Oncology and Translational Medicine
DOI 10.1007/s10330-022-0557-7

February 2022, Vol. 8, No. 1, P28–P35

REVIEW ARTICLE

Recent advances in targeted therapy for ovarian cancer

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Abstract

The global burden of ovarian cancer is gradually increasing while patients still suffer from relatively limited treatment options. With recent advances in the decoding of the molecular landscape of ovarian cancer, more options in targeted strategy were offered and can therefore be tailored in different clinical settings for individual patient. Targeting of the abnormal angiogenesis process is the first significant clinical breakthrough which revolutionized the treatment of advanced ovarian cancer, followed by the advent of poly-(ADP)-ribose polymerase (PARP) inhibitors. These two strategies represented by bevacizumab and olaparib respectively underwent tests of numerous clinical trials. In recent years, immune checkpoint inhibitors (ICIs) have been incorporated into the blueprint of ovarian cancer treatment though the effectiveness still left much to be desired. Herein, we systematically outlined recent advances in targeted therapy for ovarian cancer and summarized the landmark clinical trials for each targeted therapy including angiogenesis inhibitors, PARP inhibitors and ICIs.

Received: 7 February 2022
Revised: 15 February 2022
Accepted: 24 February 2022

Key words: ovarian cancer; targeted therapy; anti-angiogenesis; poly-(ADP)-ribose polymerase (PARP) inhibitor; immune checkpoint inhibitor (ICI); clinical trial

Ovarian cancer is one of the female reproductive tract neoplasms with the highest case fatality rate [1]. Global cancer statistics estimated that in 2020 ovarian cancer accounted for 313 959 new cases and 207 252 deaths worldwide [2]. The malignancy onset is generally insidious, with lack of typical symptoms and effective screening methods [3–4]. Therefore, by the time of clinical diagnosis most patients already present with advanced disease, often characterized by extensive dissemination in the pelvis and abdominal cavity, which may develop into malignant ascites, posing significant challenges to surgeons and oncologists. Cytoreductive surgery followed by platinum-based chemotherapy for 6–8 cycles is currently the primary therapeutic strategy for ovarian cancer [5]. Neoadjuvant chemotherapy is an alternative option for patients with bulky stage III or IV disease; however, for poor surgical candidate patients, no gross residual disease (R0) is unlikely to be achieved solely through primary cytoreduction [6]. Ovarian cancer patients have a 70% chance of relapse within 2 years after reaching a clinical complete response (CR) [7], or even multiple regressions accompanied by a gradually shortened platinum-free intervals (PFI), thereby inevitably developing platinum resistance. Due to recent progress in better understanding the biological and molecular features underpinning ovarian cancer, a generation of novel targeted drugs has been developed, gradually shaping a new treatment landscape for ovarian cancer. Among these, anti-angiogenic agents and poly-(ADP)-ribose polymerase (PARP) inhibitors have demonstrated significant potential, both in randomized controlled trials (RCTs) and clinical practice [8]. In addition immunotherapy, despite having modest effects when used as single agent [9], possibly due to the immunosuppressive tumor microenvironment (TME) of ovarian cancers [10], still holds great potential in ovarian cancer research.

Targeting angiogenesis in ovarian cancer

Abnormal angiogenesis is considered to be a hallmark of multiple malignancies [11]. Accumulated evidence has demonstrated that angiogenesis is associated with an

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unfavorable prognosis in patients with ovarian cancer [12]. The formation of new blood vessels facilitates tumor progression, and is stimulated and regulated by a series of growth factors, the most clinically relevant of which is the vascular endothelial growth factor (VEGF) [13]. The angiopoietin axis is another signaling pathway contributing to angiogenesis [14]. Angiopoietin 1 and 2 (Ang 1&2) regulate vascularization and tissue remodeling by interacting with the tyrosine kinase receptor Tie2. Hence, the vascular endothelial growth factor receptor (VEGFR) and angiopoietin pathways are promising anti-angiogenic targets.

