BRIEF REPORT

Durvalumab Combined With Pemetrexed-Based Chemotherapy in Trial-Ineligible Patients With Mesothelioma: A Brief Report

Ibiayi Dagogo-Jack, MD,[a,b,*] Aubrey Lasko, PharmD,[a] Elizabeth A. Krueger, NP,[a] Kitman Tsang, NP,[a] Revati Rao, MD,[b,c] Grace Hambelton, BA,[a] Subba R. Digumarthy, MD[b,d]

[a]Massachusetts General Hospital Cancer Center, Boston, Massachusetts
[b]Harvard Medical School, Boston, Massachusetts
[c]Department of Medicine, Newton Wellesley Hospital, Newton, Massachusetts
[d]Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts

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ABSTRACT

Introduction: Chemoimmunotherapy is associated with promising activity in mesothelioma in phase II to III trials. Studies exploring this approach in patients ineligible for clinical trials are lacking. We assembled a cohort of patients receiving pemetrexed-based chemotherapy with durvalumab outside of clinical trials.

Methods: Patients with pleural mesothelioma received pemetrexed plus durvalumab or carboplatin plus pemetrexed plus durvalumab via off-label authorization at Massachusetts General Hospital. Response to chemoimmunotherapy was assessed per modified Response Evaluation Criteria in Solid Tumors version 1.1. A retrospective chart review was conducted to assess safety per Common Terminology Criteria for Adverse Events version 5.0.

Results: Twelve patients were included in the series. Nine patients were treated with triplet chemoimmunotherapy. Three patients received doublet chemoimmunotherapy because of platinum ineligibility. Concurrent active malignancies and symptomatic cardiac disease were present in three patients (25%) and two patients (17%), respectively. Ten patients had measurable disease at baseline. With the triplet regimen, partial responses were observed in four of the seven (57%) patients with measurable disease. All three patients receiving pemetrexed plus durvalumab had measurable disease and experienced a partial response. Primary progression was not observed with either regimen. Overall, eight patients (75%) remained on treatment for more than 6 months without progression. Five patients developed immune-related adverse events (n = 1 each pyrexia, arthritis, neutropenia, Raynaud's disease, stomatitis). Three patients discontinued treatment because of toxicity or symptomatic comorbid conditions (n = 1 grade 3 heart failure, n = 1 grade 2 fever + progressive kidney cancer, n = 1 grade 2 fatigue).

Conclusions: Antitumor activity of chemoimmunotherapy reported in phase II to III clinical trials is generalizable to the broader patient population with mesothelioma. However, the tolerability of chemoimmunotherapy is impacted by comorbid conditions in real-world patients.

Keywords: Mesothelioma; Chemoimmunotherapy; Immunotherapy; Durvalumab

Introduction

Immunotherapy is a preferred first-line therapeutic strategy for pleural mesothelioma as a result of the

*Corresponding author.

Address for correspondence: Ibiayi Dagogo-Jack, MD, Department of Medicine, Massachusetts General Hospital, 32 Fruit Street, Yawkey 7B, Boston, Massachusetts 02114. E-mail: idagogo-jack@partners.org

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improved survival with ipilimumab plus nivolumab compared with platinum plus pemetrexed in the global phase 3 Checkmate 743 study.[1] Although the immunotherapy doublet outperformed chemotherapy in the overall cohort of patients with mesothelioma in Checkmate 743, the relative benefit of first-line immunotherapy was accentuated in non-epithelioid mesothelioma because of the limited activity of chemotherapy whereas the activity of chemotherapy rivaled that of immunotherapy in the epithelioid subgroup.[1] As platinum plus pemetrexed can induce durable disease stabilization for some patients with epithelioid mesothelioma, there is a rationale for evaluating chemoimmunotherapy regimens that build on the chemotherapy backbone. Notably, in other thoracic tumors, chemoimmunotherapy is associated with fewer early progression events, leading to more sustained disease control, including among patients with tumors with unfavorable molecular characteristics that confer resistance to immunotherapy.[2,3]

