Safety, tolerability and preliminary efficacy of nadunolimab, a first-in-class monoclonal antibody against IL1RAP, in combination with pembrolizumab in subjects with solid tumors

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Introduction

Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer and stromal cells of many solid tumors. IL-1α and IL-1β modulate tumor-promoting and other downstream factors (e.g. IL-6, IL-8, CRP) by signaling via IL-1 receptor type 1 (IL-1R1). For this signal transduction to occur, dimerization between IL-1R1 and IL1RAP is required. IL-1 signaling promotes an immune suppressive tumor microenvironment, e.g. by recruitment of myeloid-derived suppressor cells (MDSC). MDSC were recently demonstrated to be negatively associated with response to pembrolizumab therapy (Cristescu et al, 2022).

Nadunolimab (CAN04) is a fully humanized monoclonal IgG1 antibody targeting IL1RAP. Blockade of IL1RAP by nadunolimab offers a unique therapeutic approach compared to other IL-1-targeting concepts; it inhibits the tumor-promoting signals of both IL-1α and IL-1β and may thus dampen MDSC activity, and also mediates ADCC of IL1RAP-expressing cells.

Here, we report initial data from the phase Ib clinical trial CIRIFOUR (NCT04452214), evaluating nadunolimab with pembrolizumab in solid tumor patients who had progressed on prior anti-PD-(L)1 therapy.
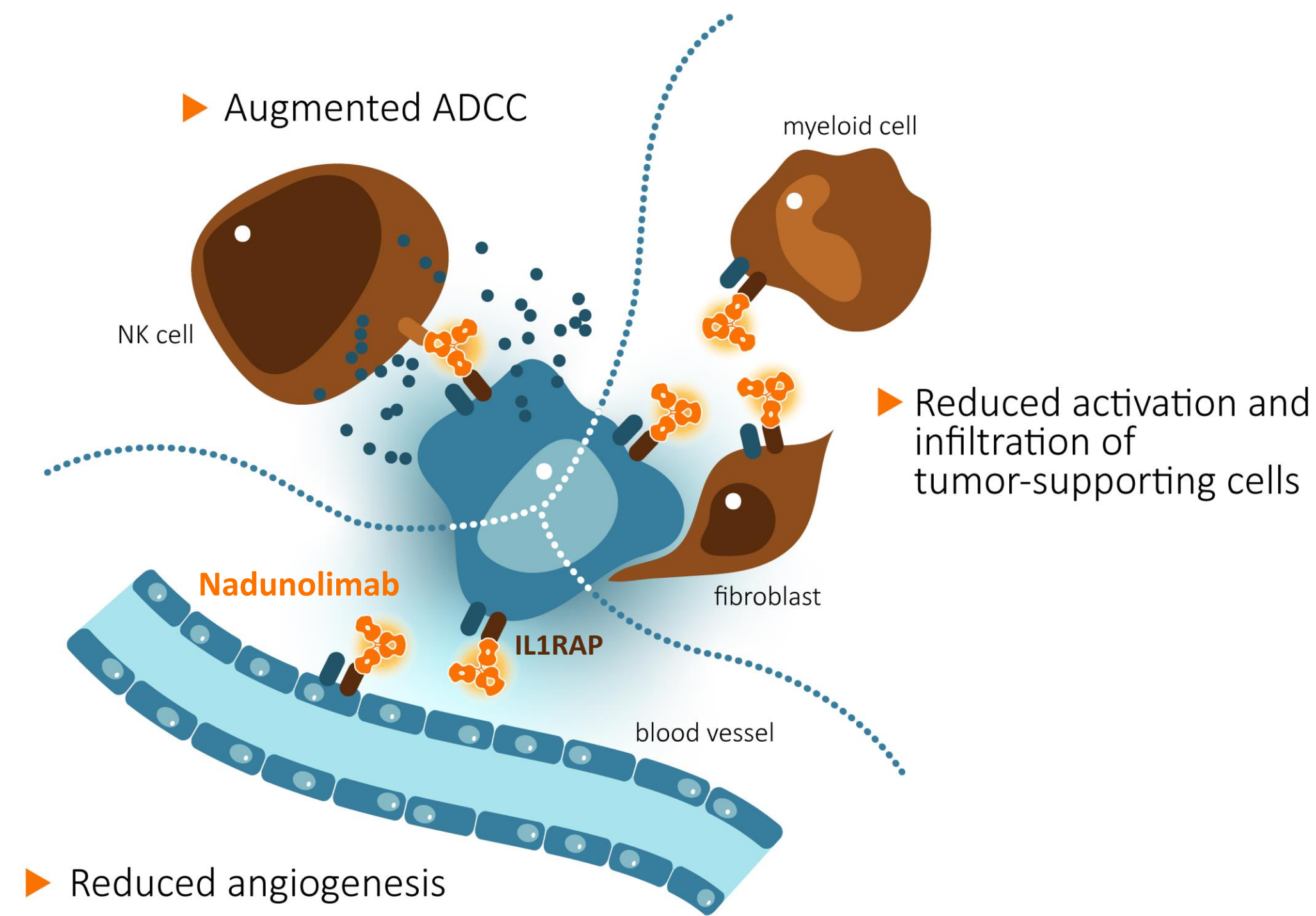

