What has changed in treatment of ovarian cancer in the past 10 years? By Prof. Nicoletta Colombo, Universtà 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 o novel and multiple pathogenic mutations

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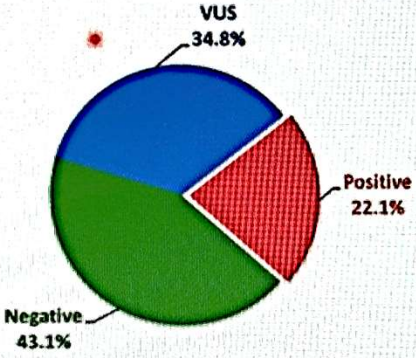
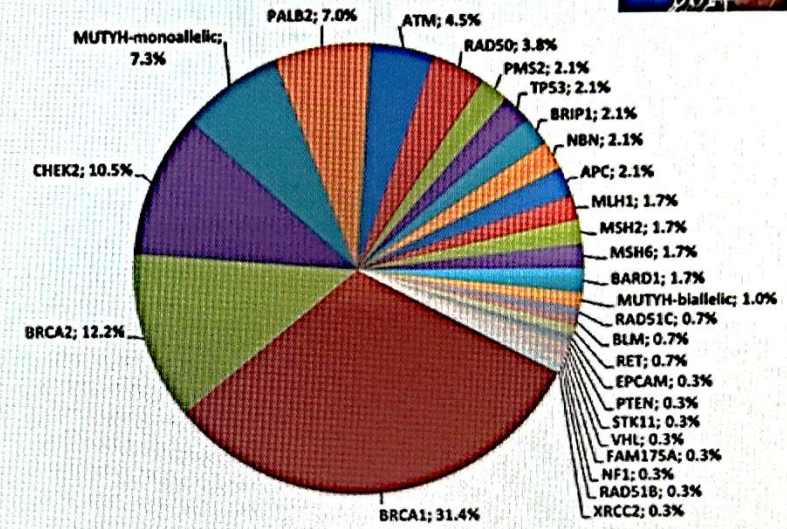
Outcomes of panel testing for the 1197 individual tested





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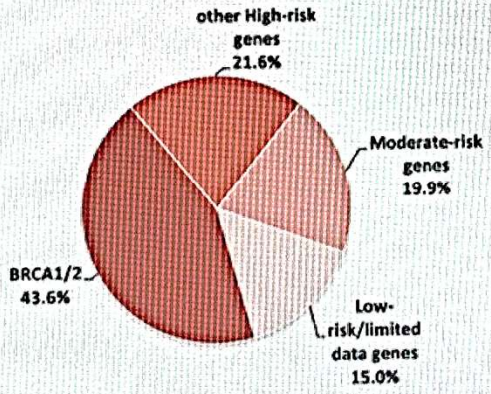


Tsaousis at al. BMC Cancer 2019

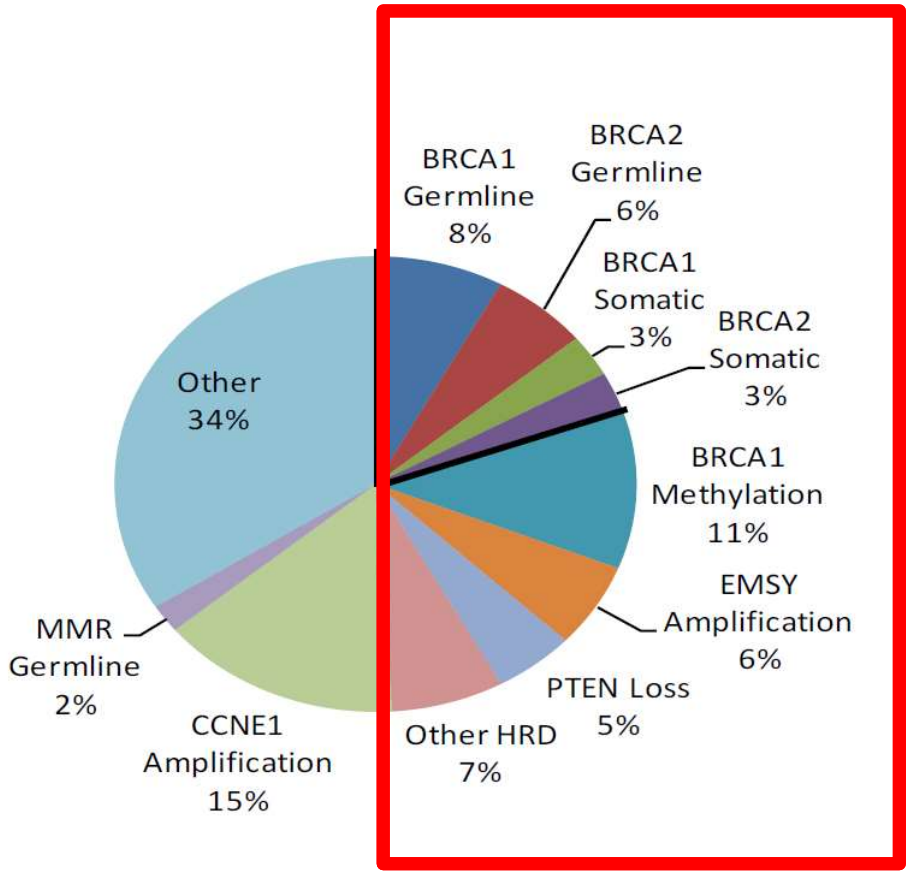
Maintenance treatment with a PARP-inhibitor

