Phase I, Dose-Escalation, 2-Part Trial of Poly(ADP-Ribose) Polymerase Inhibitor Talazoparib in Patients with Advanced Germline *BRCA1/2* Mutations and Selected Sporadic Cancers

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ABSTRACT

Talazoparib inhibits poly(ADP-ribose) polymerase (PARP) catalytic activity, trapping PARP1 on damaged DNA and causing cell death in *BRCA1/2*-mutated cells. We evaluated talazoparib therapy in this 2-part, phase I, first-in-human trial. Antitumor activity, maximum tolerated dose (MTD), pharmacokinetics, and pharmacodynamics of once-daily talazoparib were determined in an open-label, multicenter, dose-escalation study (NCT01286987). The MTD was 1.0 mg/day, with an elimination half-life of 50 hours. Treatment-related adverse events included fatigue (26/71 patients; 37%) and anemia (25/71 patients; 35%). Grade 3 to 4 adverse events included anemia (17/71 patients; 24%) and thrombocytopenia (13/71 patients; 18%). Sustained PARP inhibition was observed at doses ≥0.60 mg/day. At 1.0 mg/day, confirmed responses were observed in 7/14 (50%) and 5/12 (42%) patients with *BRCA* mutation-associated breast and ovarian cancers, respectively, and in patients with pancreatic and small cell lung cancer. Talazoparib demonstrated single-agent antitumor activity and was well tolerated in patients at the recommended dose of 1.0 mg/day.

SIGNIFICANCE: In this clinical trial, we show that talazoparib has single-agent antitumor activity and a tolerable safety profile. At its recommended phase II dose of 1.0 mg/day, confirmed responses were observed in patients with *BRCA* mutation-associated breast and ovarian cancers and in patients with pancreatic and small cell lung cancer.

INTRODUCTION

The most studied poly(ADP-ribose) polymerase (PARP) enzymes are PARP1 and 2, which play critical roles in DNA damage detection and repair (1, 2), including the repair of single-strand DNA breaks through the base excision repair pathway (3–5). It has been hypothesized that single-strand DNA breaks persist when PARP function is compromised, leading to the creation of double-strand DNA breaks during replication (6); these double-strand DNA breaks are usually repaired by homologous recombination repair (HRR), allowing replication to continue (6). However, loss of PARP activity becomes lethal when HRR is compromised. This phenomenon, known as synthetic lethality, is well established for deleterious mutations of *BRCA1* and *BRCA2* (7–9).

The PARP inhibitor, olaparib, was recently approved for the treatment of advanced ovarian cancer and remains the only approved agent. PARP inhibitors have also demonstrated antitumor activity against other tumor types with DNA repair deficiencies, including breast and prostate cancers (10–13). Talazoparib (also known as MDV3800, BMN 673) is a novel, potent, and selective inhibitor of PARP1/2 that achieves antitumor cell responses and elicits DNA repair markers at notably lower concentrations than earlier generation PARP1/2 inhibitors (14, 15). In addition to inhibiting PARP catalytic activity, talazoparib is currently the most potent PARP1/2 inhibitor *in vitro* at trapping PARP-DNA complexes at sites of single-strand DNA breaks (16). Preclinically, talazoparib has favorable metabolic stability, oral bioavailability, and pharmacokinetics (PK) that support its daily schedule in clinical trials (14).

We conducted a first-in-human, phase I dose escalation (Part 1) trial of talazoparib in patients with advanced solid malignancies and an expansion cohort (Part 2) in patients with tumors predicted to be potentially sensitive to PARP inhibition. These included: tumors harboring germline *BRCA1*/*2* mutations; triple-negative breast cancers; high-grade serous and/or undifferentiated ovarian, fallopian tube, or peritoneal cancers; and castration-resistant prostate and pancreatic cancers. Ewing's sarcoma and small cell lung cancer (SCLC) patients were also studied; the former was based on a 1000-cell line screen demonstrating antitumor activity (17, 18), and the latter was based on SCLC platinum sensitivity, increased PARP1 expression, and sensitivity of SCLC cell lines and animal models to PARP inhibition (19, 20).

RESULTS

Between January 3, 2011, and August 21, 2014, 113 patients with advanced solid tumors were enrolled at a total of six centers: five in the United States and one in the United Kingdom. A total of 110 patients received talazoparib (Table 1). Thirty-nine patients participated in Part 1 and received talazoparib at nine dose levels ranging from 0.025 to 1.1 mg/day (Fig. 1). An additional 71 patients were treated with talazoparib 1.0 mg/day in Part 2. As of the date of database cutoff (March 31, 2015), two patients in Part 1 and five patients in Part 2 continue to be treated (Fig. 1).

Safety

The number of patients per dose level, observed dose-limiting toxicities (DLTs), dose reductions, and median time on study are provided in Table 2. Dose-limiting

thrombocytopenia in cycle 1 occurred in one of six patients at 0.9 mg/day and two of six patients assessable for DLT at 1.1 mg/day. The patient treated at 0.9 mg/day experienced grade 3 thrombocytopenia with grade 3 anemia. Of the two patients treated at 1.1 mg/day, both experienced grade 3 thrombocytopenia; for one of these patients it became grade 4 thrombocytopenia. All DLTs resolved after temporary interruption of study drug; no hemorrhage was noted. As two patients experienced a DLT at the 1.1 mg/day dose level, an interim dose of 1.0 mg/day was investigated. No DLTs were observed at this dose level in a group of six assessable patients. This dose was therefore determined to be the maximum tolerated dose (MTD) and the recommended dose for Part 2.