Bevacizumab

Bevacizumab was the first humanized recombinant monoclonal IgG antibody developed against angiogenesis, and the first targeted drug approved by the Food and Drug Administration (FDA) for the treatment of ovarian cancer. Bevacizumab targets all known VEGF subtypes, thereby inhibiting VEGFR pathway activation. Two landmark randomized controlled trials (RCTs) have confirmed bevacizumab's efficacy in first-line treatment of ovarian cancer, both when combined with standard chemotherapy and when used as a single-agent for maintenance.

In the Gynecologic Oncology Group (GOG)-218 study, 1873 patients with newly diagnosed stage IV, or stage III cancer who failed to achieve R0 resection, were randomized in three groups: (1) a control group, receiving standard chemotherapy plus placebo (2–22 cycles); (2) a bevacizumab-initiation group, receiving standard chemotherapy plus bevacizumab (2–6 cycles), followed by placebo (7–22 cycles); and (3) a bevacizumab-throughout group, receiving standard chemotherapy plus bevacizumab (2–22 cycles). The median progression-free survival (PFS) for the above groups was 10.3, 11.2, and 14.1 months, respectively. Compared to chemotherapy alone the bevacizumab-throughout group achieved better PFS, although no apparent difference in overall survival (OS) between the two groups was observed [hazard ratio (HR) = 0.717; $P < 0.001$].

A second large, randomized, phase III trial, the International Collaboration on Ovarian Neoplasms (ICON7), enrolled 1528 newly diagnosed patients with either high-risk early (IA–IIA) or advanced (IIB–IV) stage disease. These patients were treated with standard chemotherapy, or chemotherapy in combination with bevacizumab plus bevacizumab maintenance for 12 additional cycles. The addition and maintenance therapy with bevacizumab significantly improved the PFS (HR = 0.81; $P < 0.004$); however, this benefit did not translate into an improvement in OS. Further exploratory analysis revealed that the high-risk subgroup with stage IV disease or inoperable/sub-optimally debulked (> 1 cm) stage III disease benefited the most from concomitant bevacizumab treatment, with a significant improvement in median OS (39.7 *vs.* 30.2 months; $P = 0.03$). It is worth mentioning that when the ICON7 high-risk definition was applied to the GOG-0218 cohort, no benefit in OS was observed in the respective GOG-0218 subgroup. However, it already has been established that the GOG-0218 stage IV subgroup alone did receive a meaningful benefit in OS compare to the control arm [HR = 0.72; 95% confidence interval (CI): 0.53–0.97] [15]. Bevacizumab was generally well-tolerated by patients in both trials, despite specific toxicities (hypertension, gastrointestinal perforation, thrombo embolism, etc.) and a slight reduction in health-related quality of life (HRQoL) [16].

Based on these seminal trials, bevacizumab was approved as first-line treatment in combination with standard chemotherapy, and as maintenance therapy for patients with advanced-stage ovarian cancer (IIIB, IIIC, and IV), by both the European Medicines Agency (EMA) and FDA in 2011 and 2018 respectively. Further, real-world observational studies, including the ROBOT and JGOG3022 trials, have validated its efficacy and safety in a clinical setting [17–18].

In addition, there is substantial clinical evidence that bevacizumab demonstrates efficacy in relapsed ovarian cancer. The OCEANS and GOG-0213 trials recruited platinum-sensitive patients with recurrent disease [19–20]. Both studies demonstrated a significantly prolonged PFS when patients were treated with a combination of chemotherapy and bevacizumab, compared to standard chemotherapy alone. The AURELIA trial was the first to explore the efficacy of bevacizumab in combination with chemotherapy in patients with platinum-resistant recurrent ovarian cancer. In this trial, 361 patients were randomly assigned to two arms: (1) a group receiving single-agent chemotherapy; and (2) a group receiving single-agent chemotherapy plus bevacizumab. The addition of bevacizumab significantly improved PFS (6.7 *vs.* 3.4 months; HR = 0.48; $P < 0.001$) and ORR (11.8% *vs.* 27.3%; $P = 0.001$). The trend in OS, however, was not significant (13.3 *vs.* 16.6 months, HR = 0.85; $P < 0.174$) [21].

