HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 3, e1902723 (6 pages)
https://doi.org/10.1080/21645515.2021.1902723

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MELANOMA IMMUNOTHERAPY SF – RESEARCH PAPER

Immune checkpoint inhibitors in adjuvant setting after radical resection of melanoma: a meta-analysis of the pivotal trials

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ABSTRACT

Beyond the overall relapse-free survival (RFS) advantage demonstrated in randomized trials (RCT) of adjuvant anti-PD-1 immunotherapy in radically resected stage III–IV melanoma, key issues about subgroups of interest have been raised in recent years, with non-conclusive results when considering single studies. In the present meta analysis, we pooled all RCT data in this setting, analyzing, overall, 3043 patients. The RFS benefit of adjuvant immunotherapy over the comparator (placebo or anti-CTLA-4) was strongly confirmed in the pooled analysis, and it was statistically significant in most subgroups, excluding patients with stage IIIA and stage IV M1c melanoma. Nevertheless, the relative benefit was not statistically significantly different when considering their IIIB-IIIC and M1a-M1b counterparts. Future trials in this setting should consider subgroups of interest for tailoring the adjuvant strategy in terms of duration and drug combination in light of literature data.

ARTICLE HISTORY
Received 30 December 2020
Revised 13 February 2021
Accepted 7 March 2021

KEYWORDS
Melanoma; immune checkpoint inhibitors; anti-PD-1; immunotherapy; adjuvant; perioperative; ICI; nivolumab; pembrolizumab; ipilimumab

Introduction

A few years ago, the therapeutic path of patients undergoing resection of infiltrating melanoma was concluded with complete lymph node dissection (CLND) in cases with metastatic sentinel lymph node.[1,2] Only a limited subgroup of patients were candidates to adjuvant therapy with high- or low-dose interferon-α, being the only available systemic intervention to prevent the distant relapse in this disease.[3–6] In both cases, the outcome in terms of overall survival (OS) was not improved in the majority of studies, and the benefit in terms of relapse-free survival (RFS) was not consistent across several prospective trials, leading to the current negative recommendation of guidelines in the case of CLND and the frequent abandonment of the adjuvant strategy with interferon-α.[7]

In 2015, the U.S. Food and Drug Administration (FDA) approved the anti-CTLA-4 ipilimumab as adjuvant therapy for stage III melanoma patients. The approval was granted based on the first pivotal trial in this setting, demonstrating the advantage of ipilimumab over placebo in obtaining longer RFS, higher rates of OS, and distant metastasis-free survival (DMFS) than placebo after surgery.[8] Since then, two anti-PD-1 immune checkpoint inhibitors (ICI) have been tested versus placebo or ipilimumab itself, to reduce the risk of recurrence following radical resection of melanoma, in certain cases also including metastatic patients with stage IV disease, rendered disease-free with radical surgery.[9–11] To date, the approved ICI drugs in this setting include nivolumab and pembrolizumab, becoming the new standard of therapy, even in the lack of adequate follow-up. Moreover, definite OS results are still missing, suggesting the likely comparable survival gain for the anti-CTLA-4 and the anti-PD-1 strategy, but with a toxicity profile favoring the latter.[9,12–14]

Beyond the clear overall advantage demonstrated in each trial, key issues about subgroups of interest have been raised in recent years, especially in sight of the radical update of the American Joint Committee on Cancer (AJCC) staging system for this disease, from the 7th version to the 8th, partially reclassifying the stages included in the adjuvant trials.[15–17] One of the crucial issues is the inclusion of the current IIIA stages in the adjuvant immunotherapy indication; another is the inclusion of patients with microsatellite only (without nodal involvement); another one is the effectiveness of adjuvant ICI in patients with BRAF-mutated melanoma. In a single trial, the subgroup analyses could underestimate the advantages of experimental therapies due to the limited sample size of the subgroup of interest and the wide margins of uncertainty demonstrated by the confidence intervals.

