

What has changed in treatment of ovarian cancer in the past 10 years? By Prof. Nicoletta Colombo, Università Milano-Bicocca, European Institute of Oncology, Milan, Clinical Chair of ENGOT

Comments by Birthe Lemley

There has been a tsunami of new drugs for o.c.

There are 300.000 new cases of ovarian cancer every year.

70 % of the o.c. patients will have a relapse.

Around 50% will survive for 5 years. However, this does not mean that the patients are cured. The relapses will still occur.

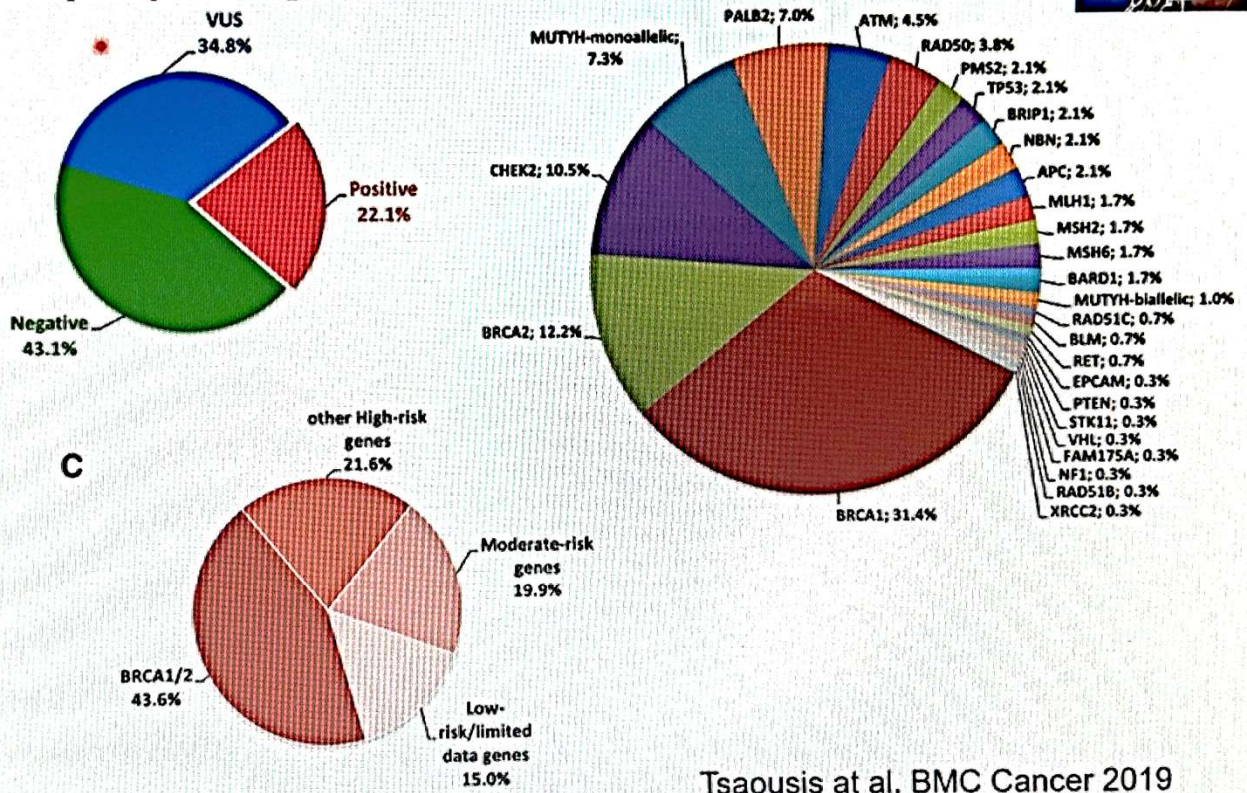
But, today the patients are living longer and longer. We are now able to control the disease for many years, however the time between relapses will become shorter and shorter along the way.

We want to find precision medicine for o.c., but the disease is incredibly unstable.

