OLAPARIB SENSITIVITY OBSERVED IN METASTATIC PANCREATIC CANCER WITH A WIDE SPECTRUM OF GERMLINE *BRCA1* AND *BRCA2* MUTATIONS

Talia Golan,[1] Hedy L Kindler,[2] Philipp Schatz,[3] Teodora Goranova,[4] Gershon Y Locker,[5] Karen Cui,[5] Katia Schlienger,[6] David McGuinness,[4] J Andrew Williams,[4] Maria Orr,[4] Thorsten Gutjahr,[4] Yu-Zhen Liu[4]

[1]The Oncology Institute, Sheba Medical Center, Tel HaShomer, Israel; [2]University of Chicago, Chicago, IL, USA; [3]AstraZeneca, Gothenburg, Sweden; [4]AstraZeneca, Cambridge, UK; [5]AstraZeneca, Gaithersburg, MD, USA; [6]Merck & Co., Inc., Kenilworth, NJ, USA

Contact and presenting author: Talia Golan

Abstract number: 4621

Introduction

- The POLO phase 3 trial demonstrated that patients with metastatic pancreatic cancer (mPaC) and germline *BRCA1* and/or *BRCA2* mutations (gBRCAm) had significantly longer progression-free survival (PFS; primary endpoint) with maintenance olaparib treatment versus placebo (median, 7.4 vs 3.8 months; hazard ratio [HR], 0.53; $p = 0.004$).[1]
- PFS benefit was observed in patients with g*BRCA1*m (HR, 0.40) and g*BRCA2*m (HR, 0.63).[1]
- POLO also represents the largest gBRCAm prevalence study in pancreatic cancer.
- We report exploratory analyses to further characterize the prevalence of gBRCAm and relationships with efficacy (PFS) in POLO.

Methods

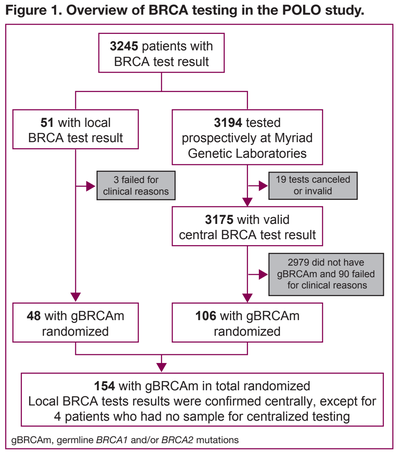
Study design and participants

- POLO was a randomized, double-blind, placebo-controlled, phase 3 trial (NCT02184195) conducted in 12 countries.
- Eligible patients were adults with a deleterious or suspected deleterious gBRCAm and metastatic pancreatic adenocarcinoma, without disease progression during at least 16 weeks of first-line platinum-based chemotherapy.
- Patients were enrolled on the basis of gBRCAm status either:
  - prospectively identified on enrollment by centralized testing using the BRACAnalysis CDx® test (Myriad Genetic Laboratories, Inc, Salt Lake City, UT, USA)
  - or previously identified from a local test result and, if a sample was available, centrally confirmed using the BRACAnalysis CDx test.
- Patients were randomized 3:2 to receive maintenance olaparib 300 mg twice daily (tablet) or placebo.

Outcomes and analyses

- Data from all screened patients with a prospective, valid germline BRCA test result (i.e. in patients with or without a gBRCAm) were retrospectively analyzed for prevalence of g*BRCA1*m and g*BRCA2*m by country, sex, race and ethnicity.

Figure 1. Overview of BRCA testing in the POLO study.



gBRCAm, germline *BRCA1* and/or *BRCA2* mutations

- Prevalence of particular types of gBRCAm, such as founder mutations, were retrospectively assessed in the randomized population of patients with a gBRCAm.
- The primary endpoint, PFS, was assessed in the randomized population by blinded independent central review (modified RECIST v1.1) and log-rank test, and per gBRCAm subgroup by Cox proportional hazards model.
- Patient characteristics in the randomized population, which were comparable in the olaparib versus placebo group, and prespecified outcomes have been reported previously.[1]

Results

BRCA testing in the POLO trial

- Of 3194 prospectively centrally tested patients, 3175 (99%) had a valid BRCA test result (**Figure 1**).
- Of those, 154 patients (106 prospectively centrally tested, 48 locally tested) were eligible for efficacy assessments (the randomized population).
  - Local test results were confirmed by centralized testing for 44 of 48 patients; 4 patients did not have a sample for centralized testing.

