SGO 2021 VIRTUAL ANNUAL MEETING ON WOMEN'S CANCER®

Society of Gynecologic Oncology

Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase III trial of niraparib in recurrent ovarian cancer

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Disclosures – Dr. Matulonis

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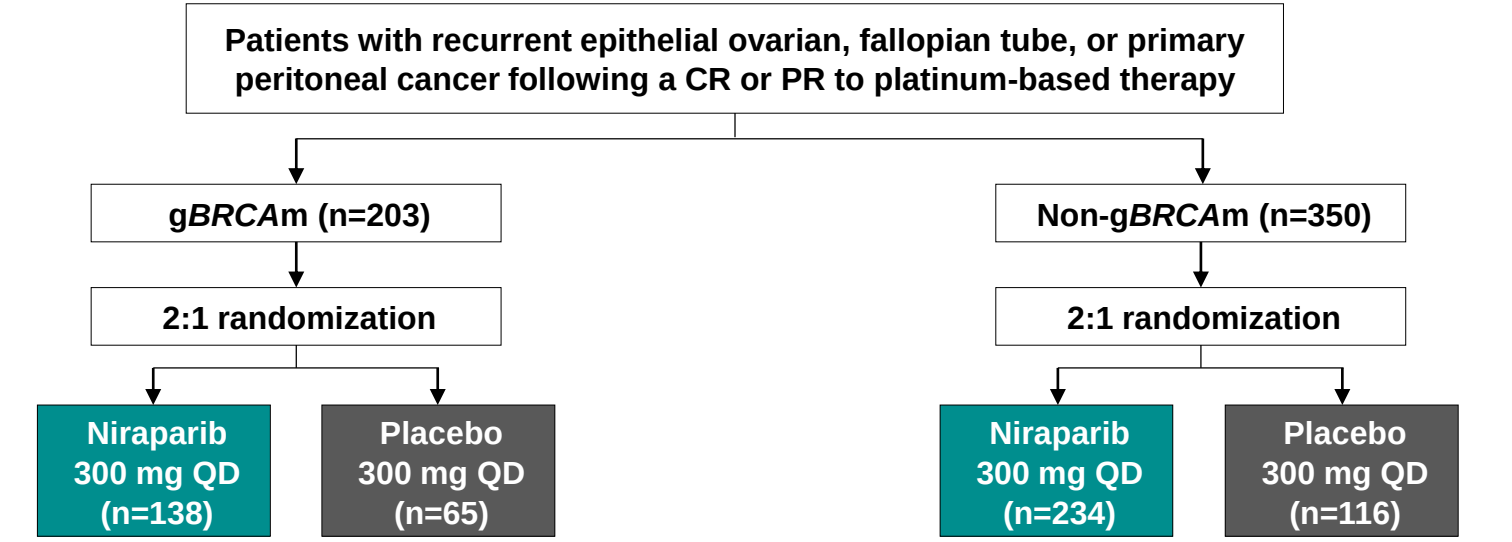
Primary PFS Endpoint: ENGOT-OV16/NOVA Study

- NOVA is a randomized, double-blind, placebo-controlled phase 3 trial of niraparib maintenance treatment for patients with platinum-sensitive recurrent OC
- Niraparib demonstrated statistically significant improvement in PFS in g*BRCA*m and non-g*BRCA*m cohorts[1]



