5568

Elucidation of PARP Inhibitor Activity in *BRCA*wt Recurrent Ovarian Cancer by HRR Mutational Gene Profile Analysis

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BACKGROUND

- Niraparib is an oral, selective poly(ADP-ribose) polymerase inhibitor approved for maintenance treatment of patients with *BRCA*-mutated (*BRCA*mut) and *BRCA* wild-type (*BRCA*wt) recurrent ovarian cancer who are in response to platinum-based chemotherapy.
- In the non-germline *BRCA*mut (non-g*BRCA*mut) cohort of the ENGOT-OV16/NOVA trial, clinical benefit with niraparib vs placebo was seen in patients regardless of their Myriad myChoice® HRD status (*BRCA*mut and homologous recombination deficiency [HRD] score), with a hazard ratio (HR) of 0.38 and 0.58 in HRD-positive (HRDpos) and HRD-negative (HRDneg) patients, respectively.[1]

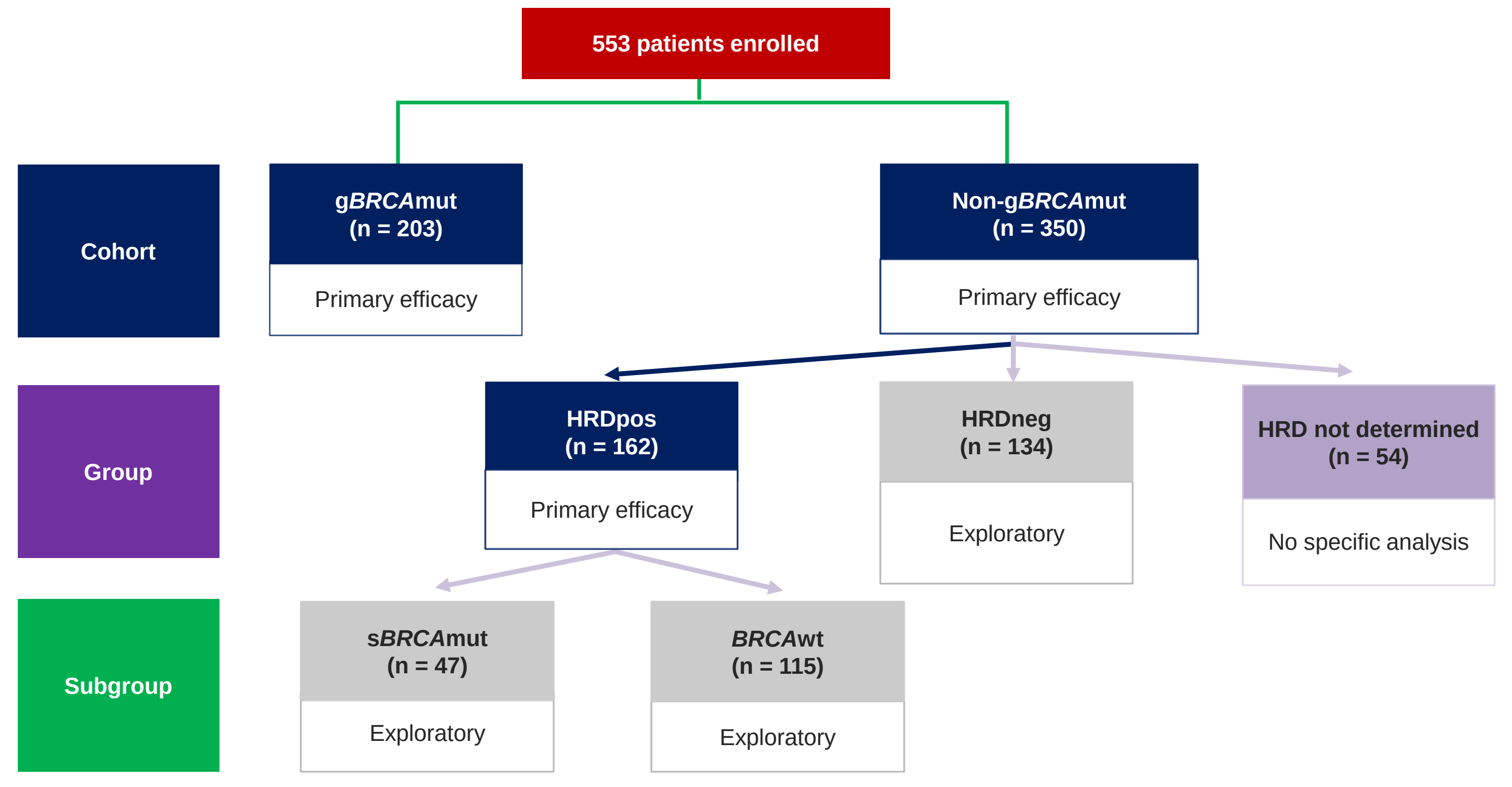
OBJECTIVES

- To determine if treatment benefit in HRDneg patients may result from mutations in other HRR genes, by examining the relationship between progression-free survival (PFS) and other homologous recombination repair (HRR) gene mutations in the ENGOT-OV16/NOVA non-gBRCAmut cohort.

METHODS

- Archival ovarian cancer specimens were required for the 553 patients randomized in ENGOT-OV16/NOVA and were sequenced using the Myriad HRD assay to identify deleterious mutations in 43 DNA damage repair (DDR) genes.
  - Tumor HRD score was detected by the Myriad myChoice® HRD assay.
  - A retrospective, exploratory biomarker analysis was conducted using all available tumor samples from 331 patients enrolled in the ENGOT-OV16/NOVA non-g*BRCA*mut cohort.
- Mutation status of HRR genes was evaluated using a 43-gene next-generation sequencing assay (Myriad Genetics), including *BRCA1/2* and 16 additional HRR genes. The 18 HRR genes are:
  - *ATM, BAP1, BARD1,* ***BRCA1***, ***BRCA2***, *BRIP1, MRE11A, NBN, PALB2, RAD50, RAD51B, RAD51C, RAD51D, RAD54B, RAD54L, ATR, XRCC2,* and *XRCC3*.