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 wtih 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

The Cancer Genome Atlas Research Network. Integrated Genomic Analyses of Ovarian Carcinoma. *Nature.* 2011;474(7353): 609–615

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:

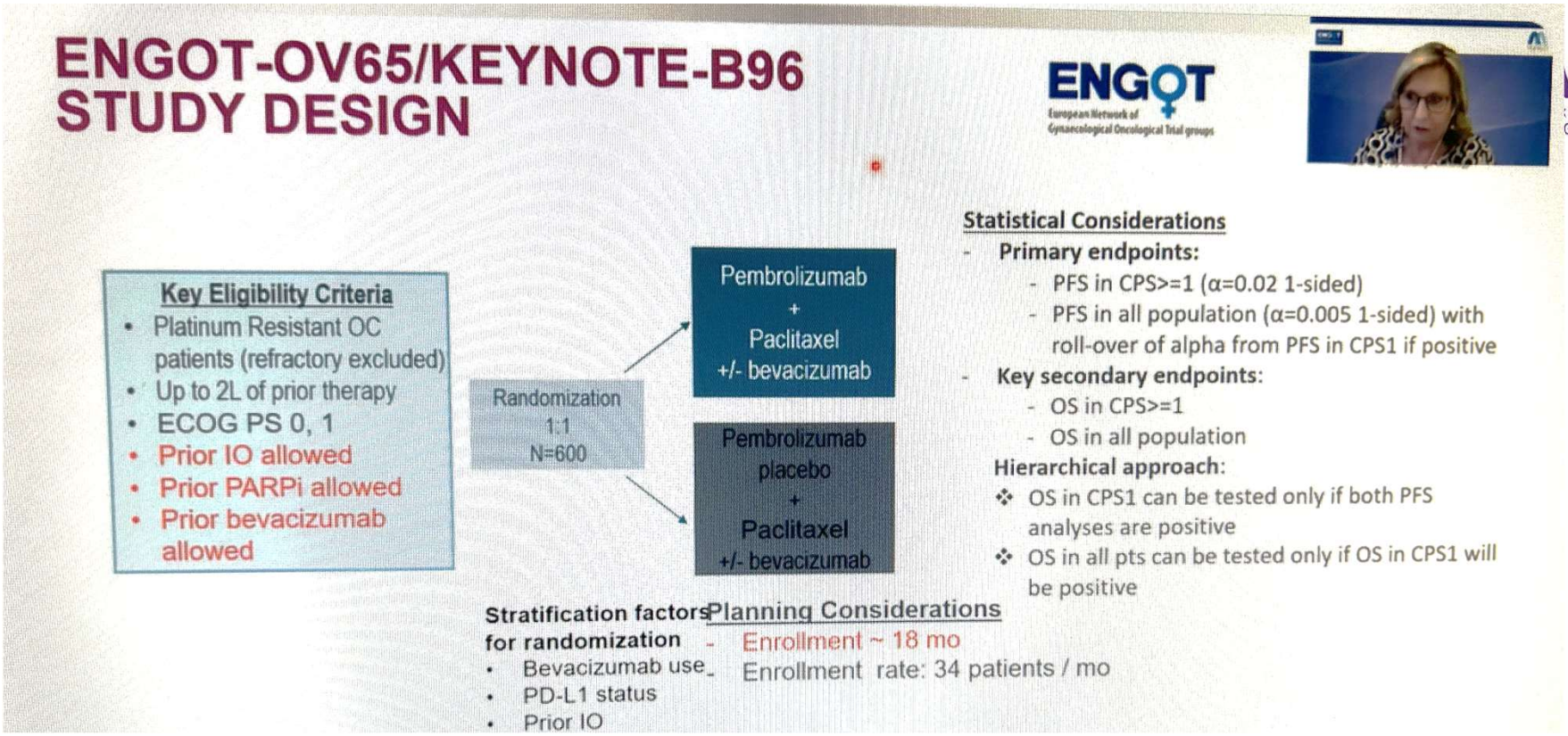
Foundation One
Thermofisher OCA Plus
Sophia DDMTM Dx HRd

