ORIGINAL RESEARCH

Phase II multicohort study of atezolizumab monotherapy in multiple advanced solid cancers

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Background: The programmed death-ligand 1 inhibitor atezolizumab had shown clinical activity against several advanced malignancies.

Patients and methods: This phase II, open-label basket study (NCT02458638) was conducted in 16 main cohorts of patients aged ≥18 years with stage III or IV solid tumors. In stage I, 12 patients were enrolled into each cohort. Treatment was atezolizumab 1200 mg intravenously every 3 weeks until loss of clinical benefit or unacceptable toxicity. The primary efficacy endpoint was the non-progression rate (NPR) at 18 weeks in treated, assessable patients. NPR ≤20% was not of interest for development as monotherapy, and NPR ≥40% was defined as the threshold of benefit/success. If ≥3 patients had non-progressive disease in stage I (interim analysis), 13 additional patients could be enrolled into stage II (final analysis). Secondary efficacy and safety endpoints were also evaluated.

Results: Overall, 474 patients were enrolled and treated; 433 were included in the efficacy set. Due partly to slow recruitment because of competing trials and limited efficacy at interim analyses, enrollment was stopped early, including in cohorts that passed stage I boundaries of success. NPR was >20% in five cohorts: cervical cancer {n = 27; NPR 44.4% [95% confidence interval (CI) 25.5% to 64.7%]}; follicular/papillary thyroid cancer [n = 11; 54.5% (95% CI 23.4% to 83.3%)]; thymoma [n = 13; 76.9% (95% CI: 46.2% to 95.0%)]; gastroenteropancreatic (GEP) and lung neuroendocrine tumors [NETs; n = 24; 41.7% (95% CI 22.1% to 63.4%)], and low/intermediate grade carcinoid GEP and lung NETs [n = 12; 58.3% (95% CI 27.7% to 84.8%)]. Treatment-related adverse events occurred in 55.3% of patients overall, and at grade 3, 4, and 5 in 10.3%, 1.7%, and 0.4%, respectively.

Conclusions: Atezolizumab monotherapy was effective in the cervical cancer cohort. The interim benefit threshold was crossed in patients with follicular/papillary thyroid cancer, thymoma, and GEP and lung NETs, but recruitment was stopped before these signals could be confirmed in stage II. Safety was consistent with previous findings.

Key words: basket study, multicohort, atezolizumab, PD-L1 checkpoint inhibitor, solid tumors

INTRODUCTION

Many human tumors express programmed death-ligand 1 (PD-L1), an immune checkpoint molecule that mediates the escape of tumor cells from immune-mediated destruction.[1] Atezolizumab is a humanized immunoglobulin G1 monoclonal antibody that targets PD-L1 and inhibits interaction with its receptors, programmed cell death protein 1 (PD-1), and B7.1 (CD80), which normally inhibit the activation of T cells.[1] Interrupting the PD-L1/PD-1 pathway is a strategy to reinvigorate tumor-specific T-cell immunity.

Atezolizumab monotherapy demonstrated clinical activity in patients with a broad range of advanced malignancies after standard-of-care therapies had failed in the phase Ia PCD4989g study (NCT01375842).[2] Objective responses were seen in patients with non-small-cell lung cancer (NSCLC),[3] small-cell lung cancer (SCLC),[4] metastatic castration-resistant prostate cancer,[5] renal cell carcinoma,[6] melanoma,[7] urothelial cancer,[8] head and neck cancer,[9] ovarian and uterine cancers,[10] glioblastoma,[11] and metastatic breast cancer.[12] Atezolizumab has subsequently been approved by the US Food and Drug Administration for advanced urothelial carcinoma and SCLC, unresectable hepatocellular carcinoma, unresectable or metastatic *BRAF* V600 mutation-positive

melanoma, PD-L1-positive metastatic NSCLC, and unresectable locally advanced or metastatic triple-negative breast cancer.

This phase II multicohort 'basket' study of atezolizumab (NCT02458638) was conducted in additional cohorts and subcohorts of patients who had locally advanced or metastatic solid tumors. The malignancies were selected based on pathologic characteristics that suggested a potential for high immunogenicity and thus, possible susceptibility to immunotherapy with atezolizumab, as well as evidence linking PD-L1 expression to pathogenesis.[1,2,13,14] Conducted to evaluate whether atezolizumab would show antitumor activity in a wide range of late-stage solid tumors, this study was designed before 2015, when limited data on checkpoint inhibitor efficacy were available.

METHODS

Patients, study design, and treatment

This was a phase II, open-label, multicohort, multinational study of atezolizumab in patients aged 18 years or older, who had advanced (i.e. stage III or IV) solid tumors. The study was planned to include 16 main cohorts of patients with the following cancers, with some cohorts divided into subcohorts (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100419): cervical; nasopharyngeal; known microsatellite instability-high (MSI-H) or mismatch repair (MMR)-deficient colorectal cancer (CRC); BRCA1/2-mutated ovarian and breast cancers; soft tissue, visceral, and bone sarcoma; mesothelioma; cholangiocarcinoma/cancer of the biliary tract; thyroid cancer; gastric adenocarcinoma/adenocarcinoma of gastroesophageal junction; other solid tumors; malignant germ cell tumors; estrogen receptor-positive/human epidermal growth factor receptor 2-negative breast cancer with known high mutation load (>100 mutations by local test); thymoma and thymic cancer; gastroenteropancreatic (GEP) and lung neuroendocrine tumors (NETs); known human papillomavirus-induced squamous cell carcinoma (SCC); and known MSI-H or MMR-deficient tumors excluding CRC and gastric cancer.

Other inclusion criteria included progressive disease (PD) at study entry, one or more lines of prior systemic treatment (unless survival-prolonging treatment was not available for their tumor type), and an Eastern Cooperative Oncology Group performance status score of 0 or 1 (see Supplementary methods for full list of eligibility criteria).

