Poster
B026

# Identification of monoallelic ATM loss-of-function and homologous recombination deficiency (HRD) in high-grade ovarian tumor with prolonged response to camonsertib and low-dose gemcitabine combination therapy


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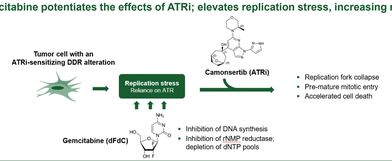
## Background

- Intra-tumor heterogeneity and the prevalent loss-of-function (LoF) mutations within DNA damage repair (DDR) genes constitute salient hallmarks of high-grade ovarian malignancies [1,2]
- Camonsertib is a highly selective ataxia telangiectasia and Rad3-related inhibitor (ATRi) that is synthetically lethal with genomic alterations affecting DNA damage response [3,4]
- Camonsertib monotherapy resulted in durable clinical benefit in several tumor types and genomic alterations [4]
  - In patients with ovarian cancer, overall response (OR) was 25%, clinical benefit rate (CBR) was 75%, and median progression free survival (PFS) was 35 weeks [4]
  - In tumors with *BRCA1/2* mutations previously treated with a poly ADP-ribose polymerase inhibitor (PARPi), CBR was 48% and responses were seen beyond hereditary breast and ovarian cancers [4]
- Additionally, both preclinical and clinical studies have demonstrated the synergy of camonsertib in combination with gemcitabine which potentiates the effects of ATRi [3,5]

**Figure 1. Gemcitabine potentiates the effects of ATRi; elevates replication stress, increasing reliance on ATR**




## Rationale

- It remains challenging to determine the specific genomic profile necessary for an effective anti-tumor response to inhibitors of DDR pathways, particularly in tumors that have LoF mutations in DDR genes other than *BRCA1/2* such as *ATM*
- Tumors with biallelic LoF mutations in DDR pathways are generally observed to have better clinical outcomes when treated with SL agents than those with monoallelic alterations [4,6,7,8]; however, other mechanisms are known to drive downstream pathway deficiency thus detailed molecular tumor profiling is often needed
- Here, we present the detailed molecular profile of a 60-year-old female with high-grade serous ovarian cancer (HGSOC) with a monoallelic *ATM* mutation who had a prolonged response to the ATRi camonsertib with low-dose gemcitabine

## Methods

- The case-study patient was enrolled in the gemcitabine combination 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

**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**

- 74 patients treated
- 60/74 patients evaluated for response (≥ 1 post-baseline scan)

Jul 2020 — Dec 2021 — Nov 2023

Monotherapy Initiated; Cam + gem Initiated; Data snapshot

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)

## Results

**Figure 2. Patient therapeutic history and timeline**

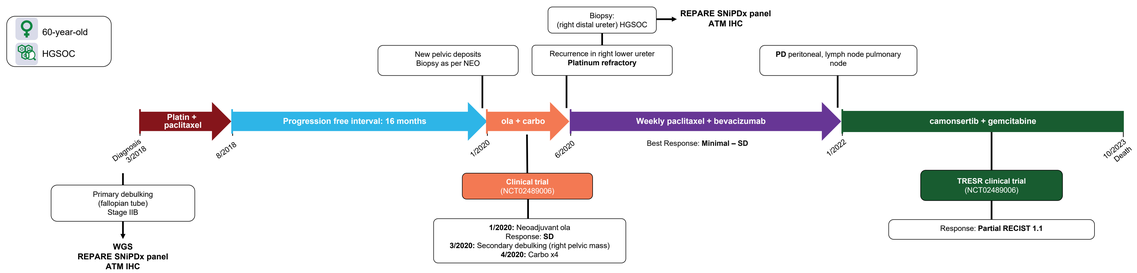
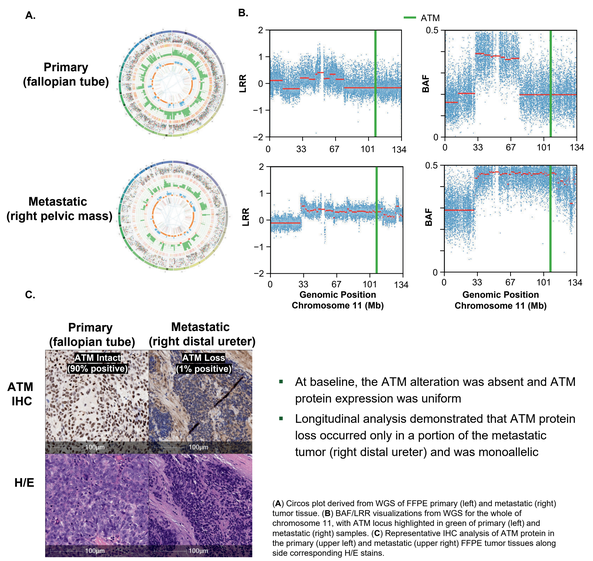



**Figure 3. Summary of retrospective genomic profiling**

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

| Sample Type | Genomic Analysis | Tumor Ploidy | Tumor Purity | *ATM* | *TP53* | Other | Genomic Signatures | ATM IHC H-score |
|---|---|---|---|---|---|---|---|---|
| Primary (fallopian tube) | SNiPDx | 2.9 | 61% | Unaltered | p.Arg248Trp (74.1%, biallelic) | *MYC* gain | ovaHRDscar GIS-I | Intact (H-score = 160, 90% positive) |
| Primary (fallopian tube) | WGS | 3.8 | 50% | Unaltered | p.Arg248Trp (76.2%, biallelic) | *MYC* gain | CHORD HRD+ (*BRCA1* Type) | Not tested |
| Metastasis (right pelvic mass) | WGS | 2.9 | 42% | c.49101G>A (20.2%, monoallelic) | p.Arg248Trp (62.1%, biallelic) | *CCNE1* gain *MYC* gain | CHORD HRD+ (*BRCA1* Type) | Not tested |
| Metastasis (right distal ureter) | SNiPDx | 2.8 | 41% | c.49101G>A (25.2%, monoallelic) | p.Arg248Trp (43.8% biallelic) | *CCNE1* gain *MYC* gain | ovaHRDscar GIS+ | Loss (H-score = 1, 1% positive) |

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 SigProfileExtractor.



