ENGAGe
ESGO European Network of Gynaecological Cancer Advocacy Groups

ENGOT
European Network of Gynaecological Oncological Trial groups

ENGAGe-ENGOT Clinical Trial Project
Webinar 2: Outcomes

Feb 24, 2021
18.30 CET

Moderators: Karina Dahl Steffensen, *Denmark* & Murat Gultekin, *Turkey*

Main Speaker: Jalid Sehouli, *Germany*

Agenda

- **Welcome word** *5 min*
  Karina Dahl Stefensen, Murat Gultekin, Birthe Lemley
- **Repeat some information from the previous webinar - What we learned?** *5 min*
  Birthe Lemley
- **How to measure the outcome (endpoints, questionnaires on QoL)** *30 min*
  Jalid Sehouli
- **Q&A** *15 min*
  All
- **Closing remarks** *5 min*
  Karina Dahl Stefensen & Murat Gultekin

Clinical endpoints in clinical trials

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ESGO Ovarian Cancer Center of Excellence
Charité Comprehensive Cancer Center
Charité Global Health
Charité/ Campus Virchow-Klinikum
University of Berlin, Germany, Europe,
ENGAGE; ENGOT, one World!

Clinical endpoints in studies

- Clinical endpoints or clinical outcomes are outcome measures referring to status of the disease, symptoms constituting a target outcome in clinical research trials.
- The primary endpoint of a clinical trial is the endpoint for which the trial is powered. Only this questions is really the questions and can be answered!
- Secondary endpoints are additional endpoints, preferably also pre-specified in the protocol (planned analysis), for which the trial may not be powered.
- Surrogate endpoints are trial endpoints that have outcomes that substitute for a clinical endpoint, often because studying the clinical endpoint is difficult (eg. PFS for OAS)

Patient reported outcomes

RR	=	Response Rate (imaging, biomarker, clinical symptoms) Clinical benefit (CR+PR+SD), only for patients with measurable disease
RD	=	Response Duration
PFS	=	Progression free Survival
DFS	=	Disease Free Survival
PFS II	=	Progression free survival after PFS I
RFS	=	Recurrence Free Survival
TTF	=	Time to subsequent therapy (eg. Chemotherapy, surgery, ascites punction))
OAS=		Overall Survival

Patient reported outcomes

- QoL, multidimensional (generally only as secpndary objective)
- Perspective (patients)
- Relevance
- Activity

Limitations:
Who are the responder?
Who are the non-responder?
Who is asking and when? and how?
What other factors impact QoL (response?, social aspects, resilience, adaptions)

What is QoL?
Who is looking on what?

