European Journal of Cancer 107 (2019) 124–132

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Long-term survival in patients with advanced non–small-cell lung cancer treated with atezolizumab versus docetaxel: Results from the randomised phase III OAK study

J. von Pawel [a,*], R. Bordoni [b], M. Satouchi [c], L. Fehrenbacher [d], M. Cobo [e], J.Y. Han [f], T. Hida [g], D. Moro-Sibilot [h], P. Conkling [i], D.R. Gandara [j], A. Rittmeyer [k], M. Gandhi [l], W. Yu [l], C. Matheny [l], H. Patel [l], A. Sandler [l], M. Ballinger [l], M. Kowanetz [l], K. Park [m]

[a] *Asklepios Fachkliniken München-Gauting, Gauting, Germany*
[b] *Georgia Cancer Specialists and Northside Hospital Cancer Institute, Atlanta, GA, USA*
[c] *Hyogo Cancer Center, Akashi, Japan*
[d] *Kaiser Permanente Medical Center, Vallejo, CA, USA*
[e] *Hospital Regional Universitario Málaga, IBIMA, Málaga, Spain*
[f] *National Cancer Center, Goyang, South Korea*
[g] *Aichi Cancer Center Hospital, Nagoya, Japan*
[h] *CHU Grenoble–Alpes, Grenoble Albert Michallon, La Tronche, France*
[i] *US Oncology Research, Virginia Oncology Associates, Norfolk, VA, USA*
[j] *UC Davis Comprehensive Cancer Center, Sacramento, CA, USA*
[k] *Lungenfachklinik Immenhausen, Immenhausen, Germany*
[l] *Genentech, Inc., South San Francisco, CA, USA*
[m] *Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Received 3 October 2018; accepted 9 November 2018
Available online 17 December 2018

KEYWORDS
Atezolizumab;
Long-term survival;
Second-line NSCLC;
PD-L1;
Cancer immunotherapy

Abstract ***Background:*** Atezolizumab (anti–programmed death-ligand 1 [PD-L1]) received approval from the US Food and Drug Administration and European Medicines Agency for previously treated advanced non–small-cell lung cancer based on OAK—a randomised, phase III trial that showed significantly improved survival with atezolizumab versus docetaxel regardless of PD-L1 expression. With longer follow-up, we summarised the characteristics of long-term survivors (LTSs).
Methods: In OAK (NCT02008227), patients were randomised 1:1 to receive atezolizumab or docetaxel until loss of clinical benefit or disease progression, respectively. Overall survival was

* *Corresponding author*: Asklepios Fachkliniken München-Gauting, Robert-Koch-Allee 2, Gauting, Germany.
E-mail address: j.pawel@asklepios.com (J. von Pawel).

https://doi.org/10.1016/j.ejca.2018.11.020

evaluated after a 26-month minimum follow-up, including in patient subgroups defined by best overall response (BOR). LTSs were defined as patients who lived ≥24 months since randomisation. Non-LTSs died within 24 months, and patients censored before 24 months were excluded from the analysis. The baseline characteristics, including biomarkers, BOR, subsequent non-protocol therapy (NPT) and safety, are reported.

Results: Survival benefit with atezolizumab was observed across all patient subgroups defined by BOR. More atezolizumab-treated patients were LTSs versus those treated with docetaxel (28% versus 18%). Most atezolizumab responders were LTSs (77%) versus only 48% of docetaxel responders. However, 21% of atezolizumab-arm LTSs had progressive disease (PD) as BOR, and more atezolizumab-arm LTSs than non-LTSs continued treatment post-PD. Fifty-two percent of docetaxel-arm LTSs received immunotherapy as subsequent NPT. Despite extended treatment duration in atezolizumab-arm LTSs (median, 18 months), atezolizumab was well tolerated.

Conclusions: After >2 years of follow-up, atezolizumab continued to provide durable survival benefit versus docetaxel, with tolerable safety. Atezolizumab-arm LTSs were enriched for patients with high PD-L1 expression and included PD-L1–negative patients. Long-term survival was not limited to responders.

1. Introduction

Globally, lung cancer is the leading cause of cancer-related mortality [1]. Patients with locally advanced or metastatic non–small-cell lung cancer (NSCLC) have historically experienced poor clinical outcomes, with a 5-year survival rate of <5% [2]. Recent advances have provided new therapeutic options for patients with advanced NSCLC, including immune checkpoint inhibitors that aim to harness the immune system to eradicate cancer.

Atezolizumab is a humanised monoclonal antibody that targets programmed death-ligand 1 (PD-L1) [3] and blocks the binding of PD-L1 to its receptors programmed death-1 (PD-1) and B7.1, thus restoring antitumour immunity [4–6]. Targeting PD-L1 with atezolizumab may also maintain immune homeostasis in normal tissue by preserving the programmed death-ligand 2/PD-1 interaction [7,8].

