Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial

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Background Outcomes are poor for patients with previously treated, advanced or metastatic non-small-cell lung cancer (NSCLC). The anti-programmed death ligand 1 (PD-L1) antibody atezolizumab is clinically active against cancer, including NSCLC, especially cancers expressing PD-L1 on tumour cells, tumour-infiltrating immune cells, or both. We assessed efficacy and safety of atezolizumab versus docetaxel in previously treated NSCLC, analysed by PD-L1 expression levels on tumour cells and tumour-infiltrating immune cells and in the intention-to-treat population.

Methods In this open-label, phase 2 randomised controlled trial, patients with NSCLC who progressed on post-platinum chemotherapy were recruited in 61 academic medical centres and community oncology practices across 13 countries in Europe and North America. Key inclusion criteria were Eastern Cooperative Oncology Group performance status 0 or 1, measurable disease by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), and adequate haematological and end-organ function. Patients were stratified by PD-L1 tumour-infiltrating immune cell status, histology, and previous lines of therapy, and randomly assigned (1:1) by permuted block randomisation (with a block size of four) using an interactive voice or web system to receive intravenous atezolizumab 1200 mg or docetaxel 75 mg/m² once every 3 weeks. Baseline PD-L1 expression was scored by immunohistochemistry in tumour cells (as percentage of PD-L1-expressing tumour cells TC3≥50%, TC2≥5% and <50%, TC1≥1% and <5%, and TC0<1%) and tumour-infiltrating immune cells (as percentage of tumour area: IC3≥10%, IC2≥5% and <10%, IC1≥1% and <5%, and IC0<1%). The primary endpoint was overall survival in the intention-to-treat population and PD-L1 subgroups at 173 deaths. Biomarkers were assessed in an exploratory analysis. We assessed safety in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01903993.

Findings Patients were enrolled between Aug 5, 2013, and March 31, 2014. 144 patients were randomly allocated to the atezolizumab group, and 143 to the docetaxel group. 142 patients received at least one dose of atezolizumab and 135 received docetaxel. Overall survival in the intention-to-treat population was 12·6 months (95% CI 9·7–16·4) for atezolizumab versus 9·7 months (8·6–12·0) for docetaxel (hazard ratio [HR] 0·73 [95% CI 0·53–0·99]; p=0·04). Increasing improvement in overall survival was associated with increasing PD-L1 expression (TC3 or IC3 HR 0·49 [0·22–1·07; p=0·068], TC2/3 or IC2/3 HR 0·54 [0·33–0·89; p=0·014], TC1/2/3 or IC1/2/3 HR 0·59 [0·40–0·85; p=0·005], TC0 and IC0 HR 1·04 [0·62–1·75; p=0·871]). In our exploratory analysis, patients with pre-existing immunity, defined by high T-effector–interferon-γ-associated gene expression, had improved overall survival with atezolizumab. 11 (8%) patients in the atezolizumab group discontinued because of adverse events versus 30 (22%) patients in the docetaxel group. 16 (11%) patients in the atezolizumab group versus 52 (39%) patients in the docetaxel group had treatment-related grade 3–4 adverse events, and one (<1%) patient in the atezolizumab group versus three (2%) patients in the docetaxel group died from a treatment-related adverse event.

Interpretation Atezolizumab significantly improved survival compared with docetaxel in patients with previously treated NSCLC. Improvement correlated with PD-L1 immunohistochemistry expression on tumour cells and tumour-infiltrating immune cells, suggesting that PD-L1 expression is predictive for atezolizumab benefit. Atezolizumab was well tolerated, with a safety profile distinct from chemotherapy.

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See **Online** for appendix

Introduction

Outcomes are poor for patients with previously treated, advanced or metastatic non-small-cell lung cancer (NSCLC); systemic chemotherapy (eg, docetaxel) provides only modest benefits.[1] Programmed death ligand 1 (PD-L1) is an immune-checkpoint protein expressed on tumour cells and tumour-infiltrating immune cells that downregulates antitumoural T-cell function through binding to programmed death 1 (PD-1) and B7.1 (also known as CD80) receptors.[2,3] The engineered, humanised IgG1 monoclonal anti-PD-L1 antibody atezolizumab (MPDL3280A; F Hoffmann-La Roche/Genentech) blocks PD-L1–PD-1 and PD-L1–B7.1 interactions, resulting in restoration of antitumour T-cell activity and enhanced T-cell priming.[4–6] Clinical studies of anti-PD-1 antibodies (eg, nivolumab or

Research in context

Evidence before this study

Outcomes are poor for patients with previously treated, advanced or metastatic non-small-cell lung cancer (NSCLC); systemic chemotherapy provides only modest benefit. Cancer immunotherapy is an exciting new treatment option. We searched PubMed from Dec 18, 2010, to Dec 18, 2015, for clinical trials with the terms "non-small cell lung cancer", "programmed-death ligand 1", "PD-L1", "programmed-death 1", "PD-1", and "cancer immunotherapy", selecting relevant English language publications within the past 5 years. We identified seven studies (phases 1–3, all of which were international and open-label) of atezolizumab, pembrolizumab, or nivolumab. Studies indicated the therapeutic value of targeting the programmed death ligand 1 (PD-L1)–programmed death 1 (PD-1) pathway to treat NSCLC, and that atezolizumab shows durable responses as monotherapy for this disease. These responses were associated with tumour cell and tumour-infiltrating immune cell PD-L1 expression, and the benefit was more pronounced in tumours with pre-existing immunity. However, these biomarker hypotheses had not been tested in an atezolizumab randomised clinical trial.

Added value of this study

POPLAR is the first study of a PD-L1 checkpoint inhibitor in a randomised clinical trial of patients with previously treated NSCLC. In our study, atezolizumab showed a significant improvement in overall survival compared with docetaxel in patients with advanced, previously treated NSCLC. We saw increasing improvement in overall survival with increasing PD-L1 expression in the atezolizumab group, whereas patients with the lowest PD-L1 expression assigned to atezolizumab experienced similar overall survival to those assigned to docetaxel. We also showed that PD-L1 expression on both tumour cells and tumour-infiltrating immune cells is independently predictive of survival improvement with atezolizumab.

