Geneva Homologous Recombination Deficiency Test Is Predictive of Survival Benefit From Olaparib and Bevacizumab Maintenance in Ovarian Cancer

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ABSTRACT

PURPOSE The ability of the Geneva homologous recombination deficiency (HRD) test to predict progression-free survival (PFS) in patients with high-grade ovarian cancer treated with poly (ADP-ribose) polymerase inhibitors has been demonstrated. Its performance with respect to overall survival (OS) has not been assessed yet.

METHODS Using the final results of the PAOLA-1/ENGOT-ov25 phase III clinical trial with a median follow-up of 5 years, we evaluated the Geneva HRD test on 468 samples as part of the ENGOT HRD European Initiative. Results were evaluated in terms of final PFS and OS in the olaparib + bevacizumab and placebo + bevacizumab arms and compared with the Myriad MyChoice HRD test.

RESULTS Final PFS was consistent with previously published data and confirmed the predictive value of the Geneva HRD test with a hazard ratio (HR) of 0.41 (95% CI, 0.30 to 0.57) for HRD-positive patients. The results for OS showed a HR of 0.56 (95% CI, 0.37 to 0.85) for HRD-positive patients and 1.6 (95% CI, 1.1 to 2.3) for HRD-negative patients. These results are consistent with those observed with the Myriad test, including the negative OS trend in the HRD-negative subgroup treated with olaparib + bevacizumab (HR, 1.2 [95% CI, 0.83 to 1.8]). A subgroup analysis of patients with intermediate HRD scores showed that the normalized large-scale state transition score used by the Geneva HRD test had both predictive and prognostic value.

CONCLUSION The Geneva HRD test predicts PFS and OS benefit from olaparib + bevacizumab. The potential detrimental effect of olaparib + bevacizumab on OS in the HRD-negative population is hypothesis-generating and needs to be confirmed prospectively.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

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INTRODUCTION

Frontline maintenance therapy with inhibitors of poly ADP-ribose polymerase (PARPi) has revolutionized the treatment of patients with high-grade serous or endometrioid ovarian carcinoma. Although several randomized phase III clinical trials have consistently shown that patients with homologous recombination deficiency (HRD) tumors have improved progression-free survival (PFS) when treated with these agents (reviewed by Foo et al[1]),[2] the overall survival (OS) benefit is debated.[3-5] PARPi monotherapy as a third or subsequent line of therapy did not show OS benefit, and trials of PARPi as maintenance therapy in patients in the recurrence setting have shown mixed results.[6] These findings led to the withdrawal of Food and Drug Administration (FDA) approval for several PARPi in the relapse settings. It is therefore important to identify patients who are likely to have OS benefit from PARPi.

Two approaches are currently used to identify HRD. The first approach is based on identifying the cause of HRR defects, mainly inactivating mutations of genes involved in homologous recombination repair pathway (HRR), such as *BRCA1* and *BRCA2*.[7] The second approach is based on the genomic consequences (or scars) of HRD, which can be identified using genomic instability scores on the basis of genomic alterations to estimate the likelihood of HRR loss. These two approaches have different advantages

CONTEXT

Key Objective

The use of olaparib and bevacizumab as frontline maintenance therapy in advanced-stage high-grade ovarian carcinoma (HGOC) is guided by the Myriad MyChoice homologous recombination deficiency (HRD) test. We aimed to evaluate the performance of the Geneva HRD test in predicting progression-free survival (PFS) and overall survival (OS) benefit in 468 patients from the PAOLA-1/ENGOT-ov25 phase III trial.

Knowledge Generated

The Geneva HRD test is predictive of PFS and OS benefit in advanced-stage HGOC treated with olaparib and bevacizumab. A detrimental effect of olaparib and bevacizumab on OS was observed in a subgroup identified by the Geneva HRD test, but not by the Myriad MyChoice HRD test.

Relevance

Our results confirm the relevance of the Geneva HRD test to guide the use of poly (ADP-ribose) polymerase inhibitors in clinical practice. The detrimental effect of olaparib and bevacizumab in a HGOC subgroup should be confirmed in further studies.

and disadvantages. In high-grade ovarian carcinoma (HGOC), the use of a genomic instability score identifies more patients who are likely to benefit from PARPi than mutations in a HRR gene panel that includes *BRCA1/BRCA2*.[8]

The choice of the primary end point in randomized controlled trials is of paramount importance. OS is considered to be the gold standard as it represents a patient-centered, objective, and an easily measured outcome.[9] PFS is a disease-centered measure that has the advantage of providing an output more rapidly than OS but is considered to be more subjective and may not necessarily identify a deleterious effect of late toxic effects or of post-treatment decreased efficacy on survival.[10,11]

In a recent issue of *JCO Precision Oncology*, we reported the results of the Geneva HRD test with respect to PFS on a large subset (N = 469) of patients with HGOC included in the PAOLA-1/ENGOT-ov25 phase III clinical trial.[12] In this trial, the primary end point was PFS and patients were randomly assigned two to one to receive olaparib + bevacizumab or placebo + bevacizumab as frontline maintenance therapy. We demonstrated that the proposed test efficiently separated the HRD-positive from HRD-negative patients (primary PFS analysis).[13] This test quantifies the number of large-scale state transitions in the tumor sample as this was shown to be the optimal metric to separate HRD-positive from HRD-negative samples. This value is normalized with respect to the number of whole-genome doubling events, which is nearly ubiquitous in HGOC.[14] Our initial analysis suggested that the other metrics used to assess HRD (loss of heterozygosity and telomeric allelic imbalance) are less discriminative.[13] *BRCA* testing is recommended in clinical routine, yet the addition of the *BRCA1/2* mutation status to the instability metric, as done by the Myriad MyChoice test and others, did not improve the performance of the Geneva HRD test in this cohort. Thanks to the technology used to quantify genomic alterations, the assay yields low rate of inconclusive results (6%, composed of 2% technical failure and 4% analytic failure) compared with 13% on the same samples for the test used in the study (Myriad MyChoice). The Geneva HRD test calls positive results at a lower cutoff than the Myriad MyChoice HRD test used in the PAOLA-1 trial, resulting in 31 more positive results among the 403 results that were valid in both tests. The Geneva HRD test is now listed among the recommended analysis methods in the European Society for Medical Oncology (ESMO) guidelines.[15] Here, we present the updated exploratory analyses of the final PFS and OS data from the PAOLA-1 trial, undertaken 3 years after the primary analysis, at 55% data maturity and a follow-up of 5 years.[3]

