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

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Introduction

The POLO phase III 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

• Patients were enrolled on the basis of gBRCAm and eligible patients were adults with a deleterious or suspected deleterious gBRCAm and metastatic or locally advanced pancreatic cancer, without previous treatment with PARP inhibitors, and adequate bone marrow, liver, and renal function; 7 palliation were excluded. Local BRCA tests results were confirmed centrally, except for 4 patients who had no sample for centralized testing.

• Patients were randomized 3:2 to receive maintenance olaparib (n = 196) or placebo (n = 130) in the POLO trial.

• 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

Methods

Study design and participants

• POLO was a randomized, double-blind, placebo-controlled, phase 3 trial (NCT02184195) conducted in 52 countries.

• Eligible patients were adults with a deleterious or suspected deleterious gBRCAm and metastatic or locally advanced pancreatic cancer, without previous treatment with PARP inhibitors, and adequate bone marrow, liver, and renal function; 7 palliation were excluded. Local BRCA tests results were confirmed centrally, except for 4 patients who had no sample for centralized testing.

• Patients were randomized 3:2 to receive maintenance olaparib 300 mg daily (196) or placebo (130) in the POLO trial.

• Patients were enrolled on the basis of gBRCAm status either:

1. prospectively identified on enrollment by centralized testing using the BRACAnalysis CDx® test (Myriad Genetic Laboratories, Inc, Salt Lake City, UT, USA) or
2. 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 daily (196) or placebo (130) in the POLO trial.

• 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 gBRCAm and gBRCAm by country, sex, race, and ethnicity.

• Overall, 3194 prospectively centrally tested patients, 3175 (99.9%) had a valid BRCA test result (Figure 1; Table 1).

• Of these, 1,154 patients (196 prospectively centrally tested, 48 locally tested) were eligible for efficacy assessments (the randomized population).

Results

BRCA testing in the POLO trial

• Of 3194 prospectively centrally tested patients, 3175 (99.9%) had a valid BRCA test result (Figure 1).

• Of these, 1,154 patients (196 prospectively centrally tested, 48 locally tested) were eligible for efficacy assessments (the randomized population).

Prevalence of gBRCAm in the prospectively tested population

• Prevalence of gBRCAm was 6.2% (n = 196) of 3175 patients with a previously identified gBRCAm.

• gBRCAm were more prevalent than gBRCAm in the overall population (4.5% vs 1.6%) and per country, sex, race and ethnicity.

• Prevalence of gBRCAm in the randomized population

1. Of 197 prospectively centrally tested patients, 61 (44%) carried founder mutations (i.e., mutations observed with high frequency in a particular population) that have previously been reported in Ashkenazi Jewish founder populations, mainly from Israel (n = 21) and the USA (n = 6), carried the following common Ashkenazi Jewish founder mutations:

• BRCA1: 187delAG (n = 13)
• BRCA1: 664C>T (n = 3)
• BRCA1: 8493delAG (n = 4)
• BRCA1: 1379delAG (n = 2)

2. 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: 664C>T (n = 3)
• BRCA1: 8493delAG (n = 4)
• BRCA1: 1379delAG (n = 2)

• In the 150 randomized patients who were centrally tested, six types of variant were identified, founder mutations were the most frequent gBRCAm (gBRCAm, 68.9%; gBRCAm, 17.1%; Figure 4).

PFS benefit 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:

  gBRCAm (4.5%) were more prevalent than gBRCAm (1.6%), in contrast to predominance of gBRCAm in patients with breast and ovarian cancer in other studies5,6

  gBRCAm were more prevalent than gBRCAm per country, sex, race and ethnicity.

• Prevalence of particular types of gBRCAm, such as founder mutations, were retrospectively assessed in the randomized population of patients with gBRCAm.

• In patients with mPaC screened for or enrolled in POLO:

  gBRCAm (4.5%) were more prevalent than gBRCAm (1.6%), in contrast to predominance of gBRCAm in patients with breast and ovarian cancer in other studies5,6

  gBRCAm were more prevalent than gBRCAm per country, sex, race and ethnicity.

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

Figure 2. Prevalence of gBRCAm in the prospectively tested population

Figure 3. Percentage of prospectively screened population (%) with valid BRCA test result per country.

Table 1. Numbers of gBRCAm by country.

Source: of gBRCAm on gBRCAm variants on screen or group (n = 150) at 196 patients were identified in 150 patients.

References


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We thank the patients who participated in this trial and their families; our co-investigators, and Michael May, PhD, and Allen Eistert, PhD, of Oxford PharmaGenesis, Cardiff, UK, who provided medical writing assistance. We thank Myriad Genetic Laboratories, Inc for performing the central testing for gBRCAm mutations in the POLO study. Philipp Schatz is now an employee of Bayer AG.

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Figure 2. Prevalence of gBRCAm and gBRCAm per country.

Figure 3. Percentage of prospectively screened population (%) with valid BRCA test result per country.

Figure 4. Prevalence of gBRCAm and gBRCAm variants.

Figure 5. Progression-free survival, grouped by types of BRCA testing and gBRCAm mutations.

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