15 December 2022
EMA/CHMP/17771/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imjudo

International non-proprietary name: tremelimumab

Procedure No. EMEA/H/C/006016/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Imjudo
Applicant:	AstraZeneca AB 151 85 Sodertalje SWEDEN
Active substance:	Tremelimumab
International Non-proprietary Name/Common Name:	tremelimumab
Pharmaco-therapeutic group (ATC Code):	monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates L01FX20
Therapeutic indication(s):	Imjudo in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	20 mg/ml
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AEX	Anion exchange chromatography
AFP	Alpha-fetoprotein
ALBI	Albumin-bilirubin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
AUC	Analytical ultracentrifugation
$AUC_{0\text{-}inf}$	Area under the serum concentration-time curve from 0 to infinity
BCLC	Barcelona clinic liver cancer
BICR	Blinded independent central review
BIP	Boehringer Ingelheim Pharma Gmbh & Co. KG
BLA	Biologics license application
BOR	Best objective response
BRAT	Benefit-risk assessment tool
BSA	Bovine serum albumin
BSE	Bovine spongiform encephalopathy
CCI	Container closure integrity
CD	Cluster of differentiation
CD	Circular dichroism
CDC	Complement-dependent cytotoxicity
CDR	Complementarity determining region
CEP	Certificate of suitability
CEX	Cation exchange chromatography
CFU	Colony-forming unit
CGE	capillary gel electrophoresis
CI	Confidence interval
cIEF	Capillary isoelectric focusing
CIP	Cleaned-in-place
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
$C_{min,1}$	Minimum serum concentration after the first dose
CPP	Critical process parameter
CQA	Critical quality attribute
CR	Complete response
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events (version 4.03)
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
D	Durvalumab 1500 mg (20 mg/kg) Q4W
DCO	Data cut-off
DCR	Disease control rate
DCR-16w	Disease control rate at 16 weeks
DCR-24w	Disease control rate at 24 weeks
DF	Diafiltration
dFBS	Dialysed fetal bovine serum
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSC	Differential scanning calorimetry
ECOG	Eastern Cooperative Oncology Group
EDQM	European Directorate For The Quality Of Medicines & Healthcare
EHS	Extrahepatic spread
ELISA	Enzyme-linked immunosorbent assay

Abbreviation or special term	Explanation
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
ES-SCLC	Extensive-stage small cell lung cancer
EU	Endotoxin unit
EVA	Ethylene vinyl acetate
FA	Final analysis
FAS	Full analysis set
FBS	fetal bovine serum
Fc region	Fragment crystallizable region
FDA	United States Food and Drug Administration
GMP	Good manufacturing practices
HBV	Hepatitis B virus
HC	Heavy chain
HCC	Hepatocellular carcinoma
HCP	Host cell protein
HCV	Hepatitis C virus
HNSCC	Head and neck squamous cell carcinoma
HPLC	high performance liquid chromatography
HPSEC	high pressure size exclusion chromatography
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
ICI	Immune checkpoint inhibitor
IDMC	Independent Data Monitoring Committee
IEC	Ion exchange chromatography
IEMT	Information Exploration Management Team (acronym used to identify supplementary data outputs)
IgG	Immunoglobulin G
imAE	Immune-mediated adverse event
IO	Immuno-oncology
IPC	In-process control
IPT	In-process test
ISI	integrated summary of immunogenicity
ISS	integrated summary of safety
IV	Intravenous
JP	Japanese Pharmacopoeia
KPP	Key process parameter
LC	Light chain
LIVCA	Limit of in vitro cell age
LRV	Log reduction value
mAb	Monoclonal antibody
MCB	Master cell bank
MTP	Multiple testing procedure
MVI	Macrovascular invasion
MVM	Minute virus of mice
nAb	Neutralizing antibody
NCCN	National comprehensive cancer network
NCPP	Non-critical process parameter
NF	National Formulary (United States)
NI	Noninferiority
NK cell	Natural killer cell
NKPP	Non-key process parameter
NOR	Normal operating range
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PACMP	Post-approval change management protocol

Abbreviation or special term	Explanation
PAR	Proven acceptable range
PD	Progressive disease
PD-1	Programmed cell death-1
PDE	Permitted daily exposure
PD-L1	Programmed cell death ligand-1
PD-L2	Programmed cell death ligand-2
PFS	Progression-free survival
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PO	Polyolefin
PopPK	Population pharmacokinetics
PP	Process parameter
PPQ	Process performance qualification
PR	Partial response
PRO	Patient reported outcome
PRS	Primary eeference atandard
PRV	Pseudorabies virus
PS	Performance status
PT	Preferred term
PV	Process validation
PVC	Polyvinyl chloride
QLQ-C30	30-item core quality of life questionnaire
QLQ-HCC18	18-item hepatocellular cancer health-related quality of life questionnaire
QoL	Quality of life
QxW	Every x weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
Reo-3	Reovirus type 3
RLP	Retrovirus-like particle
RT-qPCR	Reverse transcription quantitative real-time polymerase chain reaction
S	Sorafenib 400 mg twice daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SIP	Steamed-in-place
SMQ	Standardized MedDRA query
SoC	Standard of care
SPR	Surface plasmon resonance
T	Tremelimumab 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W
T300+D	Tremelimumab 300 mg (4 mg/kg) for a single priming dose and durvalumab 1500 mg (20 mg/kg) Q4W
T75+D	Tremelimumab 75 mg (1 mg/kg) Q4W × 4 doses and durvalumab 1500 mg (20 mg/kg) Q4W
TEM	Transmission electron microscopy
TKI	Tyrosine kinase inhibitor
TSE	Transmissible spongiform encephalopathy
TTC	Threshold of toxicological concern
TTP	Time to progression
TTR	Time to onset of objective response
UC	Urothelial carcinoma
UF	Ultrafiltration
UPB	Unprocessed bulk
US	United States
USP	United States Pharmacopoeia
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WCB	Working cell bank
WRS	Working reference standard
XMuLV	Xenotropic murine leukaemia virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 4 March 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Imjudo, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 October 2021.

The applicant applied for the following indication:

IMJUDO in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0107/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0107/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active substance status

The applicant requested the active substance tremelimumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant did seek Scientific Advice from the CHMP.

Summary of questions raised/ issues discussed in the scientific advice
The applicant received scientific advice on the development of durvalumab, tremelimumab for the treatment of hepatocellular carcinoma from the CHMP on the 18 May 2017 (EMA/CHMP/SAWP/286452/2017). The scientific advice pertained to the following clinical aspects:

- AstraZeneca intends to conduct a Phase 3 randomised study to evaluate durvalumab and durvalumab in combination with tremelimumab for the treatment of patients with unresectable HCC who are not eligible for loco-regional therapy.
- The proposed Phase 3 study design is appropriate to support registration of durvalumab and durvalumab in combination with tremelimumab at the proposed dosing regimens. In particular: the patient population has been appropriately defined in this study to support registration in HCC patients who are not eligible for loco-regional therapy; the proposed geographical recruitment and trial stratification criteria are appropriate and in turn, will support registration in this region; the sorafenib is the most appropriate active comparator for this study; the proposed endpoints and targeted magnitude of benefit; the proposed statistical analysis approach to evaluate the efficacy endpoints, as well as the multiple testing procedure to control the overall Type 1 error rate.
- The data from the Phase 1/2 Study 22 will provide sufficient evidence of contribution of components for durvalumab and for tremelimumab to support registration of durvalumab in combination with tremelimumab in patients with HCC not eligible for loco-regional therapy.
- The registrational utility of surrogate endpoints in this disease setting. Specifically, does the Agency agree that Time to Progression (TTP) (defined as time to progression or HCC-related death [i.e. non-HCC-related deaths will be censored]), if included as another primary endpoint, with appropriate control of the overall type I error rate (for example the alpha could be split between overall survival and TTP), could form the basis of regulatory approval in advance of the overall survival result being available.
- AstraZeneca's proposed biomarker development strategy.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Selma Arapovic Dzakula

The application was received by the EMA on	4 March 2022
The procedure started on	24 March 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 June 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 June 2022

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 June 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	21 July 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	09 September 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	14 October 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 October 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	10 November 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 November 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 November 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive for granting a marketing authorisation to Imjudo on	15 December 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	15 December 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Primary liver cancer (Hepatocellular carcinoma, HCC) accounts for approximately 906,000 new cases and 830,000 deaths per year globally. In Europe, there are approximately 87,000 new cases a year and around 78,000 deaths (WHO 2020). Hepatocellular carcinoma represents about 90% of primary liver cancers (EASL 2018).

The initially claimed therapeutic indication was:

TRADENAME in combination with durvalumab is indicated for the treatment of adults with unresectable hepatocellular carcinoma (uHCC).

2.1.2. Epidemiology and risk factors

The incidence of HCC increases progressively with advancing age in all populations, reaching a peak at 70 years (El-Serag 2012, White et al 2017). Rates of both incidence and mortality are 2 to 3 times higher among men than among women in most regions (Sung et al 2021).

The main risk factors for HCC are chronic infection with HBV or HCV, aflatoxin-contaminated foods, heavy alcohol intake, excess body weight, type 2 diabetes, and smoking. The major risk factors vary from region to region, which is reflected in the incidence of HCC across geographic regions (Sung et al 2021). The highest incidence rates are seen in East Asia and Sub-Saharan Africa, while lower rates are seen in Europe and North America (WHO 2019).

Worldwide, HBV causes an estimated 75% to 80% of HCC cases, while HCV causes 10% to 20% of cases (Perz et al 2006). HCV infection (particularly in the US, Japan, and Egypt [Mak et al 2018, McGlynn et al 2015]), excessive alcohol consumption, and non-alcoholic fatty liver disease (linked to the growing prevalence of obesity and type 2 diabetes) represent the main risk factors for HCC (Vogel et al 2019).

2.1.3. Biologic features

Normal liver tolerogenic mechanisms are likely responsible for chronic liver inflammation or carcinogenesis. Chronic presentation of pathological antigens in the liver can actively suppress immune responses, thus inducing a state of immune tolerance to the pathogen or tumour. Hepatocellular carcinoma takes advantage of peripheral tolerance to evade cell mediated immune responses, which allows the tumour to grow. Chronic hepatic inflammatory responses are the number one risk factor for liver tumour development (Makarova-Rusher et al 2015).

Moreover, increased expression of immunosuppressive cell populations, such as regulatory T cells and myeloid derived suppressor cells, and inhibitory signalling molecules, such as CTLA 4 and PD 1, have been observed in HCC (Gao et al 2009, Hato et al 2014, Pardee and Butterfield 2012) and is additionally associated with HBV and HCV infection. This upregulation contributes to the immunosuppressive environment for HCC and highlights the importance of the PD-(L)1 and CTLA-4 pathways in HCC (Golden-Mason et al 2007, Pardee and Butterfield 2012, Peng et al 2008).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The HCC prognosis and treatment depend on factors such as tumour burden, degree of liver dysfunction, and clinical performance status (PS) (Marrero et al 2018, Vogel et al 2019). Hepatocellular carcinoma classically develops and grows in silent fashion, making its discovery challenging prior to the development of later stage disease (Bialecki and Di Bisceglie 2005), which usually leads to a late diagnosis, with a median survival following diagnosis of approximately 6 to 20 months (McGlynn et al 2015). Hepatocellular carcinoma is a medically complex and difficult to treat disease as the majority of patients have underlying cirrhosis requiring management of both the malignancy and underlying liver disease. Hence, the 5-year survival rate for HCC is less than 20% (Sarveazad et al 2019, Villanueva 2019). Unresectable HCC remains a difficult to treat disease, and the majority of patients will ultimately die of either HCC or complications of liver disease.

2.1.5. Management

Sorafenib, an oral TKI targeting multiple kinases, including VEGFR-1, -2, and -3 and BRAF, has been the standard of care (SOC) for advanced HCC in the first-line setting since its approval in 2007, which was based on improvement compared to placebo, establishing a median OS of 10.7 months (vs 7.9 months for placebo [Llovet et al 2008]). Subsequent studies have demonstrated a median OS ranging from 10.7 to 13.4 months (Finn et al 2021, Llovet et al 2008, Yamashita et al 2020). In 2018, lenvatinib, another multiple kinase inhibitor against VEGFR-1, -2, and -3 and fibroblast growth factor receptor-1, -2, -3, and -4, was approved as first-line treatment for advanced HCC in patients without main portal vein invasion and ECOG PS 0 to 1. Lenvatinib demonstrated non-inferiority to sorafenib in a Phase III study, with a median OS of 13.6 months vs 12.3 months with sorafenib (Kudo et al 2018). Atezolizumab (a PD-L1 inhibitor) in combination with bevacizumab (an angiogenesis inhibitor targeting vascular endothelial growth factor A) has also been approved in the first-line setting, after the Phase III IMbrave150 study showed improvements in OS and PFS compared to sorafenib (Finn et al 2020b, Finn et al 2021). The NCCN, ESMO, and Japanese Society of Hepatology guidelines were updated in 2020 to recommend atezolizumab in combination with bevacizumab as the preferred option to treat first-line HCC (NCCN Guidelines 2021, JSH 2021; Vogel and Martinelli 2021 [ie, ESMO Guidelines 2021]).

Regorafenib and cabozantinib (both multitargeted TKIs) have been approved for patients with advanced HCC, who have tolerated and progressed on sorafenib (Abou-Alfa et al 2018, Bruix et al 2017). Another approved second-line therapy is ramucirumab (a monoclonal antibody against VEGFR 2), which has improved survival in patients with serum AFP $\geq$ 400 ng/mL and previous treatment with sorafenib (Zhu et al 2019). In addition, nivolumab (an anti-PD-1 mAb) in combination with ipilimumab (an anti CTLA-4 mAb) has recently received accelerated approval from the FDA for patients previously treated with sorafenib, due to results from the CheckMate 040 study, a Phase II study in which nivolumab (1 mg/kg, Q3W) plus ipilimumab (3 mg/kg Q3W × 4) (N=50; 28/50 [56%] with HBV) achieved a 32% ORR (Yau et al 2020).

Unmet medical need

Despite recent advances in treatment options, patients with uHCC continue to have a low life expectancy and the underlying liver disease and portal vein hypertension increase the risk of gastrointestinal bleeding in patients with advanced HCC, which can be potentially life-threatening. Currently available therapies provide only a modest improvement in survival with safety profiles that require management due to adverse events such as diarrhoea, hypertension, and palmar-plantar erythrodysaesthesia (PPE). Treatment with atezolizumab plus bevacizumab also carries a higher incidence of bleeding, including fatal bleeding, despite attempts to exclude patients at risk for

gastrointestinal bleeding from the pivotal study. Moreover, the underlying liver cirrhosis may result in moderate liver dysfunction, which may exacerbate the toxicity of systemic therapies such as TKIs. Hence, additional therapeutic options are needed, including options for patients with uHCC who are at higher risk of bleeding events, so there exist an unmet medical need for better and tolerable treatment options for patients with uHCC.

2.2. About the product

Tremelimumab binds to CTLA-4 that is primarily expressed on the surface of activated T lymphocytes. Binding of CTLA-4 to its target ligands (CD80 and CD86) provides a negative regulatory signal, which limits T-cell activation and blocks the interaction of the co-stimulatory receptor CD28 with CD80 and CD86, thus limiting CD28-mediated T cell co-stimulation. Tremelimumab antagonises binding of CTLA-4 to its ligands and enhances human T-cell activation as demonstrated by increased cytokine (IL-2, IFN-γ) production *in vitro* in whole blood or PBMC cultures. In addition, blockade of CD80/86 binding to CTLA-4 by anti CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumour activity in animal models, including killing of established murine solid tumours and induction of protective anti-tumour immunity. Therefore, it is expected that treatment with tremelimumab will lead to activation of the human immune system, increasing anti-tumour immunity in subjects with solid tumours.

Durvalumab binds to programmed cell death ligand-1 (PD-L1) (but not programmed cell death ligand-2) and thus blocks its interaction with programmed cell death 1 (PD-1) on T-lymphocytes (T-cells) and cluster of differentiation (CD) 80 (B7.1) on immune cells (ICs) and is engineered to reduce antibody-dependent cell-mediated cytotoxicity (ADCC). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses and may result in tumour regressions including objective responses based on tumour cell reduction as well as in stable disease due to tumour growth control. This mechanism of action may elicit eventually delay of progression and extension of survival.

The CHMP adopted a positive opinion for the following indication:

IMJUDO in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

Posology: The recommended dose of Imjudo is 300 mg as a single dose (intravenous infusion over 1 hour) administered in combination with durvalumab 1500 mg at Cycle 1/Day 1, followed by durvalumab monotherapy every 4 weeks, until disease progression or unacceptable toxicity. Dose escalation or reduction is not recommended during treatment with Imjudo in combination with durvalumab. Treatment withholding or discontinuation may be required based on individual safety and tolerability.

2.3. Type of application and aspects on development

Table 1: Summary of EMA regulatory interactions and correspondence specific to the HIMALAYA study

Date	Type of interaction	Summary of outcome
17 March 2017 – 22 May 2017	Pre-Phase III Scientific Advice	EMA agreed with the principles of the statistical analysis and commented that the proposed interim analysis may lack power and/or maturity when investigating all subgroups (including patients with low expression of PD-L1 in whom prognosis may be better and treatment efficacy less pronounced). The design of Study 22 is appropriate, but contribution of components is dependent on results and could be driven by PD-L1 expression.
19 Jan 2022	Joint Pre-submission Meeting	AstraZeneca held a joint pre-submission meeting with the Rapporteur and Co-Rapporteur to review the planned submission of tremelimumab in combination with durvalumab for the treatment of adults with unresectable hepatocellular carcinoma. The Rapporteur acknowledged that HIMALAYA was well-designed to evaluate contribution of components. It was noted, however, that the added benefit of tremelimumab relative to the safety profile of the combination would be a key consideration in the review. Additionally, study integrity will be a key consideration for the Agency during their review. The Rapporteur sought assurance to support that study integrity was maintained, as the non-inferiority margin was adopted without prior agency feedback during the conduct of the study.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 20 mg/mL of tremelimumab as active substance.

Other ingredients are: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, disodium edetate dihydrate, polysorbate 80 and water for injections.

The product is available in a 2 mL type I glass vial with an elastomeric stopper and a violet flip-off aluminum seal for the 25 mg presentation and in a 20 mL type I glass vial with an elastomeric stopper and a dark blue flip-off aluminum seal vial for the 300 mg presentation.

2.4.2. Active substance

2.4.2.1. General information

Tremelimumab (INN) active substance is a human monoclonal antibody from the immunoglobulin (Ig) G2a subclass comprising of 2 heavy chains (HC) and 2 light chains (LC) covalently linked with 6 inter-chain disulfide bonds. There is one N-linked glycosylation site at Asn-301 on each HC (Fc region). The molecular weight of tremelimumab is 149,145 Da. The theoretical and experimentally confirmed extinction coefficient is 1.43 $(mg/mL)^{-1}cm^{-1}$ and the pI is in the range of 8.5–9.0.

The mechanism of action is blocking of the interaction between CTLA-4, a cell surface receptor expressed on activated T cells, and the natural B7 ligands (CD80 and CD86) on antigen-presenting cells resulting in enhanced T cell-mediated immune response such as T cell activation, proliferation, and lymphocyte infiltration into tumours leading to tumour cell death.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturing and testing of the active substance is performed by Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, Biberach an der Riss 88397, Germany. The active substance is manufactured, packaged, stability tested and quality-control tested in accordance with Good Manufacturing Practice (GMP).

Description of manufacturing process and process controls

The active substance manufacturing process has been adequately described and is considered acceptable. It comprises of upstream process (cell culture steps) and downstream process (purification steps).

The upstream process comprises of vial thaw, inoculum expansion, seed bioreactors, production bioreactor and harvest. Cell culture process is initiated with the thaw of cells from one working cell bank (WCB) vial. One production bioreactor results in one batch of active substance (parent batch), for which a unique batch number is assigned. Subsequently, this parent batch may be subject to splitting/pooling (sub-lotting) and stored under refrigerated or frozen conditions. The applicant defined the material inputs, critical process parameters (CPPs) and non-critical process parameters (NCPPs), and process outputs (in-process controls, microbial controls, and performance attributes) for each manufacturing step and are considered acceptable. The harvest is initiated by lowering the bioreactor temperature and followed by continuous centrifugation and filtrations (depth filtration and membrane filtration). The pre-harvest samples are taken from the production bioreactor on the harvest day to perform unprocessed bulk (UPB) testing. Harvest product is tested for bioburden and endotoxins.

The protein is then purified using a series of packed bed chromatographic and membrane filtration techniques. All purification steps were sufficiently described. The used buffers and solutions, chromatography media, filters and other product contact disposables were presented. CPPs, NCPPs, in-process controls (IPCs), microbial controls and performance attributes with the proposed limits (proven acceptable range - PARs, acceptance criteria or action limits) were adequately defined for each purification step.

The purification process is followed by a formulation step, which consists of product concentration, diafiltration and dilution to formulate the bulk active substance at a concentration of 20 g/L. The formulated bulk is then filtered into a stainless-steel mobile vessel. The filtered bulk is then 0.2 µm filtered into the active substance containers (Ethyl Vinyl Acetate – EVA - bags) for long-term storage at 2-8°C. Shipment to the finished product manufacturing site is carried out using EVA bags.

There is one optional step "controlled freeze, frozen storage and controlled thaw of the active substance" during the manufacturing process, to facilitate frozen storage of the active substance. The formulated bulk active substance is transferred through a filter into cryovessels and subjected to controlled freezing. The frozen bulk can be stored in stainless-steel cryovessels for up 48 months at -40±10°C. The frozen active substance can be thawed and filtered into a stainless-steel mobile vessel. After the indicated hold times in mobile stainless-steel vessels at specified temperatures, the thawed active substance is again filtered into the EVA bags which are then shipped to the finished product manufacturing site to initiate the manufacturing process of the finished product. The applicant justified its strategy to include this optional manufacturing step as it is required for commercial supply and

inventory management. The applicant clarified that the release testing of the active substance is performed on the bulk active substance under GMP part II (i.e. freezing, thawing, filtrations, storage and transfer between storage containers). This approach is considered unusual, however, all manufacturing steps between the bulk active substance and the active substance filled in EVA bags were appropriately validated and it was shown that after these additional processing steps, all quality attributes comply with the active substance specification. Further, bioburden and endotoxin testing are routinely performed at each filtration step to ensure the microbial quality of the active substance. Stability data under frozen and refrigerated storage conditions were provided and indicated that no significant change in product quality attributes was observed over the proposed storage hold times in the individual containers (stainless steels and EVA bags). In conclusion, the proposed strategy is not considered in conflict with GMP principles. Nonetheless, it is recommended that the proposed active substance manufacturing process and control strategy should be under intensive surveillance of the GMP supervisory authority during future inspections.

Reprocessing steps have been adequately described by the applicant.

The primary packaging component for the liquid active substance stored at 2-8°C is a disposable, single-use EVA bag, constructed from a multilayer film, with the product contact layer composed of ethylene vinyl acetate (EVA) copolymer and a gas barrier film composed of ethyl vinyl alcohol. The materials of construction of the individual components were provided and a representative certificate of release from the supplier was provided. Acceptance of the EVA bags for use is based on confirmation from the supplier's CoA that all acceptance criteria were met. The bags are pre-sterilised by the vendor using validated gamma irradiation (25 kGy minimum) and a representative certificate of irradiation from the approved sub-contractor was also provided in the dossier. Compatibility of the active substance with EVA bags was demonstrated through stability studies. Extractables and leachables assessment for EVA bags was performed and the EVA bags were found to be of low risk for leachables upon review of data from the process qualification study.

The mobile vessel and the cryovessel are both made of 316L stainless-steel (manufactured from non-corroding chromium-nickel-molybdenum), cleaned-in-place (CIP), steamed-in-place (SIP) and integrity-tested via a pressure hold test prior to use. Both are equipped with a 0.2 µm liquid filter, so the active substance is filtered prior to entry into these containers. Compatibility of the active substance with stainless-steel cryovessels and mobile vessels was demonstrated through stability studies. The stainless-steel tanks are considered low risk for extractables and leachables. A risk assessment for the presence of elemental impurities has been performed by the applicant, in line with ICH Q3D, and the conclusion that no specific control of elemental impurities at the active substance level is endorsed.

Control of materials

Sufficient information regarding the raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented.

The preparation of cell culture media and nutrient feed was adequately described in the dossier. Storage temperature and storage duration were provided for both cell culture media and nutrient feed. Information related to the origin of the cell culture medium and specifications for the material were provided. No animal sourced ingredients or animal derived reagents are used in their manufacture.

Materials of animal origin were used during cell line development and also in the banking of the master cell bank (MCB) and adequate information regarding these materials was included in the dossier.

The tremelimumab antibody was initially generated in a hybridoma cell line. The genes encoding tremelimumab were isolated from hybridoma cells and were used for generation of the expression plasmid.

The host cell line (NS0 mouse myeloma cell line) was used for the preparation of the production cell line by electroporation of NS0 cells with the expression plasmid. These cells were subsequently used to prepare a pre-MCB stock, which was tested for sterility and mycoplasma.

A two-tiered cell banking system is used for tremelimumab manufacturing. Preparation of the MCB and WCB is adequately presented in the dossier. In line with ICH Q5D, 2 independent WCB storage sites are used to ensure continuous, uninterrupted production of pharmaceuticals in case of catastrophic events. The cell banks were tested for identity, purity, cell substrate stability including sterility, mycoplasma, adventitious viruses and genetic stability. MCB and limit of *in vitro* cell age (LIVCA) bank were also tested for infectious retroviruses. The range of used tests is considered sufficient in accordance with ICH Q5A requirements and all tests met the acceptance criteria. The results confirmed the identity, cell banks viability and that the cell banks are free of bacteria, fungi, mycoplasma and adventitious viruses. Phenotypic stability was demonstrated by assessing growth, productivity, and product quality for a certain number of days from the WCB thaw. The genetic stability of the expression plasmid and integrated genes for tremelimumab was characterised based on testing of the MCB, WCB, and the LIVCA bank. Based on cell line stability data and viral safety data from LIVCA, the limit of *in vitro* cell age is considered adequately justified.

The applicant has provided a stability protocol for MCB and WCB, indicating the stability tests and the acceptance criteria. The stability programme with respect to growth and viability (recoverability) of the MCB and WCB was introduced with 5 years measure intervals.

In conclusion, sufficient information is provided regarding testing of MCB and WCB and release of future WCBs.

Control of critical steps and intermediates

A comprehensive overview of the critical IPCs and critical in-process tests (IPTs) applied throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regards to critical, as well as non-critical operational parameters and IPTs. Actions taken if limits are exceeded are specified.

Process validation

A three-stage strategy is followed to define and validate the active substance manufacturing process throughout the process lifecycle. Stage 1 (process design) included the process characterisation and determination of CPPs. Stage 2 (process qualification stage) included the evaluation of the process design to determine if the process is capable of reproducible commercial manufacturing. Stage 3 (continued process verification) is considered as ongoing assurance gained during routine production that the process remains in a state of control.

The overall approach is in line with ICH Q7 Guideline and it is considered acceptable. Process validation was completed using consecutive active substance lots at the proposed commercial manufacturing scale at the proposed manufacturer (Boehringer Ingelheim Pharma GmbH & Co. KG - BIP). Continued process verification identified 2 new critical quality attributes (CQAs) which resulted in the re-classification of some process parameters and hold times. Additional concurrent validation data demonstrated that results for the process parameters and process outputs for the recently produced lots are consistent with the outcomes of the prospective validation study.

All manufacturing steps were covered during the process validation studies and the process parameters selected included all the CPPs and selected NCPPs, the latter being further classified as Key Process Parameters (KPPs) and Non-Key Process Parameters (NKPPs), based on their potential impact on process performance. Regarding the process outputs, results for IPCs, microbial controls (MCs) and performance attributes (PAs) were monitored in the process validation study. The validation acceptance criteria for monitored process parameters were established within the PARs which were determined based on process characterisation study. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the IPTs are fulfilled, demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria. Deviations observed in the process validation study were investigated and it was concluded that no impact on the process validation study could be expected.

Process intermediates and active substance hold times were validated through a small-scale study evaluating biochemical hold stability and are supported by equipment qualification hold time studies, demonstrating effective microbial control. Resin lifetime and carryover studies were also conducted at small-scale to establish the maximum number of product-contacting cycles for each chromatography resin used in the purification process and to demonstrate that the cleaning procedures for the chromatography resins are sufficient to reduce carryover of protein and host cell DNA to acceptable levels. Overall, the validation lifetime and carryover studies met the acceptance criteria and therefore the proposed maximum number of product-contacting cycles for the affinity resin and maximum cycles for both ion exchange resins are considered acceptable.

Filtration membrane studies were conducted at commercial scale to validate membrane carryover cleaning, reuse and storage for the filtration steps in the purification process. The target maximum number of membranes uses is adequately defined by the applicant. Validation of reprocessing steps was performed using small-scale studies. In line with the Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014), the verification protocols to be applied in case of the need for reprocessing at large scale were provided and are considered adequate. The applicant demonstrated the suitability of all components that come into contact with the active substance formulation during the manufacture. Materials evaluated for leachables and details regarding the risk assessment were provided.

In conclusion, the active substance manufacturing process has been adequately validated.

Manufacturing process development

Different manufacturing processes have been described. Process A to E batches were used in non-clinical and clinical studies. All clinical studies in this application were conducted by AstraZeneca utilizing Process E (the intended commercial process) active substance lots. During the development, several formulations and manufacturing sites were used. The applicant adequately described changes that were made throughout the development of the manufacturing process, as well as the comparability assessments that were conducted.

The applicant provided detailed results of analytical testing for the active substance lots manufactured from processes C, D and E. Furthermore, batch analysis data for process B and C and a summary of min-max ranges for early development Process A batches (used for early toxicology studies and non-clinical PK study) were provided. Overall, the lots met the specifications in place at the time of release. Side-by-side testing of the characterisation tests for each comparability assessment was summarised in tabular format. The results demonstrate that the active substance lots manufactured using Process C, D and E are highly comparable in terms of product quality, physicochemical and biological properties.

Characterisation

A comprehensive physicochemical and biological characterisation of the tremelimumab molecule was presented. The characterisation of tremelimumab involved primary structure, higher order structure, carbohydrate structure, charge and size heterogeneity, and biological properties.

In conclusion, the active substance has been sufficiently characterised, revealing that tremelimumab has the expected structure of a human IgG2a subclass antibody. The analytical results are consistent with the proposed structure.

Product-related impurities have been well characterised and studied. These attributes are considered CQA and the impact of these attributes on biological activity was adequately discussed. Adequate characterisation of product-related impurities has been presented, and therefore, the controls strategy for such impurities can be endorsed.

Process-related impurities comprise of impurities which arise from the cell substrates, cell culture and purification processing. Clearance and control of process-related impurities have been sufficiently discussed.

In summary, the characterisation is considered appropriate for this type of molecule.

2.4.2.3. Specification

Tremelimumab active substance specification has been defined in accordance with ICH Q6B and includes: general tests (clarity, colour, pH), oligosaccharide analysis, total protein content, identity, product-related impurities, process-related impurities), potency and safety attributes tests (bioburden, endotoxin).

Results from the statistical analysis of both release and stability data were used to support the justification of the proposed specifications. Justification for the omission of certain tests has been adequately presented by the applicant. During the assessment, acceptance criteria for several quality attributes (i.e. purity, product-related impurities and potency) were tightened upon request. In conclusion, the proposed tests panel is considered appropriate and acceptance criteria clinically justified.

The analytical methods and acceptance criteria applied during stability studies are identical to the active substance release specifications, except for certain tests conducted only at release. The stability acceptance criteria are set wider than the release acceptance criteria for several parameters, which is in principle acceptable. As the number of available batches for setting the acceptance criteria was limited, the applicant should further revise the active substance stability specification acceptance criteria for these parameters, when data from additional batches are available **(REC)**.

Analytical methods

Analytical procedures performed in accordance with Ph. Eur. are appearance (color, clarity), pH, bioburden and endotoxin. Non-compendial methods are generally described with a sufficient level of detail (including equipment, reagents, system suitability and sample acceptance criteria) and are appropriately validated in accordance with ICH guidelines. The biological activity (potency) of the active substance is determined using a cell-based potency assay.

Batch analysis

The applicant provided detailed results of analytical testing for the active substance lots manufactured from processes C, D and E. The results are within the specifications in place at the time of release and confirm consistency of the manufacturing process.

In addition, batch analyses data for Process B and Process C active substance lots were provided and min-max ranges for Process A lots were summarised.

Reference materials

The history of the used reference materials was provided. Several reference standards were used during development, however only the current primary reference standard (PRS) was used to test clinical material for this application. A two-tiered system of reference standards (PRS and working reference standard - WRS) is established and a portion of PRS was used as the first lot of WRS. Both PRS and WRS are representative of the production process and clinical performance and meet the release specifications. The preparation, storage and qualification of future standards was described in the dossier and is considered acceptable.

2.4.2.4. Stability

The applicant proposed that the active substance shelf-life is up to 48 months storage at -50°C to -30°C in stainless-steel vessels, followed by up to 24 months storage in EVA bags at 2°C to 8°C. The total storage duration should not exceed 72 months.

The applicant provided stability data to support storage of frozen bulk active substance in stainless-steel containers at -50°C to -30°C (long-term storage conditions), and 2-8°C and 23-27°C/55-65% RH (accelerated storage conditions).

Stability studies for the frozen bulk active substance were performed using reduced-scale stainless-steel containers (considered representative of the full-scale vessels) and lots manufactured at the commercial site (BIP) using the commercial manufacturing process (Process E). Long-term stability studies (48 months) are completed for 4 representative lots and for one lot data for 36 out of 48 months have been provided. No meaningful change was observed under frozen storage conditions. The results demonstrate stability of the frozen bulk active substance at -50°C to -30°C in stainless-steel vessels for up to 48 months.

Additionally, 12 months stability data have been provided for 5 bulk active substance lots stored at accelerated storage conditions (2-8°C and 23-27°C/55-65% RH). All stability lots met the acceptance criteria, however some trends in the studied parameters were observed which were more significant under storage at 23-27°C/55-65% RH. The applicant sufficiently discussed all these trends. Based on these results, the short-term storage of liquid active substance in stainless-steel containers is considered justified.

The stability of the active substance when stored in EVA bags has been demonstrated for 36 months at 5±3°C. Stability studies were performed using reduced-scale EVA bags and lots manufactured at the commercial site (BIP) using the commercial manufacturing process (Process E).

Data from long-term (2-8°C, for 36 months) and accelerated (23-27°C/55-65% RH, for 6 months) stability studies were provided. Long-term studies are completed for 3 representative lots and for one lot data for 6 out of 36 months have been provided.

Additionally, the applicant provided a summary of active substance photostability studies, conducted in accordance with ICH Q1B guideline. Based on the conclusions of these studies, the active substance should be protected from light during storage.

A sequential stability study supporting the proposed cumulative shelf-life (48 months storage at -50°C to -30°C in stainless-steel vessels followed by up to 24 months storage in EVA bags at 2°C to 8°C) has not been performed. However, 3 active substance stability batches which were included in the stability study for the active substance filled in EVA bags for 36 months at 2°C to 8°C followed the 12 months

storage in stainless steel tanks at -50°C to -30°C. Therefore, based on the overall presented stability data, the proposed cumulative shelf-life for the active substance is considered acceptable. The applicant committed to perform a sequential stability study utilizing at least one active substance batch stored in accordance with the above-mentioned conditions **(REC)**.

A post-approval stability protocol and stability commitment have been given. For ongoing studies any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

Tremelimumab finished product is a sterile, preservative-free, liquid dosage form intended for intravenous infusion after dilution. The finished product is provided in 2 single-dose presentations: a 25 mg/1.25 mL vial presentation and a 300 mg/15 mL vial presentation.

Both presentations contain 20 mg/mL tremelimumab in 20 mM histidine/histidine-HCl monohydrate, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate and 0.02% (w/v) polysorbate 80.

The finished product is filled with a volume in excess of the label-claim volume to meet the USP/Ph. Eur./JP test requirements. The proposed overfill volumes are 0.26 mL and 1 mL for 25 mg and 300 mg presentations respectively, resulting in target fill volumes of 1.51 mL and 16 mL. The proposed overfill was adequately justified based on development data. The finished product does not contain any overages.

The primary packaging components consist of a type I borosilicate glass vial (2R or 20R) and grey butyl elastomer stopper (13 mm or 20 mm) capped with an aluminium seal. The vials comply with Ph. Eur. 3.2.1 for Type I borosilicate glass. The butyl elastomer stopper complies with Ph. Eur. 3.2.9. Stoppers are silicone coated and the compliance with Ph. Eur. Monograph 3.1.8 was confirmed. Extractables and leachables from primary container components were evaluated based on a 3-stage risk-based strategy. All results were either below the Threshold of Toxicological Concern (TTC), not detected over time or found below the established and toxicologically justified Permitted Daily Exposure (PDE) level. The choice of the container closure system has been validated by finished product stability data and is adequate for the intended use of the product.

The active substance is delivered ready-to-fill and no formulation or dilution steps are performed during the finished product manufacturing process. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. No novel excipients or no excipients of human or animal origin are used in the finished product formulation. Compatibility of tremelimumab with these excipients was demonstrated in long-term stability studies.

Pharmaceutical development

The formulation composition was developed based on experience with the solubility, structural integrity and stability of the product. A summary of the formulation development studies was provided and the rationale for introduced changes to develop the intended commercial formulation was thoroughly discussed. A characterisation study was executed to evaluate the robustness of the intended commercial formulation, to identify any critical formulation parameters and to understand the impact of those critical parameters on the finished product CQAs. In conclusion, the suitability of the intended formulation has been demonstrated based on development studies.

The applicant presented 4 versions of the manufacturing process used throughout the clinical development. Process 4 for the commercial 25 mg and 300 mg finished product vials uses Process E active substance. Overall, the finished product manufacturing process development was clearly described. The rationale of the performed changes throughout the development was discussed accordingly and did not raise concerns.

Three studies were presented to demonstrate the comparability between lots produced in different stages of development. The performed comparability studies are considered well designed and in accordance with ICH Q5E guideline. The provided results demonstrate the comparability of the lots produced by different finished product manufacturing processes and sites.

Process characterisation studies were performed. Individual unit operations were evaluated regarding impact on CQAs and process performance parameters. Based on the results from the process characterisation studies, parameters that impact CQAs are classified as CPPs, while process parameters that do not impact any CQA are classified as NCPPs. Based on the tested ranges for process parameters, their respective PARs were defined. It was demonstrated that in the defined PARs there is no impact on the quality attributes of the product. As part of the characterisation study, the impact of manufacturing environment was evaluated. Leachables from in-process product contact materials were evaluated based on risk assessment. Potential leachables were found at concentrations well below the TTC limit. Therefore, the provided conclusion that the risk to patient safety is low is considered acceptable.

In-use compatibility

The finished product must be diluted into 0.9% (w/v) saline or 5% (w/v) dextrose solutions prior to dose administration. Compatibility of the finished product was assessed in 250 mL polyolefin (PO) and polyvinyl chloride (PVC) intravenous (IV) bags. Compatibility with PVC administration sets and 0.2 µm polyethersulfone in-line filters was also tested.

In summary, the physical-chemical and microbiological in-use stability of the diluted product in IV bags has been demonstrated for up to 28 days at 2°C to 8°C and for up to 48 hours at room temperature (up to 30°C) from the time of preparation. The provided results support the proposed instructions for use and handling of the finished product stated in the SmPC (i.e., if not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be normally longer than 24 hours at 2°C to 8°C or 12 hours at room temperature (up to 25°C), unless dilution has taken place in controlled and validated aseptic conditions).

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured, filled, packaged, inspected and tested in accordance with GMP at qualified vendors. The finished product is released in the EEA by AstraZeneca AB, Gärtunavägen, SE-151 85 Södertälje, Sweden. A process flow diagram for the manufacture of the finished product is provided in the dossier. Detailed descriptions of the manufacturing steps are presented. Batch formula has been provided for the intended commercial batch size ranges: for the 25 mg finished product (1.51 mL target fill volume) and for the 300 mg finished product (16 mL target fill volume).

The finished product manufacturing process consists of pre-filtration and pooling, mixing, and sterile filtration of the active substance, followed by aseptic vial filling and stoppering with sterile container closure components. There are no reprocessing steps in the finished product manufacturing process.

Process control strategy is sufficiently detailed and considered acceptable. In line with the process characterisation study, CPPs and NCPPs are defined in the manufacturing process and controlled with appropriate limits. Elements of microbial control strategy were described in detail. Process parameters are monitored and maintained within established PARs. Overall, the manufacturing process and the equipment used are considered adequately described.

The manufacturing process validation study was performed following a traditional approach. The manufacturing process was validated with consecutive lots for each vial presentation at the proposed commercial manufacturing site. Production scale process validation data were presented. All process parameters (CPPs, KPPs and NKPPS) were maintained within the specified operating ranges, based on PARs established in the characterisation study. To confirm process consistency, additional IPTs (process outputs) were monitored in the process validation study and all results fell within the predefined acceptance criteria.

The pre-filtration and pooling process is designed to enable pooling of multiple active substance bags. The provided results demonstrate that homogeneity of the bulk active substance prior to filling is achieved and therefore, pooling and mixing of active substance is considered validated.

The microbial control strategy includes process design and controls, material controls, facility controls, and testing. In the process validation study, all process steps were performed as expected and the results demonstrate adequate microbial control and sterility assurance.

Sterilisation of primary container components is performed at the manufacturing site under GMP surveillance. The performed validation studies are in line with the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015) and the provided data demonstrated the suitability of the selected sterilisation processes.

Aseptic filling process is validated using media fill runs. The matrix approach alternates the smallest and largest vial format for media fill simulations. It is therefore ensured that the commercial batches are filled within the qualified aseptic filing time.

Shipping qualification studies for the bulk vials and shipping validation for finished product packaging were performed. Details regarding the validation protocols and analytical testing results were provided in dossier and are considered acceptable.

In conclusion, the validation study demonstrated consistency and robustness of the manufacturing process for both product presentations.

2.4.3.3. Product specification, analytical procedures, batch analysis

The proposed release specifications for the finished product were defined in accordance with ICH Q6B.

The finished product specification for both 25 mg and 300 mg presentation is generally based on the active substance release specification and includes general testing (appearance, osmolarity, pH, sub-visible particles, extractable volume), quantity testing, identity testing, purity testing, charge heterogeneity testing, potency testing and safety attributes testing (sterility and endotoxin). Most of the quality attributes are also tested during stability with wider acceptance criteria.

Overall, the selection of tests is endorsed and the proposed acceptance criteria are generally acceptable. Acceptance criteria for product-related impurities and variants were revised during the procedure to better reflect the clinically qualified ranges. However, as number of available batches for setting the acceptance criteria was limited, the applicant should revise the finished product release and stability specification acceptance criteria when data from an additional 30 batches are available **(REC)**.

No additional impurities are introduced in the finished product manufacturing process. Product-related impurities are tested as part of release specification and monitored in stability studies. Process-related impurities are controlled in finished product release and stability specifications.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Detailed assessment of elemental impurities in accordance with ICH Q3D guideline was provided. It is concluded that the overall risk of a potential release of elemental impurities into the finished product is low and no specific control is considered necessary. This conclusion is agreed.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Most of the analytical methods used for the finished product testing are identical to the ones used for testing of the active substance. Transfer of analytical methods between testing sites has been successfully completed.

Batch analysis

Summary of individual batch release results for Process 3 (clinical, stability) and Process 4 (validation, commercial, clinical, stability) lots was included in the dossier. Results for finished product lots manufactured by Process 3 and finished product 25 mg lots and 300 mg lots manufactured by Process 4 were provided. Only a summary of historic ranges of quality attributes were provided for Process 1 and Process 2 finished product lots, which is acceptable. The results are within the specifications set in place at the time of release and confirm consistency of the finished product manufacturing process.

Reference materials

See active substance section on Reference materials.

2.4.3.4. Stability of the product

The finished product stability studies were performed at long-term storage conditions (2-8°C), accelerated conditions (23-27°C/55-65% RH) and stressed conditions (38-42°C/70-80% RH), in accordance with ICH guidelines. In addition, photostability studies were conducted in accordance with ICH Q1B guideline. The stability studies are performed using the proposed commercial primary container and closure systems.

Tremelimumab 25 mg and 300 mg commercial presentations (Process 4) and 400 mg presentation (Process 3, used during finished product development) were included in stability studies. Concerning the 25 mg finished product presentation, stability data are provided, with three process validation (PV) lots designated the primary stability lots. Stability testing is ongoing for additional lots manufactured post-PV. For the 400 mg strength, stability data are provided for multiple production scale lots (PV and post-PV lots). These data are included as primary data for the 300 mg finished product presentation and supporting data for the 25 mg presentation. For the 300 mg finished product presentation, stability data are provided for 3 PV lots. Results for elemental impurities from leachable studies for up to 48 months are available for the 25 mg presentation and only initial values were provided for the 300 mg presentation. The elemental impurities stability testing and the formal stability study for the 300 mg vial presentation are still ongoing and the applicant committed to submit the results for Agency review when available **(REC)**.

The claimed finished product shelf-life of 48 months at 2-8°C for both 25 mg and 300 mg presentations was established based on real-time data (up to 48 months) for the 25 mg presentation at long-term storage conditions. Data for 300 mg presentation are currently very limited (up to 6 months), however, up to 48 months of stability data were provided for the 400 mg presentation used during finished product development. The applicant proposes that a combination of stability data from the 400 mg vial presentation and 25 mg vial presentation could be considered in the assignment of shelf-life for the 300 mg vial presentation. Suitability of this approach was thoroughly discussed. An identical primary container is used for both 400 mg and 300 mg presentations. All finished product presentations have the same formulation, are produced using active substance from the commercial process and the comparability between finished product Process 3 and Process 4 materials was demonstrated. Taken together, all these considerations and the comparison of stress stability study data demonstrating the highly comparable degradation profiles between the 25 mg and the 300 mg presentations, it is agreed that the data for 25 mg and 400 mg finished product presentations may be extrapolated to support the proposed shelf-life claim for the 300 mg finished product presentation.

The provided stability data at accelerated stability conditions support the proposed finished product total time out of refrigerator of 30 days, as detectable changes are observed only after 2-6 months at 23-27°C/55-65% RH, with no significant degradation trend.

Thermal stress stability studies (38-42°C/70-80% RH) were performed to reveal the finished product degradation profile. Up to 6 months of stability data for the 400 mg and 25 mg presentations and 3 months for the 300 mg presentation are available. Clear degradation trends were observed for purity, methionine oxidation and charge heterogeneity. Slight decrease in potency was observed. It was demonstrated that changes in quality profile under stress conditions are detectable by suitable analytical methods and attributes like purity, charge heterogeneity and potency are considered stability indicating.

Finished product lots exposed to light showed an increase in acidic variants, higher methionine oxidation rate, and a slight decrease in purity. No significant differences were observed for other quality attributes, including potency. It is therefore agreed that the finished product should be stored protected from light.

In conclusion, based on the provided stability data, the proposed shelf-life for the finished product of 48 months and storage conditions as stated in the SmPC (*Store in a refrigerator (2°C - 8°C)*. *Do not freeze. Store in the original package in order to protect from light*) are acceptable. Reconstitution and in-use instructions in the SmPC are consistent with the reported stability findings of the in-use studies, as previously discussed.

A post-approval stability protocol and stability commitment have been given. For ongoing studies any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA. The ongoing stability programme will be followed up by the annual incorporation of at least one additional commercial-scale batch as stated in a stability commitment.

2.4.3.5. Adventitious agents

Materials of animal origin were used only during cell line development as well as during preparation of specified cell banks and used also during cryopreservation of the specified cell banks. Certificates of analysis including information regarding the origin and certificates of suitability (CEPs) issued by the European Directorate for the Quality of Medicines & HealthCare (EDQM) were provided for all these materials. A TSE/BSE (Transmissible/Bovine Spongiform Encephalopathy) risk assessment for all these materials was performed with the conclusion that the risk of transmission of TSE/BSE from these materials is extremely low, which is endorsed. The applicant also provided the certificate of origin for the cell culture medium. This material is considered sufficiently documented, with negligible TSE/BSE risk of transmission.

A comprehensive programme, in accordance with ICH Q5A, is employed to test, evaluate and eliminate the potential risks of adventitious and endogenous viral agents. The programme includes control of raw materials used in the manufacturing, viral testing and characterisation of the cell banks (MCB, WCB, LIVCA) used in the GMP process, virus testing of UPB and viral clearance and inactivation assessment of the purification process.

Viral clearance capability of the active substance purification process was evaluated in scale-down experiments using 4 model viruses. The viral clearance experiments were performed matching pre-defined acceptance ranges for process parameters and performance outputs. The level of purification of the scaled-down version was shown to be representative of the production procedure.

All viral clearance experiments were performed in duplicate. The lower $\log_{10}$ reduction value (LRV) from the duplicate experiments was used to calculate cumulative LRV. The viral clearance experiments demonstrated that the purification process provides a cumulative LRV of ≥21.16, ≥18.28, ≥17.05, and ≥16.49, respectively, for the 4 model viruses. For the chromatography steps, the used chromatography resin provided LRVs either comparable to (within 0.5 $\log_{10}$) or better than the new chromatography resin, demonstrating that resin reuse has no negative impact on the viral clearance capacity of the chromatography steps. The resin sanitisation and storage studies demonstrated that the solutions used for the sanitisation and storage of the resins meet acceptable levels of antimicrobial efficacy and that the risk of cross contamination is minimal.

Endogenous retrovirus-like particles (RLPs) may be present in the cell line used to produce the tremelimumab active substance. These particles are measured by TEM analysis of the UPB. A safety factor for the removal of RLPs was calculated, resulting in a factor of greater than 9.0 $\log_{10}$ for the removal of endogenous virus, which is equivalent to less than 1 retrovirus-like particle for every 1.0×10^9 doses of tremelimumab. The results are considered adequate.

2.4.3.6. GMO

Not applicable.

2.4.3.7. Post-approval change management protocol(s)

The applicant introduced a Post-Approval Change Management Protocol (PACMP) to support the use of alternative single-use disposable filters across a number of steps in the active substance manufacturing process. Details regarding the planned technical assessment, assessment of extractables and leachables, small-scale studies and at-scale verification studies for the purpose of demonstration of comparability were provided. The upcoming changes will not have an impact on the composition, active substance and finished product specifications, active substance manufacturing process, critical steps, in-process controls or hold times and at-scale active substance batches will be placed on stability. Overall, the proposed PACMP is considered acceptable.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product, which pertain to lack of data for cumulative active substance stability study, revision and potentially tightening of the active substance stability specification and finished product release/shelf-life specification acceptance criteria for product-related impurities and variants when additional data become available and submission of elemental impurity stability testing and formal stability study results for the 300 mg finished product presentation. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant should review and, if found appropriate, revise the active substance stability specification and finished product release/shelf-life specification acceptance criteria when data from an additional 30 batches are available.

2. The applicant should perform a sequential stability study according to the post-approval sequential stability protocol and provide the results supporting a shelf-life for the active substance of 48 months storage at -40°C ± 10°C in stainless-steel vessels, followed by up to 24 months storage in EVA bags at 5°C ± 3°C (for a total of up to 72 months).

3. The elemental impurities stability testing and the formal stability study for the 300 mg finished product presentation are still ongoing. The results should be submitted for Agency's review when available.

2.5. Non-clinical aspects

2.5.1. Introduction

A comprehensive package of *in vitro* and *in vivo* studies was designed to characterise the pharmacological properties of tremelimumab with respect to mechanism of action and antitumour activity, pharmacokinetics (PK), pharmacodynamics (PD), and toxicological profile.

Based on the selective binding to human and cynomolgus monkey CTLA-4, the cynomolgus monkey was considered to be the only pharmacologically relevant species for assessment of nonclinical safety of tremelimumab. Tremelimumab binds to recombinant cynoCTLA-4 (rcynoCTLA-4) with slightly lower binding affinity comparable to that for the binding to recombinant human CTLA-4.

The nonclinical safety testing strategy for tremelimumab appears to meet the requirements as outlined in relevant ICH guidance, including ICH S6(R1), 'Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals', and ICH S9, 'Nonclinical Evaluation for Anticancer Pharmaceuticals'. All pivotal nonclinical safety studies were conducted in an Organization for Economic Co-operation and Development (OECD) member country in accordance with OECD GLP guidance. The IV route of administration was used for nonclinical toxicity studies as this is the intended clinical route of administration.

2.5.2. Pharmacology

Tremelimumab (previously CP-675,206) is a fully human immunoglobulin gamma-2 (IgG2) monoclonal antibody (mAb) engineered to bind to cytotoxic T lymphocyte-associated antigen-4 (CTLA-4; CD152), a cell surface receptor expressed on activated T cells. Upon T-cell activation, CTLA-4 expression is upregulated and acts to dampen immune responses, modulating and eventually switching off T-cell activation. The natural ligands for CTLA-4 are CD80 [B7.1] and CD86 [B7.2], which are present on antigen-presenting cells (APCs). Binding of CTLA-4 to CD80/CD86 functions to limit T-cell activation, primarily by competing with CD28 for access to CD80/CD86 (Walker and Sansom 2015).

In vitro, tremelimumab enhances T-cell function, measured by increased release of interleukin 2 (IL-2), interferon gamma (IFN-γ), and other cytokines (Tarhini and Kirkwood 2008).

In animal models of cancer, blockade of CTLA-4 function using anti-mouse CTLA-4 antibodies results in enhanced T cell function and antitumour activity that is enhanced by concomitant PD-L1 blockade (Wu et al 2012).

2.5.2.1. Primary pharmacodynamic studies

In vitro pharmacology

Selectivity of tremelimumab was demonstrated by comparing binding to rhCTLA-4-Ig and 3 related proteins (hCD28-Ig, hB7.2, and hIgG1) at 1 (n=5), 10 (n=5), 100 (n=2) and 300 (n=2) µg/mL using ELISA to quantify the binding. Selectivity was >500 in most instances except one at 1 µg/mL in which the selectivity was only 14 towards B7.2.

In a more functional assay of binding, activated T cells was used to demonstrate that tremelimumab (CP-675,206 at 10 µg/mL) only bind to human and monkey CTLA-4. No binding to activated T cells from rat, mouse, hamster, or rabbit could be detected (Report 15-CP-675,206). For the mouse a positive control was included. It was stated in the report that tremelimumab in excess generally displayed ~ 3-fold higher total binding (surface plus intracellular) to stimulated human CD3+ cells than to rhesus or cynomolgus CD3+ cells as judged by median fluorescence intensities. Moreover, the affinity of tremelimumab to rhCTLA-4 and rcynoCTLA-4 was quantified using the BIAcore 2000 technology showing a slight difference in KD values for binding of tremelimumab to rhCTLA-4 and rcynoCTLA-4. KD values were 0.28 and 0.98 nM, respectively (Report 14-CP-675,206).

It was demonstrated that tremelimumab inhibited CD80 and CD86 binding in a competitive ELISA assay with sub-nanomolar EC50s (0.78 and 0.46 nM respectively, Report 03-CP-675,206).

In a functional assay of activated primary human T cells cocultured with Raji cells expressing CD80 and CD 86 an increase in secretion of IL2 (510%) and INF-γ (54%) was observed when treated with tremelimumab at 30 µg/mL as compared to the negative isotype control anti-KLH (Report 02-CP-675,206). This concentration corresponds to one third (1/3) of Cmax (~ 100 µg/mL, Table 6, Summary of Clinical Pharmacology) and therefore can be considered clinically relevant.

The involvement of CD80 and CD86 was further demonstrated in a superantigen assay (Report 08-CP-675,206) according to which, the following was concluded: Effects of B7 blockade on IL-2 production and enhancement of IL-2 by tremelimumab at 30 µg/mL were tested in staphylococcal enterotoxin A (SEA)-stimulated human PBMC and blood cultures from 3 healthy donors. Anti-B7.1 and anti-B7.2 antibodies (CD80 and CD86) and CTLA4-Ig (all at 30 µg/mL) were used to block B7 signalling. In PBMC cultures, blockade of B7.2 or B7.1 plus B7.2 reduced IL-2 baseline levels and also enhancement of IL-2 produced by tremelimumab by 89% to 100%. Blockade of B7.1 (CD80) was less effective, inhibiting both baseline IL-2 and IL-2 enhancement by tremelimumab by ~ 50%. In general, blockade of B7 in human blood cultures produced results that were similar to PBMC cultures with slightly less reduction of baseline IL-2 or enhancement of IL-2 induced by tremelimumab. These studies clearly demonstrate that SEA superantigen stimulation is highly B7 dependent (Report 08-CP-675,206).

In study 01-CP-675,206 PBMC and blood from further 15 healthy donors was used in the SEA assay to demonstrate that tremelimumab enhanced the production of IL-2 as compared to anti-KLH isotype control.

The final study using the SAE assay on human biomaterial included PBMC and blood from further 15 healthy donors and from >80 cancer patients as well (Report 13-CP-675-206). Tumour types included prostate (minimal and advanced disease), renal, rectal, colon, ovarian, melanoma, non- Hodgkin's lymphoma (NHL), and Hodgkin's lymphoma, but not HCC. Although the numerical IL-2 response was variable and PBMCs and blood from a few patients did not respond to tremelimumab, the increase in IL-2 response at 30 µg/mL tremelimumab can be considered consistent as observed across the range of tumour types in this study. Moreover, the response was also demonstrated to be concentration dependent with enhancement of IL-2 production from 10 µg/mL and to increase further at 30 and 100 µg/mL.

Similarly, cultures of whole blood from 5 cynomolgus monkeys confirmed that tremelimumab enhanced IL-2 production in the SEA assay at 30 µg/mL (Report 04-CP-675,206). Hence, the cynomolgus monkey is considered pharmacologically relevant.

As stated by Ohue, 2019, regulatory T cells (T-regs) suppress the activation of other T-cell populations and that Tegs are recruited into the microenvironment inside cancer tumours to enhance tumour immunity.

Study 11-cp-675-206 was aimed at determining if blockade of CTLA4 by tremelimumab affects the ability of peripheral blood human Treg cells (CD4+CD25+) to inhibit IFN-γ production or ^{3}H-thymidine incorporation of anti-CD3/anti-CD28 activated T responder cells (CD4+CD25-) in an *in vitro* co-culture system. Treg cells were isolated from peripheral blood mononuclear cells. FACS analyses indicated that 84% ± 5% of the isolated CD4+ Tregs were CD25+ and Foxp3+.

Under the assay conditions, a 2:1 ratio of peripheral blood Treg cells cultured with T responder cells markedly inhibited IFN-γ production and ^{3}H-thymidine incorporation compared to cultures without Treg cells. Moreover, these studies indicated that tremelimumab does not reverse the ability of human peripheral Tregs to suppress IFN-γ production or thymidine incorporation of stimulated human peripheral T responder cells at 30 or 100 µg/mL.

Studies in mice suggested that anti-CTLA-4 mAbs may also selectively deplete intratumoral FOXP3+ regulatory T cells via an Fc-dependent mechanism. In a key publication by Sharma et al, 2019, it is shown that ipilimumab and tremelimumab are not depleting intratumoral FOXP3+Tregs in human cancers and that this represents an opportunity for future improvement of these types of cancer treatments. Hence, for tremelimumab, increased activation of effector T-cells is the more likely mechanism of action.

***In vivo* pharmacology**

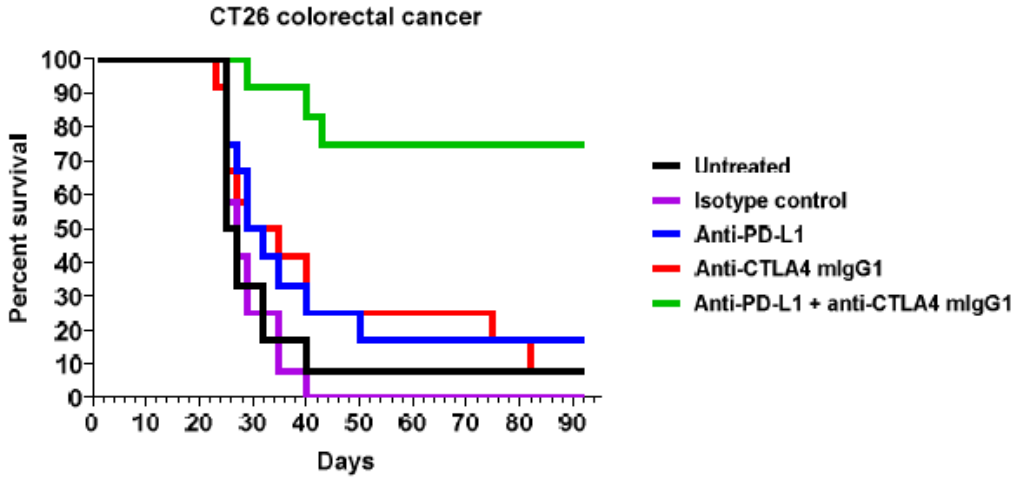
A mouse surrogate antibody (hamster anti-mouse CTLA-4 mAb named 9H10) of tremelimumab showed relevant efficacy in a mouse tumour model (12-cp-675-206). Syngeneic SA1N fibrosarcoma cells were injected subcutaneously into A/J mice (5/group). Treatment with 9H10 at 200 µg on day 0, 3 and 6 resulted in a 90% reduction in average tumour size on Day 28 compared to treatment with an isotype-control Ab. Plasma-concentrations of 9H10 24 hours after administration was 102 µg/mL and decreased to 34 µg/mL 3 days later, hence were clinically relevant (C_{max} ~ 100 µg/mL, Table 6, Summary of Clinical Pharmacology). Further studies showed a dose dependent tumour reduction at 200, 100 and 50 µg, although with no effect at 25 µg. Hence, a mouse surrogate of tremelimumab demonstrated efficacy as monotherapy in a mouse tumour model, when treatment was initiated at the same day as the inoculation.

