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Phase II Randomized Study of Ramucirumab and Pembrolizumab Versus Standard of Care in Advanced Non–Small-Cell Lung Cancer Previously Treated With Immunotherapy—Lung-MAP S1800A

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abstract

PURPOSE Resistance to immune checkpoint inhibition (ICI) in advanced non–small-cell lung cancer (NSCLC) represents a major unmet need. Combining ICI with vascular endothelial growth factor (VEGF)/VEGF receptor inhibition has yielded promising results in multiple tumor types.

METHODS In this randomized phase II Lung-MAP nonmatch substudy (S1800A), patients ineligible for a biomarker-matched substudy with NSCLC previously treated with ICI and platinum-based chemotherapy and progressive disease at least 84 days after initiation of ICI were randomly assigned to receive ramucirumab plus pembrolizumab (RP) or investigator's choice standard of care (SOC: docetaxel/ramucirumab, docetaxel, gemcitabine, and pemetrexed). With a goal of 130 eligible patients, the primary objective was to compare overall survival (OS) using a one-sided 10% level using the better of a standard log-rank (SLR) and weighted log-rank (WLR; G[rho = 0, gamma = 1]) test. Secondary end points included objective response, duration of response, investigator-assessed progression-free survival, and toxicity.

RESULTS Of 166 patients enrolled, 136 were eligible (69 RP; 67 SOC). OS was significantly improved with RP (hazard ratio [80% CI]: 0.69 [0.51 to 0.92]; SLR one-sided $P = .05$; WLR one-sided $P = .15$). The median (80% CI) OS was 14.5 (13.9 to 16.1) months for RP and 11.6 (9.9 to 13.0) months for SOC. OS benefit for RP was seen in most subgroups. Investigator-assessed progression-free survival (hazard ratio [80% CI]: 0.86 [0.66 to 1.14]; one-sided SLR, $P = .25$ and .14 for WLR) and response rates (22% RP *v* 28% SOC, one-sided $P = .19$) were similar between arms. Grade ≥ 3 treatment-related adverse events occurred in 42% of patients in the RP group and 60% on SOC.

CONCLUSION This randomized phase II trial demonstrated significantly improved OS with RP compared with SOC in patients with advanced NSCLC previously treated with ICI and chemotherapy. The safety was consistent with known toxicities of both drugs. These data warrant further evaluation.

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ASSOCIATED CONTENT

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Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

First-line treatment of metastatic non–small-cell lung cancer (NSCLC) commonly includes inhibitors of programmed death 1 (PD-1), or its ligand, programmed death ligand 1 (PD-L1), alone or in combination with chemotherapy or cytotoxic T-lymphocyte–associated antigen 4 inhibition, for tumors with PD-L1 expression.[1] However, tumor resistance ultimately develops and remains a major unmet need. Despite numerous clinical trials to date, no immune-oncology agent or combination has shown activity in this refractory setting.[2] Combinations with immune checkpoint inhibitors are being evaluated in an attempt to restore sensitivity to immunotherapy.

Vascular endothelial growth factor (VEGF) and VEGF receptor inhibitors are approved for multiple cancer indications.[3] VEGF modulates the tumor immune microenvironment by enhancing tumor infiltration of immune cells and counteracting immunosuppression by myeloid-derived suppressor cells.[4,5] Consequently, studies have evaluated immune checkpoint inhibitors combined with VEGF receptor inhibitors yielding significant clinical benefit in multiple tumor types,[3] including advanced renal cell carcinoma (axitinib and pembrolizumab,[6] axitinib and avelumab,[7] cabozantinib and nivolumab,[8] and lenvatinib and pembrolizumab[9]) compared with single-agent sunitinib, and lenvatinib and pembrolizumab in advanced endometrial cancer compared with chemotherapy.[10]

CONTEXT

Key Objective

Resistance to immunotherapy develops in most advanced non–small-cell lung cancer (NSCLC) treated with immune checkpoint inhibition (ICI). Therapeutic strategies for these patients have been lacking. Vascular endothelial growth factor (VEGF) and its receptor modulate the tumor immune microenvironment, and combined ICI and VEGF/VEGF receptor therapy demonstrated benefit across multiple malignancies. This study evaluated ramucirumab and pembrolizumab, anti-vascular endothelial growth factor receptor 2, and anti–programmed death-1 therapy in advanced NSCLC after progression on prior ICI and platinum-based doublet chemotherapy using the Lung-MAP master protocol platform.

Knowledge Generated

Ramucirumab and pembrolizumab led to improved overall survival compared with standard of care in patients with advanced NSCLC previously treated with chemotherapy and immunotherapy with acquired resistance to prior ICI in this randomized phase II trial. Similar benefit was seen across subgroups.

Relevance

To our knowledge, this is the first trial in the ICI-acquired resistance setting to demonstrate potential survival benefit compared with standard of care including docetaxel and ramucirumab.

Additionally, bevacizumab and atezolizumab demonstrated clinical benefit in advanced hepatocellular carcinoma.[11] A preliminary signal of activity with ramucirumab plus pembrolizumab (RP) was seen in a phase I study of untreated and previously treated NSCLC.[12,13] IMPower150 provides additional support for immune checkpoint inhibition plus antiangiogenic therapies in NSCLC.[14] It was the first trial to demonstrate improved progression-free survival (PFS) and overall survival (OS) with the combination of ICI and angiogenesis inhibition (bevacizumab) with chemotherapy for front-line advanced NSCLC.

S1800A, a substudy of Lung-MAP, evaluated RP versus standard of care in patients with stage IV or recurrent NSCLC after progression on prior ICI. Lung-MAP is a master protocol encompassing molecularly matched and nonmatched immunotherapy approaches for previously treated metastatic or recurrent NSCLC.[15,16]

METHODS

Lung-MAP Protocol and Biomarker Screening

Patients with pathologically proven stage IV or recurrent NSCLC were eligible to enroll in S1800A, a nonmatch substudy of Lung-MAP, if they had been screened by the original Lung-MAP screening protocol (S1400; ClinicalTrials.gov identifier: NCT03851445)[15,16] or screened under the new Lung-MAP screening protocol (LUNGMAP; ClinicalTrials.gov identifier: NCT03971474) and were not eligible for any of the actively accruing biomarker-driven Lung-MAP substudies.