Figure 1. ENGOT-OV16/NOVA trial design


553 patients enrolled

Cohort

g*BRCA*mut
(n = 203)
Primary efficacy

Non-g*BRCA*mut
(n = 350)
Primary efficacy

Group

HRDpos
(n = 162)
Primary efficacy

HRDneg
(n = 134)
Exploratory

HRD not determined
(n = 54)
No specific analysis

Subgroup

s*BRCA*mut
(n = 47)
Exploratory

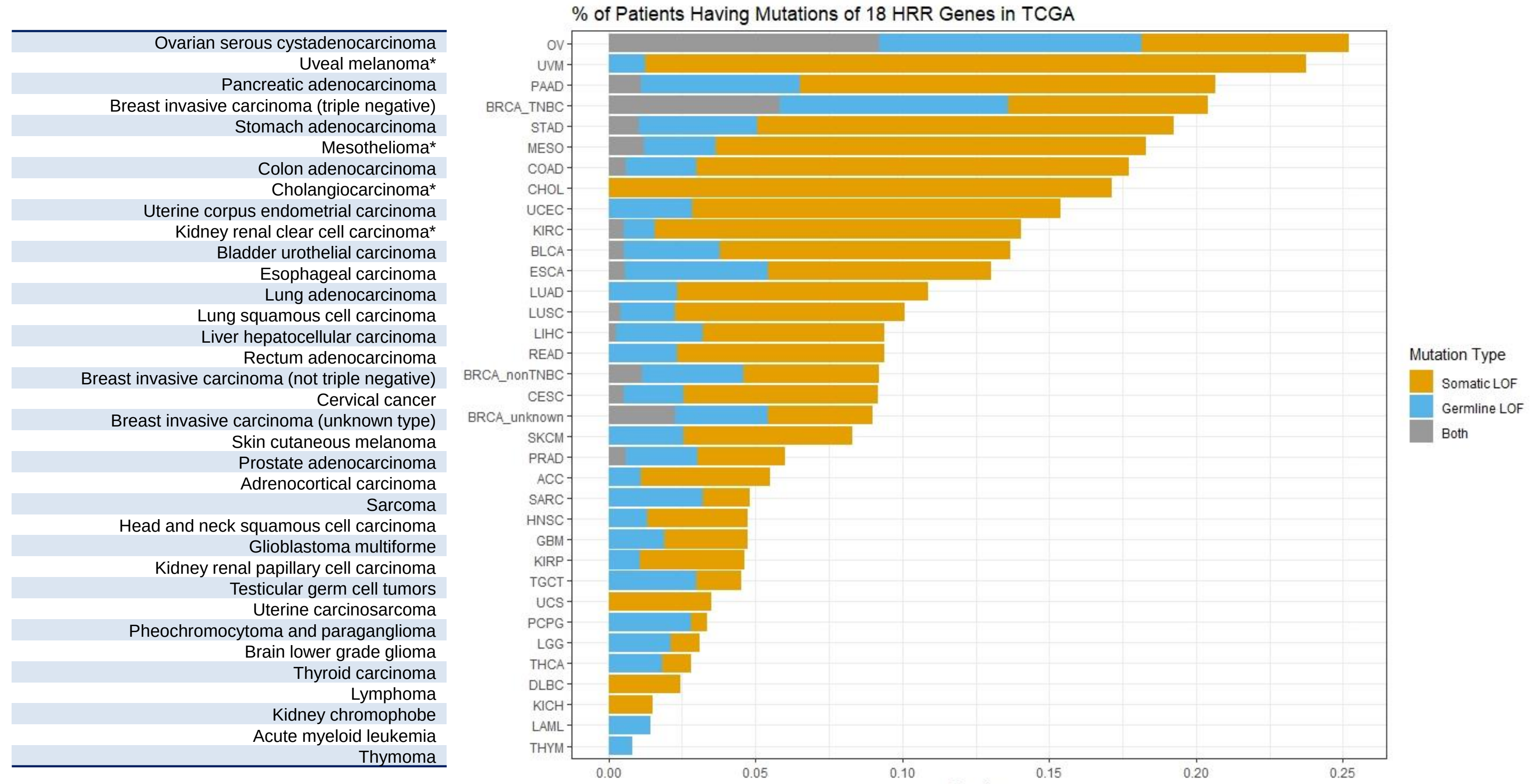
***BRCA*wt**
(n = 115)
Exploratory

s*BRCA*mut, somatic *BRCA* mutated.

RESULTS

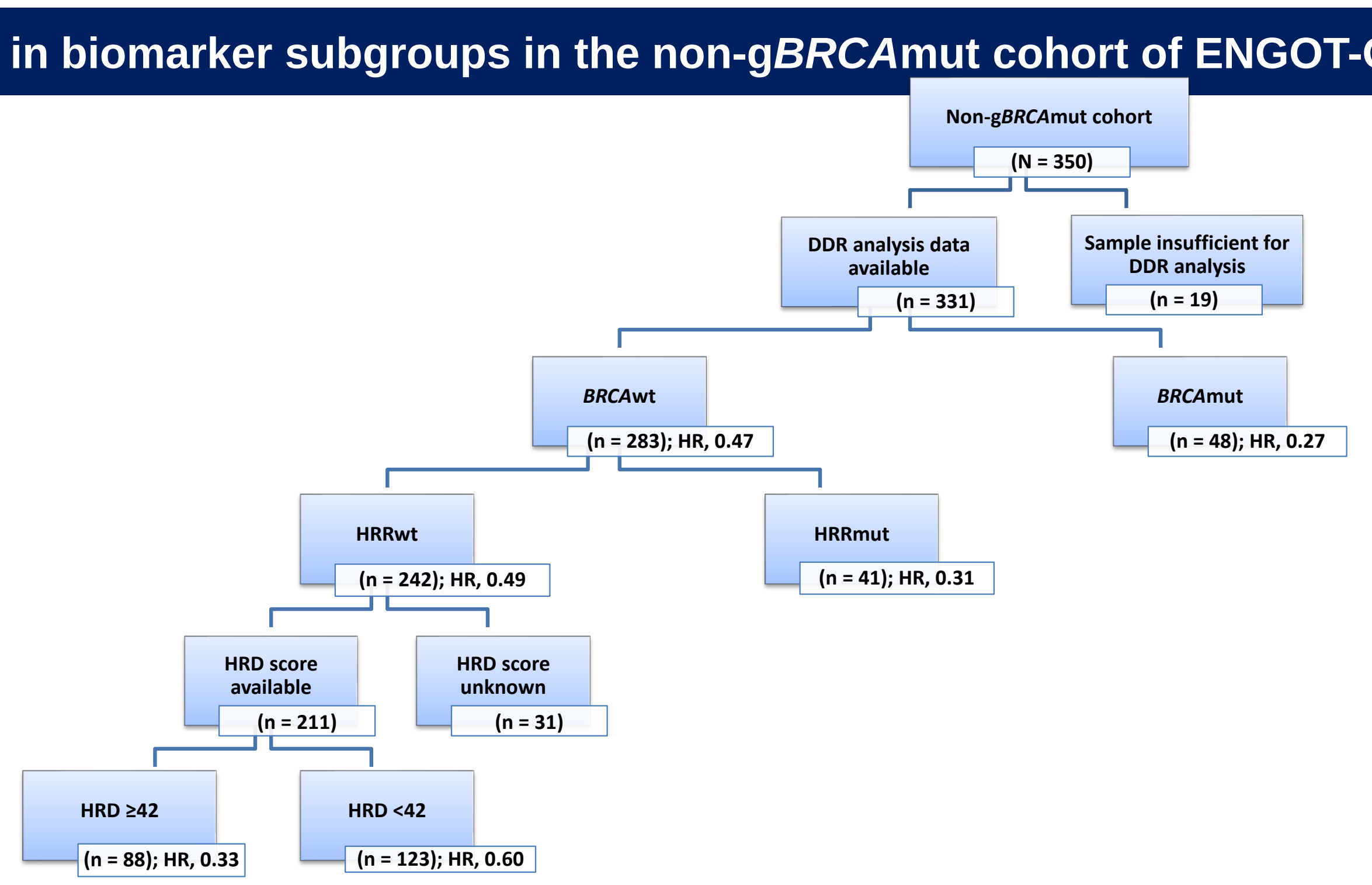
- In this exploratory analysis of the non-g*BRCA*mut cohort, niraparib demonstrated clinical benefit in patients with somatic *BRCA* mutations (s*BRCA*mut; HR, 0.27) and in *BRCA*wt patients (HR, 0.47).
- In addition, *BRCA*wt patients with other HRR gene mutations also derived benefit from niraparib (HR, 0.31), as did *BRCA*wt/HRR wild-type (HRRwt) patients (HR, 0.49).
- When *BRCA*wt/HRRwt patients were categorized by HRD score, clinical benefit was also observed in both HRDpos and HRDneg patients, with HRs of 0.33 and 0.60, respectively.