HR 0.27 (95%CI 0.17 to 0.41, p<0.001)
mPFS 21.0 vs. 5.5 months

HR 0.45 (95%CI 0.34 to 0.61,p<0.001)
mPFS 9.3 vs. 3.9 months

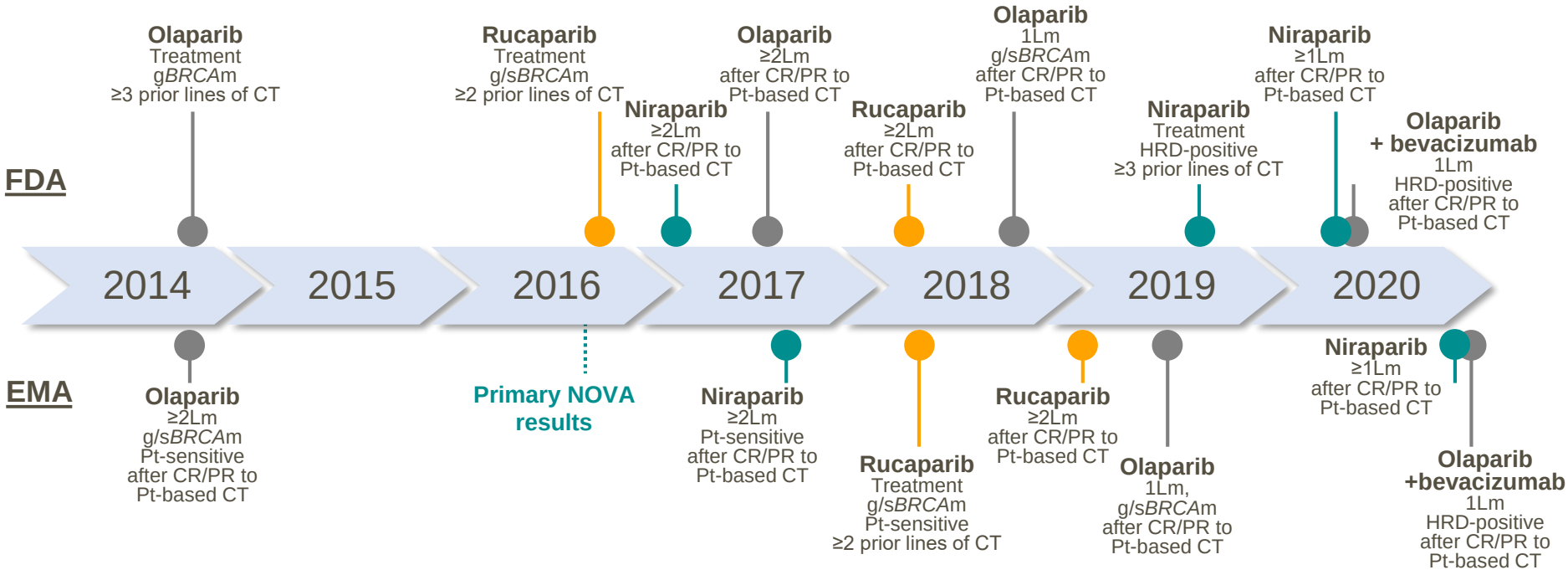
- Secondary endpoints include safety and exploratory long-term efficacy such as PFS2 and OS which were not statistically powered

Primary data cut-off was June 20, 2016 (median duration of follow up 16.9 months).

1. Mirza et al. *NEJM*, 2016;375:2154-64.

Approvals of PARPi for advanced OC

- PARP inhibitors have changed the treatment paradigm for the management of advanced OC

