KCRS 24 Kidney Cancer Research Summit

STK-012: a First-in-Class α/β IL-2 Receptor Biased Partial Agonist in Advanced Solid Tumors

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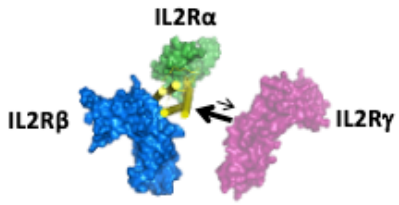
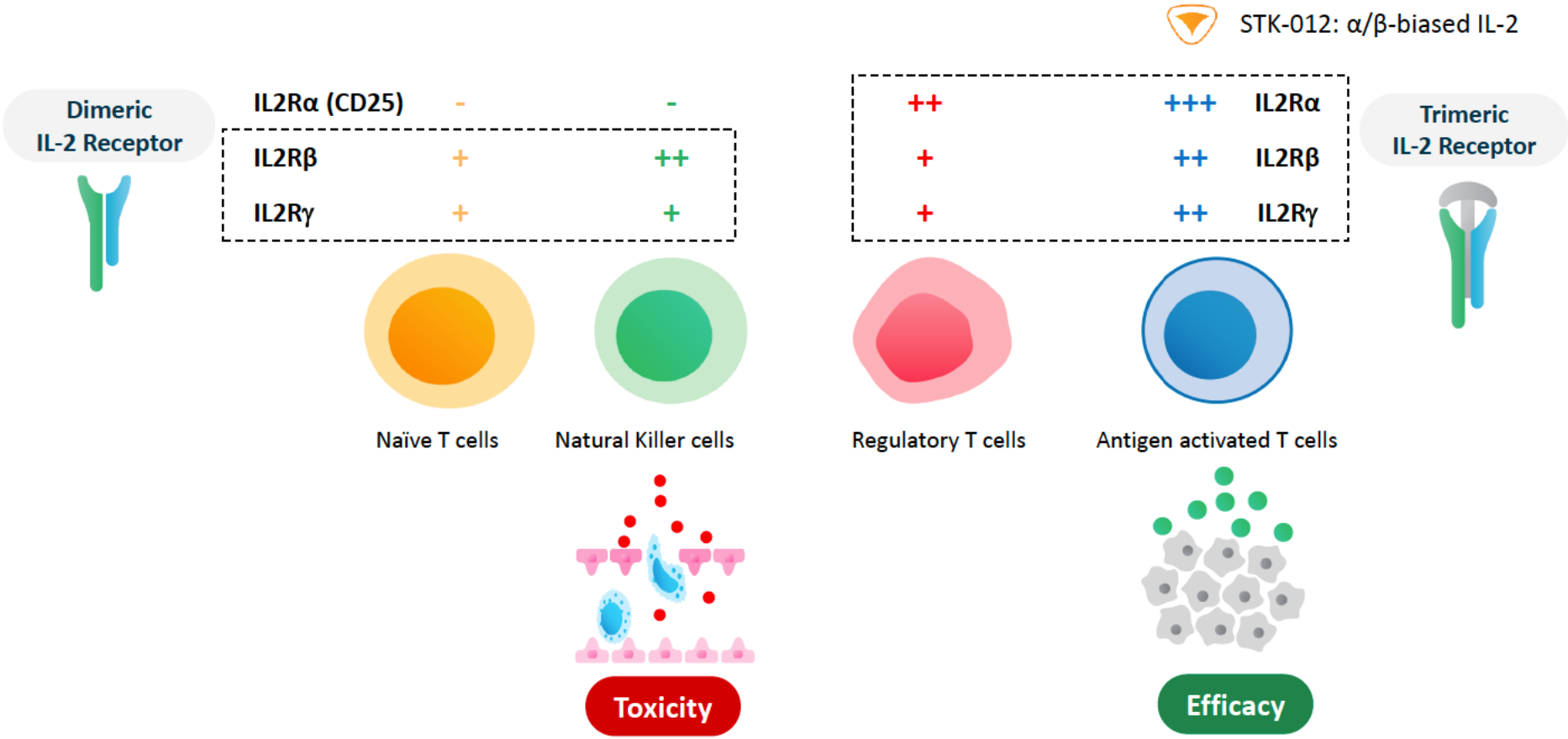
STK-012: Next Generation Pegylated α/β IL-2 Receptor Partial Agonist



