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ENGAGe-ENGOT Clinical Trials Project – 1st webinar
The background and design of a clinical trial
The PRIMA trial as an example

The Objective of a trial

- **Finding an answer to a question**
- **Define the problem**
  In the NOVA trial - the PARP-inhibitor niraparib could prolong the interval between relapses of ovarian cancer after platinum-based chemotherapy.
- **The hypothesis**
  This might also be the case after first line treatment of ovarian cancer after platinum-based chemotherapy.

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Methodology:

Randomization

In this particular trial the randomization was

2:1

2/3 of the patients would get the drug and 1/3 placebo (standard of care), which at the time was follow-up between relapses for this group of patients - no actual maintenance treatment unless they had a BRCA-mutation.

So, if there is a treatment, the new drug/procedure will be compared to the prevailing standard of care e.g., chemo, radiation, surgery or whatever. If there is no treatment, then the new treatment will be compared to placebo, which in this case is standard of care (follow-up).

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Stratification:

To avoid bias = systematic error

You have to stratify patients so that there is no bias in the treatment.

In this particular case, it means that if patients that had NACT (neoadjuvant chemotherapy) are included in the study, you have to take care that percentagewise the same number of patients with NACT are included in both arms.

Example:

600 patients included in the trial – 400 hundred in the treatment arm and 200 in the placebo arm.

150 with NACT included in the trial. This means that you have to include 100 with NACT in the treatment arm and 50 with NACT in the placebo arm in order to avoid bias

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Inclusion criteria:

High grade serous or endometrioid ovarian cancer

- **Inoperable stages III and IV**
- **Stage IV disease, regardless of postoperative residual disease status**
- **Stage III after primary debulking surgery with macroscopic visible residual disease**
- **Stage III or IV after NACT (neoadjuvant chemotherapy) and interval debulking surgery regardless of residual disease status**

Exclusion Criteria:

Long list of exclusion criteria

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Predictive factors in high grade ovarian cancer

Genetics

BRCA-mutations – hereditary or somatic

HR (homologous recombination) deficient patients and HR proficient patients

In other types of cancer there will be other gene mutations

e.g. endometrial cancer – POLEmut, P53abn, MSI and NSMP

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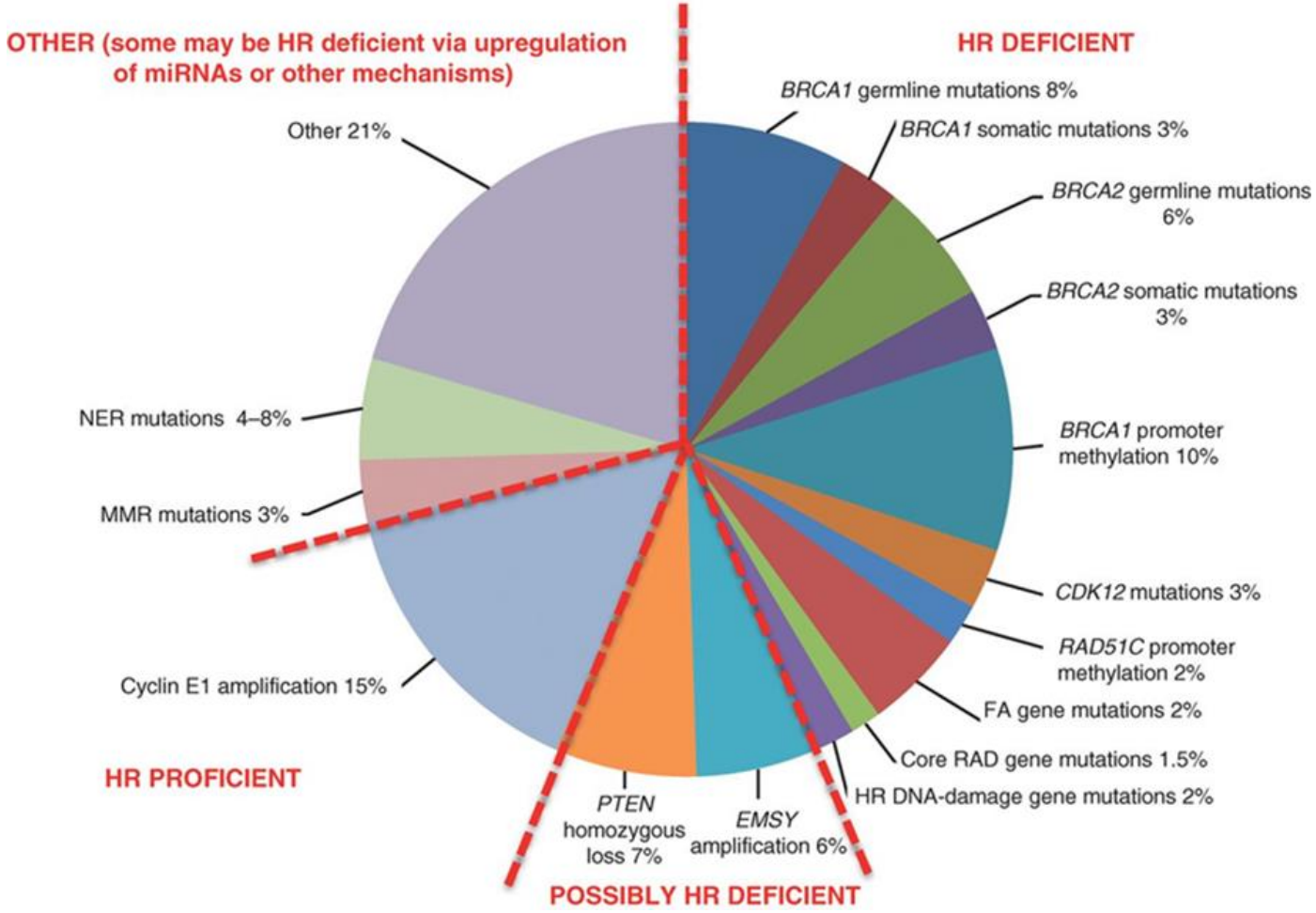

