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Molecular and clinical predictors of improvement in progression-free survival with maintenance PARP inhibitor therapy in women with platinum-sensitive recurrent ovarian cancer: A meta-analysis

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Precis:

BRCA mutation status could predict for the magnitude of PARP inhibitor benefit in platinum-sensitive recurrent high grade ovarian tumor. However, absence of a *BRCA* mutation or homologous recombinant deficiency in high grade ovarian tumor could not be used to exclude patients from such therapy.

Abstract

Background: We performed a meta-analysis to better quantify benefit of maintenance PARP inhibitor (PARPi) to inform practice in platinum-sensitive recurrent high grade ovarian cancer (PSROC) for these patient subsets: germline *BRCA* mutation (*gBRCAm*), somatic *BRCA* mutation (*sBRCAm*), wild-type *BRCA* and homologous recombinant deficient (HRD), homologous recombinant proficient (HRP), and baseline clinical prognostic characteristics.

Methods: Randomized trials comparing a PARPi versus placebo as maintenance treatment were identified from electronic databases. Treatment estimates for progression-free survival (PFS) were pooled across trials using the inverse variance weighted method.

Results: Four trials included 972 patients receiving a PARPi (olaparib, 31%; niraparib, 35%; or rucaparib, 34%), and 530 patients receiving placebo. For *gBRCAm1* (N=471), HR=0.29 (95% CI 0.23–0.37). For *gBRCAm2* (N=236), HR=0.26 (95% CI 0.17–0.39). For *sBRCAm* (N=123), HR=0.22 (95% CI 0.12–0.41). The treatment effect was similar between *gBRCAm* and s*BRCAm* (*P*=.48). In wild-type *BRCA* HRD tumors (excluding s*BRCA*m, N=309) HR=0.41 (95% CI 0.31–0.56). In wild-type *BRCA* HRP tumors (N=346), HR=0.64 (95% CI 0.49–0.83). The relative treatment effect was greater for *BRCAm* versus HRD (*P*=.03), *BRCAm* versus HRP (*P*<.00001), and HRD versus HRP subgroups (*P*<.00001) respectively. There was no difference in benefit based on age, response after recent chemotherapy, and prior bevacizumab.

Conclusions: In PSROC, maintenance PARPi improves PFS for all patient subsets. PARPi has similar magnitude of benefit for *sBRCAm* and *gBRCAm*. Although patients

with *BRCAm* derive the greatest benefit, the absence of a *BRCAm* or HRD could not be used to exclude patients from maintenance PARPi therapy.

Keywords: platinum sensitive recurrent ovarian cancer, BRCA mutation, homologous recombination deficiency, polyADP-ribose polymerase inhibitors, meta-analysis

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Introduction

Cancers of the ovary, fallopian tube and peritoneum remain the most important causes of cancer deaths for women in developed countries[1]. At diagnosis, the majority of women have advanced stage disease and approximately 80% will recur following surgery and chemotherapy**.** Women with platinum-sensitive recurrent ovarian cancer (PSROC), defined as relapse ≥6 months after the most recent platinum-based chemotherapy, are usually re-treated with further platinum-based agents. There is usually a declining likelihood of response and shorter duration of benefit with each successive line of treatment. Multiple treatment strategies have been extensively investigated in PSROC with the aim of prolonging progression-free survival (PFS) and overall survival (OS). To date the most successful strategies are concomitant chemotherapy and bevacizumab followed by maintenance bevacizumab, and maintenance poly(ADP ribose) polymerase inhibitors (PARPi).

High-grade ovarian tumors accounts for the majority of PSROC and up to 50% are deficient in homologous recombination which is a key pathway involved in DNA damage repair[2-6] and are therefore reliant on more error prone DNA repair pathways such as non-homologous end joining[7]. Various homologous recombination deficiencies have been recognized, including germline mutations of the *BRCA1*/*2* genes (*gBRCAm 1*/*2*), somatically acquired *BRCA* mutations (*sBRCAm*), epigenetic *BRCA1* inactivation, or other *BRCA*-independent pathways. To date, *sBRCAm1* were reported in 5–9% of sporadic ovarian tumors, whereas *sBRCAm2* were identified in 3–4% of cases[8-10]. *BRCAm* of either germline[11, 12] or somatic mutations[13] occurs more frequently in platinum sensitive than resistant tumors.

PARPi induce synthetic lethality in tumors with homologous recombination deficiency. Multiple randomized controlled trials (RCTs) in PSROC have reported that maintenance PARPi following response to platinum based chemotherapy significantly improves PFS and delays time to subsequent chemotherapy which has changed the standard of care[13-17] and this treatment is gradually being introduced worldwide. The SOLO2 trial also reported an OS improvement with maintenance olaparib, with 28.3% of *gBRCAm* patients alive at 60 months without need for subsequent treatment, as compared with 12.8% in the placebo arm[18]. There is ongoing interest to determine which patient subgroups, beyond those with a *gBRCAm*, will benefit from maintenance PARPi and whether it is possible to use clinico-pathologic factors to select for these patients. This information will be clinically relevant, can help inform the design and interpretation of future trials, and can aid economic analyses.

This paper reports a meta-analysis of four RCTs using published and unpublished data of patient subsets to quantify the relative treatment benefit of maintenance PARPi over placebo in women with PSROC who have responded to platinum-based chemotherapy. We also aimed to determine the variation in treatment benefit based on patient, disease, and past treatment characteristics. This meta-analysis is valuable as individual RCTs were neither designed nor adequately powered to detect differences in treatment effect in these subgroups.

Methods

Study eligibility and identification

We included RCTs of recurrent PSROC with high-grade tumors if they compared PARPi as maintenance therapy versus placebo. Eligible RCTs were identified from

MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials. Search terms used included "*BRCA*", "*BRCA*1", "*BRCA*2", "*BRCA*1 protein", "*BRCA*2 protein", "ovarian neoplasms", "platinum-sensitive", "poly(ADP Ribose) polymerase inhibitors" and "clinical trial". We retrieved relevant articles published between 2005 and 2019 with no language restrictions. Individual trial investigators were also contacted for unpublished subgroup data.

Data collection and analysis

For each RCT, we extracted the trial name, patients' clinico-pathologic characteristics and types of PARPi. Regardless of the primary endpoints of the included RCTs, this meta-analysis assessed treatment benefit based on PFS as assessed by local investigators (INV) as the primary outcome. We performed a sensitivity analysis to determine the consistency of the results based on blinded independent central review (BICR) PFS for all RCTs. BICR PFS was a pre-specified primary endpoint of one included RCT[13].

We retrieved the hazard ratio (HR) and 95% confidence interval (CI) for PFS based on homologous recombination repair (HRR) deficiency status: *gBRCAm*, *sBRCAm*, wild-type *BRCA* (*wtBRCA*) but homologous recombination deficient (HRD, excluding those with *sBRCAm*) and *wtBRCA* but homologous recombination proficient (HRP). Tumors with oncogenic germline and somatic mutations were classified as *BRCAm* and variants of unknown significance were classified as *wtBRCA*. If *BRCAm* was detected but the tumor was also tested to be HRP, these patients were classified based on their *BRCAm* status. HRD was defined differently in different RCTs. In one study[16], tumors were classified as HRD if they had high genomic loss of heterozygosity

(LOH) as detected using Foundation Medicine T5 NGS assay (cutoff of 16% or greater). Other studies[13, 19] defined HRD based on high LOH, telomeric allelic imbalance, and/or large-scale state transitions as detected using Myriad Genetics myChoice test (Genomic Instability Score of 42 or greater).

We also retrieved data on treatment effect for these clinicopathologic subgroups: age (<65 versus ≥65 years), platinum-free interval (6–12 versus >12 months), response after most recent chemotherapy (complete response versus partial response), number of previous lines of platinum chemotherapy (2 versus >2) and use of bevacizumab treatment in conjunction with last platinum regimen (yes versus no).

Two of the authors (CKL, AT) extracted the data independently, and discrepancies were resolved by a third author (CLS). The risk of bias was assessed based on methods of randomization, allocation concealment, outcome assessments, attrition and reporting of the data. We reported our data based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses *(*PRISMA) guidelines[20].

Statistical analysis

Pooled PFS HRs and 95% CIs were computed by using the inverse variance weighted method with fixed-effects models. Differences between subgroups were tested using methods described by Borenstein et al[21]. We used the χ^2 Cochran Q test to detect any heterogeneity across trials. We also evaluated publication bias by examining the funnel plot of the effect size for each RCT against the reciprocal of its standard error. The nominal level of significance was set at 5%.

Results

We identified four eligible RCTs[13-17, 19] (Figure 1). Of 1677 patients who were randomly assigned to a PARPi or placebo, we analyzed only patient data from 1502 (89.6%). A total of 175 patients (ARIEL3[16], N=59; Study 19 trial[14, 15, 19], N=62; NOVA trial[13], N=54) were excluded because HRR deficiency status were unknown. All trials recruited patients with high-grade cancers of the ovary, fallopian tube and peritoneum. The majority had predominantly serous histology, whilst only the ARIEL3[16] and SOLO2[17] trials enrolled patients with endometriod and other rare histologies (N=28, 5%, and N=25, 8%, respectively). Table 1 outlines the demographic and treatment characteristics. All included studies were evaluated as low risk for bias (details not shown).

