Selective immune activation of antigen activated T cells with STK-012, an α/β IL-2 receptor biased partial agonist, with pembrolizumab and chemotherapy in 1L PD-L1 negative non-squamous NSCLC

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Disclosure Information

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I have the following relevant financial relationships to disclose:

Employee of: NYU Langone Health
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STK-012 + SoC in 1L NSQ NSCLC with Immunotherapy Resistant Biology

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Background: Unmet Need and Disease Context

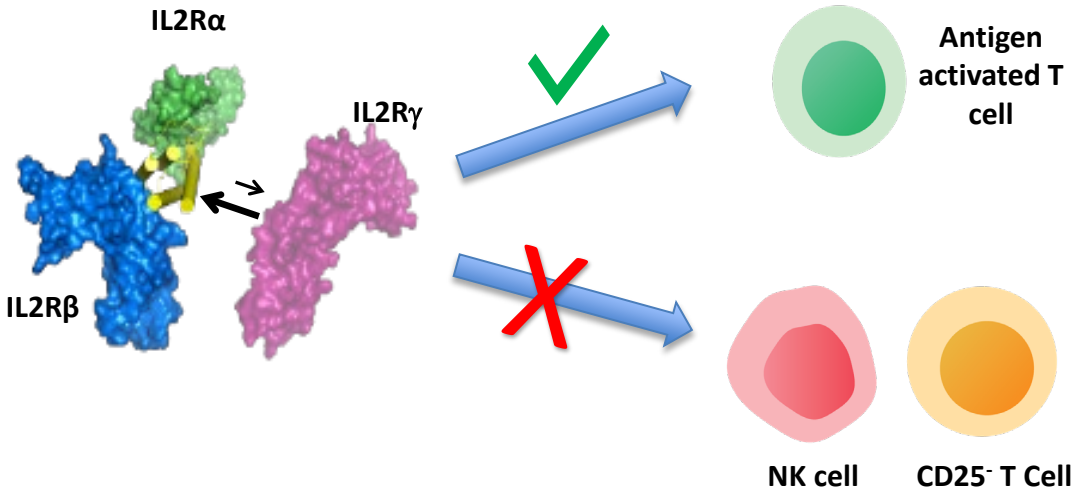
- Chemo-immunotherapy is the SoC in 1L NSQ NSCLC however, a substantial subset of patients derive limited benefit
- PD-L1 negativity (TPS <1%) is frequently associated with loss-of-function alterations in tumor suppressor genes such as *STK11, KEAP1,* and *SMARCA4*, contributing to an immunologically "cold" tumor microenvironment and immune resistance
- This biologically defined population represents >40% of patients with 1L NSQ NSCLC and remains a major unmet need, with poor outcomes with SoC chemo-immunotherapy

Population	% of 1L NSQ NSCLC	ORR (%)	mPFS (mo)	mOS (mo)	Ref
PD-L1 negative	35 – 40%	23 – 32	5.2 – 6.2	9.6 - 17.1	1, 2
≥1 TSG mutation (STK11, KEAP1, SMARCA4)	40 – 45%	22 - 36	2.7 – 6.1	8.7 – 17.4	3, 4
STK11/KEAP1 co-mutated	6 – 10%	7.1 - 15%	2.7-3	5.4 – 7.6	5, 6, 7

References: 1. Gadgeel et al. JCO 2020; 2. Makharadze et al. JTO 2023; 3.Garassino et al. JTOCRR 2022; 4. Alessi et al, JTO 2023 5. Skoulidis et al. 2024, 6. West et al., JITC 2022, 7. Anagnostou et al. ELCC 2026

STK-012 Design and Therapeutic Rationale

- STK-012 is a recombinant IL-2 precision immunotherapy engineered as an IL-2 receptor α/β-biased partial agonist
- STK-012 selectively activates and expands antigen-activated T cells to drive efficacy, while sparing NK cells and naïve T cells to avoid hallmark-IL-2 toxicities
- STK-012 is designed to promote reinvigoration of exhausted T cells and enhance trafficking of effector T cells into the TME
- STK-012 is designed to address key mechanisms underlying cold tumor biology and immunotherapy resistance, supporting combination with SoC



STK-012-101 Study Design and Baseline Characteristics in 1L NSQ NSCLC

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Enrollment Criteria

- Treatment Naïve, Stage IV non-squamous NSCLC
- No actionable genetic alterations by local testing
- Phase 1a: PD-L1 expression unrestricted
- Phase 1b: PD-L1 TPS <1% required

STK-012

- Administered subcutaneously Q3W
- Outpatient administration
- No priming dose required

STK-012 + PCT*	C1	C2	C3	C4	C5+
STK-012 2.25 mg SC	X	X	X	X	X
Pembrolizumab 200 mg IV	X	X	X	X	X
Pemetrexed 500 mg/m^2	X	X	X	X	X
Carboplatin AUC5 Q3W	X	X	X	X	

* PCT = Pembrolizumab + Chemotherapy

Baseline Characteristics Efficacy Evaluable (n=36)

	%	n
PD-L1=1%	11%	4
PD-L1<1%	89%	32
TTF-1 negative	42%	15
≥1 TSG mutation (STK11, KEAP1, SMARCA4)	50%	18
STK11 and KEAP1 co-mutation	22%	8
Mucinous	22%	8
Never Smoker	25%	9
KRAS mutation	42%	15
• KRAS + ≥1 TSG mutation	14%	5

- Efficacy clinical cutoff: 03-13-2025
- 3 subjects not efficacy evaluable (none related to PD or toxicity): 1 subject D/C during C1 for change in diagnosis (SCLC) ; 2 subjects D/C before 1st on-treatment scan (1 withdrew consent and 2nd received alternative chemo)

STK-012 + PCT Safety in 1L NSQ NSCLC (All TRAEs)