Bevacizumab's optimal treatment dosage, timing, and duration, remain to be determined by additional pre-clinical and clinical studies [22]. Moreover, biomarkers associated with bevacizumab response and patient prognosis are currently being investigated, and warrant further validation [23].

Tyrosine kinase inhibitors (TKIs)

Tyrosine kinases play a pivotal role in many biological processes, including angiogenesis, cell proliferation, and cell cycle [24–25]. TKIs prevent kinases from catalyzing the phosphorylation of tyrosine residues on their substrates, thereby blocking the activation of downstream signaling

pathways [25].

Sorafenib

Sorafenib is an oral TKI originally developed as a Raf inhibitor that has since shown affinity for various kinases, including VEGFR2 and VEGFR3 [26]. A multicenter phase II trial investigated the efficacy and tolerability of sorafenib in patients with recurrent or persistent ovarian cancer. The 71 patients received sorafenib 400 mg orally twice per day, revealing that sorafenib yielded modest benefits at the cost of substantial toxicity [27]. The TRIAS study enrolled 174 platinum-resistant ovarian cancer patients, previously treated with two or fewer chemotherapy lines. Patients were randomized on a 1:1 basis to receive: (1) topotecan in combination with sorafenib; or (2) topotecan plus placebo; a significant improvement in both PFS (6.7 *vs.* 4.4 months; HR = 0.60; P = 0.0018) and OS (17.4 *vs.* 10 months; HR = 0.65; P = 0.017) were observed in the sorafenib combination arm [28].

Pazopanib

Pazopanib is a TKI targeting VEGFR, platelet-derived growth factor receptor (PDGFR), c-kit, and c-fms [29]. Pazopanib is poorly tolerated when combined with cytotoxic therapy. Yet, in the AGO-OVAR 16 study, a phase III clinical trial of 940 stage II–IV patients, pazopanib significantly improved PFS when used as first-line maintenance therapy following chemotherapy (17.9 *vs.* 12.3 months; HR = 0.77; P = 0.021); no significant difference in OS was observed, however [30]. MITO 11, another randomized, non-blinded, phase II trial, demonstrated that weekly therapy with pazopanib in combination with paclitaxel significantly prolonged PFS in patients with platinum-resistant or refractory advanced ovarian cancer (6.35 *vs.* 33.49 months; HR = 0.42; P = 0.0002) [31]. The trade-off between pazopanib's modest efficacy and adverse effects warrant further investigation. Of note, the 2019 NCCN guidelines no longer recommended pazopanib as first-line maintenance therapy; however, its use is still recommended in the recurrent ovarian cancer setting.

Nintedanib

Nintedanib is an oral TKI targeting VEGFR, PDGFR, and fibroblast growth factor receptor (FGFR) [32], and its efficacy in the first-line ovarian cancer setting was investigated by the AGO-OVAR12 study. The 1366 postoperative chemotherapy-naive patients with stage IIB–IV ovarian cancer were randomized to receive standard chemotherapy in combination with either nintedanib or placebo, followed by maintenance treatment with each agent. The results indicated that the nintedanib combination approach significantly prolonged PFS from 16.6 to 17.3 months (HR = 0.84; P = 0.0239) [33]. Surprisingly, the low-risk subgroup benefited the most from nintedanib combination, which contradicted findings of trials evaluating other TKIs; therefore, these results warrant further investigation. In the latest results reported by the AGO-OVAR12 trial, PFS improvement appeared consistent, although it did not translate into OS benefit [34].

