v. 5, n. 3, 2025

International Journal of Health Science

MONOCLONAL ANTIBODIES AS TARGETED THERAPIES IN ADVANCED OR RECURRENT ENDOMETRIAL CANCER: A SYSTEMATIC REVIEW

Acceptance date: 09/01/2025

Isabely Guedes da Silva
Student at Universidade Nove de Julho, São Paulo/SP, Brazil

Allan Vagner Monteiro da Silva Zannon
Student at Universidade Nove de Julho, São Paulo/SP, Brazil

Ana Paula Nunes Guanaes
Student at Universidade Nove de Julho, São Paulo/SP, Brazil

Beatriz Viguetti Godoy
Student at Universidade Nove de Julho, São Paulo/SP, Brazil

Regiane dos Santos Feliciano
Professor at Universidade Nove de Julho, São Paulo/SP, Brazil

Abstract: Introduction: Advanced or recurrent endometrial cancer presents considerable therapeutic challenges, with limited options and an unfavorable prognosis. The development of target therapies, such as monoclonal antibodies, has emerged as a promising alternative for the treatment of this disease. **Objective:** This study aimed to conduct a comprehensive systematic review of clinical trials investigating the use of monoclonal antibodies in the treatment of advanced or recurrent endometrial cancer. The main focus was to elucidate the mechanisms of action, identify potential side effects and evaluate the clinical efficacy and therapeutic results of these therapies. **Methods:** The search for relevant articles was conducted in the PubMed, Embase and Scopus databases, covering the period from 1982 to 2023. Only human studies, randomized or not, in phase II or III, written in English, using the descriptors "monoclonal", "antibody", "endometrial" and "cancer" were included. The selection of studies and data extraction were carried out by four independent reviewers, following the guidelines of the PRISMA protocol. **Results:** The initial search resulted in the identification of 2069 articles, of which 25 were included in the final review after applying the eligibility criteria. The results showed that the use of monoclonal antibodies, such as pembrolizumab, dostarlimab, avelumab and durvalumab, resulted in significant improvements in overall survival (OS) and progression-free survival (PFS) in patients with advanced or recurrent endometrial cancer, especially in those with MSI-H/dMMR tumors. **Conclusions:** Monoclonal antibodies represent a promising class of targeted therapies for advanced or recurrent endometrial cancer, with the potential to improve patients' clinical outcomes. However, more studies are needed to define the optimal role of each antibody and identify the best therapeutic combinations, taking into account the individual molecular profile of each patient.

Keywords: Endometrial cancer; Monoclonal antibodies; Targeted therapies; Immunotherapy; Systematic review

INTRODUCTION

Endometrial cancer is one of the most prevalent gynecological neoplasms, with an increasing incidence worldwide. In 2024, it is estimated that approximately 67,880 new cases of endometrial cancer will be diagnosed in the United States, resulting in around 13,250 deaths, according to data from the American Cancer Society. The main risk factors for the development of endometrial cancer include hormone therapy, metabolic syndromes, obesity, diabetes and genetic predisposition.[1,2,3,4,5] In addition, patients with advanced or recurrent endometrial cancer face an unfavorable prognosis, often due to resistance to conventional treatments and the limitation of available therapeutic options.[6,7] Given this scenario, the search for more effective and specific therapeutic approaches becomes crucial.

Targeted therapies, in particular the use of monoclonal antibodies, are showing promise in the treatment of cancer. These antibodies are designed to bind to specific targets present on cancer cells, inhibiting their growth and promoting cell death.[8] The success of therapies such as trastuzumab in the treatment of breast cancer demonstrates the potential of monoclonal antibodies in oncology.[9]

The application of these agents in gynecological cancers has been the subject of several studies, and antibodies such as nivolumab and dostarlimab are being investigated and used in the treatment of endometrial cancer. These antibodies, for example, act by blocking the interaction between PD-1 (programmed cell death protein 1), present on T cells, and its ligand PD-L1, expressed on cancer cells.[18,25] This interaction prevents the cancer from escaping the immune response, allowing the immune system to attack and destroy the tumor cells, as illustrated in Figure 1.

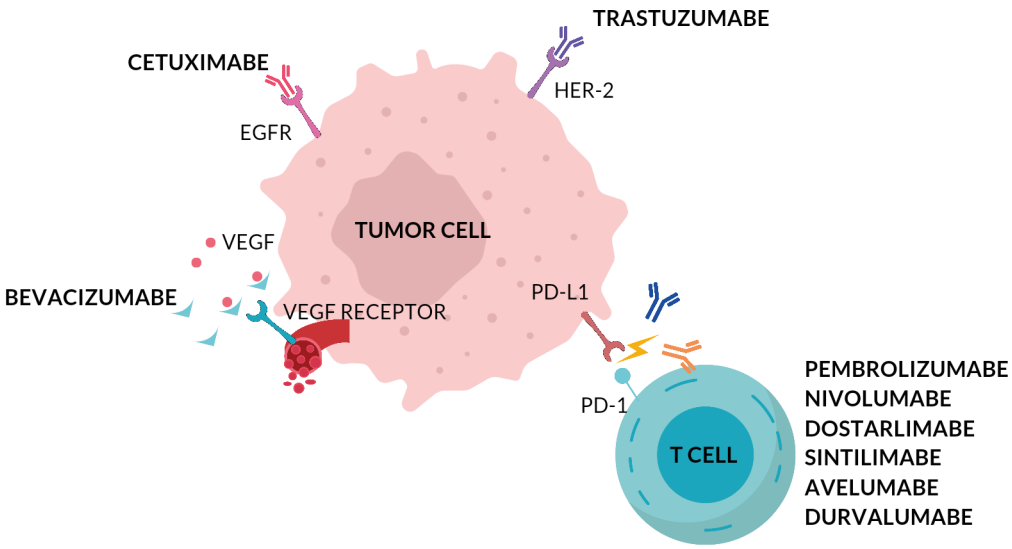

Figure 1: Mechanism of action of targeted therapies

Mechanisms of action of monoclonal antibodies in cancer treatment. The image illustrates different classes of monoclonal antibodies, each directed at specific targets involved in tumor progression. Cetuximab blocks EGFR, bevacizumab inhibits VEGF, and trastuzumab binds to the HER-2 receptor, blocking its signaling. Durvalumab and avelumab bind to PD-L1 and block its interaction with the programmed death receptor 1 (PD-1). Finally, pembrolizumab, nivolumab, dostarlimab and sintilimab act on PD-1, all with the aim of reactivating the anti-tumor immune response.

Given the urgent need to improve the treatment of advanced or recurrent endometrial cancer, this study sets out to carry out a comprehensive systematic review of randomized and non-randomized clinical trials that have investigated the use of monoclonal antibodies in this patient population. The central objective is to elucidate the mechanisms of action of these innovative therapies, identify their potential side effects and, above all, evaluate the clinical efficacy and therapeutic results achieved with their use. From this in-depth analysis, it is hoped to contribute to understanding the role of monoclonal antibodies in the treatment of advanced or recurrent endometrial cancer, providing valuable information for clinical decision-making and the development of more effective and personalized therapeutic strategies for this challenging disease.

