Checkpoint inhibitors in endometrial cancer: preclinical rationale and clinical activity

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ABSTRACT

Context: Treatment of advanced and recurrent endometrial cancer (EC) is still an unmet need for oncologists and gynecologic oncologists. The Cancer Genome Atlas Research Network (TCGA) recently provided a new genomic classification, dividing EC in four subgroups. Two types of EC, the polymerase epsilon (POLE)-ultra-mutated and the microsatellite instability-hyper-mutated (MSI-H), are characterized by a high mutation rate providing the rationale for a potential activity of checkpoint inhibitors.

Materials and Methods: We analyzed all available evidence supporting the role of tumor microenvironment (TME) in EC development and the therapeutic implications offered by immune checkpoint inhibitors in this setting. We performed a review on Pubmed with Mesh keywords ‘endometrial cancer’ and the name of each checkpoint inhibitor discussed in the article. The same search was operated on clinicaltrial.gov to identify ongoing clinical trials exploring PD-1/PD-L1 and CTLA-4 axis in EC, particularly focusing on POLE-ultra-mutated and MSI-H cancer types.

Results: POLE-ultra-mutated and MSI-H ECs showed an active TME expressing high number of neo-antigens and an elevated amount of tumor infiltrating lymphocytes (TILs). Preliminary results from a phase-1 clinical trial (KEYNOTE-028) demonstrated antitumor activity of Pembrolizumab in EC. Moreover, both Pembrolizumab and Nivolumab reported durable clinical responses in POLE-ultra-mutated patients.

Conclusions: Immune checkpoint inhibitors are an attractive option in POLE-ultra-mutated and MSI-H ECs. Future investigations in these subgroups include combinations of checkpoint inhibitors with chemotherapy and small tyrosine kinase inhibitors (TKIs) to enhance a more robust intra-tumoral immune response.

INTRODUCTION

Endometrial Cancer (EC) is expected to be the 4th most common malignancy among women and the 6th leading cause of death in 2017 [1]. EC is frequently associated with Lynch Syndrome (LS), also called hereditary non-polyposis colon cancer (HNPPC), [2], an autosomal dominant genetic disorder which confers an increased risk of developing different kind of tumours, [3]. LS, is characterized by alterations in genes involved in DNA mismatch repair (MMR), such as MLH1, MSH2, MSH6, PMS2 and EPCAM, resulting in microsatellite instability (MSI) [4]. For the 67% of EC patients diagnosed at an early stage, 5-year overall survival is of 95% after surgery with or without radiotherapy. Instead EC patients diagnosed at a late stage have a 5-year survival rate of only 17% [1, 5]; these patients are candidate to systemic treatment with
palliative intent, including chemotherapy, among which carboplatin-paclitaxel doublet is the most effective scheme [1], and endocrine treatments [6]. Up to date there is no standard second line therapy [7].

In this review, we will concentrate on the scientific background supporting the clinical development of immune checkpoint inhibitors in advanced and recurrent disease with a specific focus on the role of tumor microenvironment (TME).

**The “modern” molecular classification: beyond Bokhman’s dual scheme**

EC is an heterogeneous disease with various histological subtypes, which have different pathogenesis, prognosis and sensitivity to different therapeutic agents [8].

In the past decades, EC has been classified in two subtypes, respectively named Type I and Type II according to Bokhman’s model [9], based on clinical characteristics integrated with histological features and hormone receptor (HR) status. Type I is the most common EC (60–70% of cases); it includes grade1 and 2 endometrioid cancer with a high presence of Estrogen Receptors (ERs) and Progesteron Receptors (PgRs). It is related to increased Estrogen levels and endometrial hyperplasia and it is usually associated with a good prognosis (median 5-year survival rates of 85.6%). The most frequently altered pathway in Type I is PTEN-PIK3/AKT/mTOR (PTEN is mutated in approximately 25–50% of cases), followed by KRAS mutations (15–43%), ARID1A and B-catenin alterations [10]. MSI is present in one third of type I EC [11].

