Influence of Genomic Landscape on Cancer Immunotherapy for Newly Diagnosed Ovarian Cancer: Biomarker Analyses from the IMagyn050 Randomized Clinical Trial

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Translational Relevance

In this exploratory biomarker substudy of the placebo-controlled randomized phase III IMagyn050 trial evaluating the PD-L1 inhibitor atezolizumab combined with chemotherapy and bevacizumab for ovarian cancer, *BRCA1/2* mutations and homologous recombination deficiency (HRD) were not associated with increased sensitivity to atezolizumab, despite a modest increase in tumor mutation burden and an association with PD-L1 status. The genomic landscape of patients enrolled in IMagyn050 suggests that HRD and alterations in *BRCA2*, *RB1*, *NF1,* and *CCNE1* are prognostic regardless of the treatment administered. This is the first randomized double-blind trial in ovarian cancer demonstrating that genomic instability triggered by *BRCA1/2* mutation or HRD is not associated with improved sensitivity to immune checkpoint inhibitors.

ABSTRACT

Purpose: To explore whether patients with *BRCA1/2*-mutated or homologous recombination-deficient (HRD) ovarian cancers benefitted from atezolizumab in the phase III IMagyn050 (NCT03038100) trial.

Methods: Patients with newly diagnosed ovarian cancer were randomized to either atezolizumab or placebo with standard chemotherapy and bevacizumab. PD-L1 status of tumor-infiltrating immune cells was determined centrally (VENTANA SP142 assay). Genomic alterations, including deleterious *BRCA1/2* alterations, genomic loss of heterozygosity (gLOH), tumor mutation burden (TMB), and microsatellite instability (MSI), were evaluated using the FoundationOne assay. HRD was defined as gLOH ≥16%, regardless of *BRCA1/2* mutation status. Potential associations between progression-free survival (PFS) and genomic biomarkers were evaluated using standard correlation analyses and log-rank of Kaplan-Meier estimates.

Results: Among biomarker-evaluable samples, 22% (234/1050) harbored *BRCA1/2* mutations and 46% (446/980) were HRD. Median TMB was low irrespective of *BRCA1/2* or HRD. Only 3% (29/1024) had TMB ≥10 mut/Mb and 0.3% (3/1022) were MSI-high. PFS was better in *BRCA2*-mutated versus *BRCA2*-non-mutated tumors and in HRD versus proficient tumors. PD-L1 positivity (≥1% expression on immune cells) was associated with HRD but not *BRCA1/2* mutations. PFS was not improved by adding atezolizumab in *BRCA2*-mutated or HRD tumors; there was a trend toward enhanced PFS with atezolizumab in *BRCA1*-mutated tumors.

Conclusion: Most ovarian tumors have low TMB despite *BRCA1/2* mutations or HRD. Neither *BRCA1/2* mutation nor HRD predicted enhanced benefit from atezolizumab. This is the first randomized double-blind trial in ovarian cancer demonstrating that genomic instability triggered by *BRCA1/2* mutation or HRD is not associated with improved sensitivity to immune checkpoint inhibitors.

Background

In recent years, incorporation of immune checkpoint blockade into clinical practice has changed the treatment landscape for many cancers. However, results have been less spectacular in ovarian cancer. Two randomized phase III trials failed to show benefit from avelumab either alone or combined with chemotherapy (1,2), and more recently, results from the IMagyn050 randomized phase III trial showed no significant progression-free survival (PFS) benefit from the addition of the anti-programmed death-ligand 1 (PD-L1) immune checkpoint inhibitor (ICI) atezolizumab to standard bevacizumab and chemotherapy for newly diagnosed stage III/IV ovarian cancer (3).

Responses and an extended 'tail of the curve' in some trials suggest that a small proportion of patients with ovarian cancer may derive long-term benefit from ICIs (4,5) but to date, efforts to identify these patients prospectively have had relatively little success. Tumor mutation burden (TMB) has shown predictive potential for single-agent ICI in melanoma and lung cancer (6,7), which tend to have higher TMB (8), and in gastric cancer (9). However, its relevance and applicability across other solid tumors is less clear (10,11).

In ovarian cancer, data from non-randomized studies have suggested associations between *BRCA1/2* alterations, increased mutations, and increased PD-L1 expression, raising the possibility of enhanced sensitivity to cancer immunotherapy (12,13). To the best of our knowledge, the potential prognostic and predictive role of TMB, *BRCA1/2* mutation, and homologous recombination deficiency (HRD) has not been assessed in randomized clinical trials of ICIs for patients with newly diagnosed ovarian cancer. Therefore, in these prespecified

exploratory analyses, we evaluated TMB, *BRCA1/2* mutation status, and HRD in samples from women treated in the IMagyn050 randomized phase III trial (3) and explored associations with clinical outcome.

Patients and Methods

The design of the parent study – the multicenter, double-blind, placebo-controlled, randomized, phase III IMagyn050 trial – has been described in detail previously (3). Briefly, patients with previously untreated epithelial ovarian, peritoneal, or fallopian tube cancer (collectively referred to as ovarian cancer), either post-operative stage III with macroscopic residual disease or stage IV, or a candidate for neoadjuvant therapy with planned interval surgery, were randomized in a 1:1 ratio to receive either atezolizumab 1200 mg or placebo every 3 weeks for 22 cycles, both in combination with carboplatin plus paclitaxel chemotherapy during cycles 1–6 and bevacizumab 15 mg/kg every 3 weeks for 22 cycles. The co-primary endpoints were PFS (per Response Evaluation Criteria in Solid Tumors version 1.1) and overall survival (OS) tested in both the PD-L1-positive and the intent-to-treat (ITT) populations. Stratification factors were International Federation of Gynecology and Obstetrics (FIGO) stage (III vs. IV), Eastern Cooperative Oncology Group performance status (ECOG PS) (0 vs. 1/2), treatment approach (adjuvant vs. neoadjuvant), and PD-L1 status (PD-L1 expression in <1% vs. ≥1% of immune cells [IC] as a percentage of tumor area, as assessed by the VENTANA SP142 PD-L1 assay [VENTANA, Tucson, Arizona, USA]).

The study was conducted in full conformance with the International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the

research is conducted, whichever afforded the greater protection to the individual. The study complied with the requirements of the ICH E2A guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, U.S. FDA regulations and applicable local, state, and federal laws, and the EU Clinical Trial Directive (2001/20/EC). The protocol was approved by institutional review boards or ethics committees at each site. All patients provided written informed consent before any trial-specific procedures or treatment.

Patients were enrolled between March 8, 2017, and March 26, 2019. The data cutoff for the primary analysis, used for the *post hoc* analyses reported here, was March 30, 2020.

Next-generation sequencing (NGS; FoundationOne® CDx assay [Foundation Medicine, Cambridge, Massachusetts, USA]) was performed in samples with evaluable tumor according to local regulations to assess detection of substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements, mutation status in *BRCA1* and *BRCA2* genes, genomic loss of heterozygosity (gLOH), TMB, and microsatellite instability (MSI) status. Samples with known or likely deleterious tumor germline/somatic *BRCA1/2* mutations (excluding variants of unknown significance) were classified as *BRCA1/2* mutated. HRD was defined as gLOH ≥16%, the cutoff used in the ARIEL3 randomized phase III trial (14). Homologous recombination proficient (HRP) was defined as gLOH <16%, regardless of *BRCA1/2* mutation status. TMB was assessed according to previously described methods (15), with ≥10 mutations/megabase (mut/Mb) classified as TMB-high.

