Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial

*Brian I Rini, Thomas Powles, Michael B Atkins, Bernard Escudier, David F McDermott, Cristina Suarez, Sergio Bracarda, Walter M Stadler, Frede Donskov, Jae Lyun Lee, Robert Hawkins, Alain Ravaud, Boris Alekseev, Michael Staehler, Motohide Uemura, Ugo De Giorgi, Begoña Mellado, Camillo Porta, Bohuslav Melichar, Howard Gurney, Jens Bedke, Toni K Choueiri, Francis Parnis, Tarik Khaznadar, Alpa Thobhani, Shi Li, Elisabeth Piault-Louis, Gretchen Frantz, Mahrukh Huseni, Christina Schiff, Marjorie C Green, Robert J Motzer, on behalf of the IMmotion151 Study Group**

Summary

Background A phase 2 trial showed improved progression-free survival for atezolizumab plus bevacizumab versus sunitinib in patients with metastatic renal cell carcinoma who express programmed death-ligand 1 (PD-L1). Here, we report results of IMmotion151, a phase 3 trial comparing atezolizumab plus bevacizumab versus sunitinib in first-line metastatic renal cell carcinoma.

Methods In this multicentre, open-label, phase 3, randomised controlled trial, patients with a component of clear cell or sarcomatoid histology and who were previously untreated, were recruited from 152 academic medical centres and community oncology practices in 21 countries, mainly in Europe, North America, and the Asia-Pacific region, and were randomly assigned 1:1 to either atezolizumab 1200 mg plus bevacizumab 15 mg/kg intravenously once every 3 weeks or sunitinib 50 mg orally once daily for 4 weeks on, 2 weeks off. A permuted-block randomisation (block size of 4) was applied to obtain a balanced assignment to each treatment group with respect to the stratification factors. Study investigators and participants were not masked to treatment allocation. Patients, investigators, independent radiology committee members, and the sponsor were masked to PD-L1 expression status. Co-primary endpoints were investigator-assessed progression-free survival in the PD-L1 positive population and overall survival in the intention-to-treat (ITT) population. This trial is registered with ClinicalTrials.gov, number NCT02420821.

Findings Of 915 patients enrolled between May 20, 2015, and Oct 12, 2016, 454 were randomly assigned to the atezolizumab plus bevacizumab group and 461 to the sunitinib group. 362 (40%) of 915 patients had PD-L1 positive disease. Median follow-up was 15 months at the primary progression-free survival analysis and 24 months at the overall survival interim analysis. In the PD-L1 positive population, the median progression-free survival was 11·2 months in the atezolizumab plus bevacizumab group versus 7·7 months in the sunitinib group (hazard ratio [HR] 0·74 [95% CI 0·57–0·96]; p=0·0217). In the ITT population, median overall survival had an HR of 0·93 (0·76–1·14) and the results did not cross the significance boundary at the interim analysis. 182 (40%) of 451 patients in the atezolizumab plus bevacizumab group and 240 (54%) of 446 patients in the sunitinib group had treatment-related grade 3–4 adverse events: 24 (5%) in the atezolizumab plus bevacizumab group and 37 (8%) in the sunitinib group had treatment-related all-grade adverse events, which led to treatment-regimen discontinuation.

Interpretation Atezolizumab plus bevacizumab prolonged progression-free survival versus sunitinib in patients with metastatic renal cell carcinoma and showed a favourable safety profile. Longer-term follow-up is necessary to establish whether a survival benefit will emerge. These study results support atezolizumab plus bevacizumab as a first-line treatment option for selected patients with advanced renal cell carcinoma.

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Introduction

In patients with locally advanced or metastatic renal cell carcinoma, tyrosine kinase inhibitors targeting vascular endothelial growth factor (VEGF), such as sunitinib, have been the first-line standard of care for the past decade.[1–3] However, many patients have disease that is inherently resistant to these approaches, and almost all patients acquire resistance over time.[4] Efficacy is particularly low in some patient subgroups, including cases with a sarcomatoid differentiation[5] and disease expressing programmed death-ligand 1 (PD-L1).[6–8] Additionally, the use of these drugs can be limited by adverse events, such as diarrhoea, fatigue, palmar-plantar erythrodysaesthesia, and mucositis,

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*Investigators listed in the appendix

Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA (B I Rini MD); **Barts Cancer Institute and the Royal Free Hospital, Queen Mary University of London, London, UK** (T Powles MD); **Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA** (M B Atkins MD); **Gustave Roussy, Villejuif, France** (B Escudier MD); **Beth Israel Deaconess Medical Center, Boston, MA, USA** (D F McDermott MD); **Vall d'Hebron Institute of Oncology, Vall d´Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain** (C Suarez MD); **Azienda Ospedaliera S Maria, Terni, Italy** (S Bracarda MD); **The University of Chicago Medicine, Chicago, IL, USA** (W M Stadler MD); **Department of Oncology, Aarhus University Hospital, Aarhus, Denmark** (F Donskov DMSc); **Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea** (J L Lee MD); **The Christie NHS Foundation Trust, Manchester, UK** (R Hawkins PhD); **CHU Hôpitaux de Bordeaux–Hôpital Saint-André, Bordeaux, France** (A Ravaud MD); **P Herzen Oncology Research Institute, Moscow, Russia** (B Alekseev MD); **Klinikum der Universität München, Campus**

Großhadern, München, Germany (M Staehler MD); **Department of Urology, Osaka University Graduate School of Medicine, Osaka, Japan** (M Uemura MD); **Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, IRCCS, Meldola, Italy** (U De Giorgi MD); **Hospital Clínic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain** (B Mellado MD); **IRCCS San Matteo University Hospital Foundation, Pavia, Italy** (C Porta PhD); **Lékařská Fakulta Univerzita Palackého a Fakultní Nemocnice Olomouc, Olomouc, Czech Republic** (B Melichar MD); **Department of Clinical Medicine, Macquarie University, Sydney, NSW, Australia** (H Gurney MBBS); **Department of Urology, University of Tübingen, Tübingen, Germany** (J Bedke MD); **Dana-Farber Cancer Institute, Boston, MA, USA** (T K Choueiri MD); **Ashford Cancer Centre Research, Kurralta Park, SA, Australia** (F Parnis MBBS); **F Hoffmann–La Roche, Basel, Switzerland** (T Khaznadar MSc); **Roche Products Ltd, Welwyn Garden City, UK** (A Thobhani MSc); **Genentech, Inc, South San Francisco, CA, USA** (S Li PhD, E Piault-Louis PharmD, G Frantz PhD, M Huseni MS, C Schiff MD, M C Green MD); **and Memorial Sloan Kettering Cancer Center, New York, NY, USA** (R J Motzer MD)

Correspondence to:
Dr Brian Rini, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH 44195, USA
rinib2@ccf.org

See Online for appendix

Research in context

Evidence before this study

We searched PubMed and international congress presentations pertaining to studies in metastatic renal cell carcinoma between May 1, 2010, and May 1, 2015, for articles published in English with MeSH search terms "metastatic" AND "kidney cancer", "renal cell carcinoma", "programmed cell death 1", "PD-1", "programmed cell death ligand 1", and "PD-L1". We identified an unmet clinical need for effective and tolerable approaches to the treatment of patients with metastatic renal cell carcinoma. Approved therapies in the first-line metastatic setting included tyrosine kinase inhibitors, such as sunitinib and pazopanib, and the combination of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab with interferon alfa-2a; however, these therapies are associated with considerable morbidity due to adverse events and do not result in a sustained, durable clinical benefit. Additionally, elevated programmed death-ligand 1 (PD-L1) expression on tumour-infiltrating immune cells is often associated with a worse prognosis in renal cell carcinoma. Checkpoint inhibitors, such as atezolizumab, nivolumab, and pembrolizumab, target the PD-L1 or programmed cell death protein 1 (PD-1) pathway and represent an attractive strategy to reinvigorate tumour-specific T-cell immunity. Despite numerous advancements, metastatic renal cell carcinoma remains a largely incurable disease because a substantial majority of patients develop resistance to standard therapies, including VEGF-directed drugs or immunotherapy. Therefore, an ongoing need exists for more-efficacious and better-tolerated treatments. Collectively, the role of VEGF in the immune response and its crucial role in renal cell carcinoma pathogenesis provide a compelling rationale to test whether dual inhibition of the PD-L1–PD-1 and VEGF pathways will result in improved clinical benefit for patients with metastatic renal cell carcinoma.

