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ORIGINAL ARTICLE

Novel pembrolizumab-based treatments as first-line therapy in advanced clear-cell renal cell carcinoma: substudy 03A of the open-label, umbrella platform, phase I/II KEYMAKER-U03 trial☆

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Background: First-line triplet therapy may expand clinical benefit for advanced clear-cell renal cell carcinoma (ccRCC). The phase Ib/II KEYMAKER-U03 substudy 03A (NCT04626479) investigated novel pembrolizumab (pembro)-based regimens in this setting.

Patients and methods: Participants with advanced ccRCC and no prior systemic therapy were randomized 2 : 1 to quavonlimab (qmab)/pembro plus lenvatinib (lenva), favezelimab (fave)/pembro plus lenva, pembro plus lenva plus belzutifan (bel), and vibostolimab (vibo)/pembro plus bel or a concurrent reference treatment (pembro plus lenva). A safety lead-in of ∼10 participants occurred for all investigative treatments before randomization. Primary endpoints were objective response rate (ORR) per RECIST v1.1 by blinded independent central review in all randomized participants (excluding safety lead-in), and safety in all treated participants. Secondary endpoints included progression-free survival (PFS) and overall survival (OS).

Results: As of 31 March 2025, 393 participants were enrolled. Median follow-up for randomized participants across the five cohorts ranged between 16 and 39 months. The ORR was 80.6% [95% confidence interval (CI) 68.6% to 89.6%] with pembro plus lenva, 71.3% (95% CI 60.0% to 80.8%) with qmab/pembro plus lenva, 62.7% (95% CI 48.1% to 75.9%) with fave/pembro plus lenva, 77.5% (95% CI 66.8% to 86.1%) with pembro plus lenva plus bel, and 42.5% (95% CI 31.5% to 54.1%) with vibo/pembro plus bel. Median PFS was 26.3 months (95% CI 15.3-39.8 months) with pembro plus lenva, 18.0 months (95% CI 11.6-34.3 months) with qmab/pembro plus lenva, 26.0 months (95% CI 8.2-31.8 months) with fave/pembro plus lenva, 31.8 months [95% CI 26.3 months-not reached (NR)] with pembro plus lenva plus bel, and 15.2 months (95% CI 12.4 months-NR) with vibo/pembro plus bel. Median OS was not reached in any arm. Grade ≥3 treatment-related adverse events occurred in 71.0% (44/62) of participants treated with pembro plus lenva, 73.3% (66/90) with qmab/pembro plus lenva, 86.9% (53/61) with fave/pembro plus lenva, 70.0% (63/90) with pembro plus lenva plus bel, and 68.9% (62/90) with vibo/pembro plus bel.

Conclusions: Observed efficacy and safety of pembro plus lenva were confirmatory of prior observations for this combination. ORR was similar to reference for pembro plus lenva plus bel and qmab/pembro plus lenva, but not the other investigative arms. Further investigation of pembro plus lenva plus bel and qmab/pembro plus lenva versus pembro plus lenva is ongoing in the phase III LITESPARK-012 study.

Key words: pembrolizumab, renal cell carcinoma, lenvatinib, belzutifan

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INTRODUCTION

Doublet regimens including two immune checkpoint inhibitors (nivolumab plus ipilimumab) or an immune checkpoint inhibitor and a vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) have vastly improved outcomes for patients with previously untreated advanced clear-cell renal cell carcinoma (ccRCC) over historic single-agent VEGFR-TKI.[1,2] Nevertheless, between ∼50% and 70% of participants in the phase III clinical trials that established these regimens had progressive disease or died within 2 years of treatment initiation.[3-6] Triplet therapy may be one potential opportunity to further improve outcomes with first-line treatment.

A key challenge in developing triplet therapy is balancing improved efficacy with elevated toxicity and unmanageable safety. For example, in the phase III COSMIC-313 study, a triplet regimen of cabozantinib with nivolumab plus ipilimumab demonstrated improved progression-free survival (PFS) but a higher incidence of grade ≥3 treatment-related adverse events than nivolumab plus ipilimumab.[7,8] Overall survival (OS) was not improved for the triplet compared with nivolumab plus ipilimumab alone, and clinical benefit was potentially limited by a higher incidence of treatment discontinuation in the treatment arm versus the control arm (49% versus 26% of participants, respectively).[8] Therefore, individual treatment components within triplet therapy must be carefully selected to ensure an optimal benefit : risk ratio.

The potent and selective hypoxia-inducible factor-2α (HIF-2α) inhibitor belzutifan (bel) offers a novel mechanism of action to the treatment of advanced ccRCC and may be a potential candidate for combination with the anti-programmed cell death protein 1 inhibitor pembrolizumab (pembro) and VEGFR-TKI lenvatinib (lenva). Bel is approved as monotherapy for adult patients with advanced ccRCC following treatment with anti-programmed death-(ligand) 1 [PD-(L)1] therapy and one or more VEGF-TKI inhibitor (United States), and following anti-PD-(L)1 therapy and two or more VEGFR-targeted TKIs (European Union).[9,10] The safety profile of bel (both as monotherapy and in combination with VEGFR-TKI therapy) is manageable and distinct from current first-line advanced ccRCC therapies, and preliminary analyses of bel plus lenva in previously treated advanced RCC showed safety profiles that were consistent with each drug as monotherapy.[11-14] These results may support the potential inclusion of bel in triplet combinations.[11,12]

Other mechanisms of action that may be feasibly combined with pembro with or without lenva in the first-line treatment setting for advanced ccRCC include, but are not limited to, inhibition of the immune checkpoint cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) with a drug such as quavonlimab (qmab), inhibition of the immunomodulatory receptor lymphocyte-activation gene 3 (LAG-3) with a drug such as favezelimab (fave), and inhibition of the T-cell immunoglobulin and ITIM domain (TIGIT) receptor with a drug such as vibostolimab (vibo).[15-17] These therapies have complementary mechanisms of action to pembro and have been previously investigated with established doses in combination or coformulation with pembro. Addition of VEGFR inhibition (via lenva) to coformulations of these agents with pembro may further decrease immune suppression in the tumor microenvironment and improve clinical benefit.[18] The exploration of novel triplets that incorporate these coformulations but do not include VEGFR-TKI therapy would also be of potential interest.

We evaluated pembro-based triplet regimens as first-line therapy in advanced ccRCC in substudy 03A of the phase Ib/II KEYMAKER-U03 umbrella trial. We present the primary efficacy and safety results for four investigational regimens, including qmab coformulated with pembro (qmab/pembro) plus lenva, fave coformulated with pembro (fave/pembro) plus lenva, pembro plus lenva plus bel, and vibo coformulated with pembro (vibo/pembro) plus bel in participants with previously untreated, locally advanced or metastatic ccRCC.

