



Real-World efficacy and safety of combination nivolumab plus ipilimumab for Untreated, Unresectable, pleural Mesothelioma: The Meso-Immune (GFPC 04–2021) trial

Olivier Bylicki^{a,b,*}, Florian Guisier^c, Arnaud Scherpereel^d, Catherine Daniel^e, Aurélie Swalduz^f, Emmanuel Grolleau^g, Marie Bernardi^h, Stephane Hominalⁱ, Jean-Briac Prevost^j, Guillaume Pamart^k, Marie-Hélène Marques^l, Nicolas Cloarec^m, Simon Deshayesⁿ, Judith Raimbourg^o, Rémi Veillon^p, Youssef Oulkhoudir^q, Clarisse Audigier Valette^r, Fabien Subtil^s, Christos Chouaid^t, Laurent Greillier^u, on behalf of the GFPC

^a Department of Pneumology, Hôpital d'Instruction des Armées Sainte-Anne, Toulon, France

^b Ecole du Val-de-Grâce, Paris, France

^c Normandie Univ, UNIROUEN, LITIS Lab QuantIF team EA4108, CHU Rouen, Department of Pneumology and Inserm CIC-CRB 1404, F-76000 Rouen, France

^d Pulmonary and Thoracic Oncology, University of Lille, CHU de Lille, INSERM U1189, OncoThAI, Lille, France

^e Department of Medical Oncology, Institut Curie Hospital, Paris, France

^f Department of Medical Oncology, Léon-Bérard Cancer Center, Lyon, France

^g Acute Respiratory Disease and Thoracic Oncology Department, Lyon Sud Hospital, Hospices Civils de Lyon, 69310 Pierre-Bénite, France

^h Pneumology Department, Aix-en-Provence Hospital, Aix-en-Provence, France

ⁱ Department of Pneumology, CH d'Annecy-Genevois, Pringy, France

^j Department of Oncology, Clinique Ambroise-Paré, Beuvry, France

^k Pulmonology Department, Strasbourg University Hospital, Strasbourg, France

^l Pulmonology Department, CH Groupe Hospitalier du Havre, Le Havre, France

^m Department of Oncology, CH Henri-Duffaut, Avignon, France

ⁿ Department of Pneumology and Thoracic Oncology, CHU de Caen, Caen, France

^o Institut de Cancérologie de l'Ouest, St-Herblain, France, CRCI2NA, INSERM, Université de Nantes, 44035 Nantes, France

^p Department of Pneumology, CHU de Bordeaux, Bordeaux, France

^q Department of Pneumology, CHU Angers, Angers, France

^r Department of Medical Oncology, CH de Toulon Sainte-Musse, Toulon, France

^s Service de Biostatistique, Hospices Civils de Lyon, Lyon France, Université Lyon 1, CNRS, Laboratoire de Biométrie et Biologie Évolutive UMR 5558, Villeurbanne, France

^t Department of Pneumology, CH Intercommunal de Créteil, Créteil, France

^u Aix Marseille Univ, APHM, INSERM, CNRS, CRCM, Hôpital Nord, Department of Multidisciplinary Oncology and Therapeutic Innovations, Marseille, France

ARTICLE INFO

Keywords:

Pleural mesothelioma
Immunotherapy
Real-world data
Survival
Safety

ABSTRACT

Background: First-line standard-of-care for unresectable, pleural mesothelioma (PM) changed with the phase 3 CheckMate 743 study results, showing that nivolumab plus ipilimumab (Nivo + Ipi) significantly extended overall survival (OS) versus platinum + pemetrexed chemotherapy for PM (median OS 18.1 versus 14.1 months; hazard ratio: 0.74; $p = 0.002$). Efficacy and safety data in real-world (rw) settings are needed to confirm these results.

Methods: This French multicenter, retrospective cohort study was undertaken to assess the outcomes of treatment-naïve PM patients given Nivo + Ipi via an early-access program (EAP). The primary objective was investigator-assessed real world –progression-free survival (PFS). The secondary objectives were the combination's –overall survival (OS) and safety.

Results: From 1 April 2021 to 15 Feb 2022, the analysis included 201 of the 305 EAP-enrolled patients treated in 63 centers (79.6 % men; median age: 75 years; 91.8 % Eastern Cooperative Oncology Group performance status

* Corresponding author at: HIA Sainte-Anne-Toulon BCRM Toulon, boulevard Sainte-Anne, 83800 Toulon, France.

E-mail address: bylicki.olivier@yahoo.fr (O. Bylicki).

<https://doi.org/10.1016/j.lungcan.2024.107866>

Received 15 April 2024; Received in revised form 26 June 2024; Accepted 28 June 2024

Available online 29 June 2024

0169-5002/© 2024 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

(ECOG-PS) 0/1; 74.5 % epithelioid histology). With median (95 % CI) follow-up for all patients of 18.4 (17.7–19.2) months, –PFS and OS were 6.3 (5.3–7.5) and 18.9 (17.6–not reached (NR)) months, with 1-year OS at 66.4 % (60.1–73.3 %). Median OS and 1-year survival rates were 21.0 (18.7–NR) and 70.8 % (63.9 %–78.0.6 %), and 14.1 (10.9–21.0) months and 54.9 % (42.8 %–70.4 %) for epithelioid and non-epithelioid PM subgroups, respectively. PFS was equal between the two subgroups. Grade 3–4 adverse events occurred in 23.3 % of patients and three deaths were treatment-related.