Analysis of hereditary cancer syndromes by using a panel of novel and multiple pathogenic mutations



Outcomes of panel testing for the 1197 individual tested



Tsaousis et al. BMC Cancer 2019

New Improvements in Ovarian Cancer Treatment

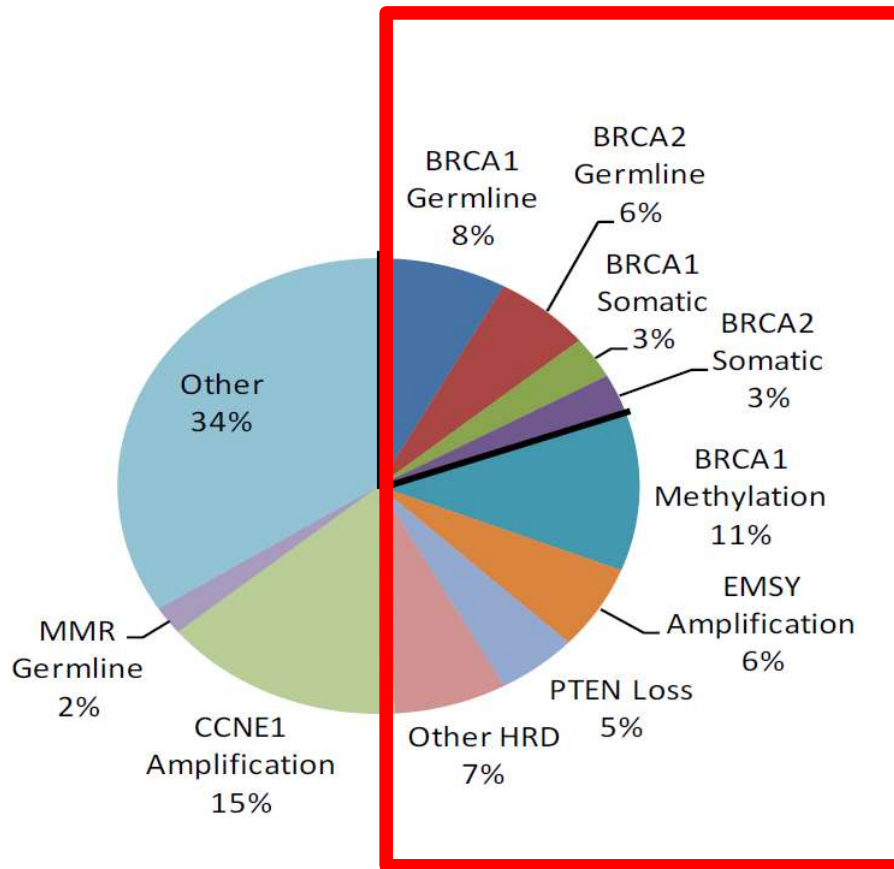
Maintenance treatment with a PARP-inhibitor

After first line treatment many patients experience complete remission, but patients still relapse.

PARP-inhibitors used in first-line might have a curable effect on some of these patients.

The study SOLO1 (olaparib) for firstline treatment included patients with a BRCA-mutation. Some of the patients from that study have now been free of progression for 7 years. They might be cured.

The study PAOLA1 (olaparib + bevacizumab) included all patients with high grade serous o.c. in stage III and IV. Overall survival data are currently immature.



Around 50% of high grade serous carcinomas show HRD, Homologous recombination deficiency



Testing HRD in tumor tissue to predict response to Chemotherapy and PARP inhibition

Maintenance treatment with a PARP-inhibitor

PRIMA with the PARP-inhibitor niraparib had another set-up as they included all patients with the worst prognosis even inoperable patients in stage IV, while the patients in stage III, who were operated up-front, were excluded although they had the best prognosis.

All patients had a beneficial outcome although the HRD negative patients only had a prolongation of a few months when receiving niraparib.

PARP-inhibitors are also used in second-line if treatment with carboplatin has worked on the patient (partial or complete response). It is, however, recommended to use a PARP-inhibitor as maintenance treatment in firstline. So far, there has been no effect of using PARP after PARP. The OReO study was negative.

Diagnostic tests – how to detect HRD?