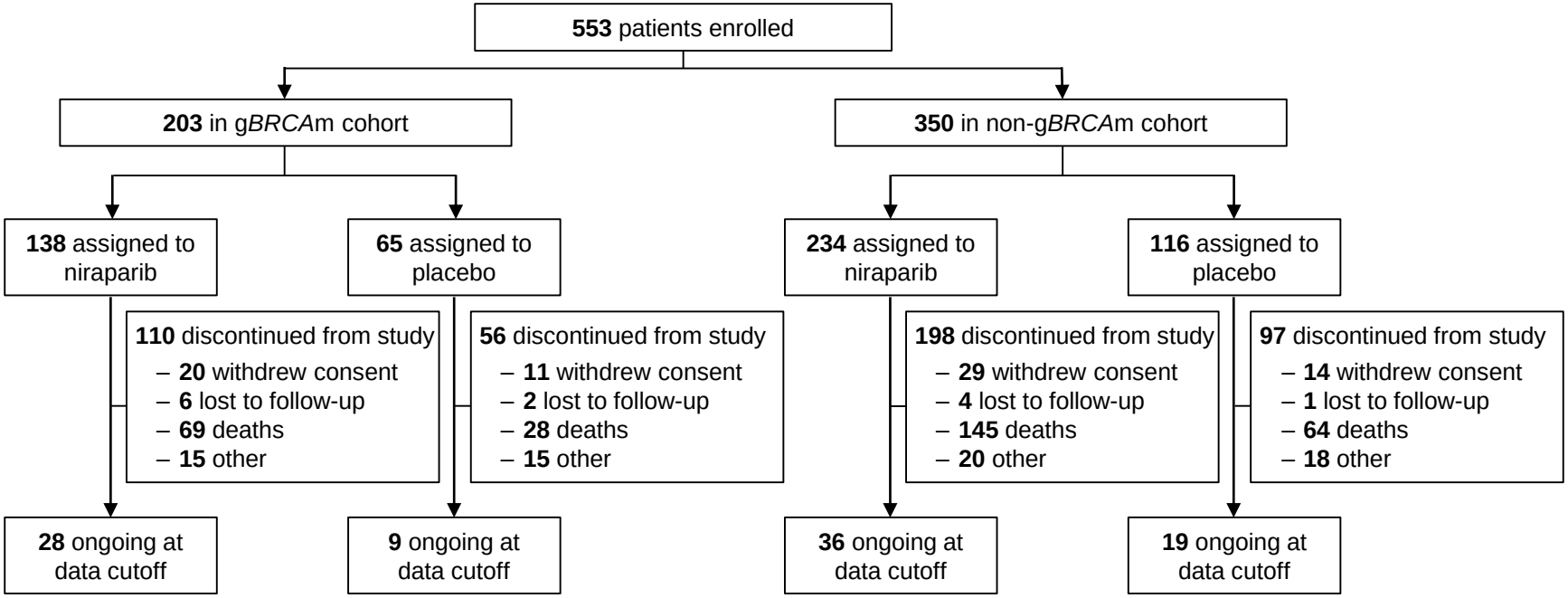


- High proportion of patients were withdrawn from the NOVA study after primary results in 2016 and post commercial availability of PARPi

2Lm, second-line maintenance; *BRCA*, breast cancer gene; CT, chemotherapy; EOC, epithelial ovarian, tubal, or primary peritoneal cancer; EMA, European Medicines Agency; FDA, Food & Drug Administration; g/s*BRCA*m, germline/somatic *BRCA* mutant; HGS, high-grade serous; HRd, homologous recombination deficient; PARPi, poly(ADP-ribose)polymerase inhibitor; Pt, platinum.

1. ZEJULA® (niraparib): US prescribing information (Apr 2020); 2. LYNPARZA® (olaparib): US prescribing information (Nov 2020); 3. RUBRACA® (rucaparib): US prescribing information (Oct 2020); 4. ZEJULA® (niraparib): EPAR – Product information - Summary of product characteristics (Nov 2020); 5. LYNPARZA® (olaparib): EPAR – Product information - Summary of product characteristics (Nov 2020); 6. RUBRACA® (rucaparib): EPAR – Product information - Summary of product characteristics (Jan 2021);

Patient Disposition and Survival Status



- In the overall population, 28% (155/553) discontinued from study for non-death reasons
  - Imbalances observed due to small sample size in each cohort
  - Early withdrawal of consent limited collection of survival and subsequent therapy data
- By final data-lock, survival status could not be retrieved for 49% (76/155) patients:
  - g*BRCA*m cohort: 14% (19/138) in niraparib group, 14% (9/65) in placebo group
  - Non-g*BRCA*m cohort: 14% (33/234) in niraparib group, 13% (15/116) in placebo group

Final data cut-off was Oct 1, 2020 (average duration of follow up for OS was 67 months).

