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Original Investigation | Oncology

Clinical Outcomes Associated With Pembrolizumab Monotherapy Among Adults With Diffuse Malignant Peritoneal Mesothelioma

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Abstract

IMPORTANCE Diffuse malignant peritoneal mesothelioma (DMPM) represents a rare and clinically distinct entity among malignant mesotheliomas. Pembrolizumab has activity in diffuse pleural mesothelioma but limited data are available for DMPM; thus, DMPM-specific outcome data are needed.

OBJECTIVE To evaluate outcomes after the initiation of pembrolizumab monotherapy in the treatment of adults with DMPM.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study was conducted in 2 tertiary care academic cancer centers (University of Pennsylvania Hospital Abramson Cancer Center and Memorial Sloan Kettering Cancer Center). All patients with DMPM treated between January 1, 2015, and September 1, 2019, were retrospectively identified and followed until January 1, 2021. Statistical analysis was performed between September 2021 and February 2022.

EXPOSURES Pembrolizumab (200 mg or 2 mg/kg every 21 days).

MAIN OUTCOMES AND MEASURES Median progression-free survival (PFS) and median overall survival (OS) were assessed using Kaplan-Meier estimates. The best overall response was determined using RECIST (Response Evaluation Criteria in Solid Tumors) criteria, version 1.1. The association of disease characteristics with partial response was evaluated using the Fisher exact test.

RESULTS This study included 24 patients with DMPM who received pembrolizumab monotherapy. Patients had a median age of 62 years (IQR, 52.4-70.6 years); 14 (58.3%) were women, 18 (75.0%) had epithelioid histology, and most (19 [79.2%]) were White. A total of 23 patients (95.8%) received systemic chemotherapy prior to pembrolizumab, and the median number of lines of prior therapy was 2 (range, 0-6 lines). Of the 17 patients who underwent programmed death ligand 1 (PD-L1) testing, 6 (35.3%) had positive tumor PD-L1 expression (range, 1.0%-80.0%). Of the 19 evaluable patients, 4 (21.0%) had a partial response (overall response rate, 21.1% [95% CI, 6.1%-46.6%]), 10 (52.6%) had stable disease, and 5 (26.3%) had progressive disease (5 of 24 patients [20.8%] were lost to follow-up). There was no association between a partial response and the presence of a *BAP1* alteration, PD-L1 positivity, or nonepithelioid histology. With a median follow-up of 29.2 (95% CI, 19.3 to not available [NA]) months, the median PFS was 4.9 (95% CI, 2.8-13.3) months and the median OS was 20.9 (95% CI, 10.0 to NA) months from pembrolizumab initiation. Three patients (12.5%) experienced PFS of more than 2 years. Among patients with nonepithelioid vs epithelioid histology, there was a numeric advantage in median PFS (11.5 [95% CI, 2.8 to NA] vs 4.0 [95% CI, 2.8-8.8] months) and median OS (31.8 [95% CI, 8.3 to NA] vs 17.5 [95% CI, 10.0 to NA] months); however, this did not reach statistical significance.

(continued)

Key Points

Question What are the clinical outcomes associated with pembrolizumab monotherapy among adults with diffuse malignant peritoneal mesothelioma (DMPM)?

Findings In this cohort study of 24 patients with DMPM treated with pembrolizumab, we observed a partial response of 21% and stable disease of 53% as the best overall response. Outcomes were numerically better for patients with nonepithelioid histology vs epithelioid histology but this was not statistically significant.

Meaning These findings suggest that pembrolizumab has clinical activity in DMPM and should be considered as a treatment option in this rare disease.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE The results of this retrospective dual-center cohort study of patients with DMPM suggest that pembrolizumab had clinical activity regardless of PD-L1 status or histology, although patients with nonepithelioid histology may have experienced additional clinical benefit. The partial response rate of 21.0% and median OS of 20.9 months in this cohort with 75.0% epithelioid histology warrants further investigation to identify those most likely to respond to immunotherapy.

