ORIGINAL ARTICLE

Phase 2 Trial of Nivolumab and Ramucirumab for Relapsed Mesothelioma: HCRN-LUN15-299

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ABSTRACT

Introduction: We hypothesized that ramucirumab could increase previously reported objective response rate (ORR) of 11% of single-agent nivolumab in the second-line therapy of unresectable mesothelioma.

Methods: This was a cooperative group, single-arm, phase 2 trial enrolling patients with unresectable mesothelioma after progression on more than or equal to one pemetrexed-containing regimen. Ramucirumab and nivolumab were given intravenously every 14 days for up to 24 months. The primary end point was ORR; secondary end points were progression-free survival (PFS) rate at 24 weeks and overall survival (OS).

Results: Between April 2018 and October 2021, 34 patients were recruited. Median age was 72 (range: 40–89) years, 12% were women, and 79% of tumors had epithelial histology. Median follow-up was 10.2 months (interquartile range 19.6 mo [4.3–23.8]). ORR was 22.6% (95% confidence interval [CI]: 9.6%–41.1%) in all population and 43% (95% CI: 10%–82%) in patients with nonepithelioid histology. Of all patients, 45.2% (95% CI: 27.3%–64.0%) had stable disease. PFS rate at 24 weeks was 32% (95% CI: 17%–51%). Median PFS was 4.2 months (95% CI: 1.9–6.4 mo). Median OS was 12.5 months (95% CI: 6.3–23.5 mo). There was no grade greater than or equal to four toxicity. Programmed death-ligand 1 expression in the tumor did not correlate with benefit from treatment. Activation of tumor-infiltrating lymphocytes in response to treatment was associated with a trend toward improvement in PFS.

Conclusions: Nivolumab and ramucirumab combination was safe and generated PFS and OS rates and ORR that compare favorably with single-agent nivolumab in a similar patient population. The primary end point of 40% ORR was not reached. Further investigation of this regimen in mesothelioma with nonepithelioid histology may be warranted. Clinical Trial Information: NCT03502746.

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Introduction

Mesothelioma is a rare yet highly aggressive cancer for which radiation and surgical therapy are typically poor options. Cisplatin or carboplatin in combination with pemetrexed[1] or ipilimumab and nivolumab[2] are currently standard first-line treatments for unresectable mesothelioma. Nevertheless, if these treatments fail to control mesothelioma, there are limited effective therapy options available.[3–5]

Antiangiogenic therapy in conjunction with standard platinum and antifolate chemotherapy has been found to be effective in patients with mesothelioma. Addition of bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, to standard cisplatin and pemetrexed resulted in improved progression-free survival (PFS) and overall survival (OS).[6] Though the survival benefits were modest, this trial established a role of targeting angiogenesis in the treatment of mesothelioma.

In mesothelioma, immune checkpoint inhibitors (ICIs) were found to have efficacy in several clinical trials highlighting the potential of therapy targeting the immune system for this disease. First-line ipilimumab and nivolumab were approved based on results of a randomized phase 3 trial revealing superior OS of combination ICI therapy than chemotherapy.[2]

The tumor microenvironment contains a vasculature that is structurally and functionally abnormal. In certain regions of tumors, the vessels are leaky, twisted, and lack stabilizing pericytes and basement membrane. The structurally abnormal tumor vessels do not provide nutritive blood flow. The immature tumor vessels contribute to an abnormal tumor microenvironment with one of the key characteristics being that of hypoxia. Abnormal tumor vasculature and subsequent tumor hypoxia contribute to immune tolerance of tumor cells by impeding the homing of cytotoxic T cells into tumor parenchyma and inhibiting their antitumor efficacy,[7] including accumulation and subsequent polarization of inflammatory cells toward immune-suppressive phenotypes, such as myeloid-derived suppressor cells,[8] tumor-associated macrophages,[9] and dendritic cells.[10]

Antiangiogenic therapy could normalize tumor vasculature and decrease hypoxic tumor area and thus may be an effective modality to potentiate immunotherapy.[11,12] The programmed cell death protein-1 (PD-1) receptor was expressed in 8% of mesothelioma cells and 24% of tumor-infiltrating lymphocytes,[13] and VEGF receptor 2 expression was found in 90%[14] of mesothelioma tumors. In the clinical setting, therapy with anti–PD-L1, atezolizumab and bevacizumab in lung cancer with high tumor mutation burden induced 42.1% overall response rate (ORR),[15] similarly activity of atezolizumab and bevacizumab resulted in 40% ORR in peritoneal mesothelioma.[16] Accordingly, we conducted a multicenter, phase 2 clinical trial using ramucirumab, a VEGF receptor 2 targeting antibody, in combination with nivolumab, a PD-1 targeting antibody, in patients with pleural and peritoneal mesothelioma.

