CT244: A Phase 1a/1b study of STK-012, an α/β IL-2 receptor selective partial agonist as monotherapy and in combination with pembrolizumab in advanced solid tumors (NCT05098132)

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BACKGROUND

- High dose intravenous (IV) interleukin-2 (IL-2) induces complete responses in certain cancers, but its use is limited due to toxicities including severe hypotension and capillary leak syndrome (CLS), and the requirement for inpatient administration.
- Recent approaches to develop IL-2 therapies with an expanded therapeutic index have targeted the dimeric form (β/γ) of the IL-2 receptor, which is predominantly expressed on naïve T cells and NK cells, rather than the high affinity trimeric form (α/β/γ), which is highly expressed on antigen activated T cells and constitutively expressed on Tregs.
- STK-012 is a pegylated, α/β IL-2R selective partial agonist engineered to preferentially stimulate antigen-activated T cells and avoid systemic NK and naïve T cell activation.

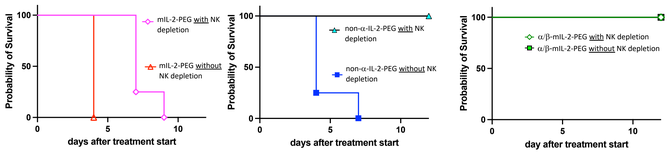
IL-2R Targeting Approaches

	1st Generation	2nd Generation Engineered IL-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 binding IL-2Rα	Reduced binding to IL-2Rγ
Cell Selectivity	No selectivity	NK cells and naïve T cells	Antigen activated T cells > Tregs

Pre-Clinical Rationale

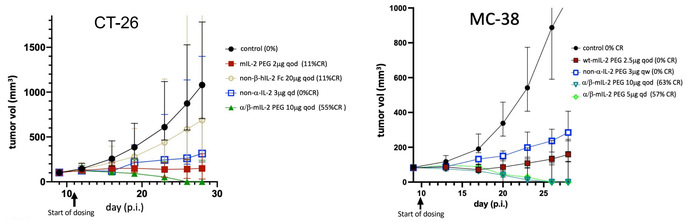
- In syngeneic tumor models, subcutaneously (SQ) injected STK-012 mouse surrogate (α/β-mIL2 PEG) demonstrated reduced toxicities and improved efficacy relative to mouse mIL-2 PEG and non-α IL-2 PEG (Figures 1 & 2). [1]
- In cynomolgus monkeys, acute lung inflammation was induced by aldesleukin and non-α-IL-2, but not by STK-012.[1]
- STK-012 mouse surrogate induced a greater CD8 expansion and higher CD8/Foxp3 ratio relative to mIL-2 PEG and non-α IL-2 PEG in MC38 colon cancer model (Figure 3)

Figure 1: IL-2 induced acute toxicity model



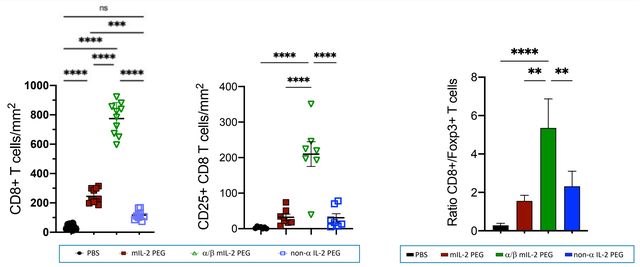
- To confirm that IL-2 toxicity is driven by NK cell stimulation, mice were depleted of NK cells (using anti-NK1.1) and treated with α/β-mIL-2-PEG (20μg), non-α-IL-2-PEG (3μg) or mIL-2-PEG (10μg).
- NK cell depletion prevented or reduced IL-2 mediated lethality in mIL-2-PEG or non-α-IL-2-PEG.
- Mice treated with α/β-mIL-2-PEG had no lethality.

Figure 2: Efficacy in mouse models



- Dosing: wt-mIL-2 PEG, non-α-IL-2 and non-α-IL-2 PEG were dosed at MTD (qd: daily; qod: every other day; qw: weekly)
- Tumor volumes plotted post tumor inoculation

Figure 3: Pharmacodynamics in MC38 colon cancer model



- Dosing: mIL-2-PEG (2.5μg every other day), non-α-IL-2-PEG (3μg weekly), α/β-mIL-2-PEG (10μg every other day).

STK-012-101 FIH STUDY

- This is a first-in-human, open-label, dose escalation and expansion study in adults with advanced solid tumors.
- The objectives of this study are to evaluate the safety, pharmacokinetics, immunogenicity, preliminary efficacy, and pharmacodynamics of STK-012 as monotherapy and in combination with pembrolizumab.
- Dose escalation will follow a standard 3+3 design for STK-012 monotherapy and in combination with pembrolizumab. STK-012 will be dosed SQ weekly, and pembrolizumab will be dosed IV every 3 weeks.

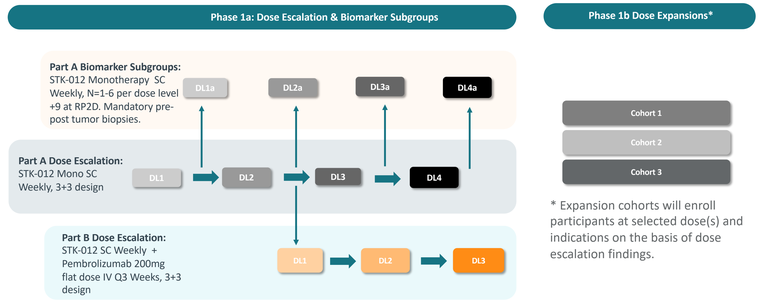
Eligibility

Eligible Tumor Types

Patients who are relapsed/ refractory to, intolerant to, or refuse standard of care treatment for the below tumor types:

- Metastatic Melanoma
- Squamous Cell Carcinoma of the Head and Neck
- Non-Small Cell Lung Cancer
- Renal Cell Carcinoma
- Ovarian Cancer
- Cervical Cancer
- MSI-H/dMMR (microsatellite instability-high or mismatch repair deficient) cancers

Study Schema



* Expansion cohorts will enroll participants at selected dose(s) and indications on the basis of dose escalation findings.

Phase	Primary Objective	Primary Endpoint
1a	To assess the safety, tolerability of STK-012 monotherapy and in combination with pembrolizumab	Including but not limited to DLTs TEAEs, SAEs, deaths, and clinical laboratory abnormalities per NCI CTCAE v5.0
1b	To assess the safety and tolerability of STK-012 in combination with pembrolizumab at the RP2D	Including but not limited to DLTs TEAEs, SAEs, deaths, and clinical laboratory abnormalities per NCI CTCAE v5.0 at RP2D

- Preliminary efficacy will be assessed as a secondary endpoint include assessments of tumor response according to RECIST v1.1.
- Exploratory biomarker assessments will include peripheral and tumor measures of immune cell populations and relevant gene/protein expression.

Study Information

- Enrollment in STK-012 monotherapy dose escalation has been initiated.
- The trial is registered with Clinicaltrials.gov, NCT05098132

References

1. Emmerich J, et al. STK-012, an alpha/beta selective IL-2 mutein for the activation of antigen-activated T cells in solid tumors. Poster # 1744, Presented at American Association of Clinical Research, 2021