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Introduction

Diffuse malignant peritoneal mesothelioma (DMPM) is a rare form of malignant mesothelioma arising from the peritoneum, with median overall survival (OS) ranging from 9 to 100 months.[1,2] Currently, patients with epithelioid DMPM achieve the best outcomes with multimodality therapy with cytoreductive surgery (CRS) and intraperitoneal chemotherapy.[3,4] However, most patients worldwide do not undergo CRS due to lack of access to surgical expertise, poor operative risk factors, or unfavorably aggressive histology (sarcomatoid and biphasic subtypes).[2,3,5] For patients with DMPM not amenable to CRS, systemic chemotherapy is the standard of care, with the combination of a platinum-based agent and pemetrexed achieving a moderate overall response rate (ORR) of 20% to 24%.[6] Other data specific to therapy choice in DMPM are limited and often extrapolated from diffuse pleural mesothelioma (DPM).

Recently, immune checkpoint inhibition (ICI) has shown promise in treating DPM, again leading to extrapolation for its use in DMPM, a clinically and genomically distinct disease.[7-10] In contrast with DPM, there is a paucity of ICI data specific to DMPM.[11] Two recent single-center studies evaluating ICIs in DMPM have been reported: the first included 20 patients and evaluated combination atezolizumab and bevacizumab (ORR, 40%; median progression-free survival [PFS], 17.6 months),[12] while the second included 29 patients (20 treated with dual ICI and 9 with single-agent ICI) and evaluated primarily dual ICI (ORR, 19.2%; median PFS, 5.5 months).[13] Although both studies provide critical information on outcomes after ICI use in this population, the inclusions of bevacizumab and the heterogeneity of dual- and single-agent ICI, respectively, limit conclusions about the true efficacy of ICI monotherapy, which is often favored for its toxicity profile. We used data from 2 academic centers to evaluate patient outcomes after pembrolizumab treatment for DMPM.

Methods

Institutional review board approval for this retrospective cohort study was obtained from 2 tertiary care academic cancer centers (University of Pennsylvania Hospital Abramson Cancer Center and Memorial Sloan Kettering Cancer Center). Informed consent was waived because deidentified data were used. This report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

All patients with pathologically confirmed DMPM who received pembrolizumab (200 mg or 2 mg/kg every 21 days) at 1 of the 2 cancer centers between January 1, 2015, and September 1, 2019, were retrospectively identified and followed until January 1, 2021. Patients with well-differentiated papillary histology were excluded. The variables included in eTable 1 in Supplement 1 were extracted from the electronic medical record. Patient-reported race and ethnicity (categorized as Black, White, and other [ie, unspecified other or unknown race or ethnicity]) was also obtained from the electronic medical record to further describe this cohort with a rare malignant neoplasm. Computed tomography images were obtained at therapy initiation and during therapy as per standard practice. The unconfirmed best overall response (BOR) and the disease control rate were determined

Table. Baseline Characteristics of Patients With Diffuse Malignant Peritoneal Mesothelioma Who Received Pembrolizumab[a]

Characteristic	Values
Total No. of patients	24
Age, median (IQR), y	
At diagnosis	62.0 (52.4-70.6)
At time of pembrolizumab receipt	65.6 (53.5-72.5)
Sex	
Male	10 (41.7)
Female	14 (58.3)
Race and ethnicity	
Black	0
White	19 (79.2)
Other[b]	5 (20.8)
Asbestos exposure[c]	
Yes	9 (37.5)
No	15 (62.5)
ECOG performance status at diagnosis	
0	5 (23.8)
1	15 (71.4)
2	1 (4.8)
Unknown	3 (12.5)
Histology	
Epithelioid	18 (75.0)
Biphasic	4 (16.6)
Sarcomatoid	1 (4.2)
Desmoplastic	1 (4.2)
Largest peritoneal implant, cm	
<2	3 (14.3)
2-5	11 (52.4)
≥5	7 (33.3)
Unknown	3 (12.5)
Ascites present	
Yes	14 (58.0)
No	10 (42.0)
Tumor PD-L1 status, %	
<1	11 (45.8)
1-49	5 (20.8)
50-100	1 (4.2)
Unknown	7 (29.2)
BAP1 alteration in tumor tissue	
Present	8 (33.3)
Absent	6 (25.0)
Not tested	10 (41.6)
Prior cytoreductive surgery	
Yes	16 (66.7)
No	8 (33.3)
Prior intraperitoneal chemotherapy	
Yes	8 (33.3)
No	16 (66.7)