All analyses were exploratory and all *P*-values are descriptive. Prevalences of TMB, *BRCA1/2* mutation status, and homologous recombination status were compared using Mann-Whitney tests.

This trial is registered with ClinicalTrials.gov, NCT03038100.

Data availability

NGS data are deposited in the European Genome-phenome Archive at the European Bioinformatics Institute (https://ega-archive.org/) under study accession number EGAS00001006838.

For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see: https://go.roche.com/data_sharing. Anonymized records for individual patients

across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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Results

Analysis population and biomarker prevalence

Among the 1301 patients enrolled in the IMagyn050 trial, samples from 1050 patients were assessable by NGS. Asian patients were under-represented in the biomarker-evaluable population compared with the ITT population (15% vs. 23%, respectively), as samples from China were not evaluated, in accordance with local regulations. Gene mutation status was available from all samples, HRD/HRP status from 980, TMB status from 1024, and MSI status from 1022.

The genomic landscape of the biomarker-evaluable population is shown in Fig. 1A. gLOH was higher in patients with high-grade serous ovarian cancers (HGSOC) than with other histotypes (median gLOH: 15.8% vs. 7.8% respectively; $P < 0.0001$). Deleterious *TP53* mutations were associated with both HGSOC and elevated gLOH ($P < 0.0001$), whereas *CCNE1* amplifications found in HGSOC tumors were associated with lower gLOH ($P < 0.0001$), and were mutually exclusive with *BRCA1* and *BRCA2* mutations (Supplementary Fig. S1). Patients with *BRCA1/2*-mutated or HRD tumors tended to be younger than those with *BRCA1/2*-non-mutated or HRP tumors, respectively, and were more likely to have PD-L1-positive tumors (Table 1). Compared with *BRCA1/2*-wild-type tumors, *BRCA*-

mutated tumors were associated with: a numerically higher proportion of patients with HRD (76% vs. 33% in the *BRCA* wild-type subgroup; $P < 0.0001$), no gross residual disease after surgery (23% vs. 16%, respectively), and baseline ECOG PS of 0 (64% vs. 58%, respectively); and a numerically lower proportion of patients with clear-cell histology (<1% vs. 5%, respectively). Compared with the HRP population, the subgroup with HRD tumors included: a numerically higher proportion patients reporting as Asian (20% vs. 13% in the HRP subgroup; $P = 0.0025$), with serous cell histology (90% vs. 82%, respectively), with *BRCA1/2*-mutated tumors (40% vs. 9%, respectively), and with no gross residual disease after surgery (20% vs. 15%, respectively); and a numerically lower proportion of White patients (74% vs. 82%, respectively) and patients with clear-cell histology (1% vs. 7%, respectively).

The vast majority of patients had low TMB: only 29 (3%) of the 1024 evaluable samples had TMB ≥10 mut/Mb. Only three (0.3%) of 1022 samples were classified as MSI-high (histologies: one mixed, one undifferentiated, one other), all of them with PD-L1 IC expression ≥1%, PD-L1 tumor cell expression <1%, *BRCA1/2* wild type, and either HRP or unknown homologous recombination status. All three patients with MSI-high tumors were randomized to the control arm. All high-grade serous cases were microsatellite stable. The overall prevalence of *BRCA1/2* mutations was 22% (234/1050; 120/537 [22%] in the atezolizumab-containing arm vs. 114/513 [22%] in the control arm). The prevalence of HRD was 46% (446/980 overall; 225/502 [45%] in the atezolizumab-containing arm vs. 221/478 [46%] in the placebo arm).

Associations between *BRCA* mutation, HRD, TMB, and PD-L1 status

HRD was associated with *BRCA1/2* mutation status (median gLOH of 22% in *BRCA1/2*-mutated vs. 12% in non-mutated tumors; Fig. 1B). However, TMB was low regardless of *BRCA1/2* mutation or HRD (Mann-Whitney $P < 0.0001$ for comparisons by both *BRCA1/2* and HRD) (Fig. 1B). High TMB (≥ 10 mut/Mb) was observed in 11 (5%) of 232 *BRCA1/2* mutated samples versus 18 (2%) of 792 *BRCA* non-mutant samples (Fisher exact test $P = 0.068$), and in 15 (3%) of 444 HRD samples versus 12 (2%) of 529 HRP samples (Fisher exact test $P = 0.33$). There was no correlation between TMB and PD-L1 status (data not shown). While *BRCA1/2* mutations were not significantly associated with PD-L1 status (19% prevalence of *BRCA1/2* mutation in PD-L1-negative tumors vs. 24% prevalence in PD-L1-positive tumors; Fisher exact test $P = 0.0637$) (Fig. 1C), deleterious alterations in *BRCA1*, but not in *BRCA2*, were moderately associated with PD-L1 positive tumors (Supplementary Fig. S2). HRD was enriched in PD-L1-positive tumors (50% prevalence vs. 37% in PD-L1-negative tumors; Fisher exact test $P < 0.0001$) (Fig. 1D).

Prognostic effects

In the pooled treatment arms, deleterious mutations in *BRCA2*, *RB1,* and *NF1* were associated with better PFS, whereas activating alterations and amplifications in *KRAS*, *CCNE1*, *FGF12,* and *AKT2* were associated with worse PFS (Fig. 2A).

In the control arm, *BRCA1/2* mutations were associated with better PFS (hazard ratio 0.62, 95% confidence interval [CI], 0.46–0.84; median 21.1 months in *BRCA1/2*-mutated tumors vs. 16.7 months in *BRCA1/2* non-mutated tumors), indicating a prognostic role of *BRCA1/2* mutation (Fig. 2B). A similar effect was seen

in the atezolizumab combination arm (hazard ratio 0.67, 95% CI, 0.49–0.91; median 21.9 vs. 18.7 months, respectively).

Likewise, in the control arm, HRD was associated with better PFS (hazard ratio 0.63, 95% CI, 0.49–0.80; median 20.7 months in the HRD subgroup vs. 15.3 months in the HRP subgroup), indicating a prognostic effect of homologous recombination status (Fig. 2C). A similar effect was seen in the atezolizumab combination arm (hazard ratio 0.73, 95% CI, 0.57–0.94; median 20.7 vs. 18.0 months, respectively).

Genomic markers, *BRCA1/2* mutation status, PD-L1, and atezolizumab treatment effect

None of the individual gene alterations from the NGS panel was associated with enhanced atezolizumab treatment effect on PFS (data not shown). Similarly, there was no clear association between atezolizumab treatment effect and *BRCA1/2* mutation status, PD-L1 status, or the combination of both (Fig. 3A). The 95% CI for the PFS hazard ratio overlapped with unity for all of the subgroups except the 509 patients with *BRCA* non-mutant PD-L1-positive tumors (hazard ratio 0.75, 95% CI, 0.59–0.96; median PFS 20.7 months with atezolizumab-containing therapy vs. 16.4 months in the control arm). The hazard ratio point estimate for the *BRCA*-mutant PD-L1-positive subgroup was the same, suggesting that the improved outcome with the addition of atezolizumab to chemotherapy and bevacizumab derived from PD-L1 positivity rather than lack of *BRCA1/2* mutation.

