Pamiparib in combination with tislelizumab in patients with advanced solid tumours: results from the dose-escalation stage of a multicentre, open-label, phase 1a/b trial

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Summary

Background Rationale exists for combined treatment with immune checkpoint inhibitors and poly (ADP-ribose) polymerase (PARP) inhibitors in a variety of solid tumours. This study aimed to investigate the safety and antitumour effects of pamiparib, an oral PARP 1/2 inhibitor, combined with tislelizumab, a humanised anti-PD-1 monoclonal antibody, in patients with advanced solid tumours and to determine the optimum doses for further evaluation.

Methods We did a multicentre, open-label, phase 1a/b study at five academic sites or community oncology centres in Australia. We recruited adults (aged ≥18 years) with advanced solid tumours who had received one or more previous lines of therapy, with an Eastern Cooperative Oncology Group performance score of 1 or less, and a life expectancy of 12 weeks or more. Patients were enrolled into one of five dose-escalation cohorts, with dose-escalation done in a 3+3 design. Cohorts 1–3 received intravenous tislelizumab 2 mg/kg every 3 weeks plus 20, 40, or 60 mg oral pamiparib twice daily, respectively; cohorts 4 and 5 received 200 mg intravenous tislelizumab every 3 weeks plus 40 or 60 mg oral pamiparib twice daily, respectively. The primary endpoints of the phase 1a dose-escalation part of the study were safety and tolerability, including the occurrence of dose-limiting toxicities and determination of the maximum tolerated dose and recommended phase 2 dose. All primary endpoints were analysed in the safety analysis set, which included all patients who received at least one dose of tislelizumab or pamiparib, with the exception of the occurrence of dose-limiting toxicities, which was analysed in the dose-limiting toxicity analysis set, which included all patients who received at least 90% of the first scheduled tislelizumab dose and at least 75% of scheduled pamiparib doses, or who had a dose-limiting toxicity event during cycle 1. Reported here are results of the phase 1a dose-escalation stage of the trial. This trial is registered with ClinicalTrials.gov, number NCT02660034, and is ongoing.

Findings Between Jan 22, 2016, and May 16, 2017, we enrolled 49 patients (median age 63 years [IQR 55–67]), all of whom received at least one dose of pamiparib or tiselzumab. Four patients had dose-limiting toxicities (intractable grade 2 nausea [n=1] and grade 3 rash [n=1] in cohort 4, and grade 2 nausea and vomiting [n=1] and grade 4 immune-mediated hepatitis [n=1] in cohort 5). The recommended phase 2 dose was tislelizumab 200 mg every 3 weeks plus pamiparib 40 mg twice daily (the dose given in cohort 4). The most common treatment-emergent adverse events were nausea (in 31 [63%] of 49 patients), fatigue (26 [53%]), diarrhoea (17 [35%]), and vomiting (15 [31%]). 23 (47%) of 49 patients had immune-related adverse events, of whom nine (39%) had asymptomatic grade 3–4 hepatic immune-related adverse events, which were reversible with corticosteroid treatment. The most common adverse event of grade 3 or worse severity was anaemia (in six [12%] patients) and no grade 5 adverse events were reported. Hepatitis or autoimmune hepatitis was the only serious adverse event to occur in two or more patients (in four [8%] patients). At a median follow-up of 8·3 months (IQR 4·8–12·8), ten (20%) of 49 patients achieved an objective response according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, including two complete responses and eight partial responses.

Interpretation Pamiparib with tislelizumab was generally well tolerated and associated with antitumour responses and clinical benefit in patients with advanced solid tumours supporting further investigation of the combination of pamiparib with tislelizumab.

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Introduction

Immune checkpoint inhibitors, such as PD-1 or PD-L1, and poly (ADP-ribose) polymerase (PARP) inhibitors targeting DNA repair mechanisms have had a substantial impact on treatment outcomes in patients with a wide range of solid tumour malignancies. Non-clinical data[1–4] have demonstrated a direct association between DNA damage and immune responses, which supports the combined use of checkpoint inhibitors and PARP inhibitors. PD-L1 expression can be upregulated by PARP

Research in context

Evidence before this study

Preclinical evidence suggests that crosstalk occurs between poly (ADP-ribose) polymerase (PARP) inhibition and the PD-1–PD-L1 immune checkpoint axis. We searched PubMed from database inception to November, 2018, and searched the proceedings of major oncology congresses (eg, American Society of Clinical Oncology and European Society for Medical Oncology) without language restrictions for controlled, prospective studies, evidence-based reviews, or case reports evaluating combination treatment with anti-PD-1 monoclonal antibodies and PARP inhibitors in patients with solid tumours. Search terms included those related to PARP inhibition (eg, "poly ADP ribose polymerase inhibitor," "PARP inhibitor," and "PARPi") and anti-PD-1 therapy (eg, "programmed cell death 1 antibody," "anti-PD-1," and "PD-1 immunotherapy"). To supplement our search, we also searched PubMed for clinical data combining PARP inhibitor and anti-PD-L1 therapy using the same search criteria, with the additional search terms "programmed cell death ligand 1 antibody," "anti-PD-L1," and "PD-L1 immunotherapy". Our search showed that there is a paucity of data about combination therapy with anti-PD-1 or anti-PD-L1 and PARP inhibitors. We identified no full-length publications on the combination of a PARP inhibitor with anti-PD-1 antibodies; however, our search did yield two 2018 American Society of Clinical Oncology Annual Meeting abstracts for studies combining an anti-PD-1 antibody with a PARP inhibitor. The first abstract described the safety and tolerability of the PARP inhibitor veliparib in combination with the anti-PD-1 antibody nivolumab and platinum doublet chemotherapy in metastatic or advanced non-small-cell lung cancer. These findings suggest combination therapy had no unanticipated safety signals and the addition of veliparib to these regimens was not associated with additional toxicity. The second abstract was from a study reporting promising safety and efficacy data from patients with recurrent ovarian cancer enrolled in a phase 1–2 study of the PARP inhibitor niraparib plus the anti-PD-1 antibody pembrolizumab. Furthermore, our search only yielded one full-text article and two congress abstracts that described the safety and clinical activity of the anti-PD-L1 antibody durvalumab in combination with a PARP inhibitor or VEGF receptor inhibitor.

Added value of this study

To the best of our knowledge, this report is the first full-text publication of a clinical trial reporting the safety, pharmacokinetic profile, and antitumour activity of combination treatment with an anti-PD-1 monoclonal antibody and PARP inhibitor for the treatment of solid tumours regardless of *BRCA* status. Our study demonstrated that pamiparib plus tislelizumab was generally well tolerated and associated with antitumour efficacy and clinical benefit. The recommended dose for further study was determined to be tislelizumab 200 mg every 3 weeks plus pamiparib 40 mg twice daily.