Several clinical trials have evaluated checkpoint inhibitors combined with platinum plus pemetrexed in pleural mesothelioma. Two phase II studies investigated durvalumab plus platinum plus pemetrexed as a first-line treatment for pleural mesothelioma. In the DREAM study, the durvalumab-based triplet yielded a six-month progression-free survival rate of 57% and median overall survival (OS) of 18.4 months.[4] The promising activity of this combination was confirmed in the multi-institution phase II prE0505 study in which a median OS of 20.4 months was observed.[5] On the basis of these results, the global randomized phase 3 DREAM3R study was launched to compare durvalumab plus platinum plus pemetrexed to standard therapy (i.e., platinum plus pemetrexed or ipilimumab plus nivolumab).[6] DREAM3R was terminated in September 2023 because of slow accrual. In contrast, the improved survival (median OS: 17.3 versus 16.1 mo) and 8% increase in the three-year survival rate of patients who received the triplet of pembrolizumab plus platinum plus pemetrexed versus those treated with platinum plus pemetrexed in a separate phase III study (IND227) led to Food and Drug Administration approval of chemoimmunotherapy for mesothelioma in September 2024.[7]

Experience with chemoimmunotherapy in patients with mesothelioma who are unable to participate in clinical trials is lacking. Here, we present a series summarizing outcomes of 12 patients with epithelioid pleural mesothelioma treated with durvalumab plus pemetrexed-based chemotherapy at Massachusetts General Hospital outside of a clinical trial. With the exception of three patients who commenced treatment after study closure, the DREAM3R study was considered for each patient but enrollment was not pursued because of concurrent oncologic or cardiac conditions, ineligibility for full-dose platinum chemotherapy, or financial constraints. Given the comparable efficacy of the immunotherapy doublet compared with doublet chemotherapy in patients with epithelioid tumors in Checkmate 743, ipilimumab plus nivolumab was not pursued as a treatment for these patients because of concerns about the potential toxicity of doublet immunotherapy.[8,9]

Materials and Methods

Data Collection and Off-Label Authorization

We identified patients with pleural mesothelioma who received one of two regimens: (1) carboplatin plus pemetrexed plus durvalumab, or (2) pemetrexed plus durvalumab at Massachusetts General Hospital and affiliated satellite centers. Consistent with the institutional practice of prioritizing carboplatin for unresectable mesothelioma, no patients received cisplatin. The decision to pursue a doublet versus triplet chemoimmunotherapy regimen was at a physician's discretion. As durvalumab plus pemetrexed-based chemotherapy is not approved by the United States Food and Drug Administration, treatment requests were reviewed by an off-label committee that included a thoracic oncologist who was not involved in the patient's care, financial services, and pharmacists. In addition to the off-label committee approval, clearance by the patient's insurance provider was mandated before initiating treatment. The administration schedule for durvalumab and chemotherapy was per prior phase II and III studies.[5,6] Ten patients received durvalumab 1500 mg once every three weeks for four cycles overlapping with chemotherapy, after which durvalumab 1500 mg was given once every four weeks per DREAM3R.[6] The remaining two patients received durvalumab 1125 mg once every three weeks with the initial 12 to 18 weeks overlapping with chemotherapy per the phase II DREAM study.[4] Pemetrexed maintenance was not pursued. Written informed consent was obtained from patients before commencing treatment. Vitamin B12, folic acid, dexamethasone, and anti-emetics were administered per standard institutional protocols. The cutoff for study follow-up was February 1, 2024.

Response and Safety Assessment

Medical records were retrospectively reviewed to collect demographics, medical histories, and treatment histories and to determine safety. During treatment, computed tomography scans were obtained approximately every two to three cycles per routine care. Response to durvalumab plus chemotherapy was assessed by a board-certified thoracic radiologist (S.R.D.) using modified Response Evaluation Criteria in Solid

Tumors version 1.1 criteria for mesothelioma.[10] Adverse events were retrospectively captured from the review of notes and graded per Common Terminology Criteria for Adverse Events version 5.0. Institutional Review Board approval was obtained before conducting the retrospective analysis.