Conclusions: For this unselected PM population, efficacy and safety outcomes compared favorably with CheckMate 743 trial results.

1. Introduction

Pleural mesothelioma (PM) is a highly aggressive cancer that is typically unresectable at diagnosis, with less than 10 % of patients surviving 5 years or beyond. [1] PM is an aggressive inflammatory cancer associated with exposure to asbestos [2]. Notably, a worse prognosis has been reported for the non-epithelioid histology than the epithelioid subtype [3]. For years, the palliative first line standard-of-care (combination of pemetrexed and cisplatin chemotherapy) [4] exhibited a response rate of ~ 40 % [5]. Moreover, there was no standard second-line therapy [6,7].

Nivolumab (Nivo), a fully human anti-programmed cell death 1 (PD-1) monoclonal antibody, and ipilimumab (Ipi), a fully human anti-cytotoxic T-lymphocyte 4 (CTLA-4) monoclonal antibody are immune-checkpoint inhibitors with distinct but complementary mechanisms of action. Ipi induces T-cell proliferation and de-novo anti-tumor T-cell responses, including in memory T cells, while Nivo restores the function of existing anti-tumor T cells [8]. The Nivo + Ipi combination has been approved as first and second-line therapy for various tumors, achieving durable overall survival (OS) benefits in patients with melanoma, renal cell carcinoma, non-small-cell lung cancer or mesothelioma [9–14].

Results of the phase 3 CheckMate 743 study, designed to assess efficacy and safety of first-line Nivo + Ipi immunotherapy versus platinum–pemetrexed chemotherapy in patients with unresectable PM [15,16], showed that the Nivo + Ipi combination significantly extended OS versus chemotherapy (median (95 % CI) OS 18.1 (16.8–21.4) versus 14.1 (12.4–16.2) months), with respective 4-year OS rates of 17 % versus 11 %. The results led to the approval of Nivo + Ipi combination in the USA then in Europe. The National Comprehensive Cancer Network® (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend Nivo + Ipi as a preferred first-line option for patients with biphasic or sarcomatoid histology, and as an option for those with epithelioid histology [17,18]. Real-world data on PM are scarce in the literature.

In France, since April 1, 2021, Nivo + Ipi combination has become accessible for newly diagnosed PM via an early access program (EAP) before reimbursed in routine practice. The patients enrolled in this program provide the unique opportunity to assess the combination therapy's efficacy and safety in a real-world setting.

2. Materials and Methods

The Meso-Immune (GFPC 04–2021) study constituted a national, retrospective, non-interventional cohort comprised of patients with PM treated with Nivo + Ipi in the French EAP. The inclusion criteria were: at least 18 years old; untreated and unresectable PM patients treated by Nivo (360 mg every 3 weeks) and Ipi (1 mg/kg every 6 weeks) in the EAP setting from April 1, 2021, to Feb 15, 2022. Patient data, obtained retrospectively from medical files, included demographics, PM characteristics, number and localization of metastatic sites, treatment characteristics, tumor response to the combination immunotherapy, and management of progression and post-treatment. Each participating center entered patients consecutively according to inclusion criteria without selection.

This non-interventional study (NCT 05308966) was conducted in

accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by a national ethics committee (Comité d'Évaluation des Protocoles de Recherche Observationnels de la Société de Pneumologie de Langue Française 2022–001, on 06/01/2022). All participating centers approved the study protocol, and all included patients still alive received information from their referring physician, with an option not to participate.

2.1. Endpoints and assessments

The primary objective was investigator-assessed real-world–progression-free survival (–PFS) from Nivo + Ipi onset, defined as the time from the first Nivo + Ipi dose to the date of disease progression, according to modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for PM or death from any cause.

Secondary endpoints included objective response rate (ORR), defined as the investigator-evaluated percentage of patients with partial or complete responses to Nivo + Ipi, according to RECIST 1.1; disease-control rate (DCR), defined as the investigator-assessed percentage of patients with partial, complete or stable responses, according to RECIST 1.1 at the time of best response.; Duration of response (DoR) is defined as the time between the date of first response to the date of the first documented tumor progression, or death due to any cause, whichever occurred first.. overall survival (OS), calculated from the start of Nivo + Ipi to the date of death from any cause; treatment duration, measured from the date of the first dose to the date of treatment discontinuation or death from any cause during the study. Immune-related adverse events (AEs), considering only Common Terminology Criteria for Adverse Events version 5.0 grades 3 to 5, were recorded. Investigators had the option of discontinuing IPI while continuing NIVO in the event of IPI-attributable toxicity, as recommended in the laboratory's Summary of Product Characteristics for the early access program.