Added value of this study

The IMmotion151 trial met its coprimary endpoint, showing improved investigator-assessed progression-free survival with atezolizumab plus bevacizumab versus sunitinib in patients with metastatic renal cell carcinoma whose disease expressed PD-L1. Clinical efficacy is further supported by higher objective response rates, especially complete response rates, with atezolizumab plus bevacizumab versus sunitinib treatment. Overall survival did not cross the significance boundary, and longer-term follow-up is necessary to establish whether a survival benefit will emerge. Patients given atezolizumab plus bevacizumab had improved progression-free survival regardless of the clinical risk group examined, including patients with previous nephrectomy, sarcomatoid histology, and established prognostic risk scores, including patients with favourable prognostic risk. The combination of atezolizumab plus bevacizumab was shown to have a tolerable safety profile consistent with previous studies and was associated with fewer high-grade treatment-related adverse events and a lower regimen discontinuation rate versus sunitinib, and low corticosteroid use. Additionally, patients reported a delay in symptom interference with daily living when given atezolizumab plus bevacizumab versus sunitinib. Results support the clinical activity of checkpoint inhibitor-based combinations in first-line metastatic renal cell carcinoma.

Implications of all the available evidence

Given that both the VEGF and PD-L1 pathways are important in renal cell carcinoma pathogenesis, concomitant inhibition of VEGF signalling might enhance the efficacy of immunotherapy in the front-line treatment of patients with metastatic renal cell carcinoma. Results from this study and others support this hypothesis.

which impair patients' quality of life,[9,10] underscoring a need for new therapeutic targets and drug combinations for patients with metastatic renal cell carcinoma. Treatment with checkpoint inhibitors, including the anti-PD-L1 antibody atezolizumab, has resulted in durable responses and improvements in overall survival in pre-treated patients with metastatic renal cell carcinoma.[7,11,12]

Bevacizumab binds to VEGF and is approved in combination with interferon alfa for metastatic renal cell carcinoma.[13] In addition to its antiangiogenic effects,[14] VEGF blockade by bevacizumab modulates the immune environment, including enhancing T-cell priming and activation via promotion of dendritic cell maturation,[15,16] increasing T-cell tumour infiltration by normalising tumour vasculature,[17,18] and establishing an immune-permissive tumour microenvironment by decreasing myeloid-derived suppressor-cell and regulatory T-cell populations.[18,19] Therefore, T-cell-mediated cancer-cell killing by atezolizumab could be enhanced through reversal of VEGF-mediated immunosuppression mechanisms by the addition of bevacizumab.[20]

Objective responses for atezolizumab plus bevacizumab were first observed in a phase 1b study[18] in metastatic renal cell carcinoma. Subsequently, a phase 2 study[11] assessed atezolizumab alone and in combination with bevacizumab versus sunitinib. Atezolizumab plus bevacizumab improved progression-free survival and the proportion of patients who achieved an objective response versus sunitinib in the subgroup of patients with disease expressing PD-L1. Atezolizumab also showed antitumour activity when administered as a single drug, supporting complementary activity of bevacizumab plus atezolizumab in patients with metastatic renal cell carcinoma.

We report the primary analysis of the efficacy and safety of atezolizumab plus bevacizumab versus sunitinib in the IMmotion151 study, the first randomised, phase 3 trial combining an anti-PD-L1–PD-1 antibody with an anti-VEGF drug as treatment for patients with metastatic renal cell carcinoma.

