Adaptive Dose Optimization Trial of Stereotactic Body Radiation Therapy (SBRT) with or without GC4419 (avasopasem manganese) in Pancreatic Cancer

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ABSTRACT

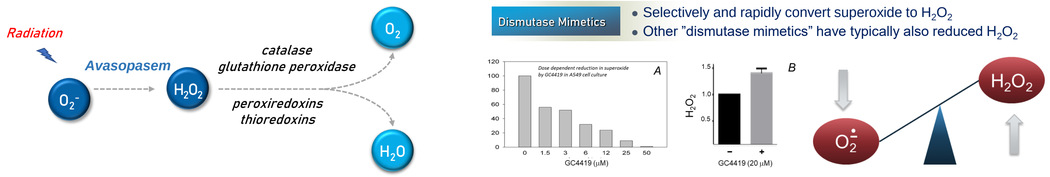
Background: Local progression causes up to 30% of deaths from pancreatic cancer (PC) and is also a significant source of morbidity. Stereotactic body radiotherapy (SBRT) offers the potential for improved therapeutic index over standard fractionation, but current regimens of 5 fractions of 5–7 Gy/fraction are constrained by nearby organ tolerance and offer only palliation without improving survival. Safe dose escalation may be necessary to improve SBRT efficacy. Avasopasem, a superoxide dismutase mimetic, selectively converts superoxide ($O2^{\bullet-}$) to hydrogen peroxide (H_2O_2) and oxygen. $O_2^{\bullet-}$ initiates normal tissue damage due to RT. Avasopasem is in a Phase III trial (NCT03689712) to reduce RT-induced oral mucositis in head and neck cancer, based on positive results in a randomized Phase II trial for that indication (Anderson *JCO* 2019). Avasopasem improved the survival of mice receiving 8.5 Gy x 5 to the upper abdomen. Cancer cells are less tolerant to elevated H_2O_2, and more tolerant to elevated $O_2^{\bullet-}$, than normal cells, and avasopasem demonstrated mechanism-dependent synergy with high dose-fraction RT in a human tumor xenograft with inducible expression of catalase (**Figure 3**; Sishc AACR 2018). Thus, adding avasopasem to SBRT may increase both the efficacy and the safety of the latter.

Methods: 48 patients with locally advanced PC, who have completed medically-indicated induction chemotherapy, are randomized 1:1 to placebo or avasopasem, 90 mg IV, prior to each of 5 consecutive daily (M–F) SBRT fractions. A Phase I/II Late Onset Efficacy/Toxicity tradeoff (LO-ET) based adaptive design adaptive model drives assignment of SBRT dose escalation in each arm based on a dual endpoint (Gr 3-4 GI toxicity or death; local stable disease or better) by 90 days post SBRT. The planned dose levels are 10, 11, and 12 Gy x 5 fractions (BED10 = 100, 112.5, and 132 Gy, respectively) as an integrated boost to the gross tumor volume (GTV).

Endpoints: Primary endpoint: Maximum tolerated dose of SBRT with avasopasem or placebo. Secondary endpoints: progression-free survival, response rate, and acute (90 day) and late (12 month) radiation toxicity with avasopasem vs placebo. Exploratory correlative studies include ctDNA, tumor exome/transcriptome sequencing and immune profiling.

BACKGROUND

Figure 1. Avasopasem Mechanistic Rationale



- Ionizing radiation induces a burst of excess superoxide ($O_2^{\bullet-}$), which initiates normal tissue damage
- Avasopasem selectively mimics the enzymatic activity of superoxide dismutase: converting $O_2^{\bullet-}$ to H_2O_2 and molecular oxygen
- No direct effect on hydroxyl radical or other reactive oxygen species

Figure 2. Combination of Avasopasem With RT More Effective in Higher Dose Per Fraction to Same BED Observed in H1299 NSCLC Tumors in Mice

