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ORIGINAL RESEARCH

Safety and efficacy of cobimetinib plus atezolizumab in patients with solid tumors: a phase II, open-label, multicenter, multicohort study

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Available online 21 March 2023

Background: Although introduction of immune checkpoint inhibitors has revolutionized the treatment of cancer, their response rates are generally low. Preclinical and early phase clinical data suggest that MEK inhibition may sensitize tumors to immune checkpoint inhibitors by upregulating tumor antigen expression, programmed death-ligand 1 (PD-L1) expression, and tumor T-cell infiltration. We evaluated the efficacy and safety of cobimetinib plus atezolizumab in patients with advanced solid tumors in the open-label, multicohort phase II COTEST study.

Patients and methods: This analysis of the COTEST trial included patients from cohorts 1-4 [1-3: anti-programmed cell death protein 1 (PD-1)/PD-L1 treatment-naive patients; 4: patients with disease progression on anti-PD-1/anti-PD-L1 treatment] who received cobimetinib 60 mg once daily for the first 21 days and intravenous infusions of atezolizumab 840 mg on days 1 and 15 of each 28-day cycle. Efficacy endpoints included objective response rate, overall survival, progression-free survival (PFS), and disease control rate.

Results: Overall, 77 patients were enrolled in cohorts 1-4 (78% male; median age 62.8 years). Objective response rate was 20% in cohort 1 [squamous cell carcinoma of the head and neck (SCCHN)], 30% in cohort 2 (urothelial carcinoma), and 18% in cohort 3 (renal cell carcinoma); there were no responders among 20 patients in cohort 4 (SCCHN). The disease control rates in cohorts 1-4 were 50%, 40%, 24%, and 25%, respectively. The median PFS was 5.5, 3.4, 3.4, and 3.6 months in cohorts 1-4, respectively, and the median overall survival was 16.8, 18.7, 21.7, and 7.7 months, respectively. Most adverse events were of grade 1/2 and were manageable.

Conclusions: Cobimetinib plus atezolizumab had moderate activity in patients with anti-PD-1/PD-L1 treatment-naive SCCHN and urothelial carcinoma, and weak activity in anti-PD-1/PD-L1 treatment-naive renal cell carcinoma, and no activity in checkpoint inhibitor-treated patients.

Key words: cobimetinib, atezolizumab, solid tumors, COTEST, phase II trial

INTRODUCTION

Immune checkpoint inhibitors (ICIs) disrupt the ability of tumor cells to escape immune surveillance by restoring antitumor T-cell responses and have been incorporated into the standard of care for many tumor types.[1,2] ICIs do this by blocking inhibitory signals of T-cell activation (immune checkpoints) that limit antitumor immune responses [e.g. anti-programmed cell death protein 1 (anti-PD-1) antibodies block the interaction of PD-1 on T cells with programmed death-ligand 1 (PD-L1) on tumor cells].[1,2] However, tumors without T-cell infiltration or low immunogenicity or tumors that were impaired by earlier checkpoints or immune suppression in the tumor microenvironment are not sensitive to ICI monotherapy.[3,4] Previous studies have shown that combination approaches using mitogen-activated protein kinase (MAPK) pathway inhibition can enhance the antitumor immune response via upregulation of T-cell antigen expression and PD-L1 expression, as well as by increased tumor T-cell infiltration.[5-7]

Cobimetinib is a reversible, potent, highly selective small-molecule inhibitor of MEK1 and MEK2, a key component of

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the MAPK signaling pathway. Inhibition of MEK1/MEK2 is known to block ERK phosphorylation, stimulating apoptosis.[8] Currently, cobimetinib is approved in combination with vemurafenib, an inhibitor of the BRAF kinase, for the treatment of advanced *BRAF*^{V600}-mutated melanoma.[9] Atezolizumab, an ICI, is a humanized immunoglobulin G1 monoclonal antibody directed against PD-L1.[10] Atezolizumab blocks the interaction of PD-L1 with PD-1 and B7-1 to enhance the magnitude and quality of tumor-specific T-cell responses. Currently, atezolizumab is approved as monotherapy or combination therapy for numerous cancers, including combination therapy with cobimetinib and vemurafenib for advanced *BRAF*^{V600}-mutated melanoma.[11]

Combination therapy of cobimetinib and atezolizumab may be a viable option for the treatment of solid tumors, including melanoma, as MEK inhibition may enhance the efficacy of immunotherapy. Results of preclinical studies have suggested that MEK inhibition may recruit immune cells to augment the activity of PD-L1 inhibitors.[5,6] In addition, results of a phase Ib, open-label study in patients with metastatic or locally advanced solid tumors showed that this combination was tolerable and had preliminary promising activity not only in melanoma, but also in microsatellite stable colorectal cancer, which is known to be insensitive to checkpoint inhibitors.[12] Furthermore, the activity of this combination was independent of *BRAF* or *KRAS* mutational status, suggesting that this combination may be effective in a variety of tumor types.[12] In the COTEST multicohort study, we evaluated the efficacy and safety of cobimetinib plus atezolizumab in patients with advanced solid tumors.

