POSTER #123

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

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DISCLOSURES

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

ACKNOWLEDGMENTS

We thank the investigative center study staff, the study patients, and their families. We thank Envision Pharma Group for their medical writing and editorial assistance, which was funded by BeiGene.

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Presented at the 2019 ASCO Annual Meeting, May 31 – June 4, 2019, Chicago, IL, USA

BACKGROUND

- Inhibitors of programmed death protein 1/ligand 1 (PD-1/PD-L1) and poly (ADP-ribose) polymerase (PARP) have improved treatment outcomes for patients with solid tumors
- Nonclinical data have demonstrated that DNA damage and immune response are directly associated, supporting the combination of PD-1/PD-L1 and PARP inhibitors[1–4]
- Tislelizumab is an anti-PD-1 inhibitor that was generally well tolerated and showed antitumor activity in a phase 1 trial[5]
- Pamiparib is a selective and potent PARP1/2 inhibitor that was generally well tolerated and showed antitumor activity in phase 1/2 trials[6,7]

OBJECTIVE

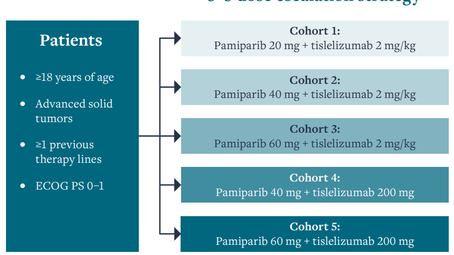
- This multicenter, open-label, phase 1a/b study (NCT02660034) aimed to evaluate the safety, tolerability, antitumor activity, and pharmacokinetics (PK) of pamiparib + tislelizumab in patients with advanced solid tumors

METHODS

Study design and outcomes

- Patients were enrolled into 5 cohorts (**Figure 1**)
- The primary endpoint was safety and tolerability (**Figure 1**)

Figure 1. Study design and endpoints



Dosing

- Pamiparib PO BD on Days 1–21 + tislelizumab IV Q3W on Day 1 (21-day cycle)
- Dose escalation until MTD* is reached or RP2D is determined

Primary endpoint

- Safety and tolerability, including DLTs, MTD, and RP2D

Secondary endpoints

- Objective response rate†
- Disease control rate‡
- Clinical benefit rate§
- PFS
- OS
- PK

Study eligibility was assessed between January 22, 2016 and May 16, 2017. Data cutoff was March 26, 2018. *Occurrence of DLT in 2/6 patients. †Proportion of patients achieving CR/PR, according to RECIST version 1.1 criteria[8] or CA-125 response criteria in ovarian cancer.[9] ‡Patients achieving CR/PR/SD. §Best overall response of CR/PR/SD lasting ≥24 weeks. BD, twice daily; CR, complete response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SD, stable disease.

Statistical analysis

- Endpoints were analyzed in the safety analysis set of all patients who received ≥1 dose of study drug except for dose-limiting toxicities (DLTs)
- DLTs were analyzed in the DLT analysis set of patients receiving ≥90% of the first tislelizumab dose and ≥75% of pamiparib doses, or who had a DLT event during cycle 1

RESULTS

Patient disposition and baseline characteristics

- A total of 49 patients were enrolled from 5 sites in Australia
  - All received ≥1 dose of pamiparib or tislelizumab
  - At data cut-off, 44 patients had discontinued both pamiparib and tislelizumab (33 due to disease progression, 11 due to adverse events [AEs])
  - Most (69%) patients had ovarian, fallopian tube, or primary peritoneal carcinoma (**Figure 2**)

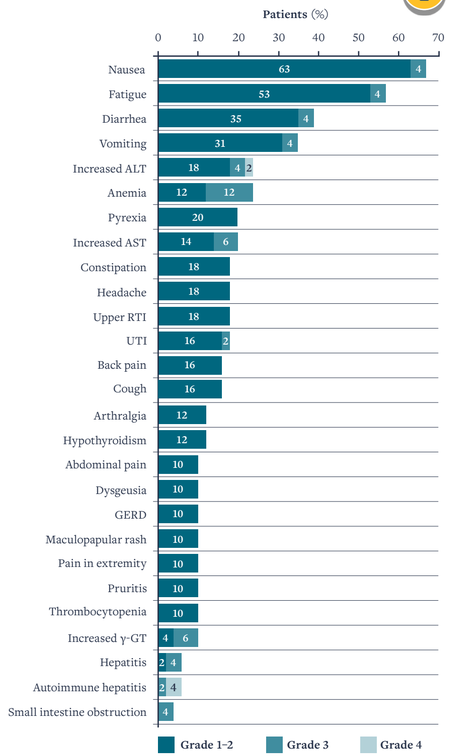
Figure 2. Baseline characteristics, follow-up, and exposure

IQR, interquartile range.