Results

Study Population

In total, 12 patients with pleural mesothelioma received off-label treatment with durvalumab plus pemetrexed-based chemotherapy at our institution between February 2021 and November 2023 (Table 1), all of whom had epithelioid mesothelioma. During this period, no other requests were made for off-label chemotherapy plus durvalumab for pleural mesothelioma (i.e., all requests were approved by the off-label committee and insurance companies). As summarized in Table 1, off-label therapy was pursued in lieu of participation in DREAM3R for nine patients as a result of the necessity of upfront dose reduction or omission of platinum, concurrent malignancy, symptomatic cardiac disease, and financial constraints limiting cross-state travel for a clinical trial. Three patients commenced chemoimmunotherapy after DREAM3R closed to accrual.

Carboplatin plus pemetrexed plus durvalumab was administered to nine patients (75%). The remaining three patients (25%) received pemetrexed plus durvalumab because of concerns about the toxicity of multiagent chemotherapy. Ten patients were treated in the first-line setting, none of whom underwent cytoreductive surgery. The remaining two patients had initially received platinum plus pemetrexed without immunotherapy alongside cytoreductive surgery. To address recurrence more than one year after pleurectomy plus decortication, the patients subsequently received pemetrexed plus durvalumab (n = 1) or carboplatin plus pemetrexed plus durvalumab (n = 1).

Table 1. Clinicopathologic Characteristics of Study Cohort

Characteristics	N = 12
Age at baseline (y)	
Median	73
Range	38-88
Sex, n (%)	
Female	4 (33)
Male	8 (67)
Ethnicity, n (%)	
White	12 (100)
Histology, n (%)	
Epithelioid	12 (100)
Non-epithelioid	0 (0)
Stage, n (%)	
T2N0M0	1 (8)
T1N1M0	3 (25)
T3N1M0	3 (25)
T4N0M0	1 (8)
T4N1M0	2 (17)
T1N0M1	1 (8)
T2N1M1	1 (8)
Prior cytoreductive surgery	
Yes	2 (17%)
No	10 (83%)
Prior chemotherapy, n (%)	
Yes	2 (17)
No	10 (83)
Chemoimmunotherapy regimen, n (%)	
Carboplatin + Pemetrexed + Durvalumab	9 (75%)
Pemetrexed + Durvalumab	3 (25%)

Safety and Efficacy of Carboplatin Plus Pemetrexed Plus Durvalumab

Nine patients received carboplatin plus pemetrexed plus durvalumab. Time on therapy ranged between one to 16 months (Table 2). Two patients had non-measurable disease per modified Response Evaluation Criteria in Solid Tumors version 1.1 at baseline. Partial responses were observed in four of seven (57%) patients with measurable disease (Fig. 1*A–C*). The best response in the remaining five patients, including the two patients with non-measurable disease, was stable disease. Five patients (55%) experienced presumed immune-related adverse events, including pyrexia, Raynaud's syndrome, inflammatory arthritis, stomatitis (i.e., oral lichen planus), and autoimmune neutropenia (Table 2). Three patients discontinued all components of treatment for toxicity. The first patient stopped therapy because of grade 2 pyrexia and progressive kidney cancer. The second patient discontinued carboplatin after cycle one owing to grade 3 heart failure in the setting of severe aortic stenosis and baseline atrial fibrillation. After transitioning to pemetrexed plus durvalumab with cycle 2, all components of therapy were eventually discontinued to pursue valve replacement. The third patient discontinued treatment after 16 months because of grade 2 fatigue. In the three cases, treatment was discontinued despite disease control.

Safety and Efficacy of Pemetrexed Plus Durvalumab

Three patients were treated with pemetrexed plus durvalumab, as they were ineligible for triplet therapy because of advanced age or baseline functional status (Table 2). The first patient experienced a transient partial response before developing an isolated progression of a lung nodule after nine months of therapy. Radiation was pursued, after which he continued chemoimmunotherapy beyond progression for an additional