The tests used are different from country to country.

The most well-known test is the Myriad Test. A sample of the tumor is sent to Myriad Genetics in Utah, US for testing. This is rather expensive and therefore many clinics in Europe have developed their own tests.

Other well-known tests are:

Foundation One

Thermofisher OCA Plus

Sophia DDMTM Dx HRd

NEWS FROM ASCO IN JUNE AND ESMO IN OCTOBER

A new drug mentioned was ADC (Antibody Drug Conjugate)
This drug is already available in the US and will also soon be available in Europe, but has to be approved by EMA and then in the individual countries.

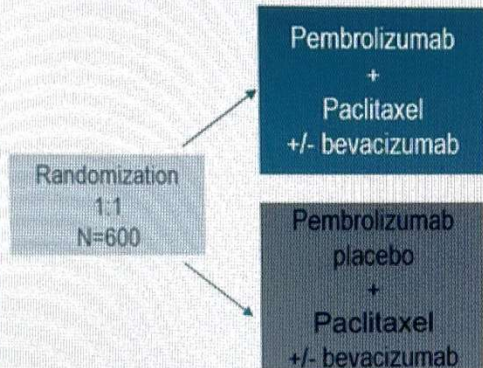
Antibody-drug conjugates or **ADCs** are a class of biopharmaceutical drugs designed as a targeted therapy for treating cancer. Unlike chemotherapy, ADCs are intended to target and kill tumor cells while sparing healthy cells. As of 2019, some 56 pharmaceutical companies were developing ADCs. Source: [Wikipedia](#).

So far there has not been much luck with **immunotherapy** in ovarian cancer, but new combinations are being tried. 600 patients will be involved in a new study with paclitaxel, bevacizumab and pembrolizumab. See next slide:

ENGOT-OV65/KEYNOTE-B96 STUDY DESIGN



- Key Eligibility Criteria**
- Platinum Resistant OC patients (refractory excluded)
 - Up to 2L of prior therapy
 - ECOG PS 0, 1
 - **Prior IO allowed**
 - **Prior PARPi allowed**
 - **Prior bevacizumab allowed**



Statistical Considerations

- **Primary endpoints:**
 - PFS in CPS \geq 1 ($\alpha=0.02$ 1-sided)
 - PFS in all population ($\alpha=0.005$ 1-sided) with roll-over of alpha from PFS in CPS1 if positive
 - **Key secondary endpoints:**
 - OS in CPS \geq 1
 - OS in all population
- Hierarchical approach:**
- ❖ OS in CPS1 can be tested only if both PFS analyses are positive
 - ❖ OS in all pts can be tested only if OS in CPS1 will be positive

Stratification factors for randomization

- Bevacizumab use
 - PD-L1 status
 - Prior IO
- Planning Considerations**
- Enrollment ~ 18 mo
 - Enrollment rate: 34 patients / mo

A PD-L1 test measures what percentage of cells in a tumor “express” PD-L1. Tumors that express high amounts of PD-L1 (50% or greater) may respond particularly well to checkpoint inhibitors (a type of immunotherapy drug).

The Combined Positive Score (CPS)¹ algorithm includes tumor and immune cells for determination of Programmed Death-Ligand 1 (PD-L1) protein expression in tumor tissues

How does T-cell transfer therapy work against cancer?

