

# Fast progression in non-small cell lung cancer: results from the randomized phase III OAK study evaluating second-line atezolizumab versus docetaxel

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## ABSTRACT

**Background** Treatment-induced accelerated tumor growth is a progression pattern reported with immune checkpoint inhibitors that has never been evaluated in randomized phase III studies because it requires two pretreatment scans. This study aimed to develop clinically relevant and applicable criteria for fast progression (FP), incorporating tumor growth kinetics and early death from disease progression to analyze data from the randomized phase III OAK study.

**Methods** The OAK study evaluated the efficacy and safety of atezolizumab versus docetaxel as second-line or third-line treatment for stage IIIb/IV non-small cell lung cancer. FP rates and associated baseline factors were analyzed. FP was defined as either a  $\geq 50\%$  increase in the sum of largest diameters (SLDs) within 6 weeks of treatment initiation or death due to cancer progression within 12 weeks (absent post-baseline scan).

**Results** Forty-two of 421 patients (10%) receiving atezolizumab and 37 of 402 (9%) receiving docetaxel had FP. Twenty patients with FP (48%) receiving atezolizumab versus 12 (30%) receiving docetaxel had a  $\geq 50\%$  SLD increase within 6 weeks. FP was significantly associated with an ECOG (Eastern Cooperative Oncology Group) performance status of 1 (vs 0),  $\geq 3$  metastatic sites at baseline, and failure of preceding first-line treatment within 6 months, but not with epidermal growth factor receptor mutation, programmed cell death 1 ligand 1 or tumor mutational burden. Overall survival in patients with FP and a  $\geq 50\%$  SLD increase at week 6 was similar with atezolizumab and docetaxel (unstratified HR 0.89 (95% CI 0.41 to 1.92)).

**Conclusions** FP rates were similar with atezolizumab and docetaxel in the OAK study, suggesting that FP may not be unique to checkpoint inhibitors, although the underlying mechanisms may differ from those of chemotherapy. Applying the FP criteria to other phase III checkpoint inhibitor trials may further elucidate the risk factors for FP.

**Trial registration number** NCT02008227.

## INTRODUCTION

Immune checkpoint inhibitors (CPIs) have transformed cancer care across multiple tumor types. Because clinical benefit is

observed in only a subset of patients treated with CPIs, identification of biological characteristics that predict benefit or harm remains an unmet need in the treatment decision-making process for this class of therapeutics.

To this point, the phenomenon of treatment-induced accelerated tumor growth—previously termed hyperprogressive disease (HPD)—was reported to be a new pattern of progression in patients receiving monotherapy with CPIs targeting programmed cell death 1 ligand 1 (PD-L1) or programmed cell death 1 protein (PD-1).<sup>1–6</sup> HPD has generally been defined as a tumor growth rate (TGR) from baseline to the first evaluation that is  $\geq 2$ -fold that of a reference TGR established by two consecutive pretreatment scans. Because there is no consensus on an optimal way to assess this phenomenon, alternative criteria have been reported.<sup>7–9</sup> Rapid tumor growth has been reported with other treatment modalities, such as targeted therapy and chemotherapy.<sup>1 10</sup> Data on HPD from randomized phase III studies comparing distinct therapeutic opportunities (notably a comparison of CPIs with other treatment strategies) are not available, largely because an assessment of TGR on two pretreatment CT scans—which are not available for patients in prospective randomized studies—is required to determine the presence of HPD.<sup>4</sup> In non-small cell lung cancer (NSCLC), HPD with CPIs has been reported to be variably associated with older age ( $>65$  years), epidermal growth factor receptor (*EGFR*) mutation, and murine double minute 2 homolog (*MDM2*) amplification, and it is consistently linked with poor overall survival (OS).<sup>1 3 4 7 11</sup> Whether these patient and disease characteristics are also associated with fast progression (FP) remains to be determined.



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To enable the investigation of rapid tumor growth after treatment initiation in randomized phase III studies and to account for early death due to cancer progression before the first restaging scan, we developed an alternative approach—termed FP. Using our FP criteria, we retrospectively analyzed data from the phase III OAK study (NCT02008227), which evaluated the efficacy and safety of atezolizumab versus docetaxel as second-line or third-line treatment for patients with advanced or metastatic NSCLC.<sup>12</sup> The OAK study showed clinically significant OS benefit with atezolizumab versus docetaxel (median OS, 13.8 months vs 9.6 months; HR 0.73 (95% CI 0.62 to 0.87);  $p=0.0102$ ).<sup>12</sup> Here, we present results from the first assessment of the phenomenon of FP in a large, randomized phase III study; we report the prevalence of FP in patients treated with atezolizumab versus docetaxel and explore the relationship of FP with baseline factors potentially associated with rapid tumor growth. Furthermore, we evaluate treatment outcomes in relation to baseline factors potentially associated with FP.

## METHODS

### Study design and patients

The randomized, open-label, international, phase III OAK study (NCT02008227) was designed to evaluate the efficacy and safety of atezolizumab monotherapy versus docetaxel in patients with locally advanced or metastatic (stage IIIb or IV) squamous or non-squamous NSCLC who had disease progression after one or two previous lines of chemotherapy. Patients with *EGFR* mutation or anaplastic lymphoma kinase (*ALK*) genetic alteration were required to have progressed on previous tyrosine kinase inhibitor therapy. The primary endpoint was OS in the intention-to-treat (ITT) population. Further details on the study design were described previously.<sup>12</sup> Patients were not involved in the design of this study.

### Treatments and assessments

Patients were randomized to receive atezolizumab 1200 mg or docetaxel 75 mg/m<sup>2</sup> intravenously every 3 weeks until radiographic progression or intolerable toxicity. Atezolizumab treatment could continue beyond progression until loss of clinical benefit. Tumors were evaluated radiographically at baseline, every 6 weeks until week 36, and every 9 weeks thereafter per Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 by the investigators. After treatment discontinuation, patients were followed up for OS every 3 months.

### Definition of FP

FP was evaluated among patients receiving study treatment and was defined as a  $\geq 50\%$  increase in the sum of largest diameters (SLDs) of target lesions, as assessed by the investigator per RECIST V.1.1, from treatment initiation within 6 weeks ( $\pm 7$  days) from first treatment. The baseline scans had to be acquired within 28 days of randomization. Additionally, our FP criteria include

death due to disease progression, with causality assessed by the investigator, within 12 weeks in patients without a radiographic response assessment. Importantly, in patients who had a post-treatment scan and also died within 12 weeks, FP was evaluated based only on the scan results and not on the death event. In addition, deaths attributed to adverse events or unknown causes were not included in the definition.

