DRAGON trial: durable remission rate with the latent TGFβ1 inhibitor linavonkibart (SRK-181) and pembrolizumab in patients with immune checkpoint inhibitor–resistant advanced cancers

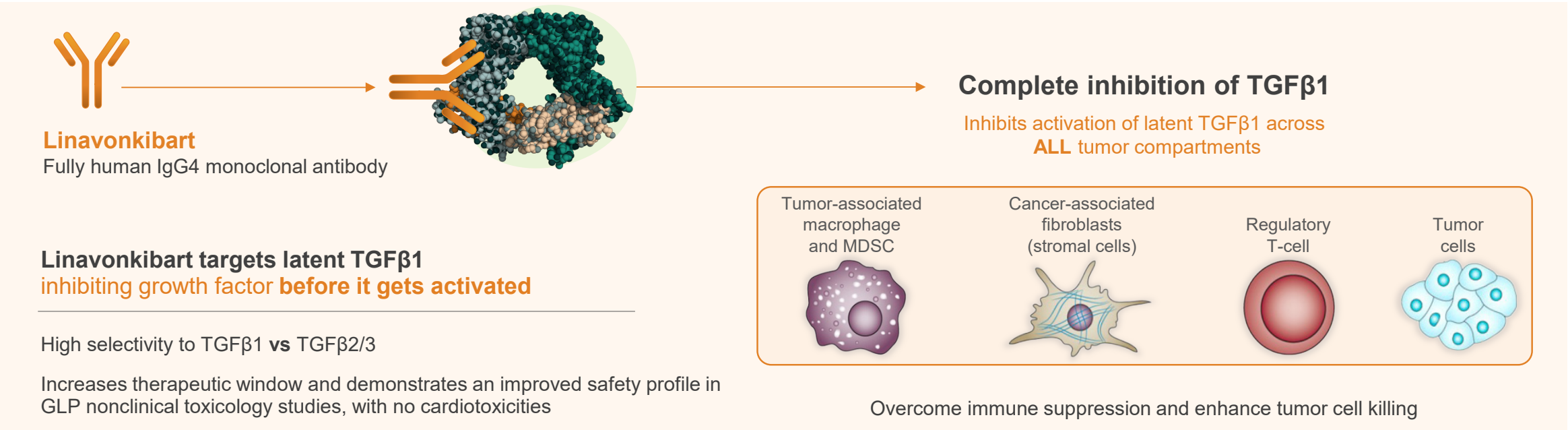
Timothy A. Yap[1], Randy F. Sweis[2], Ulka Vaishampayan[3], Deepak Kilari[4], Ahmad Tarhini[5], Justin F. Gainor[6], Minal Barve[7], Meredith Mckean[8], Guru Sonpavde[9], David Park[10], Sunil Babu[11], Rana R. McKay[12], Clara Hwang[13], Amna Sher[14], Chaitali Nangia[15], Miso Kim[16], Jungyoon Choi[17], Yawen Ju[18], Lan Liu[18], Susan Henry[18], Steve DeWall[18], Lu Gan[18]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]University of Chicago, Chicago, IL, USA; [3]University of Michigan, Ann Arbor, MI, USA; [4]Medical College of Wisconsin, Milwaukee, WI, USA; [5]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [6]Massachusetts General Hospital Harvard Medical School, Boston, MA, USA; [7]Mary Crowley Cancer Research, Dallas, TX, USA; [8]Sarah Cannon Research Institute, Nashville, TN, USA; [9]AdventHealth Medical Group, Orlando, FL, USA; [10]St. Jude Crosson Cancer Institute/Providence Medical Foundation, Fullerton, CA, USA; [11]Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, USA; [12]University of California San Diego Moores Cancer Center, San Diego, CA, USA; [13]Henry Ford Health System, Detroit, MI, USA; [14]Stony Brook Cancer Center, Stony Brook, NY, USA; [15]Hoag Memorial Hospital Presbyterian, Newport Beach, CA, USA; [16]Seoul National University Hospital, Seoul, South Korea; [17]Korea University Ansan Hospital, Ansan, South Korea; [18]Scholar Rock, Inc., Cambridge, MA, USA

Introduction

- Linavonkibart (SRK-181) is a first-in-class, fully human IgG4 monoclonal antibody that inhibits latent transforming growth factor beta-1 (TGFβ1) within the tumor microenvironment, acting in a context-independent manner (**Figure 1**)
- In mouse tumor models of bladder, melanoma, and breast cancer, linavonkibart in combination with anti–programmed cell death protein 1 (anti-PD-1) therapy overcame primary anti-PD-1 resistance and demonstrated antitumor activity[1]

Figure 1. Linavonkibart proposed mechanism of action[1,2]



Linavonkibart
Fully human IgG4 monoclonal antibody

Complete inhibition of TGFβ1
Inhibits activation of latent TGFβ1 across **ALL** tumor compartments

Linavonkibart targets latent TGFβ1
inhibiting growth factor **before it gets activated**

High selectivity to TGFβ1 **vs** TGFβ2/3

Increases therapeutic window and demonstrates an improved safety profile in GLP nonclinical toxicology studies, with no cardiotoxicities

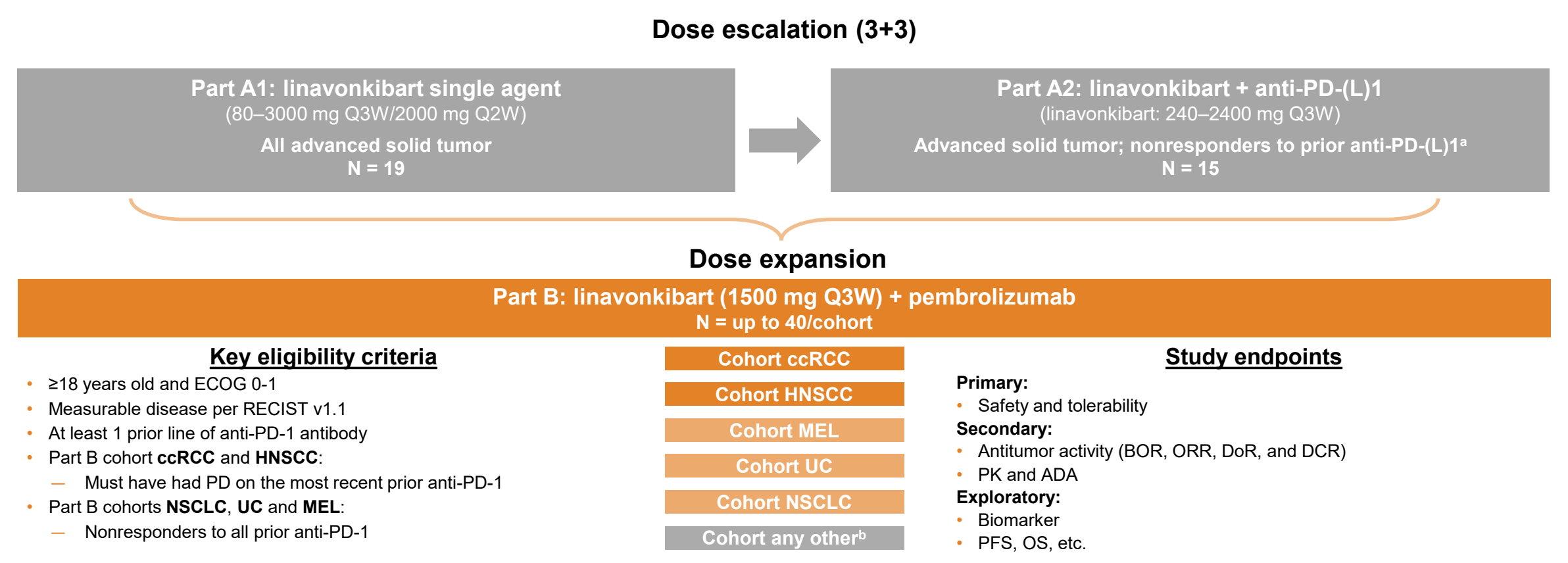
Overcome immune suppression and enhance tumor cell killing

