ORIGINAL ARTICLE

A Real-World Analysis of the Use of Systemic Therapy in Malignant Pleural Mesothelioma and the Differential Impacts on Overall Survival by Practice Pattern

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ABSTRACT

Introduction: Malignant pleural mesothelioma (MPM) is an aggressive malignancy that affects older adults with frequent comorbidities, making real-world treatment decisions challenging. This study compares the overall survival (OS) of patients with MPM by physician's choice of first-line (1L) platinum chemotherapy (PC), second-line (2L) immunotherapy versus chemotherapy, and by receipt of maintenance therapy (MT).

Methods: The study included patients diagnosed with advanced MPM in the Flatiron Health electronic health record–derived database who initiated PC with pemetrexed in the 1L setting between 2011 and 2019. Patients in the 2L therapy analysis received single-agent chemotherapy versus immunotherapy after the progression of disease from our 1L cohort. Patients in the MT cohort were identified on the basis of continued receipt of pemetrexed with or without bevacizumab after dropping PC at prespecified intervals. The OS of patients by choice of 1L PC, 2L immunotherapy versus chemotherapy, and receipt of MT was summarized by means of Kaplan-Meier survival estimates and compared in the context of propensity score matching weighted analyses.

Results: In propensity score matching weighting analysis from 2065 patients with MPM, there was no evidence of an OS difference by choice of 1L PC (hazard ratio [HR] = 1.08, 95% confidence interval [CI]: 0.89–1.31, $p = 0.43$), suggestive evidence of an OS difference by choice of 2L immunotherapy versus chemotherapy (HR = 0.68, 95% CI: 0.42–1.08; $p = 0.10$), and no evidence of an OS difference by receipt of MT (HR = 0.92, 95% CI: 0.72–1.16, $p = 0.46$).

Conclusions: Using real-world, propensity score–matched weighted analysis of MPM, we found there was no difference in OS by choice of 1L PC, 2L immunotherapy or chemotherapy, or by receipt of MT.

Keywords: Malignant pleural mesothelioma; Real-world outcomes; First-line platinum therapy; Second-line therapy; Maintenance therapy; Overall survival

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Introduction

Malignant pleural mesothelioma (MPM) is a relatively rare tumor with approximately 2400 to 2800 new diagnoses in the United States annually.[1] Asbestos exposure is the greatest risk factor for MPM development,[2–5] and the case rate remains steady owing to the 30- to 40-year latency period from exposure to diagnosis. Genomic analysis of MPM has identified germline and somatic mutations resulting in tumor suppressor inactivation, with CDKN2A, BAP1, WT1, and BRCA2 frequently implicated.[6,7]

The prognosis for MPM remains poor, with a reported median overall survival (OS) of 12 to 18 months with therapy.[8] Most patients are diagnosed with locally advanced and unresectable disease at the time of diagnosis. Cisplatin and pemetrexed combination chemotherapy became the backbone for first-line MPM management when the doublet revealed a 3-month OS benefit compared with cisplatin monotherapy.[8] The addition of bevacizumab to the platinum-doublet combination revealed an additional 3-month OS benefit and is routinely used in clinical practice, although it is not approved by the Food and Drug Administration for this indication.[9]

Medical comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and advanced age may impact the physicians' choice of platinum chemotherapy (PC). In an attempt to mitigate toxicity, carboplatin may be substituted for cisplatin given its better tolerability. Phase 3 data are lacking to support this practice, but phase 2 data comparing carboplatin with pemetrexed to cisplatin with pemetrexed revealed similar progression-free survival (PFS) and OS.[10]

Data on continuation pemetrexed maintenance with or without bevacizumab maintenance is controversial. A nonrandomized study from 2006 revealed an improvement in PFS and OS with maintenance pemetrexed[11] but a recent randomized phase 2 cooperative group trial found no statistically significant PFS or OS benefit with maintenance pemetrexed.[12] Thus, providers may be using maintenance pemetrexed with or without maintenance bevacizumab despite a lack of strong data supporting their clinical efficacy and benefit.

There is no consensus on the preferred 2L treatment after progression of disease on platinum-doublet chemotherapy with or without bevacizumab. The National Comprehensive Cancer Network guidelines identify immune checkpoint inhibitor monotherapy, immunotherapy combination therapies, and single-agent chemotherapy as therapeutic options.[13] A rationale exists for the application of immunotherapy in MPM, as previous research has revealed that resected tumors with the highest level of cytotoxic CD8-positive T cells had the best prognosis.[14] A real-world analysis of patients with MPM treated with 2L pembrolizumab (n = 93) found a high programmed death-ligand 1 (PD-L1) expression, and nonepithelioid histologic subtype was associated with greater activity to immunotherapy, thus, making immune checkpoint inhibitor therapy a potentially effective strategy in this setting.[15]

Our analysis had three main aims. The first is to describe the real-world prescribing patterns of platinum-based chemotherapy for MPM in the United States and to determine whether carboplatin may be an effective alternative to cisplatin-based chemotherapy in clinical practice. Our second aim is to describe the real-world prescribing patterns of second-line (2L) therapy, specifically evaluating OS outcomes by 2L immunotherapy versus single-agent chemotherapy. Finally, we described the prescribing patterns of continuation pemetrexed with or without bevacizumab maintenance therapy (MT) and evaluated the effect of MT on OS.

Materials and Methods

Cohorts and Exposures

We used the Flatiron Health nationwide electronic health record (EHR)–derived deidentified database to select patient cohorts of interest. The Flatiron Health database is a longitudinal database, comprising deidentified patient-level structured and unstructured data, curated by means of technology-enabled abstraction.[16,17] During the study period, the deidentified data originated from approximately 280 U.S. cancer clinics (~800 sites of care). The study was sent for institutional review board approval at our academic institution and was deemed exempt.