2.2. Statistical Analyses

Continuous variables are expressed as median (first and third quartiles [Q1–Q3]); categorical variables are expressed as number (%). Time-to-event endpoints were estimated with Kaplan–Meier curves; the median (95 % confidence intervals (95 % CI)) time-to-event and survival rates at different times were calculated. Associations between factors and time-to-event endpoints are expressed as hazard ratios (HR) with (95 % CI). Between-group comparisons were performed using with chi [2] or Fisher's exact tests. A $p < 0.05$ was considered significant. Analyses were performed with R version 4.0.2.

3. Results

Between 1 April 2021, and 15 February 2022, 305 patients were accorded EAP entry in 140 centers; 63 centers managing 201 patients accepted to participate in this analysis (Table 1). Most patients were men (79.6 %), current or former smokers (53.4 %) and 91.8 % had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0/1. The median (IQR) age was 75 (70.1–81.6) years and 51.2 % were over 75 years old; a majority of patients (61.7 %) was previously

Table 1
Baseline Characteristics of the 201 Mesothelioma Patients.

Parameter	Total, n = 201	Histological Type Epithelioid, n = 149	Non-epithelioid, n = 52	p Value
Age, y	75 (70.1–81.6)			
<65	27 (13.4 %)	21 (14.1 %)	6 (11.8 %)	0.880
≥65 to < 75	71 (35.3 %)	51 (34.2 %)	19 (37.3 %)	
≥75	103 (51.2 %)	77 (51.7 %)	26 (51.0 %)	
Male sex	160 (79.6 %)	120 (80.5 %)	40 (78.4 %)	0.903
ECOG-PS	n = 183	n = 137	n = 45	
0	78 (42.6 %)	65 (47.5.0 %)	13 (28.8 %)	0.092
1	90 (49.2 %)	61 (44.5 %)	28 (62.2 %)	
≥2	15 (8.2 %)	11 (8.0 %)	4 (9.0 %)	
Smoking status	n = 189	n = 139	n = 49	
Current or former	101 (53.4 %)	72 (51.8 %)	28 (57.1.0 %)	0.633
Never	88 (46.6 %)	67 (48.2 %)	21 (42.9.0 %)	
Asbestos exposure	n = 201	n = 149	n = 52	
Yes	124 (61.7 %)	92 (61.7 %)	32 (62.7.8 %)	0.600
No	53 (26.4 %)	38 (25.5.0 %)	15 (29.4 %)	
Unknown	24 (11.9 %)	19 (12.8 %)	4 (7.8.8 %)	
Stage, at diagnosis	n = 139	n = 104	n = 34	
I/II	28 (20.2 %)	23 (22.1 %)	5 (13.7 %)	0.797
III	69 (49.6 %)	49 (47.1 %)	19 (55.9 %)	
IV	42 (30.2 %)	32 (30.8 %)	10 (29.4 %)	
Chronic obstructive pulmonary disease	n = 201	n = 149	n = 52	
Yes	6 (3.0 %)	3 (2.0 %)	3 (5.9 %)	0.174
Arterial Hypertension	n = 201	n = 149	n = 52	
Yes	110 (54.7 %)	82 (55.0 %)	27 (52.9 %)	
Preexisting cardiovascular disease	n = 201	n = 149	n = 52	
Yes	57 (28.4 %)	40 (26.8 %)	17 (33.3 %)	0.480
Diabetes	n = 201	n = 149	n = 52	
Yes	31 (15.4 %)	22 (14.8 %)	9 (17.6 %)	
Cancer(s) other than mesothelioma	n = 201	n = 149	n = 52	
Yes	35 (17.5 %)	29 (19.5 %)	6 (11.8 %)	0.3
Loss expression BAP-1	n = 167			
Yes	92 (55.1 %)			
PD-L1 status	n = 14			
<1	8 (57.1 %)			
1–49 %	4 (28.6 %)			
>50 %	2 (14.3 %)			

ECOG-PS, Eastern Cooperative Oncology Group performance status.

exposed to asbestos, mostly of occupational origin (59.4 %). The most frequent histology was epithelioid (74.5 %, 149/201) then mixed subtype (13.5 %, 27/201) and, finally, sarcomatoid (10.0 %, 20/201). At diagnosis, 79.8 % of patients had stage-III/IV PM (eighth TNM classification for pleural mesothelioma). The tumor status of PD-1 ligand-1 (PD-L1) was not mandatory in France we have it for only 14/195 (7.2 %) patients in this cohort; 55.1 % (92/167) of patients' tumors had lost BReast CAncer gene 1-associated protein 1 (BAP-1) expression. The median diagnosis-to-treatment-onset interval was 42 (IQR: 28–63) days.

3.1. Clinical outcomes

With a median (95 % CI) follow-up of 18.4 (17.7–19.2) months, median PFS was 6.3 (5.3–7.5) months (Fig. 1A), with no difference according to histological subtype: 6.3 (5.2–7.9) months for epithelioid PMs and 6.6 (4.8–9.5) months for other histological subtypes (Fig. 1B). In patients ≥ 75 years of age, median PFS was 5.3 months, compared with 6.3 and 6.6 months for age groups < 65 and 65–75 respectively.