Implications of all the available evidence

Our results support future investigation of pamiparib, a PARP 1/2 inhibitor, combined with tislelizumab, an anti-PD-1 monoclonal antibody, in patients with advanced solid tumours, including those with homologous recombination deficiency mutations.

inhibition, primarily via glycogen synthase kinase-3β inactivation and, in the absence of a checkpoint inhibitor, can result in cancer cells that have increased resistance to T-cell-mediated cell death.[5] Additionally, tumours with *BRCA* mutations or homologous recombination deficiency (HRD) have been associated with a high neoantigen load, a high CD8 cell to CD4 cell ratio, increased peritumoural T cells, and increased PD-L1 expression.[2,3,6] The blockade of the PD-1–PD-L1 axis with a checkpoint inhibitor might potentiate PARP inhibitor-induced tumour suppression. The efficacy of PD-1 pathway blockade also correlates with DNA repair pathway mutations and neoantigen burden.[7] Tumours that respond to PARP inhibition might have an enhanced sensitivity to combined treatment with a PARP inhibitor and an anti-PD-1 antibody, and the efficacy and safety of the two drugs administered together deserves further investigation.

Pamiparib is a highly selective PARP1/2 inhibitor with oral bioavailability, potent PARP trapping, and capability to penetrate the brain.[8] In vitro, pamiparib suppressed PARP activity in patient-derived glioblastoma multiforme and small-cell-lung cancer xenografts, was shown to be ten times more potent than olaparib, and potentiated the effects of temozolamide.[8–10] In early phase clinical studies (NCT02361723 and NCT03333915), pamiparib was generally well tolerated, with a recommended phase 2 dose of 60 mg orally twice daily, and had preliminary antitumour activity. Objective responses were observed in nine of 20 patients with advanced gynaecological cancers following treatment with pamiparib.[11]

Structure–activity relationship data[12] suggest that anti-PD-1 antibodies constructed from an IgG4 isotope with the S228P mutation retain substantial binding of Fcγ-receptors (FcγRs), including FcγRI and FcγRIIB. These antibodies cross-link T cells and macrophages, which can induce antibody-dependent cellular phagocytosis. Tislelizumab is an IgG4 monoclonal antibody, with minimal to no FcγR binding via five mutations in the constant region. Engineering an antibody without the binding of FcγRs such as tislelizumab has shown reduced immune cross-linking with minimal antibody-dependent cellular phagocytosis and improved functionality in in-vitro, ex-vivo, and in-vivo models.[12]

Tislelizumab enhances T-cell-mediated production of interleukin-2 and interferon γ (IFNγ) in a dose-dependent manner, increases IFNγ production by natural killer cells, and induces cytotoxic effects against PD-L1-positive tumour cells.[13] In mouse models, tislelizumab increases

lymphocyte infiltration and PD-L1 expression in tumour tissues and substantially inhibits tumour growth.[14] Preliminary clinical data[15] in patients with solid tumours demonstrated that tislelizumab was generally well tolerated and had antitumour activity in multiple tumour types. A recommended dose of 200 mg administered intravenously every 3 weeks has been established for tislelizumab.[15]

In this study, we aimed to evaluate the safety, tolerability (including estimation of the recommended phase 2 dose), pharmacokinetics, and antitumour activity of tislelizumab plus pamiparib in patients with advanced solid tumours. We report the findings from the initial dose-escalation phase of the study, the aim of which was to evaluate the safety of the combination.

Methods

Study design and participants

We did a multicentre, open-label, phase 1a/b study at five academic sites or community oncology centres in Australia (appendix p 1). Only phase 1a dose escalation is reported here; phase 1b is ongoing.

See Online for appendix

Eligible patients were aged 18 years or older with histologically or cytologically confirmed advanced solid tumours with measurable disease (defined by Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), who had received one or more previous lines of therapy, and had an Eastern Cooperative Oncology Group performance score of 1 or less, and a life expectancy of 12 weeks or more. Patients were also required to have adequate organ function according to laboratory values and to be transfusion independent. Sensitivity to platinum was not an entry requirement. Patients with a history of severe hypersensitivity reactions to other monoclonal antibodies, a previous invasive malignancy in the 2 years before enrolment, symptomatic brain metastases, and those who had previous therapies targeting PD-1–PD-L1 or PARP were excluded. Full inclusion and exclusion criteria are in the appendix (p 3).

This study was done in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, the principles of informed consent, and the requirements of the public registration of clinical trials. Written, informed consent was obtained from each patient before screening. The protocol was approved by the institutional ethics committee at each site.

Procedures

We used a 3+3 dose-escalation strategy. Patients were enrolled to five dosing cohorts of tislelizumab and pamiparib: tiselizumab 2 mg/kg plus pamiparib 20 mg (cohort 1); tiselizumab 2 mg/kg plus pamiparib 40 mg (cohort 2); tiselizumab 2 mg/kg plus pamiparib 60 mg (cohort 3); tiselizumab 200 mg plus pamiparib 40 mg (cohort 4); and tiselizumab 200 mg/kg plus pamiparib 60 mg (cohort 5). Tislelizumab was administered every 3 weeks as an intravenous infusion on day 1, and pamiparib was administered orally twice daily on days 1–21 of every 21-day cycle until disease progression, toxicity, or patient withdrawal. Dose interruptions (tislelizumab for ≤42 consecutive days and pamiparib for ≤21 consecutive days) and dose modifications (pamiparib only) were permitted (appendix pp 4–6). Although dose reductions were not allowed for tislelizumab, tislelizumab administration was interrupted for grade 3 immune-related adverse events and infusion-related reactions. Tislelizumab was discontinued in the case of grade 4 immune-related adverse events and infusion-related reactions. Pamiparib dose reductions and interruptions were allowed for adverse events, such as renal dysfunction or low white and red blood cell counts. One or both drugs could be discontinued at any time. Treatment was generally discontinued due to progressive disease, adverse events, physician or patient withdrawal from the study, or non-compliance.

