LSD1/HDAC6 Inhibition Promotes Immunotherapy Response in Small Cell Lung Cancer

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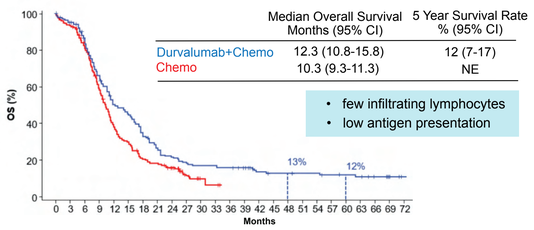
Background: JBI-802 is a novel dual inhibitior of LSD1/HDAC6

Small cell lung cancer (SCLC) has exceptionally poor prognosis

- Characterized by neuroendocrine differentiation, rapid growth, early metastasis
- Standard of care: Chemo+Immunotherapy, resistance to both is common

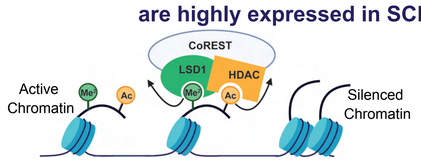


	Median Overall Survival Months (95% CI)	5 Year Survival Rate % (95% CI)
Durvalumab+Chemo	12.3 (10.8-15.8)	12 (7-17)
Chemo	10.3 (9.3-11.3)	NE

- few infiltrating lymphocytes
- low antigen presentation

Reck et al, 2024 Lung Cancer[1]

Lysine specific demethylase(LSD1) and Histone deacetylase(HDAC6) are highly expressed in SCLC, regulate epigenetic and post-translational modifications

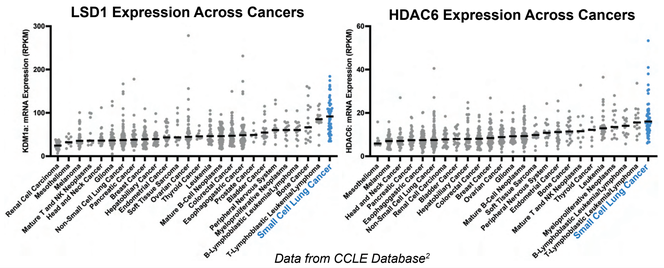


LSD1 inhibition in preclinical SCLC models[2,3,4]:

Antigen presentiation
CD8+ T cell infiltration
Response to anti-PD-1 immunotherapy

ASCL1 (master neuroendocrine transcription factor)
Neuroendocrine gene expression

Associated with SCLC patients who repond to immunotherapy

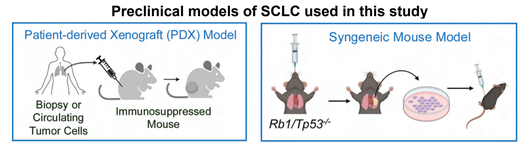


Data from CCLE Database[2]

Would targeting LSD1 *and* HDAC6 have broader anti-tumor activity than LSD1i alone in SCLC, as a single agent and with anti-PD-1?

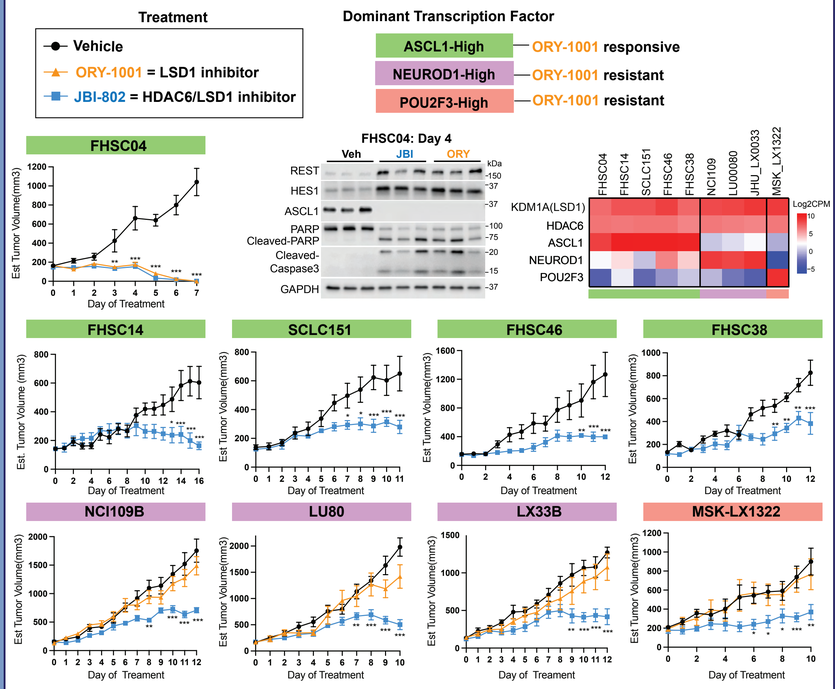
- Key therapeutic effects of LSD1 inhibition are downstream of ASCL1 supression
- Not all SCLC patients have tumors driven by ASCL1 expression
- JBI-802 has moved to phase 2 clinical trials in blood and advanced solid tumors
- In preclinical models of other cancer types, HDAC6 inhibition promotes promotes anti-tumor changes to the immune microenvironment[6,7,8]