Median (95 % CI) OS was 18.9 (17.6–not reached (NR)) months, significantly better for epithelioid than non-epithelioid PMs, respectively: 21 (18.4–NA) versus 14.1 (10.9–21.0) months (HR = 0.60 (95 % CI: 0.39–0.92); $p = 0.022$) (Fig. 1C and D). Their respective 1-year OS rates were 70.8 % and 54.9 % (Table 2), with an overall rate of 66.4 % (95 % CI 60.1–73.3 %).

The ORR (95 % CI) was 19.9 % (14.5–26.3 %): 17.5 % (11.6–24.7 %) for epithelioid PMs and 27.1 % (15.3–41.8 %) for the other subtypes ($p = 0.218$). The best overall response to treatment was stable disease for 106 patients (55.5 %) followed by progression disease for 47 patients (24.6 %) and partial response for 37 patients (19.4 %). A complete response was only observed in one patient. The median number of cycles was 7.3 with a maximum of 27 cycles.

The median treatment-onset-to-best-response interval was 3.4 (IQR: 2.4–5.1) months. The DCR was 75.4 % (95 % CI: 68.7–81.3 %). The DOR was 10.8 months for the whole cohort, 11.4 in epithelioid subtype and 9.7 months for the non-epithelioid patients.

3.2. Subsequent therapy

At the time of this analysis, 152/201 (75.6 %) patients had progressed or death on Nivo + Ipi and 101/152 (66.4 %) received a second-line treatment (Table 3). The majority received combined platinum–pemetrexed chemotherapy (86/101, 85.1 %), including 43 (42.6 %) with bevacizumab adjunction. Second-line efficacy was not available at the time of analysis.

3.3. Safety

Nivo + Ipi-related AEs occurred in 136/201 (68.3 %) patients, among which 23.3 % were grade 3 or 4 (Table 4). The median time to onset was 1.4 (IQR: 0.7–2.8) months. Immune-related AEs required hospitalization for 34.8 % of the patients. The most common of those AEs of grade ≥ 3 were respiratory (immune pneumonitis and breathing abnormalities (6 %, 12 patients)), gastrointestinal disorders (5.5 %, 11 patients), asthenia (3.5 %, 7 patients) and hepatic involvement (2.5 %, 5 patients). Investigators concluded that three deaths (hepatic cytolysis, acute myocarditis and septic shock with multiorgan failure) were treatment related AEs.

4. Discussion

Herein, we reported data on the efficacy and safety of the Nivo + Ipi combination in PM patients. Our population differed from the pivotal CheckMate 743 study [15,16] in several aspects (Table 5). Our patients were older (median age: 74.3 in our series versus 69 years in CheckMate 743), with > 50 % of them > 75 years old versus 26 %, respectively. This older age was associated by a higher number of comorbidities (> 60 % of our patients had at least one impacting comorbidity). Another difference was about the general condition, as 8.2 % of our patients had an ECOG-PS of 2/3, whereas that score was an exclusion criterion for CheckMate 743 inclusion. Our population had a higher percentage of non-epithelioid tumors, 30.8 % (62/201) versus 24 % in CheckMate 743.

In France, the estimated annual number of new cases of PM is 1100. The majority of patients will receive systemic treatment, here 305 were included in early access, the other patients had to receive chemotherapy or exclusive supportive care.

The characteristics of our unselected population reflect PM epidemiology in Europe [19]. In that registry analysis [19] of 9458 patients diagnosed with PM between 2013 and 2017 in England, median age at diagnosis was 75 years; 83.4 % were male; ECOG-PS was 0/1 for 44.5 %, ≥2 for 20.6 % and missing for 34.9 %. More patients' PMs had epithelioid (36.4 %) or not-otherwise-specified (43.3 %) histology. In a European cohort (MesoScape) of PM receiving systemic therapy (patients with comfort care were not included), median OS lasted 17.4 (95 % CI: 16.3–18.7) months, with 65 % 1-year OS; at 2 years, that rate decreased

