

Review

Immunotherapy in Gynaecological Oncology: The Italian Landscape

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Abstract

Objective: The potential of immunotherapy in gynaecological malignancies is being investigated in recent years. This review will discuss the current status of immunotherapy in endometrial (EC), ovarian (OC) and cervical (CC) cancers with particular attention to the Italian reality. **Mechanism:** The websites of Multicenter Italian Trials in Ovarian cancer (MITO) and Mario Negri Gynecologic Oncology (MaNGO) groups were consulted and an in-depth search was carried out on clinicaltrials.gov. Trials started from 2014 to September 2022 were included in the search. Monoclonal antibodies, immune checkpoint inhibitors and drug-conjugated antibodies (ADCs) therapies were considered. **Findings in Brief:** The studies with the greatest clinical impact, specifically in terms of PFS (Progression Free Survival) and adverse events reported, and with the widest participation of Italian centers have been presented. In EC the impact of immunotherapy has been considerable, as demonstrated by the inclusion of immunotherapy in today's treatment pathways. The identification of new biomarkers will make it possible to select patients who can best benefit from this type of therapy. Immunotherapy in OC has been a complex challenge for years, as early trials have shown. The results of further trials are now expected. CC seems to be one of the most interesting settings for immunotherapy and some results are already in the clinical management of advanced disease. **Conclusions:** Several trials have led to the approval of new drugs by regulatory agencies in gynaecological oncology, making immunotherapy not only an important promise for the future but also a concrete current reality for thousands of women worldwide.

Keywords: immunotherapy; endometrial cancer; ovarian cancer; cervical cancer; clinical trials

1. Introduction

Gynaecological cancers represent a major global burden, and the same is true for Italy. According to Associazione Italiana Registri Tumori (AIRTUM) 2020 data, more than 8000 new cases of endometrial carcinomas, 5000 new cases of ovarian carcinomas, and 2300 cervical carcinomas were diagnosed in 2020. 6000 Italian women lost their lives in 2020 due to these malignancies, more than half from ovarian carcinomas [1].

Two main cooperative groups, MITO (Multicenter Italian Trials in Ovarian cancer and gynaecological malignancies) and MaNGO (Mario Negri Gynecologic Oncology) are the Italian reference points for the main national and international clinical trials concerning gynaecological oncology. Working groups have also recently emerged at the regional level in order to standardize the diagnostic and therapeutic process of gynaecological cancers through the creation of shared protocols, known as PDTAs (Percorsi Diagnostico Terapeutici Assistenziali, Diagnostic Therapeutic Care Pathways).

Thanks to an ever-improving understanding of the role of the immune system in oncologic diseases, the potential of immunotherapy is being investigated in recent years in gynaecological oncologic diseases. The various types of immunotherapeutic treatments, in fact, in view of the generally poor or non-lasting response to conventional ther-

apies of advanced or relapsed gynaecological oncological malignancies, are now among the most promising therapeutic strategies on which research is focusing. Several studies have already led to the approval of new drugs by regulatory agencies, making immunotherapy not only an important promise for the future but also a concrete current reality for thousands of women worldwide.

This review will discuss the current status of immunotherapy in gynaecological cancers with particular attention to the Italian reality, which has been an active part of research in this field for years, providing what to our knowledge is the most recent update in a constantly evolving framework.

In order to obtain an accurate picture of the latest ongoing studies, the websites of the organisations MITO and MaNGO were consulted and an in-depth search was carried out on clinicaltrials.gov, entering 'Gynecological cancer', 'Gynecological neoplasm', 'Ovarian cancer', 'Ovarian neoplasm', 'Ovarian carcinoma', 'Endometrial cancer', 'Endometrial neoplasms', 'Endometrial adenocarcinoma', 'Uterine cervical cancer', 'uterine cervical neoplasm' as search terms (advanced research). The search was deepened using the terms 'Immunotherapy', 'Pembrolizumab', 'Atezolizumab', 'Dostarlimab', 'Durvalumab', and 'Cemiplimab'. All studies started from 2014 to 15 September 2022 were included in the search regardless of study type,



recruitment status, and current availability of results. Monoclonal antibodies, immune checkpoint inhibitors and drug-conjugated antibodies (ADCs) therapies were considered. It was decided not to include studies on T-cell therapy and cancer vaccines, which also provided interesting and promising results both in animal models [2] and in early phase I studies. This is in view of the absence of studies with a large number of gynaecological patients, the considerable heterogeneity between these types of immunotherapies and those already currently in use, and the current absence of such therapies registered in Italy for gynaecological malignancies. From these, the studies with the greatest clinical impact, specifically in terms of PFS (Progression Free Survival) and adverse events reported and with the widest participation of Italian centers were subsequently selected.

