STK-012, a First-in-Class α/β IL-2 Receptor Biased Partial Agonist in Advanced Solid Tumors – Initial Results of a Phase 1 study

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Synthekine, Menlo Park, CA

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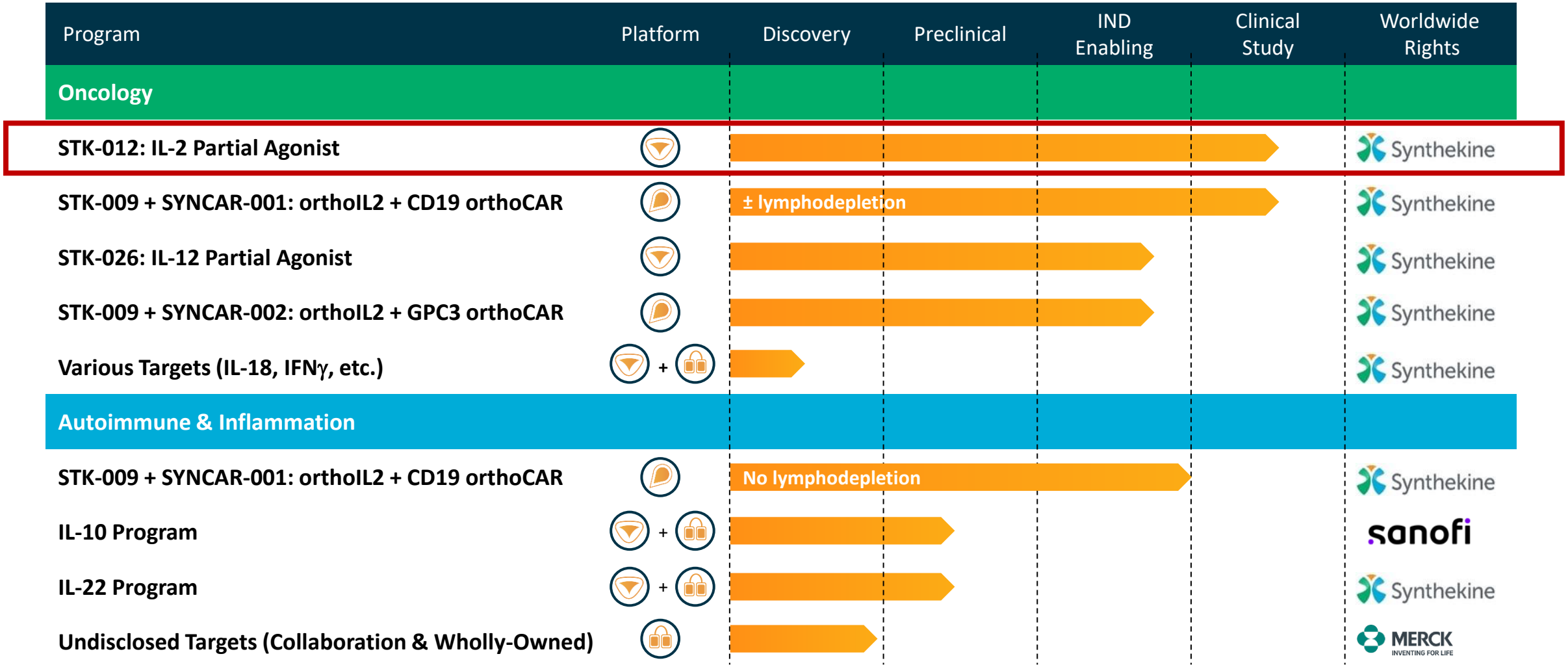
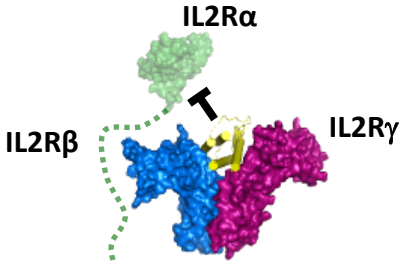
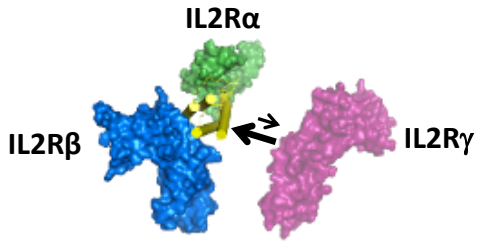
Cytokine Engineering to Increase Therapeutic Utility



Next Generation IL-2: Pegylated α/β-biased STK-012



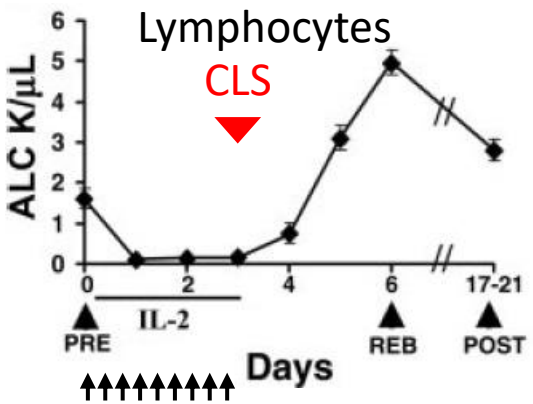


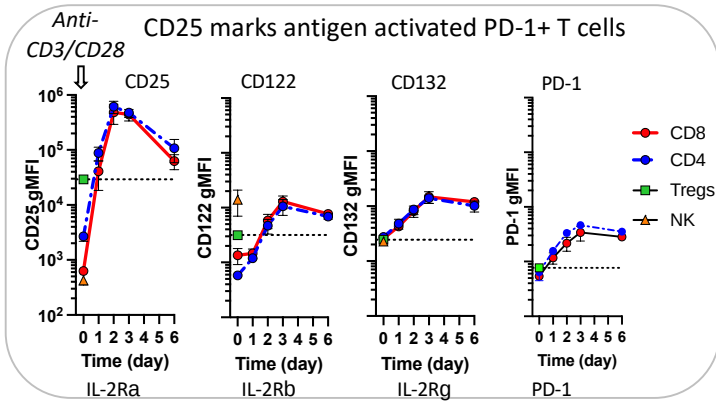
	1st Generation	2nd Generation Engineered IL-2	STK-012
	High Dose IL-2 (Aldesleukin)	"Non-α" IL-2	**α/β- IL-2**
IL-2R Bias	Trimeric >> dimeric IL-2R	Dimeric IL-2 receptor	Trimeric IL-2 receptor
IL-2R subunit sparing	None	Reduced binding IL-2Rα	Reduced binding to IL-2Rγ
Cell Selectivity	Act T cells > Tregs > NK > resting lymphocytes	Act T cells = Tregs = NK = resting lymphocytes	Act T cells > Tregs >>> NK cells and resting lymphocytes

Deep, durable responses in certain patients but limited use given toxicity

Avoids Tregs for anti-tumor function
Avoids eosinophils / endothelial cells?

