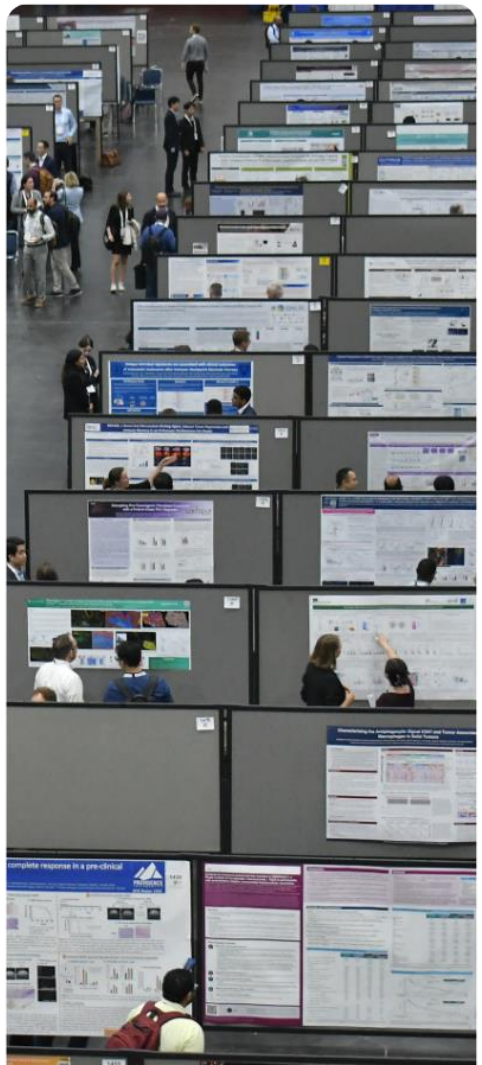


Society for Immunotherapy of Cancer

40TH ANNIVERSARY SITC 2025

Nov. 5–9 | National Harbor, MD

40th Anniversary Annual Meeting & Pre-Conference Programs

40 Years of Driving Breakthroughs in Cancer Immunotherapy.

#SITC25

Initial Phase 1a/1b Results of STK-012, an α/β IL-2 Receptor Biased Partial Agonist, with Pembrolizumab, Pemetrexed, and Carboplatin in 1L PD-L1 Negative Non-squamous NSCLC

Adam J. Schoenfeld, MD[1], Edward B. Garon, MD[2], Anne C. Chiang, MD[3], Kai He, MD, PhD[4], Jennifer A. Marks, MD[5], Brian S. Henick, MD[6], Stephen V. Liu, MD[7], Nagashree Seetharamu, MD, MBBS[8], So Yeon Kim, MD[3], Alexander I. Spira, MD[9], Timothy Larson, MD[10], Justin F Gainor, MD[11], Abraham Chachoua, MD[12], Jeffrey M. Clarke, MD, NP[13], Ticiana Leal, MD[14], Philip Lammers, MD[15], Jorge Chaves, MD[16], Alain C. Mita, MD[17], Afshin Eli Gabayan, MD[18], David J. Park, MD[19], Ricklie A. Julian, MD[20], Mary K. Crow, MD[21], Benjamin Izar, MD, PhD[6], Julio A. Peguero, MD[22], Martin Oft, MD[23], Anita Mehta-Damani, PhD[23], Natalie Busby, MHA[23], Naiyer A. Rizvi, MD[23], Alex Azrilevich, PharmD[23] and Salman R. Punekar, MD[12]

(1) Memorial Sloan Kettering Cancer Center, New York, NY, United States, (2) UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, (3) Yale University School of Medicine, New Haven, CT, (4) Ohio State University - James Comprehensive Cancer Center, Columbus, OH, (5) Dana Farber Cancer Institute, Boston, MA, (6) Columbia University Medical Center, New York, NY, (7) Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, United States, (8) Northwell Health, Lake Success, NY, United States, (9) NEXT Oncology, Virginia Cancer Specialists, Fairfax, VA, (10) HealthPartners, St. Paul, MN, (11) Massachusetts General Hospital, Boston, MA, (12)New York University, New York, NY, (13) Duke Cancer Institute, Durham, NC, (14) Winship Cancer Institute of Emory University School of Medicine, Atlanta, GA, (15) Baptist Cancer Center, Nashville, TN, (16) Northwest Medical Specialties, Tacoma, WA, (17) Hoag Family Cancer Center, Newport Beach, CA, (18) Beverly Hills Cancer Center, Beverly Hills, CA, (19) Providence Crosson Cancer Center, Fullerton, CA, (20) University of Arizona Cancer Center, Tucson, AZ, (21) Renovatio Clinical, Houston, TX, (22) Oncology Consultants, Houston, TX, (23) Synthekine, Menlo Park, CA

40TH ANNIVERSARY Society for Immunotherapy of Cancer sitc 2025

40th Anniversary Annual Meeting & Pre-Conference Programs

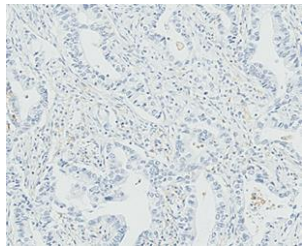
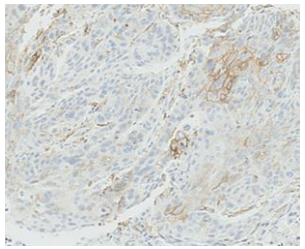
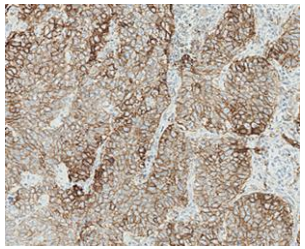
Disclosure

AJS reports consulting/advising role to J&J, Bayer, KSQ therapeutics, BMS, Merck, Astrazeneca, Synthekine, cTRL therapeutics, Regeneron, Enara Bio, Perceptive Advisors, Oppenheimer and Co, Umoja Biopharma, Legend Biotech, Iovance Biotherapeutics, Obsidian Therapeutics, Prelude Therapeutics, Immunocore, Lyell Immunopharma, Amgen and Heat Biologics. Research funding: GSK (Inst), Obsidian (Inst), Lilly (Inst), PACT pharma (Inst), Iovance Biotherapeutics (Inst), Achilles therapeutics (Inst), Merck (Inst), Synthekine (Inst), BMS (Inst), Harpoon Therapeutics (Inst), AffiniT therapeutics (Inst), Legend Therapeutics (Inst), Synthekine (Inst) and Amgen (Inst).

Introduction: STK-012 + SoC in 1L PD-L1 Negative NSQ NSCLC

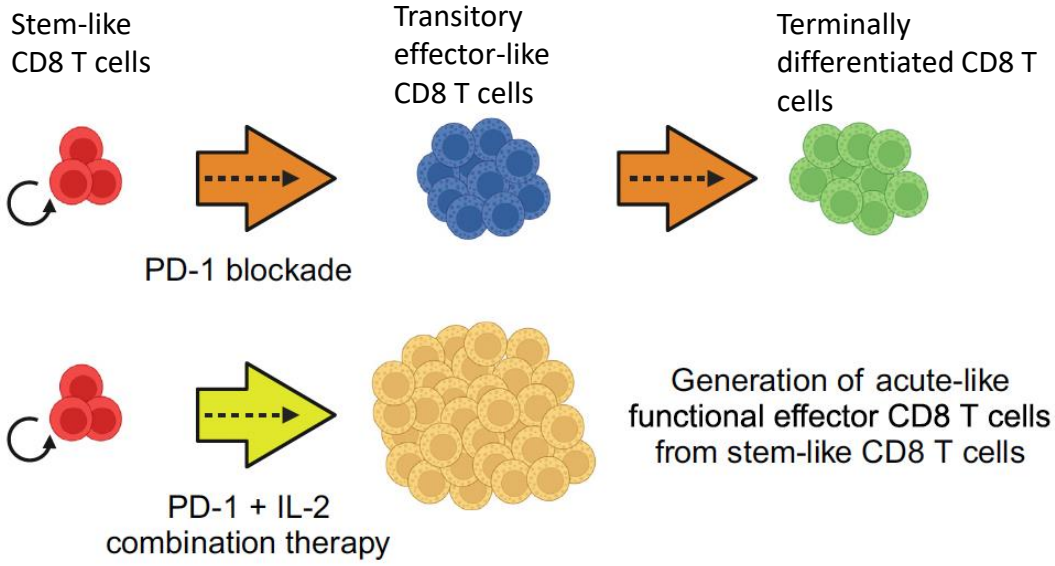
Unmet Need in 1L PD-L1 Negative NSQ NSCLC

