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Circulating tumor DNA (ctDNA) genomic and epigenomic profiling (Guardant Infinity™) for diagnosis of DNA damage repair (DDR) loss-of-function (LoF) and response monitoring in the TRESR and ATTACC trials

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Background

Camonsertib trial background and key learnings

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

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

Phase 1/2a TRESR (NCT04497116)[3]: 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.

TRESR & ATTACC studies: Key clinical findings

- 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[1]
- Low-dose regimens of camonsertib and different PARPi combinations were safe with transient hematological events; no prophylactic growth factors required[2]
- Anticancer activity observed in patients with platinum- and PARPi-resistant tumors[1,2]
- A safe, tolerable, and efficacious dose and schedule of camonsertib and gemcitabine was identified[3]

Rationale for the study

Detection of biomarkers for synthetic lethal drug targets present a unique challenge in precision oncology

- Non-invasive liquid biopsies (ctDNA panels) provide real-time data but are limited in coverage and sensitivity for DDR LoF identification in tumors, especially for deletions and structural variants
- Reversions are a validated resistance mechanism for PARPi and likely important for understanding response to other synthetic lethal therapies, but are challenging to identify due to the complexity of genomic changes
- ctDNA molecular response (MR) correlates with validated outcomes and may help identify active treatment combinations, although low tumor fraction (TF) hinder accurate assessment

Methods

Study design

Sample testing using Guardant Infinity:

- Genomic variant detection and methylation-based TF % from plasma
- % ctDNA change assessment by genomic variant- and methylation-based methods
- Paired PBMC analysis for confirmation of CH

Baseline genomic testing:

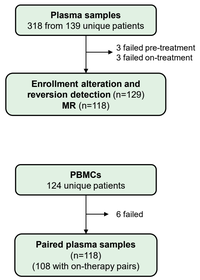
- Local genomic testing for enrollment
- Retrospective testing by SNiPDx for allele-specific copy number

Key translational questions:

- Can second-generation ctDNA assays (Guardant Infinity) better diagnose complex DDR LoF alterations and improve detection of reversions?
- Is methylation-based ctDNA monitoring a potential solution to address the sensitivity and specificity challenges linked with tissue-free genomic variant-based methods?

Methods

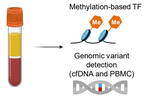
Additional coverage and optimized bioinformatics allow detection of complex LoF alterations typically missed in liquid biopsy



Parameter			TRESR (N=74)	ATTACC (N=65)	Total (N=139)
Combo agent	PARPi	Gemcitabine	38	–	**38**
		Talazoparib	36	–	**101**
		Olaparib	–	37	
		Niraparib	–	28	
Tumor type		Ovarian	20	17	**37**
		Breast	7	14	**21**
		Pancreatic	12	8	**20**
		Prostate	9	8	**17**
		Other[a]	26	18	**44**
Genotype		*BRCA2*	24	22	**46**
		ATM	19	17	**36**
		BRCA1	18	15	**33**
		PALB2	3	5	**8**
		Other[b]	10	6	**16**
Enrollment test type		Tumor tissue	42	40	**82**
		Germline	21	19	**40**
		Plasma	8	5	**13**
		IHC/unknown	3	1	**4**

[a]Other tumor types include (n=[TRESR/ATTACC]): appendix (0/1), bile duct (1/3), cervical (1/0), colorectal (4/7), endometrial (1/1), granular cell tumor, left chest mass (1/0), GI (3/1), head and neck (1/0), kidney (1/0), liver (2/0), mesothelioma (1/0), non-small cell lung (5/1), unspecified (0/1), sarcoma (5/3).
[b]Other genotypes include (n=[TRESR/ATTACC]): *CDK12* (3/2), *IDH1* (0/1), *RAD50* (1/0), *RAD51B* (2/1), *RAD51D* (0/1), *RNASEH2* (2/1), and *SETD2* (2/0).

Liquid biopsy (ctDNA) testing strategy



Assessing ctDNA MR by three methods:

1. **Guardant360 Response™ (74-gene)[a]:** ratio of somatic mVAFs between T0 and T1
2. **Guardant360 Response-CH (74-gene)[b]:** ratio of somatic mVAFs between T0 and T1, filtered for confirmed CH in PBMC samples
3. **Methylation-based ctDNA MR[c]:** methylation-based ctDNA MR ratio of methylation level in DMRs between T0 and T1

[a]Guardant360 Response: based on the genomic mVAF ratio of T1 to T0, limited to the subset of 74 genes covered by Guardant Infinity and using the same algorithm as the Guardant360 Response clinical test.
[b]Guardant360 Response-CH: Guardant360 Response, excluding genomic variants confirmed as CH in PBMC samples.
[c]Methylation-based MR: % ctDNA change measured by the ratio of the methylation levels in patient-specific DMRs between T0 and T1. DMRs are regions determined to be methylated in cancer patients and not in cancer-free donors.[4,5]

Guardant Infinity was used for genomic-variant detection and methylation-based TF assessment in plasma samples. For the purposes of this study, Guardant Infinity was also used to test paired PBMC samples for confirmation of genomic variants as CH in a subset of the patients with plasma sequencing. % ctDNA changes were assessed by genomic variant- and methylation-based methods, between T0 (measured with 3w of treatment initiation) and T1 (measured 3–12w on-treatment) for all patients and at additional longitudinal timepoints for patients of interest (i.e., clinical responders).