Assessment of Missing Subsequent PARPi Therapy

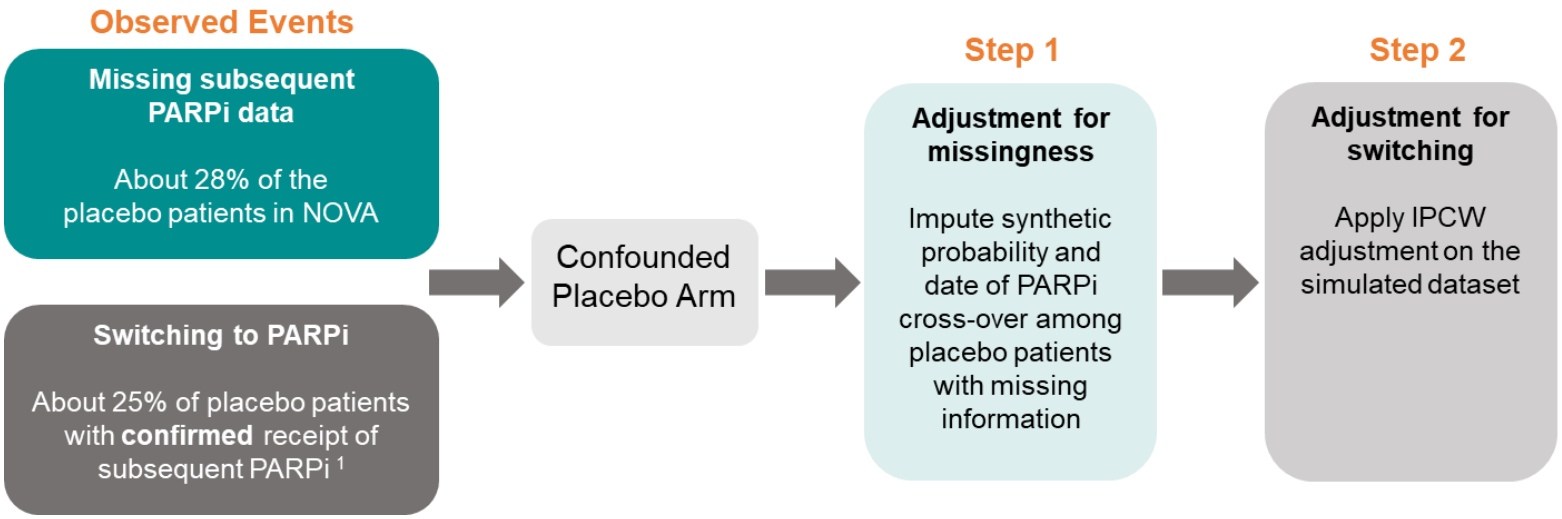
- Cross-over to PARP inhibitor (PARPi) on study was not permitted; however, patients could receive subsequent PARPi after disease progression or withdrawal from study per oncologist's clinical judgement
- Due to study discontinuation, post-progression therapy information was not available for 25% (138/553) of patients

	g*BRCA*mut		Non-g*BRCA*mut	
Subsequent PARPi treatment received on NOVA	**Niraparib (n=138)**	**Placebo (n=65)**	**Niraparib (n=234)**	**Placebo (n=116)**
Yes	**34 (25%)**	**30 (46%)**	**15 (6%)**	**15 (13%)**
No	**68 (49%)**	**15 (23%)**	**168 (72%)**	**70 (60%)**
Missing information	**36 (26%)**	**20 (31%)**	**51 (22%)**	**31 (27%)**

- Both small sample size and the missing data challenge survival analyses and interpretation

OS Sensitivity Analyses

- Adjusted OS analysis was conducted, after missing subsequent PARPi therapy data was imputed
- Inverse probability of censoring weighted (IPCW) methodology[2,3] was applied to adjust for subsequent PARPi therapy use