METHODS

Study design

COTEST was a phase II, open-label, nonrandomized, multicohort trial that enrolled patients with advanced solid tumors in the UK, Belgium, Germany, Hungary, Korea, and the USA (Clinicaltrials.gov NCT03264066). The study was planned to include seven cohorts: cohorts 1, 2, and 3 enrolled anti-PD-1 and anti-PD-L1 treatment-naive patients with squamous cell carcinoma of the head and neck (SCCHN; cohort 1), urothelial carcinoma (cohort 2), and renal cell carcinoma (RCC; cohort 3). Cohorts 4, 5, and 6 enrolled patients who progressed on anti-PD-1 or anti-PD-L1 treatment and had SCCHN (cohort 4), urothelial carcinoma (cohort 5), or RCC (cohort 6). Cohort 7 was planned to be a biopsy cohort comprising patients with solid nonmelanoma or nonhematologic tumors who had previously developed primary or secondary resistance to an anti-PD-1 or anti-PD-L1 agent, but this cohort was not opened to enrollment and is thus not discussed here.

The study protocol was approved by the institutional review board and/or an independent ethics committee at each study site. The study was carried out in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent before participation in the study.

Patients

Eligible patients were aged $\geq$18 years, with Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy $\geq$3 months, and adequate hematologic and end-organ function within 14 days of treatment initiation. All patients were required to have evidence of tumor progression on or after the last regimen received and within 6 months before enrollment, have measurable disease by RECIST version 1.1, and provide a tumor biopsy. Women of childbearing potential had to agree to remain abstinent or to use a nonhormonal contraceptive method with a failure rate of $<$1% per year during the treatment period and for $\geq$5 months after the last dose of atezolizumab and $\geq$3 months after the last dose of cobimetinib. Men were required to agree to remain abstinent or use contraceptive measures and refrain from donating sperm.

Patients were excluded if they had a history of or ongoing serous retinopathy or retinal vein occlusion at baseline; uncontrolled tumor-related pain, hypercalcemia, pleural or pericardial effusion, or ascites requiring repeated drainage more than once every 28 days; active or untreated central nervous system metastases; or left ventricular ejection fraction below the institutional lower limit of normal or $<$50%, whichever was lower. Patients were also excluded if they had received prior treatment with an MEK inhibitor. In addition, patients recruited to cohorts 1-3 were excluded if they had been previously treated with T-cell costimulating therapies or ICIs. Patients recruited to cohorts 1 and 4 were excluded if they had histologically confirmed recurrent or metastatic carcinoma of the nasopharynx and salivary gland or of nonsquamous histologies (e.g. mucosal melanoma).

Treatment

Patients in cohorts 1-6 received oral cobimetinib 60 mg once daily for the first 21 days followed by a 7-day rest for each 28-day cycle and intravenous infusions of atezolizumab 840 mg on days 1 and 15 of each cycle. Premedication was not permitted for the first infusion of atezolizumab; patients who experienced infusion-related reactions could receive premedication with antihistamines, antipyretics, and/or analgesics for subsequent atezolizumab infusions at the investigator's discretion. Treatment was continued until unacceptable toxicity or loss of clinical benefit, as determined by the investigator.

Outcomes and assessments

The primary efficacy endpoint was objective response rate (ORR), as determined by the investigators per RECIST version 1.1. Secondary efficacy endpoints were overall survival (OS; time from enrollment to death from any cause), progression-free survival (PFS; time from enrollment to first occurrence of disease progression or death from any cause), and disease control rate (DCR; proportion of patients with complete or partial response or stable disease at 16 weeks). Adverse events (AEs) and laboratory abnormalities were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version

4.0. Biomarker endpoints were assessment of outcomes according to baseline PD-L1 expression and tumor mutational burden (TMB).

Response was assessed by computed tomography or magnetic resonance imaging every 8 weeks. Biopsies were carried out at study entry to provide baseline tissue samples for biomarker analyses. Optional biopsies were carried out on day 15 (±5 days) of cycle 1 if the tumor was easily accessible and biopsy had minimal risk and caused minimal discomfort. Mandatory biopsies, unless not clinically feasible as assessed and documented by the investigator, were carried out within 14 days of disease progression or before the start of a new anticancer treatment, whichever was sooner. PD-L1 status and TMB were determined by central laboratory assessment. PD-L1 status was assessed by immunohistochemistry using the anti-human PD-L1 rabbit monoclonal antibody (SP142; Ventana Medical Systems, Oro Valley, AZ) and defined according to the proportion of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells as PD-L1 negative (<1%) or PD-L1 positive (≥1%). TMB was determined by targeted next-generation sequencing using the FoundationOne platform (Foundation Medicine, Cambridge, MA); TMB subgroups were defined as high (≥10 mutations/Mb) or low (<10 mutations/Mb).