Type II EC comprises Grade 3 endometrioid, serous or clear cell HR negative cancers, and it is usually associated with endometrial atrophy [12]. TP53 is the hallmark alteration of this subtype. Patients with type II EC generally show an advanced stage at diagnosis, a low response rate to therapies and a poor prognosis [11, 12].

This dualistic model has recently been expanded in consideration of new knowledge concerning genomic and transcriptomic analysis [13, 14]. In 2013 TGCA (The Cancer Genome Atlas Research Network) [14] published the first genomic characterisation of EC. Results of this study allowed EC classification in four different subtypes, based on somatic mutations, copy number alterations and microsatellite instability:

POLE-ultra-mutated malignancies, representing 6.4% of low-grade and 17.4% of high-grade endometrioid tumours, are characterized by a high mutation rate (232 × 10^6 mutations/Mb); their hallmarks are somatic mutations in the exonuclease domain of POLE that encodes the catalytic subunit of DNA polymerase epsilon. Loss of function of this polymerase, which plays a relevant role in DNA repair, leads to a high frequency of C>A transversions, few copy number alteration and microsatellite stability (MSS). PTEN, PIK3R1, PIK3CA, RAS are frequently mutated [12, 14, 15]. Despite the histological grade, this group is associated with good prognosis [16–20].

MSI-hyper-mutated (MSI-H) tumors represent 28.6% of low grade and 54.3% of high-grade endometrioid EC [14, 15, 21]. They show MSI and high mutation rate (18 × 10^6 mutations/Mb) related to defects in MMR system (the most implicated genes are MLH1, MSH2, MSH6, PMS2), both in sporadic and hereditary EC. PTEN mutations and subsequent alterations of the PTEN-PIK3CA pathway recur in this subgroup [22]. Further genetic abnormalities are frequent, like RPL22 frameshift deletions and KRAS mutation. There is no significant correlation between MSI and outcome in ECs patients [23].

Copy-number low EC is characterized by a low mutation rate (2.9 × 10^6 mutations/Mb) and MSS. It is frequently a low-grade endometrioid cancer (in TGCA 60%of low-grade and only 8.7% of high grade EC were MSS copy low); PTEN and PIK3CA are mutated in 77% and 53% of cases respectively [14, 15]. Other common alterations involve WNT-B catenin axis; RAS mutation is rare; PgR levels are high and this finding predicts usefulness of endocrine therapy [21, 24]. Prognosis is similar to MSI-H tumors without a clear correlation between this subtype and clinical outcome.

Copy-number high serous like subgroup includes mainly serous and mixed histology tumors with a high-grade endometrioid EC. It has a low mutation rate (2.3 × 10^6 mutations/Mb) and a small load of copy number aberrations. TP53 is commonly mutated (92%), whereas KRAS and PTEN mutation are infrequent; 25% of the serous-like tumours are ERBB2-amplified [14, 21]. Prognosis of these patients is poor [12, 15].

This new classification, reported in Figure 1, could be comparable to the already well known pathogenesis model of colon-rectal cancer [25] and may represent a step forward in defining prognosis of EC patients and may help in improving clinical trial design with targeted agents [24, 26, 27].

As recently reported, normal endometrium has a peculiar immune system; indeed, it has a dualistic role: it should be active against sexual pathogens and should allow the growth of an allogenic and “non-self” fetus [28, 29]. This behavior is regulated by sex hormones that influence therefore the TME, especially defining the typology of adaptive immune cells [30].

It is well known that immune cells can recognize and eliminate cancer cells through the identification of tumor-specific antigens (TSA) and tumor-associated antigens (TAA) [31].

