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Predicting Tarlatamab Response In Small Cell Carcinoma

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Geisel School of Medicine at Dartmouth

NNECOS 2025 Annual Meeting and Palliative Care Symposium

October 24th, 2025

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Outline

1. Background
2. Rationale
3. Data Collection
4. Results
5. Conclusion

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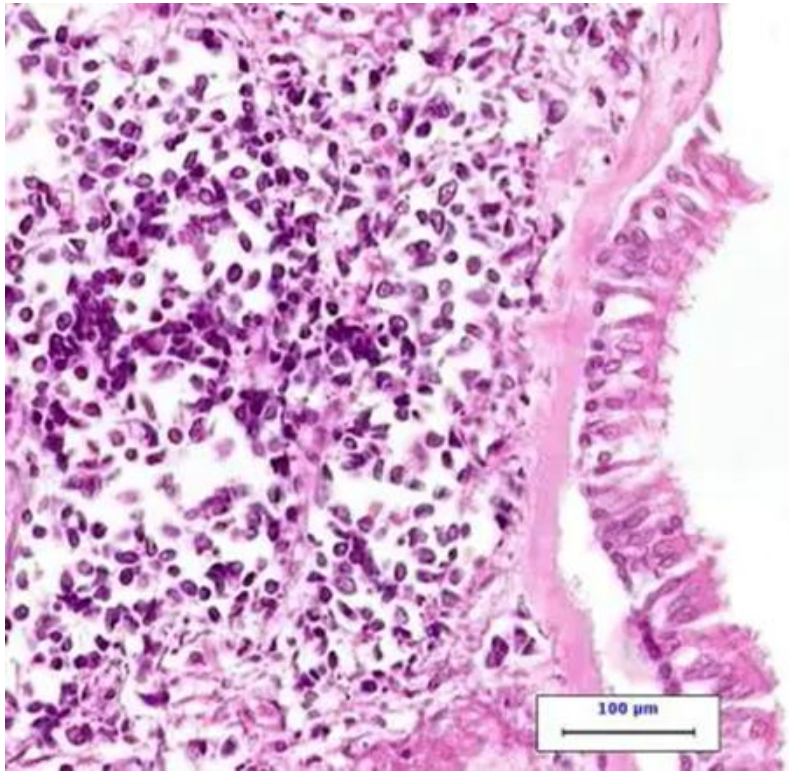
Background: Small Cell Lung Cancer

- Small cell lung cancer (SCLC) comprises **10-15%**[1,2] of lung cancers, at diagnosis most present with extensive stage[1,3] (ES) disease
- Untreated patients survive **2-4 months**[2,4], modern therapy extends overall survival to **6-13 months**[3,4] in ES disease



Credit: Medscape, Small Cell Lung Cancer (SCLC)

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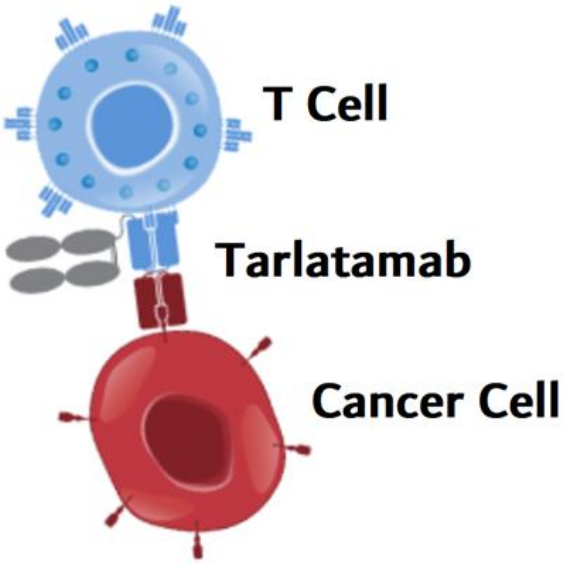
Background: Tarlatamab

- **Delta-like ligand 3**[5] (DLL3): atypical Notch ligand aberrantly expressed on the surface of SCLC cells, largely absent from adult tissues → therapeutic target
- **Tarlatamab**[5]: bispecific T-cell engager binding DLL3 on tumor cells and T cell CD3 receptors → directs cytotoxic T-cell activity towards SCLC



Credit: National Cancer Institute, Amgen

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Rationale

- **DLL3** expression is **necessary but not sufficient by itself** for tarlatamab response
- SCLC is heterogenous and divided into transcriptional subtypes
  - **ASCL1**, **NEUROD1**, **POU2F3**, and **YAP1** driven

Molecular, immunologic, and clinical correlates of tarlatamab response may elucidate mechanisms of therapeutic resistance and guide more precise patient selection.

