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# Target Therapy in Platinum-Refractory/Resistant Ovarian Cancer: From Preclinical Findings to Current Clinical Practice

**Nicoletta Staropoli, Cirino Botta, Domenico Ciliberto, Lucia Fiorillo, Antonina Maria De Angelis, Caterina Viscomi, Simona Gualtieri, Angela Salvino, Pierfrancesco Tassone, Pierosandro Tagliaferri**

Medical Oncology Unit, Department of Experimental and Clinical Medicine, Magna Græcia University and Tommaso Campanella Cancer Center, Campus Salvatore Venuta, Catanzaro, Italy.
Email: tagliaferri@unicz.it

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## ABSTRACT

Epithelial ovarian cancer (EOC) is the sixth most common malignancy in women. Ovarian tumors consist of several clinical and pathological entities that share an anatomic site. The gold standard treatment, both in front-line and in adjuvant setting, is represented by carboplatin/paclitaxel combination. Conversely, the second-line treatment is not well defined. The response to platinum is the major prognostic factor for survival. In this review we discuss the current views on platinum-refractory/resistant patient treatment only, which includes patients progressing or relapsing within 6 months from the last platinum-based course. Concerning this subgroup, the activity of several conventional drugs was confirmed in different trials without a significant impact in terms of overall survival. In the last years particular emphasis was given to targeted anti-angiogenetic therapy which produced a survival improvement with an acceptable toxicity profile. New "ad hoc" approaches, with a major attention to outcome-predictive factors, are eagerly awaited.

**Keywords:** Ovarian Cancer; Systemic Chemotherapy; Platinum Sensitivity Status

## 1. Introduction

Epithelial ovarian cancer (EOC) is the sixth most common malignancy in women [1]. The overall 5-years survival rate, despite of stage, is about 30% [2]. Serous papillary EOC is the most frequent type and the leading cause of death among gynaecological cancers. EOCs consist of several pathological entities that share anatomic site and frontline treatment [3]. Indeed, mutations that arise in EOC, such as KRAS, PIK3CA, TP53, BRCA1 and BRCA2, are unequally distributed between different subtypes [4]. Kurman *et al.* described that only serous papillary EOC seems to originate by ovary and/or fallopian tube, and in the contest of this histotype two different groups are recognized: Type I tumors arise by precursor lesion, are usually low grade with specific mutations in K-RAS, B-RAF, PTEN and b-catenin, present a normal karyotype and wild-type TP53. These mutations are frequently reported very early and typically these tumors are characterized by a worse response to platinum-based chemotherapy. The course of these lesions is indolent and has been postulated to be the result of "multi-hit oncogenesis". Conversely Type II is characterized by de novo lesions, high grade, genetic instability, TP53 mutations, RAS pathway wild-type, and BRCA mutations, both hereditary and sporadic (such as promoter methylation and failure in the DNA homologous recombination); last subgroup showed a strongly correlation with response to platinum, probably due to early loss of BRCA and TP53 function (**Table 1**) [5-13].

In 1991, a meta-analysis on 8000 patients showed that platinum-based combination regimens were more effective compared to platinum monotherapy [14]. Currently, the gold standard treatment in frontline and in adjuvant setting is carboplatin/paclitaxel [15-17]. Conversely, the treatment for recurrent or progressive EOC is not well defined. The response to platinum-containing first line chemotherapy is the major prognostic factor. Platinum-refractory status is generally considered for patients who relapse within 6 months from the last platinum-based course [7]. Concerning this subgroup, in the last years, a modest activity of several drugs such as pegylated liposomial doxorubicin (PLD), topotecan, eto-

**Table 1**. **Characteristics of Type I and Type II tumor.**

| | *Type* I | *Type* II |
|---|---|---|
| Clinical features | indolent | aggressive |
| Histological features | low-grade serous | high-grade serous |
| | low-grade endometrioid | high-grade endometrioid |
| | clear cell | undifferentiated |
| | mucinous | Carcinosarcoma |
| Molecular features | K-RAS | TP53CCNE1 |
| | B-RAF | |
| | ERBB2 | |
| | PTEN | |
| | CTNNB1 | |
| | PIK3CA | |

poside, taxanes, gemcitabine, oxaliplatin was confirmed in several trials without a significant impact in terms of overall survival (OS). Therefore, there is not a standard approach for second-line treatment [18,19].

