The Presence of Circulating Tumor DNA in Ovarian Cancer Patients After Platinum-Based Chemotherapy

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Disclosures

- No financial relationships or conflicts of interest to disclose

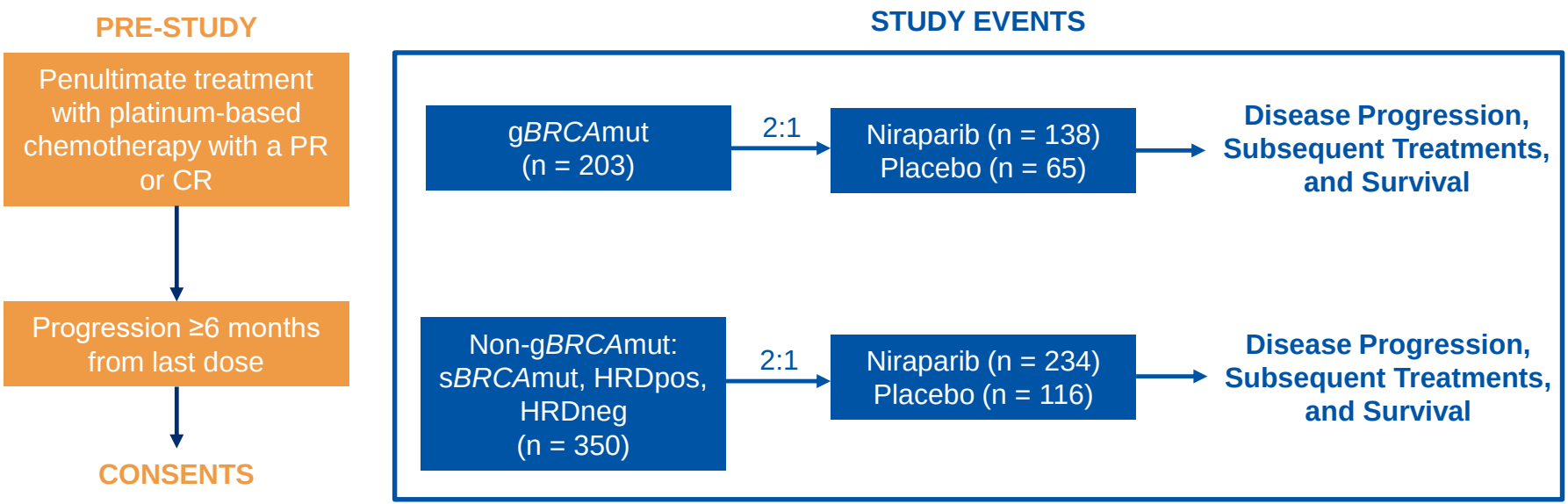
Background

- **ENGOT-OV16/NOVA Trial**
  - Niraparib: Oral poly(ADP-ribose) polymerase (PARP) inhibitor
  - Significantly longer progression-free survival (PFS) regardless of the presence of germline *BRCA* mutation (g*BRCA*mut) or homologous recombination deficiency (HRD) status

Mirza MR, et al. *N Engl J Med*. 2016;375:2154–2164.

Background

ENGOT-OV16/NOVA Trial



CR, complete response; HRDneg, HRD negative; HRDpos, HRD positive; PR, partial response; s*BRCA*mut, somatic *BRCA* mutation.

