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Poster number: B045

Camonsertib (RP-3500), an ataxia telangiectasia- and Rad3-related kinase inhibitor (ATRi) in combination with low dose gemcitabine (gem) in patients with solid tumors with DNA damage response (DDR) aberrations: Preclinical and Phase 1b results (NCT04497116)

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Background

Camonsertib, a highly selective ATR kinase inhibitor: Rationale for synergy with gemcitabine

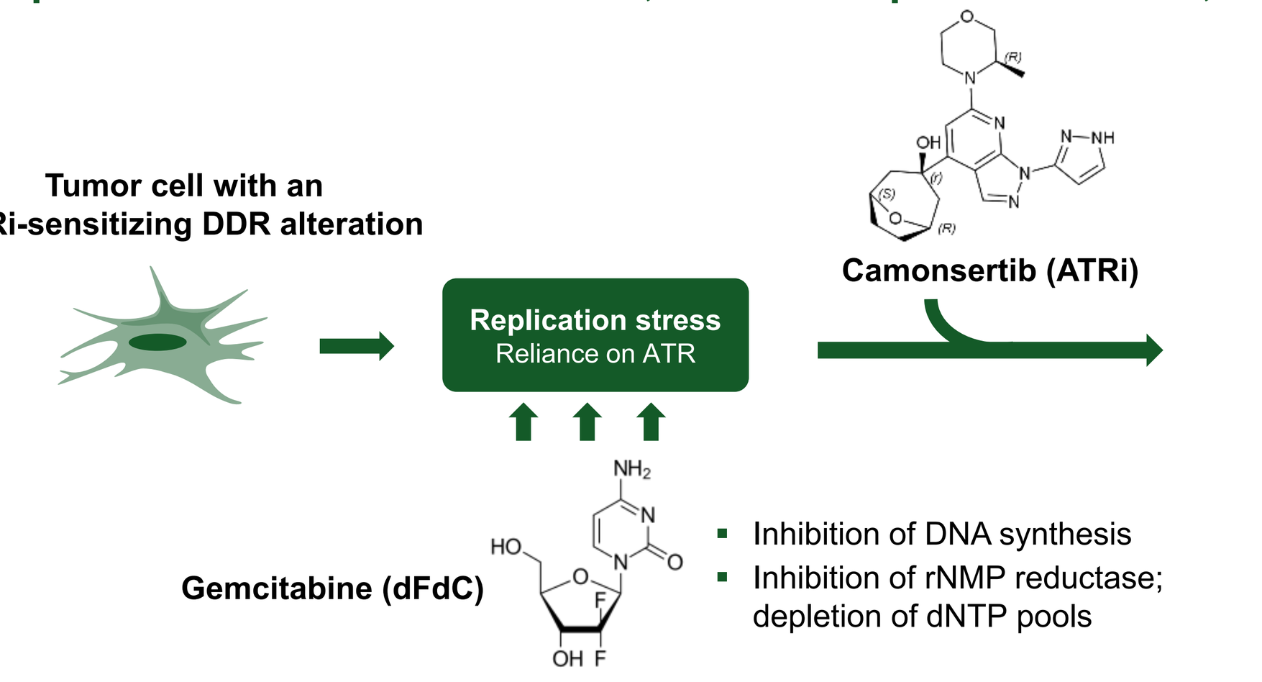
ATR inhibition is synthetically lethal with genomic alterations affecting DNA damage response[1]

- ATR: mediator of cellular DDR, activated in response to DNA replication stress
- Camonsertib is a potent, highly selective ATR inhibitor; provides relevant benefit in multiple tumors

Clinical activity of camonsertib monotherapy (> 100 mg/day) demonstrated in patients with ovarian cancer (N=20)

- Response rate: 25%
- Clinical benefit rate: 75%
- Mean progression free survival (mPFS): 35 weeks

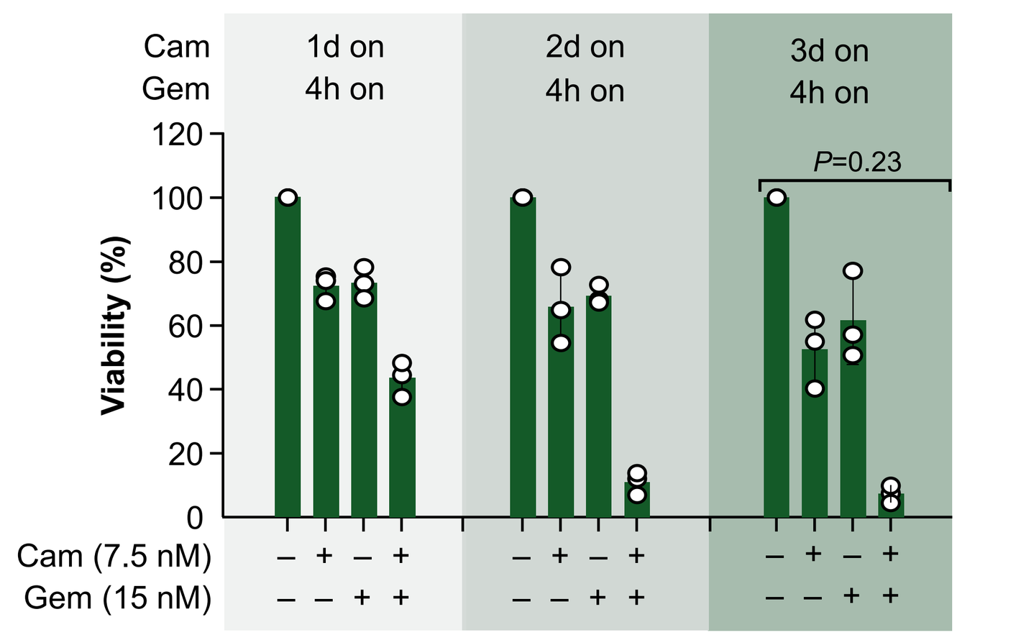
Gemcitabine potentiates the effects of ATRi; elevates replication stress, increasing reliance on ATR



