Poster
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Exceptional response to the ataxia telangiectasia and Rad3-related inhibitor (ATRi), camonsertib, in a patient with alternative lengthening of telomeres (ALT)-positive metastatic melanoma

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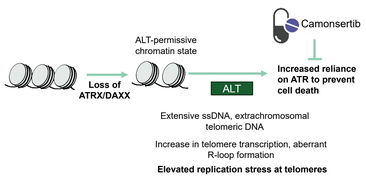
Background

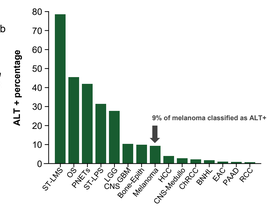
- A hallmark of cancer tumorigenesis is the maintenance of telomere length which canonically occurs through the reactivation of telomerase
- Alternative lengthening of telomeres (ALT) is a minor telomere maintenance mechanism that uses homologous recombination (HR) to maintain telomere length and is associated with replication stress and defects in genome maintenance
- In preclinical models, ALT positivity (ALT+) has been shown to sensitize tumor cells to ataxia telangiectasia and Rad3-related inhibitors (ATRi) [1,2]
- Camonsertib is a highly selective ATRi that is synthetically lethal with genomic alterations affecting DNA damage response [3,4]
- Here we describe a confirmed clinical and molecular response to the ATRi, camonsertib, in a patient with ALT+ metastatic melanoma. To our knowledge, this is the first report of clinical experience with ATRi in ALT+ tumors

Figure 1.

A. ALT is intrinsically linked to DNA repair and replication stress[a]



B. ALT prevalence in PCAWG data using machine learning classifier[5]



[a]*Adapted from Gao and Pickett, 2022, Nat. Rev. Cancer; Cesare and Reddel, 2012, Nat. Rev. Genetics.* [b]Other tumor types investigated but ALT+ percentage calculated as zero include: acute myeloid leukemia, adenocarcinomas (biliary, breast, cervical, colorectal, lung, ovarian, prostate, stomach, thyroid, and uterine), benign bone tumors, bladder transitional cell carcinoma, breast lobular carcinoma, chronic lymphocytic leukemia, ductal carcinoma in situ, pilocytic astrocytoma, squamous cell cancer (cervical, lung, and head).

Purpose

- **To understand the long and deep response to camonsertib treatment in a metastatic melanoma patient with monoallelic *BRCA2* loss of function.**

Methods

Inclusion criteria:

- Patients ≥ 18y with advanced solid tumors
- Tumors with deleterious somatic or germline gene alterations
  - *ATM, ATDRIP, BRCA1/2, CDK12, CHTF8, FZR1, MRE11, NBN, PALB2, RAD51B/C/D, RNASEH2A/B, RAD17, REV3L, RAD50, SETD2*
- ECOG PS 0 or 1
- Hemoglobin ≥ 9.5 g/dL
- Platelets ≥ 140,000/µL
- Absolute neutrophil count ≥ 1,700/µL

TRESR Overview

Camonsertib monotherapy[1]

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

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]

- The case-study patient was enrolled in the monotherapy arm of TRESR (NCT04497116), a modular, phase 1/2a, first-in-human, multicenter, open-label, non-randomized, dose-escalation, dose-expansion study of the ATRi camonsertib, administered orally as a single agent, or in combination with talazoparib or gemcitabine in patients with advanced solid tumors
- Primary and metastatic formalin-fixed paraffin-embedded (FFPE) samples were retrospectively evaluated by next-generation sequencing (NGS) using Synthetic Lethal Interactions for Precision Diagnostics (SNiPDx™), a novel, targeted sequencing panel consisting of 26 DDR genes, capable of distinguishing monoallelic and biallelic LoF alterations [9]
- Whole-genome sequencing (WGS) was retrospectively performed on DNA derived from primary and metastatic FFPE samples
- Short nucleotide variants, insertions and deletions, copy number alterations, and structural variants were filtered through custom pipelines. Mutational signatures were calculated using CHORD[10] and SigProfilerExtractor