(continued)

Table. Baseline Characteristics of Patients With Diffuse Malignant Peritoneal Mesothelioma Who Received Pembrolizumab[a] (continued)

Characteristic	Values
Prior lines of systemic chemotherapy[d]	
0	1 (4.2)
1	11 (45.8)
2	7 (29.0)
≥3	5 (20.8)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand 1.

[a] Unless noted otherwise, data are expressed as No. (%) of patients.

[b] Includes unspecified and unknown race or ethnicity.

[c] Includes both suspected occupational exposure and other sources of exposure (eg, known home exposures).

[d] Prior systemic chemotherapy includes courses of chemotherapy administered in perioperative settings (neoadjuvant and adjuvant) but does not include intraperitoneal chemotherapy.

retrospectively using RECIST (Response Evaluation Criteria in Solid Tumors) criteria, version 1.1, by dedicated study radiologists (L.R., M.S.G., and S.I.K.).[14] Clopper-Pearson exact 95% CIs were calculated for response rates.

Statistical Analysis

The Kaplan-Meier method was used to estimate PFS and OS. Progression-free survival was defined as the time from pembrolizumab initiation until radiologic progression, clinical progression, or death. Overall survival was defined as the time from pembrolizumab initiation until death or censoring at last follow-up. Subgroups were compared using the log-rank test. Associations between partial response and *BAP1* alterations, programmed death ligand 1 (PD-L1) positivity, and histology were assessed using the Fisher exact test.

Associations between partial response and the stable disease control as well as *BAP1* alterations, PD-L1 positivity, and histology were assessed separately, using 2-sided Fisher exact tests. Stata, version 14.2 (Statacorp), and R, version 4.2.1 (R Foundation for Statistical Computing), were used for analyses. Significance was set at $P < .05$. Initial statistical analysis was performed between September 2021 and February 2022.