Avoids NK cells (toxicity)
Targets Activated T cells / Tregs





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α/β-biased IL-2 is Highly Selective for Activated T Cells

Synthekine Approach

STK-012 (α/β-hIL-2)
- Synthekine's IL-2 clinical candidate
- Selective for Rα+ / Rβ+ T cells
- Modulated Rγ binding

α/β-mIL-2-PEG
- Mouse surrogate for STK-012

1st Gen. in Cancer

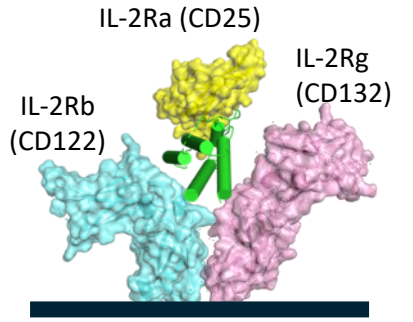
IL-2
- approved in melanoma and RCC (Proleukin®)
- mIL-2-PEG

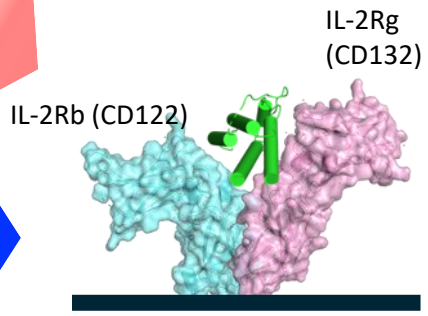
2nd. Gen. in Cancer

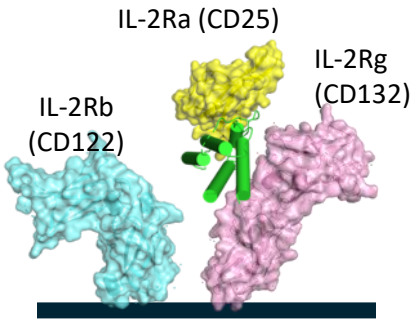
non-α-IL-2-PEG
- Engineered for reduced IL2Rα binding, IL-2 maintains binding selective for Rβ/γ
- Proxy for Super 2, NKTR-214, THOR-707, NL-201, etc.

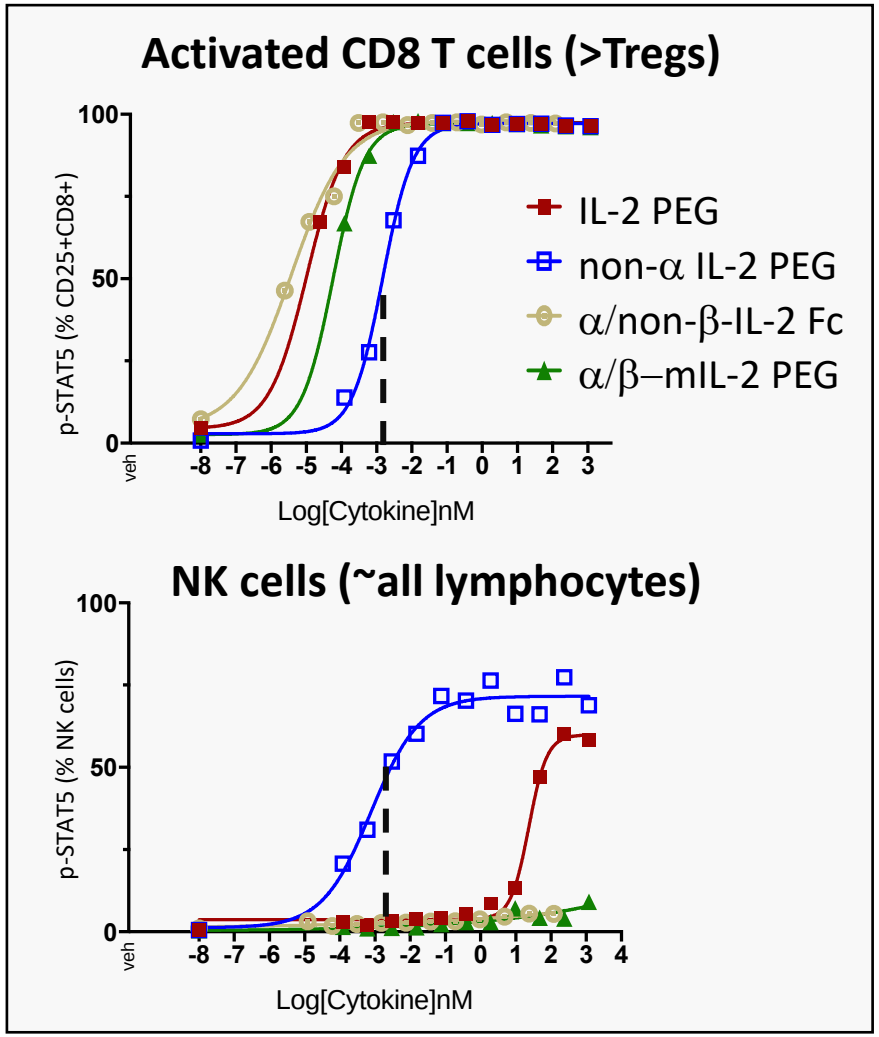
Current Approach in AI

non-β-IL-2 (Treg proliferation)
- Engineered for reduced/no Rβ binding IL-2 maintains binding selective for Rα
- Proxy for N88D, N88R, V91K, D20T, etc.









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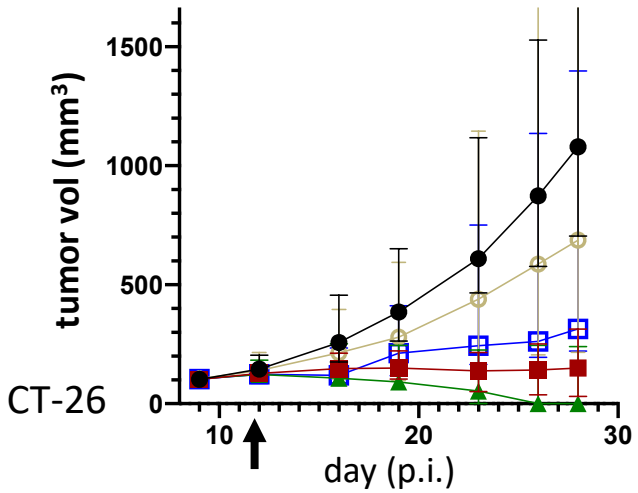
α/β-mIL-2 Retains Efficacy Compared to non-α-IL-2 and WT-IL-2

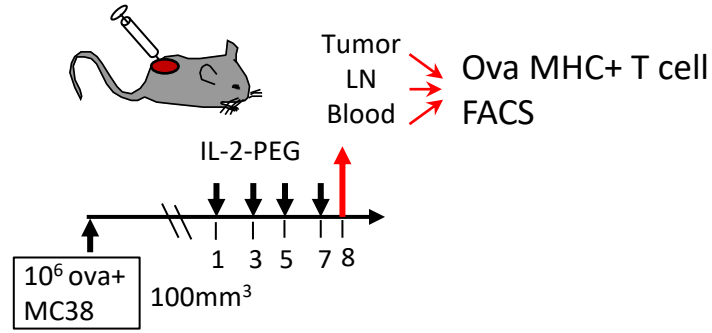
α/β-mIL-2 Retains Efficacy



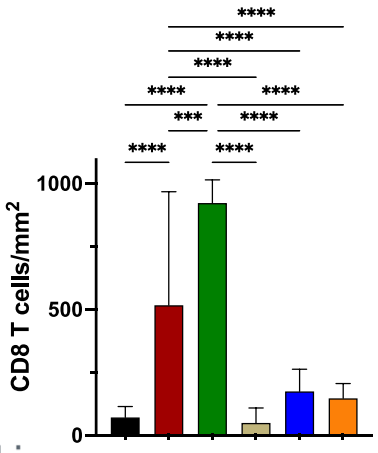
- control (CR 0/9)
- mIL-2 PEG 2μg qod (11%CR)
- non-β-IL-2-Fc 20μg qod (11%CR)
- non-α-IL-2 3μg qd (0%CR)
- α/β-mIL-2 10μg qod (55%CR)

non-α-IL-2 showed significant toxicity after 3 doses (44% death)

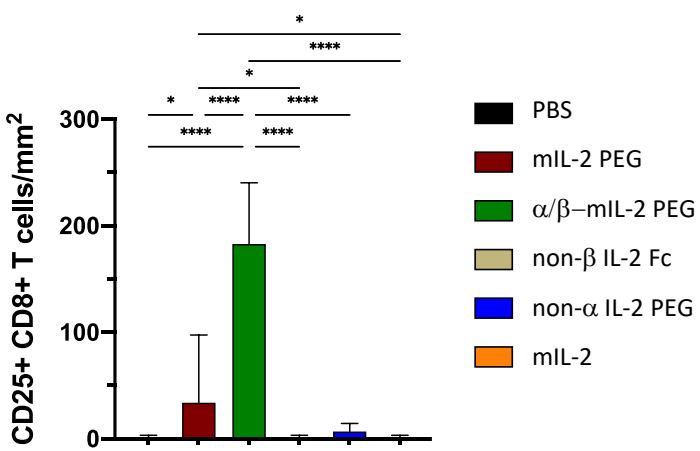
Tumor antigen specific CD8+ T cells are expanded on CD25 binding IL-2