- SoC in 1L NSQ NSCLC is immune checkpoint inhibitor (ICI) + chemotherapy however the subset of patients with PD-L1 negative (TPS <1%) tumors have poor outcomes
- As 30-40% of NSQ NSCLC tumors are PD-L1 negative this patient population is a significant unmet need with ORR of 32.3% and PFS of 6.2 months with pembrolizumab + chemotherapy (PCT) [1]

PD-L1	<1%	1-49%	>50%
			
ORR	32.3%	48.4%	61.4%
PFS	6.2 mo	9.4 mo	11.3 mo

Rationale for PD-1 + IL-2 Combination

- IL-2 is a T cell growth factor known to activate, expand, and drive effector T cells into the TME, thereby inducing tumor response
- Reversing T cell exhaustion and generating better effectors is the immunological basis for combining IL-2 with PD-1 therapy [2]



1. Gadgeel et al. JCO 2020; 2. Hashimoto et al. Nature 2022

Introduction: STK-012 + SoC in 1L PD-L1 Negative NSQ NSCLC

STK-012 Mechanism of Action

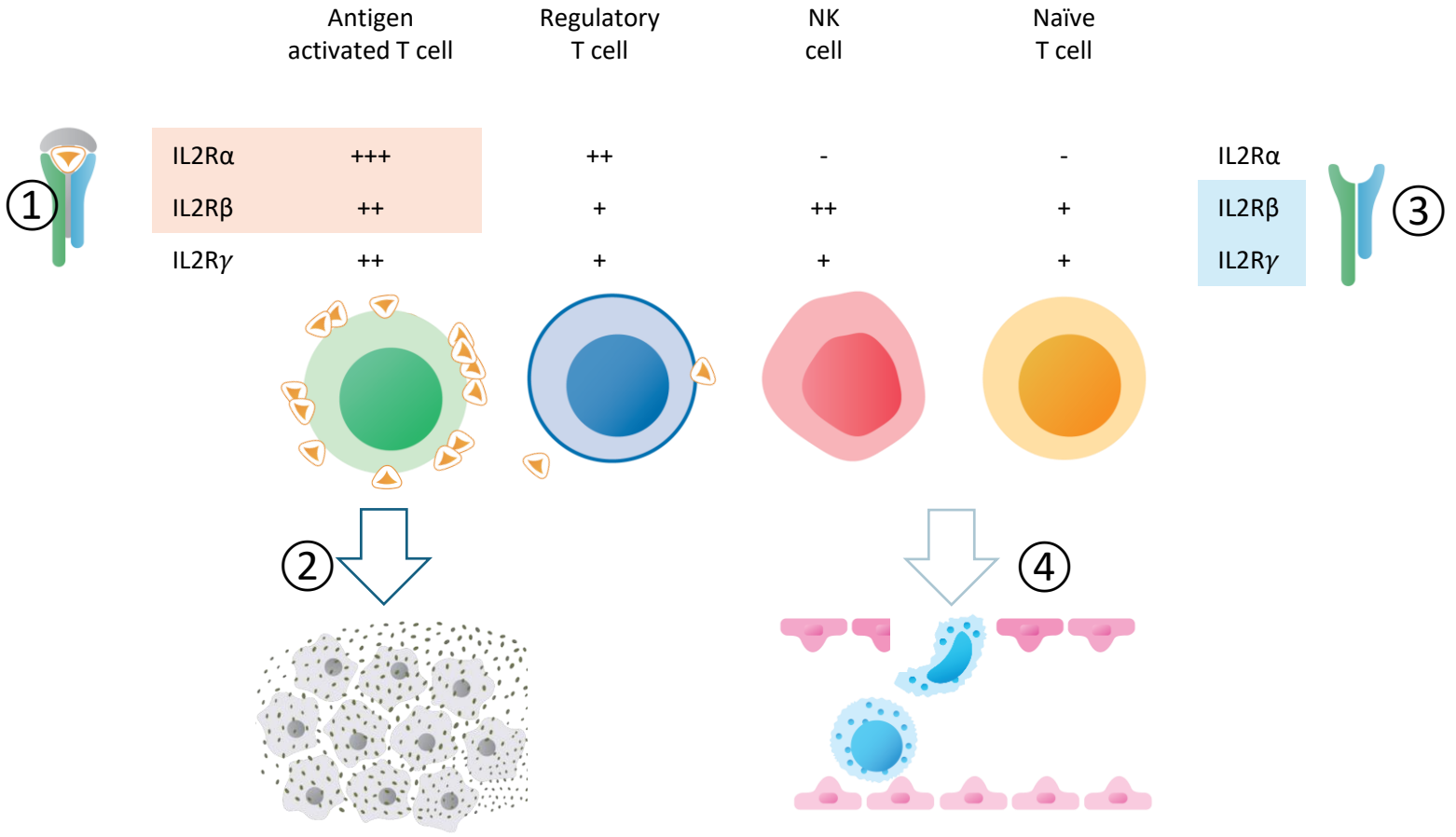
STK-012 is a recombinant IL-2 engineered as an α/β-biased partial agonist

① STK-012 binds to lymphocytes with the highest expression of trimeric IL-2 receptor

② STK-012 stimulates antigen activated T cells to drive efficacy

③ STK-012 avoids lymphocytes that express the dimeric IL-2 receptor

④ STK-012 spares NK cells and naïve T cells to avoid hallmark IL-2 toxicities



STK-012-101 Study Design in 1L NSQ NSCLC

STK-012-101: Phase 1a/1b study of STK-012 + Pembrolizumab + Chemotherapy (PCT) in 1L NSQ NSCLC

Phase 1a (n= 6-10)	→	Phase 1b (n= 20-40)	Key Endpoints
STK-012 2.25 mg + PCT Q3W		STK-012 2.25 mg + PCT Q3W	Primary: Safety
Stage IV NSQ NSCLC		Stage IV NSQ NSCLC	Secondary: ORR
Treatment naïve		Treatment naïve	
PD-L1 unselected		PD-L1 TPS<1%	
No actionable genetic alterations		No actionable genetic alterations	

STK-012 + PCT (outpatient)	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5+
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 AUC 5	X	X	X	X	

STK-012 + PCT Safety in 1L NSQ NSCLC

STK-012 + PCT Safety Population

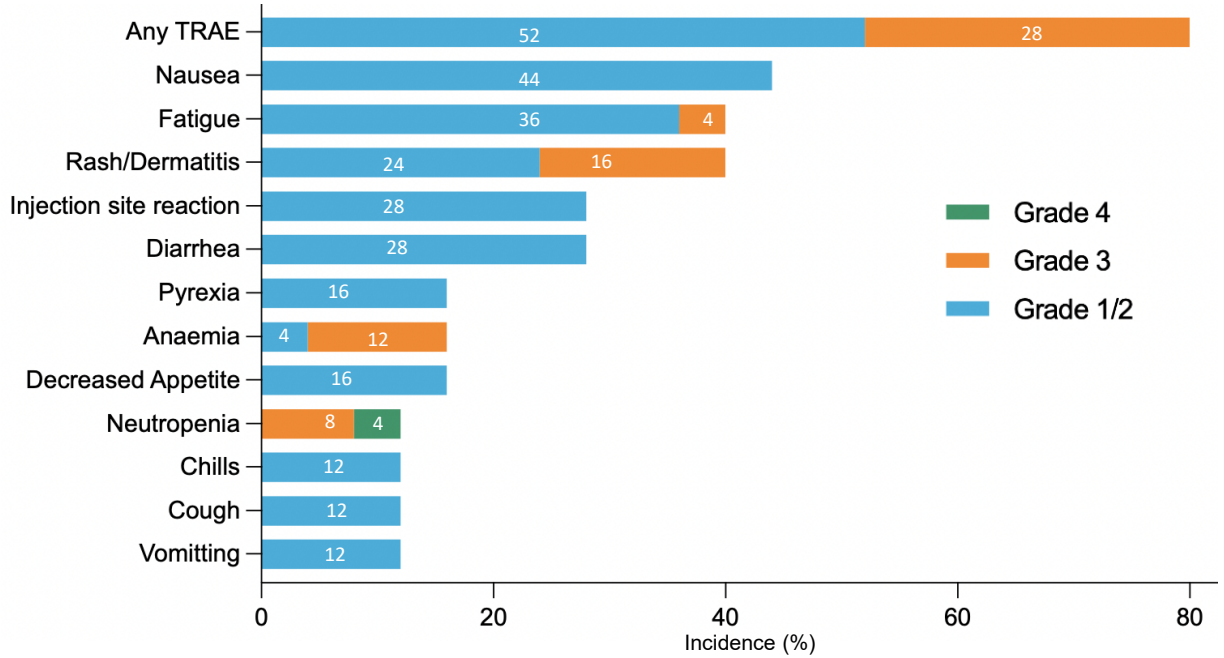
- Total Safety Evaluable (n=25)
- Phase 1a (n=10)
- Phase 1b (n=15)