## 2. Cytotoxic Chemotherapy

The platinum-refractory/resistant diseases represent an heterogeneous spectrum of tumors characterized by low response rate (RR) to previous carboplatin-based-schedule (10% - 25%) [18,20,21]. Conventional decision in this setting is exclusion of platinum in subsequent line-treatment [19]. Indeed, common recommendation can be made for the use of monotherapy with PLD, topotecan, etoposide, gemcitabine or paclitaxel, all producing a low RR without any demonstrated improvement on survival endpoints [18,21].

In 2004 results by Gordon *et al.* described a marginal progression free survival (PFS) benefit for PLD compared to topotecan (especially in platinum-sensitive subgroup) that, in view of the good tolerability of the drug, was translated in platinum-refractory setting. PLD became a "first" choice for second-line treatment in all subgroups [22]. Subsequently, several trials did not demonstrate statistically significant results in terms of survival gain for PLD compared to gemcitabine, that remains therefore a valid option in this setting with RR of 20% [23-31]. By the way gemcitabine was the most common drug used in clinical trials [32,33].

In recent studies pemetrexed, a multitarget antifolate agent, produced RR similar to historical agents without any evident impact in term of survival [34-36]. Rose *et al.* investigated prolonged oral etoposide in both platinum-sensitive and platinum-resistant patients with an overall RR of 34% and 27% respectively [37].

Paclitaxel, as single agent, represents to date, a good clinical option in term of RR and survival, in particular if we consider weekly schedule [38,39]. Furthermore, the albumin-bound formulation of paclitaxel, nab-paclitaxel too, has been investigated in this setting showing similar RR (23%) and a median PFS of 4.7 months with a good tolerability [40].

A larger study with docetaxel in monotherapy was conducted by Rose *et al.* in platinum and paclitaxel-refractory settings with a RR of 22% [41]. The potential role of docetaxel-based combination regimens has not been rigorously evaluated. A prospective phase II study was conducted to evaluate the efficacy and toxicity of a combination of docetaxel/irinotecan as salvage treatment in platinum-refractory EOC patients [42]. This non-comparative trial, demonstrated a marginal benefit in RR similar to single agent schedule, confirming that single agent chemotherapy should be considered the standard treatment for these patients. Indeed, six trials failed to demonstrate an advantage for combination treatment compared to single agent with an increased toxicity [43-51].

However, different small trials evaluating gemcitabine and oxaliplatin combination in this setting demonstrated a longer PFS and a better RR. Considering the worse prognosis of these patients, comparative studies of this doublet versus single agent are required [52,53].

In third-line treatment a randomized phase III trial comparing PLD to patupilone, a novel microtubule inhibitor, demonstrated a PFS advantage for PLD arm [54]. Similarly canfosfamide, compared to topotecan and PLD in second- and third-line treatment, have been found significantly less active than these drugs [55-58].

In the light of the dismissal activity of conventional chemotherapy, in the last years particular emphasis was given to targeted therapy which produced survival improvement with an acceptable toxicity [59-63].

## 3. Targeted Therapy in EOC

### 3.1. The Involvement of HER-Pathway in Platinum-Resistance

The epidermal growth factor receptor (EGFR)-family play an important role in different malignancies and a EGFR overexpression seems to be correlated with decreased survival [64]. About 30% - 98% of EOC present overexpression in one of these pathways. Human epidermal receptor (HER) family consist of 4 paralogs (HER1/EGFR, HER2/neu, HER3 and HER4) and is characterized by an extracellular ligand binding domain, a transmembrane lipophilic glycoprotein and an intracellular tyrosine kinase (TK) domain. Signaling cascade begins with bindings of growth factors, such as epidermal

 

growth factor (EGF), transforming growth factor alfa (TGF-$\alpha$) to the receptor and subsequent dimerization or oligomerization and has been implicated in cancer development and resistance to cisplatin [65]. EGFR determines both omo-dimerization and ethero-dimerization with HER2/neu. The receptor triggers the autophosphorylation on tyrosine residues with signal transduction cascade activation. Dysregulation in EGFR promotes cell proliferation, migration and invasion with uncontrolled cellular growth and enhanced neo-angiogenesis [66]. Dimerization activates different signaling pathways, in particular EGFR dimerization activates the RAS-RAF-mitogen-activated protein kinase pathway (RAS/RAF/MAPK pathway) which induces oncogenesis and tumor progression mainly through constitutive activation of STAT-3 and STAT-5 and the phosphatidylinositol 3-kinase pathway (PI3K). Activation of PI3K results in the activation of the PDK1, AKT/PKB pathway [67].