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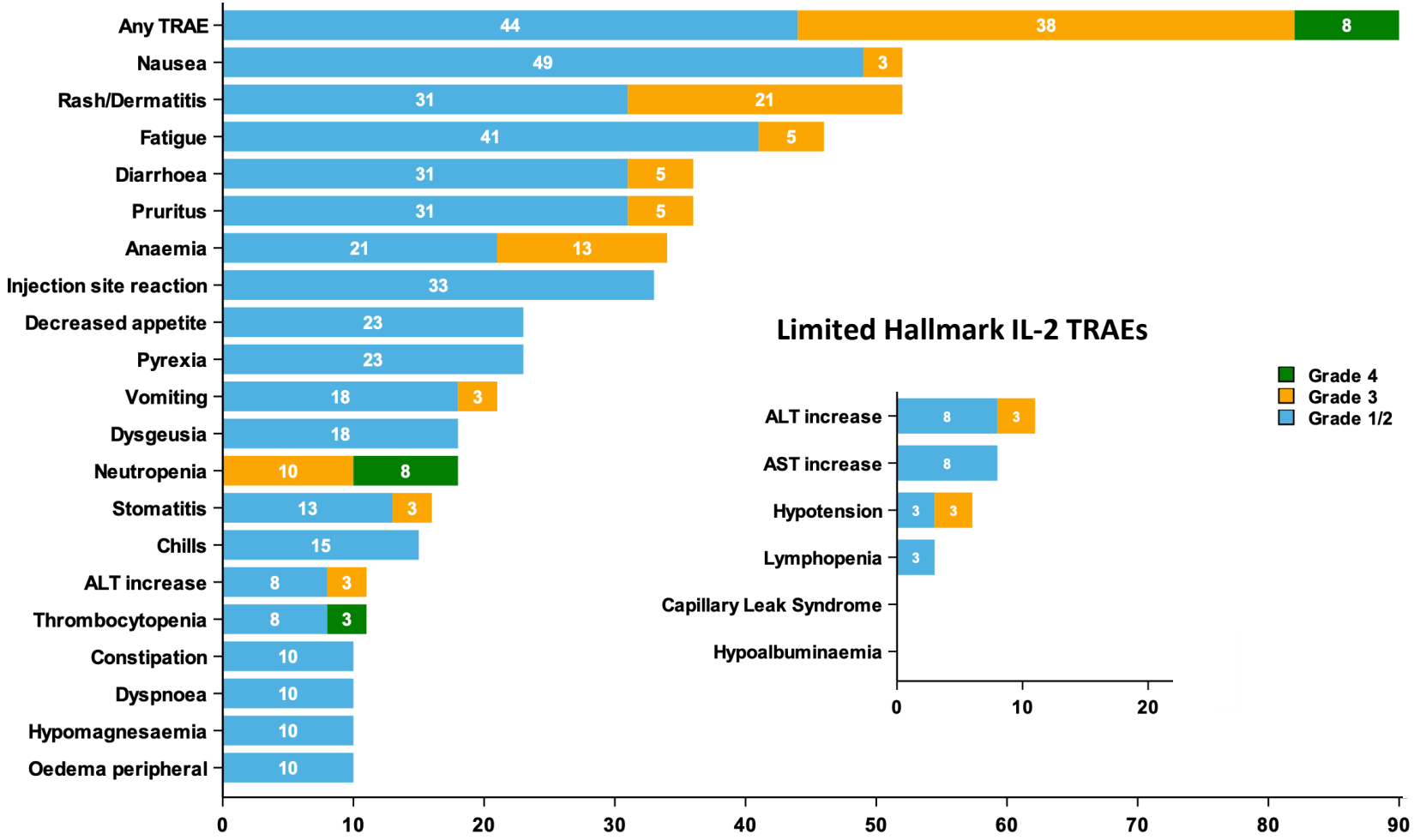
Key Safety Findings

- Total Safety Evaluable (n=39)
- No DLTs
- Most common TRAEs included manageable, reversible and rash/dermatitis (51%), nausea (51%), fatigue (46%)
- 3 subjects (7.7%) experienced Grade 4 TRAEs (hematologic) and no Grade 5 TRAEs
- Observed hematologic toxicities consistent with known chemo-immunotherapy safety profile [1]
- Limited hallmark IL-2 TRAEs
- No TRAEs led to STK-012 discontinuation

- TRAE defined as related to any component of the regimen (STK-012, Pembrolizumab, Carboplatin, Pemetrexed)
- Safety clinical cutoff: 02-17-2026
- Median Safety Follow-up (min, max): 6.44 months (1.6, 15.2)
- References: 1. Gandhi et al. NEJM 2018

Most Common TRAEs (≥10% of participants)



STK-012 + PCT Efficacy in 1L PD-L1 negative NSQ NSCLC*

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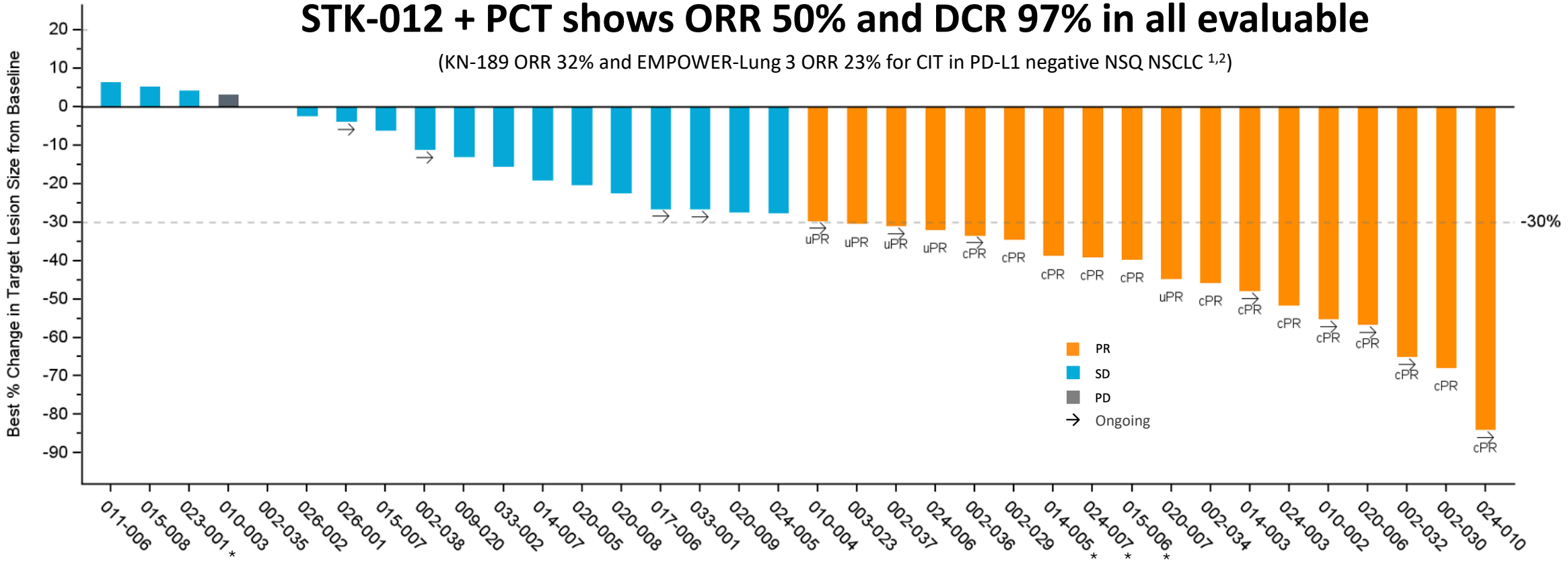
STK-012 + PCT shows ORR 50% and DCR 97% in all evaluable