The initial cohort consisted of U.S. patients diagnosed with MPM between January 2011 and July 2019 who were treated with first-line (1L) carboplatin or cisplatin with pemetrexed and with or without bevacizumab. Patients with a previous history of malignancy were excluded. Patients who did not have a documented visit, laboratory results, or vital signs within 90 days of metastatic diagnosis were also excluded to ensure all included patients were actively engaged in care at the data-providing institution (Fig. 1).

From this cohort, we then derived two secondary cohorts to analyze our secondary aims. We identified patients with MPM who were treated with 2L therapy and grouped them by receipt of single-agent chemotherapy versus single or combination immunotherapy. We also identified a sequence of MT comparison cohorts including patients who dropped all 1L therapy within a 4-week window as compared with patients who, during each 4-week window, dropped 1L PC while remaining on bevacizumab with/without

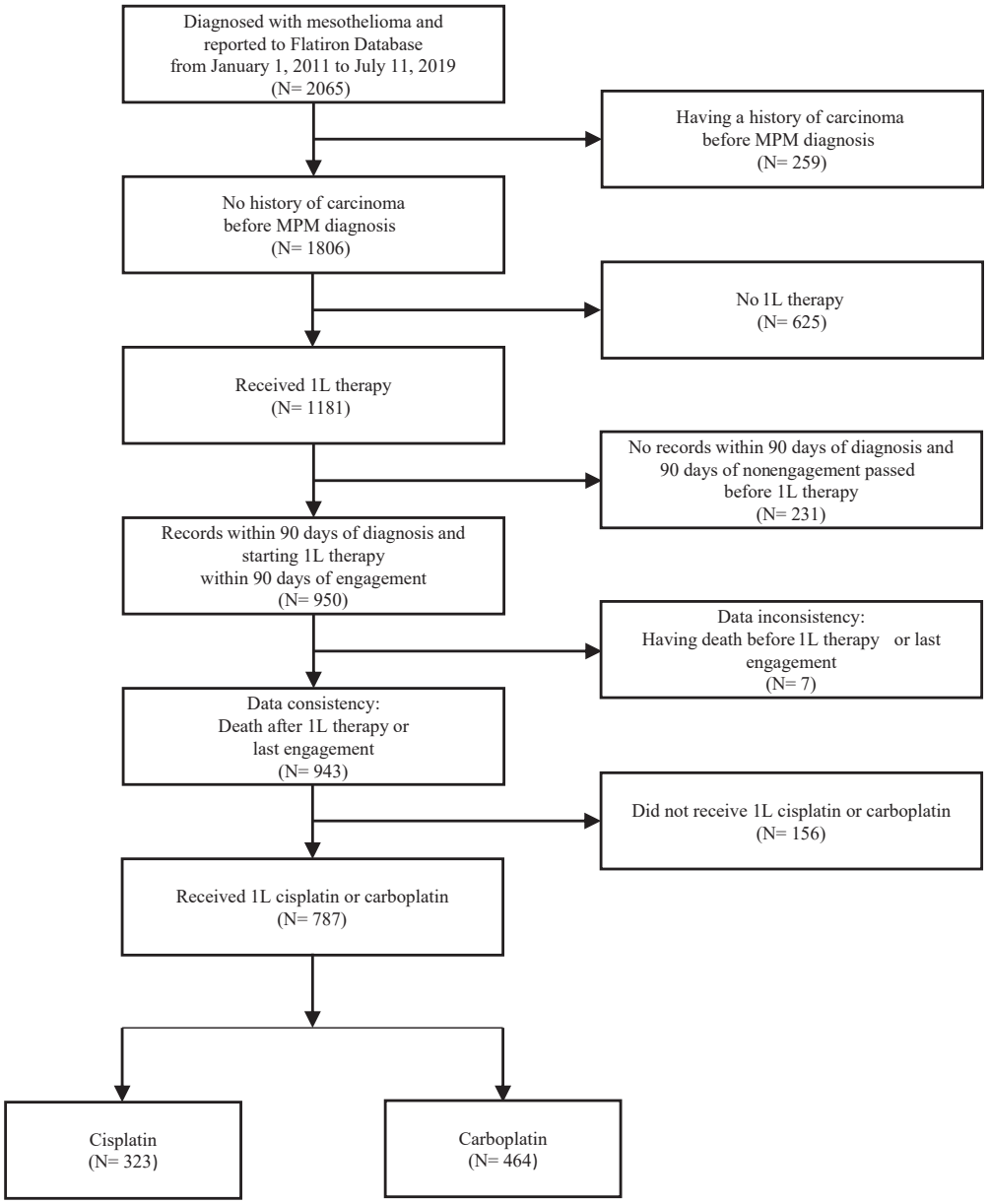

Figure 1. 1L therapy CONSORT diagram. 1L, first-line treatment; MPM, malignant pleural mesothelioma.

pemetrexed. The time of dropping a therapy was identified as the first gap in documented administrations of greater than 8 weeks.

We collected baseline demographics, asbestos exposure, smoking status, ECOG PS, relevant medical comorbidities including hearing loss, neuropathy, renal, or cardiac disease, and baseline laboratory results (Table 1). Comorbidities were identified by means of the International Classification of Diseases, Ninth or Tenth Addition diagnosis codes observed in the patients' EHRs. Data on PD-L1 testing was collected by means of abstraction and categorized as positive, negative, missing, or not tested. For each cohort, we separately collected baseline time-varying covariates within 180 days before 1L therapy, 2L therapy, or the time window for MT eligibility, respectively, depending on the cohort. For the 2L comparisons, we also collected the PC received in the 1L setting, and the time in months until starting the 2L of therapy from the start of 1L therapy.