In this review, we selected all randomized controlled clinical trials investigating the use of ICI immunotherapy in the adjuvant setting for patients with melanoma after surgical radicalization, performing a meta analysis with RFS as the primary endpoint, to offer more robust evidence on the adjuvant indication. Moreover, we performed subgroup meta analysis to improve the statistical power for subgroups of interest, to support with empowered evidence the use of adjuvant immunotherapy in special populations.

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Methods

Search strategy and inclusion criteria

We followed PRISMA guidelines for this systematic review and meta-analysis. We searched PubMed for randomized controlled trials published in English language from each database's inception to November 21, 2020. Two investigators (FP and MB) independently searched the databases. The search terms were "adjuvant" AND "melanoma" AND "immune checkpoint inhibitor" OR "anti-PD-1". We also reviewed the references of the included article for any further potential publication. Eligible studies had to be: (1) randomized trials assessing ICI alone or in combination for the adjuvant treatment of patients with any stage melanoma and (2) had to have available or calculable hazard ratios (HRs) for relapse according to patients' clinical subgroups (where RFS was compared between treated vs not treated with immunotherapy in any subgroups). We excluded non-randomized trials, non-cutaneous melanoma, and trials having other drugs as experimental arms. Two investigators (FP and MB) independently reviewed the retrieved articles to select the relevant articles, and any disagreement was resolved with the consensus of a third investigator (SB). Three reviewers (MB, SB, and FP) independently extracted data from the studies, and all discrepancies were resolved by consensus with all investigators.

Data extraction and quality assessment

From each study, SB and FP extracted the first author and year of publication, study phase, type of malignancy, number of patients, age, sex, stages, ulceration/nodal status, median follow-up, study arms, HR for RFS according to patients' characteristics (when available). We included the most updated report of any trials when duplicate publications were identified.

Statistical analysis

The primary endpoint was the difference in patients' outcome to ICI between different subgroups measured in terms of HR for RFS reported for these subgroups. Depending on available data, we applied subgroup analysis by stage (IIIA, IIIB-C, or IV), nodal status (N0 or N+), age (0–64 vs 65+ years), sex, presence of ulceration, BRAF status, PD-L1 expression. We extracted the HRs for relapse in the intervention group and control group and their 95% CIs from each study, separately for the different subgroups. We calculated the pooled HRs of RFS using the random-effects models. We assessed the heterogeneity between the two estimates using an interaction test to give P for heterogeneity. We did the Q-test to assess between-study heterogeneity and calculated the I2 statistic, which expresses the percentage of the total observed variability due to study heterogeneity. The null hypothesis was that the interaction between the covariates and immunotherapy efficacy is equal across subgroups and was tested with a $\chi 2$ test. All reported *P* values are two-sided. The analyses were performed with Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014).

Results

After selecting the pertinent publications, a total of $n = 4$ randomized studies were aggregated in the quantitative analysis according to the inclusion criteria (Figure 1). Overall, $n = 3043$ patients were analyzed. Among the included studies (Table 1), three were Phase III randomized trials, [12–14] and one was a Phase II randomized study.[11] One of the studies[11] was considered separately for nivolumab plus ipilimumab vs placebo and nivolumab vs placebo, respectively. Three had the placebo as the comparator in the control arm; only one[13] had the anti-CTLA-4 ipilimumab as the control treatment.

Overall, the pooled analysis showed a significant RFS benefit for adjuvant ICI against the control arms, with a hazard ratio (HR) of 0.60 [95% confidence interval (CI) 0.48–0.75]; $p < .0001$ (Figure 2). The heterogeneity of the included studies was significant ($P = .004$, $I^2 = 74\%$).

According to subgroup meta analysis, a statistically significant RFS benefit from ICI adjuvant therapy was confirmed across subgroups (Figure 3) considering sex (male *vs* female), age (elderly *vs* younger, cutoff 65 years), BRAF mutational status (BRAF mutated *vs* wild-type), PD-L1 expression (negative *vs* positive, where available; different cutoff at 1% or 5%), ulceration (present *vs* absent). None of the tests evidenced a significant difference among these subgroups, demonstrating that the interaction between the covariates and immunotherapy efficacy was equal across subgroups of interest.

