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Systematic or Meta-analysis Studies

Incorporation of anti-PD1 or anti PD-L1 agents to platinum-based chemotherapy for the primary treatment of advanced or recurrent endometrial cancer. A *meta*-analysis

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ABSTRACT

Importance: Various randomized trials have explored the efficacy of combining immune checkpoint inhibitors (ICIs) with first-line chemotherapy in advanced endometrial cancer. We aimed to summarize available data and clarify the benefit of adding immunotherapy according to the DNA mismatch repair status (deficient, dMMR or proficient, pMMR) and the specific type of agent used (anti-PD1 or anti-PD-L1).
Objective: To assess whether the addition of ICIs to standard platinum-based chemotherapy enhances progression-free survival (PFS) for patients with advanced endometrial cancer both overall and based on DNA mismatch repair status.
Data sources: Electronic databases (PubMed, Embase and Cochrane Library) and conference proceedings were searched for first line, randomized and controlled trials integrating ICIs with chemotherapy for the treatment of advanced endometrial cancer published or presented by November 1, 2023.
Study selection: Five studies, comprising 2456 patients (1308 received ICIs with chemotherapy and 1148 treated with chemotherapy alone) met the selection criteria and were included in the analysis. Experimental arms included pembrolizumab, dostarlimab (anti-PD1) and durvalumab, atezolizumab and avelumab (anti-PD-L1) combined with standard three-weekly carboplatin-paclitaxel chemotherapy backbone. Endometrial carcinosarcoma were included in 3 out of 5 trials.
Data extraction and synthesis: For comparison of PFS outcomes, extrapolation of hazard ratios (HRs), 95% confidence intervals (CI) and PFS events was performed for each included study in the overall population and according to subgroups. Data analysis was conducted using a random-effects model.
Results: The addition of ICIs to chemotherapy improved PFS compared to chemotherapy alone in the overall population (pooled HR, 0.63; 95 % CI, 0.52—0.76; P <.001). In the dMMR subgroup the benefit was more pronounced (pooled HR, 0.34; 95 % CI, 0.27—0.44; P <.001) and not affected by drugs used with pooled HRs of 0.39 (95 % CI, 0.28—0.55; P <.001) and 0.34 (95 % CI, 0.27—0.44; P <.001) for PD-L1 and PD1 inhibitors, respectively. For pMMR patients, a statistically significant benefit in terms of PFS was confirmed only when anti-PD1 were used (anti-PD-1: HR 0.64, 95 % CI: 0.46–0.90, P =.010 vs anti-PD-L1: HR 0.87, 95 % CI: 0.73–1.03, P =.104)

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Conclusions and relevance: This *meta*-analysis confirmed the advantage in terms of PFS of adding ICIs to standard platinum-based chemotherapy. While dMMR patients benefit from the incorporation of both anti PD-1 or anti PD-L1, this benefit is confined to the association of anti-PD1 agents in pMMR patients. Updated analysis of trials is awaited to clarify the impact of immunotherapy on overall survival.

Introduction

Immunotherapy is effective in recurrent endometrial cancer (EC), particularly in patients harboring a deficit in the DNA mismatch repair system (dMMR) or with microsatellite instability-high (MSI-H) tumors. Currently, for patients with advanced disease in progression to platinum-based chemotherapy, dostarlimab or pembrolizumab used as a monotherapy are considered the standard of care for the dMMR/MSI-H subgroup. Additionally, pembrolizumab plus lenvatinib have been approved for both pMMR and dMMR/MSI-H patients. More recently, randomized controlled trials have tested the incorporation of anti-PD1 or anti-PD-L1 monoclonal antibodies with the standard first-line, platinum-based chemotherapy in the overall population of EC patients [1,2,3,4,5]. While it appears clear that dMMR patients benefit the most from the addition of immune checkpoint inhibitors (ICIs), in patients with a conserved mismatch repair machinery, the so-called proficient subgroup (pMMR), this benefit is unclear[1,5]. In fact, in 2 trials the incorporation of avelumab and atezolizumab (anti-PD-L1) failed to demonstrate benefit in PFS and OS [1,5]. Moreover, a different mechanism of action between anti-PD1 and anti-PD-L1 yet demonstrated in other solid tumors could justify the differential effectiveness of immunotherapy in the pMMR population [6]. Even if pMMR patients represent an heterogenous subgroup for which further molecular subclassifications and targeted therapies are awaited, the efficacy of immunotherapy in pMMR needs to be clarified. We thus sought to perform a *meta*-analysis to investigate the efficacy of the incorporation of ICIs to chemotherapy in the first-line treatment of advanced EC in all-comers patients and according to the DNA mismatch repair status (proficient or deficient).

Methods

Search strategy and selection criteria

Public databases as PubMed, Embase, Cochrane Library and meeting proceeding of the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) were systematically searched for randomized controlled trials that incorporated anti-PD1/PD-L1 with platinum-based chemotherapy for advanced EC.

The research was restricted to first-line trials published or presented by November 1, 2023. The following research terms were used "immunotherapy AND endometrial cancer". We also performed a manual search using references and citations from the pivotal published studies. Screening process of article titles, abstracts, and full texts was carried out by three authors (M.B., R.M., L.M.) independently to include all relevant studies. Inclusion/exclusion criteria were verified by two authors (M.B. and R.M.). In the case of overlapping studies, we selected the most recent and/or most comprehensive manuscript. This *meta*-analysis conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.