Background

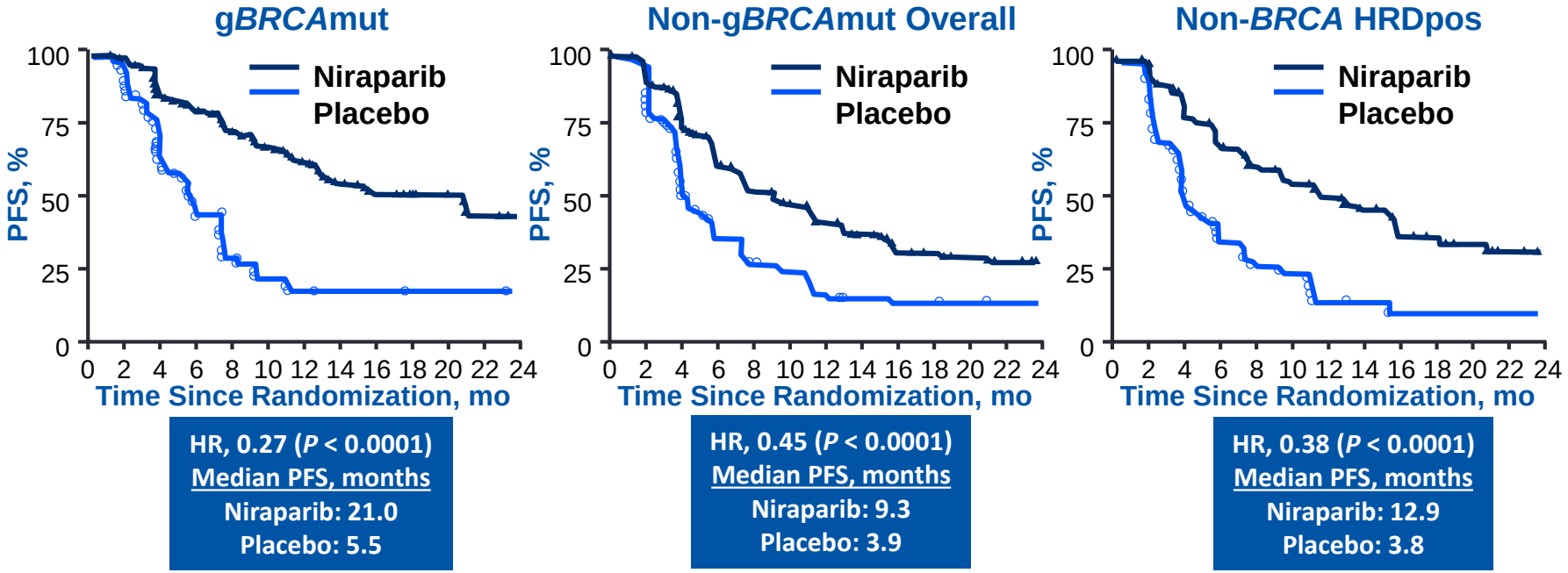
ENGOT-OV16/NOVA Trial

Study Group		N	PFI, %		Platinum Response, %		PFS, Months HR (95% CI)
			6–12 Months	>12 Months	CR	PR	
g*BRCA*mut		203	40	60	50.8	49.2	**21.0 vs 5.5** 0.27 (0.17–0.41)
Non-g*BRCA*mut	**Overall**	350	37.9	62.1	51.7	48.3	**9.3 vs 3.9** 0.45 (0.34–0.61)
	HRDpos	162					**12.9 vs 3.8** 0.38 (0.24–0.59)
	HRDneg	188					**6.3 vs 3.8** 0.58 (0.36-0.92)

CI, confidence interval; CR, complete response; HR, hazard ratio; HRDpos, HRD positive; PFI, platinum-free interval; PR, partial response.

Background

ENGOT-OV16/NOVA Trial



HR, hazard ratio; HRDpos, HRD positive; mo, months.

Background

- **FDA Approval (March 2017)**
  - Niraparib approved for maintenance treatment of recurrent ovarian cancer following a complete response (CR) or partial response (PR) to platinum-based chemotherapy
- **European Medicines Agency (EMA) Approval (Nov. 2017)**
- **National Institute for Health and Care Excellence (NICE) UK Approval (June 2018)**