Implications of all the available evidence

Targeting the PD-L1–PD-1 pathway improves outcomes for patients with NSCLC. Together with reports of the anti-PD1 antibodies pembrolizumab and nivolumab, our results affirm that not only the receptor, but also the ligand components of the PD-L1–PD-1 axis are valid targets for the treatment of lung cancer. The predictive value of PD-L1 expression on tumour cells and tumour-infiltrating immune cells (rather than tumour cells alone) suggests that an immunohistochemistry test for PD-L1 expression on both cell types would identify a broader patient population likely to benefit from atezolizumab treatment than that identified by testing tumour cells alone. Additionally, the predictive value of the T-effector and interferon-γ gene signature for improvement in overall survival might provide insights into the biology of atezolizumab efficacy and aid development of the next generation of diagnostic assays for therapies targeting this pathway.

pembrolizumab) have established the therapeutic value of targeting the PD-L1–PD-1 pathway.[7–10] Blocking PD-L1–B7.1 binding on T cells and antigen-presenting cells might additionally inhibit downregulation of immune responses, thus preventing inhibition of T-cell activation and cytokine production.[11,12] Direct targeting of PD-L1 leaves the PD-L2–PD-1 interaction intact, potentially avoiding effects on immune homoeostasis.[6,13–16] Atezolizumab is engineered to eliminate binding to Fc receptors and prevent Fc-effector function. This modification eliminates antibody-dependent cell-mediated cytotoxicity and thus avoids potential loss of PD-L1-expressing T-effector cells and reduced anticancer immunity. Early-phase clinical trials of atezolizumab monotherapy have shown durable antitumour responses in NSCLC,[4,17,18] associated with tumour cell and tumour-infiltrating immune cell PD-L1 expression when assessed with immunohistochemistry.[17,18] These studies suggest that the benefit of atezolizumab is pronounced in tumours with pre-existing immunity.[4] However, these biomarker hypotheses have not been tested in a randomised clinical trial.

Accordingly, we designed POPLAR to investigate the efficacy and safety of atezolizumab versus docetaxel in second-line and third-line NSCLC, and to further assess the predictive value of PD-L1 expression levels on tumour cells and tumour-infiltrating immune cells.

Methods

Study design

POPLAR is a multicentre, randomised, open-label, all-comer phase 2 trial, done at 61 academic medical centres and community oncology practices across 13 countries in Europe and North America. The study was done in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Protocol (and modification) approval was obtained from an independent ethics committee for each site (listed in appendix).

Patients

We enrolled 287 patients. Eligible patients were aged 18 years or older, had Eastern Cooperative Oncology Group performance status 0 or 1, measurable disease by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), adequate haematological and end-organ function, and provided tumour specimens for central PD-L1 testing on formalin-fixed paraffin-embedded sections before enrolment. Key exclusion criteria were active or untreated CNS metastases, history of pneumonitis, autoimmune or chronic viral diseases, or previous treatment with docetaxel, CD137 agonists, anti-CTLA4, anti-PD-L1, or anti-PD-1 therapeutic antibodies, or PD-L1–PD-1 pathway-targeting agents. Patients gave written informed consent.

Randomisation and masking

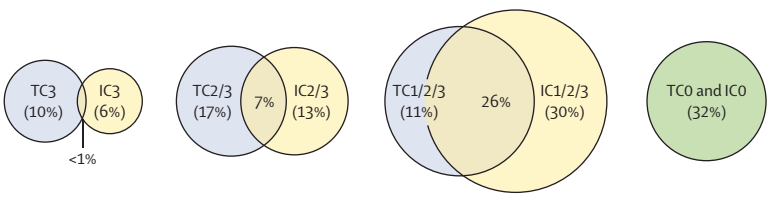
Patients were stratified by tumour-infiltrating immune cell PD-L1 expression, previous lines of chemotherapy (one *vs* two), and histology (non-squamous *vs* squamous), then permuted block-randomised (1:1) with a block size of four to receive either atezolizumab or docetaxel using an interactive voice or web response system (Bracket, San Francisco, CA, USA). The sequence was generated by Bracket; Bracket did not have any involvement in the rest of the trial. The trial centres enrolled the patients. The study was open-label, and allocation was unmasked.

Procedures

Patients received intravenous atezolizumab (1200 mg fixed dose) or docetaxel (75 mg/m²) every 3 weeks on day 1 of each 3-week cycle. Atezolizumab was continued as long as patients received clinical benefit according to investigator assessment (absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results [if available], and clinical status), and patients consented to continuation. Docetaxel was given until disease progression or unacceptable toxicity. No docetaxel-to-atezolizumab crossover was allowed.

We assessed tumours by imaging at baseline, every 6 weeks for 36 weeks after randomisation, and every 9 weeks (range 8–10 weeks) thereafter. Tumour assessments continued until progression, irrespective of treatment discontinuation. For patients in the atezolizumab group who continued beyond progression, assessments continued until discontinuation.

We assessed PD-L1 expression prospectively on tumour cells and tumour-infiltrating immune cells with the VENTANA SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ, USA). We scored tumour cells expressing PD-L1 as a percentage of total tumour cells and tumour-infiltrating immune cells expressing PD-L1 as a percentage of tumour area, as previously described (tumour cells scored as percentage of PD-L1-expressing tumour cells: TC3≥50%, TC2≥5% and <50%, TC1≥1% and <5%, and TC0<1%; tumour-inflitrating immune cells scored as percentage of tumor area: IC3≥10%, IC2≥5% and <10%, IC1≥1% and <5%, and IC0<1%; figure 1).[4] Scoring was highly reproducible among pathologists and clinical testing sites.[19] We analysed immune gene expression in pretreatment tumour specimens using a previously described Fluidigm-based gene-expression platform (Fluidigm; South San Francisco, CA, USA).[4] The T-effector and interferon-γ gene signature was defined by *CD8A*, *GZMA*, *GZMB*, *IFNγ*, *EOMES*, *CXCL9*, *CXCL10*, and *TBX21*. All of these genes had high co-expression in POPLAR tumour specimens (appendix). These genes have previously been associated with activated T cells, immune cytolytic activity, and interferon-γ expression.[20–23] We also analysed by *PD-L1, PD-1, PD-L2,* and *B7.1* gene expression. We defined the high biomarker group as gene expression at or above the median level, and the low biomarker group as gene expression below the median level. We collected serum and tumour samples for pharmacokinetic, immunogenicity, and biomarker analyses.