All study sponsors provided unpublished summary subgroup data. All RCTs had a double-blind, placebo-controlled design. The primary endpoint was PFS by BICR for the NOVA trial[13]; PFS by INV was the primary endpoint for other RCTs. The Study 19 trial[14, 15, 19] was the only trial with a randomized phase II design and the HRR gene status of the tumor was determined retrospectively.

The SOLO2 trial[17] recruited only *gBRCA*m carriers, whereas the remaining RCTs included *gBRCAm*, *sBRCAm* and *wtBRCA* patients. In the ARIEL3 trial[16], *wtBRCA* tumors with HRD was defined based on high genomic LOH. In the Study 19 and NOVA trials, *wtBRCA* tumors with HRD were those with high LOH, telomeric allelic imbalance, and large-scale state transitions.

Benefit of PARP inhibitor in subgroups according to homologous recombination repair deficiency status

Across the trials, 972 patients received a PARPi (olaparib, N=301 [31%]; niraparib, N=336 [35%]; or rucaparib, N=335 [34%]), and 530 patients received placebo.

Among the 471 *gBRCAm1* patients, the pooled PFS HR was 0.29 (95% CI 0.23–0.37, *P*<.00001; Figure 2). Among the 236 *gBRCAm2* patients, the pooled PFS HR was 0.26 (95% CI 0.17–0.39, *P*<.00001). In the 123 *sBRCA*m patients, the pooled PFS HR was 0.22 (95% CI 0.12–0.41, *P*<.00001).

The pooled PFS HR for both *gBRCAm1* and *gBRCAm2* only was 0.28 (95% CI 0.23–0.35, *P*<.00001). The pooled PFS HR for *gBRCAm1*, *gBRCAm2* and *sBRCAm* was 0.27 (95% CI 0.23–0.34, *P*<.00001).

The relative treatment effect was similar between *gBRCAm1* and *gBRCAm2* (*P*=.63). There was also no significant difference in treatment effect between *gBRCAm1/2* and *sBRCAm* (*P*=.48).

There were 309 *wtBRCA* patients with HRD tumor (excluding s*BRCAm*). The pooled PFS HR was 0.41 (95% CI 0.31–0.56, *P*<.00001). In the 346 *wtBRCA* patients with HRP tumor, the pooled PFS HR was 0.64 (95% CI 0.49–0.83, *P*=.0006). The relative treatment effect was significantly greater for HRD than HRP subgroups (*P*<.00001).

The relative treatment effect was also significantly greater for *BRCAm* (both germline and somatic) than HRD subgroups (HR 0.27 versus 0.41, *P*=.03). A similar finding was observed for the comparison of *BRCAm* (both germline and somatic) with HRP subgroups (HR 0.27 versus 0.64, *P*<.00001).

Subgroup analyses by clinico-pathologic characteristics

Subgroup outcome data were available for age, response after most recent chemotherapy, number of previous lines of platinum chemotherapy and prior bevacizumab treatment.

In the *gBRCAm* cohort, the pooled HR for patients with only two prior platinum chemotherapy lines (N=420, 58%) was 0.31 (95% CI 0.24–0.41, *P*<.00001). Among the 302 (42%) patients who had more than two prior platinum chemotherapy lines, the pooled HR was 0.20 (95% CI 0.14–0.28, *P*<.00001). The relative treatment effect was borderline significant between these subgroups (*P*=.04; Figure 3). In this *gBRCAm* cohort, the relative treatment benefit of PARPi versus placebo did not vary substantially between the subgroups, based on age, response after most recent chemotherapy, and prior bevacizumab treatment (Figure 3).

In patients with HRD tumors but without s*BRCAm*, PFS HRs did not vary substantially between the subgroups defined by clinico-pathologic characteristics. For patients with HRP tumors, PFS HRs also did not vary substantially in these clinico-pathologic subgroups (Figure 3).

Impact of platinum-free interval on progression-free survival across patient cohorts

Platinum-free interval (PFI) was a stratification factor and defined consistently across all RCTs. A total of 834 patients had PFI greater than twelve months and 545 patients had PFI between six to twelve months. PFS HRs did not vary substantially according to PFI within the *gBRCAm*, HRD, and HRP subgroups (Figure 3).

However, amongst those with PFI greater than twelve months, the pooled PFS HR was 0.29 (95% CI 0.22–0.38, *P*<.00001) in 429 (51%) *gBRCAm* patients. In the 192

(23%) patients with HRD tumor (excluding s*BRCAm*), the pooled PFS HR was 0.34 (95% CI 0.23–0.50, *P*<.00001). There was no significant difference in treatment effect between *gBRCAm* and HRD subgroups (*P*=.56). In contrast, the pooled PFS HR was 0.67 (95% CI 0.48–0.92, *P*=.01) in 213 (26%) patients with HRP tumors. The treatment effect was significantly greater for the comparisons of *gBRCAm* versus HRP (*P*=.0001), and HRD versus HRP subgroups (*P*=.009).

Amongst those with PFI between six to twelve months, 295 (54%) *gBRCAm* patients had a pooled PFS HR of 0.25 (95% CI 0.19–0.34, *P*<.00001). In the 117 (22%) patients with HRD tumors, the pooled PFS HR was 0.54 (95% CI 0.34–0.87, *P*=.01). Among the 133 (24%) patients with HRP tumor, the pooled PFS HR was 0.59 (95% CI 0.38–0.90, *P*=.02). The treatment effect was significantly greater for *gBRCAm* than HRD subgroups (*P*=.007), and for *gBRCAm* than HRP subgroups (*P*=.001). There was no significant difference in the treatment effect between HRD and HRP subgroups (*P*=.80).

Sensitivity analysis

SFigure 1 summarized the results for PFS by BICR. Data were not available for 5 patients from Study 19 trial[14, 15, 19]. For patient cohorts with *gBRCAm1*, *gBRCAm2* and *sBRCAm*, results for PFS by BICR were consistent with INV. PFS HRs by BICR did not differ significantly between *gBRCAm1* and *gBRCAm2* (*P*=.23). PFS HRs by BICR were also similar between *gBRCAm1/2* and *sBRCAm* subgroups (*P*=.51).

In *wtBRCA* patients with HRD tumor but without s*BRCAm*, PFS HR by BICR (SFigure1) was also similar to PFS HR by INV (Figure 2). However, there was a difference in PFS HR by BICR for *wtBRCA* patients with HRP tumor as compared with

PFS HR by INV. Unlike PFS INV analysis, there was no significant difference in PFS HR by BICR between HRD than HRP subgroups (*P*=.75).

The treatment effect by BICR was also significantly greater for *BRCAm* (both germline and somatic) than HRD subgroups (*P*=.004). A similar and consistent finding with BICR as INV was also observed for comparison of *BRCAm* (both germline and somatic) with HRP subgroups (*P*=.0009).

There was also a borderline significant difference in BICR PFS for patients who only had two versus those with more than two prior platinum chemotherapy lines in the *gBRCAm* cohort (*P*=.04; SFigure 2).

Publication bias

A funnel plot of the PFS effect size for each trial against the precision showed no asymmetry (data not shown).

Discussion

This meta-analysis demonstrates that maintenance PARPi improves PFS over placebo in PSROC following response to platinum-based chemotherapy in all patients. Our meta-analysis could not identify definitively a subset of patients who may not benefit from PARPi. Patients with *BRCAm* have the greatest PFS benefit, and there is no significant difference in the magnitude of benefit in those with *gBRCAm1*, *gBRCAm2*, and *sBRCAm*. In patients who did not have either a *gBRCAm* or *sBRCAm*, PARPi also significantly reduced the risk of disease progression or death by 59% and 36% in the HRD and HRP subgroups respectively.

Although *BRCAm* reliably predicts the magnitude of potential PARPi benefit, the absence of *BRCAm* does not exclude *wtBRCA* patients with PSROC benefitting from this treatment. There were statistically significant and clinically meaningful PFS improvement in HRD and HRP subgroups with maintenance PARPi. The different HRD assays used in the NOVA, Study 19 and ARIEL3 trials had not reliably identify *wtBRCA* patients that did not benefit from PARPi. These assays use different platforms, and the number and types of HRD genes analyzed also varied, thus making it difficult to compare results across different assays. Further, with assays designed to measure a putative HRD signature, there needs to be a validated cut-point for classifying patients. The European Society of Medical Oncology has performed a review and recommended that there is currently insufficient evidence to support the use of individual or panels of non-*BRCA* HRR genes for predicting a PARPi response and further prospective data collection is required[22]. Ongoing research is also required to harmonize different assays and allow for universal interpretation of test results in order to accurately identify *wtBRCA* patients that will not benefit from PARPi.

Mutations of HRR genes predict for a similar OS and platinum responsiveness as *gBRCAm* when treated with platinum-based chemotherapy[19, 23, 24]. There are multiple of these genes, and it has not been specifically clear whether *sBRCAm* predict for similar treatment benefit with PARPi as *gBRCAm*[25, 26]. This meta-analysis provides robust estimates for quantifying the treatment benefit with data pooled from three RCTs involving more than 100 patients. Although caution still needs to be exercised when interpreting our data, prospective RCTs comparing PARPi versus placebo for *sBRCAm* only is unlikely to be feasible for this relatively rare patient subgroup. Similarly, this

meta-analysis remains the only one to report on the relative treatment effect from more than 200 *gBRCAm*2 carriers with PSROC, which are much less common than *gBRCAm1*. Regardless of types of *BRCAm*, germline or somatic, results from this meta-analysis shows that these patients should be treated in an identical manner in routine practice and future trials.