Preclinical models of SCLC used in this study

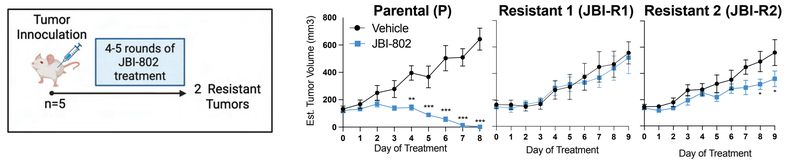


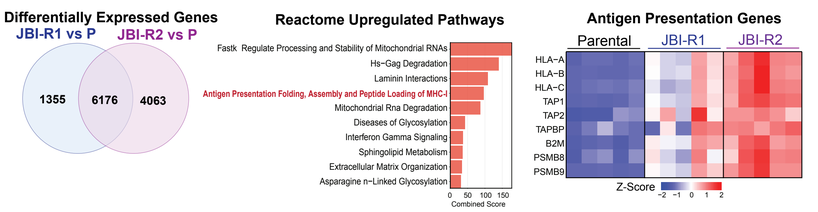
1. Single agent efficacy in hSCLC PDX models

JBI-802 restricts tumor progression accross transcriptional diversity in SCLC, even in models resistant to LSD1 inhibtion alone



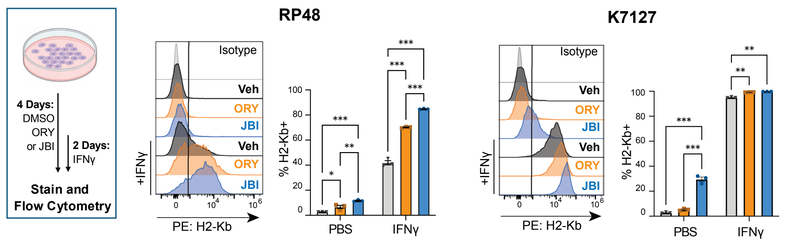
Chronic JBI-802 treatment in vivo promotes sustained antigen presentation



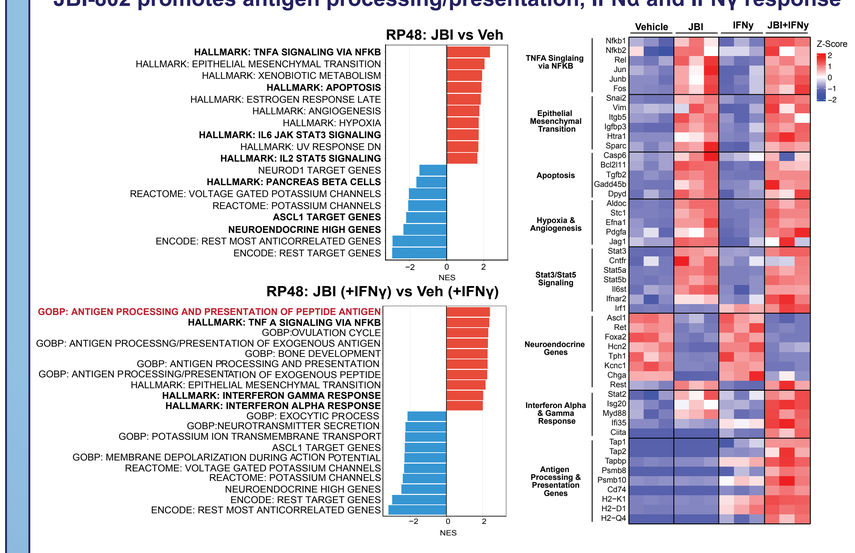


2. Increased antigen presentation *in vitro*

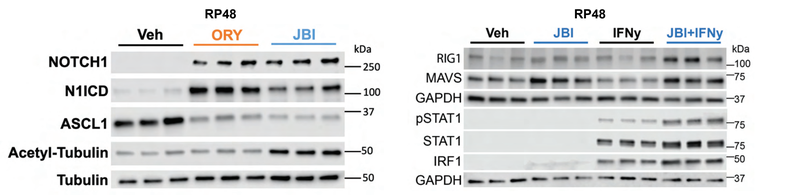
JBI-802 treatment promotes cell surface MHC-1 expression in mSCLC lines