PD-L1 tumour cell scoring		PD-L1 tumour-infiltrating immune cell scoring	
Score	Percentage of PD-L1-expressing cells	Score	Percentage of PD-L1-expressing cells
TC3	≥50%	IC3	≥10%
TC2	≥5% and <50%	IC2	≥5% and <10%
TC1	≥1% and <5%	IC1	≥1% and <5%
TC0	<1%	IC0	<1%

Overall prevalence	
Subgroup	Proportion
TC3 or IC3	16%
TC2/3 or IC2/3	37%
TC1/2/3 or IC1/2/3	68%
TC0 and IC0	32%

Figure 1: **Programmed death ligand 1 (PD-L1) scoring criteria, prevalence, and overlap between PD-L1 expression on tumour cells and tumour-infiltrating immune cells**
Percentages in Venn diagrams represent the prevalence of PD-L1 expression in non-overlapping subgroups.

Outcomes

The primary endpoint was overall survival (time from randomisation to death) in the intention-to-treat population and PD-L1 subgroups, using a hierarchical procedure, and was centrally assessed. Secondary endpoints included investigator-assessed objective response rate (per RECIST v1.1), investigator-assessed progression-free survival (time from randomisation to the first occurrence of RECIST v1.1-defined disease progression, or death from any cause), and investigator-assessed duration of response (time from first occurrence of objective response to time of RECIST v1.1-defined disease progression, or death from any cause, whichever came first).

Additionally, we assessed efficacy according to immune-modified RECIST criteria,[17] which were designed to characterise unconventional response patterns associated with cancer immunotherapy, as a secondary endpoint. Other secondary endpoints were atezolizumab pharmacokinetics, patient-reported outcomes, biomarkers, and pharmacodynamics.

We graded adverse events with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[24] Laboratory safety assessments included monitoring haematology and blood chemistry.

Statistical analysis

We did three interim overall survival analyses to monitor the efficacy and safety profile of atezolizumab. We used a small α of 0·0001, 0·0001, and 0·001 for the first, second,

and third planned interim analyses of overall survival, respectively. We did the final overall survival analysis when 173 deaths had occurred in the intention-to-treat population, using a two-sided α level of 4·88%. We calculated that the analysis on the intention-to-treat population had 82·3% power, with a two-sided α level of 5%, assuming about 180 deaths, with a HR of 0·65 (assuming event times are exponentially distributed, median overall survival in the control group would be 8 months, and patients would be enrolled over 8 months). Assuming target HRs of 0·35 for TC3 or IC3, 0·5 for TC2/3 or IC2/3, and 0·6 for TC1/2/3 or IC1/2/3, PD-L1 expression subgroup analyses of overall survival had 80% power.

We compared treatment groups for overall survival and progression-free survival individually using a stratified log-rank test in the intention-to-treat population (stratified by histology, number of previous chemotherapy regimens, and tumour-infiltrating immune cell PD-L1 level). We used an unstratified log-rank test in PD-L1 immunohistochemistry subgroups because of the small sample sizes. We used the Kaplan-Meier method to estimate median overall survival and progression-free survival and to draw survival curves, and the Brookmeyer-Crowley method for 95% CIs. We used stratified Cox-regression models to estimate HRs and 95% CIs in the intention-to-treat population (using the same stratification variables as in the log-rank test). We used unstratified Cox regression models for PD-L1 immunohistochemistry subgroup populations. We adjusted gene expression subgroup analyses for smoking status, Eastern Cooperative Oncology Group performance status, and sex, and stratified according to PD-L1 expression as measured by immunohistochemisty (IC0 and TC0 *vs* others), number of previous chemotherapy regimens (one *vs* two), and histology (non-squamous *vs* squamous).

For overall survival analyses, patients not reported as having died at the time of analysis were censored at the date they were last known to be alive. Patients without information after baseline were censored at the randomisation date plus 1 day. For progression-free survival analyses, patients who were alive without disease progression at the time of analysis were censored at the time of the last tumour assessment. Patients with no post-baseline tumour assessment were censored at the randomisation date plus 1 day.

We calculated objective response rate estimates (and 95% CIs) for the PD-L1 subgroups and overall populations using the Clopper-Pearson method. We estimated duration of response using the Kaplan-Meier method for patients with complete or partial responses (confirmed). Patients without assessment after baseline were considered non-responders. Duration of response was censored at the date of the first occurrence of complete or partial response plus 1 day if no tumour assessments were done after the first response.

We assessed primary outcomes in the intention-to-treat population, and safety in all randomised patients who received at least one dose of study drug. We did statistical analyses with SAS version 9.2.

An internal monitoring committee evaluated interim data during the course of the study. POPLAR is registered with ClinicalTrials.gov, number NCT01903993.