Study enrollment was based on Simon's optimal two-stage design.[15] Twelve fully assessable patients (defined as having received study treatment, with a baseline and at least one post-baseline tumor assessment) were enrolled into each cohort in stage I. If 3 or more of these patients had non-PD at 18 weeks (defined as the end of stage I), an additional 13 fully assessable patients could be enrolled into stage II (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100419).

Enrolled patients received a fixed dose of atezolizumab 1200 mg intravenously on the first day of each 21-day cycle. Treatment continued for as long as they experienced clinical benefit, in the opinion of an investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to PD.

Efficacy endpoints and assessments

The primary efficacy endpoint was the non-progression rate (NPR) at 18 weeks. NPR was defined as the percentage of patients who had a complete response (CR), partial response (PR), or stable disease (SD) as assessed by the investigator according to RECIST version 1.1, and by disease-specific criteria for patients with prostate cancer and malignant pleural mesothelioma.

Secondary endpoints included 24-week NPR; overall response rate [ORR (i.e. percentage of patients with CR or PR)]; best overall response until PD, death or loss to follow-up; and clinical benefit rate (i.e. CR, PR, or SD for ≥6 weeks); duration of response (DOR); time to tumor progression (TTP); and progression-free survival (PFS), all as assessed by the investigator; and overall survival (OS).

All cohorts were analyzed for futility at stage I (interim analysis) when the first 12 patients had passed the 18-week assessment, except cohorts that were stopped before 12 assessable patients had enrolled due to recruitment limitations or for safety reasons. Efficacy was assessed in all cohorts, including those where expansion was not done, with the final analysis conducted at the data cut-off of 21 December 2019. Patients with missing data were imputed as PD.

Tumor assessment per RECIST 1.1 was conducted at screening, every 6 weeks for the first 24 weeks, then every 12 weeks thereafter until loss of clinical benefit or study withdrawal.

Safety objectives and assessments

The safety objective was to evaluate the safety and tolerability of atezolizumab in patients with various solid tumors. The incidence, nature, and severity of adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs) were graded according to the National Cancer Institute Common Terminology Criteria for AE (version 4). Physical examinations, electrocardiograms, and laboratory assessments were done at screening, at all treatment visits, and at the treatment discontinuation visit. All patients were monitored for survival for ≥24 months after the last patient was enrolled in each cohort or until all patients had died, withdrawn consent or were lost to follow-up, or the study ended, whichever occurred first.

Statistical analyses

The sample size was determined by Simon's optimal two-stage design. An NPR of ≤20% (based on historical controls) was not of interest for further clinical development, whereas an NPR of ≥40% at week 18 was of clinical interest and therefore, was defined as the threshold of benefit or success (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100419). The type I error was 10% and the study had an 80% power to reject the null

hypothesis when the true NPR was 40%, with the same hypotheses and clinical assumptions applied to all cohorts individually. The stage I (futility) analysis was targeted at the first 12 patients in each cohort. The final analysis of each cohort was based on the data cut-off of 21 December 2019. Given the heterogeneity of cancer types, efficacy analysis was conducted within each cohort, rather than across cohorts.

The intent-to-treat (ITT) population was defined as all enrolled patients. Since all enrolled patients received study treatment, they were included in the safety set. The efficacy set included patients who were eligible and assessable (i.e. received study treatment, with a baseline and at least one post-baseline tumor assessment).

Binary outcomes (e.g. rates) are presented as number and percentage of patients together with two-sided 95% exact binominal confidence intervals (CIs). Kaplan—Meier methodology was used to estimate OS, PFS, DOR, and TTP, with associated two-sided 95% CIs computed using log-log transformation.

Study ethics

This study was conducted in accordance with principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent to participate. Before the study started, protocol approval was obtained from an independent ethics committee or institutional review board at each study site, which also had to approve all amendments in accordance with local regulations.

RESULTS

Patient disposition and characteristics

A total of 703 patients were screened. Between 31 May 2015 and 12 February 2018, 474 patients in the ITT population were enrolled from 47 centers in 18 countries and since they all received at least one dose of study treatment, they were included in the safety set (Figure 1). The efficacy set included 433 eligible and assessable patients. The number of patients in the safety and efficacy sets in each tumor cohort and subcohort is shown in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100419. The baseline and disease characteristics of patients are summarized by cohort in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100419.

Overall, 97% of 474 patients discontinued treatment during the study (Figure 1). The main reasons for stopping treatment were PD (n = 343; 72.3%), death (n = 34; 7.2%), and AEs (n = 33; 7.0%). Lack of clinical benefit was reported as a reason for discontinuation by 30 patients (6.3%). 'Lack of clinical benefit' was not defined in the study protocol, but was reported by the investigators when patients had symptoms that were considered to be related to PD but no documented progression of disease was available. At the clinical cut-off (21 December 2019), 14 patients were still being treated with

atezolizumab. The median duration of study participation was 9.76 months (range, 0.13-52.47 months).

Recruitment was closed before the planned number of 725 patients were enrolled. Based on emerging data on checkpoint inhibitor monotherapy, the increase in competing trials due to the availability of a growing number of treatment combinations, and the limited efficacy observed at the interim analyses, in May 2018 the decision was made to stop recruitment of new patients for all cohorts. This included cohorts that passed the boundaries of success in the stage I interim analysis and were eligible for expansion (stage II) at the time the decision was made. Patients who were experiencing clinical benefit from atezolizumab, however, were allowed to continue treatment and complete the study.

Efficacy

Because the study design involved various cancer subtypes and each malignancy had different characteristics, the interpretation of efficacy data for each individual cohort was considered more meaningful than for the combined analysis. The primary efficacy endpoint, NPR at 18 weeks, is shown by cohort in Figure 2. The planned 'other solid tumor' cohort was closed before analysis and the vaginal/vulvar cancer cohort did not recruit any patients. All remaining cohorts and subcohorts underwent stage I interim analysis, and three cohorts (cervical cancer, nasopharyngeal carcinoma, and known translocation-related sarcomas) continued enrollment into stage II (Figure 2).

