



HAL
open science

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

Arnaud Scherpereel, Julien Mazières, Laurent Greillier, Sylvie Lantuéjoul, Pascal Do, Olivier Bylicki, Isabelle Monnet, Romain Corre, Clarisse Audigier-Valette, Myriam Locatelli-Sanchez, et al.

► **To cite this version:**

Arnaud Scherpereel, Julien Mazières, Laurent Greillier, Sylvie Lantuéjoul, Pascal Do, 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 Oncology*, 2019, 20 (2), pp.239-253. 10.1016/S1470-2045(18)30765-4 . hal-02570690

HAL Id: hal-02570690

<https://hal.science/hal-02570690v1>

Submitted on 22 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Second- or third-line nivolumab or nivolumab plus ipilimumab in malignant pleural mesothelioma patients: results of the IFCT-1501 MAPS2 randomised non-comparative Phase 2 trial

Arnaud Scherpereel, Julien Mazieres, Laurent Greillier, Sylvie Lantuejoul, Pascal Dô, Olivier Bylicki, Isabelle Monnet, Romain Corre, Clarisse Audigier-Valette, Myriam Locatelli-Sanchez, Olivier Molinier, Florian Guisier, Thierry Urban, Catherine Ligeza-poisson, David Planchard, Elodie Amour, Franck Morin, Denis Moro-Sibilot, Gérard Zalcman, on behalf of the French Cooperative Thoracic Intergroup (IFCT)

Department of Pulmonary and Thoracic Oncology, University of Lille, University Hospital (CHU) of Lille, Lille, France (Prof. A Scherpereel MD, PhD); French National Network of Clinical Expert Centers for Malignant Pleural Mesothelioma Management (MESOCLIN), Lille, France (Prof. A Scherpereel MD, PhD); Department of Pneumology, University Hospital of Toulouse, Université Paul Sabatier, Toulouse, France (Prof. J Mazieres MD, PhD); Multidisciplinary Oncology and Therapeutic Innovations Department, Aix Marseille University, Assistance Publique - Hôpitaux de Marseille, Marseille, France (Prof. L Greillier MD, PhD); Department of BioPathology, MESOPATH, CLCC Léon Bérard, Lyon, and University Grenoble Alpes, France (Prof. S Lantuejoul MD, PhD); Department of Pneumology, CLCC Baclesse, Caen, France (P Dô MD); Department of Pneumology, Hôpital d'instruction des Armées, Percy, Clamart, France (O Bylicki MD); Department of Pneumology, Centre Hospitalier Intercommunal de Créteil, Créteil, France (I Monnet MD); Department of Pneumology, University Hospital of Rennes, Rennes, France (R Corre MD); Department of Pneumology, Hôpital Sainte-Musse, Toulon, France (C Audigier-Valette MD); Department of Pneumology,

Centre Hospitalier Lyon-Sud Pierre-Bénite, Lyon, France (M Locatelli-Sanchez MD); Department of Pneumology, Le Mans Regional Hospital, Le Mans, France (O Molinier MD); Department of Pneumology, University Hospital of Rouen, Rouen, France (F Guisier MD); Department of Pneumology, University Hospital of CHU Angers, Angers, France (Prof. T Urban MD, PhD); Department of Medical Oncology, Clinique Mutualiste de l'Estuaire, Saint-Nazaire, France (C Ligeza-poisson MD); Department of Thoracic Oncology, Institut Gustave Roussy, Villejuif, France (D Planchard MD, PhD); Intergroupe Francophone de Cancérologie Thoracique IFCT, Paris, France (E Amour M.Sc.; Morin F M.Sc.); Department of Pneumology, University Hospital of Grenoble, Grenoble, France (Prof. D Moro-Sibilot MD, PhD); University Hospital Bichat Claude Bernard, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris-Diderot University Paris, France (Prof. G Zalcman MD, PhD)

Corresponding author: Arnaud Scherpereel, MD, PhD

CHU de Lille, Service de Pneumologie et d'Oncologie Thoracique, F-59037 Lille;
Tel.: +33 (0)3 20 44 49 98; Fax: +33 (0)3 20 44 52 47; arnaud.scherpereel@chru-lille.fr

Summary (341 words)

Background There is no recommended therapy for malignant pleural mesothelioma (MPM) progressing after 1st-line pemetrexed-platinum treatment. Disease control rate (DCR) was below 30% with all 2nd-line drugs tested. Preliminary results suggested anti-PD-1 monoclonal antibody (mAb) could be active in this setting. We thus aimed to prospectively assess anti-PD-1 mAb alone or in combination with anti-CTLA-4 in MPM.

Methods In this multicentre randomised non-comparative, open-label phase 2 trial, patients >18 years old with PS 0-1, histologically-proven MPM progressing after 1st-/2nd-line treatments involving pemetrexed/platinum, and measurable disease, were randomly allocated (1:1) to nivolumab (3 mg/kg bodyweight intravenously) every 2 weeks), or nivolumab plus ipilimumab (3 mg/kg every 2 weeks plus 1 mg/kg, every 6 weeks, intravenously), given until progression or unacceptable toxicity. Central randomization stratified by histology (epithelioid vs non-epithelioid), treatment line (second vs third line), and chemosensitivity to previous pemetrexed-platinum doublet, used a minimization method with a 0.8 random factor. The primary endpoint was 12-week DCR \geq 40%, assessed by blinded central review, on the first 108 required eligible patients. Last patient was accrued in August 2016; we report here the final analysis. ClinicalTrials.gov: NCT02716272.

Findings During a 5-months period, 125 patients were recruited. The 12-week DCR in the first 108 eligible patients and in the intention to treat (ITT) population were with nivolumab: 44.4% [95% CI: 31.2-57.7%] (n=24/54) and 39.7% [27.6-51.8%] (n=25/63), respectively; with nivolumab+ipilimumab: 50.0% [36.7-63.3%] (n=27/54), and 51.6% [39.2-64.1%] (n=32/62), respectively. Grade (G)3-4 toxicities were 14.3% (n=8) and 26.2% (n=16), with nivolumab or the combination respectively. The most frequent G3 adverse event was asthenia, with nivolumab (n=1, 1.6%) or with the combination (n=3, 4.9%), AST or ALT asymptomatic increase (n=4, 6.6%, all in the combination arm), lipase asymptomatic increase,

with nivolumab (n=2, 3.6%) or with the combination (n=1,1.6%), with one additional G4 lipase increase (1.6%) in both arms. There were 0 and 3/62 (4.8%) toxic deaths, in the nivolumab and the combination arm respectively.

Interpretation: Single-drug anti-PD-1 nivolumab or anti-PD-1 plus anti-CTLA-4 ipilimumab combination both showed efficacy in pre-treated MPM patients, without unexpected toxicity, deserving confirmation by larger clinical trials.

Funding: The French Cooperative Thoracic Intergroup (IFCT), France

Research in context

Evidence before this study

On November 15th 2015, we searched PubMed for studies evaluating immunotherapeutic antibody use, PD-1-blocking or CTLA4-blocking antibodies, in mesothelioma patients using the following search terms: “mesothelioma” and “nivolumab OR pembrolizumab OR atezolizumab OR avelumab OR durvalumab OR ipilimumab OR tremelimumab OR PD-1 OR PD-L1, OR CTLA-4”. Additionally, we examined abstracts from the 2015, 2016 and 2017 editions of the American Society of Clinical Oncology (ASCO) annual meeting. Though several studies confirmed that mesothelioma tumour cells do express immune checkpoint proteins, including PD-L1, and that mesothelioma specimens at times demonstrate high stromal infiltration by immune cells like lymphocytes or mono-macrophage and dendritic cells, we found no published clinical studies investigating the safety or efficacy of the anti-PD-1 nivolumab and anti-CTLA-4 ipilimumab combination or anti-PD-1 nivolumab monotherapy in human malignant pleural mesothelioma (MPM) patients. One large randomised Phase IIb trial evaluating tremelimumab, an anti-CTLA-4 antibody, tested this agent administered alone *versus* placebo as second- or third-line treatment in 564 MPM patients, yet no survival gain was demonstrated compared to placebo. Also, a Phase Ib trial was recently published reporting 20% overall response rate (ORR) (95% CI: 6.8-40.7) and 52% stable disease in 25 patients with PD-L1-expressing MPM (>1% positive tumour cells) treated with the anti-PD-1 antibody pembrolizumab, mostly as second-line treatment, along with a median duration of response (DOR) of 12 months (95% CI: 3.7-not reached), without any safety concerns. Lastly, a single-arm Phase II trial (“NIBIT-MESO-1”; NCT02588131) assessed the combination of 1mg/kg anti-CTLA-4 tremelimumab and 20mg/kg anti-PDL-1 durvalumab, intravenously injected every 4 weeks in four doses and followed by maintenance durvalumab, as first- or second-line treatment in unresectable malignant mesothelioma

patients. The authors reported evidence of clinical activity, demonstrated by 27.5% (out of 40 patients) exhibiting immune-related (ir) partial response (median DOR: 16.1 months) and another 65%-patient subset exhibiting ir disease control, resulting in a median ir PFS of 8 months and mOS of 16.6 months.

Added value of this study

On Nov. 15th 2015, no second- or third-line treatment had as yet demonstrated efficacy in MPM patients who had received first-line pemetrexed-platinum-based chemotherapy with or without the anti-angiogenic agent bevacizumab, namely the current reference first-line strategy in unresectable MPM patients. Furthermore, no PD-1/PD-L1-directed antibodies, non-PD-1-directed targeted immunotherapies or dual immunotherapies had been approved for MPM indications. There is thus a significant unmet need for new therapeutic strategies assessing immunotherapies in relapsed MPM patients. This study achieved its statistical endpoint and was, to our best knowledge, the first to assess the safety and efficacy of single-therapy anti-PD-1 nivolumab or anti-PD-1 nivolumab and anti-CTLA-4 ipilimumab combination therapy in MPM patients as second- or third-line following first-line pemetrexed-platinum-based chemotherapy. These findings provide supporting evidence that both single therapy with nivolumab and combination therapy with both nivolumab and ipilimumab are effective in treating relapsed MPM patients.

Implications of all the available evidence

These findings, involving 125 randomized patients, clearly show that immune-checkpoint inhibitors (ICIs) do achieve significant clinical activity in relapsed MPM, either as single or combination therapy, at standard doses. The data revealed ICIs are capable of inducing anti-tumour objective responses according to RECIST-meso criteria, as well as significant median progression-free and overall survival rates, with a tolerable safety profile, in this orphan-

disease population. While these results require further confirmation in larger-scale trials, they could at present justify ICI use in relapsed MPM patients who have no other efficient therapeutic options available.

