ENGAGe - ENGOT
Clinical Trials Project

STUDY BOOK 2

for the participants of the Clinical Trials Project

ENGAGe
ESGO | European Network of Gynaecological Cancer Advocacy Groups

ENGOT
European Network of Gynaecological Oncological Trial groups

ESGO
European Society of Gynaecological Oncology

Introduction

This is a study guide of the second step in the education of 'patient experts' in a collaboration between ENGOT and ENGAGe.

In this second study guide we are using an actual clinical trial as an example of the theory that was introduced in the first study guide. The PRIMA trial was chosen as an example.

The participants in the project have also had access to all presentations under SoA – a virtual conference organised by ESGO and held from 14 to 16 December 2020, and they have all been invited to attend the online part of the Charité-Mayo conference in Berlin from 5 to 8 May 2021.

The first 3 webinars were held on Sept. 2, 2019 and the next 3 webinars at the beginning of 2021. The training is ongoing, and 2 more webinars are planned for 2021.

The objective is to educate a number of gynaecological cancer patients from major European countries to a level where they will be able to understand the process of a clinical trial and contribute with useful insight from a patient perspective in the design and implementation of a clinical trial.

The intent of this study guide, which consists of a report of the 3 webinars using the PRIMA trial as an example, is to enable the patient experts to understand the layout of a clinical trial and in that way be able to read and comment on any trial within their own area of disease.

The webinar is a joint project between two ESGO networks, ENGAGe and ENGOT.

ENGAGe is the European Network of Gynaecological Cancer Advocacy Groups.
Learn more at **engage.esgo.org**

ENGOT is the European Network of Gynaecological Oncological Trial groups.
Learn more at **engot.esgo.org**

Featured speakers:

Dr. Antonio González-Martín	***Webinar 1: The background and design of a clinical trial***
Prof. Jalid Sehouli	***Webinar 2: The Outcomes***
Prof. Jonathan Ledermann	***Webinar 3: Simple statistics in a clinical trial***

Moderators:

Dr. Murat Gultekin, ENGAGe Co-chair
Prof. Karina Dahl Steffensen, Vejle Hospital, Denmark
Prof. Jalid Sehouli, Charité - Universitätsmedizin Berlin, Germany

Project Manager of the Clinical Trials Project and writer of this report:

Birthe Lemley, EEG member of ESGO ENGAGe

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1st webinar

Background and design of a clinical Trial

21 Jan 2021

ENGAGe – ENGOT Clinical Trials Project, Webinar 1

Moderators: **Prof. Jalid Sehouli,** Charité University Hospital, Germany
Dr. Murat Gultekin, Turkey
Birthe Lemley, Denmark on behalf of ENGAGE

ENGOT presenter: **Dr. Antonio González-Martín**
Clínica Universidad de Navarra, Spain

Comments from Antonio González-Martín on the Clinical Trials Project:

There is much work done on this project. As I see it, we are becoming the unique professional patient network in clinical trials. We are so proud both from the ENGOT's point of view and the doctors' point of view and together we will become more and more powerful.

Everybody is talking about empowerment and engagement and cooperation with patients and relatives in the treatment decision-making process, but I think ENGAGE and even ENGOT are doing this in a rare practical way, and I am impressed by this engagement and even by this philosophy.

It's always a challenge for me to give a lecture to our patients because one of the key rules when you have to give a lecture is very simple: Know your audience and when you are talking to patients you don't know what the audience know at that moment and what their expectations are.

Birthe asked me to present a trial and to give you the background of the different parts of the trial starting with why we perform a trial, what are the exclusion criteria of the trial, the exclusion criteria and so on. Do not hesitate to interrupt me by asking questions or if you are interested in anything else that we may have time for in the discussion.

I'm going to present the PRIMA study, and the first thing you need to know is: What is a clinical trial?

What is a Clinical Trial?

A clinical trial is a methodology to answer a medical question. That is the reason why we usually start by defining the problem. And for the PRIMA study our problem was that many of the patients with advanced ovarian cancer will have a recurrence after frontline chemotherapy based on paclitaxel and carboplatin. That is the main problem that we have with this disease. When we designed the PRIMA trial, we started to introduce a concept in ovarian cancer treatment and that was the concept of maintenance. The idea is to give a treatment at the end of chemotherapy in order to maintain the response and keep the patient free of progression for as long as possible. When we decided to do the PRIMA study, we actually only had one option for maintenance treatment and that was bevacizumab. Later on, we also had a possibility of giving the PARP-inhibitor olaparib to our patients, but only to a subgroup of patients that had a BRCA mutation. This was the problem.

What could be the solution? The solution could be maintenance therapy. And why niraparib? Why niraparib frontline? Why trying maintenance treatment with niraparib after chemotherapy? Because we had data from the NOVA trial that was lead and published by doctor Mirza; and what Dr. Mirza and the rest of the colleagues from NSGO and ENGOT demonstrated was that patients that had a recurrence of ovarian cancer, and were treated with platinum-based chemotherapy again, and reached a new response, were able to live longer and without progression if they received niraparib as a maintenance therapy; so DR Mirza and colleagues demonstrated that giving niraparib after chemotherapy prolongs the progression-free interval.

Niraparib is Effective in Recurrent OC (*BRCA*mut and *BRCA*wt)

- Advanced ovarian cancer is a leading cause of cancer deaths in women with high recurrence rate after completion of standard first-line platinum-based chemotherapy[1]
- Despite current options for maintenance treatment, there is still a high unmet need for many patients
  - **Olaparib:** limited to patients with BRCA mutations, =20% of OC patients[2]
  - **Bevacizumab:** limited use due to safety concerns and limited data in the growing number of patients receiving NACT
  - **Active surveillance:** many patients undergo watchful waiting following chemotherapy
- Niraparib was the first oral PARP inhibitor approved as maintenance for all patients with recurrent OC (*BRCA*mut and *BRCA*wt)
  - NOVA study demonstrated efficacy of niraparib maintenance after platinum CT in all biomarker populations: g*BRCA*mut: hazard ratio 0.27 (95% CI 0.17-0.41, P<0.0001); homologous recombination deficient: hazard ratio 0.38 (95% CI 0.24-0.59, P<0.0001) and non-g*BRCA*mut: hazard ratio 0.45 (95% CI 0.34-0.61, P<0 0001)[3]
  - QUADRA study showed niraparib treatment benefit in patients with at least 3 prior therapies: *BRCA*mut 39% ORR, homologous recombination deficient 26% ORR, duration of response 94 months[4]

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CI, confidence interval; CT, chemotherapy; NACT, neoadjuvant chemotherapy; mut, mutant; OC, ovarian cancer; ORR, objective response rate; PARP, poly (ADP-rbose) polymerase; wt, wild-type;
1.GLOBOCAN.2018: 2. Moore. *NEJM* 2018: Mirza. *NEJM* 2016: Moore. Lancet Oncol 2019.

What we did was ask the simple question: Will Niraparib added at the end of frontline chemotheraphy produce the same effect? Will Niraparib also reduce the rate of relapse if we give this treatment as maintenance after frontline chemotheraphy? That was the hypothesis.

Hypothesis: Will niraparib also reduce the rate of relapse if we give this treatment after frontline platinum-based chemotherapy?

When you read a clinical trial of any organisation/pharmaceutical company, or if somebody asks you to review a trial, you need to understand the problem and the hypothesis. What is the intervention? What is it the trial supposed to demonstrate?

In summary **the hypothesis behind PRIMA was to test the efficacy and safety of niraparib after response to platinum-based chemotherapy in patients with newly diagnosed ovarian cancer.** When you read a protocol of a clinical trial, you need to try to understand what the hypothesis is that the trial is supposed to prove.

The Study Population

Once you have defined the problem, and you have defined your hypothesis or the question that you want to answer, you need to define the population. That is critical in order to have a methodology. To be very precise in this methodology, you need to very accurately define the population of patients that will receive the intervention. In summary what we decided was to study patients with high-grade serous or endometroid carcinoma; patients with clinically high-risk factors defined as stage IV or stage III with residual tumour after primary debulking surgery or patients with stage III that had response to neoadjuvant platinum-based chemotheraphy. That means that at the end of chemotherapy, they have all shown that they are sensitive to platinum-based chemotherapy - that they have responded.

And as a very important point for this trial, we asked the investigators to provide tumour tissue from the patients to determine biomarker status.

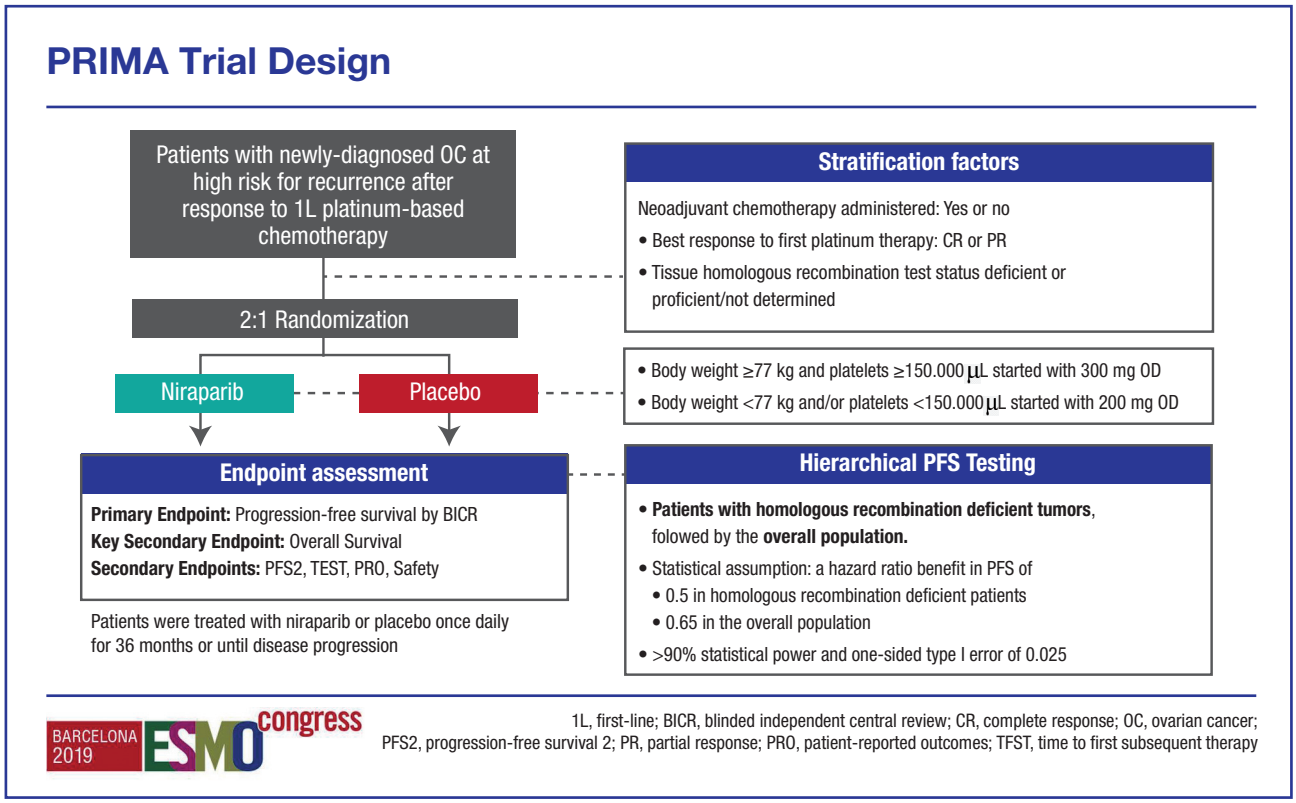
So, when we have now roughly defined our population as newly diagnosed patients with ovarian cancer and of high risk of recurrence after response to first-line platinum-based chemotherapy, I hereby introduce two concepts.

One is

- ✔ **Randomization**

and the other one is

- ✔ **Stratification factors**



Randomization

What does randomisation mean? Randomization is essentially to provide the treatment to the patient by chance – in a random way. The patients are not selected by us in the clinic as to who will receive what treatment because that would introduce a bias in the trial. In this case the randomization was between two options. One is the intervention, which is niraparib, and the other is placebo, which is standard of care. Why placebo in this case? - because you might claim that placebo is not an ethical procedure. That is another question that you probably need to ask in a trial: Is it ethical to include placebo in this trial? At the time when we designed the PRIMA study, the standard of care for many patients around the world was just chemotheraphy followed by surveillance, by follow-up. In some countries we also had the opportunity of giving the patients bevacizumab but that was not a standard of care across the world so that is the reason why using placebo was ethical in this trial.

Two out of three patients received niraparib and one out of three patients received placebo. But this distribution - this randomisation of niraparib and placebo was not completely by chance.

Stratification factors

We introduced what we call stratification factors. What is a stratification factor? This is a factor that may have an impact on the result of the trial by itself. This is a factor that if it is not well-balanced between both arms of the trial, you may have a result that is not influenced by the intervention of your drug, but instead by the influence that came from a confounding factor.

Let me give you an example:

In this trial we have included three stratification factors:

1) Neoadjuvant chemotherapy

2) Best response to platinum-based chemotherapy (CR or PR)

3) The biological characteristics of the patient (BRCAm, HRd or HRp)

If we focus on the first one, we know that patients receiving neoadjuvant chemotherapy usually have **a worse prognosis**. So, if we don't have a good balance between the group of niraparib and the group of placebo, the result of the trial might be influenced by this factor.

If you have more patients **without** neoadjuvant chemotherapy in the niraparib arm and we have a good result with niraparib, you could interpret the result as if the benefit is because of niraparib, but maybe the better result is not because of niraparib, but because you have included patients with a better prognosis in the niraparib arm.

That is the reason why we need to have these prognostic or stratification factors. The majority are **prognostic factors**; that means factors that will influence the prognosis of the patients but sometimes we also include **predictive factors**. That is a factor that may predict the benefit of the intervention – in this case niraparib. We know that patients that have homologous recombination deficient tumours have a better prognosis, a better response to niraparib. That is something that Dr Mirza showed in the NOVA trial.

So, the two concepts above were the randomisation and the stratification factors.

The next factor is **the endpoints**.

