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Recent targeted therapies addition to standard chemotherapy regimen in mismatch repair deficient (Dmmr) primary advanced or recurrent endometrial cancer, to what significance? A network meta-analysis

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Abstract

Endometrial cancer (EC) is one of the most common gynecological cancers, often diagnosed in recurrent or advanced stages. Despite various advances in chemotherapy, high mortality and morbidity persist. Immune checkpoint inhibitors (ICIs) combined with tyrosine kinase inhibitors (TKIs) are recent targeted therapies used alongside chemotherapy in primary advanced or recurrent endometrial cancer, especially in mismatch repair-deficient (dMMR) cases. This study was conducted to compare the use of ICI, TKI, and standard chemotherapy regimens (Carboplatin, Paclitaxel, and/or Doxorubicin) in primary advanced or recurrent endometrial cancer cases with known mismatch repair (MMR) status based on recent evidence. Searching and selection were conducted in adherence to the PRISMA statement across various databases. Inclusion and exclusion criteria were applied. Selected studies were assessed using the Cochrane Risk of Bias 2 (RoB2) tool. Eligible studies were extracted for characteristics and outcomes. The primary outcome of this study was progression-free survival (PFS), with the secondary outcome being overall survival (OS) and adverse events (AEs). Subgroup analysis of mismatch repair deficient (dMMR) and proficient (pMMR) cases was performed. A network meta-analysis was conducted using Review Manager 5.4. Five randomized controlled trials (RCTs) of good quality were included. The analysis found that the ICI plus chemotherapy combination regimen provided better PFS compared to the chemotherapy-only regimen in dMMR-EC subjects (OR = 0.021; 95% CI = 0.003–0.140), but not in pMMR-EC subjects. There was no significant difference in PFS between the ICI plus TKI combination regimen and ICI monotherapy compared to chemotherapy-only. No difference in OS was observed among all groups. Adverse events were higher in the ICI plus chemotherapy combination regimen, but no differences in quality of life or discontinuation rates were noted. ICI plus chemotherapy provided better PFS compared to chemotherapy alone, ICI monotherapy, and ICI plus TKI regimens, respectively in dMMR primary advanced or recurrent endometrial cancer cases. PROSPERO ID: CRD42023472033.

Keywords: Endometrial cancer, Immune checkpoint inhibitors, Mismatch repair deficient, Targeted therapy, Tyrosine kinase inhibitors.

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1. Introduction

Endometrial cancer (EC) is currently considered one of the most common gynecological cancers worldwide, affecting both developing and high-income countries, with approximately 417,000 new cases and 97,000 deaths annually, respectively [1-4]. In the United States, the American Cancer Society (2023) estimated that roughly 66,200 new cases and 13,030 deaths from uterine body or corpus cancer will occur, respectively [5]. The most recent International Federation of Gynecology and Obstetrics (FIGO) staging of endometrial cancer 2023 has integrated molecular classifications based on The Cancer Genome Atlas (TCGA), which include: polymerase-ε-mutated/ultra-mutated (*POLEmut*), mismatch repair deficient (dMMR) or microsatellite-instable hypermutated (MSI-H), no specific molecular profile (NSMP), and p53 abnormal (p53abn) [6, 7]. This integration of molecular classification is clinically relevant in determining prognostic value as *POLEmut* demonstrated a favorable prognosis, while both dMMR and NSMP, and p53abn demonstrated intermediate and poor prognoses, respectively. Other clinical relevance of molecular classification is rapidly evolving over the years, which includes de-escalation or intensification strategies of post-surgical adjuvant treatments and the additional use of targeted therapies, including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), to the standard chemotherapy regimen (*Carboplatin and/or Paclitaxel*) in primary advanced (Stage III and IV) and recurrent endometrial cancer patients with mismatch repair deficient (dMMR) molecular classification [7, 8].