At the final analysis, the lower limits of the 95% CI of NPR were >20% in five cohorts: cervical cancer; follicular or papillary thyroid cancer; thymoma; GEP and lung NETs; and low/intermediate grade carcinoid GEP and lung NETs. The benefit in the GEP and lung NETs cohort was derived from that observed in the subcohort of low/intermediate grade carcinoid GEP and lung NETs (Figure 2). In all these cohorts except cervical cancer, recruitment had been stopped before all planned patients could be enrolled into stage II, despite the positive clinical signal observed in the absence of cohort expansion.

The median 18-week NPRs in the nasopharyngeal carcinoma and translocation-related sarcoma cohorts that met the criteria for stage I success and underwent expansion to full sample size were 29.6% (95% CI 13.8% to 50.2%) and 23.1% (95% CI 9.0% to 43.6%), respectively, which were lower than the prespecified 40% benefit threshold.

ORRs in all cohorts are summarized in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100419. The cohorts in which primary endpoint efficacy exceeded the benefit threshold in the interim or final analyses are described in further detail.

Cervical cancer

Among the 27 efficacy-evaluable patients assessed in the final analysis, 51.9% had SCC, 44.4% had adenocarcinoma, 70.4% had a poorly to moderately differentiated tumor
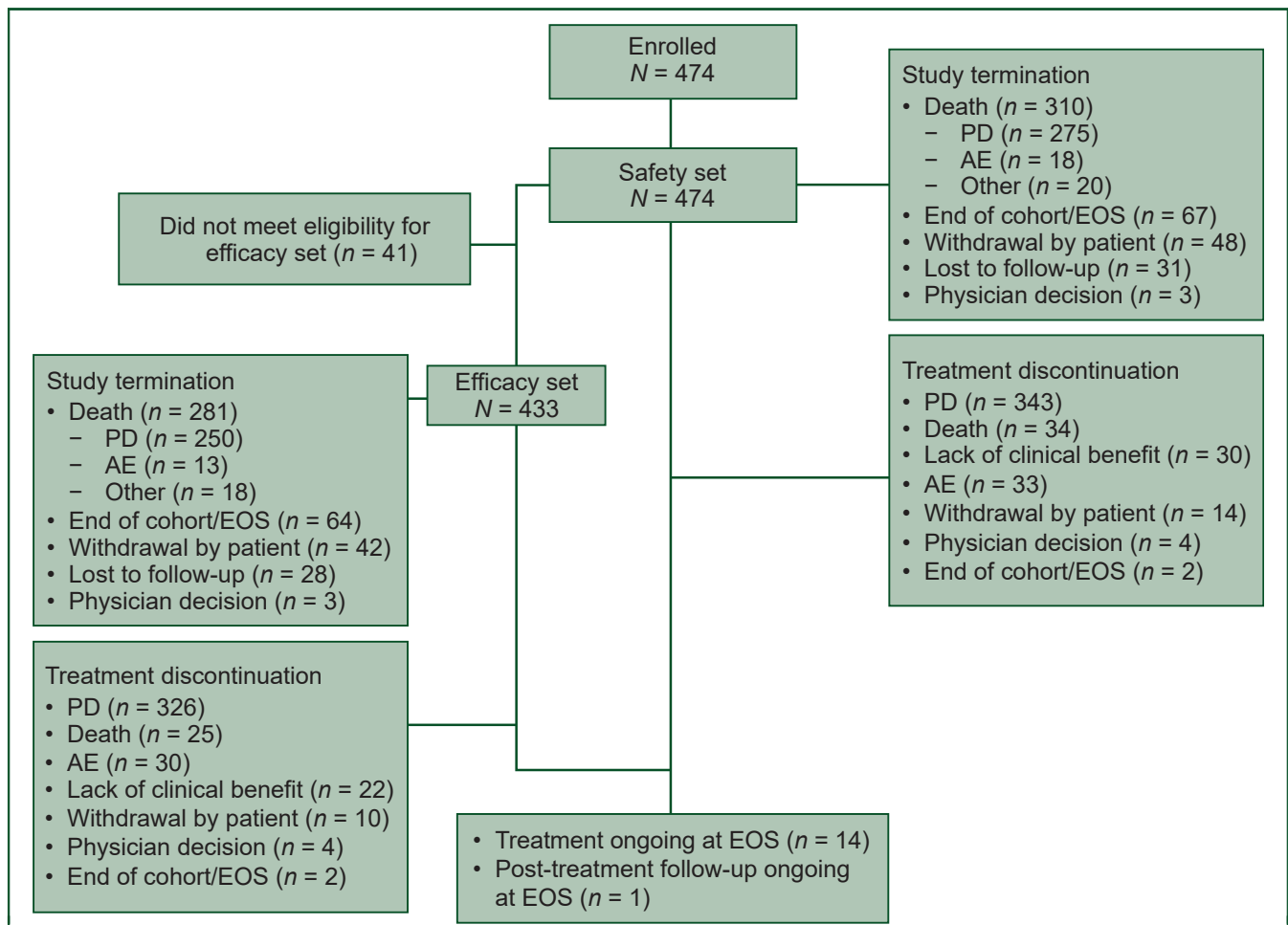
Figure 1. Trial profile.
AE, adverse event; EOS, end of study; PD, progressive disease.

grade, and 96.3% had stage IVB cervical cancer at screening. Liver and lung metastases were present in 22.2% and 48.1% of patients, respectively. The median time since primary diagnosis was 3.47 years (range, 0.4-16.3 years) and since first metastases was 1.52 years (range, 0.1-6.3 years). The median number of prior systemic anticancer therapy lines was 2.0 (range, 1-7); 70.4% of these patients had received two or more prior lines (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100419).

Overall, 12 patients had no progression at 18 weeks; the NPR was 44.4% (95% CI 25.5% to 64.7%) (Figure 2; Table 1). Tumor response and other secondary efficacy endpoint outcomes are summarized in Table 1 and Supplementary Figures S2A and S3A, available at https://doi.org/10.1016/j.esmoop.2022.100419. The ORR was 14.8%. In the four patients who had CR or PR at 18 weeks, the DORs were 2.99, 9.99, and 11.30 months (censored) and 1.27 years, respectively (Figure 3A).

