ASTRO 2024
Targeting Provider Wellness
FOR EXCEPTIONAL PATIENT CARE

Genotypically-selected pan cancer trial of camonsertib with palliative radiation in the treatment of metastatic tumors harboring an ataxia-telangiectasia mutated (ATM) mutation

Nancy Lee[1,2], Ryan Mitchell[2], Michelle Huang[2], Jeeban Das[1], Robin Guo[2,3], Wungki Park[2,3], Virginia Ferreira[2], Madeline Merrill[2], Erica Sgroe[2], TJ Unger[3], Maria Koehler[3], Jeremy Setton[1], Simon Powell[1], Ezra Rosen[2,3], Nadeem Riaz[1,2]

[1]Department of Radiation Oncology, MSKCC, NY, NY; [2]Department of Early Drug Development, MSKCC; [3]Department of Medical Oncology, MSKCC, NY, NY; [4]REPARE Therapeutics

PURPOSE/OBJECTIVES

- Pre-clinical models show that camonsertib (RP-3500), a potent/selective ataxia telangiectasia and rad3-related (ATR) inhibitor in combination with radiation, markedly radiosensitizes *ATM*$^{-/-}$ versus *ATM*^{WT} tumors, illustrating features of radiation-induced synthetic cytotoxicity.
- We conducted a Phase I trial of camonsertib to determine the MTD with low dose EBRT (4Gy x 5). A subsequent Phase II study will determine efficacy of therapy
- We hypothesized that patients with pathogenic ATM mutations versus those with variants of unknown significance (VUS) would experience markedly higher rates of clinical benefit from camonsertib in combination with radiotherapy.

MATERIALS/METHODS

- Phase I/II trial enrolled patients with metastatic tumors harboring *ATM* mutations (somatic or germline, pathogenic or VUS).
- Patients received camonsertib daily starting at 80mg up to maximum of 160mg given ~1 hour +/- 30 minutes prior to each fraction of radiation (4Gy) for 5 days followed by continuation of camonsertib for 5 additional days. (**Fig. 1**)
- The primary objective was to obtain the maximum tolerated dose (MTD) of camonsertib with radiation using a 3+3 design.
- Toxicity was assessed using CTCAEv5. Tumor response [(complete (CR, partial (PR), stable disease (SD), progressive disease (PD)] was assessed by computed tomography (RECIST) and/or positron emission tomography (PERSIST for bone lesions) at 2- and 6- months post-treatment.

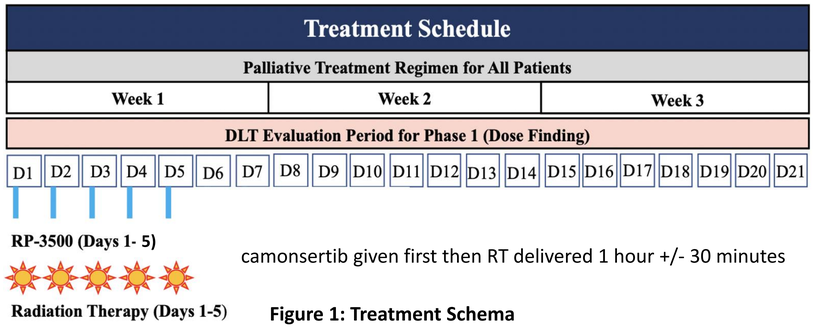


Figure 1: Treatment Schema

RESULTS

- N=17 patients were enrolled who had mutations in ATM, of which 12 where pathogenic and 5 VUS;.14 mutations were somatic and 3 were germline.
- Primary cancer histology included: gastrointestinal (n=5), pancreas (n=5), breast (n=2), lung (n=2), bladder (n=2), and thyroid (n=1).
- The median number of discrete lesions radiated per patient was 3 (range: 1-6). Sites irradiated: lung (n=9), liver (n=7), bone (n=17), node (n=8), pancreas (n=3), and rectum (n=1).
- There were 3 dose-limiting toxicities (DLTs): 80 mg (anemia); 120 mg (thrombocytopenia); 160 mg (thrombocytopenia).
- Due to the appreciation of systemic toxicity with 10 days of continuous Camonsertib, after 80 mg dose, subsequent patients were treated for only 5 days.
- **The MTD was 160 mg** given day 1-5 with 4Gy. 5.
- Interim response information was available for 16 patients at submission
  - At 2-months, there were 2 CR, 5 PR,4 SD in the pathogenic group versus 1 PR and 4 SD in the VUS group.
  - At 6-months, in 9 evaluable patients, there were 2 CR, 4 PR, 1 SD in the pathogenic group versus 1 SD, 1 PD in the VUS group.
  - Latest radiographic response for patients shown (**Fig.2)**