- ▶ Augmented ADCC
- ▶ Reduced activation and infiltration of tumor-supporting cells
- ▶ Reduced angiogenesis

Figure 1: Mode-of-action of nadunolimab.

Study Design

CIRIFOUR is an open-label phase Ib trial designed to assess safety and tolerability of nadunolimab combined with pembrolizumab in solid tumor patients who had previously progressed on PD-(L)1 inhibitor therapy.
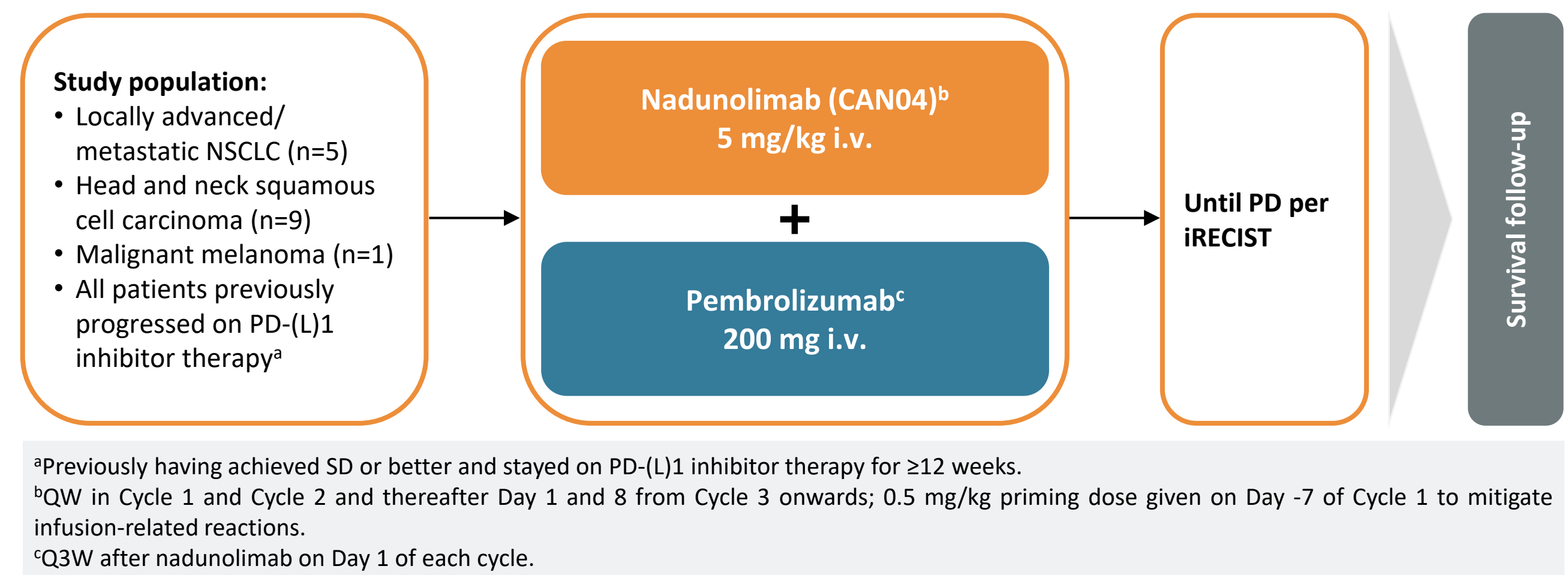

Study population:
- Locally advanced/ metastatic NSCLC (n=5)
- Head and neck squamous cell carcinoma (n=9)
- Malignant melanoma (n=1)
- All patients previously progressed on PD-(L)1 inhibitor therapy[a]

Nadunolimab (CAN04)[b] 5 mg/kg i.v.
+
Pembrolizumab[c] 200 mg i.v.