In Part 2, 71 patients received talazoparib at 1.0 mg/day via continuous daily dosing. The median relative dose intensity was high at 97.2% and the dose was well tolerated. Table 2 presents the most common toxicities at this dose related to the study drug, including fatigue (37%), anemia (35%), nausea (32%), thrombocytopenia (21%), alopecia (20%), and neutropenia (15%). Grade 3 or 4 adverse events (AEs) assessed by investigator as related were reported in 32 (45%) patients, with the most frequent being anemia (23%), thrombocytopenia (18%), and neutropenia (10%).

Of the 77 patients receiving the 1 mg/day dose, 26 patients (34%) reported at least one dose reduction, the majority of whom (20 patients) had reductions due to an AE such as anemia, thrombocytopenia, and neutropenia. Although transient dose holidays were needed as a result of these AEs, no patients permanently withdrew from treatment because of them in either Part 1 or Part 2 of the trial.

There were eight deaths associated with an AE during the study, none of which were considered to be related to study treatment. Two of the deaths occurred in patients with breast cancer enrolled in Part 1 at the entry dose of 1.1 mg/day talazoparib (both related to disease progression). Six of the deaths occurred in patients in Part 2 at 1.0 mg/day talazoparib (two patients with pancreatic cancer, both from disease progression; two patients with Ewing's sarcoma, one from dyspnea and the other from respiratory failure; and two patients with SCLC, one from hypoxia secondary to lung metastases and the other from lung infection).

Pharmacokinetics

Mean talazoparib plasma concentration-time profiles following single and multiple doses of talazoparib are provided in Fig. 2 A-D. Talazoparib PK parameters resulting from the analysis of the plasma concentration-time profiles are provided in Table 3.

Talazoparib demonstrated rapid absorption, with maximum plasma concentration (C_{max}) generally reached within 2 hours after all evaluated doses and following both single and multiple daily dosing. Steady-state plasma concentrations were reached by 2 weeks of daily dosing across all doses evaluated. Talazoparib was well distributed into tissue compartments, with apparent volume of distribution (V_z/F) estimates well in excess of the volume of the systemic circulatory space. Plasma elimination followed biphasic kinetics with a long terminal half-life ($t_{1/2}$). Linear elimination across dose levels was apparent following both single and multiple daily dosing as evidenced by parallel terminal phases of the log-linear profiles and similar apparent oral clearance (CL/F) estimates across dose levels. At the MTD dose of 1.0 mg/day, $t_{1/2}$ is approximately 2 days and mean accumulation ratio is 2.4-fold at steady-state.

Plasma concentrations, C_{max}, and area under the plasma concentration-time curve (AUC) estimates increased approximately with doses ranging from 0.025 to 1.1 mg following multiple daily dosing as shown in Fig. 2 E-H. Estimates (95% confidence interval [CI]) of the dose proportionality parameter, β, for C_{max} and AUC from 0 to 24 hours (AUC_{0-24}) following multiple daily doses of talazoparib were 1.11 (1.01–1.20) and 0.95 (0.84–1.05), respectively.

Results for urinary elimination of the parent compound suggest linear urinary elimination kinetics after daily talazoparib dosing between the 0.025 and 1.1 mg dose levels. Following single doses in Part 1, mean values for the amount of the analyte excreted in urine from 0 to 24 hours (Ae_{0-24}) and the fraction of urine excretion from 0 to 24 hours (Fe_{0-24}) generally increased with dose, and average renal clearance from time 0 to 24 hours postdose (ARC_{0-24}) values were similar across dose levels. Following multiple daily doses in Part 1, Ae_{0-24} increased with increasing dose, whereas mean Fe_{0-24} and ARC_{0-24} values were generally similar across the 0.025 and 1.1 mg/day dose levels.

Pharmacodynamics

The mean percentage baseline peripheral blood mononuclear cell (PBMC) PARP activities with multiple-dose talazoparib by dose level are provided in Table 3 and Supplementary Fig. S1. Overall, PBMC PARP activity decreased with talazoparib dose across the evaluated dose range.

The dose- and concentration-response relationships between talazoparib and PBMC PARP activity are shown in Fig. 2 E-H, and maximum inhibitory effect model parameter estimates are provided in Supplementary Table S1. In the exposure-

response curve, an estimated half maximal inhibitory concentration of AUC_{0-24} was 19,000 pg.h/mL.