METHODS

Cohort Characteristics

This study is part of the ENGOT HRD initiative led by the French Groupe des Investigateurs Nationaux pour l'Etude des Cancers de l'Ovaire (GINECO).[16] Specifically, 469 samples were selected from the PAOLA-1/ENGOT-ov25 cohort of 806 patients.[12] The study was approved by the ethics committee "Comite de Protection des Personnes SUD-EST IV," France. All patients provided written informed consent before their participation in this study. Samples with the highest content of DNA were prioritized (ARCAGY-GINECO tumor bank, Institut Curie, Paris), selected, and shared with the 10 initial participant laboratories to the ENGOT initiative. DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor slides, preferentially from patients untreated before surgery. Among these samples, 76.5% (359) were collected from prechemotherapy biopsies and 21.5% (101)

from postchemotherapy biopsies. From each sample, 100 ng tumor DNA was obtained and transferred to 96-well plates that were sent to Geneva at −80°C, after agreement from the French authority. DNA samples were analyzed with the OncoScan assay as previously described.[13]

Samples were specifically selected from the entire selected PAOLA-1 population to be representative in terms of *BRCA* and HRD status distribution. Beyond this, the major criterion for selection was that sufficient material was present to ensure that DNA could be distributed to the 10 laboratories participating in the ENGOT HRD initiative. Among the 469 patients included, benefit of olaparib + bevacizumab maintenance compared with bevacizumab was in the same range as that of the entire PAOLA-1 population of 806 patients. Within these 469 female patients with a high-grade ovarian adenocarcinoma (median age, 60 years; detailed statistics in Appendix Table A1) who responded to first-line platinum-based chemotherapy and bevacizumab, 32% had *BRCA* tumor mutation (29% in the entire PAOLA-1 cohort). The clinical database was locked on March 22, 2022, 3 years after the primary analysis, at 55% data maturity and a median follow-up of 5 years.[3] In 2024, one patient retracted her consent leading to a reduced cohort of 468 patients for this study.

Geneva HRD Test

The Geneva HRD test does not assess *BRCA* mutational status. It is solely based on an instability metrics of normalized large-scale state transition (nLST). In practice, however, *BRCA* mutational status is already known or assessed through next-generation sequencing (NGS). Within this exploratory analysis, *BRCA* mutational status and genomic instability score (GIS) were obtained from the Myriad MyChoice assay results that were performed in the PAOLA-1 trial. Of note, an « inconclusive » result could either reflect a failed experiment or a variant of unknown significance.

Statistical Analyses

All analyses were performed in R 4.2.0 with packages "survival," "survminer," and "forestplot."

RESULTS

The Geneva HRD Test Is Predictive of PFS Benefit Upon Exposure to Olaparib and Bevacizumab

Within the cohort of 468 patients, those with Geneva HRD-positive tumors had PFS benefit (hazard ratio [HR], 0.41 [95% CI, 0.30 to 0.57]) on exposure to olaparib + bevacizumab. Those with Geneva HRD-negative tumors, which includes few *BRCA*-mutated samples (15 of 189), did not have PFS benefit (HR, 1.20 [95% CI, 0.86 to 1.70]; Fig 1A). These results are very similar to those obtained with the Myriad MyChoice test.

In the *BRCA*-mutated subpopulation (n = 151), PFS benefit was observed in patients with a Geneva HRD-positive test receiving olaparib + bevacizumab (HR, 0.33 [95% CI, 0.20 to 0.54]; n = 129).

The *BRCA* wild-type group displaying a Geneva HRD-positive test showed a PFS benefit in the olaparib + bevacizumab arm (HR, 0.54 [95% CI, 0.35 to 0.84]; n = 119). Of note, the Myriad MyChoice test displayed a HR of 0.44 (95% CI, 0.26 to 0.73; n = 91) for this subpopulation but had a lower positivity rate than the Geneva test (29% [91/319] *v* 38% [119/310]). In the *BRCA* wild-type Geneva HRD-negative subpopulation, no PFS benefit was observed in patients receiving olaparib + bevacizumab (HR, 1.10 [95% CI, 0.78 to 1.60]; Fig 1B). These results are consistent with our previously published data.[13]

The Geneva HRD Test Is Predictive of OS Benefit Upon Exposure to Olaparib and Bevacizumab

For the entire cohort of 468 patients with HGOC, those having Geneva HRD-positive tumors had longer OS when treated in the olaparib + bevacizumab arm, compared with the control arm (bevacizumab monotherapy). This benefit is consistent regardless of the HRD test used, the Geneva test (HR, 0.56 [95% CI, 0.37 to 0.85]; Fig 2A), Myriad MyChoice (HR, 0.6 [95% CI, 0.39 to 0.9]), or Myriad test using GIS score only (HR, 0.52 [95% CI, 0.33 to 0.82]; Fig 2C). In the Geneva HRD-positive *BRCA* wild-type subpopulation, a nonsignificant benefit of olaparib + bevacizumab treatment was observed with a hazard ratio of 0.75 (95% CI, 0.43 to 1.3; Appendix Fig A1), which is comparable with the results reported by Ray-Coquard et al[3] on the same subgroup of the entire POALA-1 cohort with the Myriad MyChoice test (HR, 0.71 [95% CI, 0.45 to 1.13]).

