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Ovarian cancer relapse: From the latest scientific evidence to the best practice

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ABSTRACT

Ovarian cancer (OC) is the fifth most common cause of cancer death in women worldwide. Despite treatment options have continued to improve in recent years, the recurrence rate is still high; in fact around 80% of patients relapses within 18 months.

Recently, the scientific landscape is agree in asserting that the ovarian cancer is not a single disease but the outcome of patients depends from the molecular and biological characterization of tumor tissue. In this scenario, molecular targeted therapy given alone or in combination with chemotherapy is showing significant results.

We review the different options for the treatment of ovarian cancer recurrence, including the role of surgery, in order to try outlining a possible treatment algorithm evaluating the recent scientific literature and the most important trials

1. Introduction

Ovarian cancer (OC) is the fifth most common cause of cancer death in women worldwide. Despite treatment options have continued to improve in recent years, recurrence rate is still high; in fact, around 80% of patients relapses within 18 months (Luvero et al., 2014).

Although important progresses have been made over the last decades, the length of the platinum free interval (PFI) still plays a key role in the management of these patients and it influences their prognosis in terms of overall survival (OS) and progression free survival (PFS) (Markman et al., 1991; Kaye, 2008; Gore et al., 1990; Pujade-Lauraine et al., 2019; Colombo, 2013)

Recently, the scientific landscape is agreeing in asserting that ovarian cancer is not a single disease but patients' outcome depends on the molecular and biological characterization of tumor tissue (Romero and Bast, 2012). In fact, the different subtypes of OC can be divided into five main histological subtypes: high grade serous, low grade serous, clear cell, endometrioid and mucinous. These subtypes represent distinct disease's entities, both at clinical and molecular level. Furthermore, they have an influence on therapy choice, because they revealed significant genetic characteristics that can respond in different ways to the different therapies. For example, different subtypes display different levels of chemosensitivity: clear cell, mucinous and low grade OC are highly platinum resistant, while high grade OC is often platinum sensitive in the first-line setting. In this scenario, molecular targeted therapy given alone or in combination with chemotherapy is showing significant results, too. We review the different options for the treatment of ovarian cancer recurrence in order to try outlining a possible treatment algorithm according to recent scientific literature and the most important trials.

2. Role of surgery

The role of secondary cytoreductive surgery (SCS) in the management of relapsed OC is not well established. To date, only few prospective studies have focused on the effect of surgery in relapsed ovarian cancer. Isolated recurrence is rare, but it may be a condition in which there is a possible survival benefit with acceptable surgical morbidity.

However, the extent to which this procedure adds to PFS or overall survival (OS) is unclear. It is clear that if a complete resection is possible, the patient who most can benefit is the one with platinum

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resistant disease, as showed by Petrillo et al (Petrillo et al., 2014), because a platinum-resistant tumor has very low probability of responding to systemic chemotherapy (Suh et al., 2016). Lymph nodes (39%) and peritoneum (33%) were reported to be the most frequent sites of platinum-resistant relapse. If isolated relapse was located in lymph nodes or peritoneum, the survival advantage of SCS seems to be more evident (Musella et al., 2015).

The German AGO (Arbeitsgemeinschaft Gynaekologische Onkologie) group defined a possible group of patients who can benefit of surgery, in presence of at least two of the three following criteria: complete resection at first surgery, good performance status and absence of ascites (Harter et al., 2009). More recently, a group of Italian investigators reported that surgery could represent a useful adjunct to chemotherapy in the management of platinum-resistant ROC patients. Patients treated with (n = 18) or without (n = 18) cytoreductive surgery were compared. OS was significantly longer in the surgery group than in the control group (median OS, 67 months, 95% CI 38.7–95.2 months, versus 24 months, 95% CI 8.3–39.6 months; p = 0.035) (Musella et al., 2015).

In 2000, Eisenkop et al (Eisenkop and Spirtos, 2001) showed that complete cytoreduction rate was 82.1%. Multivariate analysis showed that survival was independently influenced by: DFI, the completeness of cytoreduction, the use of salvage chemotherapy before SCS, and the largest size of recurrent tumors.

Another prospective study was conducted by Scarabelli et al. in 2001 (Scarabelli et al., 2001). They reported similar results. Of three independent prognosis-associated factors, including DFI, chemotherapy before SCS, and residual tumor after SCS, residual tumor was the most strongly predictive factor of survival (hazard ratio [HR], 2.65; 95% CI 1.43–4.92).

Since the Scarabelli study, a large number of small retrospective studies have supported the clinical benefit of SCS in platinum sensitive (Tay et al., 2002; Wang et al., 2013; Ayhan et al., 2006; Park et al., 2010; Goto et al., 2011; Boran et al., 2012; Schorge et al., 2011).

In 2009, Bristow et al. published results of a meta-analysis to determine the relative effect of multiple prognostic factors on overall post recurrence survival time in patients with recurrence undergoing to SCS. The result are listed in Table 1 According to the regression model estimate, the median cohort survival time ranged from 18.0 months to 48.0 months as the proportion of patients undergoing complete SCS increased from 0% to 100% (3.0 month increase in median cohort survival time, 10% increase in the proportion of complete SCS). The absence of residual disease after SCS was the most important prognostic factor in these patients (Bristow et al., 2009).

However, most retrospective series had a small number of enrolled patients and presented a bias in the selection of patients.

Despite the longer OS (median OS, 49.9 months versus 29.7 months; adjusted HR, 0.68; p = 0.004) observed in patients who underwent SCS if compared with chemotherapy alone, Lee et al. reported that the OS benefit simply reflects the selection of patients with good prognosis (Lee et al., 2015).

With the aim to exceed the bias there are three ongoing phase III randomized controlled trials (DESKTOP III, GOG 213, and SOCceR).

