Retrospective Evaluation of the Use of Pembrolizumab in Malignant Mesothelioma in a Real-World Australian Population

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ABSTRACT

Introduction: We investigated the efficacy and toxicity of pembrolizumab in patients with mesothelioma from a real-world Australian population. We aimed to determine clinical factors and predictive biomarkers that could help select patients who are likely to benefit from pembrolizumab.

Method: Patients with mesothelioma who were treated with pembrolizumab as part of the Insurance and Care New South Wales compensation scheme were included. Clinical information was collected retrospectively. Tumor biomarkers such as programmed death-ligand 1 (PD-L1), BAP1, and CD3-positive (CD3+) tumor-infiltrating lymphocytes (TILs) were examined using archival formalin-fixed paraffin-embedded tumor samples.

Results: A total of 98 patients were included with a median age of 70 years (range, 46–91 y); 92% were men; 76% had epithelioid subtype; 21% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Pembrolizumab was used as second-line or subsequent-line treatment in 94 patients and as first-line treatment in four patients. The overall response rate was 18%, and the disease control rate was 56%. The median progression-free survival (PFS) was 4.8 months (95% confidence interval: 3.6–6.2), and the median overall survival (OS) was 9.5 months (95% confidence interval: 6.6–13.7). Immune-related adverse events occurred in 27% of patients, of which nine (9%) were of grade 3 or higher. In the multivariable analysis, factors independently associated with longer PFS included baseline ECOG status of 0 (median PFS: 12 mo versus 4 mo, p < 0.01) and PD-L1 tumor proportion score of greater than or equal to 1% (median PFS: 6 mo versus 4 mo, p < 0.01). Baseline platelet count of less than or equal to 400 × 10^9/liter was independently associated with longer PFS and OS (median PFS: 6 mo versus 2 mo, p = 0.05; median OS: 10 mo versus 4 mo, p = 0.01), whereas lack of pretreatment dexamethasone was independently associated with OS but not PFS (median OS: 10 mo versus 3 mo, p = 0.01). The odds of response were higher for patients with baseline ECOG status of 0 (p = 0.02) and with greater than or equal to 5% CD3+ TILs in the tumor (p < 0.01). PD-L1 expression, BAP1 loss, and CD3+ TILs in the stroma were not significantly associated with the overall response rate.

Conclusions: Immunotherapy is a reasonable treatment option for patients with mesothelioma. Our results are comparable to other clinical trials investigating pembrolizumab in mesothelioma in terms of response. Good performance status assessment remains the most robust predictor for patient outcomes. CD3+ TILs in the tumor may help select patients that are likely to respond to pembrolizumab, whereas factors such as PD-L1 expression, baseline platelet count, and lack of pretreatment dexamethasone may help predict survival outcomes from pembrolizumab treatment.

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Keywords: Mesothelioma; Pembrolizumab; PD-L1; Tumor-infiltrating lymphocytes; BAP1; Immunotherapy

Introduction

Malignant mesothelioma, a fatal cancer of the mesothelium, continues to have one of the poorest survival rates of any cancer, with a median overall survival (OS) ranging from 6 months to 25 months1 and a 5-year survival rate of between 4.7% and 6.1%.2 It is primarily caused by exposure to asbestos.1 Australia has one of the highest reported incidences, with around 700 to 800 patients diagnosed each year, of which 94% constitute malignant pleural mesothelioma (MPM), and the remaining 6% are mostly peritoneal mesothelioma.1,2

In MPM, the standard approved first-line treatment is currently combination chemotherapy using pemetrexed...
and cisplatin, which was reported to increase median survival time by approximately 3 months in phase 3 randomized controlled trial.³ The addition of bevacizumab, an antibody against VEGF, has also been reported to modestly increase survival.⁴ However, survival outcomes still remain poor, with a median progression-free survival (PFS) ranging from only 6 to 9 months.³⁻⁵ There is currently no approved second-line treatment for malignant mesothelioma; hence, an urgent need for improved treatment options.⁶,⁷