Primary endpoint: safety

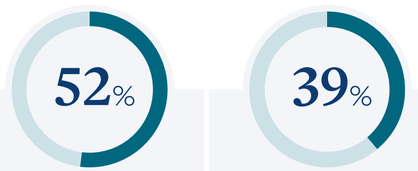
- DLTs per cohort were as follows:
  - Cohorts 1–3: no DLTs reported
  - Cohort 4: intractable nausea (grade 2; n=1) and rash (grade 3; n=1) in the first 6 patients
    - This was identified as the maximum tolerated dose
    - Additional patients were enrolled to cohort 4 (total n=13) to confirm the safety profile
  - Cohort 5: nausea and vomiting (grade 2; n=1) and immune-mediated hepatitis (grade 4; n=1)
- RP2D was identified as the cohort 4 dose: **pamiparib 40 mg twice daily (BD) plus tislelizumab 200 mg every 3 weeks (Q3W)**
- All 49 patients had ≥1 treatment-emergent AE (TEAE)
  - Nausea, fatigue, diarrhea, and vomiting were the most frequent TEAEs (**Figure 3**)
  - Most TEAEs were mild to moderate (**Figure 3**)
- AEs of interest included immune-related AEs (irAEs), which were reported in 23 patients
  - The most frequent irAEs were hepatic events (**Figure 4**)

Figure 3. TEAEs by severity (N=49)



TEAEs in order of frequency; only grade 1–2 events that occurred in 10% or more patients, and grade 3–4 events that occurred in 2 or more patients are presented. No grade 5 AEs occurred. AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GERD, gastroesophageal reflux disease; γ-GT, γ-glutamyl transferase; RTI, respiratory tract infection; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

Figure 4. Hepatic immune-related AEs*



- 12/23 patients
- 5/12 had other irAEs before or coincident with hepatic irAEs
- Four irAEs were dermatological†
- One patient had rash and hypothyroidism (both grade 2)

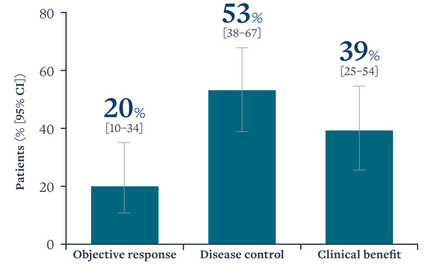
- 9/23 patients
- All events resolved with corticosteroid treatment

*Immune-mediated hepatitis or increases in alanine transaminase or aspartate transaminase of any grade. †Rash, psoriasis flare, and dermatitis. AEs, adverse events; irAE, immune-related adverse event.

Secondary endpoints: antitumor activity and PK

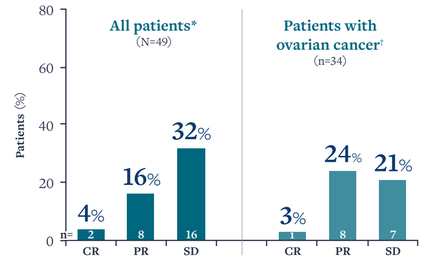
- Ten (20%) patients achieved an objective response (**Figure 5**)
- Disease control was achieved by 53% and clinical benefit by 39% (**Figure 6**)
- Antitumor responses were observed in several tumor types, including in ovarian cancer (**Figure 6**)
- Median progression-free survival was 92 days (95% confidence interval [CI]: 63–190); median overall survival was 388 days (95% CI: 253–not reached)
- Coadministration of pamiparib and tislelizumab did not have a substantial effect on the PK profile of either compound

Figure 5. Antitumor response*



*According to RECIST version 1.1 criteria.[8] CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 6. Best overall antitumor response



*According to RECIST version 1.1 criteria.[8] †Including fallopian tube and peritoneal cancer, according to Gynecological Cancer Intergroup CA-125 response criteria.[9] CR, complete response; PR, partial response; SD, stable disease ; RECIST, Response Evaluation Criteria in Solid Tumors.

Limitations

- Study limitations will be addressed in the ongoing dose-expansion phase of the trial

CONCLUSIONS

- RP2D was determined to be pamiparib 40 mg BD + tislelizumab 200 mg Q3W
- Pamiparib + tislelizumab was generally well tolerated and associated with antitumor response
- These data support further investigation of this combination in tumor-specific cohorts who are most likely to benefit, with close monitoring for hepatic irAEs

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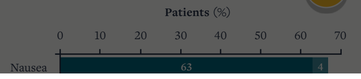

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Background: Targeting the immune response and DNA repair mechanisms in solid tumors

Inhibiting the immune checkpoint pathway

- Known as immuno-oncology or immunotherapy, antibodies that target the immune checkpoint pathway such as PD-1 or PD-L1 inhibitors are effective treatments in several solid tumors
- Tislelizumab, a humanized anti-PD-1 monoclonal antibody, was generally well tolerated and showed antitumor activity in a phase 1 trial (RP2D 200 mg Q3W)[1]

Inhibiting DNA repair mechanisms

- Inhibitors of DNA repair mechanisms such as PARP are effective treatments in several solid tumors
- Pamiparib, a highly selective and potent PARP1/2 inhibitor,[2] was generally well tolerated and showed antitumor activity in phase 1/2 trials (RP2D 60 mg BD)[3]

Inhibiting both the immune checkpoint pathway and DNA repair mechanisms

- Non-clinical data show a direct association between immune responses and DNA damage[4–7]
  - PD-L1 expression can be upregulated by PARP inhibition
  - Blockade of the PD-1/PD-L1 pathway may potentiate PARP inhibitor-induced tumor suppression
  - PARP inhibition could enhance sensitivity to PD-1/PD-L1 inhibitors when used in combination
- As such, combination treatment comprising immune checkpoint inhibitors and PARP inhibitors could be associated with a clinical benefit in patients with a range of solid tumor types

BD, twice daily; mAb, monoclonal antibody; PARP, poly (ADP-ribose) polymerase; PD-1/PD-L1, programmed cell death protein 1/ligand 1; Q3W, every 3 weeks; RP2D, recommended phase 2 dose.

