

A phase IB trial of Nivolumab for Immunoprevention of Bronchial Dysplasia Progression in high-risk current and former smokers

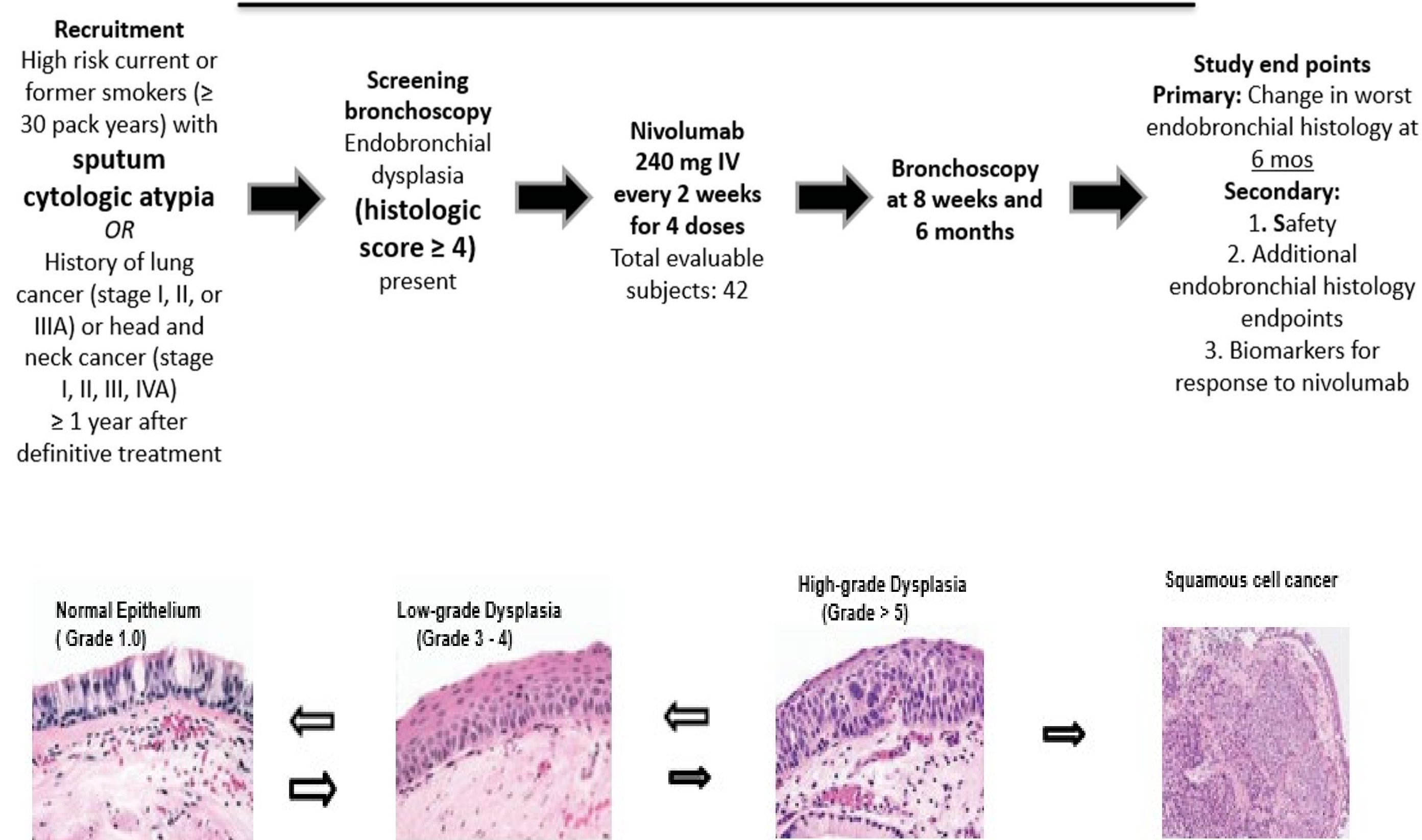
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Background

1. Cigarette smoking causes persistent chronic airway injury, which can lead to central airway dysplasia that can progress to invasive lung squamous cell carcinoma (SCC).
2. Given the success of immune checkpoint inhibitors (ICIs) in the treatment of lung cancer, we investigated the efficacy of nivolumab for immunoprevention of bronchial dysplasia progression in high-risk current and former smokers.

Study Design

Nivolumab Trial Schema



PRIMARY ENDPOINTS

1. Improvement in endobronchial dysplasia in worst histologic score at 8 weeks and 6 months.
2. Safety and tolerability of PD-1 blockade in high-risk current and former smokers and in subjects with a prior history of early-stage lung or head & neck cancer.