PATIENTS AND METHODS

Study oversight

An institutional review board or other appropriate ethics body at each study center approved the protocol and all amendments. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. An internal data-monitoring committee was established by the sponsor to monitor participant safety and review futility interim results. The data-monitoring committee was composed of sponsor staff members who were not directly associated with the study; the committee reviewed treatment-level results every 6 months and made recommendations for discontinuation of each study intervention as relevant based on safety and risk/benefit considerations. The study was sponsored by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Participants

Eligible participants were ≥18 years old with histologically confirmed locally advanced or metastatic ccRCC measurable per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 with no prior systemic therapy for advanced RCC. Neoadjuvant or adjuvant therapy ≥12 months before treatment assignment was permitted. Participants also had to have a Karnofsky performance status score of ≥70%, adequate organ function, and adequately controlled blood pressure with or without medication (≤150/90 mmHg within 1 week of assignment). Exclusion criteria included clinically significant cardiovascular disease ≤12 months before start of study intervention, prior radiotherapy ≤2 weeks of study intervention (or radiation-related toxicities requiring corticosteroids), known active central nervous system metastases and/or carcinomatous meningitis, active infection requiring systemic therapy, and immunodeficiency or use of immunosuppressive therapy ≤7 days before start of study intervention. Participants provided written informed consent before enrollment.

Study design, randomization, and treatment

Substudy 03A of the phase Ib/II, rolling-arm, multicenter, open-label KEYMAKER-U03 study (NCT04626479) consisted of a safety lead-in phase of ∼10 participants for all investigative regimens, followed by a 2 : 1 randomization to an open investigative arm or the reference treatment arm. The study employed an adaptive design in which investigative arm(s) were added and/or inactivated from the study on a rolling basis (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.10.010). For each new investigative arm, additional reference-arm participants were enrolled to the reference arm as needed to maintain the 2 : 1 randomization ratio at any given time. Randomization was carried out by interactive voice response technology and stratified according to the International Metastatic RCC Database Consortium (IMDC) risk group (favorable versus intermediate versus poor), with the number of participants in the IMDC-favorable group within each arm capped at 20% of total enrollment.

Investigational treatment arms included the following: intravenous coformulated qmab (anti-CTLA-4)/pembro 25 mg/400 mg every 6 weeks (MK-1308A) plus oral lenva 20 mg daily; intravenous coformulated fave (anti-LAG-3)/pembro 800 mg/200 mg every 3 weeks (MK-4280A) plus oral lenva 20 mg daily; intravenous pembro 400 mg every 6 weeks plus oral lenva 20 mg daily plus oral bel (HIF-2α inhibitor) 120 mg daily; intravenous coformulated vibo (anti-TIGIT)/pembro 200 mg/200 mg every 3 weeks (MK-7684A) plus oral bel 120 mg daily. The reference-arm treatment consisted of intravenous pembro 400 mg every 6 weeks plus oral lenva 20 mg daily. Stepwise dose reduction of the lenva dose (from 20 mg to 14, 10, 8, and then 4 mg daily as needed before discontinuation) and bel dose (from 120 mg daily to 80 mg and then 40 mg before discontinuation) were permitted to manage adverse events. Re-escalation of bel was permitted with sponsor consultation if the reduced dose of bel was tolerated for ≥28 days without reappearance of the original toxicity, except reductions due to grade 3 symptomatic hypoxia. Lenva dose re-escalation was not permitted.

Pembro and pembro coformulations were planned to be continued for up to ∼2 years (≤17 cycles of 400 mg every 6 weeks or ≤35 cycles of 200 mg every 3 weeks). Reasons for discontinuation of one or more agents included disease progression, unacceptable toxicity, intercurrent illness preventing treatment, investigator decision, pregnancy, or withdrawal of consent, whichever occurred first. Study treatment could continue beyond disease progression with sponsor consultation, either indefinitely for oral therapy or up to the defined 2-year duration for immunotherapy. Reinitiation of pembro as a single agent could be considered for toxicities attributed to coformulations (up to the defined 2-year duration, including the duration of treatment with the coformulation).

The fave/pembro plus lenva arm enrollment ended early in January 2023 per the data-monitoring committee's recommendation; this decision was not based on any concerns around the safety of the coformulation and participants were permitted to stay on treatment if clinical benefit was observed. The clinical development programs for vibo/pembro and fave/pembro were discontinued by the sponsor in December 2024, based on the totality of study data across both programs. At that time, there were no longer any participants receiving fave/pembro. For the vibo/pembro plus bel arm, participants were required to discontinue the vibo/pembro coformulation; treatment could then be continued with pembro and bel.

Endpoints and assessments

The primary endpoints were objective response rate (ORR), defined as the proportion of participants who had a complete or partial response per RECIST v1.1 by blinded independent central review (BICR), and safety. Secondary endpoints were clinical benefit rate (defined as the proportion of participants who had a confirmed complete or partial response, or stable disease lasting ≥6 months), duration of response (DOR, time from first documented evidence of complete or partial response until disease progression or death due to any cause, whichever occurred first), and PFS (time from randomization to first documented disease progression or death due to any cause, whichever occurred first) assessed per RECIST v1.1 by BICR, as well as OS (time from randomization to death due to any cause). Exploratory endpoints included assessment of the best percentage change in the sum of diameters of the target lesions. Median duration of follow-up was defined as the time from randomization to the database cut-off date.

Tumor response assessments were conducted by computed tomography or magnetic resonance imaging and assessed per RECIST v1.1 at screening and then 12 weeks after treatment assignment. Subsequent scans were carried out every 6 weeks up to week 54 and every 12 weeks thereafter.

Dose-limiting toxicities (DLTs) were assessed within the first 21 days of treatment based on a protocol-specified list of toxicities and are defined in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.10.010. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Adverse events were reported up to 30 days after the last study treatment, and serious adverse events were reported up to 90 days after the last dose or up to 30 days if new anticancer therapy was initiated. Immune-mediated adverse events and infusion reactions were based on a list of preferred terms intended to capture known risks of pembro and were considered regardless of attribution to study treatment by the investigator. Protocol-specified events of clinical interest for bel included anemia, fatigue, nausea, dyspnea, dizziness, and hypoxia of any grade; anemia and hypoxia were managed as clinically indicated by the investigator and there were no protocol restrictions regarding erythropoietin-stimulating agent use. Clinically significant adverse events of lenva were based on a protocol-specified list of known risks of lenva therapy. Grade ≥2 cardiac dysfunction events were also considered events of clinical interest.

Statistical analysis

Efficacy endpoints for each treatment (ORR, clinical benefit rate, median PFS, and median OS) were assessed in all

randomized participants; median PFS and median OS for the reference arm were assessed in concurrently randomized participants. DOR was assessed in all randomized participants who had a confirmed complete or partial response. A sample size of ∼80 participants in each investigative arm was calculated to power a lower 95% confidence interval (CI) bound of 59% to 64% for an observed ORR range of 70%-75%, and 40 participants in the reference arm were calculated for a lower 95% CI bound of 38% to 43% per an observed ORR of 55%-60%. Point estimates and 95% CIs for ORR were calculated using the Clopper—Pearson methodology. The Kaplan—Meier methodology was used to estimate DOR, PFS, and OS, as well as associated 95% CIs for medians and rates at select time points. In this estimation study, all efficacy comparisons were exploratory, and no formal hypothesis testing was planned. Hazard ratios (HRs) for PFS and OS were *ad hoc* and estimated for all randomized participants in each investigative regimen arm against concurrently enrolled participants in the reference arm.