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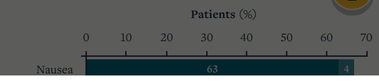

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Patient eligibility and study design

Eligible patients

- ≥18 years
- Histologically/cytologically confirmed advanced solid tumors
- Measurable disease (RECIST version 1.1)
- ≥1 previous lines of therapy
- ECOG PS ≤1
- Life expectancy ≥12 weeks
- Adequate organ function
- Transfusion independent

Patients with a history of severe hypersensitivity reactions to other mAb, a previous invasive malignancy within 2 years of enrolment, symptomatic brain metastases, and those who had previous therapies targeting PD-1/PD-L1 or PARP, were excluded.
*Patients were treated until PD, toxicity, physician/patient withdrawal, or non-compliance. Dose interruptions (pamiparib for ≤21 consecutive days and tislelizumab for ≤42 consecutive days) and dose modifications (pamiparib only) were permitted.
[†]Defined as the occurrence of a DLT (a prespecified AE/abnormal laboratory value deemed unrelated to PD, intercurrent illness, or concomitant medications, occurring during the first 21 days following the first dose of tislelizumab and pamiparib in cycle 1, that met the criteria for hematological/nonhematological toxicities) in 2/6 treated patients in a cohort.
[‡]Based on safety and PK profile.
[§]Categorized according to severity (CTCAE v4.03), seriousness, and relation to the study drug.
AE, adverse event; BD, twice daily; CT, computed tomography; CTCAE, Common Toxicity Criteria for Adverse Events; DLT, dose-limiting toxicity; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; mAb, monoclonal antibody; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PD-1/PD-L1, programmed death protein 1/ligand 1; PK, pharmacokinetics; PO, orally; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose.

1. U.S. Department of Health and Human Services. CTCAE, version 4.03. https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf (accessed July 21, 2019); 2. Eisenhauer EA, et al. *Eur J Cancer* 2009;45:228–47; 3. Rustin GJ, et al. *Int J Gynecol Cancer* 2011;21:419–23; 4. Scher HI, et al. *J Clin Oncol* 2008;26:1148–59.

3+3 dose escalation strategy

Cohort 1: Pamiparib 20 mg + tislelizumab 2 mg/kg

Cohort 2: Pamiparib 40 mg + tislelizumab 2 mg/kg

Cohort 3: Pamiparib 60 mg + tislelizumab 2 mg/kg

Cohort 4: Pamiparib 40 mg + tislelizumab 200 mg

Cohort 5: Pamiparib 60 mg + tislelizumab 200 mg

Dosing:*

- Pamiparib PO BD on Days 1–21 of a 21-day cycle
- Tislelizumab IV Q3W on Day 1 of a 21-day cycle

Dose escalation continued until either:

the MTD[†] was reached, or the RP2D[‡] was determined

Safety assessments

- At each visit: AEs,[§1] vital signs, and physical examination
- During each cycle: ECG and clinical laboratory investigations

Antitumor activity assessments

- Radiographical imaging (CT or MRI) at screening within 28 days before enrolment, every 9 weeks (± 1 week) in the first 12 months, and every 12 weeks (± 1 week) thereafter
- Tumor response: investigator assessed according to RECIST version 1.1 criteria[2]
- Ovarian/fallopian tube/primary peritoneal tumors assessed by Gynecological Cancer Intergroup CA-125 response criteria[3]
- Prostate cancer responses assessed by Prostate Cancer Working Group 2 criteria[4]

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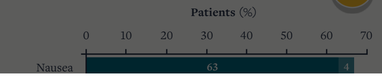
Figure 3. TEAEs by severity (N=49)



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- Most TEAEs were mild to moderate (**Figure 3**)

- AEs of interest included immune-related AEs (irAEs), which were reported in 23 patients
  - The most frequent irAEs were hepatic events (**Figure 4**)

- One patient had rash and hypothyroidism (both grade 2)

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24% 21%
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- These data support further investigation of this combination in tumor-specific cohorts who are most likely to benefit, with close monitoring for hepatic irAEs

Patient eligibility and study design

Eligible patients

- ≥18 years
- Histologically/cytologically confirmed advanced solid tumors
- Measurable disease (RECIST version 1.1)
- ≥1 previous lines of therapy
- ECOG PS ≤1
- Life expectancy ≥12 weeks
- Adequate organ function
- Transfusion independent

3+3 dose escalation strategy

- **Cohort 1:** Pamiparib 20 mg + tislelizumab 2 mg/kg
- **Cohort 2:** Pamiparib 40 mg + tislelizumab 2 mg/kg
- **Cohort 3:** Pamiparib 60 mg + tislelizumab 2 mg/kg
- **Cohort 4:** Pamiparib 40 mg + tislelizumab 200 mg
- **Cohort 5:** Pamiparib 60 mg + tislelizumab 200 mg

Dosing:*

- Pamiparib PO BD on Days 1–21 of a 21-day cycle
- Tislelizumab IV Q3W on Day 1 of a 21-day cycle

