Based on the Real-World Results From Australia, Immunotherapy Is Not a Good Option for Patients With Mesothelioma

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Introduction

In recent years, the treatment paradigm for pleural mesothelioma (PM) has been expanded after the development and rollout of immune checkpoint inhibitors (ICIs),[1] whereas the results of the Checkpoint-743 (CM-743) trial have led to the Food and Drug Administration (FDA) approval of the combination of ipilimumab and nivolumab for unresectable PM.[2] Despite the enthusiasm for this regimen in the frontline setting, we and others have previously suggested that biological rationale for using ICI for PM[3] together with the design of clinical trials in this neoplasm (including those for ICI) raises concerns owing to immunobiology and several inherent weaknesses of statistical robustness and issues with both informative censoring and clinical equipoise,[4–6] respectively.

Meta-Analysis of Clinical Trial Data

Various meta-analyses have been conducted on the current trials of ICI in PM. In an early meta-analysis of Guo et al.,[7] for studies that compared the efficacy of advanced-line ICIs with that of chemotherapy or placebo, they found that although targeted therapy had superior median overall survival (mOS) than placebo, ICIs did not have significant OS benefits over chemotherapy, yet it must be noted that a significant drawback to this meta-analysis is that it included only two studies—a cohort study and a randomized controlled trial (RCT). Furthermore, an analysis of two RCTs that compared the efficacy of ICIs with placebo was assessed, and ICIs were found to have no significant OS benefits.[7]

A second meta-analysis by Tagliamento et al.[8] found that first-line ICI resulted in an aggregated survival at 2 years of 39% (95% confidence interval [CI]: 34%–45%), but no clear evidence was presented for an estimation of the benefit of ICI plus chemotherapy with that of chemotherapy and placebo for OS. One of the main critiques of this meta-analysis is that it involved an analysis of four trials (DREAM, PrE0505, JME-001, and IND227), three of which are single-arm, making it difficult to consider analysis of OS.

Finally, in a multicancer meta-analysis of ICI (including a single mesothelioma trial) Serritella and Shenoy[9] concluded that the differences detected in OS and progression-free survival (PFS) between nivolumab plus ipilimumab and nivolumab were not clinically meaningful.

New Clinical Trial Data

The final results of the phase 3 component of IND227 have now been presented.[10] This trial was designed to compare the efficacy and safety of platinum, pemetrexed, and pembrolizumab versus platinum and pemetrexed in patients with previously untreated, advanced, unresectable PM. The primary end point for this trial was OS in all randomly assigned patients,[10] and although the authors conclude that the immune oncology regimen with the addition of pembrolizumab to standard platinum–pemetrexed chemotherapy was tolerable and resulted in a significant improvement in OS,[10] the overall benefit is minimal at best with an mOS of 16.1 months (95% CI: 13.08–18.17) for chemotherapy versus 17.3 months (95% CI: 14.36–21.29) (Table 1). Nevertheless, this marginal benefit came at a serious cost with an increase

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Table 1. Comparison of Various Elements in the IND227 Trial[10]

Element	Chemotherapy Alone	Chemotherapy Plus Pembrolizumab	Notes
Overall			
Median OS (95% CI)	16.1 mo (13.08-18.17)	17.3 mo (14.36-21.29)	Figure 2A[10]
Median duration of response	5.5 mo (4.2-6.0)	5.8 mo (5.5-7.0)	Table 3[10]
Discontinuation	The most common reason for chemotherapy discontinuation was completion of treatment.	The most common reason for chemotherapy discontinuation was completion of treatment. The most common reason for pembrolizumab discontinuation was disease progression.	Table 2[10]
Percentage AEs of grade 3 or higher	(32 of 211 patients)	(60 of 222 patients)	Table 4[10]
	15%	27%	
Hospital admissions due to SAE	16%	32%	Supplementary appendix, Table A4[10]
Deaths where relationship to one of more study drugs could not be excluded	2 (1%)	7 (3%)	Supplementary appendix, page 4[10]
Exploratory analyses			
Median OS in nonepithelioid (95% CI)	8.21 mo (5.85-10.8)	12.3 mo (8.67-21.2)	Figure 2[10]
Median OS in epithelioid (95% CI)	18.2 mo (16.0-20.4)	19.8 mo (16.0-22.2)	Figure 2[10]