The global, randomised, phase III clinical trial, OAK (NCT02008227), compared the efficacy and safety of atezolizumab versus docetaxel in patients with previously treated locally advanced or metastatic NSCLC [9]. In the primary analysis (data cut-off: July 7, 2016; median follow-up, 21 months), overall survival (OS) improved with atezolizumab (median, 13.8 months) versus docetaxel (median, 9.6 months; hazard ratio [HR], 0.73 [95% confidence interval {CI}: 0.62, 0.87]; $P = 0.0003$) in the intent-to-treat (ITT) population and across PD-L1 subgroups and NSCLC histologies [9]. These results led to approval of atezolizumab in previously treated patients with NSCLC in the United States, EU and additional countries worldwide [10,11]. The secondary analysis of the OAK study (data cut-off: January 23, 2017; median follow-up, 28 months) continued to demonstrate improved OS with atezolizumab (median, 13.8 months) compared with docetaxel (median, 9.6 months; HR, 0.75 [95% CI: 0.64, 0.89]; $P = 0.0006$) in the primary efficacy population (ITT850), with a landmark 2-year OS rate of 30.9% with atezolizumab versus 21.1% with docetaxel [12]. Patients with the highest level of PD-L1 expression (on ≥ 50% of tumour cells [TC] or on ≥10% of tumour-infiltrating immune cells [IC] [TC3 or IC3]) experienced the greatest survival benefit with atezolizumab (HR, 0.40 [95% CI: 0.27, 0.61]; $P < 0.001$), with landmark 2-year OS rates of 43.2% and 17.4%, respectively (Fig. S1) [12]. However, patients in the PD-L1–negative subgroup (expression on < 1% of TC and IC [TC0 and IC0]) also had significantly improved survival (HR, 0.77 [95% CI: 0.61, 0.97]; $P = 0.026$), with landmark 2-year OS rates of 30.0% and 18.3%, respectively (Fig. S1) [12]. An improved 2-year OS rate with atezolizumab versus docetaxel was also seen across tumour histologies: non-squamous (34.7% versus 24.4%) and squamous (19.7% versus 12.2%) [12].

Here, OS by best response and characteristics of patients who experienced long-term survival in OAK are reported.

2. Material and methods

The OAK study design was previously reported [9]. Patients had disease progression after 1–2 prior chemotherapy regimens, including ≥1 platinum-based therapy; patients with *EGFR*- or *ALK*-altered tumours were required to have received approved targeted therapy. All patients provided signed informed consent, and the study was conducted in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki.

Atezolizumab was administered intravenously (1200 mg every 3 weeks) until investigator-assessed loss of clinical benefit, in the absence of unacceptable

toxicity or symptomatic deterioration attributed to progressive disease (PD). Docetaxel was administered intravenously (75 mg/m^2 every 3 weeks) until unacceptable toxicity or PD.

Tumour assessments, per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1.1), were performed at baseline and then every 6 weeks until week 36 and every 9 weeks thereafter until PD or treatment discontinuation for patients receiving atezolizumab beyond progression. After discontinuation, patients were followed for survival and subsequent non-protocol therapy (NPT).

The co-primary end-points were OS in the ITT population and the PD-L1–positive subgroup (TC1/2/3 or IC1/2/3), compared between treatment arms in the first 850 patients enrolled. Safety was assessed in all patients who received study treatment. The incidence and severity of adverse events (AEs) and laboratory abnormalities were assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Immune-related AEs (irAEs) were defined using the Medical Dictionary for Regulatory Activities preferred terms, which included both diagnosed immune conditions and signs and symptoms potentially representative of immune-related events—regardless of investigator-assessed causality.

OS was compared between treatment arms with a stratified log-rank test at the two-sided significance level. Kaplan–Meier analysis was used to estimate median OS, and the Brookmeyer-Crowley methodology was used to estimate 95% CIs. HRs were estimated with a stratified Cox regression analysis. Progression-free survival, objective response rate (ORR) and duration of response were analysed as previously described [9].

Survival of 2 years is considered exceptional in patients with previously treated advanced NSCLC; historically, the median OS has been ≈5.5–10.4 months [13–17]. Therefore, long-term survivors (LTSs) were defined as patients who lived ≥24 months from the time of randomisation. Non-LTSs were defined as patients who died within 24 months from the time of randomisation. Patients censored prior to 24 months were excluded from these analyses.

Biomarkers were evaluated in baseline tumour samples. PD-L1 expression was evaluated by immunohistochemistry, as previously described [9]. Expression of the T-effector gene signature (*CD274*, *IFNG* and *CXCL9*) [18] was assessed by polymerase chain reaction.