METHODS

This study was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol,[10] making it a systematic review of clinical trials.

The search for relevant articles was carried out in three electronic databases: PubMed, Embase and Scopus, covering the period from 1982 to 2023. Only human studies, randomized or not, in phase II or III, written in English, using the following descriptors were included: "monoclonal", "antibody", "endometrial" and "cancer".

After searching each database, the articles were imported into Rayyan software,[11] where duplicates were automatically removed. The abstracts were then read in pairs by the researchers for screening and initial analysis.

In the process of selecting the clinical trials, four reviewers independently examined the titles and abstracts in Rayyan[11] to make the

first exclusions. The studies that met the inclusion criteria were selected for full reading. At this stage, the opinion of each of the four reviewers was considered individually, and for a study to be included in the review, the consensus of at least three reviewers was required.

The reasons for excluding studies were recorded in the folder of non-included studies generated by the Rayyan software.[11] Among the main reasons for exclusion were: book chapters, abstracts, case discussions, case reports, studies using laboratory cells, animal studies and studies that did not contain specific data on endometrial cancer.

The data was extracted independently by four reviewers and organized in a standardized table containing the following information: a) title of the text; b) authors and year of publication; c) phase of the study; d) country; e) intervention; f) administration; g) number of patients; h) age of the intervention group; i) therapeutic target; j) biomarker; k) "progression-free survival" (PFS); l) "overall survival" (OS); m) "odds ratio" (OR).

RISK OF BIAS

The risk of bias and the methodological quality of the included studies were independently assessed by four reviewers, using the Downs and Black scale (1998).[12] The results of this assessment were compiled in a table, showing the score obtained by each study in each category analyzed.

RESULTS

SELECTION OF STUDIES

The initial search for articles published between 1982 and 2023 resulted in the identification of 2069 articles. After importing them into Rayyan software,[11] 836 duplicates were identified and removed, leaving 1233 articles for peer review of the abstracts. The inclusion criteria covered clinical trials investigating the use of monoclonal antibodies in the treatment of endometrial cancer, while the exclusion criteria involved studies not written in English, reviews, book chapters and case studies. At the end of the screening, 27 articles were selected for full reading. Of these, 25 were included in the final review, while studies using Ipilimumab and Atezolizumab as target therapies were excluded because they were still ongoing and did not present available outcomes.

CHARACTERISTICS OF THE STUDIES

BIOMARKERS

Endometrial cancer is classified into four distinct molecular subtypes according to The Cancer Genome Atlas (TCGA): polymerase epsilon ultramutated (POLE), microsatellite instability hypermutated (MSI-H), low copy number and high copy number, each with specific prognoses.[13] MSI-H is a phenotype of the deficient mismatch repair (dMMR) pathway, which accelerates the accumulation of mutations in the DNA. Microsatellite stable (MSS) or proficient mismatch repair (pMMR) occurs when the DNA repair system (MMR) is functioning correctly, representing the normal state of the cells. Therapy with immune checkpoint inhibitors (ICB) has shown particular efficacy in solid tumors with dMMR, pMMR and p53 mutation.[13]

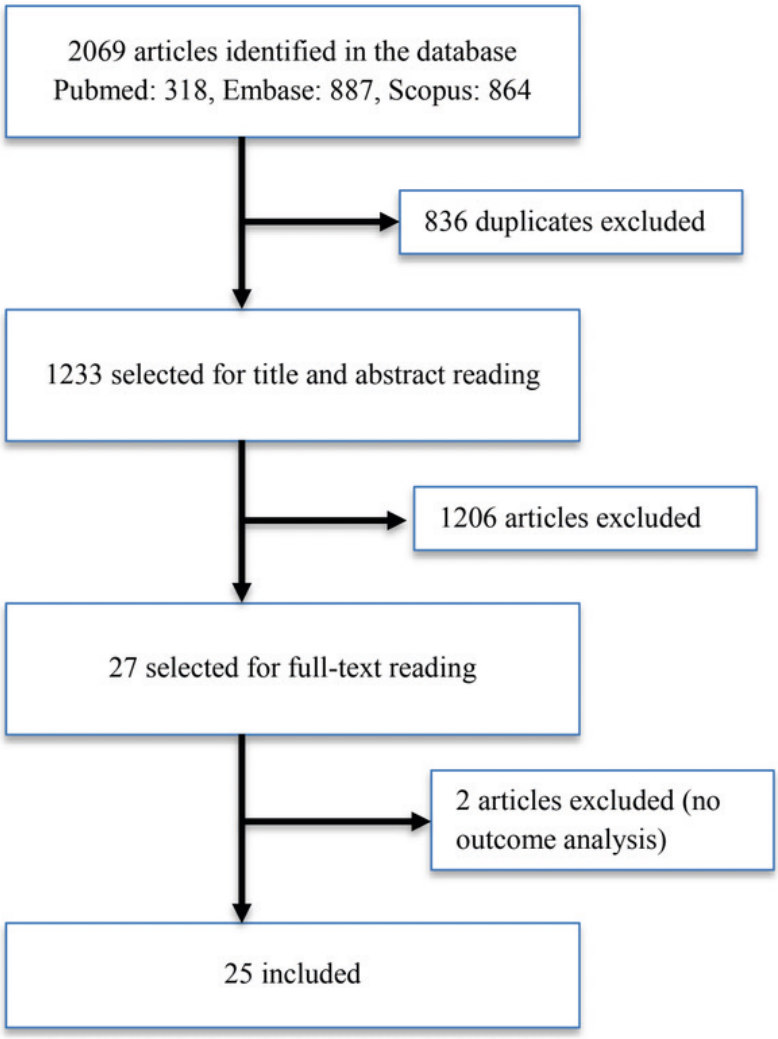

Figure 2: Study selection flowchart

Visual representation illustrating the process of identifying, screening and including studies in the systematic review. The flowchart details the number of records identified at each stage, exclusion numbers and the final number of studies included in the analysis.