### Statistical analysis

Demographic and baseline characteristics were summarized by treatment arm and FP versus non-FP status. First, a Cochran-Mantel-Haenszel (CMH) test was performed to evaluate the association of FP status with treatment arm while controlling for all factors of interest. A CMH test was additionally performed to evaluate the association of FP status with candidate baseline factors while controlling for treatment arms. P values  $\leq 0.05$  were considered significant. We used a landmark analysis of all ITT patients to determine whether there was an effect on OS in patients with a  $\geq 50\%$  increase in the SLD from baseline at week 6. Univariate Cox models were used to model the association of OS with the baseline factors associated with FP in the CMH test. P values in Kaplan-Meier plots were calculated using the log-rank test.

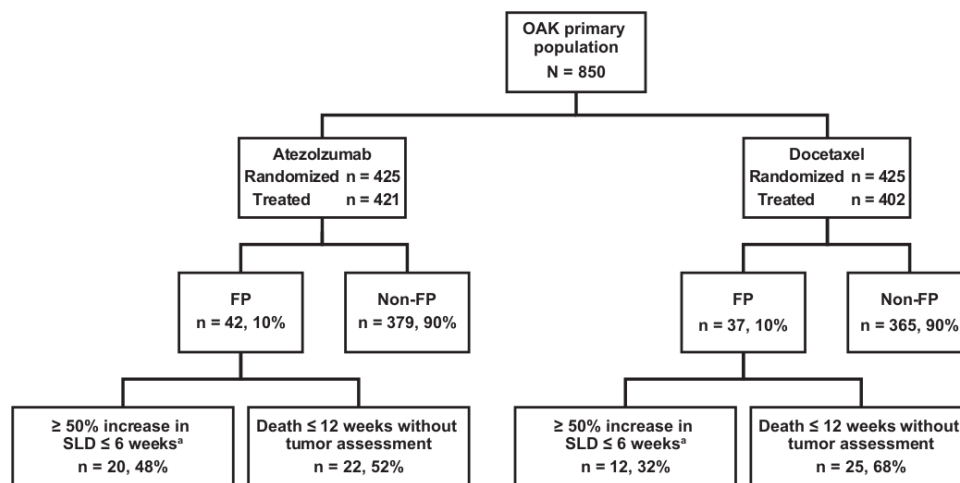
### Genomic analysis and blood-based tumor mutational burden

Tumor samples were analyzed using the FoundationOne T7 bait set panel to assess *STK11*, *KEAP1*, and *MDM2* genetic alterations. *MDM2* amplification was defined as having  $>5$  alterations after correction for tumor ploidy.<sup>13</sup> *EGFR* mutation and *ALK* rearrangement statuses were based on local testing results. Patients with unknown *EGFR* or *ALK* status were tested by a central laboratory prior to enrollment.<sup>12</sup> Blood-based tumor mutational burden (bTMB) was assessed using the same hybridization-capture methodology used in the Food and Drug Administration–approved FoundationOne next-generation sequencing assay.<sup>14</sup>

## RESULTS

### Patient population

FP was evaluated in treated patients in the primary population from the phase III OAK study, representing 823 of the 850 patients in the ITT (figure 1). Prognostic clinical factors were evaluated for potential association with FP, including lactate dehydrogenase (LDH) level, tumor burden as evaluated by SLD, time to failure of the preceding treatment, and number of metastatic sites. Demographic and baseline characteristics were well balanced between the atezolizumab and docetaxel arms.<sup>12</sup> At the time of clinical data cut-off (July 7, 2016), the minimum follow-up was 19 months and the median follow-up was 21 months. Biomarker-evaluable populations were assessed for bTMB ( $n=640$ ) and tumor mutations (*MDM2*, *STK11*, *KEAP1*;  $n=455$ ).



**Figure 1** Patients with fast progression (FP) and patients without FP patient populations in OAK. <sup>a</sup>A  $\geq 50\%$  increase in the sum of largest diameters (SLDs) within 6 weeks from baseline.

### Prevalence of FP in the OAK study

The prevalence of FP was similar in both treatment arms: 42 of 421 patients (10%) in the atezolizumab arm and 37 of 402 patients (9%) in the docetaxel arm (figure 1). FP rates were not significantly different between treatment arms, per the CMH test ( $p=0.2003$ , after control for key variables—including age, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), early prior treatment failure (defined as failure within 6 months of treatment initiation), baseline LDH levels, baseline SLD, number of metastatic sites, presence of brain metastases, histology, PD-L1 positive status, PD-L1 high status, bTMB, *EGFR* mutation status, *MDM2* amplification status, *KEAP1* mutation status, and *STK11* mutation status. The median time from baseline scan to the start of treatment was similar between patients in the FP (17 days, IQR 8–22) and non-FP (11 days, IQR 6–20) groups.

Differences were observed within the components of the FP definition between patients in the two arms of the study: FP due to a  $\geq 50\%$  increase in the SLD occurred in 20 patients (48% of all patients with FP in the arm) treated with atezolizumab versus 12 patients (32%) treated with docetaxel. Conversely, death due to disease progression within 12 weeks (without tumor assessment) occurred in 22 patients with FP (52%) in the atezolizumab arm versus 25 patients with FP (68%) in the docetaxel arm. Change in tumor burden is shown for the FP population (online supplemental figure S1). The majority of patients either discontinued scanning after the initial assessment showing FP or showed continued target lesion growth on a subsequent scan. Two patients in the atezolizumab arm and one in the docetaxel arm who continued treatment and scans beyond initial FP showed some subsequent stabilization or reversal of tumor growth at some point post-FP.

### Baseline factors of patients with versus without FP

To identify the baseline characteristics of patients likely to experience FP in response to atezolizumab or docetaxel,

baseline characteristics between patients with and without FP were compared within each treatment arm (table 1, online supplemental figure S1).<sup>15</sup> CMH testing was performed to evaluate whether FP was significantly associated with any of the characteristics of interest while controlling for treatment arms (figure 2). Three of the 15 evaluated characteristics were significantly associated with FP: ECOG PS (0 vs 1;  $p=0.032$ ), number of metastatic sites at baseline ( $<3$  vs  $\geq 3$ ;  $p=0.0213$ ), and time to prior treatment failure ( $<6$  months vs  $\geq 6$  months;  $p=0.0008$ ). No statistically significant associations were observed for age, sex, smoking history, baseline LDH levels, baseline SLD, brain metastases, tumor histology, PD-L1 positive status, PD-L1 high status, bTMB, *EGFR* mutation status, *MDM2* amplification status, *KEAP1* mutation status, or *STK11* mutation status (figure 2).<sup>6</sup>

### OS in patients with and without FP experiencing radiographic progression

To determine whether OS was different between treatment arms in patients experiencing radiographic FP, we performed an OS analysis with a 6-week conditional landmark. All patients with a tumor assessment within 6 weeks ( $\pm 1$  week) of study initiation, corresponding to the first scheduled assessment, were included in this analysis. Median OS in the subgroup of patients with FP and a  $\geq 50\%$  increase in the SLD at week 6 was 5.1 months (95% CI 3.4 to 21.5) in the atezolizumab arm and 6.8 months (95% CI 4.7 to not evaluable) in the docetaxel arm; the unstratified HR was 0.89 (95% CI 0.41 to 1.92;  $p=0.77$ ; figure 3A). In patients with a  $<50\%$  increase in the SLD, median OS was 15.5 months (95% CI 13.5 to 17.3) with atezolizumab and 10.9 months (95% CI 9.3 to 12.0) with docetaxel; the unstratified HR was 0.70 (95% CI 0.59 to 0.83;  $p<0.01$ ; figure 3B).