Until PD per iRECIST

Survival follow-up

[a]Previously having achieved SD or better and stayed on PD-(L)1 inhibitor therapy for ≥12 weeks.
[b]QW in Cycle 1 and Cycle 2 and thereafter Day 1 and 8 from Cycle 3 onwards; 0.5 mg/kg priming dose given on Day -7 of Cycle 1 to mitigate infusion-related reactions.
[c]Q3W after nadunolimab on Day 1 of each cycle.

Figure 2: Summary of study design.

Primary objectives:
- To determine the safety and tolerability of the combination of nadunolimab and pembrolizumab

Secondary objectives:
- To determine preliminary signs of clinical efficacy of nadunolimab in combination with pembrolizumab

Exploratory objectives:
- To evaluate disease-related inflammatory, immune or microenvironment-related parameters related to the study drugs, in the circulation and in tumor tissue

Results

Patient Characteristics

Table 1: Subject disposition and baseline characteristics.

Patients were arbitrarily subgrouped on the basis of duration of disease control with a cut-off at 10 therapy cycles (dotted line in Figure 4).

	All (n=15)	<10 therapy cycles (n=9)	≥10 therapy cycles (n=6)
Age; years			
Mean (Range)	64.1 (50-79)	61.7 (50-72)	67.8 (57-79)
Sex; n (%)			
Female/Male	4 (27%)/11 (73%)	2 (22%)/7 (78%)	2 (33%)/4 (67%)
ECOG PS; n (%)			
0/1	1 (7%)/14 (93%)	1 (11%)/8 (89%)	0/6 (100%)
Indication; n (%)			
HNSCC	9 (60%)	6 (67%)	3 (50%)
Malignant melanoma	1 (7%)	0	1 (17%)
NSCLC	5 (33%)	3 (33%)	2 (33%)
Prior therapies; n (%)			
Radiation	9 (60%)	6 (67%)	3 (50%)
Surgery	7 (47%)	4 (44%)	3 (50%)
Number of previous lines of therapy for stage IV			
Median (Range)	2 (1-6)	1 (1-6)	2 (1-3)
PD-L1 expression (TPS) at baseline; n (%)			
<1%	4 (27%)	3 (33%)	1 (17%)
1%-49%	7 (47%)	4 (44%)	3 (50%)
≥50%	0	0	0
Not available	4 (27%)	2 (22%)	2 (33%)
Best response to prior PD-1/PD-L1 inhibitor; n (%)			
CR/PR	7 (47%)	3 (33%)	4 (67%)
SD	7 (47%)	5 (56%)	2 (33%)
Not available	1 (7%)	1 (11%)	0
CRP; mg/l*			
Median (Range)	3.4 (<1-20.2)	4.5 (1.4-20.2)	2.4 (<1-14.3)
IL-6; pg/ml*			
Median (Range)	3.1 (0.71-9.21)	3.6 (0.71-9.21)	2.2 (0.92-6.4)
NLR; ratio*			
Median (Range)	4.4 (2.2-33.1)	4.7 (2.2-33.1)	3.7 (2.7-7.7)
Tumor burden; sum of diameters in mm			
Median (Range)	48 (16-125)	63 (39-125)	41 (16-50)

