Lung Cancer 203 (2025) 108545

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Efficacy and safety of bintrafusp alfa evaluated in a phase II single-arm clinical trial in previously treated advanced pleural mesothelioma

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ARTICLE INFO

Keywords:
Mesothelioma
Immunotherapy
PD-L1
TGF-β blockade

ABSTRACT

Objectives: We aimed to evaluate the efficacy (progression-free survival [PFS]) of bintrafusp alfa in patients with pleural mesothelioma (PM) who had progressed to platinum-based chemotherapy and had not previously received immunotherapy. We also assessed overall survival [OS], objective response rate [ORR], and safety and tolerability.

Materials and Methods: This open-label, non-randomised, multicentre, phase II, single-arm clinical trial was carried out by the Spanish Lung Cancer Group between October 2021 and March 2023 in 15 Spanish hospitals. We included patients ≥ 18 years old, with an ECOG PS of 0 or 1, with a histologically confirmed unresectable or metastatic PM, and with a life expectancy of at least three months.

Results: 46 patients were included in the analysis. Most patients were men (78.3 %), the mean age was 70.0 years (SD, 9.5), and most presented epithelioid PM (84.8 %). The median PFS was 1.9 months (95 % CI, 1.7–3.2 months), the median duration of bintrafusp alfa response was 3.8 months, and the ORR was 6.5 % (95 % CI, 2.1–18.8 %). The median OS was 11.9 months (95 % CI, 5.8–15.7 months). Grade 3 or higher adverse events were observed in 34.8 % of patients and no grade 5 adverse event was reported.

Conclusion: Bintrafusp alfa did not reach the expected efficacy in patients with advanced PM. We did not identify new safety signals with bintrafusp alfa, and no case of bleeding was reported. Our study suggested that bintrafusp alfa has limited efficacy in PM, as reported in other solid tumours.

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https://doi.org/10.1016/j.lungcan.2025.108545
Received 27 February 2025; Received in revised form 14 April 2025; Accepted 16 April 2025
Available online 17 April 2025

1. Introduction

Pleural mesothelioma (PM) is a rare and aggressive malignancy arising from the mesothelial surface of the pleura [1]. In Europe, the incidence rate per 100 000 persons is 1.7 for males and 0.4 for females [2]. Asbestos exposure is the main cause of the disease, with usually a long latency period between fibre exposure and presentation [1]. PM is divided into three histological subtypes, i.e., epithelioid and non-epithelioid—comprising biphasic and sarcomatoid [3]. Surgery remains controversial for resectable cases, especially following the results of the MARS 2 trial [4]. The prognosis remained very poor for years, with a median overall survival (OS) below 12 months [5,6], mainly due to the limited benefit of surgical resection [7] and the frequent development of drug resistance to chemotherapy [8–10]. The combination of nivolumab plus ipilimumab is currently the first-line standard of care [2,11]. However, this therapy was not available in Spain at the time of study, and first-line chemotherapy remained the standard of care [12]. Adding bevacizumab to chemotherapy moderately improved OS, but this treatment was unavailable worldwide [13]. No other therapy beyond first-line had been approved in Europe [2].

Transforming growth factor β (TGF-β) has been demonstrated to play a key role in tumour immune evasion, and neutralising it could control tumour growth by restoring effective antitumor immunity, blocking metastasis, and inhibiting angiogenesis [14–16]. Upregulation of TGF-β signalling and epithelial to mesenchymal transition were associated with a lack of benefit from nivolumab in patients with PM who had been previously treated with chemotherapy in the CONFIRM trial [17]. On the other hand, high PD-L1 expression has been found to be a significant prognostic factor for poor OS in patients with PM [18]. Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the human TGF-β receptor II (TGF-βRII or TGF-β "trap") fused via a flexible linker to the C-terminus of each heavy chain of an IgG1 antibody blocking programmed death ligand 1 (PD-L1), designed to target colocalized, simultaneous inhibition of TGF-β and PD-L1 in the tumour microenvironment [19,20]. We hypothesised that the dual targeting of PD-L1 and TGF-β of bintrafusp alfa could reduce tumour aggressiveness in PM, reverse the suppressive tumour microenvironment, and extend progression-free survival (PFS). Our primary outcome was to determine the efficacy, in terms of PFS, of bintrafusp alfa in patients with PM who had progressed to platinum-based chemotherapy and had not previously received immunotherapy. Secondary outcomes included OS and objective response rate [ORR] and the safety and tolerability profile of bintrafusp alfa in this population.

2. Methods

2.1. Study design and setting

This was an open-label, non-randomised, Phase II, single-arm, multicentre clinical trial carried out by the Spanish Lung Cancer Group (GECP) between October 2021 and March 2023 in 15 hospitals from Spain. The trial was registered at the EU Clinical Trials Register EudraCT 2020–004902–67 (and at ClinicalTrials.gov NCT05005429) and was approved by the Clinical Research Ethics Committee of Hospital Universitario Puerta de Hierro. We obtained written informed consent from all study participants. The study was carried out in accordance with the Declaration of Helsinki [21].