Tyrosine kinase inhibitors (TKIs) were first introduced in 2001 when imatinib became the first TKI to gain Food and Drug Association (FDA) approval. TKIs inhibit the transduction of protein kinases using various methods. TKIs could be grouped into five subgroups based on their binding modes, from binding to the ATP-binding site of active tyrosine kinases to allosteric sites of the ATP-binding pocket [9]. The use of TKIs in cancer has been widely recognized. However, the application of TKIs in endometrial cancer cases still requires further study. A study by Janát-Amsbury, et al. [10] found that a pan-tyrosine kinase inhibitor produced excellent outcomes in an orthotopic mouse model with endometrial cancers [10]. Another study by Lin et al. found that dual tyrosine kinase inhibitors suppressed the growth of endometrial cancer through the inhibition of matrix metalloproteinase (MMP) expression [11]. Another study by Tong et al. found that the addition of Lenvatinib, a TKI, to Pembrolizumab therapy provided a better inhibitory effect on endometrial cancer cells' growth [12]. Therefore, TKIs provided a promising prospect in the development of advanced or recurrent endometrial cancer management.

First considered as a novel treatment option in 2011, immune checkpoint inhibitor (ICI) is classified as immunotherapies, which rely on immune system components of tumor cells and T-lymphocytes; therefore, it boost anti-cancer immune responses.[13] ICIs, which consist of antibodies targeting immune inhibitory receptors such as programmed death-1 (PD-1), programmed death-ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have been widely used as immunotherapeutic agents in the last decade. Results from several studies revealed higher expression of PD-1/PD-L1 and higher infiltration of cytotoxic T cells (CD8+) in the mismatch repair deficient (dMMR) compared to the mismatch proficient (pMMR) group of endometrial cancer [13-15].

The use of ICIs as monotherapy or in combination with radiotherapy, chemotherapy, and/or tyrosine kinase inhibitors (TKIs) in advanced or recurrent endometrial carcinoma is currently the subject of ongoing clinical trials [7, 8, 16-18]. Therefore, this study was conducted to compare the efficacy and safety of a combination of ICI plus chemotherapy, ICI plus TKI, ICI monotherapy, and chemotherapy-only regimens in the treatment of advanced or recurrent endometrial cancer with known mismatch repair (MMR) status. The information obtained in this study aims to provide better guidance for the management of patients with advanced or recurrent endometrial cancer.

2. Method

This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement and was registered on the International Prospective Register of Systematic Reviews (PROSPERO): CRD42023472033 [19]. Searching was conducted in various databases such as Scopus, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. The following keywords were used: ("immune checkpoint inhibitor" OR "immunotherapy" OR "PD-1 inhibitor" OR "PD-L1 inhibitor" OR "CTLA-4 inhibitor" OR "pembrolizumab" OR "nivolumab" OR "cemiplimab" OR "dostarlimab" OR "atezolizumab" OR "avelumab" OR "durvalumab" OR "ipilimumab") OR ("chemotherapy" OR "carboplatin" OR "paclitaxel" OR "doxorubicin") OR ("tyrosine kinase inhibitor" OR "TKI") AND ("endometrial cancer" OR "endometrial carcinoma" OR "endometrial neoplasm") for databases which do not apply medical subheading (MeSH) terms; and ("Endometrial Neoplasms"[Mesh]) AND (("Chemotherapy" OR

"Carboplatin" OR "Paclitaxel" OR "Doxorubicin") OR ("Immune Checkpoint Inhibitors"[Mesh])) OR ("Tyrosine Kinase Inhibitors"[Mesh])) for databases which apply MeSH terms.

All found studies were filtered using the criteria. Inclusion criteria were set as follows: (1) randomized controlled trials; (2) involving participants with advanced or recurrent endometrial cancer (FIGO stage III–IV) aged 18 years or older; (3) studying interventions such as ICI, TKI, chemotherapy, or their combinations alongside adequate comparators; (4) studying outcomes including progression-free survival (PFS) and overall survival (OS); (5) studying safety profiles. Exclusion criteria were as follows: (1) written in languages other than English; (2) studies not yet conducted. Selected studies were gathered and identified using Mendeley to remove duplicates. All studies underwent a selection process carried out by all authors, with any discrepancies discussed to reach a consensus. All selected studies were further assessed for quality using the Cochrane Risk of Bias tool 2.0 (RoB 2.0) [20]. Studies with good qualities were included in this review.

Included studies were extracted for their characteristics, such as trial name, registration number, first author, publication year, study design, study phases, drug used, dosage and regimen, total participants, duration of follow-up, and type of financial support. The expected primary outcome was progression-free survival (PFS). Secondary outcomes were overall survival (OS) and treatment-related adverse effects (TRAE), which were defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [21]. Meta-analysis was conducted on sufficient outcome data using Review Manager 5.4 in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [22]. The fixed effect model was used if tests of heterogeneity are not significant (I^2 <50% or P >0.1); however, the random effect model was used if statistical heterogeneity is observed (I^2 >=50% or P <0.1). Network meta-analysis was conducted if the data were adequate to determine the relationship between therapy modalities. A p-value of less than 0.5 was used to determine statistical significance. Subgroup analysis of mismatch repair deficient (MMRd) and proficient (MMRp) was performed.