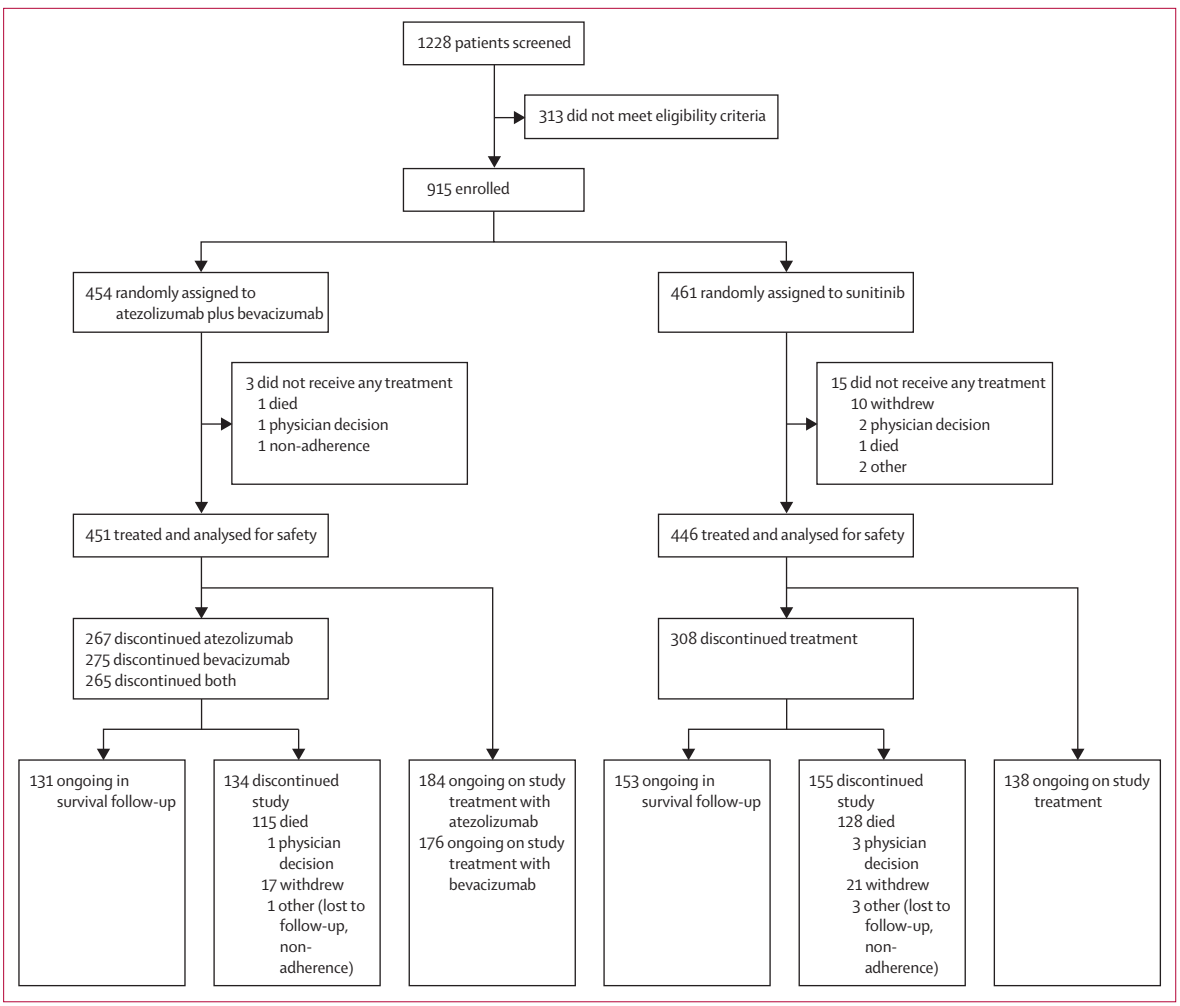

Figure 1: **Trial profile**

Methods

Study design and participants

We did a multicentre, open-label, phase 3, randomised controlled trial at 152 academic medical centres and community oncology practices in 21 countries, mainly in Europe, North America, and the Asia-Pacific region (Australia, Bosnia and Herzegovina, Brazil, Canada, Czech Republic, Denmark, France, Germany, Italy, Japan, South Korea, Mexico, Poland, Russia, Singapore, Spain, Taiwan, Thailand, Turkey, UK, and USA; appendix). Eligible patients were aged 18 years or older with unresectable locally advanced or metastatic renal cell carcinoma with any component of clear cell or sarcomatoid histology (per local pathology report), measurable disease according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1), Karnofsky performance status 70% or higher, adequate haematological and end-organ function, and tumour tissue available for PD-L1 testing. Patients were excluded if they had received previous systemic treatment or if they had untreated brain metastases. A full list of inclusion and exclusion criteria is available in the appendix. All patients gave written informed consent.

The study protocol (appendix) was approved by the institutional review board or independent ethics committee for each study site and was done in full accordance with the Guideline for Good Clinical Practice and the Declaration of Helsinki.

Randomisation and masking

Patients were randomly assigned (1:1) via an interactive voice and web response system to receive atezolizumab plus bevacizumab or sunitinib. A permuted-block randomisation (block size of 4) was applied to obtain a balanced assignment to each treatment group with respect to the stratification factors, including PD-L1 expression (<1% *vs* ≥1% of tumour-infiltrating immune cells expressing PD-L1 as assessed by immunohistochemistry [VENTANA PD-L1 SP142 assay; Ventana Medical Systems, Tucson, AZ]), presence of liver metastasis (yes *vs* no), and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk score (0, 1–2, ≥3).[21] The trial centres

	PD-L1 positive (n=362)		Intention to treat (n=915)	
	Atezolizumab plus bevacizumab (n=178)	Sunitinib (n=184)	Atezolizumab plus bevacizumab (n=454)	Sunitinib (n=461)
Age, years	62 (55–67)	59 (53–65)	62 (56–69)	60 (54–66)
Sex				
Male	120 (67%)	146 (79%)	317 (70%)	352 (76%)
Female	58 (33%)	38 (21%)	137 (30%)	109 (24%)
Geographical region				
USA and Canada	46 (26%)	35 (19%)	97 (21%)	84 (18%)
Western Europe and Australia	70 (39%)	89 (48%)	195 (43%)	219 (48%)
Asia	31 (17%)	25 (14%)	80 (18%)	73 (16%)
Eastern Europe	30 (17%)	29 (16%)	69 (15%)	70 (15%)
Central and South America	1 (1%)	6 (3%)	13 (3%)	15 (3%)
Karnofsky performance status				
<80	9 (5%)	9 (5%)	40 (9%)	35 (8%)
80–90	94 (53%)	96 (52%)	242 (53%)	228 (49%)
100	75 (42%)	79 (43%)	172 (38%)	198 (43%)
MSKCC risk score				
Favourable (0)	31 (17%)	31 (17%)	89 (20%)	90 (20%)
Intermediate (1 or 2)	128 (72%)	133 (72%)	311 (69%)	318 (69%)
Poor (≥3)	19 (11%)	20 (11%)	54 (12%)	53 (12%)
Most common metastatic sites				
Bone	32 (18%)	41 (22%)	90 (20%)	90 (20%)
Liver	30 (17%)	33 (18%)	78 (17%)	82 (18%)
Lung	135 (76%)	136 (74%)	339 (75%)	325 (71%)
Lymph node	89 (50%)	90 (49%)	211 (47%)	218 (47%)
Previous nephrectomy	150 (84%)	152 (83%)	334 (74%)	330 (72%)
Disease PD-L1 expression on tumour-infiltrating immune cells				
≥1%	178 (100%)	184 (100%)	178 (39%)	184 (40%)
<1%	0	0	276 (61%)	277 (60%)
Predominant histology				
Clear cell carcinoma	163 (92%)	160 (87%)	420 (93%)	425 (92%)
Sarcomatoid	12 (7%)	17 (9%)	22 (5%)	22 (5%)
Other*	3 (1%)	7 (4%)	12 (2%)	14 (3%)
Sarcomatoid differentiation†	36 (20%)	50 (27%)	68 (15%)	74 (16%)

Data are n (%) or median (IQR). MSKCC=Memorial Sloan Kettering Cancer Center. PD-L1=programmed death-ligand 1. *Includes papillary, chromophobe, and oncocytoma. †Any component of sarcomatoid differentiation regardless of predominant histology.

Table 1: **Baseline characteristics**

enrolled the patients. The study was open label, and investigators and participants were not masked to treatment allocation. Patients, investigators, independent radiology committee (IRC) members, and the sponsor were masked to PD-L1 expression status. The sponsor was not permitted to carry out any population-level summaries of outcome data by treatment group until the time of primary analysis.

Procedures

Patients randomly assigned to the atezolizumab plus bevacizumab group received atezolizumab 1200 mg intravenously then bevacizumab 15 mg/kg intravenous infusions once every 3 weeks. Patients randomly assigned to the sunitinib group received sunitinib 50 mg once daily orally for 4 weeks, followed by 2 weeks of rest. Atezolizumab, bevacizumab, and sunitinib were provided by the sponsor, except when sunitinib was procured as local commercial product in some countries (Japan, USA, and Canada). Patients could continue atezolizumab plus bevacizumab or sunitinib beyond disease progression according to RECIST 1.1 and the investigator's discretion if evidence of clinical benefit was observed. No prespecified crossover was planned per protocol.

Patients had tumour assessments at baseline, week 12, and then every 6 weeks up to week 78, followed by every 12 weeks thereafter, until disease progression according to RECIST 1.1 or loss of clinical benefit. Survival follow-up occurred every 3 months after treatment discontinuation. National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used to assess frequency and severity of adverse events.

Symptom severity for 17 symptoms and symptom interference with activities of daily living were captured by the MD Anderson Symptom Inventory (MDASI), which patients completed before initiating treatment (baseline), on day 1 and day 22 of each cycle, at end of treatment, and during survival follow-up. The range for each symptom severity and symptom interference score is 0–10, with higher scores indicating greater symptom severity and interference. Time to clinically relevant deterioration of day-to-day functioning was based on a 2-point or higher increase above baseline on the six-item MDASI interference subscale, where patients rated how much their symptoms interfered with work, general activity, walking, enjoyment of life, mood, and relations with other people.[22]

Outcomes

Co-primary endpoints were progression-free survival (RECIST 1.1) by investigator assessment in patients with PD-L1 positive disease (defined as ≥1% expression on tumour-infiltrating immune cells) and overall survival in the intention-to-treat (ITT) population. Key secondary objectives included overall survival in the PD-L1 positive population, progression-free survival in the ITT population, the proportion of patients who achieved an objective response, duration of response, patient-reported outcomes, and safety. Radiographic endpoints were also assessed by an IRC. A complete list of outcomes is reported in the protocol (see appendix).

