Safety and Efficacy of Three PARP Inhibitors (PARPi) Combined With the Ataxia Telangiectasia- and Rad3-related Kinase Inhibitor (ATRi) Camonsertib in Patients (pts) With Solid Tumors Harboring DNA Damage Response (DDR) Alterations

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Disclosure Information

Timothy A. Yap

I have the following financial relationships to disclose:

- Employment: University of Texas MD Anderson Cancer Center; where I am Medical Director of the Institute for Applied Cancer Science, which has a commercial interest in DNA damage response (DDR) and other inhibitors (IACS30380/ ART0380 was licensed to Artios)
- Grant/Research support (to the Institution): Acrivon, Artios, AstraZeneca, Bayer, Beigene, BioNTech, Blueprint Medicines, BMS, Boundless bio, Clovis, Constellation, Cyteir, Eli Lilly, EMD Serono, Forbius, F-Star, GlaxoSmithKline, Genentech, Haihe, Ideaya ImmuneSensor, Ionis, Ipsen, Jounce, Karyopharm, KSQ, Kyowa, Merck, Mirati, Novartis, Pfizer, Ribon Therapeutics, Regeneron, Repare Therapeutics, Rubius, Sanofi, Scholar Rock, Seattle Genetics, Tesaro, Vivace, and Zenith.
- Consultant for: AbbVie, AstraZeneca, Acrivon, Adagene, Almac, Aduro, Amphista, Artios, Athena, Atrin, Avoro, Axiom, Baptist Health Systems, Bayer, Beigene, Blueprint Medicines, Boxer, BMS, C4 Therapeutics, Calithera, Cancer Research UK, Circle Pharma, Clovis, CUHK Committee, Cybrexa, Dark Blue Therapeutics, Diffusion, Ellipses.Life, EMD Serono, F-Star, Genentech, Genmab, Gerson and Lehrman Group, Glenmark, GLG, Globe Life Sciences, GlaxoSmithKline, Guidepoint, Idience, Ignyta, I-Mab, ImmuneSensor, Institut Gustave Roussy, Intellisphere, Jansen, Kyn, LRG1, MEI pharma, Mereo, Merck, Natera, Nexys, Novocure, OHSU, OncoSec, Ono Pharma, Panangium, Pegascy, PER, Pfizer, Piper-Sandler, Pliant Therapeutics, Prolynx, Radiopharm Theranostics, Repare Therapeutics, resTORbio, Roche, Sanofi, Schrodinger, Seagen, Synthis Therapeutics, Terremoto Biosciences, Tessellate Bio, TD2 Theragnostics, Tome Biosciences, Varian, Versant, Vibliome, Xinthera, Zai Labs, Zentalis, and ZielBio
- Stockholder in: Seagen

ATR inhibition prevents recovery from PARPi-induced DNA damage via rapid, irreversible replication catastrophe and unscheduled mitosis entry

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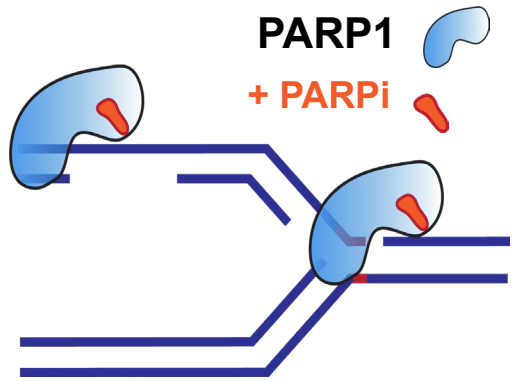

PARP trapping
Replication fork blockage
Post-replicative gaps in DNA

+ camonsertib (ATRi)

Cell cycle checkpoint
Restricted replication origin firing DNA repair by HR
Cell survival

ATR pathway active

Aberrant origin firing and replication catastrophe
Unscheduled mitotic entry
Cell death

ATR inhibited

PARPi + ATRi combination provides a rational approach to improve PARPi efficacy:

- Robust pre-clinical PARPi + ATRi synergy in HRD models, including *BRCA1/2, ATM and CDK12* alterations
- Delay/overcome acquired PARPi resistance

Zimmermann et al. *Cell Rep*. 2022;40(2):111081; Kim et al. *Clin Cancer Res*. 2017;23(12):3097–3108; Lloyd et al. *Oncogene*. 2020;39(25):4869–4883; Yazinski et al. *Genes Dev*. 2017;31(3):318–332..
ATR, ataxia telangiectasia- and Rad3-related; ATRi, ATR inhibitor; HR, homologous recombination; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor.

Camonsertib (RP-3500): a potent and selective oral ATR inhibitor with confirmed clinical activity

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Camonsertib functional selectivity

Assay IC_{50} (nM)	ATR	mTOR	ATM	DNA-PK	PI3Kα
Biochemical	1.0	120	>30,000	1,600	>10
Selectivity	–	120x	>30,000x	1,600x	>10,000x
Cell-based	0.33[a]	11[b]	>10,000[c]	>10,000[c]	780[b]
Selectivity	–	30x	>20,000x	>20,000x	2,200x

Camonsertib:

- Low nanomolar potency in biochemical (1.0 nM) and cell-based MOA assays (0.33 nM)
- >2,000-fold selectivity over ATM, DNA-PK, and PI3Kα

- **Clinical activity demonstrated with camonsertib monotherapy**
  - Efficacy in patients with ovarian cancer (N=20)
    - 90% prior PARPi; 85% platinum refractory/resistant
    - Response rate: 25%; CBR: 75%; mPFS: 35 weeks
    - Genomic alterations in responders: *BRCA1*, *RAD51C*, *SETD2*
- **Proposed monotherapy RP2D: 160 mg QD, 3 days on / 4 days off**

Yap TA et al. accepted at *Nature Medicine.*
ATM, ataxia-telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related; DNA-PK, DNA-dependent protein kinase; MOA, mechanism of action; mTOR, mammalian target of rapamycin; PI3Kα, PI3-kinase alpha; QD, once daily; RP2D, recommended phase 2 dose.
CBR:Clinical Benefit Rate; mPFS: media Progression Free Survival

Intermittent, low-dose camonsertib + PARPi is active in preclinical models

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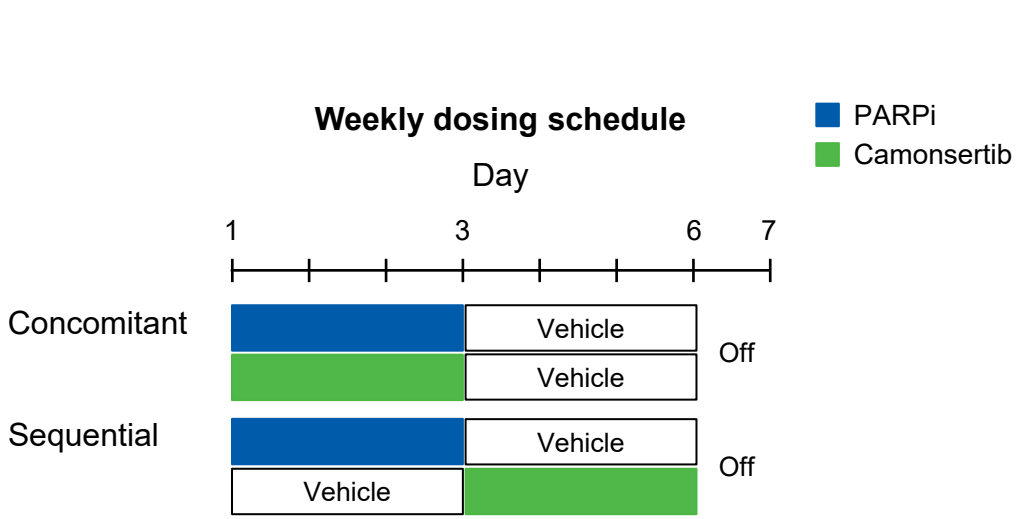