2. The Rationale for Immunotherapy in Endometrial Carcinoma (EC)

It is well known that there is an important link between the endometrium and the immune system in both physiology and cancer pathology.

The complex interaction between endometrial epithelial cells, the innate and adaptive immune systems, cytokines and hormones enables fine regulation of the immune system in the endometrium, in order to ensure effective defence against infection and, at the same time, an immunosuppressive microenvironment to allow implantation of the product of conception [3,4]. The endometrial microenvironment undergoes alterations during neoplasia development which promote carcinogenesis [5]. However, the role and the prognostic significance of each component of this process are still debated.

The incorporation of the new molecular classification, identified by the Cancer Genome Atlas Research Network (TCGA), made it possible to tailor the treatment according to the molecular subtypes [6]. PoIE and MSI-H (microsatellite instability high) tumours represent 30% of ECs. These two subtypes with a higher tumour mutation burden have a stronger expression of neoantigens resulting in higher lymphocyte infiltrate and are the best candidates to receive immunotherapy. In addition to this, a correlation was observed between PDL1 expression and MSI-H tumours [7].

Mo *et al.* [8] reported that EC has a high expression of immune checkpoints. Nearly 100% of metastatic ECs express PD1, and the expression of PD1 and PDL1 in tumour-infiltrating lymphocytes (TILs) is relevant [8]. Therefore, the PD1-PDL1 pathway has been investigated as a potential therapeutic target in many clinical trials.

3. Immunotherapy in Endometrial Cancer

The first immunotherapy drug studied in the setting of solid tumours with homologous recombination deficiency (MMRd) was Pembrolizumab. In the KEYNOTE-028/NCT02054806 study, a multi-cohort phase I basket

trial evaluating the safety and efficacy of Pembrolizumab in patients with PDL1-positive solid tumours, the results showed an Overall Response Rate (ORR) of 13% in 23 patients with advanced EC and a reduction in lesion size in 25% of patients [9].

The KEYNOTE-158/NCT02628067, an open-label, multicohort, phase II study, enrolled 233 patients with 27 different advanced solid tumour types and also Italian centres were involved. For endometrial carcinoma, the study design included two cohorts: a group with EC regardless of MSI status and a group with any type of advanced solid tumour (excluding colorectal carcinoma) with MSI-H/dMMR (mismatch repair-deficient), including endometrial carcinoma. Pembrolizumab as monotherapy demonstrated an objective response by Response Evaluation Criteria in Solid Tumours (RECIST) in 57.1% of EC patients, with manageable toxicity. EC was the most common tumour type with a reduction from baseline in tumour size (33 of 47 had a $\geq 30\%$ reduction) [10]. Based on these data, Pembrolizumab was approved by the Food and Drug Association (FDA) for patients with unresectable or metastatic, MSI-H or MMRd solid tumours who have progressed following prior treatment and who have no satisfactory alternative treatment options. This is one of the first approval in which treatment is based on a common tumour biomarker rather than on the anatomic location of origin [11].

Currently, after being approved by the European Medicines Agency (EMA) as monotherapy in advanced or metastatic endometrial cancer with disease progression during or after treatment with platinum-containing therapy, also in Italy Pembrolizumab as monotherapy is going through the process for approval.

Subsequent to these data, research focused on strategies to enhance the efficacy of immunotherapy in patients with endometrial adenocarcinoma by using combination therapies with other types of drugs. One of the first associations tested was between PD-1/PDL1 signal inhibitors and lenvatinib, a vascular endothelial growth factor (VEGF) inhibitor.

The rationale is that the VEGF/VEGF receptor 2 (VEGFR2) signalling pathway is not only critical for tumour angiogenesis but is also involved in the regulation of the immune response. Its inhibition increases the number of tumour-infiltrating lymphocytes, makes the tumour microenvironment less immunosuppressive, and alters its cellular composition [12].

The KEYNOTE 146/NCT02501096 trial enrolled patients with solid tumours from the United States, Norway and Spain, including 108 patients with metastatic endometrial cancer with ≤ 2 previous lines of therapy (94 without MSI-H or MMRd, 11 with MSI-H/MMR, and 3 in whom MSI/MMR status was not available). Regardless of MSI/MMR status and PDL1 status (positive in 49%) patients received lenvatinib 20 mg once daily orally plus Pembrolizumab 200 mg intravenously once every 3 weeks.

