Gynecologic Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Clear cell carcinoma of the endometrium

Giorgio Bogani [a,*], Isabelle Ray-Coquard [b], Nicole Concin [c,d], Natalie Y.L. Ngoi [e], Philippe Morice [f], Takayuki Enomoto [g], Kazuhiro Takehara [h], Hannelore Denys [i], Domenica Lorusso [j], Robert Coleman [k], Michelle M. Vaughan [l], Masashi Takano [m], Diane Provencher [n], Satoru Sagae [o], Pauline Wimberger [p], Robert Póka [q], Yakir Segev [r], Se Ik Kim [s], Jae-Weon Kim [s], Francisco J. Candido dos Reis [t], Andrea Mariani [u], Mario M. Leitao Jr [v], Viky Makker [v], Nadeem Abu Rustum [v], Ignace Vergote [w], Gian Franco Zannoni [j], David S.P. Tan [x], Mary McCormack [y], Marta Bini [z], Salvatore Lopez [z], Francesco Raspagliesi [z], Pierluigi Benedetti Panici [a], Violante di Donato [a], Ludovico Muzii [a], Nicoletta Colombo [aa], Giovanni Scambia [j], Sandro Pignata [ab], Bradley J. Monk [ac]

[a] Department of Maternal and Child Health and Urological Sciences, Sapienza University, Policlinico Umberto I, Rome, Italy
[b] Centre Leon Bérard, Hesper lab, EA 7425, Université Claude Bernard Lyon Est, Lyon, France
[c] Department of Gynecology and Obstetrics, Innsbruck Medical University, Innsbruck, Austria
[d] Department of Gynecology and Gynecological Oncology, Evangelische Kliniken Essen-Mitte, Essen, Germany
[e] National University Cancer Institute, Singapore, Singapore
[f] Gystave Roussy Cancer Campus, Villejuif, France
[g] Department of Obstetrics and Gynecology, Niigata University Graduate School of Medical and Dental Sciences, Japan
[h] Department of Gynecologic Oncology, National Hospital Organization Shikoku Cancer Center, Japan
[i] Medical Oncology, Department of Internal Medicine and Pediatrics, Ghent University Hospital, Ghent, Belgium
[j] Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy
[k] Department of Gynecologic Oncology and Reproductive Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA
[l] Medical Oncology, Canterbury Regional Cancer and Haematology Service, Christchurch, New Zealand
[m] Department of Obstetrics and Gynecology, National Defense Medical College, Tokorozawa, Saitama, Japan
[n] Centre hospitalier de l'Université de Montréal (CHUM), Institut du cancer de Montréal, Montréal, Canada
[o] Gynecologic Oncology Unit, Hokkaido Ohno Memorial Hospital, Sapporo, Japan
[p] Department of Gynecology and Obstetrics, Carl-Gustav-Carus University, TU Dresden, Dresden, Germany on behalf of the AGO-Ovar, Germany
[q] Institute of Obstetrics and Gynecology, Clinical Center, University of Debrecen, Debrecen, Hungary
[r] Carmel Medical Center, Affiliated to the Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[s] Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul 03080, Republic of Korea
[t] Department of Gynecology and Obstetrics, Ribeirao Preto Medical School, University of Sao Paulo, Brazil
[u] Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN, USA
[v] Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, NeJoan & Sanford I. Weill Medical College of Cornell University, New York, NY, USA
[w] University Hospital Leuven, Leuven, Belgium
[x] Department of Haematology-Oncology, National University Cancer Institute, National University Health System, Singapore; Cancer Science Institute, National University of Singapore, Singapore
[y] Department of Oncology, University College London Hospitals NHS Foundation Trust, London, UK
[z] Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy
[aa] Gynecologic Oncology Program, European Institute of Oncology, IRCCS, Milan and University of Milan-Bicocca, Milan, Italy
[ab] Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli, Italy
[ac] Arizona Oncology (US Oncology Network), University of Arizona, Creighton University, Phoenix, USA

HIGHLIGHTS

- Clear cell endometrial cancer represents uncommon uterine tumor.
- Multi-modal treatment should be considered in patient with clear cell endometrial cancer.
- Immunotherapy might play a role in patients with MMRd clear cell endometrial cancer.
- *ATr*, *PIK3CA*, *DDR*, and *HER2* might be potential targets in clear cell endometrial cancer

* Corresponding author.
E-mail address: giorgiobogani@yahoo.it (G. Bogani).

https://doi.org/10.1016/j.ygyno.2022.01.012

Please cite this article as: G. Bogani, I. Ray-Coquard, N. Concin, et al., Clear cell carcinoma of the endometrium, Gynecologic Oncology, https://doi.org/10.1016/j.ygyno.2022.01.012

ARTICLE INFO

Article history:
Received 8 November 2021
Received in revised form 4 January 2022
Accepted 7 January 2022
Available online xxxx

Keywords:
Clear cell endometrial cancer
Immunotherapy
Target therapy
Uterine cancer

ABSTRACT

Clear cell endometrial carcinoma represents an uncommon and poorly understood entity. Data from molecular/genomic profiling highlighted the importance of various signatures in assessing the prognosis of endometrial cancer according to four classes of risk (*POLE* mutated, MMRd, NSMP, and *p53* abnormal). Unfortunately, data specific to clear cell histological subtype endometrial cancer are lacking. More recently, data has emerged to suggest that most of the patients (more than 80%) with clear cell endometrial carcinoma are characterized by *p53* abnormality or NSMP type. This classification has important therapeutic implications. Although it is an uncommon entity, clear cell endometrial cancer patients with *POLE* mutation seem characterized by a good prognosis. Chemotherapy is effective in patients with NSMP (especially in stage III and IV) and patients with *p53* abnormal disease (all stages). While, preliminary data suggested that patients with MMRd are less likely to benefit from chemotherapy. The latter group appears to benefit much more from immune checkpoint inhibitors: recent data from clinical trials on pembrolizumab plus lenvatinib and nivolumab plus cabozantinib supported that immunotherapy plus tyrosine kinase inhibitors (TKI) would be the most appropriate treatment for recurrent non-endometrioid endometrial cancer (including clear cell carcinoma) after the failure of platinum-based chemotherapy. Moreover, ongoing clinical trials testing the anti-tumor activity of innovative products will clarify the better strategies for advanced/recurrent clear cell endometrial carcinoma. Further prospective evidence is urgently needed to better characterize clear cell endometrial carcinoma.