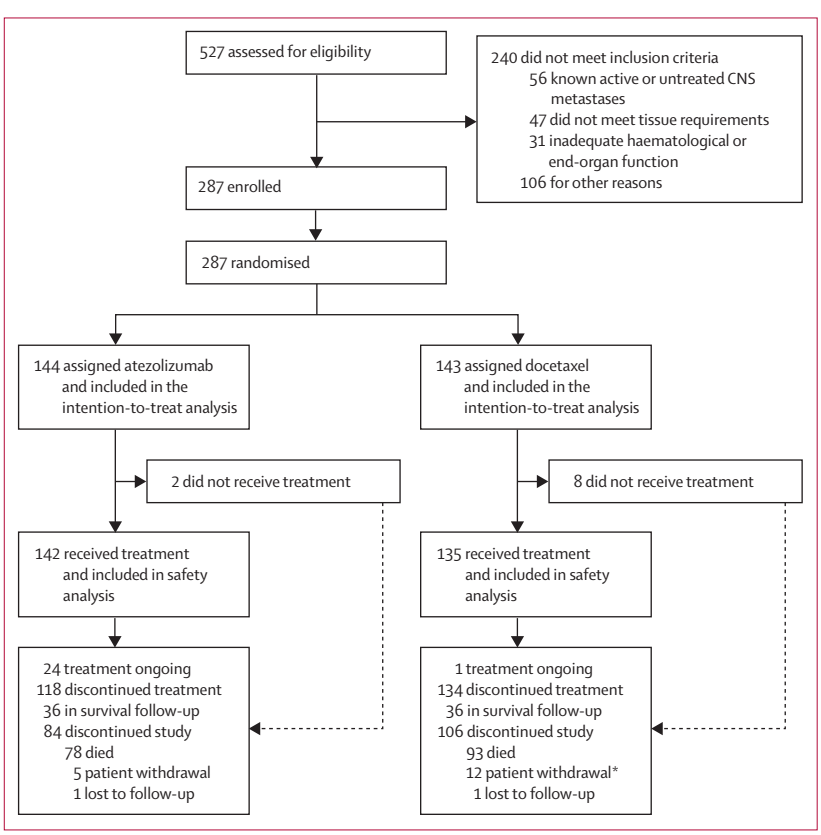


Figure 2: **Trial profile**
*Deaths determined from public records for two patients who withdrew from the docetaxel group.

Role of the funding source

F Hoffmann-La Roche/Genentech funded the study, provided study drugs, was involved in the study design, data collection, data analysis, data interpretation, and writing of the report, and gave approval to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We screened 527 patients for eligibility, enrolling 287 patients into the study between Aug 5, 2013, and March 31, 2014, at 61 academic medical centres and community oncology practices across 13 countries (figure 2). 144 patients were randomly allocated to receive atezolizumab and 143 to receive docetaxel; 142 patients received at least one dose of atezolizumab and 135 patients received at least one dose of docetaxel. The

primary analysis data cutoff was May 8, 2015. Median follow-up was 14·8 months (range 0·2+ to 19·6) in the atezolizumab group and 15·7 months (range 0·1–18·7) in the docetaxel group.

Baseline characteristics were balanced between groups, except for an 11% greater proportion of female patients in the docetaxel group (35% in the atezolizumab group *vs* 47% in the docetaxel group; table 1). Of 287 enrolled patients, 97 (34%) had squamous, and 190 (66%) had non-squamous, disease. 189 (66%) patients had one previous line of chemotherapy, and 98 (34%) patients had two previous lines of chemotherapy. PD-L1 prevalence and patterns of expression on tumour cells and tumour-infiltrating immune cells are summarised in figure 1. In addition to patients with PD-L1 expression on both cell types, we identified distinct populations of patients with PD-L1 expression on tumour cells only or on tumour-infiltrating immune cells only across all PD-L1 expression cutoffs (eg, among patients in the TC1/2/3 or IC1/2/3 group, 86 [30%] expressed PD-L1 only on tumour-infiltrating immune cells—ie, TC0 and IC1/2/3). TC3 and IC3 tumours showed minimal overlap (<1%; figure 1).

At a minimum follow-up of 13 months (60% of patients had died), atezolizumab significantly improved overall survival compared with docetaxel (12·6 *vs* 9·7 months; HR 0·73, 95% CI 0·53–0·99; p=0·04; figure 3A).

Progression-free survival was similar between groups (2·7 months with atezolizumab *vs* 3·0 months with docetaxel; HR 0·94, 95% CI 0·72–1·23; appendix). 21 (15%) patients in the atezolizumab group and 21 (15%) patients in the docetaxel group achieved an objective response (appendix).

Objective responses with atezolizumab were durable, with a median duration of 14·3 months (95% CI 11·6–non-estimable) compared with 7·2 months (5·6–12·5) for docetaxel (appendix). 12 (57%) of 21 responders in the atezolizumab group had an ongoing response versus five (24%) of 21 responders in the docetaxel group at the cutoff date.

Overall survival benefit from atezolizumab increased with increasing PD-L1 expression on tumour cells, tumour-infiltrating immune cells, or both (figure 3B–F). Overall survival improvement was significant in the TC2/3 or IC2/3 (HR 0·54, 95% CI 0·33–0·89; p=0·014) and TC1/2/3 or IC1/2/3 subgroups (HR 0·59, 95% CI 0·40–0·85; p=0·005) compared with patients receiving docetaxel, corresponding to PD-L1 expression in at least 5% of cells and 1% of cells, respectively. Overall survival in patients with TC0 and IC0 PD-L1 status in the atezolizumab group was similar to that in docetaxel group. To assess the independent contribution of each level of PD-L1 expression, we analysed non-overlapping subgroups. Each tumour cell or tumour-infiltrating immune cell level independently contributed to the improvements in overall survival in the TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 combined groups (appendix). Additionally, patients in the atezolizumab group with PD-L1 expression on tumour cells only (TC1/2/3 and IC0 subgroup) and tumour-infiltrating immune cells only (IC1/2/3 and TC0 subgroup) had improved overall survival compared with patients receiving docetaxel (appendix). Atezolizumab improved overall survival in both responding and non-responding patients compared with docetaxel (appendix). PD-L1 expression on tumour cells and tumour-infiltrating immune cells was not associated with docetaxel efficacy.

	Atezolizumab (n=144)	Docetaxel (n=143)
Age (years)	62 (42–82)	62 (36–84)
Sex		
Male	93 (65%)	76 (53%)
Female	51 (35%)	67 (47%)
Tobacco use history		
Never	27 (19%)	29 (20%)
Current	25 (17%)	21 (15%)
Previous	92 (64%)	93 (65%)
Pathology or histology		
Non-squamous	95 (66%)	95 (66%)
Squamous	49 (34%)	48 (34%)
ECOG performance status*		
0	46 (32%)	45 (32%)
1	96 (68%)	97 (68%)
PD-L1 tumour-infiltrating immune cell expression level		
0	62 (43%)	63 (44%)
1	53 (37%)	54 (38%)
2	19 (13%)	18 (13%)
3	10 (7%)	8 (6%)
PD-L1 tumour cell expression level		
0	96 (67%)	82 (57%)
1	19 (13%)	21 (15%)
2	14 (10%)	25 (18%)
3	15 (10%)	15 (11%)
Number of previous therapies in the locally advanced or metastatic setting		
1	93 (65%)	96 (67%)
2	51 (35%)	47 (33%)
EGFR mutation†		
Thr790Met	1 (1%)	0
Positive	10 (12%)	8 (10%)
Negative	72 (87%)	75 (90%)
EMLA-ALK translocation‡		
Yes	0	3 (5%)
No	61 (100%)	55 (95%)
KRAS mutation§		
Yes	14 (33%)	13 (43%)
No	28 (67%)	17 (57%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed death ligand 1.*Of 142 patients in each group. †Of 83 patients in each group with known *EGFR* mutation status. ‡Of 61 patients in the atezolizumab group and 58 in the docetaxel group with known *EMLA-ALK*translocation status. §Of 42 patients in the atezolizumab group and 30 in the docetaxel group with known *KRAS* mutation status.

