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Atezolizumab in patients with advanced non-small cell lung cancer and history of asymptomatic, treated brain metastases: Exploratory analyses of the phase III OAK study

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ABSTRACT

Objectives: To assess the safety and efficacy of atezolizumab and docetaxel in patients with and without a history of asymptomatic, treated brain metastases in the phase III OAK trial.

Materials and methods: Patients received 1200 mg atezolizumab or 75 mg/m^2 docetaxel every 3 weeks until unacceptable toxicity, disease progression, or loss of clinical atezolizumab benefit. Patients with asymptomatic, treated supratentorial metastases were eligible. Patients had brain scans before enrollment; follow-up brain scans and treatment were required when clinically indicated.

Results: Approximately 14% of patients in each arm had a history of asymptomatic, treated brain metastases (61/425 in the atezolizumab arm and 62/425 in the docetaxel arm).

Fewer treatment-related adverse events (AEs), serious AEs, and treatment-related neurologic AEs were reported with atezolizumab than with docetaxel, regardless of history of asymptomatic, treated brain metastases. In patients with a history of asymptomatic, treated brain metastases, median overall survival (OS) was longer with atezolizumab than with docetaxel (16.0 vs 11.9 months; hazard ratio = 0.74; 95% CI: 0.49–1.13). Median OS was also longer with atezolizumab in patients without a history of asymptomatic, treated brain metastases (13.2 vs 9.3 months; hazard ratio = 0.74; 95% CI: 0.63–0.88). Landmark analyses showed that patients with a history of asymptomatic, treated brain metastases had a lower probability of developing new symptomatic brain lesions with atezolizumab vs docetaxel at 6–24 months. Patients without a history had a lower probability with atezolizumab at 18–24+ months.

Conclusion: Atezolizumab had an acceptable neurologic safety profile, showed a trend toward an OS benefit, and

Abbreviations: AE, adverse event; CNS, central nervous system; CRF, case report form; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IC, tumor-infiltrating immune cells; ITT, intention-to-treat; NE, not evaluable; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TC, tumor cells

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led to a prolonged time to radiographic identification of new symptomatic brain lesions compared with docetaxel in patients who had a history of asymptomatic, treated brain metastases.

Clinicaltrials.gov registration number: NCT02008227.

1. Introduction

Brain metastases are a frequent complication of advanced non-small cell lung cancer (NSCLC); they occur in 20%–40% of patients (often within the first 2 years of primary diagnosis), are associated with poor survival, and have very few systemic treatment options [1–4].

Atezolizumab (TECENTRIQ®; F. Hoffmann-La Roche Ltd, Basel, Switzerland/Genentech, Inc., South San Francisco, CA), is an anti–programmed death-ligand 1 (PD-L1) monoclonal antibody that selectively inhibits PD-L1 interactions with programmed death-1 (PD-1) and B7.1 and reinvigorates and enhances anticancer immunity while potentially preserving immune homeostasis [5,6].

The phase III open-label OAK study compared the efficacy and safety of atezolizumab with docetaxel in patients with PD-L1–unselected, previously treated advanced or metastatic NSCLC [7]. At the time of the primary analysis (median follow-up, 21 months), the study demonstrated a 4.2-month improvement in median overall survival (OS) in the atezolizumab arm compared with the docetaxel arm (hazard ratio [HR] = 0.73, 95% CI: 0.62–0.87; $p = 0.0003$) and a favorable atezolizumab safety profile relative to docetaxel [7]. Based on these and phase II data [8,9], atezolizumab was approved for the treatment of metastatic NSCLC in patients who had disease progression during or following platinum-containing chemotherapy (and an approved therapy for *EGFR* or *ALK* genomic tumor aberrations, in applicable patients). However, data from randomized trials regarding efficacy and safety of PD-L1/PD-1–directed agents as monotherapy in patients with brain metastases are limited: a pooled analysis of the CheckMate 063, 017, and 057 studies showed that patients with advanced NSCLC and pretreated central nervous system metastases had similar OS with nivolumab or docetaxel [10].

Here we present safety and efficacy data from OAK in patients with and without a history of asymptomatic, treated brain metastases, the most detailed analyses of this patient population to date.