Data extraction and objectives

Data extraction and quality assessment were conducted across all

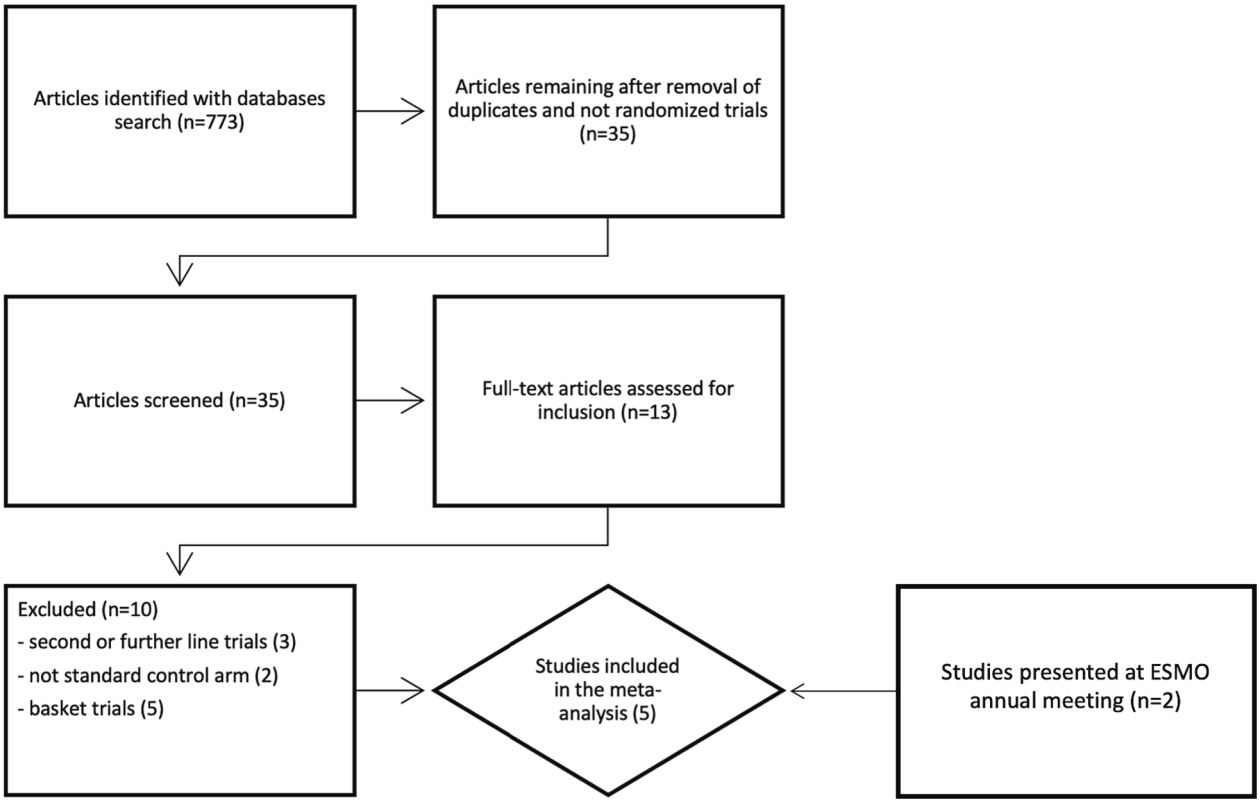

Fig. 1. PRISMA workflow.

Table 1
Summary of selected trials.

Trial	Recruitment period	Phase	Experimental Group	Control Group	Sample size	HR 95 % CI	Median follow-up (months)	Median PFS (months) experimental vs control
MITO END-3 trial Pignata S et al.	2018–2021	II	CP + avelumab x 6 cycles + maintenance with avelumab	CP + placebo x 6 cycles + maintenance with placebo	Overall 125 pMMR 57 dMMR 64	Overall 0.78 (0.65–0.93) p = 0.085 dMMR 0.46 (0.22–0.94) pMMR 1.17 (0.65–2.10)	Overall 23.3	Overall 9.6 vs 9.9
RUBY trial Mirza M. et al.	2019–2021	III	CP + dostarlimab x 6 cycles + maintenance with dostarlimab	CP + placebo x 6 cycles + maintenance with placebo	Overall 494 dMMR 118 pMMR 376	Overall 0.64 (0.51–0.80) p < 0.001 dMMR 0.28 (0.16–0.50) p < 0.001 pMMR 0.76 (0.59–0.98)	Overall 25.4 dMMR 24.8 pMMR NA	NA
NRG GY018 trial Eskander R et al.	2019–2022	III	CP + pembrolizumab x 6 cycles + maintenance with pembrolizumab	CP + placebo x 6 cycles + maintenance with placebo	Overall 816 dMMR 225 pMMR 591	Overall NE dMMR 0.30 (0.19–0.48) p < 0.001 pMMR 0.54 (0.41–0.71) p < 0.001	Overall NE dMMR 12 pMMR 7.9	Overall NE dMMR NR vs 7.6 pMMR 8.7 vs 13.1
DUO-E trial (durva vs placebo) Westin S. et al.	2020–2022	III	CP + durvalumab x 6 cycles + maintenance with durvalumab	CP + placebo x 6 cycles + maintenance with placebo	Overall 479 dMMR 95 pMMR 384	Overall 0.71 (0.57–0.89) p = 0.003 dMMR 0.42 (0.22–0.80) pMMR 0.77 (0.60–0.97)	Control 12.6 Experimental 15.4 dMMR 10.2 pMMR 12.8	Overall 10.2 vs 9.6 dMMR NR vs 7 pMMR 9.9 vs 9.7
AtTEnd trial Colombo N. et al.	2018–2022	III	CP + atezolizumab x 6 cycles + maintenance with atezolizumab	CP + placebo x 6 cycles + maintenance with placebo	Overall 549 dMMR 125 pMMR 409	Overall 0.74 (0.61–0.91) p = 0.0219 dMMR 0.36 (0.23–0.57) p = 0.0005 pMMR 0.92 (0.73–1.16)	Overall 28.3 dMMR 26.2 pMMR NA	Overall 10.1 vs 8.9 dMMR NR vs 6.9 pMMR 9.5 vs 9.2

