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# Systemic therapy de-escalation in advanced ovarian cancer: a new era on the horizon?

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## ABSTRACT

Poly(ADP-ribose) polymerase inhibitors (PARPi) have sculpted the current landscape of advanced ovarian cancer treatment. With the advent of targeted maintenance therapies, improved survival rates have led to a timely interest in exploring de-intensified strategies with the goal of improving quality of life without compromising oncologic outcomes. The emerging concept of systemic treatment de-escalation would represent a new frontier in personalizing therapy in ovarian cancer. PARPi are so effective that properly selected patients treated with these agents might require less chemotherapy to achieve the same oncologic outcomes. The fundamental key is to limit de-escalation to a narrow subpopulation with favorable prognostic factors, such as patients with *BRCA*-mutated and/or homologous recombination-deficient tumors without macroscopic residual disease after surgery or other high-risk clinical factors. Potential de-escalation strategies include shifting PARPi in the neoadjuvant setting, de-escalating adjuvant chemotherapy after primary debulking surgery, reducing PARPi maintenance therapy duration, starting PARPi directly after interval debulking surgery, omitting maintenance therapy, and continuing PARPi beyond oligoprogression (if combined with locoregional treatment). Several ongoing trials are currently investigating the feasibility and safety of de-escalating approaches in ovarian cancer and the results are eagerly awaited. This review aims to discuss the current trends, drawbacks, and future perspectives regarding systemic treatment de-escalation in advanced ovarian cancer.

## BACKGROUND



Finding the optimal balance between treatment efficacy and side effects is a key strategic principle in oncology therapeutics. This is critical as the maximum tolerated therapy criterion has become obsolete and has been replaced by the principles of minimum effective dose and personalized treatment. There is an emerging need to focus not only on areas of escalation, where new treatments and cocktail strategies are leveraged to increase overall efficacy, but also on de-escalation, where optimal care can be achieved with less treatment. In the era of precision medicine, de-escalation of cytotoxic treatments in favor of biomarker-driven individualized therapies is of paramount importance. De-escalation of cancer treatment aims to reduce the intensity and/or duration of treatment without compromising survival, thereby improving quality

of life. More treatment is not always better; less, if targeted and right, could be more. Indeed, an even better term for ‘de-escalation of treatment’ might be ‘optimization of treatment’.

The introduction of poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) marked a new era in the treatment of advanced ovarian cancer, resulting in unprecedented survival rates that significantly improved the prognosis of patients after several years of disappointing trials in this field.<sup>1</sup> Figure 1 provides an overview of the current indications for PARPi maintenance therapy in the upfront and recurrent settings. PARPi have now become the new standard of care in the primary maintenance treatment of ovarian cancer. Nevertheless, the PARPi landscape continues to evolve and there are many unanswered questions and potential future opportunities that need to be further explored. The increased overall survival associated with PARPi underscores a potential role for de-escalated treatment paradigms that minimize the toxicity burden while maintaining oncologic control in a narrow subset of selected patients.<sup>2</sup> While patients with homologous recombination-proficient tumors and an unfavorable response to platinum would potentially benefit from escalated approaches with PARPi combination regimens (eg, with anti-angiogenics, PI3K inhibitors, ATR inhibitors, WEE1 inhibitors, immune checkpoint inhibitors), properly selected patients with *BRCA*-mutated and/or homologous recombination-deficient tumors may be candidates for de-escalated approaches.

De-escalation of treatment is not a new concept in cancer care. Following the lead of pediatric oncologists who pioneered the de-escalation of treatment for highly curable childhood malignancies, examples of de-escalation treatment for selected adult patients with solid tumors, especially breast cancer, have gradually emerged with the goal of achieving little or no loss in long-term survival rates with gains in quality of life.<sup>3–5</sup> Based on multiple attempts at de-escalation in cancer research, gynecologic oncologists and medical oncologists have begun to wonder whether de-escalating approaches might be feasible for selected ovarian cancer patients. This review aims to critically discuss the current trends, challenges and future directions concerning systemic treatment de-escalation in advanced ovarian cancer.

## Review

	Olaparib		Niraparib	Rucaparib
<b>UPFRONT</b>				
<b>Shared prerequisites</b>	<ul style="list-style-type: none"> <li>Advanced stage (FIGO III-IV), epithelial</li> <li>High-grade disease (serous or endometrioid)</li> <li>Response (complete or partial) to platinum-based CHT</li> </ul>			
<b>Pivotal trial(s)</b>	SOLO1	PAOLA1 (combined with bevacizumab)	PRIMA and PRIME	ATHENA-MONO
<b>Mutational status</b>	g/sBRCAm	g/sBRCAm* and/or HRD * In some countries, not reimbursed in combination with bevacizumab for g/sBRCAm	All-comers* * In some countries, not reimbursed for stage III with R0 after PDS	All-comers (not licensed)
<b>Duration</b> (if no unacceptable toxicity or progression)	2 years	Olaparib: 2 years Bevacizumab: 15 months	3 years	2 years
<b>RECURRENCE</b>				
<b>Shared prerequisites</b>	<ul style="list-style-type: none"> <li>Platinum-eligible disease (PFI ≥ 6 months)</li> <li>Response (complete or partial) to platinum-based CHT</li> </ul>			
<b>Pivotal trial(s)</b>	SOLO2		NOVA and NORA	ARIEL3
<b>Mutational status</b>	All-comers* *In some countries, reimbursed only for g/sBRCAm		EMA  Regardless of BRCA status	FDA  gBRCAm
<b>Duration</b>	Upon unacceptable toxicity or further progression			

**Figure 1** Overview of the current indications for PARPi maintenance therapy in ovarian cancer. BRCA, BReast CAncer genes; CHT, chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; FIGO, International Federation of Gynecology and Obstetrics; gBRCA, germline BRCA mutation; HRD, homologous recombination deficiency; PARPi, poly(ADP-ribose) polymerase inhibitors; PDS, primary debulking surgery; PFI, platinum-free interval; R0, no gross residual tumor after surgery; sBRCA, somatic BRCA mutation.