(KN-189 ORR 32% and EMPOWER-Lung 3 ORR 23% for CIT in PD-L1 negative NSQ NSCLC [1,2])



- PD-L1<1% in 32/36 and PD-L1 1% in 4/36 *
- Efficacy clinical cutoff: 03-13-2025; median follow-up (min, max): 6.8 months (1.6, 15.2)
- References: 1. Gadgeel et al. JCO 2020; 2. Makharadze et al. JTO 2023

STK-012 + PCT drives sustained and selective increase in circulating Th1 cytokines and chemokines

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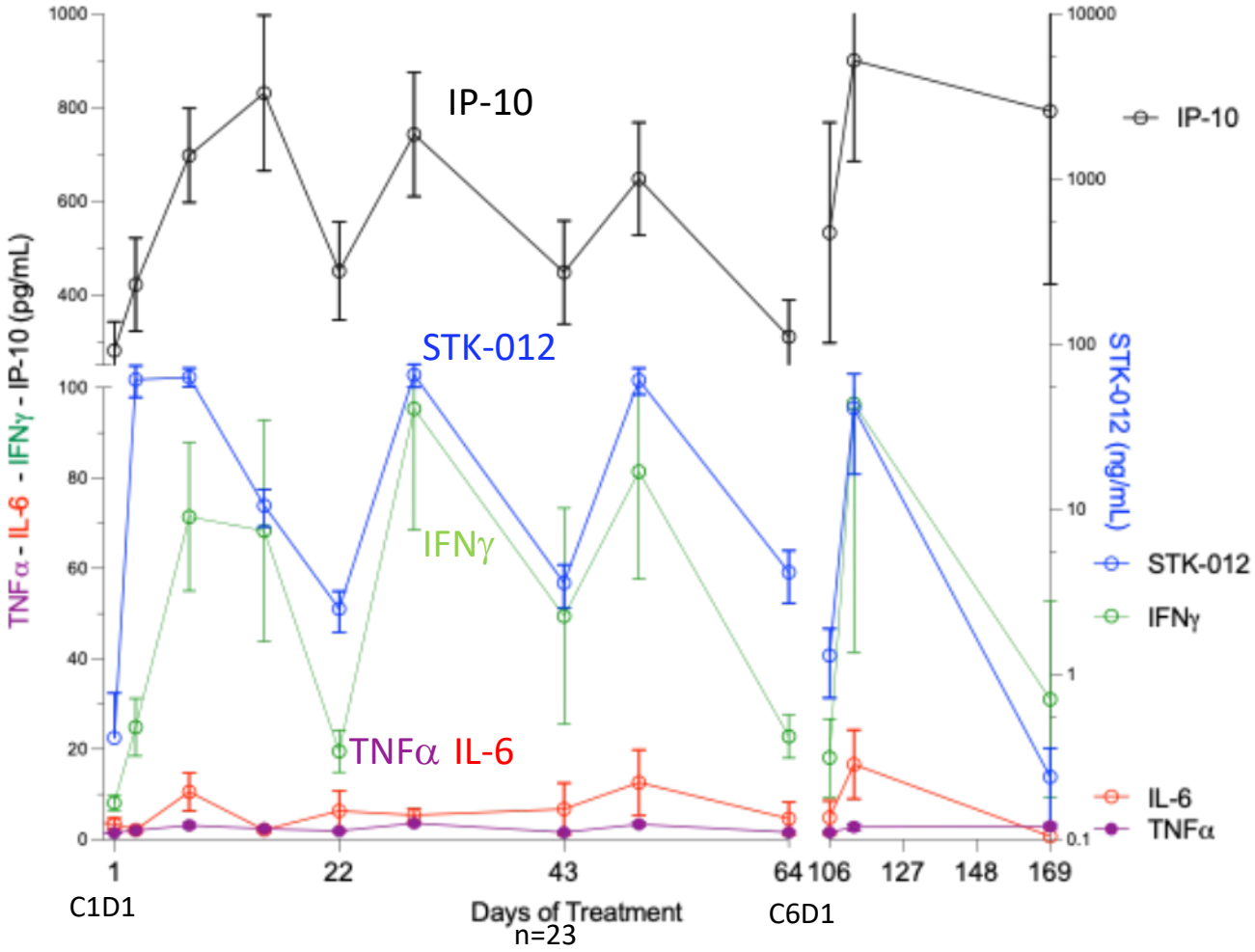
- Long $T_{1/2}$ of ~5.7 days supports sustained exposure with Q3W dosing
- Robust induction of IFNγ and IP-10 (CXCL10) observed across treatment cycles, consistent with activation of a Type 1 immune response
- IP-10 induction, an IFNγ-inducible chemokine, supports recruitment of activated T cells into tissues
- Cytokine induction is sustained over multiple cycles, indicating durable pharmacodynamic activity
- Minimal induction of TNFα and IL-6 with repeat dosing, indicating reduced risk of vascular leak and cytokine storm



STK-012 + PCT Selectively Induces Proliferation of Circulating Activated CD8+ T Cells