Over the past decade, immunotherapy has emerged as a promising treatment option for several cancers.⁷,⁸ In MPM, up to 60% of patients express programmed death-ligand 1 (PD-L1), an immune-suppressing receptor that binds to the programmed cell death protein 1 (PD-1) receptor on T-cells to suppress their tumor-killing function.⁹,¹⁰ Hence, a number of clinical trials have investigated the safety and efficacy of immunotherapies that block the PD-1 or PD-L1 pathway as the first-line or subsequent-line treatment for patients with MPM (Table 1).⁷,¹¹ Although preliminary results, in general, revealed good treatment tolerability, the overall response rate (ORR) ranges only from 10% to 30%. This suggests only a small proportion of patients may benefit from this therapy and highlights the urgent need for predictive biomarkers to select patients for immunotherapy.⁷,¹¹⁻¹³ In this study, we investigated the efficacy and toxicity of pembrolizumab, a PD-1 antibody, in patients from a real-world Australian population. We aimed to identify predictive clinical factors and the role of PD-L1 expression, BAP1 expression, and tumor-infiltrating lymphocytes (TILs) as predictive biomarkers from pembrolizumab treatment.

### Materials and Methods

#### Study Patients
Pembrolizumab was provided to individual patients at the request of their treating physician by the Insurance and Care (iCare) Dust Diseases Authority of New South Wales (NSW), which is a workers’ compensation scheme

### Table 1. Comparison of Currently Available Results From Studies Using PD-1 or PD-L1 Checkpoint Inhibitors in Mesothelioma

| Trial                  | Intervention                        | Target            | Phase | N   | ECOG PS | ORR (%) | DCR (%) | mOS (mo) | mPFS (mo) | Grade ≥3 Toxics |
|------------------------|-------------------------------------|-------------------|-------|-----|---------|---------|---------|----------|-----------|-----------------|
| PrE0505²⁴              | Durvalumab + chemo (cisplatin or pemetrexed) first-line | PD-L1             | 2     | 55  | 0-1     | 56.4    | 96.4    | 20.4     | (69.1%)   | –               |
| DREAM²²                | Durvalumab + chemo (cisplatin or pemetrexed) first-line | PD-L1             | 2     | 54  | 0-1     | 50³     | NR      | NR       | 6.9       | 8/54 (15%)      |
| JapicCTI-163247        | Nivolumab                           | PD-1              | 2     | 34  | 0-1     | 29      | 68      | 17.3     | 6.1       | 26/34 (76%)     |
| INITIATE¹⁰             | Nivolumab + ipilimumab              | PD-1 + CTLA-4     | 2     | 34  | 0-1     | 29      | 68      | NR       | 6.2       | 12/35 (34%)     |
| NIBIT-MESO-1¹⁶         | Tremelimumab + durvalumab           | CTLA-4 + PD-L1    | 2     | 40  | 0-1     | 28      | 65      | 16.6     | 8         | 7/40 (18%)      |
| NivoMes¹²              | Nivolumab                           | PD-1              | 2     | 34  | 0-1     | 24      | 47      | 11.8     | 2.6       | 9/34 (26%)      |
| PROMÉE-Meso²³          | Pembrolizumab vs. chemo (gemcitabine or vinorelbine) | PD-1              | 3     | RCT | 73 vs. 71 | (99%)  | 22 vs. 38 | 10.7 vs. 11.7 | 2.5 vs. 3.4 | 19.4% vs. 24.3% |
| KEYNOTE-028¹⁷          | Pembrolizumab                       | PD-1              | 1b    | 25  | 0-1     | 20      | 72      | 18       | 5.4       | 5/25 (20%)      |
| NCT02054806            | Pembrolizumab                       | PD-1              | 2     | 65  | 0-1     | 19      | 66      | 11.5     | 4.5       | 12/65 (18%)     |
| NCT02399371⁹           | Pembrolizumab                       | PD-1              | 2     | 65  | 0-1     | 19      | 66      | 11.5     | 4.5       | 12/65 (18%)     |
| Metaxas et al. (2018)¹⁶| Pembrolizumab                       | PD-1 RCS          | 93    | 0-1 | 18      | 48      | 7.2     | 3.1      | 7/93 (7.5%) |               |
| MAPS²²                 | Pembrolizumab alone vs. nivolumab + ipilimumab | PD-1 vs. PD-1 + CTLA-4 | 2     | RCT | 63 vs. 62 | (99%)  | 17 vs. 30 | 11.9 vs. 15.9 | 4.0 vs. 5.6 | 9/63 (14%) vs. 16/61 (26%) |
| JAVELIN²⁹              | Avelumab                            | PD-L1             | 1b    | 53  | 0-1     | 9      | 58      | 10.7     | 4.1       | 5/53 (9%)       |
| Current study          | Pembrolizumab                       | PD-1 RCS          | 98    | 0-1 | 18      | 56      | 9.5     | 4.8      | 9/98 (9%)  |               |

