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European Journal of Cancer 180 (2023) 117–124

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Immune checkpoint blockers in patients with unresectable or metastatic thymic epithelial tumours: A meta-analysis

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Received 13 October 2022; received in revised form 24 November 2022; accepted 5 December 2022
Available online 12 December 2022

KEYWORDS
Immune checkpoint blockers;
Advanced thymic epithelial tumours;
Pembrolizumab;
Nivolumab;
Atezolizumab;
Avelumab

Abstract ***Background:*** For patients with advanced thymic epithelial tumours (TET), there is no standard second-line treatment after platinum-based chemotherapy. Although immune checkpoint blockers (ICB) are a potential treatment strategy, their efficacy seems limited with an increased risk of immune-related adverse events (ir-AEs), thus hampering their application in daily clinical practice.
Methods: We performed a meta-analysis to better evaluate the existing evidence about the activity and safety of ICB in the setting of unresectable or metastatic advanced TET previously treated with platinum-based chemotherapy.
Results: Six phase I/II trials met the eligibility criteria including a total of 166 evaluable patients (77% thymic carcinoma, 23% thymoma) evaluable for activity after being treated with pembrolizumab, nivolumab, avelumab or atezolizumab. The overall response rate to ICB

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https://doi.org/10.1016/j.ejca.2022.12.005

was 18.4% (95% CI: 12.3–26.5), and the one-year progression-free survival rate and one-year overall survival rate were 26.0% (95% CI: 19.6–34.6) and 66.9% (95% CI: 59.6–75.2%), respectively. The incidence of grade 3–5 ir-AEs was 26.4%, with 17.1% in thymic carcinoma and 58.3% in thymoma.

Conclusions: Despite the absence of a robust demonstration of efficacy in the context of randomised trials, our results suggest ICB as a potential strategy in patients with pretreated TET, mainly among patients with thymic carcinoma. Close monitoring is strongly advised to detect severe immune-toxicity.

1. Introduction

Thymic epithelial tumours (TET) encompass a group of rare and heterogeneous intrathoracic malignancies. TETs are histologically classified according to the World Health Organisation as thymomas (T) subtypes A, AB, B1, B2, B3 or thymic carcinoma (TC) and thymic neuroendocrine tumours [1]. The histologic classification of TETs in T and TC has prognostic value and correlates with the risk of autoimmune disorders (AID). The risk to be diagnosed in an advanced stage increases with a higher histological subtype, with the highest risk for TC which has a greater tendency for metastatic spread [2]. In contrast, the risk of AID, reported in up to one-third of patients with TET, is higher in low-grade thymomas (i.e. from A to B2), being very uncommon in TC (<5%). Myasthenia gravis is the most common AID associated with TETs, although many other AIDs have been reported [3]. For those patients with advanced TET non-eligible for a loco-regional treatment, platinum-based chemotherapy remains the standard of care treatment in the first-line setting. For patients with disease recurrence who have already received at least one line of chemotherapy, there is no standard treatment in the second line and beyond. Unfortunately, in contrast with oncogene-driven non-small cell lung cancer (NSCLC), a personalised treatment approach is not yet a reality in TET. Although 10% of TC may have a c-*KIT* mutation, imatinib (a c-KIT inhibitor) did not result in responses in unselected patients with TET [4]. Chemotherapy, mTOR inhibitors and antiangiogenic drugs have been accepted as potential treatment strategies in the platinum-refractory setting [5,6]. Indeed, for patients with non-resectable recurrences, several consecutive lines of therapy may be administered, which positively impact patients' outcome [7,8]. The immune checkpoint blockers (ICB) are the most recent therapeutic strategies assessed in patients with TETs. ICB have been tested in several tumour types, and numerous studies have correlated the efficacy of ICB with the expression of the programmed-death ligand-1 (PD-L1) in the tumour. Because of the high PD-L1 expression in TET, mainly in TC [9–11], ICB were expected to achieve a breakthrough therapy in these tumours mirroring the data reported in other thoracic malignancies. In the setting of pretreated advanced TET, mainly among patients with TC but also in patients with thymoma, ICB, such as pembrolizumab [12–14], nivolumab [15,16], avelumab [17] and atezolizumab [18], have been tested, yielding a clinical activity. However, concerning rates of severe immune-related adverse events (ir-AEs) have been observed during treatment with ICB secondary to abnormal immune responses promoted by these drugs. The risk–efficacy ratio of ICB must be balanced before the widespread application of this therapeutic strategy in daily clinical practice. Therefore, we performed a systematic review and meta-analysis to obtain a comprehensive evaluation of the clinical outcomes and the risk of ir-AEs with ICB in the setting of pre-treated TET.

