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Durvalumab for the treatment of non-small cell lung cancer

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Abstract

Introduction: The prognosis of patients with advanced non-small cell lung cancer (NSCLC) remains poor, with a 5-year overall survival rate of around 15%. Immune checkpoint inhibitors, such as programmed cell death protein 1 and programmed death-ligand 1 (PD-L1) inhibitors, have opened a new era in the management of NSCLC. Three checkpoint inhibitors (nivolumab, pembrolizumab, and atezolizumab) are currently approved by the US Food and Drug Administration (FDA) for advanced NSCLC. Durvalumab, an anti-PD-L1 antibody, is under investigation in several trials.

Areas covered: This article reviews the pharmacological properties, clinical efficacy, and safety of durvalumab as monotherapy and in combination with other drugs for the treatment of locally advanced and advanced NSCLC.

Expert opinion: Durvalumab as monotherapy or in combination with tremelimumab was effective with well-tolerated safety profiles for advanced NSCLC in several phase I or II studies.

The PACIFIC study assessed the effectiveness of durvalumab as maintenance therapy following definitive chemoradiotherapy for unresectable stage III NSCLC, and met its primary endpoints of progression-free survival and overall survival. These results led to FDA approval for this NSCLC population. It will be exciting to follow ongoing phase III studies assessing how durvalumab fits into the rapidly evolving therapeutic landscape for advanced NSCLC.

Keywords: durvalumab; NSCLC; PD-1; PD-L1; immune checkpoint inhibitors

Article highlights

- Durvalumab specifically binds to human PD-L1 and inhibits its interactions with PD-1 and CD80 expressed on immune cells.
- Phase I and II studies of durvalumab monotherapy suggested it showed similar effects to two PD-1 immune checkpoint inhibitors (ICIs; nivolumab and pembrolizumab) and a PD-L1 ICI (atezolizumab).
- In a phase I study, durvalumab in combination with tremelimumab exhibited antitumor activity irrespective of PD-L1 status.
- Durvalumab maintenance treatment following definitive chemoradiotherapy showed robust effects in locally advanced NSCLC.
- Durvalumab is being investigated in phase III studies as monotherapy and in combination with tremelimumab for first-line treatment of advanced NSCLC. However, the primary endpoints were not met with durvalumab monotherapy (MYSTIC study) or durvalumab plus tremelimumab (MYSTIC and NEPTUNE studies).

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with an estimated 2.1 million newly diagnosed cases and 1.8 million deaths globally in 2018 [1]. The main cause of lung cancer is smoking, which accounts for about 70% of cases [2]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 80% of all primary lung cancers.

The tumor-node-metastasis stage indicates the level of disease progression and the malignant potential of the primary lung cancer, and is used to select the optimal treatment plan [3]. Most NSCLC patients are diagnosed with locally advanced or metastatic disease [4]; only 25% of lung cancer patients are potentially curable by surgery [5]. However, many patients experience recurrence, even after curative resection. About 30% of patients with locally advanced NSCLC present with unresectable, locally advanced disease at diagnosis (stage III). Concurrent chemoradiotherapy is currently recommended as standard treatment for these patients. Although chemoradiotherapy is considered curative treatment, the median progression-free survival (PFS) is around 8 months and only about 20% of patients survive to 5 years [6-8]. Patients with recurrent or metastatic disease are candidates for systemic

chemotherapy, which may improve survival and quality of life measures, but are still considered palliative. Therefore, lung cancer, with a 5-year overall survival (OS) rate of about 15% [3], remains a major challenge to oncological care today.

To improve the outcomes of NSCLC patients, advances in systemic therapy are needed and the development of novel systemic therapy regimens has become an important research focus. Several previous studies of platinum-based combination chemotherapy for advanced NSCLC have shown comparable response rates of 20%–40% and a median OS of about 12 months [9]. However, the efficacy of cytotoxic chemotherapy has reached a plateau.

Targeted therapies have been developed to inhibit aberrant oncogenic pathways and have dramatically changed the treatment paradigm for advanced NSCLC patients with oncogenic driver mutations. Therapies that target oncogenic driver mutations, such as sensitizing mutations in the epidermal growth factor receptor gene (*EGFR*) and fusions of echinoderm microtubule-associated protein-like 4 (*EML4*) and anaplastic lymphoma kinase (*ALK*), have dramatically improved the prognosis of advanced NSCLC, with response rates of about 60%–80% and median OS of >2 years [10-14]. However, these benefits are limited to patients with oncogenic driver mutations. Therefore, for patients without these mutations,

chemotherapy has remained the standard treatment. Although targeted agents were beneficial in stage IV patients with oncogenic driver mutations in *EGFR* or *EML4-ALK*, for example, the role of targeted agents in locally advanced NSCLC has not been fully evaluated.

