SITC 2018 NOVEMBER 7–11 • WASHINGTON, D.C.

Immune Monitoring After NKTR-214 Plus Nivolumab (PIVOT-02) in Previously Untreated Patients With Metastatic Stage IV Melanoma

ClinicalTrials.gov Identifier: NCT02983045

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Presenter Disclosure Information

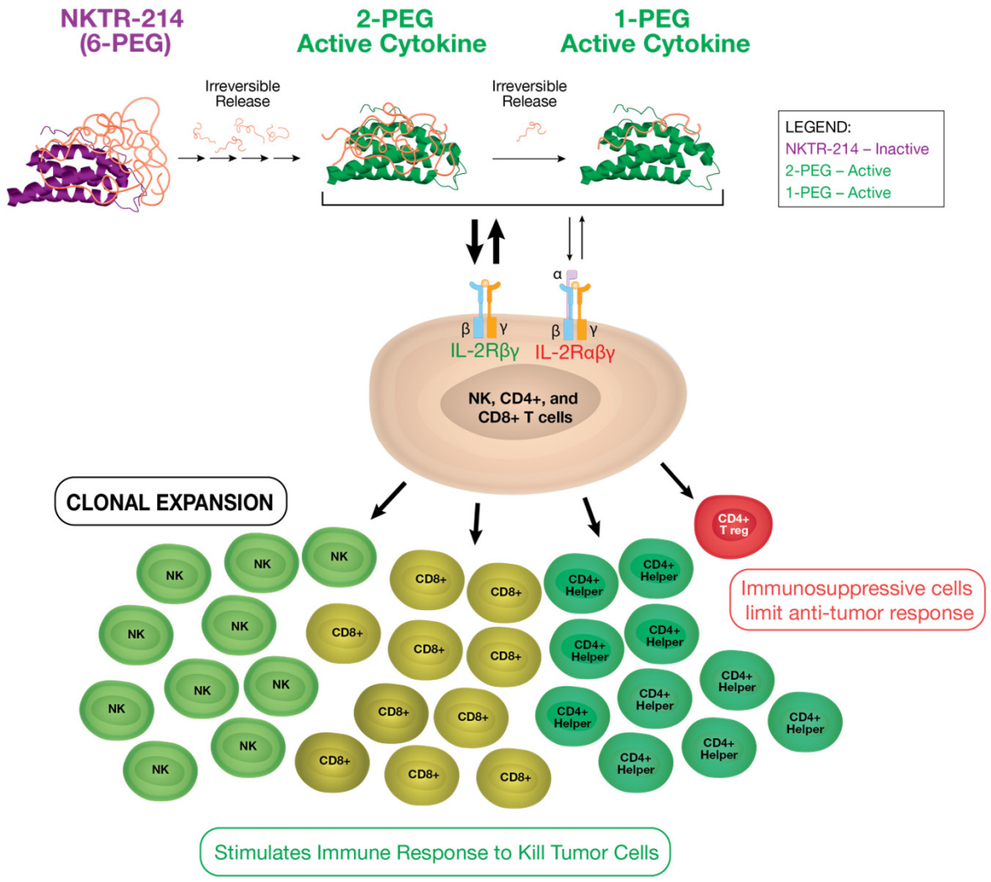
Adi Diab, MD, The University of Texas MD Anderson Cancer Center

The following relationships exist related to this presentation:

Research funding (institution): Nektar Therapeutics, Bristol-Myers Squibb, Idera Pharmaceuticals, Jounce Therapeutics, Apexigen

Consultation Fees & Advisory Boards: Nektar Therapeutics, Idera Pharmaceuticals, Jounce Therapeutics, Array BioPharma

NKTR-214 Background: Harnessing the IL-2 Pathway to Increase TILs



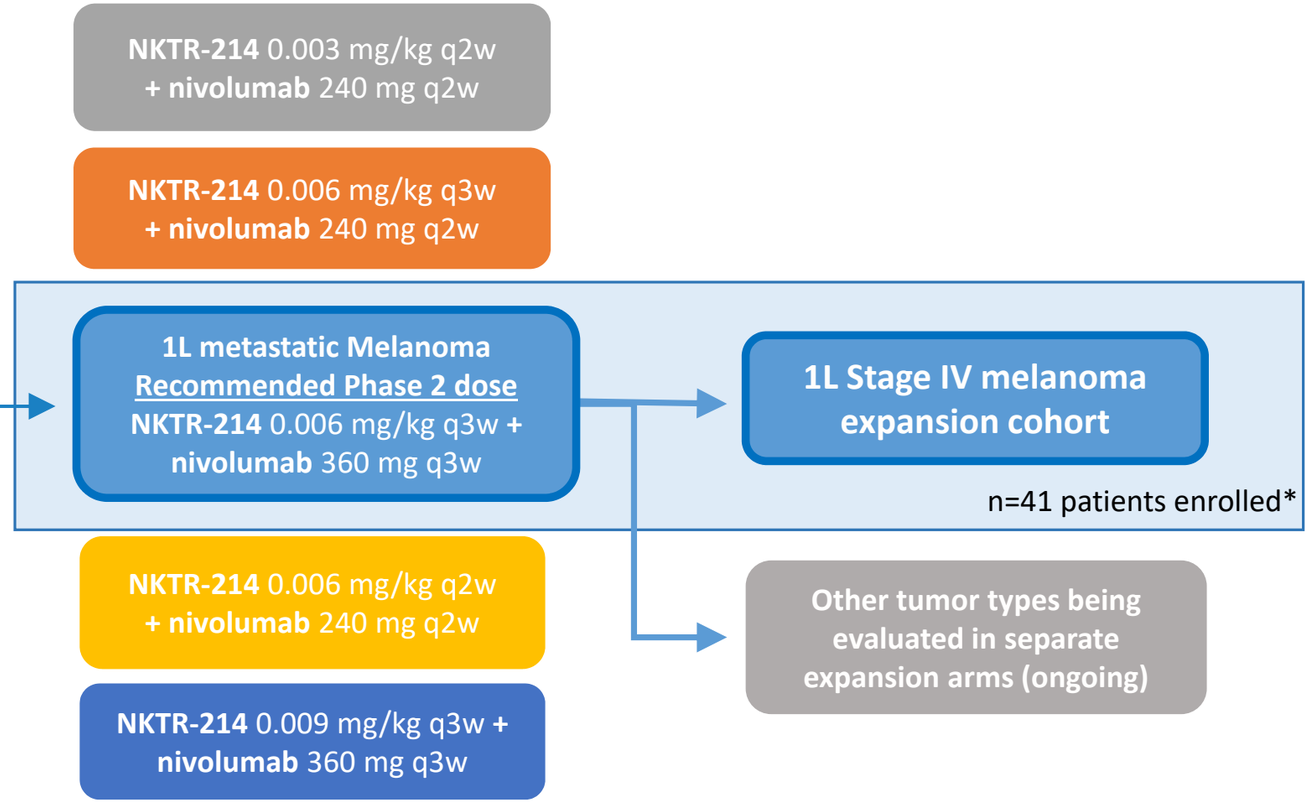
- NKTR-214 prodrug design results in potent immune activation with every 3 week dosing
- Biased signaling through IL-2βγ receptor preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- NKTR-214 creates a favorable tumor microenvironment for combination with checkpoint inhibitors including increased TILs, CD8+ PD1 expression and T cell clonality
- NKTR-214 has been shown to convert baseline PD-L1(-) tumors to PD-L1(+)*
- NKTR-214 is a systemic therapy with broad mechanistic applicability across multiple tumors

*Diab, A., et al., ASCO 2018; Bentebibel, S. et al., SITC 2017; Diab, A., SITC 2016

PIVOT-02: Dose-Escalation and Recommended Phase 2 Dose Expansion Trial of NKTR-214 + Nivolumab

Key inclusion criteria

- Locally advanced or metastatic solid tumour
  - 1L Melanoma (with known BRAF status)
  - 1L–2L RCC
  - 1L–2L NSCLC (EGFR and ALK WT)
- Measurable disease per RECIST v1.1
- ECOG PS 0–1
- Adequate organ function
- Fresh biopsy and archival tissue



RP2D: recommended Phase 2 dose.
*41 1L melanoma patients enrolled across 12 clinical sites; includes 7 patients from dose escalation cohort

Primary endpoints:

- Safety and tolerability per CTCAEv4.03
- ORR per RECIST v1.1 assessed every 8 (±1) weeks
- Per protocol, efficacy evaluable is defined as patients with ≥ 1 post baseline scan

Secondary and exploratory endpoints:

- Duration of response, OS, PFS, clinical benefit rate, PK

Biomarker endpoints (subset of patients in each cohort):

- Absolute Lymphocyte Count, Blood immuno-phenotyping
- Baseline and on-treatment biopsies (3 weeks) were collected in patients, when clinically feasible.