The DESKTOP III trial is a randomized multicenter study with the aim to compare the efficacy of additional tumor debulking surgery vs chemotherapy alone in recurrent platinum-sensitive ovarian cancer in terms of OS, PFS and QoL. The trial included patients with a positive AGO-score in which the complete resection of the tumor by median laparotomy seemed possible. There are no results about OS in these patients, but preliminary results show a median PFS of 19.6 months, compared with 14 months in patients who receive tumor debulking surgery vs only second-line chemotherapy (HR 0.66; CI 0.52–0.83, p < 0.001) respectively. At the same time, median time to start of first subsequent therapy was 21 vs 13.9 months in favor of the surgery arm (HR 0.61; 95% CI 0.48–0.77; p < 0.001) (NCT01166737). The second ongoing trial, GOG 213 (NCT00565851), is a phase III randomized controlled trial of secondary surgical cytoreduction (SSC) followed by platinum-based combination chemotherapy, with or without bevacizumab in platinum-sensitive, recurrent ovarian cancer. Data are listed in Table 1. SSC can be safely performed in patients with platinum sensitive disease, but did not improve OS in this population. Additional analyses such as impact of PFI, SSC outcome, disease burden and chemotherapy regimen on OS by SSC allocation are underway we are awaiting the final data (Abstract 5501 ASCO 2018 Coleman et al., 2018)

The last randomized controlled trial is SOCceR; it is conducted by the Netherlands study group (NTR3337) (van de Laar et al., 2014). The primary objective of the SOCceR study is to determine whether SCS followed by platinum-based chemotherapy increases progression-free survival in patients with platinum sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer and data are not mature yet.

Many issues remain unsolved. First, is the decision to use SCS in addition to chemotherapy only depending on survival benefit?

Absolutely not, but it depends also from the quality of life (QoL). Recently, Plotti et al published the first case-control prospective study to compare, through validated assessment tools, QoL of platinum-sensitive ROC patients treated with SCS followed by chemotherapy, versus chemotherapy alone. Data showed that both surgery followed by chemotherapy and chemotherapy alone seem to have a negligible impact on quality of life (QOL). Secondary cytoreduction surgery plus chemotherapy seems to be an effective and tolerable therapeutic option in platinum-sensitive recurrences (Plotti et al., 2015).

Second, could further surgery beyond secondary cytoreduction in ROC be beneficial?

In literature, there are only 11 retrospective studies on surgery beyond SCS with conflicting results (Leitao et al., 2004; Karam et al., 2007; Gultekin et al., 2008; Shih et al., 2010a; Fotopoulou et al., 2011; Hizli et al., 2012; Fotopoulou et al., 2013a, b; Tang et al., 2013; Fanfani et al., 2015; Shih et al., 2010b). Completed data are reported in Table 2.

Some studies showed that the residual tumor after surgery beyond secondary cytoreduction had a prognostic relevance in terms of OS. Moreover, residual tumor in the preceding (secondary) cytoreductive surgery also showed prognostic significance in concordance with the previous studies. Regarding the upper abdominal tumor involvement, it might not be an absolute contraindication to TCS (tertiary cytoreductive surgery). More large prospective studies are needed to clarify the real beneficial of tertiary (TCS) and quaternary cytoreductive surgery (QCS) in future.

The last noteworthy issue in this review is the role of SCS when recurrence including biochemical relapse is detected earlier. The Medical Research Council (MRC)/EORTC randomized trial

Table 1
Studies evaluating the role of secondary cytoreductive surgery.

Study	N. patients	N. previous lines	PFI	OS(months)	PF
MUSELLA(Musella et al., 2015)	36	1	< 6	67	RD
BRISTOW(Bristow et al., 2009)	2019	1	> 6	30.3	RD
DESKTOP III	407	1	> 6	NA	RD
GOG213 (Abstract 5501 ASCO 2018 Coleman et al., 2018)	485	1	> 6	53,6	NA
SOCceR (van de Laar et al., 2014)	230	1	> 6	NA	NA

Table 2
Main trials beyond secondary cytoreductive surgery.

Study	N. patients	N. previous lines	PFI	OS(months)	DSS	PF
M.M. Leitao Jr. (Leitao et al., 2004)	77	2	NA	NA	33.4 months (95%CI, 20.4–46.4)	TFI RD
A.K. Karam, (Karam et al., 2007)	47	2	NA	Statistically longer in patients with microscopic versus macroscopic residual disease(24 versus 16 months, p = 0.03).	NA	RD
M. Gultekin,M. (Gultekin et al., 2008)	20	≥ 2	NA	NA	NA	NA
K.K. Shih, (Shih et al., 2010a)	77	2	NA	NA	47.7 (25.5–69.9)	RD Number of recurrence sites
C. Fotopoulou, (Fotopoulou et al., 2011)	135	2	NA	NA	NA	RD Serous papillary histology Interval to primary diagnosis ≥ 3 years
D. Hizli, (Hizli et al., 2012)	23	2	NA	NA	NA	NA
C. Fotopoulou (Fotopoulou et al., 2013a)	406	2	NA	NA	NA	RD Decreasing interval to second relapse Ascites Upper abdominal tumor involvement Nonplatinum third line chemotherapy
C. Fotopoulou (Fotopoulou et al., 2013b)	49	3	NA	NA	NA	Systemic chemotherapy after quaternary citoreduction
J. Tang (Tang et al., 2013)	83	2	NA	Limited survival benefit from tertiary cytoreductive surgery was observed in patients with platinum-sensitive secondary relapsed ovarian cancer	NA	Microscopic residual disease
F. Fanfani (Fanfani et al., 2015)	53	≥2	NA	PFS (16 vs. 21 months; p = 0.032) and OS (152 vs. 116 months; p = 0.015) in patients submitted to cytoreduction with respect to those treated with chemotherapy were observed	NA	TFI > 12 months
K.K. Shih (Shih et al., 2010b)	15	3	NA	NA	NA	RD Number of recurrence sites

PF: prognostic factor; TFI Treatment free interval; OS: overall survival; NA Not Applicable; RD: residual disease; PF Prognostic factor.

demonstrated that early chemotherapy in asymptomatic patients based only on increased CA-125 does not prolong survival (Rustin et al., 2010). However, this trial was not focused on the role of SCS and the authors underline the fact that randomized trials showing a benefit from surgery for relapsed disease are essential before CA125 follow-up is routinely recommended to trigger radiological detection of relapse amenable to surgical treatment. On the other hand, Tanner et al. showed that detection of asymptomatic recurrences, by routine surveillance testing, was associated with a high likelihood of optimal SCS in operative candidates, and extended OS in platinum-sensitive ROC. Fleming et al. reported that each week of delay after the first CA-125 elevation correlated with a 3% increased chance of suboptimal resection at SCS (Fleming et al., 2011), highlighting the important role of SCS as salvage therapy.