Materials and Methods

Study Design and Participants

This multicenter, single-arm, open-label phase 2 trial, enrolling patients with unresectable pleural or peritoneal mesothelioma after progression on more than or equal to one pemetrexed-containing regimen, was performed in four institutions of the Hoosier Cancer Research Network. Patients were required to have measurable disease according to modified Response Evaluation Criteria in Solid Tumors version 1.1 (modified RECIST v1.1)[17] and adequate organ function within 28 days of starting therapy. The complete list of inclusion and exclusion criteria can be found in the study protocol in Supplementary Material 1. The institutional review board at all participating centers approved the study protocol. All patients provided informed consent before study interventions were initiated. The primary end point was to evaluate objective response rate (ORR) using mesothelioma modified RECIST v1.1.[17] Secondary end points were to characterize adverse events and PFS rate at 24 weeks and to measure OS at 2 years.

Ramucirumab was sourced from Eli Lilly and Company (Indianapolis, IN), and nivolumab was provided by Bristol-Myers Squibb Company (New York, NY). Ramucirumab 8 mg/kg and nivolumab 240 mg were given intravenously on day 1 every 14 days until disease progression, intolerable toxicity, or up to 2 years from treatment initiation.

Imaging of the chest, abdomen, and pelvis was performed every 6 weeks. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Exploratory Studies

The whole blood for serum submission was collected pre-dose on days 1 (cycle 1, day 1) and 57 (cycle 5, day 1) for analysis of soluble programmed death-ligand 1 (sPD-L1) levels. Programmed death-ligand 1 (PD-L1) protein levels in the serum were determined using the CHECKMARK ELISA (Martell Diagnostic Laboratories, Inc., Roseville, MN).

Tumor tissues were obtained by computed tomography (CT)-guided biopsies (before starting treatment and during treatment before day 1 of cycle 5). Details of tissue analysis performed by Clinical and Translational Laboratory of HiberCell (Roseville, MN) are in Supplementary Material 2. Briefly, the tumor tissue slides stained with the myeloid panel were analyzed for PD-L1, CD80 (a marker of M1 macrophages associated with resistance to pathogen and tumor control), and CD206 (a marker of M2 macrophages associated with functions in metabolism, tissue remodeling, immunoregulation, and tumor progression). Subpopulations of myeloid and tumor cells were determined for PD-L1, CD80, and CD206. A myeloid activation index (MAI) was calculated for each sample. This index is based on the ratio of myeloid cells to tumor cells and the M1:M2 status of the myeloid cells. A higher value indicates an increase in infiltration and activation of myeloid cells.

Tumor tissue slides stained with the lymphoid panel were analyzed for CD8 cells, CD4 cells, Ki67, FOXP3, and granzyme B. A lymphoid activation index (LAI) was calculated for each sample. This value is based on the ratio of total T cells to tumor cells and the activation status of the T cells. A higher value indicates an increase in infiltration and activation of lymphoid cells in the tumor.

Baseline and change in PD-L1 during therapy relative to baseline were evaluated in relation to the best clinical response, PFS, and OS. Similarly, changes in MAI and LAI during therapy relative to baseline were evaluated in relation to the best clinical response, PFS, and OS. Correlations with best response were done using Fisher's exact test, and correlations with PFS and OS were done using Cox regression model. All analyses were performed using R Statistical Software (version 4.2.2; R Core Team 2022).

Statistical Analysis

The primary study end point was ORR (partial response [PR] or complete response [CR]) as assessed by modified RECIST v1.1.[17]

At the time of study design, there were no data on single activity of nivolumab in mesothelioma, and therefore we used a 20% response rate found with pembrolizumab in patients with mesothelioma as a reference.[18] With 33 patients, there was 80% power to detect an ORR of 40% with combination therapy, with one-sided type 1 error constrained to 0.05. Sample size analyses were conducted using the PASS software (NCSS, Kaysville, UT).