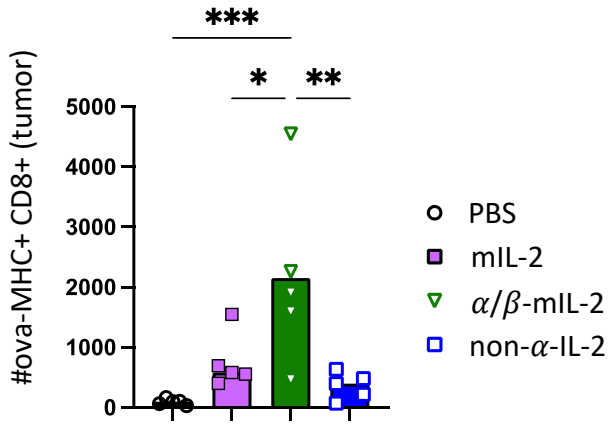
Tumor infiltrating CD8 T cells



Tumor infiltrating CD25+ CD8 T cells



Tumor Antigen specific CD8+ TILs



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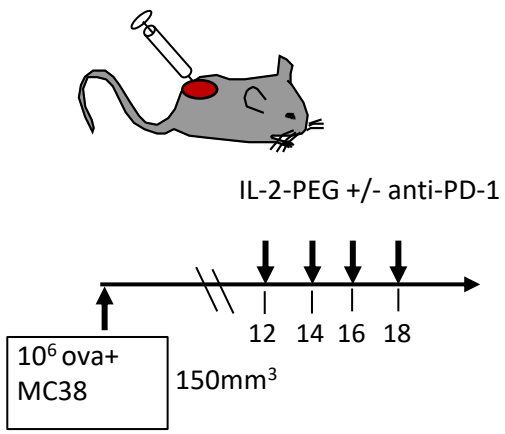
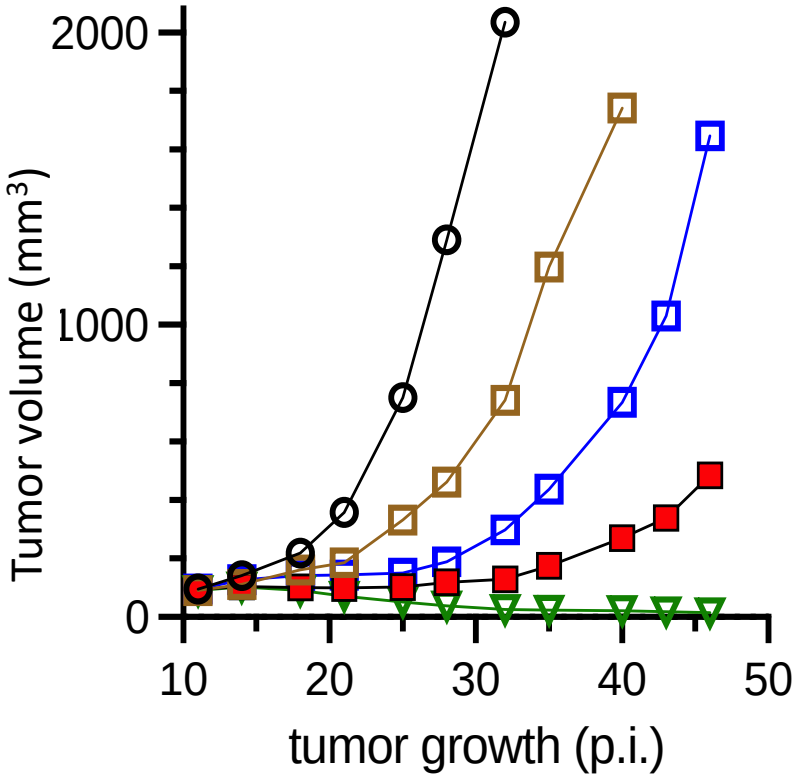
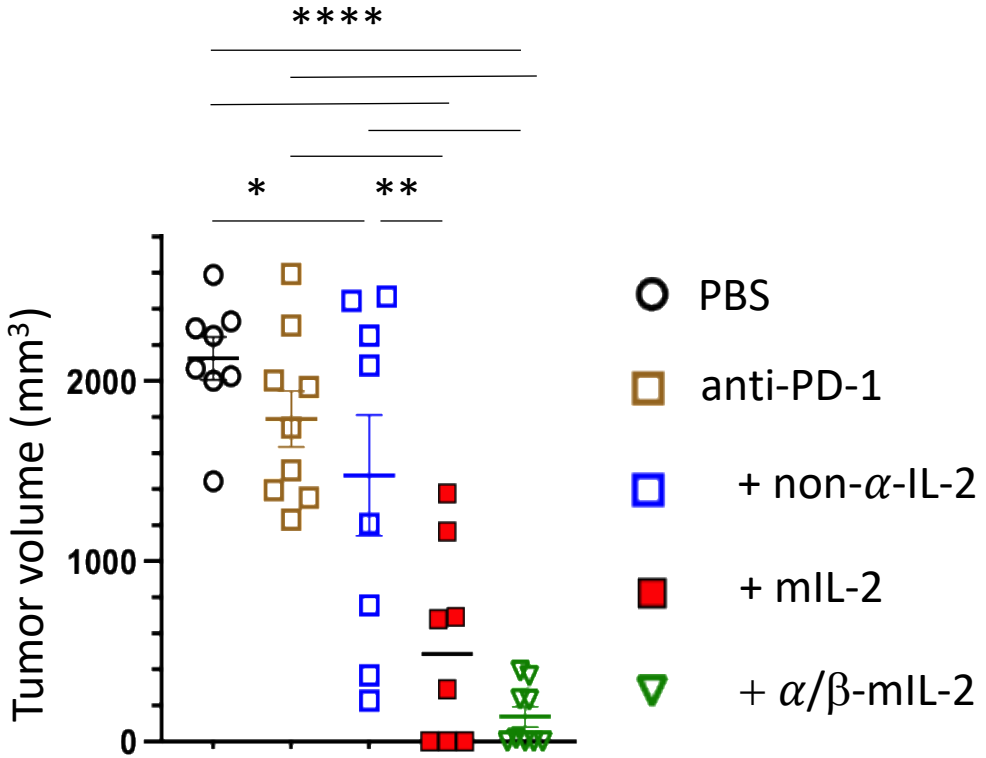
α/β-mIL-2 But Not non-α-IL-2 Combines with anti-PD-1