In conclusion, currently, the strongest predictor of OS in patients with ROC who undergo SCS is maximal cytoreduction with minimal residual disease, at best, no residual disease. Complete resection should become the ultimate goal of SCS. However, there is no consensus on how much survival gain can justify operative morbidity and mortality. In order to exquisitely balance between the two, maximal survival gain and minimal operative morbidity and mortality, needs to refer to highly specialized centers and appears crucial to identify the criteria for selecting optimal candidates which can beneficiate of SCS, TCS or QCS.

PF: prognostic factor; PFI Platinum free interval; OS: overall survival; NA Not Applicable; RD: residual disease; PF Prognostic factor

3. Role of chemotherapy

3.1. Platinum sensitive recurrence

The choice of chemotherapy after recurrence is based on the interval between the completion of last platinum therapy and the relapse, called platinum free interval (PFI) (Luvero et al., 2014). This is the most important predictive factor for response to platinum rechallenge and the most important prognostic factor for progression free survival (PFS) and overall survival (OS) (Luvero et al., 2014; Gore et al., 1990; Pujade-Lauraine et al., 2019).

Probably, after the fifth Consensus conference in Japan (Wilson et al., 2017), it would be more correct referring to treatment free interval (TFI) instead PFI in order to choose the best therapy for patients: in fact, we know the importance of clinical judgement on the decision whether to continue a patient's therapy or change it. In the same way, as we know, many patients, looking on web, decide to make a diagnostic exam such as PET/CT scan or serum markers without contact their oncologist or gynecologist. This fact could generate a mistake in the calculation of PFI, resulting in a mistake in the choice of treatment.

Regarding treatment, platinum based chemotherapy remains the principal choice used to treat cancer that relapses after 6 months after primary treatment (Luvero et al., 2014).

As Parmar showed in 2003 in ICON 4/OVAR 2.2 randomized phase III trial, paclitaxel added to platinum therapy, in particular carboplatin, extended the PFS (from 10 to 13 months) with a smaller benefit in OS of patients with recurrent ovarian cancer (57% with paclitaxel vs 50% without). Because of the high neuro-toxicity and hair loss rate with paclitaxel, the CALYPSO trial was designed and showed a better safety profile with the association of carboplatin and pegylated liposomal doxorubicin (PLD) than carboplatin and paclitaxel, with a better PFS, but not different OS (Pujade-Lauraine et al., 2010).

Raja et al also investigated the choice between platinum in monotherapy and in combination in a meta-analysis in which benefit both in PFS and OS for platinum doublet was showed. However, quality of life needs to be further investigated in future trials (Raja et al., 2013).

In 2009, trabectedin was approved in this setting of patients in combination with PLD. A large multicenter randomized trial, the OVA 301, confirmed an improved PFS and 41% reduction in the risk of death with trabectedin + PLD if compared with PLD alone (7.3 vs 5.8 months in PFS and 27.7 vs 18.7 months in OS, respectively) in patients with partially platinum-sensitive disease (Monk et al., 2010). Interestingly, it was noted that patients treated with trabectedin and PLD, which were re-treated with platinum later, showed a better OS by a median 8.9 months compared with PLD alone. This clinical evidence may support the hypothesis that artificially prolonging PFI by introducing a non-platinum based chemo (NPBC) might improve the sensitivity to following platinum.

Based on this important data ESMO guidelines recommend the combination with trabectedin and PLD in patients with relapsed partially platinum sensitive (6–12 months) ovarian cancer (Monk et al., 2010).

MITO 8 (Pignata et al., 2017), a phase III multicenter study testing the effect on survival of prolonging platinum-free interval (PFI) in patients with ovarian cancer (OC) recurring, between 6 and 12 months, after previous platinum-based chemotherapy, randomized to receive experimental NPBC (pegylated liposomal doxorubicin or topotecan or gemcitabine, standard dose and timing) followed at progression by PBC (carboplatin/paclitaxel or carboplatin/gemcitabine if residual neurotoxicity, standard dose and timing) or the reverse standard treatment sequence. The study was closed prematurely due to slow recruitment and the final analysis was anticipated. Neverthless, with 215 patients enrolled (108 in the standard arm, 107 in the experimental arm) the data showed that prolonging PFI by introducing a NPBC did not improve efficacy outcomes in patients with partially platinum sensitive ROC (median OS median, 21.8 v 24.5 months; hazard ratio, 1.38; 95% CI, 0.99–1.94; P = 0.06)

Data showed that prolonging PFI by introducing a NPBC does not improve efficacy outcomes in patients with partially platinum sensitive recurrent ovarian cancer (median OS 21.8 months in experimental arm vs 24.5 months in standard arm, p = 0.06; median PFS was 12.8 months in experimental arm vs 16.4 months in standard arm, p = 0.025) (Pignata et al., 2017)

We are waiting for the results from INOVATYON, that compared the non-platinum trabectedin + PLD combination and a platinum + PLD combination (NCT01379989).

Regarding the role of targeted therapy, two classes of drugs have been explored in this setting of patients: antiangiogenics (anti VEGF, anti VEGF-Receptor) and poly-ADP ribose polymerase (PARP) inhibitors.

3.1.1. Antiangiogenics

VEGF plays an important role in neo-angiogenesis and bevacizumab is the most important monoclonal antibody under study. In particular, it is directed against vascular endotelial growth factor (VEGF) A.

In 2012, results from a big trial, OCEANS (See Table 3), that compared carboplatin and gemcitabine with or without bevacizumab, in

Table 3
Randomized, Phase III, controlled trials of antiangiogenics in platinum sensitive ovarian cancer recurrences.