Cetuximab is a chimeric monoclonal antibody able to inhibit the binding of EGF and the autophosphorylation of the receptor with its internalization from the cell surface that prevents further interaction with ligand [68]. A small phase II trial designed on platinum-refractory/resistant EGFR positive setting on cetuximab as single agent demonstrated marginal benefit in term of PFS [69]. Matuzumab, a humanized anti-EGFR monoclonal antibody, in patients heavily pretreated, did not show activity in this setting [70].

Erlotinib, a reversible EGFR-specific tyrosine kinase inhibitor (TKI), was evaluated as single-agent in two phase II trials that enrolled patients with platinum-resistant status obtaining a marginal activity limited for patients with EGFR-positive EOC. These trials reported a median OS of 8 months and disease control rate (DCR) in 50% of patients with acceptable tolerability [71].

Gefitinib was evaluated in phase II trial in patients with platinum-resistant setting and EGFR positive, with median PFS 2.2 months and RR 9% [72]. Another trial in this setting, evaluated the combination gefitinib/tamoxifen with a median time-to-progression of 58 days and median survival of 253 days [73]. Furthermore gefitinib was evaluated in combination with carboplatin and paclitaxel in patients stratified for platinum-sensitivity and EGFR positive and suggested advantages for platinum-sensitive setting only [74].

Trastuzumab, a monoclonal antibody targeting the HER2/neu, was investigated in a phase II trial on the basis of HER2/neu expression. This trial showed that activity of trastuzumab in this setting is limited by the low frequency of HER2 overexpression and low rate of objective response among patients with HER2 overexpression [75]. CI-1033 (canertinib), another panERB inhibitor also failed to demonstrate activity in platinum-refractory/resistant patients [76]. Lapatinib a 4-anilinoquinazoline, is an inhibitor of the intracellular TK domains of both EGFR and HER2. It was investigated in phase II trials both as single agent and in combination with topotecan but was not effective. Interestingly, in this trial, a subset analysis about prognostic factors suggested that Ki-67 expression may be associated with better prior platinum free interval (PFI) and PFS [77,78].

Pertuzumab is a recombinant, humanized monoclonal antibody directed against human HER2 that inhibits ligand-activated heterodimerization with other HERs, most notably HER3 [79]. A phase II trial evaluated pertuzumab in combination with gemcitabine in platinum-resistant EOC treatment demonstrated a significant advantage in term of RR and PFS for experimental arm compared to gemcitabine/placebo. Furthermore, it was suggested that patients with low HER3 mRNA expression, had an increase treatment benefit with pertuzumab [80].

### 3.2. Potential Role of mTOR Inhibitors and Platinum-Refractory/Resistant Ovarian Cancer

mTOR is a serine and threonine protein kinase. The mTOR pathway is involved in cell proliferation, motility and survival, protein synthesis and transcription. Preclinical findings indicated that this pathway has a crucial role in survival and drug-resistance of cancer cells. A small phase II trial evaluated efficacy and toxicity profile of mTOR inhibitor, temsirolimus, in platinum-resistant EOC disease and showed a modest activity. Cyclin D1 and circulating tumors cells (CTCs) measures where suggested as markers of outcome [81].

### 3.3. PARP Inhibitors

About 50% of EOC display defects in the homologous recombination (HR) pathway. This condition, like hereditary mutation in BRCA1-2, correlated to a good response to platinum-chemotherapy. However, Kaye *et al.*, evaluated use of olaparib, a PARP inhibitor, compared to PLD in patients who relapsed within 12 months did not reach pre-specified endpoints, failing to demonstrate any advantage for olaparib [82].