Outcomes and Analyses

The primary outcome measured was OS from the date of 1L therapy, 2L therapy, and MT, respectively, for each of the three cohorts. Patients were censored at their last date of engagement, before a gap exceeding 90 days without any recorded visits, episodes, laboratory results, or vital signs in the patient's EHR, to limit potential

Table 1. Patient Demographics for the First-line Platinum Chemotherapy Analysis

Demographics	Carboplatin (n = 464)	Cisplatin (n = 323)	SMD
Diagnosis y (centered), median (IQR)	0.67 (−1.49 to 2.49)	0.05 (−1.75 to 1.80)	0.174
Age, median (IQR)	77.00 (72.00-80.00)	70.00 (65.00-76.00)	0.78
Asbestos, n (%)			0.157
No	67 (14.4)	60 (18.6)	
Unknown/not documented	82 (17.7)	42 (13.0)	
Yes	315 (67.9)	221 (68.4)	
Smoking status, n (%)			0.073
History of smoking	317 (68.3)	210 (65.0)	
No history of smoking	145 (31.2)	111 (34.4)	
Unknown not documented	2 (0.4)	2 (0.6)	
Region, n (%)			0.153
Midwest	57 (12.3)	33 (10.2)	
Northeast	77 (16.6)	46 (14.2)	
South	191 (41.2)	131 (40.6)	
West	52 (11.2)	51 (15.8)	
Unknown or unclassified	87 (18.8)	62 (19.2)	
Practice type—community, n (%)	384 (82.8)	267 (82.7)	0.003
Race-ethnicity, n (%)			0.205
White (Non-Hispanic)	352 (84.6)	239 (79.7)	
Black (Non-Hispanic)	16 (3.8)	13 (4.3)	
Hispanic	17 (4.1)	19 (6.3)	
Asian (Non-Hispanic)	6 (1.4)	1 (0.3)	
Other	25 (6.0)	28 (9.3)	
Cardiac disease, n (%)	14 (3.0)	1 (0.3)	0.213
Kidney disease, n (%)	18 (3.9)	2 (0.6)	0.221
Neuropathy, n (%)	6 (1.3)	1 (0.3)	0.11
Otopathology, n (%)	1 (0.2)	1 (0.3)	0.018
PD-L1 expression, n (%)			0.058
Positive	6 (1.3)	3 (0.9)	
Negative/not detected	17 (3.7)	11 (3.4)	
Not tested or missing	430 (92.7)	299 (92.6)	
Tested and unknown	11 (2.4)	10 (3.1)	
Histology, n (%)			0.168
Epithelioid	285 (61.4)	181 (56.0)	
Sarcomatoid	66 (14.2)	50 (15.5)	
Biphasic (mixed) or Other	64 (13.8)	63 (19.5)	
Unknown/not documented	49 (10.6)	29 (9.0)	
Serum creatinine, mg/dL, median (IQR)	0.87 (0.72-1.10)	0.80 (0.70-0.93)	0.35
Hemoglobin g/dL, median (IQR)	12.10 (10.80-13.30)	12.40 (11.10-13.60)	0.127
Absolute neutrophil count, k/μL, median (IQR)	7.30 (5.40-10.10)	7.30 (5.30-10.10)	0.012
Platelet count k/μL, median (IQR)	323.00 (253.50-405.50)	346.00 (258.00-438.00)	0.139
White blood cell count, k/μL, median (IQR)	9.40 (7.40-12.42)	9.10 (7.30-12.65)	0.022
Serum albumin, g/dL, median (IQR)	35.00 (32.00-38.00)	36.00 (32.50-40.00)	0.203
Height, cm, median (IQR)	172.72 (165.10-177.80)	172.72 (167.00-177.80)	0.057
Weight, kg, median (IQR)	76.29 (66.22-87.09)	80.20 (69.67-91.90)	0.246
ECOG $\geq$2, n (%)	53 (11.4)	20 (6.2)	0.185

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-L1, programmed death-ligand 1; SMD, standardized mean difference.

impacts of patient receipt of care outside the data-providing institution.

The R software version 4.0.11[18] was used for the analysis, and the multivariate imputation by chained equations package[19] was used for multiple imputations. Missing data were multiply-imputed using predictive mean matching on 50 chained equations.[20] For each cohort, we estimated a propensity score for treatment choice using a logistic regression conditioning on baseline covariates and missingness of covariates. Restricted cubic splines, with three knots, were placed on continuous covariates to allow for nonlinear predictors of treatment. In the 2L therapy cohort, the propensity score model excluded diagnosis year, given its strong association with 1L therapy and practice type that yielded singularities in the estimation of the propensity score.

Instead, we adjusted for diagnosis year when comparing 2L therapies weighted by the propensity score.[21] In the MT cohort, we dropped neutrophil count from the propensity score model because of its high correlation with white blood cell count.

The cohorts were reweighted using matching weights,[22] and we fit a marginal Cox proportional hazards model comparing treatment groups on the outcomes of interest. The proportional hazards assumption was checked using Schoenfeld's residuals.[23]

We tested for effect modifications by interacting treatment with subgroups of interest, sarcomatoid subtype (Y/N), ECOG PS (≥2, <2), baseline body mass index (underweight defined as <18.5, normal plus overweight defined as 18.5–29.9, and obese defined as ≥30), baseline albumin (≥35 g/dL, <35 g/dL), baseline hemoglobin (≥12 g/dL, <12 g/dL), ever-smoker (Y/N), age (≥70 y, <70 y), and ever-exposed to asbestos (Y/N). For each cohort, baseline body mass index, albumin, and hemoglobin were the most recent patient value within 180 days before 1L therapy, 2L therapy, or the time window for MT eligibility, respectively. PD-L1 positivity was defined as greater than or equal to 1%. PD-L1 status had too high of a rate of missingness to be reliably tested for an effect modification. Causal effects within each subgroup were estimated analogously to the primary analyses.