2.2. Participants

We included patients ≥ 18 years old, with an Eastern Cooperative Oncology Group performance status of 0 or 1, with a histologically confirmed unresectable or metastatic PM, and with a life expectancy of at least three months. Included patients were required to have had disease progression to one or two regimens of chemotherapy, including platinum-based chemotherapy with pemetrexed. Bevacizumab during chemotherapy was allowed. We included patients with evaluable or measurable disease as assessed according to the modified RECIST v1.1 criteria.

We excluded all patients who had received immune checkpoint therapy with an anti–PD-1, anti–PD-L1, anti-CD137, or anti–CTLA-4 antibody; pregnant women; those with known severe hypersensitivity to bintrafusp alfa or recent (history of uncontrollable asthma; patients with other previous malignant disease within the last three years (except cervical carcinoma in situ, superficial or non-invasive bladder cancer, localised prostate cancer or basal cell or squamous cell carcinoma *in situ* previously treated with curative intent and endoscopically resected gastrointestinal cancers limited to the mucosal layer without recurrence); patients with active central nervous system metastases and/or carcinomatous meningitis; patients with unstable or unresolved surgical or chemotherapy-related toxicity; patients with active and serious autoimmune diseases requiring immunosuppressive treatment; patients with drug-induced interstitial lung disease or history of drug-induced pneumonitis requiring oral or intravenous corticosteroids; and those with previous organ transplantation.

2.3. Treatment

Participants received 1200 mg of bintrafusp alfa over 60 min of intravenous infusion within one to five days from enrolment. Treatment was administered at day 1 and day 14 (14 days ± 3 days) of a 28-day cycle. The treatment was administered for a maximum of two years or until disease progression, unacceptable toxicity, loss of clinical benefit, or patient-consent withdrawal. If pseudo-progression was suspected, patients could continue the treatment until loss of clinical benefit as judged by the principal investigator.

2.4. Outcomes and measures

During the screening phase, a physical examination, laboratory testing, electrocardiogram, and chest and abdomen computed tomography (CT) scan with intravenous contrast were conducted in all patients. Every two weeks, patients underwent a physical examination. Blood pressure and laboratory testing were performed on participants before treatment administration. Tumour assessment by chest and abdomen CT scan with intravenous contrast was conducted every eight weeks after initiating bintrafusp alfa. PFS was defined as the time from the start of bintrafusp alfa to the date of disease progression or death, whichever occurred first. OS was defined as the time from the start of bintrafusp alfa to death from any cause. ORR was defined as the percentage of patients with a confirmed complete or partial response, while disease control rate was defined as the percentage of patients with a confirmed complete or partial response or stable disease. Patients who were still alive at the time of data analysis were censored at the date of the last contact. We graded adverse events (AEs) according to the NCI Common Terminology Criteria for Adverse Events version 4.0. Safety was assessed in the as-treated population, which included all patients who received at least one dose of bintrafusp alfa.

Serum TGF-β levels were measured in the serum using an Enzyme-Linked Immunosorbent Assay (ELISA) with the Quantikine DB100C kit (R&D Systems), according to the manufacturer's instructions, at three timepoints: baseline (prior to treatment initiation), week 8 (first tumor assessment) and at tumor progression or end of treatment.

2.5. Statistical analysis and sample size

The study was designed to show that bintrafusp alfa would achieve a median PFS of 4.5 months with a statistical power of 90 % and a one-sided type I error of 10 %. On these bases and considering the Lachin design, 45 patients were needed over a period of 18 months with a minimum median follow-up of 12 months to perform an exponential test. Considering 5 % of dropout patients and a hazard of 0.04 for

dropouts, enrolling 47 patients was required for the study.

We used absolute frequencies and percentages to describe categorical variables and mean and standard deviation (SD) for quantitative variables (median and range when normality could not be assumed). We assessed PFS, OS, and 95 % confidence interval (CI) with the Kaplan-Meier product-limit method, using the log-rank test to compare curves for independent groups. We calculated two-sided P-values and set the statistical significance level at $P \leq 0.05$. We carried out all analyses using Stata 18.0 for Microsoft Windows (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC).

3. Results

3.1. Baseline characteristics and treatment information

A total of 47 patients were assessed for eligibility and 46 were finally analysed (Fig. 1). Most patients were male (36, 78.3 %) and the mean age was 70.0 years (SD, 9.5). The majority presented epithelioid histology (39, 84.8 %) and received bintrafusp alfa as the second-line of therapy (39, 84.8 %). The most common comorbidities were hypertension (21, 45.7 %) and dyslipidaemia (13, 28.3 %) (Table 1). The median follow-up of our cohort was 16.4 months (range, 0.2–24.6 months). The median number of bintrafusp alfa doses received was 4 (range, 1–21 doses) and the median duration of treatment was 56 days (range, 13–379 days). Patients terminated the treatment during the study period because of disease progression (38, 82.6 %), death (3, 6.5 %), toxicity (3, 6.5 %), or the principal investigator's decision (2, 4.4 %) (Fig. 1).

3.2. Efficacy: progression-free survival, objective response rate and overall survival

Of the 46 patients analysed, 43 (93.5 %) had disease progression during the follow-up period. The median PFS of our cohort was 1.9 months (95 % CI, 1.7–3.2 months) (Fig. 2). The median PFS for epithelioid PM was 1.9 months (95 % CI, 1.8–3.2 months), while in non-epithelioid PM was 1.8 months (95 % CI, 1.1 months-Not estimable; P = 0.473) (Fig. 3A). Similarly, the median PFS for second-line bintrafusp alfa was 1.9 months (95 % CI, 1.8–3.3 months), while in third-line therapy was 1.8 months (95 % CI, 0.7 months-not estimable; P = 0.096) (Fig. 3B).