2. Materials and methods

2.1. Study design

The overall study design has been reported previously [7]. Briefly, OAK (NCT02008227) was a randomized, controlled, open-label, international, phase III trial conducted in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each participant. An independent data monitoring committee reviewed safety. Protocol approval was obtained from independent ethics committees for each site.

2.2. Patients

In addition to the published eligibility criteria [7], those related to central nervous system (CNS) metastases included the presence of measurable disease outside the CNS; only allowing asymptomatic supratentorial metastases (no infratentorial, spinal, or leptomeningeal disease; patients with new asymptomatic CNS metastases detected at the screening scan must have received radiation therapy and/or surgery for CNS metastases); no history of intracranial hemorrhage; no ongoing requirement for corticosteroids; no stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to Cycle 1, Day 1; and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study.

In the primary [7] and updated analyses [11], “baseline brain metastases” was defined by the investigator as being a site of metastasis present at baseline (OS HR = 0.57, 95% CI: 0.33–0.97 at the updated analysis using the same cut-off as the current analysis). The definition was expanded for the current analysis to include additional patients with a history of brain radiotherapy, as this strongly implied that such patients also had a history of asymptomatic, previously treated brain metastases.

2.3. Procedures

Patients received 1200 mg fixed-dose intravenous atezolizumab or 75 mg/m^2 docetaxel every 3 weeks until unacceptable toxicity or investigator-determined disease progression [7]. Crossover to atezolizumab was not allowed.

Patients in the atezolizumab arm could continue treatment beyond progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) if they met the protocol criteria for continuation, including continued clinical benefit as assessed by the investigator [7].

2.4. Assessments

All known sites of disease were assessed and documented at baseline, every 6 weeks until week 36, and every 9 weeks thereafter until disease progression, regardless of treatment discontinuation. Assessments were performed until treatment discontinuation for those receiving atezolizumab beyond progression [7].

Patients were followed for survival throughout the study and every 3 months following treatment discontinuation [7].

Patients had brain scans prior to enrollment in the study, but follow-up scans after enrollment and treatment were required only when clinically indicated. Since preexisting brain metastases that had been treated but were still observable were classified as nontarget lesions, intracranial response and progression were not assessed. Assessment of baseline brain metastases for the primary analysis was based on “sites of metastasis at baseline” on the lung cancer history case report form (CRF) plus the RECIST v1.1 baseline lesions from the tumor assessment (screening) CRF. The additional patients for the current analysis were identified by indication of prior brain radiotherapy on the prior cancer radiotherapy CRF.

The National Cancer Institute’s Common Terminology Criteria for Adverse Events version 4.0 was used to grade adverse events (AEs) and laboratory abnormalities [7].

2.5. Statistical analysis

The OAK primary analysis population comprised the first 850 randomized patients (of a total of 1225) [7]. The primary analysis population was analyzed here. Safety (actual treated) and intention-to-treat populations (all randomized) were used for safety and efficacy analyses, respectively.

Safety analyses were conducted for all-cause and treatment-related AEs at all grades, with an emphasis on treatment-related neurologic AEs. Safety data were summarized separately for patients with and without a history of asymptomatic, treated brain metastases. Differences in AEs were compared between atezolizumab and docetaxel.

OS and time to radiographic identification of new symptomatic brain lesions were evaluated separately in patients with and without a history of asymptomatic, treated brain metastases. Time-to-event differences between atezolizumab and docetaxel in OS and in time to

Table 1
Baseline demographics and tumor characteristics for the intention-to-treat population.