First you have a hypothesis. The hypothesis is that if you give niraparib to these patients after platinum-based chemotherapy, they will have a better outcome. But you need to be very precise again how to define that outcome. This is the **primary endpoint of the trial**. You need to identify the primary endpoint in a trial, which is the main reason for which the trial was designed, and also **the secondary endpoints.** They are aspects that you are also exploring or analysing but they are not the main reason you are doing the trial. The main reason is to demonstrate the benefit in progression-free survival, to demonstrate the benefit of giving niraparib in the outcome of the trial, and the way that we decide to measure the outcome was as **PFS - progression-free survival.** This is a concept that is essentially defined by the time from the randomisation of the patient to the date of progression or death due to any cause. The methodology of a clinical trial needs to be very clear as to how you are going to measure your endpoint. As to progression-free survival we decided to measure the disease using certain procedures every 12 weeks. This can be done using the RECIST criteria, which means that if we see an increment in the size of a nodule or disease that disappeared with chemotherapy, it will be considered **progression of the disease.**

In this trial the CT scan or the MRI was the imaging study that was performed every 12 weeks. There were other criteria for defining progression of disease, for instance the increment of the tumour marker CA125 in addition to very clear symptoms or signs of progression of disease, for instance abdominal pain and bowel obstruction, which are clinical features that are clearly related to progression of the disease.

Another important issue in the PRIMA study regarding methodology is that all the imaging procedures were reviewed by a blinded independent radiologist **(BICR - Blinded Independent Central Review)**; so this in addition to the use of placebo and the trial being double-blinded (as regards medication, doctors and patients) gives the trial a more robust conclusion because everything that diminishes the potential bias of the investigator assessing the results is something that we should avoid in order to improve the robustness of the trial and the possibility of making this new intervention a future intervention in the clinic.

Secondary endpoints are important aspects that we would like to analyse in the trial, but they are not the top priority. In this case they were overall survival, which is obviously very important, and PROs – patient-reported outcomes.

In the PRIMA study we used four different tools for measuring patient-reported outcomes periodically.

- ✔ Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI)
- ✔ The European Quality of Life five-dimension, five-level questionnaire (EQ-5D-5L)
- ✔ The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC-QLQ-C30)
- ✔ The EORTC Quality of Life Questionnaire Ovarian Cancer module (EORTC-QLQ-OV28)

In addition to the primary endpoint, which was time to first progression, we included some additional **surrogate endpoints** that are also reflecting what is happening when you give niraparib to your patients. For instance, the time to first subsequent therapy (TFST). That means the time between randomization and the day of the next treatment after niraparib or placebo, or time to progression on the next anti-cancer therapy (PFS2). Imagine that the patient has progressed on niraparib or placebo and receive another treatment, and then progress again and again, so the time from the beginning to the second progression or time to the CA125 tumour marker progression, and also of essential importance **the safety and tolerability of niraparib**; so, these are the endpoints of the trial.

Statistical Analyses

Another important piece of information that you need to identify in the trial, which is much more technical but also important to identify, is the statistical assumption of your trial. It is something that you need to define before starting the trial. Or in any case BEFORE finishing the trial or analysing the trial. You need to define in advance what is the level of benefit that you expect with the drug because that will also influence the number of patients that you need to include in order to demonstrate that benefit. In this case we performed what we call a hierarchical analysis, which means that we first analyse a group of patients - in this case patients with molecular recombination deficiency (HRD). If that analysis was shown to be statistically positive, then we would analyse the whole population. What we expected from

the trial was for niraparib to demonstrate a reduction in the risk of a relapse of at least the 50% in the homologous recombination deficient group of patients. If that was positive, then we would move to the ITT population (the Intention to Treat Population) i. e. the overall population and the reduction in the risk of progression should be 35%. That was the statistical assumption of the trial. If you – as a patient – read the trial, you need to understand what the investigator is expecting from the intervention. Maybe you don't have the knowledge to adequately interpret the hazard ratio or other statistical information but at least to have an idea of what is expected from the statistical analyses.

Patient Population and inclusion/exclusion criteria

PRIMA Was Designed to Address the Unmet Need in 1L Advanced OC

Hypothesis: PRIMA/ENGOT-OV26/GOG-3012 was designed to test the efficacy and safety of niraparib therapy after response to platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer, induding those at high risk of relapse (ClinicalTrials.gov: NCT02655016)

Key Inclusion Criteria

- High grade serous or endometroid pathology
- Stage III: PDS with visible residual disease post surgery, NACT, or inoperable
- Stage IV: PDS regardless of residual disease, NACT, or inoperable
- CR or PR following platinum first-line treatment
- Tissue for homologous recombination testing was required at screening (Myriad MyChoice)

Key Exclusion Criteria

- Patients with Stage III disease who have had complete cytoreduction (i.e., no visible residual disease) after PDS

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1L, first-line; CR, complete response; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; PDS, primary debulking surgery; PR, partial response

In the slide above you see the population that was included in the PRIMA trial. They had high-grade serious or endometroid tumours, stage III or IV disease where the patients could be inoperable or could have stage IV disease regardless of post-operative residual tumour or a stage III with macroscopic disease after primary debulking surgery or any patients receiving neoadjuvant chemotherapy regardless of residual tumour. All patients needed to have a response to platinum-based chemotherapy.

PRIMA Trial Inclusion Criteria

- Intraperitoneal chemotherapy allowed;
- Completed ≥6 and ≤9 cycles of platinum-based therapy;
- ≥3 cycles of platinum therapy before and after surgery (NACT patients);
- Complete or partial tumor response to platinum-based regimen after ≥4 cycles of therapy (per physician assessment)
- Any residual tumor after chemotherapy must measure ≤2 cm;
- Either CA-125 in the normal range, or CA-125 decrease ≥90% during that is stable for at least 7 days (i.e., no increase >15% from nadir)
- Patients must be randomized within 12 weeks of the first day of the last cycle of chemotherapy.

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Vocabulary: nadir = the lowest point

But in the inclusion criteria of the trial there is a very long list of criteria because we need to have a very homogenous population to avoid the bias of balance in prognostic factors and in patient characteristics; so, we need to have a very homogeneous population and in addition to that we need to have stratification factors. Therefore, in this case we defined the number of cycles of chemotheraphy and the need of complete or partial response to therapy. We defined the quality of the response. It is not the same if the patient has a partial response to platinum-based chemo than if she has a very good response to platinum-based chemotherapy. The patients that we included in PRIMA trial were patients with a very good response to platinum-based chemotherapy and who had a reduction in the level of the tumour marker CA125. Also, the time from the end of chemotherapy and the randomization needed to be defined, and it was defined as a period of 12 weeks.

Homologous Recombination testing

Patients with ovarian cancer and specifically high-grade ovarian cancer are a heterogeneous population. One of the most important biological features that they have is mutations in the BRCA gene and also some kind of deficiency in the repair mechanism of the DNA that leads to some sort of genomic instability in the tumour. That is something that happens approximately in half of the patients. It's a predictive factor of response to PARP-inhibitors and also to chemotherapy. It is such an important factor that we need to have it under control in the trial.

PRIMA Trial Inclusion Criteria

Patients must agree to undergo tumor HRD testing.

- The HRD test result must be available for randomization as it is a stratification factor. Patients with documented gBRCA1 or gBRCA2 mutation or sBRCA1/2 mutation may be randomized without HRD test results
- The tumor sample may be submitted for HRD testing prior to the screening period if it appears the patient is likely to meet other eligibility requirements. Patients are not required to have repeat HRD testing if HRD result is „not determined“ (eg, due to insufficient tumor specimen)

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Vocabulary: gBRCA1, gBRCA2 = germline BRCA (hereditary)
sBRCA1/2 = somatic BRCA (not hereditary)

That was the reason why we asked the doctors to provide a piece of tumour that was obtained during surgery to analyse this tumour using Next-Generation Sequencing of the DNA. The test was done at Myriad Genetics, which is an American company using the Myriad Choice Test. This test is done in order to identify and separate the patients with deficient tumours from patients with proficient tumours, i.e., those patients who have problems in the repair of the damage of the DNA from those patients who can easily repair the damage in the DNA. This is a rather complicated test using 3 different alterations in the DNA that can be detected by the technology of NGS (next generation sequencing).

This type of testing is another important topic in the clinical trials that we are running right now. We are requesting tumour tissue at the beginning and sometimes during the treatment in order to be able to analyse the changes in the tumour produced by the treatment. From a scientific point of view, it is very important to have a good biomarker. Sometimes many biopsies are taken, which can be a discomfort to the patient, but if the biopsy is really necessary and well explained to the patient, then that could be one of the ways to improve our treatment of cancer in the future.

Exclusion Criteria

We also have a long list of why we need to exclude patients with specific problems that should not be treated with our intervention. For instance, when you are treating a patient with niraparib, the patient needs to have a good bone marrow function and that is the reason why we exclude patients with problems during chemotherapy.

Exclusion Criteria (2)

- Patient has received bevacizumab with their first-line platinum based therapy
- Patient has had investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study
- Patient has had any known ≥Grade 3 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted >4 weeks
- Patient has any known history or current diagnosis of MDS or AML
- Patient has undergone major surgery (per Investigator judgment) within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery
- Patient has had drainage of ascites within 4 weeks prior to enrollment
- Patient has undergone palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment

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Study treatments / dose interruptions / amendment of the trial

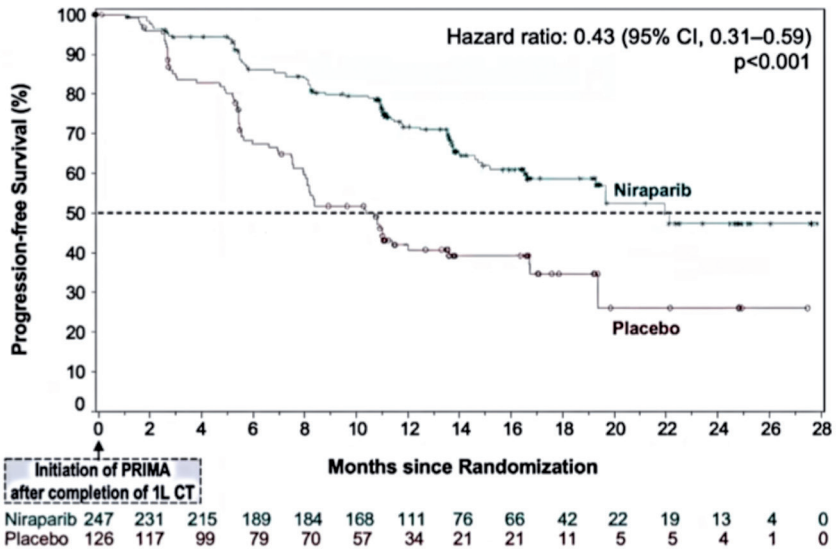
The last thing I would like to highlight is that we have a clear definition of the treatment: the dosing, modifications, dose interruptions, transitory interruption or definitive interruption of the treatment based on the effect that the treatment is producing on the patients, for instance before the amendment of the trial, we treated all patients with 300 mg of niraparib; that means 3 capsules of niraparib. In cases where we had some adverse events or serious adverse events, we interrupted the treatment, stopped and waited for up to 28 days before restarting, re-initiating the treatment.

If the patient e.g., had a platelet count of less than 75.000 you must interrupt the treatment, and you have to take weekly blood counts until you reach 100.000 and then you can resume the treatment with a reduced dose. This is just an example to show you how detailed the protocol of the intervention is in a clinical trial.

Conclusion

My conclusion is in the two slides below: With this intervention we used niraparib and we were able to demonstrate that niraparib prolonged the time without progression significantly in patients with recombination deficiency and also in the overall population regardless of homologous recombination status. So, in summary niraparib provide a new option for our patients to prolong the progression-free survival after chemotherapy.

Patients at the 50% mark – HRD



57% reduction in hazard of relapse or death with niraparib

	Niraparib (n=247)	Placebo (n=126)
Median PFS		
months (95% CI)	21.9 (19.3–NE)	10.4 (8.1–12.1)
Patients without PD or death (%)		
6 months	86%	68%
12 months	72%	42%
18 months	59%	35%

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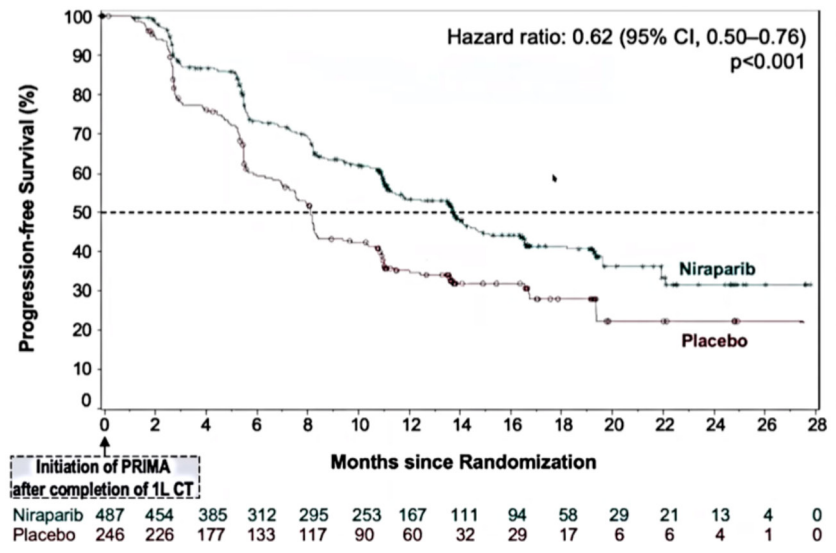
1L, first-line; CI, confidence interval; CT, chemotherapy; HR, homologous recombination; NE, not estimable; PD, progressive disease; PFS, progression-free survival; Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.

Patients at 50% mark – Overall population



38% reduction in hazard of relapse or death with niraparib

	Niraparib (n=487)	Placebo (n=246)
Median PFS		
months (95% CI)	13.8 (11.5–14.9)	8.2 (7.3–8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

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1L, first-line; CI, confidence interval; CT, chemotherapy; PD, progressive disease; PFS, progression-free survival; Discordance in PFS event between investigator assessment vs BICR = 12%.

Questions
from the Audience at 1st webinar

How do we define the number of patients that is needed in a trial?