Table 2. Efficacy, Safety, and Survival Outcomes with Chemoimmunotherapy

Patient	Chemoimmunotherapy Regimen	Reason for Off-Label Combination Instead of DREAM3R	Best Response Tx Duration	Treatment Prematurely Discontinued	Treatment-Related Adverse Events	Survival from Initiation of ChemoIO
1	Carboplatin + Pemetrexed + Durva	Chronic infection, Upfront dose reduction	PR (−82%) 7 mo	No	Fatigue (grade 1), Raynaud's syndrome	9.6+ mo
2	Carboplatin + Pemetrexed + Durva	Upfront dose reduction	SD (−22%) 7 mo	No	Fatigue (grade 1)	10.0+ mo
3	Carboplatin + Pemetrexed + Durva	Limited financial resources for travel	PR (−57%) 16+ mo	Yes[a]	Arthritis (grade 1), Fatigue (grade 2)	13.3+ mo
4	Carboplatin + Pemetrexed + Durva	Concurrent breast cancer	SD (−7%) 7 mo	No	Fatigue (grade 1), Anemia (grade 3)	17.8 mo
5	Carboplatin + Pemetrexed + Durva	Upfront dose reduction	PR (−50%) 13 mo	No	Immune-related neutropenia (grade 3)	9.2+ mo
6	Carboplatin + Pemetrexed + Durva	Upfront dose reduction, Recent surgery	SD◆ 10 mo	No	Fatigue (grade 1)	10.2+ mo
7	Carboplatin + Pemetrexed + Durva	Concurrent kidney cancer	PR (−38%) 2 mo	Yes[a]	Pyrexia (grade 2), Hyperglycemia (grade 3)	13.8 mo
8	Carboplatin + Pemetrexed + Durva	N/A, Study closed	SD◆ 1 mo	Yes[b]	Heart failure (grade 3), Fatigue (grade 1)	2.9+ mo
9	Carboplatin + Pemetrexed + Durva	N/A, Study closed	SD (−12%) 4+ mo	No	Fatigue (grade 1), oral lichen planus (grade 1)	3.5+ mo
10	Pemetrexed + Durva	Symptomatic, uncontrolled arrhythmia	PR (−35%) 15 mo[c]	No	Fatigue (grade 1)	36.1+ mo
11	Pemetrexed + Durva	Concurrent prostate cancer, advanced aged	PR (−30%)[d] 7 mo	No	Fatigue (grade 1)	6.4+ mo
12	Pemetrexed + Durva	N/A, Study closed	PR (−39%) 3+ mo	No	Creatinine elevation (grade 1)	2.6+ mo

"+mo" indicates ongoing response.
[a]Treatment discontinued owing to pyrexia and progression of kidney cancer for patient 7 and considerable fatigue despite ongoing response for patient 3, partial response unconfirmed.
[b]Treatment six months beyond progression after radiation to enlarging lung nodule; transient PR evidence of growth on next scan.
[c]Carboplatin held after cycle 1 and treatment stopped after cycle 2.
[d]Unconfirmed partial response; ◆Given non-measurable disease, stable disease indicates non-complete response, non-progression.
Chemo, chemotherapy; Durva, durvalumab; IO, immunotherapy; N/A, not applicable; PR, partial response; SD, stable disease; Tx, treatment.