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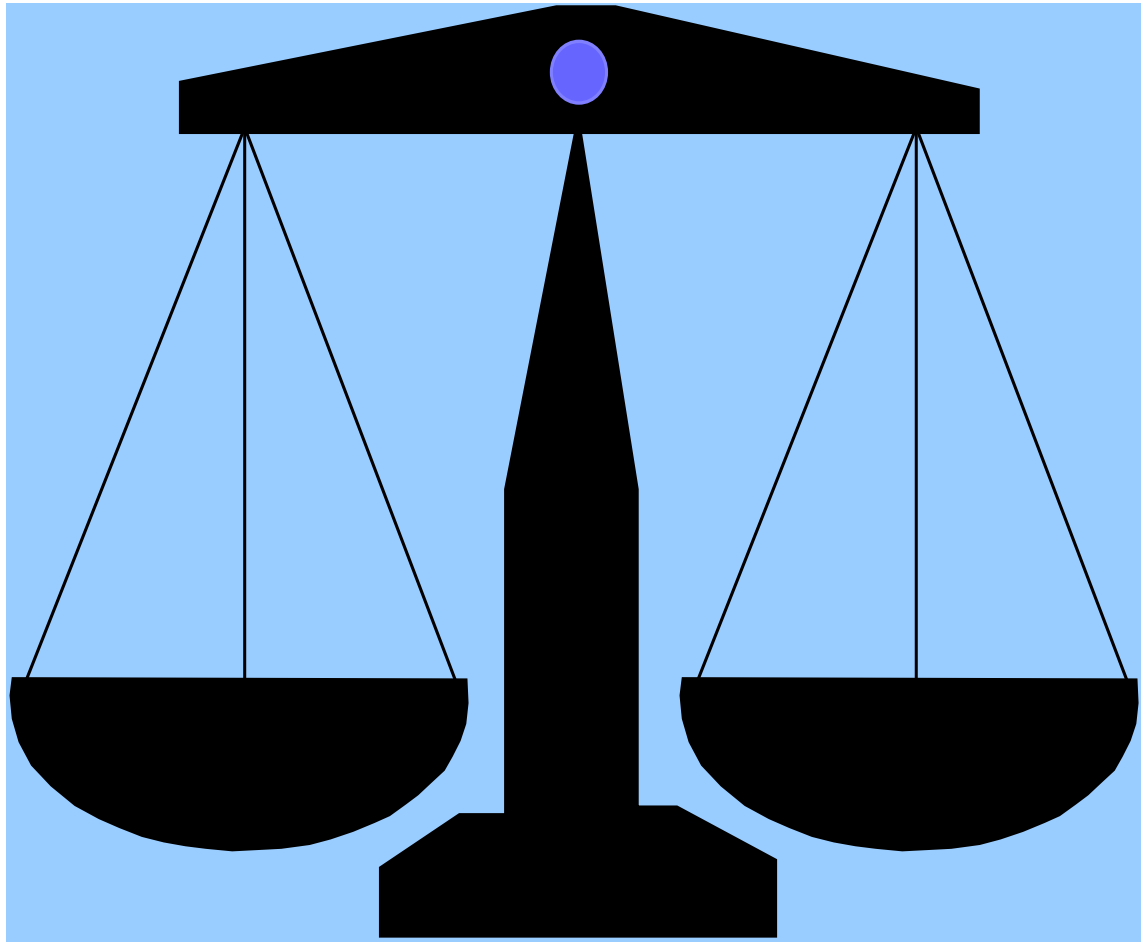
Quality of Life

… To Tell the Brain

What

The Heart Can Feel



Quality of Life/ Survival

PRIMA Trial Design

Once-daily oral maintenance therapy evaluated in patients with newly diagnosed advanced ovarian cancer

Patients with stage III or IV ovarian cancer who had high risk for progressive disease and who had achieved a CR or PR following front line platinum-based chemotherapy, regardless of *BRCA* and HR status

Stratification Factors

- Neoadjuvant chemotherapy administered: Yes or No
- Best response to 1st platinum therapy: CR or PR
- HR status: deficient or proficient/not determined

2:1 Randomization

Niraparib Daily

Placebo Daily

Endpoint assessment

Primary Endpoint	**Hierarchical Testing for PFS (radiologic, central review)** ・PFS in HR-deficient population ・PFS in ITT population
Key Secondary Endpoints	・**Overall Survival** ・**Safety & Tolerability** ・**Patient Reported Outcomes (FOSI, EQ-5D-5L, EORTC-QLQ-30 & -OV28)** ・**PFS2** ・**Time to CA-125 Progression**
Exploratory Endpoints	・**Population PK** ・**PK parameters for niraparib and major metabolite** ・**HR Diagnostic Test**

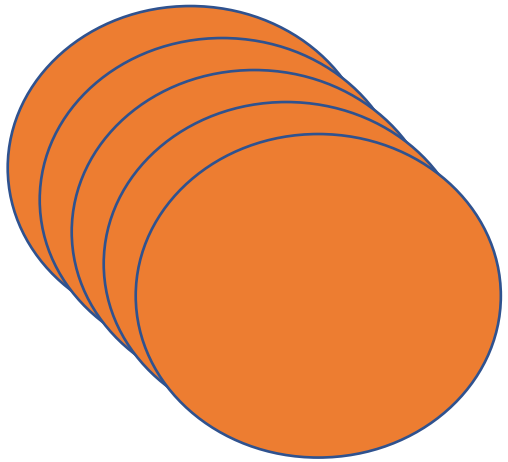
The PRIMA study protocol was modified to prospectively investigate a starting dose of either 300 mg or 200 mg of niraparib (or placebo) based on baseline body weight and platelet counts (individualized starting dose).