Platinum sensitivity is a strong predictor of the '*BRCA*ness' phenotype caused by defective homologous recombination due to mechanisms other than *gBRCAm1/2*[7, 27]. We observed similar treatment benefit between HRD and *gBRCAm* if the PFI was greater than twelve months (HR 0.34 versus 0.29). In contrast, if the PFI was between six to twelve months, the treatment benefit was inferior for HRD than *gBRCAm* (HR 0.54 versus 0.25). However, for HRP patients with PFI greater than twelve months, the treatment effect (HR 0.67) was significantly inferior to *gBRCAm* and HRD subgroups. Therefore, platinum sensitivity is also an imperfect biomarker to predict for response to PARPi, and a robust assay for HRD is still required, even in the context of a PFI greater than twelve months. Interestingly, among the *gBRCAm* only, women who had more than two prior platinum chemotherapy lines had greater PFS benefit as compared to those who only had two chemotherapy lines (HR 0.20 versus 0.31). This finding is hypothesis-generating, as this variable was not a stratification factor in any of the included RCTs, and the difference was of borderline significance (*P*=.04). Furthermore, prior platinum chemotherapy lines were not predictive in HRD and HRP subgroups.

Strengths and limitations

This study has several strengths. We have conducted a comprehensive review and reported on a number of previously unpublished subgroup data. With a combined

total number of more than 1500 patients from four well-conducted placebo-controlled RCTs, this analysis has greater power to detect differences in subgroups that may be associated with improved PFS benefit. Specifically, having subgroup data available according to HRR gene status allowed us to assess it adequately as predictive biomarkers for benefit with PARPi. Importantly, we were also able to provide a better estimate of the treatment benefit of PARPi in the *wtBRCA* patient without *sBRCAm* but had HRD tumors. These patient populations were distinct but several publications[13, 16] had combined these patient cohorts in the reporting of treatment benefit from PARPi. Our work is further strengthened by the consistencies of the results according to INV and BICR PFS assessments. Our study also has several limitations. We assumed that all PARP inhibitor agents, including olaparib, niraparib, and rucaparib, have equivalent therapeutic efficacy when pooling the data across trials. Data on treatment effect of olaparib remained limited for *wtBRCA* patients, with only a non-randomized Phase IIIB single-arm study reporting a median PFS of 9.2 months in PSROC treated with olaparib as maintenance treatment[28]. We acknowledged that the frequency of imaging assessment was different across the RCTs and it could impact on the PFS estimates. We also did not have access to individual patient data to allow missing data be dealt with consistently across trials and to perform multivariable analysis to account for potential confounders. Most importantly, our current analysis is not based on the OS outcome which might be considered to be a more clinically relevant endpoint for this patient population with an incurable cancer. Despite these limitations, this meta-analysis addressed many of the questions important for future research and clinical practice.

Conclusions

In PSROC, maintenance PARPi improves PFS over placebo in women who responded to platinum-based chemotherapy regardless of their *gBRCAm* status. Patients with *sBRCAm* treated with maintenance PARPi have similar magnitude of treatment benefit as those with *gBRCAm*. Although patients with *BRCAm* derive the greatest benefit, the absence of a *BRCAm* or HRD cannot be used to exclude patients from maintenance therapy with a PARPi. As PARPi are being used widely in the first-line setting, there is now greater urgency to identify patients that could potentially be cured with platinum-based chemotherapy followed by maintenance PARPi. Robust tests to identify non-*BRCA* HRR genes and other molecular markers that predict for PARPi benefit is of top priority in future research.

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Table I: Demographic and treatment characteristics†

	poly-ADP ribose polymerase inhibitor arm			Placebo		
	Germline *BRCA* N=469‡ (%)	Homologous Recombinant Deficient* N=193 (%)	Homologous Recombinant Proficient N=225 (%)	Germline *BRCA* N=255‡(%)	Homologous Recombinant Deficient* N=116 (%)	Homologous Recombinant Proficient N=121 (%)
Age≤65 years old	374 (80)	123 (64)	118 (52)	201 (79)	77 (66)	57 (47)
Platinum-free interval >12 months	280 (60)	121 (63)	135 (60)	149 (58)	71 (61)	78 (64)
Partial response to platinum chemotherapy	251 (54)	109 (56)	135 (60)	136 (53)	63 (54)	73 (60)
2 prior lines of platinum chemotherapy	260 (55)	119 (62)	169 (75)	160 (63)	77 (66)	91 (75)
No prior bevacizumab	379 (81)	148 (77)	173 (77)	204 (80)	91 (78)	88 (73)
SOLO2 trial	196 (42)	NA	NA	99 (51)	NA	NA
Study 19 trial	53 (11)	16 (8)	26 (12)	43 (22)	20 (17)	25 (21)
ARIEL3 trial	82 (17)	106 (55)	107 (48)	48 (25)	52 (45)	54 (45)
NOVA trial	138 (29)	71 (37)	92 (41)	65 (25)	44 (38)	42 (35)
Olaparib	249 (53)	16 (8)	26 (12)	NA	NA	NA
Rucaparib	82 (17)	106 (55)	107 (48)	NA	NA	NA
Niraparib	138 (29)	71 (37)	92 (41)	NA	NA	NA
Germline BRCA 1	308 (66)	NA	NA	163 (64)	NA	NA
Germline BRCA 2	151	NA	NA	85	NA	NA

	(32)			(33)		

†somatic *BRCA* mutations (N=123) are not included in this Table 1. Trials contributed to somatic *BRCA* mutations pool are outlined in Figure 2.

‡The number of patients listed in this table with germline *BRCA* mutations do not match Figure 2 because some patients either had both germline *BRCA* 1 and germline *BRCA* 2 mutations, or types of germline *BRCA* mutation were unknown.

*Patients with somatic BRCA mutation were excluded from this subgroup with homologous recombinant deficiency. ARIEL 3 trial defined HRD based on high genomic loss of heterozygosity as detected using Foundation Medicine T5 NGS assay. NOVA and Study 19 defined HRD based on high LOH, telomeric allelic imbalance, and/or large-scale state transitions as detected using Myriad Genetics myChoice test.

Figure Legends

Figure 1: Flow diagram showing inclusion and exclusion of studies

Figure 2: Relative efficacy analysis according to patient cohorts with germline *BRCA1* mutation, germline *BRCA2,* somatic *BRCA* mutation, wild-type *BRCA* but homologous recombination deficient (excluding those with somatic *BRCA* mutation) and wild-type *BRCA* but homologous recombination proficient (HRP).

Forest plot of hazard ratios (HRs) for investigator-assessed progression-free survival for the relative comparison of poly(ADP-ribose) polymerase (PARP) inhibitors versus placebo in each of the patient cohorts. Hazard ratio for each trial is represented by the square, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamond represents the pooled overall effect size.

†For the NOVA trial, blinded independent central review progression-free survival was the pre-specified primary endpoint of the study, but investigator-assessed progression-free survival result is displayed here.

Figure 3: Relative efficacy analysis according to age, platinum-free interval, response after most recent chemotherapy, number of previous lines of platinum chemotherapy and use of bevacizumab treatment in conjunction with last platinum regimen within patient cohorts with germline *BRCA* mutation, wild-type *BRCA* but homologous recombination deficient (excluding those with somatic *BRCA* mutation) and wild-type *BRCA* but homologous recombination proficient (HRP).

Forest plot of pooled hazard ratios (HRs) for investigator-assessed progression-free survival across all trials for the relative comparison of poly(ADP-ribose) polymerase (PARP) inhibitors versus placebo in each of the patient cohorts. Hazard ratio for

each trial is represented by the square, and the horizontal line crossing the square represents the 95% confidence interval (CI).

Molecular and clinical predictors of improvement in progression-free survival with maintenance PARP inhibitor therapy in women with platinum-sensitive recurrent ovarian cancer: A meta-analysis

Running Title: Predicting benefit with PARP inhibitor

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Conception and design: CKL, MF, CS

Collection and assembly of data: CKL, AT, RB, SG, PW

Data analysis and interpretation: All authors

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Precis:

BRCA mutation status could predict for the magnitude of PARP inhibitor benefit in platinum-sensitive recurrent high grade ovarian tumor. However, absence of a *BRCA* mutation or homologous recombinant deficiency in high grade ovarian tumor could not be used to exclude patients from such therapy.

Abstract

Background: We performed a meta-analysis to better quantify benefit of maintenance PARP inhibitor (PARPi) to inform practice in platinum-sensitive recurrent high grade ovarian cancer (PSROC) for these patient subsets: germline *BRCA* mutation (*gBRCAm*), somatic *BRCA* mutation (*sBRCAm*), wild-type *BRCA* and homologous recombinant deficient (HRD), homologous recombinant proficient (HRP), and baseline clinical prognostic characteristics.

Methods: Randomized trials comparing a PARPi versus placebo as maintenance treatment were identified from electronic databases. Treatment estimates for progression-free survival (PFS) were pooled across trials using the inverse variance weighted method.

