Phase II Trial of SM-88 in Non-Metastatic Biochemical Recurrent Prostate Cancer

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BACKGROUND

- Androgen deprivation therapy (ADT) is a standard treatment for recurrent non-metastatic prostate cancer (nmPC) after local therapy that produces declines in prostate-specific antigen (PSA).
- ADT is not curative and in many cases, is associated with significant side effects including hot flashes, fatigue, muscle wasting, bone loss and changes in cognition.
- SM-88 is an oral non-hormonal investigational agent (D,L-alpha-metyrosine, (racemetyrosine) with responses across multiple cancers including prostate[1,2]. It has been used with methoxsalen, phenytoin, and sirolimus (MPS).
- It is hypothesized that methoxsalen, phenytoin, and sirolimus (MPS) enhance the anti-cancer properties of both the D- and L- isomers of SM-88.
- Both the D- and L- isomers of SM-88 correlate with a reduction in CTCs[3].
- The present study updates the safety and antitumor effects of SM-88 in men with non-castrate non-metastatic prostate cancer.
- Antitumor effects were assessed by post-therapy changes in PSA and the number of circulating tumor cells (CTCs).

OBJECTIVES

- To evaluate SM-88 with MPS prior to ADT in patients with rapid rising PSA levels after local therapy.
- To evaluate the safety and side effect profile of SM-88.
- The primary endpoint was disease control assessed by: PSA progression (WG3), local progression by CT at trial end), the development of metastatic disease (by CT and bone scan) and/or death.
- Secondary endpoints included: changes in CTC number.

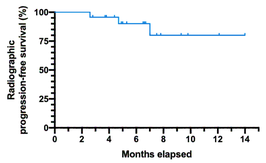
RESULTS

Table 1. **DEMOGRAPHICS AND BASELINE CHARACTERISTICS (n=23)**

Age, mean ± SD	70.6 ± 7.4
Weight (kg), mean ± SD	87.4 ± 15.7
BMI, mean ± SD	28.9 ± 4.5
Race, n (%)	
White	16 (69.6%)
Black	5 (21.7%)
Other	2 (8.7%)
Prior Surgery, n (%)	7 (30.4%)
Prior Radiotherapy, n (%)	14 (60.9%)
Time Since Completion of Most Recent Prior Therapy (years), mean ± SD	4.6 ± 3.7
Previous Androgen Deprivation Therapy, n (%)	17 (73.9%)
Current Androgen Deprivation Therapy, n (%)	1 (4.3%)
PSA (ng/mL), median (range)	6.4 (1.7 – 80.1)
PSA Doubling Time (months), median (range)	6.2 (1.4 – 37.6)
CTCs Detected, n (%)	23 (100%)
ECOG Performance Status Score, median (range)	0 (0 – 1)
Gleason Score, median (range)	7 (6 – 10)
Concomitant Disease States, n (%)	
Coronary Artery Disease	3 (13.0%)
Diabetes	4 (17.4%)
Hypertension	15 (65.2%)

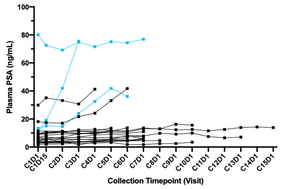
- As of September 2019, 34 subjects were screened, 23 subjects were enrolled and had received SM-88, and of those, 21 subjects remained on study for ≥ 12 weeks.
- 12 subjects completed 6 or more cycles of SM-88 therapy.
- The cumulative exposure of the entire cohort was 149 months of daily dosing. Median duration of therapy was 6.5 months (range 2.6 to 14.0 months).
- 3 patients did not report any prior surgery or radiotherapy.

Figure 1. **PROGRESSION RADIOGRAPHIC FREE SURVIVAL (PFS)**



- No subject developed metastatic disease (MFS = 100%, median duration of therapy 6.5 (2.6 – 14.0) months).
- All radiographic PD were regional (2 lymph nodes, 1 prostate bed).