CR = complete response; PR = partial response; HR = homologous recombination;; PFS = progression-free survival; ITT = intent to treat; FOSI = Functional Assessment of Cancer Therapy-Ovarian Symptom Index; EQ-5D-5L = European Quality of Life 5-Dimensions 5-Level Scale; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire; EORTC-QLQ-OV28 = EORTC Quality of Life Questionnaire Ovarian Cancer Module; PFS2 = Progression-free survival 2; PK = pharmacokinetics

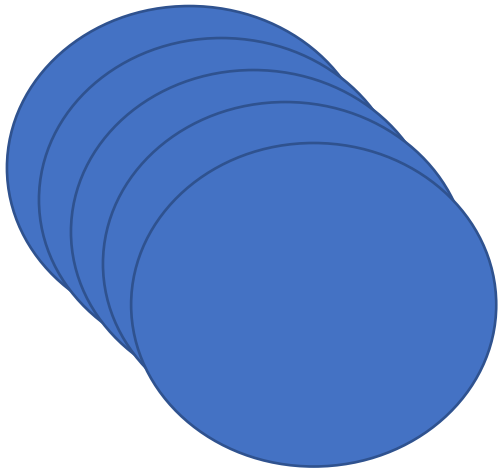
Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402.

Randomization

GROUP A



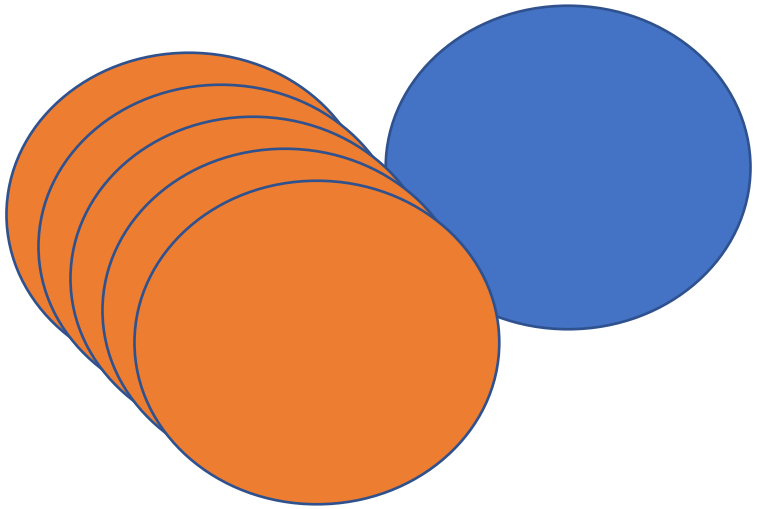
GROUP B

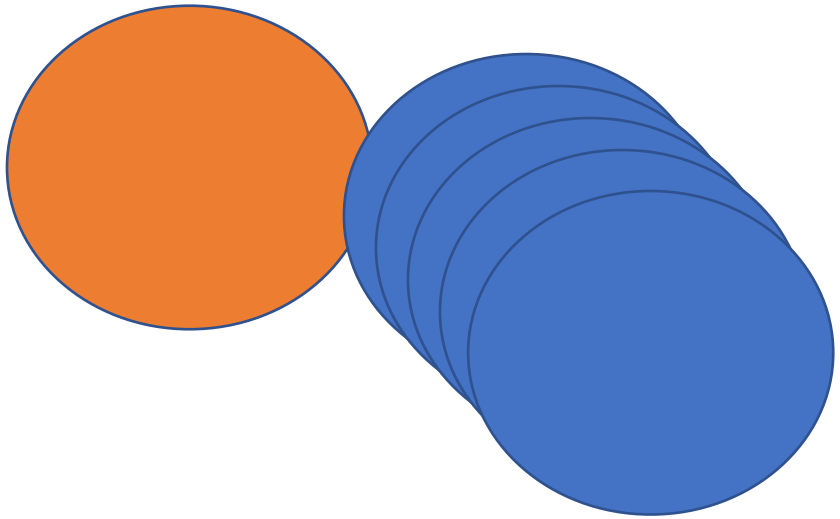


Randomization

GROUP A

GROUP B





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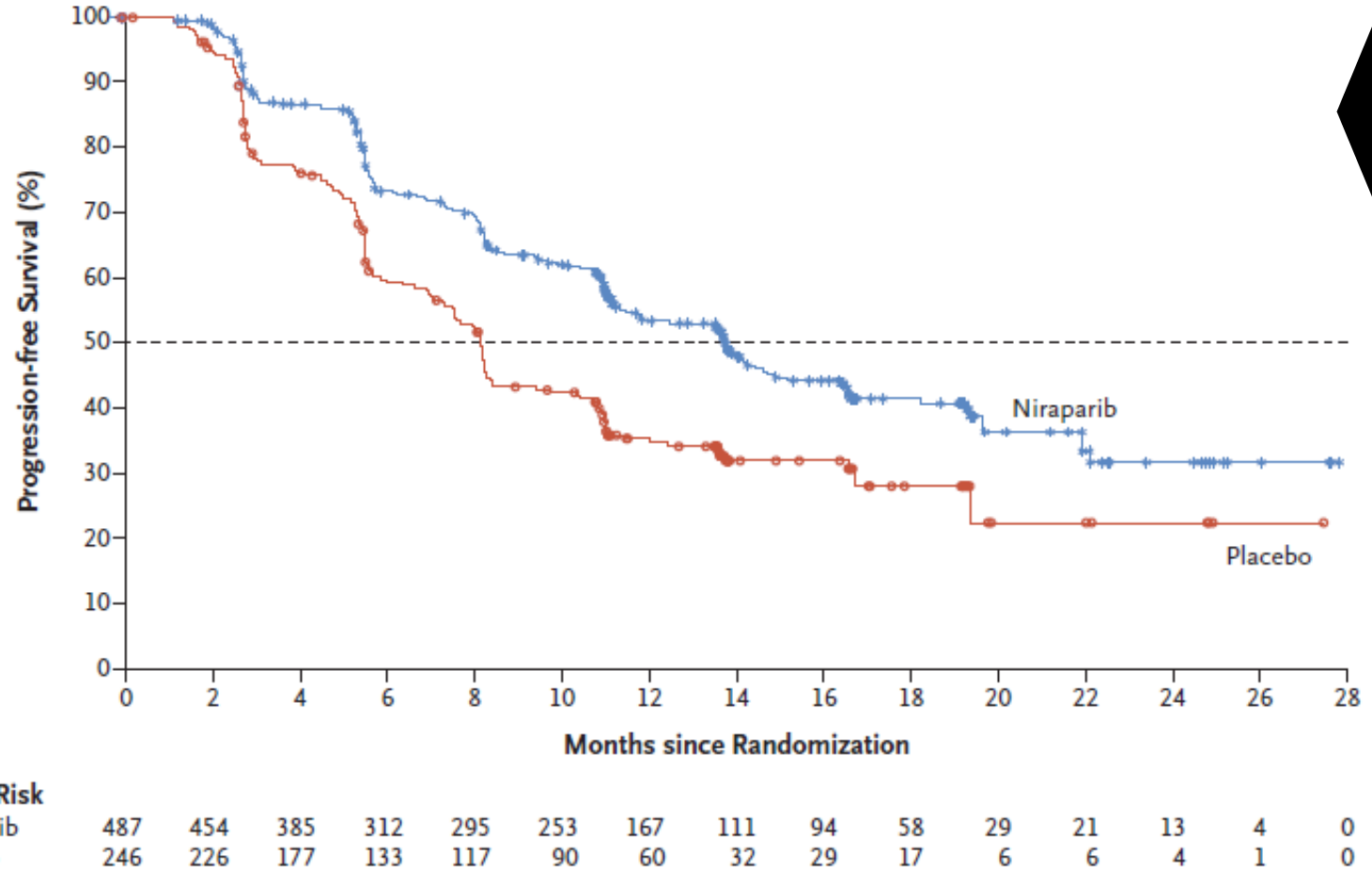
Primary Endpoint: PFS in the Overall Population

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



HR (95% CI) for disease progression or death: 0.62 (0.50–0.76; P<0.001)