### POTENTIAL DE-ESCALATION STRATEGIES IN THE FIRST-LINE

There is a strong rationale for de-escalating systemic treatment in the first-line setting of ovarian cancer. PARPi are so effective, especially in patients with *BRCA*-mutated and/or homologous recombination-deficient tumors, that selected patients treated with these agents may require less chemotherapy to achieve the same effect. However, attempting to de-escalate chemotherapy is challenging and appropriate selection criteria are essential to avoid undertreatment. Key requirements for this opportunity in ovarian cancer include: (1) the reliability of *BRCA* gene mutations and homologous recombination deficiency as positive predictive biomarkers of PARPi efficacy; (2) the absence of high-risk clinical factors, such as macroscopic residual disease after surgery.

Theoretically, five different strategies can be attempted to de-escalate systemic therapy (figure 2):

- ▶ **Shifting PARPi in the neoadjuvant setting:** Using PARPi as a neoadjuvant treatment in lieu of chemotherapy or with reduced chemotherapy.
- ▶ **De-escalating adjuvant chemotherapy after primary debulking surgery:** Reducing the number of cycles of adjuvant chemotherapy after primary debulking surgery, before starting PARPi maintenance therapy.
- ▶ **Reducing PARPi maintenance therapy duration:** Discontinuing PARPi before the two (olaparib and rucaparib) or three (niraparib) years currently planned for first-line maintenance therapy.
- ▶ **Starting PARPi directly after interval debulking surgery:** Limiting the use of chemotherapy to the neoadjuvant setting

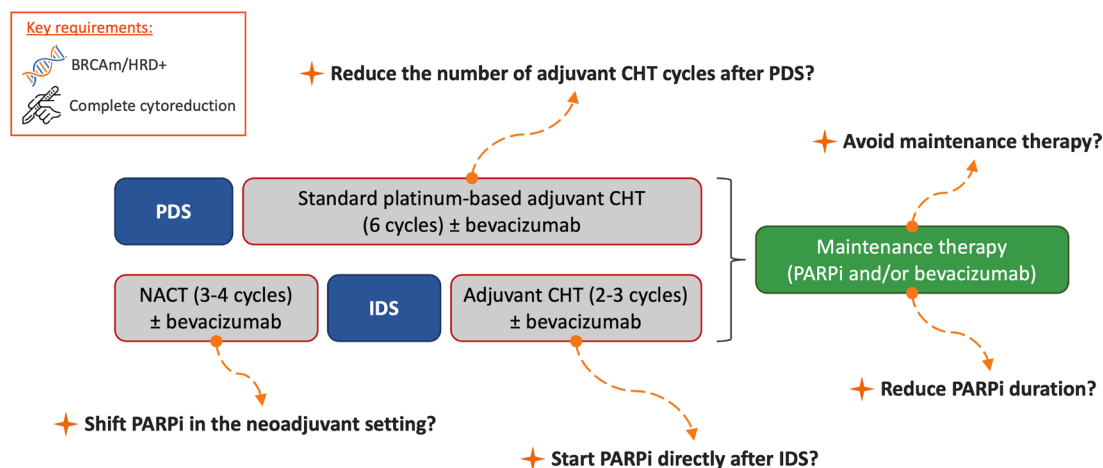
in patients triaged to neoadjuvant chemotherapy and then starting PARPi immediately after interval debulking surgery.

- ▶ **Omitting maintenance therapy:** Avoiding maintenance treatment with PARPi and/or bevacizumab after chemotherapy in carefully selected patients with favorable prognostic factors.

Several clinical trials are currently investigating the feasibility and safety of tailored de-escalation approaches for the primary treatment of ovarian cancer. Extreme caution should be exercised when attempting to reduce or even replace chemotherapy in the definitive treatment of ovarian cancer patients, even when using effective targeted therapies. It is unlikely that chemotherapy-free strategies using PARPi will completely replace the carboplatin-paclitaxel milestone in the primary setting. However, there is room to explore chemotherapy de-escalation strategies for selected patients to personalize patient care, reduce unnecessary toxicity, improve quality of life, and optimize outcomes.

### Shifting PARPi in the Neoadjuvant Setting

Much has changed since the introduction of PARPi in the treatment of ovarian cancer. Early PARPi clinical trials focused on the recurrent setting and led to Food and Drug Administration (FDA) approval of PARPi first as a single-agent treatment for patients with *BRCA*-mutated, platinum-sensitive disease and then as maintenance therapy following platinum-based chemotherapy. Maintenance with PARPi has become the standard of care in the first-line treatment of patients with *BRCA*-mutated and/or homologous recombination-deficient ovarian cancer, while updated survival data in the recurrent setting prompted the withdrawal of the PARPi indication as



**Figure 2** Potential systemic therapy de-escalation strategies in selected patients with advanced ovarian cancer. BRCA, BRCA1/2; CHT, chemotherapy; HRD, homologous recombination deficiency; IDS, interval debulking surgery; PARPi, poly(ADP-ribose) polymerase inhibitors; PDS, primary debulking surgery.

single-agent therapy and warranted caution in using PARPi maintenance in unselected (*BRCA* wild-type) patients.<sup>6</sup> Overall, these data underline that the earlier PARPi are used, the better their efficacy and benefit-risk profile, raising interesting questions about their potential use even earlier, in the neoadjuvant setting. The rationale is compelling: to deliver a targeted therapy as early as possible in a biomarker-selected population, given that the first-line setting is the optimal setting to achieve a potential cure. Nevertheless, along with the appealing benefits, there are potential drawbacks that need to be addressed.