The ORR was 6.5 % (95 % CI, 2.1 – 18.8 %, Table 2) and the disease control rate was 34.8 % (95 % CI, 22.2 – 49.9 %, Table 2). Three (6.5 %) patients showed partial response, 13 (28.3 %) stable disease, and 26 (56.5 %) progressive disease. Treatment response was not determined in 4 (8.7 %) patients. The median duration of bintrafusp alfa response was 3.8 months.

A total of 29 (63.0 %) patients died during the study period. The median OS was 11.9 months (95 % CI, 5.8–15.7 months) (Fig. 4). The median OS for epithelioid PM was 13.2 months (95 % CI, 6.2–15.7 months), longer than that of non-epithelioid PM (5.8 months; 95 % CI, 2.7-not estimable), although these differences were not statistically significant (P = 0.302) (Fig. 5A). The median OS for second-line bintrafusp alfa was 13.2 months (95 % CI, 11.5–24.2 months), whereas in third-line, it was significantly shorter (3.6 months; 95 % CI, 0.9-Not estimable; P = 0.003) (Fig. 5B).

Figure 1

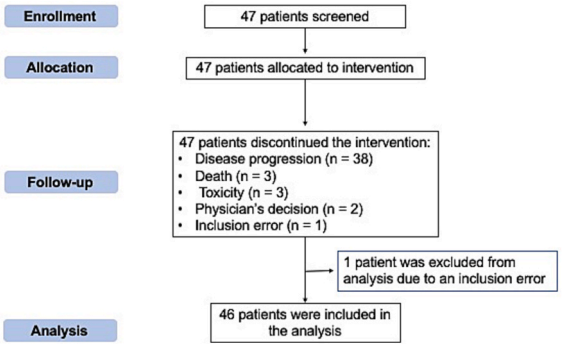

Fig. 1. Patient flow chart.

Table 1
Demographic and clinical characteristics of study participants.

	Total (n = 46)
Sex, *No.* (%)	
Female	10 (21.7)
Male	36 (78.3)
Age (years), *mean* (SD)	70.0 (9.5)
Smoking history, *No.* (%)	
Never (≤ 100 cigarettes/lifetime)	18 (39.1)
Former smoker (≥ 1 year)	22 (47.8)
Active smoker	6 (13.1)
Histology, *No.* (%)	
Epitheloid	39 (84.8)
Non-epitheloid	5 (10.9)
Mixed	3 (6.5)
Sarcomatoid	1 (2.2)
Desmoplastic	1 (2.2)
NOS / Undifferentiated	2 (4.3)
T Clinical Stage, *No.* (%)	
T1	9 (19.6)
T2	10 (21.7)
T3	8 (17.4)
T4	16 (34.8)
Unknown	3 (6.5)
N Clinical Stage, *No.* (%)	
Nx	1 (2.2)
N0	24 (52.2)
N1	14 (30.4)
N2	4 (8.7)
Unknown	3 (6.5)
M Clinical Stage, *No.* (%)	
M0	35 (76.1)
M1	8 (17.4)
Unknown	3 (6.5)
Bintrafusp line of therapy, *No.* (%)	
Second-line	39 (84.8)
Third-line	7 (15.2)
Most common comorbidities, *No.* (%)	
Hypertension	21 (45.7)
Dyslipidaemia	13 (28.3)
Diabetes mellitus	8 (17.4)
Chronic obstructive pulmonary disease	6 (13.0)
Benign prostatic hypertrophy	5 (10.9)
Asthma	3 (6.5)
Heart disease	3 (6.5)
Hypercholesterolemia	3 (6.5)
Vasculopathy	3 (6.5)

Abbreviations: NOS, not otherwise specified.

3.3. Safety

Table 3 summarises the recorded AEs related to treatment present in > 5 % of the population or grade ≥ 3. No grade 5 AEs were reported in our cohort. A total of 29 patients (63.0 %) presented treatment-related AEs. The most common AEs were pruritus (17, 37.0 %), anaemia (16, 34.8 %), and rash maculo-papular (8, 17.4 %). We did not observe any case of bleeding. Of the 120 reported AEs, 22 (18.3 %) were serious AEs, but most were grade 1 (75, 62.5 %) and grade 2 (29, 24.2 %). A total of 14 patients (11.7 %) had grade 3 AEs consisting of anaemia (n = 5), maculo-papular rash (n = 2), pruritus, diarrhoea, serum amylase increased, colitis, allergic reaction, acute kidney injury, and eczema (n = 1 each). Two patients (1.7 %) had grade 4 AEs consisting of lipase increase and adrenal insufficiency (n = 1 each).

