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Simple statistics in a clinical trial

The PRIMA trial as an example

- **Inclusion/exclusion criteria which are strictly adhered to in a randomized clinical trial.**

- **Primary endpoints**
- **Secondary endpoints**

- **Stratification**

PRIMA: Study design: Randomised, double-blind, placebo-controlled, Phase III trial

Patient population

- N=733
- ≥18 years of age
- Newly diagnosed, histologically confirmed advanced ovarian cancer
- High-grade, predominantly serous or endometrioid histological features*
- Complete or partial response to first-line platinum-based chemotherapy
- Stage III patients with visible residual disease after primary debulking surgery
- Stage III and IV* patients with inoperable disease
- Tumour sample testing for *BRCA* mutations or HRd

R 2:1

- Body weight ≥77 kg and platelets ≥150,000/µL started with 300 mg OD
- Body weight <77 kg and/or platelets <150,000/µL started with 200 mg OD

Niraparib
300 mg OD or ISD
n=487

Matching placebo
n=246

Primary endpoint

- PFS

Secondary endpoints

- OS
- TFST
- PFS 2
- PROs
- AEs

Stratified by:

- Clinical response after first-line platinum-based chemotherapy (complete vs. partial response)
- Receipt of neoadjuvant chemotherapy (yes or no)
- Tumour homologous recombination status (deficient or proficient/undetermined)

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 dose; OS, 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.

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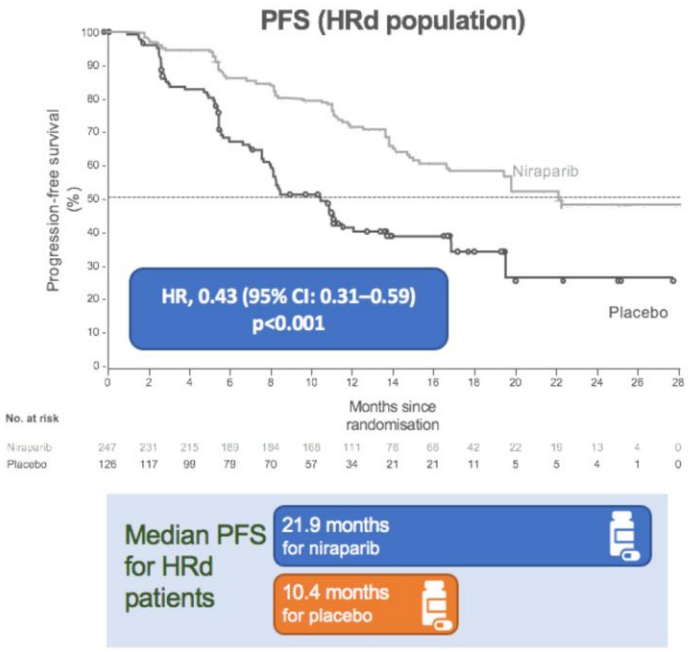
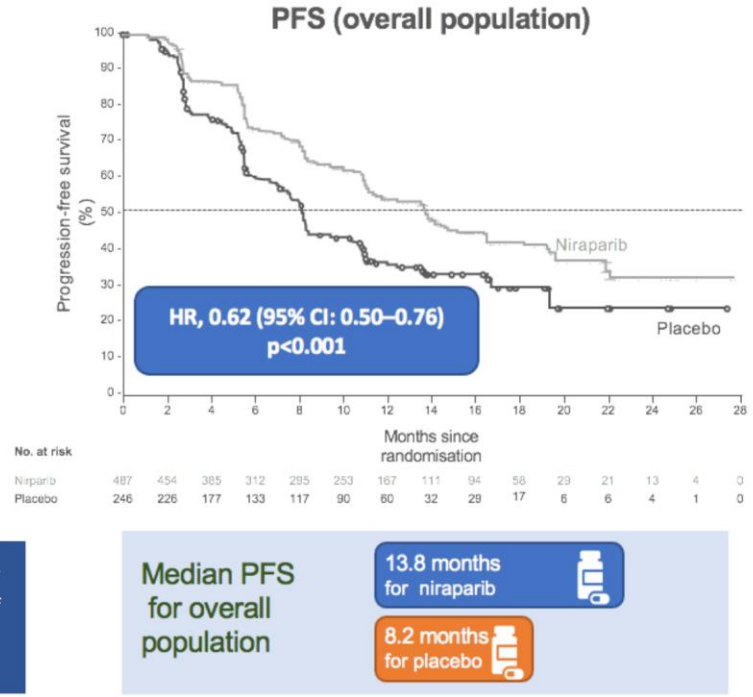
Progression-Free survival in the HRD population and overall population



Median duration of follow-up at time of data cut-off: **13.8 months**



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.