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Institutional Data Collection

- Demographic characteristics, treatment details, and clinical course obtained through chart review
- Restaging imaging characterized using **RECIST 1.1 criteria**

- **Pre-treatment** FFPE biopsies with IHC available for all patients
- Analysis was performed using the Clinical DHCancerSeq assay using joint exome and transcriptome data and analyzed using AUGMET platform

Patient Characteristics

13 patients

CRS: 4 (31%)

ICANS: 4 (31%)

- **6** responders
- **5** non-responders
- **23%** complete response

Table 1: Patient and sample characteristics

	All cases (N = 13)
Age	
Mean (SD)	65 (9.7)
Range	47 - 82
Gender	
M	5 (38%)
F	8 (62%)
Smoking	
Mean pack years (SD)	51 (21)
Range	26 - 78.6
Prior lines of therapy	
Mean (SD)	1.7 (0.63)
Tarlatamab Response	
Response	6 (46%)
No response	5 (38%)
Stable disease	1 (8%)
Non-evaluable	1 (8%)
RECIST criteria	
Complete response	3 (23%)
Partial response	3 (23%)
Stable disease	1 (8%)
Progressive disease	5 (38%)
Specimen type	
Primary resection	2 (15%)
Biopsy	7 (54%)
Cytology (FNA)	4 (31%)
Biopsy/cytology site	
Primary lung tumor	5 (39%)
Lymph nodes	6 (46%)
Metastasis	2 (15%)
SCLC type	
ASCL1	9 (69%)
NEUROD1	2 (15%)
YAP1	1 (8%)

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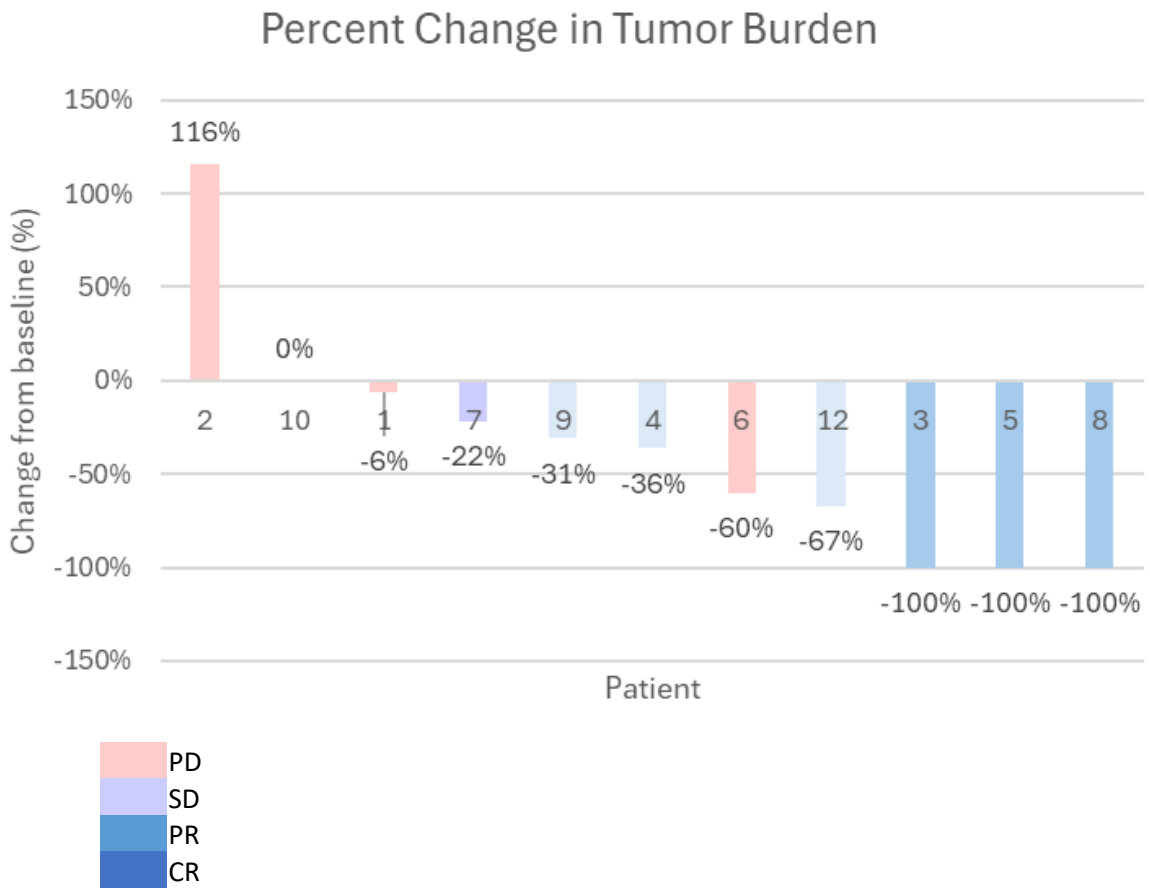
Patient Characteristics