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:



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 Programed 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

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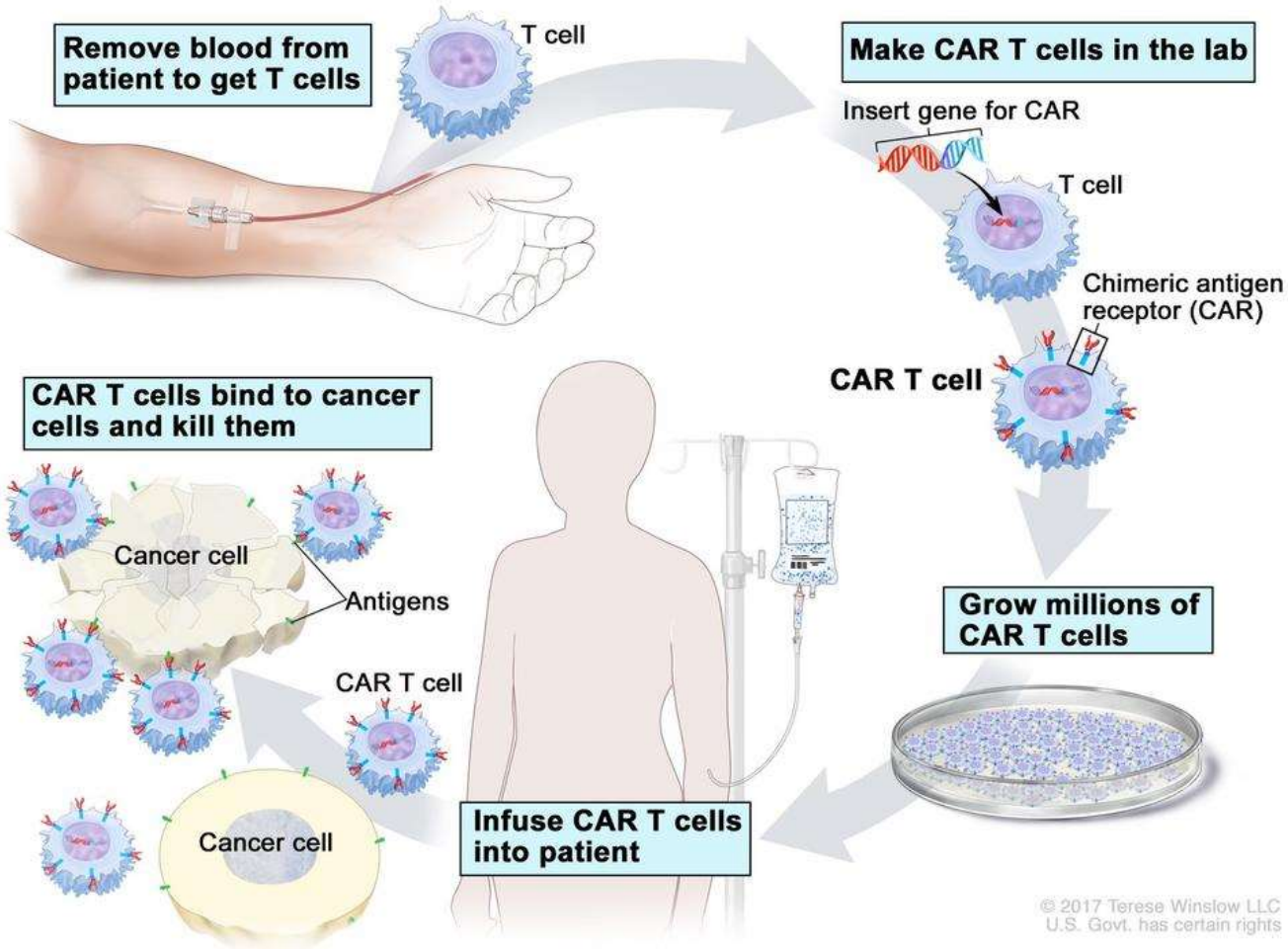
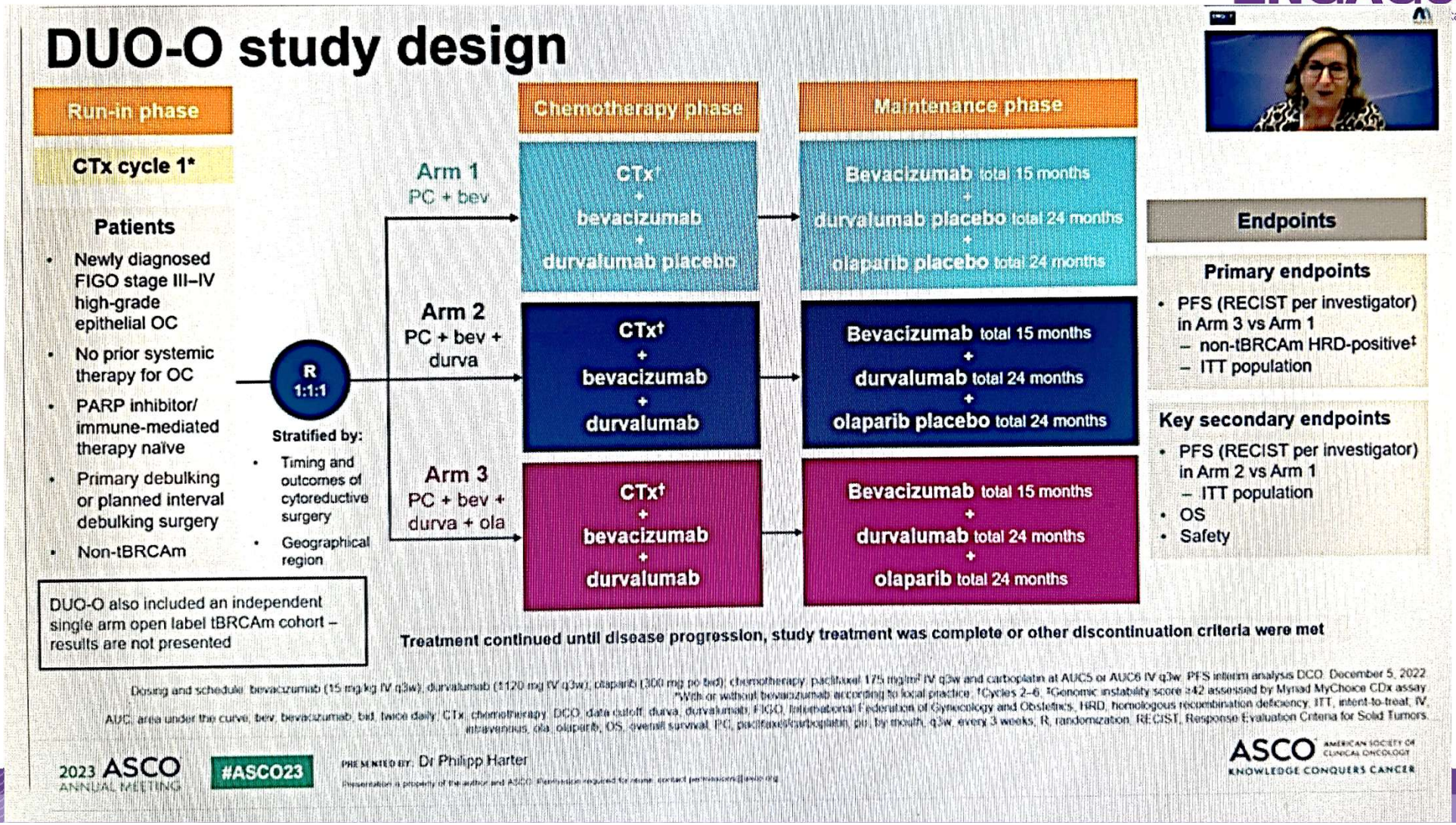
CAR T-cell Therapy



