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

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Background

- In-patient tumor heterogeneity and the present lower loss-of-function (LoF) mutations within DNA damage repair (DDR) gene could account for suboptimal outcomes of high-grade ovarian malignancies.
- ATM variants is highly reflective about trisomies and facio-scuttle-related inhibitor (ATR) that is systemically altered with germline/HRD affecting DDR damage repair.

- ATM/p53 monotherapy resulted in limited clinical benefit in several tumor types and genomics

Rationale

- The challenge in determining the specific genomic profile necessary for an effective endo-therapy, response to therapies of DDR pathways, particularly in tumors that have LoF mutations in DDR genes other than BRCA1/2 such as ATM.
- Tumors with biallelic ATM loss-of-function (LOF) pathways are generally observed to have better clinical outcomes when treated with ASO drugs than those with monoallelic alterations. In vitro, however, other mechanisms are known to allow downstream pathway deficiency thus delayed molecular response.
- Here, we present the detailed molecular profile of a 60-year-old female with high-grade serous ovarian cancer (HGSOC) who had a prolonged response to the ATM inhibitor camosertib with concurrent gemcitabine.

Methods

- The study included 19 patients with advanced-stage HGSOC and/or high-grade serous tumors.
- Primary and metastatic formalin-fixed, paraffin-embedded (FFPE) samples were retrospectively evaluated using Cancer Genome Landscape Explorer (CGLEx) (https://cglx.mdx.uiuc.edu), a tool thatscreened panel consisting of 120 DDR genes capable of distinguishing monoallelic and biallelic DDR alterations.
- Whole-genome sequencing (WGS) was retrospectively performed on DNA derived from primary and metastatic FFPE samples.
- Short-read variants, insertions and deletions, copy number variations, and structural variants were filtered through custom pipelines.
- Tumor frequencies were calculated using COSMIC and the Pan-Cancer project.
- The study was reviewed and approved by the institutional review boards.

Results

- In patients with ovarian cancer, overall response rate (ORR) was 20%, clinical benefit rate (CBB) was 76%, and median progression-free survival (PSF) was 4.4 months.
- In tumors with BRCA1/2 mutations previously treated with a poly-ADP ribose polymerase inhibitor (PARPi), ORR was 33%, and CBB was 67% with median PFS of 2.4 months.

- ATM IHC staining was absent in metastatic (right distal ureter) samples. (right distal ureter) HGSOC metastatic (right distal ureter) HGSOC (left) and (right distal ureter) HGSOC (left) and (right distal ureter) HGSOC (left) and (right distal ureter) HGSOC (left) and

- Table 1. Description characteris of patient population used in the analysis

Case Description

- A 60-year-old female diagnosed with metastatic HGSOC.
- Treated with 3 prior lines of therapy and was both platinum and PAPR resistant.

- Patient had a prolonged response to the ATM inhibitor camosertib with concurrent gemcitabine.

- Due to a lack of tolerability (primarily hematological), patient underwent dose reductions to reach a tolerable combination dose of 50 mg camosertib (3rd on/4th off) + 200 mg/m2 gemcitabine on a 2x4 cycles (2x4 on/8 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), camosertib dose was increased to 80 mg while gemcitabine dose was maintained at 200 mg/m2.

- At baseline, the ATM alteration was absent and ATM protein loss occurred only in a portion of the metastatic (right distal ureter) tumor.

- The ATM protein loss occurred only in a portion of the metastatic tumor.

- The case-study patient was enrolled in the gemcitabine combination arm of TRESR (NCT04497116), a National Cancer Institute of Canada Clinical Trials Group study for patients aged 60 years or older with recurrent/stage IV HGSOC.

- A partial RECIST 1.1 response was observed at 4 months and sustained despite the significant dose reductions.

- Significant inter- and intra-tumor heterogeneity in the tumor molecular profile was detected. ATM protein loss occurred only in a portion of the metastatic (right distal ureter) tumor.

Conclusions

- Despite significant dose-reductions due to tolerability, this patient achieved a prolonged response to low-dose gemcitabine and camosertib.
- Significant inter- and intra-tumor heterogeneity in the tumor molecular profile was detected. ATM protein loss occurred only in a portion of the metastatic (right distal ureter) tumor.

- This case highlights the complexity of clinical evolution in high grade ovarian cancer tumors and importance of ‘functional’ HRD on an apparent monosomatic driver was identified.

Questions

1. How did the patient achieve a prolonged response to camosertib and low-dose gemcitabine combination therapy?

2. What were the key findings from the genomic analysis of the patient's tumors?

3. How did the patient's ATM protein expression change during the course of treatment?

4. What were the implications of the observed heterogeneity in the tumor molecular profile?

5. What is the significance of ATM protein loss in high-grade serous ovarian cancer?