Results

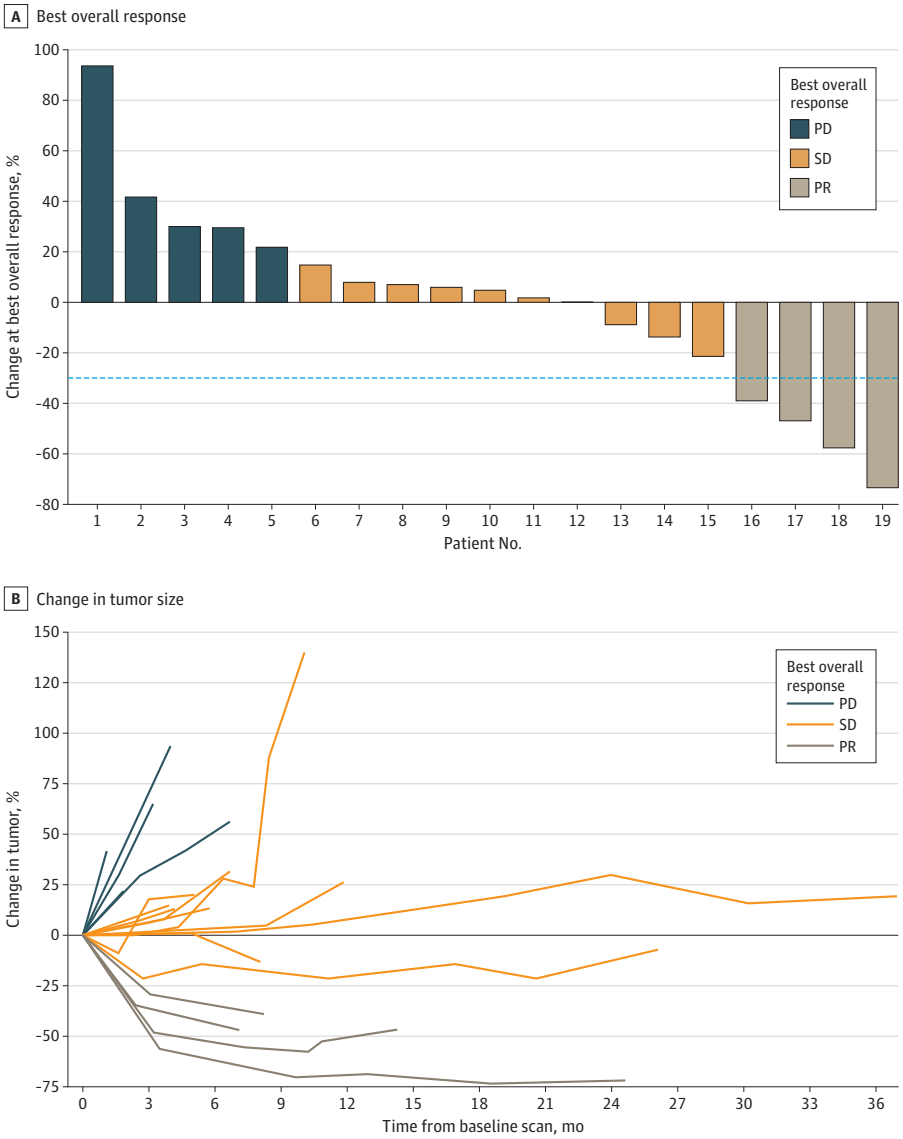
This cohort study included 24 patients with DMPM. They had a median age of 62 years (IQR, 52.4-70.6 years); 14 (58.3%) were women and 10 (41.7%) were men. No patients were Black (0%), 19 (79.2%) were White, and 5 (20.8%) reported being of unspecified other or unknown race or ethnicity. There were 23 patients (95.8%) with prior exposure to intravenous systemic chemotherapy, with 12 (50.0%) receiving 2 or more lines of prior therapy (range, 0-6 prior lines). Nine patients (37.5%) had a self-reported history of potential prior asbestos exposure. Epithelioid histology was predominant (18 of 24 [75.0%]) compared with biphasic (4 [16.6%]), sarcomatoid (1 [4.2%]), and desmoplastic (1 [4.2%]) histology. Six patients (25.0%) had tumors with known positive PD-L1 expression (range, 1.0%-80.0%), 11 patients (45.8%) had tumors with negative expression, and 7 (29.2%) did not have tumors tested (**Table**).

Targeted next-generation sequencing was conducted on tumor tissue from 14 patients (58.3%). *BAP1* alterations were detected for 8 patients (57.1%) who underwent next-generation sequencing. Among 11 patients who underwent germline *BAP1* testing, 1 variant of unknown significance (9.1%) was found. Six patients (25.0%) reported a family history of a *BAP1*-related tumor such as breast

cancer, melanoma, or renal cell carcinoma.[15] The most commonly detected alterations besides *BAP1* were *SETD2* (4 [28.6%]), *TP53* (2 [14.2%]), *NF2* (2 in the same patient), and *PBRM1* (2 [14.2%]). Other alterations detected included point mutations in *CDKN2A*, *CDKN2B*, and *MSH6* and a *PPP1R10-KMT2B* fusion.