Efficacy

In 14 patients with breast cancer (all with deleterious *BRCA1*/*2* mutations) treated with talazoparib at 1.0 mg/day, the objective response rate (ORR) was 50% and included one complete response (CR; Table 4). Five patients had stable disease (SD) lasting at least 24 weeks, resulting in a clinical benefit rate (CBR) of 86% for at least 24 weeks. Median progression-free survival (PFS) was 34.6 weeks (95% CI, 27.1–54.0) (Table 4). For the total of 18 patients with breast cancer with deleterious *BRCA1*/*BRCA2* mutations treated at any talazoparib dose level, the ORR and CBR were higher in patients whose tumors carried the *BRCA2* mutation (ORR, 55%, 6/11 patients; CBR, 91%, 10/11 patients) compared with those who had the *BRCA1* mutation (ORR, 38%, 3/8 patients; CBR, 50%, 4/8 patients; percentage change in target lesion size summarized in Fig. 3A). Of note, one patient had aberrations in both *BRCA1* and *BRCA2*, although the *BRCA2* aberration detected may not be deleterious (Y3098X). Interestingly, in the *BRCA*-mutated breast cancer patients, higher antitumor activity was observed in patients with non–triple-negative breast cancer (n = 9) than in those with triple-negative disease (n = 9) (CBR, 89% *vs.* 56% ≥24 weeks; median PFS, 38.3 weeks [95% CI, 2.6–67.4] *vs.* 20.4 weeks [95% CI, 3.1–36.1]). Six of the 18 *BRCA*-mutated breast cancer patients had received prior platinum therapy, of whom two had an objective response.

In 12 patients with ovarian cancer with deleterious germline *BRCA1/2* mutations with measurable disease treated with talazoparib 1.0 mg/day, ORR and CBR lasting at least 24 weeks equaled 42% and 67%, respectively, with a median PFS of 36.4

241 weeks (Table 4). For all patients with *BRCA*-mutated ovarian cancer treated at any
242 talazoparib dose level with measurable disease (*n* = 25), ORR and CBR lasting at
243 least 24 weeks was 48% (including one CR) and 76%, respectively (percentage
244 change in target lesion size is summarized in Fig. 3B). All 25 patients had received
245 prior platinum-based chemotherapy; the ORR in platinum-sensitive patients was
246 55% (11/20 patients) compared with 20% (1/5 patients) in platinum-resistant
247 patients.

248 All 23 SCLC patients were enrolled in Part 2 and treated with 1.0 mg/day. Median
249 number of prior regimens was 1, ranging from 0 to 2. Two patients had a partial
250 response (PR) (ORR, 9%, with duration of response, 12.0 and 15.3 weeks,
251 respectively), and a further four had SD lasting at least 16 weeks (CBR, 26% ≥16
252 weeks; Table 4). For the two patients with an objective response, both had had an
253 objective response to the last prior platinum therapy, with a platinum-free interval of
254 6 months or less. Median PFS for this group was 11.1 weeks (95% CI, 4.3–13.0).

255 Of the 13 patients with pancreatic cancer from Part 1 and Part 2, four had clinical
256 benefit (CBR, 31% ≥16 weeks): two patients had a PR, one with *BRCA2* mutation,
257 the other with a *PALB2* mutation (Table 4). For patients with Ewing's sarcoma, no
258 objective response was observed, and the CBR (SD ≥16 weeks) was 23%.

259 For the seven patients currently receiving talazoparib on the study as of the data
260 cutoff of March 31, 2015, four have ovarian cancer (continuing on study for 27.4,
261 28.1, 31.5, and 36.6 months, and one patient each has breast, pancreatic, and
262 prostate cancer (24.2, 22.8, and 8.4 months, respectively). The starting dose for
263 these patients ranged between 0.9 and 1.0 mg/day; current dose is between 0.5 and
264 1.0 mg/day.

DISCUSSION

Talazoparib is a potent oral PARP1/2 inhibitor that has equivalent catalytic activity to olaparib and rucaparib, but is superior in trapping PARP-DNA at the site of DNA damage by comparison (16). This first-in-human study demonstrated that talazoparib results in single-agent activity in patients harboring germline deleterious *BRCA* mutations or whose tumors harbor other mutations sensitive to PARP inhibition. The clinical activity observed with talazoparib suggests that targeting of PARP1/2 may also be an effective strategy for those patients whose tumors harbor other genomic abnormalities involved in DNA repair mechanisms (13).

Talazoparib was well tolerated overall. The primary toxicity of talazoparib was hematological, with transient and reversible cytopenias (thrombocytopenia, neutropenia, and anemia), primarily managed with drug interruption and/or dose reduction and otherwise routine medical intervention; transfusions were uncommon. All episodes of DLT involved brief thrombocytopenia without hemorrhage. Nonhematological toxic effects were mild in severity and manageable. The relative dose intensity was high at 97.2% and overall the dose was well tolerated. Furthermore, no patients permanently withdrew from talazoparib treatment because of toxicity, in either Part 1 or 2 of this study.

Talazoparib demonstrated favorable PK properties with good oral bioavailability, rapid absorption, and dose proportional increases in total exposure (AUC) over a wide dose range (0.025–1.1 mg/day). Steady-state was reached approximately 2 weeks after initiation of daily dosing. Linear urinary elimination kinetics were reported with daily dosing. At the recommended phase 2 dose of 1.0 mg/day, the terminal

289 half-life was approximately 2 days upon multiple dosing; trough talazoparib plasma
290 concentrations were maintained above 10 nM, suggesting that systemic
291 concentrations of talazoparib are sufficient to inhibit PARP activity.