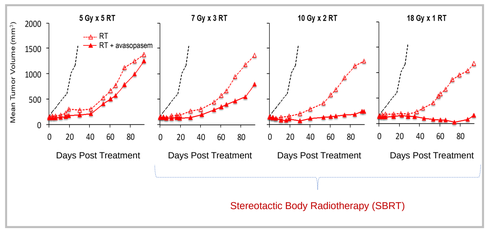
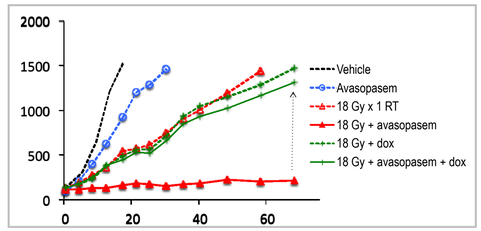
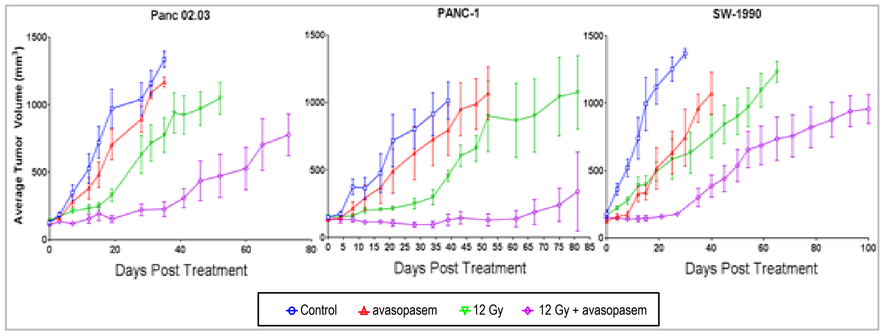


Figure 3. Mechanism-dependent Antitumor Synergy of Avasopasem with SBRT in the Lung Cancer Xenograft H1299; Synergy Abrogated by Induction of Catalase Production (Doxycycline Promoter)



Presented by Sishc BJ et al. AACR Annual Meeting 2018; April 14-18, 2018; Abstract 667: The radioprotector avasopasem (GC4419) ameliorates radiation induced lung fibrosis while enhancing the response of non-small cell lung cancer tumors to high dose per fraction radiation exposures. BED, biologically effective dose; dox, doxycycline; SBRT, stereotactic body radiotherapy.

Figure 4. Avasopasem Enhances the Response of Three Human PDAC Xenografts to High Dose Per Fraction Radiation Exposure



Presented by Sishc BJ et al. AACR Annual Meeting 2019: 2019:Abstract C52: The radioprotector avasopasem (GC4419) enhances the response of pancreatic ductal adenocarcinoma tumors to high dose per fraction radiation exposure.

TRIAL IN PROGRESS (NCT03340974): AVASOPASEM + SBRT IN PANCREATIC CANCER

Figure 5. Trial Design

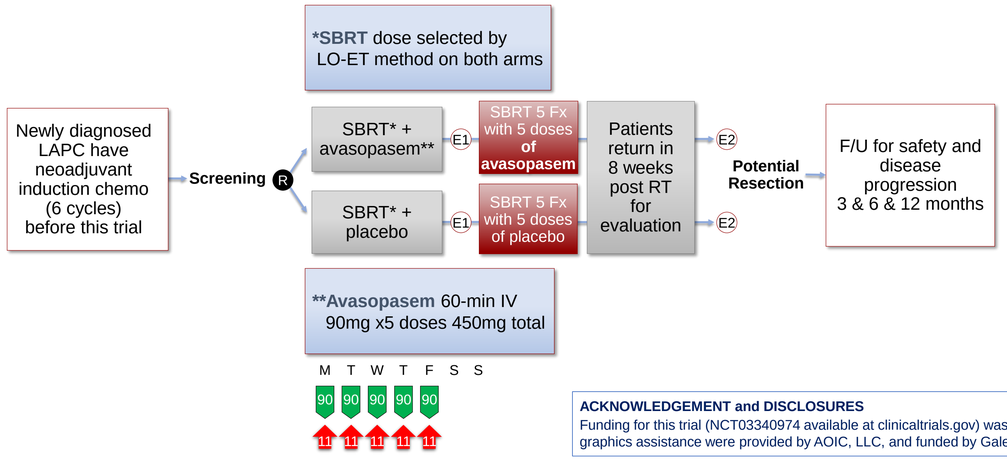
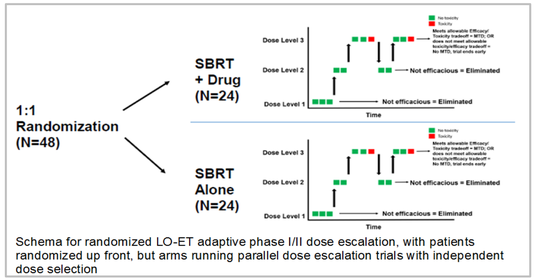


Figure 6. Adaptive Trial Dose Levels in Each Arm



Schema for randomized LO-ET adaptive phase I/II dose escalation, with patients randomized up front, but arms running parallel dose escalation trials with independent dose selection

REFERENCES

1. Anderson CM et al. *JCO* 2018;36(15_suppl):6006; **2.** Sishc BJ et al. American Association for Cancer Research Annual Meeting 2018:Abstract 667; **3.** Sishc BJ et al. American Association for Cancer Research Annual Meeting 2019:Abstract C52.

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