Cediranib

Cediranib is a highly potent VEGFR inhibitor, exerting similar inhibitory activity to PDGFR and c-kit [35]. The ICON-6 trial investigated the efficacy of cediranib in patients with platinum-sensitive recurrent ovarian cancer. Four hundred fifty-six patients were randomized to receive either of the following: (1) chemotherapy in combination with placebo, followed by placebo maintenance; (2) chemotherapy in combination with cediranib, followed by placebo maintenance; and (3) chemotherapy in combination with cediranib, followed by cediranib maintenance. PFS in the above groups was 8.7, 9.9, and 11 months, respectively. However, increased adverse reactions during cediranib maintenance therapy may reduce patient compliance [36]. Of note, the ICON-6 data released at the 2013 European Society of Medical Oncology (ESMO) annual meeting demonstrating a significant improvement in PFS and OS (20.3% *vs.* 17.6%; HR = 0.70; P = 0.0419), were the first data reporting an OS benefit as a result of combining chemotherapy with anti-angiogenic agents.

Angiopoietin axis inhibitor

Trebananib is a newly developed peptibody that neutralizes both Ang1 and Ang2 through interaction with the Tie2 receptor, thereby inhibiting endothelial sprouting, and decreasing blood vessel density and vascular permeability [37–38].

TRINOVA-3 is a randomized placebo-controlled phase III clinical trial investigating trebananib in combination with single-agent weekly paclitaxel in patients with recurrent ovarian cancer. One thousand fifteen patients were selected and randomized to receive either of the following: (1) 6 cycles of paclitaxel and carboplatin plus weekly trebananib, followed by trebananib maintenance for up to 18 additional months; and (2) 6 cycles of paclitaxel and carboplatin plus weekly trebananib, and placebo maintenance. Unfortunately, no significant benefit in PFS was observed in TRINOVA-3, thereby diminishing the utility of trebananib in first line management of ovarian cancer [39].

The TRINOVA-1 trial assessed the addition of trebananib to single-agent weekly paclitaxel in patients with recurrent ovarian cancer. In this setting, median PFS was significantly prolonged in the trebananib group compared toplacebo (7.2 *vs.* 5.4 months; HR = 0.66; P < 0.0001) [40]. A later study evaluating HRQoL in TRINOVA-1, reported that the improvement in PFS in the trebananib arm did not significantly compromise patients' HRQoL [41]. However, the clinical applications of

trebananib require further investigation.

Poly-(ADP)-ribose polymerase (PARP) inhibitors

The advent of PARP inhibitors has fundamentally transformed the clinical management of patients with ovarian cancer carrying mutationsin the *BRCA1/2* genes. DNA single-strand breaks (SSBs) are common DNA damage events [42]; PARP recognizes and orchestrates the repair of SSBs, thereby maintaining DNA stability [43]. PARP inhibition leads to persistent unresolved SSBs, which during DNA replication give rise to stalled replication forks and subsequent accumulation of double-strand breaks (DSBs). Cells with homologous recombination deficiency (HRD), such as *BRCA1/2*-mutant cells, cannot efficiently repair these DSBs, thus giving rise to the "synthetic lethality" phenotype [44].

Olaparib

Olaparib was the first PARP inhibitor introduced in the clinical setting by the FDA in 2014 and has since transformed the landscape of ovarian cancer treatment [45].

The SOLO-1 trial compared olaparib maintenance treatment to placebo in a front-line setting, among newly diagnosed patients with *BRCA1/2* mutations (388 patients with germline mutations, and 2 with somaticmutations). A total of 391 International Federation of Gynecology and Obstetrics (FIGO) stage III or IV patients who previously achieved complete or partial response to platinum-based chemotherapy were randomly assigned to receive olaparib 300 mg twice a day or placebo tablets as maintenance therapy until disease progression. When the median follow-up duration reached 40.7 months, 60% of the patients in the olaparib arm achieved the primary endpoint of PFS, compared to 27% in the placebo arm (HR = 0.3; $P < 0.001$) [46]. In the latest 5-year follow-up of the SOLO-1 study, the PFS benefit was sustained (56 *vs.* 13.8 months; HR = 0.33) beyond the end of treatment, with an extension of median progression-free survival past 4.5 years [47]. Based on the robust SOLO-1 data, the FDA and EMA have approved olaparib as a new standard of care.