3. Results

Of the first 850 patients enrolled in OAK, 425 were randomised to receive atezolizumab and 425 to docetaxel [9]. At the time of data cut-off (January 23, 2017), the median follow-up was 28 months with a minimum follow-up of 26 months.

3.1. OS by best overall response

Across subgroups defined by best overall response (BOR), OS improved with atezolizumab versus docetaxel (Fig. 1). Patients who had a response experienced the greatest OS benefit with atezolizumab (HR, 0.35 [95% CI: 0.19, 0.64]; Fig. 1). However, non-responders also had improved survival with atezolizumab: stable disease (SD) (HR, 0.73 [95% CI: 0.57, 0.95] and PD (HR, 0.76 [95% CI: 0.59, 0.98]) (Fig. 1).

In the atezolizumab arm, the 2-year OS rate was 77% in patients who had a response, 33% in patients who had SD and 17% in patients who had PD as best response; in the docetaxel arm, the respective values were 48%, 27% and 7%. The OS benefit observed with atezolizumab versus docetaxel across subgroups defined by BOR was observed in patients with both non-squamous and squamous histology (Fig. S2).

3.2. Long-term survivors

In the atezolizumab arm, 398 patients were included in the analysis (27 patients censored before 24 months were excluded). Of these, 119 patients (30%) were LTSs (Fig. 2), and 279 (70%) were non-LTSs. In the docetaxel arm, 376 patients were included (49 patients censored before 24 months were excluded), and 77 (20%) were LTSs (Fig. S3), and 299 (80%) were non-LTSs.

In both arms, baseline characteristics showed enrichment for female patients, non-squamous histology and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 in LTSs versus non-LTSs (Table 1). History of tobacco use, number of prior therapies and *EGFR* mutation status were similar between LTSs and non-LTSs in both treatment arms.

3.3. Evaluation of biomarkers in LTSs

Atezolizumab-arm LTSs were enriched for patients with the highest level of PD-L1 expression (TC3 or IC3) and who had higher expression of the T-effector gene signature compared with non-LTSs (Table 1). Twenty-four percent of atezolizumab-arm LTSs were TC3 or IC3 versus 14% of non-LTSs. Median T-effector gene signature expression was 1.7-fold higher in atezolizumab-arm LTSs versus non-LTSs (−1.61 versus −2.40). Long-term survival was not limited to patients with PD-L1–expressing tumours; 40% of atezolizumab-arm LTSs had PD-L1–negative tumours (TC0 and IC0), comparable to atezolizumab-arm non-LTSs (43%).

3.4. Sites of disease at baseline and progression

At baseline, LTSs in both treatment arms had fewer bone and liver metastases compared with non-LTSs, while the frequencies of brain and adrenal metastases were similar (Fig. S4A). Eighty-five atezolizumab-arm LTSs (71%)

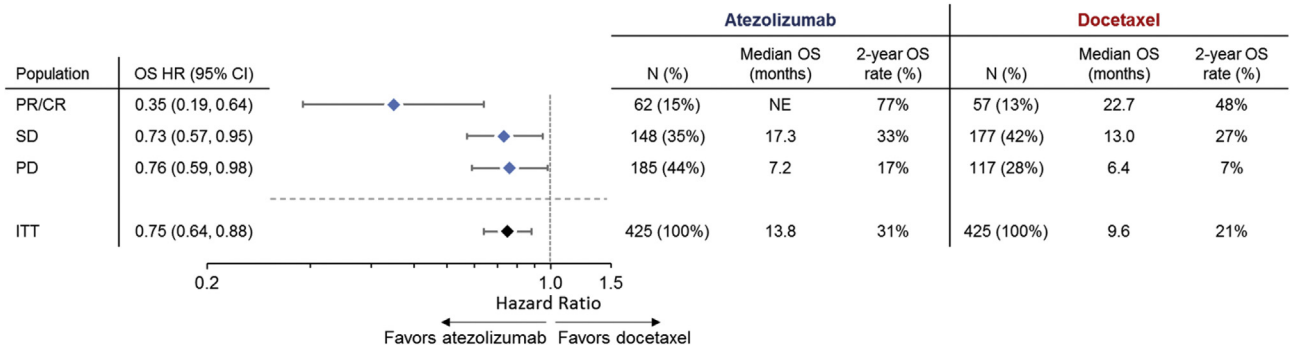

Fig. 1. Long-term survival by best overall response in the OAK study with ≥26 months of follow-up. Hazard ratios for overall survival (OS) in subgroups defined by best overall response. CR, complete response; ITT, intent-to-treat; PD, progressive disease; PR, partial response; SD, stable disease.