Characteristic	Without history of brain metastases		With history of brain metastases	
	Atezolizumab n = 364	Docetaxel n = 363	Atezolizumab n = 61	Docetaxel n = 62
Median age (range), y	63.5 (33–82)	64.0 (34–85)	59.0 (39–79)	62.5 (39–83)
Male patients, n (%)	227 (62.4)	226 (62.3)	34 (55.7)	33 (53.2)
ECOG performance status, n (%)				
0	132 (36.3)	132 (36.4)	23 (37.7)	28 (45.2)
1	232 (63.7)	231 (63.6)	38 (62.3)	34 (54.8)
History of tobacco use, n (%)				
Never	73 (20.1)	60 (16.5)	11 (18.0)	12 (19.4)
Current	48 (13.2)	54 (14.9)	11 (18.0)	13 (21.0)
Previous	243 (66.8)	249 (68.6)	39 (63.9)	37 (59.7)
Histology, n (%)				
Nonsquamous	261 (71.7)	261 (71.9)	52 (85.2)	54 (87.1)
Squamous	103 (28.3)	102 (28.1)	9 (14.8)	8 (12.9)
PD-L1 expression, n/N (%)[a]				
TC3 or IC3	63/359 (17.5)	57/359 (15.9)	9/61 (14.8)	8/62 (12.9)
TC2/3 or IC2/3	112/358 (31.3)	117/358 (32.7)	17/61 (27.9)	19/62 (30.6)
TC1/2/3 or IC1/2/3	206/360 (57.2)	191/359 (53.2)	35/61 (57.4)	31/62 (50.0)
TC0 and IC0	154/360 (42.8)	168/359 (46.8)	26/61 (42.6)	31/62 (50.0)
Tissue tumor mutational burden				
n	157	161	17	25
Mean (SD)	10.6 (8.6)	12.3 (10.2)	12.7 (10.1)	12.0 (9.2)
≥16, n (%)	34 (21.7)	44 (27.3)	5 (29.4)	6 (24.0)
< 16, n (%)	123 (78.3)	117 (72.7)	12 (70.6)	19 (76.0)
Time between any prior radiotherapy on the brain to first treatment/randomization, months				
n	0	0	55	51
Median (range)	NE	NE	3.0 (0–25.1)	5.1 (0.3–37.7)
History of brain radiotherapy, n (%)				
Had prior radiotherapy on the brain	0	0	55 (90.2)	51 (82.3)
No radiotherapy on the brain	364 (100)	363 (100)	6 (9.8)	11 (17.7)
Last prior radiotherapy (any, not just brain) ended within one month of first treatment/randomization, n/N (%)	9/144 (6.3)	20/143 (14.0)	17/57 (29.8)	12/58 (20.7)

ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; NE, not evaluable; PD-L1, programmed death-ligand 1; TC, tumor cells.

[a] TC1/2/3 or IC1/2/3 = PD-L1 expression on 1% or more of TC or IC; TC2/3 or IC2/3 = PD-L1 expression on 5% of TC or IC; TC3 = PD-L1 expression on 50% or more of TC; IC3 = 10% or more of IC; TC0 = PD-L1 expression on less than 1% of TC; IC0 = PD-L1 expression on less than 1% of IC. [7] N-numbers differ due to some patients not having baseline PD-L1 data.

Table 2
Safety summary in the safety population.

Patients, n (%)	Without history of brain metastases		With history of brain metastases	
	Atezolizumab n = 362	Docetaxel n = 346	Atezolizumab n = 60	Docetaxel n = 55
Any AE	339 (93.6)	336 (97.1)	59 (98.3)	54 (98.2)
Any treatment-related AE	221 (61.0)	304 (87.9)	44 (73.3)	47 (85.5)
Treatment-related grade 3–5 AE[a]	55 (15.2)	147 (42.5)	14 (23.3)	28 (50.9)
Any treatment-related SAE	30 (8.3)	61 (17.6)	10 (16.7)	12 (21.8)
Any neurologic AE	112 (30.9)	147 (42.5)	27 (45.0)	19 (34.5)
Any treatment-related neurologic AE	35 (9.7)	121 (35.0)	11 (18.3)	15 (27.3)
Treatment-related grade 3 neurologic AE[b]	4 (1.1)	10 (2.9)	3 (5.0)[c]	1 (1.8)[d]
Treatment-related neurologic SAE	3 (0.8)	2 (0.6)	1 (1.7)	0

AE, adverse event; SAE, serious adverse event.
[a] One grade 5 event in the docetaxel arm.
[b] No grade 4 or 5 events.
[c] Dizziness, headache, depressed level of consciousness.
[d] Peripheral neuropathy.

development (diagnosis) of new symptomatic brain lesions were compared using an unstratified log-rank test. Time to identification of new symptomatic brain lesions was censored at the last tumor assessment time.