Statistical analysis

We randomly assigned 915 patients, including 362 patients with a PD-L1 immunohistochemistry tumour-infiltrating immune cell score of 1% or higher. The type 1 error (α) for the entire study is 0·05 (two-sided), which we split between the co-primary endpoints of progression-free survival in patients with PD-L1 positive disease (α=0·04) and overall survival in the ITT population (α=0·01) to

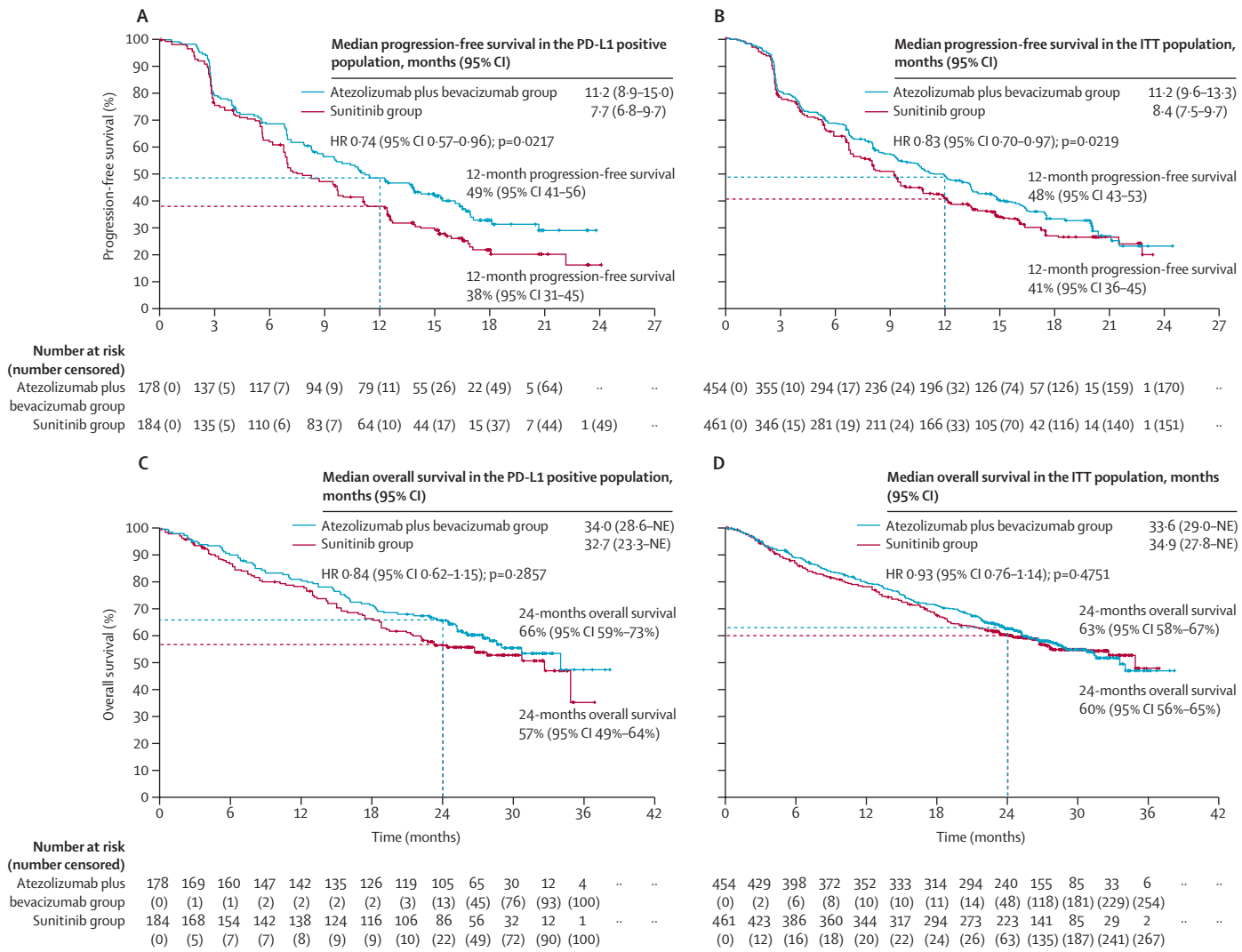

Figure 2: **Progression-free survival (investigator-assessed) and overall survival**

Progression-free survival in the PD-L1 positive (A) and intention-to-treat populations (B). Progression was defined according to Response Evaluation Criteria in Solid Tumours, version 1.1. Overall survival in the PD-L1 positive (C) and intention-to-treat populations (D) at the second interim analysis. The overall survival analysis in the intention-to-treat population did not pass the prespecified α boundary. p values reported for results other than the co-primary endpoints are provided for descriptive purposes only. HR=hazard ratio. ITT-intention to treat. NE=not estimable. PD-L1=programmed death-ligand 1.

ensure sufficient power to test both co-primary endpoints. If progression-free survival was significant, we recycled the α=0·04 to the overall survival in the ITT poulation.[23,24] We defined the ITT population as all randomly assigned patients regardless of whether they received the assigned study treatment. We defined the PD-L1 positive population as patients in the ITT population whose PD-L1 expression was 1% or higher on tumour-infiltrating immune cells at the time of randomisation. We assessed progression-free survival in patients with PD-L1 positive disease at an α level of 0·04, with a power of 90% based on a target hazard ratio (HR) of 0·65 under the stratified log-rank test. We then back-calculated the total number of patients based on the number of events required. The primary analysis of progression-free survival was triggered by 236 progression-free survival events (65% event-to-patient ratio) in the PD-L1 positive population (362 patients) at the projected data cutoff date of Sept 29, 2017. The co-primary endpoint of progression-free survival was met; therefore, the α level for overall survival testing was 0·05. We planned the first interim analysis of overall survival at the time of progression-free survival primary analysis. We used an adjusted α level of 0·0009 for the first interim analysis of overall survival based on an O'Brien-Fleming α spending function calculated on the number of overall survival events.[25] We added a second interim analysis of overall survival to the protocol after the primary progression-free survival analysis to fulfil health authority

	PD-L1 positive (n=362)		Intention to treat (n=915)	
	Atezolizumab plus bevacizumab (n=178)	Sunitinib (n=184)	Atezolizumab plus bevacizumab (n=454)	Sunitinib (n=461)
Proportion of patients who achieved a confirmed objective response*	76 (43%; 35–50)	64 (35%; 28–42)	166 (37%; 32–41)	153 (33%; 29–38)
Complete response	16 (9%)	8 (4%)	24 (5%)	10 (2%)
Partial response	60 (34%)	56 (30%)	142 (31%)	143 (31%)
Stable disease	56 (32%)	64 (35%)	178 (39%)	178 (39%)
Progressive disease	34 (19%)	38 (21%)	80 (18%)	87 (19%)
Not evaluable†	12 (7%)	18 (10%)	30 (7%)	42 (9%)
Duration of response, months	NR (12–NR)	12·9 (10–NR)	16·6 (15–NR)	14·2 (11–NR)
Ongoing responder	49 (64%)	34 (53%)	107 (64%)	90 (59%)

Data are n (%), n (%; 95% CI), or median (95% CI). Investigator-assessed according to Response Evaluation Criteria in Solid Tumours, version 1.1. NR=not reached. PD-L1=programmed death-ligand 1. *Objective response assessed by investigators in patients with measurable disease at baseline. †Including patients with no post-baseline tumour assessment.

Table 2: **Confirmed best objective response**

requirements. We did the second interim overall survival analysis approximately 10 months after the first interim analysis, with an adjusted α level of 0·0076 based on an O'Brien-Fleming α spending function calculated on the number of overall survival events. We did not update any other study endpoints at that time. We compared treatment groups for progression-free survival and overall survival using a two-sided, stratified log-rank test. We used stratified Cox regression models to estimate HRs and 95% CIs. We assessed the proportional hazards assumption of the Cox regression model and no evidence of violation was observed. We provide p values for results other than the co-primary endpoints for descriptive purposes only. We used the Kaplan-Meier method to estimate survival curves and time to patient-reported deterioration in symptom interference. We estimated patient-reported symptom-severity score changes from baseline up to end of treatment and differences between groups using linear mixed-effects models. We assessed safety analyses, including summaries of adverse events, in patients who received any amount of any component of study treatment.

