Biomarker Analysis (CTC and ctDNA/RNA) of GT0918 (Proxalutamide) New AR blocker in Phase I mCRPC Patients with Dose Escalation

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Background
- Androgen receptor (AR) blockade is an important treatment option of prostate cancer in clinic and enzalutamide and apalutamide were approved by US FDA as part of standard of care.
- GT0918 is a second-generation AR antagonist with new chemical entity binding directly to the androgen receptor, impairing unclear translocation and decreasing AR protein expression.
- A phase I/II dose escalation, PK, tolerability study was performed in pts with mCRPC progressed on multiple lines of SOC and experimental therapies. Daily oral administration of GT0918 has shown better clinical outcomes in 400mg and 500mg cohorts with no comprised toxicities.
- To study the tumor biology in response to study drug

Method
- Eligible pts were collected blood samples for biomarkers at baseline and on tx every 8 wks during the trial. Pts on tx over 16 wks (≥ 3 blood tests) were qualified for assays for CTCs and cfDNA via EPIC and PredicincPlus platforms.

Result
- Total 40 pts were enrolled with oral administration of GT0918 daily in dose escalation of 50, 100, 200, 300, 400, 500 and 600 mg and shown well tolerated with mild to moderate toxicities. Pts received GT0918 over 16 weeks were run biomarkers in Predicinc and/or EPIC platforms. ctDNA/RNA based variants and CTCs are all detectable in selected pts samples. AR splicing variants (AR-V3 and AR-V7), AR hotspot mutations (W742C, T878A and S889G) and amplifications were detected and shown interesting trends with the clinical outcomes. Both exploratory biomarkers and CTCs suggested higher doses of GT0918 resulted in better clinical outcomes.

Conclusion
- This is a preliminary data from Phase I/II study to explore genomics alterations and the CTC enumeration in late stage of mCRPC pts in response to GT0918 treatment with dose increasing. As non-invasive assays, both CTC and ctDNA/RNA assays provided valuable molecular insights of tumor biology for the monitoring treatment effects besides PSA and imaging scan. Early detection of possible drug sensitivity or resistance from mechanism will facilitate clinical development programs.

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