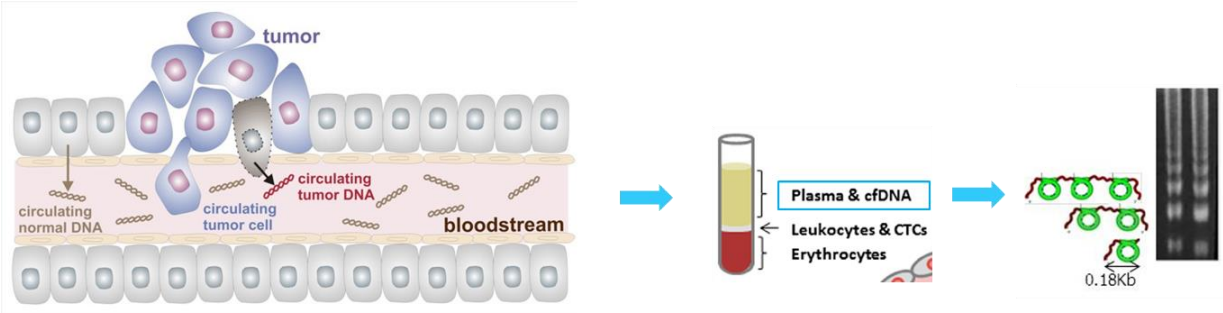
FDA, Food and Drug Administration.

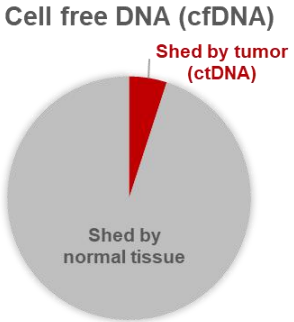
Background

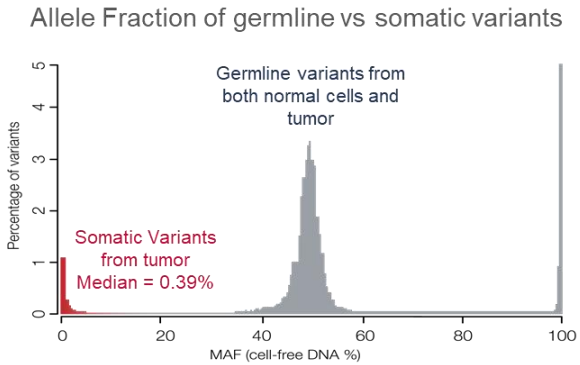
- **Circulating Tumor DNA (ctDNA)**
  - Potential origins of ctDNA
  - Brief history of ctDNA
  - Use in cancer diagnosis and prognosis
    - Half-life of 1.5–2.0 hours[1]
    - Potential marker of tumor burden or risk of relapse in pancreatic[2], breast[3], and colorectal cancer[4]

1. Yao W, et al. *Gene*. 2016;590:142-8.
2. Bernard V, et al. *Gastroenterology*. 2019;156(1):108-118.
3. Wang R, et al. *Oncotarget*. 2017; 8(43): 75742–75755.
4. Osumi H, et al. *Cancer Sci*. 2019;110(4):1148-1155.

Background





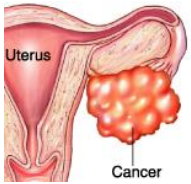


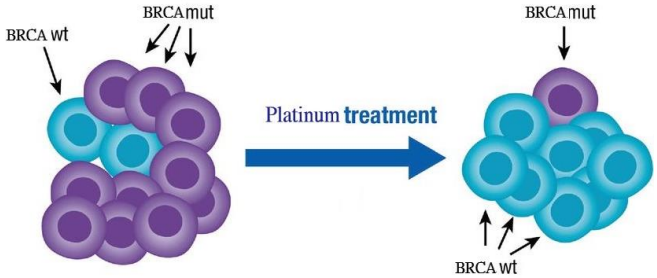
Cell Free DNA is shed from both normal and tumor tissue

Objective

- Assess the presence of tumor derived DNA fragments in circulation for NOVA patients with demonstrated response to chemotherapy
- Identify treatment and biomarker strategies for NOVA patients with recurrent ovarian cancer following a complete or partial response to platinum-based chemotherapy
- Determine the utility of defining the homologous recombination repair (HRR) status in ctDNA in the maintenance setting

Methods





Stage III/IV OC

50% Primary Surgery

50% NACT

Interval debulking

1L Chemo

1L Maintenance

2L Chemo

2L Maintenance

If there is utility of ctDNA to determine HRR status in maintenance setting

NOVA randomization

1L, first-line; 2L, second-line; *BRCA*wt, *BRCA* wild-type; Chemo, chemotherapy; HRR, homologous recombination repair; Maint, maintenance; NACT, neoadjuvant chemotherapy; OC, ovarian cancer.