2. Methods

We performed a systematic review of the literature to identify clinical trials that tested ICB (anti-programmed cell death protein-1 [anti-PD-1] or anti-programmed cell death protein (ligand)-1 [anti-PD(L)-1]) in TET. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19].

2.1. Eligibility criteria

To be included in the meta-analysis potentially eligible studies had to satisfy the following criteria: (i) prospective clinical trials studying anti-PD(L)-1 as monotherapy, (ii) patients with unresectable or metastatic pretreated TET, (iii) available information on efficacy endpoints and (iv) published or presented before June 2022. Histologies other than thymoma or TC were not included in this meta-analysis. All studies that met the inclusion criteria were selected for the analysis.

2.2. Search strategy

PubMed database was used to identify all potential eligible published studies. Additionally, a review of

conference proceedings from the European Society of Medical Oncology (ESMO) congress and the American Society of Oncology (ASCO) annual meeting up to the same time period was also conducted to identify relevant unpublished studies (more details in Supplement Fig. 1).

2.3. Collected data

The following variables were extracted if available: name of the first author, year of publication, study sample size, specific ICB used, number of patients with objective response rate (ORR: complete and partial response, CR and PR) and with disease control rate (DCR: CR, PR and stable disease, SD), all progression-free survival (PFS) and overall survival (OS) outcomes and frequency of any grade ir-AEs.

2.4. Endpoints and statistical analysis

To summarise evidence from published studies, an overall estimation was calculated for (i) ORR, (ii) DCR, (iii) 6- and 12-month of PFS, (iv) 6- and 12-month of OS and (v) grade ≥3 ir-AEs. For binary endpoints (ORR, DCR and ir-AEs), a random effect model with logit transformation was fitted to estimate the overall proportion along with the 95% confidence interval (95% CI). The amount of heterogeneity was calculated by means of the I^2. For survival endpoints (PFS and OS), we used the published survival curves to reconstruct individual patient data [20] in order to calculate the pooled estimation using the Kaplan–Meier method along with the 95% CI. Risks of bias of included trials and publication bias were not assessed due to the lack of randomisation [21]. All analyses were undertaken using R statistical software.

3. Results

Six phase I/II trials met the eligibility criteria and were included in the analysis: two trials with pembrolizumab [12–14]; two trials with nivolumab [15,16]; one trial with avelumab [17]; other trail with atezolizumab (only efficacy data available for the thymoma cohort of this basket study) [18]. A total of 166 patients with TET were enrolled, of whom 164 were evaluated for safety and 158 patients were evaluable for efficacy endpoints as outcome data were available.

Table 1 summarises population characteristics and reported results for the selected trials. Most of the patients received ICB as third-line treatment or beyond. The median age was 56.8 years, most patients were males (68%), and 38 patients had a T and 128 a TC.

The ORR in patients treated with ICB was 18.4% (95% CI: 12.3–26.5; I^2 = 14%), and the DCR was 72.8% (95% CI: 65.3–79.2; I^2 = 0%) with 115 out of 158 patients having CR, PR or SD as a best response (Fig. 1A and B, n = 158). In terms of PFS (n = 150), the 6-month PFS estimation ranged from 28.0% to 76.9%, with an overall 6-month PFS estimation of 51.7% (95% CI: 44.2–60.5). The 12-month PFS estimation ranged from 9.0% to 46.1% with an overall estimation of 26% (95% CI: 19.6–34.6) (Fig. 1C and D). Regarding the OS endpoint (n = 150), the 6-month OS was above 78% in all the studies being 83.2% (95%C: 77.3–89.4) in the pooled estimation. The 12-month OS

Table 1
Clinical trials testing immune checkpoint blockers as monotherapy in patients with pre-treated advanced thymic epithelial tumours.