Data cut-off is at 13.8 months.
How can we compare the two curves? We have median 50% value when half of the patients have progressed or died.
Difference in median PFS for HRD 11.5 months
Difference in median PFA for overall population 5.6 months. The numbers at the bottom diminishes over time.

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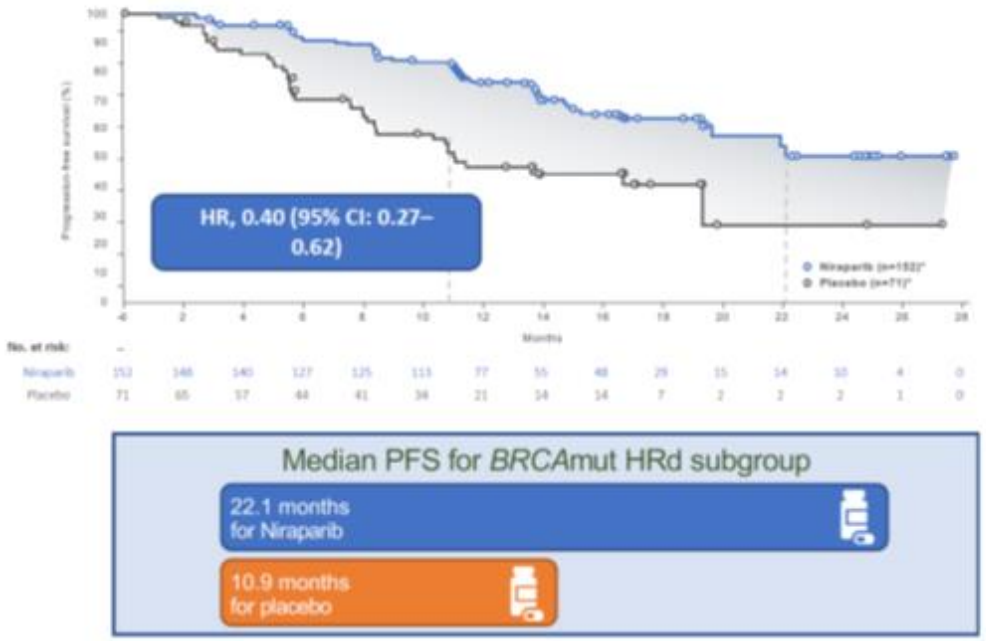
The Hazard ratio – PFS for BRCAmut HRD subgroup



BRCA, breast cancer susceptibility gene; *BRCA*mut, *BRCA* mutant; HR, hazard ratio; HRd, homologous-recombination deficiency; PFS, progression-free survival; mut, mutation.
Monk BJ, et al. Oral presentation 31 at the Society of Gynecologic Oncology (SGO) 2020 Webinar Series.

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. A ratio of 0.4 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.

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Confidence Limits

HR, 0.40 (95% CI: 0.27–0.62)

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 a 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.

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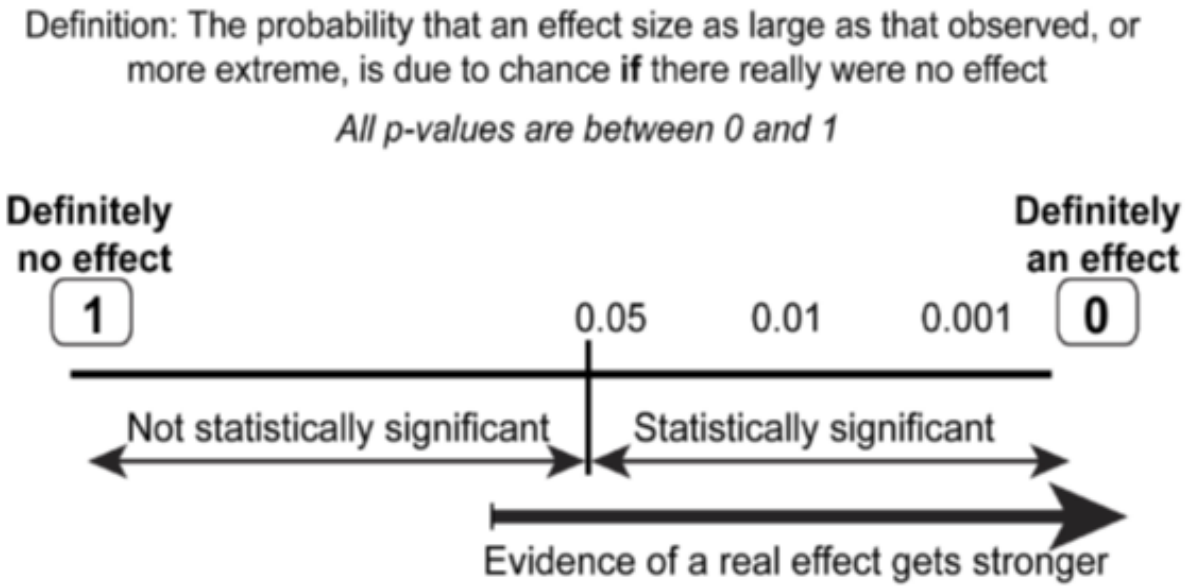
Statistical P-value



