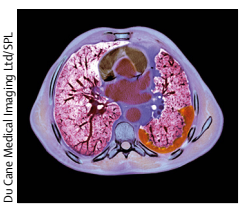
Checkpoint inhibitors in mesothelioma: hope for the future?



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Malignant pleural mesothelioma is an aggressive, asbestos-related tumour of the thoracic cavity, with increasing global incidence.[1] Prognosis is poor and treatment options are scarce. Pemetrexed and platinum doublet chemotherapy has been the standard first-line therapy for non-resectable malignant pleural mesothelioma since 2003, when a phase 3 randomised trial showed a survival benefit of 2·8 months compared with cisplatin alone.[2] Treatment remained unchanged for more than a decade, until 2016, when the Mesothelioma Avastin plus Pemetrexed-cisplatin Study (MAPS) trial showed that adding the vascular endothelial growth factor antagonist, bevacizumab, to first-line chemotherapy extended survival to 18·8 months compared with 16·1 months with chemotherapy alone.[3] Unfortunately, no second-line or third-line treatment has been established for relapsed or progressive malignant pleural mesothelioma, despite substantial academic endeavour.

In this context, the publication this month of two promising phase 2 studies in previously treated malignant pleural mesothelioma is important progress.[4,5] Both trials investigated immune checkpoint inhibitors (ICIs), used alone or in combination. These drugs, which enable preservation of antitumour immune activity by preventing downregulation of antigen-specific T cells, have yielded impressive results in other malignancies with poor prognosis and have earned the scientists behind their discovery the Nobel Prize in Medicine. ICIs exert their effect by targeting inhibitory checkpoint receptors and their ligands (including the programmed cell death 1 [PD-1] receptor and its ligand, PD-L1), preventing interactions that would otherwise lead to apoptosis of effector T cells and maintenance of regulatory T cells. This approach is of interest in malignant pleural mesothelioma, a tumour that can co-opt inhibitory pathways by expressing PD-L1, and thus might be vulnerable to checkpoint blockade.

Reported in *The Lancet Oncology*, the French Cooperative Thoracic Intergroup describe the MAPS2 randomised controlled trial,[4] in which they assessed nivolumab (a PD-1 inhibitor) alone (n=63) or in combination with ipilimumab (an ICI targeting cytotoxic T-lymphocyte protein 4 [CTLA-4]; n=62) until disease progression or unacceptable toxicity. Patients had an Eastern Cooperative Oncology Group performance status of 0–1 and histologically proven, non-resectable malignant pleural mesothelioma that had progressed radiologically after at least one line of standard chemotherapy. Notably, this well-organised French research collaborative completed recruitment within 5 months.

The primary outcome was 12-week disease control (defined as complete response, partial response, or stable disease) in the initial 108 eligible participants. The intention was not to compare the two regimens, and the study was not powered to do so, but rather to describe the efficacy and tolerability in each group, with a view to design a subsequent comparative phase 3 trial. Disease control was achieved by 24 (44%; 95% CI 31–58) of 54 patients in the nivolumab group and 27 (50%; 37–63) of 54 patients in the combination group. Secondary analyses showed median progression-free survival of 4·0 months (95% CI 2·8–5·7) in the nivolumab group and 5·6 months (3·1–8·3) in the combination group, median overall survival of 11·9 months (95% CI 6·7–17·7) and 15·9 months (10·7–not reached), and 1-year overall survival of 49·2% (36·9–61·6) and 58·1% (45·8–70·3).

In the second trial, INITIATE, published in *The Lancet Respiratory Medicine*, Maria Disselhorst and colleagues[5] treated 34 patients with combination ipilimumab and nivolumab for up to 2 years, or until disease progression or unacceptable toxicity. Patients had received at least one previous cycle of platinum-based chemotherapy, with six patients (18%) receiving multiple lines of treatment, including some experimental drugs. 12-week disease control (the primary outcome) was achieved in 23 patients (68%), with a median duration of response of 14·3 months (95% CI 6·4–not reached). Median overall survival was not reached but was estimated, with 95% confidence, to exceed 12·7 months. 1-year overall survival was achieved by 64% of patients (95% CI 50–83).