All previous studies were conducted at Pfizer Groton. A new proof of concept study was sponsored by AstraZeneca (experimental work in 2017 and 2018, report signed 2021) demonstrating pharmacological activity of murine surrogates for tremelimumab and durvalumab in mouse syngeneic tumour models (ONC1123-0001).

In this study, treatment was initiated when the tumours reached 100 to 150 mm^{3} and can therefore be considered more clinically relevant than study 12-CP-675,206 in which treatment was initiated at the time of inoculation.

The anti-mouse CTLA-4 mIgG1 tremelimumab surrogate mAb demonstrated modest antitumour activity as monotherapy, but good effect in combination with anti-PD-L1 in the EMT6 breast and CT26 colon syngeneic mouse tumour models (tumour growth and survival).

Figure 1: Survival curves for CT26 antitumour efficacy study - Experiment 1



Likewise, the tremelimumab surrogate showed combination activity with anti-PD-L1 therapy in the MCA205 fibrosarcoma model, but no relevant effect as monotherapy. However, the effects were not fully comparable, while the addition of tremelimumab to durvalumab monotherapy increase the efficacy in colon model, in breast model, the combination effect is mainly due to durvalumab, thus in this case, addition of tremelimumab do not provide an increase in efficacy compared to durvalumab monotherapy. Due to this heterogenic data and since an uHCC mouse model has not been studied, the effect in the proposed indication cannot be anticipated. Monotherapy and combination with anti-PD-L1 also induced in-tumour CD4+ or CD8+ T cell proliferation in these 3 mouse tumour models, demonstrating the pharmacodynamic activity of the tremelimumab surrogate with respect to T-cell activation. As shown previously *in vitro* for tremelimumab, that peripheral Tregs was not depleted (11-CP-675,206), the tremelimumab surrogate did not deplete peripheral Tregs *in vivo*, establishing the mAb as a relevant surrogate to explore the pharmacodynamic and antitumour activity in these mouse syngeneic tumour models.

A study entitled "Profiling of Biomarkers Relevant to Immunotherapies in Paediatric Solid Tumours" was included in the submission. Immunohistochemistry data for PD-L1 and CD8 were generated for 76 and 77 paediatric tumours, respectively. Only one sample was positive for PD-L1 staining, defined as ≥ 1% of TC expression of PD-L1. The level of CD8 T-cell infiltration within the paediatric tumours was relatively low as compared to adult tumours. Overall, these IHC data suggest a limited immune response against these paediatric tumours.

It was further concluded that these data were illustrative of a group of samples with relatively low levels of mutation and with a limited degree of immunogenicity and immune activation. These characteristics suggest that checkpoint blockade, using molecules such as durvalumab and tremelimumab, would be unlikely to result in significant activity in paediatric tumours, and is in keeping with the relatively low levels of activity observed to date for similar molecules in this setting.

2.5.2.2. Secondary pharmacodynamic studies

Study 07-CP-675,206 showed that plate-bound tremelimumab did not inhibit T cell activation in the SEA assay (0.01-100 µg/mL) as the IL-2 response was not changing in any direction at any plating-concentration. This is presented as a surrogate measure of non-specific surface bound or aggregated tremelimumab *in vivo* in which then tremelimumab is not expected to have any effect.

In study 05-CP-675,206 tremelimumab was added to unstimulated human whole blood from healthy volunteers at concentrations of 10 or 100 µg/mL and did not induce levels of TNF-α, IL-6, or IL-1β *in*

vitro that would be predictive of cytokine release syndrome *in vivo*. The positive control anti-CD3 induced cytokine release as expected in this assay. Hence, tremelimumab is not expected to induce spontaneous cytokine release *in vivo*, which is confirmed in clinical trials.

Study 10-CP-675,206 evaluated whole blood incubated with tremelimumab and a positive control antibody CP-642,570. Only the positive control reduced platelet number in the incubations. Tremelimumab and the negative control antibody anti-KLH did not reduce platelet numbers over the 24 -hour period the experiment lasted. It should be noted that the testing concentration was only 30 µg/mL and is therefore not covering C_{max}, i.e. no safety margin is established. Immune thrombocytopenia has been observed in clinical trials with tremelimumab, however not in the HCC pool.

A human IgG1 antibody has much higher affinity for most human Fcγ receptors compared to a human IgG2 antibody such as tremelimumab. A study (16-CP-675,206) of competitive binding between a low concentration of ^{125}I-labeled antibody compared to when added 500-fold excess of unlabelled antibody to blood leucocytes, showed that an average of 53%, 43%, and 62% of the binding of hIgG1 antibody was inhibited by addition of excess unlabelled IgG1 antibody to human healthy donor, human prostate cancer patient, or cynomolgus monkey peripheral blood leukocytes. An average of 0%, 15%, and 2% of the binding of tremelimumab was inhibited by addition of excess unlabelled tremelimumab to human healthy donor, human prostate cancer patient, or cynomolgus monkey peripheral blood leukocytes. These results indicate that tremelimumab shows minimal specific binding to Fc receptor-bearing leukocytes, whether originating from humans or cynomolgus monkeys or cancer patients. Hence, Fc binding is not anticipated to be part of the mechanism of action of tremelimumab. Moreover, the tremelimumab binding to FcγRI, FcγRIIa, FcγRIIb and FcγRIII was evaluated using SPR assays and the KD obtained are not expected to be reached in the clinical setting.

In a study of antibody-dependent cell-mediated cytotoxicity (ADCC) against naïve and activated human T cells using a FACS-based assay (09-cp-675-206), it was demonstrated that tremelimumab (100 µg/mL) added to naïve or anti-CD3/CD28 activated human T cells ± IL-2- activated NK cells (up to an effector-to-target ratio of 25:1) produced no increases in ADCC compared to the no-treatment controls. The positive control anti-CD3 (Mu-IgG2a) did induce T-cell toxicity in both naïve and activated T cells in this assay. Hence, ADCC is not anticipated to be part of the mechanism of action of tremelimumab.

CDC risk was evaluated using doses below clinical concentration (5 µg/ml). CDC activity was not seen in cells incubated with tremelimumab under this condition. However, given the lack of effects on T cell depletion in the non-clinical *in vivo* studies and clinical studies, it is likely that the occurrence of CDC *in vivo* does not occur at biological relevant levels.

2.5.2.3. Safety pharmacology programme

No stand-alone safety pharmacology studies were conducted for tremelimumab. This is acceptable and according to guideline, especially when non-human primate is the only relevant species.

ECG, heart rate, blood pressure and vital signs (respiration rate and body temperature) was evaluated twice pre-dose and 5 min post dose in the GLP single dose study (t_{max}) and on several occasions during the dosing and recovery phase in the two repeat-dose studies. No dose-related changes from normal were observed in any study or on any occasion.

No dedicated CNS safety study was conducted. Instead, daily observations of the behaviour of the animals during the studies served this purpose. This is also acceptable as it is not expected that tremelimumab will cross the blood brain barrier. Any CNS effects is expected to be secondary to the

pharmacological effect of increased systemic inflammation. Histopathology revealed mononuclear cell infiltration of choroid plexus of the brain and pituitary in the 6 months repeat-dose study. Dose-related mononuclear cell inflammation was present in kidney. Clinical signs of diarrhoea in the 50 mg/kg/week group generally correlated with inflammation in the cecum and colon.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies of tremelimumab were submitted.

2.5.3. Pharmacokinetics

Methods of analysis

Bioanalysis

An ELISA bioanalytical method was developed and revised over the time providing versions each of which was validated according to GLP and used for the three pivotal studies in monkeys. For the 6-month toxicity and the EFD study an ELISA method validated as described in report DM2004-675206-014 was used. These studies were conducted in 2005 and 2007, prior to issuing of the current bioanalytical guidelines. Hence, incurred sample reproducibility was not demonstrated. Nevertheless, the bioanalytical method appears to have been in good control and to be validated in GLP compliance according to common practice at the time of conduct including e.g. dilutional integrity up to 2000-fold, hook effect and specificity.

In the assay, the ELISA plate was coated with a capture antigen (human CD152/CTLA-4). The samples were aliquoted in duplicate and allowed to incubate. The drug-antigen complex was then detected using a biotin-mouse anti-human IgG2 conjugate and a streptavidin HRP conjugate. A colorimetric signal is produced using a commercial TMB substrate solution. The intensity of colour generated is directly proportional to the concentration of tremelimumab in the sample. Sample concentrations were determined by interpolation from a standard curve which was fit using a four-parameter curve fit. The minimum required dilution (MRD) for all samples was 1:20 and the required sample volume was 0.050 mL in duplicate. The quantitation range was 156 to 3000 ng/mL. Samples were stored at a nominal temperature of -80°C prior to analysis. Using this method, stability at -80°C was demonstrated in monkey plasma for 174 days.

ADA analysis

GLP compliant ADA analysis was used in the 1 month and 6 months toxicity studies (validation report DM2007-675206-022 from 2001). Samples were collected in the EFD study, but not analysed, since pharmacokinetics implied that this was not necessary. This is accepted.

The ADA method was a qualitative sandwich ELISA assay in which the plate was coated with F(ab')2 fragments prepared from tremelimumab. Anti-tremelimumab antibodies in plasma was then captured by the immobilised tremelimumab F(ab')2- fragment, washed and then detected and visualised by Protein G conjugated to horseradish peroxidase (HRP) and tetramethylbenzidine (TMB). A normal cynomolgus sodium heparin plasma pool and a reference standard plasma (diluted 1:500, 1:1500, and 1:4500) were included on each plate as negative and positive controls, respectively. Results were reported as the net signal at the 1:500 dilution if not ≥3.0, then the 1:1500 was reported.

The reference standard plasma was pooled plasma from eighteen monkeys that received a single dose of tremelimumab. The plasma was collected following clearance of tremelimumab as measured by ELISA. This reference standard served as a quality control sample in all subsequent assays.

This is not the state of the art, however it appears to be a feasible way of determining ADA.

Reference range, dilution effects, stability, lot to lot variation of the negative control and intra/inter assay variability (robustness) was included in the validation. Long term stability was not presented. ADA could not be detected in the presence of tremelimumab above LLOQ of the bioanalytical method. A new method was developed for clinical samples with good assay drug tolerance.

NAb assay

Positive samples identified in the ADA assay were subjected to a nAb assay, which was also validated (validation report DM2007-675206-023).

A non-functional qualitative sandwich enzyme immunoassay technique was utilised to determine anti-tremelimumab neutralizing antibodies to tremelimumab F(ab')2 in cynomolgus sodium heparin plasma. with specificity and sufficient affinity to disrupt the binding of tremelimumab to its ligand (CTLA4) in cynomolgus sodium heparin plasma.

Samples were diluted with CTLA4/Ig and incubated with F(ab')2 fragments prepared from tremelimumab which had been immobilised on an ELISA plate. After incubation, unbound material was washed away and CTLA4/Ig was detected using goat anti-mouse Ig-HRP and visualised with TMB. A normal cynomolgus sodium heparin plasma pool and a reference standard plasma (diluted 1:10, 1:50, and 1:100) were included on each plate as negative and positive controls. The presence of nAb is indicated by a reduction in signal intensity as compared to normal cynomolgus monkey plasma (naive to tremelimumab). Study samples were run at 1:10 and 1:50 dilution, and the results were reported as the percentage of normal plasma signal generated by a dilution of test plasma in a given concentration of CTLA4IIg (10 ng/mL). This is considered an acceptable strategy for a nAb assay. It should be mentioned that the nAb assay was not functional in the presence of tremelimumab above LLOQ of the bioanalytical assay.

Absorption

Absorption was evaluated for the subcutaneous route at 5 mg/kg. Bioavailability was 54% when comparing clearance/F for SC administration with mean clearance from two studies of 0.75 mg/kg IV. It should be noted that tremelimumab is for intravenous administration together with durvalumab in a hospital setting. Hence this study is of minor clinical relevance. Pharmacokinetics after intravenous administration is discussed in section Other pharmacokinetic studies below.

Distribution

As expected for a monoclonal antibody, volume of distribution is mostly confined to the vascular space as the volume of distribution in monkey demonstrate (Vss = 54 mL/kg).

Metabolism

There is no evidence of nonlinearity of the pharmacokinetics of tremelimumab over the dose range of 0.75 to 100 mg/kg single dose. Therefore, it can be assumed that tremelimumab is not cleared via target mediated disposition but only through proteolytic degradation and catabolism.

Excretion

Excretion was not studied for tremelimumab. This is acceptable due to nature of the molecule and that it is expected to be cleared as small peptides or aminoacids or incorporated in the endogenous aminoacid pool.

Pharmacokinetic drug interactions

Pharmacokinetic drug interactions were not studied. This is acceptable as PK drug interactions are not expected.

Other pharmacokinetic studies

Single dose IV pharmacokinetics

Pharmacokinetics of clonally and non-clonally derived tremelimumab was evaluated after IV administration of 0.75 mg/kg to cynomolgus monkey. This is a very low dose compared to the highest doses used in the toxicity studies (50 and 30 mg/kg/week). Minor differences in Vss (0.0705 and 0.0538 L/kg), clearance (0.00339 and 0.00300 mL/min/kg) and resulting half-life (11 and 9.1 days), for clonally and non-clonally derived tremelimumab were observed.

A single dose toxicity study was performed in cynomolgus monkeys at dose levels of 10, 30 and 100 mg/kg. The toxicokinetic report was very brief providing only C_{max}, T_{max} and AUC and no pharmacokinetic profiles. A trend towards lower increments in systemic levels at lower dose ranges in all pharmacokinetic and toxicokinetic studies were observed. For example, when comparing $AUC_{0\text{-tlast}}$ for 0.75 and 10 mg/kg, the increase in dose of 13.3-fold (from 0.75 to 10 mg/kg) only increased AUC by 7.8 and 6.8, the increase in dose of 3-fold (from 10 to 30 mg/kg) increased AUC by 2.3 and the increase in dose of 3.3-fold (from 30 to 100 mg/kg) increased AUC by 3.1. In addition, in the 1-mont and 6-month toxicity studies, accumulation on Day 29 was more pronounced at the lowest dose ($AUC_{0\text{-}24h}$ D29/ $AUC_{0\text{-}24h}$ D1 were 1.8 and 1.6 at 5 mg/kg, 1.1 at 15 mg/kg and 1.4 at 50 mg/kg).

New submitted PK data support that the higher accumulation observed at the lowest dose might be due to lower CL, although the high variability in exposure hinders understanding the PK profile of tremelimumab in animals. Despite the observed variability in exposure might be due to the impact of ADA on clearance of tremelimumab, it should be noted that the ADA analysis was limited to samples that showed pre-dose exposure below LLOQ (8/30 and 7/28 animals in the 1-month and 6 months toxicity studies, respectively) and thus, are limited to conclude the impact of ADA in exposure variability.

It should be noted that the dose of 0.75 mg/kg is clinically relevant. The dose in patients is a flat single dose of 300 mg providing geometric mean C_{max} of 100 µg/mL. This is in close range to C_{max} in the monkeys administered a single dose of 0.75 mg/kg of 25-30 µg/mL.

Repeat-dose IV Pharmacokinetics

Repeat-dose toxicokinetics was evaluated in the 1-month toxicology study in which tremelimumab was administered IV once weekly at 5, 15 and 50 mg/kg (DM2001-675206-006). A few animals showed concentrations of tremelimumab above LLOQ at Day 1. However, so low as this is not anticipated to impact the conclusions of the study.

No gender-related differences in exposure was observed, why data was pooled across gender. AUC increased according to increase in dose on day 1, however slightly more than dose-proportional on Day 29.

Slight accumulation was observed as a result of pre-dose plasma concentration being 30-50% of C_{max} over the following doses. The accumulation was most pronounced at the highest dose. This could be due to neutralising antidrug antibodies at the lower dose levels, see below.

Antidrug antibodies were detected in 8/12 monkey in the recovery phase. As expected, variability in plasma concentrations tended to increase from Day 22 and onwards. On Day 29 at the mid dose of 15 mg/kg, 5/8 animals showed lower plasma concentrations indicating antibody mediated increased

clearance in selected animals. At the low dose only 2/8 and at the high dose only 1/8 showed lower plasma concentrations demonstrating that the animals were, in general, exposed as intended.

Repeat-dose toxicokinetics was evaluated in the 6-month toxicology study in which tremelimumab was administered IV once weekly at 5 and 15 mg/kg/week, n=4 (DM2001-675206-006) for 26 weeks. The high dose group of 50 mg/kg/week was terminated on Day 78 due to excess toxicity (last dose on day 43). Two male and two females continued in to a 100-day recovery phase (Study day 177). There were no recovery animals allocated for the low and the mid dose. Pre-dose samples were below LLOQ (0.156 µg/mL) on Day 1 and so were all samples collected from control animals. The observed slight gender differences in exposure were ascribed to variability due to neutralising antibodies and resulting waning exposure later in the study in some animals. Hence, the pharmacokinetic data were pooled across gender.

As expected, slight accumulation was observed between day 1 and 29. A slight decrease was evident on Day 176 probably due to increased clearance in some animals. Only one animal (34F, 15 mg/kg dose) developed antidrug antibodies already on day 22 were the predose sample was below LLOQ. From day 43, 3 more animals (28F, 12M and 14M) showed up with exposure at or below LLOQ and from Day 141 one more (12F). When pre-dose samples showed exposure below LLOQ, these were subjected to ADA assays. Anti-tremelimumab antibodies were detected in animal 12M, 14M and 34F in predose samples from Day 44, 44 and 23, respectively correlating with waning exposure in predose samples.

The systemic exposure to tremelimumab appeared to increase with increase in dose in a linear manner on Day 1. On day 29, the increase was slightly lower than the increase in dose. This was even more obvious on Day 176 due to the increase in neutralising antidrug antibodies and waning exposure in some animals. However, on Day 176, a 3-fold increase in dose still increased the exposure 2-fold. All monkeys at 5 and 15 mg/kg dose groups had measurable plasma concentrations of tremelimumab throughout the 6-month treatment period following each dose except one, which reached LLOQ on Day 141. Hence, the animals were subjected to adequate dose-related exposure during the dosing phase and the validity of the study.

Since exposure was relatively stable during the study, the $AUC_{day1-30}$ can be acceptable as a rough estimate of for calculating exposure margins. No NOAEL could be established in this 6-months study as the monkeys also at the low dose experienced diarrhoea requiring supportive care and skin rash. The low dose provided exposure from Day 1 to 30 of 94700 µg/mL*h ((=94700/30)/(19104/28)) = 3157/682 ~ 5 times higher than clinical exposure.

Exposure was also followed in the EFD study. Pregnant female monkeys (n=12 or 14) per group were dosed 5, 15 or 30 mg/kg/week IV from GD20 to GD49 (5 doses). Systemic exposure (C_{max} and $AUC_{GD20-49}$) appeared to increase with increase in dose in a linear manner. Slight increase in exposure was observed between GD20 and GD 49 as expected for a product with a half-life longer than the dosing interval. ADA samples were obtained in the study, but since only very few animals showed increased clearance during the study as evident from low plasma concentrations in pre-dose samples on day 48 (12884 in the low dose group, 12702 and 13004 in the mid dose group and animal 12836 in the high dose group), these samples were not subjected to ADA analysis.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Two single dose toxicity studies were presented for tremelimumab. The first one was with only a 10 mg/kg dose in one female and one male monkey and 12 weeks treatment-free observation period (Study 00-1985-06, non-GLP). This dose was well tolerated with no clinical signs, only a slight increase in lymphocyte counts was considered related to the pharmacological effect of tremelimumab. Exposure ($AUC_{0\text{-}tlast}$) was documented to be similar to the same dose level in next study (Study 99-1985-01) and the female monkey was found positive for ADA.

The second study was GLP compliant and included 3 monkeys of each sex in each group (control, 10, 30 and 100 mg/kg) and a 15-week treatment free observation period (Study 99-1985-01).

This study included core end points such as mortality, clinical signs (daily), body weight, food consumption, physical examinations, haematology, clinical chemistry, inspection of administration site, gross pathology, microscopic pathology. Only the control and high dose group was subjected to necropsy on Day 106. The others were returned to colony. Moreover, this study included evaluation of some safety pharmacology parameters (ECG, heart rate, respiration rate and blood pressure 5 min post dosing).

$AUC_{0\text{-}tlast}$ was proportional to the increase in dose and all 9 animals were found positive for ADA.

All animals survived until the end of the study. The most prominent clinical sign was diarrhoea/loose stool which was dose related in incidence and severity. However, this did not result in change in food intake or body weight.

Haematology revealed a general drug-related increase in lymphocyte counts, which occurred in both males and females at ≥30 mg/kg. Moreover, a general drug-related increase in eosinophil counts was observed in females at all dose levels and males at 100 mg/kg. These effects are considered a result of the pharmacological effect of tremelimumab. The increase in circulating lymphocytes was not associated with corresponding microscopic changes in the organs examined. Other changes in haematology were consistent with stress leucogram profile as they were also observed in the control group or were characteristic for an inflammatory response against a foreign protein (human CTLA4 antibody; tremelimumab).

All microscopic findings were comparable between drug-treated and control animals and consistent with those commonly or sporadically found in non-human primates.

Safety pharmacology evaluation was included in this study by assessing vital signs (heart rate, respiration rate and body temperature) and ECG/blood pressure twice pre-study and 5 minutes (T_{max}) after dosing. Hence, only acute effects were monitored. No acute drug-related changes were observed. This is endorsed.

2.5.4.2. Repeat dose toxicity

1-month i.v toxicity study with 2 months post-dose observation in cynomolgus monkey (Study 00-1985-04, GLP)

The 1 month repeat-dose toxicity study was performed in compliance with GLP as a multi-site study with Pfizer, Groton, CT, USA as the primary site. Only the immunophenotyping and serology was not performed to GLP.

Animals (5/sex/group) were administered tremelimumab at 5, 15 or 50 mg/kg via once-weekly IV bolus injection on Day 1, 8, 15, 22 and 29. Control animals (5/sex) received vehicle according to the same dosing schedule. Scheduled necropsies were conducted on Day 30 (3/sex/group), and following a 2-month treatment-free period (Day 105; 2/sex/group). I.e. there were recovery animals in all four groups.

Weekly IV bolus administration of tremelimumab over a period of 1 month was associated with intermittent diarrhoea or loose stool in individual animals across all treated groups during the dosing phase. In the 2-month treatment-free period, this effect was only observed in the high dose group. As expected from the primary pharmacodynamics of tremelimumab, reversible increases in the absolute number and/or percent of peripheral blood lymphocytes that correlated with increases in circulating T cells and/or B cells at 15 and 50 mg/kg/week was observed. Histopathology revealed periportal mononuclear cell infiltrates in the liver at 15 and 50 mg/kg/week, which reversed in females but not in males after a 2-month treatment-free period. Additional histopathology findings included lymphoid hyperplasia in the spleen and mesenteric lymph node, which was observed at all dose levels. Again, these changes were considered consistent with the primary pharmacodynamics of tremelimumab and reversed or showed a trend towards reversal after a 2-month treatment-free period. Based on the above findings, the 5 mg/kg/week dose was considered to be the NOAEL and the 50 mg/kg/week dose was considered to be the highest non-severely toxic dose (HNSTD) for tremelimumab in this study.

6-month i.v toxicity study in cynomolgus monkey (study 2004-0150, GLP)

The 6 month repeat-dose toxicity study was performed in compliance with GLP as a multi-site study with Pfizer, Kalamazoo, MI, USA as the primary site. Test formulation and analysis was performed at Pfizer, Chesterfield, MO. Plasma analysis at Pfizer, Richmond, VA, ADA analysis and TK, immune-phenotyping were performed at Pfizer Groton, CT and finally the ECG analysis by an associate professor at Michigan University, East Lansing, MI, USA. The quality assurance statement includes dates of audits/inspections which cover from draft protocol across in-life phases to ECG, necropsy and study reporting. Individual quality assurance statement was provided for bioanalysis, toxicokinetics, immunophenotyping and ADA reports. No quality assurance statement was associated with the report of analysis of the dosing solutions.

The plasma concentration of tremelimumab collected from the control group animals at 0.5-hour post-dose on treatment Days 1, 29 and 176 and recovery Day 99 were less than the LLOQ (0.156 µg/mL).

Cynomolgus monkeys were administered a solution of tremelimumab in vehicle intravenously at doses of 5, 15, and 50 mg/kg/week for 6 months (the same dose levels as in the 1-month study).

Six monkeys/sex were assigned to the 0 (control) and 50 mg/kg/week groups (with 4 monkeys/sex designated as main study monkeys and 2 monkeys/sex designated as recovery-phase monkeys). Four monkeys/sex were assigned to the 5 and 15 mg/kg/week groups (no recovery-phase monkeys).

Dosing had to be suspended in the high dose group already after 6 or 7 weeks due to persistent diarrhoea and what seems to be rather severe adverse skin conditions. Several of the animals failed to improve after suspension of dosing and had to be euthanised despite supportive treatment of fluids, snacks, benadryl and prednisolone. On Day 79, the remaining 50 mg/kg/week monkeys (2/sex) and the control monkeys originally designated as recovery monkeys (2/sex) were placed in a newly designated 99-day recovery phase. Mortality was observed in the low dose group, which were not associated with treatment (broken forearm and peracute diarrhoea due to acute infection).

As expected from the pharmacodynamic effects of tremelimumab, changes were observed in hematological, immunophenotyping and clinical chemistry endpoints, such as increased numbers of white blood cells and lymphocytes and slightly decreased A/G ratio.

A decrease in thyroid hormones (T3 and T4) in combination with increased TSH was observed in one male and 1 female in each of the mid and high dose. These changes correlated with moderate to marked thyroid atrophy as observed microscopically at day 170 at the mid dose and at Day 42 at the high dose. Immune mediated hypothyroidism was observed in clinical trials. In section 4.4 in SmPC a recommendation of monitoring for abnormal thyroid function. Hypothyroidism is classified as a very common adverse effect (13.3%) in section 4.8 of SmPC.

Tremelimumab-related histologic findings were generally consistent with the intended pharmacology of increased immune reactivity. All treated groups had a dose-related increase in the incidence of mononuclear cell infiltration and mononuclear cell inflammation in numerous organs apart from skin and intestinal system in which adverse effects were obvious by clinical signs.

Dose-related mononuclear cell infiltration was present in the cecum, colon, skin, brain (choroid plexus), oesophagus, eye (conjunctiva), heart, liver (periportal area), kidney, skeletal muscle, pancreas (acinar), parathyroid, pituitary, prostate, salivary gland, thyroid, tongue and uterus of the 5, 15, and 50 mg/kg/week groups.

Histological evaluation of the recovery animals showed minimal inflammation of salivary gland (1/4 animals) and skin (3/4 animals).

NOAEL was not determined based on clinical observations that required supportive care (prednisolone, benadryl, IV or gavage fluids, snacks) in the 5 mg/kg/week and 50 mg/kg/week groups and mononuclear cell inflammation in the kidney, skin and salivary gland of all tremelimumab-treated groups. Exposure to tremelimumab, assessed by mean C_{max} and AUC values, was largely maintained throughout the dosing phase despite antidrug antibodies in individual animals and there were no consistent gender differences in mean exposure. The maximum tolerated dose was considered to be 15 mg/kg/week. At 15 mg/kg/week on Day 176 the combined-sex C_{max} and $AUC_{Day1-30}$ means were 444 µg/mL and 212000 µg•h/mL, respectively. This is much higher than C_{max} of 100 µg/ml and $AUC_{0-28days}$ of 19104 µg/mL*h in patients after a single dose of 300 mg. Exposure at 5 mg/kg/week was also 5 times higher than in patients indicating that the dose setting in this study was too high. Mean $AUC_{1-30days}$ was 94700 µg/mL*h in the monkey. $AUC_{0-28days}$ in patients was 19104 µg/mL*h. Hence, exposure margin to the lowest dose was (94700/30)/(19104/28) = ~ 5. Nevertheless, the majority of the findings appeared to be clinically relevant, even the palliative treatment of corticosteroids in the most affected animals.

2.5.4.3. Genotoxicity

No genotoxicity studies were conducted with tremelimumab.

2.5.4.4. Carcinogenicity

No carcinogenicity studies were conducted with tremelimumab.

2.5.4.5. Reproductive and developmental toxicity

Tremelimumab potential for influencing fertility and early embryonic development was not evaluated.

In the 6 months toxicity study (Study 2004-0150; GLP), mammary gland, uterus, vagina, oviduct, cervix, ovary, epididymides, prostate, seminal vesicle and testes were included in the list of organs subjected to histopathology on Day 177, where the low and mid dose animals had been dosed weekly up until sacrifice and the high dose animals had been off dosing for 99 days.

As for the male reproductive organs, mononuclear cell inflammation/infiltration was observed as minimal or mild in seminal vesicle (1/4 in High dose), testes (1/4 in Low dose and Mid dose with 1/4 with mild inflammation in the high dose), epididymides (1/4 in control, 1/4 in Low dose, 1/4 in Mid dose and 2/4 in High dose). Prostate was more affected in incidence and severity compared to the other male reproductive organs, as one of the four high dose animals also showed moderate mononuclear cell inflammation.

As for the female reproductive organs, mononuclear cell inflammation/infiltration was observed as minimal or mild in uterus (0/4 in control, 3/4 in low dose, 1/4 in mid dose and 3/4 in high dose). In vagina, this finding was dose related in incidence and severity and was found to be moderate in 1/4 in mid dose and 2/4 in the high dose. In mammary gland, mononuclear infiltration was mild in 1/4 in low and mid dose and mononuclear inflammation was present in the 3/4 of the high dose animals with one classified as moderate. Other findings were only present in one animal and is considered incidental.

The embryofoetal development study of tremelimumab was a multisite study performed with Covance, Münster, Germany as the primary site with a comprehensive audit programme covering most phases of the study (2501-001). Analysis of a stock solution took place at Covance using UV absorbance. Bioanalysis (GLP) was conducted at Nerviano Medical Sciences, Italy and toxicokinetics (GLP) at Pfizer, Groton, CT. ADA analysis was decided not to be performed, since the pharmacokinetics appeared to be minimally affected by possible neutralising antibodies towards tremelimumab. Moreover, exposure was dose-related and similar to the repeat-dose toxicity studies.

In this study, the animals were dosed once weekly with tremelimumab from day 20 to 50 of gestation (e.g. on days 20, 27, 34, 41, and 48 of gestation) at dose levels of 0, 5, 15 or 30 mg/kg/week.

Toxicokinetic samples were collected: days 20 and 48 of gestation: predose, and at approximately 0.5, 8, and 24 hours post-dose and days 27, 34, and 41, of gestation: predose and at approximately 0.5 hours post-dose, hence exposure was well-covered throughout the study.

All animals were observed once daily for behaviour and appearance. A second examination was performed on all animals later in the day as a cage side observation, including another faeces evaluation. Additionally, a detailed fur examination was performed at weekly intervals for each individual animal.

The only clinical signs assigned to treatment was slight dose-related increase in the incidence of days with diarrhoea.

Foetuses were delivered via Caesarean section and euthanised on day 100 ± 1 of gestation, followed by examination for weight, external, visceral, and skeletal abnormalities, and weights of selected organs. Placentae were examined for weight and gross appearance.

There was no effect of treatment on the incidence of prenatal loss. There were no treatment-related changes in foetal body or organ weights, foetal body measurements, or placental weights among the live foetuses. External and visceral examination revealed several minor findings in foetuses of all groups including the control group. Type, frequency and pattern of those findings did not show any dose-relationship.

Hence, there were no signs of tremelimumab having adverse effects on the outcome of pregnancy and embryofoetal development at doses up to 30 mg/kg/week during pregnancy (GD20 to GD48) in the monkey providing sufficient margin of exposure.

A pre- and postnatal development study (PPND) study was not performed.

Studies in juvenile animals were not performed.

2.5.4.6. Toxicokinetic data

Table 2: Key findings in toxicity studies with tremelimumab in cynomolgus monkeys

Dose (mg/kg)	Key Findings	C_{max}[a] (µg/mL)	AUC[a] (µg·hr/mL)
Single-dose with 3-month observation period after dosing (3 animals/sex)			
10	↑ eosinophil counts; ADA detected	251	29000
30	↑ eosinophil counts loose stools;↑ lymphocyte counts; ADA detected	688	66900
100	↑ eosinophil counts loose stools;↑ lymphocyte counts; ADA detected No gross or microscopic findings after 3-month observation period	2970	209000
1-month repeat-dose with 2-month observation period after dosing (5 animals/sex)[b]			
5 (NOAEL)	Loose stools; lymphoid hyperplasia in the spleen and mesenteric lymph nodes; ADA detected	107 164	69500 88600
15	Loose stools; lymphoid hyperplasia in the spleen; ↑ peripheral blood CD3+CD4+ T cells; periportal infiltration of mononuclear cells ADA detected	357 433	186000 210000
50 (HNSTD)	Loose stools with supportive care; lymphoid hyperplasia in the spleen;↑ peripheral blood lymphocytes; ↑ peripheral blood CD3+CD4+ T cells, CD3+ T cells, and/or CD20+ B cells; ↓ RBC, hemoglobin, and hematocrit	1,090 1,480	590000 775000
6-month repeat-dose (4 or 6 animals/sex)[c]			
5	Diarrhoea requiring supportive care; skin rash; lymphoid hyperplasia; ↑incidence and severity of mononuclear cell infiltration and/or inflammation in skin and tissues that have a spontaneous background incidence of mononuclear cell aggregates; ADA detected	145 234 192	94700
15 (HNSTD)	Diarrhoea; skin rash (requiring supportive care in 1 male); lymphoid hyperplasia; ↑ incidence and severity of mononuclear cell infiltration and/or inflammation in skin and tissues that have a spontaneous background incidence of mononuclear cell aggregates; ↑ CD3+CD4+ peripheral blood lymphocytes; inflammation of cecum and colon; thyroid atrophy; ADA detected	418 505 444	212000
50	Diarrhoea; skin rash; lymphoid hyperplasia; ↑ incidence and severity of mononuclear cell infiltration and/or inflammation in skin and tissues that have a spontaneous background incidence of mononuclear cell aggregates; ↑ CD3+CD4+ peripheral blood lymphocytes; inflammation of duodenum, cecum, and colon; acinar pancreatic and thyroid atrophy; ADA detected; early euthanasia due to progressive skin condition, diarrhea, and ↓ body weight	1400 2030 NC	776000
Embryo-Fetal Development (16 females/group)[d]			
5	Slight increase in diarrhoea	154 187	76800
15		498 707	208000
30 (NOAEL)		954 1230	454000

↑ = increased; ↓ = decreased; ADA = antidrug antibody; AUC = area under the plasma concentration-timecurve; $AUC_{0\text{-}Tlast}$ = area under the plasma concentration-time curve from time 0 to last measurable concentration; $AUC_{Days1\text{-}30}$ = area under the plasma concentration-time curve from Day 1 to Day 30; $AUC_{Day\ 20\text{-}49}$ = area under the concentration-time curve from GD 20 to GD 49; C_{max} = maximum observed concentration; GD = gestation day; NC = not calculated; NOAEL = no-observed-adverse-effect level; HNSTD = highest non-severely toxic dose; RBC = redblood cell.

[a] In the single-dose study, AUC is $AUC_{0\text{-}Tlast}$ from Day 1 through Day 105. In the 1-month repeat-dose study, C_{max} values are on Day 1 and Day 29 and AUC values are $AUC_{Days1\text{-}30}$ and $AUC_{0\text{-}Tlast}$, where T_{last} is from Day 1 through the end of the observation period (Day 105). In the 6 month repeat-dose study, C_{max} values are from Days 1, 29 and 176 and AUC values are $AUC_{Days1\text{-}30}$. In the EFD study, C_{max} values are from GD 20 and 48 and AUC values are $AUC_{GD20\text{-}49}$

[b] Tremelimumab was administered on Days 1, 8, 15, 22, and 29.

[c] Tremelimumab at dose levels of 5 and 15 mg/kg was administered once weekly for 26 consecutive weeks, and at dose level of 50 mg/kg once weekly for 7 consecutive weeks.

[d] Tremelimumab was administered on GD 20, 27, 34, 41, and 48.

2.5.4.7. Local Tolerance

Local tolerance was assessed in both single and repeat-dose toxicity studies. When changes were observed, these were considered procedurally related and similar in incidence and severity between control and tremelimumab dosed animals.

2.5.4.8. Other toxicity studies

Tissue cross reactivity

Tissue cross reactivity studies of tissue binding of a fluorosceinated version of tremelimumab to cynomolgus monkey and human tissues was presented in reports IM645 and IM676. The studies were conducted according to GLP at Pathology Associates, a Charles River Company, Maryland, USA. The range of tissue was sufficiently broad and covered tissues of vital organs such organs of reproduction, heart and lung apart from expected target organs of gastrointestinal system, thymus, pancreas and lymph system. Human lymphocytes and human cerebellum tissue were used as positive and negative control, respectively.

The tissue binding profile of the two species was remarkably similar. The tissues binding tremelimumab were tonsils, lymphocytes in stomach, colon, spleen, lymph nodes and thymus in monkey. In human tissues it was tonsils, lymph nodes, thymus, lymphocytes in spleen, colon and small intestine with low binding in 1 out of three donors of thyroid. Tissue binding correlates with expected pharmacological effect and adverse findings in the monkey and adverse effects in patients.

Antigenicity

Tremelimumab did give rise to antidrug antibodies in the monkeys, however with limited impact on exposure. Only few animals showed decreasing exposure over time due to neutralising antidrug antibodies. This seems to be the case in patients as well, where 12.1% tested positive for ADAs and 10.0% for neutralising ADAs. The presence of ADAs did not impact tremelimumab pharmacokinetics, and there was no apparent effect on efficacy and safety (SmPC).

Immunotoxicity

Tremelimumab is a product, which enhance the reactivity of the immune system by inhibiting one of the down-regulating functions (CTLA4). This gives rise to general inflammation (in essence autoimmune reactions) in a range of organs - most severely in the intestinal system and skin as observed from clinical signs in the monkey. The increase in general inflammation seems to be well documented in the studies in cynomolgus monkeys also on the cellular level but may be less obvious in the patient population in which leucopenia and neutropenia are very common adverse effects.

2.5.5. Ecotoxicity/environmental risk assessment

Tremelimumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), tremelimumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

It is acknowledged that tremelimumab inhibits CTLA4 and thereby activate T cells. A range of both *in vitro*, *in vivo* pharmacology and repeat-dose toxicity studies documents this effect, which *in vivo* translates into severe systemic inflammation and mortality after repeat-dosing. However, the lack of effects on Tregs ability to dampen IFN-γ production by activated T cells is a concern. According to e.g. Ohue, 2019, Tregs may be part of cancer tumours microenvironment to enhance tumour immunity providing a possibility for evading the activated T cells.

To further explain this trait of tremelimumab not targeting the intratumoral Tregs limiting its efficacy in cancer treatment, a scientific discussion was provided. Depletion of Tregs is dependent on ADCC of which tremelimumab is not capable mainly due to lack of FcR affinity. Selby et al. demonstrated that in mouse tumour models surrogate antibodies with higher affinity for FcR showed both the ability of depleting Tregs and enhanced antitumour activity.

There is a difference in affinity of IgG isotypes for FcR between mouse and human. IgG2a is a mouse isotype, with relatively potent Fc binding properties and is broadly equivalent to human IgG1. Additionally, human IgG2 (such as tremelimumab) has very minimal Fc binding properties and is broadly equivalent to mouse IgG1 (as used in the *in vivo* studies described below) (Stewart et al 2014).

This discrepancy between nonclinical and clinical findings could be summarised as translational challenges associated with: 1) differences between IgG isotypes across species; 2) type of effector cells infiltrated in tumour and expression of different FcγRs on the surface between mouse and human; 3) varying CTLA-4 expression level on Tregs.

To conclude, tremelimumab is not capable of performing ADCC and therefore does not reduce Tregs number. In the context of immune related adverse events, that property is desirable, but intratumoral Tregs might be potential target for more efficient therapy because reducing Tregs inside tumours is associated with superior antitumour activity. Tremelimumab achieves its effect by targeting CTLA-4 on activated effector T cells and should be administered in combination with anti-PD-L1 antibody. Results from nonclinical studies showed that combination is superior to monotherapy with tremelimumab in cancer treatment, but similar to anti-PD-L1 monotherapy. Totality of data suggest that not affecting Tregs might be the reason for weaker efficacy of tremelimumab.

Key *in vitro* and *in vivo* studies highlight applicant´s statement that tremelimumab is not capable of affecting Tregs, however, the absence might be associated with weaker clinical outcomes and questionable contribution of tremelimumab in antitumour efficacy.

This deficiency might also explain the modest effect in the *in vivo* mouse cancer models.

Despite the principle of abrogating the T-cell inhibition was studied *in vitro* as well as *in vivo*, different results have been obtained from different animal disease models. A proof of principle specific for the tumour type included in the indication was not demonstrated. Thus, the relevance for the current proposed indication, uHCC, was not provided. According to e.g. Chulpanova et al 2020, the syngeneic mouse tumour models lack the complexity of the tumour microenvironment observed in patients, hence the translational value of the mouse model is questionable.

Pharmacokinetics

As expected for a monoclonal antibody, volume of distribution is mostly confined to the vascular space as the volume of distribution in monkey demonstrate (Vss = 54 mL/kg). The major elimination pathway of tremelimumab is expected to be through protein catabolism. Pharmacokinetic drug-drug interactions of tremelimumab with other therapeutics are not anticipated.

The pharmacokinetics of tremelimumab appear to be independent of dose and providing a linear relation between exposure and dose within the dose range tested (0.75 to 100 mg/kg), which also is the case in humans over the dose range of 1 to 20 mg/kg.

Antidrug antibodies (ADAs) were observed in several animals during the repeat-dose toxicology studies and in some cases appeared to increase clearance. However, the overall exposure was deemed sufficient securing the validity of the studies.

Toxicology

Repeat-dose toxicity studies were conducted in monkeys of 1- or 6- months duration. In the 1-mont study findings were consistent with tremelimumab pharmacology by inducing inflammation but not severe.

In the chronic 6-month study in cynomolgus monkeys, treatment with tremelimumab was associated with dose-related incidence in persistent diarrhoea and skin rash, scabs and open sores, which were dose-limiting. These clinical signs were also associated with decreased appetite and body weight and swollen peripheral lymph nodes. Histopathological findings correlating with the observed clinical signs included reversible chronic inflammation in the cecum and colon, and mononuclear cell infiltration in the skin and hyperplasia in lymphoid tissues. A dose-dependent increase in the incidence and severity of mononuclear cell infiltration with or without mononuclear cell inflammation was observed in the salivary gland, pancreas (acinar), thyroid, parathyroid, adrenal, heart, oesophagus, tongue, periportal liver area, skeletal muscle, prostate, uterus, pituitary, eye (conjunctiva, extra ocular muscles), and choroid plexus of the brain. No NOAEL was found in this study with animals treated with the lowest dose of 5 mg/kg/week requiring supportive care. This dose provided an exposure-based safety margin of 1-2 to clinically relevant exposure (taking species difference in potency into account).

Mononuclear cell infiltration in prostate and uterus was observed in repeat dose toxicity studies. Since animal fertility studies have not been conducted with tremelimumab, the clinical relevance of these findings for fertility is unknown. In reproduction studies, administration of tremelimumab to pregnant Cynomolgus monkeys during the period of organogenesis was not associated with maternal toxicity or effects pregnancy losses, foetal weights, or external, visceral, skeletal abnormalities or weights of selected foetal organs.

Tremelimumab potential for influencing fertility and early embryonic development was not evaluated or discussed by the applicant. According to ICH S9, effects on reproductive organs from the repeat-dose toxicity studies can make the basis for this evaluation.

Pre- and postnatal development studies were not performed, and this is acceptable and in line with ICH S9.

No studies in juvenile animals were performed, and this is acceptable since the sought indication is only including adult patents.

Tremelimumab was not evaluated for genotoxic potential, and this is acceptable for a monoclonal antibody. Carcinogenic potential of tremelimumab was not evaluated, and this is acceptable given the indication sought in the treatment of unresectable hepatocellular carcinoma (uHCC).

RMP

The findings observed in the pivotal repeat-dose general toxicity studies of inflammation in cecum, colon and skin were also observed in patients. Moreover, clinical chemistry findings in patients and monkeys related to liver toxicity correlated to histological changes. As for toxicity to reproduction, it is acknowledged that the EFD study in monkeys did not give rise to concerns. However, inflammatory

markers were present in organs of reproduction of both male and female animals even after 99 days of recovery.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical data submitted support the marketing authorisation of tremelimumab.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study	**Phase**	**Objectives of study**	**Study design and type of control**	**Route of administration and dosage regimen**	
Pivotal study					
HIMALAYA (D419CC00002) Randomised, Open-label, Multicentre Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma (HIMALAYA)	III	Efficacy and safety of durvalumab and tremelimumab in combination versus durvalumab alone and sorafenib as SoC	Randomised, open-label	Durvalumab 1500 mg Q4W	
				Durvalumab 1500 mg Q4W Tremelimumab 300 mg single dose	
				Durvalumab 1500 mg Q4W Tremelimumab 75 mg 4 doses	
				Sorafenib (SoC) 400 mg BID	
Supporting studies					
Study 22 (D4190C00022) A study of safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, or durvalumab in combination with tremelimumab or bevacizumab in subjects with advanced unresectable HCC	I/II	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, randomised	*Part 1*	Tremelimumab 75 mg (1 mg/kg) × 4 doses Durvalumab 1500 mg (20 mg/kg) Q4W
				Part 2A & China Cohort	Durvalumab monotherapy 1500 mg (20 mg/kg) Q4W Tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W Tremelimumab 75 mg (1 mg/kg) × 4 doses + Durvalumab IV 1500 mg (20 mg/kg) Q4W
				Part 2B	Tremelimumab IV 300 mg (4 mg/kg) × 1 dose + Durvalumab IV 1500 mg (20 mg/kg) Q4W

				Part 3	Durvalumab monotherapy 1500 mg (20 mg/kg) Q4W Tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W Tremelimumab 75 mg (1 mg/kg) × 4 doses + Durvalumab 1500 mg (20 mg/kg) Q4W Tremelimumab 300 mg (4 mg/kg) × 1 dose + Durvalumab 1500 mg (20 mg/kg) Q4W
				Part 4	Durvalumab 1120 mg (15 mg/kg) + Bevacizumab 15 mg/kg Q3W
Study 11 (D4190C00011) Phase I multicentre, open-label, doseexploration, and dose-expansion study of Durvalumab in combination with Tremelimumab in subjects with recurrent or metastatic SCCHN	I	Evaluate safety, tolerability, and efficacy of Durvalumab in combination with Tremelimumab	Non-randomised, open-label	*Dose exploration*	
				Cohort 1	Durvalumab 15 mg/kg Q4W Tremelimumab 3 mg/kg Q4W
				Cohort 2	Durvalumab 10 mg/kg Q2W Tremelimumab 1 mg/kg Q4W
				Cohort 3	Durvalumab 20 mg/kg Q4W Tremelimumab 1 mg/kg Q4W
				Cohort 4	Durvalumab 20 mg/kg Q2W Tremelimumab 3 mg/kg Q4W
				Dose exploration	
				Cohort A PD-L1 High	Durvalumab 20 mg/kg Q4W Tremelimumab 1 mg/kg Q4W then Durvalumab 10 mg/kg Q2W
				Cohort B PD-L1 Low or Negative	Durvalumab 20 mg/kg Q4W Tremelimumab 1 mg/kg Q4W then Durvalumab 10 mg/kg Q2W
				Cohort C prior IMTtreatment	Durvalumab 20 mg/kg Q4W Tremelimumab 1 mg/kg Q4W then Durvalumab 10 mg/kg Q2W
HAWK (D4193C00001) Phase II, multicentre, single-arm, global study of Durvalumab monotherapy in SCCHN	II	Efficacy of durvalumab monotherapy and health-related quality of life	Open-label, single-arm	Durvalumab IV 10 mg/kg Q2W for 12 months or until progression of disease	

Study 21 (D4190C00021) Phase Ib/II study to evaluate the safety, tolerability, and clinical activity of durvalumab in combination with tremelimumab, of durvalumab monotherapy, and of tremelimumab monotherapy in second- and third-line subjects with metastatic or recurrent gastric or gastroesophageal junction adenocarcinoma	Ib/II	Evaluate the safety, antitumour activity, PK, and immunogenicity of Durvalumab in combination with Tremelimumab, of Durvalumab monotherapy, and of Tremelimumab monotherapy	Randomised, multicentre, open-label, comparative study	*Phase 1b*	Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg
				Phase 2	
				Arm A	Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg
				Arm B	Durvalumab 10 mg/kg
				Arm C	Tremelimumab 10 mg/kg
				Arm D	Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg
				Arm E	Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg
Study 1108 (CD-ON-MEDI4736-1108) Phase I/II study to evaluate the safety, tolerability, and pharmacokinetics of MEDI4736 in subjects with advanced solid tumours	I/II	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, nonrandomised	*Dose-escalation phase*	
				Durvalumab 0.1, 0.3, 1, 3, 10 mg/kg Q2W + 15 mg/kg Q3W for up to 12 months or until PD	
				Dose-exploration phase	
				Durvalumab 20 mg/kg Q4W for up to 12 months	
				Dose-expansion phase	
				Durvalumab 10 mg/kg Q2W up to 12 months	
Study 06 (D4190C00006) Phase Ib open-label study to evaluate the safety and tolerability of durvalumab (MEDI4736) in combination with tremelimumab in subjects with advanced NSCLC [a]	Ib	Safety, tolerability, and efficacy of durvalumab in combination with tremelimumab	Open-label	*Dose-escalation phase - combination*	
				Durvalumab IV 3-20 mg/kg Q4W or 10 mg/kg Q2W + Tremelimumab IV 1-10 mg/kg Q4W for 6 doses, then Q12W for 3 doses	
				Dose-expansion phase - combination	
				Durvalumab 20 mg/kg Q4W for 4 doses then IV 20 mg/kg Q4W for 9 doses + Tremelimumab 1 mg/kg Q4W for 4 doses	

Japan Study 02 (D4190C00002) A Phase I, open-label, multicentre study to evaluate the safety, tolerability, and PK of MEDI4736 in patients with advanced solid tumours	I	Safety and tolerability of durvalumab monotherapy or in combination with tremelimumab	Open-label, Non-randomised	Durvalumab monotherapy *Dose-escalation phase* Durvalumab IV 1, 3, 10 mg/kg Q2W; 15 mg/kg Q3W; 20 mg/kg Q4W Dose-expansion phase Durvalumab IV 10 mg/kg Q2W
				Combination therapy *Dose-expansion phase* Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 20 mg/kg Q4W + Tremelimumab IV 1 mg/kg Q4W for 4 doses
Study 10 (D4190C00010) Phase I study of MEDI4736 (anti-PD-L1 antibody) in combination with tremelimumab (anti-CTLA-4 antibody) in subjects with advanced solid tumours	I	Safety, tolerability, and efficacy of the combination of durvalumab and tremelimumab	Open-label	Combination therapy *Dose-exploration phase* Durvalumab IV at 20 mg/kg Q4W for 12 months AND Tremelimumab IV 1 mg/kg Q4W (7 doses) then Q12W (2 doses) OR Durvalumab IV 10 mg/kg Q2W for 12 months AND Tremelimumab 3 mg/kg Q4W (7 doses) then Q12W (2 doses) Dose-expansion phase – combination therapy Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W + Tremelimumab IV 1 mg/kg Q4W for 4 doses
DANUBE (D419BC00001) Phase III study of Durvalumab alone and in combination with Tremelimumab in patients with unresectable stage IV urothelial cancer	III	Efficacy and safety of Durvalumab monotherapy and in combination with Tremelimumab versus SoC	Randomised, open-label, controlled (SoC), multicentre	Durvalumab 1500 mg Q4W alone
				Durvalumab 1500 mg Q4W + Tremelimumab 75 mg Q4W for 4 doses
				SoC
KESTREL (D419LC00001) Phase III study of Durvalumab alone and in combination with Tremelimumab in patients with metastatic SCCHN	III	Efficacy and safety of Durvalumab monotherapy and in combination with Tremelimumab versus SoC	Randomised, open-label, multicentre, global study	Durvalumab 1500 mg Q4W alone
				Durvalumab 1500 mg Q4W + Tremelimumab 75 mg Q4W for 4 doses
				SoC
POSEIDON (D419MC00004) Phase III, randomised, global study to determine the efficacy of durvalumab or	III	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Randomised, multicentre, open-label, comparative active comparator	Durvalumab 1500 mg Q3W for 4 doses + SoC, then Durvalumab 1500 mg Q4W until PD

durvalumab and tremelimumab in combination with platinum-based chemotherapy for first-line treatment in patients with metastatic NSCLC				Durvalumab 1500 mg Q3W for 4 doses + SoC, then Durvalumab 1500 mg Q4W until PD Tremelimumab 75 mg Q3W for 4 doses + 1 dose at week 16
				SoC (abraxane + carboplatin, pemetrexed + cisplatin or carboplatin, or gemcitabine + cisplatin or carboplatin)
ATLANTIC (D4191C00003) Phase II non-comparative, open-label, multicentre, international study of MEDI4736 in patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen	II	Efficacy, safety, tolerability, PK, and immunogenicity	Open-label, single-arm, non-randomised	Durvalumab 10 mg/kg Q2W for up to 12 months
PACIFIC (D4191C00001) Phase III, randomised, double-blind, placebo-controlled, multicentre, international study of durvalumab as sequential therapy in patients with locally advanced, unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based concurrent chemoradiation therapy	III	Efficacy, safety, tolerability, PK, immunogenicity, and health-related quality of life versus SoC	Randomised, double-blind, placebo-controlled	Durvalumab 10 mg/kg Q2W for up to 12 months
MYSTIC (D419AC00001) Phase III, randomized, open-label, multicentre, global study of durvalumab monotherapy and durvalumab in combination with tremelimumab	III	Efficacy versus SoC	Open-label, randomised, active comparator	*Durvalumab monotherapy* Durvalumab IV 20 mg/kg Q4W

compared to SoC in patients with advanced or metastatic NSCLC				*Combination therapy* Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 20 mg/kg Q4W until PD AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
NEPTUNE (D419AC00003) Phase III randomised, open-label, multicentre, global study of MEDI4736 in combination with tremelimumab therapy versus standard of care platinum-based chemotherapy in first line treatment of patients with advanced or metastatic NSCLC	III	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Open-label, randomised, active comparator	*Combination therapy* Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 20 mg/kg Q4W AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
ARCTIC (D4191C00004) Phase III, open-label, randomised, multicentre, international study of durvalumab, given as monotherapy or in combination with tremelimumab, determined by PD-L1 expression, versus SoC in patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen and do not have known EGFR TK activating mutations or ALK rearrangements	III	Efficacy, safety, tolerability, PK, and immunogenicity versus SoC	Open-label, randomised, active comparator	*Durvalumab monotherapy* Durvalumab IV 10 mg/kg Q2W for up to 12 months
				Tremelimumab monotherapy Tremelimumab IV 10 mg/kg IV Q4W for 24 weeks followed by 10 mg/kg IV Q12W for 24 weeks
				Combination therapy Durvalumab IV 20 mg/kg Q4W for 12 weeks then IV 10 mg/kg Q2W for 34 weeks + Tremelimumab IV 1 mg/kg Q4W for 12 weeks (maximum of 22 doses of durvalumab + 4 doses of tremelimumab)

CASPIAN (D419QC00001) Phase III, randomised, multicentre, open-label, comparative study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for the first-line treatment in patients with extensive disease SCLC	III	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Open-label, randomised, active comparator	Durvalumab IV 1500 mg Q3W for 4 doses then durvalumab IV 1500 mg Q4W until PD + EP for 4 cycles
				Combination therapy (D + T + EP) Durvalumab IV 1500 mg Q3W for 4 doses then Durvalumab IV 1500 mg Q4W until PD + Tremelimumab IV 75 mg Q3W for 4 doses + EP for 4 cycles
				SoC EP for up to 6 cycles [b]
CONDOR (D4193C00003) Phase II, randomised, open-label, multicentre, global study of durvalumab monotherapy, tremelimumab monotherapy, and durvalumab in combination with tremelimumab in patients with recurrent or metastatic SCCHN	II	Efficacy of durvalumab in combination with tremelimumab and health-related quality of life	Open-label, randomised	*Durvalumab monotherapy* Durvalumab IV 10 mg/kg Q2W for up to 12 months
				Tremelimumab monotherapy Tremelimumab IV 10 mg/kg Q4W for 7 doses then Q12W for 2 doses for up to 12 months
				Combination therapy Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W to complete 12 months of treatment + Tremelimumab IV 1 mg/kg Q4W for 4 doses
EAGLE (D4193C00002) Phase III, randomised, open-label, multicentre, global study of durvalumab monotherapy and durvalumab in combination with tremelimumab versus SoC in patients with recurrent or metastatic SCCHN	III	Efficacy of durvalumab monotherapy and durvalumab in combination with tremelimumab versus SoC	Open-label, randomised	*Durvalumab monotherapy* Durvalumab IV 10 mg/kg Q2W
				Combination therapy Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W for 12 months or until PD + Tremelimumab IV 1 mg/kg Q4W for 4 doses

D4884C00001 Phase II multicentre, open-label study of tremelimumab monotherapy in patients with advanced solid tumours	II	Efficacy and safety	Open-label	*Durvalumab monotherapy* Durvalumab IV 1500 mg Q4W for up to 12 months
				Tremelimumab monotherapy Tremelimumab IV 750 mg Q4W for 7 doses then Q12W for 2 doses
				Combination therapy Durvalumab IV 1500 mg Q4W for 4 doses + Tremelimumab IV 75 mg/kg Q4W for 4 doses then Durvalumab IV 1500 mg Q4W for up to 8 months
DETERMINE (D4880C00003) Phase IIb, randomised, double-blind study comparing tremelimumab to placebo in second- or third-line treatment of subjects with unresectable pleural or peritoneal malignant mesothelioma	IIb	Efficacy and safety	Randomised, double-blind, placebocontrolled	*Tremelimumab monotherapy* Tremelimumab IV 10 mg/kg Q4W for 7 doses (6 months) then Q12W

[a] For Study 06, an NCA was done for an interim dataset (DCO 28 February 2017). As the final dataset (DCO 19 November 2019) only had 343 additional samples (all in the dose-expansion phase) compared to the interim, it was determined that an additional NCA for the final dataset was not required. This was supported by the sparse sampling in the dose-expansion phase patients (~2 samples per patient per treatment), which would contribute little to no value to a NCA, which typically relies on intense sampling in order to accurately estimate key PK parameters such as half-life and AUC. Therefore, only the results of the interim NCA are presented.
[b] Patients in the EP alone group were permitted an additional 2 cycles of EP (up to 6 cycles total) per the Investigator's discretion.
Abbreviations; ALK, anaplastic lymphoma kinase; AUC, area under the serum concentration-time curve; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; D, durvalumab; DCO, data cutoff; EGFR, epidermal growth factor receptor; EP, etoposide and either carboplatin or cisplatin; IV, intravenous; NCA, noncompartmental analysis; NSCLC, non-small cell lung cancer; PD, progression of disease; PD-L1, programmed cell death ligand-1; PK, pharmacokinetics; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q12W, every 12 weeks; SCCHN, head and neck squamous cell carcinoma; SoC, standard of care; T, tremelimumab; TK, tyrosine kinase.

All studies included male and female patients aged 18 years and older with advanced solid tumours. No PK data has been obtained from healthy volunteers.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Tremelimumab and durvalumab are human monoclonal antibodies (mAb) that act as checkpoint inhibitors with distinct yet complementary mechanisms of action with respect to enhancing the antitumour immune response.

In 2018 durvalumab (Imfinzi) was approved in the EU as monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy

The applicant is currently seeking marketing approval for the use of a single priming dose of tremelimumab in combination with durvalumab for the treatment of patients with unresectable hepatocellular carcinoma (uHCC).

The PK of durvalumab and tremelimumab have been investigated in patients enrolled in the studies listed below.

