Received: 5 August 2022 | Revised: 15 December 2022 | Accepted: 15 December 2022

DOI: 10.1002/cncr.34662

ORIGINAL ARTICLE

A phase 1 dose-escalation study of the poly(ADP-ribose) polymerase inhibitor senaparib in Australian patients with advanced solid tumors

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Funding information
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Abstract

Background: Senaparib is a novel, selective poly(ADP-ribose) polymerase-1/2 inhibitor with strong antitumor activity in preclinical studies. This first-in-human, phase 1, dose-escalation study examined the safety and preliminary efficacy of senaparib in patients with advanced solid tumors.

Methods: Patients with advanced solid tumors were enrolled from three centers in Australia, using a conventional *3 + 3* design. Dose-escalation cohorts continued until the maximum tolerated dose or a recommended phase 2 dose was determined. Patients received one dose of oral senaparib and, if no dose-limiting toxicity occurred within 7 days, they received senaparib once daily in 3-week cycles. The primary end points were safety and tolerability.

Results: Thirty-nine patients were enrolled at 10 dose levels ranging from 2 to 150 mg. No dose-limiting toxicities were observed in any cohort. Most treatment-emergent adverse events were grade 1–2 (91%). Seven patients (17.9%) reported hematologic treatment-emergent adverse events. Treatment-related adverse events occurred in eight patients (20.5%), and the most frequent was nausea (7.7%). Two deaths were reported after the end of study treatment, one of which was considered a complication from senaparib-related bone marrow failure. Pharmacokinetic analysis indicated that senaparib the accumulation index was 1.06–1.67, and absorption saturation was 80–150 mg daily. In 22 patients with evaluable disease, the overall response rate was 13.6%, and the disease control rate was 81.8%. The overall response rate was 33.3% for the BRCA mutation-positive subgroup and 6.3% for the nonmutated subgroup.

Conclusions: Senaparib was well tolerated in Australian patients with advanced solid tumors, with encouraging signals of antitumor activity. The recommended phase 2 dose for senaparib was determined to be 100 mg daily.
ClinicalTrials.gov ID: NCT03507543.

KEYWORDS
Australia, BRCA mutation, PARP inhibitor, recommended phase 2 dose, senaparib, solid tumors

INTRODUCTION

Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPis) are a class of anticancer drugs developed based on the theory of synthetic lethality.[1–3] The PARP enzymes, and PARP1 in particular, are critical for the maintenance of genetic stability by repair of DNA damage, such as single-strand breaks and double-strand breaks.[2–4] PARP1 acts by binding to damaged DNA at the site of single-strand breaks, inducing PARylation and the recruitment of DNA-repair effectors; upon completion of the repair, the enzyme is released.[2,3] PARPis trap PARP onto the chromatin at the damage site, preventing repair, leading to stalling of the replication fork and subsequent conversion of single-strand breaks to one-sided double-strand breaks.[2,5–7] In healthy cells, double-strand breaks are generally repaired through the high-fidelity homologous recombination repair pathway.[2,7] However, high-fidelity homologous recombination repair–deficient cells, such as those harboring breast cancer susceptibility (BRCA) gene mutations, must rely primarily on the error-prone, nonhomologous, end-joining pathway, inducing DNA fragmentation, genomic instability, and ultimately cell death.[2,3] The advantage of PARPi-induced synthetic lethality is the specific targeting of tumor cells that harbor a BRCA gene mutation while leaving healthy cells intact.[8,9]

BRCA1 and *BRCA2* are tumor-suppressor genes, mutations of which can lead to uncontrolled cell growth. Individuals who harbor a germline BRCA mutation are predisposed to the development of several cancer types, including breast, ovarian, pancreatic, and prostate cancers.[10,11] Sensitivity to PARP inhibition has been observed in high-fidelity homologous recombination repair–deficient malignancies, such as BRCA mutation-positive tumors.[3,8,12] To date, four PARPis have been approved in Europe and/or the United States for the treatment of four solid tumor types, including BRCA mutation-positive tumors.[13–20]

Senaparib (formerly IMP4297) is a novel, selective, oral PARP1 and PARP2 inhibitor that has shown strong antitumor activity in preclinical studies, with 20-fold higher in vivo activity than olaparib (the most well developed of the currently approved PARPis).[21–23] A phase 1, first-in-human study of senaparib was conducted in Australian patients with advanced solid tumors (ClinicalTrials.gov identifier NCT03507543). The safety, tolerability, and pharmacokinetic (PK) profiles of single and multiple doses of senaparib were explored, and preliminary antitumor responses were documented.

MATERIALS AND METHODS

Patients

Adult patients (aged 18 years or older) with a histologically or cytologically documented incurable, advanced, solid malignancy (breast, ovarian, or prostate cancer were preferred) who had progressed on or failed to respond to one or more prior systemic therapy, or for whom there was no suitable standard therapy, were enrolled from three study centers in Australia. A full account of the patient eligibility criteria is provided in Table S1.