Introduction

Malignant pleural mesothelioma (MPM) is a rare but aggressive malignancy of the pleural surface, commonly associated with occupational asbestos exposure, and its incidence is increasing worldwide.¹ MPM patients display usually a dismal prognosis, with a median overall survival (mOS) of approximately 12 months, even if some selected MPM patients could exhibit surprisingly long tumour doubling time indicative of a more indolent tumour, specifically in second or third-line setting. Moreover, they often exhibit strong resistance to chemotherapy, and only few patients are suitable candidates for multimodal treatment including “radical” surgery.² In 2015, our group initiated a Phase 3 randomised open-label IFCT 0701 MAPS (Mesothelioma Avastin Cisplatin Pemetrexed Study) trial that revealed an overall survival (OS) benefit when adding bevacizumab to standard cisplatin plus pemetrexed chemotherapy (18.8 vs. 16.1 months; hazard ratio [HR]=0.77; p=0.017).³ Nonetheless, an optimal second-line MPM treatment has not yet been defined by most recent guidelines.^{2,4-7}

Our understanding of MPM pathogenesis has significantly improved over recent years, leading to innovative drugs and strategies,^{8,9} with targeted therapies and immunotherapies sparking new hope for MPM patients.^{3,9-11} By instigating chronic inflammation and localized tumour immunosuppression, the immune system has proven paramount in MPM pathogenesis, with improved outcomes correlating with higher intra-tumour infiltration by cytotoxic T CD8+ cells¹². Conversely, high tumour expression of programmed cell death-ligand 1 (PD-L1), as it inhibits T-cell function *via* binding the programmed cell death-1 (PD-1), has been associated with poor prognosis in mesothelioma (mOS: 5.0 months in PD-L1-positive patients vs. 14.5 months in PD-L1-negative patients).^{9,13,14}

Among the different immunotherapies evaluated so far to restore anti-tumour immune response in MPM, immune checkpoint inhibitors (ICI) have garnered the most attention based

on their efficacy, particularly in melanoma and non-small cell lung cancer (NSCLC).^{9,10} Cytotoxic T lymphocyte-associated protein (CTLA-4) is a checkpoint inhibitor that blocks interactions between antigen-presenting cells, such as dendritic and naïve T cells, occurring early in the anti-tumour cycle. Following encouraging Phase II trial results, tremelimumab, an anti-CTLA-4 antibody, was tested alone vs. placebo in 2nd- or 3rd-line treatment in MPM in a large randomised Phase IIb trial ('DETERMINE'), yet no survival gain was obtained compared to placebo.¹⁵ In contrast, several studies assessing ICIs targeting the PD-1/PD-L1 pathway generated promising results.^{9,16} In a Phase Ib trial, 25 patients with PD-L1-expressing MPM ($\geq 1\%$ positive tumour cells) treated with the anti-PD-1 antibody pembrolizumab, mostly as second-line, exhibited a 20% overall response rate, with 52% achieving stable disease (SD). The median duration of response (DOR) was 12 months, with no safety concerns.¹⁶ Other trials assessing anti-PD-1/PD-L1 antibodies in MPM have demonstrated similar response rates.^{9,10} Another anti-PD-1 antibody, nivolumab (Nivo), is currently under evaluation as third line alone or versus placebo in the UK in a randomised Phase III ("CONFIRM") trial (*Cancer Research UK* trial number CRUK/16/022).

Checkpoint antibody combination trials represent another area of great interest. Combined 1mg/kg tremelimumab and 20mg/kg durvalumab given in four intravenous doses every 4 weeks, followed by maintenance durvalumab at the same dose and schedule for nine doses, was tested in a single-arm Phase II trial ("NIBIT-MESO-1"; NCT02588131) as first- or second-line treatment on unresectable malignant mesothelioma patients.¹⁷ This trial met its primary endpoint with 11/40 (27.5%) patients exhibiting immune-related (ir)-partial response (median DOS: 16.1 months) and 25/40 (65%) ir-disease control, leading to a median ir-progression free survival (PFS) of 8 months and an mOS of 16.6 months (95% CI: 13.1–20.1). Baseline tumour PD-L1 expression had no predictive or prognostic value.

Based on this rationale, we aimed to assess, in MPM patients, the value of anti-PD-1 mAb nivolumab (Nivo) as a single agent or in combination with anti-CTLA-4 mAb ipilimumab (Ipi) in a second- or third-line setting by means of a randomised non-comparative Phase II trial.

Methods

Study design and participants

This multicentre, randomised, controlled but non-comparative, open-label Phase II trial involving 21 French hospitals recruited patients aged >18 years old with MPM histologically-proven by pleural biopsy (thoracoscopy recommended), irrespective of PD-L1 tumour status, demonstrating progression according to modified RECIST-meso criteria¹⁸ (centrally assessed on computed tomography [CT] by three MPM-experienced radiologists) and having already received one or two systemic chemotherapy lines, at least one involving pemetrexed-platinum salt doublet line (triplet including bevacizumab also accepted), without mandatory washout period. Eligible patients had 0-1 ECOG performance status (PS), had not lost >10% body weight over the previous 3 months and were not candidates for curative surgery (according to an MPM-dedicated multidisciplinary board, including a thoracic surgeon), with at least one lesion (pleural tumour, solid thickening) measurable on CT and life expectancy >12 weeks. They also had to exhibit adequate haematological, hepatic and renal function (creatinine clearance ≥ 60 mL/min) within 7 days of enrolment and available tumour tissue (fresh or archived) for PD-L1 immunohistochemistry (IHC) evaluation.

Non-inclusion criteria comprised active or history of inflammatory bowel disease (*e.g.* haemorrhagic rectocolitis or Crohn's disease) central nervous system metastases, peritoneal or pericardial mesothelioma without any pleural involvement at the time of diagnosis, known primary immunodeficiency or immunosuppressive treatment within 28 days preceding

inclusion, corticosteroid treatment of >10mg/day prednisone or equivalent within 14 days preceding inclusion and known lung interstitial disease history. Other previous not permitted treatments were anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

The research protocol was approved by the Nord-Ouest III ethics committee (*Comité de Protection des Personnes*) of the University Hospital (CHU) of Caen, France, and the trial was carried out in line with the Helsinki Declaration and Good Clinical Practice guidelines. Prior to inclusion, all patients provided written informed consent to participate in the trial.

Randomisation and masking

We used an interactive web-response system to generate random, non-masked treatment allocation. We randomly assigned patients enrolled by investigators (1:1) to the two treatment groups. Randomisation was centrally performed by computer. We used a minimisation method (random factor of 0.8) and stratified patients by histology (epithelioid vs sarcomatoid or mixed-histological subtypes), treatment line (second vs third line), and chemosensitivity to pemetrexed-platinum doublet (progression ≥ 3 months after completing pemetrexed-platinum doublet or < 3 months).

Procedures

Patients received intravenous anti-PD-1 nivolumab (Nivo) at 3mg/kg of their body weight (60 min infusion) every 2 weeks, or 3mg/kg Nivo every 2 weeks given first (60 min infusion) followed by 1mg/kg anti-CTLA4 ipilimumab (Ipi) (90 min infusion) every 6 weeks. Patients received open-label treatment until progression or unacceptable toxicity, for a maximum of two years. No dose reduction or modifications was permitted for nivolumab or ipilimumab. Whenever \geq Grade 3 immune toxicity occurred, the immune treatment (Nivo in Arm A or

Nivo+Ipi in Arm B) was interrupted until recovery (<Grade 2). Any Nivo dose delay associated with treatment interruption of >6 weeks required treatment discontinuation. Treatment delay of Ipi interruption for >12 weeks also required treatment discontinuation, except for delays due to drug-related adverse events (DRAEs) needing slow steroid tapering off until <10mg daily steroid dose for full recovery from immunotherapy-related DRAE. Criteria for permanent treatment discontinuation included the following treatment-related adverse events: grade 3 non-skin events lasting 7 days or more, grade 3 laboratory abnormalities of thrombocytopenia or liver function test, and all grade 4 events, as well as laboratory abnormalities, except for asymptomatic amylase or lipase elevations.

Other potential treatment termination reasons included tumour progression, death, intercurrent illness, protocol violation, non-compliance, and patient consent withdrawn.

Following progression or unacceptable toxicity, further treatment lines could be initiated at the discretion of the investigators, although crossover and further Ipi or Ipi plus Nivo were not permitted in the Nivo arm.

Baseline laboratory tests required to assess eligibility included white blood cell counts, neutrophils, platelets, haemoglobin, serum creatinine, alanine aminotransferase, aspartate amino transferase, alkaline phosphatase, total bilirubin, albumin, lipase, and was performed at baseline and at every treatment infusion. TSH was measured at baseline and monitored prior every 12 weeks.

Adverse event monitoring was performed prior to each treatment infusion thus every two weeks until off protocol therapy and until three months post-discontinuation.

At baseline, disease assessment was performed using chest CT-scan including abdominal exploration and brain magnetic resonance imaging (MRI) or CT. Tumour node metastasis (TNM) classification was centrally assessed post-hoc by expert thoracic radiologists, blinded to the allocation arm, on thoracic CT-scans at diagnosis, and by reviewing the pathological

and surgical reports in cases involving initial diagnostic thoracoscopy, according to the 8th TNM classification for MPM.¹⁹ We performed CT scans every 12 weeks from randomisation, at the same time points in both arms, with response assessed at 12 weeks by modified Response Evaluation Criteria in Solid Tumours criteria for mesothelioma.¹⁸ CTs were centrally reviewed by three blinded independent MPM-experienced radiologists. Patients were contacted every 12 weeks in order to assess survival upon follow-up. Adverse events (AEs) and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

We assessed quality of life (QoL) using the Lung Cancer Symptom Score (LCSS)-Meso at baseline, treatment initiation and every 12 weeks. For each scale or item in LCSS-Meso, a linear transformation was applied to standardise the raw score to a 0-100 range (100=best possible function or QoL for functional scales and highest symptom burden for symptom scales and symptom items). A 10-point change in an item or domain was considered clinically meaningful³. QoL was defined as improved when a ≥ 10 -point increase was recorded for functioning scales and ≥ 10 -point reduction for symptom domains or items between baseline and 12-week assessments. We deemed QoL stable when variations of < 10 points were recorded for functioning scales and symptom domains and items, and as worsened with ≥ 10 -point decreases for functioning scales and ≥ 10 -point increases for symptom domains or items. To compute treatment exposure, we calculated the ratio of the dose intensity measured as a proportion of the theoretical dose intensity.

Formalin-fixed tumour samples were collected and PD-L1 expression was assessed by immunohistochemistry at a central laboratory (Lyon, Léon Bérard Cancer Center) by PD-L1 IHC, using both 28.8 Dako pharmDx™ and SP-263 monoclonal antibody clones, on a Dako AS Link48 platform, according to previously-described laboratory-developed tests for SP-263

clones using the Dako platform²⁰ with formalin-fixed tumour samples obtained by thoracoscopy or CT- guided core-needle biopsies by the National Reference Center (NRC) for MPM pathological diagnosis certification MESOPATH (F. Galateau-Sallé and S. Lantuejoul).²¹ The pathologist in charge of analysing the specimens was blinded to treatment and patient response. Expression was categorized according to tumour proportion scores (*i.e.*, percentage of tumour cells with membranous PD-L1 staining, regardless of intensity). An exploratory cut-off threshold of 25% tumour cells presenting membranous PD-L1 staining was chosen based on data resulting from a post-hoc analysis to ensure there were sufficient numbers of patients in each subset.

Outcomes

The primary outcome was the rate of patients with controlled disease (disease control rate, DCR), defined as the number of patients with complete response, partial response or stable disease at 12 weeks post-randomisation, assessed by the independent central review involving three radiologists blinded to treatment arm, using modified RECIST criteria for mesothelioma¹⁸, divided by the number of patients in each group.

Secondary outcomes were OS (defined as the time from randomisation to death from any cause), PFS (time from randomisation to documented disease progression or death, whichever occurred first), QoL as evaluated by Lung Cancer Symptom Scale (LCSS) questionnaires at each infusion, safety and correlation between PD-L1 tumour expression and ORR, DCR, PFS and OS.

Patients were considered as assessable for response or survival provided they had the 12-weeks tumour evaluation (for response) or if they progressed before the 12 weeks evaluation (either clinically or by CT-scan evaluation), and provided they were eligible.

Statistical analysis

The primary study endpoint included the first 108 eligible patients, while the intention-to-treat (ITT) population included all randomised patients for efficacy analyses; the 'safety population' for safety analyses included all patients who received at least one cycle of study treatment.

