A phase I study of highly potent oral ATR inhibitor (ATRi) tuvusertib plus oral PARP inhibitor (PARPi) niraparib in patients with solid tumors

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Conclusions

- A novel dose-finding model enabled efficient exploration of multiple tuvusertib and niraparib doses and schedules
- Intermittent schedules of both drugs showed manageable safety profiles and two regimens were selected as RDEs:
  - Tuvusertib 90 mg QD + niraparib 200 mg QD 1w on/1w off, and
  - Tuvusertib 180 mg QD + niraparib 100 mg QD 1w on/1w off
- Myelosuppression, mainly anemia, remains the most frequent toxicity; no new safety signals were observed
- Tuvusertib exposure when administered with niraparib was consistent with monotherapy exposure, suggesting a lack of clinically meaningful mutual drug-drug interactions
- Encouraging activity was observed in heavily pretreated patients with an ORR of 19% and molecular response rate of 47% reported
- Activity was especially pronounced in patients with EOC (ORR: 38%; molecular response rate: 60%), despite 12/13 patients having had prior PARPis
- This combination will be further explored in patients with PARPi-resistant EOC (DDRiver EOC 302; NCT06433219)

EOC, epithelial ovarian cancer; MRR, molecular response rate; ORR, objective response rate; PARPi, poly-ADP ribose polymerase inhibitor; QD, once daily; RDE, recommended dose for expansion; w, week.

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Background and overall study design

- ATR and PARP protein kinases are crucial components of the DNA damage response[1]
- PARPis show synergism with ATRis *in vitro* and *in vivo*[2–4]
- In preclinical models, tuvusertib + niraparib showed greater anti-tumor activity than either drug alone[4,5]
- Tuvusertib (M1774) is a potent, oral and selective ATRi with a manageable safety profile[6]
- Combining tuvusertib and the PARPi niraparib may result in synthetic lethality, triggering replication fork collapse, mitotic catastrophe and cancer cell death[5,7]
- The DDRiver 301 study is assessing tuvusertib in patients with advanced solid tumors[6]
  - Part B1 is investigating safety, PK, PD, and preliminary efficacy of tuvusertib in combination with niraparib

In **Part A1** of DDRiver 301, tuvusertib 180 mg QD was determined as the MTD, with anemia as the main toxicity[6]

Part A1 dose escalation: safety and tolerability, MTD, RDE, PK, and PD of **tuvusertib monotherapy**

Part A2: effect of food on tuvusertib PK

Part A3: preliminary efficacy of tuvusertib in BM-selected patients

Part B1: safety, tolerability, MTD, RDE, PK, PD, and preliminary efficacy of **tuvusertib** + **niraparib**

ATR, ataxia telangiectasia and Rad3-related kinase; ATRi, ataxia telangiectasia and Rad3-related kinase inhibitor; BM, biomarker; MTD, maximum tolerated dose; PARP, poly-ADP ribose polymerase; PD, pharmacodynamic;PK, pharmacokinetic; QD, once daily; RDE, recommended dose for expansion.

1. Blackford N, Jackson P. *Mol Cell*. 2017;66:801–817; 2. Zenke FT, et al; *Cancer Res*. 2019;79(13_Suppl.):369; 3. Kim H, et al. *Nat. Commun*. 2020;11(1):3726; 4. Zimmermann A, et al. AACR 2022:P2588; 5. Hao J, et al. *Cancer Res*. 2023;83(7_Suppl):6210 6. Yap T, et al. *Clin Cancer Res*. 2024 OF1–OF11; 7. Shah PD, et al. *Gynecol Onc*. 2021;163:246–253.