Prevalence of gBRCAm in the prospectively tested population

- Prevalence of gBRCAm was 6.2% (n = 196) of 3175 patients with no previously identified gBRCAm.
- g*BRCA2*m were more prevalent than g*BRCA1*m in the overall population (4.5% vs 1.6%) and per country, sex, race and ethnicity (**Figures 2 and 3**).
- In countries with more than 100 patients prospectively tested (n = 8), the highest gBRCAm prevalence was 9.2% (USA) and the lowest was 4.0% (Spain) (**Figure 2**).
- Prevalence by race (for those groups with more than 100 patients) was 6.4% in White and 4.6% in Asian patients; African Americans had the highest prevalence of gBRCAm (15.4%), although this was based on only 39 patients (**Figure 3**).

Prevalence of types of gBRCAm in the randomized population

- Of 154 randomized patients, 61 (40%) carried founder mutations (i.e. mutations observed with high frequency in particular populations) that have previously been reported in Ashkenazi Jewish or European populations.[2–4]
- Of the randomized population, 37 patients (24%), mainly from Israel (n = 21) and the USA (n = 6), carried the following common Ashkenazi Jewish founder mutations:
  - *BRCA1*:187delAG (n = 13)
  - *BRCA1*:5385insC (n = 4)
  - *BRCA2*:6174delT (n = 19)
  - *BRCA1*:5385insC and *BRCA2*:6174delT (n = 1).
- In the 150 randomized patients who were centrally tested, six types of variant were identified; frameshift mutations were the most frequent (g*BRCA1*m, 69.6%; g*BRCA2*m, 71.4%) (**Figure 4**).

PFS according to BRCA testing and gBRCAm types in the randomized population

- The efficacy (PFS) of olaparib versus placebo was consistent across different gBRCAm subgroups and with the full analysis set (**Figure 5**).

Conclusions and key messages

- In patients with mPaC screened for or enrolled in POLO:
  - g*BRCA2*m (4.5%) were more prevalent than g*BRCA1*m (1.6%), in contrast to predominance of g*BRCA1*m in patients with breast and ovarian cancer in other studies[5,6]
  - g*BRCA2*m were more prevalent than g*BRCA1*m per country, sex, race and ethnicity
  - frameshift mutations were the most common type of mutation, comprising 69.6% of g*BRCA1*m and 71.4% of g*BRCA2*m
  - PFS benefit of maintenance olaparib was consistent across a heterogeneous spectrum of gBRCAm and with the previously reported full analysis set.[1]

Author contact details: talia.golan@sheba.health.gov.il

References

1. Golan T *et al. N Engl J Med* 2019;381:317–27.
2. Ferla R *et al. Ann Oncol* 2007;18:93–8.
3. Janavicius R *et al. EPMA J* 2010;1:397–412.
4. Niell B *et al. J Natl Cancer Inst* 2004;96:15–21.
5. Robson *et al. N Engl J Med* 2017;377:523–33.
6. Moore K *et al. N Engl J Med* 2018;379:2495–505.

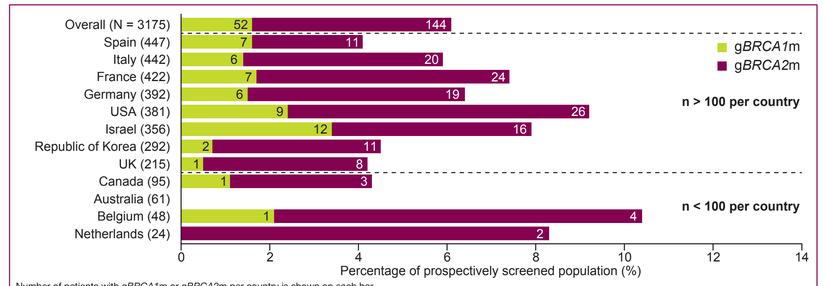
Funding

This study (NCT02184195) was funded by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD).

