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Revisiting IL-1 Antagonism in Lung Cancer Therapeutics: Lessons from Failure and Pathways to Precision Therapy

Sitong Feng[1], Cong Xu[1], Chuang Qi [4], Yi Li[4], Bo Shen[1,2,3]*

[1]Department of Oncology, The Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing 210009, Jiangsu, China

[2]Department of Oncology, The Affiliated Dongtai Hospital of Nanjing Medical University, Dongtai People's Hospital, Dongtai 224200, Jiangsu, China

[3]Department of Oncology, The Affiliated Dafeng Hospital of Xuzhou Medical University, Dafeng People's Hospital of Yancheng, Yancheng 224100, Jiangsu, China

[4]Changchun Gene Science Pharmaceuticals Co., Ltd, Shanghai 200030, China

***Corresponding author:** *Bo Shen, shenbo987@njmu.edu.cn*

Abstract: Despite compelling preclinical and epidemiological evidence (e.g., reduced lung cancer incidence in the CANTOS trial), IL-1β inhibition with canakinumab failed to achieve the expected therapeutic effect in the Phase III clinical trials (CANOPY series) of non-small cell lung cancer (NSCLC). This perspective analyzes the disconnect between mechanistic promise and clinical outcomes. IL-1β drives NSCLC progression by promoting immunosuppression, angiogenesis, and metastasis. However, CANOPY-2 showed no overall survival (OS) benefit, though a trend emerged in patients with an elevated baseline of high-sensitivity C-reactive protein (hs-CRP). Similarly, CANOPY-1 and adjuvant CANOPY-A missed primary endpoints for progression-free survival (PFS) and disease-free survival (DFS), respectively. These failures highlight limitations of IL-1 monotherapy in advanced, immunosuppressive microenvironments and underscore inadequate patient selection. We propose that IL-1 antagonism retains therapeutic potential but requires refined strategies: biomarker-driven enrichment (e.g., inflammation signatures like hs-CRP), rational combinatorial regimens informed by successful multi-target agents (e.g., cadonilimab), and early-stage intervention. Repositioning IL-1 blockers through precision approaches could unlock their value in immuno-oncology.

Keywords: Canakinumab; Clinical trial failure; Biomarker-driven enrichment

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1. Introduction

The IL-1β inhibitor canakinumab demonstrated significant anti-tumor potential in preclinical models and

epidemiological studies (e.g., reduced lung cancer incidence in the CANTOS trial) [1]. Nevertheless, its failure in the Phase III clinical trials (CANOPY series) of non-small cell lung cancer (NSCLC) underscores critical gaps in patient selection and therapeutic context [2]. This viewpoint contends that IL-1 blockade retains mechanistic promise but requires redefined clinical strategies, including biomarker-driven enrichment, optimized combinatorial regimens, and early-stage intervention. Integrating insights from successful multi-target agents (e.g., cadonilimab in gastric cancer), we propose a roadmap to reposition IL-1 antagonists within the evolving landscape of immuno-oncology.

2. IL-1β in lung cancer: Mechanistic promise and clinical setbacks

IL-1β, a pivotal mediator of inflammation, drives lung cancer progression by fostering immunosuppression, angiogenesis, and metastatic niche formation [3]. Preclinical studies highlight its role in recruiting myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), while dampening cytotoxic T-cell activity. Despite this rationale, Phase III trials of the IL-1β inhibitor canakinumab (CANOPY series) in NSCLC yielded disappointing outcomes [4]. In CANOPY-2 (NCT03631199), combining canakinumab with docetaxel failed to improve overall survival (OS; HR = 0.93, $p = 0.29$), though a trend emerged in patients with elevated baseline of high-sensitivity C-reactive protein (hs-CRP; ≥ 10 mg/L). Similarly, CANOPY-1 (NCT03626545), which tested canakinumab alongside pembrolizumab and chemotherapy in first-line NSCLC, showed no significant progression-free survival (PFS) or OS benefit, underscoring the limitations of IL-1 monotherapy in advanced, immunosuppressive microenvironments. CANOPY-A (NCT03447769), evaluating adjuvant canakinumab post-resection, also missed its disease-free survival (DFS) endpoint, likely due to residual tumor heterogeneity. These failures suggest that unselected patient populations and late-stage intervention may obscure IL-1β's therapeutic potential, rather than invalidating its mechanistic relevance.

3. Unmasking failure: The critical role of biomarkers and timing

The CANOPY trials' shortcomings stem from a "one-size-fits-all" approach, neglecting the heterogeneity of IL-1β-driven tumorigenesis. For instance, KRAS-mutant NSCLCs exhibit inflammasome hyperactivity and inflammatory cytokine profiles (e.g., IL-6, CXCL1/2), rendering them plausible candidates for IL-1 blockade [5]. Retrospective analyses of CANOPY-2 hinted at OS benefits in patients with elevated hs-CRP, mirroring the CANTOS trial's finding that CRP reduction correlated with reduced lung cancer incidence [6]. However, the critical absence of prospective biomarker stratification (notably tumor IL-1β expression, peripheral cytokine quantification, or inflammasome-related transcriptional signatures) precluded rigorous validation of these mechanistic hypotheses. Additionally, the trials focused on advanced NSCLC, where entrenched immunosuppressive networks (e.g., VEGF, TGF-β) may overwhelm single-pathway inhibition. Conversely, CANTOS revealed canakinumab's striking cancer-preventive efficacy through a 67% reduction in lung cancer incidence among high-risk cardiovascular cohorts, strongly implying that therapeutic interception during premalignant/early-stage disease may achieve superior clinical impact.