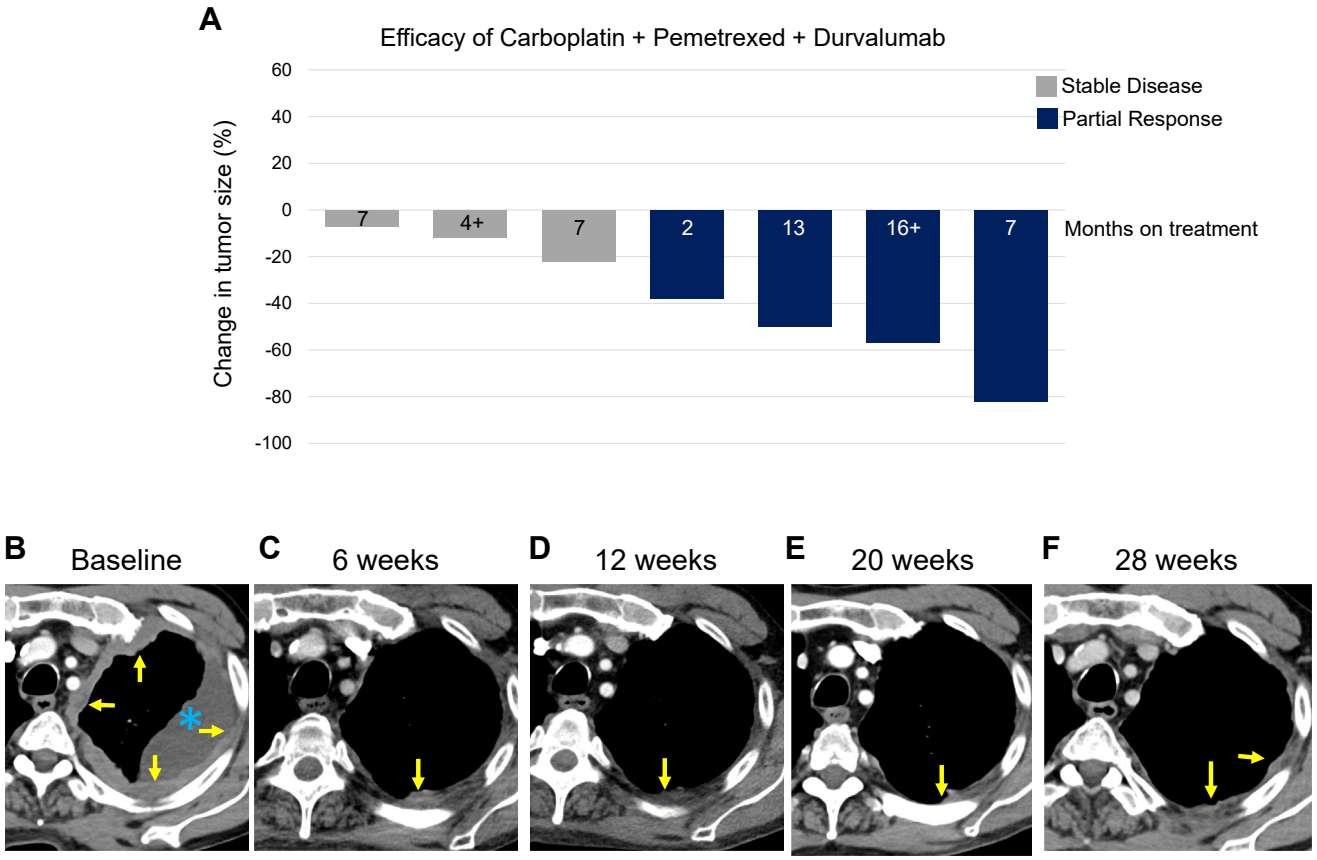

Figure 1. Efficacy of Chemoimmunotherapy Triplet Regimen. *(A)* The waterfall plot depicts the best response per RECIST version 1.1 to carboplatin plus pemetrexed plus durvalumab in seven patients with mesothelioma and measurable baseline disease. *(B)* Axial computed tomography images show circumferential nodular thickening of the left pleura (arrows) and pleural effusion (asterisk). *(C-E)* Partial response with a decrease in pleural thickening and pleural effusion at six, 12, and 20 weeks after starting treatment with carboplatin plus pemetrexed plus durvalumab. *(E)* Disease progression at 28 weeks with new and increased pleural thickening (arrows). RECIST, Response Evaluation Criteria in Solid Tumors.

6.5 months before stopping therapy for multifocal progression. The second patient continues on doublet therapy at seven months with partial response. The final patient has been on chemoimmunotherapy for three months with partial response; pemetrexed has been intermittently held to address intermittent creatine elevation. None of the patients experienced immune-related adverse events. Premature discontinuation of immunotherapy was not required for any of the three patients.

Discussion

The doublet of ipilimumab plus nivolumab has replaced platinum plus pemetrexed as the favored approach for the initial treatment of many patients with unresectable pleural mesothelioma.[1] Given the older age of patients with mesothelioma, frequent overlapping medical conditions, and the increased toxicity of ipilimumab plus nivolumab in elderly patients,[11] alternative regimens with promising efficacy are warranted. Checkpoint inhibitor plus chemotherapy combinations have reported encouraging results in phase II to III studies, with a median OS of 17 to 20 months and median progression-free survival of six to seven months.[5,7] The efficacy and safety of chemoimmunotherapy regimens in the general population are not well described. We, therefore, compiled a series of 12 patients with epithelioid mesothelioma who received off-label durvalumab plus pemetrexed-based chemotherapy at a single institution to summarize the efficacy and safety of this approach.