Part B1 eligibility criteria and patient demographics

Main eligibility criteria:

- Patients with locally advanced or metastatic solid tumors refractory to standard therapy (prostate cancer was excluded)
- Patients with platelets <150,000/μL or weight <77 kg (patient population for whom the niraparib 200 mg QD dose is licensed)

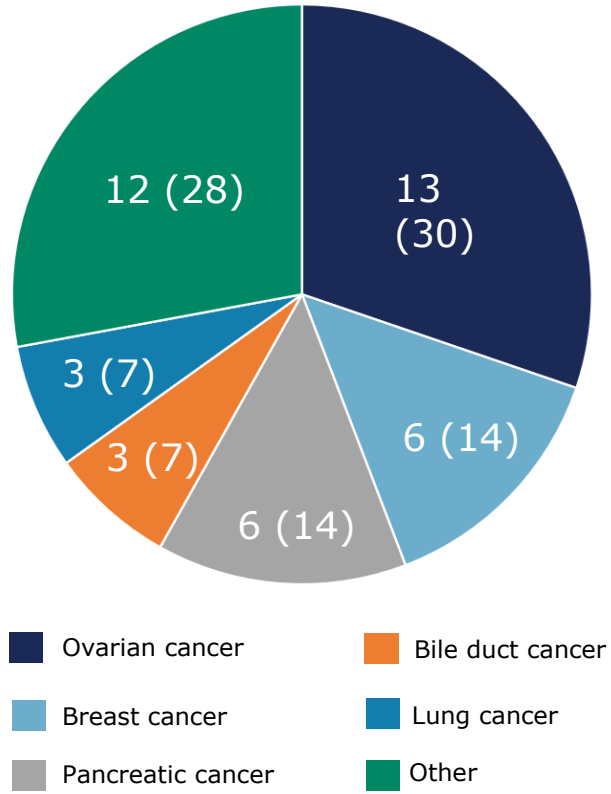
HRR genetic alterations (N=37)[a]

Gene	n (%)	Gene	n (%)
BRCA1	10 (27)	*ATM*	4 (11)
BRCA2	10 (27)	*RAD51D*	3 (8)
RAD51B	6 (16)	*PALB2*	2 (5)

Patient characteristics

Parameter	N=43
Age, median years (IQR)	64 (30–79)
Sex, n (%) Female Male	 32 (74) 11 (26)
ECOG PS, n (%) 0 1	 10 (23) 33 (77)
Prior lines of therapy for advanced disease, n (%) 1 2 3 ≥4, n (%)	 6 (14) 6 (14) 7 (16) 21 (49)
Prior platinum treatment, n (%)	36 (84)
Prior PARPi treatment, n (%) EOC, n (%)	14 (33) 12 (92)

Tumor types, n (%)



[a]37 pts had NGS data available.

ECOG PS, Eastern Coperative Oncology Group Performance Status; EOC, epithelial overian cancer; HRR, homologous recombination repair; IQR, interquartile range; NGS, next-generation sequencing; PARPi, poly-ADP ribose polymerase inhibitor; QD, once daily