#### Potential Advantages

The use of PARPi in the neoadjuvant setting could potentially lead to several advantages:

1. De-escalate (or even omit?) chemotherapy.
2. Optimize neoadjuvant treatment. Since the mortality rate for patients with newly diagnosed advanced ovarian cancer remains high despite advances in treatment, and since the alternative approach of interval debulking surgery has gradually gained acceptance in routine practice, there is an unmet need to optimize neoadjuvant therapy. The use of PARPi in the neoadjuvant setting may yield promising results.
3. Overcome cross-resistance to PARPi. The use of PARPi prior to platinum exposure would be better tolerated and avoid potential cross-resistance mechanisms, thus providing full activity as targeted treatments. Indeed, PARPi and platinum agents share complementary mechanisms of action that are critically dependent on the DNA Damage Repair (DDR) response, and cross-resistance mechanisms between these two therapeutic classes have been well documented in both preclinical and clinical settings.<sup>7,8</sup>
4. Improve patient performance status prior to surgery by avoiding or minimizing chemotherapy-induced toxicity.
5. Flexibility in scheduling. PARPi treatment can be easily extended or discontinued without the need to reschedule day hospital access as with chemotherapy, and this would facilitate possible adjustments of neoadjuvant treatment related to hospital organizational logistics.

#### Potential Drawbacks

1. Cross-resistance to subsequent platinum. The other side of the coin is that the use of upfront PARPi may induce resistance to platinum agents. There is solid preclinical and clinical evidence that PARPi can reduce subsequent response to platinum through cross-resistance mechanisms.<sup>9-11</sup> A post hoc analysis of the SOLO2 trial showed that among *BRCA*-mutated patients who received platinum-based chemotherapy as their first subsequent treatment after progression, the time to second progression was significantly longer in the placebo arm compared with the olaparib arm (14.3 vs 7.0 months).<sup>9</sup> Similar real-world data from the MITO group<sup>10</sup> and a large multicenter series by Romeo *et al*<sup>11</sup> demonstrated lower objective response rates to platinum after PARPi in the cohort of *BRCA*-mutated patients. Although these data derive from the recurrent setting and therefore refer to patients who could be heavily pretreated, it seems reasonable that the same may apply to the first-line setting. Ultimately, the potential negative impact on first-line adjuvant platinum-based chemotherapy should be carefully considered.
2. Long-term risk of myeloid neoplasms. With the progressive use of PARPi as maintenance treatment for patients with ovarian cancer, secondary myeloid neoplasms are gradually emerging as delayed and life-threatening toxicities. It is unlikely that PARPi alone are responsible for this increasing incidence; instead, multiple risk factors seem to play a pivotal role, including genetic predisposition and the synergistic interaction between PARPi and cumulative platinum exposure.<sup>12</sup> In this context, the impact of using PARPi in the neoadjuvant setting, in addition to adjuvant maintenance therapy, needs to be clarified.

#### Ongoing Clinical Trials

Six early phase trials are currently exploring the feasibility and efficacy of PARPi in the neoadjuvant setting (table 1). Four trials are using olaparib (NOW, OPALem, NUVOLA, IMPACT) and two are using niraparib (NANT, OPAL-C). The NUVOLA and IMPACT trials are not investigating a de-escalation approach per se, but are included in this discussion because they may still provide useful data on the use of PARPi in the neoadjuvant setting. There is wide heterogeneity

## Review

**Table 1** Ongoing clinical trials investigating the use of PARPi for systemic therapy de-escalation strategies in ovarian cancer

Trial (NCT identifier)	Design	PARPi	Adjuvant therapy	Biomarker status	Primary endpoints	Estimated enrollment	Status
Upfront: neoadjuvant							
NOW (NCT03943173)	Monocenter, single-arm, phase I	Olaparib 300 mg orally twice daily for two 28-day cycles	Either surgery → CHT for up to four cycles or NACT for up to four cycles → surgery, followed by olaparib, at the physician's discretion	BRCA-mutated	Feasibility	17	Recruiting
OLAPem (NCT04417192)	Multicenter, single-arm, phase II	Olaparib 300 mg orally twice daily for two 21-day cycles ± pembrolizumab	NR	HRD	ORR	30	Active, not recruiting
NUVOLA (NCT04261465)	Multicenter, single-arm, phase II	Olaparib 300 mg orally twice daily for three consecutive days (D1-D3), every week for each cycle plus weekly carboplatin and paclitaxel for three cycles	Carboplatin and paclitaxel	BRCA-mutated	Pathological complete response	35	Unknown
IMPACT (NCT03378297)	Monocenter, single-arm, phase I, randomized window-of-opportunity study	Olaparib for 10–14 days	NR	NR	Changes in the expression of biomarkers	Olaparib: 32 Control: 16	Completed
NANT (NCT04507841)	Multicenter, single-arm, phase II	Niraparib 100–300 mg once daily	NR	HRD	ORR, R0 resection rate	53	Recruiting
OPAL-C (NCT03574779)	Multicenter, phase II, multicohort umbrella, randomized	Niraparib 100–300 mg once daily for three 21-day cycles vs standard of care plus one run-in cycle of carboplatin-paclitaxel during pre-screening	Up to three 21-day cycles of platinum-taxane doublet ± bevacizumab followed by niraparib ± bevacizumab	HRD	ORR	125	Recruiting
Upfront: adjuvant							
N-PLUS (NCT05460000)	Multicenter, phase III, randomized (1:1)	Niraparib 100–300 mg once daily following PDS with R0	Six cycles vs three cycles of carboplatin and paclitaxel	HRD	RFS	640	Recruiting
Recurrence (platinum-eligible)							
NEO (NCT02489006)	Multicenter, phase II, randomized	Olaparib 300 mg orally twice daily for six weeks (± two weeks) prior to surgery	Olaparib, 300 mg orally twice daily ± standard chemotherapy	All-comers	Difference in levels of PAR or PARP-1 before and after olaparib. Mutations in HR genes in germline tissue compared with tumor tissue.	71	Active, not recruiting
BRCA, BRCA1/2; CHT, chemotherapy; HR, homologous recombination; HRD, homologous recombination deficiency; NACT, neoadjuvant chemotherapy; NCT, National Clinical Trial identifier number; NR, not reported; ORR, overall response rate; PAR, poly(ADP-ribose); PARPi, poly(ADP-ribose) polymerase inhibitors; PDS, primary debulking surgery; R0, no gross residual tumor after surgery; RFS, recurrence-free survival.							