Could the Hazard Ratio value of 0.4 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.

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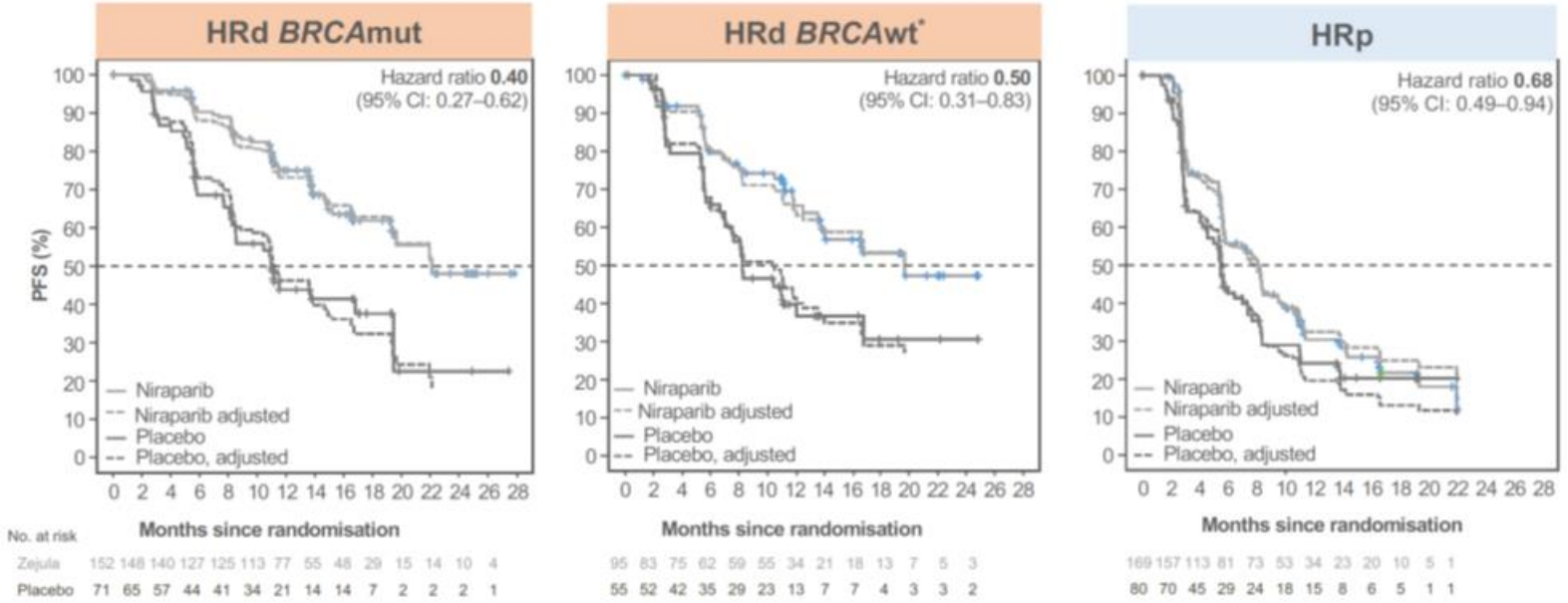
Progression-free survival across three defined subgroups, HRD BRCAmut; HRD BRCAwt; HRP



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

We have already seen the hazard ratios of the HRd BRCAmut is 0.40. Here you see the HRd BRCAwt 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 50% or 0.32% respectively. They all have a confidence interval of 95%. Statistics have in time chosen that everything below 0.05 turned significant. This means that P-value of 0.001 is highly significant. All of them have a confidence interval below 1.