	1st Generation IL-2: (Proleukin®)	2nd Generation Engineered IL-2: (NKTR-214, THOR-707, etc.)	Next Generation Engineered IL-2: STK-012
Design	High Dose IL-2	"Non-α" IL-2	**α/β-biased IL-2**
IL-2R Bias	Binds to high & intermediate affinity IL-2Rs	Binds selectively to dimeric intermediate affinity IL-2R	Binds selectively to trimeric high affinity 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

STK-012 is Designed to Decouple Efficacy and Toxicity, Based on Expression of IL-2 Receptors



STK-012-101: a Phase 1a/1b study of STK-012 Administered Subcutaneously in Advanced Solid Tumors

Monotherapy Escalation		Combination Escalation
STK-012 monotherapy 0.375 mg QW	STK-012 monotherapy 0.75 mg Q3W	STK-012 + pembro 0.375 mg Q3W
STK-012 monotherapy 0.75 mg QW	STK-012 monotherapy 1.125 mg Q3W	STK-012 + pembro 0.75 mg Q3W
	STK-012 monotherapy 1.5 mg Q3W	STK-012 + pembro 1.125 mg Q3W
	STK-012 monotherapy 3 mg Q3W	STK-012 + pembro 1.5 mg Q3W
Candidate RP2D	STK-012 monotherapy 2.25 mg Q3W	STK-012 + pembro 2.25 mg Q3W

Ongoing Dose Expansions

- STK-012 monotherapy 2.25 mg Q3W NSCLC (1-2 priors)
- STK-012 monotherapy 2.25 mg Q3W ccRCC (1-2 priors)

STK-012 Ph1a Monotherapy Baseline Disease Characteristics, N=47	
Prior lines in advanced setting	
1	10 (21.3)
2	9 (19.1)
≥3	28 (59.6)
Prior immune checkpoint inhibitor	
0	10 (21.2)
≥1	37 (78.7)
Disease type	
NSCLC	15 (31.9)
ccRCC	6 (12.8)
Ovarian	6 (12.8)
Mucosal Melanoma	4 (8.5)
Other	13 (27.7)

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STK-012 Monotherapy Ph1a Safety

- Treatment-related adverse events (TRAEs) were reversible with standard management (eg, dose hold/reduction, supportive meds).
- No CLS and very few associated TRAEs.
- No DLTs during the DLT period (Cycle 1 [21 days]).
- The majority of TRAEs were Grade 1 or 2;
  - 1 subject experienced a Grade 4 TRAE (anaphylactic reaction-resolved same day) and
  - no subjects experienced Grade 5 TRAEs.
- All 3 subjects treated at the maximum dose of 3 mg Q3W experienced Grade 3 GI SAEs (Small bowel Obstruction, Enterocolitis, Vomiting) in Cycle 2 (after the DLT period).
- An intermediate dose of 2.25 mg Q3W was then explored and selected as candidate RP2D.

Most Common TRAEs (in ≥10% of subjects) on STK-012 monotherapy, N=47

TRAE	All Grade, N (%)	Grade ≥3, N (%)
Rash maculo-papular	19 (40.4)	5 (10.6)
Fatigue	12 (25.5)	1 (2.1)
Injection site reaction	11 (23.4)	0
Nausea	11 (23.4)	1 (2.1)
Diarrhea	9 (19.9)	2 (4.3)
Pruritis	7 (14.9)	0
Vomiting	6 (12.8)	2 (4.3)
Arthralgia	5 (10.6)	1 (2.1)
Total (TRAEs)	**37 (78.7)**	**15 (31.9)**

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 Increase	1(2.1)	1(2.1)
CLS	0	0
LFT increase	0	0
Lymphopenia	0	0