Patient Demographics and Disease Characteristics at Study Entry: 1st-Line Stage IV Melanoma

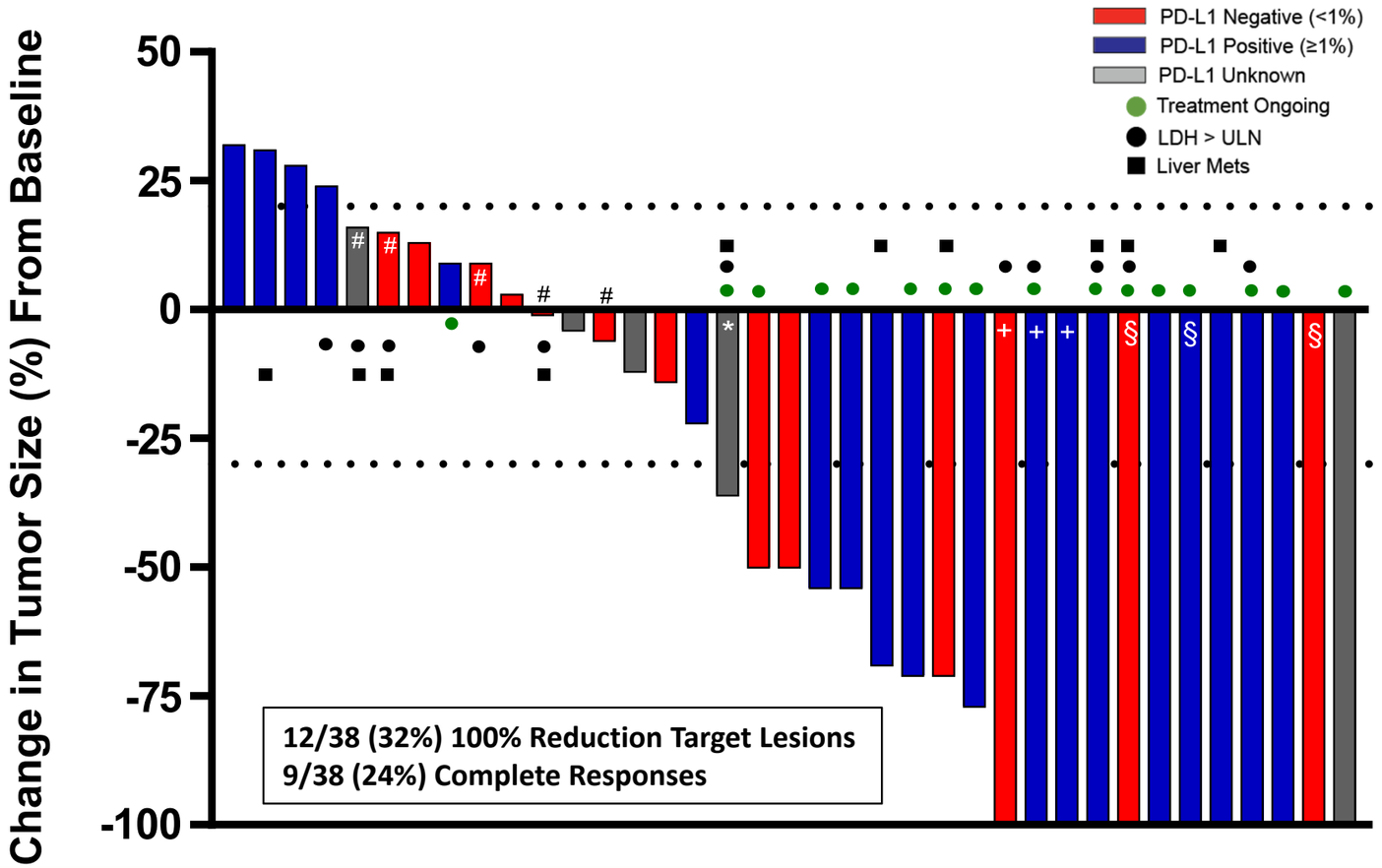
	Total (n=41)
Sex	
Female	17 (41.5%)
Male	24 (58.5%)
Age (years)	
Median (Range)	63 (22-80)
ECOG Performance Status	
0	32 (78.0%)
1	9 (22.0%)

	Total (n=38)
PD-L1 status* (Efficacy Evaluable)	
Positive ≥1%	19 (50.0%)
Negative <1%	14 (36.8%)
Unknown	5 (13.2%)

	Total (n=41)
BRAF status	
Mutant (V600E, V600K)	13 (32%)
Wild-Type or non-V600 mutation	27 (66%)
Unknown	1 (2%)
LDH‡	
Normal	29 (70.7%)
Elevated >ULN#	12 (29.3%)
Stage (7th edition AJCC)	
M0	0 (0%)
M1a	5 (12%)
M1b	16 (39%)
M1c	20 (49%)
Liver metastases	
Yes**	11 (26.8%)
No	30 (73.2%)

Demographics of biomarker subgroup are representative of overall population
*PD-L1 status determined by 28-8 diagnostic on fresh or archival tumor, or investigator reported
‡Based on maximum value prior to dosing
#8 patients with ≥ 2X ULN; 1 patient with elevated LDH not evaluable for efficacy
**1 patient with liver metastases not evaluable for efficacy

Stage IV IO-Naïve 1L Melanoma Cohort at RP2D Best Overall Response by Independent Radiology