CP: carboplatin-paclitaxel; dMMR: Mismatch repair deficient; HR: hazard ratio; NA: not available; NE: not evaluated; NR: not reached; pMMR: Mismatch repair proficient.

retrieved studies based on full-text articles. We registered the following information from each report: authors, year of study publication, study design, number of patients, immunotherapy type (anti-PD1 vs anti-PD-L1), recruitment period, adverse events, median follow-up, median progression-free survival (PFS), number of PFS events in the experimental group and in the control group, hazard ratio (HR) and related *p* values.

The primary outcome analyzed was PFS in the intention-to-treat population (all comers patients) and according to mismatch repair status (dMMR vs pMMR). Secondary endpoints were PFS according to the type of ICIs used in the pMMR subgroup (PD1 vs PD-L1). For the comparison of time-to-event PFS outcomes, HR and associated 95 % confidence intervals (CIs) were extracted for all comers, dMMR and pMMR patients, according to reported subgroup analysis. For the NRG018 study, the HR for PFS in the all-comer population was not analyzed. However, the study was included twice (dMMR and pMMR) when the overall population was considered. For the DUO-E trial including a third arm of durvalumab plus olaparib in the maintenance phase, the HR for the comparison between placebo and ICIs alone was only considered.

Statistical analysis

Meta-analysis on all patients and subgroups was carried out using a random effect model (method of DerSimonian & Laird). Results are reported as pooled HRs and relative 95 % CIs. Heterogeneity was assessed with I [2] statistic. Sensitivity analysis was carried out to assess the effect of NRG study on the *meta*-analysis results. Publication bias was not accessed due to the small number of studies included. Data were analyzed using STATA statistical software (version 14.2).

In the PROSPERO online database, the present *meta*-analysis was registered with ID CRD42023491732.

Assessment of risk of bias

The risk of bias for each trial was assessed by using the criteria outlined in the RoB 2, Cochrane risk-of-bias tool for randomized trials [7]. The domains were the following: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result. Review authors' judgments will be categorized as "low risk", "high risk" or "some concerns" of bias (Fig. 1, supplementary).

Results

Search results and study characteristics

Five randomized, phase II-III trials for a total number of 2456 patients were included according to inclusion/exclusion criteria. The PRISMA workflow is presented in Fig. 1.

In the experimental arms, 1308 received ICIs with chemotherapy and 1148 patients were treated with chemotherapy alone. Pembrolizumab,