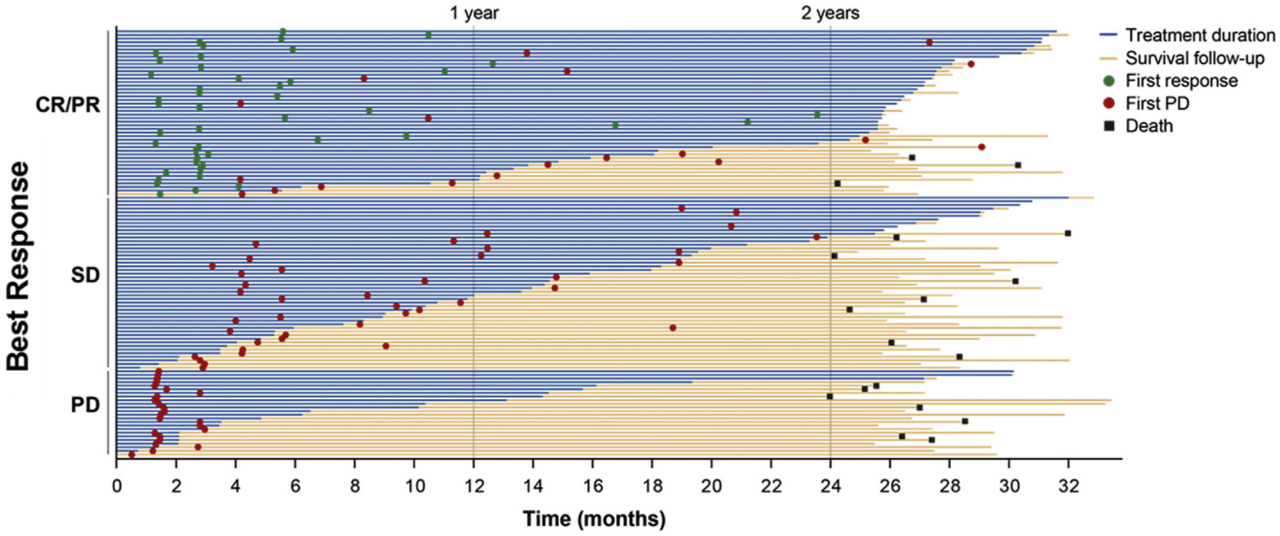

Fig. 2. Profile of long-term survivors (LTSs) in the atezolizumab-arm. Duration of atezolizumab treatment and survival with best overall response in LTSs (n = 119) Patients are grouped by best overall response and sorted by duration of treatment. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

and 62 docetaxel-arm LTSs (81%) experienced PD, while 231 atezolizumab-arm (83%) and 216 docetaxel-arm non-LTSs (72%) experienced PD (Table 2).

The occurrence of PD at both existing and new sites in the atezolizumab-arm LTSs was less frequent (18%) versus non-LTSs (30%), while PD at both existing and new sites was similar between docetaxel-arm LTSs (19%) and non-LTSs (21%; Table S1). Of the atezolizumab-arm patients who had a new lesion at the time of PD, non-LTSs had more new liver (14% versus 4%) and bone (10% versus 6%) lesions compared with LTSs (Fig. S4B).

3.5. ORR in LTSs

Atezolizumab- and docetaxel-arm LTSs had higher ORR (39% and 33%, respectively) compared with non-LTSs (5% and 9%, respectively; Table 3). However, 77% (46 of 60) of atezolizumab-arm responders were LTSs, while only 48% (25 of 52) of docetaxel-arm responders were LTSs. Twenty-one percent of atezolizumab-arm LTSs had a BOR of PD versus 9% of docetaxel-arm LTSs (Table 3; Figs. 2 and S3).

3.6. Treatment beyond progression and subsequent NPT

Of the atezolizumab-arm patients with PD, more LTSs than non-LTSs were treated beyond progression (62% versus 45%; Table 2). Fifty-three percent of atezolizumab-arm LTSs and 71% of docetaxel-arm LTSs received subsequent NPT; 52% of docetaxel-arm LTSs received immunotherapy (e.g. checkpoint inhibitor) as subsequent NPT. Erlotinib, bevacizumab and osimertinib were the most common targeted therapies given in all groups.

3.7. Duration of treatment in LTSs

The median treatment duration with atezolizumab was 18 months (range, 0–32) in LTSs and 2.1 months (range, 0–19) in non-LTSs (Table 4). Thirty-eight

Table 1
Baseline characteristics in LTSs and non-LTSs.

