SUPPLEMENTARY DATA

Supplementary Methods

Tumors eligible for dose escalation phase

1. Breast cancer
    - Triple-negative breast cancer
    - Known *BRCA1/2*-mutated breast cancer
    - Platinum sensitive breast cancer
2. Ovarian cancer
    - High-grade serous and/or undifferentiated ovarian, fallopian tube, or peritoneal cancer
    - Known *BRCA1/2*-associated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer
    - Platinum-sensitive recurrent ovarian cancer
3. Uterine carcinosarcoma or endometrioid endometrial carcinomas
4. Non-small cell lung cancer
5. Metastatic castration-resistant prostate cancer
6. Pancreatic cancer
7. Colorectal cancer, mismatch repair positive
8. Any recurrent locally advanced or metastatic disease proven to harbor DNA repair deficiencies
9. Suspected hereditary cancers based on family history only
    - Hereditary breast and ovarian cancer
    - Hereditary nonpolyposis colorectal cancer
    - Cowden syndrome
    - Li–Fraumeni syndrome

Tumors eligible for dose expansion phase

1. *BRCA1/2*-mutated tumors
    - Epithelial ovarian, fallopian tube, or primary peritoneal cancer
    - Breast cancer
    - Pancreatic cancer
    - Metastatic castration-resistant prostate cancer
2. *BRCA*-like tumors
    - Triple-negative breast cancer
    - High-grade serous and/or undifferentiated ovarian, fallopian tube, or peritoneal cancer
3. *PTEN*-loss tumors
    - Uterine carcinosarcoma or endometrioid endometrial carcinomas
    - Non-small cell lung cancer
    - Metastatic and castration-resistant prostate cancer
    - Pancreatic cancer
    - Breast cancer
    - Ovarian cancer
4. Other tumor types were considered if there was evidence of response in the dose escalation portion of the study

Patients enrolled using a local laboratory

For patients enrolled using a local laboratory, the prior germline *BRCA* analysis must have indicated a deleterious mutation on *BRCA* function (subsequent confirmatory testing [MYRIAD, Salt Lake City, Utah] was performed). Patients with small cell lung cancer (SCLC),

Ewing's sarcoma or a documented DNA repair defect (such as partner and localizer of *BRCA2* (*PALB2*) gene mutations, or ataxia telangiectasia-mutated [*ATM*] gene mutations) were also eligible.

Study design and participants

The Part 2 dose expansion enrolled approximately 70 patients, of whom approximately 40 patients had *BRCA*-associated cancers, including approximately 10 with breast cancer, 10 with ovarian cancer (including fallopian or primary peritoneal cancer) with pathogenic or deleterious *BRCA* mutations, 10 with prostate cancer with pathogenic or deleterious *BRCA* or somatic mutation in *ATM*, 10 with pancreatic cancer with *BRCA* and/or *PALB2* pathogenic or deleterious mutations; the remaining patients included approximately 20 patients with SCLC and 10 patients with Ewing's sarcoma.

Additional inclusion criteria

Other inclusion criteria included measurable disease by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) or increased tumor markers, adequate organ function, ability to take oral medications, and willing to use highly effective contraception throughout the study and for 30 days after the last dose of talazoparib. Although no limits on the number of prior cytotoxic regimens, including prior platinum, were made in Part 1, patients enrolled in Part 2 had to have received ≤4 prior regimens (ovarian, breast cancer), ≤3 prior regimens (Ewing's sarcoma), ≤2 prior regimens (prostate, pancreatic cancers) or ≤1 prior regimen (SCLC). For Part 2, progression on prior platinum-based chemotherapy must have occurred >8 weeks after the last dose (ovarian, breast cancer) or >3 months after last dose (SCLC); prior treatment with poly(ADP-ribose) polymerase (PARP) inhibitors was prohibited.

Key exclusion criteria included: persistent grade ≥2 toxicities (per National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events version 4.03 [CTCAE]) from previous therapy (excluding alopecia or laboratory abnormalities); having received any antitumor therapy within 28 days before starting talazoparib (6 weeks for nitrosoureas or mitomycin-C); having undergone high-dose chemotherapy followed by transplant; history of central nervous system (CNS) metastases (with the exception of patients with SCLC and history of adequately treated brain metastasis off corticosteroids). A full list of exclusion criteria is given below.

Full list of exclusion criteria

Individuals who met any of the following criteria were ineligible to participate in the study:

- Not recovered (defined as NCI CTCAE grade ≤1) from acute toxicities of previous therapy except treatment-related alopecia or laboratory abnormalities and otherwise meeting inclusion criteria
- Prior treatment with a PARP inhibitor (Part 2)
- History of CNS metastasis (NB, patients with SCLC and history of adequately treated brain metastasis without corticosteroids for management of CNS symptoms were eligible)
- Any antitumor systemic cytotoxic therapy within 28 days (6 weeks for nitrosoureas or mitomycin-C) before cycle 1 day 1, treatment with immune modulators such as corticosteroids at prednisone-equivalent dose of >10 mg/day, cyclosporine and tacrolimus or radiotherapy within 28 days before cycle 1 day 1; locally active treatments such as Beconase allowed
- Prior high-dose chemotherapy with bone marrow or stem cell transplant
- Known to have human immunodeficiency virus or active hepatitis C or B virus
- Major surgery within 28 days before cycle 1 day 1
- Active peptic ulcer disease
- Active gastrointestinal tract disease with malabsorption syndrome