Study	Regimen	PFS	OS
OCEANS (Aghajanian et al., 2015)	CG + placebo vs CG + bev	8.4 12.4	33.6 32.9
ICON 6 (Ledermann et al., 2016)	Arm A: PBC + placebo + placebo in M Arm B: PBC + cediranib + placebo in M Arm C: PBC + cediranib + cediranib in M	8.7 9.9 11.0	19.9 26,6 27,3
MITO 16 b	CT + BEV CT	11.8 8.8	26.7 27.1

PFS: progression free survival; OS: overall survival; CP: Carboplatin + Paclitaxel; Bev: Bevacizumab; CG: Carboplatin + Gemcitabine; CT: Chemotherapy; P: Paclitaxel; PLD: pegylated liposomal doxorubicin; Top: Topotecan; M: maintenance.

patient with platinum sensitive recurrence, showed an improvement in PFS (12,4 months vs 8,4 months) and in RR (response rate) (78,5% vs 57,4%) with the use of bevacizumab. Treatment was well tolerated and hypertension and proteinuria were the most common side effects (Aghajanian et al., 2015).

The other remarkable targeted agents of which the results of phase III randomized trials (ICON 6) were published in 2016 were cediranib, an oral antiangiogenic vascular endothelial growth factor receptor (VEGFR) 1–3 inhibitor. Data published by Ledermann et al (Ledermann et al., 2016) are showed in Table 3

Diarrhea, neutropenia, hypertension, and voice changes were significantly more common during chemotherapy with cediranib, while diarrhea, hypothyroidism and voice changes were more common during maintenance.

Cediranib significantly increased PFS. The interim survival analysis (85%) showed an improvement in median OS of 7.4 months and an incremental benefit with increased cediranib use. This study showed the potential role of cediranib in platinum-sensitive recurrent ovarian cancer. Further explorations of cediranib in this setting are needed and we are waiting for the final data.

Recently, data from MITO16b trial were presented during ASCO 2018 and ESMO 2018.

The MITO 16b trial is a multicenter phase III randomized study with second line chemotherapy ± bevacizumab in patients with platinum sensitive ovarian cancer recurrence after a bevacizumab/chemotherapy first line. 405 patients were included according to inclusion criteria. PFS was 11.8 vs 8.8 in patients that received respectively chemotherapy + bevacizumab and chemotherapy alone (HR 0.51; 95% CI 0.41–0.64; $p < 0.001$). The median OS was 27.1 months in patients who did not receive Bevacizumab and 26.7 in patients who received Bevacizumab. Unfortunately, these results were not statistically significant.

3.1.2. PARP inhibitors

Inhibitors of poly (ADP-ribose) polymerase (PARP) have emerged as one of the most active new therapies for the treatment of ovarian cancer, directed to cancer's cells with defective DNA-damage repair. In 2014, PARP inhibitors received regulatory approval for the treatment of ovarian cancer by both United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) (Evans and Matulonis, 2017).

The greatest efficacy for the use of PARP inhibitors in ovarian cancers has been observed for patients with cancers harboring BRCAm (either germline BRCA mutations (gBRCAm) or somatic/tumor BRCA mutations (tBRCAm)), extending the benefit of PARP inhibitors to all in high-grade serous OC (HGSCs) in this clinical setting (Alsop et al., 2012).The PARPi trials in recurrent ovarian cancer are listed in Table 4.

The estimated prevalence of a BRCA1/2 mutations in patients with newly diagnosed high-grade serous ovarian cancer is 20–25% and might be higher in patients with platinum-sensitive, relapsed ovarian cancer (Alsop et al., 2012; Cancer Genome Atlas Research Network, 2011; Zhang et al., 2011; Dann et al., 2012).

These mutations result in deficiency of homologous recombination repair (HRD) of DNA damage.

PARP inhibitors are active also in BRCA wild type cancers (BRCAwt), particularly in those women with a 'platinum-sensitive' relapse (phenotype BRCAness) (Dann et al., 2012). This fact suggests that PARP inhibitors may have a wider role, in particular olaparib, the most extensively tested PARP inhibitor.

Olaparib is currently approved in the European Union and other countries as maintenance treatment for patients with platinum-sensitive, relapsed ovarian cancer and a germline or somatic BRCA1/2 mutation, and in the USA as monotherapy for advanced ovarian cancer patients with a germline BRCA1/2 mutation (European Medicines Agency, 2014; FDA Lynparza, 2019).

In 2012 and 2014, two trials were performed to identify a possible role for olaparib as a single agent: The study 19 is a randomized, phase 2 trial, published by Ledermann et al., 2016 In this study it was evaluated the maintenance treatment with olaparib in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens and had a partial or complete response to their most recent platinum-based regimen. Patients were randomly assigned to receive olaparib, at a dose of 400 mg twice daily, or placebo and were treated until disease progression.

Olaparib reduced the risk of progression by 65% (HR 0.35; 95% CI 0.25–0.49; $p < 0.001$), increasing the median time to progression on maintenance therapy from 4.8 to 8.4 months (Gelmon et al., 2011).

In a more recent analysis, it was found that 51% of patients in the trial had a BRCA mutation. Olaparib showed the greatest effect in this subgroup, reducing the risk of progression by 82% (HR 0.18; 95% CI 0.11–0.31; $p < 0.00001$), with a median PFS of 11.2 versus 4.3 months respectively.

A benefit was also seen in the BRCA wild type group, but the difference was less marked (HR 0.54; 95% CI 0.33–0.84; $p = 0.007$). An advantage in OS for patients randomized to olaparib maintenance monotherapy vs placebo in the total study population (HR 0.73, 95% CI 0.55–0.95; nominal $P = 0.02138$; Fig. 2a) did not meet the threshold defined for statistical significance ($P < 0.0095$). At the final data cut off, this resulted in an adjusted OS HR of 0.68 (95% CI 0.49–0.95; BRCAm) although Study 19 was not designed or powered to show a statistically significant difference in OS, this OS advantage with olaparib is consistent with previously published analyses. (Friedlander et al., 2018)

A phase 3 study (SOLO-2), olaparib maintenance treatment (given as a tablet formulation) in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation led to a significant improvement in progression-free survival compared with placebo. This study was designed similarly to Study 19, except eligibility is restricted to ovarian cancers with a gmBRCA or tBRCAm (Ledermann et al., 2012)

SOLO2 data support treatment's benefit observed in Study 19 for

Table 4
PARPi trials in recurrent ovarian cancer.