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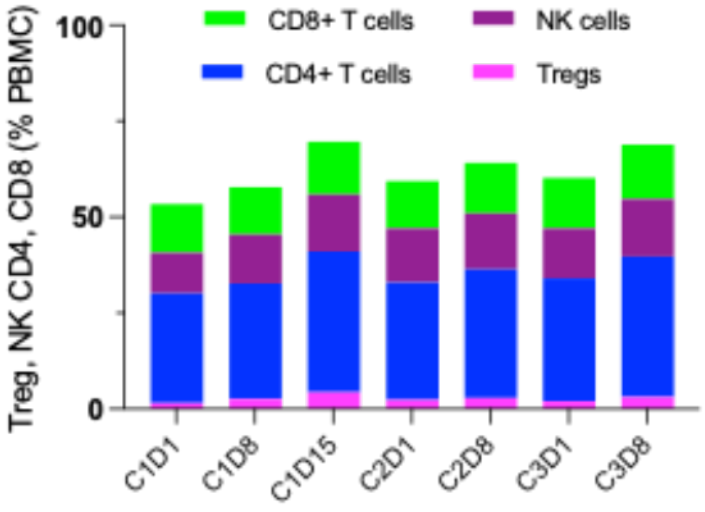
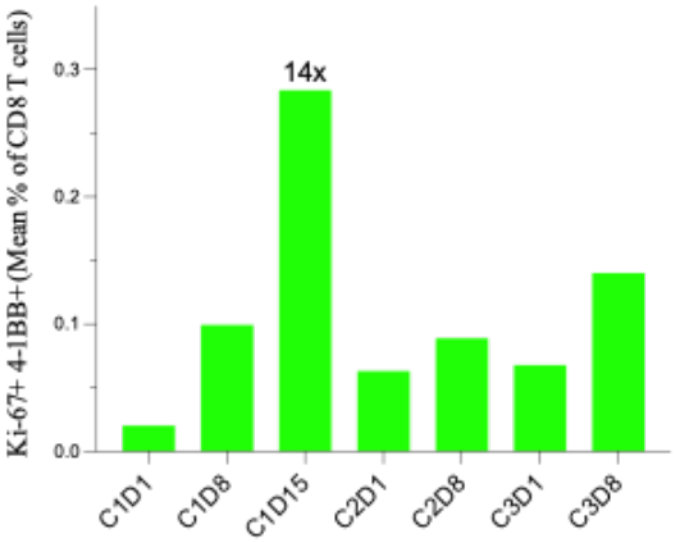
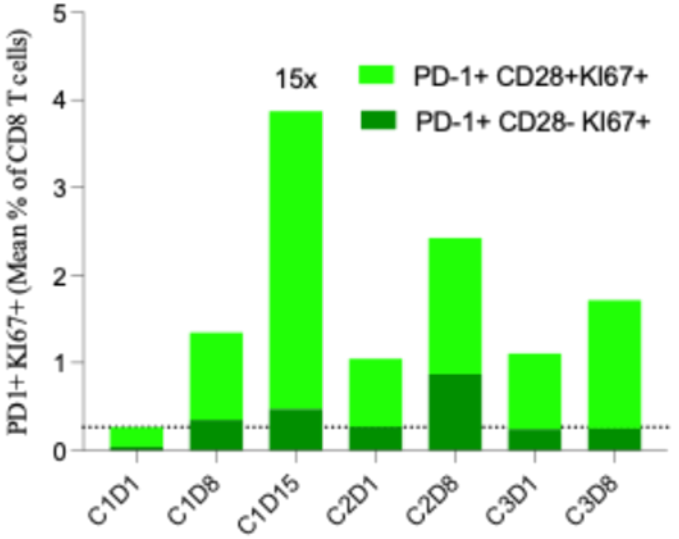
Limited expansion of NK and Tregs

Robust proliferation of antigen-activated CD8+ T cells (Ki-67+41BB+)

Reinvigoration of exhausted T cells, demonstrated by increased proliferation of PD-1+ CD8+ T cells (Ki-67+)







- Peripheral blood flow cytometry analysis (n=36) on Cycle 1: Days 1/8/15; Cycle 2 and 3: Days 1/8
- Preferential expansion of CD28+ PD-1+ T cells, consistent with activation of a costimulation-competent, memory-capable T-cell population
- Consistent activation across effector subsets, including HLA-DR+, CD38+ CD8+ T cells, supporting broad engagement of antigen-activated T cells (data not shown)

STK-012 + PCT Leads to Robust TCR Clonal Expansion in Peripheral Blood

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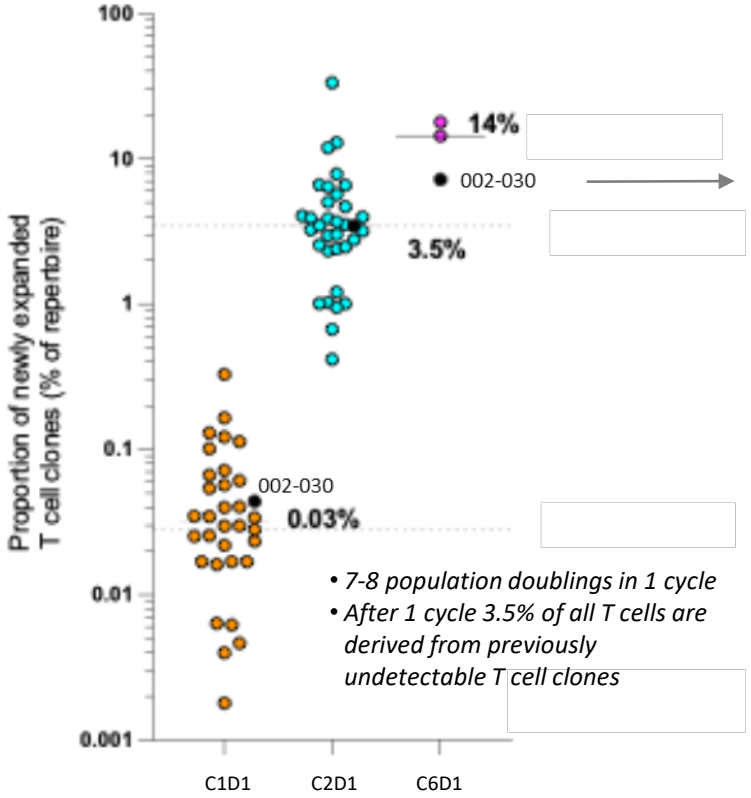
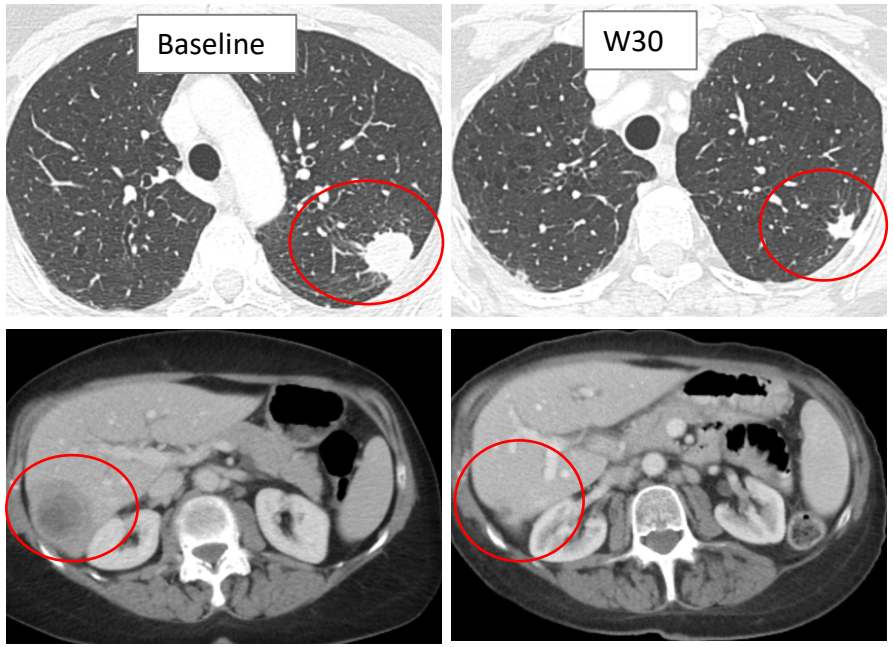
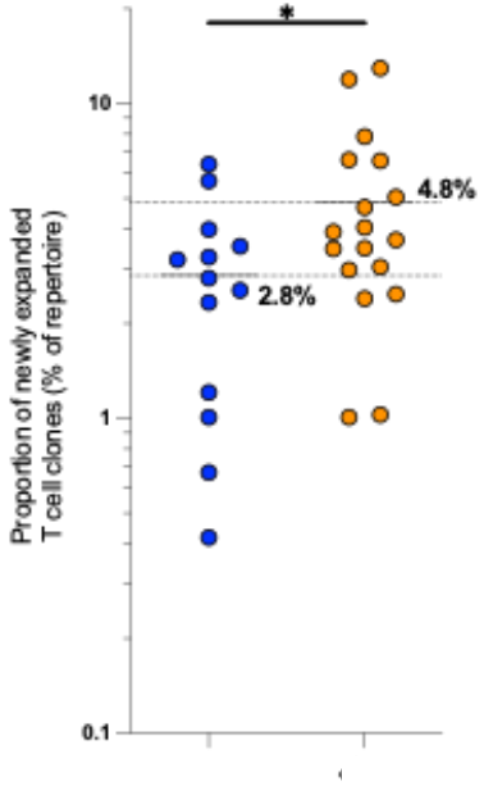
Robust expansion of newly detectable T cell clones



