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New Drugs

# Tyrosine-kinases inhibitors in recurrent platinum-resistant ovarian cancer patients

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ABSTRACT

For many decades, ovarian cancer (OC) has been one of the most common gynecological cancer.

Despite advances in OC diagnosis and treatment, the risk of recurrence is ever present and approximately 85% of patients will experience relapse. Recurrent OC after first-line therapy is almost always incurable. Multiple novel therapies, including tyrosine-kinases inhibitors (TKI), have shown promising results, but their role needs to be clarified.

In this review we describe the rationale and the clinical evidence regarding the use of TKI for the treatment of recurrent platinum-resistant OC patients.



## Introduction

Ovarian cancer (OC) is the 9th most common cancer in the female population and the 2nd most common gynecological cancer after cancer of corpus uteri, with 21980 new cases in US in 2014 and 67,000 new cases in Europe in 2008 [1,2]. In the last decades, survivals of women with epithelial OC has improved, especially thanks to more aggressive surgical techniques, aimed to achieve optimal cytoreduction, and to the introduction of platinum-based treatment [3]. Nonetheless, approximately 60% of patients with advanced disease at primary diagnosis will experience recurrent disease within 5 years from diagnosis [4], and some of them will develop resistance to chemotherapy. Patients who relapse within 6 months have a very poor overall response rate (ORR): the most active agents have shown an ORR of about only 10%, with a progression free survival (PFS) < 4 months and an overall survival (OS) of approximately 1 year [5]. With the aim to obtain a better ORR and to counteract the occurrence of mechanisms of resistance to chemotherapy in particular in patients who develop recurrent disease, new therapeutic approaches are required and target therapies recently gained great attention.

These agents, which interfere exclusively with specific molecular targets, promise greater selectivity and lower toxicities than traditional cytotoxic drugs; indeed, it is noteworthy to consider that also a prolonged toxicity may decrease the efficiency of an antitumor treatment [6,7]. Furthermore, even if cure is not yet an objectively valid goal of therapy, the emerging strategies should essentially be designed to focus equally on the quality of life (QoL) as well as on the length of survival. Several molecules have been evaluated and used in OC including agents that target vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR), epidermal growth factor receptor (EGFR), poly (ADP-ribose) polymerase (PARP) tumor suppressor gene and phosphate tensin homolog (PTEN) [8]. Of these, bevacizumab has recently been included in the currently recommended National Comprehensive Cancer Network (NCCN) guidelines for OC. Moreover, the publication of the results of the AURELIA study urges the addition of bevacizumab to traditional chemotherapy for treatment of platinum-resistant recurrent OC. In fact, the trial has shown an increase in PFS when bevacizumab was associated to single-agent chemotherapy paclitaxel or pegylated liposomal doxorubicin or topotecan (3.4 months vs 6.7 months respectively; HR: 0.48, 95%

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CI, 0.38–0.60). However, no statistically significant difference in OS between the regimens (13.3 months vs 16.6 months HR: 0.85; 95% CI 0.66–1.08) has been observed [9].

Probably more target agents are likely to appear in national and international guidelines soon [1,10,11]. Furthermore, the biological behavior of tumors in these groups can be different as some patients have rapidly progressive symptomatic disease whilst others are asymptomatic and may have slow-growing disease. As a result, even in randomized trials interpretation of the results can be difficult. It is important that trials in 'platinum-resistant' OC include other endpoints such as patient-reported outcome. This review will provide an updated overview of existing investigational drugs that are potentially suitable for the treatment of platinum-resistant OC patients, with a special focus on emerging target therapies. The aim is to provide the scenario of the tyrosine-kinases inhibitors (TKI) that are potentially suitable for the treatment of recurrent, platinum-resistant OC patients, by focusing on the drugs that are already in clinical development phases and especially on target therapies.

## Platinum resistance definition

Patients with recurrent OC are categorized by their "platinum sensitivity", which is defined by the length of the treatment-free interval. Platinum resistance eventually occurs in virtually all patients with recurrent OC. It includes patients with a very heterogeneous group of tumors; those who do not respond to first-line therapy (platinum refractory), relapse within 6 months of treatment, or relapse within 6 months of several lines of treatment for recurrent disease. Clinical trials in 'platinum-resistant' disease often include patients from some or all of these categories.

## Tyrosine-kinases inhibitors (TKI)

Platinum resistant patients have a low probability of responding to alternative regimens, especially those who do not respond to second-line chemotherapy.