Results

1L Therapy Analysis—Cisplatin Versus Carboplatin Doublet Chemotherapy

The cohort identification flowchart for comparison of 1L cisplatin and carboplatin is illustrated in Figure 1. Of the 787 patients with MPM in this cohort, 464 were treated with carboplatin, and 323 were treated with cisplatin-based chemotherapy in the 1L setting. The baseline characteristics of the study population by treatment are summarized in Table 1. Carboplatin-treated patients were older (median age = 77 y versus 70 y), had worse ECOG PS (ECOG ≥2 11.4% versus 6.2%), and were more likely to have relevant medical comorbidities including kidney (3.9% versus 0.7%) and cardiac (3.0% versus 0.3%) disease. There were no notable imbalances between groups (standardized mean difference [SMD] <0.1) in smoking status, documented PD-L1 expression, or practice type by exposure. There were many instances of lack of documented testing for PD-L1 expression in this cohort. After propensity score matching weighting, all the potential confounders achieved adequate balance (SMD <0.1) (Supplementary Fig. 1).

The median OS from the start of 1L therapy was 10.8 months (95% confidence interval [CI]: 9.33–12.1) and 12.3 months (95% CI: 11.27–13.9) for patients treated with carboplatin and cisplatin, respectively (Fig. 2*A*). After propensity score matching weighting, the median OS was 12.1 months (95% CI: 10.4–14.3) and 11.9 months (95% CI: 10.5–13.8) for patients treated with carboplatin and cisplatin, respectively (Fig. 2*B*). After propensity score matching weighting, we had insufficient evidence to suggest an OS difference between cisplatin and carboplatin ($p = 0.43$). We estimated the causal hazard ratio (HR) of cisplatin compared with carboplatin to be 1.08 (95% CI: 0.89–1.31). We did not find evidence for effect modification within subgroups; however, we provided estimates of the causal effects by subgroup (Supplementary Fig. 2).

2L Therapy—Immunotherapy Versus Single-Agent Chemotherapy

Of the 192 patients with MPM who received 2L therapy in this cohort, 104 patients were treated with single-agent chemotherapy, and 88 received single or combination immunotherapy. After propensity score matching weighting, a slight imbalance remained in race-ethnicity (SMD = 0.12) with other potential confounders, except for diagnosis year, achieving balance (SMD <0.1) (Supplementary Fig. 3). Diagnosis year and race-ethnicity were included as covariates in the primary matching weighted models for the 2L therapy comparisons.

The median OS from the start of 2L therapy was 4.90 months (95% CI: 3.78–6.08) and 8.05 months (95% CI: 7.13–11.43) for patients treated with chemotherapy and immunotherapy, respectively (Fig. 3*A*). After propensity score matching weighting, the median OS was 4.90 months (95% CI: 3.78–6.08) and 8.05 months (95% CI: 7.13–11.43) for patients treated with chemotherapy and immunotherapy, respectively (Fig. 3*B*). After propensity score matching weighting, there was no strong evidence suggesting that the use of 2L immunotherapy improved OS, though estimates of the causal effect reveal more support for benefit than harm with an HR of 0.68 (95% CI: 0.42–1.08, $p = 0.10$). After adjusting for diagnosis year and race-ethnicity, the evidence became weaker with an HR of 0.79 (95% CI: 0.45–1.40, $p = 0.42$).

There was evidence that sarcomatoid histology may be an effect modifier ($p = 0.04$). 2L immunotherapy was associated with better outcomes than single-agent chemotherapy in patients with sarcomatoid histology, with an HR of 0.21 (95% CI: 0.06–0.71, $p = 0.01$). We did not find evidence for effect modification within other subgroups; however, we provided estimates of the causal effects by subgroup (Supplementary Fig. 4). Furthermore, we did not find evidence that time to second therapy was associated with 1L platinum ($p = 0.45$).

