Plasma-based exploratory biomarker analysis to evaluate GT0918 in a Phase 1/2 study in mCRPC patients

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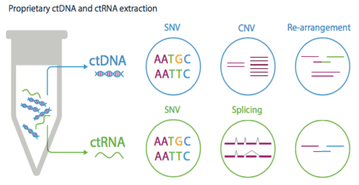
Background

Metastatic castration resistant prostate cancer (mCRPC) is a complex disease with distinct molecular features in relation to genomic instability and selective treatment pressure. Circulating tumor DNA and RNA fragments (ctDNA & ctRNA) found in blood offer the potential of disease diagnosis, monitoring, and resistance mechanism interrogation by detecting genomic alterations from tumor. GT0918, a novel potent androgen receptor antagonist, has been evaluated in a ph1/2 study in mCRPC patients for its safety and efficacy (NCT02826772). Here using patient plasma samples, we explored cell-free DNA & RNA-based biomarkers to assess their associations with clinical response of GT0918.

Methods and Materials

Blood samples were prospectively collected from mCRPC patients at baseline, on- and after study during the trial. PredicinePLUS cfDNA+cfRNA assay, a 180-gene targeted NGS Panel, was used to detect genomic alterations in plasma. Statistical analyses were performed in R 3.5.1.

- Enhanced sensitivity of variant detecdtion with combined ctDNA and ctRNA information
- Detection of functional fusions in a robust, super -efficient mean
- Broader coverage of 565kb genomic regions, enables estimation of TMB and discovery of novel biomarkers
- Clinical grade NGS assay to identify RNA- and DNA-based SNV, Indel, fusion, and RNA splicing variants



Parameter	Description
Regions Analyzed	180 genes
Panel Size	565 kb
Assay Sensitivity	0.25%, report down to 0.1%
Sequencing Coverage	>20,000X for plasma/urine >1,000X for tissue
Turnaround Time	2-4 weeks
Input Sample Type	Plasma (5ml), Urine (40ml) Tissue (5-10 FFPE slides)

Alterations	Report Range	Sensitivity	PPV*
SNV	>0.25% AF	94.4%	99.7%
SNV	0.1%-0.25% AF	78.6%	94.3%
CNV	2.3 copies	95.0%	100%

Results

In total, 58 blood samples were collected at multiple time points from 20 mCRPC patients. The detailed information is listed in Table 1.

Patient ID	Age	Disease Stage	GT0918 Dosage	Treatment Duration (wks)	Over 6 months (Y/N)	Timepoints
003-002	73	IV	100mg	13	N	5
003-004	58	IV	100mg	9	N	3
004-001	73	IV	100mg	13	N	2
004-002	87	III	100mg	41	Y	5
001-001	52	IV	200mg	9	N	2
002-004	74	IV	200mg	7	N	2
004-003	74	IV	200mg	9	N	1
001-002	71	IV	300mg	8	N	1
006-002	66	IV	300mg	10	N	2
006-005	60	IV	300mg	14	N	2
003-007	63	IV	400mg	21	N	4
004-006	NA	NA	400mg	26	Y	4
005-003	62	NA	400mg	17	N	4
006-006	87	III	400mg	23	N	4
006-007	74	NA	400mg	15	N	2
003-009	68	NA	500mg	15	N	3
004-009	54	NA	500mg	>20	NA	3
006-008	69	NA	500mg	17	N	3
006-009	73	NA	500mg	17	N	3
006-010	66	NA	500mg	13	N	3

Figure 1. ctDNA-based mutations are detected in all patients. The most frequent mutations are *AR* and *TP53*. Combined mutation rates in PTEN-PI3K-AKT and DNA damage repair pathways (BRCA1/BRCA2/ATM) are approximately 56.89% respectively.