Figure 2. **PSA VALUES BY CYCLE***



- Median baseline PSA for subjects with radiographic progression was 13.4 versus 5.6 for for subjects with no radiographic progression.
- 52% (12/23) of subjects experienced an improvement in PSA Doubling Time on trial.
- PSA Doubling Time improved 34.4% from 6.1 months to 8.2 months for all subjects completing 3 cycles of therapy (n=20).
- 3 subjects with regional radiographic PD are shown in blue.

*PSA progressions have not yet been adjudicated.

Figure 3. **CTC VALUES BY CYCLE ON SM-88**

Fig 3a. Individual and Median CTC Results by Radiographic Progression

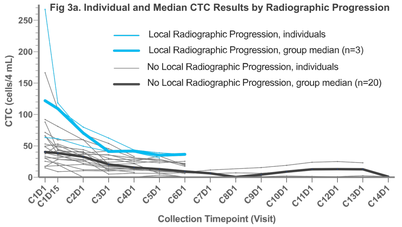


Fig 3b. CTC By Radiographic Progression

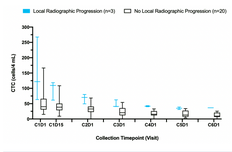
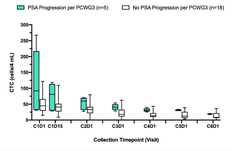


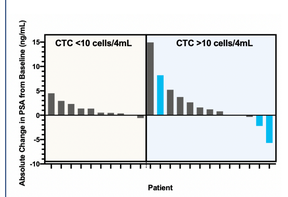
Fig 3c. CTC By PSA Progression



- All patients had detectable CTCs at baseline.
- All patients with available CTC results for at least 3 cycles (n=19) achieved a decrease from baseline, with a median decrease of 65.3% at the end of 3 cycles.*
- 94.7% (18/19) of patients maintained CTCs below baseline for the duration of therapy after cycle 3.
- Median baseline CTC (per 4 ml) for subjects with radiographic progression (n=3) was 122 cells vs 40 for subjects with no radiographic progression (p<0.003).

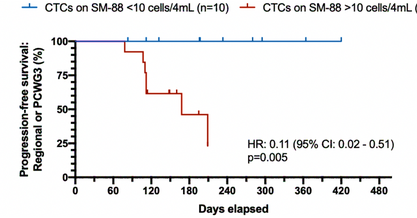
*One patient did not have a CTC result at 12 weeks but did have results thereafter.

Figure 4. **PSA CHANGE BY CTC NADIR**



- Among patients with CTCs >10 cells/4mL, PSA rose 46.6% on treatment (mean baseline PSA = 15.1 to 22.2 ng/mL at C6D1), while those who achieved CTCs <10 cells/4mL had an average PSA rise of 15.1% (p=0.09).
- PSA changes were not associated with regional radiographic progression. Disease progression was associated with CTC changes (see Figure 5).

Figure 5. **CTC NADIR ON SM-88 AND PSA OR RADIOGRAPHIC PROGRESSION**



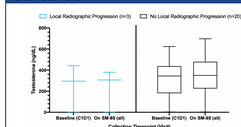
- Progression included regional radiographic PD and PCWG3 PSA progression.
- Patients experiencing radiographic progression (n=3) had median baseline uNTx of 72 (median 26 throughout treatment) vs. patients with no radiographic progression (n=20) had median baseline uNTx of 23.5 (median 25 throughout treatment).
- uNTx also increased among patients on treatment with CTCs >10 largely due to one of the patients with regional PD. There were no differences in other markers of metastases, including LDH and bone-specific alkaline phosphatase.