Note: a According to mRECIST.
Chemo, chemotherapy; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; mOS, median overall survival; mPFS, median progression-free survival; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NR, not reported; ORR, overall response rate; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; RCS, retrospective cohort study; RCT, randomized controlled trial.
in NSW, Australia that funds access to treatment for patients with dust-related diseases. The eligibility criteria to receive iCare compensation include individuals who developed mesothelioma as a result of occupational exposure to dust, such as asbestos, while employed in an NSW workplace. Pembrolizumab was then given off-label by the physicians to eligible patients who were deemed suitable candidates for immunotherapy and who were unable to access the treatment locally through a clinical trial setting. There were no strict inclusion and exclusion criteria set out for accessing pembrolizumab as part of this compensation scheme. Pembrolizumab was given at the request of the treating physician as the iCare Medical Advisory Committee had previously approved such use. Oncologists were invited to provide retrospective data of patients with mesothelioma who were treated with pembrolizumab between August 2015 and July 2019. This study was approved by the Sydney Local Health District Human Research Ethics Committee of the Concord Repatriation General Hospital (HREC/16/CRGH/177) with a waiver of informed consent.

**Baseline Variables**

Clinical and pathologic data were collected retrospectively from medical records of the participating cancer centers using a predefined template. Fields included age, sex, histologic subtype, baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS), location of mesothelioma, smoking history, extrapleural pneumonectomy, line of pembrolizumab therapy, and cycles of pembrolizumab and dexamethasone pre pembrolizumab (defined as patients who were already receiving dexamethasone medication at the time of commencement of pembrolizumab treatment). Differential blood counts and prognostic inflammatory markers were also collected, as reported previously, including neutrophil-to-lymphocyte ratio (NLR), defined as the absolute neutrophil count divided by the absolute lymphocyte count. An NLR of five or greater was considered to be elevated.

**Clinical Outcomes**

The following clinical information was collected and measured: (1) response to pembrolizumab, assessed as per the standard modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria for mesothelioma; (2) toxicity according to Common Terminology Criteria for Adverse Events version 4.03; (3) OS from the start date of pembrolizumab treatment until the date of death from any cause; and (4) PFS from the start date of pembrolizumab treatment until the date of disease progression or date of death from any cause (whichever occurred first). Patients were censored at the last follow-up date if they were still alive at the end of the study. Responses were obtained from radiologic imaging and reported by the operating oncologist. ORR was defined as the number of patients with complete response (CR) or partial response (PR) as a percentage of the total number of patients. Disease control rate (DCR) was defined as the number of patients with CR, PR, or stable disease as a percentage of the total number of patients.

**Immunohistochemistry**

All available archival formalin-fixed paraffin-embedded tumor samples were collected and evaluated in a central location (Royal Prince Alfred Hospital, Sydney, Australia) by an experienced thoracic pathologist who was blinded to the clinical outcome data. Immunohistochemistry was performed on a Bond III Autostainer PTLink using the Bond Polymer Refine Detection Kit (Leica Biosystems Nussloch GmbH, Nüßloch, Germany), with a high-pH target retrieval buffer (Leica Biosystems), as per manufacturer’s instructions. Formalin-fixed paraffin-embedded tumor samples were stained for PD-L1 (E1L3N clone, 1:75 dilution; XP Rabbit Monoclonal Antibody, Cell Signaling Technology, Danvers, MA), BAP1 (C-4 clone, 1:100 dilution; Santa Cruz Mouse Monoclonal Antibody, Dallas, TX), and TILs in the intratumoral component and the tumor-associated stroma (CD3-positive [CD3þ]; LN10 clone, 1:200 dilution; Novocastra, Newcastle Upon Tyne, United Kingdom).

PD-L1 expression was assessed by the tumor proportion score (TPS), defined as the percentage of tumor cells with any membranous staining of any intensity (0%–100%). PD-L1 expression was considered positive if TPS was greater than or equal to 1%. BAP1 expression was considered as positive or negative based on nuclear staining, with negative indicating abnormal loss of protein expression. CD3þ TILs were assessed in the intratumoral component and in the tumor-associated stroma.

