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 telomerase is the characteristic of telomere length which can result in increasing telomere length.
- The target lesions continued to decrease with a best decline of -74% after about 1 year of treatment.
- In preclinical models, ALT positivity (ALT+) has been shown to sensitize tumor cells to ataxia telangiectasia and Rad3-related inhibitors (ATRi).
- Camonsertib is a highly selective ATRi that is synthetically lethal with genomic alterations affecting DNA replication, and has shown clinical activity in all tumor types investigated.
- Here we describe a confirmed clinical and molecular response to the ATRi camonsertib, in a patient with ALT-positive metastatic melanoma.

Case Description

- A 53-year-old male diagnosed with stage IV (CT7, N0, M1b (1)) metastatic melanoma.
- 5 prior lines of therapy including PARPi.
- In June 2021, the patient received camonsertib monotherapy.
- The patient had an initial RECIST PR (30%) at 3 months with one radiographic lesion.
- The target lesions continued to decrease with a best decline of -74%, after about 1 year of treatment.

Results

- The target lesions continued to decrease with a best decline of -74% after about 1 year of treatment.
- Inclusion criteria:
- Objectives and key endpoints:

Methods

- The study was conducted at the MD Anderson Cancer Center (Houston, TX, USA) and included 26 DDR genes.
- Other tumor types investigated but ALT+ percentage varied across tumor types.
- Whole-genome sequencing (WGS) was retrospectively performed on DNA derived from primary and metastatic FFPE samples.
- Conclusions:

Purpose

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

Figure 1

A. ALT+ is intimately linked to DNA repair and replication stress.

Figure 2

B. ALT prevalence in PCa using machine learning classifiers.

Figure 3

3. Tumor and ctDNA response in camonsertib

Figure 4

4. Characterization of genomic structure and signatures

Table 1

<table>
<thead>
<tr>
<th>Sample</th>
<th>Tumour (dilution)</th>
<th>BRCA2</th>
<th>DNA</th>
<th>TP53</th>
<th>Other-Signature</th>
<th>Genetic Signatures</th>
</tr>
</thead>
</table>

References

1. Kyn, MEI Pharma, Mereo, Merck, Natera, Nexys, Novocure, OHSU, OncoSec, Ono Pharma, Pegascy, PER, Pfizer, Piper-Sandler, Prolynx, Repare, resTORbio, Roche, Schrodinger, Theragnostics, Varian, Versant, Vibliome, Xinthera, Zai Labs, and ZielBio; and is a stockholder in Seagen.

Disclosures

- Both the BRCA2 and gBRCA2 variants were monoallelic and genomic signature analysis defined the tumor as HR-positive, consistent with the lack of benefit from olaparib.
- WGS confirmed a frameshift loss of ATM with a germline signature consistent with an ALT+ phenotype.
- The clinical experience of ATRi therapy in patients with ALT+ tumors is limited but further investigation of ATRi as a monotherapy is warranted in this patient population.

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