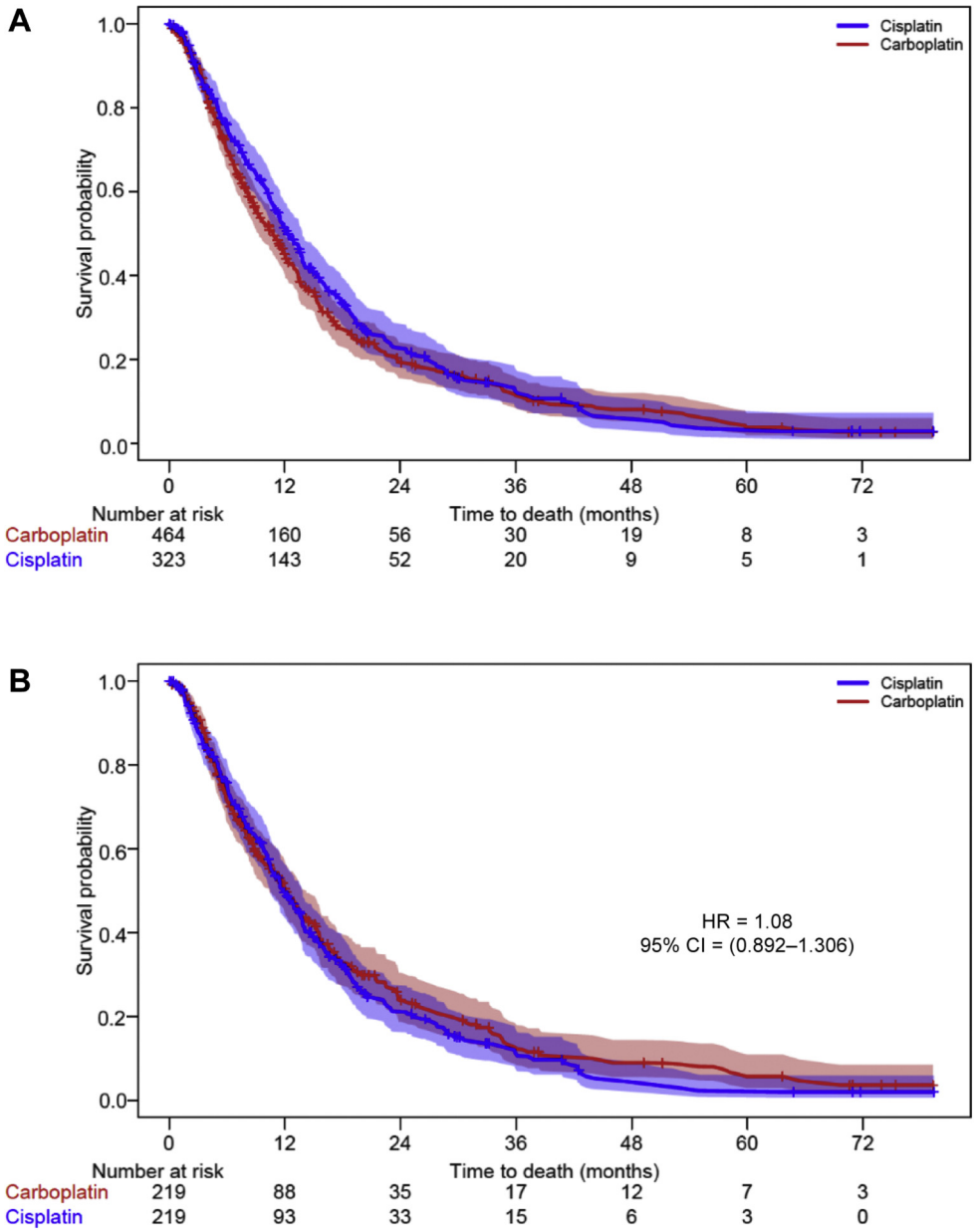

Figure 2. (A) Kaplan-Meier overall survival estimates for 1L platinum unadjusted analysis. (B) Kaplan-Meier overall survival estimates for 1L platinum on the basis of propensity score weighted analysis. 1L, first-line treatment; CI, confidence interval; HR, hazard ratio.

Maintenance Therapy—Continuation Pemetrexed With or Without Bevacizumab After Completion of PC Versus No Additional Therapy

From the 1L cohort, 482 patients were identified who were treated with 1L cisplatin or carboplatin in combination with pemetrexed with or without bevacizumab and stopped platinum agents between 8 and 28 weeks. Of these, 315 patients stopped both platinum and pemetrexed and/or bevacizumab within a particular 4-week time window, and these patients were identified as eligible for, but not receiving, MT (no maintenance arm, red points in Supplementary Fig. 5). The remaining 167 patients stopped platinum within the 4-week time window but continued pemetrexed with or without bevacizumab beyond the time window, and these patients were identified as receiving MT (maintenance arm, blue points in Supplementary Fig. 5).

The median OS from the MT eligibility date was 8.38 months (95% CI: 7.56–10.2) and 10.58 months (95% CI: 9.26–11.9) for patients who did not receive and did receive MT, respectively (Fig. 4*A*). After propensity score matching weighting, the median OS was similar at 9.0 months (95% CI: 7.82–12.0) and 10.5 months (95% CI: 9.17–11.4) for patients who did not and who did receive