Agent	Trial	Line of treatment
Olaparib	SOLO-2 (NCT01874353): Phase III maintenance (olaparib vs placebo)	≥2 prior lines platinum based CT
	SOLO-3 (NCT02282020): Phase III olaparib vs physician choice CT (standard of care non-platinum based)	≥2 prior lines of platinum based CT
Rucaparib	ARIEL 2 (part 2) (NCT01891344): Single arm study	≥2 prior lines of CT
	ARIEL 3 (NCT01968213): Phase III maintenance (rucaparib vs placebo)	≥2 prior lines of platinum based CT
	ARIEL 4 (NCT02855944): Phase III rucaparib vs chemotherapy	Received ≥2 lines prior CT
Niraparib	QUADRA study (NCT02354586): Single arm phase II study	≥ 3/4 prior lines of CT
	AVANOVA study (NCT02354131): Phase I/II niraparib ± bevacizumab	No limits for previous lines of CT
Talazoparib	Phase I/II study (NCT01989546)	after standard CT
	Phase II study (NCT02326844)	Progression following a PARPi

CT : chemotherapy.
Vs: versus.

patients with BRCA1/2 mutation, using a two-tablet twice-daily dosing schedule of olaparib. Patients with germline or somatic BRCA1/2 mutations were eligible for the SOLO2 trial. In particular, the median progression-free survival was significantly longer with olaparib (19·1 months [95% CI 16·3–25·7]) than with placebo (5,5 months; hazard ratio [HR] 0·30 [95% CI 0·22–0·41], p < 0·0001). The most common adverse events of grade 3 or worse severity were anaemia (19% patients in the olaparib group vs 2% of patients in the placebo group), fatigue or asthenia (4% vs 2%), and neutropenia (5% vs 4%).

The study also showed a significant improvement in time to first subsequent therapy, time to second progression, and time to second subsequent therapy in favor of olaparib (Pujade-Lauraine et al., 2017).

In terms of quality of life, there was no significant detrimental effect of olaparib versus placebo, and the quality adjusted progression free survival (QAPFS) is significantly longer with the use of olaparib vs placebo. In addition, the time without symptoms of disease or toxicity (TWIST) is longer in Olaparib group than in placebo group (13,5 vs 7,1 months respectively)

Two PARP inhibitor trials with niraparib or rucaparib include patients without BRCA mutations (Mirza et al., 2016).

Niraparib was approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy in BRCAmut and BRCAwt both.

In the randomized, placebo-controlled, phase III trial performed by the European Network for Gynecological Oncological Trial (ENGOT) groups, a total of 553 patients (203 with gmBRCA and 350 without gmBRCA) were randomly assigned to receive niraparib 300 mg or placebo.

Median PFS of niraparib and placebo groups was 21.0 vs. 5.5 months in the patients with gmBRCA (HR = 0.27; 95% CI = 0.17–0.41; p < 0.001) as compared with 9.3 vs. 3.9 months in the patients without gmBRCA (HR = 0.45; 95% CI = 0.34–0.61; p < 0.001) and 12.9 vs. 3.8 months in the patients without gmBRCA but with HRD (HR = 0.38; 95% CI = 0.24–0.59; p < 0.001).

The ENGOT-OV16/NOVA trial demonstrated that PFS was significantly longer in patients receiving niraparib than in those receiving placebo, despite more than 10% of patients had grade ≥3 adverse events following treatment with niraparib (33.8% had thrombocytopenia, 25.3% had anemia, and 19.6% had neutropenia) (Pujade-Lauraine et al., 2017).

Data from QOL reported at ESMO 2017 showed that no significant difference in mean PRO (patient reported outcomes) scores was observed between niraparib and placebo arms in either cohort. Adjusted HUI scores (health utility index) were similar in both arms at baseline. Moreover, average adjusted HUI pre-progression scores trended higher in the niraparib arm (0.812 vs 0.803 in gBRCAmut cohort; 0.845 vs 0.828 in non-gBRCAmut cohort) suggesting that treatment with niraparib improves patient QoL in certain aspects; in particular there was a trend toward lower pain levels in niraparib-treated patients compared to those receiving placebo. While nausea increased initially, it returned to baseline levels over time (abstract 930 ESMO 2017).

Rucaparib was studied in ARIEL 2 study which enrolled patients with platinum – sensitive recurrent EOC with BRCA mutation. This study tested a new HRD assay and algorithm to predict rucaparib sensitivity by assessing tumor BRCA status and LOH. Patients received 600 mg of Rucaparib twice a day and were divided in three HRD subgroups: BRCAmut, BRCAwt/LOHhigh, BRCAwt/LOHlow. The response rate was 69%, 39% and 11% respectively; and occurred either in gBRCAmut or sBRCAmut (Swisher et al., 2017).

Recently, data derived from the large phase 3 trial (ARIEL 3) have been presented, regarding the use of rucaparib vs placebo in patients with platinum sensitive disease.

Data showed an improvement in terms of PFS in the BRCAmut group vs placebo group (16.6 vs 5,4 months respectively), and an improvement of 8 months and 5 months in the groups with HRD and wild type (ITT) using Rucaparib (13,6 vs 5,4 months in HRD, 10,8 and 5,4 months in ITT group).

This improvement in spite of a liver toxicity in 33% of cases with a 10% more than G3 toxicity.

The combination between a PARP inhibitor with anti-angiogenic drug (olaprarib and cediranib vs olaparib alone) showed interesting data with a better PFS in the combination arm compared to the single arm (17.7 months vs 9 months respectively). G3, G4 fatigue, diarrhea and hypertension were more common in the combination therapy (Liu et al., 2014). The side-effect profile suggests that it could be useful to include assessments of quality of life and patient-reported outcomes to compare the effects of continuing oral regimen and intermittent chemotherapy.