Follicular or papillary thyroid cancer

In 11 patients in this cohort, thyroid cancers were papillary in 63.6% or follicular in 36.4%. All patients had stage IVC cancer and lung metastases (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100419);

81.8% also had metastases at other sites. The median time since primary diagnosis was 9.01 years (range, 1.3-27.7 years) and since first metastases was 4.3 years (range, 0.9-20.8 years). These patients had received a median 2.0 (range, 1-4) lines of prior systemic anticancer therapy and 63.6% had received ≥2 prior lines.

At the interim analysis, six patients had no progression at 18 weeks; the NPR was 54.5% (95% CI 23.4% to 83.3%) (Figure 2; Table 1). Tumor response and other secondary efficacy endpoint outcomes are summarized in Table 1 and Supplementary Figures S2B and S3B, available at https://doi.org/10.1016/j.esmoop.2022.100419. The ORR was 9.1%, with none of these patients having a CR or PR at 18 and 24 weeks; however, a PR was observed in one patient at day 258 (week 36), which lasted for 2.09 years (Figure 3B). Despite the positive signal observed for clinical activity, this subcohort did not progress to stage II due to the decision to stop recruitment for the whole trial.

Thymoma

Of these 13 efficacy-evaluable patients, 15.4% had poorly/moderately differentiated tumors and 15.4% had well differentiated tumors (tumor grade was unknown in 69.2% of patients); 76.9% had stage IVB cancer. Liver metastases
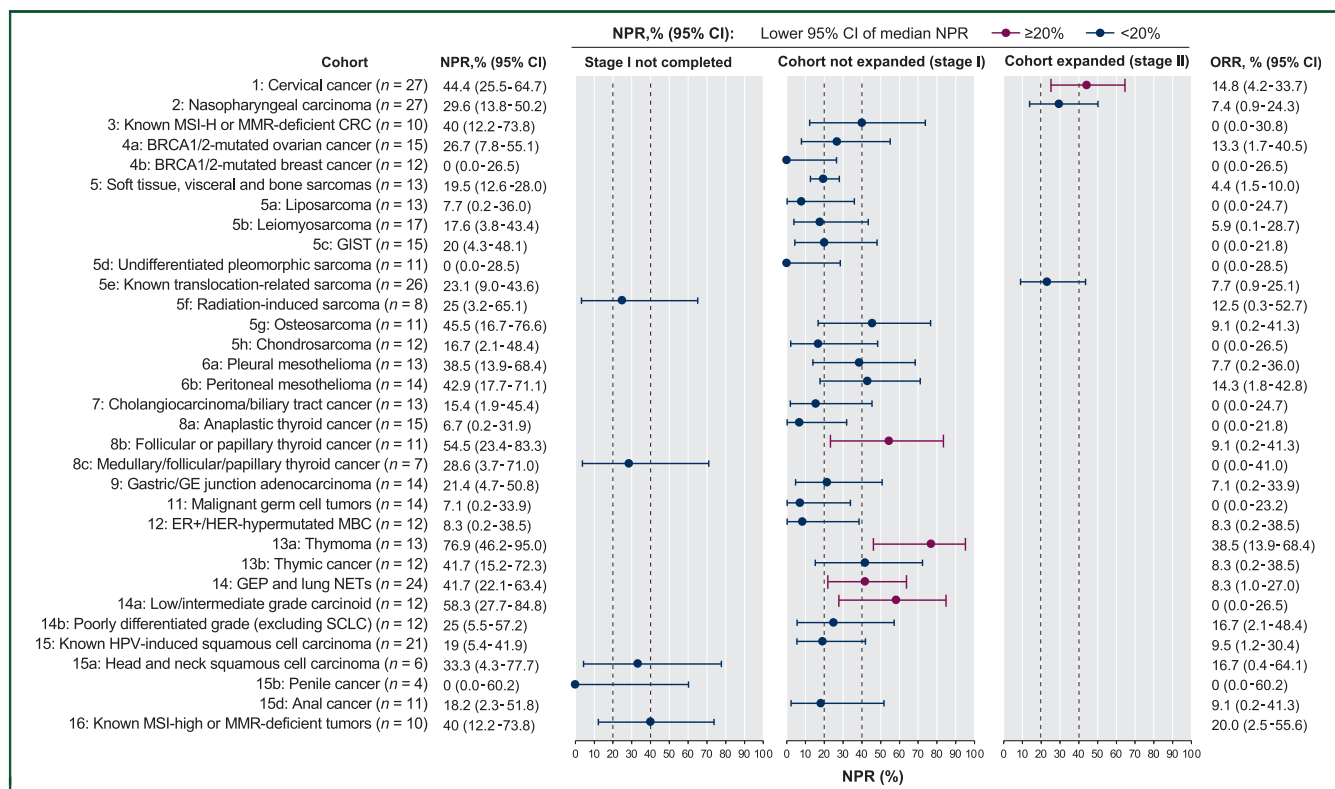
Figure 2. NPR at 18 weeks by cohort at interim analysis (stage I) or final analysis (stage II) in the efficacy set.
Cohort data shown in red passed the boundary of interim analysis; cohort data shown in blue did not pass the boundary of interim analysis. Cohorts for which only interim analyses are shown did not reach stage II due to low accrual or because recruitment was stopped. Interim analysis was not conducted for cohorts that were stopped before 12 eligible, assessable patients had been enrolled.
CI, confidence interval; CRC, colorectal cancer; ER, estrogen receptor; GE, gastroesophageal; GEP, gastroenteropancreatic; GIST, gastrointestinal stromal tumor; HER, human epidermal growth factor receptor; HPV, human papillomavirus; MBC, metastatic breast cancer; MMR, mismatch repair; MSI-H, microsatellite instability-high; NET, neuroendocrine tumor; NPR, non-progression rate; SCLC, small-cell lung cancer.

were present in 7.7% of patients, lung metastases in 53.8%, and 100% also had metastases at other sites. The median number of prior systemic anticancer therapy lines was 2.0 (range, 0-9); 53.8% had received 2 or more prior lines. The median time since primary diagnosis was 6.10 years (range, 1.1-17.8 years) and since first metastases was 3.99 years (range, 0.6-14.8 years).