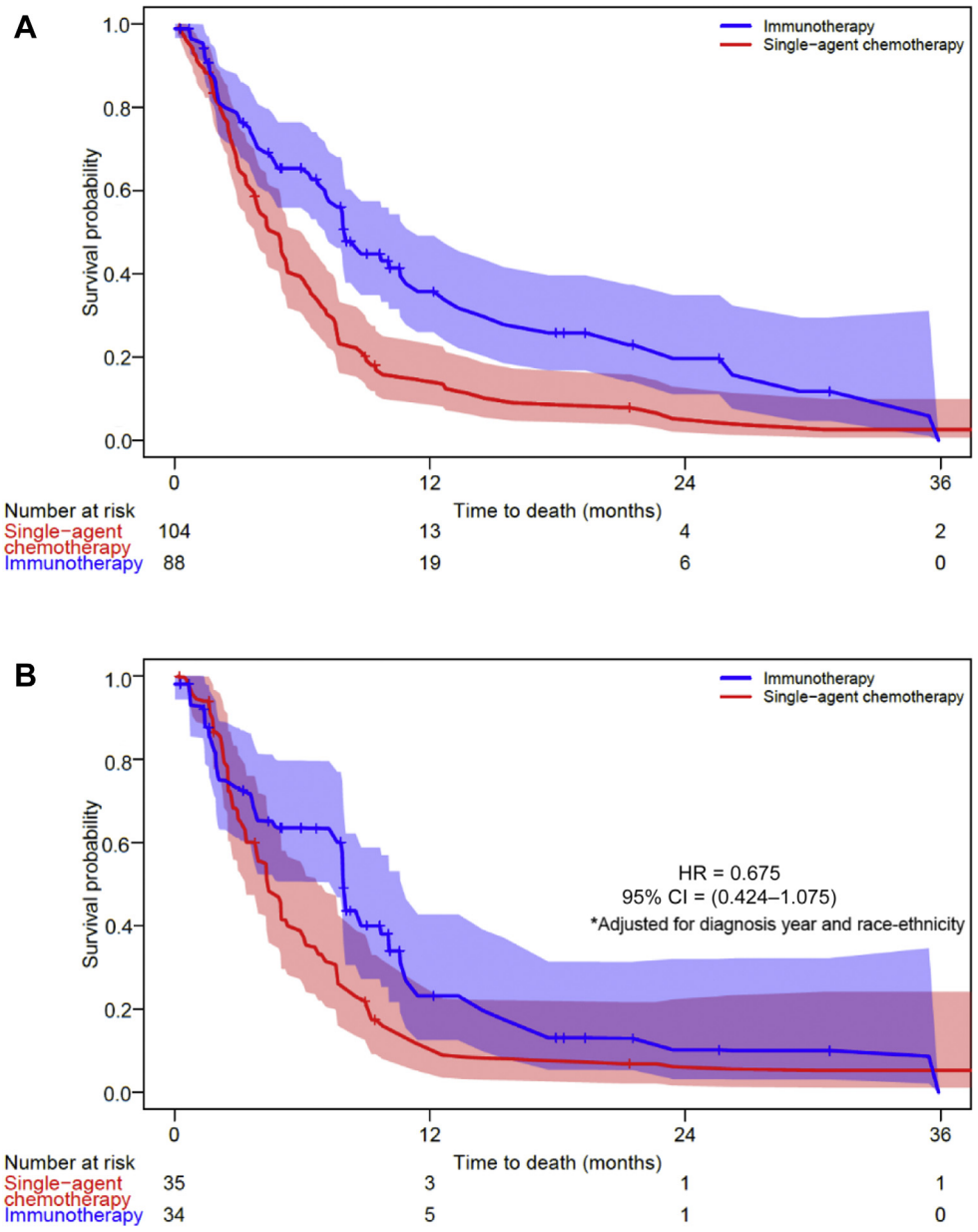

Figure 3. Kaplan-Meier overall survival estimates comparing 2L immunotherapy and single-agent chemotherapy: (A) unadjusted analysis and (B) propensity score weighted analysis. 2L, second-line treatment; CI, confidence interval; HR, hazard ratio.

MT, respectively (Fig. 4*B*). After propensity score matching weighting and stratified by cohort, we had insufficient evidence to find MT as beneficial (HR = 0.92, 95% CI: 0.72–1.16, $p = 0.46$). We did not find evidence for effect modification within subgroups; however, we provided estimates of the causal effect by subgroup (Supplementary Fig. 6). A crude unadjusted Cox analysis was performed for comparison each of the 1L, 2L, and MT analyses and is reported in the Supplementary Table 1.

Discussion

To the best of our knowledge, this is the largest real-world cohort of U.S. patients diagnosed with MPM and analyzed by physician's choice of 1L PC, 2L therapy, and MT. In our 1L platinum plus pemetrexed analysis, there was no statistically significant difference in OS by choice of platinum agent. By applying propensity score matching weights, we largely removed the confounding risk of age and other measured variables and found an SMD of less than 0.1 for all baseline features. This gives us increased confidence that these baseline features are not confounding our estimated causal effect of cisplatin on OS. Our analysis found no evidence that cisplatin is superior to carboplatin in the real-world setting; we, therefore, conclude that carboplatin is a suitable alternative to cisplatin-based chemotherapy for patients with