Dose escalation continued until the maximum tolerated dose was reached, defined as the occurrence of a dose-limiting toxicity in two of six treated patients in a cohort, or the recommended phase 2 dose was determined for the combination (appendix p 2). If the maximum tolerated dose could not be established after evaluation of all planned doses, the recommended phase 2 dose would be determined based on safety and pharmacokinetic profile. A dose-limiting toxicity was defined as a prespecified adverse event or an abnormal laboratory value that was deemed unrelated to disease progression, intercurrent illness, or concomitant medications, occurring during the first 21 days following the first dose of tislelizumab and pamiparib in cycle 1, and that met the criteria for haematological and non-haematological toxicities (appendix p 7). The pharmacokinetic profiles of tislelizumab and pamiparib were evaluated following coadministration of both drugs.

Safety assessments included monitoring of adverse events, vital signs, and physical examinations, which were documented at each study visit. Electrocardiograms, ophthalmological examinations, and clinical laboratory investigations (eg, haematology and serum chemistry) were also done during each cycle. Adverse events were categorised according to their severity (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03[16]), seriousness, and relation to the study treatment. Antitumour activity was assessed by radiographical imaging (computed tomography or MRI) at screening within 28 days before enrolment, every 9 weeks (or within 1 week either side of this timepoint) in the first 12 months, and every 12 weeks (or within 1 week either side of this timepoint) thereafter. Tumour response was evaluated locally by the investigator according to RECIST version 1.1 criteria[17] for all tumour types. Ovarian, fallopian tube, or primary peritoneal tumours were also assessed by Gynecological Cancer Intergroup CA-125 response criteria[18] and prostate cancer responses were assessed by Prostate Cancer Working Group 2 criteria.[19]

Because preclinical data supported the activity of the combination in tumour types with and without HRD-positive status, *BRCA* or HRD positivity was not a requirement for study entry. *BRCA* status was determined at sites based on testing guidelines and HRD status was determined centrally using the Myriad MyChoice HRD CDx assay (Salt Lake City, UT, USA) if tumour tissue was available.

Outcomes

The primary endpoints of the dose-escalation phase of the study were the safety and tolerability of pampiparib and tiselizumab, including the incidence and nature of dose-limiting toxicities, and determination of the maximum tolerated dose and recommended phase 2 dose. The maximum tolerated dose was defined as the occurrence of a dose-limiting toxicity in two of six patients. Secondary endpoints were antitumour response outcomes, including the proportion of patients achieving an objective response (a complete response or partial response, according to RECIST version 1.1 [overall population] and CA-125 response criteria [patients with ovarian cancer]), the proportion of patients achieving disease control (patients with a complete response, partial response, or stable disease), the proportion of patients achieving clinical benefit (best overall response of complete response, partial response, or stable disease lasting ≥24 weeks), progression-free survival (time from the first dose of study medication to the first documented objective disease progression or death, whichever occurred first), overall survival (time from the date of the first dose of study drug to the date of death), pharmacokinetics of pamiparib and tiselizumab, and tislelizumab immunogenicity. At the time of writing, tislelizumab immunogenicity data were not available, and will be reported in a later publication.

Statistical analysis

Although no formal power calculations were done, on the basis of the estimation that five dose-limiting toxicities would occur, we determined that enrolment of up to 50 patients in the dose-escalation phase would be required to establish the recommended phase 2 dose of combination treatment with tislelizumab and pamiparib. A safety monitoring subcommittee oversaw the study. Analyses were done in the following populations: the enrolled set, which included all patients who provided informed consent; the safety analysis set, which included all patients who received at least one dose of tislelizumab or pamiparib (the primary

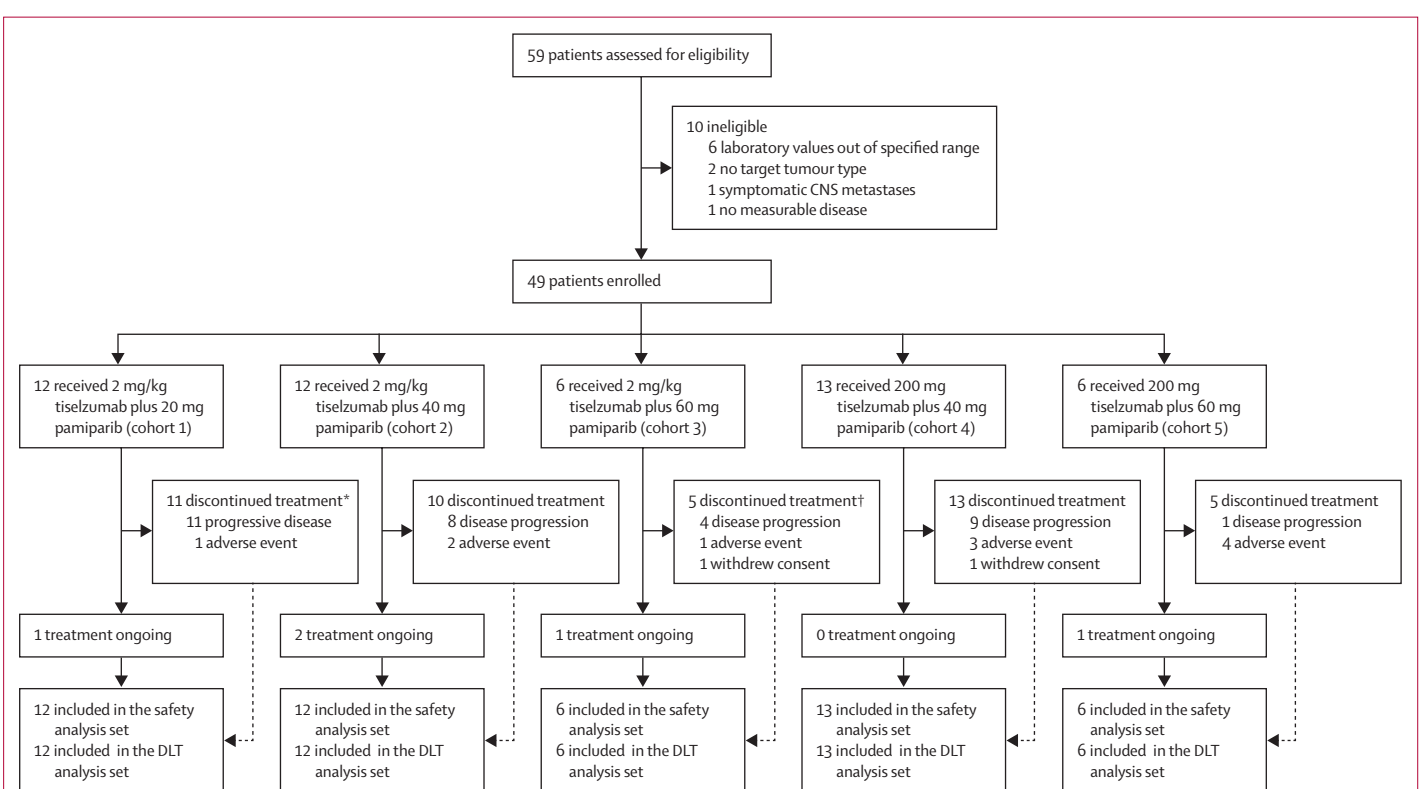

Figure 1: **Study profile**

Patients could withdraw each drug independently, thus the number of reasons for discontinuation in cohorts 1 and 3 exceeds the overall number of patients in the cohort. CNS=central nervous system. DLT=dose-limiting toxicity. *One patient discontinued tislelizumab due to adverse events and discontinued pamiparib due to disease progression. †One patient discontinued tislelizumab due to an adverse event and discontinued pamiparib due to consent withdrawal.