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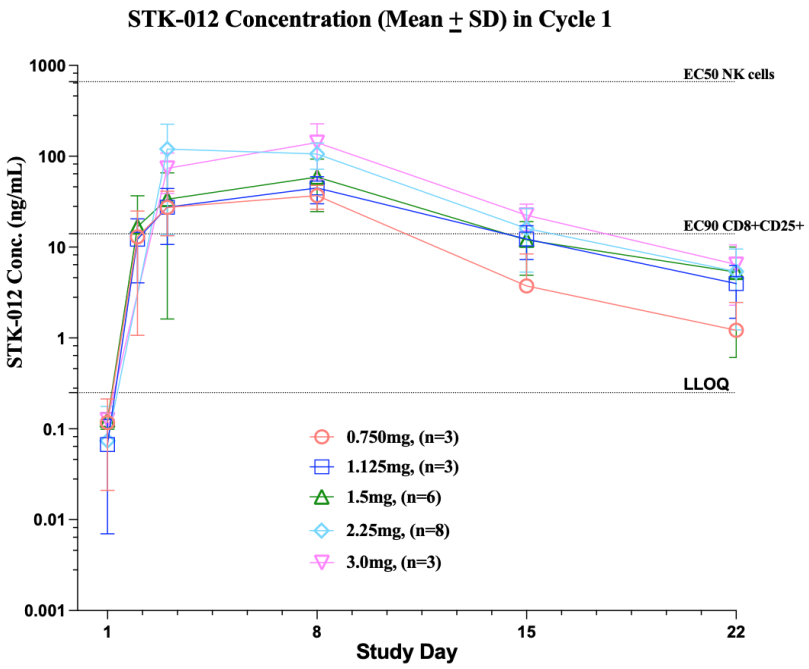
STK-012 Monotherapy Ph1a PK-PD

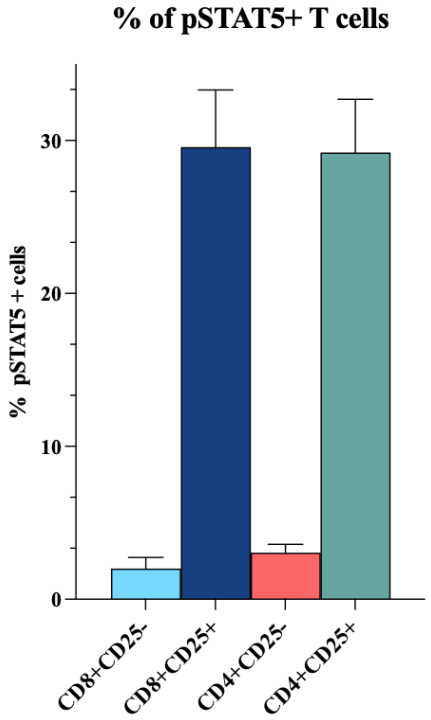
PK

- Observed Half-life is ~4 days.
- Exposure (AUC) is dose proportional.



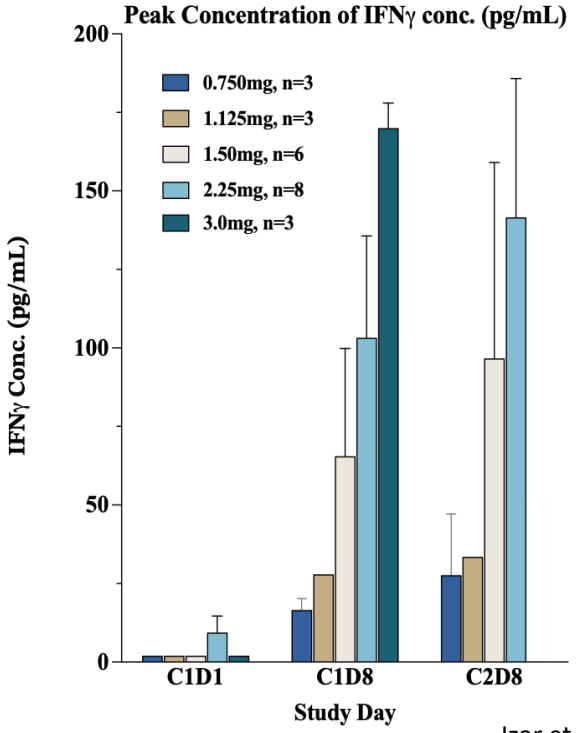
pSTAT5

- STK-012 demonstrates selectivity for T cells that express CD25 (IL-2Rα).



