T cell and Immune Activation from a Phase 1 Study of STK-012, a first-in-class IL-2R α/β Selective Partial Agonist in Advanced Solid Tumors

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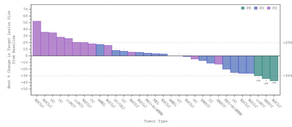
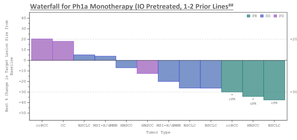
Background

- STK-012 is a first-in-class α/β-IL-2R biased partial agonist designed to drive antitumor activity by selectively stimulating CD25+ antigen activated T cells, while avoiding hallmark IL-2 toxicities by sparing pleotropic activation of lymphocytes including NK cells.
- Initial clinical findings showed a favorable safety profile and single agent efficacy of STK-012 in advanced, relapsed/refractory solid tumors (Figures below). [1]

Waterfall for Phase 1a Monotherapy[#]



Waterfall for Ph1a Monotherapy (IO Pretreated, 1-2 Prior Lines)[##]



IL-2- Receptor Targeting Strategies			
	1st Generation[2]	2nd Generation Engineered IL-2[2]	STK-012
IL-2 Construct	High dose IL-2 (Aldesleukin)	"Non-α" IL-2	α/β-biased IL-2
IL-2R Bias	No bias / Binds to high & intermediate affinity IL-2R	Dimeric IL-2 receptor / Binds to intermediate affinity IL-2R	Trimeric IL-2 receptor / Binds to high affinity receptor IL-2R
IL-2R Subunit Sparing	None	Reduced or No binding to IL-2Rα	Reduced binding to IL-2Rγ
Cell Selectivity	No selectivity	NK cells and naïve T cells	Antigen-activated T cells

Analysis Population and Methods

- The STK-012-101 study design and preliminary clinical data from 47 subjects treated with STK-012 monotherapy in Phase 1a were previously presented. [1]
- This analysis describes peripheral translational and correlative findings in the same population:

Part A: STK-012 QW escalation 0.375 mg → 0.75 mg N=19

Part B: STK-012 Q3W escalation 0.75 mg → 3 mg N=28

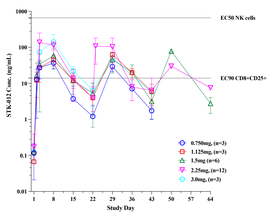
Candidate RP2D → **2.25 mg Q3W**

- Analysis of STK-012 and cytokines in serum samples was assessed using an immunoassay and MSD multiplex U-plex kits. Immunophenotype profile of the immune cells was performed using spectral flow cytometry on Cytek Aurora platform using custom developed panels.
- TCR-Seq was performed using gDNA and conducted at Adaptive Technologies. CITE-Seq was conducted on the 10x Genomics platform using CD8+ T cells isolated from pre and post STK-012 treated patient PBMCs.
- Pharmacokinetic (PK) and Pharmacodynamic (PD) data are presented for subjects receiving STK-012 Q3W only (except for TCR Seq), while correlative data are presented for all evaluable subjects in the analysis set (Q3W and QW).
- Best overall response (BOR)*, progression free survival and adverse event assessment is as of July 17, 2024.

STK-012 PK & Cytokine PD Data

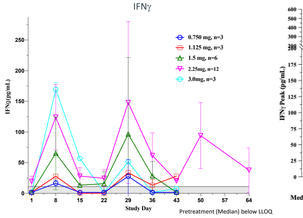
Serum PK

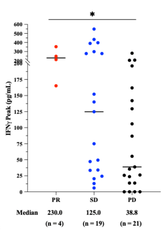
- Exposure increased in linear proportion to dose
- No evidence of time-dependent changes in PK
- Effective Half-life is 5.7 days.



Serum IFNγ PD and correlation to BOR

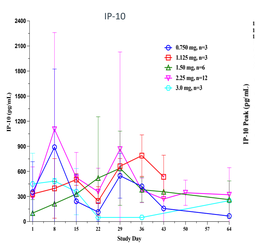
- Sustained Dose Dependent Serum IFNγ induction
- Serum IFNγ peak correlated to improved BOR

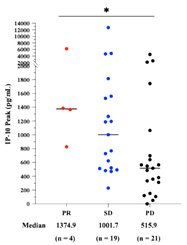




Serum IP-10 (CXCL10) PD and correlation to BOR

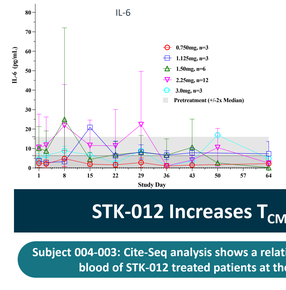
- Serum IP-10 increase across STK-012 dose levels
- Serum IP-10 peak is correlated to improved BOR





Serum IL-6

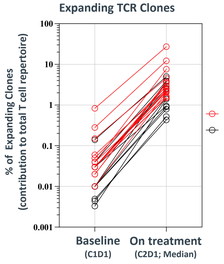
- Limited serum IL-6 increase across dose levels