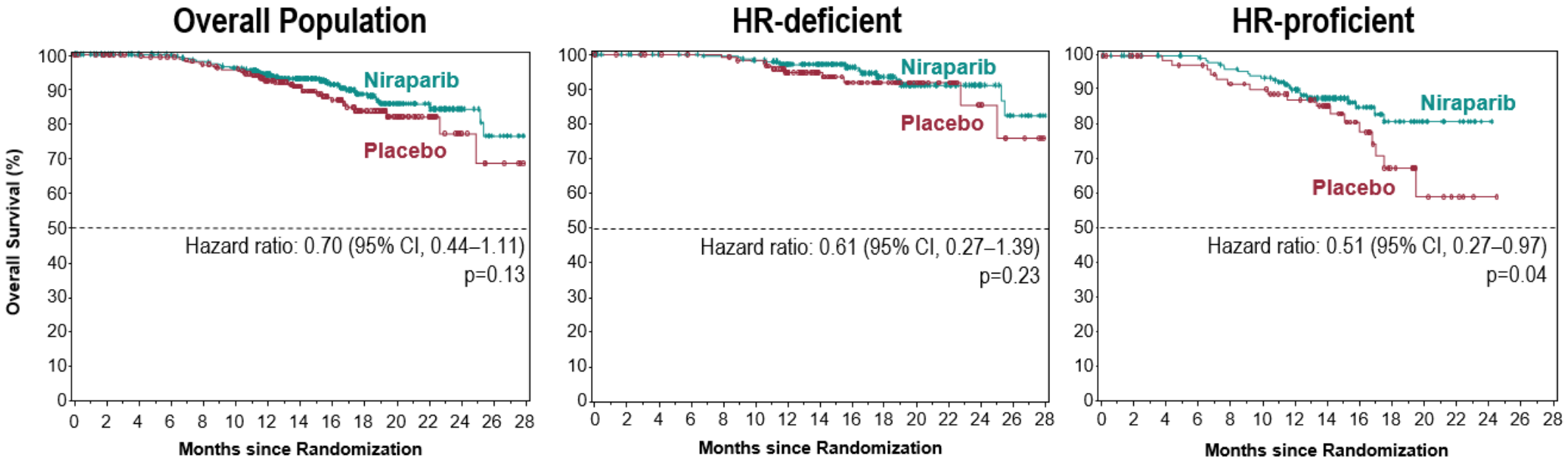
	Niraparib (n = 487)	Placebo (n = 246)
Median PFS		
months (95% CI)	13.8 (11.5 – 14.9)	8.2 (7.3 – 8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

CI = confidence interval; HR = hazard ratio; PD = progressive disease; PFS = progression-free survival

Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402; Gonzalez-Martin A, et al. Presented at ESMO 2019. Barcelona, Spain.

Key Secondary Endpoint: Overall Survival

At 2 years, more women treated with niraparib were alive vs those on placebo, regardless of HR status (11% data maturity)



Overall survival at 2 years	Niraparib	Placebo
Overall population	84%	77%
HR-deficient	91%	85%
HR-proficient	81%	59%

