P2.243: BTN1A1 Expression and Spatial Immune Profiling as Predictive Biomarkers for Nelmastobart in NSCLC

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ABSTRACT

Introduction

Advanced/metastatic NSCLC remains difficult to treat after platinum-based chemotherapy and immunotherapy. Nelmastobart is a novel monoclonal antibody targeting BTN1A1, an immune-regulatory molecule in the tumor microenvironment [1]. We investigated BTN1A1 expression and immune biomarkers associated with nelmastobart plus docetaxel in advanced NSCLC (NCT07306624).

Methods

Tumor tissues from a multicenter, single-arm phase 2 study were analyzed by BTN1A1 IHC and multiplex IHC using Opal™ or CellDIVE. Immune and tumor markers included CD3, CD4, CD8, FOXP3, CD68, PD-1, PD-L1, CK, Ki-67, SLFN11, and YAP1. Biomarker profiles and spatial immune features were explored in relation to clinical response.

Results

BTN1A1 was frequently expressed in prescreened NSCLC tumors, with 51/92 patients (55%) showing TPS ≥50. Among 10 BTN1A1-high patients included in the current analysis, histology was equally distributed between non-squamous and squamous NSCLC. Multiplex IHC revealed associations of BTN1A1 with Ki-67, SLFN11, and YAP1, together with increased $CD8^+$ T-cell infiltration and distinct spatial immune patterns.

Conclusions

BTN1A1-high NSCLC exhibited distinct tumor-intrinsic and spatial immune features, supporting BTN1A1 as a potential predictive biomarker for nelmastobart plus docetaxel. Ongoing enrollment and larger-scale analyses will further evaluate associations with clinical efficacy.

INTRODUCTION

BTN1A1 Expression and Tumor Microenvironment (TME)

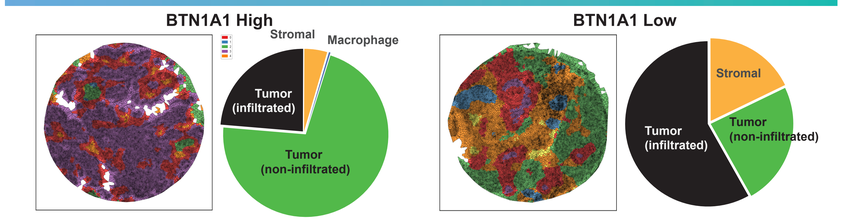


Figure 1. Higher BTN1A1 expression is associated with a reduced proportion of CD8+ T-cell–infiltrated tumor regions. Relative area of representative colorectal TMA cores by microenvironmental component. BTN1A1-high tumors (left) showed a higher proportion of non-infiltrated tumor regions, whereas BTN1A1-low tumors (right) showed a greater proportion of immune-infiltrated regions.[2]

BTN1A1 expression is associated with distinct patterns of TME remodeling.

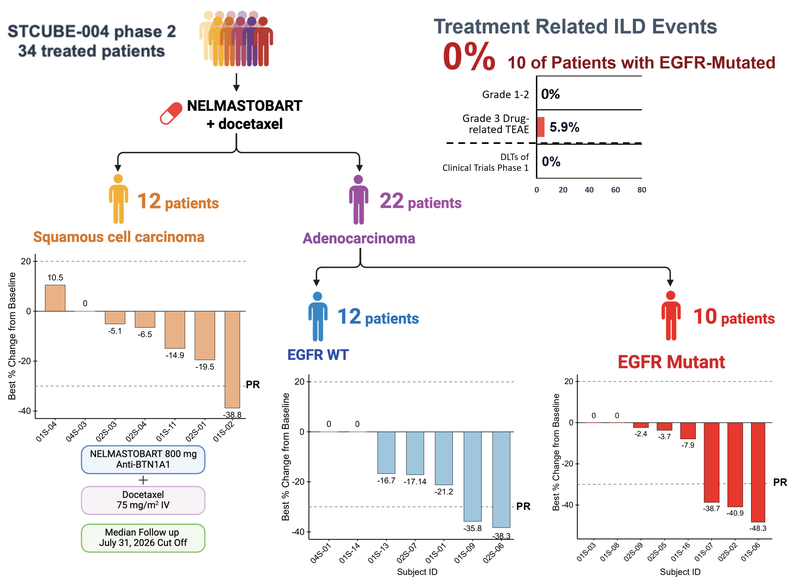
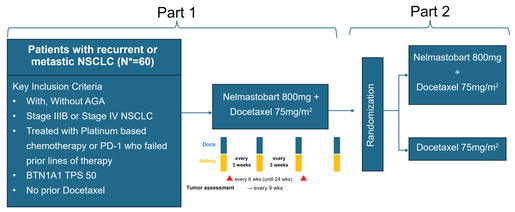


Figure 2. Safety signal associated with osimertinib plus durvalumab and Nelmastobart. Among 34 treated patients, 12 had squamous cell carcinoma and 22 had adenocarcinoma; within the adenocarcinoma cohort, 12 patients were EGFR wild type and 10 had EGFR-mutant disease. Waterfall plots show best percentage change from baseline in target lesions, including partial responses in both EGFR wild-type and EGFR-mutated subgroups. Notably, no ILD-related adverse events were observed among the 10 EGFR-mutated patients. Treatment-related adverse events were 0% of grade 1–2, with 2.9% grade 3 drug-related TEAEs.