Baseline characteristics	Atezolizumab (n = 398)		Docetaxel (n = 376)	
	LTSs (n = 119)	Non-LTSs (n = 279)	LTSs (n = 77)	Non-LTSs (n = 299)
Median age (range), years	63 (35–81)	64 (33–82)	62 (41–84)	64 (34–85)
Aged ≥ 65 years, n (%)	52 (44%)	127 (46%)	31 (40%)	149 (50%)
Sex, n (%)				
Male	61 (51%)	183 (66%)	45 (58%)	186 (62%)
Female	58 (49%)	96 (34%)	32 (42%)	113 (38%)
Race, n (%)				
White	84 (71%)	205 (74%)	52 (68%)	217 (73%)
Asian	27 (23%)	46 (17%)	20 (26%)	61 (20%)
Black	1 (1%)	4 (1%)	3 (4%)	6 (2%)
Other[a]	3 (3%)	10 (4%)	1 (1%)	4 (1%)
Unknown	4 (3%)	14 (5%)	1 (1%)	11 (4%)
ECOG PS, n (%)				
0	60 (50%)	89 (32%)	48 (62%)	95 (32%)
1	59 (50%)	190 (68%)	29 (38%)	204 (68%)
Prior lines of therapy, n (%)				
1	89 (75%)	209 (75%)	55 (71%)	231 (77%)
2	30 (25%)	70 (25%)	22 (29%)	68 (23%)
Tobacco use history, n (%)				
Never	29 (24%)	47 (17%)	14 (18%)	45 (15%)
Current	18 (15%)	36 (13%)	10 (13%)	49 (16%)
Previous	72 (61%)	196 (70%)	53 (69%)	205 (69%)
EGFR mutation, n (%)				
Positive	11 (9%)	26 (9%)	10 (13%)	24 (8%)
Negative	96 (81%)	204 (73%)	59 (77%)	214 (72%)
Unknown	12 (10%)	49 (18%)	8 (10%)	61 (20%)
EML4-ALK translocation, n (%)				
Positive	2 (2%)	0	0	0
Negative	69 (58%)	142 (51%)	36 (47%)	131 (44%)
Unknown	48 (40%)	137 (49%)	41 (53%)	168 (56%)
KRAS mutation, n (%)				
Positive	9 (8%)	17 (6%)	6 (8%)	24 (8%)
Negative	32 (27%)	62 (22%)	22 (29%)	62 (21%)
Unknown	78 (66%)	200 (72%)	49 (64%)	213 (71%)
Histology, n (%)				
Non-squamous	100 (84%)	195 (70%)	65 (84%)	209 (70%)
Squamous	19 (16%)	84 (30%)	12 (16%)	90 (30%)
PD-L1 expression, n (%)				
TC3 or IC3	28 (24%)	39 (14%)	10 (13%)	49 (16%)
TC2/3 or IC2/3	42 (35%)	81 (29%)	27 (35%)	92 (31%)
TC1/2/3 or IC1/2/3	71 (60%)	156 (56%)	45 (58%)	149 (50%)
TC0 and IC0	48 (40%)	119 (43%)	32 (42%)	147 (49%)
T-effector gene expression[b]				
Median	−1.61	−2.40	−2.01	−2.41
Interquartile range	−2.64, −0.58	−3.39, −0.87	−3.76, −1.21	−4.13, −1.27
Below the limit of detection, n (%)	6 (5%)	13 (17%)	29 (10%)	37 (12%)

ECOG PS, Eastern Cooperative Oncology Group performance status; IC, tumour-infiltrating immune cell; PD-L1, programmed death-ligand 1; TC, tumour cell; LTSs, long-term survivors.
TC3 or IC3 = PD-L1 expression of ≥50% on TC or ≥10% on IC; TC2/3 or IC2/3 = PD-L1 expression of ≥5% on TC or IC; TC1/2/3 or IC1/2/3 = PD-L1 expression of ≥1% on TC or IC; TC0 and IC0 = PD-L1 expression of <1% on TC and IC.
[a] 'Other' includes American Indian, Alaska native, Hawaiian native, other Pacific Islanders, other and multiple.
[b] 355 patients in the atezolizumab arm and 336 patients in the docetaxel arm were evaluable for T-effector gene expression.

percent of atezolizumab-arm LTSs were treated beyond 24 months, and many LTSs in the atezolizumab arm who were non-responders received treatment for an extended duration (Fig. 2).

3.8. Safety profile in LTSs

Similar rates of grade 3–4 treatment-related AEs (TRAEs) were reported in atezolizumab-arm LTSs and non-LTSs (19% and 15%, respectively), and AEs leading to treatment discontinuation were similar (9% and 8%, respectively; Table 4). A higher rate of AEs leading to treatment interruption was reported in LTSs (43%) versus non-LTSs (19%). The most frequently occurring TRAEs in atezolizumab-arm LTSs were grade 1–2 and included diarrhoea (14%), fatigue (12%) and pruritus (12%) (Fig. S5A). Atezolizumab-arm LTSs had an irAE rate of 30% (Table 4); most of these irAEs were grade

Table 2
Treatment beyond progression and subsequent NPT in LTSs and non-LTSs.