Immunotherapy based on immune checkpoint inhibitors (ICIs) has opened a new era in the management of several cancer types [15-22]. Inhibitors of target cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway have demonstrated the most promise. Four agents targeting the PD-1/PD-L1 pathway, nivolumab (Opdivo), pembrolizumab (Keytruda), atezolizumab (Tecentriq), and durvalumab (Imfinzi), have been approved for clinical use in NSCLC. This review provides an overview of the preclinical and clinical efficacy of durvalumab in the treatment of NSCLC.

2. Overview of the market

Several ICIs targeting the PD-1/PD-L1 pathway have been developed in recent years for advanced NSCLC. Anti-PD-1/PD-L1 antibodies, including two PD-1 inhibitors (nivolumab and pembrolizumab) and one PD-L1 inhibitor (atezolizumab), were initially approved for advanced NSCLC patients following chemotherapy owing to their improvements in OS and durable

responses compared with standard chemotherapy [23-26]. The second-line treatments nivolumab and atezolizumab are prescribed independently of PD-L1 expression, while pembrolizumab is indicated for patients with PD-L1 expression on >1% of tumor cells. Pembrolizumab was subsequently approved as first-line treatment for advanced NSCLC patients with PD-L1 expression on more than 50% of tumor cells [27]. More recently, pembrolizumab combined with platinum-doublet chemotherapy and atezolizumab combined with platinum-doublet chemotherapy and bevacizumab were approved as first-line treatments for advanced NSCLC, irrespective of PD-L1 expression on tumor cells [28-30]. Additionally, durvalumab was initially approved as consolidation therapy after definitive chemoradiotherapy in patients with locally advanced NSCLC.

Other PD-L1 antibodies, such as avelumab [31,32] and durvalumab, are under development for advanced NSCLC and anti-PD-1/PD-L1 antibodies other than durvalumab are under development for locally advanced NSCLC [33,34]. Moreover, combinations with other agents, including other ICIs and drugs targeting oncogenic driver mutations, are expected. Anti-CTLA-4 antibodies are recognized as promising partners for combination therapy, and are

expected to provide additive or synergetic effects on the immune response [35,36], although these drugs are not yet approved for NSCLC as monotherapy or combination therapy.

3. Introduction to durvalumab

3.1. Chemistry

Durvalumab (Imfinzi, MEDI 4736) is a fully human immunoglobulin G1 (IgG1) monoclonal anti-PD-L1 antibody [37] that blocks interactions of PD-L1 with PD-1 and CD80 and releases the inhibition of immune responses. Antibodies of the IgG1 isotype exert cytotoxic effector activities, including antibody-dependent cell-mediated cytotoxicity (ADCC) activity, against cells expressing their targets. The fragment crystallizable (Fc) domain of the antibody contains a triple mutation in the constant domain of the IgG1 heavy chain, reducing binding to the complement component C1q and the Fcγ receptors responsible for mediating ADCC. The structural modification of the Fc domain of durvalumab ensures the absence of ADCC effector function.

3.2. Pharmacodynamics

In vitro [38], durvalumab specifically binds to human PD-L1, with no detectable cross reactivity to other related proteins (PD-L2 and CD276(B7-H3)), and inhibits its interactions with PD-L1 and CD80 expressed on immune cells. A competitive binding assay, based on homogenous time-resolved fluorescence, showed that durvalumab completely blocked the binding of PD-1 and CD80, with IC_{50} values of 0.1 and 0.04 nmol/L, respectively. A subsequent *in vitro* T cell activation assay showed that durvalumab overcomes PD-L1-mediated inhibition of CD4 T cell activation in a concentration-dependent manner.

In vivo [38], the ability of durvalumab to enhance T cell-mediated tumor cell killing was investigated *in vivo* using xenografts of human melanoma (A375) or pancreatic (HPAC) tumor cell lines. Durvalumab significantly inhibited tumor growth of A375 and HPAC xenografts by 74% and 77%, respectively. Critically, this activity was entirely dependent on the presence of tumor-reactive human T cells, supporting the immunological mechanism of action for durvalumab.