(Antonio)

You probably have access to the webinar that we did in 2019 in which we explained the different types of clinical trials and that we have different phases: phase 1, phase 2 phase 3 because the number of patients depends on many factors. First of all, the phase of the trial. In phase 1 when you start to study a drug in a population, you need a smaller number of patients - usually less than one hundred but sometimes nowadays we are increasing the number of patients in phase 1. Then you go to phase 2, in which you define the drug, the safety and how to use it. In phase 2 you need to have some notion of the activity of that drug in a specific population. That is a trial where we have between 30 to 100 patients, no more than that. And then you go to phase 3 when you want to demonstrate that your drug will improve the outcome of the patients in comparison with standard of care through the intervention, surgery, or other methods. And that is a crucial point because you have to define how many patients you are going to treat with the new drug/the intervention or without the intervention in the randomisation. The main factor to define the number of patients is first of all what we call HAZARDATION. Hazardation is the probability of success. If the probability of reducing the risk of something is 50%, then you need few patients. But if you say: well, I want to reduce the risk by 20%, then you need a much higher number of patients to demonstrate the same from a statistical point of view. The second crucial point is the DURATION OF THE RECRUITMENT. If you want to recruit patients over 1 year, 2 years, or 3 years that will also influence the number of patients in the trial and finally – I would say the concept that we call the DROP OUT. That is the number of patients that you select, but in the end, you cannot include them in the trial, or they start but they will not be able to continue. If you have a huge number of dropouts, you need more patients because at the end of the day you need to have a sufficient number of patients that have received the intervention and the follow-up.

There was a request for a list of medical abbreviations.

(Antonio)

If the protocol is well written, you will find – at the very beginning – a list of abbreviations. If not, the protocol is not well-written because we use a lot of abbreviations and if they are not included in the protocol, it is poor quality. So, there is a very simple way to have an idea of the quality of the protocol: look for the list of the abbreviations!

(Birthe)

In the first Study Book there is a list of abbreviations and acronyms. All the abbreviations and acronyms of the PRIMA study are attached to this Study Book. But as Antonio said all trials should have a list of abbreviations and acronyms.

Patient

How do we know if the patient is at high risk of recurrence?

(Antonio and Murat)

We know that ovarian cancer patients for example have a poor prognosis if they have not undergone primary surgery. This is different in endometrial cancer, and also different in cervical cancer. Doctors learn from experience over time, but sometimes a trial includes all patients. Sometimes it includes low-risk patients and sometimes it includes high-risk patients. The PRIMA trial is exclusive because in this trial – as you saw in the last slides – the drug is working both in the genetically mutated and non-mutated population.

Patient

What is the next step? Approval by the authorities to use it as standard of care.

(Antonio)

The next step is of course approval by the authorities (FDA, EMA) and after the authorities' approval by the local authorities in the individual countries for reimbursement. It really takes time.

Could the patient representative have a role in this step?

(Antonio)

Honestly, what we can influence is to provide evidence that something is really good for the patients. That is our responsibility, that is our task. Once we have provided data, the approval by the authorities, the reimbursement, the commercialisation are a very complicated processes with many challenges depending on the country, depending on the economic situation or even the region. So our task is to provide good evidence for drugs to cure patients.

There was a question to the exclusion criteria.

■ Can the doctor change the exclusion criteria during the trial if a patient wants to enter the trial?

(Antonio)

Usually, the inclusion and exclusion criteria are very stable along the duration of the trial, but you are right that sometimes when you have new significant information you may change the trial while it is running. For instance, we have got several trials in ENGOT where we have started with immunotherapy and after a number of patients were included, we realised that it would be important to have a new stratification factor based on the expression of a protein. That is something that we can include in a trial. We can change it, if it is justified. The way in which we change the protocol is called an amendment. We have to submit the protocol to the health authorities again with our proposal of change and that needs to be accepted by the health authorities and the ethics committees. If it is well justified, you usually get the approval of the amendment.

I just want to add that if you think that you can change the criteria to include a single patient, that is not possible. The inclusion criteria are very stringent and cannot be changed to accommodate a patient to enter the trial if that was your question.

■ Wasn't it the case in the prima trial there was an amendment from 300 milligrams to 200 milligrams during the trial?

(Antonio)

After the NOVA trial Mansoor and colleagues demonstrated that patients with a weight under 77 kilograms or less than 150 000 platelets in the baseline blood test did not tolerate the 300 milligrams very well, but if they instead started with 200 milligrams, they could have the same efficacy with much less haematological side effects. When we made that important observation, we included an amendment in PRIMA trial to these individualized starting doses according to the body weight and the baseline platelets counts because it was in the favour of our patients.

Are you telling the patients once you finished the trial if they were in the placebo group?

(Antonio)

That's something I have also prepared. Let me show you this slide.

- Patients, investigators and associates, and TESARO scientific study will be blined to HRD status and treatment assignment
- The investigator may be unblinded to HRD status and/or study treatment for **important medical reasons** (as determined by the investigator) and for **specific non-urgent medical events**
  - Study treatment assignment and tumor BRCA status will be available to the investigator upon request for post-study treatment planning
- The process for unblinding the identity of the assigned treatment is outlined in the Pharmacy Manual
- Once a patient's HRD and/or treatment status is unblinded, the patient will be permanently discontinued from study

BARCELONA 2019 ESMO congress

That is the unblinding procedure. The patient needs to understand that when she started the treatment, the patient and the doctor were both blinded to the treatment. We don't know if the patient is taking niraparib or if the patient is taking placebo. And there are some rules for opening the blinding. For instance, if the patient has an important medical reason or is suffering from some unexpected side effect, then the doctor needs to know if the patient is taking another medication which could be a reason for asking the sponsor of the trial to unblind the treatment, or if the patient has a relapse one year after she has participated in the trial. Then you need to know whether the patient received the PARP-inhibitor niraparib during the trial; so that could be another reason for a request of unblinding. So there are some procedures to do that. What we do not do is to inform all of the patients at the end of the trial if they were receiving the intervention (in this case niraparib) or placebo.

I recall an exception though. There was a case in a trial with breast cancer patients where treatment in one of the arms was clearly inferior to treatment in the other arms. There was an interim analysis carried out by an independent data monitoring committee. Such a committee consist of external people that periodically review that a trial is safe and is carried out in accordance with good clinical practice and so on. They detected that one of the arms was clearly inferior, and in that case, you have to stop that arm and inform the patients that they are receiving an inferior treatment and offer the patients to receive a better treatment. So, there is a lot of protection for the patient when you participate in a clinical trial.

In the clinical trial – beside the medical criteria that you have provided – do you also take the social background, the social support of the patient into consideration since this can affect the results?

One criterion in the long list of inclusion criteria is – generally speaking – that the patient has to be able to follow the procedures of the study. That means that if you have a patient who has some kind of psychiatric illness so that patient might not be able follow all the procedures that we need her to follow, or imagine a patient that lives in another country and does not have enough resources to come to the scheduled consultations or staying in contact with the centre running the trial, then we cannot include the patient in the trial. Most of the patients that we see in our clinics are patients that have some kind of support from family or friends. They are very committed to the disease, the treatment, and the trial.

Patient

The reason why I asked this question was that I am in various groups on Facebook, and I see sometimes that there are people who have no support, or they may be living alone, and they are in a really bad state when they go into treatment compared to others who might have a good family background and full family support. That was my question because that might have an influence on the outcome. Maybe the drug is good, the clinical trial is good, but this can affect the result of the trial. That was my question.

(Jalid)

Yes, so again, I think this is one of the reasons why we need your input, because, again, regarding quality of life it is not only the drug that has an influence on quality of life but in the trials that is what we are looking at because the environments of social activity, support and resilience in general are not covered in the trials and are not documented. I think this can be a new field to bring much more reality in this part of research so I totally agree it is not enough to believe that the drug can have an influence on everything, especially on quality of life and so maybe we have to include that kind of thinking in our trials.

Patient

What can we tell the patient beforehand about the outcome of the trial as to chance of cure or better quality of life?

(Antonio)

When you participate in a clinical trial, you cannot know in advance what the result will be. That is impossible for us. We cannot guarantee anything in a clinical trial. What we can guarantee is your safety, your protection, that the procedures are safe, and that the procedures are really needed but we cannot guarantee the result. We can explain to the patient the reasons why we are performing the trial, what the background is, the prior studies with that drug and why we think that it will improve the outcome of patients; but we have done a lot of trials that have demonstrated that the result is the same as the standard of care, or that the new drug is not adding any benefit.

(Jalid)

Yes, but nevertheless in most of the trials even being in the placebo arm is better than the classical standard of care because you are involved in a program and you will be monitored closely by doctors trained in the disease - and your outcome will be better in general – no matter which arm you are in. I think this is a very important message.

(Murat)

You are so right, Jalid. At least you will have the benefit that many doctors in the clinic will monitor you because you are a trial participant, and any type of side effect or tumour progression is so closely monitored and timely managed. At least potentially this may be an advantage.

ENGOT - ENGAGE collaboration

In connection with this first webinar there was also a discussion among the participating doctors as to where patients' insight may have a valuable impact on a clinical trial.

The question came from a patient.

Below are some of the comments from the doctors' side: Murat Gultekin, Antonio González Martín, and Mansoor Rasa Mirza

(Murat)

What point of the design of a clinical do you think patients could take part in as to the PRIMA trial, Antonio? What was the point when you would really have wanted to include patients' input if you had had the opportunity?

(Antonio)

That is something that we haven't done before. It is something that we are now starting to consider in some trials. I see that Laura Farrelly is connected to this webinar. I think she is the person with the most experience in engaging patients in the design of clinical trials because they have defined this process very well in the UK.

I can give you my thoughts. The patients are needed – **at the beginning when you design the trial** - specifically for some procedures. One very important thing is to review the ICF - **the Inform Consent Form** - just to give their opinion as to whether it is understandable or not. I think that they could also provide some feedback on the **number of procedures** and also even concerning **the endpoints**, e.g., in the **Patient Reported Outcome**. Does it make sense to them or are they missing something important points that are not included? That is a process that we would like to start but so far we haven't started it.

(Mansoor)

I think I made it very clear what we want to do:

Involve patients to comment on the informed consent and also to discuss **the endpoints** and get their opinion. Is it something that they feel would change their outcome? This is what we could start out with.

(Murat)

Yes, I totally agree. I think first of all at every step in the clinical trial from starting the idea and up to the interpretation and even giving feedback to the community there is always space for the patients and advocacy groups. And the second thing is that we always talk about **quality of life but we know that quality of life based on patient's perspective and doctor's perspective are sometimes different** and we have not really solved that problem so I think this might be a challenge: we can really take the next step in quality of life, or daily activity, or patient expectations by including patients in the secondary endpoints. We might even be able to define **the weakness of our research and the strength of our research**. That might be the benefit of such a collaboration.

Summary of the doctors' expectations to patient engagement:

- ✔ **At the design of a trial**
- ✔ **The Informed consent**
- ✔ **The endpoints – especially the secondary endpoints**
- ✔ **PROs on Quality of Life**
- ✔ **The Outcome – Is this something that will benefit the patient?**

Laura Farrelly, Trials Group Lead at Cancer Research UK and UCL Cancer Trials Centre, London, UK

Laura Farrelly was also present at the webinar. Below are some of her statements:

I think it is vitally important to have patient representatives involved in trials right from the very beginning; so, in our unit what we have done is, we have set up a group of women.

So, there is a group of women who we have engaged through the charity sector, and we have recruited them to be in our participant representative group.

We get them involved from the very beginning to give their feedback on whether they think the trial will be acceptable to women, to patients. Then we ask them to be on our trial management groups.

We have one of our ladies who has joined our trust hearing committee and who review all the gynaecological trials that are currently going through the gynae group so that is really, really helpful.

There is a lot of training involved sometimes and actually that's a good thing because it means that they get to learn, and they can ask specific questions.

2st webinar

Outcomes

February 24, 2021

ENGAGe – ENGOT Clinical Trials Project, Webinar 2

Outcomes

Moderators: **Karina Dahl Steffensen,** Vejle Hospital, Denmark
Dr. Murat Gultekin, Turkey

ENGOT presenter: **Prof. Jalid Sehouli**

Quote from Prof. Sehouli

"The endpoints in a trial are defined by doctors and scientists – not by patients. You have to learn how to be critical when studying a clinical trial - what is a strong point in a trial and what is not, and where can we improve the trial?"

Prof. Sehouli started by talking about clinical endpoints and evidence-based medicine. We need prospective randomized trials to get evidence-based medicine. There might be a hypothesis based on a retrospective argument which could result in a prospective randomized trial in order to find a solution. Is this treatment beneficial to the patient? This is the first barrier. The endpoints are not defined by patients, but by doctors, researchers, and authorities but at the end of the day we want to see if it is beneficial for the patient.

If we look at the PRIMA trial, what was the primary objective?

The primary objective of the trial was to test the efficacy and safety of niraparib maintenance therapy after a response to platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer at high risk of relapse.

The secondary objective in a trial might not be statistically powered enough to give a definitive answer – it might just be descriptive. The statistical power regarding number of patients or so-called events might not be strong enough. That is the reason why it is placed as a secondary objective. So, secondary objectives might be important from the patients' perspective, but from the trial, they are supportive information.

Statistical analysis

There can be a superiority or inferiority problem in the statistical analysis to identify a difference, but no difference does not mean the same as equal. It takes more time and more patients to show that something is equal. Conclusions from trials should not be too optimistic and not too conservative.

So, you should always check the primary objective. Is it realistic? The researchers are trying to find a difference.

Sometimes the budget is limited or there are not enough patients in the trial, then we have to be careful when interpreting the outcome. *Science must be authentic, realistic, and transparent. We have to look at transparency.*

The primary endpoint is the endpoint for which the trial is powered.

There must be a statistical analysis plan including demographics, stage of disease, residual tumour mass, comorbidity etc. Data must be evidence-based, otherwise you might find something that you never had in mind, but the statistical power is weak. The statistical analysis plan must be pre-planned and pre-specified.

Surrogate endpoints are trial endpoints that have outcomes that substitute a clinical endpoint. In most cases you are looking for a cure, but you have to look for a very long time - 5-10 years. You might not be able to wait that long. The company might be pressuring for secondary surrogate events.

The endpoint PFS might give you a hint for OS. You look for response on the tumour marker. This is a hint for survival, but not a surrogate marker for survival. PSF is not one to one with OS.