Results

Additional coverage and optimized bioinformatics allow detection of complex LoF alterations typically missed in liquid biopsy

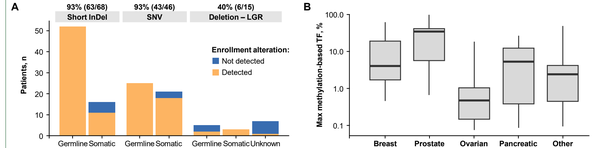


Figure 3: Detection of enrollment alterations and tumor-type-specific TF by Guardant Infinity. (**A**) Patients enrolled based on presence of a genomic alteration in pre-existing local genomic tests (tissue- and plasma-based). Alterations were grouped into 1) short InDels (insertions, deletions, and InDels < 50 nt), 2) SNVs, and 3) Deletions – LGR (duplications, rearrangements, and deletions ≥ 50 nt). Germline status was defined based on interpretation of NGS from tumor, blood, and/or plasma where available. Patients enrolled by IHC (n=4) or with local alterations confirmed negative by central tissue (n=6) were not included in the confirmatory analysis. (**B**) The maximum methylation-based TF from one or more successful ctDNA tests per patient was plotted by tumor type.

- **129 patients with evaluable enrollment alterations and at least one successful ctDNA test**
  - 87% (112/129) of enrollment alterations were detected in at least one timepoint
  - 63% (5/8) of unconfirmed somatic alterations were due to low TF

Results

Reversion alterations are detected in 41% (26/64) of patients with HRD-associated tumors exposed to PARPi or platinum treatment

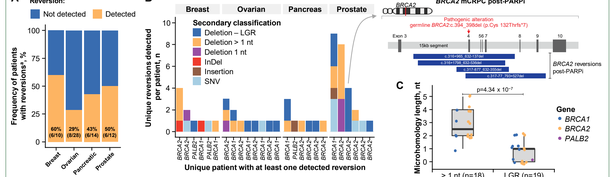
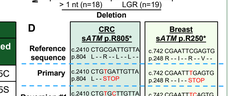


Table 2. Detection of novel ATM reversions in two patients with somatic biallelic LoF

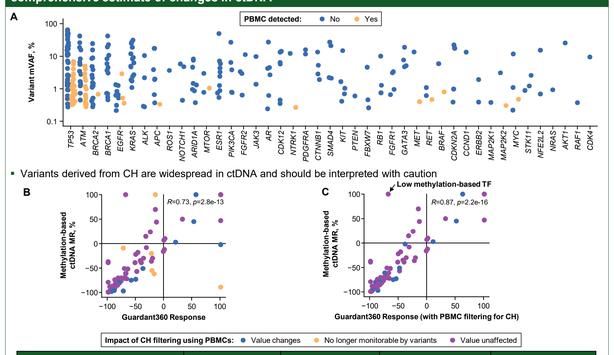
Tumor type	Prior lines of treatment	Prior platinum or PARPi	Primary		Reversions	
			cDNA	AA	Secondary cDNA	Reverted AA
CRC	4	2 lines of FOLFOX	c.2413C>T	p.R805*	c.2415A>C	p.R805C
					c.2414G>C	p.R805S
Breast	8	Carboplatin	c.748C>T	p.R250*	c.749G>C	p.R250S
					c.748_749delCGinsGT	p.R250V



*Methylation-based ctDNA tumor fraction was significantly lower in non-reverted patients and overall lower in ovarian tumors.

Figure 4. (**A**) **and** (**B**) **Reversions were evaluated in patients with HRD-associated tumors** (breast, ovary, pancreas, prostate) with *BRCA1*, *BRCA2,* or *PALB2* mutations who were previously treated with platinum or PARPi. Reversions were classified into five categories: 1) missense, 2) insertion, 3) deletion = 1 nt, 4) deletions > 1 nt and < 50 nt, 5) deletions (≥ 50 nt [LGR]). (**C**) Micrhomology evaluated in deletions > 1 nt and determined by comparing either side of the internal deletion sequence to the opposite flanking sequence. (**D**) Two additional patients with CRC (n=1) and breast cancer (n=1) both previously treated with platinum-containing treatments had novel *ATM* reversions.