Two subgroups did not reach statistically significant RFS benefit from adjuvant ICI immunotherapy: those of patients with stage IIIA melanoma according to the AJCC 7th ed., [9] (HR 0.74 [95% CI 0.47–1.17], $p = .20$; Figure 3f) and with stage IV disease M1c (HR 0.58 [95% CI 0.23–1.51], $p = .27$; Figure 3g). Nevertheless, the test for subgroup difference was not statistically significant in both cases.

Discussion

This meta-analysis confirmed a significantly improved RFS in patients with radically resected stage IIIA or worse melanoma treated with ICI compared with placebo/comparator. The overall estimate (HR = 0.60) strengthens the encouraging results of the individual trials.[8–14] Moreover, the significant efficacy of ICI was confirmed in sub-analysis with relevant effects among both women and men, young and elderly patients, in wild type and mutated BRAF types, in positive and negative PD-L1, for ulcerated and not ulcerated melanomas, in stage IIIB-C, and IV (M1a-b).

Regarding stage IIIA, it was available in two of the analyzed studies and with a relatively limited sample size: overall, 175 treated patients vs 163 controls were pooled in the present analysis. The HR point estimate showed a better RFS for ICI (0.74) but the confidence intervals overlapped the unit. Stage III is expected to have a central role in the clinical debate about translating experimental results on ICI efficacy in the real-world. In fact, all the four analyzed trials included patients according to the 7th version of the AJCC staging system. Unfortunately, the current (8th) AJCC version has a variable agreement with the previous