3. Result and Discussion

We found five studies after thorough searching and selection (Figure 1). All studies were randomized controlled trials that demonstrated good quality in terms of proper randomization processes, minimal deviations from the intended interventions, appropriate handling of missing outcome data, accurate measurement of outcomes, and proper selection of reported results (Figure 2) [23-27].

There were five studies conducted between 2022 and 2023 that addressed the novelty of this topic. Randomized controlled trials (RCTs) were conducted between phases 2 and 3. Three studies compared the ICI plus chemotherapy combination to a chemotherapy-only regimen, one study compared the ICI plus TKI combination to a chemotherapy-only regimen, and one study compared the ICI plus TKI combination to ICI monotherapy. All studies involved 2,321 subjects with a minimum follow-up period of 10.7 months. All studies were funded by either private or public funds (Table 1) [23-27].

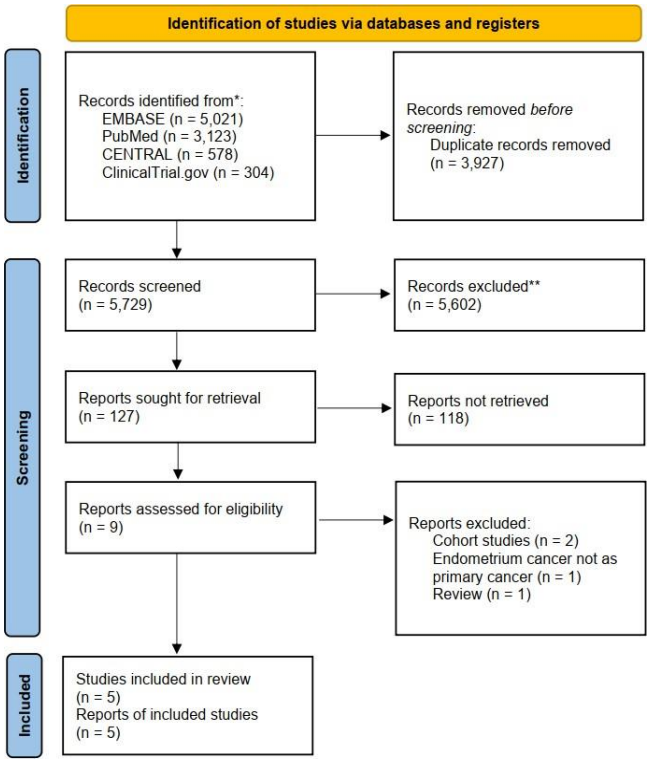

Figure 1.
PRISMA flowchart of searching and selection of included studies [19].

