Poster
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Detection and characterization of DDR reversion alterations in baseline tissue and plasma samples from patients enrolled in the TRESR and ATTACC Phase I clinical trials

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Background

- Reversions, secondary mutations reverting the gene back into frame and restoring gene function, in DNA damage repair (DDR) and homologous recombination (HR) genes are an established mechanism of acquired resistance in patients treated with poly(ADP-ribose) polymerase inhibitors (PARPi) and platinum-based therapies
- Camonsertib is a highly selective ataxia telangiectasia and Rad3-related inhibitor (ATRi) that is synthetic lethal (SL) with genomic alterations affecting DNA damage response [1,2]
- Despite increasing clinical development of novel SL agents in this population, baseline detection and characterization of reversions is not widely reported; thus, interpreting the efficacy data of these agents may be confounded by reversion mutations
- Here we report the baseline DDR reversions in the Phase I trials TRESR (NCT04497116) and ATTACC (NCT04972110), which evaluated safety and efficacy of the ATRi camonsertib as monotherapy or in combination with a PARPi or gemcitabine

Key Translational Questions

Patients treated with 2nd generation SL agents in phase I clinical trials have likely been treated with prior PARPi and/or platinum therapies and thus may have pre-existing resistance

- What type and frequency of reversion alterations exist in this population?
- Which biospecimen (tissue vs. plasma) identifies the most reversions?
- Can reversions be comprehensively identified by pre-existing local genomic test results or is contemporaneous central sequencing required?
- Will SL agents in clinical development be as effective in tumors with pre-existing reversions?

Camonsertib trial clinical cohorts and key learnings

Phase 1/2a TRESR (NCT04497116)[2]: Module 1 - camonsertib monotherapy

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

Phase 1b/2 ATTACC (NCT04972110)[3]: camonsertib + niraparib or olaparib

Phase 1/2a TRESR (NCT04497116)[4]: Module 4 – camonsertib + gemcitabine

Main eligibility criteria:

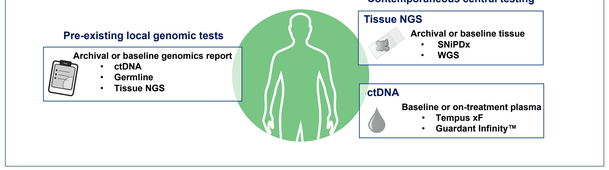
- Patients ≥ 18 years of age with advanced solid tumors
- Tumors with deleterious somatic or germline alterations[b]
  - *ATM, ATRIP, BRCA1/2[c], CDK12[c], CHTF8, FZR1, MRE11, NBN, PALB2[c], RAD51B/C/D[c], RNASEH2A/B[c], RAD17, REV3L, RAD50, SETD2*
- ECOG PS 0 or 1
- Prior PARPi treatment permitted
-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

[a]Talazoparib was provided by Pfizer Inc. [b]Centrally reviewed by the Precision Oncology Decision Support group (MD Anderson Cancer Center). [c]Subset of TRESR genes used for ATTACC enrollment.

- Camonsertib monotherapy is well-tolerated and mechanism-based anemia is well controlled [1]
- Durable clinical benefit in several tumor types and genomic alterations, including the high-unmet-need group of PARPi-exposed recurrent ovarian cancer [2]
- Low-dose regimens of camonsertib and different PARPi combinations were safe with transient hematological events; no prophylactic growth factors required [3]
- Anticancer activity observed in patients with platinum- and PARPi-resistant tumors [2,3]
- Camonsertib and gemcitabine combination recommended phase 2 dose identified, with antitumor activity observed primarily in patients with gynecological cancers [4]

Methods

Figure 1. Genomic data collection methods for identifying reversions



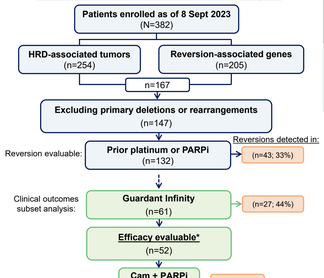
Results

Figure 2. One hundred thirty-two patients met the criteria for reversion evaluation

Criteria for reversion evaluation

- HRD-associated tumor type (breast, ovarian, pancreatic, prostate)
- Pathogenic alteration in a gene known to revert (*BRCA1, BRCA2, PALB2, RAD51C, RAD51D*)
- Revertible alteration (excluding deletions and rearrangements)
- Prior treatment with platinum and/or PARPi

Flow chart of patients used in this analysis



*Clinical outcomes were analyzed in the cam + PARPi patient population alone due to insufficient numbers in the Guardant Infinity profiled cam + gem (n=15) or cam monotherapy (n=0) groups.