The results were encouraging in both the groups of patients with MSI-H/MMRd and, particularly interestingly, in patients without MSI-H/MMRd (MMRp), with an ORR of 63.3% and 36.2%, respectively; the median duration of response (DoR) was reached only in the MSI-H/MMRd group and was of 21.2 months. A potentially problematic aspect emerged from toxicities; the most common adverse event (AE) was hypertension (32.4% of patients). Twenty per cent of patients reported toxicities which led to discontinuation of at least one drug. Any grade of immune-related AEs occurred in 57.4% of patients: the most common was hypothyroidism (47.2%). Among severe toxicities (grade ≥ 3) 4.6% of patients experienced severe skin reactions [13]. Data obtained in the MMRp population led the FDA to provide approval in September 2019 for the treatment of patients with advanced endometrial carcinoma who do not have MSI-H or MMRd, progressing after previous systemic therapy, that are not candidates for curative surgery or radiation therapy.

Since this was an important result for a patient population previously devoid of innovative therapies, two additional trials were conducted: KEYNOTE 775/NCT03517449 and the ENGOT-en9/LEAP-001/NCT03884101 trial. In both cases, Italian centres were involved. In the former, 827 patients (including 697 with MMRp and 130 with MMRd) with advanced endometrial carcinoma already treated with at least one line of platinum-based chemotherapy were randomized in a 1:1 ratio to receive lenvatinib plus Pembrolizumab versus physician's choice chemotherapy (Doxorubicin or Paclitaxel). Overall the median progression-free survival (PFS) was longer with lenvatinib plus Pembrolizumab than with chemotherapy, with similar results in both the all-comers and MMRp populations: 7.2 months with Pembrolizumab plus lenvatinib versus 3.8 months with chemotherapy in the 'all comers' patient group and 6.6 months versus 3.8 months in the MMRp patient group, while median overall survival (OS) was 18.3 months versus 11.4 months ($p < 0.0001$) and 17.4 months versus 12 months ($p = 0.0001$), respectively [14]. The ENGOT-en9/LEAP-001/NCT03884101 trial, which has completed enrollment and whose results are expected in mid-2023, is the first study to evaluate the application of immunotherapy as first-line therapy in endometrial cancer compared with chemotherapy. Seven hundred-twenty patients with stage III/IV endometrial adenocarcinoma with residual or measurable disease were randomized 1:1 to receive Pembrolizumab in combination with lenvatinib or paclitaxel in combination with carboplatin. The dual primary endpoints are PFS, and OS and patients were stratified by MMR status [15]. From March 2022 also in Italy the combination of Pembrolizumab and Lenvatinib is approved for the treatment of advanced or recurrent MMRp endometrial carcinoma, progressing during or after treatment with platinum-containing therapy [16].

In addition to this, the KEYNOTE-C93/GOG-3064/ENGOT-en15/NCT05173987 trial is currently recruiting patients with advanced or recurrent dMMR endometrial carcinoma in order to assess the safety and efficacy of treatment with Pembrolizumab compared to a combination of carboplatin and paclitaxel as first-line therapy. Results are expected in 2026 [17].

The GARNET/NCT02715284 trial was a phase I, multicenter, nonrandomized trial in which another PD1 inhibitor, Dostarlimab, was evaluated as monotherapy in patients with advanced or recurrent endometrial cancer already treated with one or two lines of therapy and progressing after treatment with a platinum-based doublet. The trial enrolled two cohorts of patients: one MMRd and one MMRp. The MMRd subgroup was the most responsive (ORR 44.7% versus 13.4%) and even though the disease control rate was not so different, the duration of response was longer in the MMRd group. The drug was well tolerated overall, the most frequent side effect being an increase in transaminase levels [18]. From September 16, 2022 in Italy, Dostarlimab has been approved and is paid for by the national health care system as monotherapy for the treatment of patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) advanced or recurrent endometrial cancer that has progressed during or after previous treatment with a platinum-based regimen, thus becoming the new standard of care in this subgroup of patients [19].

For a long time, it was thought that it was not possible to combine immunotherapy with chemotherapy, mainly because of the immunosuppressive action of the latter. More recently, the option has been explored in numerous clinical trials. The rationale is complex, and numerous mechanisms have been proposed: DNA damage induced by chemotherapy drugs would induce the activation of specific pathways capable of upregulating the MHC (Major Histocompatibility Complex) presentation system, a modification of the immunosuppressive tumour microenvironment and a better tumour penetration by lymphocytes [20]. In this context, Dostarlimab was also one of the first monoclonal antibodies to be combined with chemotherapy in the setting of gynaecological cancers.