### 3.4. The Strict Interplay between Inflammation, Immune-System and Angiogenesis

The role of inflammation, immune system and angiogenesis in the onset and development of EOC has been extensively investigated during the past years [83,84]. The synthesis of cytokines such as TNF-$\alpha$, IL-1$\beta$, IL-6, PGE-2 and vascular endothelial growth factor (VEGF)

 

by cells from the microenvironment (especially activated immune cells and stromal cells), as well as the increased expression of STAT-3, NF-kB, iNOS and COX-2 in tumor and tumor-surrounding cells, has been linked to poor prognosis, disease stage progression, residual disease status and the presence of ascites [83,85,86]. Among these molecules, IL-6 seems to play a key role in determining platinum-resistance. Wang *et al.* recently reported that IL-6 production by different EOC cell lines is directly associated to treatment resistance. Furthermore, IL-6 induced cisplatin and paclitaxel-resistance when administered to IL-6-non-producing cell lines [87]. The ERK signaling pathway seems the principal mediator of this effect. Furthermore, IL-6 is able to induce HIF-1 via STAT-3, and HIF-1, in turn, promotes VEGF expression [88-90]. VEGF is able to enhance the malignant potential of EOC cells through the induction of ascites, by increasing peritoneal permeability and immune suppression, by impairing dendritic cells maturation and Th1 response and increasing tumor-infiltration by T regulatory cells [91-93]. Moreover, Bamias *et al.* described an association between VEGF levels in ascites and platinum-resistance and an inverse correlation of VEGF with $CD3^+$ $CD56^+$ Natural Killer (NK) cells [94]. On these basis it emerges the central role of inflammation in platinum-refractory EOC: the inflammatory microenvironment induces the production and release of IL-6 and VEGF which in turn lead to neo-angiogenesis, ascites formation and immune suppression on both adaptive (DCs and Th1) and NK immunity.

Tumor infiltration by different inflammatory cells has been correlated with prognosis and tumor progression in different tumors including EOC [95-98]. Among these cells, tumor associated macrophages (TAMs) have recently demonstrated to exert a significant immune suppressive effect together with a pro-angiogenic activity (M2 polarization) [99]. M2-TAMs are characterized by the expression of the angiopoietin receptor TIE-2 and are thought to be implied in VEGF-independent neo-angiogenesis [100]. These aspects are extremely relevant in a translational view, offering a solid rationale for the use of anti-angiogenic agents in platinum-resistant EOC.

### 3.5. Anti-Angiogenetic Agents in Platinum-Resistant Ovarian Cancer

Bevacizumab, antibody targeting VEGF-A, demonstrated clinical activity in recurrent EOC [101,102]. A small trial reported for heavily pre-treated patients with platinum-resistant treated with bevacizumab as single agent a median PFS of 4.4 months and a median OS of 10.7 months [59].

Preclinical studies showed an improvement of anti-tumor activity when anti-VEGF or anti-VEGFR targeting agents were associated to cytotoxic agent, probably due to vascular normalization [103,104]. A phase II trial described that the association of bevacizumab and metronomic oral cyclophosphamide produced a median OS of 16.9 months [105]. Another phase II trial, that investigated a combination of bevacizumab and nab-paclitaxel reported a median PFS of 8.3 months and a median OS of 16.5 months [106].

Recently results of AURELIA trial, designed for this setting, reported that association of bevacizumab to conventional agents (PLD, topotecan or paclitaxel) was able to prolong PFS. In particular the arm containing weekly-paclitaxel/bevacizumab determined a 10.4 months PFS [60].

Aflibercept, is a recombinant fusion protein between the constant region (Fc) of an IgG1, the second domain of VEGFR-1 and the third domain of VEGFR-2 that binds and neutralizes VEGF A, B and placental growth factor (PIGF) [107]. This agent seems particularly active in recurrent EOC patients with malignant ascites [108, 109].

Imatinib and dasatinib, selective inhibitors of PDGFR and C-KIT, were evaluated in small phases II trials in recurrent EOC without any improvement both in RR and in survival endpoints [110,111].

Sorafenib, a multitarget inhibitor of B-RAF, VEGFR-2 and -3, PDGFR-b, FLT-3, and C-KIT, was evaluated in phase II trials in second and third line treatment, demonstrating a modest activity and substantial toxicity [112, 113]. Sunitinib, another multi-target TKI for VEGFR, PDGFR-A, PDGFR-B, C-KIT, FLT-3 and cediranib, a potent inhibitor of VEGFR, PDGFR-B and C-KIT, were evaluated as single agents and in combination schedules, in recurrent EOC patients with modest activity in terms of RR and and mostly restricted to the platinum-sensitive setting [114-117].