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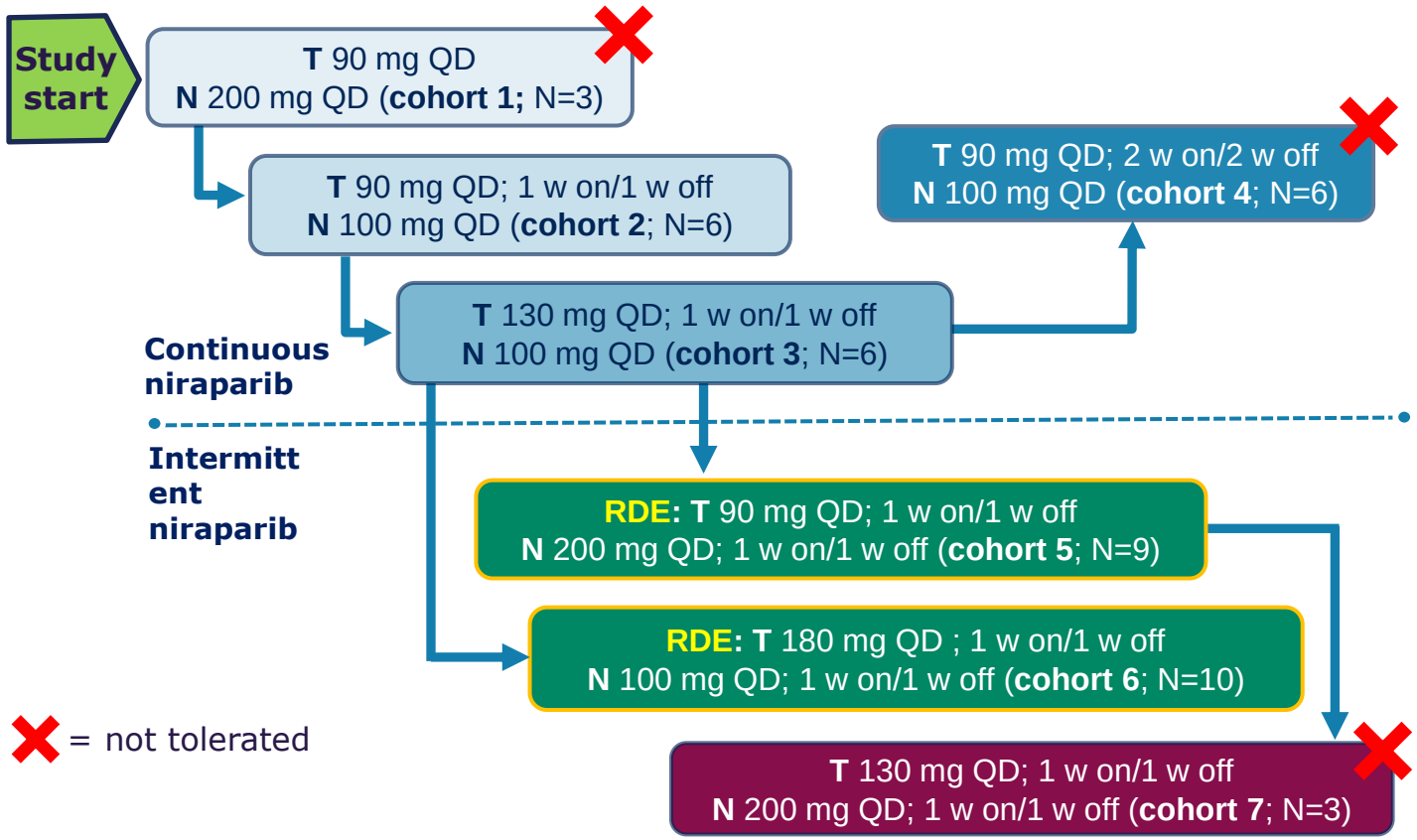
Dose-finding strategy and RDEs

Dose-finding steps (N=43)



- The Bayesian **Partial Ordering Continual Reassessment Method (POCRM)** model was used
- Continuous and intermittent schedules of tuvusertib (90–180 mg) and niraparib (100 or 200 mg) were explored.
- **Two RDEs** for tuvusertib + niraparib were declared
  - Tuvusertib (90 mg) + niraparib (200 mg) 1 w on /1 w off (**cohort 5**; N=8 DLT-evaluable patients): no DLTs occurred
  - Tuvusertib (180 mg) + niraparib (100 mg) 1 w on /1 w off (**cohort 6**; N=7 DLT-evaluable patients); DLTs were:

One patient
- G3 fatigue (n=1)

One patient
- G4 platelet count decreased (n=1)
- G4 neutrophil count decreased (n=1)
- G3 anemia requiring transfusion (n=1)

DLT, dose-limiting toxicity; G, grade; N, niraparib; QD, once daily; RDE, recommended dose for expansion; T, tuvusertib; w, week.

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Related TEAEs[a,b] at declared RDEs[c]

- Tuvusertib + niraparib demonstrated a manageable safety profile; no unexpected safety signals were identified

Related TEAEs	Tuvusertib 90 mg QD + niraparib 200 mg QD 1w on/1w off (N=9) n (%)		Tuvusertib 180 mg QD + niraparib 100 mg QD 1w on/1w off (N=10) n (%)	
Preferred term	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Anemia	5 (56)	3 (33)	6 (60)	3 (30)
Neutropenia[d]	2 (22)	0	2 (20)	2 (20)
Platelet count decreased	1 (11)	0	3 (30)	3 (30)
WBC count decreased	2 (22)	0	0	0
Constipation	4 (44)	0	2 (20)[e]	0
Diarrhea	2 (22)	1 (11)	0[f]	0
Dyspepsia	1 (11)	0	2 (20)	0
Nausea	6 (67)	0	7 (70)	0
Vomiting	5 (56)	0	2 (20)	0
Fatigue	3 (33)	0	3 (30)	1 (10)

[a]TEAEs were assessed as related to both tuvusertib and niraparib; [b]Assessed using MedDRA version 26.1; [c]Occurring in ≥2 patients in one of the cohorts; [d]Includes terms neutropenia and neutrophil count decreased; [e]One more event of constipation related to niraparib alone; [f]One more event of diarrhea related to niraparib alone
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; RDEs, recommended doses for expansion; TEAE, treatment-emergent adverse event; w, week; WBC, white blood cell .