292 In pharmacodynamic (PD) testing, talazoparib demonstrated PARP inhibition in
293 PBMCs over a relatively wide range of doses. For doses at and above 0.6 mg/day,
294 PARP activity was consistently inhibited in all patients evaluated. Pharmacodynamic
295 results suggest that effective PARP inhibition could still be achieved at reduced dose
296 levels.

297 Talazoparib demonstrated promising antitumor activity in patients with heavily
298 pretreated breast and ovarian cancers associated with deleterious germline
299 *BRCA1*/*2* mutations. Single-agent activity in patients with advanced breast cancer
300 (including patients with triple-negative disease) equaled 50% (ORR) and 86% (CBR).
301 Similarly, in the 12 *BRCA*-mutated ovarian cancer patients treated with 1.0 mg/day of
302 talazoparib, ORR and CBR equaled 42% and 67%, respectively.

303 Of note, one responding patient with pancreatic cancer harbored a *PALB2* mutation
304 (21); as this mutation is known to recruit *BRCA2* and *RAD51* to DNA breaks, such
305 findings support a trial in a broader population (those with additional DNA repair
306 deficiencies as opposed to *BRCA* mutations only), potentially expanding applications
307 for PARP inhibitor therapy.

308 In conclusion, the findings from this study demonstrate the effectiveness of single-
309 agent talazoparib for treatment of patients with and without germline *BRCA1/2*
310 mutations in ovarian, breast, small cell lung, and pancreatic cancers. Talazoparib
311 has a tolerable safety profile in multiple patients seen over a treatment period
312 exceeding 2 years. The PK properties of talazoparib support once-daily dosing. Data

313 from this phase 1 trial supports a role for talazoparib in treatment of patients with
314 advanced tumors (inherited and sporadic cancers with DNA repair deficiencies).
315 Talazoparib is currently undergoing further clinical investigation against multiple
316 tumor types, including a phase 3 trial in patients with metastatic breast cancer with a
317 deleterious *BRCA1/2* mutation.

318

319 **METHODS**

320 **Study Design and Participants**

321 We undertook a phase I study of talazoparib in patients with advanced solid tumors
322 and either germline *BRCA1/2* mutations or a strong preclinical rationale for use of a
323 PARP inhibitor. Eligible patients were aged 18 years or older and had: histologically
324 or cytologically documented unresectable, locally advanced, or metastatic solid
325 tumors not suitable for established therapy or for which standard therapy had failed;
326 Eastern Cooperative Oncology Group Performance Status of 0 or 1; and adequate
327 hematological and liver function.

328 Patients enrolled in Part 1 (dose escalation) had tumors known to harbor DNA repair
329 deficiencies (Supplementary Methods); provision of documentation (genomic or
330 immunohistochemistry) was not required. Enrollment in Part 2 was restricted to
331 patients with selected tumors with confirmed *BRCA1/2* germline pathogenic or
332 deleterious mutations by BRACAnalysis® (Myriad Genetics, Salt Lake City, Utah) or
333 local laboratory evaluation (ovarian or peritoneal, breast, prostate, or pancreatic
334 cancers), patients with DNA repair deficiency, or patients with SCLC or Ewing's
335 sarcoma (Supplementary Methods). Patient eligibility, including a full list of exclusion
336 criteria is provided in the Supplementary Methods.

The study was conducted in accordance with the protocol, good clinical practice standards, and the Declaration of Helsinki and the International Conference on Harmonisation. The appropriate institutional review board or ethics committee at each participating institution approved the protocol. All enrolled patients provided written informed consent before undergoing study specific procedures.

Study Treatment

For Part 1, fasted patients received a single dose of talazoparib at the start of the study and then underwent PK and PD assessments 1 week later. Following assessments, patients received talazoparib once daily, continuously for 28-days, again followed by a 1-week break from treatment (defined as cycle 1) to assess PK and PD. Dosing was continuous thereafter without breaks except as needed for toxicity. A standard 3+3 design was used for dose escalation (22), with a starting talazoparib dose of 0.025 mg/day. Dose doubling occurred provided toxicities were Common Terminology Criteria for Adverse Events grade 1 or less during cycle 1; dose escalations were limited to 25%–50% once grade 2 drug-related toxicities were observed (25% for grade 3 drug-related toxicity). For each cohort, the first patient was observed for 15 days prior to additional patient enrollment. To be eligible for DLT assessment, a patient must have received at least 24 of the planned 28 doses of talazoparib between days 8 and 35. A DLT was defined as any of the following events occurring during cycle 1: grade 4 neutropenia associated with grade 2 or greater infection or lasting at least 5 days; grade 4 thrombocytopenia (or grade 3 with either hemorrhage or dose interruption for ≥5 days); any AE of grade 3 or greater considered related to talazoparib, except a nonhematologic asymptomatic grade 3 laboratory AE, grade 3 nausea, vomiting, and/or diarrhea medically managed to grade 2 or less within 24 hours, or grade 3 fatigue that improved to

grade 2 or less in no more than 5 days (additional information provided in the Supplementary Methods).