METHODS



Part 1 is a single arm trial where mPFS from 62 subjects who are administered with Nelmastobart 800mg combined with Docetaxel 75mg/m² will be tested against the mPFS from historical control of Docetaxel monotherapy. Safety and efficacy data from Part 1 will be evaluated concurrently to assess the feasibility of a subsequent two arm, randomized Part 2 study. Purpose of part 2 is to further assess and compare the mPFS of each arm.

20-Marker CellDIVE Panel for the NSCLC Tumor Microenviroment

A multiplex panel spanning tumor identity, immune regulation, effector function, lineage, and stromal remodeling

1. Tumor identity & signaling	2. Immune checkpoints	3. Effector & DNA sensing	4. Immune lineages	5. Stroma & CAF
NSCLC epithelial state	*Tumor–immune suppression*	*Antitumor activity and stress*	*Immune-cell composition*	*Tumor-supportive compartment*
PanCK, EpCAM, β-catenin, YAP1, Ki-67, BCL-2	PD-1, PD-L1, BTN1A1	CTL, Granzyme B; Granzyme B, STING, SLFN11	T cell, Mφ, DC, Treg; CD45, CD68, CD3ε, CD4, CD8, FOXP3	Vimentin, α-SMA
Defines epithelial tumor cells, proliferation, survival, and oncogenic signaling.	Captures canonical and alternative checkpoint-mediated immune evasion.	Measures cytotoxic potential, innate sensing, and DNA-damage/replication-stress biology.	Resolves leukocytes, macrophages, T-cell subsets, and regulatory T cells.	Identifies mesenchymal/EMT features, CAFs, myofibroblasts, and remodeling.

NSCLC spatial readout | Integrated single-cell phenotypes and spatial relationships across tumor, immune, and stromal compartments

RESULTS

Key Findings

- BTN1A1-positive tumor cells displayed response-associated differences in their local immune contexture.
- In responders, BTN1A1-positive tumor cells and the YAP1-positive, Ki-67-negative, and SLFN11-positive subgroups generally showed greater separation from CD8 T cells and lower local CD8 T-cell density.
- The strongest nominal density differences were observed for the YAP1-positive and SLFN11-positive subgroups; these signals did not remain significant after correction for multiple testing.
- The results support a hypothesis in which a spatially immune-excluded BTN1A1-positive tumor niche may be associated with benefit from nelmastobart-based treatment.
- These exploratory findings require validation because the current response comparison included only two responders and eight non-responders.

Spatial Differences Between Responders and Non-responders

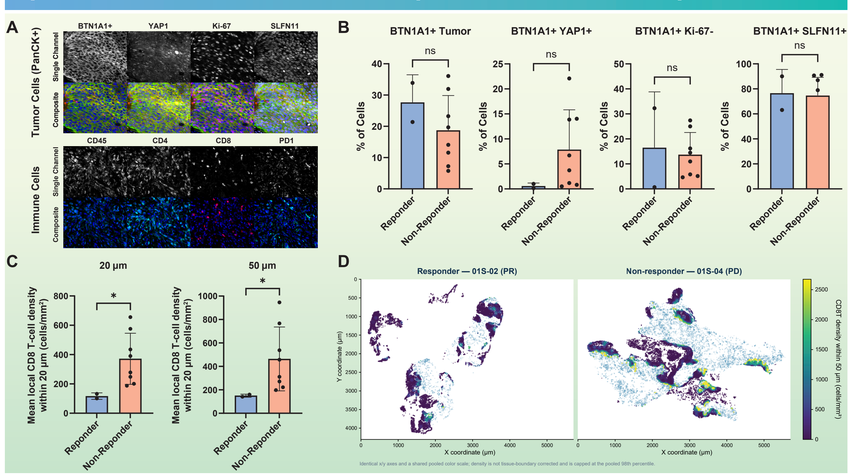


Figure 3. BTN1A1-positive tumor phenotypes and their spatial relationship with CD8 T cells according to clinical response. BTN1A1-positive tumor-cell abundance and tumor-intrinsic subgroups were compared by response (**A, B**), and their spatial relationship with CD8 T cells was assessed using nearest-neighbor distance and local density within 20 and 50 μm (**C, D**). Responders generally exhibited a more CD8 T-cell-excluded BTN1A1-positive tumor niche. Because only two responders were available and subgroup signals did not remain significant after multiple-testing correction, the findings are hypothesis-generating.