The median number of pembrolizumab cycles administered was 7 (range, 1-42 cycles). The ORR as determined by the BOR to pembrolizumab was 21.1% (95% CI, 6.1%-46.6%). Of the 24 patients in this study, 5 (20.8%) did not have radiologic images available for review. Of the 19 patients with radiologic data, 4 (21.0%) exhibited a partial response, 10 (52.6%) had stable disease, and 5 (26.3%) had progressive disease as the BOR (**Figure 1**). With a median follow-up of 29.2 (95% CI, 19.3 to not available [NA]) months, the median PFS was 4.9 (95% CI, 2.8-13.3) months from pembrolizumab initiation, whereas the median OS was 20.9 (95% CI, 10.0 to NA) months from pembrolizumab initiation and 81.6 (95% CI, 63.2 to NA) months from initial diagnosis. Progression-free survival did not differ based on PD-L1 status, with a median PFS of 3.1 (95% CI, 2.5 to NA) months for positive status vs 5.7 (95% CI, 4.0 to NA) months for negative status (log-rank P = .30). Three patients experienced PFS of 2 years or more, with the following characteristics: (1) epithelioid histology,

Figure 1. Tumor Response After Pembrolizumab Treatment



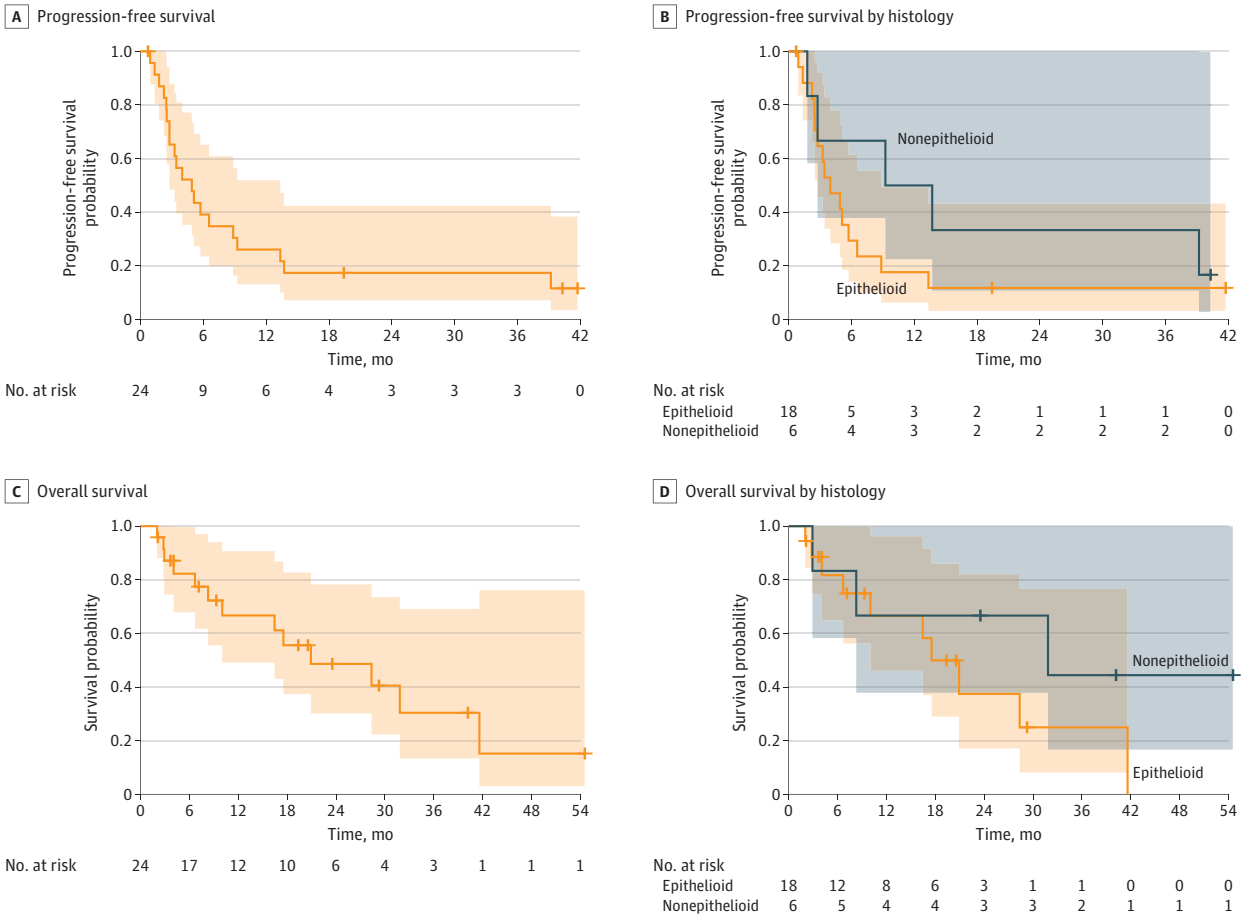
A, Best overall response to pembrolizumab determined by RECIST (Response Evaluation Criteria in Solid Tumors) criteria, version 1.1. The dashed blue line indicates a partial response (PR) threshold of −30%. Additional patient information is provided in eTable 1 in Supplement 1. B, Spider plot showing tumor percent change compared with baseline over time. PD indicates progressive disease; SD, stable disease.