in the design of ongoing trials, particularly with regard to the duration of neoadjuvant PARPi treatment, the number of chemotherapy cycles, and the type and duration of adjuvant and maintenance therapies. Therefore, if the use of neoadjuvant PARPi treatment is confirmed to be feasible, future prospective studies with more rigorous designs will be required before this attractive indication can be implemented in clinical practice.

## Olaparib: NOW Trial

NOW (NCT03943173) is a single-institution, single-arm, open-label, phase I, pilot study assessing the feasibility of neoadjuvant

olaparib in lieu of chemotherapy in patients with newly diagnosed, high-grade, advanced ovarian, primary peritoneal, or fallopian tube cancer who are ineligible for upfront surgery and harbor a germline mutation in either the *BRCA1/2*, *RAD51C/D*, or *PALB2* genes. Patients received olaparib (300 mg orally twice daily) for two 28-day cycles, followed by interval debulking surgery and chemotherapy for up to four cycles, or vice versa, and then PARPi maintenance at the discretion of the treating physician. The primary objective was to determine the feasibility of olaparib window treatment in the neoadjuvant setting, defined as the absence of unacceptable

toxicity (dose interruption of more than two weeks or two dose reductions) or disease progression, with at least 80% of patients able to undergo surgery immediately after olaparib. Patients with disease progression or a response not amenable to surgery would receive chemotherapy with paclitaxel and carboplatin, followed by surgery (if feasible), additional chemotherapy and PARPi maintenance. Secondary endpoints included Response Evaluation Criteria In Solid Tumors (RECIST) response rate, proportion of patients able to undergo directly interval cytoreductive surgery, progression-free survival, complete pathologic response and toxicity. Notably, tumor tissue samples were collected before and after olaparib treatment for translational research purposes.

Exciting preliminary results from the NOW trial were recently presented at the Society of Gynecologic Oncology (SGO) 2023 Annual Meeting on Women's Cancer and demonstrated that neoadjuvant olaparib is feasible in aiding optimal resection in ovarian cancer patients with germline mutations.<sup>13</sup> A total of 64 patients were screened and 51 underwent genetic testing. Of these patients, 20 had a germline mutation and 15 received olaparib. The median age of the patients was 56 years (range, 44–88). Most patients had stage IIIC disease (60%), followed by IVA (20%) and IVB (20%). Treatment was feasible and all 15 patients were able to receive two cycles of olaparib without unacceptable toxicity or progression. The partial response rate was 53.8%, while 46.2% of patients had stable disease. The vast majority of patients underwent surgery immediately after olaparib administration (86.6%), one (6.7%) underwent interval surgery after chemotherapy, while one (6.7%) was ineligible for surgery even after receiving standard chemotherapy due to poor performance status. Surgical outcomes were impressive with only two cycles of olaparib. Indeed, neoadjuvant olaparib resulted in a 100% optimal resection rate (less than 1 cm of residual disease) and, notably, 85.7% of cases achieved no gross residual disease, with one patient showing complete pathological response. In terms of tumor markers, 93% of patients had a reduction in CA-125 levels and 73% of patients had a 75% decrease. With a median follow-up of 11.7 months (range, 2.0–32.2), the estimated 12-month progression-free survival rate was 81%. Regarding safety, neoadjuvant olaparib was well tolerated with only one patient requiring dose interruption and dose reduction due to grade 3 anemia. Although preliminary, these findings provide an encouraging template for how PARPi could be used earlier in the treatment continuum. In the future, we may be able to shift to fully targeted therapy in the upfront setting for advanced ovarian cancer patients with germline mutations. Definitive results together with a detailed translational analysis are highly anticipated.

#### Olaparib: OLAPem Trial

OLAPem (NCT04417192) is a multicenter, single-arm, open-label, phase II pilot study to address the efficacy and safety of preoperative olaparib with or without pembrolizumab in patients with untreated, advanced (International Federation of Gynecology and Obstetrics (FIGO) stage III–IV), high-grade (serous or endometrioid) and homologous recombination-deficient ovarian cancer. Patients in cohort 1 receive olaparib monotherapy (300 mg orally twice daily) for two 21-day cycles, while those in cohort 2 receive olaparib plus pembrolizumab (200 mg intravenously every three weeks) combination therapy. Details of the type of adjuvant chemotherapy given

after interval surgery are not available. The primary endpoint is overall response rate based on RECIST.