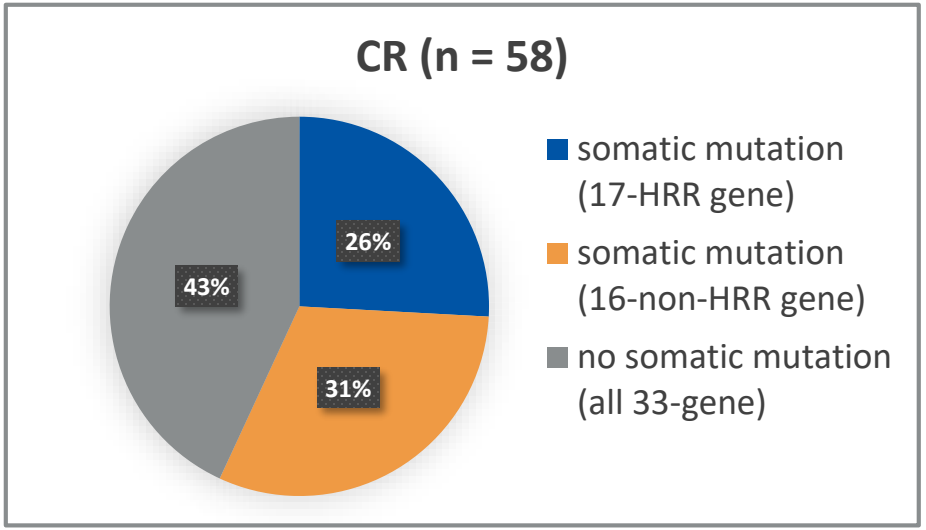
Methods

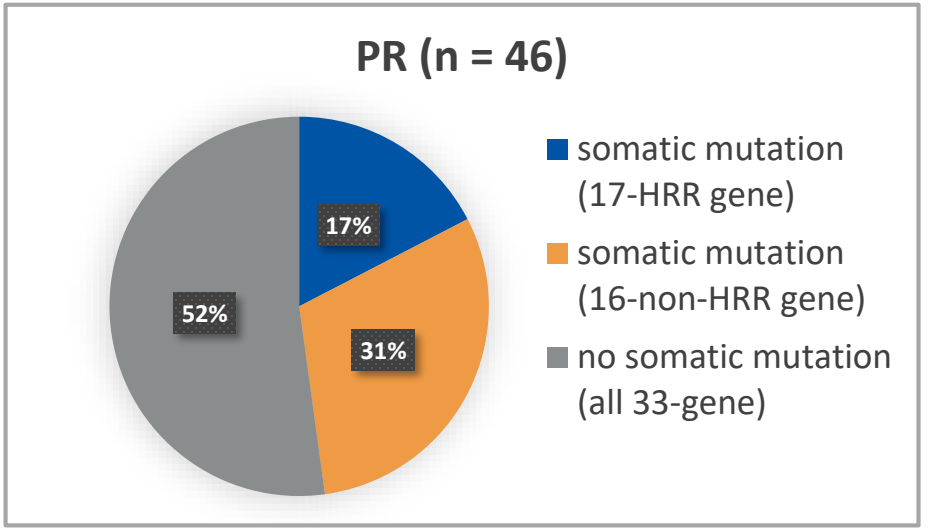
- **NOVA Samples (n = 104)**
  - Following completion of platinum-based chemotherapy and within the first 2 cycles of niraparib
  - CR 56%; PR 44%
  - De-identified and unlinked from patient level clinical information
- **Analysis**
  - ctDx-HRR Assay (Resolution Bioscience, Kirkland, WA, USA)
    - Next-generation sequencing
    - Sample requirement: as low as 2ml plasma prepared from 5ml blood
    - Custom investigator use only (IUO) panel which detects 33 cancer-related genes including *BRCA1*, *BRCA2*, and 16 other homologous recombination repair (HRR) genes
    - Analytically validated for Investigational Use