Contents

1. Introduction

Endometrial cancer is one of most common gynecological cancers, with more than 65,000 newly diagnosed cases in the United States in 2021 [1]. The prevalence of endometrial cancer is rapidly growing, with an estimated increase of about 20,000 cases *per* year, over the last decade [1]. Endometrial cancer is not a single disease, but a heterogeneous group of separate entities. According to histological classification, endometrioid endometrial cancer is the most common type of endometrial cancer, accounting for about 75–80% of cases [2]. Other types of endometrial cancer include serous carcinoma (10%), undifferentiated carcinoma (5%), carcinosarcoma (2–5%), clear cell carcinoma (2–5%), mesonephric like (1%) and the gastric-type (1%) [2,3]. Non-endometrioid endometrial cancer is characterized by a higher risk of recurrence and worse prognosis than endometrioid endometrial cancer [2]. These aggressive forms are responsible for 40% of the total number of endometrial cancer-related deaths [2,3].

Clear cell endometrial carcinoma is a rare type of uterine malignancy, and it is more prevalent amongst East Asian patients [3]. Clear cell endometrial carcinoma represents a poorly understood disease entity, and few clinical trials have exclusively recruited this patient population [3]. In contrast with other more common subtypes of endometrial cancer, limited data are available regarding the carcinogenesis and natural history of clear cell endometrial cancer. Clear cell endometrial carcinomas are aggressive cancers with poorer prognosis and chemotherapy resistance [4,5]. Owing to the rarity of clear cell endometrial cancer, several features regarding this condition are still unclear. In the present review, we performed a thorough discussion on the pathological and molecular landscape of clear cell endometrial cancer, focusing on emerging therapeutic options.

2. Pathological characteristics

The diagnosis of clear cell endometrial carcinoma represents a challenge for pathologists, since there is a significant inter-observer variability which can be as high as 30% [6,7]. The morphological features are similar to its ovarian counterpart but, according to the World Health Organization (WHO) classification, the diagnosis of clear cell endometrial carcinoma requires specific criteria: polygonal or hobnail or cells with clear or eosinophilic/oxyphilic cytoplasm and nuclear atypia, with different architectural pattern of growth, such as papillary, tubulocystic, or solid [8]. The vast majority of cases show a combination of different histologic patterns, the most common being the tubulo-cystic, which is represented by tubules or glands characterized by cystic dilation and abundant inter-glandular stroma [7–9]. The predominant histologic pattern is papillary, in the form of small rounded papillae hyalinized stroma and hyaline bodies [7–9]. The solid pattern is composed both by clear and oxyphilic cells, which constitute a sheet of polygonal cells with well-defined cell borders, interspersed thin fibrous septa, and is almost always interlaced with other patterns. From the cytologic point of view, large pleomorphic nuclei included in scattered or clustered cells with a low mitotic index is often shown, while nuclear atypia and high mitotic index are not typical features [7–9]. Usually, clear cell endometrial carcinoma are “high-grade”. Fig. 1 shows pathological characteristics of clear cell endometrial carcinoma. Diagnosis is mainly based on morphological features, but immunohistochemistry can help to

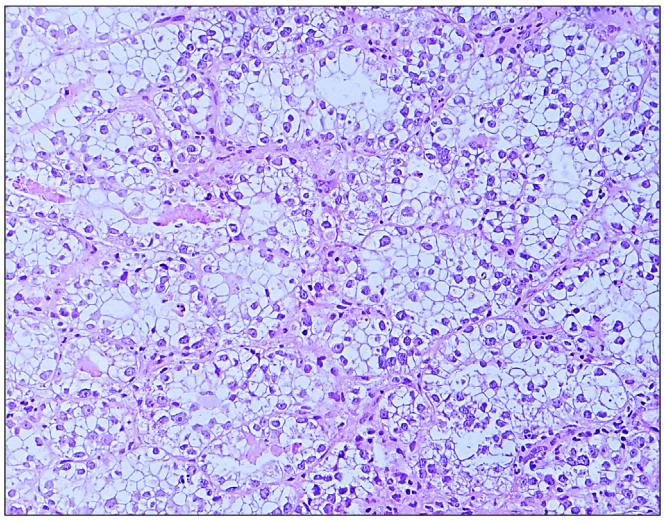

Fig. 1. Pathological characteristics of clear cell endometrial cancer.

distinguish it from serous and endometroid carcinomas. A clear cell endometrial carcinoma is usually HNF1B positive, WT1 negative, Napsin A and/or p504S positive, and estrogen receptor (ER)/progesterone receptor (PR) negative [7–9]. An expert gynecologic pathology review is highly recommended [10–11].

2.1. Molecular and genomic profile of clear cell endometrial cancer

In 2013, The Cancer Genome Atlas (TCGA) highlighted the importance of molecular/genomic profiling in endometrial cancer. As surrogate markers of the TCGA molecular subtypes, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) subdivided different endometrial carcinomas into four prognostic molecular subgroups *POLE* mutated/ultramutated (*POLE* mut), microsatellite-unstable/hypermutated (MSI or mismatch repair deficient (MMRd)), copy-number-low/*TP53*-wild-type (CNL/NSMP) and copy-number- high/*TP53*-abnormal (CNH/*p53* abn) [4]. Notably, no clear cell endometrial carcinomas were involved in the study. Since then, other groups have described the molecular classification of clear cell endometrial carcinomas [12]. Results are consistent across different reports, and demonstrated that the most prevalent subgroups were the *p53* abnormal and NSMP subgroups, while the MSI and *POLE* mut subgroups were less common [12]. Data extracted from a recently published review suggest that *POLE* mut, MMRd, *p53* abn and NSMP wild type accounted for about 4%, 10%, 44%, and 42% of patients with pure clear cell endometrial carcinoma, respectively [12,13] This molecular classification has also prognostic value. The *p53* abnormal subgroup displays aggressive features with the highest proportion of LVSI, deep myometrial invasion, node positivity and advanced stage (III/IV) disease among the endometrial cancer patients. Patients with MMRd or *POLE* mutation are typically younger, and usually show higher tumor infiltrating lymphocytes (TILs), which might confer better outcome (especially for those receiving immunotherapy). Understanding response to therapies in these molecular subgroups will be fundamental to optimal clinical practice: post hoc subgroup analysis of PORTEC 3 trial data suggested that some subgroups do not need adjuvant therapy due to their intrinsically good prognosis (e.g., the *POLE* subgroups), or possibly they need only radiation therapy (e.g., the MMRd subgroup) [14,15]. Instead, *p53* abnormal endometrial cancer benefit from both chemotherapy with or without radiotherapy [14,15]. The most frequently mutated group of genes in clear cell endometrial carcinoma are those involved in chromatin remodeling and transcriptional regulation (i.e., *ARID1A*, *ZFHX, PIK3CA,* and *TSPYL2*) and genes involved in ubiquitin-mediated proteolysis (i.e., *SPOP* and *FBXW7*); *TP53* missense mutation is also frequently found. Mutations in the *PIK3R1* and *KRAS* genes are found in 18% and 14% of cases, respectively. Interestingly patients with clear cell carcinoma are characterized by synchronous mutation of the PIK3CA and KRAS genes [17]. Mutations in *CTNNB1* and *PTEN* are not usually reported in patients with clear cell endometrial cancer [12,13,16,17].