Tumor cell with an ATRi-sensitizing DDR alteration
Replication stress
Reliance on ATR
Camonsertib (ATRi)
Gemcitabine (dFdC)
Replication fork collapse
Pre-mature mitotic entry
Accelerated cell death
Inhibition of DNA synthesis
Inhibition of rNMP reductase; depletion of dNTP pools

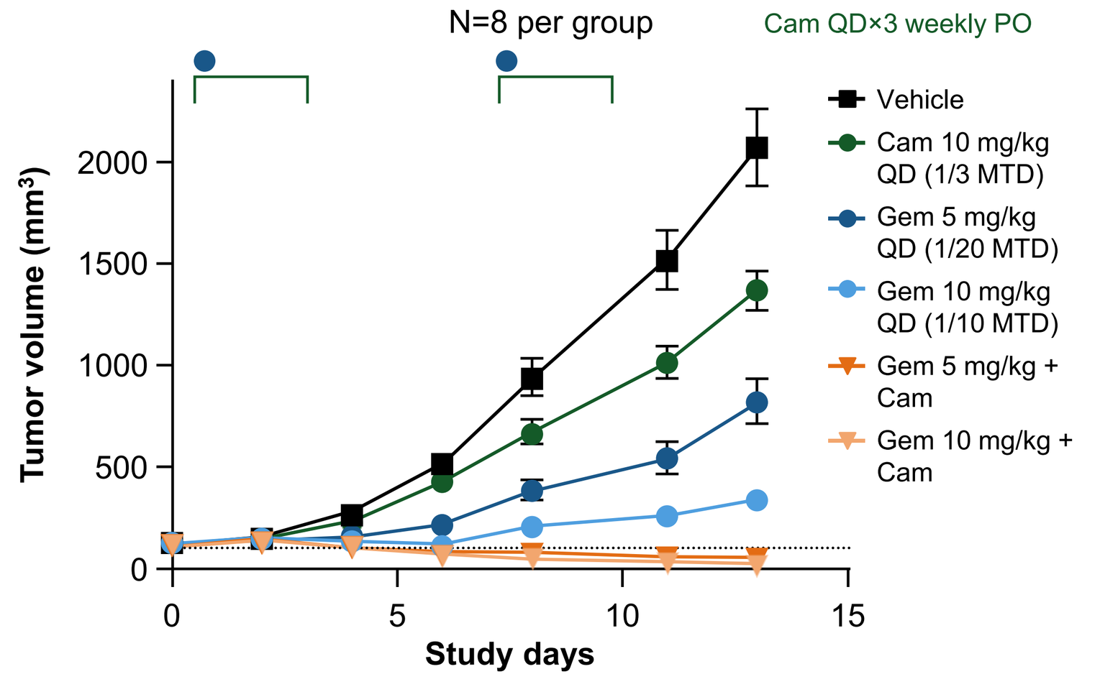
Figure 1. Preclinical data demonstrate combination synergy at low doses of cam and gem

A. SUM149PT (BRCA1m) 8d CTG assay



In vitro, low doses of cam (≤IC_{50}) and gem strongly synergize to kill tumor cells with ZIP synergy scores of > 40

B. Granta-519 ATMmut



In vivo, cam (1/3 MTD) combined with low dose gem (1/10-1/20 MTD) results in tumor regression. No impact on body weight was observed (data not shown).

Methods

Inclusion criteria:

- Patients ≥ 18y with advanced solid tumors
- Tumors with deleterious somatic or germline gene alterations
  - *ATM, ATRIP, BRCA1/2, CDK12, CHTF8, FZR1, MRE11, NBN, PALB2, RAD51B/C/D, RNASEH2A/B, RAD17, REV3L, RAD50, SETD2*
- ECOG PS 0 or 1
- Hemoglobin ≥ 10 g/dL
- Platelets ≥ 140,000/µL
- Absolute neutrophil count ≥ 1,700/µL
- Prior gemcitabine permitted

Camonsertib monotherapy[1]

- Preliminary RP2D: 160 mg QD (3/4)

Camonsertib with gemcitabine

- 64 patients treated
- 52/64 patients evaluated for response (≥ 1 post-baseline scan)

Jul 2020 – Monotherapy Initiated; Dec 2021 – Cam + gem Initiated; Jul 31, 2023 – Data cut-off date