**Statistical Analysis**

Survival curves and survival proportions were estimated using the method of Kaplan-Meier and compared using a log-rank test. The median follow-up time was estimated using the reverse Kaplan-Meier method. Scores for CD3þ TILs and blood counts were dichotomized on the basis of the distributions to ensure sufficient numbers in each group. A cutoff of greater than or equal to 5% was used to categorize CD3þ TILs in the tumor and stroma. Cox proportional hazards models were used to investigate the association of each marker with OS and PFS. Factors with a known or statistically significant prognostic association were then entered into a multivariable Cox regression model to determine their independent effect.
| Variable                      | All patients (N = 98) |
|-------------------------------|-----------------------|
|                              | N  | %    |
| Age, y                        |    |      |
| <65                           | 26 | 27   |
| ≥65                           | 72 | 73   |
| Sex                           |    |      |
| Female                        | 8  | 8    |
| Male                          | 90 | 92   |
| Histologic subtype            |    |      |
| Epithelioid                   | 74 | 76   |
| Sarcomatoid                   | 8  | 8    |
| Biphasic                      | 8  | 8    |
| Missing                       | 8  | 8    |
| ECOG PS                       |    |      |
| 0                             | 21 | 21   |
| 1                             | 55 | 56   |
| 2                             | 18 | 18   |
| 3                             | 2  | 2    |
| Missing                       | 2  | 2    |
| Location of Mesothelioma      |    |      |
| Pleural                       | 95 | 97   |
| Peritoneal                    | 3  | 3    |
| EPP                           |    |      |
| Yes                           | 8  | 8    |
| No                            | 89 | 91   |
| Missing                       | 1  | 1    |
| Pembrolizumab line of therapy |    |      |
| First line                    | 4  | 4    |
| Second line                   | 63 | 64   |
| Third line                    | 21 | 21   |
| More than third line          | 10 | 10   |
| Cycles of pembrolizumab       |    |      |
| Median                        | 6  |      |
| Range                         | 1-35 |    |
| Dexamethasone prepembrolizumab|    |      |
| Yes                           | 12 | 12   |
| No                            | 85 | 87   |
| Missing                       | 1  | 1    |
| Dexamethasone dose, mg (n = 9)|    |      |
| Median                        | 4  |      |
| Range                         | 1.0-7.5 |    |
| irAEs                         |    |      |
| No                            | 71 | 72   |
| Yes                           | 26 | 27   |
| Missing                       | 1  | 1    |
| Postpembrolizumab treatment   |    |      |
| Yes                           | 13 | 13   |
| No                            | 85 | 87   |
| Blood counts                  |    |      |
| NLR                           |    |      |
| <5                            | 56 | 57   |
| ≥5                            | 36 | 37   |
| Missing                       | 6  | 6    |
| Baseline white blood count (×10⁶/liter) | | |
| <8.3                          | 52 | 53   |
| ≥8.3                          | 40 | 41   |
| Missing                       | 6  | 6    |

(continued)
The relationship between ORR and significant clinical factors and biomarkers was analyzed using logistic regression. The OR with the corresponding 95% confidence interval (CI) was used to assess the relationship. For variables with insufficient numbers to conduct logistic regression, Fisher’s exact test was applied to determine the relationship. A p value of 0.05 or less was considered statistically significant. Stata SE 14.2 software was used for the statistical analysis.

Results

Patient Demographics and Outcomes

A total of 98 patients were included in the study, and 76 tumor samples were available for analysis. At the end of the study period, 27 patients were alive. Baseline characteristics are provided in Table 2. The median age was 70 years (range, 46–91 y). Most patients were men (92%) diagnosed with MPM (97%) of the epithelioid subtype (76%), had ECOG PS 0 to 1 (78%), and did not undergo extrapleural pneumonectomy (91%). Most patients received previous treatments, predominantly combination chemotherapy, before commencing pembrolizumab (Supplementary Table 1). Four patients (4%) received pembrolizumab as first-line treatment as they were unfit for chemotherapy for a variety of reasons. A total of 63 patients (64%) received pembrolizumab as second-line treatment and 31 patients (32%) as third-line or later. None of the patients were selected based on biomarker expression. The dose of
Figure 1. Kaplan-Meier curves for (A) PFS in the entire cohort and according to (B) ECOG PS, (C) baseline platelet count, (D) PD-L1 expression, and (E) histologic subtype. ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.
pembrolizumab was 200 mg (flat dose) administered every 3 weeks for 73% of patients and 2 mg/kg (weight-based) every 3 weeks for 27% of patients. The number of cycles of pembrolizumab treatment, 12 patients (12%) were on dexamethasone medication, which was given to boost energy, stimulate appetite, or palliate symptoms.