The results of preclinical studies demonstrate that durvalumab is a highly potent PD-L1 antagonistic antibody, and it has since been studied in a range of clinical trials.

3.3. Pharmacokinetics and metabolism

The pharmacokinetics (PK) of durvalumab were studied at doses ranging from 0.1 to 20 mg/kg administered every 2, 3, or 4 weeks. The PK exposure of durvalumab increases more than dose proportionally at doses of <3 mg/kg and dose proportionally at doses of ≥3 mg/kg, with the steady state achieved at around 16 weeks [39]. Durvalumab clearance decreases over time, with a terminal half-life of approximately 17 days [39]. PK modeling indicated that administration of 10 mg/kg every 2 weeks would maintain exposure at >40 µg/mL throughout the dosing interval. The PK of durvalumab are not clinically affected by age (19–96 years), body weight (34–149 kg), sex, albumin levels, lactate dehydrogenase levels, creatinine levels, soluble PD-L1, tumor type, race, mild and moderate renal impairment (creatinine clearance 60–89 and 30–59 mL/min), mild hepatic impairment (bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN or bilirubin > 1.0–1.5 × the ULN and any AST), or Eastern Cooperative Oncology Group performance status. However, it is unknown whether severe renal impairment or moderate or severe hepatic impairment influences the PK of durvalumab.

3.4. Clinical efficacy

3.4.1. Second-line or Later Treatment

Durvalumab monotherapy

A phase I/II study evaluated durvalumab monotherapy in patients with advanced solid tumors (Study 1108, NCT01693562) [40]. This was an open-label, first-in-human, dose-escalation, expansion study performed across multiple centers worldwide. The primary objectives were to assess the safety, PK, pharmacodynamics, and immunogenicity of durvalumab (dose-escalation part) as well as the safety and antitumor activity in NSCLC and urothelial cancer cohorts (expansion part).

In the dose-escalation part of the study, durvalumab was administered intravenously every 2 or 3 weeks for up to 12 months in 26 patients with various malignancies including NSCLC, using a standard 3 + 3 design. Treatment-related adverse events (AE) were observed in 34% of patients, and the AEs were mostly grade 1 or 2 toxicities. The 10 mg/kg dose was chosen to ensure a mean trough concentration of 50 μg/mL. Dose-limiting toxicities were not observed at the 10 mg/kg dose. Following completion of the dose-escalation phase,

the dose of 10 mg/kg every 2 weeks was selected for the tumor-specific expansion phase, which enrolled patients with a variety of tumor types. Recently, the long-term follow-up results of durvalumab in 304 patients with advanced NSCLC (2 in the dose-escalation phase and 302 in the expansion phase) who had been treated with durvalumab at 10 mg/kg every 2 weeks in study 1108 were reported [40]. Initially, patients were enrolled regardless of tumor PD-L1 expression, which was determined using an immunohistochemical assay (Ventana SP263 assay). After assay validation, PD-L1 was defined as positive if ≥25% of tumor cells expressed PD-L1. Protocol amendment required that all remaining non-squamous patients have positive PD-L1 expression. Most of the NSCLC patients (78.9%) had received at least one prior line of chemotherapy, 15.1% were never smokers, and 165 patients had PD-L1 expression of ≥25%. The confirmed objective response rate (ORR) was 15.3% out of 275 evaluable patients. The ORR was 21.8% in patients with PD-L1 expression ≥25% and 6.4% in patients with PD-L1 expression of <25%. Patients were followed for a median of 40.05 months (range, 0.3–52.2 months). Some patients showed a durable response, with 40.6% of responses ongoing in patients with PD-L1 expression of ≥25%. The duration of response was 17.74 months (range, 1.4+ to 41.2+ months). The median OS was 12.4 months overall, and was 16.4 and 7.6 months

in patients with PD-L1 expression of ≥25% and <25%, respectively. The median PFS was 1.7 months overall, and was 2.6 and 1.4 months in patients with PD-L1 expression of ≥25% and <25%, respectively. PD-L1 expression on ≥25% of tumor cells was associated with greater antitumor responses and longer survival. Durvalumab also showed a manageable safety profile in patients with advanced NSCLC. Grade 3 or 4 treatment-related AEs occurred in 10.2% of patients and 5.6% of patients discontinued the study discontinuation due to treatment-related AEs. Treatment-related AEs leading to death occurred in one (0.3%) patient with pneumonia who had ongoing Grade 3/4 treatment-related pneumonitis.