3.2. Platinum resistant recurrence

In platinum-resistant ovarian cancer (OC), single-agent chemotherapy is the standard. Unfortunately, most of these studies are not randomized and may suffer from selection bias, making it difficult to interpret the value of published results. The most active single agents are paclitaxel (PTX), pegylated liposomal doxorubicin (PLD), topotecan and gemcitabine (Buda et al., 2004; Gordon et al., 2001a; Vergote et al., 2009a; Mutch et al., 2007; Bokkel Huinink et al., 1997; Gordon et al., 2004; Eisenhauer et al., 1994)

Different studies compared PLD efficacy to common drugs employed in this setting of disease. Gordon et al. matched PLD 50 mg/m2 as a 1 -h infusion every 4 weeks to topotecan 1.5 mg/m2/days 1–5 every 3 weeks. No differences were found in terms of PFS and OS in a total of 474 patients, with more G3-G4 toxicity in topotecan group (myelosuppresion, stomatitis and palmar-plantar erythrodysesthesia) (Gordon et al., 2001a). Comparable efficacy was found in other phase III studies in which PLD was matched with PTX (PFS of 5.4 versus 6 months and OS of 11.4 and 14.0 months for PLD versus PTX group respectively p < 0.05) (Gordon et al., 2001b; O'Byrne and Graham, 2002). In conclusion, non-platinum combination therapy has not been shown to be superior to sequential single agent treatment.

Paclitaxel (PTX) is one of the most active single agents. In a large, randomized, international study, 407 patients affected by OC recurrence were assessed to receive 175 or 135 mg/m2 of PTX over either 24 or 3 h (O'Byrne and Graham, 2002). Among these women 62% had PR disease. RR varied from 14% to 24%. At the approved dose of 175 mg/m2 over 3 h every 21 days, the RR was 15%. To find the most effective dosage, Rosemberg tested 108 patients who had developed a PR recurrence: they were randomly assigned to weekly or three weekly Paclitaxel treatments (Rosenberg et al., 2002). No difference between groups were found concerning to objective response rate (ORR), progression free survival (PFS) or overall survival (OS). Osman compared weekly Paclitaxel (group 1) versus tri-weekly (group 2) paclitaxel in 55 platinum resistant patients. They demonstrated that weekly paclitaxel, instead of tri-weekly paclitaxel, had a PFS and OS higher (PFS of 7 months versus 4.5 months, respectively (p:0.02) and OS was 16 months versus 11.9 months, respectively) (Osman et al., 2016) after a 24 months follow-up period. The median overall survival (OS) was approximately 12 months (Naumann and Coleman, 2011). Several trials have shown that combining chemotherapy agents increases toxicity without improving efficacy (Vergote et al., 2009b; Sehouli et al., 2008; Lortholary et al., 2012).

PM1183 is a compound under clinical investigation. It is an inhibitor of RNA polymerase II. This enzyme is essential for the transcription process that is over-activated in tumors with transcription addiction. The antitumor efficacy of lurbinectedin is being investigated in various types of solid tumors, including a Phase III study for platinum-resistant ovarian cancer, a Phase II study for BRCA 1 and BRCA 2- associated metastatic breast cancer and a Phase III study for small cell lung cancer. It showed activity in platinum-resistant ovarian cancer patients in a randomized phase II trial in comparison to topotecan

(Lortholary et al., 2012; Poveda et al., 2017). In a phase III CORAIL (Gaillard et al., 2016) trial patients were randomly assigned (1:1) to receive L 3.2 mg/m^2 q3wk (Arm A), or investigator choice of PLD (P) 50 mg/m^2 q4wk or topotecan (T) 1.5 mg/m^2/day D1–5 q3wk (Arm B) until progression or discontinuation due to toxicity. Median (95% CI) PFS by IRC was 3.5 months in arm A vs 3.6 mo in arm B (HR 1.04, 95% CI 0.84–1.29). ORR by IRC was 14.0% (9.7–19.3%) in arm A vs 12.2% (8.2–17.3%) for arm B (p = NS). Interim OS was 11.2 mo in arm A vs 11.1 months in arm B. Related adverse events were reported in 92% of patients in Arm A vs 198/213 (93%) in Arm B; grade ≥ 3 AEs in 105 (48%) vs 136 (64%) (p = 0.001), respectively. In arm B, Topotecan accounted for a higher percentage of AEs than PLD. Treatment-related dose reductions, delays and discontinuations were more frequent in Arm B. Finally, the global QoL scores were not different between the arms. In conclusion, although the primary endpoint (30% of reduction in PFS) was not met, the similar efficacy results between arms and the favorable safety profile indicate a potential role for Lurbinectedin in the difficult-to-treat platinum resistant setting.

A new phase II Italian study is starting in this subgroup of patients. It will randomize the use of Decitabine in combination with Carboplatin versus physician's choice chemotherapy in platinum resistant ovarian cancer.

3.2.1. Target therapy

Antiangiogenic agents play an important role in all phases of treatment, including 'platinum-resistant' disease. The original studies with bevacizumab showed that it is active both as monotherapy (Burger et al., 2007; Cannistra et al., 2007) and combined with chemotherapy - (Mc Gonigle et al., 2011).

When used as single agent, tumor response occurred in 16% of patients when used alone or in combination with low-dose cyclophosphamide (Garcia et al., 2008).

Recently, AURELIA trial (see Table 5) evaluated the combination of bevacizumab and chemotherapy in platinum-resistant recurrent ovarian cancer. Three hundred sixty one patients were enrolled and randomized to receive chemotherapy alone (paclitaxel 80 mg/m2 weekly, topotecan 4 mg/m2 weekly or PLD 40 mg/m2 every four weeks) or with bevacizumab (10 mg/Kg administered every 2 weeks). The study demonstrated a prolongation of PFS in the group treated with bevacizumab. The best survival benefit was obtained in the group treated with paclitaxel plus bevacizumab versus paclitaxel alone with an increase even on OS (Garcia et al., 2008). The results related to safety showed that patients of the CT arm had adverse events in 40,3% of cases while patients of the BEV-CT arm were affected by adverse events in 57% of cases. There was an increased incidence of grade 2 hypertension and proteinuria with bevacizumab. Grade 2 of gastro-intestinal (GI) perforation was observed in four patients (2.2%) receiving BEV-CT (grade 3, 1.7%) and none of those receiving CT alone. To reduce the risk of GI perforation, previously reported at a high incidence in patients receiving bevacizumab for heavily pretreated ovarian cancer (Sorio et al., 2017), AURELIA trial used strict exclusion criteria. Grade 3 hematologic toxicity occurred at a similar incidence in the two treatment arms. Adverse events such as severe abdominal pain, vomiting, fatigue, and dyspnea, were less common with BEV-CT. Patients with ascites at baseline underwent paracentesis after starting study treatment in 17% of cases if treated with CT alone, in 2% receiving BEV-CT.