Enrollment in Part 2 proceeded once the MTD was determined. Patients received talazoparib at the MTD of 1.0 mg/day starting from cycle 1, day 1 (28-day cycles). Participation in the study could be discontinued at any time at the discretion of the investigator and in accordance with clinical judgment.

Adverse events were recorded from the time of first dose of talazoparib until 30 days after the last dose.

Study Procedures

At screening, patients underwent physical examination (with vital signs and performance status assessment). Safety laboratory tests (complete blood count with differential and platelets, chemistry) were obtained weekly; coagulation and urinalysis were obtained weekly (cycle 1) and at the beginning of each cycle thereafter. Hematology evaluations were conducted more frequently upon observation of grade 2 or greater neutropenia or thrombocytopenia. Further details of study procedures are given in the Supplementary Methods.

Pharmacokinetic Analysis

Plasma and urine samples were assayed for talazoparib concentrations using a validated high-performance liquid chromatography with tandem mass spectrometry detection method. For plasma, the lower limit of quantitation (LLOQ) was 5.0 pg/mL; for urine, the LLOQ was 25.0 pg/mL. Talazoparib PK parameters (following single and multiple daily dosing) were obtained using standard noncompartmental analysis methods in Phoenix® WinNonlin® Version 6.4 (Certara L.P., Princeton, New Jersey). Pharmacokinetic parameters estimated included: C_{max}; time to C_{max}; AUC_{0-24}, AUC

from time 0 to time of last quantifiable concentration, and AUC from time 0 extrapolated to infinity; CL/F; V_z/F; and $t_{1/2}$. The multiple-dose PK parameters also estimated included minimum plasma concentration and CL/F at steady-state. Dose proportionality following single and multiple daily dosing of talazoparib was assessed using a power model approach (23).

Pharmacodynamic Analysis

See the Supplementary Methods for details.

Statistical Analysis

The primary objective in Part 1 of this study was to determine the MTD and recommended dose of daily oral talazoparib; secondary objectives included safety, PK, and PD profiles. For Part 2, efficacy parameters in the selected tumor types were investigated per a prespecified analysis based on Response Evaluation Criteria In Solid Tumors version 1.1 through investigator assessment of lesion measurements, including ORR (in patients with measurable disease) or disease-specific changes in tumor markers using standard definitions (24–26). The number and percentage of patients achieving a response were summarized with an exact 95% CI calculated using the Clopper-Pearson method. The PFS was summarized using the Kaplan-Meier method. The data cutoff was March 31, 2015. SAS® Analytics Software (version 9.1; SAS Institute, Inc., Cary, North Carolina) was used for data analyses.

Role of the Funding Source

Medivation, Inc., has assumed responsibility for talazoparib effective October 6, 2015, and was involved in the trial data analysis and interpretation; Medivation was acquired by Pfizer, Inc., in September 2016. BioMarin Pharmaceutical, Inc., was

involved in the study design, data collection, analysis, and interpretation. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

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References

1. Rouleau M, Patel A, Hendzel MJ, Kaufmann SH, Poirier GG. PARP inhibition: PARP1 and beyond. Nat Rev Cancer 2010;10:293–301.

2. Satoh MS, Lindahl T. Role of poly(ADP-ribose) formation in DNA repair. Nature 1992;356:356–58.

3. Ame JC, Rolli V, Schreiber V, Niedergang C, Apiou F, Decker P, et al. PARP-2, a novel mammalian DNA damage-dependent poly(ADP-ribose) polymerase. J Biol Chem 1999;274:17860–68.

4. Shall S, de Murcia G. Poly(ADP-ribose) polymerase-1: what have we learned from the deficient mouse model? Mutat Res 2000;460:1–15.

5. Dantzer F, Schreiber V, Niedergang C, Trucco C, Flatter E, De La Rubia G, et al. Involvement of poly(ADP-ribose) polymerase in base excision repair. Biochimie 1999;81:69–75.

6. De Vos M, Schreiber V, Dantzer F. The diverse roles and clinical relevance of PARPs in DNA damage repair: current state of the art. Biochem Pharmacol 2012;84:137–46.

7. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy. Nature 2005;434:917–21.

8. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005;434:913–17.

449 9. Lord CJ, Tutt AN, Ashworth A. Synthetic lethality and cancer therapy: lessons
450 learned from the development of PARP inhibitors. Annu Rev Med 2015;66:455–70.

451 10. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of
452 poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. N Engl J Med
453 2009;361:123–34.

454 11. Fong PC, Yap TA, Boss DS, Carden CP, Mergui-Roelvink M, et al. Poly(ADP)-
455 ribose polymerase inhibition: frequent durable responses in *BRCA* carrier ovarian
456 cancer correlating with platinum-free interval. J Clin Oncol 2010;28:2512–19.

457 12. Lee JM, Ledermann JA, Kohn EC. PARP Inhibitors for *BRCA1/2* mutation-
458 associated and *BRCA*-like malignancies. Ann Oncol 2014;25:32–40.

459 13. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al.
460 DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med
461 2015;373:1697–708.

462 14. Shen Y, Rehman FL, Feng Y, Boshuizen J, Bajrami I, Elliott R, et al. BMN 673, a
463 novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with
464 DNA repair deficiency. Clin Cancer Res 2013;19:5003–15.