The ATLANTIC (NCT02087423) study [41] was a phase 2, open-label, single-arm, three-cohort study that evaluated durvalumab (10 mg/kg every 2 weeks) as third-line or later treatment in patients with locally advanced or metastatic stage IIIB–IV NSCLC. This study included three independent patient cohorts defined by *EGFR*/*ALK* status and tumor PD-L1 expression: *EGFR*/*ALK* mutation-positive tumors (cohort 1), *EGFR*/*ALK* wild-type tumors (cohort 2), *EGFR*/*ALK* wild-type tumors and PD-L1 expression on ≥90% of tumor cells (cohort 3). Cohorts 1, 2, and 3 comprised 111, 265, and 68 patients, respectively. The ORRs were 12.2%, 16.4% and 30.9%, respectively. The proportions of patients showing a response was lower in

cohort 1 (*EGFR*/*ALK* mutation-positive NSCLC) than in cohorts 2 and 3 (*EGFR*/*ALK* wild-type NSCLC). In cohorts 1 and 2, patients with PD-L1 expression on ≥25% showed higher ORR than patients with PD-L1 expression on <25%, irrespective of the *EGFR*/*ALK* status. In cohort 1, the median PFS was 1.9 and 1.9 months in patients with PD-L1 expression on ≥25% and PD-L1 expression on <25%. In cohort 2, the median PFS was 3.3 and 1.9 months in patients with PD-L1 expression on ≥25% and PD-L1 expression on <25%. In cohort 3, the median PFS was 2.4 months. In cohort 1, the 1-year OS rate was 40.0% and 54.8% in patients in patients with PD-L1 expression on ≥25% and PD-L1 expression on <25%. In cohort 2, the 1-year OS rate was 34.5% and 47.7% in patients in patients with PD-L1 expression on ≥25% and PD-L1 expression on <25%. In cohort 3, the 1-year OS rate was 50.8%. Most AEs were low-grade and manageable with standard treatment guidelines. Treatment-related serious AEs occurred in 6% of patients overall, and 2% discontinued durvalumab due to treatment-related AEs. The most common serious AEs were pneumonitis (1%), fatigue (1%), and infusion-related reactions (1%).

Durvalumab with other drugs

Several phase I studies have evaluated durvalumab in combination with other drugs, including CTLA-4 antibodies. A phase Ib dose-escalation study (NCT02000947) [42] assessed the combination of durvalumab with the anti-CTLA4 antibody tremelimumab in 102 patients. The maximum tolerated dose was durvalumab (20 mg/kg every 4 weeks) plus tremelimumab (1 mg/kg every 4 weeks). This dose was selected for the expansion phase and for use in further studies. Thirty-seven (36%) patients developed serious treatment-related AEs, 29 (28%) patients discontinued due to treatment-related AEs, and 3 patients died following treatment-related AEs. The ORR was 23% (6/26 patients) in patients who received durvalumab (20 mg/kg every 4 weeks) combined with tremelimumab (1 mg/kg every 4 weeks). The antitumor activity of durvalumab plus tremelimumab was observed irrespective of PD-L1 status, with an ORR of 22% (2/9) in patients with PD-L1-positive tumors and 29% (4/14) in patients with PD-L1-negative tumors.

A phase I study investigated durvalumab in combination with gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), in TKI-naive patients with advanced NSCLC harboring *EGFR* mutations (NCT02088112) [43]. In the expansion phase, 10 patients received concurrent durvalumab plus gefitinib (arm 1) and 10 patients received

gefitinib alone for 28 days followed by the combination (arm 2). Grade 3–4 AEs led to treatment discontinuation in four patients, all from arm 2, that included pneumonitis in one patient. The ORRs were 77.8% and 80% in arms 1 and 2, respectively.

The TATTON study (NCT02143466) [44] was a multi-arm phase Ib study that assessed the safety and tolerability of osimertinib, a third-generation EGFR-TKI, in combination with targeted therapy (MET inhibitor and MEK inhibitor), and durvalumab in patients with advanced NSCLC harboring *EGFR* mutations. In the durvalumab plus osimertinib arm, enrollment into the dose-escalation phase (part A) involving TKI-pretreated patients and the dose-expansion phase (part B) involving TKI-naive patients was terminated due to pulmonary toxicity. Pulmonary toxicities occurred in 26% of EGFR-TKI-pretreated patients and 64% of EGFR-TKI-naive patients in parts A and B, respectively, including grade 3–4 severe pneumonitis in 9% and 27% of patients. The combination of osimertinib and durvalumab increased the occurrence of pneumonitis over that expected with either drug alone. As a result, enrolment into the osimertinib plus durvalumab combination arm of the TATTON study was suspended.