At the interim analysis, 10 patients had no progression at 18 weeks and the NPR was 76.9% (95% CI 46.2% to 95.0%) (Figure 2; Table 1). The NPR remained unchanged at 24 weeks, with four patients (30.8%) having a PR (Table 1). Tumor response and secondary efficacy endpoint outcomes are summarized in Table 1 and Supplementary Figures S2C and S3C, available at https://doi.org/10.1016/j.esmoop. 2022.100419. The ORR was 38.5%; the DOR in the five patients who had a PR ranged from 46 days to 2.52 years (censored), with four patients having a PR >1.4 years (Figure 3C). Despite the positive signal for clinical activity, this subcohort did not progress to stage II for the safety reasons described in the following sections.

Tumor grades were either moderately (41.7%) or well differentiated (58.3% of patients). All these patients had stage IV disease. Liver and lung metastases were reported in 75.0% and 16.7% of patients, respectively. The median time since primary diagnosis was 4.90 years (range, 0.5-16.3 years). The median time since first metastases was 3.9 years (range, 0.5-13.1 years). The median number of prior systemic regimens was 2.5 (range, 1 to 6) and 75% of these patients had received two or more prior treatment lines.

The interim analysis showed that seven patients had no progression at 18 weeks; the NPR was 58.3% (95% CI 27.7% to 84.8%) (Figure 2, Table 1). The ORR was 0%; none of these patients had a CR or PR (Figure 3D). Tumor response and secondary efficacy endpoint outcomes are summarized in Table 1 and Supplementary Figures S2D and S3D, available at https://doi.org/10.1016/j.esmoop.2022.100419. Despite the positive signal for clinical activity, this subcohort did not progress to stage II due to the decision to stop recruitment for the whole trial.

Low/intermediate grade GEP and lung NETs

The main locations for the primary tumor in these 12 efficacy-evaluable patients were the ileum and pancreas (each 33.3%); 66.7% of patients had carcinoid tumors.

Safety

The median duration of study treatment in the combined safety set was 2.51 months (range, 0.03-52.47 months). The median number of atezolizumab doses was 4 (range, 1-71).

Table 1. Efficacy in cohorts that exceeded the benefit threshold (efficacy set)

	Cervical cancer (n = 27)[a]	Follicular or papillary thyroid cancer (n = 11)[b]	Thymoma (n = 13)[b]	Low/intermediate grade carcinoid GEP and lung NETs (n = 12)[b]
Primary efficacy endpoints				
NPR at 18 weeks, n (%) [95% CI][c]	12 (44.4) [25.5-64.7]	6 (54.5) [23.4-83.3]	10 (76.9) [46.2-95.0]	7 (58.3) [27.7-84.8]
Response rate at 18 weeks, n (%) [95% CI]	4 (14.8) [4.2-33.7]	0 [0.0-28.5]	3 (23.1) [5.0-53.8]	0.0 [0.0, 26.5]
CR	1 (3.7)	0	0	0
PR	3 (11.1)	0	3 (23.1)	0
SD	8 (29.6)	6 (54.5)	7 (53.8)	7 (58.3)
PD	14 (51.9)	5 (45.5)	2 (15.4)	4 (33.3)
Missing/out of window[d]	0	0	0	1 (8.3)
Secondary efficacy endpoints				
NPR at 24 weeks, n (%) [95% CI]	11 (40.7)[e] [22.4-61.2]	6 (54.5) [23.4-83.3]	10 (76.9) [46.2-95.0]	7 (58.3) [27.7-84.8]
BOR rate, n (%) [95% CI][f]	4 (14.8) [4.2-33.7]	1 (9.1) [0.2-41.3]	5 (38.5) [13.9-68.4]	0 [0.0-26.5]
CR	1 (3.7)	0	0	0
PR	3 (11.1)	1 (9.1)	5 (38.5)	0
SD	11 (40.7)	8 (72.7)	6 (46.2)	12 (100)
PD	11 (40.7)	2 (18.2)	1 (7.7)	0
Missing	1 (3.7)	0	1 (7.7)	0
Clinical benefit rate, n (%) [95% CI]	15 (55.6) [35.3-74.5]	9 (81.8) [48.2-97.7]	11 (84.6) [54.6-98.1]	12 (100.0) [73.5-100.0]
Median TTP (95% CI), months	4.14 (1.31-8.34)	8.48 (1.31-15.41)	12.58 (3.22-37.22)	8.54 (4.07-10.94)
Median PFS (95% CI), months	4.14 (1.31-8.34)	8.48 (1.31-15.41)	11.76 (3.22-37.22)	8.54 (4.07-13.67)
Median OS (95% CI), months	14.78 (10.55-26.51)	24.02 (4.11-NE)	NE	27.20 (17.02-NE)

NPR = exact binomial estimate of CR + PR + SD; ORR = exact binomial estimate of CR + PR; clinical benefit rate = CR + PR + SD.
BOR, best overall response; CI, confidence interval; CR, complete response; GEP, gastroenteropancreatic; NE, not estimable; NET, neuroendocrine tumor; NPR, non-progression rate; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression.
[a]Stage II final analysis.
[b]Interim analysis; this subcohort did not progress to stage II due to the decision by the steering committee and sponsor to stop recruitment.
[c]RECIST 1.1 by investigator assessment, includes confirmed and unconfirmed responses.
[d]Out of window: no assessment of CR, PR, or SD within days 112 to 209; and no PD, death, or study discontinuation up to day 142.
[e]One patient withdrew from the study.
[f]Best overall response rate (i.e. ORR) with a breakdown by BOR in the following rows.

As of the clinical cut-off date (21 December 2019), 91.8% of 474 patients in the safety set reported at least one treatment-emergent AE (TEAE) (Table 2). Most patients (87.6%) reported grade 1-2 events. A safety overview by cohort is shown in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100419.