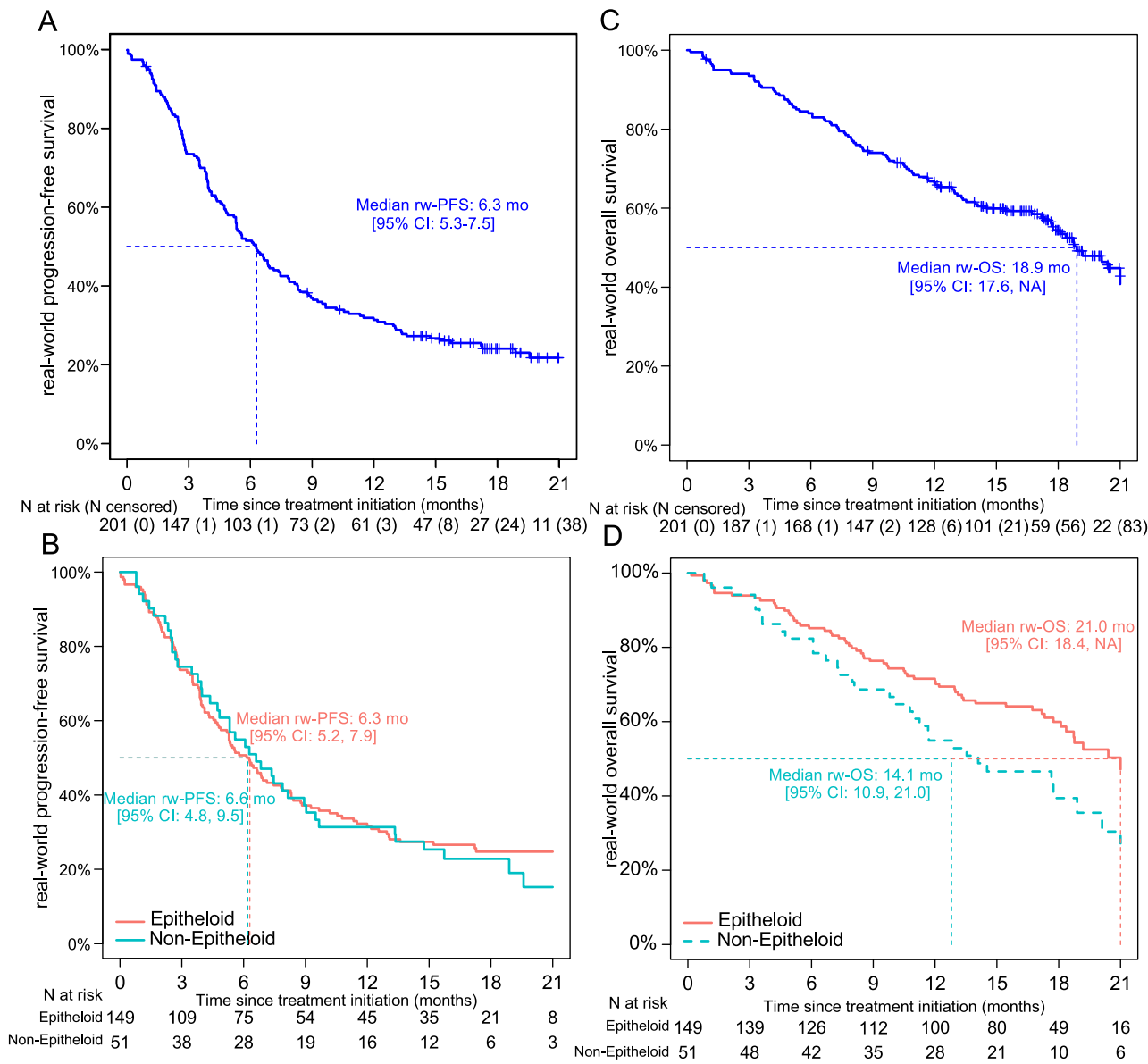


Fig. 1. Real-world progression-free survival (PFS) and overall survival (OS), respectively, for the entire population (A and C), epithelioid subtypes and non-epithelioid histology (B and D).

Table 2			
Efficacy and Survival Rates According to Histological Subtype.			
	All, n = 201	Epithelioid, n = 149	Non-epithelioid, n = 52
ORR, % (95 % CI)	19.9 % (14.5–26.3 %)	17.5 % (11.6–24.7 %)	27.1 % (15.3–41.8 %)
Median PFS (months) (95 % CI)	6.3 (5.3–7.5)	6.3 (5.2–7.9)	6.6 (4.8–9.5)
Median OS (months) (95 % CI)	18.9 (17.6–NR)	21.0 (18.4–NR)	14.1 (10.1–21.0)
1-year OS, % (95 % CI)	66.4 % (60.1–73.3 %)	70.8 (63.0–78.6 %)	54.9 (42.8–70.4 %)

ORR, objective response rate; PFS, real-world progression-free survival, OS, real-world overall survival; NR, not reached.

Table 3	
Subsequent Therapy for the 136 out of 201 patients with disease progression after Nivolumab + Ipilimumab.	
Status or Treatment	n (%)
Disease progression	136/201 (67.7 %)
Second-line regimen (n = 101)	101/136 (74.3 %)
Platinum–pemetrexed–bevacizumab	43 (42.6 %)
Platinum–pemetrexed	43 (42.6 %)
Mono-chemotherapy	11 (10.9 %)
Pemetrexed	7 (7 %)
Gemcitabine	2 (2 %)
Navelbine	2 (2 %)
Clinical Trial	1 (1 %)
Missing data	3 (3 %)

Table 4
Immune-Related Adverse Events Observed in the 201 Mesothelioma Patients.