Table 1: **Baseline characteristics of the intention-to-treat population**

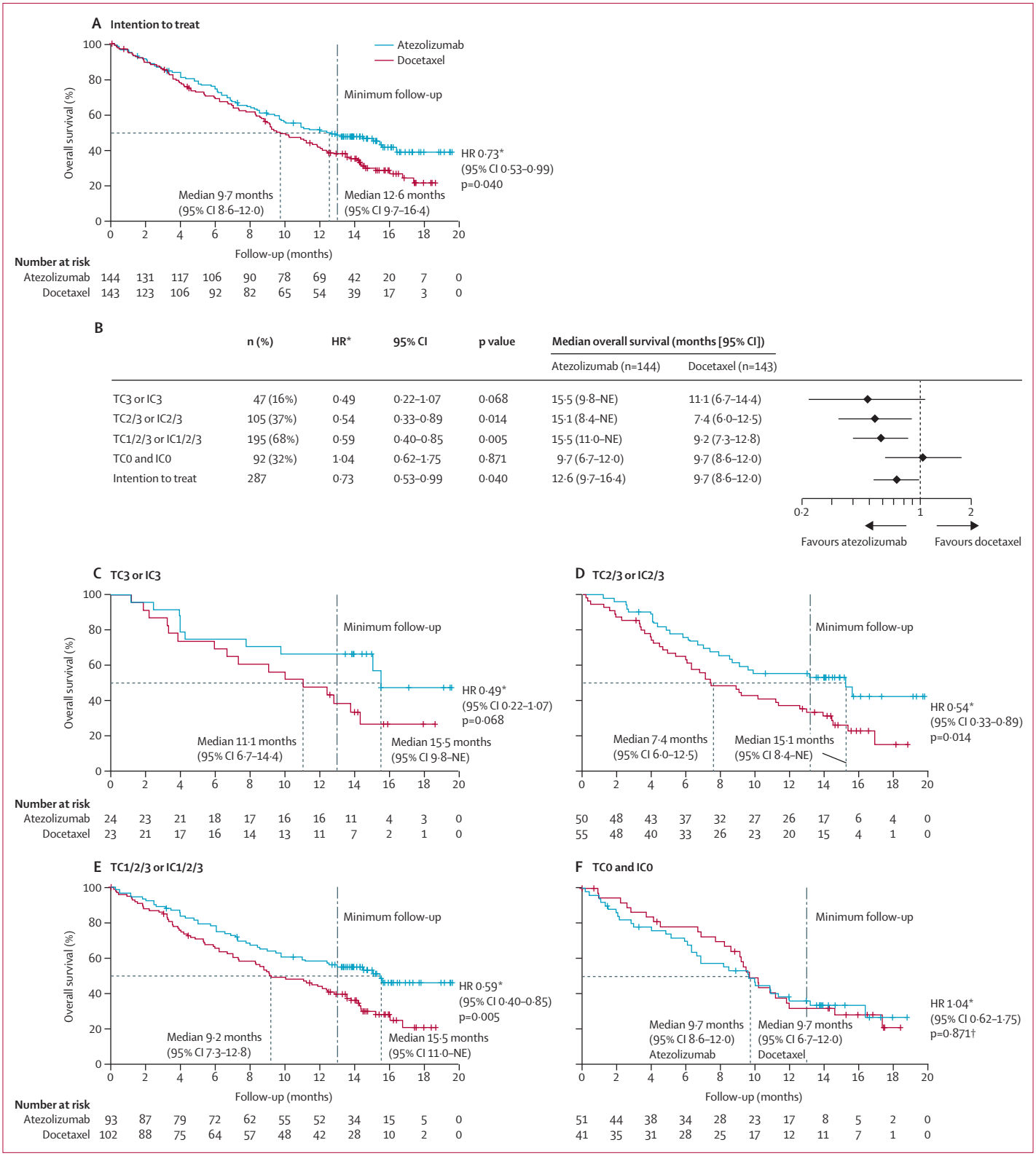


Figure 3: **Overall survival**

(A) Kaplan-Meier estimates in intention-to-treat population. (B) HRs for overall survival in programmed death ligand 1 (PD-L1) subgroups. (C) Kaplan-Meier estimates in the TC3 or IC3 population. (D) Kaplan-Meier estimates in the TC2/3 or IC2/3 population. (E) Kaplan-Meier estimates in the TC1/2/3 or IC1/2/3 population. (F) Kaplan-Meier estimates in the TC0 and IC0 population. Grey dashed line represents minimum follow-up of 13 months. NE=non-estimable. HR=hazard ratio. TC=tumour cell. IC=immune cell. *Unstratified hazard ratios were used for subgroup analyses. †p value for exploratory purposes only.

Overall survival was also improved in atezolizumab-treated patients with high *PD-L1* gene expression, as well as in patients with high expression of other PD-L1–PD-1 pathway genes in tumour tissue (PD-L1 receptors *PD-1* and *B7.1*, and the alternative ligand, *PD-L2;* figure 4A). Furthermore, atezolizumab improved overall survival in patients with tumours characterised by high expression of T-effector-associated and interferon-γ-associated genes (HR 0·43; 95% CI 0·24–0·77; figure 4B). The T-effector-associated and interferon-γ-associated gene signature was also associated with PD-L1 expression on tumour-infiltrating immune cells, suggesting that PD-L1 expression on tumour-infiltrating immune cells indicates pre-existing immunity within the tumour tissue (appendix). We did not see an association of the T-effector-associated and interferon-γ-associated gene signature with PD-L1 expression on tumour cells.