Physiologically, when TAA are recognized by T cells they are handled, converted into small fragments and finally presented by antigen-presenting cells (APCs) after loading on major histocompatibility complex (MHC) class I and II. Usually, immune response activation is elicited if two positive signals are present. The first one is the interaction between MHC molecules and T cell
receptors (TCR); the second one is the connection of the co-stimulatory receptor CD28, present on T cells’ surface, with its ligand B7 on APCs. In order to avoid autoimmune reaction CD28 has a competitor for binding B7, the cytotoxic T lymphocyte antigen-4 (CTLA-4), which carries an inhibitory signal. This negative feedback is mostly represented within secondary lymphoid organs, while the inhibitory pathway more frequently present within peripheral TME is the connection between the programmed cell death-1 (PD-1) receptor on the T cells, and the programmed cell death ligand-1 and 2 (PD-L1 and PD-L2) on the tumor cells surface [32, 33]. Different molecular patterns are involved downstream this interaction, such as inhibition of PI3K/AKT and Ras/MEK/Erk pathways, through down-regulation of PTEN and PLC-γ1 respectively [34–36] (Figure 2). Inflammatory cytokines, as interferon, IL-4 and IL-10, generated after recognition of TAA and TSA stimulates PD-1 and PD-L1 over-expression, lead to down-regulation of T-cell reaction and create the mechanism called “adaptive immune resistance” [37]. Other immune checkpoints seem to play a role in adaptive immune resistance, such as Lymphocyte Activation Gene 3 (LAG-3) and indoleamine 2,3-dioxygenase (IDO), both up-regulated in POLE and MSI-H subtypes [38, 39]. Among gynecological cancer, EC show the highest expression of PD-1 and PD-L1,75 % and 25–100% respectively [40]. Moreover, Vanderstraeten and coll. analyzed other immune-related molecules and reported that B7-H4, responsible of another inhibitory pathway of CD4+ and CD8+ T cells, is present in 90% of EC specimens, while IDO is expressed only in 21% of EC samples [39]. These findings confirm an important role of PD-1/PD-L1 pathway and suggest B7-H4 signal as a potential new therapeutic target.

The correlation between PD-L1 expression and patient’s outcome is controversial, since has been associated with a worse prognosis in some tumors, like non-small cell lung cancer (NSCLC) [41], kidney [42–44] and bladder [45] cancer, and with a good one in melanoma [46]. Currently, PD-L1 is routinely analyzed in advanced NSCLC in order to prescribe checkpoint inhibitors, even if is still controversial which is the best cut-off to define positivity and which the best antibody to detect the expression on immunohistochemistry (IHC) assay [47]. PD-L1 detection is regularly used also in the treatment of kidney and bladder cancers [48].

The prognostic value of the expression of this inhibitory pathway, as the role of other components of tumor microenvironment (TME), such as tumor infiltrating lymphocytes (TILs), is currently under investigation in EC. PD-1 and PD-L1 are more frequently reported in POLE-mutated and MSI-H tumors. This pathway might account for more aggressive histopathologic features observed in POLE-mutated, as reported above, even if these tumors have a good prognosis related to a higher number of CD3+ and CD8+ TILs that prevent disease dissemination [49, 50]. POLE-mutated and MSI tumors have an active TME not only for the high number of TILs, but also for the huge amount of tumor specific neo-antigens, generated by genetic alteration acquired due to impaired DNA replication fidelity (POLE) and defective DNA MMR system (MSI-H) [4, 14] (Figure 3). Recent studies have characterized the different cell populations constituting TME. The presence of TILs

Figure 1: Shows the ECs classification according to TGCA including the most common genetic alteration in each subtype. POLE: polymerase epsilon; MMR:mismatch repair; p53: tumor protein p53; PTEN: phosphatase and tensin homolog; PIK3: phosphatidylinositol-4,5-bisphosphate 3 kinase; KRAS: Kirsten rat sarcoma viral oncogene homolog; MMS: microsatellite stability; MSI: microsatellite instability; MLH: mutL homolog 1; MSH2: mutS homolg 2; MSH6: mutS homolog 6; RPL22: 60S ribosomal protein L22; ERBB2: human receptor tyrosine-protein kinase erbB-2; WNT-B: WNT-beta catenin pathway; PgR: progesteron receptor.
appears associated with a better outcome in many different kinds of cancers such as melanoma [51], esophageal [52], breast [53], colorectal [54] and ovarian cancer [55, 56]. In EC, in 2009 de Jong and colleagues assessed the number of CD8+ (cytotoxic T-lymphocytes, CTL), FOXP3+ (regulatory T-lymphocytes, Treg) and CD45R0+ (memory T-lymphocytes) TILs by IHCon tissue microarrays [57]. High numbers of CTL and a high CD8+/FOXP3+ ratio were correlated with a longer disease free survival (DFS), while high levels of CTL and presence of CD45R0+ memory cells were associated with a greater overall survival (OS). In the multivariate analyses high presence of CTL was an independent prognostic factor for longer OS in the entire EC population (HR 0.48,