All analyses were exploratory and post hoc; there was no stratification for presence of brain metastases.

3. Results

3.1. Population

Data cutoff for this analysis was 23 January 2017 (an additional 7 months of follow-up over the primary analysis). Baseline characteristics for each subgroup are shown in Table 1. Approximately 14% of patients in each arm had a history of asymptomatic, treated brain metastases (61/425 in the atezolizumab arm and 62/425 in the docetaxel arm). In patients with a history of asymptomatic, treated brain metastases, the median age was 59.0 years in the atezolizumab arm and 62.5 years in the docetaxel arm, 37.7% and 45.2% had an Eastern Cooperative Oncology Group performance status of 0, and 42.6% and 50.0% had tumor cell (TC) 0 and tumor-infiltrating immune cell (IC) 0 PD-L1 expression.

In patients with a history of asymptomatic, treated brain metastases, 29.8% and 20.7% of patients' last prior radiotherapy (any, not just brain) ended within 1 month of first treatment/randomization in the atezolizumab and docetaxel arms, respectively. In those without a history of asymptomatic, treated brain metastases, these proportions were 6.3% and 14.0%. The median time between any prior radiotherapy on the brain to first treatment/randomization was 3.0 months (range, 0–25.1) in the atezolizumab arm and 5.1 months in the docetaxel arm (0.3–37.7). A higher proportion of patients with a history of asymptomatic, treated brain metastases in the docetaxel arm did not receive brain radiation, compared with those in the atezolizumab arm. The patient disposition for the intention-to-treat population is shown in Table A.1 (Supplementary material).

3.2. Safety

Fewer treatment-related AEs, serious AEs, and treatment-related neurologic AEs were reported in patients treated with atezolizumab vs docetaxel, regardless of history of brain metastases (Table 2). Grade 3 treatment-related neurologic AEs were higher in the atezolizumab arm in patients with a history of asymptomatic, treated brain metastases. The rate of neurocognitive AEs was low in both arms, and there were no treatment-related grade 4–5 neurologic AEs in either treatment arm (Table 2). The most common treatment-related neurologic AE was headache in the atezolizumab arm and peripheral neuropathy in the docetaxel arm, which accounted for the high rate in this arm (Table A.2 in Supplementary material).

3.3. Overall survival

In patients with a history of asymptomatic, treated brain metastases, there was a trend toward OS benefit in the atezolizumab arm (16.0 months) versus the docetaxel arm (11.9 months) (HR = 0.74, 95% CI: 0.49–1.13; $p = 0.1633$) (Fig. 1A).

In patients without a history of asymptomatic, treated brain metastases, median OS was longer in patients treated with atezolizumab (13.2 months compared with 9.3 months in the docetaxel arm) (HR = 0.74, 95% CI: 0.63–0.88; $p = 0.0007$) (Fig. 1B).

Landmark OS estimates were higher in the atezolizumab arm than in the docetaxel arm at all time points in patients with and without a history of asymptomatic, treated brain metastases. In patients with a history of asymptomatic, treated brain metastases, OS estimates were 26.6% (95% CI: 15.1–38.1) in the atezolizumab arm and 19.3% (95% CI: 8.2–30.4) in the docetaxel arm at 24 months (Table 3A). In those without a history of asymptomatic, treated brain metastases, estimates were 31.6% (95% CI: 26.7–36.5) and 21.4% (95% CI: 16.9–25.9), respectively, at this time point (Table 3A).

3.4. Time to radiographic identification of new symptomatic brain lesions

Time to radiographic identification of new symptomatic brain lesions is shown in Fig. 2. In patients with a history of asymptomatic, treated brain metastases, the median time was not reached in the atezolizumab arm and was 9.5 months in the docetaxel arm (HR = 0.38, 95% CI: 0.16–0.91; $p = 0.0239$).