Patients with negative Geneva HRD test had shorter OS when treated with olaparib + bevacizumab (HR, 1.6 [95% CI, 1.1 to 2.3]; Fig 2B), compared with the control arm. This result confirms the trend toward shorter survival observed with the Myriad MyChoice test in this cohort (Fig 2C) and in the entire PAOLA-1 cohort (HR, 1.19 [95% CI, 0.88 to 1.63]) as reported by Ray-Coquard et al.[3] Of note, the HR difference in the HRD-negative subpopulation between the Geneva HRD test and the Myriad MyChoice assay cannot be attributed to the fact that the latter includes the *BRCA* mutational status in its algorithm. Indeed, OS results on the basis of the instability metrics from the Myriad MyChoice test show that the HR remained at 1.2 (95% CI, 0.81 to 1.7).

Fifteen patient had tumors that were *BRCA*-mutated but HRD-negative with the Geneva HRD test. Of these, four were heterozygous (no loss of the second copy of the *BRCA* gene) and could reasonably be classified as *BRCA*-proficient. In seven other samples, there was evidence of insufficient tumor cell content in the samples analyzed with the Geneva HRD test (few if any copy-number abnormalities detected). Thus, only four samples (<1%) seemed to have complete

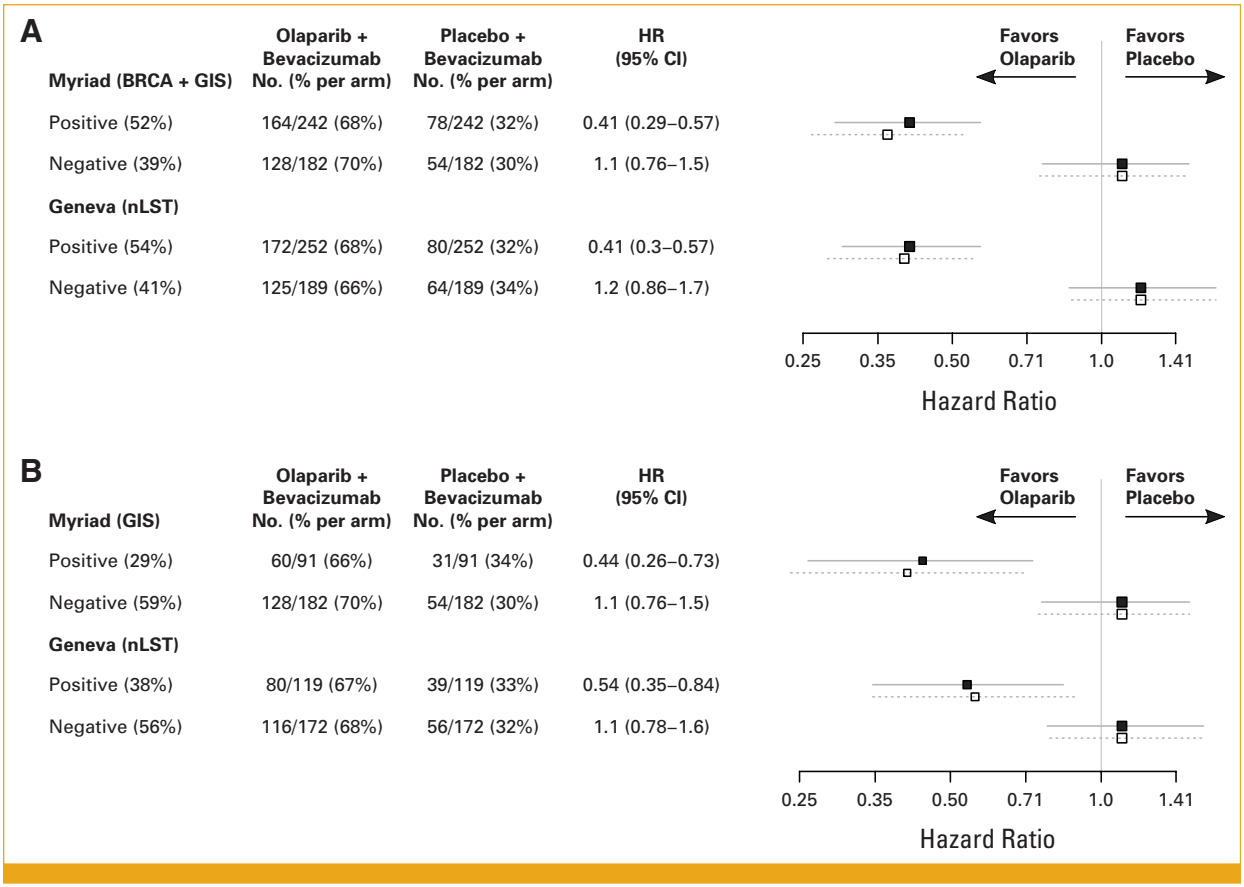

FIG 1. HR with the updated PFS for (A) the entire cohort (N = 468) and (B) *BRCA* wild-type tumors (n = 310). The dotted lines with the empty squares represent the data previously reported. GIS, genomic instability score; HR, hazard ratio; nLST, normalized large-scale state transition; PFS, progression-free survival.

BRCA loss with absence of HRD phenotype. These 15 patients did not seem to benefit from olaparib and bevacizumab, similarly to the *BRCA* wild-type HRD negative subpopulation.