Dose escalation continued until either:

the MTD[†] was reached, or the RP2D[‡] was determined

Patients with a history of severe hypersensitivity reactions to other mAb, a previous invasive malignancy within 2 years of enrolment, symptomatic brain metastases, and those who had previous therapies targeting PD-1/PD-L1 or PARP, were excluded.
*Patients were treated until PD, toxicity, physician/patient withdrawal, or non-compliance. Dose interruptions (pamiparib for ≤21 consecutive days and tislelizumab for ≤42 consecutive days) and dose modifications (pamiparib only) were permitted.
[†]Defined as the occurrence of a DLT (a prespecified AE/abnormal laboratory value deemed unrelated to PD, intercurrent illness, or concomitant medications, occurring during the first 21 days following the first dose of tislelizumab and pamiparib in cycle 1, that met the criteria for hematological/nonhematological toxicities) in 2/6 treated patients in a cohort.
[‡]Based on safety and PK profile.
AE, adverse event; BD, twice daily; CR, complete response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PD-1/PD-L1, programmed death protein 1/ligand 1; PFS, progression-free survival; PK, pharmacokinetic; PO, orally; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SAS, safety analysis set; SD, stable disease.

Primary endpoint (dose escalation phase)

- **Safety and tolerability:** DLT, MTD (defined as DLT in 2/6 patients), RP2D

Secondary endpoints

- **Antitumor response:** ORR (CR/PR, according to RECIST version 1.12 [overall population] and CA-125 response criteria[3] [patients with ovarian cancer]); disease control rate (patients with CR/PR/SD); clinical benefit rate (CR/PR/SD lasting ≥24 weeks); PFS; OS
- **PK**

Antitumor activity assessments

- **SAS:** all patients who received ≥1 dose of pamiparib or tislelizumab
- **DLT analysis set:** patients receiving ≥90% of the first tislelizumab dose and ≥75% of pamiparib doses, or who had a DLT event during cycle 1
- **Efficacy evaluable set:** all patients in the SAS with measurable disease at baseline and ≥1 post-baseline tumor assessment, unless they had discontinued treatment due to PD or died before tumor assessment

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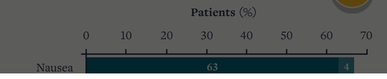

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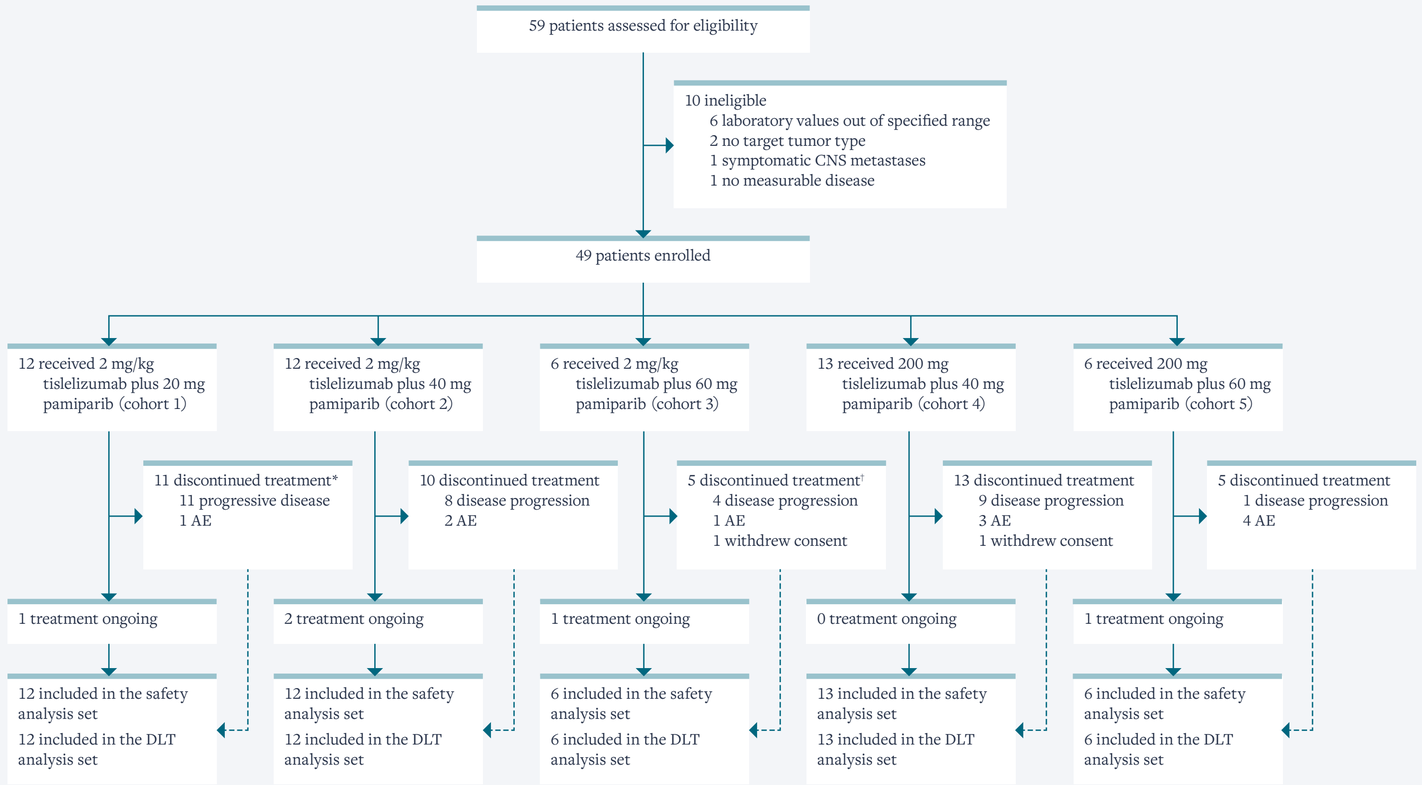
Patient flow diagram



