



P2.045: Effects of ATR Inhibition in Small Cell Lung Cancer Differ According to Transcription Factor-Defined Subtype

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INTRODUCTION

- Small cell lung cancer (SCLC) is an aggressive malignancy with limited treatment options.
- Although transcription factor-based subtyping provides a biological framework, subtype-specific vulnerabilities remain unclear.
- This study investigated subtype-specific ATR inhibitor sensitivity and explored a subtype-guided therapeutic strategy.

METHODS

- SCLC specimens, with expression of the transcriptional factors ASCL1, NEUROD1, and POU2F3 assessed using the H-score and categorized as low (H-score<1) or high (H-score≥1).
- Tumors were classified into corresponding molecular subtypes, based on transcription factor expression, allowing overlapping classification, while tumors negative for all three transcription factors were defined as triple-negative (TN).
- Representative SCLC cell lines from each molecular subtype along with Non-SCLC cell lines as controls, were used to evaluate sensitivity to the ATR inhibitor VE-822.
- Antitumor activity of VE-822 was assessed by CCK-8 assay in vitro and by tumor growth in xenograft mouse models in vivo.

RESULTS

Table 1. Clinicopathological characteristics of patients with small cell lung cancer

Characteristic of patients	
Variables	n=94
Median age (range), y	70 (44 - 87)
Sex, n (%)	
Male	78 (87)
Female	16 (13)
Smoking history, n (%)	
Current / Former	88 (93.6)
Never	3 (3.2)
N/A	3 (3.2)
pStage	
I	52 (55.3)
II	27 (28.7)
III	15 (16.0)
IV	0 (0)
Adjuvant, n (%)	56 (59.6)

Figure 1. Representative immunohistochemical staining patterns of transcription factors in small cell lung cancer.