Study is ongoing: ***NCT04497116***

Objectives and key endpoints:

- Safety and tolerability; RP2D and schedule
- Response: response evaluation in solid tumors (RECIST v1.1), confirmed PSA (PCWG3 criteria) or CA-125 response (GCIG criteria)
- Clinical benefit: response or treatment duration ≥ 16 w without progression
- Camonsertib pharmacokinetics
- Genomic analysis and ctDNA molecular response (MR) (≥ 50% decline in methylation-based TF)[2]

Results

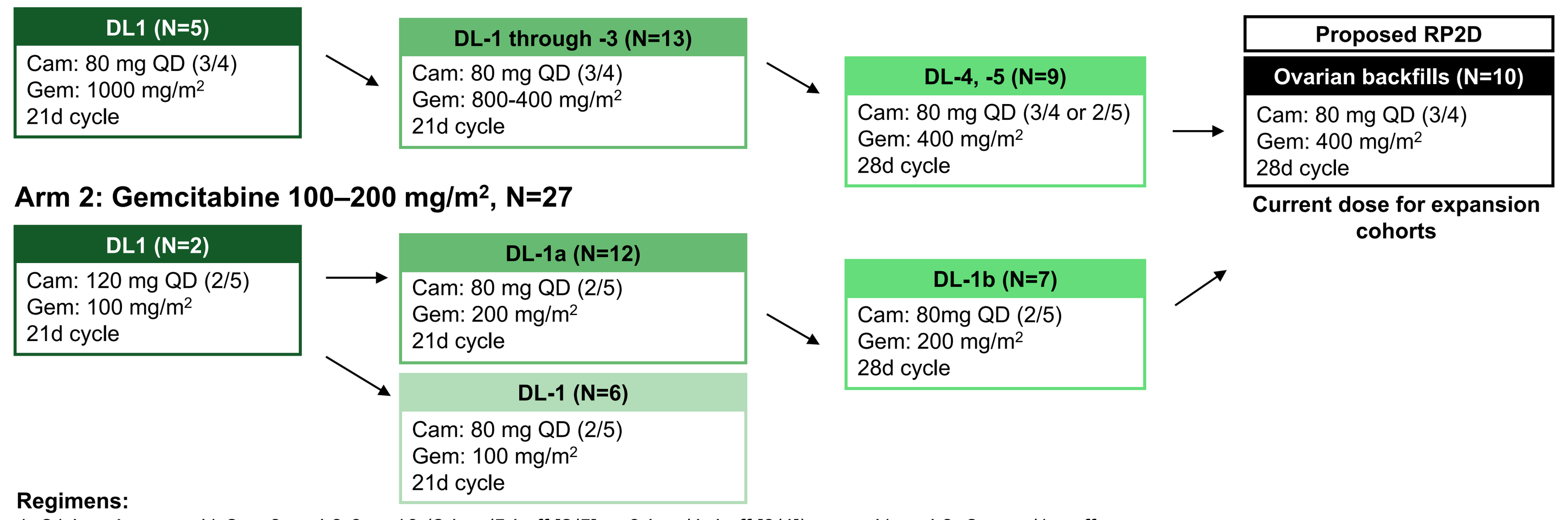
Table 1. Patient demographics

Parameter	All patients (N=64)	
Age (years) Median (IQR)	61 (55–69)	
Sex, n (%)		
Male	15 (23)	
Female	49 (77)	
ECOG PS, n (%)		
0	26 (41)	
1	38 (59)	
Prior systemic therapies	*All patients (N=64)*	*Ovarian Cancer (N=29)*
Median (IQR)	**3 (2–4)**	**3 (2–4)**
≥ 3, n (%)	39 (61)	20 (69)
PARPi, n (%)	37 (58)	23 (79)
Platinum, n (%)	55 (86)	28 (97)
Gemcitabine, n(%)	12 (19)	8 (28)

Parameter	All patients (N=64)
Tumor types, n (%)	
Ovarian	29 (45)
Pancreatic	8 (13)
Breast	6 (9)
Colorectal	4 (6)
Prostate	3 (5)
Lung	3 (5)
Endometrial	2 (3)
Liver	2 (3)
Other[a]	7 (11)
Genotypes, n (%)	
BRCA1	23 (36)
BRCA2	17 (27)
ATM	14 (22)
PALB2	2 (3)
CDK12	2 (3)
SETD2	2 (3)
Other[b]	4 (6)

[a]Other tumor types included cervical (n=1), gastrointestinal (n=1), head and neck (n=1), kidney (n=1), ampullary (n=1), mesothelioma (n=1), and uterine carcinosarcoma (n=1). [b]Other genotypes included *RAD50* (n=1), *RAD51B* (n=1), *RAD51C* (n=1), and *MRE11A* (n=1).