So, surrogate markers are nice but not strong enough because the translation of response, progression-free survival, relapse-free survival are not one-to-one with overall survival. That is very critical. There are trials where you have significant differences in progression-free survival, but no differences in overall survival.

There can be a long PFS, but no difference in OS. Sometimes it is the other way round. This is the case in all cancer diseases – not only in ovarian cancer.

The point is to be critical when studying a clinical trial. What is a strong point in a trial and what is not, and where we must improve the trial?

In the first webinar there was a lot of discussion about acronyms and abbreviations. Below is a description by Prof. Sehouli of some essential acronyms:

IMPORTANT ACRONYMS

RR Response Rate (imaging, biomarker, clinical symptoms) Clinical benefit (CR+PR+SD), only for patients with measurable disease. Response is when you can see that the disease is shrinking e.g., after chemotherapy or maintenance treatment - where you can see the tumour. If you resect the tumour by surgery, then there is no measurable disease – even if there is less than 1 cm; you cannot see it on imaging (CT/MRI). You can only talk about response rate where you are able to see the tumour; then the results can be **CR** = complete response, **PR** = partial response or **SD** = stable disease. If there is no residual tumour mass, you cannot talk about Response Rate. Then it is called no evidence of disease - **NED**. Response rate cannot be used as a primary endpoint like PFS or OS. It is not strong enough. It is used in a palliative setting to show **clinical benefit** including **stable disease**.

The biomarker CA125 is used in ovarian cancer, but it is not sensitive enough. It does not work in endometroid ovarian cancer, in low grade ovarian cancer, nor in clear cell ovarian cancer. After surgery it decreases but it is like a curve and has to be measured over a period of several months after surgery.

RD Response Duration – tumour is shrinking, but for how long? When we know also depends on how often the patients has a scan. For instance, the definition of platinum-resistance is that if you give chemo, complete response in general is zero, partial response in general is 20 %, but the duration is generally only 2-4 months. It is not very long. And that's the reason why you have to look at response duration, which depends on how frequently you see the patient and what methods you use.

DFS Disease Free Survival – no tumour, no measurable disease or **RFS** = Recurrence Free Survival means that there is no measurable disease, and you look at the time until there is a relapse. These are both defined as events on the curves if you look at the PRIMA trial or other trials.

PFS Progression free Survival - the time from randomization until objective tumor progression or death from any cause, whichever occurs first

PFS II Progression free survival after PFS I – when you see the progression, the treatment is stopped (in this case treatment with niraparib), but you measure the time to progression in the next relapse although this is not part of the study. But even here you see a longer progression free survival in the second relapse after treatment with a PARP-inhibitor. The patient has a longer time without ascites, without bowel obstruction, etc. However, the authorities want to see OS.

RFS Recurrence Free Survival - the length of time after primary cancer treatment that the patient survives without any signs or symptoms of the cancer.

TFST Time to first subsequent therapy (e.g., chemotherapy, surgery, ascites puncture, medical intervention)

OS Overall Survival – Studies are not powered for overall survival. Most studies are approved on PFS - not OS. We would have to wait for a very long time for the results of a study and the patient populations would have to be very large. There is no study, no drug in ovarian cancer - and we now have more than 15 drugs - that was approved on overall survival. They are all approved based on progression-free survival. Besides the treatment is so heterogeneous that sometimes the ensuing treatments might destroy the effect of the previous treatments. This is called **confounding factors**. It could also be the case that the patient has the opportunity of getting a second surgery with the lucky outcome that there is no residual tumour. Would it then be the treatment with a PARP-inhibitor or the surgery that had prolonged the patient's life – or a combination of the two?

Quality of life

QoL, multidimensional (generally only as a secondary objective)

PROMs – Patient Reported Outcome Measures – questionnaires that patients complete on their health and quality of life are very important. However, some of them are not suitable for maintenance treatment with a PARP-inhibitor.

EORTC QLQ-c30 and other questionnaires

We are still using quality of life measurement with the EORTC QLQ-c30 questionnaire from EORTC, which was developed 30 years ago for patients with lung cancer and then translated into many languages. The questionnaire is not strong enough to measure low toxicity. They were never developed for long term treatment.

What other factors impact QoL – response, social aspects, resilience, adaptations?

Quality of life studies should always be multi-dimensional with social, physical, and psychological aspects. 50 % of the items that influence QoL are scientifically unclear, and that is the reason why we have to develop better questionnaires. That is a problem in the PRIMA trial.

It also matters when the patient gets her questionnaire. Is it right after surgery or chemotherapy? We don't know where the patient started. We don't know the patient's social aspects, resilience, or educational level.

Limitations of QoL:

Who are the responders?
Who are the non-responders?
Who is asking and when? and how?

Questionnaires should be filled out by 80 % of the patients, and yet we don't know who the 20 % missing patients are. If the percentage is below 80 %, we should not trust the answers.

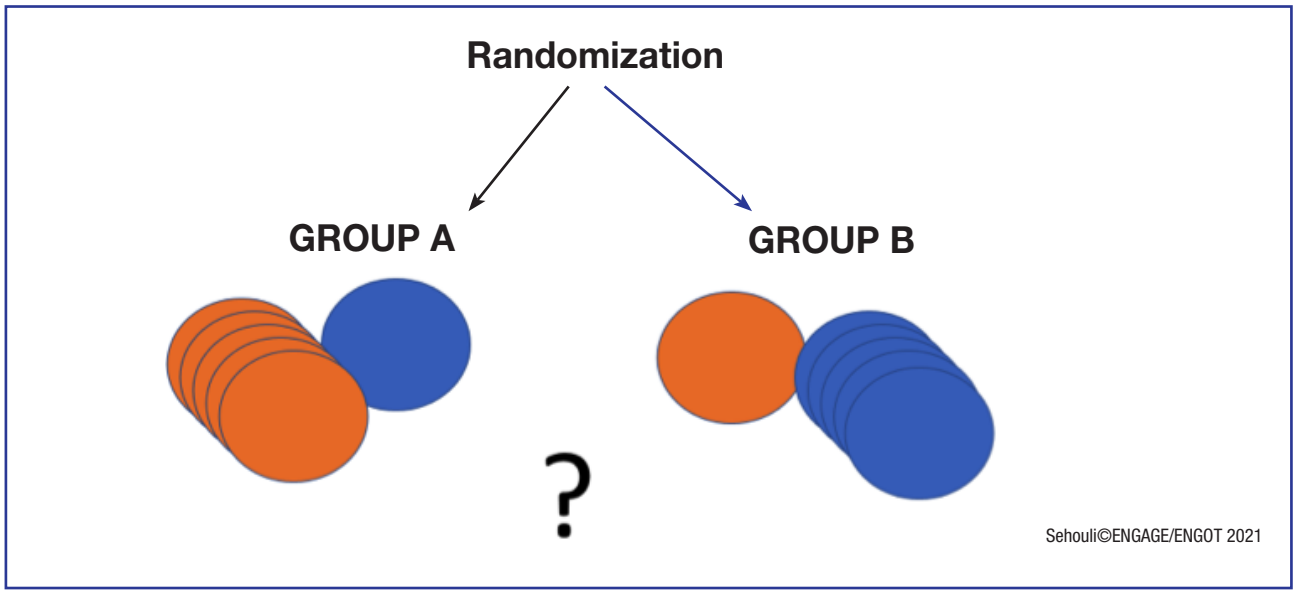
Discussion of Quality of Life versus Survival from the patient perspective

In the primary outcome of a trial what is most important to the patient OS, PFS or QoL? Survival is higher than quality of life - even poor quality of life. That is mostly the patient's answer in all studies involving QoL.

The ITT principle

The PRIMA trial is a randomized trial with a 2:1 randomization.

There was now a question from the professor on what to do if one of the patients in the trial got the wrong pill. One patient got the blue pill but should have received the orange pill. And another patient got the orange pill but should have received the blue pill.



Some of the members of the project suggested including the patient anyhow, and others suggested excluding the patient so as not to disrupt the general picture.

In a clinical trial there is the ITT principle. The ITT is the **Intention to Treat** population.

The right answer was that the patients should be analysed in the group where they are according to the so-called **Intention-to-Treat Analysis**.

The most important aspect in randomization is the randomization process because with the randomization process you try to balance known and unknown confounders that may influence the outcome of the patient: age, tumour load, etc. And this balancing of randomization is always from the perspective of evidence-based medicine of higher importance than any medical intervention. That is the reason why the patient will be analysed in the intention-to-treat analysis. No individual patient will be excluded. And in the ideal analysis you have a so-called Intention to-Treat Analysis and a secondary patient Per-Protocol Analysis, because in the Intention-to-Treat Analysis, even the patient in the wrong group will be analysed, and in the patient Per-Protocol Analysis you will look to see if the patient was really in the adequate group when she was treated.

This is a key point in a prospective trial. And even if you have made a mistake in a drug delivery, this is not as strong evidence as the Intention-to-Treat Analysis, and the statistical approach is not based on individual mistakes. It is always based on the group from the randomization process.

So, there is the Intention-To-Treat Analysis and the Patient Per-Protocol Analysis:

The Intention-to-treat analysis *is a method for analyzing results in a prospective randomized study where all participants who are randomized are included in the statistical analysis and analyzed according to the group they were originally assigned, regardless of what treatment (if any) they received. This method allows the investigator (or consumer of the medical literature) to draw accurate (unbiased) conclusions regarding the effectiveness of an intervention. This method preserves the benefits of randomization, which cannot be assumed when using other methods of analysis.*

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5654877/

Per-Protocol Analysis *This analysis will begin according to who actually received the intervention assigned by the protocol. This method of analyzing the data is called per-protocol analysis, also referred to as efficacy, explanatory analysis, or analysis by treatment administered.*

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5654877/

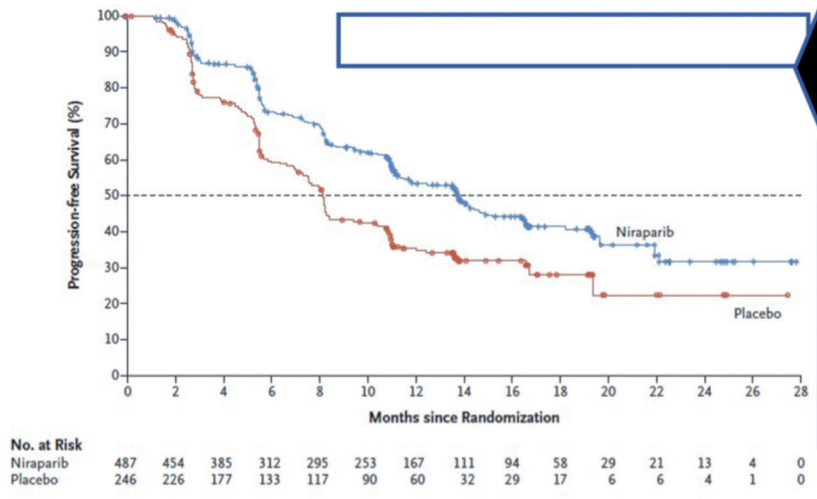
The PRIMARY endpoint:

PFS was discussed in the Overall Population and in the individual subgroups of the PRIMA trial. The hazard ratio should preferably be below 0.50. This was not the case in the overall population, but data are not mature yet. In the PRIMA trial there was **an event-driven cut-off date** for analysis after 13.8 months.

Explanation: Event-driven COD = Reaching a required number of events for overall survival or progression-free survival analysis that are pre-specified in the protocol and where the statistical analysis plan triggers formal analysis

Primary Endpoint: PFS in the Overall Population

Niraparib significantly reduced the risk of progression or death by 38% in the overall PRIMA population of women with newly diagnosed advanced ovarian cancer



	Niraparib (n = 487)	Placebo (n = 246)
Median PFS		
months (95% CI)	13.8 (11.5–14.9)	8.2 (7.3–8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

CI = confidence interval; HR = hazard ratio; PD = progressive disease; PFS = progressionfree survival
Gonzales Martin A, et al. N Eng J Med. 2019; 381:23912402; Gonzales Martin A, et al Presented at ESMO 2019, Barcelona Spain

Questions from the Audience at 2nd webinar

Unblinding

■ If a patient relapses, she will know if she received placebo or the actual drug, but if she doesn't relapse will she ever know?

If the trial is double blinded, the doctor does not know either. In general, nobody knows, but with major side effect e.g., in drugs like PARP-inhibitors where the patients in one arm are getting placebo, the patient and doctor will know, even though the trial is double-blinded. There will be drug-related side effects, e.g., leukopenia. (Leukopenia is a decrease in the number of leukocytes in the blood; they are the white blood cells and are the body's primary defense against infection.)

In immunotherapy where one of the side effects might be pneumonitis (inflammation of lung tissue), you need to know.

■ Is there a review upfront with the authors of the protocol?

Both at the FDA (US) and EMA (Europe) there is a possibility for trial groups/pharma companies to discuss a potential trial. They give advice.

EUnetHTA and Early Dialogue

Participation of a patient representative in Early Dialogues through HTAB (Health Technology Assessment Bodies) when a company/an organisation wants to find out if the drugs/procedure that they have in mind, has a chance of being reimbursed in the various European countries. Final meeting is at EMA between HTAB, the producer and a patient rep. who has had the disease.

The patient rep. has to study the same material as everyone else. She is interviewed for an hour beforehand and is asked to give her opinion at the meeting with the various representative from pharma, EMA and HTAB at EMA in Amsterdam.

(Birthe Lemley)

Is there a box in the Informed Consent where the patient can cross off that she wants to know the outcome of the trial?

Actually, that is not the case. In general, there is no information given to the patient after the trial. There is no structure to do that, but many patients would want to know. Something we could be working at altering?

Has COVID19 had an impact on the outcome of ongoing trials?