AE, adverse event; CI, confidence interval; OS, overall survival; SAE, serious adverse event.

in grade 3 to 5 treatment-related adverse events (TRAEs) involving hospitalization and toxicity resulting in increased deaths in the immune oncology arm versus chemotherapy (discussed in depth in a later section).

Although these analyses and RCTs provide emerging data that suggest a limited benefit of ICI, an emerging area of concern for the IND227 trial and other RCTs involving ICIs is the issue of informative censoring bias,[11] and we believe that this is also true for RCTs involving ICI in PM and others (Meirson et al., manuscript in preparation).

The Issue of Histologic Subtype

One of the major considerations from the latest RCTs and meta-analyses is the potential benefit that may accrue to patients with the nonepithelioid histological subtype. In an exploratory subgroup analysis of CM-743 trial (Table 2), the hazard ratio (HR) for OS of 0.46 (95% CI: 0.31–0.68) with mOS of 18.1 months (95% CI: 12.2–22.8) for ICI versus 8.8 months (95% CI: 7.4–10.2) for chemotherapy suggested that this was a significant improvement for this subtype. The IND227 trial exploratory analyses also support this possibility with a HR for OS of 0.57 (95% CI: 0.36–0.89) and mOS of 12.3 months (95% CI: 8.67–21.2) for chemotherapy plus pembrolizumab versus 8.21 months (95% CI: 5.85–10.8) for chemotherapy.[10] In contrast, the epithelioid subtypes have not even a week suggestion of survival benefit in both trials.

One of the most pressing issues moving forward will be the exact determination of which nonepithelioid histotype achieves the most benefit. Currently, the CM-743 trial data were based off a 50.0% sarcomatoid and 50.0% mixed or other histological subtypes in the nivolumab plus ipilimumab arm and 62.5% and 37.5%, respectively, in the chemotherapy arm (Supplementary Table 9)[12] but did not do any exploratory analyses with respect to different histologies in the nonepithelioid patients. Likewise, the data from the IND227 exploratory analyses failed to segregate the nonepithelioid subtypes.[10]

Real-World Data of ICI in the PM Setting

The analyses described previously are, however, based off clinical trials involving highly selected cohorts of patients which may not accurately reflect real-world realities.[13] Emerging studies on real-world evidence of ICI in PM patient treatment have recently been published as abstracts. Wu et al.[14] reported that combining ipilimumab and nivolumab had a mOS of 22.3 months, whereas the ImmunoMeso study by Aguirre et al.[15] reported the regimen mOS of 30 months in the first-line setting of patients with unresectable or metastatic malignant PM. Both real-world analyses did not directly compare ICI

Table 2. Comparison of Various Elements in the CM-743 Trial[12]

Element	Chemotherapy Alone	Chemotherapy Plus ICI	Notes
Overall mOS (all patients) (95% CI)	14.1 mo (16.8-21.0)	18.1 mo (12.4-16.3)	Figure 2[12]
Median duration of complete or partial response (95% CI)	6.7 mo (5.6-7.1)	11.6 mo (8.2-16.8)	Figure 3 and Supplementary Table 4[12]
Median PFS (95% CI)	7.2 mo (6.9-8.0)	6.8 mo (5.6-7.4)	Figure 3
Percentage AEs of grade 3 or higher	32%	30.7%	Supplementary Table 5[12]
Any AEs leading to discontinuation of any component of the regimen	23%	38%	Supplementary Table 5. Safety summary[12]
AEs leading to discontinuation of all components of the regimen	12.3%	30.3%	Supplementary Table 5. Safety summary[12]
Serious AEs	13.7%	37%	Supplementary Table 5. Safety summary[12]
Deaths associated with treatment	0.4%	1%	Supplementary Table 5. Safety summary[12]
Exploratory analyses			
mOS (nonepithelioid subset) (95% CI)	8.8 mo (7.4-10.2)	18.1 mo(12.2-22.8)	Figure 2[12]
mOS (nonepithelioid subset) (95% CI)	16.5 (14.9-20.5)	18.7 (16.9-22.0)	Figure 2[12]