Patients

Patients must have received at least one line of anti–PD-1 or anti–PD-L1 (anti–PD-L1) therapy for stage III, IV, or recurrent disease and at most one line of anti–PD-L1 therapy for stage IV or recurrent disease, given sequentially or combined with platinum-based chemotherapy with disease progression at least 84 days after initiation of anti–PD-L1 therapy. Patients must have received platinum-based chemotherapy for stage IV/recurrent disease or for stage I-III with disease progression within 1 year from the last dose. Progression on prior therapy was based on investigator assessment. Exclusions included active autoimmune disease that required systemic treatment in the past 2 years, history of primary immunodeficiency, an immune-related adverse event, organ transplant that required use of immunosuppressives, and history of pneumonitis that required steroids or current pneumonitis/interstitial lung disease. Full eligibility criteria are given in the Protocol (online only).

Study Procedures and Treatment

The study was approved by an Independent Ethics Committee, and all patients provided written informed consent. Patients were randomly assigned to open label ramucirumab (10 mg/kg intravenous [IV]) plus pembrolizumab (200 mg IV) once every 21 days or investigator's choice standard-of-care (SOC) chemotherapy. Chemotherapy options were limited to docetaxel (75 mg/m^2) IV; ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) IV once every 21 days; gemcitabine (1,000 mg/m^2) IV on days 1 and 8 every 21 days; or for nonsquamous NSCLC patients only, pemetrexed (500 mg/m^2) IV once every 21 days. Random assignment was done using a dynamic balancing algorithm stratifying by PD-L1 tumor status ($< 1\%$ *v* $\geq 1\%$ or unknown), tumor histology (squamous *v* nonsquamous), and whether the planned treatment would include ramucirumab (yes *v* no) if randomly assigned to SOC. Treatment continued until disease progression as defined in RECIST 1.1, symptomatic deterioration, unacceptable toxicity, treatment delay for any reason > 84 days, or patient choice. Full information about guidance regarding treatment decisions is provided in the Protocol.

Tumor imaging was performed at baseline and every 6 weeks for the first year and then every 12 weeks until disease progression and discontinuation of protocol treatment. After off-protocol treatment following progression, laboratory tests and scans were required every 6 months for 2 years and then at the end of year 3. Adverse events were reported using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Statistical Methods

The primary end point was OS, defined as the duration from random assignment to death due to any cause. OS was chosen as the primary end point because neither response nor PFS has been demonstrated to be a robust and reliable end point in the immunotherapy relapsed setting. The primary analysis was based on a one-sided testing at the 10% level using a modified intention-to-treat analysis including only eligible patients. As many studies evaluating immunotherapy in NSCLC appear to have a delayed separation in time-to-event curves which can result in nonproportional hazards, testing was performed using a standard stratified log-rank test and a weighted log-rank test with weights equal to 1-S(t), where S(t) is the pooled survival estimate at time t (G[rho = 0, gamma = 1]).[17] The weighted test weights later events over earlier events and has more power than the standard log-rank test under a delayed separation in the curves. If either *P* value from the two tests was < .0972, the study would be considered to have rejected the null at the one-sided 10% level. The study design had an accrual goal of 130 eligible patients with the analysis when at least 90 deaths occurred. The study had 90% power to detect the scenario with overlapping curves up to 3 months and a hazard ratio (HR) of 0.5 after 3 months, assuming exponentially distributed survival times (piece-wise for the investigational arm), a median OS of 10.5 months in the SOC arm, and uniform accrual over 21-24 months. The study included two interim analyses evaluating early closure of accrual for futility. The first interim analysis was based on a single-arm assessment of response and disease control at 12 weeks among patients randomly assigned to RP when the first 18 eligible patients reached at least 24 weeks of follow-up. The second futility analysis took place when 50% of expected events (45 deaths) with at least 30 events with 3 months after random assignment were reported. The study was monitored by the SWOG Data and Safety Monitoring Committee.

Nominal *P* values are reported for secondary analyses. Secondary end points included investigator-assessed progression-free survival (IA-PFS) defined as the time from random assignment to the date of first progression, symptomatic deterioration, or death due to any cause. IA-PFS for patients last known to be alive without a report of progression, symptomatic deterioration, or death was censored at the date of last disease assessment. Best objective response was defined as complete, partial, unconfirmed complete, or unconfirmed partial response by RECIST 1.1. Patients not known to achieve a response were coded as nonresponders.

Survival distributions were estimated using the method of Kaplan-Meier (OS, PFS, and duration of response [DOR]). IA-PFS was compared using both the standard and weighted log-rank tests as described for OS. Treatment effects for time-to-event outcomes were summarized using a Cox proportional hazards model including the stratification factors and 80% CIs. Binary proportions were compared using a chi-squared test at the one-sided 5% level. Subgroup analyses were performed comparing OS and IA-PFS between the arms within the stratification factors (PD-L1 and histology), tumor mutational burden (TMB), and performance status (PS) using a Cox proportional hazards model.

RESULTS

Patients and Treatments

Between May 2019 and November 2020, 166 patients were randomly assigned to receive RP (n = 82) or SOC (n = 84) and 136 met eligibility (RP n = 69, SOC n = 67). The study CONSORT diagram is shown in Figure 1 and describes reasons for ineligibility in detail. Patient characteristics are described in Table 1. The median age of patients was 66 years (range, 38-85), and 61% were male. Most patients were current or former smokers (91%), and more patients with an Eastern Cooperative Oncology Group performance score 1 were in SOC versus RP arms (87% *v* 67%; Table 1). On the RP arm, of the 62 (90%) with known PD-L1 levels, 47%, 34%, and 19% had PD-L1 < 1%, 1%-49%, and ≥ 50%, respectively. For the SOC arm, of the 64 (96%) with known PD-L1 levels, 41%, 34%, and 25% had PD-L1 < 1%, 1%-49%, and ≥ 50%, respectively. Other patient baseline demographics and clinical characteristics were similar between the two treatment groups.

Protocol Treatment

Among 67 eligible in the SOC arm, 45 (67%) received ramucirumab and docetaxel; 12 (18%) received gemcitabine; three (4%) received docetaxel; one (1%) received pemetrexed; and six (9%) did not receive therapy. Reasons patients did not receive therapy included withdrawal (2), symptomatic deterioration (2—hemorrhage from large occipital mass and dyspnea), disease status improvement, and death.