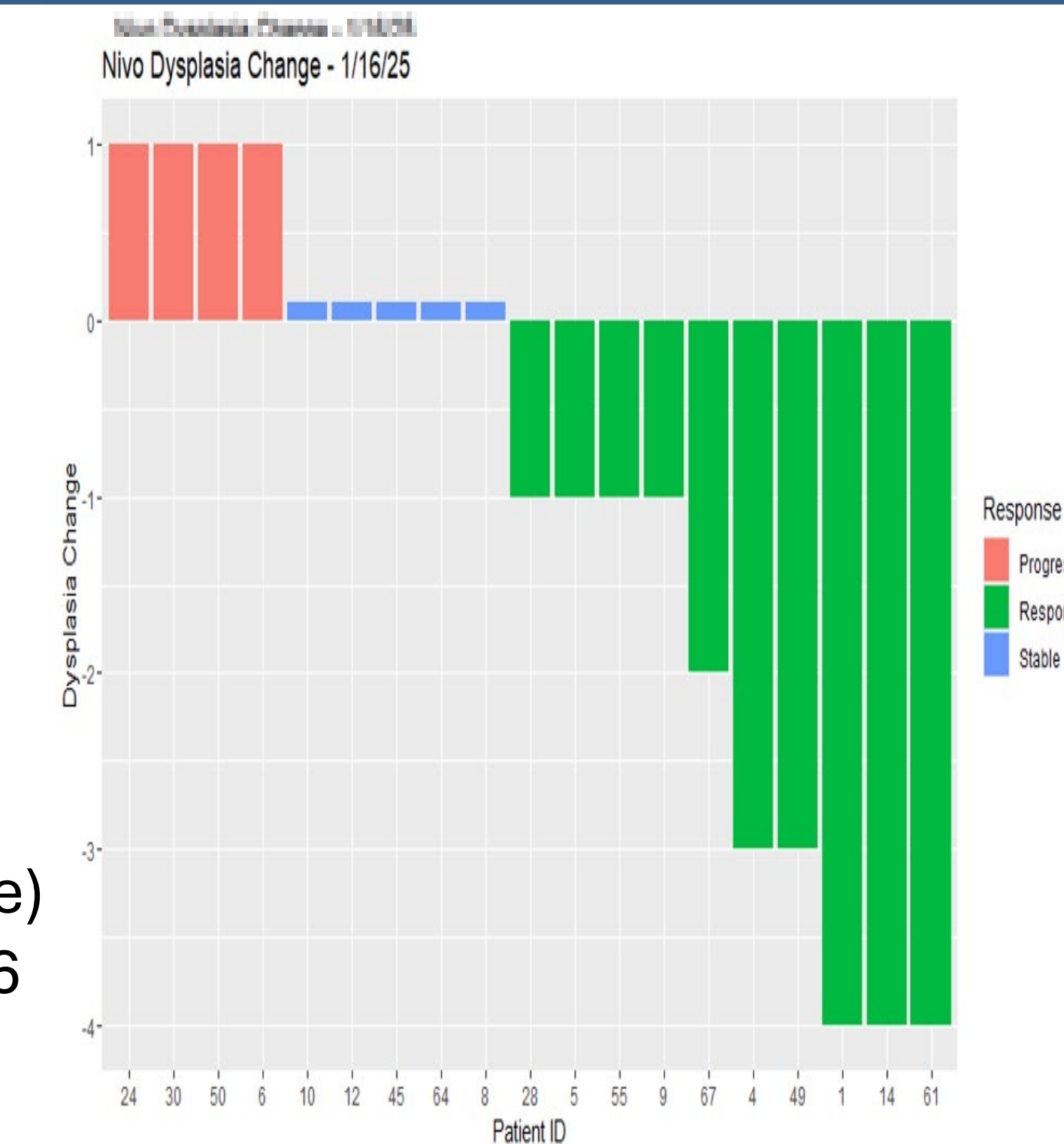
SECONDARY ENDPOINTS

1. Explore the correlation of ICI response with alterations in the immune microenvironment [Phenoimager multiplex immunofluorescence (mIF) imaging].
2. Examine the association between mutational burden and nivolumab response by whole exome sequencing (WES).