Figure 2. Comprehensive dose and schedule finding



Arm 1: Gemcitabine 400–1000 mg/m², N=37
DL1 (N=5)
Cam: 80 mg QD (3/4)
Gem: 1000 mg/m²
21d cycle
DL-1 through -3 (N=13)
Cam: 80 mg QD (3/4)
Gem: 800-400 mg/m²
21d cycle
DL-4, -5 (N=9)
Cam: 80 mg QD (3/4 or 2/5)
Gem: 400 mg/m²
28d cycle
Proposed RP2D
Ovarian backfills (N=10)
Cam: 80 mg QD (3/4)
Gem: 400 mg/m²
28d cycle
Current dose for expansion cohorts
Arm 2: Gemcitabine 100–200 mg/m², N=27
DL1 (N=2)
Cam: 120 mg QD (2/5)
Gem: 100 mg/m²
21d cycle
DL-1a (N=12)
Cam: 80 mg QD (2/5)
Gem: 200 mg/m²
21d cycle
DL-1 (N=6)
Cam: 80 mg QD (2/5)
Gem: 100 mg/m²
21d cycle
DL-1b (N=7)
Cam: 80mg QD (2/5)
Gem: 200 mg/m²
28d cycle

Regimens:
1. 21d cycle: cam d1-2 or 3 and 8-9 or 10 (2d on/5d off [2/5] or 3d on/4 d off [3/4]), gem d1 and 8; 2 w on/1w off.
2. 28d cycle: cam d1-2 or 3 and 15-16 or 17 (2/5 or 3/4); gem d1 and 15; 1w on/1w off.

Treatment-related adverse events and neutrophil dynamics

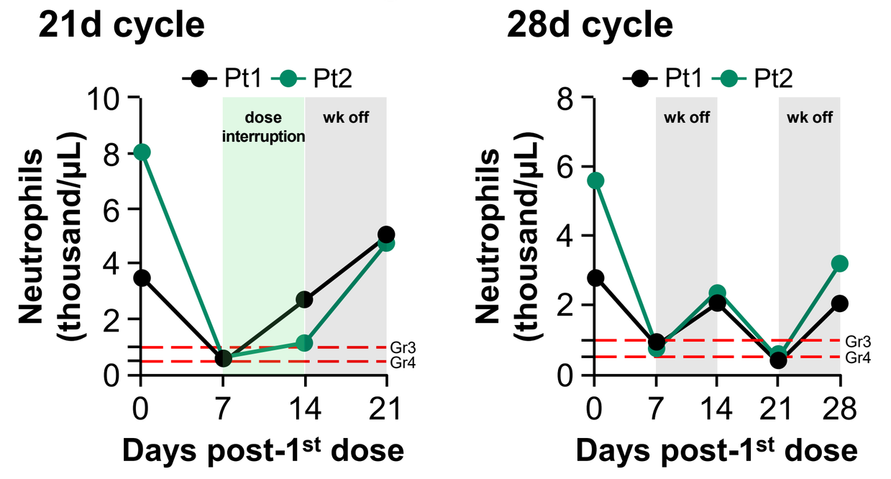
Table 2. Treatment-related adverse events (TRAEs)

AE term, %	Arm 1 N=37			Arm 2 N=27		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Neutropenia	62	30	27	56	33	7
Fatigue	49	3	0	63	7	0
Anemia	49	22	0	56	22	0
Alopecia	43	0	0	44	0	0
Nausea	38	0	0	41	0	0
Thrombocytopenia	35	8	0	41	19	4
Pyrexia	38	0	0	15	0	0
Vomiting	27	0	0	30	0	0
Leukopenia	30	19	0	26	11	0
Stomatitis	30	5	0	11	4	0
Chills	24	0	0	15	0	0
Decreased appetite	14	0	0	19	0	0
Headache	16	0	0	15	0	0

TRAE of all grades that occurred in ≥ 15% of patients treated.
Most frequent dose-limiting toxicities: neutropenia/anemia (Arm 1); neutropenia (Arm 2).

Neutropenia, the most frequent TRAE across dose levels, was transient and occurred in the absence of fever, typically with spontaneous recovery.

Figure 3. Neutrophil dynamics: 21d vs 28d cycle (representative examples)