Predictive Value of Intermediate nLST Scores

We previously reported that patients with a nLST score between 15 and 20 with the Geneva HRD test (hereafter referred to as HRD positive-mid) had an initial good response to olaparib + bevacizumab but early relapse. This observation was confirmed with the final PFS analysis (Appendix Fig A2; 57 (13%) HRD-positive–mid patients).

In terms of treatment, HRD-positive–mid patients had comparable PFS benefit (HR, 0.42 [95% CI, 0.21 to 0.86]) from olaparib + bevacizumab as HRD-positive–high patients (HR, 0.37 [95% CI, 0.25 to 0.53]; Fig 3). Consistently, HRD-positive–mid patients had comparable OS benefit (HR, 0.46 [95% CI, 0.21 to 0.98]) from olaparib + bevacizumab as HRD-positive–high patients (HR, 0.55 [95% CI, 0.34 to 0.9]; Fig 3).

Of note, the HRD-positive–mid subgroup (Geneva test) had the most discordant results with the Myriad MyChoice test: 40% (23/57) of the patients in this group were predicted to be HRD-negative by the Myriad test, whereas only 2.6% (5/195) in the Geneva HRD-positive–high subgroup were discordant between the two tests (chi-square *P* value of 2×10^{-14}). Within the 23 Geneva HRD-positive–mid but Myriad HRD-negative samples, a trend toward olaparib benefit is observed with respect to OS (HR, 0.45 [95% CI, 0.12 to 1.7]). Such a trend is not observed in the Geneva HRD-negative but Myriad HRD-positive samples (HR, 5.0 [95% CI, 1.6 to 15]; n = 20).

Prognostic Value of Geneva HRD Test in the Placebo Arm

In the placebo + bevacizumab arm and compared with HRD-positive–high patients, the HRD-positive–mid subgroup had a shorter 2-year PFS rate (16% *v* 39%; Fig 4A) and a lower 5-year OS rate (23% *v* 57%; Fig 4B). Although the number of HRD-positive–mid patients in this arm is low (14), the OS difference with the HRD-positive–high patients is nonetheless significant (log-rank *P* value of .0142). The HRD-positive–mid subgroup have a trend toward shorter survival than HRD-negative patients, although not statistically significant (log-rank *P* value of .256). A multivariate Cox analysis on OS within the placebo + bevacizumab arm showed that the difference between HRD-positive–mid and HRD-positive–high (nLST ≥20) remained significant (*P* = .0061) when taking into account the *BRCA* mutation,

