A Phase 1b/2, Open-Label, Dose Escalation Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of TYME-88 (SM-88) in Patients with Prostate Cancer

Giuseppe Del Priore,1,2,3, Steve Hoffman,1 Daniel Nixon MD1
1Tyme Inc, New York, NY; 2Grady Memorial Hospital, 3Morehouse School of Medicine

BACKGROUND
- Treatment options for recurrent non-metastatic prostate cancer (nmPC) are limited and generally include toxic systemic treatments e.g. hormone therapy (ADT)
- Testosterone depletion through ADT has dramatic quality of life implications for patients while the resulting clinical benefit is currently under debate
- Progression to other more toxic therapies is linked to increased serious adverse events and can meaningfully compromise patient health
- With over 160,000 new cases of prostate cancer estimated annually by the ACS, there is a substantial need for less toxic therapies that can control disease while maintaining a higher quality of life in the non-metastatic population

TYME-88 THERAPY
- TYME-88 is a relatively non-toxic therapy that has shown effectiveness in both non-metastatic and metastatic prostate cancer
- Initial data reported activity in solid tumors without significant toxicity (Hoffman et al J Clin Oncol 2013; e22095, Hoffman et al Ann Onc 2016; v555)
- TYME-88’s mechanism of action uses the innate metabolic process of cancer (glycolysis) to selectively enter tumor cells and breakdown cellular defenses against the immune system and oxidative stress
- The core component of TYME-88 is a dysfunctional tyrosine derivative that interferes with cancer’s protein synthesis process
- In addition, TYME-88 includes microdevices of three repurposed agents (a CYP3a4 inducer, mTOR inhibitor and an oxidative catalyst) designed to selectively increase tyrosine uptake and oxidative stress within cancer cells

STUDY OBJECTIVES
- Demonstrate that a relatively non-toxic alternative to ADT can:
  1. Show quantitative therapeutic benefit through reduction in circulating tumor cells (CTCs)
  2. Prevent radiographic progression (rPFS)
  3. Delay time to or prevent subsequent toxic therapy (TFS), including ADT or chemotherapeutics
  4. Maintain baseline testosterone levels
  5. Maintain or improve patient reported outcomes (PROs)

STUDY DESIGN
- Six-month, open-label, multi-center Phase 1b/2
- Completed Phase 1b (n=4): Dose escalation to determine safe and effective dose
- On-going Phase 2 (n=30): Single-arm study of safety and efficacy

RESULTS
- Preliminary summary of efficacy (details reported elsewhere at ASCO)
  - CTC count undetectable or significantly improved: 87.5%
  - Radiographic progression free survival (rPFS): 100%
  - Need for subsequent toxic therapy: None
  - PSA doubling stable or improved: All subjects
  - PROs improved or stable: All subjects

DISCUSSION
- Although the results are still early and with a small sample size, the consistency of response across subjects is encouraging that TYME-88 may be a viable alternative for maintenance therapy in recurrent nmPC
- As a relatively non-toxic treatment, TYME-88 could provide clinicians an option that is in-between an observation strategy and more toxic treatments, whether using chemical castration with ADT or other systemic therapies
- The ability to significantly reduce or eliminate CTCs and maintain radiographic progression free survival, while also preserving normal testosterone levels, raises the question of the necessity of chemical castration to control non-metastatic biochemical recurrent prostate cancer
- In addition, we believe this supports the growing body of evidence that circulating tumor cells are a better prognostic biomarker than PSA levels, especially in earlier-stage prostate cancer where PSA levels may be affected by multiple non-cancerous influences

DEMOGRAPHICS
- As of May 30, 2017, 10 subjects have received the study medications.

SAFETY AND DOSING
- In the Phase 1b dose ranging stage of the trial, the first subject showed therapeutic benefit at the lowest dose (230mg tyrosine derivative QD) with no significant toxicities
- Three additional subjects were then given 460mg tyrosine derivative (230mg BID) and all demonstrated therapeutic benefit with no significant toxicities
- The Phase 2 stage of the trial was then commenced, with all subjects receiving the 460mg dose
- No dose limiting toxicities or drug-related serious adverse events have been identified in either Phase 1b or Phase 2 subjects
- Subjects received lowest clinically available doses of three repurposed agents that represented approximately 10-25% of lowest effective dose for their original approved applications
- Levels of repurposed agents were not varied during the dose escalation stage as they are intended to improve the effectiveness of the tyrosine derivative, but not have an independent therapeutic effect

REFERENCES
- Hoffman et al. SMK/SM-88 toxicity, efficacy and patient reported outcomes in metastatic pancreatic cancer. (J Clin Oncol 35, 2017 e14060)
- Hoffman et al. SM-88/SMK non-hormonal therapy in recurrent or untreated prostate cancer. (J Clin Oncol 35, 2017 e16540)
- Del Priore et al. SMK-88 in non-metastatic rising PSA-recurrent prostate cancer. (J Clin Oncol e16567)
- Del Priore et al. Phase Ib pharmacokinetics of non-hormonal SM-88 in patients with non-metastatic recurrent prostate cancer. (J Clin Oncol e14061)