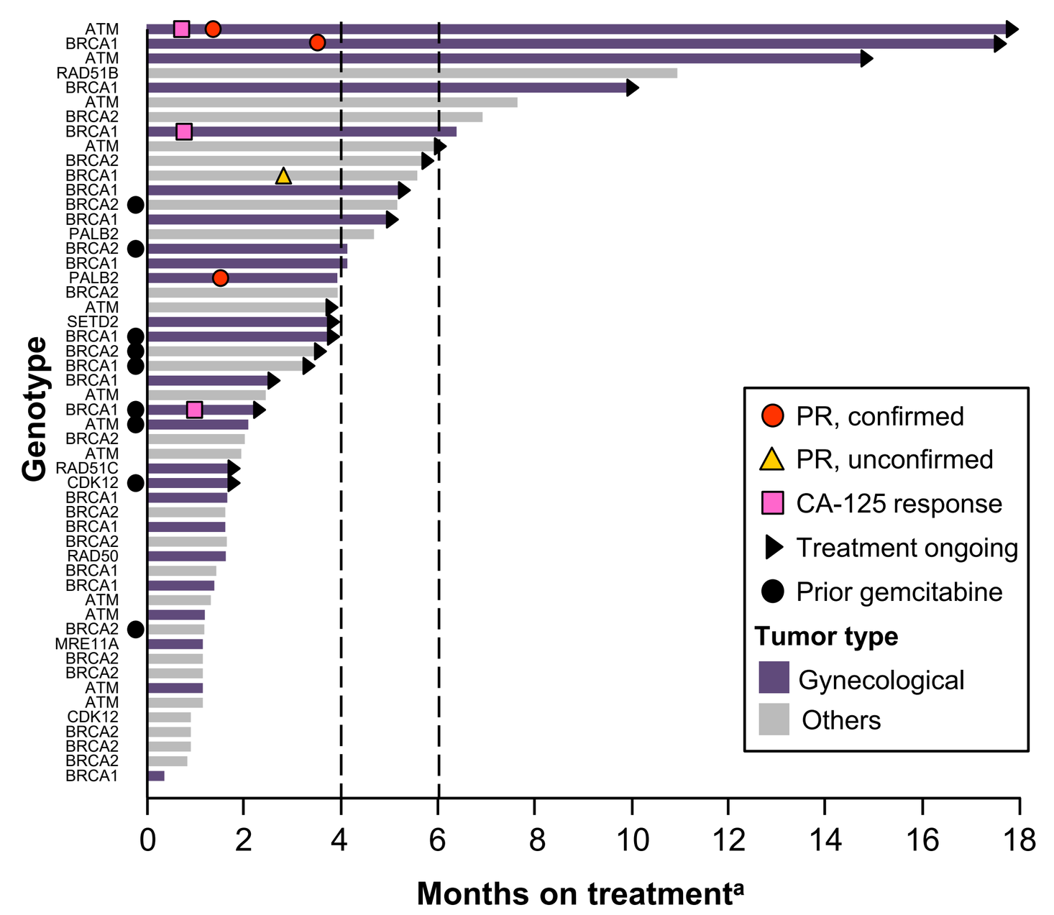
At proposed RP2D/schedule neutrophil nadir occurred during planned week off, with recovery by next scheduled dose, resulting in fewer dose interruptions/reductions.

- Arm 1, 21d cycle: 72% (13/18) of patients had a dose interruption and/or reduction due to neutropenia.
- Proposed RP2D, 28d cycle: no patients had a dose interruption due to neutropenia; 1 patient (6% [1/16]) required a dose reduction due to neutropenia.

Results

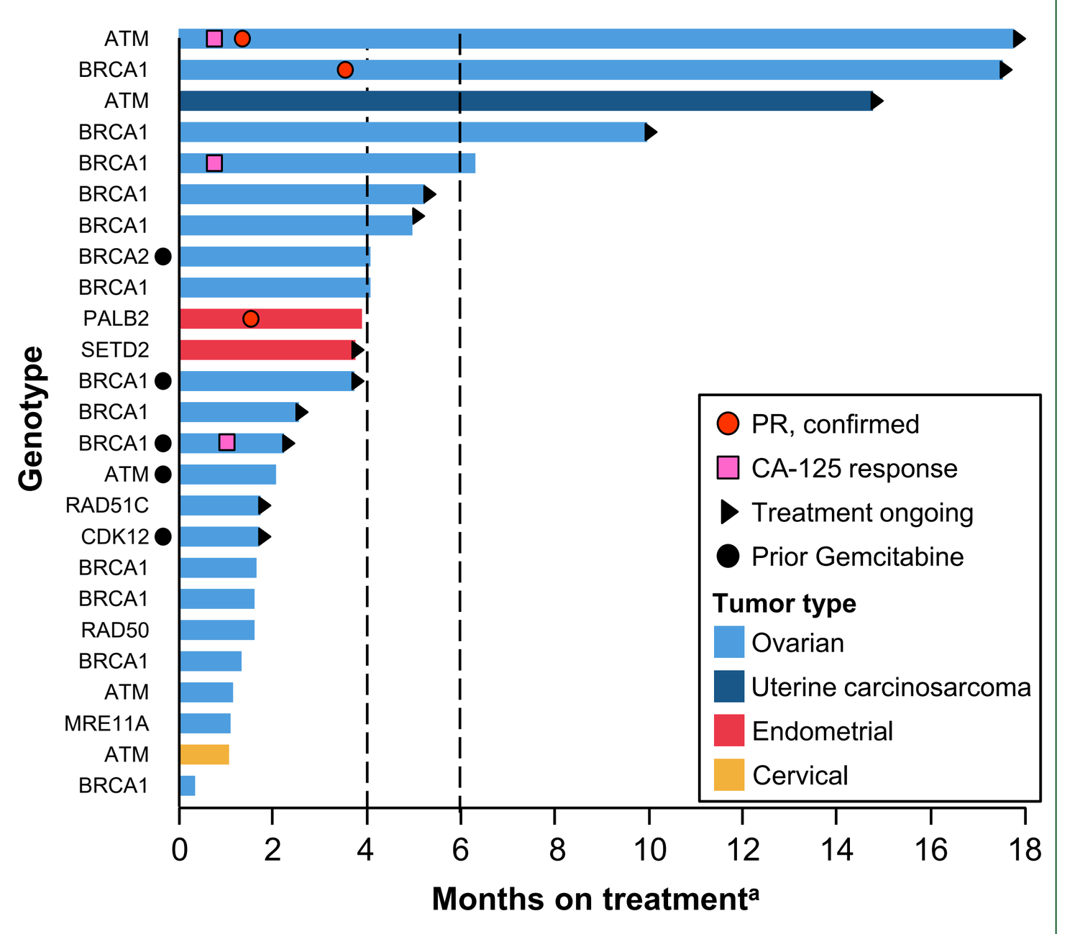
Figure 4. Preliminary antitumor activity of combination: study ongoing