Confirmed response in a patient with PD-L1 <1% and STK11-mutant disease (002-030)



Greater clonal expansion associated with clinical response



- STK-012 + PCT in 1L NSQ NSCLC TCR sequencing (n=32) at Adaptive Biotech
- T cell clones expanding >10× and emergence of new clonotypes supports activation of antigen-specific T cell responses

STK-012 + PCT in ≥1 TSG mutations: ORR 61%

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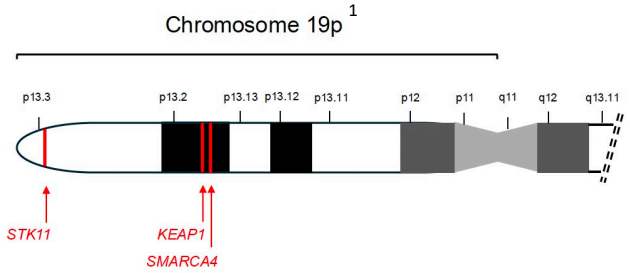

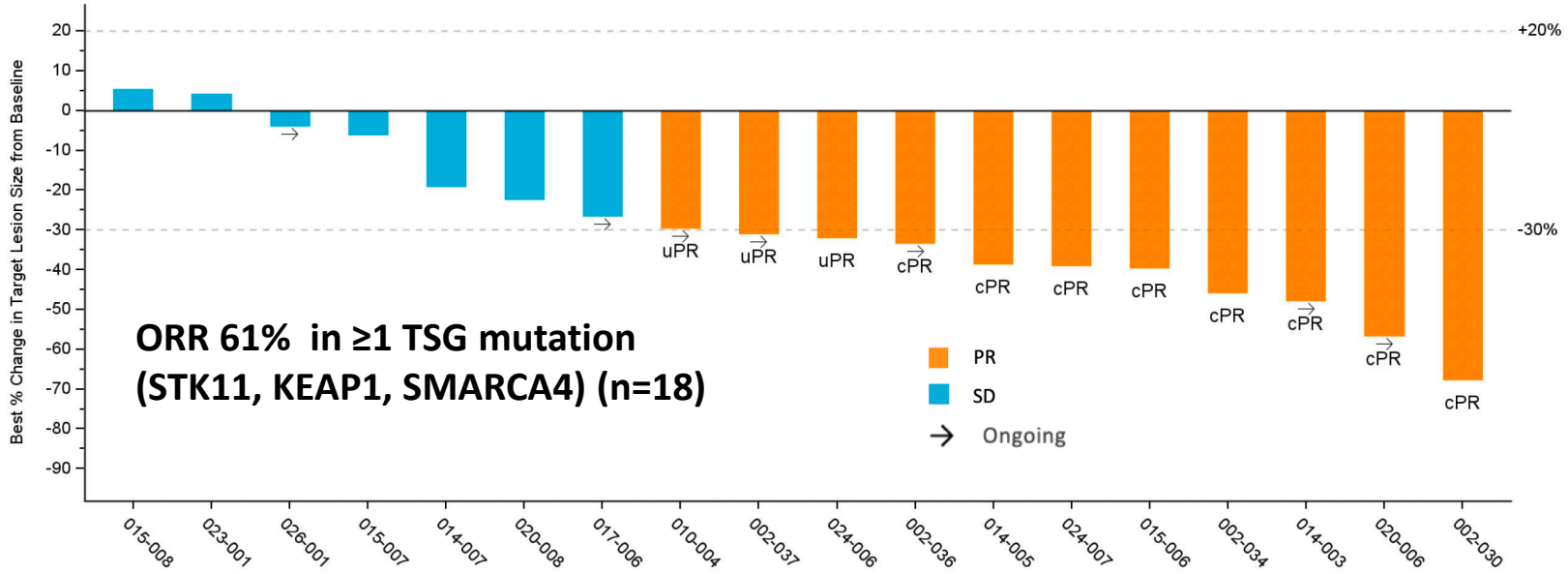

PD-L1 <1%	x	1%	x	x	x	x	x	x	x	x	x	1%	1%	1%	x	x	x	x
STK11	x	x	x		x	x	x	x		x		x	x	x	x			x
KEAP1	x		x	x	x	x		x				x	x		x			
SMARCA4			x						x		x				x	x	x	
KRAS		x	x		x			x					x	x				