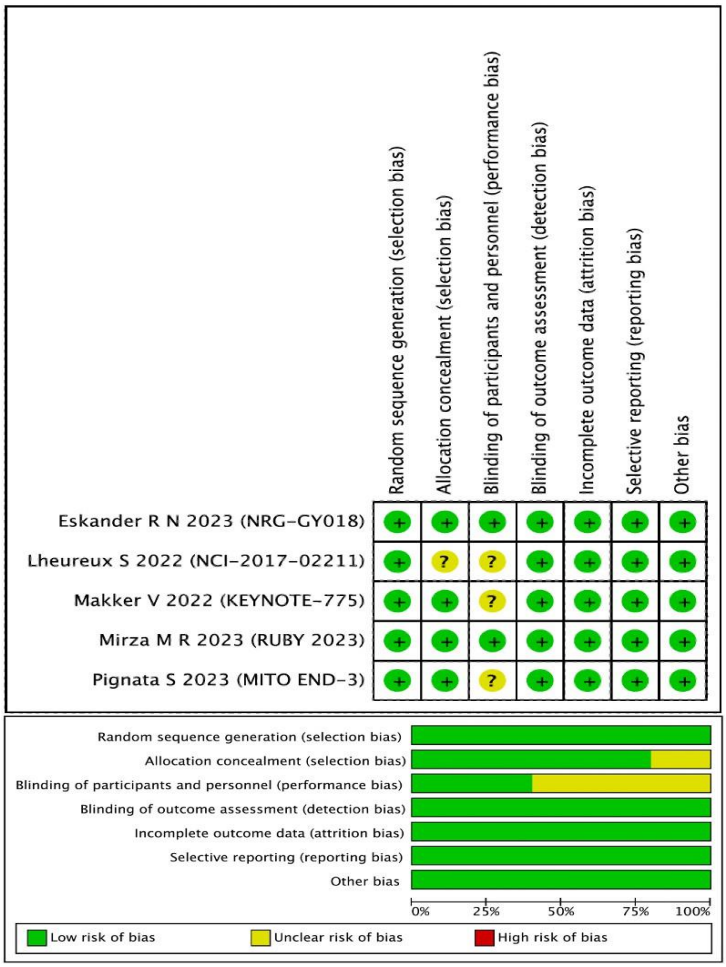

Figure 2.
Critical appraisal of included studies according to Cochrane Risk of Bias 2 tool [20, 23-27].

Table 1.
Characteristics of included studies [23-27].

Trial		First Author	Publication Year	Design	Phase	Name of drug	Dosage and regimen	Subjects size	Follow up (months)	Financial support
Name	Registration No									
MITO END-3	NCT03503786	Pignata, et al. [23]	2023	RCT	2	Carboplatin and Paclitaxel plus Avelumab v. Carboplatin and Paclitaxel	Carboplatin (AUC 5 mg/mL x min) and Paclitaxel (175 mg/m2) every 3 weeks for 6-8 cycles plus Avelumab (10 mg/kg IV) v. Carboplatin and Paclitaxel	125	23.3 (IQR 13.2-29.6)	Yes (Pfizer)
KEYNOTE-775	NCT03517449	Makker, et al. [24]	2022	RCT	3	Lenvatinib plus Pembrolizumab v.Chemotherapy	Lenvatinib (20 mg) once daily plus pembrolizumab (200 mg) IV every 3 weeks vs. Doxorubicin (60 mg/m2 IV) every 3 weeks or Paclitaxel (80 mg/m2 IV) every 3 weeks and 1 week off	827	12.2 v. 10.7	Yes (Eisai & Merck)
RUBY 2023	NCT03981796	Mirza, et al. [25]	2023	RCT	3	Dostarlimab plus Carboplatin and Paclitaxel followed by Dostarlimab v. Placebo plus Carboplatin and Paclitaxel followed by Placebo	Dostarlimab (500 mg) plus Carboplatin (AUC 5 mg/mL x min) and Paclitaxel (175 mg/m2) every 3 weeks for the first six cycles, followed by Dostarlimab (1000 mg) every 6 weeks up to 3 years v. Placebo plus Carboplatin and Paclitaxel, followed by Placebo.	494	24.8 (19.2-36.9)	Yes (GSK)
NRGY018	NCT03914612	Eskander, et al. [26]	2023	RCT	3	Paclitaxel plus Carboplatin and Pembrolizumab followed by Pembrolizumab v. Paclitaxel plus Carboplatin and placebo followed by Placebo	Palixatel (175 mg/m2) every 3 weeks plus carboplatin (AUC 5 mg/mL x min) and Pembrolizumab (200 mg) for 6 cycles followed by Pembrolizumab (200 mg) every 6 weeks v. Paclitaxel plus Caboplatin and Placebo followed by Placebo	816	12.0 v. 7.9	Yes (Merck)
NCI-2017-02211	NCT03367741	Lheureux, et al. [27]	2022	RCT	2	Cabozantinib plus Nivolumab v. Nivolumab	Cabozantinib 40 mg/day for 28 days and Nivolumab 240 mg/day for every 14 days vs. Nivolumab 240 mg every 28 days	59	15.9	Yes (NCI & ASCO)

Source: Abbreviations: RCT = randomized-controlled trials; AUC = area under the curve; IV = intravenous; IQR = inter-quartile range; GSK = Glaxo SmithKline; NCI = National Cancer Institute; ASCO = American Society of Clinical Oncology

Analysis among studies showed that ICI plus chemotherapy combination provided better PFS among dMMR recurrent or advanced endometrial cancer patients compared to a chemotherapy-only regimen (OR = 0.021; 95% CI = 0.003–0.140). However, PFS among ICI monotherapy and ICI plus TKI were not statistically different when compared to the chemotherapy-only regimen with an odds ratio of 1.6 (95% CI = 0.016–130.000) and 0.490 (95% CI = 0.020–10.000) (Figure 3). The ICI plus chemotherapy combination provided the highest rank among other regimens in the rank probabilities plot. Analysis of studies through leverage versus residual deviance graph suggested that there was no risk of outlier study which could cause any bias, thus the result has enough power and low to no risk of deviation (Figure 4).