465 15. Aoyagi-Scharber M, Gardberg AS, Yip BK, Wang B, Shen Y, Fitzpatrick PA.
466 Structural basis for the inhibition of poly(ADP-ribose) polymerases 1 and 2 by BMN
467 673, a potent inhibitor derived from dihydropyridophthalazinone. Acta Crystallogr F
468 Struct Biol Commun 2014;70:1143–49.

469 16. Murai J, Huang SY, Renaud A, Zhang Y, Ji J, Takeda S, et al. Stereospecific
470 PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol
471 Cancer Ther 2014;13:433–43.

17. Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, et al. Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature 2012;483:570–75.

18. Lee HJ, Yoon C, Schmidt B, Park DJ, Zhang AY, Erkizan HV, et al. Combining PARP-1 inhibition and radiation in Ewing sarcoma results in lethal DNA damage. Mol Cancer Ther 2013;12:2591–600.

19. Byers LA, Wang J, Nilsson MB, Fujimoto J, Saintigny P, Yordy J, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov 2012;2:798–811.

20. Cardnell RJ, Feng Y, Diao L, Fan YH, Masrorpour F, Wang J, et al. Proteomic markers of DNA repair and PI3K pathway activation predict response to the PARP inhibitor BMN 673 in small cell lung cancer. Clin Cancer Res 2013;19:6322–28.

21. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature 2015;518:495–501.

22. Simon R, Freidlin B, Rubinstein L, Arbuck SG, Collins J, Christian MC. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst 1997;89:1138–47.

23. Gough K, Hutchison M, Keene O, Byrom B, Ellis S, Lacey L, et al. Assessment of dose proportionality: report from the statisticians in the pharmaceutical industry/pharmacokinetics UK joint working party. Drug Inf J 1995;29:1039–48.

24. Rustin GJ, Quinn M, Thigpen T, du Bois A, Pujade-Lauraine E, Jakobsen A, et al. New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst 2004;96:487–88.

496 25. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al.
497 Design and end points of clinical trials for patients with progressive prostate cancer
498 and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical
499 Trials Working Group. J Clin Oncol 2008;26:1148–59.

500 26. Melnik MK, Webb CP, Richardson PJ, Luttenton CR, Campbell AD, Monroe TJ,
501 et al. Phase II trial to evaluate gemcitabine and etoposide for locally advanced or
502 metastatic pancreatic cancer. Mol Cancer Ther 2010;9:2423–29.

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504 **TABLES**

505 **Table 1.** Demographics and baseline clinical characteristics

Demographic parameter	**Dose escalation (part 1) (*n* = 39)**	**Dose expansion (part 2) (*n* = 71)**	**Overall (*N* = 110)**
Median age, years (range)	58.0 (19–81)	57.0 (18–88)	57.0 (18–88)
Male, *n* (%)	6 (15.4)	28 (39.4)	34 (30.9)
ECOG Performance Status, *n* (%)			
0	23 (59.0)	37 (52.1)	60 (54.5)
1	16 (41.0)	34 (47.9)	50 (45.5)
Tumor type, *n* (%)			
Breast	8 (20.5)	12 (16.9)	20 (18.2)
Ovarian/peritoneal	23 (59.0)	11 (15.5)	34 (30.9)
Prostate	1 (2.6)	3 (4.2)	4 (3.6)
Pancreatic	3 (7.7)	10 (14.1)	13 (11.8)
Ewing's sarcoma	2 (5.1)	12 (16.9)	14 (12.7)
Small cell lung cancer	0	23 (32.4)	23 (20.9)
Colorectal cancer	2 (5.1)	0	2 (1.8)
Deleterious mutation, *n* (%)			
g*BRCA1*	16 (41.0)	13 (18.3)	29 (26.4)
g*BRCA2*	7 (17.9)	20 (28.2)	27 (24.5)
g*BRCA1/2*	1 (2.6)	2 (2.8)	3 (2.7)
Median prior chemotherapy regimens, *n* (range)	4.0 (1.0–13.0)	2.0 (0.0–6.0)	2.5 (0.0–13.0)
Median prior platinum regimens, *n* (range)	2.0 (0.0–4.0)	1.0 (0.0–4.0)	1.0 (0.0–4.0)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; g*BRCA*, germline *BRCA* mutated.			

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508 **Table 2.** Part 1 dose escalation schema, DLTs, dose reductions, and common
509 adverse events (>15%) or grade 3–4 adverse event (>4%) assessed by investigator
510 as related at the recommended dose