The phase 3 ENGOT-EN6/NSGO-RUBY/NCT03981796 trial has currently completed the recruitment phase, enrolling more than 750 patients in 20 countries, including Italy, to evaluate the efficacy and safety of Dostarlimab associated with chemotherapy. Patients were randomized to receive Carboplatin-Paclitaxel with Dostarlimab, or placebo followed by maintenance with Dostarlimab or placebo for 3 years. Stratifications based on MSI status, previous pelvic radiotherapy, and disease status are also planned. The trial is estimated to be completed in 2026 [21].

In addition to PD1 inhibitors, PDL1 inhibitors are also under trial. Atezolizumab, already approved for urothelial

Table 1. Immunotherapy for endometrial cancer: main ongoing trials in Italy.

Study	Treatment	Number of patients	Patient population	Status
ENGOT-en9/MK-7902-001/NCT03884101	Pembrolizumab plus Lenvatinib vs Chemotherapy	875 (estimated enrollment)	Stage III, IV or recurrent EC not previously treated with systemic chemotherapy	Active, not recruiting. Estimated Study Completion Date: April 2023
KEYNOTE-C93/GOG-3064/ENGOT-en15/NCT05173987	Pembrolizumab vs Carboplatin and Paclitaxel	350 (estimated enrollment)	Advanced or recurrent dMMR EC	Active, recruiting
ENGOT-EN6/NSGO-RUBY/NCT03981796	Dostarlimab plus Carboplatin-Paclitaxel versus Placebo plus Carboplatin Paclitaxel	785 participants (actual enrollment)	Stage III, IV or recurrent EC	Active, not recruiting. Estimated Study Completion Date: 2026
AtTEnd/NCT03603184	Atezolizumab plus Carboplatin-Paclitaxel versus Placebo plus Carboplatin Paclitaxel	550 participants (estimated enrollment)	Stage III, IV or recurrent EC	Active, not recruiting. Estimated Study Completion Date: 2026

EC, endometrial carcinoma.

carcinoma and non-small cell lung cancer (NSCLC) is the focus of the Italian AtTEnd trial (NCT03603184). This trial, with Mario Negri Institute as the sponsor and Prof. Nicoletta Colombo (IEO, European Institute of Oncology) as principal investigator, enrolled patients (40% of them in Italy) with stage III–IV EC inoperable or with residual disease after surgery or recurrent disease. The experimental arm consisted of paclitaxel and carboplatin with Atezolizumab or placebo every 21 days for 6–8 cycles, thereafter Atezolizumab or placebo every 21 days until disease progression or intolerable toxicity. Evaluation of the results is ongoing, and their publication is expected soon [22].

The gradual and increasingly widespread application of molecular classification is changing the carcinoma therapeutic algorithm, with new perspectives for both the adjuvant and metastatic or advanced settings. From the numerous ongoing trials (Table 1), new immunotherapies and combinations with other drugs are expected to be approved by the Italian regulatory body. Future challenges will focus on the identification of new predictive biomarkers of response, effective therapies for the MSI-Low/MMRp population, and the use of immunotherapy in the first-line setting.

4. The Rationale for Immunotherapy in Ovarian, Tubal and Peritoneal Carcinoma

Trials on the applicability of immunotherapy in ovarian carcinoma patients find their rationale in the high expression of immune checkpoints in these carcinomas and the correlation between the number of TILs and overall survival. PDL1 expression is associated with poorer survival and an increased risk of peritoneal dissemination [23]. In addition to this, increased expression of PD1-

PDL1 was noted in tumours with *BRCA1/2* mutation compared with homologous recombination-proficient tumours [24,25]. A mechanism for the formation of an immunosuppressive microenvironment involving regulatory T lymphocytes, myeloid-derived suppressor cells, the release of inhibitory cytokines, and alterations to the PD1-PDL1 axis has also been demonstrated in ovarian carcinoma [26].

5. Immunotherapy in Ovarian Carcinoma (OC)

Given the high sensitivity to chemotherapy in ovarian cancer and the therapeutic centrality that poly (ADP-ribose) polymerase (PARP) inhibitors have achieved, various combinations of immunotherapy with chemotherapy, VEGF inhibitors, and PARP inhibitors, have been evaluated. Since the earliest trials, however, the high complexity of the immune response to ovarian cancer and the need to identify predictive factors for better selection of patients to whom immunotherapy should be proposed have emerged.