Methylation-based ctDNA MR circumvents noise from CH providing an accurate and more comprehensive estimate of changes in ctDNA



- Variants derived from CH are widespread in ctDNA and should be interpreted with caution

Analysis	Sample fail, n	ctDNA low, n	Evaluable, n (rate)	≥ 50% decline, n (rate)
Methylation-based ctDNA MR	11	6	91 (84%)	49 (54%)
Guardant360 Response[a]	9	21	78 (72%)	45 (58%)
Guardant360 Response-CH	9	30	69 (64%)	43 (62%)

Figure 5. (**A**) mVAF (across timepoints) for CH-associated (*TP53* and *ATM*) and non-CH-associated genes in patients with matched PBMC sequencing. Variants that were not detected in matched PBMC sequencing (confirmed somatic) are highlighted in blue, while variants that were detected in PBMCs are in yellow. Correlation analysis between methylation-based MR and (**B**) Guardant360 Response or (**C**) Guardant360 Response-CH for the PBMC-matched subset (n=108). One outlier in the Guardant360 Response-CH vs. methylation-based ctDNA MR was undetectable at baseline and just above the methylation-based TF LoQ at the on-treatment time point. [a]Guardant360 Response: using the same algorithm as the Guardant360 Response clinical test.

Results

Methylation-based ctDNA MR shows the greatest mean PFS separation among efficacy-evaluable patients

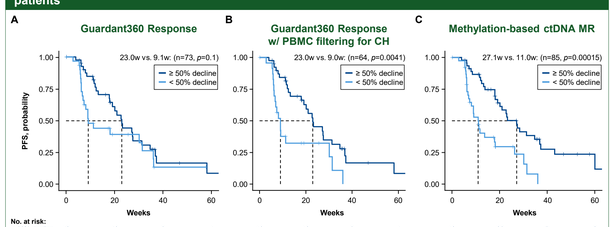


Figure 6: Kaplan-Meier estimate of PFS in those with a ≥ 50% decline vs. without using variant- and methylation-based approaches for ctDNA monitoring. A cutoff of 50% decline from BL within 3–12 weeks on-treatment with either camonsertib + PARPi or camonsertib + gemcitabine was used.

Conclusions

- Broad panel coverage allowed high sensitivity for LoF SNVs and InDels detection in DDR genes, and the ability to detect deletions and duplications
- Guardant Infinity showed a high reversion detection rate (> 40%) in HRD-associated tumors and genotypes with prior PARPi or platinum treatments
  - Reversions derived from LGR were detected in multiple tumor and genotypes, and may be missed by other panels
  - Microhomology was observed in short deletions (> 1 nt and < 50 nt), but not in larger deletions (≥ 50 nt)
  - Novel reversions detection in two patients with somatic biallelic *ATM* alterations
- Methylation-based ctDNA MR overcomes sensitivity and CH challenges and allows accurate monitoring in more patients than genomic variant-based MR assessment
  - Removing CH-variants, especially in *TP53* and *ATM*, decreased the number of patients evaluable by Guardant360 Response
  - A strong correlation was observed between genomic variant-based Guardant360 Response and methylation-based MR after filtering the former for CH variants confirmed in PBMCs
  - Methylation-based ctDNA MR showed the strongest relationship with PFS and increased the number of evaluable patients
    - CH filtering of Guardant360 Response scores showed a significant improvement in PFS association but decreased the number of evaluable patients

References

1. Yap TA, et al. *Nat Med*. 2023 Jun;29(6):1400–1411. 2. Yap TA, et al. In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; Cancer Res 2022;82(12_Suppl):Abstract nr CT030. 3. Rosen E, et al. Poster B045 at: ANE; 2023; Boston, MA. 4. Chen et al. Cancer Res (2023) 83 (7_Supplement): 3123. 5. Jiang (Chuang) Cancer Res (2023) 83 (7_Supplement): 6601.

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Abbreviations

AA, amino acid; ANC, absolute neutrophil count; CH, clonal hematopoiesis; cDNA, complementary DNA; ctDNA, cell-free DNA; CRC, colorectal cancer; ctDNA, circulating tumor DNA; del, deletion; DDR, DNA damage response; DMR, differentially methylated regions; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HRD, homologous recombination deficiency; IHC, immunohistochemistry; InDel, insertion or deletion; ins, insertion; LGR, large genomic rearrangement; LoF, loss of function; LOQ, limit of quantification; max, maximum; mCRPC, metastatic castration-resistant prostate cancer; MR, molecular response; mVAF, mean variant allele frequency; NGS, next-generation sequencing; nt, nucleotide; PARPi, poly ADP-ribose polymerase inhibitor; PBMC, peripheral blood mononuclear cell; PFS, progression free survival; SNiPDx, SyNthetic Lethal Interactions for Precision Diagnostics panel; SNV, short nucleotide variants; TD, timepoint3; T1, timepoint 1; TF, tumor fraction; w, week