Key Safety Findings

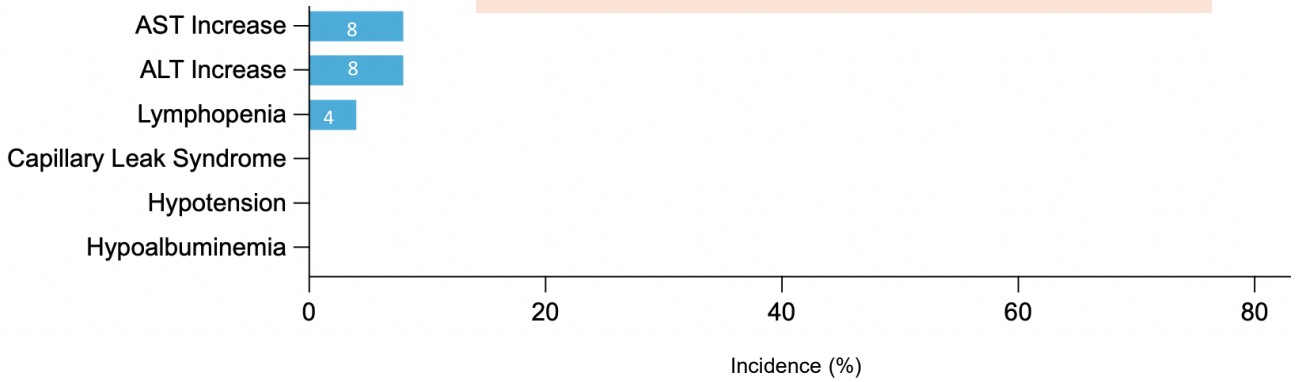
- No DLTs
- Most common TRAES included manageable, reversible nausea (44%), fatigue (40%), and rash (40%)
- One Grade 4 TRAE (Neutropenia) and no Grade 5 AEs
- No significant hallmark IL-2 TRAEs
- No TRAEs led to treatment discontinuation
- One subject had TRAE leading to dose reduction (Gr 3 Dermatitis)

- Safety clinical cutoff: 08-08-2025
- Median Follow-up (min, max): 3.12 months (0.1, 11.0)

Most Common TRAEs (≥10%)



No Significant Hallmark IL-2 TRAEs Observed



STK-012 + PCT Baseline Characteristics in 1L NSQ NSCLC

Baseline Characteristics Efficacy Evaluable (n=22), n (%)	
Median age, years (range)	69 (30, 82)
Male,	12 (55%)
ECOG PS	
0	13 (59%)
1	9 (41%)
Smoking status	
Current / former	16 (73%)
Never	6 (27%)
PD-L1 Tumor Proportion Score (TPS, local or central)	
PD-L1<1%	18 (82%)
PD-L1=1%	4 (18%)
Histology	
Adeno, non-mucinous	17 (77%)
Adeno, mucinous	5 (23%)

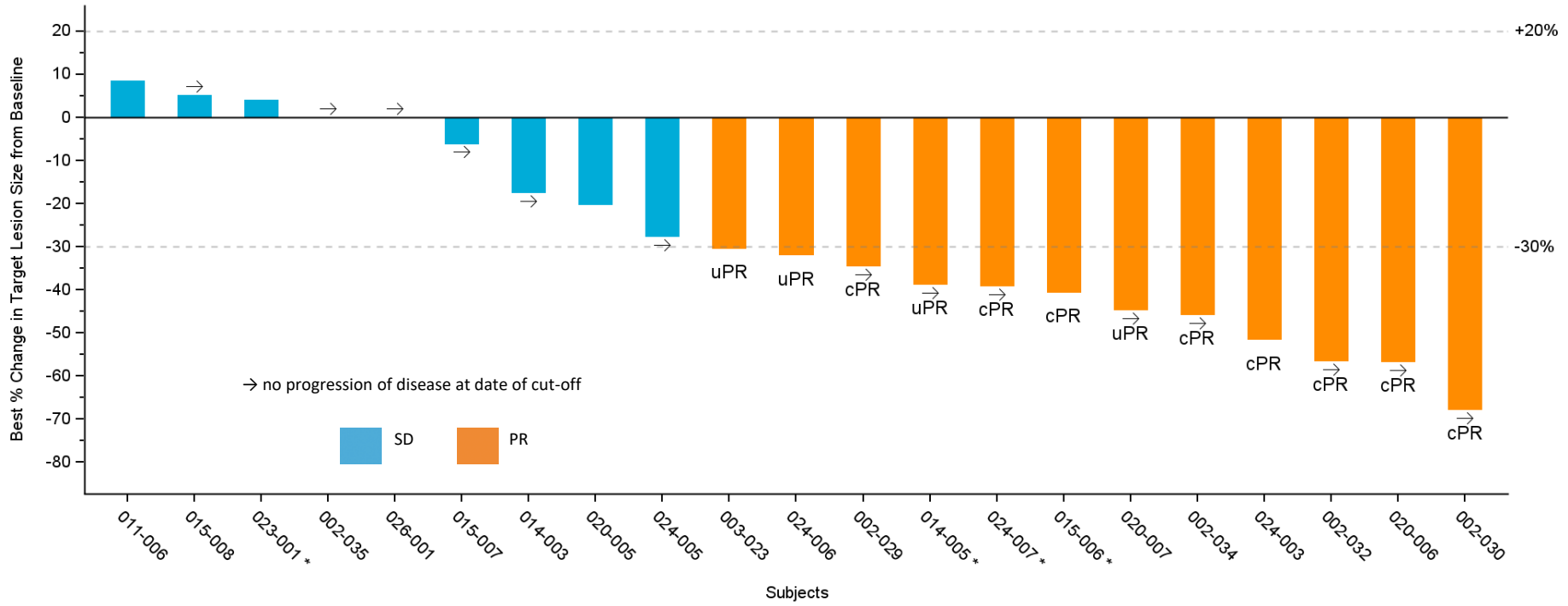
Baseline Molecular Efficacy Evaluable (n=22)	
≥1 TSG, n (%)	11 (50%)
STK11	10
KEAP1	4
SMARCA4	2
≥2 TSG, n (%)	4 (18%)
STK11 + KEAP1	3
STK11 + KEAP1 + SMARCA4	1
KRAS, n (%)	8 (36%)
G12D (3), G12V (2), G13D (1), G12C (1), Q61H (1)	
Co-occurring with STK11	4

- TSG: Known mutation in tumor suppressor gene associated with primary ICI resistance
- Efficacy clinical cutoff: 09-15-2025
- Median follow-up (min, max): 4 months (1.3, 12.2)
- 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 in 1L NSQ NSCLC (All subjects PD-L1<1% except 4 PD-L1=1%)

STK-012 + PCT shows ORR 55% and DCR 96% in 1L NSQ NSCLC (N=22, all PD-L1<1% except 4 PD-L1=1%)

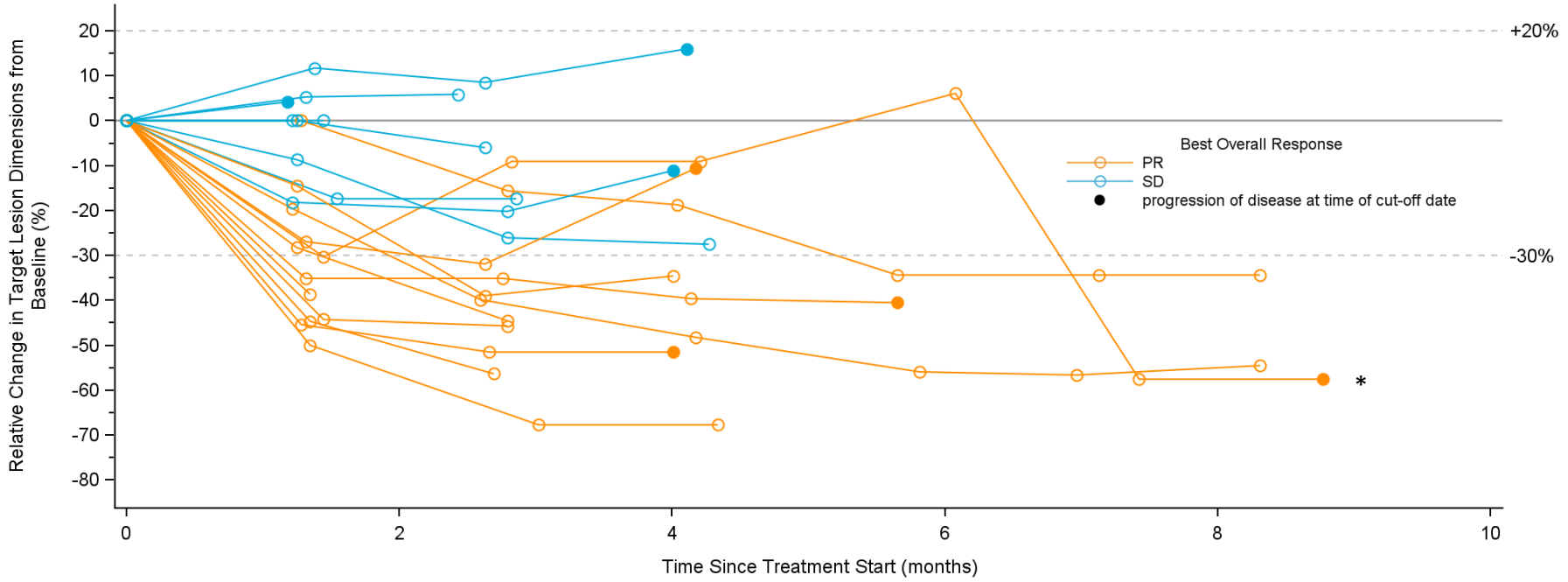
All Efficacy Evaluable (N=22)	
ORR	55%
DCR	96%
BOR	
CR	0
PR	12 (55%)
SD	9 (41%)
PD	0
NE	1 (5%)