Results

Clinical Outcome

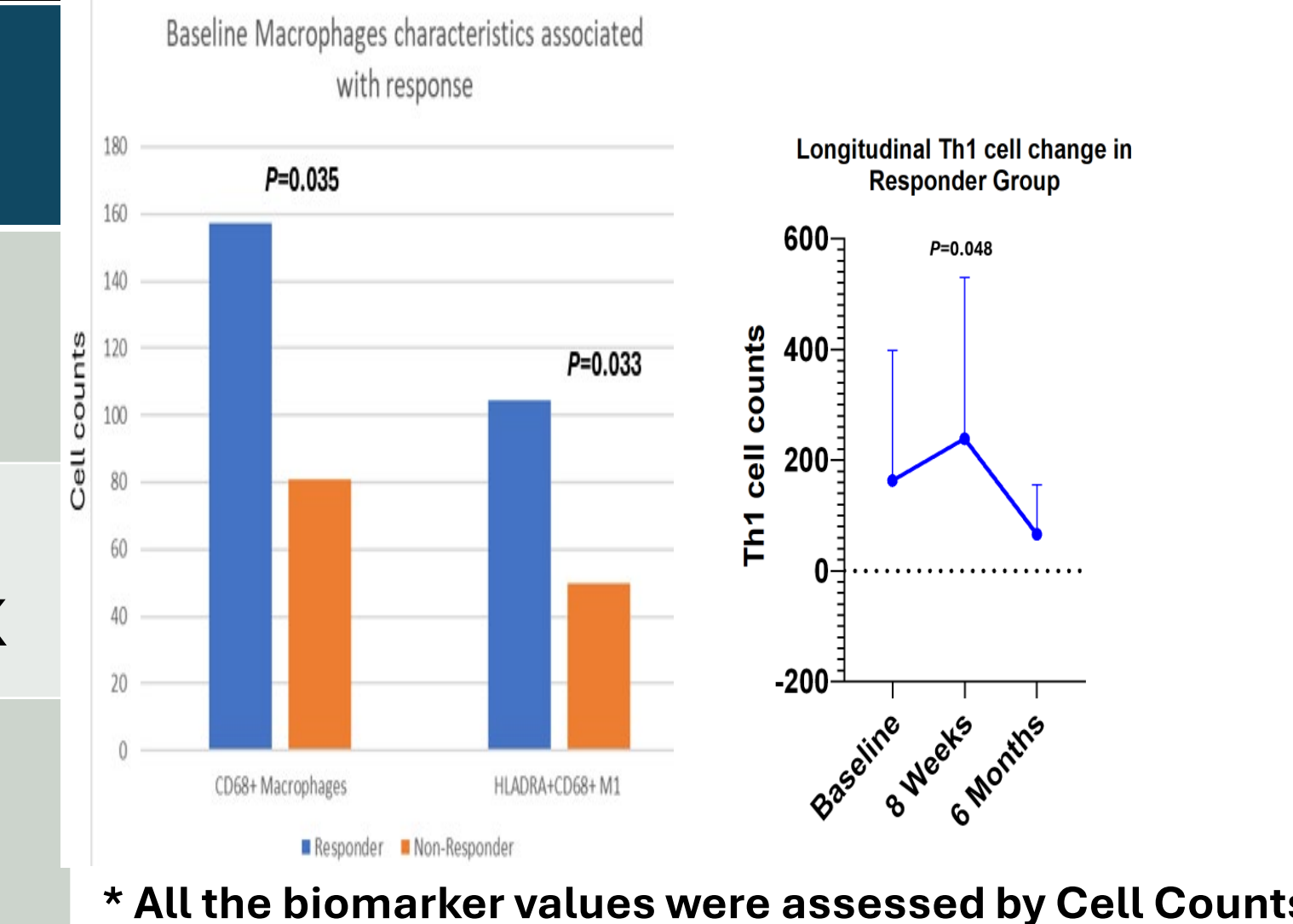
1. A total of 19 patients completed treatment.
2. The treatment was well tolerated. The main treatment related adverse events were hypothyroidism, fatigue, and headache.
3. Histologic improvement (defined as a max score decreasing by at least one grade) was observed in 10 patients at 6 months. Five subjects showed stable dysplasia and four subjects showed progression.



Waterfall plot showing changes in max histologic score at 6 months.

Phenoimager Multiplex Immunofluorescence (mIF)