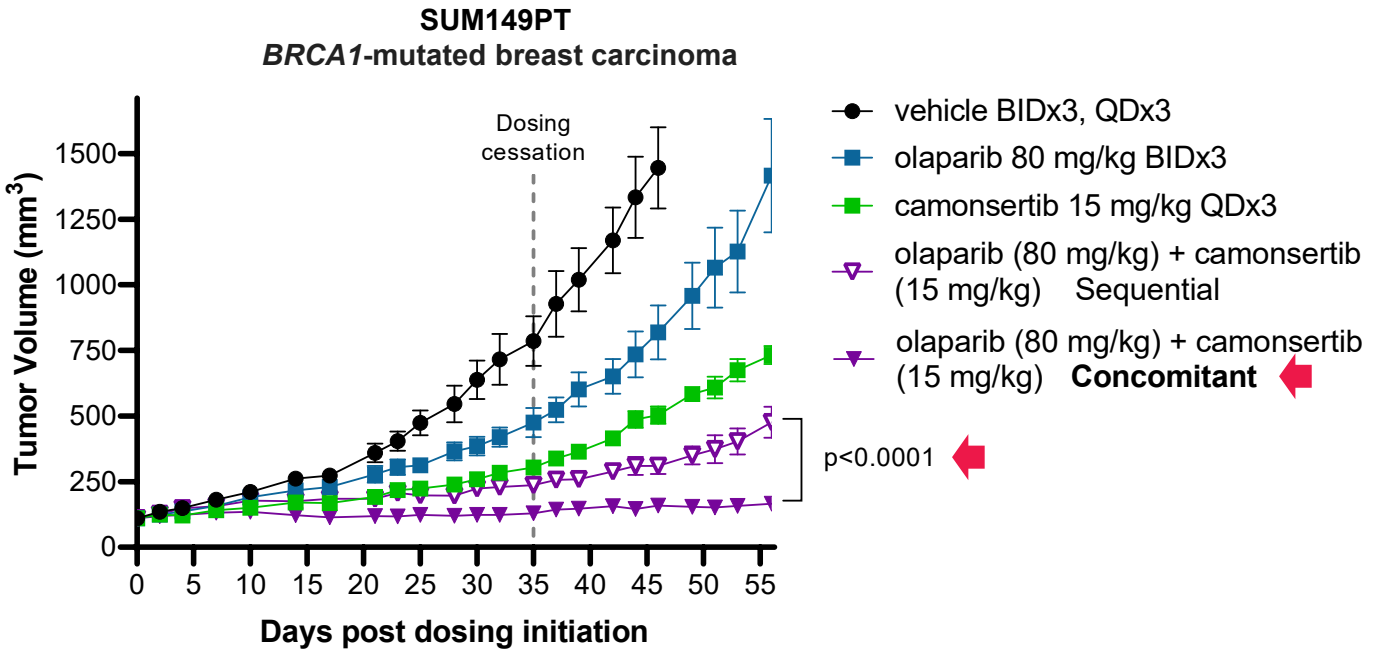

- **A 3 days on / 4 days off weekly schedule of low camonsertib + olaparib** doses shows sustained tumor growth inhibition compared to each single agent
- Intermittent combination schedules are well tolerated in mice, with no body weight loss
- Concomitant administration of camonsertib and olaparib shows more sustained efficacy than sequential administration
- Efficacy on intermittent schedules were similar with **multiple PARPi (niraparib, talazoparib, olaparib)**

Zimmermann et al. *Cell Rep*. 2022; Roulston et al. *Mol Cancer Ther*. 2022.
BID, twice daily; d, days; MTD, maximum tolerated dose; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; QD, once daily.

TRESR and ATTACC studies: populations and endpoints

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Phase 1/2a TRESR:
Module 3 – camonsertib + talazoparib[a]
(NCT04497116)

+

Phase 1b/2 ATTACC:
camonsertib + niraparib or olaparib
(NCT04972110)

107 patients treated

90/107 patients evaluable for efficacy (≥1 post-baseline scan, treated at least 13 weeks prior to data cutoff date)

Main eligibility criteria:

- Patients ≥18 years of age with advanced solid tumors
- Deleterious SNIPRx[1] gene alterations[b]; somatic or germline
  - *ATM, ATRIP, BRCA1/2, CDK12, CHTF8, FZR1, MRE11, NBN, PALB2, RAD51B/C/D, RNASEH2A/B, RAD17, REV3L, RAD50, SETD2*
- ECOG PS 0 or 1
- Prior PARPi treatment permitted
- Hemoglobin ≥10 g/dL
  - **TRESR:** Platelets ≥140 K/uL, ANC ≥1.7 K/uL
  - **ATTACC:** Platelets ≥ 120 K/uL, ANC ≥1.5K/uL

Primary objectives/key endpoints:

- Safety and tolerability; RP2D and schedule

Secondary objectives/key endpoints:

- Overall response (RECIST v1.1, PSA, or CA-125 response)
- Clinical benefit (response or ≥16 weeks on treatment without progression)
- PK parameters of camonsertib in combination with PARPi

Exploratory objectives/key endpoints:

- Genomic analysis and ctDNA molecular response

Data cutoff date for this presentation is February 27, 2023. [a]Talazoparib was provided by Pfizer Inc. [b]Centrally reviewed by the Precision Oncology Decision Support group (MD Anderson Cancer Center).

1. Glodzik D et al. *J Mol Diagn*. 2023:S1525-1578(23)00050-8.

ANC, absolute neutrophil count; ATTACC, ATRi and PARPi in patients with molecularly selected cancers; CA-125, cancer antigen 125; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SNIPRx, SyNthetic Lethal Interactions for Precision Therapeutics platform; TRESR, treatment enabled by SNIPRx; w, weeks.

TRESR and ATTACC studies: patient demographics

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Treatment combination	Cam + tala	Cam + nira	Cam + ola	Total
Number of patients treated	43	29	35	107

Parameter	N=107
Age (years)	
Median (IQR)	58 (52–66)
Sex, n (%)	
Male/female	43 (40) / 64 (60)
ECOG PS, n (%)	
0	42 (39)
1/2[a]	64 (60) / 1 (1)
Prior lines of systemic therapy, n (%)	
Median (IQR)	3 (2–4)
≥3, n (%)	67 (63)
Prior platinum, n (%)	74 (69)
Platinum resistant/refractory, n (%)	58 (78)
Prior PARP inhibitor, n (%)	42 (39)
Ovarian, n (%)	18 (82)
Prior PD-(L)1 inhibitor, n (%)	17 (16)

Tumor types, n (%)	N=107
Ovarian	22 (21)
Breast	22 (21)
Pancreatic	16 (15)
Prostate	14 (13)
Colorectal	7 (7)
Soft tissue sarcoma	6 (6)
Bile duct	5 (5)
Other[b]	15 (14)
Genotypes, n (%)	
BRCA2	35 (33)
ATM	28 (26)
BRCA1	21 (20)
PALB2	9 (8)
Other[c]	14 (13)

[a]ECOG PS of 2 was due to Parkinson's disease.
[b]Lung non-small cell (n=4), upper gastric (n=3), anal squamous cell carcinoma (n=1), endometrial (n=1), head and neck (n=1), mesothelioma (n=1), kidney (n=1), bone sarcoma (n=1), left chest mass granular cell (n=1), and unknown (colorectal/gastric profile) (n=1).
[c]*CDK12* (n=4), *RNASEH2* (n=3), *RAD51B* (n=2), *IDH1* (n=2), *NBN* (n=1), *RAD51D* (n=1), and *SETD2* (n=1).
cam, camonsertib; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; nira, niraparib; ola, olaparib; PARP, poly (ADP-ribose) polymerase; PD-(L)1, programmed death (ligand)-1; tala, talazoparib.

Escalation/de-escalation strategy for dose optimization

Combination dose utilizes ~1/2 of ATRi and ~ 1/3 – 1/4 of PARPi single agent doses

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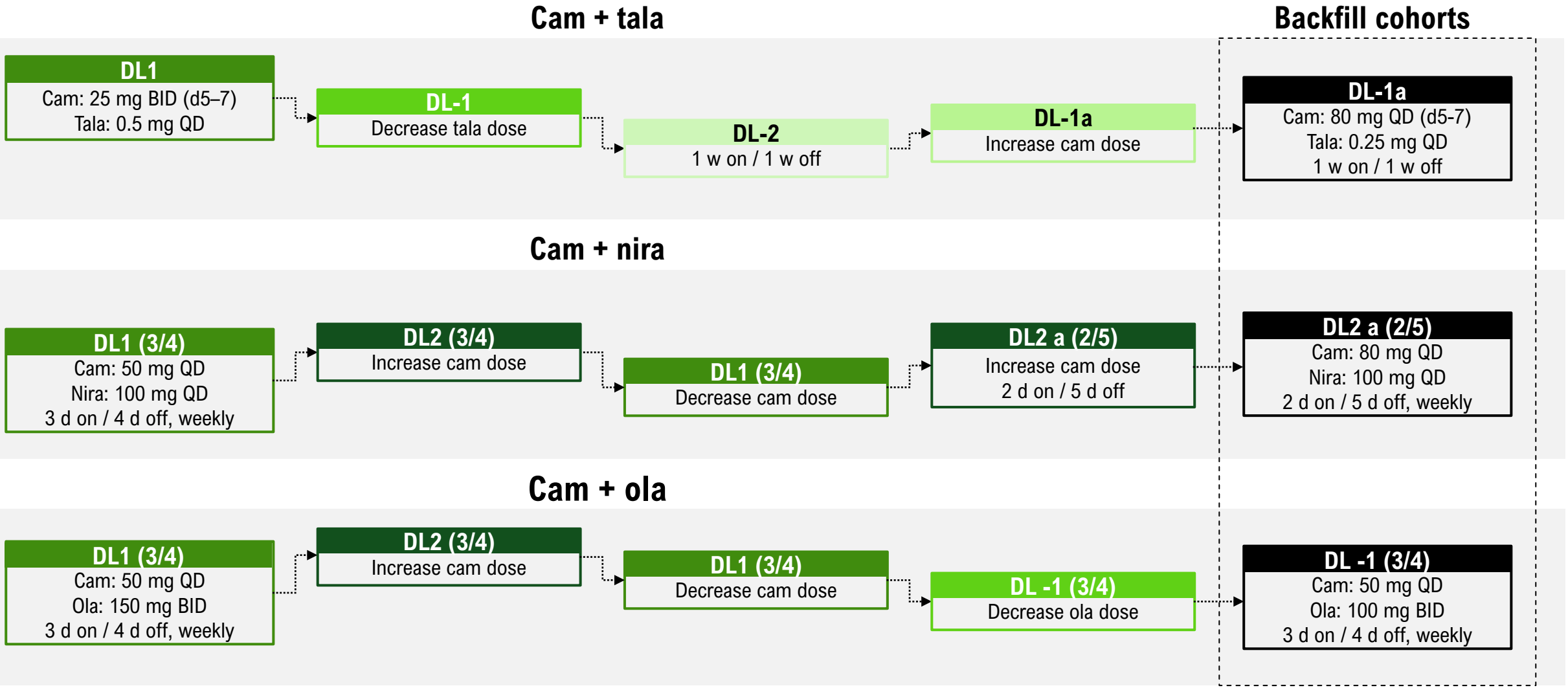

BID, twice daily; cam, camonsertib; d, days; DL, dose level; nira, niraparib; ola, olaparib; QD, once daily; tala, talazoparib; w, week.