Figure 2. Mutation prevalence of 18 HRR genes in TCGA[2]



*Four tumor types with high mutation prevalence of HRR genes in TCGA (uveal melanoma, mesothelioma, cholangiocarcinoma, and kidney renal clear cell carcinoma) were driven by the high *BAP1* mutation prevalence.
LOF, loss of function; TCGA, The Cancer Genome Atlas.

Figure 3. Clinical benefit in biomarker subgroups in the non-g*BRCA*mut cohort of ENGOT-OV16/NOVA


Non-g*BRCA*mut cohort
(N = 350)

DDR analysis data available
(n = 331)

Sample insufficient for DDR analysis
(n = 19)

***BRCA*wt**
(n = 283); HR, 0.47

***BRCA*mut**
(n = 48); HR, 0.27

HRRwt
(n = 242); HR, 0.49

HRRmut
(n = 41); HR, 0.31

HRD score available
(n = 211)

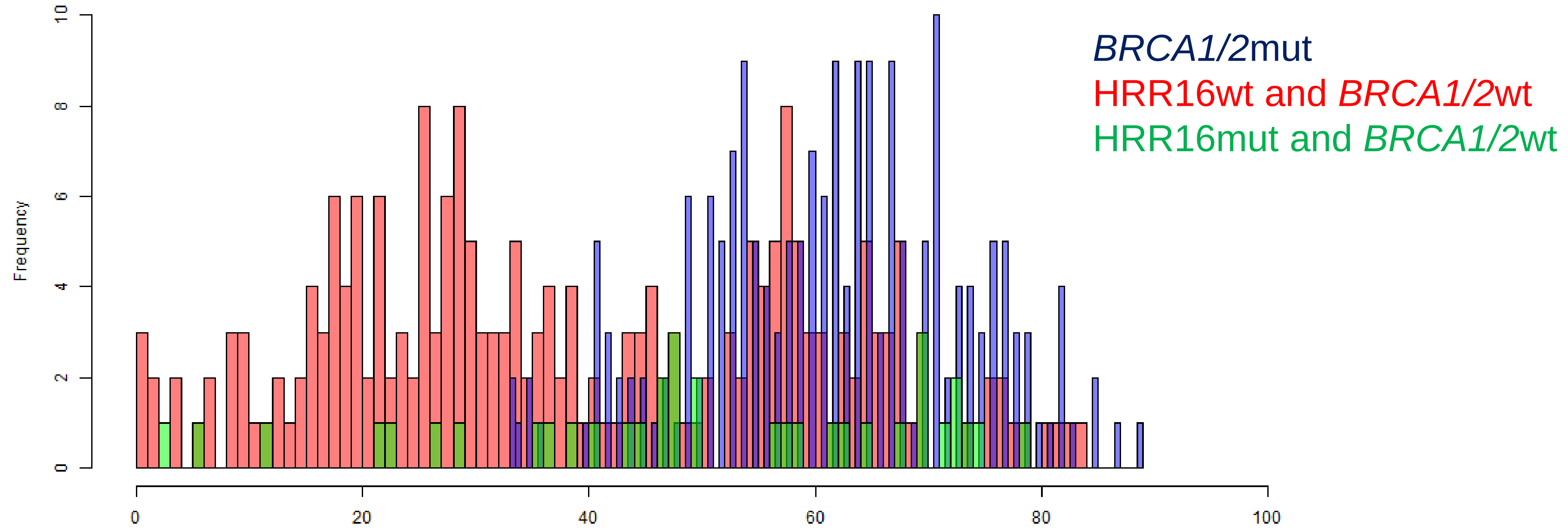
HRD score unknown
(n = 31)