A. Treatment duration for all patients (median 3 prior systemic therapies)



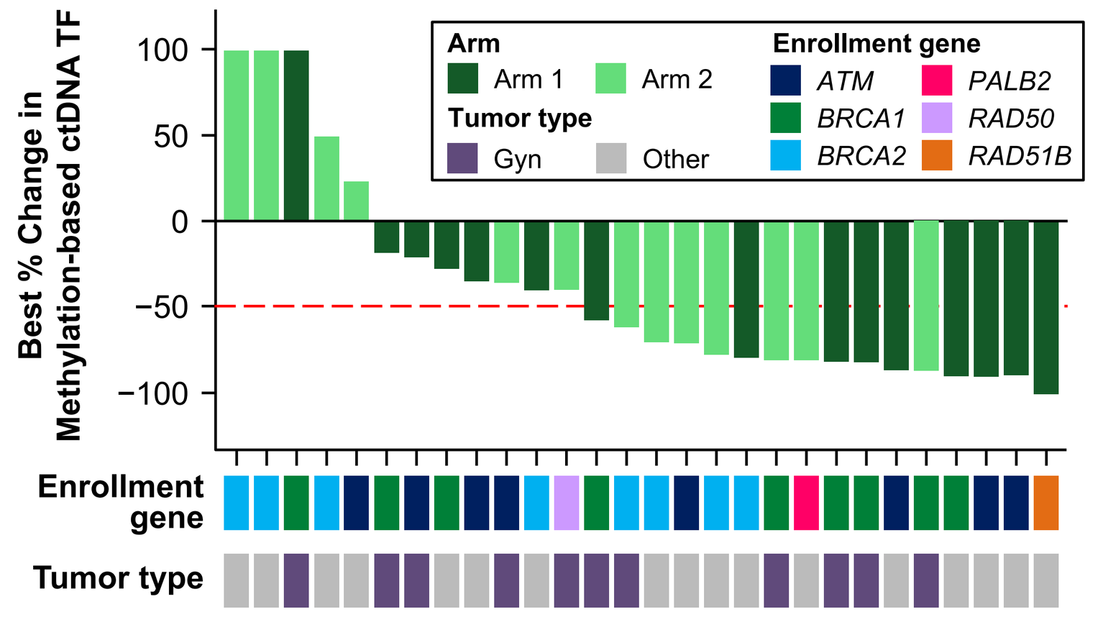
- Response rate: 12% (6/52)
- CBR[b]: 44% (18/41)

B. Treatment duration for patients with gynecologic cancers (median 3 prior systemic therapies)



- Response rate: 20% (5/25)
- CBR[b]: 59% (10/17)

C. ctDNA molecular response analysis



- Methylation-based TF reduction[c] is a more sensitive approach for ctDNA monitoring[3].
- On-treatment time-points analyzed for MR; median timepoint for data shown is 6w (range 4-12 w)
- Molecular response rate (MRR): 57% (16/28)
- ctDNA decreases seen in 82% (23/28)
- Responses observed across range of gem doses
  - Arm 1: Gem doses ≥ 400 mg/m² (9/15; 60% MRR)
  - Arm 2: Gem doses ≤ 200 mg/m² (7/13; 54% MRR)

[a]1 month = 4 weeks. [b]CBR evaluable population: ≥1 post-baseline scan, 16 w follow up. [c]Methylation-based TF determined using Guardant Infinity™

Table 3. Patients with responses to cam + gem combination

Tumor type	Enrollment gene	Retrospective genomics	Prior lines (N/Parp/gem)	Time on treatment (months)	Best response	Best decrease in TL from baseline
Ovarian	*ATM*	Monoallelic/HRD+	3/Y/N	20+	cPR	-52%
	BRCA1	Monoallelic	1/Y/N	19+	cPR	-31%
	BRCA1	Rearrangement	1/Y/N	12+	uPR[a]	-32%
	gBRCA1	Biallelic	3/Y/N	6	CA-125	No decrease
	gBRCA1	Pending	5/Y/Y	4+	CA-125[b]	-28%
Endometrial	*gPALB2*	Pending	3/N/N	4	cPR	-64%
Breast	*gBRCA1*	Pending	3/Y/N	4	uPR[c]	-31%

Data cut-off date for Table 3 is 21SEP23. 1 mo = 4 w. [a]Response observed after 31JUL23. [b]Enrolled at proposed RP2D, evaluation ongoing. [c]PR unconfirmed due to progression of brain lesions though sustained reduction in target lesions (TLs).