Results: Four trials included 972 patients receiving a PARPi (olaparib, 31%; niraparib, 35%; or rucaparib, 34%), and 530 patients receiving placebo. For *gBRCAm1* (N=471), HR=0.29 (95% CI 0.23–0.37). For *gBRCAm2* (N=236), HR=0.26 (95% CI 0.17–0.39). For *sBRCAm* (N=123), HR=0.22 (95% CI 0.12–0.41). The treatment effect was similar between *gBRCAm* and s*BRCAm* (*P*=.48). In wild-type *BRCA* HRD tumors (excluding s*BRCA*m, N=309) HR=0.41 (95% CI 0.31–0.56). In wild-type *BRCA* HRP tumors (N=346), HR=0.64 (95% CI 0.49–0.83). The relative treatment effect was greater for *BRCAm* versus HRD (*P*=.03), *BRCAm* versus HRP (*P*<.00001), and HRD versus HRP subgroups (*P*<.00001) respectively. There was no difference in benefit based on age, response after recent chemotherapy, and prior bevacizumab.

Conclusions: In PSROC, maintenance PARPi improves PFS for all patient subsets. PARPi has similar magnitude of benefit for *sBRCAm* and *gBRCAm*. Although patients

with *BRCAm* derive the greatest benefit, the absence of a *BRCAm* or HRD could not be used to exclude patients from maintenance PARPi therapy.

Keywords: platinum sensitive recurrent ovarian cancer, BRCA mutation, homologous recombination deficiency, polyADP-ribose polymerase inhibitors, meta-analysis

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Introduction

Cancers of the ovary, fallopian tube and peritoneum remain the most important causes of cancer deaths for women in developed countries[1]. At diagnosis, the majority of women have advanced stage disease and approximately 80% will recur following surgery and chemotherapy**.** Women with platinum-sensitive recurrent ovarian cancer (PSROC), defined as relapse ≥6 months after the most recent platinum-based chemotherapy, are usually re-treated with further platinum-based agents. There is usually a declining likelihood of response and shorter duration of benefit with each successive line of treatment. Multiple treatment strategies have been extensively investigated in PSROC with the aim of prolonging progression-free survival (PFS) and overall survival (OS). To date the most successful strategies are concomitant chemotherapy and bevacizumab followed by maintenance bevacizumab, and maintenance poly(ADP ribose) polymerase inhibitors (PARPi).

High-grade ovarian tumors accounts for the majority of PSROC and up to 50% are deficient in homologous recombination which is a key pathway involved in DNA damage repair[2-6] and are therefore reliant on more error prone DNA repair pathways such as non-homologous end joining[7]. Various homologous recombination deficiencies have been recognized, including germline mutations of the *BRCA1*/*2* genes (*gBRCAm 1*/*2*), somatically acquired *BRCA* mutations (*sBRCAm*), epigenetic *BRCA1* inactivation, or other *BRCA*-independent pathways. To date, *sBRCAm1* were reported in 5–9% of sporadic ovarian tumors, whereas *sBRCAm2* were identified in 3–4% of cases[8-10]. *BRCAm* of either germline[11, 12] or somatic mutations[13] occurs more frequently in platinum sensitive than resistant tumors.

PARPi induce synthetic lethality in tumors with homologous recombination deficiency. Multiple randomized controlled trials (RCTs) in PSROC have reported that maintenance PARPi following response to platinum based chemotherapy significantly improves PFS and delays time to subsequent chemotherapy which has changed the standard of care[13-17] and this treatment is gradually being introduced worldwide. The SOLO2 trial also reported an OS improvement with maintenance olaparib, with 28.3% of *gBRCAm* patients alive at 60 months without need for subsequent treatment, as compared with 12.8% in the placebo arm[18]. There is ongoing interest to determine which patient subgroups, beyond those with a *gBRCAm*, will benefit from maintenance PARPi and whether it is possible to use clinico-pathologic factors to select for these patients. This information will be clinically relevant, can help inform the design and interpretation of future trials, and can aid economic analyses.

This paper reports a meta-analysis of four RCTs using published and unpublished data of patient subsets to quantify the relative treatment benefit of maintenance PARPi over placebo in women with PSROC who have responded to platinum-based chemotherapy. We also aimed to determine the variation in treatment benefit based on patient, disease, and past treatment characteristics. This meta-analysis is valuable as individual RCTs were neither designed nor adequately powered to detect differences in treatment effect in these subgroups.

Methods

Study eligibility and identification

We included RCTs of recurrent PSROC with high-grade tumors if they compared PARPi as maintenance therapy versus placebo. Eligible RCTs were identified from

MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials. Search terms used included "*BRCA*", "*BRCA*1", "*BRCA*2", "*BRCA*1 protein", "*BRCA*2 protein", "ovarian neoplasms", "platinum-sensitive", "poly(ADP Ribose) polymerase inhibitors" and "clinical trial". We retrieved relevant articles published between 2005 and 2019 with no language restrictions. Individual trial investigators were also contacted for unpublished subgroup data.

Data collection and analysis

For each RCT, we extracted the trial name, patients' clinico-pathologic characteristics and types of PARPi. Regardless of the primary endpoints of the included RCTs, this meta-analysis assessed treatment benefit based on PFS as assessed by local investigators (INV) as the primary outcome. We performed a sensitivity analysis to determine the consistency of the results based on blinded independent central review (BICR) PFS for all RCTs. BICR PFS was a pre-specified primary endpoint of one included RCT[13].

We retrieved the hazard ratio (HR) and 95% confidence interval (CI) for PFS based on homologous recombination repair (HRR) deficiency status: *gBRCAm*, *sBRCAm*, wild-type *BRCA* (*wtBRCA*) but homologous recombination deficient (HRD, excluding those with *sBRCAm*) and *wtBRCA* but homologous recombination proficient (HRP). Tumors with oncogenic germline and somatic mutations were classified as *BRCAm* and variants of unknown significance were classified as *wtBRCA*. If *BRCAm* was detected but the tumor was also tested to be HRP, these patients were classified based on their *BRCAm* status. HRD was defined differently in different RCTs. In one study[16], tumors were classified as HRD if they had high genomic loss of heterozygosity

(LOH) as detected using Foundation Medicine T5 NGS assay (cutoff of 16% or greater). Other studies[13, 19] defined HRD based on high LOH, telomeric allelic imbalance, and/or large-scale state transitions as detected using Myriad Genetics myChoice test (Genomic Instability Score of 42 or greater).

We also retrieved data on treatment effect for these clinicopathologic subgroups: age (<65 versus ≥65 years), platinum-free interval (6–12 versus >12 months), response after most recent chemotherapy (complete response versus partial response), number of previous lines of platinum chemotherapy (2 versus >2) and use of bevacizumab treatment in conjunction with last platinum regimen (yes versus no).

Two of the authors (CKL, AT) extracted the data independently, and discrepancies were resolved by a third author (CLS). The risk of bias was assessed based on methods of randomization, allocation concealment, outcome assessments, attrition and reporting of the data. We reported our data based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses *(*PRISMA) guidelines[20].

Statistical analysis

Pooled PFS HRs and 95% CIs were computed by using the inverse variance weighted method with fixed-effects models. Differences between subgroups were tested using methods described by Borenstein et al[21]. We used the χ^2 Cochran Q test to detect any heterogeneity across trials. We also evaluated publication bias by examining the funnel plot of the effect size for each RCT against the reciprocal of its standard error. The nominal level of significance was set at 5%.

Results

We identified four eligible RCTs[13-17, 19] (Figure 1). Of 1677 patients who were randomly assigned to a PARPi or placebo, we analyzed only patient data from 1502 (89.6%). A total of 175 patients (ARIEL3[16], N=59; Study 19 trial[14, 15, 19], N=62; NOVA trial[13], N=54) were excluded because HRR deficiency status were unknown. All trials recruited patients with high-grade cancers of the ovary, fallopian tube and peritoneum. The majority had predominantly serous histology, whilst only the ARIEL3[16] and SOLO2[17] trials enrolled patients with endometriod and other rare histologies (N=28, 5%, and N=25, 8%, respectively). Table 1 outlines the demographic and treatment characteristics. All included studies were evaluated as low risk for bias (details not shown).

All study sponsors provided unpublished summary subgroup data. All RCTs had a double-blind, placebo-controlled design. The primary endpoint was PFS by BICR for the NOVA trial[13]; PFS by INV was the primary endpoint for other RCTs. The Study 19 trial[14, 15, 19] was the only trial with a randomized phase II design and the HRR gene status of the tumor was determined retrospectively.

The SOLO2 trial[17] recruited only *gBRCA*m carriers, whereas the remaining RCTs included *gBRCAm*, *sBRCAm* and *wtBRCA* patients. In the ARIEL3 trial[16], *wtBRCA* tumors with HRD was defined based on high genomic LOH. In the Study 19 and NOVA trials, *wtBRCA* tumors with HRD were those with high LOH, telomeric allelic imbalance, and large-scale state transitions.

Benefit of PARP inhibitor in subgroups according to homologous recombination repair deficiency status

Across the trials, 972 patients received a PARPi (olaparib, N=301 [31%]; niraparib, N=336 [35%]; or rucaparib, N=335 [34%]), and 530 patients received placebo.