	Cohort 1 (n=12)	Cohort 2 (n=12)	Cohort 3 (n=6)	Cohort 4 (n=13)	Cohort 5 (n=6)	All enrolled patients (n=49)
Age, years	63 (56–70)	61 (55–65)	53 (48–64)	65 (55–68)	64 (59–68)	63 (55–67)
Sex						
Women	9 (75%)	11 (92%)	5 (83%)	12 (92%)	5 (83%)	42 (86%)
Men	3 (25%)	1 (8%)	1 (17%)	1 (8%)	1 (17%)	7 (14%)
Ethnicity						
White	10 (83%)	12 (100%)	5 (83%)	11 (85%)	6 (100%)	44 (90%)
Asian	2 (17%)	0	1 (17%)	2 (15%)	0	5 (10%)
Primary site of tumour						
Ovary, fallopian tube, or peritoneum	8	8	4	9	5	34*
Pancreas	1	1	1	0	0	3
Prostate	1	0	0	1	1	3
Breast	1	1	0	1	0	3
Bile duct	0	0	1	0	0	1
Bladder	0	1	0	0	0	1
Lung	1	0	0	0	0	1
Peripheral nerve sheath	0	0	0	1	0	1
Uterus	0	0	0	1	0	1
Cervix	0	1	0	0	0	1
BRCA mutation status†						
Positive	2	0	2	0	3	7
Wild-type	4	8	2	8	2	24
Missing or unknown	2	0	0	1	0	3

Data are median (IQR), n (%), or n.*16 patients had platinum-sensitive tumours and 18 patients had platinum-resistant tumours. †Data from patients with ovarian, fallopian tube, or peritoneal cancer (n=34).

Table 1: **Patient demographics and baseline characteristics (safety analysis set; n=49)**

	Grade 1–2	Grade 3	Grade 4
Nausea	31 (63%)	2 (4%)	0
Fatigue	26 (53%)	2 (4%)	0
Diarrhoea	17 (35%)	2 (4%)	0
Vomiting	15 (31%)	2 (4%)	0
Pyrexia	10 (20%)	0	0
Increased alanine aminotransferase	9 (18%)	2 (4%)	1 (2%)
Constipation	9 (18%)	0	0
Headache	9 (18%)	0	0
Upper respiratory tract infection	9 (18%)	0	0
Back pain	8 (16%)	0	0
Cough	8 (16%)	0	0
Urinary tract infection	8 (16%)	1 (2%)	0
Increased aspartate aminotransferase	7 (14%)	3 (6%)	0
Anaemia	6 (12%)	6 (12%)	0
Arthralgia	6 (12%)	0	0
Hypothyroidism	6 (12%)	0	0
Abdominal pain	5 (10%)	0	0
Dysgeusia	5 (10%)	0	0
Gastroesophageal reflux disease	5 (10%)	0	0
Maculopapular rash	5 (10%)	0	0
Pain in extremity	5 (10%)	0	0
Pruritus	5 (10%)	0	0
Thrombocytopenia	5 (10%)	0	0
Increased γ-glutamyl transferase	2 (4%)	3 (6%)	0
Hepatitis	1 (2%)	2 (4%)	0
Small intestinal obstruction	0	2 (4%)	0
Autoimmune hepatitis	0	1 (2%)	2 (4%)

Data are n (%). Only grade 1–2 events that occurred in 10% or more patients, and grade 3 and 4 events that occurred in two or more patients are presented. No grade 5 adverse events occurred. Adverse events, grade 3 or worse treatment-emergent adverse events by cohort, immune-related adverse events, and treatment-related adverse events are shown in the appendix (pp 9–13).

Table 2: **Treatment-emergent adverse events in the safety analysis set (n=49)**

endpoints were evaluated in this population, with the exception of dose-limiting toxicities, which were analysed in the dose-limiting toxicity analysis set); the efficacy evaluable set, which included all patients in the safety analysis set who had measurable disease at baseline and had at least one post-baseline tumour assessment, unless they had discontinued treatment due to disease progression or died before tumour assessment; and the dose-limiting toxicity analysis set, which included all patients who received at least 90% of the first scheduled tislelizumab dose and at least 75% of scheduled pamiparib doses, or who had a-limiting toxicity event during cycle 1. All patients with a dose-limiting toxicity event were included in the dose-limiting toxicity analysis set regardless of dosing or follow-up status, and thus the estimated dose-limiting toxicity rates were more conservative (ie, no lower) than those based on the safety population.

SAS (version 9.4) was used for statistical analyses. Descriptive statistics were used to summarise all study data. Continuous variables were summarised by number, mean (SD), and median (IQR) values. Categorical variables were summarised on the basis of the number and percentage of patients. The Kaplan–Meier method was used to estimate median progression-free survival and overall survival and accompanying 95% CIs. A formal interim analysis was done on June 23, 2017, when the dose-escalation phase was complete. This trial is registered with ClinicalTrials.gov, number NCT02660034.

Role of the funding source

The study protocol was developed by the funder in collaboration with the study investigators. The funder was also involved in data collection, analysis, interpretation of results, and writing of the report. The corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication.

Results

Between Jan 22, 2016, and May 16, 2017, 59 adult patients were assessed for eligibility, of whom 49 were enrolled (figure 1): 12 into cohort 1, 12 into cohort 2, six into cohort 3, 13 into cohort 4, and six into cohort 5. The median duration of follow-up was 8·3 months (IQR 4·8–12·8). At the data cutoff (March 26, 2018), 44 patients had discontinued both tislelizumab and pamiparib, with disease progression (n=33) being the most common reason. 11 patients discontinued treatment due to adverse events (appendix p 8), including two patients who discontinued tislelizumab independently of pamiparib.