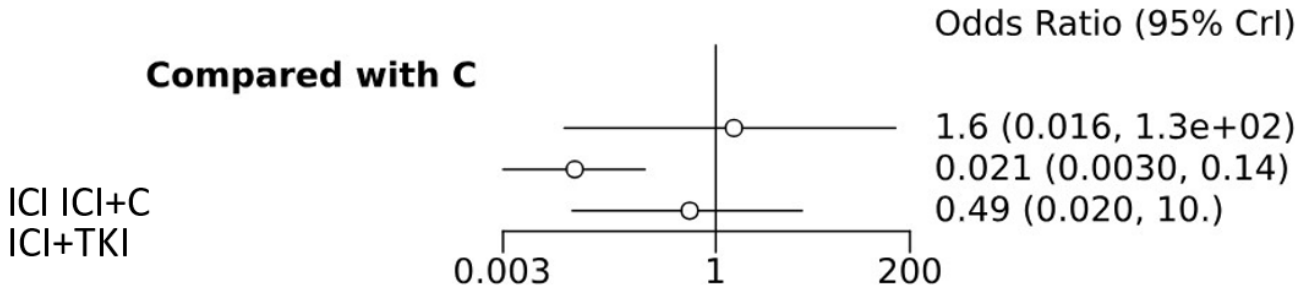

Figure 3.
Forest plot of ICI plus C vs ICI plus TKI vs ICI monotherapy vs C-only regimen towards PFS among dMMR primary advanced or recurrent endometrial cancer patients [23-27].

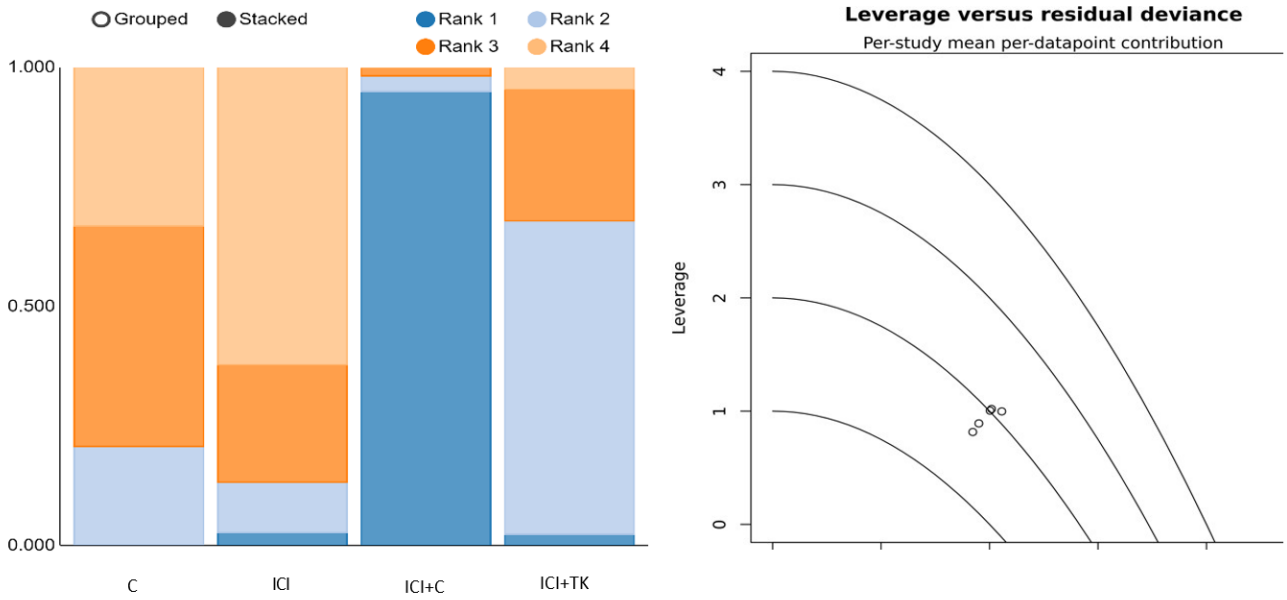

Figure 4.
Left to right: (a) Ranked probability of ICI plus C vs ICI plus TKI vs ICI monotherapy vs C-only regimen towards PFS among dMMR primary advanced or recurrent endometrial cancer patients; (b) Residual deviance plot of studies involved in analysis of ICI plus C vs ICI plus TKI vs ICI monotherapy vs C-only therapy towards PFS among dMMR primary advanced endometrial or recurrent cancer patients [23-27].