Statistical analysis

COTEST was designed for hypothesis generation only. Enrollment to cohorts 1-6 was planned to be ∼20 patients per cohort. No power analysis was carried out because no formal hypothesis testing or inference analysis was carried out. Cohort-specified ORR and the corresponding 95% Clopper—Pearson confidence intervals (CIs) were calculated. PFS and OS were estimated using the Kaplan—Meier method, and 95% CIs were constructed with the Brookmeyer and Crowley method. Efficacy was assessed in the intention-to-treat population, which comprised all enrolled patients. The safety population included all patients who received one or more dose of the study medication. Biomarker analyses were carried out in patients with available biomarker data who received one or more dose of the study medication. The database lock date for analysis was 7 August 2020. Analyses were carried out using SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Results for cohorts 1-4 are reported herein. Cohorts 5 and 6 closed early due to slow recruitment ($n = 7$ in cohort 5 and $n = 3$ in cohort 6) and lack of efficacy in cohort 4. Consistent with what was seen in cohort 4, no responses were observed in the small number of patients enrolled in cohorts 5 and 6; these cohorts were therefore excluded from the analysis. Cohort 7 did not open for enrollment.

Patients were enrolled in cohorts 1-3 from November 2017 to July 2018 and in cohort 4 from August 2018 to May 2019. Cohorts 1, 2, and 3 enrolled 20, 20, and 17 patients, respectively, and cohort 4 enrolled 20 patients. The safety-evaluable population included 20, 19, and 17 patients in cohorts 1, 2, and 3, respectively, and 20 patients in cohort 4. One patient in cohort 2 did not receive any study treatment and was excluded from the safety and biomarker populations. The median follow-up was 11.3, 17.9, and 19.6 months in cohorts 1, 2, and 3, respectively, and 6.3 months in cohort 4. Baseline characteristics of patients in cohorts 1-4 are summarized in Table 1.

Efficacy

The best overall confirmed response by RECIST version 1.1 for each cohort is summarized in Table 2. The ORR was 20% (95% CI 0% to 40%) in cohort 1, 30% (95% CI 7% to 53%) in cohort 2, 18% (95% CI 0% to 39%) in cohort 3, and 0% (95% CI 0% to 3%) in cohort 4 (Table 2). All were partial responses. The DCR at 16 weeks was 50% (95% CI 26% to 74%), 40% (95% CI 16% to 64%), 24% (95% CI 0% to 47%), and 25% (95% CI 4% to 46%) in cohorts 1-4, respectively. The median PFS was 5.5 months (95% CI 2.1-14.8 months) in cohort 1, 3.4 months (95% CI 2.3-5.8 months) in cohort 2, 3.4 months (95% CI 1.8-4.2 months) in cohort 3, and 3.6 months (95% CI 2.0-5.1 months) in cohort 4 (Figure 1). The median OS was 16.8 months (95% CI 6.9-25.8 months) in cohort 1, 18.7 months (95% CI 11.0-26.2 months) in cohort 2, 21.7 months (95% CI 17.4 months-not estimable) in cohort 3, and 7.7 months (95% CI 4.0 months-not estimable) in cohort 4 (Figure 2).

Biomarker analysis

For outcomes by PD-L1 status, the biomarker analysis included 50 anti-PD-1/PD-L1 treatment-naive patients from cohorts 1-3, and 18 patients who had previously progressed on anti-PD-1/PD-L1 treatment from cohort 4. For outcomes by TMB, the TMB data were available for 33 anti-PD-1/PD-L1 treatment-naive patients from cohorts 1-3, and 18 patients who had previously progressed on anti-PD-1/PD-L1 treatment from cohort 4.

Among anti-PD-1/PD-L1 treatment-naive patients in cohorts 1-3, the median PFS was longer for patients with PD-L1-positive tumors ($n = 23$) compared with those with PD-L1-negative tumors ($n = 27$) [7.3 versus 2.3 months; hazard ratio 0.34 (95% CI 0.18-0.64); $P = 0.0008$; Supplementary Figures S1 and S2A, available at https://doi.org/10.1016/j.esmoop.2023.100877]. The median OS was not reached for patients with PD-L1-positive tumors versus 13.6 months for patients with PD-L1-negative tumors [hazard ratio 0.46 (95% CI 0.20-1.02); $P = 0.0478$; Supplementary Figure S2B, available at https://doi.org/10.1016/j.esmoop.2023.100877]. No statistically significant differences were observed between anti-PD-1/PD-L1 treatment-naive patients with TMB ≥10 mutations/Mb ($n = 5$) and TMB <10 mutations/Mb ($n = 28$) for PFS [median 4.2 versus 5.5 months; hazard ratio 1.74 (95% CI 0.63-4.81); $P = 0.3078$; Supplementary Figure S3A, available at https://doi.org/10.1016/j.esmoop.2023.100877] or OS [median 13.6 versus 19.7 months; hazard ratio 1.11 (95% CI 0.32-3.88); $P = 0.8661$; Supplementary Figure S3B, available at https://doi.org/10.1016/j.esmoop.2023.100877].