- Here, we present preliminary safety, efficacy, and biomarker results from DRAGON (NCT04291079), a phase 1 study that evaluates linavonkibart alone or in combination with pembrolizumab in patients who received prior anti-PD-1 therapy

Phase 1 clinical trial overview

- DRAGON (NCT04291079) is an ongoing, open-label, phase 1 study that evaluates linavonkibart as a single agent or in combination with pembrolizumab (**Figure 2**)
- In the phase 1, part A dose escalation, linavonkibart was well tolerated, with no dose-limiting toxicities or grade ≥4 treatment-related adverse events (TRAEs), and efficacy results were promising[3,4] The recommended dose for part B was 1500 mg once every 3 weeks

Figure 2. DRAGON study design



Dose escalation (3+3)

Part A1: linavonkibart single agent
(80–3000 mg Q3W/2000 mg Q2W)
All advanced solid tumor
N = 19

Part A2: linavonkibart + anti-PD-(L)1
(linavonkibart: 240–2400 mg Q3W)
Advanced solid tumor; nonresponders to prior anti-PD-(L)1[a]
N = 15

Dose expansion

Part B: linavonkibart (1500 mg Q3W) + pembrolizumab
N = up to 40/cohort

Key eligibility criteria

- ≥18 years old and ECOG 0-1
- Measurable disease per RECIST v1.1
- At least 1 prior line of anti-PD-1 antibody
- Part B cohort **ccRCC** and **HNSCC**:
  - Must have had PD on the most recent prior anti-PD-1
- Part B cohorts **NSCLC**, **UC** and **MEL**:
  - Nonresponders to all prior anti-PD-1

Cohort ccRCC
Cohort HNSCC
Cohort MEL
Cohort UC
Cohort NSCLC
Cohort any other[b]

Study endpoints

Primary:
- Safety and tolerability

Secondary:
- Antitumor activity (BOR, ORR, DoR, and DCR)
- PK and ADA

Exploratory:
- Biomarker
- PFS, OS, etc.

[a]Anti-PD-1 and/or anti-PD-L1. [b]The "any other" cohort was terminated early, and the HNSCC cohort was added.

Phase 1 dose expansion

Patient demographics and disposition

- Of those enrolled, all patients had a best response of stable disease (SD) or progressive disease (PD) on prior anti-PD-1, and all but 2 patients with melanoma had disease progression on the last prior anti-PD-1 therapy (**Table 1**)

Safety

- There was only 1 grade 4 TRAE (dermatitis exfoliative generalized) and no grade 5 TRAEs
- Treatment-related serious adverse events occurring in >2% of patients included colitis and pemphigoid in 2 patients each (immune-related adverse events)
  - TRAEs occurring in >5% of patients are shown in (**Table 2**)

Table 1. Baseline characteristics and patient disposition

Baseline characteristics	All[a]
N	78
Age, median (range)	65 y (32–81 y)
Gender, M, n (%)	56 (71.8)
Prior lines of therapy, median (range)	3 (1–9)
Number of lines of prior anti-PD-(L)1, n (%)	
1	48 (61.5)
2	23 (29.5)
3	6 (7.7)
4	1 (1.3)
Best response to last prior anti-PD-(L)1, n (%)	
Stable disease	28 (35.9)
Progressive disease	50 (64.1)
Disease progressed from the last prior anti-PD-1, n (%)	76 (97.4)[b]
Patient disposition	**All[a]**
Enrolled	78
On study, n (%)	4 (5.1)
Stopped treatment, n (%)	74 (94.9)
Reason for completion/discontinuation, n (%)	
Disease progression based on RECIST v1.1	44 (56.4)
Clinical progression	5 (6.4)
Adverse event	19 (24.4)[c]
Withdrawal of consent	5 (6.4)
Investigator decision	1 (1.3)

Data cutoff: September 9, 2024. [a]Includes patients with ccRCC (30), HNSCC (11), MEL (11), UC (11), NSCLC (11), and 4 patients in "any other" cohort. [b]Two MEL patients discontinued the last prior anti-PD-(L)1 due to other reasons instead of disease progression. [c]Eleven (14.1%) patients discontinued due to AEs related to linavonkibart (rash maculo-papular [3 patients]; dermatitis exfoliative generalized, immune-mediated vasculitis, lichenoid keratosis, pneumonitis, rash erythematous, stomatitis, squamous cell carcinoma of skin [1 patient each]; and immune-mediated myocarditis and pemphigoid in the same patient); 13 (16.7%) patients discontinued due to AEs related to linavonkibart or pembrolizumab (those listed prior, plus colitis and pneumonitis [1 patient each]).

Table 2. Treatment-related adverse events

Treatment-related adverse event[a]	All grades (>5%) N = 78	≥Grade 3 N = 78
Rash[b]	26 (33.3%)[c]	11 (14.1%)[c]
Pruritus	21 (26.9%)[c]	1 (1.3%)[c]
Fatigue	17 (21.8%)	1 (1.3%)
Diarrhea	12 (15.4%)	0
Nausea	6 (7.7%)	1 (1.3%)
Arthralgia	5 (6.4%)	0
ALT increased	4 (5.1%)	2 (2.6%)
AST increased	4 (5.1%)	1 (1.3%)
Decreased appetite	4 (5.1%)	0
Dyspnea	4 (5.1%)	0
Pyrexia	4 (5.1%)	0
Stomatitis	4 (5.1%)	1 (1.3%)
Vomiting	4 (5.1%)	0

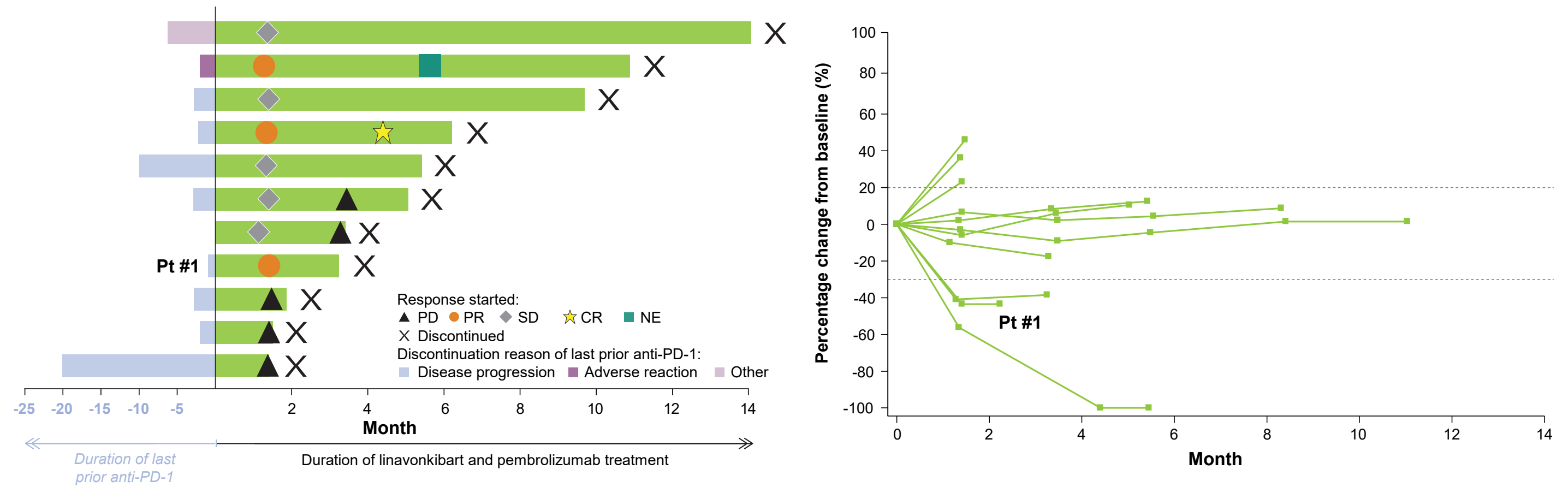
Data cutoff: September 9, 2024. [a]A treatment-related adverse event is an event with either a relationship to linavonkibart or a relationship to anti-PD-(L)1 drug categorized as "Related." [b]Rash includes rash, rash macular, rash maculo-papular, rash erythematous, and rash pruritic. [c]Treatment-related immune-related adverse event.