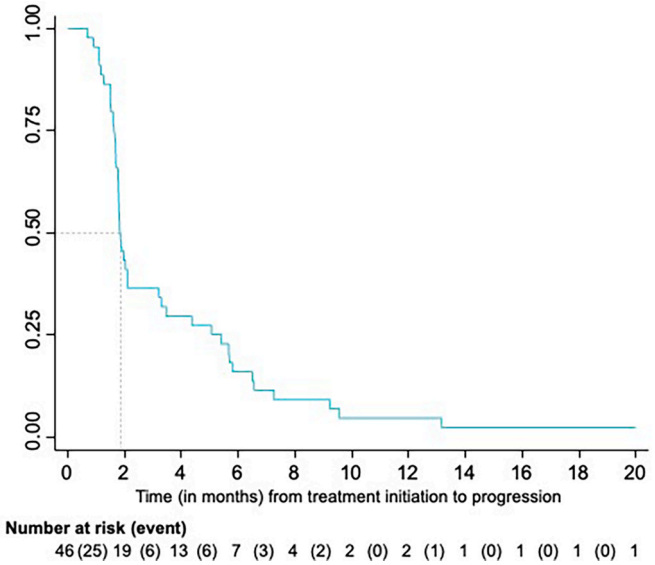

Fig. 2. Progression-free survival (PFS) of the cohort. Median PFS: 1.9 months (95 % confidence interval [CI]: 1.7–3.2 months; interquartile range: 1.7–5.4 months). Estimated probability of survival without disease progression at 6 months: 15.9 % (95 % CI: 7.0–28.1 %), at 12 months: 4.6 % (95 % CI: 0.8–13.6 %), and at 18 months: 2.3 % (95 % CI: 0.2–10.4 %).

3.4. TGF-β measurement in serum

Serum TGF-β levels were quantified by ELISA, revealing a significant reduction at the first tumor assessment (week 8) compared to baseline (Fig. 6**A**). At disease progression, most patients kept similar serum levels of TGF-β compared to week 8. These results suggest that, despite the limited efficacy observed in the study, bintrafusp alfa was able effectively reduced TGF-β levels. No significant differences in the TGF-β levels were observed at baseline among patients with a median PFS below 2 months or above 6 months (Fig. 6**B**).

Table 2
Efficacy outcomes.

Best Overall Response, No (%)	
CR	0
PR	3 (6.5 %)
SD	13 (28.3 %)
PD	26 (56.5 %)
NE	4 (8.7 %)
Overall response rate, % (95 % CI)	6.5 (2.1–18.8)
Disease control rate, % (95 % CI)	34.8 (22.2–49.9)
Median DoR, months	3.8
Median PFS, months (95 % CI)	1.9 (1.7–3.2)
Median OS, months (95 % CI)	11.9 (5.8–15.7)

Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; OS, overall survival; PR, partial response; SD, stable disease.

4. Discussion

This study evaluated the efficacy and safety of bintrafusp alfa in patients with PM who had progressed to platinum-based chemotherapy and had not previously received immunotherapy. Nearly all patients had disease progression during the study period and the median PFS was shorter than expected. More than half of the study participants died during the follow-up and the median OS was below one year, with a marked difference between epithelioid and non-epithelioid PM. The toxicity profile of bintrafusp alfa was manageable, although a non-negligible number of patients presented serious AEs.

The baseline characteristics of our study population were consistent with the Epidemiologic Spanish Malignant Mesothelioma Database (BEMME) [22]. The baseline characteristics of our study patients were also akin to those reported in the CONFIRM [23] and PROMISE-meso [24] trials, with the exception that in the CONFIRM trial, most patients received nivolumab or placebo as third-line of treatment. In contrast, in our study, patients were mainly treated with bintrafusp in second-line.

Despite the median PFS achieved in our cohort treated with bintrafusp alfa (1.9 months; 95 % CI, 1.7–3.2 months) was shorter than those reported for treatment with pembrolizumab (2.5 months; 95 % CI, 2.1–4.2 months) [24] and with nivolumab (3.0 months, 95 % CI,