*Baseline values collected at Day -7
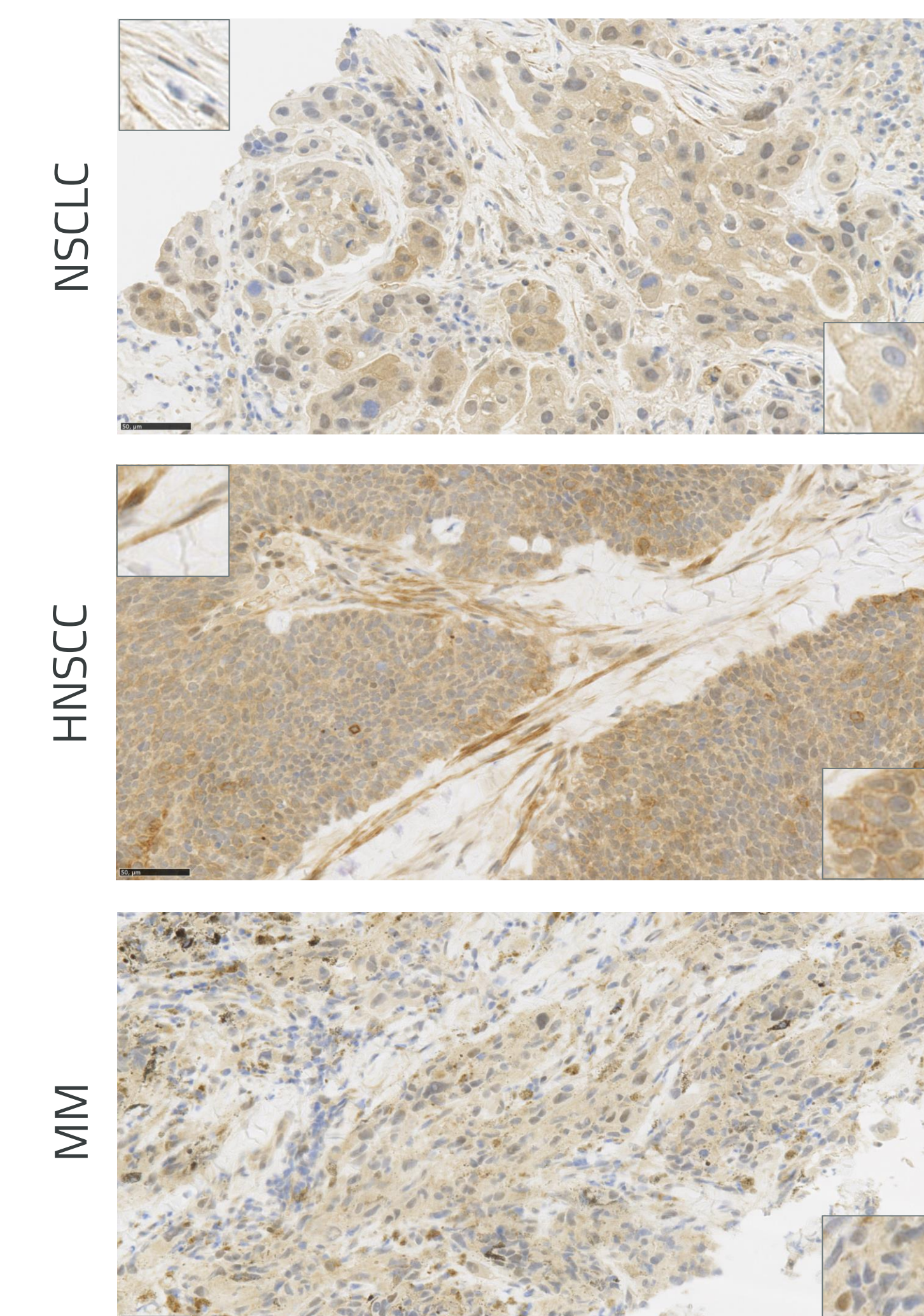
Target Expression

Figure 3: IL1RAP expression on tumor and stromal cells in NSCLC, HNSCC and MM biopsies.

Study-specific needle biopsies were taken at time of inclusion and at Cycle 2 Day 8 and stained for IL1RAP by immunohistochemistry. IL1RAP was detected on tumor and stromal cells in all indications included in the study.

Images from one representative screening biopsy per indication are shown. In upper left and lower right corners, positive IL1RAP staining of stromal cells and tumor cells are presented, respectively.

Thirteen screening biopsies, and eight Cycle 2 Day 8 biopsies were collected and stained for IL1RAP and scored by H-score. The median H-score of both screening and Cycle 2 Day 8 biopsies was 200.

PD-L1 expression on tumor cells was also evaluated in the biopsies by TPS and a range from 0 to 40% PD-L1 positive tumor cells was detected. No change in PD-L1 expression was observed by treatment.

Safety

Table 2: Most frequent (n>2) all grade TEAE per patient with corresponding grade 3-4 TEAE.