As of April 14, 2022, 129 patients (62 RP and 67 SOC) had gone off protocol treatment and seven patients on RP remained on study treatment. Treatment discontinuation reasons were progressive disease for 87 patients (47 RP; 40 SOC), adverse events for 18 (seven RP; 11 SOC), death for nine (three RP; six SOC), and not protocol specified for nine (four RP; five SOC). Three patients withdrew consent after treatment initiation (one RP, two SOC). No patients were lost to follow-up. Patients on RP received a median (range) of six (1-37) cycles of ramucirumab and six (0-35) cycles of pembrolizumab. Patients on SOC received a median (range) of five (1-27)

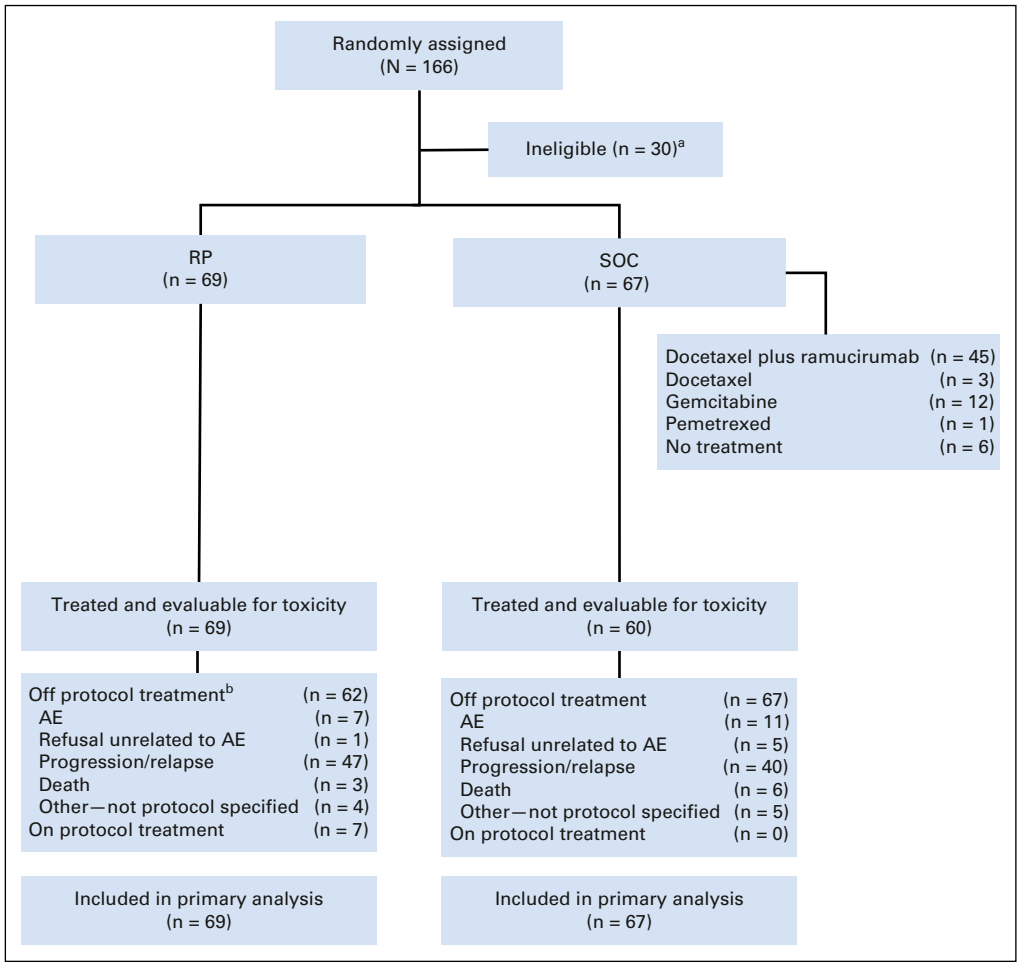

FIG 1. CONSORT diagram of patient disposition. [a]Of the 84 patients randomly assigned to the SOC arm, 17 patients were not eligible because of the following reasons: not progressing from platinum-based chemotherapy (four), not receiving or progressing from anti–PD-1/PD-L1 therapy per protocol-specified timeframe (two), permanent discontinuation of prior anti–PD-1/PD-L1 therapy because of toxicity (two), baseline scans for measurable disease not performed within the protocol timeframe (two), brain metastases requiring continued steroid treatment beyond the time of registration (two), not receiving and progressing on all SOC–targeted therapies for an oncogenic driver alteration, no measurable disease identified before registration, baseline blood pressure outside of protocol-specified range, receiving more than one line of anti–PD-1/PD-L1 therapy, and baseline scans for measurable disease not of diagnostic quality (one patient each). Of the 82 patients randomly assigned to the investigational arm, 13 patients were not eligible because of the following reasons: not receiving or progressing from anti–PD-1/PD-L1 therapy per protocol-specified timeframe (four), receiving more than one line of anti–PD-1/PD-L1 therapy (two), not progressing from platinum-based chemotherapy (two), no measurable disease identified before registration, receiving systemic therapy within 21 days before random assignment, not receiving platinum-based chemotherapy, receiving radiation therapy within 14 days before random assignmentand inadequate renal function, and receiving corticosteroids for brain metastasis within 7 days before random assignment (one patient each). [b]Of the 55 on the RP arm with reported progression, 41 (75%) went off-RP at the time of progression (PD), four (7%) discontinued treatment before PD, and 10 received treatment after PD. Of the 10, durations were four for $<$ 1 month, two for 1-3 months, one for 3-6 months, and two 6-18 months, and one remains on treatment as of last follow-up at 2.1 months after PD. AE, adverse event; PD, progression of disease; PD-1, programmed death 1; PD-L1, programmed death ligand 1; RP, ramucirumab plus pembrolizumab; SOC, standard of care.

cycles of ramucirumab, five (1-28) cycles of docetaxel (with or without ramucirumab), or 5.5 (1-19) cycles of gemcitabine. The one patient on pemetrexed received six cycles. Ten (14%) patients on the RP arm received study therapy beyond progression, with six for $<$ 3 months and two for $>$ 6 months.