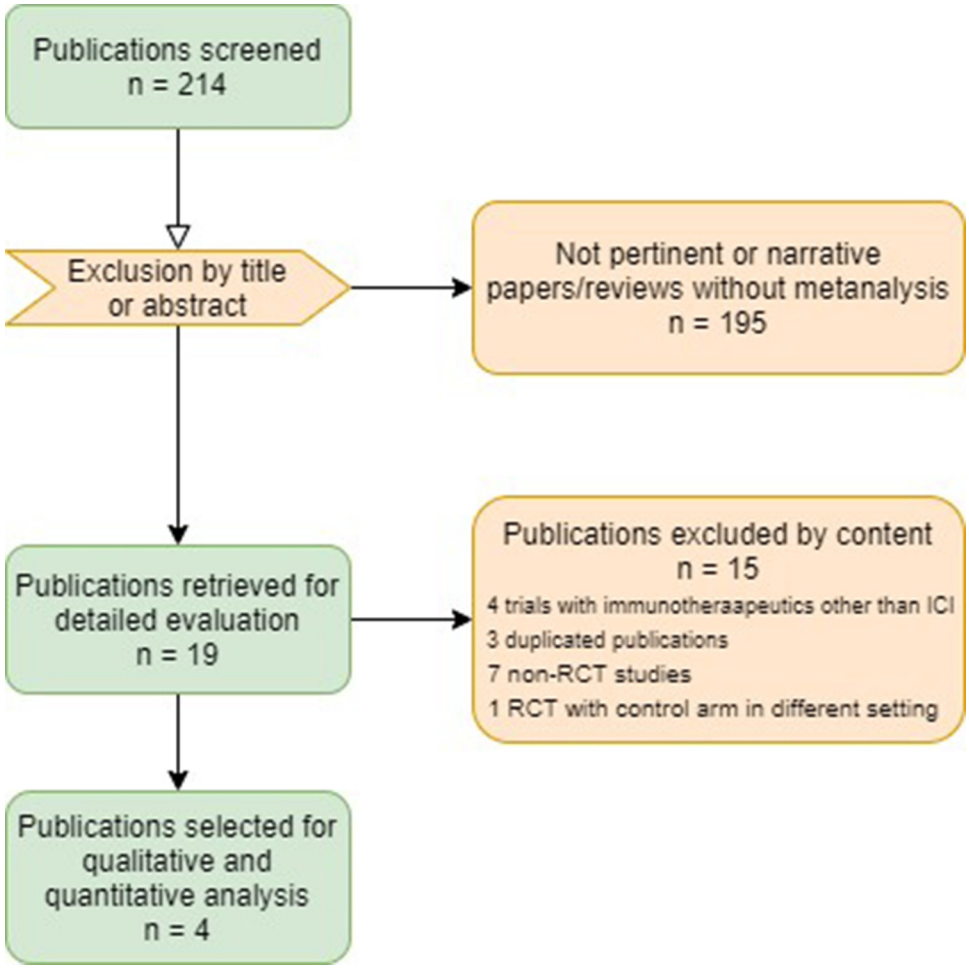

Figure 1. Flow diagram of the study selection process for the qualitative and quantitative analysis.

one.[15,18] An extremely poor agreement has been documented in real-world populations for stage III (K = 8.1%), due to the shift of former IIIB into IIIA.[18] The majority of studies' recurrent pitfall in this setting is the patient selection based on AJCC 7th edition; moreover, the 8th update was based on data gathered when checkpoint inhibitors were not used as adjuvant therapy in stage III melanoma. Of note, recent evidence demonstrated that AJCC-8 staging had a robust prognostic importance for RFS but no predictive importance toward adjuvant immunotherapy.[19] Studies involving greater sample sizes are needed to fully understand the real efficacy of ICI in patients with stage IIIA melanoma.

Also, in patients with stage IV M1c melanoma, 56 treated cases and 37 controls were available across three trials, with an extremely limited sample: consequently, even in the pooled analysis, the results for this subgroup are not conclusive. On the other hand, at least one of the RCT included had negative results for this subgroup[13] and, moreover, the lack of benefit in the meta analysis could be due to the early discontinuation of ICI treatment after 1 year, as provided by the majority of RCT, probably not enough for such high-risk patients.

The pooled analysis's usefulness to confirm significant RFS benefit, despite single-trial data not reaching statistically significant subgroup results, emerged for the subgroups of elderly and patients with PD-L1-negative tumors. Previously, at least two of the four trials considered reported non-statistically significant RFS benefit for adjuvant ICI in these subgroups of interest.[11,12,14] Our results finally confirm statistically significant and clinically meaningful benefit (absolute decrease of relapse of 28% and 50%, respectively) for the elderly and patients with PD-L1-negative melanoma.

Despite the unreliability of a comparative analysis regarding the safety of different adjuvant ICI regimens, indirect comparison of literature data about immune-related adverse events (irAEs) in these RCTs allows considering anti-PD-1 monotherapy as the best option in terms of tolerability (both over combinations and over single-agent anti-CTLA-4). On the other hand, the statistical strength of the results obtained in each of the analyzed subgroups with the combination of ipilimumab and nivolumab, in a single trial, with a huge improvement of RFS across all patients when compared to placebo, is undoubtedly attractive even in the face of greater toxicity.[11]

Finally, considering the possibility of different adjuvant treatment choices for patients with BRAF-mutated melanoma, [20] the present meta-analysis provides evidence that the expected magnitude of benefit from ICI adjuvant therapy is maintained in this population. The strength of each single-trial subgroup is overcome with 963 patients BRAF-

Table 1. Studies included in the present review and meta analysis.