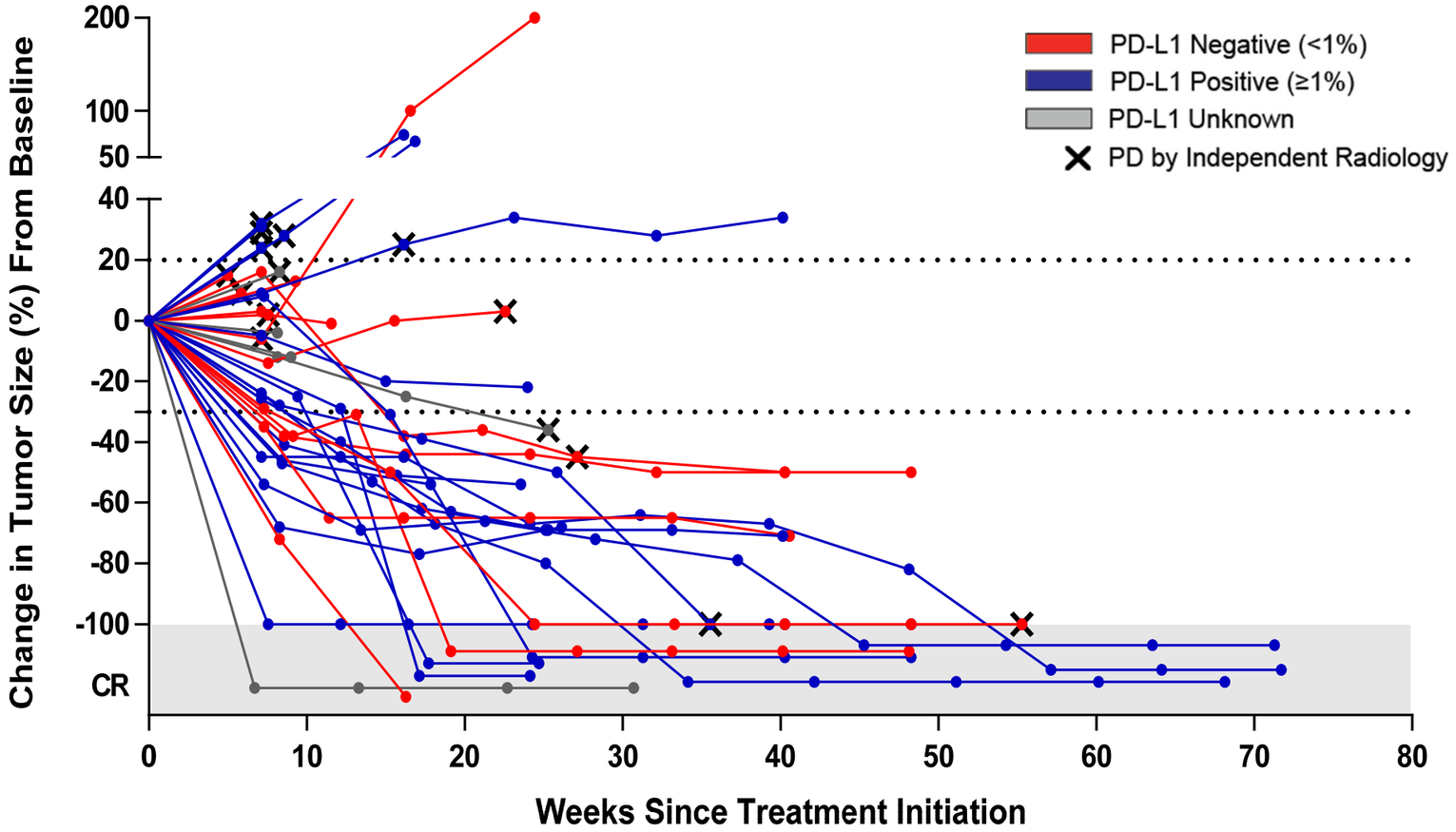


1L Melanoma (n=38 Efficacy Evaluable)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	9 (24%)
DCR (CR+PR+SD)	29 (76%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=19)	13 (68%)
PD-L1 unknown (n=5)	1 (20%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

High level of concordance in ORR between independent central radiology (53%) and investigator-assessed 19/38 (50%).

Per protocol, efficacy evaluable is defined as patients with ≥ 1 post baseline scan. 3 patients discontinued prior to 1st scan due to an unrelated TEAE [n=1] and Patients Decision [n=2].
One patient not represented in plot had target lesions per protocol by investigator assessment but did not have target lesions at baseline by independent central radiology; patient achieved SD based on non-target lesions during the study.
#: Best overall response is PD. *: Best overall response is SD. + Best overall response is PR with -100% reduction of target lesions. §: Best overall response of CR is unconfirmed; PR confirmed.

Stage IV IO-Naïve 1L Melanoma Cohort at RP2D
Target Lesion Change Over Time Per Independent Radiology



1L Melanoma (n=38)	
Median Time of Follow-Up (months)	7.2
Patients with Ongoing Responses	17/20 (85%)
Median Duration of Response (months)	NR (2.6, NR)
Median Time to Response (months)	2.0
Median % Reduction from Baseline as of 1Oct2018 (ongoing)	-50%

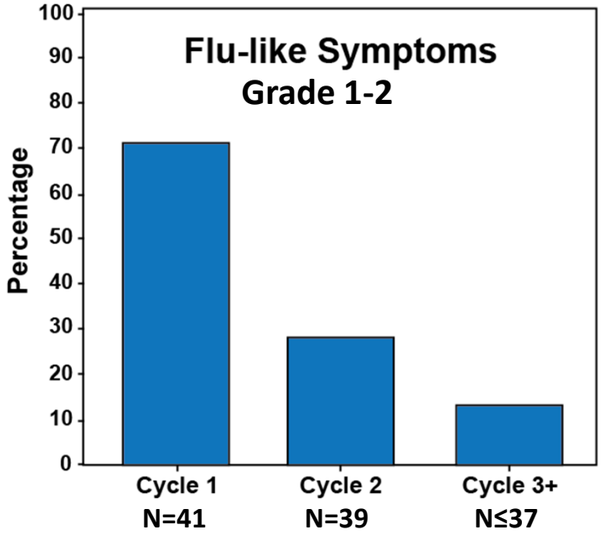
Per protocol, efficacy evaluable is defined as patients with ≥ 1 post baseline scan. 3 patients discontinued prior to 1st scan due to TEAE [n=1] and Patients Decision [n=2].
Three responders progressed after 6 months of treatment. All three patients sustained tumor control of target lesions (-100%, -100%, -50%) with 2 patients having non-target, new subcutaneous lesions and one patient with new mediastinal lymph node deemed as progression by independent radiology. One patient not represented in plot had target lesions per protocol by Investigator assessment but did not have target lesion at baseline by BICR. Patient achieved non-target SD based on non-target lesion during the study.

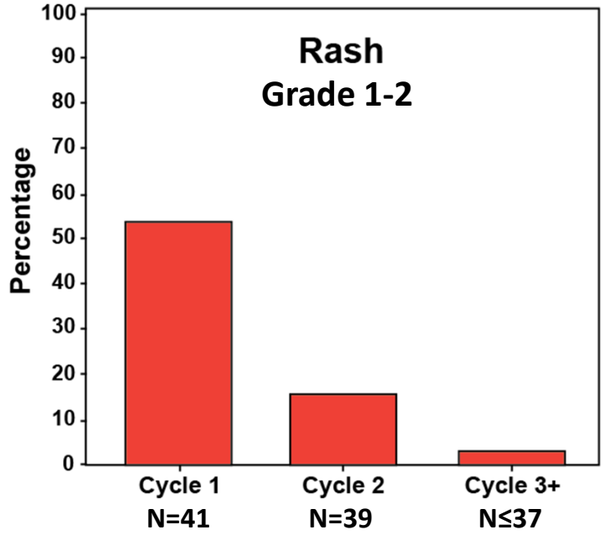
Stage IV IO-Naïve 1L Melanoma Treatment-Related Adverse Events (AEs) at RP2D

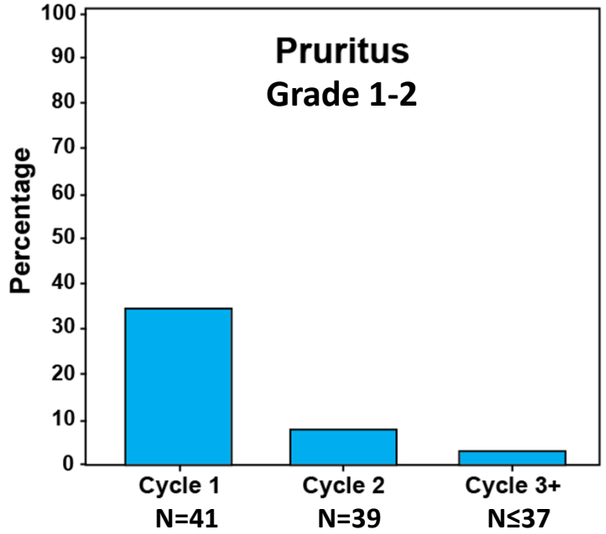
Preferred Term[1]	Total (N=41)
Grade 3-4 Treatment-Related AEs	8 (19.5%)
Lipase increased	3 (7.3%)
Atrial fibrillation*	2 (4.9%)
Acute kidney, injury, Blood creatinine increased, Cellulitis, Dyspnea, Hyperglycemia, Hypoxia	1 each (2.4%)
Grade 1-2 Treatment-Related AEs (>30% listed below)	
Flu like symptoms**	32 (78.0%)
Rash***	29 (70.7%)
Fatigue	26 (63.4%)
Pruritus	19 (46.3%)
Nausea	18 (43.9%)
Arthralgia	15 (36.6%)
Myalgia	13 (31.7%)
Any imAE (Grade ≥3) (blood creatinine increased, lipase increased)	2 (4.9%)
Patients requiring dose reductions of NKTR-214 (serum amylase increase, fatigue, pharyngitis)	3 (7.3%)
Patients who discontinued due to a TRAE (blood creatinine increased, stroke)	2 (4.9%)