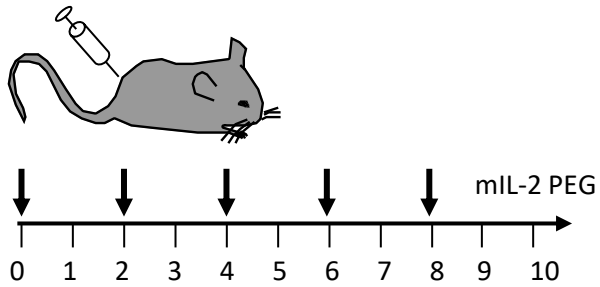




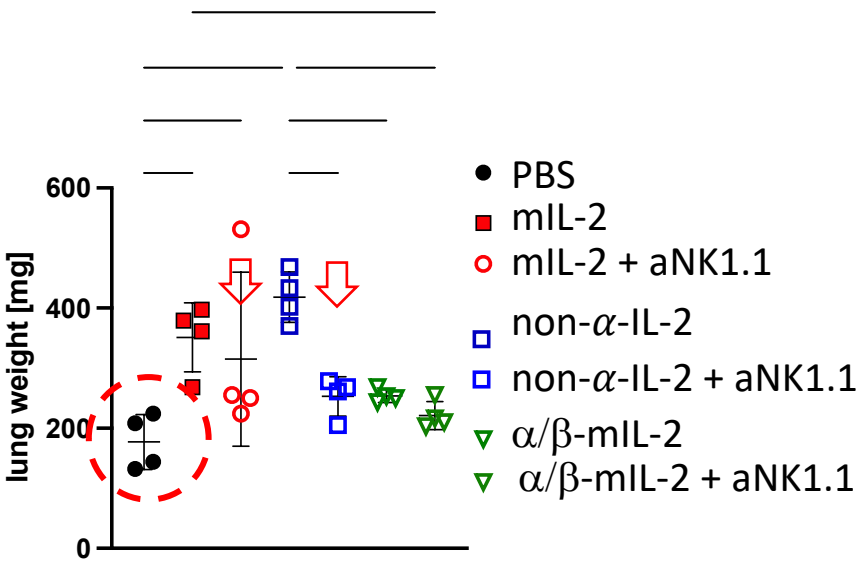


NK Cells Mediate the Capillary Leak Syndrome for WT-IL-2 and non-α-IL-2

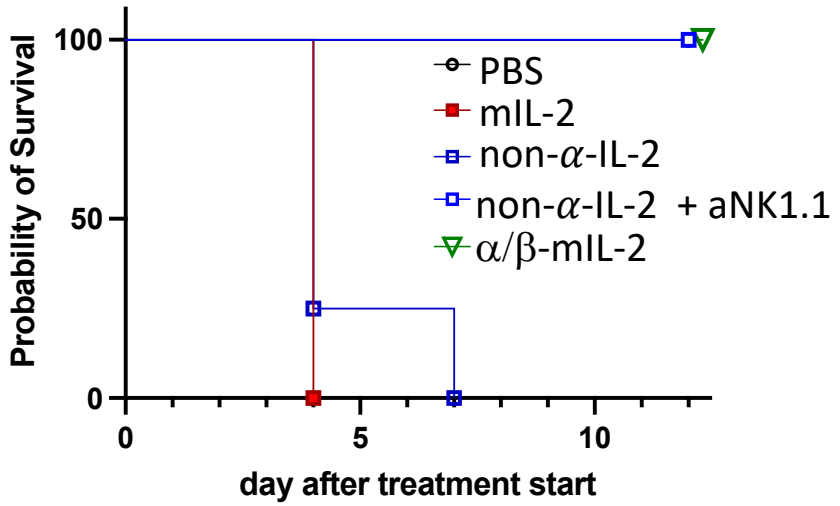
- Wild-Type IL-2 and non-α-IL-2 increase NK cells, T cells and myeloid cells in the lung
- In mice – NK cells depletion (anti-NK1.1) avoids CLS



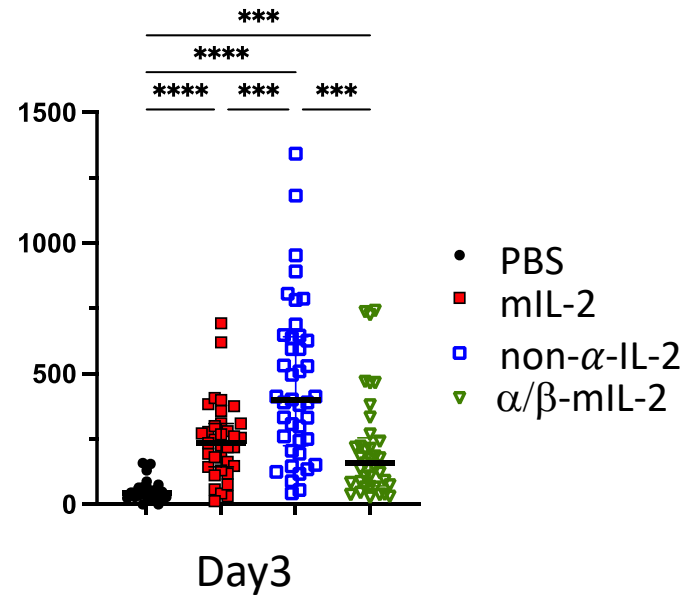
IL-2 Capillary Leak Syndrome



IL-2 Lethality



NK cells in the lung



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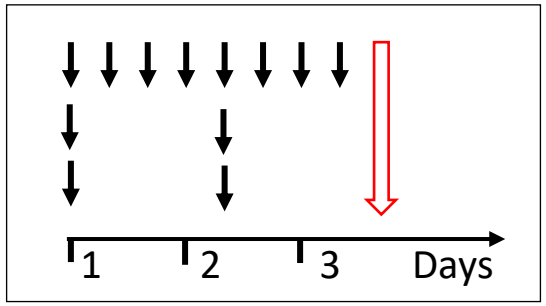
STK-012 Avoids IL-2 Induced Capillary Leak Syndrome in Cynos



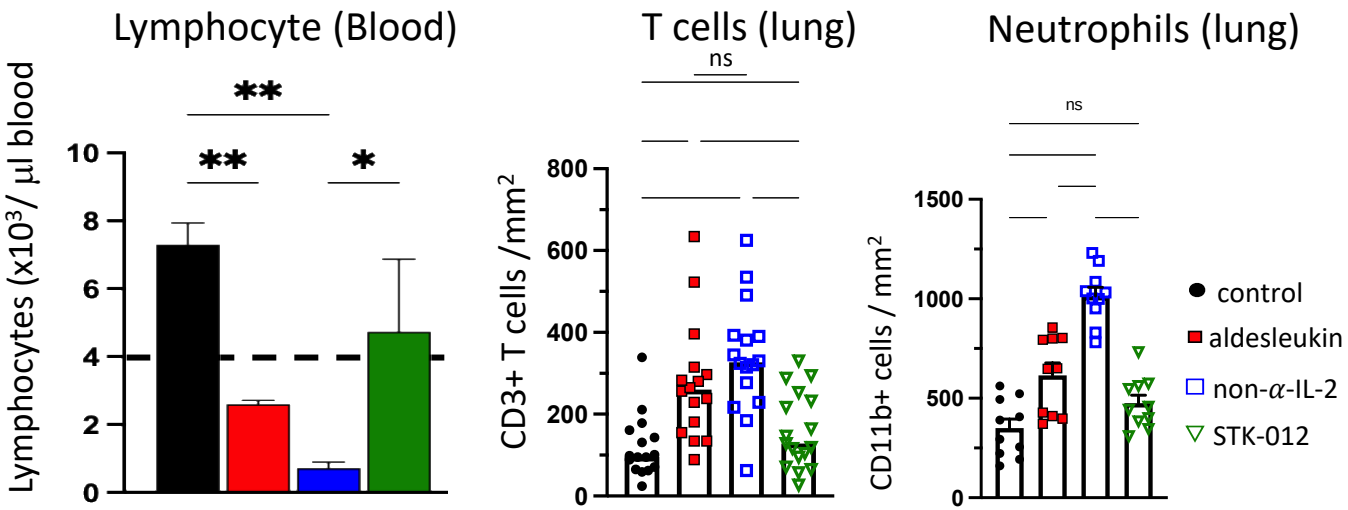
8x Proleukin® (37µg/kg/ 600.00IU/kg, 3x/day IV)