### OS by baseline factors potentially prognostic for FP

In addition to evaluating FP subgroups for baseline characteristics, we also examined OS in subgroups of the ITT population defined by baseline factors which were significantly associated with FP. OS was greater with atezolizumab

**Table 1** Baseline characteristics by FP status in the treated population (N=823)

Characteristic, n (%) <sup>*</sup>	FP		Non-FP	
	Atezolizumab (n=42)	Docetaxel (n=37)	Atezolizumab (n=379)	Docetaxel (n=365)
Age ≥65 years	20 (48)	17 (46)	168 (44)	176 (48)
Male	32 (76)	20 (54)	228 (60)	226 (62)
Never smoker	7 (17)	3 (8)	75 (20)	61 (17)
ECOG PS 1	33 (79)	26 (70)	234 (62)	225 (62)
Early prior Tx failure <6 months <sup>†</sup>	10 (31)	15 (50)	62 (22)	53 (20)
Baseline LDH ≥ULN <sup>‡</sup>	20 (53)	19 (54)	140 (39)	162 (46)
Baseline SLD ≥80 mm <sup>§</sup>	20 (48)	18 (49)	138 (37)	147 (40)
Metastatic sites ≥3	31 (74)	25 (68)	204 (54)	219 (60)
Brain metastases	1 (2)	3 (8)	37 (10)	38 (10)
NSCLC histology				
Non-squamous	30 (71)	25 (68)	280 (74)	269 (74)
Squamous	12 (29)	12 (32)	99 (26)	96 (26)
PD-L1 status <sup>¶</sup>				
Positive	24 (57)	21 (57)	216 (58)	189 (52)
Negative	18 (43)	16 (43)	159 (42)	173 (48)
High <sup>**</sup>	9 (21)	5 (14)	63 (17)	57 (16)
bTMB <sup>††</sup>				
≥16	11 (31)	9 (26)	67 (23)	72 (26)
<16	25 (69)	26 (74)	220 (77)	210 (74)
EGFR-mutation positive <sup>‡‡</sup>	3 (9)	1 (3)	39 (12)	37 (12)
MDM2-amplification positive <sup>§§</sup>	2 (11)	1 (5)	8 (4)	11 (5)
KEAP1-mutation positive <sup>§§</sup>	2 (11)	3 (16)	36 (17)	28 (14)
STK11-mutation positive <sup>§§</sup>	3 (17)	5 (26)	35 (17)	27 (13)

<sup>\*</sup>Percentages may not sum to 100 because of rounding.

<sup>†</sup>Includes only patients with one prior treatment (FP, n=62; non-FP, n=556).

<sup>‡</sup>Percentages based on patients with available LDH data (FP, n=73; non-FP, n=719).

<sup>§</sup>Dichotomized using the method of Contal and O'Quigley.<sup>15</sup> Percentages based on patients with available SLD data (FP, n=79; non-FP, n=743).

<sup>¶</sup>Number of unknown in the non-FP group: atezolizumab, n=4; docetaxel, n=3.

<sup>\*\*</sup>TC ≥50% or IC ≥10%.

<sup>††</sup>Percentages based on patients with available bTMB data (FP, n=71; non-FP, n=569).

<sup>‡‡</sup>Percentages based on patients with available EGFR mutation data (FP, n=63; non-FP, n=625).

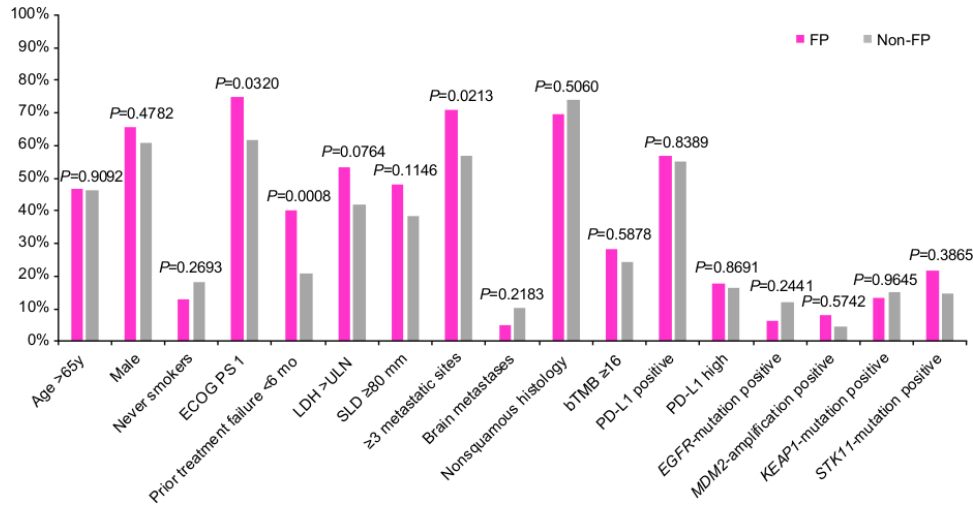
<sup>§§</sup>Percentages based on patients with available MDM2, KEAP1, and STK11 mutation data (FP, n=71; non-FP, n=569).

bTMB, blood-based tumor mutational burden; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FP, fast progression; ITT, intention to treat; LDH, lactate dehydrogenase; MDM2, murine double minute 2 homolog; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death 1 ligand 1; SLD, sum of longest diameters; Tx, treatment; ULN, upper limit of normal.

than with docetaxel, regardless of the three baseline prognostic factors examined: ECOG PS of 1 (HR 0.68; 95% CI 0.56 to 0.84), ≥3 metastatic sites (HR 0.75; 95% CI 0.61 to 0.93), or early failure of the preceding treatment (in second-line patients only) within 6 months (HR 0.69; 95% CI 0.48 to 1.00) (figure 4; online supplemental figure S3A-F). Treatment arm-by-factor interactions in univariate Cox models were also analyzed for these three baseline factors associated with FP, but they were not statistically significant.