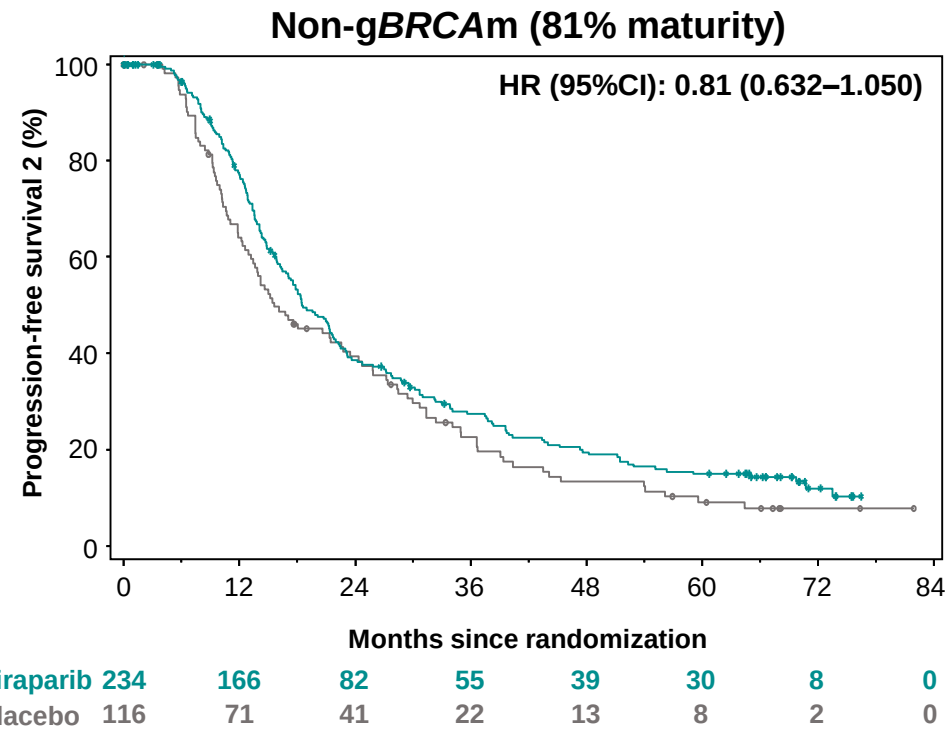


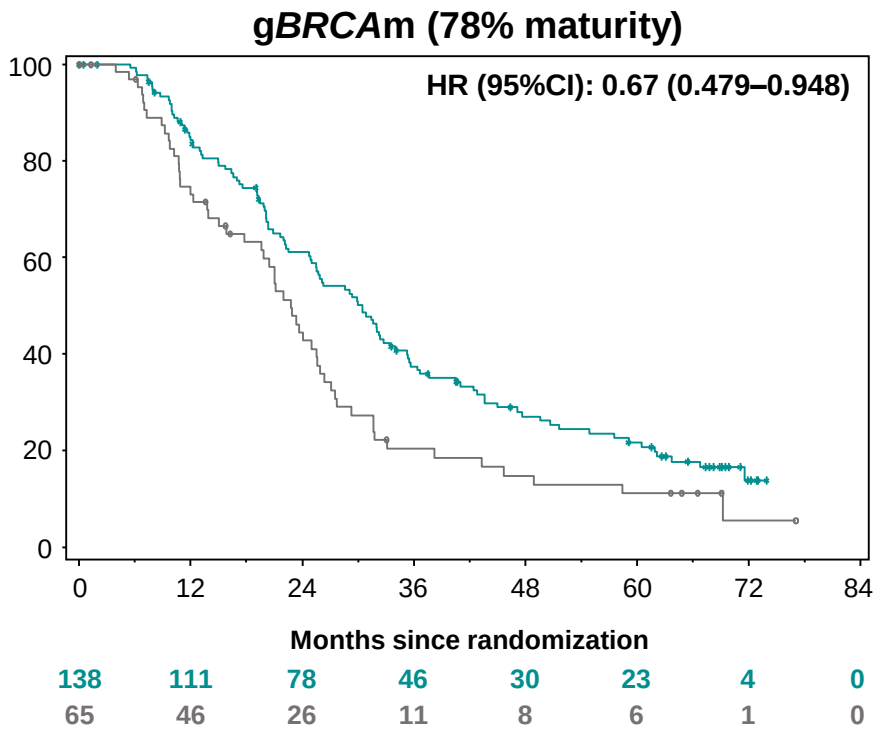
- Restricted mean survival time (RMST) analysis was conducted when non-proportional hazards were observed

1. 46% on the g*BRCA*m and 13% in the non-g*BRCA*m.
2. Ishak et al. Methods for Adjusting for Bias Due to Crossover in Oncology Trials, PharmacoEconomics (2014) 32:533–546
3. NICE DSU TSU 16, Latimer et al. Adjusting survival time estimates in the presence of treatment switching, 2014

PFS2: non-g*BRCA*m and g*BRCA*m Cohorts

- Benefit of niraparib extends beyond first progression based on updated analysis



