ADPORT-601 (TT-10-101): First-in-Human Study of Adenosine 2A (A2A) and Adenosine 2B (A2B) receptor antagonists in Participants with Selected Advanced Solid Tumors

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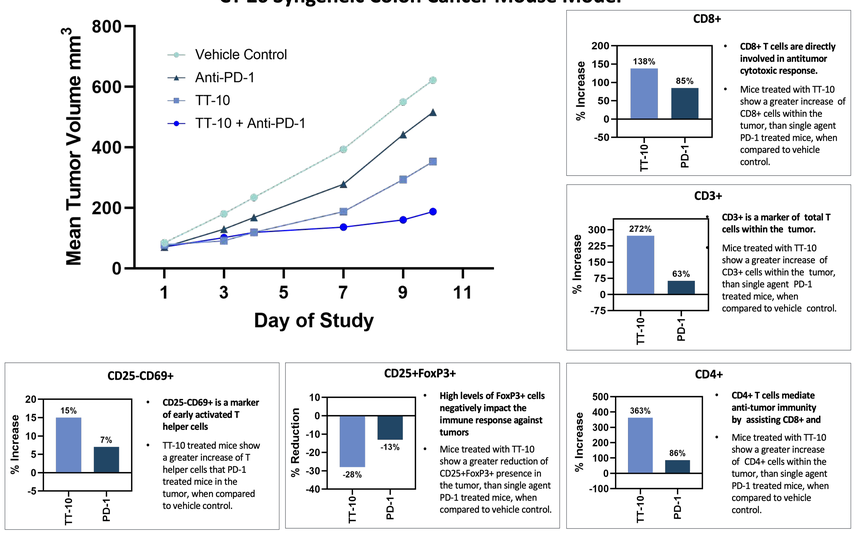
Background:

- Hypoxic tumors possess high levels of extracellular adenosine within the tumor microenvironment, suppressing both innate and adaptive immune responses
- Adenosine binding of the A2A and A2B receptors reduces cytotoxicity of NK and T cells, as well as impairs T cell effector function, while increasing immunosuppressive functions of DCs, T regs and macrophages
- TT-10 (PORT-6) and TT-4 (PORT-7) are novel, potent and selective antagonists of A2AR and A2BR, respectively
- Preclinical studies further demonstrate that PORT-6 exhibits high-affinity receptor binding with a long dissociation rate ($t_{1/2}$ >10 hours) and is characterized by very slow displacement in the presence of super-physiologic concentrations of adenosine
- Both PORT-6 and PORT-7 have shown monotherapy activity in traditionally non-immunogenic tumor mouse models (4T-1) as well as immunogenic models (CT-26, **Figure 1**)

Figure 1: PORT-6 (TT-10): Increased Immune Response vs. Anti-PD-1

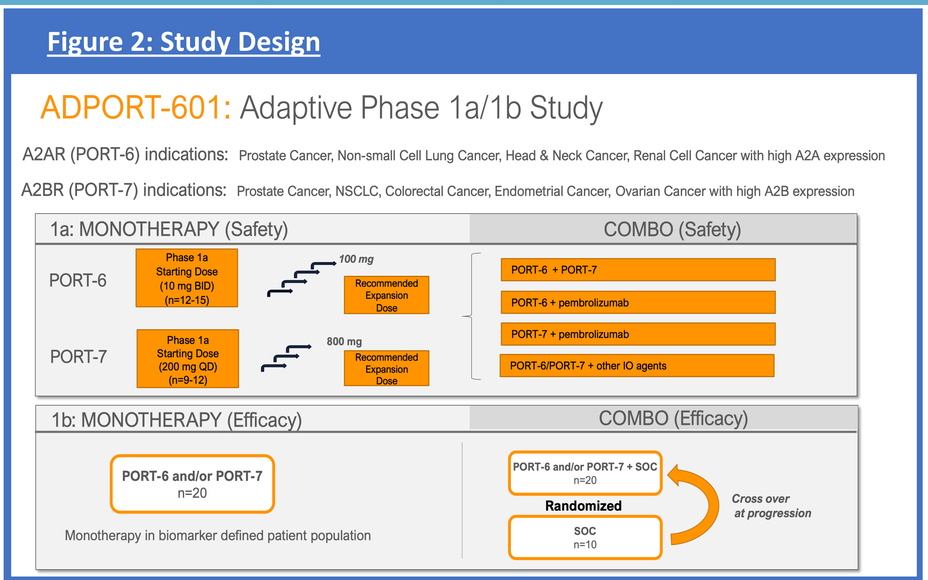


Methods:

Study Design:

- Study schema is shown in **Figure 2**
- ADPORT-601 is a multi-center, open-label Phase 1 study
- Phase 1 cohorts utilize a standard 3+3 design at each dose level
- The Primary Phase 1 endpoint is safety, as defined by the number of patients experiencing Dose-Limiting Toxicities (DLT) and the incidence of Grade ≥ 3 treatment-related adverse events
- Secondary endpoints include Overall Response Rate, Duration of Response, Progression-free Survival, and pharmacokinetics, as well as pharmacodynamic and translational endpoints

Figure 2: Study Design



Summary:

- The ADPORT-601 study design allows for targeting of the A2A and A2B receptors individually and in combination with novel, potent and selective antagonists
- In preclinical models PORT-6 demonstrated single agent activity associated with favorable changes in multiple immune cell populations
- Patients with high levels of A2A and/or A2B receptor expression will be identified via a novel IHC-based assay, optimizing the overall risk/benefit profile for participants
- Optimizing inhibition of A2AR and A2BR provides an opportunity to dissect the role and relative contribution of each signaling pathway in suppressing anti-tumor immunity via multi-omic analyses
- The study is actively recruiting participants at 8 US research centers

Eligibility:

- PORT-6 (A2A) Dose Escalation: histologically confirmed metastatic castration-resistant prostate cancer (CRPC), non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), or renal cell carcinoma (RCC) that is refractory to standard therapy
- PORT-7 (A2B) Dose Escalation: CRPC, NSCLC, colorectal cancer (CRC), endometrial cancer or ovarian cancer that is refractory to standard therapy
- High adenosine receptor expression as assessed by a novel IHC-based companion diagnostic
- Measurable disease per RECIST 1.1, with the exception of CRPC (patients with metastatic non-measurable CRPC, including bone-only disease, are eligible)
- ECOG 0-1
- Prior immunotherapy is permitted

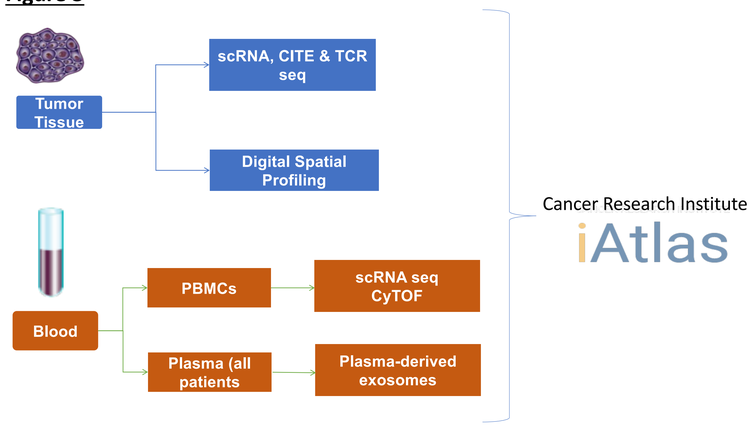
Study Status:

- First patient first visit was achieved in June 2023
- Enrollment is ongoing, with 8 US study centers activated
- A total of 4 patients have been treated, and the second dose cohort is open for enrollment

Translational Study Collaboration

- A novel collaboration is being planned among Portage Biotech, Cancer Research Institute, MD Anderson Cancer Center and University of California San Francisco (**Figure 3**)
- Prospective longitudinal blood and tissue collection will enable a multi-omic translational approach to studying the adenosine pathway
- The ADPORT-601 study design provides a unique opportunity to study the effect of potent A2A and A2B receptor inhibition individually
- Results will be added to CRI's iAtlas portal

Figure 3



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