## DISCUSSION

Here we presented results of the first comparative assessment of the phenomenon of rapid and early progression in a large, randomized phase III study using the FP criteria defined by rapid tumor growth or early death following initiation of CPI treatment or standard-of-care chemotherapy. Although both HPD and FP describe patient populations with poor outcomes related to immediate progressive disease, they are different concepts: the determination of FP does not require documentation of TGR pretreatment, but does incorporate those patients who have a large initial increase in tumor

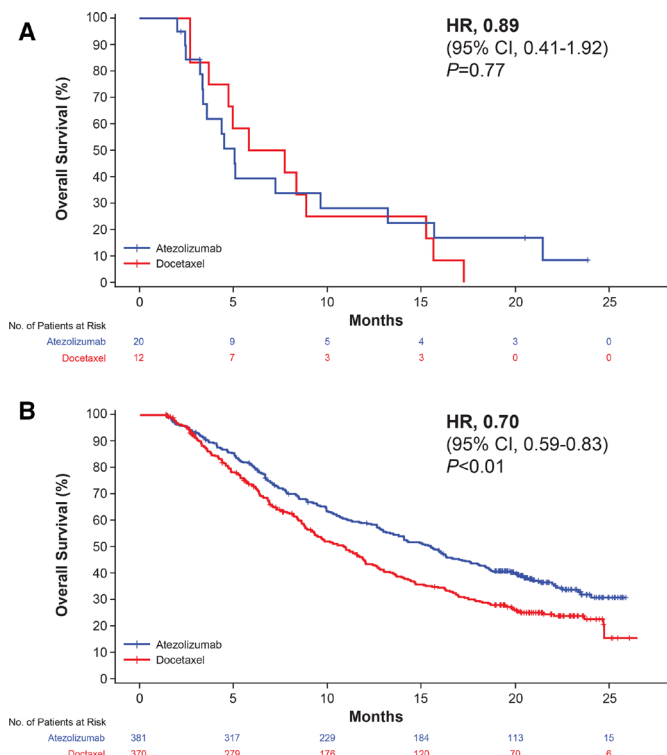


**Figure 2** Cochran-Mantel-Haenszel test for the association between fast progression (FP) and baseline characteristics of interest while controlling for treatment arm. Percentages were calculated from patients with non-missing data. bTMB, blood-based tumor mutational burden; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; KEAP1, kelch like ECH associated protein 1; LDH, lactate dehydrogenase; MDM2, murine double minute 2 homolog; PD-L1, programmed cell death 1 ligand 1; SLD, sum of longest diameters; STK11, serine/threonine kinase 11.

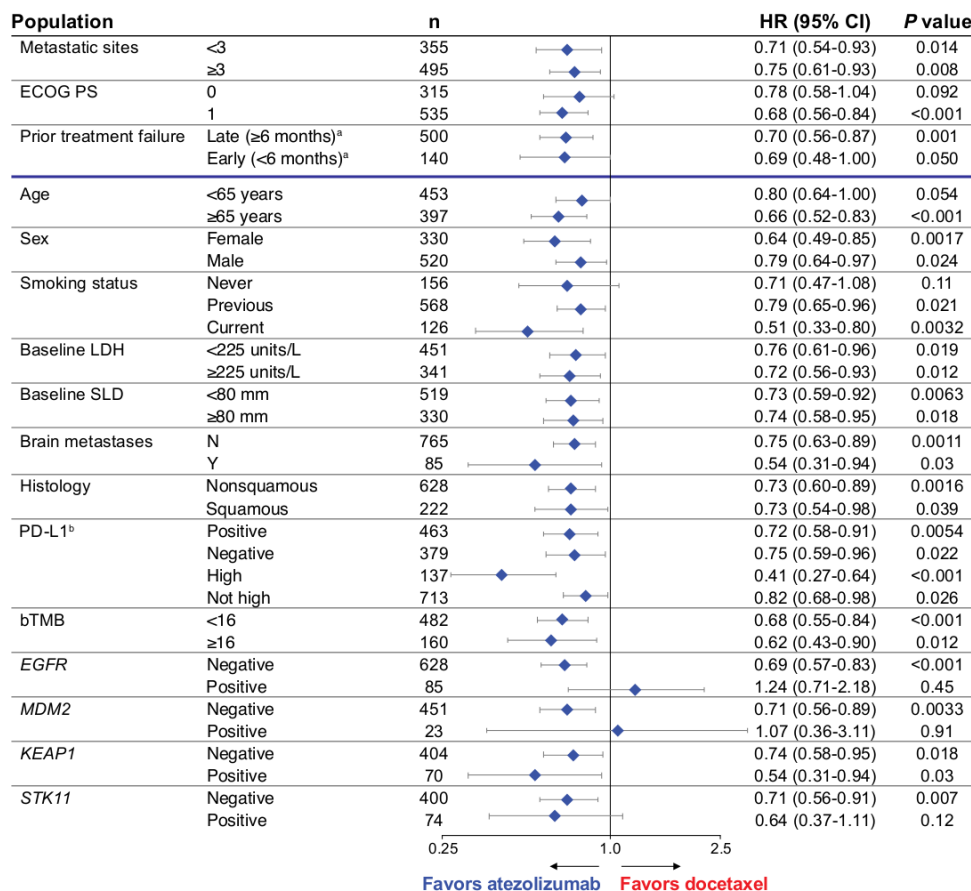
burden or die early of rapid progressive disease without any post-baseline scan assessments. FP criteria are not intended as a surrogate for HPD but constitute an alternative and complementary approach with an increased scope to enable retrospective analyses of the many randomized phase III studies and advance the understanding of the phenomenon of rapid

tumor growth after treatment initiation. In such randomized trials, a control arm allows comparative evaluation between patient and tumor characteristics and enables their correlation with patterns of treatment failure.

Similar rates of FP were observed in the atezolizumab and docetaxel arms when these criteria were applied to the phase III OAK study,<sup>12</sup> suggesting that FP is not specific to CPI treatment but happens at a similar frequency with chemotherapy in this disease setting. One non-randomized institutional study has proposed that PD-L1/PD-1–targeting CPIs might cause higher rates of HPD than chemotherapy.<sup>1</sup> Our results do not support this hypothesis, potentially reflecting differences in assessment criteria but possibly the imbalanced patient characteristics inherent to an unmatched, non-randomized clinical trial comparison. HPD is defined by an increase in TGR, requiring two pretreatment scans to establish a baseline rate, whereas FP measures a large ( $\geq 50\%$ ) increase in tumor burden at the first post-treatment assessment. In contrast with HPD, FP also accounts for early deaths due to disease progression in the absence of radiographic assessment. Early deaths may reflect the worst cases of rapid progression and the worst efficacy outcomes, representing about 10% of patients in the OAK study. A recent study that applied FP criteria to the previously reported institutional HPD analysis population (n=406) reported that 9 of 72 patients with available scans within 6 weeks from the start of treatment had a  $\geq 50\%$  increase in target lesions from baseline—8 of whom also met the criteria for HPD. This subgroup was also found to have poor OS.<sup>116</sup> Another set of criteria aiming to address the rapid progression phenomenon in NSCLC was recently published.<sup>7</sup> This institutional study, which was conducted without a chemotherapy comparator, evaluated patients with NSCLC treated with CPIs in various lines of treatment and defined patients with hyperprogression as meeting  $\geq 3$  of the 5 HPD criteria: time to treatment failure <2 months, a  $\geq 50\%$  increase in the SLD,  $\geq 2$  new lesions in an organ already involved, a new lesion



**Figure 3** Kaplan-Meier plots of overall survival landmark, by increase in the sum of largest diameters at week 6. Kaplan-Meier overall survival estimates in patients with a  $\geq 50\%$  (A) or a  $< 50\%$  (B) increase in the sum of largest diameters at week 6. Patients without a tumor assessment were excluded. Unstratified HRs are displayed.