Study	Agent	N	Male/female (%)	Median age (y)	Previous therapy	TC/T	ORR (%)	PFS (mo.)	OS (mo.)	G3-4 ir AEs (%)
Giaccone [12,13]	**Pembrolizumab** 200 mg Q3W. **EP:** RR	41	70/30	57	2 (1–6)[a]	41/0	22.5	4.2	25.4 1-y OS: 71%	15
Cho [14]	**Pembrolizumab** 200 mg Q3W. **EP:** RR	33	64/36	57	≥2 (57.6%)	26/7	19.2/28.6	6.1/6.1	14.5 vs. NR 1-y OS: NR	15.4/71.4
PRIMER[b] [15]	**Nivolumab** 3 mg/kg Q2W. **EP:** RR	15	80/20	55	≥2 (73.3%)	15/0	0	3.8	14.1 1-y OS: 60%	13.3
NIVOTHYM Cohort 1[c] [16]	**Nivolumab** 240 mg Q2W. **EP:** PFS-6	55	64/36	58	≥1 (100%)	45/10	12	6.0	21.3 1-y OS: 68%	26
Rajan [17]	**Avelumab** 10–20 mg/kg Q2W	8	63/37	53	3.5 (2–10)[a]	1/7	0/57	NA	NA	38
Tabernero[d] [18]	**Atezolizumab** 1200 mg Q3W	14	54/46	61	≥2 (61.5%)	0/14	38.5	11.7	NE	35.7

TC: thymic carcinoma; T: thymoma; RR: response rate; PFS: progression-free survival; PFS-6: progression-free survival at six months; OS: overall survival; G3-4 ir-AEs: grade 34 immune-related adverse events; Y.: years; EP: endpoint of the trial; NR: not reached; NA: not available; NE: not estimable; Q3W: every 3 weeks; Q2W: every 2 weeks.
In the Cho trial [14], 28.6% of patients with T and 3.8% of patients with TC had myasthenia gravis.
[a] Median number and range of previous therapies (in the NIVOTHYM trial [16], 100% of patients had received at least one previous line of platinum-based chemotherapy). In Cho *et al.*, the RR, PFS and OS are reported: thymic carcinoma versus thymoma.
[b] Study was closed prematurely, and no responses were found.
[c] Cohort 1 did not achieve the prespecified 6-month PFS of 40% (6-month PFS: 35%).
[d] The safety efficacy population was 13 patients with thymoma. This sub-cohort did not progress to stage II for safety reasons.