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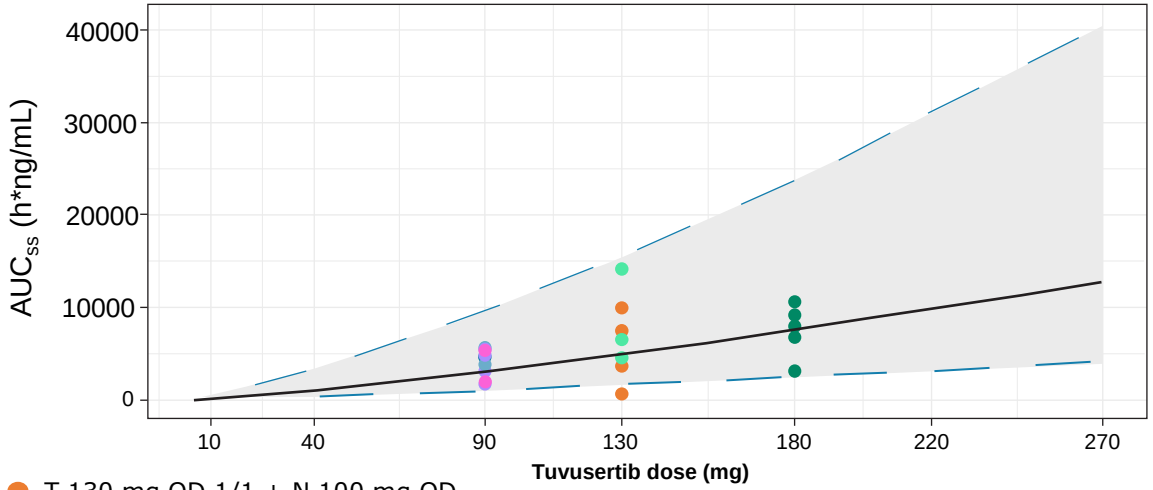
PK and PD outcomes in line with tuvusertib monotherapy experience

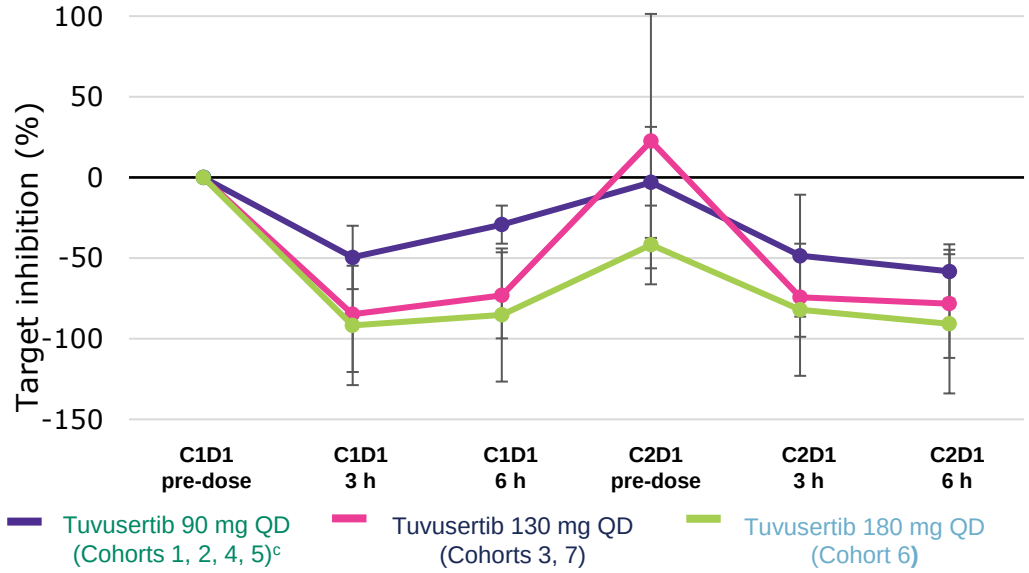
- Tuvusertib exposure when combined with niraparib was consistent with monotherapy exposure, suggesting a lack of any clinically meaningful mutual drug-drug interactions