In the full cohort, the ORR was 18% (95% CI: 12%–28%), which included one CR and 17 PR. The DCR was 56% (95% CI: 47%–66%), which included 37 stable diseases. For patients who had a PR or CR (n = 18), the median duration of treatment was 12.9 months (interquartile range: 10.4–18.9 mo), defined as the time from date of pembrolizumab treatment to date of disease progression, date of death, or date of censoring, whichever occurred first. Three patients had pseudoprogression, defined as a patient who seemed to progress initially on imaging (RECIST progression), followed by a response. Two of these patients were reported previously.15 Response in one patient was not assessable as the patient passed away before imaging. A total of 13 patients received other treatments post-pembrolizumab, such as combination chemotherapy with or without bevacizumab (Supplementary Table 2). Of these, two patients (15%) had PR. Overall, the median PFS was 4.8 months (95% CI: 3.6–6.2 mo) (Fig. 1A), and the median OS was 9.5 months (95% CI: 6.6–13.7 mo) (Fig. 2A). The median follow-up was 21.3 months (95% CI: 17.9–22.9 mo), and the OS rate at 12 and 24 months was 41% and 21%, respectively.

Immune-related adverse events (irAEs) of any grade occurred in 26 patients (27%), with eight patients (8%) experiencing grade 3 or higher irAEs. These included pneumonitis (four cases, 4%), nephritis (one case, 1%), scleroderma (one case, 1%), and hepatitis (one case, 1%), with one patient experiencing grade 3 myasthenia gravis (1%) and diarrhea or colitis (1%). Other irAEs included grade 1 to 2 rash or pruritus (six cases, 6%), grade 2 pneumonitis (one case, 1%), grade 1 to 2 diarrhea or colitis (three cases, 3%), grade 2 nephritis (one case, 1%), grade 1 arthralgia (two cases, 2%), grade 1 dry mouth (one case 1%), grade 1 to 2 hyperthyroidism (three cases, 3%), grade 1 thyroid function test abnormalities (one case, 1%) and grade 2 synovitis (one case, 1%) (Supplementary Table 3).

**Biomarkers: PD-L1 TPS Score, BAP1, and TILs**

Examples of cytoplasmic staining of each biomarker are illustrated in Figure 1. BAP1 score was not assessable in one patient, and CD3+ TILs in the stroma was not assessable in five patients. PD-L1 TPS of greater than or
equal to 1% was observed in 31 of 76 patients (41%), and loss of nuclear BAP1 was observed in 35 of 75 patients (47%). CD3+ TILs (≥5%) was observed in 36 of 76 patients (47%) within the tumor and in 64 of 71 patients (90%) within the stroma.

Factors Associated With Response, OS, and PFS

The odds of a response to pembrolizumab were higher for patients with baseline ECOG PS 0 (OR for ECOG ≥1: 0.25; 95% CI: 0.08–0.77; p = 0.02). In addition, there was an association between ORR and CD3+ TILs (≥5%) within the tumor (ORR: 28% versus 5%; p < 0.01) but not in the stroma (p = 0.26). PD-L1 expression and BAP1 loss were not significantly associated with ORR (Table 3), although the ORR was numerically higher for patients with PD-L1 TPS score of greater than or equal to 1% (23% versus 11%) and patients who had BAP1 loss (20% versus 13%).

In univariate analysis (Supplementary Table 4), factors predictive of better PFS included ECOG PS 0 (median PFS: 12 mo versus 4 mo, p < 0.01), baseline platelet count of less than or equal to 400 × 10^9/liter (median OS: 6 mo versus 2 mo, p = 0.01) and CD3+ TILs (≥5%) in the tumor (median PFS: 6 mo versus 4 mo, p = 0.02). In the multivariable analysis (Fig. 1), factors independently predictive of PFS included ECOG PS greater than or equal to 1 (hazard ratio [HR] = 3.85; 95% CI: 1.54–9.64; p < 0.01) (Fig. 1B), baseline platelet count of greater than 400 × 10^9/liter (HR = 1.93; 95% CI: 1.01–