We assumed a $\leq 20\%$ DCR at 12 weeks (null hypothesis), thus of no therapeutic interest (*i.e.*, DCR below which the treatment would be deemed inactive), validated by a blinded independent central review by one of three radiologists, and a target $\geq 40\%$ DCR (alternative hypothesis), thus indicating clinical activity, along with a one-sided α error of 0.05. We thus calculated that a total of 54 eligible patients in each arm (108 in total) would enable us to detect an effect on the primary outcome with 95% power. Assuming 5% were ineligible, we had to recruit 57 patients to each arm. Based on these assumptions, ≥ 17 failure-free patients had to be independently observed at 12 weeks in either arm, using a one-step Fleming procedure, to enable us to conclude on the activity of the corresponding regimen. No interim analysis was planned.

For patients exhibiting no events, the cut-off point was last contact. We plotted PFS and OS by means of Kaplan-Meier curves, with follow-up censored on December 28th, 2017. In subgroup analyses, HRs and 95% CIs were estimated using a Cox model adjusted for stratification factors. For statistical analyses, SAS software Version 9.4 was employed, with all p values and CIs two-sided. We tested the prognostic effect of PD-L1 tumour expression (28.8 PharmDX or SP263 Assays) using a non-adjusted Cox model. This IFCT-1501 trial was registered beforehand with the European Union Clinical Trials Register (number 2015-004475-75) and ClinicalTrials.gov (number NCT 02716272). The whole protocol study is available in the supplementary web appendix (pp 1-75).

Role of the funding source

Nivolumab, Ipilimumab and an unrestricted research grant were provided by Bristol-Myers-Squibb (BMS) (France). The *Intergroupe Francophone de Cancérologie Thoracique* (IFCT) designed the whole trial, collected and interpreted the data. IFCT investigators and staff participated in study design and data analysis. BMS had no role in designing the research, analyzing the data or writing the report. The corresponding author (AS) and co-principal investigator (GZ) had full access to all study raw data and took final responsibility in the decision to publish the trial data.

Results

Between March 24, 2016, and August 25, 2016, we randomly assigned 125 patients to Nivo (63 [50.4%]) or Nivo+Ipi (62 [49.6%]), with 63 (100%) receiving Nivo and 61 (>98%) receiving Nivo+Ipi. Since accrual ran faster than anticipated, 11 patients providing consent on the last day of accrual were enrolled in addition to the 114 initially planned (Figure 1).

Five patients were deemed ineligible in the nivolumab arm, since one had no evidence of progression at inclusion, three had received more than three treatment lines at inclusion, and one had only a cytological evidence to sustain the MPM diagnosis. Two additional patients were deemed ineligible in the combination arm, one having no evidence of progression at inclusion, another one having received more than three previous treatment arms. In total, 63 patients were randomized in the nivolumab arm and all received at least one infusion of treatment, 62 were randomized in the combination arm, with only 61 treated since one patient died before receiving any treatment.

Median age was 72.3 [32.5-87.2] in the Nivo arm and 71.2 [48.1-88.1] in Nivo+Ipi. The Nivo arm comprised 25% (n=16) women and Nivo+Ipi 15% (n=9); 89% of Nivo (n=56) and 82% of Nivo+Ipi (n=51) patients exhibited Stage III-IV disease, while 31% of Nivo (n=19) and 40% of Nivo+Ipi (n=25) patients had ECOG PS 0.

MPM histology was epithelioid in 52 (83%) and biphasic or sarcomatoid in 11 (17%) of the Nivo patients; vs. 53 and nine (85% and 15%) in the Nivo+Ipi patients, respectively, as assessed by central review of the NRC MESOPATH (Table 1). Most patients experienced progression beyond a period of 3 months after receiving first-line pemetrexed-platinum-based chemotherapy (59% Nivo, n=37; 66% Nivo+Ipi, n=41); the majority of patients had received only one therapy line prior to inclusion (70% and 68%, respectively). Blood counts were balanced (leukocytes, red cells, estimated by haemoglobin concentration, and platelets) between both arms (Table 1).

At the cut-off date, all but one patient had received at least one dose of Nivo or Nivo+Ipi, and one Nivo+Ipi patient died before receiving the allocated treatment (Figure 1). Drug delivery was relatively good: approximately 70% received the first six infusions (Nivo or Nivo+Ipi) as initially planned, at 100% of the planned drug dose; 49.2% Nivo patients (n=31) and 38.7% Nivo+Ipi (n=24) received 10 planned infusions (both drugs injected by infusion on Days 1, 4, 7 and 10 in the Nivo+Ipi arm).

After a median follow-up of 20.1 months (IQR: 18.4–20.8), 59 patients had discontinued treatment in the Nivo arm, 50 of whom (84.7%) exhibited disease progression, three (5.1%) toxicity (detailed in Figure 1), with one patient having died without toxicity or progression, another exhibiting a second unrelated cancer, one patient presenting an intercurrent disease, one patient having decided to stop treatment by his own choice, two patients for both toxicity and progression, only four remaining patients continuing treatment (Figure 1). In the Nivo+Ipi arm, 58 patients withdrew from the study, 38 of whom (65.5%) had disease progression and 13 (22.4%) toxicity (detailed in Figure 1), five patients having died without toxicity or progression, one patient having an intercurrent disease and one patient by decision of the investigator, with only three patients still on treatment at the data cut-off point (Figure 1).

To conform to CONSORT guidelines, we report the primary efficacy analysis as estimated by

DCR at 12 weeks post-randomisation in the first 108 eligible patients (54 patients in each arm), the population anticipated by the statistical analysis plan. This primary endpoint which was met in both arms, with a 44.4% [31.2-57.7%] 12-week DCR (n=24/54) in the Nivo group and 50% [36.7-63.3%] 12-week DCR (n=27/54) in Nivo+Ipi, as centrally assessed by an independent blinded radiological expert panel. Objective response rates were 18.5% [8.2-28.9%] (n=10/54) and 27.8% [15.8-39.7%] (n=15/54) in Nivo and Nivo+Ipi, respectively. In the ITT population, comprising 125 patients, the 12-week DCR was 39.7% [27.6-51.8%] (n=25/63) and 51.6% [39.2-64.1%] (n=32/62) in Nivo and Nivo+Ipi, respectively (supplementary Table 1, webappendix p.3). Figure 2 presents waterfall plots of percentage changes in tumour size between baseline and 12 weeks in Nivo vs. Nivo+Ipi groups for the 114 patients evaluable at 12 weeks, revealing major tumour response irrespective of histological subtype. In contrast, as early as the 12th week of treatment at the first tumour response evaluation, 6 out of 59 (10.1%) and 2 out of 55 (3.6%) patients treated with nivolumab or nivolumab+ipilimumab, respectively, exhibited over 80% increase in size of their target lesions suggesting hyper-progression, with no obvious correlation with the histological subtype found. Treatment duration, time to response and treatment response duration are presented on the swimmer plots in Figure 3 for patients with objective response. Median DORs were 7.4 months (4.1-11.9) and 8.3 months (3.0-14.0) in Nivo and Nivo+Ipi, respectively, with four (one still on Nivo) and seven (two still on the combination) patients still responding at 15 months in Nivo and Nivo+Ipi, respectively.

After a median follow-up of 20.1 months (95% CI: 19.6-20.3), median PFS were 4.0 months (95% CI: 2.8-5.7) and 5.6 months (95% CI: 3.1-8.3) in Nivo and Nivo+Ipi, respectively with 58/63 and 53/62 events (i.e. progression or death) recorded at study cut-off (Figure 4A). One-year PFS were 15.9% (95% CI: 6.8%-24.9%) and 22.6% (95% CI: 12.2%-33%) in Nivo and Nivo+Ipi, respectively.

mOS was 11.9 months (95% CI: 6.7-17.7) and 15.9 months (95% CI: 10.7-NR) in Nivo and Nivo+Ipi, respectively, with 41/63 and 32/62 events (ie deaths) (Figure 4B). One-year survival rates were 49.2% (95% CI: 36.9%-61.6%) and 58.1% (95% CI: 45.8%-70.3%) in Nivo and Nivo+Ipi, respectively. No significant differences in the post-discontinuation treatments received by patients were detected between the arms (supplementary Table 2, webappendix p.4).

All-grade DRAEs were observed in 88.9% (n=56/63) and 93.4% (n=57/61) of Nivo and Nivo+Ipi patients, respectively. Grade 3-4 DRAEs were less frequent in Nivo than in Nivo+Ipi patients (14.3% vs. 26.2% incidence). Grade 3-4 DRAEs were 14.2% (n=9/63) and 31.1% (n=19/61) in the nivolumab and the nivolumab plus ipilimumab arms respectively (Table 3). There were 3/63 (4.8%) and 17/61 (27.8%) all-grade serious drug-related AEs in the nivolumab and the combination arms respectively (Table 3). Three DRAEs of 63 patients (4.8%) and 13/61 (21.3%) led to treatment discontinuation in the nivolumab and the combination arms respectively (Table 3). There were three treatment-related deaths reported by investigators in the combination arm (Table 3): one fulminant hepatitis, one encephalitis (normal cerebrospinal fluid cellular and biochemical composition, normal brain MRI and no blood cerebrospinal fluid neuronal self-antibodies found) and one acute kidney failure in a patient with (end of life) disease progression exhibiting recurrent pleural and peritoneal effusions needing daily punctures. These three lethal events (4.9%) occurred within the first 4 study months, with no other toxic deaths reported later on in the trial. No treatment-related death was reported in the nivolumab arm. The incidence of Grade 4 adverse events proved low in both arms (1.6%, n=1, for Nivo; 3.3%, n=2, for Nivo+Ipi).

Table 2 presents all drug-related non-haematological AEs of any grade, in 124 patients evaluable for safety, for all treatment injections, involving 10% of patients, with very low Grade 4 (0 and 1/61, 1.6% for Nivo and Nivo+Ipi, respectively) or Grade 3 incidences (2/63,

3.2% and 5/61, 8.2% for Nivo and Nivo+Ipi, respectively). All-grade diarrhoea events occurred frequently in Nivo+Ipi and Nivo patients (9/63, 14.3% and 18/61, 29.5 % for Nivo and Nivo+Ipi, respectively). All-grade pruritus were frequent in both arms (6/63, 9.5% and 15/61, 24.6% for Nivo and Nivo+Ipi, respectively). No differences in drug-related haematological AE rates were noted (0% Grade 3-4 in both arms). Immune-related AEs (irAEs), listed in Table 3, ranged from 0 to 4/63, 6.34% and 0 to 7/61, 11.4% in Nivo and Nivo+Ipi, respectively, for any-grade toxicities. No Grade 4 irAEs were reported, except for 1.6% of cases exhibiting increased lipase levels in both arms. Most all-grade immune-related toxicities were biological, causing neither relevant clinical consequences nor treatment interruption. There also were all-grade asymptomatic elevations of aminotransferase ALT levels in both arms (n=1/63, 1.6% in Nivo vs. n= 8/61, 13.1% in Nivo+Ipi). The incidence of Grade 3, 4, 5 and all-grade AEs is summarized in the dataset of Supplementary Table 3 (webappendix p.5).

Patient-reported outcomes (PROs) were collected using the LCSS questionnaire, expressed as a percentage of patients who reported deteriorating quality of life between the 12-week and baseline questionnaires. A graphical representation of the rate of decline for 10 items is depicted in the supplemental Figure 1 (webappendix p.2). There were no major differences detected between arms in the numbers of patients reporting score decline at 12 weeks in each item, taking into account the exploratory nature of such unpowered analyses precluding any formal statistical test. Longitudinal QoL studies, using time until definitive deterioration (TUDD), and thus long-term QoL data, will be presented in a separate paper.