As with overall survival, progression-free survival and objective response rate tended to show increased atezolizumab benefit with increasing PD-L1 expression (appendix). The greatest improvement was in the TC3 or IC3 subgroup, with progression-free survival of 7·8 months with atezolizumab versus 3·9 months with docetaxel (HR 0·60, 95% CI 0·31–1·16) and nine (38%) of 24 patients achieving an objective response with atezolizumab versus three (13%) of 23 with docetaxel. However, analysis of non-overlapping subgroups suggested that, unlike overall survival, improved progression-free survival and objective response rate with atezolizumab were limited to only those patients with the highest level of PD-L1 expression: the TC3 or IC3 subgroup (appendix). Objective response, as measured by immune-modified RECIST criteria, was achieved in 24 (17%; 95% CI 11·0–23·8) patients in the atezolizumab intention-to-treat population, similar to the objective response in 21 (15%; 9·3–21·4) patients, as measured by RECIST v1.1 criteria.

In patients with squamous disease, overall survival was 10·1 months in 49 patients in the atezolizumab group and 8·6 months in 48 patients in the docetaxel group (HR 0·80; 0·49–1·30) in favour of atezolizumab. In the non-squamous group, overall survival was 15·5 months in 95 patients in the atezolizumab group and 10·9 months in 95 patients in the docetaxel group (HR 0·69; 95% CI 0·47–1·01). Patients showed overall survival benefit with atezolizumab compared with docetaxel irrespective of tobacco use history (HR 0·75 [0·54–1·04] for patients with current or previous tobacco use *vs* 0·55 [0·24–1·25] for patients with no tobacco use history).

Therapies received after discontinuing study treatment are summarised in the appendix. No patients in the atezolizumab group received subsequent PD-1 or PD-L1 inhibitors but seven patients in the docetaxel group received subsequent PD-1 or PD-L1 inhibitors.

Despite longer median treatment duration (atezolizumab 3·7 months [range 0–19] *vs* docetaxel 2·1 months [range 0–17]), 57 (40%) patients in the atezolizumab group experienced grade 3–4 adverse events versus 71 (53%) in the docetaxel group (table 2). This difference was more evident in grade 3–4 adverse events assessed as related to treatment by the investigator (16 [11%] *vs* 52 [39%]). The most common atezolizumab-related grade 3 adverse events were pneumonia (three [2%] patients) and increased aspartate aminotransferase (three [2%] patients). No atezolizumab-related grade 4 adverse events were reported. The most common adverse events from any cause differing by 5% or more between

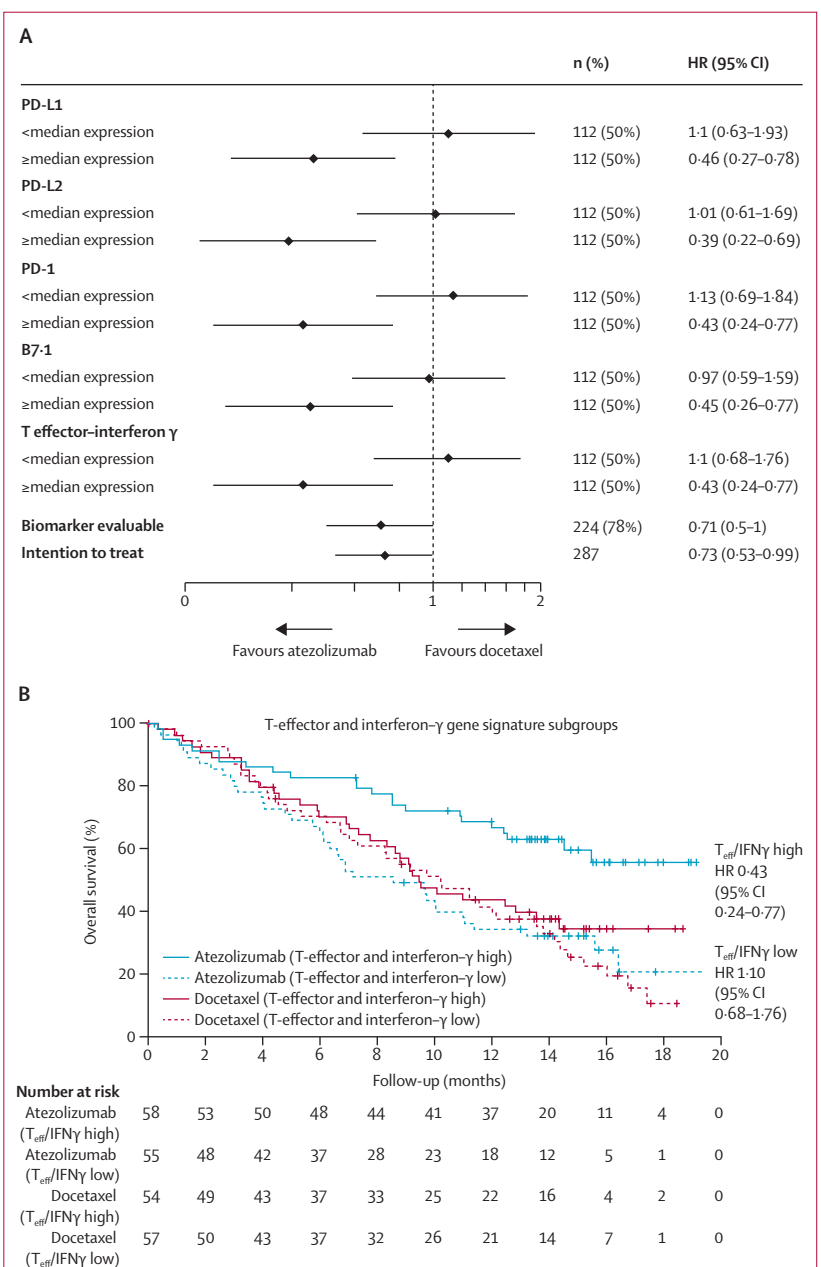


Figure 4: **Overall survival in subgroups defined by gene expression in tumour tissue**
(A) HRs and 95% CIs for overall survival in subgroups defined by gene expression. (B) Kaplan-Meier estimates in the T-effector and interferon-γ gene signature subgroups. HR=hazard ratio. Teff/IFNγ=T effector and interferon γ.