Pazopanib a TKI targeting VEGFR, PDGFR, and C-KIT, and BIBF-1120, a VEGFR, PDGFR, and FGFR multi-targeted TKI were recently evaluated in combination-schedules and as single agents in EOC patients. Data available, to date, showed activity of these agents and major trials are still ongoing [61,62,118].

Recently a phase II trial evaluated AMG-386, an investigational peptide-Fc fusion protein that neutralizes the interaction between the TIE-2 receptor and angiopoietin-1/2, in combination with weekly paclitaxel demonstrated the potential efficacy of this agent, with a good toxicity profile, warranting further studies [119].

Many authors proposed proangiogenic protein concentration in plasma or urine (e.g., VEGF, PDGF, PIGF) as markers that would predict response to anti-angiogenic

 

therapy. Several ongoing trials could confirm this hypothesis.

### 3.6. MicroRNAs, New Potential Targets in Platinum-Refractory/Resistant EOC

MicroRNAs (miRNAs), are short non-coding RNA molecules of about 19 - 25 nucleotides able to regulate gene expression at post-trascriptional level by binding specific target mRNAs [120,121]. Several recently published studies focus their attention on the role played by these molecules in EOC initiation and progression. miR-21 is one of the most widely investigated miRNA due to its pro-oncogenic activity demonstrated in different malignancies [122]. This miRNA is upregulated by the IL-6 downstream (described in previous section) and was found to be overexpressed in platinum-resistant EOC cell lines. In the same study, Lou *et al.* reported that the down-regulation of miR-21induced apoptosis and inhibited invasion and migration capabilities of EOC cell line, making this miRNA a possible candidate for future clinical translation [123].

About 63% of platinum-resistant EOC presented a dysfunctional TP53 pathway [124]. This event leads to the reduction of intracellular of the oncosuppressor miR-34a, thus improving cell capability to survive and metastatize [125]. In different studies *in vitro* and *in vivo*, in different tumors, miR-34 replacement/overexpression induced apoptosis and reduced cellular migration, proliferation and tumor growth [125,126].

The miR-200 family represents another widely studied group of miRNA in EOC. They appeared to be implied in epithelial to mesenchimal transition and in resistance to both paclitaxel and platinum [120]. However, contrasting data on activity and expression of these miRNAs in EOC are available in literature and its role is far to be completely understood.

Non-coding RNAs represent one of the most exciting recent discovery in cancer biology and other different miRNAs, such as miR-29b or miR-221/222 are currently under investigation in different malignancies for their potential clinical application as anticancer agents [127-132].

## 4. Conclusions

**Figure 1** and **Table 2**, describe all major pathways mentioned in our review. In the light of clinical trials results it is evident, to date, that only antiangiogenic agents (in particular bevacizumab) when associated to cytotoxic drugs are able to improve EOC patient outcome. Concerning other described pathway, probably pertuzumab