In the subgroup of patients with high PD-L1 expression (IC ≥5%), there was no difference in clinical outcome according to *BRCA1/2* mutation status (Supplementary Fig. S3).

In additional analyses, subgroups were defined according to *BRCA1* versus *BRCA2* mutations. Tumors harbored *BRCA1* mutations in 152 patients (14%; 91 germline, 24 somatic, 37 unknown), *BRCA2* mutations in 78 patients (7%; 51 germline, 14 somatic, 13 unknown), and both *BRCA1* and *BRCA2* alterations in four patients (0.4%). In both treatment arms, there was a suggestion that PFS was more favorable in patients with *BRCA2*-mutated tumors than *BRCA1*-mutated tumors (Fig. 3B), although this was less pronounced in the atezolizumab-containing arm. However, there was no evidence of a treatment benefit from atezolizumab in patients with *BRCA2*-mutated tumors, but a suggestion of improved PFS with the addition of atezolizumab to chemotherapy and bevacizumab in patients with *BRCA1*-mutated tumors, particularly those with PD-L1-positive tumors (median PFS of 25.8 months with atezolizumab-containing therapy vs. 18.4 months in the control arm) (Fig. 3C).

HRD and atezolizumab treatment effect

There was no association between atezolizumab treatment effect and homologous recombination status or PD-L1 status (Fig. 4). When combining these two factors, the predictive effect of PD-L1 status seemed more pronounced in patients with HRD tumors. However, in the subgroup of patients with PD-L1 IC ≥5% there was no difference in PFS hazard ratio between subgroups with HRD versus HRP tumors (Supplementary Fig. S3).

TMB and atezolizumab treatment effect

Subgroup analyses of PFS according to TMB showed a numerically improved effect of atezolizumab in patients with TMB ≥10 mut/Mb, but this was a very small subgroup and 95% CIs were wide (Supplementary Fig. S4).

Discussion

IMagyn050 is the first randomized double-blind trial in ovarian cancer to demonstrate that neither deleterious *BRCA1* or *BRCA2* mutations nor HRD improves sensitivity to therapeutic PD-L1 blockade. Similarly, TMB is generally not increased and plays no clear predictive role in ovarian cancer. None of these biomarkers can be recommended for use as a selection criterion for PD-L1-targeting immunotherapy in newly diagnosed ovarian cancer.

In tumor types with higher TMB, such as melanoma and lung cancer, *BRCA1/2* alterations are associated with increased neoantigen load and greater sensitivity to ICIs. In a retrospective study of more than 37,000 samples across multiple indications, *BRCA1/2*-altered tumors had higher median TMB than *BRCA1/2* wild-type tumors (16). However, ovarian tumors represented only 2% of samples and of those, only 41 (5%) were *BRCA1/2* mutated. Survival analysis in a subset of these patients treated with ICIs showed that those with *BRCA2* alteration and high TMB appeared to have the best OS outcome, but outcomes specifically in the ovarian cancer subgroup were not described (16). Furthermore, as all patients received an ICI, potential differences may simply reflect the prognostic effect of *BRCA2* alterations.

In the IMagyn050 trial in ovarian cancer, we observed low TMB (<10 mut/Mb) in almost all tumors (97%), irrespective of *BRCA1/2* or homologous recombination status. We also found that genomic instability due to *BRCA1/2* mutations or HRD was associated with statistically significant but not biologically meaningful increases in TMB. These biological findings are consistent with previous reports of a higher neoantigen load in HRD versus HRP HGSOC (12). We show that the minor TMB

increase in HRD or *BRCA1/2*-mutated tumors is not associated with sensitivity to ICIs nor hypermutation, such as described for tumors with high MSI that are deficient in DNA mismatch repair.

The prognostic role of *BRCA* mutations (particularly in *BRCA2*) and HRD observed in IMagyn050 is consistent with previous reports (17,18), highlighting the importance of stratifying according to *BRCA1/2* and/or HRD status in future trials in newly diagnosed ovarian cancer. Our findings are also consistent with the lack of predictive value of *BRCA1/2* alterations in patients receiving an ICI (atezolizumab) in the randomized IMpassion130 trial of atezolizumab combined with nanoparticle albumin-bound (nab)-paclitaxel in triple-negative breast cancer (TNBC) (19).

More specifically, *BRCA2* status was associated with improved prognosis in IMagyn050 but without a predictive role for atezolizumab. Of note, there was a numerical effect favoring atezolizumab-containing therapy among the subgroup of patients with *BRCA1*-mutated tumors, notwithstanding the caveat of the small sample size. Superficially, this contrasts with findings reported by Samstein et al. (20), which suggested that mutations in *BRCA2* but not *BRCA1* were associated with improved outcomes. However, all patients received ICIs and therefore it is impossible to differentiate between prognostic and predictive effects. Moreover, few patients in Samstein et al.'s study had ovarian cancer and neither of the patients with HGSOC and deleterious *BRCA2* mutations showed a clinical response to the ICI. It is plausible, therefore, that those who responded to ICIs had a very different tumor microenvironment from the *BRCA2*-mutated HGSOCs. Interestingly, polyADP ribose polymerase (PARP) inhibitors are clinically active in both ovarian cancer and TNBC; therefore, the tumor characteristics where the *BRCA2* mutation resides may differentially predispose to ICI sensitivity.

There is no evidence from the present analysis to support use of TMB as a predictive biomarker for immunotherapy in ovarian cancer. Emerging data suggest that weighting all mutations identically when calculating TMB score may miss important information about the type of mutation, with certain mutations generating more immunogenic neoantigens than the more common nonsynonymous single-nucleotide mutations. There may also be differences between inflamed and noninflamed tumors (10). In an analysis of almost 1,000 patients with ovarian cancer reported by Fan et al. (21), higher TMB was associated with higher CD8+ T-cell infiltration but also better PFS and OS, lower clinical stages, and tumor-free status.

Our analyses showing no correlation between PD-L1 status and *BRCA1/2* mutation in ovarian cancer contradict early reports that *BRCA1/2*-mutated HGSOC was associated with increased PD-L1 expression in tumor-infiltrating immune cells (but not tumor cells) compared with HRP tumors (12) but are consistent with recently published analyses from the randomized IMpassion130 trial in metastatic TNBC (19).

This analysis of a double-blind, randomized, placebo-controlled trial offers an important strength compared with most previous reports in the literature. While Liu et al. (22) found no association between clinical benefit from immunotherapy and *BRCA1/2* mutation, HRD, or TMB in recurrent ovarian cancer, it is not possible to differentiate between prognostic and predictive effects in a single-arm study. In contrast, the efficacy of immunotherapy versus placebo was assessed in our analyses, thus enabling separation of disease-related versus treatment-related effects.