Camonsertib PK with three PARPi similar to monotherapy PK

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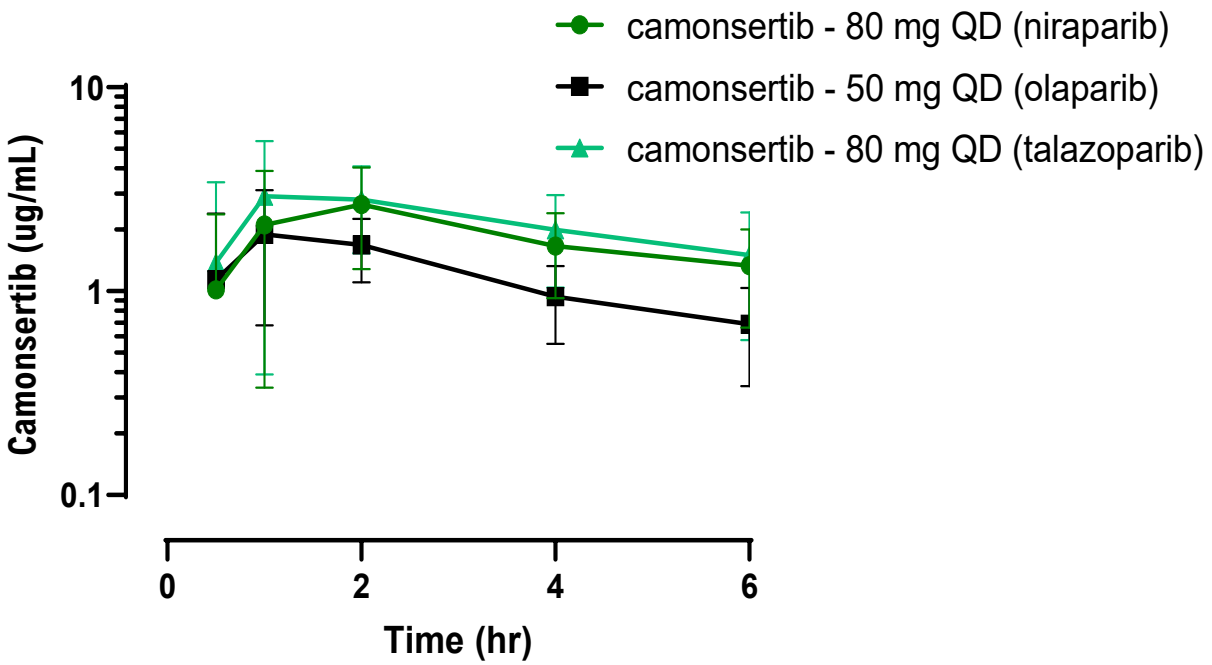
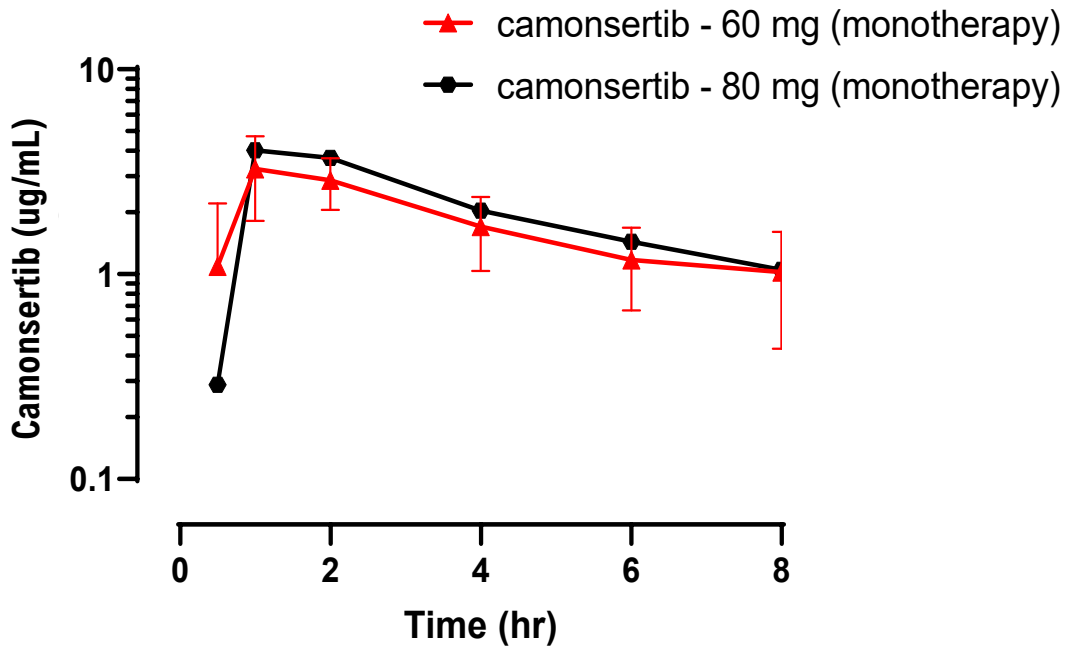
Combination PK



Monotherapy PK



Mean ± SD (N)	Cam 80 mg QD + nira	Cam 50 mg QD + ola	Cam 80 mg QD + tala	Cam 60 mg monotherapy	Cam 80 mg monotherapy
C_{max}/dose (µg/mL/mg)	0.0403 ± 0.0185 (16)	0.0471 ± 0.0203 (25)	0.0494 ± 0.223 (27)	0.0522 ± 0.0211 (4)	0.0708 (1)
$AUC_{0–6}$/dose (µg•hr/mL/mg)	0.139 ± 0.057 (16)	0.147 ± 0.049 (24)	0.157 ± 0.076 (26)	0.196 ± 0.066 (4)	0.189 (1)

$AUC_{0–6}$, area under the concentration-time curve from 0 to 6 hours; cam, camonsertib; C_{max}, maximum concentration; hr, hours; nira, niraparib; ola, olaparib; PARPi, poly (ADP-ribose) polymerase inhibitor; PK, pharmacokinetics; QD, once daily; SD, standard deviation; tala, talazoparib.

Related TEAEs throughout treatment at preliminary combination doses[a]

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Preliminary combination dose utilizes ~1/2 of ATRi and ~ 1/3 – 1/4 of PARPi single agent doses

	Cam 80mg QD 3/4 + tala 0.25 mg QD 1wk on/1wk off schedule (n=32)		Cam 80 mg QD + nira 100 mg QD 2/5 schedule (n=17)		Cam 50 mg QD + ola 100 mg BID 3/4 schedule* (n=19)	
Preferred term, %	**All grades**	**Grade 3+**	**All grades**	**Grade 3+**	**All grades**	**Grade 3+**
Anemia	72	22	82	29	89	47
Neutrophil count decrease/neutropenia	56	41	59	24	68	47
Platelet count decreased/thrombocytopenia	38	16	41	6	37	11
Fatigue	38	6	41	6	26	0
Nausea	25	0	47	6	16	0
Vomiting	13	0	24	0	5	0
Decreased appetite	16	0	6	0	11	0
Diarrhea	13	0	6	0	16	0
DLTs in the 68 patients treated with the proposed combination doses were related to myelotoxicity only (anemia 3%, thrombocytopenia 6%, neutropenia 7%, and febrile neutropenia 3%)						

[a]Related TEAE of all grades that occurred in ≥10% of patients treated at preliminary combination doses. 3/4, 3 days on, 4 days off; 2/5, 2 days on, 5 days off. ATRi, ataxia telangiectasia- and Rad3-related inhibitor; cam, camonsertib; DLT, dose limiting toxicities; nira, niraparib; ola, olaparib; PARPi, poly (ADP-ribose) polymerase inhibitor; tala, talazoparib; TEAE, treatment-emergent adverse event.

*47% in ola arm had history of anemia vs <30% in nira/tala arms. 78% in ola arm with history of anemia had on-trial G3 anemia vs 20% without previous anemia (p=0.023). This difference was not present in nira/tala arms possibly due to lower frequency of previous myelotoxicity. Further dose refinement of ola arm is ongoing.

Durable clinical benefit seen across various tumor types regardless of camonsertib's PARPi partner