Median number of cycles = 9. Median duration of exposure = 5.8 months. Per protocol, safety evaluable is defined as patients with ≥ 1 dose of study treatment. (1) Patients are only counted once under each preferred term using highest grade.
*1 patient with previous history of atrial fibrillation since 2015; 1 patient experienced atrial fibrillation 1 month after last dose of study drug. ** Flu-like symptoms included the following MedDRA PTs: Chills, Influenza, Influenza-like Illness, Pyrexia.
***Rash included the following MedDRA PTs: Erythema, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Exfoliative rash

Cytokine-Related AEs: Decreased Frequency with Continuous Dosing



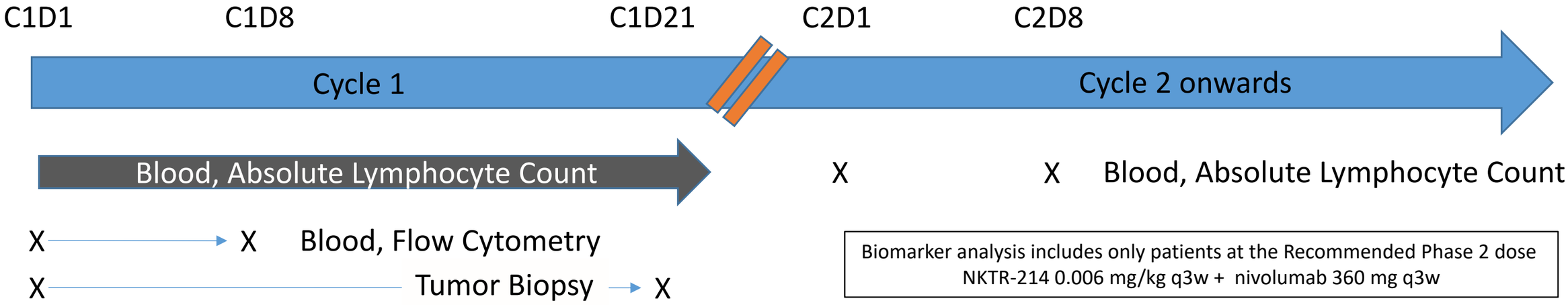




- Cytokine related AEs decreased with subsequent cycles of treatment.
  - All were low grade (no Grade ≥3 or higher).
  - Easily managed with NSAIDs/OTCs.
  - No dose delays, dose reductions or study discontinuations due to cytokine related AE's.
- Hydration guidelines effective: no Grade ≥3 TRAEs of hypotension.
- Prodrug design of NKTR-214 accounts for lower frequency of cytokine-related AE's compared to high dose IL-2.

Cycle 3+ symptoms equals average of % per cycle for cycles 3-25.

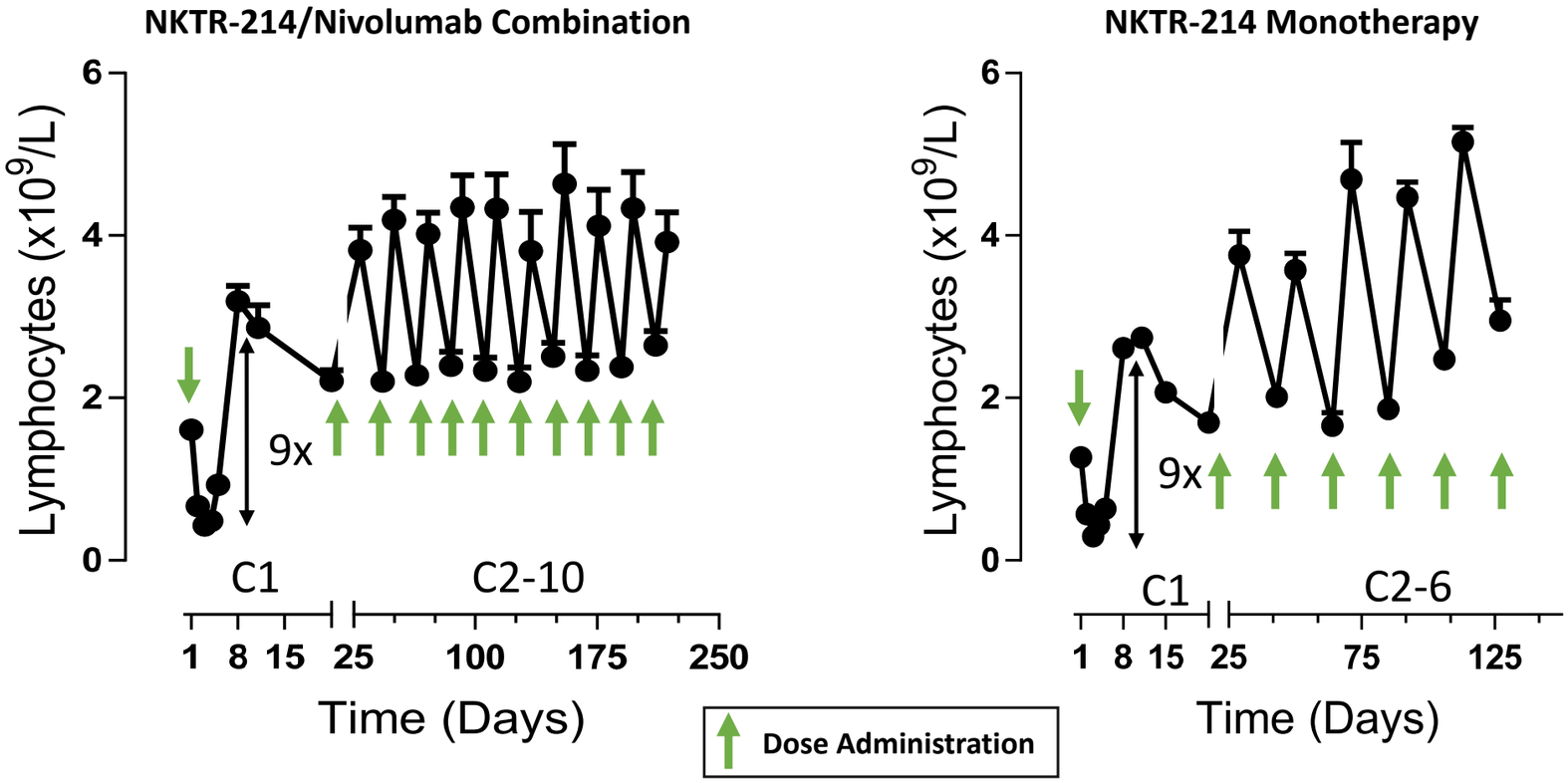
Biomarker Sampling and Methodology for Stage IV Melanoma Cohort



Biomarker analysis includes only patients at the Recommended Phase 2 dose NKTR-214 0.006 mg/kg q3w + nivolumab 360 mg q3w

- Multiple methods included in the biomarker plan to demonstrate activation of the IL-2 receptor pathway
  - Lymphocyte analysis in blood for all patients over duration of treatment (n=41)
  - Baseline tumor biopsies evaluated for PD-L1, CD8 T cells (n=26)
  - Baseline tumor biopsies evaluated for gene expression using EdgeSeq (n=11)
  - Immunophenotype analysis for matched Day 1 and Day 8 samples (n=9)
  - Cellular analysis of tumor biopsy using immunofluorescence (n=4) and IHC (n=8) with matched Day 1 and Day 21 samples
  - TCR repertoire analysis using immunoSEQ (n=7)