Data for ISS PK/anti-drug antibody (ADA) and for PopPK were taken from the following studies (most of these studies provided data for both durvalumab and tremelimumab but some for durvalumab or tremelimumab only, as indicated below):

HIMALAYA (D419CC00002) Phase III

Study 22 (D4190C00022) Phase I/II

PACIFIC (D4191C00001) Phase III (durvalumab only)

DETERMINE (D4880C00003) Phase IIb (tremelimumab only)

ATLANTIC (D4191C00003) Phase II (durvalumab only)

D4884C00001 Phase II

Study 1108 (CD-ON-MEDI4736-1108) Phase I/II (durvalumab only)

Study 06 (D4190C0000) Phase Ib

Japan Study 02 (D4190C00002) Phase I

Study 10 (D4190C00010) Phase I

Additional data for ISS PK/ADA outputs only were taken from the following studies:

MYSTIC (D419AC00001) Phase III

ARCTIC (D4191C00004) Phase III

EAGLE (D4193C00002) Phase III

NEPTUNE (D419AC00003) Phase III

DANUBE (D419BC00001) Phase III

KESTREL (D419LC00001) Phase III

Study 21 (D4190C00021) Phase II

HAWK (D4193C00001) Phase II (durvalumab only)

CONDOR (D4193C00003) Phase II

Study 11 (D4190C00011) Phase I

Additional data for PopPK only were taken from the following studies:

POSEIDON (D419MC00004) Phase III

CASPIAN (D419QC00001) Phase III

Details of the studies are described in table 1

Key tremelimumab PK results from studies conducted in patients with unresectable hepatocellular carcinoma (uHCC)

HIMALAYA (D419CC00002)

Himalaya was a randomised, open-label, multicentre Phase III study of durvalumab and tremelimumab as first-line treatment in patients with advanced uHCC.

Patients were randomly assigned (1:1:1:1) to treatment with one of the following 4 treatment arms:

- durvalumab 1500 mg every 4 weeks (Q4W) (D)

- tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W (T300 + D)

- tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W (T75 + D)

- sorafenib 400 mg twice daily (BID) (S)

Patients were stratified according to macrovascular invasion (yes or no), etiology of liver disease (confirmed HBV vs confirmed HCV vs others), and Eastern Cooperative Oncology Group (ECOG) PS (0 vs 1).

The study population included adult patients (aged ≥ 18 years) with confirmed uHCC (based on histopathology) with preserved liver function (Child-Pugh Score class A), Barcelona Clinic

Liver Cancer stage B (not eligible for locoregional therapy) or C, ECOG PS score of 0 or 1, with a life-expectancy of > 12 weeks, and no prior systemic therapy for uHCC. A total of 1324 patients were randomised to one of the four treatment arms in the study.

Tremelimumab PK Results and Conclusions

Tremelimumab PK data were available for a total of 528 patients (386 in the T300 + D arm and 142 in the T75 + D arm). Eighteen patients were excluded from the tremelimumab PK Analysis Set either because they did not receive study treatment or because they had no post-dose data.

No formal noncompartmental analysis was conducted due to the sparse PK sampling scheme in this study.

Following a single dose of tremelimumab 300 mg plus durvalumab Q4W, geometric mean concentrations (n, geometric CV%) were: Cycle 2 trough = 10.7 µg/mL (221, 84.7%) and follow up (3 months) = 0.5 µg/mL (55, 140.4%) (Table 2).

Tremelimumab PK concentrations were within the expected exposure range following a single 300 mg dose.

Following tremelimumab 75 mg Q4W in combination with durvalumab Q4W, geometric mean concentrations (n, geometric CV%) were: Cycle 2 trough = 3.2 µg/mL (132, 67.8%); Cycle 4 trough = 4.3 µg/mL (86, 85.4%); and follow-up (3 months) = 0.4 µg/mL (30, 106.1%) (Table 3:).

Tremelimumab PK concentrations were within the expected exposure range following 75 mg Q4W.

Overall, trough concentrations of tremelimumab at Cycle 2 were 3.3 times higher in the T300 + D arm than the T75 + D arm. In addition, similar tremelimumab exposures were observed in patients rechallenged with tremelimumab.

Table 3: Summary of tremelimumab concentrations over time (µg/mL) (PK Analysis Set) (HIMALAYA)

Analysis timepoint/parameter	Number of patients	
	T300 + D (N = 388)	T75 + D (N = 142)
Cycle 1 pre-infusion		
N	380	140
Mean (SD)	NQ (NC)	NQ (NC)
Median (min, max)	NQ (NQ, 135.7)	NQ (NQ, 3.8)
CV%	NC	NC
Geometric mean [a]	NC	NC
Geometric CV% [a]	NC	NC
Number of BLQ	360	129
Cycle 1 post-infusion		
N	379	0
Mean (SD)	92.70 (34.30)	
Median (min, max)	90.80 (0.2,217.1)	
CV%	37.0	
Geometric mean [a]	78.0	
Geometric CV% [a]	117.2	
Number of BLQ	5	0
Cycle 2 pre-infusion		
N	221	132
Mean (SD)	13.00 (8.40)	3.70 (2.50)
Median (min, max)	12.90 (0.2, 97.2)	3.40 (0.2, 19.0)
CV%	64.3	66.5
Geometric mean [a]	10.7	3.2
Geometric CV% [a]	84.7	67.8
Number of BLQ	1	1
Cycle 4 pre-infusion		
N	0	86
Mean (SD)		5.30 (3.30)
Median (min, max)		4.60 (0.3, 21.0)
CV%		62.3
Geometric mean [a]		4.3
Geometric CV% [a]		85.4
Number of BLQ	0	0
Cycle 4 post-infusion		
N	113	0
Mean (SD)	4.2 (16.50)	
Median (min, max)	1.30 (0.2, 117.2)	
CV%	396.3	
Geometric mean [a]	1.3	
Geometric CV% [a]	156.5	
Number of BLQ	8	0
3-month follow-up (Follow-up)		
N	55	30
Mean (SD)	0.80 (0.90)	0.60 (0.50)
Median (min, max)	0.50 (0.2,4.4)	0.40 (0.2,1.8)
CV%	106.2	86.8
Geometric mean [a]	0.5	0.4
Geometric CV% [a]	140.4	106.1
Number of BLQ	18	9

[a] Calculated using log transformed data.
At a time point where less than or equal to 50% of the concentration values were NQ, all NQ values were set to LLOQ, and all descriptive statistics were calculated accordingly. At a time point where more than 50% (but not all) of the values were NQ, the gmean and gCV% was set to NC. The maximum value was reported from the individual data, and the minimum, mean, and median were set to NQ. If all concentrations are NQ at a time point, no descriptive statistics were calculated for that time point. The gmean, minimum, mean, median, and maximum are reported as NQ and the gCV% as NC.
Abbreviations; BLQ, below the limit of quantitation (< 0.156 µg/mL); CV, coefficient of variation; LLOQ, Lower Limit of Quantification; max, maximum; min, minimum; N/A, not available; NC, Not calculated; NQ, Not Quantifiable; PK, pharmacokinetic; Q4W, every 4 weeks; SD, standard deviation; T75 + D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300 + D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Study 22 (D4190C00022)

Study 22 was a Phase I/II, randomised, open-label, multicentre study examining the safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, or durvalumab in combination with tremelimumab or bevacizumab in patients with advanced uHCC.

Tremelimumab PK Results and Conclusions

In Parts 2 and 3 of the study, the PK Analysis Set comprised 319 patients (99 in the D arm,74 in the T300 + D arm, 66 in the T arm, and 80 in the T75 + D arm). At the final data cutoff (DCO), 603 PK data points from the evaluable PK population were available for a total of 216 patients following tremelimumab administered over 60 minutes (1 mg/kg: 81 data points from 36 patients; 10 mg/kg: 94 data points from 33 patients; 75 mg: 134 data points from 43 patients; 300 mg: 187 data points from 72 patients; and 750 mg: 107 data points from 32 patients).

Table 4 summarises the tremelimumab data.

Table 4: Summary of PK parameters of tremelimumab following IV dose of tremelimumab to patients with advanced hepatocellular carcinoma (Parts 2 and 3) (PK Analysis Set) (Study 22)

Dose	Summary	C_{max} (µg/mL)			C_{trough} (µg/mL)		
		Week 1	Week 13	Week 25	Week 5	Week 13	Week 25
1 mg/kg Q4W	N	34	12	—	—	14	—
	AM	23.06	23.87	—	—	5.478	—
	SD	6.175	4.964	—	—	2.964	—
	ACV (%)	26.8	20.8	—	—	54.1	—
	Median	22.95	21.95	—	—	5.720	—
	Minimum	10.30	17.40	—	—	0.7780	—
	Maximum	36.80	35.40	—	—	12.16	—
	GM	22.22	23.43	—	—	4.545	—
	GCV (%)	29.1	19.8	—	—	82.1	—
	95% CI	(20.12, 24.54)	(20.69, 26.54)	—	—	(3.003, 6.879)	—
10 mg/kg Q4W	N	31	6	5	—	14	7
	AM	221.0	255.2	203.2	—	48.61	39.56
	SD	62.82	121.6	20.24	—	22.68	7.832
	ACV (%)	28.4	47.6	10.0	—	46.7	19.8
	Median	209.1	275.0	211.7	—	41.85	42.82
	Minimum	150.2	31.80	173.3	—	15.80	24.64
	Maximum	502.0	388.0	225.2	—	93.00	47.22
	GM	214.7	203.7	202.4	—	43.90	38.78
	GCV (%)	23.3	116.5	10.3	—	50.5	22.9
	95% CI	(197.3, 233.6)	(77.08, 538.3)	(178.2, 229.9)	—	(33.34, 57.82)	(31.47, 47.78)
75 mg Q4W	N	40	11	—	32	11	—
	AM	30.91	29.54	—	4.862	5.867	—
	SD	21.96	9.870	—	2.402	3.606	—
	ACV (%)	71.0	33.4	—	49.4	61.5	—
	Med	25.65	30.00	—	4.260	7.100	—
	Min	14.10	14.10	—	0.3820	0.5740	—
	Max	129.5	42.70	—	10.52	10.42	—
	GM	26.99	27.80	—	4.178	4.113	—
	GCV (%)	49.6	39.9	—	71.1	146.0	—

Dose	Summary	C_{max} (µg/mL)			C_{trough} (µg/mL)		
		Week 1	Week 13	Week 25	Week 5	Week 13	Week 25
	95% CI	(23.23, 31.36)	(21.47, 35.99)	—	(3.317, 5.262)	(2.006, 8.430)	—
300 mg	N	68	—	—	48	—	—
	AM	103.4	—	—	13.08	—	—
	SD	34.31	—	—	5.437	—	—
	ACV (%)	33.2	—	—	41.6	—	—
	Median	95.75	—	—	13.23	—	—
	Minimum	57.70	—	—	2.740	—	—
	Maximum	239.0	—	—	26.32	—	—
	GM	99.06	—	—	11.67	—	—
	GCV (%)	28.6	—	—	57.3	—	—
	95% CI	(92.55, 106.0)	—	—	(9.997, 13.62)	—	—
750 mg Q4W	N	29	11	—	23	16	5
	AM	241.8	260.0	—	32.43	37.79	35.96
	SD	101.9	130.1	—	18.81	23.84	5.806
	ACV (%)	42.1	50.0	—	58.0	63.1	16.1
	Median	219.7	232.0	—	26.12	34.52	33.14
	Minimum	130.3	52.00	—	4.092	4.718	30.73
	Maximum	471.0	487.5	—	83.20	98.90	44.90
	GM	224.8	225.2	—	26.69	31.25	35.61
	GCV (%)	39.0	68.2	—	81.6	78.1	15.6
	95% CI	(194.8, 259.4)	(148.7, 341.2)	—	(19.59, 36.35)	(21.63, 45.13)	(29.38, 43.16)

ACV, arithmetic coefficient of variation is calculated in the original scale with the equation: 100 × (SD/AM); AM, arithmetic mean; CI, confidence interval of the geometric mean; Cmax, concentration at the end of infusion (TAD < 1 day) in that visit; C_{trough}, predose concentration (40 day < TAD > 23 day) in that visit; GCV, geometric coefficient of variation is calculated in the natural log scale; with the equation: 100 × sqrt(exp(σ2) – 1), where σ2 is the observed variance on the natural log scale; GM, geometric mean; IV, intravenous; N, number of patients; PK, pharmacokinetic; Q4W, every 4 weeks; SD, standard deviation; TAD, time after dose.

Similar exposures were observed following the weight-based 1 mg/kg and the equivalent fixed 75 mg dose. Additionally, similar exposures were observed following the weight-based 10 mg/kg and the equivalent fixed 750 mg dose.

Maximum serum concentration (C_{max}) values were 3.3-fold (arithmetic mean) or 3.7-fold (geometric mean) higher following a 300 mg dose compared to a 75 mg dose. Exposures increased generally dose-proportionally with increasing weight-based doses from 1 to 10 mg/kg and fixed doses from 75 to 750 mg, respectively.

The data in **Error! Reference source not found.** above show that there was no observed accumulation of tremelimumab (C_{max} or trough serum concentration [C_{trough}]) following repeated dosing in any of the cohorts and the geometric mean of the accumulation index ranged from 0.949 to 1.17, where adequate data were available for assessment. The C_{max} (geometric mean) for tremelimumab in the T300 + D arm was approximately 3.7 times that in the T75 + D arm.

Dose rationale for tremelimumab and durvalumab in HIMALAYA

Dose selection for tremelimumab and durvalumab in HIMALAYA was aligned with results from the dose-finding results of Study 22, in which 1500 mg durvalumab Q4W was administered in combination with tremelimumab for 4 cycles followed by durvalumab 1500 mg Q4W monotherapy.

A fixed dose of tremelimumab 75 mg Q4W (equivalent to 1 mg/kg Q4W for an average body weight of 75 kg) is predicted to result in similar AUC and only provide a modest difference in median peak and trough levels at steady state compared to tremelimumab 1 mg/kg Q4W, based on simulations in a Population PK model developed for tremelimumab using data from Study 10, Japan Study 02, Study 06, BASKET, DETERMINE, and POSEIDON. The Population PK model indicated that body weight is not a significant covariate on the PK of tremelimumab.

Administration of tremelimumab in combination with durvalumab has demonstrated significant elevations in proliferating CD4 + Ki67 + T cell quantities (Study 06 and Study 10). These elevations were proportional to the tremelimumab dose (Study 06). A dose of tremelimumab 1 mg/kg Q4W in combination with durvalumab 15 or 20 mg/kg Q4W was sufficient to achieve the significant elevation in

proliferating T cell quantities. It was hypothesised that a single high-dose of tremelimumab may provide a stronger pharmacodynamic effect in uHCC than tremelimumab 1 mg/kg, while potentially avoiding the toxicity typically observed with repeated cycles of tremelimumab administration. This led to the proposal of evaluating a higher dose of tremelimumab in uHCC, achieved by combining the 4 doses of tremelimumab 1 mg/kg from the T75 + D regimen into a single priming dose of tremelimumab 4 mg/kg added to the first treatment cycle of durvalumab 20 mg/kg Q4W. Based on PK simulations, the predicted C_{max} for a single dose of tremelimumab 4 mg/kg was approximately 3- to 4-fold higher than the predicted C_{max} for tremelimumab 1 mg/kg (compared to any of the 4 tremelimumab doses in the T75 + D regimen). Based on the expectation of minor impact of body weight on PK exposure, a fixed dose of tremelimumab 300 mg was considered equivalent to tremelimumab 4 mg/kg. In Study 22, pharmacodynamic results revealed that patients receiving T300 + D or T demonstrated the highest peak CD8 + Ki67 + T cell counts, and this corresponded with best overall responses of complete or partial response.

HIMALAYA results confirmed that durvalumab 1500 mg Q4W with tremelimumab 300 mg as a priming dose followed by durvalumab 1500 mg Q4W monotherapy is an appropriate dose for patients with uHCC by showing a clinically meaningful efficacy and manageable safety profile following this dosing regimen.

Bioanalytical Methods

Bioanalysis methods for quantitation of tremelimumab drug concentration, anti-drug antibodies (ADA), and neutralizing antibodies (nAb) were developed and validated.

Population PK analyses for tremelimumab and durvalumab

The tremelimumab population PK analysis was updated with sparse data from Study 22 and HIMALAYA in HCC patients and pooled with the previous dataset (Studies D4190C00002, D4190C00006, D4190C00010, DETERMINE, BASKET and POSEIDON). 7039 serum PK samples from 2406 patients administered tremelimumab were available in the final dataset for analysis of which 1801 samples came from HCC patients. Structurally, the final model remained the same as the previous model: a 2-compartment model with linear CL and an additional time-dependent CL component for patients on combination therapy only. Residuals were described by a combined additive and proportional error model. The following covariates were identified as statistically significant and included in the final model: body weight and sex on both CL and V1; albumin, primary indication and combination therapy (chemotherapy vs. no chemotherapy) on CL.

The final model was evaluated by means of non-parametric bootstrap analysis, RSEs, GOF-plots and pcVPCs.

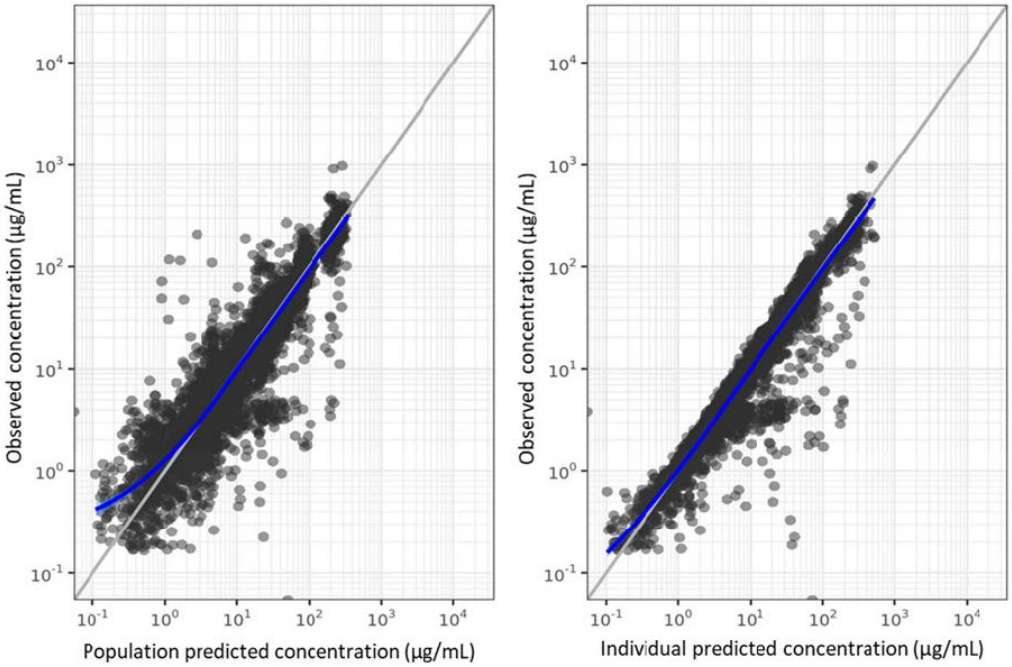
Parameter estimates of the final model for tremelimumab and selected diagnostic plots are shown in Table 5 and Figure 2 and Figure 3.

Table 5: Tremelimumab PopPK model parameter estimates (final model)

Parameter	Estimate	RSE (%)	bootstrap 95%CI	Shrinkage (%)	Unit
Population Parameter					
CL	0.295	1.35	[0.283 ; 0.308]	-	L/day
V1	3.59	1.11	[3.54 ; 3.65]	-	L
Q	0.480	6.94	[0.383 ; 0.624]	-	L/day
V2	2.69	3.55	[2.48 ; 2.98]	-	L
Tmax change CL	-0.134	15.3	[-0.283 ; -0.0219]	-	L/day
TC50 change CL	63.1	7.22	[4.06 ; 468]	-	days
Covariate					
Body weight on V1	0.467	7.99	[0.404 ; 0.539]	-	-
Sex on V1	-0.116	15.4	[-0.144 ; -0.0892]	-	-
Body weight on CL	0.384	10.5	[0.304 ; 0.469]	-	-
Albumin on CL	-0.780	5.74	[-0.896 ; -0.669]	-	-
Sex on CL	-0.0985	18.4	[-0.135 ; -0.0634]	-	-
Comb2 on CL	-0.124	15.2	[-0.166 ; -0.0772]	-	-
Primary tumor 6-7 on CL	-0.146	17.2	[-0.202 ; -0.0872]	-	-
Interindividual Variability					
ETA CL	0.108	3.67	[0.0873 ; 0.131]	21.8	-
Covariance CL-V1	0.0621	3.84	[0.0420 ; 0.0862]	-	-
ETA V1	0.0619	1.71	[0.0377 ; 0.0932]	24.3	-
Covariance CL-V2	0.0898	9.68	[0.0468 ; 0.138]	-	-
Covariance V1-V2	0.112	7.48	[0.0694 ; 0.158]	-	-
ETA V2	0.212	12.3	[0.119 ; 0.312]	28.3	-
ETA T_{max}	1.42	10.6	[0.784 ; 8.14]	65.2	-
Residual Variability					
Proportional component	0.285	0.799	[0.271 ; 0.300]	18.3	-
Additive component	0.369	0.915	[0.134 ; 0.506]	18.3	µg/mL

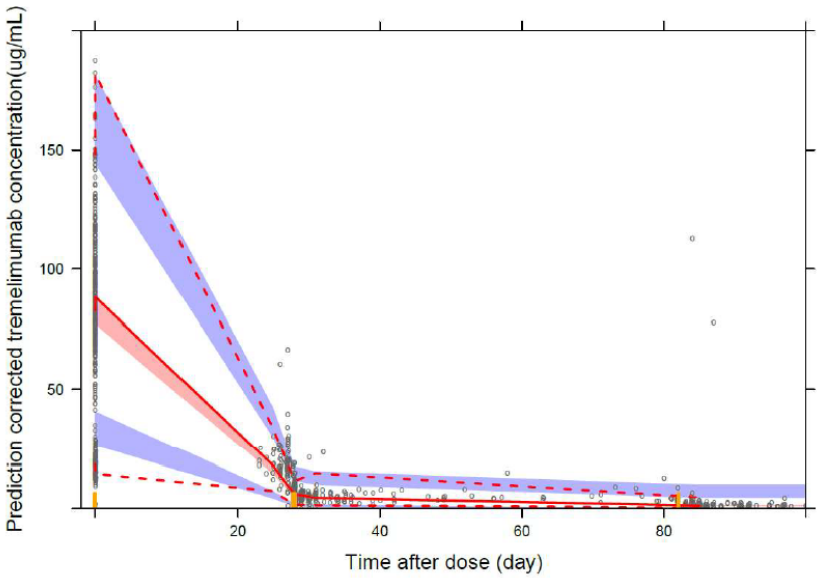
Source: az-tremelimumab-pk-model-himalaya-V1.0.Rmd, Reference: 04e0e5:7ef181
CI=confidence interval, CL=clearance, Comb2=durvalumab, tremelimumab and chemotherapy (standard of care), as compared to treatment arms without chemotherapy, ETA=random effect, IIV=inter-individual variability, PK=pharmacokinetics, V1=central volume of distribution, primary indication 6=biliary tract carcinoma, primary indication 7=esophagus carcinoma, Q=inter-compartmental clearance, V2=peripheral volume of distribution, RSE=relative standard error, TC50=time to 50% clearance reduction, Tmax=maximum change of CL over time.
Source: Table 16, Population PK and Exposure-Response Report, Module 5.3.3.5

Figure 2: Final model GOF plots for serum tremelimumab concentration: observations vs predictions



Note: The blue line is a trend line through the data points, and the blue area is the 95% confidence interval around it.
GOF, goodness-of-fit.
Source: Figure 8, Population PK and Exposure-Response Report, Module 5.3.3.5

Figure 3: pcVPC of the final model vs time after dose – HIMALAYA Study



Note: The solid and dashed lines represent the median, 5th, and 95th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model.
Abbreviations: CI=confidence interval, pcVPC=prediction-corrected visual predictive check
Source: /projects/qcp/QCP_MODELING/ONC/durvalumab/poppk_20210729_himalaya/Scripts/s04_vpc.R

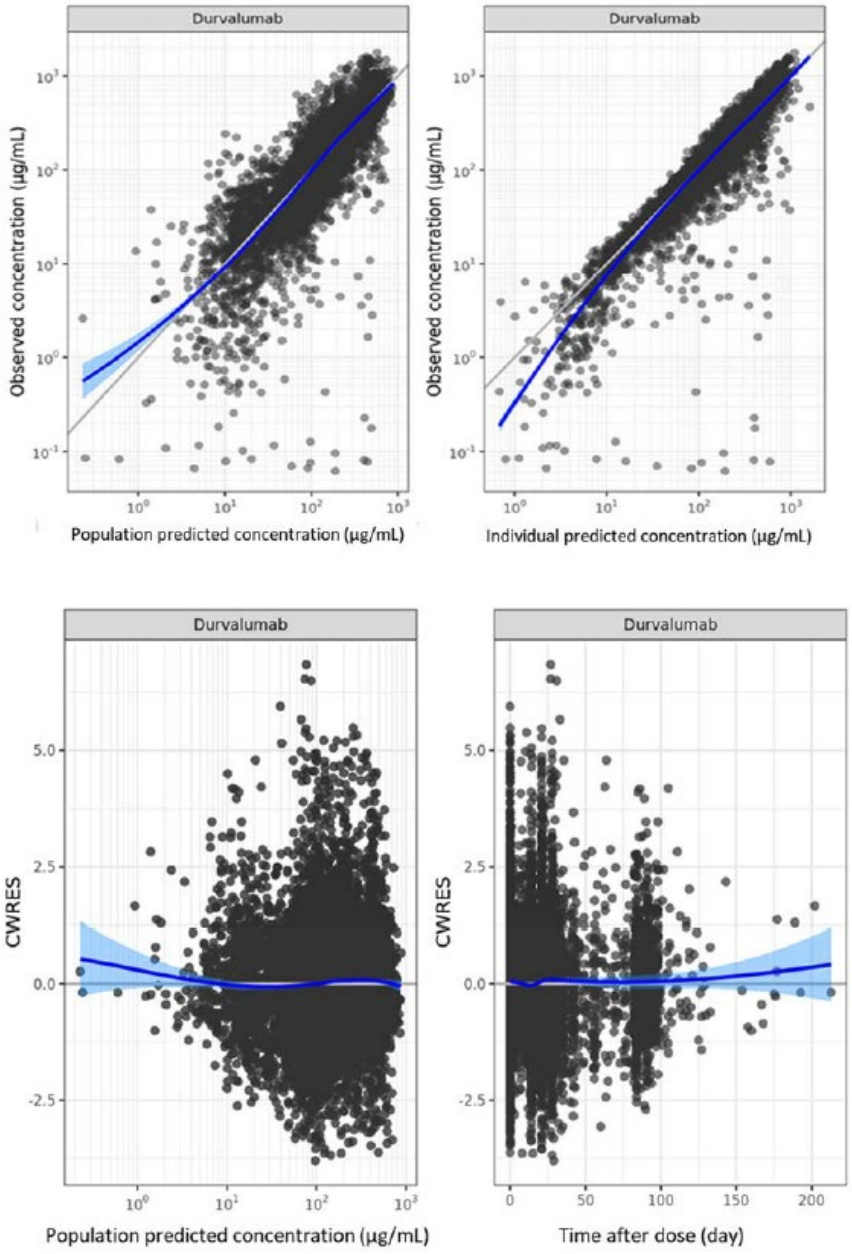
The durvalumab population PK model was updated with sparse data from HIMALAYA and Study 22 and pooled with the previous dataset (Studies CASPIAN, PACIFIC, ATLANTIC, POSEIDON and CD-ON-MEDIA-

4736-1108). The final model of durvalumab PK was a 2-compartment model with time-dependent CL. The final model included the following covariate effects on CL: WT, ALB, combination therapy, sex, CrCL, LDH, ECOG and tumour type; and on V1: WT and sex. The final model was evaluated by means of non-parametric bootstrap analysis, RSEs, GOF-plots and pcVPCs. Parameter estimates of the final model for durvalumab and selected diagnostic plots are shown in Table 6 and Figure 4 and Figure 5.

Table 6: Population PK model parameter estimates durvalumab (final model)

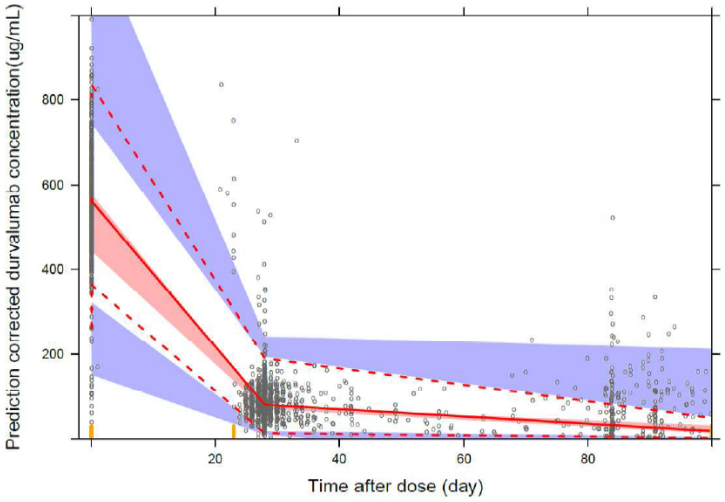
Parameter	Estimate	RSE (%)	bootstrap 95%CI	Shrinkage (%)	Unit
Population Parameter					
CL	0.277	2.01	[0.263 ; 0.292]	--	L/day
V1	3.45	0.807	[3.40 ; 3.49]	--	L
V2	2.13	2.02	[1.98 ; 2.29]	--	L
Q	0.469	5.15	[0.411 ; 0.535]	--	L/day
Tmax	-0.372	4.99	[-0.419 ; -0.327]	--	L/day
TC_{50}	88.7	9.92	[58.3 ; 150]	--	day
LAM	1.00	--	--	--	-
Covariate					
Albumin on CL	-0.659	2.87	[-0.834 ; -0.506]	--	--
Creatinine clearance on CL	0.121	15.6	[0.0800 ; 0.162]	--	--
ECOG status on CL	-0.0516	20.7	[-0.0720 ; -0.0278]	--	--
LDH on CL	0.0442	23.3	[0.0208 ; 0.0642]	--	--
Sex on CL	-0.149	7.95	[-0.172 ; -0.126]	--	--
COMB1 on CL	-0.0459	27.0	[-0.0688 ; -0.0195]	--	--
COMB2 on CL	-0.0417	43.2	[-0.0886 ; 0.00746]	--	--
Body weight on CL	0.376	8.32	[0.317 ; 0.443]	--	--
Tumor type 1 on CL	-0.0393	46.1	[-0.0750 ; -0.00306]	--	--
Tumor type 2 on CL	0.0622	55.8	[-0.0131 ; 0.137]	--	--
Tumor type 3 on CL	0.0472	46.1	[0.00497 ; 0.0932]	--	--
Sex on V1	-0.140	7.60	[-0.163 ; -0.118]	--	--
Body weight on V1	0.499	5.01	[0.449 ; 0.549]	--	--
Interindividual Variability					
ETA CL	0.0896	2.85	[0.0803 ; 0.0982]	17.6	--
Cov CL-V1	0.0389	5.34	[0.0338 ; 0.0441]	-	--
ETA V1	0.0524	3.32	[0.0451 ; 0.0598]	29.9	--
ETA T_{max}	0.0665	9.03	[0.0436 ; 0.109]	59.3	--
Residual Variability					
Proportional component	0.250	0.541	[0.241 ; 0.258]	15.0	--
Additive component	4.28	6.70	[3.39 ; 5.29]	15.0	µg/mL

Figure 4: Final durvalumab PopPK model – basic GOF



Note: The blue line is a trend line through the data points, and the blue area is the 95% CI around it.
Source: Figure 2, Population PK and Exposure-Response Report, Module 5.3.3.5.
CI, confidence interval; CWRES=conditional weighted residuals.

Figure 5: pcVPC of the final model vs time after dose – HIMALAYA Study



Note: The solid and dashed lines represent the median, 5th, and 95th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model.
Abbreviations: CI=confidence interval, pcVPC=prediction-corrected visual predictive check
Source: /projects/qcp/QCP_MODELING/ONC/durvalumab/poppk_20210729_himalaya/Scripts/s04_vpc.R

Tremelimumab & durvalumab exposure-response modelling analyses

The ER analysis for both efficacy and safety was based on patients from HIMALAYA study administered 1500 mg Q4W durvalumab and a 300 mg single dose tremelimumab IV. 388 and 397 patients were included in the ER analysis for durvalumab and tremelimumab, respectively. The final durvalumab/tremelimumab PopPK models were used to obtains EBEs of individual PK parameters.

Exposure-efficacy:

The exposure-efficacy relationships in the HIMALAYA study were explored by Kaplan-Meier plots stratified by durvalumab and tremelimumab exposure quartiles. Several exposure metrics for tremelimumab and durvalumab were derived. For both efficacy outcomes, OS and PFS, Cox Proportional Hazard (CPH) models were developed and a stepwise covariate selection was performed (α = 1% and 0.1%). No significant exposure-efficacy relationships were identified for durvalumab or tremelimumab. The CPH models for OS suggested that AST and NLR were associated with shorter survival in T300+D arm as they were identified as statistically significant covariates. Maximum concentration following the first dose (Cmax, dose 1) for tremelimumab was also identified as a marginally statistically significant exposure metric (LRT: 11.92 > 10.83) but was removed due to non-significance in the Wald test (p = 0.199), the standard error of coefficient (β) being large and the 95% CI of β containing the null. Likewise, trough concentration following the first dose (Cmin, dose 1) for tremelimumab was also identified as a marginally significant covariate within PFS based on the LRT but was removed for the same reasons. No other covariates were identified to be significant with PFS.

Exposure-safety:

Logistic regression modelling did not identify any significant impact of durvalumab or tremelimumab exposure on the incidence of investigated adverse effects.

QTcF modelling analysis

Linear mixed-effects exposure-response modelling with an intercept was conducted to characterise the relationship of change from baseline of QTcF (ΔQTcF) with durvalumab or tremelimumab serum concentrations. The concentration-ΔQTcF analysis population consisted of 293 observations from 67 patients administered durvalumab and 254 observations from 66 patients administered tremelimumab from Study 06. Unscheduled concentration-QTcF observations and non-central ECG records were excluded from the analysis.

For durvalumab, the slope for the relationship of ΔQTcF to durvalumab concentration was 0.0048 ms per µg/mL (p = 0.112), with a mean intercept of 0.082 ms (p = 0.950; 90% CI: -2.07, 2.24 ms; Table).

The slope for the relationship of ΔQTcF to tremelimumab concentration was -0.012 ms per µg/mL (p = 0.531), and the mean intercept was 0.581 ms (p = 0.629; 90% CI: -1.41, 2.57 ms; Table).

The slope or the intercept for tremelimumab and durvalumab were not significantly different from zero.

Table 7: Parameter estimates of durvalumab PK – ΔQTcF relationship

Parameter estimates						
Parameter	**Estimate**	**Standard error**	***p*- value**	**90% confidence limits**		**Gradient**
Intercept (ms)	0.08205	1.2916	0.9495	-2.0726	2.2367	0.000012
Slope (ms/µg/mL)	0.004841	0.003007	0.1123	-0.00018	0.009858	0.003814
Inter individual variability on intercept	7.8721	0.8472	<.0001	6.4588	9.2855	0.000021
Model error	9.4501	0.4275	<.0001	8.7369	10.1633	-8.91E-6

PK pharmacokinetic

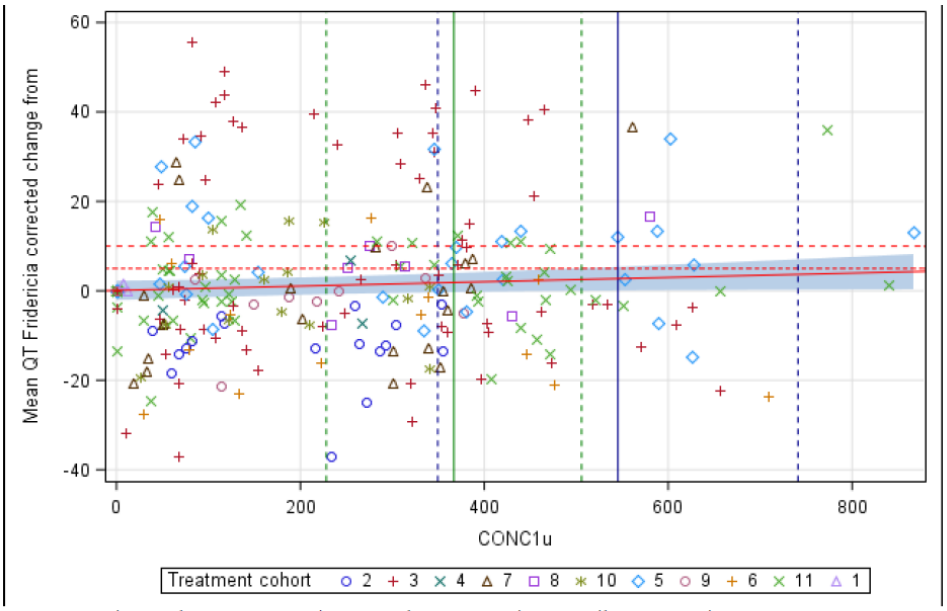
Table 8: Parameter estimates of tremelimumab PK – ΔQTcF relationship

Parameter estimates						
Parameter	**Estimate**	**Standard error**	***p*- value**	**90% confidence limits**		**Gradient**
Intercept (ms)	0.5806	1.1952	0.6288	-1.4137	2.5749	-1.01E-6
Slope (ms/ µg/mL)	-0.01225	0.01945	0.5312	-0.04470	0.02021	-0.00007
Inter individual variability on intercept	7.5385	0.8414	<.0001	6.1345	8.9425	-2.99E-6
Model error	9.2338	0.4544	<.0001	8.4755	9.9921	4.764E-6

PK pharmacokinetic

The upper bound of the 90% 2-sided CI for ΔQTcF was less than 10 ms, and the highest observed concentration of durvalumab and tremelimumab had a predicted mean ΔQTcF of less than 5 ms (Figure 6, Figure 7 and Table 8).

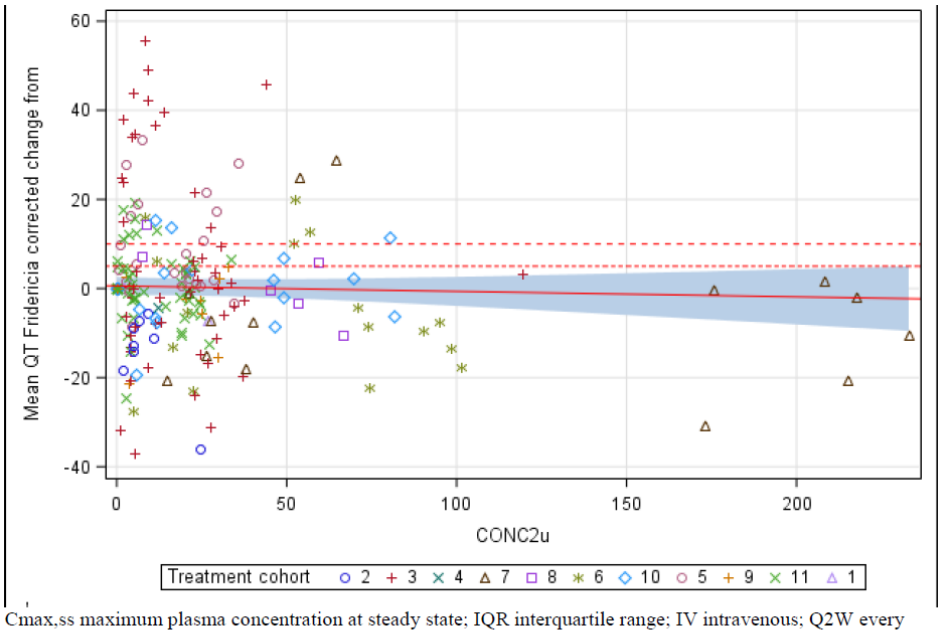
Figure 6: QTcF (change from baseline) versus concentration of durvalumab on intercept full data



Cmax,ss maximum plasma concentration at steady state; IQR interquartile range; IV intravenous; Q2W every 2 weeks; Q4W every 4 weeks

Note: Red line is the linear regression line and the shaded area is the 90% CI based on the linear mixed-effects model prediction. Red short dashed horizontal line is 5 msec change from baseline identity line. Red long dashed horizontal line is 10 msec change from baseline identity line. Green dashed vertical lines are observed median +/- IQR predicted Cmax,ss for a 10 mg/kg Q2W IV durvalumab dosing. Green solid line is median predicted Cmax,ss for a 10 mg/kg Q2W IV durvalumab dosing. Blue dashed vertical lines are observed median +/- IQR(interquartile range) predicted Cmax,ss for a 20 mg/kg Q4W IV durvalumab dosing. Blue solid line is median predicted Cmax,ss for a 20 mg/kg Q4W IV durvalumab dosing. Treatment cohorts are 1: 3 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 2: 10 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab;3: 15 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 4: 10 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 5: 20 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 6: 15 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 7: 15 mg/kg durvalumab (Q4W) + 10 mg/kg

Figure 7: QTcF (change from baseline) versus concentration of tremelimumab on intercept full data



Cmax,ss maximum plasma concentration at steady state; IQR interquartile range; IV intravenous; Q2W every 2 weeks; Q4W every 4 weeks

Note: Red line is the linear regression line and the shaded area is the 90% CI based on the linear mixed-effects model prediction. Red short dashed horizontal line is 5 msec change from baseline identity line. Red long dashed horizontal line is 10 msec change from baseline identity line. Treatment cohorts are 1: 3 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 2: 10 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab;3: 15 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 4: 10 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 5: 20 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 6: 15 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 7: 15 mg/kg durvalumab (Q4W) + 10 mg/kg Tremelimumab; 8: 20 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 9: 10 mg/kg durvalumab (Q2W) + 1 mg/kg Tremelimumab; 10: 10 mg/kg durvalumab (Q2W) + 3 mg/kg Tremelimumab; 11: 20 mg/kg durvalumab (Q4W) + 1 mg/kg tremelimumab (Q4W)/ 20 mg/kg durvalumab (Q4W)

Table 9: Summary of maximum observed durvalumab or tremelimumab serum concentration and predicted mean and CI of ΔQTcF

	Observed Cmax (µg/mL)	Cohort	Dosing regimen	Predicted mean ΔQTcF (ms)	90% CI of predicted mean ΔQTcF (ms)
Durvalumab	866.6	10	20mg/kg durvalumab, 1mg/kg tremelimumab	4.28	(0.36, 8.20)
Tremelimumab	233	4	10mg/kg durvalumab, 15mg/kg tremelimumab	-2.27	(-9.49, 4.96)

ΔQTcF change from baseline of QTcF; CI confidence interval; Cmax maximum plasma concentration; QTcF Fridericia's heart rate corrected QT interval.

Absorption

The product is intended for intravenous administration. Clinical studies were not conducted to evaluate the bioavailability or bioequivalence compared to other formulations.

Dose-normalised tremelimumab PK Parameters (C_{max} and AUC_{0-28}) from the dose finding study (Study 06) following administration of tremelimumab in combination with durvalumab are given in Table 10:10.

Table 10: Dose-normalised tremelimumab PK parameters following administration of tremelimumab and durvalumab combination (Study 06)

Dose level	Tremelimumab geometric mean (n, geometric %CV)	
	Cmax_D (µg/mL/mg)	AUC0-28_D (µg·day/mL/mg)
T1 Q4W Escalation (N = 59)	0.319 (55, 37.8)	2.82 (36, 39.3)
T3 Q4W Escalation (N = 34)	0.258 (32, 60.7)	2.83 (17, 21.1)
T10 Q4W Escalation (N = 9)	0.261 (9, 26.1)	2.45 (9, 32.2)
T1 Q4W Expansion (N = 251)	0.288 (200, 41.3)	3.41 (14, 45.9)

Note: All data are depicted as geometric mean (n, geometric %CV), and rounded to 3 significant digits.
AUC0-28_D, dose-normalised area under the serum concentration-time curve from Day 1 to Day 29; Cmax_D, dose-normalised maximum serum concentration after the first dose; CV, coefficient of variation; PK, pharmacokinetic; Q4W, every 4 weeks; T1, tremelimumab 1 mg/kg; T3, tremelimumab 3 mg/kg; T10, tremelimumab 10 mg/kg.

Distribution

Study 22 evaluated PK parameters in patients with advanced hepatocellular carcinoma, who received a single IV dose of 300 mg on Day 1. In a subset of patients from this study (N=11) for whom intensive PK sampling was done, the estimated geometric mean volume of distribution was 7.6 L (Table).

Based on population PK analysis that included 1605 patients who received tremelimumab monotherapy or in combination with durvalumab with or without chemotherapy in the dose range of ≥ 1 mg/kg, the geometric mean steady-state volume of distribution (V_{ss}) was 6.33 L.

Table 11: Individual values and descriptive statistics of tremelimumab serum PK parameters following single IV dose of 300 mg tremelimumab on Day 1 of Week 1 to patients with advanced hepatocellular carcinoma (PK analysis set) (Study 22)

Allocation number	Tremelimumab PK parameters						
	AUC_{last} (µg/mL*day)	AUC_{inf} (µg/mL*day)	C_{max} (µg/mL)	T_{max} (h)	Apparent terminal $t_{1/2}$ (day)	CL (L/day)	Vz (L)
D4190C00022/20015120016	1814	1903	102.7	1.58	28.2	0.158	6.42
D4190C00022/20015220014	1212	1469	100.9	3.24	67.9	0.204	20.0
D4190C00022/20015240015	1784	1828	73.60	1.18	23.6	0.164	5.59
D4190C00022/20016520005	1009	1022	95.40	1.01	16.0	0.293	6.76
D4190C00022/20018500022	1362	1377	68.50	1.08	25.7	0.218	8.09
D4190C00022/20021190008	1422	1636	117.8	1.25	21.7	0.183	5.73
D4190C00022/20021190009	1267	1310	89.30	1.13	24.3	0.229	8.02
D4190C00022/20021200007	1225	1728	122.1	1.22	18.3	0.174	4.59
D4190C00022/20021200010	1223	1273	84.60	1.27	19.4	0.236	6.58
D4190C00022/20021210007	1303	1597	92.10	1.06	39.4	0.188	10.7
D4190C00022/20021210011	895.5	913.5	80.30	1.13	18.6	0.328	8.83
Number of patients	11	11	11	11	11	11	11
Arithmetic mean	1320	1460	93.39	NR	27.6	0.216	8.30
Standard deviation	279.5	317.4	16.87	NR	14.8	0.0539	4.24
ACV (%)	21.2	21.7	18.1	NR	53.8	25.0	51.1
Median	1267	1469	92.10	1.18	23.6	0.204	6.76
Minimum	895.5	913.5	68.50	1.01	16.0	0.158	4.59
Maximum	1814	1903	122.1	3.24	67.9	0.328	20.0
Geometric mean	1294	1426	92.02	NR	25.1	0.210	7.64
GCV (%)	21.1	23.7	18.2	NR	43.0	23.7	41.3
95% CI	(1124, 1489)	(1219, 1668)	(81.50, 103.9)	NR	(19.1, 33.2)	(0.180, 0.246)	(5.85, 9.97)

ACV, arithmetic coefficient of variation is calculated in the original scale with the equation: 100 × (SD/AM); AUC_{inf}, area under the concentration versus time curve from 0 to infinity; AUC_{last}, area under the concentration versus time curve from 0 to the time of the last quantifiable sample; AUC_{inf}, area under the concentration versus time curve from 0 to infinity after dosing; CI, confidence interval of the geometric mean; CL, clearance; C_{max}, concentration at the end of infusion (TAD < 1 day) in that visit; GCV, geometric coefficient of variation is calculated in the natural log scale with the equation: $100 \times \sqrt{(\exp(\sigma^2) - 1)}$, where σ^2 is the observed variance on the natural log scale; IV, intravenous; NR, not reported; PK, pharmacokinetic; $t_{1/2}$, apparent first-order terminal elimination half-life; TAD, time after dose; T_{max}, time to maximum serum concentration; V_z, volume of distribution during the terminal phase.

Elimination

Tremelimumab, as a typical mAb, is not cleared renally due to its large molecular weight. The primary elimination pathways are protein catabolism via the reticuloendothelial system (RES) or target-mediated disposition.

Based on the findings from the subset of patients from Study 22, for whom intensive PK sampling was done, the geometric mean clearance was 0.21 L/day and the apparent terminal half-life was 25.1 days (Table).

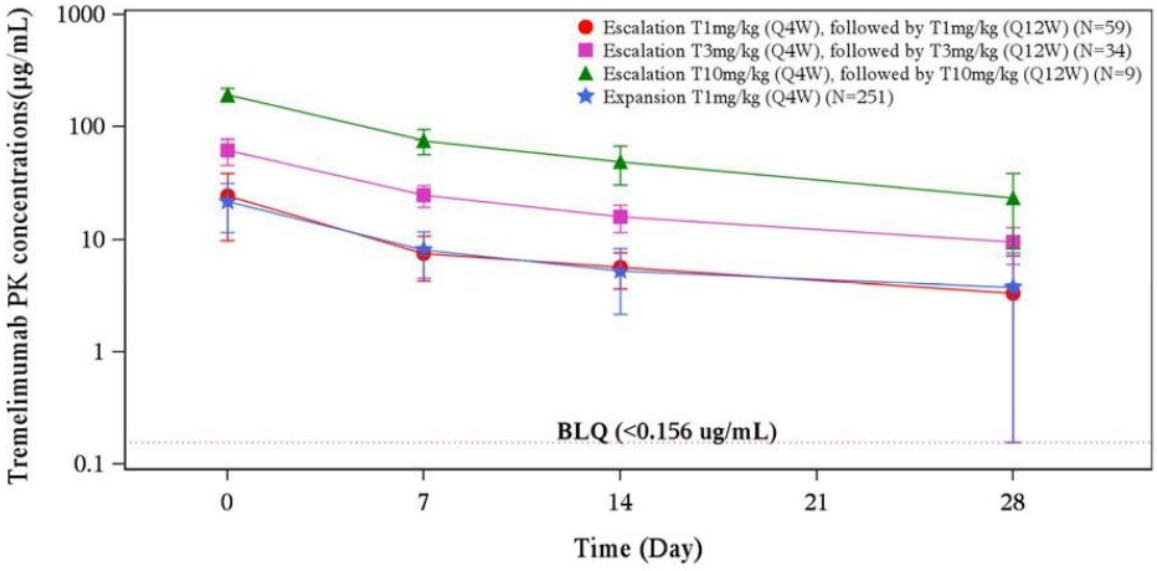
Based on population PK analysis, the geometric mean steady-state clearance (CL_{ss}) was 0.309 L/day and the geometric mean terminal half-life was approximately 14.2 days.

Dose proportionality and time dependencies

In a dose finding study conducted in patients with NSCLC (Study 06) an approximately dose-proportional increase in PK exposure (C_{max} and AUC_{0-28}) of tremelimumab was observed over the dose range of 1 to 10 mg/kg tremelimumab Q4W when administered in combination with durvalumab (Table above).

Exposure following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. The PK profile for tremelimumab is shown in Figure 8.

Figure 8: Mean (SD) tremelimumab PK concentration-time profiles after the first dose by tremelimumab dose following IV administration of the combination of durvalumab and tremelimumab (Study 06)



BLQ, below the limit of quantification; IV, intravenous; PK, pharmacokinetic; Q4W, every 4 weeks; Q12W, every 12 weeks; SD, standard deviation.

Based on the final Population PK model, time-dependent CL was identified for tremelimumab in combination with durvalumab, but not for tremelimumab as monotherapy.

Intra- and inter-individual variability

For the tremelimumab population PK model, estimates of inter-individual variability (CV%) were 32.9% on CL, 24.9% on V1, 46.0% on V2 and 119.2% on T_{max}.

For the durvalumab population PK model, estimates of inter-individual variability (CV%) were 29.9% on CL, 22.9% on V1 and 25.8% on T_{max}.

Special populations

The effect of intrinsic factors (i.e., renal function, hepatic function, age, race, gender, and body weight) on the PK of tremelimumab has not been studied through specific dedicated studies.

The effect of body weight, age, gender, race, renal and hepatic function and disease severity on the PK of tremelimumab has, however, been evaluated in the Population PK analysis.

In summary, the final Population PK modeling indicated that the baseline patient characteristics of age, race, renal function, and hepatic function had no effect on the PK of tremelimumab. In contrast, body weight, ALB, gender, combination therapy and primary indication had a statistically significant impact on clearance. Body weight and sex had a statistically significant impact on central volume of distribution. However, all identified covariates changed tremelimumab population parameter estimates by less than or about 20% and were therefore regarded of minor clinical relevance.

Impaired renal function

Mild (creatinine clearance (CrCL) 60 to 89 ml/min) and moderate renal impairment (creatinine clearance (CrCL) 30 to 59 ml/min) had no clinically significant effect on the PK of tremelimumab. The effect of severe renal impairment (CrCL 15 to 29 ml/min) on the PK of tremelimumab is unknown.

Impaired hepatic function

Mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST) and moderate hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) had no clinically significant effect on the PK of tremelimumab. The effect of severe hepatic impairment (bilirubin > 3.0 x ULN and any AST) on the PK of tremelimumab is unknown.

Gender

Based on the final PopPK model of tremelimumab, gender had a statistically significant impact on CL and V1. However, since the impact was less than 20% this was not regarded as of clinical relevance.

Age

Age (range 18 to 87 years) was not identified as a significant covariate in the final PopPK model of tremelimumab.

	D alone	**D + T75**	**D + T300**	**SoC**	**All patients in PopPK**
N	388	152	388	374	2406
Age sub-group (yr)					
<65	201 (51.8%)	74 (48.7%)	193 (49.7%)	188 (50.3%)	1246 (51.8%)
>=65-75	130 (33.5%)	55 (36.2%)	142 (36.6%)	130 (34.8%)	875 (36.4%)
>=75	57 (14.7%)	23 (15.1%)	53 (13.7%)	56 (15.0%)	285 (11.8%)

Race

Race was not identified as a significant covariate in the final Population PK model of tremelimumab, and race did not seem to influence PK of tremelimumab. .

Weight

Body weight (range 34 to 149 kg) had a statistically significant effect on CL and V1. However, since body weight changed tremelimumab population parameter estimates by less than 20% it was regarded of minor clinical relevance.

Table shows the simulated tremelimumab AUC, C_{max}, and C_{min} across body weight quartiles. At the highest weight quartile, the simulated geometric mean AUC, C_{max}, and C_{min} decreased by 7.67%, 11.8%, and 8.88%, respectively, compared to the geometric mean of the overall population. At the lowest quartile, the simulated AUC, C_{max}, and C_{min} increased by 7.73%, 14.5%, and 7.89%, respectively, compared to the mean of the overall population. These differences in exposure were not considered clinically relevant but due to the potential concern the weight limit for body weight-based dosing has been increased to 40 kg.

Table 12: Tremelimumab exposure across body weight quartiles

	Q1	Q2	Q3	Q4
Individuals				
N	97	100	95	95
Body weight (kg)				
Geometric mean (%CV)	52.5 (9.81)	65.4 (4.80)	75.0 (3.97)	91.9 (11.8)
Median [min-max]	53.7 [40.5-59.4]	66.0 [59.6-70.0]	74.9 [70.1-80.0]	89.0 [80.3-140]
AUC, dose 1				
Geometric mean (%CV)	835 (21.7)	785 (23.6)	767 (19.9)	715 (25.6)
Median [min-max]	825 [391-2320]	784 [373-1560]	766 [501-1490]	705 [419-2190]
%change	7.73	1.37	-1.04	-7.67
Cmax, dose 1				
Geometric mean (%CV)	99.7 (15.2)	89.1 (16.6)	84.0 (15.3)	76.8 (18.5)
Median [min-max]	100 [64.0-174]	89.1 [52.8-134]	81.7 [61.8-141]	76.8 [45.8-137]
%change	14.5	2.34	-3.59	-11.8
Cmin, dose 1				
Geometric mean (%CV)	13.1 (34.3)	12.4 (36.7)	12.2 (26.4)	11.1 (38.0)
Median [min-max]	13.3 [3.70-74.8]	12.4 [4.21-48.5]	12.4 [6.50-24.3]	11.1 [4.88-71.9]
%change	7.89	1.54	-0.0657	-8.88
AUC0-inf				
Geometric mean (%CV)	1140 (23.1)	1070 (26.3)	1050 (21.4)	955 (26.7)
Median [min-max]	1160 [460-2130]	1080 [500-1810]	1060 [643-1960]	957 [527-2000]
%change	8.28	1.71	-0.299	-9.16

Note: % change is computed with the geometric mean of the entire population as a reference

Pharmacokinetic interaction studies

No formal drug-drug interaction studies have been conducted with durvalumab or tremelimumab. PK drug-drug interaction of durvalumab or tremelimumab with other therapeutics is not anticipated given that durvalumab and tremelimumab are not primarily cleared via hepatic or renal pathways; instead, the primary elimination pathways are protein catabolism via reticuloendothelial system (RES) or target-mediated disposition.

Durvalumab and tremelimumab are not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways.

Pharmacokinetics using human biomaterials

No *in vitro* permeability, *in vitro* metabolism, or *in vitro* metabolic drug-drug interaction studies that used human biomaterials have been performed.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Immunogenicity of tremelimumab is based on pooled data in 2075 patients who were treated with tremelimumab 75 mg or 1 mg/kg and evaluable for the presence of anti-drug antibodies (ADAs). Two-hundred fifty-two patients (12.1%) tested positive for treatment-emergent ADAs. Neutralising antibodies against tremelimumab were detected in 10.0% (208/2075) patients. The presence of ADAs did not impact tremelimumab pharmacokinetics, and there was no apparent effect on efficacy and safety.

In the HIMALAYA study, of the 182 patients who were treated with Imjudo 300 mg as a single dose in combination with durvalumab and evaluable for the presence of ADAs against tremelimumab, 20 (11.0%) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against tremelimumab were detected in 4.4% (8/182) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.

2.6.2.2. Pharmacodynamics

Mechanism of action

Tremelimumab is a human IgG2 mAb directed against cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). CTLA-4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell activation, T cells upregulate CTLA-4, which binds to CD80 and CD86 ligands on antigen-presenting cells, sending an inhibitory signal and preventing CD28-mediated T-cell co-stimulation, thus limiting T-cell activation. Tremelimumab blocks these events, leading to prolongation and enhancement of T-cell activation and expansion.

Durvalumab is a human IgG1k mAb that binds to programmed cell death ligand-1 (PD-L1) and blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Expression of PD-L1 can be induced by inflammatory signals and can be expressed on both tumour cells and tumour-associated immune cells in the tumour microenvironment. PD-L1 blocks T-cell function and activation through interactions with PD-1 and CD80 (B7.1). By binding to its receptors PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody-dependent cell-mediated cytotoxicity (ADCC).

Tremelimumab and durvalumab are checkpoint inhibitors with distinct yet complementary mechanisms of action with respect to enhancing the antitumour immune response. Tremelimumab mediated blockade of CTLA-4 functions early in the immune response, lowering the threshold for T cell activation, allowing more T cells to be activated and increasing the diversity of the T cell population. This increases the probability that a T cell recognizing a tumour neoantigen can become activated. Durvalumab blockade of PD-L1 is expected to function mainly during the effector phase of T cell function, once T cells enter the tumour, where it acts to block local suppression of T-cell function by PD-L1, enhancing the ability of activated anti-tumour T cells to target and kill tumour cells.

Primary pharmacology

Data from Study 06, Study 10 and Study 22 indicate that a pharmacodynamic effect exists on proliferating CD4+ and CD8+ T cell quantities consistent with the proposed mechanisms of action of both therapeutic agents.

Data from Study 1108, Japan Study 02, Study 06 and Study 10 indicate that durvalumab treatment (with or without tremelimumab) reduces free Soluble Programmed Cell Death Ligand-1 (sPD-L1) in serum.

No PD biomarkers are proposed for monitoring of effect.

Secondary pharmacology

Concentration-QTc Analysis

Overall, concentration-QTc-analysis did not identify a significant linear relationship between tremelimumab or durvalumab serum concentrations and ΔQTcF. The predicted mean ΔQTcF and upper 90% CI at the maximum observed concentration for tremelimumab or durvalumab in the dataset were below the threshold of clinical concern.

Exposure-response relationships

Assessment of an exposure-efficacy relationship was conducted using OS and PFS as efficacy parameters in patients from HIMALAYA, for whom the different exposure metrics could be calculated.

For the exposure-response analysis for efficacy (OS and PFS), only the T300 + D cohort was used, but with the SoC cohort as a comparator in some of the analyses. The exposure-response Cox proportional-hazards (CPH model) for OS and PFS was developed based on durvalumab and tremelimumab-treated patients in the HIMALAYA study. Simulated durvalumab and tremelimumab serum concentration-time PK profiles, based on individual post-hoc PK parameters, were used as a measure of exposure after T300 + D. Of the 388 patients in this cohort, 1 did not have tremelimumab exposure metrics, and therefore, 387 patients were included in the E-R analysis for tremelimumab.