Analysis among pMMR primary advanced or recurrent endometrial cancer patients showed that there was no superiority of either of ICI monotherapy, ICI plus chemotherapy, nor ICI plus TKI regimens towards the chemotherapy-only regimen, along with an odds ratio of 1.600 (95% CI = 0.020–140.000), 1.600 (95%

CI = 0.290–9.900), and 0.470 (95% CI = 0.022–9.500) (Figure 5). Rank probabilities plot, however, favored the ICI plus TKI combination over other regimens. Leverage versus residual deviance showed that there was no risk of bias as all studies were similarly distributed (Figure 6).

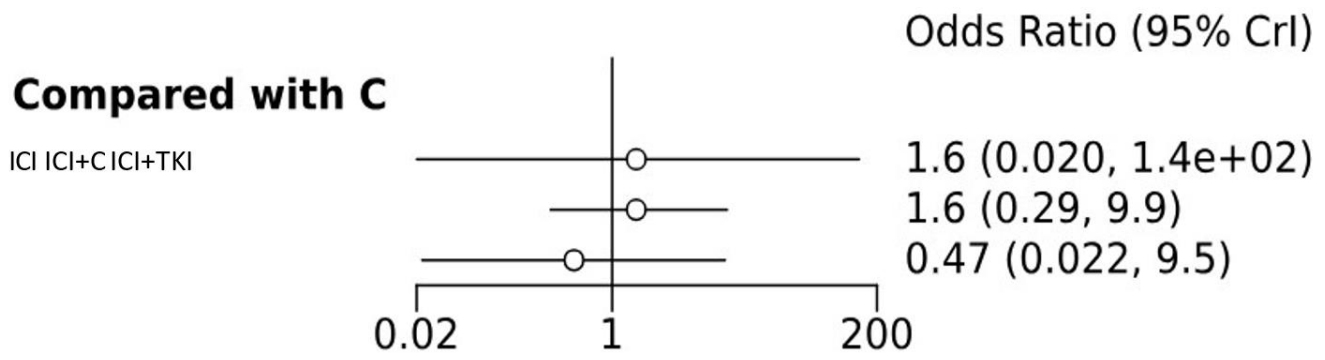

Figure 5.
Forest plot of ICI plus C vs ICI plus TKI vs ICI monotherapy vs C-only regimen towards PFS among pMMR primary advanced or recurrent endometrial cancer patients [23-27].