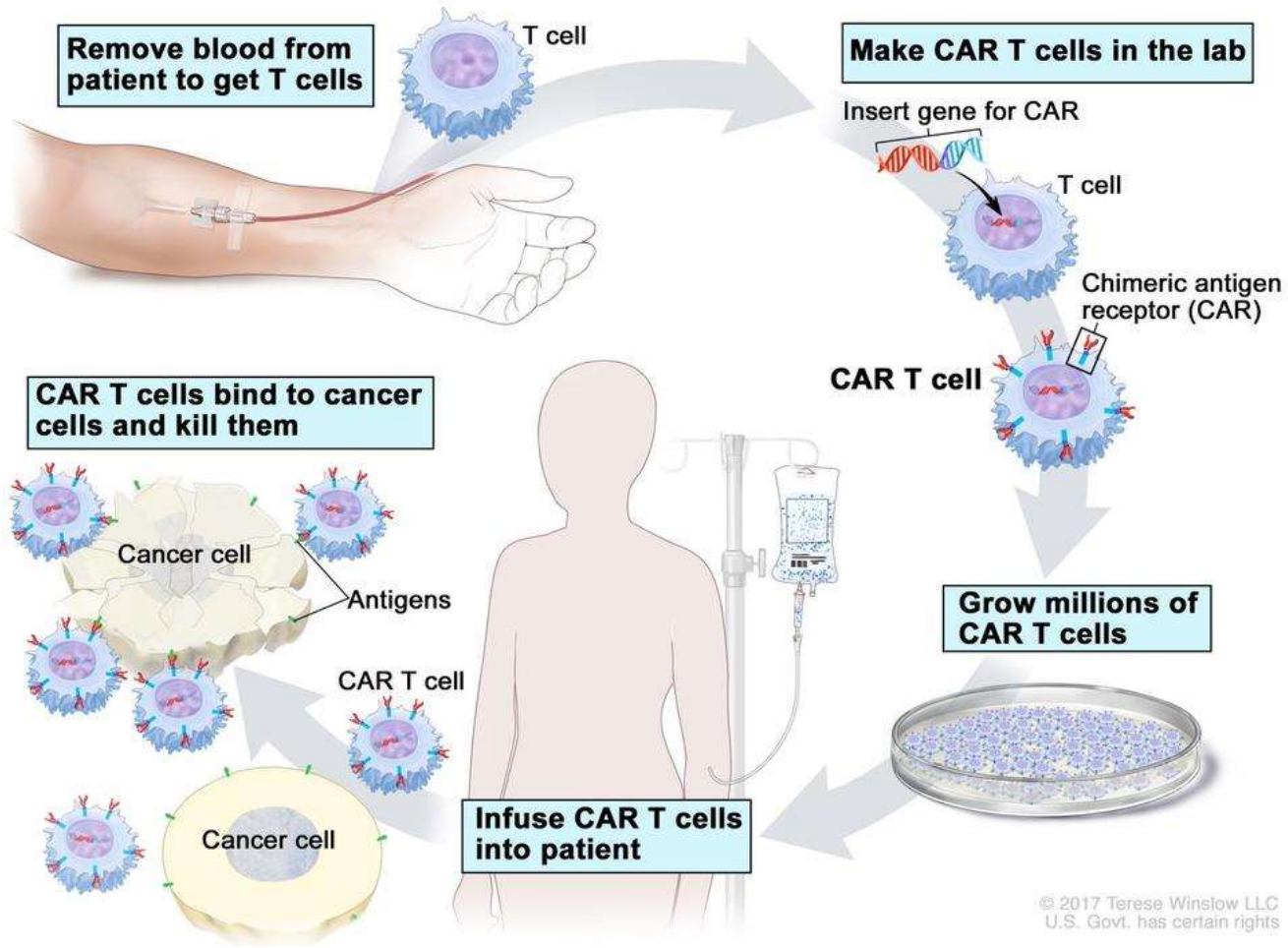
T-cell transfer therapy is a type of immunotherapy that makes your own immune cells better able to attack cancer. There are two main types of T-cell transfer therapy: tumor-infiltrating lymphocytes (or TIL) therapy and CAR T-cell therapy. Both involve collecting your own immune cells, growing large numbers of these cells in the lab, and then giving the cells back to you through a needle in your vein. T-cell transfer therapy is also called adoptive cell therapy, adoptive immunotherapy, and immune cell therapy.

The process of growing your T cells in the lab can take 2 to 8 weeks. During this time, you may have treatment with chemotherapy and, maybe, radiation therapy to get rid of other immune cells. Reducing your immune cells helps the transferred T cells to be more effective. After these treatments, the T cells that were grown in the lab will be given back to you via a needle in your vein.