Safety was assessed in all participants who received one or more dose of investigative study treatment or reference therapy, including participants enrolled in the safety lead-in phase. A DLT rate of 30% per the modified toxicity probability interval evaluation criteria was used in the safety lead-in phase for dose determination for the efficacy phase.[19]

Statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Participant disposition

A total of 393 participants (including safety lead-in) were enrolled in substudy 03A: reference arm pembro plus lenva (total $n = 62$), qmab/pembro plus lenva ($n = 90$), fave/pembro plus lenva ($n = 61$, due to early stoppage of enrollment), pembro plus lenva plus bel ($n = 90$), or vibo/pembro plus bel ($n = 90$). Median (range) follow-up time from allocation to the data cut-off date (31 March 2025) in all treated participants was 21.2 months (11.9-44.4 months) in the reference arm, 24.0 months (13.5-48.2 months) for qmab/pembro plus lenva, 41.8 months (28.8-50.8 months) for fave/pembro plus lenva, 25.7 months (14.1-46.5 months) for pembro plus lenva plus bel, and 16.9 months (11.8-26.7 months) for vibo/pembro plus bel. Baseline demographics and disease characteristics were generally balanced across all arms (Table 1). At the time of data cut-off, 31 (50.0%) participants in the reference arm, 53 (58.9%) in the qmab/pembro plus lenva arm, 49 (80.3%) in the fave/pembro plus lenva arm, 36 (40.0%) in the pembro plus lenva plus bel arm, and 48 (53.3%) in the vibo/pembro plus bel arm had discontinued study therapy; progressive disease was the most common reason for discontinuation in all arms of the study (Figure 1). Summary of treatment exposure is shown in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.10.010; median (range) number of study treatment cycles was 11 (1-32) for the reference arm, 12 (1-34) for qmab/pembro plus lenva, 12 (1-30) for fave/pembro plus lenva, 14 (1-33) for pembro plus lenva plus bel, and 9 (1-19) for vibo/pembro plus bel. The median duration of therapy ranged from 12.6 months (range 0.7-26.4 months) with vibo/pembro plus bel to 19.8 months (range 0.6-45.7 months) with pembro plus lenva plus bel (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.10.010). Prior adjuvant therapy was received by one participant in the reference arm (sorafenib), two in the qmab/pembro plus lenva arm (nivolumab plus ipilimumab and sunitinib), three in the fave/pembro plus lenva arm (axitinib, placebo in a clinical study, and pembrolizumab), one in the pembro plus lenva plus bel arm (sorafenib), and one in the vibo/pembro plus bel arm (durvalumab plus tremelimumab).

Efficacy

The primary efficacy endpoint of ORR by BICR per RECIST v1.1 was 80.6% (95% CI 68.6% to 89.6%) for the reference treatment, 71.3% (95% CI 60.0% to 80.8%) for qmab/pembro plus lenva, 62.7% (95% CI 48.1% to 75.9%) for fave/pembro plus lenva, 77.5% (95% CI 66.8% to 86.1%) for pembro plus lenva plus bel, and 42.5% (95% CI 31.5% to 54.1%) for vibo/pembro plus bel (Table 2). Complete responses were observed with all regimens (Table 2). Best percentage change in lesion size for all treatment arms in this study are shown in Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.10.010. Beyond the primary endpoint of ORR, efficacy results for all treatment arms are shown in the tables and figures, but the main text will focus on the reference arm, qmab/pembro plus lenva, and pembro plus lenva plus bel. Clinical benefit rate was 88.7% (95% CI 78.1% to 95.3%), 75.0% (95% CI 64.1% to 84.0%), and 83.8% (95% CI 73.8% to 91.1%), respectively (Table 2). Median DOR is presented in Figure 2. Median time to response was ∼3 months across all arms, in line with the first planned radiological assessment after start of study therapy (Figure 2).

At the time of data cut-off, documented disease progression or death had occurred in 33.8% of 80 participants in the pembro plus lenva plus bel arm and ∼50% of participants in each of the other treatment arms (Table 2 and Figure 3). Pembro plus lenva (reference) was associated with a median PFS of 26.3 months and a 24-month estimated PFS rate of 52.9%. For qmab/pembro plus lenva, median PFS was 18.0 months and the 24-month estimated PFS rate was 46.0% (HR 0.96 versus concurrent reference of 41 participants, 95% CI 0.57-1.61). For pembro plus lenva plus bel, median PFS was 31.8 months and the 24-month estimated PFS rate was 67.1% (HR 0.45 versus concurrent reference of 37 participants, 95% CI 0.25-0.83).

Deaths occurred in 22.6% of participants in the reference arm, 27.5% with qmab/pembro plus lenva, and 16.3% with pembro plus lenva plus bel. Median OS was not reached in any arm (Figure 4). The estimated proportion of participants alive at 24 months was 76.5% (95% CI 60.2% to 86.9%) for the reference arm, 73.3% (95% CI 60.4% to 82.6%) for qmab/pembro plus lenva, and 85.5% (95% CI 73.4% to 92.4%) for pembro plus lenva plus bel. HRs for OS against concurrently enrolled participants in the reference were not presented due to immature data and the limited number of available events.