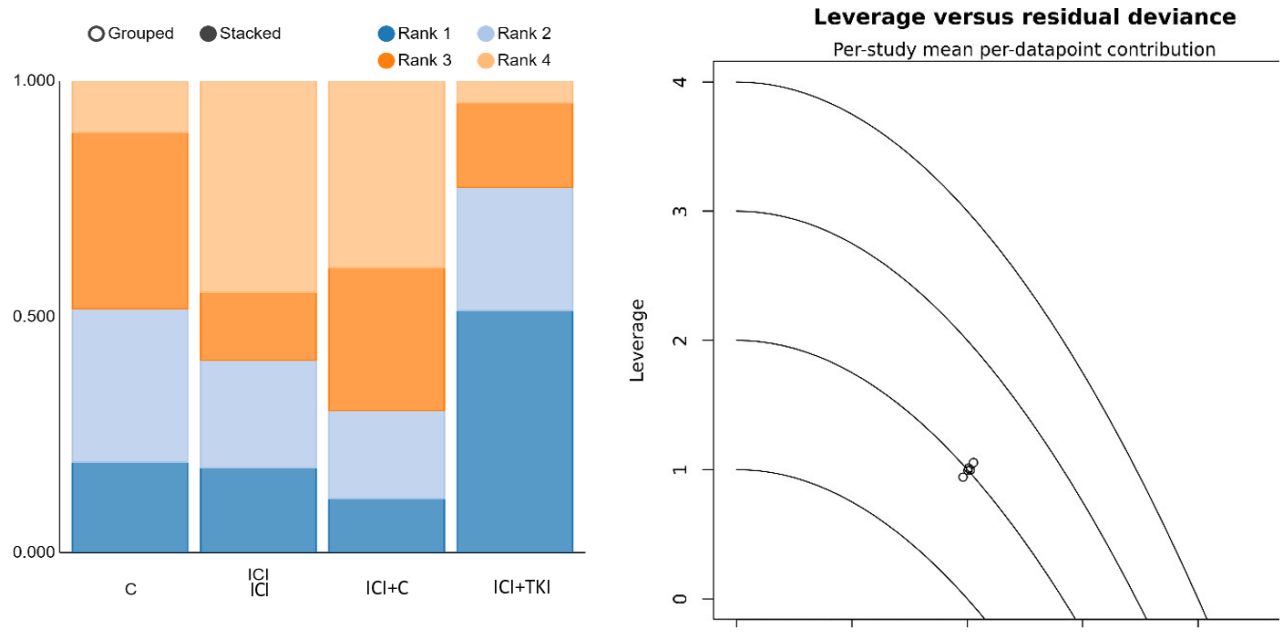

Figure 6.
Left to right: (a) Ranked probability of ICI plus C vs ICI plus TKI vs ICI monotherapy vs C-only regimen towards PFS among pMMR recurrent or advanced endometrial cancer patients; (b) Residual deviance plot of studies involved in analysis of ICI plus C vs ICI plus TKI vs ICI monotherapy vs C-only regimen towards PFS among pMMR primary advanced or recurrent endometrial cancer patients [23-27].

Data on the overall response rate was not available; hence, it was not analyzed. Overall survival was higher among patients receiving ICI plus TKI combination and ICI plus C combination compared to chemotherapy-only regimens in dMMR and pMMR advanced or recurrent endometrial patients (Table 2). In terms of adverse events, there were more adverse events observed among the ICI plus chemotherapy regimen and the ICI plus TKI regimen compared to the chemotherapy-only regimen. However, there was no significant difference in severe and life-threatening adverse events among groups in most studies. The MITO END-3 study reported that there were more serious adverse events in the ICI plus chemotherapy group, but no certain deaths caused by treatment. RUBY 2023 reported more grade 3 or higher adverse events in the ICI plus chemotherapy group, but also reported that there were no treatment-related deaths during the follow-up period. The NCI-2017-02211 study indicated that the ICI plus TKI regimen was considered more toxic compared to ICI monotherapy in terms of serious treatment-related adverse events (Table 3). Results of this study were considered high in GRADE based on BMJ Best Practice, as the authors have a lot of confidence that the true effect is similar to the estimated effect. This was based on a low risk of bias in selected studies, precision of analysis, consistency within results, and directness of outcomes.

Table 2.
Comparison of overall survival between recurrent or advanced endometrial cancer patients receiving various regimens of therapies [24, 25, 27].

Trial Name	Registration No	Regimen	Mean	SD	n	Mean	Control SD	n
KEYNOTE-775	NCT03517449	ICI+TKI v. C	18.3	1.325	411	11.4	0.6	416
RUBY 2023	NCT03981796	ICI+C v. C	71.3	3.15	245	56.0	3.4	249
NCI-2017-02211	NCT03367741	ICI+TKI v. ICI	13.0	2.05	36	7.9	1.89	18

Source: Abbreviations: ICI = immune checkpoint inhibitor; C = chemotherapy; TKI = tyrosine kinase inhibitor; SD = standard deviation.

Table 3.
Comparison of adverse events between treatment regimens of primary advanced or recurrent endometrial cancer [23-27].