AE, adverse event; CI, confidence interval; ICI, immune checkpoint inhibitor; mOS, median overall survival; OS, overall survival; PFS, progression-free survival.

with chemotherapy. Nevertheless, in the study by Wu et al.,[14] the 95% CIs for the HR for OS of chemotherapy (0.63–0.92; $p = 0.004$) and ICI (0.28–0.90; $p = 0.02$) compared with best supportive care (BSC) suggest no significant benefit between the two regimens. Furthermore, the marginal p value (0.02) indicates that the reported survival benefit of ICI over BSC lacks statistical robustness. Nevertheless, caution is warranted in interpreting these results due to the small sample size, and the full-text articles have yet to be published.

Two studies have been recently published regarding the use of ICI in real-world settings. The first, known as Australian RIOMeso by McNamee et al.,[16] includes 119 patients with malignant PM. Of these patients, 75% received dual ICI as first-line treatment, whereas the remaining underwent second-line therapy. The meta-analysis reported a mOS of only 14.5 months in first-line patients[16] (Table 3), comparable with and numerically lower than the mOS of the arm in CM-743 (14.1 mo)[12] and IND227 (16.1 mo),[10] respectively.

The second real-world data set to emerge concerns the combination of ipilimumab and nivolumab for 184 patients treated in the Netherlands between January 2021 and August 2022.[13] mOS for this data set was reported as 14.1 months (Table 3), which is again comparable with the mOS reported for the chemotherapy arm in CM-743 or numerically lower than IND227.[12] Despite the inherent limitations of cross-comparison of clinical studies, these observations are noteworthy.[16]

In terms of the potential benefit accruing for the nonepithelioid subtype, Australian RIOMeso found that there was no statistically significant difference in mOS for the epithelioid histological subtype compared with nonepithelioid,[16] whereas the analysis from the Netherlands data set concluded that no correlations could be found between PFS and OS with histologic subtype.[13] Similar outcomes have also been reported in the unpublished real-world data sets. The ImmunoMeso study found no statistical difference in PFS between patients with epithelioid versus nonepithelioid tumors.[15] The absence of outcome differences between subtypes, despite the nonepithelioid being linked to a poorer prognosis, supports a distinct benefit for this subtype, yet the exact benefit for nonepithelioid subtypes (sarcomatoid versus biphasic/mixed/other) remains to be determined.

The data from real-world treatment of PM with ICI within the second-line setting ICI also reveal contrasting results when compared with trial-based outcomes. Kerrigan et al.[17] reported no evidence of an improved OS treated with single or combination immunotherapy as compared with single-agent chemotherapy, and the Australian RIOMeso study also found no significant difference between first-line and second-line combination immunotherapy.[16] Nevertheless, in the RCT setting, the CONFIRM trial (nivolumab versus placebo) revealed an OS benefit,[18] whereas PROMISE-meso (pembrolizumab versus chemotherapy) failed to find any OS benefit.[19] Such disparities may however reflect an issue with clinical equipoise[4] in the design of these trials.

Is Toxicity an Emerging Additional Area of Concern?