HRD ≥42
(n = 88); HR, 0.33

HRD <42
(n = 123); HR, 0.60

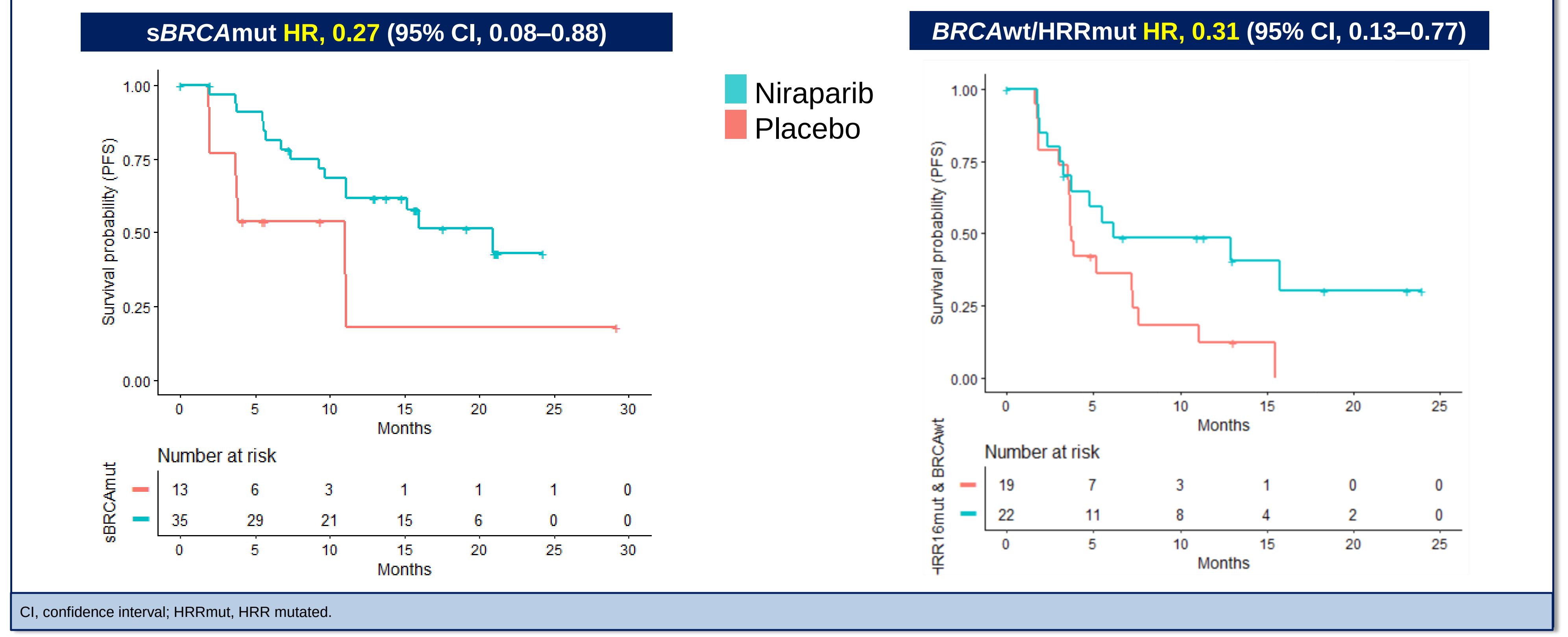
HRRmut, HRR mutated.