≥1 TSG mutation outcomes in literature (STK11, KEAP1, SMARCA4)

- LoF TSG alterations (STK11, KEAP1, SMARCA4) define an immune-resistant NSQ NSCLC subset frequently co-mutated and associated with an immunosuppressed, non-inflamed TME
- Real-world outcomes with pembrolizumab + chemotherapy remain poor: STK11m ORR 33% / mPFS 4.8 mo; KEAP1m ORR 14.3% / mPFS 2.8 mo; SMARCA4m ORR 21.9% / mPFS 2.7 mo; STK11m+KEAP1m ORR 7.1% / mPFS 2.7 mo. [2, 3]

- Efficacy clinical cutoff: 03-13-2025; Median follow-up (min, max): 8.6 months (2.5, 15.2); References: 1. Gandhi et al. JTO 2025; 2. Skoulidis et al, Nature 2024; 3. Alessi et al, JTO 2023

STK-012 + PCT in STK11/KEAP1 co-mutated 1L NSQ NSCLC: ORR 50%

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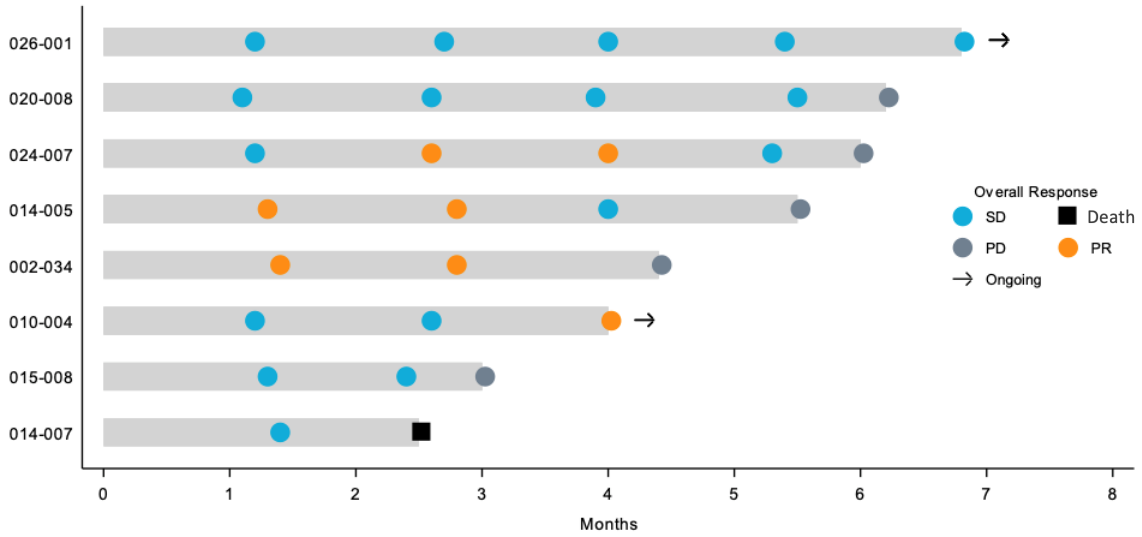
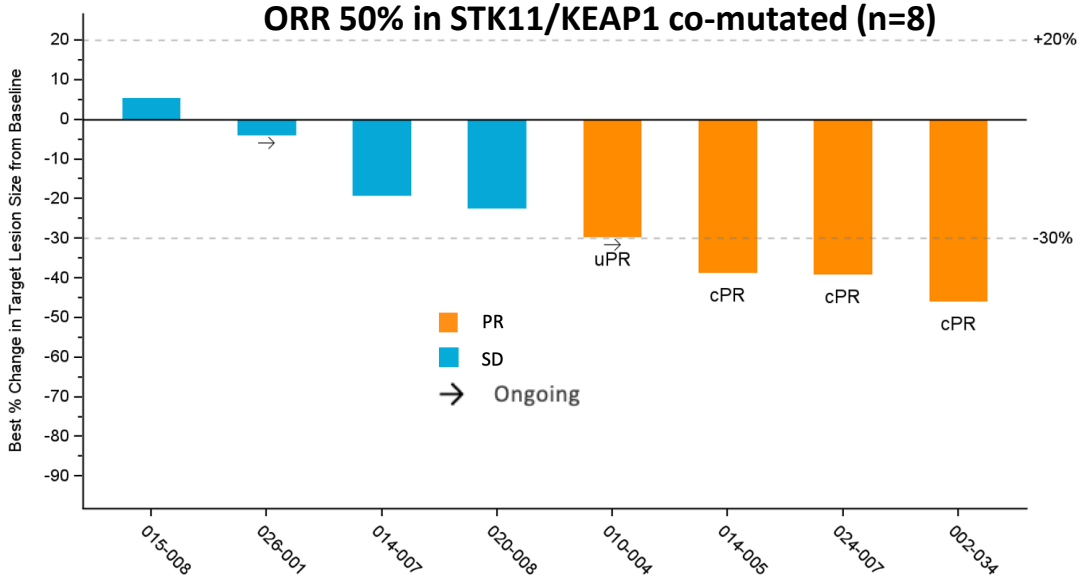
BOR PR/SD 100% in STK11/KEAP1 co-mutated (n=8)



ORR 50% in STK11/KEAP1 co-mutated (n=8)



	015-008	026-001	014-007	020-008	010-004	014-005	024-007	002-034
PD-L1 <1%	x	x	x	x	x	1%	1%	x
STK11	x	x	x	x	x	x	x	x
KEAP1	x	x	x	x	x	x	x	x
SMARCA4		x						x
KRAS		x	x		x		x	

STK11/KEAP1 co-mutated outcomes in literature

- STK11/KEAP1 co-mutations represent 6.6 to 10% of 1L NSQ NSCLC eligible for chemo-immunotherapy
- Academic retrospective analysis in STK11/KEAP1 co-mutated showed an ORR 7%, BOR PD in 43%, mPFS 3 months , and OS 7.6 months with pembrolizumab + chemotherapy[1]
- Impower150 reported mPFS 3 months and OS 5.4 months across the 3 arms (ABCP/ACP/BCP) in STK11/KEAP1 co-mutated[2]
- EMPOWER-Lung 3 reported an ORR of 15.4% (2/13) with cemiplimab + chemotherapy in STK11/KEAP1 co-mutated[3]