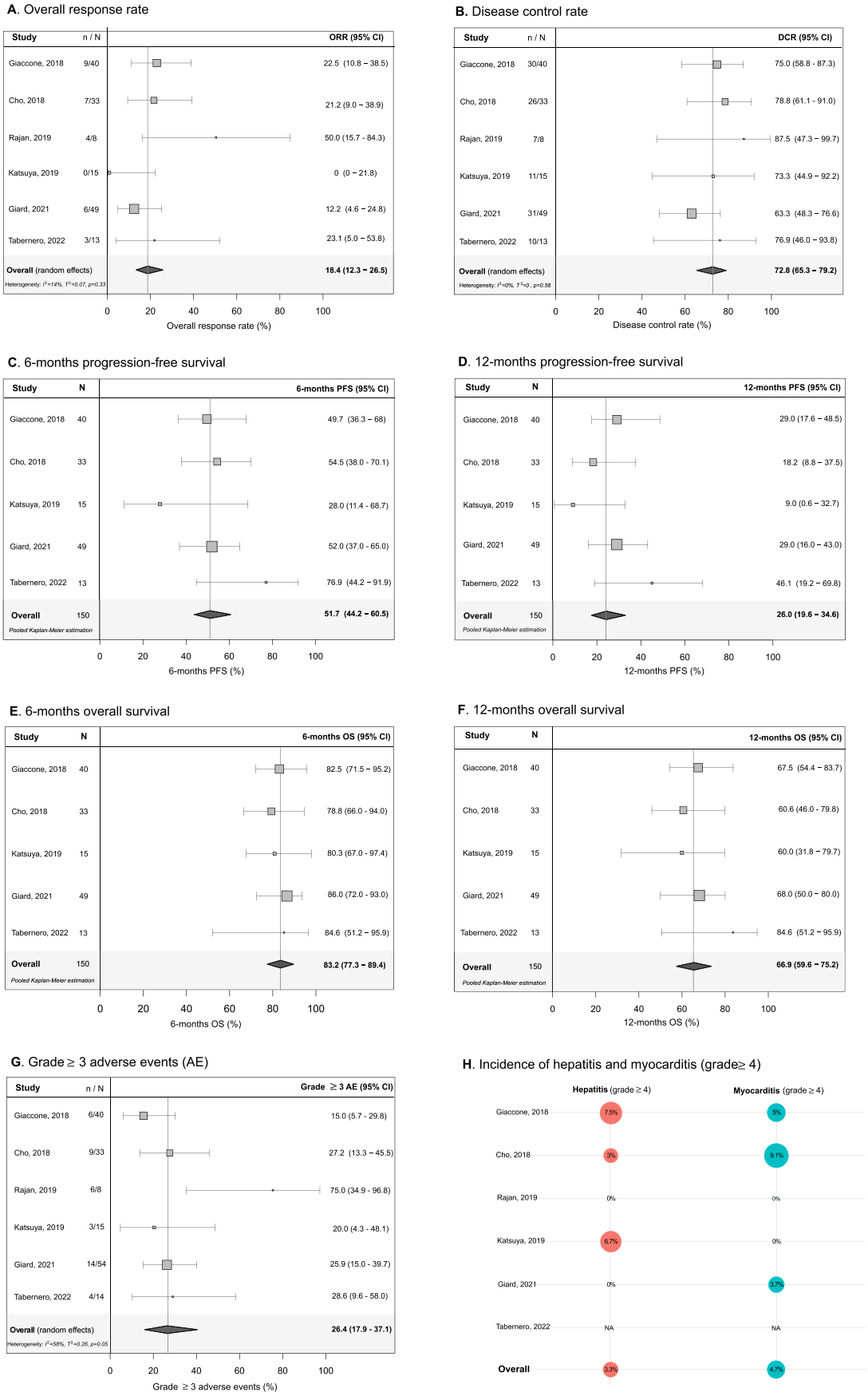

Fig. 1. In patients treated with immune checkpoint blockers, the overall response rate and disease control rate (A–B, n = 158); the 6- and 12-month progression-free survival (C–D, n = 150); the 6- and 12-month overall survival (E–F, n = 150); the treatment-related grade 3 or higher AEs (G), frequency to develop hepatitis or myocarditis (grade 4–5 AEs, H).

Table 2
Ongoing clinical trials with immune checkpoint blockers in patients with advanced thymic epithelial tumours (TET). RR: response rate; PFS: progression-free survival; Q3W: every 3 weeks; Q2W: every 2 weeks.

Trial	Treatment	Endpoint
NCT03076554	Avelumab 10 mg/kg Q2W	RR by RECIST and safety
NCT04321330	Atezolizumab 1200 mg Q3W	RR by RECIST
NCT04469725	KN046 5 mg/kg Q2W	RR by RECIST
NCT04417660	Bintrafusp alfa 1200 mg Q2W	RR by RECIST
NCT03134118	Nivolumab 240 mg Q2W + ipilimumab 1 mg/kg Q6W 1 year	PFS rate at 6 months
NCT03463460	Pembrolizumab 200 mg Q3W + sunitinib 50 mg 2 weeks on/1 week off	RR by RECIST
NCT04710628	Pembrolizumab 200 mg Q3W + lenvatinib 20 mg QD	PFS rate at 5 months

was 66.9% (95% CI: 59.6–75.2) with an individual trial estimation range from 60% to 84.6% (Fig. 1E and F).

For patients with data available, the ORR was 33.3% (95% CI: 17.2–54.0) for those with T (n = 23) and 17.1% (95% CI: 10.0–27.3) for those with TC (n = 82).

In terms of safety profile, 26.4% of patients with TET developed a grade 3 or higher ir-AE (Fig. 1G). However, the percentage of grade ≥3 ir-AEs was higher in patients with T (58.3%, n = 28) compared with patients with TC (17.1%, n = 82). An extensive analysis was carried out to estimate the frequency to develop hepatitis or myocarditis (grade 4–5 AEs). Overall, the risk of grade ≥ 4 hepatitis was 3.3%, and the risk of myocarditis grade ≥ 4 was 4.7% (Fig. 1H). One grade 5 AEs was reported in one patient with T.

4. Discussion

This meta-analysis does not support ICB as a potent treatment option for patients with low-grade thymomas progressing after platinum-based chemotherapy given the risk of grade ≥3 ir-AEs. This treatment option should be restricted to patients with TC and patients with AID should be excluded from this strategy.