As patients could withdraw each drug independently, the number of reasons for discontinuation in cohorts 1 and 3 exceeds the overall number of patients in the cohorts

*One patient discontinued tislelizumab due to AE and discontinued pamiparib due to disease progression.
†One patient discontinued tislelizumab due to an AE and discontinued pamiparib due to consent withdrawal.
AE, adverse event; CNS, central nervous system; DLT, dose-limiting toxicity.

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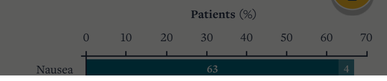

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- These data support further investigation of this combination in tumor-specific cohorts who are most likely to benefit, with close monitoring for hepatic irAEs

Patient demographics and baseline characteristics

- Median age was 63 years (IQR: 55–67)
- Most patients were women (86%), White (90%), and had ovarian, fallopian tube, or primary peritoneal carcinoma (69%)

Duration of study follow-up and duration of exposure

- Median duration of study follow-up was 8.3 months (IQR: 4.8–12.8)
- Median number of treatment cycles was 5 (IQR: 2–10)

	Cohort 1 (n=12)	Cohort 2 (n=12)	Cohort 3 (n=6)	Cohort 4 (n=13)	Cohort 5 (n=6)	All patients (N=49)
Median age (IQR), years	63 (56–70)	61 (55–65)	53 (48–64)	65 (55–68)	64 (59–68)	63 (55–67)
Sex, n (%)						
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, n (%)						
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 tumor, n						
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, n†**						
Positive	2	0	2	0	3	7
Wild type	4	8	2	8	2	24
Missing/unknown	2	0	0	1	0	3

The safety analysis set comprised all patients who received ≥1 dose of pamiparib or tislelizumab.
*16 patients had platinum-sensitive tumors and 18 patients had platinum-resistant tumors.
[†]Data from patients with ovarian, fallopian tube, or peritoneal cancer (n=34).
BRCA, breast cancer gene; IQR, interquartile range.

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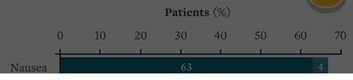

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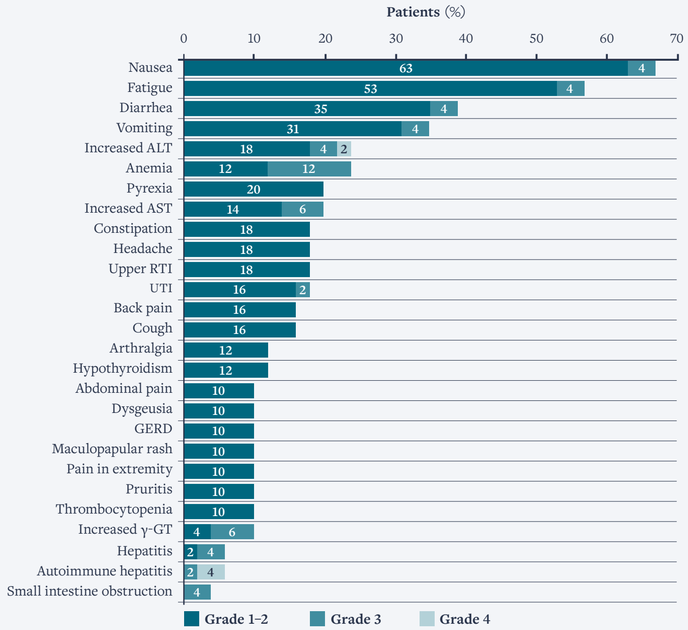
Safety: TEAEs and irAEs

- All 49 patients had ≥1 TEAE
- Most TEAEs were mild or moderate
- The most common grade 1–2 TEAEs were:
  - Nausea (31/49 [63%])
  - Fatigue (26/49 [53%])
  - Diarrhea (17/49 [35%])
  - Vomiting (15/49 [31%])
- The most common grade 3–4 TEAEs were:
  - Anemia (6/49 [12%])
  - Increased ALT (3/49 [6%]
  - Increased AST (3/49 [6%])
  - Increased γ-GT (3/49 [6%])
  - Autoimmune hepatitis (3/49 [6%])
- Hepatitis/autoimmune hepatitis were the only SAEs reported in ≥2 patients (4/49 [8%])
- No fatal AEs were reported
- AEs of interest included irAEs, which were reported in 23 patients
- The most frequent irAEs were hepatic (12/23 [52%])
  - Grade 3–4 hepatic irAEs were reported in 9/23 (39%) patients; all resolved with corticosteroid treatment