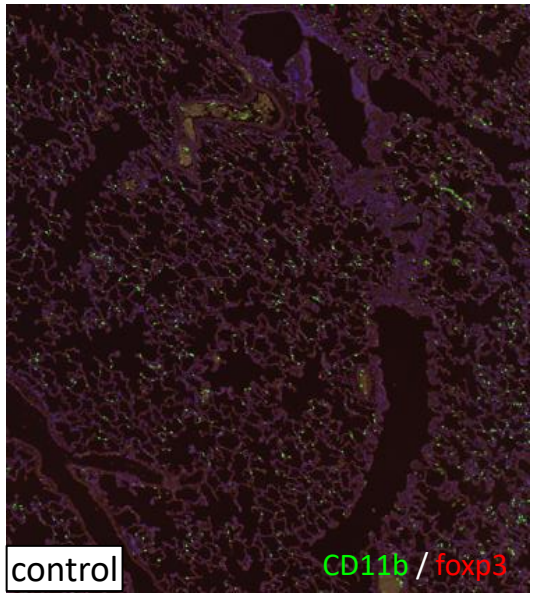
2x non-α-IL-2-PEG

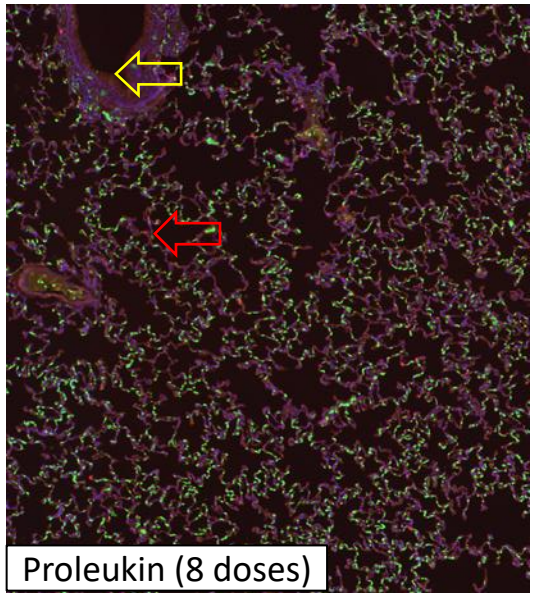
2x STK-012 (PEG)

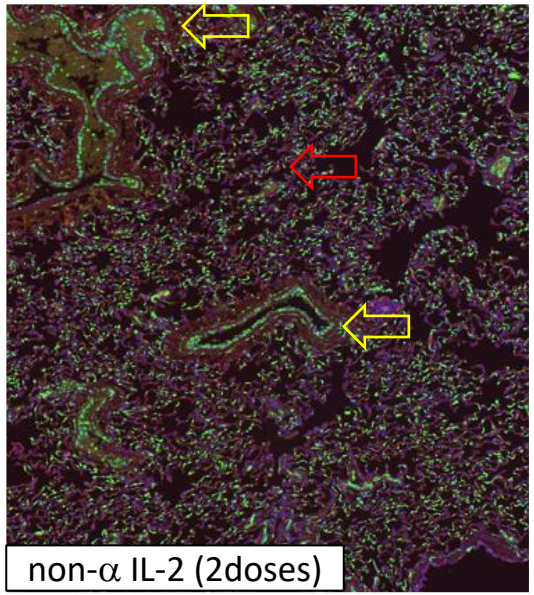
⇩ Analysis for acute capillary leak

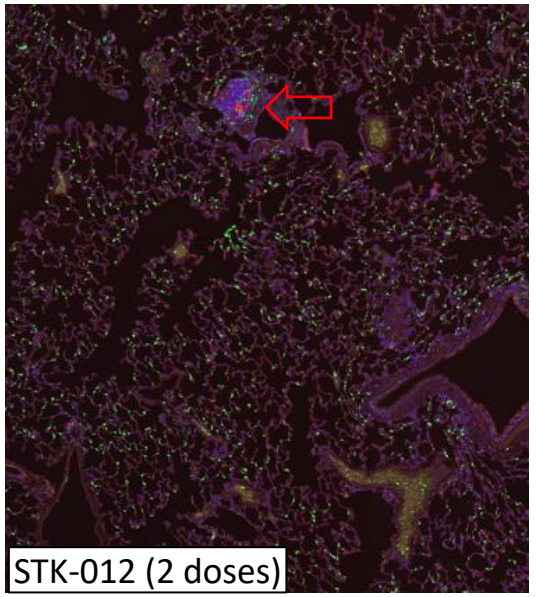
WT IL-2 and Non-a-IL-2 cause lymphocyte extravasation











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STK-012 Phase 1 Design and Patients in Monotherapy Escalation

- **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)**
- **Part C: STK-012 Q3W escalation 0.75 mg ⇢ 3 mg + Pembro Q3W**
- **Part D: STK-012 Ph1b expansions at 2.25 mg Q3W**

Candidate RP2D

→ **2.25 mg Q3W**

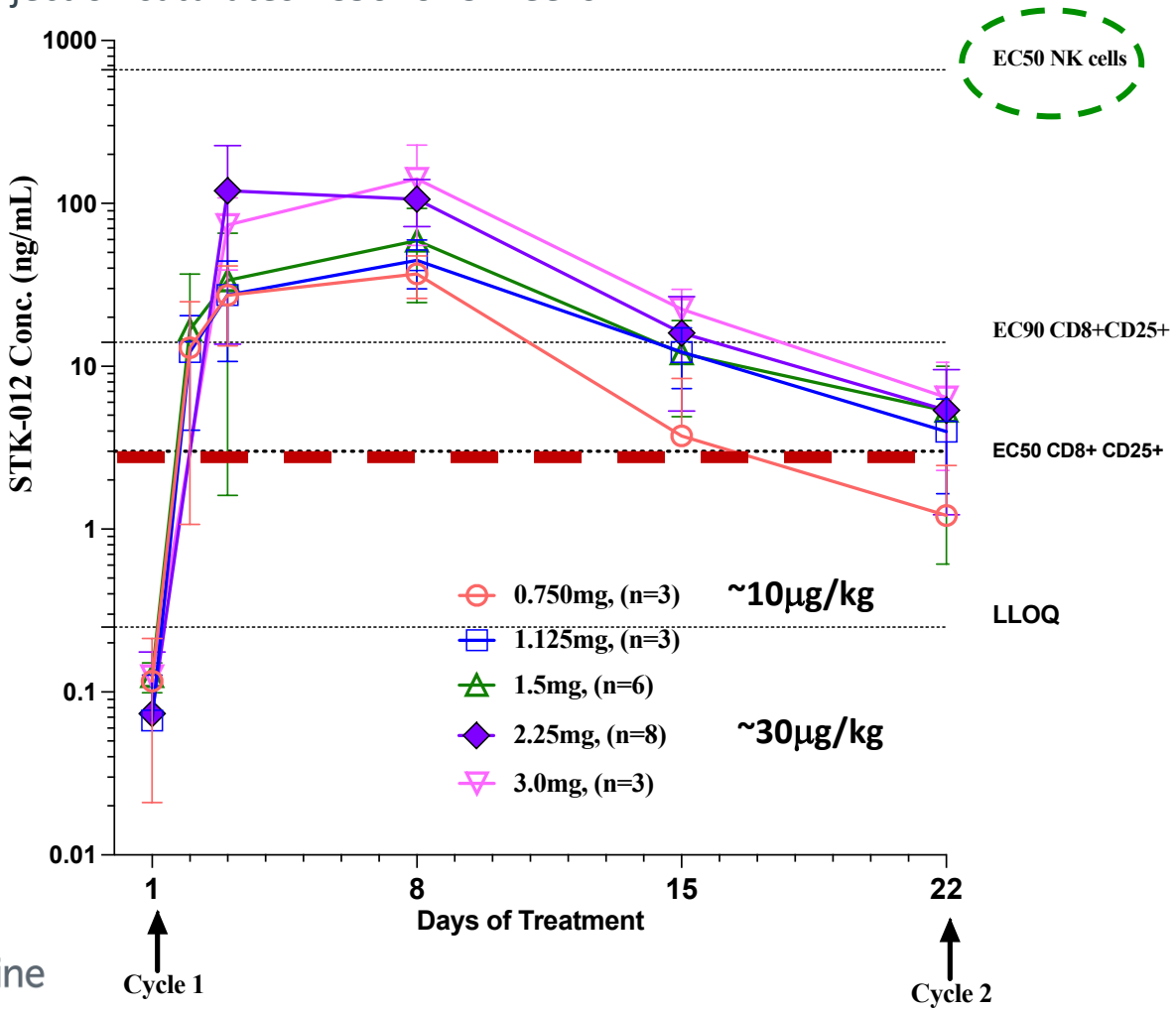
Enrolling to Ph1b expansions and biomarker backfill