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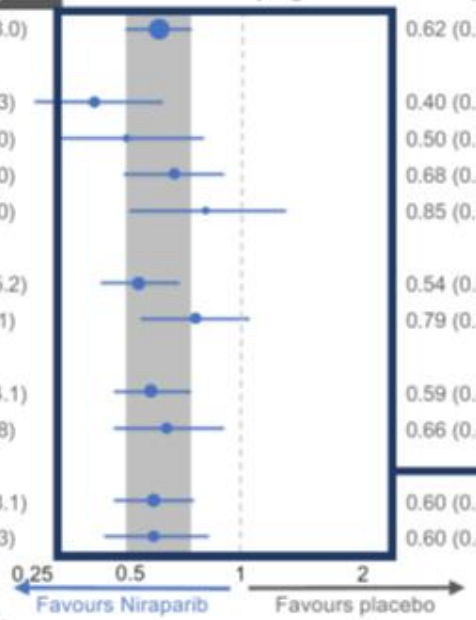
Risk of disease progression or death across a variety of subgroups: Niraparib is compared to placebo- Forest Plot

Patient subgroup	Niraparib n/N (%)	Placebo n/N (%)	HR for disease progression or death (95% CI)
All patients	232/487 (47.6)	155/246 (63.0)	0.62 (0.50–0.76)
HRd/HRp status			
*BRCA*mut	49/152 (32.2)	40/71 (56.3)	0.40 (0.27–0.62)
HRd, *BRCA*wt	32/95 (33.7)	33/55 (60.0)	0.50 (0.31–0.83)
HRp	111/169 (65.7)	56/80 (70.0)	0.68 (0.49–0.94)
Not determined	40/71 (56.3)	26/40 (65.0)	0.85 (0.51–1.43)
Stage of disease at initial diagnosis			
III	143/318 (45.0)	103/158 (65.2)	0.54 (0.42–0.70)
IV	89/169 (52.7)	52/88 (59.1)	0.79 (0.55–1.12)
Neoadjuvant chemotherapy			
Yes	151/322 (46.9)	107/167 (64.1)	0.59 (0.46–0.76)
No	81/165 (49.1)	48/79 (60.8)	0.66 (0.46–0.94)
Best response to platinum therapy			
Complete response	146/337 (43.3)	100/172 (58.1)	0.60 (0.46–0.77)
Partial response	86/150 (57.3)	55/74 (74.3)	0.60 (0.43–0.85)



All patient subgroups showed an improved HR for disease progression or death in those given Zejula compared with placebo

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)

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.

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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%	

PFS 2 can often be used as surrogate for overall survival. Early data for PFS2 in the PRIMA trial was mentioned at SGO last year. 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.

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

PFS 2 event rates are low; therefore, no definitive conclusions can be drawn.

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Adverse Events

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 <u>Unexpected</u> 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.

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Questions from the audience:

How could there be side effects in the placebo arm?

The explanation was that the patients had just come of chemotherapy when they started on niraparib, and when they start to relapse again, there are side effects from the cancer.)