Study	CheckMate-238 Ascierto 2020	EORTC-18071 Eggermont 2019	KEYNOTE-054 Eggermont 2020	IMMUNED Zimmer 2020
Phase	III	III	III	II
Arms	Nivolumab *vs* Ipilimumab	Ipilimumab *vs* Placebo	Pembrolizumab *vs* Placebo	Nivolumab + Ipilimumab *vs* Nivolumab *vs* Placebo
Primary endpoint	Recurrence-free survival	Recurrence-free survival	Recurrence-free survival in the overall population and in PD-L1-positive tumors	Recurrence-free survival
Treatment duration	1 year	3 years	1 year	1 year
Total patients enrolled	906 (453 *vs* 453)	951 (475 *vs* 476)	1019 (514 *vs* 505)	167 (56 *vs* 59 *vs* 22)
Median follow-up (months)	51.1 *vs* 50.9	63.6	36.6	28.4
Included stages	IIIB-C, IV	III	III	IV
AJCC version	VII	VII	VII	VII
Sex				
- Male	258 *vs* 269	296 *vs* 293	324 *vs* 304	31 *vs* 31 *vs* 33
- Female	195 *vs* 184	179 *vs* 183	190 *vs* 201	25 *vs* 18 *vs* 19
Age	(cutoff 65 years)	(cutoff 65 years)	(cutoff 65 years)	(cutoff 65 years)
- Younger	333 *vs* 339	394 *vs* 389	389 *vs* 379	45 *vs* 43 *vs* 35
- Elderly	120 *vs* 114	81 *vs* 87	125 *vs* 126	11 *vs* 16 *vs* 17
BRAF		not available		
- Mutation	187 *vs* 194		245 *vs* 262	27 *vs* 27 *vs* 21
- Wild type	197 *vs* 212		233 *vs* 214	29 *vs* 32 *vs* 31
- Not reported	69 *vs* 47		36 *vs* 29	0
PD-L1	(cutoff 5%)	not available	(cutoff 1%)	(cutoff 5%)
- Positive	153 *vs* 154		428 *vs* 425	28 *vs* 28 *vs* 25
- Negative	300 *vs* 299		59 *vs* 57	28 *vs* 31 *vs* 27
- Unknown	0		36 *vs* 29	0
Ulceration				Not available
- Present	145 *vs* 133	197 *vs* 203	208 *vs* 197	
- Absent	187 *vs* 199	257 *vs* 244	230 *vs* 251	
- Not reported	38 *vs* 34		76 *vs* 57	
Stage				
- IIIA	0	98 *vs* 88	77 *vs* 75	0
- IIIB-C	368 *vs* 366	377 *vs* 388	437 *vs* 430	0
- IV	82 *vs* 87*	0	0	56 *vs* 59 *vs* 52
M stage				
- M1a-b	62 *vs* 66	0	0	38 *vs* 41 *vs* 36
- M1c	20 *vs* 21	0	0	18 *vs* 18 *vs* 16†

*1 case not reported.
†Including history of brain metastases in 22 patients.

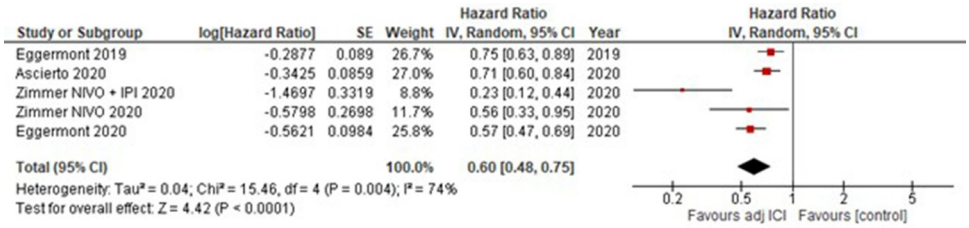

Figure 2. Forest plot resulting from the meta analysis of the included studies for the primary endpoint of relapse free survival (RFS).

mutated melanoma included in our analysis (see Table 1), confirming the efficacy of the immunotherapeutic strategy in this setting and offering the opportunity of basing the adjuvant treatment choice on the toxicity profile according to the patient comorbidities

The limitations of the current study are represented by the following: significant heterogeneity among RCT included, with various comparator arms (placebo or anti-CTLA-4 active therapy) and different inclusion criteria (i.e., stage III only or stage IV included); relatively limited sample size for specific subgroups; outdated AJCC version used for the trial inclusion criteria; relatively small numerosity of RCT published in this setting for melanoma patients.