3.4.2. First-line treatment

Durvalumab monotherapy or durvalumab plus tremelimumab

Based on the results of phase I and II studies of durvalumab monotherapy, the phase III PEARL study (NCT03003962) [45] was started as a randomized study to determine the efficacy and safety of durvalumab versus platinum-based chemotherapy as first-line treatment of advanced NSCLC in patients with PD-L1 expression of ≥25%.

At present, there are three ongoing phase III studies (MYSTIC, ARCTIC, and NEPTUNE), which are investigating the efficacy of durvalumab plus tremelimumab in patients with advanced NSCLC.

The MYSTIC study (NCT02453282) [46] is a phase III study assessing durvalumab (20 mg/kg every 4 weeks) as monotherapy or in combination with tremelimumab (1 mg/kg every 4 weeks) versus platinum-based chemotherapy as first-line treatment of advanced NSCLC. This study has completed enrolment of 1092 patients. A press release published on 27 December 2017 [47] revealed that the combination of durvalumab plus tremelimumab did not meet the primary endpoint of improving PFS compared with platinum-based chemotherapy in patients with PD-L1 expression on ≥25% of tumor cells. Moreover, the results of two additional primary

endpoints of OS for durvalumab monotherapy and OS for durvalumab plus tremelimumab were reported in a press release on 16 December 2018 [48], and revealed that the study did not meet its primary endpoints of improving OS compared with platinum-based chemotherapy. The OS rates were not statistical significant, but the HRs for OS were <1 for both durvalumab monotherapy (HR 0.76, 95% confidence interval [CI] 0.564, 1.019) and durvalumab plus tremelimumab (HR 0.85, 95% CI 0.611, 1.173). A preplanned exploratory analysis examined survival according to tumor mutational burden (TMB) in the blood, which was determined in 72.4% of patients [49]. In patients with high TMB (≥16 mutations per megabase [mut/Mb]), which accounted for 40% of patients in whom TMB was assessed, the median OSs were 16.5, 11.0, and 10.5 months for durvalumab plus tremelimumab, durvalumab monotherapy, and platinum-based chemotherapy, respectively. The corresponding 2-year OS rates were 39%, 30%, and 18%, respectively. The HR for OS was 0.64 in the durvalumab plus tremelimumab arm compared with platinum-based chemotherapy.

The ARCTIC study (NCT02352948) [50] was a phase III, randomized, open-label multicenter study in patients with advanced NSCLC that evaluated the efficacy and safety of durvalumab versus standard of care (SoC) in patients with PD-L1 expression on ≥25% of tumor

cells (sub-study A) and the combination of durvalumab plus tremelimumab or either agent as monotherapy versus SoC in patients with PD-L1 expression on <25% of tumor cells (sub-study B). In sub-study A, the median OS was 11.7 and 6.8 months for durvalumab and SoC (HR 0.63, 95% CI 0.42, 0.93) with 1-year OS rates of 49.3% and 31.3%, respectively. The median PFS was 3.8 and 2.2 months (HR 0.71, 95% CI 0.49, 1.04). Durvalumab monotherapy reduced the risk of death compared with chemotherapy, but the study was not sufficiently powered to detect statistical significance. In sub-study B, the median OS was 11.5 and 8.7 months for durvalumab plus tremelimumab and SoC (HR 0.80, 95% CI 0.61, 1.05) with 1-year OS rates of 49.5% and 38.3%, respectively. The median PFS was 3.5 and 3.5 months, respectively (HR 0.77, 95% CI 0.59, 1.01). Durvalumab plus tremelimumab did not meet the primary endpoints of statistically significant and clinically meaningful improvements in PFS and OS versus SoC.

The NEPTUNE study (NCT02542293) [51] was a phase III study that determined the efficacy and safety of durvalumab plus tremelimumab versus platinum-based chemotherapy as first-line treatment for advanced NSCLC patients. This study has completed recruitment and the estimated primary completion date is 22 August 2019. On 6 June 2019, the primary endpoint of this study was changed from OS in all patients to OS in patients with blood TMB

(bTMB) ≥20 mut/Mb. A press release on 21 August 2019 [52], reported that the combination of durvalumab plus tremelimumab did not meet the primary endpoint of improving OS versus platinum-based chemotherapy.