None of the doctors believed there would be an impact. Patients entering trials during a pandemic are normally strong patients. 😉

3rd webinar

Statistics in a clinical trial

March 18, 2021

ENGAGe – ENGOT Clinical Trials Project, Webinar 3

Moderators: Jalid Sehouli
Murat Gultekin

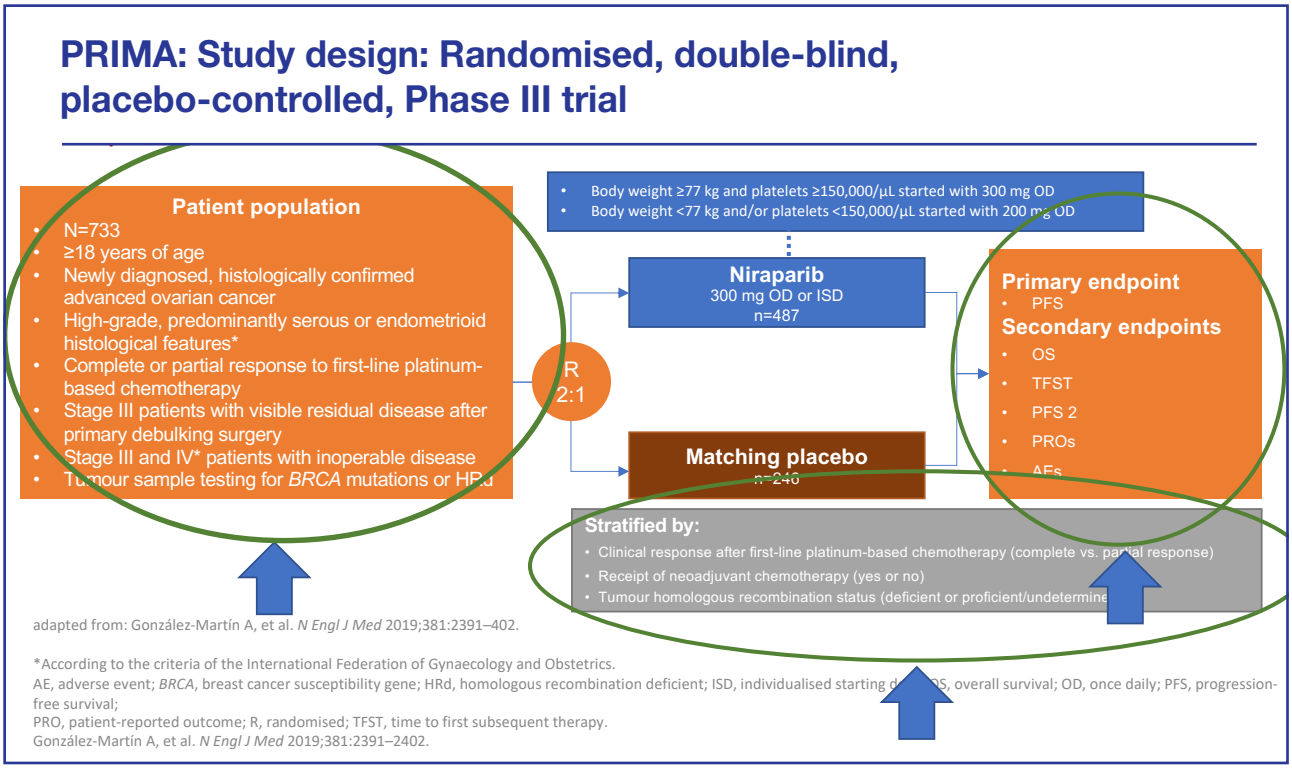
ENGOT presenter: Jonathan Ledermann professor of medical oncology in the UCL Cancer Institute, UK

Professor Jonathan Ledermann had been asked to talk about simple statistics in a clinical trial using the PRIMA trial as an example.

Simple statistics

Understanding simple statistics in a clinical trial and particularly with a focus on the PRIMA trial is the main topic for today with focus almost entirely on the PRIMA - niraparib trial, but one or two slides from other studies will be used for illustration.

The slide below shows the design structure in relation to the statistical analysis.



adapted from: González-Martín A, et al. *N Engl J Med* 2019;381:2391–402.

*According to the criteria of the International Federation of Gynaecology and Obstetrics.
AE, adverse event; *BRCA*, breast cancer susceptibility gene; HRd, homologous recombination deficient; ISD, individualised starting d…S, overall survival; OD, once daily; PFS, progression-free survival;
PRO, patient-reported outcome; R, randomised; TFST, time to first subsequent therapy.
González-Martín A, et al. *N Engl J Med* 2019;381:2391–2402.

Inclusion and exclusion Criteria

We have a population of patients where there are clear inclusion and exclusion criteria to enroll the patients, who are most likely to derive a benefit from the trial, and to exclude patients where it might not be safe to give the drug or where no benefit is expected. So, that is the population, and inclusion and exclusion criteria are very strictly adhered to in clinical trials.

The slide shows the trial schematically. As you already know it is a randomized trial. You will also see **the patient population, the primary and secondary endpoints, and the stratification factors.**

In his presentation the professor went on to give us an interpretation of the primary endpoints from a statistical viewpoint and also an explanation of the stratification factors.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Niraparib		Placebo	
	HRD Population (N=247)	Overall Population (N=487)	HRD Population (N=126)	Overall Population (N=246)
Median age (range) — yr	58 (32–83)	62 (32–85)	58 (33–82)	62 (33–88)
ECOG score — no. (%)†				
0	182 (73.7)	337 (69.2)	97 (77.0)	174 (70.7)
1	65 (26.3)	150 (30.8)	29 (23.0)	72 (29.3)
International FIGO stage — no. (%)‡				
III	161 (65.2)	318 (65.3)	78 (61.9)	158 (64.2)
A	4 (1.6)	7 (1.4)	1 (0.8)	4 (1.6)
B	10 (4.0)	16 (3.3)	9 (7.1)	12 (4.9)
C	140 (56.7)	285 (58.5)	67 (53.2)	138 (56.1)
Not specified	7 (2.8)	10 (2.1)	1 (0.8)	4 (1.6)
IV	86 (34.8)	169 (34.7)	48 (38.1)	88 (35.8)
Primary tumor location — no. (%)				
Ovary	201 (81.4)	388 (79.7)	105 (83.3)	201 (81.7)
Fallopian tube	32 (13.0)	65 (13.3)	13 (10.3)	32 (13.0)
Peritoneum	14 (5.7)	34 (7.0)	8 (6.3)	13 (5.3)
Histologic type — no. (%)§				
Serous	234 (94.7)	465 (95.5)	116 (92.1)	230 (93.5)
Endometrioid	5 (2.0)	11 (2.3)	6 (4.8)	9 (3.7)
Other	8 (3.2)	11 (2.3)	4 (3.2)	6 (2.4)
Receipt of neoadjuvant chemotherapy — no. (%)				
Yes	156 (63.2)	322 (66.1)	80 (63.5)	167 (67.9)
No	91 (36.8)	165 (33.9)	46 (36.5)	79 (32.1)
Clinical response after platinum-based chemotherapy — no. (%)				
Complete response	185 (74.9)	337 (69.2)	93 (73.8)	172 (70.0)
Partial response	62 (25.1)	150 (30.8)	33 (26.2)	74 (30.0)
Cancer antigen 125 level — no. (%)				
≤ULN	236 (95.5)	450 (92.4)	120 (95.2)	226 (91.9)
>ULN	9 (3.6)	34 (7.0)	5 (4.0)	18 (7.3)
Missing data	2 (0.8)	3 (0.6)	1 (0.8)	2 (0.8)
No. of cycles of platinum-based chemotherapy — no. (%)				
6	165 (66.8)	333 (68.4)	84 (66.7)	170 (69.1)
7–9	52 (21.1)	124 (25.5)	28 (22.2)	62 (25.2)
Missing data	30 (12.1)	30 (6.2)	14 (11.1)	14 (5.7)

Baseline Characteristics

- Factors that are important for entry
  - Relevant inclusion criteria
- Factors that might affect outcome
  - Eg stage III and stage IV patients
- Balance is needed
  - Can be achieved by large numbers
  - Randomisation by minimisation

Here there were two main subgroups HRD population and all with balance between niraparib and placebo

Explanation of terms in Table 1

International FIGO stage = International Federation of Gynecology and Obstetrics (FIGO) staging system

≤ULN = less than or equal to upper limit of normal

>ULN = greater than upper limit of normal

Above you see table 1 from the New England Journal of Medicine showing characteristics of the patients at baseline.

This is a table showing the baseline patient characteristics – niraparib versus placebo and on the left-hand side you will see the important factors that were considered for entry because some of these factors may have a bearing on the outcome of the trial. We know for example that patients with stage IV disease do less well than people with stage III disease. So, you want to make sure that there is a balance between the niraparib and the placebo arms in relation to stage III and stage IV disease. The patients have had chemotherapy, and neoadjuvant chemotherapy or postoperative chemotherapy, and you look across the table to see that there is balance. You will immediately see that there are 4 columns – two with niraparib and two with placebo, so why is that?

There was a major stratification into subgroups on the left-hand side, but if the trial is too small you may by chance just happen to have an imbalance.

Stratification

There are important factors for entering the trial. There are patients with stage III and stage IV disease. We know that patients with stage IV disease do worse than patients with stage III disease. Therefore, there needs to be a balance between the niraparib and the placebo arms in relation to stage III and stage IV disease.

You will also see that important inclusion criteria are listed both in the trial population in the first slide and also in the first column in Table 1.

In table 1 there are two columns with niraparib and two columns with placebo. This is because we need a major stratification into subgroups. If we have a large trial with hundreds of patients, the balance is usually pretty good, but if the trial is small – you may have an imbalance in the trial, which you should try to solve to avoid criticism of the outcome.

If the trial is very large trial with hundreds of patients, the chances are you may have a good balance across all those points on the left-hand side, but if the trial is too small, you may just by chance have an imbalance.

That is a problem when you are analyzing a trial because people might say you have too many patients with this or too few patients with that so in order to help achieve that balance in addition to stratification there are other ways in which the patients can be grouped when they are randomized this is sometimes called randomization by minimization to ensure that there is good balance and you can see it through all those variables here. There is a pretty good balance.

An example was shown with oranges and red ar

If we want to study round fruits in a clinical trial, we have to look at the subgroup of oranges apart from the group of red and green apples. That is what stratification does. It separates the groups that may be the key to affecting the outcome of a trial.

Stratification

So, when we had to look into the stratification, we had to look at a number of variables – e.g., response to platinum-based chemotherapy and whether the patient had surgery or neoadjuvant chemotherapy.

Then we looked at whether the tumour had HRD (Homologous Recombination Deficiency) as HRD was a key element in the trial.

When the results were first presented, they were first analysed on the HR deficient group of patients as this was the way the statistics were structured. The expectations were that niraparib would be most beneficial for this group of patients as a subgroup as we know that HR deficiency makes a tumour more likely to respond to a PARP-inhibitor. If the outcome was successful, then we would look at the statistics for the whole group of patients.

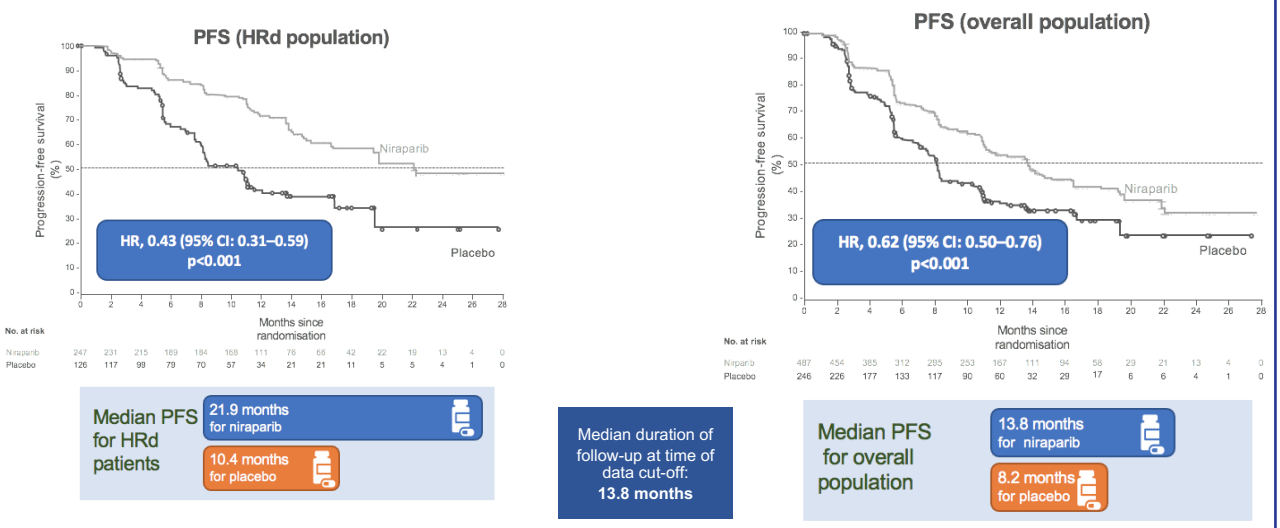
If you look at the slide below: **Progression-free Survival in the HRD population and the Overall Population,** you can see the PFS of the HRD group of patients (the oranges) and the PFS of the overall population (all the fruit).

The Primary Endpoint - PFS

We will now take a look at the curves and the primary endpoint PFS. PFS is defined as the time from random assignment in a clinical trial to disease progression or death from any cause. Progression in this trial is defined as a radiological progression (tumour now visible or enlarging) on a CT-scan according to RECIST (Response Evaluation Criteria in Solid Tumours). This can either be judged by the investigator or independently by BICR (Blinded Independent Central Review).

The survival is plotted as a 'Kaplan-Meier' plot, or Cox regression analysis and the two groups are compared.

Progression-Free survival in the HRD population and overall population



BRCA, breast cancer susceptibility gene; *BRCA*mut, *BRCA* mutant; HR, hazard ratio; HRd, homologous-recombination deficiency; PFS, progression-free survival; mut, mutation.
González-Martín A, et al. *N Engl J Med* 2019;381:2391–2402.