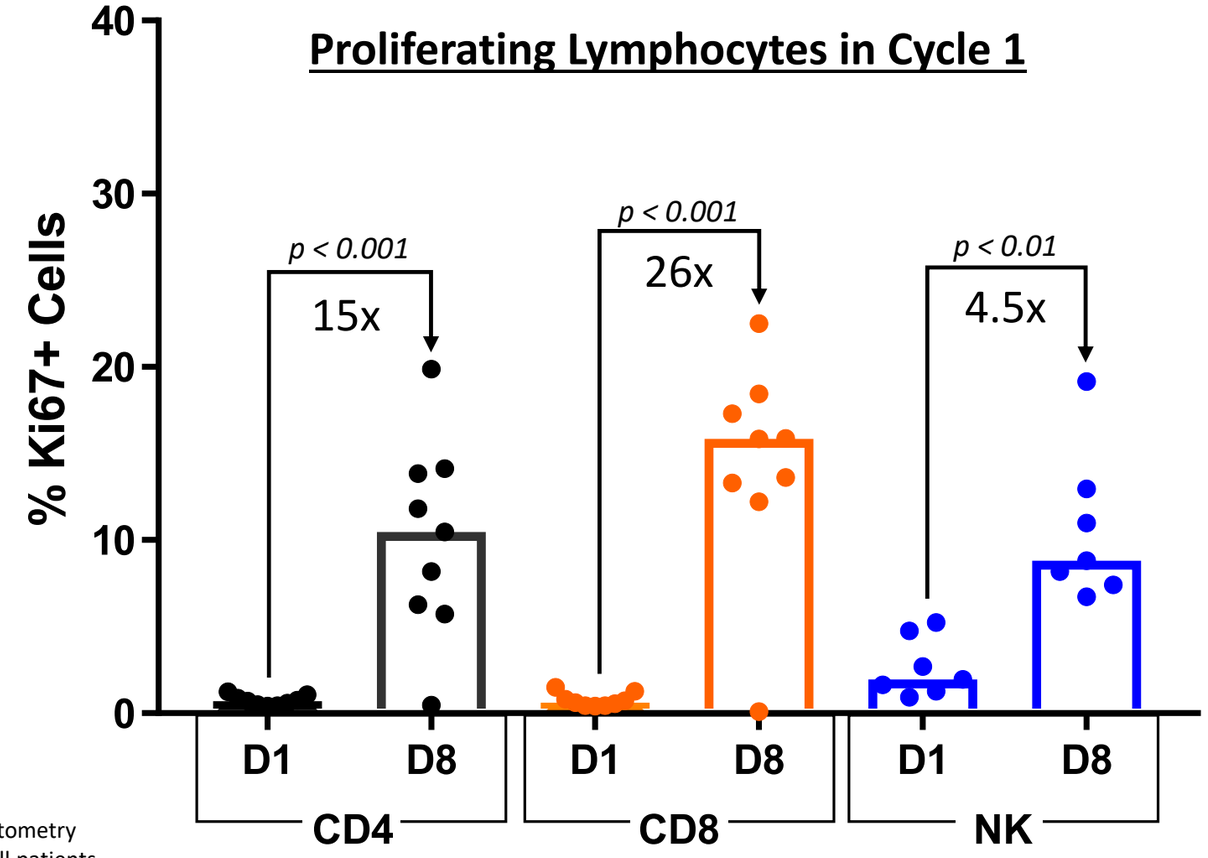
NKTR-214 Drives Continuous Mobilization of Lymphocytes After Every Cycle



- NKTR-214 provides rapid activation of the immune system.
- Effect of lymphocyte mobilization is consistent and maintained with successive treatment cycles.
- Lymphocyte effects of the NKTR-214/nivolumab combination are driven by NKTR-214, as a similar pattern is observed with monotherapy

Lymphocyte levels were obtained from standard hematology analysis. All patients with data from the monotherapy trial EXCEL (N=17) and all 1L Melanoma patients in the NKTR-214/nivolumab combination enrolled in PIVOT-02 (N=41, Mean±SE) were included in the analyses.

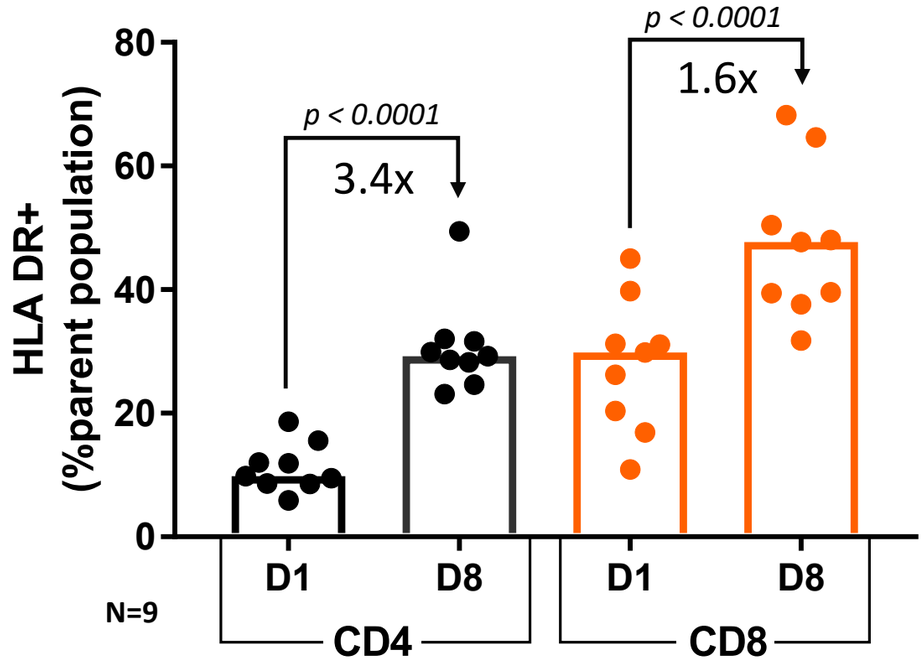
Peripheral Blood Demonstrates Proliferation of CD4, CD8 and NK Cells 1L IO-Naïve Melanoma



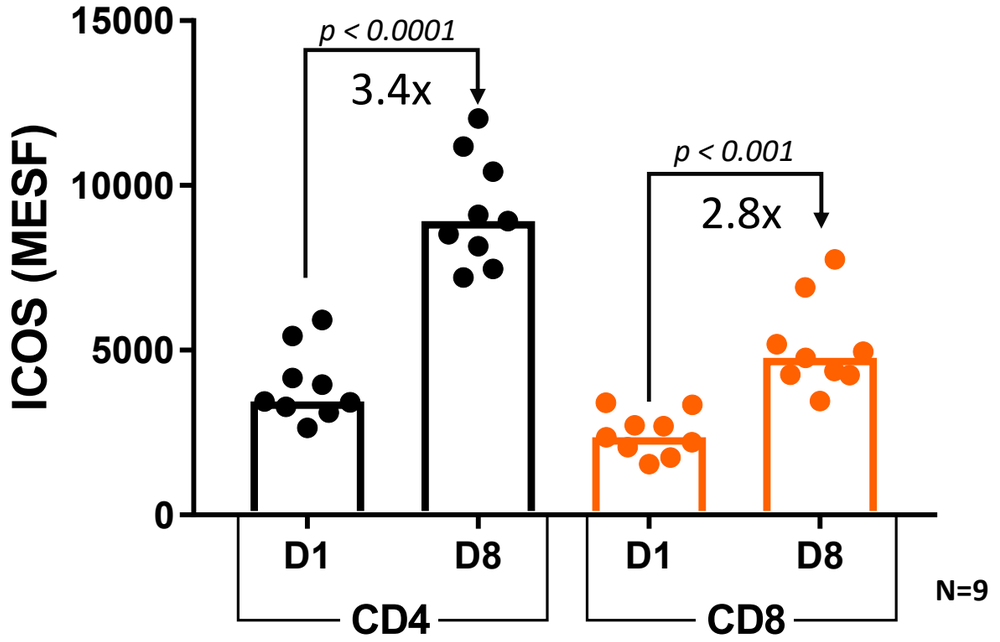
Ki67 positive lymphocytes were enumerated using flow cytometry and presented as proportion (%) of each cell population. All patients at RP2D with matched D1 and D8 samples were included in the analysis (CD4: N=9, CD8: N=9, NK: N=7). Median is shown, fold change and paired T-test was used for statistical significance.