2.2. Surgical approaches

Surgery is the mainstay of treatment for endometrial cancer. Hysterectomy (plus salpingo-oophorectomy) allows primary tumor removal and identification of major prognostic factors (e.g., myometrial invasion, lymph vascular space invasion) [18]. Fertility-sparing procedures are not recommended in patients with clear cell endometrial cancer [10,11]. International guidelines recommend, the execution of peritoneal and retroperitoneal staging, even in presence of apparent early-stage disease. Minimally invasive surgery should be the preferred surgical approach [11]. Minimally invasive surgery correlates with improved short-term outcomes and similar long-term oncologic outcomes than open surgery [11]. Cytoreductive surgery (with the removal of bulky nodes) is recommended in locally advanced and metastatic disease (III-IVB) [10,11]. The role of retroperitoneal staging deserves special attention. Full nodal dissection (pelvic and para-aortic) is still recommended by several guidelines [10,11]. Only few data on the use of sentinel node mapping in clear cell carcinoma are available [19], the National Comprehensive Cancer Network® (NCCN®) guidelines open to the adoption of this approach even in non-endometroid endometrial cancer (including those with clear cell histology) [10]. Also, the ESGO/ESTRO/ESP guidelines stated that sentinel node is an acceptable alternative to systematic lymphadenectomy for staging purpose in early stage endometrial cancer with high/intermediate and high risk disease (including clear cell endometrial cancer) [11]. However, sentinel node mapping should be done in institutions with expertise in this type of approach. Ongoing prospective studies will clarify the role of sentinel node mapping in clear cell endometrial cancer [20]. According to the ESGO/ESTRO/ESP guidelines, infracolic omentectomy can be omitted in early-stage clear cell endometrial carcinoma, as the low rate of omental metastases does not justify this staging procedure [11].

2.3. Adjuvant therapy

The role of adjuvant therapy in early-stage clear cell endometrial carcinoma is still debated. Both the NCCN and ESGO/ESTRO/ESP guidelines grouped together clear cell endometrial carcinoma with other non-endometrioid histological types. [10,11] According to the NCCN guidelines, clear cell endometrial carcinoma are classified as a high-risk disease and warrant adjuvant treatments in most cases [10].

Importantly, the ESGO/ESTRO/ESP guidelines introduced molecular classification as fundamental integrated information for prognostic risk group stratification and for tailoring adjuvant therapy in endometrial carcinoma patients. These Triple-European guidelines apply a differentiated approach in patients with clear cell carcinoma of the endometrium and discriminate the situation of known and unknown molecular marker profile, respectively. In the situation of known clinico-pathological markers only (without molecular profiling) the ESGO/ESTRO/ESP guidelines classify patients with stage IA clear cell endometrial carcinoma without myometrial invasion as intermediate risk, while patients with stage I-IVA clear cell endometrial carcinoma with myometrial invasion are classified as high risk disease [11].

If molecular classification is known, these guidelines classify clear cell carcinoma patient with stage I and II *POLE* mut disease as low risk with no need for adjuvant treatment, while stage I-IVa p53abn clear cell carcinomas with myometrial invasion are categorized into the high risk group, and treatment according to high risk group with chemotherapy +/− radiotherapy is recommended. Clear cell carcinoma of stages I-IVa with the molecular profile MMRd or NSMP and myometrial invasion are not allocated to a prognostic risk group in the

ESGO/ESTO/ESP guidelines as at the time point of publication insufficient data were available for their prognostic relevance. Thus, for these patients also no adjuvant treatment recommendations are provided, but inclusion into prospective registries is recommended.

A recently meta-analysis including 114 pure clear cell endometrial carcinoma patients from six studies highlighted that molecular and genomic classification might predict patients outcomes [12]. The 5-year overall survival rates for POLE mutated, MMRd, NSMP and p53 abnormal subgroups were 100%, 91%, 49% and 35%, respectively [12]. In literature, patients with POLE mutation are considered at low risk of recurrence, and adjuvant therapy in this group can be avoided in stage I, II while more reliable date are waited for stage III-IV disease and prospective registries are encouraged [12]. Similarly, molecular analysis of the PORTEC-3 trial suggested no, or limited benefit of adding chemotherapy in patients with MMRd disease [15]. Therefore, in this latter group of patients, chemotherapy could be considered as an option and discussed on a case-by-case basis. Adjuvant therapy has an important role in patients with p53 abnormalities and potentially also to certain extent in the NSMP group. These two latter groups also represent the large majority of clear cell endometrial carcinoma. Overall, 30–50% of patients with clear cell endometrial cancer are characterized by *p53* abnormalities. The prevalence is generally higher in case of tumors characterized by mixed histology (e.g., clear cell plus serous endometrial cancer) [12–15]. However, we have to highlight that patients with mixed endometrioid and clear cell carcinoma are characterized by MMMRd [21]. The NSMP group accounts for about 45–50% of clear cell endometrial carcinoma. Hence, the majority of clear cell endometrial carcinoma is characterized by poor prognosis and deserve to be treated with adjuvant treatment. Generally, the preferred adjuvant regimen includes a multimodal treatment with chemotherapy and radiotherapy [10–12]. Fig. 2 displays the recommendation for adjuvant therapy in clear cell endometrial carcinoma, according to clinical-pathological features and molecular / genomic characteristics. However, we would like to emphasize that only limited data are available for stage IA (with myometrial invasion), stage IB, II, III and IVA clear cell endometrial carcinoma characterized by MMRd and NSMP. Similarly, data regarding *POLE* mutated, stage III and IV, clear cell endometrial carcinoma are also limited. Therefore, the level of evidence is not sufficient to draw strong conclusions, further prospective data are needed to better define prognosis and role of adjuvant therapy in clear cell endometrial cancer.