In patients without a history of brain metastases, median time to radiographic identification of new symptomatic brain lesions was not reached in either arm (HR = 0.99, 95% CI: 0.50–1.97; $p = 0.9803$). Landmark new brain lesion-free probabilities are shown in Table 3B and were higher with atezolizumab at all time points in patients with a history of brain metastases, while a potential atezolizumab benefit was not seen until 18 months in those without a history of brain metastases.

3.5. Atezolizumab overall exposure and treatment beyond progression

Overall, patients in the atezolizumab arm with a history of asymptomatic, treated brain metastases received atezolizumab for a median of 2.89 months (range: 0–30.8 months) and a median of 5.0 doses (range: 1–42). Those without a history of asymptomatic, treated brain metastases received atezolizumab for a median of 3.53 months (range: 0–32.0 months) and a median of 6.0 doses (range: 1–47).

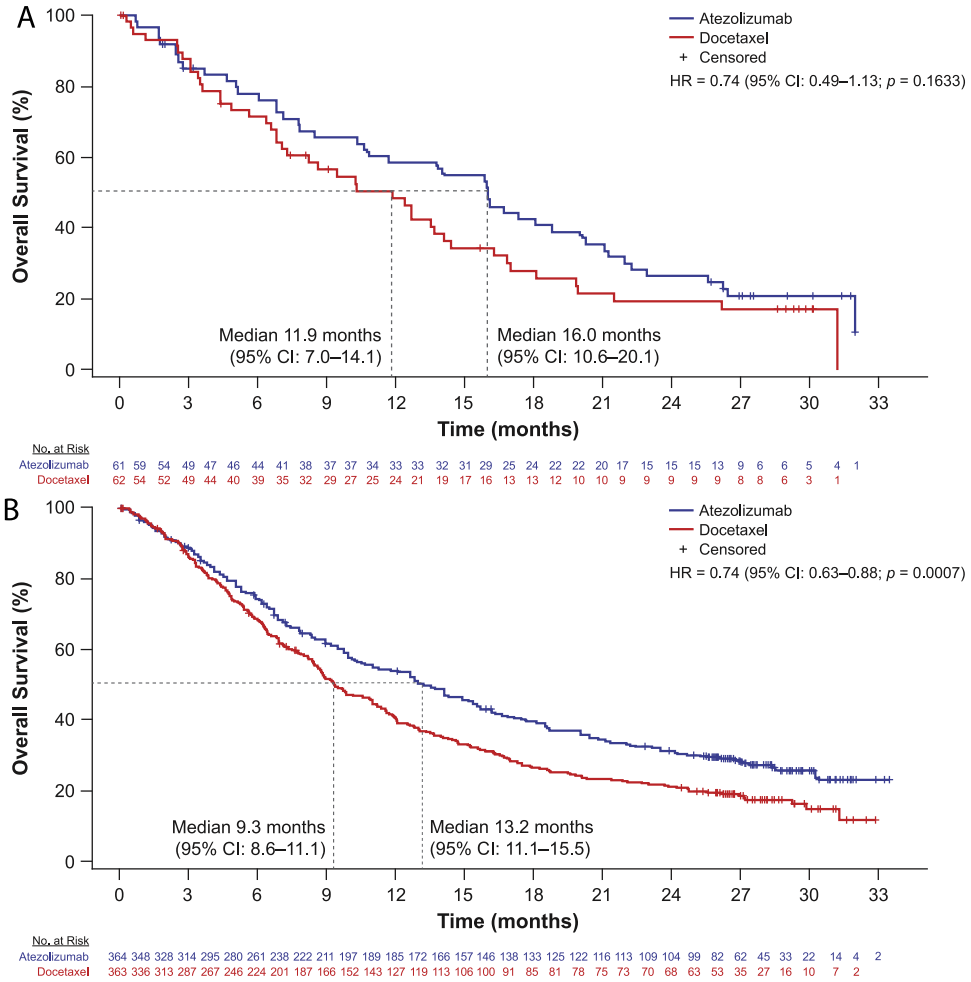

Fig. 1. Overall survival (A) in patients with a history of brain metastases and (B) in patients without a history of brain metastases. HR, hazard ratio. HR based on log-rank test. *P* value for descriptive purposes only.