In this meta-analysis, the ICB achieved an ORR and DCR that mirrors the data reported in the third-line setting and beyond with other potential therapeutic strategies, including chemotherapy or sunitinib according to real-world databases, with an ORR in TC of 18% and median PFS of 6–7 month [7,8]. Of note, the ORR was the primary endpoint in three out of six trials included in the current meta-analysis [12,14,15]. However, due to the metastatic spread pattern of TET in the pleura or mediastinum, it is not always feasible to assess the response rate by RECIST criteria in this disease. Similarly, many TET, mainly thymomas, show slow growth and therefore stable disease as the best response cannot be considered as proof of the actual efficacy of therapies. This may explain why despite the low ORR, the DCR on ICB in TET is >70%, suggesting a potential selection of patients with slowly progressive disease. Finally, the ORR under ICB may poorly correlate with the 6-month PFS or the 12-month OS rates [22]. This could explain the 12-month OS > 65% reported in the meta-analysis, despite an ORR below 20%. Therefore, other surrogate endpoints, such as 6-month PFS or the 12-month OS rates, would be more suitable in future clinical trials for assessing the efficacy of ICB in these malignancies. In this regard, despite the limitation of the exercise of cross-trial comparisons, the 12-month PFS and OS rate within ICB reported in the current meta-analysis is similar to the 12-month PFS rate of ~20%, and the 12-month OS rate of 50%–~65% achieved in real-world populations with the currently available treatment strategies in second- or third-line setting, such as chemotherapy or targeted therapies (such as sunitinib or everolimus) [7,23]. However, in a phase II trial, lenvatinib (a multi-kinase inhibitor with antiangiogenic properties) tested in patients with previously treated TC reported a 12-month PFS and OS rates of 41% and 83%, respectively [24]. In a real-world population (N = 29), lenvatinib resulted in similar outcomes with a 12-month PFS and OS of 30% and 79%, respectively [25], supporting the role of antiangiogenic agents in this disease. Although ICB are not better than the current available therapeutic strategies, our current meta-analysis supports that ICB may enlarge the number of potential treatment strategies available for this population. In contrast to other thoracic malignancies, patients with TET are younger, in good medical condition and without co-morbidities, allowing to receive several subsequent treatment lines after the initial platinum-based chemotherapy, which may positively impact on patients' survival. As an example, patients with TC exclusively treated with subsequent systemic treatments, not including ICB, may achieve a median OS of 32.9 months (95% CI: 20.6–45.1) [8]. This outcome could be potentially enlarged with the ICB, as pembrolizumab has reported long-term survivors in patients with TC, with 18% of patients alive at five years, supporting ICB as a feasible therapeutic strategy in this malignancy [13]. The identification of predictive biomarkers is an urgent challenge in this disease. The PD-L1 expression has been correlated with better response rate and outcome on pembrolizumab in patients with TC [12,14], and alterations in genes or pathways that correlated with PD-L1 expression (CYLD and BAP1) could be also potential predictive biomarkers in TC [26]. However, the evidence remains limited due to small sample size and probably

the PD-L1 expression should not be considered a predictive biomarker, as PD-L1 expression is a hallmark of any epithelial cell originating from the thymus, thus not reflecting the presence of an antitumour immune response [26]. Similarly, the TET have the lowest tumour mutational burden of all adult cancers (average of 0.48 mutations per megabase, with a significant increase in the tumour mutational burden in TC compared with thymoma), and microsatellite instability is uncommon in TET [27,28] not supporting their utility as predictive biomarkers of ICB efficacy in this malignancy. Finally, the tumour microenvironment analysis in TET based on flow cytometric data revealed that type B3-thymoma and TC belonged to the hot cluster to be targeted for anti-tumour immunotherapy [29].

We report that the ORR is higher in T than TC. However, one limitation of our meta-analysis is that due to the lack of efficacy data available, we could not provide difference in the outcome according to the TET histologic subtype (thymomas versus TC). Although our meta-analysis reports that patients with T may experience clinical benefit with ICB, the benefit is limited by the prohibitive increased risk of toxicity [14,17,18]. Some of these trials allowed patients with previous AID or low-grade T (<B3-thymoma) [14,17], which may explain the rate of grade 3–5 ir-AEs of 58.3% in this population, as ICB may induce an exacerbation of pre-existing AID in up to 35% of cases and induce *de novo* ir-AEs in other third of patients [30]. For this reason, patients with low-grade T or with AID must be excluded from the ICB strategy. Likewise, in the NCCN guidelines, the ICB are being integrated as a potential treatment strategy in patients with previously treated TC [31]. However, even in this population, the safety is of concern, as the incidence of grade 3–4 ir-AEs in our meta-analysis in TC reached 17.1%, including polymyositis and myocarditis [12]. This incidence is higher than expected in comparison with the incidence grade 3–4 ir-AEs reported in other thoracic malignancies such as NSCLC when treated with ICB (<10%) [32]. Therefore, in patients with TC, the ICB should not be delivered in an off-label setting and should be more considered a potential option rather than a standard of care, which requires close monitoring of patients.