- RECIST and CA-125 responses observed primarily in patients with gynecologic cancers
- Late response observed; efficacy evaluation of patients at proposed RP2D ongoing

Results

Figure 5. Prolonged tumor response in patient with HR deficient ovarian cancer

Response sustained following multiple gemcitabine dose reductions

59-year-old patient with **HGSOC and *ATM* mutation (monoallelic)**

- 3 lines of prior therapy: platinum and PARPi resistant

Duration of Treatment: 20+ months

- Starting dose of 80 mg cam (3/4),1000 mg/m² gem, 21d cycle; continued tumor decrease after series of reductions: 200 mg/m² gem since month 6
- Upon CA-125 increase, cam increased from 50 mg to 80 mg, after which target lesions returned to nadir, CA-125 decreased

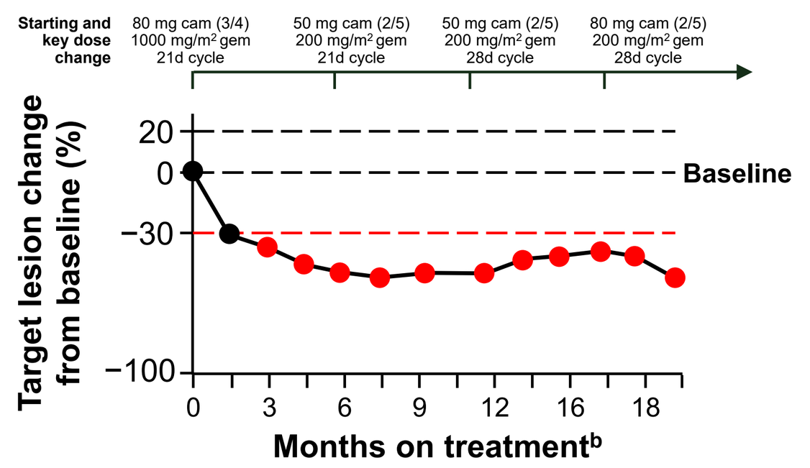
ctDNA (methylation-based) TF[a]

- ctDNA TF signal low and goes to undetectable at month 8 after gem reduction to 200 mg/m²

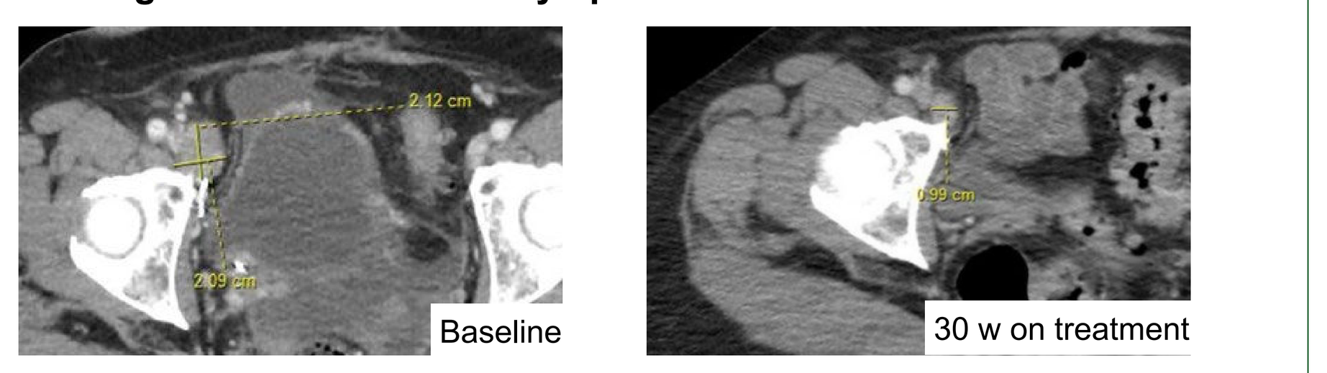
Exploratory whole genome sequencing

- HRD+ (*BRCA1*-Type)[4]
- Mutational signatures; SBS3 (43%) and SBS8 (29%), associated with HR deficiency