Baseline Disease Characteristics & Demographics , 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	
Non-Small Cell Lung Cancer	15 (31.9)
Clear Cell Renal Cell Carcinoma	6 (12.8)
Ovarian Cancer	6 (12.8)
Mucosal Melanoma	4 (8.5)
Other (HNSCC, GEJ, GC, CC, non-ccRCC, MSI-H/dMMR CRC and HNSCC)	13 (27.7)
Age (median)	63.1y
female	44.3%
ECOG 1/0	42.6 / 57.4

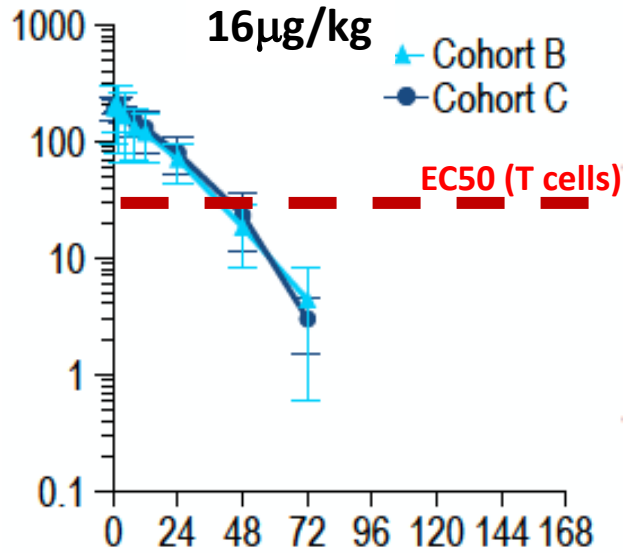
CD25 Selectivity Leads to Slow Clearance of STK-012

- Observed Half-life is ~4 days.
- Exposure (AUC) is dose proportional
- Single injection saturates EC50 for 3 weeks

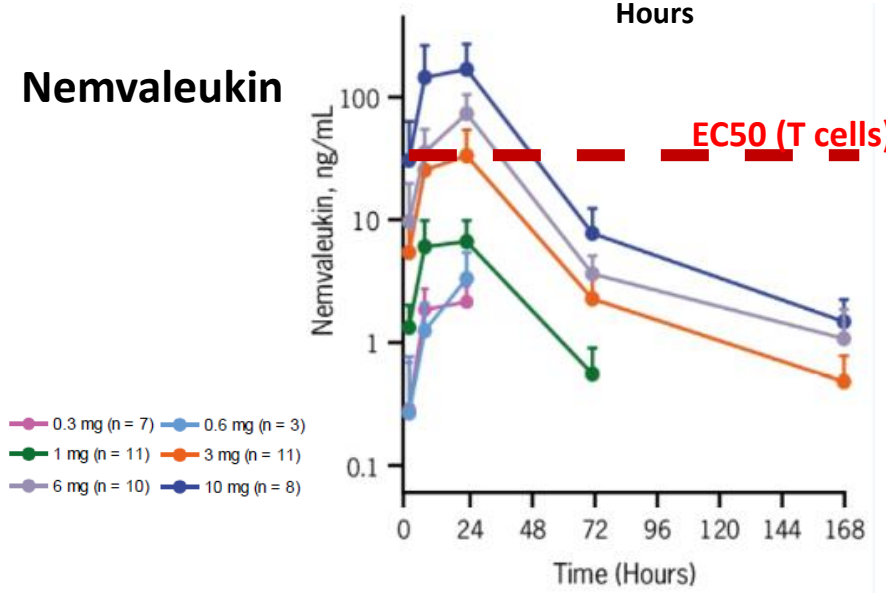
STK-012
(N-term. 40kD PEG)



THOR-707
(40kD PEG)



Nemvaleukin



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STK-012 Monotherapy Safety

- Treatment-related adverse events (TRAEs) were reversible with standard management (eg, dose hold/reduction, supportive meds)
- No subjects experienced CLS and very few had associated TRAEs
- No dose-limiting toxicities (DLT period: 21 days)
- The majority of TRAEs were Grade 1 or 2 in severity
- 1 subject experienced a Grade 4 TRAE (Anaphylactic reaction occurred at C9D1 (1.5 mg Q3W) and no subjects experienced Grade 5 TRAEs
- All 3 subjects treated at the maximum dose of 3 mg Q3W experienced Grade 3 GI SAEs (in Cycle 2 (after the DLT period)
- 2.25 mg Q3W was selected as candidate RP2D

Most Common TRAEs (≥10% of subjects)
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
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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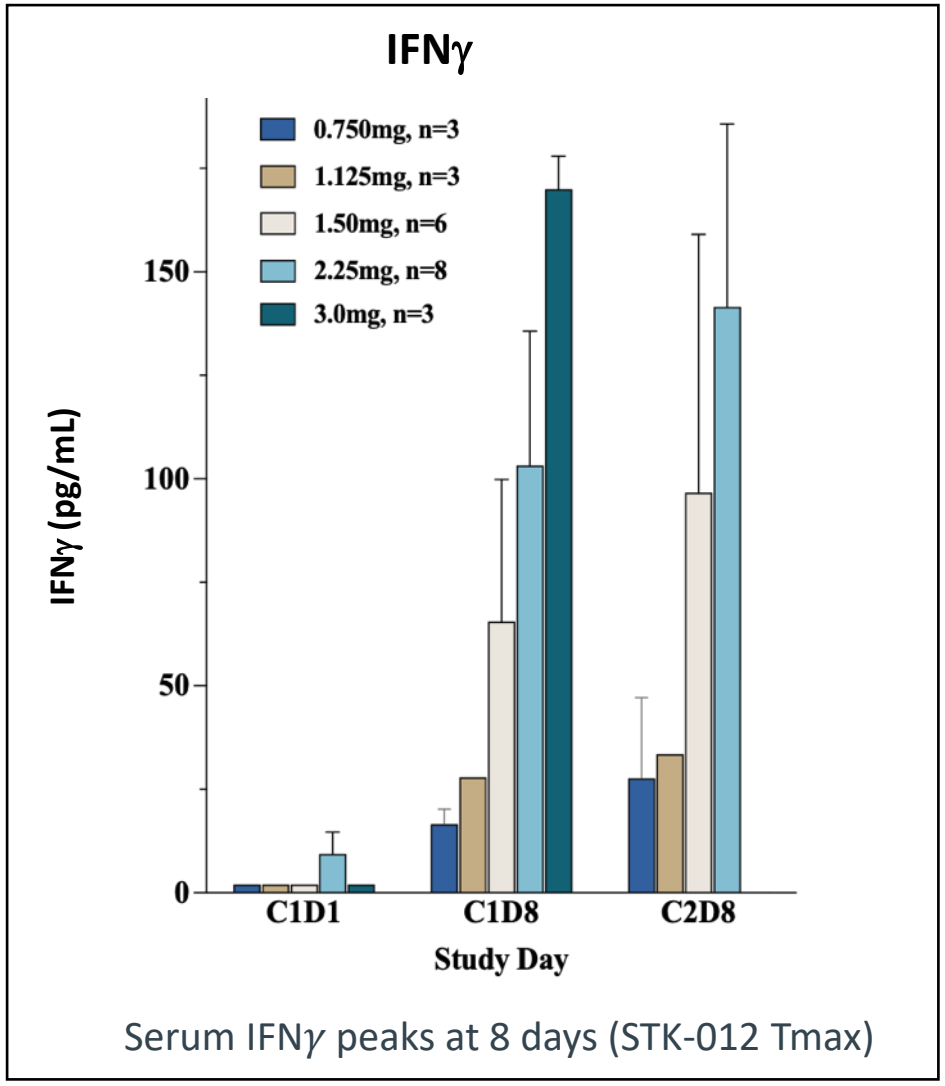
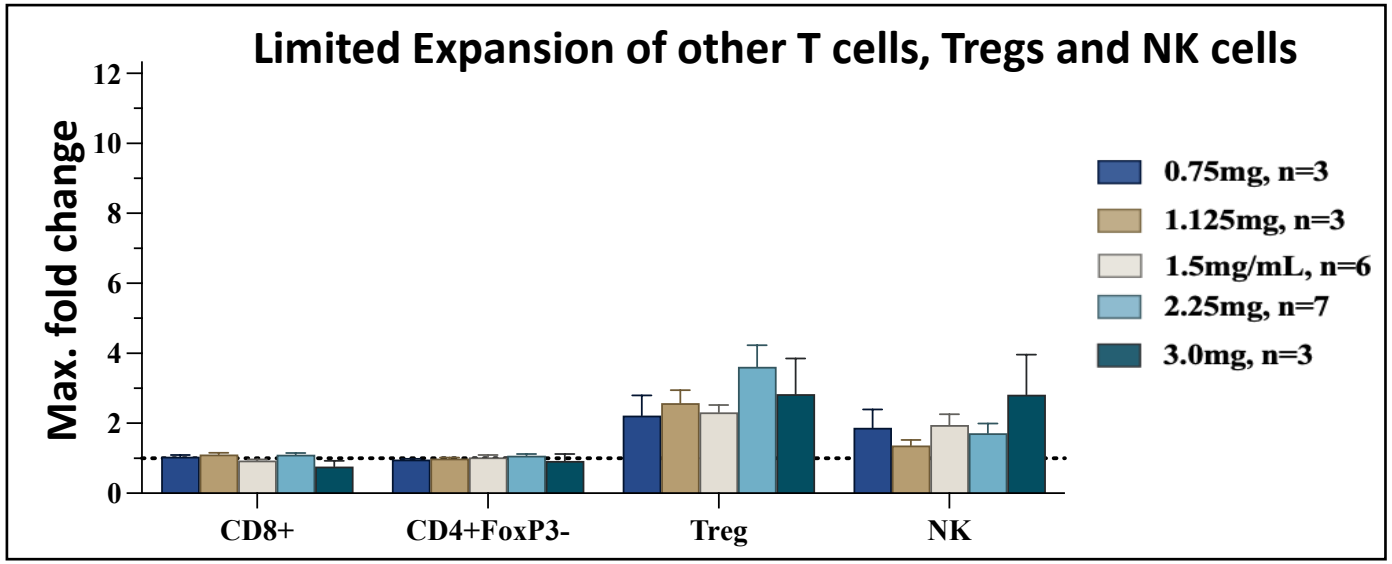
STK-012 Dose Dependent Increase of IFNγ and T Cell Proliferation