Name	Trial Registration No	Regimen	Safety
MITO	NCT03503786	ICI+C v. C	More serious adverse events (38.7% vs. 11.1%)
END-3			Less neutrophil count decrease (31% vs. 43%)
			Two deaths occurred in the experimental group (one
			respiratory failure following severe myositis, probably
			related to treatment; one cardiac arrest, not related to
			treatment)
KEYNOTE-	NCT03517449	ICI+TKI v. C	No difference in grade 5 adverse events (5.7% vs. 4.9%)
775			Higher adverse events of grade 3 or higher in
			experimental (88.9% vs. 72.7%)
RUBY 2023	NCT03981796	ICI+C v. C	Rash and maculopapular rash were largely different
			(22.8% vs. 13.8% and 14.1% vs. 3.7%)
			Incidence of grade 3 or higher adverse events and
			Serious adverse events were higher (70.5% vs. 59.8% and
			37.8% vs. 27.6%)
			More discontinuation (17.4% vs. 9.3%)
			More hypothyroidism (11.2% vs. 2.8%)
			More elevation of alanine aminotransferase (5.8% vs.
			0.8%)
NRGY018	NCT03914612	ICI+C v. C	Similar frequencies of grade 3 or 4 adverse events
			Expected grade 5 adverse events in both groups
			One death is possibly related to the intervention in
			experimental group
NCI-2017-	NCT03367741	ICI+TKI v. ICI	More treatment-related toxicities in combination
02211			therapy
			More serious treatment-related adverse events (31% vs.
			0%)

Source: Abbreviations: ICI = immune checkpoint inhibitor; C = chemotherapy; TKI = tyrosine kinase inhibitor.

4. Discussion

The addition of ICI to chemotherapy provided better outcomes compared to a chemotherapy-only regimen in the treatment of dMMR primary advanced or recurrent endometrial cancer patients. Dostarlimab, an ICI, has shown potential in many other studies. It was reported in several studies that administration of dostarlimab gave significant benefits as a second-line treatment in dMMR primary advanced or recurrent endometrial cancer patients who failed platinum-based chemotherapy [28-31]. This was an addition to studies that had been conducted previously, which stated that there was no significant superiority of PD-1 and/or PD-L1 inhibitors over chemotherapy in recurrent or metastatic endometrial cancers. The earlier studies could only report slight to minimal improvements among patients receiving ICIs [29, 32-34].

MMR status was expected to be predictive of the superiority of combination therapy. It was known that dMMR status was more responsive to ICI and chemotherapy combination therapy due to its less malignant nature. pMMR tumors tend to be more heterogeneous and are at higher risk among histological subtypes, for example, carcinosarcomas. Therefore, pMMR tumors were more challenging to treat compared to dMMR tumors, which explained this study's inability to demonstrate the superiority of combination therapy over chemotherapy-only regimens in patients with dMMR recurrent or advanced endometrial cancer [35, 36]. Those findings also suggested that testing for MMR status was important in order to predict treatment success rates and patients' prognosis [37-39]. However, pMMR tumors express high levels of PD-1, hence providing promising prospects for further study and development of ICI applications towards pMMR endometrial cancers [29].

Reports on ICI toxicity suggested that there were no life-threatening direct adverse effects attributable to ICI administration. There were no adverse effects caused by immune reactions towards ICI administration, according to a study [40]. A study by Mirza, et al. [25] reported that there was a 10 percent higher number of serious and severe adverse events

observed with the ICI plus chemotherapy combination regimen. However, the same study reported that there were no differences in discontinuation rates and quality of life between the ICI plus chemotherapy regimen and the chemotherapy-only regimen [25]. Those findings showed that the risks associated with the ICI plus chemotherapy combination regimen were outweighed by the benefits; therefore, the administration of the ICI plus chemotherapy regimen was considered beneficial for patients with recurrent or advanced endometrial cancer, especially those with the dMMR subtype.

This was the first systematic review to compare efficacy between ICI, TKI, and chemotherapy, to the authors' knowledge. Therefore, the knowledge obtained by this study was intended to help clinicians provide better medical care for patients with recurrent or advanced endometrial cancers and to assist researchers in conducting further studies on this topic. However, the analysis in this study was based on five studies, and it could be improved if more studies were included. Therefore, more high-quality, randomized controlled studies involving diverse populations should be conducted to produce an updated systematic review on this topic, utilizing the knowledge gained from this study.

5. Conclusion

Immune checkpoint inhibitor plus chemotherapy combination regimen yielded better progression-free survival among mismatch repair-deficient primary advanced or recurrent endometrial cancer patients compared to chemotherapy, yet suggested better outcomes compared to immune checkpoint inhibitor monotherapy or immune checkpoint inhibitor plus tyrosine kinase inhibitor combination regimen. The immune checkpoint inhibitor plus chemotherapy combination regimen had few serious adverse effects and treatment-related deaths; thus, benefits outweighed risks, and it should be given to mismatch repair-deficient advanced or recurrent endometrial cancer patients.

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