2.4. Follow-up schedule

Patients with clear cell endometrial cancer are candidates for regular follow-up visits after primary treatment. Follow-up schedules include regular gynecological examination performed every 3–4 months during the first two years, and every six months during the next three years. Radiological examination (contrast enhanced abdominal computed tomography [CT] scan) is recommended annually [22]. To date, no data support the role of more intensive follow-up schedule even in patients with clear cell endometrial cancer. The intensive versus minimalist follow-up in patients treated for endometrial cancer (TOTEM) study, was presented at the American Society for Clinical Oncology (ASCO) 2021 annual meeting [22]. Analyzing data of 1884 endometrial cancer patients, the authors observed that intensive follow-up schedules showed a weak and uncertain advantage in detecting earlier asymptomatic relapses, but did not improve 5-year overall survival, even in the high-risk group, nor influenced quality of life. However, only 8.1% of patients with non-endometrioid histology were included [22]. Further evidence is needed to assess the preferred follow-up schedule. However, frequent routine use of imaging and laboratory exams (i.e., serum markers) in these patients should be discouraged.

2.5. Treatment of recurrent / progressive disease

Patients with recurrent disease are characterized by poor prognosis and have only limited therapeutic options. The treatment of recurrent disease depends on several features, including the patients' demographic characteristics, comorbidities, performance status, response to previous treatments, and metastatic sites. Treatment of recurrent disease is usually multimodal, and includes surgery, radiotherapy, and chemotherapy. Surgery and/or radiotherapy (with or without chemotherapy) might be offered in patients with oligometastatic disease and loco-regional recurrence, even when relapses are repeated [23]. Surgery should only be offered if R0-resection is possible [23]. Chemotherapy is the mainstay of treatment in patients with peritoneal and/or hematogenous dissemination and platinum-based chemotherapy is the standard first-line regimen. The phase III GOG209 study compared paclitaxel-doxorubicin-cisplatin with carboplatin plus paclitaxel in stage III/IV, and recurrent endometrial cancers. Carboplatin plus paclitaxel showed similar efficacy in terms of progression-free survival and overall survival, but more favorable safety profile, compared to paclitaxel-doxorubicin-cisplatin. However, the GOG209 included only 47 (3.4%) with clear cell endometrial carcinoma **[24]**. Although no specific prospective data on clear cell endometrial cancer are available as yet, several immune checkpoint inhibitors have been studied in patients with recurrent endometrial cancer [25]. Recently, based on the results from phase II studies, the US Food and Drug Administration (FDA) approved the use of the immune-checkpoint inhibitor, pembrolizumab, in patients with MSI-H/MMRd disease (progressed after conventional therapy), and pembrolizumab plus the antiangiogenic agent, lenvatinib, as second line treatment in patients with microsatellite stable endometrial cancer [25]. Interestingly, the combination of pembrolizumab and lenvatinib in second line showed a clinically meaningful (and statistically significant) improvement in progression-free survival, overall survival, and objective response rate, regardless of MMR status, in endometrial cancer patients after failure of platinum-based chemotherapy [25]. Makker et al., reported results of a phase II study (the KEYNOTE-146/Study-111) evaluating the role of lenvatinib plus pembrolizumab in a cohort of patients with advanced endometrial carcinoma [25]. In this trial, patients were treated with lenvatinib 20 mg once daily orally plus pembrolizumab 200 mg intravenously once every 3 weeks, in three-week cycles. The objective response rate at 24 weeks was 63.6% (95% CI: 30.8% to 89.1%) in patients with MSIH/MMRd ($n = 11$), and 36.2% (95%CI: 26.5% to 46.7%) in patients with microsatellite-stable tumors ($n = 94$). The results of this study highlight that pembrolizumab plus lenvatinib have promising antitumor activity, regardless of tumors' MSI status [25]. However, only about 5% of patients included in the KEYNOTE-146/Study-111 were affected by clear cell endometrial carcinoma [25]. More recently, dostarlimab was granted accelerated approval for the treatment of patients with recurrent or advanced endometrial cancer with MMRd that has progressed on, or following prior treatment with platinum-based chemotherapy. In the single-arm, multi-cohort GARNET trial (NCT02715284), patients received 500 mg of dostarlimab once every 3 weeks for 4 doses, followed by 1000 mg once every 6 weeks until disease progression. This trial showed an effective anti-tumor activity in the MMRd cohort. Moreover, the updated results of the trial (presented at the European Society for Medical Oncology - ESMO 2020 Congress) showed that in 103 patients with MMRd endometrial cancer, the disease control rate was 57.3% and the objective response rate was 44.7% [26]. Overall, 11, 35, and 13 patients experienced complete response, partial response, and stable disease, respectively [26]. Lower rates of response were also seen in a separate cohort of patients with microsatellite stable endometrial cancer patients. Table 1 summarizes the most relevant available data on anti-tumor activity of immune-checkpoint inhibitors in patients with recurrent endometrial cancer. Fig. 3 summarizes the recommendation for the treatment of advanced and metastatic disease according to the NCCN and ESGO/ESTRO/ESP guidelines [10,11]. At the present time, only dostarlimab gained approval or reimbursement in Europe and approval for lenvatinib and pembrolizumab is awaited at the end of this year. Further evidence from ongoing trials will clarify the benefit of adding immunotherapy, or other target therapies in patients with recurrent clear cell endometrial carcinoma.

for stage III-IVa POLE mut endometrial carcinoma (incl. clear cell) insucifient data are available to allocate patients to a prognostic risk group and to give robust treatment recommendations
*, Only few data are avialable on stage IA (with myometrial invasion), stage IB, II, III and IVA clear cell endometrial cancer with MMRd and NSMP.
The level of evidence is not sufficient to draw definitive conclusions on prognosis and to give robust adjuvant treatment recommendations , further prospective data are needed
** , There are no available data supporting the addition of chemotherapy in this group of patients

Fig. 2. Recommendation for adjuvant treatments according to pathological and molecular analyses.

Table 1
The role of immune checkpoint inhibitors in advanced / recurrent endometrial cancer.