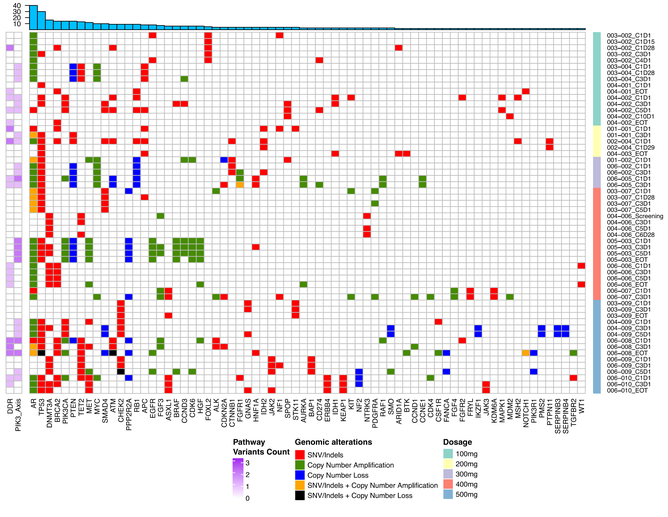


Figure 2. ctRNA-based detection of TMPRSS2-ERG fusions, AR splicing transcripts (A) and TMPRSS2-ERG fusion detection is highly concordant at cfDNA and cfRNA levels (B).

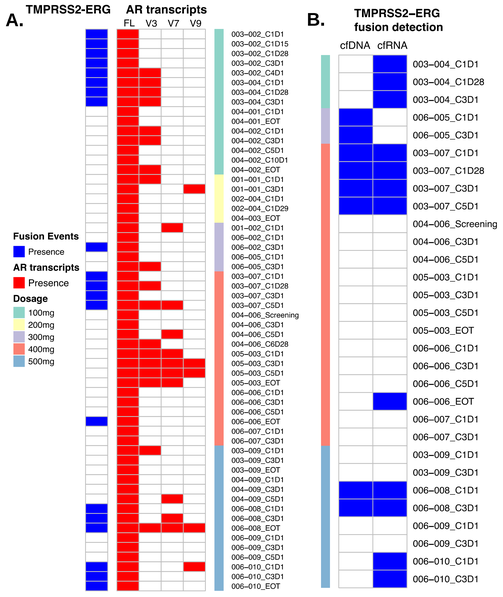


Figure 3. AR hotspot mutation allele frequency (A) and AR copy number (B) changes during the course of treatment.

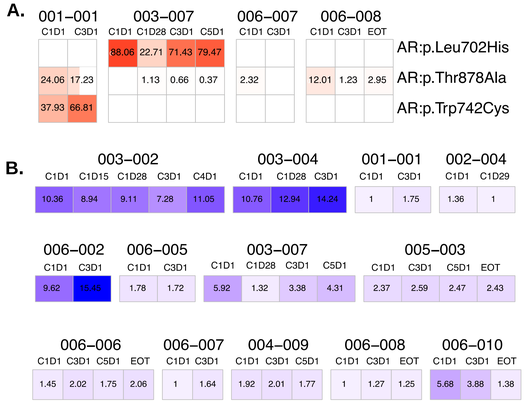


Figure 5. Patient 003-007 has similar change in cfDNA yield, cfRNA yield, AR copy number, and mutation frequency.

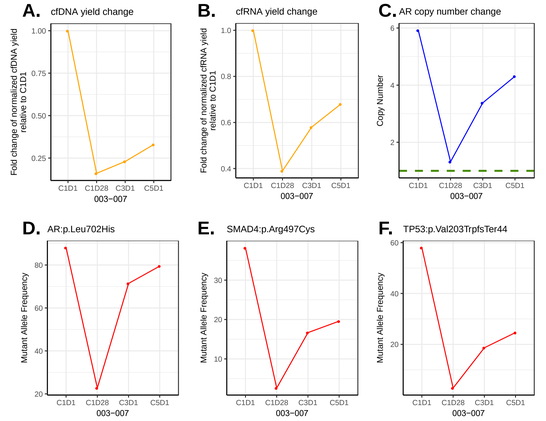
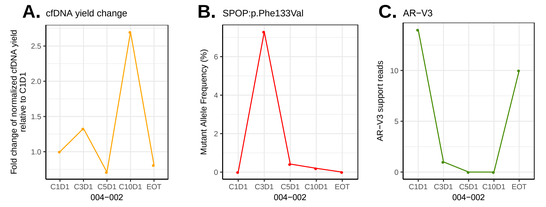


Figure 6. Patient 004-002 had continual increase in PSA over treatment cycles, however, he had disease controlled over 11 cycles and had relatively stable cfDNA amount detected in blood. Prostate-specific SPOP mutation frequency also continuously decreased during treatment.



Conclusion

This is a preliminary study to explore genomic alterations in mCRPC during the GT918 treatment. As an non-invasive assay, PredicinePLUS ctDNA + ctRNA assay provided valuable molecular insights for monitoring treatment effects and identifying possible drug sensitivity/resistance mechanisms.