An exploratory analysis of PD-L1 tumour expression, using both 28.8 and SP-263 anti-PD-L1 assays, was performed, with centralized immunohistochemistry and pathological review, on samples containing a minimum of 100 viable tumour cells. Such exploratory study was possible in only 104 patients for SP263 and 99 for 28.8 antibodies, since there were no longer

any tissue remaining for the other patients. 28.8 Dako pharmDx™ (supplementary Table 4, webappendix p.6) PD-L1 expression in $\geq 1\%$ of cells was found to be significantly associated with objective response to immunotherapy (39.0% vs. 12.1% ORR, $p=0.002$), yet not with 12-week DCR. Typically, the same two cut-offs are used in the literature to define patients with high PD-L1 tumour expression: 25% or more tumour cells expressing PD-L1 regardless of the intensity^{20,21} or 50% or more²². A post-hoc analysis was performed with the 25% cut-off since there were not enough patients with 50% cells or more expressing PD-L1 in this series (zero and three in the nivolumab and combination groups respectively). When comparing patients with the highest PD-L1 tumour expression ($\geq 25\%$, $n=7$ with 28.8 assay, $n=16$ with SP-263 assay) to others ($n=92$ and $n=88$, respectively), both ORR and DCR were demonstrated to be significantly greater in the high-expression subgroups. ORRs were 71.4% ($n=5$) and 62.5% ($n=10$) vs. 19.6% ($n=18$) and 14.8% ($n=13$) ($p=0.007$ or <0.001) with 28.8 and SP-263 assays, respectively, and DCRs were 85.7% and 75.0% vs. 43.5% and 38.6% ($p=0.047$ or 0.003) with 28.8 and SP-263 assays, respectively. Thus, while the concordance kappa index was low ($\kappa = 0.56$), reflecting differences in sensitivity for low PD-L1 expressing tumours, analyses of response rates or DCR were similar whether using the 28.8 or Dako™ PD-L1 (SP263) assay. This observation further supports how consistently valuable PD-L1 expression is in predicting response to ICI and survival.

Lastly, we conducted exploratory subgroup post-hoc analyses for known prognostic factors in MPM, using an adjusted Cox model for the stratification variables, represented as a forest plot, in both arms, separately (Figure 5).

Discussion

Our findings show that nivolumab monotherapy and nivolumab plus ipilimumab provide clinically meaningful activity for patients with pre-treated MPM who progressed after one or

two lines of treatment including pemetrexed-platinum doublet, despite an excess of adverse events and three toxic deaths in the combination arm. Indeed, following the publication of a few small-sized trials suggesting that anti-PD-1/anti-PD-L1 antibodies exert activity in relapsed or refractory MPM, the MAPS-2 academic phase 2 randomised trial reached its disease control rate primary endpoint in both groups of patients treated also leading to remarkable overall survivals reaching or exceeding one year.

The nivolumab plus ipilimumab combination has likewise been evaluated in several different doses and schedules as first-line therapy in advanced NSCLC patients, such as in Checkmate CA209012 Phase I trial²². Early cohorts evaluated two different dosing schedules, of which nivolumab 3mg/kg plus ipilimumab 1 mg/kg, every 3 weeks resulted in significant toxicity, with 37% of patient discontinuing treatment due to treatment-related adverse events. Thus, four other combination cohorts were studied, including nivolumab 3 mg/kg every 2 weeks + ipilimumab 1mg/kg every 6 weeks, which was selected for the recently published NSCLC phase 3 first-line trial CheckMate 227²³ and then was selected for our MPM trial.

The stratified, randomised nature of this trial ensured that both groups were well balanced. Another strength of this study was its very fast accrual for such a disease that, given its rare incidence, could have been limited to an overly restrictive selection of patients. However, we acknowledge that our patients population could still be selected, good-prognosis group of patients, taking into account the favourable PS selection (PS 0-1), usual for a clinical trial but not necessarily representative of a wider population of 2nd or 3rd-line MPM patients.

We made a pragmatic choice to select the 12-weeks disease control rate (DCR) as the primary endpoint rather than overall response rate since patients displaying long-term control without any formal objective response criteria could also drive an essential part of the survival effect. This methodological choice should be considered in the time context in which the trial was designed, namely in mid-2015. At that time, we only had scarce data on the efficacy of

immunotherapy in MPM or the ICI tolerance of MPM patients, who are slightly older than patients with NSCLC or melanoma patients, typical cancer types evaluated in the vast majority trials assessing ICI. We also had no idea about the best regimen to choose, either single anti-PD-1 mAb or dual immunotherapy combination, and thus were undecided about the optimal statistical comparative hypothesis to propose with survival (PFS or OS) as primary endpoint, supposing a preconceived idea about the best ICI regimen. Such considerations led us to choose a classical non-comparative design for a randomised phase 2 trial, not powered for face to face comparisons, but instead allowing to study simultaneously two ICI regimens. The Phase 2 nature of this trial was a conservative choice aimed solely to detect early efficacy (and tolerance) signals of two different immunotherapy regimens at the same time, with no preconceptions, and to select at least one of these regimens for a future comparative Phase 3 trial.

An impressive response was achieved with nivolumab and nivolumab+ipilimumab in second- or third-line MPM treatment. Additionally, ORR as assessed by central review were clinically meaningful, and mOS were also noteworthy in that setting (up to the significant values of 11.9 and 15.9 months, respectively), compared to what was previously reported with standard chemotherapies or investigational targeted therapies. Thus, the MAPS-2 study was able, by its randomised design to assess that both regimens demonstrated activity signs yet distinct safety profiles, providing clear data for selecting adequate experimental arms in future prospective comparative trials. Of note is that the MAPS-2 results do already support a recent NCCN panel decision (NCCN guidelines Malignant Pleural Mesothelioma, Version 2.2018-February 26, 2018) to recommend nivolumab or nivolumab+ipilimumab as options for second/third-line therapy in MPM.⁷ Interestingly, another small and non-randomised trial (“INITIATE”; n=34) by P. Baas *et al.* was recently presented at the 2018 International Mesothelioma Interest Group (iMig) meeting, similarly assessing the value of nivolumab (240mg every 2 weeks in

contrast to 3mg/kg every 2 weeks in MAPS-2) plus ipilimumab (1mg/kg every 6 weeks) as second-/third-line treatment in MPM (85% of patients) or peritoneal mesothelioma²⁴. Their tolerance and efficacy results were likewise similar to those of the MAPS-2 trial. However, these exciting data now require confirmation with a comparative randomised Phase 3 trial that could determine whether the nivolumab+ipilimumab combination is superior or not to nivolumab alone or another single chemotherapy drug, such as vinorelbine or gemcitabine, which are commonly used in this setting, despite the lack of any data from prospective randomised trials. In fact, larger randomised trials are also needed in order to assess the reproducibility of the survival results, as well as evaluating their external validity, to confirm that the MAPS-2 patients are wholly representative of standard pre-treated MPM patients. This would also be valuable in excluding the possibility that our patients who exhibited good general status after one or two treatment lines might exhibit more indolent tumour biology than the majority of the MPM population.

Some large Phase 3 randomized trials are, in fact, already ongoing in mesothelioma patients testing ICIs alone or in combination with chemotherapy or targeted therapies, as frontline or second/third-line treatment.⁹ Taking into account for the increased toxicity observed in the combination arm, with 22.4% of withdrawals due to toxicity, three toxic deaths, we recognize that this regimen could be debatable in such 2nd and 3rd-line setting, although the 15.9 months long-term survival is also appealing. Only a Phase 3 trial would be able to provide definitive conclusions on that issue. At least, a large randomised Phase 3 trial (“CheckMate BMS CA209-743”; NCT 02899299; n=600) is currently assessing the benefit of nivolumab+ipilimumab vs. standard frontline chemotherapy in MPM patients, with PFS and OS as co-primary endpoints. Another ongoing Phase 3 trial is evaluating pembrolizumab+cisplatin-pemetrexed vs. cisplatin-pemetrexed in the same setting (Canadian Cancer Trials Group; NCT 02784171). Finally, two single-arm Phase 2 trials are assessing

durvalumab+cisplatin-pemetrexed in the USA (NCT 02899195; n=55) and Australia (“DREAM” trial; n=54). The response results for the first 31 patients of this last trial were presented at the 2018 ASCO meeting, reporting an excellent dose-intensity of both chemotherapy (95%) and durvalumab (94%), a median PFS of 7.3 months, 95% CI [5.8-11], leading to a 65% 6-month PFS and a remarkable 84% DCR²⁵.

While MPM patients have been shown to display low tumour mutational burden (TMB)⁸, a potential predictive biomarker for ICI in other tumour types, the pathogenesis of MPM seems to be mostly driven by inflammation. Accordingly, the MAPS-2 results suggest that nivolumab or nivolumab+ipilimumab efficacy may be strongest in PD-L1+ MPM patients, and particularly in high PD-L1 expressers ($\geq 25\%$ positive tumour cells: PD-L1^{hi $\geq 25\%$}). These subjects exhibit a 71.4% ORR and 62.5% ORR, respectively (28.8 assay is less sensitive than SP263 assay, respectively). However, there is a weakness with this finding related to the *post-hoc* choice of a 25% cut-off point (data driven), given that, as previously reported in the literature^{14,26}, we found relatively low numbers of tumours with very high PD-L1 expression (*i.e.*, over 50% of positive tumour cells) in our patients, compared to NSCLC patients as previously reported^{13,14,28}. Another weakness comes from the fact this biomarker study was only possible in roughly 80% of patients with enough tumour tissue remaining. The 25% cut-off point was therefore a pragmatic choice taken from among all the different thresholds used in the literature so as to ensure a sufficient patient number in each subset to allow for statistical comparison. Similarly, as the non-comparative nature of our trial did not enable analysis of PD-L1 prognostic value arm by arm, we simply observed that the two groups of patients were well balanced in terms of PD-L1 high expression between (Table 1).

In an Australian cohort, PD-L1^{high>50%} subjects exhibited 50% ORR vs. 22% in PDL1^{low <5%} patients²⁷, with a similar trend observed in a US cohort.²⁸ A subgroup of mesothelioma patients thus seemingly benefit from ICIs, as already described in melanoma and NSCLC.

Nevertheless, it is still unclear how to accurately select the patients best suited for such immunotherapy.²⁸ The complex interplay of tumour-infiltrating lymphocytes and immune checkpoints probably impacts on response to ICIs in MPM. More in-depth studies of immunohistochemistry markers and tumour infiltration by immune cells in MAPS-2 patients are thus ongoing. Therefore, it is of paramount importance that patient clinical characteristics (histologic subtype, previous chemosensitivity, PS) and biomarkers (such as tumour PD-L1 IHC status, CD8 or myelomonocytic infiltration extent, TMB, genomic signatures,⁸ expression of multiple checkpoint inhibitors, specific mutations, *etc.*²⁹⁻³⁴) be prospectively investigated in all future immunotherapy trials for MPM patients.²¹

We reported relatively high rates of drug-related adverse events with close to 90% rates of all-grade AEs in both arms and more Grade 3 AEs in the combination arm *vs.* the nivolumab arm (approximately 23% *vs.* 13%, respectively). However, It should be noted that all the three treatment-related deaths (all in the combination arm) occurred in the first months of the trial, with no other toxic deaths subsequently occurring over 14 months. This observation may suggest that our investigators experienced a learning curve in identifying immune-related adverse events and optimising treatment for these patients, as well as simultaneously optimising care for the NSCLC patients they started to treat routinely with anti-PD-1 at that time. It should also be underlined that the safety profiles of nivolumab alone or combined with ipilimumab compared favourably with what has already been posited in the literature for platinum-based chemotherapy, and that AEs observed in our trial were similar in type to those reported for immunotherapy drugs used in other settings and in numerous previous trials.