Among the 471 *gBRCAm1* patients, the pooled PFS HR was 0.29 (95% CI 0.23–0.37, *P*<.00001; Figure 2). Among the 236 *gBRCAm2* patients, the pooled PFS HR was 0.26 (95% CI 0.17–0.39, *P*<.00001). In the 123 *sBRCA*m patients, the pooled PFS HR was 0.22 (95% CI 0.12–0.41, *P*<.00001).

The pooled PFS HR for both *gBRCAm1* and *gBRCAm2* only was 0.28 (95% CI 0.23–0.35, *P*<.00001). The pooled PFS HR for *gBRCAm1*, *gBRCAm2* and *sBRCAm* was 0.27 (95% CI 0.23–0.34, *P*<.00001).

The relative treatment effect was similar between *gBRCAm1* and *gBRCAm2* (*P*=.63). There was also no significant difference in treatment effect between *gBRCAm1/2* and *sBRCAm* (*P*=.48).

There were 309 *wtBRCA* patients with HRD tumor (excluding s*BRCAm*). The pooled PFS HR was 0.41 (95% CI 0.31–0.56, *P*<.00001). In the 346 *wtBRCA* patients with HRP tumor, the pooled PFS HR was 0.64 (95% CI 0.49–0.83, *P*=.0006). The relative treatment effect was significantly greater for HRD than HRP subgroups (*P*<.00001).

The relative treatment effect was also significantly greater for *BRCAm* (both germline and somatic) than HRD subgroups (HR 0.27 versus 0.41, *P*=.03). A similar finding was observed for the comparison of *BRCAm* (both germline and somatic) with HRP subgroups (HR 0.27 versus 0.64, *P*<.00001).

Subgroup analyses by clinico-pathologic characteristics

Subgroup outcome data were available for age, response after most recent chemotherapy, number of previous lines of platinum chemotherapy and prior bevacizumab treatment.

In the *gBRCAm* cohort, the pooled HR for patients with only two prior platinum chemotherapy lines (N=420, 58%) was 0.31 (95% CI 0.24–0.41, *P*<.00001). Among the 302 (42%) patients who had more than two prior platinum chemotherapy lines, the pooled HR was 0.20 (95% CI 0.14–0.28, *P*<.00001). The relative treatment effect was borderline significant between these subgroups (*P*=.04; Figure 3). In this *gBRCAm* cohort, the relative treatment benefit of PARPi versus placebo did not vary substantially between the subgroups, based on age, response after most recent chemotherapy, and prior bevacizumab treatment (Figure 3).

In patients with HRD tumors but without s*BRCAm*, PFS HRs did not vary substantially between the subgroups defined by clinico-pathologic characteristics. For patients with HRP tumors, PFS HRs also did not vary substantially in these clinico-pathologic subgroups (Figure 3).

Impact of platinum-free interval on progression-free survival across patient cohorts

Platinum-free interval (PFI) was a stratification factor and defined consistently across all RCTs. A total of 834 patients had PFI greater than twelve months and 545 patients had PFI between six to twelve months. PFS HRs did not vary substantially according to PFI within the *gBRCAm*, HRD, and HRP subgroups (Figure 3).

However, amongst those with PFI greater than twelve months, the pooled PFS HR was 0.29 (95% CI 0.22–0.38, *P*<.00001) in 429 (51%) *gBRCAm* patients. In the 192

(23%) patients with HRD tumor (excluding s*BRCAm*), the pooled PFS HR was 0.34 (95% CI 0.23–0.50, *P*<.00001). There was no significant difference in treatment effect between *gBRCAm* and HRD subgroups (*P*=.56). In contrast, the pooled PFS HR was 0.67 (95% CI 0.48–0.92, *P*=.01) in 213 (26%) patients with HRP tumors. The treatment effect was significantly greater for the comparisons of *gBRCAm* versus HRP (*P*=.0001), and HRD versus HRP subgroups (*P*=.009).

Amongst those with PFI between six to twelve months, 295 (54%) *gBRCAm* patients had a pooled PFS HR of 0.25 (95% CI 0.19–0.34, *P*<.00001). In the 117 (22%) patients with HRD tumors, the pooled PFS HR was 0.54 (95% CI 0.34–0.87, *P*=.01). Among the 133 (24%) patients with HRP tumor, the pooled PFS HR was 0.59 (95% CI 0.38–0.90, *P*=.02). The treatment effect was significantly greater for *gBRCAm* than HRD subgroups (*P*=.007), and for *gBRCAm* than HRP subgroups (*P*=.001). There was no significant difference in the treatment effect between HRD and HRP subgroups (*P*=.80).

Sensitivity analysis

SFigure 1 summarized the results for PFS by BICR. Data were not available for 5 patients from Study 19 trial[14, 15, 19]. For patient cohorts with *gBRCAm1*, *gBRCAm2* and *sBRCAm*, results for PFS by BICR were consistent with INV. PFS HRs by BICR did not differ significantly between *gBRCAm1* and *gBRCAm2* (*P*=.23). PFS HRs by BICR were also similar between *gBRCAm1/2* and *sBRCAm* subgroups (*P*=.51).

In *wtBRCA* patients with HRD tumor but without s*BRCAm*, PFS HR by BICR (SFigure1) was also similar to PFS HR by INV (Figure 2). However, there was a difference in PFS HR by BICR for *wtBRCA* patients with HRP tumor as compared with

PFS HR by INV. Unlike PFS INV analysis, there was no significant difference in PFS HR by BICR between HRD than HRP subgroups (*P*=.75).

The treatment effect by BICR was also significantly greater for *BRCAm* (both germline and somatic) than HRD subgroups (*P*=.004). A similar and consistent finding with BICR as INV was also observed for comparison of *BRCAm* (both germline and somatic) with HRP subgroups (*P*=.0009).

There was also a borderline significant difference in BICR PFS for patients who only had two versus those with more than two prior platinum chemotherapy lines in the *gBRCAm* cohort (*P*=.04; SFigure 2).

Publication bias

A funnel plot of the PFS effect size for each trial against the precision showed no asymmetry (data not shown).

Discussion

This meta-analysis demonstrates that maintenance PARPi improves PFS over placebo in PSROC following response to platinum-based chemotherapy in all patients. Our meta-analysis could not identify definitively a subset of patients who may not benefit from PARPi. Patients with *BRCAm* have the greatest PFS benefit, and there is no significant difference in the magnitude of benefit in those with *gBRCAm1*, *gBRCAm2*, and *sBRCAm*. In patients who did not have either a *gBRCAm* or *sBRCAm*, PARPi also significantly reduced the risk of disease progression or death by 59% and 36% in the HRD and HRP subgroups respectively.

Although *BRCAm* reliably predicts the magnitude of potential PARPi benefit, the absence of *BRCAm* does not exclude *wtBRCA* patients with PSROC benefitting from this treatment. There were statistically significant and clinically meaningful PFS improvement in HRD and HRP subgroups with maintenance PARPi. The different HRD assays used in the NOVA, Study 19 and ARIEL3 trials had not reliably identify *wtBRCA* patients that did not benefit from PARPi. These assays use different platforms, and the number and types of HRD genes analyzed also varied, thus making it difficult to compare results across different assays. Further, with assays designed to measure a putative HRD signature, there needs to be a validated cut-point for classifying patients. The European Society of Medical Oncology has performed a review and recommended that there is currently insufficient evidence to support the use of individual or panels of non-*BRCA* HRR genes for predicting a PARPi response and further prospective data collection is required[22]. ~~A consensus on the type of bioinformatics algorithm used to define HRD is required.~~ Ongoing research is also required~~vital~~ to harmonize ~~these~~ different assays and allow for universal interpretation of test results in order to accurately identify *wtBRCA* patients that will not benefit from PARPi.

Mutations of HRR genes predict for a similar OS and platinum responsiveness as *gBRCAm* when treated with platinum-based chemotherapy[19, 23, 24]. There are multiple of these genes, and it has not been specifically clear whether *sBRCAm* predict for similar treatment benefit with PARPi as *gBRCAm*[25, 26]. This meta-analysis provides robust estimates for quantifying the treatment benefit with data pooled from three RCTs involving more than 100 patients. Although caution still needs to be exercised when interpreting our data, prospective RCTs comparing PARPi versus placebo for *sBRCAm*

only is unlikely to be feasible for this relatively rare patient subgroup. Similarly, this meta-analysis remains the only one to report on the relative treatment effect from more than 200 *gBRCAm*2 carriers with PSROC, which are much less common than *gBRCAm1*. Regardless of types of *BRCAm*, germline or somatic, results from this meta-analysis shows that these patients should be treated in an identical manner in routine practice and future trials.

Platinum sensitivity is a strong predictor of the '*BRCA*ness' phenotype caused by defective homologous recombination due to mechanisms other than *gBRCAm1/2*[7, 27]. We observed similar treatment benefit between HRD and *gBRCAm* if the PFI was greater than twelve months (HR 0.34 versus 0.29). In contrast, if the PFI was between six to twelve months, the treatment benefit was inferior for HRD than *gBRCAm* (HR 0.54 versus 0.25). However, for HRP patients with PFI greater than twelve months, the treatment effect (HR 0.67) was significantly inferior to *gBRCAm* and HRD subgroups. Therefore, platinum sensitivity is also an imperfect biomarker to predict for response to PARPi, and a robust assay for HRD is still required, even in the context of a PFI greater than twelve months. Interestingly, among the *gBRCAm* only, women who had more than two prior platinum chemotherapy lines had greater PFS benefit as compared to those who only had two chemotherapy lines (HR 0.20 versus 0.31). This finding is hypothesis-generating, as this variable was not a stratification factor in any of the included RCTs, and the difference was of borderline significance (*P*=.04). Furthermore, prior platinum chemotherapy lines were not predictive in HRD and HRP subgroups.