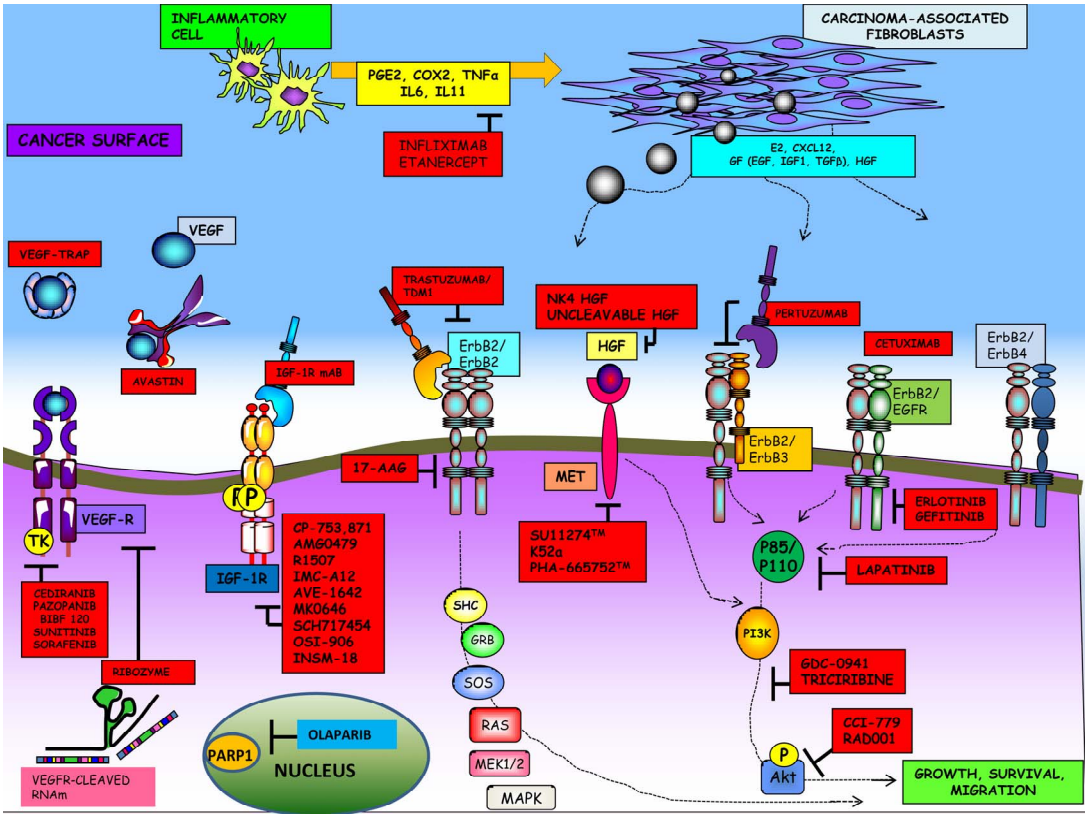


**Figure 1. Major pathways involved in EOC pathogenesis and new potential targets.**

 

**Table 2. Phase II III studies targeting EOC.**

| *Study No. pts* | *Patients* | *Treatment* | *RR* | *SD* | *Median PFS* | *Median OS* | *Most common grade ≥ 3 AE* |
|---|---|---|---|---|---|---|---|
| Cannistra *et al.* [59] No. 44 | Platinum-resistant EOC/PSC after 2 - 3 CT regimens | Bevacizumab 15 mg/kg IV q3 weeks; median no. of cycles, 5 | 16% | 61% | 4.4 months | 10.7 months | GI perforation (11%), small intestinal obstruction (9%), Hy (9%), Fg (5%), abdominal pain (5%), or digestion (5%) and dyspnea (5%) |
| Pujade-Lauriaine *et al*. [60] No. 361 | Platinum/resistent EOC after 1 - 2 CT regimens No history of bowel obstruction/abdominal fistula, or clinical/radiological evidence of rectosigmoid encolvement | Bevacizumab 15 mg/kg IV q3 weeks and/or CT[a] | NR | NR | 6.7 months | NR | Netropenia (23% with P; 19% with T), PSN (35% grade ≥2 with P), HFS (28% grade ≥2 with PLD), Hy (12% with PDL) |
| Burger *et al.* [102] No. 62 | Persistent/recurrent EOC or PPC after 1 - 2 CT regimens | Bevacizumab 15 mg/kg IV q3 weeks; median no. of cycles, 7 | 21% | 52% | 4.7 months | 16.9 months | Hy (10%) and GI events (7%) |
| Garcia *et al.* [104] No. 70 | Recurrent EOC or PPC after 1 - 3 CT regimens | Bevacizumab 10 mg/kg IV q2 weeks and cyclophosphamide 50 mg daily orally; median no. of cycles, 5 | 24% | 63% | 6 months | 16.9 months | Lymphopenia (14 episodes), pain (13 episodes), Hy (11 episodes), Fg (6 episodes), and GI obstruction (5 episodes). |
| Tillmanns *et al.* [106] No. 48 | Recurrent/platinum-resistant EOC/PPC after ≥1 prior regimen | Bevacizumab 10 mg/kg IV q2 weeks and nabpaclitaxel 100 mg/m$^2$; median no. of cycles, until progression | 46% | 30.8 | 8.3 months | 16.5 months | Bowel obstruction (4%), nausea (4%), and nose bleed (4%) |
| Wagner *et al.* [73] No. 56 | Recurrent/platinum-resistant EOC/FTC/PPC; had previously received first-line platinum/taxane treatment only | Tamoxifen 40 mg/day PO and gefitinib 500 mg/day PO until progression or unacceptable toxicity | NR | NR | 58 days | 253 days | Diarrhea (NR%) and acne-like skin rash (NR%) |
| Pautier *et al.* [74] No. 28 | Recurrent/platinum-resistant EOC/FTC/PPC; had previously received first-line platinum/taxane treatment only | Gefitinib 500 mg/day PO, P (175 mg/m$^2$ 3 h infusion) and C (AUC 5) every 3 weeks, followed by gefitinib alone, median no. of received cycles 6 - 8. | NR | NR | 6.1 months | 16.9 months | Neutropenia (59%), diarrhea (25%), leukopenia (22%), anemia (13%), and acne (13%). |
| Weroha *et al.* [77] No. 18 | Recurrent/platinum-resistant EOC/PPC; had previously received first-line platinum/taxane treatment only | Topotecan 3.2 mg/m$^2$ IV on day 1, 8 and 15 and lapatinib 1250 mg daily, continuously in 28 day cycles. PO | NR | NR | 3.5 months | 15.5 months | Neutropenia (56%), Thrombocytopenia (28%), and diarrhea (22%). |