Table 1. Participant demographics and clinical characteristics at baseline

	Qmab/pembro plus lenva *n* = 90	Fave/pembro plus lenva *n* = 61	Pembro plus lenva plus bel *n* = 90	Vibo/pembro plus bel *n* = 90	Reference: pembro plus lenva *n* = 62
Age, years, median (range)	60 (36-81)	60 (40-82)	61 (38-84)	63 (37-83)	61 (39-81)
<65 years, *n* (%)	59 (65.6)	40 (65.6)	55 (61.1)	50 (55.6)	41 (66.1)
Sex, *n* (%)					
Male	68 (75.6)	38 (62.3)	69 (76.7)	67 (74.4)	49 (79.0)
Female	22 (24.4)	23 (37.7)	21 (23.3)	23 (25.6)	13 (21.0)
Race, *n* (%)					
American Indian or Alaska Native	1 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.6)
Asian	11 (12.2)	17 (27.9)	7 (7.8)	0 (0.0)	4 (6.5)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Multiple	2 (2.2)	0 (0.0)	1 (1.1)	3 (3.3)	0 (0.0)
Native Hawaiian or other Pacific Islander	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	71 (78.9)	38 (62.3)	78 (86.7)	84 (93.3)	53 (85.5)
Missing	4 (4.4)	6 (9.8)	3 (3.3)	3 (3.3)	3 (4.8)
Ethnicity, *n* (%)					
Hispanic or Latino	29 (32.2)	1 (1.6)	26 (28.9)	45 (50.0)	20 (32.3)
Not Hispanic or Latino	55 (61.1)	54 (88.5)	54 (60.0)	40 (44.4)	38 (61.3)
Not reported or unknown	6 (6.7)	6 (9.8)	10 (11.1)	5 (5.6)	4 (6.5)
Region, *n* (%)					
EU	26 (28.9)	22 (36.1)	31 (34.4)	28 (31.1)	24 (38.7)
Non-EU	64 (71.1)	39 (63.9)	59 (65.6)	62 (68.9)	38 (61.3)
ECOG performance status, *n* (%)					
0	54 (60.0)	36 (59.0)	50 (55.6)	44 (48.9)	31 (50.0)
1	35 (38.9)	25 (41.0)	40 (44.4)	44 (48.9)	30 (48.4)
2	1 (1.1)	0 (0.0)	0 (0.0)	2 (2.2)	1 (1.6)
KPS, *n* (%)					
90/100	70 (77.8)	44 (72.1)	70 (77.8)	58 (64.4)	48 (77.4)
70/80	20 (22.2)	17 (27.9)	20 (22.2)	32 (35.6)	14 (22.6)
IMDC risk category, *n* (%)					
Favorable	20 (22.2)	17 (27.9)	18 (20.0)	20 (22.2)	14 (22.6)
Intermediate	60 (66.7)	36 (59.0)	62 (68.9)	53 (58.9)	39 (62.9)
Poor	10 (11.1)	8 (13.1)	10 (11.1)	17 (18.9)	9 (14.5)
Prior nephrectomy, *n* (%)	61 (67.8)	43 (70.5)	54 (60.0)	52 (57.8)	36 (58.1)
Number of organs involved, *n* (%)					
1	14 (15.6)	15 (24.6)	18 (20.0)	20 (22.2)	11 (17.7)
≥2	72 (80.0)	45 (73.8)	71 (78.9)	67 (74.4)	49 (79.0)
Missing	4 (4.4)	1 (1.6)	1 (1.1)	3 (3.3)	2 (3.2)
Sites of metastasis, *n* (%)					
Lung	62 (68.9)	44 (72.1)	63 (70.0)	62 (68.9)	40 (64.5)
Lymph node	47 (52.2)	27 (44.3)	46 (51.1)	34 (37.8)	32 (51.6)
Bone	27 (30.0)	17 (27.9)	30 (33.3)	39 (43.3)	24 (38.7)
Liver	12 (13.3)	14 (23.0)	12 (13.3)	15 (16.7)	9 (14.5)
Adrenal gland	13 (14.4)	5 (8.2)	10 (11.1)	12 (13.3)	6 (9.7)

Bel, belzutifan; ECOG, Eastern Cooperative Oncology Group; EU, European Union; fave, favezelimab; IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; lenva, lenvatinib; pembro, pembrolizumab; qmab, quavonlimab; vibo, vibostolimab.

Safety

DLTs occurred in 3 (5.4%) DLT-assessable participants in the reference arm, 2 (2.5%) in the qmab/pembro plus lenva arm, 12 (21.1%) in the fave/pembro plus lenva arm, and 2 (2.3%) in the vibo/pembro plus bel arm; no DLTs were reported with pembro plus lenva plus bel (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.10.010). Treatment-related adverse events led to any study therapy discontinuation in 19 (30.6%) participants within the reference arm, 31 (34.4%) with qmab/pembro plus lenva, 23 (37.7%) with fave/pembro plus lenva, 22 (24.4%) with pembro plus lenva plus bel, and 28 (31.1%) with vibo/pembro plus bel (Table 3). Treatment-emergent adverse events led to dose reduction in 46 (74.2%) participants within the reference arm, 59 (65.6%) with qmab/pembro plus lenva, 28 (45.9%) with fave/pembro plus lenva, 60 (66.7%) with pembro plus lenva plus bel, and 30 (33.3%) with vibo/pembro plus bel.

All participants experienced treatment-related adverse events; grade ≥3 events were reported in 71.0% of participants with the reference treatment, 73.3% with qmab/pembro plus lenva, 86.9% with fave/pembro plus lenva, 70.0% with pembro plus lenva plus bel, and 68.9% with vibo/pembro plus bel (Table 3, and Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.10.010). Hypertension was the most common grade ≥3 treatment-related adverse event with lenva-containing regimens (incidence range of 26.7%-33.9%). Grade ≥3 anemia was most common with bel-containing regimens (incidence range of 24.4%-33.3%; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.10.010). Serious treatment-related adverse events occurred in 30.6% of participants in the reference arm, 34.4% in the qmab/pembro plus lenva arm, 36.1% in the fave/pembro plus lenva arm, 22.2% in the pembro plus lenva plus bel arm, and 27.8% in the vibo/pembro plus bel arm (Table 3). Four treatment-related

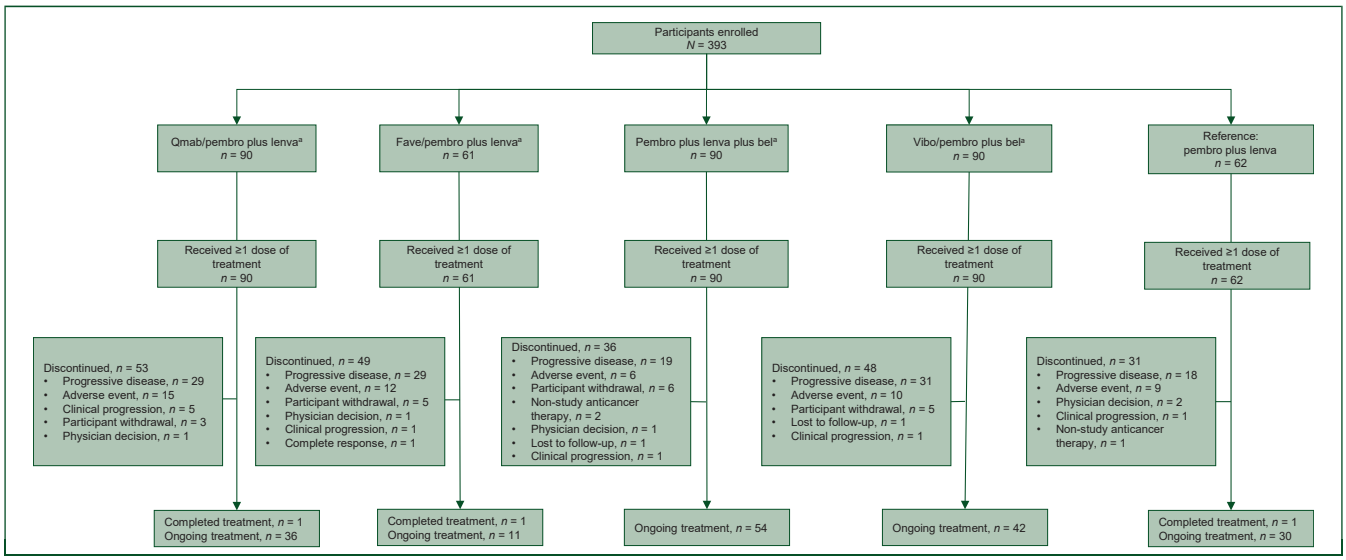

Figure 1. CONSORT diagram.
Bel, belzutifan; fave, favezelimab; lenva, lenvatinib; pembro, pembrolizumab; qmab, quavonlimab; vibo, vibostolimab.
[a]Includes a safety run-in phase of 10 participants for each investigative arm.

deaths were reported: one case each of enterocolitis and immune-mediated enterocolitis in the reference arm, one case of diabetic ketoacidosis in the fave/pembro plus lenva arm, and one case of pneumonitis with pembro plus lenva plus bel.