HRD is a frequent feature of HGSOC, as observed in this analysis, thus a potential weakness of the present trial is the grouping of all histologies for analyses

according to homologous recombination status. Non-HGSOC tumors are usually HRP and *BRCA1/2* wild type; therefore, segmenting histologic subgroups within *post hoc* biomarker-identified subgroups would result in sample sizes too small for meaningful interpretation. Another potential criticism is the lack of information on tumor-infiltrating lymphocytes (TILs), which have also shown prognostic value in ovarian cancer independent of HRD (23). Analyses of TILs and other tumor immune biomarkers, such as T-cells (cytotoxic and regulatory), myeloid populations, and other immune-based gene expression signatures are ongoing in the IMagyn050 trial.

Notwithstanding these limitations, the analyses reported here provide important new information from a randomized phase III trial challenging the hypothesis that *BRCA2* mutation status, HRD, and/or high TMB predict clinical benefit from immune checkpoint blockade in ovarian cancer. On the other hand, we observed an intriguing hint that *BRCA1* mutation may predict for enhanced effect of atezolizumab-containing therapy on PFS. There was a hint that the prognosis for patients with *BRCA1*-mutated tumors, which was less favorable than for those with *BRCA2*-mutated tumors, can perhaps be improved with the addition of atezolizumab to chemotherapy and bevacizumab. Sample sizes are small, but this finding merits exploration in other datasets to try to establish robust markers potentially enabling identification of those patients with newly diagnosed ovarian cancer who may benefit from immunotherapy. This may also have implications for ongoing trials of immunotherapy in combination with PARP inhibitors, which may show higher benefit in patients with *BRCA1*-mutated disease.

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Authors' Contributions

C. N. Landen: Data analysis and interpretation, manuscript writing, final approval of manuscript. **L. Molinero:** Conception and design, collation and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript. **H. Hamidi:** Manuscript writing, final approval of manuscript. **J. Sehouli:** Manuscript writing, final approval of manuscript. **A. Miller:** Manuscript writing, final approval of manuscript. **K. N. Moore:** Conception and design, manuscript writing, final approval of manuscript. **C. Taskiran:** Manuscript writing, final approval of manuscript. **M. Bookman:** Conception and design, manuscript writing, final approval of manuscript. **K. Lindemann:** Manuscript writing, final approval of manuscript. **C. Anderson:** Manuscript writing, final approval of manuscript. **R. Berger:** Manuscript writing, final approval of manuscript. **T. Myers:** Manuscript writing, final approval of manuscript. **M. Beiner:** Manuscript writing, final approval of manuscript. **T. Reid:** Manuscript writing, final approval of manuscript. **E. Van Nieuwenhuysen:** Manuscript writing, final approval of manuscript. **A. Green:** Manuscript writing, final approval of manuscript. **A. Okamoto:** Manuscript writing, final approval of manuscript. **C. Aghajanian:** Manuscript writing, final approval of manuscript. **P. H. Thaker:** Manuscript writing, final approval of manuscript. **S. V. Blank**: Manuscript

writing, final approval of manuscript. **V. K. Khor:** Conception and design, data analysis and interpretation, manuscript writing, final approval of manuscript. **Y. G. Lin:** Conception and design, data analysis and interpretation, manuscript writing, final approval of manuscript. C.-W. Chang: Data analysis and interpretation, final approval of manuscript. **S. Pignata:** Conception and design, manuscript writing, final approval of manuscript.

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Table 1. Baseline characteristics of the study participants.

Characteristic	ITT population (*n* = 1301)	*BRCA*-evaluable population		HR-evaluable population	
		BRCA mutant (*n* = 234)	*BRCA* wild type (*n* = 816)	HRD (*n* = 446)	HRP (*n* = 534)
Median age, years (range)	59 (18–84)	57 (32–81)	61 (18–84)	58 (27–81)	62 (24–84)
Race					
White	925 (71)	183 (78)	645 (79)	329 (74)	439 (82)
Asian	305 (23)	36 (15)	126 (15)	87 (20)	67 (13)
Black or African American	21 (2)	7 (3)	11 (1)	10 (2)	7 (1)
Other/unknown	50 (4)	8 (3)	34 (4)	20 (4)	21 (4)
ECOG PS[a]					
0	708 (54)	149 (64)	471 (58)	270 (61)	304 (57)
1 or 2	593 (46)	85 (36)	345 (42)	176 (39)	230 (43)
Treatment approach[a]					
Neoadjuvant	332 (26)	63 (27)	186 (23)	121 (27)	112 (21)

Primary surgery	969 (74)	171 (73)	630 (77)	325 (73)	422 (79)
Outcome of surgery					
No gross residual disease	238 (18)	53 (23)	130 (16)	89 (20)	79 (15)
Residual disease ≤1 cm	565 (43)	95 (41)	351 (43)	181 (41)	230 (43)
Residual disease >1 cm	458 (35)	81 (35)	312 (38)	164 (37)	210 (39)
Not applicable	40 (3)	5 (2)	23 (3)	12 (3)	15 (3)
PD-L1[a]					
IC <1%	517 (40)	72 (31)	307 (38)	129 (29)	223 (42)
IC ≥1%	784 (60)	162 (69)	509 (62)	317 (71)	311 (58)
Stage[a,b]					
III	896 (69)	154 (66)	560 (69)	297 (67)	372 (70)
IV	404 (31)	80 (34)	256 (31)	149 (33)	162 (30)
Primary tumor site[b]					
Epithelial ovarian	965 (74)	174 (74)	592 (73)	334 (75)	398 (75)
Fallopian tube	211 (16)	40 (17)	147 (18)	73 (16)	87 (16)
Primary peritoneal	124 (10)	20 (9)	77 (9)	39 (9)	49 (9)

Histology					
Serous	1118 (86)	207 (88)	691 (85)	403 (90)	440 (82)
Endometrioid	35 (3)	3 (1)	29 (4)	7 (2)	22 (4)
Clear cell	51 (4)	1 (<1)	42 (5)	3 (1)	37 (7)
Mucinous/undifferentiated/mixed/other	97 (7)	23 (10)	54 (7)	33 (7)	35 (7)
Abnormal CA-125 level[c]	1124 (86)	168 (72)	562 (69)	324 (73)	359 (68)
gLOH status					
HR deficient	446 (34)	178 (76)	268 (33)	446 (100)	0
HR proficient	534 (41)	48 (21)	486 (60)	0	534 (100)
HR not evaluable	321 (25)	8 (3)	62 (8)	0	0
BRCA1/2 mutation status					
Mutant	234 (18)	234 (100)	0	178 (40)	48 (9)
Wild type	816 (63)	0	816 (100)	268 (60)	486 (91)
Not evaluable	251 (19)	0	0	0	0

Note: data are *n* (%) unless otherwise specified.

Abbreviation: HR, homologous recombination.

[a]Stratification factor. [b]Missing in one patient in the placebo arm. [c]Missing in 18 patients in the ITT population.

Figure Legends

Figure 1.

A, Genomic landscape of biomarker-evaluable population from IMagyn050 (pooled treatment arms) according to FoundationOne® CDx assay. **B,** Relationships between TMB, *BRCA1/2* mutation status, and HR status. **C,** Prevalence of *BRCA1/2* mutation by PD-L1 status. **D,** Prevalence of HRD by PD-L1 status. [a]*BRCA1/2* Mut: known and likely deleterious tumor germline/somatic *BRCA1/2* mutations; variants of unknown significance excluded. [b]HRD: gLOH ≥16%; HRP: gLOH <16%, regardless of *BRCA1/2* mutation status. For visualization purposes, patients with TMB=0 were set to TMB=0.01 and those with gLOH=0 were set to gLOH=0.1. Patients with no data are blank. HR, homologous recombination; LGSOC, low-grade serous ovarian cancer.