Table 5
Randomized control trials of antiangiogenics in platinum resistant ovarian cancer recurrences.

Study	Regimen	PFS	OS
MITO 11	weeklyP vs	3.49	13.7
(Pignata et al., 2015)	weeklyP + pazopanib	6.35	19.1
AURELIA	CT (PLD,P,Top) vs	3.4	13.3
(Sorio et al., 2017)	CT + Bev	6.7	16.6

PFS: progression free survival; OS: overall survival; CT: Chemotherapy; P: Paclitaxel; PLD: pegylated liposomal doxorubicin; Top: Topotecan.

The results of another important study, the MITO11, where published by Pignata et al. in 2015. This is a open-label, randomized phase 2 trial that included 74 patients with platinum-resistant or platinum-refractory ovarian cancer previously treated with a maximum of two lines of chemotherapy. Patients were randomly assigned to receive weekly paclitaxel with or without pazopanib. The increase in progression-free survival noted in this trial was comparable to that reported with the addition of bevacizumab, an anti-VEGF monoclonal antibody, to in a phase 3 trial published by Pujade-Lauraine in 2014. Data about PFS and OS are reported in Table 5. As expected, adverse events were more common in patients who received paclitaxel and pazopanib, although were not recorded any unexpected side-effects or any deaths related to toxic effects. Unfortunately, one limitation of this study is that no patients had previously received an anti-angiogenic treatment. In fact, when the trial was designed, anti-VEGF treatments were not the standard of care for ovarian cancer in Italy. (Pignata et al., 2015)

Olaparib showed a response rate of about 30% in different Phase II study in resistant ovarian cancer. Different studies are currently evaluating this option of treatment (Kaufman et al., 2015).

A randomized phase II trial, PRECEDENT, compared PLD with PLD and vintafolide (EC 145), a folic acid–desacetyl vinblastine conjugate that targets FR-positive cells. The combination increased the median PFS from 2.7 to 5.0 months (HR 0.63; 95% CI 0.41–0.96; p = 0.031) (Naumann et al., 2013).

Trebananib, a peptibody that blocks binding of angiopoietin-1 and -2 to Tie2, significantly prolonged progression-free survival (PFS) in patients with recurrent epithelial ovarian cancer in the phase 3 TRINOVA-1 study. Median OS was not significantly improved with trebananib compared with placebo (19.3 versus 18.3months; HR, 0.95; 95% CI, 0.81–1.11; P = 0.52) in the intent-to-treat population. In subgroup analysis, trebananib improved median OS compared with placebo (14.5 versus 12.3months; HR, 0.72; 95% CI, 0.55-0.93; P = 0.011) in patients with ascites at baseline. In the intent-to-treat population, trebananib significantly improved the time to second disease progression (PFS-2) compared with placebo (12.5 versus 10.9months; HR, 0.85; 95% CI, 0.74-0.98; P = 0.024) (Monk et al., 2016).

Trebananib also demonstrated anticancer activity if associated with pegylated liposomal doxorubicin in TRINOVA 2 trial. Probably the safety profile is not so good: adverse events with a greater incidence in the trebananib arm included localized oedema (61% versus 32%), ascites (29% versus 9%) and vomiting (45% versus 33%) (Marth et al., 2017).

3.2.2. Immunotherapy

Immunotherapies based on anti-programmed death 1/programmed death ligand 1 (PD-1/PD-L1) pathway inhibitors may turn out effective in ovarian cancer treatment. They can be used in combination with standard therapy and are especially promising in recurrent and platinum-resistant OC. The mechanism of the PD-1/PD-L1 pathway can be specific for a particular histological cancer type: in fact, data have shown that the PD-1/PD-L1 pathway blockade may be effective, especially in the endometrioid type of OC.

Most of clinical trials are Phase I or PhaseI/II studies, as well as targeting cytotoxic T-lymphocyte associated protein 4 (CTLA-4) or the anti-programmed cell death ligan-1/programmed cell death-1 (PD-L1/PD-1). Ipilimumab, the more tested, is a fully humanized mAb that blocks the immunosuppressive signal by cytotoxic T-lymphocyte antigen 4. Nivolumab is an anti-PD-1 monoclonal antibody. It has achieved an overall response rate of 17% in Phase 1 clinical trial for patient with platinum-resistant ovarian cancer. Results demonstrated that the combined treatment with nivolumab and cisplatin effectively inhibited platinum-resistant ovarian cancer cells via induction of cell apoptosis and inhibition of ADAM17 expression (Sun et al., 2017;

Hamanishi et al., 2015).

Among these agents, avelumab is one of the most promising. In JAVELIN Solid tumour phase Ib study (NCT01772004) a total of 124 unselected patients with heavily pre-treated 'platinum-resistant' ovarian cancer were enrolled, making this the largest reported dataset of patients with ovarian cancer and immune checkpoint inhibitors. The overall response rate was 9.7%. The most common side effects were fatigue, nausea/vomiting, diarrhea/constipation, infusion-related reactions, rash and hypothyroidism.

JAVELIN Ovarian 200 is a Phase III, Multicenter, Randomized, Open-label Study that compares avelumab alone, avelumab plus PLD and PLD alone in patients with platinum-resistant/refractory resistent ovarian cancer. Unfortunately, Avelumab alone or in combination with pegylated liposomal doxorubicin (PLD) did not induce a statistically significant improvement in OS or PFS versus PLD alone in patients with platinum–resistant/refractory ovarian cancer. It was reported in a press release that avelumab plus PLD led to an HR for PFS of 0.78, which did not meet the prespecified criteria for superiority. [RCI 0.587–1.244; one-sided P value = .0301]. The OS endpoint with the avelumab combination was also not met (HR, 0.89; RCI, 0.744–1.241; one-sided P value = .2082). (NCT02580058).