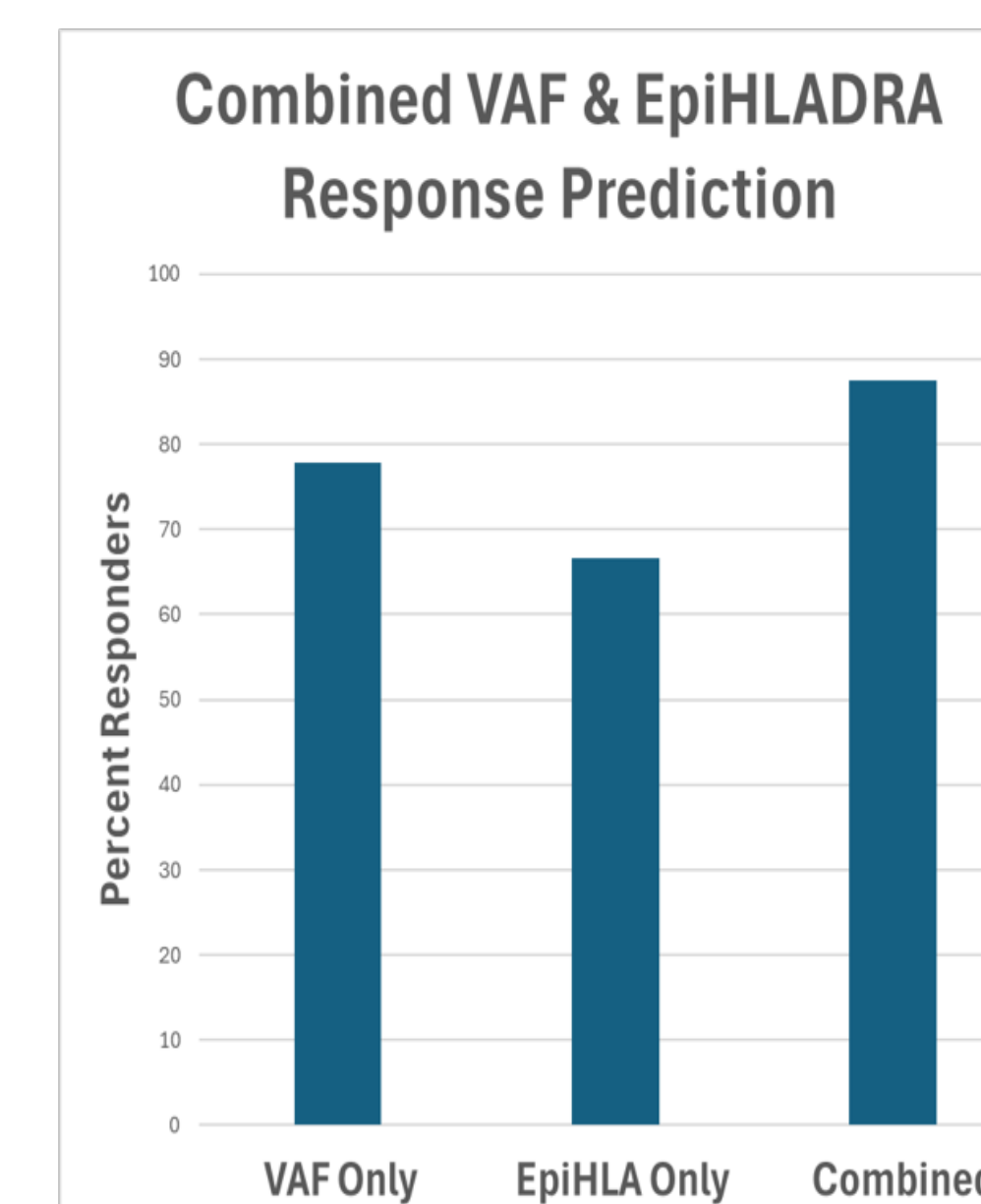
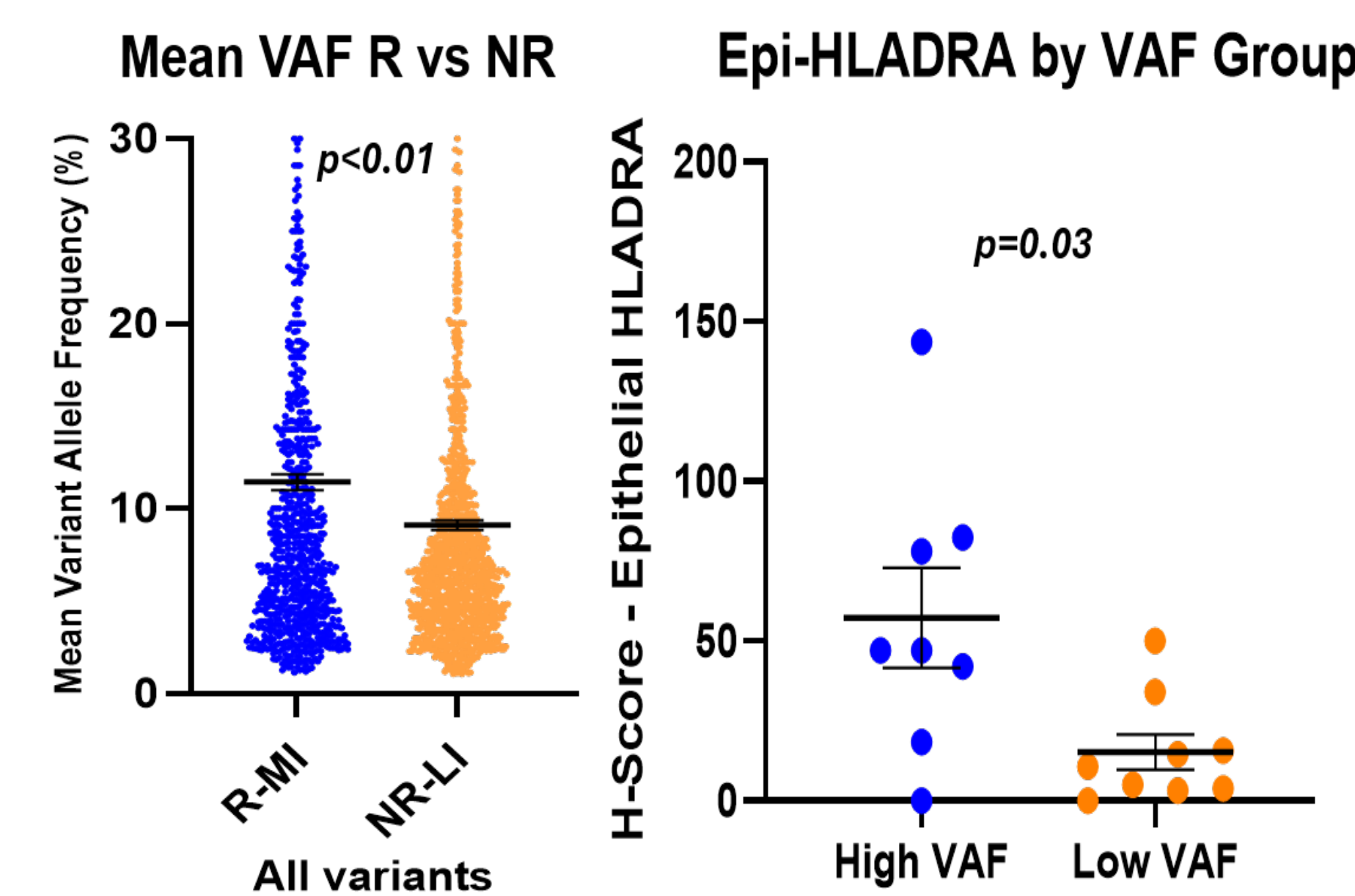
Phenoimager Analysis Panels (N=19)	
Panel 1 (Th1/Th2)	CD4/CD8/PD-L1/PD1/Tbet/GATA3
Panel 2 (M1/M2)	CD68/CD206/HLA-DR/PD-L1/PD1/Pan-CK
Panel 3 (Treg/Th17)	CD4/IFN γ /IL-1 β /IL-17/FoxP3/Pan-CK