Durvalumab plus tremelimumab and chemotherapy

The POSEIDON study (NCT03164616) [53] is an ongoing randomized phase III study that is designed to determine the efficacy and safety of durvalumab plus tremelimumab and platinum-based chemotherapy or durvalumab monotherapy and platinum-based chemotherapy versus platinum-based chemotherapy alone as first-line treatment in patients with advanced NSCLC. This study is still ongoing, but participants are not currently being recruited. The primary endpoints are PFS according to blinded independent central review and OS. The estimated primary data of completion is April 2021.

3.4.3. Consolidation after Chemoradiotherapy

The PACIFIC trial (NCT0212546) [54,55] was a phase III trial designed to evaluate the effectiveness of durvalumab (10 mg/kg every 2 weeks) as maintenance therapy following

definitive chemoradiotherapy for unresectable stage III NSCLC. In this study, 713 patients were randomized to either durvalumab or placebo, every 2 weeks for up to 12 months, starting 1–42 days after completing at least two cycles of platinum-based chemoradiotherapy. The co-primary endpoints were PFS and OS. An interim analysis of PFS was initially reported [54], followed by the 2-year OS [55] and the 3-year OS [56]. The median PFS from randomization was 17.2 months for durvalumab versus 5.6 months for placebo with a hazard ratio (HR) of 0.51 ($P < 0.001$). The ORR was greater with durvalumab versus placebo (28.4% versus 16.0%, $P < 0.001$). In addition, 72.8% of patients who responded to durvalumab had an ongoing response after 18 months of follow-up versus 46.8% with placebo. The 2- and 3-year OS rate with durvalumab and placebo were 66.3% versus 55.3%, and 57.0% versus 43.5%. The median OS was not reached with durvalumab and was 29.1 months with placebo, with a HR of 0.69 (95% CI 0.55, 0.86). The PFS and OS benefits of durvalumab were observed across all prespecified subgroups, which included PD-L1 status (PD-L1-positive [≥25%] or not). Regarding safety, grade 3/4 AEs occurred in 30.5% and 26.1% of patients in the durvalumab and placebo groups, respectively. The most common grade 3/4 AE was pneumonia, which occurred in 4.4% and 3.8% of patients, respectively. Discontinuation due to AEs occurred in 15.4% and 9.8% of

patients, respectively, and death due to AEs occurred in 4.4% and 5.6% of patients, respectively. Based on the PACIFIC study, the US Food and Drug Administration (FDA) approved durvalumab as maintenance treatment following chemoradiotherapy for locally advanced NSCLC. In a subgroup analysis in *EGFR* mutation-positive patients, PFS was not prolonged significantly owing to the low number of events, but the HR was <1 (HR 0.76). Because there were too few events, a subgroup analysis of OS was not performed in *EGFR* mutation-positive patients. In a *post hoc* analysis of patients with PD-L1 expression of <1%, PFS results showed an improvement in durvalumab-treated patients (HR 0.73), but the HR for OS was >1 (HR 1.36). However, PD-L1 expression was not an inclusion criterion in the PACIFIC trial and baseline tissue samples were only available for 64% of patients.

The PACIFIC II trial (NCT03519971) [57] is an ongoing randomized phase III study that was designed to assess the additional efficacy and safety of durvalumab when given concurrently with definitive chemoradiotherapy in patients with locally advanced NSCLC, as compared with chemoradiotherapy alone. The primary endpoints are PFS and ORR, assessed via blinded independent central review. The estimated primary completion date is September 2020.

Several phase III studies have also assessed the efficacy of durvalumab in patients with locally advanced and advanced NSCLC. These ongoing phase II and III studies are listed in Table 1.

3.4.4. Biomarkers

Biomarker expression is an important issue that should be addressed when considering personalized medicines to avoid unnecessary exposure to potential toxicities and to provide the greatest effectiveness. PD-L1 expression on tumor cells is a predictive biomarker for the efficacy of PD-1/PD-L1 checkpoint inhibitors and is often used to determine the treatment strategy. However, PD-L1 expression alone does not fully predict the response to PD-1/PD-L1 ICIs. Rather, a greater somatic mutation burden was shown to be associated with a greater response to immunotherapy in several tumor types, including NSCLC [58,59]. Indeed, recent analyses of the CheckMate 568 [60] and CheckMate 227 [61] studies established the importance of using the TMB to identify which patients are more likely to show a benefit from nivolumab plus ipilimumab. Similarly, a preplanned exploratory analysis of the MYSTIC study [46], showed that bTMB is a potential biomarker for selecting patients for

durvalumab plus tremelimumab therapy. In that study, durvalumab plus tremelimumab showed durable response and a higher 2-year OS rate in patients with high TMB than in patients with a low TMB. Recently, however, it was disappointing to see the negative results of the ongoing phase III study (NEPTUNE) [51], in which the primary endpoint was not met in patients with blood TMB ≥20 mut/Mb.