TEAE; n (%) events	All TEAE (n=15)	Grade 3-4 TEAE (n=15)
Fatigue	7 (47%)	1 (7%)
Pruritus	6 (40%)	
Diarrhea	4 (27%)	
Dyspnea	4 (27%)	1 (7%)
Rash	3 (20%)	
Hypotension	3 (20%)	
Dizziness	3 (20%)	
Musculoskeletal pain	3 (20%)	

In addition, one TEAE of grade 3 febrile neutropenia, which occurred during Cycle 1, was observed.
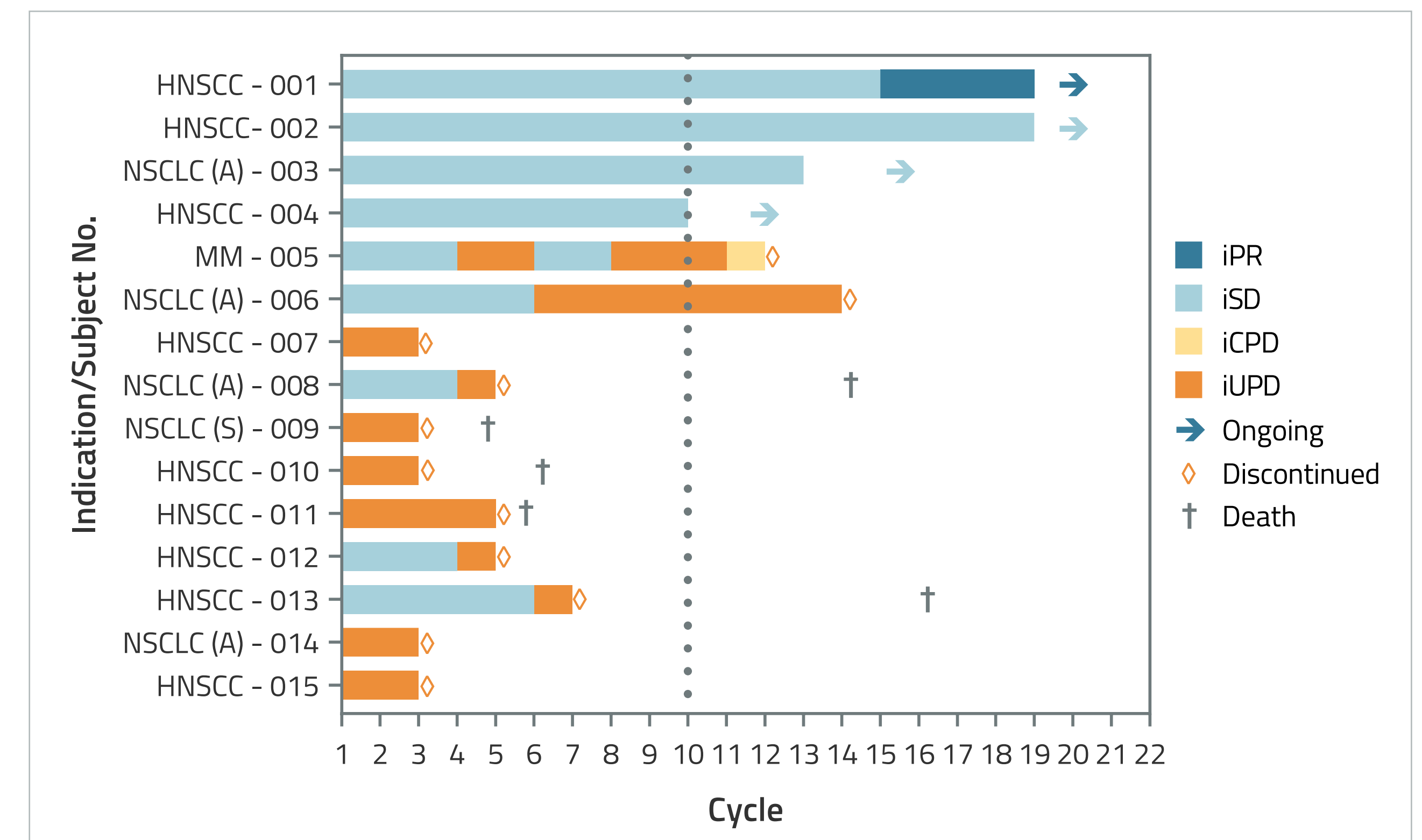
Efficacy