Prior Treatment

Of the 136 eligible patients, 74 (54%) previously received immunotherapy combined with platinum-based chemotherapy, 59 (43%) received platinum-based chemotherapy, followed by immunotherapy, and three (2%) received

TABLE 1. Baseline Demographics and Characteristics

Characteristic	SOC (n = 67)	RP (n = 69)
Age, years, median (range)	65.8 (45.6-84.3)	66.4 (37.6-85.3)
Sex		
Male	42 (63)	41 (59)
Female	25 (37)	28 (41)
Race		
White	58 (87)	60 (87)
Black	6 (9)	5 (7)
Asian	2 (3)	1 (1)
Native American		1 (1)
Multiracial	1 (1)	
Unknown		2 (3)
Hispanic		2 (3)
Smoking status		
Current smoker	18 (27)	19 (28)
Past smoker	43 (64)	44 (64)
Never smoked	6 (9)	6 (9)
PS		
0	9 (13)	23 (33)
1	58 (87)	46 (67)
Tumor histology		
Adenocarcinoma	39 (58)	36 (52)
Squamous cell	27 (40)	28 (41)
Mixed < 50% squamous cell	1 (1)	
Mixed ≥ 50% squamous cell		1 (1)
Other non–small-cell, NOS		4 (6)
Prior lines of treatment for stage IV disease		
0	4 (6)	4 (6)
1	33 (49)	35 (51)
2	17 (25)	19 (28)
≥ 3	13 (19)	11 (16)
PD-L1 status[a]		
< 1%	26 (41)	29 (47)
≥ 1%	38 (59)	33 (53)
1%-49%	22 (34)	21 (34)
≥ 50%	16 (25)	12 (19)
Unknown	3 (4)	7 (10)
Tumor mutational burden by F1CDX[a]		
Median (range, IQR range)	7.6 (0-25.2, 3.8-12.6)	10.1 (0-40.4, 5.0-15.1)
≥ 10	25 (40)	33 (51)

NOTE. Data are represented as No. (%) unless otherwise stated.

Abbreviations: IQR, interquartile range; NOS, not otherwise specified; PD-L1, programmed death ligand 1; PS, performance status; RP, ramucirumab plus pembrolizumab; SOC, standard of care.

[a]Percentages in categories are calculated among those with known status only.

immunotherapy, followed by platinum-based chemotherapy (Table 2). Twenty-three patients received additional chemotherapy after their platinum-based chemotherapy and immunotherapy regimens; 50 patients received chemotherapy before combination immunotherapy and chemotherapy (16 for stage I-III disease and 34 for stage IV disease). Most patients received prior pembrolizumab (82, 60%), followed by nivolumab (27, 20%), durvalumab (23, 17%), and atezolizumab (four, 3%). Best response to prior immune checkpoint inhibitor-containing therapy was partial response for 48 (35%), stable disease for 66 (49%), progressive disease for 21 (15%), and unknown for one patient. The time between initiation of prior immunotherapy and progression for patients with progression as best response ranged between 3 and 14.7 months with a median (interquartile range) of 4.9 (3.8-7.1) months.

Toxicity

Grade 3-5 treatment-related adverse events for all grade 4 and 5 events and grade 3 events reported in at least 5% of patients are summarized in Table 3. Of 69 patients on RP assessed for adverse events, there were three treatment-related deaths: one due to cardiac arrest, one due to respiratory failure, and one where exact cause of death could not be determined. Additionally, four patients experienced treatment-related grade 4 events as the highest grade. Twenty-nine patients on RP experienced grade 3-5 adverse events, and nine (31%) were classified as immune-related adverse events (Appendix Table A1, online only) by the study chairs.

Of 60 patients on SOC assessed for adverse events (44 on docetaxel/ramucirumab and 16 on single-agent chemotherapy), there were four treatment-related deaths (three on docetaxel/ramucirumab and one single-agent chemotherapy): two due to sepsis (one docetaxel/ramucirumab) and two due to respiratory failure (both on docetaxel/ramucirumab). Additionally, 15 patients experienced treatment-related grade 4 events as their highest grade (12 of 15 on docetaxel/ramucirumab). The grade 4 adverse event listed as GI disorders–other was due to ischemic bowel. Table 4 describes the adverse events on SOC by type of treatment.

OS

At the time of analysis, 96 deaths had been reported, and the median (range) of follow-up among those still alive (n = 40) was 17.9 months (1-30). OS was significantly longer with RP, with the one-sided *P* value from the standard log-rank test equal to .05 and .15 from the weighted log-rank test. RP reduced the risk of death by 31% (HR: 0.69 [80% CI, 0.51 to 0.92]; Fig 2A), and the median OS (80% CI) was 14.5 (13.9 to 16.1) months in this arm versus 11.6 (9.9 to 13.0) months in the SOC arm.

Interpretation of subgroup analyses is limited by small sample sizes. The magnitude of OS benefit did not

TABLE 2. Summary of Patient Characteristics and Randomized Treatment On the Basis of Type of Regimen Including Prior Treatment With Immunotherapy and Chemotherapy Treatment

Patient Characteristics and Treatment	Chemotherapy Followed by Immunotherapy (n = 59)	Combination Immunotherapy and Chemotherapy (n = 74)	Total[a] (N = 136)
Randomized treatment			
RP	36	32	69
SOC (investigator's choice)	23	42	67
Histology			
Adenocarcinoma	26	47	75
Squamous cell carcinoma	32	23	55
Mixed < 50% squamous cell carcinoma		1	1
Mixed ≥ 50% squamous cell carcinoma			1
Other non–small-cell, NOS	1	3	4
Prior immunotherapy received			
Pembrolizumab	13	66	82
Nivolumab	27	0	27
Durvalumab	18	5	23
Atezolizumab	1	3	4
Additional treatment order			
Chemotherapy received before combination Immunotherapy and chemotherapy	NA	50	50
Chemotherapy received after immunotherapy	12	11	23
Stage when chemotherapy first received			
I-III	34	17	52
IV	25	57	84
Best response on prior immunotherapy			
Partial response	17	31	48
Stable disease	30	34	66
Progression	12	8	21
Unknown		1	1
Time on prior immunotherapy			
Median, months (range)	8.3 (2.8-56.8)	7.8 (0-43.7)	8.0 (0-56.8)
< 6	18	22	41
6 to < 12	23	36	59
≥ 12	18	16	36
Time between prior immunotherapy and random assignment			
Median, months (range)	2.6 (0.7-21.4)	2.4 (0.7-16.3)	2.5 (0.7-21.4)
< 6	43	62	105
6 to < 12	4	7	13
≥ 12	12	5	18

Abbreviations: NA, not available; NOS, not otherwise specified; RP, ramucirumab plus pembrolizumab; SOC, standard of care.
[a]Total to include all patients, but three patients who received immunotherapy followed by chemotherapy not described separately.

appear to differ by PD-L1 or TMB subgroups (Fig 3A). OS benefits were consistent across the majority of pre-specified subgroups examined. Appendix Table A2 (online only) describes genomic alterations detected with next-generation sequencing as part of Lung-MAP screening.