Figure 2.

A, Gene mutations associated with PFS (univariate analysis). **B,** PFS according to *BRCA1/2* mutation status in the placebo, chemotherapy, and bevacizumab control arm and the atezolizumab, chemotherapy, and bevacizumab arm. **C,** PFS according to homologous recombination status in the placebo-containing control arm and the atezolizumab-containing arm.

Figure 3.

A, Association between PFS outcome, *BRCA1/2* mutation status, and PD-L1 status. **B,** PFS according to treatment arm and *BRCA1* versus *BRCA2* status.[a] **C,** Forest plot of PFS according to treatment arm, PD-L1 status, and *BRCA* mutation status.

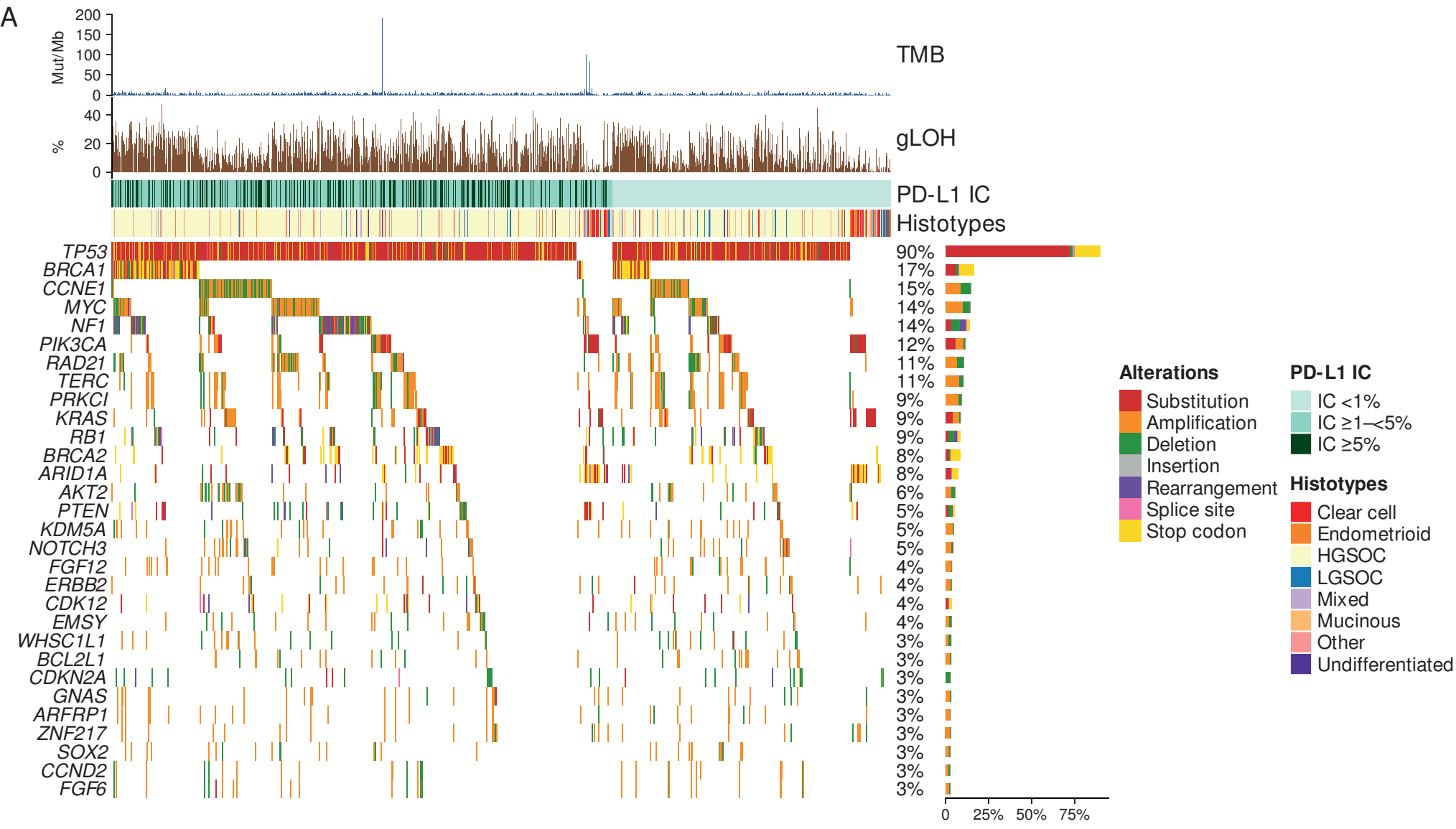
[a]Four patients with both *BRCA1* and *BRCA2* mutations are excluded from Panel B (one patient in the placebo arm with PFS of 12.5+ months; three in the atezolizumab-containing arm with PFS of 17.1, 18.1+, and 12.7+ months). CPB, paclitaxel, carboplatin, and bevacizumab.

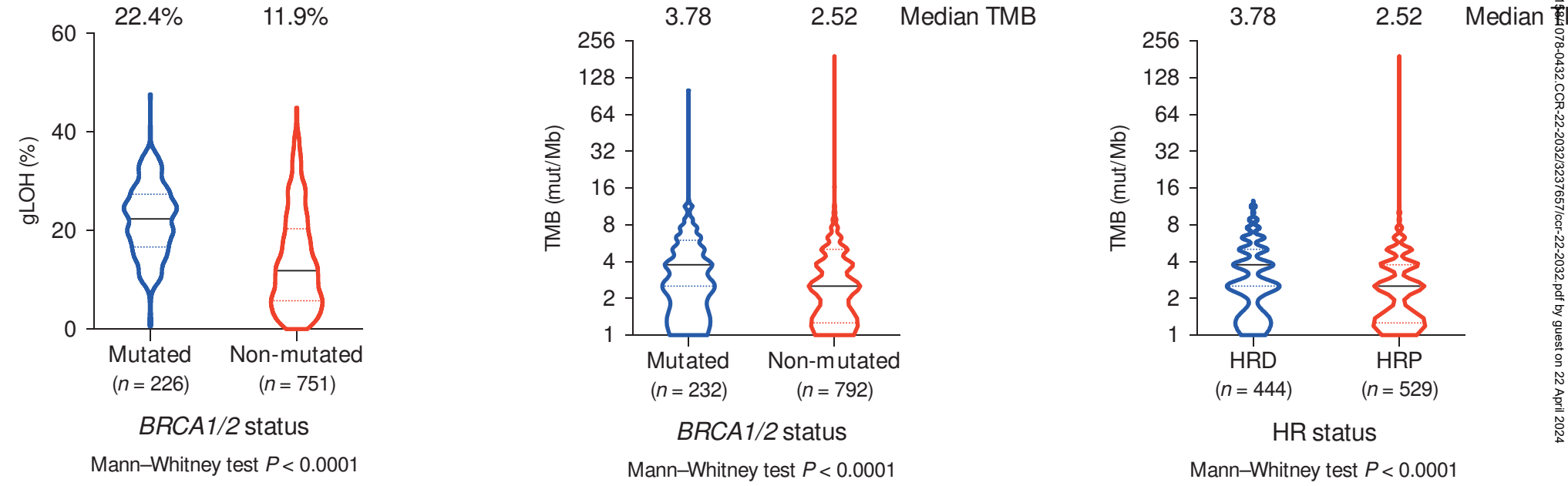
Figure 4.