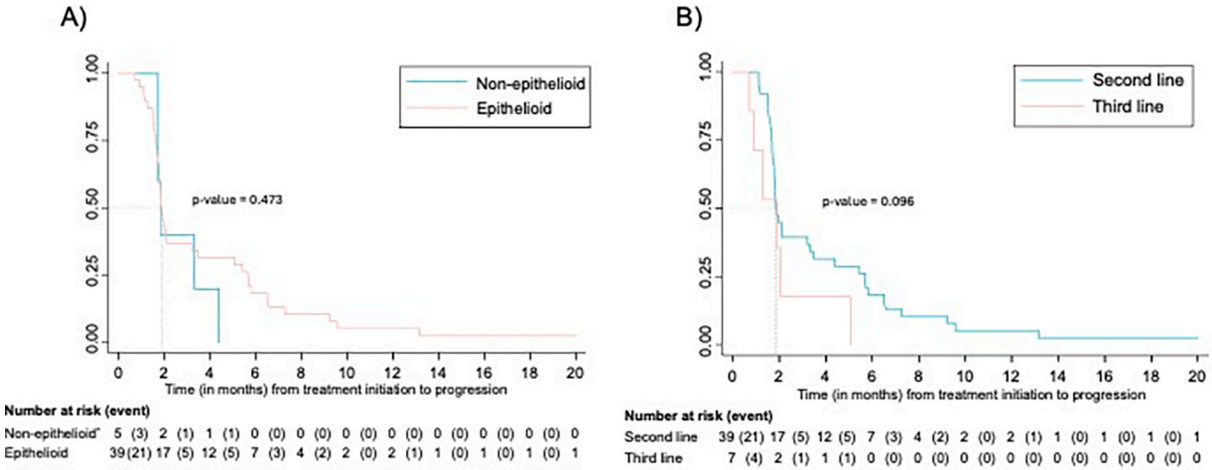

Fig. 3. Progression-free survival (PFS) of the cohort according to A) histology[a] and B) line of therapy. [a]Patients with "non-specified" histology (n = 2) were not included in this analysis. A) Median PFS for epithelioid mesothelioma: 1.9 months (95 % confidence interval [CI]: 1.8–3.2 months; interquartile range [IQR]: 1.6–5.7 months). Median PFS for non-epithelioid mesothelioma: 1.8 months (95 % CI: 1.1 months-not estimable; IQR: 1.7–3.3 months). For epithelioid mesothelioma, the estimated PFS rate at 6 months: 18.5 % (95 % confidence interval [CI]:8.1–32.1 %), at 12 months: 5.3 % (95 % CI: 0.9–15.6 %), and at 18 months: 2.6 % (95 % CI: 0.2–11.8 %). For non-epithelioid mesothelioma, the PFS rate at the 6, 12, and 18 months could not be estimated. B) Median PFS for second-line bintrafusp alfa: 1.9 months (95 % CI: 1.8–3.3 months; IQR: 1.6–5.7 months). Median PFS for third-line bintrafusp alfa: 1.8 months (95 % CI: 0.7 months-not estimable; IQR: 1.7–5.7 months). For second-line bintrafusp alfa, the estimated PFS rate at 6 months: 18.5 % (95 % CI: 8.1–32.1 %), at 12 months: 5.3 % (95 % CI: 0.9–15.6 %), and at 18 months: 2.6 % (95 % CI: 0.2–11.8 %). For third-line bintrafusp alfa, the PFS rate at the 6, 12, and 18 months could not be estimated.

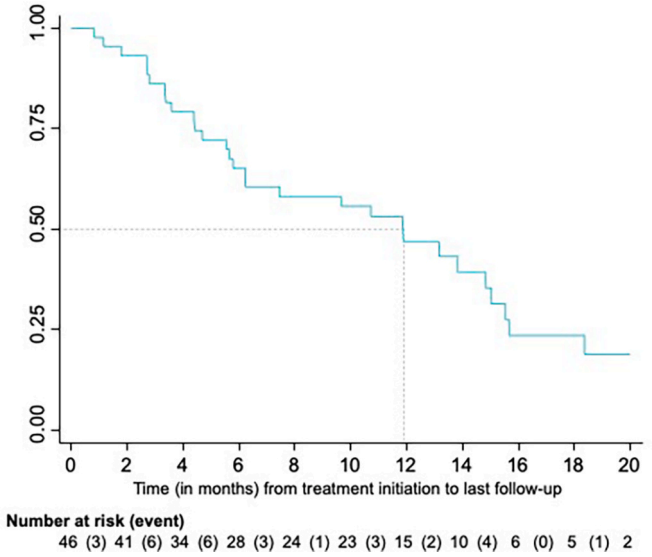

Fig. 4. Overall survival (OS) of the cohort. Median OS: 11.9 months (95 % confidence interval [CI]: 5.8–15.7 months; interquartile range: 4.4–15.7 months). Estimated probability of survival at 6 months: 65.3 % (95 % CI: 49.1–77.4 %), at 12 months: 47.0 % (95 % CI: 31.0–61.4 %), and at 18 months: 23.6 % (95 % CI: 10.4–39.9 %).

2.8–4.1 months) [23], there is an overlap with the confidence intervals reported in the three studies. Although no control arm treated was included in our study, the median PFS achieved in our cohort was similar to that of the placebo group in the CONFIRM trial (1.8 months; 95 % CI, 1.4–2.6 months) [23] but was shorter than the observed in the chemotherapy-treated group of the PROMISE-meso study (3.4 months; 95 % CI, 2.1–4.2 months) [24]. This would support the fact that treatment with bintrafusp alfa had limited efficacy and could be inferior to single-agent chemotherapy, such as gemcitabine or vinorelbine [25]. The lack of efficacy of bintrafusp alfa may be partly attributed to several factors. First, the dual role of the TGF-β pathway, not only promoting immune suppression but also exerting tumor-suppressive functions in certain contexts, may have limited its therapeutic benefit. Second, although a reduction of serum TGF-β levels was observed in most patients receiving bintrafusp alfa, this effect did not translate into meaningful clinical efficacy. This suggests that immune evasion may be driven by other cytokines beyond TGF-β, rendering a single-targeted approach insufficient. Third, the absence biomarker-based patient selection in this trial in this trial likely further limited the potential for therapeutic benefit.

The analysis by histology showed similar PFS for patients with epithelioid PM compared with those with non-epithelioid PM, which was in contrast with previous studies of other therapies. However, these differences were not statistically or clinically significant in previous clinical trials [11,23,24].