Most patients were women (n=42), white (n=44), and had been diagnosed with ovarian, fallopian tube, or primary peritoneal carcinoma (n=34; table 1). The median age of the study population was 63 years (IQR 55–67). Among the study population, the median number of previous anticancer therapies was two (IQR 1–2), with 27 (55%) of 49 patients having received two or more previous treatment regimens.

BRCA testing was done in 31 (91%) of 34 patients with ovarian, peritoneal, or fallopian tube cancer at individual sites in accredited Australian laboratories. Six patients had a germline *BRCA1* (g*BRCA1*), mutation, one patient had a g*BRCA2* mutation, 24 were *BRCA* wild-type, and three had an unknown *BRCA* mutation status. Additionally, of the 34 samples from patients with ovarian, fallopian tube, or peritoneal tumours, 23 were submitted for HRD evaluation; 14 were positive for HRD, two were negative, and seven could not be evaluated due to insufficient DNA content (appendix pp 14, 15). Four additional tumour samples were submitted for HRD evaluation, which included three prostate cancer samples and one triple-negative breast cancer sample. The sample for triple-negative breast cancer and one prostate sample were positive for HRD, while the remaining two samples were not analysed due to insufficient DNA content.

Patients received a median of five (IQR 2–10) on-study treatment cycles with a median duration of exposure to tislelizumab of 85 days (IQR 43–191) and to pamiparib of 91 days (43–190). Tislelizumab infusion interruption occurred in one patient in cohort 2, who had a grade 1 infusion-related reaction. Interruptions in pamiparib administration occurred in 19 patients (four patients in cohort 1, three patients in cohort 2, three patients in cohort 3, five patients in cohort 4, and four patients in cohort 5), of whom eight patients required pamiparib dose reductions (one patient each in cohorts 1, 2, and 3; two patients in cohort 4; and three patients in cohort 5).

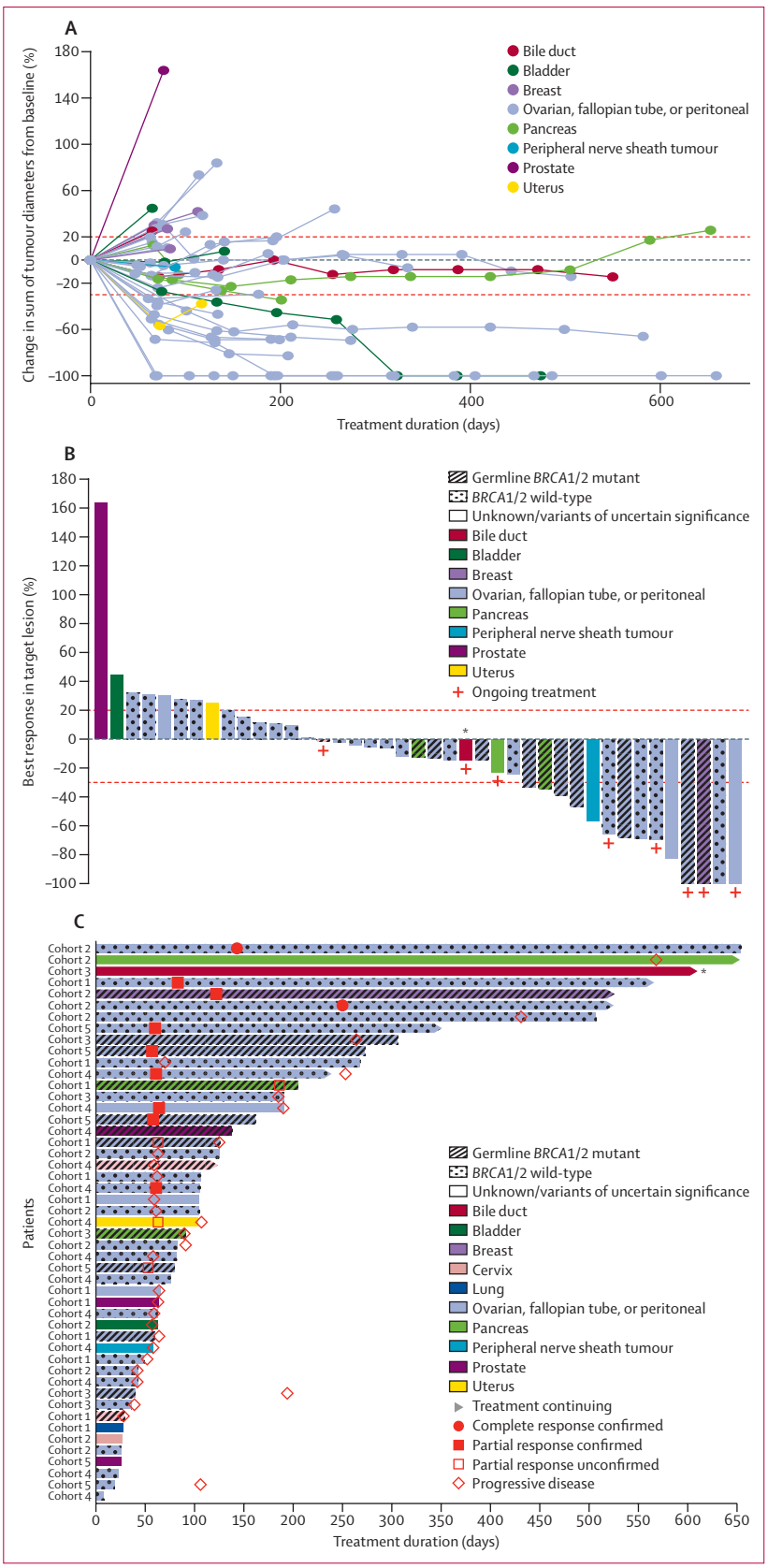

Figure 2: **Antitumour activity by tumour type**
(A) Change in tumour burden over time. Dotted lines at –30% and 20% indicate boundries for response and progression, respectively. (B) Best response in target lesion. Dotted lines at –30% and 20% indicate boundries for response and progression, respectively. (C) Treatment duration, time to best overall response, and time to first progression by tumour type. Each bar represents an individual patient. *Patient with cholangiocarcinoma with Lynch syndrome.