The SOLO-1 trial excluded patients receiving bevacizumab-containing therapy. These patients were explored by the PAOLA-1 study, which included bevacizumab in both treatment arms. Eight hundred and six newly diagnosed ovarian cancer patients who responded to first-line platinum-taxane chemotherapy plus bevacizumab were eligible for inclusion, regardless of surgical outcome and *BRCA* status. At a median follow-up of 22.9 months, the addition of olaparib yielded a 5.5 months PFS benefit (22.1 *vs.* 16.6 months; HR = 0.59; $P < 0.0001$). Subgroup analysis revealed that patients with HRD tumors demonstrated a robust prolonged PFS (37.2 *vs.* 17.7 months; HR = 0.33). The disease progression or death hazard ratio was 0.43 in patients with *BRCA* wild-type and HRD-positive tumors (PFS 28.1 *vs.* 16.6 months) [48]. The results of the PAOLA-1 trial prompted the FDA to approve olaparib in combination with bevacizumab as first-line maintenance for HRD-positive ovarian cancer patients.

Pivotal clinical trials of olaparib in the setting of relapsed ovarian cancer include Study 19, SOLO-2, and SOLO-3. Study 19 is an international randomized phase II trial that enrolled 265 patients with recurrent ovarian cancer and unselected *BRCA* status. Participants were treated with either olaparib or placebo, and the trial met the primary endpoint of PFS (8.4 *vs.* 4.8 months; HR = 0.35; $P < 0.001$). In apre-planned retrospective analysis, the *BRCA* mutation sub-group in the olaparib arm showed substantially improved PFS (11.2 *vs.* 4.3 months; HR = 0.18; $P < 0.0001$). Interestingly, the non-*BRCA* mutation subgroup also obtained a significant benefit in PFS (7.4 *vs.* 5.5 months; HR = 0.54; $P = 0.0075$), albeit less pronounced [49]. As a landmark trial, the encouraging data from Study 19 led to EMA approval of olaparib for maintenance therapy in a recurrent setting, regardless of *BRCA* status. The SOLO-2 trial prospectively evaluated the efficacy of olaparib in patients with *BRCA* mutations. The 295 patients with recurrent disease were randomized to receive olaparib or placebo, and olaparib maintenance was associated with significantly prolonged PFS (19.1 *vs.* 5.5%; HR = 0.30; $P < 0.0001$) [50]. The SOLO-3 study was the first phase III trial evaluating the efficacy and safety of olaparib monotherapy compared to chemotherapy, in patients with germline *BRCA* mutations. The SOLO-3 olaparib arm achieved a significantly higher BICR-assessed ORR compared to the standard chemotherapy arm (72.2% *vs.* 51.4%, OR = 2.53; $P = 0.002$); BICR-assessed PFS also favored the olaparib arm (13.4 *vs.* 9.2 months, HR = 0.62; $P = 0.013$). In a sub-group analysis, patients who had received two prior lines of treatment seemed to benefit the most, with an OR of 3.44 [51].

Niraparib

Niraparib is a potent selective inhibitor of the PARP1/2 nuclear proteins [52]. The efficacy and safety of niraparib were examined in the QUADRA study, a single-arm phase II trial. The 463 patients were enrolled and stratified according to their HRD and germline *BRCA* mutation status tests. The trial met its primary endpoint, resulting in an ORR of 29% among HRD-positive subpopulations, 39% among platinum-sensitive *BRCA*-positive patients, and 27% among platinum-resistant *BRCA*-positive patients. Hematological toxicity was the most common drug-related adverse event, and was effectively managed

by dose modification [53].

The NOVA study explored the role of niraparib maintenance therapy in relapsed, platinum-sensitive ovarian cancer. In this randomized phase III trial, 553 patients with high-grade serous, platinum-sensitive ovarian cancer were categorized based on their *BRCA* mutation status in two cohorts, gBRCA and non-gBRCA. Homologous recombination capacity was tested in 345 non-gBRCA-mutated patients to identify the HRD subpopulation of ovarian cancers. There was a significant improvement in PFS regardless of gBRCA and HRD status, including 21.0 vs. 5.5 months in the gBRCA cohort (HR = 0.27); 12.9 *vs.* 3.8 months in the non-gBRCA HRD cohort (HR = 0.38); and 9.3 vs. 3.9 months in the HR proficient cohort (HR = 0.45) [54].