Figure 2: Shows the interactions of PD-1 and CTLA-4 expressed on the surface of the T cells with the respective ligands and the subsequent activation of immune checkpoint signalling pathways that inhibit lymphocytes survival and proliferation. CTLA-4: Cytotoxic T-Lymphocyte Antigen 4; MHC: Major histocompatibility complex; MMR: Mismatch repair PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; TAA: Tumor associated antigen; TCR: T-cell receptor.

Figure 3: Shows proteins involved in DNA mismatch repair system and the formation of neoantigens resulting from their deficiency. TAA: tumor associated antigen.
with a major impact in type II EC (HR 0.17, \( p = 0.019 \)), with a higher CD8\(^+\)/FOXP3\(^+\) ratio and response to checkpoint inhibitors, a significant step forward in the identification of predictors of response, as discussed in the next section.

Recently, Ott and colleagues published the results of KEYNOTE-028 trial, a phase Ib study involving 24 patients with advanced EC [76]. All patients were treated with Pembrolizumab 10 mg/kg every two weeks for up to 24 months or until confirmed progression, intolerable toxicity, death, or consent withdrawal. Overall Response rate observed was 13%. Three patients obtained a partial response and other three achieved a stable disease. Authors reported a six-months PFS and OS rates of 19.0% and 68.8% respectively. Drug-related adverse events occurred in 54.2% of patients; most common were pruritus, asthenia, fatigue, pyrexia, and decreased appetite. No patients died or discontinued Pembrolizumab because of toxicities. Interestingly, Ganesan and colleagues reported the case of a durable partial response with Pembrolizumab in one patient with POLE-mutation [77]. Pembrolizumab has been tested in metastatic EC also in combination with Lenvatinib, a multikinase-inhibitor with antiangiogenic activity. Makker and colleagues recently presented the results of a phase I / II trial in which 23 patients received Lenvatinib 20 mg/day and Pembrolizumab 200 mg every three weeks. The authors reported an ORR of 48% and a DCR of 96%. The most common adverse events were hypertension, fatigue, arthralgia, diarrhea and nausea [78].

In 2016 Santin and colleagues reported the cases of two patients with recurrent EC refractory to surgery, chemotherapy and radiotherapy treated with the anti-PD-1 Nivolumab [79]. The two women were respectively affected by a mixed clear cell and endometrioid POLE mutated EC and by a serous MSH6 mutated EC. Both patients were treated with Nivolumab 3 mg/kg biweekly. CTL infiltration and PD-L1 expression were evaluated on a pretreatment biopsy. The first patient showed a moderate amount of peri and intratumoral lymphocytic infiltrate. Moreover, a weak membranous PD-L1 expression was reported in about 5% of the tumor cells, whereas the peri- and intratumoral lymphocytes were PD-L1 negative. In the second patient the peri-tumoral lymphocytic infiltrate was moderate, whereas there were fewer CD8-positive lymphocytes within the tumor cell nests. PD-L1 was observed in approximately 20% of peri- and intratumoral lymphocytes, while no significant PD-L1 expression was observed for cancer cells. In this case authors evaluated also p53 expression by immune histochemistry which revealed a wild type pattern. Both patients obtained a persistent clinical response to Nivolumab confirmed by a CT scan respectively at 7 and 9 months from the start of immunotherapy. No severe toxicities were reported.

Antibodies against PD-L1 were also tested for the treatment of endometrial carcinoma.

Fleming and colleagues reported the results of a phase Ia study in which 15 women with EC received Atezolizumab 15 mg/m\(^2\) every three weeks. The majority
discussed above another possible target for checkpoint inhibitors is CTLA-4, in order to prevent binding with its ligand B7. Ipilimumab and Tremelimumab are monoclonal antibodies able to disrupt this interaction. This approach has proven to be effective in the treatment of melanoma [82, 83], but data supporting the effectiveness of anti-CTLA4 in the treatment of EC have not been reported so far.