TIL therapy uses T cells called tumor-infiltrating lymphocytes that are found in your tumor. Doctors test these lymphocytes in the lab to find out which ones best recognize your tumor cells. Then, these selected lymphocytes are treated with substances that make them grow to large numbers quickly.

Source: [National Cancer Institute](#)

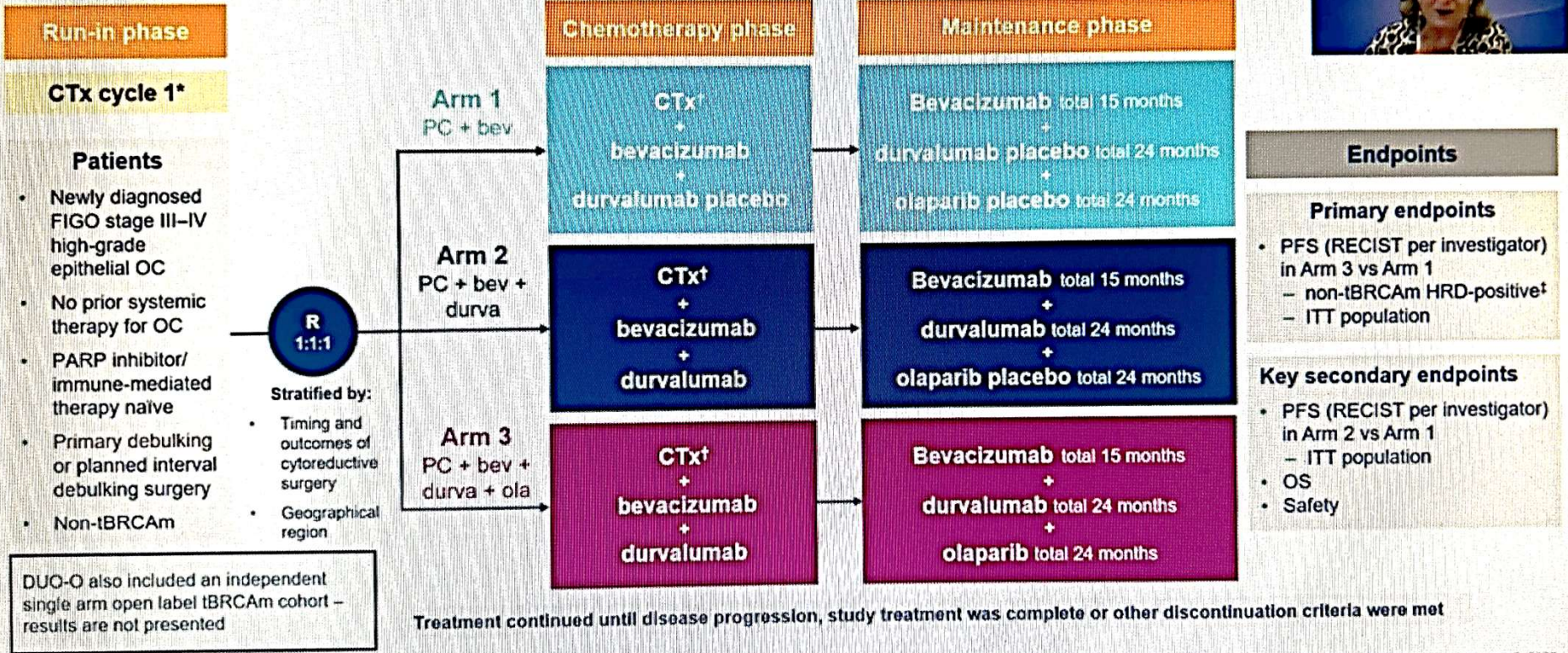
CAR T-cell Therapy



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DUO-O study design



DUO-O also included an independent single arm open label tBRCAm cohort – results are not presented

Dosing and schedule: bevacizumab (15 mg/kg IV q3w), durvalumab (1200 mg IV q3w), olaparib (300 mg po bid), chemotherapy: paclitaxel 175 mg/m² IV q3w and carboplatin at AUC5 or AUC6 IV q3w. PFS interim analysis DCO, December 5, 2022. *With or without bevacizumab according to local practice. †Cycles 2–6. ‡Genomic instability score ≥42 assessed by Myriad MyChoice CDx assay. AUC, area under the curve; bev, bevacizumab; bid, twice daily; CTx, chemotherapy; DCO, date cutoff; durva, durvalumab; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; ola, olaparib; OS, overall survival; PC, paclitaxel/carboplatin; po, by mouth; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria for Solid Tumors.