Adverse Event	Grade	
	Any	≥3
All	136 (67.7 %)	44 (21.9 %)
Leading to study drug discontinuation	50 (24.9 %)	
Leading to study drug interruption	22 (10.9 %)	
Leading to hospitalization	47 (23.4 %)	
Leading to Death	3 (1.5 %)	
Hepatocellular damage	1 (0.5 %)	
Renal failure	1 (0.5 %)	
Myocarditis	1 (0.5 %)	
Any grade in ≥ 10 patients	n = 201	
Asthenia	51 (25.4 %)	7 (3.5 %)
Gastrointestinal disorders	48 (23.9 %)	11 (5.5 %)
Musculoskeletal & connective tissue, pain & discomfort	35 (17.4 %)	4 (2 %)
Breathing abnormalities	32 (15.9 %)	12 (6 %)
Rashes, eruptions and exanthems	41 (20.4 %)	1 (0.5 %)
Endocrine disorders		
Hypothyroidism	8 (4.0 %)	0
Adrenal insufficiency	6 (3.0 %)	2 (1.0 %)
Hyperthyroidism	5 (2.5 %)	0
Diabetes	3 (1.5 %)	1 (0.5 %)
Hypophysitis	2 (1.0 %)	0
Hepatic disorders	13 (6.5 %)	5 (2.5 %)

Table 5
Comparison between the CheckMate 743 results^{15,16} and Meso-Immune GFPC 04–2021.

Parameter	CheckMate 743		Meso-Immune GFPC 04–2021 n = 201
	Pemetrexed, n = 284	Nivo + Ipi, n = 300	
Population			
Age, y (IQR)	69 (62–75)	69 (65–75)	75.3 (70.1–80.7)
Sex			
Male	77 %	77 %	79.6 %
Female	23 %	23 %	20.4 %
ECOG-PS			
0	42 %	38 %	42.6 %
1	57 %	62 %	49.2 %
2			7.1 %
≥2			1.1 %
Histology			
Epithelioid	75 %	76 %	74.5 %
Non-epithelioid	25 %	24 %	25.5 %
Sarcomatoid	12 %	12 %	10 %
Mixed/other	13 %	13 %	15.5 %
Efficacy			
ORR	43 %	40 %	19.9 %
PFS (mo) (95 % CI)	7.2 (6.9–8.0)	6.8 (5.6–7.4)	6.3 (5.3–7.5)
OS (mo) (95 % CI)	14.1 (12.4–16.3)	18.1 (16.8–21.0)	18.9 (17.6–NR)
1-year OS (95 % CI)	58 % (51.7–63.2)	68 % (62.3–72.8)	66.4 % (60.1–73.3)
Safety			
Any-cause adverse event			
All	239 (84.2 %)	232 (77.3 %)	136 (68.3 %)
Grade > 3	91 (32.0 %)	91 (30.3 %)	44 (34.4 %)
Leading to study-drug withdrawal	45 (15.8 %)	69 (23 %)	50 (24.9 %)

Nivo + Ipi, nivolumab + ipilimumab; ECOG-PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; PFS, progression-free survival, OS, overall survival; NR, not reached.

to 36 %. Median OS for the patients with epithelioid subtype was 20.4 months, significantly longer than for the patients with non-epithelioid histology, 11.0 months ($p < 0.001$). Despite those age and ECOG-PS differences, the PFS and OS outcomes in this analysis are similar to those of CheckMate 743, respectively: 6.3 versus 6.8 months and 18.9

versus 18.1 months. However, unlike this clinical trial, our results favored more epithelioid PM subtypes, with an OS of 21 months versus only 14.1 months (95 % CI 10.9–21.0) for non-epithelioid PM, whereas, in CheckMate 743, the benefit of Nivo + Ipi combination compared to chemotherapy one was less impressive for the epithelioid subtype versus non-epithelioid cases. CheckMate-743 demonstrated comparable OS between both histologic PM groups (18.7 vs 18.1 months) [15]. However in the data presented here, OS was inferior for the non-epithelioid subgroup but characteristics between the 2 groups were not well balanced, with more ECOG 1/2 patients and more patients with a second malignant tumor other than PM in the non-epithelioid group which might have influenced the OS. The most likely hypothesis for the difference in OS between the two subgroups despite equal PFS is the efficacy of subsequent treatments in the non-epithelioid subtype. Second-line chemotherapy may be less effective in this subtype. The ORR herein was lower than in that study (19.9 % versus 40.0 %) but CT-scan assessment was not centralized.

These findings should be compared to observed chemotherapy efficacy before the immunotherapy era. In the study by Baas et al., [19] only 33.4 % of the patients received systemic anticancer therapy as first-line therapy, mainly platinum– pemetrexed: their median OS lasted 14.0 (95 %CI,13.6–14.4) months [19]. After adjusting for age, sex and ECOG-PS, PMs with sarcomatoid, biphasic and not-otherwise-specified histology were significantly associated with shorter OS than epithelioid PMs. In a retrospective analysis of 667 chemotherapy-treated patients managed in a university hospital, median OS lasted 17.4 months, but only 12.7 months for patients ≥ 75 years [21]. According to the analysis of a European population, median OS lasted 17.4 (95 % CI: 16.3–18.7) months, with 65 % 1-year OS; at 2 years, that rate decreased to 36 %. Median OS for the patients with epithelioid subtype was 20.4 months, significantly longer than for the patients with non-epithelioid histology, 11.0 months ($p < 0.001$) [20].