Table 1. Baseline demographics and disease characteristics in the intention-to-treat population

Demographics and disease characteristics	Anti-PD-1/PD-L1 treatment naive			Postprogression on anti-PD-1/PD-L1 treatment
	Cohort 1: SCCHN ($n = 20$)	Cohort 2: UC ($n = 20$)	Cohort 3: RCC ($n = 17$)	Cohort 4: SCCHN ($n = 20$)
Age, years				
Median (range)	60.5 (45-76)	69.0 (41-76)	61.0 (34-76)	60.5 (53-75)
18-64, *n* (%)	12 (60)	6 (30)	10 (59)	12 (60)
≥65, *n* (%)	8 (40)	13 (65)	7 (41)	8 (40)
Sex, *n* (%)				
Male	18 (90)	12 (60)	11 (65)	19 (95)
Female	2 (10)	8 (40)	6 (35)	1 (5)
Race, *n* (%)				
Asian	2 (10)	10 (50)	10 (59)	0
White	18 (90)	10 (50)	7 (41)	20 (100)
ECOG PS, *n* (%)				
0	9 (45)	6 (30)	6 (35)	5 (25)
1	11 (55)	13 (65)	11 (65)	15 (75)
2	0	1 (5)	0	0
PD-L1 status by SP142 assay, *n* (%)				
Positive (≥1%)	10 (50)	8 (40)	5 (29)	10 (50)
Negative (<1%)	8 (40)	11 (55)	9 (53)	8 (40)
Unknown/missing	2 (10)	1 (5)	3 (18)	2 (10)

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; UC, urothelial carcinoma.

Among anti-PD-1/PD-L1-treated patients following progression, no statistically significant differences were observed between patients who were PD-L1 positive ($n = 10$) and PD-L1 negative ($n = 8$) for PFS [median 4.6 versus 2.0 months; hazard ratio 0.39 (95% CI 0.12-1.24); $P = 0.1083$; Supplementary Figure S4A, available at https://doi.org/10.1016/j.esmoop.2023.100877] or OS [median 9.3 versus 4.8 months; hazard ratio 0.43 (95% CI 0.13-1.45); $P = 0.1746$; Supplementary Figure S4B, available at https://doi.org/10.1016/j.esmoop.2023.100877]. Similarly, no statistically significant differences were observed between patients with ≥10 mutations/Mb ($n = 5$) versus TMB <10 mutations/Mb ($n = 13$) for PFS [median 4.6 versus 3.5 months; hazard ratio 0.83 (95% CI 0.28-2.46); $P = 0.7405$]; Supplementary Figure S5A, available at https://doi.org/10.1016/j.esmoop.2023.100877) or OS [median 8.0 versus 7.4 months; hazard ratio 1.13 (95% CI 0.33-3.89); $P = 0.8457$; Supplementary Figure S5B, available at https://doi.org/10.1016/j.esmoop.2023.100877].

Safety

The median cobimetinib treatment duration was 1.9 months (range 0-26 months), 3.4 months (range 0-26 months), and 3.3 months (range 1-28 months) in cohorts 1-3, respectively, and 1.7 months (range 0-9) in cohort 4. The median cobimetinib dose intensity was 100% (range 22%-105%), 91% (range 36%-100%), and 70% (range 36%-100%) in cohorts 1-3, respectively, and 98% (range 62%-100%) in cohort 4.

The median atezolizumab treatment duration was 3.3 months (range 0-25 months), 5.0 months (range 0-26 months), and 3.3 months (range 0-28 months) in cohorts 1-3, respectively, and 1.9 months (range 0-9 months) in cohort 4. The median atezolizumab dose intensity was 100%

Table 2. Best confirmed overall response

Outcome	Anti-PD-1/PD-L1 treatment naive			Postprogression on anti-PD-1/PD-L1 treatment
	Cohort 1: SCCHN ($n = 20$)	Cohort 2: UC ($n = 20$)	Cohort 3: RCC ($n = 17$)	Cohort 4: SCCHN ($n = 20$)
Objective response rate, *n* (%)	4 (20)	6 (30)	3 (18)	0 (0)
95% CI	(0-40)	(7-53)	(0-39)	(0-3)
Complete response, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Partial response, *n* (%)	4 (20)	6 (30)	3 (18)	0 (0)
Stable disease, *n* (%)	8 (40)	6 (30)	6 (35)	7 (35)
Progressive disease, *n* (%)	6 (30)	6 (30)	8 (47)	5 (25)
Not evaluable, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Missing, *n* (%)	2 (10)	2 (10)	0 (0)	8 (40)
Disease control rate at 16 weeks, *n* (%)	10 (50)	8 (40)	4 (24)	5 (25)
95% CI	(26-74)	(16-64)	(0-47)	(4-46)

All values presented as *n* (%) unless stated otherwise.
CI, confidence interval; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma, SCCHN, squamous cell carcinoma of the head and neck; UC, urothelial carcinoma.