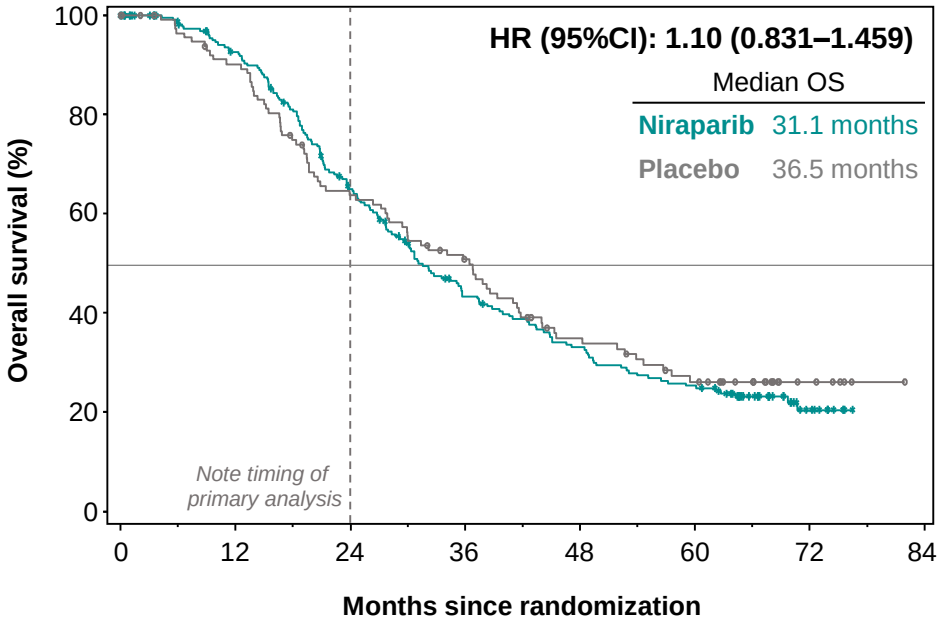


Final data cut-off was Oct 1, 2020 (average duration of follow up for OS was 67 months).
PFS2 was measured from time of randomization to progression on subsequent chemotherapy.

OS: Non-g*BRCA*mut Cohort

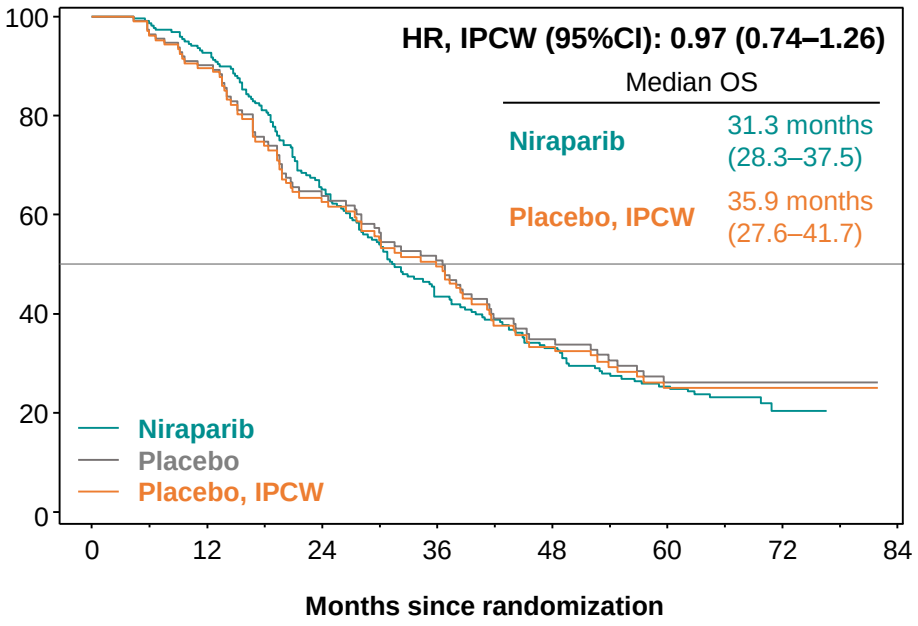
- At the time of the final analysis, average follow up time was 5.6 years
- Based on adjusted analysis for subsequent PARPi therapy, no difference in survival observed

Non-g*BRCA*m (68% maturity)