In our series, the efficacy of the triplet regimen was comparable to that observed in prospective trials, with most patients remaining on therapy for six months or longer.[4,5] Yet, the rate of treatment discontinuation was higher in our series, with three of nine (33%) patients stopping treatment for toxicity. In two such cases, a competing medical condition (n = 1 worsening cardiac disease in the setting of chemoimmunotherapy, n = 1 treatment-related pyrexia plus progressive advanced kidney cancer) contributed to the decision to stop

treatment. In comparison, fewer than 10% of patients discontinued treatment for adverse events in DREAM and PrE0505,[4,5] likely reflecting the overall healthier group of patients enrolled in these studies. Although the small number of patients in our series precludes us from concluding that toxicity is greater in a "real world" population, our findings resonate with larger "real world" studies. For example, in the RIOMeso study, 44% of patients treated with first-line ipilimumab plus nivolumab required hospitalization and 31% of patients ceased treatment to address toxicity.[12] Similarly, in an analysis of patients with mesothelioma receiving ipilimumab plus nivolumab via expanded access programs in the Netherlands, premature treatment discontinuation occurred in 25% of patients.[8] In both of these cohorts, the rates of toxicity with ipilimumab plus nivolumab were greater than reported in Checkmate 743.[1]

Although the DREAM3R study was open at our institution, nine patients in this series were not trial candidates. In parallel with pursuing off-label strategies, our site enrolled three patients in DREAM3R. The "attrition rate" at our institution and the early closure of DREAM3R highlight the challenges of conducting first-line clinical trials for rare diseases. Considering the goal of translating promising trial findings to the overall population, the higher utilization of off-label strategies to access chemoimmunotherapy is noteworthy as it emphasizes the gap between a "trial eligible" population and all-comers with mesothelioma. Thus, future trials should employ creative strategies to boost enrollment, such as synthetic and external control cohorts, decentralized trials, and pragmatic designs with lenient eligibility criteria.[13]

The limitations of our series include its retrospective nature, lack of rigorous assessment of toxicity, small sample size, inconsistent imaging intervals, the focus on epithelioid mesothelioma, and heterogeneous regimens used. Nonetheless, our findings suggest that patients with epithelioid mesothelioma with clinical characteristics precluding trial enrollment can derive benefit from chemoimmunotherapy, though close attention should be paid to toxicity management given the frequency of treatment-related toxicity.

CRediT Authorship Contribution Statement

Ibiayi Dagogo-Jack: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing.

Aubrey Lasko: Data curation, Methodology, Writing - review & editing.

Elizabeth A. Krueger: Data curation, Investigation, Writing - review & editing.

Kitman Tsang: Data curation, Investigation, Writing - review & editing.

Revati Rao: Data curation, Investigation, Writing - review & editing.

Grace Hambelton: Data curation, Writing - review & editing.

Subba R. Digumarthy: Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing.

Disclosure

Dr. Dagogo-Jack has received honoraria from Foundation Medicine, Creative Education Concepts, OncLive, ASCO Post, DAVA Oncology, Medscape, Research to Practice, Total Health, Aptitude Health, American Lung Association, PeerView; consulting fees from AstraZeneca, Boehringer Ingelheim, Bayer, BostonGene, Bristol Myers Squibb, Catalyst, Genentech, Gilead, Janssen, Merus, Novocure, Pfizer, Roche, Sanofi-Genzyme, Syros, ThermoFisher Scientific, and Xcovery, research support from Array, Genentech, Novartis, Pfizer, and Guardant Health; and travel support from Array and Pfizer. Mrs. Lasko has received consulting fees from Janssen. Mrs. Krueger has received consulting fees from Pfizer. Dr. Digumarthy provides independent image analysis for hospital-contracted clinical research trials programs for Merck, Pfizer, Bristol Myers Squibb, Novartis, Roche, Polaris, Cascadian, Abbvie, Gradalis, Bayer, Zai laboratories, Biengen, Riverain, Resonance, AstraZeneca, Analise. Research grants from Lunit Inc, GE, Qure AI, Vuno, honorarium from Siemens, and book royalties from Elsevier. The remaining authors declare no conflict of interest.

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