#### Olaparib: NUVOLA Trial

This is a multicenter, single-arm, open-label, phase II study (NCT04261465) evaluating the safety and efficacy of olaparib plus weekly carboplatin/paclitaxel in patients with *BRCA*-mutated, unresectable, advanced (FIGO stage III or IV), high-grade (serous or endometrioid) epithelial ovarian, fallopian tube, or primary peritoneal cancer. Preclinical data suggested that olaparib may enhance the efficacy of platinum-based chemotherapy and achieve a higher pathological response rate with an acceptable toxicity profile. Chemotherapy is administered weekly for three cycles. Olaparib (300 mg orally twice daily) is given intermittently for three consecutive days (D1–D3) every week for each cycle. Adjuvant chemotherapy consists of carboplatin plus paclitaxel at the investigator's discretion. The primary endpoint is complete pathological response after three cycles of neoadjuvant chemotherapy plus olaparib.

#### Olaparib: IMPACT Trial

IMPACT (NCT03378297) is a single-institution, single-arm, open-label, randomized, early phase 1, window-of-opportunity study of novel and repurposed therapeutic agents in patients with advanced (FIGO stage III–IV) high-grade serous ovarian cancer. Women who agree to participate and are triaged for primary cytoreduction following diagnostic laparoscopy receive a study agent for 10–14 days before tumor reduction surgery, starting on the day of laparoscopic surgery. Among the primary investigational agents being tested is the PARP inhibitor olaparib. Treatment is discontinued at the time of cytoreductive surgery. Controls receive neither study drug nor placebo as the study is unblinded. Following debulking surgery, all women receive standard chemotherapy with or without bevacizumab. For each drug, a specific biomarker will be selected and a characterization of the tumor tissue from each patient will be performed. Changes in the expression of the defined biomarkers represent the primary outcome parameters.

#### Niraparib: NANT Trial

This is a multicenter, single-arm, open-label, phase II study (NCT04507841) to evaluate the safety and efficacy of niraparib (100–300 mg orally once daily) monotherapy as neoadjuvant therapy in patients with homologous recombination-deficient, high-grade (serous or endometrioid) advanced (FIGO stage III or IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer who are considered unfit for complete debulking surgery based on imaging, clinical, and/or laparoscopic evaluation. Data on the type of adjuvant chemotherapy administered after interval surgery are not specified. Primary endpoints are complete resection rate and overall response rate after neoadjuvant treatment. Secondary endpoints include disease control rate, complete pathological response rate, progression-free survival, overall survival, quality of life, patient-reported outcome, rate of treatment interruption and termination, treatment-related adverse events, and overall response rate during niraparib maintenance.

#### Niraparib: OPAL-C trial

OPAL-C (NCT03574779) is a multicenter, multicohort, open-label, randomized, phase II trial comparing neoadjuvant niraparib to standard of care before interval debulking surgery in patients with

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homologous recombination-deficient, high-grade non-mucinous, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients receive one run-in cycle of carboplatin-paclitaxel chemotherapy during pre-screening (while awaiting the results of the homologous recombination deficiency test). They are then randomized to receive either three 21-day cycles of standard chemotherapy or three 21-day cycles of niraparib (100–300 mg orally once daily) prior to surgery, followed by up to three cycles of chemotherapy with or without bevacizumab, and then maintenance with niraparib with or without bevacizumab. The primary endpoint is overall response rate before interval debulking surgery as assessed by RECIST. Secondary endpoints include the number of participants with CA-125 progression, progression-free survival, overall survival, and time to first subsequent treatment.

### De-escalating Adjuvant Chemotherapy After Primary Debulking Surgery

Given the extraordinary efficacy of PARPi in selected patients with a favorable biomarker profile, it is reasonable to speculate that these patients could maintain their good prognosis with a reduced amount of adjuvant chemotherapy after complete primary cytoreduction. Platinum salts and taxanes can cause cumulative, dose-dependent, long-term sensory neurotoxicity, among other adverse events. Therefore, there is interest in assessing the non-inferior efficacy of de-escalated chemotherapy to reduce the risk of short- and long-term toxicity, and prospective research is ongoing.

#### Ongoing Clinical Trials: N-PLUS Trial

The N-PLUS trial (NCT05460000) is a multicenter, open-label, randomized, phase III, non-inferiority trial to assess whether the use of niraparib (100–300 mg once daily) maintenance after chemotherapy could allow clinicians to reduce the number of adjuvant chemotherapy cycles from six to three in patients with advanced, high-grade, homologous recombination-deficient ovarian cancer who have been optimally debulked at primary surgery (table 1). Patients are randomized 1:1 to receive either three (arm A) or six (arm B) cycles of carboplatin and paclitaxel followed by niraparib maintenance. The hypothesis is that recurrence-free survival in patients receiving three cycles of chemotherapy followed by niraparib will not be inferior to patients receiving six cycles of chemotherapy followed by niraparib. Secondary endpoints include overall survival, time to first subsequent treatment, time without symptoms of disease progression or treatment toxicity, time from randomization to the date of second objective disease progression or death, quality of life, safety and cost-effectiveness. Approximately 60 centers in five European countries will participate in this study to recruit 640 patients over 36 months. The results of this trial are eagerly awaited.

#### Future Perspectives

In this context, another interesting trial could be designed with olaparib for patients with *BRCA*-mutated tumors, who represent an even more selective subpopulation with a favorable prognosis. Moreover, in this case there would be no bias related to the potential fallibility of available homologous recombination deficiency tests and the risk of false-positive results.