Immune-mediated adverse events and infusion reactions are summarized in Supplementary Tables S4 and S5, available at https://doi.org/10.1016/j.annonc.2025.10.010; the most common immune-mediated event was hypothyroidism (incidence range 23.3%-61.3%). Summaries of protocol-defined events of clinical interest observed with bel and lenva-associated clinically significant adverse events are presented in Supplementary Tables S6 and S7, available at https://doi.org/10.1016/j.annonc.2025.10.010, respectively. Events of clinical interest related to cardiac dysfunction occurred in three participants in the pembro

Table 2. Key efficacy endpoint data by BICR per RECIST v1.1 in all randomized participants

Participants *n* (%)	Efficacy population				
	Qmab/pembro plus lenva *n* = 80	Fave/pembro plus lenva *n* = 51	Pembro plus lenva plus bel *n* = 80	Vibo/pembro plus bel *n* = 80	Reference: pembro plus lenva *n* = 62
Median follow-up (range), months	22.1 (13.5-40.6)	39.2 (28.8-44.6)	23.4 (14.1-41.0)	16.4 (11.8-23.4)	21.2 (11.9-44.4)
Objective response rate, % (95% CI)	71.3 (60.0-80.8)	62.7 (48.1-75.9)	77.5 (66.8-86.1)	42.5 (31.5-54.1)	80.6 (68.6-89.6)
Clinical benefit rate, % (95% CI)[a]	75.0 (64.1-84.0)	66.7 (52.1-79.2)	83.8 (73.8-91.1)	63.8 (52.2-74.2)	88.7 (78.1-95.3)
Confirmed best objective response, *n* (%)					
Complete response	5 (6.3)	5 (9.8)	10 (12.5)	4 (5.0)	4 (6.5)
Partial response	52 (65.0)	27 (52.9)	52 (65.0)	30 (37.5)	46 (74.2)
Stable disease[b]	14 (17.5)	12 (23.5)	12 (15.0)	32 (40.0)	8 (12.9)
Progressive disease	7 (8.8)	4 (7.8)	2 (2.5)	12 (15.0)	3 (4.8)
Not evaluable[c]	0 (0.0)	1 (2.0)	1 (1.3)	0 (0.0)	0 (0.0)
No evidence of disease[d]	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
No assessment[e]	2 (2.5)	1 (2.0)	3 (3.8)	2 (2.5)	1 (1.6)
Median duration of response (range), months	25.0 (2.4 to 37.1+)	26.3 (1.4+ to 34.4+)	33.4 (2.6 to 37.6+)	14.0 (2.7+ to 18.2+)	25.6 (1.4+ to 41.2+)
Median progression-free survival (95% CI), months	18.0 (11.6-34.3)	26.0 (8.2-31.8)	31.8 (26.3-NR)	15.2 (12.4-NR)	26.3 (15.3-39.8)
24-month progression-free survival rate (95% CI), %	46.0 (33.0-58.1)	53.4 (37.9-66.7)	67.1 (53.0-77.9)	NR (NR-NR)	52.9 (36.8-66.7)

Bel, belzutifan; BICR, blinded independent central review; CI, confidence internal; fave, favezelimab; lenva, lenvatinib; NR, not reached; pembro, pembrolizumab; qmab, quavonlimab; RECIST; Response Evaluation Criteria in Solid Tumors; vibo, vibostolimab.
[a]Includes participants with complete response, partial response, or stable disease of ≥6 months.
[b]Includes participants with stable disease and participants with non-complete response/non-progressive disease.
[c]Insufficient data for assessment of response per RECIST v1.1.
[d]No lesions were identified at baseline assessment, and there remained no lesions at post-baseline assessment.
[e]No post-baseline assessment available on the data cut-off date.