Our rw-Nivo + Ipi safety findings also appear to agree with the CheckMate-743 data with 23.3 % of the patients experiencing a grade 3–4 AE versus 30.3 % in this pivotal phase 3 trial, but with more serious AEs (34.8 % versus 21.3 %). We also observed a higher AE rate requiring hospitalization (34.8 % versus 15 %), partly explained by the unselected population in routine, including older and more ECOG-PS ≥ 2 patients. However, the profile of immune-mediated AEs was similar to the one reported for CheckMate 743, with predominant gastrointestinal (23.4 %), musculoskeletal and osteoarticular (17.4 %) and respiratory (15.9 %) AEs. Those AEs led to Nivo + Ipi discontinuation for 24.9 % of our PM patients, compared to only 15 % of CheckMate 743 participants.

Recently, two other real-world cohorts (one Australian and one Netherlands) have been published [22,23]. 189 patients were included in the Netherlands cohort, with a median age of 71 (66–76) years. OS and PFS were 14.1 months and 5.1 months respectively, with an AE > 3 rate of 26 % [22]. The Australian cohort included 119 patients, 89 (75 %) of whom had not been pretreated. Median age was 72 (19–89) years, with ECOG-PS ≥ 1 in 66 % of cases. OS and PFS here were 14.5 months and 6.7 months in first-line treatment [23]. These cohorts show similar results to our own, with an older population and poorer ECOG-PS than the CM743 study, but similar efficacy.

Our study has some limitations inherent in conducting a retrospective analysis. First, not all the patients enrolled in an EAP were included in the analysis. Second, no standardized method for patient follow-up was applied, no standardization of assessment (depending on the local practices of each center), and tumor responses were not subjected to independent review. Finally, safety was estimated based on patients' medical files, which could underestimate AE frequencies, especially those of low-to-moderate grade. Nevertheless, this analysis concerned a large series of PM patients, managed in numerous centers that exhaustively included all Nivo + Ipi-treated patients with a new PM diagnosis during the EAP-inclusion period, limiting the risk of bias.

Interestingly, outcome of the IND227/IFCT1901 phase 3, randomized trial [24] were recently reported. This trial evaluating first line

standard chemotherapy alone or combined with pembrolizumab, reported a 17.3 months mOS for the chemo-pembro arm versus 16.1 for the chemotherapy alone arm ($p = 0.03$, $HR = 0.79$), and a 3-years survival of respectively 25 % and 17 %. Similarly to CheckMate743, the benefit of chemo-pembro was more important in the subset of patients with non-epithelioid mesothelioma, with 12.3 and 8.1 mOS respectively ($HR = 0.57$, 95 % CI (0.36–0.89)). Thus, this new potential therapeutic option does not impressively outperform Nivo + Ipi based on results from the French EAP program.

5. Conclusion

While the characteristics of our study population differed from recruited patients in the CheckMate 743 trial, notably being older and with less preserved performance status, the efficacy of the checkpoint inhibitors in the real world compared favorably with the outcome observed in that pivotal trial. As expected, the toxicity of Nivo + Ipi in this unselected and more fragile PM population was higher than in the CheckMate 743 trial, but overall, the tolerance of the combo appears to be acceptable and routinely manageable despite a discontinuation rate of 25 % due to toxicity.

CRediT authorship contribution statement

Olivier Bylicki: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Florian Guisier:** Writing – review & editing, Investigation, Conceptualization. **Arnaud Scherpereel:** Writing – review & editing, Investigation. **Catherine Daniel:** Writing – review & editing, Investigation. **Aurélien Swalduz:** Writing – review & editing, Investigation. **Emmanuel Grolleau:** Investigation. **Marie Bernardi:** Investigation. **Stephane Hominal:** Investigation. **Jean-Briac Prevost:** Investigation. **Guillaume Pamart:** Investigation. **Marie-Hélène Marques:** Investigation. **Nicolas Cloarec:** Investigation. **Simon Deshayes:** Investigation. **Judith Raimbourg:** Investigation. **Rémi Veillon:** Investigation. **Youssef Oulhouir:** Investigation. **Clarisse Audigier Valette:** Investigation. **Fabien Subtil:** Writing – review & editing, Methodology, Formal analysis. **Christos Chouaid:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Laurent Greillier:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This trial received financial support from Bristol Myers Squibb (BMS), which was not involved in the design and conduct of the study, the collection, management, analysis and interpretation of the data, the writing of the manuscript or the decision to publish.