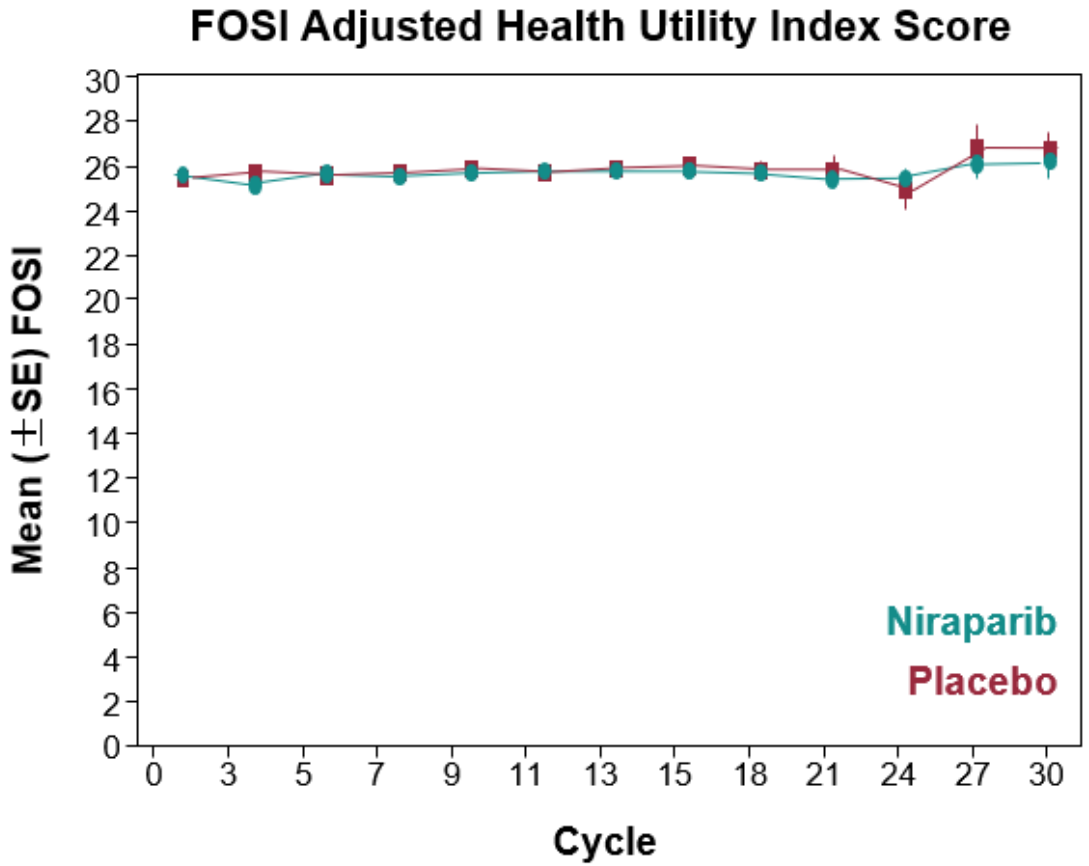
At 2 years, 84% of women on niraparib were alive vs 77% on placebo

CI = confidence interval; HR = homologous recombination; OS = overall survival.

Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402; Gonzalez-Martin A, et al. Presented at ESMO 2019. Barcelona, Spain.

Patient Reported Outcomes

No indication of between-group differences in HRQoL scores among patients receiving niraparib compared with placebo



FOSI = Functional Assessment of Cancer Therapy-Ovarian Symptoms Index; HRQoL = health-related quality of life; SE = standard error.

Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402; Gonzalez-Martin A, et al. Presented at ESMO 2019. Barcelona, Spain.

Patient´s preferences and expectations Why it can be important to know these

- Patients preference is important for the adjuvant and palliative setting
- Dissatisfaction is associated with Non-Compliance (*Coulter et al., 1999, Elwyn et al., 2003)*
- Compliance and Non-Compliance correlate with quality of life and survival
- Expectations and preferences from patients and physicians are different (*Oskay-Oezcelik, Sehouli, 2006)*

Berlin Dialogue
2020, Int J Gyn Cancer

1. **Quality of Life: Should quality of life (QoL) be introduced as outcome parameter into clinical trials and how should this be done?**
2. **Side Effects: How can we help physicians and patients in the reporting of side effects due to chemotherapy and maintenance therapy?**
3. **Treatment decision-making process: How can we strengthen the patient´s role in the treatment decision-making process?**
4. **Sexuality: What is the role of sexuality during chemotherapy or maintenance therapy?**
5. **Study Participation: Do we include all relevant social groups? How can we improve study participation?**
6. **Second Opinion: Is there a right for second opinion for patients and how should physicians deal with this demand?**
7. **Long Term Survivors (LTS): Should we prolong follow-up screening for long term survivors?**

Results of the interprofessional and interdisciplinary Berlin round table on patient-reported outcomes, quality of life, and treatment expectations of patients with gynecological cancer under maintenance treatment. Armbrust R, Alavi S, Pirmorady A, Chen F, Colombo N, Gultekin M, Hierro C, Lemley B, Mirza MR, Urkmez E, Fotopoulou C, Vinzent J, Gonzalez Martin A, Krull A, Heepe J, Rose M, Sehouli J.Armbrust R, et al. Int J Gynecol Cancer. 2020 Oct;30(10):1603-1607. doi: 10.1136/ijgc-2019-001070. Epub 2020 Aug 16.