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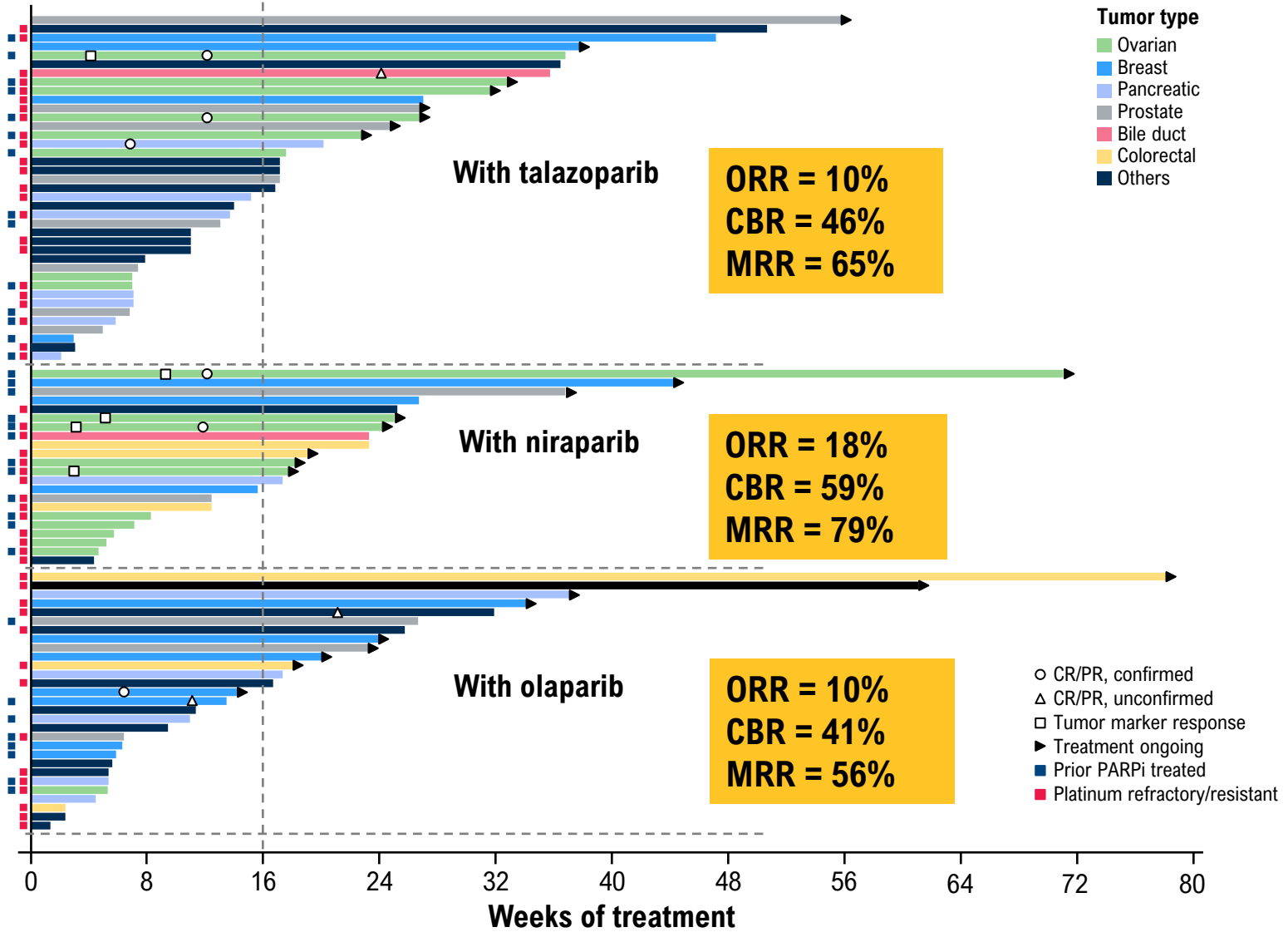
- **Overall CBR** (tumor response or ≥16 w of therapy) for all patients was **48%**
- Benefit was observed **across multiple tumors** and **regardless of previous PARPi treatment**
- **Patients with platinum-resistant tumors (ORR 12%, CBR 49%) benefited similarly to non-platinum-resistant tumors (ORR 13%, CBR 46%)**



Included patients from efficacy analysis set.
ORR is based on overall response as best response of confirmed or unconfirmed CR or PR per RECIST v1.1 criteria or confirmed CA-125 response per Gynecological Cancer Intergroup; CBR is based on overall response or ≥16 weeks on treatment without progression; MRR is based on ctDNA molecular response as >50% decline in mVAF assessed by GuardantINFINITY or Tempus xF gene panel for patients with detectable somatic alterations.
CBR, clinical benefit rate; CR, complete response; ctDNA, circulating tumor DNA; MRR, molecular response rate; mVAF, mean variant allele frequency; PARPi, poly (ADP-ribose) polymerase inhibitor; PR, partial response; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Antitumor activity by tumor type

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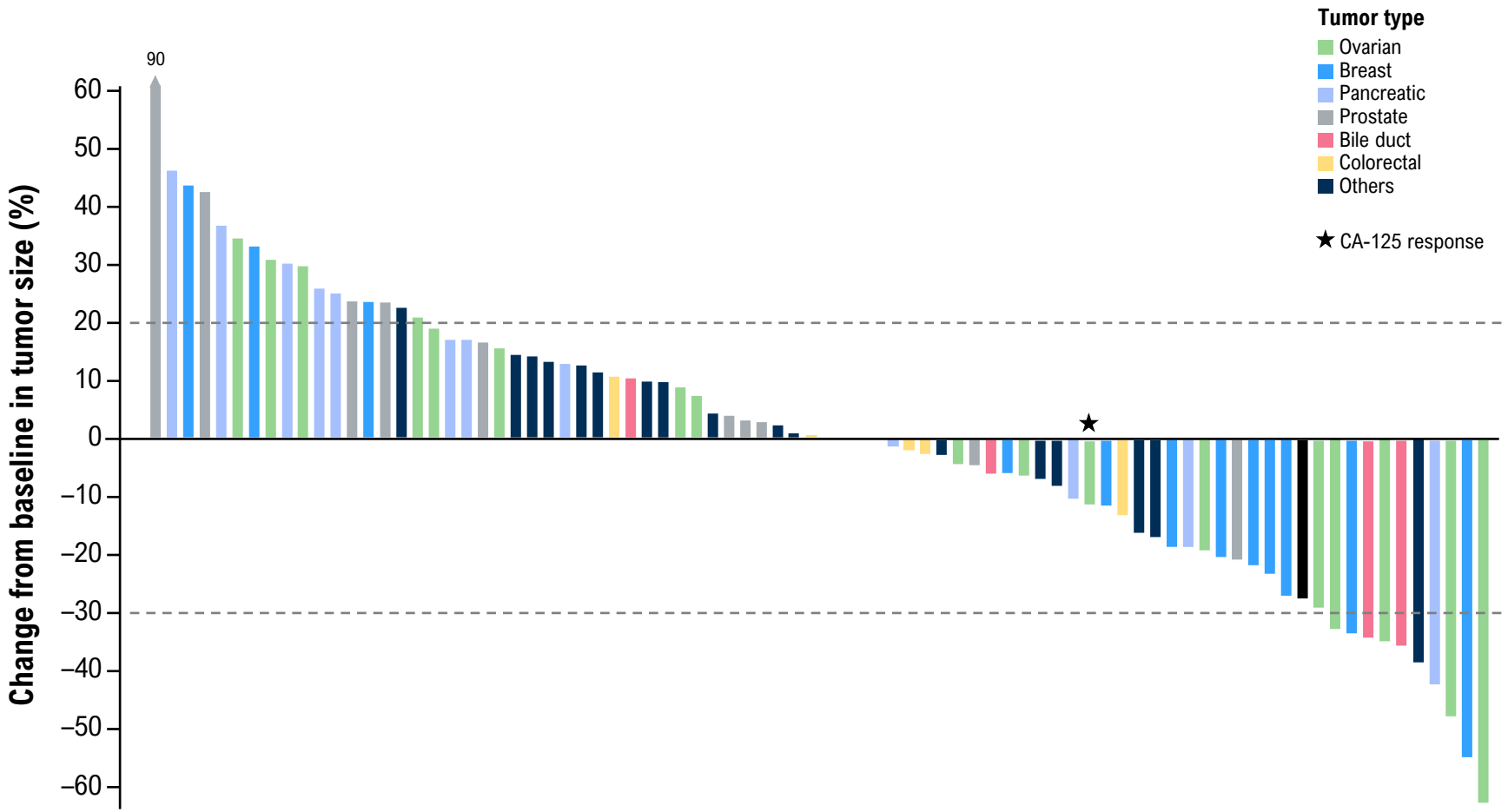
- **Responses seen across:**
  - **Tumor types**
  - Mutation type
  - PARPi combinations
  - Prior PARPi exposure
  - Platinum sensitivity

- RECIST cPR (n=6), uPR (n=3) in the following:
  - Ovarian, breast, pancreatic, bile duct among responding tumors



Included only those patients in the efficacy analysis set with measurable disease; n=82. Eight other patients did not have measurable disease.
One patient with unknown primary tumor of germline ATM mutation that is platinum resistant and PARPi naïve, treated with camoncertib and olaparib combination in the study had uPR in target lesion but developed new bone lesion was not considered as a responder.
CA-125, cancer antigen 125; cPR, confirmed partial response; PARPi, poly (ADP-ribose) polymerase inhibitor; uPR, unconfirmed partial response.