This AE incidence could certainly raise questions regarding the chosen dosing schedule in the combination arm. As mentioned above, we chose what was considered to be the most tolerable of six schemes previously tested in the Checkmate 012 Phase 1 trial²², ~~and~~ this

scheme being subsequently selected for the NSCLC Phase 3 Checkmate 227 trial²³ and the ongoing first-line Phase 3 Checkmate 743 trial in MPM patients (NCT02899299). It is also paramount to note that most AEs were classed as Grade 1-2, including a substantial number that were purely biological or asymptomatic, rapidly resolving either spontaneously or once treatment was interrupted. Moreover, our preliminary QOL analysis failed to detect any obvious consequences on patient-reported outcome items at Week 12. Taking into account potential immunotherapy-induced harm, it was crucial to early report some QOL data, even if these data were unpowered and incomplete. We are aware that the scientific considerations regarding estimating a minimally clinically important difference (MCID) are challenging and that our choice of a 10-point change in the scores as a cut-off point has not been prospectively validated for MPM patients in the literature. To resolve this, additional studies of health-related quality of life data from the MAPS-2 trial are underway, modeling longitudinal QOL based on the time until definitive deterioration (TUDD), the results of which will be reported in a separate paper dedicated to this outcome. Additionally, it should be underlined that the study's open-label design could have influenced the QoL analysis.

We provide exploratory subset analysis, although carefully avoiding to directly compare the two groups of patients, according to methodological rules for a randomized Phase 2 trial, which was not powered for such comparisons. Dual PD-1/CTLA-4 inhibition in "more indolent" tumours (*i.e.*, patients relapsing more than 3 months after pemetrexed-based chemotherapy was stopped) provided a 0.35 [0.19-0.67] adjusted HR for death *vs.* those with more "aggressive" cancers. However, such exploratory analyses should be considered as purely hypothesis-generating and must thus not be over-interpreted, taking into account the wide-ranging 95% confidence intervals observed, reflecting the low patient numbers in each subset, and considering, although these analyses were adjusted for stratification factors, that some biases could have been induced by the prognosis influence of other variables. Hence,

the optimal strategy in view of a better efficacy/safety (and cost) ratio remains to be defined for all patients. Of note, we suspected in our trial that a few patients would exhibit hyper-progression under ICIs, as previously described in some NSCLC cases.³⁵ Additional studies for these patients are on-going, in particular to assess whether their tumour growth rate, defined as a >50% increase in tumour volume over time, could actually correspond to the still-debated criteria for hyper-progressive disease, thus requiring to analyze two CT scans performed before the ICI treatment was initiated.

In conclusion, as previously observed in melanoma and NSCLC patients, immunotherapy appears to offer real hope for patients with MPM, a cancer which, until now, had very few therapeutic options. Thus, ICIs are likely to change our standard of care in MPM, as already emphasized for nivolumab alone or combined with ipilimumab in the NCCN guidelines⁷. Yet many questions remain unanswered, and more data is required from randomised Phase 2 or 3 trials to select the best candidates suited for ICIs (pretreated *vs.* frontline patients, biomarkers, tolerance, *etc.*) and to define the long-term survival benefit, as well as the optimal treatment regimen (anti-PD-1 monotherapy *vs.* combination with ICIs, chemotherapy or targeted therapy, or even surgery or radiotherapy). It is essential that MPM expert centres from all over the world collaborate to speed-up the recruitment of patients with this rare cancer into large, randomised trials and translational studies, to bring new hope and real progress in the future of mesothelioma patient care.

Contributors

AS and GZ were the principal investigators of the trial and were involved in conception and study design. All investigators, including FM and EA, were involved in the data collection. SL contributed to pathological review and diagnostic certification, immunohistochemistry analysis. All authors contributed to the data analysis, data interpretation, the writing and the approval of the final manuscript.

Declaration of interests

AS reports personal fees and non-financial support from BMS, personal fees and non-financial support from Roche, personal fees and non-financial support from MSD, personal fees from Boehringer-Ingelheim, outside the submitted work;

LG reports grants, personal fees and non-financial support from ROCHE, personal fees and non-financial support from LILLY, grants, personal fees and non-financial support from NOVARTIS, personal fees and non-financial support from PFIZER, personal fees and non-financial support from BRISTOL-MYERS SQUIBB, personal fees and non-financial support from BOEHRINGER INGELHEIM, personal fees and non-financial support from ASTRA ZENECA, personal fees and non-financial support from ABBVIE, personal fees and non-financial support from MSD, outside the submitted work;

OB reports personal fees and non-financial support from MSD, non-financial support from Roche, outside the submitted work;

IM reports other from BMS (medical congress), during the conduct of the study;

RC reports participation to board with Roche and BMS.

CAV reports personal fees from Roche, personal fees from Pfizer, personal fees from Boehringer Ingelheim, personal fees from Novartis, personal fees from AstraZeneca, personal fees from Lilly, personal fees from Amgen, personal fees from Bristol-Myers Squibb, personal fees from Sysmex, personal fees from MSD, personal fees from Clovis Oncology, from Abbvie, outside the submitted work;

OM reports personal fees from Bristol-Myers Squibb, outside the submitted work;

FG reports personal fees and non-financial support from 3MS, personal fees from MSD/MERCK US, personal fees from AstraZeneca, personal fees from Roche, grants and personal fees from Boehringer Ingelheim, non-financial support from Chugai, outside the submitted work;

DP reports personal fees from Astrazeneca, personal fees from Boehringer, personal fees from BMS, personal fees from Celgene, personal fees from Novartis, personal fees from MSD, personal fees from Pfizer, personal fees from Roche, outside the submitted work;

DMS reports personal fees and non-financial support from BMS, during the conduct of the study; personal fees from Roche, personal fees from MSD, personal fees from Lilly, personal fees from Novartis, personal fees from Pfizer, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Takeda, personal fees from Leurquin Mediolanum, outside the submitted work;

GZ reports grants, personal fees and non-financial support from BMS, during the conduct of the study; non-financial support from Roche, personal fees and non-financial support from AstraZeneca, non-financial support from MSD, non-financial support from Pfizer, personal fees from DA Voltera, outside the submitted work;

JM, SL, PD, EA, FM, CLP, TU and MLS have nothing to disclose

Data sharing statement

The Data Sharing statement is available in the webappendix (p. 8)

Acknowledgments

Bristol-Myers-Squibb (BMS) (France) supplied nivolumab/ipilimumab and a research grant to *Intergroupe Francophone de Cancérologie Thoracique* (IFCT) for the MAPS-2 biomarkers studies. We thank the participating patients and their families as well as the study teams involved in the trial, the clinical research assistants, study coordinators and IFCT operations staff, as well as Dr. G. Cremer at Cremer Consulting (Strasbourg, France) for medical writing support. We thank also the French National Cancer Institute (INCa) and the French League against Cancer.

References

- 1 Robinson BW, Musk AW, Lake RA. Malignant mesothelioma. *Lancet* 2005; **366**: 397–408.
- 2 Scherpereel A, Astoul P, Baas P, et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *Eur Respir J* 2010; **35**: 479–95.
- 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 Baas P, Fennell D, Kerr KM, Van Schil PE, Haas RL, Peters S; ESMO Guidelines Committee. *Ann Oncol* 2015; **26**: v31–9.
- 5 Woolhouse I, Bishop L, Darlison L, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. *Thorax* 2018; **73**: i1–i30.
- 6 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.
- 7 NCCN Malignant Pleural Mesothelioma guidelines Version 2.2018 — February 26, 2018 https://www.nccn.org/professionals/physician_gls/pdf/mpm_blocks.pdf
Accessed: Sept 09, 2018.
- 8 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.

- 9 Scherpereel A, Wallyn F, Albelda SM, Munck C. Novel therapies for malignant pleural mesothelioma. *Lancet Oncol* 2018; **19**: e161–e72.
- 10 Yap TA, Aerts JG, Popat S, Fennell DA. Novel insights into mesothelioma biology and implications for therapy. *Nat Rev Cancer* 2017; **17**: 475–88.
- 11 Grosso F, Steele N, Novello S, et al. Nintedanib Plus Pemetrexed/Cisplatin in Patients With Malignant Pleural Mesothelioma: Phase II Results From the Randomised, Placebo-Controlled LUME-Meso Trial. *J Clin Oncol* 2017; **35**: 3591–600.
12. Yamada N, Oizumi S, Kikuchi E, et al. CD8+ tumor-infiltrating lymphocytes predict favorable prognosis in malignant pleural mesothelioma after resection. *Cancer Immunol Immunother* 2010;59(10):1543-9.
13. Mansfield AS, Roden AC, Peikert T, et al. B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis. *J Thorac Oncol* 2014; **9**: 1036–40.
14. Cedrès S, Ponce-Aix S, Zugazagoitia J, et al. Analysis of Expression of Programmed Cell Death 1 Ligand 1 (PD-L1) in Malignant Pleural Mesothelioma (MPM). Gangopadhyay N, editor. *PLOS ONE* 2015; **10**: e0121071.
- 15 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.
16. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol* 2017; **18**: 623–30.

17. Calabro L, Morra A, Giannarelli D, et al. Tremelimumab in combination with durvalumab in first or second line mesothelioma patients: final analysis of the NIBIT-MESO-1 phase 2 study. *Lancet Respir Med* 2018 (in press).
18. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol* 2004; **15**: 257–60.
19. Rusch VW, Chansky K, Kindler HL, et al; IASLC Staging and Prognostic Factors Committee, advisory boards, and participating institutions. The IASLC Mesothelioma Staging Project: Proposals for the M Descriptors and for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Mesothelioma. *J Thorac Oncol* 2016; **11**: 2112–9.
20. Adam J, Le Stang N, Rouquette I, et al. Multicenter harmonization study for PD-L1 IHC testing in non-small-cell lung cancer. *Ann Oncol* 2018; **29**: 953–8.
21. Lantuejoul S, Le Stang N, Damiola F, Scherpereel A, Galateau-Sallé F. PD-L1 Testing for Immune Checkpoint Inhibitors in Mesothelioma: For Want of Anything Better? *J Thorac Oncol* 2017; **12**:778–81.
22. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012 : results of an open-label, phase 1, multicohort stud. *Lancet Oncol* 2017; **18**: 31-41
23. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018; **378**:2093-2104
24. Baas P, Disselhorst M, Harms E, Quispel J, K M, Burgers S. Phase II trial of Nivolumab and Ipilimumab in patients with malignant mesothelioma. *J Thorac Oncol* 2017;12(11, suppl.2):S292-S93, OA 9389

25. Nowak AK, Lesterhuis WJ, Maxwell Hughes BG, et al. DREAM: A phase II study of durvalumab with first line chemotherapy in mesothelioma - First results. *J Clin Oncol* 36, 2018 (suppl; abstr 8503)
26. Antonia SJ, Villegas A, Daniell D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer *N Engl J Med* 2017; 377:1919-29
27. Rivalland G, Chuan-Hao Kao S, Pavlakis N, et al. Outcomes of anti-PD-1 therapy in mesothelioma and correlation with PD-L1 expression. *J Clin Oncol* 2017 ASCO;(abstr 8514).
28. Kindler HL, Karrison TG, Rose B, et al. Biomarkers of pembrolizumab (P) activity in mesothelioma (MM): Results from a phase II trial. *J Clin Oncol* 2017 ASCO;(abstr 8557).
29. Reck M, Rodríguez-Abreu D, Robinson AG et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016; 375:1823-1833
30. 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**: 850–9.
31. Suzuki K, Kadota K, Sima CS, et al. Chronic inflammation in tumor stroma is an independent predictor of prolonged survival in epithelioid malignant pleural mesothelioma patients. *Cancer Immunol Immunother.* 2011; **60(12)**: 1721–8.
32. Ujiie H, Kadota K, Nitadori JI, et al. The tumoral and stromal immune microenvironment in malignant pleural mesothelioma: A comprehensive analysis reveals prognostic immune markers. *Oncoimmunol.* 2015; **4**: e1009285.