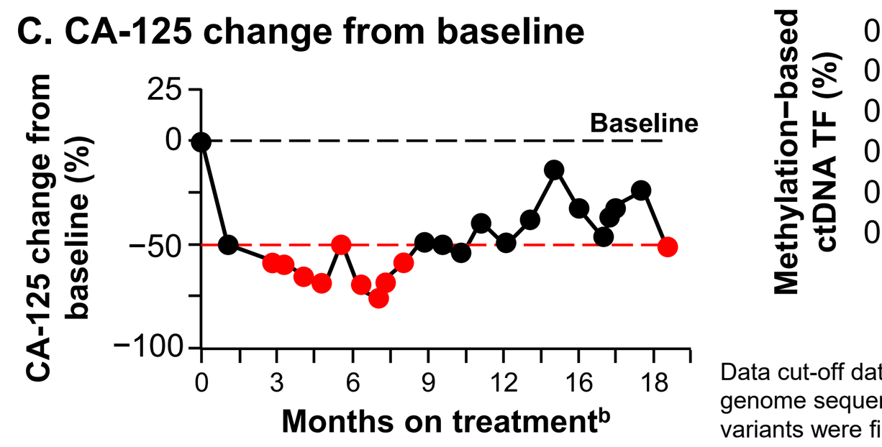
A. Target lesion change from baseline



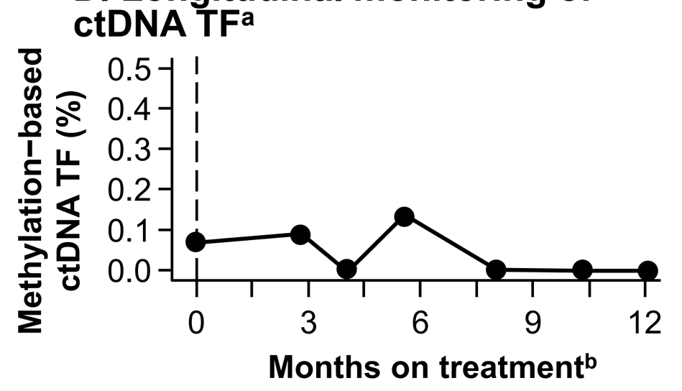
B. Target lesion: abdominal lymph node



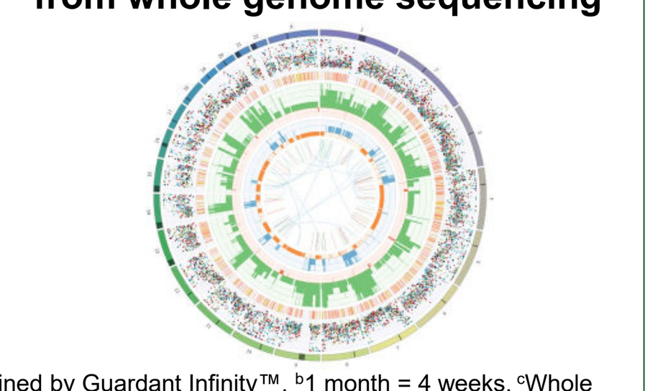
C. CA-125 change from baseline



D. Longitudinal monitoring of ctDNA TF[a]



E. Mutational signature analysis from whole genome sequencing[c]



Data cut-off date for Fig. 5 is 21SEP23. [a]Methylation-based TF determined by Guardant Infinity™. [b]1 month = 4 weeks. [c]Whole genome sequencing was performed on FFPE tumor tissue. Short nucleotide variants, insertions and deletions, and structural variants were filtered through custom pipelines. Mutational signatures were calculated using CHORD and SigProfileExtractor.

Conclusions

- The synergy of low doses of cam + gem, demonstrated in preclinical studies, was confirmed in this trial.
- Combination therapy required comprehensive dose and schedule evaluation; antitumor activity was observed at low doses of gem.
- Transient Grade 3+ neutropenia, the main drug-related toxicity, recovered promptly without complications; the 1w on/1w off schedule enabled neutrophil recovery during the scheduled week off and allowed for planned treatment.
- No drug-drug interaction was observed.
- Antitumor activity of low dose cam (half the RP2D) + low dose gem (≤ 400 mg/m²) was observed in this heavily pretreated population, primarily in patients with gynecological cancers (including patients with prior gem).
- Proposed RP2D: 80 mg cam (D1-3, 15-17) + 400 mg/m² gem (D1, 15), 28d cycle
- Efficacy assessment is ongoing at proposed RP2D in patients with ovarian cancer.

References

1. Yap TA, et al. *Nat Med*. 2023 Jun;29(6):1400-1411. 2. Chen S, et al. *Cancer Res.* 2023 Apr;83(7_Supplement):3123 3. Rosen E, et al. See ANE poster A123. 4. Nguyen L, et al. *Nat Commun*. 2020 Nov 4;11(1):5584.

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Abbreviations

2/5, 2 days on, 5 days off; 3/4, 3 days on, 4 days off; AE, adverse event; ATRi, ataxia telangiectasia and Rad3-related inhibitor; CA-125, cancer antigen 125; cam, camonsertib; CBR, clinical benefit rate; cPR, confirmed partial response; ctDNA, circulating tumor DNA; CTG, CellTiter-Glo®; d, day; DDR, DNA damage response; dFdC, difluorodeoxycytidine; DL, dose level; dNTP, deoxynucleotide triphosphate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FFPE, formalin fixed paraffin embedded; GCIG, Gynecological Cancer Integroup; gem, gemcitabine; gr, grade; HGSOC, high-grade serous ovarian cancer; IQR, interquartile range; mo = month; mPFS, mean progression free survival; MR, molecular response; MRR, MR rate; MTD, maximum tolerated dose; mVAFR, best percent change in methylation-based TF; PARPi, poly (ADP-ribose) polymerase inhibitor; PCWG, Prostate Cancer Working Group; PD, progressive disease; PO, orally; PR, partial response; PSA, prostate-specific antigen; QD, once daily; QW, once weekly; RECIST, Response Evaluation Criteria in Solid Tumors; rNMP, ribonucleotide; TF, tumor fraction; TL, target lesion; TRAE, treatment-related adverse event; uPR, unconfirmed partial response; w, week.

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