An even more challenging and provocative question is the following: ‘Could chemotherapy even be omitted in the primary

setting?’ With increasing understanding of the exact types and locations of *BRCA* mutations and their predictive roles, could it be oncologically safe to use PARPi alone before and/or after surgery in selected patients? Some challenging attempts to use PARPi without chemotherapy are currently underway. In the preliminary results of the NOW trial, three patients were so enthusiastic about their response to neoadjuvant PARPi and complete cytoreduction that they declined adjuvant chemotherapy and instead switched to PARPi immediately after surgery. Larger studies are needed to determine if this is an effective and safe approach.

### Reducing PARPi Maintenance Therapy Duration

Another opportunity for de-escalation exists in the maintenance setting for properly selected patients who have completed primary therapy. First-line maintenance with PARPi is currently continued for two years (olaparib, rucaparib) or three years (niraparib) based on study design and results from randomized clinical trials.<sup>14–16</sup>

The rationale behind the temporal cut-off used in these trials, and subsequently adopted in regulatory approvals and reimbursement policies, is based on the concept that most patients with advanced ovarian cancer typically relapse within two to three years of diagnosis despite complete cytoreduction and primary systemic treatment. Therefore, maintenance therapy is aimed at reducing the risk of disease recurrence during this critical window. However, there is room for speculating that a shorter PARPi maintenance exposure may be sufficient for a selected subpopulation. Indeed, in each of the three single-agent phase III trials (SOLO1,<sup>14</sup> PRIMA,<sup>15</sup> ATHENA-MONO<sup>16</sup>), the event rate in the PARPi and placebo arms reached unity several months before the planned completion of PARPi therapy. In other words, the Kaplan-Meier survival curves of the PARPi and placebo arms, which initially split progressively, indicating an effective role of PARPi maintenance treatment, then achieve a fixed vertical gap and seem to flatten and become parallel lines. This suggests that the biggest benefit with PARPi maintenance is seen in the first 12–15 months, but then the difference between the treatment and control groups remains constant with almost the same probability of progression or death. Ultimately, the optimal duration of PARPi maintenance should probably be re-discussed and further investigated. Reducing the overall PARPi exposure would lower the risk of long-term toxicities such as myeloid neoplasms.

### Starting PARPi Directly After Interval Debulking Surgery

Neoadjuvant chemotherapy followed by interval debulking surgery has gradually become an alternative approach for patients with advanced-stage ovarian cancer for whom complete primary cytoreduction is not feasible. Another possible de-escalating strategy for ovarian cancer patients would be to give chemotherapy only in the neoadjuvant setting (standard three–four cycles) and then start PARPi immediately after interval debulking surgery without further cycles of adjuvant chemotherapy. Obviously, this concept is only a hypothesis and there are currently no data to support it. Nevertheless, this approach would not be new in cancer management, but would follow what is already done in other solid tumors, such as early-stage breast cancer, where – when neoadjuvant chemotherapy is given – surgery is performed at the end of chemotherapy and patients with hormone receptor-positive disease then receive hormone maintenance therapy without additional cycles of chemotherapy.<sup>17</sup> Platinum sensitivity, which is a prerequisite for starting

PARPi, would be assessed based on clinical and pathological response to neoadjuvant chemotherapy. In addition, as for PARPi therapy duration, the concept of starting PARPi within eight weeks (olaparib, rucaparib) or twelve weeks (niraparib) after the last dose of chemotherapy is based on the design of currently available randomized clinical trials, but further prospective evidence is warranted to shed more light on this potential de-escalating approach.

### Omitting Maintenance Therapy

The clinical efficacy of PARPi in ovarian cancer is well established, but much remains to be clarified. A major challenge will be to accurately distinguish those patients who would be long-term survivors regardless of PARPi maintenance therapy from those who would benefit from PARPi. The ability to avoid PARPi maintenance therapy in selected patients would reduce the risk of life-threatening toxicities such as myeloid neoplasms.

While 5–20% of patients with *BRCA*-mutated and homologous recombination-deficient tumors will progress within 6 months of starting PARPi, approximately 25% of patients with *BRCA*-mutated tumors have a good prognosis without the need for PARPi.<sup>14–16</sup> In addition, the PRIMA trial showed a 35% reduction in the risk of progression or death in patients with homologous recombination-proficient tumors who received niraparib, with approximately 10–15% achieving sustained long-term benefit.<sup>18</sup> This risk reduction was also confirmed in the PRIME<sup>19</sup> and ATHENA-MONO<sup>16</sup> trials, which used different homologous recombination deficiency tests and reported risk reductions of 59% and 35%, respectively, in the same setting. Collectively, these data underscore that simply categorizing tumors as *BRCA*-mutated, homologous recombination deficiency test-positive and homologous recombination deficiency test-negative is not sufficient and that a deeper insight into molecular details is imperative. First, not all *BRCA* mutations are the same and understanding the predictive value of each type and location of *BRCA* mutation in terms of PARPi sensitivity would help optimize maintenance therapy. Second, currently available homologous recombination deficiency tests are not completely reliable and need further improvement. Indeed, a positive or negative test result does not guarantee that tumors with a deficiency or proficiency, respectively, in the homologous recombination pathway have been correctly identified without the risk of false-positive or false-negative results. Therefore, in addition to unraveling the type and location of *BRCA* mutations, there is an unmet need to implement functional homologous recombination deficiency assays to predict sensitivity to PARPi. Although the primary impact of current PARPi is the induction of DNA double-strand breaks over time, other PARPi effects may affect DNA repair and ultimately PARPi sensitivity, which can only be properly documented by functional evaluation.