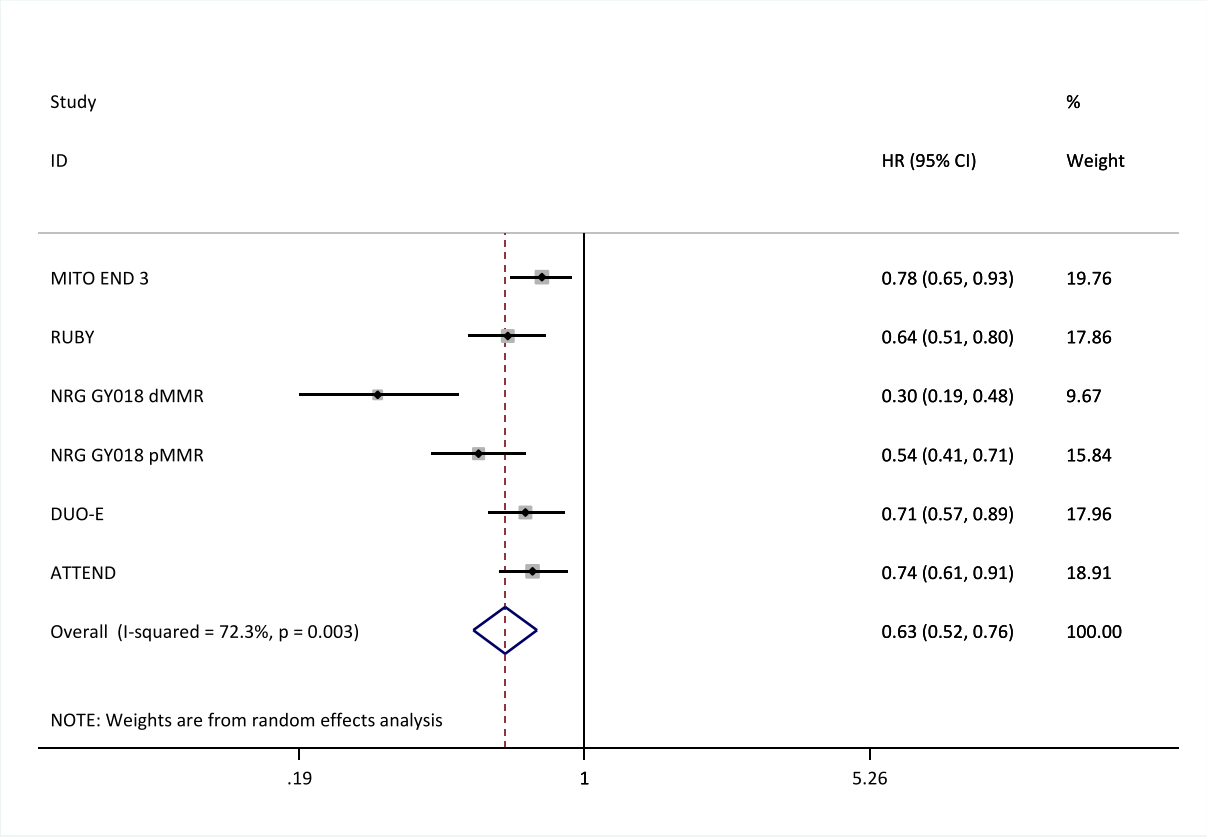

Fig. 2a. Forest plot of effect sizes for overall population (including NRG trial).

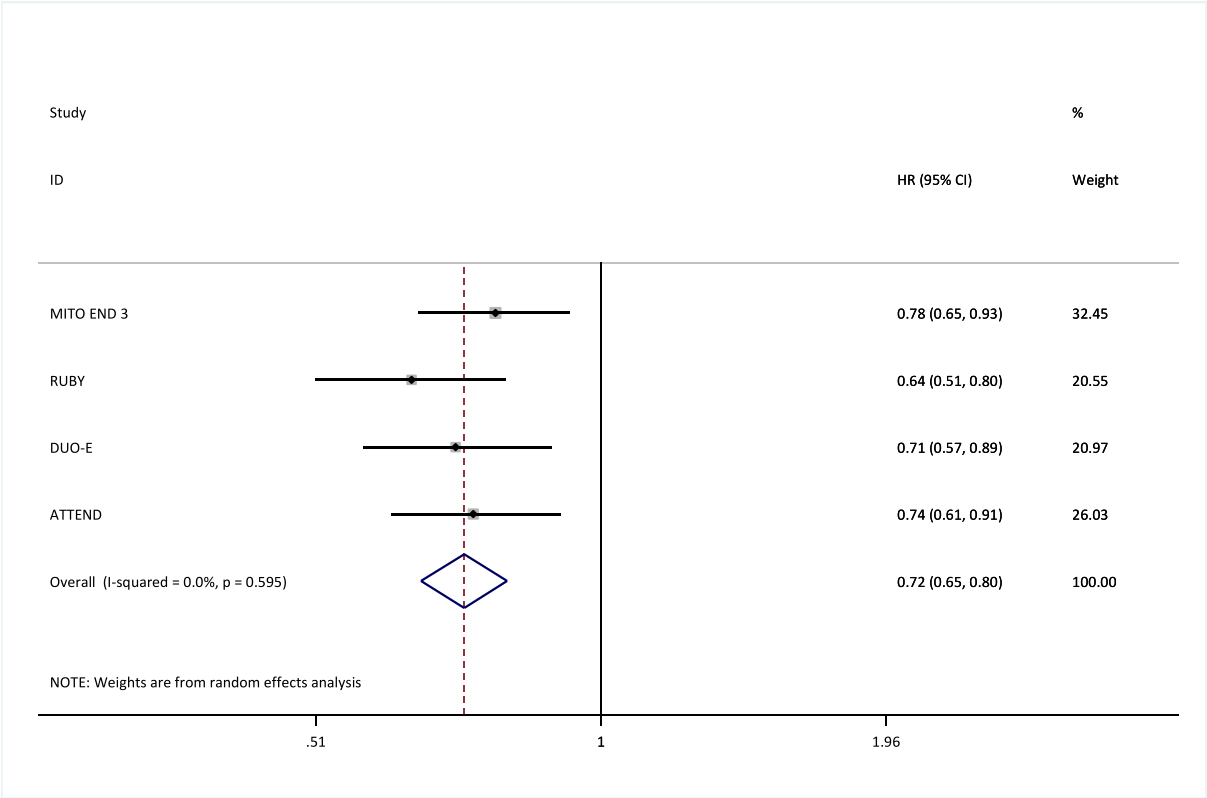

Fig. 2b. Forest plot of effect sizes for overall population excluding NRG trial.

