**Figure 1:** Ad is injected intraarterially and production of IL-12 in the tumor microenvironment is regulated through the administration of V leading to controlled T cell activation toward tumor-associated antigens and driving a cytotoxic immune response against distant tumors.

**Figure 2:** Schema

**Key Eligibility Criteria**

- **Inclusion:**
  - Women ≥18 years with locally advanced or metastatic breast cancer; any histology
  - Standard chemotherapy or immunotherapy
  - Anti-HER2+ in patients with chemotherapy-resistant locally advanced or metastatic breast cancer
  - HER2+ or HER2- in patients with chemotherapy resistant metastatic breast cancer

- **Exclusion:**
  - Patients with prior exposure to Ad

**Study Population**

- **Objects:**
  - Evaluate the safety and tolerability of one cycle of Ad-V immunotherapy following a first- or second-line standard treatment in HER2- subjects, or together with a first- or second-line anti-HER2 antibody therapy in HER2+ subjects
  - Estimate progression rate, overall response rate (ORR), and disease control rate (DCR)
  - Evaluate number of subjects whose baseline tumor status improves to PR or better
  - Explore impact on tumor and serum immune biomarkers

**Study Design**

- **Primary:**
  - Single-arm, single-center phase 1b/2 study
  - Ad-V immunotherapy is given as a chemotherapy holiday and is started within 4 weeks of stopping the pre-study standard chemotherapy
  - Safety and efficacy is being evaluated separately for HER2- and HER2+ patients
  - Stopping rules have been implemented for both safety (Grade 3/4 events) and efficacy (12-week progression rate)

**Periheral Response**

- **Figure 3:** An increase in plasma level of IL-12 protein was observed with a corresponding increase in downstream IFNγ. Each histogram is the mean SEM.

**Immunfluorescence and Tumor Cytokines**

- **Figure 6:** Ad-V effects on tumor cytotoxic T cells (CD3+CD8+) at baseline and 6 weeks posttreatment. Metastatic liver tumor biopsy (15x) at baseline and 6 weeks posttreatment from subject A showing increase in cytotoxic T cell (red).

**Conclusion**

- **Ad-V provided a meaningful drug holiday for subjects with durable responses to 18 and 35 weeks.
- Ad-V consistently elicited production of IL-12 and IFNγ with a net influx in CD8+ cytotoxic T cells and sustained intratumoral IFNγ production.
- DCR (SD or better) was 44% at Week 6 and 22% at Week 12; ORR (PR or better) was 11% at Week 12.
- All 12 toxicities 3 toxicities reversed promptly upon discontinuation of V, including CRS.
- The observed immune modulation and influx of cytotoxic T cells (CD3+CD8+) into the tumor suggest that combination of Ad-V with a checkpoint inhibitor warrants exploration.
- Higher than expected frequency of CRS (6 of 9 subjects) was likely related to CPR 344 drug interactions with V (8 mg), resulting in enhanced peak cytokine expression.
- These encouraging data with Ad-V warrant further evaluation.

**Table 2:** Response at Week 6 and Week 12 represents changes from pre-Ad-V baseline (RECIST v1.1). Baseline represents response from pre-study first- or second-line standard chemotherapy. Subjects A and C reported progression post-study at 35 and 18 weeks, respectively.

**Table 3:** Response at Week 6 and Week 12 represents changes from pre-Ad-V baseline (RECIST v1.1). Baseline represents response from pre-study first- or second-line standard chemotherapy. Subjects A and C reported progression post-study at 35 and 18 weeks, respectively.

**Figure 7:** An increase in IFNγ at Week 6 indicates immune activation within the tumor microenvironment. This histogram shows the mean SEM. Asterisk indicates statistical significance vs. baseline (P<0.05).

**Reference**