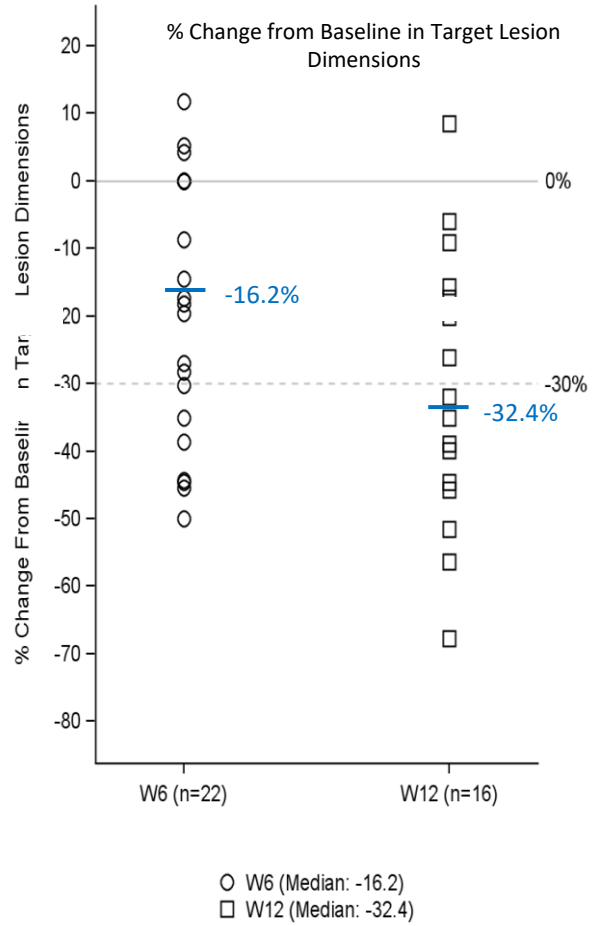


- All subjects PD-L1<1% except 4 PD-L1 TPS =1% *
- Efficacy clinical cutoff: 09-15-2025
- Median follow-up (min, max): 4 months (1.3, 12.2)
- One subject with BOR of NE (1st scan TETE) who is still on treatment is not represented on the waterfall plot

STK-012 + PCT in 1L NSQ NSCLC (All subjects PD-L1<1% except 4 PD-L1=1%)

STK-012 + PCT shows deepening of response over time with 15/22 subjects ongoing



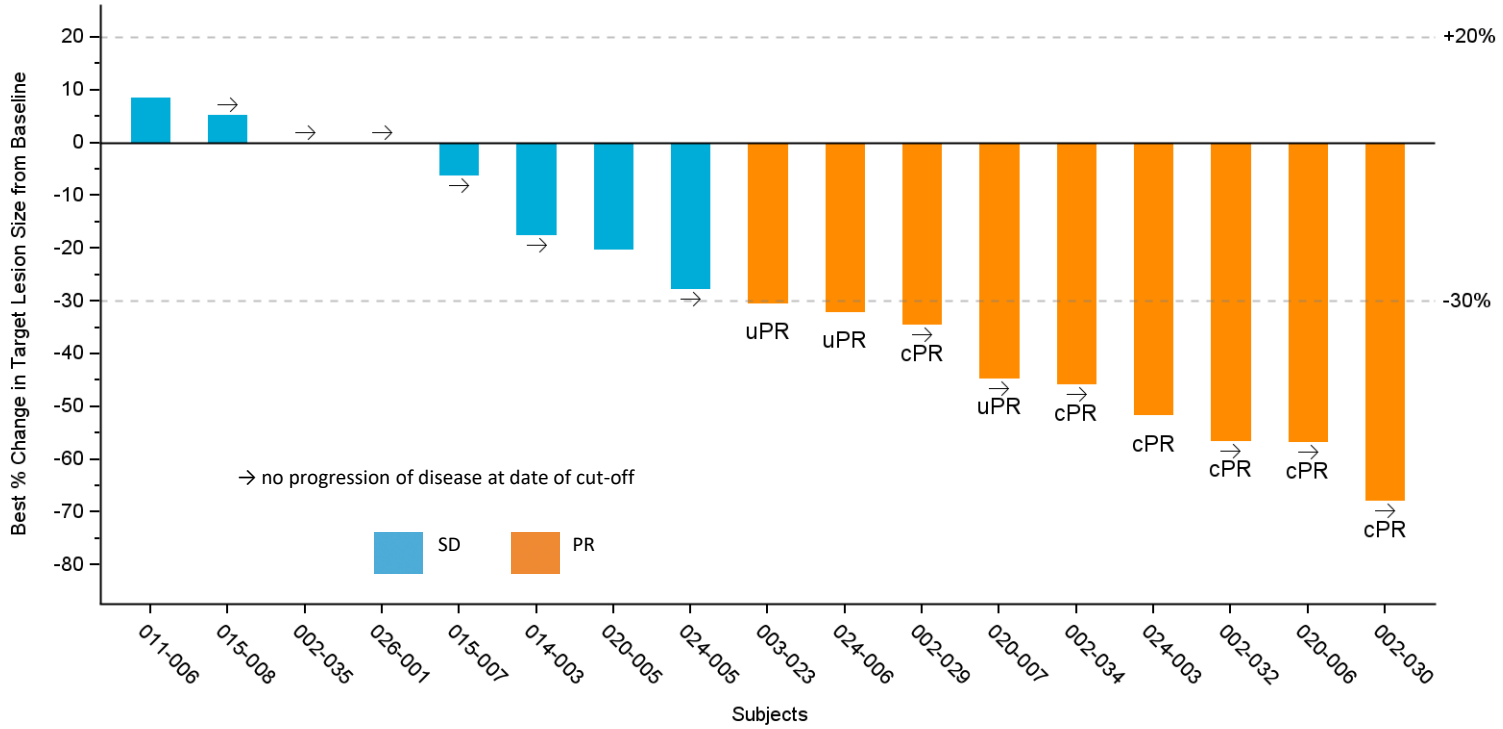


- Efficacy clinical cutoff: 09-15-2025
- Median follow-up (min, max): 4 months (1.3, 12.2)
- One subject with BOR of NE (1st scan TETE) who is still on treatment is not represented on the spider plot
- All subjects PD-L1<1% except 4 PD-L1=1%
- Subject 003-023 uPR by investigator assessment however cPR by central blinded radiology assessment *

STK-012 + PCT Efficacy in 1L PD-L1<1% NSQ NSCLC

STK-012 + PCT shows ORR 50% and DCR 94% in 1L PD-L1<1% NSQ NSCLC (N=18)

PD-L1<1% (N=18)	
ORR	50%
DCR	94%
BOR	
CR	0
PR	9 (50%)
SD	8 (44%)
PD	0
NE	1 (5%)