From these data, ICIs appear more efficacious than second-line chemotherapy, which is associated, at best, with median progression-free survival of 3·8 months and median overall survival of 10·5 months.[6] The results reinforce other early-phase studies of ICIs in malignant pleural mesothelioma, including the non-randomised NivoMes trial[7] in patients with malignant pleural mesothelioma treated with nivolumab monotherapy,

in which disease control was achieved by 16 (47%) of 34 patients and 1-year overall survival was 50% (95% CI 36–70). Combination nivolumab and ipilimumab has not been previously studied in malignant pleural mesothelioma, but an alternative combination of durvalumab and tremelimumab, also targeting PD-1 and CTLA-4, was used in the NIBIT-MESO-1 trial.[8] 40 patients were treated, in the first-line or second-line setting, of whom 25 (63%) achieved disease control, with a progression-free survival of 5·7 months (95% CI 1·7–9·7) and median overall survival of 16·6 months (13·1–20·1).[8]

However, ICIs are not without side-effects, especially when used in combination. More than 93% of patients who received nivolumab and ipilimumab in MAPS2 and INITIATE had an adverse event, with 16 (26%) of 61 patients in MAPS2 and 12 (34%) of 35 participants in INITIATE having at least one treatment-related adverse event of grade 3–4 severity. Additionally, there were three (5%) treatment-related deaths in the combination group of MAPS2, and 13 (21%) of patients discontinued treatment because of side-effects. Nivolumab monotherapy was less toxic, with nine (14%) of 63 patients having a grade 3–4 adverse event, and no treatment-related deaths. In keeping with previous experience, the most common adverse events in these two studies were fatigue, diarrhoea, and anorexia, with acute kidney injury and increases in liver enzyme concentrations as the most important non-haematological events. However, perspective is required. Chemotherapy is associated with much higher complication rates; 44% of patients treated with pemetrexed and cisplatin have grade 3 or 4 neutropenia, and more than 75% have some degree of nausea and vomiting.[3] As with all treatments, the deciding factor will be whether clinicians and patients consider the risk of side-effects to be outweighed by potential benefit—a decision that is likely to vary between individuals.

These two trials inspire optimism for several reasons. First, the speed of recruitment in a subpopulation of patients with a rare disease is impressive. Improved public engagement, patient involvement in trial design, and wider dissemination of results has led to increased awareness of research among patients with malignant pleural mesothelioma, carers, and other stakeholders. This is a welcome development and researchers must respond by ensuring that patients have optimal and equitable access to malignant pleural mesothelioma trials, both for their benefit and to expedite further therapeutic advances.

Second, the trial results are encouraging, and their consistency with each other and existing data suggest they are reliable. However, we must be mindful of the limitations of non-comparative trials, including selection bias and, in the second-line or third-line setting, survivorship bias. External validity is also unverified; participants were of good performance status and both studies excluded patients with some poor-prognosis indicators (eg, weight loss and uncontrolled chest pain). Above all, history has taught us that promising phase 2 data are no guarantee of demonstrable efficacy in suitably powered randomised trials—eg, the two tremelimumab studies, MESOTREM[9] and DETERMINE.[10] In the initial single-arm study, 29 patients with mesothelioma were treated with tremelimumab and 15 (52%) achieved disease control, but the subsequent randomised, double-blind, placebo-controlled trial of 569 patients showed no difference in survival between patients given tremelimumab versus placebo (hazard ratio 0·92 [95% CI 0·76–1·12], p=0·41).[9,10]

Well designed phase 3 trials are needed to assess the clinical efficacy of ICIs in the second-line and third-line setting. Several studies are underway investigating PD-1 inhibitors as monotherapy in this context, including pembrolizumab in PROMISE-meso (NCT02991482) and nivolumab in CONFIRM (NCT03063450). Phase 3 trials of combinations of ICIs in previously treated relapsed patients with malignant pleural mesothelioma are awaited, although CheckMate743 (NCT02899299) is evaluating nivolumab plus ipilimumab combination therapy in untreated patients compared with standard chemotherapy.