**Figure 4** Overall survival in clinically relevant patient subgroups. Forest plot of overall survival HRs in patient subgroups defined by characteristics associated with fast progression (above the blue line) and the remaining characteristics analyzed (below the blue line). <sup>a</sup>Includes only patients with one prior treatment. <sup>b</sup>Positive: TC ≥1% or IC ≥1%; negative: TC <1% and IC <1%; high: TC ≥50% or IC ≥10%; not high: TC <50% and IC <10%. bTMB, blood-based tumor mutational burden; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; KEAP1, kelch like ECH associated protein 1; LDH, lactate dehydrogenase; MDM2, murine double minute 2 homolog; PD-L1, programmed cell death 1 ligand 1; SLD, sum of longest diameters; STK11, serine/threonine kinase 11.

in a new organ, and an increase in ECOG PS of ≥2 within the first 2 months of treatment.<sup>7</sup> On the basis of these obviously broader and biologically distinct criteria, the reported 25.6% of patients who experienced hyperprogression exceeded the prevalence that we observed in the OAK study based on the FP criteria. Of note, the study authors state that a clinical trial is ongoing to validate the rate of hyperprogression.<sup>7</sup> Another study (n=335) of patients treated with CPI monotherapy radiographically evaluated tumor volume and used criteria of (1) time to treatment failure <2 months, (2) twofold increase in tumor growth kinetics between pre-baseline to baseline versus baseline to post-baseline, or (3) 50% increase in volume from baseline, and found a 14% prevalence of rapid progression. Multivariate analysis showed rapid progression was associated with worse survival, lower ECOG performance status, and lower neutrophil-to-lymphocyte ratio.<sup>8</sup>

The baseline characteristics and OS outcomes of patients with FP were largely similar between the atezolizumab and docetaxel arms. Our analyses showed that FP was significantly associated with ECOG PS (1 vs 0), the number of metastatic sites at baseline (<3 vs ≥3), and early failure of the preceding first-line treatment (within 6 months). Confirmation of these

associations would require evaluation of FP criteria across several additional phase III studies. In contrast with studies evaluating HPD using TGR, our study found no association between FP and older age (>65 years), EGFR mutation, or MDM2 amplification. Similarly, FP was not associated with lower bTMB (<16). The presence of CD163+/PD-L1+/CD33+ tumor-infiltrating macrophages with epithelioid morphology—a potential predictive biomarker recently identified<sup>7</sup>—was not assessed in samples from patients with FP in the OAK study. Tumor mutations in STK11 and KEAP1, which have been retrospectively shown to be associated with poor outcomes in response to immunotherapy, were not associated with FP in the OAK study.

Because of the small patient numbers and the exploratory nature of this analysis, the results should be interpreted with caution. The multiple testing associated with this analysis has to be carefully considered. Although we did not adjust the p values for multiplicity, we consider the CMH test to be the optimal approach because it aids in the analysis of multiple subgroups. The interpretation of our results is limited by the small number of patients with FP in the OAK study; however, the similar and short OS observed in patients experiencing

radiographic FP in both treatment arms of OAK suggests that outcomes associated with large increases in tumor burden are similarly poor with CPI treatment or chemotherapy. We noticed that the proportions of patients meeting the radiographic versus early death due to disease progression component of FP criteria differed by treatment arm, but this observation may have been due to the small number of patients in each subgroup. Another potential factor could have been delayed treatment effect in the atezolizumab arm. While classic pseudoprogression (response relative to original baseline after disease progression) is rare, especially in NSCLC, an analysis of patients who continued treatment with atezolizumab beyond progression showed that a majority had subsequent reduction or stabilization in target lesions relative to the initial progression.<sup>17</sup> In this analysis, 2 patients continued atezolizumab treatment for multiple cycles beyond FP with some subsequent reversal of SLD growth, potentially reflecting a delayed benefit from treatment despite the initial progression.

Consistent with the OS benefit broadly observed across baseline characteristic subgroups as previously described with atezolizumab versus docetaxel (including patients with central nervous system metastases),<sup>12,18</sup> the subgroups defined by baseline factors associated with FP also demonstrated OS benefit with atezolizumab compared with docetaxel. These findings suggest that the factors identified are prognostic in nature and do not differentially affect the treatment effects of CPIs versus chemotherapy. Accordingly, the findings do not allow identification of patient subpopulations in which docetaxel should be preferred and demonstrate that the atezolizumab benefit is not restricted to patients who have more indolent disease at initiation of therapy.

A key question behind the studies assessing rapid tumor growth is whether this phenomenon is caused primarily by CPI treatment or due to a lack of CPI efficacy in some patients. Biological mechanisms potentially supporting a causative link between CPI treatment and hyperprogression have been proposed, including Fc receptor triggering of clustered epithelioid macrophages with a specific immunophenotype,<sup>7</sup> induction of *MDM2* expression by higher levels of interferon regulatory factor 8 triggered by CPI-mediated interferon- $\gamma$ ,<sup>11</sup> enhanced viability with the blockade of PD-1 expressed on tumor cells,<sup>19</sup> or facilitation of the proliferation of highly suppressive PD-1+ effector regulatory T cells<sup>20</sup>; however, these mechanisms have not formally been clinically or prospectively validated to date. Our results suggest that a subgroup of disease can demonstrate aggressive behavior and result in FP regardless of the therapeutic strategy. However, the underlying biological mechanism possibly differs between treatments.<sup>21</sup> This study points to the need for further research into these mechanisms and questions the attribution of FP with treatment over underlying disease biology.

In the OAK study,<sup>9</sup> CPI monotherapy was evaluated against an active chemotherapy comparator. A prospective, randomized, placebo-controlled study to investigate tumor growth kinetics with chemotherapy, with immunotherapy, or in the absence of antineoplastic treatment is currently not possible because it would withhold standard-of-care treatment for

a group of patients. Therefore, new methodologies will be required to fully understand whether CPI treatment may accelerate tumor growth beyond the natural course of a patient's disease.