Antitumor activity by mutation type

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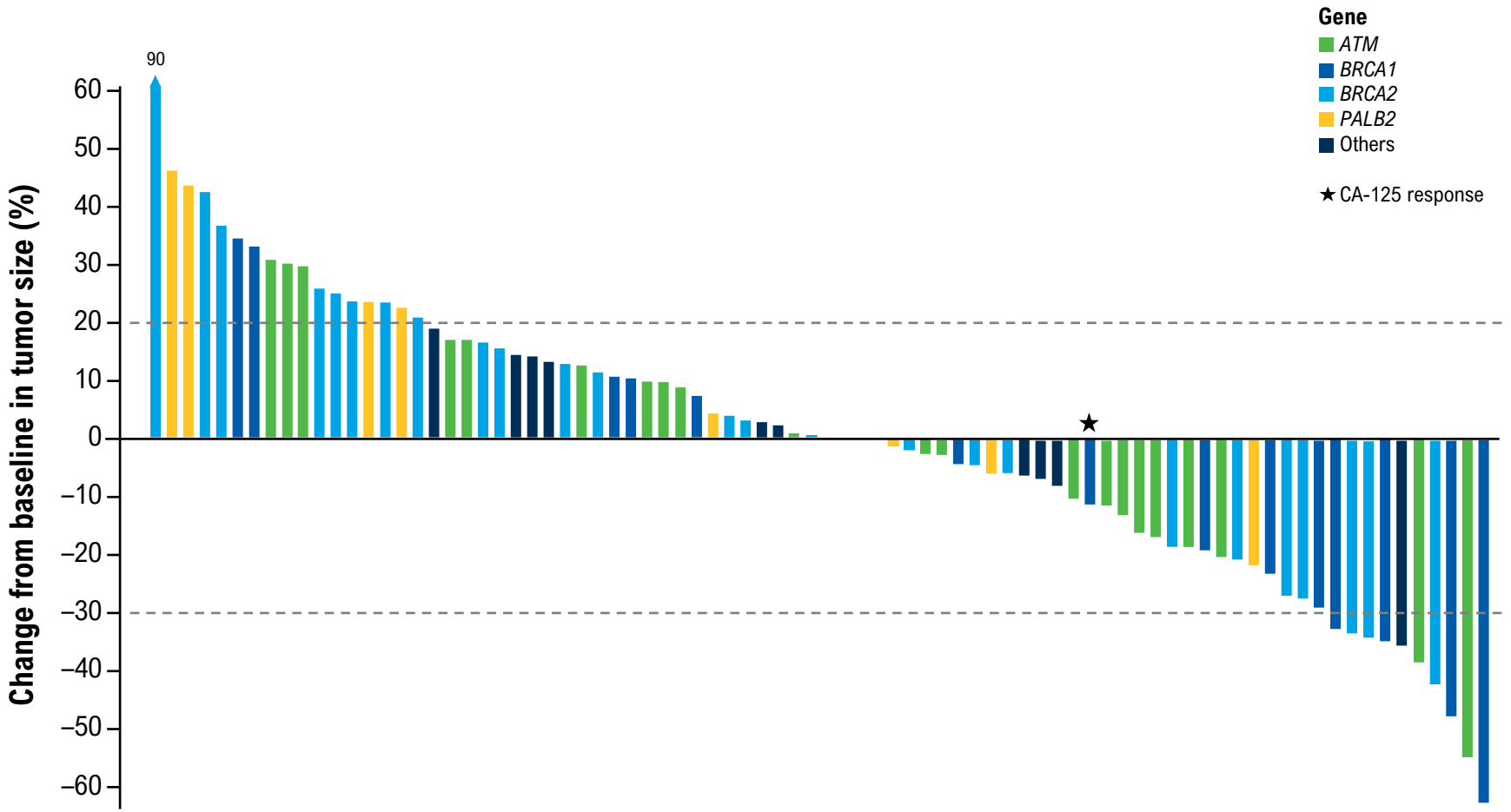
- **Responses seen across:**
  - Tumor types
  - **Mutation type**
  - PARPi combinations
  - Prior PARPi exposure
  - Platinum sensitivity

- In efficacy evaluable tumors with *BRCA1* mutation (n=17):
  - ORR: 35%
    - cPR: n=4;
    - CA-125 response: n=2
  - CBR: 71%



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ORR is based on overall response as best response of confirmed or unconfirmed CR or PR per RECIST v1.1 criteria or confirmed CA-125 response per Gynecological Cancer Intergroup; Clinical benefit rate is based on overall response or ≥16 weeks on treatment without progression.
CA-125, cancer antigen 125; CBR, clinical benefit rate; CR, complete response; cPR, confirmed partial response; ORR, overall response rate; PR, partial response; uPR, unconfirmed partial response.

Antitumor activity independent of PARPi combination partner

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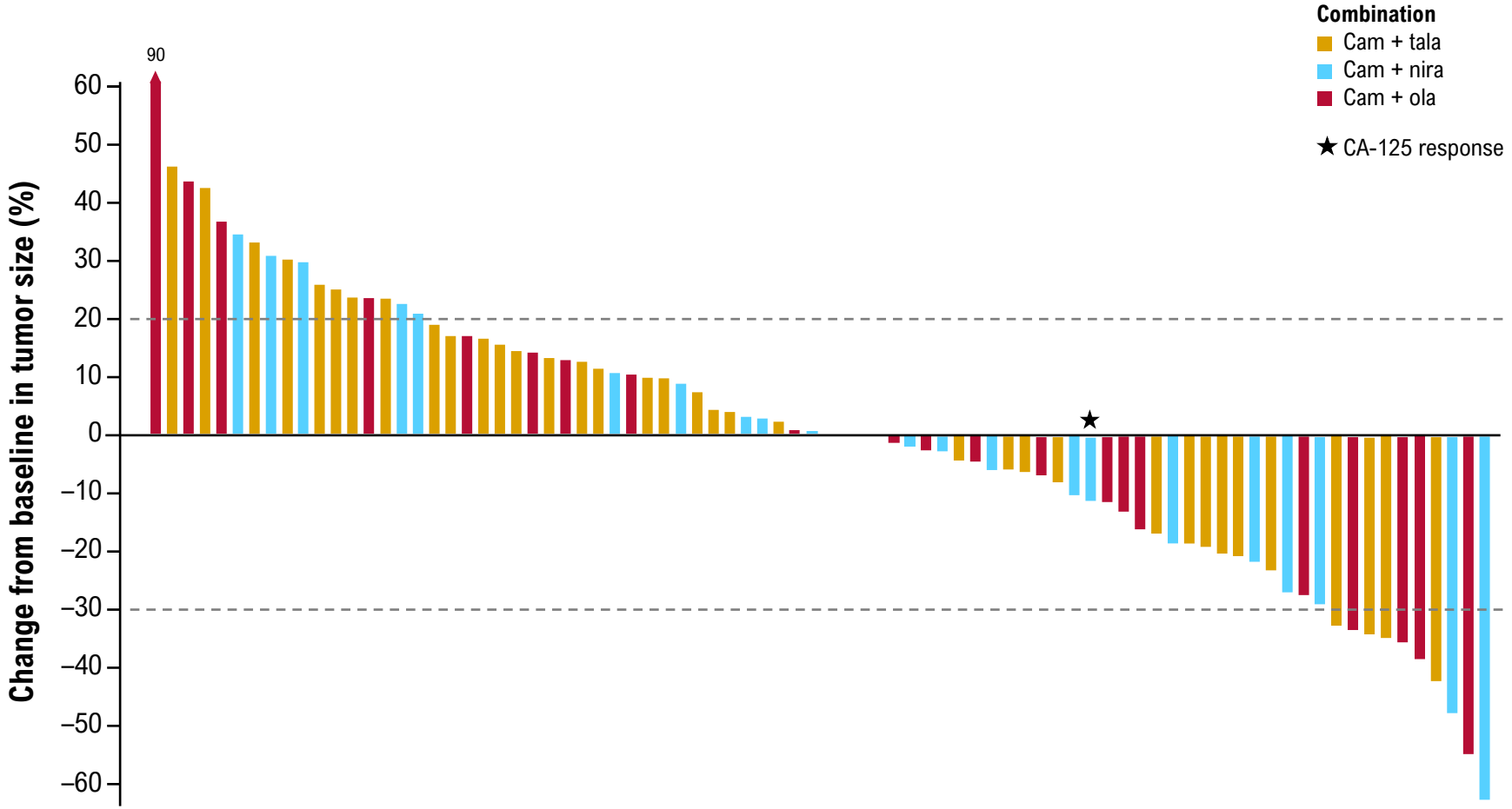
- **Responses seen across:**
  - Tumor types
  - Mutation type
  - **PARPi combinations**
  - Prior PARPi exposure
  - Platinum sensitivity



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CA-125, cancer antigen 125; cam, camonsertib; nira, niraparib; ola, olaparib; PARPi, poly (ADP-ribose) polymerase inhibitor; tala, talazoparib; uPR, unconfirmed partial response.

Antitumor activity regardless of prior PARPi exposure

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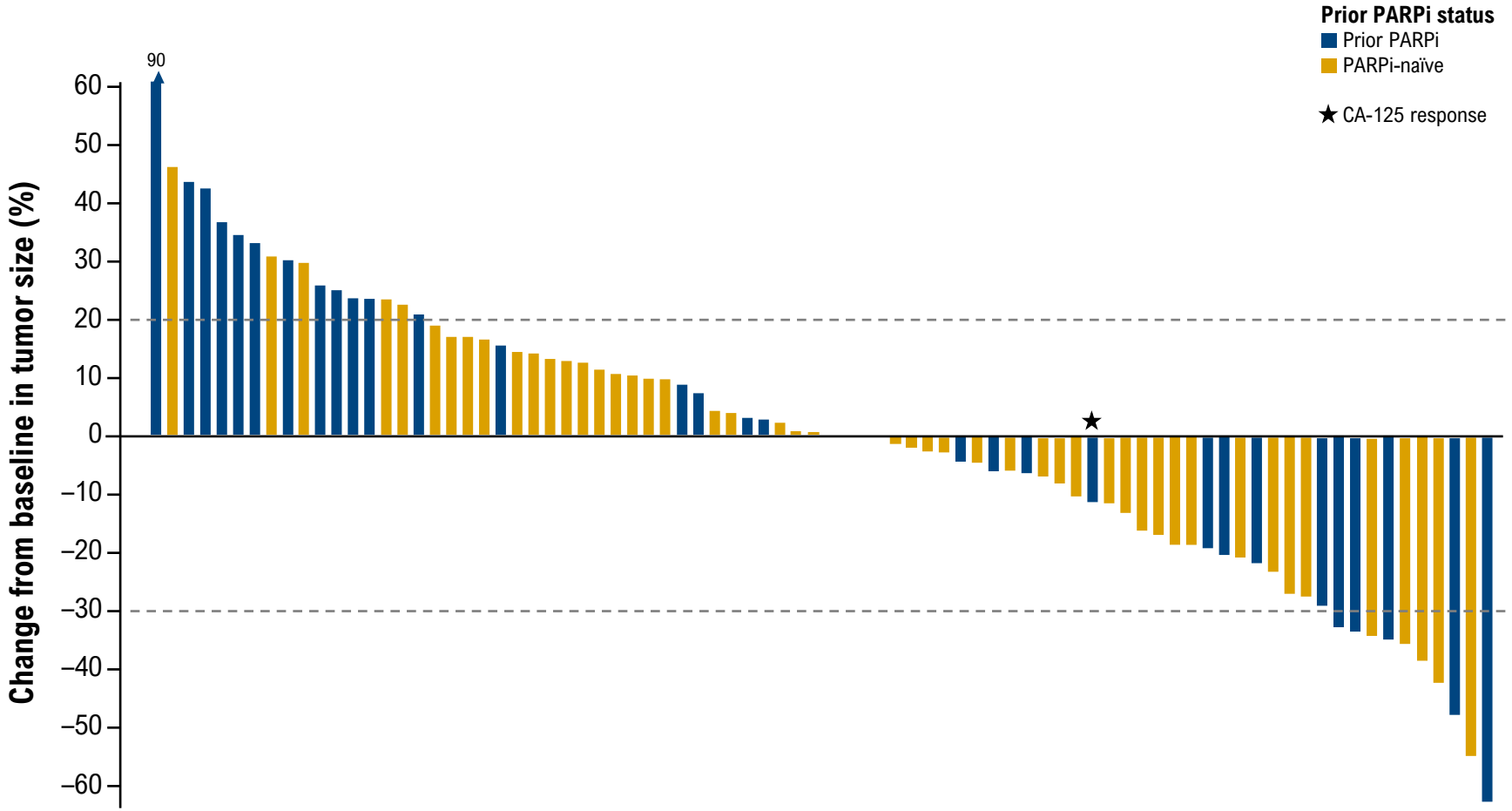
- **Responses seen across:**
  - Tumor types
  - Mutation type
  - PARPi combinations
  - **Prior PARPi exposure**
  - Platinum sensitivity