Serum IFNγ

- Serum IFNγ is dose dependent and peaks approximately at STK-012 T_{max} (~8 days).



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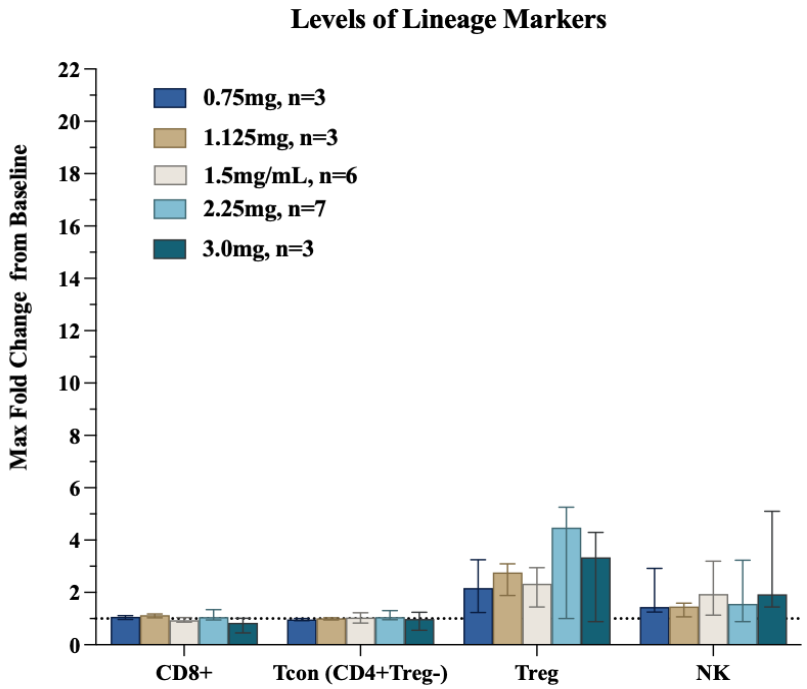
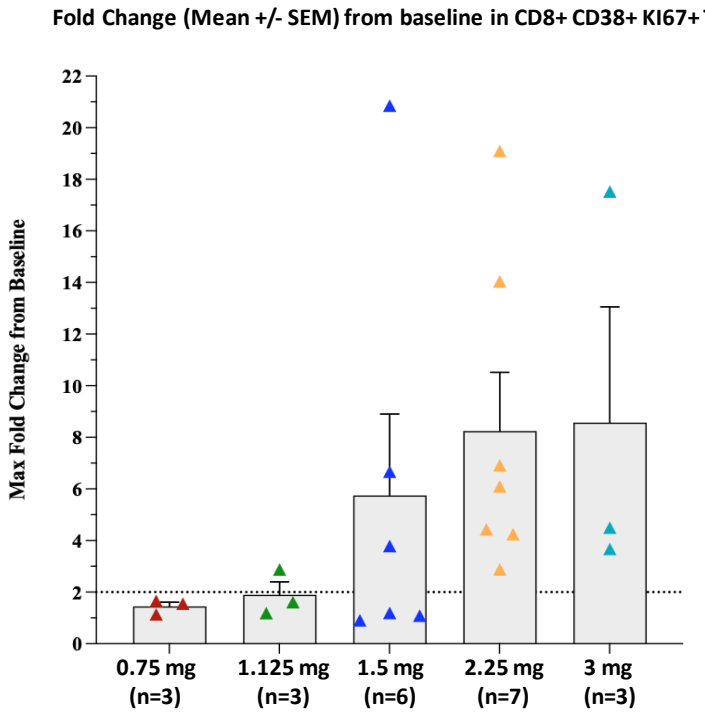
STK-012 Monotherapy Ph1a PD: Selectivity for Antigen Activated CD8 T cells

- Peripheral Flow Cytometry showed that STK-012 has limited increase in broad lymphocyte populations.



- Activated (CD38+), proliferating (KI67+), CD8 T cells increased in a dose dependent manner.