The ORR and 95% confidence interval (CI) were computed using SAS 9.4 software (Cary, NC). Kaplan-Meier analysis was used to calculate PFS and OS with associated 95% CI. The effect of epithelioid versus nonepithelioid histology on ORR and PFS was analyzed using logistic and Cox regression models.

The proportion of subjects with each grade of adverse events, as defined by the Common Terminology Criteria for Adverse Events version 4, was computed along with 95% CI and reported in a tabular and descriptive manner.

Correlative study analyses were performed using R Statistical Software (version 4.2.2; R Core Team 2022).

Results

Patient Characteristics

Between April 2018 and October 2021, 34 patients were enrolled: 30 were men and four were women, with median age of 72 (range: 40–89) years. There was one African American, two Hispanic, and 31 White patients. There were 30 (88%) who had a diagnosis of pleural mesothelioma and four (12%) had peritoneal mesothelioma. Furthermore, 27 patients had tumors with epithelioid, four with biphasic, and three with sarcomatoid histology. Most patients (24, 71%) received only one treatment regimen of platinum (carboplatin or cisplatin) and pemetrexed chemotherapy before starting treatment on this study. Bevacizumab was included as first-line therapy in eight patients (26%). No patient received prior ICI therapy. Table 1 describes the characteristics of subjects and the number of prior therapies received.

Treatment Outcomes

One patient was not assessable for response after he withdrew from the study because of generalized weakness one day after first infusion of ramucirumab and nivolumab. In two patients, progression was recorded as clinical progression. Response was found in seven patients with ORR of 22.6% (95% CI: 9.6%–41.1%) in all patients, and 43% (95% CI: 10%–82%) in patients with nonepithelioid histology, all revealing partial responses. Of all patients, 45.2% (95% CI: 27.3%–64.0%) had stable disease. Figure 1*A* illustrates a waterfall plot of responses. Figure 1*B* illustrates treatment duration. At the time of data cutoff, two patients were still receiving treatment.

The median time to response was 56 days (range 28–200), and median duration of response was 168 days (95% CI: 91–280). The median duration of ramucirumab and nivolumab treatment was 3.2 months (interquartile range, 1.4–6.1). Overall, patients received 100% planned per cycle doses of both drugs; median dose of ramucirumab was 8 mg/kg and nivolumab was 240 mg per cycle.

Median follow-up was 10.2 months (interquartile range, 19.6 mo [4.3–23.8]). PFS rate for overall study

Table 1. Patient Characteristics

Characteristic	N = 34
Age, y, median (range)	72 (40-89)
Sex, n (%)	
Female	4 (12)
Male	30 (88)
Ethnicity	
Hispanic or Latino	2 (5.9)
Non-Hispanic	31 (91)
Unknown	1 (2.9)
Race, n (%)	
Black or African American	1 (2.9)
Unknown	2 (5.9)
White	31 (91)
Primary, n (%)	
Pleural	30 (88)
Peritoneal	4 (12)
Histology, n (%)	
Epithelial	27 (79)
Biphasic	4 (12)
Sarcomatoid	3 (9)

population at 24 weeks was 32% (95% CI: 17%–51%), and median PFS was 4.2 months (95% CI: 1.9–6.4 mo). Figure 2*A* illustrates the Kaplan-Meier PFS curve. Patients with nonepithelioid histology had a median PFS of 6.0 months (95% CI: 1.64–11.53). Median OS was 12.5 months (95% CI: 6.3–23.5 mo). Figure 2*B* illustrates the Kaplan-Meier OS curve. Patients with nonepithelioid histology had median OS of 11.4 months (95% CI: 3.8–18.5).