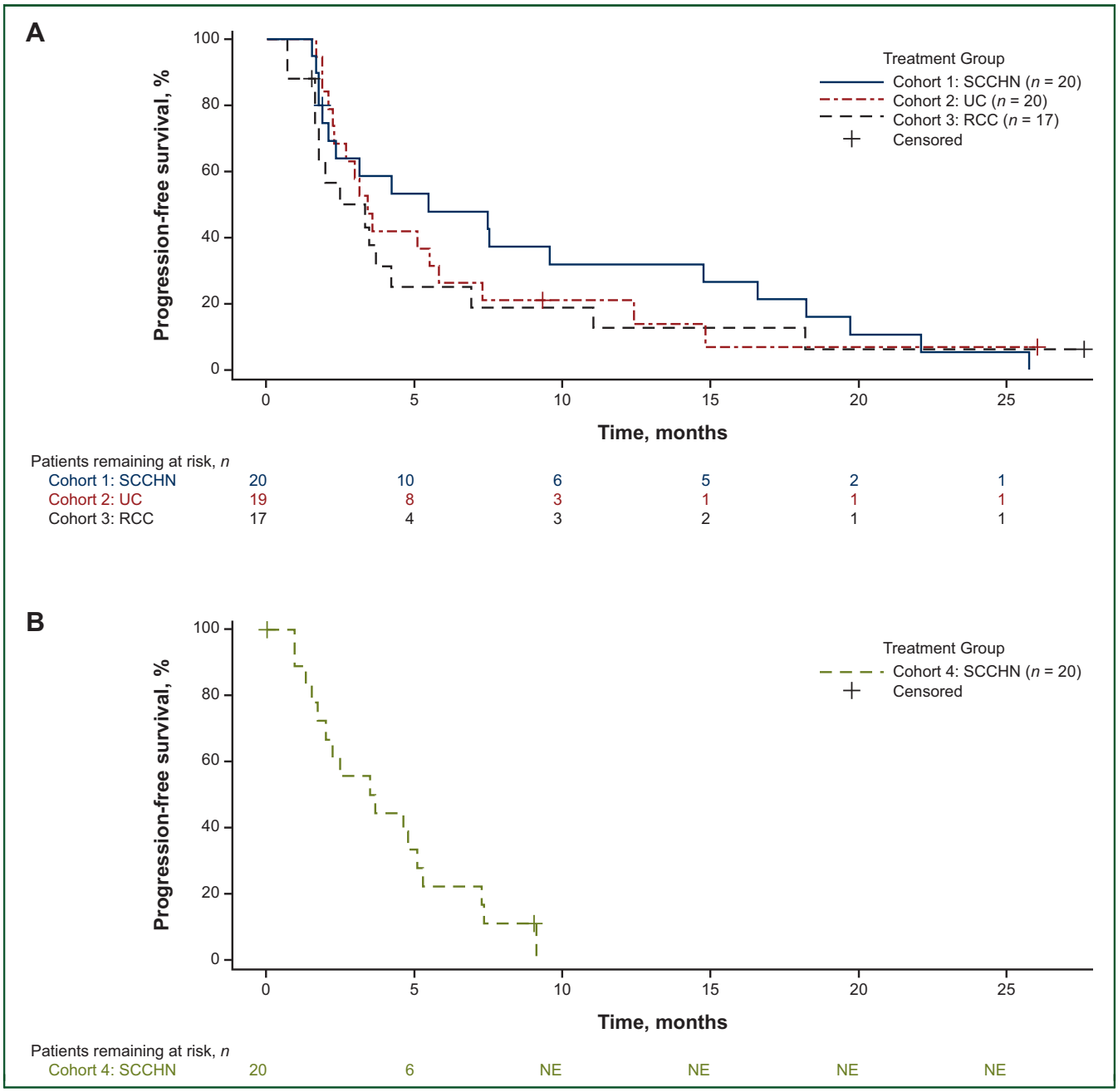

Figure 1. Kaplan–Meier curves for progression-free survival in (A) cohorts 1-3 (anti-PD-1/PD-L1 treatment naive) and (B) cohort 4 (following progression on anti-PD-1/PD-L1 treatment).

PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma, SCCHN, squamous cell carcinoma of the head and neck; UC, urothelial carcinoma.

(range 80%-102%), 93% (range 56%-100%), and 96% (range 57%-110%) in cohorts 1-3, respectively, and 100% (range 80%-100%) in cohort 4.

The incidence of AEs in each cohort is summarized in Table 3. All patients experienced one or more AEs. The most frequently reported AEs of any grade reported in ≥20% of patients across all cohorts were diarrhea, rash, fatigue, nausea, anemia, pyrexia, and vomiting (Table 3). The most commonly reported grade 3/4 AEs (≥5% of patients across all cohorts) were anemia, rash, and pneumonia (Table 3). In cohorts 1-3, 13 (65%), 9 (47%), and 8 (47%) patients, respectively, experienced one or more serious AEs. In cohort 4, 10 (50%) patients experienced one or more serious AEs. Three grade 5 AEs of pneumonia occurred in one patient each in cohorts 1, 2, and 4. One event of grade 5 pneumonia was assessed as related to atezolizumab by the investigator; the other two were considered unrelated to study treatment.

