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

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Type de publication	Article de revue
Auteur	Scherpereel, Arnaud [1], Mazières, Julien [2], Greillier, Laurent [3], Lantuejoul, Sylvie [4], Do, Pascal [5], Bylicki, Olivier [6], Monnet, Isabelle [7], Corre, Romain [8], Audigier-Valette, Clarisse [9], Locatelli-Sanchez, Myriam [10], Molinier, Olivier [11], Guisier, Florian [12], Urban, Thierry [13], Ligeza-Poisson, Catherine [14], Planchard, David [15], Amour, Elodie [16], Morin, Franck [17], Moro-Sibilot, Denis [18], Zalcman, Gérard [19]
Organisme	French Cooperative Thoracic Intergroup [20]
Editeur	Elsevier
Type	Article scientifique dans une revue à comité de lecture
Année	2019
Langue	Anglais
Date	Février 2019
Numéro	2
Pagination	239-253
Volume	20
Titre de la revue	Lancet Oncology
ISSN	1474-5488

Résumé en anglais	BACKGROUND: There is no recommended therapy for malignant pleural mesothelioma that has progressed after first-line pemetrexed and platinum-based chemotherapy. Disease control has been less than 30% in all previous studies of second-line drugs. Preliminary results have suggested that anti-programmed cell death 1 (PD-1) monoclonal antibody could be efficacious in these patients. We thus aimed to prospectively assess the anti-PD-1 monoclonal antibody alone or in combination with anti-cytotoxic T-lymphocyte protein 4 (CTLA-4) antibody in patients with malignant pleural mesothelioma. METHODS: This multicentre randomised, non-comparative, open-label, phase 2 trial was done at 21 hospitals in France. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0-1, histologically proven malignant pleural mesothelioma progressing after first-line or second-line pemetrexed and platinum-based treatments, measurable disease by CT, and life expectancy greater than 12 weeks. Patients were randomly allocated (1:1) to receive intravenous nivolumab (3 mg/kg bodyweight) every 2 weeks, or intravenous nivolumab (3 mg/kg every 2 weeks) plus intravenous ipilimumab (1 mg/kg every 6 weeks), given until progression or unacceptable toxicity. Central randomisation was stratified by histology (epithelioid vs non-epithelioid), treatment line (second line vs third line), and chemosensitivity to previous treatment (progression ≥3 months vs <3 months after pemetrexed treatment) and used a minimisation method with a 0·8 random factor. The primary outcome was the proportion of patients who achieved 12-week disease control, assessed by masked independent central review; the primary endpoint would be met if disease control was achieved in at least 40% of patients. The primary endpoint was assessed in the first 108 eligible patients. Efficacy analyses were also done in the intention-to-treat population and safety analyses were done in all patients who received at least one dose of their assigned treatment. This trial is registered at ClinicalTrials.gov, number NCT02716272. FINDINGS: Between March 24 and August 25, 2016, 125 eligible patients were recruited and assigned to either nivolumab (n=63) or nivolumab plus ipilimumab (n=62). In the first 108 eligible patients, 12-week 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 nivolumab plus ipilimumab group. In the intention-to-treat population, 12-week disease control was achieved by 25 (40%; 28-52) of 63 patients in the nivolumab group and 32 (52%; 39-64) of 62 patients in the combination group. Nine (14%) of 63 patients in the nivolumab group and 16 (26%) of 61 patients in the combination group had grade 3-4 toxicities. The most frequent grade 3 adverse events were asthenia (one [2%] in the nivolumab group vs three [5%] in the combination group), asymptomatic increase in aspartate aminotransferase or alanine aminotransferase (none vs four [7%] of each), and asymptomatic lipase increase (two [3%] vs one [2%]). No patients had toxicities leading to death in the nivolumab group, whereas three (5%) of 62 in the combination group did (one fulminant hepatitis, one encephalitis, and one acute kidney failure). INTERPRETATION: Anti-PD-1 nivolumab monotherapy or nivolumab plus anti-CTLA-4 ipilimumab combination therapy both showed promising activity in relapsed patients with malignant pleural mesothelioma, without unexpected toxicity. These regimens require confirmation in larger clinical trials. FUNDING: French Cooperative Thoracic Intergroup.
URL de la notice	http://okina.univ-angers.fr/publications/ua18894 [21]
DOI	10.1016/S1470-2045(18)30765-4 [22]
Lien vers le document	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045 [23](18)30765-4/fulltext
Titre abrégé	Lancet Oncol.
Identifiant (ID) PubMed	30660609 [24]

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