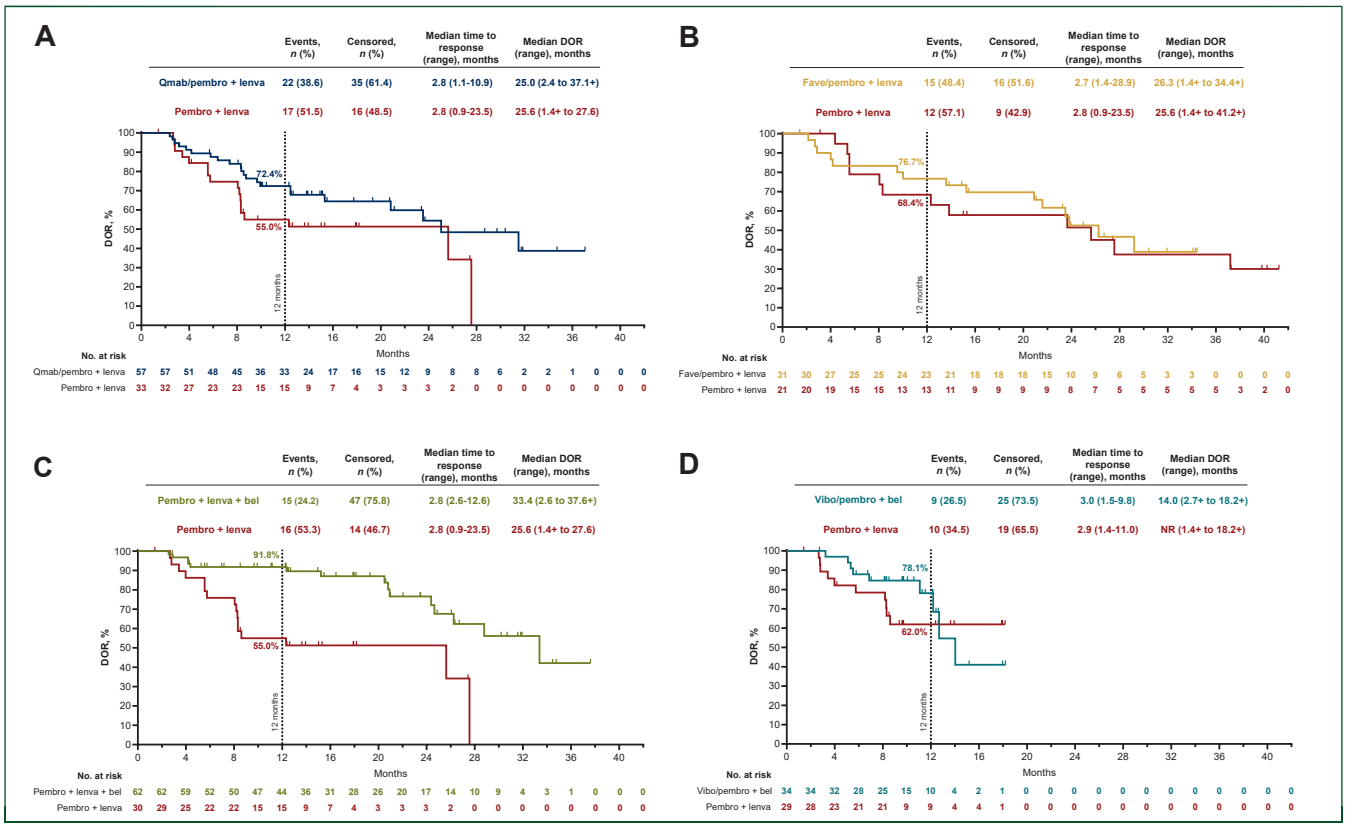

Figure 2. DOR per RECIST v1.1 by BICR in all concurrently randomized participants. Panels depict results from participants with a confirmed response who received (A) qmab/pembro plus lenva, (B) fave/pembro plus lenva, (C) pembro plus lenva plus bel, and (D) vibo/pembro plus bel. Tick marks represent data censored at the last time the participant was known to have a confirmed response. Reference arm for each panel includes concurrently randomized participants.
Bel, belzutifan; BICR, blinded independent central review; DOR, duration of response; fave, favezelimab; lenva, lenvatinib; NR, not reached; pembro, pembrolizumab; qmab, quavonlimab; RECIST, Response Evaluation Criteria in Solid Tumors; vibo, vibostolimab.

plus lenva plus bel arm (grade 2 and grade 3 cardiac failure, both considered treatment-related, and congestive cardiac failure considered unrelated to treatment); none were reported in the reference or other treatment arms.

DISCUSSION

In substudy 03A, objective responses were observed in the majority of participants (~63%-81%) with previously untreated advanced ccRCC across all pembro plus lenva-containing regimens (including the reference arm). The qmab/pembro plus lenva and pembro plus lenva plus bel regimens yielded a similar ORR to the reference arm in substudy 03A; responses were potentially less favorable with fave/pembro plus lenva and vibo/pembro plus bel compared with pembro plus lenva. The reference treatment of pembro plus lenva within this study had numerically the highest observed ORR and appeared to outperform prior results for this combination in the phase III CLEAR/KEYNOTE-581 study (ORR of 71%).[20] Baseline characteristics in the present study appear similar to those reported in CLEAR/KEYNOTE-581, with the possible exception of a slightly lower median age in substudy 03A (61 years for the reference arm in substudy 03A, and 64 years in the pembro plus lenva arm of CLEAR).[6] Therefore, reasons for the higher-than-expected ORR in the reference arm were not directly identifiable. Notably, ORR 95% CIs were wide across treatment arms (in accordance with the small sample sizes reported here) and overlap with historic ORR benchmarks for the doublet, suggesting no meaningful difference.[6]

Results were hypothesis-generating only and are to be interpreted with caution due to the exploratory nature of this study. Formal comparisons for PFS were not powered as evidenced by the wide CIs for medians and HRs. While conclusions are thereby limited, the triplet of pembro plus lenva with added bel, but not the other investigative arms, may have been associated with a higher proportion of complete responses, prolonged DOR, and prolonged PFS compared with pembro plus lenva. Specifically, Kaplan—Meier curves of PFS for pembro plus lenva with or without bel showed separation at ~8 months after randomization. Future investigations may reveal whether bel has a possible role in promoting durable antitumor activity and delaying disease progression rather than an upfront increase in initial ORR. OS results were not mature at this primary readout (total OS event rates between 16% and 39% across treatment arms). Based on reports for other anti-CTLA-4 antibodies such as ipilimumab, the duration of study follow-up may have been insufficient to detect long-term contributions to efficacy (including OS) by the qmab