Figure 4. Histogram of Myriad HRD scores for all samples



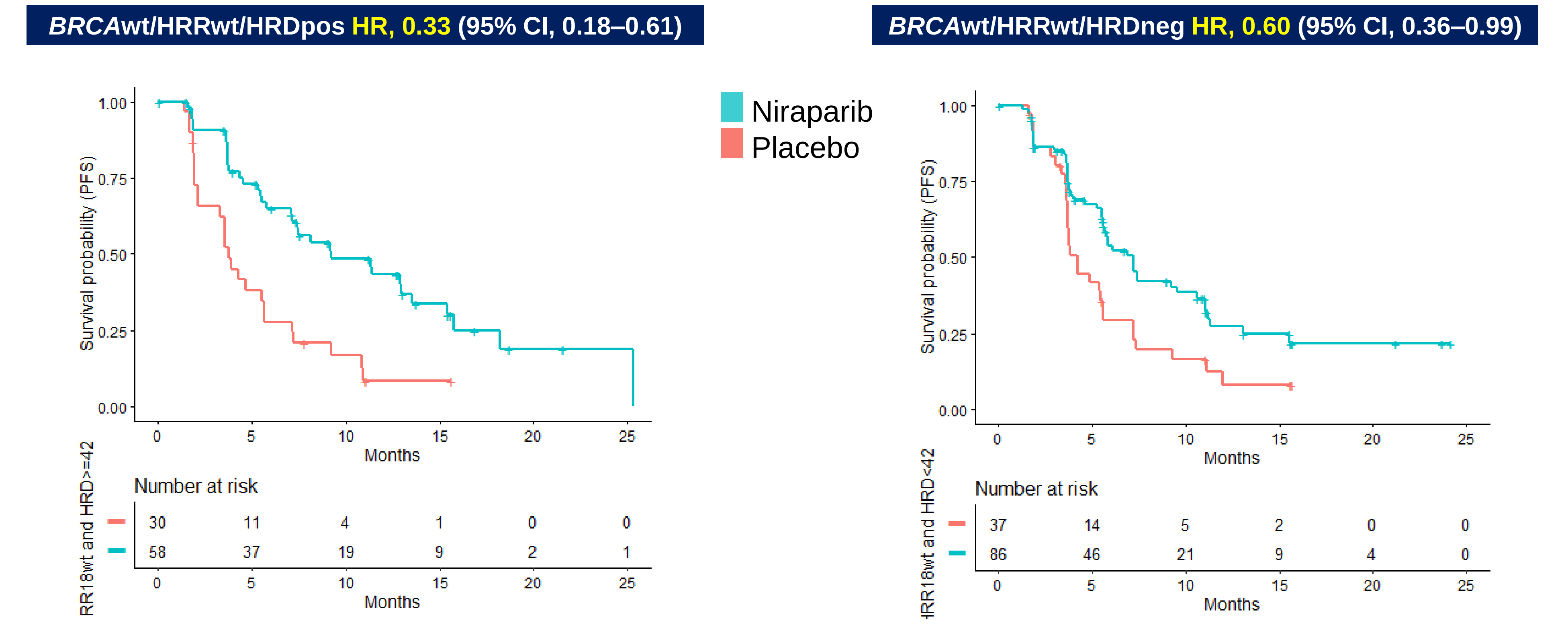
BRCA1/2 wild-type samples showed a bimodal distribution.

Figure 5. Comparable clinical benefit of niraparib in *BRCA*wt patients with other HRR mutations vs patients carrying somatic *BRCA* mutations



CI, confidence interval; HRRmut, HRR mutated.

Figure 6. Benefit of niraparib in *BRCA*wt/HRRwt patients with HRDneg or HRDpos ovarian cancers



CI, confidence interval.

CONCLUSIONS

- This retrospective, exploratory analysis of the ENGOT-OV16/NOVA non-g*BRCA*mut cohort suggests that, although patients with somatic *BRCA* and other HRR mutations benefit from niraparib treatment, clinical benefit is also seen in HRDneg patients without HRR mutations, perhaps related to other genomic, epigenetic, or functional alterations within ovarian tumors yet to be defined.
- These results suggest that, although these biomarkers have good positive predictive value, they are not good negative predictors for niraparib benefit in this indication.

REFERENCES

1. Mirza MR, et al. *N Engl J Med*. 2016;375:2154–2164.
2. The Cancer Genome Atlas (TCGA) Research Network. http://cancergenome.nih.gov/.

Presented at the American Society of Clinical Oncology (ASCO) Annual Congress | May 31–June 4, 2019 | Chicago, IL