Treatment beyond progression	Atezolizumab (n = 398)		Docetaxel (n = 376)	
	LTSs (n = 119)	Non-LTSs (n = 279)	LTSs (n = 77)	Non-LTSs (n = 299)
PD per RECIST v1.1, n (%)	85 (71%)	231 (83%)	62 (81%)	216 (72%)
Treated beyond PD, n/N (%)	53/85 (62%)	105/231 (45%)	NA	NA
Received subsequent NPT, n (%)[a]	63 (53%)	149 (53%)	55 (71%)	142 (47%)
Immunotherapy	17 (14%)	7 (3%)	40 (52%)	38 (13%)
Nivolumab	15 (13%)	6 (2%)	37 (48%)	26 (9%)
Chemotherapy	47 (40%)	136 (49%)	28 (36%)	107 (36%)
Docetaxel	22 (19%)	91 (33%)	2 (3%)	8 (3%)
Vinorelbine	11 (9%)	23 (8%)	13 (17%)	30 (10%)
Carboplatin	9 (8%)	28 (10%)	8 (10%)	27 (9%)
Gemcitabine	8 (7%)	31 (11%)	12 (16%)	45 (15%)
Paclitaxel	7 (6%)	13 (5%)	3 (4%)	12 (4%)
Pemetrexed	6 (5%)	17 (6%)	8 (10%)	23 (8%)
Gimeracil/oteracil potassium/tegafur	5 (4%)	5 (2%)	2 (3%)	3 (1%)
Paclitaxel albumin	4 (3%)	4 (1%)	2 (3%)	4 (1%)
Cisplatin	1 (1%)	5 (2%)	1 (1%)	10 (3%)
Targeted therapy	27 (23%)	41 (15%)	21 (27%)	48 (16%)
Erlotinib	11 (9%)	24 (9%)	12 (16%)	36 (12%)
Bevacizumab	4 (3%)	4 (1%)	5 (6%)	6 (2%)
Osimertinib	4 (3%)	0	2 (3%)	2 (1%)
Afatinib	3 (2%)	2 (1%)	1 (1%)	5 (2%)
Crizotinib	2 (2%)	0	2 (3%)	0

LTSs, long-term survivors; NA, not applicable; NPT, non-protocol therapy; PD, progressive disease; RECIST, response evaluation criteria in solid tumors.
[a] Only subsequent NPT received by ≥ 2% of all LTSs or all non-LTSs are listed individually.

1–2 (Fig. S5B). The most frequently reported irAEs in both populations were changes in liver function test results (14%, LTSs; 6%, non-LTSs) and hypothyroidism (9%, LTSs; 4%, non-LTSs).

4. Discussion

An updated OS analysis of OAK with extended follow-up demonstrating a continued survival benefit with atezolizumab versus docetaxel was recently reported [12]. The responses and characteristics of the LTSs are reported here. Atezolizumab treatment provided durable and superior OS benefit versus docetaxel across all patient subgroups defined by BOR. While responders had the greatest OS benefit, patients with SD or PD as best response also had improved survival with atezolizumab, indicating that non-responders also benefit from atezolizumab treatment.

The percentage of patients who were 2-year LTSs (28%) differed from the 2-year OS rate (30.9%) in the ITT population [12] because patients censored before 24 months were excluded. Long-term survival was associated with known favourable prognostic factors at baseline (non-squamous histology, female sex, ECOG PS and sites of metastatic disease) in both treatment arms, suggesting that these factors may similarly affect immunotherapy and chemotherapy benefit.

Consistent with prior results showing clinical benefit across PD-L1 expression subgroups [9], long-term survival in the atezolizumab arm was not restricted to patients with high PD-L1–expressing tumours; 40% of atezolizumab-arm LTSs had PD-L1–negative tumours. However, atezolizumab-arm LTSs were enriched for high PD-L1–expressing tumours compared with atezolizumab-arm non-LTSs; no comparable enrichment was observed in the docetaxel arm.

Table 3
Best overall response, DOR and PFS in the atezolizumab- and docetaxel-arm LTSs and non-LTSs.

Treatment beyond progression	Atezolizumab (n = 398)		Docetaxel (n = 376)	
	LTSs (n = 119)	Non-LTSs (n = 279)	LTSs (n = 77)	Non-LTSs (n = 299)
ORR, n (%)	46 (39%)	14 (5%)	25 (33%)	27 (9%)
CR	5 (4%)	0	1 (1%)	0
PR	41 (35%)	14 (5%)	24 (31%)	27 (9%)
SD, n (%)	48 (40%)	97 (35%)	44 (57%)	122 (41%)
PD, n (%)	25 (21%)	142 (51%)	7 (9%)	104 (35%)
Median DOR, months (95% CI)	26.3 (17.6, NE)	6.2 (4.2, 9.4)	8.7 (6.2, 13.2)	4.6 (3.5, 6.4)
Median PFS, months (95% CI)	11.3 (5.7, 14.8)	1.7 (1.5, 2.6)	8.8 (7.0, 10.4)	2.9 (2.8, 3.6)

CI, confidence interval; CR, complete response; DOR, duration of response; LTSs, long-term survivors; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 4
Safety summary of atezolizumab-arm LTSs and non-LTSs.