Kaplan-Meier plot explained:

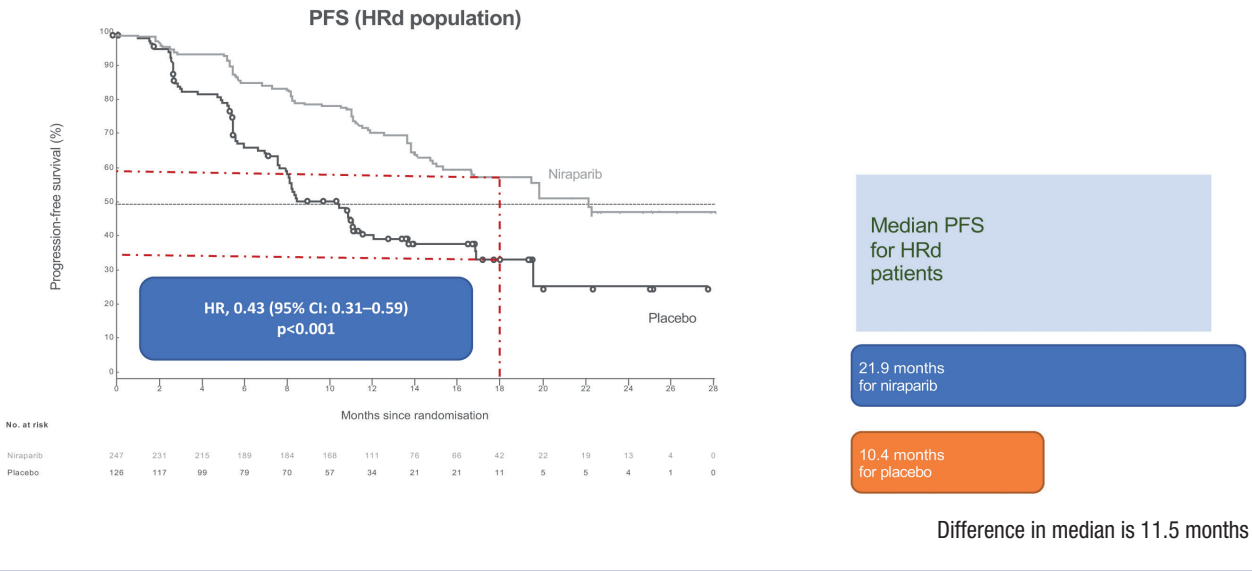
A plot of the Kaplan–Meier estimator is a series of declining horizontal steps which, with a large enough sample size, approaches the true survival function for that population. On the plot, small vertical tick-marks state individual patients whose survival times have been right-censored. *(Wikipedia)*

So having plotted the points of progression or death, you can plot the outcome against time and the proportion of patients being free of progression using the Kaplan Meier plot and by doing that you can compare the two groups of niraparib and placebo in trial. The numbers at risk (numbers at the bottom of the graph) become smaller with time. As the numbers become smaller, comparison of the two curves at later time points becomes harder and the maturity of the curve data becomes unreliable. Numbers will diminish as time goes on.

How can we compare the two curves? We have the median 50% value when half of the patients have progressed or died, and we can look at them in two groups and we call that the median i.e, the median time to progression. We measure the curves in months or sometimes in years using the 50% mark which gives us a point in time. What we really want to look at is the way the whole population is behaving over time. And to compare the two curves in that way across the whole period of time, we compare the difference between the two curves and that gives us the risk reduction of progression or death between the two curves, which is called the hazard ratio.

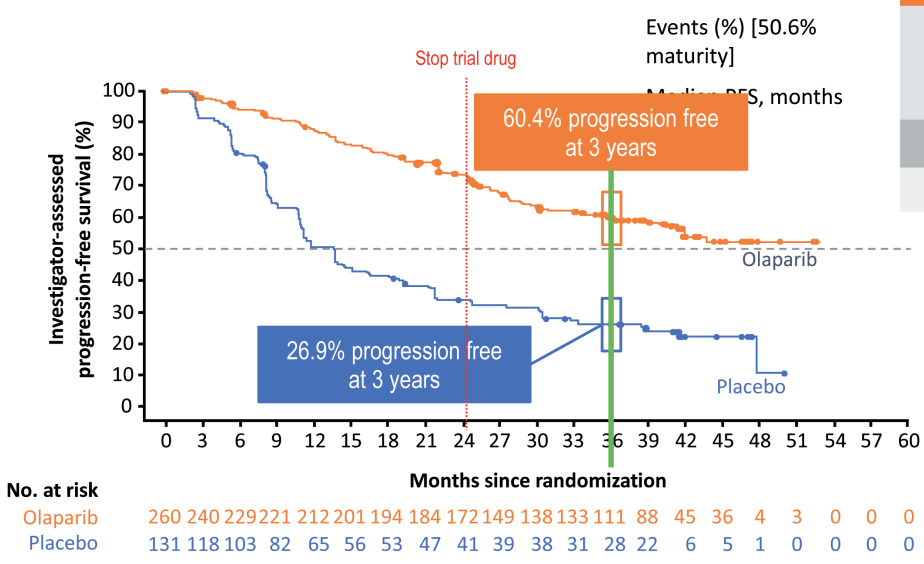
A third analysis that is sometimes done is **the landmark analysis** – which is a fixed-point analysis. What percentages are free of progression e.g., at 18 months?

PRIMA: Progression-Free survival in HRD population



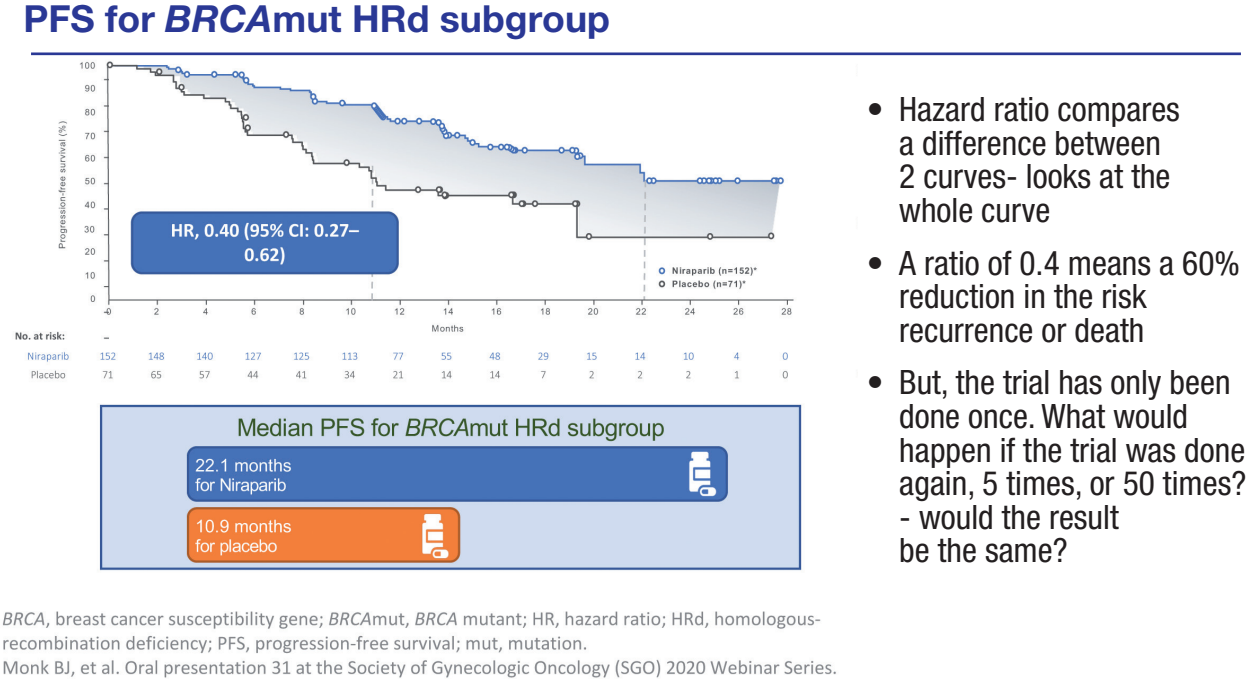
If we look at the HRD population, the curves are separated at the 50% mark by 21.9 months and 10.4 months, which means that there is a difference of 11.5 months – also called median PFS. You can see the red dotted line on the graph. That gives a fixed point of the 50% mark with a hazard ratio of 0.43, a confidence interval of 95% (0.31-0.59) and a P-value of less than 0.001. As we go through the numbers at the bottom of the graph, there are really very few patients out there. Is this a reliable figure at 18 months?

The SOLO1 trial as an example:



It becomes more reliable with the SOLO 1 trial with olaparib, when data are more mature at 36 months with a hazard ration of 0.30, when 60% in the olaparib arm are still alive compared to 27% in the placebo arm at three years.

The hazard ratio



The hazard ratio is a bit more complicated to understand. The slide shows the curves in the subgroup of the BRCA mutated population. The hazard ratio compares a difference between 2 curves and looks at the whole curve. The difference between the two curves – the grey area of difference - means that there is a 60% reduction in the risk of recurrence or death. The curves look at the whole area and gives a risk

reduction. A ratio of 0.40 means a 60% reduction in the risk of recurrence or death. Would we get the same result if we did the same trial 100 times? Probably not but the statistical confidence range is 95%. The result would still be within the 0.27-0.62 range. If the range is small, it is still true until it crosses 1.0 reading. If the range is wide and crosses 1.0, it may not be reliable. So, a confidence range well below one e.g., 0.40, is likely a real value. When we do a study, it gives us a higher degree of certainty.

The hypothesis in the study is that there is no difference – the null hypothesis. We have disproved the hypothesis. The P-value (probability value) is 0.001.

A P-value of 0.001 means that there is a 1 in 1000 chance of this being wrong.

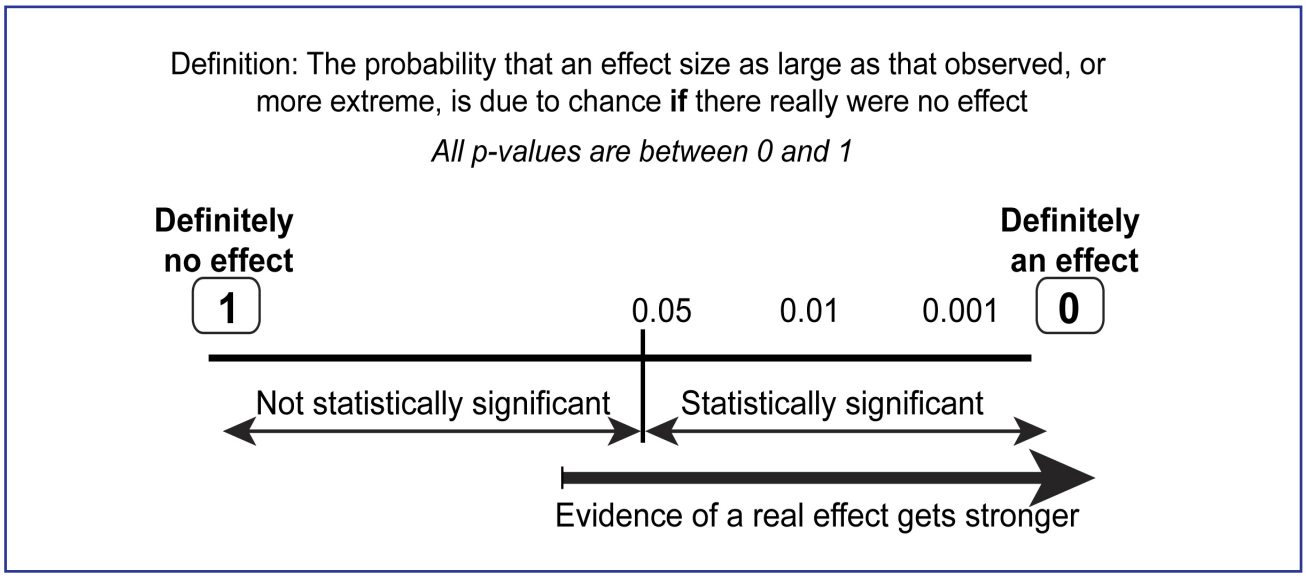
Confidence Limits

The confidence limits are 0.27 to 0.62. What does this mean? If there was no true difference between the curves, the Hazard Ratio would be 1.0. If the trial was done 100 times, on 95 occasions the hazard ratio would lie between 0.27-0.62.

The true effect of niraparib will lie between 0.27 and 0.62. The smaller the difference in range, the stronger the confidence of the effect.

As the 95% CI does not cross 1.0 there is good evidence that the observed value shows a reliable difference between the two groups.

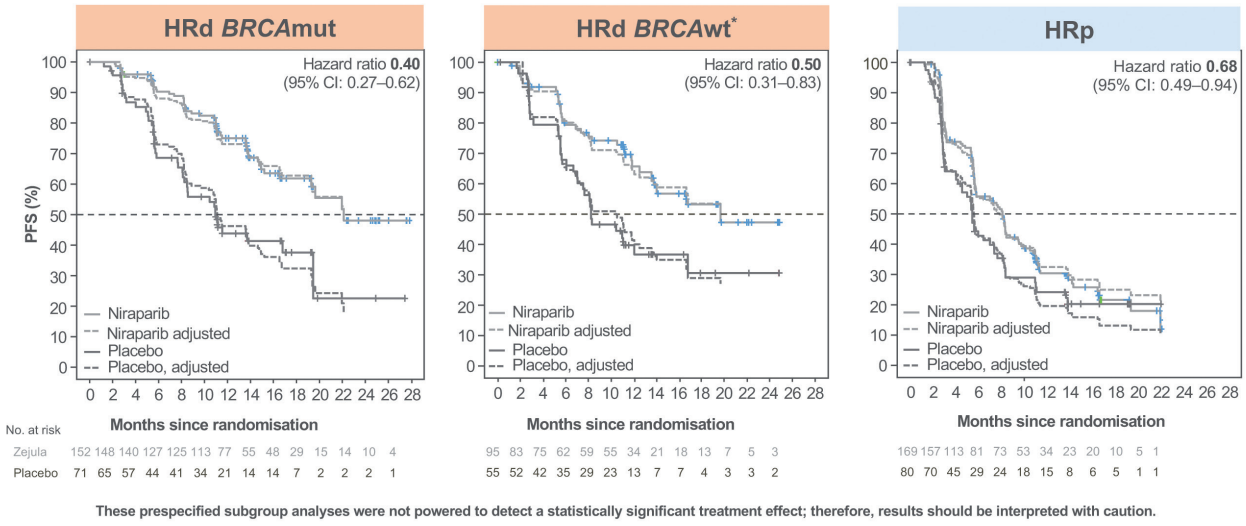
Statistical P-value



Could the Hazard Ratio value of 0.40 have come about by chance? Yes, possibly. How certain can we be that this finding is real? A hypothesis is set at the beginning of the trial that there is no difference between niraparib and placebo. The P value gives an indication of the probability that the HR is a real finding with P<0.001.