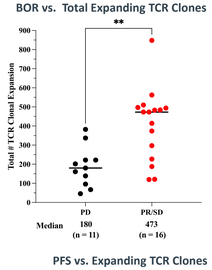
STK-012 Drives TCR Clonal Expansion

- Significant T cell clonal expansion upon treatment with STK-012 monotherapy (N=27, 80-fold median change)
- Total number of TCR clonal expansion correlated to longer PFS and improved BOR

Expanding TCR Clones



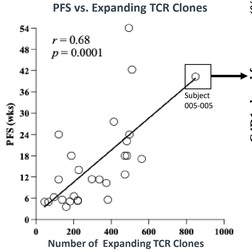
BOR vs. Total Expanding TCR Clones



Expanding TCR Clones		
Median T Cell Burst (%)	Pre-treatment (%)	On-treatment (%)
PR/SD (n = 16)	0.03	2.7
PD (n = 11)	0.01	1.4
All (n = 27)	0.03	2.4

Median fold change for all patients: 80
PR/SD and PD showed significant difference
Pre- ($p < 0.01$) and Post-treatment ($p < 0.05$)
On treatment samples analyzed C2D1(Median), C3D1, C4D1)

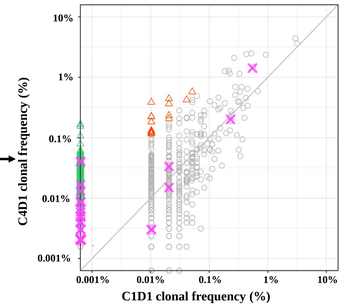
PFS vs. Expanding TCR Clones



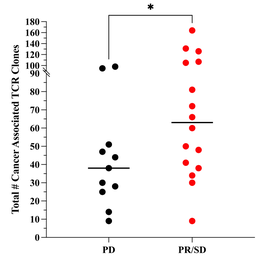
Subject 005-005: STK-012 expands new and existing TCR clones including cancer associated MIRA TCR clones

Clinical Background:
- 49-year-old male with Stage IV MSI-H HNSCC
- Treated with STK-012 0.75mg QW after progressing on 2 prior lines: pembrolizumab → atezolizumab + anti-TIGIT antibody
- Subject achieved stable disease (best TL change -20%) for 9 months and came off study for unrelated AE.
- ctDNA reduction of 77% and 83% after 5 and 10 cycles of STK-012, respectively

Clonal Expansion Observed:
- A total of 848 TCRs were expanded, consisting of 832 newly detected ones and 16 that showed ≥ 10-fold increase
- Very few clones contracted. Simpson clonality increased (C1D1: 0.05; C4D1:0.084)
- A total of 36 known cancer-associated MIRA TCR clones (see right side panel) were expanded within the repertoire. Of a total of 41 known cancer associated clones 88% were expanded in the C4D1 sample, compared to the baseline (C1D1).



BOR vs. Expanding Cancer Associated MIRA TCR Clones

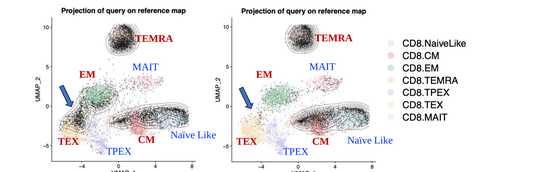


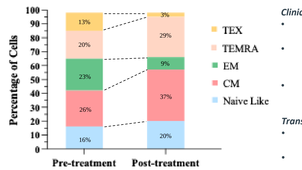
Cancer Associated Clones were identified by Comparing the TCR repertoire of patients to TCRs identified by Adaptive Bio in "Multiplexed Identification of T-cell Receptor Antigen Specificity Assay" (MIRA) TCR Sequencing for Cancer Association:
- MIRA TCRs associated with cancer epitopes were found with increased frequency in expanded T cell clones.
- MIRA clones associated with viral epitopes were also analyzed but were not associated with expanded T cell clones.

Methods:
Clonal Expansion: Patient samples (pre-treatment (C1D1) or on treatment (C2-C4D1; Median C2D1)) were subjected to deep TCR sequencing at Adaptive Biotechnologies. Clonotypes expanding ≥ 10-fold or newly detected TCR clonotypes with ≥5 copies detected were considered "expanding". Clonotypes contracting ≥ 10-fold or clones with ≥ 5 copies becoming undetectable are considered "contracting" TCR clones. Very few clones were contracting.
Cancer Associated TCRs: MIRA is a high-throughput assay that helps identify the antigen-specificity of T-cell receptors (TCRs) in the context of antigen pools, such as cancer cells, oncogenes and cancer antigens or viral antigens. Using Adaptive TCR sequencing, this method detects TCRs that have been identified as reactive to cancer-related antigens by using large pools of overlapping peptide fragments derived from tumor antigens. These TCRs are assessed for their ability to recognize specific tumor antigens, which provides insights into the clonal expansion of T-cells and the immune response to cancer.