One of the elements that may be a factor is the potential issue of toxicity associated with ICI therapy. In

Table 3. Comparison of Various Elements in the Australian RIOMeso and the Netherlands Real-Time Studies[13,16]

Element	Dual ICI in First-Line Setting	Dual ICI in Second-Line or Later Settings	Notes
RIOMeso (Australian study)			
Median OS	14.5 mo	15.4 mo	Main text[16]
Percentage AEs of grade 3 or higher	22%	30%	Main text[16]
Hospital admissions due to AEs	44%	40%	Main text[16]
Discontinuation due to drug toxicities	31%	30%	Main text[16]
Deaths associated with treatment	3%		Table 2[16]
Dumoulin et al.[13] (Netherlands study)			
	Dual ICI (first-line and beyond)		Notes
Median OS (95% CI)	14.1 mo (11.1-18.2)		Main text[13]
Percentage AEs of grade 3 or higher	32%		(Based off data presented in Table 2[13])
Discontinuation due to drug toxicities	25%		Main text[13]

AE, adverse event; CI, confidence interval; ICI, immune checkpoint inhibitor; OS, overall survival.

the JME-011 phase 2 trial, Miyamoto et al.[20] reported that 55.6% of patients receiving ICI (nivolumab) experienced grade 3 or worse AEs suggesting that ICI may cause significant AEs in PM. In a similar vein, in the MAPS2 phase 2 clinical trial, no grade 5 AEs were reported for patients treated just with nivolumab, whereas in the combination arm 5% of patients had grade 5 AEs leading to death.[21] CM-743 reported that, overall, any-grade serious AEs occurred in 21% of patients in the nivolumab plus ipilimumab arm and 8% in the chemotherapy arm, whereas there was a 1% grade 5 AE[12] (Table 2). It must also be noted that according to the protocol of CM-743,[12] only events that led to death within 24 hours were documented as grade 5 AEs which could lead to an underestimation of treatment-related deaths.

In the IND227 trial, 3% deaths were reported as possibly being related to pembrolizumab plus chemotherapy versus 1% deaths for chemotherapy alone (Table 1). In this regard, a death was recorded as related to study therapy if it occurred at any point after the onset of the event in contrast to CM-743.[12] In this trial, grade 3 to 4 AEs related to treatment occurred in 60 of 222 patients (27%) in the pembrolizumab group and 32 of 211 patients (15%) in the chemotherapy-alone group. In addition, hospital admissions for serious AEs related to one or more study drugs were reported in 40 of 222 patients (18%) in the pembrolizumab group and 12 of 211 patients (6%) in the chemotherapy-alone group.[10] Moreover, discontinuation of any protocol therapy owing to AEs was much higher in the pembrolizumab plus chemotherapy arm versus chemotherapy alone (n = 82 [37%] versus n = 42 [20%], respectively),[10] and although reasons for discontinuation should not be considered as a surrogate for adverse event or efficacy, the double rate of discontinuation in the ICI arm is concerning.

In the real-world setting, the Australian RIOMeso study reported 3% grade 5 toxicities, all classified as treatment-related deaths[16] (Table 3). Moreover, 24% of patients had a grade greater than or equal to 3 AE, 44% of patients required hospital admission during first-line treatment, and treatment cessation owing to toxicity occurred in 31% (n = 28 of 89) of patients treated in the first-line ICI setting.[16] In the second real-world setting, in the Netherlands, TRAEs of grades 2 to 5 requiring additional treatment were found to involve 46.7% of patients,[13] and of these, grades 3 to 5 TRAEs were of the order of 32% (Table 3).

All the above-mentioned suggest that toxicity may be a real issue of concern to clinicians treating patients with PM moving forward.

The Issue of Cost

The next issue arising relates to the heavy cost burden of not only the ICI themselves but also the associated issue of increased hospitalizations as identified through the real-world data for this frontline regimen.[16] Initial analyses suggest that for many countries, the cost-effectiveness of ICI in PM determined as the incremental cost-effectiveness ratio is too high and is often above the threshold for willingness-to-pay (WTP)[5] (Table 4). More recent analyses have determined that in the People's Republic of China, nivolumab is not cost effective and above the WTP threshold,[22] and separate cost-effective analyses for the dual ICI combination of nivolumab/ipilimumab also exceeded the WTP in both the People's Republic of China and Switzerland[23,24] (Table 4). On top of this, a major area of concern to whether the addition of ipilimumab to the first-line therapy involving nivolumab adds any true clinical benefit or whether it just adds an extreme element of toxicity.[6,21]