Phase 1 dose expansion: efficacy

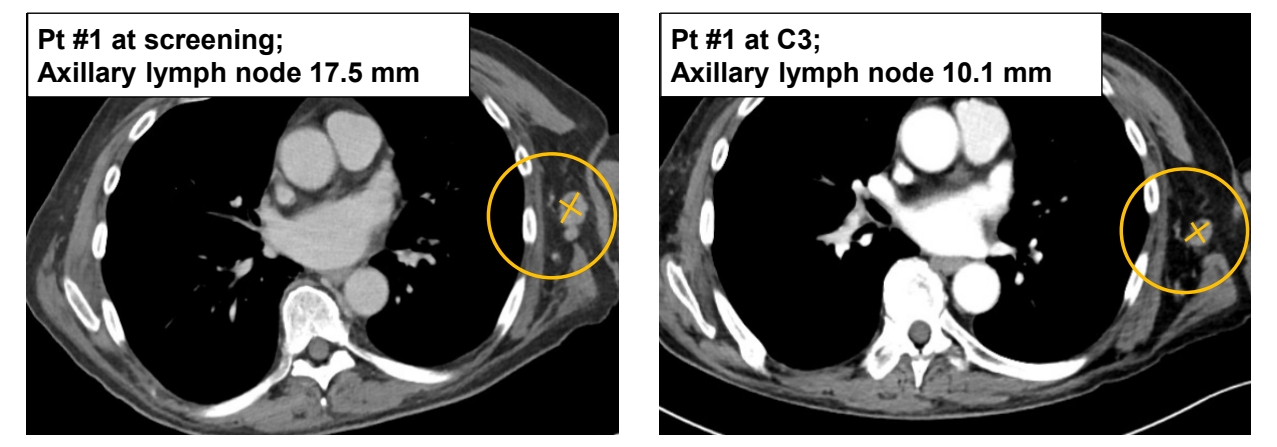
Melanoma

- Median lines of prior cancer therapy: 3 (range, 1–7)

Figure 3. Clinical responses in melanoma



Efficacy	Intention-to-treat N = 11
ORR	3 (27.3%)
CR (unconfirmed)	1 (9.1%)
PR (confirmed)	2 (18.2%)
mDoR (months)	4.9 (4.0, 7.2)
DCR	8 (72.7%)



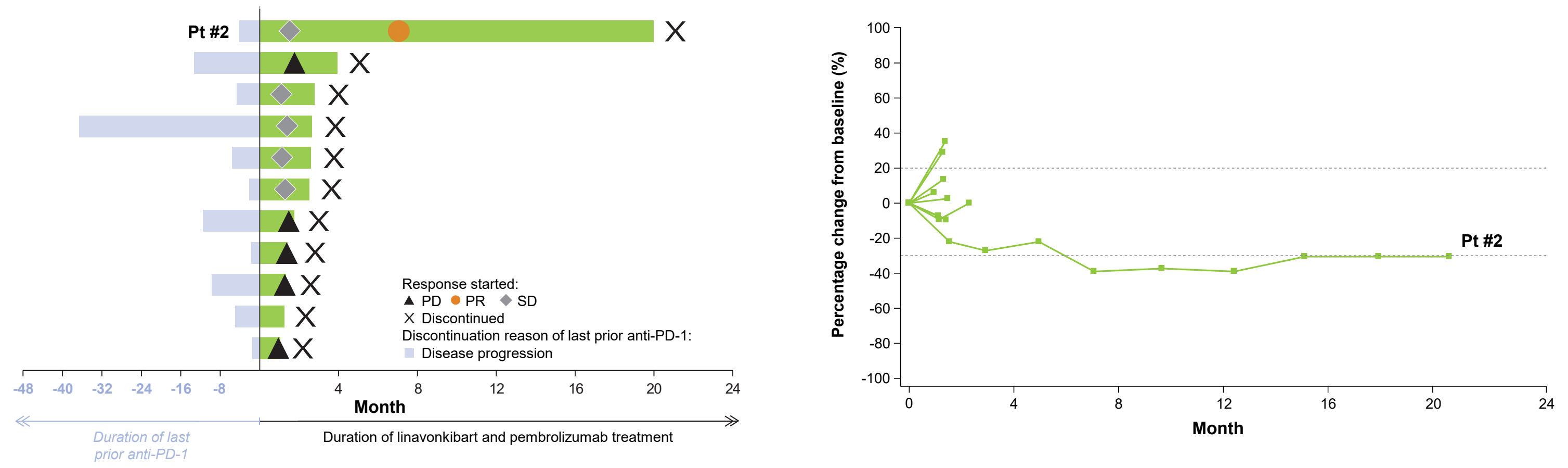
Pt #1 at screening; Axillary lymph node 17.5 mm

Pt #1 at C3; Axillary lymph node 10.1 mm

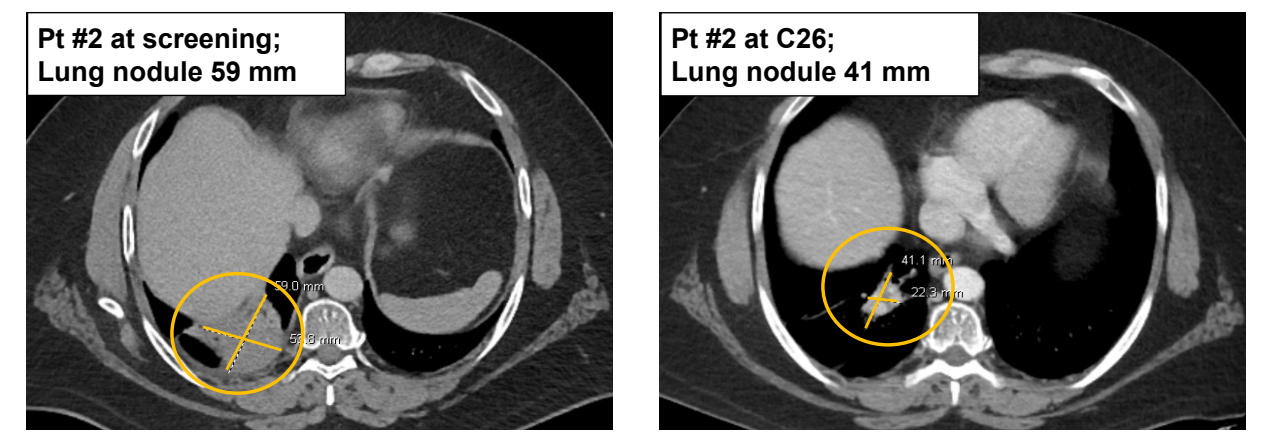
Urothelial carcinoma

- Median lines of prior cancer therapy: 4 (range, 2–5)