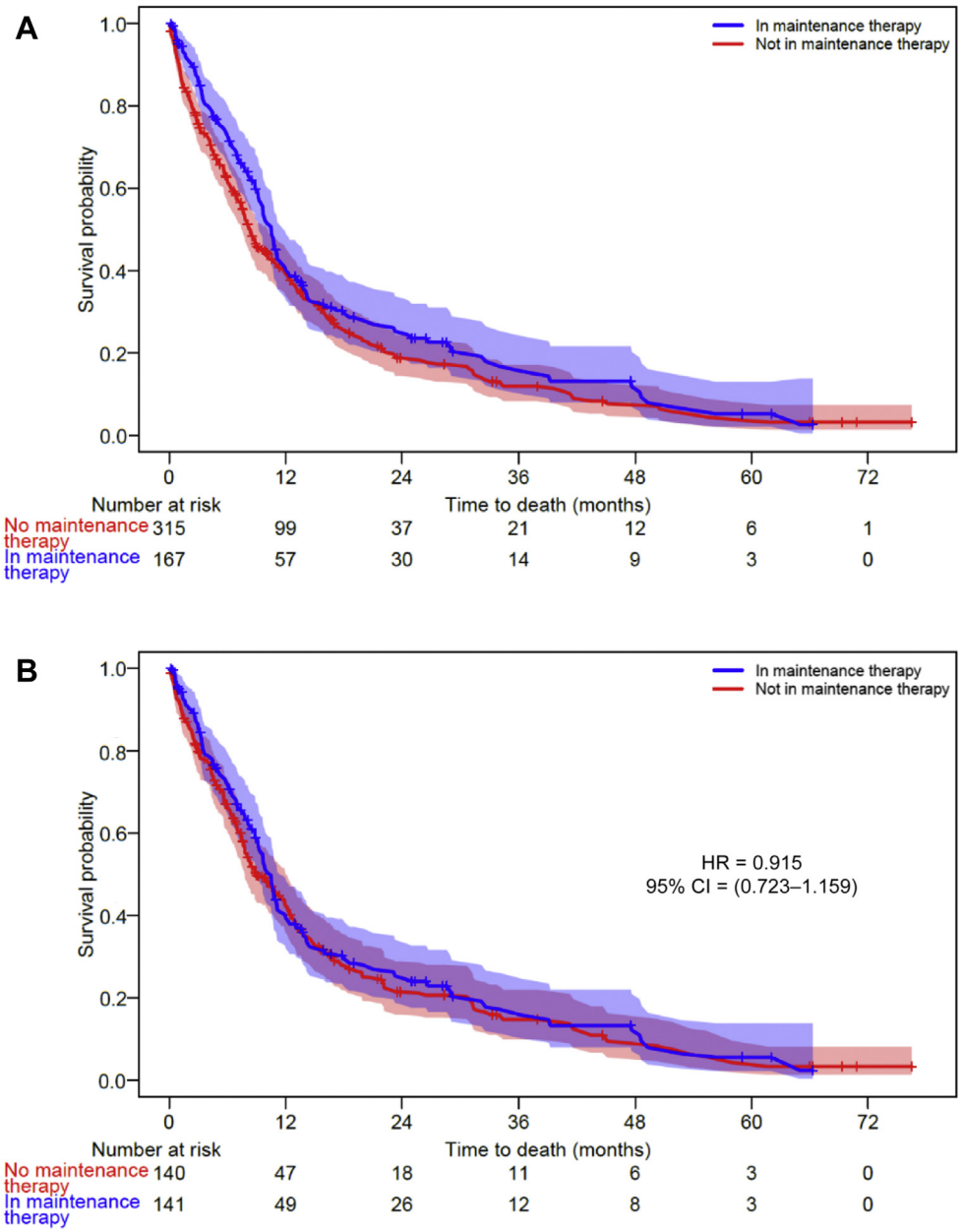

Figure 4. Kaplan-Meier overall survival estimates comparing patients in MT and not in MT: (A) unadjusted analysis and (B) propensity score weighted analysis. CI, confidence interval; HR, hazard ratio; MT, maintenance therapy.

MPM, with a similar OS, and a generally improved safety and tolerability profile. This real-world data corroborate the previous phase 2 data exhibiting a similar PFS and OS among the platinum agents.[10]

In the 2L setting, we found no statistically significant difference in OS between patients treated with single-agent and combination immunotherapy as compared with single-agent chemotherapy. This is in line with published data from randomized studies, which have yet to report a survival benefit for 2L immunotherapy over chemotherapy. The PROMISE-meso trial found a similar PFS and OS of 2L pembrolizumab versus gemcitabine plus vinorelbine in relapsed patients with MPM.[24] Data from the IFCT-1501 MAPS trial revealed that nivolumab (n = 63) and nivolumab plus ipilimumab (n = 62) have activity in relapsed patients with MPM, with objective response rates and disease control rates that were at least parallel to single-agent chemotherapy activity,[25] but long-term data on OS are currently unavailable. In this real-world data set, patients with MPM with sarcomatoid histology exhibited the greatest benefit from immunotherapy treatment (n = 46) in the 2L setting. These findings corroborate recently published data[26–28] and should continue to be evaluated prospectively.

In addition, we sought to answer the survival impact that maintenance pemetrexed and/or bevacizumab provided in a real-world patient population with MPM. After propensity score matching weighting, there was little evidence of an OS difference between patients who received and did not receive maintenance therapy, even when adjusted for 1L platinum therapy (Supplementary Table 2). Our findings further support recently published data reporting a lack of PFS and OS benefit with maintenance pemetrexed,[12] and call this clinical practice into question.

It is currently unclear how this real-world analysis will impact the treatment paradigm for patients with MPM because, in 2020, practice-changing data from the phase 3 international CheckMate743 trial were presented and published. The investigators revealed that the 1L combination of nivolumab and ipilimumab exhibited a statistically and clinically significant 4-month improvement in OS compared with platinum-pemetrexed chemotherapy (18.1 vs. 14.1 mo, HR = 0.74, $p = 0.002$).[27,28] In addition, some patients in this trial experienced durable benefit, with 2-year OS rates approaching 41% in the combination immunotherapy group compared with 27% in the chemotherapy arm.[27,28] The toxicity profiles were generally similar. The regimen subsequently received Food and Drug Administration approval for 1L use in October 2020.[29] It is currently unknown how U.S.-based oncologists are using this new data in the clinic, and whether the same benefits and toxicity profiles are observed in a real-world patient population. Specifically, patients with an ECOG PS of greater than or equal to two were excluded from this trial, but are often seen in medical oncology clinics. Similarly, patients with autoimmune disease, a history of interstitial lung disease, previous history of malignancy within 3 years, those with prespecified abnormal laboratory parameters, and those with untreated or unstable central nervous system metastasis were excluded. Thus, we cannot extrapolate the efficacy and toxicity data from CheckMate 743 to this patient population and it remains unclear what is the best treatment approach for said patients.

This study has several limitations. An important limitation of using real-world data abstracted from the EHR is the completeness of the data set and the possibility of unmeasured confounding. Real-world EHR data is subject to shifting practice patterns, EHR use, testing, and time trends, with additional variation among individual providers and practice sites within the data set. In this data set, there was a high degree of missingness and/or lack of testing for PD-L1 status. As such, firm conclusions cannot be drawn regarding the role of this biomarker and how it should impact treatment selection in any line.

A strength of our study is its relatively large sample size from a deidentified nationwide cohort of U.S.-treated patients with MPM who have medical comorbidities, older age, and trends toward a worse PS as compared with those patients who are enrolled in clinical trials. In this real-world data analysis, we have addressed clinically relevant questions that are unlikely to ever be studied in prospective randomized clinical trials.