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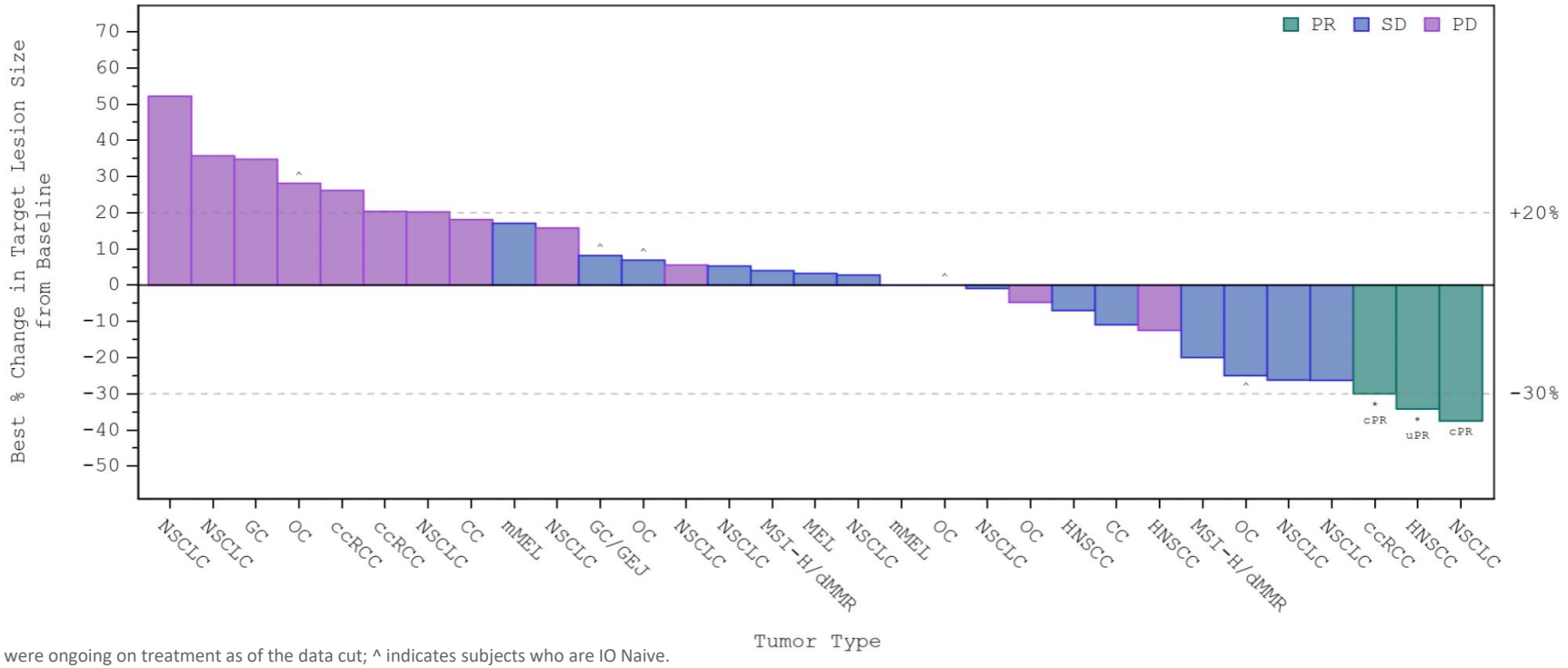
STK-012 Monotherapy Ph1a Efficacy

- Of 40 efficacy evaluable subjects, 3 had partial response (PR) and 12 had stable disease (SD) as their best overall response (BOR) by RECIST V1.1.
- The partial responses included 2 confirmed (anti-PD-1 pretreated NSCLC and RCC) and 1 unconfirmed (anti-PD-1 pretreated HNSCC).



* Indicates subjects who were ongoing on treatment as of the data cut; ^ indicates subjects who are IO Naive.