Figure 4. Clinical responses in urothelial carcinoma



Efficacy	Intention-to-treat N = 11
ORR	1 (9.1%)
PR (confirmed)	1 (9.1%)
mDoR (months)	12.9 (12.9, 12.9)
DCR	5 (45.5%)



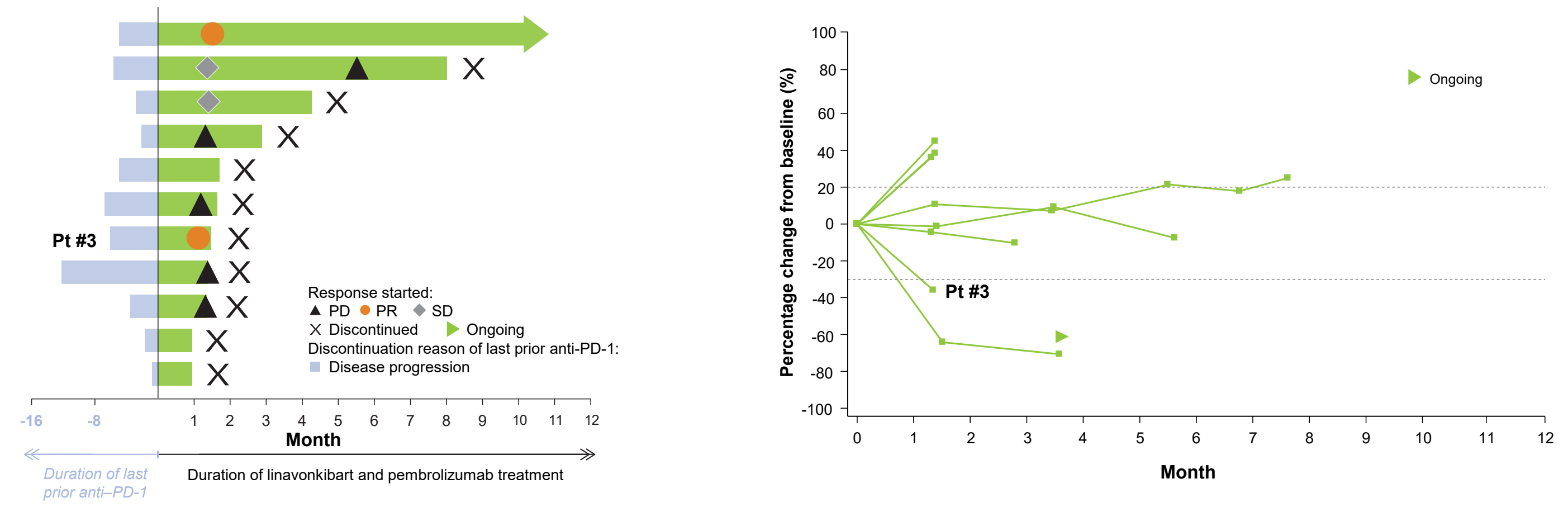
Pt #2 at screening; Lung nodule 59 mm

Pt #2 at C26; Lung nodule 41 mm

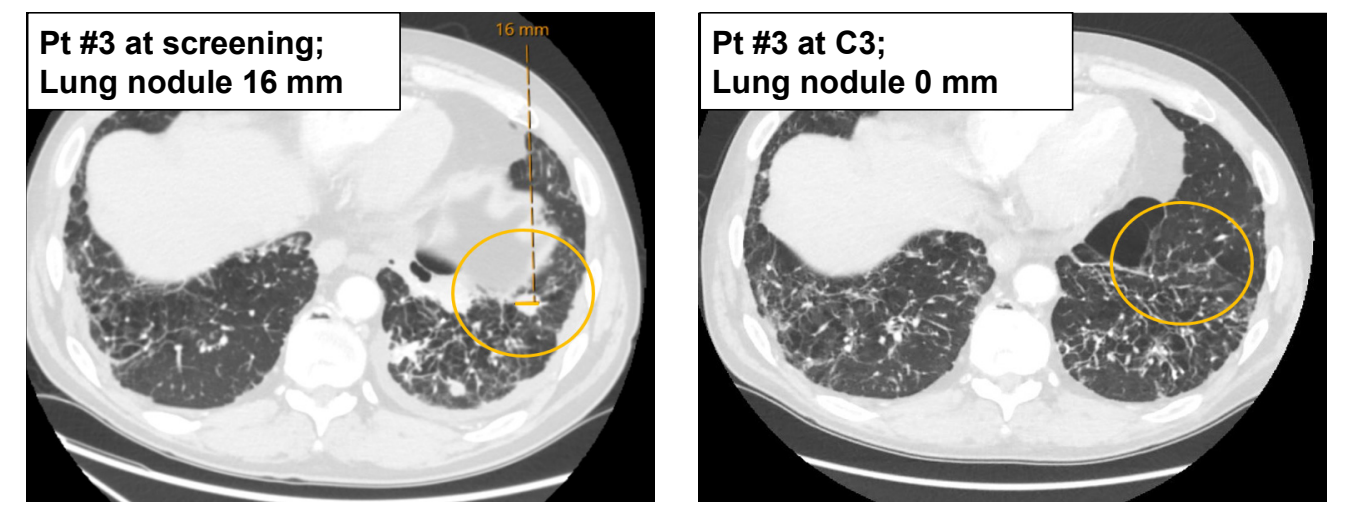
Head and neck squamous cell carcinoma cohort

- Median lines of prior cancer therapy: 3 (range, 1–7)

Figure 5. Clinical responses in head and neck squamous cell carcinoma



Efficacy	Intention-to-treat N = 11
ORR	2 (18.2%)
PR (confirmed)	1 (9.1%)
PR (unconfirmed)	1 (9.1%)
mDoR (months)	4.7 (0.1, 9.3+)
DCR	4 (36.4%)