Association between PFS outcome, homologous recombination status,[a] and PD-L1 status.

[a]HRD: gLOH ≥16%; HRP: gLOH <16%. CPB, paclitaxel, carboplatin, and bevacizumab.

Figure 1





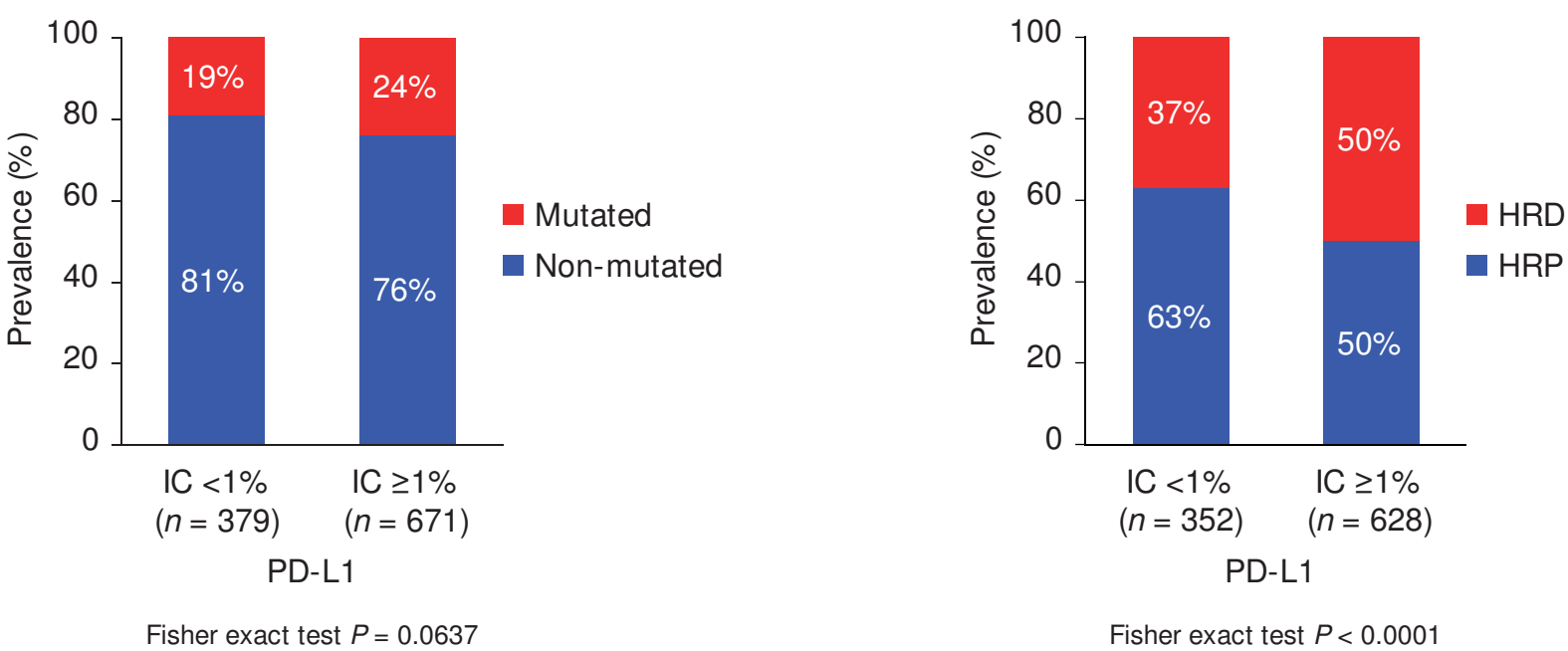
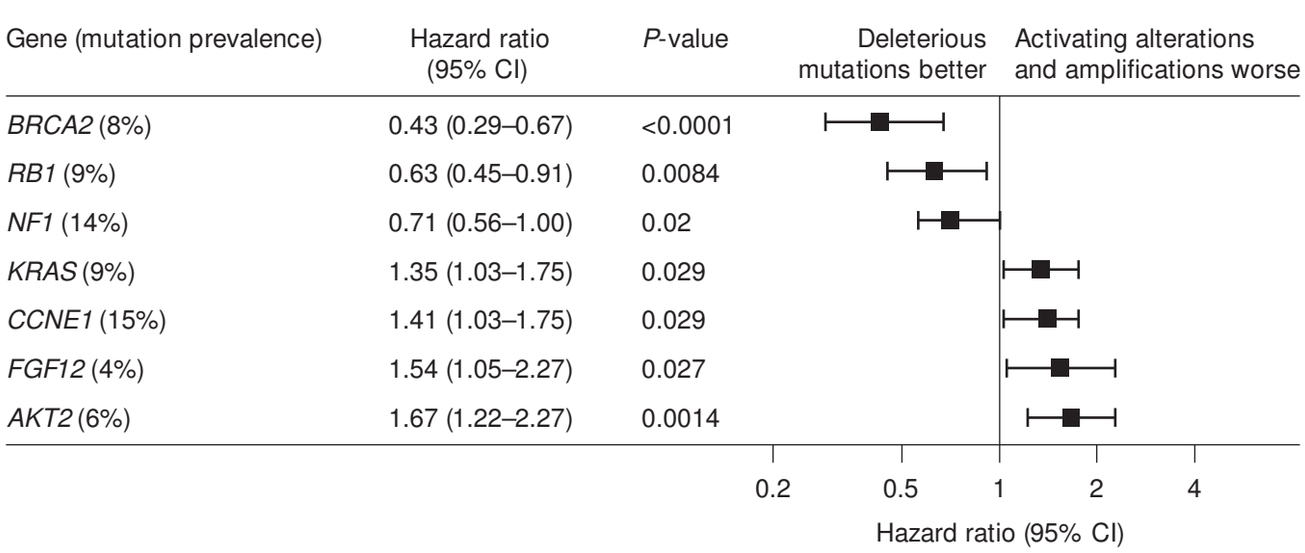