Serum IFNγ peaks at 8 days (STK-012 Tmax)



IL-2 variants in clinical trials

Max Fold Change	FOXP3+ Treg	NK cells	IFNg (pg/ml)	T1/2
STK-012*	**3.6x**	**1.6x**	**>100**	**4d**
Nemvaleukin [1]	2.3x	7.9x	400	~5h
SAR'245 [2]	3.5x	29.0x	(250x)	~11h
Transcon IL-2β/γ [3]	3x	20.2x	NA	35h
AMG592 [4]	17x	2.9x	-	24h

- *STK-012 2.25mg*

1. ASCO 2021
2. ESMO 2022
3. Corp Pres. 2023
4. ARD 2022
NA=not available

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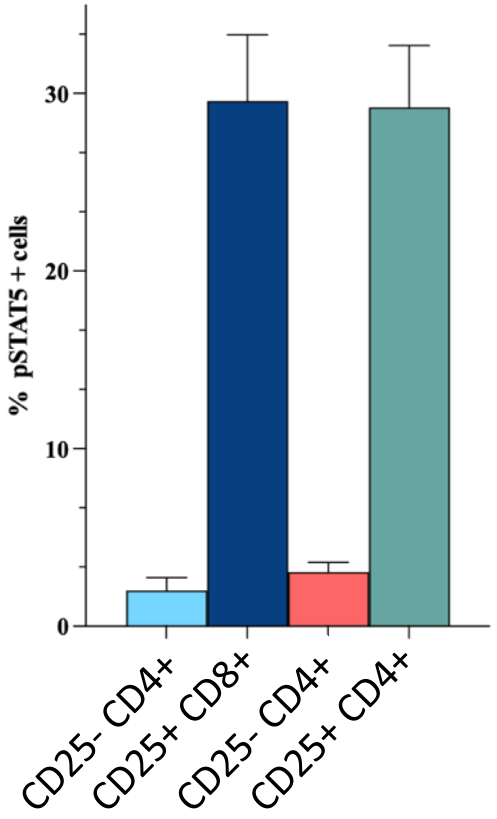
STK-012 Selective Activation of CD25+ T Cells