Study Identifier	KEYNOTE-158	KEYNOTE-775/Study 309	NCT01375842	GARNET trial (NCT02715284)	NCT03367741	
Medication used	Pembrolizumab	Pembrolizumab lenvatinib vs. chemotherapy	Atezolizumab	Dostarlimab	Nivolumab	Nivolumab plus cabozantinib
Study design	Phase II	Phase III	Phase Ia	Phase II	Phase II	Phase II
Number of patients	49 dMMR patients	411 in the control group vs. 416 in the experimental arm	15	126 dMMR and 145 MMRp	20	39
Number of patients with non-endometrioid histology	47%	NR	5 (33%)	NR	NR	NR
Number of patients with clear cell histology	2%	NR	0%	NR	NR	NR
Objective response rate	57%	31.9%	13%	44.7% (dMMR); 13.4% (MMRp)	11%	25%
Partial response	20%	25.3%	13%	33.9%	NR	NR
Complete response	8%	6.6%	0%	10.6%	NR	NR
Duration of response	Not reached (NR; range, 3–27+ mo)	14.4	7.3–8.1	Not reached	NR	NR
Progression-free survival	26 mo	7.2 mo	1.7 mo	NR	1.9 mo	5.3 mo
Overall survival	Not reached (95% CI, 27 mo-NR)	18.3 mo	9.6 mo	Not reached	7.9 mo	13 mo

Abbreviations; NR, not reported; mo, months.

2.6. Ongoing trials and future directions

Several ongoing trials are testing various types of novel agents in patients with advanced or recurrent endometrial cancer, however only few trials specifically focus on the treatment of clear cell endometrial carcinoma patients. In order to provide a clear overview on emerging therapies, we performed a search from the clinicaltrials.gov database (www.clinicaltrials.gov), on August 2021 [27]. The key word: “clear

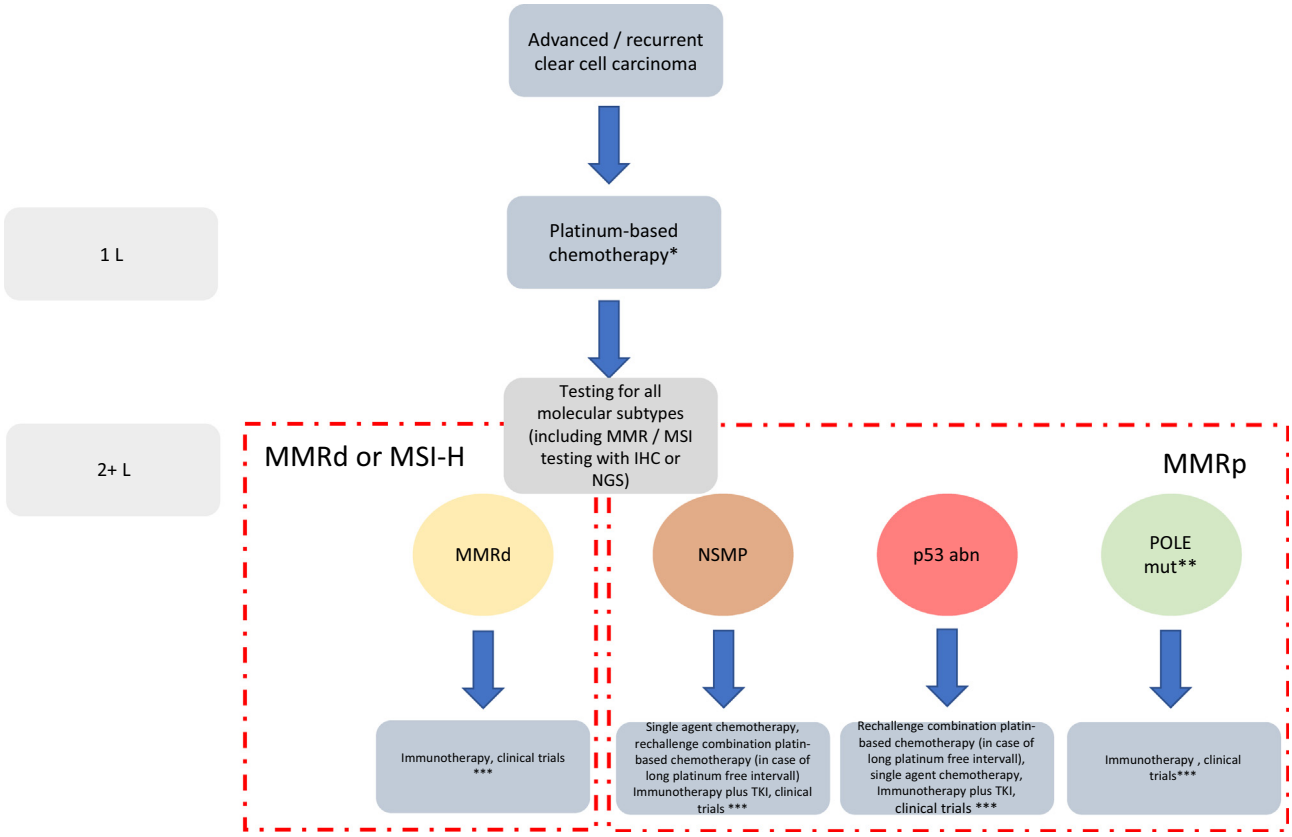

Fig. 3. Systematic treatment in advanced / recurrent endometrial cancer.
Abbreviations: IHC, immunohistochemistry; NGS, next generation sequencing; MMRd, mismatch repair–deficient; MMRp, mismatch repair–proficient; MSI-H, microsatellite instability–high

Table 2
Ongoing trials on clear cell endometrial carcinoma.