Figure 2. Kaplan-Meier curves for (A) overall survival in the entire cohort and according to (B) baseline platelet count, (C) dexamethasone prepembrolizumab, and (D) histologic subtype.
Figure 3. Examples of MPM tumor sections stained for PD-L1, BAP1, and CD3-positive TILs in the tumor and stroma. MPM, malignant pleural mesothelioma; TIL, tumor-infiltrating lymphocyte; PD-L1, programmed death-ligand 1.
than or equal to 1% (HR: 0.31; 95% CI: 0.52–0.63; p < 0.01) (Fig. 1D). The presence of CD3+ TILs (≥5%) in the tumor was not independently predictive of PFS (p = 0.40).

Factors predictive of longer OS in our univariate analysis included ECOG PS 0 (median OS: 18 mo versus 8 mo, p = 0.01), lack of dexamethasone pre pembrolizumab (median OS: 10 mo versus 3 mo, p < 0.01) and baseline platelet count of less than or equal to 400 × 10^9/liter (median OS: 10 mo versus 4 mo, p < 0.01) (Supplementary Table 5). In the multivariable analysis (Fig. 2), factors that were independently predictive of OS included baseline platelet count of greater than 400 × 10^9/liter (HR: 2.37; 95% CI: 1.21–4.63; p = 0.01) (Fig. 2B) and dexamethasone pre pembrolizumab (HR: 4.37; 95% CI: 1.45–13.13; p = 0.01) (Fig. 2C). Neither BAP1 loss nor CD3+ TILs (≥5%) in the stroma were predictive of PFS nor OS. Histologic subtype was not associated with a response, nor with PFS and OS (Figs. 1E and 2D). This may be because of the uneven distribution of data, with a small number of patients having nonepithelioid subtype (n = 16) and most patients having epithelioid subtype (n = 74).

Discussion

We presented the outcomes to pembrolizumab from a large real-world cohort of patients with mesothelioma and explored predictive factors that correlated with outcome. We observed an ORR of 18%, DCR of 56%, median PFS of 4.8 months, and median OS of 9.5 months. Our outcomes were comparable to similar real-world data recently reported by Metaxas et al. In addition, our data exhibited that pembrolizumab was well tolerated, given that only eight patients (8%) experienced grade 3 or higher irAEs, which were similar to those reported in clinical trials (Supplementary Table 3). Our study suggests that the use of pembrolizumab monotherapy in malignant mesothelioma patients is safe, with activity in line with the available literature.

It is clear from our study that not all patients benefit from this immunotherapeutic approach. This observation is consistent with the results from the phase 3 prospective randomized PROMISE-Meso trial, which compared pembrolizumab with chemotherapy with either single-agent gemcitabine or vinorelbine in the second-line setting. Although pembrolizumab treatment led to a superior ORR, it did not provide a survival advantage in terms of either PFS or OS compared with chemotherapy despite correcting for crossover. Given the somewhat disappointing results of the PROMISE-Meso trial, two broad strategies have been suggested to improve patient outcomes. The first is to combine PD-1 or PD-L1 inhibition with other treatments with the hope of potentiating efficacy. Promising results have emerged in mesothelioma and other tumor settings by combining immunotherapy with chemotherapy or through combined targeting of different immune checkpoint inhibitors (ICIs). In the DREAM study, a phase 2 single-arm trial (n = 54), durvalumab (PD-L1 antibody) was combined with cisplatin plus pemetrexed as first-line treatment in patients with MPM. The objective tumor response was 48% according to modified RECIST and 50% according to immune RECIST, which is one of the highest reported so far. In the MAPS2 study, combined targeting of PD-1 and CTLA-4 also exhibited a high response rate (30%) and comparable median OS and PFS (Table 1). Similar ORRs were observed in the INITIATE and NIBIT-MESO-1 trials, which combined PD-1 and PD-L1 blockade, respectively, with CTLA-4 inhibitors, with low and manageable toxicity. These results suggest that combination immunotherapy or chemimmunotherapy may be viable treatment options for patients with mesothelioma.