In conclusion, MPM is an aggressive malignancy affecting older patients which creates therapeutic challenges for the practicing oncologist. In this analysis, we found no statistically significant differences in OS by choice of 1L PC, physician's choice of 2L chemotherapy versus immunotherapy, or by physician's choice of use of MT. As such, the selection of therapy for patients with advanced MPM should be on the basis of shared decision making, patient comorbidities, and ECOG PS.

CRediT Authorship Contribution Statement

Kathleen Kerrigan, Shiven Patel: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original and final draft, Editing, Resources, Supervision, Project administration, Funding.

Yeonjung Jo, Jonathan Chipman, Benjamin Haaland: Methodology, Software, Data curation, Analysis, Validation, Writing - original and final draft, Editing, Funding.

Sonam Puri, Wallace Akerley: Conceptualization, Writing - final draft, Supervision, Editing, Funding.

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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.2022.100280.

References

1. Mesothelioma and Asbestos Awareness Center. Statistics 2021 guide. https://www.maacenter.org/mesothelioma/statistics/. Accessed January 20, 2021.
2. Liu B, van Gerwen M, Bonassi S, Taioli E. International Association for the Study of Lung Cancer Mesothelioma Task Force. Epidemiology of Enviornmental exposure and malignant mesothelioma. *J Thorac Oncol*. 2017;12:1031-1045.
3. McDonald JC, McDonald AD. The epidemiology of mesothelioma in historical context. *Eur Respir J*. 1996;9:1932-1942.

4. Lin RT, Takahashi K, Karjalainen A, et al. Ecological association between asbestos-related diseases and historical asbestos consumption: an international analysis. *Lancet*. 2007;369:844–849.
5. Selikoff IJ, Churg J, Hammond EC. Asbestos exposure and neoplasia. *JAMA*. 1964;188:22–26.
6. Panou V, Gadiraju M, Wolin A, et al. Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. *J Clin Oncol*. 2018;36:2863–2871.
7. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet*. 2016;48:407–416.
8. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 2003;21:2636–2644.
9. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the mesothelioma Avastin cisplatin pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2016;387:1405–1414.
10. Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. *J Thorac Oncol*. 2008;3:756–763.
11. van den Bogaert DP, Pouw EM, van Wijhe G, et al. Pemetrexed MT in patients with malignant pleural mesothelioma. *J Thorac Oncol*. 2006;1:25–30.
12. Dudek AZ, Wang X, Gu L, et al. Randomized study of maintenance pemetrexed versus observation for treatment of malignant pleural mesothelioma: CALGB 30901. *Clin Lung Cancer*. 2020;21:553–51.e1.
13. Ettinger DS, Wood DE, Aiser DL, et al. NCCN Guidelines Insights: Malignant Pleural Mesothelioma, Version 1. 2021. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf. Accessed January 15, 2021.
14. Lievense LA, Sterman DH, Cornelissen R, Aerts JG. Checkpoint blockade in lung cancer and mesothelioma. *Am J Respir Crit Care Med*. 2017;196:274–282.
15. Metaxas Y, Rivalland G, Mauti LA, et al. Pembrolizumab as palliative immunotherapy in malignant pleural mesothelioma. *J Thorac Oncol*. 2018;13:1784–1791.
16. Ma X, Long L, Moon S, et al. Comparison of population characteristics in real-world clinical oncology databases in the US: flatiron health, SEER, and NPCR. MedRxiv. https://www.medrxiv.org/content/10.1101/2020.03.16.20037143v2. Accessed March 2, 2021.
17. Birnbaum B, Nussbaum N, Seidl-Rathkopf K, et al. *Model-Assisted Cohort Selection With Bias Analysis for Generating Large-Scale Cohorts From the EHR for Oncology Research*. Ithaca, NY: Cornell University; 2020.
18. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. https://www.R-project.org/. Accessed July 5, 2021.
19. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate Imputation by Chained Equations in R. *J Stat Softw*. 2011;45:1–67.
20. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399.
21. Nguyen TL, Collins GS, Spence J, et al. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. *BMC Med Res Methodol*. 2017;17:78.
22. Li L, Greene T. A weighting analogue to pair matching in propensity score analysis. *Int J Biostat*. 2013;9:215–234.
23. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69:239–241.
24. Popat S, Curioni-Fontecedro A, Dafni U, et al. A multicentre randomized phase III trial comparing pembrolizumab (P) versus single-agent chemotherapy (CT) for advanced pretreated malignant pleural mesothelioma (MPM): results from the European Thoracic Oncology Platform (ETOP 9–15) PROMISE-meso trial. *Ann Oncol*. 2020;31:1734–1735.
25. Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. *Lancet Oncol*. 2019;20:239–253.
26. Brockwell NK, Alamgeer M, Kumar B, Rivalland G, John T, Parker BS. Preliminary study highlights the potential of immune checkpoint inhibitors in sarcomatoid mesothelioma. *Transl Lung Cancer Res*. 2020;9:639–645.
27. Bass P, Scherpereel A, Nowak A, et al. First-line nivolumab + ipilimumab vs chemotherapy in unresectable malignant pleural mesothelioma: CheckMate 743. *J Thorac Oncol*. 2020;15(suppl):E42.
28. Baas P, Scherpereel A, Nowak AK, et al. 1L nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet*. 2021;397:375–386.
29. US Food and Drug Administration. Center for Drug Evaluation and Research. Nivolumab plus ipilimumab approval letter. https://www.fda.gov/news-events/press-announcements/fda-approves-drug-combination-treating-mesothelioma. Accessed April 3, 2021.