Agents	Phase	Mechanism of action	Participants	Primary endopoint	Estimated completion date
Target therapy					
Onapristone, Anastrozole	II	Synthetic and steroidal antiprogestogen with additional antiglucocorticoid activity, aromatese inhibitor	77 pts. with advanced or recurrent EC, including also CCEC	Objective response rate	December 2023
AZD6738, + Olaparib	II	ATR inhibitor and PARP inhibitor	40 pts. with Ovarian cancer and EC, including also CCEC	Objective response rate	March 2023
VSV-hIFNbeta-NIS, with/without Ruxolitinib	I	Oncolytic vesicular stomatitis virus-human interferon beta-sodium iodide symporter	77 pts. with advanced or recurrent EC, including also CCEC	Maximum tolerated dose of VSV-hIFNbeta-NIS	June 2021
Nintedanib	II	Triple kinase inhibitor blocking VEGFR, PDGFR and FGFR	120 pts.; 90 with ovarian clear cell carcinoma and up to 30 with CCEC	Progression-free survival	March 2021
Immunotherapy					
Atezolizumab + Bevacizumab + Rucaparib		Anti PD1, Anti-VEGF PARP ihibitor	30 pts. with advanced or recurrent EC, including also CCEC	Objective response rate	June 2026
Tislelizumab	I	Anti PD1	20 pts. with advanced or recurrent EC with MSI high or evidence of LS, including also CCEC	T-cell receptor (TCR) profiles, clonality, and diversity	December 2024
Pembrolizumab + Lenvatinib	III	Anti PD1 TKI	875 pts. with advanced or recurrent EC, including also CCEC	Progression-free and overall survivals	September 2024
Atezolizumab + platinum-based chemotherapy	III	Anti PD1	550 pts. with advanced or recurrent EC, including also CCEC	Progression-free and overall survivals	December 2023
Pembrolizumab (MK-3475) + platinum-based chemotherapy	III	Anti PD1	810 pts. with advanced or recurrent EC, including also CCEC	Progression-free survival	June 2023
Atezolizumab + Bevacizumab	II	Anti PD1, Anti-VEGF	20 pts. with advanced or recurrent EC, including also CCEC	Objective response rate	May 2023
Nivolumab + BMS-986205	II	Anti PD1, Anti-IDO	50 pts. with advanced or recurrent EC, including also CCEC	Objective response rate	September 2022
Nivolumab + Cabozantinib	II	Anti PD1, TKI	50 pts. with advanced or recurrent EC, including also CCEC	Progression-free survival	Januray 2022
Pembrolizumab + Doxorubicin	II	Anti PD1, Chemotherapy	51 pts. with advanced or recurrent EC, including also CCEC	Progression-free survival	June 2021
Nivolumab + Ipilimumab	II	Anti PD1, Anti-CTLA4	60 pts. with advanced or recurrent EC, including also CCEC	Objective response rate	December 2020

Abbreviations: EC, endometrial cancer; CCEC, Clear cell endometrial carcinoma; pts., patients; PD-1, Programmed cell death protein 1; TKI, Tyrosine Kinase Inhibitors; PARP, Poly (ADP-ribose) polymerase; MSI, microsatellite instability; LS, Lynch syndrome.
These studies are extracted from Clinical Trial (www.clinicaltrial.gov) on August 30, 2021 [27,28].

cell endometrial carcinoma" was used to identify the available studies. Details of these studies are reported in Table 2. Several promising trials including both endometrioid and non-endometrioid advanced or recurrent endometrial cancer are presently ongoing [26,27]. In particular, several ongoing phase III trials are testing the role of different immunotherapy agents (e.g, pembrolizumab, nivolumab with or without ipilimumab, atezolizumab, and dostarlimab). As reported before, preliminary analyses of the KEYNOTE-755 and GARNET trials showed exciting results in the treatment of advanced / recurrent endometrial cancer. No data about the AtTEnd and NCI10104 trial are still available [27]. Testing patients for programmed death - 1 (PD-1) and PD-ligand 1 (PD-L1) would be important to identify patients who might benefit from immune checkpoint inhibitors [27]. Moreover, no specific data on clear cell endometrial carcinoma are still available. Similarly, no data on the role of various targeted therapies are mature in this setting. In few cases, ATr, PIK3CA, DDR, and HER2 would be potential targets in a selected group of patients. Interestingly, ATr inhibitors (alone or in combination with PARP inhibitors) are under investigation in patients characterized by *ARId1A* loss [17,28,29]. The ATARI trial is going to investigate whether ceralasertib (AZD6738), an *ATr* inhibitor, has anti-tumor activity as a single agent and in combination with the olaparib, in patients with *ARID1A* 'loss' and 'no loss' clear cell carcinomas and other relapsed gynecological cancers [29]. In the era of precision cancer medicine, further evidence is warranted in order to provide the best therapeutic options for patients affected by clear cell endometrial carcinoma.

3. Conclusions

In the present paper, we summarize the current evidences and further perspectives on the management of clear cell endometrial carcinoma. Clear cell endometrial cancer represents an uncommon disease entity, with distinct characteristics between endometrioid and other non-endometrioid uterine cancers. Centralization of clear cell endometrial carcinoma cases in a referral center, pathologic review, multidisciplinary management, and genomic/molecular analysis are of paramount importance. According to the molecular classification, *POLE* mutated, MMRd, NSMP and *p53* abnormal disease accounted for about 4%, 10%, 44%, and 42% of clear cell endometrial carcinoma, respectively. Theoretically, adjuvant therapy could be omitted in patients with uterine confined disease harboring *POLE* mutation, whereas adjuvant therapy is recommended in patients with NSMP and *p53* abnormal disease. Immunotherapy seems to be the more promising treatment option for patients with advanced or recurrent clear cell endometrial cancer characterized by MMRd. In other patients, platinum-based chemotherapy and the combination of pembrolizumab and lenvatinib would be the preferred treatment modalities, for first and second line, respectively. Ongoing clinical trials testing the anti-tumor activity of checkpoint inhibitors and targeted therapy will clarify the better strategies for advanced / recurrent clear cell endometrial cancer. Moreover, the wide adoption of molecular and genomic profiling will be useful in tailoring the most appropriate treatments modalities for every patient.

Author contribution

Conceptualization: GB, BJM; Methodology: All authors.; Project administration: BJM.; Supervision: BJM.; writing – original draft: All authors; writing – review & editing: All authors.

Declaration of Competing Interest

Giorgio Bogani: Novartis AG Pharma (C/A, H), Italian Ministry of Health (RG).

Nicole Concin: AstraZeneca (C/A, SH), Seattle Genetics (C/A, SH), MSD (SAB), Mersana (C/A, SH), eTheRNA immunotherapies NV (C/A, SH), Roche (travel expenses), Genmab (travel expenses), Amgen (travel expenses).

Isabelle Ray-Coquard: Honoraria from AstraZeneca, Clovis, GSK/Tesaro and PharmaMar; Consulting/advisory board fees from AstraZeneca, Roche, Clovis, GSK/Tesaro, Genmab, PharmaMar, MSD, Mersana, Deciphera, OncXea, Esai, BMS, Novartis and Pfizer; Research funding from MSD;Travel expenses from AstraZeneca, GSK and Roche.