Strengths and limitations

This study has several strengths. We have conducted a comprehensive review and reported on a number of previously unpublished subgroup data. With a combined total number of more than 1500 patients from four well-conducted placebo-controlled RCTs, this analysis has greater power to detect differences in subgroups that may be associated with improved PFS benefit. Specifically, having subgroup data available according to HRR gene status allowed us to assess it adequately as predictive biomarkers for benefit with PARPi. Importantly, we were also able to provide a better estimate of the treatment benefit of PARPi in the *wtBRCA* patient without *sBRCAm* but had HRD tumors. These patient populations were distinct but several publications[13, 16] had combined these patient cohorts in the reporting of treatment benefit from PARPi. Our work is further strengthened by the consistencies of the results according to INV and BICR PFS assessments. Our study also has several limitations. We assumed that all PARP inhibitor agents, including olaparib, niraparib, and rucaparib, have equivalent therapeutic efficacy when pooling the data across trials. Data on treatment effect of olaparib remained limited for *wtBRCA* patients, with only a non-randomized Phase IIIB single-arm study reporting a median PFS of 9.2 months in PSROC treated with olaparib as maintenance treatment[28] ~~with HRD and HRP tumors~~. We acknowledged that the frequency of imaging assessment was different across the RCTs and it could impact on the PFS estimates. We also did not have access to individual patient data to allow missing data be dealt with consistently across trials and to perform multivariable analysis to account for potential confounders. Most importantly, our current analysis is not based on the OS outcome which might be considered to be a more clinically relevant endpoint for this patient population with an incurable cancer. Despite these

limitations, this meta-analysis addressed many of the questions important for future research and clinical practice.

Conclusions

In PSROC, maintenance PARPi improves PFS over placebo in women who responded to platinum-based chemotherapy regardless of their *gBRCAm* status. Patients with *sBRCAm* treated with maintenance PARPi have similar magnitude of treatment benefit as those with *gBRCAm*. Although patients with *BRCAm* derive the greatest benefit, the absence of a *BRCAm* or HRD cannot be used to exclude patients from maintenance therapy with a PARPi. As PARPi are being used widely in the first-line setting, there is now greater urgency to identify patients that could potentially be cured with platinum-based chemotherapy followed by maintenance PARPi. Robust tests to identify non-*BRCA* HRR genes and other molecular markers that predict for PARPi benefit is of top priority in future research.

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Table I: Demographic and treatment characteristics†

	poly-ADP ribose polymerase inhibitor arm			Placebo		
	Germline *BRCA* N=469‡ (%)	Homologous Recombinant Deficient* N=193 (%)	Homologous Recombinant Proficient N=225 (%)	Germline *BRCA* N=255‡(%)	Homologous Recombinant Deficient* N=116 (%)	Homologous Recombinant Proficient N=121 (%)
Age≤65 years old	374 (80)	123 (64)	118 (52)	201 (79)	77 (66)	57 (47)
Platinum-free interval >12 months	280 (60)	121 (63)	135 (60)	149 (58)	71 (61)	78 (64)
Partial response to platinum chemotherapy	251 (54)	109 (56)	135 (60)	136 (53)	63 (54)	73 (60)
2 prior lines of platinum chemotherapy	260 (55)	119 (62)	169 (75)	160 (63)	77 (66)	91 (75)
No prior bevacizumab	379 (81)	148 (77)	173 (77)	204 (80)	91 (78)	88 (73)
SOLO2 trial	196 (42)	NA	NA	99 (51)	NA	NA
Study 19 trial	53 (11)	16 (8)	26 (12)	43 (22)	20 (17)	25 (21)
ARIEL3 trial	82 (17)	106 (55)	107 (48)	48 (25)	52 (45)	54 (45)
NOVA trial	138 (29)	71 (37)	92 (41)	65 (25)	44 (38)	42 (35)
Olaparib	249 (53)	16 (8)	26 (12)	NA	NA	NA
Rucaparib	82 (17)	106 (55)	107 (48)	NA	NA	NA
Niraparib	138 (29)	71 (37)	92 (41)	NA	NA	NA
Germline BRCA 1	308 (66)	NA	NA	163 (64)	NA	NA
Germline BRCA 2	151	NA	NA	85	NA	NA

	(32)			(33)		

†somatic *BRCA* mutations (N=123) are not included in this Table 1. Trials contributed to somatic *BRCA* mutations pool are outlined in Figure 2.

‡The number of patients listed in this table with germline *BRCA* mutations do not match Figure 2 because some patients either had both germline *BRCA* 1 and germline *BRCA* 2 mutations, or types of germline *BRCA* mutation were unknown.

*Patients with somatic BRCA mutation were excluded from this subgroup with homologous recombinant deficiency. ARIEL 3 trial defined HRD based on high genomic loss of heterozygosity as detected using Foundation Medicine T5 NGS assay. NOVA and Study 19 defined HRD based on high LOH, telomeric allelic imbalance, and/or large-scale state transitions as detected using Myriad Genetics myChoice test.

Figure Legends

Figure 1: Flow diagram showing inclusion and exclusion of studies

Figure 2: Relative efficacy analysis according to patient cohorts with germline *BRCA1* mutation, germline *BRCA2,* somatic *BRCA* mutation, wild-type *BRCA* but homologous recombination deficient (excluding those with somatic *BRCA* mutation) and wild-type *BRCA* but homologous recombination proficient (HRP).

Forest plot of hazard ratios (HRs) for investigator-assessed progression-free survival for the relative comparison of poly(ADP-ribose) polymerase (PARP) inhibitors versus placebo in each of the patient cohorts. Hazard ratio for each trial is represented by the square, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamond represents the pooled overall effect size.

†For the NOVA trial, blinded independent central review progression-free survival was the pre-specified primary endpoint of the study, but investigator-assessed progression-free survival result is displayed here.

Figure 3: Relative efficacy analysis according to age, platinum-free interval, response after most recent chemotherapy, number of previous lines of platinum chemotherapy and use of bevacizumab treatment in conjunction with last platinum regimen within patient cohorts with germline *BRCA* mutation, wild-type *BRCA* but homologous recombination deficient (excluding those with somatic *BRCA* mutation) and wild-type *BRCA* but homologous recombination proficient (HRP).

Forest plot of pooled hazard ratios (HRs) for investigator-assessed progression-free survival across all trials for the relative comparison of poly(ADP-ribose) polymerase (PARP) inhibitors versus placebo in each of the patient cohorts. Hazard ratio for

each trial is represented by the square, and the horizontal line crossing the square represents the 95% confidence interval (CI).