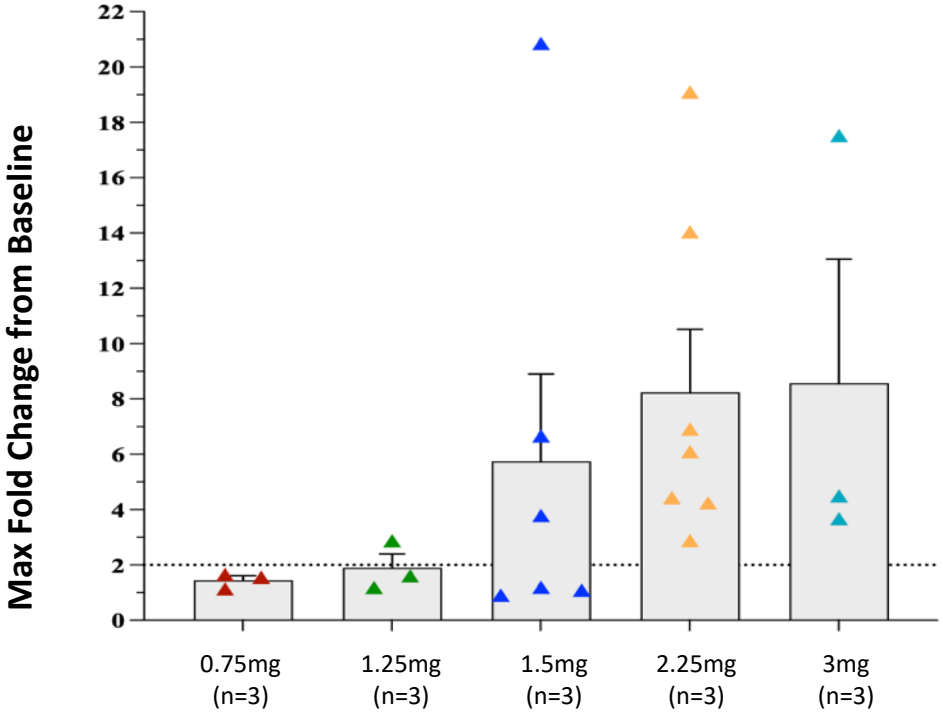
CD25 Selective pSTAT5 Induction

pSTAT5 in peripheral T cells



Expansion of Antigen Activated CD8 T Cells

KI67+ CD38+ CD8 T cells



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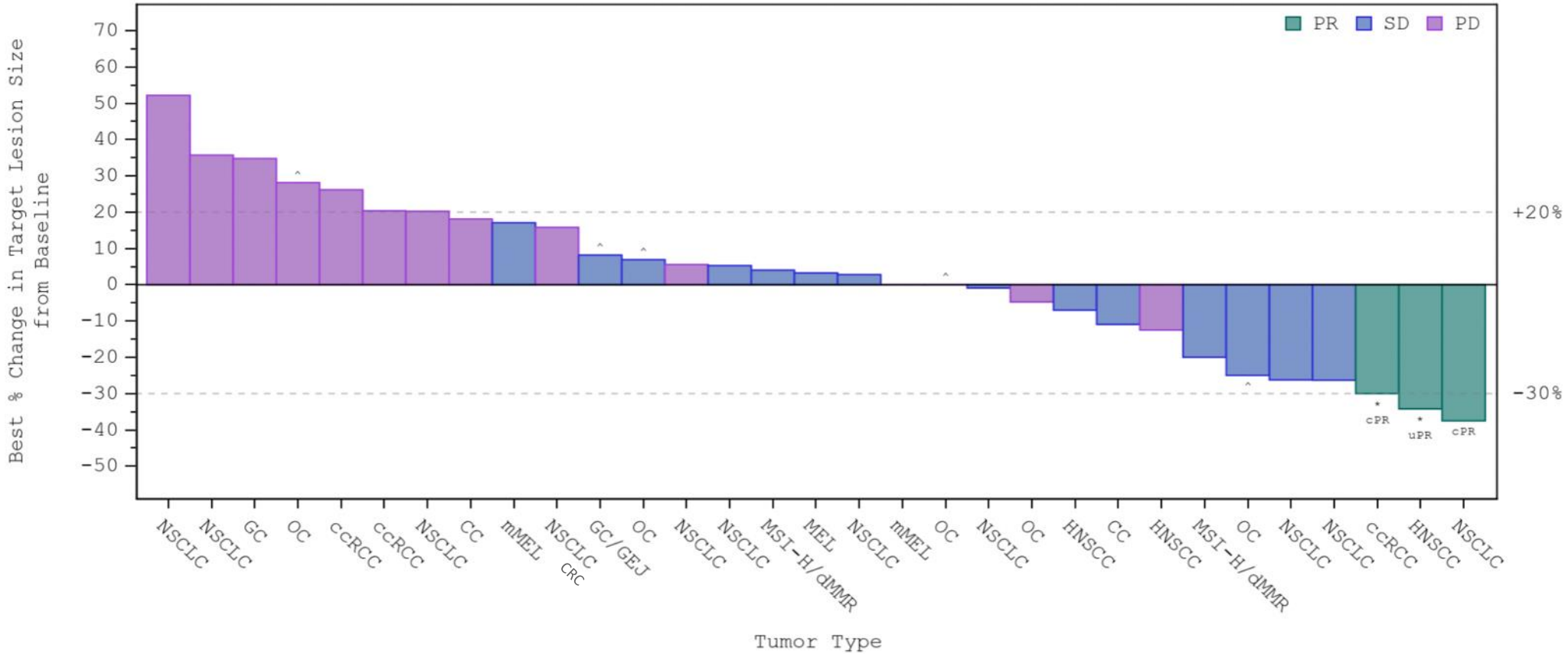
STK-012 Monotherapy Efficacy

- 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).



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.
* Indicates subjects who are ongoing treatment; ^ indicates subjects who are IO Naive.

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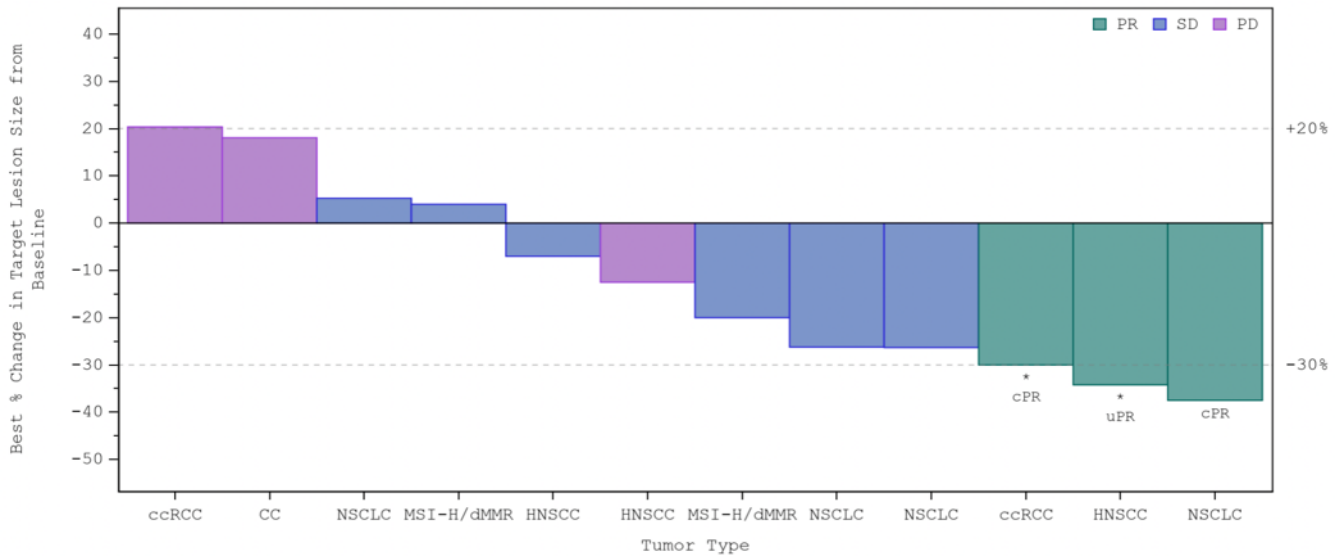
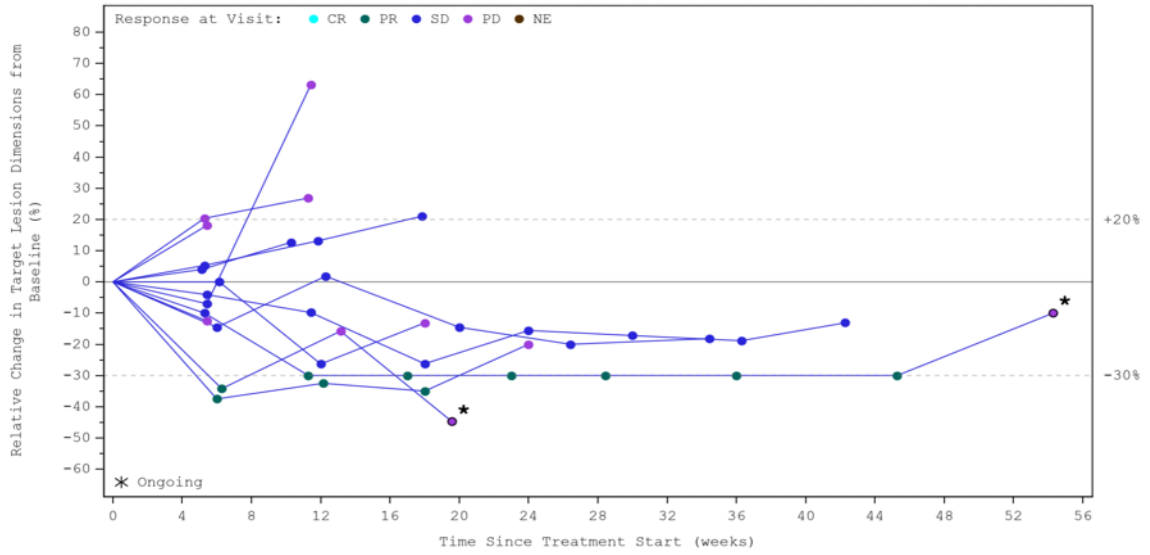
STK-012 Monotherapy Efficacy in Patients with 1-2 Prior Lines

- 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
- ccRCC responder who maintained response for >9 months.





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Conclusions

- Monotherapy STK-012 showed favorable safety, PK, and PD profiles with distinct differences from aldesleukin and non-α IL-2 analogues
  - No capillary leak syndrome observed with STK-012 treatment
- Selectivity for IL-2R α/β, selective expansion of activated CD8 T cells, and dose dependent increase of serum IFNγ
- Preliminary efficacy with monotherapy STK-012 (3 partial responses in Phase 1a) was observed in subjects who progressed on/after prior immunotherapy
- Further development is warranted and enrollment in STK-012 monotherapy dose expansions (Phase 1b) in advanced NSCLC and ccRCC is ongoing