Author, year and country	Study phase/N. patients/age (mean or range)	Intervention/target therapy/biomarker	PFS	OS	OR
Simpkins et al., 2014 (USA)	Phase 2 / 15 / (63)	Paclitaxel, Carboplatin and Bevacizumab / VEGF	6 months 93% (95% CI)	mOS 58 months	73%
Viswanathan et al., 2015 (USA)	Phase 2 / 34 / (59)	Radiotherapy, Cisplatin, Bevacizumab and chemotherapy	DFS 2 years 79.1%	OS 2 years 96.7%	-
Aghajanian et al., 2018	Phase 2 / 349 / (63)	Chemotherapy [CP] and Bevacizumab (1) vs CP and Temsirolimus (2) vs Ixabepilone, Carboplatin and Bevacizumab (3) vs Reference CP	HR PFS 0.81 (1) vs 1.22 (2) vs 0.87 (3)	mOS 34 (1) vs 25 (2) vs 25.2 (3) vs 22.7 months	59% (1) vs 55% (2) vs 53% (3) vs 51%
Lorusso et al., 2019 (ITA)	Phase 2 / 108 / (63)	Carboplatin and paclitaxel (PC) and Bevacizumab vs PC / VEGF	13.7 vs 10.5 months (95% CI)**	40 vs 29.7 months**	74.4% vs 53.1%**

Konstantinopoulos et al., 2019 (USA)	Phase 2 / 33	Avelumab / PD-1 / dMMR and pMMR	PFS 6 months 40% (dMMR) and 6.25% (pMMR)	-	26.7% (dMMR) and 6.25% (pMMR)
Slomovitz et al., 2020 (USA)	Phase 2 / 30 / (64)	Cetuximab (erbitux) / EGFR	-	-	-
Makker et al., 2020 (USA)	Phase 1b and 2 / 108 / (65.1)	Lenvatinib and Pembrolizumab / VEGF and PD-1 / pMMR and dMMR	7.4 months (95% CI)	16.7 months	38% (week 24) 63.6% (dMMR) and 36.2% (pMMR)
Bellone et al., 2021 (USA)	Phase 2 / 24 / (69)	Pembrolizumab / PD-1 / dMMR	mPFS 23.5 months	mOS 40 months	58%
Antill et al., 2021 (AUS)	Phase 2 / 71 / (67)	Durvalumab / PD-1 / dMMR and pMMR	mPFS 8.3 dMMR vs 1.8 months pMMR	12 months 71% dMMR vs 51% pMMR	OTRR 47% dMMR vs 3% pMMR
Post et al., 2022 (HOL)	Phase 2 / 55 / (69)	Durvalumab and Olaparib / PD-1 and PARP / dMMR	PFS of ≥ 6 months in 50% was not achieved	mOS 8.4 months (95% CI)	16%
Konstantinopoulos et al., 2022 (USA)	Phase 2 / 35 / (67.9)	Talazoparib and Avelumab / PARP and PDL-1 / pMMR	6 months 22.9% (95% CI)		11.40% (95% CI)
Yonemori et al., 2022 (JAP)	Phase 3 / 104 / (62.5)	Lenvatinib and Pembrolizumab vs Doxorubicin or Paclitaxel / VEGF and PD-1 / pMMR and dMMR	mPFS pMMR: 5.6 vs 5.6 months overall mPFS: 7.2 vs 5.4 months**	mOS pMMR: 16.7 vs 12.2 months general mOS: NR vs 12 months**	ORR pMMR: 31.8% vs 29.8% Overall ORR: 36.5% vs 26.9%
Kelkar et al., 2022 (USA)	140 / (66)	Chemotherapy and Bevacizumab (1) vs hormone therapy (2) / PD-1 / dMMR and pMMR	rwPFS 5 (1) vs 5.5 months (2)	mOS 10 (1) vs 9 months (2)	-
O'Malley et al., 2022	Phase 2 / 90 / (64) (cohort D)	Pembrolizumab / PD-1 / dMMR	mPFS 13.1 months	NR	48%
Lheureux et al., 2022 (USA and CAN)	Phase 2 / 82 / (69.5)	Cabozantinib and Nivolumab (A and C) vs Nivolumab (B) / MET, VEGF, RET, AXL	mPFS 5.3 (A) vs 1.9 months (B) (90% CI)	mOS 13 (A) vs 7.9 months (B)	25% (A) vs 11% (B)
Liao et al., 2022 (CHI)	93 / (45.9)	Nivolumab and Bevacizumab vs Bevacizumab and chemotherapy / PD-1 and VEGF / dMMR and	-	mOS 33.2 vs 21.8 months**	-
Wei et al., 2022 (CHI)	Phase 2 / 23 / (56)	Sintilimab and anlotinib / PD-1 and VEGF / dMMR and pMMR	PFS > 6 months 76.7% and > 12 months 57.1%	-	73.9%
De Jaeghere et al., 2022 (BEL)	Phase 2 / 25 / (67) endometrial section	Pembrolizumab, radiotherapy and immunomodulator cocktail / PD-1	irPFS 3.6 weeks	mOS 37.4 weeks	irORR 12%
Westin et al., 2023	Phase 3 / 718 / (63)	Chemotherapy (CP) vs CP and Durvalumab vs CP, Durvalumab and Olaparib****/ PD-1 / dMMR and pMMR	mPFS 9.6 vs 10.2 vs 15.1 months****	18.6 vs 18.4 and 18.7 months	-
Meric-Bernstam et al., 2023 (USA)	Phase 2 / 40 / (67)	Trastuzumab deruxtecan (T-DXd) / HER2	11.1 months	26 months	57.5%
Rodrigues et al., 2023 (FRA)	80 / (69)	Dostarlimab / PD-1 / dMMR	-	-	35%
Mirza et al., 2023	Phase 3 / 494 / (64)	Dostarlimab and chemotherapy / PD-1 / dMMR	PFS 24 months dMMR: 61.4% vs 15.7%*** PFS 24 months overall: 36.1% vs 18.1%***	24 months 83.3% vs 58.7%*** OS 24 months general 71.3% vs 56%***	-

Eskander et al., 2023 (USA, CAN, JAP, KOR)	Phase 3 / 816 / (66)	Pembrolizumab and chemotherapy / PD-1 / dMMR and pMMR	74% vs 38% mPFS pMMR 13.1 vs 8.7 months***	-	-
Makker; Aghajanian et al., 2023	Phase 1b and 2 / 108 / (65.1)	Lenvatinib and Pembrolizumab / VEGF and PD-1 / pMMR and dMMR	mPFS 7.4 months = 7.4 (pMMR) vs 26.4 months (dMMR)	17.7 months = 17.2 (pMMR) vs NE (dMMR)	39.8% = 38.3% (pMMR) vs 63.6% (dMMR)
Makker; Colombo et al., 2023	Phase 3 / 827 / (64)	Lenvatinib and Pembrolizumab / VEGF and PD-1 / pMMR	mPFS 6.7 vs 3.8 months (pMMR)** and 7.3 vs 3.8 months (general)**	mOS 18 vs 12.2 months (pMMR)** and 18.7 vs 11.9 months (general)**	32.4% vs 15.1%**

Table 1: Overview of the included studies and summary table illustrating the main characteristics of the studies.

** Experimental group vs. control group (chemotherapy)

*** Experimental group vs placebo group

**** Control group vs Durvalumab group vs Durvalumab group + Olaparib

Information from studies that were not identified was listed by indent. Studies that did not specify the phase they were in were included by the remaining inclusion criteria listed.

