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

Karl Zhou, Phoebe Zhang, Youzhi Tong, Liandong Ma

Kintor Pharmaceuticals, Inc

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 of 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 in clinical setting, CTC and ctDNA/RNA based biomarkers were explored.

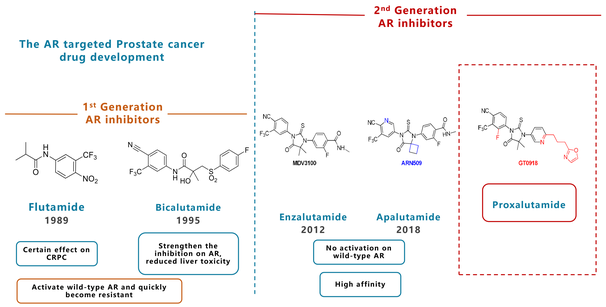


Figure 1. GT0918 Proxalutamide, 2nd Generation of AR Antagonist

Method

- All pts with mCRPC had progressive disease based on rising prostate-specific antigen (PSA) or/and imaging scans, PS 0-2, life-expectancy of 3 months. Prior lines of therapies of bicalutamide, radiation, abiraterone, enzalutamide, sipuleucel-T, docetaxel, or other experimental therapies were allowed.
- Eligible pts (3-6 pts per cohort) were planned for dose-escalation and 5 dose levels (50, 100, 200, 300, 400, 500 mg) were tested. One level of 600 mg was added for safety margin. All pts were treated with oral GT0918 daily for 28 days +7 days for safety, DLT, and PK. If pts tolerated the study drug well, then continuously on treatment until PD, intolerable toxicity or withdraw. All pts had safety lab and PSA every 4 wks and scans every 8wks

- 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/RNA via EPIC and PredicinePlus platforms

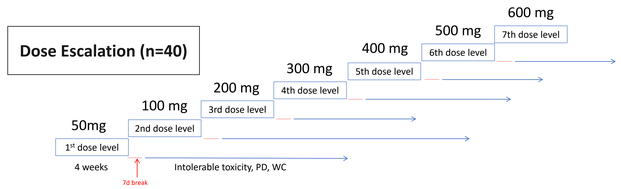


Figure 2. Phase I Trial Scheme of GT0918

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 Predicine 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.

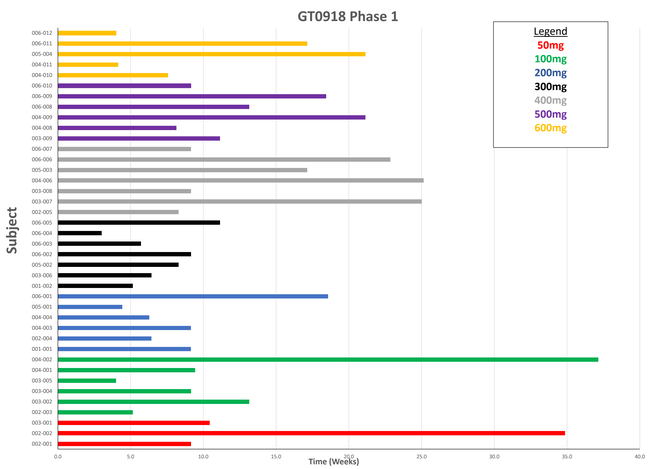


Figure 3. "SWIM Plot" of Treatment Duration GT0918 in Ph I mCRPC Patients Who Failed Lines of Therapies (Abi, Enza, Doc, etc.)

	50mg	100mg	200mg	300mg	400mg	500mg	600mg
>20 wks (Responders)	1	1	1	0	3	1	1
>10 wks but <20 wks	1	1	1	1	2	4	1
<10 wks (Non-responders)	1	4	4	6	2	1	3
Total	3	6	6	7	7	6	5