Safety and Adverse Events

The median number of 2-week treatment cycles was 7 (range, 1–52), corresponding to 3 months (range, 0–24 mo). Dose delays due to adverse events occurred in one patient (2.9%). The rate of treatment discontinuation because of adverse events was 12% (n = 4). The causes of treatment discontinuation were as follows: grade 3 muscle weakness in one patient, grade 2 heart failure in one patient, and grade 1 anorexia, nausea, and vomiting in one patient. In all instances, treatment discontinuation was attributed to both drugs. The incidence of adverse events at least possibly related to nivolumab was 82.3% and to ramucirumab was 79.4%. The incidence of grade 3 treatment-related adverse events was 33% and included the following: hypertension (9%), hyponatremia (6%), diarrhea (3%), hyperkalemia (3%), muscle weakness (3%), myocardial infarction (3%), proteinuria (3%), and syncope (3%). There were no treatment-related grade 4 or 5 toxicities. The following were the grade 3 immune-related toxicities: diarrhea (3%) and muscle weakness (3%). A list of all treatment-related toxicities is provided in Table 2.

Exploratory Studies

There were 34 individuals who had available serum for sPD-L1 analysis on day 1 of cycle 1 and 24 individuals on day 1 of cycle 5. Neither baseline nor change in sPD-L1 (neither increase nor decrease) correlated with best response, PFS, or OS.

Only 12 subjects had sufficient tissue at screening for analysis of PD-L1 expression, and only 10 subjects had tumor tissue available for analysis at screening paired with second biopsy before day 1 of cycle 5. There was no correlation between best response and any of the following: baseline PD-L1 expression, change in PD-1, change in MAI, and change in LAI. There was no correlation between PFS or OS and the following variables: baseline PD-L1 expression, change in PD-1, and change in MAI. PFS in patients with increasing MAI was 5.4 ± 1.4 months versus 2.6 ± 0.7 months in patients with decreasing MAI, with hazard ratio (HR) of 0.96 (0.76–1.23) ($p = 0.751$). Patients with tumors that had increasing activation of T lymphocytes had PFS of 6.6 ± 1.7 months versus 2.6 ± 0.5 months in patient with decreasing fraction of activated T lymphocytes that approached level of significance (HR 0.91 [95% CI: 0.81–1.02], $p = 0.104$) (Table 3).

Discussion

Our study did not meet the primary end point to reject an ORR rate of 20% based on historical data of pembrolizumab alone,[18] in favor of an ORR rate of 40% with the combination of nivolumab and ramucirumab. ORR was found in seven patients (ORR of 22.6%), although in patients with nonepithelioid histology, ORR was 43%. Interestingly, the higher effect of ICI treatment in nonepithelioid histology was also found in CheckMate 743 study.[2]

In the randomized CONFIRM study which evaluated 332 patients with relapsed mesothelioma, treatment with single-agent nivolumab resulted in 11% ORR.[19] When our study was designed, we did not have data on single-agent nivolumab activity in relapsed mesothelioma and had to rely on reference activity of pembrolizumab in a study of only 25 patients.[18]

The efficacy of nivolumab and ramucirumab was reflected in the PFS rate at 24 weeks of 32%, median PFS of 4.2 months, and median OS of 12.5 months. This compares favorably to activity of single-agent nivolumab (median PFS of 3.0 mo and median OS of 10.2 mo)[19] or ipilimumab and nivolumab after progression after first- or second-line pemetrexed and platinum regimen (ORR of 28%, median PFS of 5.6 mo, and median OS of 15.9 mo).[20] It also compares favorably to activity of gemcitabine and ramucirumab (ramucirumab dose: 10 mg/kg) combination for treatment of unresectable pleural mesothelioma after progression from first-line therapy with