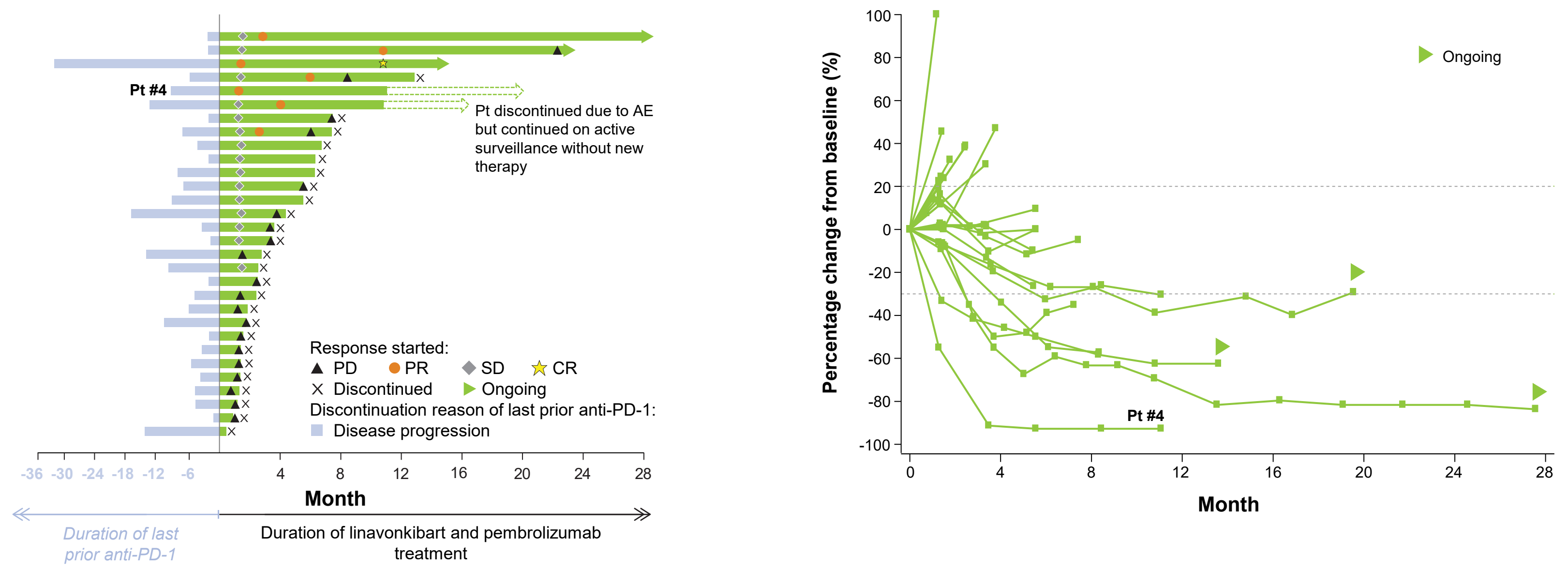
Pt #3 at screening; Lung nodule 16 mm

Pt #3 at C3; Lung nodule 0 mm

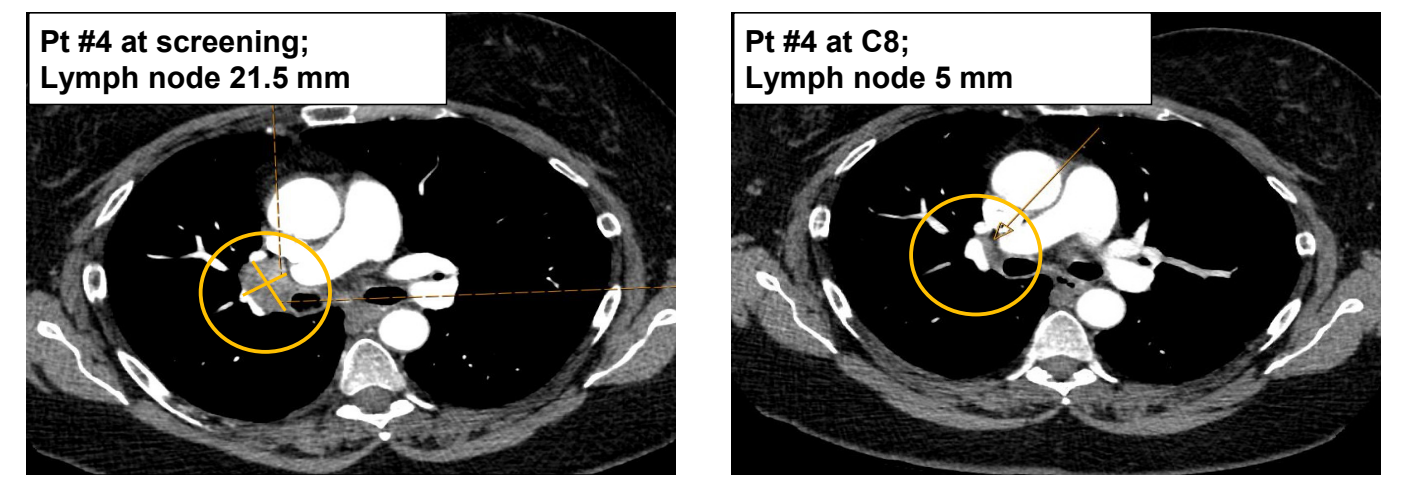
Clear cell renal cell carcinoma cohort

- IMDC score: intermediate, 67%; poor, 30%
- Median lines of prior cancer therapy: 2 (range, 1–9), with 29 (97%) patients receiving at least 1 prior anti-PD-1 and tyrosine kinase inhibitor

Figure 6. Clinical responses in clear cell renal cell carcinoma

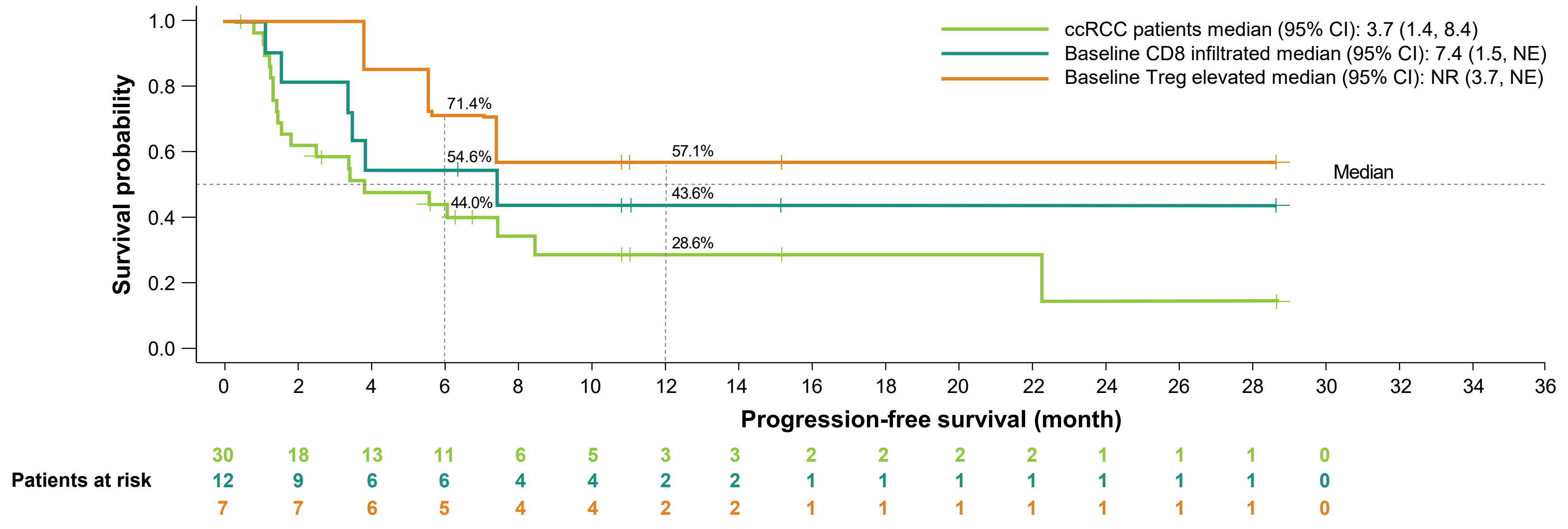


Efficacy	Intention-to-treat N = 30
ORR	7 (23.3%)
CR (confirmed)	1 (3.3%)
PR (confirmed)	5 (16.7%)
PR (unconfirmed)	1 (3.3%)
mDoR (months)	9.8 (2.5, 25.9+)
DCR	17 (56.7%)



Pt #4 at screening; Lymph node 21.5 mm

Pt #4 at C8; Lymph node 5 mm



Patients at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
ccRCC patients	30	18	13	11	6	5	3	3	2	2	2	2	1	1	1	0
Baseline CD8 infiltrated	12	9	6	6	4	4	2	2	1	1	1	1	1	1	1	0
Baseline Treg elevated	7	7	6	5	4	4	2	2	1	1	1	1	1	1	1	0

Data cutoff: September 9, 2024. There were no responses observed in the NSCLC cohort.