Table 3
Landmark overall survival (A) and new brain lesion-free probabilities (B) in the intention-to-treat population.

(A)

	Without history of brain metastases		With history of brain metastases	
	Atezolizumab n = 364	Docetaxel n = 363	Atezolizumab n = 61	Docetaxel n = 62
Overall survival probability, % (95% CI)				
6 months	74.4 (69.8–78.9)	68.2 (63.3–73.2)	77.9 (67.3–88.5)	71.4 (59.6–83.3)
12 months	54.1 (48.9–59.3)	40.0 (34.6–45.3)	58.4 (45.7–71.2)	48.5 (35.0–61.9)
18 months	39.7 (34.5–44.8)	26.7 (21.9–31.6)	42.5 (29.7–55.4)	27.9 (15.5–40.3)
24 months	31.6 (26.7–36.5)	21.4 (16.9–25.9)	26.6 (15.1–38.1)	19.3 (8.2–30.4)

(B)

	Without history of brain metastases		With history of brain metastases	
	Atezolizumab n = 364	Docetaxel n = 363	Atezolizumab n = 61	Docetaxel n = 62
New brain lesion-free probability, % (95% CI)				
6 months	94.8 (92.0–97.7)	94.8 (91.1–98.4)	85.1 (74.7–95.6)	64.1 (45.8–82.4)
12 months	90.0 (85.3–94.6)	90.8 (84.3–97.2)	76.6 (62.0–91.3)	42.8 (13.9–71.6)
18 months	85.9 (79.6–92.3)	81.6 (68.3–95.0)	76.6 (62.0–91.3)	42.8 (13.9–71.6)
24 months	85.9 (79.6–92.3)	72.6 (52.0–93.1)	76.6 (62.0–91.3)	0 (0–NE)

NE, not estimable.