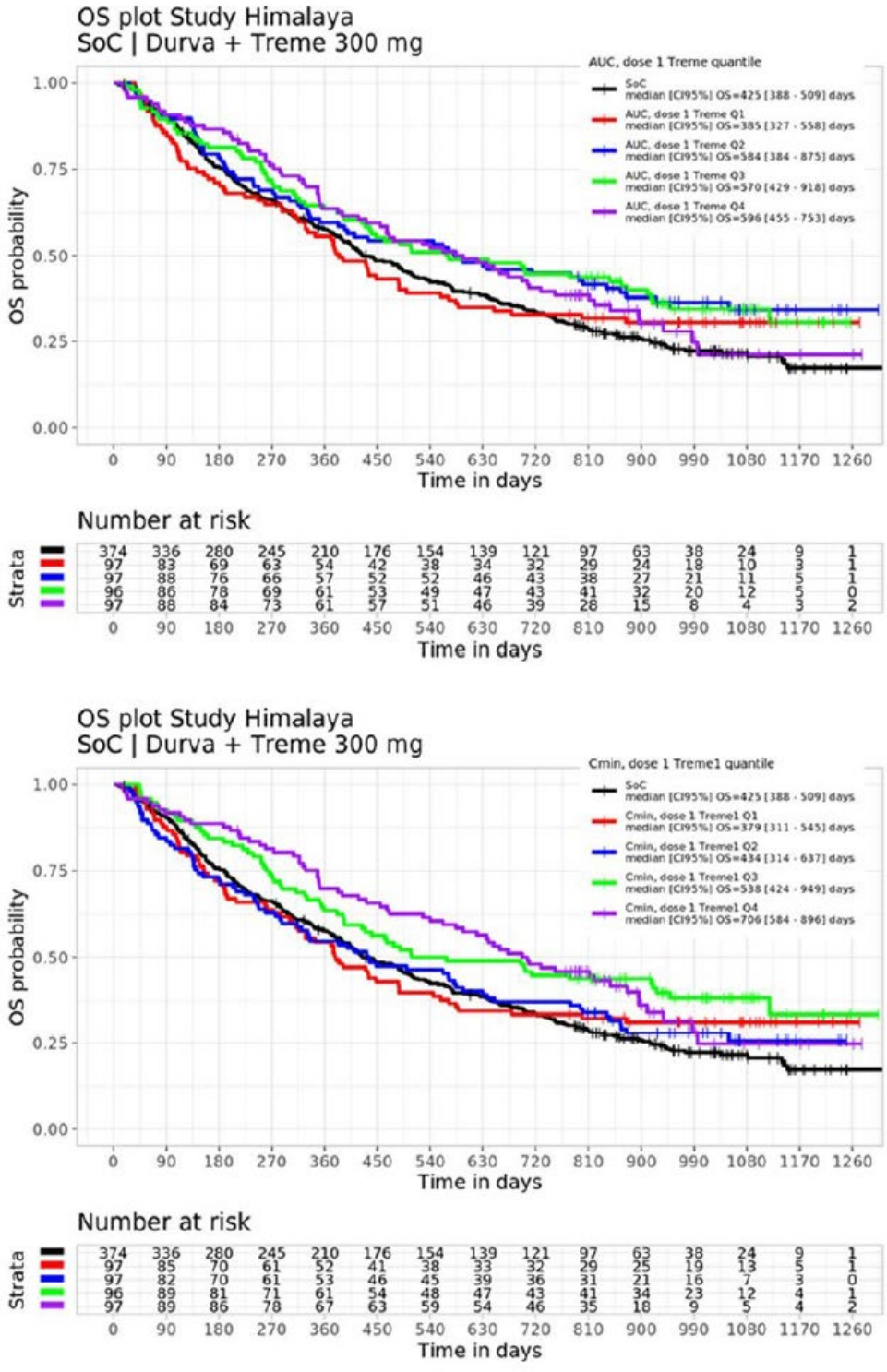
Exposure-efficacy relationship

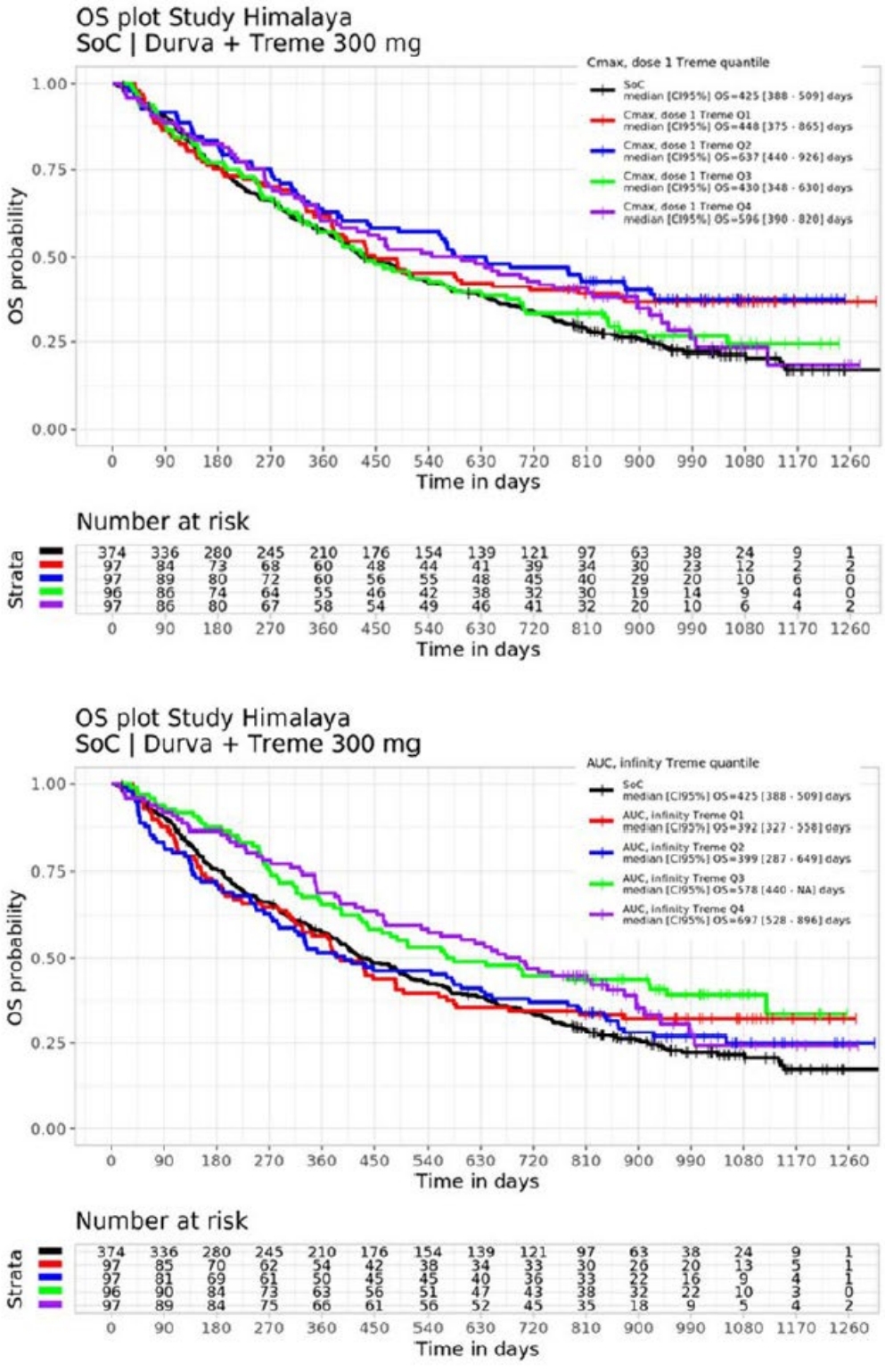
Overall survival (OS)
The data for OS were stratified by model-predicted exposure metrics and overlaid with data from patients in the SoC arm. There were 4 exposure metrics used for tremelimumab ($AUC_{dose\ 1}$, $C_{min,\ dose\ 1}$, $C_{max,dose\ 1}$, and $AUC_{0\text{-}inf}$).

Figure shows the OS Kaplan-Meier (KM) plots for exposure metrics of tremelimumab. The number of patients at risk is indicated below each plot. The KM plots indicated that there was no clear relationship between efficacy and exposure to tremelimumab, with all quartiles overlapping each other.

Additional explorative analyses of the covariates, body weight, and ADA status indicated that there is no clear association between OS and body weight or ADA status. However, the results for ADA status must be considered with caution due to the small number of ADA-positive patients in the tremelimumab treatment cohort.

Figure 9: OS Kaplan-Meier plots for tremelimumab exposure metrics by quartiles at Dose 1





The covariates, aspartate aminotransferase (AST) and neutrophil-to-lymphocyte ratio (NLR) were identified as significant in the final model. Higher AST and NLR were associated with shorter survival in T300 + D arm, suggesting they are prognostic factors for OS. The OS Kaplan Meier plot stratified by these 2 significant covariates can be found in Figure 10. A Forest plot of the final CPH model for OS is showed in Figure.

Figure 10: OS Kaplan Meier plots stratified by significant covariates

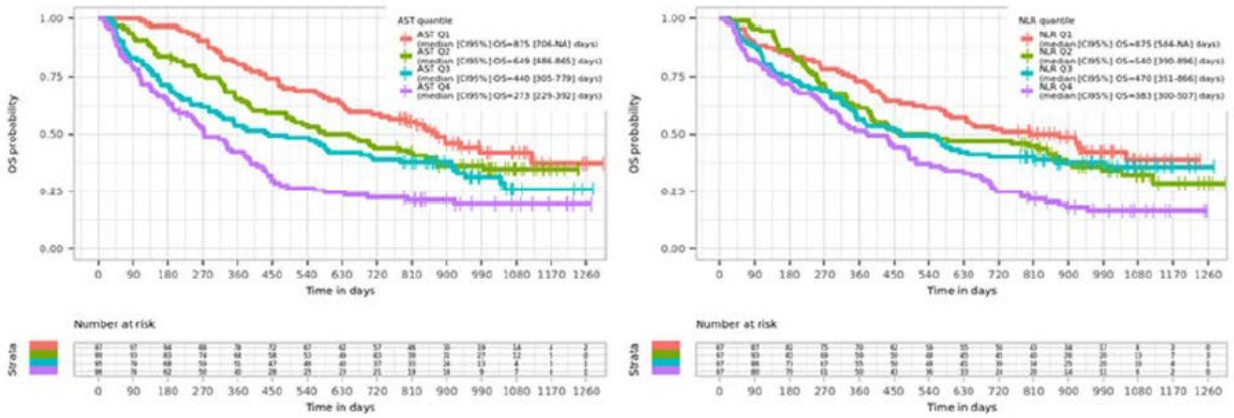
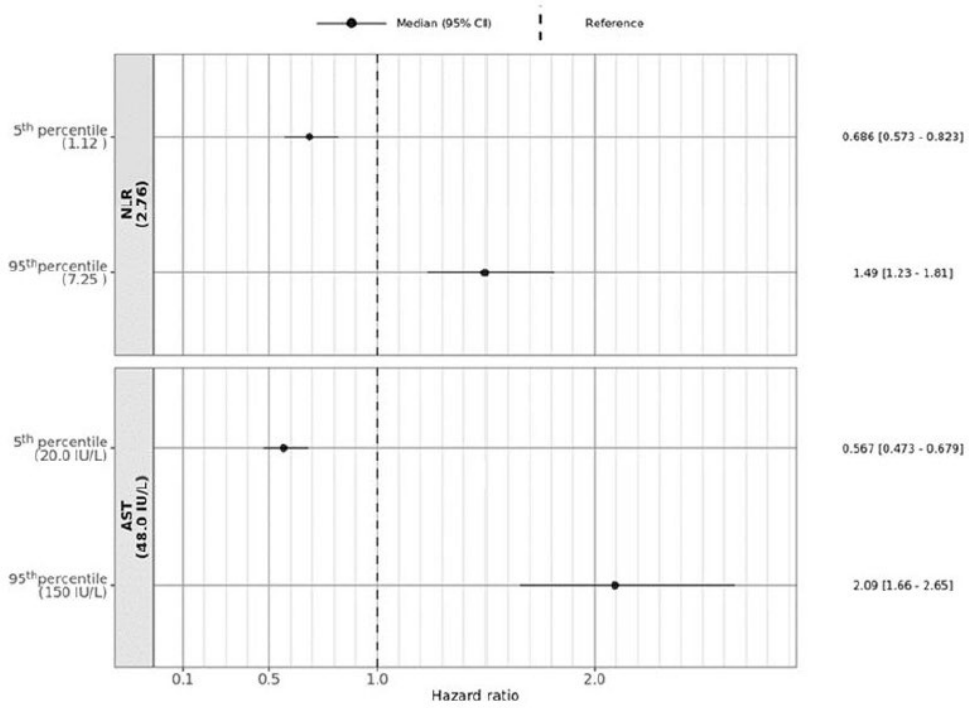


Figure 11: Forest plot of the final Cox proportional-hazards model for OS



Note: Numbers at the right of the graph are the predicted HR and associated 95% CI.

Progression-free survival (PFS)

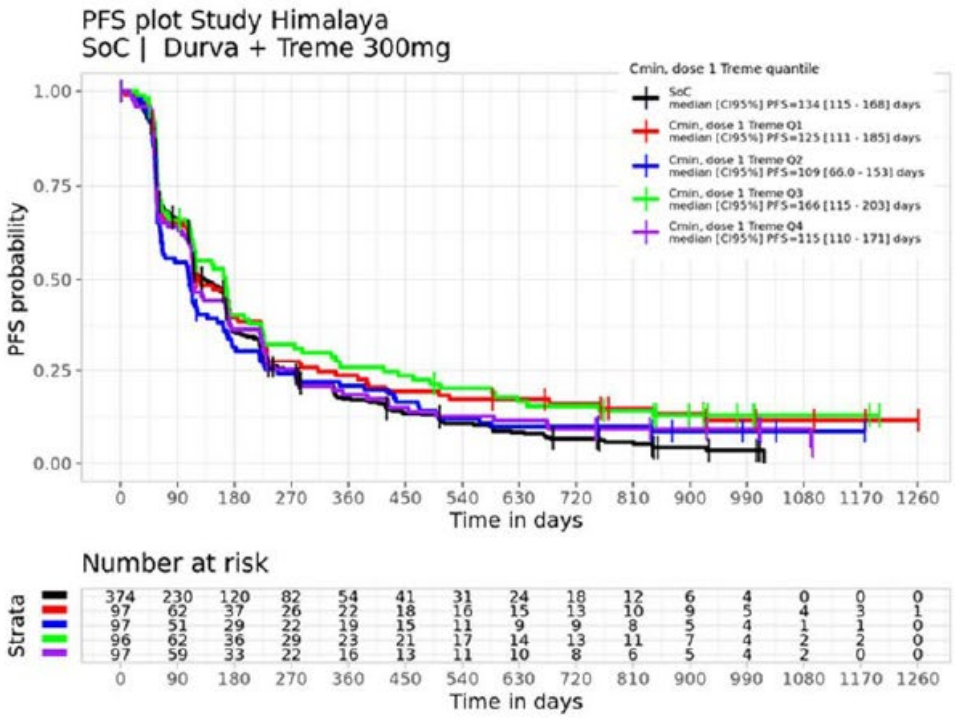
Figure shows PFS Kaplan-Meier curves for patients receiving durvalumab in combination with tremelimumab, data stratified by model-predicted exposures metrics and overlaid with data from patients in the SoC arm ($C_{min,\ dose\ 1}$, $AUC_{0\text{-}inf}$). The number of patients at risk is indicated below the plot.

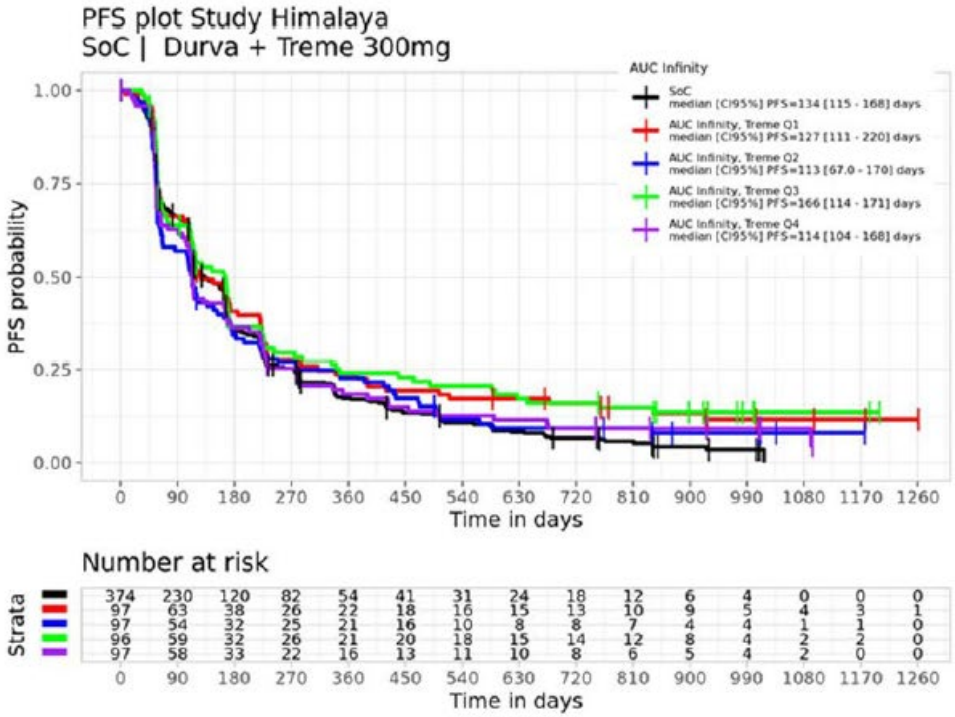
These plots indicated no clear efficacy relationship to tremelimumab exposure, with all quartiles overlapping each other.

Overall, no covariate was identified to be related with PFS in this analysis.

Additional explorative analyses of the covariates, body weight, and ADA status for tremelimumab exposure did not indicate any clear trend between PFS and body weight or ADA status. However, the small number of ADA-positive patients after tremelimumab treatment mean that the Kaplan-Meier plots for ADA status should be interpreted with caution.

Figure 12: PFS Kaplan-Meier plots for tremelimumab exposure metrics by quartiles at Dose 1





Note: Shaded areas are the 95% CI around the Kaplan-Meier curves. Vertical ticks represent the right censoring. AUCss, area under the serum concentration-time curve at steady state; CI, confidence interval; C_{max}, maximum concentration, C_{min}, minimum concentration; SoC, standard of care.

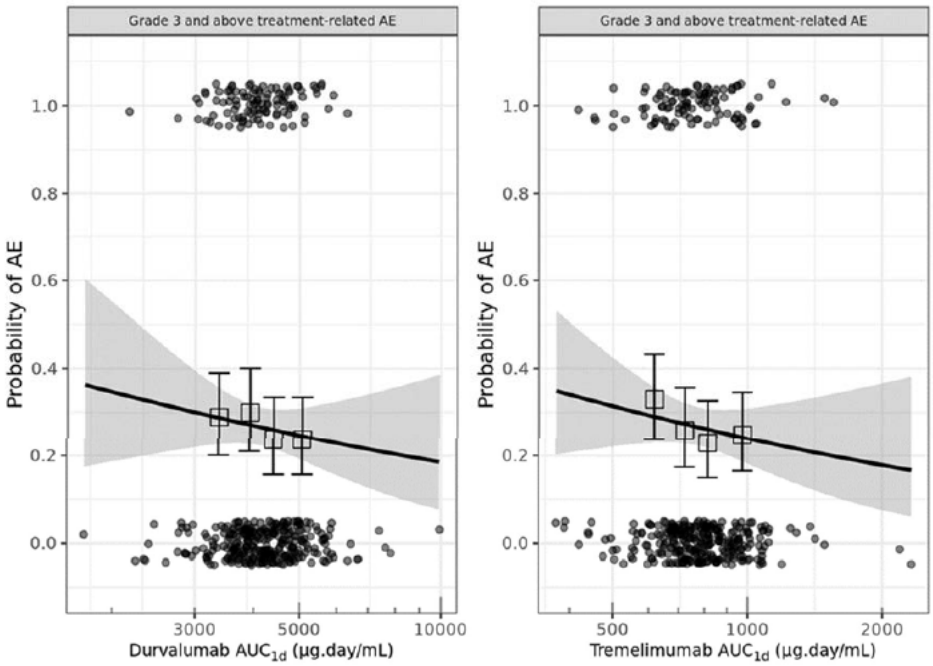
Exposure-safety relationship

For assessment of an exposure-safety relationship, the evaluated safety endpoints were Grade 3 and above treatment-related AEs from HIMALAYA, Grade 3 and above AESIs, and AEs leading to durvalumab treatment discontinuation.

Grade 3 and above treatment-related AEs

The probability of AEs calculated in quartiles of the $AUC_{dose\ 1}$ exposure metrics for durvalumab and tremelimumab is shown in Figure 13. This figure summarises the logistic regression results assessing the impact of exposure on the probability of AEs. The p-values associated with exposure effects were relatively large, indicating that the relationship was not statistically significant.

Figure 13: Relationship between the probability of having Grade 3 and above treatment-related AEs and $AUC_{dose\ 1}$ for durvalumab and tremelimumab



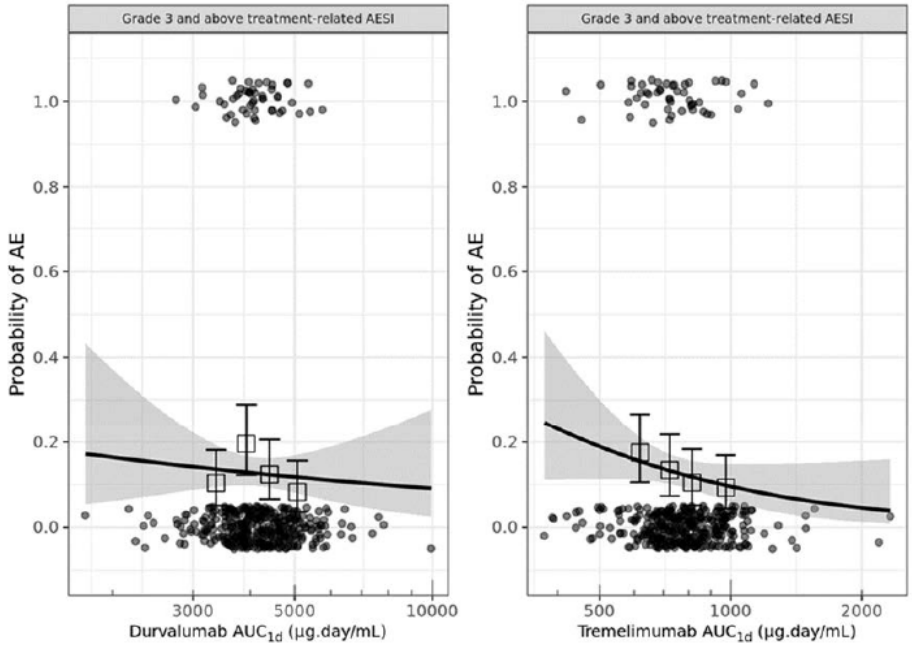
Note: The black solid circles are the observed AE, and the open squares with error bars are the observed probability of response at each exposure quartile. The black lines are the logistic regression between two variables, and the gray area represents the associated confidence interval.
AE, adverse event; AUC, area under the serum concentration-time curve.

Grade 3 and Above Treatment-related AESIs

The probability of AESIs calculated in quartiles of the $AUC_{dose\ 1}$ exposure metrics for durvalumab and tremelimumab is shown in Figure.

The p-values associated with exposure effects were relatively large, indicating that the relationship was not statistically significant.

Figure 14: Relationship between the probability of having Grade 3 and above treatment-related AESIs and AUC$_{,\ dose\ 1}$ for durvalumab and tremelimumab



Note: The black solid circles are the observed AEs, and the open squares with error bars are the observed probability of response at each exposure quartile. The black lines are the logistic regression between two variables, and the gray area represents the associated confidence interval.
Abbreviations: AE, adverse event; AUC, area under the serum concentration-time curve.

In conclusion, none of the tremelimumab or durvalumab exposure metrics in a logistic regression analysis were identified to have an influence on safety events defined as Grade 3 and above treatment-related AEs, Grade 3 and above AESIs, or AEs leading to durvalumab treatment discontinuation.

2.6.3. Discussion on clinical pharmacology

The pharmacokinetics (PK) of tremelimumab was assessed for Imjudo as monotherapy and in combination with durvalumab.

The PK of tremelimumab was studied in patients with doses ranging from 75 mg to 750 mg or 10 mg/kg administered intravenously once every 4 or 12 weeks as monotherapy, or at a single dose of 300 mg. PK exposure increased dose proportionally (linear PK) at doses ≥ 75 mg. Steady state was achieved at approximately 12 weeks. Based on population PK analysis that included patients who received tremelimumab monotherapy or in combination with other medicinal products in the dose range of ≥ 75 mg (or 1 mg/kg) every 3 or 4 weeks, the estimated tremelimumab clearance (CL) and volume of distribution (Vd) were 0.309 l/day and 6.33 l, respectively. The terminal half-life was approximately 14.2 days.

HIMALAYA assessed the efficacy and safety of durvalumab and tremelimumab in combination versus durvalumab alone and sorafenib as SoC. In the two arms of the study that included tremelimumab treatment, tremelimumab was administered either as a single dose of 300 mg (in combination with durvalumab 1500 mg Q4W) or as 4 doses of 75 mg tremelimumab Q4W (in combination with durvalumab 1500 mg Q4W).

Tremelimumab PK concentrations were within the expected exposure range following a single 300 mg dose as well as following four doses of 75 mg Q4W.

Overall, trough concentrations of tremelimumab at Cycle 2 were 3.3 times higher in the T300 + D arm than the T75 + D arm. In addition, similar tremelimumab exposures were observed in patients rechallenged with tremelimumab.

Furthermore, PK profiles of durvalumab were overall similar between patients treated in the D arm and those in the T300 + D and T75 + D arms, suggesting that tremelimumab did not have an impact on the PK of durvalumab when administered in combination.

Study 22 evaluated the safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, or durvalumab in combination with tremelimumab or bevacizumab in subjects with advanced unresectable HCC, similar exposures were observed following a weight-based dosing of 1 mg/kg and the equivalent fixed 75 mg dose. Additionally, similar exposures were observed following a weight-based dose of 10 mg/kg and the equivalent fixed 750 mg dose.

No accumulation of tremelimumab was observed following repeated dosing in any of the cohorts in Study 22. In contrast, accumulation of durvalumab was observed following repeated dosing at 1500 mg. Overall, durvalumab PK parameters were similar between patients treated with durvalumab monotherapy and those treated with durvalumab and tremelimumab combination therapy.

The PK of tremelimumab could be described by a 2-compartment model with linear CL and an additional time-dependent CL component for patients on combination therapy only. Body weight, albumin, sex, combination therapy and primary indication were identified as statistically significant covariates on CL. Body weight and sex were identified as statistically significant covariates on V1. The effect of body weight was allometrically scaled with estimated exponents of 0.384 and 0.467 for CL and V1, respectively, indicating that the effect of body weight was less than proportional. Low-to-high inter-individual variability (%CV) was identified on CL (32.9%), V1 (24.9%), V2 (46.0%) and Tmax (119.2%). The adequacy of the model was confirmed based on the GOF-plots but some deviation was observed in the DV vs. IPRED plot. The same deviation was present in the previous model which suggests this deviation is not specific to HCC patients. In general, the model seems able to describe the overall tendency of the experimental data and parameters were estimated precisely.

Age (18–87 years), body weight (34-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, tumour type, race or ECOG/WHO status had no clinically significant effect on the PK of tremelimumab.

The exposure-efficacy relationships in the HIMALAYA study were explored by Cox Proportional Hazard (CPH) models. The assumption of proportional hazards of OS analysis are not fully supported for AST and the utilisation of the CPH model with this covariate should be interpreted with caution.

The clinical pharmacology programme in special populations is considered adequate and typical for a monoclonal antibody product being administered intravenously. The effect of hepatic and renal impairment was not formally tested in dedicated clinical trials, and data from patients with severe renal impairment are too limited to draw conclusions on this population. Based on pop PK analyses, age, gender, race, mild/moderate renal impairment, or mild hepatic impairment had no impact on the exposure of tremelimumab. Accordingly, no dose adjustment is recommended in patients with mild or moderate renal impairment and patients with mild or moderate hepatic impairment (see section 5.2). No dose adjustment is required for elderly patients ($\geqslant$ 65 years of age) (see section 5.2). Data on patients aged 75 years of age or older are limited.

The use of systemic corticosteroids or immunosuppressants before starting tremelimumab, except physiological dose of systemic corticosteroids ($\leqslant$ 10 mg/day prednisone or equivalent), is not recommended because of their potential interference with the pharmacodynamic activity and efficacy of tremelimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting tremelimumab to treat immune related adverse reactions (see section 4.4).

No formal pharmacokinetic (PK) drug drug interaction studies have been conducted with tremelimumab. Since the primary elimination pathways of tremelimumab are protein catabolism via reticuloendothelial system or target mediated disposition, no metabolic drug-drug interactions are expected.

Assessment of an exposure-efficacy relationship was conducted using OS and PFS as efficacy parameters in patients from HIMALAYA. OS and PFS were explored by Kaplan-Meier (KM) estimates and analyzed by Cox proportional-hazards models.

For OS the KM plots indicate that there was no clear relationship between efficacy and exposure to tremelimumab, with all quartiles overlapping each other.

The covariates, aspartate aminotransferase (AST) and neutrophil-to-lymphocyte ratio (NLR) were identified as significant in the final model. Higher AST and NLR were associated with shorter survival in T300 + D arm, suggesting they are prognostic factors for OS.

For PFS the KM plots indicate no clear efficacy relationship to tremelimumab exposure, with all quartiles overlapping each other. Overall, no covariate was identified to be related with PFS in this analysis.

Additional explorative analyses of the covariates, body weight, and ADA status for tremelimumab exposure did not indicate any clear trend between OS or PFS and body weight or ADA status. However, the small number of ADA-positive patients after tremelimumab treatment mean that the Kaplan-Meier plots for ADA status should be interpreted with caution.

For assessment of an exposure-safety relationship, the evaluated safety endpoints were Grade 3 and above treatment-related AEs from HIMALAYA, Grade 3 and above AESIs, AEs leading to durvalumab treatment discontinuation.

None of the tremelimumab or durvalumab exposure metrics in a logistic regression analysis were identified to have an influence on safety events defined as Grade 3 and above treatment-related AEs, Grade 3 and above AESIs or AEs leading to durvalumab treatment discontinuation. In the HIMALAYA study, no patients received BW-based dosing of tremelimumab (4 mg/kg).

There appeared to be no clear trend between increasing body weight and the probability of AEs.

In terms of immunogenicity, the prevalence of anti-drug antibodies (ADA) and neutralizing antibodies (nAb) as well as incidence of ADA for tremelimumab in HIMALAYA were higher in the T75 + D arm than in the T300 + D arm. This could be related to the different number of tremelimumab doses in the 2 treatment arms.

The development of treatment-emergent ADA to tremelimumab did not have any apparent effect on serum concentrations of tremelimumab, efficacy or safety.

2.6.4. Conclusions on clinical pharmacology

Considering the nature of the product, the pharmacology package is considered adequate.

2.6.5. Clinical efficacy

The current marketing authorisation application for tremelimumab is based on efficacy data from HIMALAYA, a randomised, open-label, multicentre Phase III study in patients with unresectable hepatocellular carcinoma (HCC) not eligible for locoregional therapy and with no prior systemic therapy

for HCC. Additional supportive evidence of clinical efficacy is provided from study 22, a randomised, phase I/II, open-label study.

Table 13: Overview of studies in the clinical development programme for durvalumab in combination with tremelimumab and durvalumab monotherapy in patients with uHCC

Table 1 Overview of Studies in the Clinical Development Program for Durvalumab in Combination With Tremelimumab and Durvalumab Monotherapy in Patients With uHCC

Study number and acronym	Study title	Study design	Objective	DCO date(s)	Location in Module 5
Pivotal Study					
D419CC00002 **HIMALAYA**	A Randomized, Open-label, Multicenter Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma (HIMALAYA)	Phase III, randomized, open-label, sponsor-blind, multicenter, global study	To assess the efficacy and safety of T300+D vs S and D vs S	**FA:** 27 August 2021	5.3.5.1
Supportive Study					
D4190C00022 **Study 22**	A Study of Safety, Tolerability, and Clinical Activity of Durvalumab and Tremelimumab Administered as Monotherapy, or Durvalumab in Combination With Tremelimumab or Bevacizumab in Subjects with Advanced Hepatocellular Carcinoma	Phase I/II, randomized, open-label, multicenter, international study	Parts 2 and 3: To assess the safety, tolerability, and clinical activity of T300+D, D, and T.	**FA:** 06 November 2020	5.3.5.2

Abbreviations: D = durvalumab 1500 mg (20 mg/kg) Q4W; DCO = data cut-off; FA = Final Analysis; Q4W = every 4 weeks; Q12W = every 12 weeks; T = tremelimumab 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W; T300+D = tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W; uHCC = unresectable hepatocellular carcinoma.

2.6.5.1. Dose response studies

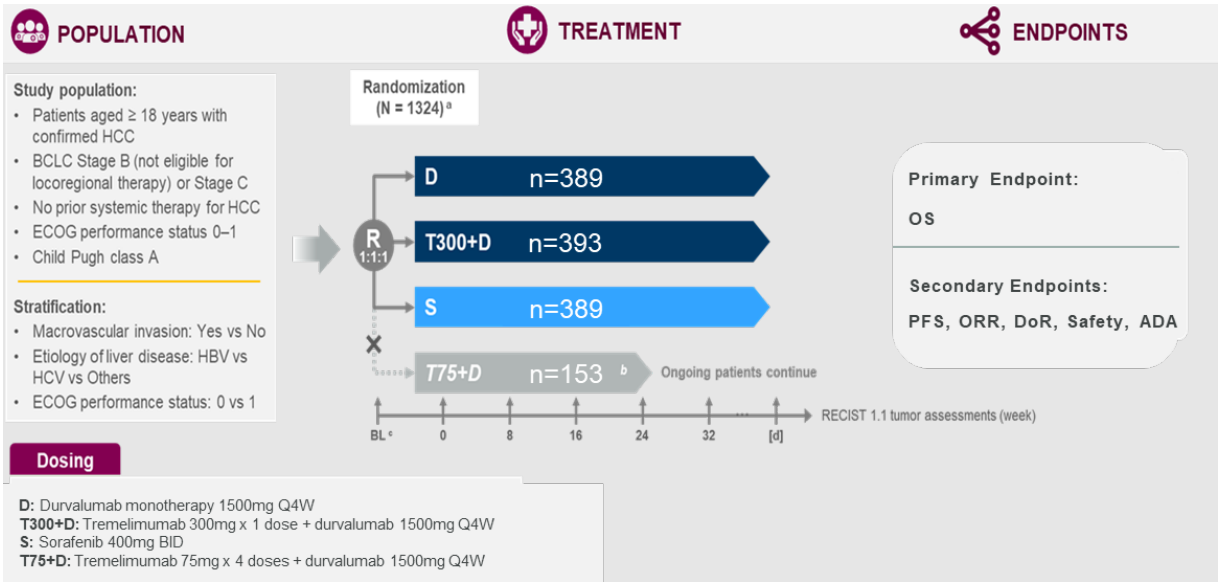
See section 2.6.2.1.

2.6.5.2. Main study

A randomised, open-label, multicentre phase III study of durvalumab and tremelimumab as first-line treatment in patients with advanced hepatocellular carcinoma (HIMALAYA)

Study design for the pivotal trial is illustrated in Figure 15.

Figure 9: HIMALAYA study design



Patient numbers shown correspond to the actual enrollment.

Enrollment into the T75+D arm was closed following protocol edition 4.0 (29 November 2018). Patients randomised to T75+D prior to protocol amendment 3 could continue on their assigned study treatment, provided the Investigator and patient agreed this was in the patient's best interest. Patients randomised to T75+D arm who had not completed or started all 4 doses of tremelimumab could either complete the full schedule or continue with durvalumab monotherapy only

Methods

- **Study Participants**

Patients were enrolled at 181 sites and randomised at 170 study centres in 16 countries: Brazil (13 centres), Canada (9), France (14), Germany (10), Hong Kong (5), India (10), Italy (8), Japan (27), South Korea (8), Russian Federation (10), Spain (6), Taiwan (9), Thailand (9), Ukraine (8), United States of America (21), and Vietnam (3).

Inclusion Criteria

For inclusion in the study, patients had to fulfill all of the following criteria:

1. Age ≥ 18 years at the time of screening.

2. Body weight > 30 kg.

3. Written informed consent and any locally required authorisation obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

4. Confirmed HCC based on histopathological findings from tumour tissues.

5. Must not have received prior systemic therapy for HCC.

6. Ineligible for locoregional therapy for unresectable HCC. For patients who progressed after locoregional therapy for HCC, locoregional therapy must have been completed ≥ 28 days prior to the baseline scan for the current study.

7. BCLC stage B (ie, not eligible for locoregional therapy) or stage C.

8. Child-Pugh score class A.

9. ECOG performance status of 0 or 1 at enrollment.

10. Patients with HBV infection, characterised by positive HBsAg and/or anti-HBcAb with detectable HBV DNA (≥ 10 IU/mL or above the limit of detection per local or central laboratory standard), must be treated with antiviral therapy, per institutional practice, to ensure adequate viral suppression (HBV DNA ≤ 2000 IU/mL) prior to enrollment. Patients were to remain on antiviral therapy for the study duration and for 6 months after the last dose of study treatment. Patients who tested positive for HBc with undetectable HBV DNA (< 10 IU/mL or under the limit of detection per local or central laboratory standard) did not require antiviral therapy prior to enrollment. These patients were tested at every cycle to monitor HBV DNA levels and antiviral therapy initiated if HBV DNA was detected (≥ 10 IU/mL or above the limit of detection per local or central laboratory standard). HBV DNA detectable patients were to initiate and remain on antiviral therapy for the study duration and for 6 months after the last dose of study treatment.

11. Patients with HCV infection: Confirmed diagnosis of HCV characterised by the presence of detectable HCV RNA or anti-HCV antibody upon enrollment.

12. At least 1 measurable lesion, not previously irradiated, that could be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥ 15 mm) with CT or MRI, and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines. A lesion which progressed after previous ablation or transarterial chemoablation could be measurable if it met these criteria.

13. Adequate organ and marrow function, as defined below. Criteria "a", "b," "c," and "f" could not be met with transfusions, infusions, or growth factor support administered within 14 days of starting the first dose.

a. Hemoglobin ≥ 9 g/dL

b. Absolute neutrophil count ≥ 1000/μL

c. Platelet count ≥ 75000/μL

d. TBL ≤ 2.0 × ULN

e. AST and ALT ≤ 5 × ULN

f. Albumin ≥ 2.8 g/dL

g. INR ≤ 1.6. Note: INR prolongation due to anticoagulants for prophylaxis (eg, atrial fibrillation) in patients without liver cirrhosis could be an exception

h. Calculated creatinine clearance ≥ 50 mL/min as determined by Cockcroft-Gault (using actual body weight) or 24 h urine creatinine clearance

14. Evidence of postmenopausal status or negative urinary or serum pregnancy test for female premenopausal patients.

15. Life expectancy of at least 12 weeks.

Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

2. Previous study treatment (s) assignment in the present study.

3. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

4. Received an IP within 28 days prior to the first dose of study treatment.

5. Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria:

a. Patients with Grade ≥ 2 neuropathy were evaluated on a case-by-case basis after consultation with the Study Physician

b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab could be included only after consultation with the Study Physician.

6. Any concurrent chemotherapy, study treatment, or biologic or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) was acceptable.

7. Known allergy or hypersensitivity to any of the study treatments or any of the study treatment excipients.

8. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 28 days of the first dose of study treatment.

9. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study treatments. Note: Local surgery of isolated lesions for palliative intent was acceptable.

10. History of allogeneic organ transplantation (eg, liver transplant).

11. History of hepatic encephalopathy within the past 12 months or requirement for medications to prevent or control encephalopathy (eg, no lactulose, rifaximin, etc if used for purposes of hepatic encephalopathy).

12. Clinically meaningful ascites, defined as any ascites requiring non-pharmacologic intervention (eg, paracentesis) to maintain symptomatic control, within 6 months prior to the first scheduled dose. Patients on stable doses of diuretics for ascites for ≥ 2 months were eligible.

13. Patients with main portal vein thrombosis (ie, thrombosis in the main trunk of the portal vein, with or without blood flow) on baseline imaging.

14. Active or prior documented GI bleeding (eg, esophageal varices or ulcer bleeding) within 12 months. Note: For patients with a history of GI bleeding for more than 12 months or assessed as high risk for esophageal varices by the Investigator, adequate endoscopic therapy according to institutional standards was required).

15. Current symptomatic or uncontrolled hypertension defined as DBP > 90 mmHg or SBP > 140 mmHg.

16. Any condition interfering with swallowing pills, uncontrolled diarrhoea, or other contraindication to oral therapy.

17. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). Patients without active disease in the last 5 years were excluded unless discussed with the Study Physician and considered appropriate for study participation.

The following were exceptions to this criterion:

1 Vitiligo or alopecia

2 Hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement

3 Any chronic skin condition not requiring systemic therapy

4 Patients with celiac disease controlled by diet alone

18. Co-infection with HBV and HCV or HBV and HDV. HBV positive (presence of HBsAg and/or anti-HBcAb with detectable HBV DNA); HCV positive (presence of anti-HCV antibodies); or HDV positive (presence of anti-HDV antibodies).

19. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, ILD, serious chronic GI conditions associated with diarrhoea, inferior vena cava thrombosis, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase the risk of incurring AEs, or compromise the ability of the patient to give written informed consent.

20. History of another primary malignancy except for:

1. Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of study treatment and of low potential risk for recurrence
2. Patients with a history of prostate cancer of stage ≤ T2cN0M0 without biochemical recurrence or progression and who, in the opinion of the Investigator, are not deemed to require active intervention
3. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
4. Adequately treated carcinoma in situ without evidence of disease

21. History of leptomeningeal carcinomatosis.

22. History of, or current, brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT, each preferably with IV contrast of the brain prior to study entry.

23. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.

24. History of active primary immunodeficiency.

25. Active infection including TB (clinical evaluation that included clinical history, physical examination and radiographic findings, and TB testing in line with local practice), or HIV (positive HIV1/2 antibodies)

26. Current or prior use of immunosuppressive medication within 14 days before the first dose of study treatment, with the exception of the following:

- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent
- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

27. Receipt of live attenuated vaccine within 30 days prior to the first dose of study treatment. Note: Patients, if enrolled, should not receive live vaccine while receiving study treatment and up to 30 days after the last dose of study treatment.

28. Female patients who were pregnant or breastfeeding, or male or female patients of reproductive potential who were not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab plus tremelimumab combination therapy. Not engaging in sexual activity, as per the patient' s preferred and usual lifestyle, for the total duration of the treatment and washout periods was an acceptable practice.

29. Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.

30. Patients who had received anti-PD-1, anti-PD-L1, or anti-CTLA-4 prior to the first dose of study treatment.

- **Treatments**

Table 7: Study treatments

Treatment arm	Description
D	Durvalumab monotherapy 1500 mg Q4W until confirmed PD, unacceptable toxicity, or any discontinuation criteria were met
T75+D	Tremelimumab (75 mg) × 4 doses + durvalumab (1500 mg) Q4W followed by durvalumab monotherapy (1500 mg) Q4W until confirmed PD, unacceptable toxicity, or any discontinuation criteria were met. [a]
T300+D	Tremelimumab (300 mg) × 1 dose + durvalumab (1500 mg) Q4W, followed by durvalumab 1500 mg monotherapy Q4W until confirmed PD, unacceptable toxicity, or any discontinuation criteria were met
S	Sorafenib 400 mg (2 × 200 mg tablets) orally BID, until confirmed PD at the Investigator's discretion, unacceptable toxicity, or any discontinuation criteria were met. (Suspected sorafenib-related toxicities were managed based on the approved product label for each country). [b]

[a] Following protocol amendment 3, enrollment into the T75+D arm was closed. Patients randomized to T75+D prior to protocol amendment 3 could continue on assigned study treatment (provided the Investigator and patient agreed it was in the best interest of the patient) until confirmed PD or any other discontinuation criteria were met. If a patient assigned to T75+D had not completed or started all 4 doses of tremelimumab, the patient was able to continue to complete the full schedule or continue with durvalumab monotherapy only.

[b] In countries where sorafenib was not approved, the following modification was followed: sorafenib dose may be reduced to 400 mg (2 × 200 mg tablets) orally once daily. If additional dose reduction was required, the sorafenib dose could be reduced to a single 400 mg dose (2 × 200-mg tablets) orally every other day.

BID, twice daily; CSP, Clinical Study Protocol; Q4W, every 4 weeks; PD, disease progression.

The proposed dosing regimen for the relevant arm for this procedure (T300+D, arm C) is new and encompasses one single initial dose of tremelimumab 300 mg in combination with durvalumab 1500 mg and thereafter, durvalumab monotherapy iv Q4W until PD or unacceptable toxicity.

The relevant comparator arm for the current procedure is the standard of care arm (SOC, arm D), which contains sorafenib 400 mg orally twice daily as standardly dosed, and treatment should also be given until PD or unacceptable toxicity. No cross-over was allowed.

The two other treatment arms with D (durvalumab 1500 mg Q4W, arm A) and T75+D (tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W, followed by durvalumab 1500 mg Q4W, arm B) are not of relevance for this procedure.

It is noted that although the combination of a CTLA-4 inhibitor, such as tremelimumab, and an immunecheckpoint inhibitor such as durvalumab is not new, it is the first time that the anti-CTLA-4 is given only as an induction dose and then monotherapy with durvalumab is continued until PD.

Moreover, the already approved combination therapy with ipilimumab + nivolumab differs as nivolumab is PD-1 inhibitor, while durvalumab is a PD-L1 inhibitor.

The applicant claims that pharmacodynamic results reported for tremelimumab and durvalumab in Study 006 suggest that the pharmacodynamic effects of anti-CTLA-4 are mainly associated with the first dosing cycle and subside in subsequent cycles regardless of dose. Moreover, these results led to the hypothesis that a single dose of tremelimumab might accomplish similar pharmacodynamic effects as seen in Study 006 and also seen for ipilimumab, while also limiting the toxicity associated with the second (and subsequent) anti-CTLA-4 dosing cycles.

- **Objectives**

Table 8. Study objectives and endpoints

Objective	Outcome measure
Primary objective:	**Primary endpoint/variables:**
To assess the efficacy of T300+D vs S (for superiority)	• OS
Key secondary objectives:	**Key secondary endpoint/variables:**
To assess the efficacy of D vs S (for non-inferiority)	• OS
To assess the efficacy of D vs S (for superiority)	• OS
Secondary objectives:	**Secondary endpoint/variables:**
To assess the efficacy of D vs S and T300+D vs S	• OS18, OS24, and OS36 • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w, and DoR, according to RECIST 1.1 using Investigator assessments
To assess the efficacy of D and T300+D in patients with an opportunity for 32 weeks of follow-up	• ORR, BOR, and DoR according to RECIST1.1 and mRECIST by BICR
To assess the efficacy of D vs S and T300+D vs S by PD-L1 expression	• OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w, and DoR according to RECIST 1.1 using Investigator assessments
To assess disease-related symptoms, impacts, and HRQoL in D vs S and T300+D vs S	• EORTC QLQ-C30: Time to deterioration in global health status/QoL, functioning (physical), multi-term symptom (fatigue), single-item symptoms (appetite loss, nausea) • EORTC QLQ-HCC18: Time to deterioration in single-item symptoms (shoulder pain, abdominal pain, abdominal swelling)
To investigate the immunogenicity of D and T300+D	• Presence of ADA for durvalumab and tremelimumab
To evaluate the population PK and pharmacodynamics in D and T300+D	• Durvalumab and tremelimumab concentrations and PK parameters in individual arms
Safety objectives:	**Safety endpoint/variables:**
To assess the safety and tolerability profile across all treatment arms	• AEs and laboratory findings [a]
Exploratory objectives:	**Exploratory endpoint/variables:**
To assess PFS from rechallenge in the T300+D arm and to assess PFS from first post-discontinuation therapy in D, T300+D, and S [b]	• PFSFR and PFSNT using Investigator assessments

Objective	Outcome measure
To assess the efficacy of D vs S and T300+D vs S using irRECIST and mRECIST for HCC [b]	• PFS, TTP, ORR, DCR, DCR-16w, DCR-24w, and DoR according to irRECIST and mRECIST and by BICR, if performed
To investigate the relationship between the progressive changes in AFP level and efficacy parameters [b]	• Association of AFP expression level with: ○ OS ○ PFS, TTP, ORR, DoR, DCR, DCR-16w, and DCR-24w according to RECIST 1.1 using Investigator assessments
To investigate the efficacy of D vs S and T300+D vs S by baseline gene expression [b]	• Association of interferon-gamma and immune-related gene expression, as measured by mRNA levels from baseline tumor biopsies and blood, with ○ OS ○ PFS, TTP, ORR, DoR, DCR, DCR-16w, and DCR-24w according to RECIST 1.1 using Investigator assessments
To investigate the efficacy of D vs S and T300+D vs S by candidate biomarkers that may correlate with drug activity or identify patients likely to respond to treatment [b]	• Association of intratumoral immune cell numbers (specifically CD8+ T cells), ctDNA, and/or tumor mutations with: ○ OS ○ PFS, TTP, ORR, DoR, DCR, DCR-16w and DCR-24w according to RECIST 1.1 using Investigator assessments
To investigate the efficacy of D vs S in patients who are at low risk of early mortality based on baseline characteristics [b]	• OS
To assess the efficacy of D vs T300+D in the overall population and in the population defined by PD-L1 expression [b]	• OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w and DoR, by according to RECIST 1.1 using Investigator assessments
To assess patient-reported treatment tolerability directly using specific items of the PRO-CTCAE questionnaire in D vs S and T300+D vs S	• PRO-CTCAE symptoms (11 items)
Healthcare resource utilization	• EQ-5D-5L • Hospital admission form
To assess physician-reported patient outcome in D vs S and T300+D vs S	• ECOG performance status
To assess the efficacy of the discontinued immunotherapy arm (T75+D) for descriptive purposes	• OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w, and DoR according to RECIST 1.1 using Investigator assessments

- **Outcomes/endpoints**

Please refer to Table 11 above regarding the objectives and endpoints for the pivotal study Himalaya.

- **Sample size**

This study will screen approximately 1650 patients, with no prior systemic therapy for hepatocellular carcinoma (HCC) and not eligible for locoregional therapy, in order to randomise approximately 1310 patients. (This includes 1155 patients randomised to Arms A (Durvalumab monotherapy), C (T300+D), D (S) with 385 per arm; and approximately 155 patients in Arm B (T75+D), randomised prior to the closure of this arm). The study is sized to characterize the OS benefit of Arm C vs. Arm D (T300+D vs S).

The sample size estimation assumes an exponentially distributed OS and a 2-month delay in separation of the OS curves for Arm C vs. Arm D. A non-uniform accrual of patients with a duration of 22 months is assumed when estimating the analysis times.

For the efficacy comparisons, the median OS for sorafenib (Arm D) is assumed to be 11.5 months, with an 18-month OS rate of 33.8%.

Durvalumab 1500 mg plus tremelimumab 300 mg × 1 dose (Arm C) versus sorafenib 400 mg BID (Arm D) (OS in FAS [ITT])

The assumed OS treatment effect is an average HR of 0.70 for Arm C versus Arm D. This translates to an increase in median OS from 11.5 months to 16.5 months, and in the 18-month OS rate from 33.8% to 46.8% in Arm C versus Arm D. Final analysis of OS will be performed when approximately 515 events in Arm C and Arm D combined (~67% maturity) have occurred. This number of OS events will provide 97% power to demonstrate a statistically significant difference in OS at a 2-sided 4.25% significance level. The smallest treatment difference that could be observed as statistically significant at the final analysis is an average HR of 0.84 (an increase in median OS from 11.5 months to 13.7 months in Arm C versus Arm D).

No formal sample size calculations were associated with the analyses planned for IA1. However, global enrollment was required to be completed prior to the DCO for IA1.

There were 2 IAs and a FA planned for HIMALAYA. Any major changes to the planned analyses were addressed in protocol amendments finalised prior to the date of the first DCO for Interim analysis 1 for ORR (02 September 2019). These changes were informed by the open-label Study 22 and study read-outs from external studies in the same disease area, including KEYNOTE-240 and CheckMate-459. No HIMALAYA data were available for use to modify the protocol design or statistical analysis plan.

The sample size calculations were updated several times while the study was ongoing. Major changes were implemented in the Protocol version 4 (29 Nov 2018) and in Protocol version 6 (20 Aug 2019). In protocol version 4, the arm durvalumab + tremelimumab 75 mg was closed due to unfavourable results obtained in the supportive Study 22. At this point, the sample size for the remaining arms was increased to 385 and the number of required events at the second interim analysis and at the final analysis was changed. In protocol version 6, the median OS and 18-month OS rate for sorafenib was increased from 10 months and 28.7 % to 11.5 months and 33.8 %, respectively. The required number of events at the second interim analysis and at the final analysis were also changed.

The applicant claimed that the changes made in the protocol and SAP were solely informed by external data including Study 22 and KEYNOTE-240 and CheckMate-459. Nevertheless, changes in the sample size while the study is ongoing can jeopardise the interpretation of the results since they may alter the behaviour of study participants and personnel. The changes were implemented between 1 and 2 years from study start, and one month before the first interim analysis (2 Sep 2019). Therefore, the sample size calculations are not considered relevant and the study results will be assessed based on the size of the confidence intervals.

- **Randomisation and Blinding (masking)**

Subjects will be randomised in a 1:1:1:1 ratio to one of the following 4 arms:

1) Arm A: Durvalumab 1500 mg monotherapy

2) Arm B: Tremelimumab 75 mg × 4 doses plus Durvalumab 1500 mg combination therapy

3) Arm C: Tremelimumab 300 mg × 1 dose plus Durvalumab 1500 mg combination therapy

4) Arm D: Sorafenib 400 mg BID.

Protocol amendment 4 closed enrolment to Arm B. As a result of protocol amendment 4, subjects will be randomised in a 1:1:1 ratio to Arm A, Arm C and Arm D. Subjects randomised to Arm B prior to amendment 4 can remain on study as planned until discontinuation criteria are met at the discretion of the investigator.

Randomisation will be stratified according to macrovascular invasion (yes versus no), aetiology of liver disease (hepatitis B virus [confirmed HBV] versus hepatitis C virus [confirmed HCV] versus others), and ECOG PS (0 versus 1).

A randomisation list was produced for each of the randomisation stratum. A blocked randomisation was generated, and all centres used the same list in order to minimise any imbalance in the number of patients assigned to each treatment arm.

The study was open-label. Measures were in place to ensure that the Study team was blinded to treatment assignment and results from the interim analyses. An IDMC assessed safety data ongoing and performed the interim analyses.

- **Statistical methods**

Full analysis set
The full analysis set (FAS) was to include all randomised patients, including patients who were randomised in error. The FAS will be used for all efficacy analyses (including PROs). Treatment arms were to be compared on the basis of randomised study drug(s), regardless of the study drug(s) actually received. Patients who were randomised but did not subsequently go on to receive study drug(s) were included in the analysis in the treatment arm to which they were randomised.

For IA1 an additional analysis set will be defined: FAS subjects with an opportunity for 32 weeks of follow up at the time of IA1 (FAS-32w, i.e., randomised ≥ 32 weeks prior to IA1 DCO).

The primary analysis was performed using the FAS, which includes all randomised patients. For the first IA, only subjects who had the opportunity to attend at least 32 weeks of follow-up were included. The results of the first IA are not related to the primary objectives of the study.

Statistical analyses

Table 14: Formal statistical analyses to be conducteed and pre-planned sensitivity

Table 13 Formal Statistical Analyses to be Conducted and Pre-planned Sensitivity Analyses

Endpoint	Analysis
Overall survival (OS)	Primary analysis: Stratified log-rank test (for p-value), HR from Cox model (with 95% CI) Sensitivity analyses: - Attrition bias. Kaplan-Meier plot of time-to-censoring where the censoring indicator of the primary analysis is reversed. - Exploratory analysis using max-combo test. - Impact of COVID19. OS analysis will be repeated but subjects who died from COVID-19 Infection will be censored at their COVID infection death date.
Progression Free Survival (PFS)	Primary analysis: Stratified log-rank test using Investigator assessments per RECIST 1.1 (for p-value), HR from Cox model (with 95% CI)
Time to progression (TTP)	Primary analysis: Stratified log-rank test using Investigator assessments per RECIST 1.1 (for p-value), HR from Cox model (with 95% CI)
Objective response rate (ORR)	IA1: Exact confidence intervals; IA2 and FA: Logistic regression using Investigator assessments per RECIST 1.1 (odds ratio with 95% CI and p-value)
Best Objective Response (BoR)	Descriptive statistics
Duration of response (DoR)	Descriptive statistics including KM plot
Disease control rate (DCR, DCR-16w, DCR-24w)	Descriptive statistics
Proportion of subjects alive at 18m (OS18)	KM estimates of OS at 18 months
Proportion of subjects alive at 24m (OS24)	KM estimates of OS at 24 months
Proportion of subjects alive at 36m (OS36)	KM estimates of OS at 36 months Stratified chi-square test of difference in KM estimators at a fixed time point (36 months) (for p-value)
PFS from rechallenge	Summarized by treatment arm using Investigator assessments per RECIST 1.1.
PFS on next treatment	Summarized by treatment arm
Time to deterioration (EORTC QLQ-C30 and EORTC QLQ-HCC18)	Stratified log-rank test (for p-value), HR from Cox model (with 95% CI), KM plot
EORTC QLQ-C30, EORTC QLQ-HCC18	Average change from baseline using an MMRM analysis, Summary statistics
Improvement based best overall response (EORTC QLQ-C30, EORTC QLQ-HCC18)	Logistic regression with odds ratio, 95% CI and p-value
EQ-5D-5L, PGIC, PRO-CTCAE	Summary statistics

EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQoL 5-Dimension, 5-Level health state utility index; MMRM Mixed effect model repeat measurement; OS overall survival; QLQ-C30 30-item core quality of life questionnaire; QLQ-HCC18 18-item hepatocellular cancer health-related quality of life questionnaire.

Overall survival

The primary OS endpoint was to be analysed using a stratified log-rank tests adjusting for aetiology of liver disease (confirmed HBV versus confirmed HCV versus others), ECOG (0 versus 1), and macrovascular invasion (yes versus no) for generation of the p-value and using rank tests for association as the testing approach, which corresponds to Cox regression with the Breslow approach for handling ties (Breslow, 1974).

The effect of Arm C vs. Arm D treatment was to be estimated by the HR from stratified Cox proportional hazards model (with ties=Efron and stratification variables as listed above) together with its corresponding 95% confidence interval (CI) calculated using a profile likelihood approach. The stratification variable used the values recorded in the randomisation system (IWRS).

If there is >10% discordance in stratification factors as recorded in IWRS versus the Case Report Form (CRF), then a sensitivity analysis of the primary endpoint OS were to be performed using CRF based stratification factors.

Secondary OS analyses were to be performed using the same methodology as for primary analysis described above.

Censoring rules for OS

Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive

Assumptions of Proportionality

The assumption of proportionality of hazard was to be assessed first by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality of hazard is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time periods. The Grambsch-Therneau test and Schoenfeld residuals may also be used to check violation of the proportional hazards assumption. As a lack of proportionality is expected (due to delayed effect in IO agents), a three-component stratified MaxCombo test will be used as a sensitivity analysis with the same stratification factors as the primary analysis. The Restricted Mean Survival Time (RMST) will also be analysed up to the minimum of the largest observed event time in each of the two arms and /or suitable clinically relevant timepoint. In addition, an area-under-the-curve approach (Kaplan-Meier method) and Royston-Parmar model (Royston and Parmar 2011, 2013) may also be used.

Sensitivity analysis

- Censoring patterns: A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias, achieved by a Kaplan-Meier plot of time-to-censoring where the censoring indicator of OS is reversed.
- Impact of switching (crossover outside of this study) to other immunotherapies (or other potentially active investigational agents) on OS analyses: Exploratory analyses of OS adjusting for the impact of subsequent switching of immunotherapy or the investigational treatment may be performed, if a sufficient proportion of subjects switch.
- Effect of COVID-19: A sensitivity analysis will be conducted to assess for the potential impact of COVID deaths on OS. This was to be assessed by repeating the OS analysis except that any subject who had a death with primary/secondary cause as COVID-19 Infection will be censored at their COVID infection death date.

- Effect of covariates on the HR estimate: Cox proportional hazards modelling was to be employed to assess the effect of pre-specified covariates on the HR estimate for the primary OS treatment comparisons. As an exploratory analysis, the covariates from the model in the primary analysis and the model containing additional covariates may be presented.

OS12, OS18, OS24, and OS36

OS12, OS18, OS24, and OS36 were to be defined as the Kaplan-Meier estimate of OS at 12 months, 18 months, 24 months, and 36 months. OS12, OS18, OS24, and OS36, along with their 95% CI, will be summarised (using the Kaplan- Meier curve) and presented by treatment arm. An analysis of OS36 will be performed to compare Arm C vs. Arm D using a stratified chisquare test for the difference in KM estimators (cloglog transformed) for Arms C and D at a fixed time point (36 months). The test will be conducted using the methods described in (Klein et al., 2007), including cloglog transformation on KM estimators, with randomisation stratification factors (macrovascular invasion, etiology of liver disease, and ECOG). Note that the adjustment for the stratification factors will be applied only if there are sufficient number of events and subjects at risk available in each strata at 36 months. Otherwise, an unstratified chisquare test will be used to compare the difference in KM estimators at 36 months.