* All the biomarker values were assessed by Cell Counts

Whole Exome Sequencing (WES): Mutational-Immune

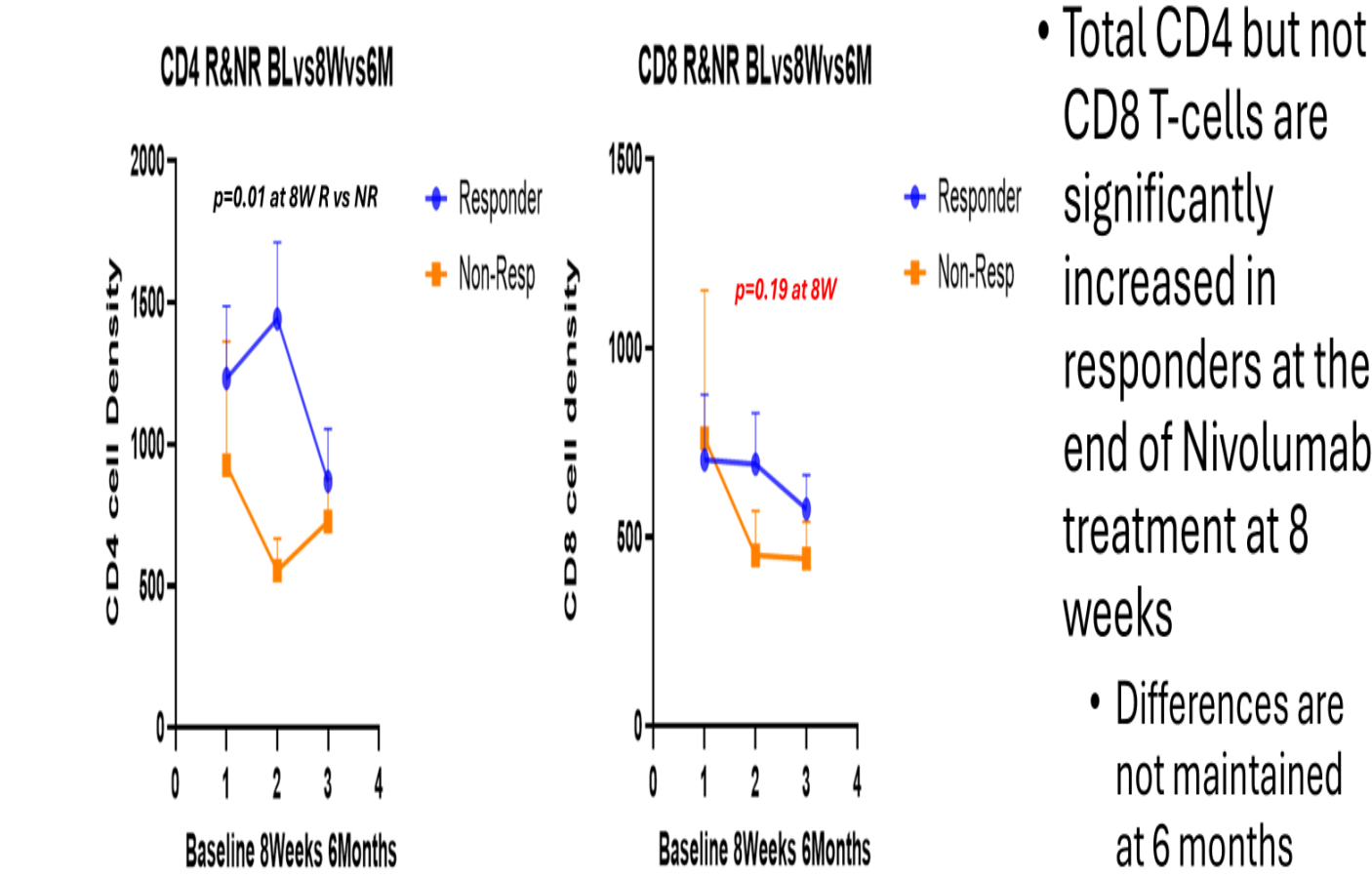
- Responders associated with high mean variant allele frequency (VAF)
- Correlation of high VAF cases with associated immune features in responders