Acknowledgments

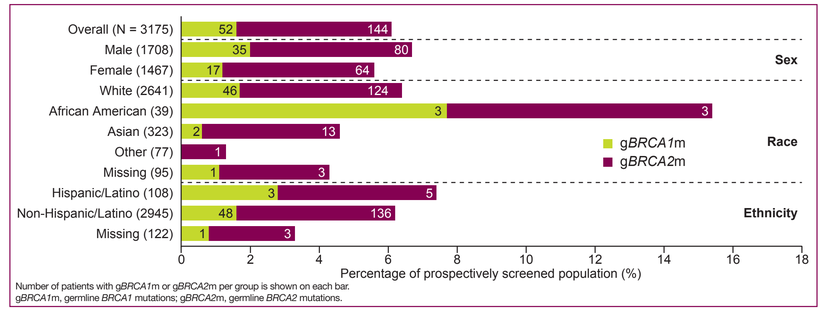
We thank the patients who participated in this trial and their families, our co-investigators, and Michael Riley, PhD, and Adam Errington, PhD, of Oxford PharmaGenesis, Cardiff, UK, who provided medical writing assistance. We thank Myriad Genetic Laboratories, Inc for performing the central testing for gBRCA mutations in the POLO study. Philipp Schatz is now an employee of Bayer AG, Pharmaceuticals, Oncology SBU, Berlin, Germany.

Figure 2. Prevalence of g*BRCA1*m and g*BRCA2*m per country.



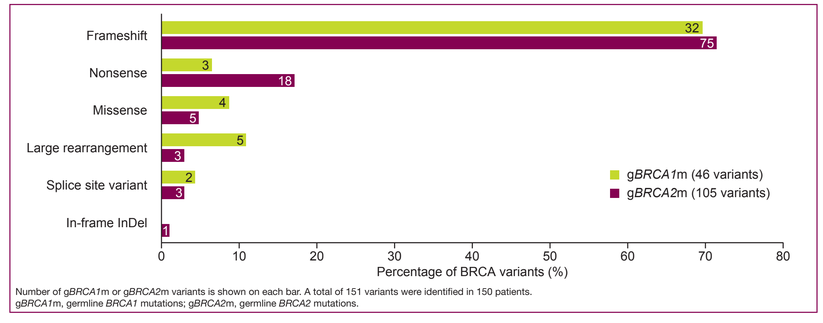
Number of patients with g*BRCA1*m or g*BRCA2*m per country is shown on each bar.
g*BRCA1*m, germline *BRCA1* mutations; g*BRCA2*m, germline *BRCA2* mutations.

Figure 3. Prevalence of g*BRCA1*m and g*BRCA2*m by sex, race and ethnicity.



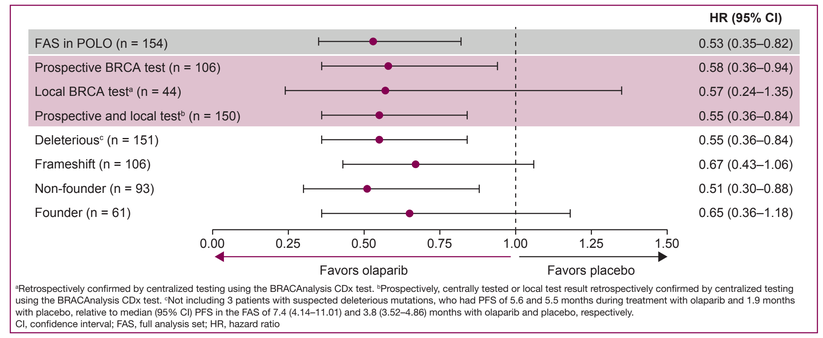
Number of patients with g*BRCA1*m or g*BRCA2*m per group is shown on each bar.
g*BRCA1*m, germline *BRCA1* mutations; g*BRCA2*m, germline *BRCA2* mutations.

Figure 4. Prevalence of g*BRCA1*m and g*BRCA2*m variants.



Number of g*BRCA1*m or g*BRCA2*m variants is shown on each bar. A total of 151 variants were identified in 150 patients.
g*BRCA1*m, germline *BRCA1* mutations; g*BRCA2*m, germline *BRCA2* mutations.

Figure 5. Progression-free survival, grouped by types of BRCA testing and g*BRCA*m, during treatment with olaparib compared with placebo.



[a]Retrospectively confirmed by centralized testing using the BRACAnalysis CDx test. [b]Prospectively, centrally tested or local test result retrospectively confirmed by centralized testing using the BRACAnalysis CDx test. [c]Not including 3 patients with suspected deleterious mutations, who had PFS of 5.6 and 5.5 months during treatment with olaparib and 1.9 months with placebo, relative to median (95% CI) PFS in the FAS of 7.4 (4.14–11.01) and 3.8 (3.52–4.86) months with olaparib and placebo, respectively.
CI, confidence interval; FAS, full analysis set; HR, hazard ratio

Presented at ASCO 2020 Virtual Poster (29–31 May 2020)