OS was analysed using a stratified log-rank tests adjusting for the factors used at randomisation: etiology of liver disease (confirmed HBV versus confirmed HCV versus others), ECOG (0 versus 1), and macrovascular invasion (yes versus no). The HR will be estimated using a stratified Cox model. The fulfilment of the proportional hazard assumption was investigated using a graphical approach and a maxcombo test. Sensitivity analyses were planned to explore the impact of treatment switch, covid 19 and effect of covariates. Censoring pattern were examined using the reverse Kaplan-Meier method. Patients not known to have died were censored at the last observation date.

The statistical method implemented to analysis OS is overall endorsed. The applicant has clarified that he concordance rate between stratification factors entered in the IWRS vs eCRF at screening and baseline is high and due to <10% discordance rate, the threshold for triggering the sensitivity analysis was not met. Hence, no sensitivity analysis for primary efficacy analysis of OS adjusted for eCRF stratification factors at baseline has been conducted, which is acceptable.

Objective response rate based on Investigator assessment (ORR)

Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Subjects who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR. ORR based on at least one confirmed response will also be derived and reported in CSR.

Logistic regression models adjusting for the same factors as the primary endpoint (etiology of liver disease, ECOG, and macrovascular invasion) will be fitted. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood 95% CI (e.g. using the option 'LRCI' in SAS procedure GENMOD) and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

Additionally, at IA2 and FA a stratified Cochran Mantel–Haenszel (CMH) test will be performed using randomisation stratification factors (macrovascular invasion, etiology of liver disease, and ECOG). CMH test results will include odds ratios and p-values.

Progression Free Survival by Investigator (PFS)

Analysis of PFS (time to first progression) will be performed to compare Arm C vs. Arm D and Arm A vs. Arm D using the same methodology as for OS. Exploratory analyses will compare Arm A vs. Arm C.

Table 15: Censoring rules for PFS

Assessment	Outcome	Date of Progression or Censoring
No baseline assessments or no evaluable response visits (excluding deaths within 2 visits of baseline)	Censored	Randomization date
No baseline or evaluable tumor assessments and death within 2 visits of baseline	Progressed	Date of death
Progression documented between scheduled visits	Progressed	Date of assessment of progression
No progression (or death) at time of analysis	Censored	Date of last evaluable tumor assessment
Death between assessment visits	Progressed	Date of death
Death or progression after 2 or more missed visits	Censored	Date of last evaluable tumor assessment prior to the 2 missed visits

PFS Progression-free survival.

Interim analyses

Two interim analyses and a final analysis are planned as described below:

Interim Analysis 1 (IA1): The first interim analysis will be performed after approximately 100 subjects per treatment arm have had the opportunity for 32 weeks of follow-up and not prior to the last subject enrolled. The objective is to evaluate the efficacy of Arm A and Arm C in terms of ORR and DoR. The analysis set for ORR and DoR will be the FAS-32wA BICR of radiological scans will be performed on all subjects included in IA1 who have been randomised and have had the opportunity for at least 32 weeks follow-up. Both Investigator (using RECIST 1.1) and BICR (using RECIST 1.1 and mRECIST) assessments are planned for IA1. Therefore, ORR and DoR (for both confirmed and unconfirmed responses) according to both Investigator using RECIST 1.1 and BICR using RECIST 1.1 and mRECIST will be reported for IA1.

Interim Analysis 2 (IA2): The second interim analysis will be performed when approximately 404 OS events in Arm C and Arm D combined (~52% maturity), approximately 30 months after the first subject is randomised. The goal is to evaluate the efficacy of Arm C vs. Arm D (for superiority) and then Arm A vs. Arm D (for non-inferiority, then superiority) in terms of OS. It is anticipated that approximately 453 OS events will have occurred across Arms A and D combined (~59% maturity) at the time of the DCO for IA2.

Final Analysis (FA): The final analysis is expected to be performed when approximately 515 OS events in Arm C and Arm D combined (~67% maturity), approximately 37.5 months after the first subject is randomised. The primary objective is to assess the efficacy of Arm C vs. Arm D in terms of OS for superiority. The key secondary objectives are to assess the efficacy of Arm A vs. Arm D in terms of OS (for non-inferiority, then superiority). It is anticipated that approximately 560 OS events will have occurred across Arms A and D combined (~73% maturity) at the time of the DCO for the final analysis. Efficacy data for Arm B (which was closed for enrollment with Amendment 4) will be summarised descriptively, however will not be formally analysed.

Multiplicity

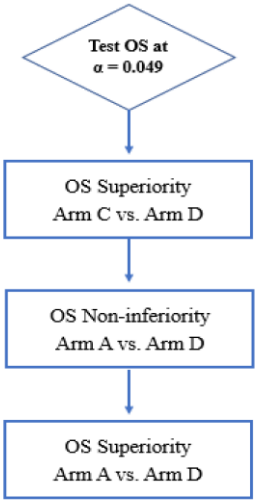
To strongly control the familywise error rate (FWER) at the 5% level (2-sided), an alpha level of 0.1% will be spent on the interim ORR analysis (IA1) while the remaining 4.9% alpha level will be spent on

all OS analyses. The primary objective of OS will be tested (H1: Arm C vs. Arm D) with 4.9% for this comparison.

Since two analyses of OS are planned (Interim Analysis, Final Analysis), the Lan DeMets approach (Lan and DeMets 1983) that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided 4.9% type I error across the two planned analyses of OS (Interim and Final) for the primary comparison (H1: Arm C vs. Arm D).

If all the OS analyses (H1, H2, and H3) are considered successful (superiority tests are statistically significant and non-inferiority is achieved), the 4.9% alpha level will be passed to test the difference in the three-year survival rates (OS36) between Arm C and Arm D; Otherwise the test will not be conducted. The study will be considered positive (a success) if the primary OS analysis result is statistically significant at either IA2 or FA. If significance is achieved at IA2, it does not need to be tested again at FA.

Figure 16: Multiple testing strategy



The MAH planned to perform 2 interim and 1 final analyses. The first interim analysis was planned to be performed after 100 subjects per treatment arm have had the opportunity for 32 weeks of follow-up. The objective is to evaluate the efficacy of Arm A and Arm C in terms of ORR and DoR. This analysis was not related to the primary objective of the study. The second interim analysis was related to OS and planned to be performed after 404 OS events were observed (~52% maturity). The final OS analysis was planned to be performed after 515 OS events (~67% maturity) had been observed. The MAH implemented a hierarchical approach to protect the type I error due to multiple hypotheses being tested (OS superiority for T300+D vs S, OS non-inferiority for D vs S, OS superiority D vs S). An inflation of the type I error due to multiple looks was avoided using an alpha spending function.

The implemented strategy to control the type I error is endorsed. Of note, the results presented in the CSR corresponds to the final analysis for OS.

Changes to Planned Analyses

Changes to the statistical analyses planned are shown in Table . The AstraZeneca study team was responsible for all changes to the planned statistical analyses. All major changes were made prior to the DBL for the final analysis (DCO: 27 August 2021) (data not shown). Minor changes to the algorithms for counting the number of dose delays for S and for determination of analysis windows for T and D were made after the SAP was finalised.

Table 16: Changes to planned analyses

Key Details of Change (Section of Report Affected)	Reason for Change
Two additional efficacy endpoints that were not detailed in the CSP were calculated: time to response and time from randomization to first subsequent therapy or death. Neither endpoint is reported in the CSR	To support the payer analysis
Section 6.5 of the CSP (see Appendix 16.1.1) does not define or provide instructions for determining AEPIs. The latest list of PTs was used to determine both AESIs and AEPIs (Section 9.8.6.2)	For completeness
The following details of the non-inferiority approach were added to the SAP (see Sections 1.3 and 4.2.2.1 of Appendix 16.1.9) to supplement the information provided on the non-inferiority margin in Sections 8.2 and 8.5 of the CSP (see Appendix 16.1.1): • results of the 3 studies used to determine the non-inferiority margin • clarification that the assumed HR for the comparison of D vs S is based on the results in Checkmate 459 for nivolumab vs sorafenib in the same population (Yau et al 2019) • results from 4 other studies that were designed with non-inferiority to a sorafenib control in first-line HCC Section 4.2.2.1 also specifies that for the interim and final analyses of the primary OS and key secondary analyses (including non-inferiority), adjusted alpha levels are derived based on the exact number of OS events using the Lan and DeMets approach that approximates the O'Brien Fleming spending function. Section 4.2.2.1 clarifies that the primary analysis method (log-rank test) will be used to assess non-inferiority and superiority for the OS comparisons of D vs S	Provision of additional details and sources for the chosen statistical analysis methods
The CSP indicated that details of the China cohort and the corresponding analysis plan would be outlined in a China-specific amendment and SAP. As no patients were enrolled in the China cohort, a China-specific SAP was not prepared	No longer required
A test of the 3-year overall survival rate (OS36) between T300+D and S was added to the MTP in SAP Section 4.2.1. The test is described in SAP Section 4.2.3.7. Section 4.2.1 clarifies that only in the case that all OS analyses were statistically significant and non-inferiority was achieved for D vs S, would the 4.9% alpha level be passed to test the difference in the 3-year survival rates (OS36) between T300 +D and S. Section 4.2.3.7 provides the details of the test for OS36; the test would be performed using the stratified method described in (Klein et al 2007), using stratification factors collected at randomization (macrovascular invasion, etiology of liver disease, and ECOG). The adjustment for stratification factors would be applied only if there are sufficient number of events and number of subjects at risk available in each stratum at 36 months, otherwise unstratified methods from (Klein et al 2007) would be used.	To further assess efficacy between T300+D and S

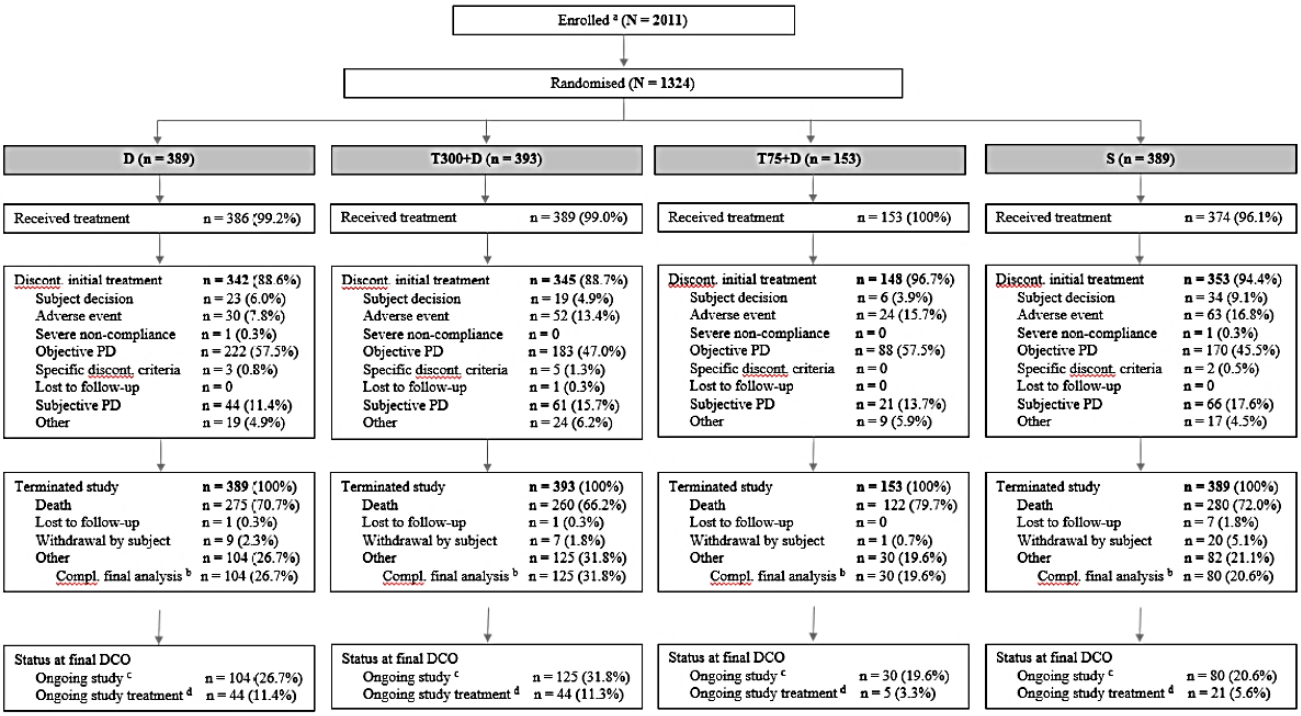
AEPI, adverse event of possible interest; AESI, adverse event of special interest; CSP, clinical study protocol; CSR, clinical study report; D, durvalumab monotherapy 1500 mg Q4W; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; OS36, OS at 36 months; PT, preferred term; S, sorafenib 400 mg twice daily; SAP, statistical analysis plan; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

There are 4 versions of the SAP: SAP edition 1 (25 Oct 2017), SAP edition 2 (23 Aug 2019), SAP edition 3 (15 May 2020), and SAP edition 4 (30 July 2021). Several amendments were done to the study protocol throughout the study and the SAP was therefore updated. Major changes to the study design were made in Protocol version 5 (20 Aug 2019) where the objectives of the study, primary endpoints and the testing hierarchy were modified.

Results

- **Participant flow**

Figure 17: Patient disposition



[a] Informed consent received. The reported value of 2011 includes 61 rescreened subjects who each received a new subject ID code during the rescreening phase per protocol. The actual number of subjects enrolled was 1950.

[b] Patients confirmed alive in follow-up or on active study treatment at the time of final analysis reported 'study completion' on the disposition eCRF.

[c] Patients ongoing in study are the same as patients who completed the final analysis.

[d] Percentages are calculated from the number of patients who received treatment in the Global Study. For combination therapy patients durvalumab reason is reported.

Compl., completed; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cutoff; Discont., discontinued or discontinuation; PD, disease progression; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W

Source: Table 14.1.1

Table 17: Subject Disposition (All subjects, DCO 27 Aug 2021)

AstraZeneca
Durvalumab (MEDI4736) and Tremelimumab Protocol D419CC00002
Data Cut-Off: 27AUG2021

Table 14.1.1 Subject disposition (All subjects)

	Number (%) of subjects				
	Durva 1500 mg	Treme 300 mg x1 dose + Durva 1500 mg	Treme 75 mg x4 doses + Durva 1500 mg	Sora 400 mg BID	Total
Subjects enrolled[a]					2011
Subjects randomized	389	393	153	389	1324
Subjects who were not randomized[b]					687
Eligibility criteria not fulfilled					654 (95.2)
Other					33 (4.8)
Subjects who received treatment	386 (99.2)	389 (99.0)	153 (100)	374 (96.1)	1302 (98.3)
Subjects who did not receive treatment	3 (0.8)	4 (1.0)	0	15 (3.9)	22 (1.7)
Subjects ongoing study treatment at data cut-off[c]	44 (11.4)	44 (11.3)	5 (3.3)	21 (5.6)	114 (8.8)
Subjects who discontinued initial study treatment[cd]	342 (88.6)	345 (88.7)	148 (96.7)	353 (94.4)	1188 (91.2)
Subject decision	23 (6.0)	19 (4.9)	6 (3.9)	34 (9.1)	82 (6.3)
Adverse event	30 (7.8)	52 (13.4)	24 (15.7)	63 (16.8)	169 (13.0)
Severe non-compliance to protocol	1 (0.3)	0	0	1 (0.3)	2 (0.2)
Objective disease progression	222 (57.5)	183 (47.0)	88 (57.5)	170 (45.5)	663 (50.9)
Development of study specific discontinuation criteria	3 (0.8)	5 (1.3)	0	2 (0.5)	10 (0.8)
Subject lost to follow-up	0	1 (0.3)	0	0	1 (0.1)
Subjective disease progression	44 (11.4)	61 (15.7)	21 (13.7)	66 (17.6)	192 (14.7)
Other	19 (4.9)	24 (6.2)	9 (5.9)	17 (4.5)	69 (5.3)
Subjects ongoing study[ef]	0	0	0	0	0
Subjects who terminated study[e]	389 (100)	393 (100)	153 (100)	389 (100)	1324 (100)
Death	275 (70.7)	260 (66.2)	122 (79.7)	280 (72.0)	937 (70.8)
Lost to follow-up	1 (0.3)	1 (0.3)	0	7 (1.8)	9 (0.7)
Screen failure	0	0	0	0	0
Withdrawal by subject	9 (2.3)	7 (1.8)	1 (0.7)	20 (5.1)	37 (2.8)
Other	104 (26.7)	125 (31.8)	30 (19.6)	82 (21.1)	341 (25.8)
Completed final analysis[f]	104 (26.7)	125 (31.8)	30 (19.6)	80 (20.6)	339 (25.6)

[a] Informed consent received.
[b] Percentages are calculated from the number of not randomized subjects.
[c] Percentages are calculated from the number of subjects who received treatment in the Global Study. For combination therapy subjects durvalumab reason is reported.
[d] Initial study treatment refers to originally assigned treatment and does not include rechallenge with tremelimumab.
[e] Percentages are calculated from the number of subjects randomized into the Global Study.
[f] Subjects confirmed alive in follow-up or on active study treatment at the time of final analysis reported 'study completion' on the disposition CRF.
Subjects are summarized using the planned treatment arm in this table.
The reported value of 2011 includes 61 rescreened subjects who each received a new subject ID code during the rescreening phase per protocol. The actual number of subjects enrolled was 1950.

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Table 18: Important protocol deviations (FAS)

Table 13 Important Protocol Deviations (FAS)

Important protocol deviations [a]	N (%) of patients				
	D (N = 389)	T300+D (N = 393)	T75+D (N = 153)	S (N = 389)	Total (N = 1324)
Number of subjects with at least 1 important deviation	3 (0.8)	9 (2.3)	3 (2.0)	21 (5.4)	36 (2.7)
Active or prior documented autoimmune or inflammatory disorders [b]	0	0	0	1 (0.3)	1 (0.1)
Additional investigational systemic anticancer therapy concurrent with those under investigation in this study (as specified in CSP Section 7.7)	0	1 (0.3)	0	0	1 (0.1)
Baseline tumor assessments (RECIST1.1) performed more than 28 days before the first dose of study treatment	0	0	0	2 (0.5)	2 (0.2)
Child-Pugh score was not class A	0	1 (0.3)	1 (0.7)	3 (0.8)	5 (0.4)
Concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment other than those under investigation in this study while the patient is on study treatment(s)	0	1 (0.3)	1 (0.7)	0	2 (0.2)
Patient randomized but did not receive study treatment	3 (0.8)	4 (1.0)	0	15 (3.9)	22 (1.7)
Patient received / used incorrect medication (ie, expired medication, incorrect kit ID, incorrect dose, alternative study treatment to what which they were randomized)	0	2 (0.5)	0	0	2 (0.2)
Patients co-infected with HBV and HCV, or co-infected with HBV and hepatitis D virus (HDV). [c]	0	1 (0.3)	0	0	1 (0.1)
Patients with main portal vein tumor thrombosis (Vp4)	0	1 (0.3)	1 (0.7)	0	2 (0.2)

[a] The same patient may have had more than 1 important protocol deviation.

[b] Includes inflammatory bowel disease (eg, colitis or Crohn's disease), diverticulitis (with the exception of diverticulosis), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.). Active disease (outside of the allowed exceptions) in the last 5 years that has not been discussed with the Study Physician and considered appropriate for study participation

[c] HBV positive (presence of HbsAg and/or anti-HbcAb with detectable HBV DNA); HCV positive (presence of anti-HCV antibodies); HDV positive (presence of anti-HDV antibodies)

Table 19: Not randomised patients with "other" reason for screening failure

Reason for screening failure	Number of patients
Because it was possible that selection criterion 12 would not be satisfied.	1
Eligibility was not able to be verified within 28 days so patient was reconsented with a new screening id:.	1
Exceeded screening time (new screening number)	1
Incorrect activation of the patient	1
Issue due to sorafenib shipment	1
Not recorded	7
Patient died due to progression disease, before randomisation.	1
Patient doesn't meet inclusion criteria 3, as patient withdrew informed consent	1
Patient was withdrawal	1
Screen fail due to insurance reasons	1
Screen failure	2
Screening assessment could not be completed during screening date	1
Screening assessments were not completed during screening.	2
Screening period was greater than 28 days because some examinations was missing	1
Sf due to death	1
Subject does not come to site	1
Subject fell out of screening window.	1
Subject was unable to provide tumour sample	1
Subject withdrawn in the middle of screening	1
Time for screening was exceeded.	1
Screening assessments were not completed during screening.	1
Unable to be randomised within 28 days of icf	1
Unable to submit tumour sample	1
Withdrawal during screening	2

Of 1950 patients enrolled in the pivotal study, 61 were rescreened and 1324 were randomised to 1 of the 4 original treatment arms. The applicant has clarified that of the 687 non-randomised patients, 654 did not fulfil eligibility criteria and 33 were not randomised due to other reasons. The screen failure reasons of these 33 patients as collected as free text field in CRF are summarised in Table : 10/33 patients were not randomised due to inability to complete screening procedures within the 28-day window, 6/33 withdrew informed consent or failed to return to clinic, 2/33 were unable to provide the required tumour tissue sample, and 2/33 died prior to randomisation. In addition, 9/33 did not report more specific screen failure reasons. Other reasons were reported in 1 patient each and included insurance coverage issues, incorrect screening, inability to verify eligibility, or local issues with sorafenib supply. The clarification is accepted and the screen failure reasons are in line with what could be expected for a clinical trial with the targeted patient population.

- **Recruitment**

The first patient was enrolled on 11 October 2017 and the last patient on 19 June 2019. The median follow-up for OS at DCO (27 August 2021) was ~33 months in the T300+D arm and ~32 months in the S arm.

- **Conduct of the study**

Table 20: Protocol amendments and other significant changes to study conduct

Table 11 Protocol Amendments and Other Significant Changes to Study Conduct

Key details of amendment (section of this report affected)	Reason for amendment
Protocol amendment 1, Protocol version 2.0 (20 December 2017)	
Updated descriptions of risks for durvalumab, tremelimumab, and the combination of durvalumab with tremelimumab (Section 12.2.4). Toxicity Management Guidelines replaced with new version from 01 November 2017.	To align with updates across the clinical program and Investigator's Brochure
Inclusion of the exploratory objective: to assess PFS from rechallenge in the durvalumab plus tremelimumab combination arms only, and to assess PFS from first post-IP discontinuation therapy in all arms	Additional exploratory objective of interest
Section 9.3 • IC10 amended to clarify treatment of patients with HBV infection with antiviral therapy to ensure adequate viral suppression prior to enrollment, and to further clarify that patients who test positive for HBc with undetectable HBV DNA (< 10 IU/ml) do not require antiviral therapy prior to enrollment. These patients were to be tested at every cycle to monitor HBV DNA levels and initiate antiviral therapy if HBV DNA was detected (≥ 10 IU/ml). HBV DNA detectable patients were to initiate and remain on antiviral therapy for the study duration and for 6 months after the last dose of IP • New IC15 requiring patients to have a life expectancy of at least 12 weeks • EC12 amended to specify "clinically meaningful ascites (defined as ascites requiring non-pharmacologic intervention eg, paracentesis or escalation in pharmacologic intervention to maintain symptomatic control), within 6 months prior to the first scheduled dose", rather than "ascites that require ongoing paracentesis, within 6 weeks prior to the first scheduled dose to control symptoms." The amended EC12 also indicates patients on stable doses of diuretics for ascites for ≥ 2 months are eligible • EC22 qualified to indicate that a history of, or current, brain metastases was an exclusion	• IC10: to ensure patients receive antiviral medication as clinically indicated • IC15: for compliance with new CSP template • EC12: to clarify protocol definition of clinically meaningful ascites • EC22: to ensure patient safety
Updated AESI terminology (Section 12.2.4)	To align with updates across the clinical program
Protocol amendment 2, Protocol version 3.0 (23 January 2018)	
No major updates	Released to correct errors noted in CSP version 2.0
Protocol amendment 3, Protocol version 4.0 (29 November 2018)	

Key details of amendment (section of this report affected)	Reason for amendment
Enrollment into the T75+D arm was closed, based on results from a pre-planned IA evaluating tolerability and clinical activity in Study D419CC00022. All other arms were unchanged (Section 9.1)	In the ongoing Study 22, safety data showed that the T75+D regimen was tolerable with no new safety signals. However, efficacy data for the T75+D regimen did not differentiate it from the durvalumab monotherapy arm. Thus, there was insufficient clinical activity observed to warrant continuing enrollment in the T75+D arm in the current study
Following closure of enrollment in the T75+D arm, the primary and secondary objectives were re-aligned: The original primary objective of OS for T75+D vs S was replaced with D vs S and T300+D vs S for OS. Other supportive endpoints were clarified for consistency across the CSP, and a new endpoint (DCR-16w) was added (Section 8)	To align with study design changes
The multiple testing strategy was updated to reflect the procedure for controlling the type 1 error as a result of the changes to the primary and secondary objectives. PRO endpoints were added to the MTP (Section 9.8.3)	To align with study design changes
Update such that IA1 was performed after approximately 100 patients per treatment arm had the opportunity for 32 rather than 24 weeks of follow-up (Section 9.8.9)	To ensure 24 weeks of imaging follow-up, the baseline scan needs to be 8 weeks prior to the first follow-up scan, ie, a total of 32 weeks
The sample size was updated to align with closure of enrollment in the T75+D arm. The number of events, maturity, power and 2-sided significance levels for these analyses were updated accordingly and the MTP was updated to reflect the revised procedure for controlling the type 1 error. No changes were made to the assumed HRs, timelines, or median OS. The statistical methods were revised to indicate the T75+D arm would be summarized descriptively, but not formally analyzed (Section 9.8.1)	To align with study design changes
Patients in the T75+D arm could continue to receive their assigned treatment according to the CSP (Section 9.4)	To align with study design changes
Patients in the T75+D arm who were eligible for rechallenge could be rechallenged with either 75 mg tremelimumab × 4 doses or 300 mg tremelimumab × 1 dose in combination with durvalumab 1500 mg (with prior approval from the AstraZeneca clinical team) (Section 9.4.1.5)	To align with study design changes
EC19 amended to include "inferior vena cava thrombosis" (Section9.3.2)	Patients with inferior vena cava thrombosis were excluded due to the risk of pulmonary embolism and sudden death
Protocol amendment 4, Protocol version 5.0 (17 December 2018)	

No major updates	Released to correct administrative errors noted in CSP version 4.0
Protocol amendment 5, Protocol version 6.0 (20 August 2019)	
Statistical analysis methods revised to change dual primary objectives to hierarchical approach with a single primary objective (T300+D vs S for superiority) and 2 key secondary objectives (D vs S for non-inferiority, then D vs S for superiority) of OS (Section 9.8): • The multiple testing strategy was updated to reflect the procedure for controlling the type 1 error given the update from dual primary objectives to a hierarchical approach with a single primary objective and 2 key secondary objectives of OS • ORR and PRO endpoints were removed from the MTP • The number of events, maturity, power and 2-sided significance levels for these analyses were updated	An IA of the ongoing Study 22 suggested that the best clinical benefit (in terms of ORR and OS) was observed in patients who received the T300+D combination when compared to durvalumab monotherapy, tremelimumab monotherapy, or T75+D. As a result, the primary analysis for the current study was revised
Efficacy assessments in IA1, ie, RECIST 1.1 and mRECIST analyses (ORR, BOR, DoR) by BICR for the IA1 set of patients with an opportunity for 32 weeks of follow-up were added as a secondary objective. It was also clarified that enrollment had to be completed before IA1 could be performed (Section 8)	To clarify analyses in IA1
The order of hypotheses for superiority was changed: H1: T300+D vs S and H3: D vs S. A new hypothesis was added - H2: for non-inferiority D vs S (Section 9.8)	To align with revised objectives
The assessment of efficacy for the comparison of D vs T300+D in the overall population and in the population defined by PD-L1 expression was changed from a secondary to an exploratory objective (Section 8)	Archival tissue up to 3 years of age was allowed for the HIMALAYA study. Data suggest that sample age may affect PD-L1 expression status (eg, PD-L1 expression measured in an older sample might be lower than PD-L1 expression at the current time for a patient). Therefore, it was decided to change the assessment of efficacy by PD-L1 expression to an exploratory objective
An exploratory objective relating to patients with early mortality risk was added (Section 8)	This was an exploratory objective of interest
Protocol amendment 6, Protocol version 7.0 (22 September 2021)	

Key details of amendment (section of this report affected)	Reason for amendment
The OS at 36 months (OS36) was added to the secondary objectives (proportion of patients alive at 36 months after randomization [OS36]). The OS36 was defined as the KM estimate of OS at 36 months after randomization (Section 9.8.4.1). Clarified that patients in all treatment arms, not just durvalumab, may continue to receive treatment following the final primary analysis DCO. Added that long-term follow-up data may be collected in eCRFs post final primary analysis for approximately 3 years and defined end of study, if long-term follow-up is collected post final primary analysis, as the last visit of the last patient in the study.	To further assess efficacy

AESI, adverse event of special interest; BICR, blinded independent central review; BOR, best overall response; CSP, Clinical Study Protocol; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; DCR-16w, disease control rate at 16 weeks; DNA, deoxyribonucleic acid; DoR, duration of response; EC, exclusion criterion; HBc, hepatitis B core; HBV, hepatitis B virus; HR, hazard ratio; IA1, interim analysis 1; IC, inclusion criterion; IP, investigational product; KM, Kaplan-Meier; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MTP, multiple testing procedure; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PRO, patient-reported outcome; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 21: Summary of overall survival: T300+D versus sorafenib and D versus sorafenib (PD-L1 analysis set)

Subgroup	Treatment	Number of Patients	Events (%)	Median (months) (95% CI)	Hazard Ratio (95% CI)
PD-L1 Evaluable patients[a]	T300+D	337	229 (68.0)	16.00 (13.11, 19.58)	0.84 (0.70, 1.00)
	D	344	248 (72.1)	16.46 (13.83, 19.12)	0.90 (0.76, 1.08)
	Sorafenib	329	248 (75.4)	14.55 (12.75, 16.85)	
TIP <1%[b]	T300+D	189	128 (67.7)	14.26 (11.43, 21.29)	0.83 (0.65, 1.05)
	D	190	141 (74.2)	15.06 (12.68, 18.53)	0.93 (0.73, 1.17)
	Sorafenib	181	138 (76.2)	13.93 (12.39, 16.69)	
TIP ≥1%[b]	T300+D	148	101 (68.2)	17.35 (13.50, 23.03)	0.85 (0.65, 1.11)
	D	154	107 (69.5)	17.22 (12.29, 24.38)	0.87 (0.66, 1.13)
	Sorafenib	148	110 (74.3)	15.93 (10.68, 21.72)	-

- The analysis was performed using stratified log-rank test adjusting for treatment, aetiology of liver disease (HBV versus HCV versus others), ECOG PS (0 versus 1), and macro-vascular invasion (yes versus no). The values of the stratification factors were obtained from the interactive web response system.

Unstratified analyses.

CI = confidence interval; D = durvalumab 1500 mg Q4W; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; PD-L1 = programmed cell death ligand 1; PS = performance status; QxW = every X weeks; T300+D = tremelimumab 300 mg for a single dose and durvalumab 1500 mg Q4W; TIP = Tumour and Immune Cell Positivity. Source:CSR table 14.2.1.3

- **Baseline data**

Table 22: Demographic and baseline patient characteristics in HIMALAYA (pivotal study) and Study 22 (supportive study)

Study Analysis set (DCO)	HIMALAYA FAS (Final Analysis)			Study 22 (Parts 2 and 3) FAS (Final Analysis)	
	D (N = 389)	T300+D (N = 393)	S (N = 389)	D (N = 104)	T300+D (N = 75)
Age (years)					
Mean	62.6	63.0	63.5	64.0	64.4
SD	11.47	11.65	11.12	10.81	11.24
Median	64.0	65.0	64.0	64.5	66.0
Min	20	22	18	32	26
Max	86	86	88	89	86
Age group (years), n (%)					
< 65	203 (52.2)	195 (49.6)	195 (50.1)	52 (50.0)	34 (45.3)
≥ 65 – < 75	130 (33.4)	145 (36.9)	137 (35.2)	33 (31.7)	31 (41.3)
≥ 75	56 (14.4)	53 (13.5)	57 (14.7)	19 (18.3)	10 (13.3)
Sex, n (%)					
Male	323 (83.0)	327 (83.2)	337 (86.6)	92 (88.5)	65 (86.7)
Female	66 (17.0)	66 (16.8)	52 (13.4)	12 (11.5)	10 (13.3)
Region group, n (%)					
Asia (excl. Japan)	167 (42.9)	156 (39.7)	156 (40.1)	47 (45.2)	31 (41.3)
Rest of World (incl. Japan)	222 (57.1)	237 (60.3)	233 (59.9)	57 (54.8)	44 (58.7)
Race, n (%)					
White	160 (41.1)	182 (46.3)	179 (46.0)	35 (33.7)	27 (36.0)
Black or African American	2 (0.5)	7 (1.8)	10 (2.6)	10 (9.6)	4 (5.3)
Asian	212 (54.5)	195 (49.6)	189 (48.6)	55 (52.9)	44 (58.7)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	0	2 (1.9)	0
American Indian or Alaska Native	0	0	0	1 (1.0)	0
Other	15 (3.9)	7 (1.8)	5 (1.3)	1 (1.0)	0
Ethnic group, n (%)					
Hispanic or Latino	13 (3.3)	21 (5.3)	21 (5.4)	5 (4.8)	4 (5.3)
Not Hispanic or Latino	376 (96.7)	372 (94.7)	362 (93.1)	99 (95.2)	71 (94.7)
Weight group (kg), n (%)					
< 70	218 (56.0)	190 (48.3)	202 (51.9)	47 (45.2)	49 (65.3)
≥ 70 – < 90	130 (33.4)	158 (40.2)	137 (35.2)	41 (39.4)	20 (26.7)

Table 22: Demographic and baseline patient characteristics in HIMALAYA (pivotal study) and Study 22 (supportive study)

Study Analysis set (DCO)	HIMALAYA FAS (Final Analysis)			Study 22 (Parts 2 and 3) FAS (Final Analysis)	
	D (N = 389)	T300+D (N = 393)	S (N = 389)	D (N = 104)	T300+D (N = 75)
≥ 90	41 (10.5)	45 (11.5)	50 (12.9)	15 (14.4)	5 (6.7)
BMI group (kg/m^2), n (%)					
Underweight (< 18.5)	15 (3.9)	19 (4.8)	17 (4.4)	7 (6.7)	4 (5.3)
Normal (≥ 18.5 – < 25.0)	210 (54.0)	188 (47.8)	195 (50.1)	47 (45.2)	47 (62.7)
Overweight (≥ 25.0 – < 30.0)	114 (29.3)	128 (32.6)	125 (32.1)	32 (30.8)	17 (22.7)
Obese (≥ 30.0)	47 (12.1)	56 (14.2)	48 (12.3)	17 (16.3)	6 (8.0)
Alcohol use, n (%) [a]					
Never	150 (38.6)	162 (41.2)	147 (37.8)	NA	NA
Current	62 (15.9)	54 (13.7)	60 (15.4)	NA	NA
Former	176 (45.2)	176 (44.8)	182 (46.8)	NA	NA
Missing	1 (0.3)	1 (0.3)	0	NA	NA

[a] Alcohol use was not captured in the Study 22 eCRF.

Baseline is the last assessment prior to the intake of the first dose of any study drug; for patients not treated, the last assessment on or prior to treatment allocation (Study 22 Part 2B) or randomisation (HIMALAYA and Study 22 Parts 2A and 3) was used.

Abbreviations: BMI = body mass index; DCO = data cut-off; eCRF = electronic case report form; Excl. = excluding; FAS = full analysis set; Max = maximum; Min = minimum; N = total number of patients; n = number of patients in a treatment arm; NA = not applicable; SD = standard deviation.

Table 23: Disease characteristics at screening in HIMALAYA (pivotal study) and Study 22 (supportive study)

Study Analysis set (DCO)	HIMALAYA FAS (Final Analysis)			Study 22 (Parts 2 and 3) FAS (Final Analysis)	
	D (N = 389)	T300+D (N = 393)	S (N = 389)	D (N = 104)	T300+D (N = 75)
ECOG performance status, n (%)					
0	244 (62.7)	246 (62.6)	239 (61.4)	52 (50.0)	46 (61.3)
1	145 (37.3)	147 (37.4)	148 (38.0)	52 (50.0)	29 (38.7)
BCLC stage, n (%) [a]					
Early (A)	NA	NA	NA	1 (1.0)	1 (1.3)
Intermediate (B)	80 (20.6)	77 (19.6)	66 (17.0)	9 (8.7)	13 (17.3)
Advanced (C)	309 (79.4)	316 (80.4)	323 (83.0)	80 (76.9)	58 (77.3)
Etiology of liver disease, n (%)					
HBV-positive	119 (30.6)	122 (31.0)	119 (30.6)	40 (38.5)	27 (36.0)
HCV-positive	107 (27.5)	110 (28.0)	104 (26.7)	29 (27.9)	21 (28.0)
Others	163 (41.9)	161 (41.0)	166 (42.7)	35 (33.7)	27 (36.0)
MVI and/or EHS, n (%)					

Table 23: Disease characteristics at screening in HIMALAYA (pivotal study) and Study 22 (supportive study)

Study Analysis set (DCO)	HIMALAYA FAS (Final Analysis)			Study 22 (Parts 2 and 3) FAS (Final Analysis)	
	D (N = 389)	T300+D (N = 393)	S (N = 389)	D (N = 104)	T300+D (N = 75)
MVI = Yes and/or EHS = Yes [b]	255 (65.6)	263 (66.9)	251 (64.5)	72 (69.2)	58 (77.3)
MVI = No and EHS=No	133 (34.2)	128 (32.6)	137 (35.2)	12 (11.5)	13 (17.3)
Child-Pugh score, n (%)					
A/5	284 (73.0)	295 (75.1)	277 (71.2)	79 (76.0)	51 (68.0)
A/6	96 (24.7)	92 (23.4)	102 (26.2)	23 (22.1)	23 (30.7)
B/7	1 (0.3)	2 (0.5)	10 (2.6)	2 (1.9)	1 (1.3)
Alpha-fetoprotein, n (%)					
< 400 ng/ml	247 (63.5)	243 (61.8)	256 (65.8)	62 (59.6)	39 (52.0)
≥ 400 ng/ml	137 (35.2)	145 (36.9)	124 (31.9)	39 (37.5)	35 (46.7)
Missing	5 (1.3)	5 (1.3)	9 (2.3)	3 (2.9)	1 (1.3)
ALBI score					
1	198 (50.9)	217 (55.2)	203 (52.2)	NA	NA
2	189 (48.6)	174 (44.3)	185 (47.6)	NA	NA
3	2 (0.5)	1 (0.3)	1 (0.3)	NA	NA
Missing	0	1 (0.3)	0	NA	NA
PD-L1 expression level, n (%) [c]					
Positive (TIP ≥ 1%)	154 (39.6)	148 (37.7)	148 (38.0)	55 (52.9)	27 (36.0)
Negative (TIP < 1%)	190 (48.8)	189 (48.1)	181 (46.5)	35 (33.7)	38 (50.7)
Missing	42 (10.8)	52 (13.2)	45 (11.6)	14 (13.5)	10 (13.3)
Prior treatment with sorafenib/VEGFR TKI, n (%) [d]					
Yes	NA	NA	NA	66 (63.5)	55 (73.3)
No	NA	NA	NA	38 (36.5)	20 (26.7)

[a] In HIMALAYA, patients were enrolled only if they had BCLC Stage B (not eligible for locoregional therapy) or Stage C. In Study 22, BCLC Stage was not specified in the inclusion criteria and collection of BCLC scores was not mandated at screening until protocol amendment 3 (20 July 2017); as a result, baseline BCLC scores were missing for some patients in Part 2A (see Section 9.2.2, Study 22 CSR, Module 5.3.5.2).

[b] Includes all patients with "MVI = Yes and EHS = No/Missing," "MVI = No/Missing and EHS = Yes," and "MVI = Yes and EHS = Yes."

[c] PD-L1 expression level was defined as "Positive" if PD-L1 staining of any intensity in tumour cell membranes and/or tumour-associated immune cells covered ≥ 1% of tumour area (TIP ≥ 1%), and "Negative" if PD-L1 staining of any intensity in tumour cell membranes and/or tumour-associated immune cells covered < 1% of tumour area (TIP < 1%).

[d] Per inclusion criteria, no patients in HIMALAYA received prior systemic therapy for HCC (first-line setting only). In Study 22, patients were required to be immunotherapy-naïve and had either progressed on, were intolerant to, or have refused treatment with sorafenib or another approved VEGFR TKI (first-line and second-line settings).

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; eCRF = electronic case report form; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; FAS = full analysis set; HBV = hepatitis B virus; HCV = hepatitis C virus; MVI = macrovascular invasion; N = total number of patients; n = number of patients in a treatment arm; NA, not applicable; PD-L1 = programmed cell death ligand-1; TIP = tumour immune percentage; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

Prior cancer therapy

Per inclusion criteria, no patients in HIMALAYA received prior systemic therapy for HCC (first-line setting only). Overall, the most common disease-related medical procedures prior to study entry, including ablative therapy, therapeutic embolisation, regional chemotherapy, and HCC-related surgery, were similar across treatment arms and consistent with that typically seen in the target patient population.

In study 22, the prior anticancer treatment modalities reported were prior treatment with sorafenib/VEGFR TKI (55/75 patients, 73.3%). Most patients had undergone prior TACE or RFA Per protocol, all patients were immunotherapy-naïve.

Post-IP Discontinuation Anticancer Systemic Therapy

Table 24: Post- discontinuation anticancer systemic therapy

	Number (%) of patients				
Anticancer therapy [a]	D (N = 389)	T300+D (N = 393)	T75+D (N = 153)	S (N = 389)	Total (N = 1324)
Total number of subjects	168 (43.2)	160 (40.7)	67 (43.8)	175 (45.0)	570 (43.1)
Immunotherapy	20 (5.1)	15 (3.8)	5 (3.3)	89 (22.9)	129 (9.7)
Atezolizumab	11 (2.8)	6 (1.5)	1 (0.7)	14 (3.6)	32 (2.4)
Avelumab	0	0	0	1 (0.3)	1 (0.1)
Cancer Vaccines	0	0	0	1 (0.3)	1 (0.1)
Durvalumab	0	0	0	2 (0.5)	2 (0.2)
Immunotherapy	0	0	0	4 (1.0)	4 (0.3)
Investigational Immunotherapy	1 (0.3)	0	0	0	1 (0.1)
Ipilimumab	2 (0.5)	0	0	2 (0.5)	4 (0.3)
Mgd 013	0	2 (0.5)	0	2 (0.5)	4 (0.3)
Monoclonal Antibodies	3 (0.8)	2 (0.5)	1 (0.7)	7 (1.8)	13 (1.0)
Nivolumab	5 (1.3)	5 (1.3)	3 (2.0)	47 (12.1)	60 (4.5)
Pembrolizumab	1 (0.3)	0	0	17 (4.4)	18 (1.4)
Spartalizumab	0	0	0	1 (0.3)	1 (0.1)
Tremelimumab	0	0	0	2 (0.5)	2 (0.2)
Cytotoxic chemotherapy	18 (4.6)	20 (5.1)	7 (4.6)	25 (6.4)	70 (5.3)
Capecitabine	5 (1.3)	3 (0.8)	1 (0.7)	4 (1.0)	13 (1.0)
Capecitabine;oxaliplatin	1 (0.3)	0	0	0	1 (0.1)
Carboplatin	0	0	0	1 (0.3)	1 (0.1)
Carboplatin;etoposide	0	1 (0.3)	0	0	1 (0.1)
Cisplatin [b]	9 (2.3)	6 (1.5)	5 (3.3)	5 (1.3)	25 (1.9)
Cisplatin;doxorubicin	0	2 (0.5)	0	0	2 (0.2)
Cisplatin;fluorouracil	0	1 (0.3)	0	2 (0.5)	3 (0.2)
Cyclophosphamide	1 (0.3)	0	0	1 (0.3)	2 (0.2)
Doxorubicin	0	4 (1.0)	1 (0.7)	7 (1.8)	12 (0.9)
Fluorouracil	5 (1.3)	5 (1.3)	3 (2.0)	7 (1.8)	20 (1.5)
Folfox	0	4 (1.0)	0	2 (0.5)	6 (0.5)
Gemcitabine	3 (0.8)	1 (0.3)	0	2 (0.5)	6 (0.5)
Gemcitabine;oxaliplatin	0	0	0	1 (0.3)	1 (0.1)

Anticancer therapy [a]	Number (%) of patients				
	D (N = 389)	T300+D (N = 393)	T75+D (N = 153)	S (N = 389)	Total (N = 1324)
Irinotecan	1 (0.3)	0	0	1 (0.3)	2 (0.2)
Oxaliplatin[b]	7 (1.8)	2 (0.5)	1 (0.7)	8 (2.1)	18 (1.4)
Tegafur	0	0	0	1 (0.3)	1 (0.1)
Uracil	0	0	0	1 (0.3)	1 (0.1)
Vinorelbine	0	1 (0.3)	0	0	1 (0.1)
Targeted therapy	155 (39.8)	147 (37.4)	64 (41.8)	108 (27.8)	474 (35.8)
Cabozantinib	20 (5.1)	24 (6.1)	6 (3.9)	26 (6.7)	76 (5.7)
Capmatinib	0	0	0	1 (0.3)	1 (0.1)
H3b 6527	0	1 (0.3)	0	0	1 (0.1)
Lenvatinib	68 (17.5)	55 (14.0)	23 (15.0)	32 (8.2)	178 (13.4)
Olaparib	1 (0.3)	0	0	0	1 (0.1)
Pegargiminase	1 (0.3)	1 (0.3)	0	1 (0.3)	3 (0.2)
Regorafenib	26 (6.7)	29 (7.4)	17 (11.1)	62 (15.9)	134 (10.1)
Sorafenib	98 (25.2)	105 (26.7)	51 (33.3)	12 (3.1)	266 (20.1)
Tyrosine Kinase Inhibitors	0	2 (0.5)	0	0	2 (0.2)
Antiangiogenic therapy	20 (5.1)	11 (2.8)	9 (5.9)	19 (4.9)	59 (4.5)
Bevacizumab	12 (3.1)	6 (1.5)	1 (0.7)	16 (4.1)	35 (2.6)
Ramucirumab	8 (2.1)	7 (1.8)	7 (4.6)	3 (0.8)	25 (1.9)
Thalidomide	2 (0.5)	0	1 (0.7)	0	3 (0.2)
Homeopathic therapy	1 (0.3)	0	0	2 (0.5)	3 (0.2)
Herbal anticancer remedies	1 (0.3)	0	0	2 (0.5)	3 (0.2)
Other	1 (0.3)	3 (0.8)	0	9 (2.3)	13 (1.0)
Fenbendazole	0	0	0	1 (0.3)	1 (0.1)
Folinic Acid	1 (0.3)	1 (0.3)	0	3 (0.8)	5 (0.4)
Investigational Antineoplastic Drugs	0	2 (0.5)	0	3 (0.8)	5 (0.4)
Investigational Drug	0	0	0	2 (0.5)	2 (0.2)

[a] Therapies taken following discontinuation of IP.

[b] Includes intra-arterial administrations.

Patients may have received more than 1 post-IP discontinuation therapy.

D, durvalumab monotherapy 1500 mg Q4W; FAS, Full Analysis Set; N, number of patients in treatment group; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Source: Table 14.1.17.

- **Numbers analysed**

Table 25: Analysis sets

	Durva 1500 mg	Treme 300 mg x1 dose + Durva 1500 mg	Treme 75 mg x4 doses + Durva 1500 mg	Sora 400 mg BID	Total
Subjects randomized	389	393	153	389	1324
Subjects included in full analysis set	389	393	153	389	1324
Subjects included in safety analysis set	388	388	152	374	1302
Subjects excluded from safety analysis set	3	4	0	15	22
Did not receive treatment	3	4	0	15	22
Subjects included in Durvalumab PK analysis set	357	348	142		847
Subjects excluded from Durvalumab PK analysis set[a]	34	44	10		88
Did not receive treatment	3	4	0		7
No post-dose data available	31	40	10		81
Subjects included in Tremelimumab PK analysis set		386	142		528
Subjects excluded from Tremelimumab PK analysis set[b]		6	12		18
Did not receive treatment		4	2		6
No post-dose data available		2	10		12

Full analysis set - all randomized subjects analysed on an ITT basis.
Safety analysis set - all subjects who received at least one dose of study treatment.
PK analysis sets - all subjects who received at least 1 dose of study drugs and for whom any postdose data are available.
ADA evaluable sets - all subjects who have non-missing baseline ADA and at least one non-missing post-baseline ADA result.
Results in categories 'Subjects included in safety analysis set', 'Subjects included in PK analysis set' and 'Subjects included in ADA evaluable set' are calculated on basis of actual arm , in other categories on basis of planned arm.
[a] Subjects excluded from the Durvalumab PK analysis are either not part of the safety analysis set or belong to the safety analysis set but are missing a Durvalumab postdose PK assessment.
[b] Subjects excluded from the Tremelimumab PK analysis are either not part of the safety analysis set or belong to the safety analysis set but are missing a Tremelimumab postdose PK assessment.

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- **Outcomes and estimation**

Primary endpoint: Overall survival

Table 26. Overall Survival in HIMALAYA (Pivotal Study)

Study **Analysis set (DCO)**	**HIMALAYA** **FAS (Final Analysis)**		
	D **(N = 389)**	**T300+D** **(N = 393)**	**S** **(N = 389)**
HR (compared to sorafenib) [a]	**0.86**	**0.78**	-
95% CI [a]	0.73 - 1.02	0.66 - 0.92	-
96.02% CI for HR (T300+D vs S) [a, b]	-	0.65 - 0.93	**-**
2-sided p-value (T300+D vs S)	**-**	**0.0035**	-
95.67% CI for HR (D vs S) [a, c]	0.73 - 1.03	-	**-**
2-sided p-value (D vs S) [d]	**0.0674**	-	-
Median OS (months) [e]	**16.56**	**16.43**	**13.77**
95% CI for median OS [e]	**14.06 - 19.12**	**14.16 - 19.58**	**12.25 - 16.13**
OS rate at 12 months, % [e]	59.3	60.2	56.2
OS rate at 18 months, % [e]	47.4	48.7	41.5
OS rate at 24 months, % [e]	39.6	40.5	32.6
OS rate at 36 months, % [e]	24.7	30.7	20.2
Deaths, n (%)	280 (72.0)	262 (66.7)	293 (75.3)
Censored patients, n (%)	109 (28.0)	131 (33.3)	96 (24.7)
Still in survival follow-up at DCO [f]	104 (26.7)	125 (31.8)	79 (20.3)
Terminated prior to death [g]	109 (28.0)	131 (33.3)	96 (24.7)
Lost to follow-up	1 (0.3)	1 (0.3)	7 (1.8)
Withdrawn consent	4 (1.0)	5 (1.3)	10 (2.6)
Median (range) duration of follow-up in censored patients (months) [h]	31.61 (1.91 – 45.70)	32.36 (6.18 – 42.84)	30.36 (0.03 – 43.60)
Median (95% CI) duration of follow-up in all patients (months) [i]	32.56 (31.57 – 33.71)	33.18 (31.74 – 34.53)	32.23 (30.42 – 33.71)

[a] The HR was calculated using a Cox proportional hazards model adjusting for treatment arm, etiology of liver disease (HBV vs HCV vs all others), ECOG (0 vs 1), and MVI (yes vs no). An HR < 1 favors either the T300+D arm or the D arm compared with the S arm in terms of being associated with a longer OS.

[b] T300+D vs S (primary objective in HIMALAYA). Statistical significance for T300+D vs S was based on a 2-sided interim $p < 0.0419$ (overall alpha 4.9%), as defined in the MTP.

[c] D vs S (key secondary objective in HIMALAYA). The non-inferiority margin for D vs S was 1.08, as defined in the MTP.

[d] The analysis was performed using a stratified log-rank test adjusting for treatment arm, etiology of liver disease (HBV vs HCV vs all others), ECOG (0 vs 1), and MVI (yes vs no).

[e] Calculated using the Kaplan-Meier method.

[f] Patients confirmed alive in follow-up or on active study treatment at the time of final analysis reported "study completion" on the disposition CRF.

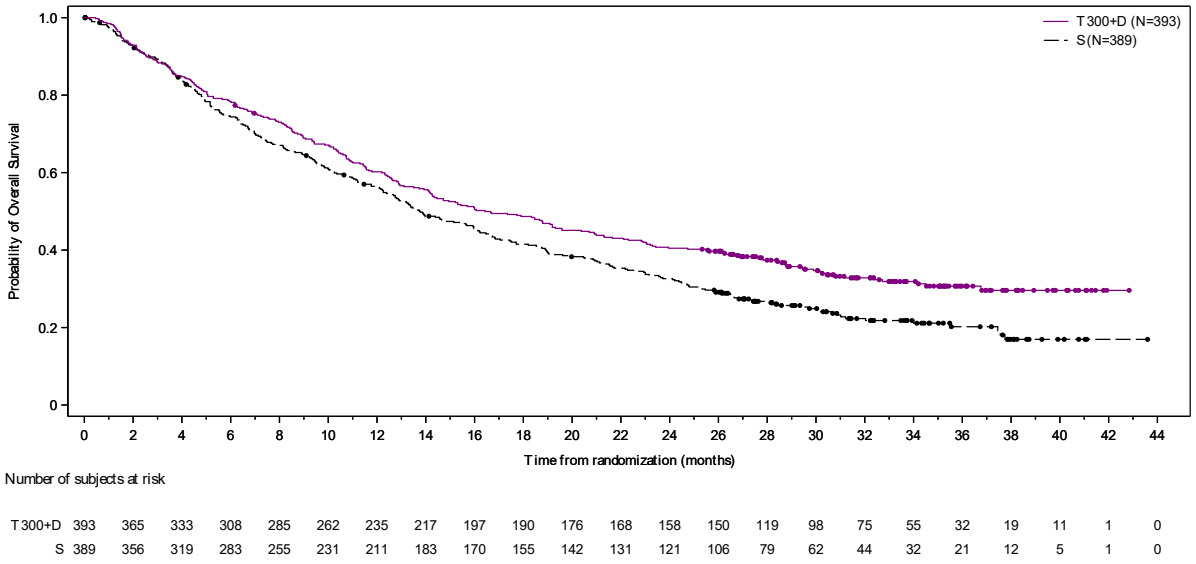
[g] Includes patients with unknown survival status or patients who were lost to follow-up.

[h] Median for duration of follow-up is the arithmetic median.

[i] Calculated using the reverse Kaplan-Meier technique (with censor indicator reversed).

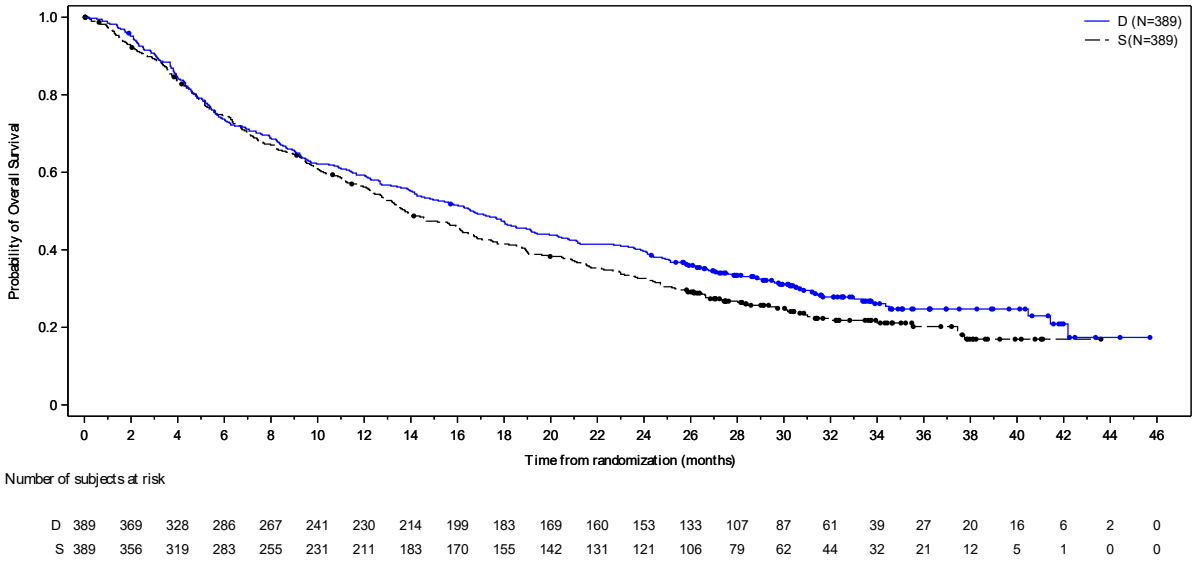
Abbreviations: CI = confidence interval; CRF = case report form; DCO = data cut-off; FAS = full analysis set; HR = hazard ratio; IA = interim analysis; OS = overall survival.

Figure 18 Kaplan-Meier Plot of Overall Survival in the T300+D and S Arms in HIMALAYA, FAS (Final Analysis)



Abbreviations: FAS = Full Analysis Set; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Figure 19 Kaplan-Meier Plot of Overall Survival in the D and S Arms in HIMALAYA, FAS (Final Analysis)



Abbreviations: D = durvalumab monotherapy 1500 mg Q4W; FAS = Full Analysis Set; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily

Secondary endpoints:

Progression-free survival (PFS)

Table 27: Progression-free Survival by Investigator Assessment According to RECIST 1.1 (FAS)

	Number (%) of patients		
	D (N = 389)	**T300+D (N = 393)**	**S (N = 389)**
Hazard ratio (D vs S and T300+D vs S)	1.02	0.90	-
95% CI for hazard ratio	0.88 - 1.19	0.77 - 1.05	-
2-sided p-value	0.7736	0.1625	-
Median PFS (months) [a]	3.65	3.78	4.07
95% CI for median PFS [a]	3.19 - 3.75	3.68 - 5.32	3.75 - 5.49
Total PFS events, n (%) [b]	345 (88.7)	335 (85.2)	327 (84.1)
Median (range) duration of follow-up in all patients (months)	3.61 (0.03 - 44.02)	3.75 (0.03 - 41.46)	3.75 (0.03 - 33.41)
Median (range) duration of follow-up in censored patients (months)	27.63 (0.03 - 44.02)	27.55 (0.03 - 41.46)	1.95 (0.03 - 33.18)

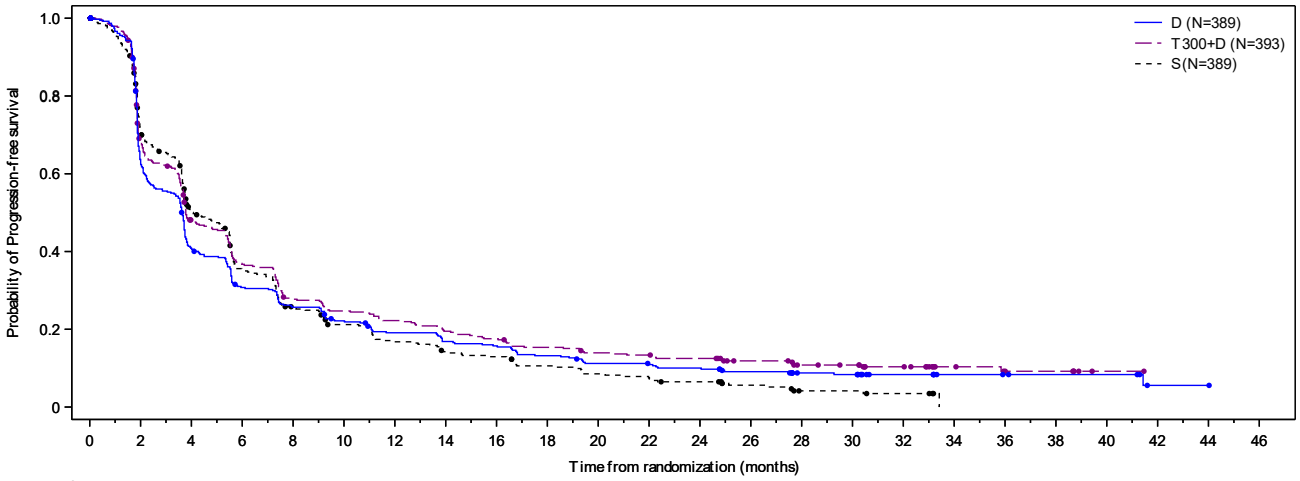
- Calculated using the Kaplan-Meier technique.
- Patients who had not progressed or died, or who progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST 1.1 assessment, or Day 1 if there were no evaluable visits. Patients who have no evaluable visits or baseline data were censored at Day 1 unless they died within 2 visits of baseline. Patients who die without tumour progression will be censored at the time of death.