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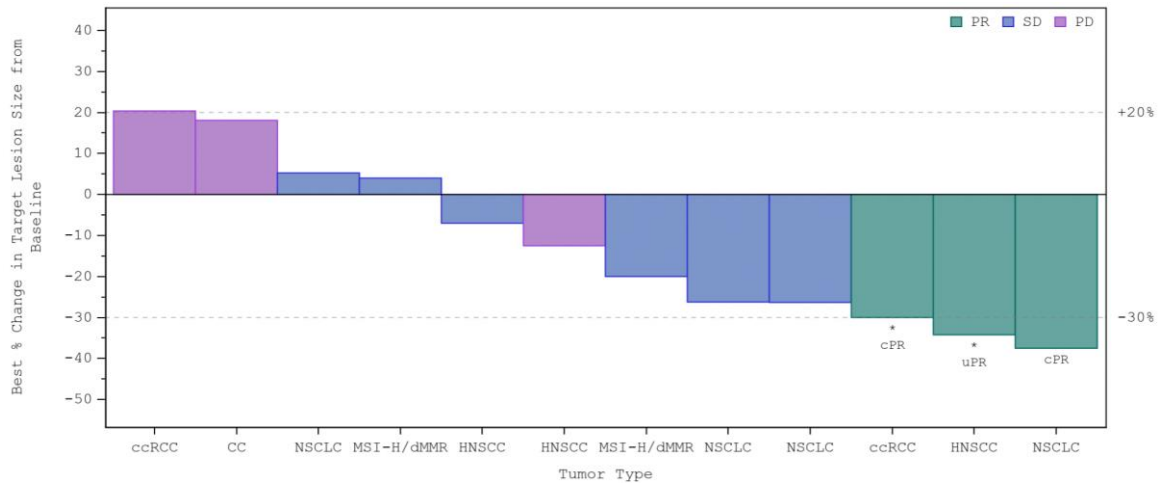
STK-012 Monotherapy Ph1a Efficacy

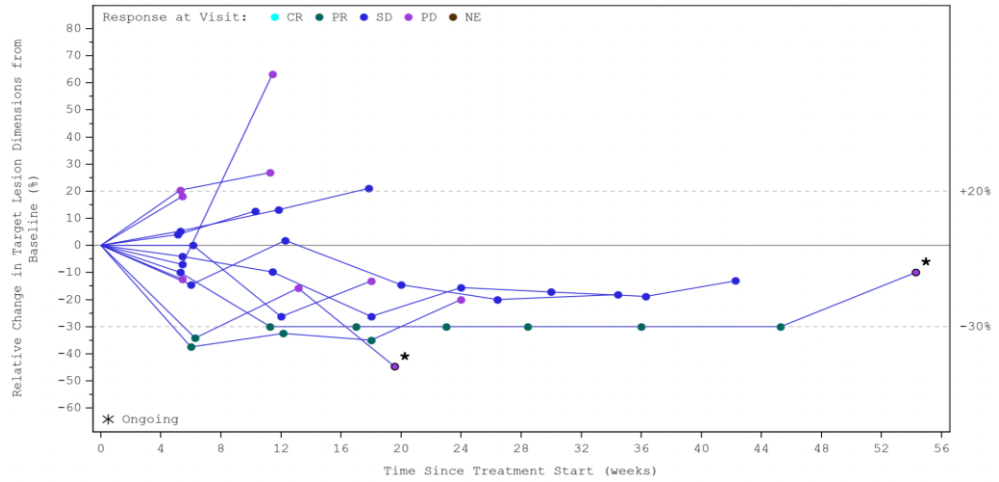
Greater Efficacy in IO Pretreated Subjects With 1-2 Prior Lines

- In subjects who progressed on/after prior immunotherapy who also had 1-2 prior lines in the advanced setting (N=15 efficacy evaluable), 3 had BOR of PR and 6 BOR of SD.
- Durability of effect was observed in multiple subjects with BOR of SD and the ccRCC responder who maintained response for >9 months.