CURRENT MONOCLONAL ANTIBODY THERAPIES FOR ENDOMETRIAL CANCER

PEMBROLIZUMAB

Pembrolizumab is a humanized monoclonal antibody of the IgG4 type that acts by inhibiting the PD-1 receptor, promoting the reactivation of the immune response against tumor cells. In May 2017, the FDA approved pembrolizumab for the treatment of metastatic or unresectable MSI-H or dMMR solid tumors, recommending doses of 200 mg intravenously every 3 weeks or 400 mg every 6 weeks.[14] This approval was based on five clinical trials that included patients with MSI-H and/or dMMR endometrial cancer.[14]

Additionally, in 2019, pembrolizumab in combination with lenvatinib received approval for advanced MSI-H or dMMR endometrial cancer, with subsequent studies demonstrating significant clinical benefits and leading to full approval in 2021. The phase IB/II KEYNOTE-146 trial showed a median progression-free survival (PFS) of 7.4 months (95% CI 5.2 to 8.7) and a median overall survival (OS) of 17.7 months (95% CI 15.5 to 25.8).[15]

As for adverse effects, selected adverse reactions began within the first 10 weeks of treatment.[16] Fatigue, hypertension and nausea of severity ≥3 occurred in ≥5% of patients. The overall incidence of hypothyroidism was 51%, mainly grade 2 (46%).[16]

Another study involving 108 patients with endometrial carcinoma treated with pembrolizumab and lenvatinib showed an objective response rate (ORR) of 38.0% (95% CI, 28.8% to 47.8%).[17] In specific subgroups, the ORR was 63.6% (95% CI, 30.8% to 89.1%) in patients with MSI-high tumors and 36.2% (95% CI, 26.5% to 46.7%) in patients with MSI-stable tumors.[17] For previously treated patients, regardless of the tumor's MSI status, the median duration of response was 21.2 months (95% CI, 7.6 months to not estimable), the median PFS was 7.4 months (95% CI, 5.3 to 8.7 months) and the median OS was 16.7 months (95% CI, 15.0 months to not estimable). Grade 3 or 4 treatment-related adverse events occurred in 66.9% of patients.[17]

DOSTARLIMABE

Dostarlimab is an IgG4 monoclonal antibody directed against PD-1. In April 2021, the FDA granted accelerated approval to dostarlimab for the treatment of adult patients with recurrent or advanced dMMR endometrial cancer. This approval was based on the results of the A1 cohort of the GARNET study, which included 71 patients with dMMR whose cancer progressed during or after platinum-containing chemotherapy.[18] The confirmed objective response rate was 42.3%, with a complete response rate of 12.7% and a partial response rate of 29.6%.[18]

A phase III clinical trial (RUBY) evaluated the efficacy of adding dostarlimab to chemotherapy in patients with advanced or recurrent endometrial cancer. Of the 494 patients randomized, 118 (23.9%) had tumours with mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H). In the dMMR-MSI-H population, the estimated progression-free survival at 24 months was 61.4% (95% CI, 46.3 to 73.4) in the dostarlimab group and 15.7% (95% CI, 7.2 to 27.0) in the placebo group (hazard ratio for progression or death, 0.28; 95% CI, 0.16 to 0.50; P<0.001).[19] In the general population, progression-free survival at 24 months was 36.1% (95% CI, 29.3 to 42.9) in the dostarlimab group and 18.1% (95% CI, 13.0 to 23.9) in the placebo group (hazard ratio, 0.64; 95% CI, 0.51 to 0.80; P<0.001). Overall survival at 24 months was 71.3% (95% CI, 64.5 to 77.1) with dostarlimab and 56.0% (95% CI, 48.9 to 62.5) with placebo (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.87).[19]

The most common adverse events that occurred or worsened during treatment included nausea (53.9% of patients in the dostarlimab group and 45.9% in the placebo group), alopecia (53.5% and 50.0%) and fatigue (51.9% and 54.5%). Serious and severe adverse events were more frequent in the dostarlimab group compared to the placebo group.[(19)]

AVELUMAB

Avelumab is an IgG1 antibody that blocks PD-L1 and is used in the treatment of certain types of cancer, such as urothelial carcinoma and renal cell carcinoma.[20] In a phase II clinical trial for endometrial cancer, avelumab demonstrated an objective response rate (ORR) of 6.25% in patients with dMMR disease and an ORR of 40% in patients with pMMR mutations.[20] Microsatellite status and the presence of mutations in the POLE gene appear to influence the response to avelumab, even in patients who are PD-L1 negative.[20]

Another phase II trial investigated the efficacy of combining avelumab with talazoparib (a poly [ADP-ribose] polymerase inhibitor, PARPi) in recurrent endometrial cancer. Up to the cutoff date of November 30, 2020, progression-free survival (PFS) was 3.6 months (95% CI, 2.4-5.4 months), with a median follow-up of 12.9 months (range, 1.3-20.9 months).[21]

DURVALUMAB

Durvalumab is an immunoglobulin G1 kappa monoclonal antibody that blocks the interaction of PD-L1 with PD1 and CD80. The phase III trial investigated carboplatin/paclitaxel plus durvalumab followed by durvalumab maintenance with or without olaparib (PARP inhibitor) placebo in 718 patients.[22] A significant benefit in progression-free survival (PFS) was observed in the group receiving durvalumab (hazard ratio [HR], 0.71 [95% CI, 0.57 to 0.89]).[22]

A phase II trial evaluated the anti-tumor activity of durvalumab in a cohort of 71 patients with MMRp and MMRd advanced endometrial cancer.[23] MMR status was determined by immunohistochemistry to assess loss of protein expression. In the MMRp cohort, 1 to 3 lines of prior chemotherapy were allowed, while in the MMRd cohort, no prior treatment was required or up to 3 lines of prior chemotherapy were allowed.[23] The objective respon-

se rate (ORR) was 3% (1/35) in the MMRp cohort and 47% (17/36) in the MMRd cohort. Durvalumab was well tolerated, with 19% of patients experiencing grade 1 and 2 treatment-related adverse events.[23]

In the DOMEC study, the efficacy of durvalumab was evaluated in combination with olaparib, a PARP (Poly ADP-Ribose Polymerase) inhibitor, in patients with metastatic or recurrent endometrial cancer.[24] It was observed that 34% of patients had no disease progression at six months. The treatment response rate was 16%, with one patient achieving a complete response and seven showing partial responses.[24] With a median follow-up of 17.6 months, the patients had a median disease progression-free survival of 3.4 months and an overall survival (OS) of 8.0 months.[24] Grade 3 treatment-related adverse events were observed in 8 patients (16%), mainly anemia, with no reports of grade 4 or 5 treatment-related adverse events.([24])

NIVOLUMAB

Nivolumab is a fully humanized anti-human PD-1 monoclonal antibody of the IgG4 class. A comparative study investigated the efficacy of nivolumab in combination with bevacizumab versus bevacizumab in conjunction with paclitaxel chemotherapy. The results indicated that in the intervention group, median overall survival was not reached for patients with MMR deficiency (dMMR), while it was 29.2 months for patients with proficient mismatch repair (pMMR). In contrast, in the group treated with chemotherapy alone, overall survival was 12.4 months for patients with dMMR and 24.1 months for patients with pMMR.[25]