The satisfactory outcomes of NOVA prompted the investigation of niraparib in a front-line setting. The PRIMA study is a double-blinded, randomized phase III trial investigating the efficacy of niraparib monotherapy as maintenance therapy in newly diagnosed ovarian cancer. Seven hundred thirty-three patients were classified based on their HRD status, and randomized to receive maintenance therapy with either niraparib or placebo. The overall population achieved a modest benefit in median PFS (13.8 *vs.* 8.2 months, HR = 0.62; $P < 0.0001$), which was more pronounced among patients with HRD tumors (21.9 *vs.* 10.4 months; HR = 0.43; $P < 0.001$) [55]. The PRIMA results were concordant with the results obtained from the NOVA trial.

Rucaparib

Rucaparib is another oral, small-molecule inhibitor of PARP1/2/3, approved by the FDA for clinical applications [56]. Its approval was mainly based on two open-label, multicenter, single-arm clinical trials. The ARIEL 2 study, which is comprised of two parts, is a multicenter phase II trial investigating the effectiveness of rucaparib in pretreated ovarian cancer patients. Part 1 of ARIEL 2 included 204 patients previously treated with ≥ 1 line of chemotherapy, while Part 2 included patients previously treated with 3 or 4 lines. The findings of Part 1 indicated that HR-related gene status could determine responders to PARP inhibitors regardless of *BRCA* status. The *BRCA*-mutated subgroup had the longest PFS (12.8 months; HR = 0.27, $P < 0.0001$), followed by the *BRCA* wild-type and loss of heterozygosity (LOH) high subgroup (5.7 months; HR = 0.62, $P = 0.011$); the *BRCA* wild-type and LOH low subgroup had a PFS of 5.2 months [57]. Results of the ARIEL 2 Part 2 are still pending. In the latest analysis of data derived by both parts of ARIEL 2, it was reported that RAD51C and RAD51D status correlated with meaningful clinical activity of rucaparib, similar to that of *BRCA* status in high-grade ovarian cancer [58].

Rucaparib was also evaluated in the Study 10 trial, which consisted of three parts: part 1 established the recommended dose of rucaparib in a dose dependent manner; part 2A enrolled 42 pretreated platinum-sensitive patients with a germline *BRCA* mutation, investigated ORR based on RECIST, and reached an ORR at 60%; part 2B enrolled 40 patients previously treated with 3 or 4 lines of chemotherapy. Part 2B results of Study 10, however, are still pending [59].

The ARIEL 3 study provided further evidence that rucaparib could be used as standard of care for patients with ovarian cancer, in a second- or later-line maintenance setting. This randomized multicenter phase 3 trial recruited 564 patients with platinum-sensitive disease who had previously received ≥ 2 platinum-based chemotherapy regimens. The overall population was divided into the following three nested cohorts for subgroup analysis: (1) patients with *BRCA* mutations; (2) patients with HRD disease; and (3) the intention-to-treat population. The biomarkers established by the ARIEL 2 study were employed in the interpretation of data obtained from ARIEL 3. The median PFS for *BRCA*-mutated patients was 16.6 months in the rucaparib arm, compared to 5.4 months in the placebo arm (HR = 0.23; $P < 0.0001$). For the HRD cohort, median PFS was 13.6 *vs.* 5.4 months (HR = 0.32; $P < 0.0001$). The intention-to-treat cohort reached a PFS of 10.8 months versus 5.4 months (HR = 0.36; $P < 0.0001$). Thus, rucaparib monotherapy in the second- or later-line maintenance achieved significant improvement in PFS across all three sub-groups [60]. The currently ongoing ARIEL 3 trial compares rucaparib with standard chemotherapy for relapsed ovarian cancer patients with *BRCA* mutations who were previously treated with ≥ 2 lines of chemotherapy regimens [61].