Table 4. Cost Analyses for ICI in PM (Without Stratification by Histological Subtype)

Drug Comparison	Country	ICER per QALY	Comments
Nivolumab plus ipilimumab vs. chemotherapy (first-line setting)	USA	$475,677/QALYs	Above the theoretical willingness-to-pay threshold in the United States[5,25]
Nivolumab plus ipilimumab vs. chemotherapy (first-line setting)	USA	$375,656/QALYs in all randomized patients	Above the theoretical willingness-to-pay threshold in the United States[5,26]
Nivolumab plus ipilimumab vs. platinum plus pemetrexed (with and without bevacizumab) (first-line setting)	Switzerland	$201,829/QALYs	May be cost effective if priced at 48% across all histologies[23]
Nivolumab in relapsed PM (second-line setting)	People's Republic of China	$75,805.11/QALYs	Above the willingness-to-pay threshold in the People's Republic of China[22]
Nivolumab plus ipilimumab (first-line setting)	People's Republic of China	$375,656/QALYs	Above the willingness-to-pay threshold in the People's Republic of China[24]

ICER, incremental cost-effectiveness ratio; ICI, immune checkpoint inhibitor; PM, pleural mesothelioma; QALY, quality-adjusted life-year; USA, United States of America.

In terms of potential cost-savings, should ICI therefore be given to all-comers (i.e., all histologic subtypes), or should it be given to nonepithelioid patients? In the various trials, results have suggested that all histologic subtypes benefit,[8,12] yet exploratory subgroup analyses for both the CM-743 and IND227 trials suggest that the nonepithelioid subgroup benefits from the combination or addition of ICI with standard chemotherapy.[10,12]

Conclusions

Despite all the hype, we believe that at the present moment, the current data for ICI for treatment of PM are not sound enough to currently warrant its use for all-comers. Although evidence supporting survival benefits for all-comers is limited, the use of ICI is associated with a twofold increase in drug discontinuation, up to three times more serious AEs or treatment-related deaths, and nearly half of the patients' requiring hospitalizations or additional treatment. Despite methodological limitations, emerging data suggest that there may be the potential to have ICI used in the first-line setting for patients with nonepithelioid histologies. More needs to be done to better assess AEs associated with ICI, and more observational studies and ongoing trials[27] may help shed light on this taxing issue. Essentially, one subgroup (epithelioid) experiences severe toxicity with no apparent benefit, whereas the nonepithelioid subtype has the same toxicities with a strong suggestion for benefit.

The potential mOS benefit for the nonepithelioid subtype is highly important given its traditionally reported poor outcomes for chemotherapy. Nevertheless, it is interesting to note that, in the ETOP/ESTS real-world mesothelioma data set analysis,[28] patients with the nonepithelioid histological subtype (regardless of treatment and inclusive of BSC) had a mOS of 11 months (95% CI: 9.5–13.0).[25,26,28] This is similar to the reported mOS for the chemotherapy plus pembrolizumab with a mOS of 12.3 months (95% CI: 8.67–21.2) in IND227.[10] In contrast, the reported mOS benefit for checkpoint inhibitors in CM-743 was 18.1 months (95% CI: 12.2–22.8),[12] and although it is not possible to make any direct comparisons with respect to these three studies, from a clinician's perspective, it is clear that more data will be required to tease out the potential benefit of checkpoint inhibitors in the nonepithelioid setting. We propose that to answer this, a new specific, phase 3, randomly controlled clinical trial specifically designed to compare between ICI monotherapy versus dual ICI in the nonepithelioid subset will be required.

CRediT Authorship Contribution Statement

Luciano Mutti: Conceptualization, Investigation, Project administration, Supervision.

Steven Gray: Data curation, Investigation, Visualization, Roles/Writing—original draft, Writing—review and editing.

Tomer Meirson: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Roles/Writing—original draft, Writing—review and editing.

Disclosures

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