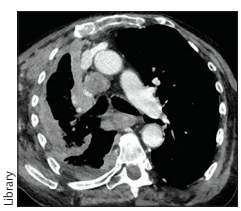
Immune checkpoint inhibitors in mesothelioma: a turning point



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Malignant pleural mesothelioma (MPM) is an asbestos-related tumour with a poor prognosis.[1] Most patients are diagnosed with a diffuse disease unamenable to surgery, and are candidates for medical therapy only. First-line treatment with pemetrexed and platinum chemotherapy has not changed in the past two decades, with no standard further-line therapies available, and nearly all patients dying due to the disease.[2]

High interpatient heterogeneity and genetic heterogeneity have been major hurdles in developing effective treatment for MPM.[3] Moreover, several studies investigating the tumour microenvironment have shown a spectrum of heterogeneous entities with distinct immune cell infiltrates and checkpoint expression.[4] Expression of programmed cell death ligand 1 (PD-L1) has been correlated with a negative prognosis in MPM;[5] however, trials of immune checkpoint inhibitors report conflicting results on the association between PD-L1 and efficacy.[6,7] Immunosuppressive cells such as T-regulatory and myelomonocytic cells frequently infiltrate MPM samples, and a role of M2-polarised tumour-associated macrophages in resistance to immune checkpoint inhibitors has been hypothesised.[8]

In *The Lancet*, Paul Baas and colleagues[9] report results from the interim analysis of CheckMate 743, a global, open-label, randomised, phase 3 study investigating first-line nivolumab plus ipilimumab versus standard platinum plus pemetrexed chemotherapy. 605 adult patients with previously untreated unresectable MPM were randomly assigned (1:1) to either nivolumab (3 mg/kg intravenously once every 2 weeks) plus ipilimumab (1 mg/kg intravenously once every 6 weeks) for up to 2 years or platinum plus pemetrexed chemotherapy (pemetrexed [500 mg/m^2 intravenously] plus cisplatin [75 mg/m^2 intravenously] or carboplatin [area under the concentration-time curve 5 mg/mL per min intravenously]) once every 3 weeks for up to six cycles. Baseline patient characteristics were well balanced between treatment groups; overall, 467 (77%) of 605 participants were male, median age was 69 years (IQR 64–75), and 456 (75%) had epithelioid histology. Most patients were enrolled at European sites (352 [58%]). Immunotherapy significantly extended overall survival, with a median value of 18·1 months (95% CI 16·8–21·4) in the nivolumab plus ipilimumab group versus 14·1 months (12·4–16·2) in the chemotherapy group, and a hazard ratio (HR) of 0·74 (96·6% CI 0·60–0·91); 2-year overall survival rates were 41% (95% CI 35·1–46·5) versus 27% (21·9–32·4). Based on these data, the authors suggest that nivolumab plus ipilimumab should be considered a new standard of care for previously untreated patients with unresectable MPM, regardless of histological subtype.

Checkmate 743 is an important study in unresectable MPM. However, considering the potential impact of its results on clinical practice worldwide, there are several issues that should be highlighted.

First, a substantial difference was seen in overall survival gain between the patients with non-epithelioid and epithelioid histology in the nivolumab plus ipilimumab group (HR 0·46 [95% CI 0·31–0·68] *vs* 0·86 [0·69–1·08]). In the overall study population, overall survival data of patients enrolled in the chemotherapy group supported a negative prognostic role of PD-L1, which was somewhat reverted by treatment with the double checkpoint inhibitor. These findings suggest the need for stratified data according to PD-L1 expression for the more heterogeneous epithelioid subtype.

Second, notably, progressive disease was observed in 55 (18%) patients treated with nivolumab plus ipilimumab versus 14 (5%) treated with chemotherapy.[9] The progression-free survival curve shows that progression with immunotherapy often occurred in the first months of treatment. Other trials have reported the occurrence of early progression or even hyperprogressive disease in patients with MPM treated with immune checkpoint inhibitors in the second-line and further-line settings.[10] Moreover, Baas and colleagues reported grade 3–4 treatment-related adverse events leading to treatment discontinuation in 45 (15%) patients treated with nivolumab plus ipilimumab versus 21 (7%) treated with chemotherapy. Clinicians and patients should therefore be aware of the possibility of hyperprogression and early treatment discontinuation with nivolumab and ipilimumab.