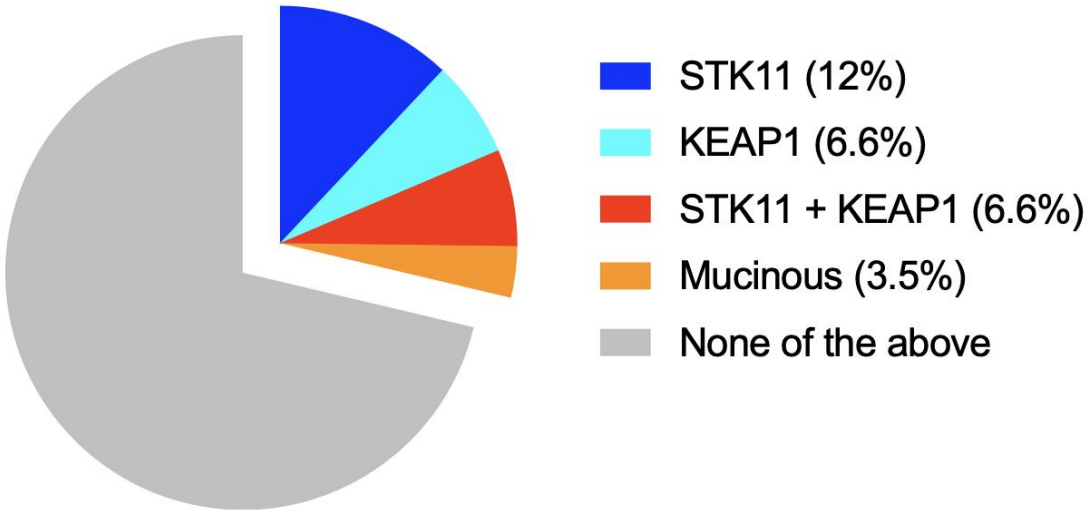


- Efficacy clinical cutoff: 09-15-2025
- Median follow-up (min, max): 4 months (1.3, 12.2)
- One subject with BOR of NE (1st scan TETE) who is still on treatment is not represented on the waterfall plot

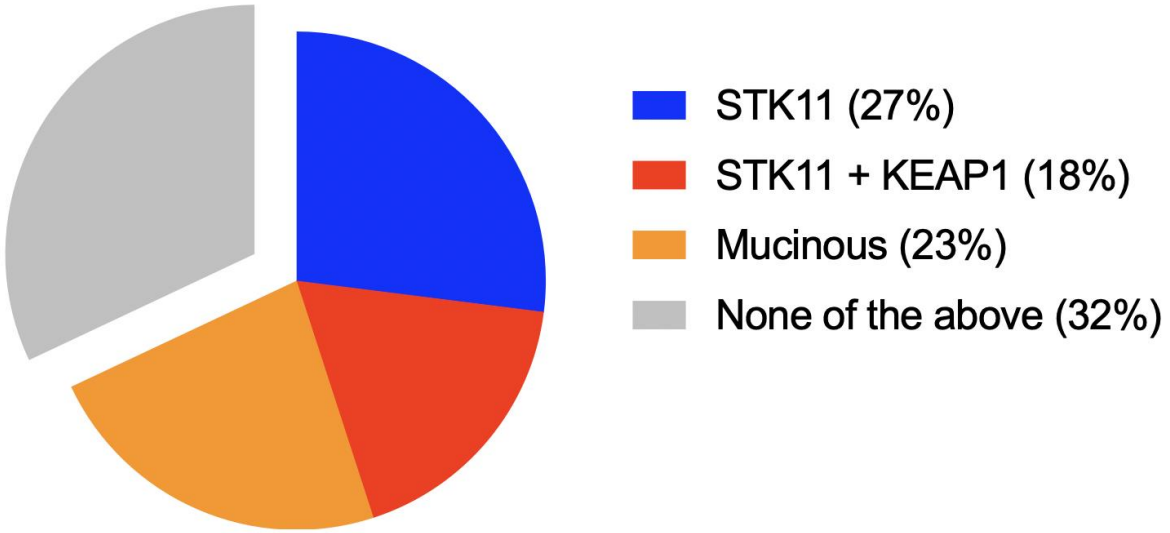
Prevalence of ICI Resistance Characteristics in 1L NSQ NSCLC

The majority of subjects enrolled to STK-012-101 had loss-of-function tumor suppressor gene (TSG) mutations or mucinous histology associated with primary immune resistance

Real world prevalence of ICI resistance in NSQ NSCLC



Prevalence of ICI resistance in STK-012-101



Adapted from Skoulidis et al, Nature 2024; Kim et al, WCLC 2024

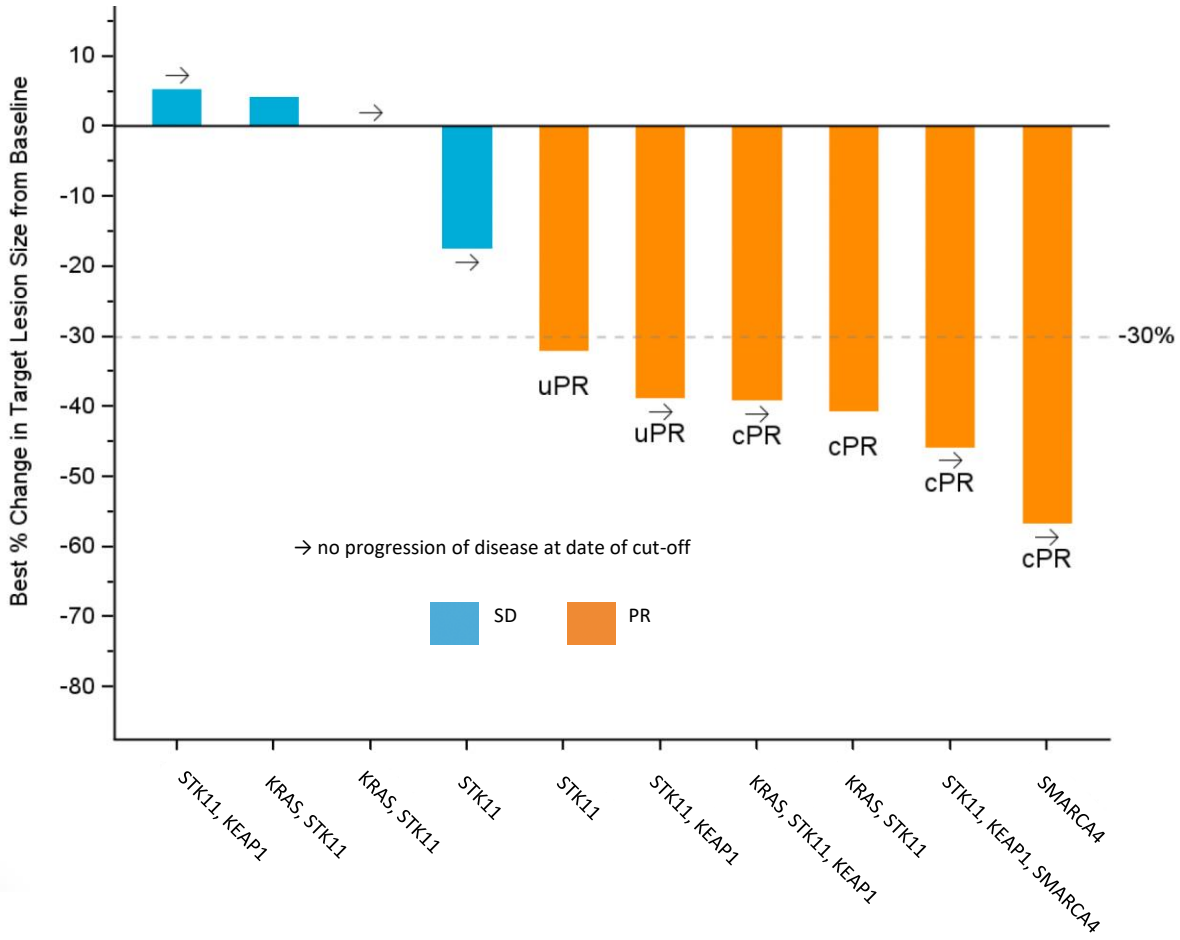
STK-012 + PCT Efficacy in 1L NSQ NSCLC with IO Resistance TSG mutations

STK-012 + PCT shows a 55% ORR in ≥ 1 TSG (N=11) and 75% in 2 TSG (N=4)

STK-012 + PCT in ≥1 TSG (N=11)

- STK11 mutant ORR with pembro + CT (KN189) = 30.6%[1]
- TSG = Known mutation in STK11and/or KEAP1 and/or SMARCA4
- All PD-L1<1% (n=7) or PD-L1=1% (n=4)
- KRAS co-mutation in 4/11
- ORR 55% in ≥1 TSG
- ORR 75% in 2 TSG

- Efficacy clinical cutoff: 09-15-2025
- One subject with STK11 mutation and a BOR of NE (1st scan TETE) who is still on treatment is not represented on the waterfall plot



[1] Garassino et al, JTO Clin Res Rep 2022

STK-012 + PCT Efficacy in 1L NSQ NSCLC with IO Resistance TSG mutations

STK-012 + PCT shows ORR 55% with ≥ 1 TSG (N=11) and ORR 75% in 2 TSG (N=4)

Real World Outcomes with PCT [1]

- 20% ORR in ≥1 TSG mutation (STK11 and/or KEAP1)
- 7.1% ORR in 2 TSG co-mutations (STK11 and KEAP1)
- ~40% with PD as best overall response