33. Awad MM, Jones RE, Liu H, et al. Cytotoxic T Cells in PD-L1-Positive Malignant Pleural Mesotheliomas Are Counterbalanced by Distinct Immunosuppressive Factors. *Cancer Immunol Res* 2016; **4**: 1038–48.
34. Ayers M, Lunceford J, Nebozhyn M, et al. IFN- γ -related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest* 2017; **127**: 2930–40.
35. Champiat S, Derclé L, Ammari S, et al. Hyperprogressive Disease is a new pattern of progression in cancer patients treated by Anti-PD-1/PD-L1. *Clin Cancer Res* 2017; **23**: 1920–8.

Figure legends

Figure 1: Patient flow chart

Figure 2: Percentage changes in tumour size between baseline and Week 12 follow-up

Figure 3: Treatment duration, time to response and treatment response duration

Figure 4: Progression-free survival and overall survival curves

Figure 5: Exploratory analyses of response predictors

Tables

Patient baseline characteristics	Nivo arm (n=63)	Nivo+Ipi arm (n=62)
Gender N (%)		
Male	47 (75)	53 (85)
Female	16 (25)	9 (15)
Age (years)		
Mean +/- SD	71.2 ± 9.5	70.4 ± 9.0
Median [Range]	72.3 [32.5-87.2]	71.2 [48.1-88.1]
Histological subtype N (%)		
Epithelioid	52 (83)	53 (85)
Sarcomatoid or mixed (biphasic)	11 (17)	9 (15)
Performance status N (%)		
0	19 (31)	25 (40)
1	42 (69)	36 (58)
2	0 [2 missing]	1 (2)
Pem chemosensitivity N (%)		
Progression <3 months	26 (41)	21 (34)
Progression >3 months	37 (59)	41 (66)
Smoking status N (%)		
Smoker / never-smoker	34 (54) / 29 (46)	36 (58) / 26 (42)
Number of prior line(s) N (%)		
1 (2 nd line patients)	44 (70)	42 (68)
2 (3 rd line patients)	17 (27)	19 (30)
>2	2 (3)	1 (2)
TNM (1995)		
Stages III-IV N (%)	56 (89.0%)	51 (82.3%)
Leucocytes		
<8.3 x 10 ⁹ /L	43 (68)	41 (66)
≥8.3 x 10 ⁹ /L	20 (32)	21 (34)
Haemoglobin		
>12 g/L	33 (52)	37 (60)
≤12 g/L	30 (48)	25 (40)
Platelets		
<350 x 10 ⁹ /L	46 (73)	43 (69)

$\geq 350 \times 10^9/L$	17 (27)	19 (31)
PD-L1 status available (28·8 mAb, Dako PharmDx™)	50 (79%)	49 (79%)
Negative	31 (62%)	27 (55%)
$\geq 1\%$	19 (38%)	22 (45%)
$\geq 25\%$	2 (4%)	5 (10%)
$\geq 50\%$	0	3 (6%)

Nivo=nivolumab. Nivo+Ipi=nivolumab plus ipilimumab.SD=standard deviation. Pem= pemetrexed. TNM=Tumour Node Metastasis classification. PD-L1=programmed cell death-ligand 1. mAb=monoclonal antibody

Table 1: Baseline patient characteristics per treatment arm

Drug-related non-haematological AE	Nivo arm (n=63)			Nivo+Ipi arm (n=61)		
	Grade1-2	Grade 3	Grade 4	Grade1-2	Grade 3	Grade 4
Asthenia/fatigue	25 (39.7%)	1 (1.6%)	0%	31 (50.8%)	3 (4.9%)	0%
Diarrhoea	9 (14.3%)	0%	0%	16 (26.2%)	1 (1.6%)	1 (1.6%)
Decreased appetite	14 (22.2%)	0%	0%	11 (18%)	0%	0%
Nausea/vomiting	11 (17.5%)	1 (1.6%)	0%	12 (19.7%)	0%	0%
Pruritus	6 (9.5%)	0%	0%	15 (24.6%)	0%	0%
Constipation	7 (11.1%)	0%	0%	9 (14.8%)	0%	0%
Weight loss	6 (9.5%)	0%	0%	7 (11.5%)	1 (1.6%)	0%
Dry skin	3 (4.8%)	0%	0%	9 (14.8%)	0%	0%

AE=adverse event. Nivo=nivolumab. Nivo+Ipi=nivolumab plus ipilimumab. NS=not significant

Table 2: Drug-related non-haematological adverse events per treatment arm.

Grade 1 or 2, any occurring in $\geq 10\%$ of patients are reported. All grade 3, 4, 5 events are reported in the table

Drug-related Adverse Events (AE)	Nivo arm (n=63)				Nivo+Ipi arm (n=61)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Any AE	47 (74.6%)	8 (12.7%)	1 (1.6%)	0 (0%)	38 (62.3%)	14 (22.9%)	2 (3.3%)	3 (4.9%)
Serious AE	1 (1.6%)	2 (3.2%)	0%	0%	7 (11.5%)	6 (9.8%)	1 (1.6%)	3 (4.9%)
Led to discontinuation	2 (3.2%)	1(1.6%)	0%	0%	4 (6.6%)	7 (11.5%)	2 (3.2%)	0%
Led to death	0%	0%	0%	0%	0%	0%	0%	3 (4.9%)
Immune-related AEs	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Stomatitis	4 (6.3%)	1 (1.6%)	0%	0%	4 (6.6%)	0%	0%	0%
Arthritis	3 (4.8%)	0%	0%	0%	7 (11.5%)	0%	0%	0%
AST increase	2 (3.2%)	0%	0%	0%	3 (4.9%)	4 (6.6%)	0%	0%
ALT increase	1 (1.6%)	0%	0%	0%	4 (6.6%)	4 (6.6%)	0%	0%
Lipase increase	1 (1.6%)	2 (3.2%)	1 (1.6%)	0%	2 (3.2%)	1 (1.6%)	1 (1.6%)	0%
Oedema peripheral	4 (6.3%)	0%	0%	0%	3 (4.9%)	1 (1.6%)	0%	0%
Gamma-glutamyltransferase increased	1 (1.6%)	0%	0%	0%	3 (4.9%)	3 (4.9%)	0%	0%
Amylase increased	1 (1.6%)	1 (1.6%)	0%	0%	3 (4.9%)	0%	0%	0%
General physical health deterioration	3 (4.8%)	0%	0%	0%	0 %	2 (3.3%)	0%	0%
Acute kidney failure	0%	0%	0%	0%	0%	0%	1 (1.6%)	1 (1.6%)
Blood alkaline phosphatase increased	0%	0%	0%	0%	2 (3.2%)	2 (3.2%)	0%	0%
Colitis	1 (1.6%)	0%	0%	0%	1 (1.6%)	1 (1.6%)	0%	0%
Pneumonitis	1 (1.6%)	0%	0%	0%	1 (1.6%)	1 (1.6%)	0%	0%
Polyneuropathy	0%	0%	0%	0%	0%	1 (1.6%)	0%	0%
Acute respiratory distress syndrome	0%	0%	0%	0%	0%	1 (1.6%)	0%	0%
Cardiac failure	0%	0%	0%	0%	0%	1 (1.6%)	0%	0%
Dermatitis bullous	0%	0%	0%	0%	0 %	1 (1.6%)	0%	0%
Encephalitis	0%	0%	0%	0%	0%	0%	0%	1 (1.6%)
Hepatitis	0%	0%	0%	0%	0 %	2 (3.2%)	0%	1 (1.6%)
Hyperbilirubinaemia	0%	0%	0%	0%	0 %	1 (1.6%)	0%	0%
Hyponatraemia	0%	0%	0%	0%	0 %	1 (1.6%)	0%	0%
Hypophysitis	0%	0%	0%	0%	0 %	1 (1.6%)	0%	0%
Interstitial lung disease	0%	0%	0%	0%	0 %	1 (1.6%)	0%	0%
Pericardial effusion	0 %	1 (1.6%)	0%	0%	0%	0%	0%	0%
Pleural effusion	0 %	1 (1.6%)	0%	0%	0%	0%	0%	0%

AE=adverse event. Nivo=nivolumab. Nivo+Ipi=nivolumab plus ipilimumab.
AST=aspartate aminotransferase. ALT=alanine aminotransferase

Table 3: Immune-related adverse events per treatment arm

All grade 3, 4, 5 events are listed. For such events, the rate of grade 1-2 of the same event is also provided. For other grade 1-2 events, only events for which the cumulative rate in both arms is superior to 10% are listed

Randomized
n = 125

From March 2016
to early Aug. 2016

A

Allocated
NIVOLUMAB
n = 63

Received treatment
n = 63

Ongoing
n = 4

B

Allocated
NIVOLUMAB
+ IPILIMUMAB
n = 62

Received treatment
n = 61

Ongoing
n = 3

Ineligible (n=5)

- No progression to inclusion (n=1)
- Received 3 or more treatment lines before inclusion (n=3)
- No histological evidence (n=1)

Ineligible (n=2)

- No progression to inclusion (n=1)
- Received 3 or more treatment lines before inclusion (n=1)

Did not receive allocated treatment

- Death (n=1)

Study withdrawn (n=59)

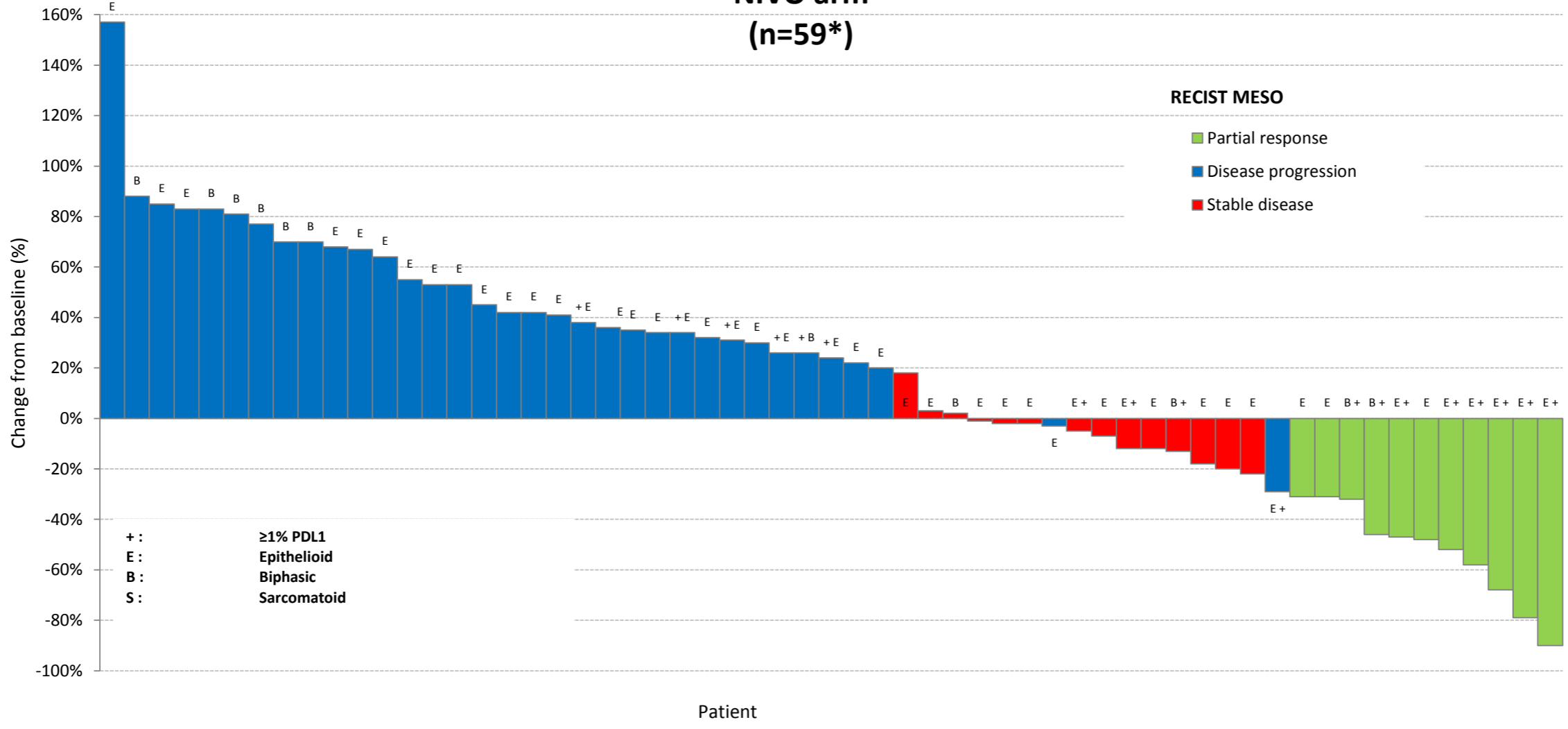
- Disease Progression (n=50, 84.7%)
- Toxicity (n=3, 5.1%)
 - Renal failure (n=1)*
 - Pericardial effusion (n=1)*
 - Keratitis (n=1)*
- Death (n=1, 1.7%)
- Second cancer (n=1, 1.7%)
- Intercurrent disease (n=1, 1.7%)
- Patient's choice (n=1, 1.7%)
- Other : Prog+Tox (n=2, 3.4%)