RESULTS

Spatial LDA Identifies Recurrent Immune–Tumor Neighborhoods

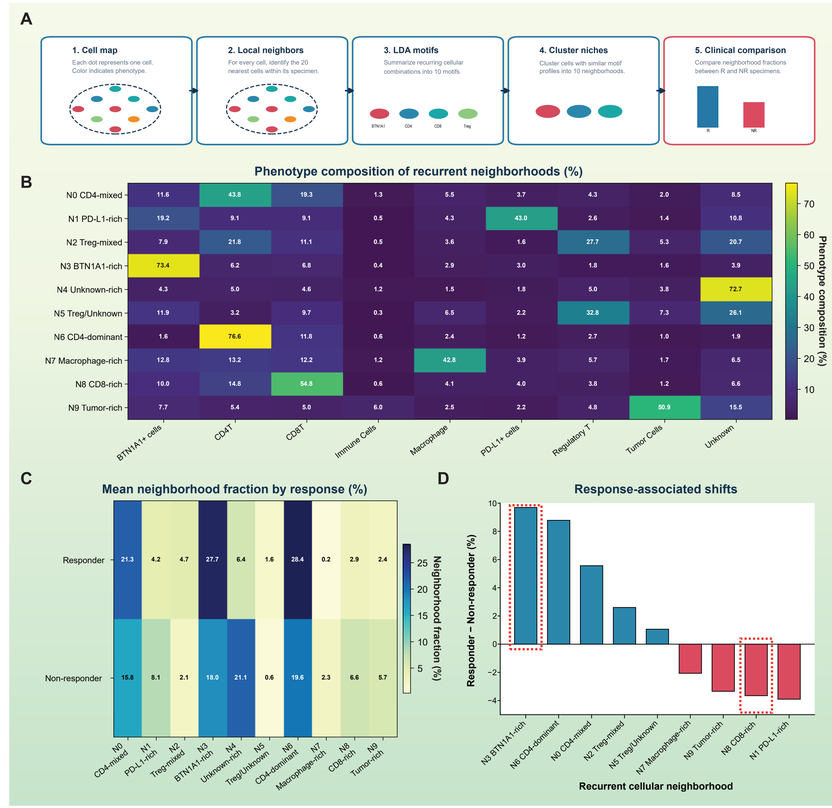


Figure 4. Spatial LDA analysis of cellular neighborhoods. (**A**) Schematic of the spatial LDA workflow. Phenotypes of the 20 nearest neighboring cells were collected for each cell within each specimen. Recurrent cellular combinations were summarized into 10 LDA motifs and subsequently grouped into 10 recurrent cellular neighborhoods using k-means clustering. Neighborhood fractions were then compared between responders and non-responders. (**B**) Heatmap showing the phenotype composition of each neighborhood. The analysis identified distinct BTN1A1-rich, PD-L1-rich, CD4-dominant, CD8-rich, regulatory T-cell–rich, macrophage-rich, and tumor-rich spatial niches. Values represent the percentage of each phenotype within a neighborhood. (**C**) Mean specimen-level neighborhood fractions in responders (n=2) and non-responders (n=8). (**D**) Differences in mean neighborhood fractions between response groups, calculated as responder minus non-responder. Blue bars indicate neighborhoods enriched in responders, whereas red bars indicate neighborhoods enriched in non-responders. Responders showed higher fractions of BTN1A1-rich and CD4-dominant neighborhoods and a lower fraction of the CD8-rich neighborhood.
None of the neighborhood comparisons reached statistical significance by the two-sided Mann–Whitney test.
Spatial LDA was performed using 1,956,768 cells from 14 specimens. Samples without response information were included in LDA training but excluded from the response-group comparison.

CONCLUSION

BTN1A1-high NSCLC exhibited distinct tumor-intrinsic phenotypes and spatial immune architectures. The cellular composition surrounding $BTN1A1^+$ tumor cells—particularly $CD8^+$ T-cell proximity and local density—may be associated with clinical response to nelmastobart plus docetaxel. These findings support spatial profiling of the $BTN1A1^+$ tumor niche as a potential predictive biomarker. Validation in a larger cohort is required to determine its relationship with treatment efficacy.

REFERENCES

1. Kim, Young-Seung, et al. "BTN1A1 is a novel immune checkpoint mutually exclusive to PD-L1." Journal for immunotherapy of cancer 12.3 (2024): e008303.
2. Nirmal, Ajit J, and Peter K Sorger. "SCIMAP: A Python Toolkit for Integrated Spatial Analysis of Multiplexed Imaging Data." ArXiv arXiv:2405.02076v1. 3 May. 2024 Preprint.