Table 1. GT0918 Preliminary Activities In Heavily Pretreated mCRPC Patients

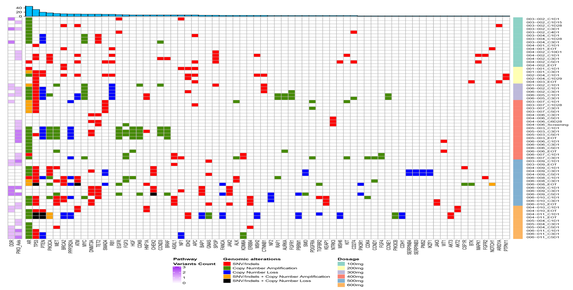


Figure 4. Mutation Landscape of mCRPC in Ph I Trial of GT0918

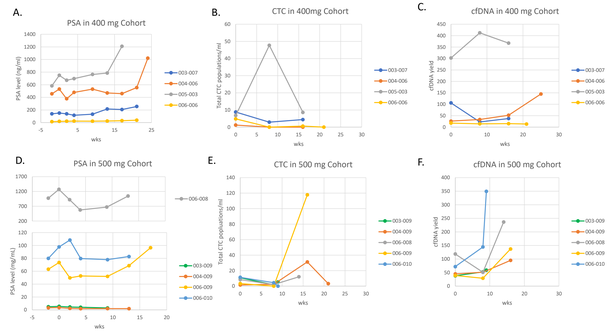
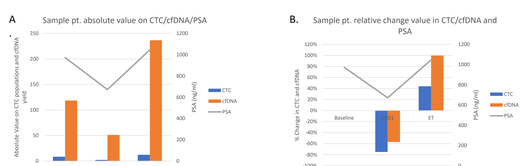


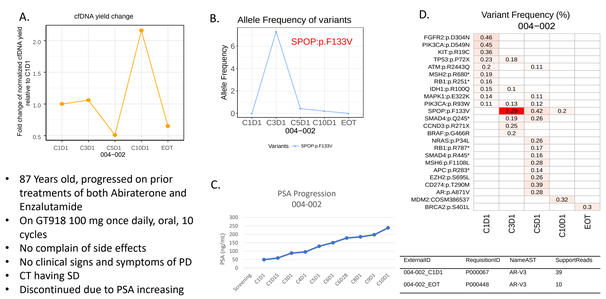
Figure 5. Changes of PSA, CTC and cfDNA in mCRPC Patients on GT0918 Treated with 400 mg or 500 mg



C.

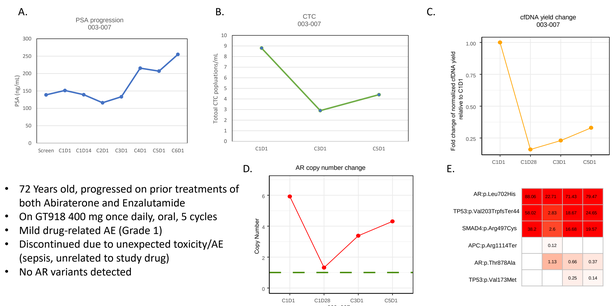
Pt case.	Baseline	C3D1	End of Study
CTC	8.4	2.1	12.1
cfDNA yield	118.5	51	236.5
PSA (ng/ml)	972.3	671.5	1045.1

Figure 6. Changes in CTC, cfDNA level and PSA in a Single Patient. Sugests that CTC or cfDNA Could Function as One of the Indicator for Disease Progression



ExternalID	RequisitionID	NameAST	SupportReads
004-002_C1D1	P000067	AR-V3	39
004-002_EOT	P000448	AR-V3	10

Figure 7. Case of Interest: 004-002. Unmatched Trends in PSA and cfDNA.



- 72 Years old, progressed on prior treatments of both Abiraterone and Enzalutamide
- On GT918 400 mg once daily, oral, 5 cycles
- Mild drug-related AE (Grade 1)
- Discontinued due to unexpected toxicity/AE (sepsis, unrelated to study drug)
- No AR variants detected

Figure 8. Case of Interest: 003-007. Unmatched Trends in PSA and cfDNA

Conclusion

This is a preliminary data from Phase I/II study to explore genomic 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. More patients will be tested in phase II study GT0918 in mCRPC progressed on either abiraterone or enzalutamide.

Acknowledgment

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Contact Information

- This poster was presented at the 2020 ASCO-GU San Francisco. CA
- Contact: Phoebe Zhang, PhD. pzhang@kintor.com.cn
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