Results

Case Description

- A 63-year-old male diagnosed with stage IV (cTX, cNX, pM1c[1]) metastatic melanoma
- 5 prior lines of therapy including PARPi
- Genomic profiling of a liver biopsy collected at the time of progression identified somatic alterations in *TP53* (p.S127F, p.R65fs), *NF1* (p.K1263*), *BRCA2* (p.R2482C) and *ATRX* (p.R418*), a germline *CHEK2* mutation (p.T376fs), and high tumor mutational burden
- In June 2021, the patient received camonsertib monotherapy at an initial dose of 120 mg QD 3 on/4 off in the phase I TRESR trial (NCT04497116)
- The patient had an initial RECIST PR (-36%) at 3 months with ctDNA clearance
- The target lesions continued to decrease with a best decline of -74% after about 1 year of treatment
- The cancer progressed at 20 months (+105% from nadir, -47% from baseline) though due to ongoing clinical benefit treatment was continued for a total duration of 22 months

Figure 2. Therapeutic history and case timeline

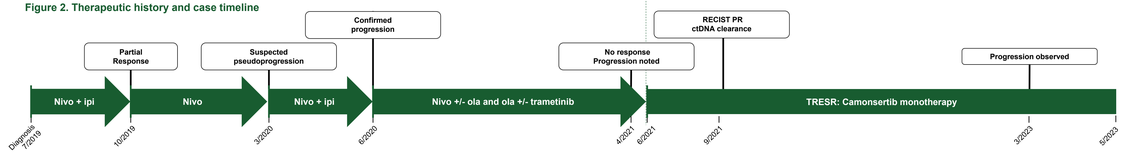
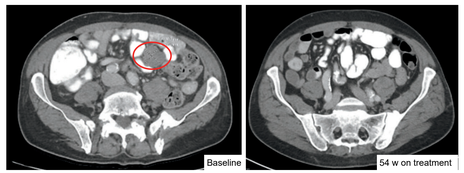
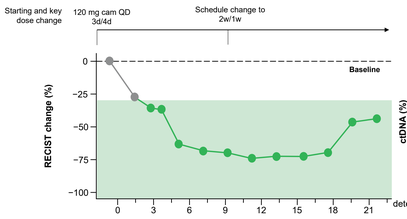


Figure 3. Tumor and ctDNA response to camonsertib

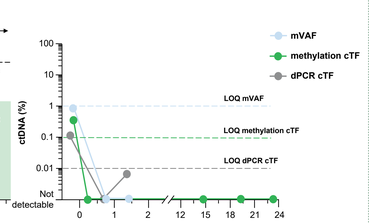
A. Target lesion: Peritoneal mass



B. Target lesion change from baseline



C. ctDNA clearance[b]



- The target lesions continued to decrease with a best decline of -74% after about 1 year of treatment
- ctDNA clearance was observed by 3 weeks and remained around or below the limit of detection throughout treatment using mVAF (mean variant allele frequency) as well as methylation- and dPCR-based assays

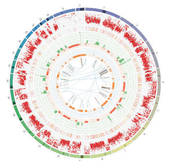
[a]1 month = 30.4 days. [b]ctDNA assessments were determined by a tumor uninformed variant-based approach using Tempus xF, a genomic-variant detection and methylation-based TF assessment using Guardant Infinity™, and TracerDx a tumor-informed dPCR-based approach from Tracer Biotechnologies.