CETUXIMAB

Cetuximab is an IgG1 monoclonal antibody that blocks the epidermal growth factor receptor (EGFR) on the surface of cancer cells. Overexpression of the epidermal growth factor receptor (EGFR) is a common finding in endometrial cancer and has been associated with advanced stages of the disease and a worse prognosis. Activation of the receptor by ligands initiates signaling pathways that play important roles in tumorigenic processes, including continuation of the cell cycle, angiogenesis, protection against apoptosis. The Erbitux study evaluated 20 patients with progressive or recurrent endometrial cancer, of whom three (15%) showed a beneficial clinical response: one complete response and two stable disease.[26] The patient with a beneficial clinical response received a total of 27 cycles of treatment, while the two patients with stable disease were withdrawn from the study due to progression after four and six cycles, respectively.[26] Of the 10 non-evaluable patients, nine received ≤1 cycle due to clinical deterioration, and one patient had an anaphylactic reaction. One patient developed a grade 3 rash, which resolved after a delay in treatment, without the need for a dose reduction.([26]

BEVACIZUMAB

Bevacizumab is a monoclonal antibody that acts by inhibiting the vascular endothelial growth factor (VEGF), which is overexpressed in endometrial cancer and is associated with a higher histological grade and myometrial invasion, as well as a worse prognosis.

In addition to the study associating nivolumab mentioned above, another study also investigated its combination with a PD-1 inhibitor and compared its use to conventional chemotherapy. The proportion of patients with mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H) was similar between the two groups. Patients in the

combined treatment group had a significantly prolonged overall survival compared to those in the control group (33.2 months versus 21.8 months). Notably, in the combined treatment group, median overall survival was not reached for dMMR patients, while it was 29.2 months for pMMR patients (P <0.01). In contrast, in the control group, median overall survival was 12.4 months for dMMR patients and 24.1 months for pMMR patients (P <0.01).[27]

In a randomized phase II study, 349 patients with advanced or recurrent endometrial cancer were divided into three treatment groups: one receiving paclitaxel and carboplatin (PC) plus bevacizumab, another PC plus temsirolimus, and the third IC plus bevacizumab. Overall survival was significantly higher only in the group receiving PC plus bevacizumab.[28]

Another study evaluated the effect of treatment with paclitaxel, carboplatin and bevacizumab in patients with endometrial carcinoma. During the study, a total of 127 cycles of the combined therapy were administered, with a median of 8 cycles per patient (ranging from 1 to 20). Fourteen of the 15 patients (93%, 95% CI: 82-100) were progression-free after 6 months. The median follow-up was 36 months (ranging from 7 to over 58 months). The median progression-free survival was 18 months (CI: 11-25 months). The study recorded five complete responses and six partial responses, resulting in an overall response rate of 73% (CI: 45-91%). The median overall survival was 58 months (CI: 48-68 months).[29]

TRASTUZUMAB

Trastuzumab is a monoclonal antibody directed at the HER-2 receptor. HER2 overexpression is associated with a biologically aggressive tumor phenotype, poor prognosis and increased risk of disease recurrence. The most recent study, DESTINY-PanTumor02, used Trastuzumab deruxtecan (T-DXd), which combines a monoclonal antibody (trastuzumab) with a topoisomerase I inhibiting chemotherapeutic agent. The primary analysis included 267 patients treated in seven tumor cohorts: endometrial, cervical, ovarian, bladder, biliary tract, pancreatic and others. The median follow-up was 12.75 months. In all patients, the objective response rate (ORR) was 37.1% (n = 99; 95% CI: 31.3 to 43.2), with responses observed in all cohorts. The median duration of response (DOR) was 11.3 months (95% CI: 9.6 to 17.8), the median progression-free survival (PFS) was 6.9 months (95% CI: 5.6 to 8.0), and the median overall survival (OS) was 13.4 months (95% CI: 11.9 to 15.5).[30]

SINTILIMAB

Sintilimab is a human monoclonal antibody that selectively binds to the PD-1 receptor. One study also combined this antibody with anlotinib - an oral multi-target tyrosine kinase inhibitor that affects angiogenesis and tumor proliferation - demonstrating positive therapeutic effects in terms of overall survival (OS).[31] Of the 23 patients studied, 47.8% had received ≥ 2 lines of prior chemotherapy; 39.1% had high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR), while 60.9% were microsatellite stable (MSS) or proficient in mismatch repair (pMMR).[31] An OS of 17.8 months (95% CI: 9.4 to 26.3 months) was observed. MSI-H patients demonstrated a superior OS to MSS patients (not available versus 13.3 months; HR 0.15, 95% CI: 0.33-0.70; P = 0.006).[31]

ADVERSE EFFECTS

Table 2 presents data on the 10 adverse effects associated with the use of monoclonal antibodies in the treatment of endometrial cancer that appeared most frequently in the compilation of clinical trials. The analysis covers the following side effects: fatigue, diarrhea, arthralgia, nausea, hypothyroidism, loss of appetite or anorexia, vomiting, anemia, neutropenia and hypertension.

Author	Intervention	Arm	Fatigue	Diarrhea	Arthralgia	Nausea	Hypothyroidism	Lack of Appetite/ Anorexia	Vomiting	Anemia	Neutropenia	Hypertension
David M. O'Malley et al	Pembrolizumab		21%	16%	14%	14%	13%	9%	6%	-	-	-
Ramez N. Eskander et al			71,60%	42,20%	29,40%	50,50%	12,80%	-	20,20%	57,80%	25,70%	-
			63,40%	35,90%	22,50%	43,80%	13,40%	-	19,20%	55,10%	31,50%	-
Emiel A De Jaeghere et al		-	32%	44%	-	24%	-	24%	12%	20%		-
Vicky Makker; Nicoletta Colombo et al	Pembrolizumab and Lenvatinib	-	34,00%	55,70%	32,30%	51,70%	58,90%	46,60%	37,70%	28,10%	9%	65%
Matthew H. Taylor et al		-	58%	52%	28%	32%	42%	39%	19%	-	-	47%
Vicky Makker; Matthew H. Taylor et al		-	51,90%	52,80%	31,50%	39,80%	44,40%	47,20%	-	-	-	61,10%
Kan Yonemori et al		-	-	44%	25,00%	48%	75,00%	46,20%	36,50%	42,30%	23,10%	78,80%
Vicky Makker; Carol Aghajanian et al		-	53,70%	53,70%	31,50%	43,50%	46%	50,00%	30,60%	-	-	60,20%
Wei Wei et al			-	-	-	-	-	-	-	-	-	-
Fiona Simpkins et al	Bevacizumab	-	-	33,33%	-	40%	80,00%	53,33%	-	100%	80%	-
D. Lorusso; G et al		-	-	-	-	1,90%	-	-	-	11,30%	57%	21%
Carol Aghajanian et al		Arm 1	-	-	-	-	-	-	-	25,00%	85,70%	16,10%
		Arm	-	-	-	-	-	-	-	35,10%	78,10%	16,70%
A.M. Westermann et al	Durvalumab	-	44%	26%	-	38%	8%	24%	16%	32%	-	2%
Yoland Antill et al		dMMR	-	-	-	-	9%	-	-	-	-	-
		pMMR	-	-	-	-	9%	-	-	-	-	-
Shannon N et al		-	54,20%	29,20%	24,40%	54,60%	-	23,10%	25,60%	61,80%	41,60%	-
		-	43,00%	31,50%	30,20%	40,90%	-	17,90%	20,90%	47,70%	35,70%	-
Stephanie Lheureux et al	Nivolumab	Arm A	39%	50%	-	22%		31%	-	17%		31%
		Arm B	33%	6%	-	11%	6%	6%	-	6%		-
		Arm C	53%	30%	-	37%	30%	20%	-	43%	-	33%
Manuel Rodrigues et al	Dostarlimabe	-		3%	3%	-	-	-	-	-	-	-
M.R. Mirza et al		-	52%	31%	36%	53%	-	21%	-	34%	-	-
Panagiotis A. Konstantinopoulos, Weixiu Luo et al	Avelumab	-	35%	9%	-	16%	12%	-	-	9%	12%	-
Brian M Slomovitz et al	Cetuximab (Erbitux)	-	63%	20%	-	33%	-	13%	-	-	-	-
Funda Meric-Bernstam et al	Trastuzumab Deruxtecan (T-DXd)	-	25%	40%	-	72%	-	20%	40%	17%	10%	-
Xiaohua Ban et al	sintilimab	-	-	39,1%	-	-	69,6%	26,1%	-	-	17,4%	39,1%