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CA-125, cancer antigen 125; PARPi, poly (ADP-ribose) polymerase inhibitor; uPR, unconfirmed partial response.

Antitumor activity is independent of platinum sensitivity

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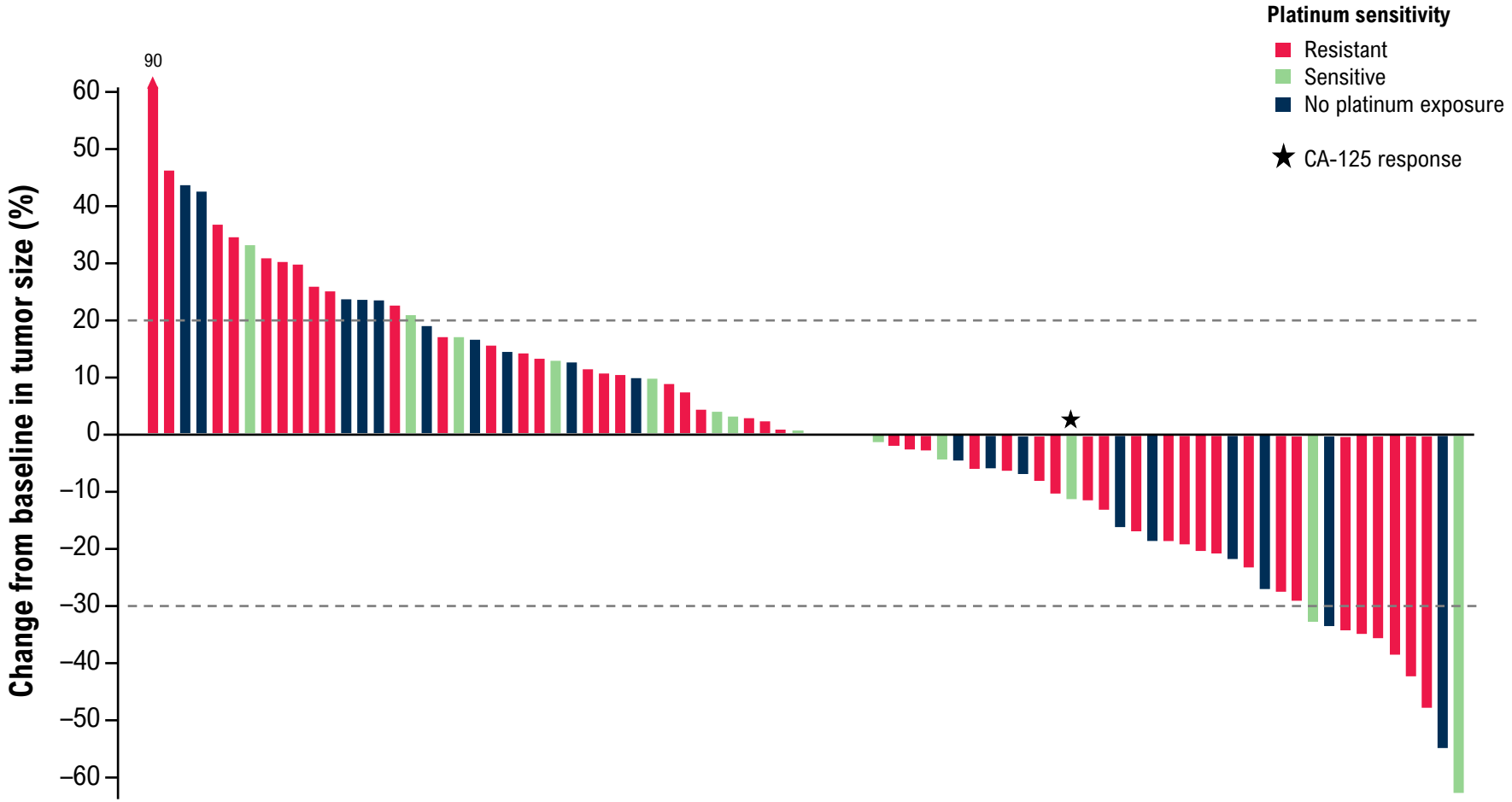
- **Responses seen across:**
  - Tumor types
  - Mutation type
  - PARPi combinations
  - Prior PARPi exposure
  - **Platinum sensitivity**



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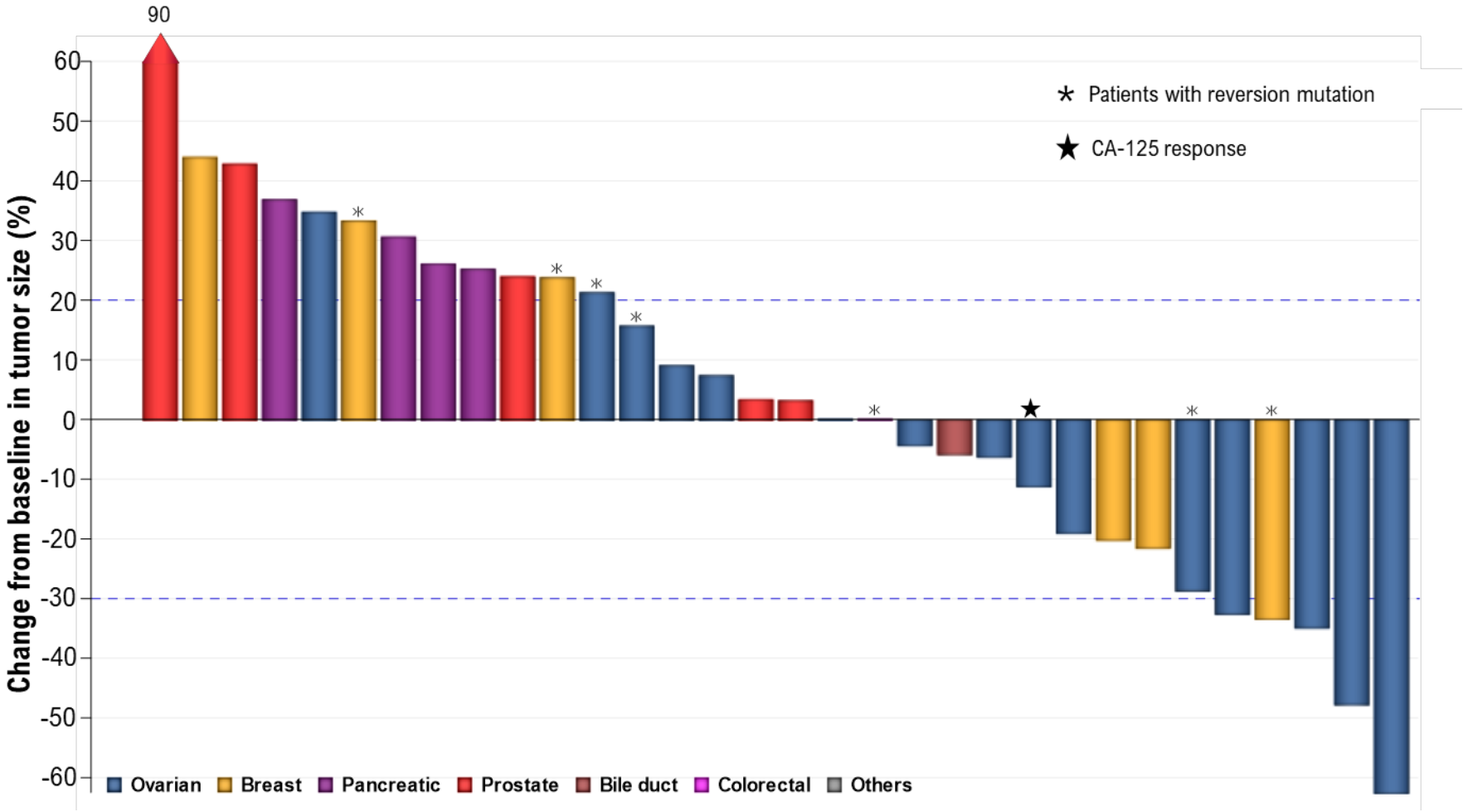
Platinum resistant is defined as platinum treated tumors progressed within 6 months of treatment; Platinum sensitive is defined as platinum treated tumors that did not progress within 6 months of treatment.
CA-125, cancer antigen 125; PARPi, poly (ADP-ribose) polymerase inhibitor; uPR, unconfirmed partial response.