Figure 4. Characterization of genomic structure and signatures

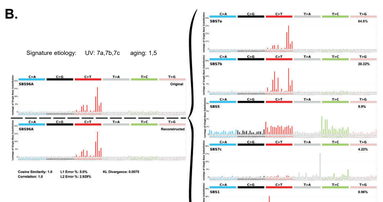
Sample	Genomic/Functional Assay	*BRCA2*	*ATRX*	*TP53*	Other Alterations	Genomic Signatures
Liver Metastasis 02/27/2020	Tempus xT (DNA/RNA)	p.R2842C (24.2%)	p.R418* (53.5%)	p.S127F (25.9%), p.R65fs (9.6%)	*NF1, gCHEK2*	TMB = 43.7 mut/mb, MSS
Retroperitoneum Metastasis 06/02/2021	SNiPDx™	p.R2842C (23.5%) monoallelic	Not on Panel	p.S127F (25.7%) monoallelic	-	-
	WGS	p.R2842C (28.6%) monoallelic	p.R418* (40.9%) biallelic	p.S127F (24.6%) monoallelic	*NF1, gCHEK2* (monoallelic), *GRIN2A, KMT2B*	TMB = 98.29 mut/mb, MSS, ALT+, UV-Signature, HRD-
Plasma (baseline)	Tempus xF (ctDNA)	p.R2842C (0.5%)	Not on Panel	p.S127F (0.5%)	*NF1*	MSS
	Guardant Infinity™	p.R2842C (0.42%)	p.R418* (0.87%)	p.S127F (0.35%)	*NF1*	bTMB = 86.47 mut/mb, MSS

WGS was performed on FFPE tumor tissue. Short nucleotide variants, insertions and deletions, copy number alterations, and structural variants were filtered through custom pipelines. Mutational signatures were calculated using CHORD and SigProfilerExtractor.

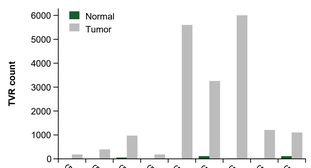
A.



B.



C.



(A) Circos plot derived from WGS of the metastasis. **(B)** Mutational signature decomposition plots of original (left) and 5 mutational signature plots (right). Using machine learning model TelomereHunter software previously published and trained using PCAWG data the **(C)** telomere variant repeats (TVRs) derived from the WGS data are plotted for normal and tumor tissues.

Conclusions

- Both the *BRCA2* and *gCHEK2* mutations were monoallelic and genomic signature analysis defined the tumor as HR-proficient, consistent with the lack of benefit from ola
- WGS confirmed a biallelic loss of ATRX with a genomic signature consistent with an ALT+ phenotype
- The clinical experience of ATRi therapy in patients with ALT+ tumors is limited but further investigation of ATRi such as camonsertib is warranted in this patient population

References

1. Flynn et al. *Science*. 2015 Jan 16;347(6219):273-7. 2. Zimmermann et al. *Cell Rep*. 2022 Jul 12; 40(2):111081. 3. Roulston et al. *Mol. Canc. Ther*. 2022. 21(2):245-56. 4. Yap et al. *Nature Med*. 2023. Jun; 29(6):1400-11. 5. de Nonneville et al. *Nat Commun*. 2021; 12:1552.

Acknowledgments

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Disclosures

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Abbreviations

2w/1w: 2 weeks on/1 week off; 3d/4d, 3 days on/4days off; ALT, alternative lengthening of telomeres; APB, ALT-associated PML bodies; ATRi, ataxia telangiectasia and Rad3-related inhibitor; BNHL, B-cell non-Hodgkin's lymphoma; CA-125, cancer antigen-125; cam, camonsertib; ChRCC, chromophobe renal cell carcinoma; ctDNA, circulating tumor DNA; cTF, circulating tumor fraction; EAC, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; epith, epithelial; GBM, glioblastoma multiforme; Gynecological Cancer Integroup gem, gemcitabine; HCC, hepatocellular carcinoma; HR, homologous recombination; ipi, ipilimumab; LGG, low-grade gliomas; LMS, leiomyosarcoma; LPS, liposarcoma; mVAF, mean variant allele frequency; nivo, nivolumab; ola, olaparib; OS, osteosarcoma; PAAD, pancreatic adenocarcinoma; PARPi, poly ADP-ribose polymerase inhibitor; PCAWG, pan-cancer analysis of whole genomes; PNETs, pancreatic neuroendocrine tumors; PR, partial response; PSA, prostate-specific antigen; QD, once daily; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SNiPDx, Synthetic Lethal Interactions for Precision Diagnostics; ssDNA, single stranded DNA; ST, soft tissue; TF, tumor fraction; TVR, telomere variant repeats; w, week; WGS, whole genome sequencing; y, years.

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