Figure 4: Preliminary tumor response evaluated according to iRECIST. Each cycle corresponds to three weeks of treatment. HNSCC, head and neck squamous cell carcinoma; MM, malignant melanoma; NSCLC, non-small cell lung carcinoma; A, adenocarcinoma; S, squamous.
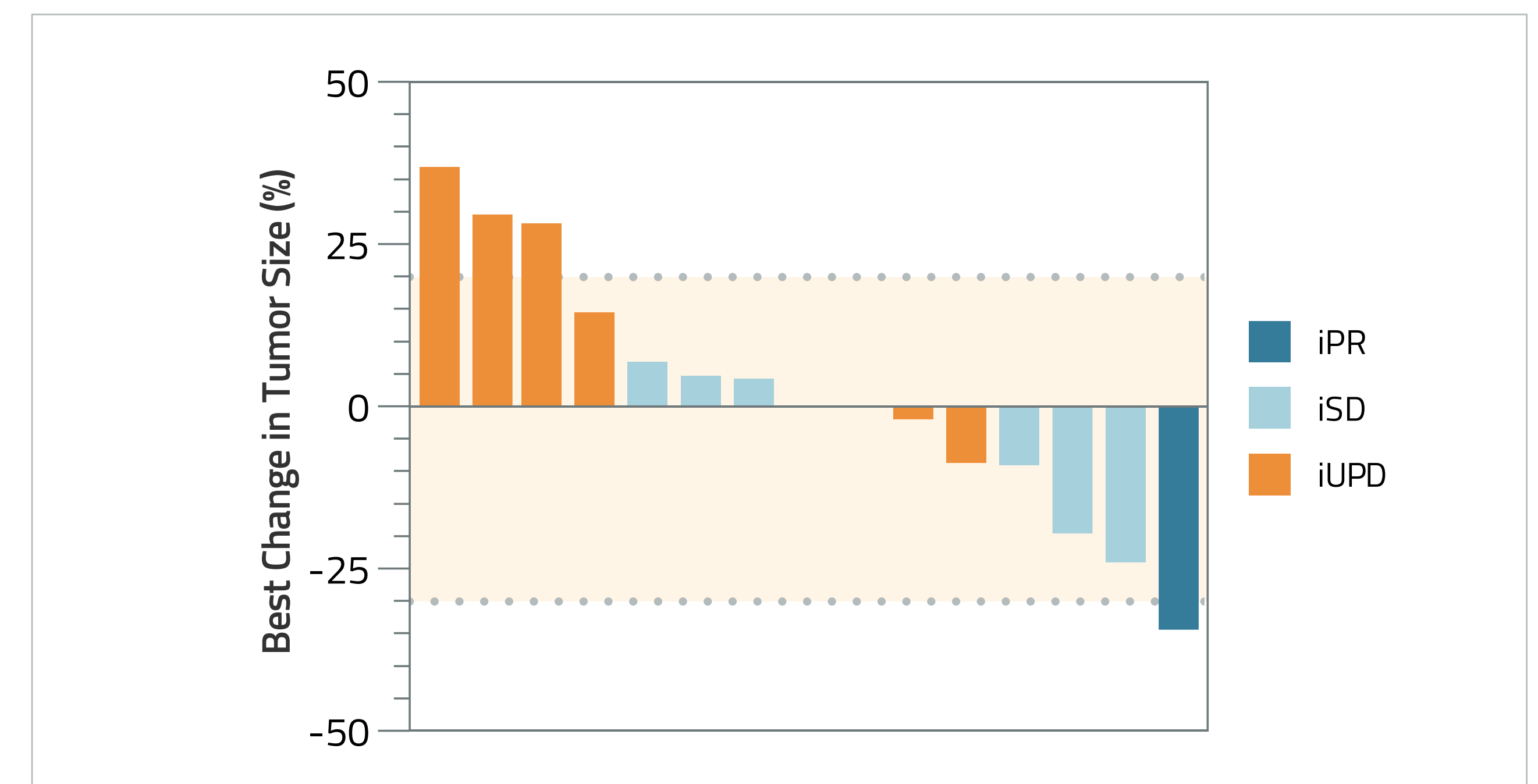

Figure 5: Best change in tumor size and best overall response.