Results

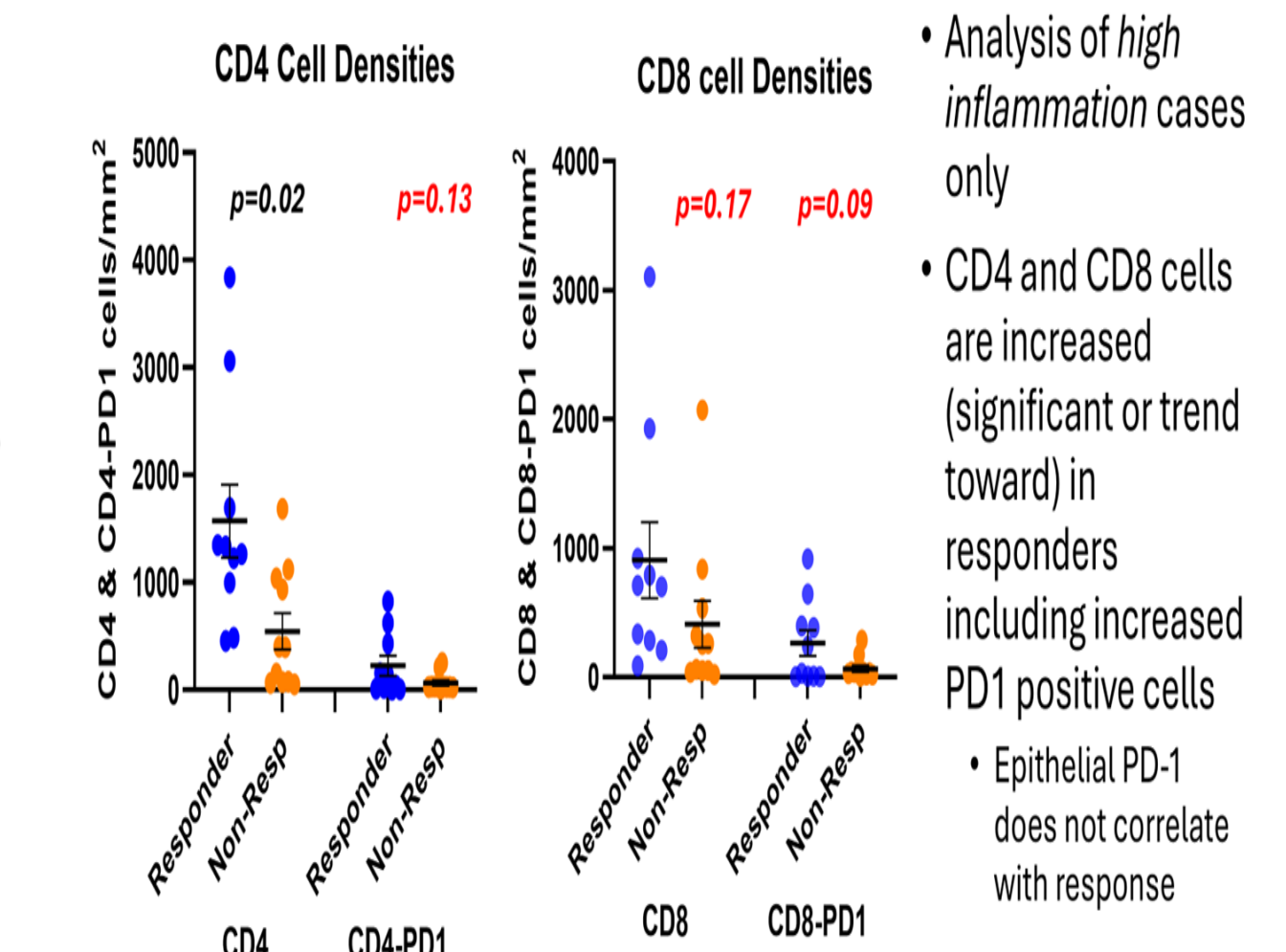
Phenoimager Multiplex Immunofluorescence (mIF)-Evaluated by Cell Density