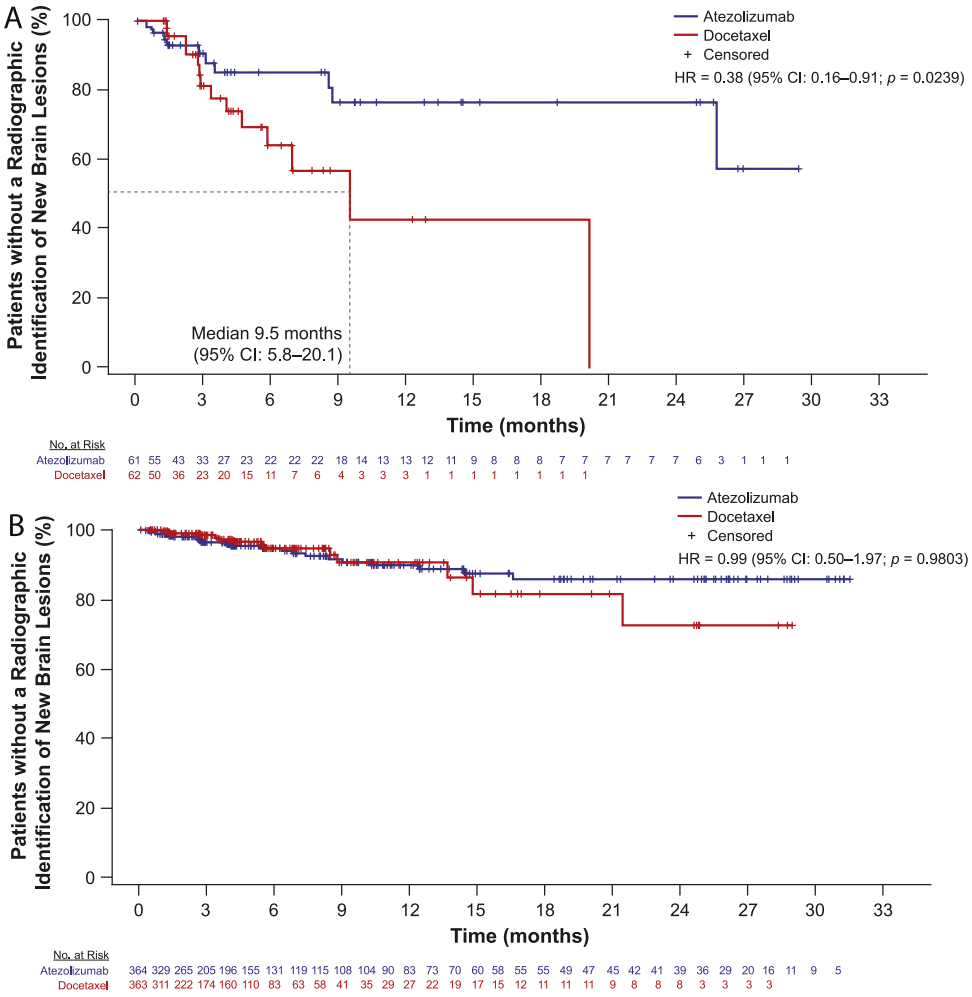

Fig. 2. Time to radiographic identification of new symptomatic brain lesions (A) in patients with a history of brain metastases and (B) in patients without a history of brain metastases.
HR, hazard ratio. HR based on log-rank test. *P* value for descriptive purposes only.

Patients with a history of asymptomatic, treated brain metastases discontinued atezolizumab due to progressive disease (46/61 [75.4%]) and AEs (10/61 [16.4%]) (Table A.1 in Supplementary material). In those without a history of asymptomatic, treated brain metastases, the numbers were 288/364 (79.1%) and 26/364 (7.1%), respectively (Table A.1 in Supplementary material).

Patients in the atezolizumab arm with and without a history of asymptomatic, treated brain metastases received atezolizumab beyond disease progression at approximately the same proportions (29/51 [56.9%] and 139/281 [49.5%], respectively).

4. Discussion

Data from this subgroup analysis of OAK demonstrate that atezolizumab has an acceptable safety profile in second- or third-line advanced or metastatic NSCLC patients who have asymptomatic and previously treated stable brain metastases and that its efficacy in this subgroup is comparable to its efficacy in patients without a history of asymptomatic, treated brain metastases.

No treatment-related grade 4–5 neurologic AEs or SAEs were observed in patients with a history of asymptomatic, treated brain metastases, and there was a low incidence of treatment-related grade 3 neurologic AEs (5%). Fewer treatment-related AEs and SAEs, and treatment-related neurologic AEs, were reported in patients treated with atezolizumab vs docetaxel. While the incidence of radiation necrosis was not formally tracked (leading to underdetection), there were no clinically concerning scenarios or pathologically proven cases of radiation necrosis in patients with a history of asymptomatic, treated brain metastases who received atezolizumab.

In patients with a history of asymptomatic, treated brain metastases, treatment with atezolizumab showed a trend toward OS benefit versus treatment with docetaxel (as the CIs crossed “1,” superiority could not be concluded), and the extent of benefit with additional follow-up was similar to the benefit observed in the overall population of the primary analysis [7].

The risk of identifying new symptomatic brain lesions in patients with a history of asymptomatic, treated brain metastases appeared to be lower with atezolizumab than with docetaxel. In patients without a history of asymptomatic, brain metastases, the small probability of identifying new symptomatic brain metastases suggests that a larger sample size with longer follow-up is needed in order to generate sufficient data to draw a conclusion. It should be noted that, although all patients had a brain scan at baseline, regularly scheduled follow-up scans were not mandatory and were instead symptom-directed.

Our findings may have implications regarding the activity of anti–PD-L1 immunotherapy in patients with CNS metastases. Beyond the OAK study, a genomic characterization analysis of matched brain metastases, primary tumors (mostly lung, breast, and renal cell carcinomas), and normal tissue showed that brain metastases appeared to have a significantly different mutational profile from the primary tumor in approximately half of cases studied, and they often exhibited mutations that were not found in the primary tumor [12]. It is possible that

this mutational difference may improve response to immunotherapy in the brain. A further potential mechanism is that it is possible that treatment of the CNS metastases with radiation (whole-brain or stereotactic radiosurgery) serves to prime the immune system for the PD-L1–directed therapy. It may do so by exposing tumor-specific epitopes, altering (increasing) the tumor mutational burden of the CNS metastases and altering the immune profile of the tumor microenvironment. Finally, as observed in the case of trastuzumab [13–15], atezolizumab may also lead to improved CNS control via improved penetration of atezolizumab through a disrupted blood-brain barrier and/or via modulation of the immune response in the extra-CNS space. The fact that OS was longer in both study arms in patients with a history of asymptomatic, brain metastases compared with those without a history may be reflective of differing disease biology between advanced stage NSCLC patients predisposed to brain metastases versus those who were not.