	All enrolled patients (n=49)
Complete response	2 (4%)
Partial response	8 (16%)
Stable disease	16 (32%)
Objective response*(95% CI)	20% (10–34)
Disease control† (95% CI)	53% (38–67)
Clinical benefit‡ (95% CI)	39% (25–54)
Ovarian cancer response§	
Complete response	1/34 (3%)
Partial response	8/34 (24%)
Stable disease	7/34 (21%)

Data are n (%) or n/N (%), unless otherwise specified. *Proportion of patients who achieved a complete response or partial response, according to RECIST version 1.1 criteria.[17] †Proportion of patients who achieved a complete response, partial response, or stable disease, according to RECIST version 1.1 criteria.[17] ‡Proportion of patients who achieved a complete response, partial response, or had durable stable disease for 24 weeks or longer, according to RECIST version 1.1 criteria.[17] §According to Gynecological Cancer Intergroup CA-125 response criteria.[18]

Table 3: **Best overall antitumour response in the safety analysis set (n=49)**

	BRCA wild-type (n=24)	*BRCA1/2* (n=7)	Unknown (n=3)
Complete response	2 (8%)	0	0
Partial response	4 (17%)	2 (29%)	1 (33%)
Stable disease	6 (25%)	4 (57%)	0
Objective response*	6 (25%)	2 (29%)	1 (33%)
Disease control†	12 (50%)	6 (86%)	1 (33%)

Data are n (%). *Proportion of patients who achieved complete or partial response, according to RECIST version 1.1 criteria.[17] †Proportion of patients who achieved complete response, partial response, or stable disease, according to RECIST version 1.1 criteria.[17]

Table 4: **Best overall antitumour response in patients with ovarian, fallopian tube, or peritoneal cancer by *BRCA* mutation status**

No dose-limiting toxicities were reported or observed in cohorts 1–3. During dose escalation, cohorts 1 and 2 enrolled additional patients to further evaluate safety before proceeding to the next dose level; thus, a total of 12 patients were enrolled into each of these two cohorts. Intractable grade 2 nausea (n=1) and grade 3 rash (n=1) were reported in the first six patients enrolled to cohort 4. In cohort 5, one patient had grade 2 nausea and vomiting and one patient had grade 4 immune-mediated hepatitis. Additional patients were enrolled to cohort 4 (total n=13) to confirm the safety profile. The recommended dose for further study (recommended phase 2 dose) was identified as the dose given in cohort 4: tislelizumab 200 mg intravenously every 3 weeks plus pamiparib 40 mg orally twice daily.

All 49 patients had one or more treatment-emergent adverse events (appendix p 9). The most commonly reported grade 1–2 treatment-emergent adverse events were nausea (31 [63%] of 49 patients), fatigue (26 [53%]), diarrhoea (17 [35%]), and vomiting (15 [31%]). The most common treatment-emergent adverse events of grade 3 or worse severity were anaemia (six [12%] patients), increased alanine transaminase concentration (three [6%]), increased aspartate aminotransferase concentration (three [6%]), increased γ-glutamyl transferase concentration (three [6%]), and autoimmune hepatitis (three [6%]); no fatal adverse events were reported (table 2). Hepatitis or autoimmune hepatitis were the only serious adverse events reported in two or more patients (four [8%] patients). Adverse events considered related to either pamiparib or tislelizumab are shown in the appendix (p 10). Grade 3 or worse treatment-related adverse events reported in at least two patients are listed by cohort in the appendix (p 11).

Immune-related adverse events observed in this study are in the appendix (pp 12, 13). Of the 23 patients who had an immune-related adverse event (four patients in cohort 1, four patients in cohort 2, three patients in cohort 3, six patients in cohort 4, and six patients in cohort 5), 12 (52%) had hepatic immune-related adverse events (immune-mediated hepatitis or increases in alanine transaminase and aspartate transaminase of any severity grade). In some patients, increased transaminase concentrations resolved after withdrawal of both treatments in the absence of corticosteroid treatment; in four patients, restarting pamiparib triggered an increase in transaminase concentrations. Grade 3–4 hepatic immune-related adverse events were reported in nine (39%) of the 23 patients with immune-related adverse events, all of whom were successfully treated with corticosteroids. Of the 12 patients who had hepatic immune-related adverse events, five had other immune-related events before, or that were coincident with, the hepatic immune-related adverse events; four events were dermatological (rash, psoriasis flare, and dermatitis) and one patient had grade 2 hypothyroidism in addition to a grade 2 rash.

The proportion of patients who achieved an objective response according to RECIST 1.1 was 20% (95% CI 10–34). Of the ten patients who achieved an objective response, two (4%) achieved a complete response and eight (16%) achieved a partial response (figure 2A, figure 2B; table 3). Both patients who achieved complete response were enrolled in cohort 2 and had *BRCA* wild-type ovarian cancers. Of the eight patients who achieved a partial response (one patient from cohort 1, one patient from cohort 2, three patients from cohort 4, and three patients from cohort 5), seven had ovarian, fallopian, or peritoneal cancer and one had breast cancer. 16 (32%) of 49 patients achieved stable disease; the proportion of patients achieving disease control was 53% (95% CI 38–67) and the proportion of patients who achieved clinical benefit was 39% (25–54).

Nine (26%) of the 34 patients with ovarian, fallopian tube, or peritoneal cancer achieved clinical responses according to RECIST 1.1 (two complete and seven partial responses), of whom six had platinum-sensitive tumours and three had platinum-resistant tumours (appendix

pp 14, 15). Responses were observed in patients with both wild-type and g*BRCA* status (figure 2C; table 4). Six patients with *BRCA* wild-type ovarian cancer had a complete response (n=2) or partial response (n=4); two patients with a *BRCA1/2* mutation and one patient for whom *BRCA* status was unknown had a partial response; the proportion of patients who achieved an objective response was similar between the *BRCA* wild-type (six [25%] of 24 patients) and *BRCA1/2* mutation (two [29%] of seven patients) groups. Best overall response, according to CA-125 response criteria, was assessed in the 34 patients with ovarian, fallopian tube, or peritoneal cancer. Of these 34 patients, one (3%) patient achieved a complete response, eight (24%) patients achieved a partial response, and seven (21%) patients had stable disease. Across the dose-escalation phase, 13 (27%) of 49 patients remained on treatment for more than 200 days.

The median progression-free survival was 92 days (95% CI 63 to 190) and median overall survival was 388 days (95% CI 253 to not reached; appendix pp 16, 17).

Coadministration of tislelizumab and pamiparib did not have a substantial effect on the pharmacokinetic profile of either compound. On day 1 of cycle 4, the mean steady-state trough and peak serum concentrations of tislelizumab were 24828 ng/mL (SD 9279) and 61111 ng/mL (20780), respectively. Time to maximum concentration for pamiparib across all three doses ranged from 1·9 to 2·2 h (data not shown). Pamiparib exposure (area under the curve and maximum plasma concentration) increased with increasing doses; however, the increases were less than dose proportional (data not shown).