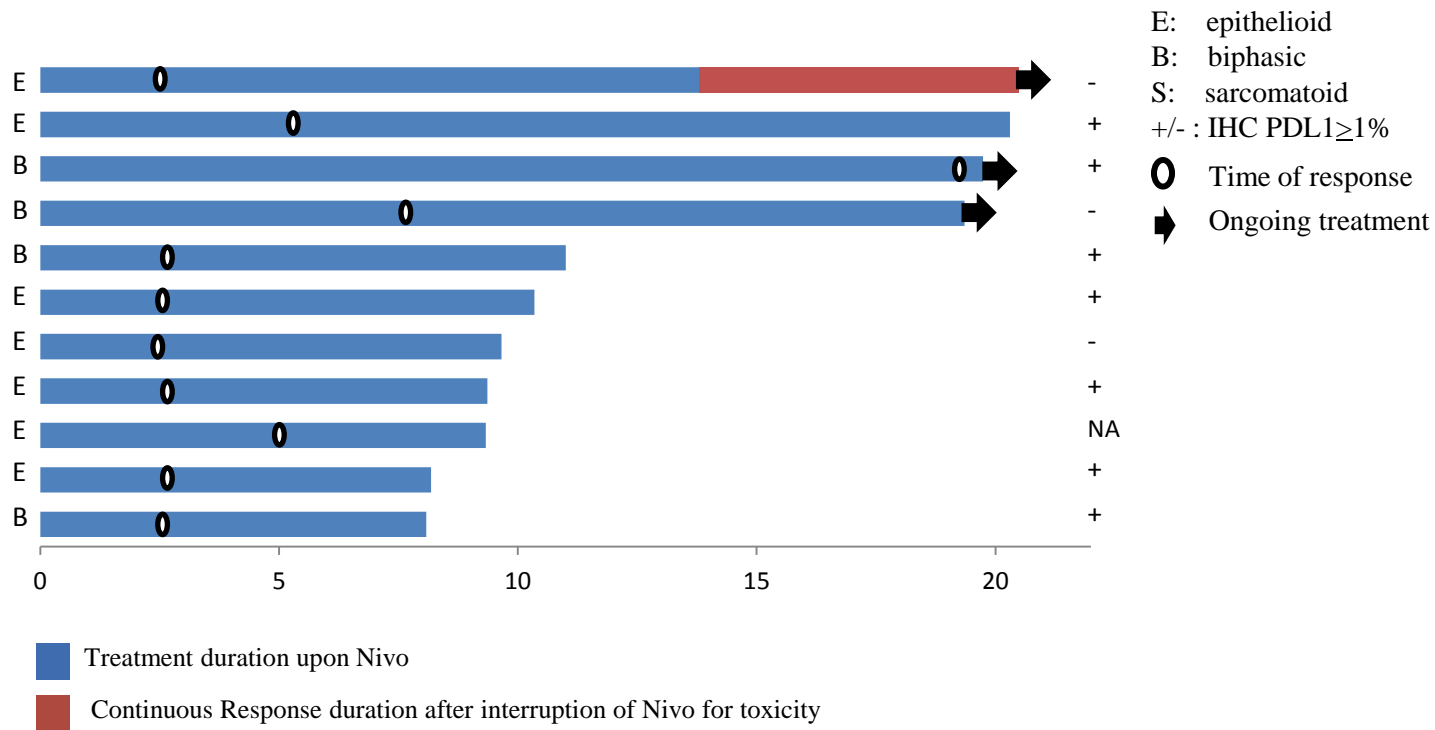
Study withdrawn (n=58)

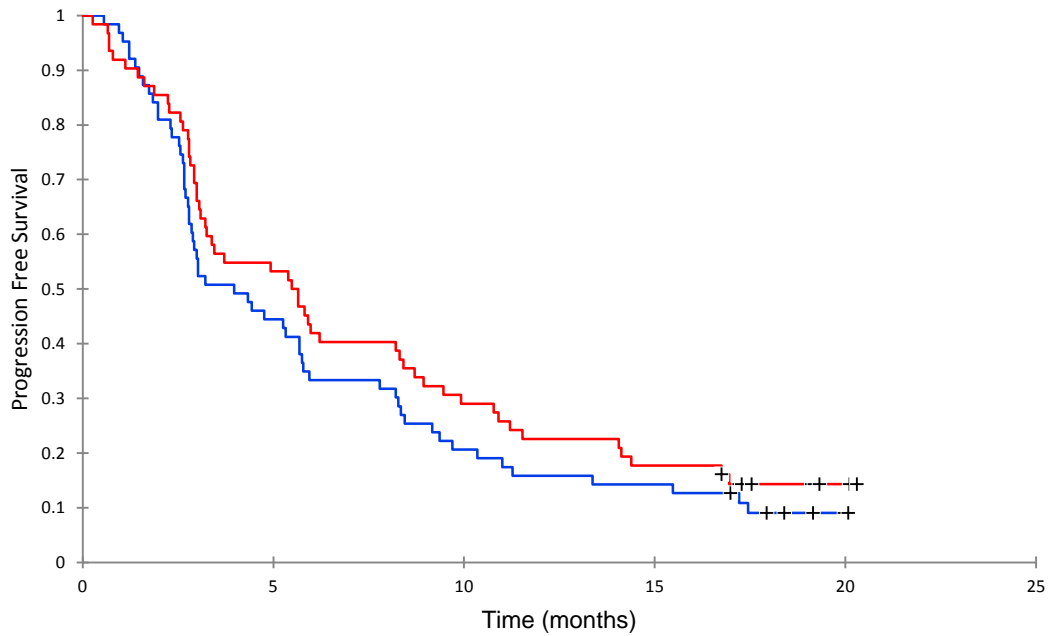
- Disease Progression (n=38, 65.5%)
- Toxicity (n=13, 22.4%)
 - Cardiac failure (n=1)*
 - Lipase increased (n=1)*
 - Pneumopathy (n=1)*
 - Gastritis (n=1)*
 - Dermatitis bullous (n=1)*
 - Pneumonitis (n=1)*
 - Atrioventricular block (n=1)*
 - Hepatitis (n=2)*
 - Colitis (n=1)*
 - Atrial fibrillation (n=1)*
 - Polyneuropathy (n=1)*
 - Diarrhoea (n=1)*
- Death (n=5, 8.6%)
- Intercurrent disease (n=1, 1.7%)
- Other (n=1, 1.7%)

txNumInclusion	Response	RECIST_MESO	TRTGRP	marquage_mb_numerique	dec_typhisto	histo	marquage_mb_numeriquebis	toto	Position	Partial response	Disease progression	Stable disease
	157%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	1	0	157%	0
	88%	Disease progression	A - Nivolumab	0	Biphasique (mixte)	B		B	2	0	88%	0
	85%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	3	0	85%	0
	83%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	4	0	83%	0
	83%	Disease progression	A - Nivolumab	0	Biphasique (mixte)	B		B	5	0	83%	0
	81%	Disease progression	A - Nivolumab	0	Biphasique (mixte)	B		B	6	0	81%	0
	77%	Disease progression	A - Nivolumab	0	Biphasique (mixte)	B		B	7	0	77%	0
	70%	Disease progression	A - Nivolumab		Biphasique (mixte)	B		B	8	0	70%	0
	70%	Disease progression	A - Nivolumab	0	Biphasique (mixte)	B		B	9	0	70%	0
	68%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	10	0	68%	0
	67%	Disease progression	A - Nivolumab		Épithélioïde	E		E	11	0	67%	0
	64%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	12	0	64%	0
	55%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	13	0	55%	0
	53%	Disease progression	A - Nivolumab		Épithélioïde	E		E	14	0	53%	0
	53%	Disease progression	A - Nivolumab		Épithélioïde	E		E	15	0	53%	0
	45%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	16	0	45%	0
	42%	Disease progression	A - Nivolumab		Épithélioïde	E		E	17	0	42%	0
	42%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	18	0	42%	0
	41%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	19	0	41%	0
	38%	Disease progression	A - Nivolumab	1	Épithélioïde	E +		+ E	20	0	38%	0
	36%	Disease progression	A - Nivolumab		Épithélioïde	E		E	21	0	36%	0
	35%	Disease progression	A - Nivolumab		Épithélioïde	E		E	22	0	35%	0
	34%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	23	0	34%	0
	34%	Disease progression	A - Nivolumab	10	Épithélioïde	E +		+ E	24	0	34%	0
	32%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	25	0	32%	0
	31%	Disease progression	A - Nivolumab	10	Épithélioïde	E +		+ E	26	0	31%	0
	30%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	27	0	30%	0
	26%	Disease progression	A - Nivolumab	1	Épithélioïde	E +		+ E	28	0	26%	0
	26%	Disease progression	A - Nivolumab	10	Biphasique (mixte)	B +		+ B	29	0	26%	0
	24%	Disease progression	A - Nivolumab	1	Épithélioïde	E +		+ E	30	0	24%	0
	22%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	31	0	22%	0
	20%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	32	0	20%	0
	18%	Stable disease	A - Nivolumab	0	Épithélioïde	E		E	33	0	0	18%
	3%	Stable disease	A - Nivolumab	0	Épithélioïde	E		E	34	0	0	3%
	2%	Stable disease	A - Nivolumab	0	Biphasique (mixte)	B		B	35	0	0	2%
	-1%	Stable disease	A - Nivolumab	0	Épithélioïde	E		E	36	0	0	-1%
	-2%	Stable disease	A - Nivolumab		Épithélioïde	E		E	37	0	0	-2%
	-2%	Stable disease	A - Nivolumab	0	Épithélioïde	E		E	38	0	0	-2%
	-3%	Disease progression	A - Nivolumab	0	Épithélioïde	E		E	39	0	-3%	0
	-5%	Stable disease	A - Nivolumab	10	Épithélioïde	E +		E +	40	0	0	-5%
	-7%	Stable disease	A - Nivolumab	0	Épithélioïde	E		E	41	0	0	-7%
	-12%	Stable disease	A - Nivolumab	10	Épithélioïde	E +		E +	42	0	0	-12%
	-12%	Stable disease	A - Nivolumab	0	Épithélioïde	E		E	43	0	0	-12%
	-13%	Stable disease	A - Nivolumab	10	Biphasique (mixte)	B +		B +	44	0	0	-13%
	-18%	Stable disease	A - Nivolumab	0	Épithélioïde	E		E	45	0	0	-18%
	-20%	Stable disease	A - Nivolumab	0	Épithélioïde	E		E	46	0	0	-20%
	-22%	Stable disease	A - Nivolumab		Épithélioïde	E		E	47	0	0	-22%
	-29%	Disease progression	A - Nivolumab	10	Épithélioïde	E +		E +	48	0	-29%	0
	-31%	Partial response	A - Nivolumab		Épithélioïde	E		E	49	-31%	0	0
	-31%	Partial response	A - Nivolumab	0	Épithélioïde	E		E	50	-31%	0	0
	-32%	Partial response	A - Nivolumab	10	Biphasique (mixte)	B +		B +	51	-32%	0	0
	-46%	Partial response	A - Nivolumab	30	Biphasique (mixte)	B +		B +	52	-46%	0	0
	-47%	Partial response	A - Nivolumab	30	Épithélioïde	E +		E +	53	-47%	0	0
	-48%	Partial response	A - Nivolumab		Épithélioïde	E		E	54	-48%	0	0
	-52%	Partial response	A - Nivolumab	1	Épithélioïde	E +		E +	55	-52%	0	0
	-58%	Partial response	A - Nivolumab	10	Épithélioïde	E +		E +	56	-58%	0	0
	-68%	Partial response	A - Nivolumab	1	Épithélioïde	E +		E +	57	-68%	0	0
	-79%	Partial response	A - Nivolumab	10	Épithélioïde	E +		E +	58	-79%	0	0
	-90%	Partial response	A - Nivolumab	1	Épithélioïde	E +		E +	59	-90%	0	0
			A - Nivolumab	0	Épithélioïde	E		E	60	0	0	0
			A - Nivolumab		Épithélioïde	E		E	61	0	0	0
			A - Nivolumab		Épithélioïde	E		E	62	0	0	0
			A - Nivolumab	1	Épithélioïde	E +		E +	63	0	0	0