## CONCLUSION

The similar rates of FP in the two treatment arms of the phase III OAK study suggest that the phenomenon of rapid disease progression after initiation of treatment is not unique to CPIs. This retrospective analysis provides a framework in which to examine the potential phenomenon of FP more broadly in phase III CPI studies, which by design do not capture two scans performed prior to trial treatment. Our results further suggest that patients with FP-associated factors at baseline have a higher risk of FP, independent of the treatment given (CPI vs chemotherapy). More research is needed to identify characteristics that can predict the benefit or lack thereof of CPI treatment, such as a biomarkers.

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**Data availability statement** Qualified researchers may request access to individual patient-level data through the clinical study data request platform (<https://vivli.org/>). Further details on Roche's criteria for eligible studies are available here (<https://vivli.org/members/ourmembers/>). 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](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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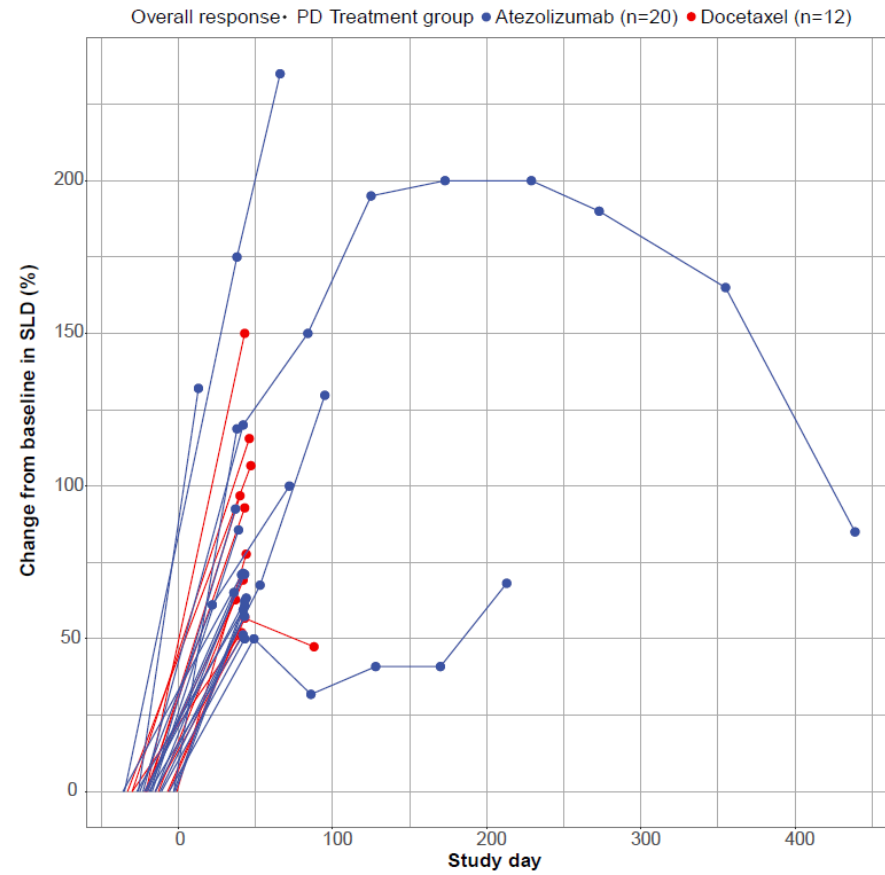
## **ONLINE-ONLY MATERIAL**