Study design

Details of the dose-escalation protocol can be found in the Supporting Methods. Patients were initially administered one dose of oral senaparib; after a 7-day washout period, senaparib was administered once daily in 3-week cycles (from day 1 [D1] to D21). If no dose-limiting toxicity (DLT) emerged, the dose was increased from 6 to 40 mg once daily in dose cohorts in a stepwise manner. For subsequent dose levels, the study followed a conventional *3 + 3* design[24] to determine the maximum tolerated dose (MTD; the maximum dose at which one in six patients from a single cohort experienced a DLT during the first treatment cycle [C1]) or the recommended phase 2 dose (RP2D; based on the toxicity end point—the MTD or one dose level below; Figure S1 and Table S2). Treatment with senaparib continued for up to 1 year until disease progression or unacceptable toxicity or until the investigator determined there was no benefit to the patient.

This study was conducted in accordance with the protocol, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use good clinical practice guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles originating in the Declaration of Helsinki. All patients provided written informed consent to participate before their inclusion in the study.

End points

Primary end points were the incidence and nature of DLTs, and the incidence, nature, relatedness, and severity of treatment-emergent

adverse events (TEAEs). The secondary end point was the PK parameters of senaparib. Exploratory efficacy end points were the overall response rate (ORR), the disease control rate (DCR; complete responses [CRs] + partial responses [PRs] + stable disease [SD] lasting ≥6 weeks), the duration of response, progression-free survival (PFS), and, where applicable, serum prostate-specific antigen (PSA) and cancer antigen 125 (CA-125) concentrations. A full list of all efficacy end points and their definitions can be found in Table S3.

Study assessments

TEAEs and serious adverse events (SAEs) were recorded throughout the study, and patients were followed for safety for 30 days after the last dose of senaparib or at treatment discontinuation, whichever occurred later. All TEAEs were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03),[25] and their relatedness was investigator assessed according to protocol-defined criteria Tables (see S4 and S5). Dose modifications to manage any toxicities were allowed after C1 (see Table S6). The window for DLT assessment was C1D1 to C1D21. DLTs were defined as the occurrence of any of the following during the assessment window: any grade ≥3 nonhematologic toxicity, grade 4 neutropenia lasting >7 days, febrile neutropenia (absolute neutrophil count [ANC] <1000 cells/mm^3 and fever ≥38.5° C) or documented grade ≥3 infection with an absolute neutrophil count ≤1000 cells/mm^3, grade 4 thrombocytopenia lasting >48 hours or requiring intervention or associated with increased bleeding, or dose interruption for >14 days because of toxicity. Any patient experiencing a DLT was treated according to standard clinical practice and discontinued from the study treatment.

Blood sampling for measurement of PK and PSA/CA-125 concentrations and assessments for antitumor efficacy are described in the Supporting Methods. Antitumor efficacy was assessed in patients with a measurable lesion using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[26]

Statistical analyses

The method of sample size determination is provided in the Supporting Methods. A sample size of approximately 20 patients was planned for the dose-escalation phase.

The *all-patients* population was based on the entire enrolled cohort and dose level, regardless of which dose level the patient actually received, and was used to summarize patient baseline and demographic data. The safety population included all patients who received any amount of senaparib. The DLT population comprised patients in the escalation stage who experienced DLT and those who did not experience DLT but completed C1. Safety data were summarized as numbers and frequencies, with numbers of events.

The PK population included all patients who received any amount of senaparib and had an evaluable PK profile. PK parameters were estimated from the plasma concentration data using standard noncompartmental methods. Dose proportionality was determined based on the single-dose data of the area under the plasma concentration time curve (AUC) and the maximum plasma concentration (C_{max}) using the power model on a log-transformed scale.

The preliminary efficacy population comprised all patients who received at least one dose of the study drug and was based on the enrolled cohort and dose level, regardless of which dose level the patient received. For ORR and DCR, 95% confidence intervals (CIs) were calculated using the Clopper–Pearson method[27] for each group in all evaluable patients and for the subgroup with BRCA mutation-positive disease. The duration of response and PFS were summarized using Kaplan–Meier statistics, with 95% CIs for each dose group separately; the Greenwood formula was used to calculate the standard error of the estimates from the Kaplan–Meier curve. Serum concentrations of PSA and CA-125 were summarized for each dose group, including absolute values and changes from baseline; a PSA or CA-125 response was defined as a decrease >50% in the serum concentration from baseline.

All statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., North Carolina, USA). The data cutoff date was April 15, 2020.