One patient (7%) had confirmed iPR as best response, onset after 43 weeks, and duration of >10.1 weeks. Eight patients (53%) showed iSD and six (40%) had iUPD. At the time of analysis, four patients (27%) were still receiving therapy. Among these, two patients had been on therapy for over 34 weeks, another two for over 58 weeks.
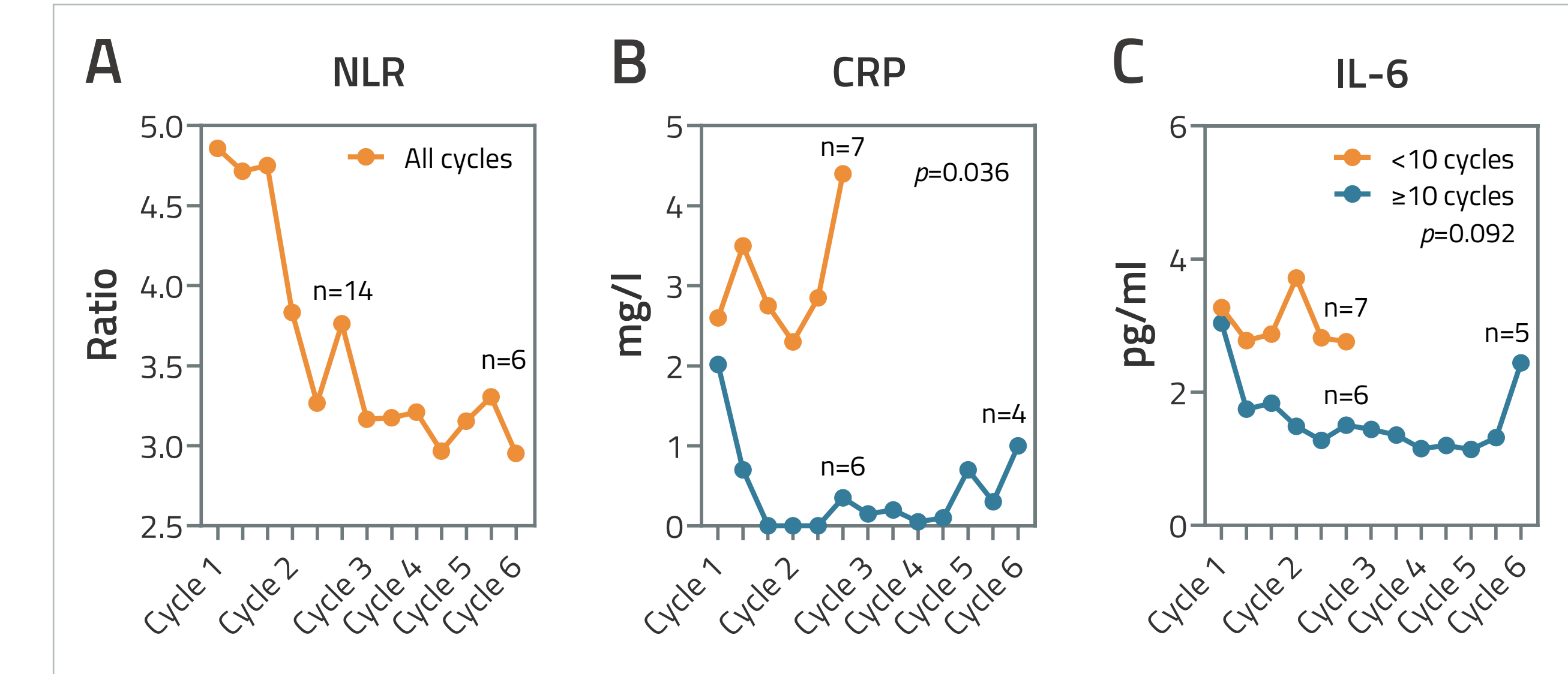
Biomarker Effects

Figure 6: Neutrophil-to-lymphocyte (NLR) ratio, CRP and IL-6 serum levels; median of absolute values.