BOR	WT	≥1 TSG	2 TSG (STK11+KEAP1)
Total n	72	69	28
CR/PR	48.6%	20%	7.1%
SD	37.5%	42%	50%
PD	14.9%	38%	42.9%

STK-012 + PCT

- 55% ORR in ≥ 1 TSG *
- 75% ORR in 2 TSG co-mutations (STK11 and KEAP1)
- No patients with PD as best overall response

BOR	≥ 1 TSG	2 TSG (STK11+KEAP1)
Total n	11	4
CR/PR	6 (55%)	3 (75%)
SD	4 (36%)	1 (25%)
PD	0	0

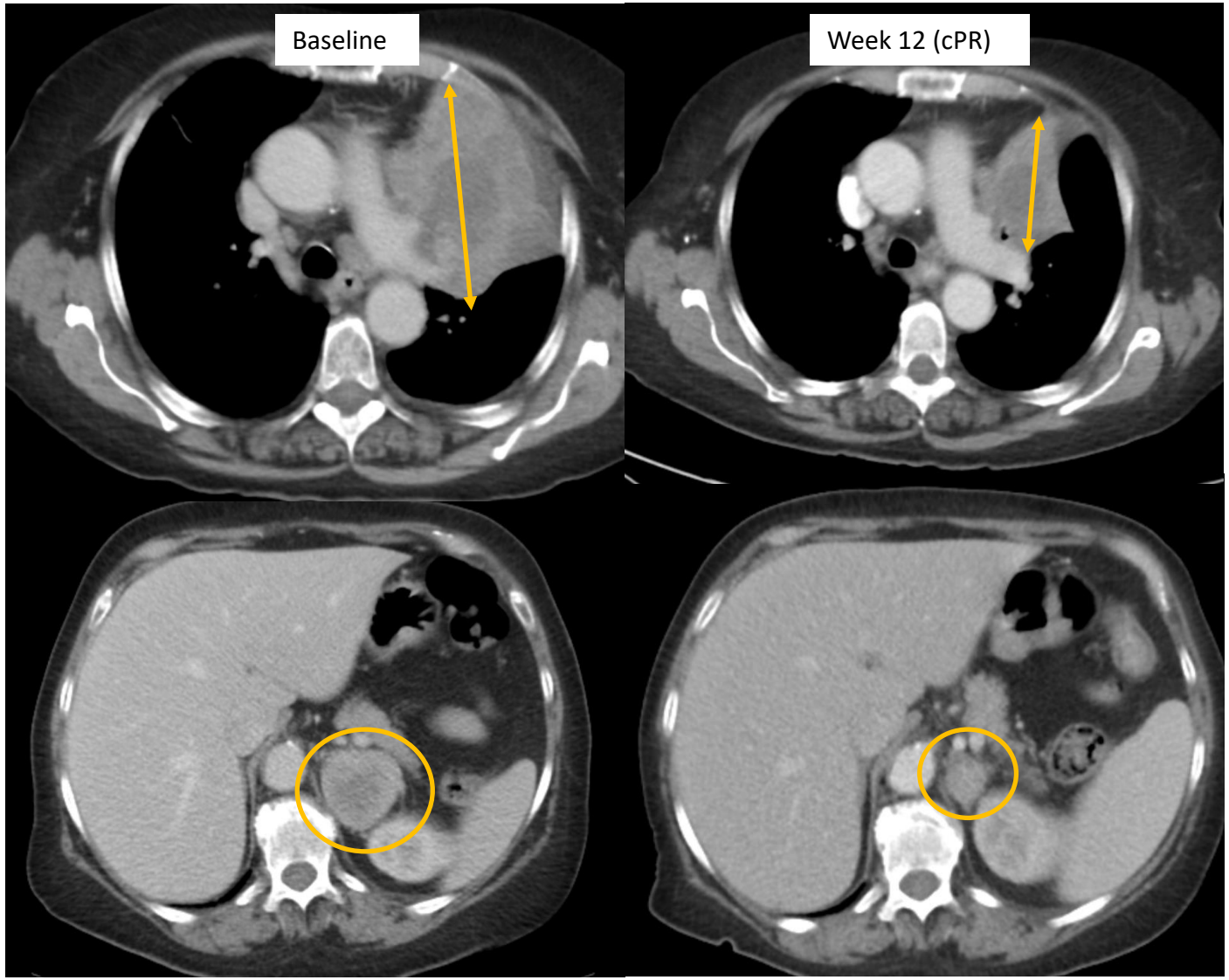
- One additional subject with STK11 mutation and BOR of NE (1st scan TETE) who is still on treatment is not represented in the table
- * STK11 only (n=6), STK11 and KEAP1 (n=4), SMARCA4 only (n=1)

1. Adapted from Skoulidis et al, Nature 2024

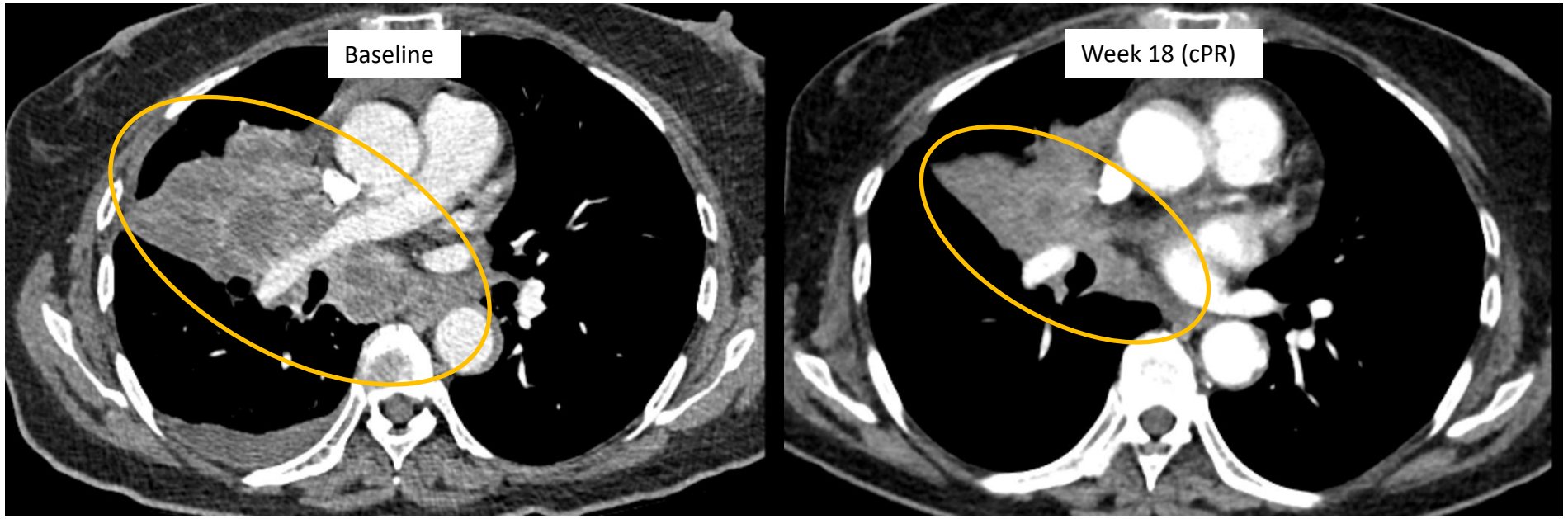
STK-012 + PCT Efficacy in 1L NSQ NSCLC with IO Resistance TSG mutations

Case study 002-034

- 63 yo female with PD-L1<1% NSQ NSCLC with disease in lung and metastases to mediastinal LNs, adrenal, bone, and brain
- Molecular: STK11, KEAP1, SMARCA4 triple co-mutations
- 46% maximum reduction in target lesions and BOR of confirmed PR
- Treatment response in extensive lung mass and adrenal metastasis shown