DISCUSSION

COTEST was a phase II, open-label, nonrandomized, multicohort study that evaluated the safety and potential mechanism of cobimetinib to sensitize advanced solid tumors to atezolizumab. Results suggest that the combination of cobimetinib plus atezolizumab had moderate activity in SCCHN (cohort 1) and urothelial carcinoma (cohort 2), weak

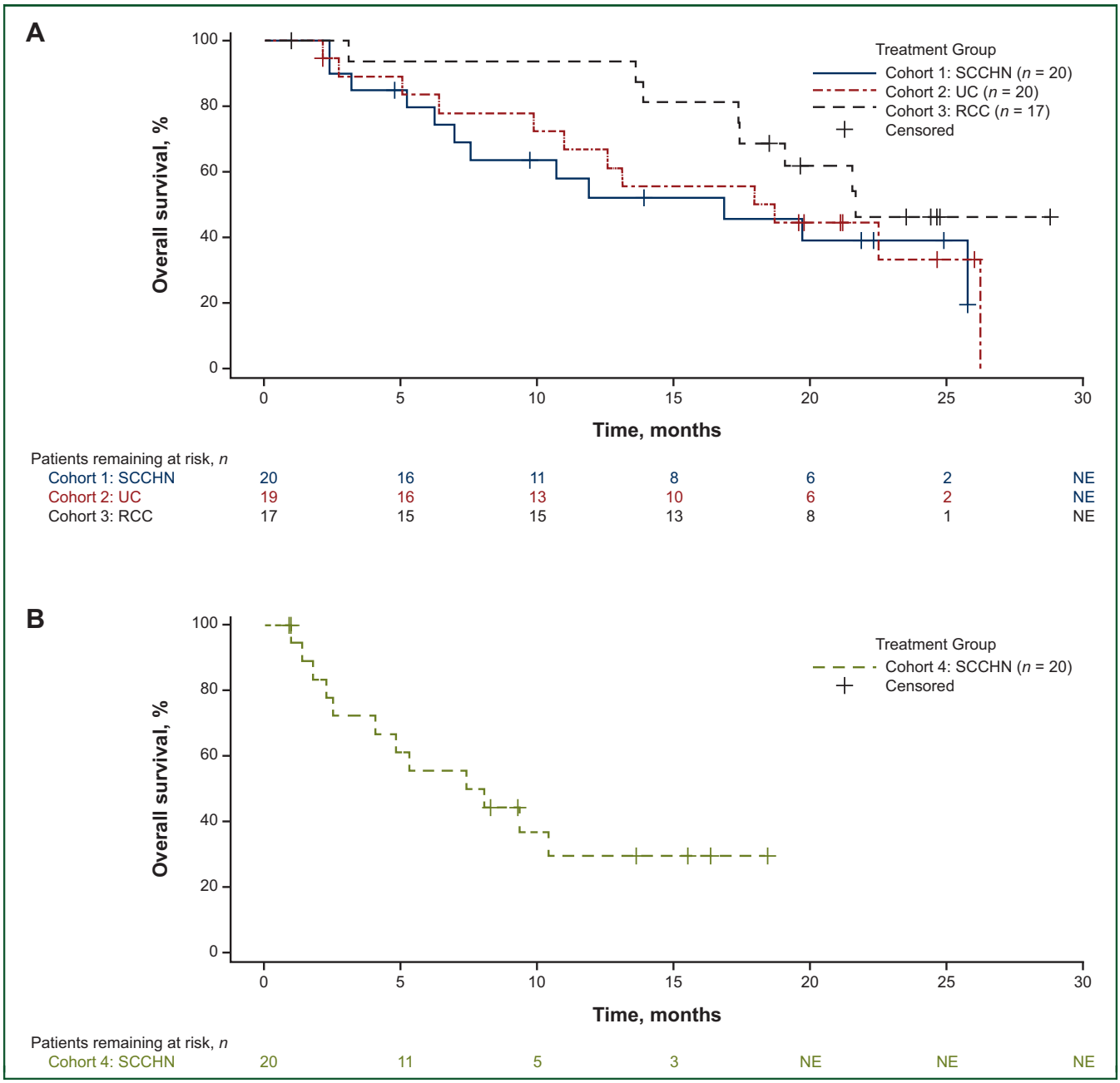

Figure 2. Kaplan–Meier curves for overall survival in (A) cohorts 1-3 (anti-PD-1/PD-L1 treatment naive) and (B) cohort 4 (following progression on anti-PD-1/PD-L1 treatment).

PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma, SCCHN, squamous cell carcinoma of the head and neck; UC, urothelial carcinoma.

activity in RCC (cohort 3), and minimal activity in checkpoint inhibitor treatment-experienced SCCHN (cohort 4).

For patients with anti-PD-1/PD-L1 treatment-naive SCCHN, cobimetinib plus atezolizumab provided a similar ORR (20%) to that observed with pembrolizumab monotherapy (17%), but a slightly longer median PFS (5.5 versus 2.3 months) and median OS (16.8 versus 11.6 months).[13] In patients with anti-PD-1/PD-L1 treatment-naive urothelial carcinoma, the observed ORR of 30% and the median PFS and OS of 3.4 and 18.6 months, respectively, with atezolizumab plus cobimetinib in the present study were higher/longer than that observed with atezolizumab alone in patients with metastatic urothelial carcinoma who had progressed after platinum-based chemotherapy in the phase III IMvigor211 trial (13%; 2.1 months and 11.1 months, respectively),[14] and in those who had progressed following up to three prior platinum- or nonplatinum-based treatments in the phase IIIB SAUL trial (13%; 2.2 months and 8.7 months).[15] In patients with anti-PD-1/PD-L1 treatment-naive RCC, the ORR of 21% with cobimetinib plus atezolizumab was comparable to that observed with the historical benchmark of cabozantinib (21%), whereas the median PFS (3.4 months) appeared shorter than that observed with cabozantinib (7.4 months).[16]