Statistical analyses were done using SAS version 9.4. Full details of the statistical plan are included in the appendix. An independent data monitoring committee reviewed safety data during the study on a periodic basis (approximately every 6 months). This trial is registered with ClinicalTrials.gov, number NCT02420821.

Role of the funding source

F Hoffmann–La Roche Ltd and Genentech Inc sponsored the study and collaborated with academic authors regarding study design and data collection, data analysis, and data interpretation. All authors verify that this study was done according to the protocol and attested for data accuracy and completeness. All authors had full access to all the data in the study, contributed to drafts of the manuscript, and gave final approval to publish. The corresponding author had final responsibility for the decision to submit for publication.

Results

The study enrolled 915 patients in the ITT population between May 20, 2015, and Oct 12, 2016, at 152 sites across 21 countries; 454 patients were randomly assigned to receive atezolizumab plus bevacizumab and 461 patients to receive sunitinib (figure 1). A total of 362 (40%) of 915 patients had PD-L1 positive tumours. Baseline characteristics were well balanced between study groups and between the PD-L1 positive and ITT populations (table 1). Overall, 142 (16%) patients had tumours with a component of sarcomatoid differentiation. At data cutoff for the primary progression-free analysis, the minimum survival follow-up was 12 months (median survival follow-up was 16 months in the PD-L1 positive population and 15 months in the and ITT population).

Of 362 patients with PD-L1 positive disease, 243 (67%) had disease progression or died. The study met the co-primary endpoint of investigator-assessed progression-free survival, with a median progression-free survival of 11·2 months with atezolizumab plus bevacizumab and 7·7 months with sunitinib; stratified HR was 0·74 (95% CI 0·57–0·96; p=0·0217). At 12 months, progression-free survival was 49% (41–56) with atezolizumab plus bevacizumab versus 38% (31–45) with sunitinib (figure 2A; appendix). 76 (43%) of 178 patients (35–50) achieved a confirmed objective response in the atezolizumab plus bevacizumab group, with 16 (9%) achieving a complete response; 64 (35%) of 184 patients (28–42) in the sunitinib group achieved a confirmed objective response, with eight (4%) patients achieving a complete response (table 2). At the data cutoff, 49 (64%) of 76 responses in the atezolizumab plus bevacizumab group and 34 (53%) of 64 responses in the sunitinib group were ongoing (table 2; appendix).

In the ITT population, 592 (65%) of 915 patients had disease progression or death. Progression-free survival benefit was also identified in the atezolizumab plus bevacizumab group (median progression-free survival was 11·2 months) versus the sunitinib group (8·4 months) in the ITT population; stratified HR was 0·83 (95% CI 0·70–0·97). At 12 months, 196 (48%) of 454 patients (43–53) in the atezolizumab plus bevacizumab group had progression-free survival versus 166 (41%) of 461 patients (36–45) in the sunitinib group (figure 2B; appendix). 166 (37%) of 454 patients (32–41) in the atezolizumab plus bevacizumab group achieved a confirmed objective response in the ITT population, with 24 (5%) achieving a complete response; and 153 (33%) of 461 patients (29–38) in the sunitinib group achieved a confirmed objective response, with 10 (2%) achieving a complete response (table 2). At the data cutoff, 107 (64%) of 166 responses

in the atezolizumab plus bevacizumab group and 90 (59%) of 153 responses in the sunitinib group were ongoing (table 2; appendix).

Progression-free survival benefit was observed with atezolizumab plus bevacizumab versus sunitinib in patients across key clinical subgroups, including MSKCC risk groups, sarcomatoid histology, liver metastasis, and previous nephrectomy (figure 3A; appendix). Notably, the progression-free survival HR in patients with sarcomatoid histology was 0·46 (95% CI 0·28–0·78) in the PD-L1 positive population and 0·56 (0·38–0·83) in the ITT population. In this subgroup of the ITT population, 33 (49%) of 68 patients achieved an objective response with atezolizumab plus bevacizumab versus ten (14%) of 74 patients with sunitinib. Progression-free survival was also analysed by extent of PD-L1 status, showing a gradient of increasing benefit with increasing PD-L1 expression (figure 3B).

Radiographic efficacy endpoints were also assessed by an IRC as a secondary endpoint. IRC-assessed progression-free survival resulted in a stratified HR of 0·93 (95% CI 0·72–1·21) in the PD-L1 positive population and 0·88 (0·74–1·04) in the ITT population when comparing the atezolizumab plus bevacizumab group versus the sunitinib group. Notably, in the IRC analysis, patients with PD-L1 negative disease (PD-L1 tumour-infiltrating immune cell immunohistochemistry expression <1%) unexpectedly showed an improved HR (0·84 [0·67–1·04]) compared with patients with PD-L1 positive disease (appendix). In the PD-L1 positive population, 36% (64 of 178) of patients achieved an objective response with atezolizumab plus bevacizumab and 33% (60 of 184) with sunitinib, including 15% (26 of 178) who achieved a complete response with atezolizumab plus bevacizumab and 8% (15 of 184) with sunitinib (appendix). Progressive disease event concordance rates between investigator and IRC assessment were high at approximately 80% and were similar between the PD-L1 positive and ITT populations and between both treatment groups.

No imbalances in progressive disease event concordance between treatment groups were observed in the ITT population. However, numerically more patients had disease progression according to IRC assessment than with investigator assessment in the atezolizumab plus bevacizumab group (n=22) than in the sunitinib group (n=10) of the PD-L1 positive population. The difference between groups was primarily caused by disease progression with appearance of new lesions (most commonly in lymph nodes) in the atezolizumab plus bevacizumab group, while the total number of target lesion and non-target lesion progression events was similar between groups (appendix). The difference between the IRC progressive disease event and the last investigator assessment or death exceeded 6 months in approximately 50% of the patients and 12 months in approximately 20% of patients. Most of these patients were still on study at data cutoff.