STK-012 + PCT Efficacy in 1L NSQ NSCLC with IO Resistance TSG mutations



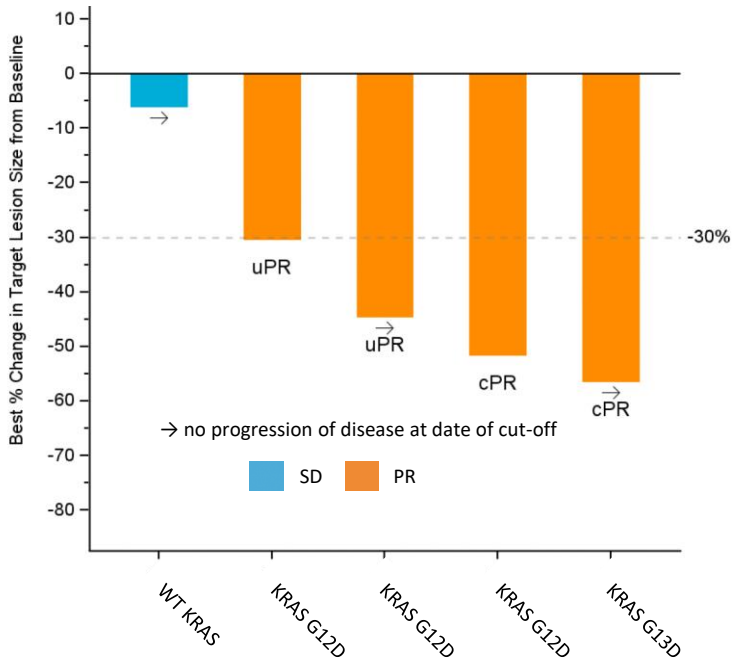
Case study 024-007

- 65 yo female with PD-L1=1% NSQ NSCLC and metastases from lung to mediastinal LNs, bone, and brain
- Molecular: KRAS Q61H, STK11+ KEAP1 co-mutations
- 39% maximum reduction in target lesions and BOR of confirmed PR
- Treatment response in extensive lung mass and mediastinal LNs shown

STK-012 + PCT Efficacy in 1L NSQ NSCLC with Mucinous Histology

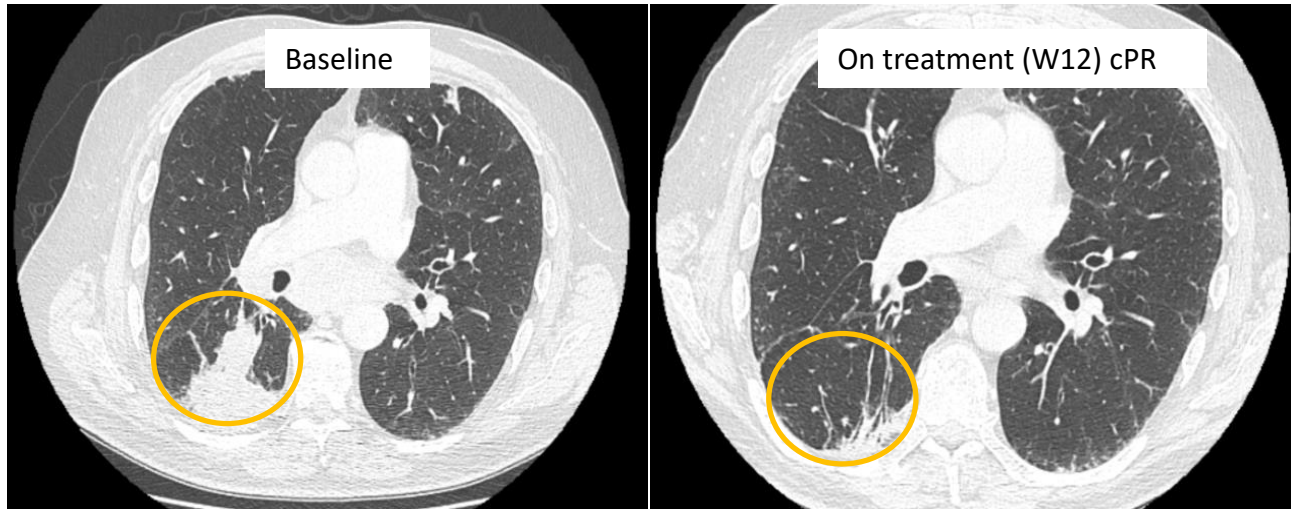
STK-012 + PCT in mucinous adenocarcinoma

- Mucinous adenocarcinoma has a poor response to SoC PCT with an ORR of 21.3% and PFS of 5 months [1]
- STK-012 + PCT ORR: 80% (N= 4/5)



Case study 002-032

- 68 yo male never smoker with PD-L1<1% mucinous adenocarcinoma with lung to hilar, mediastinal and supraclavicular LNs
- Molecular: KRAS G13D mutation with
- 59% maximum decrease in target lesions and BOR of confirmed PR
- Treatment response in lung mass shown

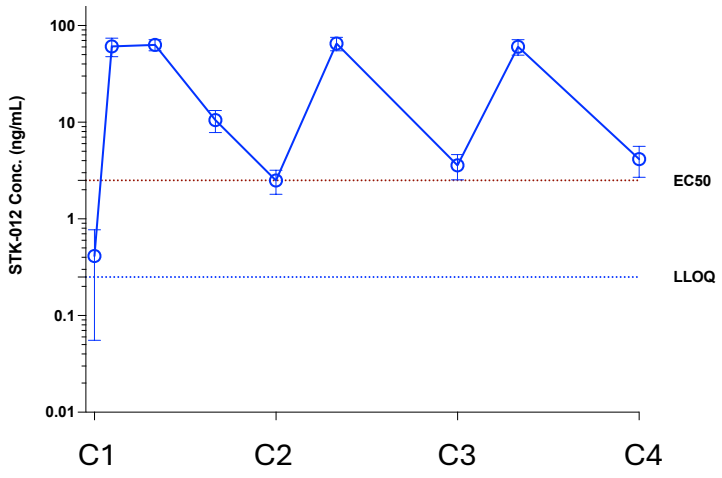


1. Federico et al, Ann Oncol 2024

Pharmacokinetics and Peripheral Induction of IFNγ and Chemokines

STK-012 Pharmacokinetics

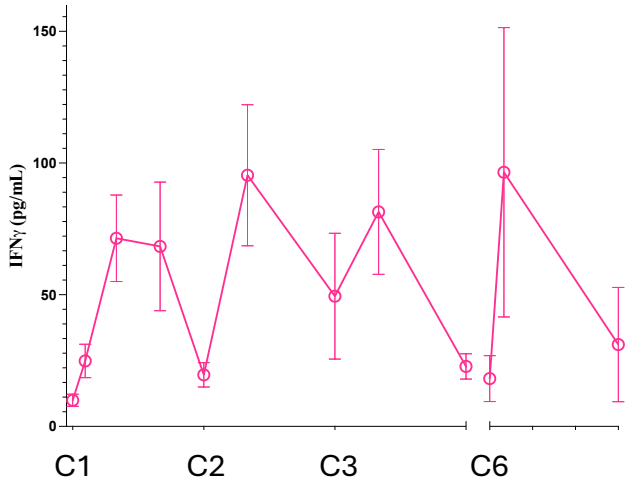
5.7 day half life demonstrates selectivity and supports Q3W dosing



n=22

STK-012 + PCT induction of IFNγ

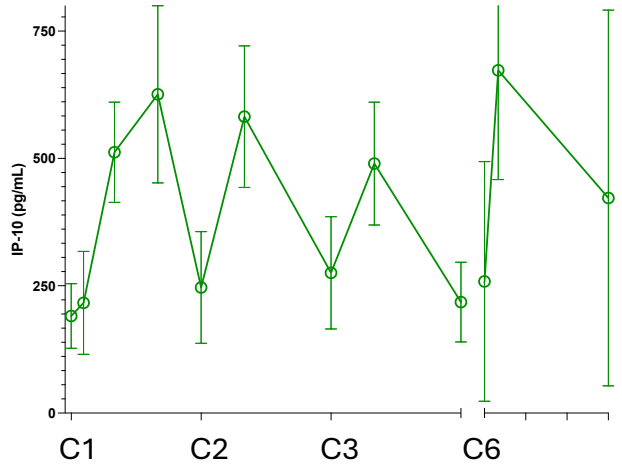
Persistent and predictable induction of IFNγ, a hallmark cytokine of activated CD8+ T cells



n=22

STK-012 + PCT induction of IP10

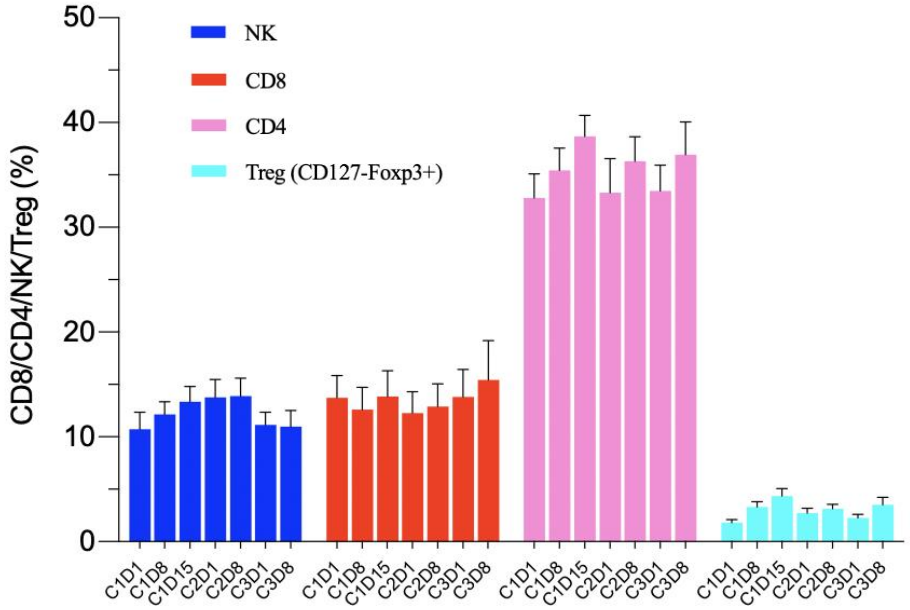
Persistent and predictable induction of IP10 (CXCL10) enables enhanced T cell trafficking into tissue