Table 2: Main side effects of the included studies

The results indicate a varied incidence of adverse effects between the different studies. Fatigue, for example, showed a prevalence of 21% in the study by Davi M. O'Malley et al. (Pembrolizumab), while Ramez N. Eskander et al. (Pembrolizumab) reported rates of 71.6% in patients with poor mismatch repair (dMMR) and 63.4% in patients with proficient mismatch repair (pMMR).

Diarrhea also showed significant variation, with rates ranging from 16% in the Davi M. O'Malley et al. study to 55.7% in the Vicky Makker et al. study (pembrolizumab plus Lenvatinib). This adverse effect was particularly prevalent in patients treated with monoclonal antibodies, suggesting a need for continuous monitoring and appropriate interventions to manage this debilitating symptom.

Arthralgia, or joint pain, was reported to a lesser degree, with rates of 14% in the study by Davi M. O'Malley et al. and up to 32.3% in the study by Vicky Makker et al. This variation may indicate differences in individual response to monoclonal antibodies or possible variations in the treatment regimens used in each study.

Nausea showed remarkable variability, with 1.90% in the study by D. Lorusso et al. (Bevacizumab) and 72% in the study by Funda Meric-Bernstam et al. (Trastuzumab deruxtecan), indicating that this adverse effect is relatively common in patients undergoing treatment with monoclonal antibodies. This high incidence of nausea highlights the importance of effective symptom management strategies to improve adherence to treatment and patients' quality of life.

Hypothyroidism was a significant adverse effect, especially in the study by Fiona Simpkins et al. (Bevacizumab), which reported an incidence of 80% and Kan Yonemori et al. (pembrolizumab plus Lenvatinib) with 75%. Other studies have shown lower rates, such as 13% in the study by Davi M. O'Malley et al. This discrepancy suggests that the risk of developing hypothyroidism may vary depending on the monoclonal antibody used.

Loss of appetite or anorexia was also an important adverse effect, ranging from 9% in the study by O'Malley et al. to 53.33% in the study by Fiona Simpkins a et al. This adverse effect can significantly impact patients' nutritional status and general health, highlighting the need for appropriate nutritional interventions during treatment.

Vomiting, anemia and neutropenia were relevant adverse effects. Vomiting ranged from 6% in the study by O'Malley et al. to 40% in the study by Funda Meric-Bernstam et al. Anemia had variable rates, with 100% in the study by Fiona Simpkins et al. and 6% in arm b patients in the study by Stephanie Lheureux et al. (Nivolumab). On the other hand, neutropenia had the highest rate of 85.7% observed in arm 1 patients in the study by Carol Aghajanian et al. (Bevacizumab). These variations highlight the importance of regular hematological monitoring during treatment with monoclonal antibodies.

Finally, hypertension ranged from 78.8% of patients in the study by Kan Yonemori et al. to 2% in the study by A.M. Westermann et al (Durvalumab), standing out as an adverse effect with great variation depending on the antibody used.

RISK OF BIAS IN STUDIES

GENERAL ANALYSIS OF THE METHODOLOGICAL QUALITY OF THE STUDIES

The table presents an assessment of the methodological quality of academic articles, using the criteria of Downs and Black (1998).[12] Each article is assessed in five categories: "Reporting", "External Validity", "Internal Validity, Bias", "Internal Validity, Confounding Factors" and "Total". Higher scores

International Journal of Health Science ISSN 2764-0159 DOI https://doi.org/10.22533/at.ed.159532509015

First author, year of publication	Report (maximum of 10)	External validity (maximum of 3)	Internal validity, bias and confounding factors (maximum of 7)	Internal validity, confounding factors (maximum 6)	Total (maximum of 26)
Viswanathan et al. 2015	8	3	5	1	17
Bellone et al. 2021	8	1	5	2	16
Slomovitz et al. 2020	8	1	5	1	15
Post. et al. 2022	8	3	5	3	19
Aghajanian et al. 2018	7	2	5	4	18
Lorusso et al. 2019	9	1	5	4	20
O'Malley et al. 2022	8	3	5	2	18
De Jaeghere et al. 2023	8	3	5	3	19
Simpkins et al. 2014	8	3	5	1	17
Meric-Bernstam et al. 2023	9	1	5	3	18
Yonemori et al. 2022	8	2	7	4	21
Mirza et al. 2023	9	3	7	5	24
Rodrigues et al. 2023	7	1	4	1	13
Konstantinopoulos et al. 2022	9	3	5	3	20
Konstantinopoulos et al. 2019	9	3	5	3	20
Eskander et al. 2023	9	2	7	5	23
Westin et al. 2023	9	1	7	4	21
Kelkar et al. 2022	7	0	5	3	15
Lheureux et al. 2022	8	3	5	1	17
Makker et al. 2020	9	3	5	3	20
Vicky Makker et al. 2023	8	2	6	3	19
Vicky Makker et al. 2023	8	2	4	2	16
Wei et al. 2022	8	2	5	3	18
Liao et al. 2022	7	2	5	3	17
Antill et al. 2021	8	3	5	3	19

Table 3: Risk of bias using the Downs and Black tool for the studies included in the analysis (n= 24 studies)

26 criteria are used to assess the risk of bias. Each criterion is scored as Yes (1), No (0) or unable to determine (0). An overall score is calculated from the sum, as well as four sub-scales representing "reporting" (total of 10), "external validity" (total of 3) and "internal validity, bias (total of 7) and confounding factors (total of 16)". Higher scores represent a lower risk of bias. Assessment adapted.

in each category and in total indicate a lower risk of bias in the study. The methodological quality of the articles evaluated varied considerably, with total scores ranging from 13 to 24. Most of the articles showed good quality in terms of "Reporting", indicating that the objectives, methods and results were clearly described. However, the "External Validity" of the studies was limited, suggesting that the generalizability of the results to other populations may be restricted. With regard to "Internal Validity", most of the articles presented a low risk of bias, but some studies may not have fully controlled for confounding factors, which could influence the results. The article by M.R. Mirza et al. (2023) had the best methodological quality, while that by Manuel Rodrigues et al. (2023) had the lowest.