### **Supplementary Methods**

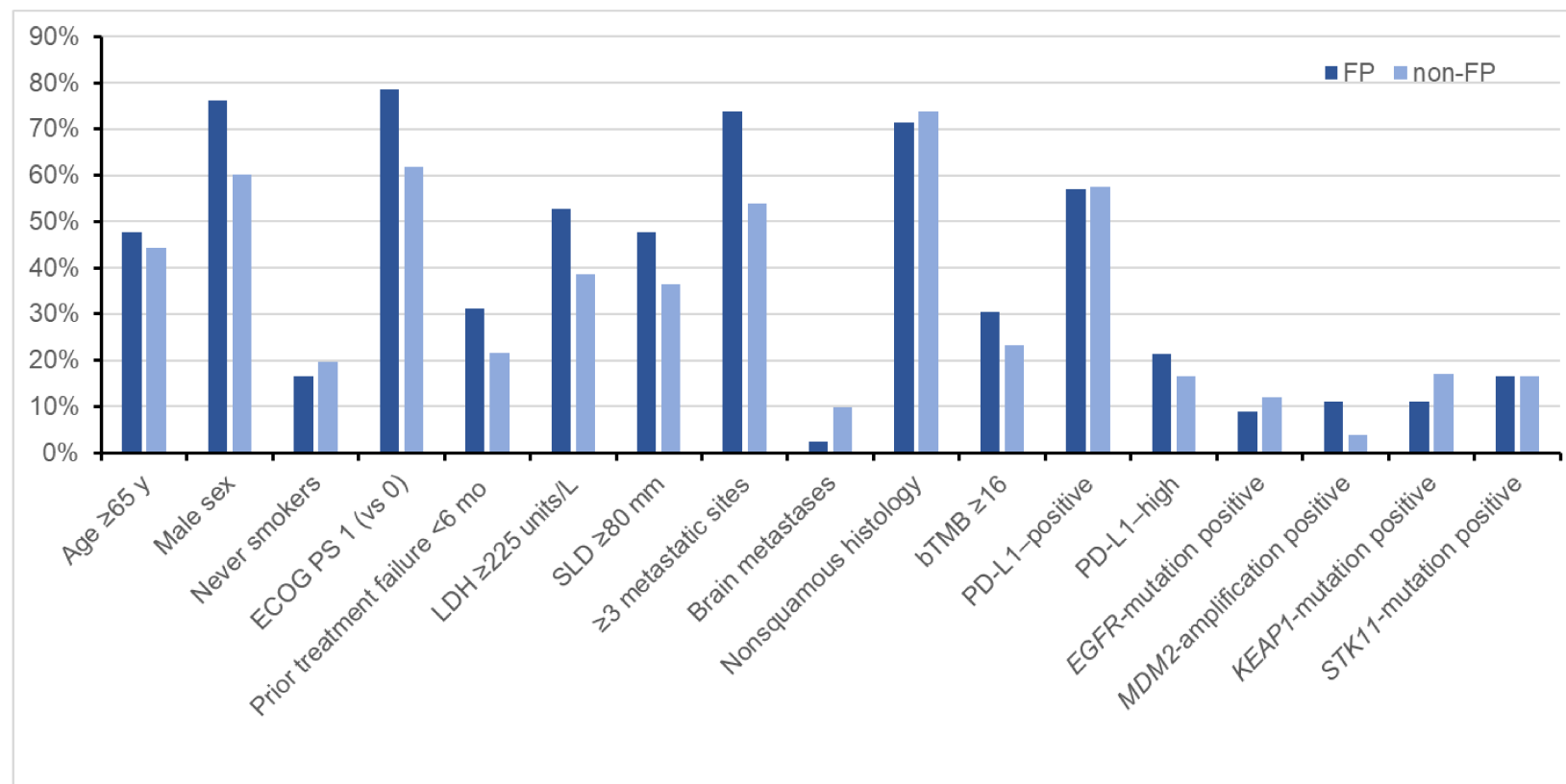
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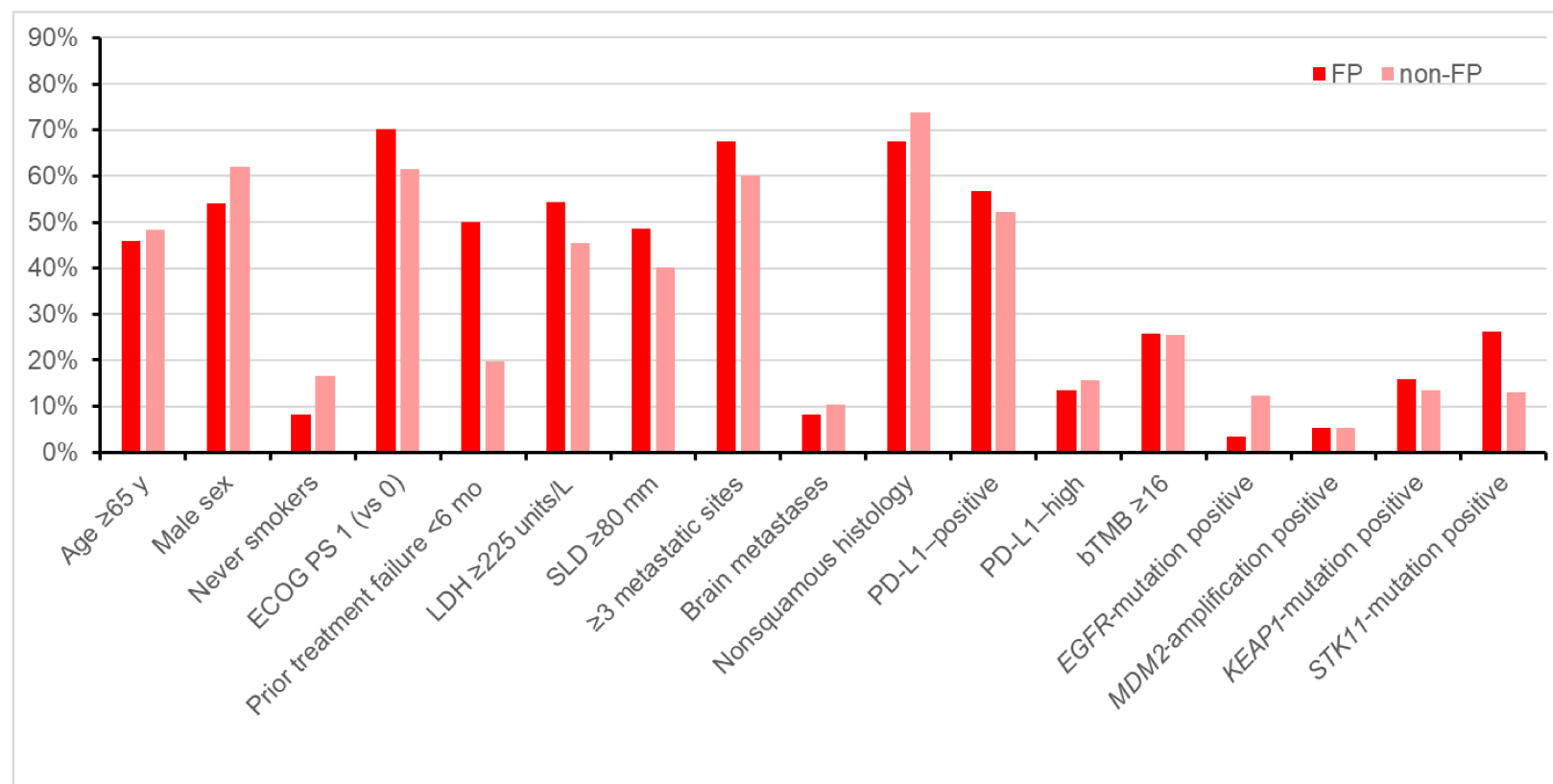
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**Supplementary Figure S1.** Percent change in sum of longest diameters. FP only by study day. Only RECIST target lesions were included.



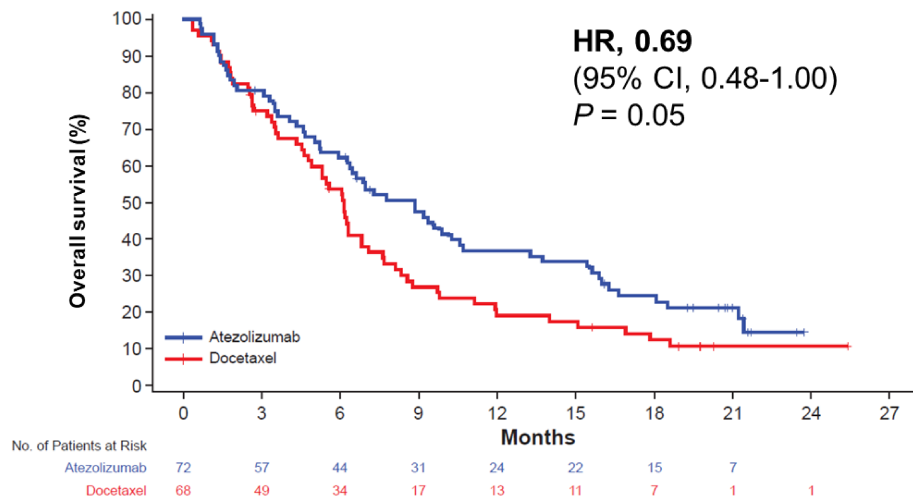
**Supplementary Figure S2.** Exploratory association of baseline characteristics. Comparison of baseline characteristics between atezolizumab-treated patients with fast progression (FP) and without (*A*) and between docetaxel-treated patients with FP and without (*B*). Percentages were calculated from patients with nonmissing data (see **Supplementary Table S1**). bTMB, blood-based tumor mutational burden; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; LDH, lactate dehydrogenase; *MDM2*, murine double minute 2 homolog; PD-L1, programmed death-ligand 1; SLD, sum of largest diameters.