Figure 2

A



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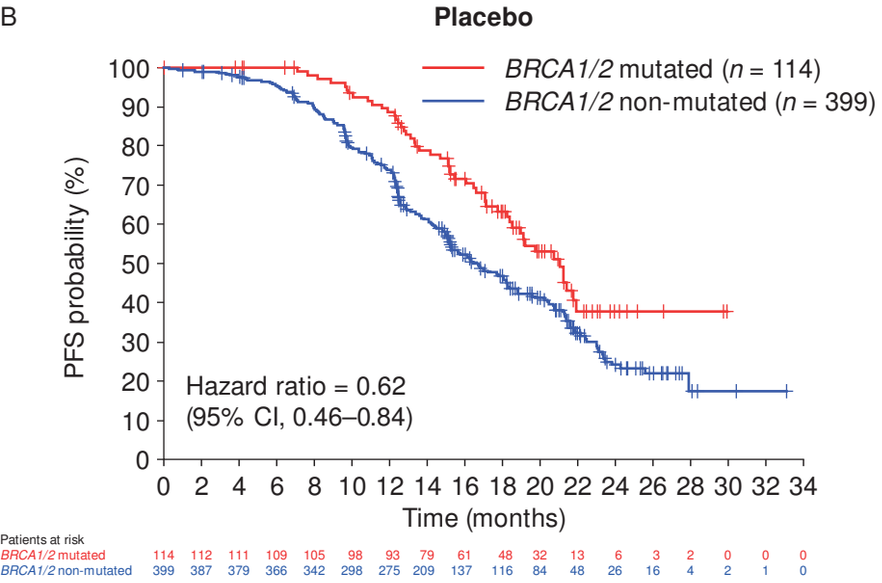

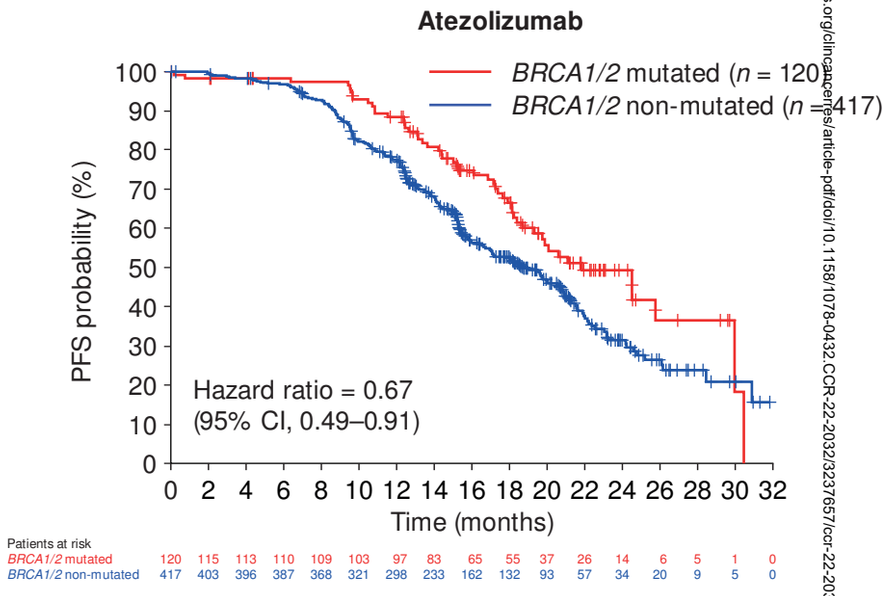

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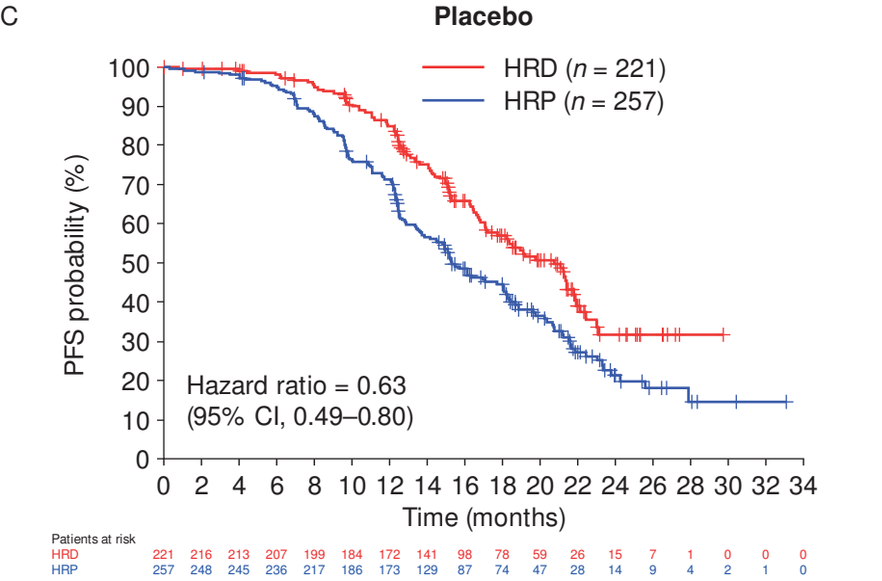


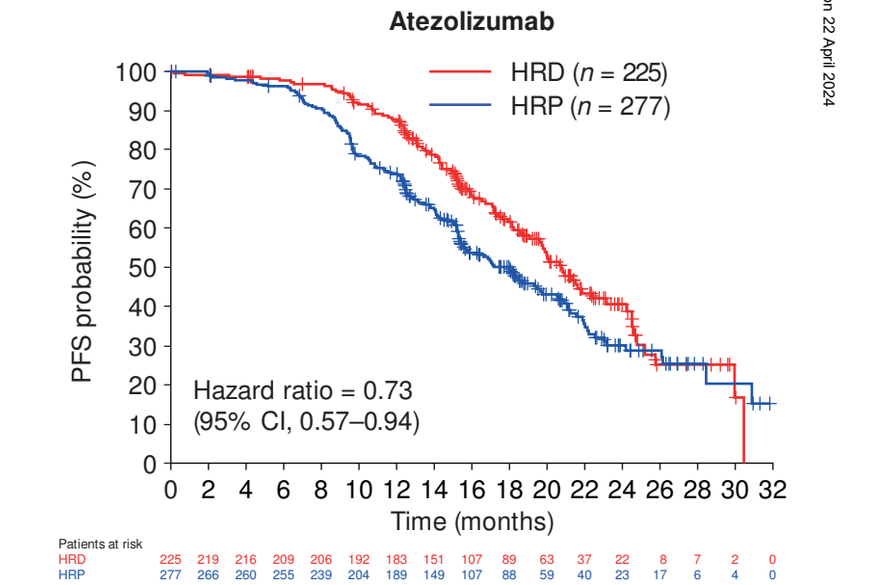
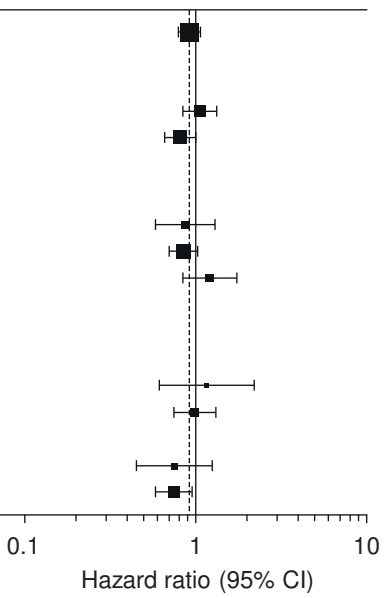