### Type and Location of *BRCA* Mutations: Prognostic and Predictive Value

The association of specific mutations in the *BRCA1* or *BRCA2* genes with breast and ovarian cancer risk has been well documented in the literature and has implications for risk assessment and cancer prevention in *BRCA* mutation carriers.<sup>20</sup> The prognostic role of *BRCA* mutations, depending on the exact type and location, is also well established. For instance, *BRCA1* mutations outside of exon 11 are associated with improved survival,<sup>21</sup> as are mutations in the *RAD51*-binding domain (*RAD51*-BD) of the *BRCA2* gene.<sup>22</sup>

Since most patients with high-grade epithelial ovarian cancer are treated with platinum agents, the prognostic value of *BRCA* mutations most likely reflects sensitivity to these agents. However, the predictive value of specific *BRCA* genotypes in terms of sensitivity to DNA damaging agents such as platinum and PARPi remains to be elucidated. Preclinical data have provided evidence for a genotype-phenotype correlation. In genetically engineered murine models, *BRCA1* mutations in the Really Interesting Gene (RING) domain conferred decreased sensitivity to platinum and PARPi,<sup>23,24</sup> whereas *BRCA2* mutations in the DNA-binding domain (DBD) were associated with increased sensitivity to platinum salts and PARPi.<sup>25</sup> Some clinical evidence in the recurrent setting has shown that long-term responders to platinum are more likely to have *BRCA2* mutations<sup>26</sup> or *BRCA* structural variants.<sup>27</sup> In the primary setting, interesting data were recently reported in an exploratory subgroup analysis of the PAOLA1 trial,<sup>28</sup> which assessed the magnitude of benefit from olaparib and bevacizumab according to the location of mutations in the functional domains of *BRCA1* (RING, DBD, or C-terminal domain) and *BRCA2* (*RAD51*-BD or DBD). The benefit of adding olaparib to bevacizumab was particularly high in patients with mutations in the DNA-binding domain of *BRCA1*, and an excellent outcome was also reported for mutations in the DNA-binding domain of *BRCA2*. Larger biochemical and functional studies with adequate statistical power are needed to better understand the *BRCA* domain-related sensitivity to platinum and PARPi, as gathering this information would optimize decision-making regarding primary systemic therapy in ovarian cancer.

### POTENTIAL DE-ESCALATION STRATEGIES FOR THE RECURRENCE

PARPi have revolutionized the management of advanced high-grade epithelial ovarian cancer; however, a significant number of patients still progress under or after PARPi. Traditionally, chemotherapy has represented the mainstay of treatment for recurrent ovarian cancer, but there has been increasing interest in developing valid chemotherapy-free strategies based on combinations of PARPi, immunotherapy and anti-angiogenics, among others, to reduce cumulative toxicity and delay the time to next chemotherapy. Indeed, in the natural history of ovarian cancer, once the disease relapses, it is largely incurable and multiple relapses or progressions occur almost inevitably and at increasingly shorter intervals.

The efficacy of PARPi in terms of overall survival has also been confirmed in the recurrent setting, at least in patients with somatic or germline *BRCA* mutations.<sup>29–32</sup> De-escalation approaches exploiting the efficacy of PARPi could be implemented in the recurrent setting for (1) patients who did not receive PARPi in the first-line or in those cases where PARPi could be (2) rechallenged or (3) continued beyond oligoprogression in combination with locoregional therapy. Two recent retrospective studies have suggested that patients with oligometastatic progression on PARPi may continue to benefit from PARPi maintenance if managed with locoregional treatment, either surgery or radiotherapy. Palluzzi *et al.*<sup>33</sup> retrospectively studied 186 ovarian cancer patients with oligometastatic progression under PARPi maintenance who underwent surgery or stereotactic body radiotherapy and continued PARPi until

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further progression. The median prolongation of the treatment-free interval in patients treated with surgery or stereotactic body radiotherapy was 6 and 10 months, respectively. Similar results were reported by Gauduchon *et al*<sup>34</sup> who evaluated the survival benefit of PARPi continuation or reintroduction in 74 patients with oligometastatic progression treated with local therapy and suggested the feasibility and potential benefit of this strategy with almost one year without progression or initiation of a new line of chemotherapy. However, these studies are retrospective and did not reach statistical significance. Moreover, it could be argued that the benefit was due to the local treatment and not to the PARPi. Therefore, the impact of such strategies on survival remains unclear and warrants large-scale prospective research.

### Ongoing Clinical Trials: NEO Trial

NEO (NCT02489006) is an ongoing multicenter, open-label, randomized, phase II trial designed to evaluate the role of olaparib as neoadjuvant treatment before surgery in patients with platinum-sensitive recurrent high-grade ovarian, primary peritoneal, or fallopian tube cancer, regardless of mutational status (table 1). Previous use of a PARPi was an exclusion criterion. According to the study protocol, patients will receive olaparib (300 mg orally twice daily) for six weeks ( $\pm$  two weeks) before secondary surgery and will then be randomized to receive adjuvant olaparib with or without standard chemotherapy. Therefore, there is an arm in which patients will receive PARPi both before and after secondary surgery without standard chemotherapy. Primary endpoints include measuring the difference in levels of poly(ADP-ribose) (PAR) or poly(ADP-ribose) polymerase-1 (PARP-1) before and after olaparib and the rate of homologous recombination gene mutations in germline tissue compared with tumor tissue. Secondary endpoints include the incidence of adverse events, response rate to olaparib in the neoadjuvant setting and progression-free survival.