RESULTS

Patient disposition and baseline characteristics

From January 10, 2017, to April 15, 2020, 39 patients were enrolled across 10 dose cohorts ranging from 2 to 150 mg. At the time of data cutoff on April 15, 2022, the median duration of treatment was 91 days (range, 1–805 days). Thirty-two patients (82.1%) had discontinued from the study, and seven (17.9%) remained on trial at the cutoff date (Figure 1). The most common reason for study discontinuation was disease progression (n = 19, 48.7%); other reasons included physician decision (n = 7; 17.9%), withdrawal by patient (n = 3; 7.7%), adverse events (n = 1; 2.6%), and other (n = 2; 5.1%). All 39 patients were included in the all-patients, safety, efficacy, and PK populations. Six patients were excluded from the DLT population (n = 33) because they missed 1 dose in C1.

The median patient age was 70 years (range, 42–83 years; Table 1 and Table S7). Eight of the 34 patients (20.5%) with available data were BRCA mutation-positive. The most common malignancy was ovarian cancer (n = 11; 28.2%), followed by prostate cancer (n = 10; 25.6%) and breast cancer (n = 3; 7.7%). More than one third of the patients (n = 15; 38.5%) had received three or more prior lines of systemic therapies.

Safety and tolerability

Overall, 38 patients (97.4%) experienced at least one TEAE (267 events in total; Table 2). The incidence and severity of TEAEs did not

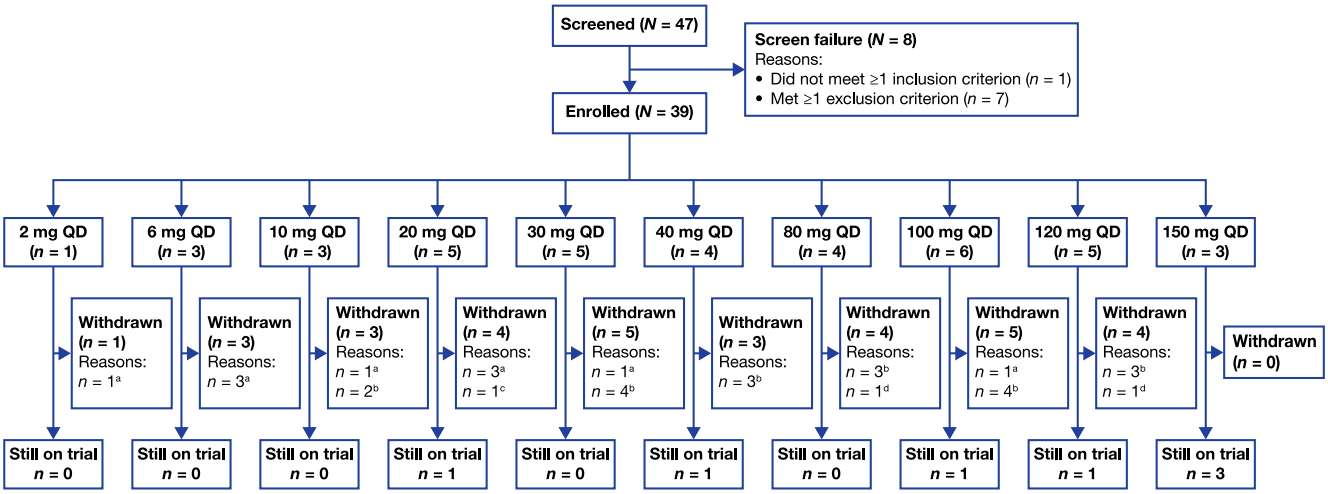

FIGURE 1 Patient disposition. [a]Patient or physician decision to discontinue for other reasons. [b]Evidence of disease progression. [c]Intolerable toxicity or cumulative toxicity preventing the patient from continuing. [d]Other. QD indicates once daily.

TABLE 1 Demographic and baseline characteristics of all patients: All-patients population, *N* = 39

Characteristic	No. (%)
Age: Median [range], years	70 [42–83]
Sex	
Men	17 (43.6)
Women	22 (56.4)
Race	
White	35 (89.7)
Asian	2 (5.1)
Other	2 (5.1)
Ethnicity	
Hispanic or Latino	1 (2.6)
Not Hispanic or Latino	38 (97.4)
ECOG PS	
0	18 (46.2)
1	21 (53.8)
Primary tumor	
Ovarian[a]	11 (28.2)
Breast	3 (7.7)
Prostate	10 (25.6)
Other[b]	15 (38.5)
Overall tumor staging	
III	3 (7.7)
IV	30 (76.9)
Missing	6 (15.4)
Target lesion at baseline	
Yes	26 (66.7)
Prior lines of therapy	
0[c]	1 (2.6)
1–2	16 (41.0)
≥3	15 (38.5)
Missing	7 (17.9)
BRCA mutation status[d]	
Positive	8 (20.5)
Negative	26 (66.7)
Not tested	5 (12.8)

Abbreviations: BRCA, breast cancer susceptibility genes *BRCA1* and/or *BRCA2*; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]Including ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.

