



P3.118: Triplet Therapy Improves Outcomes in SMARCA4-Mutant Lung Cancer: Integrated Clinical Evidence and Spatial Transcriptomic Insights

Xiaonan Zhang, Xiangyu Sun, Xuantang Lu, Zhongyi Dong, Xue Bai

Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, China,

Correspondence: baixue1990@i.smu.edu.cn



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INTRODUCTION

SMARCA4-mutant lung cancer is an aggressive subtype with poor clinical outcomes. Although chemo-immunotherapy is widely used, responses remain heterogeneous and durable benefit is limited.

Aberrant angiogenesis may contribute to treatment resistance and an immunosuppressive tumor microenvironment, providing a rationale for combining antiangiogenic therapy with chemo-immunotherapy. However, the clinical benefit and underlying biological basis of this strategy in SMARCA4-mutant lung cancer remain unclear.

Here, we integrated retrospective clinical data, Xenium spatial transcriptomics, and a prospective pilot study to evaluate triplet therapy and characterize its vascular and immune microenvironmental context.

METHODS

This study integrated retrospective clinical analysis, Xenium spatial transcriptomics, and a prospective pilot study.

Patients with locally advanced or metastatic SMARCA4-mutant lung cancer were retrospectively analyzed to compare chemo-immunotherapy (C+I) with chemo-immunotherapy plus antiangiogenic therapy (C+I+A), with progression-free survival and overall survival as major endpoints.

Xenium spatial transcriptomics was performed on SMARCA4-mutant and wild-type tumors to characterize vascular and immune microenvironmental features using dimensional reduction, gene-set enrichment, and pseudotime analyses. A prospective single-arm pilot study evaluated platinum-based chemotherapy combined with enavoflimab and endostar for preliminary assessment of efficacy and safety.

REFERENCES & ACKNOWLEDGEMENTS

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RESULTS

Triplet Therapy Improves Clinical Outcomes in SMARCA4-Mutant Lung Cancer

In the retrospective cohort, chemo-immunotherapy plus antiangiogenic therapy (C+I+A) demonstrated superior clinical efficacy compared with chemo-immunotherapy (C+I) alone. The addition of antiangiogenic therapy was associated with significantly prolonged progression-free survival and overall survival, together with improved tumor response. Notably, the survival benefit was particularly pronounced in patients with SMARCA4-deficient undifferentiated tumors, suggesting that this aggressive subgroup may derive substantial benefit from triplet therapy. Loss of BRG1 expression by immunohistochemistry further confirmed SMARCA4 deficiency. Representative longitudinal CT images showed progressive tumor shrinkage after treatment, providing radiological evidence of durable tumor control. Collectively, these clinical and imaging findings support the potential benefit of incorporating antiangiogenic therapy into chemo-immunotherapy for patients with SMARCA4-mutant lung cancer.

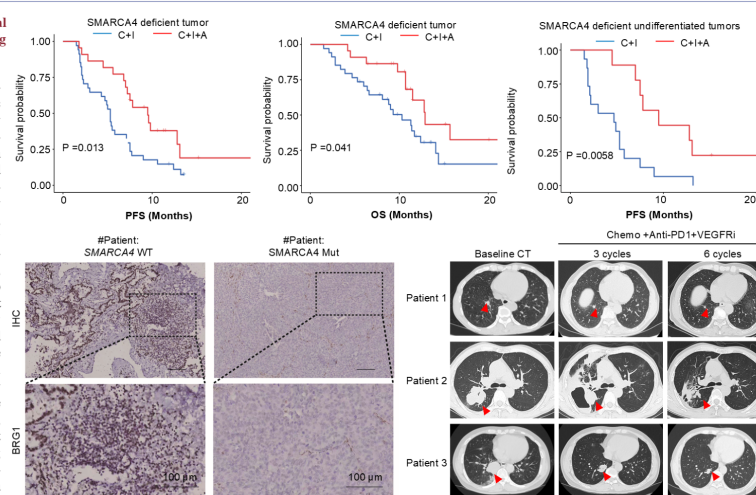


Figure 1. Triplet therapy improves clinical outcomes in SMARCA4-mutant lung cancer.