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



Spider for Ph1a Monotherapy (IO Pretreated with 1-2 Prior Lines)



* Indicates subjects who are ongoing treatment as of the data cut

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STK-012 Monotherapy RCC Response in Ongoing Phase 1b Dose Expansion

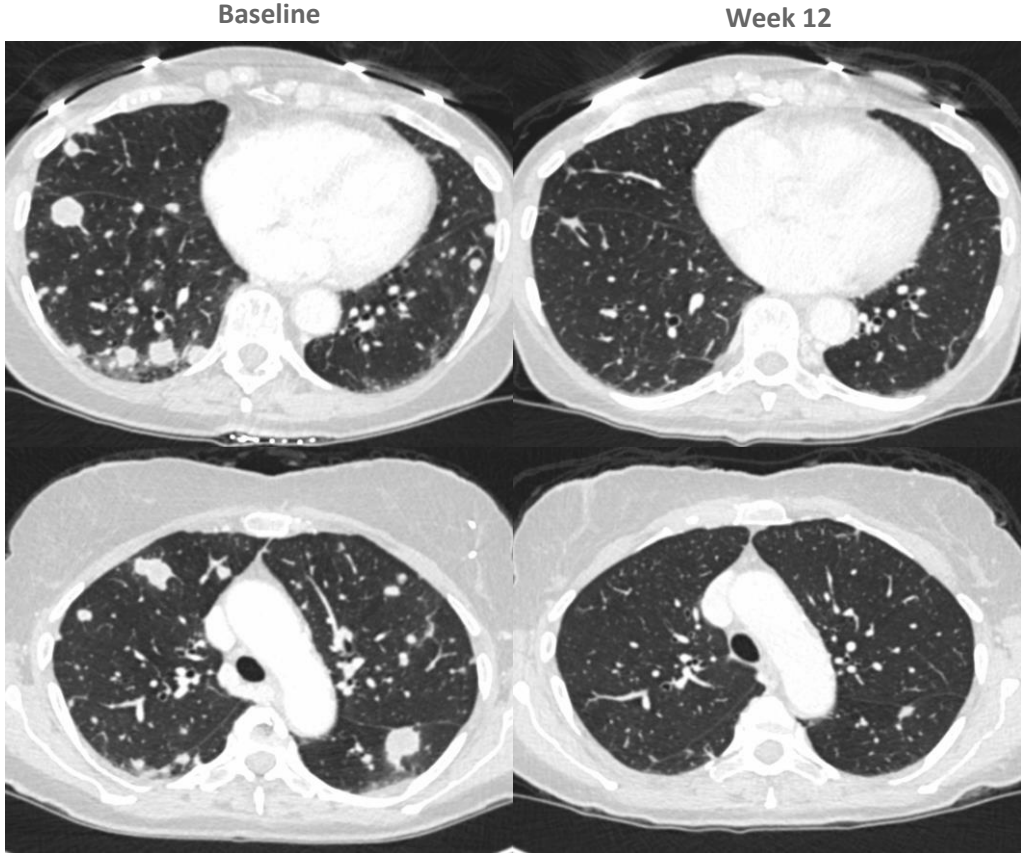
Subject History: 72-year-old female with Stage IV ccRCC and 2 prior lines of therapy before receiving STK-012 monotherapy

Prior lines:

1. Nivolumab + ipilimumab: Aug 2022-Mar 2023 (BOR: cPR)
2. Cabozantinib + Nivolumab: Apr 2023 – Aug 2023 (BOR: PD)

STK-012 Tumor Response: Baseline: Subject enrolled with ”innumerable” lung metastases and a large primary renal mass (non target)

Week	Change From Baseline
6	↓50% (PR)
12	↓80% (cPR)
18	↓85% (cPR)
24	↓76% (PD)



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Conclusions

- In the ongoing STK-012-101 study, monotherapy STK-012 showed favorable safety, PK, and PD profiles with distinct differences from aldesleukin and non-α IL-2 analogues.
- Preliminary PK-PD data support selectivity for IL-2R α/β, selective expansion of activated CD8 T cells, and dose dependent serum IFNγ increase.
- Preliminary efficacy with monotherapy STK-012 (3 partial responses in Phase 1a) was observed in subjects who progressed on/after prior immunotherapy.
- Preliminary evidence of activity was observed in the ongoing Phase 1b.
- Further development is warranted and enrollment in STK-012 monotherapy dose expansions (Phase 1b) in ccRCC is ongoing.