Immune checkpoint inhibitors (ICIs)

ICIs have profoundly enriched and revolutionized the treatment landscape of various cancers. By releasing inhibitory brakes present on T cells, ICIs induce a robust antitumor effect by harnessing both the innate and adaptive arms of the human immunesystem [62]. Unfortunately, not all tumor types and patients respond to ICIs, and even patients that initially respond can develop acquired resistance. FDA-approved ICIs can be classified into three categories based on their target: monoclonal antibodies targeting the cytotoxic T lymphocyte-associated protein 4 (CTLA-4), monoclonal antibodies targeting the programmed cell death protein 1 (PD-1), and monoclonal antibodies targeting the programmed cell death one ligand 1 (PD-L1). To date, the efficacy of ICIs as single agents in preclinical studies and clinical trials of ovarian cancer remains poor. This is mainly due to the immunosuppressive microenvironment of ovarian cancer. Nonetheless, conventional chemotherapies can

stimulate anticancer immunity, leading to the possibility that synergistic combinatorial regimens may potentially enhance the effectiveness of ICIs monotherapy [63]. ICIs entering Phase III clinical trials include nivolumab, avelumab, and atezolizumab.

The NINJA study is a multicenter randomized phase III study, investigating the efficacy and safety of nivolumab against chemotherapy in platinum-resistant ovarian cancer patients in Japan. Three hundred sixteen patients were randomly assigned to receive either nivolumab or gemcitabine/pegylated liposomal doxorubicin (PLD). Unfortunately, the study failed its primary endpoint, observing no significant difference between the two arms (HR = 1.0, $P = 0.808$); in fact, median PFS was longer in the gemcitabine/PLDNINJA arm (2.0 *versus* 3.8 months; HR = 1.5; $P = 0.002$) [64].

JAVELIN 200 is a multicenter three-arm randomized phase III trial. A total of 566 platinum-resistant or -refractory patients were randomized to receive (1) avelumab monotherapy; (2) avelumab in combination with PLD; and (3) PLD monotherapy. The median OS for the above three groups was 11.8, 15.7, and 13.1 months, respectively, and the median PFS 1.9, 3.7, and 3.5 months, respectively. Neither avelumab monotherapy nor combination therapy significantly prolonged PFS or OS compared to PLD. This outcome suggests that proper patient selection is necessary in future studies [65].

IMagyn050 is a multicenter placebo-controlled phase III trial, investigating the addition of atezolizumab to standard chemotherapy and bevacizumab as first-line treatment for advanced ovarian cancer. The 1301 patients were randomized to receive atezolizumab combined with standard chemotherapy plus bevacizumab, or placebo with standard chemotherapy plus bevacizumab. The median PFS in the intention-to-treat subpopulation was 19.5 versus 18.4 months respectively (HR = 0.92; stratified log-rank $P = 0.28$). In the PD-L1 positive subpopulation, PFS was 20.8 versus 18.5 months (HR = 0.80; $P = 0.038$). This limited benefit in PFS did not translate into a statistically significant extension in OS [65].

Summary

The molecular targeted therapies introduced in this article are gradually creating a paradigm shift in the clinical management of ovarian cancer. While some have demonstrated great success in both preclinical and clinical settings, others warrant further validation and investigation. Exploring biomarkers that can predict prognosis and response, selecting patient populations more likely to benefit from particular treatments, and designing rational drug combinations and optimal dosages, are of paramount importance and should be a priority. In this review, we underline critical studies on targeted therapies for the treatment of ovarian cancer. We anticipate that ample evidence addressing the aforementioned issues will be reported by currently ongoing and future studies and trials.

Acknowledgments

Not applicable.

Funding

Not applicable.

Conflicts of interest

The authors indicated no potential conflicts of interest.

Author contributions

All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version of this manuscript.

Data availability statement

Not applicable.

Ethical approval

Not applicable.

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DOI 10.1007/s10330-022-0557-7
Cite this article as: Qin TY, Chen G. Recent advances in targeted therapy for ovarian cancer. Oncol Transl Med. 2022;8(1):28-35.