Progression determined by Investigator assessment. Lost to follow-up is defined as patients who have no RECIST 1.1 progression or death at the time of the DCO and have a termination status of 'Lost to follow-up' from the Disposition module. Withdrawn consent is defined as patients who have no RECIST 1.1 progression or death at the time of DCO and whose termination status is 'Withdrawn consent' on the Disposition module. The analysis methods used to obtain the hazard ratio, confidence interval, and 2-sided p-value are the same as for the primary OS analysis.

A hazard ratio of < 1 favours IO treatment arms to be associated with a longer progression-free survival than sorafenib.

Abbreviations: CI = confidence interval; D = durvalumab monotherapy 1500 mg; Q4W; DCO = data cut-off; ECOG PS, Eastern Cooperative Oncology Group performance status; FAS = Full Analysis Set; IO = immuno-oncology; HBV, hepatitis B virus; HCV, hepatitis C virus; N = total number of patients; n = number of PFS events; PFS = progression-free survival; Q4W = every 4 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1; S = sorafenib 400 mg twice daily; T75+D = tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Figure 20: Kaplan-Meier plot for progression-free survival by investigator assessment according to RECIST 1.1 (FAS)



Number of subjects at risk

D	389	243	155	115	96	81	68	60	56	47	39	37	34	28	21	20	12	7	6	5	5	1	1	0
T300+D	393	262	177	135	101	90	81	71	64	55	49	47	43	35	28	26	19	10	7	6	1	0	0	0
S	389	257	173	118	85	67	53	44	40	31	25	22	18	12	6	6	4	0	0	0	0	0	0	0

Abbreviations: D = durvalumab monotherapy 1500 mg; Q4W; FAS = Full Analysis Set; Q4W = every 4 weeks; N = total number of patients; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1; S = sorafenib 400 mg twice daily; T75+D = tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 28: Progression-free survival (FAS 32w FUP) based on BICR assessments per RECIST 1.1 (DCO 27-AUG-2021)

	Number (%) of subjects			
	Durva 1500 mg (N=236)	Treme 300 mg x1 dose + Durva 1500 mg (N=234)	Treme 75 mg x4 doses + Durva 1500 mg (N=153)	Sora 400 mg BID (N=236)
Total events[a], n (%)	194 (82.2)	172 (73.5)		163 (69.1)
RECIST progression	175 (74.2)	148 (63.2)		137 (58.1)
Target Lesions[b]	106 (44.9)	81 (34.6)		76 (32.2)
Non Target Lesions[b]	101 (42.8)	74 (31.6)		68 (28.8)
New Lesions[b]	50 (21.2)	53 (22.6)		45 (19.1)
Death in the absence of progression	19 (8.1)	24 (10.3)		26 (11.0)
Censored subjects, n (%)	42 (17.8)	62 (26.5)		73 (30.9)
Censored RECIST progression[c]	0	0		1 (0.4)
Censored death[d]	11 (4.7)	17 (7.3)		44 (18.6)
Progression-free at time of analysis	0	0		0
Lost to follow-up	0	0		2 (0.8)
Withdrawn consent	0	0		2 (0.8)
Study completion[e]	31 (13.1)	45 (19.2)		24 (10.2)
Median progression-free survival (months)[f]	3.48	3.65		3.78
95% CI for median progression-free survival[f]	2.17 - 3.68	3.52 - 3.94		3.68 - 5.32
Hazard ratio	1.19	0.96		
95% CI for hazard ratio	0.97 - 1.47	0.77 - 1.19		
2-sided p-value	0.0971	0.6668		
Median (range) duration of follow-up in all subjects (months)	3.07 (0.03 - 19.42)	3.61 (0.03 - 16.59)		3.61 (0.03 - 16.43)
Median (range) duration of follow-up in censored subjects (months)	8.99 (0.03 - 19.42)	9.33 (0.03 - 16.59)		5.49 (0.03 - 13.96)

Progression is determined by BICR, RECIST 1.1. CI=Confidence interval. NR = Not reached. FAS 32w FUP = Full analysis set with opportunity for 32 weeks of follow-up at IA1 DCO.
Lost to follow up is defined as subjects whom have no RECIST 1.1 progression or death at the time of the data cutoff and have a termination status of 'Lost to follow-up' from the Disposition module.
Withdrawn consent is defined as all subjects whom have no RECIST 1.1 progression or death at the time of data cut off and whose termination Status is 'Withdrawn consent' on the Disposition module.
[a] Subjects who have not progressed or died, or who progress or die after two or more missed visits, are censored at the latest evaluable RECIST assessment, or day 1 if there are no evaluable visits. Subjects who have no evaluable visits or do not have baseline data will be censored at study day 1 unless they die within 2 visits of baseline.
[b] Target Lesions, Non Target Lesions and New Lesions are not necessarily mutually exclusive categories. [c] RECIST progression event occurred after 2 or more missed visits after last evaluable RECIST assessment (or randomization).
[d] Death occurred after 2 or more missed visits after last evaluable RECIST assessment (or randomization).
[e] Other recorded on disposition eCRF with specified status of 'Study terminated by sponsor. [f] Calculated using the Kaplan-Meier technique.
The analysis methods used to obtain the hazard ratio, confidence interval and 2-sided p-value are the same as for the primary OS analysis. A hazard ratio < 1 favours IO treatment arms to be associated with a longer progression-free survival than sorafenib.
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PFS by BICR by mRECIST was also performed in the FAS 32w FUP (not shown), and this did not show a statistically significant difference of PFS between the three arms (D vs T300+D vs S) either.

Overall response rate (ORR) and best objective response

Table 29: Objective response rate based on investigator assessment (confirmed responses) according to RECIST 1.1 (FAS)

Treatment arm	N	Number of patients with response [a]	Response rate (%)	Comparison between arms		
				Odds ratio [b]	95% CI	2-sided p-value
D	389	66	17.0	3.80	2.29, 6.57	<0.0001
T300+D	393	79	20.1	4.69	2.85, 8.04	<0.0001
S	389	20	5.1	-	-	-

[a] Responses include only confirmed responses. [b] Comparator arm for the odds ratio is S.

The analysis was performed using a logistic regression model adjusted for treatment with factors for etiology of liver disease, ECOG PS, and MVI. An odds ratio of > 1 favors IO treatment arms.

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; FAS = Full Analysis Set; IO = immuno-oncology; MVI = macrovascular invasion; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 30: Best objective response based on investigator assessment (confirmed response) according to RECIST 1.1 (FAS)

Response status	BOR	Number (%) of patients		
		D (N = 389)	T300+D (N = 393)	S (N = 389)
Response	Total	66 (17.0)	79 (20.1)	20 (5.1)
	Complete response	6 (1.5)	12 (3.1)	0
	Partial response	60 (15.4)	67 (17.0)	20 (5.1)
Non-response	Total	323 (83.0)	314 (79.9)	369 (94.9)
	Stable disease	147 (37.8)	157 (39.9)	216 (55.5)
	Progression	160 (41.1)	141 (35.9)	118 (30.3)
	RECIST progression	143 (36.8)	117 (29.8)	91 (23.4)
	Death	17 (4.4)	24 (6.1)	27 (6.9)
	Not evaluable	16 (4.1)	16 (4.1)	35 (9.0)

Abbreviations: BOR = best objective response; D = durvalumab monotherapy 1500 mg; Q4W; FAS = Full Analysis Set; N = total number of patients; Q4W = every 4 weeks; RECIST 1.1 = Response Evaluation Criteria In Solid Tumours Version 1.1; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 31: Objective response rate based on BICR assessment (confirmed response) according to RECIST 1.1 (FAS 32w FUP) – DCO 27 AUG 2021

	Durva 1500 mg (N=236)	Treme 300 mg x1 dose + Durva 1500 mg (N=234)	Treme 75 mg x4 doses + Durva 1500 mg (N=153)	Sora 400 mg BID (N=236)
Subjects with Objective response, n (%)	36 (15.3)	44 (18.8)		12 (5.1)
Objective response rate (%)	15.3	18.8		5.1
95% exact CI	10.92, 20.49	14.01, 24.41		2.65, 8.71

CI=Confidence interval.
RECIST version 1.1.
Lost to follow up and withdrawn consent are defined as subjects who have no RECIST 1.1 progression or death at the time of the DCO and have a termination status of 'Lost to follow-up' or 'Withdrawn consent,' respectively in the Disposition module. FAS 32w FUP = Full analysis set with opportunity for 32 weeks of follow-up at IA1 DCO.

Table 32: Disagreements between investigator and BICR of RECIST progression per RECIST 1.1 (FAS 32w FUP) – DCO 27 AUG 2021

	Number (%) of subjects				Difference	
	Durva 1500 mg (N=236)	Treme 300 mg x1 dose + Durva 1500 mg (N=234)	Treme 75 mg x4 doses + Durva 1500 mg (N=153)	Sora 400 mg BID (N=236)	Durva 1500 mg - Sora 400 mg BID	Treme 300 mg x1 dose + Durva 1500 mg - Sora 400 mg BID
RECIST progression[a] declared by:						
Investigator and central review	160 (67.8)	138 (59.0)		123 (52.1)		
Progression date agreement (within 2 weeks)	90 (38.1)	61 (26.1)		63 (26.7)		
Progression date >=2 weeks earlier by central review than by Investigator	47 (19.9)	61 (26.1)		46 (19.5)		
Progression date >=2 weeks earlier by Investigator than by central review	23 (9.7)	16 (6.8)		14 (5.9)		
Investigator but not central review	26 (11.0)	36 (15.4)		45 (19.1)		
Central review but not Investigator	15 (6.4)	10 (4.3)		14 (5.9)		
No Progression by both	35 (14.8)	50 (21.4)		54 (22.9)		
Early Discrepancy Rate (EDR)[b]	0.26	0.30		0.35	-0.09	-0.05
Late Discrepancy Rate (LDR)[c]	0.56	0.58		0.50	0.05	0.07

[a] Progression events that do not occur within two visits of the last evaluable assessment (or randomization) are censored.
[b] EDR is the frequency of Investigator declared progressions before central review as a proportion of all Investigator progressions.
[c] LDR is the frequency of Investigator declared progressions after central review as a proportion of all discrepancies.
RECIST version 1.1.

Duration of response and time to response

Table 33: Duration of response and time to onset of objective response in HIMALAYA (final analysis) according to investigator assessment per RECIST 1.1 (FAS)

Study Analysis set (DCO)	**HIMALAYA** **FAS (Final Analysis)**		
Response assessment	**Investigator per RECIST 1.1 [a]**		
	D **(N = 66)**	**T300+D** **(N = 79)**	**S** **(N = 20)**
Patients with objective response, n (%)	38	44	13
DoR from onset of response (months) [b, c]			
25th percentile	7.43	8.54	6.51
Median	16.82	22.34	18.43
75th percentile	NR	NR	25.99
Percentage remaining in response [c]			
At 6 months	81.8	82.3	78.9
At 12 months	57.8	65.8	63.2
TTR from randomisation (months)			
25th percentile	1.87	1.84	1.89
Median	2.09	2.17	3.78
75th percentile	3.98	3.98	8.44

[a] Confirmed responses only.

[b] DoR is the time from the first documentation of CR/PR until the date of progression, death, or the last evaluable RECIST assessment for patients who do not progress.

[c] Calculated using the Kaplan-Meier method.

Abbreviations: CR = complete response; DCO = data cut-off; DoR = duration of response; FAS = full analysis set; N = total number of patients; n = number of patients in a treatment arm; NR = not reached; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; TTR = time to onset of objective response.

Patient-reported outcomes (PROs)

Patient-reported symptoms, function, and health-related quality of life (HRQoL) were collected in the HIMALAYA study using the EORTC QLQ C30 and its HCC module (EORTC QLQ HCC18). At baseline, patient-reported symptoms, functioning, and HRQoL scores were comparable between the HIMALAYA study arms.

Table 34: Summary of change from baseline using MMRM in EORTC QLQ-30 (FAS)

Symptom Scale Item	Statistic	Number (%) of patients			
		D (N = 389)	T300+D (N = 393)	T75+D (N = 153)	S (N = 389)
GHS/QoL					
GHS/QoL	n	282	249	116	254
	Adjusted mean (SE)	-1.8 (1.26)	-5.8 (1.29)	-6.2 (2.04)	NE
	95% CI	-4.30, 0.65	-8.37, -3.32	-10.22, -2.21	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Function					
Physical functioning	n	282	249	116	254
	Adjusted mean (SE)	-0.9 (1.16)	-2.7 (1.19)	-4.4 (1.87)	NE
	95% CI	-3.18, 1.37	-5.05, -0.39	-8.05, -0.71	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Symptoms					
Fatigue	n	282	249	116	254
	Adjusted mean (SE)	1.7 (1.40)	1.9 (1.43)	4.3 (2.27)	NE
	95% CI	-1.09, 4.43	-0.91, 4.72	-0.14, 8.75	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Appetite loss	n	282	249	116	254
	Adjusted mean (SE)	3.8 (1.62)	1.7 (1.65)	2.8 (2.63)	NE
	95% CI	0.64, 7.00	-1.58, 4.91	-2.36, 7.97	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Nausea	n	282	249	116	254
	Adjusted mean (SE)	1.2 (1.18)	0.7 (1.20)	3.1 (1.91)	NE
	95% CI	-1.16, 3.47	-1.64, 3.08	-0.61, 6.87	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Diarrhea	n	282	249	116	254
	Adjusted mean (SE)	1.2 (1.43)	-1.0 (1.45)	5.7 (2.31)	NE
	95% CI	-1.62, 3.97	-3.83, 1.86	1.20, 10.28	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-

The analysis set includes a subset of the FAS with an evaluable baseline assessment and at least 1 evaluable post-baseline assessment. Change from baseline is derived using a MMRM analysis of all the post-baseline scores for each visit. The model includes treatment, visit, and treatment by visit interaction as explanatory variables and the baseline score as a covariate.

All scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. A high score for functional scales (physical, role, emotional, cognitive, social) and global health status/QoL represents a high functioning/QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

Adjusted mean: adjusted mean change from baseline.

95% CI: 95% CI for adjusted mean change.

Estimated difference: overall estimate of the treatment difference between D (monotherapy or combination therapy) and S.

CI, confidence interval; D, durvalumab monotherapy 1500 mg; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire; FAS, Full Analysis Set; MMRM, mixed-effect model for repeated measurement; N, number of patients in treatment arm; NE, not evaluable; QoL, Quality of Life; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SE, standard error; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 35: Summary of change from baseline in EORTC QLQ-HCC19 symptoms (FAS)

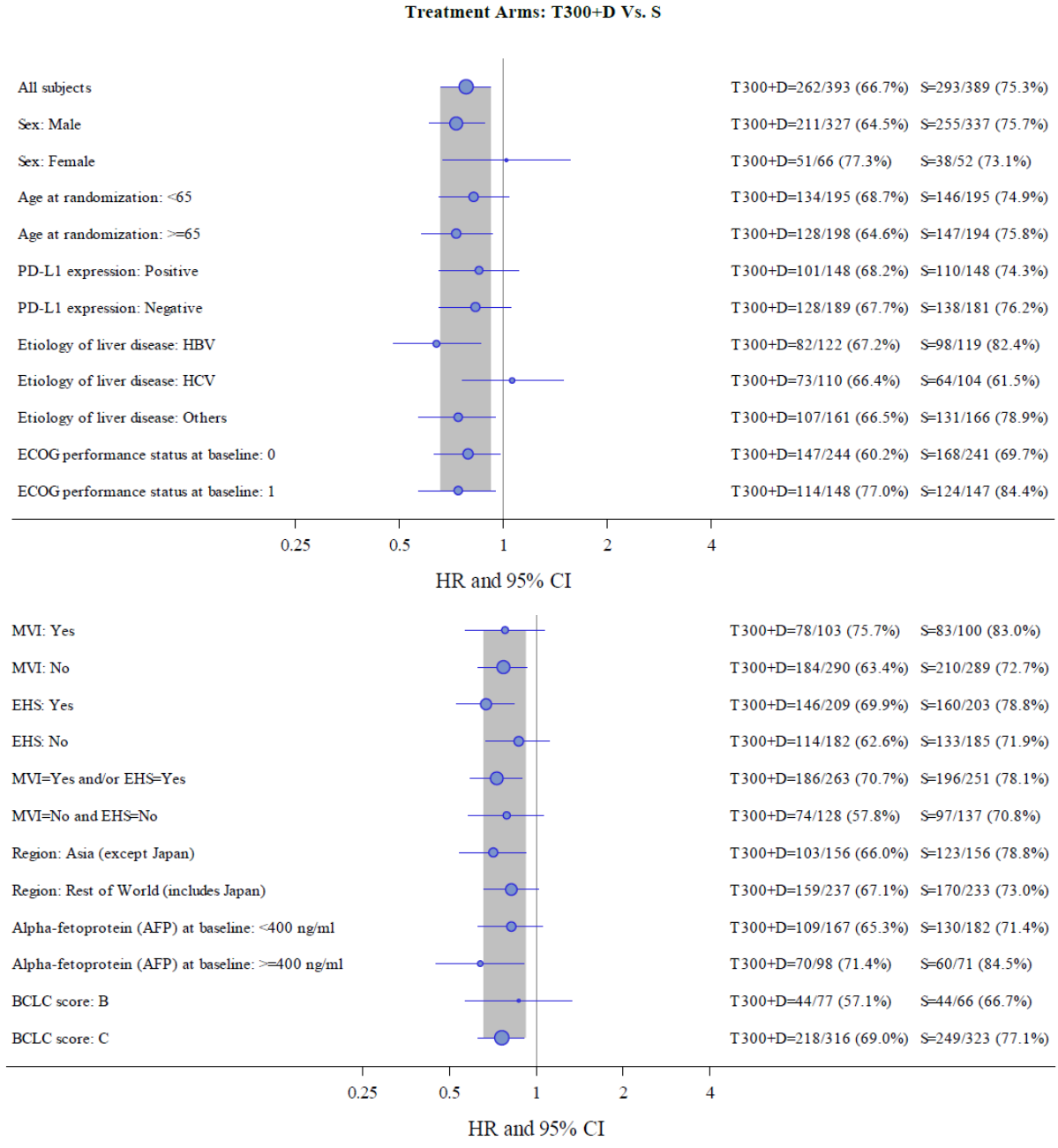
Symptom Scale Item	Statistic	Number (%) of patients			
		D (N= 389)	T300+D (N= 393)	T75+D (N = 153)	S (N= 389)
Abdominal swelling	n	280	238	112	253
	Adjusted mean (SE)	1.0 (1.32)	-0.1 (1.37)	-0.7 (2.15)	NE
	95% CI	-1.64, 3.56	-2.84, 2.55	-4.93, 3.52	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Abdominal pain	n	280	238	112	253
	Adjusted mean (SE)	0.6 (1.49)	-1.4 (1.54)	-0.5 (2.42)	NE
	95% CI	-2.30, 3.53	-4.41, 1.62	-5.29, 4.20	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Shoulder pain	n	280	238	112	253
	Adjusted mean (SE)	-2.4 (1.51)	-1.7 (1.56)	-4.8 (2.46)	NE
	95% CI	-5.35, 0.59	-4.75, 1.35	-9.66, 0.01	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-

EORTC Score Interpretation: All scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. A high score for functional scales (physical, role, emotional, cognitive, social) and global health status/QoL represents a high functioning/QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.
CI, confidence interval; D, durvalumab monotherapy 1500 mg; EORTC QLQ-HCC18, European Organization for Research and Treatment of Cancer 18-item hepatocellular cancer health-related quality of life questionnaire; FAS, Full Analysis Set; N, number of patients in treatment arm; NE, not evaluable; QoL, Quality of Life; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SE, standard error; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.
Source: Table 14.2.9.1.

- **Ancillary analyses**

Subgroup analyses

Figure 21: Forest plots of overall survival, subgroup analysis, FAS, DCO 27 AUG 2021



Hazard ratio and 95% CI.
A hazard ratio <1 implies a lower risk of death for the Treme 300 mg x 1 dose + Durva 1500 mg treatment arm.
For analysis methods, refer to Table 14.2.1.3.
Subgroup analyses for stratification factors, etiology of liver disease (HBV versus HCV versus others) and macro-vascular invasion (yes versus no) are performed using values collected from the pathology at screening eCRF. Others (for etiology of liver disease) is defined as no active viral hepatitis identified.
Values of ECOG are obtained from performance status eCRF.
Size of circle is proportional to the number of events.
Grey band represents the 95% confidence interval for the overall (all subjects) hazard ratio.
D = Durva 1500 mg,T300+D = Treme 300 mg x1 dose + Durva 1500 mg, S = Sora 400 mg BID
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Abbreviations: AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; FAS = full analysis set; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard ratio; MVI = macrovascular invasion; OS = overall survival; PD-L1 = programmed cell death ligand-1; TIP = tumour immune percentage.

Table 36: Subgroup analysis of overall survival by PD-L1 expression level, HIMALAYA (FAS)

PD-L1 expression subgroup	Treatment arm	N	Number (%) of events	Comparison to S	
				HR [a]	95% CI
Positive: TIP ≥ 1% [b]	D	154	107 (69.5)	0.87	0.66, 1.13
	T300+D	148	101 (68.2)	0.85	0.65, 1.11
	S	148	110 (74.3)	–	–
Negative: TIP < 1% [b]	D	190	141 (74.2)	0.93	0.73, 1.17
	T300+D	189	128 (67.7)	0.83	0.65, 1.05
	S	181	138 (76.2)	–	–
Positive: TIP ≥ 5% [c]	D	70	47 (67.1)	0.90	0.59, 1.38
	T300+D	67	44 (65.7)	0.94	0.60, 1.47
	S	66	46 (69.7)	–	–
Negative: TIP < 5% [c]	D	274	201 (73.4)	0.92	0.75, 1.12
	T300+D	270	185 (68.5)	0.84	0.69, 1.03
	S	263	202 (76.8)	–	–
Positive: TIP ≥ 10% [c]	D	37	26 (70.3)	0.88	0.47, 1.66
	T300+D	34	21 (61.8)	0.88	0.44, 1.79
	S	33	21 (63.6)	–	–
Negative: TIP < 10% [c]	D	307	222 (72.3)	0.89	0.74, 1.08
	T300+D	303	208 (68.6)	0.83	0.69, 1.01
	S	296	227 (76.7)	–	–

[a] HR < 1 favors the IO treatment arm.

[b] HR and 95% CI were estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and using the Efron method to control for ties.

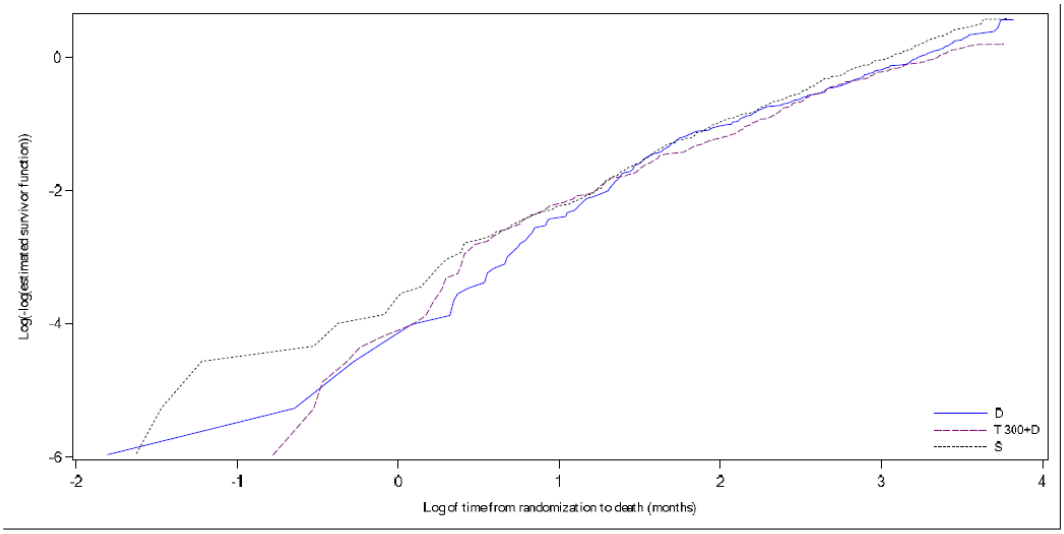
[c] HR and 95% CI were estimated from a Cox proportional hazards model adjusting for treatment, etiology of liver disease (HBV vs HCV vs others), ECOG performance status (0 vs 1), and MVI (yes vs no).

PD-L1 expression level is based on the TIP score method as: PD-L1 Positive (TIP ≥ 1%) or PD-L1 Negative (TIP < 1%). The TIP 1% cut-off is the only validated cut-off at which HIMALAYA patient samples were read. Additional PD-L1 TIP cut-offs of 5% and 10% should be interpreted in an exploratory manner.

Abbreviations: CI = confidence interval; D = durvalumab monotherapy 1500 mg Q4W; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; HR = hazard ratio; IO, immuno-oncology; MVI = macrovascular invasion; PD-L1 = programmed cell death ligand 1; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TIP = tumour and immune cell positivity.

Sensitivity analyses

Figure 22: Complementary log-log(event) vs log(time) to assess assumptions of proportionality of hazards for OS (FAS)



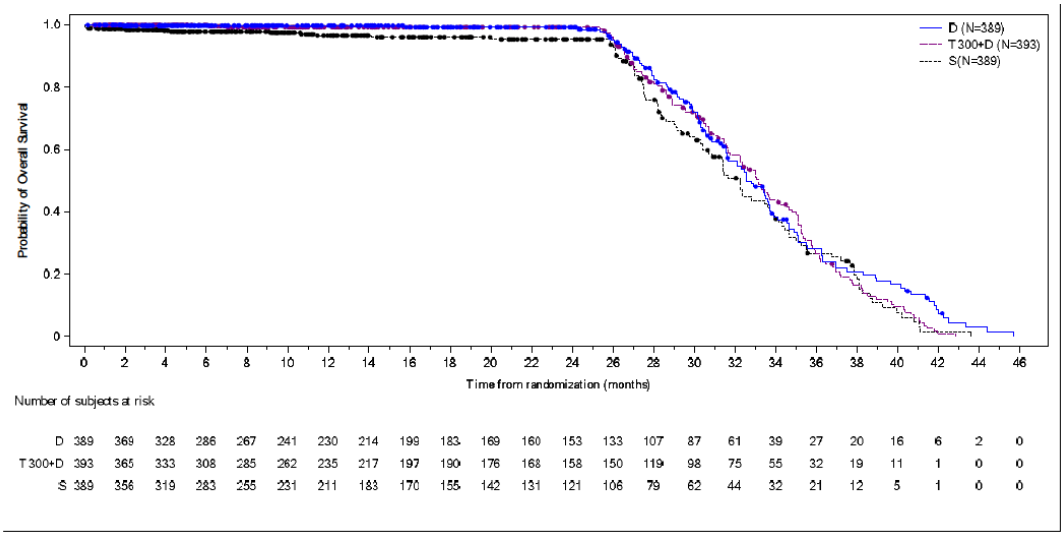
D, durvalumab monotherapy 1500 mg Q4W; FAS, Full Analysis Set; Q4W, every 4 weeks; OS, Overall Survival; S, sorafenib 400 mg twice daily; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Source: Figure 14.2.1.9.

Inversed Censoring

The reverse KM survival curve shown in Figure is constructed by reversing the "censor" and "event" of the standard KM curve (data not shown). Figure 8 shows that the curves for arms D, T300+D and S remain close to 1 for the first 26 months post randomisation, indicating nearly complete follow-up for this period of time. No meaningful difference in the length of follow-up among arms D, T300+D and S can be seen in the figure, which is also evidenced by similar median follow-up times in censored patients (D: 31.61 months, T300+D: 32.36 months, and S: 30.36 months).

Figure 23: Overall survival, sensitivity analysis, KM plot with inversed censoring indicators (FAS)



D, durvalumab monotherapy 1500 mg Q4W; FAS, Full Analysis Set; KM, Kaplan Meier; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.
Source: Figure 14.2.1.1.3.

Contribution of components

Table 37: Data From HIMALAYA (pivotal study) and Study 22 (supportive study) relevant to the recommended T300+D regimen in patients with uHCC

Study Analysis set	**HIMALAYA** **FAS (Final Analysis)**		**Study 22 (Parts 2 and 3)** **FAS (Final Analysis)**		
	D **(N = 389)**	**T300+D** **(N = 393)**	**D** **(N = 104)**	**T300+D** **(N = 75)**	**T** **(N = 69)**
Median OS (months) [a]	16.56	16.43	12.91	17.05	17.05
95% CI for median OS	14.06, 19.12	14.16, 19.58	8.74, 16.79	10.55, 22.83	11.33, 20.24
HR (95% CI) for T300+D vs D	0.90 (0.76, 1.07)		–	–	–
OS rate at 12 months, % [a]	59.3	60.2	50.4	57.6	59.8
OS rate at 18 months, % [a]	47.4	48.7	34.0	47.8	43.3
OS rate at 24 months, % [a]	39.6	40.5	26.2	38.3	30.9
OS rate at 36 months, % [a]	24.7	30.7	–	–	–
Tumour response assessment	**Investigator assessment per RECIST 1.1**		**BICR per RECIST 1.1**		
	D **(N = 389)**	**T300+D** **(N = 393)**	**D** **(N = 104)**	**T300+D** **(N = 75)**	**T** **(N = 69)**
Median PFS [a]	3.65	3.78	2.07	2.17	2.69
95% CI for median PFS	3.19, 3.75	3.68, 5.32	1.84, 2.86	1.91, 5.42	1.87, 5.29
Progression-free at DCO n (%)	32 (8.2)	49 (12.5)	8 (7.7)	11 (14.7)	4 (5.8)
ORR (%) [b]	17.0	20.1	11.5	24.0	7.2
Complete Response [b]	6 (1.5)	12 (3.1)	0	1 (1.3)	0
Partial Response [b]	60 (15.4)	67 (17.0)	12 (11.5)	17 (22.7)	5 (7.2)

Table 37: Data From HIMALAYA (pivotal study) and Study 22 (supportive study) relevant to the recommended T300+D regimen in patients with uHCC

Study Analysis set	HIMALAYA FAS (Final Analysis)		Study 22 (Parts 2 and 3) FAS (Final Analysis)		
DCR (%) [c]	54.8 [d]	60.1 [d]	37.5 [b]	45.3 [b]	49.3 [b]
Median DoR (months) [d, e]	16.82	22.34	14.95	18.43	23.95
Median TTR (months) [d, f]	2.09	2.17	3.65	2.28	1.81

[a] Calculated using the Kaplan-Meier method.

[b] Confirmed responses only.

- Disease control = complete response + partial response + stable disease.

[d] Response did not require confirmation.

[e] DoR is the time from the first documentation of CR/PR until the date of progression, death, or the last evaluable RECIST assessment for subjects that do not progress.

[f] TTR is the time to onset of confirmed response from from randomisation (HIMALAYA; Study 22 Parts 2A and 3) or from treatment allocation (Study 22 Part 2B).

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCO = data cut-off; DCR = disease control rate; DoR = duration of response; FAS = Full Analysis Set; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; TTR = time to onset of objective response; uHCC = unresectable hepatocellular carcinoma.

Additional sensitivity analyses following inaccurate survival information at site 6208

GCP findings from the PMDA concerning the HIMALAYA trial, indicated that survival information was inaccurate for 4 subjects at site 6208. Following question regarding this issue, the supplementary analysis of OS with the corrected data was provided.

In total the site 6208 enrolled 14 patients in HIMALAYA study. Overall survival data for 4/14 enrolled patients was affected, and no discrepancies in survival information were identified for the remaining 10/14 patients after onsite review.

Table 38: **Overall survival data for affected 4/14 enrolled patients at site 6208**

Subject Number	Randomisation Date (mm/dd/yyyy)	Treatment Arm	Survival Status/Date of Death (mm/dd/yyyy)				Variance (days): CRF vs death certificate
			CRF	Source document/medical record	Local oncology registry	Death certificate	
	01/26/2018	S	03/05/2018	N/A	03/04/2018	03/04/2018	1
	04/05/2018	S	Alive on 09/03/2021	Alive on 09/03/2021	08/12/2021	08/12/2021	22
	07/15/2019	T300+D	08/05/2019	08/05/2019	07/25/2019	07/25/2019	11
	07/16/2019	D	04/23/2020	04/23/2020	07/23/2019	07/23/2019	275

D = durvalumab 1500mg Q4W; N/A = not applicable; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg for a single dose and durvalumab 400 mg Q4W; T75+D = tremelimumab 75 mg Q4W x 4 doses and durvalumab 1500 mg Q4W.

Table 39: Sensitivity analysis of OS by removing site 6208 (full analysis set)

	Number (%) of subjects			
	D (N=385)	T300+D (N=391)	T75 +D (N=151)	S (N=383)
Deaths, n (%)	277 (71.9)	260 (66.5)	121 (80.1)	288 (75.2)
Censored subjects, n (%)	108 (28.1)	131 (33.5)	30 (19.9)	95 (24.8)
Median overall survival (months)[a]	16.56	16.66	16.56	13.77
95% CI for median overall survival[a]	14.06 - 19.12	14.19 – 20.37	12.71 - 19.78	12.25 - 16.13
Hazard ratio[b]	0.87	0.77		-
95% CI for hazard ratio[b]	0.73 - 1.02	0.65 - 0.91		-

Calculated using the Kaplan-Meier technique.
The analysis was performed using a Cox proportional hazards model adjusting for treatment, etiology of liver disease (hepatitis B virus vs. hepatitis C virus vs. others), Eastern Cooperative Oncology Group performance status (0 vs. 1), and macro-vascular invasion (yes vs. no). Values of the variables used for adjustment were obtained from the Interactive Voice Response System.
Note: Table does not include subjects from Russian site 6208. A hazard ratio < 1 favors IO treatment arms to be associated with a longer overall survival than sorafenib. A hazard ratio < 1 favors IO treatment arms to be associated with a longer overall survival than sorafenib.
CI = confidence interval; D = durvalumab 1500 mg Q4W; IO = immuno-oncology; NR = not reached; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg for a single dose and durvalumab 400 mg Q4W; T75+D = tremelimumab 75 mg Q4W × 4 doses and durvalumab 1500 mg Q4W.

Figure 24: KM plot of OS by removing site 6208 (full analysis set)

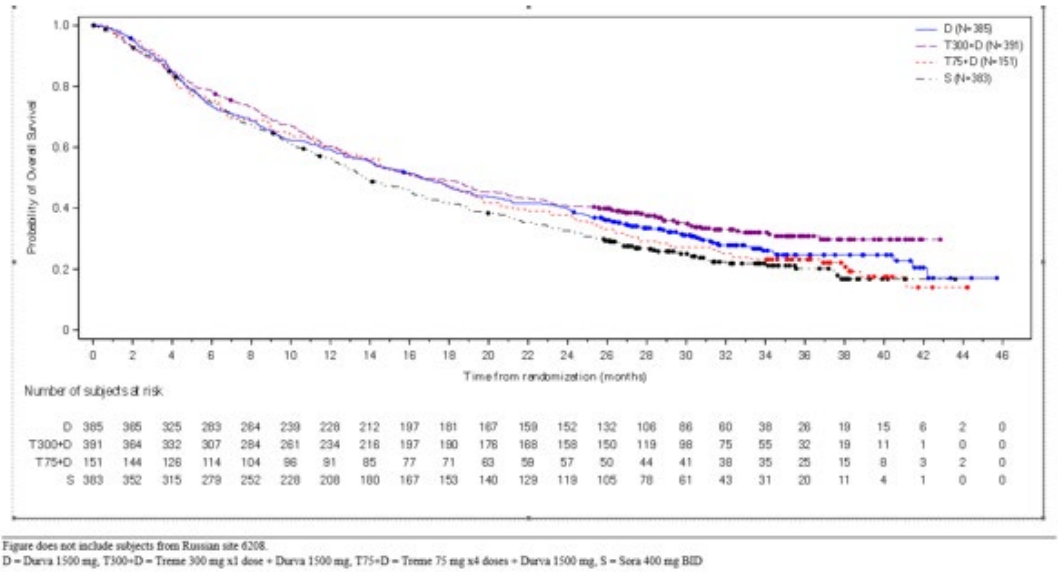


Figure does not include subjects from Russian site 6208.
D = Durva 1500 mg, T300+D = Treme 300 mg x1 dose + Durva 1500 mg, T75+D = Treme 75 mg x4 doses + Durva 1500 mg, S = Sora 400 mg BID

The applicant has provided the requested sensitivity analysis, using the most conservative approach by removing all 14 patients enrolled at this site and this showed that the OS HR was of 0.77 (95%CI: 0.65, 0.91) for T300+D vs. S comparison, which is the main scope of the current procedure. There is overall consistency between the sensitivity analysis and the primary analysis, which is considered reassuring.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

- **Table 40: Summary of efficacy for trial HIMALAYA**

Title: A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma (HIMALAYA)			
Study identifier	EudraCT number: 2016-005126-11, NCT number: NCT03298451		
Design	Randomised, open-label, multicentre Phase III study		
	Duration of main phase:	Not applicable	
	Duration of Run-in phase:	Not applicable	
	Duration of Extension phase:	Not applicable	
Hypothesis	Superiority for T300+D vs S		
	D	Durvalumab 1500 mg Q4W until PD or unacceptable toxicity, N=389	
	T300+D	Tremelimumab 300 mg as single dose plus durvalumab 1500 mg Q4W followed by durvalumab monotherapy 1500 mg Q4W until PD or unacceptable toxicity, N=393	
	S	Sorafenib monotherapy 400 mg twice daily until PD or unacceptable toxicity, N=389	
	T75+D	Tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W, followed by durvalumab monotherapy 1500 mg Q4W. Arm closed prematurely, results not shown.	
Endpoints and definitions	Primary endpoint	OS	OS of T300+D vs S
	Key Secondary endpoints	OS	Non-Inferiority of D vs S and superiority of D vs S.
	Other secondary endpoints	PFS, ORR, DoR	Progression-free survival, overall response rate and duration of response
Database lock	27 August 2021		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat, final analysis			
Descriptive statistics and estimate variability	Treatment group	D	T300+D	S
	Number of subjects	389	393	389
	OS (Months)	16.56	16.43	13.77
	95%CI	14.06; 19.12	14.16; 19.58	12.25; 16.13
	PFS by INV (months)	3.65	3.78	4.07
	95%CI	3.19; 3.75	3.68; 5.32	3.75; 5.49
	ORR (%)	17	20.1	5.1
	DoR (%)	16.82	22.34	18.43

Effect estimate per comparison	Primary endpoint OS	Comparison groups	T300+D vs S
		Stratified HR	0.78
		95% CI	0.66, 0.92
		P-value	0.0035
	Secondary	Comparison groups	D vs S (non-inferior)

Title: A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma (HIMALAYA)			
Study identifier	EudraCT number: 2016-005126-11, NCT number: NCT03298451		
	endpoint OS	Stratified HR	0.86
		95.67% CI	0.73; 1.03*
		P-value	NA
	Secondary endpoint OS	Comparison groups	D vs S (superior)
		Stratified HR	0.86
		95.67% CI	0.73; 1.03
		P-value	0.0674 (NS)
Notes	*below prespecified clinical NI (non-inferiority) margin of 1.08		

2.6.5.3. Clinical studies in special populations

Table 41: Patient counts by age category-controlled trial versus non-controlled trial (full analysis set)

Age	**Controlled trials** (N=1324)	**Non-controlled trials (N=332)**
< 65	667 (50.4)	175 (52.7)
65-74	467 (35.3)	108 (32.5)
75-84	181 (13.7)	46 (13.9)
85+	9 (0.7)	3 (0.9)

Note: Controlled trial includes only HIMALAYA and non-controlled trail includes only Study 22.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

PD-L1 testing

The relationship between PD-L1 expression level and clinical outcomes (eg, OS, PFS, and ORR) was investigated, and the results are presented by treatment arm.

PD-L1 expression was determined by the analytically validated VENTANA PD-L1 (SP263) assay using the TIP score method. The TIP score was defined as the total percentage of the tumour area covered by tumour cells with PD-L1 membrane staining at any intensity and/or tumour-associated immune cells with any pattern of PD-L1 staining at any intensity. Two PD-L1 expression subgroups were defined:

- PD-L1 TIP ≥ 1% (Positive): PD-L1 staining of any intensity in tumour cell membranes and/or tumour-associated immune cells covering ≥ 1% of the tumour area
- PD-L1 TIP < 1% (Negative): PD-L1 staining of any intensity in tumour cell membranes and/or tumour-associated immune cells covering < 1% of the tumour area.

Collection of patient samples for analysis of PD-L1 expression

Patients were strongly encouraged to provide a fresh tissue biopsy for the purpose of PD-L1 expression analyses at screening. The tumour specimen submitted to the central laboratory for PD-L1 expression analysis should be of sufficient quantity and quality (with pathology quality control) to allow for PD-L1 immunohistochemical (IHC) analyses. Newly acquired or archived specimens with limited tumour content and fine needle aspirates were not acceptable for defining tumour PD-L1 expression.

- MANDATORY: Provision of a tumour biopsy, formalin fixed and embedded in paraffin, for the purpose of PD-L1 expression analyses (and for enabling exploratory analyses as described in the proceeding section). A newly acquired tumour biopsy (<3 months) was strongly preferred; however, if not feasible with an acceptable clinical risk, an archival sample taken ≤3 years prior

to screening could have been submitted. Note: the tumour biopsy was optional for the China cohort.

- Samples should have been collected via an image-guided core needle (at least 18 gauge) or an excisional archival tumour biopsy sample. Where institutional practice, in this setting, uses a smaller gauge needle, samples should have been submitted with tissue adequate to ensure that a valid result can be achieved (ie, total tissue quantity submitted should have been similar to core needle or excisional biopsy requirements).
- When fresh tissue was obtained, 2 cores should have been placed in formalin and processed to a single paraffin-embedded block. It was anticipated that 4 passes of an 18 gauge core needle would provide sufficient tissue for both PD-L1 analyses and exploratory analyses as described below. Tumour lesions used for fresh biopsies should not have been the same lesions used as RECIST 1.1 TLs, unless there were no other lesions suitable for biopsy, and in this instance, only core needle (not excisional/incisional) biopsy was allowed. For patients with a single TL, if screening biopsy was collected prior to screening imaging for baseline tumour assessment, allowed approximately 2 weeks before imaging scans were acquired.
- OPTIONAL: Additional archived tumour tissue block (formalin fixed and paraffin embedded), where such samples exist in a quantity sufficient to allow for analysis. Tumour tissue block was preferred. If a tissue block was unavailable, unstained sections from the tissue block may be submitted.
- OPTIONAL: Tumour biopsy at the time of progression was requested
- OPTIONAL: Additional tumour biopsies collected as part of clinical care (eg, for mixed responses or upon PD) could have been submitted for further analysis.
- Additional archived tissue not intended for PD-L1 testing, and optional biopsies obtained at the time of progression or part of clinical care were not to be collected in China. Additionally, China study sites were not to submit tumour tissue blocks and only unstained sections from the tissue block were to be submitted for analysis.
- The Ventana SP263 IHC assay was to be used to determine PD-L1 expression in all available specimens. To meet the requirement of the United States Food and Drug Administration for approval of a companion diagnostic, sections of the tumour were to be retained at Ventana and/or at the Investigation Use only testing laboratory for potential additional studies to support potential test approval.

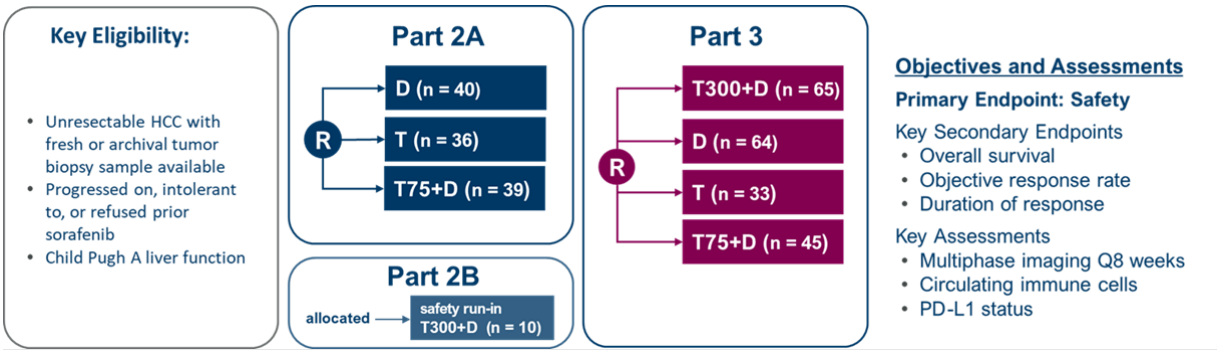
The Ventana SP163 PD-L1 assay was validated as an appropriate method for the selection of patients who would obtain benefit from durvalumab monotherapy in the PACIFIC trial, whose outcome led to the PD-L1 restricted indication of this anti-PD-L1 product in the locally advanced unresectable NSCLC setting after chemoradiotherapy. Thus, the choice of PD-L1 assay is acceptable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.6. Supportive study – Study 22

Figure 25: Study 22 study design



Following protocol amendment 5, enrollment into the T75+D arm in Part 3 was closed. Patients already randomised to T75+D could continue on assigned study treatment (provided the Investigator and patient thought it in the best interests of the patient) until confirmed progressive disease or any other discontinuation criteria were met. Weight-based dosing regimen was used in Parts 2A; fixed-dosing regimens were used in Part 2B and Part 3 (durvalumab only).

Abbreviations: D = durvalumab 1500 mg (20 mg/kg) Q4W; DoR, duration of response; HCC = hepatocellular carcinoma; n = number of subjects in a treatment arm; PD-L1 = programmed cell death ligand-1; OS, overall survival; ORR, objective response rate; Q8W, every 8 weeks; Q4W = every 4 weeks; Q8 = every 8 weeks; Q12W = every 12 weeks; T = tremelimumab 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W; T300+D = tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W; T75+D = tremelimumab 75 mg (1 mg/kg) Q4W × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W, followed by durvalumab 1500 mg (20 mg/kg) Q4W.

Study 22 was a randomised, multicentre, international, open-label, multipart study designed to evaluate the safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab, in patients with advanced HCC. The study was comprised of multiple parts but only Parts 2 and 3 of Study 22 are relevant for this procedure.

The primary objectives of Parts 2 and 3 were to:

- Assess the safety and tolerability of durvalumab and tremelimumab administered as monotherapy and durvalumab administered in combination with tremelimumab to subjects with advanced HCC.

The secondary objectives were to:

- Evaluate the efficacy of durvalumab and tremelimumab administered as monotherapy and durvalumab in combination with tremelimumab in subjects with advanced HCC.
- Evaluate the relationship between baseline and pharmacodynamic biomarkers and measures of clinical outcomes of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab in subjects with advanced HCC.

The final analysis of data in all study parts was performed 12 months after the first dose of investigational product was given to the last patient enrolled in the study (DCO: 06 November 2020).

Patient population

In Study 22, eligible patients were aged ≥ 18 years (≥ 20 years for Japanese patients) with advanced HCC confirmed pathologically or with non-invasive methods. This study enrolled immunotherapy-naïve patients who progressed on, were intolerant to, or refused treatment with sorafenib or another approved VEGFR TKI. Patients with co-infection of viral hepatitis B and hepatitis C, active or prior documented GI bleeding within 12 months, ascites requiring non-pharmacologic intervention within 6 months, hepatic encephalopathy within 12 months before the start of treatment, and active or prior documented autoimmune or inflammatory disorders were excluded.

In Part 2A of Study 22, eligible patients were randomised in a 1:1:1 ratio to each of the following 3 treatment arms: D: Durvalumab 20 mg/kg Q4W; T: Tremelimumab 10 mg/kg Q4W × 7 doses followed by Q12W; T75+D: Tremelimumab 1 mg/kg Q4W × 4 doses + durvalumab 20 mg/kg Q4W, followed by durvalumab 20 mg/kg Q4W

Part 2B was a safety run-in for the combination regimen consisting of a single, priming dose of tremelimumab (300 mg) added to durvalumab Q4W. Part 3 was a dose expansion cohort of patients enrolled in Parts 2A and B. Eligible patients were randomised in a 2:2:1:2 ratio to each of the following 4 treatment arms: D: Durvalumab 1500 mg (20 mg/kg) Q4W; T300+D: Tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W; T: Tremelimumab 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W; T75+D: Tremelimumab 75 mg (1 mg/kg) Q4W× 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W, followed by durvalumab 1500 mg (20 mg/kg) Q4W.

In Part 2A, patients were stratified based on viral status (uninfected, HCV infected, or HBV infected) and PD-L1 expression (positive, negative, or non-evaluable). In Part 3, patients were stratified based on viral status (uninfected, HCV infected, or HBV infected) and sorafenib-based therapy (refusers or all others).

Table 42: Previous disease-related treatment modalities in Parts 2 and 3 (FAS)

	Number (%) of patients				
	D (N = 104)	T300+D (N = 75)	T (N = 69)	T75+D (N = 84)	Total (N = 332)
Systemic therapy [a]	66 (63.5)	55 (73.3)	44 (63.8)	55 (65.5)	220 (66.3)
Carotuximab	1 (1.0)	0	0	0	1 (0.3)
Regorafenib	1 (1.0)	0	0	0	1 (0.3)
Sorafenib	66 (63.5)	55 (73.3)	44 (63.8)	55 (65.5)	220 (66.3)
Radiotherapy	16 (15.4)	22 (29.3)	15 (21.7)	22 (26.2)	75 (22.6)
Cancer-related surgery	37 (35.6)	34 (45.3)	23 (33.3)	37 (44.0)	131 (39.5)
Other	49 (47.1)	25 (33.3)	31 (44.9)	39 (46.4)	144 (43.4)

[a] Based on World Health Organization Drug Global B3-format (September 2020).

D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; FAS, Full Analysis Set; Q4W, every 4 weeks; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.

Results

A total of 326 (98.2%) patients in the FAS of Parts 2 and 3 received study treatment. At the final DCO, 93.3% of patients across all treatment arms discontinued study treatment. The most frequently reported reason for discontinuing study treatment was HCC disease progression in 66.6% of patients; 11% of patients discontinued due to AEs. The rate of study treatment discontinuation due to PD or AEs was similar across the T300+D and D treatment arms.

The number of patients in Parts 2 and 3 with important protocol deviations with the potential to affect the analyses was low (13 patients overall [3.9%]).

For patient demographics and disease characteristics, please refer to Table and **Error! Reference source not found.** in the Results section above (2.6.5.2.).

Table 43: Overall survival in Parts 2 and 3 (FAS)

	D (N = 104)	T300+D (N = 75)	T (N = 69)	T75+D (N = 84)
Median OS (months) [a]	12.91	17.05	17.05	11.30
95% CI for median OS [a]	8.74-16.79	10.55-22.83	11.33-20.24	8.38-14.95
Deaths, n (%)	78 (75.0)	49 (65.3)	55 (79.7)	64 (76.2)
Censored patients, n (%)	26 (25.0)	26 (34.7)	14 (20.3)	20 (23.8)
Still in survival follow-up [b]	20 (19.2)	23 (30.7)	12 (17.4)	15 (17.9)
Terminated prior to death [c]	6 (5.8)	3 (4.0)	2 (2.9)	5 (6.0)
Lost to follow-up	0	1 (1.3)	0	2 (2.4)
Withdrawn consent	3 (2.9)	2 (2.7)	2 (2.9)	2 (2.4)
Other	3 (2.9) [d]	0	0	1 (1.2) [e]
OS rate at 12 months, % [a]	50.4	57.6	59.8	49.4
95% CI for OS rate at 12 months [a]	40.3-59.7	45.5-68.0	47.1-70.4	38.1-59.7
OS rate at 18 months, % [a]	34.0	47.8	43.3	35.5
95% CI for OS rate at 18 months [a]	24.9-43.3	35.9-58.7	31.3-54.7	25.2-45.9
OS rate at 24 months, % [a]	26.2	38.3	30.9	30.3
95% CI for OS rate at 24 months [a]	17.9-35.3	26.9-49.6	20.3-42.2	20.7-40.6
Duration of follow-up in censored patients (months), median (range) [f]	23.18 (1.84-44.29)	24.61 (0.95-35.58)	31.03 (1.81-44.02)	29.82 (0.03-43.14)

[a] Calculated using the Kaplan-Meier technique.

[b] Includes patients known to be alive at the data cut-off.

[c] Includes patients with unknown survival status who terminated study participation and patients who were lost to follow-up.

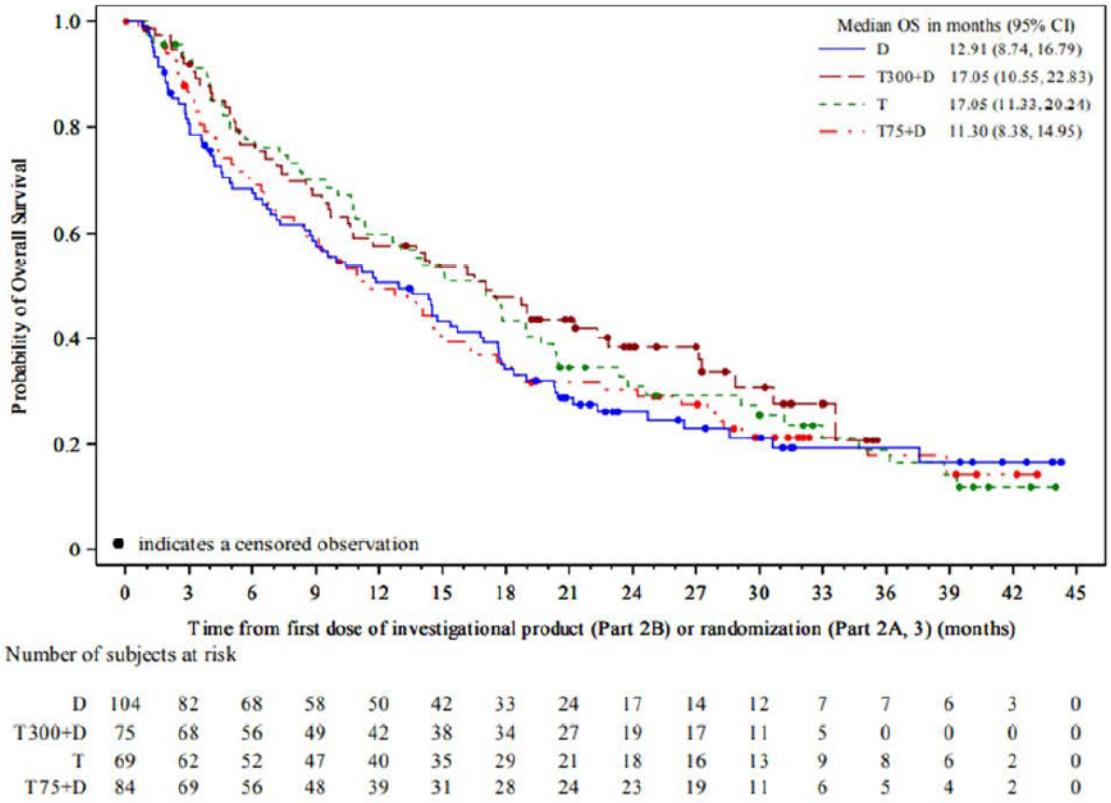
[d] 'Other' reasons (1 patient each): psychiatric issues and study compliance, adverse event, and patient did not receive treatment.

[e] 'Other' reason: patient did not receive treatment.

[f] Median for duration of follow-up is the arithmetic median. Duration of follow-up was calculated from date of randomization (Part 2A, Part 3) or date of first study treatment dose (Part 2B).

CI, confidence interval; D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; FAS, Full Analysis Set; OS, overall survival; Q4W, every 4 weeks; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.

Figure 26: Kaplan-Meier plot of overall survival in Parts 2 and 3 (FAS)



CI, confidence interval; D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; FAS, full analysis set; OS, overall survival; Q4W, every 4 weeks; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.
Source: Figure 14.2.1.

Table 44: Confirmed objective response rate in parts 2 and 3 based on BICR according to RECIST 1.1 (FAS)

	D (N = 104)	T300+D (N = 75)	T (N = 69)	T75+D (N = 84)
Patients with objective response, n (%) [a]	12 (11.5)	18 (24.0)	5 (7.2)	8 (9.5)
ORR (%)	11.5	24.0	7.2	9.5
95% exact CI	6.1, 19.3	14.9, 35.3	2.4, 16.1	4.2, 17.9

[a] Patients with confirmed complete response or confirmed partial response.

BICR, blinded independent central review; CI, confidence interval; D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; FAS, Full Analysis Set; ORR, objective response rate; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.

Table 45: Duration and onset of objective response in patients with confirmed objective response in parts 2 and 3 based on BICR according to RECIST 1.1 (FAS)

	D (N = 104)	T300+D (N = 75)	T (N = 69)	T75+D (N = 84)
Number of patients with objective response, n (%)	12 (11.5)	18 (24.0)	5 (7.2)	8 (9.5)
Number of responders who subsequently progressed or died, n	6	9	3	4
Duration of response from onset of response (months) [a, b]				
Median	14.95	18.43	23.95	13.21
25th, 75th percentile	8.54, NR	5.59, 23.95	4.07, NR	10.15, NR
Percentage remaining in response [b]				
6 months	83.3	71.8	60.0	87.5
12 months	56.3	64.6	60.0	58.3
Time to onset of response from randomization (Parts 2A and 3)/treatment allocation (Part 2B) (months)				
Median	3.65	2.28	1.81	2.86
25th, 75th percentile	2.71, 5.59	1.81, 3.68	1.81, 1.84	1.84, 3.83

[a] Duration of response is the time from the first documentation of a confirmed complete response/partial response until the date of progression, death, or the last evaluable RECIST assessment.

[b] Calculated using the Kaplan-Meier technique.

BICR, blinded independent central review; D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; FAS, Full Analysis Set; NR, not reached; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.

Overall Survival (Part 2 Only)

A total of 125 patients were randomised/allocated to treatment in Part 2: 40 in the D arm, 10 in the T300+D arm, 36 in the T arm, and 39 in the T75+D arm. At the final DCO, 81.6% of patients in part 2 had died (FAS): 80.0% in the D arm, 70.0% in the T300+D arm, 80.6% in the T arm, and 87.2% in the T75+D arm. The percentage of patients alive at the final DCO and in survival follow-up (including those still receiving study treatment) was highest in the T300+D arm (30.0%) compared to the other 3 arms (10.3% to 17.5%).

The Kaplan-Meier estimate of median OS was highest for patients receiving T300+D (28.06 months) compared to patients receiving D (11.78 months), T (17.05 months), or T75+D (13.34 months).

Overall Survival (Part 3 Only)

Part 3 included the following number of patients per treatment arm: 64 in D arm; 65 in T300+D arm; 33 in T arm; 45 in T75+D arm. Median OS was higher for patients in the T300+D (16.16 months) and T arms (17.54 arms) compared to D (13.57 months) and T75+D (11.30 months).

ADA Response to tremelimumab (in Parts 2 and 3)

At the final DCO, immunogenicity data for tremelimumab were available for 56.9% of patients evaluable for ADA.

ADA prevalence for tremelimumab was 12.7% in the T300+D arm, 15.6% in the T arm, and 7.3% in the T75+D arm and the majority of ADA-positive patients were classified as treatment-emergent ADA positive. ADA incidence for tremelimumab appeared to be numerically higher in the T treatment arm (15.6%) relative to the T300+D (7.3%) and T75+D (7.3%) arms (

Table). However, due to the small number of ADA-positive patients in all treatment arms (≤ 5 in all arms), it is not possible to draw a definitive conclusion.

All 12 of the tremelimumab treatment-emergent ADA positive patients in the study were classified as persistently ADA positive. However, 11 of these were classified as such due to the last ADA assessment being positive, rather than based on the duration of the ADA response being ≥ 16 weeks.