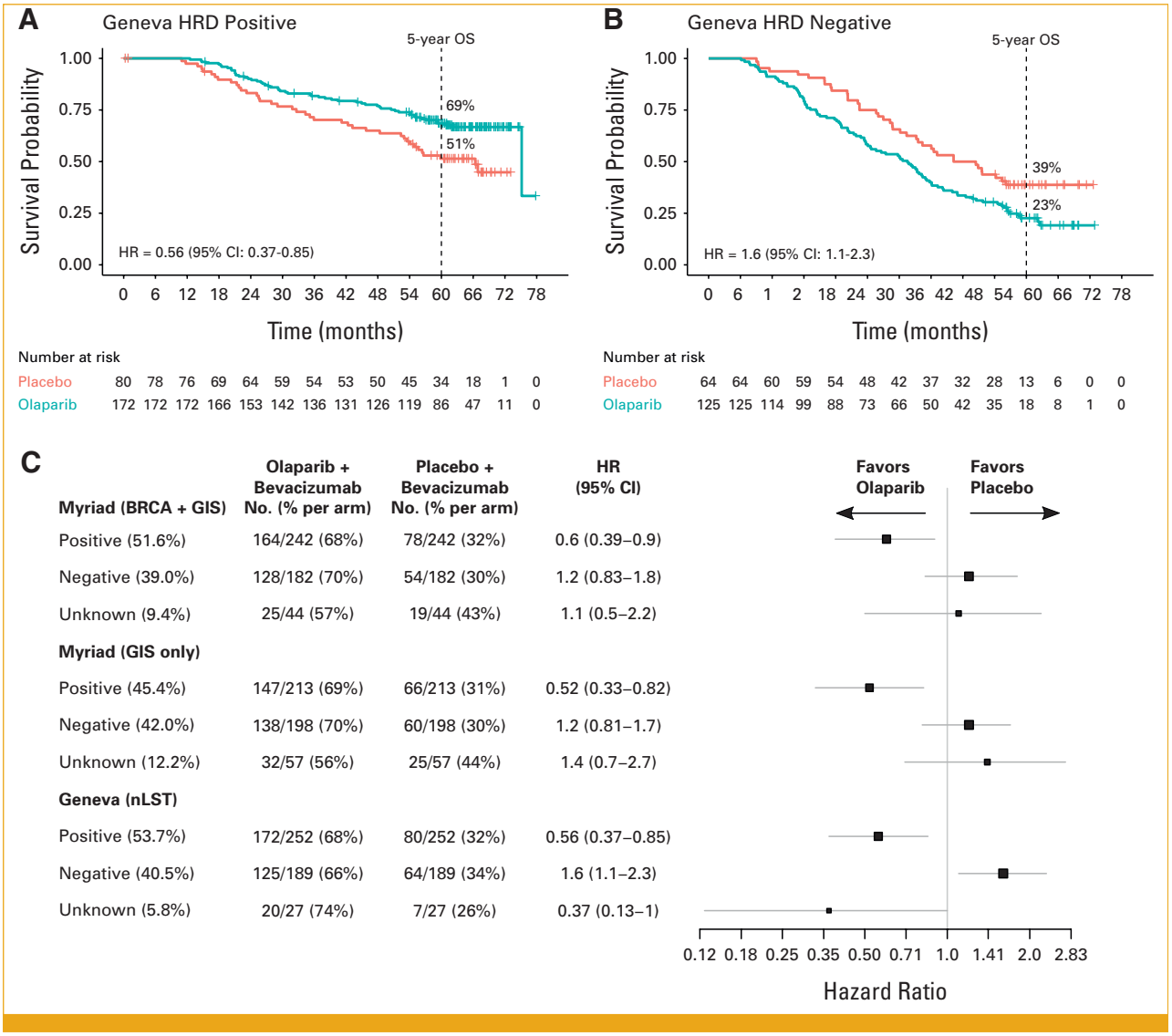

FIG 2. OS with respect to HRD test. Kaplan-Meier OS curves for (A) HRD-positive and (B) HRD-negative subpopulation by the Geneva HRD test with respect to the treatment arm. (C) HR of OS according to HRD test results (Geneva test and Myriad MyChoice). GIS, genomic instability score; HR, hazard ratio; HRD, homologous recombination deficiency; nLST, normalized large-scale state transition; OS, overall survival.

response to primary chemotherapy, and subsequent PARPi therapy (Appendix Table A2).

DISCUSSION

In the current study, we confirmed that the Geneva HRD test had prognostic and predictive value in terms of PFS and OS in the PAOLA-1 study. In this context, the HRD test allows to identify subgroups of patients with different outcomes according to their HRD score (≥20, 15-20, or <15). The subgroup with HRD score <15 has a bad prognosis and, in addition, the maintenance combination of olaparib + bevacizumab appears to have in this subgroup a detrimental effect on OS compared with placebo + bevacizumab. By contrast, patients with an HRD score ≥15 show a benefit when olaparib is added to bevacizumab in maintenance therapy. Irrespective of the treatment arm, patients with HRD score between 15 and 20 have a worse prognosis than patients with HRD score ≥20 but derive similar PFS and OS benefit from olaparib + bevacizumab combination.

Of note, although the Geneva HRD and the Myriad MyChoice tests are similar, they are not equivalent. The Myriad test includes the *BRCA* mutation status in its algorithm and the HRD score is computed with a different method. These differences might explain why the trend toward a detrimental effect on OS of olaparib + bevacizumab in the HRD-negative subpopulation was not significant with the Myriad test.

These results, obtained on a subpopulation of the PAOLA-1 trial (N = 468), should be considered hypothesis-generating

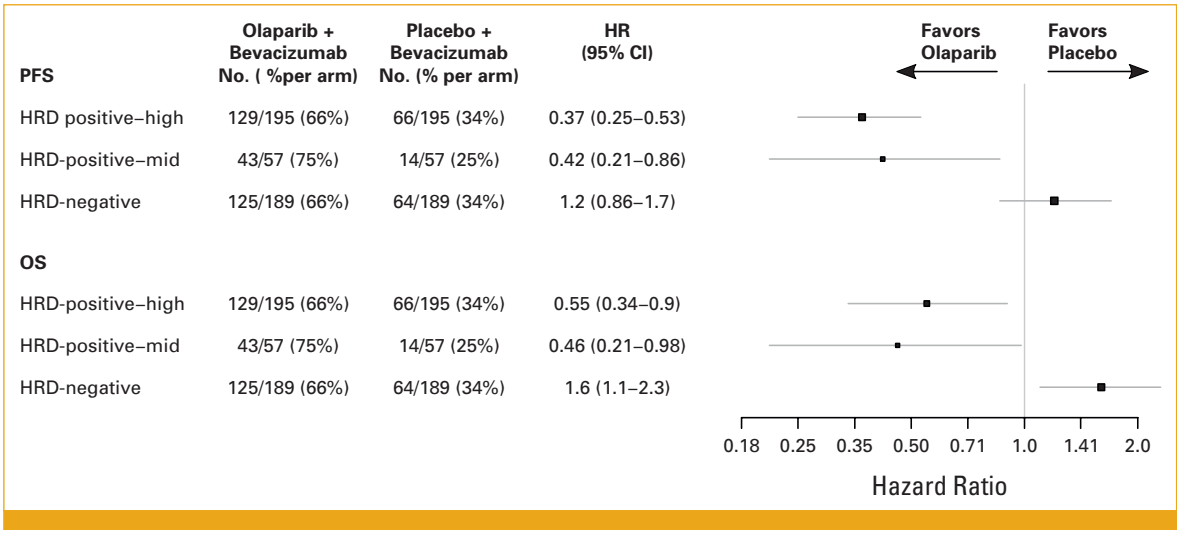

FIG 3. Predictive value (hazard of ratio of olaparib + bevacizumab *v* placebo + bevacizumab) of the Geneva HRD test on PFS and OS according to the three categories of nLST score (HRD-negative: nLST <15; HRD-positive–mid: 15 ≤ nLST < 20; HRD-positive–high: nLST ≥20). HRD, homologous recombination deficiency; nLST, normalized large-scale state transition; OS, overall survival; PFS, progression-free survival.

and have to be confirmed with the Geneva HRD test on the entire PAOLA-1 cohort and, ideally, using this or other HRD tests in other prospective studies. The potential detrimental effects of PARPi on survival in the HRD-negative subgroup of HGOC in first-line maintenance therapy need to be better understood. The data should be interpreted in the context of the trend toward shorter OS observed with the Myriad MyChoice in the PAOLA-1 cohort as reported by Ray-Coquard et al[3] and recent withdrawals of several PARPi (olaparib, niraparib, and rucaparib) by the US Food and Drug Administration in relapsing HGOC. The final OS results of the PRIMA trial showed no OS benefit in either the HRD-positive or HRD-negative subgroups, as defined by the Myriad test.[4] Other ongoing large phase III trials will provide a better understanding of the impact and the potential role of subsequent therapy. These studies may offer an explanation

