Preliminary Analysis of a US Phase II Study of the Safety And Tolerability Of Proxalutamide (GT0918) In Subjects With mCRPC Who Had Progressed On Either Abiraterone (Abi) Or Enzalutamide (Enza)

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Background

Prostate cancer is the most common malignant tumor in men and is the second leading cause of cancer-related deaths in men. Recently there are several 2nd generations of anti-androgen therapies approved and used widely in clinics. However, many patients (pts) relapse after a period of treatment in clinic due to various resistant mechanisms and require new drug or additional therapy.

GT0918 (Proxalutamide) is a new chemical entity of androgen receptor (AR) antagonist with more specificity and activity in inhibiting ARs with reduced drug accumulation in the CNS and also show activities on AR mutations including ART878A leading AR drug resistance in cell assays.

In early phase I clinical trial of dose escalation study (NCT02826772), GT0918 was shown well tolerated in mCRPC pts progressed lines of standard and experimental therapies with some durable responses. 400mg and 500mg orally once daily were selected warranted for further clinical testing.

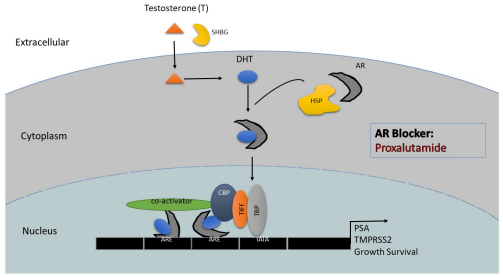


Figure 1. MoA of GT0918 As The Androgen Receptor Blocker

Trial Design

- Study start date: May 2019
- Total study duration: approximately 30 months
- Eligible patients from 10 US sites are randomized in a 1:1 ratio to orally take 400 mg or 500 mg of GT0918 once daily.
- Patients will continue treatment with GT0918 up to 24 months at their assigned dose until disease progression, intolerable toxicities (AEs), or withdrawn consent.
- Subjects will assessment of circulating tumor cells (CTC), ct-DNA and ct-RNA obtained at baseline and every 3 months during the study

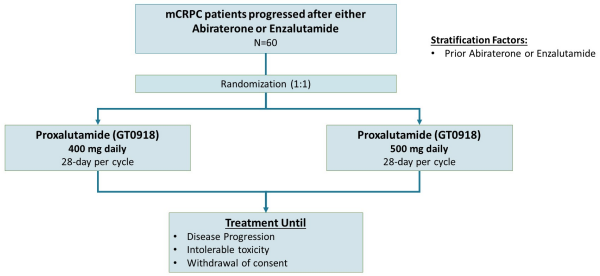


Figure 2. Phase II Trial Scheme of GT0918

Study Objectives

The primary objectives

To evaluate the safety and tolerability of GT0918 either 400 mg or 500 mg daily dose to determine the RP2D for Ph III and/or other confirming studies.

The secondary objectives

To evaluate efficacy endpoints including≥ 50% PSA suppression, the percentage of radiographic disease progression, the time to radiographic and bone progression, the time to PSA progression.

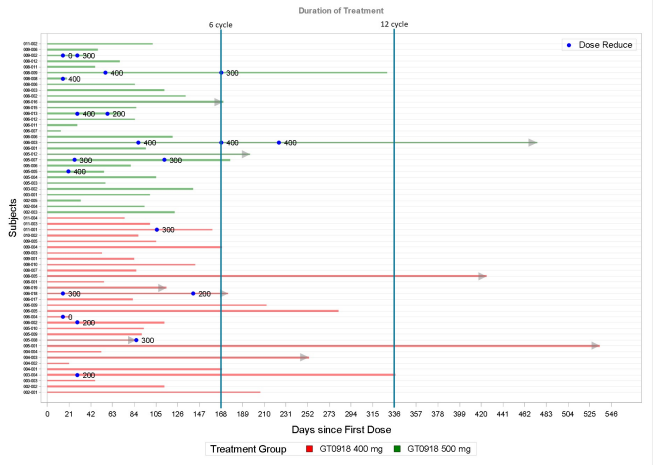
Major Inclusion/Exclusion Criteria

- Inclusion:
  - Histologically confirmed metastatic castrate resistant prostate cancer (mCRPC)
  - Prior failed therapy either abiraterone or enzalutamide (only 1 prior chemotherapy is allowed)
  - Progression defined by PCWG 3 criteria
  - Adequate bone-marrow, renal, and liver function
  - ECOG performance status of 0-1
  - Life expectancy of ≥ 6 months (at screening)
- Exclusion:
  - Discontinuation of enzalutamide or abiraterone less than 3 weeks, prior to the start of study medication.
  - Prior chemotherapy, radiation, sipuleucel-T or other experimental immunotherapy less than 3 weeks prior to the start of study medication
  - Prior chemotherapies more than 1 line.