[b]Mesothelioma (*n* = 3; 7.7%); small cell lung cancer (*n* = 2; 5.1%); urothelial cancer (*n* = 2; 5.1%); and pancreatic cancer, fallopian tube cancer, peritoneal cancer, gastric cancer, esophageal cancer, chondrosarcoma, cancer of unknown primary, and anaplastic oligodendroglioma (*n* = 1 each; 2.6% each).

[c]Patients with no prior chemotherapy, immunotherapy, or endocrine therapy.

[d]BRCA mutation status of blood samples collected at baseline and tested by central laboratory testing.

appear to be dose-dependent. The most common TEAEs of any grade were fatigue, headache (*n* = 10; 25.6% for each), and nausea (*n* = 9; 23.1%; Table 3). The majority of TEAEs were grade 1 or 2 (*n* = 25; 64.1%; Table 2). TEAEs resulted in dose discontinuation or interruption in six patients (15.4%) and eight patients (20.5%), respectively. Two deaths were reported, and both occurred after the end of study treatment. One death was attributed to progression of metastatic

TABLE 2 Summary of treatment-emergent adverse events: Safety population, $n = 39$[a]

	Dose group, no. (%)										
	2 mg daily, $n = 1$	**6 mg daily, $n = 3$**	**10 mg daily, $n = 3$**	**20 mg daily, $n = 5$**	**30 mg daily n = 5**	**40 mg daily, $n = 4$**	**80 mg daily, $n = 4$**	**100 mg daily, $n = 6$**	**120 mg daily, $n = 5$**	**150 mg daily, $n = 3$**	**Total no. (%)**
Any TEAEs	1 (100.0)	2 (66.7)	3 (100.0)	5 (100.0)	5 (100.0)	4 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)	3 (100.0)	38 (97.4)
Related[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	2 (50.0)	1 (16.7)	4 (80.0)	0 (0.0))	8 (20.5)
TEAEs grade ≥3	0 (0.0)	2 (66.7)	0 (0.0)	2 (40.0)	2 (40.0)	1 (25.0)	1 (25.0)	2 (33.3)	3 (60.0)	0 (0.0)	13 (33.3)
Related[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (20.0)	0 (0.0)	2 (5.1)
Leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	0 (0.0)	1 (25.0)	1 (16.7)	2 (40.0)	0 (0.0)	6 (15.4)
Related[c]	0 (0.0)	(0.0)0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Leading to interruption	0 (0.0)	1 (33.3)	0 (0.0)	1 (20.0)	2 (40.0)	2 (50.0)	1 (25.0)	0 (0.0)	1 (20.0)	0 (0.0)	8 (20.5)
SAEs	0 (0.0)	1 (33.3)	0 (0.0)	3 (60.0)	2 (40.0)	2 (50.0)	1 (25.0)	3 (50.0)	3 (60.0)	0 (0.0)	15 (38.5)
Related[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Related[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)

Abbreviations: Related, related to the study drug; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]There were no dose-limiting toxicities or TEAEs leading to dose adjustment.

[b]Considered by the investigator to be attributable to senaparib.

[c]SAE of grade 5 bone marrow failure, which led to study drug discontinuation and death.

TABLE 3 Incidence of treatment-emergent adverse events occurring in ≥10% of patients, including incidence of grade ≥3 and those considered to be related to the study drug (safety population, $n = 39$), by preferred term

	All grades, no. (%)		Grade ≥3, no. (%)	
TEAE	**All TEAEs**	**Related to study drug**	**All TEAEs**	**Related to study drug**
Any TEAE	38 (97.4)	8 (20.5)	13 (33.3)	2 (5.1)[a]
Fatigue	10 (25.6)	2 (5.1)	0 (0.0)	—
Headache	10 (25.6)	—	0 (0.0)	—
Nausea	9 (23.1)	3 (7.7)	0 (0.0)	—
Back pain	8 (20.5)	—	0 (0.0)	—
Constipation	8 (20.5)	—	0 (0.0)	—
Arthralgia	6 (15.4)	—	0 (0.0)	—
Pain in extremity	6 (15.4)	—	0 (0.0)	—
Urinary tract infection	6 (15.4)	—	0 (0.0)	—
Dizziness	6 (15.4)	—	0 (0.0)	—
Diarrhea	5 (12.8)	—	0 (0.0)	—
Abdominal pain	4 (10.3)	—	0 (0.0)	—
Vomiting	4 (10.3)	—	0 (0.0)	—
Anemia	4 (10.3)	—	0 (0.0)	—
Appetite decreased	4 (10.3)	—	0 (0.0)	—
Lethargy	4 (10.3)	—	0 (0.0)	—
Pleural effusion	4 (10.3)	—	0 (0.0)	—

Abbreviation: TEAE, treatment-emergent adverse event

[a]Platelet count decrease in one patient and bone marrow failure in another.