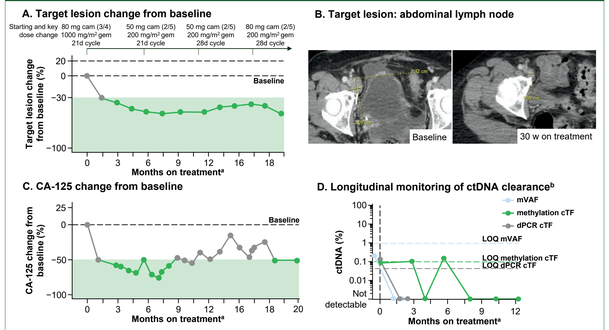

- At baseline, the ATM alteration was absent and ATM protein expression was uniform
- Longitudinal analysis demonstrated that ATM protein loss occurred only in a portion of the metastatic tumor (right distal ureter) and was monoallelic

(**A**) Circos plot derived from WGS of FFPE primary (left) and metastatic (right) tumor tissue. (**B**) BAF/LRR visualizations from WGS for the whole of chromosome 11, with ATM locus highlighted in green of primary (left) and metastatic (right) samples. (**C**) Representative IHC analysis of ATM protein in the primary (upper left) and metastatic (upper right) FFPE tumor tissues along side corresponding H/E stains.

## Case Description

- A 60-year-old female diagnosed with HSGOC
- Treated with 3 prior lines of therapy and was both platinum and PARPi resistant
- Phase Ib TRESR trial enrollment
- Received a starting dose of 80 mg camonsertib (3d on/4d off) + 1000 mg/m$^2$ gemcitabine on a 21d cycle (2w on/1 w off)
- Due to a lack of tolerability (primarily hematologic), patient had sequential dose reductions to reach a tolerated combination dose of 50 mg camonsertib (2d on/5d off) + 200 mg/m$^2$ gemcitabine on a 28d cycle (1w on/1w off)
- A partial RECIST 1.1 response was observed at 4 months and sustained despite the significant dose reductions
- After an increase in target lesions and CA-125 (at month 13), camonsertib dose was increased to 80 mg while gemcitabine dose was maintained at 200 mg/m$^2$
- After which the target lesions decreased to nadir at 76w with concomitant CA-125 decrease
- Patient achieved a durable response and remained on treatment for 1 year and 7 months

**Figure 4. RECIST and tumor marker response**




- A partial RECIST 1.1 response was observed at 4 months and sustained
- At 13 months, the target lesions began increasing in size (-50% to -43%), after which the target lesions decreased to nadir (-52%) at 76w with concomitant CA-125 decrease
- Circulating tumor fraction (cTF), measured by mVAF as well as methylation- and dPCR-based profiling, remained at or below the limit of quantitation of the assay through 12 months

[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.

## Conclusions

- Despite significant dose-reductions due to tolerability, this patient achieved a prolonged response to low-dose gemcitabine and camonsertib
- Significant inter- and intra- tumor heterogeneity in the tumor molecular profile was detected. ATM protein loss and monoallelic ATM alteration were detected at metastasis but not in the primary tumor suggesting the ATM alteration was a late event in the clonal evolution of the tumor
- HRD positivity was observed in the primary tumor (as well as the metastasis) in the absence of a known DDR alteration
- This case highlights the complexity of clonal evolution in high grade serous ovarian tumors and importance of "functional" HRD as no apparent mutational driver was identified


**References**

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**Abbreviations**

3/4, 3 days on/4days off; ATM, ataxia telangiectasia and Rad3-related; ATRi, ataxia telangiectasia and Rad3-related inhibitor; BAF, B allele frequency; CA-125, cancer antigen-125; cam, camonsertib; carbo, carboplatin; CBR, clinical benefit response; CHORD, classifier of homologous recombination deficiency; chr, chromosome; ctDNA, circulating tumor DNA; d, day; DDR, DNA damage response; dNTP, deoxynucleotide triphosphate;ECOG PS, Eastern Cooperative Oncology Group Performance Status; FFPE, formalin-fixed paraffin-embedded; GIS, genomic instability score; Gynecological Cancer Intergroup; gem, gemcitabine; H/E, hematoxylin/eosin; HRD, homologous recombination deficient; HSGOC, high-grade serous ovarian cancer; IHC, immunohistochemistry; LoF, loss-of-function; NGS, next-generation sequencing; ola, olaparib; OR, overall response; PARPi, poly ADP-ribose polymerase inhibitor; PCWG, Prostate Cancer Working Group; PD, progressive disease; PFS, progression free survival; PSA, prostate-specific antigen; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; rNMP, ribonucleoside monophosphate; RP2D, recommended phase 2 dose; SD, stable disease; SL, synthetic lethal; SNiPDx, Synthetic Lethal Interactions for Precision Diagnostics; TF, tumor fraction; w, week; WGS, whole genome sequencing; WT, wildtype; y, years.

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