unknown tumor PD-L1 status, stable disease (BOR), and a 2.0% change in tumor size; (2) desmoplastic histology, 0% tumor PD-L1 status, stable disease (BOR), and a −21.0% change in tumor size; and (3) biphasic histology, 80.0% tumor PD-L1 status, partial response (BOR), and a −70.0% change in tumor size. There was a numeric benefit in clinical outcomes among patients with nonepithelioid tumors, although it did not reach statistical significance for median PFS (11.5 [95% CI, 2.8 to NA] vs 4.0 [95% CI, 2.8-8.8] months; *P* = .24) or median OS (31.8 [95% CI, 8.3 to NA] vs 17.5 [95% CI, 10.0 to NA] months; log-rank *P* = .24) (**Figure 2**). Outcomes after pembrolizumab treatment were better for patients with fewer prior lines of chemotherapy but did not differ based on a history of prior CRS (eTable 2 in Supplement 1). The 5 patients with missing radiologic data had PFS of 0.6, 1.3, 2.5, 4.0, and 9.2 months (mean [SD] PFS, 3.5 [3.1] months).

Discussion

The results of this dual-center retrospective cohort study of patients with DMPM suggest that treatment with pembrolizumab is clinically active. Our results were similar to a previous study of outcomes of patients with DMPM treated primarily with dual ICI regimens (ORR, 19.2%; median PFS, 5.5 months).[13] Given the favorable toxicity profile of single-agent ICI over dual ICI, our findings of similar clinical outcomes support pembrolizumab use as a treatment option for patients with DMPM.

Figure 2. Clinical Outcomes After Pembrolizumab Treatment



A and B, Probability of progression-free survival after initiation of pembrolizumab in the overall cohort (A) and by histology (B). C and D, Probability of overall survival after initiation of pembrolizumab in the overall cohort (C) and by histology (D). Shaded areas represent 95% CIs.

Although we did not identify a statistical difference between histologies, patients with nonepithelioid DMPM had numerically superior clinical outcomes compared with those with epithelioid DMPM. In our cohort, two-thirds of patients with PFS of 2 years or more with pembrolizumab had nonepithelioid histology. The retrospective nature of this analysis and pembrolizumab use in later lines of therapy could select for patients with nonepithelioid DMPM with less aggressive biology; however, the median time receiving a prior line of therapy was shorter in the nonepithelioid group compared with the epithelioid group (1.0 vs 7.7 months), suggesting that the disease is still aggressive for these individuals.

Limitations

There are limitations of this retrospective cohort study. Since patients did not always receive all of their treatment at single locations, radiologic data were missing for 5 patients (20.8%). The mean PFS for these 5 patients was 3.5 months, which was near the median PFS of the whole cohort, suggesting that these images were missing at random. In addition, we did not control for potential confounders (eg, burden of disease); however, patients with disease not amenable to second-line treatment were generally excluded, given this largely pretreated cohort. Nonetheless, this data set represents, to our knowledge, the largest cohort of patients with DMPM treated with single-agent ICI to date and is the only such report combining patients from multiple centers.