Key Points:

- DUO-O assessed safety and efficacy of maintenance therapy with bevacizumab monotherapy versus bevacizumab in combination with durvalumab and olaparib in patients with newly diagnosed advanced ovarian cancer and no *BRCA* mutations.
- PFS with the triplet maintenance therapy was significantly greater than with bevacizumab monotherapy.
- 35% of the patients in the triplet arm experienced adverse events leading to discontinuation of 1 or more of the triplet drugs.
- Final analysis data are awaited to fully assess the overall clinical benefit. **Source ASCO**



Dr. Phillip Harter, P. I., Kliniken
Essen, Germany

New drugs for Ovarian Cancer:

The ADCs have increased toxicity – ocular problems among others, but Nicoletta Columbo explained that this was also the case with paclitaxel when they first started using it.

The doctors will learn along the way, how to treat these various toxicities.

The next slide will show a phase III study named Mirasol with an ADC. In the doctors opinion this is a new drug with a lot of potential.

Mirvetuximab soravtansine (MIRV), an antibody drug conjugate targeting FR α (frequent overexpression of folate receptor), demonstrated clinically meaningful antitumor activity in a single arm trial reported previously (Matulonis, JCO 2023). MIRASOL is a randomized phase 3 trial to confirm the efficacy of MIRV vs standard-of-care chemotherapy in patients (pts) with PROC (platinum-resistant ovarian cancer). Kilde: [Journal of Clinical Oncology](#)



MIRASOL STUDY DESIGN: PHASE 3 REGISTRATION TRIAL FOR MIRVETUXIMAB SORAVTANSINE USING PS2+ SCORING IN FR α HIGH PATIENTS

MIRASOL

Enrollment and Key Eligibility

- 430 patients/330 events for PFS by INV
- Platinum resistant disease (<6 months PFI)
- Prior Bev and PARP allowed
- BRCAmut patients allowed

Statistical Assumptions

- $\alpha=0.05$ (two-sided), Power = 90%, HR=0.7; control arm mPFS 3.5 mo

Mirvetuximab Soravtansine

6 mg/kg (adjusted ideal body weight) once every 3 weeks

1:1 Randomization

STRATIFICATION FACTORS
 IC Chemotherapy Choice (Paclitaxel, PLD, Topotecan)
 Prior therapies (1 vs 2 vs 3)

Investigator's Choice Chemotherapy

Paclitaxel, PLD[†], or Topotecan

Paclitaxel: 80 mg/m² weekly
 PLD: 40 mg/m² once every 4 weeks
 Topotecan: 4 mg/m² on Days 1, 8, and 15 every 4 weeks; or 1.25 mg/m² on Days 1-5 every 3 weeks

Primary Endpoint

Progression-free survival by INV
 BICR* for sensitivity analysis

Secondary Endpoints

Overall response rate by INV
 Overall survival
 Patient reported outcomes

*BICR: Blinded Independent Central Review
 †PLD: pegylated liposomal doxorubicin

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 †PLD: pegylated liposomal doxorubicin

Take home messages



- This past year has seen many foundational advances in OC with newly identified therapeutic opportunities in components of the DNA repair pathway.
- We are witnessing a revolution in the therapeutic management of ovarian cancer in multiple settings, with the 1L data of PARP inhibitors raising the hope of potential cure
- Several combination strategies including IO are currently being explored in clinical trials in the front-line setting
- ADC are among the most promising drugs
- With the increased use of PARP inhibitors in front line, overcoming therapeutic resistance emerge as a key research priority and several combination strategies are currently being explored in clinical trials .
- The correct sequence of available drugs should represent an important area of research over the coming years, possibly associated with translational strategies to improve therapeutic precision.