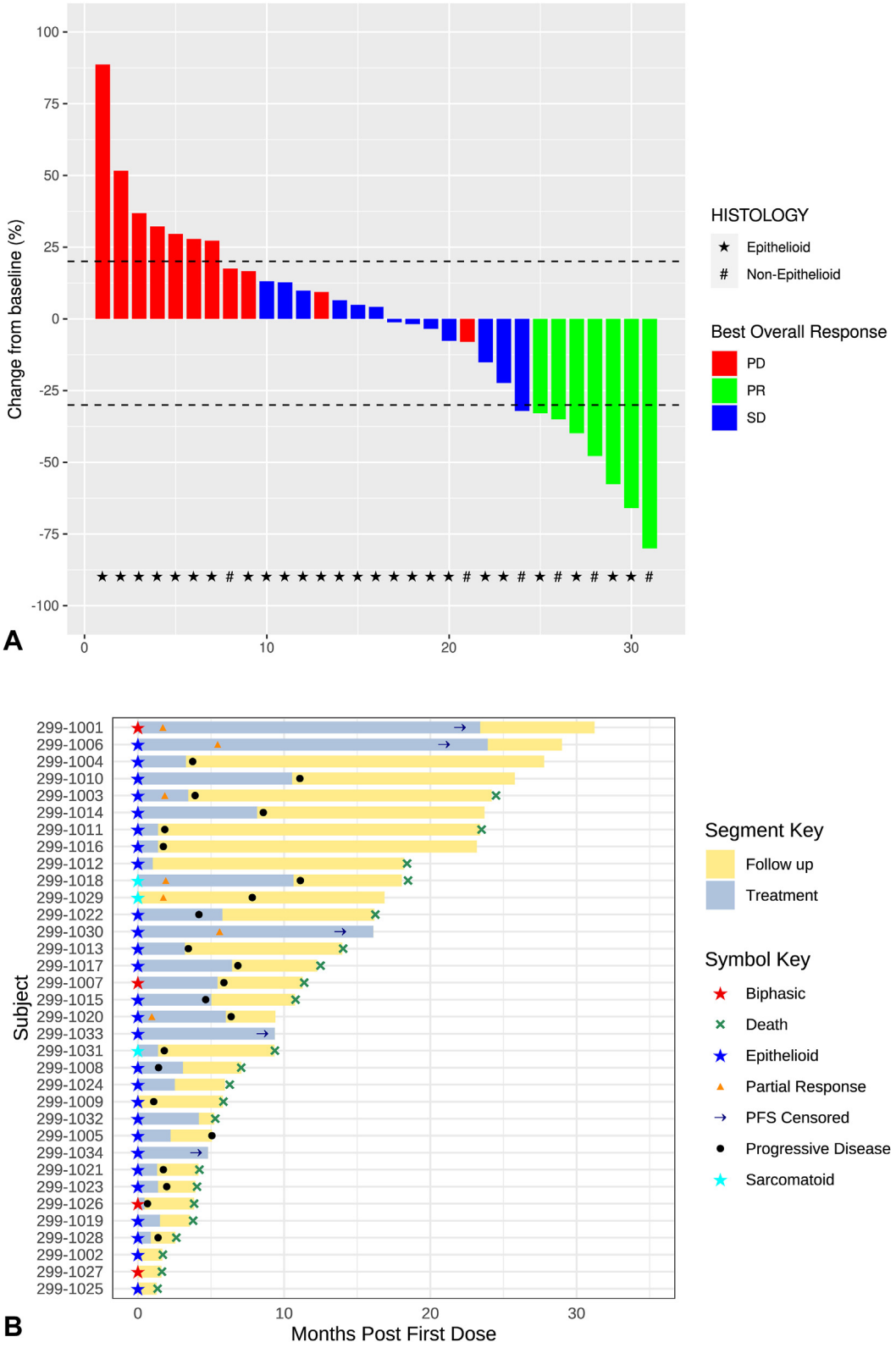

Figure 1. (*A*) Waterfall plot of the best response by modified RECIST version 1.1 and (*B*) swimmer plot of duration of treatment. In panel (*A*), bars represent best overall response. Stars represent epithelioid histology and hashtags non-epithelioid histology of the tumor. In panel (*B*), x axis represents months from first dose of treatment, and y axis represents individual subjects. PD, progressive disease; PR, partial response; SD, stable disease.