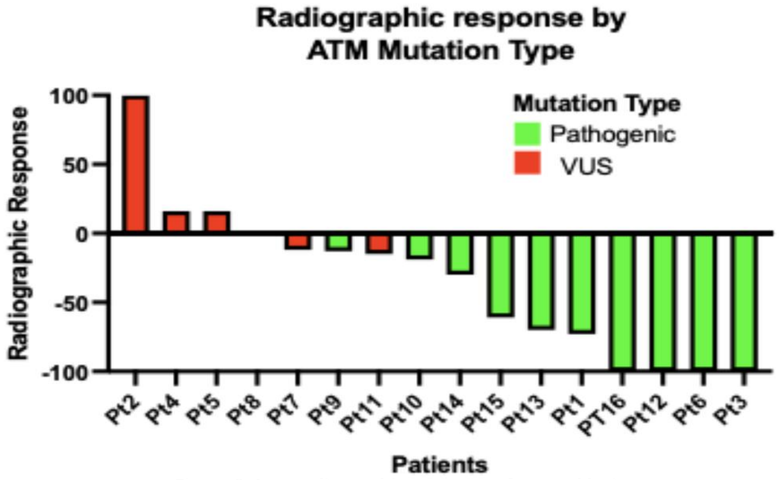
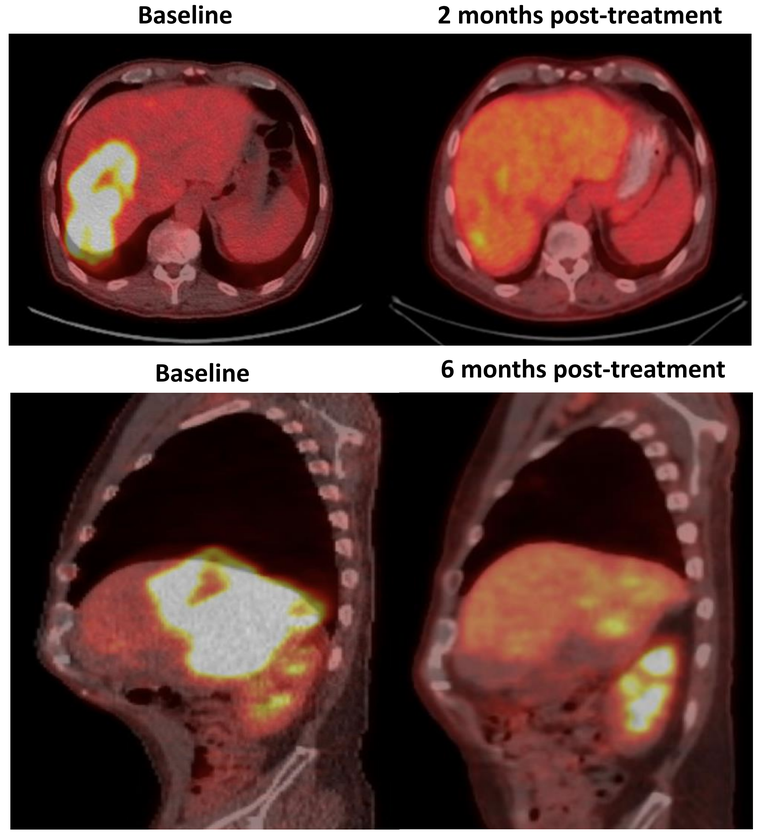


Figure 2: Last radiographic response of treated lesions

A patient with pathogenic ATM mutation: met pancreatic cancer to liver axial (top) view and sagittal (bottom) view of a positron emission tomography (PET)



Conclusions

- The recommended phase II dose of camonsertib is 160mg.
- Encouraging response rates (including 15 patients enrolled on the phase II trial, response evaluation on-going) were observed for the pathogenic versus VUS ATM mutation group in this first genotypically selected drug and radiation combination study.