The safety analysis set (N=49) comprised all patients who received ≥1 dose of tislelizumab or pamiparib. No grade 5 AEs occurred.
*Immune-mediated hepatitis or increases in ALT/AST.
†Rash, psoriasis flare, and dermatitis.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; GERD, gastroesophageal reflux disease; irAE, immune-related adverse event; RTI, respiratory tract infection; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

TEAEs in order of frequency



AE, n (%)	Grade 1–2	Grade 3	Grade 4
Nausea	31 (63)	2 (4)	0
Fatigue	26 (53)	2 (4)	0
Diarrhea	17 (35)	2 (4)	0
Vomiting	15 (31)	2 (4)	0
Increased ALT	9 (18)	2 (4)	1 (2)
Anemia	6 (12)	6 (12)	0
Pyrexia	10 (20)	0	0
Increased AST	7 (14)	3 (6)	0
Constipation	9 (18)	0	0
Headache	9 (18)	0	0
Upper RTI	9 (18)	0	0
UTI	8 (16)	1 (2)	0
Back pain	8 (16)	0	0
Cough	8 (16)	0	0
Arthralgia	6 (12)	0	0
Hypothyroidism	6 (12)	0	0
Abdominal pain	5 (10)	0	0
Dysgeusia	5 (10)	0	0
GERD	5 (10)	0	0
Maculopapular rash	5 (10)	0	0
Pain in extremity	5 (10)	0	0
Pruritis	5 (10)	0	0
Thrombocytopenia	5 (10)	0	0
Increased γ-GT	2 (4)	3 (6)	0
Hepatitis	1 (2)	2 (4)	0
Autoimmune hepatitis	0	1 (2)	2 (4)
Small intestine obstruction	0	2 (4)	0

Hepatic irAEs* of any severity

- 12/23 patients
- 5/12 had other irAEs before or coincident with hepatic irAEs
- Four irAEs were dermatological†
- One patient had rash and hypothyroidism (both grade 2)

Grade 3–4 hepatic irAEs

- 9/23 patients
- All events resolved with corticosteroid treatment

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Best overall antitumor response* in the SAS (N=49)

Objective response
- Achieved in 20% (95% CI 10–34) of patients

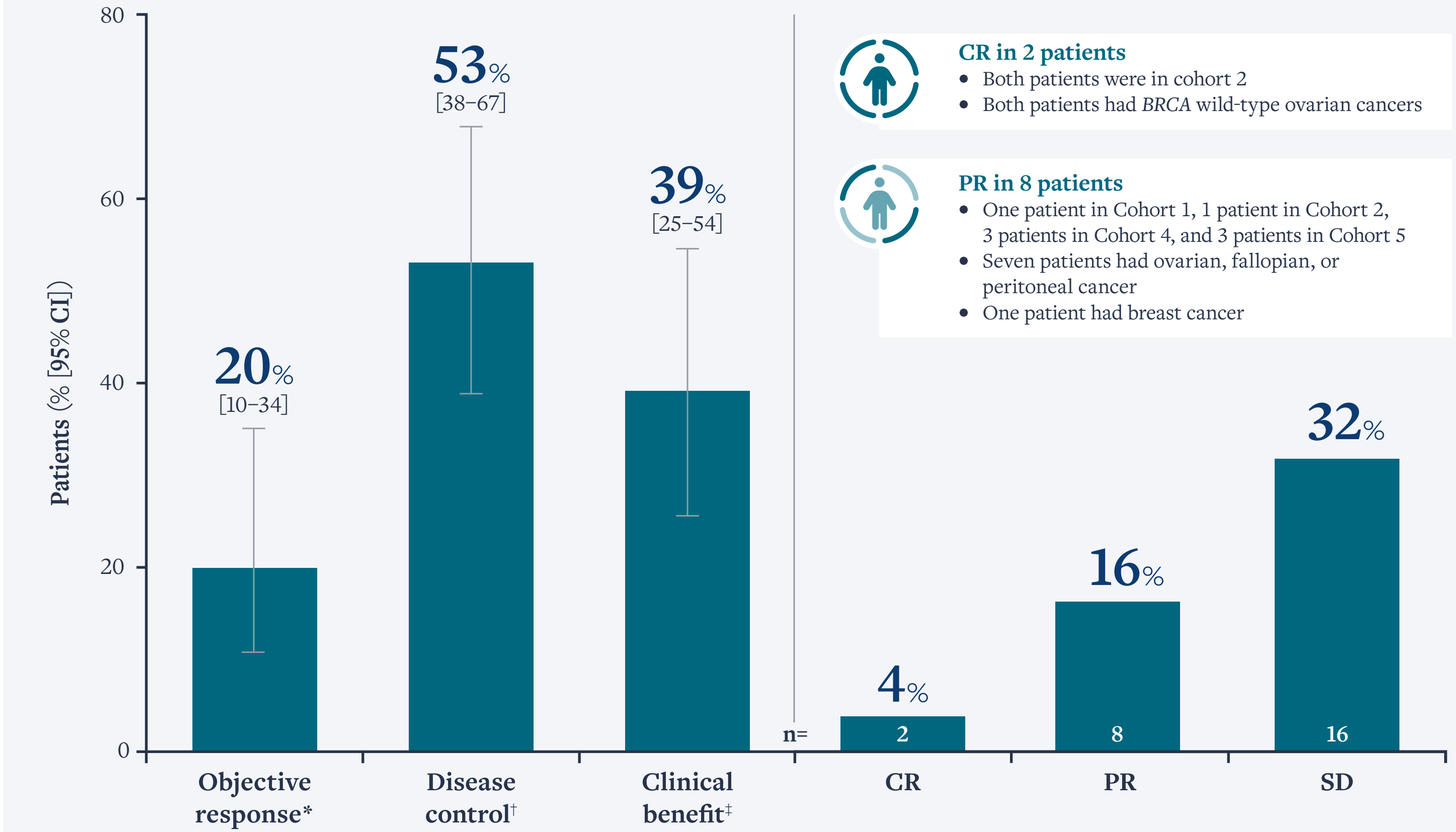
Disease control
- Achieved in 53% (95% CI 38–67) of patients