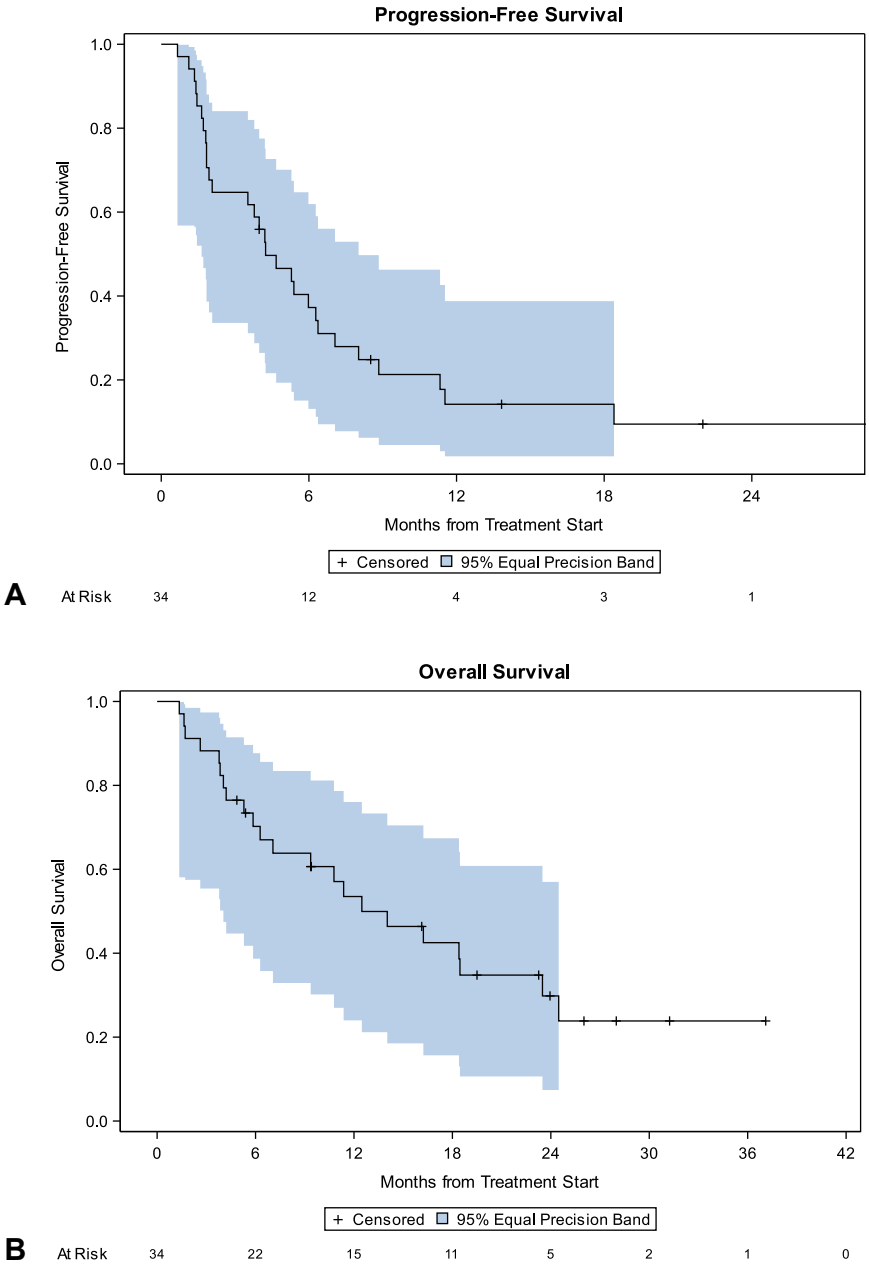

Figure 2. (*A*) Progression-free survival and (*B*) overall survival. Kaplan-Meier analysis.

pemetrexed and platinum,[3] where no CR and only 6% PR were found, with median PFS of 6.4 months and median OS of 13.8 months.

We selected ramucirumab dose of 8 mg/kg every 2 weeks (as indicated for treatment of metastatic gastric cancer), rather 10 mg/kg every 21 days as indicated for treatment of lung cancer, to align with every 2-week administration of nivolumab. Because the ramucirumab exposure is similar in both regimens, we do not feel that selection of the dose of 8 mg/kg of ramucirumab had a negative effect on activity of the combination regimen in our study.

None of the patients who received bevacizumab in their prior treatment regimen had a tumor response, but all who completed at least one cycle of treatment (seven of eight) had stable disease with median PFS of 4.2 month, and median OS of 14.0 months. This would suggest that prior treatment with bevacizumab does not negatively affect the potential benefit from nivolumab and ramucirumab.