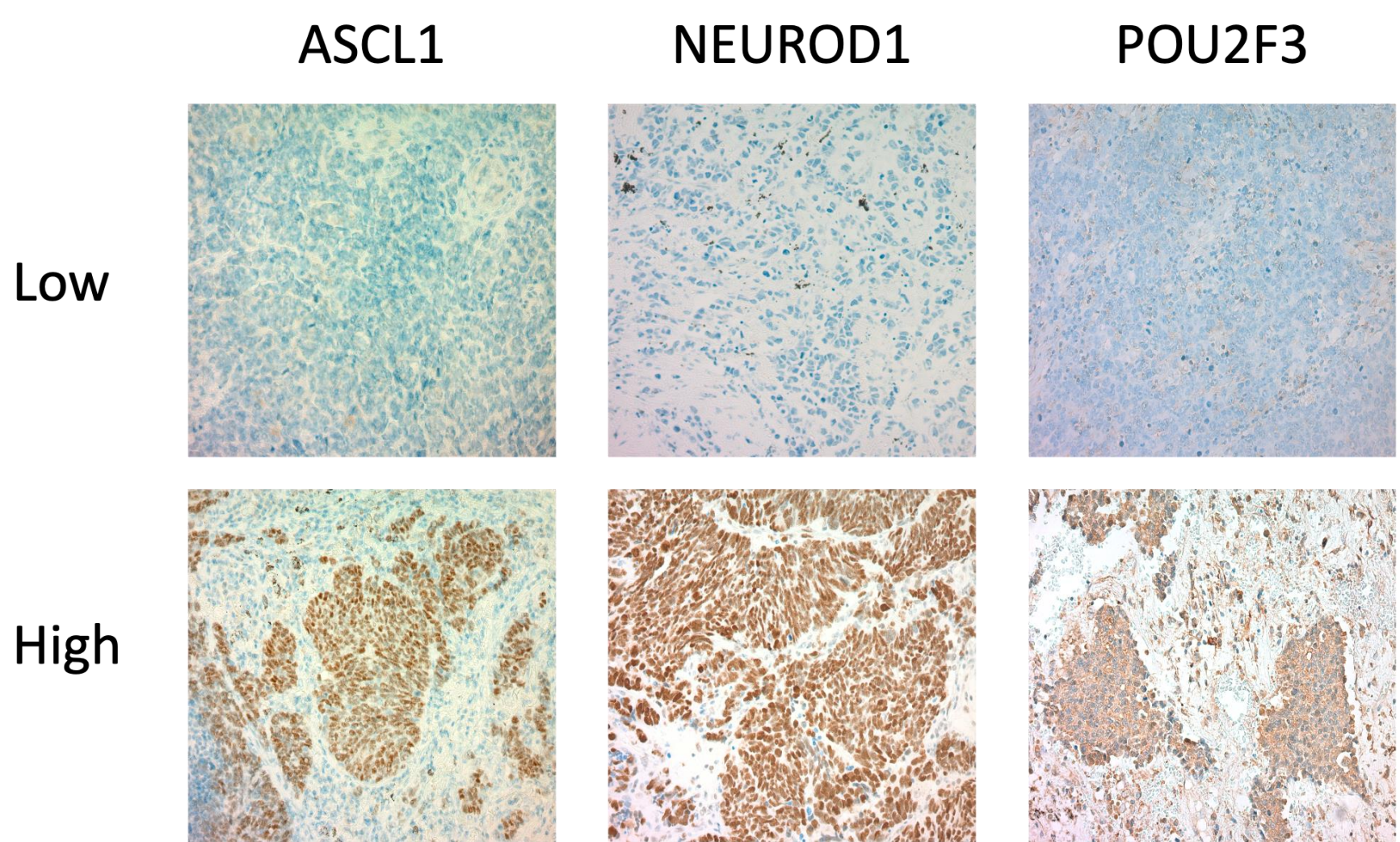


Table 2. Univariable and multivariable analyses of prognostic factors for disease-free survival and overall survival

Cox proportional hazards analyses for disease-free survival and overall survival					
Outcome	Variable	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
DFS	Age, per 1-year increase	1.028 (0.987–1.071)	0.185	—	—
	Sex, male vs female	1.177 (0.491–2.822)	0.715	—	—
	pStage, Stage 2–3 vs Stage 1	1.979 (1.023–3.828)	0.043	2.956 (1.375–6.355)	0.005
	ASCL1, high vs low	2.411 (1.053–5.519)	0.037	3.682 (1.340–10.119)	0.011
	Adjuvant chemotherapy, yes vs no	0.469 (0.230–0.959)	0.038	0.245 (0.111–0.542)	<0.001
OS	Age, per 1-year increase	1.018 (0.974–1.064)	0.422	—	—
	Sex, male vs female	2.111 (0.639–6.979)	0.22	—	—
	pStage, Stage 2–3 vs Stage 1	2.144 (1.022–4.501)	0.044	2.672 (1.212–5.891)	0.015
	ASCL1, high vs low	2.129 (0.811–5.588)	0.125	2.973 (1.013–8.727)	0.047
	Adjuvant chemotherapy, yes vs no	0.433 (0.204–0.923)	0.03	0.335 (0.155–0.720)	0.005