**A Comparison of baseline characteristics between atezolizumab-treated patients with FP and without**

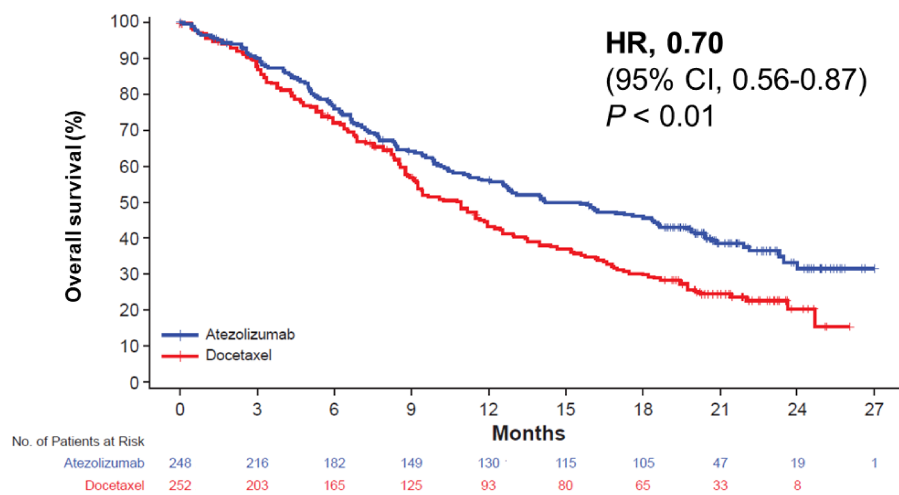
**B Comparison of baseline characteristics between docetaxel-treated patients with FP and without**

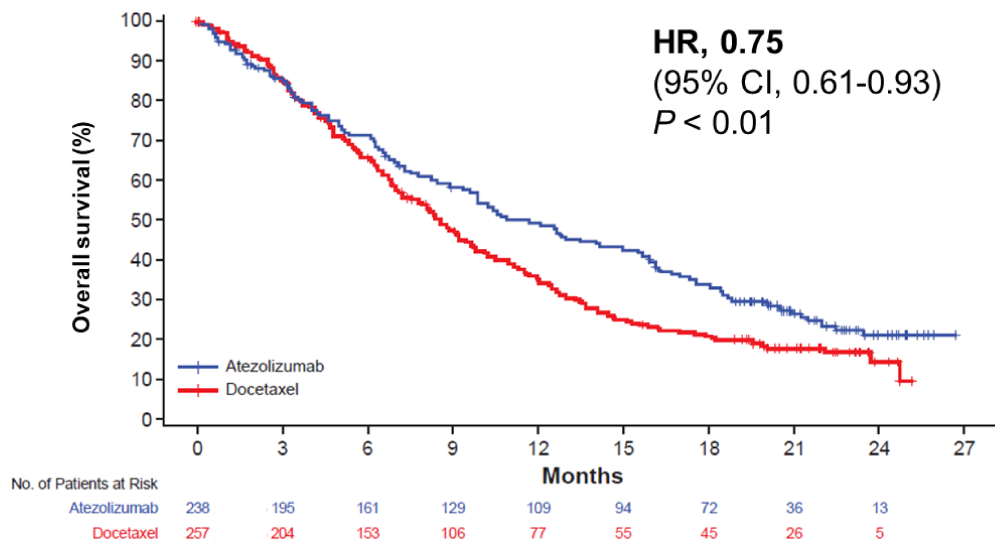
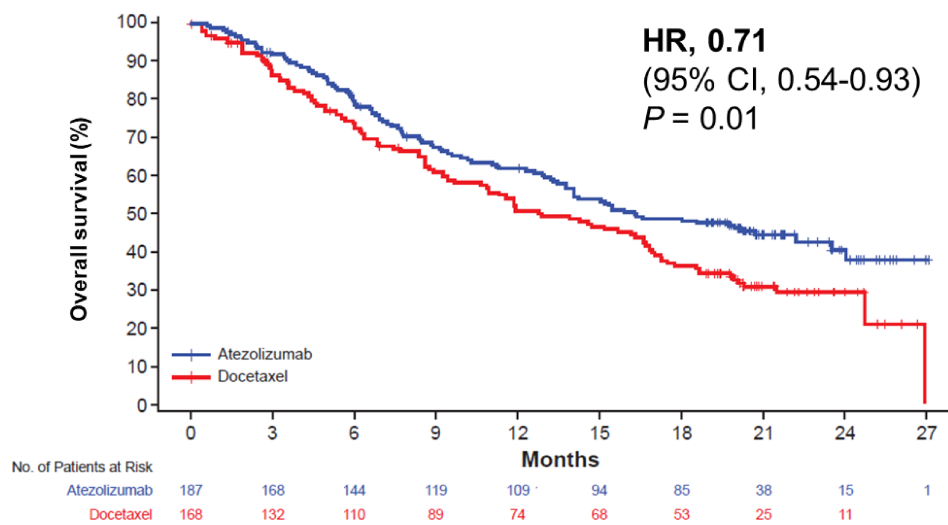
**Supplementary Figure S3.** Kaplan-Meier plots of overall survival (OS) in clinically relevant patient subgroups. 1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

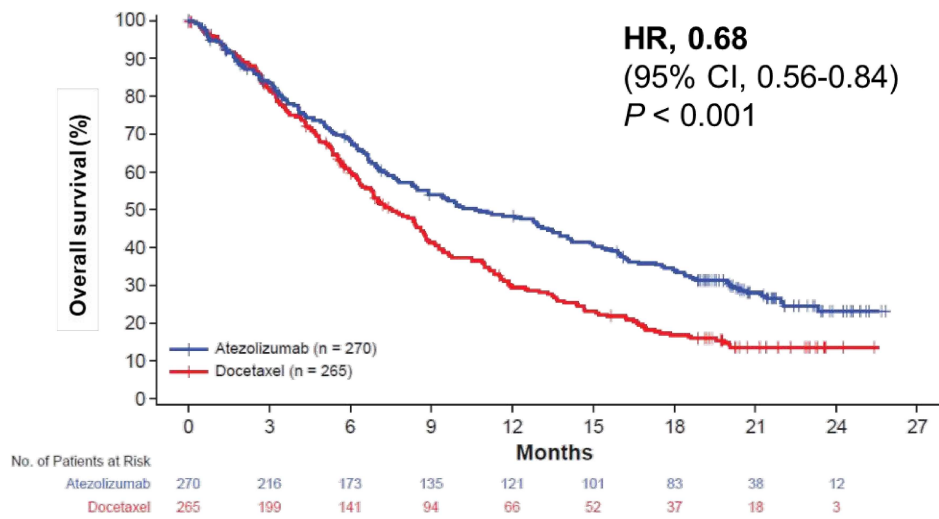
**A OS for failure of preceding 1L treatment  $\leq 6$  months**



**B OS for failure of preceding 1L treatment  $>6$  months**



**C OS for  $\geq 3$  metastatic sites****D OS for  $< 3$  metastatic sites****E OS for ECOG PS 1**



**F OS for ECOG PS 0**