NIVO arm (n=59*)



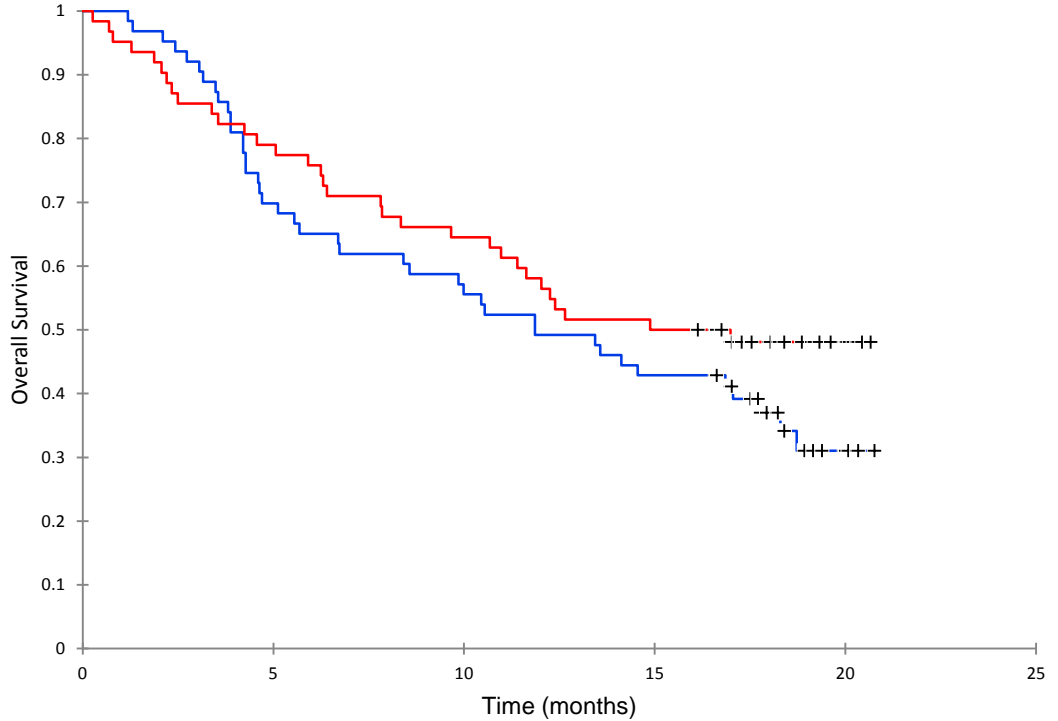




— A - Nivolumab — B - Nivolumab et Ipilimumab

Number at risk (number censored)

	0	5	10	15	20
Nivo Arm	63 (0)	28 (0)	13 (0)	9 (0)	1 (5)
Nivo+Ipi Arm	62 (0)	34 (0)	19 (0)	11 (0)	2 (7)



— A - Nivolumab — B - Nivolumab et Ipilimumab

Number at risk (number censored)

Nivo Arm	63 (0)	44 (0)	35 (0)	27 (0)	5 (17)	0 (22)
Nivo+Ipi Arm	62 (0)	49 (0)	40 (0)	32 (0)	8 (22)	0 (30)

Instructions for the use of Forest Plot Excell sheet:

This sheet does not allow you to calculate anything, or to perform a meta-analysis. It only plots results in a forest-plot like graph.

It's previously set to have nine entries, but you can change this easily.

To enter data, just enter in each line the upper limit, the lower limit of the confidence interval and the estimate point in this sequence. If you want each line to have a label in the graph, type it in the column label.

Unfortunately, the Excel does not allow us to rotate the graph, so you have to use another trick: Copy the graph to a Power Point blank slide. Select the graph. In the Draw menu click in "Ungroup", accept the prompt and then in "Group". In the same menu, choose "Rotate or Flip" and then "Rotate Left".

Be careful to not click in other places while in the group/ ungroup process. You will have to select all parts of the ungrouped graph if this happens.

In Excel, its possible to change any of the parameters that you want, by changing the proprieties of the graph.

This sheet can be changed and distributed free of charge. We ask you to give us the appropriate credit using any kind of citation we included this sugestion in the sheet: Clark O; Djulbegovic B. Forest plots in excel software(Data sheet). 2001. Available at www.evidencias.com.

Otavio Clark

Benjamin Djulbegovic

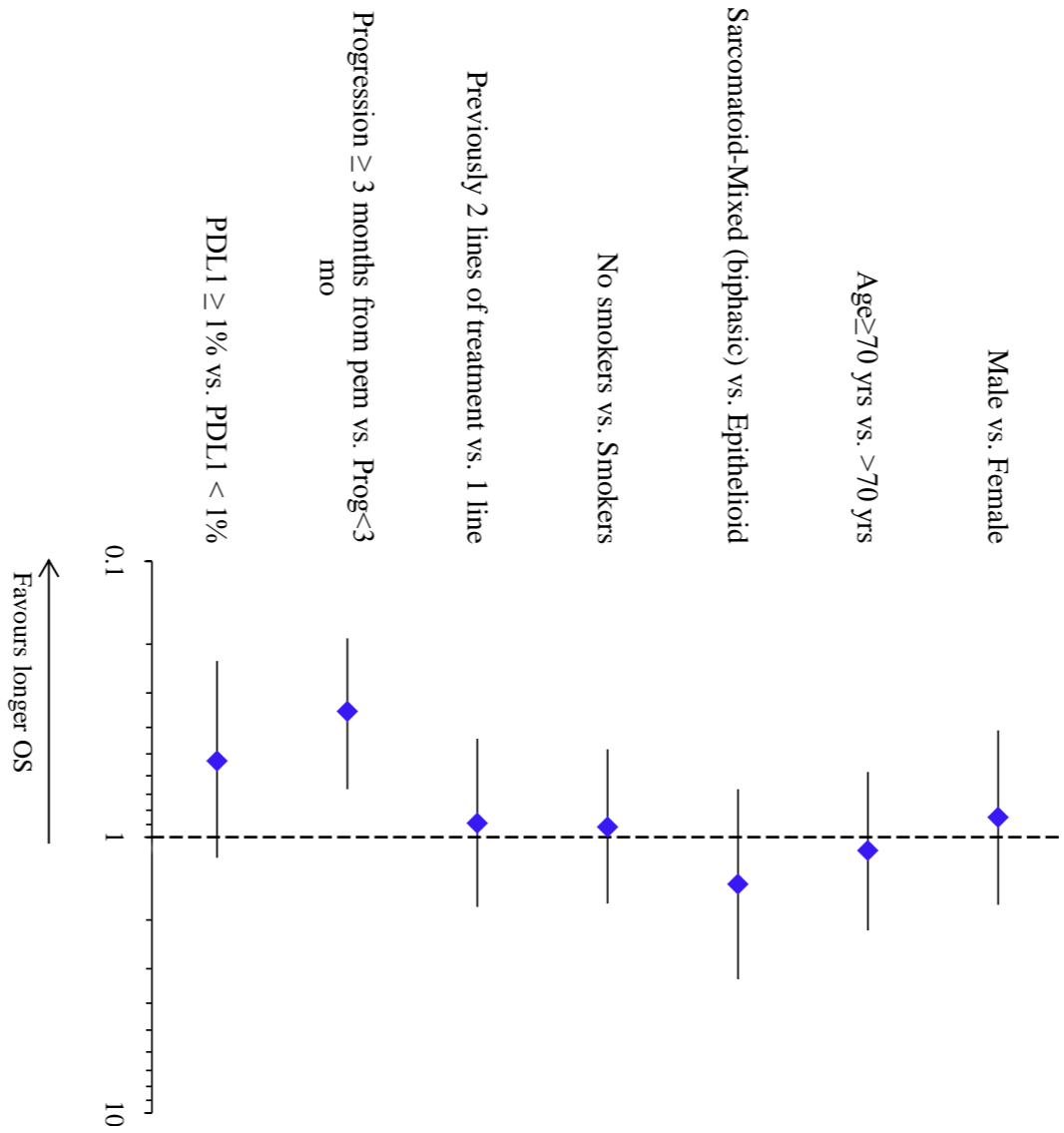
H Lee Moffitt Cancer Center

Tampa, FL, USA

clark@evidencias.com

Upper limit of the confidence interval	Lower limit of the confidence interval	Point estimate	LABELS for the graph	n
1.19	0.23	0.53	PDL1 ≥ 1% vs. PDL1 < 1%	1
0.67	0.19	0.35	Progression ≥ 3 months from pem vs. Prog<3 mo	2
1.79	0.44	0.89	Previously 2 lines of treatment vs. 1 line	3
1.74	0.48	0.92	No smokers vs. Smokers	4
3.27	0.67	1.48	Sarcomatoid-Mixed (biphasic) vs. Epithelioid	5
2.18	0.58	1.12	Age≥70 yrs vs. >70 yrs	6
1.76	0.41	0.85	Male vs. Female	7

Suggested citation: Clark O, Djuribegovic B. Forest plots in excel software(Data sheet). 2001.Available at www.evidencias.com.



Upper limit of the confidence interval	Lower limit of the confidence interval	Point estimate	LABELS for the graph	n
2.76	0.51	1.19	PDL1 ≥ 1% vs. PDL1 < 1%	1
1.61	0.36	0.76	Progression ≥ 3 months from pem vs. Prog<3 mo	2
1.54	0.31	0.69	Previously 2 lines of treatment vs. 1 line	3
2.45	0.6	1.21	No smokers vs. Smokers	4
1.54	0.14	0.46	Sarcomatoid-Mixed (biphasic) vs. Epithelioid	5
1.89	0.39	0.86	Age≥70 yrs vs. >70 yrs	6
1.42	0.25	0.6	Male vs. Female	7

Suggested citation: Clark O; Djulbegovic B. Forest plots in excel software(Data sheet). 2001.Available at www.evidencias.com.