Study allowed patients with peritoneal mesothelioma although not identical, but have sufficiently similar genomic landscape,[21] to justify inclusion of both mesothelioma subtypes in our study. In addition, patients with peritoneal mesothelioma diagnosis are frequently

Table 2. Treatment-Related Adverse Events (All Grades)

Possibly or Probably Related to Nivolumab or Ramucirumab		Number (%) of Patients (n = 34) With Adverse Events by Severity Grade[a]			
System organ class[b]	Adverse event preferred term[b]	Grade 1	Grade 2	Grade 3	Number of Events
Blood and lymphatic system disorders	Anemia	1 (3)			1
	Platelet count decreased	1 (3)			1
Cardiac disorders	Heart failure		1 (3)		1
	Myocardial infarction			1 (3)	1
Ear and labyrinth disorders	Vertigo	1 (3)			1
Eye disorders	Watering eyes	1 (3)			1
Endocrine disorders	Hyperthyroidism	1 (3)			1
	Hypothyroidism	2 (6)	3 (9)		5
Gastrointestinal disorders	Constipation	1(3)			1
	Diarrhea	3 (9)		1(3)	4
	Nausea	2 (6)			2
	Oral mucositis	1 (3)			1
	Stomach pain	2 (6)			2
	Vomiting	1 (3)			1
General disorders	Chills	1 (3)			1
	Edema limbs	4 (12)			4
	Fatigue	9 (26)	6 (18)		15
	Fever	1 (3)			1
	Infusion-related reactions	2 (6)			2
	Infusion site extravasation	1 (3)			1
	Irritability	1 (3)			1
	Pain	2 (6)			2
Infections and infestations	Sinusitis		1 (3)		1
Investigations	AST increased	2 (6)			2
	Creatinine increased	1 (3)			1
	Weight loss	1 (3)			1
Metabolism and nutrition disorders	Anorexia	4 (12)			4
	Dehydration	1 (3)			1
	Hyperkalemia			1 (3)	1
	Hypokalemia	1 (3)			1
	Hypomagnesemia	1 (3)			1
	Hyponatremia			2 (6)	2
Musculoskeletal disorders	Arthralgia	6 (18)			6
	Back pain	1 (3)			1
	Chest wall pain	2 (6)			2
	Myalgia	1 (3)			1
	Muscle weakness	3 (9)	2 (6)	1 (3)	6
Nervous system disorders	Dizziness	3 (9)	1 (3)		4
	Dysgeusia	1 (3)			1
	Headache	6 (18)			6
	Memory impairment	2 (6)			2
	Peripheral sensory neuropathy	1 (3)			1
	Syncope			1 (3)	1
Psychiatric disorders	Confusion	1 (3)			1
	Insomnia	1 (3)			1
Renal and urinary disorders	Hematuria	1 (3)			1
	Proteinuria		6 (8)	1 (3)	7
Respiratory, thoracic, and mediastinal disorders	Cough	2 (6)			2
	Dyspnea	2 (6)			2
	Epistaxis	1 (3)			1
	Nasal congestion	1 (3)			1
	Pneumonitis		1(3)		1

(continued)

Table 2. Continued

Possibly or Probably Related to Nivolumab or Ramucirumab		Number (%) of Patients (n = 34) With Adverse Events by Severity Grade[a]			
System organ class[b]	Adverse event preferred term[b]	Grade 1	Grade 2	Grade 3	Number of Events
Skin and subcutaneous tissue disorders	Angioma	1 (3)			1
	Atopic dermatitis		1 (3)		1
	Dry skin	1 (3)			1
	Erythema multiforme	1 (3)			1
	Pruritus	2 (6)			2
	Rash maculopapular	5 (15)			5
	Skin hypopigmentation	1 (3)			1
Vascular disorders	Hypertension			3 (9)	3

[a]Patients are counted once for multiple occurrences of the same adverse event, according to the worst severity grade (CTCAE, version 4.0, published: May 28, 2009 [version 4.03: June 14, 2010]).
[b]Coded with MedDRA Version 20.0.
AST, aspartate transaminase; CTCAE, Common Terminology Criteria for Adverse Events.

excluded from clinical trials, and in participating institutions, they did not have experimental therapeutic options. The similar sentiment allowed inclusion of both peritoneal and pleural mesotheliomas in CONFIRM[19] and DETERMINE[22] clinical trials.