For patients who had progressed on anti-PD-1/PD-L1 treatment in this study, there was no evidence of activity or reversal

Table 3. Most common adverse events irrespective of causality in the safety population

Adverse event[a], *n* (%)	Anti-PD-1/PD-L1 treatment naive									Postprogression on anti-PD-1/PD-L1 treatment		
	Cohort 1: SCCHN ($n = 20$)			Cohort 2: UC ($n = 19$)			Cohort 3: RCC ($n = 17$)			Cohort 4: SCCHN ($n = 20$)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any	20 (100)	12 (60)	1 (5)	19 (100)	13 (68)	2 (11)	17 (100)	9 (53)	2 (12)	20 (100)	13 (65)	1 (5)
Diarrhea	7 (35)	0 (0)	0 (0)	11 (58)	0 (0)	0 (0)	10 (59)	1 (6)	0 (0)	13 (65)	0 (0)	0 (0)
Rash	9 (45)	0 (0)	0 (0)	9 (47)	1 (5)	0 (0)	12 (71)	2 (12)	0 (0)	5 (25)	0 (0)	0 (0)
Fatigue	6 (30)	0 (0)	0 (0)	9 (47)	0 (0)	0 (0)	5 (29)	1 (6)	0 (0)	5 (25)	0 (0)	0 (0)
Nausea	6 (30)	0 (0)	0 (0)	3 (16)	0 (0)	0 (0)	5 (29)	0 (0)	0 (0)	6 (30)	1 (5)	0 (0)
Anemia	9 (45)	5 (25)	0 (0)	6 (32)	4 (21)	0 (0)	4 (24)	2 (12)	0 (0)	2 (10)	1 (5)	0 (0)
Pyrexia	2 (10)	0 (0)	0 (0)	7 (37)	0 (0)	0 (0)	5 (29)	0 (0)	0 (0)	2 (10)	1 (5)	0 (0)
Vomiting	7 (35)	0 (0)	0 (0)	4 (21)	0 (0)	0 (0)	3 (18)	0 (0)	0 (0)	4 (20)	2 (10)	0 (0)
Blood CPK increased	4 (20)	0 (0)	0 (0)	7 (37)	2 (11)	0 (0)	3 (18)	1 (6)	0 (0)	1 (5)	0 (0)	0 (0)
Decreased appetite	4 (20)	0 (0)	0 (0)	7 (37)	0 (0)	0 (0)	3 (18)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	1 (5)	0 (0)	0 (0)	5 (26)	0 (0)	0 (0)	3 (18)	0 (0)	0 (0)	4 (20)	0 (0)	0 (0)
Stomatitis	2 (10)	0 (0)	0 (0)	5 (26)	0 (0)	0 (0)	2 (12)	0 (0)	0 (0)	4 (20)	0 (0)	0 (0)
Pruritus	2 (10)	0 (0)	0 (0)	3 (16)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	4 (20)	0 (0)	0 (0)
Dermatitis acneiform	0 (0)	0 (0)	0 (0)	2 (11)	0 (0)	0 (0)	3 (18)	1 (6)	0 (0)	5 (25)	0 (0)	0 (0)
Urinary tract infection	0 (0)	0 (0)	0 (0)	6 (32)	2 (11)	0 (0)	2 (12)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Dysphagia	4 (20)	2 (10)	0 (0)	2 (11)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	4 (20)	1 (5)	0 (0)
Weight decreased	2 (10)	0 (0)	0 (0)	3 (16)	1 (5)	0 (0)	1 (6)	0 (0)	0 (0)	4 (20)	0 (0)	0 (0)
Dyspnea	1 (5)	0 (0)	0 (0)	4 (21)	0 (0)	0 (0)	3 (18)	1 (6)	1 (6)	2 (10)	1 (5)	0 (0)
Dry skin	3 (15)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	4 (20)	0 (0)	0 (0)
Dyspepsia	2 (10)	0 (0)	0 (0)	4 (21)	0 (0)	0 (0)	3 (18)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypoalbuminemia	0 (0)	0 (0)	0 (0)	3 (16)	2 (11)	0 (0)	6 (35)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Dizziness	0 (0)	0 (0)	0 (0)	4 (21)	0 (0)	0 (0)	2 (12)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)
Hyponatremia	0 (0)	0 (0)	0 (0)	3 (16)	2 (11)	0 (0)	1 (6)	1 (6)	0 (0)	1 (5)	1 (5)	0 (0)
Pneumonia	3 (15)	2 (10)	0 (0)	2 (11)	1 (5)	0 (0)	2 (12)	1 (6)	0 (0)	2 (10)	1 (5)	0 (0)

CPK, creatine phosphokinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; UC, urothelial carcinoma.

[a]Adverse events of any grade occurring in ≥20% of patients in any cohort and grade 3/4 adverse events occurring in ≥10% of patients in any cohort are reported.

of anti-PD-1/PD-L1 resistance by adding cobimetinib to the atezolizumab regimen. Among patients with SCCHN, the ORR was 0% and the median PFS was 3.6 months relative to the historical benchmarks of 5.8% and 2.3 months, respectively, with standard chemotherapy.[17] Likewise, no activity was seen in the limited number of patients recruited into cohort 5 ($n = 7$) and cohort 6 ($n = 3$). Overall, no responses were seen for this combination in 30 anti-PD-1/PD-L1-resistant patients with SCCHN, urothelial carcinoma, or RCC.