### Future Perspectives

In the NOW trial, patients who had previously received a PARPi were excluded. However, the vast majority of patients with advanced ovarian cancer now receive a PARPi in the upfront setting. Prior exposure to PARPi is an important consideration when discussing de-escalation strategies in the recurrent setting, and it is particularly important to distinguish between patients with and without progression on PARPi maintenance. Indeed, patients progressing on PARPi maintenance have worse expected outcomes when rechallenged with platinum, even in the presence of a long platinum-free interval, compared with those – mostly with *BRCA*-mutated tumors – who completed first-line PARPi maintenance without progression. The phase IIIb OREO/ENGOT-ov38 trial evaluated the role of olaparib maintenance rechallenge after standard chemotherapy in patients with platinum-sensitive recurrent ovarian cancer and reported a very modest but statistically significant benefit, irrespective of *BRCA*/homologous recombination deficiency status.<sup>35</sup> However, the potential role of PARPi-based de-escalation approaches in the recurrent setting for those patients who have already received a PARPi in the first-line remains to be clarified and requires prospective investigation in dedicated clinical trials.

As for the primary setting, it is important to consider the type and location of mutations in *BRCA* carriers, as there is evidence that reversion mutations in *BRCA* genes, a frequent mechanism

of secondary resistance to platinum and PARPi, exhibit a position dependence. Depending on the specific domain where they are located, *BRCA* mutations can be more or less easily reverted by secondary mutations and this could serve as a proxy for PARPi sensitivity. For instance, reversion mutations located in the C-terminus of *BRCA2* are extremely rare, suggesting that mutations in this domain are less reversible, which may explain the excellent prognosis of these patients.<sup>36</sup>

Finally, another key question to be explored in the relapsed setting is whether it is possible, in properly selected patients, to consider the use of PARPi for a limited and predetermined time, as in the first-line setting, rather than continuing until further relapse or progression. Indeed, this approach would have the potential to reduce the risk of post-PARPi platinum resistance and long-term toxicities such as myeloid malignancies.

### PITFALLS AND CHALLENGES

Learning to surf the balance between escalation and de-escalation with ease will be the greatest challenge of the future. For a disease with a high mortality rate such as ovarian cancer, extreme caution is required when considering de-escalation of systemic therapy in the primary setting. Improved biomarkers of PARPi sensitivity are urgently needed. In particular, there is an unmet need to better understand the predictive value of each type and location of *BRCA* and homologous recombination gene mutations and to develop more reliable homologous recombination deficiency tests and functional assays to properly identify homologous recombination-deficient tumors and minimize the risk of false-positive and false-negative results. An even more challenging endeavor may be to investigate combination regimens with PARPi and other targeted therapies as neoadjuvant treatment in lieu of chemotherapy for patients with homologous recombination-proficient tumors. Moreover, next-generation highly selective PARPi, such as the PARP-1-specific inhibitor AZD5305,<sup>37</sup> are gradually emerging with the goal of increasing efficacy while minimizing toxicity, and it will be interesting to explore their role in the neoadjuvant setting.

Well-designed, large, randomized, biomarker-driven trials are needed before systemic de-escalation regimens can be implemented in clinical practice. However, conducting such trials may be demanding for several reasons:

1. Patient non-compliance. De-escalation can be a difficult concept for patients to understand, especially under the psychological distress of a cancer diagnosis. There is a high probability that patients will misunderstand the intent of a de-escalation clinical trial. Most patients consider chemotherapy as life-saving and want to receive the maximum amount of treatment, while they may be less aware of long-term side effects and why tailoring treatment is so important. Therefore, accurate counseling is essential to clearly explain to patients the reasons why de-escalation is being tested and how it can optimize outcomes in terms of efficacy, safety, and quality of life.
2. The need for large sample sizes and long accrual periods. De-escalation of therapy is inherently a non-inferiority question, which poses trial design challenges in the context of a low-risk population where events are rare and may occur over a long period of time.



- Non-inferiority trial design. Since the goal of a non-inferiority trial is to demonstrate that an experimental treatment is no worse than the standard of care, a single trial that fails to demonstrate non-inferiority of the de-escalated treatment would be sufficient to lose clinical equipoise and undermine ethical principles for further trials addressing the same or analogous hypotheses.
- Single-arm study design. Because random assignment to standard care versus de-escalation typically requires large sample sizes, some hypotheses could be tested in selected patient populations using single-arm designs. However, this raises the question of whether de-escalation trials without a control arm can yield practice-changing results.
- Poorly designed non-inferiority trials have the potential to claim non-inferiority where there is none, thereby adversely affecting standard of care guidelines.
- Underfunding. Another major concern with de-escalation trials is often limited interest from the pharmaceutical industry, resulting in inadequate sample sizes and consequently insufficient statistical power to produce robust results.

More attention should be paid to the rigorous design of de-escalation trials. The Breast International Group–North American Breast Cancer Group Collaboration developed a roadmap to improve the design and conduct of de-escalation trials, with recommendations on how to (a) minimize treatment non-adherence, outcome heterogeneity, and the risk of undertreatment; (b) appropriately select patients; and (c) support the selection of recurrence-free interval, recurrence-free survival, and distant metastasis-free survival as desirable endpoints.<sup>3</sup> This roadmap can help investigators conduct de-escalation trials with robust, patient-centered, practice-changing results.

## CONCLUSION

In the era of targeted therapies, the development of oncologically safe de-escalation regimens may be an attractive strategy for selected ovarian cancer patients. Advances in genetics and multi-omics are drawing an unprecedented roadmap for more personalized treatments and encouraging new opportunities to improve quality of life. The extent to which systemic de-escalation approaches will change ovarian cancer treatment remains to be seen. Rigorous, biomarker-driven clinical trials with appropriate patient selection are warranted to establish a de-escalated treatment paradigm for ovarian cancer patients that optimizes oncologic outcomes while reducing toxicities.

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