- Efficacy clinical cutoff: 03-13-2025; Median follow-up (min, max): 6.8 months (2.5, 9.2); References: 1. Skoulidis et al. Nature 2024, 2. West et al., JITC 2022, 3. Anagnostou et al. ELCC 2026

STK-012 + PCT PFS and OS in STK11/KEAP1 co-mutated 1L NSQ NSCLC

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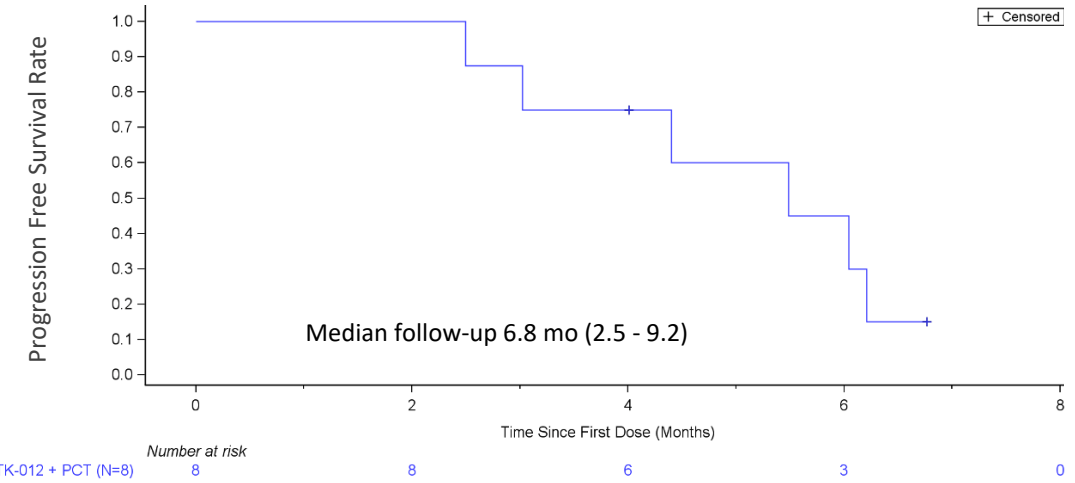
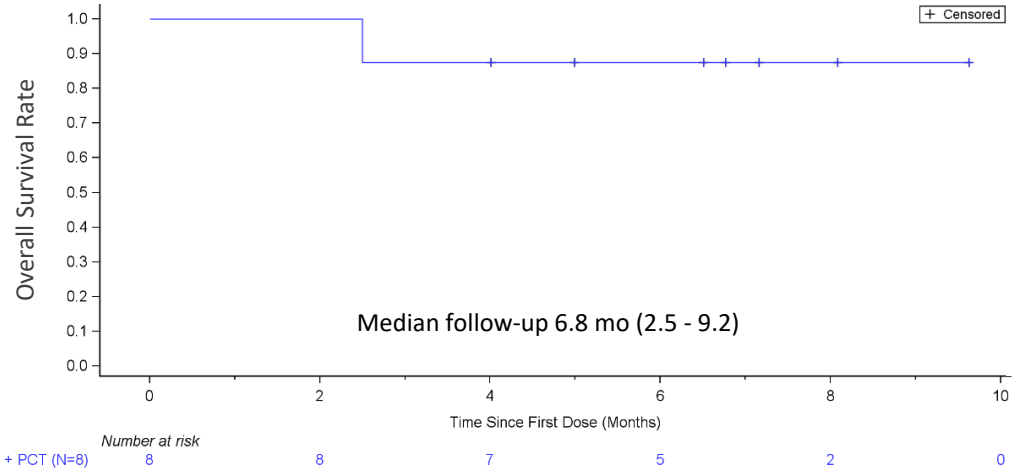
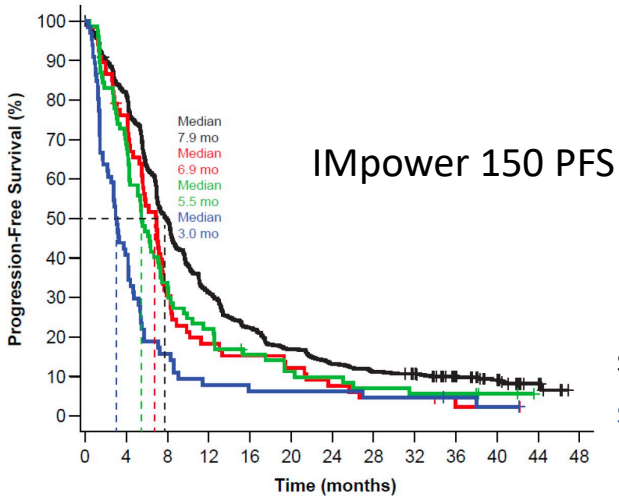
STK11/KEAP1 co-mutated mPFS 5.5 mo



STK11/KEAP1 co-mutated mOS NR, 6mo OS rate 88%



IMpower 150 PFS [1, 2]

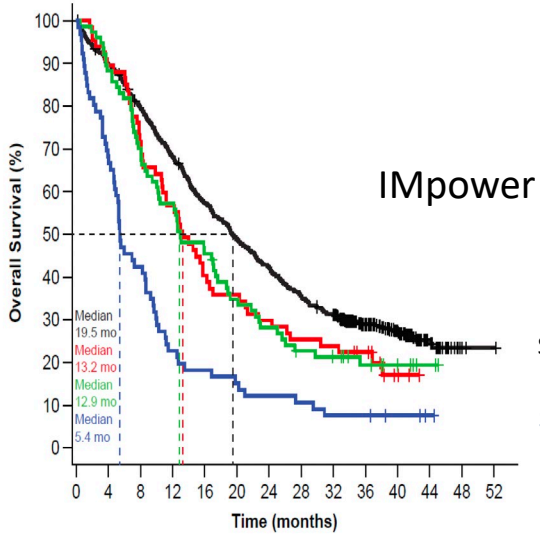


STK11wt/KEAP1wt
mSTK11/KEAP1wt
mKEAP1/STK11wt
mSTK11/mKEAP1

STK11wt/KEAP1wt PFS = 7.9 mo

STK11m/KEAP1m PFS = 3 mo

IMpower 150 OS [1, 2]



STK11wt/KEAP1wt OS = 19.5 mo

STK11m/KEAP1m OS = 5.4 mo

1. KM curves shown for pooled treatment arms ACP, BCP, ABCP; 2. Reference: West et al., JITC 2022

STK-012 + PCT Overcomes Immune Suppression in the STK11/KEAP1 Co-mutated Population