Figure 3. Survival curves according to ASCL1 expression

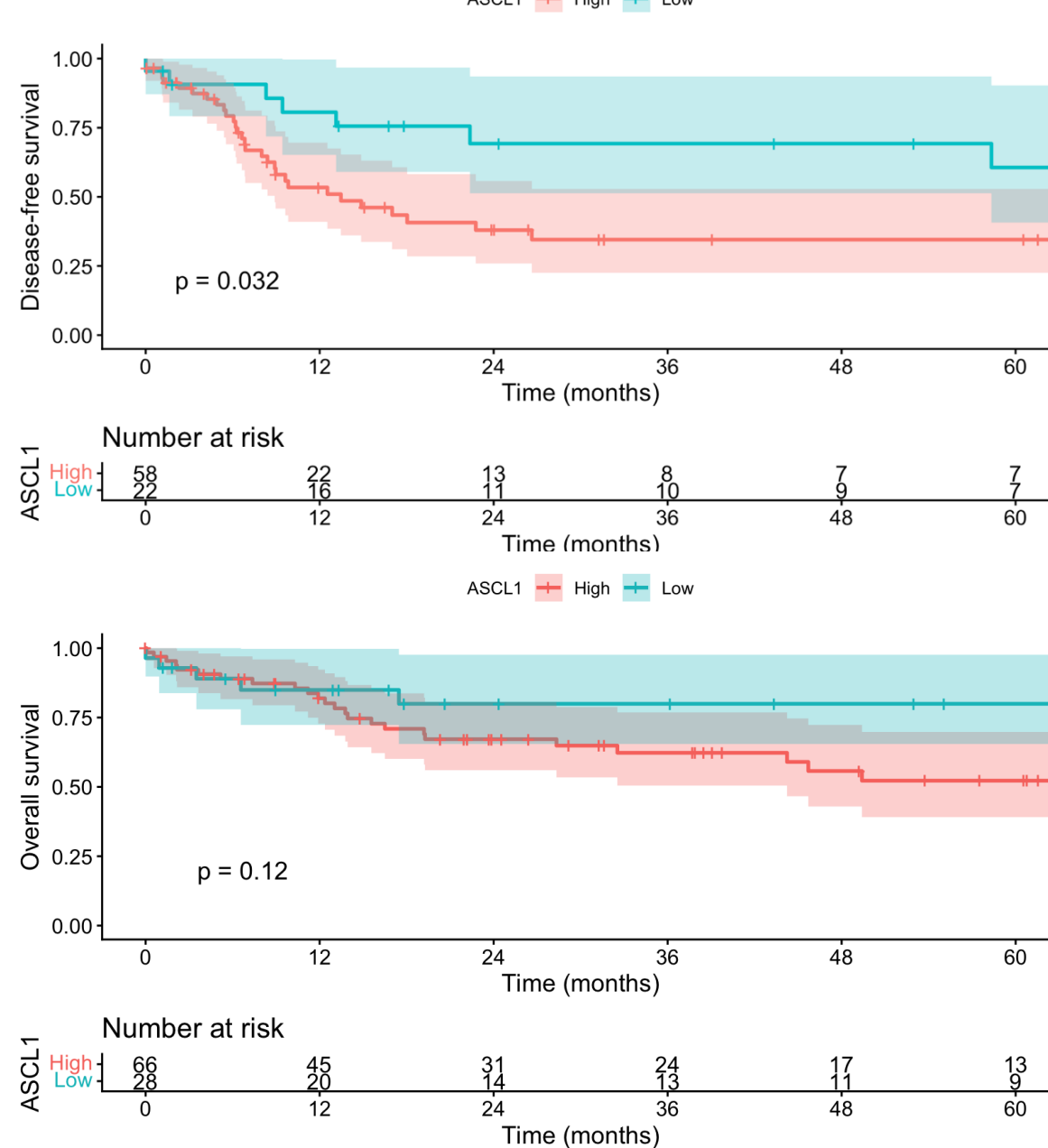


Figure 2. Distribution of molecular subtypes in SCLC

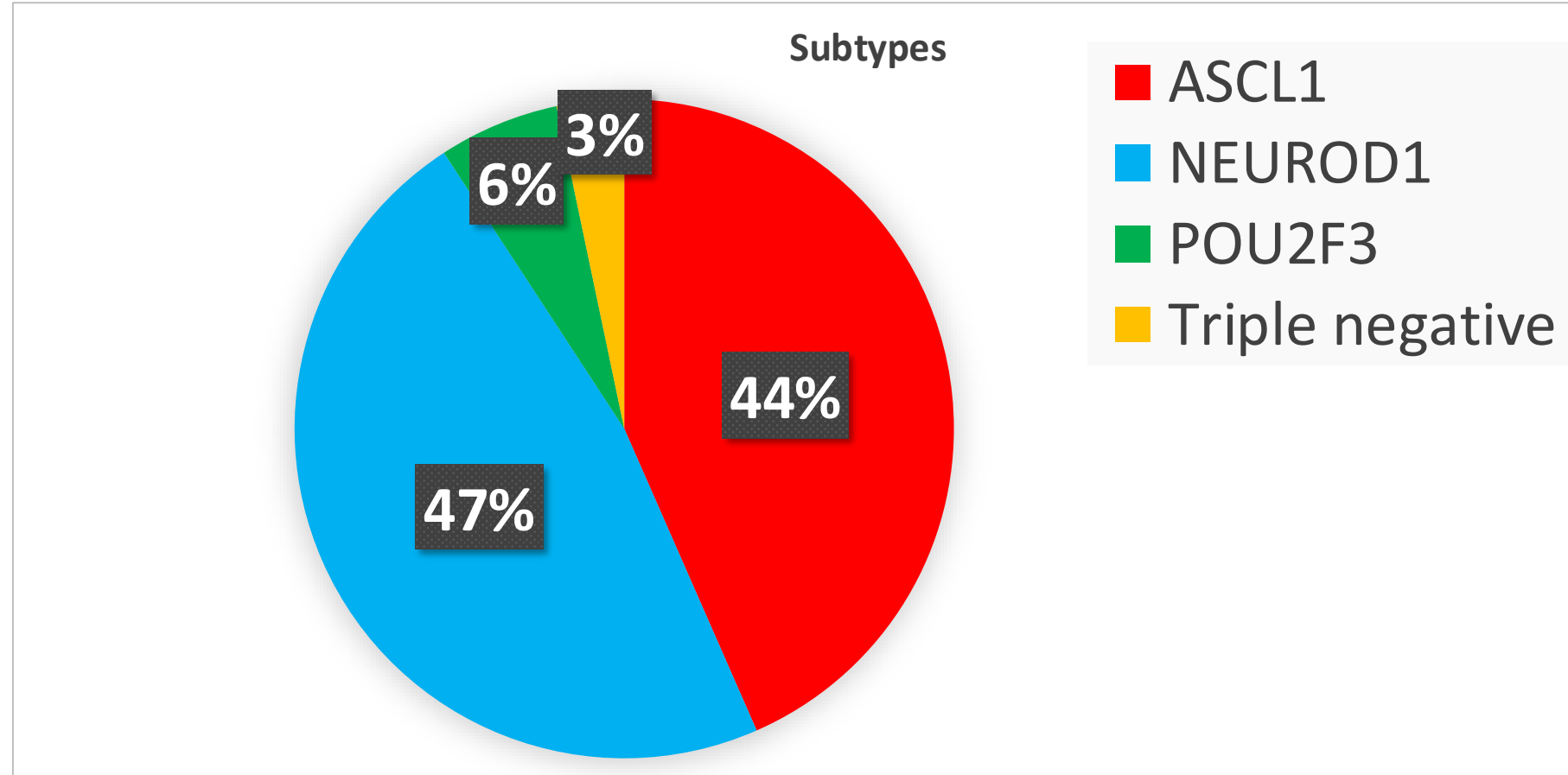
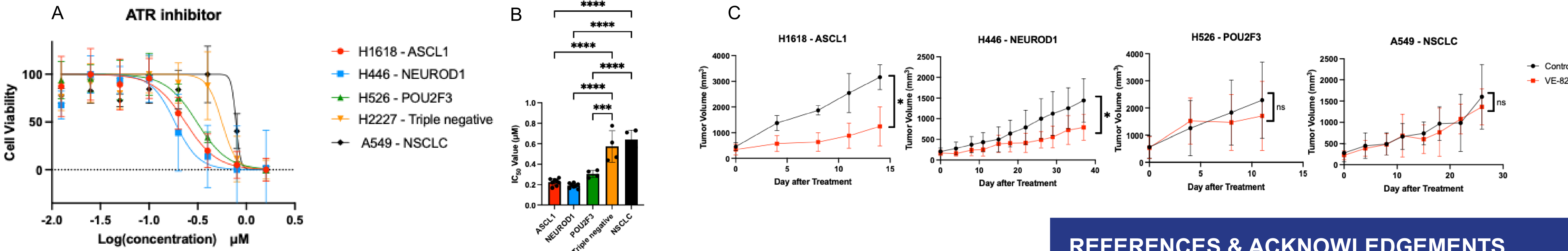


Figure 4. Antitumor effects of an ATR inhibitor in vitro (A, B) and in vivo (C)



REFERENCES & ACKNOWLEDGEMENTS

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ChatGPT (OpenAI) was used for language editing.
All scientific content and interpretations were reviewed and verified by the authors.

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DISCUSSION AND CONCLUSION

Actionable Take Away Message

- ASCL1-high SCLC identifies a poor-prognosis subgroup, with significantly shorter DFS and OS, supporting its potential as a prognostic biomarker.
- SCLC is highly sensitive to ATR inhibition, with greater sensitivity than NSCLC in both in vitro and in vivo models.
- Among SCLC molecular subtypes, ASCL1- and NEUROD1-expressing tumors showed particularly high sensitivity to ATR inhibition, highlighting molecular subtyping as a potential strategy for personalized ATR inhibitor therapy.

Future Direction for Research

- Define the mechanisms of subtype-specific ATR inhibitor sensitivity.
- Develop rational combination therapies toward precision medicine in SCLC.