JBI-802 promotes TNF-α, EMT, hypoxia,and apoptosis signaling, while downregulating neuroendocrine genes. With IFNγ, JBI-802 promotes antigen processing/presentation, IFNα and IFNγ response

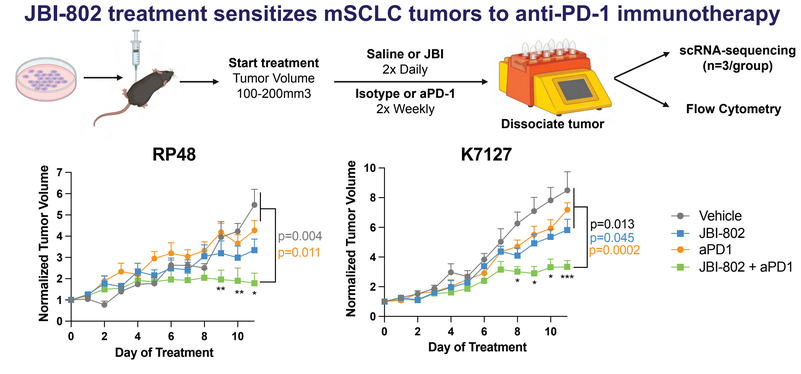


JBI-802 promotes accumulation of acetylated-Tubulin (known HDAC6 target), promotes viral sensing pathway and interferon gamma response

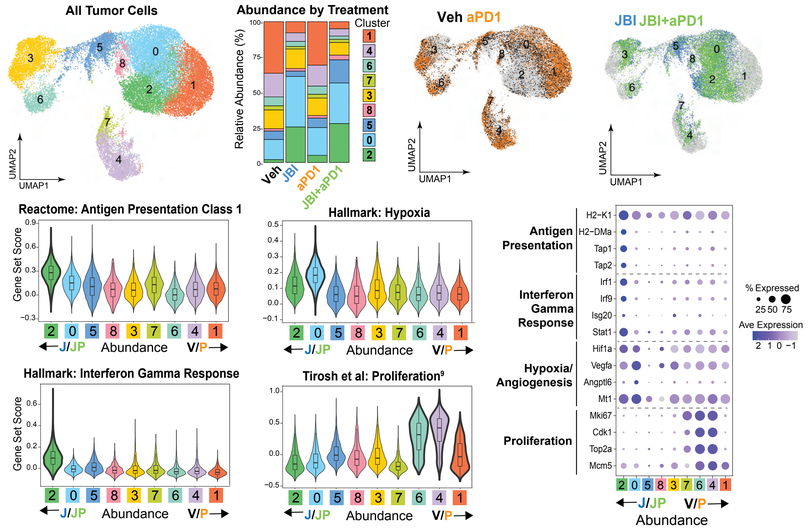


3. Synergy with anti-PD-1 immunotherapy

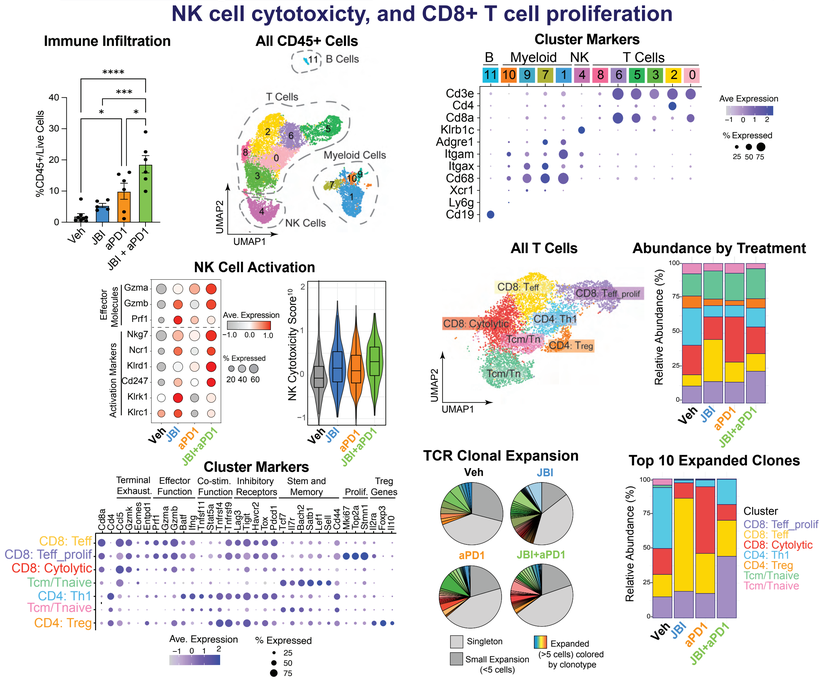
JBI-802 treatment sensitizes mSCLC tumors to anti-PD-1 immunotherapy