Relationship of tuvusertib steady-state AUC (AUC_{ss}) and dose[a]



- Reduction in γ-H2AX in PBMCs immediately after dosing serves as proximal PD marker for tuvusertib
  - In line with monotherapy experience, almost complete inhibition of γ-H2AX expression observed after tuvusertib 130 and 180 mg doses

Target modulation[b] according to tuvusertib dose



[a]Symbols represent individual patient tuvusertib AUC_{ss} data in combination with niraparib; the solid black line and the shaded grey area represent the model-predicted AUC_{tau} and the 97.5% probability interval from tuvusertib monotherapy, respectively; [b]4-NQO-only valid data used for analysis; [c]Only one patient available in cohort 1 with a C1D1 6 h valid time point

γ-H2AX, phosphorylation of the Ser-139 residue of the histone variant; 1/1, 1 week on/1 week off; 2/2, 2 weeks on/2 weeks off; AUC, area under the curve; AUC_{ss}, area under the drug concentration-time curve at steady state; C, cycle; D, day; h, hour; N, niraparib; PBMC, peripheral blood mononuclear cells; PD, pharmacodynamic; PK, pharmacokinetic; QD, once daily; T, tuvusertib; w, week

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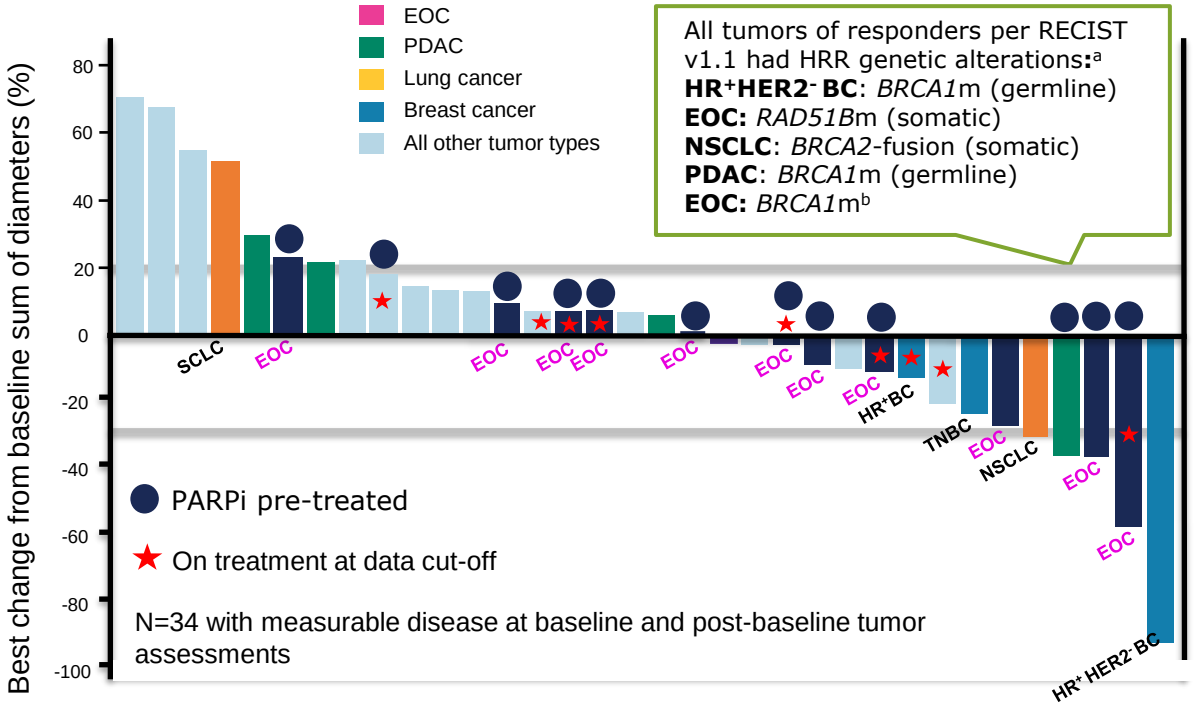
Clinical responses across dose levels, including patients with EOC