The second strategy to improve patient outcomes is to identify those that are likely to benefit from immunotherapy alone. Predictive biomarkers of PD-1 or PD-L1 inhibition in malignant mesothelioma have not been clearly defined, and our study aimed to explore this vexing question. In MPM, PD-L1 expression has been suggested as an adverse prognostic biomarker and associated with the nonepithelioid subtype. However, response to pembrolizumab has been observed in patients with MPM regardless of PD-L1 status, and no clear correlation has yet been found between PD-L1 expression and response to immunotherapy using PD-1 or PD-L1 checkpoint blockade. Nevertheless, it seems that a higher proportion of patients with PD-L1 TPS score of greater than or equal to 5% respond to pembrolizumab and have prolonged PFS and OS, compared with those that do not stain for PD-L1. This was observed in our study and in the MERIT study involving patients treated with nivolumab (PD-1 antibody). Similarly, in the JAVELIN study involving patients treated with avelumab (PD-L1 antibody), higher ORR and prolonged PFS and OS was observed in those with PD-L1 TPS score of greater than or equal to 5%. In a retrospective cohort of Metaxas et al., PD-L1 expression was significantly associated with response in MPM, with ORRs of 11%, 42%, and 44% for PD-L1 expressions of less than 5%, 5% to 49%, and greater than or equal to 50%, respectively. In other studies, PD-L1 expression was found to be a predictive biomarker of ICIs in NSCLC and bladder, cervical, and gastric or gastroesophageal junction cancers. However, the methodologies across clinical trials are inconsistent, including the use of variable PD-L1 antibodies, assays,
cutoff points (1%, 5%, and 50%) and detection methods (PD-L1 expression measured either on tumor cells or tumor-infiltrating immune cells, or both). Overall, the role of PD-L1 as a predictive biomarker for immunotherapy still remains unclear, and larger prospective studies are required to verify its predictive power.

Emerging evidence suggests that TILs may have predictive value for anti–PD-L1 or PD-1 therapy. In a small-scale study, an association was found between the ratio of CD8-positive (CD8+)/CD4-positive TILs and response to anti–PD-1 treatment in NSCLC and metastatic melanoma. Furthermore, in the KEYNOTE-119 trial, high TILs were significantly associated with better clinical outcomes from pembrolizumab, but not from chemotherapy, in metastatic triple-negative breast cancer. Similarly, in our study, TILs were associated with response to pembrolizumab. To understand this relationship, it is important to characterize the tumor microenvironment. Clinical responses to anti–PD-L1 or PD-1 therapy generally occur in patients with inflamed tumors. An inflamed phenotype suggests that there is a preexisting antitumor activity in the tumor microenvironment. We previously reported that most MPM patients had an inflamed tumor irrespective of PD-L1 status. It is possible that in an inflamed tumor microenvironment, TILs are restimulated during immunotherapy, triggering a response. However, not all patients with TILs in the tumor respond, suggesting that other factors are involved in the highly heterogenous MPM tumor microenvironment. Although we only investigated CD3+ TILs in our study, other subtypes of TILs contribute to an immune response, such as CD4-positive and CD8+ T-lymphocytes, Foxp3-positive regulatory T-cells, and CD20-positive B-lymphocytes. Therefore, combining different lymphocyte subsets and multiple biomarkers could help better determine the importance of TILs as a predictive biomarker for immunotherapy.

Markers such as NLR and differential blood counts have exhibited prognostic value in MPM. However, they have not been widely investigated in clinical trials, and it is not known whether they can predict response to immunotherapy. In the phase 2 NivoMes trial, lymphocytes, lactate dehydrogenase, C-reactive protein, and NLR were investigated for their predictive value in addition to PD-L1. Neither of these markers correlated with response to nivolumab nor with progressive disease; however, an increase in NLR from baseline to week 6 was significantly associated with the nonresponse. In our study, differential blood counts did not predict outcomes from pembrolizumab (Supplementary Tables 4 and 5), with the exception of elevated baseline platelet count (>400 × 10^9/liter), which was an independent predictor of lower OS and PFS. This is consistent with previous observations, as platelets are known to release a large number of proangiogenic factors, for example, VEGF, which is an adverse prognostic factor and predicts a worse outcome in MPM.

There are scarce data regarding other predictive biomarkers for immunotherapy. We investigated the predictive role of BAP1, a tumor suppressor gene. BAP1 is involved in regulating transcription by deubiquitinating target histones. Loss of BAP1 has been associated with aberrant activity of enhancer of zeste homolog 2, which is involved in gene expression and histone methylation. Recently, BAP1 loss was associated with an inflamed tumor microenvironment in peritoneal mesothelioma and uveal melanoma, suggesting that it could be a candidate predictive biomarker for immunotherapy. Although we did not observe an association between BAP1 loss and clinical outcomes to pembrolizumab treatment in our study, our results may have been limited by our small sample size. Larger studies are encouraged to further explore the role of BAP1 as a predictive biomarker.