No patients showed a complete response to bintrafusp alfa, which was in line with trials evaluating pembrolizumab [24] and nivolumab [23]. Nonetheless, the ORR of bintrafusp alfa (6.5 %) was much lower than that reported for pembrolizumab (22 %) [24] and nivolumab (11 %) [23], being closer to the ORR for chemotherapy (6 %) [24]. Notably, the number of deaths in our study was very similar to that of other treatments [11,13,23,24], implying that the tested therapy did not seem harmful to the participants. The median OS achieved by our cohort was in agreement with that found for pembrolizumab [24] and for nivolumab [23]. The only statistically and clinically significant difference found in our study was in the OS between second- and third-line treatment with bintrafusp alfa, highlighting the need for effective therapies in patients with refractory disease.

Observed AEs were in agreement with those previously found in studies with bintrafusp alfa, except that a higher proportion of anaemia and a lower proportion of diarrhoea and decreased appetite were seen in our study [26,27]. This discrepancy could be explained by the similar sample size between our study and the phase I trial [26] and by the difference with the much larger population evaluated in the study comparing bintrafusp alfa with pembrolizumab [27]. Also in line with these previous reports [26,27], no grade 5 treatment-related AEs were recorded. However, while no bleeding events were observed in our study, they were rather common (36.4 %) in a previous study with bintrafusp alfa, where it was associated with TGF-β inhibition [27]. Again, this disagreement could be explained by the difference in sample size and differences in the tumour location.

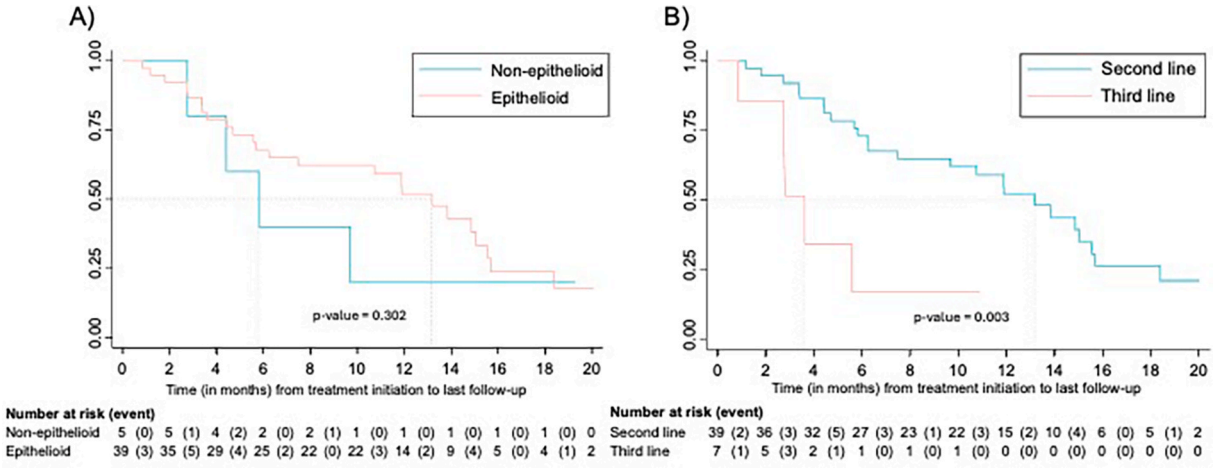

Fig. 5. Overall survival (OS) according to A) histology[a] and B) line of therapy. [a]Patients with "non-specified" histology (n = 2) were not included in this analysis. A) Median OS for epithelioid mesothelioma: 13.2 months (95 % confidence interval [CI]: 6.2–15.7 months; interquartile range [IQR]: 4.7–15.7 months). Median OS for non-epithelioid mesothelioma: 5.8 months (95 % CI; 2.7- not estimable; IQR: 4.4–9.7 months). For epithelioid mesothelioma, the estimated OS rate at 6 months: 67.8 % (95 % confidence interval [CI]: 50.3–80.3 %), at 12 months: 51.9 % (95 % CI: 34.0–67.1 %), and at 18 months: 23.8 % (95 % CI: 9.3–41.9 %). For for non-epithelioid mesothelioma, the estimated OS rate at 6 months: 40.0 % (95 % CI: 5.2–75.3 %), at 12 months: 20.0 % (95 % CI: 0.8–58.2 %), and at 18 months: 20.0 % (95 % CI: 0.8–58.2 %). B) Median OS for second-line bintrafusp alfa: 13.2 months (95 % CI: 11.5–24.2 months; IQR: 5.8–18.4 months). Median OS for third-line bintrafusp alfa: 3.6 months (95 % CI: 0.9- not estimable; IQR: 2.7–5.6 months). For second-line bintrafusp alfa, the estimated OS rate at 6 months: 73.1 % (95 % CI: 55.7–84.5 %), at 12 months: 52.1 % (95 % CI: 34.4–67.2 %), and at 18 months: 26.3 % (95 % CI: 11.4–43.8 %). For third-line bintrafusp alfa, the estimated OS rate at 6 months: 17.1 % (95 % CI: 7.9–52.6 %), while atthe 12 and 18 months could not be estimated.