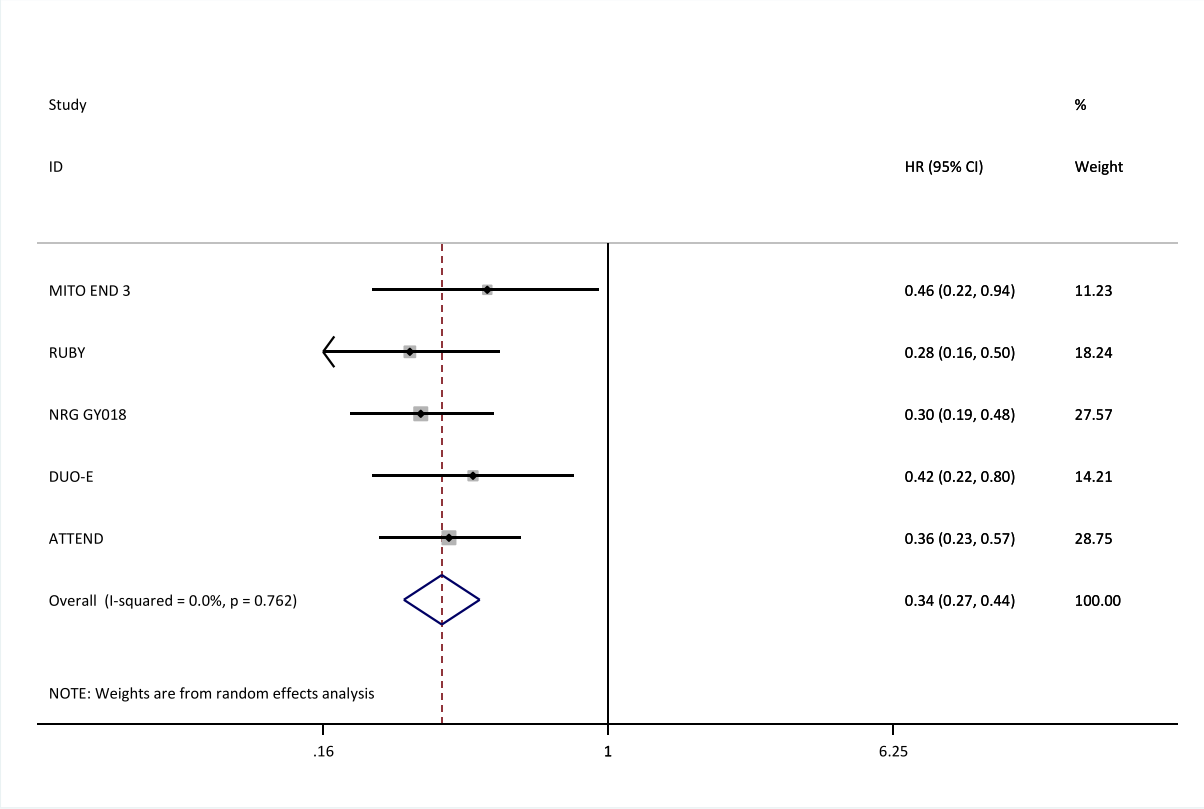

Fig. 3a. Forest plot of effect sizes for dMMR population.

dostarlimab (anti-PD1) and durvalumab, atezolizumab and avelumab (anti-PD-L1) were incorporated to standard three-weekly carboplatin-paclitaxel chemotherapy backbone. Endometrial carcinosarcoma were included in 3 out of 5 trials. Patients previously treated with adjuvant chemotherapy were accepted in all included studies, but the treatment-free interval allowed was different between trials (more than 6 months vs more than 12 months). In Table 1 are summarized the main characteristics of the studies.

Efficacy

ICIs plus platinum-based chemotherapy were associated with a substantial improvement in PFS compared to chemotherapy alone in all comers (pooled HR, 0.63; 95 % CI, 0.52—0.76; P <.001; I^2 = 72.3 %) (Fig. 2a).

A sensitivity analysis was performed excluding the NRG GY018 trial [3] in which the HR for PFS was not evaluated in the all comer population. The pooled HR without the study by Eskander et al was 0.72; 95 % CI, 0.65—0.80; P <.001; I^2 = 0 %) (Fig. 2b).

In the dMMR population the benefit from the addition of immunotherapy was more pronounced (pooled HR, 0.34; 95 % CI, 0.27—0.44; P <.001; I^2 = 0 %) (Fig. 3a) and not affected by ICIs type used with pooled HRs of 0.39 (95 % CI, 0.28—0.55; P <.001; I^2 = 0 %) and 0.34 (95 % CI, 0.27—0.44; P <.001; I^2 = 0 %) for dMMR patients treated with PD-L1 or PD1 inhibitors, respectively. (Fig. 3b).

A PFS benefit was also confirmed in the pMMR population who received chemo-immunotherapy (pooled HR of 0.77; 95 % CI, 0.63—0.95; P =.015; I^2 = 62.4 %) (Fig. 4a). However, in the subgroup analysis by ICI class, only pMMR patients treated with anti-PD1 agents retained a statistically significant benefit in terms of PFS (anti-PD1: HR 0.64, 95 % CI: 0.46–0.90, P =.010; I^2 = 68.9 % vs anti-PD-L1: HR 0.87, 95 % CI: 0.73–1.03, P =.104; I^2 = 8.8 %) (Fig. 4b).

Discussion

Endometrial cancer lagged behind major oncologic innovations until the advent of immunotherapy. Approximately 20 % to 30 % of patients harboring a dMMR/MSI-H disease represents the group who benefits the most from ICIs [8]. ICIs alone, as confirmed by pembrolizumab and dostarlimab as single agents, showed deep and sustained antitumor activities in terms of response rate in phase I-II not randomized trials [10,11,12]. Pembrolizumab plus lenvatinib have demonstrated to be superior in terms of progression-free survival and overall survival when compared to standard non platinum, second-line chemotherapies regardless of the biomarker status (dMMR or pMMR) [9]. Consequently, dostarlimab and pembrolizumab for patients with dMMR EC as well as lenvatinib plus pembrolizumab for all comers are in the treatment armamentarium for recurrent EC previously treated with platinum-based chemotherapy.