These data are consistent with results of other clinical studies with this combination in patients with solid tumors.[12,18,19] Similarly, the combination did not improve the primary endpoint of OS versus regorafenib in heavily pretreated patients with metastatic colorectal cancer in a phase III study,[19] or the primary endpoint of PFS versus pembrolizumab in patients with *BRAF*^{V600} wild-type advanced melanoma in a phase III study.[18] Preclinical and early phase clinical data suggested significant potential for enhanced antitumor activity with the combination of an MEK inhibitor with ICIs.[5,6,12] Together with previous findings, the results of the COTEST study suggest at best only modest activity for this combination with evidence of increased toxicity over ICI alone. Further biomarker analysis may be needed to identify subgroups of patients in whom MEK inhibition may enhance the response to ICIs compared with monotherapy.

The safety profile of the combination observed in this study was consistent with that seen in other trials of cobimetinib and atezolizumab,[12,18,19] with the most commonly reported AEs being diarrhea, rash, and fatigue. No new safety signals were identified, and no unexpected immune-mediated AEs were observed in any of the cohorts.

The study has several limitations. The study was a non-randomized, open-label design. In addition, the response assessment was carried out by investigators and not an independent review committee. The sample size of groups was relatively small, which may have introduced bias and limits the confidence on estimates of efficacy.

Conclusions

Data from this study may suggest some benefit from the combination of cobimetinib plus atezolizumab in patients with anti-PD-1/PD-L1 treatment-naive SCCHN or urothelial carcinoma, but not in patients previously treated with anti-PD-1/PD-L1 treatment. The small patient numbers require that data should be interpreted with caution. No additional trials on cobimetinib plus atezolizumab in advanced solid tumors are currently planned.

ACKNOWLEDGMENTS

The authors thank Lieke Kusters for her contribution in designing and initiating the study and review of results. The authors also thank all patients and their families, and investigators and research teams who participated in this study. Medical writing and editorial support for this manuscript was provided by Nishad Parkar, PhD, and Melanie Sweetlove, MSc (ApotheCom, San Francisco, CA), and was funded by F. Hoffmann-La Roche Ltd.

FUNDING

This work was supported by F. Hoffmann-La Roche Ltd (no grant number). The sponsor collaborated with academic authors on study design and the collection, analysis, and interpretation of data. All drafts of the manuscript were prepared together with the authors, with professional editorial and writing assistance funded by the sponsor.

DISCLOSURE

All authors report nonfinancial support from Roche for the preparation of the manuscript. ES has received grants from Regeneron and Eli Lilly and is an advisory board member for Eisai, Exelixis, Regeneron, Eli Lilly, and Roche/BluePrint outside the submitted work. JLL is an advisory board member for Pfizer Korea, Ipsen Korea, Sanofi Aventis, Astellas Korea, BMS Korea, MSD, and Merck; has received grants from Pfizer Korea, Ipsen Korea, BMS Korea, MSD, Merck, Esai, Roche, AstraZeneca, Exelixis, and Seagen; has received personal fees from Pfizer Korea, Ipsen Korea, Sanofi Aventis, Novartis Korea, Astellas Korea, BMS Korea, MSD, and AstraZeneca; and has stock ownership with Merck, Amgen, Myovant Sciences, and Johnson & Johnson outside the submitted work. PRD has received a grant from Pfizer; has received personal fees from BMS, Merck/Pfizer, MSD, Roche, and Bayer outside the submitted work; has received travel support from Janssen; and has stock ownership with Alkermes. BK has received grants from Ono Pharmaceuticals, MSD Oncology, and AstraZeneca and has received personal fees from MSD Oncology, AstraZeneca, Genexine, Handok, and CBS Bio outside the submitted work. IC, KS, RA, and YY are employees and stockholders of Genentech/Roche. RH reports grants from MSD and Roche and personal fees from MSD, Roche, Nektar Pharmaceuticals, Janssen, Bayer, Astellas, and Pfizer outside the submitted work. TP reports grants and personal fees from Roche, AstraZeneca, BMS, Exelixis, Ipsen, Merck, MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, and Eisai; and personal fees from Incyte.

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).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was carried out in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and the study protocol was approved by the institutional review boards and/or an independent ethics committee at each study site. The institutional review boards of this study were Memorial Sloan Kettering Cancer Center Institutional Review Board (303071, 306949, 306974), Western Institutional Review Board (303115, 304982), Chesapeake IRB (303116), South Central — Oxford A Research Ethics Committee (303121, 303267, 311307), Seoul National Univ. Ethics Committee (303122), Asan Medical Center Ethics Committee (303124), EK an der Med. Fakultät d. (303129), AZ Groeninge Commissie voor Medische Ethiek (303132), Severance Hospital — Yonsei University (304256), and Medical Research Council, Ethics Committee for Clinical Pharmacology (304510, 304511, 304512). All patients provided written informed consent before participation in the study.

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