Table 1. Descriptive characteristics of the patient population used in the analysis*

Parameter		TRESR (N=82)	ATTACC (N=50)	Total (N=132)
Monotherapy	Camonsertib	35	-	35
Combination therapy (camonsertib +)	Gemcitabine	31	–	31
	PARPi: Talazoparib	16	–	66
	PARPi: Olaparib	–	27	
	PARPi: Niraparib	–	23	
Tumor type	Ovarian	45	19	64
	Breast	17	14	31
	Pancreatic	14	6	20
	Prostate	6	11	17
Genotype	*BRCA1*	46	16	62
	BRCA2	28	26	54
	PALB2	4	7	11
	RAD51C	4	0	4
	RAD51D	0	1	1

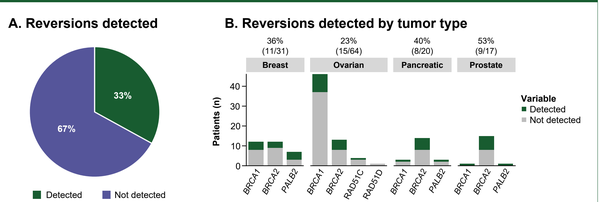
* Includes patients from both studies with HRD-associated tumor types, pathogenic alterations known to revert, and prior platinum and/or PARPi.

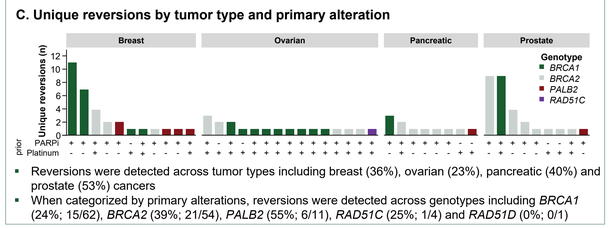
Table 2. Enrollment genotypes by tumor type*, n

Gene	Breast	Ovarian	Pancreatic	Prostate
BRCA1	12	46	3	1
BRCA2	12	13	14	15
PALB2	7	0	3	1
RAD51C	0	4	0	0
RAD51D	0	1	0	0

* Includes patients from both studies with HRD-associated tumor types, pathogenic alterations known to revert, and prior platinum and/or PARPi.

Figure 3. Ninety-one unique reversions detected in 33% (43/132) cases

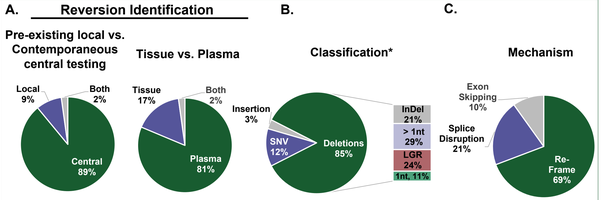




- Reversions were detected across tumor types including breast (36%), ovarian (23%), pancreatic (40%) and prostate (53%) cancers
- When categorized by primary alterations, reversions were detected across genotypes including *BRCA1* (24%; 15/62), *BRCA2* (39%; 21/54), *PALB2* (55%; 6/11), *RAD51C* (25%; 1/4) and *RAD51D* (0%; 0/1)

Results

Figure 4. Classification of reversion alterations



Of the 91 unique reversions detected the majority were:

- identified by contemporaneous central testing alone (89%; n=81) with 81% detected using plasma samples (n=74)
- classified as deletions (85%), with short insertions (3%; n=3) and SNVs (12%; n=11) also detected
- mechanistically near-complete restoration of the coding sequence (69%; n=63) with other larger-scale reversions affecting whole exons by deletion (10%; n=9) or splice-site disruption (21%; n=19)

*Reversions were classified into three categories: 1) insertion, 2) SNV, and 3) deletions (= 1 nt, > 1 nt to < 50 nt, InDel, and LGR [≥ 50 nt]).

Figure 5. Unexpected reversions identified in patients with *BRCA*1/2 deletions and *ATM*/*NBN* mutations

Two patients enrolled based on pathogenic mutations that were later determined to be reversions of unreported primary alterations

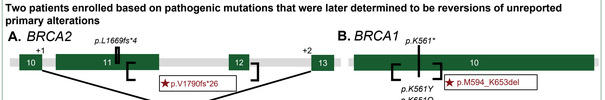


Table 3. Descriptive characteristics of patients with reversions of unreported primary alterations

Tumor type	Gene	Prior platinum/ PARPi	Enrollment Test	Primary (Not reported in enrollment test) cDNA	Primary (Not reported in enrollment test) AA	Reversions Secondary cDNA	Reversions Combined AA	Reversions Mechanism
Ovarian	*BRCA2*	Y/Y	Oncopanel (Tissue)	c.5007_5053del	p.L1669fs*4	**c.5367_6937+943del (enrollment alteration)**	**★ p.V1790fs*26 (enrollment alteration)**	Splice Disruption
Ovarian	*BRCA1*	Y/Y	Tempus xT (Tissue)	c.1951A>T	p.K651*	**c.1751_1960del (enrollment alteration)**	**★ p.M594_K653del (enrollment alteration)**	Re-Frame
						c.1951_1953delinsTAC	p.K651Y	Re-Frame
						c.1951A>C	p.K651Q	Re-Frame
						c.1951A>G	p.K651E	Re-Frame