3.5. Regulatory affairs

As a result of the PACIFIC study, the FDA and the Japan Pharmaceuticals and Medical Devices Agency (PMDA) approval of durvalumab was expanded to include patients with unresectable stage III NSCLC whose disease had not progressed following concurrent platinum-based chemotherapy and radiotherapy. Durvalumab is the first immunotherapy to be approved for this indication. However, in Europe, the European Medical Agency (EMA) has only approved durvalumab for adults with tumors expressing PD-L1 on ≥1% of tumor cells based on the post-hoc analysis of PACIFIC study of patients with PD-L1 <1%. Durvalumab is not approved for use in advanced NSCLC patients by the FDA, EMA or PMDA.

4. Conclusion

In preclinical studies, durvalumab monotherapy showed high affinity and selectivity for its target, PD-L1, induced immune responses and killed tumor cells. In the ATLANTIC study [41], durvalumab monotherapy showed greater clinical activity in patients with PD-L1 expression in ≥25% of tumor cells, and showed durable responses in patients unselected by tumor PD-L1 expression. These data for suggested durvalumab monotherapy was similar to two PD-1 ICIs (nivolumab and pembrolizumab) and a PD-L1 ICI (atezolizumab). Recent developments have shifted towards first-line treatment and combinations with other agents. In this environment, durvalumab is under evaluation as monotherapy and in combination with tremelimumab in the phase III trials MYSTIC [46] and NEPTUNE [51] as a first-line treatment for advanced NSCLC. However, durvalumab monotherapy did not meet the primary endpoint of OS versus chemotherapy in patients with PD-L1 expression ≥25% in the MYSTIC study, and durvalumab plus tremelimumab did not meet the primary endpoints in the MYSTIC and NEPTUNE studies. Therefore, durvalumab in combination with tremelimumab is unlikely to become a standard treatment based on current patient selection criteria. Instead, patients may need to be selected by evaluating more selective biomarkers in future trials. Based on the

positive results of several studies that evaluated anti-PD-1/PD-L1 antibodies, other than durvalumab, in combination with chemotherapy, we would expect similar results using durvalumab in combination with chemotherapy, and this treatment strategy is being investigated in the POSEIDON study [53].

In locally advanced NSCLC, robust data were obtained for durvalumab maintenance treatment following definitive chemoradiotherapy in the PACIFIC study [54,55]. Based on the results of this study, maintenance therapy with durvalumab for 1 year is now considered as the new SoC [62], but there are still many questions to be answered. Which is suitable timing of durvalumab with chemoradiotherapy between concurrent or maintenance? What is the optimal radiation dose to activate the tumor immune system? The ongoing clinical trials could help us to define more suitable timing and duration of ICI therapy in stage III NSCLC.

5. Expert opinion

Immunotherapy based on immune checkpoint blockade has opened a new era for patients with advanced NSCLC by improving survival outcomes with potentially lower toxicity than chemotherapy. PD-1/PD-L1 checkpoint inhibitors, including nivolumab [23,24],

pembrolizumab [25], and atezolizumab [26], have been shown to increase PFS and OS in patients with advanced NSCLC, initially in a second-line setting, and have been approved as standard therapeutic agents. In addition to prolonging the PFS and OS in these patients, PD-1/PD-L1 checkpoint inhibitors showed durable clinical benefits, especially in patients who responded to these agents with ongoing tumor responses. Some patients remained relapse-free even after treatment discontinuation and survived for at least 5 years. The finding that some patients are expected to be cured by systemic treatment has greatly influenced the value of such treatment for patients with advanced NSCLC and a poor prognosis, and has renewed our interest in the long-term survival rate.