breast cancer and was considered unrelated to senaparib: the patient died 27 days after the withdrawal of treatment. The other death occurred to a patient with non-BRCA–mutated ovarian cancer, and it was attributed to a grade 5 event of bone marrow failure related to senaparib, for which the bone marrow biopsy did not indicate myelodysplastic syndrome (MDS); this patient also had grade 3 anemia, grade 4 neutropenia and grade 4 thrombocytopenia. The patient had a response of SD to the treatment at dose level of 80 mg daily, 10.9 months free of disease progression, and died 96 days after the withdrawal of treatment. Eight patients (20.5%) reported treatment-related AEs; the most common were nausea ($n = 3$; 7.7%), fatigue, and thrombocytopenia ($n = 2$; 5.1% for each; see Table S8). In total, 15 patients (38.5%) experienced 28 SAEs (see Table S9), of which 22 events (78.6%) in 14 patients were grade 2 or 3. The most frequent SAEs were hematuria (two events in two patients [5.1%], both grade 3) and pulmonary embolism (two events in two patients [5.1%], one each at grades 2 and 3). Almost all reported SAEs were considered either not related or unlikely to be related to senaparib; the exception was the SAE of grade 5 bone marrow failure already mentioned.

Hematologic TEAEs occurred in seven patients (17.9%). Anemia was reported in four patients (10.3%; three at grade 2 and one at grade 3), thrombocytopenia in three patients (7.7%; two at grade 1 and one at grade 3), and neutropenia in one patient (2.6%; grade 4). The final hematologic TEAE was the grade 5 bone marrow failure, which was considered to be probably related to the study drug. This patient was diagnosed with a grade 4 SAE of decreased platelet count on study day 239, leading to study drug discontinuation, and was further diagnosed with bone marrow failure on study day 263, leading to death on day 353. There were no cases of secondary hematologic malignancies among the patients in this study.

No DLTs were observed during the protocol-defined DLT period at any dose level. Therefore, the MTD was not reached. Considering the absorption of senaparib tended to be saturated during the 80–150 mg dose range, and the preliminary efficacy was a 20% ORR at 100 mg, the RP2D of senaparib was determined to be 100 mg daily.

Pharmacokinetics

The senaparib single-dose PK data are presented in Figure 2A and Table S10. The median time to reach C_{max} of senaparib was 1.00–2.08 hours across dose levels. Senaparib exposure parameters (C_{max} and AUC) demonstrated an increasing trend with increasing doses in the dose range from 2 to 80 mg but were comparable in the range from 80 to 150 mg. The relationships between dose and senaparib exposure supported a plateau commencing at 80 mg daily.

Data for the senaparib multiple-dose PK parameters are presented in Figure 2B and Table S11. The PKs of senaparib after