Avelumab, a fully human antibody targeting the PD1 pathway, has been tested in the first line (JAVELIN Ovarian 100/NCT02718417) and in recurrent setting in platinum-resistant/refractory disease (JAVELIN Ovarian 200/NCT02580058) in combination with chemotherapy and alone without advantages in terms of PFS [27,28].

Several Italian centres have been involved in the ENGOTov39 Imagyn 050/NCT03038100, a phase III trial to evaluate the efficacy, safety, and pharmacokinetics of Atezolizumab administered with paclitaxel, carboplatin and bevacizumab in patients with newly diagnosed untreated primary ovarian, fallopian tube, and/or peritoneal carcinoma. Preliminary OS results showed no significant benefit from Atezolizumab, even if a slightly better PFS emerged for the

PLD-L1-positive population in the immunotherapy group [29].

Pembrolizumab is actually involved in several protocols either in first-line and in recurrent settings and patients with ovarian cancer were already included in the KEYNOTE 028/NCT02054806 basket trial. Patients with platinum-resistant OC are burdened by a response rate to platinum chemotherapy of less than 10%, a reduced PFS, and a median OS of 13 months. Immunotherapy is being investigated also in this setting. The KEYNOTE-B96/ENGOT-ov65/NCT05116189 trial evaluates the addition of Pembrolizumab to paclitaxel compared with paclitaxel alone with or without bevacizumab in platinum-resistant disease, in terms of PFS, both in patients with Combined Positive Score (CPS) ≥ 1 and in the whole enrolled population. The trial is in the recruitment phase, also in many Italian centres [30].

CPS is calculated as the percentage of cells with PD-L1 staining (tumour cells, lymphocytes, macrophages). The Italian phase II trial MITO 27/NCT03539328 is precisely aimed at evaluating the OS efficacy of Pembrolizumab monotherapy for patients with ovarian cancer already treated with no more than 2 lines of chemotherapy and CPS score $>$ or equal to 1 [31].

Among trials evaluating the safety and activity of the combination of PARP inhibitors and immunotherapy, there was the MEDIOLA/NCT02734004 trial, a basket trial testing the combination of durvalumab and olaparib for germline *BRCA*-mutated metastatic breast cancer, ovarian cancer, gastric cancer and relapsed small-cell lung cancer [32].

The ENGOT-OV43/NCT03740165 trial, whose results are expected in 2023, is aimed at evaluating the safety and efficacy of carboplatin-paclitaxel treatment combined with Pembrolizumab and followed by Pembrolizumab and olaparib for the first-line treatment of women with *BRCA* non-mutated advanced epithelial ovarian cancer [33].

The European trial ENGOT-Ov41/GEICO 69-O/ANITA/NCT03598270, on the other hand, will evaluate the results obtained by combining Atezolizumab with platinum-based chemotherapy and Niraparib in platinum-sensitive relapse of OC. Recruitment has been completed and results are expected in 2025 [34].

Results are expected in the next year from the DUO ENGOT-OV46/NCT03737643 trial, whose design enrolled patients with newly diagnosed advanced ovarian cancer. Patients with *BRCA* mutated disease received therapy with Carboplatin, Paclitaxel, Durvalumab, and optionally Bevacizumab, followed by maintenance with Olaparib and Durvalumab. In contrast, patients with *BRCA* wild-type disease were randomized into 3 arms with chemotherapy associated with only bevacizumab (arm 1), bevacizumab and durvalumab (arm 2) and bevacizumab, durvalumab and olaparib (arm 3), respectively [35].

At present, there are no non-antiangiogenic immunotherapy drugs approved for ovarian cancer in Italy. Nevertheless, in the next two years, the results of several ongoing trials (Table 2) are expected to be published, and predictive factors could be revealed to identify the subpopulations of patients more suitable to respond to immunotherapy. This is especially urgent for patients with platinum-resistant carcinomas and for patients already treated with multiple lines of chemotherapy, who to date lack satisfactory treatment options. It will also be critical to determine the details of combination therapies with chemotherapy and especially with bevacizumab and PARP inhibitors to ensure the best clinical response and optimal management of toxicities.

6. Rationale of Immunotherapy for Cervical Cancer (CC)

The rationale for the use of immunotherapy in cervical cancer finds its cornerstone in the interactions between the immune system, the human papilloma virus (HPV) infection and the CC progression. Immunotherapy could play an important role facilitated by the fact that the immune system is in a pro-inflammatory condition of potential activation against viral antigens [36].