Niraparib	234	200	136	85	64	49	11	0
Placebo	116	100	69	52	33	23	6	0

Non-g*BRCA*m adjusted IPCW analysis

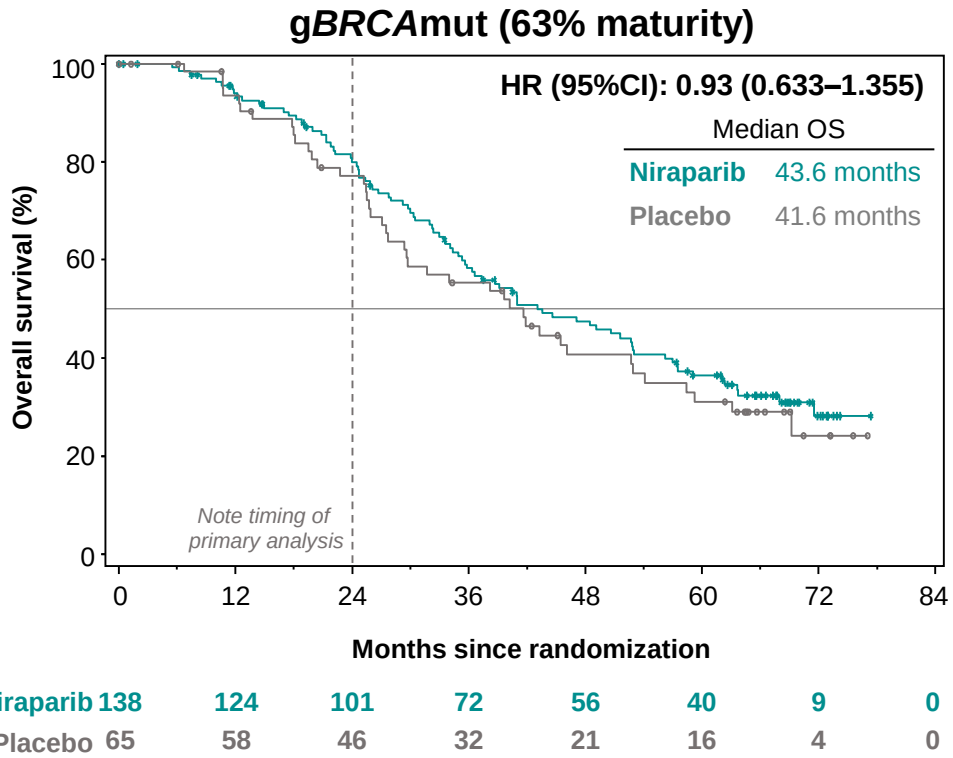


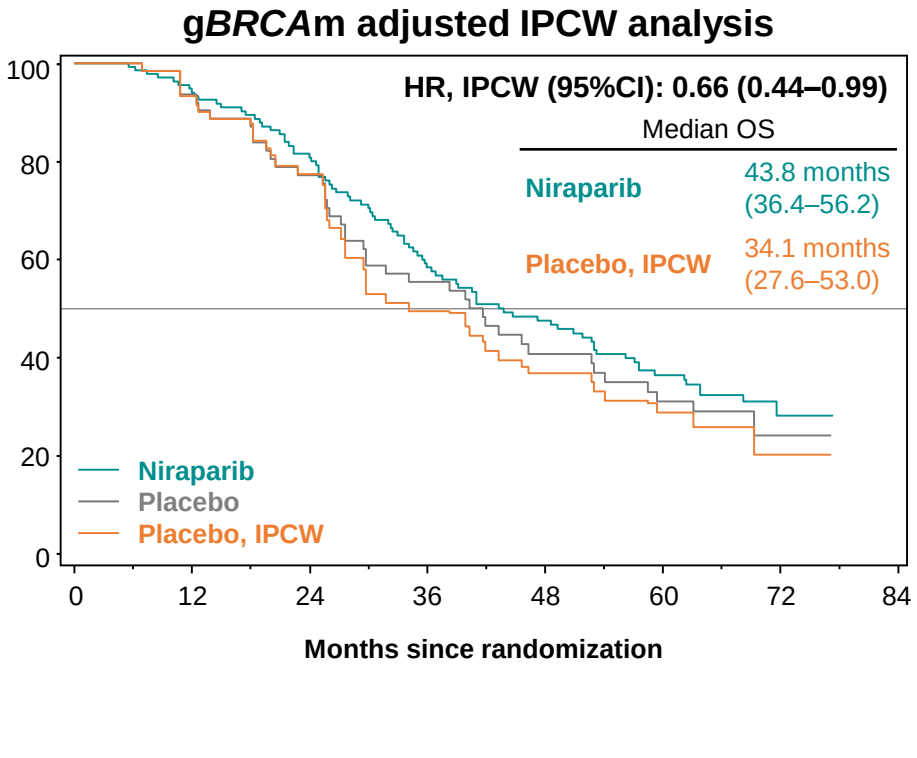
- Given evidence of non-proportional hazards, RMST analysis was conducted in ITT population to estimate the difference in restricted mean values (area under the curve).
  - **up to 24 months:** 20.6 months in placebo vs 21.3 months niraparib (Δ of 0.7, 95% CI: -0.5, 1.9)
  - **up to 72 months:** 39.1 months in placebo vs 38.5 months in niraparib (Δ of -0.7, 95% CI: -6.0, 4.7)

Final data cut-off was Oct 1, 2020

OS: g*BRCA*mut Cohort

- At the time of the final analysis, average follow up time was 5.6 years
- Adjusted analysis indicates a trend for improved survival with niraparib maintenance with a HR 0.66 and increased mOS by 9.7 months