Peripheral Lymphocytes Mobilized by NKTR-214 + Nivolumab Exhibit an Activated Phenotype

Antigen-Experienced T Cells in Cycle 1



Increased Cell Surface Expression of ICOS on T Cells in Cycle 1



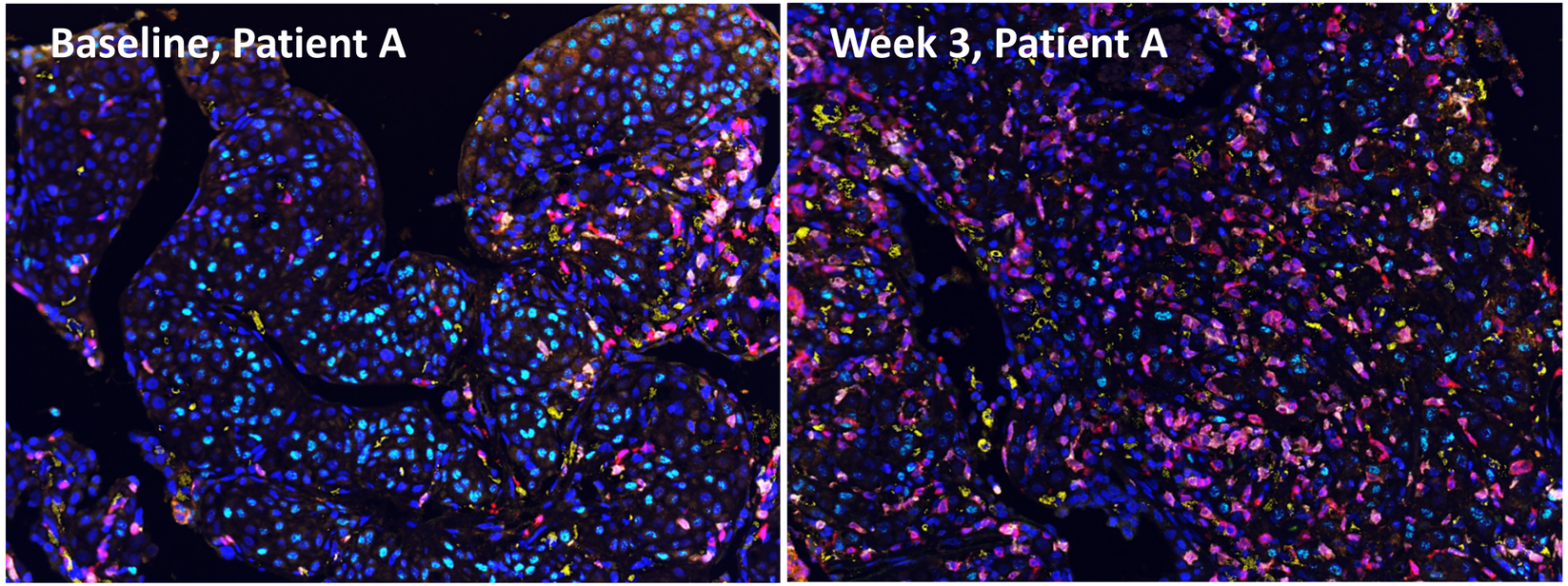
- ICOS increase also observed with NKTR-214 monotherapy

HLA-DR positive T cells were enumerated using flow cytometry and presented as proportion (%) of each parent cell population. All patients at RP2D with matched D1 and D8 Cycle 1 samples were included in the analysis. (N=9; bars show median for each population). Median fold change and statistical analysis is paired T-test between D8 and D1.

ICOS positive T cells were enumerated using flow cytometry and cell surface expression of ICOS was calculated from a reference curve of Molecules of Equivalent Staining Fluorochrome (MESF). All patients at the RP2D with matched D1 and D8 Cycle 1 samples were included in the analysis (N=9, bars show median for each population). Median fold change and statistical analysis is paired T-test between D8 and D1.

NKTR-214 + Nivolumab Promotes Increase of T cells

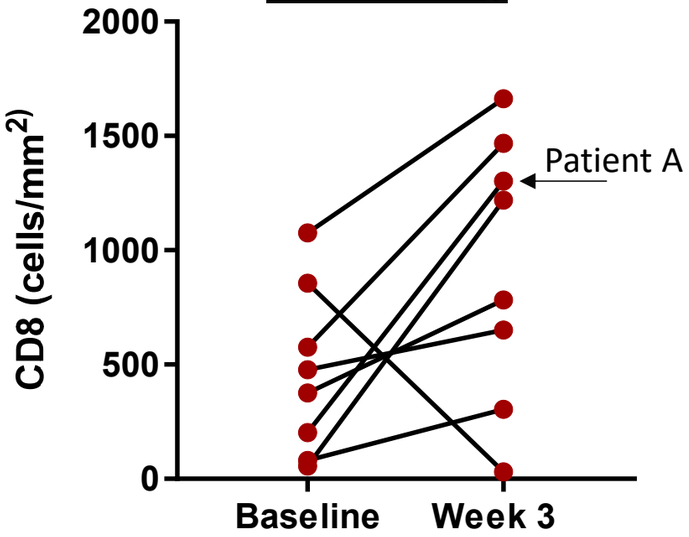
Immunofluorescence Microscopy of Tumor Biopsy