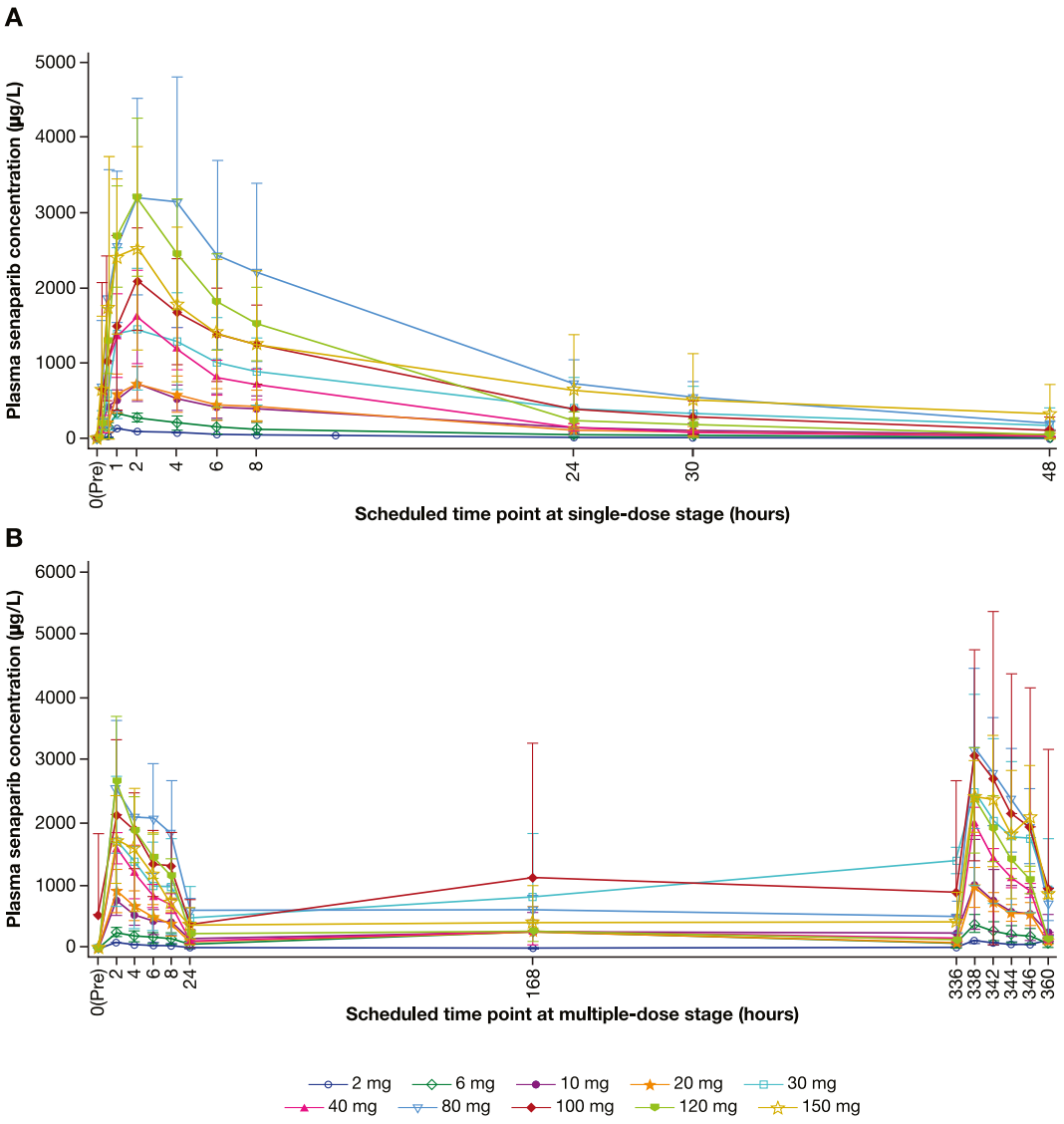

FIGURE 2 Plasma senaparib concentration–time curves (A) over a 48-hour period after a single dose and (B) during cycle 1 of the multiple-dose stage. Pre indicates before dosing.

multiple-dose administration followed the same pattern as the single-dose administration (Figure 2B). The median time to reach C_{max} of senaparib was 1.97–2.13 hours after single-dose administration of 2–150 mg during this multiple-dose stage (D1). The mean elimination half-life ranged from 5.86 to 13.30 hours for D1 and from 5.68 to 8.39 hours for D15. There was no apparent accumulation of senaparib in the body after multiple dosing (accumulation index, 1.06–1.67).

Efficacy

Of the 22 patients who were evaluable for tumor response by RECIST 1.1 criteria, six patients were confirmed as carriers of *BRCA1* or *BRCA2* mutations (see Table S12). Among these 22 patients, three (all with ovarian cancer) experienced a PR (one each in the 20-mg, 100-mg, and 120-mg dose groups), with an ORR of 13.6% (95% CI, 2.9%–34.9%). Two of the responders had BRCA mutation-positive tumors (one each in the 20-mg and 100-mg dose groups), for an ORR in the BRCA mutation-positive subgroup of 33.3% (two of six patients; 95% CI, 4.3%–77.7%). The ORR was 6.3% (one of 16 patients) for the nonmutated subgroup. An additional 15 patients (68.2%) overall had SD. The DCR was 81.8% (95% CI, 59.7%–94.8%) overall and was similar for the BRCA mutation-positive subgroup (83.3%; 95% CI, 35.9%–99.6%). In the 100-mg group, the ORR was 20% (95% CI, 0.5%–71.6%), and the DCR was 40% (95% CI, 5.3%–85.3%). A waterfall plot of the best change in target lesion size for all evaluable patients is shown in Figure 3. All three responders were still alive without disease progression at the data cutoff date, with response durations of 1.4 months for the patient with BRCA wild type and 2.8 and 22.1 months for the two patients with BRCA mutation-positive disease. Median PFS was 5.7 months (95% CI, 2.7%–7.4%) in the efficacy population and 7.4 months (95% CI, 1.77% to not reached) in the BRCA mutation-positive subgroup (see