Final data cut-off was Oct 1, 2020

Long-term Safety: Grade ≥3 Adverse Events

- Hematologic TEAEs primarily occurred in the first year of niraparib treatment
- Incidence of grade ≥3 thrombocytopenia decreased from 33.8% to 2.8%, anemia decreased from 25.6% to 0.7%, and neutropenia decreased from 19.3% to 2.1% from year 1 to year 2–3, respectively
- 49 (13%) patients remained on niraparib vs. 9 (5%) on placebo for more than 3 years

	Niraparib Arm				Placebo Arm			
Adverse Event, n (%)	**Overall (N=367)**	**Year 1 n=367**	**Year 2-3 n=143**	**Year 3+ n=49**	**Overall (N=179)**	**Year 1 n=179**	**Year 2-3 n=31**	**Year 3+ n=9**
Thrombocytopenia	131 (35.7)	124 (33.8)	4 (2.8)	6 (12.2)	1 (0.6)	1 (0.6)	0	0
Anemia	99 (27.0)	94 (25.6)	1 (0.7)	5 (10.2)	0	0	0	0
Neutropenia	76 (20.7)	71 (19.3)	3 (2.1)	4 (8.2)	3 (1.7)	3 (1.7)	0	0
Hypertension	36 (9.8)	32 (8.7)	7 (4.9)	4 (8.2)	4 (2.2)	4 (2.2)	0	0
Fatigue	31 (8.4)	30 (8.2)	0	1 (2.0)	1 (0.6)	1 (0.6)	0	0
GI disorders	30 (8.2)	24 (6.5)	4 (2.8)	2 (4.1)	9 (5.0)	8 (4.5)	1 (3.2)	0

Final data cut-off was Oct 1, 2020 (average duration of follow up for OS was 67 months).
The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count. The category of fatigue includes reports of fatigue, asthenia, malaise. The category of anemia includes reports of anemia and decreased hemoglobin count. The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia. The category of GI disorders includes constipation, diarrhea, nausea, vomiting, abdominal pain.

Summary of MDS/AML

- At the time of the primary analysis, incidence of MDS/AML was 1.4% (5/367) in the niraparib arm vs 1.1% (2/179) in the placebo arm[1]
- With long term follow up and administration of subsequent therapies, 3.5% (13/367) of patients in the niraparib arm vs. 1.7% (3/179) in the placebo arm developed MDS/AML

	Niraparib Arm			Placebo Arm		
Adverse Event, n (%)	**All (N=367)**	**g*BRCA*m n=136**	**Non-g*BRCA*m n=231**	**All (N=179)**	**g*BRCA*m n=65**	**Non-g*BRCA*m n=114**
MDS/AML All	**13* (3.5)**	9 (6.6)	4 (1.7)	**3 (1.7)**	2 (3.1)	1 (0.9)
TEAE (treatment)	9 (2.5)	7 (5.1)	2 (0.9)	0	0	0
TEAE (follow-up)	4 (1.1)	2 (1.5)	2 (0.9)	3 (1.7)	2 (3.1)	1 (0.9)

Final data cut-off was Oct 1, 2020 (average duration of follow up for OS was 67 months).
*Total 16 events of MDS/AML reported in 13 patients treated with niraparib; 1 patient had MDS then AML; 1 patient had MDS grade 1, MDS grade 4, then AML

1. Mirza et al. *NEJM*, 2016;375:2154-64.

Final NOVA Analysis In Platinum-sensitive Recurrent Ovarian Cancer

- Clinical benefit of niraparib was demonstrated in the primary PFS analysis in non-g*BRCA*m and g*BRCA*m patients

- Final PFS2 analysis indicates benefit of niraparib maintenance therapy extends beyond first progression

- OS was a secondary endpoint and not statistically powered in the NOVA study
  - Interpretation is challenged by a high rate of subsequent PARPi use and missing data
  - No difference in survival was observed in non-g*BRCA*m patients
  - Trend towards improved survival was observed in g*BRCA*m patients based on the adjusted analyses, with 9.7 months increase in survival

- Long term safety analysis supports use of niraparib for maintenance treatment
  - Hematologic adverse events decreased after first year of maintenance

Acknowledgments

We thank the 553 patients and their families for participating in this trial

NSGO	AGO	GEICO	GINECO	NCRI	MITO MaNGO	BGOG	ISGO	CEEGOG	AGO			
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