Results

- **Somatic Variant Mutations**
  - Detected in 53% regardless of radiologic response to platinum-based chemotherapy
    - 57% of complete responders
    - 48% of partial responders

Results

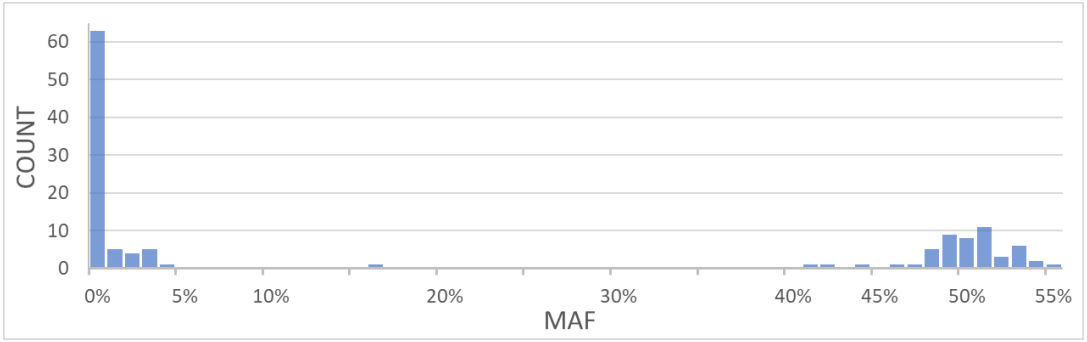




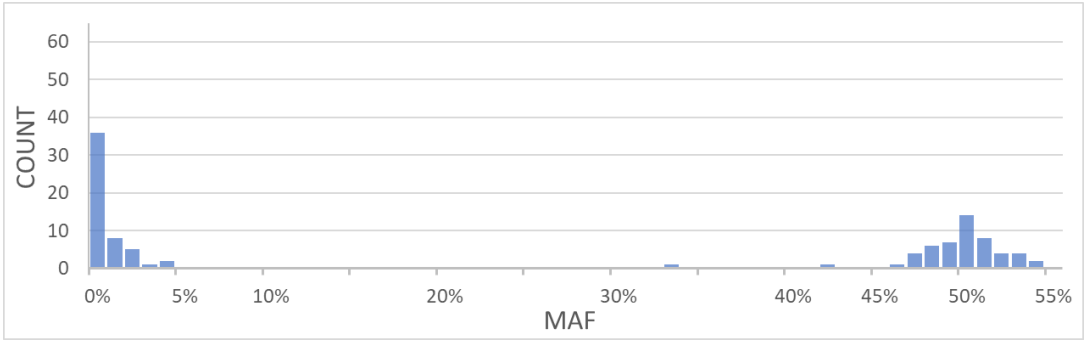
- Presence of somatic mutation demonstrates DNA shed from tumor cells in CR and PR patients

Results

Complete Response



Partial Response



Count, number of mutations within different ranges of mutational allele frequency; MAF, mutational allele frequency.

Conclusions

- **Residual Disease**
  - ctDNA present despite CR at time of sampling
  - Both PR and CR patients have detectable somatic mutations in ctDNA
  - Possible contribution to high recurrence rate and poor outcomes

- **Potential Benefit of Maintenance Therapy**
  - Suppression of incipient disease

- **Future Research**
  - ctDNA for detection of minimal residual disease and assessment of the efficacy of platinum-based chemotherapy or PARPi therapy

Thank You!

Questions?

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