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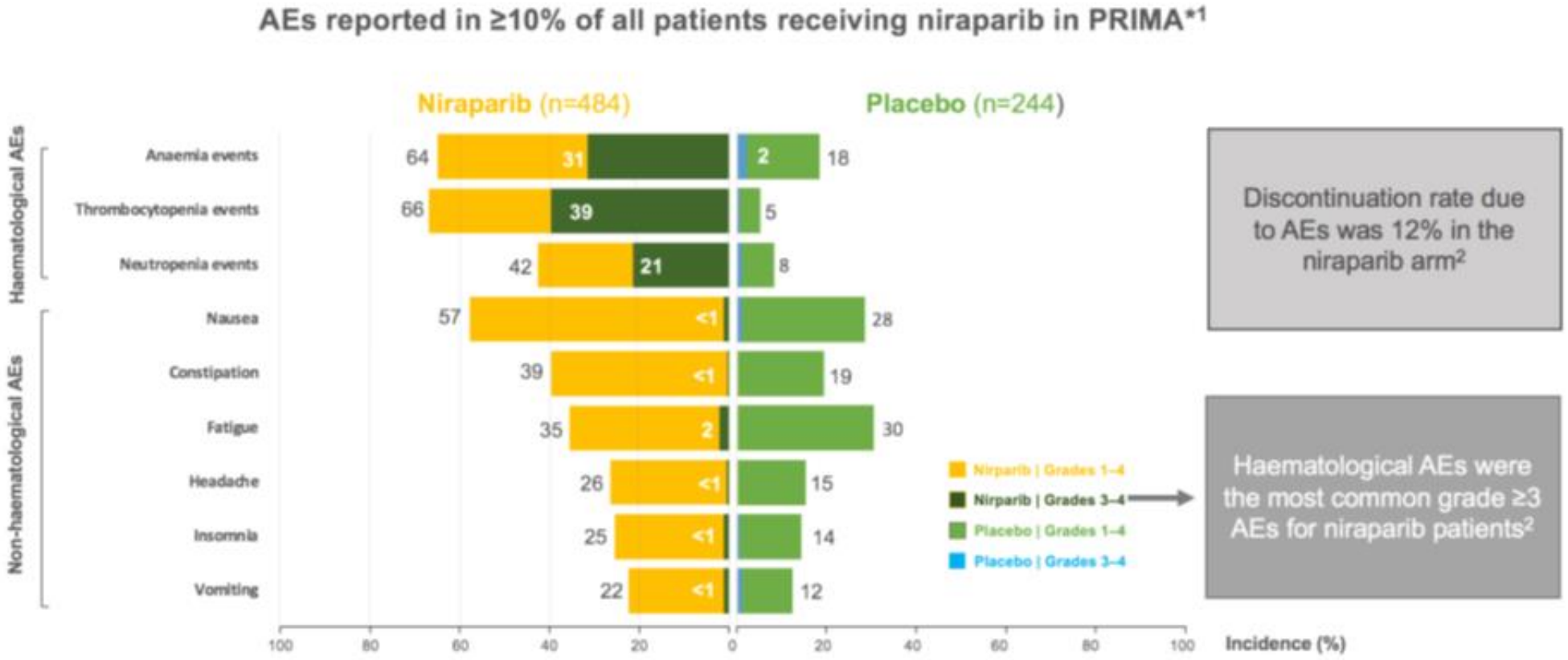
PRIMA Trial: Side effects or niraparib and placebo



Discontinuation rate due to AEs was 12% in the niraparib arm[2]

Haematological AEs were the most common grade ≥3 AEs for niraparib patients[2]

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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%.

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Question to the Forest Plot on slide No. 12

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?
Answer: 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?
Answer: The experts couldn't 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 on the HRP group of patients and that both the FDA and EMA have recommended the use of niraparib for all groups of patients.

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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 shouldn't 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). There has been huge effect of SOLO1 (Olaparib) for BRCAm patients on OS. There are now mature data up to 5 years.

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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 (standard of care) = 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.

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You find all the material at ENGAGe https://engage.esgo.org/for-members/ct-project-participant

- There is now a study book of the first 3 webinars in 2019
- A study book for the 3 webinars in 2021
- All presentations as pdf-files are also uploaded to the ENGAGe website
- Charité-Mayo Conference May 5 – 8, 2021
- 5th Webinar – Endometrial cancer and cervical cancer
- Test based on your present knowledge followed by course certificate
- Precision medicine and genomics? Molecular Pathology & Targeted Therapy in gynae oncology

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My experience of involvement followed by yours:

EUnetHTA and Early Dialogue (https://eunethta.eu)
Patient Participation 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. 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 at EMA in Amsterdam.

A foundation in Switzerland as a patient reviewer. A foundation in Belgium as a patient reviewer

Patient representative for ovarian and endometrial cancer in the Danish Medicines Council.

Numerous research applications for the Danish Cancer Society.

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Objective

To get the patient insight and patient perspective into the design and implementation of clinical trials.

To develop strategies to increase the awareness of and participation in clinical trials.

To facilitate that gynaecological cancer patients can cross borders in Europe to participate in clinical trials appropriate for their disease in other European countrird.

To dessiminate the results of clinical trials to the individual patients and the public at large.

To use our knowledge in any other way which may benefit the work of ESGO, ENGOT and other affiliated organisations and ultimately benefit the patients.

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What is the next step? – Understanding precision medicine, biomarkers and genomics?

In endometrial cancer, cervical cancer, ovarian cancer and rare cancers?

Round table discussion – feedback from the CT project members