RP48 tumor cells: JBI-802 promotes IFNγ response and antigen presentation



RP48 infiltrating immune cells: JBI-802 promotes immune infiltration, NK cell cytotoxicty, and CD8+ T cell proliferation



Conclusions

JBI-802 exhibits broad anti-tumor activity in SCLC preclinical models

- In PDX models, LSD1/HDAC6 inhibition supresses tumor progression accross a broad panel, even in models resistnat to LSD1 inhibition alone
- LSD1/HDAC6 inhibition promotes innate immune sifnaling and antigen presentation
- LSD1/HDAC6 inhibition sensitizes SCLC tumors to anti-PD-1 immunotherapy *in vivo*
- In the tumor microenvironment, LSD1/HDAC6 inhibition promotes cytolytic gene expression in NK cells and more proliferative effector CD8+ T cells, particularly in the top 10 expanded T cell clones
- Further study of the mechanisms underlying these effects, downstream of LSD1/HDAC6 targets are underway

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References

1. Reck M, Dziadziuszko R, Sugawara S, Kao S, Hochmair M, et al. Five-year survival in patients with extensive-stage small cell lung cancer treated with atezolizumab in the Phase III IMpower133 study and the Phase III IMbrella A extension study. Lung Cancer. 2024 Oct;196:107924. doi: 10.1016/j.lungcan.2024.107924.
2. Augert A, Eastwood E, Ibrahim AH, Wu N, Grunblatt E, et al. Targeting NOTCH activation in small cell lung cancer through LSD1 inhibition. Sci Signal. 2019 Feb 5;12(567):eaau2922. doi: 10.1126/scisignal.aau2922.
3. Nguyen EM, Taniguchi H, Chan JM, Zhan YA, Chen X, et al. Targeting Lysine-Specific Demethylase 1 Rescues Major Histocompatibility Complex Class I Antigen Presentation and Overcomes Programmed Death-Ligand 1 Blockade Resistance in SCLC. J Thorac Oncol. 2022 Aug;17(8):1014-1031. doi: 10.1016/j.jtho.2022.05.014.
4. Hiatt JB, Sandborg H, Garrison SM, Arnold HU, Liao SY, et al. Inhibition of LSD1 with Bomedemstat Sensitizes Small Cell Lung Cancer to Immune Checkpoint Blockade and T-Cell Killing. Clin Cancer Res. 2022 Oct 14;28(20):4551-4564. doi: 10.1158/1078-0432.CCR-22-1128.
5. Ghandi, Mahmoud, et al. "Next-generation characterization of the Cancer Cell Line Encyclopedia." Nature 569.7757 (2019): 505–516.
6. Adeegbe DO, Liu Y, Lizotte PH, Kamihara Y, Aref AR, et al. Synergistic Immunostimulatory Effects and Therapeutic Benefit of Combined Histone Deacetylase and Bromodomain Inhibition in Non-Small Cell Lung Cancer. Cancer Discov. 2017 Aug;7(8):852-867. doi: 10.1158/2159-8290.CD-16-1020.
7. Laino AS, Betts BC, Veerapathran A, Dolgalev I, Sarnaik A, et al. HDAC6 selective inhibition of melanoma patient T-cells augments anti-tumor characteristics. J Immunother Cancer. 2019 Feb 6;7(1):33. doi: 10.1186/s40425-019-0517-0.
8. Liu Y, Li Y, Liu S, Adeegbe DO, Christensen CL, et al. NK Cells Mediate Synergistic Antitumor Effects of Combined Inhibition of HDAC6 and BET in a SCLC Preclinical Model. Cancer Res. 2018 Jul 1;78(13):3709-3717. doi: 10.1158/0008-5472.CAN-18-0161. 2.
9. Tirosh I, Izar B, Prakadan SM, Wadsworth MH 2nd, Treacy D, et al. Dissecting the multicellular ecosystem of metastatic melanoma by single-cell RNA-seq. Science. 2016 Apr 8;352(6282):189-96. doi: 10.1126/science.aad0501.
10. de Andrade LF, Lu Y, Luoma A, Ito Y, Pan D, et al. Discovery of specialized NK cell populations infiltrating human melanoma metastases. JCI Insight. 2019 Dec 5;4(23):e133103. doi: 10.1172/jci.insight.133103.