### *Overview*

Tyrosine-kinases are a group of enzymes with a catalytic subunit, which transfers a phosphate from nucleotide triphosphate to the hydroxyl group of one or more tyrosine residues on signal transduction molecules, resulting in a conformational change affecting protein function [12]. When activated, they can both auto-phosphorylate or phosphorylate other signaling molecules playing a central role in signal transduction and acting as relay points on a variety of biological processes, including cell growth, migration, differentiation and apoptosis [13]. TK receptors can induce specific cellular behavior by activating different signaling pathways as a result of its own activation that is controlled by extracellular ligand concentration. The most important cytoplasmic signaling pathways activated are the phosphoinositide 3-kinase/Akt pathway/mammalian target of rapamycin (PI3K/AKT/mTOR), the Ras/Raf mitogen-activated protein kinase (MAPK) pathway, the Raf/MEK/Erk pathway and the protein kinase C pathway [14]. These pathways, in turn influences cell proliferation, endothelial cell migration, apoptosis as well as increased vascular permeability eventually leading to blood vessel formation. Inhibition of these pathways has shown to might be useful in overcoming resistance to VEGF blockade. Several TKIs are being investigated that inhibit the VEGFRs directly rather than the binding of the VEGF ligand. Ongoing trials' details are listed in Table 1.

### *Nintedanib (BIBF 1120)*

Nintedanib (BIBF 1120) is an orally administered potent blocker of the receptors of vascular endothelial growth factor (VEGFR-1–3), platelet-derived growth factor (PDGFR-α/β) and fibroblast growth factor (FGFR-1–3).

It has recently been shown to have activity as maintenance treatment for relapsed OC in a randomized, double-blind, controlled phase II trial [15]. In this trial, 83 patients who had just completed chemotherapy for relapsed OC, with evidence of response, but at high risk of further early recurrence were randomly assigned to receive maintenance therapy using BIBF 1120 250 mg or placebo, twice per day, continuously for 36 weeks. Thirty-six-week PFS rates were 16.3% and 5.0% in the BIBF 1120 and placebo groups, respectively (HR 0.65; 95% CI, 0.42–1.02; $p = 0.06$). This drug was generally well tolerated with no significant toxicities. In particular, the proportion of patients with any grade 3 or 4 adverse events was similar between the groups (34.9% for BIBF 1120 versus 27.5% for placebo; $p = 0.49$). However, more patients on BIBF 1120 experienced diarrhea, nausea, or vomiting (mainly grade 1 or 2 and no grade 4) and grade 3 or 4 hepatotoxicity in patients on BIBF 1120 (51.2%) compared with patients on placebo (7.5%; $p < 0.001$), but this was rarely of clinical significance.

BIBF 1120 has also been evaluated in combination with cytotoxic agent, pegylated liposomal doxorubicin hydrochloride (PLD) in platinum-resistant cancer, in a phase I/II trial presented at ASCO 2014 [16]. BIBF 1120 was given orally twice a day and PLD was given intravenously at 40 mg/m$^2$ every 28 days, in a 3 + 3 dose escalation model, starting with BIBF at 150 mg BID. Eleven patients were enrolled in phase I. The association PLD plus BIBF 1120 was tolerated at 40 mg/m$^2$ and 100 mg BID. One patient with history of chemotherapy induced myelosuppression had grade 4 neutropenia and other toxicities were diarrhea (36.4%), fatigue (36.4%), vomiting (27.3%), headache (27.3%), allergic reaction (9.1%) and oral pain (9.1%). Three women had partial response, 3 stable disease and 4 progression; 1 was not evaluable. An expanded cohort using generic liposomal doxorubicin and BIBF 1120 at level −1 is planned before initiation of the phase II cohort. The potential effect of BIBF 1120 nearly tripling PFS, when compared to the placebo, has warranted a 1300 patients, phase III study of this drug in the LUME-Ovar 1 trial in the first line setting, which showed a significant improvement of the sole PFS [17].

BIBF 1120 is currently being evaluated in a two phase II trials including platinum resistant patients, one in which BIBF 1120 is associated with low dose (metronomic) cyclophosphamide (see Table 1).

### *Pazopanib*

Pazopanib is a TKI targeting VEGFR, PDGFR, and c-kit, recently approved by the US FDA for the treatment of patients with advanced renal cell carcinoma [18].

In the Phase I trial of other cancers, pazopanib demonstrated a manageable toxicity profile and considerable activity [19]. In the last years it has been also investigated in OC, in both primary and recurrent setting, with interesting as well as controversial results [20].

In a Phase II, open-label study evaluating pazopanib in patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma it was administrated at 800 mg once daily [21]. Thirty-six evaluable patients entered the study, 11 (31%) had a CA-125 response. ORR was 18% in patients with measurable disease at baseline. The median time to response was 29 days and median response duration was 113 days. The grade 3 alanine transaminase (ALT) (8%) and aspartate aminotransferase (AST) (8%) elevation appeared to be the most common AEs unacceptable to patients. After this study, showing promising activity of the drug