Conclusion

The benefit of ICI-based adjuvant immunotherapy for radically resected melanoma patients was confirmed in this pooled analysis of all randomized trials in this setting, with no significant differences across subgroups. The prolongation of therapy over 1 year could represent the possible evolution of the adjuvant approach in future trials for radically resected stage IV melanoma, and the selection of high-risk patients suitable to be candidates to anti-PD -1/anti-CTLA-4 combinations instead of a monotherapy. Eventually, an unsolved issue in the field of adjuvant immunotherapy in melanoma is represented by the lack of data about patients who did not undergo radical lymph

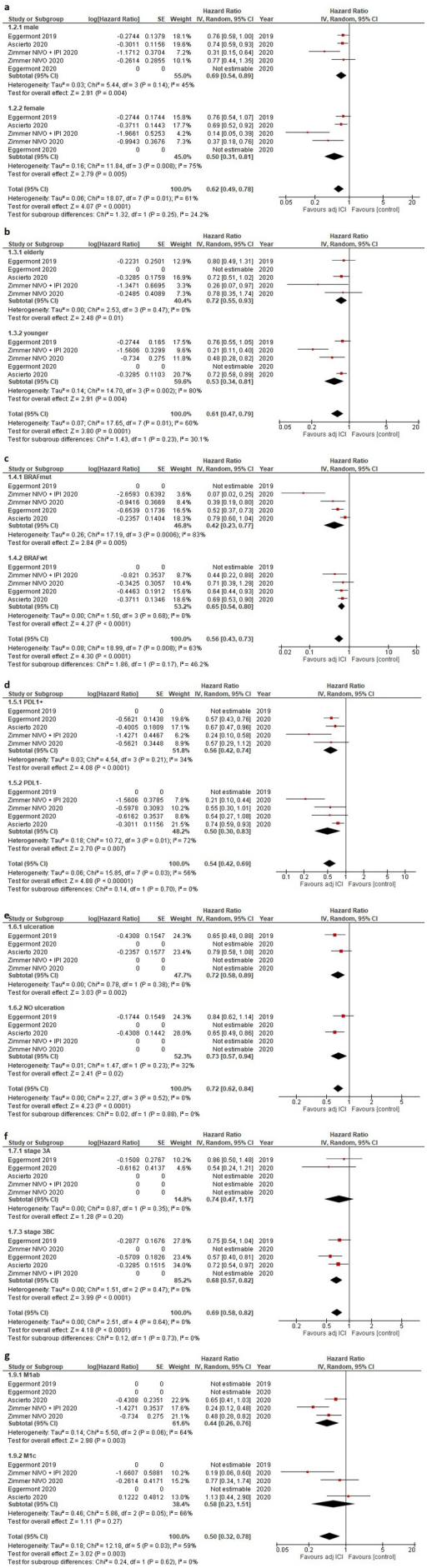

Figure 3. Subgroup meta analysis for sex (a), age (b), BRAF mutational status (c), PD-L1 expression (d), ulceration (e), stage (f), M substage (g).

node dissection in the case of sentinel biopsy positivity, currently dramatically increasing in clinical practice, but still missing in pivotal clinical trials.

Disclosure of potential conflicts of interest

Melissa Bersanelli received research funding from Seqirus UK, Pfizer, Novartis, BMS, Astra Zeneca, Roche S.p.A., and Sanofi Genzyme; honoraria as speaker at scientific events by Bristol-Myers Squibb (BMS), Novartis, Astra Zeneca, and Pfizer and as consultant for advisory role by Novartis, BMS, and Pfizer; she also received fees for copyright transfer by Sciclone Pharmaceuticals.

Sebastiano Buti received honoraria as speaker at scientific events and advisory role by Bristol-Myers Squibb (BMS), Pfizer; MSD, Ipsen, Roche, Eli-Lilly, AstraZeneca and Novartis; he also received research funding from Novartis.

Ignazio Stanganelli received honoraria as speaker at scientific meetings by BMS, Novartis, MSD.

The other authors have no conflict of interest to declare.

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