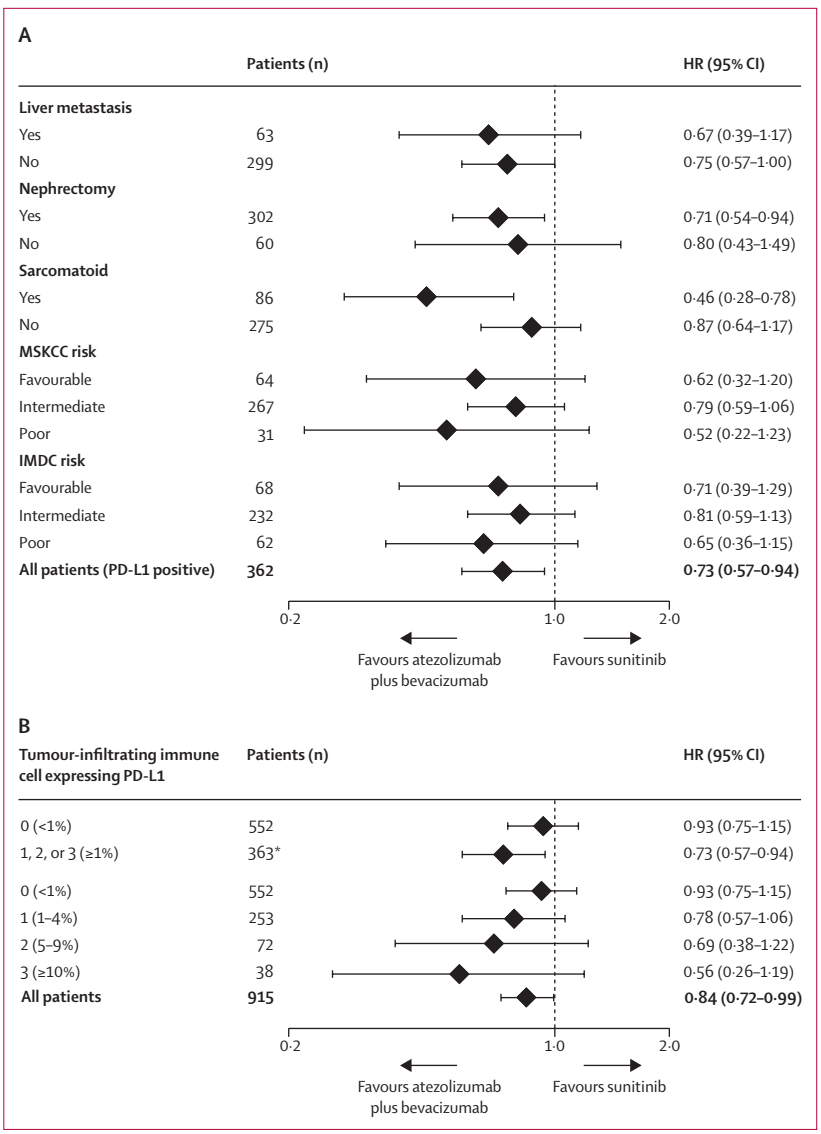

Figure 3: **Progression-free survival subgroup analyses**
(A) Subgroup analyses of investigator-assessed progression-free survival in the PD-L1 positive population. The MSKCC prognostic risk groups are based on the presence of 0 (favourable), 1, or 2 (intermediate), or 3 or more (poor) of the prognostic factors Karnofsky performance status less than 80, corrected serum calcium concentration higher than 10 mg/dL, lactate dehydrogenase concentration higher than 1·5 times the upper limit of normal, haemoglobin concentration lower than the lower limit of normal, time from nephrectomy to systemic therapy 12 months or less. The IMDC risk group was derived ad hoc from baseline data collected in electronic case report forms. (B) Subgroup analyses of investigator-assessed progression-free survival in the intention-to-treat population based on PD-L1 tumour-infiltrating immune cell expression status according to central laboratory (VENTANA PD-L1 [SP142] assay). HR=hazard ratio. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium. MSKCC=Memorial Sloan Kettering Cancer Center. PD-L1=programmed death-ligand 1. *One patient had a PD-L1 tumour-infiltrating immune cell immunohistochemistry expression less than 1% according to interactive voice and web response system and PD-L1 tumour-infiltrating immune cell immunohistochemistry expression 1% or higher according to central laboratory.

For the co-primary endpoint of overall survival in the ITT population, 123 (27%) of 454 patients in the atezolizumab plus bevacizumab group and 141 (31%) of 461 patients in the sunitinib group had died at the data cutoff for the first interim analysis; stratified HR was 0·81 (95% CI 0·63–1·03; p=0·0895). The results did not

cross the prespecified significance boundary of α=0·0009. In the PD-L1 positive population, 45 (25%) of 178 patients in the atezolizumab plus bevacizumab group and 64 (35%) of 184 patients in the sunitinib group had died at data cutoff; stratified HR was 0·68 (0·46–1·00; p=0·0470). Of the 166 (36%) of 461 patients receiving subsequent systemic cancer therapy in the sunitinib group, approximately half received treatment with a PD-L1–PD-1 inhibitor (appendix).

At the data cutoff for the second overall survival interim analysis, 194 (43%) of 454 patients in the atezolizumab plus bevacizumab group and 192 (42%) of 461 patients in the sunitinib group had died; stratified HR was 0·93 (95% CI 0·76–1·14; p=0·4751) in the ITT population (figure 2D). The results did not cross the prespecified significance boundary of α=0·0076, and survival follow-up is continuing to the next planned survival analyses. In the PD-L1 positive population, 74 (42%) of 178 patients in the atezolizumab plus bevacizumab group and 83 (45%) of 184 patients in the sunitinib group had died at data cutoff; stratified HR was 0·84 (0·62–1·15; p=0·2857; figure 2C). 238 (52%) of 461 patients had received subsequent systemic cancer therapy, and 139 (30%) received subsequent treatment with a PD-L1–PD-1 inhibitor in the sunitinib group (appendix). 103 (22%) had received a PD-L1–PD-1 inhibitor as second-line therapy immediately after study treatment in the sunitinib group versus less than 1% in the atezolizumab plus bevacizumab group.

A total of 897 patients received atezolizumab plus bevacizumab (n=451) or sunitinib (n=446); safety outcomes analysed at the primary progression-free survival analysis are summarised in the appendix. Patients had a median treatment duration of 12·0 months in the atezolizumab (IQR 4·8–16·5) plus bevacizumab (4·2–15·9) group and 9·2 months (3·6–15·5) in the sunitinib group. A total of 143 (32%) patients in the atezolizumab plus bevacizumab group and 124 (28%) patients in the sunitinib group were treated beyond investigator-assessed, RECIST-defined progression, as permitted according to the protocol. Treatment-related adverse events occurred in 411 (91%) patients in the atezolizumab plus bevacizumab group and 429 (96%) in the sunitinib group. Patients given atezolizumab plus