	Atezolizumab (n=142)	Docetaxel (n=135)
Total patients with at least one adverse event	136 (96%)	130 (96%)
Total events	1354	1325
Treatment-related adverse events	95 (67%)	119 (88%)
Grade 3 or 4 adverse events	57 (40%)	71 (53%)
Treatment-related grade 3 or 4 adverse events	16 (11%)	52 (39%)
Grade 5 adverse events	6 (4%)	5 (4%)
Treatment-related grade 5 adverse events	1 (1%)	3 (2%)
Serious adverse events	50 (35%)	46 (34%)
Adverse events leading to withdrawal from treatment	11 (8%)	30 (22%)
Treatment-related adverse events leading to withdrawal from treatment	2 (1%)	24 (18%)
Adverse events leading to dose modification or interruption	34 (24%)	44 (33%)
Treatment-related adverse events leading to dose modification or interruption	15 (11%)	32 (24%)

Table 2: **Overall safety profile**

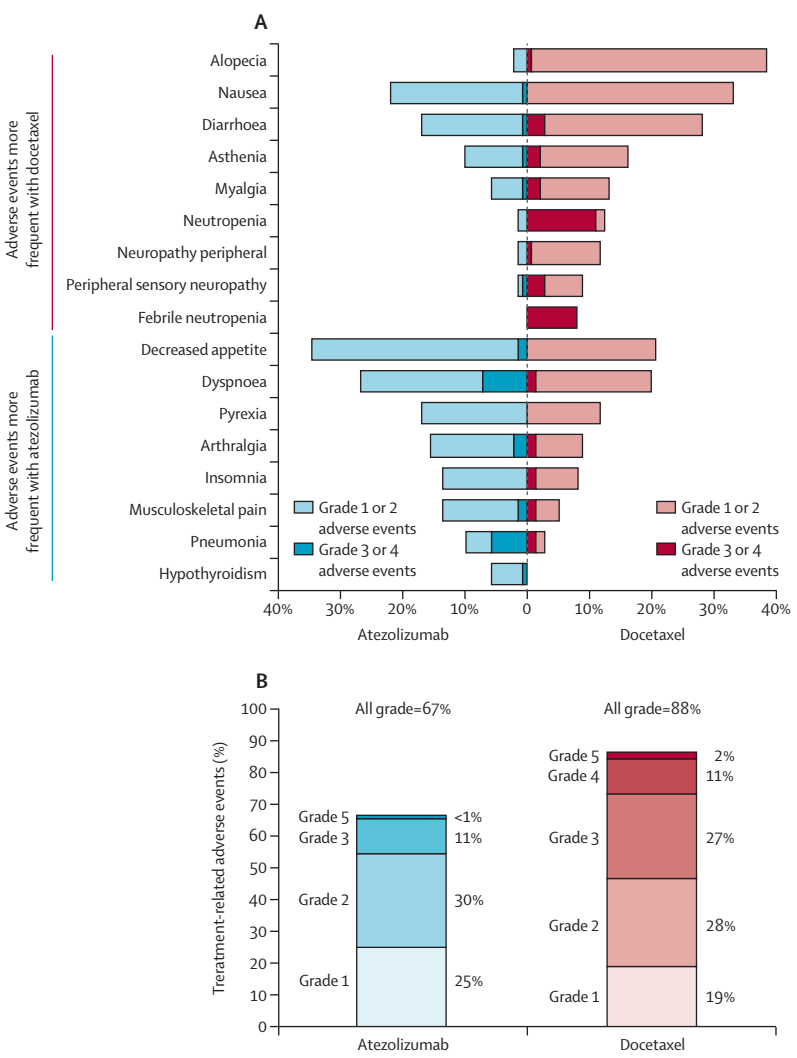


Figure 5: **All-cause and treatment-related adverse events in the safety population**
(A) All-cause adverse events that differed by 5% or more between study groups. (B) Proportions of patients having treatment-related adverse events, by grade.

groups are shown in figure 5A, and proportions of treatment-related adverse events by grade are shown in figure 5B. Related adverse events differing by 10% or more between groups are shown in the appendix. Other immune-mediated adverse events of any grade with atezolizumab were increased aspartate aminotransferase (six [4%] patients, three at grade 3–4), increased alanine aminotransferase (six [4%] patients, three at grade 3–4), pneumonitis (four [3%] patients, one at grade 3–4), colitis (two [1%] patients, one at grade 3–4), and hepatitis (one [1%] patient, grade 1–2). Fewer patients discontinued treatment with atezolizumab than with docetaxel (11 [8%] *vs* 30 [22%]). Grade 5 adverse events were cardiac failure (related to study treatment), pneumonia, ulcer haemorrhage, pneumothorax, pulmonary embolism, and embolism in the atezolizumab group (one patient each) and sepsis (two patients; one related to study treatment), death from unknown causes (two patients; one related to study treatment), and acute respiratory distress syndrome (one patient; related to study treatment) in the docetaxel group (table 2).

Discussion

Atezolizumab showed significant improvement in overall survival compared with docetaxel in patients with advanced, previously treated NSCLC, unselected for PD-L1 expression. Improvement in overall survival increased with increasing PD-L1 expression, whereas patients with the lowest PD-L1 expression levels experienced overall survival similar to that in the docetaxel group. Efficacy outcomes of patients in the docetaxel group compared favourably with those in previous clinical trials in the second-line setting.[25–29] Baseline characteristics were balanced except for the higher proportion of female patients in the docetaxel group; in some studies, female sex has been associated with improved survival in patients with advanced NSCLC, which could have resulted in increased survival in the docetaxel group of our study.[30] Patients with either squamous or non-squamous NSCLC exhibited a numerical improvement in overall survival with atezolizumab compared with docetaxel.