 

**Continued**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Makhija *et al.* [80] No. 130 | Recurrent EOC/PPC; had previously received first-line treatment | gemcitabine plus either pertuzumab or placebo | NR | NR | 2.9 months | 13.2 months | Neutropenia (39 %), diarrhea (11%), back pain (9%) and Fg (22%) |
| Bebakht *et al.* [81] No. 60 | Persistent/recurrent EOC/PPC who had received 1 - 3 prior regimens | Temsirolimus 25 mg weekly IV until progression or intolerable toxicity | NR | NR | 3.1 months | NR | Metabolic (8 pts), GI (8 pts), pain (6 pts), and pulmonary (4 pts) |
| Colombo *et al.* [109] No. 16 | Advanced chemo-resistant EOC and symptomatic malignant ascites | Aflibercept 4mg/kg every 2 weeks IV | NR | NR | 59.5 days | NR | Hy and weight loss (1 pt) and intestinal perforation (1 pt) |
| Baumann *et al.* [114] No. 73 | recurrent platinum-resistant ovarian cancer who were pretreated with up to three chemotherapies | sunitinib (arm 1: 50 mg daily orally for 28 days followed by 14 days off drug; and arm 2: 37.5 mg daily continuously | NR | NR | 4.8 months 2.9 months | 13.6 months 13.7 months | cardiovascular, GI and abdominal symptoms, hematologic and hepatic laboratory abnormalities |
| Biagi *et al.* [115] No. 30 | measurable disease and one or two prior chemotherapies, at least one platinum based. Platinum-sensitiveor resistant disease was allowed. | 50 mg daily, 4 of 6 weeks 37.5 mg daily continuously | NR | NR | NR | 4.1 months | Fg (3 pts), GI symptoms (4 pts), HFS (3 pts) and Hp (1 pt). |

Abbreviations: RR, response rate; SD, stable disease; PFS, progression-free survival; OS, overall survival; NR, not reported; EOC, epithelial ovarian carcinoma; PSC, peritoneal serous carcinoma; PPC, primary peritoneal cancer; FTC, fallopian tube cancer; CT, chemotherapy; IV, intravenously; PO, oral dose; AUC, area under the concentration-time curve; AEs, adverse events; GI, gastrointestinal; Hp, hypertension; PSN, peripheral sensory neuropathy; HFS, hand-foot syndrome; Fg, fatigue. [a]CT options (investigator's choice): Paclitaxel (P) 80 mg/m$^2$ days 1, 8, 15, & 22 q4w; Topotecan (T) 4 mg/m$^2$ days 1, 8, & 15 q4w (or 1.25 mg/m$^2$, days 1 - 5 q3w); pegylated liposomal doxorubicin (PLD) 40 mg/m$^2$ day 1 q4w.

only may be a promising therapeutic option.

It could be interest to achieve additional information on the role of miRNAs as predictive factors of outcome and/or as new therapeutic agents. Further studies are eagerly awaited to disclose the real potential of both miRNA and miRNA inhibitors as new drugs to translate into clinical practice.

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