Discussion

The underlying hypothesis of this study was that treatment with pamiparib would enhance the antitumour effects of tislelizumab PD-1 inhibition and combination treatment would be associated with a clinical benefit in patients with a range of tumour types, particularly in tumours that are commonly associated with HRD. The combination of pamiparib and tislelizumab exploits the potential accumulation of DNA damage resulting from PARP inhibition, which in turn might increase infiltration of immune cells into the tumour microenvironment, thereby increasing cancer cell killing. The recommended regimen for further investigation was determined to be 200 mg tislelizumab every 3 weeks and 40 mg pamiparib twice daily. The adverse events reported in this dose-escalation cohort were generally of low grade, and reversible with standard of care treatments; immune-related adverse events reported with the recommended dose (cohort 4) occurred in six of 13 patients. The dose-limiting toxicities observed in this cohort occurred in two of 13 patients, which met the protocol-specified criteria for continuation of the study. The safety profile of the combination was generally consistent with the safety profiles of each drug given as monotherapy and with other drugs in the checkpoint and PARP inhibitor class, with the exception of a higher frequency of hepatic adverse events. Most of the adverse events were grade 1 or 2 in severity and were not dose limiting. The causality assessment for adverse events was challenging because treatment included the use of two investigational products. Adverse events of interest included immune-related adverse events, which were reported in 23 patients, the most frequent of which were hepatic events.

Pharmacokinetic parameters were not presented due to the small sample size from which data were generated. In our analyses of the pharmacokinetic data, coadministration of the drugs did not affect the pharmacokinetic profiles of either agent, with the pharmacokinetic results for pamiparib similar to those observed in single-agent pamiparib trials.[20] Although pamiparib exposure increased with increasing doses, these increases were less than dose proportional, probably due to the small sample size.

Immune-related hepatic adverse events have previously been associated with PD-1 inhibitors,[21,22] especially when administered in combination with other drugs, such as cytotoxic T lymphocyte-associated protein 4 inhibitors. Increases in transaminase levels have been reported with PARP inhibition, most notably with rucaparib,[23,24] but this has generally not been observed in patients treated with pamiparib or tislelizumab monotherapy. In early-phase monotherapy studies, less than 5% of patients had liver enzyme elevation with pamiparib[20] and less than 6% of patients had elevations when treated with tislelizumab.[25]

The elevations in hepatic enzymes observed most likely represent a drug-induced reaction, but do not meet the criteria for drug-induced liver injury, which by consensus includes an increase in serum alanine transaminase or aspartate transaminase concentrations greater than five times the upper limit of normal or previous baseline concentration on two consecutive examinations; serum alkaline phosphatase concentrations greater than two times the upper limit of normal; bilirubin concentrations greater than 2·5 mg/dL with any elevation in liver enzymes; or an international normalised ratio greater than 1·5 with any elevation in liver enzymes.[26] Considering the rapid onset and resolution with corticosteroid treatment in the current study, these hepatic adverse events are likely to have an inflammatory, and possibly an immune-mediated, component. In some patients, resolution of the increased transaminase concentrations occurred after withdrawal of both treatments in the absence of corticosteroid treatment. Hepatic synthetic function was not impaired in any of the patients. Although transaminase elevation resolved with temporary treatment discontinuation, and without corticosteroid treatment in some patients, restarting pamiparib triggered an increase in transaminase concentrations in four patients, suggesting an upregulated inflammatory response with the

combination therapy. Hepatic adverse events were observed at all dose levels, and it is unclear whether these hepatic immune-related adverse events were associated with the exposure to, or treatment duration of, the combined therapy.[27] Other potential contributory factors, such as concomitant medication use, extensive liver metastases, or viral hepatitis, were ruled out. All patients in this study were carefully monitored with frequent liver function test evaluations to facilitate early diagnosis and corticosteroid treatment. Evaluation of risk factors for these hepatic adverse events is ongoing and includes hepatic biopsy when feasible. Clinical diagnosis of immune-mediated hepatitis can be difficult, which explains why some patients were reported to have an increase in transaminases without being assigned a specific diagnosis and others were reported as having immune-related hepatitis. Considering the small sample size of this study and the broad range of patients included, it is unclear whether the hepatic adverse events are associated with a specific disease type or genetic or biomarker profile that would help identify patients at higher risk. By contrast with data suggesting an association between immune-related adverse events and tumour response,[28] when considering the responses achieved by the patients who had hepatic adverse events, these events did not seem to be associated with an increased proportion of patients achieving an objective response in this study (responses ranged from progressive disease to complete response), suggesting that in some patients the elevated transaminases might not necessarily be a manifestation of an immune-mediated reaction.

Since these data are from a small non-randomised dose-escalation study, several limitations exist, which might affect the generalisability of the results. For the dose-escalation phase of this study, we recruited a heterogeneous group of patients with a variety of advanced solid tumours, many of whom were heavily pretreated. Although these results showed modest benefits, it is possible the combination therapy would have greater activity if these patients were treated earlier in their disease trajectory. Another potential limitation was that known *BRCA* status and HRD testing were not a requirement for inclusion in the trial. As such, data on germline *BRCA* mutations were not available for all patients, and no data were available on germline mutations in other homologous recombination genes such as *RAD51C*, *ATM*, and *BARD1*. Similar to many phase 1 trials with a 3+3 dose-escalation scheme, dose-limiting toxicities were determined after one cycle of treatment. Some checkpoint inhibitor toxicities, especially immune-related adverse events, can occur later in treatment. These limitations have been addressed in the dose-expansion phase of the study, which is ongoing, and will be reported separately.

The results of this study, and the observed activity of the combination, support continuation of the trial and exploration of the activity of pamiparib plus tislelizumab in disease-specific cohorts. The selection of disease-specific cohorts in phase 1b was based on pathological subtypes that might be associated with endogenous loss of DNA damage repair or exogenous DNA damage. Endogenous mutational damage and exogenous DNA damage might limit the capacity of cancer cells to repair DNA, making cancer cells susceptible to PARP inhibition. Moreover, high somatic non-synonymous mutation burden has been associated with the clinical efficacy of PD-1 inhibition.[29] Overall, the data presented support the continued investigation of pamiparib and tislelizumab, with close monitoring of liver function tests, in tumour-specific cohorts who are most likely to benefit from this combination therapy.