Data from the KEYNOTE-028 study (NCT02054806) suggested that pembrolizumab (pembro) had clinical activity in patients (pts) with PD-L1 + advanced ovarian cancer (AOC). These data were recently confirmed by the study Keynote 100 that showed a ORR of 9% (95% CI, 4, 17). ORR was higher in pts with PD-L1 expression: 14% (8/59) with CPS ≥ 1 and 25% (5/20) with CPS ≥ 10. 73% of patients had treatment-related (TR) AEs and 17% had grade 3–5 TR AEs.

Unfortunately, therapies based on immune checkpoint have some disadvantages. The treatment based on PD-1/PD-L1 pathway inhibitors may cause adverse effects, including fatal colitis, severe diarrhea, pneumonitis, fatigue, arthrodynia, vomiting and headache. Nevertheless, the adverse events of these mAbs are most frequently mild and temporary. It is also necessary to conduct subsequent studies to confirm in which OC cases the treatment is effective and how to select patients and combine drugs to improve patient survival.

The main check-point inhibitor studied in OC recurrence are listed in Table 6

4. Conclusions and future prospectives

Despite the fact that there have been several studies about ovarian cancer therapy, the rate of cure has increased little over the last two decades, and recurrence is a common event in 80% of endothelial ovarian cancer (EOC) patients.

Recent advances have led to novel targeted treatments for recurrent OC that offer opportunities to improve response rates and prolong progression-free intervals. However, the survival rate and the time to second disease progression (PFS-2) in patients with ovarian cancer recurrence is still poor.

Recently, different strategies were studied to improve these data. In platinum sensitive recurrence disease with a TFI > 12 months, so "fully sensitive", the possible options, based on the previous use of bevacizumab, could be:

1) A platinum based chemotherapy + PARP inhibitors (Niraparib if BRCAwt or BRCAmut; Olaparib if BRCAmut). BRCAmut include both germiline and somatic mutations.
2) A platinum based chemotherapy + Bevacizumab (if not used in first line)
3) A platinum based chemotherapy

The choice of the most appropriate treatment is based on treatment free interval, molecular characteristics and biological profile of the disease such as the presence of a BRCA mutation or HRD (homologous recombination deficiency), previous lines of chemotherapy, toxicities,

Table 6
ZZZ.

Study	Checkpoint inhibitors	Arms	N. patients	N. previous lines	PFS	OS (months)
UMIN000005714 (Sun et al., 2017)	Nivolumab	1	20	≥ 2	3.5 months (95% CI, 1.7 to 3.9 months),	20.0 months (95% CI, 7.0 months to not reached)
NCT02580058 (Pujade-Lauraine et al., 2018)	Avelumab	avelumab alone avelumab plus PLD PLD alone	Data are currently being analyzed	Up to 3	PFS of 0.78 (criteria for superiority not met)	HR, 0.89; RCI, 0.744-1.241; one-sided P value = .2082 (criteria for superiority not met)
NCT03038100 (Moore and Pignata, 2019)	Atezolizumab	atezolizumab + paclitaxel + carboplatin + bevacizumab	1300	NA	NA	NA
NCT02054806 (Varga et al., 2018)	Pembrolizumab	placebo + paclitaxel + carboplatin + bevacizumab 1	26	NA	1.9 months (95% CI, 1.8–3.5)	13.8 months (95% CI, 6.7–18.8)
NCT03267589	Durvalumab	MEDI9447 (CD73) + durvalumab MEDI0562 (OX40) + durvalumab MEDI0562 (OX40) + tremelimumab combination	75	NA	Still recruiting	Still recruiting

NA: not applicable; NS: not significative.

and tumor load (if ascites, gross tumor volume…)

After about 40 years, antiangiogenics therapies such us Bevacizumab and PARP inhibitors are changing the scenario and are offering a possibility to improve the outcome in these patients: bevacizumab, as maintenance, have showed important results in terms of outcome, either in first line or in patients with platinum sensitive recurrent disease. With the PARPi, we observed the best PFS curves over the last years, with a great familiar and personal involvement and finally the possibility to choice the best strategy tailored on patient's history.

Combinations of PARPi with other molecularly targeted therapies, especially anti-angiogenic drugs, are also showing promising encouraging results, but we need to confirm them.

It should be highlighted that ovarian cancer is a heterogeneous disease, at a genomic level too, and progression depends on many different factors, for example e.g. the histological type. OC is also heterogeneous at phenotypical level, and can be associated with increased copy alterations that correlate with the lack of response to the immune checkpoint inhibitor therapy.

For this reason, studies about checkpoint inhibitors have demonstrated an activity in melanoma and lung cancer and for this reason they have inspired further investigation of these agents in multiple other solid tumors, including ovarian cancer.

It could look in the future to use the PDL-1 and PD-1 and the other check-points as a biomarker to select patients for therapy. Their role in the treatment of ovarian cancer is unclear, but many trials are enrolling, and we hope that the benefit of these drugs, yet seen in other solid cancers, may extend to the treatment of ovarian cancers.

When TFI is between 6 and 12 months ("partially sensitive"), a possible strategy is to prolong the platinum free interval with non-platinum drugs, like trabectedin in association with pegylated liposomal doxorubicin, and then a rechallange with platinum.

Unfortunately a big issue remains platinum resistant disease (< 6 months) with its poor prognosis: a possibility could be the use of dose-dense schedule of platinum, either cisplatin or carboplatin given weekly with the addition etoposide or paclitaxel (Van Der Burg et al., 2002; Sharma et al., 2009; Rose et al., 2003), or weekly paclitaxel with the addiction of bevacizumab.

In conclusion, the most important thing to remember is to offer to our patients all potential combinations of therapies that we have, in order to reduce toxicities and improve the outcome, without forgetting the quality of life.

Declarations of interest

None.

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