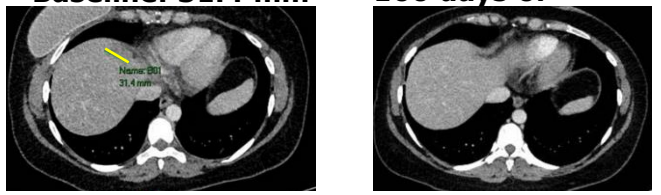
Waterfall plot showing best change in the sum of diameters, according to BOR and tumor type (N=34)



- 12/13 patients with EOC had received prior PARPis
- Across all dose levels, 19% of all patients and 38% of patients with EOC had an objective response
  - Five patients (15%) experienced a response per RECIST v1.1:
  - Two patients with EOC, one with NSCLC, and another with PDAC experienced PR
  - One patient with plt-sensitive, PARPi-naive HR+HER2- *BRCA1*m BC experienced a CR in the target lesion

Clinical outcomes	All cohorts (N=43)	Patients with EOC (N=13)
ORR[c]	**19**% (8/43)	**38**% (5/13)[d]
CBR[e]	37% (16/43)	62% (8/13)

Patient with HR+HER2- *BRCA1*m BC and CR of liver metastases



[a]For 4/5 responders the mutations were detected by NGS in liquid biopsies, tumor analysis is ongoing; [b]For 1 of the 5 responders the mutations were detected in local tumor biopsy analysis only; [c]ORR=best response of confirmed or unconfirmed CR or PR per RECIST v1.1 or confirmed CA-125 response per Gynecological Cancer Intergroup; [d]According to RECIST v1.1; [e]CBR=PR, CR, or ≥16 weeks on treatment without progression

BC, breast cancer; BOR, best overall response; *BRCA1*m, breast cancer gene-1 mutated; CBR, clinical benefit rate; CR, complete response; EOC, epithelial ovarian cancer; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; HRR, homologous recombination repair; m, mutated; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; PARPi, poly-ADP ribose polymerase inhibitor; PDAC, pancreatic ductal adenocarcinoma; plt, platinum; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer

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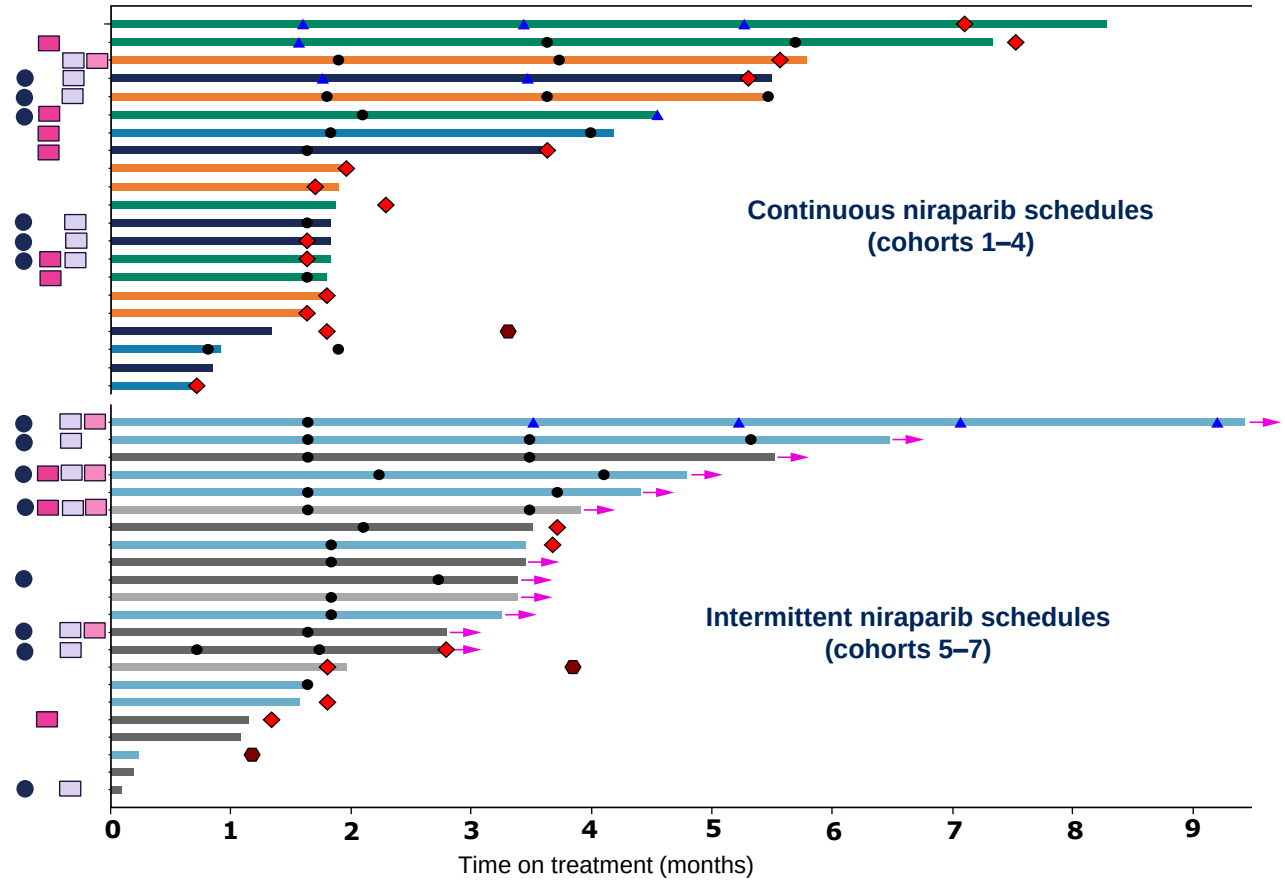
Time on treatment across dose levels, including patients with EOC

Swimmer plot showing time on treatment per niraparib schedule



- Median DoT was longer in patients receiving tuvusertib + intermittent niraparib (**14.1** weeks; range: **1.4–42.0**) than patients receiving continuous niraparib (**8.1** weeks; range: **3.1–42.0**)
- Median DoT in patients with EOC was **18.0** weeks (range: **1.4–42.0**)

Cohorts

- **C1**: T 90 mg QD + N 200 mg QD
- **C2**: T 90 mg QD 1/1 + N 100 mg QD
- **C3**: T 130 mg QD 1/1 + N 100 mg QD
- **C4**: T 90 mg QD 2/2 + N 100 mg QD
- **C5:** T 90 mg QD 1/1 + N 200 mg QD 1/1
- **C6**: T 180 mg QD 1/1 + N 100 mg QD 1/1
- **C7**: T 130 mg QD 1/1 + N 200 mg QD 1/1

Response key

- Partial response
- Stable disease
- Progressive disease
- Death
- Ongoing in trial

Additional patient data

- MR (n=19 patients with available data; analysis ongoing)
- Patients with EOC (n=13)
- Confirmed CA-125 response (n=12 patients with available data); some values were obtained after data cut off[a]
- PARPi pre-treated

[a]One patient who only borderline met the CA-125 baseline requirements (per Gynecological Cancer Intergroup) was included as a CA-125 responder
1/1, 1 week on/1 week off; 2/2, 2 weeks on/2 weeks off; C, cohort; CA-125, cancer antigen-125; DoT, duration of treatment; EOC, epithelial ovarian cancer; MR, molecular response; N, niraparib; QD, once daily; T, tuvusertib; w, week