Pie chart of mutations in high grade ovarian cancer

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Endpoints:

The endpoint can be PFS (progression free survival). How many months to the next relapse? The patients need 6 months or more to receive treatment with platinum-based chemotherapy again.

An endpoint can also be OS (overall survival). These endpoints are usually measured by RECIST (Response Evaluation Criteria in Solid Tumors)

The next relapse is usually measured by blinded radiologists. This is again done to avoid bias.

Secondary endpoints:

OS can also be a secondary endpoint together with quality of life measured by various questionnaires, e.g., PROs (patient reported outcomes).

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The trial population – the cohort:

The patients included in this trial have stage III or stage IV ovarian cancer. Some were inoperable, some had residual tumour after surgery. They all had very good response to platinum-based chemotherapy.

Some have BRCA-mutations, some are HR deficient, some have HR not-determined, some are HR proficient.

Final conclusion:

Niraparib is a new option for patients with high grade serous ovarian cancer to avoid/postpone progression of disease after first line treatment.

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Questions from the audience:

<u>Where do we find list of acronyms and abbreviations</u>?

Answer from Antonio González: In a well-written protocol there is always a list of abbreviations/acronyms, and it is always a good idea to look at the list before reading the protocol.

Many of the acronyms are used in all protocols, but for each trial there will also be new abbreviations/acronyms. If we e.g., compare ovarian cancer and endometrial cancer, the acronyms for the various mutations are different because the mutations are different.

You have all received a list of acronyms and abbreviations for the PRIMA trial.

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How does the drug get from a successful outcome in a trial to the patients at large?

- In Europe, the drug first has to be approved by EMA (The European Medicines Agency), and afterwards there are medicines councils in the various European countries that also have to approve the use of the drug as standard of care. They don't only look at the outcome of the trial, but also at the cost of the drug, so some drugs can be available in some European countries, but not in others.
- If the study has been initiated by an American pharma company, it has to be approved by the FDA (Food and Drug Administration) and then by EMA in Europe and then by the councils/HTA in the individual countries.
- This is where we as patients might have an influence or might even be able to help other patients get the drugs in the individual European country and also to disseminate the results of a trial.

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Where and when can patients' insights be taken into account in a clinical trial?

- Questionnaires on quality of life. It has been proven that the opinions of patients and doctors differ quite a lot in that respect.
- PROs (patient reported outcomes). Looking at the questions asked.
- Spreading the knowledge of the trial and disseminate the outcome of the trial.
- Help getting the new drug/procedure approved in the individual countries.
- General information in our various countries of what it means to participate in a clinical trial is also important, as there might be misconceptions.
- Sometimes even the patients on placebo do better than what they would have done if they had not been in a clinical trial because they are monitored much more closely.

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<u>Can the exclusion criteria change while the trial is running</u>?

The answer was no. But there can be an amendment to a trial. As explained during the presentation, there was an amendment to the daily dose of the drug in the PRIMA trial.

- **The amendment in the PRIMA trial was based on the patient's weight and her number of platelets.**
- **It can also happen that the blinding is opened for medical reasons – unexpected side effects – a drug that in one arm is inferior to the other drugs in other arms (e.g. umbrella trial).**
- **Amendments to a running trial must be approved by the health authorities and the ethics committee.**

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When will the patient know whether she was in the treatment or placebo arm?

When she has a relapse, she will know. Sometimes there can be a possibility of cross-over. Changing from one arm to the other, but not in the PRIMA trial.

Not only the drug but also the patient's quality of life have an influence on how the patient is doing.

Does she have support from family and friends? Is that something that is taken into account when she enters a trial? In the inclusion criteria it says that the patient must be able to follow the procedure of the study, but maybe attention should be paid to this factor as it might have an influence on the outcome of the trial.

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<u>How do doctors know that the patient is in high risk of recurrence?</u>

With ovarian cancer in stages IIIC and IV there is a high risk of recurrence – around 80 %. The doctors know that from experience.

<u>What if a patient lives in another country than where the trial is taken place</u>?

This is something we ought to try to solve at ENGAGe as this is a real problem, and something that should be made possible for the patient.