TABLE 3. Grade 3 Treatment-Related AEs ≥ 5% and All Grade 4 and 5 Treatment-Related AEs

	SOC (n = 60)			RP (n = 69)		
	Grade			Grade		
AE	3	4	5	3	4	5
Acidosis		1 (2)				
Acute kidney injury		1 (2)		4 (6)		
ALT increased	1 (2)	1 (2)		1 (1)		
Anemia	4 (7)					
AST increased	1 (2)	1 (2)		2 (3)		
Bronchopulmonary hemorrhage					1 (1)	
Cardiac arrest						1 (1)
Colonic perforation	1 (2)	1 (2%)				
Death NOS						1 (1)
Dehydration	3 (5)					
Dyspnea	2 (3)	1 (2)		2 (3)	1 (1)	
Fatigue	4 (7)			4 (6)		
Febrile neutropenia	2 (3)	1 (2)		1 (1)		
GI disorders—others, specify		1 (2)				
Hypertension	2 (3)			9 (13)		
Hypotension	2 (3)	1 (2)				
Hypoxia	1 (2)	1 (2)		1 (1)	1 (1)	
Lung infection	4 (7)			3 (4)	1 (1)	
Lymphocyte count decreased	10 (17)	1 (2)		3 (4)		
Mucositis oral	3 (5)	1 (2)				
Multiorgan failure		1 (2)				
Nausea	3 (5)			1 (1)		
Neutrophil count decreased	6 (10)	14 (23)		2 (3)	1 (1)	
Pericardial effusion		1 (2)				
Platelet count decreased	3 (5)					
Pneumonitis	1 (2)				1 (1)	
Pneumothorax					1 (1)	
Respiratory failure			2 (3)		1 (1)	1 (1)
Sepsis	2 (3)	1 (2)	2 (3)	2 (3)	1 (1)	
Wheezing				1 (1)	1 (1)	
WBC decreased	13 (22)	4 (7)		1 (1)		
Maximum grade all hematologic AEs	13 (22)	15 (25)		5 (7)	1 (1)	
Maximum grade all nonhematologic AEs	13 (22)	4 (7)	4 (7)	21 (30)	4 (6)	3 (4)
Maximum grade any AE	17 (28)	15 (25)	4 (7)	22 (32)	4 (6)	3 (4)

NOTE. Data are represented as No. (%).

Abbreviations: AE, adverse event; NOS, not otherwise specified; RP, ramucirumab plus pembrolizumab; SOC, standard of care.

PFS

At the time of analysis, 119 PFS events had been reported. PFS was not significantly longer with RP, with the one-sided *P* value from the standard log-rank test equal to .25 and .14 from the weighted log-rank test (HR: 0.86 [80% CI, 0.66 to 1.14]; Fig 2B). The median PFS (80% CI) was 4.5 (4.2 to 6.1) months for RP and 5.2 (4.2 to 5.7) months in the SOC arm. Subgroup analyses were consistent with those for OS (Fig 3B).

Response and Disease Control

On RP, there were 12 confirmed partial responses and three unconfirmed partial responses for an objective

TABLE 4. Grade 3 Treatment-Related AEs ≥ 5% and All Grade 4 and 5 Treatment-Related AEs on Standard of Care by Type of Treatment

	Docetaxel Plus Ramucirumab (n = 44)			Chemomonotherapy (n = 16)		
	Grade			Grade		
AE	3	4	5	3	4	5
Acidosis					1 (6)	
Acute kidney injury					1 (6)	
ALT increased	1 (2)				1 (6)	
Anemia	4 (9)					
AST increased	1 (2)				1 (6)	
Colonic perforation	1 (2)				1 (6)	
Dehydration	3 (7)					
Diarrhea	2 (5)					
Dyspnea	1 (2)	1 (2)		1 (6)		
Fatigue	3 (7)			1 (6)		
Febrile neutropenia	2 (5)	1 (2)				
GI disorders—others, specify					1 (6)	
Hypertension	2 (5)					
Hypoalbuminemia	2 (5)					
Hypotension	2 (5)				1 (6)	
Hypoxia	1 (2)				1 (6)	
Lung infection	3 (7)			1 (6)		
Lymphocyte count decreased	6 (14)			4 (25)	1 (6)	
Mucositis oral	3 (7)	1 (2)				
Multiorgan failure					1 (6)	
Muscle weakness lower limb				1 (6)		
Nausea	3 (7)					
Neutrophil count decreased	2 (5)	12 (27)		4 (25)	2 (13)	
Pericardial effusion		1 (2)				
Platelet count decreased	2 (5)			1 (6)		
Pleural effusion				1 (6)		
Respiratory failure			2 (5)			
Sepsis	2 (5)	1 (2)	1 (2)			1 (6)
Thromboembolic event	2 (5)					
Vomiting	2 (5)					
WBC decreased	9 (20)	3 (7)		4 (25)	1 (6)	
Maximum grade all hematologic AEs	8 (18)	12 (27)		5 (31)	3 (19)	
Maximum grade all nonhematologic AEs	13 (30)	3 (7)	3 (7)		1 (6)	1 (6)
Maximum grade any AE	12 (27)	12 (27)	3 (7)	5 (31)	3 (19)	1 (6)

NOTE. Data are represented as No. (%).
Abbreviation: AE, adverse event.

response rate of 22% (15 of 69; 90% CI, 14 to 30). On SOC, there was one confirmed complete response, 13 confirmed partial responses, and five unconfirmed partial responses for an objective response rate of 28% (19 of 67; 90% CI, 19 to 37). Of the 19 responders on SOC, 18 received docetaxel and ramucirumab and one received gemcitabine. Thirty-seven patients on RP and 30 on SOC achieved stable disease as best response for a DCR of 75% (90% CI, 67 to 84) in the RP arm and 73% (90% CI, 64 to 82) in the SOC arm ($P = .38$). The median DOR (90% CI) was 12.9 (2.8 to not available) months for RP and 5.6 (4.6 to 7.8) months in the SOC arm. Eight and nine patients had a DOR ≥ 6 months on RP and SOC, respectively.