Figure 1 Study flow diagram

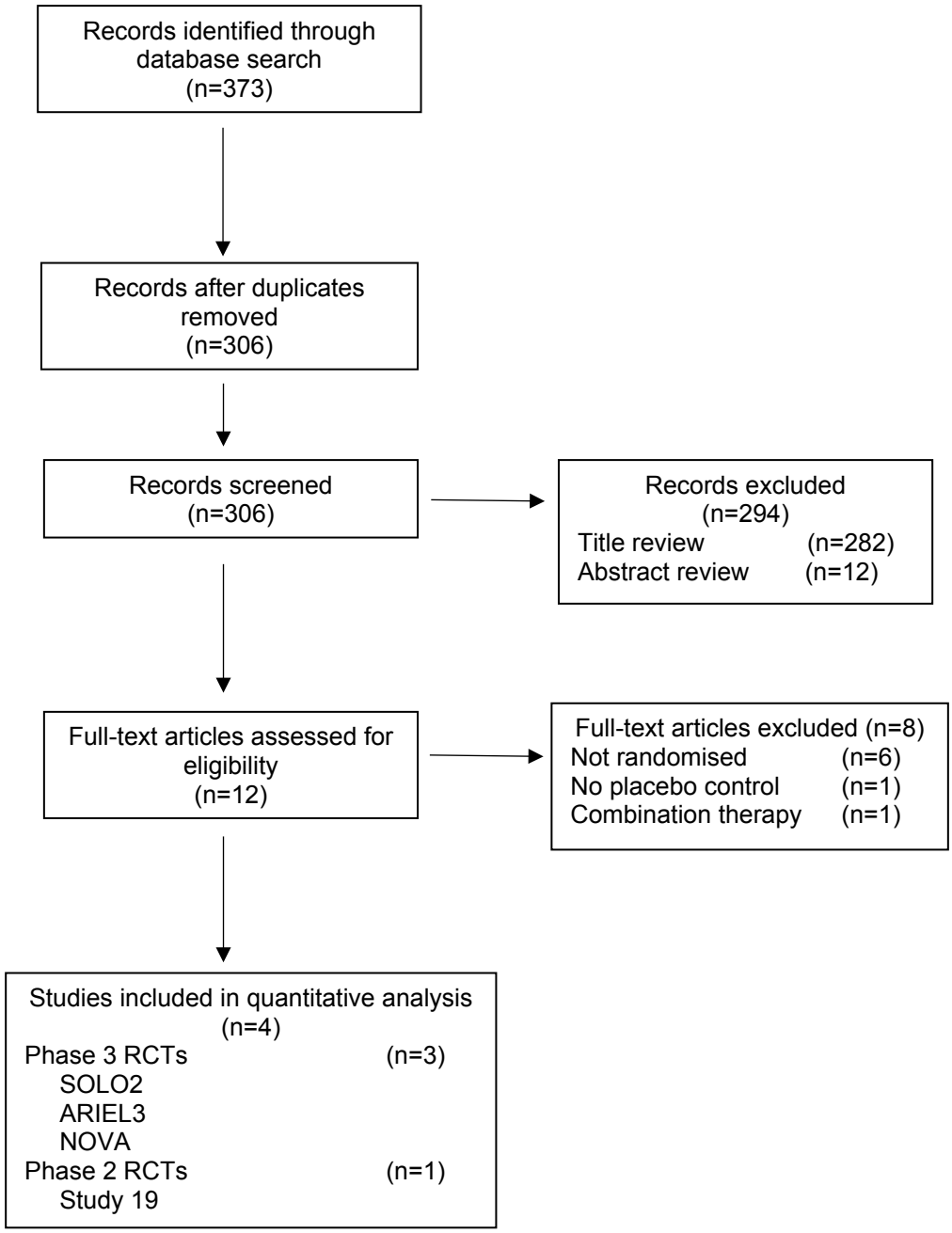
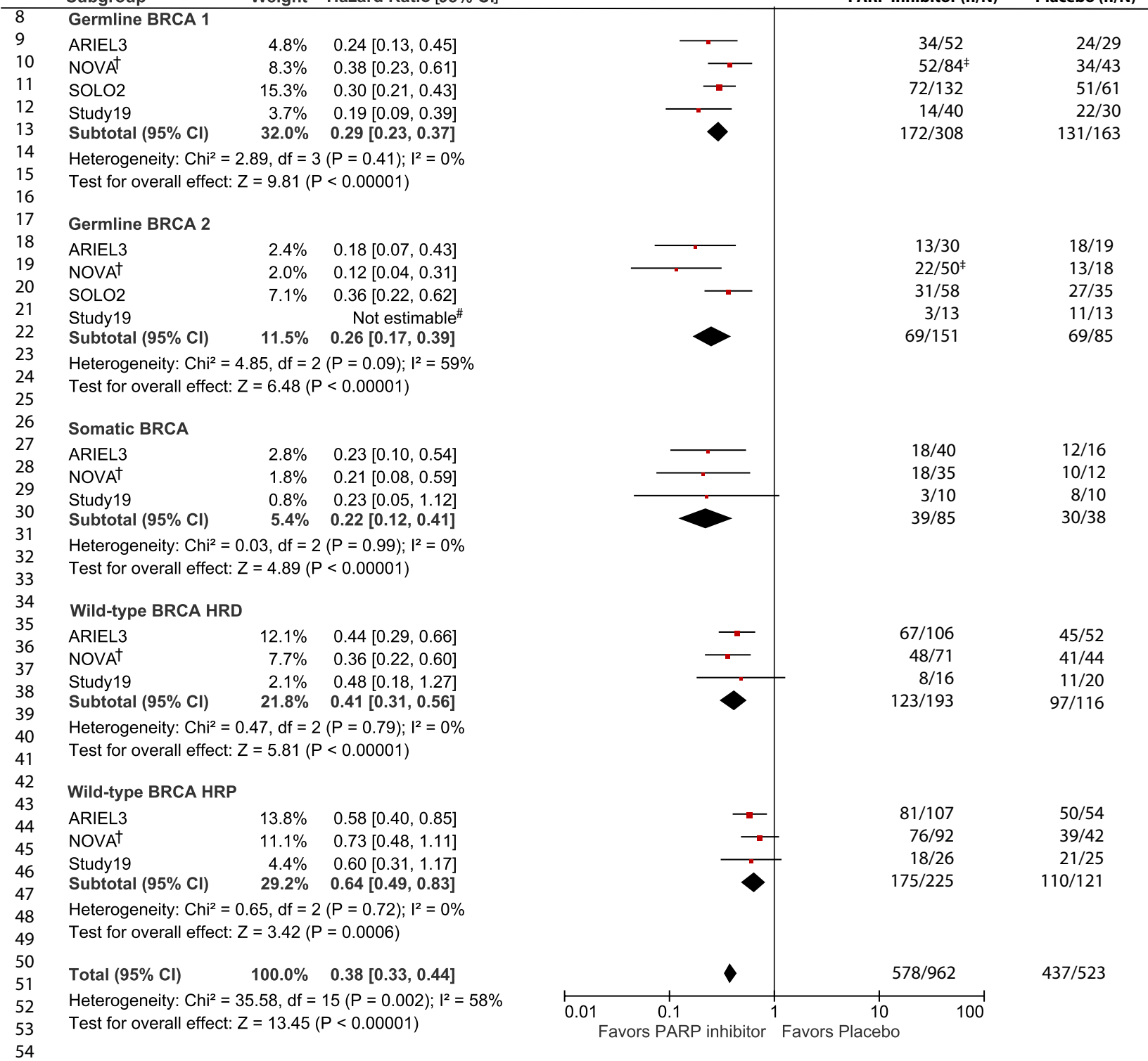


Figure 2

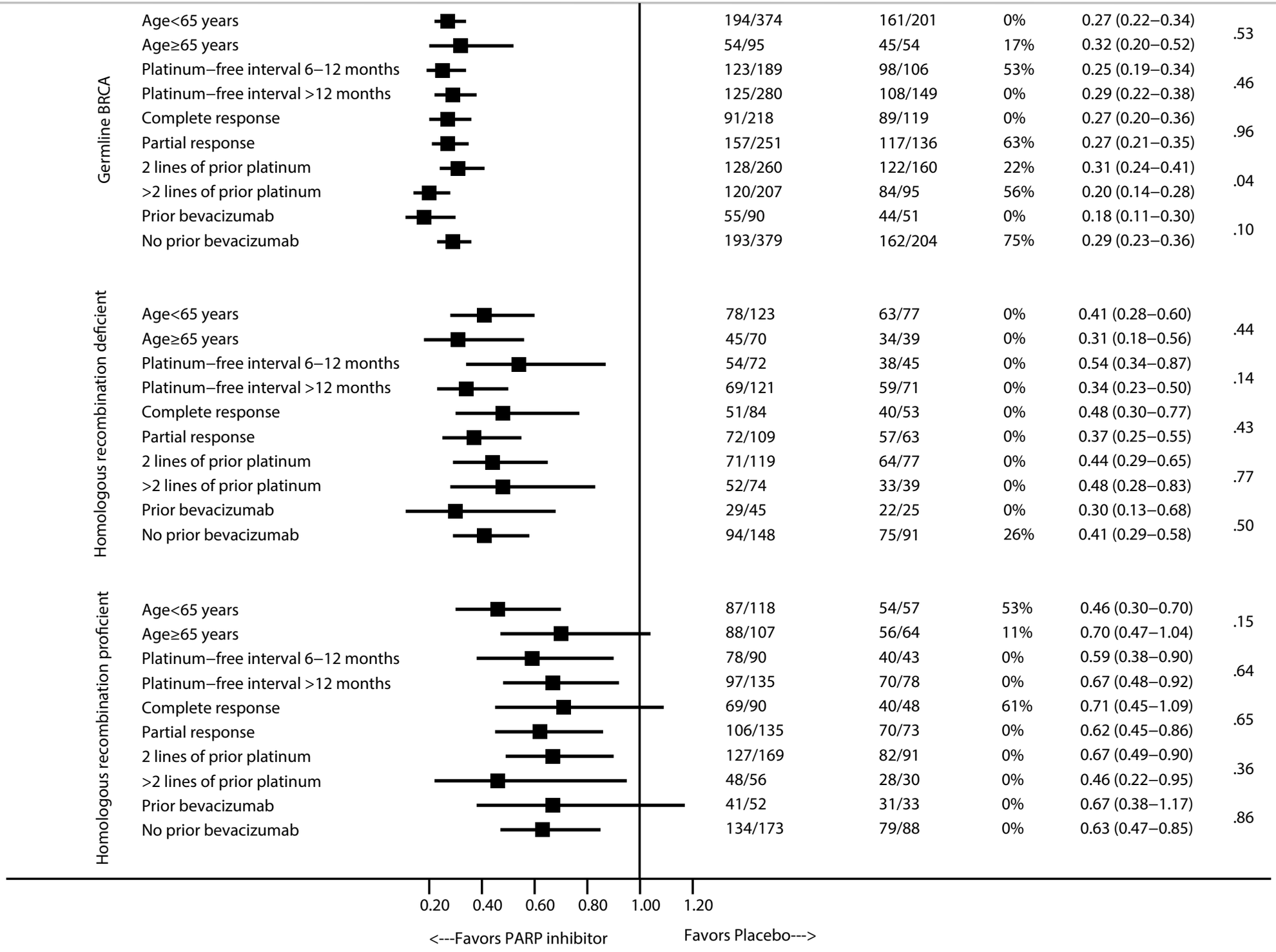


* n refers to number of progression-free survival events; N refers to total number of evaluable patients

Hazard ratio is not estimable due to insufficient number of events

‡ one patient with both germline BRCA 1 and germline BRCA 2 mutations were excluded from analysis