Treatment-related TEAEs were reported by 55.3% of patients overall. Most were mild, with grade 3 and 4 events reported by 10.3% and 1.7% of patients, respectively. The most frequent treatment-related TEAEs were fatigue (n = 60, 12.7%), diarrhea (n = 36, 7.6%), rash (n = 34, 7.2%), asthenia (n = 26, 5.5%), pyrexia (n = 26, 5.5%), pruritus (n = 24, 5.1%), and nausea (n = 24, 5.1%). Seventeen patients (3.6%) discontinued treatment as a result of a treatment-related TEAE.

Treatment-related SAEs occurred in 39 patients (8.2%); among these, 19 patients (4%) had grade 3 SAEs and 8 patients (1.7%) had grade 4 SAEs. The most frequently reported SAEs were pyrexia (n = 5, 1.1%), with colitis, pancreatitis, fatigue, febrile neutropenia, thrombocytopenia and myasthenia gravis, pneumonitis, inappropriate antidiuretic hormone, and type 1 diabetes mellitus reported in two patients (0.4%) each. Twelve patients (2.5%) died due to SAEs during the study; deaths in two patients (0.4%) were treatment-related and due to pneumonitis and myasthenia gravis, respectively. The latter patient had asymptomatic myasthenia gravis at screening.

Overall, 170 patients (35.9%) had AESIs (Table 2), of whom 23 (4.9%) had AESIs considered serious by the

investigator. The most frequently reported AESIs of any grade in >2% of patients were rash (n = 41, 8.6%), hypothyroidism (n = 38, 8.0%), increased aspartate aminotransferase (AST) (n = 25, 5.3%), increased alanine aminotransferase (ALT, n = 23, 4.9%), infusion-related reactions (n = 17, 3.6%), and hyperthyroidism (n = 14, 3.0%). Grade 3 AESIs were reported by 32 patients (6.8%). Grade 3 events reported in more than one patient were colitis in four patients (0.8%), increased AST, increased gammaglutamyltransferase, diabetes mellitus in three patients each (0.6%), and rash, increased ALT, increased blood bilirubin, and pancreatitis in two patients each (0.4%). Five patients (1.1%) had grade 4 AESIs; two patients (0.4%) had type 1 diabetes mellitus and one patient (0.2%) had each of increased blood bilirubin, increased amylase, hepatitis, immune-mediated encephalitis, and meningitis. The highest rate of AESIs [in 9 of 14 patients (64.3%)] was reported in the thymoma cohort. Eight patients (57.1%) in this cohort had treatment-related AESIs and five patients (35.7%) had serious AESIs, with two patients each reporting hepatitis and myasthenia gravis; the latter was fatal in one patient. Recruitment into this cohort was stopped due to the observed AEs.

DISCUSSION

Despite the study being stopped early, atezolizumab monotherapy showed antitumor activity (as defined in the protocol) in five cohorts overall: cervical cancer, follicular or
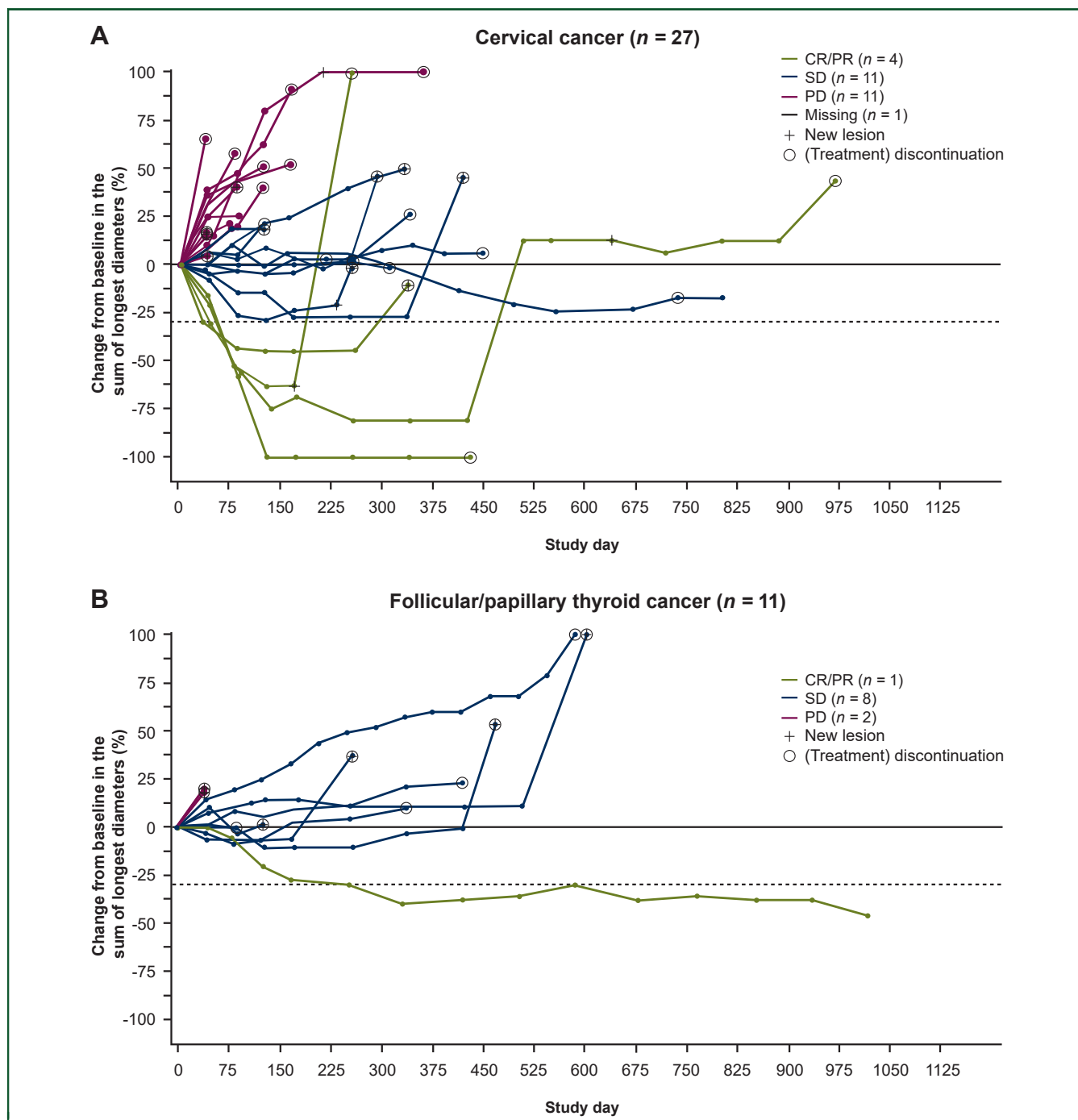
Figure 3. Tumor response shown as change in sum of tumor diameter over time (efficacy set).
The sum of the diameters of baseline target lesions is shown. Treatment discontinuation is shown at the time of the last tumor assessment carried out on or before discontinuation.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