- Requirement for intravenous alimentation
- Prior surgical procedure affecting absorption
- Uncontrolled inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
- Myocardial infarction within 6 months before starting therapy, symptomatic congestive heart failure (New York Heart Association > Class II), unstable angina, or unstable cardiac arrhythmia requiring medication
- Breastfeeding at screening or planning pregnancy (self or partner) any time during study
- Any investigational product or investigational medical device within 28 days before cycle 1 day 1
- Concurrent disease or condition that would interfere with study participation or safety, such as the following:
  - Active, clinically significant infection requiring parenteral antimicrobial agent or grade >2 by NCI CTCAE within 14 days before cycle 1 day 1
  - Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorder
  - Nonhealing wound, ulcer, or bone fracture
  - Bone marrow disorder including myelodysplasia

Study treatment

Intrapatient dose escalation was permitted in Part 1 after cycle 1 if a patient demonstrated clinical benefit and the next higher dose was demonstrated to be tolerable. In the event of grade 3–4 toxicity, treatment was interrupted and could be resumed with dose reduction if toxicity resolved to grade ≤1 or returned to baseline within 7 days. The start of any cycle subsequent to cycle 1 could be delayed for up to 28 days for recovery from toxicity (treatment delays exceeding 28 days were considered if agreed upon by the sponsor and investigator).

Study procedures

For Part 1, plasma samples were collected for talazoparib concentration measurements on days 1 and 35 at predose and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, and 10 hours postdose (± 5 minutes), and on days 2, 3, 4, 5, 36, 37, 38, and 39 at approximately the same time (± 1 hour) as dosing on days 1 and 35, and at predose on days 8, 15, 22, and 29. Additional predose samples were collected weekly through cycle 3, and then on day 1 of cycles 4 and 5. Twenty-four hour urine collections for parent drug excretion were performed on days 1 and 35 during cycle 1. For Part 2, more limited plasma pharmacokinetic (PK) sampling was collected. Tumor response was assessed by RECIST (1) at the end of cycles 1, 3, and 5, and every 3 months thereafter, or as clinically indicated. The efficacy variable for patients with nonmeasurable disease was disease-specific tumor marker response. During Part 1, peripheral blood mononuclear cell (PBMC) samples were taken for PARP enzyme activity assessments at baseline, following a single dose of talazoparib on day 1 at 2 and 4 hours postdose, and days 2, 3, 5, and 8. Additional assessments occurred on days 15, 22, and 35 (predose) and at 2, 24, and 96 hours postdose (day 35). In Part 2, PBMC PARP enzyme activity was not assessed.

Pharmacodynamic (PD) analysis

The PBMC samples were collected by lymphopreparation and resuspended in culture medium containing 10% dimethyl sulfoxide (as cryopreservative). Samples were shipped on dry ice and stored at -80º C until analysis. All samples were analyzed using a previously validated and published activity assay using quantitative immunologic detection of poly(ADP-ribose) formation ex vivo (2, 3). To minimize interassay variability, all samples from an individual patient were assayed in one batch; no significant deterioration of PARP inhibition had been observed over the sample storage period (376 days; data not shown). Inhibition of

PBMC PARP activity was estimated by normalizing the measured activity in postdose assessments by the measured activity in the baseline assessment within patients. The percentage inhibition upon multiple dosing of talazoparib within patients was determined by taking the mean of the normalized activities in the predose assessments collected on days 15, 22, and 35 in cycle 1.

The inhibition of PBMC PARP activity as a function of talazoparib dose and talazoparib exposure ($AUC_{0\text{-}24}$ on cycle 1 day 35) was estimated using a maximum inhibitory effect (I_{max}) model.

Inhibition of PBMC PARP activity

The inhibition of PBMC PARP activity as a function of talazoparib dose and talazoparib exposure ($AUC_{0\text{-}24}$ on cycle 1 day 35) was estimated using an I_{max} model shown in equation 1 and equation 2, respectively.

$$\%PARP_{Activity} = A_o\left(1 - \frac{I_{max} * Dose^h}{Dose^h + ID_{50}^h}\right) \quad (1)$$

$$\%PARP_{Activity} = A_o\left(1 - \frac{I_{max} * AUC_{0-24}^h}{AUC_{0-24}^h + IC_{50}}\right) \quad (2)$$

Where A_o is the estimated baseline activity, I_{max} is the estimated maximum activity inhibition, and ID_{50} and IC_{50} are the estimated dose and $AUC_{0\text{-}24}$, respectively, where activity inhibition is half maximal, and h is the hill coefficient. The PK/PD model parameter estimates were obtained using nonlinear least-squares mean in R (R Foundation for Statistical Computing, Vienna, Austria).

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References

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