Nivolumab Trial: Longitudinal T-Cell Change



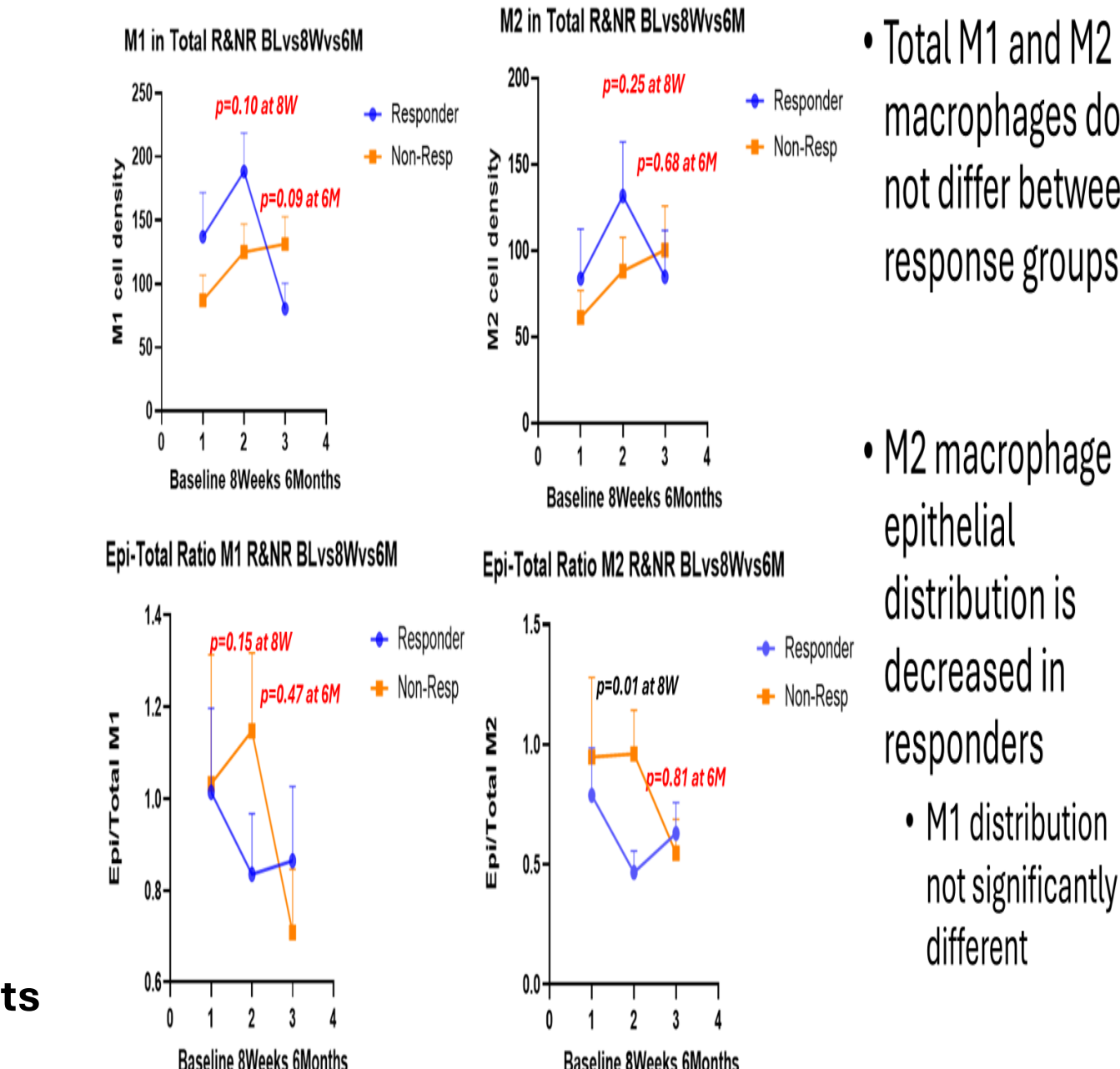
- Total CD4 but not CD8 T-cells are significantly increased in responders at the end of Nivolumab treatment at 8 weeks
- Differences are not maintained at 6 months