papillary thyroid cancer, GEP and lung NETs (driven largely by activity in low- or intermediate-grade carcinoid tumors), and thymoma. The immunotherapy landscape evolved rapidly after the study was designed, with data emerging on checkpoint inhibitor mechanisms of action, efficacy of treatment combinations, and on predictive tumor markers for atezolizumab and other PD-L1 inhibitors as our study was getting underway.[2,6,13,16-19] This rendered the study outdated while it was still ongoing. In addition, slow rates of accrual occurred in many cohorts. The sponsor and the

steering committee therefore decided to terminate recruitment for all cohorts, including those that passed the boundaries of the interim analysis at stage I, but to complete the study in the patients who were still deriving clinical benefit from study treatment.

The efficacy data from the final analysis of the cervical cancer cohort, including the ORR of 14.8%, are consistent with positive findings with other checkpoint inhibitors in cervical cancer.[20] An ORR of 17% was reported with pembrolizumab.[21] Several phase I-III studies of nivolumab and
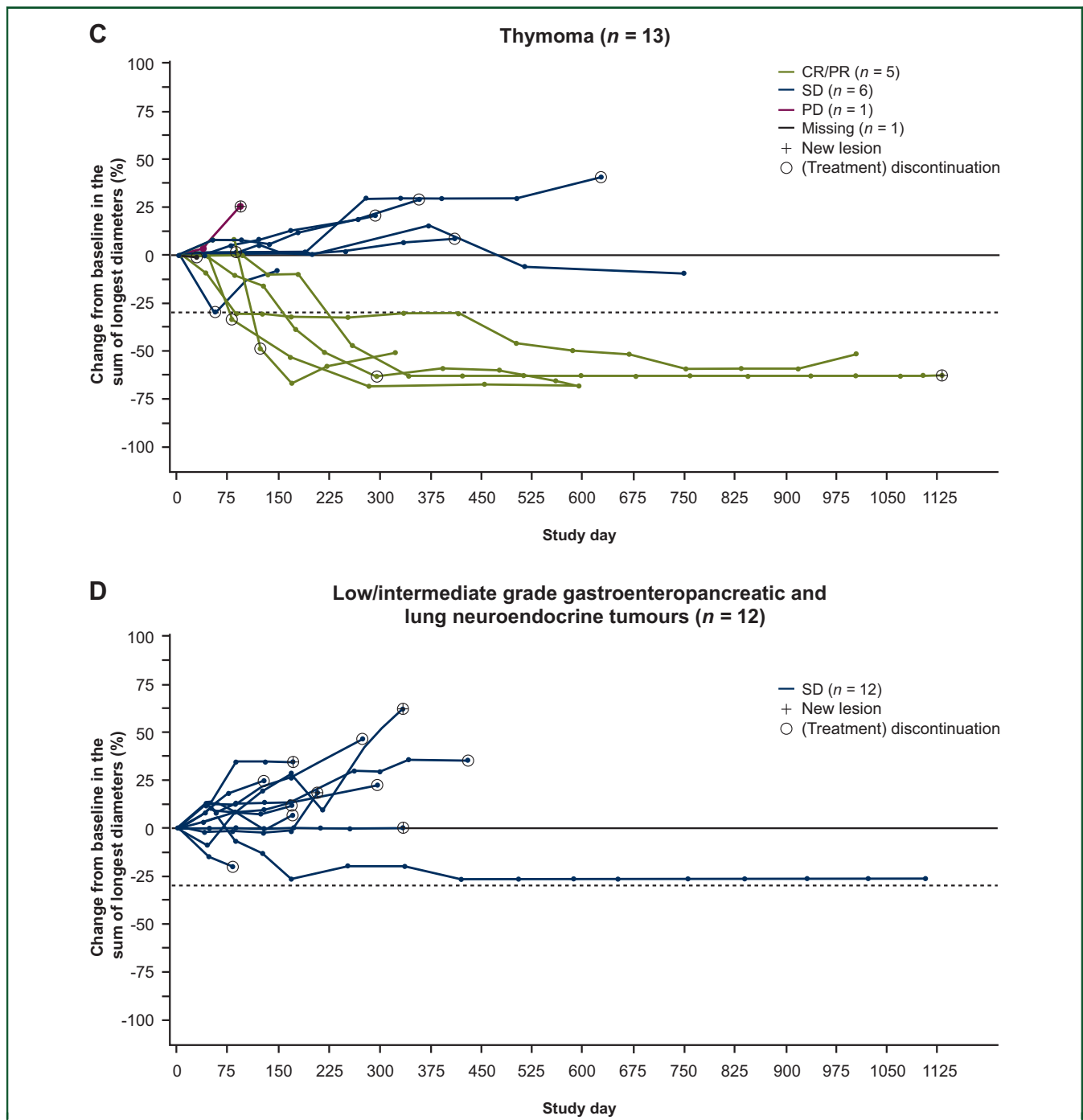
Figure 3. Continued.