The potential synergism between chemotherapy and ICIs was tested in recent phase II-III randomized and controlled trials showing a clear benefit of the combination strategy in dMMR population, irrespective of agent used (anti-PD1 or anti-PD-L1). Accordingly, the Food and Drugs Administration and the European Medicine Agency, have recently approved dostarlimab in combination with first-line platinum-based chemotherapy in advanced/recurrent dMMR EC [13]. Since the benefit of ICIs in combination to chemotherapy is remarked in dMMR but not so clear in the pMMR subgroup, we performed a *meta*-analysis to summarize the results of recently presented trials and clarify the effect size in the pivotal subgroups of dMMR and pMMR patients. We confirmed that adding ICIs to chemotherapy improved the HR for PFS in the intention-to treat population. In the dMMR subgroup the effect size was more pronounced and appeared to be independent from the ICIs used (anti-PD1 or anti-PD-L1) while in pMMR patients the benefit was limited to the use of anti-PD1 ICIs. These results could broaden the use of immunotherapy in EC and are in line with previous reports, where anti-PD1

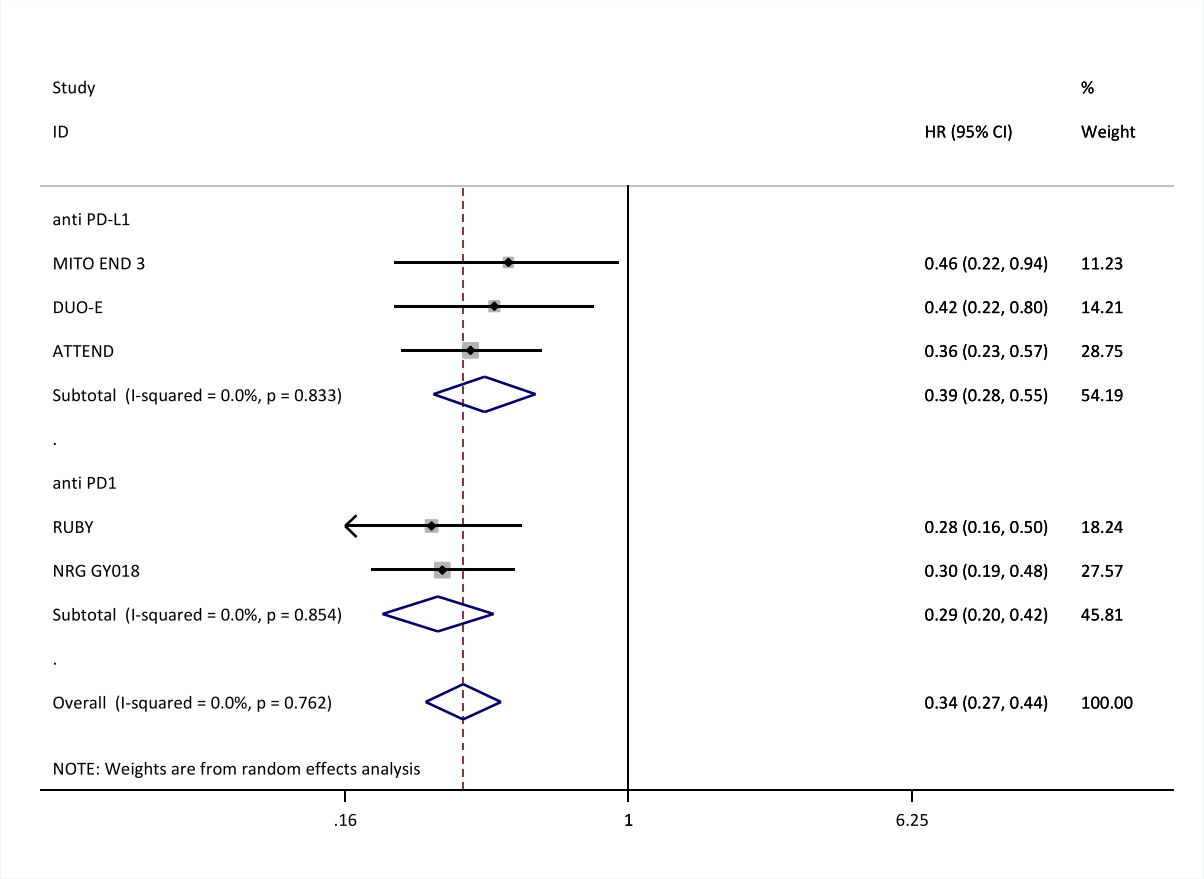

Fig. 3b. Forest plot of effect sizes for dMMR by treatment type (PD1 vs PD-L1).

strategy was correlated with better outcomes in patients with advanced solid tumors [6], even when combined with chemotherapy in non-small cell lung cancers [14].

We recognized that other treatment strategies are coming and could enrich the treatment algorithm for pMMR patients. In fact, the combination of durvalumab and olaparib as maintenance after durvalumab plus chemotherapy improved PFS compared to chemotherapy alone in pMMR population according to results of the DUO-E trial [2]. The third arm of this trial was not included in the current *meta*-analysis and the absence of an olaparib-alone arm limited the estimation of a synergism between ICIs and PARP inhibitors.

Moreover, the pMMR subgroup presents as a heterogenous cohort that requires a more refined classification according to the TCGA molecular subgroups and emerging molecular biomarkers (e.g., TP53, HER2, hormone receptors status, *PIK3CA status*, Homologous Recombination Deficiency) [15]. This stratification will pave the way for biomarker-driven trials aimed at testing targeted agents. Conversely, in the case of dMMR patients the question to address is the role of chemotherapy when combined with ICIs. Two ongoing phase 3 trials are randomizing dMMR patients to receive ICIs alone (experimental arm) or chemotherapy (standard arm) in the setting of advanced EC [16,17]. In this changing scenario, a control arm with chemotherapy alone in dMMR patients could be considered outdated according to the results of trials here presented. However, these two ongoing studies are pivotal to explore the possibility of avoiding chemotherapy in this specific subgroup.