Other new treament options and studies mentioned during Prof. Colombo's lecture:



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:

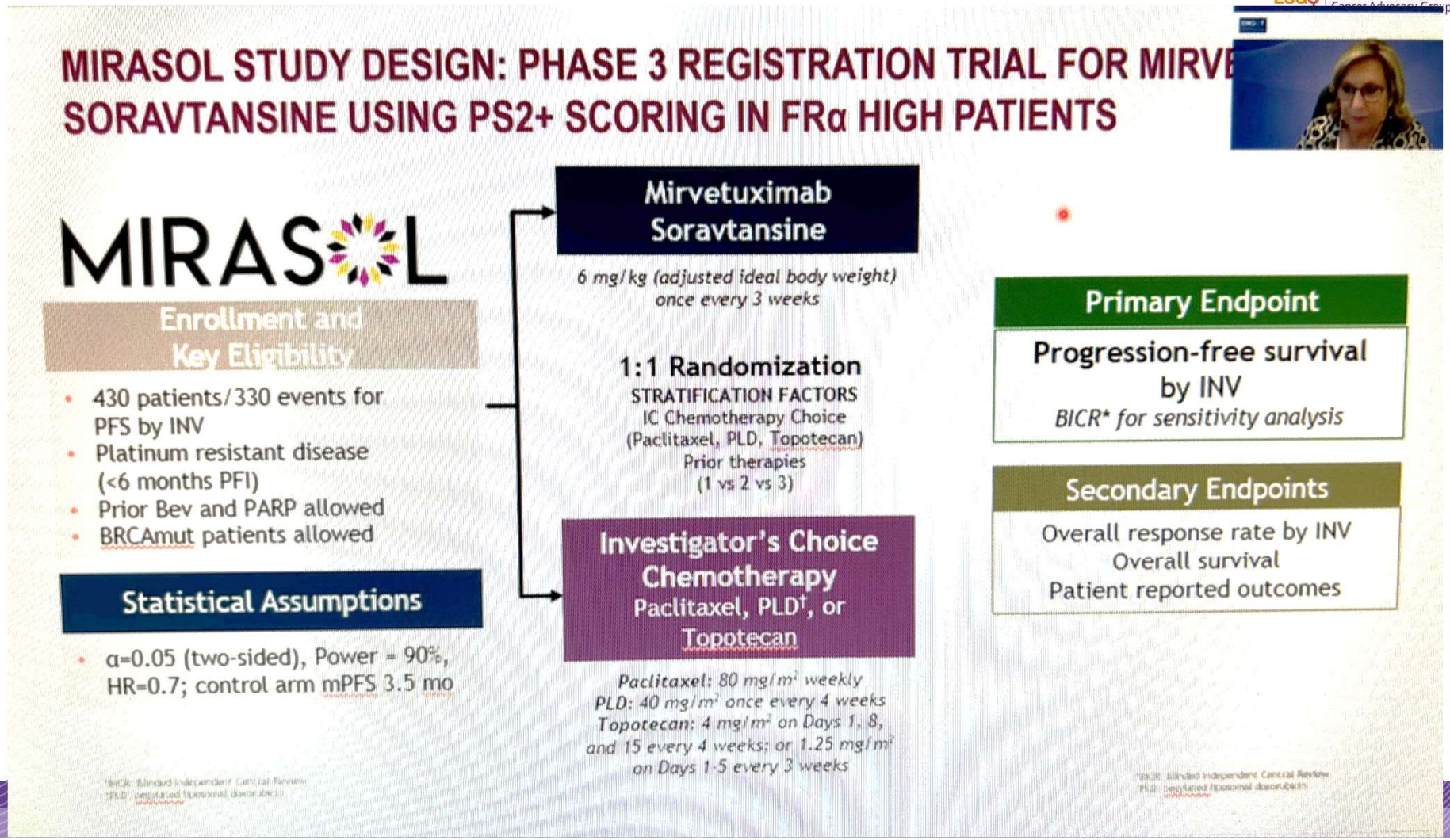
The ADCs have increased toxicity – ocular problems among others, but Nicoletta Columbo explained that this was also the case with paclitaxel when they first started using it.

The doctors will learn along the way, how to treat these variaous 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 FRα (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

Mirvetuximab Soravtansine – ADC for O.C. patients with platinum resistant disease



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 been 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.