Numerous trials have focused on mechanisms that allow a tumour with such a high level of neoantigens to escape the immune system. HPV has been shown to promote a “non-lytic life cycle”, thereby reducing the number of neoantigens released and the subsequent activation and migration of dendritic cells to lymph nodes. The same result is achieved by low expression of viral E6 and E7 proteins, which can block Langerhans cell activity and significant expression of immunosuppressive proteins leading to an immune-tolerant status [37,38].

High expression of immune checkpoints, such as CTLA4 and PD1/PD-L1, has been demonstrated in intraepithelial lesions and CC. Furthermore, there is a correlation between PD-L1 expression and TILs which can predict response to neoadjuvant chemotherapy [39]. About 8% of cervical cancers have also microsatellite instability [40].

7. Immunotherapy for Cervical Cancer (CC)

Pembrolizumab was the first checkpoint inhibitor approved by the FDA, in 2018, for the treatment of metastatic, PDL1-positive cervical cancer progressing after first-line treatment. The studies that led to this approval were the Keynote 028/NCT02054806 and Keynote 158/NCT02628067 basket trials. Specifically, in the latter, 98 patients with pretreated advanced cervical cancer were enrolled, including 82 with PD-L1 positive, and treated with Pembrolizumab monotherapy every 3 weeks for 2 years or until progression or intolerable toxicity. An overall ORR of 12.2% was measured, including 3 complete responses. In the PD-L1-positive population, the ORR was 14.6% [41]. Pembrolizumab as monotherapy is not cur-

Table 2. Immunotherapy for ovarian cancer: main ongoing trials in Italy.

Study	Treatment	Number of patients	Patient population	Status
ENGOTov39/Imagyn 050/NCT03038100	Atezolizumab + paclitaxel + carboplatin + bevacizumab versus placebo + paclitaxel + carboplatin + bevacizumab	1301 (Actual enrollment)	Stage III, IV OC not previously treated with systemic chemotherapy	Active, not recruiting. Estimated Study Completion Date: 2023
KEYNOTE-B96/ENGOT-Ov65/NCT05116189	Pembrolizumab + paclitaxel vs placebo + paclitaxel	616 (estimated enrollment)	Platinum resistant OC	Recruiting. Estimated Study Completion Date: 2027
ENGOT-Ov43/GOG-3036/NCT03740165	Carboplatin Paclitaxel followed by Pembrolizumab + Olaparib or Pembrolizumab + Placebo for Olaparib or Placebo for Pembrolizumab plus Placebo for Olaparib	1284 (estimated enrollment)	Stage III, IV OC <i>BRCA</i> non-mutated not previously treated with systemic chemotherapy	Active, not recruiting. Estimated Study Completion Date: 2025
ENGOT-Ov41/GEICO 69-O/ANITA/NCT03598270	Chemotherapy With or Without Atezolizumab Followed by Niraparib Maintenance with or Without Atezolizumab	414 (Estimated enrollment)	Recurrent Platinum sensitive OC	Active, not recruiting. Estimated Study Completion Date: 2025
ENGOT-Ov46/DUO-O/NCT03737643	Chemotherapy with or without Durvalumab followed by Durvalumab and/or Olaparib	1374 (estimated enrollment)	Stage III, IV OC not previously treated with systemic chemotherapy	Active, Recruiting. Estimated Study Completion Date: 2027

OC, ovarian carcinoma.

rently approved by the European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA) for this indication.

The route of combining checkpoint inhibitors with chemotherapy has also been pursued in cervical cancer. Italian centres participate in many trials (Table 3), including the multicenter, randomized, phase III KEYNOTE-826/NCT03635567 trial, which was designed precisely to investigate the addition of Pembrolizumab to a platinum-based chemotherapy regimen, with or without bevacizumab. A total of 617 patients with persistent, recurrent or metastatic cervical cancer who had not been treated with chemotherapy, except when used concomitantly as a radiosensitizing agent, were enrolled, regardless of tumour PD-L1 expression status (89% of tumours expressed PD-L1 with CPS \geq to 1). In the 548 patients with CPS $>$ 1, the median PFS was 10.4 months in the Pembrolizumab group and 8.2 months in the placebo group. Similarly, in the 317 patients with a CPS of 10 or more, PFS was 10.4 months and 8.1 months, respectively. Overall survival at 24 months was 53.0% in the Pembrolizumab group and 41.7% in the placebo group [42].