The combination was tolerated without grade 4 or 5 toxicities and a grade 3 toxicity rate of 33% with a treatment discontinuation rate of 12%. These safety data are similar to 28% grade 3 or higher toxicity rate and treatment-related discontinuation rate of 14% of single-agent nivolumab.[19] These safety data are favorable as compared with gemcitabine and ramucirumab combination that had grade 3 or higher toxicity rate of 44% and 11% treatment-related discontinuation rate,[3] 26% grades 3 to 4 toxicity, and 5% treatment-related death on ipilimumab and nivolumab.[20]

Activity and toxicity of ramucirumab and nivolumab in second- or higher-line therapy for mesothelioma seem to be at least as good as that of single-agent avelumab in second-line treatment, with ORR of 9%, median PFS of 4.1 months, median OS of 10.7 months, and 9% rate of grade 3 or 4 toxicities.[23]

High PD-L1 expression has been reported to be associated with worse OS in patients with mesothelioma.[13] In our study, there was no correlation between expression of baseline PD-L1 or change in PD-L1 expression and either best response or OS. Mesothelioma tumors with higher expression of CD68+ macrophages are associated with a lesser response to chemotherapy and shorter survival.[24] In our study, we observed that in 70% of tumors, there was an increase in macrophages expressing CD80 and a decrease in CD206, suggesting that ramucirumab was increasing fraction of macrophages that are associated with tumor control. Increase in lymphocyte activation index correlated with longer PFS that approached level of significance (HR of 0.91, $p = 0.104$).

Table 3. Correlative End Point and Progression-Free Survival and Overall Survival

End Point: Progression-Free Survival (N = 10)		
Variable	HR (95% CI)	*p* Value
Increase in PD-L1	1.07 (0.98-1.17)	0.110
Increase in MAI	0.96 (0.76-1.23)	0.751
Increase in LAI	0.91 (0.81-1.02)	0.104
End Point: Overall Survival (N = 10)		
Variable	HR (95% CI)	*p* Value
Increase in PD-L1	0.99 (0.92-1.08)	0.894
Increase in MAI	1.00 (0.76-1.33)	0.982
Increase in LAI	0.98 (0.89-1.09)	0.747

Note: HR from univariate Cox regression models with one covariate entered per model.
CI, confidence interval; HR, hazard ratio; LAI, lymphoid activation index; MAI, myeloid activation index; PD-L1, programmed death-ligand 1.

Our study includes the following shortcomings: assumptions for desired effect of combination were based on results of a study with only 25 patients with different checkpoint inhibitor,[18] high heterogeneity of patient population who had either one or more prior therapies, including prior bevacizumab use, and unknown benefit to current clinical practice where use of ICIs in the frontline setting is accepted based on activity of ipilimumab and nivolumab.[2] In addition, in near future, we will see outcomes of ICIs in combination with platinum and pemetrexed,[25,26] or in combination of bevacizumab and chemotherapy (BEAT-meso study; ClinicalTrials.gov identifier: NCT03762018), likely bringing additional ICI to the frontline treatment of mesothelioma.

In conclusion, this study of combination of nivolumab and ramucirumab in patients with pleural mesothelioma that progressed on prior therapy did not meet its primary end point to reject an ORR rate of 20% based on historical data of pembrolizumab alone, in favor of 40% ORR, but the drug combination had an acceptable toxicity profile comparable with single-agent nivolumab in this setting. Except for increased activation of tumor-infiltrating lymphocytes correlating with a trend of longer PFS, no other predictive biomarkers in the tissue or blood were identified. The drug combination of nivolumab and ramucirumab could be further tested in a patient population with treatment-naive, unresectable mesothelioma with nonepithelioid histology. It is conceivable in this population that there might be a high disease control rate with favorable toxicity as compared with ipilimumab and nivolumab.

CRediT Authorship Contribution Statement

Arkadiusz Z. Dudek: Conceptualization, Investigation, Formal analysis, Writing—original draft preparation, Writing—reviewing and editing.

Min X. Xi: Formal analysis, Writing—reviewing and editing.

Katherine A. Scilla: Investigation, Writing—reviewing and editing.

Hirva Mamdami: Investigation, Writing—reviewing and editing.

Benjamin C. Creelan: Investigation, Writing—reviewing and editing.

Andreas Saltos: Investigation, Writing—reviewing and editing.

Tawee Tanvetanon: Investigation, Writing—reviewing and editing.

Alberto Chiappori: Investigation, Writing—reviewing and editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100584.

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