Clinical benefit
- Achieved in 39% (95% CI 25–54) of patients

CR in 2/49 (4%) patients

PR in 8/49 (16%) patients

Stable disease in 16/49 (32%) patients



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CI, confidence interval; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SAS, safety analysis set; SD, stable disease.
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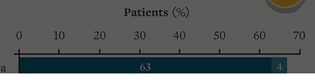

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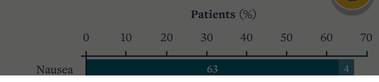

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Antitumor response in patients with ovarian, fallopian tube, or peritoneal cancer overall and by *BRCA* mutation status (n=34)

Objective response in subgroup of patients with ovarian, fallopian tube, or peritoneal cancer (n=34)

Best overall response

- 1/34 (3%) patients achieved CR
- 8/34 (24%) achieved PR
- 7/34 (21%) had stable disease

Objective response by *BRCA* status

BRCA wild-type

- Two patients achieved CR
- Four patients achieved PR

BRCA1/2 mutation

- Two patients achieved PR

Unknown *BRCA* status

- One patient achieved PR
- Similar proportions of patients with *BRCA* wild-type versus *BRCA1/2* mutations achieved objective response (25% vs 29%)

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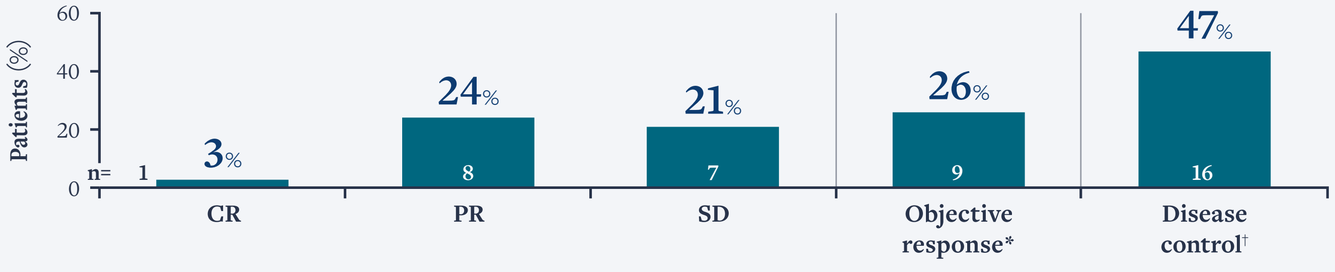

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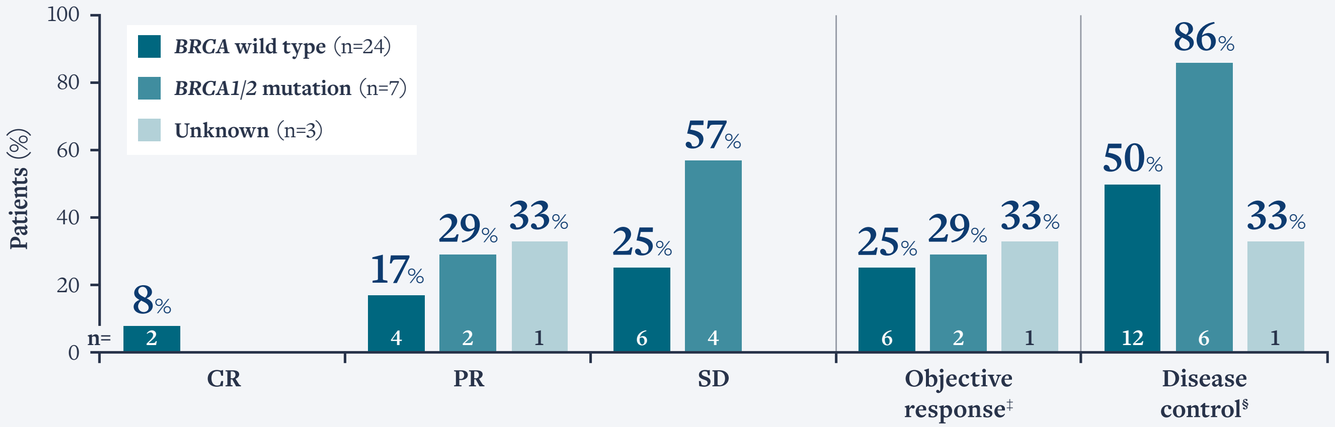

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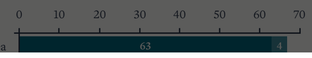