Phase 3 trials will also enable clarification of ongoing areas of uncertainty. Of particular interest is the role of tumour PD-L1 expression in predicting treatment response, as well as the most sensitive assay with which to measure it and the optimal threshold to define high or low expression. Larger trials will also enable exploration and further quantification of the characteristics of patients with hyperprogression—an important phenomenon that is poorly understood. This information could facilitate a move towards

personalised treatment for malignant pleural mesothelioma, with the potential to improve outcomes and enhance patients' quality of life.

In summary, the publication of these two promising studies is an important and encouraging advance for malignant pleural mesothelioma. ICIs have had an enormous impact on the treatment of other malignancies with poor prognoses, such as melanoma and non-small-cell lung cancer. They might do the same for malignant pleural mesothelioma in time; however, for now all efforts must be directed toward supporting definitive trials, for it is these that have the potential to transform the treatment landscape of malignant pleural mesothelioma.

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1 Woolhouse I, Bishop L, Darlison L, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. *Thorax* 2018; **73** (suppl 1): i1–30.
2 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:** 2636–44.
3 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:** 1405–14.
4 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; published online Jan 16. http://dx.doi.org/10.1016/S1470-2045(18)30765-4.
5 Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. *Lancet Respir Med* 2019; published online Jan 16. http://dx.doi.org/10.1016/S2213-2600(18)30420-X.
6 Ceresoli GL, Zucali PA, De Vincenzo F, et al. Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma. *Lung Cancer* 2011; **72:** 73–77.
7 Quispel-Janssen J, van der Noort V, de Vries JF, et al. Programmed death 1 blockade with nivolumab in patients with recurrent malignant pleural mesothelioma. *J Thoracic Oncol* 2018; **13:** 1569–76.
8 Calabrò L, Morra A, Giannarelli D, et al. Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study. *Lancet Respir Med* 2018; **6:** 451–60.
9 Calabrò L, Morra A, Fonsatti E, et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. *Lancet Respir Med* 2015; **3:** 301–09.
10 Maio M, Scherpereel A, Calabrò L, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. *Lancet Oncol* 2017; **18:** 1261–73.

More evidence for implant-based breast reconstruction


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The scarcity of randomised controlled trials is a key issue in surgical research. The dearth of trials results from several methodological challenges, and because of surgeons' reluctance to be involved in study design.[1] Nonetheless, experimental research is crucial to the generation of high-quality data to assess the effects of new procedures or devices before introducing them into standard practice. This insufficiency of high-level evidence becomes a paradox when dealing with implant-based breast reconstruction. Despite this technique being the most common surgical procedure for breast reconstruction worldwide, the number of patients involved in randomised trials is very low.[2]

In the iBRA study, Shelley Potter and colleagues investigated short-term outcomes of immediate implant-based breast reconstruction with or without mesh in a large prospective cohort of 2108 patients (2655 reconstructions) across 81 breast and plastic surgical units in the UK.[3] This study was designed to identify key questions and suitable outcomes to be investigated with adequate power in forthcoming randomised trials. Mesh-based reconstruction (1376 [65%] patients) was by far the most common method, followed by dermal sling implants (440 [21%] patients) and non-mesh submuscular or subfascial implants (181 [9%] patients). The results highlight that the proportion of patients with complications is far higher than proposed standards: nearly a tenth of patients had implant loss, almost a fifth were readmitted or re-operated for complications within 3 months, and a quarter needed treatment for infection.[3,4] Further, these levels of complications have not decreased since the 2008–09 UK National Mastectomy and Breast Reconstruction Audit (NMBRA).[5] In our opinion, these worrisome conclusions could be a direct consequence of the poor evidence available to inform choices about the best method of reconstruction to use, which generates unreliable and confusing information about indications, risk factors, and outcomes.