4. Rebuilding the strategy: biomarkers, combinations, and early intervention

To resurrect IL-1 antagonists, future trials must prioritize biomarker-driven patient enrichment and

combinatorial synergy. Prospective validation of IL-1β pathway biomarkers, such as tumor NLRP3 expression, dynamic CRP monitoring, or inflammatory gene signatures, could identify responsive subsets, including KRAS/TP53-mutant tumors with cytokine-rich microenvironments [7,8]. Mechanistically, IL-1β blockade may synergize with PD-1 inhibitors by reversing T-cell exhaustion and MDSC-mediated suppression, as seen in preclinical models. Clinically, combining canakinumab with anti-angiogenics (e.g., bevacizumab) or KRAS-G12C inhibitors could address pathway redundancy, akin to cadonilimab's success in gastric cancer through dual PD-1/CTLA-4 targeting. Early-stage applications, such as neoadjuvant or adjuvant therapy for resectable NSCLC with elevated inflammatory markers, offer a strategic niche, leveraging IL-1β's role in micrometastatic progression. Furthermore, repurposing IL-1 inhibitors for cancer interception in high-risk populations (e.g., COPD patients with precancerous lesions) aligns with CANTOS' preventive insights, bridging cardiology and oncology paradigms.

5. Lessons from cadonilimab: Multi-target synergy and adaptive design

The breakthrough of cadonilimab, a PD-1/CTLA-4 bispecific antibody, in gastric cancer (COMPASSION-15 trial) underscores the power of multi-target strategies to broaden efficacy and mitigate resistance[9]. By engaging two immune checkpoints, cadonilimab achieved responses across PD-L1 expression levels, including PD-L1-negative tumors—a lesson applicable to IL-1 antagonists. Combining IL-1β inhibition with complementary targets (e.g., IL-6R, VEGF) could counteract compensatory cytokine activation, while dynamic biomarker monitoring (e.g., serial CRP/IL-6 measurements) might enable adaptive therapy adjustments. Additionally, cadonilimab's favorable safety profile compared to combination checkpoint inhibitors highlights the importance of balancing efficacy and tolerability in IL-1-based regimens. Translating these principles, future IL-1 trials should adopt modular designs, integrating biomarker stratification, combination partners, and stage-specific contexts to unlock its full potential.

6. Conclusion

The inability of IL-1β blockade in NSCLC trials reflects not mechanistic futility but a disconnect between biological rationale and clinical execution. By embracing precision oncology, prospectively defining responsive subsets, optimizing combinatorial logic, and shifting to early-stage or preventive settings, canakinumab and next-generation IL-1 inhibitors may yet carve a niche in lung cancer therapy. As cadonilimab redefined dual checkpoint inhibition, a similarly innovative framework, rooted in biomarker-driven adaptation and multi-modal synergy, could resurrect IL-1 antagonism as a strategic component of the immuno-oncology arsenal.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Wong C, Baum J, Silvestro A, et al., 2020, Inhibition of IL1β by Canakinumab May Be Effective Against Diverse Molecular Subtypes of Lung Cancer: An Exploratory Analysis of the CANTOS Trial. Cancer Res, 80(24): 5597–5605.

[2] Garon E, Lu S, Goto Y, et al., 2024, Canakinumab as Adjuvant Therapy in Patients With Completely Resected Non-Small-Cell Lung Cancer: Results From the CANOPY-A Double-Blind, Randomized Clinical Trial. J Clin Oncol, 42(2): 180–191.

[3] Malkova A, Gubal A, Petrova A, et al., 2023, Pathogenetic Role and Clinical Significance of Interleukin-1β in Cancer. Immunology, 168(2): 203–216.

[4] Lythgoe M, Prasad V, 2022, Repositioning Canakinumab for Non-Small Cell Lung Cancer—Important Lessons for Drug Repurposing in Oncology. Br J Cancer, 127(5): 785–787.

[5] Yuan B, Clowers M, Velasco W, et al., 2022, Targeting IL-1β as an Immunopreventive and Therapeutic Modality for K-Ras-Mutant Lung Cancer. JCI Insight, 7(11): e157788.

[6] Paz-Ares L, Goto Y, Lim D, et al., 2024, Canakinumab in Combination With Docetaxel Compared With Docetaxel Alone for the Treatment of Advanced Non-Small Cell Lung Cancer Following Platinum-Based Doublet Chemotherapy and Immunotherapy (CANOPY-2): A Multicenter, Randomized, Double-Blind, Phase 3 Trial. Lung Cancer, 189: 107451.

[7] Tengesdal I, Dinarello C, Marchetti C, 2023, NLRP3 and Cancer: Pathogenesis and Therapeutic Opportunities. Pharmacol Ther, 251: 108545.

[8] Jeon W, Guo M, Gavralidis A, et al., 2024, Unlocking Therapeutic Potential: IL-1β as a Target in Non-Small Cell Lung Cancer With Oncogenic Mutations—Prognostic and Predictive Insights. J Clin Oncol, 42(Suppl 16): 8030.

[9] Lythgoe M, Prasad V, 2022, Repositioning Canakinumab for Non-Small Cell Lung Cancer—Important Lessons for Drug Repurposing in Oncology. Br J Cancer, 127(5): 785–787.