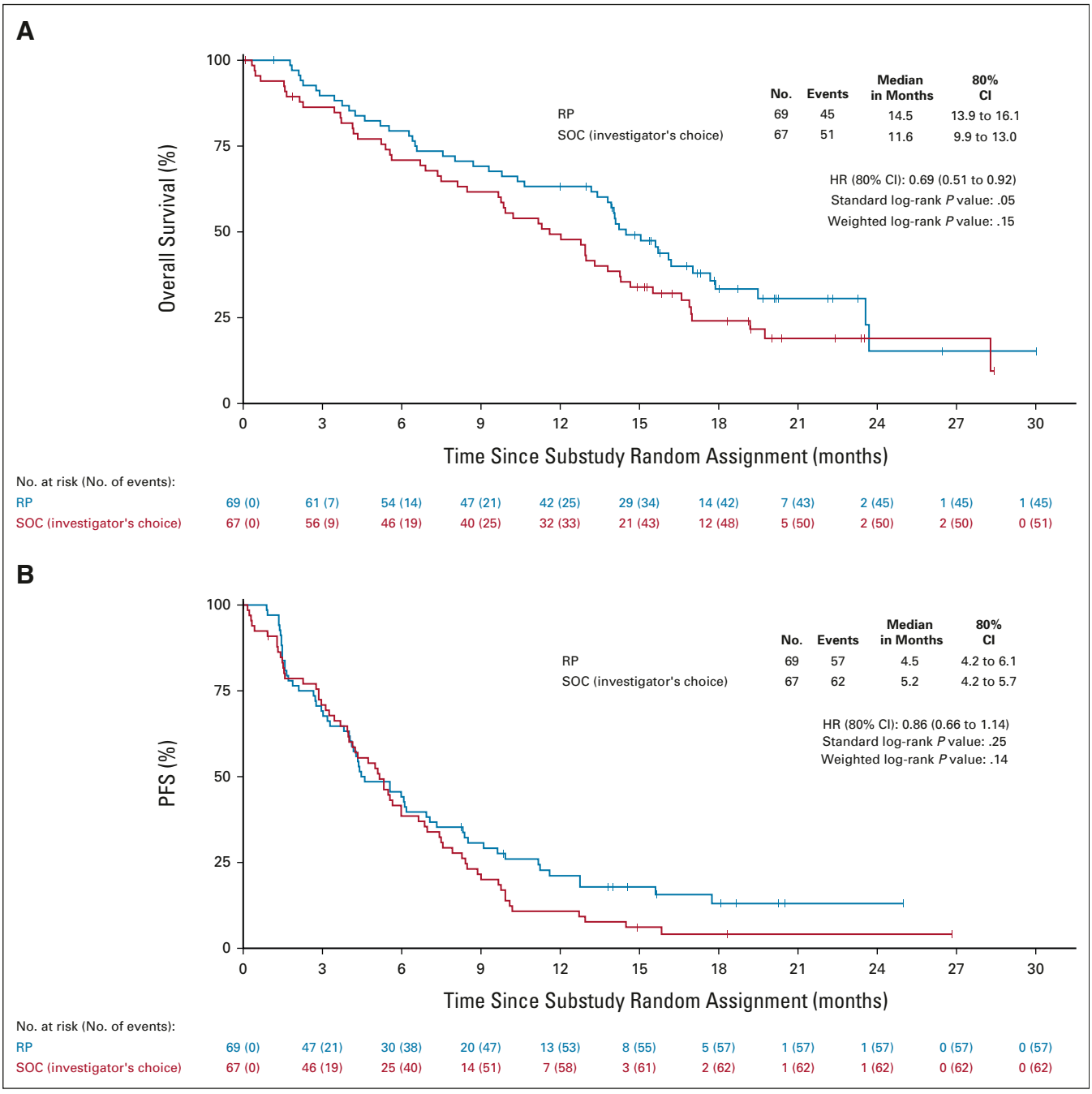

FIG 2. (A) Overall survival and (B) PFS. *P* values from the standard log-rank test. HR, hazard ratio; PFS, progression-free survival; RP, ramucirumab plus pembrolizumab; SOC, standard of care.

Postprotocol Treatment

Sixty-seven patients had postprotocol systemic therapy reported with nine (five SOC, four RP) receiving treatment before progression and 58 (30 SOC, 28 RP) after progression on study. The type of postprotocol therapy and a description of the therapies are included in Appendix Table A3 (online only). Appendix Table A4 (online only) includes an extended description of post-treatment therapy.

DISCUSSION

S1800A represents a positive signal in immune checkpoint inhibitor-refractory cancers, arguably one of the greatest unmet needs in oncology. The rapid accrual of S1800A was facilitated by the unique Lung-MAP infrastructure. To our knowledge, this is the first trial for previously treated NSCLC without a chemotherapy backbone to demonstrate a potential survival benefit compared with SOC regimens including docetaxel and ramucirumab. The safety seen with