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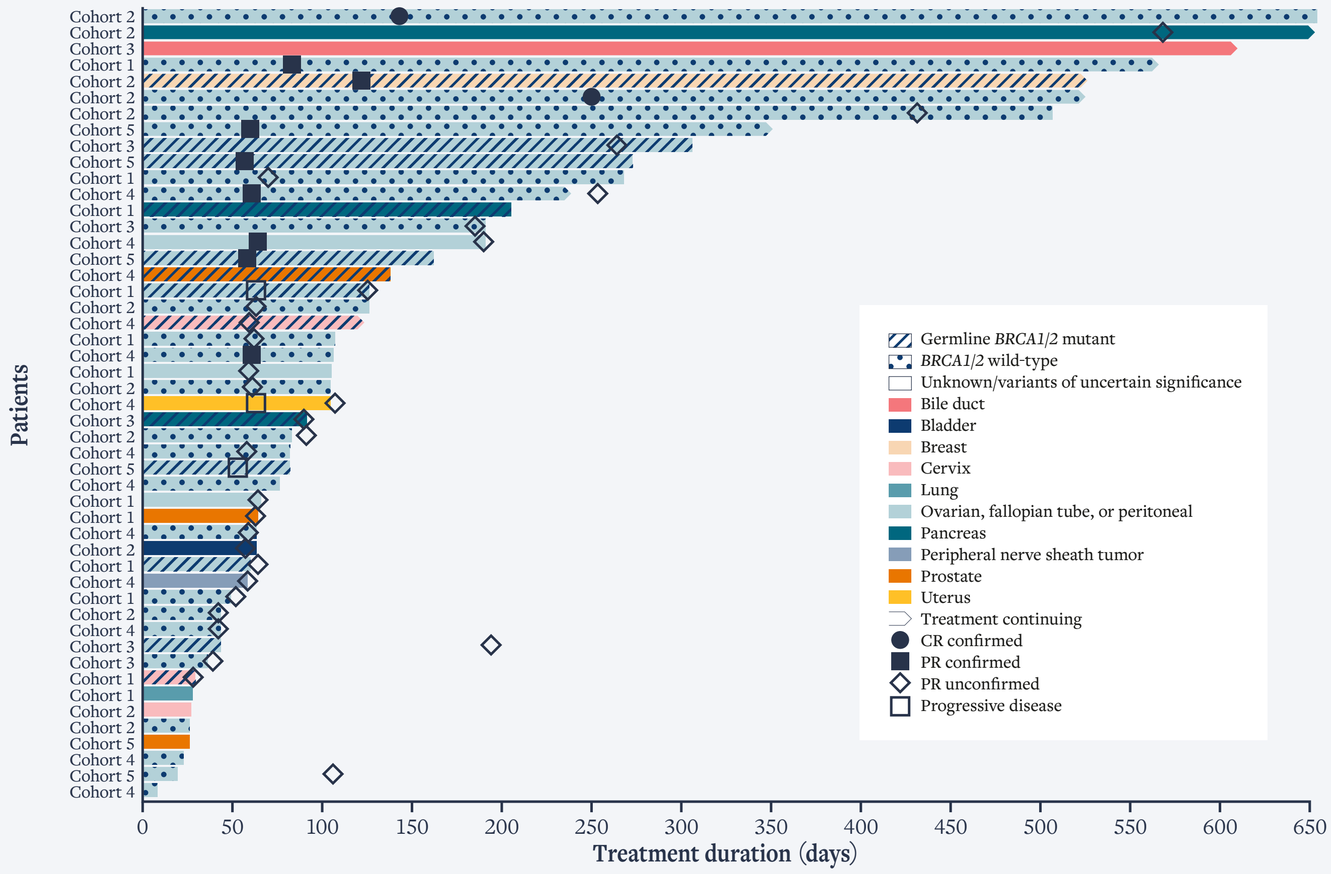
Antitumor activity by tumor type: Treatment duration, time to best overall response, and time to first progression by tumor type

Responses were observed in patients with both wild-type and germline *BRCA* mutation status



Each bar represents an individual patient.
*Patient with cholangiocarcinoma with Lynch syndrome.
BRCA, breast cancer gene; CR, complete response; PR, partial response.

In the efficacy evaluable set (all patients in the safety analysis set with measurable disease at baseline and ≥1 post-baseline tumor assessment, unless they had discontinued treatment due to progressive disease or died before tumor assessment).

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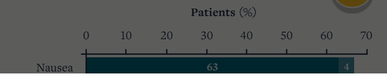

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Study limitations

In the dose-escalation phase, a heterogeneous group of patients with a variety of advanced solid tumors, many of whom were heavily pretreated

- Although this study suggested modest antitumor activity, it is possible that the combination therapy would have greater activity if these patients were treated earlier in their disease trajectory

Known *BRCA* status and HRD testing were not inclusion criteria

- Tumors with *BRCA* mutations or HRD have been associated with increased PD-L1 expression[1]
- 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, DLTs were determined after 1 cycle of treatment

- Some immune checkpoint inhibitor toxicities, particularly irAEs, can occur later in treatment and therefore would not have been reported as DLTs in this part of the study

These limitations will be addressed in the ongoing dose-expansion phase of the study

BARD1, *BRCA1*-associated RING domain protein 1; *BRCA*, breast cancer gene; DLT, dose-limiting toxicity; HRD, homologous recombination deficiency; irAEs, immune-related adverse events; PD-L1, programmed death ligand 1.

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