Results

Parameter	Category/ Statistic	GT0918 400 mg/day Prior Enzalutamide (N=13)	GT0918 400 mg/day Prior Abiraterone (N=16)	GT0918 500 mg/day Prior Enzalutamide (N=9)	GT0918 500 mg/day Prior Abiraterone (N=19)
Age (Years)	n	13	16	9	19
	Mean	74.3	71.1	72.3	75.4
	SD	8.16	9.46	10.99	5.48
	Max	87	90	85	85
Race	American Indian or Alaskan Native	0	0	0	0
	Asian	0	0	0	0
	Black or African American	1 (7.7)	1 (6.3)	3 (33.3)	4 (21.1)
	Native Hawaiian or Pacific Islander	0	0	0	0
	White	12 (92.3)	14 (87.5)	5 (55.6)	13 (68.4)

Table 1. The demographic characteristics of subjects in Phase II trial of GT0918.



As of Dec. 30th. 2020,, 61 pts were enrolled at 9 US sites and randomized 1:1 to 400 mg (n=31) or 500 mg (n=30) daily dose. Fifteen pts finished 6 cycles. Among them, three finished 12 cycles and remained on the treatment. Treatment duration showed more pts in the 400 mg cohort with stable disease (SD) on imaging (10/31 finished 6 cycles) compared to the 500 mg cohort (5/30 finished 6 cycles). Further, three out of four pts who finished 12 cycles had progressed on Abi indicating that GT0918 might be a good treatment option for pts who had progressed on Abi.

	GT0918 400 mg Prior Enzalutamide (N=13)	GT0918 400 mg Prior Abiraterone (N=16)	GT0918 500 mg Prior Enzalutamide (N=9)	GT0918 500 mg Prior Abiraterone (N=19)
Adverse Events	11 (84.6)	15 (93.8)	9 (100)	18 (94.7)
Drug-Related Adverse Events	10 (76.9)	13 (81.3)	8 (88.9)	15 (78.9)
Serious Adverse Events	2 (15.4)	3 (18.8)	3 (33.3)	7 (36.8)
Drug-Related Serious Adverse Events	1 (7.7)	1 (6.3)	1 (11.1)	5 (26.3)
Grade 3 or Higher Treatment-Emergent Adverse Events	3 (23.1)	4 (25.0)	3 (33.3)	6 (31.6)
Adverse Events Leading to Permanent Discontinuation of Study Drug	0	1 (6.3)	3 (33.3)	3 (15.8)
Drug-Related Adverse Events Leading to Permanent Discontinuation of Study Drug	0	1 (6.3)	3 (33.3)	3 (15.8)
Deaths	0	0	0	0

Table 2. The current incidence of drug related adverse events in Phase II trial of GT0918.

Most of the reported AEs related to GT0918 were grade 1 or 2 as per CTCAE v4.03, but 22 AEs (5.3%) were reported as grade ≥ 3, such as fatigue, increase ALT/AST, rhabdomyolysis, or muscle weakness. Some AEs were due to drug-drug interaction with lipid-lowering medications leading to early discontinuation (26.2%).

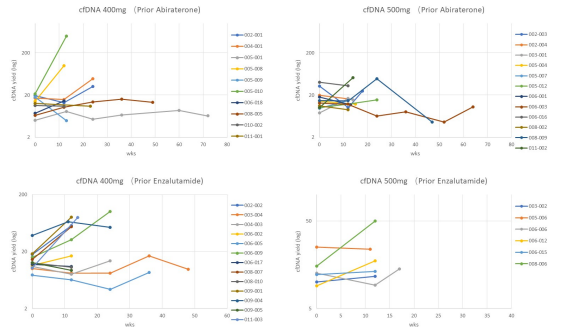


Figure 4. The changes of cfDNA in mCRPC pts on GT0918 treated with 400 mg or 500 mg

As an exploratory biomarker and a potentially valuable insight in addition to imaging scan, the cfDNA data was investigated using Predicine platform (180 gene panel). ctDNA/RNA based variants including AR splicing variants (AR-V3 and AR-V7), AR hotspot mutations (W742C, T878A and S889G) and amplifications were detected. The current results suggest that pts who had failed enza may not benefit from 500 mg GT0918 dosage. However, due to the limitation on the number of pts in this study, further investigation will be needed to get more confirmative result.

Conclusion

Proxalutamide (GT0918) administrated orally once a day is well tolerated and resulted in SD in pts who had progressed on either Abi or Enza. The 400 mg/day will be considered as the recommended phase II dose for further clinical trials. GT0918 is warranted for pts who have failed either Abi or Enza

Acknowledgment

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