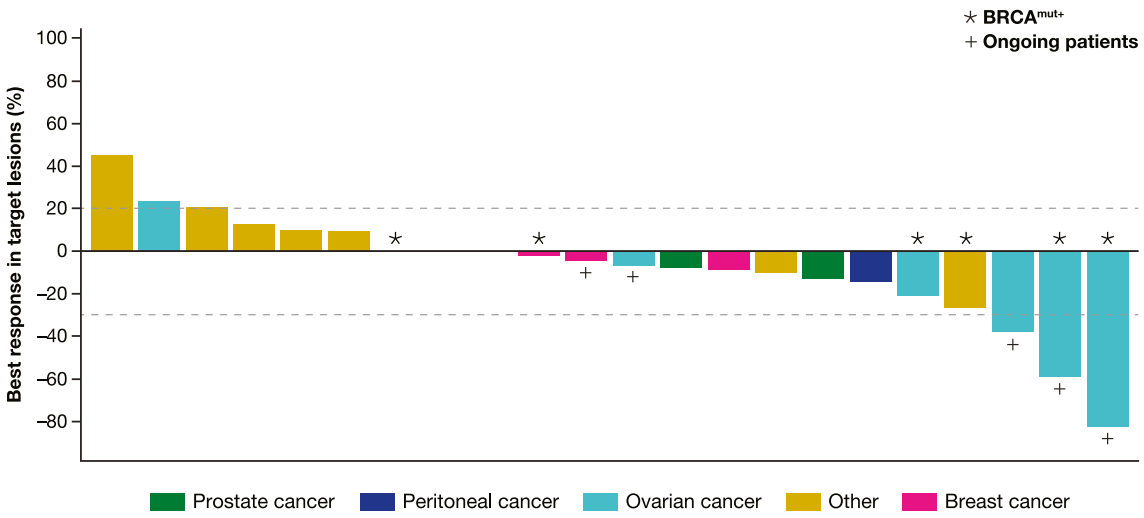

FIGURE 3 Waterfall plot showing best change in target lesion for all evaluable patients and tumor type and BRCA gene mutation status. BRCA indicates breast cancer susceptibility; BRCA^{mut+}, positive for *BRCA1* and/or *BRCA2* mutation.

Table S13 and Figure S2). One of the 10 patients (10%) with prostate cancer experienced a PSA response; he had BRCA wild-type and was in the 40-mg dose group.

DISCUSSION

This first-in-human study of senaparib showed good tolerability and promising antitumor activity in patients with advanced solid tumors. There were no DLTs observed in any cohorts, and the MTD was not reached. TEAEs were predominantly mild to moderate (only 9% of TEAEs were grade ≥3), and most had returned to normal, baseline, or stable status by the end of the study. Senaparib demonstrated encouraging preliminary data of antitumor activity, with indications of particular benefit among the BRCA mutation-positive patients. The C_{max} and AUC of senaparib increased with the increasing dose during the 2–80 mg range. However, the exposure results were comparable among the 80-mg, 100-mg, 120-mg, and 150-mg dose groups, indicating that the absorption of senaparib tended to be saturated during the 80–150 mg dose range. The efficacy results in the 100-mg dose group showed that one patient (20%) had the best ORR (CR + PR), and two patients (40%) had the best overall response as CR + PR + SD. Based on the safety, PK, and preliminary efficacy data, the RP2D of senaparib was determined to be 100 mg daily.[13]

The observed safety profile of senaparib in this study, including the development of bone marrow failure in one patient, was consistent with the known side effects of the PARPi class.[13–16] Some of the most common adverse events associated with PARPi monotherapy are hematologic toxicities, and the most reported grade ≥3 adverse events are hematologic.[28] In the current study, anemia (10.3%) was the most frequently reported hematologic TEAE in PARPi-treated patients, and neutropenia (2.6%) was lower than reported for currently approved PARPis in phase 3 maintenance studies (37%–50% and 18%–30%, respectively). Grade ≥3 anemia and neutropenia were also less common with senaparib (2.6% for both in the current study vs. 19%–25% and 5%–20%, respectively).[28] One grade 5 SAE bone marrow failure in one patient (2.6%) on study day 263 was reported who had concurrent grade 3 anemia, grade 4 neutropenia, and grade 4 thrombocytopenia, but the bone marrow biopsy did not indicate myelodysplastic syndrome (MDS). The bone marrow failure or suppression presented with multiple hematologic AEs, including neutropenia, anemia, and thrombocytopenia, and these hematologic toxicities were usually recoverable after withdrawal and rarely fatal.[28] Detailed data about the death caused by hematologic toxicities or bone marrow failure were not reported in the publication of approved PARPis.[28] Among the more common gastrointestinal toxicities observed with single-agent PARPis, both nausea and vomiting were less prevalent with senaparib than with other such agents (23.1% vs. 75% and 10.3% vs. 34%–37%, respectively).[28] However, in consideration of the small sample size of this study, further studies are needed.

The US Food and Drug Administration labels for all four of the currently approved PARPis include a boxed warning of a potential increased risk of secondary hematologic tumors (acute myeloid leukemia [AML] or MDS) associated with their use. The reported incidence of PARPi-associated AML/MDS is 0.73% (vs. 0.47% with placebo), and it is ultimately fatal in approximately 45% of patients.[13–16,29,30] The reported median latency period from the first PARPI to AML/MDS was 17.8 months, and median the exposure duration was 9.8 months.[29] There were no secondary hematologic tumors among patients in that study. However, a further study with larger patient numbers and longer follow-up durations is needed to clarify the risk of delayed hematologic toxicity. The US Food and Drug Administration label for olaparib also contains warnings for pneumonitis (<1% of exposed patients in clinical trials) and venous thromboembolic events (in 7% of patients with metastatic, castration-resistant prostate cancer),[13] neither of which arose in the current trial population.