Yakir Segev: AstraZeneca (CA), GSK (CA).

Pauline Wimberger: Amgen (SH, RF, SAB), AstraZeneca (SH, RF, H, SAB), Clovis (SH, RF, SAB), Eisai (SH, SAB), GSK (SH, SAB), Lilly (SH, SAB), MSD (SH, RF, SAB), Novartis (SH, RF, SAB), Pfizer (SH, RF, SAB), Roche (SH, RF, H, SAB), TEVA (SH, SAB).

Natalie YL Ngoi: AstraZeneca (SH), Janssen (SH).

Kazuhiro Takehara: AstraZeneca (SH), Chugai (SH, RF), Eisai (SH), MSD (SH), Mochida (SH), Takeda (SH).

Takayuki Enomoto: Takeda (SH), Astra Zeneca (SH), Eisai (SH), Chugai Pharma (SH, RF), MSD (SH), Mochida (SH).

Domenica Lorusso: AstraZeneca (H, CA), Clovis (H, CA, RF), GSK/Tesaro (H, CA), Roche (CA), Genmab (CA), PharmaMar (CA, RF), MSD (CA, RF), Esai (CA), Merck Serono (CA), Novartis (CA) and PharmaMar (H); Consulting/advisory board fees from AstraZeneca, Roche, Clovis, GSK/Tesaro.

Diane Provencher: AstraZeneca (CA, SH, SAB), GSK (CA, SH, SAB).

Nadeem Abu-Rustum: NIH/NCI Cancer Center Support Grant P30 CA008748 (F).

Hannelore Denys: Roche (CA, SH, SAB), Pfizer (CA, SH, SAB), AstraZeneca (SH, SAB), Lily (SAB), GSK (SAB), Novartis (SH), Pharmamar (SH).

Bradley J Monk: AstraZeneca (SH, SAB), GSK (SH, SAB), Incyte (SAB), Merck (SH, SAB), Roche/Genentech (SH, SAB), Eisai (SAB), GOG-Foundation (E), US Oncology (E).

The other authors indicated no financial relationship.

Legend: consulting/advisory relationship (CA); speaker honoraria (SH); honoraria (H); research funding (RF); ownership interest (OI); intellectual propriety/patent holder (IP); scientific advisory board (SAB).

References

[1] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer statistics, CA Cancer J. Clin. 71 (2021) 7–33, https://doi.org/10.3322/caac.21654 Epub 2021 Jan 12. Erratum in: CA Cancer J Clin. 2021 ;71:359.

[2] G. Bogani, I. Ray-Coquard, N. Concin, N.Y.L. Ngoi, P. Morice, T. Enomoto, et al., Uterine serous carcinoma, Gynecol. Oncol. 162 (2021) 226–234, https://doi.org/10.1016/j.ygyno.2021.04.029 Epub 2021 Apr 30. PMID: 33934848.

[3] E.B. Jeans, W.G. Breen, T.C. Mullikin, B.A. Looker, A. Mariani, G.L. Keeney, et al., Adjuvant brachytherapy for FIGO stage I serous or clear cell endometrial cancer, Int. J. Gynecol. Cancer 31 (2021) 859–867, https://doi.org/10.1136/ijgc-2020-002217.

[4] Cancer Genome Atlas Research Network, C. Kandoth, N. Schultz, A.D. Cherniack, R. Akbani, Y. Liu, et al., Integrated genomic characterization of endometrial carcinoma, Nature 497 (7447) (2013 May 2) 67–73, https://doi.org/10.1038/nature12113 Erratum in: Nature. 2013 Aug 8;500(7461):242. PMID: 23636398; PMCID: PMC3704730.

[5] S.R. Kim, B.T. Cloutier, S. Leung, D. Cochrane, H. Britton, A. Pina, et al., Molecular subtypes of clear cell carcinoma of the endometrium: Opportunities for prognostic and predictive stratification, Gynecol. Oncol. 158 (2020 Jul) 3–11, https://doi.org/10.1016/j.ygyno.2020.04.043 Epub 2020 Apr 21. PMID: 32331700.

[6] G. Han, R.A. Soslow, S. Wethington, D.A. Levine, F. Bogomolniy, P.B. Clement, et al., Endometrial Carcinomas With Clear Cells: A Study of a Heterogeneous Group of Tumors Including Interobserver Variability, Mutation Analysis, and Immunohistochemistry With HNF-1β, Int. J. Gynecol. Pathol. 34 (4) (2015 Jul) 323–333, https://doi.org/10.1097/PGP.0000000000000162 PMID: 25851704.

[7] E. Spoor, P. Cross, Audit of Endometrial Cancer Pathology for a Regional Gynecological Oncology Multidisciplinary Meeting, Int. J. Gynecol. Pathol. 38 (6) (2019 Nov) 514–519, https://doi.org/10.1097/PGP.0000000000000547 PMID: 30252729.

[8] R. Zaino, S.G. Carinelli, L.H. Ellenson, et al., Epithelial tumours and precursors, in: R.J. Kurman, M.-L. Carcangiu, C.S. Herrington (Eds.), World Health Organization classification of tumours of female reproductive organs, Lyon, IARC Pres 2014, pp. 125–134.

[9] R. Murali, B. Davidson, O. Fadare, et al., High-grade endometrial carcinomas: morphologic and immunohistochemical features, diagnostic challenges and recommendations, Int. J. Gynecol. Pathol. 38 (2019) S40–S63.

[10] N.R. Abu-Rustum, C.M. Yashar, K. Bradley, S.M. Campos, J. Chino, H.S. Chon, et al., NCCN Guidelines® Insights: Uterine Neoplasms, Version 3.2021, J. Natl. Compr. Cancer Netw. 19 (8) (2021 Aug 1) 888–895, https://doi.org/10.6004/jnccn.2021.0038 PMID: 34416706.

[11] N. Concin, X. Matias-Guiu, I. Vergote, D. Cibula, M.R. Mirza, S. Marnitz, et al., ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma, Int. J. Gynecol. Cancer 31 (2021) 12–39, https://doi.org/10.1136/ijgc-2020-002230 Epub 2020 Dec 18. PMID: 33397713.