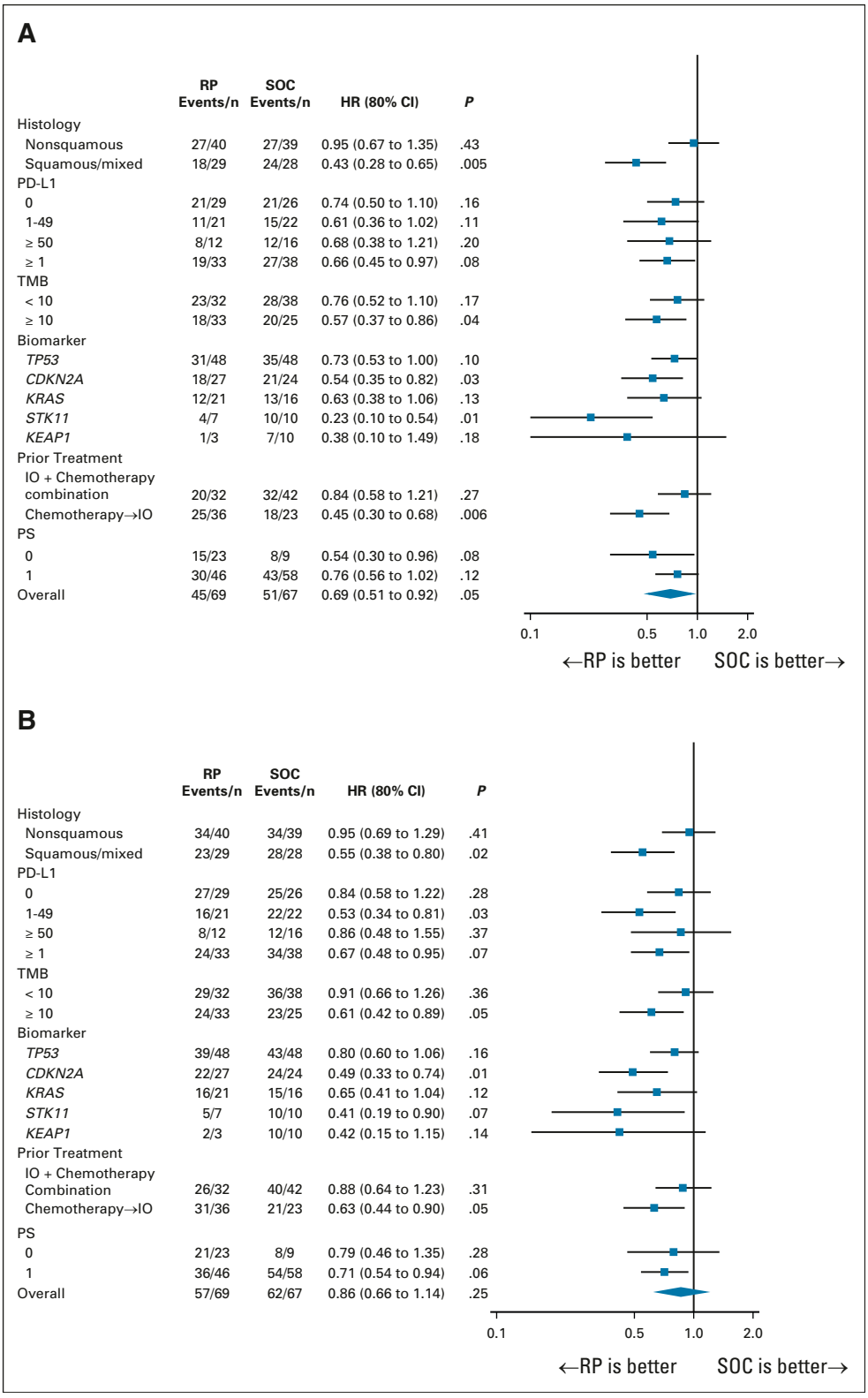

FIG 3. Subgroup analysis of (A) overall survival and (B) Progression-free survival. One-sided *P* values from the standard log-rank test. HR, hazard ratio; IO, immuno-oncology; PD-L1, programmed death ligand 1; PS, performance status; RP, ramucirumab plus pembrolizumab; SOC, standard of care; TMB, tumor mutational burden.

RP was consistent with expected toxicities and fewer patients on RP versus SOC requiring treatment discontinuation because of adverse events.

Although SOC choice included single-agent chemotherapy, two-thirds of patients on SOC received docetaxel and ramucirumab. In the REVEL study, ramucirumab and docetaxel improved clinical outcomes compared with docetaxel alone in previous platinum-based doublet therapy treated, immunotherapy-naive, advanced NSCLC.[18] A retrospective study evaluating docetaxel and ramucirumab after progressive disease on nivolumab suggested clinical benefit using a historical comparison.[19] Together, this implies that most on SOC received the most active therapy available.

S1800A evaluated RP in patients who experienced disease progression at least 84 days after start of ICI, our definition of acquired resistance. Multiple trials are evaluating combination therapies in the acquired resistance setting, but a standardized definition has not been established.[2] Definitions of acquired resistance are further complicated for combination ICI plus chemotherapy regimens in the frontline setting, where the component contributing to efficacy and resistance is not easily discerned.

Importantly, the OS hazard ratios for all subgroups were less than one and relatively consistent across PD-L1 expression and TMB levels. There was some variability, but suggested benefit, by mutations (notably *STK11,* Fig 3A), despite other studies suggesting reduced efficacy of single-agent ICI in these populations.[20,21] Finally, of note was the effect size in squamous histology. ICI is beneficial in squamous NSCLC,[22] and contrary to nonsquamous histologies, independent of PD-L1 status for second line.[23,24] Thus, the squamous population should be evaluated further as ramucirumab is not restricted to nonsquamous histology.

Although this is a randomized phase II trial, we choose OS as the primary end point because response and PFS benefit are not always seen with ICI in advanced NSCLC potentially because of increased immune cell infiltration or prolonged time to tumor reduction, which is not seen with cytotoxic regimens.[24,25] Lack of PFS benefit with RP is consistent with postprogression prolongation of survival seen in other studies with PD-1 and PD-L1 antibody therapy.[25] The postprogression prolongation of survival phenomenon is likely to be responsible for the OS findings, especially since patients who were progressing immediately on ICI-achieved OS improvement similar to the overall population in the subgroup analysis.

The randomized phase II design and resulting smaller sample size imply that the study results should not be interpreted as definitive and limits interpretation of subgroup effects. Heterogeneity in type of prior immune checkpoint inhibitor-containing regimen is a potential limitation that reflects real-world therapy for advanced NSCLC. An imbalance in patients with PS 1 was seen in the SOC arm, and we analyzed the overall treatment effect adjusting for PS, which demonstrated that directionally the treatment effects remain in favor of RP. Additionally, the population was not completely unselected as S1800A excluded patients who had qualifying genomic alterations for Lung-MAP substudies S1900A (*BRCA*LOH) and S1900C (*STK11*) and met the substudy eligibility criteria. Additionally, most next-generation sequencing and PD-L1 expression were based on archival tissue.

In summary, RP demonstrated improved OS over investigator's choice SOC, which largely consisted of docetaxel and ramucirumab, suggesting modulation of the immune microenvironment by an antiangiogenic agent, allowing resensitization to ICI. Further evaluation of this approach is warranted.

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DISCLAIMER

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Phase II Randomized Study of Ramucirumab and Pembrolizumab Versus Standard of Care in Advanced Non–Small-Cell Lung Cancer Previously Treated With Immunotherapy—Lung-MAP S1800A

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APPENDIX

TABLE A1. Grade 3-5 irAEs on RP

	RP (n = 9)		
	Grade		
irAE	3	4	5
Acute kidney injury	2 (22)		
Adrenal insufficiency	2 (22)		
ALT increased	1 (11)		
Arthralgia	2 (22)		
AST increased	2 (22)		
Blood bilirubin increased	1 (11)		
Cough	1 (11)		
Dyspnea	2 (22)	1 (11)	
Encephalopathy	1 (11)		
Fatigue	1 (11)		
Hypoxia		1 (11)	
Lung infection		1 (11)	
Pneumonitis		1 (11)	
Respiratory failure			1 (11)
Wheezing	1 (11)	1 (11)	
Maximum grade any irAE	6 (67)	2 (22)	1 (11)

NOTE. Data are represented as No. (%).