Although single-agent PARPis have demonstrated efficacy in various solid tumors, and particularly in tumors harboring alterations

in DNA damage-repair genes (eg, BRCA mutation-positive), not all patients benefit from the treatment.[3,8,12,31–33] In patients with PARPi-treated solid tumors, PARPis were associated with a 41% reduction in the hazard for PFS events overall regardless of BRCA mutation status in a meta-analysis, although PFS rates varied according to the type of malignancy and the PARPi used across trials.[34] The other systematic review of PARPis showed a mean response rate of 47%, and the median PFS ranged from 6.8 to 24 months in BRCA mutation-positive patients.[35] The preliminary data of antitumor activity observed in the current small population of unselected, relatively heavily pretreated patients with advanced solid tumors were encouraging and appeared to favor the BRCA mutation-positive subgroup (ORRs of 13.6% and 33.3%, respectively). Greater than 80% of both the efficacy population and those harboring BRCA mutation-positive tumors achieved disease control, and the median PFS was 5.7 and 7.4 months, respectively (see Table S12). However, these preliminary efficacy data should be considered in light of the phase 1, single-arm study design with multiple dose cohorts and a small patient population. Dosing was not optimal across patients, and much of the reported data were obtained at doses other than the RP2D.

Similar to most contemporary therapies for patients with recurrent solid tumor malignancies, efficacy decreased with successive lines of therapy, and drug resistance was inevitable. In an effort to improve or prolong response, several trials have used PARPis in doublet or triplet combination. Augmented toxicity, particularly hematologic and gastrointestinal toxicity, was observed.[36] The favorable adverse effect profile observed in this phase 1 trial may provide senaparib with an advantage in the future development of combination regimens with the aim of improving efficacy while maintaining an acceptable safety profile.

CONCLUSIONS

Overall, senaparib was well tolerated in Australian patients with advanced, pretreated solid tumors and demonstrated preliminary evidence of antitumor activity. The current findings support further phase 2 and 3 investigations of senaparib in patients with solid tumors at the RP2D of 100 mg daily.

AUTHOR CONTRIBUTIONS

Bo Gao: Conceptualization, data curation, investigation, formal analysis, methodology, and writing–review and editing. **Mark Voskoboynik:** Conceptualization, data curation, investigation, formal analysis, methodology, and writing–review and editing. **Adam Cooper:** Data curation, investigation, and formal analysis. **Kate Wilkinson:** Data curation, investigation, and formal analysis. **Siao Hoon:** Data curation, investigation, and formal analysis. **Chih-Yi Hsieh:** Conceptualization, formal analysis, and writing–review and editing. **Suixiong Cai:** Conceptualization and writing–review and editing. **Ye Edward Tian:** Conceptualization and writing–review and editing. **Jun Bao:** Conceptualization, funding acquisition, and writing–review and editing. **Ning Ma:** Methodology, validation, and writing–review and editing. **Chen Wang:** Data curation, formal analysis, writing–original draft, and writing–review and editing. **Ming Zhang:** Formal analysis and writing–review and editing. **Baoyue Li:** Formal analysis, visualization, and writing–review and editing. **Mingchuan Guo:** Formal analysis and writing–review and editing. **Ruiyu Zhou:** Formal analysis and writing–review and editing. **Xiaozhu Wang:** Methodology, project administration, visualization, and writing–review and editing. **Cong Xu:** Conceptualization and writing–review and editing. **Paul de Souza:** Conceptualization, data curation, investigation, formal analysis, methodology, supervision, and writing–review and editing.

ACKNOWLEDGMENTS

We acknowledge and thank the study patients and their families, the investigators, and the study teams at each of the participating centers. These trials were sponsored by IMPACT Therapeutics Inc. Writing and editorial assistance was provided by Jacqueline Kolston and Jing Yi Lee at Parexel and was funded by IMPACT Therapeutics Inc.

CONFLICTS OF INTEREST

Mark Voskoboynik reports consulting fees from AstraZeneca and IMPACT Therapeutics and honoraria from MSD and IMPACT Therapeutics outside the submitted work. Siao Hoon reports travel support from Merck outside the submitted work. Chih-Yi Hsieh owns stock options in IMPACT Therapeutics. The remaining authors made no disclosures.

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How to cite this article: Gao B, Voskoboynik M, Cooper A, et al. A phase 1 dose-escalation study of the poly(ADP-ribose) polymerase inhibitor senaparib in Australian patients with advanced solid tumors. *Cancer*. 2023;129(7):1041-1050. doi:10.1002/cncr.34662