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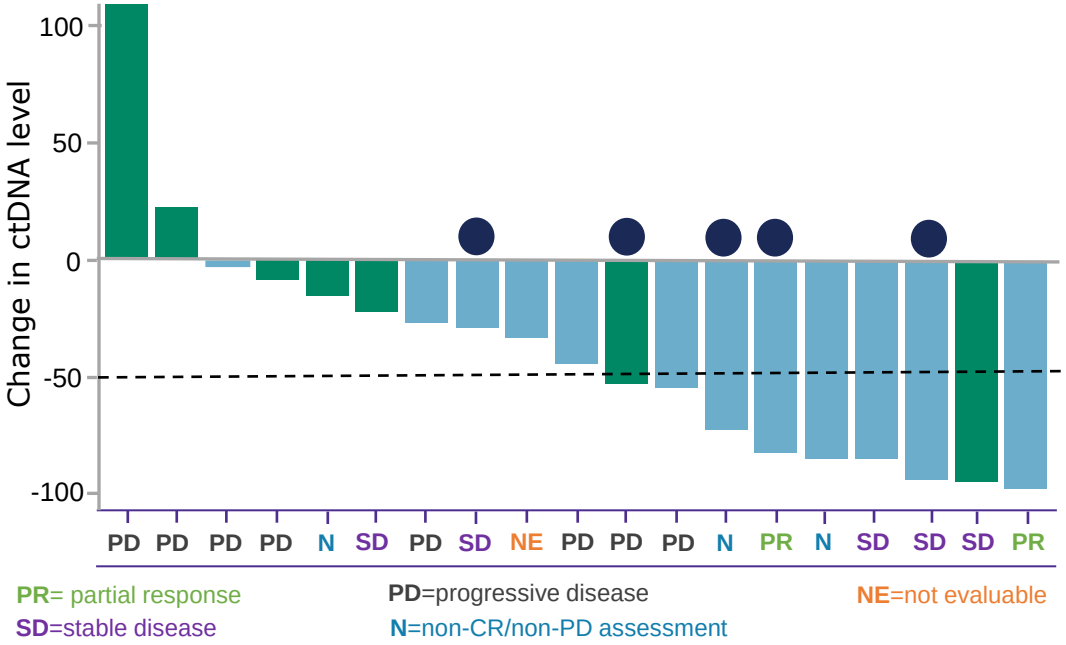
Molecular response outcomes overall and according to BRCA status[a]

- Nineteen patients were able to be assessed for MR[b]; MRs occurred in 47% of patients across all dose levels
- MRs were more frequent in patients with *BRCA1/2*-mutated tumors who received ≥130 mg tuvusertib QD

BRCA1/2 status and change in methylated ctDNA

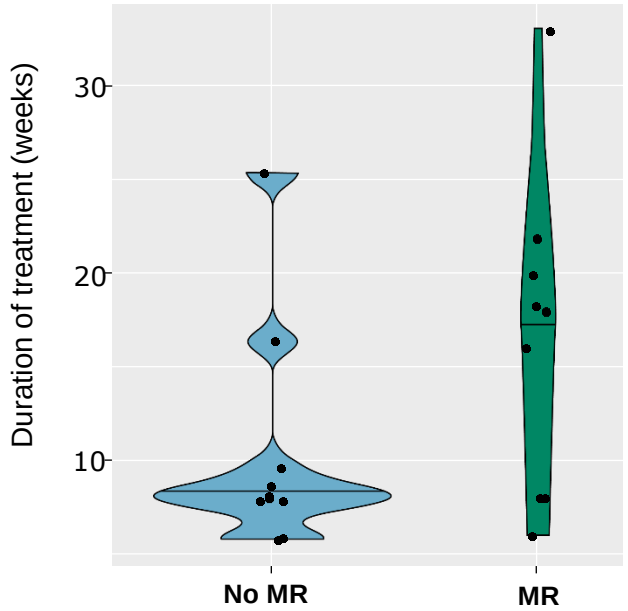


MRR in all cohorts and in patients with EOC

	All cohorts (N=19)	Patients with EOC (N=5)
MR, % (n/N)	47% (9/19)	60% (3/5)

- There appeared to be a trend for patients with *BRCA1/2*-mutated tumors and MR to stay on treatment longer

Duration of treatment and MR



[a]N=19 participants with available data, analysis is ongoing; [b]MR is based on >50% reduction from baseline in ctDNA, according to tumor-specific DNA methylation levels
BRCA1/2, breast cancer gene 1 and 2; ctDNA, circulating tumor DNA; EOC, epithelial ovarian cancer; MR, molecular response; MRR, molecular response rate; QD, once daily

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