Table 3
Treatment-related[a] adverse events (AEs) in the as-treated population.[b,c]

	Total (n = 47)				
	Any Grade[d,e]	Grade 1	Grade 2	Grade 3	Grade 4
Total[f], *No. (%)*	120 (100)	75 (62.5)	29 (24.2)	14 (11.7)	2 (1.7)
Pruritus, *No.* (%)	17 (37.0)	13 (28.3)	3 (6.5)	1 (2.2)	0 (0.0)
Anaemia, *No.* (%)	16 (34.8)	4 (8.7)	7 (5.2)	5 (10.9)	0 (0.0)
Rash maculo-papular, *No.* (%)	8 (17.4)	4 (8.7)	2 (4.3)	2 (4.3)	0 (0.0)
Fatigue, *No.* (%)	6 (13.0)	5 (10.9)	1 (2.2)	0 (0.0)	0 (0.0)
Other skin and subcutaneous disorders, *No.* (%)	6 (13.0)	6 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia, *No.* (%)	5 (10.9)	2 (4.3)	3 (6.5)	0 (0.0)	0 (0.0)
Epistaxis, *No.* (%)	4 (8.7)	4 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Rash acneiform, *No.* (%)	4 (8.7)	3 (6.5)	1 (2.2)	0 (0.0)	0 (0.0)
Diarrhoea, *No.* (%)	3 (6.5)	1 (2.2)	1 (2.2)	1 (2.2)	0 (0.0)
Creatinine increase, *No.* (%)	3 (6.5)	1 (2.2)	2 (4.3)	0 (0.0)	0 (0.0)
Lipase increase, *No.* (%)	3 (6.5)	2 (4.3)	0 (0.0)	0 (0.0)	1 (2.2)
Serum amylase increase, *No.* (%)	3 (6.5)	1 (2.2)	1 (2.2)	1 (2.2)	0 (0.0)
Arthralgia, *No.* (%)	3 (6.5)	2 (4.3)	1 (2.2)	0 (0.0)	0 (0.0)
Myalgia, *No.* (%)	3 (6.5)	2 (4.3)	1 (2.2)	0 (0.0)	0 (0.0)
Adrenal insufficiency, *No.* (%)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Colitis, *No.* (%)	1 (2.2)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)
Allergic reaction, *No.* (%)	1 (2.2)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)
Acute kidney injury, *No.* (%)	1 (2.2)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)
Eczema, *No.* (%)	1 (2.2)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)

[a] Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case-report form.
[b] The as-treated population included all patients who received at least one dose of bintrafusp alfa.
[c] No grade 5 adverse events were reported.
[d] Here are summarised the adverse events that occurred with a frequency ≥ 5 % or grade 3 or 4 AEs.
[e] Events are listed in descending order of frequency in the total population.
[f] Total number of adverse events regardless of frequency.

At the time of our study, a phase III trial comparing bintrafusp alfa and pembrolizumab for patients with non–small-cell lung cancer was being conducted. This work yielded a negative result, proving that bintrafusp alfa was not superior to pembrolizumab [27]. Our findings were consistent with those of other studies published in the last years demonstrating that bintrafusp alfa was not more beneficial than chemotherapy [27,28].

The main limitations of our study stem from its single-arm design and the absence of a control group. Another limitation was the relatively small sample size, particularly for non-epithelioid PM, which may hinder the generalizability of our results to larger studies.

5. Conclusion

Bintrafusp alfa did not reach the expected efficacy in patients with advanced PM who were previously treated with platinum-based chemotherapy. We did not identify new safety signals with bintrafusp alfa, and no case of bleeding was reported. Future correlative studies with the tissue and blood samples collected in the present study will help understand the role of TGF-β in the context of PM.

CRediT authorship contribution statement

Ernest Nadal: Writing – original draft, Supervision, Investigation, Conceptualization. **Paloma Martín-Martorell:** Writing – review & editing, Investigation. **Jose Carlos Benítez:** Writing – review & editing, Investigation. **Maria Ángeles Sala:** Writing – review & editing, Investigation. **Susana Cedrés:** Writing – review & editing, Investigation. **Carlos Álvarez:** Writing – review & editing, Investigation. **Manuel Dómine:** Writing – review & editing, Investigation. **Elia Sais:** Writing – review & editing, Investigation. **Maria Saigí:** Writing – review & editing, Investigation. **Rafael López:** Writing – review & editing, Investigation. **Laia Vilà:** Writing – review & editing, Investigation. **Bartomeu Massutí:** Writing – review & editing, Investigation. **Rosario García-Campelo:** Writing – review & editing, Investigation. **Andres Mesas-Ruiz:** Writing – review & editing, Investigation. **Amelia Insa:** Writing – review & editing, Investigation. **Sílvia Plans-Marín:** Conceptualization, Investigation, Visualization. **Sara Hijazo-Pechero:** Investigation, Visualization. **Cristina Muñoz-Pinedo:** Investigation, Visualization, Writing – review & editing. **Jesús Brenes:** Writing – review & editing, Investigation. **Mariano Provencio:** Writing – review & editing, Investigation.