Moreover, pembrolizumab prolonged PFS and OS in a first-line setting compared with platinum-based chemotherapy in metastatic NSCLC patients with PD-L1 expression on ≥50% of tumor-cells [27]. These findings highlight the importance of careful patient selection, although some patients with strong PD-L1 expression (on ≥50% of tumor cells) exhibit disease progression immediately after treatment. Although PD-L1 expression on tumor cells and TMB are currently most promising biomarkers, but additional biomarker reflecting the immune status of patients are required.

Recent some clinical studies (KEYNOTE-189 [28], KEYNOTE-407 [29], and IMpower150 [30]) in which PD-1/PD-L1 checkpoint inhibitors were combined with platinum-based chemotherapy, have shown significant improvements in PFS and OS regardless of the PD-L1 expression on tumor cells. The combination of PD-1/PD-L1 checkpoint inhibitors and chemotherapy has overcome the weakness of early progression associated with PD-1/PD-L1 checkpoint inhibitor monotherapy. However, the follow-up duration of studies to date has been insufficient to clarify whether combination therapy improves long-term survival as compared with PD-1/PD-L1 checkpoint inhibitor monotherapy. To evaluate the true value of combination therapy with chemotherapy, we must obtain long-term follow-up data.

The next problems to be solved are the mechanism of acquired resistance to PD-1/PD-L1 checkpoint inhibitors and identifying potential sequential treatments for patients with non-durable responses. For this purpose, the HUDSON study (NCT03334617) [63], an ongoing phase II umbrella study, will examine the use of durvalumab and novel anti-cancer agents for patients with NSCLC who progressed on PD-1/PD-L1 checkpoint inhibitor-based therapy.

Oncologic immunotherapy is a rapidly growing area, and has led to important changes in the SoC for locally advanced or metastatic NSCLC. In the future, the results of ongoing clinical studies examining durvalumab in combination with tremelimumab, chemotherapy, and small targeted molecules could lead to important changes in clinical practice. However, such combinations could increase toxicities, raising the importance of careful patient selection based on biomarker expression.

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Table 1. Ongoing phase II and III studies of durvalumab as monotherapy or in combination with other drugs

Study phase	Description	Clinical trials gov identifier	Tumor types	Start date	Status
III	Monotherapy or combination with tremelimumab versus SoC (MYSTIC)	NCT02453282	Stage IV NSCLC	Jul 2015	Active, not recruiting
III	Combination with tremelimumab versus SoC (NEPTUNE)	NCT02542293	Stage IV NSCLC	Nov 2015	Active, not recruiting
III	Durvalumab or durvalumab and tremelimumab combination with chemotherapy	NCT03164616	Stage IV NSCLC	Jun 2017	Active, not recruiting

	(POSEIDON)				
III	Monotherapy versus SoC (PEARL)	NCT03003962	Stage IV NSCLC PD-L1 high expression	Jan 2017	Active, not recruiting
III	Combination with chemoradiotherapy versus placebo with chemoradiotherapy (PACIFIC2)	NCT03519971	Unresectable stage III NSCLC	Mar 2018	Active, not recruiting
III	Durvalumab or placebo following chemoradiotherapy (PACIFIC5)	NCT03706690	Unresectable stage III NSCLC	Nov 2018	Recruiting
II	Monotherapy	NCT02879617	Stage IIIB or IV NSCLC, PS2	Apr 2017	Recruiting
II	Monotherapy	NCT03345810	Frail and Elder	Dec 2017	Recruiting

	(DURATION)		Patients With stage IV NSCLC		
II	combination with novel agents (Olaparib, AZD9150, AZD6738, Vistusertib, Oleclumab) (HUDSON)	NCT03334617	metastatic NSCLC, progressed on an anti-PD-1/PD-L1 containing therapy	Dec 2017	Recruiting
II	Durvalumab and Tremelimumab combination with chemotherapy (ILLUMINATE)	NCT03994393	Metastatic EGFR Mutant NSCLC	Oct 2018	Recruiting
II	Durvalumab and Olaparib or	NCT03775486	Stage IV NSCLC	Dec 2018	Recruiting

	Durvalumab After Durvalumab and Chemotherapy (ORION)				
II	Monotherapy or combination with Oleclumab or combination with Monalizumab following chemoradiotherapy (COAST)	NCT03822351	Unresectable stage III NSCLC	Dec 2018	Recruiting
II	Durvalumab following sequential chemoradiotherapy (PACIFIC6)	NCT03693300	Unresectable stage III NSCLC	Apr 2019	Recruiting

NSCLC: non-small cell lung cancer; SoC: standard of care.