Dose level	**Patients (*n* = 39)**	**DLTs in first cycle**		**Dose reductions (any cycle)**	**Number of treatment days**
		Number	**Description**	**Number**	**Median (range)**
0.025 mg	3	0	-	2	35 (35–98)
0.05 mg	3	0	-	2	99 (34–205)
0.10 mg	3	0	-	2	119 (65– 253)
0.20 mg	3	0	-	2	281 (35 –427)
0.40 mg	3	0	-	1	226 (97–268)
0.60 mg	6	0	-	4	185 (58–289)
0.90 mg	6	1	Grade 3 TCP	5	261 (30–1114)
1.00 mg	6	0	-	5	214 (84–960)
1.10 mg	6[a]	2	Grade 3–4 TCP	4	60 (14–196)
Adverse event				**All grade (*n* = 71)**	**Grade 3-4 (*n* = 71)**
Any treatment-emergent adverse event, *n* (%)				55 (77)	32 (45)
Blood and lymphatic system disorders, *n* (%)				40 (56)	30 (42)
Anemia				25 (35)	16 (23)
TCP				15 (21)	13 (18)
Neutropenia				11 (15)	7 (10)
Gastrointestinal disorders, *n* (%)				27 (38)	-
Nausea				23 (32)	-
General disorders and administration site conditions, *n* (%)				27 (38)	2 (3)
Fatigue				26 (37)	2 (3)
Skin and subcutaneous tissue disorders, *n* (%)				19 (27)	-
Alopecia				14 (20)	-

Abbreviations: DLT, dose-limiting toxicity; TCP, thrombocytopenia.

[a]One patient discontinued from the trial on study day 21 for progressive disease, having received only 8 days of continuous dosing.

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513 **Table 3.** Pharmacokinetic parameters and PARP inhibition following single and multiple daily dosing

	Single talazoparib dose, mg								
PK parameter	**0.025 (*n* = 3)**	**0.05 (*n* = 3)**	**0.1 (*n* = 3)**	**0.2 (*n* = 3)**	**0.4 (*n* = 3)**	**0.6 (*n* = 6)[a]**	**0.9 (*n* = 6)[b]**	**1.0 (*n* = 5)**	**1.1 (*n* = 7)[c]**
T_{max}, median (min, max), h	7.92 (1.95, 9.95)	1.00 (0.80, 1.02)	1.02 (1.00, 3.98)	1.03 (1.00, 2.32)	2.03 (0.75, 2.95)	0.835 (0.75, 1.95)	2.00 (1.02, 9.98)	1.03 (0.73, 2.07)	1.00 (0.73, 2.05)
C_{max}, mean (SD), pg/mL	60.0 (15.9)	79.7 (7.50)	214 (50.9)	788 (369)	1,830 (699)	4,100 (1,400)	6,100 (3,060)	10,600 (4,220)	13,200 (3,220)
AUC_{0-24}, mean (SD), pg·h/mL	952 (386)	1,160 (166)	3,160 (1,270)	9,130 (3,540)	13,500 (5,200)	37,900 (12,900)	58,200 (24,300)	85,100 (29,100)	91,600 (31,800)
AUC_{0-t}, mean (SD), pg·h/mL	3,600 (1,360)	5,340 (1,960)	16,600 (5320)	39,300 (11,700)	43,700 (15,000)	97,900 (30,000)	160,000 (66,100)	182,000 (62,400)	201,000 (93,400)
$AUC_{0-\infty}$, mean (SD), pg·h/mL	5,330 (1,840)	8,320 (1,960)	37,600 (6,620)	92,700 (48,500)	60,100 (15,900)	120,000 (26,000)	188,000 (85,700)	200,000 (64,000)	235,000 (111,000)
$t_{1/2}$, mean (SD), h	100 (11.9)	129 (42.6)	229 (158)	212 (126)	102 (27.2)	58.6 (17.3)	60.4 (10.9)	52.9 (13.4)	71.0 (20.6)
CL/F, mean (SD), L/h	5.17 (2.10)	6.27 (1.66)	2.72 (0.532)	2.61 (1.35)	6.95 (1.71)	5.19 (0.99)	5.49 (2.08)	5.39 (1.59)	5.32 (1.64)
V_z/F, mean (SD), L	756 (351)	1240 (742)	839 (487)	678 (217)	1050 (431)	441 (143)	468 (169)	415 (170)	549 (232)
	Multiple daily talazoparib dosing, mg/day								
	0.025 (*n* = 3)[d,e]	**0.05 (*n* = 2)**	**0.1 (*n* = 2)[f]**	**0.2 (*n* = 3)**	**0.4 (*n* = 3)**	**0.6 (*n* = 6)[g]**	**0.9 (*n* = 5)[h]**	**1.0 (*n* = 6)**	**1.1 (*n* = 4)[i]**

