Circulating tumor cells (CTCs) N-terminal androgen receptor expression to identify patients (pts) with castrate resistant prostate cancer (CRPC) who are more sensitive to chemotherapy

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BACKGROUND
We initiated a multicenter phase II randomized trial of abiraterone/prednisone (AA/pred) followed by cabazitaxel (CBZ) upon abiraterone failure versus the combination (AA/CBZ) at treatment initiation in patients (pts) with castration-resistant prostate cancer (CRPC) with circulating androgen receptor (AR) expression as a biomarker for selecting pts who may benefit from CBZ. CBZ is FDA approved for pts whose tumors are AR deficient or who have shown progression on prior AR signaling inhibitors. AR expression has been linked to cancer progression and is associated with increased tumor proliferation. However, a phase II trial showed no benefit from adding CBZ to AA/pred in mCRPC patients. Although several biomarkers have been studied in mCRPC, none have been FDA approved for ctDNA-based stratification of pts.

MATERIALS AND METHODS:
Pts with chemotherapy naïve mCRPC were treated with AA 1000 mg po daily + prednisone 5 mg po bid either in combination with or followed by CBZ 25 mg/m2 iv q 3 weeks upon progression. The primary endpoint was progression-free survival with a planned accrual of 80 patients. Correlative studies were performed including baseline tumor biopsies/explants, RB status based on immunohistochemistry/FISH and RB gene signature on tissue and CTCs, and pre- and post-treatment serum androgen levels.

RESULTS:
To date, 39 pts have been accrued: 21 pts started on AA/pred alone (Arm 1), and 18 pts started on AA/pred in combination with CBZ (Arm 2). At time of recent analysis of 34 pts, 7 pts from Arm 1 crossed over to CBZ; 11 pts completed 9 cycles of CBZ on Arm 2 and remain on AA/pred alone. Baseline biopsies or archival tissue samples have been collected from all patients and CTCs are being collected throughout treatment. Correlative analysis is ongoing.

CONCLUSIONS:
The concurrent use of AA with CBZ was well-tolerated. The real-time collection of tumor biopsies and CTCs is feasible. The current platform of CTC analysis has enabled close follow up of changes in RB status as pts transition to resistant disease.


diagram

**Objective 1:** Positive AR N-terminal expression (AR+): based on presence of at least 1 CTC or CK+ cell with AR N-terminal signal expression above the 3.0 positivity threshold.

**Objective 2:** Blood from 35 pts underwent CTC analysis: 27/35 (77%) had detectable CTCs with 11/35 (31%) had AR overexpression.

**Objective 3:** Of pts with AR- CTCs, 1/5 pts treated with AA and 5/6 pts treated with AA/CBZ had a PSA decline >50% from baseline.

**Objective 4:** RB1 focal deletions and Chromosome 13 loss in CTCs associates with higher CTC burden counts for patients in both Arm 1 and Arm 2.

**Objective 5:** RB1 loss co-occurs in CTCs with either AR overexpression or no detectable presence of AR

**Ex vivo Explant Assay**
Pre-treatment fresh tissue was subbed and cultured for 6 days on dental sponges in cell culture media with different treatments. Tissue was formalin-fixed, paraffin-embedded, and stained with Hematoxylin and Eosin (H&E) or antibodies directed against Ki67 or RB, counterstained with Eosin. In blue are AR positive nuclei, Ki67 and HIC score 0.3 for nuclear RB. Ki67 is significantly reduced by CBZ alone or in combination with AA, indicative of reduced tumor cell proliferation.

**Intra-patient CTC Diversity of RB1 Status and AR Expression**

**Updated Trial Summary and Conclusions**
- The concurrent use of AA with CBZ was well-tolerated.
- Real-time collection of tumor explants and CTCs is feasible.
- Data suggest that this may identify a cohort of pts who may benefit from the combination of CBZ with AA.
- The current platform of CTC analysis has enabled close follow up of changes in RB status as pts transition to resistant disease.
- Further studies are ongoing to evaluate cellular heterogeneity and RB expression in CTCs play a role in identifying pts who would benefit from chemotherapy.

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