Contributors

MF was the principle Investigator. MF, JW, and VP conceptualised and designed the study. VP and JW were involved in the collection and analysis of the data. All authors were responsible for data analysis and interpretation, contributed to the preparation and writing of the manuscript, and approved the final manuscript.

Declaration of interests

MF has received honoraria from AstraZeneca, Merck Sharp & Dohme, Lilly, and Takeda; serves in a consulting or advisory role for AstraZeneca and Merck Sharp & Dohme; and has received research funding from BeiGene and AstraZeneca. TM has received honoraria from and serves in a consulting or advisory role for AstraZeneca; has received research funding from AstraZeneca, Bayer, BeiGene, Bristol-Myers Squibb, Incyte, Merck Serono, Regeneron, and Roche; and has received reimbursement for travel, accommodation, and expenses from Roche. BM serves in a consulting or advisory role for Novartis and has received reimbursement for travel, accommodation, and expenses from BeiGene. LM has received travel, accommodations, and expenses from BeiGene and Roche. MM serves in a consulting or advisory role for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Roche; and has received reimbursement for travel, accommodation, and expenses from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Roche. AF has received research funding from BeiGene. SM, JW, and VP are employees of BeiGene. PH, JL, CN, and BG declare no competing interests.

Data sharing

Upon request, and subject to certain criteria, conditions, and exceptions, BeiGene will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines for indications that have been approved or in programmes that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests can be submitted to medicalinformation@beigene.com.

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References

1 Gasser S, Raulet D. The DNA damage response, immunity and cancer. *Semin Cancer Biol* 2006; **16:** 344–47.
2 Strickland KC, Howitt BE, Shukla SA, et al. Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer. *Oncotarget* 2016; **7:** 13587–98.
3 Nausch N, Cerwenka A. NKG2D ligands in tumor immunity. *Oncogene* 2008; **27:** 5944.
4 Mouw KW, D'Andrea AD. DNA repair deficiency and immunotherapy response. *J Clin Oncol* 2018; **36:** 1710–13.

5 Jiao S, Xia W, Yamaguchi H, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. *Clin Cancer Res* 2017; **23:** 3711–20.

6 Huang J, Wang L, Cong Z, et al. The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a Brca1(-/-) murine model of ovarian cancer. *Biochem Biophys Res Commun* 2015; **463:** 551–56.

7 Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015; **348:** 124–28.

8 Gupta SK, Carlson BL, Schroeder MA, Bakken KK, Tuma AC, Sarkaria JN. Inhibition of PARP activity by BGB-290 potentiates efficacy of temozolomide in patient derived xenografts of glioblastoma multiforme. *Cancer Res* 2015; **75** (suppl 15)**:** 3505.

9 Tang Z, Liu Y, Zhen Q, et al. BGB-290: A highly potent and specific PARP1/2 inhibitor potentiates anti-tumor activity of chemotherapeutics in patient biopsy derived SCLC models. *Cancer Res* 2015; **75** (suppl 15)**:** 1653.

10 Tang Z, Jiang B, Shi Z, et al. BGB-290, a novel PARP inhibitor with unique brain penetration ability, demonstrated strong synergism with temozolomide in subcutaneous and intracranial xenograft models. *Cancer Res* 2015; **75** (suppl 15)**:** 1651.

11 Lickliter JD, Gan HK, Meniawy T, et al. A phase I dose-escalation study of BGB-290, a novel PARP1/2 selective inhibitor in patients with advanced solid tumors. *Proc Am Soc Clin Oncol* 2016; **34** (suppl 15)**:** e17049.

12 Zhang T, Song X, Xu L, et al. The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. *Cancer Immunol Immunother* 2018; **67:** 1079–90.

13 Zhang T, Song J, Li Y, et al. Anti-human PD-1 antibody BGB-A317 exhibits potent immune cell activation. *Cancer Res* 2016; **76** (suppl 14)**:** 2226 (abstr).

14 Song X, Tang Z, Zhang T, et al. Anti-tumor activity of a novel anti-human PD-1 antibody BGB-A317 in mouse models. *Cancer Res* 2016; **76** (suppl 14)**:** 5002 (abstr).

15 Desai J, Markman B, Sandhu SK, et al. A phase I dose-escalation study of BGB-A317, an anti-programmed death-1 (PD-1) mAb in patients with advanced solid tumors. *Proc Am Soc Clin Oncol* 2016; **34** (suppl 15)**:** 3066.

16 US Department of Health and Human Services. Common Termiology Criteria for Adverse Events (CTCAE), version 4.03. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (accessed July 21, 2019).

17 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

18 Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *Int J Gynecol Cancer* 2011; **21:** 419–23.

19 Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008; **26:** 1148–59.

20 Lickliter JML, Mileshkin L, Voskoboynik M, et al. Dose escalation/expansion study to investigate the safety, pharmacokinetics, food effect, and antitumor activity of BGB-290 in patients with advanced solid tumors. European Society for Medical Oncology Congress; Madrid; Sept 8–12, 2017. 368PD.

21 Zhang X, Ran Y, Wang K, Zhu Y, Li J. Incidence and risk of hepatic toxicities with PD-1 inhibitors in cancer patients: a meta-analysis. *Drug Des Devel Ther* 2016; **10:** 3153–61.

22 Amin A, Plimack ER, Infante JR, et al. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with sunitinib or pazopanib in patients with metastatic renal cell carcinoma (mRCC). *Proc Am Soc Clin Oncol* 2014; **32** (suppl 15)**:** 5010.

23 Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **390:** 1949–61.

24 Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. *J Clin Oncol* 2015; **33:** 2092–99.

25 Desai J MM, Millward M, Chao Y, et al. Preliminary results from subsets of patients with advanced gastric cancer and esophageal carcinoma in a dose-escalation/expansion study of BGB-A317, an anti-PD-1 monoclonal antibody. European Society for Medical Oncology Congress; Madrid; Sept 8–12, 2017. 387P.

26 Hayashi PH. Drug-Induced Liver Injury Network Causality Assessment: criteria and experience in the United States. *Int J Mol Sci* 2016; **17:** 201.

27 Haanen J, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28** (suppl 4)**:** iv119–42.

28 Shafqat H, Gourdin T, Sion A. Immune-related adverse events are linked with improved progression-free survival in patients receiving anti-PD-1/PD-L1 therapy. *Semin Oncol* 2018; **45:** 156–63.

29 Chabanon RM, Pedrero M, Lefebvre C, Marabelle A, Soria JC, Postel-Vinay S. Mutational landscape and sensitivity to immune checkpoint blockers. *Clin Cancer Res* 2016; **22:** 4309–21.