Identification of three patients with novel reversions detected in *ATM* and *NBN* genes

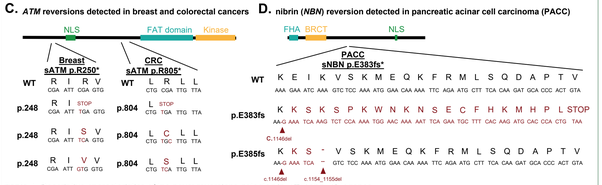
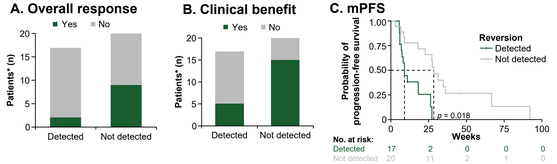


Table 4. Descriptive characteristics of the novel reversions detected in *ATM* and *NBN* genes

Tumor type	Gene	Prior lines	Prior platinum or PARPi	Primary cDNA	Primary AA	Reversion Secondary cDNA	Reversion Combined AA
Breast	*ATM*	8	Carboplatin	c.748C>T	p.R250*	c.749G>C	p.R250S
						c.748_749delCGinsGT	p.R250V
CRC	*ATM*	4	2 lines of FOLFOX	c.2413C>T	p.R805*	c.2415A>C	p.R805C
						c.2414G>C	p.R805S
PACC	*NBN*	2	Oxaliplatin	c.1146del	p.E383fs*21	c.1154_1155del	p.E383_K385delinsKS

Results

Figure 6. Clinical outcomes in patients treated with camonsertib/PARPi combination and uniformly tested with Guardant Infinity



- The overall response seen in patients without reversions (45%; 9/20) was significantly higher compared to those with reversions (12%; 2/17; $p = 0.037$, fisher's exact test)
- Significantly higher clinical benefit rate seen in patients without reversions (75%; 15/20) vs. those with reversion (29%; 5/17; $p = 0.009$, fisher's exact test)
- Patients without reversions showed a significantly longer median progression-free survival (mPFS; 28 weeks) vs. those with reversions (9 weeks; $p = 0.018$, log-rank test)

*In patients profiled by Guardant Infinity (n=61) and restricted to efficacy evaluable patients treated with camonsertib + PARPi (n=37). Guardant Infinity is a genomic and epigenomic liquid biopsy NGS platform. Overall response rate was defined as the proportion of patients with best response or complete response or partial response according to RECIST 1.1, confirmed CA-125 response based on GCIG criteria or PSA response based on PCWG3. Clinical benefit response was defined as the proportion of patients with a response by RECIST 1.1 or confirmed CA-125 by GCIG criteria or PSA response based on PCWG3 or a treatment duration of at least 16 weeks without prior evidence of progression.

Conclusions

- These data highlight the genomic complexity and current diagnostic challenges to detect and characterize baseline reversion alterations in heavily pre-treated, DDR-selected patients
- Patients whose tumors harbor DDR/HR alterations and enrolled in early phase clinical studies often have pre-exiting resistance to PARPi or platinum and may not respond as well to next-generation DDR agents
- Reversions may occur in genes outside of the canonical HR genes or be misdiagnosed as pathogenic alterations
- Contemporaneous central ctDNA analysis with a panel that includes intron coverage and can call large genomic events is critical for more sensitive reversion detection
- Interrogation of ctDNA or tumor biopsies with better diagnostic tools that include broad intron coverage and enhanced reversion calling will aid in interpretation of efficacy data for next-generation DDR agents and guide more targeted patient selection

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Abbreviations

ANC, absolute neutrophil count; ATRi, ataxia telangiectasia and Rad3-related inhibitor; cam, camonsertib; CRC, colorectal cancer; cDNA, complimentary DNA; cfDNA, cell-free DNA; ctDNA: circulating tumor DNA; CRC, colorectal cancer; DDR, DNA damage response; del, deletion; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FAT, focal adhesion targeting; FHA, forkhead-associated; FOLFOX, folinic acid, fluorouracil and oxaliplatin; GCIG, gynecologic cancer intergroup; gem, gemcitabine; HR, homologous recombination; HRD, HR deficient; InDel, insertion/deletion; ins, insertion; LGR, large genomic rearrangements; mPFS, median progression free survival; NGS, next generation sequencing; NLS, nuclear localization sequence; nt, nucleotide; PACC, pancreatic acinar cell carcinoma; PARPi, Poly (ADP-ribose) polymerase inhibitor; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PK, pharmacokinetics; PR: partial response; PSA, prostate specific antigen; pts, patients; RECIST, response evaluation criteria in solid tumors; SL, synthetic lethal; SNiPDx, SyNthetic lethal Interactions for Precision Diagnostics; SNV, single nucleotide variant; WGS, whole genome sequencing; WT, wildtype; Y, yes.

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