EVALUATION LIMITATIONS AND RECOMMENDATIONS

The assessment of methodological quality was limited by the absence of the "Power" category of the Downs and Black checklist, which assesses the statistical power of studies. Furthermore, the analysis was based on adapted criteria.

DISCUSSION

The results of this review highlight the transformative potential of monoclonal antibodies in the treatment of endometrial cancer, particularly in patients with MSI-H/dMMR tumors. PD-1/PD-L1 inhibition with pembrolizumab, dostarlimab, avelumab and durvalumab, alone or in combination with other immune-mediated agents or chemotherapy, has shown promising results in terms of overall survival (OS) and progression-free survival (PFS). However, the heterogeneity of the studies, both in terms of design and patient population, makes it difficult to directly compare the different monoclonal antibodies.

The limitations most commonly found in studies include varying population sizes, definition of the control group, different biomarkers, different time and type of study, selection of patients which may have hindered data collection and/or the efficacy of the drugs. The sample size has a direct impact on the power and reliability of the results, suggesting that the study may be undersized. Most of the studies included in this review have a relatively short follow-up period, which limits the assessment of the long-term efficacy and safety of these treatments. In addition, the different metrics used may hinder comparative analysis.

Despite these limitations, the results of this review have important implications for clinical practice, health policy and future research. The growing evidence of the efficacy of monoclonal antibodies in the treatment of endometrial cancer reinforces the need to incorporate these agents into the therapeutic arsenal available to patients with this neoplasm.

In terms of future research, studies with greater statistical power and longer follow-up are needed to assess long-term efficacy and safety. In addition, randomized controlled trials are essential to compare the efficacy of different monoclonal antibodies and identify the best therapeutic combinations. In addition, the identification of predictive biomarkers of response is essential to optimize the use of these treatments, ensuring that patients receive the most appropriate therapy for their individual molecular profile.

OTHER INFORMATION

REVIEW REGISTRATION

Our systematic review entitled "Monoclonal Antibodies as Targeted Therapies in Advanced or Recurrent Endometrial Cancer: A Systematic Review" has been registered in the PROSPERO international register of systematic reviews under the number CRD42024569935. The detailed protocol of the review, including the eligibility criteria, search strategy and analysis methods, can be accessed on the PROSPERO register via the following link: https:

SOURCES OF FINANCIAL SUPPORT

This systematic review received no external financial support. The support for this study was provided exclusively by the Universidade Nove de Julho, through the Medicine course, which offered academic support and infrastructure to conduct the research. The funders had no role in the design, collection, analysis, interpretation of the data, writing of the manuscript or the decision to submit the article for publication.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in relation to this systematic review. There was no financial, commercial, personal or professional influence that could affect the conduct or results of this study.

REFERENCES

1. MILLION WOMEN STUDY COLLABORATORS et al. Endometrial cancer and hormone-replacement therapy in the Million Women Study. **The Lancet**, v. 365, n. 9470, p. 1543-1551, 2005. Disponível em: https://pubmed.ncbi.nlm.nih.gov/15866308/. Acesso em: 4 jul. de 2024.

2. ESPOSITO, Katherine et al. Metabolic syndrome and endometrial cancer: a meta-analysis. **Endocrine**, v. 45, p. 28-36, 2014. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23640372/. Acesso em: 4 jul. de 2024.

3. AUNE, Dagfinn et al. Anthropometric factors and endometrial cancer risk: a systematic review and dose–response meta-analysis of prospective studies. **Annals of Oncology**, v. 26, n. 8, p. 1635-1648, 2015. Disponível em:https://pubmed.ncbi.nlm.nih.gov/25791635/. Acesso em: 4 jul. de 2024.

4. TSILIDIS, Konstantinos K. et al. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. **Bmj**, v. 350, 2015. Disponível em:https://pubmed.ncbi.nlm.nih.gov/25555821/. Acesso em: 4 jul. de 2024.

5. WIN, Aung Ko; REECE, Jeanette C.; RYAN, Shae. Family history and risk of endometrial cancer: a systematic review and meta-analysis. **Obstetrics & Gynecology**, v. 125, n. 1, p. 89-98, 2015. Disponível em:https://pubmed.ncbi.nlm.nih.gov/25560109/. Acesso em: 4 jul. de 2024.

6. LONGORIA, Teresa C.; ESKANDER, Ramez N. Immunotherapy in endometrial cancer-an evolving therapeutic paradigm. **Gynecologic oncology research and practice**, v. 2, p. 1-9, 2015. Disponível em:https://gynoncrp.biomedcentral.com/articles/10.1186/s40661-015-0020-3. Acesso em: 4 jul. de 2024.

7. GORDHANDAS, Sushmita et al. Current evidence-based systemic therapy for advanced and recurrent endometrial cancer. **Journal of the National Comprehensive Cancer Network**, v. 21, n. 2, p. 217-226, 2023. Disponível em:https://pubmed.ncbi.nlm.nih.gov/36791759/. Acesso em: 4 jul. de 2024.

8. NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES. **LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]**. Bethesda (MD), 2012–. Monoclonal Antibodies. 2024 Jul 8. PMID: 31644151. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK547852/. Acesso em: 4 jul. 2024

9. KREUTZFELDT, Jordyn et al. The trastuzumab era: current and upcoming targeted HER2+ breast cancer therapies. **American journal of cancer research**, v. 10, n. 4, p. 1045, 2020. Disponível em:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7191090/. Acesso em: 4 jul. de 2024.

10. PAGE, M. . J. et al. (2022). A declaração PRISMA 2020: diretriz atualizada para relatar revisões sistemáticas. ***Epidemiologia e Serviços de Saúde***, *31*(2), e2022107. Disponível em: http://scielo.iec.gov.br/scielo.php?script=sci_arttext&pid=S1679-49742022000201700 . Acesso em 6 ago. de 2024.

11. OUZZANNI, M. et al. (2016). Rayyan — a web and mobile app for systematic reviews. ***Systematic Reviews***, 5(210). Disponível em: https://doi.org/10.1186/s13643-016-0384-4. Acesso em 6 ago. de 2024.

12. DOWNS, S. H.; BLACK, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. **J Epidemiol Community Health**, v. 52, n. 6, p. 377-84, 1998. doi: 10.1136/jech.52.6.377. PMID: 9764259. Disponível em: https://pubmed.ncbi.nlm.nih.gov/9764259/. Acesso em: 6 ago. de 2024.