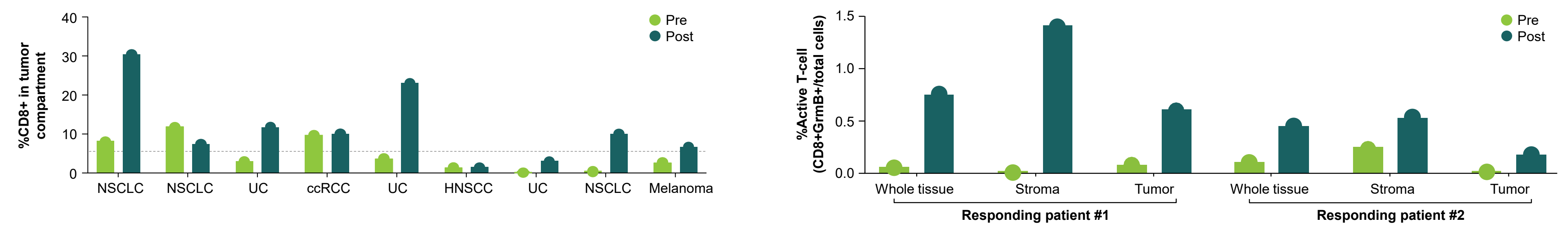
Proof of mechanism

- Linavonkibart combined with pembrolizumab increased CD8+ T-cell tumor infiltration (**Figure 7A**) and activation (CD8+GrmB+; **Figure 7B**) in responding patients
- Tumor shrinkage was associated with a lower ratio of regulatory T-cells (Treg) to activated CD8+ T-cells (**Figure 7C**)
- Circulating (**Figure 7D**) and tumor (**Figure 7E**) granulocytic myeloid-derived suppressor cells decreased in responding patients

Figure 7. Linavonkibart combined with pembrolizumab establishes a proinflammatory tumor microenvironment across multiple tumor types

A) Linavonkibart and pembrolizumab increased CD8+ T-cell infiltration across multiple tumor types

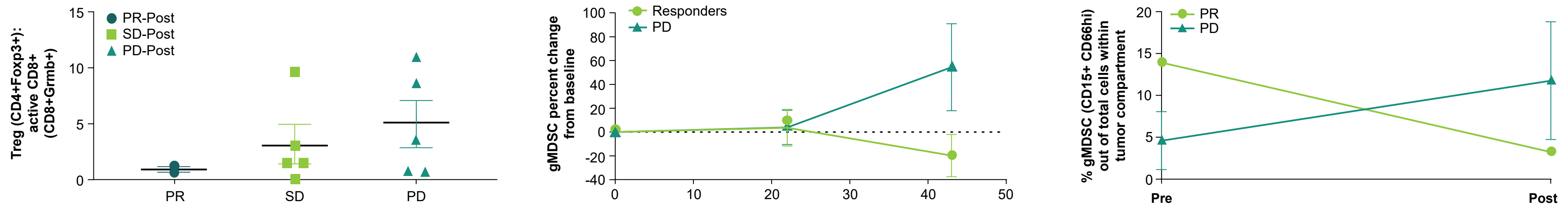
B) CD8 + T-cells were activated in responding patients



C) Treg: active CD8 + T-cell ratio lower in responders compared to nonresponders

D) Circulating gMDSC were suppressed in responders and elevated in PD

E) gMDSC were suppressed in tumor microenvironment of responders and elevated in PD

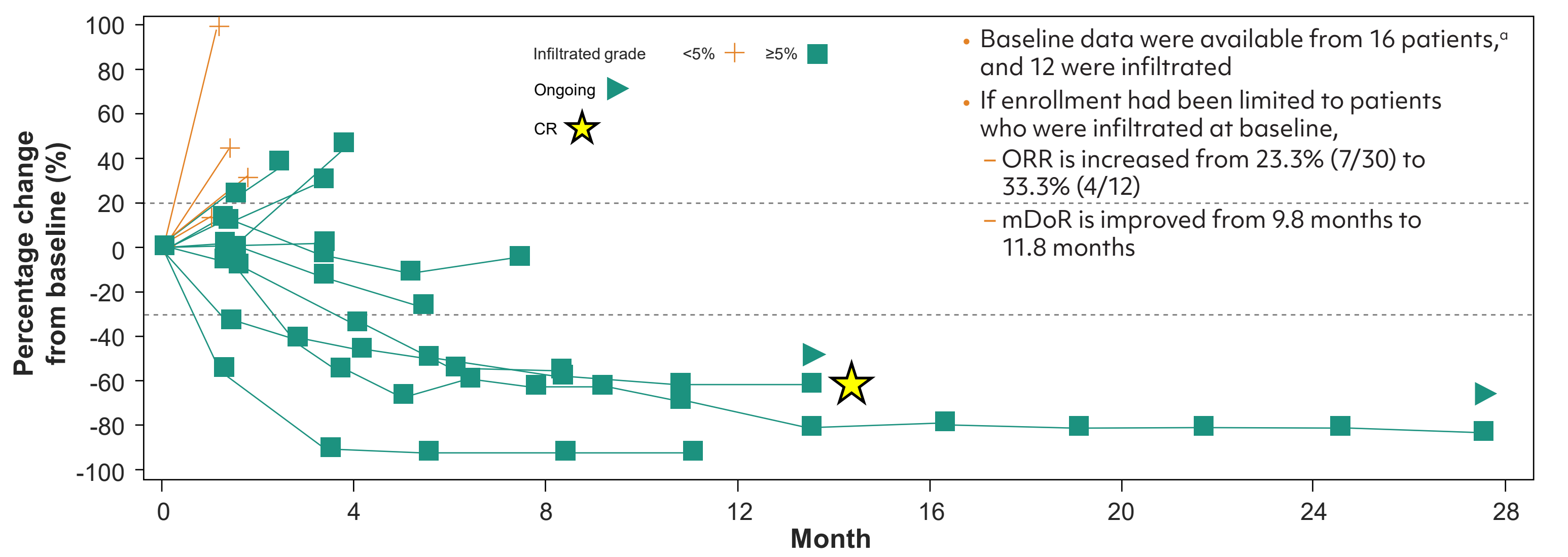


Biopsies were collected at baseline and post-treatment between day 28 to 48. Tumor expression data were generated from biopsies using either immunohistochemistry or in situ hybridization. Circulating gMDSC data were generated by flow cytometry.

- Elevated baseline CD8+ T-cell (**Figure 8A**), Treg (**Figure 8B**), and TGFβ1 (**Figure 8C**) levels in the tumor may suggest a higher chance of clinical response with linavonkibart combination therapy for patients with ccRCC

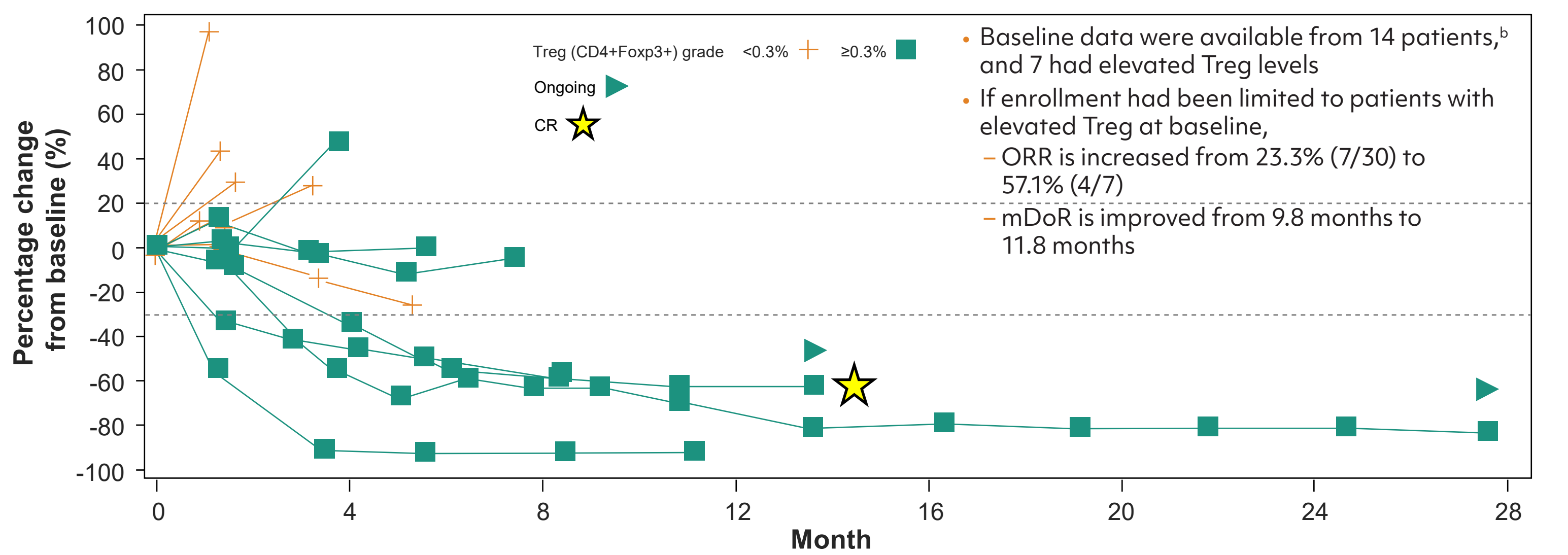
Figure 8. Biomarker data may provide a strategy for selection of ccRCC patients with a higher chance of response