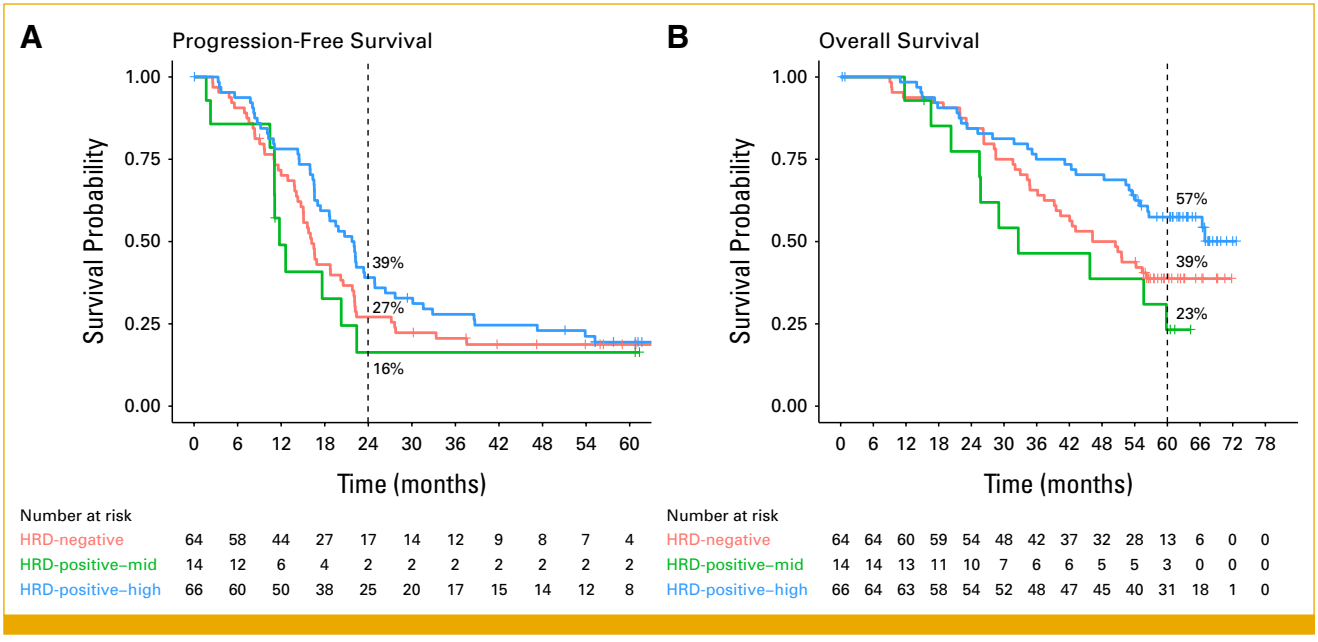

FIG 4. PFS and OS in the placebo + bevacizumab arm with respect to the nLST score divided in three categories (HRD-negative: nLST <15; HRD-positive–mid: 15 ≤ nLST < 20; HRD-positive–high: nLST ≥20). (A) PFS and (B) OS. HRD, homologous recombination deficiency; nLST, normalized large-scale state transition; OS, overall survival; PFS, progression-free survival.

both for our results and those in relapsed HGOC where PARPi as maintenance therapy in a nonselected population (NOVA and ARIEL3) suggested a trend toward poorer survival that was not completely explained by cross-over.[17-20]

The mechanism by which maintenance PARPi treatment results in a worse prognosis in patients with HRD-negative tumors that responded at least partially to first-line platinum therapy is not clear. It does not seem to be related to side effects of the treatment, as these were not more frequent in HRD-negative than in HRD-positive patients.[3] At first view, this difference does not seem to be related to tumor progression as no difference in PFS was reported, although the biological characteristics of the recurring tumor might be different at the time of recurrence. High-grade serous ovarian carcinoma is characterized by high genomic instability related to the ubiquitous *TP53* mutations found in these tumors. Inevitably, this genomic instability is a source of intratumoral heterogeneity that may be both spatial and temporal.[21-23] In patients with advanced-stage HGOC, multiple clones evolve over time and with therapy, and are major contributors to disease relapse and drug resistance.[24] Selective pressure because of continuous exposure to PARPi could accelerate the emergence of preexisting drug-tolerant clones leading to higher levels of drug resistance at the time of identifiable disease relapse,[25] assuming that there is at least some overlap between the mechanisms of resistance to PARPi and to subsequent lines of therapy. Alternatively, PARPi therapy, through its inhibition of base excision repair, may increase the diversity of tumor clones at the time of relapse. The characteristics of the clones selected by PARPi may be different in HRD-positive and HRD-negative tumors, leading to a difference in survival. Given the cross-resistance between platinum and PARPi in *BRCA*-mutated tumors,[26-28] patients with HRD-negative tumors that relapse during or after maintenance therapy with PARPi are more likely to be platinum-resistant and thus be less responsive to further lines of platinum therapy leading to shorter survival.[29]

In contrast to the predictive value, the prognostic value of the Geneva HRD test seems to have different cutoff with patients whose tumors have a high level of nLST showing longer OS than patients with mid-level nLST or whose tumors were HRD-negative. The biological basis of the quantitative differences in nLST levels is not clear, although three possibilities, that are not mutually exclusive, present themselves. The first variable is time from loss of HRR. Tumors that have acquired a deficiency in HRR just before diagnosis and analysis would be expected to have lower nLST values since accumulation of genomic anomalies is time-dependent. Although this would explain the variability in nLST levels, the underlying biological mechanism is unchanged and is thus unlikely to contribute to prognosis. The second variable is incomplete loss of HRR either because of lower expression of HRR gene RNA through partial methylation of the *BRCA1* promoter,[30] or mutations that result in partial activity of HRR pathway. The prognostic effect of different *BRCA* mutations has been investigated but no correlation with nLST levels is available yet.[31] Both would be predicted to result in lower levels of HRD and thus lower nLST values, leading to poorer prognosis by facilitating the emergence of PARPi-resistant clones. Finally, clonal heterogeneity within the tumor leads to subclones that are partly HRD and others partly HRR-competent, forming a mix that results in a lower nLST score when the whole tumor is analyzed.[21-24] This tumor heterogeneity would be expected to result in the earlier recurrence because of the selective advantage of the HRR-competent subclone and thus shorter survival.