NLR is a prognostic marker for cancer and reflects the inflammatory status of the patient. NLR reduction was observed (Figure 6A), driven by a moderate reduction in circulating neutrophils, while lymphocyte levels remained stable. A trend towards higher lymphocyte counts in patients with treatment duration ≥10 cycles was also observed. Reductions in CRP (Figure 6B) and IL-6 (Figure 6C) were most pronounced in patients with treatment duration ≥10 cycles. This was evident during the first two weeks and remained stable throughout the study.
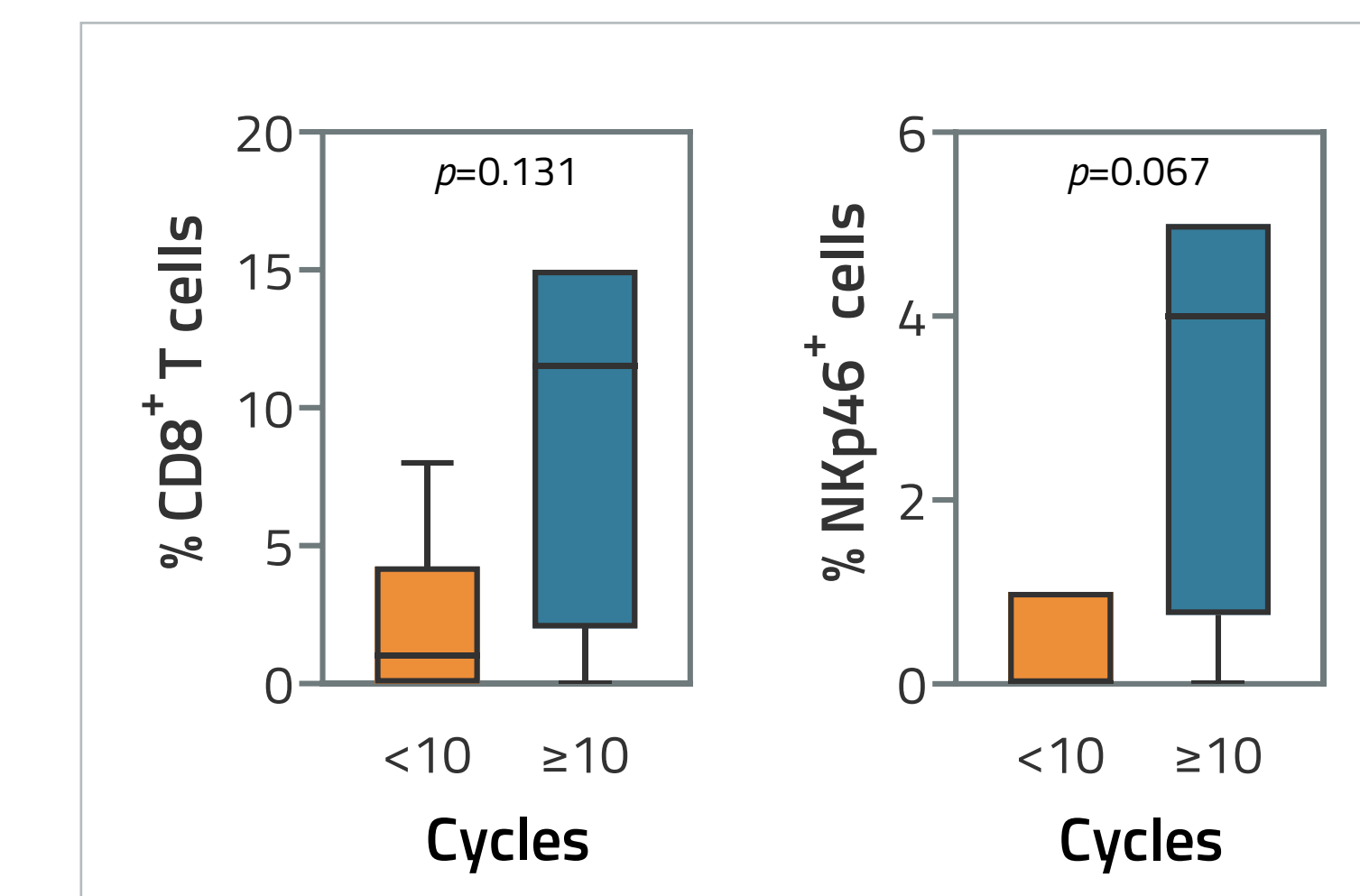

Figure 7: Frequency of CD8+ T cells and NKp46+ cells in tumor tissue at baseline.

Study-specific needle biopsies were taken before therapy start and stained for the cytotoxic T cell marker, CD8, and the Natural Killer (NK) cell marker, NKp46. Stainings were scored as percent positive cells. <10 cycles, n=8; ≥10 cycles, n=4.

Baseline biopsies from patients with the longest disease control showed a trend towards a higher percent of CD8+ T cells and NK cells in the tumor.

Conclusions

- Nadunolimab in combination with standard pembrolizumab treatment was safe and tolerable.

- 40% of patients receiving combination therapy had >30 of weeks disease control after previous progression on anti-PD-(L)1 therapy.

- Prolonged disease control correlated with:
  - Higher baseline levels of immune cells (CD8+ T cells, NK cells) in tumor tissue.
  - Reduction in markers of systemic inflammation (CRP, IL-6) during treatment.

- The results support further development of nadunolimab in combination with PD-(L)1 inhibitor therapy.

Acknowledgements