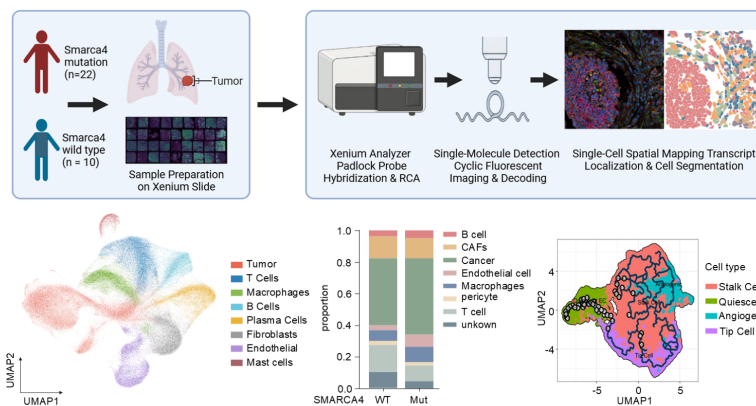


Figure 2. Spatial transcriptomic profiling characterizes the cellular and vascular landscape of SMARCA4-mutant lung cancer

Their differential distribution indicated substantial endothelial heterogeneity and provided a basis for dissecting mutation-associated vascular remodeling. Together, these spatial data established a detailed cellular framework for subsequent analyses of angiogenic activation, endothelial differentiation, and immune-vascular interactions in SMARCA4-mutant lung cancer.

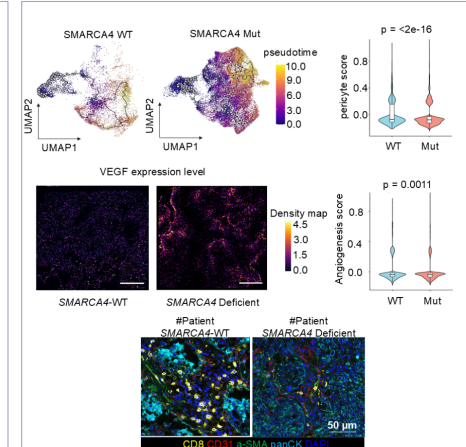


Figure 3. SMARCA4 deficiency is associated with an angiogenic and immunosuppressive vascular microenvironment

SMARCA4 Deficiency Promotes an Angiogenic and Immunosuppressive Vascular Microenvironment

Spatial analyses revealed profound vascular remodeling in SMARCA4-deficient tumors. Endothelial pseudotime trajectories indicated a shift toward angiogenic and tip-cell-like states, suggesting enhanced endothelial activation. SMARCA4-deficient tumors also displayed increased VEGF-associated spatial signals and altered angiogenesis-related programs. Multiplex immunofluorescence further demonstrated reduced CD8⁺ T-cell infiltration together with prominent vascular and perivascular remodeling. Collectively, these findings indicate that SMARCA4 deficiency is associated with an angiogenesis-dominant, immune-suppressed tumor microenvironment, providing a biological rationale for combining antiangiogenic therapy with chemo-immunotherapy.

DISCUSSION

Discussion

Our findings suggest that SMARCA4-mutant lung cancer is characterized not only by aggressive clinical behavior but also by a distinct vascular and immune microenvironment. The superior outcomes observed with chemo-immunotherapy plus antiangiogenic therapy indicate that aberrant angiogenesis may represent a therapeutically actionable vulnerability in this population.

Spatial transcriptomic profiling further revealed prominent vascular remodeling, endothelial activation, and reduced CD8⁺ T-cell infiltration in SMARCA4-deficient tumors, supporting the presence of an angiogenesis-dominant and immunosuppressive microenvironment. These features may partly explain the limited and heterogeneous benefit of chemo-immunotherapy alone and provide a biological rationale for incorporating antiangiogenic therapy.

Together, the concordant clinical and spatial findings support triplet therapy as a promising strategy for SMARCA4-mutant lung cancer and highlight vascular remodeling as a potential key mechanism underlying treatment response. Larger prospective studies are warranted to validate these observations.