Phase 1b/2 study of intratumoral Ad-RTS-hIL-12+veledimex in patients with chemotherapy-responsive locally advanced or metastatic breast cancer

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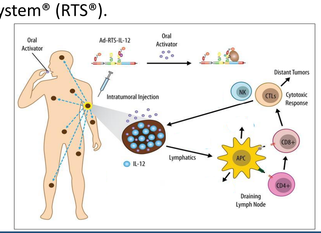
Background

- Interleukin-12 (IL-12) is a pro-inflammatory cytokine that can reverse immune escape mechanisms induced by myeloid-derived suppressor cells (MDSCs) and dendritic cells (DCs) and significantly improve the function of activated CD8+ T cells .
- Ad-RTS-hIL-12 (Ad) is a novel gene therapy candidate expressing IL-12 under the control of an orally administered activator ligand, veledimex (V) through the proprietary RheoSwitch Therapeutic System® (RTS®).

Figure 1: Ad is injected intratumorally 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.



Objectives

Primary:

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

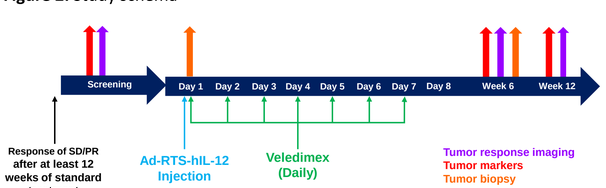
Secondary:

- 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

- Single-arm, single-center phase 1b/2
- 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)

Figure 2: Study schema



Key Eligibility Criteria

Inclusion:

- Women ≥ 18 years with locally advanced or metastatic breast cancer; any histology
- SD or PR after at least 12 weeks of pre-study first- or second-line standard chemotherapy
- At least 2 measurable lesions

Exclusion:

- Auto-immune diseases, chronic immune suppression, and untreated brain metastases

Study Population

- As of 30-Aug-2016, 9 Subjects have been enrolled (8 HER2- disease and 1HER2+ disease); enrollment is ongoing.

Table 1. Subject characteristics

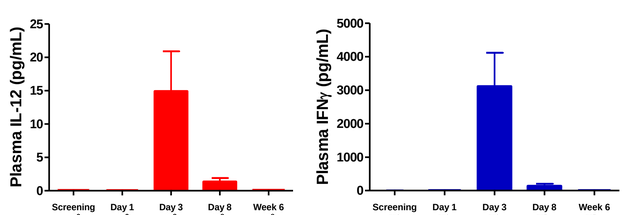
Median age in years (min, max)	52 (33, 63)
Mean prior lines of treatment	1.4
Mean V dosing days (% of assigned dose)	4.56 (65.1%)
Proportion subjects taking CYP 3A4 medication	9 (100%)

Safety

- All 9 subjects had related AEs; the related AEs with 2 or more occurrences included: pyrexia, fatigue, myalgia, chills, nausea, vomiting, GERD, hypotension, ALT/AST increased, lymphocyte count decreased.
- Cytokine release syndrome ǂ (CRS) was seen in 6 subjects out of 9 (4 Grade 2 and 2 Grade 1).
- 2 subjects had related SAEs, including:
  - One with Grade 3 ALT/AST increased, Grade 2 malaise, and Grade 3 fatigue
  - One with Grade 4 hypotension and Grade 4 febrile neutropenia
- All related SAEs and AEs ≥ Grade 3 were predictable and rapidly reversed upon discontinuation of V.

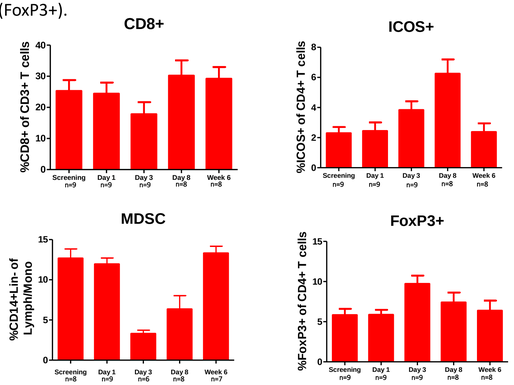
Peripheral Response

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.



Peripheral Response

Figure 4: Blood FACS analysis results (mean ±SEM) for immunosuppressive T cells (MDSC), T cell activation (ICOS+), cytotoxic T cells (CD3+CD8+), and regulatory T cells (FoxP3+).



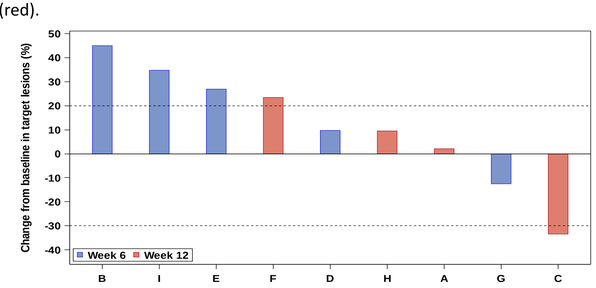
Tumor Response via Imaging

Table 2: Response at Week 6 and Week 12 represents change 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.

Subject	Baseline	Week 6	Week 12
A	SD	SD	SD (until Week 35)
B	PR	PD	-
C	SD	SD	PR (until Week 18)
D	SD	SD*	-
E	SD	PD	-
F	SD	PD	PD
G	PR	PD	-
H	PR	SD	PD
I	SD	PD	-

*Clinical progression

Figure 5: Percent change of sum of target lesions at Week 6 (blue) or Week 12 (red).



Immunofluorescence 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 cells (red).

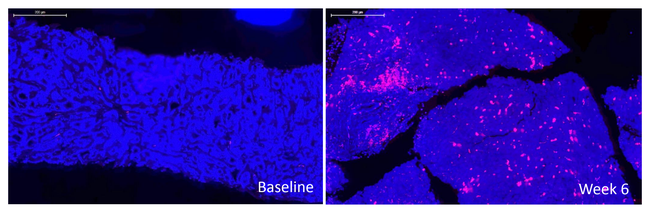
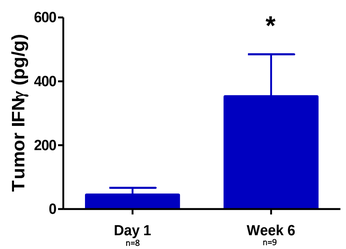


Figure 7: An increase in IFNγ at Week 6 indicates immune activation within the tumor microenvironment. This histogram shows the mean ±SEM. Asterisk indicates statistical significance vs. baseline (P<0.05).



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 ≥ Grade 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 CYP 3A4 drug interactions with V (80 mg), resulting in enhanced peak cytokine expression.
- These encouraging data with Ad+V warrant further evaluation.

Reference

ǂ Daniel W. Lee, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood, 2014, 124: 188