Third, patients enrolled in Checkmate 743 had a good (0–1) Eastern Cooperative Oncology Group

performance status. This feature is not applicable to every patient with MPM. More importantly, 157 (26%) patients were aged 75 years or older. This subset of patients clearly did not benefit from nivolumab plus ipilimumab compared with chemotherapy (HR for death 1·02 [95% CI 0·70–1·48]). Similar data with the same drug combination were reported in patients with metastatic non-small-cell lung cancer.[11] Overestimating the benefits from a new intervention can cause harm to subsets of patients who are given treatments that are not proven to be effective in their specific subgroup, with risk of adverse effects and personal costs.

Checkmate 743 represents a turning point in the treatment of unresectable MPM and supporting a new standard of care in this population. However, as in other thoracic cancers, the long-term benefit of immunotherapy in MPM appears to be limited to a small fraction of patients. Longer follow-up and translational studies, including assessment of circulating immune cells and cytokines,[12] will shed more light on predictors of treatment efficacy. Ongoing trials exploring the addition of chemotherapy and antiangiogenics to immune checkpoint inhibitors will assess a potential extension of survival benefit to a larger group of patients with MPM, particularly those with epithelioid histology, thus possibly leading to treatment stratification in different histological subtypes.

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1 Carbone M, Adusumilli PS, Alexander HR Jr, et al. Mesothelioma: scientific clues for prevention, diagnosis, and therapy. *CA Cancer J Clin* 2019; **69:** 402–29.
2 Kindler HL, Ismaila N, Armato SG 3rd, et al. Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2018; **36:** 1343–73.
3 Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet* 2016; **48:** 407–16.
4 Pasello G, Zago G, Lunardi F, et al. Malignant pleural mesothelioma immune microenvironment and checkpoint expression: correlation with clinical-pathological features and intratumor heterogeneity over time. *Ann Oncol* 2018; **29:** 1258–65.
5 Thapa B, Salcedo A, Lin X, et al. The immune microenvironment, genome-wide copy number aberrations, and survival in mesothelioma. *J Thorac Oncol* 2017; **12:** 850–59.
6 Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. *Lancet Oncol* 2019; **20:** 239–53.
7 Popat S, Curioni-Fontecedro A, Dafni U, et al. A multicentre randomised phase III trial comparing pembrolizumab versus single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. *Ann Oncol* 2020; **31:** 1734–45.
8 Ceresoli GL, Mantovani A. Immune checkpoint inhibitors in malignant pleural mesothelioma. *Lancet Oncol* 2017; **18:** 559–61.
9 Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural 1 mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet* 2021; published online Jan 21. https://doi.org/10.1016/S0140-6736(20)32714-8.
10 Zalcman G, Mazieres L, Greillier L, et al. Second or third line nivolumab versus nivolumab plus ipilimumab in malignant pleural mesothelioma patients: long-term results of the IFCT-1501 MAPS2 randomized phase 2 trial with a focus on hyperprogression. *Ann Oncol* 2019; **30** (suppl 5)**:** 747.
11 Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med* 2019; **381:** 2020–31.
12 Mankor JM, Disselhorst MJ, Poncin M, Baas P, Aerts JGJV, Vroman H. Efficacy of nivolumab and ipilimumab in patients with malignant pleural mesothelioma is related to a subtype of effector memory cytotoxic T cells: translational evidence from two clinical trials. *EBioMedicine* 2020; **62:** 103040.

High burden of postoperative cancer mortality in LMICs

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Low-income and middle-income countries (LMICs) have a large burden of cancer mortality compared with high-income countries, with as many as 70% of global cancer deaths in these regions and a paucity of data to drive cancer policies.[1,2] Several factors contribute to this burden, ranging from late presentation of disease to poor access to diagnosis and treatment.[2] Access to surgical interventions is reduced in LMICs, and the risk of complications of surgery is high in these regions.[3–5] When surgical interventions are available, knowledge about how to avoid complications can be scant.

In *The Lancet*, the GlobalSurg Collaborative and National Institute for Health Research Global Health Research Unit on Global Surgery report findings of a multicentre, international, prospective cohort study to better understand the factors attributable to poor surgical outcomes in LMICs.[6] 30-day mortality and 30-day complications associated with surgery for primary breast, colorectal, or gastric cancer were assessed. The investigators included 15 958 patients from 428 hospitals in 82 countries; more than 4000 patients were from 28 low-income and lower-middle-income