**DISCUSSION AND FUTURE PERSPECTIVES**

The use of checkpoint inhibitors has a strong rationale in EC, however clinical development is at very beginning and, despite preliminary encouraging results, several issues need to be addressed.

First of all, few data are available regarding predictive biomarkers of response to checkpoint inhibitors. In order to select patients who mostly benefit from these therapies more and more studies analyze cancer genome and its correlation with TME. PD-L1 expression level has been reported as a predictive biomarker of response in NSCLC [63, 65] but its predictive role is not consistent across different cancers types. This may be related to various detection strategies and different specimens analyzed (before, during or after treatments) [66]. Moreover, a crucial role in immune surveillance is played by the others cells expressing PD-L1 present in TME, as reported in a translational study by Webb and colleagues for tumor-associated macrophages (TAMs) on the basis of tissue microarrays of optimally debulked ovarian cancers [84].

Recently, huge progress has been achieved regarding the relationship between cancer genome and response to checkpoint inhibitors [85, 86]. A relationship between response to PD-1/PDL-1 inhibitors and somatic mutations load has been reported in melanoma and lung cancer [67, 68] according to the hypothesis that identifying neo-antigens generated by mutations is an essential step for immune response. Indeed, mutational burden defines immunogenicity of cancers [87, 88]. Besides the neo-antigens loads, some studies were conducted in the melanoma to identify mechanisms related to resistance to PD-1 inhibitors. Shin and colleagues found that loss of function mutations in JAK1 and JAK2, where associated with a deficiency of interferons that physiologically induce PD-L1 upregulation, in several melanoma cells lines which correlate to resistance to checkpoints inhibitors. Moreover, they reported beta-2 microglobulin deletions or mutations leading to beta-2 microglobulin inactivation and subsequent inability for T cells to recognize the tumor. These mutations are responsible for primary resistance or can be developed during treatment, arising secondary resistance to checkpoints inhibitors [89, 90]. The importance of the interferon associated pathways for the response to anti PD-1 and CTLA-4 was confirmed also by an MD Anderson report [91].

As reported above, two subgroups of EC, POLE-ultra-mutated and MSI-H, are characterized by higher number of neo-antigens and the elevated amount of TILs [15]. The consequent high immunogenicity of POLE-ultramutated EC is speculated to be responsible for the good prognosis and possibly for likelihood of responding to immune checkpoint inhibitors [92]. Neo-antigen load could possibly be a biomarker of response also in hypomutated EC, as reported by Shukla and colleagues [93]. Indeed they observed that hypo-mutated tumors with highest neo-antigen load have a better PFS. Moreover, they reported that a lower neo-antigens number is associated with particular gene alterations, CTNNB1 and PIK3CA mutations and MYC amplifications. The above variations could be used as indicators of less immunogenicity and, consequently, of lower response rate to checkpoint inhibitors. These discoveries could help clinicians to identify EC patients that could benefit from checkpoint inhibitors.

The need to identify possible biomarkers of response is also crucial for the ongoing clinical trials, reported in Table 2, which, following evidence derived from other cancers, are exploring combinations of checkpoints inhibitors or associations of checkpoints inhibitors with chemotherapy, small tyrosine kinase inhibitors (TKIs) and mTOR inhibitors.

The study published by Pakish evaluating the immune infiltrate in MSI-H EC suggests for the first time...
Table 1: Published and preliminary data of trials evaluating the activity of checkpoint inhibitors in the treatment of endometrial cancer