[12] A. Travaglino, A. Raffone, A. Santoro, D. Raimondo, G. Angelico, M. Valente, et al., Clear cell endometrial carcinomas with mismatch repair deficiency have a favorable prognosis: A systematic review and meta-analysis, Gynecol. Oncol. 162 (2021) 804–808, https://doi.org/10.1016/j.ygyno.2021.07.007 Epub 2021 Jul 12. PMID: 34266691.

[13] A. Santoro, G. Angelico, A. Travaglino, F. Inzani, D. Arciuolo, M. Valente, et al., New Pathological and Clinical Insights in Endometrial Cancer in View of the Updated ESGO/ESTRO/ESP Guidelines, Cancers (Basel) 13 (2021) 2623, https://doi.org/10.3390/cancers13112623 PMID: 34073635; PMCID: PMC8198052.

[14] M. Le Gallo, M.L. Rudd, M.E. Urick, N.F. Hansen, S. Zhang, NISC Comparative Sequencing Program, et al. Somatic mutation profiles of clear cell endometrial tumors revealed by whole exome and targeted gene sequencing, Cancer 123 (17) (2017 Sep 1) 3261–3268, https://doi.org/10.1002/cncr.30745 Epub 2017 May 9. PMID: 28485815; PMCID: PMC5587124.

[15] C.L. Creutzberg, A. Leon-Castillo, S.M. de Boer, M.E. Powell, L.R. Mileshkin, H.J. Mackay, et al., Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on adjuvant therapy, Ann. Oncol. 30 (2019) 899–900.

[16] E. Stelloo, T. Bosse, R.A. Nout, et al., Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative, Mod. Pathol. 28 (2015) 836–844.

[17] G.F. Zannoni, A. Santoro, G. Angelico, S. Spadola, D. Arciuolo, M. Valente, et al., Clear cell carcinoma of the endometrium: an immunohistochemical and molecular analysis of 45 cases, Hum. Pathol. 92 (2019 Oct) 10–17, https://doi.org/10.1016/j.humpath.2019.06.005 (Epub 2019 Jun 30).

[18] G. Bogani, A. Papadia, A. Buda, J. Casarin, V. Di Donato, M.L. Gasparri, et al., Sentinel node mapping vs. sentinel node mapping plus back-up lymphadenectomy in high-risk endometrial cancer patients: Results from a multi-institutional study, Gynecol. Oncol. 161 (2021) 122–129, https://doi.org/10.1016/j.ygyno.2021.01.008 Epub 2021 Jan 20 PMID: 33485641.

[19] B.A. Schlappe, A.L. Weaver, M.E. McGree, J. Ducie, A.G. Zahl Eriksson, S.C. Dowdy, et al., Multicenter study comparing oncologic outcomes after lymph node assessment via a sentinel lymph node algorithm versus comprehensive pelvic and paraaortic lymphadenectomy in patients with serous and clear cell endometrial carcinoma, Gynecol. Oncol. 156 (1) (2020 Jan) 62–69, https://doi.org/10.1016/j.ygyno.2019.11.002 Epub 2019 Nov 24. PMID: 31776037; PMCID: PMC6980738.

[20] U.S. NIH, National Library of Medicine, ClinicalTrial.gov , Available at: https://clinicaltrials.gov/ct2/results?cond=Endometrial+Cancer&term=sentinel+node&cntry=&state=&city=&dist= last view: 9/11/2021.

[21] M. Köbel, B. Tessier-Cloutier, J. Leo, L.N. Hoang, C.B. Gilks, R.A. Soslow, et al., Frequent Mismatch Repair Protein Deficiency in Mixed Endometrioid and Clear Cell Carcinoma of the Endometrium, Int. J. Gynecol. Pathol. 36 (2017) 555–561, https://doi.org/10.1097/PGP.0000000000000369.

[22] P. Zola, G. Ciccone, E. Piovano, L. Fuso, E. Peirano, D. Di Cuonzo, et al., Intensive versus minimalist follow-up in patients treated for endometrial cancer: A multicentric randomized controlled trial (The TOTEM study—NCT00916708), J. Clin. Oncol. 39 (15_suppl) (2021) 5506.

[23] A. Papadia, F. Bellati, A. Ditto, G. Bogani, M.L. Gasparri, V. Di Donato, et al., Surgical Treatment of Recurrent Endometrial Cancer: Time for a Paradigm Shift, Ann. Surg. Oncol. 22 (13) (2015 Dec) 4204–4210, https://doi.org/10.1245/s10434-015-4504-5 Epub 2015 Mar 17. PMID: 25777095.

[24] D.S. Miller, V.L. Filiaci, R.S. Mannel, D.E. Cohn, T. Matsumoto, K.S. Tewari, et al., Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209), J. Clin. Oncol. 38 (33) (2020 Nov 20) 3841–3850.

[25] V. Makker, M.H. Taylor, C. Aghajanian, A. Oaknin, J. Mier, A.L. Cohn, et al., Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer, J. Clin. Oncol. 38 (26) (2020) 2981–2992.

[26] A. Oaknin, S.L. Ellard, C. Leath III, V. Moreno, R. Kristeleit, W. Guo, et al., Preliminary safety, efficacy, and PK/PD characterization from GARNET, a phase I clinical trial of the anti–PD-1 monoclonal antibody, TSR-042, in patients with recurrent or advanced MSI-H endometrial cancer, Ann. Oncol. 29 (2018) 334.

[27] U.S. NIH, National Library of Medicine, ClinicalTrial.gov , Available at https://clinicaltrials.gov/ct2/results?cond=Clear+Cell+Endometrial+Carcinoma&term=immunotherapy&cntry=&state=&city=&dist= last view: 9/11/2021.
[28] U.S. NIH, National Library of Medicine, ClinicalTrial.gov , Available at https://clinicaltrials.gov/ct2/results?cond=Clear+Cell+Endometrial+Carcinoma&term=target+therapy&cntry=&state=&city=&dist= last view: 9/11/2021.
[29] S. Banerjee, J. Stewart, N. Porta, C. Toms, A. Leary, S. Lheureux, et al., ATARI trial: ATR inhibitor in combination with olaparib in gynecological cancers with ARID1A loss or no loss (ENGOT/GYN1/NCRI), Int. J. Gynecol. Cancer (2021 Sep 13) https://doi.org/10.1136/ijgc-2021-002973 ijgc-2021-002973. Epub ahead of print. PMID: 34518240.