T_{max}, median (min, max), h	1.02 (0.58, 3.98)	5.43 (0.77, 10.1)	0.76 (0.75, 0.82)	1.97 (1.00, 3.02)	0.98 (0.75, 2.00)	1.04 (0.73, 5.98)	1.02 (0.97, 2.07)	1.02 (0.75, 2.00)	1.48 (0.98, 2.00)
C_{max}, mean (SD), pg/mL	300 (78.8)	615 (74.2)	1,880 (332)	5,620 (3,530)	6,560 (1,500)	11,300 (3,230)	15,400 (1,540)	21,000 (7,990)	23,400 (4,810)
AUC_{0-24}, mean (SD), pg·h/mL	3,960 (759)	9,770 (2,440)	30,000 (4,490)	83,100 (49,300)	67,300 (22,600)	119,000 (19,900)	157,000 (24,500)	202,000 (54,000)	188,000 (29,200)
$t_{1/2}$, mean (SD), h	107 (84.2)	132 (12.3)	98.2 (4.83)	50.9 (19.1)	90.7 (32.7)	63.7 (12.7)	71.0 (14.5)	50.0 (16.6)	52.8 (23.2)
CL_{ss}/F, mean (SD), L/h	6.43 (1.23)	5.28 (1.32)	3.37 (0.502)	3.12 (1.91)	6.40 (2.07)	5.15 (0.897)	5.86 (0.951)	5.24 (1.39)	5.96 (0.837)
V_z/F, mean (SD), L	1,070 (971)	1,020 (345)	475 (47.8)	264 (249)	818 (326)	477 (136)	604 (169)	373 (144)	472 (254)
C_{min}, mean (SD), pg/mL	169 (58.0)	299 (133)	1,020 (107)	2,880 (1,710)	2,230 (957)	3,470 (1,050)	3,180 (802)	3,720 (1,590)	2,910 (803)
	PARP activity, % baseline								
	0.025 (*n* = 3)	**0.05 (*n* = 3)**	**0.1 (*n* = 3)**	**0.2 (*n* = 3)**	**0.4 (*n* = 3)**	**0.6 (*n* = 4)**	**0.9 (*n* = 4)**	**1.0 (*n* = 4)**	**1.1 (*n* = 2)**
PARP activity, mean (SD)	172 (206)	141 (52.5)	102 (98.0)	14.7 (5.04)	111 (96.5)	24.7 (8.19)	34.7 (27.4)	21.1 (14.9)	16.3 (5.63)

Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve (AUC) from 0 to 24 h; $AUC_{0-\infty}$, AUC from time 0 extrapolated to infinity; AUC_{0-t}, AUC from time 0 to last quantifiable concentration; CL/F, apparent oral clearance; CL_{ss}/F, CL/F at steady-state; C_{max}, maximum plasma concentration; PARP, poly(ADP-ribose) polymerase; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, terminal half-life; T_{max}, time to C_{max}; V_z/F, apparent volume of distribution.

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515 **Table 4.** Clinical response rate (RECIST) by cancer type in patients treated with

516 talazoparib 1.0 mg/day (recommended phase 2 dose)

Response	Breast[a] (*n* = 14)	Ovarian/ peritoneal[a] (*n* = 12)	SCLC (*n* = 23)	Pancreatic (*n* = 10)	Ewing's sarcoma (*n* = 13)
ORR,%	50.0	41.7	8.7	20.0	0
CR, *n*	1	1	0	0	0
PR, *n*	6	4	2	2	0
SD, *n*	5[b]	3[b]	4[c]	1[c]	3[c]
CBR,%[b,d]	85.7	66.7	26.1	30.0	23.1
Median PFS, weeks	34.6	36.4[§]	11.1	ND	ND

Abbreviations: CBR, clinical benefit rate; CR, complete response; ND, not determined; ORR, objective response rate; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SCLC, small cell lung cancer; SD, stable disease.

[a]Patients had *BRCA1/2* mutation.

[b]Clinical benefit = CR + PR + SD ≥24 weeks for breast and ovarian cancers.

[c]Analysis on 14 patients, as two patients who did not have measurable disease at baseline were included in the PFS analysis but not in the response analysis.

[d]Clinical benefit = CR + PR + SD ≥16 weeks for SCLC, pancreatic cancer, Ewing's sarcoma.

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FIGURE LEGENDS

Figure 1. Patient enrollment and disposition. Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Figure 2. Pharmacokinetic and pharmacodynamic features of talazoparib. **A-D,** mean concentration-time profiles of talazoparib. Linear mean talazoparib plasma concentration-time profiles over the initial 24 hours postdose and log-linear mean talazoparib plasma concentration-time profilers over the complete sampling interval following: **A, B,** single doses of talazoparib; **C, D,** multiple daily doses of talazoparib. **E-H,** dose proportionality of talazoparib pharmacokinetics and dose-response and exposure-response relationships between talazoparib and PBMC PARP activity. **E,** plasma C_{max} following multiple daily doses ranging from 0.025 to 1.1 mg. **F,** AUC_{0-24} following multiple daily doses ranging from 0.025 to 1.1 mg. Filled circles represent the mean value at each dose level and error bars represent the standard deviations. Solid line represents the power model fit through the data. **G,** dose-response relationship between talazoparib and PBMC PARP activity. **H,** exposure-response relationship between talazoparib and PBMC PARP activity. Percentage baseline PBMC PARP activity defined as the mean of the predose PARP activity assessments during the multiple dosing assessment phase (i.e., predose assessments on days 15, 22, and 35 of cycle 1). Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve from 0 to 24 h; C_{max}, maximum plasma concentration; IC_{50}, half maximal inhibitory concentration; ID_{50}, inhibitory dose 50%; PARP, poly(ADP-ribose) polymerase; PBMC, peripheral blood mononuclear cells.

Figure 3. Percentage change in target lesion for patients undergoing treatment with talazoparib who have: **A,** g*BRCA* breast cancer; **B,** g*BRCA* ovarian cancer. Positive values indicate tumor growth, negative values indicate tumor reduction, and the dashed line represents the definition of partial response from Response Evaluation Criteria In Solid Tumors guidelines. Abbreviations: g*BRCA*, germline *BRCA* mutated; SLD, sum of longest diameter.

Figure 1