<table>
<thead>
<tr>
<th>Study name/First author</th>
<th>Combination</th>
<th>Treatment setting</th>
<th>Phase</th>
<th>Class of experimental agent</th>
<th>Line of therapy</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
<th>Study name/First author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab 10 mg/kg every 2 weeks</td>
<td>Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>Ib</td>
<td>Anti-PD-1</td>
<td>2L+</td>
<td>13%</td>
<td>19% at six months</td>
<td>68.8% at six months</td>
<td>KEYNOTE-028</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab 20 mg/day + Pembrolizumab 200 mg every 3 weeks</td>
<td>Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>Ib/II</td>
<td>Multikinase inhibitor + Anti-PD-1</td>
<td>2L+</td>
<td>48%</td>
<td>Not estimable</td>
<td>Not estimable</td>
<td>Vicky Makker</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab 1200 mg or 15 mg/kg IV q3w</td>
<td>Pembrolizumab in Ultramutated and Hypermutated EC</td>
<td>1a</td>
<td>Anti-PD-L1</td>
<td>2L+</td>
<td>13%</td>
<td>1.7 months</td>
<td>9.6 months</td>
<td>Gini F. Fleming</td>
<td></td>
</tr>
</tbody>
</table>

PFS = Progression Free Survival; ORR = Overall Response Rate; OS = Overall Survival.

Table 2: Ongoing trials using checkpoint inhibitors in endometrial cancer

<table>
<thead>
<tr>
<th>Combination</th>
<th>Treatment setting</th>
<th>Phase</th>
<th>Class of experimental agent</th>
<th>Line of therapy</th>
<th>Primary endpoint</th>
<th>Status</th>
<th>Trial identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPD-L1</td>
<td>Avapetam in Patients With MSS, MSI-H and POLE-mutated</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>ORR, safety by CTCAE v4</td>
<td>Recruiting</td>
<td>NCT02912572</td>
</tr>
<tr>
<td>aPD-1</td>
<td>Pembrolizumab in Ultramutated and Hypermutated EC</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>1 L</td>
<td>1 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-1</td>
<td>Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>1L</td>
<td>Pembrolizumab + Lenvatinib</td>
<td>Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>1 L</td>
<td>2 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-1 + Bev/C/PLD</td>
<td>Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>1 L</td>
<td>2 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-1 + Chemo</td>
<td>Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>1L+</td>
<td>Pembrolizumab + Lenvatinib</td>
<td>Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers</td>
<td>1 L</td>
<td>2 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-1 + TIL</td>
<td>Pembrolizumab + TIL PBL and aldesleukin</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab + Lenvatinib + TIL PBL and aldesleukin</td>
<td>1 L</td>
<td>2 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-1 + TKI</td>
<td>Pembrolizumab + Itacitinib</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab + Itacitinib</td>
<td>1 L</td>
<td>2 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-L1 + aCTLA-4</td>
<td>Pembrolizumab + Tremelimumab</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab + Tremelimumab</td>
<td>2 L</td>
<td>2 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-L1 + Chemo</td>
<td>Pembrolizumab + Chemotherapy</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab + Chemotherapy</td>
<td>2 L</td>
<td>2 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-L1 + aCTLA-4</td>
<td>Pembrolizumab + Ipilimumab</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab + Ipilimumab</td>
<td>2 L</td>
<td>2 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-L1 + mTORi</td>
<td>Pembrolizumab + Temsirolimus/ Nivolumab + CT</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab + Temsirolimus/ Nivolumab + CT</td>
<td>2 L</td>
<td>2 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-L1 + aCTLA-4</td>
<td>Pembrolizumab + Ipilimumab in rare tumors</td>
<td>1L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab + Ipilimumab in rare tumors</td>
<td>1 L</td>
<td>2 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-L1 + Chemo</td>
<td>Pembrolizumab + Carboplatin-cyclophosphamide</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab + Carboplatin-cyclophosphamide</td>
<td>2 L</td>
<td>1 L</td>
<td>Recruiting</td>
</tr>
<tr>
<td>aPD-L1 + IDO Inhibitor</td>
<td>Pembrolizumab + IP-10109</td>
<td>2L+</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab + IP-10109</td>
<td>2 L</td>
<td>1 L</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

Chemo: chemotherapy; Bev: bevacizumab; C: Carboplatin; PLD: pegylated liposomal doxorubicin; TKI: tyrosine kinase inhibitor; TIL: tumor infiltrating lymphocytes; mTORi: mTOR inhibitor; IDO: indoleamine 2,3-dioxygenase; L, line (regime of chemotherapy); PFS6, progression free survival at 6 months; ORR, overall response rate; CTCAE v4.03, Common Terminology Criteria for Adverse Events, version 4.03; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; MTD, maximum tolerated dose; DLT, dose-limiting toxicities; RP2D, recommended phase 2 dose; NCT, National Clinical Trial.

that among patients with MSI, there may be differences in the TME on the basis of hereditary or sporadic nature of the MMR deficiency [4]. These data have been recently confirmed at the Society for Gynecologic Oncology Annual Meeting on Women’s Cancer by Ring and colleagues, who reported that EC related to LS has a stronger expression of PD-L1, in particular for LS caused by MSH6 loss [94].