There is a 1 in a 1000 chance that the trial was wrong and that there was no difference, i.e., we could find no difference if we ran the same trial 1000 times, so highly unlikely that niraparib and placebo have the same effect and that the observed difference occurred by chance.

Progression-free survival across three defined subgroups, HRD BRCAmut; HRD BRCAwt; HRP



These prespecified subgroup analyses were not powered to detect a statistically significant treatment effect; therefore, results should be interpreted with caution.

Note: All subgroups were also analysed using the adjusted Cox regression method to account for stratification imbalances.
*HRd *BRCA*wt population represents all HRd patients who are not *BRCA*mut.
BRCA, breast cancer susceptibility gene; *BRCA*mut, *BRCA* mutant; *BRCA*wt, *BRCA* wild type; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PFS, progression-free survival.
Monk BJ, et al. Oral presentation 31 at the Society of Gynaecologic Oncology (SGO) 2020 Webinar Series.

We have already seen that the hazard ratios of the HRd BRCAmut is 0.40. Here you see the HRd BRCA-wt with a hazard ratio of 0.50 and the HRp – proficient with a hazard ratio of 0.68 which means a risk reduction of recurrence or death of 60 %, 50% or 0.32% respectively in the three groups. They all have a confidence interval of 95%. Statisticians have in time chosen that anything that has a P-value below 0.05 is significant. This means that P-value of 0.001 is highly significant. All of them have a confidence interval below 1.

Risk of disease progression or death across a variety of subgroups: Niraparib is compared to placebo- Forest Plot

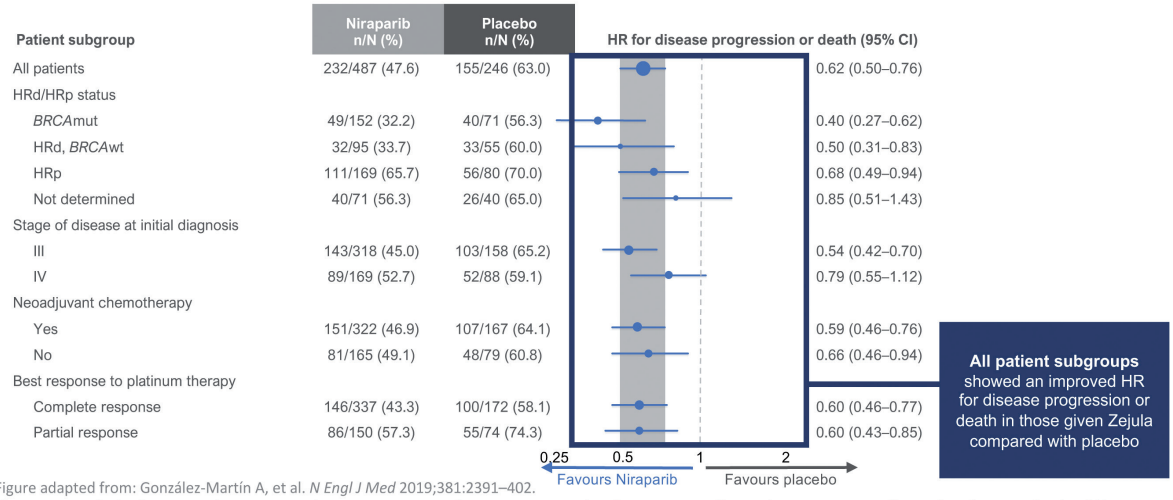
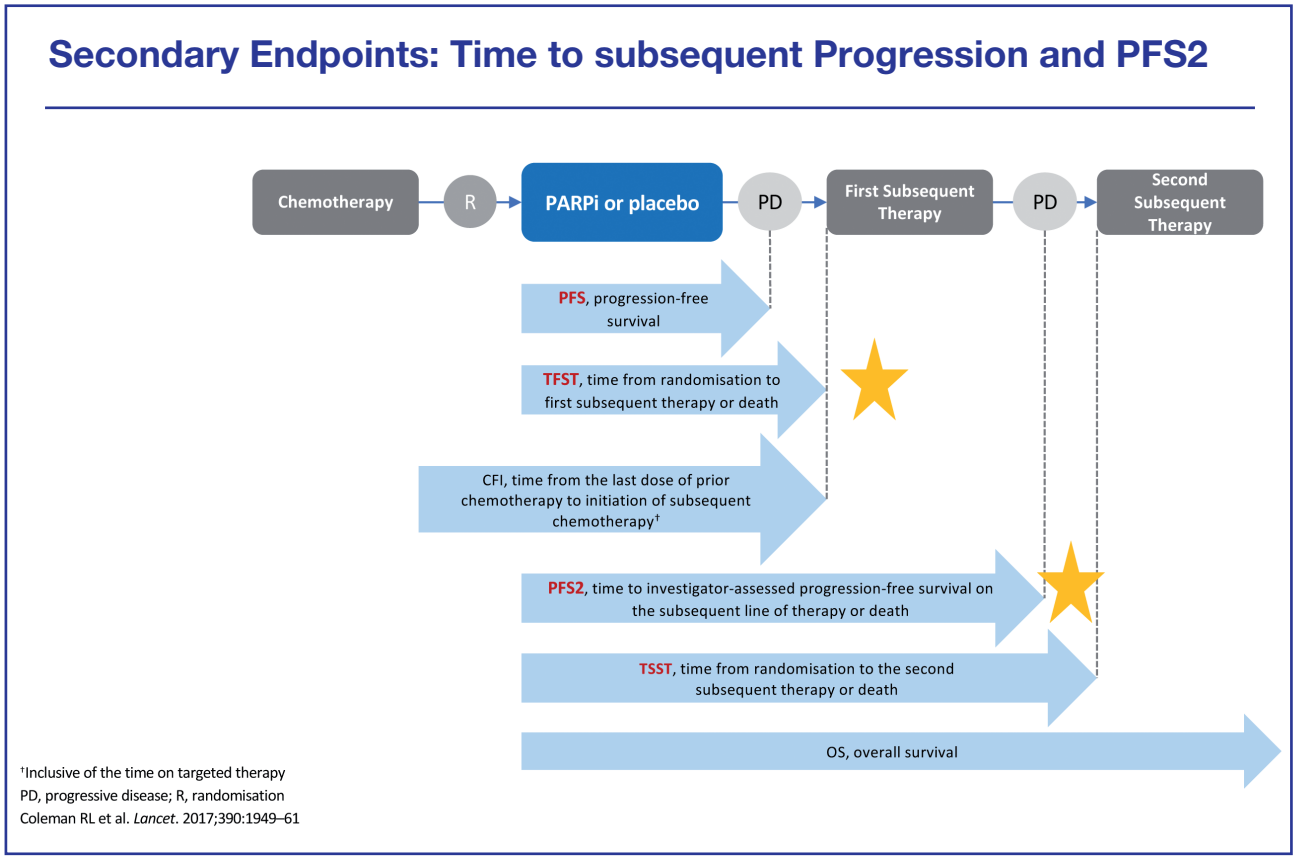


Figure adapted from: González-Martín A, et al. *N Engl J Med* 2019;381:2391–402.
These prespecified subgroup analyses were exploratory in nature and were not powered to detect statistically significant treatment effects; therefore, results should be interpreted with caution.*BRCA*, breast cancer susceptibility gene; *BRCA*mut, *BRCA* mutant; *BRCA*wt, *BRCA* wild type; CI, confidence interval; HR, hazard ratio; HR(d/p), homologous recombination (deficient/proficient)
González-Martín A, et al. *N Engl J Med* 2019;381:2391–2402.

The slide above looks at other effects that might influence the outcome of the trial. Some patients are in stage three and others are in stage 4. Some had received neoadjuvant chemotherapy. Some patients had complete response to carboplatin treatment. Others had partial response to the treatment. The grey shaded area contains 96% of the whole group of patients. If you look at the horizontal lines, you can see that patients in stage III fared better than patients in stage IV. The size of the blue plot indicates the size of the patient population. The smaller the plot, the few the number of patients. The plots are called also Forest plots.



Time to subsequent progression – PFS2

Patients that might have progressed on first subsequent progression or death.

PFS2 can often be used as surrogate for overall survival. Early data for PFS2 in the PRIMA trial was mentioned at SGO in 2020. These data are used to see if the effect of niraparib is diminishing, but there was very low maturity of the data last year, so we will have to wait for the hazard ratio when the data are more mature.

PFS2: Prespecified Interim Analysis of Secondary Endpoint

	HRd		Overall		HRp	
Patients	**Niraparib (n=247)**	**Placebo (n=126)**	**Niraparib (N=487)**	**Placebo (N=246)**	**Niraparib (n=169)**	**Placebo (n=80)**
Hazard ratio (95% CI)	0.84 (0.49–1.45)		0.81 (0.58–1.14)		0.56 (0.34–0.91)	
Maturity rate	15%		20%		27%	

Preliminary data numerically favour niraparib maintenance in all biomarker subgroups, including HRp.

PFS 2 event rates are low; therefore, no definitive conclusions can be drawn. It is difficult to know what the hazard ratios means given the maturity. We need to look at this again when the data are more mature.

Adverse Event Reporting

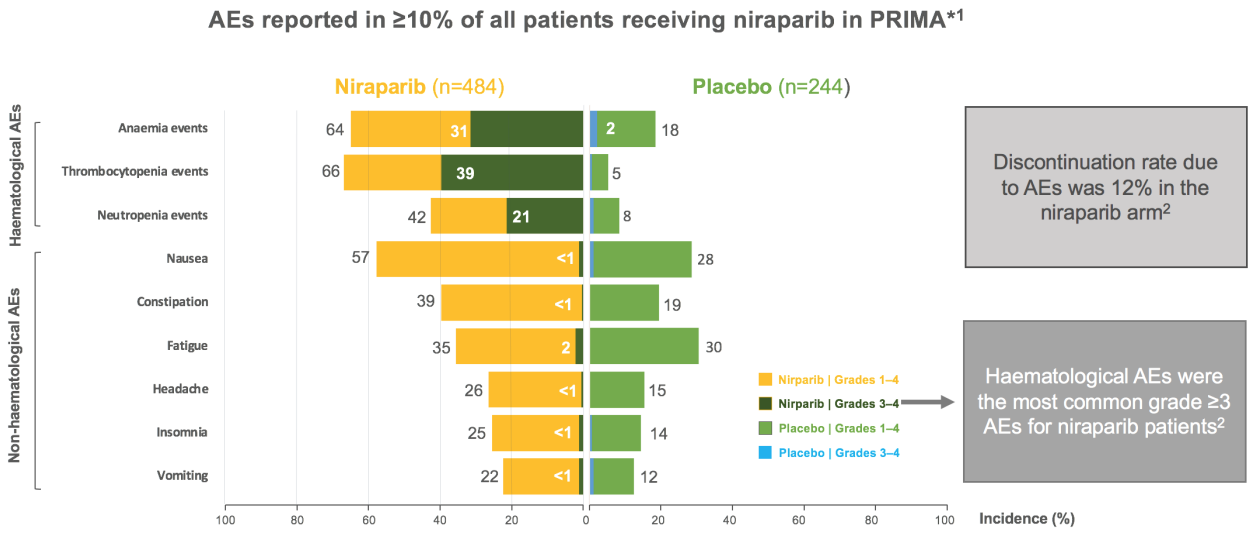
There are 5 grades of toxicity according to NCI CTC AE v.4.03 – National Cancer Institute Common Terminology Criteria for Adverse Events

- ✔ **Scale 1-5 (where 5 = death)**
- ✔ **SAE – Serious Adverse Events (24 hours)**
- ✔ **SUSAR – Suspected Unexpected Serious Adverse Reaction**

Serious adverse events have to be reported to sponsor within 24 hours.

SUSAR are critically important and have to be reported as a matter of urgency.

PRIMA Trial: Side effects or niraparib and placebo



The above is called a tornado plot. As you will see, there are also side effects in the placebo arm. There was a question to Jonathan how that could happen. His explanation was that some of the patients on placebo have just come out of chemotherapy and might still be suffering from anemia, nausea, and fatigue due to that. Later on, when they progress, there are symptoms from the cancer, which can also explain the side effects that we see; so even if the patient is on placebo, there will still be side effects.

Dose Adjustment in the PRIMA trial

Most patients today are started on 2 capsules a day. Only patients who weigh more than 77 kg and with a platelet count of ≥150.000 are given 3 capsules a day. There were few problems with blood count after the dose adjustment.

Quality of life

We have previously talked about the EORTC questionnaires EORTC QLQ-C30, EORTC QLQ-C28 and FOSI – Functional Assessment of Cancer Therapy-Ovarian Symptoms Index, which are very old measures meant for patients on cytotoxic drugs like chemotherapy – not for patients on maintenance therapy. The answers to the questionnaires show no deterioration in quality of life no matter whether the patients are on maintenance treatment or of placebo.

Questions
from the Audience at the 3rd webinar

Oranges and apples

There was a question as to the example with the orange group and the apple group. Are they equally divided?

It depends on how we split them up. We all know that 30% of the patients with high-grade serous ovarian cancer have a BRCA-mutation. If we want to analyze this group separately, there will be a 30 – 70 division with 30% of the patients in the orange group and 70% in the apple group. If we split up according to HRD and HRP, we have a 50–50 split between the apples and the oranges, as the group with BRCA and HRD amounts to approx. 50% of the patients, and the HRP group makes up the other 50%.

Questions to the Myriad test and the patient group: Not determined.

Why was there a group of patients where the BRCA, HRD or HRP status was not determined?

This could be due to a technical failure in the test.

Why did this group have a much worse outcome than all the other patients?

The experts could not explain that. The MYRIAD test is the only validated test to distinguish between HRD and HRP patients. The test is done in Utah, in the US, costs rather a lot of money and is not 100% effective. However, we know from the PRIMA and the NOVA study that niraparib is also effective in the HRP group of patients and that both the FDA and EMA have recommended the use of niraparib for all groups of patients.

A question on dose reduction

Was there a lower outcome from the patients who had dose reduction?

According to Professor Ledermann that was not the case.

When chemotherapy first came on the market and in the 1970s, it was attempted to give the patients as high a dose as possible. That should not be done with PARP-inhibitors nor with check-point inhibitors. Most doctors today probably give 200 mg as a starting dose as there is much less toxicity but good effect.

Will PARP-inhibitors be moved to first-line treatment?