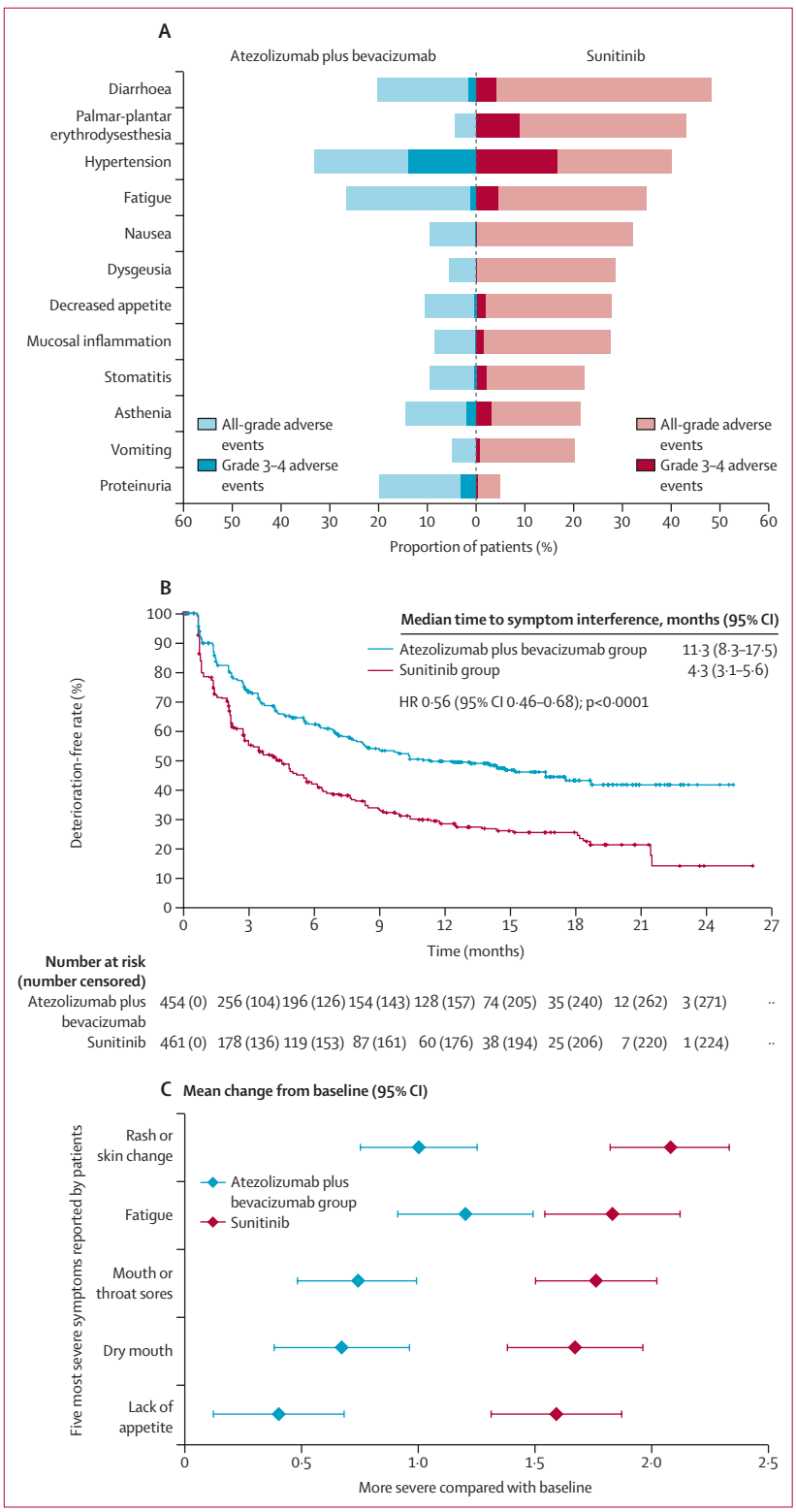

Figure 4: **Treatment-related adverse events and patient-reported outcomes**
(A) Treatment-related adverse events with 20% or higher frequency in either group and more than 5% difference between groups are shown in the tornado plot. (B) Kaplan-Meier estimates denote time to clinically relevant deterioration (defined as a patient's first ≥2-point MDASI interference score increase above baseline) of patients' daily functioning in the intention-to-treat population. Time to deterioration in MDASI interference scores included patient-reported outcome data collected at study treatment visits every 3 weeks. p values reported for results other than the co-primary endpoints are provided for descriptive purposes only. (C) The five most severe symptoms reported by patients based on largest numeric MDASI symptom score increase from baseline in either group. MDASI score range, 0–10. Range across 17 symptom severity mean scores (SD) at baseline: 0·2 (0·7) for mouth or throat sores to 2·6 (2·8) for fatigue in the atezolizumab plus bevacizumab group versus 0·3 (0·9) for mouth or throat sores to 2·5 (2·6) for fatigue in the sunitinib group. HR=hazard ratio. MDASI=MD Anderson Symptom Inventory.

bevacizumab versus sunitinib had fewer treatment-related grade 3–4 adverse events (182 [40%] of 451 *vs* 240 [54%] of 446) and had fewer treatment regimen discontinuations due to treatment-related adverse events (24 [5%] *vs* 37 [8%]); in the atezolizumab plus bevacizumab group, additional patients had adverse events leading to discontinuation of one component of the study treatment (atezolizumab, nine [2%]; bevacizumab, 23 [5%]). The median time to treatment discontinuation for atezolizumab and bevacizumab was 12 months. The most common grade 3–4 treatment-related adverse event in the atezolizumab plus bevacizumab group was hypertension (63 [14%]); in the sunitinib group, hypertension (75 [17%]), thrombocytopenia (24 [5%]), and palmar-plantar erythrodysaesthesia (40 [9%]) occurred most commonly (appendix). Treatment-related adverse events occurring with more than 5% difference between treatment groups are shown in figure 4A. Five treatment-related deaths occurred in the atezolizumab plus bevacizumab group, and one death occurred in the sunitinib group. The most common adverse events of special interest were rash, hypothyroidism, hyperthyroidism, and liver function test abnormalities, with most events being low grade (appendix). 74 (16%) of 451 patients given atezolizumab plus bevacizumab received systemic corticosteroids and 42 (9%) received high-dose systemic corticosteroids within 30 days of an adverse event of special interest (high-dose systemic corticosteroid use was defined as prednisone ≥40 mg per day or equivalent).

Among all randomly assigned patients, 386 (86%) of 451 patients in the atezolizumab plus bevacizumab group and 369 (83%) of 446 patients in the sunitinib group completed the MDASI at baseline. The proportion of patients who completed the MDASI until cycle 7 day 22 (week 57), when day-22 clinic visits were no longer required for patients receiving sunitinib, were similar between groups (both ≥70%). In the ITT population, median time to clinically relevant deterioration of daily functioning due to treatment-related and disease-related symptoms was significantly longer in patients receiving atezolizumab plus bevacizumab (11·3 months) than in patients receiving sunitinib (4·3 months); stratified HR was 0·56 (95% CI 0·46 to 0·68; figure 4B). Change from baseline to end of treatment in symptom severity favoured atezolizumab plus bevacizumab over sunitinib for 17 symptoms: lack of appetite, rash or skin change, diarrhoea, mouth or throat sores, dry mouth, nausea, fatigue, sad feelings, vomiting, shortness of breath, distress, drowsiness, disturbed sleep, pain, numbness or tingling, difficulty remembering things, and headache—listed from highest difference in least-squares mean change (–1·19 [–1·46 to –0·91] for lack of appetite) to the lowest (–0·05 [–0·26 to 0·16] for headache). The five most severe symptoms reported by patients during study treatment are displayed in figure 4C.

Discussion

This phase 3 study met its co-primary endpoint by showing improved progression-free survival with atezolizumab plus bevacizumab over sunitinib in patients with metastatic renal cell carcinoma whose disease expressed PD-L1. Clinical efficacy is supported by a higher proportion of patients in the atezolizumab plus bevacizumab group achieving an objective response than those in the sunitinib group, most notably the proportion achieving a complete response. The observed progression-free survival benefit of atezolizumab plus bevacizumab extended across different examined clinical groups, including previous nephrectomy, sarcomatoid histology, and established prognostic risk groups.

In the primary analysis, IRC-assessed progression-free survival was generally consistent with investigator-assessed progression-free survival in the ITT population. However, progression-free survival results differed in the PD-L1 positive population. Notably, investigators and IRC reviewers were masked to patient PD-L1 status, suggesting that an evaluation bias limited to this subgroup was unlikely. Sensitivity analyses indicated that patients with progressive disease according to IRC, but not investigator, in the atezolizumab plus bevacizumab group were key contributors to the difference observed in the PD-L1 positive population. Among the 22 patients in this subgroup, identification of new lesions was the primary reason that led to differing progressive disease assessments. Lymph nodes were the most common site of new lesions, a finding that might, in part, reflect the mode of action of immunotherapy rather than clinically relevant disease progression. Half of these patients had been followed up for more than 6 months beyond IRC-assessed progressive disease, with stable or decreasing target lesions according to both IRC and investigator, an observation that supports continued disease control and treatment benefit.

For the second overall survival interim analysis, 386 (42%) of 915 patients had experienced an overall survival event at data cutoff. Results did not cross the prespecified α boundary, and the study will continue until the next planned survival analyses. Differing HRs for the two overall survival interim analyses highlight the need for more mature survival data to establish whether a survival benefit will emerge.