Limitations

This research has several limitations. First, the subgroup analysis of the pMMR population drew data from only 3 randomized trials, one of which was a phase II study involving 120 patients [1]. Consequently, the effectiveness of anti PD-L1 in pMMR patients cannot be excluded and it should be tested in a properly dimensioned clinical trial involving pMMR-only patients. Second, we limited the analysis to PFS that seems to correlate to overall survival in first-line trials of EC [18]. Despite this, an updated analysis encompassing OS data is imperative. Third, the current study did not incorporate an analysis of safety data.

Conclusion

This *meta*-analysis of 5 randomized trials involving 2456 EC patients confirmed the benefit in terms of progression-free survival by adding ICIs to standard chemotherapy in first-line setting of advanced endometrial cancer. While dMMR patients benefit from the incorporation of both anti PD-1 or anti PD-L1, the gain in PFS is restricted to the incorporation of anti-PD1 agents in dMMR patients. Further analysis from updated trials is awaited to clarify the impact of immunotherapy on overall survival.

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CRediT authorship contribution statement

Michele Bartoletti: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Marcella Montico:** Methodology, Resources, Data curation, Project administration. **Domenica Lorusso:** Writing – review & editing, Visualization, Supervision. **Roberta Mazzeo:** Methodology,

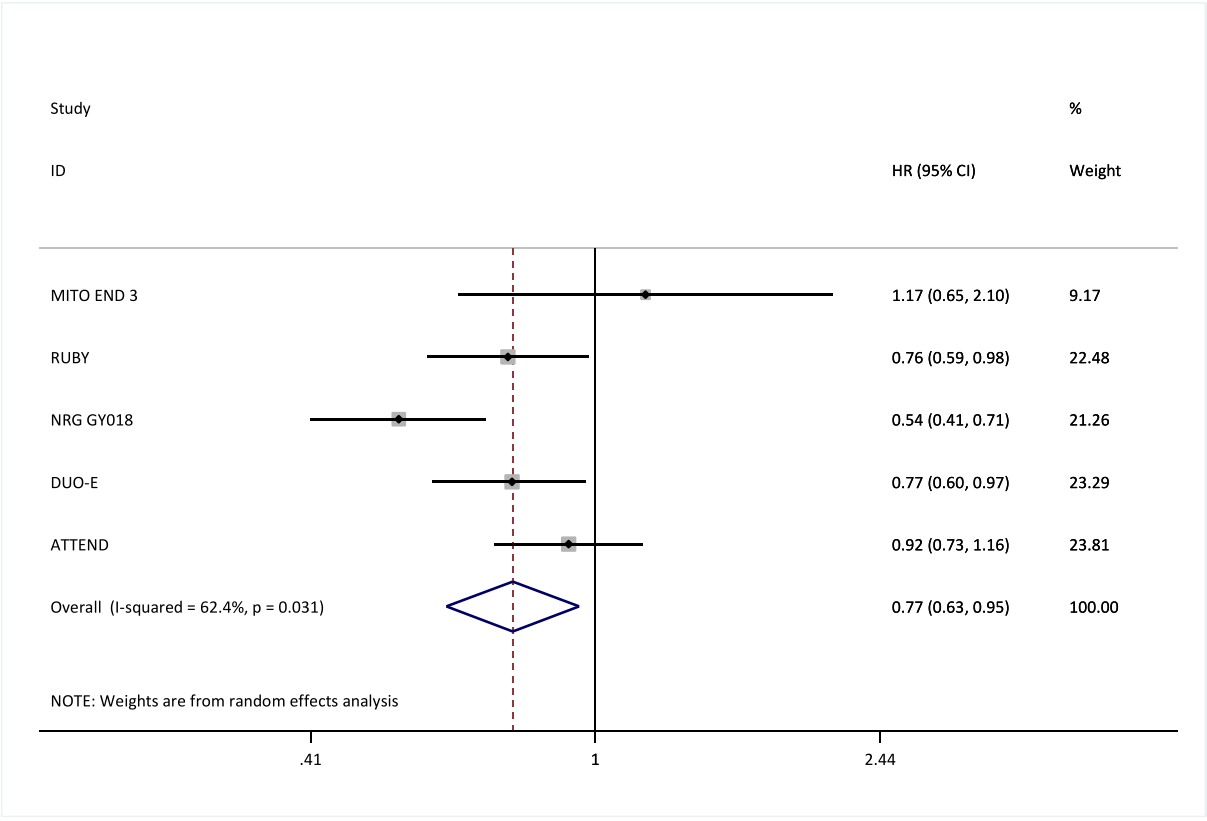

Fig. 4a. Forest plot of effect sizes for pMMR

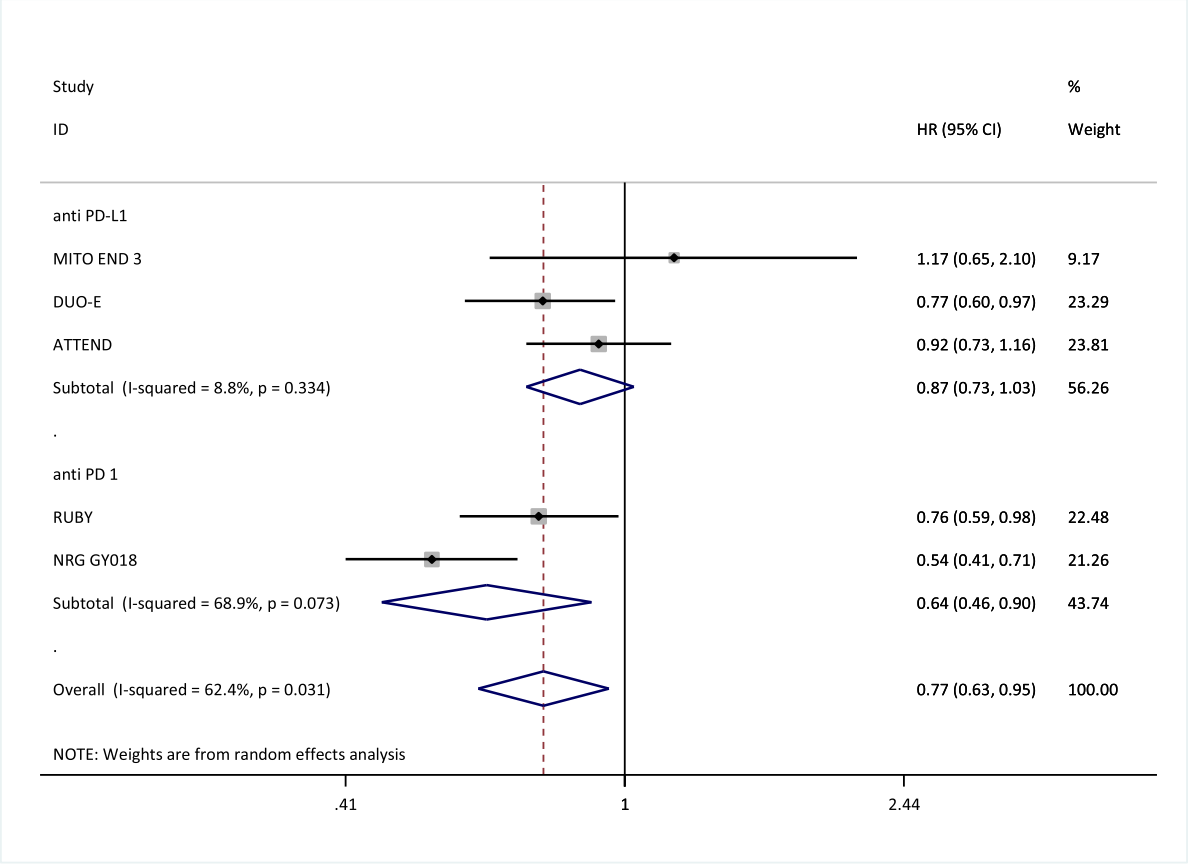

Fig. 4b. Forest plot of effect sizes for pMMR by treatment type.

Software, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Ana Oaknin:** Writing – review & editing, Supervision. **Lucia Musacchio:** Writing – original draft, Writing – review & editing, Visualization. **Giovanni Scambia:** Writing – review & editing, Supervision. **Fabio Puglisi:** Writing – review & editing, Supervision. **Sandro Pignata:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [**MB** reports advisory board from GSK, MSD, EISAI, Roche; speaker fees form