Table 46: Summary of anti-drug antibody responses to tremelimumab in parts 2 and 3 (safety analysis set)

Category, n (%)	T300+D (N = 74)	T (N = 69)	T75+D (N = 82)
Tremelimumab ADA evaluable patients	55 (74.3)	32 (46.4)	41 (50.0)
ADA positive at any visit (ADA prevalence) [a]	7 (12.7)	5 (15.6)	3 (7.3)
Treatment-emergent ADA positive (ADA incidence) [b]	4 (7.3)	5 (15.6)	3 (7.3)
Treatment-boosted ADA [c]	0	1 (3.1)	0
Treatment-induced ADA (Positive post-baseline only)	4 (7.3)	4 (12.5)	3 (7.3)
ADA positive at baseline only	2 (3.6)	0	0
ADA positive post-baseline and positive at baseline	1 (1.8)	1 (3.1)	0
Persistently positive [d]	5 (9.1)	5 (15.6)	3 (7.3)
Transiently positive [e]	0	0	0
nAb positive at any time	5 (9.1)	5 (15.6)	0

Refer to Table 48 for footnote definitions.
ADA, anti-drug antibody; nAb, neutralizing antibody; Q4W, every 4 weeks; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.
Source: Table 14.3.9.2.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the new active substance, tremelimumab (T), in combination with the already approved PD-L1 inhibitor durvalumab (D) for the treatment of unresectable hepatocellular carcinoma (uHCC) is primarily based on the pivotal Himalaya study. This was a randomised, open-label, multicentre Phase III study in patients with uHCC not eligible for locoregional therapy. Patients were recruited from 181 sites across 16 countries, mostly from countries with an EU-like population. No prior systemic therapy was allowed and only patients with mild or no symptoms pertaining to the HCC and/or liver cirrhosis were eligible, which is not considered reflective of the general patient population with uHCC. However, the inclusion and exclusion criteria are reflected in the SmPC section 5.1, so this is acceptable. 1324 patients were randomised to 4 arms, durvalumab monotherapy (D, n=389); tremelimumab single dose 300 mg + durvalumab (T300+D, n=393); Tremelimumab 75 mg x 4 + durvalumab (T75+D, n=153); and sorafenib (S, n=389). Randomisation was stratified according to macrovascular invasion (yes versus no), etiology of liver disease (hepatitis B virus [confirmed HBV] versus hepatitis C virus [confirmed HCV] versus others), and ECOG PS (0 versus 1). The stratification factors are considered clinically relevant as they are important prognostic factors for the outcome of uHCC. Other important prognostic factors could have been added, such as AFP levels; however, considering the size of the pivotal trial, it is considered appropriate to limit the number of stratification

factors to three. Additional supportive evidence of clinical efficacy was provided from study 22, a randomised, phase I/II, open-label study.

The overall design of the pivotal Himalaya study is endorsed as it allows to assess the efficacy of the proposed dosing of tremelimumab single dose 300 mg + durvalumab 1500 mg iv followed by durvalumab monotherapy 1500 mg iv Q4W (T300+D) versus standard of care (Sorafenib - S) in the proposed first-line setting. Moreover, the applicant included a durvalumab monotherapy arm and an arm with another combination regimen of T75+D, which was abolished after some time.

Baseline characteristics for patients included in the Himalaya study showed that the median age in the relevant arms (T300+D vs the S arm vs the T300+D arm of study 22) were 65 vs 64 vs 66 years of age; however, approximately half of the patients were <65 years of age and the vast majority of the patients were male (83.2% vs 86.6% vs 86.7%) and of white (46.3% vs 46% vs 36%) or Asian (49.6% vs 48.6% vs 58.7%) race. Alcohol use was only registered in the pivotal Himalaya study and it is noted that a large proportion was never users (~40%) or former users (~45%). The baseline characteristics are well balanced between the arms, but only approximately 46% of the study population are considered EU like according to region and race characteristics. Moreover, the alcohol use in the study population is considered lower than for the EU population.

Disease characteristics showed that most patients were ECOG PS 0 (~60%) and of advanced Barcelona Clinic Liver Cancer (BCLC) stage C (~80%). Additionally, macrovascular invasion and/or extrahepatic spread was observed for many (~65%). However, the poor prognostic factor of AFP >400 ng/ml was observed in approximately a third of the patients, which is also reflected by the distribution of the Child-Pugh score categories, showing that many of the included patients have a favourable prognosis.

It is noted that only a third of the included patients had tumours that were PD-L1 positive (TIP≥1%) and that there were ~13% of the patients in the D+T containing arms, who had missing data on PD-L1 status. Overall, the important disease characteristics are well distributed between the treatment arms. Regarding the level of poor prognostic factors, it is considered that these are lower than expected for the targeted patient population, which should be kept in mind when interpreting the results of the studies.

The primary objective of the pivotal Himalaya study was to assess superiority of efficacy of T300+D vs standard of care (sorafenib) regarding OS for the ITT population. The two key secondary objectives of the trial were to assess non-inferiority of the efficacy of durvalumab monotherapy versus SoC (sorafenib) regarding OS and superiority of the efficacy of durvalumab monotherapy versus SoC (sorafenib) regarding OS. Other important secondary endpoints are PFS and overall response rate plus duration of response. The current MAA for tremelimumab is based on efficacy results from the primary objective of the pivotal study. The primary objective and key secondary objectives pertain to overall survival, and this is endorsed, considering the targeted patient population and the robustness of OS as an endpoint.

Although it does not preclude a benefit/risk assessment, the overall conduct of the study is considered suboptimal due to the changes in primary endpoints and sample size especially considering the open label design. Additionally, interpretation of radiological assessments of tumour response is hindered because of the lack of blinded central review of the assessments in the final analysis.

Efficacy data and additional analyses

<u>The pivotal Himalaya study:</u>

The primary objective was met as treatment with T300+D showed a statistically significant and clinically relevant improvement in **OS** compared to standard of care, sorafenib. Median OS was improved from 13.77 months to 16.43 months, HR 0.78 (96.02% CI: 0.65, 0.92). The analysis was

performed after ~33 months of follow up and 66.7% of events in the T300+D arm and 75.3% events in the S arm, respectively, so the OS data are considered mature. The KM curves begin to separate after 4 months of therapy and stay separated.

It is acknowledged that Himalaya was primarily designed to demonstrate superiority of T300+D vs S in terms of OS and was amended to demonstrate non-inferiority of D vs S for OS as the next analysis in the hierarchical testing. Moreover, the study design allowed for assessment of the contribution of tremelimumab to the combination regimen, through prespecified exploratory analyses of T300+D vs D, which showed an HR of 0.90 (95%CI: 0.76, 1.07) for OS, which was 16.43 months vs 16.56 months, respectively. The applicant has further argued that due to the complementary mechanisms of action of tremelimumab and durvalumab, the reduction in risk of death, more patients achieving a BOR of CR plus more durable responses in the T300+D arm that the addition of tremelimumab is justified. Additionally, a post-hoc analysis calculating piecewise constant treatment effects favoured T300+D independent of selected time interval when compared to either S or D, further illustrating the OS benefit offered by T300+D compared with D. . However, there are remaining uncertainties regarding the optimal dosing regimen e.g. would more than one single dose of tremelimumab have had a significant contribution to added efficacy compared to T300+D and is 300 mg the optimal dose or could the same efficacy and maybe a better safety profile have been obtained with several but lower doses of tremelimumab.

The secondary endpoint of **ORR** by investigator was 20.1% for the T300+D arm compared to 5.1% in the sorafenib arm, while 3.1% of the patients in the T300+D arm had a complete response (CR) vs no patients in the S arm. Confirmed ORR by BIRC was slightly lower in the T300+D arm (18.8%), but this is not directly comparable with ORR by Investigator, since the evaluation was only done in a subset of patients. The improvement of the response rate both by INV and by BIRC is considered borderline clinically meaningful in its magnitude; however, the responders in the T300+D arm (n=79) had durable responses with a median **DoR** of 22.34 months.

The **PFS** analyses were not in the testing hierarchy, so they are not controlled for multiplicity. PFS by investigator was not clinically significantly improved, since the median PFS was 3.78 months in the T300+D arm versus 4.07 months in the S arm; HR 0.90 (95%CI: 0.77, 1.05). The PFS analyses are mature with 85.2% and 84.1% events in the T300+D and S arms, respectively and the KM curves do not clearly separate at any time. This finding is considered consistent with the pattern of efficacy generally observed for immunotherapy, where PFS benefit is often lacking or of a small magnitude, while OS is often clinically significantly improved. Hence, this could be considered an acceptable result as the primary endpoint was OS, and that an OS benefit has been shown for the proposed treatment regimenT300+D vs S.

However, there are uncertainties when interpreting PFS and ORR considering that the final analysis in an open label setting was done by investigators. Additionally, assessments were performed using RECIST 1.1. although in the immunotherapy setting, irRECIST may have been more appropriate/more informative. Nevertheless, rate of possible pseudoprogression of HCC with CTLA-4/PD-L1 inhibition is currently unknown, which creates uncertainty around PFS and ORR data, since patients with confirmed PD (according to RECIST 1.1) were discontinued from IP. Confirmation of PD required a follow-up scan evaluated by Confirmation of Radiological Progression criteria preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD. In the HIMALAYA study, confirmation of PD was not mandatory as RECIST 1.1 used for final analysis does not require confirmation of progression and therefore was not done in the study. The lack of data on potential pseudoprogression is of concern as patients could be denied potentially beneficial treatment. This issue remains to be answered in clinical practice.

Additionally, assessments by BICR were performed only on a subset of patients evaluable for 32 weeks of follow up (for interim analysis 1), and included RECIST 1.1, irRECIST, and mRECIST. Following interim analysis 1, no further BICR assessments were performed. In view of the robustness of the primary endpoint (OS) the applicant's approach regarding PFS can be accepted.

The study design of Himalaya allowed for assessment of the contribution of tremelimumab to the combination regimen, through prespecified exploratory analyses of T300+D vs D, which showed an HR of 0.90 (95%CI: 0.76, 1.07) for OS, which was 16.43 months vs 16.56 months, respectively. The applicant has also provided a rationale for the addition of tremelimumab to durvalumab for the HCC indication, which is primarily based on the following: The combined blockade of CTLA-4 and PD-(L)1 to increase effector T-cell response through two distinct yet complementary mechanisms of action and an approximately 10% reduction in the average risk of death was observed with T300+D versus D. Moreover, while the objective response rates with T300+D and D were similar in HIMALAYA (20.1% vs. 17.0%), twice as many BORs of CR were observed in HIMALAYA with T300+D (12 [3.1%]) compared to D (6 [1.5%]).

The provided arguments are acknowledged and it is accepted that the applicant seeks an approval for the T300+D regimen. However, there remains to be unanswered questions to what would have been the optimal dosing regimen e.g. would more than one single dose of tremelimumab have had a significant contribution to added efficacy compared to T300+D and is 300 mg the optimal dose or could the same efficacy and maybe a better safety profile have been obtained with several but lower doses of tremelimumab. This remains to be unknown.

PRO data was collected as a secondary endpoint. Since the pivotal study was open-label and PRO endpoints were not multiplicity-protected, clinical meaningfulness of PRO data is not considered relevant and the applicant has agreed to delete them from the SmPC.

No additional information on changes in AFP were provided as these data were not collected in the HIMALAYA study.

Relevant **subgroup analyses** of the primary endpoint of OS show that the benefit of T300+D vs S is maintained across important subgroups of age of less than or ≥ 65 years, HBV or other reasons for liver disease, ECOG performance status, macrovascular invasion (MVI), AFP at baseline and BCLB score C.

<u>The supportive Study 22:</u>

The supportive study 22 was a randomised, multicentre, open-label, multipart study designed to evaluate the safety and efficacy of durvalumab and/or tremelimumab in patients with advanced HCC in the 2L+ setting. The study was comprised of multiple parts, but the results from the T300+D arm is considered of most relevance for the proposed indication (n=75), although the study randomised patients to 4 treatment arms. Patients were immunotherapy-naïve patients with advanced HCC, who had progressed on, were intolerant to, or refused treatment with sorafenib or another approved Vascular endothelial growth factor receptor (VEGFR) TKI. Due to different stratification factors in Parts 2A and 3 and lack of randomisation altogether in Part 2B, pooling of efficacy data is inappropriate. Fortunately, OS data from Part 2 and 3 is available separately as well. Although there were no interim analyses planned in the Original Protocol (09 April 2015), in the end 6 interim analyses were performed (and added through Protocol Amendments).

Baseline data for the T300+D arm showed that the median age was 66 years and the vast majority of the patients were male (86.7%) and of white (36%) or Asian (58.7%) race. Disease characteristics show that the vast majority of patients were ECOC PS 0 (61.3%) and disease of advanced BCLC stage C (77.3%) plus macrovascular invasion and/or extrahepatic spread (77.3%).

In conclusion, Study 22 is an early phase, exploratory study that was amended several times. The primary objective of the study was to assess the safety and tolerability, whereas efficacy was a secondary objective and there was no hierarchical testing procedure or correction for multiplicity. The efficacy data quality should be viewed in this light. Moreover, out of the 75 patients in Study 22, who were treated with T300+D, only 55 patients had received prior treatment with sorafenib and were thus truly 'second line'. Due to the lack of a SoC comparator arm in Study 22, there is no benchmark for the results of the T300+D study arm, as there is insufficient understanding of the relevance of the efficacy as observed in the other study arms. In addition, the exploratory design of Study 22 and in particular the lack of a SAP that would provide for formal comparisons between the study arms, hampers both the contextualisation and interpretation of the efficacy results obtained in these 55 patients. As a consequence, the time-to-event endpoints cannot be interpreted adequately. It is noted that the ORR in these 55 patients was only 20%, which cannot be considered dramatic (EMA/CHMP/205/95 Rev.5).

The final analysis showed a median OS of 17 months (65.3% events) for patients who received the proposed dosing regimen of T300+D, while the ORR was 24% and the duration of response (DoR) was 18 months. The applicant compares this result to durvalumab monotherapy; however, this is not approved for or is standard of care (SOC) in the 2L+ setting, so this comparison is not considered relevant for the current application. Since none of the arms of Study 22 contained any SOC, the results for the T300+D arm are considered supportive of efficacy for the proposed dosing regimen in the first-line setting.

2.6.7. Conclusions on the clinical efficacy

The results from the pivotal Himalaya study show a statistically significant and clinically relevant OS benefit over standard of care in the first-line setting of unresectable HCC.

2.6.8. Clinical safety

Table 47: Summary of clinical studies included in the submission package

Study Name (Study Number) Status DCO	**Phase Study Design**	**Patient Population**	**No. of patients Assigned and Treated (Treatment group)**
Studies in HCC			
HIMALAYA (D419CC00002) Ongoing 27 Aug 2021	Phase III Randomised, open-label, comparative, multicentre	Advanced HCC with no prior systemic therapy for HCC	1324 (total) **393 (T300+D)** 389 (D) 389 (Sorafenib) 153 (T75+D)
Study 22 (D4190C00022) Complete 06 Nov 2020	Phase II Randomised, open-label, comparative, multicentre	Advanced unresectable HCC	326 (total) **74 (T300+D)** 101 (D) 82 (T75+D) 69 (T)

HCC-tumour Pools

The pivotal safety dataset used to characterise the safety profile of durvalumab in combination with tremelimumab in the proposed indication was derived from pooled data from HIMALAYA and Study 22. The populations in the HCC-tumour pools are described below:

- **HCC T300+D pool:** This population consists of all patients who have received at least 1 dose of durvalumab given at a dose of 1500mg IV Q4W (or equivalent) in combination with tremelimumab 300 mg IV x 1 dose (or equivalent) for HCC.

- **HCC D pool:** This population consists of all patients who have received at least 1 dose of durvalumab monotherapy given at a dose of 20 mg/kg Q4W IV (or equivalent) for HCC.

2.6.8.1. Patient exposure

Table 48: Summary of study treatment exposure (safety analysis set)

	HCC-tumour pool		Pan-tumour pool		
	T300+D	D	D	T75+D	T750
	(N = 462)	(N = 492)	(N = 4045)	(N = 3319)	(N = 643)
Total treatment duration (weeks) [a]					
n	462	492	4045	3319	643
Mean (SD)	41.9 (44.34)	38.0 (41.49)	28.9 (32.18)	30.1 (37.06)	17.1 (18.46)
Median (min, max)	20.0 (2, 185)	19.9 (1, 193)	16.1 (0, 220)	16.0 (1, 222)	12.0 (1, 176)
Total treatment years	370.6	358.6	2240.4	1912.2	210.5
Total treatment duration (weeks); n (%)					
≥ 24	222 (48.1)	225 (45.7)	1671 (41.3)	1219 (36.7)	129 (20.1)
≥ 52	131 (28.4)	120 (24.4)	793 (19.6)	590 (17.8)	36 (5.6)
≥ 76	92 (19.9)	82 (16.7)	246 (6.1)	292 (8.8)	14 (2.2)
≥ 104	66 (14.3)	53 (10.8)	179 (4.4)	219 (6.6)	6 (0.9)

Table 49: Duration of exposure (Safety analysis set)

		D (N = 388)	T300+D (N = 388)			T75+D (N = 152)			S (N = 374)
			Tremelimumab		Durvalumab	Tremelimumab		Durvalumab	
		Total study [a]	Initial treatment [b]	Rechallenge	Total study [a]	Initial treatment [b]	Rechallenge	Total study [a]	
Total treatment duration [c] (months)	N	388	388	30	388	152	12	152	374
	Mean (SD)	9.7 (10.16)	0.9 (0.04)	0.9 (0.00)	10.6 (10.82)	3.0 (1.14)	2.2 (1.27)	9.3 (10.38)	7.5 (8.48)
	Median (min, max)	5.5 (0.2, 44.4)	0.9 (0.4, 0.9)	0.9 (0.9, 0.9)	5.5 (0.4, 42.7)	3.6 (0.7, 5.6)	1.9 (0.9, 3.7)	4.6 (0.7, 44.2)	4.1 (0.1, 38.6)
	Total treatment years	312.7	29.6	2.3	341.7	38.6	2.2	118.0	234.9
Actual treatment duration [d] (months)	N	388	388	30	388	152	12	152	374
	Mean (SD)	9.3 (9.84)	0.9 (0.04)	0.9 (0.00)	10.1 (10.47)	2.9 (1.02)	2.1 (1.26)	8.9 (9.98)	7.2 (8.35)
	Median (min, max)	4.6 (0.2, 44.4)	0.9 (0.4, 0.9)	0.9 (0.9, 0.9)	5.5 (0.4, 42.6)	3.6 (0.7, 3.7)	1.8 (0.9, 3.7)	4.6 (0.7, 41.9)	3.7 (0.1, 38.6)
	Total treatment years	301.4	29.6	2.3	326.2	36.6	2.1	112.7	224.5
Total duration of cycle delays – total study (months)	N	180	0		194	60		88	182
	Mean (SD)	0.7 (1.22)	NA		1.0 (1.28)	0.4 (0.54)		0.7 (0.95)	0.7 (0.69)
	Median (min, max)	0.3 (0.0, 10.3)	NA		0.5 (0.0, 94)	0.1 (0.0, 1.9)		0.3 (0.0, 5.4)	0.5 (0.0, 3.7)

[a] Total study exposure includes initial treatment and rechallenge phase, where rechallenge occurred.

[b] Initial treatment phase includes the start of study treatment to last treatment or last treatment prior to rechallenge, where rechallenge occurred.

[c] Total treatment duration for immunotherapies = (last dose date + 27 days or date of death or DCO, whichever occurred earlier − first dose date + 1)/(365.25/12). Total treatment duration for S = (last dose date or date of death or DCO, whichever occurred earlier − first dose date + 1)/(365.25/12).

[d] Actual treatment duration = (intended exposure – total duration of dose delays)/(365.25/12).

Patients who took infusion earlier than planned were set to 0 for calculation.

D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; max, maximum; min, minimum; NA, not applicable; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SD, standard deviation; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Source: Table 14.3.1.1.

2.6.8.2. Adverse events

Table 50: Overview of AEs in the HIMALAYA T300+D and S arms and the HCC T300+D pool (safety analysis set)

	Number (%) of patients [a]		
	HCC T300+D pool	HIMALAYA T300+D arm	HIMALAYA S arm
AE category	**(N = 462)**	**(N = 388)**	**(N = 374)**
Any AE	451 (97.6)	378 (97.4)	357 (95.5)
Any AE possibly related to any study treatment [b]	355 (76.8)	294 (75.8)	317 (84.8)
Any AE possibly related to durvalumab [b]	349 (75.5)	288 (74.2)	NA
Any AE possibly related to tremelimumab [b]	224 (48.5)	175 (45.1)	NA
Any AE possibly related to sorafenib [b]	NA	NA	317 (84.8)
Any AE of CTCAE Grade 3 or 4 [c]	240 (51.9)	196 (50.5)	196 (52.4)
Any AE of CTCAE Grade 3 or 4 [c] possibly related to any study treatment [b]	127 (27.5)	100 (25.8)	138 (36.9)
Any AE with outcome of death	34 (7.4)	30 (7.7)	27 (7.2)
Any SAE (including events with outcome of death) [d]	189 (40.9)	157 (40.5)	111 (29.7)
Any AE leading to discontinuation of any study treatment	63 (13.6)	53 (13.7)	63 (16.8)
Any AE leading to discontinuation of any study treatment, possibly related to any study treatment [b]	41 (8.9)	32 (8.2)	41 (11.0)
Any AE leading to dose delay or interruption of any study treatment [e]	149 (32.3)	134 (34.5)	178 (47.6)
Any AE leading to dose delay or interruption of any study treatment [e], possibly related to any study treatment [b]	NE	83 (21.4)	144 (38.5)

[a] Patients with multiple events in the same category are counted only once in that category; patients with events in more than 1 category are counted once in each of those categories.

[b] As assessed by the investigator. Missing responses are counted as related.

[c] All CTCAE grades per patient, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.

[d] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

[e] Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.

Note: Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study treatment or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

AE, adverse event; CRF, case report form; CSR, Clinical Study Report; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); HCC, hepatocellular carcinoma; HCC T300+D pool, all patients from HIMALAYA and Study 22 who have received at least 1 dose of durvalumab given at a dose of 1500 mg IV Q4W (or equivalent) in combination with tremelimumab 300 mg IV × 1 dose (or equivalent) for HCC for any line of therapy; IV, intravenous; NA, not applicable; NE, not evaluated; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SAE, serious adverse event; T300+D, tremelimumab 300 mg (4 mg/kg) for a single priming dose and durvalumab 1500 mg (20 mg/kg) Q4W.

Table 51: Adverse events by preferred term occurring in ⩾10% of patients in any treatment arm (safety analysis set)

System organ class MedDRA preferred term	Number (%) of patients [a] D (N = 388)	 T300+D (N = 388)	 T75+D (N = 152)	 S (N = 374)
Patients with any AE	345 (88.9)	378 (97.4)	145 (95.4)	357 (95.5)
Gastrointestinal disorders	195 (50.3)	236 (60.8)	79 (52.0)	265 (70.9)
Diarrhoea	58 (14.9)	103 (26.5)	32 (21.1)	167 (44.7)
Constipation	42 (10.8)	36 (9.3)	12 (7.9)	35 (9.4)
Abdominal pain	37 (9.5)	46 (11.9)	26 (17.1)	63 (16.8)
Nausea	37 (9.5)	47 (12.1)	14 (9.2)	53 (14.2)
Skin and subcutaneous tissue disorders	135 (34.8)	198 (51.0)	70 (46.1)	243 (65.0)
Pruritus	56 (14.4)	89 (22.9)	27 (17.8)	24 (6.4)
Rash	40 (10.3)	87 (22.4)	27 (17.8)	51 (13.6)
Alopecia	5 (1.3)	2 (0.5)	1 (0.7)	53 (14.2)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.3)	3 (0.8)	3 (2.0)	174 (46.5)
Investigations	123 (31.7)	155 (39.9)	50 (32.9)	122 (32.6)
Aspartate aminotransferase increased	56 (14.4)	48 (12.4)	16 (10.5)	24 (6.4)
Alanine aminotransferase increased	44 (11.3)	36 (9.3)	10 (6.6)	20 (5.3)
Metabolism and nutrition disorders	101 (26.0)	145 (37.4)	42 (27.6)	123 (32.9)
Decreased appetite	53 (13.7)	66 (17.0)	25 (16.4)	67 (17.9)
General disorders and administration site conditions	149 (38.4)	180 (46.4)	73 (48.0)	174 (46.5)
Asthenia	49 (12.6)	39 (10.1)	20 (13.2)	44 (11.8)
Fatigue	38 (9.8)	66 (17.0)	25 (16.4)	71 (19.0)
Pyrexia	36 (9.3)	50 (12.9)	16 (10.5)	33 (8.8)
Oedema peripheral	24 (6.2)	33 (8.5)	16 (10.5)	19 (5.1)
Respiratory, thoracic and mediastinal disorders	73 (18.8)	90 (23.2)	34 (22.4)	95 (25.4)
Cough	31 (8.0)	30 (7.7)	17 (11.2)	22 (5.9)
Psychiatric disorders	41 (10.6)	57 (14.7)	14 (9.2)	26 (7.0)
Insomnia	21 (5.4)	40 (10.3)	10 (6.6)	16 (4.3)
Endocrine disorders	41 (10.6)	92 (23.7)	32 (21.1)	20 (5.3)
Hypothyroidism	19 (4.9)	47 (12.1)	20 (13.2)	16 (4.3)
Vascular disorders	31 (8.0)	48 (12.4)	12 (7.9)	73 (19.5)
Hypertension	17 (4.4)	23 (5.9)	6 (3.9)	68 (18.2)

[a] Each patient has only been represented with the maximum reported CTCAE grade for each system organ class/preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).

Preferred terms are ordered by decreasing frequency in the D arm.

Patients with an AE of maximum CTCAE Grade 5 after the DCO have been reset to 'unknown' at the DCO. This affected 0 patients in the D arm, 0 patients in the T300+D arm, 0 patients in the T75+D arm, and 0 patients in the S arm.

MedDRA version 23.1. CTCAE version 4.03.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 52: Adverse events and event rate occurring in ⩾ 10% of patients in any treatment group by preferred term (safety analysis set)

MedDRA preferred term	HCC-tumour pool				Pan-tumour pool					
	T300+D		D		D		T75+D		T750	
	(N = 462)		(N = 492)		(N = 4045)		(N = 3319)		(N = 643)	
	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]
Patients with any AE	451 (97.6)	121.7	443 (90.0)	123.5	3825 (94.6)	170.7	3151 (94.9)	164.8	609 (94.7)	289.3
Pruritus	118 (25.5)	31.8	76 (15.4)	21.2	463 (11.4)	20.7	623 (18.8)	32.6	173 (26.9)	82.2
Diarrhoea	117 (25.3)	31.6	78 (15.9)	21.7	650 (16.1)	29.0	780 (23.5)	40.8	257 (40.0)	122.1
Rash	115 (24.9)	31.0	53 (10.8)	14.8	395 (9.8)	17.6	442 (13.3)	23.1	128 (19.9)	60.8
Fatigue	83 (18.0)	22.4	62 (12.6)	17.3	997 (24.6)	44.5	775 (23.4)	40.5	150 (23.3)	71.3
Decreased appetite	76 (16.5)	20.5	68 (13.8)	19.0	769 (19.0)	34.3	687 (20.7)	35.9	166 (25.8)	78.9
Aspartate aminotransferase increased	71 (15.4)	19.2	85 (17.3)	23.7	277 (6.8)	12.4	268 (8.1)	14.0	35 (5.4)	16.6
Pyrexia	64 (13.9)	17.3	44 (8.9)	12.3	525 (13.0)	23.4	494 (14.9)	25.8	100 (15.6)	47.5
Abdominal pain	58 (12.6)	15.7	54 (11.0)	15.1	318 (7.9)	14.2	307 (9.2)	16.1	84 (13.1)	39.9
Nausea	57 (12.3)	15.4	49 (10.0)	13.7	678 (16.8)	30.3	625 (18.8)	32.7	166 (25.8)	78.9
Hypothyroidism	55 (11.9)	14.8	33 (6.7)	9.2	380 (9.4)	17.0	378 (11.4)	19.8	29 (4.5)	13.8
Alanine aminotransferase increased	53 (11.5)	14.3	70 (14.2)	19.5	256 (6.3)	11.4	242 (7.3)	12.7	31 (4.8)	14.7
Lipase increased	46 (10.0)	12.4	28 (5.7)	7.8	87 (2.2)	3.9	212 (6.4)	11.1	37 (5.8)	17.6
Constipation	45 (9.7)	12.1	54 (11.0)	15.1	652 (16.1)	29.1	571 (17.2)	29.9	103 (16.0)	48.9
Cough	45 (9.7)	12.1	43 (8.7)	12.0	643 (15.9)	28.7	435 (13.1)	22.7	102 (15.9)	48.5
Anaemia	43 (9.3)	11.6	36 (7.3)	10.0	509 (12.6)	22.7	532 (16.0)	27.8	96 (14.9)	45.6
Arthralgia	43 (9.3)	11.6	45 (9.1)	12.5	559 (13.8)	25.0	376 (11.3)	19.7	54 (8.4)	25.7
Asthenia	42 (9.1)	11.3	52 (10.6)	14.5	463 (11.4)	20.7	437 (13.2)	22.9	77 (12.0)	36.6
Vomiting	34 (7.4)	9.2	23 (4.7)	6.4	423 (10.5)	18.9	405 (12.2)	21.2	107 (16.6)	50.8
Weight decreased	32 (6.9)	8.6	15 (3.0)	4.2	285 (7.0)	12.7	349 (10.5)	18.3	71 (11.0)	33.7
Back pain	30 (6.5)	8.1	50 (10.2)	13.9	448 (11.1)	20.0	329 (9.9)	17.2	41 (6.4)	19.5
Dyspnoea	28 (6.1)	7.6	26 (5.3)	7.2	598 (14.8)	26.7	456 (13.7)	23.8	151 (23.5)	71.7

[a]Number (%) of patients with AEs, sorted in decreasing frequency of preferred term (HCC-tumour pool T300+D column).

[b]Number of patients with AEs divided by the total duration of treatment across all patients in given group, multiplied by 100.

Patients with multiple AEs are counted once for each preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.MedDRA version 23.1.

AE, adverse event; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; pt, patient; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumour types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumour types). Source: Table 2.7.4.2.5, Pooled Safety Outputs, Module 5.3.5.3.

Table 53: Adverse events of maximum CTCAE grade 3 or 4 by system organ class and preferred term (frequency ⩾5% in any treatment arm) (safety analysis set)

System organ class MedDRA preferred term	Number (%) of patients [a]			
	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
Patients with AE of maximum CTCAE Grade 3 or 4	144 (37.1)	196 (50.5)	60 (39.5)	196 (52.4)
Investigations	56 (14.4)	69 (17.8)	27 (17.8)	53 (14.2)
Aspartate aminotransferase increased	26 (6.7)	20 (5.2)	10 (6.6)	12 (3.2)
Lipase increased	16 (4.1)	24 (6.2)	5 (3.3)	11 (2.9)
Vascular disorders	5 (1.3)	11 (2.8)	5 (3.3)	23 (6.1)
Hypertension	4 (1.0)	7 (1.8)	3 (2.0)	23 (6.1)
Skin and subcutaneous tissue disorders	1 (0.3)	15 (3.9)	4 (2.6)	49 (13.1)
Palmar-plantar erthyrodysaesthesia syndrome	0	0	1 (0.7)	34 (9.1)

[a] Each patient is only represented with the maximum reported CTCAE grade for each system organ class / preferred term.

Preferred terms are ordered by decreasing frequency in the D arm.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).

MedDRA version 23.1. CTCAE version 4.03.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 54: Adverse events of maximum CTCAE grade 3 or 4 by preferred term (⩾ 5% of patients in any treatment group) (safety analysis set)

MedDRA preferred term	Number (%) of patients [a]				
	HCC-tumour pool		Pan-tumour pool		
	T300+D	D	D	T75+D	T750
	(N = 462)	(N = 492)	(N = 4045)	(N = 3319)	(N = 643)
Patients with any AE of maximum CTCAE Grade 3 or 4	222 (48.1)	188 (38.2)	1600 (39.6)	1642 (49.5)	344 (53.5)
Aspartate aminotransferase increased	34 (7.4)	36 (7.3)	83 (2.1)	73 (2.2)	15 (2.3)
Lipase increased	33 (7.1)	17 (3.5)	51 (1.3)	143 (4.3)	20 (3.1)
Diarrhoea	18 (3.9)	8 (1.6)	34 (0.8)	92 (2.8)	81 (12.6)
Anaemia	13 (2.8)	11 (2.2)	177 (4.4)	169 (5.1)	20 (3.1)
Colitis	10 (2.2)	0	10 (0.2)	44 (1.3)	32 (5.0)
Dyspnoea	3 (0.6)	4 (0.8)	126 (3.1)	93 (2.8)	40 (6.2)

[a]Number (%) of patients with AEs, sorted in decreasing frequency of preferred term (HCC-tumour pool T300+D column).

Patients with multiple AEs are counted once for each preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication, or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.

MedDRA version 23.1.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumour types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumour types).

Table 55: Adverse events with CTCAE grade 3 or 4, possibly related to investigational product (frequency of ⩾ 2%) by system organ class, preferred term and maximum reported CTCAE grade (HCC pool; safety analysis set)

		Number (%) of patients [a]	
		HCC-tumour pool	
System organ class / MedDRA Preferred term	Maximum reported CTCAE grade	T300 + D (N = 462)	D (N = 492)
Patients with any treatment-related AE	Total	57 (12.3)	27 (5.5)
	Grade 3	50 (10.8)	24 (4.9)
	Grade 4	7 (1.5)	3 (0.6)
Gastrointestinal disorders	Total	14 (3.0)	6 (1.2)
	Grade 3	14 (3.0)	6 (1.2)
Diarrhoea	Total	14 (3.0)	6 (1.2)
	Grade 3	14 (3.0)	6 (1.2)
Investigations	Total	44 (9.5)	22 (4.5)
	Grade 3	37 (8.0)	19 (3.9)
	Grade 4	7 (1.5)	3 (0.6)
Amylase increased	Total	15 (3.2)	3 (0.6)
	Grade 3	14 (3.0)	2 (0.4)
	Grade 4	1 (0.2)	1 (0.2)
Aspartate aminotransferase increased	Total	18 (3.9)	12 (2.4)
	Grade 3	18 (3.9)	11 (2.2)
	Grade 4	0	1 (0.2)
Lipase increased	Total	22 (4.8)	8 (1.6)
	Grade 3	16 (3.5)	7 (1.4)
	Grade 4	6 (1.3)	1 (0.2)

Each patient has only been represented with the maximum reported CTCAE grade for each system organ class / preferred term.
Number (%) of patients with AEs, sorted by international SOC order and alphabetical PT and then maximum grade.
Table includes events occurring in greater than or equal to 2% of patients in either group.
Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Possibly related to treatment, as assessed by the investigator. Missing responses are counted as related.
MedDRA version 23.1.
CTCAE (version 4.03).
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; D = durvalumab 1500 mg Q4W; HCC = hepatocellular carcinoma; PT = preferred term; MedDRA = Medical Dictionary for Regulatory Activities; QxW = every X weeks; SOC = System Organ Class; T300+D = tremelimumab 300 mg for single dose and durvalumab 1500 mg Q4W.

Adverse drug reactions (ADRs)

Table 56: Adverse reactions in patients with HCC treated with tremelimumab 300 mg in combination with durvalumab

	Tremelimumab 300 mg in combination with durvalumab (n=462)			
Adverse Reaction	**Frequency of any Grade**		**Frequency of Grade 3-4**	
Infections and infestations				
Upper respiratory tract infections[a]	Common	39 (8.4%)		
Pneumonia[b]	Common	20 (4.3%)	Common	6 (1.3%)
Influenza	Common	10 (2.2%)		
Dental and oral soft tissue infections[c]	Common	6 (1.3%)		
Oral candidiasis	Uncommon	3 (0.6%)		
Blood and lymphatic system disorders				
Immune thrombocytopenia[d]	Not known			
Endocrine disorders				
Hypothyroidism[e]	Very common	60 (13.0%)		

	Tremelimumab 300 mg in combination with durvalumab (n=462)			
Adverse Reaction	**Frequency of any Grade**		**Frequency of Grade 3-4**	
Hyperthyroidism[f]	Common	44 (9.5%)	Uncommon	1 (0.2%)
Thyroiditis[g]	Common	8 (1.7%)		
Adrenal insufficiency	Common	6 (1.3%)	Uncommon	1 (0.2%)
Hypopituitarism/Hypophysitis	Uncommon	4 (0.9%)		
Diabetes insipidus[d]	Not known			
Type 1 diabetes mellitus[d]	Not known			
Nervous system disorders				
Myasthenia gravis	Uncommon	2 (0.4%)		
Meningitis	Uncommon	1 (0.2%)	Uncommon	1 (0.2%)
Guillain-Barré syndrome[d]	Not known			
Encephalitis[d]	Not known			
Cardiac disorders				
Myocarditis	Uncommon	2 (0.4%)		
Respiratory, thoracic and mediastinal disorders				
Cough/Productive cough	Very common	50 (10.8%)	Uncommon	1 (0.2%)
Pneumonitis[h]	Common	11 (2.4%)	Uncommon	1 (0.2%)
Dysphonia	Uncommon	4 (0.9%)		
Interstitial lung disease	Uncommon	1 (0.2%)		
Gastrointestinal disorders				
Diarrhoea	Very common	117 (25.3%)	Common	18 (3.9%)
Abdominal pain[i]	Very common	91 (19.7%)	Common	10 (2.2%)
Lipase increased	Common	46 (10.0%)	Common	33 (7.1%)
Amylase increased	Common	41 (8.9%)	Common	20 (4.3%)
Colitis[j]	Common	16 (3.5%)	Common	12 (2.6%)
Pancreatitis[k]	Common	6 (1.3%)	Uncommon	3 (0.6%)
Intestinal perforation[d]	Not known			
Large intestine perforation[d]	Not known			
Hepatobiliary disorders				
Aspartate aminotransferase increased/Alanine aminotransferase increased[l]	Very common	83 (18.0%)	Common	41 (8.9%)
Hepatitis[m]	Common	23 (5.0%)	Common	8 (1.7%)
Skin and subcutaneous tissue disorders				
Rash[n]	Very common	150 (32.5%)	Common	14 (3.0%)
Pruritus	Very common	118 (25.5%)		
Dermatitis[o]	Common	6 (1.3%)		
Night sweats	Common	6 (1.3%)		
Pemphigoid	Uncommon	1 (0.2%)		
Musculoskeletal and connective tissue disorders				
Myalgia	Common	16 (3.5%)	Uncommon	1 (0.2%)
Myositis	Uncommon	3 (0.6%)	Uncommon	1 (0.2%)
Polymyositis	Uncommon	1 (0.2%)	Uncommon	1 (0.2%)
Renal and urinary disorders				
Blood creatinine increased	Common	21 (4.5%)	Uncommon	2 (0.4%)
Dysuria	Common	7 (1.5%)		
Nephritis[p]	Uncommon	3 (0.6%)	Uncommon	2 (0.4%)
Cystitis noninfective[d]	Not known			
General disorders and administration site conditions				
Pyrexia	Very common	64 (13.9%)	Uncommon	1 (0.2%)
Oedema peripheral[q]	Very common	48 (10.4%)	Uncommon	2 (0.4%)
Injury, poisoning and procedural complications				
Infusion-related reaction[r]	Common	6 (1.3%)		

[a] Includes nasopharyngitis, pharyngitis, rhinitis, tracheobronchitis and upper respiratory tract infection.

[b] Includes pneumocystis jirovecii pneumonia and pneumonia.

[c] Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.

[d] Adverse reaction was not observed in the HCC pool, but was reported in patients treated with durvalumab or durvalumab + tremelimumab in AstraZeneca-sponsored clinical studies.

[e] Includes blood thyroid stimulating hormone increased, hypothyroidism and immune-mediated hypothyroidism.

[f] Includes blood thyroid stimulating hormone decreased and hyperthyroidism.

[g] Includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis and thyroiditis subacute.

[h] Includes immune-mediated pneumonitis and pneumonitis.

[i] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

[j] Includes colitis, enteritis and enterocolitis.

[k] Includes pancreatitis and pancreatitis acute.

[l] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.

[m] Includes autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity and immune-mediated hepatitis.

[n] Includes eczema, erythema, rash, rash macular, rash maculo-papular, rash papular and rash pruritic.

[o] Includes dermatitis and immune-mediated dermatitis.

[p] Includes autoimmune nephritis and immune-mediated nephritis.

[q] Includes oedema peripheral and peripheral swelling.

[r] Includes infusion-related reaction and urticaria.

Adverse events of special interest

Table 57: Overview of imAEs in the HIMALAYA T300+D and S arms and the HCC T300+D pool (safety analysis set)

	Number (%) of patients [a]		
	HCC T300+D pool	HIMALAYA T300+D arm	HIMALAYA S arm
AE category	**(N = 462)**	**(N = 388)**	**(N = 374)**
Any AE	167 (36.1)	142 (36.6)	28 (7.5)
Any AE of CTCAE Grade 3 or 4	62 (13.4)	51 (13.1)	9 (2.4)
Any SAE (including AEs with outcome of death) [b]	47 (10.2)	40 (10.3)	4 (1.1)
Any AE with outcome of death	6 (1.3)	6 (1.5)	0
Received systemic corticosteroids	119 (25.8)	97 (25.0)	15 (4.0)
Received high dose corticosteroids	94 (20.3)	78 (20.1)	7 (1.9)
Received endocrine therapy	69 (14.9)	65 (16.8)	13 (3.5)
Received other immunosuppressants	15 (3.2)	15 (3.9)	0
Any AE leading to discontinuation of study treatment	26 (5.6)	22 (5.7)	6 (1.6)

[f] Patients with multiple events in the same category are counted only once in that category; patients with events in more than 1 category are counted once in each of those categories.

[g] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

Note: Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study treatment or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

AE, adverse event; CSR, Clinical Study Report; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); HCC, hepatocellular carcinoma; HCC T300+D pool, all patients from HIMALAYA and Study 22 who have received at least 1 dose of durvalumab given at a dose of 1500 mg IV Q4W (or equivalent) in combination with tremelimumab 300 mg IV × 1 dose (or equivalent) for HCC for any line of therapy; IV, intravenous; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SAE, serious adverse event; T300+D, tremelimumab 300 mg (4 mg/kg) for a single priming dose and durvalumab 1500 mg (20 mg/kg) Q4W.

Table 58: Immune-mediated adverse events categories reported for > 2% of patients in the HCC pool (safety analysis set)

	Number (%) of patients [a]			
	HCC T300+D Pool (N = 462)		HCC D Pool (N = 492)	
imAE category	**Any Grade**	**CTCAE Grade 3 or 4**	**Any Grade**	**CTCAE Grade 3 or 4**
Any imAE	167 (36.1)	62 (13.4)	81 (16.5)	31 (6.3)
Hypothyroid events	45 (9.7)	0	25 (5.1)	0
Hepatic events	34 (7.4)	23 (5.0)	31 (6.3)	21 (4.3)
Diarrhoea/colitis	30 (6.5)	17 (3.7)	7 (1.4)	3 (0.6)
Dermatitis/rash	26 (5.6)	9 (1.9)	4 (0.8)	1 (0.2)
Hyperthyroid	21 (4.5)	1 (0.2)	6 (1.2)	0
Other rare/ miscellaneous	10 (2.2)	2 (0.4)	2 (0.4)	0

[h] Patients with multiple events in the same category are counted only once in that category; patients with events in more than one category are counted once in each of those categories.

Includes AEs with an onset date on or after the date of first date or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study treatment or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (20 mg/kg) Q4W; HCC, hepatocellular carcinoma; imAE, immune-mediated adverse event; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg (4 mg/kg) for a single priming dose and durvalumab 1500 mg (20 mg/kg) Q4W.

In the HCC pool (n=462), the following immune mediated adverse drug reactions have been reported:

- immune-mediated pneumonitis occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient and Grade 5 (fatal) in 1 (0.2%) patient. The median time to onset was 29 days (range: 5-774 days). Six patients received systemic corticosteroids, and 5 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received other immunosuppressants. Treatment was discontinued in 2 patients. Resolution occurred in 3 patients.

- immune-mediated hepatitis occurred in 34 (7.4%) patients, including Grade 3 in 20 (4.3%) patients, Grade 4 in 1 (0.2%) patient and Grade 5 (fatal) in 3 (0.6%) patients. The median time to onset was 29 days (range: 13-313 days). All patients received systemic corticosteroids, and 32 of the 34 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Nine patients also received other immunosuppressants. Treatment was discontinued in 10 patients. Resolution occurred in 13 patients.

- immune-mediated colitis or diarrhoea occurred in 31 (6.7%) patients, including Grade 3 in 17 (3.7%) patients. The median time to onset was 23 days (range: 2-479 days). All patients received systemic corticosteroids, and 28 of the 31 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also received other immunosuppressants. Treatment was discontinued in 5 patients. Resolution occurred in 29 patients.

Intestinal perforation was observed in patients receiving Imjudo in combination with durvalumab (rare) in studies outside of the HCC pool.

- immune-mediated hypothyroidism occurred in 46 (10.0%) patients. The median time to onset was 85 days (range: 26-763 days). One patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement

therapy . Resolution occurred in 6 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 patients.

- immune-mediated hyperthyroidism occurred in 21 (4.5%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 30 days (range: 13-60 days). Four patients received systemic corticosteriods, and all of the four patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 17 patients.

- immune-mediated thyroiditis occurred in 6 (1.3%) patients. The median time to onset was 56 days (range: 7-84 days). Two patients received systemic corticosteroids, and 1 of the 2 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy, Resolution occurred in 2 patients.

- immune-mediated adrenal insufficiency occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 64 days (range: 43-504 days). All patients received systemic corticosteroids, and 1 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in 2 patients.

- immune-mediated hypophysitis/hypopituitarism occurred in 5 (1.1%) patients. The median time to onset for the events was 149 days (range: 27-242 days). Four patients received systemic corticosteroids, and 1 of the 4 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also required endocrine therapy. Resolution occurred in 2 patients.

- immune-mediated nephritis occurred in 4 (0.9%) patients, including Grade 3 in 2 (0.4%) patients. The median time to onset was 53 days (range: 26-242 days). All patients received systemic corticosteroids, and 3 of the 4 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 2 patients. Resolution occurred in 3 patients.

- immune-mediated rash or dermatitis (including pemphigoid) occurred in 26 (5.6%) patients, including Grade 3 in 9 (1.9%) patients and Grade 4 in 1 (0.2%) patient. The median time to onset was 25 days (range: 2-933 days). All patients received systemic corticosteroids and 14 of the 26 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants. Treatment was discontinued in 3 patients. Resolution occurred in 19 patients.

Immune-mediated type 1 diabetes mellitus was observed in patients receiving Imjudo in combination with durvalumab (uncommon) in studies outside of the HCC pool.

2.6.8.3. Serious adverse event/deaths/other significant events

Table 59: Serious adverse events by system organ class and preferred term (⩾ 2% patients in any treatment arm; safety analysis set)

System Organ Class MedDRA Preferred Term	Number (%) of patients [a]			
	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
Patients with any SAE	115 (29.6)	157 (40.5)	52 (34.2)	111 (29.7)
Gastrointestinal disorders	22 (5.7)	48 (12.4)	14 (9.2)	35 (9.4)
Oesophageal varices haemorrhage	4 (1.0)	1 (0.3)	3 (2.0)	2 (0.5)
Diarrhoea	2 (0.5)	9 (2.3)	4 (2.6)	6 (1.6)
Infections and infestations	21 (5.4)	43 (11.1)	10 (6.6)	23 (6.1)
Sepsis	4 (1.0)	8 (2.1)	2 (1.3)	0
Pneumonia	3 (0.8)	7 (1.8)	6 (3.9)	8 (2.1)
General disorders and administration site conditions	18 (4.6)	11 (2.8)	7 (4.6)	9 (2.4)
Death	8 (2.1)	4 (1.0)	5 (3.3)	5 (1.3)
Hepatobiliary disorders	16 (4.1)	14 (3.6)	8 (5.3)	15 (4.0)
Hepatitis	1 (0.3)	3 (0.8)	4 (2.6)	0
Respiratory, thoracic, and mediastinal disorders	11 (2.8)	9 (2.3)	6 (3.9)	9 (2.4)
Pneumonitis	2 (0.5)	4 (1.0)	3 (2.0)	1 (0.3)
Blood and lymphatic system disorders	2 (0.5)	6 (1.5)	4 (2.6)	3 (0.8)
Anaemia	1 (0.3)	5 (1.3)	3 (2.0)	2 (0.5)

[a] Each patient has only been represented with the maximum reported CTCAE grade for each system organ class/preferred term.

Preferred terms are ordered by decreasing frequency in the D arm.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).

Patients with an AE of maximum CTCAE Grade 5 after the DCO have been reset to 'unknown' at the DCO. This affected 0 patients in the D arm, 0 patients in the T300+D arm, 0 patients in the T75+D arm, and 0 patients in the S arm.

MedDRA version 23.1. CTCAE version 4.03.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

17.5% of the SAEs (40.5%) in the T300+D arm were treatment-related. The below table describes treatment-related SAEs for the T300+D and S arms of the Himalaya study and the HCC pool (frequency more than 1%).

Table 60: Time to onset, discontinuation, resolution and duration of treatment related serious adverse events (frequency of ⩾ 1%) by preferred term

Preferred term	Parameters (days)	Descriptive statistics	HIMALAYA			HCC-tumour pool	
			T300 + D (N = 388)	D (N = 388)	S (N = 374)	T300 + D (N = 462)	D (N = 492)
Colitis	Time to onset	n	6	2	0	9	2
		Mean	219.5	104.0		228.2	104.0
		Minimum	8	11		8	11
		Median	21.5	104.0		25.0	104.0
		Maximum	815	197		815	197
	Duration of events	n	6	2	0	9	2
		Mean	54.2	39.5		50.3	39.5
		Minimum	7	36		7	36

Preferred term	Parameters (days)	Descriptive statistics	HIMALAYA			HCC-tumour pool	
			T300 + D (N = 388)	D (N = 388)	S (N = 374)	T300 + D (N = 462)	D (N = 492)
		Median	51.0	39.5		43.0	39.5
		Maximum	99	43		99	43
	Time to discontinuation	n	2	1	0	2	1
		Mean	1.0	1.0		1.0	1.0
		Minimum	1	1		1	1
		Median	1.0	1.0		1.0	1.0
		Maximum	1	1		1	1
	Time to resolution	n	6	1	0	9	1
		Mean	54.2	43.0		50.3	43.0
		Minimum	7	43		7	43
		Median	51.0	43.0		43.0	43.0
		Maximum	99	43		99	43
Diarrhoea	Time to onset	n	7	1	6	9	2
		Mean	24.1	63.0	78.7	37.8	39.5
		Minimum	2	63	25	2	16
		Median	14.0	63.0	67.5	24.0	39.5
		Maximum	66	63	162	115	63
	Duration of events	n	7	1	6	9	2
		Mean	37.3	82.0	22.3	34.6	43.5
		Minimum	7	82	1	7	5
		Median	52.0	82.0	4.5	25.0	43.5
		Maximum	72	82	112	72	82
	Time to discontinuation	n	0	0	1	0	1
		Mean			102.0		1.0
		Minimum			102		1
		Median			102.0		1.0
		Maximum			102		1
	Time to resolution	n	7	0	5	9	1
		Mean	37.3		4.4	34.6	5.0
		Minimum	7		1	7	5
		Median	52.0		4.0	25.0	5.0
		Maximum	72		8	72	5
Hepatic function abnormal	Time to onset	n	1	5	1	2	9
		Mean	36.0	119.2	7.0	257.0	115.1
		Minimum	36	15	7	36	15
		Median	36.0	29.0	7.0	257.0	43.0
		Maximum	36	467	7	478	467
	Duration of events	n	1	5	1	2	9
		Mean	141.0	133.8	37.0	169.5	124.2
		Minimum	141	13	37	141	9
		Median	141.0	92.0	37.0	169.5	57.0
		Maximum	141	413	37	198	413
	Time to discontinuation	n	1	0	0	2	3
		Mean	29.0			200.5	112.0
		Minimum	29			29	1
		Median	29.0			200.5	57.0
		Maximum	29			372	278
	Time to resolution	n	1	3	1	1	4
		Mean	141.0	66.3	37.0	141.0	52.0
		Minimum	141	13	37	141	9
		Median	141.0	92.0	37.0	141.0	52.5
		Maximum	141	94	37	141	94

Note: Table includes events occurring in ≥ 1% of patients in either group.
D = durvalumab 1500 mg Q4W; HCC = hepatocellular carcinoma; QxW = every X weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg for single dose and durvalumab 1500 mg Q4W.

Deaths

Table 61: All deaths (full analysis set) – DCO: 27 AUG 2021

Category	Number (%) of subjects			
	Durva 1500 mg (N=389)	Treme 300 mg x1 dose + Durva 1500 mg (N=393)	Treme 75 mg x4 doses + Durva 1500 mg (N=153)	Sora 400 mg BID (N=389)
Total number of deaths	280 (72.0)	262 (66.7)	123 (80.4)	293 (75.3)
Death related to disease under investigation only	245 (63.0)	221 (56.2)	103 (67.3)	256 (65.8)
AE with outcome of death only	19 (4.9)	24 (6.1)	9 (5.9)	20 (5.1)
AE with outcome of death only (AE start date falling after 90 days follow up period)	2 (0.5)	3 (0.8)	1 (0.7)	0
Number of subjects with death related to disease progression and an AE with outcome of death	6 (1.5)	8 (2.0)	4 (2.6)	7 (1.8)
Other deaths[a]	8 (2.1)	6 (1.5)	6 (3.9)	10 (2.6)

[a] Subjects who died and are not captured in the earlier categories.
Death related to disease under investigation is determined by the investigator.
Rows are mutually exclusive, subjects are only reported in one category.

Table 62: Adverse events with outcome of death by preferred term (safety analysis set)

MedDRA Preferred Term	Number (%) of patients [a]			
	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
Immune-mediated hepatitis	0	2 (0.5)	0	0
Internal haemorrhage	0	1 (0.3)	0	0
Myocarditis	0	1 (0.3)	0	0
Liver abscess	0	0	0	1 (0.3)
Peritonitis	0	0	0	1 (0.3)
Pneumonia	0	0	2 (1.3)	2 (0.5)
Sepsis	0	1 (0.3)	1 (0.7)	0
Cerebral haematoma	0	0	0	1 (0.3)
Cerebral haemorrhage	0	1 (0.3)	0	0
Haemorrhage intracranial	0	2 (0.5)	0	0
Hepatic encephalopathy	0	0	0	1 (0.3)
Myasthenia gravis	0	1 (0.3)	0	0
Nervous system disorder	0	1 (0.3)	0	0
Thrombocytopenia	0	1 (0.3)	0	0
Haematuria	0	0	0	1 (0.3)
Acute respiratory distress syndrome	0	1 (0.3)	0	0
Dyspnoea	0	0	0	1 (0.3)
Epistaxis	0	0	0	1 (0.3)
Pneumonitis	0	2 (0.5)	0	0
Pulmonary embolism	0	1 (0.3)	0	1 (0.3)
Respiratory failure	0	0	0	1 (0.3)

[a] Each patient has only been represented with the maximum reported CTCAE grade for each preferred term.
Preferred terms are ordered by decreasing frequency in the D arm.
Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).
Patients with an AE of maximum CTCAE Grade 5 after the DCO have been reset to 'unknown' at the DCO. This affected 0 patients in the D arm, 0 patients in the T300+D arm, 0 patients in the T75+D arm, and 0 patients in the S arm.
MedDRA version 23.1. CTCAE version 4.03.

Below is the table of the treatment-related (as assessed by the investigator) AEs leading to death.

Table 63: Adverse events with outcome of death, possibility related to investigational product by system organ class, preferred term and maximum reported CTCAE grade (safety analysis set)

System organ class / MedDRA Preferred term	Maximum reported CTCAE grade	Number (%) of subjects[a]			
		Durva 1500 mg (N=388)	Treme 300 mg x1 dose + Durva 1500 mg (N=388)	Treme 75 mg x4 doses + Durva 1500 mg (N=152)	Sora 400 mg BID (N=374)
Subjects with any AE	Grade 5	0	9 (2.3)	2 (1.3)	3 (0.8)
Infections and infestations	Grade 5	0	0	1 (0.7)	0
Septic shock	Grade 5	0	0	1 (0.7)	0
Nervous system disorders	Grade 5	0	2 (0.5)	0	1 (0.3)
Cerebral haematoma	Grade 5	0	0	0	1 (0.3)
Myasthenia gravis	Grade 5	0	1 (0.3)	0	0
Nervous system disorder	Grade 5	0	1 (0.3)	0	0
Cardiac disorders	Grade 5	0	1 (0.3)	0	0
Myocarditis	Grade 5	0	1 (0.3)	0	0
Respiratory, thoracic and mediastinal disorders	Grade 5	0	2 (0.5)	0	0
Acute respiratory distress syndrome	Grade 5	0	1 (0.3)	0	0
Pneumonitis	Grade 5	0	1 (0.3)	0	0
Hepatobiliary disorders	Grade 5	0	4 (1.0)	1 (0.7)	1 (0.3)
Hepatic failure	Grade 5	0	1 (0.3)	1 (0.7)	1 (0.3)
Hepatitis	Grade 5	0	1 (0.3)	0	0
Immune-mediated hepatitis	Grade 5	0	2 (0.5)	0	0
Renal and urinary disorders	Grade 5	0	0	0	1 (0.3)
Haematuria	Grade 5	0	0	0	1 (0.3)
General disorders and administration site conditions	Grade 5	0	0	1 (0.7)	0
Multiple organ dysfunction syndrome	Grade 5	0	0	1 (0.7)	0

[a] Each subject has only been represented with the maximum reported CTCAE grade for each system organ class / preferred term.
Number (%) of subjects with AEs, sorted by international SOC order and alphabetical PT and then maximum grade.
Includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Subjects who have a maximum CTCAE grade 5 post the DCO, have been reset to unknown at the DCO. This affects 0 subjects in group 'Durva 1500 mg' and 0 subjects in group 'Treme 300 mg x1 dose + Durva 1500 mg' and 0 subjects in group 'Treme 75 mg x4 doses + Durva 1500 mg' and 0 subjects in group 'Sora 400 mg BID'.
Possibly related to treatment, as assessed by the investigator. Missing responses are counted as related.
MedDRA version 23.1.
CTCAE = Common Terminology Criteria for Adverse Events (version 4.03).
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2.6.8.4. Laboratory findings

Haematology

Table 64: Clinically important changes in haematology and clinical chemistry parameters (safety analysis set) – DCO: 27 AUG 2021

	n/N# (%) of subjects											
	Durva 1500 mg (N=388)			Treme 300 mg x1 dose + Durva 1500 mg (N=388)			Treme 75 mg x4 doses + Durva 1500 mg (N=152)			Sora 400 mg BID (N=374)		
Parameter	>= 1 CTCAE grade changes	>= 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	>= 1 CTCAE grade changes	>= 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	>= 1 CTCAE grade changes	>= 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	>= 1 CTCAE grade changes	>= 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
B-Hemoglobin	158/ 373 (42.4)	24/ 373 (6.4)	18/ 373 (4.8)	195/ 378 (51.6)	26/ 378 (6.9)	18/ 378 (4.8)	61/ 148 (41.2)	14/ 148 (9.5)	8/ 148 (5.4)	142/ 352 (40.3)	25/ 352 (7.1)	21/ 352 (6.0)
B-Leukocytes	112/ 370 (30.3)	11/ 370 (3.0)	5/ 370 (1.4)	76/ 376 (20.2)	8/ 376 (2.1)	3/ 376 (0.8)	35/ 147 (23.8)	2/ 147 (1.4)	2/ 147 (1.4)	106/ 352 (30.1)	11/ 352 (3.1)	4/ 352 (1.1)
B-Lymphocytes	160/ 371 (43.1)	64/ 371 (17.3)	32/ 371 (8.6)	156/ 377 (41.4)	78/ 377 (20.7)	42/ 377 (11.1)	62/ 147 (42.2)	25/ 147 (17.0)	19/ 147 (12.9)	138/ 351 (39.3)	68/ 351 (19.4)	35/ 351 (10.0)
B-Neutrophils	58/ 372 (15.6)	20/ 372 (5.4)	5/ 372 (1.3)	48/ 378 (12.7)	15/ 378 (4.0)	3/ 378 (0.8)	22/ 148 (14.9)	7/ 148 (4.7)	2/ 148 (1.4)	48/ 351 (13.7)	21/ 351 (6.0)	7/ 351 (2.0)
B-Platelets	108/ 372 (29.0)	12/ 372 (3.2)	8/ 372 (2.2)	109/ 378 (28.8)	14/ 378 (3.7)	6/ 378 (1.6)	41/ 148 (27.7)	7/ 148 (4.7)	5/ 148 (3.4)	122/ 352 (34.7)	16/ 352 (4.5)	11/ 352 (3.1)

Table 65: Clinically important changes in haematology parameters (safety analysis set)

	n/N (%) of patients									
	HCC-tumor pool				Pan-tumor pool					
	T300+D (N = 462)		D (N = 492)		D (N = 4045)		T75+D (N = 3319)		T750 (N = 643)	
Parameter	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Hemoglobin	31/452 (6.9)	22/452 (4.9)	31/476 (6.5)	23/476 (4.8)	209/3868 (5.4)	193/3868 (5.0)	195/3162 (6.2)	178/3162 (5.6)	28/538 (5.2)	25/538 (4.6)
Leukocytes	14/450 (3.1)	5/450 (1.1)	15/473 (3.2)	6/473 (1.3)	75/3868 (1.9)	22/3868 (0.6)	59/3158 (1.9)	16/3158 (0.5)	11/585 (1.9)	4/585 (0.7)
Lymphocytes - Low	86/431 (20.0)	51/431 (11.8)	81/450 (18.0)	38/450 (8.7)	738/3828 (19.3)	506/3828 (13.2)	617/3126 (19.7)	418/3126 (13.4)	48/513 (9.4)	37/513 (7.2)
Neutrophils	19/431 (4.4)	4/431 (0.9)	24/451 (5.3)	6/451 (1.3)	119/3833 (3.1)	37/3833 (1.0)	87/3104 (2.8)	18/3104 (0.6)	15/544 (2.8)	5/544 (0.9)
Platelets	14/452 (3.1)	6/452 (1.3)	16/475 (3.4)	14/475 (2.9)	64/3865 (1.7)	44/3865 (1.1)	59/3154 (1.9)	36/3154 (1.1)	14/585 (2.4)	9/585 (1.5)

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first).