STK-012 Increases T_{CM} and T_{EMRA} CD8 T Cells

Subject 004-003: Cite-Seq analysis shows a relative increase of T_{CM} and T_{EMRA} Phenotypes in the blood of STK-012 treated patients at the expense of of exhausted CD8+ T cells





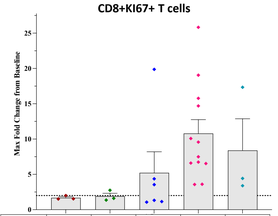
Clinical Background:
- 71-year-old male with Stage IV Malignant Melanoma
- Treated with STK-012 0.375mg QW after progressing on 5 prior lines including PD-1 and CTLA-4 blockade
- Subject was on treatment with stable disease for 4 months before progressing

Translational Findings:
- Tex (exhausted CD8+ T cells) decreased from 13% to 3%
- CM (central memory T cells) increased from 26% to 37%

STK-012 Induces CD8 T Cell Activation/Expansion

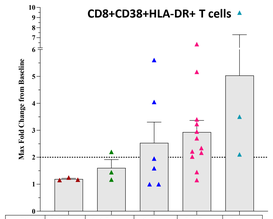
- Dose dependent increase in CD8+KI67+ and CD8+CD38+HLA-Dr+ T cells
- Max fold change (FC) CD8+CD38+HLA-DR+ T cells is correlated to improved BOR
- Limited expansion of Tregs and NK Cell[5]

CD8+KI67+ T cells



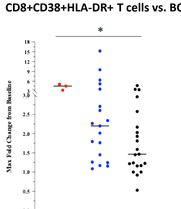
DL	0.75mg	1.125mg	1.5mg	2.25mg	3.0mg
FC ≥ 2.0	0/3	1/3	3/6	12/12	3/3

CD8+CD38+HLA-DR+ T cells



DL	0.75mg	1.125mg	1.5mg	2.25mg	3.0mg
FC ≥ 2.0	0/3	1/3	2/6	10/12	3/3

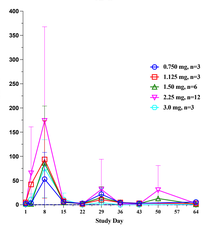
CD8+CD38+HLA-DR+ T cells vs. BOR

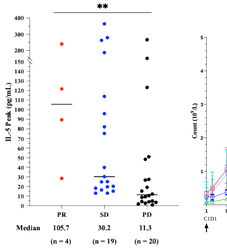


STK-012 Induces IL-5 and Eosinophil Increase which is Correlated to BOR and Not to Capillary Leak

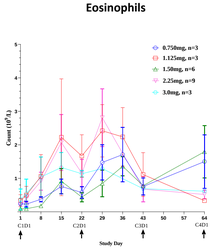
- STK-012 use resulted in a dose dependent increase in serum IL-5
- Serum IL-5 peak is correlated to improved BOR
- Peripheral eosinophils were increased across STK-012 Q3W dose levels
- Despite eosinophil elevations, no subjects experienced Capillary leak and very few had associated TRAEs (Table 1)

IL-5





Eosinophils



Eosinophils vs TRAE

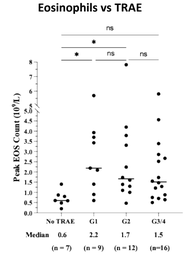


Table 1. Capillary Leak associated TRAEs on STK-012 monotherapy, N=47

TRAE	All Grade, N (%)	Grade ≥3, N (%)
Hypotension	2 (4.3)	0
Pyrexia	2 (4.3)	0
Flu-like symptoms	2 (4.3)	0
Peripheral edema	2 (4.3)	0
CRS	1 (2.1)	0
Creatinine ↑	1 (2.1)	1 (2.1)
CLS	0	0
LFT increase	0	0
Lymphopenia	0	0

Conclusions

- STK-012 induced peripheral IFNγ, T-cell proliferation and clonal expansion, consistent with selective expansion of antigen-activated T-cells.
- These endpoints correlated with improved outcomes on study.
- STK-012 demonstrated a PK and cytokine PD profile which supports selectivity for antigen-activated T-cells and is distinct from that of aldesleukin and non-α-IL-2 analogues.
- Further development is warranted and enrollment in Phase 1a/b cohort of STK-012 + Pembrolizumab + Pemetrexed + Carboplatin in 1L NSCLC is ongoing (NCT05098132).

References:
1. Izar B. et al. Cancer Res (2024) 84 (7_Supplement): CT183.
2. Raeber ME et al. The Lancet. 2023;90: 104539

#: Note: 31 subjects are represented on this waterfall plot. 9 efficacy evaluable subjects are not represented due to (1) Clinical PD before 1st scan OR (2) target lesions not evaluable at baseline OR (3) discontinued due to related AE prior to scans OR (4) BOR NE with no other evaluable scan timepoints. - Subjects are censored after the first reporting of radiographic or clinical PD.
* Indicates subjects who are ongoing treatment,^ indicates subjects who are IO Naive.

##: Note: 12 subjects are represented on this waterfall plot. 3 efficacy evaluable subjects are not represented due to (1) Clinical PD before 1st scan.
- Subjects are censored after the first reporting of radiographic or clinical PD.
* Indicates subjects who are ongoing treatment as of the data extract date .

* Of 4 Partial Responders represented in BOR plots, 3 were confirmed, 1 was unconfirmed