Abbreviations: irAE, immune-related adverse event; RP, ramucirumab plus pembrolizumab.

TABLE A2. Alterations Detected by FoundationOne CDx on Lung-MAP Screening

Other Concomitant Gene Alterations	Total (N = 136), No. (%)
Short variants	
TP53	94 (69)
KRAS	36 (26)
CDKN2A	22 (16)
KEAP1, STK11	12 (9)
RBM10	11 (8)
PTEN, SMARCA4	10 (7)
EGFR	9 (7)
ARID1A, MLL2, NF1, NOTCH1	8 (6)
PIK3CA	7 (5)
ATM	6 (4)
DNMT3A, RB1	5 (4)
APC, NFE2L2, SMAD4	4 (3)
ATRX, CHEK2, CTNNB1, FGFR3, KDM6A, NBN, NF2, TERT, U2AF1	3 (2)
ASXL1, ATR, BARD1, BRAF, BRCA1, BRCA2, BRIP1, CTCF, EP300, ERBB2, ERRFI1, FBXW7, FGFR2, KDM5C, KEL, MAP3K13, MET, MSH3, MUTYH, NOTCH2, PARK2, PBRM1, RAF1, SETD2, SGK1, TET2, TSC2	2 (1)
AKT3, BAP1, BCOR, BRD4, BTG1, BTK, CDH1, CDKN1A, CIC, CTNNA1, CUL3, EPHB1, ERBB4, ESR1, FAM123B, FANCC, FANCL, FGF6, FH, FLT1, FUBP1, GATA3, GATA4, GNAS, HSD3B1, IDH1, IKZF1, INPP4B, IRF2, JAK3, KDM5A, KDR, LRP1B, MSH6, MTOR, MYCN, NOTCH3, NPM1, NRAS, NTRK2, P2RY8, PALB2, PARP4, PIK3R1, PTPN11, RAD51C, RAD51D, SDHA, SH2B3, SMARCB1, SMO, SPEN, TBX3, TGFBR2, TSC1, WHSC1L1, WT1, XPO1	1 (1)
Copy number alterations	
CDKN2A	29 (21)
CDKN2B	27 (20)
MTAP	18 (13)
NKX2-1	13 (10)
SOX2	11 (8)
NFKBIA	10 (7)
PIK3CA	9 (7)
CCND1, FGF19, FGF3, PRKCI, RAD21, TERC	8 (6)
MYC	7 (5)
FGF12, FGF4, MCL1, WHSC1L1	6 (4)
AURKA, FGFR1, MDM2	5 (4)
CCNE1, CDK4, EGFR, ZNF703	4 (3)
ARFRP1, BCL2L1, BCL2L2, EPHB4, ERBB2, GNAS, KRAS, MET, NTRK1, STK11, ZNF217	3 (2)
AKT2, C17orf39, CDK6, EMSY, EPHA3, FGF10, KDM5A, MAPK1, PDGFRA, PTEN, REL, RICTOR, TP53	2 (1)
AKT1, CCND2, CD274, CDKN1B, CRKL, CUL4A, ERBB4, FGF23, FGF6, GATA6, HGF, IKBKE, IRS2, JAK2, KDR, KEAP1, KIT, MAP2K4, MDM4, MITF, MYCL1, MYCN, MYST3, NF1, PDCD1, PDCD1LG2, PIK3C2B, PIM1, SMAD4, SMARCA4	1 (1)
Rearrangements	
STK11	2 (1)
APC, BRCA2, CBL, CTNNA1, FGFR3, MLL2, MSH6, MTAP, NBN, NOTCH1, PALB2, PDGFRA, PTPRO, RB1, RET, TMPRSS2, WT1	1 (1)

TABLE A3. Reported First Postprotocol Therapy by the Randomized Treatment Arm

Therapy	SOC (n = 35)	RP (n = 32)	Total (n = 67)
Before RECIST progression	5	4	9
Chemomonotherapy	3	1	4
Chemotherapy plus VEGF	1		1
IO plus VEGF		1	1
Platinum doublet plus IO		2	2
Targeted therapy	1		1
Post-RECIST progression	30	28	58
Chemotherapy plus IO	1		1
Chemotherapy plus other	1		1
Chemotherapy plus VEGF	1	3	4
Chemomonotherapy	11	14	25
IO	7		7
IO plus other	1		1
Platinum doublet	3	6	9
Platinum doublet plus VEGF		1	1
Targeted therapy	5	4	9

Abbreviations: IO, immunotherapy; RP, ramucirumab plus pembrolizumab; SOC, standard of care; VEGF, vascular endothelial growth factor/receptor therapy.

TABLE A4. Details of Reported First Postprotocol Therapy

Therapy	Total (n = 67)
Chemotherapy regimen without immunotherapy	n = 45
Chemomonotherapy (n = 29)	
Docetaxel	9
Gemcitabine	13
Paclitaxel	2
Pemetrexed	3
Vinorelbine	2
Platinum doublet (n = 9)	
Carboplatin/gemcitabine	4
Carboplatin/paclitaxel	3
Carboplatin/pemetrexed	2
Chemotherapy plus VEGF (n = 5)	
Docetaxel/ramucirumab	5
Platinum doublet plus VEGF (n = 1)	
Bevacizumab/carboplatin/paclitaxel	1
Chemotherapy plus other (n = 1)	
Docetaxel/selinexor	1
Treatment including immunotherapy	n = 12
Immunotherapy alone (n = 7)	
Atezolizumab	1
Avelumab	1
Ipilimumab/nivolumab	4
ONC-392/pembrolizumab	1
Platinum doublet plus immunotherapy (n = 2)	
Carboplatin/ipilimumab/nivolumab/pemetrexed	1
Carboplatin/paclitaxel/pembrolizumab	1
Chemomonotherapy plus immunotherapy (n = 1)	
Pembrolizumab/pemetrexed	1
Immunotherapy plus VEGF (n = 1)	
Pembrolizumab/ramucirumab	1
Immunotherapy plus other (n = 1)	
NC318/pembrolizumab	1
Treatment with targeted therapy	n = 10
Abemaciclib	1
Afatinib	1
Amivantamab	1
BI-1206	1
Capmatinib	1
Erdafitinib	1
Everolimus	1
Olaparib	1
TAK-981	1
Temsirolimus	1

Abbreviation: VEGF, vascular endothelial growth factor.