On April 29, 2022, just in consideration of the results of the phase 3 KEYNOTE-826/NCT03635567 trial, the approval by the European Commission of Pembrolizumab in combination with chemotherapy, with or without be-

vacizumab, for the treatment of persistent, recurrent or metastatic cervical cancer which expresses PD-L1 (CPS \geq 1) was announced [43].

To date, however, Pembrolizumab, even in combination with chemotherapy, has not yet been listed in Italy as a fully paid-for drug under the national health care system for the treatment of cervical cancer.

The phase III trial Platinum Chemotherapy Plus Paclitaxel With Bevacizumab and Atezolizumab in Metastatic Carcinoma of the Cervix (BEATcc/NCT03556839) completed enrollment of 404 patients with stage IVB cervical cancer, persistent or recurrent, naive for systemic anti-cancer therapy for metastatic or recurrent disease and results will be available in 2024 [44].

Another example of the association between chemotherapy and checkpoint inhibitors is the randomized, multicenter, phase 3 CALLA/NCT03830866 trial. The trial enrolled 770 patients with advanced cervical cancer (stage III-IVA or IB2-IIIB with positive lymph nodes) who had never received therapy. Patients were randomized to receive concurrent chemo-radiotherapy (CRT) in association with Durvalumab or placebo. Unfortunately, in a March 24 note, it was reported that the trial did not reach statistical significance for the primary endpoint of improved PFS compared with CRT alone in the treatment of patients with locally advanced cervical cancer [45].

Table 3. Immunotherapy for cervix carcinoma (CC): main ongoing trials in Italy.

Study	Treatment	Number of patients	Patient population	Status
KEYNOTE-826/NCT03635567	Pembrolizumab plus Chemotherapy versus Placebo plus chemotherapy	600 (estimated enrollment)	Metastatic, Persistent or Recurrent CC	Active, not recruiting. Estimated Study Completion Date: 2023
BEATcc/ENGOT-cx10/NCT03556839	Cis/Carboplatin + Paclitaxel + Bevacizumab with or without Atezolizumab	404 (Actual enrollment)	Metastatic, Persistent or Recurrent CC	Active, not recruiting. Estimated Study Completion Date: 2023
KEYNOTE-A18/ENGOT-cx11/NCT04221945	Chemoradiotherapy with or without Pembrolizumab	980 (estimated enrollment)	Locally Advanced CC	Active, recruiting. Estimated Study Completion Date: 2024
MITO CERV3/NCT04238988	Carboplatin + Paclitaxel + Pembrolizumab	45 (estimated enrollment)	Locally Advanced CC	Active: recruiting. Estimated Study Completion Date: 2023
InnovaTV205/MK3475/Engot-cx8/NCT03786081	Tisotumab Vedotin with or without chemotherapy, Bevacizumab or Pembrolizumab	220 (estimated enrollment)	Recurrent or stage IVB CC	Active: recruiting. Estimated Study Completion date: 2024

Trial MK-3475-A18/KEYNOTE-A18/ENGOT-cx11/GOG-3047/NCT04221945 is currently recruiting patients with locally advanced cervical cancer to evaluate the efficacy and safety of Pembrolizumab plus concurrent chemoradiotherapy. The primary outcomes are PFS and OS [46].

The Italian phase II, noncomparative MITO CERV 3/NCT04238988 trial, sponsored by Fondazione Policlinico Universitario A. Gemelli IRCCS, is currently recruiting patients with locally advanced cervical cancer (IB2-IIB) with CPS ≥ 1 to evaluate the role of Pembrolizumab in combination with carboplatin-Paclitaxel in locally advanced cervical cancer patients. The primary objective is to compare PFS versus historical controls.

The rationale is based on the possibility of treating locally advanced cervical cancer by using the combination of chemotherapy and immunotherapy instead of the combination of chemo-radiotherapy and radiotherapy, so that radiotherapy treatment can be reserved for cases of disease recurrence [47].

Data from the long-term survival analysis of the phase 3 EMPOWER-Cervical 1/NCT03257267 study were shown during the 2022 European Society for Medical Oncology Congress (ESMO) [48].

This is a phase III trial designed to compare the anti-PD1 antibody Cemiplimab with the chemotherapy of choice in 608 patients with persistent or metastatic cervical cancer after progression on first-line platinum-based chemotherapy, regardless of PD1 status.

The results presented showed, over a mean follow-up of 30 months, that Cemiplimab significantly improved OS compared with chemotherapy (11.7 months vs 8.5, respectively), reducing the risk of death by 34% in the overall population. Cemiplimab presented an acceptable safety profile, with grade ≥ 3 adverse events occurring in 45% of patients

treated with Cemiplimab compared with 53.4% of patients treated with chemotherapy [49].