Treatment beyond progression	LTSs (n = 118)	Non-LTSs (n = 278)
Median treatment duration (range), months	18.0 (0–32)	2.1 (0–19)
Patients treated ≥ 24 months, n (%)	45 (38%)	0
AE, all grade, n (%)	116 (98%)	258 (93%)
Grade 3–4	46 (39%)	107 (39%)
Grade 5	0	7 (3%)
Treatment-related AE, all grade, n (%)	91 (77%)	162 (58%)
Grade 3–4	22 (19%)	42 (15%)
Grade 5	0	0
Serious AE, n (%)	29 (25%)	98 (35%)
Immune-related AE, all grade, n (%)	35 (30%)	43 (16%)
AE leading to withdrawal from treatment, n (%)	10 (9%)	23 (8%)
AE leading to dose modification or interruption, n (%)	51 (43%)	54 (19%)

AE, adverse event; LTSs, long-term survivors.

Atezolizumab-arm LTSs also had higher T-effector gene signature expression versus atezolizumab-arm non-LTSs without comparable enrichment in the docetaxel arm. This is consistent with previous data showing that patients with high T-effector gene signature expression derive greater benefit from atezolizumab than from docetaxel [18,19]. Together, these data suggest that patients with tumours that express markers of preexisting immunity (i.e. T-effector gene signature or PD-L1) may derive long-term survival with atezolizumab more frequently. However, these analyses are limited by selection of a single time point to define long-term survival (i.e. 24 months), which may influence the magnitude of difference in biomarker expression.

Long-term survival with atezolizumab was not restricted to patients who experienced an objective response; more atezolizumab-arm LTSs than docetaxel-arm LTSs experienced PD as BOR. In the atezolizumab arm, more LTSs than non-LTSs received treatment beyond progression, suggesting that treatment with atezolizumab beyond progression may result in an improved survival benefit in selected patients [20]. At the time of PD, atezolizumab-arm LTSs had a lower frequency of new liver and brain lesions compared with atezolizumab-arm non-LTSs; whereas, the frequency of new liver and brain lesions in docetaxel-arm LTSs and non-LTSs was similar. This suggests that atezolizumab-arm LTSs develop new lesions with poor prognosis at a lower frequency than non-LTSs; however, further confirmatory studies are needed.

Use of subsequent NPT was lower in atezolizumab-arm versus docetaxel-arm LTSs, and more than half of docetaxel-arm LTSs received immunotherapy as subsequent NPT. Given the established efficacy of immune checkpoint inhibitors in this setting, this suggests that frequent use of these agents may have contributed to the extended survival among docetaxel-arm LTSs. Patients who received epidermal growth factor receptor tyrosine kinase inhibitors (TKIs) as subsequent NPT and had an *EGFR* mutation at study start received EGFR TKI therapy both before and after study treatment, whereas patients without *EGFR* mutations at study start received EGFR TKIs as subsequent NPT despite lack of an *EGFR* mutation at baseline.

The large difference in atezolizumab treatment exposure between LTSs and non-LTSs makes comparing the safety profile between these populations challenging. Nevertheless, despite longer treatment exposure, atezolizumab was similarly well-tolerated in LTSs and non-LTSs, and no significant differences in grade 3–4 TRAEs or AEs leading to treatment discontinuation were observed. A higher rate of AEs leading to treatment interruption was reported among LTSs, possibly because of the substantially longer exposure period. The TRAE and irAE profile of atezolizumab-arm LTSs was consistent with that of prior OAK analyses [9,12].

5. Conclusion

This analysis encompasses a large study population representative of patients with advanced NSCLC across histologies with extended survival follow-up. Owing to the durable responses and extended survival observed in a subset of patients receiving atezolizumab, further follow-up will be of interest to better evaluate these patients. Overall, this analysis of long-term follow-up of the phase III OAK study and expanded description of LTS demonstrates that the OS benefit with atezolizumab versus docetaxel is durable, extends across all best response subgroups and includes patients with PD-L1–negative tumours. In addition, extended atezolizumab exposure is well-tolerated.