For this reason, future clinical trials should stratify patients considering Lynch related and sporadic MSI-H tumor.

More recently, the European Society of Medical Oncology (ESMO) provided a practical guidance for MMR-deficiency testing in EC [95] underlying its emerging importance both to guide adjuvant treatment and to identify LS cases. Although there is not a general agreement on testing EC patients for LS, the above data suggest that MMR-deficiency could be predictive of response to immunotherapy and help clinicians in their therapeutic choices. At present, both MSI (pentaplex panel) and IHC are validated methods in EC testing [96, 97].

Clinical settings and associations

Considering its important role in EC, one of the most promising partners of checkpoint inhibitors is radiotherapy. In particular, as suggested for other malignancies, the so-called out-of-the-field responses in patients receiving radiation therapy during immunotherapy may be relevant also in EC [98]. Another important direction of clinical research is represented by the association of chemotherapy and immune checkpoint inhibitors [99]. Although chemotherapies are believed to be immunosuppressive, when given at the right dose and sequence may provide a “priming” effect for the immune system. Trials have shown already that platinum based chemotherapy associated with immune checkpoint inhibitors is active in NSCLC [100]. Since chemotherapy (especially platinum based chemotherapy) is also active in EC, it is likely to obtain similar results with the addition of a checkpoint inhibitor.

Considering other malignancies where the development of immune checkpoint inhibitors is more advanced (e.g. melanoma), there is no clear evidence...
suggesting a significant improvement in survival [69]. Accordingly, it is therefore more likely that patients with advanced endometrial cancer (stage III and IV) may benefit best from immune checkpoint inhibitors.

CONCLUSIONS

ECs have already proved to be an immunogenic diseases suggesting a potential role for checkpoints inhibitors in their treatment. As reviewed above, the TCGA classification is a step forward towards individualized therapies and should be considered in future clinical trials, to assess which subsets of EC patients are more likely to benefit from an immunotherapeutic approach. Further investigations should include the identification of which dominant immunosuppressive pathway characterizes each subtype in order to better identify reliable biomarkers of response. Future strategies will explore different clinical settings and combinations of chemo and radiotherapy with checkpoint inhibitors to boost immune response and improve patients outcomes.

MATERIALS AND METHODS

Search strategy

We conducted a search on Medline with Mesh keywords: endometrial cancer, endometrial carcinoma, endometrial neoplasm, endometrium cancer, endometrium carcinoma, and endometrium neoplasm. Moreover, the search strategy included terms for endometrial cancer matched with immunotherapy; tumor infiltrating lymphocytes (TILs); polymerase epsilon (POLE)-ultra-mutated; microsatellite instability (MSI); tumor-microenvironment; programmed death-1 (PD-1); programmed death-ligand 1 (PD-L1); cytotoxic T-lymphocyte-associated protein 4 (CTLA-4); the name of all checkpoint inhibitors discussed in the paper. The literature search was performed up to June 2017. Moreover had searched abstract books of conference proceedings between 2010 and 2017 to identify potentially eligible studies. With the same keywords we operated a search on clinicaltrials.gov.

Selection criteria

Retrieved articles were examined by all coauthors to assess their consistency with the aims of the article.

Abbreviations

Not applicable.

Author contributions

GM and GV conceived of the concept. EG, GM, SG, GG participated in data collection and interpretation, GV, GM, and MA analyzed data and wrote the manuscript. All authors read and approved the final manuscript.

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Not applicable.

CONFLICTS OF INTEREST

The authors declare the absence of conflicts of interest.

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