Table 2. **REPORTED ADVERSE EVENTS BY CAUSALITY**

	UNRELATED	POSSIBLY/ PROBABLY RELATED
Subjects Experiencing Any AE	7	12
Total Number of AEs	17	18
Grade 1	10	17
Grade 2	6	1
Grade 3	1	0
Grade 4	0	0

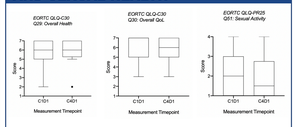
- Overall, 12/23 (52.2%) subjects reported experiencing any AE that was possibly or probably related to SM-88. 18/35 (51.4%) AEs were deemed at least possibly related to SM-88.
- The majority of Grade 1 AEs possibly or probably related to SM-88 were gastrointestinal in nature, including: intestinal bloating, diarrhea, flatulence, loose stool, and nausea. One Grade 2 AE possibly related to SM-88 was fatigue.
- One unrelated Grade 3 AE was hyperkalemia in a subject taking a K+ sparing antihypertensive.
- None of the study subjects reported seizures, Posterior Reversible Encephalopathy Syndrome (PRES), hypersensitivity reactions, ischemic heart disease, falls, or fractures.
- SM-88 was well-tolerated in all subjects. There were no treatment-related serious adverse events. No adverse events resulted in dose delay, discontinuation, or reduction.

Figure 6. **TESTOSTERONE VALUES ON SM-88**



Patients without progression (n=20) had slightly higher testosterone levels at baseline and throughout treatment on SM-88 (median at baseline 343.9, range 2.5 to 624.0 ng/dL; median throughout treatment 351.0 range 2.5 to 913.7 ng/dL, respectively) than those who experienced local radiographic progression (n=3) (median at baseline 295.0, range 2.5 to 442.0 ng/dL; median throughout treatment 319.5, range 2.5 to 433.0 ng/dL).

Figure 7. **QUALITY OF LIFE AND SEXUAL HEALTH**



- Globally, overall health and quality of life scores as reported by patients on the EORTC questionnaire were relatively high, and demonstrated that patients did not experience poor health or low quality of life on SM-88.
- Generally, patients reported a stable level of sexual activity after about 3 cycles of SM-88.
- There was no detectable worsening in any domain of EORTC QLQ-C30 or QLQ-PR25.

Table 3. **AREAS OF COMMON ADT TOXICITY**

	Baseline	Average on Treatment
Testosterone (ng/ml), mean ± SD	319.1 ± 161.3	359.8 ± 194.5
Weight[1] (kg), mean ± SD	87.2 ± 15.6	87.6 ± 16.0
Hematocrit (%), mean ± SD	42.6 ± 3.5	41.7 ± 3.5
Glucose (mg/dL), mean ± SD	116.9 ± 56.4	120.0 ± 51.4
QTc (ms), mean ± SD	424.6 ± 25.6	426.4 ± 23.8
Mean Arterial Pressure (mmHg) Normotensive subjects[2], mean ± SD	90.4 ± 2.6	92.9 ± 6.0
Mean Arterial Pressure (mmHg) Hypertensive subjects[2] , mean ± SD	100.5 ± 5.6	94.2 ± 5.1
Calcium (mg/dL), mean ± SD	9.5 ± 0.4	9.4 ± 0.8
Triglycerides (mg/dL), mean ± SD	104.3 ± 53.9	125.8 ± 41.2
Total Protein (g/dL), mean ± SD	7.0 ± 0.6	6.9 ± 0.4
Albumin (g/dL), mean ± SD	4.4 ± 0.3	4.3 ± 0.2

[1] Last Weight on Treatment was used instead of average of all measures on treatment.

[2] Normotensive subjects had both Systolic BP ≤130 and Diastolic BP ≤80; Hypertensive subjects had Systolic BP >130 or Diastolic BP >80.

- One subject began the trial with a QTc >480 and remained stable, and was not clinically significant according to Investigator.