n=22

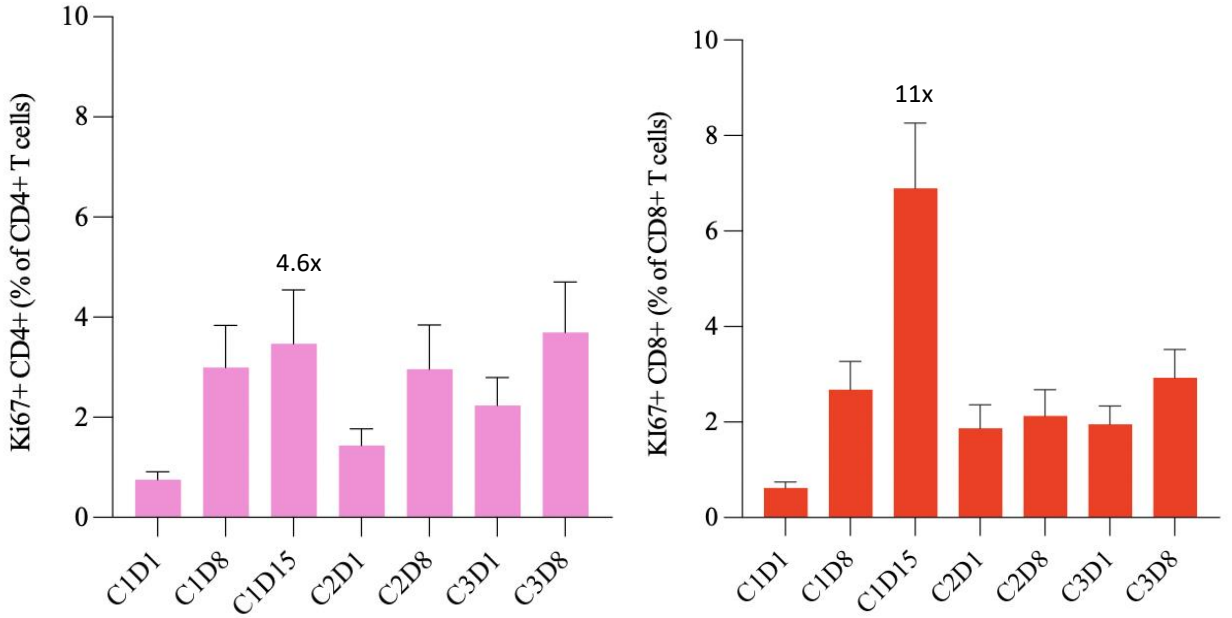
Peripheral Pharmacodynamics: Selective Proliferation of Activated T Cells

Limited expansion of NK and Tregs with STK-012 + PCT



n=22

STK-012 + PCT ↑ in proliferating activated CD8+ and CD4+ T cells



n=22

- Proliferating cells demonstrate markers of antigen activation such as CD38, 4-1BB, CD27, PD-1 (not shown)

Conclusion: STK-012 + PCT in 1L PD-L1 Negative NSQ NSCLC

STK-012 + PCT safety data

- STK-012 is administered SC Q3W in an outpatient setting
- STK-012 + PCT demonstrated manageable safety profile with most common TRAEs being reversible nausea, fatigue, and rash
- No TRAEs led to treatment discontinuation

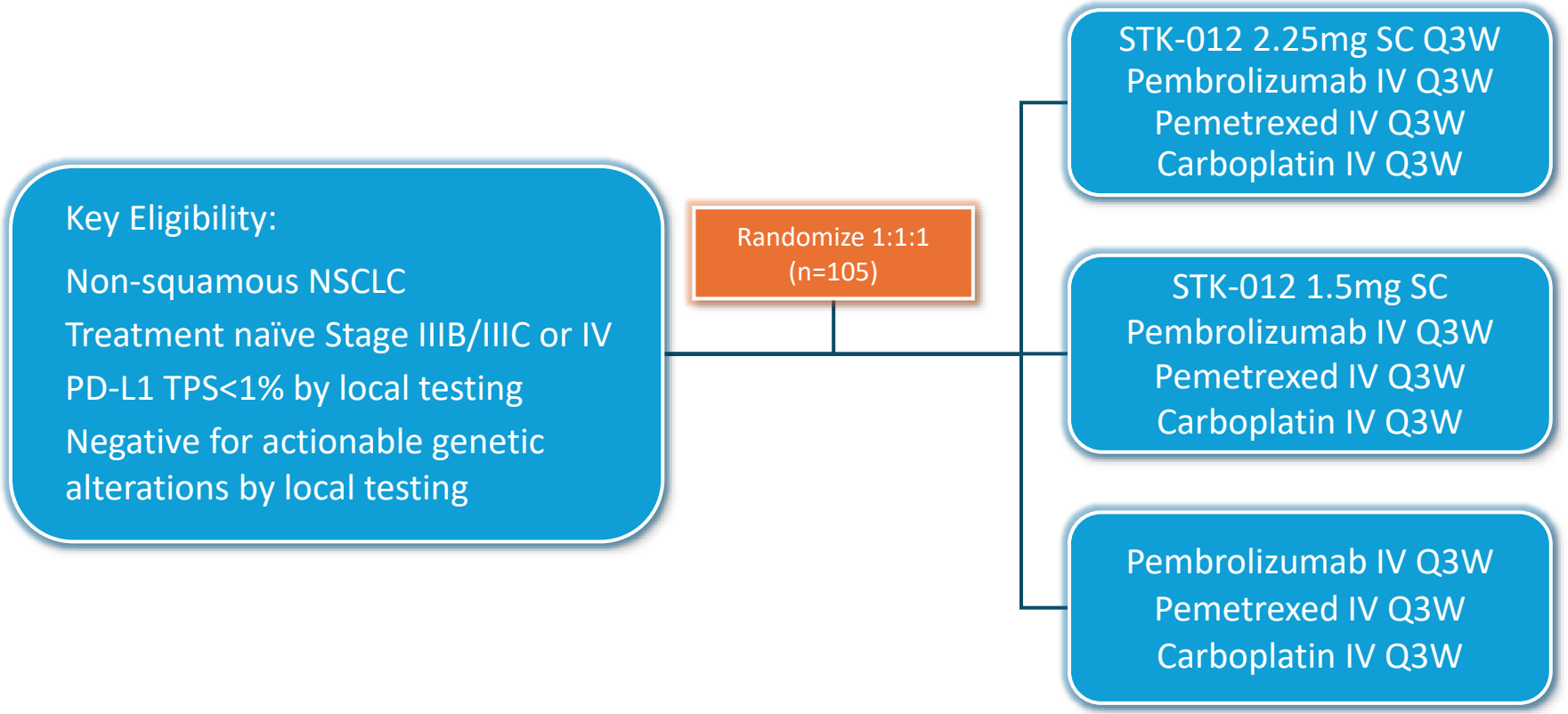
STK-012 + PCT translational data

- STK-012 $T_{1/2}$ = 5.7 days supports Q3W dosing
- Selective ↑ in proliferating activated T cells
- Persistent and predictable induction of IFNγ and CXCL10

STK-012 + PCT efficacy data

- ORR 50% (9/18) in PD-L1<1% NSQ NSCLC
- ORR 55% (6/11) in subjects with ≥ 1 immune resistance mutation (STK11,KEAP1, SMARCA4)
- ORR 75% (3/4) in subjects with highly resistant tumors harboring both STK11 *and* KEAP1 mutations
- Randomized global phase 2 with pembrolizumab, pemetrexed, carboplatin ± STK-012 in 1L PD-L1<1% NSQ NSCLC (NCT05098132) has been initiated

SYNERGY-101: rPh2 in PD-L1 Negative NSQ NSCLC (NCT05098132)



- Primary Endpoint: BICR ORR
- Stratification factors: ECOG (0 or 1) and smoking status (current or prior vs never)

Acknowledgements

- We would like to thank the patients, families, and clinical study teams who participated and made the trial possible.
- This study was supported by Synthekine. All authors contributed to and approved the presentation
- Writing and editing assistance was provided by Dora Miedaner, DVM PhD of Synterex, Inc., and funded by Synthekine.