The problem is that the study was not powered for overall survival, and this is what payers and doctors want to see. We will have to look at PFS2 when we get more mature data. There will also be cross-over in second line (patients on placebo in the trial getting niraparib when they have a relapse followed by a treatment with platinum-based chemotherapy).

There has been huge effect of SOLO1 (olaparib) for BRCAm patients on OS. There are now mature data up to 5 years.

Placebo - does it mean that the patient is not getting any treatment?

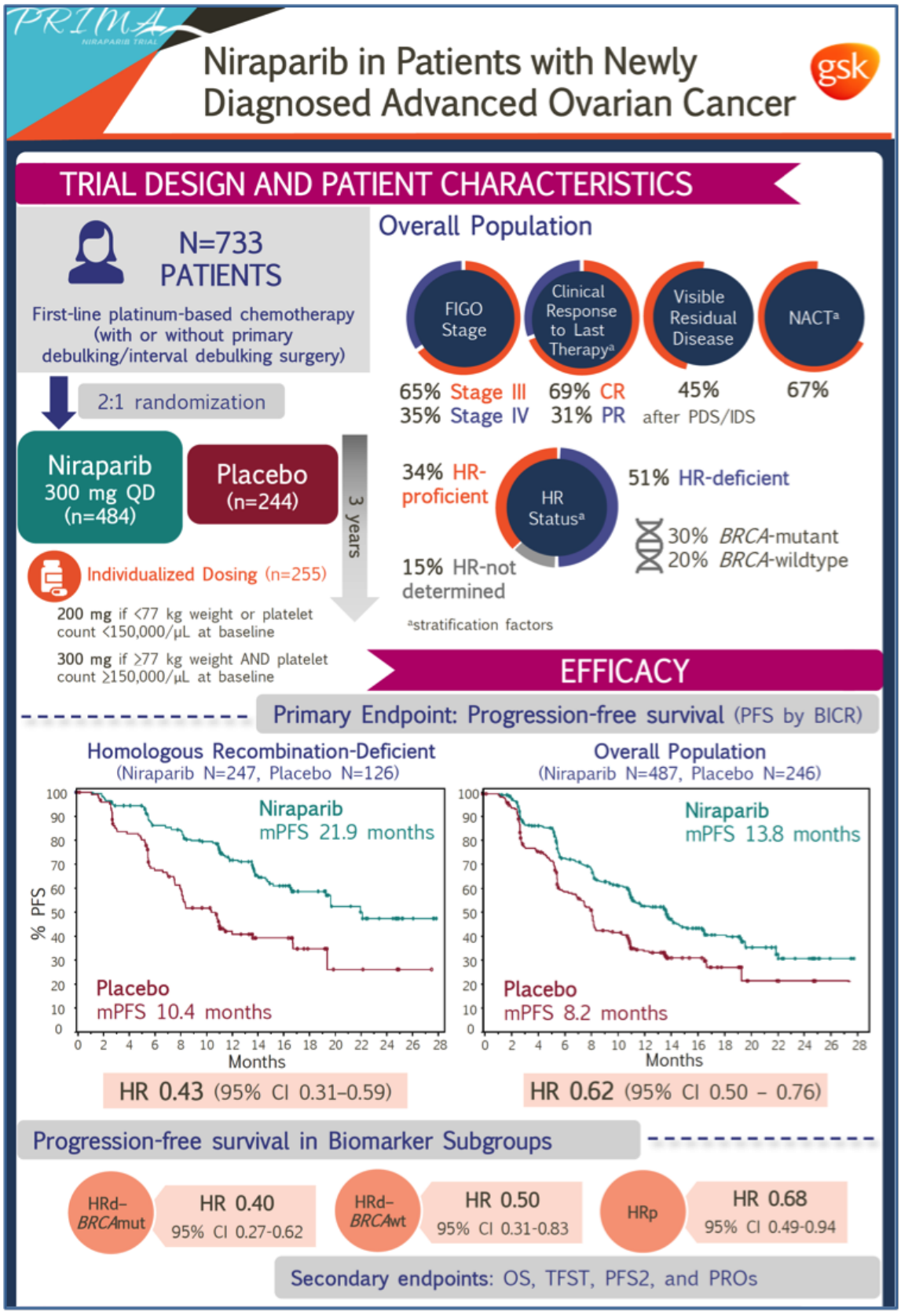
If the trial is repeated, who will accept to be in the placebo group?

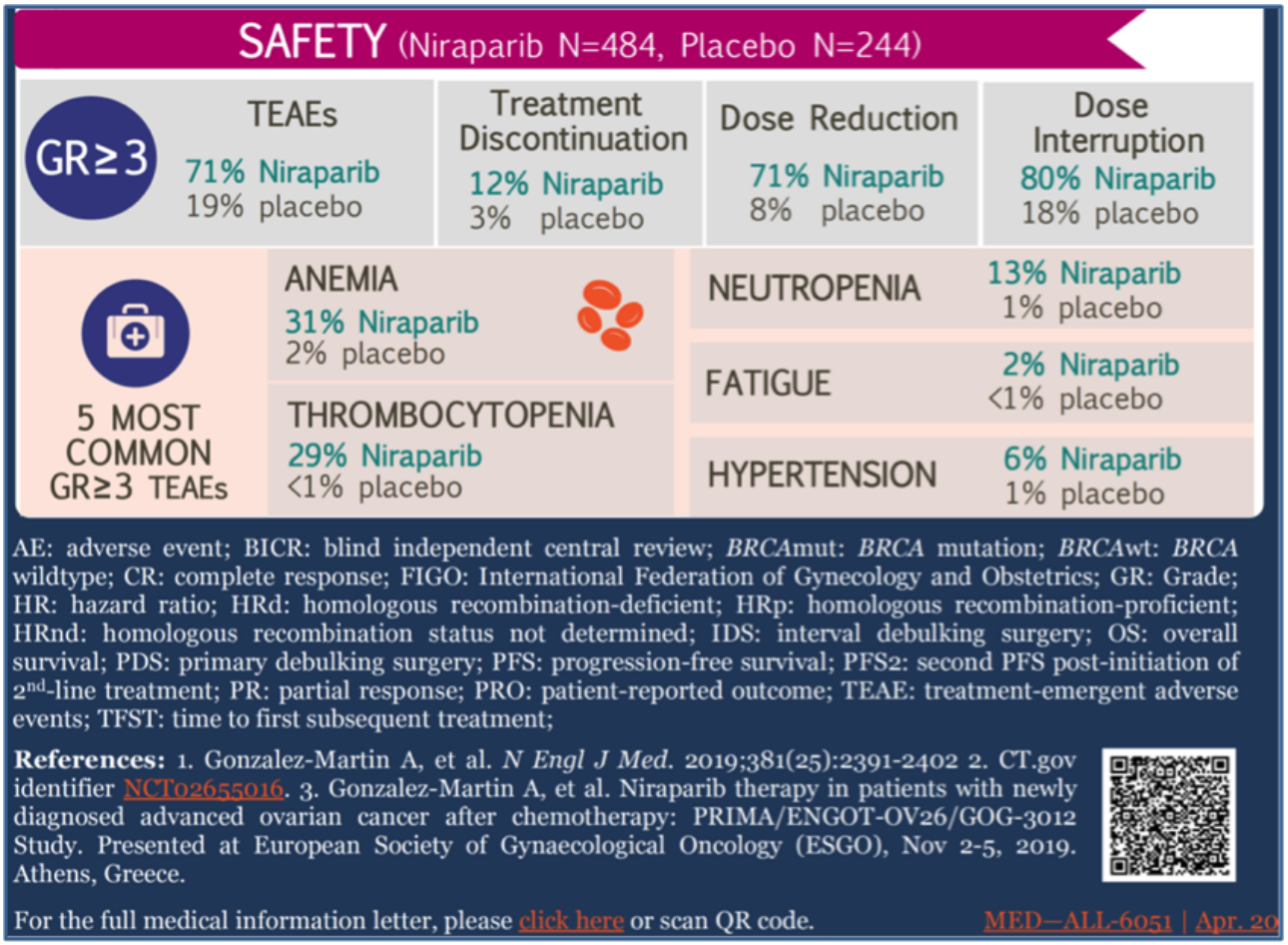
That is an ethical question. If placebo is standard treatment = watch and wait, the answer is yes.

But it would now be difficult ethically to do the same trial again. If there is a maintenance therapy available, the possibility of using placebo has gone.

Infographics

supplied by GSK on the PRIMA Trial





AE: adverse event; BICR: blind independent central review; *BRCA*mut: *BRCA* mutation; *BRCA*wt: *BRCA* wildtype; CR: complete response; FIGO: International Federation of Gynecology and Obstetrics; GR: Grade; HR: hazard ratio; HRd: homologous recombination-deficient; HRp: homologous recombination-proficient; HRnd: homologous recombination status not determined; IDS: interval debulking surgery; OS: overall survival; PDS: primary debulking surgery; PFS: progression-free survival; PFS2: second PFS post-initiation of 2nd-line treatment; PR: partial response; PRO: patient-reported outcome; TEAE: treatment-emergent adverse events; TFST: time to first subsequent treatment;

References: 1. Gonzalez-Martin A, et al. *N Engl J Med.* 2019;381(25):2391-2402 2. CT.gov identifier NCT02655016. 3. Gonzalez-Martin A, et al. Niraparib therapy in patients with newly diagnosed advanced ovarian cancer after chemotherapy: PRIMA/ENGOT-OV26/GOG-3012 Study. Presented at European Society of Gynaecological Oncology (ESGO), Nov 2-5, 2019. Athens, Greece.

For the full medical information letter, please click here or scan QR code.

MED—ALL-6051 | Apr. 20

List of acronyms and Abbreviations from the PRIMA trial

Abbreviations and definition of terms

AE	adverse events
ADR	adverse drug reaction
AUC	area under the curve
BICR	blinded, independent central review
BRCA	BReast CAncer
BRCAm	BRCA mutated
BRCAwt	BRCA wildtype
CA125	cancer antigen 125
CI	confidence interval
CNS	central nervous system
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
ENGOT	The European Network for Gynaecological Oncological Trial groups is a research network of the European Society of Gynaecological Oncology
EORTC	The European Organisation for Research and Treatment of Cancer
EORTC-QLQ-C30	EORTC Quality of Life Questionnaire; a validated, 30-item, health-related quality-of-life instrument developed to assess health outcomes from a wide variety of interventions on a common scale.
EORTC-QLQ-OV28	The EORTC Quality of Life Questionnaire Ovarian Cancer module; a scale which assesses ovarian cancer patients' abdominal/gastrointestinal symptoms, other chemotherapy side effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment an
EPAR	European public assessment report
EQ-5D-5L	European Quality of Life 5-dimension, 5-level questionnaire; a generic quality of life scale which measures the patient's perceived health state in the following 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Eac
FACT-O	Functional Assessment of Cancer Therapy - Ovarian Cancer
FACT-O TOI	Functional Assessment of Cancer Therapy - Ovarian Trial Outcome Index
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy–Ovarian Symptom Index; a validated 8-item measure of symptom response to treatment for ovarian cancer based on a subset of questions from the Functional Assessment of Cancer Therapy - Ovarian Cancer questionnaire. F
GI	gastrointestinal
GOG	Gynecologic Oncology Group
HR	hazard ratio
HRD	homologous recombination deficient

HRP	homologous recombination proficient
HRQoL	health-related quality of life;
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	intravenous
MCID	minimal clinically important difference
MRI	magnetic resonance imaging
NACT	neoadjuvant chemotherapy
NE	not estimable
NR	not reported
NVRD	no visible residual disease
OS	overall survival
PARP	poly (ADP ribose) polymerase
PDX	patient-derived xenograft tumours
PFS	progression-free survival
PFS2	progression-free survival 2. The time from randomisation to the earlier date of assessment of progression on the next anticancer therapy following trial treatment or death from any cause
PRO	patient-reported outcome(s)
PVC	polyvinyl chloride
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
RR	relative risk
SPC	summary of product characteristics
TOI	Trial Outcome Index

Link to all material in the clinical trials project

https://engage.esgo.org/for-members/ct-project-participant/

The link to the study materials is here:

https://engage.esgo.org/for-members/ct-project-participant/study-materials/

There is also a link to the slides from the last three presentations in the spring of 2021. You find them here: https://engage.esgo.org/for-members/ct-project-participant/webinars/

On this website you can also find a link to many trials on gynaecological cancer supplied by various pharma companies. You find them here: https://engage.esgo.org/for-members/ct-project-participant/examples-clinical-trials-supplied-pharma/

The links to the ENGOT ongoing clinical trials:

https://engot.esgo.org/clinical-trials/current-clinical-trials/ovarian/

https://engot.esgo.org/clinical-trials/current-clinical-trials/endometrial/

https://engot.esgo.org/clinical-trials/current-clinical-trials/cervial/

https://engot.esgo.org/clinical-trials/current-clinical-trials/vulvar/

https://engot.esgo.org/clinical-trials/current-clinical-trials/translational/

https://engot.esgo.org/clinical-trials/current-clinical-trials/basket/

The links to the ENGOT closed clinical trials:

https://engot.esgo.org/clinical-trials/publications/

The link to the individual webinars on YouTube:

September 2, 2019 – 3 webinars on theory in a clinical trial

https://youtu.be/Sc3gW2SwhBM

The links to the 3 webinars in the spring of 2021 on YouTube:

January 21, 2021 – 1st webinar

https://youtu.be/8TOHcV7tP4U

February 24, 2021 – 2nd webinar

https://youtu.be/9T3P4kmjVjs

March 18, 2021 - 3rd webinar

https://youtu.be/UihXiTr1sdU

Acknowledgements

ENGAGe would like to thank all presenters and all the moderators from ENGOT and ENGAGe for their availability and work on the webinars.

Special thanks go to Ms. Birthe Lemley (DK) for writing this report, to Ms. Icó Tóth (HU) for her help with the supporting materials for the report and to Prof. Murat Gultekin (TR), Prof. Jalid Sehouli (GE), Prof. Mansoor Raza Mirza (DK), Prof. Antonio Gonzalez (ES) and Prof. Jonathan Ledermann (UK) for their constant remarks and support.

ENGAGe would also like to thank all participants of the ENGAGe-ENGOT Clinical Trials Project.

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ENGOT
European Network of Gynaecological Oncological Trial groups

ESGO
European Society of Gynaecological Oncology