CD8 T cells: Baseline – 108 cells/mm2 **CD8 T cells: Week 3 – 712 cells/mm2**

DAPI SOX-10 CD3 CD8 PD-L1 PD-1 CD68

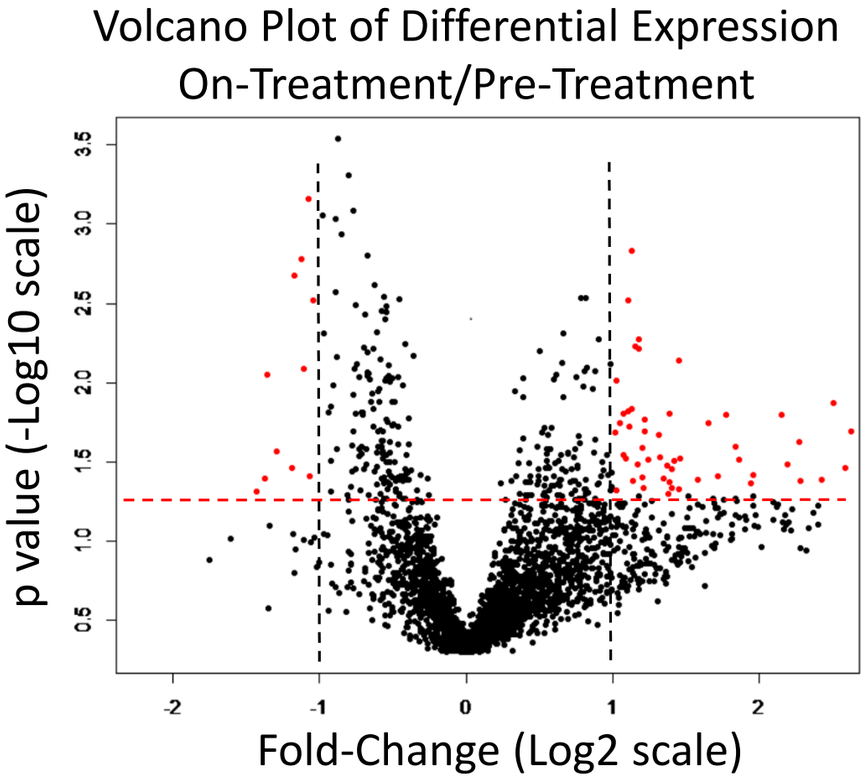
Change in CD8 Infiltrate IHC Staining

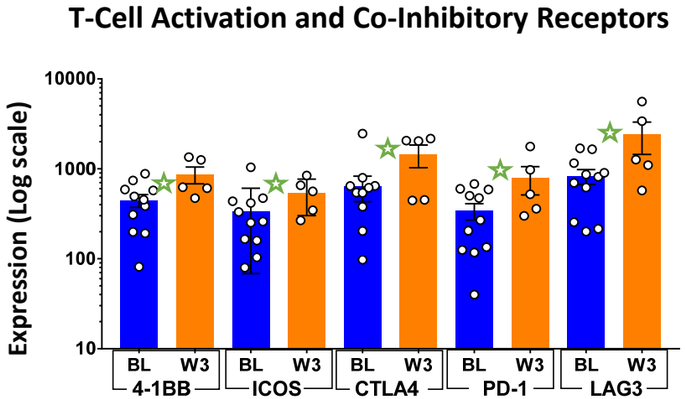


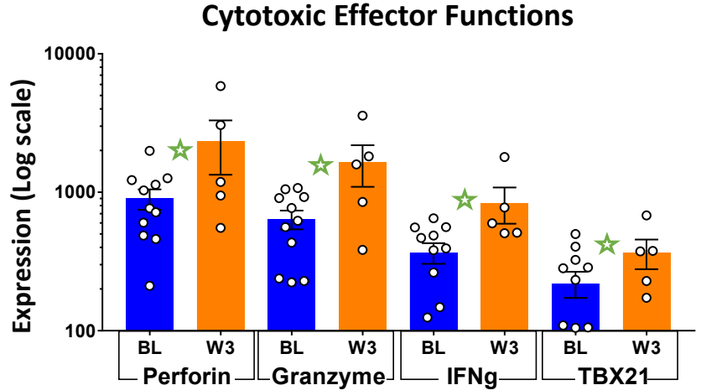
Good concordance between immunofluorescence and IHC methods

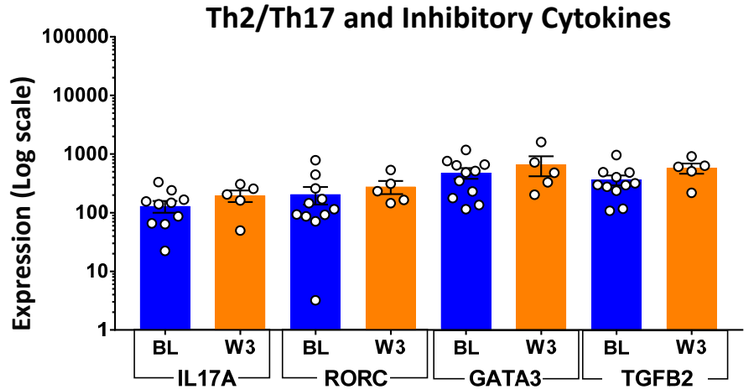
Immunofluorescence staining was performed using Vectra with the indicated staining reagents. Images shown obtained at 20X magnification. DAPI stains DNA, SOX-10 is a melanoma tumor antigen, CD3/CD8 stain T cells, CD68 stains macrophage. IHC for CD8 was obtained by standard methods. All 1L Melanoma patients with matched Baseline and Week 3 biopsy (N=8) were included in the analysis.

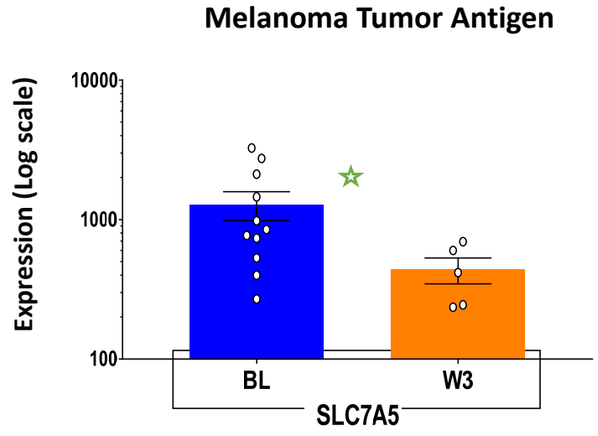
NKTR-214 + Nivolumab Promotes Favorable Anti-Tumor Gene Expression Changes and Antigen Reduction in the Tumor





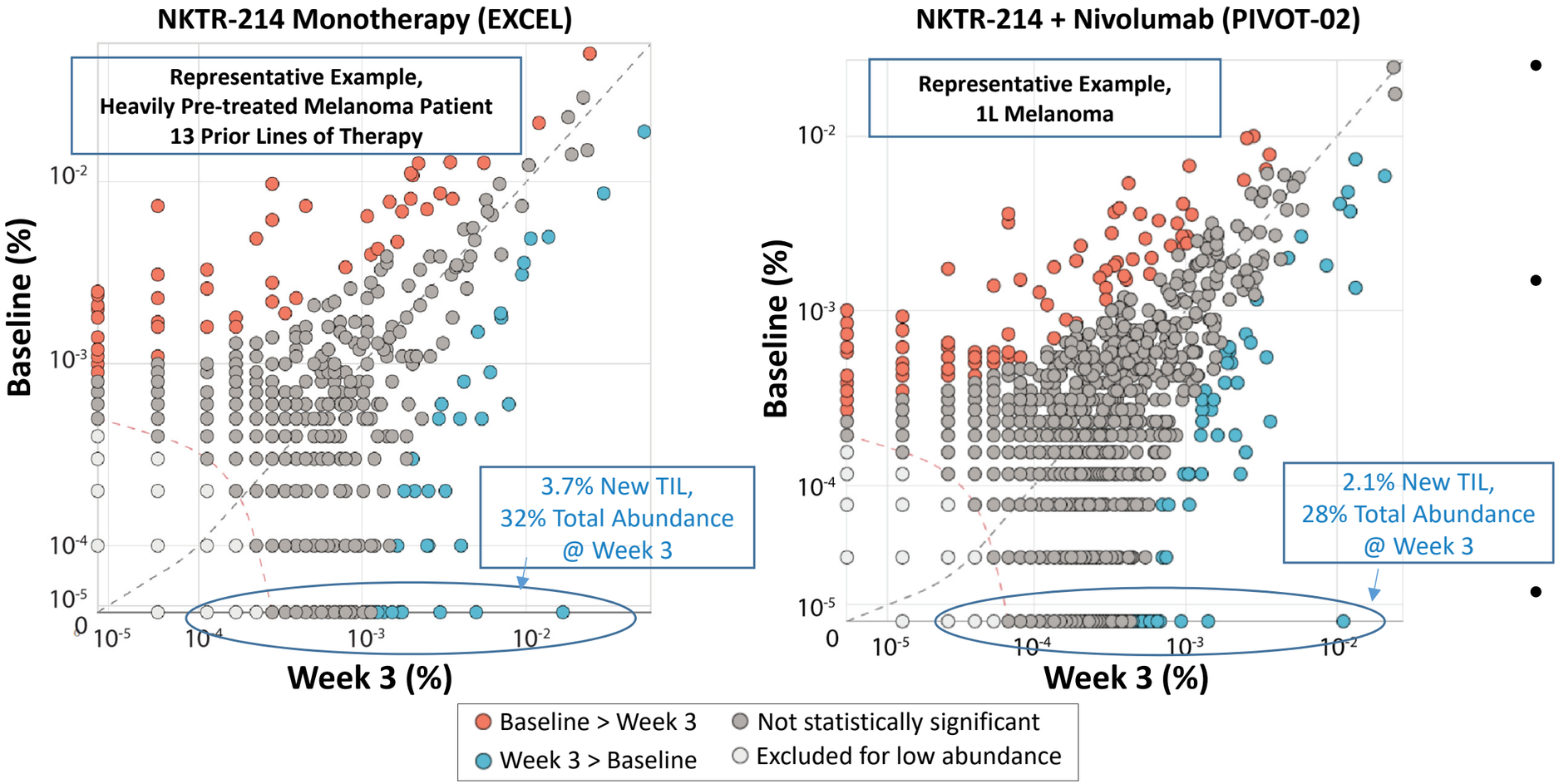






EdgeSeq was performed on all available samples, Baseline (BL) N=11 and Week 3 (W3) N=5. Only 2 patients had matched BL and W3 samples. Volcano Plot N=2: red points are both statistically significant (p-value<=0.05) and are over 2 fold higher (in linear space). Black dashed lines show 2-fold increase/decrease, red dashed line shows threshold for statistical significance. Bar Charts / Scatter Plots: Green stars indicate statistically significant genes (p-value<=0.05).