A) Baseline CD8+ T-cell infiltration status



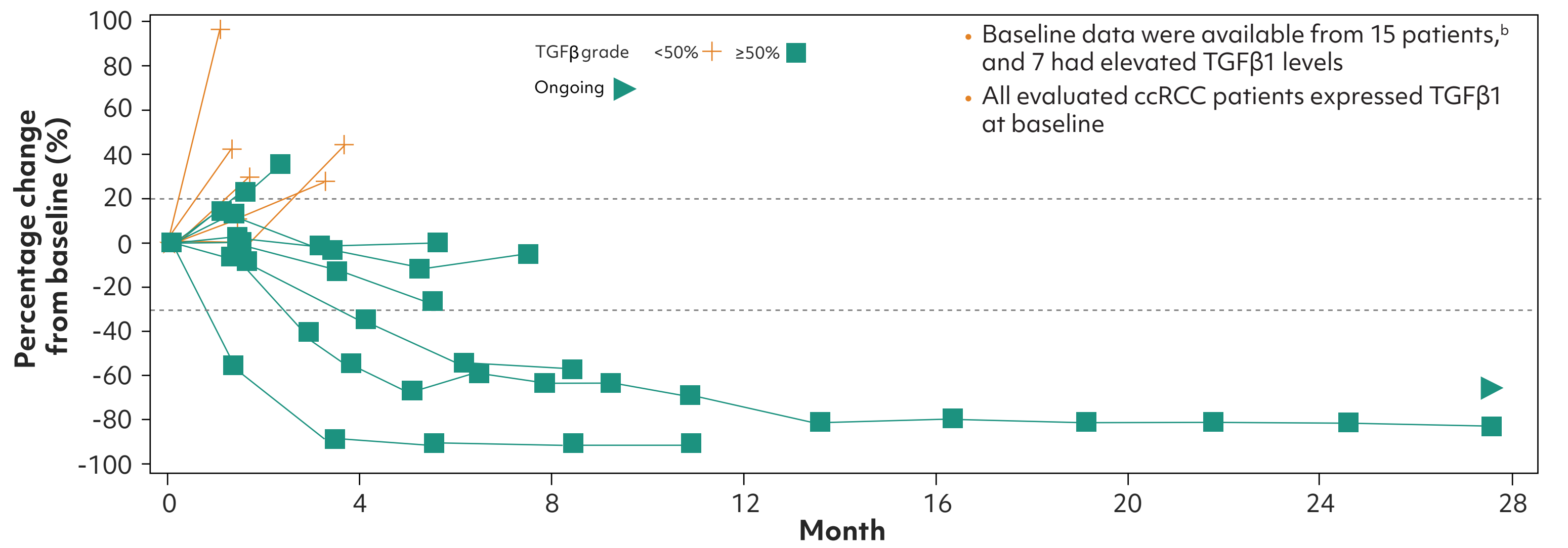
- Baseline data were available from 16 patients,[a] and 12 were infiltrated
- If enrollment had been limited to patients who were infiltrated at baseline,
  - ORR is increased from 23.3% (7/30) to 33.3% (4/12)
  - mDoR is improved from 9.8 months to 11.8 months

B) Elevated baseline Treg (CD4+Foxp3+) levels within the tumor compartment



- Baseline data were available from 14 patients,[b] and 7 had elevated Treg levels
- If enrollment had been limited to patients with elevated Treg at baseline,
  - ORR is increased from 23.3% (7/30) to 57.1% (4/7)
  - mDoR is improved from 9.8 months to 11.8 months

C) Elevated baseline TGFβ1 levels within tumor compartment



- Baseline data were available from 15 patients,[b] and 7 had elevated TGFβ1 levels
- All evaluated ccRCC patients expressed TGFβ1 at baseline

Data cutoff: September 9, 2024. [a]Two patients progressed prior to the first scan and are not represented in the spider plot. [b]One patient progressed prior to the first scan and is not represented in the spider plot.

Conclusions

- The combination of linavonkibart and pembrolizumab demonstrated a manageable safety profile
- The combination treatment demonstrated durable antitumor activity in heavily pretreated patients with anti–PD-1–resistant cancer across multiple cancer types
- Biomarker data support a proof of mechanism and identify a potential patient selection strategy
  - Linavonkibart combination therapy induced a proinflammatory tumor microenvironment
  - Both ORR and mDOR were improved in ccRCC subgroups with elevated baseline CD8+, Treg, and TGFβ1; each of these individually or some combination thereof could be further developed as a possible patient selection strategy
- These data warrant further investigation of linavonkibart

Abbreviations

ADA, antidrug antibody; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BOR, best overall response; ccRCC, clear cell renal cell carcinoma; CD, cluster of differentiation; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; Foxp3, forkhead box p3; GLP, Good Laboratory Practice; gMDSC, granulocytic myeloid-derived suppressor cells; GrmB, granzyme B; HNSCC, head and neck squamous cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; M, male; mDoR, median DoR; MDSC, myeloid-derived suppressor cell; MEL, melanoma; NE, not evaluable; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PD-(L)1, PD-1/PD-L1; PFS, progression-free survival; PK, pharmacokinetic; Post, post-treatment; PR, partial response; PRE, pretreatment; Pt, patient; Q2W, once every 2 weeks; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TGFβ1, transforming growth factor beta-1; TGFβ2, transforming growth factor beta-2; TGFβ3, transforming growth factor beta-3; Treg, regulatory T-cell; UC, urothelial carcinoma.

References

1. Martin CJ, et al. *Sci Transl Med*. 2020;12(536).
2. Batlle E, et al. *Immunity*. 2019;50(4):924-40.
3. Vaishampayan UN, et al. *JCO*. 2024;42(suppl 16):2507.
4. Yap TA, et al. *ESMO Open*. 2023;8(1):100967

Acknowledgments

Medical writing support was provided by Tony Sallese, PhD, of Red Nucleus, and funded by Scholar Rock, Inc. (Cambridge, MA, USA), and was in accordance with Good Publication Practice. Project management support was provided by Christabella Cherubino, DC, MS, CME, and Alyssa Brunal, PhD, of Scholar Rock, Inc. Funding for this trial is provided by Scholar Rock, Inc.