Atezolizumab was well tolerated with a safety profile consistent with previous studies,[4] and we identified no new safety signals. The safety profile was distinct from that of docetaxel, with lower rates of drug discontinuations due to adverse events, grade 3–4 adverse events, and adverse events common to chemotherapy, including nausea, cytopenias, and peripheral neuropathy; most atezolizumab-associated toxicities were low grade. Potential immune-mediated adverse events, such as increased aspartate aminotransferase, increased alanine aminotransferase, pneumonitis, colitis, and hepatitis occurred at low frequencies (<5%) in the atezolizumab group and were generally manageable and reversible.

POPLAR is the first randomised study showing that PD-L1 expression on tumour cells and tumour-infiltrating immune cells has non-redundant roles in

regulation of antitumour immunity and predicting response to therapy.

Very few patients (<1%) had co-expression of PD-L1 on both tumour cells and tumour-infiltrating immune cells at the highest levels (ie, TC3 and IC3), suggesting that TC3 and IC3 are distinct subpopulations in NSCLC. The association of PD-L1 expression on tumour-infiltrating immune cells with the T-effector and interferon-γ gene signature, a hallmark of pre-existing immunity, further supports the hypothesis that PD-L1 expression is regulated by different mechanisms in NSCLC: an intrinsic mechanism on tumour cells and an adaptive mechanism on immune cells.[4] An adaptive mechanism on immune cells is consistent with previous reports of adaptive PD-L1 regulation in highly inflamed tumours.[31]

Importantly, PD-L1 expression on tumour cells and tumour-infiltrating immune cells independently predicted improved overall survival with atezolizumab. This finding contrasts with anti-PD-1 studies that showed an association with tumour cell PD-L1 expression only.[7–10] PD-L1 expression on tumour-infiltrating immune cells as a predictive biomarker is further supported by the association of T-effector and interferon γ gene signature with improved overall survival. These data are also consistent with the hypothesis that benefit from checkpoint inhibition is pronounced in tumours with pre-existing immunity. Taken together, these findings confirm the importance of assessing PD-L1 on tumour-infiltrating immune cells, in addition to tumour cells, as a predictive biomarker to identify patients most likely to benefit from atezolizumab. Neither PD-L1 immunohistochemistry nor T-effector and interferon-γ gene expression was associated with prognostic significance on overall survival for docetaxel-treated patients.

High expression of PD-L2 from within the tumour was associated with improved overall survival for atezolizumab treatment, despite atezolizumab leaving the PD-L2–PD-1 interaction intact. Expression of PD-L2 has previously been associated with that of PD-L1,[32] and does not seem to confer inhibition of the anticancer immunity generated by atezolizumab therapy. These data suggest that blocking the PD-L1–PD-1 and PD-L1–B7.1 interactions and not the PD-L2–PD-1 interaction is sufficient to provide strong efficacy in patients expressing the highest levels of PD-L2, but the role of PD-L2 in anticancer immunity remains unclear.

Our results also highlight a unique relation between measures of atezolizumab efficacy (overall survival, progression-free survival, and objective response rate). Namely, overall survival, but not progression-free survival or objective response rate, improved with atezolizumab treatment in the intention-to-treat population and in PD-L1 expression subgroups defined by 1% or more and 5% or more tumour cell or tumour-infiltrating immune cell staining. The strong improvement in overall survival without an improvement in progression-free survival or objective response rate in these populations, together with the observation that overall survival improved with atezolizumab in both responding and non-responding patients, implies that standard radiographic endpoints might underestimate treatment benefit with atezolizumab. These results suggest that some patients benefit after RECIST-defined progression, possibly because of delayed anticancer immune effects.

A key strength of POPLAR was that this study enrolled patients irrespective of PD-L1 status, which was prospectively assessed on both tumour cells and tumour-infiltrating immune cells. The main limitation of POPLAR was the moderate size of the trial, reducing the ability to draw conclusions about atezolizumab benefit in smaller subgroups of patients. Therefore, further assessment of atezolizumab efficacy in this patient population, including more precise assessment of treatment effects in subgroups, will be provided by the phase 3 OAK study (ClinicalTrials.gov, number NCT02008227).

In conclusion, our data show that atezolizumab provides survival benefit in previously treated patients with NSCLC, and that PD-L1 expression on tumour cells and tumour-infiltrating immune cells is predictive of this benefit. Additionally, the exploratory analyses of T-effector and interferon γ gene signature deepens our understanding of mechanisms of response to anti-PD-L1 blockade and provides a starting point for development of future predictive biomarkers for cancer immunotherapies. These data, along with those from other atezolizumab studies in patients with previously treated NSCLC, demonstrate the clinical efficacy and safety of targeting PD-L1 with atezolizumab in this patient population.

Contributors

All authors reviewed the data analyses, contributed to data interpretation and writing of the report, approved the final version of the submitted report, and are accountable for all aspects of the report.

Declaration of interests

AA-C, LF, JM, DS, JV, CL declare no competing interests. MB is a Genentech employee, and holder of Roche, Exelixis, and Sunesis stock. JY and husband are Genentech employees. KP reports personal fees from Astellas, AstraZeneca, Aveo, Boehringer Ingelheim, Clovis, Eli Lilly, Hanmi, KHK Novartis, Ono, and Roche, and grants and research funding from AstraZeneca. AR reports grants from Roche, Lilly, Bristol-Myers Squibb, AstraZeneca, MSD, Boehringer Ingelheim, and Pfizer. ASp reports grants, personal fees, and clinical trial funding from Roche. DW is a Genentech employee. WZ is a Genentech employee. MK is a Genentech employee and holder of Genentech/Roche stock, royalties or other IP, and has a patent "Biomarkers and methods of treating PD-1 and PD-L1 related conditions" pending. FB reports personal fees from Agendia, Amgen/Onyx, Bayer, Bristol-Myers Squibb, Caris Life Sciences, Celgene, Foundation Medicine, Genomic Health, Incyte, Insys, Novartis, Pfizer, Saladax, and Sanofi. PH is a Genentech employee. DSC is a Genentech employee and stock holder, and has a patent "Biomarkers and methods of treating PD-1 and PD-L1 related conditions" pending; ASa is a Genentech employee with stock. Additionally Roche/Genentech has compensated for consultant and advisory services and expert testimony, provided honoraria, and provided research funding to the author's institution.

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