METHODS

- Tyme2016b (NCT02796898) is a Phase 1b/2, open-label, dose escalation study to evaluate SM-88.
- Inclusion Criteria:
  - Recurrent non-metastatic prostate cancer, i.e. no visible disease on CT and bone scans
  - All patients had primary curative intent treatment (see Table 1)
  - Rising PSA according to Prostate Cancer Working Group 3 (PCWG3) criteria
  - ECOG score ≤ 1, PSA ≥ 1 ng/mL
  - Males ≥18 years of age with any testosterone level
- All subjects in phase 2 received 230 mg BID of SM-88 orally.
- Subjects also received oral doses of MPS (The lowest clinically available doses of repurposed methoxsalen (10 mg), phenytoin (50 mg), and sirolimus (0.5 mg)) once per day.
- CTCs were determined by a 3rd generation ultra-sensitive assay using 4 variations including an invasion enrichment step (LineaRx, Stony Brook NY). CTCs were sampled on a monthly basis.
- Data presented is as of September 2019.

CONCLUSIONS

- Favorable changes in PSA kinetics including rising values to stable (non-rising) values were observed in cases with NO declines in serum testosterone levels (see Figure 2).
- Testosterone levels were generally maintained. Higher testosterone was not associated with worse outcomes.
- The median duration on therapy was 6.5 months (range 2.6 to 14.0 months).
- Improvement in PSA Doubling Time and CTCs were demonstrated.
- While on treatment or during follow-up, no metastatic disease was detected.
- Favorable effects on PSA and CTC kinetics were observed, consistent with a favorable treatment effect.
- The adverse profile included only 1 Grade 2 (fatigue) and 1 Grade 3 (hypokalemia) event. The majority were Grade 1 GI events, markedly different from standard ADT.
- Patient-reported overall health, overall quality of life, and sexual activity were largely retained while on treatment.
- SM-88 may provide disease control without the side effects associated with the ADT standard, delaying the need for ADT or other systemic therapy.

DISCUSSION

- These results suggest a clinically meaningful prolongation of the castrate free interval in prostate cancer patients with rising PSA.
- SM-88 can be considered in cases where testosterone lowering treatments may compromise function.
- Reductions in CTC number may be a more informative indicator of benefit than changes in PSA for further study with SM-88 and other non-testosterone modifying agents.
- Prospective trials to confirm these results are planned.

REFERENCES

1. Stega et al. A first-in-human study of the novel metabolism-based anti-cancer agent SM-88 in subjects with advanced metastatic cancer. Invest New Drug 2019.
2. A Phase Ib/II, Open-label, Dose Escalation Study to Evaluate the Safety, Pharma-cokinetics, and Efficacy of SM-88 in Patients with Prostate Cancer. Del Priore et al. J Clin Oncol 35, 2017 (suppl; abstr e16540)
3. Fernandez-Zapico M et al. Therapeutic Potential of Targeting Amino Acid Metabolism in Pancreatic Cancer. AACR Special Conference on Pancreatic Cancer; 2019 Sep 6-9; Boston (MA): AACR; 2019. Abstract nr 78677080. Poster nr B15.
4. Phase II trial of SM 88 in non-metastatic biochemical recurrent prostate cancer. Roach et al. J Clin Oncol 36, 2018 (suppl 6S; abstr 175).
5. Evaluating non-hormonal therapy in a phase II trial of SM-88 for rising PSA prostate cancer. Gartrell et al. J Clin Oncol 37, 2019 (suppl 7S; abstr 83).
6. Typical hormone deprivation side effects compared to SM-88 therapy for rising PSA. Gartrell et al. J Clin Oncol 37, 2019 (suppl 7S; abstr 79).
7. Scher et al. (2019). Circulating Tumor Cells in Prostate Cancer: From Discovery to Clinical Utility. Clin Chem, 65(1), 87-99. doi: 10.1373/clinchem.2018.287102.
8. Scher et al. (2018). Drug development for noncastrate prostate cancer in a changed therapeutic landscape. Nat Rev Clin Oncol, 15(3):150. doi: 10.1038/nrclinonc.2017.177.

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