13. BATTE, B. A. L. et al. (2014). Consequences of universal MSI/IHC in screening ENDOMETRIAL cancer patients for Lynch syndrome. **Gynecol. Oncol.**, 134(2):319-25. doi: 10.1016/j.ygyno.2014.06.009. 2014. Disponível em: https://pubmed.ncbi.nlm.nih.gov/24933100/. Acesso em: 6 ago. de 2024.

14. MARABELLE, A. et al. (2020). Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. **J Clin Oncol**, 38(1), 1-10. doi: 10.1200/JCO.19.02105. PMID: 31682550. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8184060/. Acesso em: 6 ago. de 2024.

15. MAKKER, V. et al. (2023). A Phase Ib/II Study of Lenvatinib and Pembrolizumab in Advanced Endometrial Carcinoma (Study 111/KEYNOTE-146): Long-Term Efficacy and Safety Update. **J. Clin. Oncol**., 41(5), 974-979. doi: 10.1200/JCO.22.01021. Disponível em: https://pubmed.ncbi.nlm.nih.gov/36608305/. Acesso em: 6 ago. de 2024.

16. MAKKER, V. et al. (2021). Characterization and management of adverse reactions in patients with advanced endometrial carcinoma treated with lenvatinib plus pembrolizumab. **Oncologist**, 26(9), e1599-e1608. doi: 10.1002/onco.13883. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34190370/. Acesso em: 6 ago. de 2024.

17. MAKKER, V. et al. (2020). Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. **J. Clin. Oncol.**, 38(26), 2981-2992. doi: 10.1200/JCO.19.02627. Disponível em: https://pubmed.ncbi.nlm.nih.gov/32167863/. Acesso em: 6 ago. de 2024.

18. ANDRÉ, T. et al. (2023). Antitumor activity and safety of dostarlimab monotherapy in patients with mismatch repair deficient solid tumors: A nonrandomized controlled trial. **JAMA Netw. Open**, 6(11):e2341165. doi: 10.1001/jamanetworkopen.2023.41165. Disponível em: https://pubmed.ncbi.nlm.nih.gov/37917058/. Acesso em: 6 ago. de 2024.

19. MIRZA, M. R. et al. (2023). Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. **N. Engl. J.** Med. doi: 10.1056/NEJMoa2216334. Disponível em: https://pubmed.ncbi.nlm.nih.gov/36972026/. Acesso em: 6 ago. de 2024.

20. KONSTANTINOPOULOS, Panagiotis A. et al. Phase II study of avelumab in patients with mismatch repair deficient and mismatch repair proficient recurrent/persistent endometrial cancer. **Journal of Clinical Oncology**, v. 37, n. 28, p. 2434-2441, 2019. DOI: 10.1200/JCO.19.01021. PMID: 31461377. PMCID: PMC9798913.

21. KONSTANTINOPOULOS, P. A. et al. (2022). Evaluation of Treatment With Talazoparib and Avelumab in Patients With Recurrent Mismatch Repair Proficient Endometrial Cancer. **JAMA Oncol.**, 8(9), 1317-1322. doi: 10.1001/jamaoncol.2022.2181. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35900726/. Acesso em: 6 ago. de 2024.

22. WESTIN, S. N. et al. (2024). Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: The phase III DUO-E trial. **J. Clin. Oncol.**, 42(3), 283-299. doi: 10.1200/JCO.23.02132. Disponível em: https://pubmed.ncbi.nlm.nih.gov/37864337/. Acesso em: 6 ago. de 2024.

23. ANTILL, Y. et al. (2021). Clinical activity of durvalumab for patients with advanced mismatch repair-deficient and repair--proficient endometrial cancer. A nonrandomized phase 2 clinical trial. **J. Immunother. Cancer**, 9(6), e002255. doi: 10.1136/jitc-2020-002255. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34103352/. Acesso em: 6 ago. de 2024.

24. POST, C. C. B. et al. (2022). Efficacy and safety of durvalumab with olaparib in metastatic or recurrent endometrial cancer (phase II DOMEC trial). **Gynecol. Oncol.**, 165(2), 223-229. doi: 10.1016/j.ygyno.2022.02.025. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35287967/. Acesso em: 6 ago. de 2024.

25. LIAO, Ying et al. Efficacy of PD-1 Inhibitor Combined with Bevacizumab in Treatment of Advanced Endometrial Cancer Patients with Mismatch Repair Deficiency (dMMR)/High-Level Microsatellite Instability (MSI-H). **Medical Science Monitor : International Medical Journal of Experimental and Clinical Research**, v. 28, p. e934493-1–e934493-9, 2022. Disponível em: https://www.medscimonit.com/abstract/index/idArt/934493. Acesso em 19 ago. 2023.

26. SLOMOVITZ, B. M. et al. (2020). Phase 2 study of cetuximab (Erbitux) in patients with progressive or recurrent endometrial cancer. ***Gynecologic oncology***, 111(3), 365-369. PMID: 33020204. DOI: 10.1136/ijgc-2020-001859 Disponível em: https://ijgc.bmj.com/content/30/11/1733. Acesso em: 6 ago. de 2024.

27. LIAO, Y. et al. (2022). Efficacy of PD-1 inhibitor combined with bevacizumab in treatment of advanced endometrial cancer patients with mismatch repair deficiency (dMMR)/high-level microsatellite instability (MSI-H). **Med Sci Monit**, 28:e934493. doi: 10.12659/MSM.934493. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35322001/. Acesso em: 1 ago. de 2024.

28. AGHAJANIAN, C. et al. (2018). A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. **Gynecol. Oncol**., 150(2), 274-281. doi: 10.1016/j.ygyno.2018.05.018. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29804638/. Acesso em: 1 ago. de 2024.

29. LORUSSO, D. et al. Carboplatin-paclitaxel compared to Carboplatin-Paclitaxel-Bevacizumab in advanced or recurrent endometrial cancer: MITO END-2 - A randomized phase II trial. **Gynecologic Oncology**, v. 155, n. 3, p. 406-412, dez. 2019. Epub 31 de outubro de 2019. DOI: 10.1016/j.ygyno.2019.10.013. PMID: 31677820. Acesso em: 19 de ago de 2024.

30. MERIC-BERNSTAM, Funda et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. **Journal of Clinical Oncology**, v. 42, n. 1, p. 47-58, 1 jan. 2024. Epub 23 de outubro de 2023. DOI: 10.1200/JCO.23.02005. Acesso em: 19 de ago de 2024.

31. Wei, W., Ban, X., Yang, F., Li, J., Cheng, X., Zhang, R., Huang, X., Huang, Y., Li, Q., Qiu, Y., Zheng, M., Zhu, X., & Li, J. (2023). Phase II trial of efficacy, safety and biomarker analysis of sintilimab plus anlotinib for patients with recurrent or advanced endometrial cancer. *Journal for ImmunoTherapy of Cancer*. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35623659/. Acesso em: 1 ago. de 2024.