Other studies have reported efficacy of cancer immunotherapies in patients with NSCLC or melanoma and both treated and untreated brain metastases [16–18], highlighting a role for these agents in this subgroup of patients. Atezolizumab monotherapy has also shown activity in CNS tumors, in a small cohort of patients with recurrent glioblastoma [19]; however, OAK is the first randomized phase III study evaluating a PD-L1–directed agent to report efficacy in subset of patients with NSCLC and a history of asymptomatic, treated brain metastases. Recent data have also suggested that cancer immunotherapies may show improved outcomes for patients if immunogenicity of brain metastases can be overcome, or if T-cell trafficking to those brain metastases can be improved [20]. Other interesting avenues of research include whether cranial radiotherapy before cancer immunotherapy is necessary in patients with asymptomatic brain metastases, and whether it does or does not improve outcomes or reduce toxicity.

As a subgroup analysis of a large phase III trial, these findings have certain limitations. Since post-baseline brain scans were symptom-directed rather than mandatory, patients with a history of brain metastases had a variable frequency of follow-up brain scans, which could impact results. A longer follow-up time and defined radiologic assessment may be required to evaluate the time to radiographic identification of new symptomatic brain lesions in patients without a history of brain metastases in a more robust manner. Time to brain response may be a more meaningful and clinically relevant endpoint, as it would provide direct evidence for atezolizumab benefit in the brain; however, given the patient inclusion criteria (asymptomatic, previously treated CNS metastases) in OAK, few brain lesions could be monitored by RECIST criteria, and thus brain-specific response could not be analyzed here. Using radiographic scans to measure time to identification of new symptomatic brain lesions could also be potentially confounded by unconventional immunotherapy response and progression patterns (e.g., “pseudoprogression”); however, the low frequency of new symptomatic brain lesions identified and lack of subsequent resolution observed in atezolizumab-treated patients implies that this was rare. Other limitations include a lack of molecular analyses (e.g., tumor mutational burden, PD-L1 expression) from brain metastases, the fact that statistical significance cannot be claimed due to the exploratory and post hoc nature of this analysis, and the fact that this remains a very selected group of patients with brain metastases (i.e, brain metastases were treated and asymptomatic, and patients were non-progressing and off steroids).

5. Conclusion

In this exploratory subgroup analysis of the OAK study, atezolizumab had an acceptable neurologic safety profile, showed a trend toward an OS benefit, and led to a prolonged time to radiographic identification of new symptomatic brain lesions compared with docetaxel in patients who had a history of asymptomatic, treated brain metastases. These results were consistent with the primary analysis of the OAK study and suggest a positive benefit-risk profile of atezolizumab in this patient population. These results also support further investigations of atezolizumab in patients with NSCLC and untreated brain metastases.

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SMG reports personal fees for advisory board participation/travel to scientific meetings for presentation of data from Genentech, Inc./F. Hoffmann-La Roche Ltd, and personal fees for advisory board participation from AstraZeneca, outside the submitted work.

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JDP reports an advisory role for Genentech, Inc., outside the submitted work.

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CO is an employee of Genentech, Inc. and owns stock in F. Hoffmann-La Roche Ltd.

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MB reports personal fees from Genentech, Inc./F. Hoffmann-La Roche Ltd during the conduct of the study and personal fees and other relevant financial relationships from F. Hoffmann-La Roche Ltd, outside the submitted work.

AS is an employee of Genentech, Inc. and owns stock in F. Hoffmann-La Roche Ltd.

MG is an employee of Genentech, Inc.

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Data statement

Qualified researchers may 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 (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.12.017.

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