Antitumor activity in PARPi pre-treated patients

- In 32 PARPi pre-treated tumors, activity largely seen in breast and ovarian cancers
- In 21 breast or ovarian tumors:
  - PR: n=5
  - CA-125 response: n=1
- Reversion mutations (∗) were confirmed in 8 PARPi pre-treated tumors:
  - PR: n=1 (*gBRCA2*)
  - CA-125 response: n=1 (non-measurable disease (*sBRCA1*))



Included only those PARPi pre-treated patients in the efficacy analysis set with measurable disease; n=32. Two other PARPi pre-treated patients did not have measurable disease.
PR based on RECIST v1.1 criteria; Confirmed CA-125 response based on Gynecological Cancer Intergroup criteria.
CA-125, cancer antigen 125; g, germline; PARPi, poly (ADP-ribose) polymerase inhibitor; PR, partial response; RECIST, Response Evaluation Criteria in solid Tumors; s, somatic.

Antitumor activity in patients with ovarian cancer

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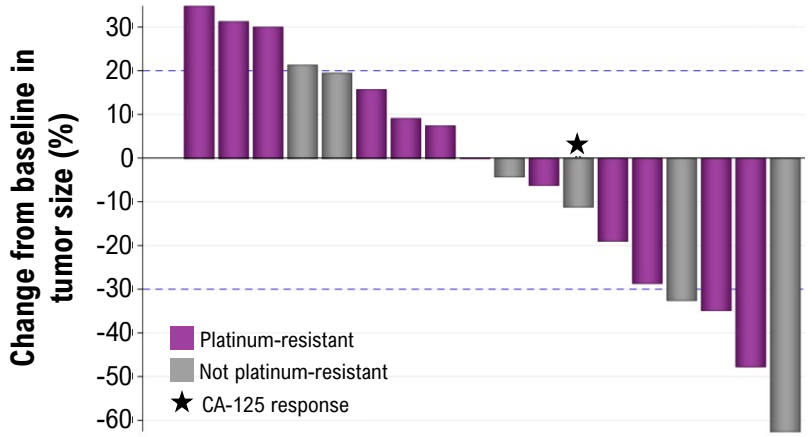
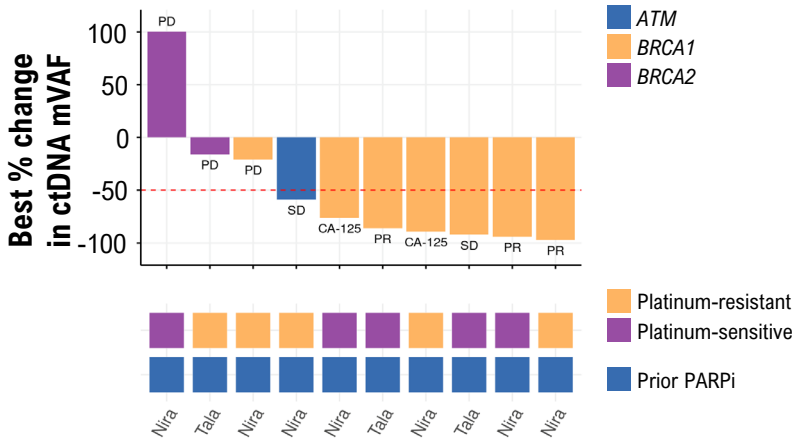
- In 19 efficacy evaluable ovarian cancers:
  - Overall response: 6 (32%)
  - CBR: 58%
  - mPFS: ~7 months
  - Treatment >16 weeks and ongoing in 9 patients
- In 13 platinum resistant/ refractory ovarian tumors:
  - Overall response: 3 (23%)
  - CBR: 54%
- In patients with evaluable ctDNA, MRR: 7/10 (70%)

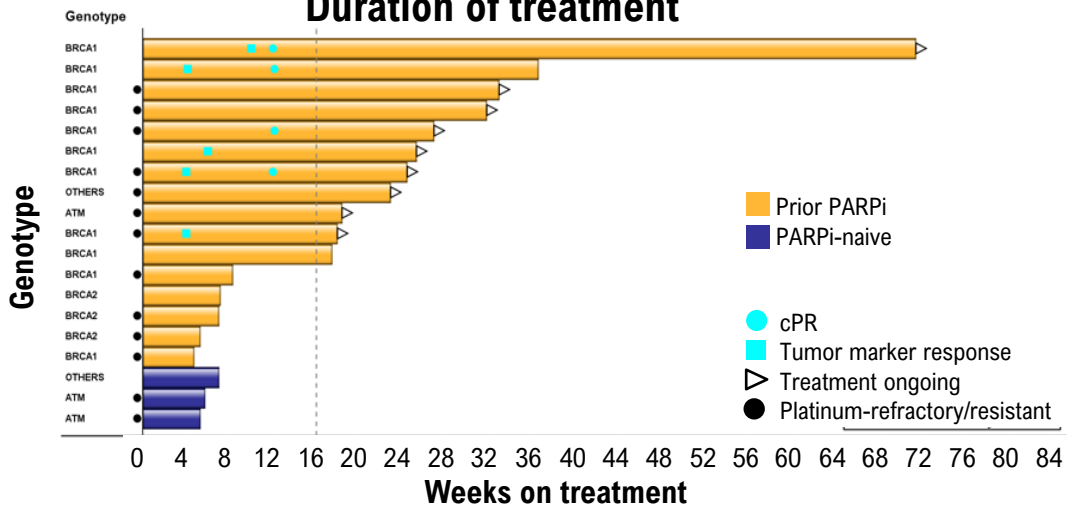
Tumor shrinkage



Early mVAF decrease



Duration of treatment



Early antitumor activity seen in patients despite PARPi pretreatment

Median time to molecular response 22 days [IQR: 20.5–25 days]

Overall response is best response of confirmed or unconfirmed CR or PR per RECIST v1.1 criteria or confirmed CA-125 response per Gynecological Cancer Intergroup; Clinical benefit rate is based on overall response or ≥16 weeks on treatment without progression; MRR is based on ctDNA molecular response as >50% decline in mVAF assessed by GuardantINFINITY or Tempus xF gene panel for patients with detectable somatic alterations.
Waterfall plot only included ovarian cancer patients in the efficacy analysis set with measurable disease; n=18. One other ovarian cancer patient did not have measurable disease.
CA-125, cancer antigen 125; CBR, clinical benefit rate; cPR, confirmed partial response; ctDNA, circulating tumor DNA; IQR, interquartile range; mPFS, median progression-free survival; MRR, molecular response rate; mVAF, mean variant allele frequency; PARPi, poly (ADP-ribose) polymerase inhibitor; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

ctDNA mVAF decrease as an antitumor activity marker

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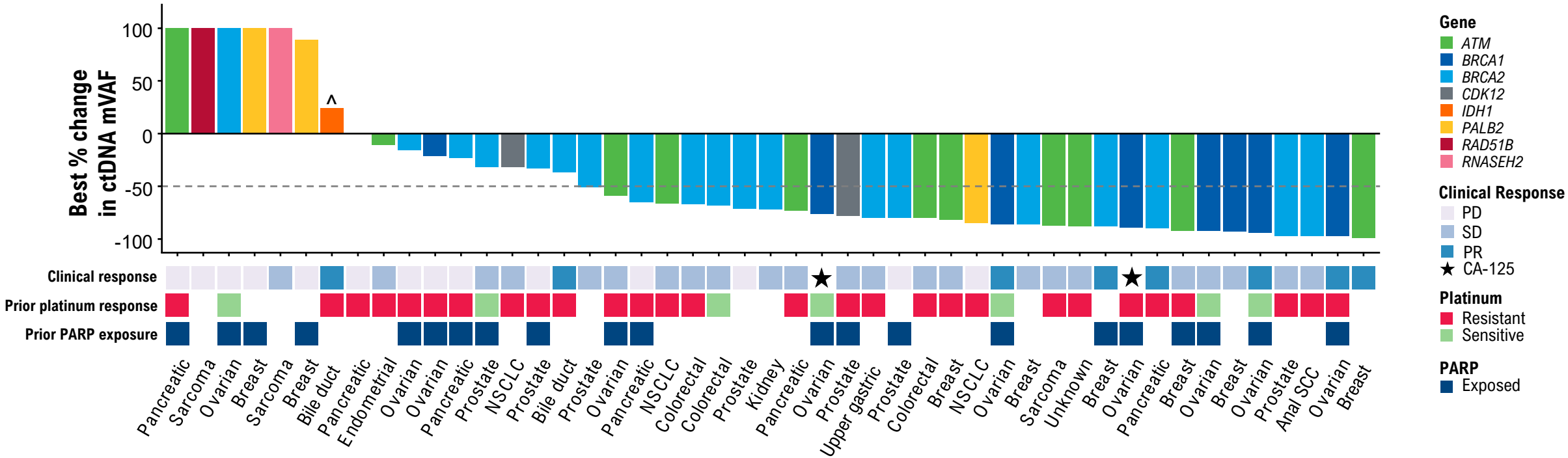
Early (median 21 days [IQR:21–31]) ctDNA molecular responses[a] in 66% (31/47) of evaluable patients supports antitumor activity of low dose, intermittent PARPi + ATRi therapy

- MRR was significantly higher in patients with clinical benefit (83%) versus those without (48%; p=0.015), supporting treatment effect
- MRs were observed in patients with prior PARPi (57%) and platinum resistance (64%)