In Italy, Cemiplimab for cervical cancer of the uterus can be administered as compassionate therapy after approval by the centre's ethics committee.

Building on experience in other solid malignancies, such as lung and breast cancer, research is testing antibody-drug (AD) conjugates for the treatment of advanced cervical cancer. Tisotumab Vedotin is a combination of tisotumab, a monoclonal antibody against tissue factor, and monomethyl auristatin E (MMAE), an antimetabolic agent.

The multicenter, open-label, single-arm, phase 2 innovaTV 204/GOG-3023/ENGOT-cx6/NCT03438396 trial enrolled 102 patients at 35 centres in Europe (including Italy) and USA. Patients had a recurrent or metastatic squamous cell, adenocarcinoma, or adenosquamous cervical carcinoma with disease progression during or after chemotherapy plus bevacizumab and who had received two or fewer prior systemic regimens for recurrent or metastatic disease. Patients received intravenous tisotumab vedotin once every 3 weeks until disease progression or unacceptable toxicity. The confirmed objective response rate was 24% (95% confidence interval (CI) 16–33), with 7 (7%) complete responses and 17 (17%) partial responses [50].

A second and more structured multicenter, phase IB/II InnovaTV205/MK3475/Engot-cx8/NCT03786081 trial is enrolling patients with recurrent or stage IV cervical cancer, evaluating Tisotumab Vedotin as monotherapy or in addition to chemotherapy, to Bevacizumab or Pembrolizumab. Results are expected in 2024 [51].

8. Discussion

Since the basket studies, immunotherapy in gynaecological oncology has been undergoing continuous expansion and growth, particularly in immune checkpoint in-

hibitors. The Italian context is particularly lively in this field, thanks to the presence of numerous research centres of excellence and cooperative groups involved in both national and international projects.

The efficacy of this type of therapy in gynaecological cancers has now been demonstrated in numerous trials, but a careful analysis of individual diseases and treatment settings is required.

With regard to EC, the impact of immunotherapy has been considerable, as demonstrated by the stable inclusion of immunotherapy in today's treatment pathways for these patients, made possible above all by an increasingly in-depth molecular knowledge of EC. The identification of new biomarkers will make it possible to select patients who can best benefit from this type of therapy, potentially reducing the use of conventional chemotherapy.

Immunotherapy in OC has been a complex challenge for years, as early trials have shown. The results of further important trials are now expected, potentially changing the standard of care, particularly for relapsed and platinum-resistant diseases.

CC seems to be one of the most interesting settings for immunotherapy and some results are already starting to be seen in the clinical management of the advanced disease.

As far as we know this review is to date the most up-to-date narrative review on immunotherapy in gynaecological tumours specifically dedicated to the Italian scenario. The main pivotal studies in the field have been included to provide a complete picture of the progress of research. Some limitations of this work may be noted. First of all, the results of numerous studies presented are not yet available, just as we are still awaiting the decision of the regulatory authorities on numerous drugs and specific settings. Furthermore, for the necessity of conciseness, many studies have not been included and some of the more advanced types of immunotherapies, such as those based on vaccines or T-cells, have not been examined.

9. Conclusions

The numerous trials of immunotherapy in gynaecological cancers show that overall, it is a set of therapies that can provide significant results, even in settings with few effective treatment options such as in advanced, relapsed, or metastatic disease.

Despite this, the challenges for clinical application outside of scientific trials are still many: first, the identification of new standardized predictive factors of response to immunotherapy in order to select subgroups of patients capable of the best clinical responses. It is also critical to establish the best timing and modalities for integrating immunotherapy with current gold-standard therapies and constant novelties such as PARP inhibitors, new biosimilar drugs, and new radiotherapy regimens.

The Italian gynaecological cancer immunotherapy landscape is changing accordingly, as evidenced by recent

regulatory body approvals and the increasing involvement of Italian centres in clinical research.

In the coming years, the publication of the results of the numerous ongoing trials is expected, with the hope of seeing new effective immunotherapies approved in Italy as well.

Author Contributions

LP performed literature analysis and wrote the manuscript. MV and RM provided design, revision and editing of the manuscript. DA and MG performed literature search, revision and editing of the manuscript. AF provided conceptualisation, supervised and validated the final manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest. Annamaria Ferrero is serving as one of the Editorial Board members of this journal. We declare that Annamaria Ferrero had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Hiroshi Matsushita.

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