Conflicts of interest statement

The support of the parent study and funding of editorial support was provided by F. Hoffmann-La Roche to all authors. J.v.P. received personal fees from AbbVie, Bristol-Myers Squibb, Novartis and Pfizer. M.S. received honoraria from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, MSD, Novartis, Ono Pharmaceutical, Pfizer Japan and Taiho Pharmaceutical and has received research grants from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, MSD, Novartis, Ono Pharmaceutical and Pfizer Japan. L.F. has received research grants from Roche/Genentech. J-Y.H. has received personal fees from MSD Oncology and Novartis and has received research grants from Roche. T.H. has received personal fees and research grants from

AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Clovis Oncology, Eli Lilly, Ignyta, Kissei, MSD, Nippon Boehringer Ingelheim, Novartis, Ono Pharmaceutical, Pfizer and Taiho Pharmaceutical and has received research grants from AbbVie, Astellas Pharma, Daiichi Sankyo, Sumitomo Dainippon Pharma, Eisai, Kyowa Hakko Kirin, Merck Serono, Servier and Takeda Pharmaceutical. D.M.S. has received honoraria from and has had a consultant or advisory role with AstraZeneca, Bristol-Myers Squibb, Eli Lilly, MSD, Novartis, Pfizer, and Roche and has received travel, accommodations and expenses paid for or reimbursed by AstraZeneca, Bristol-Myers Squibb, MSD, Pfizer and Roche. D.R.G. has received research grants and personal fees from Genentech and has had a consultant role with AstraZeneca and Merck. A.R. has received personal fees from AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, MSD, Pfizer and Roche/Genentech. M.G., W.Y., C.M., P.H., H.P., A.S., M.B. and M.K. are/were all employees of Genentech. M.G. has stock or other ownership interest in Acadia Pharmaceuticals, Merck, Neurocrine and Spark Therapeutics. C.M., H.P., A.S., M.B. and M.K. have stock or other ownership interest in Roche. C.M. has a patent with Stanford University. P.H. has stock or other ownership interest in Allergan, Amgen and Gilead Sciences. M.K. has a patent pending titled 'Biomarkers and methods treating PD-1− and PD-L1−related conditions'. K.P. has had a consultant or advisory role with Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis Oncology, Lilly, GlaxoSmithKline, Hanmi, Kyowa Hakko Kirin, Novartis, Ono Pharmaceutical and Roche and participated in speakers' bureaus for AstraZeneca and Boehringer Ingelheim. The remaining authors declare no additional conflicts of interest.

Acknowledgements

The authors thank Daniel Waterkamp of Genentech, Inc., for contribution to the OAK study design, execution and data interpretation. Third-party medical writing support was provided by Minna Balbas, PhD, of Health Interactions, with funding from F. Hoffmann-La Roche, Ltd.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.11.020.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.

[2] Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271–89.

[3] Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563–7.

[4] Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy–inhibiting programmed death-ligand 1 and programmed death-1. Clin Canc Res 2012;18:6580–7.

[5] Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39:1–10.

[6] Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008;8:467–77.

[7] Akbari O, Stock P, Singh AK, Lombardi V, Lee WL, Freeman GJ, et al. PD-L1 and PD-L2 modulate airway inflammation and iNKT-cell-dependent airway hyperreactivity in opposing directions. Mucosal Immunol 2010;3:81–91.

[8] Matsumoto K, Fukuyama S, Eguchi-Tsuda M, Nakano T, Matsumoto T, Matsumura M, et al. B7-DC induced by IL-13 works as a feedback regulator in the effector phase of allergic asthma. Biochem Biophys Res Commun 2008;365:170–5.

[9] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255–65.

[10] Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2018.

[11] Tecentriq (atezolizumab) [summary of product characteristics]. Welwyn Garden City, UK: Roche Registration Limited; 2018.

[12] Fehrenbacher L, von Pawel J, Park K, Rittmeyer A, Gandara DR, Ponce Aix S, et al. Updated efficacy analysis including secondary population results for OAK: a randomized phase III study of atezolizumab vs docetaxel in patients with previously treated advanced non-small cell lung cancer. J Thorac Oncol 2018;13:1156–70 [Epub ahead of print].

[13] Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354–62.

[14] Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589–97.

[15] Ramlau R, Gorbunova V, Ciuleanu TE, Novello S, Ozguroglu M, Goksel T, et al. Aflibercept and docetaxel versus docetaxel alone after platinum failure in patients with advanced or metastatic non-small-cell lung cancer: a randomized, controlled phase III trial. J Clin Oncol 2012;30:3640–7.

[16] Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095–103.

[17] Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123–32.

[18] Kowanetz M, Zou W, McCleland M, Gandara DR, Gadgeel S, Rittmeyer A, et al. Pre-existing immunity measured by Teff gene expression in tumor tissue is associated with atezolizumab efficacy in NSCLC. J Thorac Oncol 2017;12:S1817–8.

[19] Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

[20] Gandara DR, von Pawel J, Sullivan R, Helland A, Han J-Y, Ponce Aix S, et al. Impact of atezolizumab (atezo) treatment beyond disease progression (TBP) in advanced NSCLC: results from the randomized phase III OAK study. J Clin Oncol 2017; 35(15 suppl) [abstract 9001].