Figure 3



* n refers to number of progression-free survival events; N refers to total number of evaluable patients

Supplementary online content

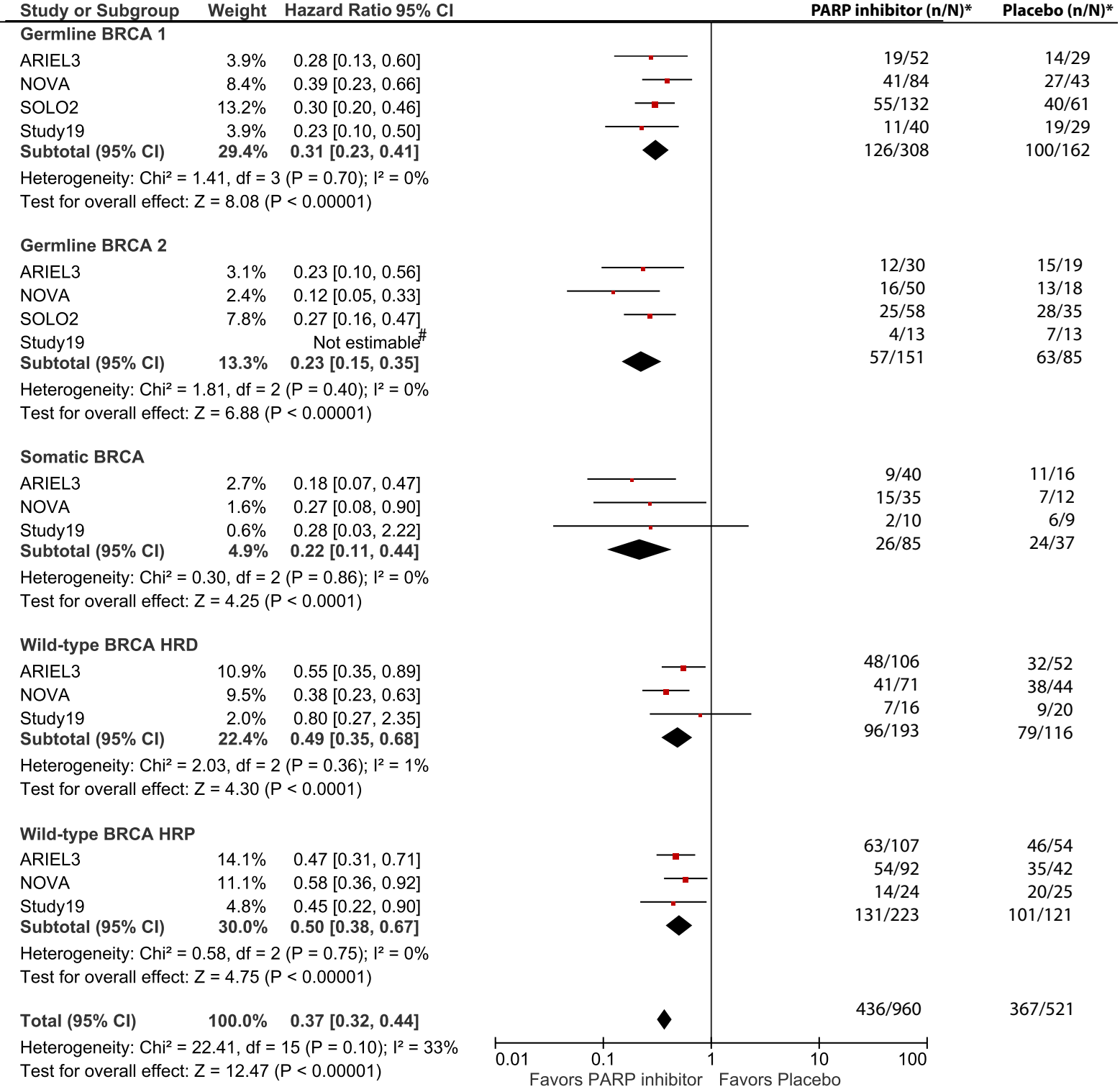
SFigure 1: Relative efficacy analysis according to patient cohorts with germline *BRCA1* mutation, germline *BRCA2,* somatic *BRCA* mutation, wild-type *BRCA* but homologous recombination deficient (excluding those with *sBRCA*) and wild-type *BRCA* but homologous recombination proficient (HRP).

Forest plot of hazard ratios (HRs) for blinded independent central review progression-free survival for the relative comparison of poly(ADP-ribose) polymerase (PARP) inhibitors versus placebo in each of the patient cohorts. Hazard ratio for each trial is represented by the square, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamond represents the pooled overall effect size.

SFigure 2: Relative efficacy analysis according to age, platinum-free interval, response after most recent chemotherapy, number of previous lines of platinum chemotherapy and use of bevacizumab treatment in conjunction with last platinum regimen within patient cohorts with germline *BRCA* mutation, wild-type *BRCA* but homologous recombination deficient (excluding those with *sBRCA*) and wild-type *BRCA* but homologous recombination proficient (HRP).

Forest plot of pooled hazard ratios (HRs) for blinded independent central review progression-free survival across all trials for the relative comparison of poly(ADP-ribose) polymerase (PARP) inhibitors versus placebo in each of the patient cohorts. Hazard ratio for each trial is represented by the square, and the horizontal line crossing the square represents the 95% confidence interval (CI).

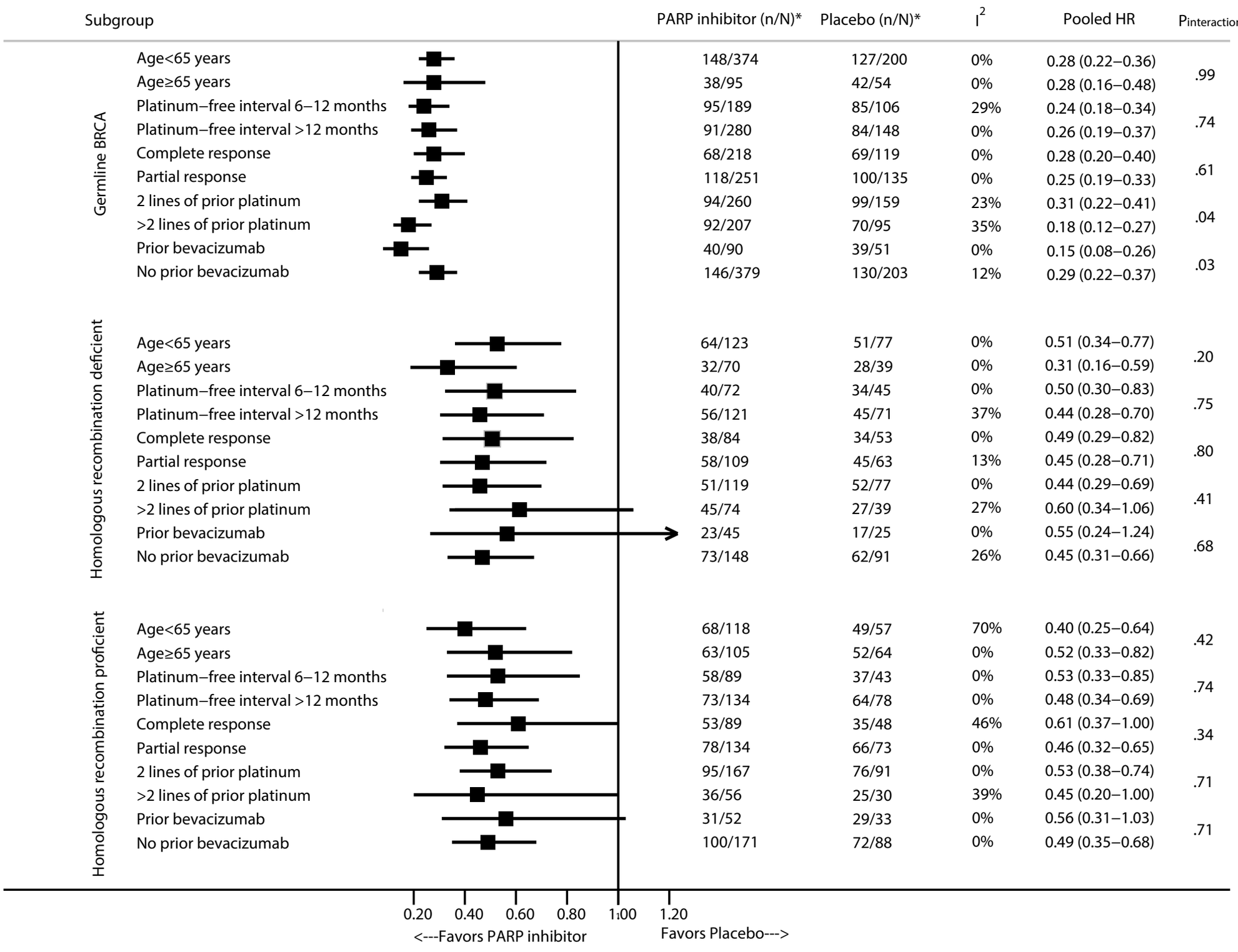
SFigure 1



* n refers to number of progression-free survival events; N refers to total number of evaluable patients

Hazard ratio is not estimable due to insufficient number of events

SFigure 2



* n refers to number of progression-free survival events; N refers to total number of evaluable patients