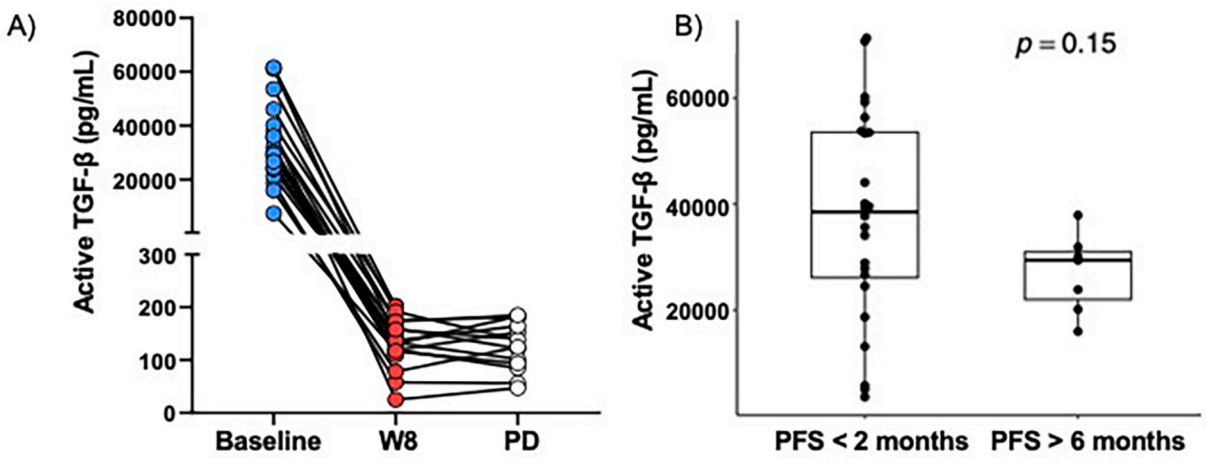

Fig. 6. Quantification of serum TGF-β in patients participating in the study. A) Serum active TGF-β levels at three timepoints: baseline, tumor assessment at week 8 (W8) and at progressive disease (PD), in patients with available samples from all timepoints. A statistically significant reduction in serum TGF-β levels was observed between baseline and week 8 ($p = 4.8 \times 10^{-7}$), as determined by a paired Wilcoxon test. B) Baseline serum active TGF-β levels at baseline comparing patients who experienced early progression with those who had a median PFS greater than 6 months.

Funding

This study was sponsored by the Spanish Lung Cancer Foundation (Fundación GECP) and financially supported by Merck (CrossRef Funder ID: https://10.13039/100009945).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ernest Nadal received research funding from Roche, Pfizer, Merck-Serono, Nanostring, and Bristol Myers Squibb (BMS), participated in advisory boards or received honoraria from Roche, BMS, Merck Sharp & Dohme (MSD), Merck-Serono, Sanofi, Pfizer, Lilly, Janssen, Amgen, Daiichi-Sankyo, Boehringer-Ingelheim, AstraZeneca, Takeda, Sanofi, Pierre Fabre, Qiagen, Apollomics, Genmab and Janssen, and received travel support from Roche, Takeda, Janssen, and MSD. Paloma Martín-Martorell received support for attending meetings and/or travel from Roche, Takeda, MSD, AstraZeneca, and Pfizer. Maria Ángeles Sala received payment or honoraria from AstraZeneca, Pfizer, Deciphera, and Roche, received support for attending meetings and/or travel from Roche, Pfizer, AstraZeneca, and PharmaMar, and participated in advisory boards of Roche. Susana Cedrés received consulting fees from Amphera, received payment or honoraria from BMS, Roche, and Pfizer, is the recipient of a grant from F. Hoffmann-La Roche, received support for attending meetings and/or travel from BMS and Roche, and participated in advisory boards of Amphera. Manuel Dómine received consulting fees from AstraZeneca, BMS, MSD Oncology, PharmaMar, Pfizer, Roche, and Takeda, received payment or honoraria from AstraZeneca, BMS, MSD Oncology, Pfizer, Roche, and Takeda, and received support for attending meetings and/or travel from AstraZeneca, MSD Oncology, Pfizer, and Takeda. Elia Sais received payment or honoraria from Roche, AstraZeneca, and BMS, received support for attending meetings and/or travel from Roche, Takeda, and BMS, and participated and advisory boards of BMS. Rafael López received payment or honoraria from Takeda, AstraZeneca, Amgen, BMS, Roche, and Pierre-Fabre, and received support for attending meetings and/or travel from Roche, AstraZeneca, MSD, Takeda, and Merck Serono. Laia Vilà received payment or honoraria from Regeneron, BMS, and AstraZeneca, and received support for attending meetings and/or travel from Takeda and MSD. Bartomeu Massutí received consulting fees from AstraZeneca and Amgen, received payment or honoraria from Roche, BMS, and MSD, received support for attending meetings and/or travel from MSD and AstraZeneca, and has a leadership or fiduciary role in the Spanish Lung Cancer Group and the Lung Ambition Alliance.

Acknowledgements

We thank the clinical research team of the Spanish Lung Cancer Group (GECP) for their study support. EN received support from Instituto de Salud Carlos III (PI21/00789 and INT22/00066), co-funded by European Regional Development Fund. ERDF, a way to build Europe. The authors are grateful to Joaquim Moreno from the Bellvitge Biomedical Research Institute (IDIBELL) for storing the patients' samples collected during the study. The authors thank the CERCA Program/Generalitat de Catalunya for institutional support. We thank Matías Rey-Carrizo at BCN Medical Writing for his editorial and medical writing support, which was funded by the GECP in accordance with Good Publication Practice (GPP 2022) guidelines.

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