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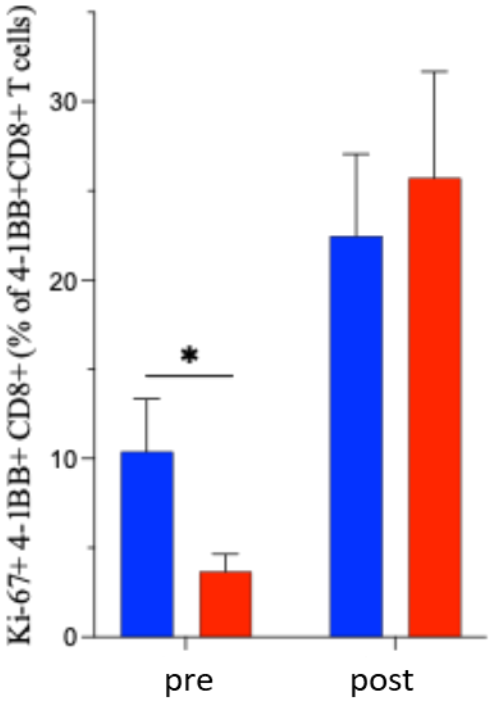
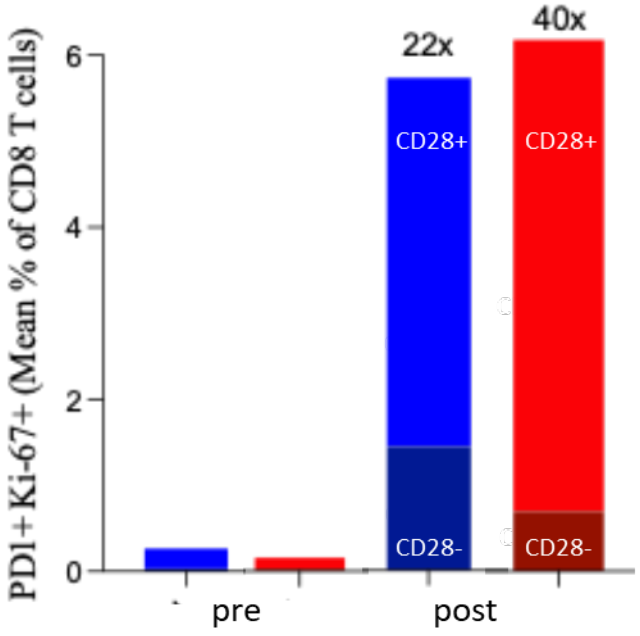
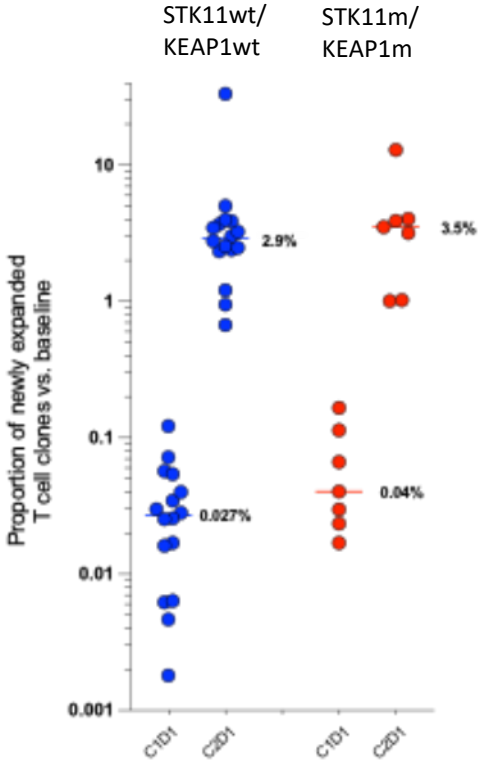
Proliferation of antigen-activated CD8+ T cells increased substantially in STK11/KEAP1 co-mutated, overcoming the baseline deficit



Exhausted CD8+ T cells reinvigorated in both groups, with marked post-treatment increases in PD-1+Ki-67+ cells, including CD28+ populations



Newly expanded T cell clones increased from baseline to C2D1 in both groups



- At baseline, flow cytometry analysis of peripheral blood CD8+ T cells from STK11/KEAP1 co-mutated patients (n=8) showed significantly lower proliferation of antigen-activated CD8+ T cells (Ki-67+41BB+) than WT (n=16), consistent with a more immunosuppressed phenotype
- Newly expanded T cell clones increased from baseline to C2D1 in both groups, supporting induction of novel antigen-specific immune responses

STK-012 + PCT Demonstrates Robust Immune Activation and Efficacy in 1L NSQ NSCLC with Immune Resistant Biology

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STK-012 + PCT Efficacy Data in 1L NSQ NSCLC

- **Encouraging efficacy in overall population:** **ORR 50% (18/36)** in a predominantly PD-L1–negative population
- **STK11, KEAP1, SMARCA4:** **ORR 61% (11/18)** in tumors harboring at least 1 TSG mutation
- **STK11/KEAP1 co-mutated tumors:** **ORR 50% (4/8)** in STK11/KEAP1 co-mutated tumors; **mPFS 5.5 months** (4.4, NR) and **6-month OS of 88%**
- **SYNERGY-101** (NCT05098132), **a global rPh2 study of PCT ± STK-012 in 1L NSQ NSCLC with immune resistant biology is enrolling.**

STK-012 + PCT Translational data

- **Persistent and predictable immune activation**: Robust induction of IFNγ and IP-10 with minimal IL-6 and TNFα, supporting selective immune engagement rather than broad cytokine release
- **Reinvigoration of exhausted T cells**: Marked expansion of proliferating PD-1+ Ki67+ CD8 T cells, with approximately 22× expansion overall and up to 40× in STK11/KEAP1 co-mutants
- **De novo expansion of anti-tumor T-cell clones**: Emergence of previously undetectable T cell clones across populations, including in highly immunosuppressed STK11/KEAP1 tumors

STK-012 + PCT Safety Data in 1L NSQ NSCLC

- **Manageable safety profile**: Hematologic, GI and constitutional AEs comparable to chemo-immunotherapy benchmarks
- **Limited hallmark IL-2 toxicities**
- **On-mechanism effects:** Increased incidence of dermatologic events and low-grade pyrexia, consistent with the mechanism of STK-012

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