We found that other clinical factors, such as the use of corticosteroids and onset of irAEs, may also affect outcomes to pembrolizumab. Corticosteroids are typically used to manage the adverse effects of chemotherapy, such as nausea, pain, vomiting, and rash. They are also often prescribed in patients with advanced mesothelioma for symptom palliation. Baseline corticosteroid use has been associated with poorer outcomes in patients with NSCLC treated with ICIs and is considered a surrogate for poor PS. However, there is also evidence to suggest that corticosteroids may reduce the efficacy of ICIs. In a preclinical mesothelioma mouse model, the addition of corticosteroids reduced the response to gemcitabine chemotherapy plus anti–CTLA-4 and anti–PD-1 ICIs. Dexamethasone was also reported to reduce the effectiveness of ICIs through suppression of interleukin-2 and potentially blunt the proliferative burst of CD8+ T-lymphocytes. In our study, the significant association of dexamethasone with the shorter OS, but not PFS, suggests it could be a surrogate for poorer PS. However, it remains unclear whether dexamethasone reduced the efficacy of pembrolizumab or had an impact on ECOG PS, given that ECOG PS was measured at the commencement of pembrolizumab treatment and not at the commencement of dexamethasone medication.

The onset of irAEs may also affect outcomes to pembrolizumab; however, larger studies are needed to exhibit its effect. IrAEs can represent bystander effects from activated T-cells; therefore, patients responding to immunotherapy would have a higher likelihood of toxicities. This theory has encouraged studies to investigate the onset of irAEs as a predictive biomarker of
immunotherapy in cancers such as melanoma and lung cancer (reviewed in Das and Johnson\textsuperscript{48}). Similar studies are encouraged to further investigate their role in the efficacy of immunotherapy in mesothelioma.

Finally, we reported that the functional status of a patient is a significant factor in their response to treatment. Although it is difficult to infer a causative relationship, it is not surprising that patients with better functional status would perform best after treatment. ECOG score of greater than 0 is considered to be an independent predictor of poor outcome,\textsuperscript{49} and we found that patients with ECOG score of 0 have longer survival and better response to pembrolizumab than patients with ECOG score of 1 or higher. It is important to note that our real-world study included a small number of patients with an ECOG score of greater than 1. Although this did not have an effect on the outcomes in our study, it may have contributed to our relatively lower survival outcomes than clinical trials, which selected patients with an ECOG score of 0 to 1 (Table 1).

The retrospective design and size of our study are its main limitations. It did not allow us to select for pre-defined patient populations or standardize treatment regimens. Although data from a real-world population can provide a more practical perspective of pembrolizumab toxicity and efficacy, larger prospective trials are needed to confirm the benefits of immunotherapy compared with chemotherapy. Further information will be known after the results of CheckMate 743 (NCT02899299), a large-scale, randomized phase 3 trial, which compared combination immunotherapy versus combination chemotherapy as first-line treatment in MPM.\textsuperscript{50} Interim unpublished results revealed promising outcomes, with combination immunotherapy exhibiting significant improvements in OS compared with combination chemotherapy.\textsuperscript{51}

**Summary and Conclusion**

We have presented real-world data on the safety and efficacy of pembrolizumab in mesothelioma from the largest patient cohort analyzed to date. We found that single-agent pembrolizumab is well tolerated by patients and is effective in a small proportion. Although the immuno-oncology field in mesothelioma is moving toward the combination strategy with chemotherapy, there still remains a strong clinical desire to better select patients for whom single-agent immunotherapy is the optimal choice. We illustrated that traditional PS assessment remains the most robust predictor for patient outcome with an ECOG status of 0 associated with better ORR and PFS. Other factors such as the lack of pretreatment dexamethasone, nonelevated absolute platelet count, and PD-L1 expression may predict for longer survival, whereas TILs in the tumor may help select patients that are likely to respond to pembrolizumab. These factors should be evaluated in a larger cohort and considered when designing protocols for prospective clinical trials. Larger studies are also required to verify the predictive value of PD-L1 and BAP1 for immunotherapy.

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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.jtocr.org and at https://doi.org/10.1016/j.jtocr.2020.100075.

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