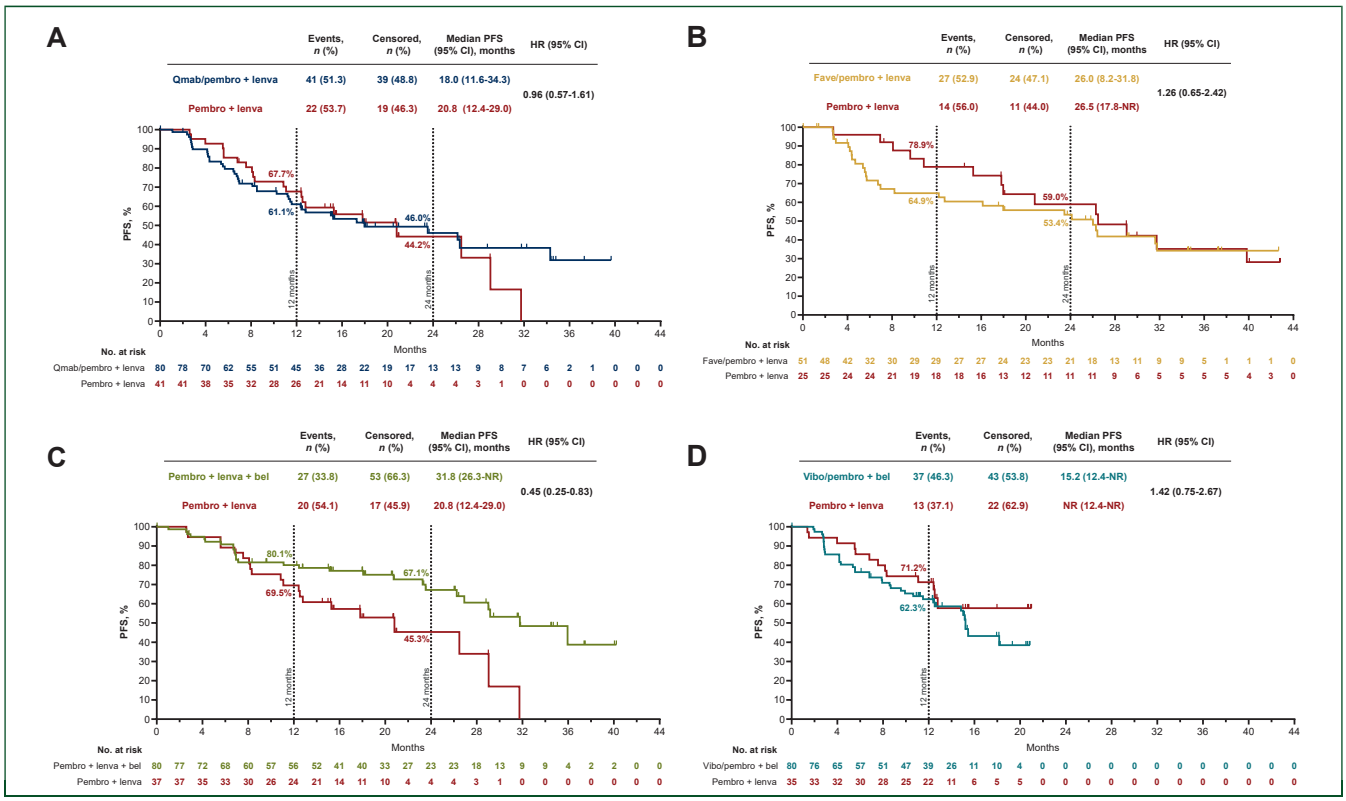

Figure 3. PFS per RECIST v1.1 by BICR in all concurrently randomized participants. Panels depict results for (A) qmab/pembro plus lenva, (B) fave/pembro plus lenva, (C) pembro plus lenva plus bel, and (D) vibo/pembro plus bel versus concurrent reference-arm participants. Tick marks represent data censored at the last time the participant was known to be alive and progression free. Reference arm for each panel includes concurrently randomized participants. HRs were *ad hoc* and calculated against concurrent reference-arm participants.
Bel, belzutifan; BICR, blinded independent central review; CI, confidence interval; fave, favezelimab; HR, hazard ratio; lenva, lenvatinib; NR, not reached; pembro, pembrolizumab; PFS, progression-free survival; qmab, quavonlimab; RECIST, Response Evaluation Criteria in Solid Tumors; vibo, vibostolimab.

component of the qmab/pembro plus lenva regimen.[5] These open questions will be addressed by the phase III LITESPARK-012 trial of first-line pembro plus lenva plus bel or qmab/pembro plus lenva versus pembro plus lenva in advanced RCC.[21]

Safety profiles for all investigative study regimens were generally consistent with the profiles of the individual drugs, and with that of the reference treatment.[12,15-17,20,22] No notable safety signals or DLTs were reported with the addition of bel to pembro plus lenva as compared with the reference regimen. The safety profile of qmab/pembro plus lenva was largely similar to the reference treatment. Fave/pembro plus lenva had a higher incidence of grade $\geq$3 and serious treatment-related adverse events, as well as treatment-related adverse events leading to treatment discontinuation. The vibo/pembro plus bel arm had a similar overall safety profile to the reference treatment but had the lowest proportion of treatment-emergent adverse events leading to dose reduction across arms, consistent with the lack of a lenva component within that regimen. With the exception of fave/pembro plus lenva, incidence of grade $\geq$3 treatment-related adverse events across arms was similar to rates observed with the standard-of-care pembro plus lenva doublet in CLEAR (72%) and for the triplet investigated in COSMIC-313 (73%).[6,7,20] Treatment-related adverse events leading to discontinuation of any study therapy for the three other arms were similar to pembro plus lenva in CLEAR (36%), and, importantly, lower than rates observed for the triplet in COSMIC-313 (45%).

In conclusion, these results support the established efficacy and safety of standard-of-care pembro plus lenva in advanced ccRCC and the feasibility of investigating first-line triplet regimens in a platform design against an active reference.[21]

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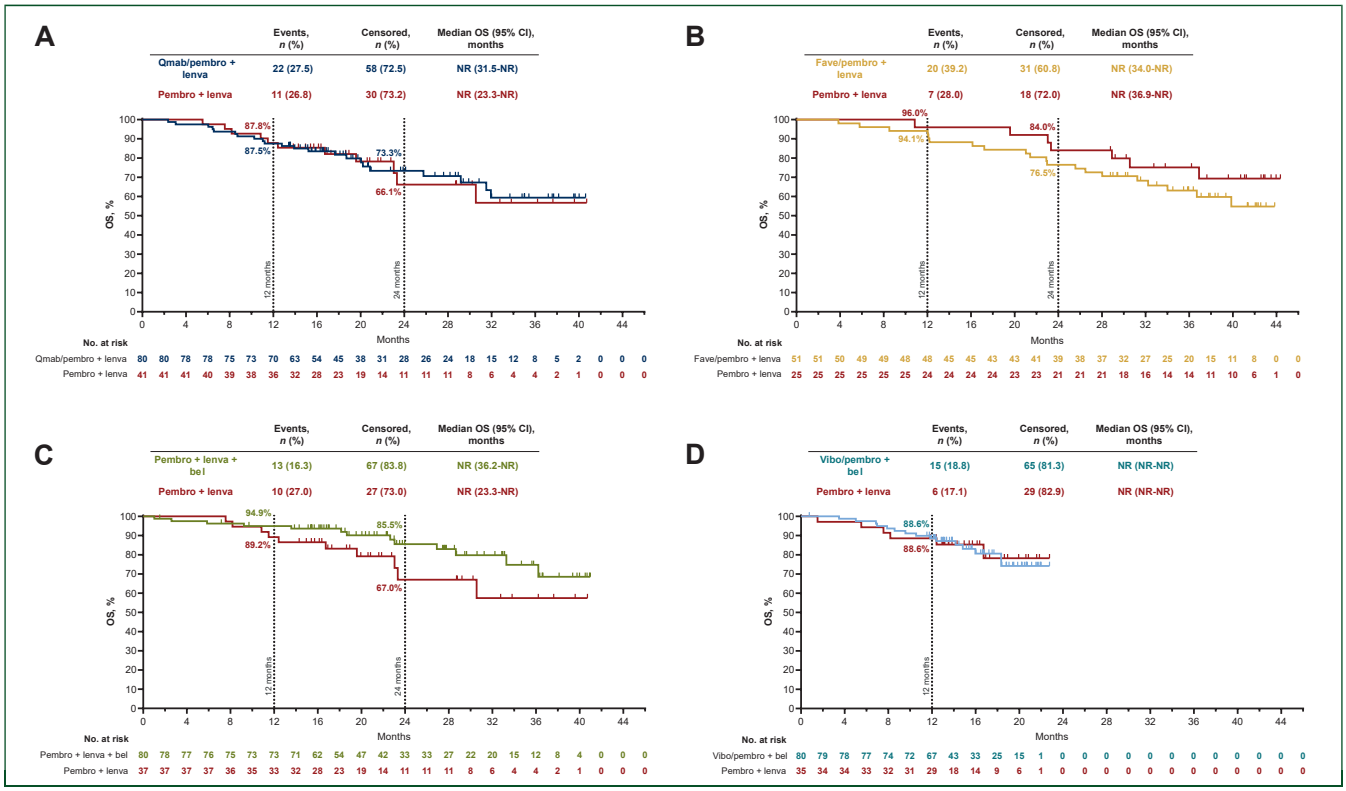

Figure 4. OS in all randomized participants. Panels depict results from participants who received (A) qmab/pembro plus lenva, (B) fave/pembro plus lenva, (C) pembro plus lenva plus bel, and (D) vibo/pembro plus bel. Tick marks represent data censored at the last time the participant was known to be alive. Reference arm for each panel includes concurrently randomized participants.
Bel, belzutifan; CI, confidence interval; fave, favezelimab; lenva, lenvatinib; NR, not reached; pembro, pembrolizumab; OS, overall survival; qmab, quavonlimab; vibo, vibostolimab.