In conclusion, although olaparib has brought unprecedented and historic survival benefit as first-line maintenance monotherapy in *BRCA*-mutated HGOC (SOLO1), and in combination with bevacizumab in HRD-positive patients (PAOLA-1), our results suggest a potential detrimental effect of frontline maintenance with olaparib + bevacizumab in the HRD-negative population as defined by the Geneva HRD test. These results will be validated on the remaining samples of the PAOLA-1 trial and should be challenged in the setting of other randomized phase III trials, such as ATHENA (ClinicalTrials.gov identifier: NCT03522246),[5] that used another HRD test and a different PARP inhibitor. Overall, these findings emphasize the importance of HRD testing for precision medicine and choosing the appropriate frontline maintenance therapy for patients with HGOC.

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DATA SHARING STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Speakers' Bureau: AbbVie (Inst), AstraZeneca (Inst), Eisai (Inst), GlaxoSmithKline (Inst), MSD (Inst)
Research Funding: Amgen (Inst), Roche (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: MSD/Merck (Inst), Immunogen (Inst), GlaxoSmithKline (Inst), PharmaMar (Inst), AstraZeneca (Inst)

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Sutro Biopharma, Novartis, Daiichi Sankyo, Immunogen, PMV Pharma, Immunocore
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Travel, Accommodations, Expenses: Roche, AstraZeneca, Tesaro, PharmaMar, GlaxoSmithKline, Clovis Oncology, BMS, Advaxis
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APPENDIX

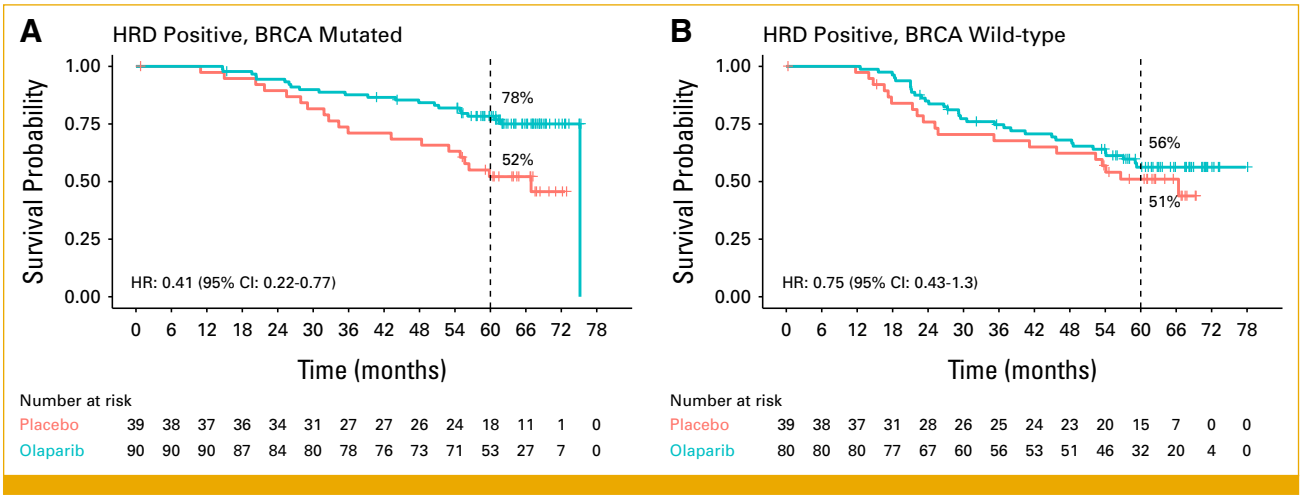

FIG A1. Kaplan-Meier OS curves for the HRD-positive subpopulation, according to the Geneva HRD test, with respect to the BRCA mutation status (given by the Myriad test). (A) *BRCA* mutated and (B) *BRCA* wild-type. HR, hazard ratio; HRD, homologous recombination deficiency; OS, overall survival.