Patient's worst (highest CTCAE grade) changes from baseline are used.

Percentages had been calculated using the number of patients with a baseline value and a post baseline value.

CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types).

Source: Table 2.7.4.10.2, Pooled Safety Outputs, Module 5.3.5.3.

Clinical chemistry

Table 66: Clinically important changes in clinical chemistry parameters (safety analysis set)

Clinical chemistry parameter	n/N [a] (%) of patients											
	D (N = 388)			T300+D (N = 388)			T75+D (N = 152)			S (N = 374)		
	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
ALT	194/374 (51.9)	52/374 (13.9)	49/374 (13.1)	212/377 (56.2)	71/377 (18.8)	67/377 (17.8)	76/148 (51.4)	24/148 (16.2)	22/148 (14.9)	185/352 (52.6)	41/352 (11.6)	43/352 (12.2)
Albumin	89/370 (24.1)	62/370 (16.8)	2/370 (0.5)	116/371 (31.3)	66/371 (17.8)	2/371 (0.5)	42/147 (28.6)	26/147 (17.7)	1/147 (0.7)	130/350 (37.1)	81/350 (23.1)	6/350 (1.7)
ALP	145/371 (39.1)	22/371 (5.9)	30/371 (8.1)	154/374 (41.2)	34/374 (9.1)	31/374 (8.3)	70/148 (47.3)	11/148 (7.4)	18/148 (12.2)	156/351 (44.4)	17/351 (4.8)	19/351 (5.4)
AST	205/373 (55.0)	65/373 (17.4)	86/373 (23.1)	238/377 (63.1)	87/377 (23.1)	101/377 (26.8)	80/148 (54.1)	28/148 (18.9)	40/148 (27.0)	191/350 (54.6)	48/350 (13.7)	74/350 (21.1)
Bilirubin	153/374 (40.9)	62/374 (16.6)	28/374 (7.5)	156/377 (41.4)	76/377 (20.2)	31/377 (8.2)	64/147 (43.5)	22/147 (15.0)	14/147 (9.5)	167/352 (47.4)	71/352 (20.2)	37/352 (10.5)
Calcium increased	16/367 (4.4)	9/367 (2.5)	6/367 (1.6)	11/367 (3.0)	2/367 (0.5)	2/367 (0.5)	4/146 (2.7)	1/146 (0.7)	0/146	8/344 (2.3)	3/344 (0.9)	2/344 (0.6)
Calcium decreased	130/367 (35.4)	1/367 (0.3)	1/367 (0.3)	123/367 (33.5)	5/367 (1.4)	0/367	50/146 (34.2)	2/146 (1.4)	0/146	148/344 (43.0)	3/344 (0.9)	1/344 (0.3)
Creatinine	70/372 (18.8)	6/372 (1.6)	1/372 (0.3)	78/374 (20.9)	10/374 (2.7)	5/374 (1.3)	25/148 (16.9)	7/148 (4.7)	0/148	52/352 (14.8)	11/352 (3.1)	3/352 (0.9)
Glucose increased	142/368 (38.6)	63/368 (17.1)	31/368 (8.4)	144/370 (38.9)	70/370 (18.9)	50/370 (13.5)	55/145 (37.9)	22/145 (15.2)	21/145 (14.5)	101/347 (29.1)	43/347 (12.4)	13/347 (3.7)
Glucose decreased	16/368 (4.3)	6/368 (1.6)	3/368 (0.8)	22/370 (5.9)	12/370 (3.2)	4/370 (1.1)	5/145 (3.4)	3/145 (2.1)	2/145 (1.4)	19/347 (5.5)	8/347 (2.3)	3/347 (0.9)
Magnesium increased	0/12	0/12	0/12	0/18	0/18	0/18	0/9	0/9	0/9	0/5	0/5	0/5
Magnesium decreased	0/12	0/12	0/12	2/18 (11.1)	1/18 (5.6)	0/18	0/9	0/9	0/9	1/5 (20.0)	0/5	0/5
Potassium increased	94/369 (25.5)	27/369 (7.3)	17/369 (4.6)	105/370 (28.4)	31/370 (8.4)	14/370 (3.8)	35/147 (23.8)	9/147 (6.1)	4/147 (2.7)	75/352 (21.3)	24/352 (6.8)	9/352 (2.6)
Potassium decreased	35/369 (9.5)	5/369 (1.4)	5/369 (1.4)	57/370 (15.4)	11/370 (3.0)	11/370 (3.0)	25/147 (17.0)	4/147 (2.7)	4/147 (2.7)	46/352 (13.1)	10/352 (2.8)	10/352 (2.8)
Sodium increased	17/371 (4.6)	0/371	0/371	19/372 (5.1)	2/372 (0.5)	1/372 (0.3)	13/147 (8.8)	0/147	0/147	23/352 (6.5)	3/352 (0.9)	1/352 (0.3)
Sodium decreased	139/371 (37.5)	23/371 (6.2)	25/371 (6.7)	171/372 (46.0)	57/372 (15.3)	57/372 (15.3)	70/147 (47.6)	15/147 (10.2)	15/147 (10.2)	140/352 (39.8)	39/352 (11.1)	39/352 (11.1)

[a] N corresponds to the number of patients with baseline value recorded.

Only worsening of CTCAE grades are presented.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study treatment or until the initiation of the first subsequent therapy (whichever occurred first).

CTCAE version 4.03.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Source: Table 14.3.7.1.2.2.

Table 67: Clinically important changes in clinical chemistry parameters (safety analysis set)

Parameter	HCC-tumor pool			
	T300+D (N = 462)		D (N = 492)	
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
AST	101/451 (22.4)	121/451 (26.8)	87/476 (18.3)	112/476 (23.5)
Alkaline phosphatase	38/448 (16.0)	35/448 (7.8)	30/474 (6.3)	44/474 (9.3)
ALT	85/451 (18.8)	80/451 (17.7)	62/477 (13.0)	56/477 (11.7)
Albumin	71/445 (16.0%)	2/445 (0.4)	74/473 (15.6)	7/473 (1.5)
Total bilirubin	91/451 (20.2%)	35/451 (7.8)	81/477 (17.0)	40/477 (8.4)
Creatinine	22/448 (4.9)	8/448 (1.8)	19/475 (4.0)	3/475 (0.6)
GGT	9/93 (9.7)	20/93 (21.5)	8/116 (6.9)	20/116 (17.2)
Lipase	117/423 (27.7)	101/423 (23.9)	75/460 (16.3)	54/460 (11.7)
Amylase	81/426 (19.0)	63/426 (14.8)	37/459 (8.1)	32/459 (7.0)
Glucose (high)	86/444 (19.4)	65/444 (14.6)	75/471 (15.9)	39/471 (8.3)
Potassium (high)	36/444 (8.1)	17/444 (3.8)	38/471 (8.1)	21/471 (4.5)
Sodium (low)	64/446 (14.3)	64/446 (14.3)	35/474 (7.4)	37/474 (7.8)
Corrected Calcium (low)	5/367 (1.4)	0/367 (0)	1/367 (0.3)	1/367 (0.3)

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first).Patient's worst (highest CTCAE grade) changes from baseline are used. Percentages had been calculated using the number of patients with a baseline value and a post baseline value. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (or equivalent); GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; IV, intravenous; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumour types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumour types).

Table 9: Hyperglycaemia/new onset diabetes mellitus SMQ AEs in the HCC T300+D tumour pool

					Received intervention					Event outcome		
SMQ Category/ MedDRA Preferred Term	Any AE	Any SAE[a]	CTCAE Grade 3-4	CTCAE Grade ≥ 3	Systemic Cortico-Steroids	High Dose Steroid	Other Immuno Suppre-ssants	Requires Endocrine Therapy	Leading to Dis-contin-uation of Study Drug	Resul-ted in Death	Not Resol-ved	Resol-ved
Hyperglycaemia/new onset diabetes mellitus	39 (8.4)	8 (1.7)	16 (3.5)	16 (3.5)	0	0	0	0	2 (0.4)	0	18 (3.9)	21 (4.5)
Diabetes mellitus	11 (2.4)	4 (0.9)	4 (0.9)	4 (0.9)	0	0	0	0	0	0	7 (1.5)	4 (0.9)
Diabetes mellitus inadequate control	2 (0.4)	0	0	0	0	0	0	0	0	0	0	2 (0.4)
Diabetic ketoacidosis	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0	0	0	0	0	1 (0.2)
Hyperglycaemia	22 (4.8)	2 (0.4)	10 (2.2)	10 (2.2)	0	0	0	0	1 (0.2)	0	7 (1.5)	15 (3.2)
Type 2 diabetes mellitus	6 (1.3)	2 (0.4)	2 (0.4)	2 (0.4)	0	0	0	0	1 (0.2)	0	4 (0.9)	2 (0.4)

[a] As assessed by the investigator.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after date of first dose up to and including 90 days following the date of last dose of study medication, or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

MedDRA Version 23.1

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; HCC = hepatocellular carcinoma; Q4W = every 4 weeks; SAE = serious adverse event; T300+D = tremelimumab 300 mg for a single dose and durvalumab 1500 mg Q4W; SMQ = Standardised MedDRA Query.

Source: IEMT 0316.2b0.

Liver chemistry

Table 69: Proportin of patients with elevated ALT or AST (⩾3 x ULN), and elevated total bilirubin (⩾ 2 x ULN; safety analysis set)

	Number (%) of patients			
Category	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
ALT or AST ≥ 3 × ULN and BILI > 2 × ULN [a]	46 (11.9)	51 (13.1)	17 (11.2)	47 (12.6)
ALT or AST ≥ 3 × ULN and BILI > 2 × ULN and no ALP ≥ 2 × ULN [a]	19 (4.9)	15 (3.9)	3 (2.0)	23 (6.1)

[a] The onset date of ALT or AST elevation occurred within 14 days prior to or on the date of total bilirubin elevation.

Percentages were calculated based on the number of patients with measurements.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of IP or until initiation of the first subsequent therapy (whichever occurred first).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, total bilirubin; D, durvalumab monotherapy 1500 mg Q4W; Q4W, every 4 weeks; IP, investigational product; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; ULN upper limit of normal.

Source: Table 14.3.7.1.4.

Table 70: Liver function abnormalities (safety analysis set)

	Number (%) of patients				
	HCC-tumour pool		Pan-tumour pool		
Category	T300+D (N = 462)	D (N = 492)	D (N = 4045)	T75+D (N = 3319)	T750 (N = 643)
ALT or AST					
≥ 3 × to ≤ 5 × ULN	93 (20.1)	84 (17.1)	242 (6.0)	217 (6.5)	27 (4.2)
> 5 × to ≤ 8 × ULN	65 (14.1)	56 (11.4)	127 (3.1)	111 (3.3)	16 (2.5)

Category	Number (%) of patients				
	HCC-tumour pool		Pan-tumour pool		
	T300+D (N = 462)	D (N = 492)	D (N = 4045)	T75+D (N = 3319)	T750 (N = 643)
> 8 × to ≤ 10 × ULN	26 (5.6)	31 (6.3)	57 (1.4)	28 (0.8)	7 (1.1)
> 10 × to ≤ 20 × ULN	39 (8.4)	33 (6.7)	67 (1.7)	66 (2.0)	4 (0.6)
> 20 × ULN	14 (3.0)	11 (2.2)	29 (0.7)	36 (1.1)	5 (0.8)
TBL					
≥ 2 × to ≤ 3 × ULN	29 (6.3)	41 (8.3)	67 (1.7)	39 (1.2)	6 (0.9)
> 3 × to ≤ 5 × ULN	16 (3.5)	18 (3.7)	48 (1.2)	33 (1.0)	1 (0.2)
> 5 × ULN	19 (4.1)	22 (4.5)	56 (1.4)	32 (1.0)	7 (1.1)
Potential Hy's law [a]	57 (12.3)	65 (13.2)	131 (3.2)	85 (2.6)	7 (1.1)

[a] The onset date of ALT or AST elevation should be prior to or on the date of TBL elevation.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first).

Patients were counted only once in the worst reported subcategory.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumour types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumour types); TBL, total bilirubin; ULN, upper limit of normal.

Thyroid function

Table 71: Abnormal thyroid function (safety analysis set)

Category	Number (%) of patients			
	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
Elevated TSH > ULN	150 (38.7)	157 (40.5)	67 (44.1)	178 (47.6)
Elevated TSH > ULN with TSH ≤ ULN at baseline	94 (24.2)	107 (27.6)	47 (30.9)	114 (30.5)
Elevated TSH > 3 × ULN	40 (10.3)	66 (17.0)	28 (18.4)	30 (8.0)
Elevated TSH > 3 × ULN with TSH ≤ ULN at baseline	21 (5.4)	42 (10.8)	18 (11.8)	4 (1.1)
Elevated TSH > 10 × ULN	15 (3.9)	37 (9.5)	13 (8.6)	6 (1.6)
Elevated TSH > 10 × ULN with TSH ≤ ULN at baseline	8 (2.1)	25 (6.4)	11 (7.2)	1 (0.3)
Low TSH < LLN	66 (17.0)	129 (33.2)	43 (28.3)	35 (9.4)
Low TSH < LLN with TSH ≥ LLN at baseline	60 (15.5)	114 (29.4)	39 (25.7)	31 (8.3)

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of investigational product or until initiation of the first subsequent therapy (whichever occurred first).

D, durvalumab monotherapy 1500 mg Q4W; Q4W, every 4 weeks; LLN, lower limit of normal; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

Source: Table 14.3.7.1.6.

Table 72: Abnormal on-treatment thyroid tests (safety analysis set)

Category	Number (%) of patients				
	HCC-tumour pool		Pan-tumour pool		
	T300+D (N = 462)	D (N = 492)	D (N = 4045)	T75+D (N = 3319)	T750 (N = 643)
On-treatment elevated TSH > ULN	180 (39.0)	180 (36.6)	1269 (31.4)	1152 (34.7)	127 (19.8)
On-treatment elevated TSH > ULN with TSH ≤ ULN at baseline *	124	116	780	697	76
with at least one T3 free/T4 free < LLN [a]	73 (58.9)	68 (58.6)	456 (58.5)	420 (60.3)	21 (27.6)
with all other T3 free/T4 free ≥ LLN [a]	41 (33.1)	38 (32.8)	270 (34.6)	216 (31.0)	19 (25.0)
with T3 free/T4 free missing [a]	10 (8.1)	10 (8.6)	54 (6.9)	61 (8.8)	36 (47.4)
On-treatment low TSH < LLN	154 (33.3)	82 (16.7)	880 (21.8)	896 (27.0)	86 (13.4)
On-treatment low TSH < LLN with TSH ≥ LLN at baseline *	136	74	709	778	66
with at least one T3 free/T4 free > ULN [a]	72 (52.9)	28 (37.8)	310 (43.7)	364 (46.8)	11 (16.7)
with all other T3 free/T4 free ≤ ULN [a]	57 (41.9)	36 (48.6)	348 (49.1)	353 (45.4)	19 (28.8)
with T3 free/T4 free missing [a]	7 (5.1)	10 (13.5)	51 (7.2)	61 (7.8)	36 (54.5)
Number of patients with at least one baseline and post-baseline TSH result *	437	464	3679	3028	543
On-treatment elevated TSH > ULN and above baseline [a]	165 (37.8)	162 (34.9)	1108 (30.1)	1011 (33.4)	106 (19.5)
On-treatment decreased TSH < LLN and below baseline [a]	148 (33.9)	80 (17.2)	816 (22.2)	848 (28.0)	76 (14.0)

[a] Percentage is based on number of patients in the main category above denoted with a *.

Baseline is defined as the last result obtained prior to the start of study treatment.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first).

D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; LLN, lower limit of normal; Q4W, every 4 weeks; T3, free triiodothyronine; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T4, free thyroxine; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumour types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumour types); TSH, thyroid stimulating hormone; ULN, upper limit of normal.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

Age

Table 73: Adverse events in any category – patient level by age group

AE category	Number (%) of patients [a]				
	HCC-tumour pool		Pan-tumour pool		
	T300+D (N1 = 226) (N2 = 173) (N3 = 63)	D (N1 = 254) (N2 = 163) (N3 = 75)	D (N1 = 2250) (N2 = 1356) (N3 = 439)	T75+D (N1 = 1852) (N2 = 1126) (N3 = 341)	T750 (N1 = 315) (N2 = 253) (N3 = 75)
Any AE possibly related to any study treatment [b]					
< 65 years	163 (72.1)	132 (52.0)	1287 (57.2)	1223 (66.0)	214 (67.9)
≥ 65 to < 75 years	138 (79.8)	93 (57.1)	804 (59.3)	781 (69.4)	182 (71.9)
≥ 75 years	54 (85.7)	42 (56.0)	248 (56.5)	249 (73.0)	64 (85.3)
Any AE possibly related to durvalumab [b]					
< 65 years	162 (71.7)	132 (52.0)	1283 (57.0)	1201 (64.8)	0
≥ 65 to < 75 years	136 (78.6)	93 (57.1)	801 (59.1)	770 (68.4)	0
≥ 75 years	51 (81.0)	42 (56.0)	248 (56.5)	244 (71.6)	1 (1.3)
Any AE possibly related to tremelimumab [b]					
< 65 years	102 (45.1)	0	0	1137 (61.4)	208 (66.0)
≥ 65 to < 75 years	87 (50.3)	0	0	720 (63.9)	180 (71.1)
≥ 75 years	35 (55.6)	0	0	231 (67.7)	64 (85.3)
Any AE with outcome of death					
< 65 years	9 (4.0)	11 (4.3)	112 (5.0)	110 (5.9)	19 (6.0)
≥ 65 to < 75 years	19 (11.0)	13 (8.0)	90 (6.6)	80 (7.1)	20 (7.9)
≥ 75 years	6 (9.5)	6 (8.0)	29 (6.6)	39 (11.4)	5 (6.7)
Any AE leading to discontinuation of any study treatment					
< 65 years	19 (8.4)	19 (7.5)	188 (8.4)	261 (14.1)	62 (19.7)
≥ 65 to < 75 years	29 (16.8)	19 (11.7)	156 (11.5)	200 (17.8)	69 (27.3)
≥ 75 years	15 (23.8)	9 (12.0)	53 (12.1)	89 (26.1)	24 (32.0)
Any AE leading to discontinuation of durvalumab					
< 65 years	19 (8.4)	19 (7.5)	183 (8.1)	235 (12.7)	0
≥ 65 to < 75 years	29 (16.8)	19 (11.7)	151 (11.1)	189 (16.8)	0
≥ 75 years	15 (23.8)	9 (12.0)	53 (12.1)	77 (22.6)	0
Any AE leading to discontinuation of tremelimumab					
< 65 years	2 (0.9)	0	0	166 (9.0)	62 (19.7)
≥ 65 to < 75 years	3 (1.7)	0	0	128 (11.4)	68 (26.9)
≥ 75 years	2 (3.2)	0	0	58 (17.0)	24 (32.0)

[i] Patients with multiple events in the same category are counted only once in that category. patients with events in more than 1 category are counted once in each of those categories.

[j] As assessed by the investigator. Missing responses are counted as related.

Percentages are calculated from N1, N2, and N3 for < 65 years, ≥ 65 to < 75 years, and ≥ 75 years, respectively.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.

AE, adverse event; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; N1, total number of < 65 years patients, N2, total number of ≥ 65 to < 75 years patients, N3, total number of ≥ 75 years patients; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumour types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumour types).

Table 74: adverse events by age category in the HCC T300+D tumour pool

AE Category or System Organ Class	Number (%) of patients		
	< 65 years (N = 226)	≥ 65 - < 75 years (N = 173)	≥ 75 years (N = 63)
Any AE	218 (96.5)	170 (98.3)	63 (100.0)
Any SAE	91 (40.3)	72 (41.6)	26 (41.3)
Hospitalisation/prolong existing hospitalisation	88 (38.9)	66 (38.2)	25 (39.7)
Life-threatening	14 (6.2)	18 (10.4)	9 (14.3)
Disability/incapacity	3 (1.3)	11 (6.4)	1 (1.6)
Other (medically significant)	23 (10.2)	29 (16.8)	8 (12.7)
Any AE with outcome of death	9 (4.0)	19 (11.0)	6 (19.5)
Any AE leading to discontinuation of study treatment	19 (8.4)	29 (16.8)	15 (23.8)
Psychiatric disorders	24 (10.6)	28 (16.2)	10 (15.9)
Nervous system disorders	30 (13.3)	39 (22.5)	12 (19.0)
Injuries, poisoning, and procedural complications	9 (4.0)	15 (8.7)	11 (17.5)
Cardiac disorders	7 (3.1)	11 (6.4)	5 (7.9)
Vascular disorders	18 (8.0)	28 (16.2)	8 (12.7)
Cerebrovascular disorders	0	0	0
Infections and infestations	824 (36.6)	550 (40.6)	167 (38.0)
Cholinergic syndrome	0	0	0
Sum of selected AEs (e.g. postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures, etc) [b]	5 (2.2)	13 (7.5)	5 (7.9)
Anticholinergic syndrome	0	0	0
Ataxia	0	0	0
Dizziness	4 (1.8)	9 (5.2)	2 (3.2)
Fall	1 (0.4)	2 (1.2)	2 (3.2)
Hand fracture	0	0	0
Multiple fractures	0	0	0
Orthostatic hypotension	0	0	0
Spinal fracture	0	0	0
Syncope	1 (0.4)	2 (1.2)	1 (1.6)
Other AEs appearing more frequently in older patients [c]			
Anaemia	14 (6.2)	17 (9.8)	12 (19.0)

AE Category or System Organ Class	Number (%) of patients		
	< 65 years (N = 226)	≥ 65 - < 75 years (N = 173)	≥ 75 years (N = 63)
Hypothyroidism	21 (9.3)	23 (13.3)	11 (17.5)
Hyperkalaemia	7 (3.1)	9 (5.2)	6 (9.5)
Pneumonitis	1 (0.4)	4 (2.3)	5 (7.9)
Abdominal pain	35 (15.5)	17 (9.8)	6 (9.5)
Constipation	24 (10.6)	18 (10.4)	3 (4.8)
Diarrhoea	55 (24.3)	48 (27.7)	14 (22.2)
Nausea	24 (10.6)	19 (11.0)	14 (22.2)
Pruritus	51 (22.6)	54 (31.2)	13 (20.6)
Rash	58 (25.7)	44 (25.4)	13 (20.6)
Fatigue	33 (14.6)	33 (19.1)	17 (27.0)
Oedema peripheral	14 (6.2)	24 (13.9)	7 (11.1)

AE = adverse event; HCC = hepatocellular carcinoma; Q4W = every 4 weeks; SAE = serious adverse event; T300+D = tremelimumab 300 mg for a single dose and durvalumab 1500 mg Q4W.

[a] The details of each SAE and the criteria met individually are found in the patient narratives

[b] Patients with multiple AEs are counted once for each category and sub-category.

[c] >5% difference between the <65, 65 to 74, and ≥75 age categories.

Body weight

In the HCC D pool, a slight increasing trend for Grade 3 to 4 AEs was observed for patients with **body weight** ≥ 90 kg (N=55), compared to patients < 70 kg (54.5% vs 36.2%), and similarly for SAEs (49.1% vs 29.4%). A similar trend was observed in the Pan-tumour D pool.

ECOG performance status

In both of the HCC-tumour pools, patients with a **baseline ECOG status** of 1 experienced a higher incidence of Grade 3 to 4 AEs (T300+D pool: 56.6% vs 49.1%) and AEs leading to death (T300+D pool: 10.3% vs 5.6%). In the HCC-tumour pools, no other clinically meaningful differences were observed in the safety profile of T300+D versus D alone with respect to performance status.

Geographical region

In the HCC tumour pools, the applicant claimed that there were no clinically meaningful differences in the safety profile of the T300+D pool compared with the D pool with respect to **geographical region**.

2.6.8.7. Immunological events

Table 75: Adverse events in any category, by ADA category to durvalumab (safety analysis set)

AE category [a]	Number (%) of patients											
	D (N = 388)				T300+D (N = 388)				T75+D (N = 152)			
	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]
Number of durvalumab ADA evaluable patients in the category	8	2	20	262	9	5	24	270	5	0	8	100
Any AE	6 (75.0)	2 (100)	18 (90.0)	235 (89.7)	9 (100)	5 (100)	23 (95.8)	264 (97.8)	5 (100)	0	8 (100)	97 (97.0)
Any AE possibly related to treatment [e]	4 (50.0)	0	9 (45.0)	148 (56.5)	5 (55.6)	3 (60.0)	17 (70.8)	213 (78.9)	4 (80.0)	0	5 (62.5)	76 (76.0)
Any AE of CTCAE Grade 3 or 4	2 (25.0)	0	9 (45.0)	89 (34.0)	5 (55.6)	3 (60.0)	10 (41.7)	135 (50.0)	2 (40.0)	0	2 (25.0)	40 (40.0)
Any AE of CTCAE grade 3 or 4, possibly related to treatment [e]	0	0	2 (10.0)	32 (12.2)	2 (22.2)	1 (20.0)	5 (20.8)	66 (24.4)	0	0	0	19 (19.0)
Any AE with outcome of death	0	0	1 (5.0)	9 (3.4)	0	0	2 (8.3)	8 (3.0)	1 (20.0)	0	1 (12.5)	5 (5.0)
Any AE with outcome of death, possibly related to treatment [e]	0	0	0	0	0	0	0	2 (0.7)	0	0	0	1 (1.0)
Any SAE (including events with outcome of death)	0	0	5 (25.0)	65 (24.8)	3 (33.3)	2 (40.0)	8 (33.3)	103 (38.1)	3 (60.0)	0	3 (37.5)	30 (30.0)
Any SAE (including events with outcome of death), possibly related to treatment [e]	0	0	0	17 (6.5)	0	0	1 (4.2)	43 (15.9)	1 (20.0)	0	1 (12.5)	16 (16.0)
Any AE leading to discontinuation of study treatment [f]	0	0	1 (5.0)	13 (5.0)	1 (11.1)	1 (20.0)	2 (8.3)	26 (9.6)	0	0	0	15 (15.0)
Any AE leading to discontinuation of study treatment, possibly related to treatment [e,f]	0	0	0	6 (2.3)	1 (11.1)	1 (20.0)	1 (4.2)	16 (5.9)	0	0	0	8 (8.0)
Any AE leading to dose delay/interruption [g]	0	0	4 (20.0)	73 (27.9)	4 (44.4)	0	11 (45.8)	99 (36.7)	1 (20.0)	0	2 (25.0)	39 (39.0)
Any AESI	1 (12.5)	0	4 (20.0)	113 (43.1)	4 (44.4)	2 (40.0)	12 (50.0)	193 (71.5)	5 (100)	0	6 (75.0)	62 (62.0)
Any AESI, possibly related to treatment [e]	1 (12.5)	0	1 (5.0)	81 (30.9)	4 (44.4)	1 (20.0)	10 (41.7)	162 (60.0)	4 (80.0)	0	5 (62.5)	53 (53.0)
Any infusion reaction AEs [h]	0	0	0	5 (1.9)	0	0	0	16 (5.9)	0	0	0	3 (3.0)

[a] Positive and negative results are with respect to durvalumab. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] Treatment-emergent ADA positive is defined as either treatment-induced or treatment-boosted.

[c] ADA positive, ie, positive ADA result at any time, baseline or post-baseline.

[d] ADA negative, ie, without any ADA positive results (at baseline or post-baseline).

[e] Possibly related to any of the study treatments, as assessed by the Investigator. Missing responses are counted as related.

[f] AEs on the AE eCRF with action taken of 'drug permanently discontinued' for at least one treatment.

[g] AEs on the AE eCRF with action taken of 'drug interrupted' for either molecule.

[h] As assessed by the Investigator.

MedDRA version 23.1. CTCAE version 4.03.

Denominator is the number of ADA evaluable patients (patients in the Safety Analysis Set who have a non-missing baseline ADA and at least one non-missing post-baseline result) in the ADA category.

Includes TEAEs.

ADA, anti-drug antibody; AE, adverse event; AESI, adverse event of special interest; eCRF, electronic case report form; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; nAb, neutralizing antibody; Q4W, every 4 weeks; SAE, serious adverse event; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TE, treatment-emergent.

Source: Table 14.3.9.3.

Table 76: Adverse events in any category, by ADA category to tremelimumab (safety analysis set)

AE category [a]	Number (%) of patients							
	T300+D (N = 388)				T75+D (N = 152)			
	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]
Number of tremelimumab ADA-evaluable patients in the category	20	8	29	153	23	16	30	72
Any AE	19 (95.0)	8 (100)	28 (96.6)	150 (98.0)	23 (100)	16 (100)	30 (100)	70 (97.2)
Any AE possibly related to treatment [e]	15 (75.0)	8 (100)	23 (79.3)	120 (78.4)	18 (78.3)	13 (81.3)	23 (76.7)	54 (75.0)
Any AE of CTCAE Grade 3 or 4	9 (45.0)	6 (75.0)	13 (44.8)	77 (50.3)	10 (43.5)	8 (50.0)	12 (40.0)	27 (37.5)
Any AE of CTCAE Grade 3 or 4, possibly related to treatment [e]	4 (20.0)	3 (37.5)	7 (24.1)	37 (24.2)	1 (4.3)	1 (6.3)	1 (3.3)	15 (20.8)
Any AE with outcome of death	0	0	0	5 (3.3)	2 (8.7)	1 (6.3)	4 (13.3)	2 (2.8)
Any AE with outcome of death, possibly related to treatment [e]	0	0	0	2 (1.3)	0	0	1 (3.3)	0
Any SAE (including events with outcome of death)	9 (45.0)	5 (62.5)	12 (41.4)	58 (37.9)	5 (21.7)	3 (18.8)	8 (26.7)	24 (33.3)
Any SAE (including events with outcome of death), possibly related to treatment [e]	6 (30.0)	3 (37.5)	7 (24.1)	25 (16.3)	1 (4.3)	1 (6.3)	3 (10.0)	13 (18.1)
Any AE leading to discontinuation of study treatment [f]	3 (15.0)	2 (25.0)	4 (13.8)	14 (9.2)	3 (13.0)	3 (18.8)	4 (13.3)	10 (13.9)
Any AE leading to discontinuation of study treatment, possibly related to treatment [e,f]	2 (10.0)	2 (25.0)	3 (10.3)	11 (7.2)	0	0	1 (3.3)	7 (9.7)
Any AE leading to dose delay/interruption [g]	8 (40.0)	2 (25.0)	10 (34.5)	57 (37.3)	9 (39.1)	8 (50.0)	10 (33.3)	28 (38.9)
Any AESI	16 (80.0)	6 (75.0)	20 (69.0)	104 (68.0)	15 (65.2)	9 (56.3)	19 (63.3)	46 (63.9)
Any AESI, possibly related to treatment [e]	14 (70.0)	6 (75.0)	17 (58.6)	89 (58.2)	12 (52.2)	9 (56.3)	16 (53.3)	40 (55.6)
Any infusion reaction AEs [h]	2 (10.0)	1 (12.5)	2 (6.9)	10 (6.5)	0	0	0	3 (4.2)

[a] Positive and negative results are with respect to tremelimumab. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] Treatment-emergent ADA positive is defined as either treatment-induced or treatment-boosted.
[c] ADA positive, ie, positive ADA result at any time, baseline or post-baseline.
[d] ADA negative, ie, without any ADA positive results (at baseline or post-baseline).
[e] Possibly related to any of the study treatments, as assessed by the Investigator. Missing responses are counted as related.
[f] AEs on the AE eCRF with action taken of 'drug permanently discontinued' for at least one treatment.
[g] AEs on the AE eCRF with action taken of 'drug interrupted' for either molecule.
[h] As assessed by Investigator.

MedDRA version 23.1. CTCAE version 4.03.

Denominator is the number of ADA evaluable patients (patients in the Safety Analysis Set who have a non-missing baseline ADA and at least one non-missing post-baseline result) in the ADA category.

Includes TEAEs.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; eCRF, electronic case report form; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; nAb, neutralizing antibody; Q4W, every 4 weeks; SAE, serious adverse event; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TE, treatment-emergent.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Durvalumab and tremelimumab are immunoglobulins, therefore, no formal pharmacokinetic drug-drug interaction studies have been conducted.

2.6.8.9. Discontinuation due to adverse events

Table 77: Adverse events leading to discontinuation of study medication by system organ class, preferred term and maximum reported CCAE grade (safety analysis aet) – DCO: 27 AUG 2021

System organ class / MedDRA Preferred term	Maximum reported CTCAE grade	Number (%) of subjects[a] Durva 1500 mg (N=388)	Treme 300 mg x1 dose + Durva 1500 mg (N=388)	Treme 75 mg x4 doses + Durva 1500 mg (N=152)	Sora 400 mg BID (N=374)
Subjects with any AE	Total	32 (8.2)	53 (13.7)	23 (15.1)	63 (16.8)
	Grade 1	0	2 (0.5)	0	2 (0.5)
	Grade 2	6 (1.5)	7 (1.8)	5 (3.3)	16 (4.3)
	Grade 3	13 (3.4)	21 (5.4)	6 (3.9)	27 (7.2)
	Grade 4	2 (0.5)	4 (1.0)	5 (3.3)	1 (0.3)
	Grade 5	11 (2.8)	19 (4.9)	7 (4.6)	17 (4.5)
	Grade >=3	26 (6.7)	44 (11.3)	18 (11.8)	45 (12.0)
	Grade 3-4	15 (3.9)	25 (6.4)	11 (7.2)	28 (7.5)

Table 78: Adverse events leading to discontinuation by system organ class and preferred term (⩾ 1% patients in any treatment group) (safety analysis set)

	Number (%) of patients [a]				
	HCC-tumour pool		Pan-tumour pool		
	T300+D	D	D	T75+D	T750
MedDRA preferred term	(N = 462)	(N = 492)	(N = 4045)	(N = 3319)	(N = 643)
Patients with any AE leading to discontinuation of any study treatment	63 (13.6)	47 (9.6)	397 (9.8)	550 (16.6)	155 (24.1)
Respiratory, thoracic and mediastinal disorders	4 (0.9)	2 (0.4)	84 (2.1)	113 (3.4)	9 (1.4)
Pneumonitis	2 (0.4)	1 (0.2)	36 (0.9)	49 (1.5)	2 (0.3)
Gastrointestinal disorders	14 (3.0)	9 (1.8)	41 (1.0)	125 (3.8)	98 (15.2)
Colitis	2 (0.4)	1 (0.2)	6 (0.1)	32 (1.0)	26 (4.0)
Diarrhoea	3 (0.6)	2 (0.4)	8 (0.2)	37 (1.1)	63 (9.8)
Investigations	8 (1.7)	6 (1.2)	25 (0.6)	42 (1.3)	11 (1.7)
Aspartate aminotransferase increased	5 (1.1)	3 (0.6)	6 (0.1)	8 (0.2)	1 (0.2)

k Number (%) of patients with AEs leading to discontinuation, sorted by international order for system organ class and alphabetically for preferred term.

Patients with multiple AEs are counted once for each system organ class/preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication, or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.

Percentages are based on the total numbers of patients in the treatment group (N).

MedDRA version 23.1.

AE, adverse event; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumour types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumour types).

Table 79: Adverse events leading to dose delay/interruption by system organ class and preferred term (⩾ 1% patients in any treatment group) (safety analysis set)

	Number (%) of patients [a]				
	HCC-tumour pool		Pan-tumour pool		
	T300+D	D	D	T75+D	T750
MedDRA preferred term	(N = 462)	(N = 492)	(N = 4045)	(N = 3319)	(N = 643)
Patients with any AE leading to dose delay/interruption of any study treatment	149 (32.3)	112 (22.8)	1120 (27.7)	945 (28.5)	144 (22.4)
Infections and infestations	22 (4.8)	12 (2.4)	255 (6.3)	183 (5.5)	18 (2.8)
Pneumonia	6 (1.3)	1 (0.2)	88 (2.2)	63 (1.9)	7 (1.1)
Blood and lymphatic system disorders	12 (2.6)	11 (2.2)	64 (1.6)	53 (1.6)	9 (1.4)
Anaemia	6 (1.3)	4 (0.8)	39 (1.0)	28 (0.8)	7 (1.1)
Endocrine disorders	9 (1.9)	6 (1.2)	75 (1.9)	88 (2.7)	7 (1.1)
Hyperthyroidism	5 (1.1)	0	28 (0.7)	34 (1.0)	0
Respiratory, thoracic and mediastinal disorders	7 (1.5)	5 (1.0)	171 (4.2)	116 (3.5)	12 (1.9)
Pneumonitis	3 (0.6)	1 (0.2)	48 (1.2)	39 (1.2)	3 (0.5)
Gastrointestinal disorders	23 (5.0)	12 (2.4)	140 (3.5)	186 (5.6)	54 (8.4)
Colitis	5 (1.1)	0	4 (< 0.1)	25 (0.8)	1 (0.2)
Diarrhoea	16 (3.5)	4 (0.8)	48 (1.2)	82 (2.5)	43 (6.7)
Hepatobiliary disorders	18 (3.9)	15 (3.0)	44 (1.1)	38 (1.1)	1 (0.2)
Hepatic function abnormal	3 (0.6)	5 (1.0)	8 (0.2)	7 (0.2)	1 (0.2)
Hepatitis	6 (1.3)	1 (0.2)	6 (0.1)	9 (0.3)	0
Skin and subcutaneous tissue disorders	21 (4.5)	12 (2.4)	64 (1.6)	91 (2.7)	19 (3.0)
Rash	10 (2.2)	3 (0.6)	14 (0.3)	34 (1.0)	7 (1.1)
General disorders and administration site conditions	13 (2.8)	3 (0.6)	147 (3.6)	112 (3.4)	19 (3.0)
Pyrexia	9 (1.9)	1 (0.2)	43 (1.1)	25 (0.8)	5 (0.8)
Investigations	47 (10.2)	45 (9.1)	214 (5.3)	203 (6.1)	19 (3.0)
Alanine aminotransferase increased	13 (2.8)	15 (3.0)	47 (1.2)	52 (1.6)	2 (0.3)
Amylase increased	14 (3.0)	1 (0.2)	22 (0.5)	34 (1.0)	2 (0.3)
Aspartate aminotransferase increased	12 (2.6)	23 (4.7)	64 (1.6)	53 (1.6)	4 (0.6)
Lipase increased	11 (2.4)	7 (1.4)	27 (0.7)	58 (1.7)	6 (0.9)
Injury, poisoning and procedural complications	5 (1.1)	0	73 (1.8)	40 (1.2)	4 (0.6)
Radiation pneumonitis	0	0	41 (1.0)	1 (< 0.1)	0

Number (%) of patients with AE leading to dose delay or interruption, sorted by international order for system organ class and alphabetically for preferred term.

Patients with multiple AEs are counted once for each system organ class/preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.

MedDRA version 23.1.

AE, adverse event; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumour types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumour types).

2.6.8.10. Post marketing experience

Tremelimumab is not yet approved for use in any country.

2.6.9. Discussion on clinical safety

The safety population of interest are patients with unresectable HCC (uHCC), who have received the proposed dosing regimen of a single dose of Tremelimumab 300 mg + durvalumab in combination followed by durvalumab monotherapy (T300+D), which consists of 388 patients from the pivotal Himalaya study and 74 patients from the supportive study 22, in total 462 patients.

The median treatment duration in the Himalaya study were 5.5 months, while the median treatment duration was 4.1 months in the Sorafenib arm (n=374). In the HCC pool, the median duration of exposure was 20 weeks and approximately 50% of patients received at least 24 weeks of treatment at DCO, while ~28% had 52 weeks of treatment. Hence, the exposure to the proposed regimen and the size of the safety database are considered sufficient for a safety assessment.

Almost all patients in the HCC pool, who received T300+D, experienced at least one **adverse event** (AE) (97.6%), and 51.9% experienced a grade 3 or 4 AEs. For the Himalaya study, a similar pattern was observed in T300+D arm: 97.4% experienced at least one AE, 50.5% experienced a grade 3 or 4 AE, and SAEs were observed in 40.5% of the patients, noting 7.7% had an SAE leading to death. The discontinuation rate due to AEs was 13.7%. In comparison, 95.5% of the patients in the Sorafenib arm also experienced at least one AE, and 52.4% experienced a grade 3 or 4 AE. SAEs were observed in 29.7% of the patients, of which 7.2% had an SAE leading to death, while the discontinuation rate due to AEs was 16.8%.

Treatment-related AEs or adverse drug reactions (ADRs) in the T300+D arm of the pivotal Himalaya study were rash (19.6%), pruritus (17%), diarrhoea (16.5%), and hypothyroidism (10.8%). In comparison, common ADRs in the Sorafenib arm were diarrhoea (38.8%), palmar-plantar erythrodysaesthesia (PPE) (43.9%), hypertension (15%), and fatigue (14.7%). The most common grade 3 or 4 ADRs in the T300+D arm were increased lipase (4.4%), diarrhoea (3.4%), amylase increased (2.6%) and ASAT increased (2.3%). Common grade 3 or 4 ADRs in the S arm were PPE (8.8%), hypertension (5.3%), and diarrhoea (4%), so in comparison there are more high-grade toxicity with sorafenib in favour of T300+D.

Adverse events of special interest for T300+D include immune-mediated AEs (imAEs) and as expected, the occurrence of imAEs are much more common in the HCC pool vs the Sorafenib arm (36.1% vs 7.5%), and these were of grade 3 or 4 in 13.4% vs 2.4% of the patients, respectively. Serious imAEs are considered common (10.2% vs 1.1%) and 6 patients (1.3%) died from these, while a quarter of the patients need systemic corticosteroids in the HCC pool versus only 4% in the Sorafenib arm. Moreover, many patients needed endocrine therapy, when treated with T300+D vs Sorafenib (14.9% vs 3.5%). It is noted that very few patients had to discontinue treatment due to imAEs (5.6% vs 1.6%), which is reassuring. Other common imAEs with T300+D were hepatic events (7.4%) and diarrhoea/colitis (6.5%). Grade 3 or 4 hepatic events (5%) and diarrhoea/colitis (3.7%) were the most frequent high-grade events, and these are difficult to manage in the clinic, so it is important that this is clear from the SmPC section 4.4, which is the case. Overall, imAEs were frequently reported and the number of AESIs and imAEs significantly differ for dermatitis/rash, pancreatic events, hepatic events, diarrhoea/colitis, hypothyroid and hyperthyroid events, pneumonitis. Some imAEs such as endocrinopathies, hepatotoxicity, dermatitis/rash are expected to be more manageable than others, such as diarrhoea/colitis, pancreatic events and pneumonitis. The latter are more difficult to manage, often require hospitalisation, and might not be assumed as immune-mediated events by clinicians.

Events of Stevens-Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors and CTLA-4 inhibitors. Patients should be monitored for signs and symptoms of rash or dermatitis and managed through dose interruption, treatment discontinuation and/or corticosteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Patients should be monitored for alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels prior to initiation of treatment and prior to each subsequent infusion. Additional monitoring is to be considered based on clinical evaluation. Patients should be monitored for abnormal renal function tests prior to and periodically during treatment. Patients should also be monitored for signs and symptoms of immune-mediated pancreatitis and myocarditis. Immune mediated hepatitis, nephritis, pancreatitis and myocarditis should be managed through dose interruption, treatment discontinuation and/or corticosteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed through dose interruption, treatment discontinuation and corticosteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Patients should be monitored for signs and symptoms of colitis/diarrhoea and intestinal perforation and managed through dose interruption, treatment discontinuation and/or corticosteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-mediated hypothyroidism, hyperthyroidism, and thyroiditis should be managed through dose interruption, symptomatic treatment or thyroid hormone replacement as clinically indicated (see sections 4.2 and 4.4 of the SmPC).

Immune mediated adrenal insufficiency occurred in patients receiving Tremelimumab AstraZeneca in combination with durvalumab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed through dose interruption, corticosteroid treatment and hormone replacement (see sections 4.2 and 4.4 of the SmPC).

Immune mediated type 1 diabetes mellitus, which can first present as diabetic ketoacidosis that can be fatal if not detected early, occurred in patients receiving tremelimumab in combination with durvalumab and chemotherapy. Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed via treatment with insulin as clinically indicated (see sections 4.2, 4.4 and 4.8 of the SmPC).

Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended through dose interruption and corticosteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Given the mechanism of action of tremelimumab in combination with durvalumab, other potential immune mediated adverse reactions may occur. The following immune-related adverse reactions have been observed in patients treated with tremelimumab in combination with durvalumab: myasthenia gravis, myositis, polymyositis, meningitis, encephalitis, Guillain-Barré syndrome, immune thrombocytopenia and cystitis noninfective. Patients should be monitored for signs and symptoms and managed through dose interruption, treatment discontinuation and/or corticosteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Although the rate of imAEs with the T300+D is considered high, these are considered generally clinically manageable.

Patients should also be monitored for signs and symptoms of IRRs. IRRs should be managed through dose interruption, treatment discontinuation, prophylaxis and appropriate treatment (see sections 4.2 and 4.4 of the SmPC).

Serious adverse events (SAEs) were very common in the T300+D arm vs the S arm in Himalaya study (40.5% vs 29.7%) and it is noted that 10% less SAEs were observed with durvalumab monotherapy, suggesting that the addition of the single dose of 300 mg tremelimumab significantly adds toxicity. The most frequent SAEs in the T300+D arm vs the S arm were diarrhoea (2.3% vs 1.6%), sepsis (2.1% vs 0), and pneumonia (1.8% vs 2.1%). Overall, the high level of SAEs with T300+D is worrisome although the targeted patient population is previously untreated patients and this may influence the tolerability in the general patient population in the first-line setting. Of note, diarrhoea and colitis are important identified risks of the anti-CTLA-4 agent ipilimumab, which has a similar mechanism of action as tremelimumab. Moreover, the targeted patient population from the 2L+ setting is expected to have even more serious toxicity.

AEs leading to death occurred in 34 patients (7.4%) in the HCC T300+D pool and 30 patients (7.7%) in the T300+D arm of the Himalaya study.

The overall **discontinuation rate** due to AEs in the HCC pool was 13.6%, while it was 13.7% of the patients in the pivotal Himalaya study. Most commonly the patients discontinued treatment due to AST increased and diarrhoea, which reflects the safety profile of T300+D. Dose delays were very common in the patients who had T300+D in the HCC pool (32.3%) and mostly due to diarrhoea and increased liver enzymes.

Laboratory findings showed that the changes in haematological parameters were mostly of low grade and pertaining to a decrease in lymphocytes ≥grade 2 for 20% of the patients and grade 3 or 4 in 11.8%. This is in line with the findings in the pivotal Himalaya study. Laboratory shifts for clinical chemistry parameters were rare and mostly to low grade events. It is noted that increased glucose was common in the HCC pool (19.4%) and that grade 3 or 4 were observed in 14.6% of the patients. New onset diabetes mellitus was identified in 39 (8.4%) of 462 patients in the T300+D HCC pool and 30 (6.1%) of 492 patients in the D monotherapy HCC pool. Eight (1.7%) SAE reports of hyperglycaemia occurred in the T300+D HCC pool and most patients did not receive therapy for the hyperglycaemic event and the reported events were resolved in 21 (4.5%) of the patients in the T300+D HCC pool. One patient with hyperglycaemia and one patient with T2DM discontinued treatment. Liver toxicity was very often observed regarding elevated hepatic laboratory parameters in the HCC pool. Potential Hy's law cases were reported for 57 patients (12.3%) in the HCC pool and the narratives for the 4 patients, who met the Hy's law criteria in the T300+D arm of the pivotal Himalaya study are all agreed.

Increased toxicity with increasing age was observed in the HCC pool, as the incidence of ADRs were 72.1% in the patients of <65 years of age vs 79.8% in patients of 65-75 years of age and 85.7% in those of ≥75 years of age. A trend towards more discontinuations with increasing age was also observed.

Safety and tolerability profiles were similar in patients with ADAs and in those without ADAs. According to the applicant, there were no new types of events or events clearly suggestive or indicative of infusion reactions or immune complex disease.

Overall, the toxicity observed in the first-line study Himalaya was significantly less than what was observed for the entire HCC pool, which is to be expected for the included study population, who was previously systemically untreated patients, who are usually more fit and able to tolerate toxicities. The toxicity observed with Sorafenib is similar to the toxicity level observed in the HCC pool and in some cases worse than what was observed for the T300+D arm of the Himalaya study. However, the toxicity

profiles of T300+D and Sorafenib differs due to different mechanisms of action mainly between immune checkpoint inhibition and a tyrosine kinase inhibitor (TKI).

2.6.10. Conclusions on the clinical safety

The toxicity of the proposed dosing regimen of T300+D is considerable, since approximately half of the patients experience grade 3 or 4 adverse events and 40% of the patients have serious adverse events, mostly pertaining to diarrhoea and immune-mediated adverse events. The discontinuation rate is however relatively low (~13%) and most of the toxicity observed is clinically manageable and the toxicity profile of T300+D is not considered significantly worse than that of Sorafenib, the current standard of care.

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 90: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Immune-mediated adverse reactions
Important potential risks	None
Missing information	None

2.7.2. Pharmacovigilance plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

2.7.3. Risk minimisation measures

Table 91: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Identified Risks		
Immune-mediated adverse reactions	**Routine risk minimisation measures:** • SmPC Sections 4.2, 4.2, and 4.8 • PL Sections 2 and 4 • Prescription-only medicine **Additional risk minimisation measures:** • Patient card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None. **Additional pharmacovigilance activities:** • None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.10.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

A justification to consider the package leaflet user testing report for the POSEIDON MAA (EMEA/H/C/004650) as relevant for this application has been provided. This is considered acceptable on the basis of the similarities in the text of both package

2.9.2. Labelling exemptions

A request to use minimum particulars on the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group. However the QRD Group would like the applicant to take note of the following remarks:

- Vial label: The short pharmaceutical form can be used as proposed on the multilingual label. However on the single language labels the full pharmaceutical form should be used. If not possible, 'after dilution' should be added next to the route of administration, i.e. "IV after dilution".
- Outer carton: The statement "Keep out of the sight and reach of children" can be grey-shaded in Annex IIIA, and there is no need to print it on the actual carton as the product will be handled by healthcare professionals only. This will leave more space on the carton to improve readability of the rest of information.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Imjudo (tremelimumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of

new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved therapeutic indication is:

IMJUDO in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

The aim of the applied dosing regimen of tremelimumab plus durvalumab (T300+D) in comparison to Sorafenib (SOC) in the targeted population is to prolong overall survival (OS).

3.1.2. Available therapies and unmet medical need

The first-line treatment of uHCC includes sorafenib (a tyrosine-kinase inhibitor - TKI) based on OS benefit when compared to placebo (10.7 vs 7.9 months) and lenvatinib, another TKI, which is non-inferior when compared to sorafenib (median OS 13.6 vs 12.3 months). Atezolizumab (a PD-L1 inhibitor) in combination with bevacizumab (a vascular endothelial growth factor receptor inhibitor) has also been approved in the first-line setting, based on the Phase III IMbrave150 study showing improvements of OS and PFS compared to sorafenib i.e. the median OS was 19.2 months with atezolizumab + bevacizumab vs 13.4 months with Sorafenib (HR, 0.66 [95%CI: 0.52, 0.85]), while the PFS by blinded review was 6.9 vs. 4.3 months (HR 0.65 [95%CI: 0.53, 0.81]).

Despite recent advances in treatment options, patients with uHCC continue to have a short life expectancy and the underlying liver disease and portal vein hypertension increase the risk of gastrointestinal bleeding, which can be potentially life-threatening. Currently available therapies provide only a modest improvement in survival with safety profiles that require management due to adverse events such as diarrhoea, hypertension, and palmar-plantar erythrodysaesthesia (PPE). Treatment with atezolizumab plus bevacizumab also carries a higher incidence of bleeding, including fatal bleeding, despite attempts to exclude patients at risk for gastrointestinal bleeding from the pivotal study. Moreover, the underlying liver cirrhosis may result in moderate liver dysfunction, which may exacerbate the toxicity of systemic therapies such as TKIs. Hence, additional therapeutic options are needed, including options for patients with uHCC, who are at higher risk of bleeding events, so there exist an unmet medical need for better and more tolerable treatment options for patients with uHCC.

3.1.3. Main clinical studies

The pivotal study Himalaya is a randomised, open-label, multicentre Phase III study in patients with unresectable HCC not eligible for locoregional therapy, which compared tremelimumab + durvalumab (T300+D) to standard of care, sorafenib, in the first-line setting. The primary endpoint was OS in the ITT population.

Additional supportive evidence of clinical efficacy was provided from Study 22, a randomised, phase I/II, open-label study conducted in the 2L+ setting, comparing the efficacy of T300+D and durvalumab monotherapy.

3.2. Favourable effects

The primary endpoint for the Himalaya study was met as treatment with T300+D showed a statistically significant improvement in **overall survival (OS)** compared to standard of care, Sorafenib.

- At data cutoff 27 August 2021 and after ~33 months of follow up, 66.7% OS events had occurred in the T300+D arm versus 75.3% OS events in the Sorafenib arm, treatment with T300+D showed a statistically significant survival benefit as compared with SoC: Median OS was improved from 13.77 months to 16.43 months, HR 0.78 (96.02% CI: 0.65, 0.93).
- The secondary endpoint of **ORR** by investigator was 20.1% for the T300+D arm compared to 5.1% in the sorafenib arm, and the median duration of response was 22.34 months in the T300+D arm vs 18.43 months in the sorafenib arm.
- The **PFS** analyses were not controlled for multiplicity. PFS by investigator was not significantly improved, since the median PFS was 3.78 months in the T300+D arm versus 4.07 months in the S arm; HR 0.90 (95%CI: 0.77, 1.05). The event rates were 85.2% and 84.1% in the T300+D and S arms, respectively.
- Relevant **subgroup analyses** of the primary endpoint of OS show that the benefit of T300+D vs S is maintained across important subgroups of age of less than or ≥ 65 years, HBV or other reasons for liver disease, ECOG performance status, macrovascular invasion (MVI), AFP at baseline and BCLB score C.

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

The safety populations of interest are the 388 patients from the pivotal Himalaya study and the patients included in the HCC pool (n=462), which also contains patients from the supportive study 22. The median treatment duration in the Himalaya study were 5.5 months, while the median treatment duration was 4.1 months in the Sorafenib arm (n=374).

Almost all of the patients in the HCC pool, who received T300+D, experienced at least one **adverse event** (AE) (97.6%), and 51.9% experienced a grade 3 or 4 AE. For the Himalaya study, a similar pattern was observed.

Adverse drug reactions (ADRs) in the T300+D arm of the pivotal Himalaya study were rash , pruritus , diarrhoea , and hypothyroidism. In comparison, common ADRs in the Sorafenib arm were diarrhoea, palmar-plantar erythrodysaesthesia (PPE), hypertension, and fatigue. The most common grade 3 or 4 ADRs in the T300+D arm were increased lipase, diarrhoea, amylase increased and ASAT increased. Common grade 3 or 4 ADRs in the S arm were PPE, hypertension, and diarrhoea.

Adverse events of special interest for T300+D include immune-mediated AEs (imAEs) and as expected, the occurrence of imAEs are much more common in the HCC pool vs the Sorafenib arm (36.1% vs 7.5%), and these were of grade 3 or 4 in 13.4% vs 2.4% of the patients, respectively. Serious imAEs were observed in 10.2% vs 1.1% and 6 patients (1.3%) died from these.

The most common **serious adverse reactions** in the T300+D HCC pool are colitis (2.6%), diarrhoea (2.4%), pneumonia (2.2%), and hepatitis (1.7%).

In the pivotal Himalaya study, 6.1% of the patients in the T300+D arm **died from an adverse event**, while it was 7.4% in the HCC pool.

The overall **discontinuation rate** due to ADRs was 6.5%. Most commonly the patients discontinued treatment due to ADRs of hepatitis (1.5%) and aspartate aminotransferase increased/alanine aminotransferase increased (1.3%).

Laboratory findings showed that the changes in haematological parameters and clinical chemistry were mostly to low grade events. It is noted that increased glucose was common in the HCC pool (19.4%) and that grade 3 or 4 were observed in 14.6% of the patients. Liver toxicity was often observed regarding elevated hepatic laboratory parameters in the HCC pool and potential Hy's law cases were reported for 57 patients (12.3%) in the HCC pool.

3.5. Uncertainties and limitations about unfavourable effects

There are very limited safety data on elderly aged 75 years and older (see section 4.8 of the SmPC).

3.6. Effects Table

Table 92: Effects table for T300+D in the treatment of uHCC for the Himalaya Study (data cut-off: 27 August 2021)

Effect	Short Description	Unit	Treatment T300+D	Control Sorafenib	Control Durvalumab	Uncertainties/ Strength of evidence	Ref
Favourable Effects			**N=393**	**N=389**	**N=389**		
OS	Median overall survival	Months 95%CI	**16.43** 14.16; 19.58	**13.77** 12.25; 16.13	16.56 14.06; 19.12	At 71% events, HR for T300+D vs S **0.78** (96.02%CI: 0.65; 0.93) P=0.0035	
PFS by INV	Progression-free survival	Months 95%CI	3.78 3.68; 5.32	4.07 3.75; 5.49	3.65 3.19, 3.75	Comparison was not formally tested; no BICR assessment	
ORR	Overall response rate	%	20.1	5.1	17.0		
DoR	Duration of response	Months	22.34	18.43	16.82		
Unfavourable Effects							
Any AE	Any adverse event	%	97.4	95.5	90.0	Incidences from the Himalaya study, except for the Durvalumab monotherapy arm; which are from the HCC D pool	
Grade 3 or 4 AEs	High-grade AEs	%	50.5	52.4	38.2		
Grade 5 AEs	AEs leading to death	%	7.7	7.2	6.1		
SAEs	Serious AEs	%	40.5	29.7	32.7		
AEs disc.	AEs leading to dis-continuation	%	13.7	16.8	9.6		
ImAEs	Immune-mediated AEs	%	36.1	7.5	16.5	Incidences from the HCC pool for T300+D group	

Effect	Short Description	Unit	Treatment T300+D	Control Sorafenib	Control Durvalumab	Uncertainties/ Strength of evidence	Ref
	Hepatic events	%	7.4	NA	1.6		
	Diarrhoea/ colitis	%	6.5	NA	1.4		

Abbreviations: OS: Overall survival; PFS: Progression free survival; INV: Investigator; ORR: Objective response rate; DoR: Duration of response; AE: Adverse event; SAE: Serious adverse event; ImAEs: Immune-mediated adverse events; HCC: hepatocellular carcinoma; BICR: Blinded independent central review.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The proposed dosing regimen of tremelimumab + durvalumab provides a statistically significant and clinically meaningful survival benefit compared to the current standard of care, sorafenib, in a head-to-head comparison from the pivotal Himalaya study, in a population of patients with unresectable hepatocellular carcinoma, who had not received prior systemic treatment. The ORR was also significantly improved; however, the magnitude of patients who had an objective response with T300+D is still low (~20%). The few objective responses were durable (~22 months), which is considered clinically significant. Hence, the efficacy of T300+D in the first-line setting could be considered shown. Supportive evidence for the application comes from Study 22, which compared T300+D to durvalumab monotherapy in the 2L+ setting.

The safety profiles of T300+D versus sorafenib are distinct as they have different mechanisms of action (immune checkpoint inhibition vs TKI) and the toxicity does not seem worse than sorafenib regarding grade 3 or 4 AEs (50.5% vs 52.4%), AEs leading to discontinuation (13.7% vs 16.8%), and AEs leading to death (7.7% vs 7.2%) as reported in the pivotal Himalaya study. The safety profile of tremelimumab in combination with durvalumab in the HCC setting is serious and has to be weighed against the seriousness of palliative setting and individual patient (ECOG status, age, comorbidities). This is of particular importance since a significant proportion of the immune-mediated adverse events observed with the T300+D regimen were serious (e.g. diarrhoea/colitis, pancreatitis and pneumonitis), expected to be less manageable and often require hospitalisation. Immune-mediated AEs have therefore been included as important identified risks in the list of safety concerns for tremelimumab.

3.7.2. Balance of benefits and risks

The shown overall survival benefit and the fact that the safety profile of T300+D is not worse than that of standard of care, sorafenib, support a positive benefit-risk balance in the first-line treatment setting of advanced, unresectable HCC.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit /risk balance of tremelimumab + durvalumab in the first line treatment of uHCC is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Imjudo is favourable in the following indication(s):

Imjudo in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Imjudo in each Member State the MAH will agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The additional risk miniminsation measure is aimed at increasing awareness and providing information concerning the symptoms of immune-mediated adverse reactions.

The MAH shall ensure that in each Member State where Imjudo is marketed, all physicians who are expected to use Imjudo have access to/are provided with the following to provide to their patients:

Patient card

Key messages of the Patient Card include:

- A warning that immune-mediated adverse reactions (in lay terms) may occur and that they can be serious.
- A description of the symptoms of immune-mediated adverse reactions.
- A reminder to contact a healthcare professional provider immediately to discuss signs and symptoms.
- Space for contact details of the prescriber.
- A reminder to carry the card at all times.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tremelimumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.