Conclusions

In summary, these preliminary data suggest that pembrolizumab has clinical activity in DMPM. Furthermore, we observed potentially superior outcomes in patients with nonepithelioid DMPM, representing an important pathway for further research in this population with limited treatment options. Future immunotherapy trials in DMPM should leverage novel immunotherapy targets and a multi-institutional approach to increase the sample size and power to detect disease response and determine the predictive role of histology and biomarkers in this rare disease.

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Author Contributions: Dr Marmarelis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Marmarelis and Wang contributed equally to this work.

Concept and design: Marmarelis, Wang, Cercek, Foote, Nash, Cengel, Katz, Zauderer, Langer, Offin.

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Administrative, technical, or material support: Roshkovan, Miura, Ginsberg, Ciunci, Egger, Walker, Zauderer, Langer.

Supervision: Marmarelis, Zauderer, Langer, Offin.

Conflict of Interest Disclosures: Dr Marmarelis reported receiving research funding (paid to the University of Pennsylvania Health System) from Eli Lilly, Trizell, and AstraZeneca as well as consulting fees from AstraZeneca, Blueprint Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Ikena, Janssen, Novocure, and Takeda outside the submitted work. Dr Marmarelis also reported owning stock in Gilead Sciences, Portola Pharmaceuticals, Merck, Bluebird Bio, Johnson & Johnson, and Pfizer and receiving previous medical writing support from Novartis outside the submitted work. Dr Ciunci reported receiving research funding (paid to the University of Pennsylvania Health System) from Celgene, Merck, BMS, and MacroGenics as well as honoraria from iMedX outside the submitted work. Dr Cercek reported receiving grants from GlaxoSmithKline (GSK) and Seagen as well as personal fees for serving on the advisory boards of Bayer, Seagen, Merck, GSK, and Pfizer outside the submitted work. Dr Haas reported having a consulting role with Olympus America and Novocure outside the submitted work. Dr Karakousis reported receiving personal fees for serving on the Merck advisory board outside the submitted work. Dr Cengel reported receiving grants from the National Institutes of Health during the conduct of the study. Dr Zauderer reported receiving grants (paid to Memorial Sloan Kettering Cancer Center) from Curis, Takeda, GSK, Epizyme, Polaris, Sellas Life Sciences, BMS, and Atar as well as personal fees from Curis, Ikena, Takeda, GSK, Novocure, and Aldeyra Therapeutics outside the submitted work. Dr Zauderer also serves as chair of the board of directors (uncompensated) of the Mesothelioma Applied Research Foundation outside the submitted work. Dr Langer reported receiving research funding (paid to the University of Pennsylvania Health System) from Merck, Advantagene, Clovis Oncology, Celgene, Inovio Pharmaceuticals, ARIAD, GSK, Genentech/Roche, Stemcentrx, Lilly, and Trizell outside the submitted work. Dr Langer also reported receiving honoraria from BMS, Genentech/Roche, Lilly/ImClone, AstraZeneca, and Takeda Science Foundation; having a consulting role with Genentech/Roche, Lilly/ImClone, Merck, Abbott Biotherapeutics, Bayer/Onyx, Clarient, Cancer Support Community, BMS, ARIAD, Takeda, AstraZeneca, Pfizer, Novocure, and Gilead Sciences; and having other relationships with Lilly, Amgen, Peregrine Pharmaceuticals, and Synta outside the submitted work. Dr Offin reported receiving grants from LUNGevity and consulting fees or honoraria from Novartis, Jazz Pharmaceuticals, PharmaMar, Targeted Oncology, OncLive, and the American Society for Radiation Oncology outside the submitted work. No other disclosures were reported.

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SUPPLEMENT 1.

eTable 1. Cohort Characteristics and Outcomes
eTable 2. Median Progression-Free and Overall Survival by Baseline Tumor and Treatment Characteristics

SUPPLEMENT 2.

Data Sharing Statement