GSK, Astrazeneca, MSD; travel grant from Pharmamar outside the submitted work. **DL** reports grants from Clovis Oncology and GSK; personal fees from Amgen, AstraZeneca, Clovis Oncology, MSD and Pharmamar; advisory board from AstraZeneca, GSK, MSD; Institutional grants from Clovis Oncology, Genmab, GSK and MSD outside the submitted work. **AO** reports advisory board from Agenus, AstraZeneca, Clovis Oncology, Corcept Therapeutics, Deciphera Pharmaceuticals, Eisai, Exelisis, EMD Serono, F. Hoffmann-La Roche, Genmab, GSK, ImmunoGen, Itheos, Merck Sharps & Dohme de España, SA, Mersana Therapeutics, Novocure, OneXerna Therapeutics, Inc., PharmaMar, Regeneron, Sattucklabs, Seagen and Sutro Biopharma; personal fees for travel/accommodation from AstraZeneca, PharmaMar and Roche; institutional funding from Abbvie Deutschland, Advaxis Inc., Aeterna Zentaris, Amgen, Aprea Therapeutics AB, Bristol Myers Squibb, Clovis Oncology Inc, EISAI limited LTD, F. Hoffmann –La Roche LTD, Immunogen Inc, Merck, Sharp & Dohme de España SA, Millennium Pharmaceuticals Inc, PharmaMar SA, Regeneron Pharmaceuticals and Tesaro Inc. outside the submitted work. **GS** reports grants from MSD, and honoraria from Clovis Oncology, Tesaro, Johnson & Johnson, outside the submitted work; **FP** reports honoraria for advisory boards, activities as a speaker, travel grants, research grants from Amgen - Astrazeneca - Daiichi Sankyo - Celgene - Eisai - Eli Lilly- Exact Sciences- Gilead - Ipsen – Menarini- MSD - Novartis - Pierre Fabre - Pfizer - Roche - Seagen - Takeda – Viatris; Research funding from Astrazeneca – Eisai - Roche, outside the submitted work. **SP** reports grants from Roche; personal fees from Roche, grants and personal fees from MSD, grants and personal fees from AZ, personal fees from Clovis, personal fees from GSK, personal fees from Pharmamar, grants and personal fees from Pfizer, outside the submitted work. All the above disclosures are outside the submitted work. The other Authors have no conflict to disclose.].

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MB and MM had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2024.102701.

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