References

- [1] M. VanGerwen, N. Alpert, A. Wolf, et al., Prognostic factors of survival in patients with malignant pleural mesothelioma: an analysis of the National Cancer Database, *Carcinogenesis* 40 (2019) 529–536.
- [2] M.T. Milano, H. Zhang, Malignant pleural mesothelioma: a population-based study of survival, *J Thorac Oncol.* 5 (2010) 1841–1848.
- [3] A. Billé, L.M. Krug, K.M. Woo, V.W. Rusch, M.G. Zauderer, Contemporary analysis of prognostic factors in patients with unresectable malignant pleural mesothelioma, *J Thorac Oncol.* 11 (2016) 249–255.
- [4] H.L. Kindler, N. Ismaila, S.G. Armato 3rd, et al., Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline, *J Clin Oncol.* 36 (2018) 1343–1373.
- [5] N.J. Vogelzang, J.J. Rusthoven, J. Symanowski, et al., Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma, *J Clin Oncol.* 21 (2003) 2636–2644.
- [6] L. Trizzi, A. Catalano, G. Vianale, et al., Vascular endothelial growth factor is an autocrine growth factor in human malignant mesothelioma, *J Pathol.* 193 (2001) 468–475.
- [7] G. Zalcman, J. Mazieres, J. Margery, 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* 387 (2016) 1405–1414.
- [8] S.C. Wei, C.R. Duffy, J.P. Allison, Fundamental mechanisms of immune checkpoint blockade therapy, *Cancer Discov.* 8 (2018) 1069–1086.
- [9] J. Larkin, V. Chiarion-Sileni, R. Gonzalez, et al., Five-year survival with combined nivolumab and ipilimumab in advanced melanoma, *N Engl J Med.* 381 (2019) 1535–1546.
- [10] R.J. Motzer, B.I. Rini, D.F. McDermott, et al., Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial, *Lancet Oncol.* 20 (2019) 1370–1385.
- [11] M.D. Hellmann, L. Paz-Ares, R. Bernabe Caro, et al., Nivolumab plus ipilimumab in advanced non-small-cell lung cancer, *N Engl J Med.* 381 (2019) 2020–2031.
- [12] A. Scherpereel, J. Mazieres, L. Greillier, 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.* 20 (2019) 239–253.
- [13] J. Quispel-Janssen, V. van der Noort, J.F. de Vries, et al., Programmed death 1 blockade with nivolumab in patients with recurrent malignant pleural mesothelioma, *J Thorac Oncol.* 13 (2018) 1569–1576.
- [14] M.J. Disselhorst, J. Quispel-Janssen, F. Lalezari, et al., Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial, *Lancet Respir Med.* 7 (2019) 260–270.
- [15] P. Baas, A. Scherpereel, A.K. Nowak, et al., First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial, *Lancet* 397 (2021) 375–386.
- [16] S. Peters, A. Scherpereel, R. Cornelissen, et al., First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743, *Ann Oncol.* 33 (2022) 488–499.
- [17] NCCN Guidelines, Mesothelioma: Pleura, Version 1.2023 Available at <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1512>; accessed November 2023.
- [18] S. Popat, P. Baas, C. Faivre-Finn, et al., Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, *Ann Oncol.* 33 (2022) 129–142.
- [19] P. Baas, M.J. Daumont, L. Lacoïn, et al., Treatment patterns and outcomes for patients with malignant pleural mesothelioma in England in 2013–2017: A nationwide CAS registry analysis from the I-O Optimise initiative, *Lung Cancer* 162 (2021) 185–193.
- [20] I. Opitz, A. Bille, U. Dafni, et al., European epidemiology of pleural mesothelioma-real-life data from a joint analysis of the Mesoscape database of the European Thoracic Oncology Platform and the European Society of Thoracic Surgery Mesothelioma Database, *J Thorac Oncol.* 18 (2023) 1233–1247.
- [21] K. Kerrigan, Y. Jo, J. Chipman, et al., A real-world analysis of the use of systemic therapy in malignant pleural mesothelioma and the differential impacts on overall survival by practice pattern, *JTO Clin Res Rep.* 3 (2022) 100280.
- [22] D.W. Dumoulin, L.H. Douma, M.M. Hofman, et al., Nivolumab and ipilimumab in the real-world setting in patients with mesothelioma, *Lung Cancer* 187 (2024 Jan) 107440.
- [23] N. McNamee, C. Harvey, L. Gray, et al., Brief Report: Real-World Toxicity and Survival of Combination Immunotherapy in Pleural Mesothelioma-RIOMeso, *J Thorac Oncol.* 19 (4) (2024 Apr) 636–642.
- [24] Q.S. Chu, M.C. Piccirillo, L. Greillier, F. Grosso, G. Lo Russo, M. Florescu, M. Mencoboni, P.A. Bradbury, A. Morabito, F.L. Cecere, S. Delfanti, A. Scherpereel, M. Locatelli-Sanchez, G. Zalcman, D.E. Dawe, J. Sederias, S.A. Laurie, C.W. Lee, W. Tu, L. Seymour, IND227: Phase III (P3) study of Cisplatin/Pemetrexed (CP) with or without Pembrolizumab (Pembro) in Patients (pts) with Malignant Pleural Mesothelioma (PM): A CCTG, NCIN and IFCT Trial, *Lancet*, 2023 in press.