Progression-free survival and response benefit was observed in the context of a favourable safety profile with atezolizumab plus bevacizumab versus sunitinib. The safety profile was consistent with previous studies,[11] and no new or additive safety signals were identified. Atezolizumab plus bevacizumab was associated with fewer severe treatment-related adverse events, a lower regimen discontinuation rate, and low need for corticosteroid use. Except for proteinuria, a well described adverse event associated with bevacizumab treatment, all treatment-related adverse events were reported more commonly in the sunitinib group, including

gastrointestinal and skin adverse events often associated with quality-of-life impairment. Results of the prespecified patient-reported outcomes analyses further supported this finding. A meaningful interference of symptoms with patients' daily functioning occurred significantly later in the atezolizumab plus bevacizumab group than the sunitinib group, with a 7-month median delay. The median time to symptom interference with daily living coincided with median progression-free survival with atezolizumab plus bevacizumab, whereas patients in the sunitinib group had functional impairment significantly earlier than radiographic progression. In addition, patients in the atezolizumab plus bevacizumab group reported milder treatment-related and disease-related symptoms than those in the sunitinib group.

Results reported here corroborate the clinical activity of PD-L1–PD-1 checkpoint inhibitor-based combinations in previously untreated metastatic renal cell carcinoma, as published for the combinations of nivolumab plus ipilimumab and avelumab plus axitinib.[8,26] Although cross-trial comparisons are limited by study design and patient populations, results from these investigations add to the growing evidence of PD-L1 expression on either tumour cells or tumour-infiltrating immune cells being associated with enriched clinical benefit with checkpoint inhibition and negative prognostic value in metastatic renal cell carcinoma.[6,7,27,28]

PD-L1 expression on tumour-infiltrating immune cells was previously reported to be strongly associated with expression of T-effector and interferon gamma gene signatures, a hallmark of pre-existing antitumoural immunity.[11] A consistent pattern of improved progression-free survival with increasing levels of PD-L1 tumour-infiltrating immune cell expression was observed in IMmotion151. This finding underscores the relevance of pre-existing immunity in differentiating the clinical activity of atezolizumab plus bevacizumab versus sunitinib and substantiates PD-L1 immunohistochemistry as a supporting tool for treatment selection in patients with metastatic renal cell carcinoma.

The combination of nivolumab plus ipilimumab showed improved overall survival and objective response in patients with intermediate and poor prognostic risk as assessed by the International Metastatic Renal Cell Carcinoma Database Consortium score, whereas patients with favourable risk showed numerically superior results for overall survival, progression-free survival, and objective response with sunitinib.[8] The results reported here, with combined VEGF and checkpoint inhibition, corroborated by phase 3 results for avelumab plus axitinib,[26] suggest a progression-free survival benefit across prognostic risk groups, including in patients with favourable prognostic risk.

Additionally, this trial showed substantial efficacy in patients with a sarcomatoid histology component, a patient group with a particularly poor prognosis and limited response to VEGF inhibition.[29] PD-L1 expression was enhanced in this histological subgroup, with 86 (61%) of 142 patients expressing PD-L1. However, patients in the atezolizumab plus bevacizumab group showed improved progression-free survival and a higher proportion achieved a response compared with those in the sunitinib group, with and without PD-L1 expression, supporting an independent predictive value of histology.

In summary, this trial showed a progression-free survival advantage with the combination of atezolizumab plus bevacizumab over sunitinib in patients with previously untreated metastatic renal cell carcinoma, with a favourable safety profile. Overall survival did not cross the significance boundary, and longer-term follow-up is necessary to establish whether a survival benefit will emerge.

Contributors

BIR, TP, MBA, BE, DFM, CSu, and RJM designed the study. All authors contributed to data collection, data analysis, and data interpretation. All authors contributed to the writing of the manuscript, approved the final version, and agree to be accountable for all aspects of the report.

Declaration of interests

BIR has received grants and honoraria from Roche–Genentech and Pfizer during the conduct of the study and has received grants to his institution and honoraria for consulting roles from Merck, Peloton, Aveo, Bristol-Myers Squibb, grants to his institution from AstraZeneca, honoraria for consulting roles from Novartis, Synthorx, Compugen, Corvus, Exelixis, and holds stock in PTC therapeutics, all outside of the submitted work. TP has received research funding from AstraZeneca and Roche, and honoraria from AstraZeneca, Roche, Bristol-Myers Squibb, Pfizer, Novartis, Exelixis, and Merck Sharp & Dohme outside of the submitted work. MBA has received grants from Roche–Genentech during the conduct of the study and honoraria for consulting roles outside of the submitted work from Roche–Genentech, Bristol-Myers Squibb, Merck, Novartis, Pfizer, Exelixis, and Esai. BE has received grants and honoraria from Bristol-Myers Squibb, Novartis, Ipsen, and EUSA outside of the submitted work. DFM has received grants from Bristol-Myers Squibb and Prometheus and honoraria for consulting roles from Bristol-Myers Squibb, Pfizer, Merck, Novartis, Eisai, Exelixis, Array BioPharm, and Genentech BioOncology outside of the submitted work. SB has received honoraria and travel support for advisory roles from Novartis, Astellas, Janssen, Pfizer, Bristol-Myers Squibb, Roche, and Ipsen, honoraria from Merck Sharp & Dohme, and travel support from Exelixis outside the submitted work. WMS has received honoraria from Roche and Pfizer for advisory roles outside of the submitted work. FD has received grants from Pfizer, Novartis, and Ipsen outside of the submitted work. JLL has received study medication for investigator-sponsored trials from Pfizer and Samyang and honoraria from Bristol-Myers Squibb outside of the submitted work. RH has received honoraria from Novartis, Ipsen, EUSA, and Pfizer, honoraria and travel support from Bristol-Myers Squibb, and patent royalties outside of the submitted work. AR has received honoraria and travel support for advisory roles from Pfizer, Novartis, Roche, and Bristol-Myers Squibb during the conduct of the study. BA has received grants from Roche during the conduct of the study and grants, honoraria, and travel support from Roche, AstraZeneca, Janssen, Pfizer, Merck, and Sanofi outside of the submitted work. MS has received institutional grants from Roche–Genentech during the conduct of the study, grants and honoraria from Pfizer, Novartis, and Ipsen, and honoraria from EUSA Pharma and Bristol-Myers Squibb outside of the submitted work. MU has received honoraria for advisory roles from Chugai Pharmaceuticals outside of the submitted work. UDG has received honoraria from Bristol-Myers Squibb, Pfizer, Novartis, Ipsen, Astellas, Bayer, Sanofi, and Janssen outside of the submitted work. CP has received honoraria from Bristol-Myers Squibb, Pfizer, Novartis, Ipsen, EUSA, Eisai, and Janssen outside of the submitted work. BMeli has received honoraria and travel support for advisory roles from Roche, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, and Merck Serono, and honoraria for advisory roles from Pfizer, Astellas, AstraZeneca, Bayer, Pierre Fabre, and Janssen outside of the submitted work. HG has received grants and

honoraria from Pfizer, and honoraria from Roche and Bristol-Myers Squibb outside of the submitted work. JB has received grants and honoraria from Roche, Bristol-Myers Squibb, Pfizer, Novartis, Eisai, and Merck Sharp & Dohme and honoraria from Ipsen, EUSA Pharma, and Nektar outside of the submitted work. TKC has received grants and honoraria from Bristol-Myers Squibb and honoraria from Roche, Pfizer, Merck, Eisai, and Novartis during the conduct of the study. TK is an employee of F Hoffmann–La Roche, Ltd. AT is an employee of Roche Products Ltd. SL, EP-L, GF, MH, CSc, and MCG are employees of Genentech Inc. RJM has received honoraria for advisory roles from Roche–Genentech, Pfizer, Novartis, Exelixis, Eisai, and Merck, and institutional support from Bristol-Myers Squibb, Roche–Genentech, Pfizer, Novartis, Exelixis, and Eisai outside of the submitted work. CSu, FP, and BMell have nothing to disclose.

Data sharing

Qualified researchers can request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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