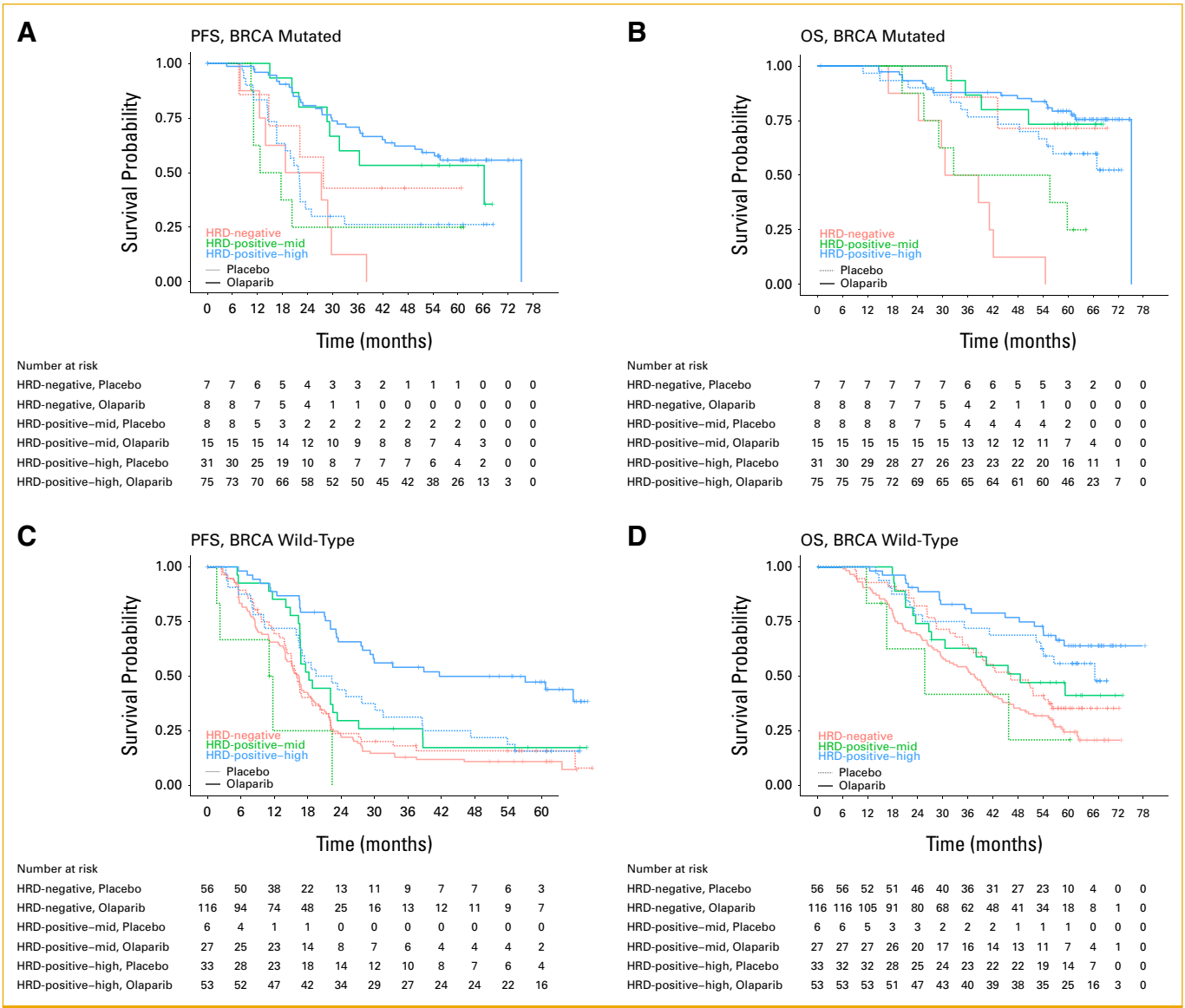

FIG A2. PFS and OS with respect to the treatment arm, subdivided by the nLST amplitude (negative: <15; positive-mid: 15 ≤ nLST < 20; positive-high: nLST ≥20) and the *BRCA* mutational status (given by the Myriad test). (A) PFS on *BRCA*-mutated patients, (B) OS on *BRCA*-mutated patients, (C) PFS on *BRCA* wild-type patients, and (D) OS on *BRCA* wild-type patients. HRD, homologous recombination deficiency; nLST, normalized large-scale state transition; OS, overall survival; PFS, progression-free survival.

TABLE A1. Demographics of the 468 Patients With Respect to the Geneva HRD Test Results

Variable	HRD-Positive–High	HRD-Positive–Mid	HRD-Negative	Unknown
Age, years, median	58	60	62	59
FIGO staging				
III B	21	4	9	0
III C	136	32	129	17
IV	38	21	51	10
Adenocarcinoma type				
Serous	180	56	182	27
Endometrioid	11	1	3	0
Other	4	0	4	0

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency.

TABLE A2. Multivariate Model of PFS and OS in the Placebo + Bevacizumab Arm According to the Three Categories of nLST Score of the Geneva Test (HRD-negative: nLST <15; HRD-positive–mid: 15 ≤ nLST < 20; HRD-positive–high: nLST ≥20)

Variable	2-Year PFS Rate, % (95% CI)	HR (95% CI)	*P*	5-Year OS Rate, % (95% CI)	HR (95% CI)	*P*
HRD score						
Positive-high	39 (29 to 53)	1		57 (46 to 71)	1	
Positive-mid	16 (5 to 57)	1.81 (0.93 to 3.54)	.0823	23 (9 to 63)	2.82 (1.34 to 5.93)	.0061
Negative	27 (18 to 41)	1.15 (0.76 to 1.73)	.5054	39 (28 to 53)	1.37 (0.82 to 2.29)	.2352
BRCA status						
Wild-type	29 (21 to 40)	1		39 (31 to 50)	1	
Mutated	35 (23 to 52)	0.65 (0.41 to 1.02)	.0580	56 (43 to 72)	0.60 (0.34 to 1.04)	.0706
Primary response to chemotherapy						
Complete response	32 (25 to 42)	1		46 (37 to 56)	1	
Partial response	26 (15 to 45)	1.12 (0.72 to 1.73)	.6170	37 (24 to 57)	1.52 (0.92 to 2.52)	.1018
Subsequent PARPi therapy						
No				45 (35 to 58)	1	
Yes				43 (33 to 56)	0.91 (0.58 to 1.43)	.6722

NOTE. The subsequent PARPi therapy is not accounted for PFS since it is a posterior event.
Abbreviations: HR, hazard ratio; HRD, homologous recombination deficiency; nLST, normalized large-scale state transition; OS, overall survival; PARPi, inhibitors of poly ADP ribose polymerase; PFS, progression-free survival.