pembrolizumab in combination with other agents are ongoing in patients with cervical cancer.[20] The safety and efficacy of atezolizumab monotherapy is being compared with atezolizumab plus tiragolumab in an ongoing phase II cervical cancer study (NCT04300647). Atezolizumab is also being investigated further in this setting in combination with radiotherapy and chemotherapy in several phase II and III studies.[20]

The interim analysis showed clinical activity with atezolizumab against follicular or papillary thyroid cancer, and GEP and lung NETs driven by a signal in low- or intermediate-grade carcinoid tumors. Because recruitment had been stopped, however, additional patients were not recruited into stage II to confirm these positive signals. Pembrolizumab monotherapy has also shown antitumor activity in these settings, with respective ORRs of 9% and 12% observed in patients with PD-L1-positive follicular or papillary thyroid cancer,[22] and PD-L1-positive, moderately or well-differentiated NETs.[23]

High PD-L1 expression levels on tumor cells and abundant CD8+ lymphocytes provide a strong rationale for using immune-checkpoint inhibitors to treat thymic

Table 2. Overview of AEs in the safety set—combined analysis	
	Safety set N = 474
Any AE	435 (91.8)
Any related AE	262 (55.3)
Any AESI	170 (35.9)
Serious AESIs	23 (4.9)
Any SAE	142 (30.0)
Related SAEs	39 (8.2)
SAEs leading to death	12 (2.5)
Related SAEs leading to death	2 (0.4)
AEs leading to treatment discontinuation	31 (6.5)
AEs by grade[a]	
1-2	415 (87.6)
1	347 (73.2)
2	317 (66.9)
3-4	206 (43.5)
3	200 (42.2)
4	24 (5.1)
5	12 (2.5)
Related AEs by grade[a]	
1-2	245 (51.7)
1	191 (40.3)
2	135 (28.5)
3-4	53 (11.2)
3	49 (10.3)
4	8 (1.7)
5	2 (0.4)
AEs by maximum grade	
1-2	222 (46.8)
1	65 (13.7)
2	157 (33.1)
3-4	201 (42.4)
3	178 (37.6)
4	23 (4.9)
5	12 (2.5)
Related AEs by maximum grade	
1-2	207 (43.7)
1	98 (20.7)
2	109 (23.0)
3-4	53 (11.2)
3	45 (9.5)
4	8 (1.7)
5	2 (0.4)

Results are presented as n (%).
AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event.
[a]Patients can appear under multiple grades.

epithelial tumors.[24] Although the highest median NPR in this study was observed in the thymoma cohort, and encouraging antitumor activity against thymic cancers has also been observed with pembrolizumab,[25,26] the relatively high incidence of severe immune-related AEs in thymic epithelial tumors (especially thymoma) remains a concern and cancer immunotherapies should be avoided in these patients.[25]

Although the overall prognosis in patients with MSI-H cancer is favorable (less so for those with advanced MSI-H CRC),[27] the patients included in either of the two MSI-H cohorts in this study all had stage IV disease and many had rapidly progressing disease at baseline (the protocol did not preclude such patients). More than half these patients had PD within 3 months, and a similar proportion had received three or more prior lines of treatment. Hence, our cohorts of patients with MSI-H

cancers may not be comparable to those in studies where more encouraging activity with atezolizumab has been observed, which may explain why the treatment response we observed was less than anticipated. We did observe that among patients for whom MSI-H status was confirmed, all but one survived longer than the median OS in these cohorts, regardless of their response at 18 weeks. These cohorts of patients closed early, however, so the sample size is very small and inference is very limited.

Other than in the thymoma cohort, which had the highest rate of AESIs (78.6%) and related SAEs (35.7%) among its 14 patients, no new safety signals or trends in treatment-related AEs were observed. Atezolizumab was well tolerated in this study, as demonstrated by the 8.2% rate of SAEs (pyrexia being the most common), and only 3% of patients withdrawing from treatment because of an atezolizumab-related TEAE. The safety profile was consistent with previous phase I clinical studies of atezolizumab monotherapy, and as expected from this agent.[6,8,14]

A basket study provides an excellent opportunity to evaluate the efficacy and safety of a new treatment across numerous different types of malignancies. It also increases the risk that cohorts may be too small to show meaningful outcomes, however, particularly if tumors are rare and accrual is slow. In this study, the recruitment rate was too low in several cohorts, and recruitment was stopped before positive interim signals could be confirmed in stage II. Another study limitation was the choice of a single target for efficacy across all tumor types, which have different characteristics and thus potentially different levels of response to PD-L1 inhibition. The primary endpoint (NPR at 18 weeks) was chosen for the purposes of signal seeking. It allowed a Simon's staged design with an endpoint that could be assessed relatively early after the start of treatment, and based on which the steering committee could decide whether or not a cohort should progress to stage II (in combination with other non-efficacy-related factors, such as safety and toxicity, feasibility of recruitment, and emerging knowledge in the field). We acknowledge, however, that NPR at 18 weeks is not a very clinically meaningful outcome for the final analysis. Furthermore, non-progression at 18 weeks in patients with slow-growing, indolent tumors such as GEP, lung NETS, and thymoma might occur even without treatment intervention. Points to consider when designing a basket trial should therefore include the frequency or rarity of tumor types in relation to study timelines, which tumor types can be pooled in the same cohort and still show a clinically actionable signal, and an efficacy endpoint that will be sensitive enough to detect a positive signal across malignancies.

In conclusion, based on the protocol rules for stage II, atezolizumab monotherapy showed antitumor activity in the cervical cancer cohort. Interim analyses also showed that the protocol-defined threshold of benefit had been crossed in patients with follicular or papillary thyroid cancer, thymoma, and GEP and lung NETs (driven by those with low- or intermediate-grade carcinoid tumors), but recruitment was stopped before the signal could be confirmed in a

larger sample. The safety profile of atezolizumab was generally tolerable across the cohorts and consistent with previous findings.

DISCLOSURE

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DATA SHARING

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).

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