Figure 3

A

	Total N	Placebo + CPB (n = 650) n	Placebo + CPB (n = 650) Median (months)	Atezolizumab + CPB (n = 651) n	Atezolizumab + CPB (n = 651) Median (months)	Hazard ratio (95% Wald CI)
All patients	1301	650	18.4	651	19.5	0.92 (0.79–1.07)
PD-L1 IC status						
IC <1%	517	257	18.3	260	17.4	1.06 (0.84–1.33)
IC ≥1%	784	393	18.5	391	20.8	0.81 (0.66–1.00)
BRCA1/2 status						
Mutated	234	114	21.1	120	21.8	0.87 (0.59–1.29)
Non-mutated	816	399	16.7	417	18.7	0.85 (0.70–1.02)
Not evaluable	251	137	20.3	114	18.4	1.21 (0.84–1.74)
Combined *BRCA1/2* and PD-L1 status						
BRCA1/2 mutated, IC <1%	72	35	19.7	37	18.1	1.16 (0.61–2.20)
BRCA1/2 non-mutated, IC <1%	307	144	16.7	163	16.0	0.99 (0.74–1.32)
BRCA1/2 mutated, IC ≥1%	162	79	21.4	83	25.8	0.75 (0.45–1.25)
BRCA1/2 non-mutated, IC ≥1%	509	255	16.4	254	20.7	0.75 (0.59–0.96)



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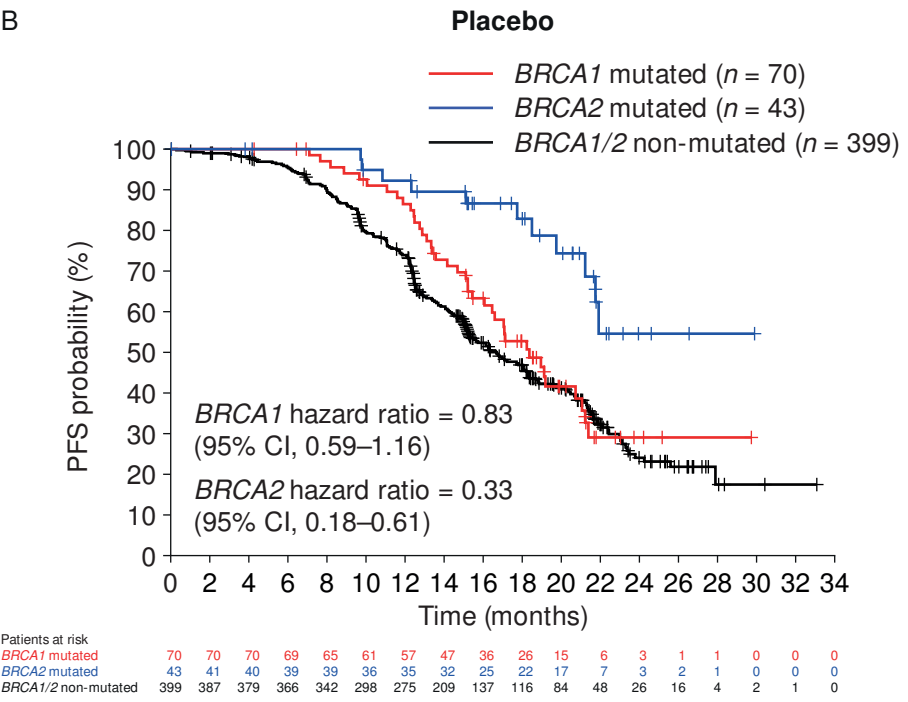

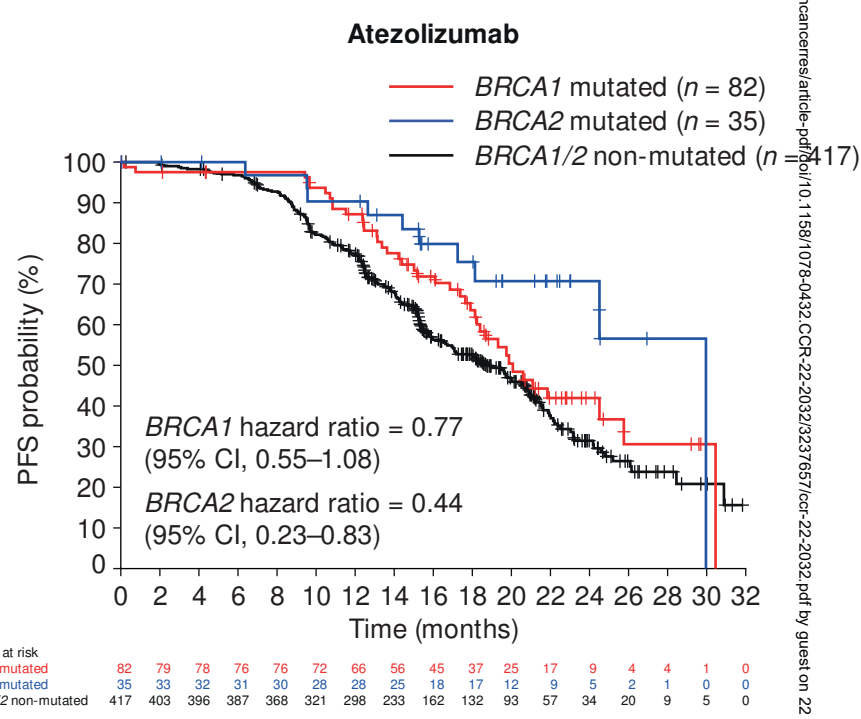

C

	Subgroup	No. of patients Placebo	No. of patients Atezolizumab	Median PFS, months Placebo	Median PFS, months Atezolizumab	Hazard ratio (95% CI)
BRCA1 mutated	All patients (n = 156)	71	85	18.4	20.1	0.76 (0.48–1.18)
	PD-L1+ (n = 109)	49	60	18.4	25.8	0.60 (0.34–1.08)
BRCA2 mutated	All patients (n = 82)	44	38	NE	30.0	1.05 (0.44–2.48)
	PD-L1+ (n = 57)	31	26	NE	30.0	1.12 (0.41–3.09)

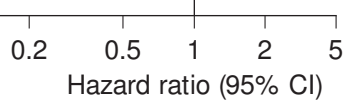

Figure 4

	Total N	Placebo + CPB (*n* = 650) *n*	Placebo + CPB (*n* = 650) Median (months)	Atezolizumab + CPB (*n* = 651) *n*	Atezolizumab + CPB (*n* = 651) Median (months)	Hazard ratio (95% Wald CI)
All patients	1301	650	18.4	651	19.5	0.92 (0.79–1.07)
PD-L1 IC status						
IC <1%	517	257	18.3	260	17.4	1.06 (0.84–1.33)
IC ≥1%	784	393	18.5	391	20.8	0.81 (0.66–1.00)
Homologous recombination status						
HRD	446	221	20.7	225	20.8	0.92 (0.70–1.21)
HRP	534	257	15.3	277	18.0	0.82 (0.66–1.02)
Not evaluable	321	172	20.5	149	19.3	1.09 (0.78–1.51)
Combined homologous recombination and PD-L1 status						
HRD, IC <1%	129	61	20.7	68	17.4	1.76 (1.10–2.82)
HRP, IC <1%	223	105	15.2	118	17.0	0.82 (0.58–1.14)
HRD, IC ≥1%	317	160	21.3	157	24.8	0.69 (0.49–0.97)
HRP, IC ≥1%	311	152	16.1	159	18.4	0.81 (0.60–1.09)