DISCLOSURE

CS reports advisory board participation for Astellas, AstraZeneca, Bristol Myers Squibb (Inst), Ipsen, and MSD; travel accommodations from Bayer; speakers' bureau participation for AstraZeneca, Astellas, Bristol Myers Squibb (Inst), Ipsen, and MSD; invited speaker participation for Bristol Myers Squibb (Inst) and MSD; expert testimony for Bristol Myers Squibb (Inst) and MSD; research funding from Bristol Myers Squibb (Inst), Ipsen, MSD, Pfizer, and Roche; and funding (to institution) for the conduct of the study from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. CR reports advisory board participation for BMS, MSD, Pfizer, Roche, and Sanofi; invited speaker participation for AstraZeneca, BMS, Knight, MSD, and Pfizer; board of directors' membership for Bradford Hill; and funding (to institution) for the conduct of the study from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. SJS reports advisory board participation from Astellas Korea, AstraZeneca, Merck, MSD, and Pfizer; and funding (to institution) for the conduct of the study from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. PYW reports funding (to institution) for the conduct of the study from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. LA reports consulting roles for Amgen, Astellas, BMS, Daiichi Sankyo, Eisai, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer, Roche, Telix Pharmaceuticals, and Xencor; honoraria from Novartis; clinical trial steering committee participation from Aveo, AstraZeneca, BMS, Exelixis, Ipsen, MSD, Pfizer, Roche, and Telix Pharmaceuticals; membership in the American Society of Clinical Oncology, the medical steering committee for the Kidney Cancer Association, and the Renal Cell Carcinoma Guidelines Panel for the European Association of Urology; and funding (to institution) for the conduct of the study from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. RM reports advisory board participation for Exelixis, Incyte, and Merck; institutional study funding from Aveo, Bristol Myers Squibb, Eisai, Exelixis, Genentech/Roche, Merck, and Pfizer; and funding (to institution) for the conduct of the study from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. HH reports honoraria from Bristol Myers Squibb; consulting or advisory roles for ARMO BioSciences, Bayer, Bristol Myers Squibb, Corvus Pharmaceuticals, Exelixis, Lilly, Merck, Novartis, Pfizer, and Surface Oncology; institutional research funding from Aveo, Bristol Myers Squibb, Exelixis, Hibercell, Merck, NGM Biopharmaceuticals, NiKang Therapeutics, Surface Oncology, and Werewolf Therapeutics; travel/accommodations/expenses from Bristol Myers Squibb, Lilly, Merck, Novartis, and Pfizer; and funding (to institution) for the conduct of the study from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. AP reports advisory board participation from Astellas, Bayer, BMS, Eisai, Janssen, Medison Pharma, MSD, and Novartis; invited speaker participation from Astellas, Bayer, BMS, Eisai, Exelixis, Janssen, Medison Pharma, MSD, Novartis, and Roche; travel grants from Astellas, BMS, and MSD; and funding (to institution) for the conduct of the study from

Table 3. Summary of treatment-related adverse events in all treated participants

Participants, *n* (%)	Qmab/pembro plus lenva *n* = 90	Fave/pembro plus lenva *n* = 61	Pembro plus lenva plus bel *n* = 90	Vibo/pembro plus bel *n* = 90	Reference: pembro plus lenva *n* = 62
Any-grade TRAE	90 (100.0)	61 (100.0)	90 (100.0)	90 (100.0)	62 (100.0)
Grade ≥3 TRAE	66 (73.3)	53 (86.9)	63 (70.0)	62 (68.9)	44 (71.0)
TRAEs leading to discontinuation of any study therapy	31 (34.4)	23 (37.7)	22 (24.4)	28 (31.1)	19 (30.6)
Serious TRAEs[a]	31 (34.4)	22 (36.1)	20 (22.2)	25 (27.8)	19 (30.6)
TRAEs leading to death	0 (0.0)	1 (1.6)	1 (1.1)	0 (0.0)	2 (3.2)
TEAEs leading to dose reduction	59 (65.6)	28 (45.9)	60 (66.7)	30 (33.3)	46 (74.2)
TRAEs in ≥20% of participants in any arm, *n* (%)					
Hypertension	55 (61.1)	37 (60.7)	39 (43.3)	3 (3.3)	38 (61.3)
Diarrhea	51 (56.7)	32 (52.5)	42 (46.7)	13 (14.4)	34 (54.8)
Hypothyroidism	51 (56.7)	27 (44.3)	41 (45.6)	20 (22.2)	35 (56.5)
Fatigue	37 (41.1)	21 (34.4)	46 (51.1)	31 (34.4)	30 (48.4)
Decreased appetite	35 (38.9)	22 (36.1)	29 (32.2)	9 (10.0)	15 (24.2)
Proteinuria	34 (37.8)	30 (49.2)	31 (34.4)	4 (4.4)	19 (30.6)
Palmar-plantar erythrodysesthesia syndrome	30 (33.3)	23 (37.7)	21 (23.3)	2 (2.2)	19 (30.6)
Pruritus	30 (33.3)	16 (26.2)	21 (23.3)	36 (40.0)	17 (27.4)
Nausea	29 (32.2)	20 (32.8)	33 (36.7)	21 (23.3)	18 (29.0)
Alanine aminotransferase increased	28 (31.1)	19 (31.1)	33 (36.7)	22 (24.4)	9 (14.5)
Arthralgia	27 (30.0)	10 (16.4)	17 (18.9)	18 (20.0)	9 (14.5)
Aspartate aminotransferase increased	26 (28.9)	19 (31.1)	27 (30.0)	23 (25.6)	8 (12.9)
Rash	23 (25.6)	11 (18.0)	22 (24.4)	24 (26.7)	10 (16.1)
Stomatitis	22 (24.4)	12 (19.7)	11 (12.2)	1 (1.1)	8 (12.9)
Hyperthyroidism	20 (22.2)	14 (23.0)	4 (4.4)	6 (6.7)	8 (12.9)
Vomiting	20 (22.2)	14 (23.0)	17 (18.9)	7 (7.8)	7 (11.3)
Asthenia	19 (21.1)	20 (32.8)	23 (25.6)	6 (6.7)	8 (12.9)
Weight decreased	19 (21.1)	9 (14.8)	16 (17.8)	4 (4.4)	14 (22.6)
Mucosal inflammation	18 (20.0)	9 (14.8)	15 (16.7)	0 (0.0)	8 (12.9)
Dysphonia	14 (15.6)	9 (14.8)	11 (12.2)	0 (0.0)	17 (27.4)
Lipase increased	13 (14.4)	14 (23.0)	13 (14.4)	8 (8.9)	5 (8.1)
Anemia	10 (11.1)	5 (8.2)	68 (75.6)	73 (81.1)	4 (6.5)

Bel, belzutifan; fave, favezelimab; lenva, lenvatinib; pembro, pembrolizumab; qmab, quavonlimab; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; vibo, vibostolimab.

[a]Serious adverse events were recorded from randomization through to 90 days after treatment discontinuation, or to 30 days after treatment discontinuation if participant initiated subsequent anticancer therapy.

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DATA SHARING

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data-sharing website (available at https://externaldatasharing-msd.com/) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the United States and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either carry out the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can carry out the proposed analyses.

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