Disclosures

TAY reports grants and personal fees from Acrivon, Artios, AstraZeneca, Bayer, BeiGene, Blueprint, Clovis, EMD Serono, F-Star, Genentech, ImmuneSensor, Merck, and Pfizer; grants from Bristol Myers Squibb, Boundless Bio, BioNTech, Constellation, Cyteir, Forbius, GSK, Haihe, Ideaya, Ionis, Ipsen, Jounce, Karyopharm, KSQ, Kyowa, Lilly, Mirati, Novartis, Regeneron, Repare, Ribon Therapeutics, Rubius, Sanofi, Scholar Rock, Inc., Seattle Genetics, Tesaro, Vivace, and Zenith; personal fees from AbbVie, Adagene, Aduro, Almac, Amphista, Athena, Atrin, Ayoro, Axiom, Baptist Health System, Boxer, Bristol Myers Squibb, C4 Therapeutics, Calithera, Cancer Research UK, Circle Pharma, CUHK Committee, Cybrexa, Dark Blue Therapeutics, Diffusion, Ellipses Life, Genmab, Gerson and Lehrman Group, Glenmark, GLG, Globe Life Sciences, GSK, Guidepoint, Idience, Ignyta, I-Mab, Institut Gustave Roussy, Intellisphere, Janssen, Kyn, LRG1, MEI Pharma, Mereo, Natera, Nexys, Novocure, OHSU, OncoSec, Ono Pharma, Panangium, Pegascy, PER, Piper-Sandler, Pliant Therapeutics, Prolynx, Radiopharm Theranostics, resTORbio, Roche, SchrÖdinger, Synthis Therapeutics, Terremoto Biosciences, Tessellate Bio, TD2 Theragnostics, Tome Biosciences, Varian, Versant, Vibliome, Xinthera, Zai Labs, Zentalis, and ZielBio; and personal fees and other support from Seagen. **RFS** reports consulting fees from Astellas, AstraZeneca, AVEO, BMS, Editas, Eisai, EMD Serono, Exelixis, Gilead, Janssen, Lilly, Loxo, Mirati, Pfizer, Silverback, and Seattle Genetics; institutional research support from ALX Oncology, Astellas, Ascendis, AstraZeneca, Bayer, BMS, CytomX, Eisai, Genentech/Roche, Gilead, Immunocore, Jounce, Lilly, Loxo, Merck, Mirati, Moderna, Novartis, Pfizer, Pionyr, Pyxis, QED Therapeutics, and Scholar Rock, Inc.; equity in AbbVie; and the following patents: neo-antigens in cancer, PCT/US2020/031357. **UV** reports grants and personal fees from Merck for the work under consideration; grants from Astellas and Bristol Myers Squibb; and personal fees from AAA, Alkermes, Astellas, Bayer, Bristol Myers Squibb, Exelixis, and Pfizer. **AT** reports consulting or advisory roles for Bayer, BioNTech, Bristol Myers Squibb, Clinigen Group, ConcertAI, Eisai, Genentech/Roche, Instil Bio, Merck, Novartis, Partner Therapeutics, and Sanofi/Regeneron and has received institutional research funding from Acrotech Biopharma, Agenus, Bristol Myers Squibb, Clinigen Group, Genentech/Roche, InflaRx (Inst), Merck, OncoSec, Pfizer, Sanofi/Regeneron, and Scholar Rock, Inc. **JFG** reports personal fees and other support from Adaptimmune, AIProteins, Alexo, Array Biopharma, AstraZeneca, Blueprint Medicines, Bristol Myers Squibb, Genentech/Roche, Merck, Moderna, Palleon, and Tesaro; equity in AI Proteins; personal fees from Gilead, iTeos, Jounce Therapeutics, Karyopharm, Lilly, Mariana Therapeutics, Merus Pharmaceuticals, Mirati Therapeutics, Novocure, Nuvalent, Pfizer, Sanofi, Silverback, and Takeda; and grants, personal fees, and other support from Novartis. JFG has an immediate family member who is an employee with equity in Ironwood Pharmaceuticals. **MB** reports personal fees from Tempus Labs and personal fees from Texas Oncology outside the submitted work. **MM** reports consultancy for Castle Biosciences, Eisai, IQVIA, Merck, Moderna, and Pfizer and research funding from Aadi Biosciences, Alpine Immune Sciences, Arcus Biosciences, Arvinas, Ascentage Pharma Group, ASCO, Astellas, Aulos Bioscience, Bayer, Bicycle Therapeutics, Biomed Valley Discoveries, BioNTech, Bristol Myers Squibb, C4 Therapeutics, Dragonfly Therapeutics, EMD Serono, Epizyme, Erasca, Exelixis, Foghorn Therapeutics, G1 Therapeutics, Genentech/Roche, Gilead Sciences, GSK, IDEAYA Biosciences, Ikena Oncology, ImmVira Pharma, Infinity Pharmaceuticals, Jacobio Pharmaceuticals, Kechow Pharma, Kezar Life Sciences, Kinnate BioPharma, MedImmune, Mereo BioPharma, Metabomed, Moderna, NBE Therapeutics, Nektar, Novartis, NucMito Pharmaceuticals, OncoC4, Oncorus, OnKure, PACT Pharma, Pfizer, Plexxikon, Poseida, Prelude Therapeutics, Pyramid Biosciences, Regeneron, Sapience Therapeutics, Scholar Rock, Inc., Seattle Genetics, Synthrox, Tenebio, Tempest Therapeutics, Tizona Therapeutics, TMUNITY Therapeutics, TopAlliance Biosciences, and Xilio. **GS** reports serving on advisory boards of AstraZeneca, Bicycle Therapeutics, Bristol Myers Squibb, Ellipses Pharma, EMD Serono, Exelixis, G1 Therapeutics, Genentech, Gilead, IMV, Infinity Pharmaceuticals, Janssen, Lilly/Loxo Oncology, Lucence Health, Merck, Pfizer, PrecisCa, Primum, Sanofi, Scholar Rock, Inc., Seattle Genetics/AstellasSyapse, Tempus, and Vial; consultant/scientific advisory boards of Merck, Servier, Suba Therapeutics, Syapse, and Syncorp; received institutional research support from AstraZeneca, Bristol Myers Squibb, EMD Serono, Gilead, Helsinn, Jazz Therapeutics, Lucence, and Sanofi; received speaker's fees from AVEO, Bayer, Exelixis, Gilead, Janssen, Natera, and Seagen; received data safety monitoring committee honorarium from Mereo; received writing/editing fees from Onviv, Practice Update, and UpToDate; and a spouse employed by Myriad. **RRM** reports serving on the consulting/advisory boards for AstraZeneca, AVEO, Bayer, Blue Earth Diagnostics, Bristol Myers Squibb, Calithera, Caris, Denderon, Exelixis, Janssen, Merck, Myovant, Pfizer, Sanofi, Seagen, Sorrento Therapeutics, and Tempus and has received institutional research funding from Artera, AstraZeneca, Bayer, Bristol Myers Squibb, Exelixis, Oncternal, and Tempus. **CH** reports stock holdings in Johnson & Johnson; research funding to institution from AstraZeneca, Bausch Health, Bayer, Genentech, and Merck; consultant fees from EMD Sorono, Genzyme, and Tempus; speaking fees from OncLive/MJH Life Sciences, travel fees from Merck, all outside the submitted work. **MK** reports serving in a consulting or advisory role for Astellas Pharma, Bayer, Bristol Myers Squibb/Ono Pharmaceutical, Boryung, Eisai, Ipsen, Janssen, Merck, MSD, Pfizer, Roche, Yuhan and honoraria from Astellas Pharma, Merck, Novartis, and Yuhan. **DK, DP, SB, AS, CN,** and **JC** have no disclosures to report. **YJ, LL, SH, SD,** and **LG** are employees of Scholar Rock, Inc.