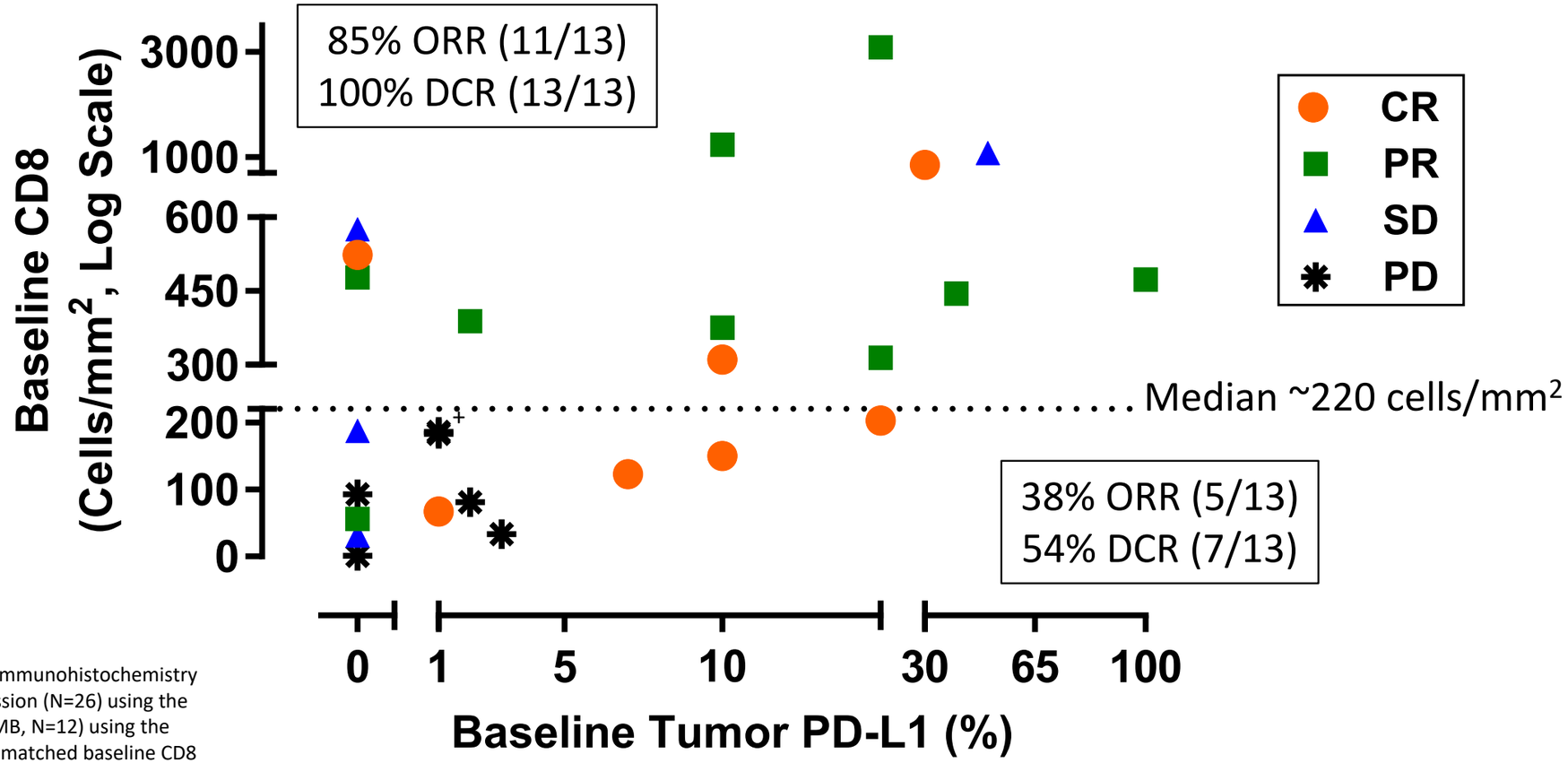
NKTR-214 Drives New T Cell Clones into the Tumor Microenvironment



- All patients evaluated demonstrated new clones at Week 3 that were not present at Baseline
- New TIL fraction and proportional abundance driven by NKTR-214 since effects are similar in monotherapy and combination
- Results indicate that therapy promotes new priming and T cell trafficking into the tumor

Tumor biopsy was processed to nucleic acid and used for TCR repertoire analysis using immunoSEQ. All 1L Melanoma patients (N=7) with matched Baseline and Week 3 samples are reported as % productive frequency. TCR Clones more abundant at Baseline are shown in red and clones more abundant at Week 3 are shown in blue. Dark grey dots are not significant between timepoints and light gray dots are excluded for low abundance. The gray dashed line lists frequency equality and the red dashed line identifies the population used for statistical comparison. New T Cell infiltrates are shown in the oval and summarized for N=7 in the box above. EXCEL: NKTR-214 Monotherapy clinical trial.

NKTR-214 + Nivolumab Provides Efficacy Regardless of Baseline CD8 Tumor Infiltrating Lymphocytes and PD-L1 Expression



+: 2 patients with PD

Baseline tumor biopsies were evaluated by immunohistochemistry for CD8 cell counts (N=26), and PD-L1 expression (N=26) using the 28-8 method, or tumor mutation burden (TMB, N=12) using the Foundation TMB method. Each patient with matched baseline CD8 and %PD-L1 were plotted as x/y coordinates and correlated with BOR. Each symbol represents an individual patient (CR: N=7, PR: N=9, SD: N=4, and PD: N=6).

Conclusions

- NKTR-214 plus nivolumab is well tolerated with deep and durable responses in 1L Stage IV melanoma patients, including a high rate of complete responses
- Clear activation of the IL-2 pathway demonstrated by increase in absolute lymphocyte count with activated and proliferating CD4, CD8 and NK cells in blood
- Combination demonstrated T cell infiltration and activation in the tumor microenvironment
- TCR repertoire analysis demonstrates the presence of newly trafficked clonal infiltrates after treatment with NKTR-214 plus nivolumab
- These findings support further evaluation of NKTR-214 plus nivolumab in randomized clinical trials, including the recently initiated 1L melanoma phase 3 trial (CA045-001/NCT03635983)

Acknowledgments

A special thank you is extended to the patients, their families and all study staff who are participating and have participated in the PIVOT-02 study

MD Anderson
- Adi Diab, MD
- Michael Wong, MD, PhD
- Jianjun Gao, MD, PhD
- Nuhad K. Ibrahim, MD
- Vali Papadimitrakopoulou, MD
- Arlene O. Siefker-Radtke, MD
- Nizar Tannir, MD
- Debu Tripathy, MD

Inova Cancer Center
- Sekwon Jang, MD

Instytut MSF Sp Zoo
- Ewa Kalinka Warzocha, MD

Yale University
- Michael Hurwitz, MD, PhD
- Harriet Kluger, MD
- Mario Sznol, MD
- Scott Gettinger, MD

New York University
- Daniel Cho, MD
- David Wise, MD, PhD

Providence Cancer Institute
- Brendan Curti, MD

Roswell Park Cancer Institute
- Igor Puzanov, MD

Seattle Cancer Center Alliance
- Scotty Tykodi, MD, PhD

Virginia Cancer Specialists
- Alexander Spira, MD

UOC Immunoterapia Oncologica
- Michele Maio, MD

University of California San Diego
- Greg Daniels, MD, PhD

University of Colorado Anchutz Cancer Center
- Karl Lewis, MD

Nektar, Bristol-Myers Squibb and ONO Pharmaceuticals