[a]ctDNA molecular response is defined as 50% or greater decline in mVAF assessed by GuardantINFINITY or Tempus xF gene panel for patients with detectable somatic alterations; best mVAFR capped at +100%.
^Patient with m*IDH1* (not a SNIPRx sensitivity gene) cholangiocarcinoma enrolled as "other alterations" had a short lasting uPR, but no molecular response.
ATRi, ataxia telangiectasia- and Rad3-related inhibitor; CA-125, cancer antigen 125; CCA, cholangiocarcinoma; ctDNA, circulating tumor DNA; IQR, interquartile range; MR, molecular response; MRR, MR rate; mVAF, mean variant allele frequency; mVAFR, mVAF response; NSCLC, non-small cell lung cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease; SCC, squamous cell carcinoma; uPR, unconfirmed partial response.

ctDNA mVAF decline correlates with tumor volume decrease and longer mPFS

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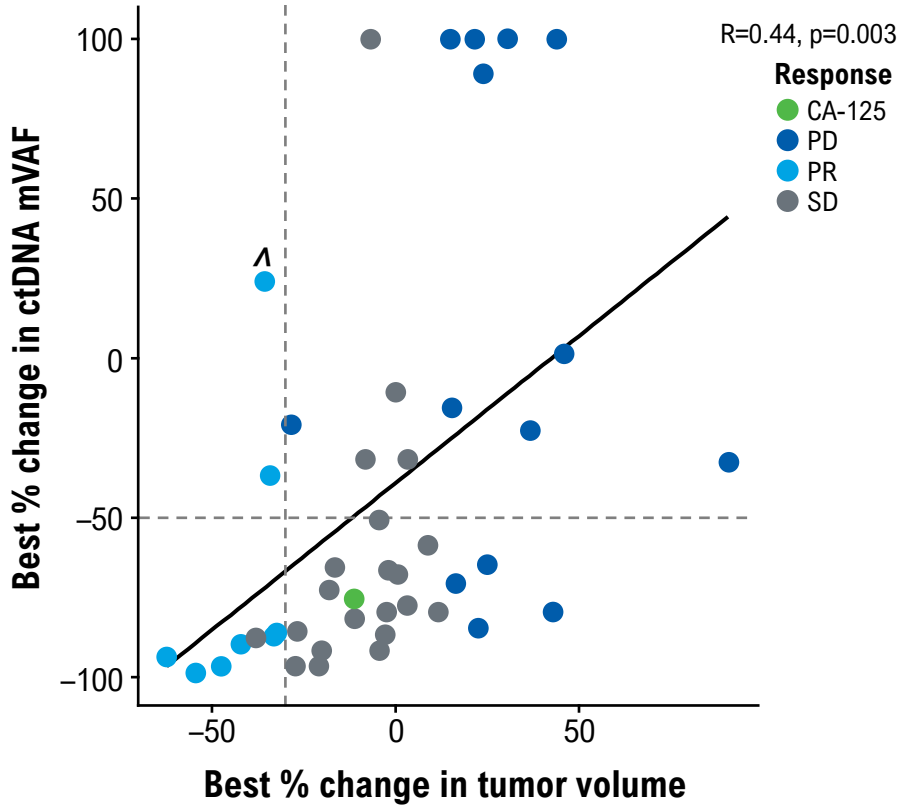
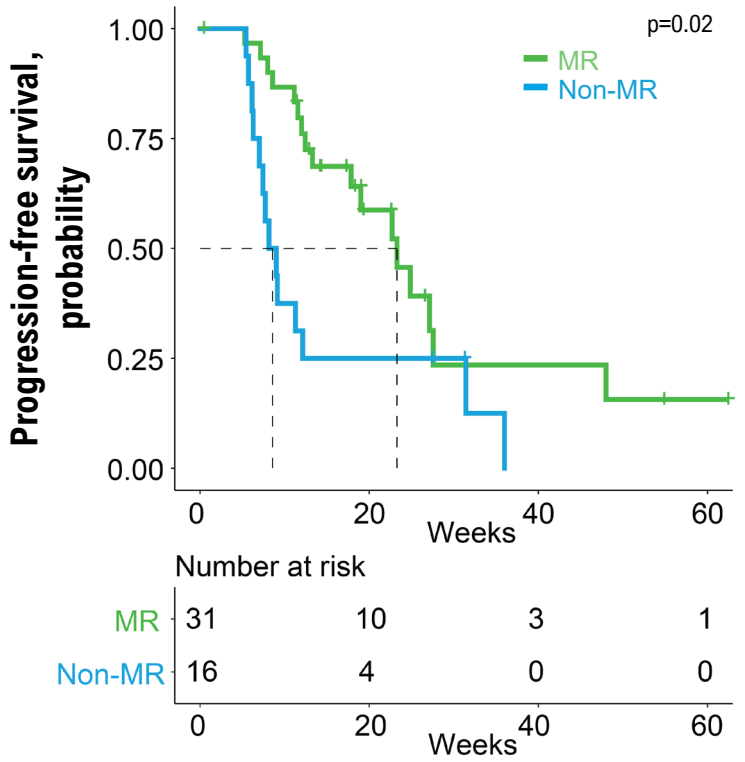
- Best % change in mVAF positively correlated with change in tumor volume (R=0.44; p=0.003)
- Molecular responders had longer mPFS (23 weeks) versus non-molecular responders (9 weeks; p=0.02)



Subset of patients with available ctDNA data; n=47



Subset of patients with available ctDNA data; n=47

CA-125, cancer antigen 125; ctDNA, circulating tumor DNA; MR, molecular response; mPFS, median progression-free survival; mVAF, mean variant allele frequency; PD, progressive disease; PR, partial response; SD, stable disease. R: Pearson correlation coefficient; Log-rank test used for comparison of PFS. ^Patient with m*IDH1* (not a SNIPRx sensitivity gene) cholangiocarcinoma enrolled as "other alterations" had a short lasting uPR, but no molecular response.

Summary and conclusions

- Low-dose intermittent regimens of camonsertib and different PARPi combinations were safe with transient hematological events; no prophylactic growth factors required

- Anticancer activity observed in patients with platinum and PARPi resistant tumors with predefined genomic alterations:
  - Durable antitumor activity was encouraging, with CBR of 48% in the efficacy population (n=90)
  - Patients with late-line ovarian cancer (n=19) derived the most benefit from therapy (Overall Response 32%, CBR 58%, mPFS ~7 months), which compares favorably to current therapeutic options for patients
  - MRR was 66% in 47 evaluable patients, supporting antitumor activity of the combinations

- Dose optimization to refine a tailored combinatorial dose in tumor-specific expansions is ongoing; this approach could represent a novel strategy in areas of unmet clinical need

Overall response is best response of confirmed or unconfirmed CR or PR per RECIST v1.1 criteria or confirmed CA-125 response per Gynecological Cancer Intergroup; Clinical benefit rate is based on overall response or ≥16 weeks on treatment without progression; MRR is based on ctDNA molecular response as >50% decline in mVAF assessed by GuardantINFINITY or Tempus xF gene panel for patients with detectable somatic alterations.
CA-125, cancer antigen 125; CBR, clinical benefit rate; CR, complete response; ctDNA, circulating tumor DNA; mPFS, median progression-free survival; MRR, molecular response rate; mVAF, mean variant allele frequency; ORR, overall response rate; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Acknowledgements

The authors would like to thank all patients, their families and caregivers, and all investigators involved in both ATTACC and TRESR studies

Participating TRESR and ATTACC study sites for their work and contributions

- Billy Hoadley, Christian Brown, Desirae Dufner, Morgan Williams, Melissa Pham MD, Natalie Ngoi MD – University of Texas MD Anderson Cancer Center, TX
- Mary Liebers, Ava Greenberg – Dana Farber Cancer Institute, MA
- Brooke Petrasovits – Sarah Cannon Research Institute/Tennessee Oncology, TN
- Christopher Tapia Pichardo – Memorial Sloan Kettering Cancer Center, NY
- Paula Lee – Duke Cancer Institute, NC
- Jocelyn Hubbard – Massachusetts General Hospital, MA
- Emily Roth, Victoria Nelson – Rhode Island Hospital/Lifespan, RI
- Ramya Myneni – Robert H. Lurie Comprehensive Cancer Center; Northwestern University, IL
- Ashley Adile – Princess Margaret Cancer Center, ON
- Jane Halliwell, Vivienne Tsui – The Christie NHS Foundation Trust, UK
- Helen Porteous – Newcastle Hospital NHS Foundation Trust, UK
- Saba Mahmud, Lisa Ng – Sarah Cannon Research Institute, UK
- Cecilia Sonander Westphal, Emma-Sofie Sønderskov Darre – Righospitalet, Denmark
- Vivek Suri – Columbia University Medical Center, NY
- Carol Goldener, Kai Hajos – The Johns Hopkins University, MD
- Arati Khanna-Gupta, Karen Rodriguez-Vasquez – Yale University School of Medicine, CT
- Sierra Mitchell – Huntsman Cancer Institute, UT
- Catharine Frost – University of Michigan, MI
- Pyone Lei Phone, Renee Bradshaw – The Mayo Clinic, MN

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Precision Oncology Decision Support (PODS) Group at the University of Texas MD Anderson Cancer Center

ProPharma Group and ICON, Clinical Research Organizations

Talazoparib was provided by Pfizer Inc.

This study was funded by Repare Therapeutics.

Editorial support, including layout, figure redraws, and editorial review was provided by Onyx (London, UK), supported by Repare Therapeutics according to good publication practices.

ATTACC, ATRi and PARPi in patients with molecularly selected cancers; TRESR, treatment enabled by SNIPRx.