The results of our meta-analysis could serve as a benchmark to evaluate the additive efficacy of the ICB in combination with other strategies, especially with multi-tyrosine kinase inhibitors with antiangiogenic properties [24] and others, which are being tested in several ongoing clinical trials (Table 2). Recently, in the phase II CAVEATT study, the combination of avelumab and axitinib in B3-thymoma and TC resistant to chemotherapy reported an ORR of 34% and 12-month PFS and OS rate of 29% and 83%, respectively, with 12% of patients reporting severe ir-AEs [33]. This data support the potential benefit of combo-immune strategies without increasing the percentage of severe toxicity as compared with ICB as monotherapy in this population. The ongoing multicentre PECATI trial (NCT04710628), testing the combination of pembrolizumab and lenvatinib in a similar patient population, will provide further evidence on the activity of the combination of ICB plus antiangiogenic agents. However, the potential role of these strategies in the first-line setting remains unknown.

In conclusion, the current meta-analysis provides insights about the potential role of ICB as a therapeutic approach in a subset of patients with previously treated advanced TET, mainly those with TC. Patients with B3-thymoma could also be considered after a strict initial work up ruling out AID, but not low-grade T as the risk of severe toxicity is prohibitive. Close monitoring of patients is strongly advised to detect severe ir-AEs. To improve the efficacy of ICB, combination strategies are being explored, and further assessment of predictive biomarkers for response and risk of ir-AEs are warranted.

Financial support

Not applicable. We did not receive any external financial support.

Author contribution

Jordi Remon: conceptualisation, methodology, formal analysis, validation, writing original draft.

Guillermo Villacampa: methodology, formal analysis, writing, review and editing.

Francesco Facchinetti: conceptualisation, review and editing.

Marcello Tiseo, Florit Marcuse, Massimo di Maio, Monique Hochstenbag, Lizza Hendriks, Benjamin Besse: review and editing.

Conflict of interest statement

None of all authors have declared any conflict of interest that may inappropriately influence this manuscript. Others are reported below.

JR: reports advisory from MSD, Boehringer, Janssen. Speaker: Janssen. Travel: Pfizer, personal fees and other from OSE immunotherapeutics, BMS, AstraZeneca, Roche, Bayer, Sanofi, Takeda, outside the submitted work.

FF: reports editorial activities from Roche and BMS outside the submitted work.

LL: reports other from Boehringer Ingelheim, other from BMS, other from Roche Genentech, grants from Roche Genentech, grants from Boehringer Ingelheim, other from AstraZeneca, personal fees from Quadia, grants from AstraZeneca, other from Eli Lilly, other from Roche Genentech, other from Pfizer, other from

MSD, other from Takeda, non-financial support from AstraZeneca, non-financial support from Novartis, non-financial support from BMS, non-financial support from MSD/Merck, non-financial support from GSK, non-financial support from Takeda, non-financial support from Blueprint Medicines, non-financial support from Roche Genentech, other from Amgen, non-financial support from Janssen Pharmaceuticals, non-financial support from Mirati, outside the submitted work.

BB: Dr. reports grants from Abbvie, grants from Amgen, grants from AstraZeneca, grants from Biogen, grants from Blueprint Medicines, grants from BMS, grants from Celgène, grants from Eli-Lilly, grants from GSK, grants from Ignyta, grants from IPSEN, grants from Merck KGaA, grants from MSD, grants from Nektar, grants from Onxeo, grants from Pfizer, grants from Pharma Mar, grants from Sanofi, grants from Spectrum Pharmaceuticals, grants from Takeda, grants from Tiziana Pharma, outside the submitted work.

MT, MdM, GV, FM, MH: have not reported additional COI outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.12.005.

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