Nivolumab Trial: Baseline T-Cell Predictors



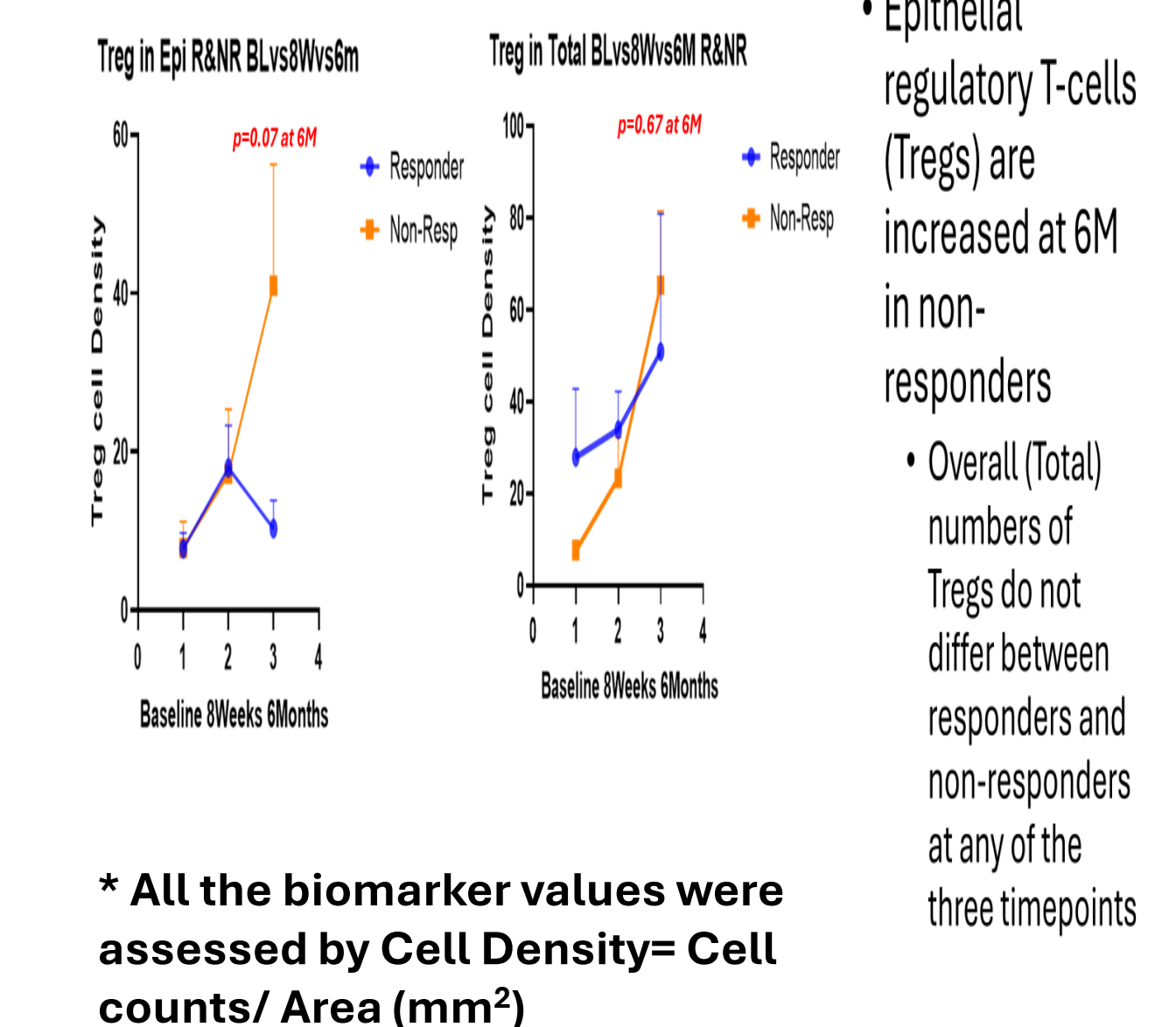
- Analysis of high inflammation cases only
- CD4 and CD8 cells are increased (significant or trend toward) in responders including increased PD1 positive cells
- Epithelial PD-1 does not correlate with response

Nivolumab Trial: Long. Macrophages Changes



- Total M1 and M2 macrophages do not differ between response groups
- M2 macrophage epithelial distribution is decreased in responders
- M1 distribution not significantly different

Nivolumab Trial: Longitudinal Treg Cell Changes



- Epithelial regulatory T-cells (Tregs) are increased at 6M in non-responders
- Overall (Total) numbers of Tregs do not differ between responders and non-responders at any of the three timepoints

* All the biomarker values were assessed by Cell Density= Cell counts/ Area (mm²)

Conclusions

- ❖ The PD-1 inhibitor nivolumab improves endobronchial dysplasia in high-risk current and former smokers and those with a history of early-stage lung or head/neck cancer. It may ultimately prevent progression of dysplasia to SCC.
- ❖ Nivolumab is well tolerated in this population. No subjects dropped out during treatment.
- ❖ Phenoimager mIF analysis showed:
 - Increased CD4 T cells at baseline may promote response to nivolumab
 - Dynamic changes in immune cell populations occur at 8 weeks that correlate with response including increased CD4⁺ T cells and altered macrophages activation status within the epithelium.
- ❖ Whole Exome Sequencing:
 - An increase in mean VAF was found in responders, suggesting dysplastic lesions that show clonal outgrowth may be more susceptible to nivolumab.
 - A potential synergistic relationship between mean VAF and epithelial HLADRA expression was seen. The combined presence of high VAF and epithelial HLADRA showed the highest accuracy in identifying responders.