- Objective response rate: **46%**
- Disease control rate: **54%**
- Average change in tumor burden: **-37%**



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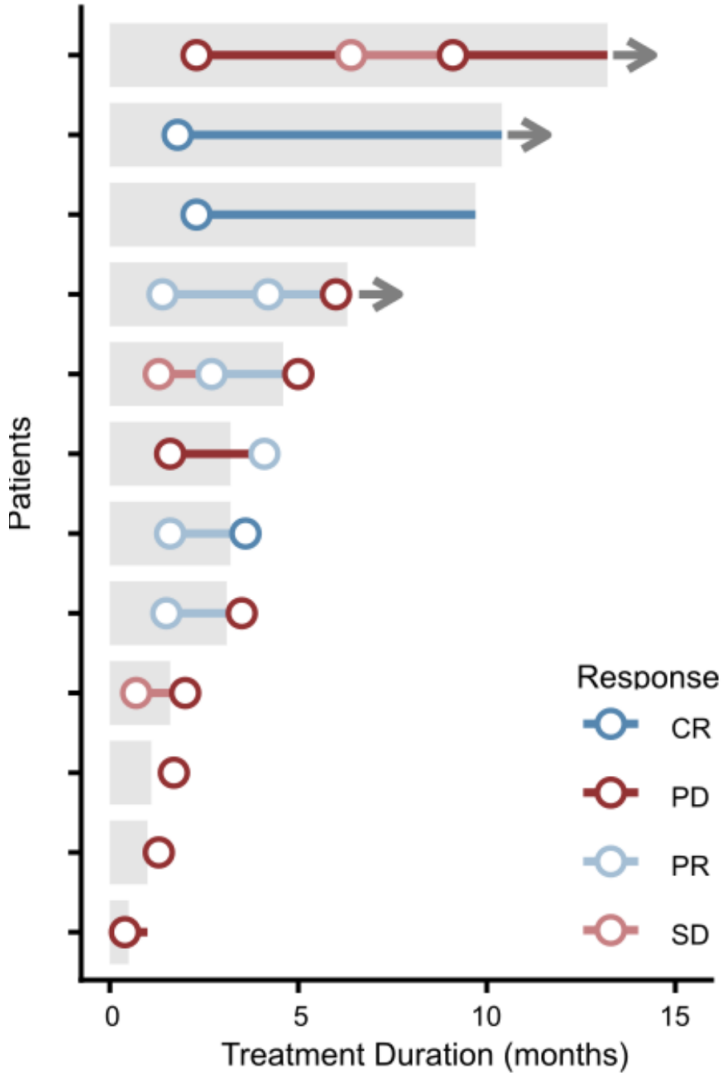
Patient Characteristics



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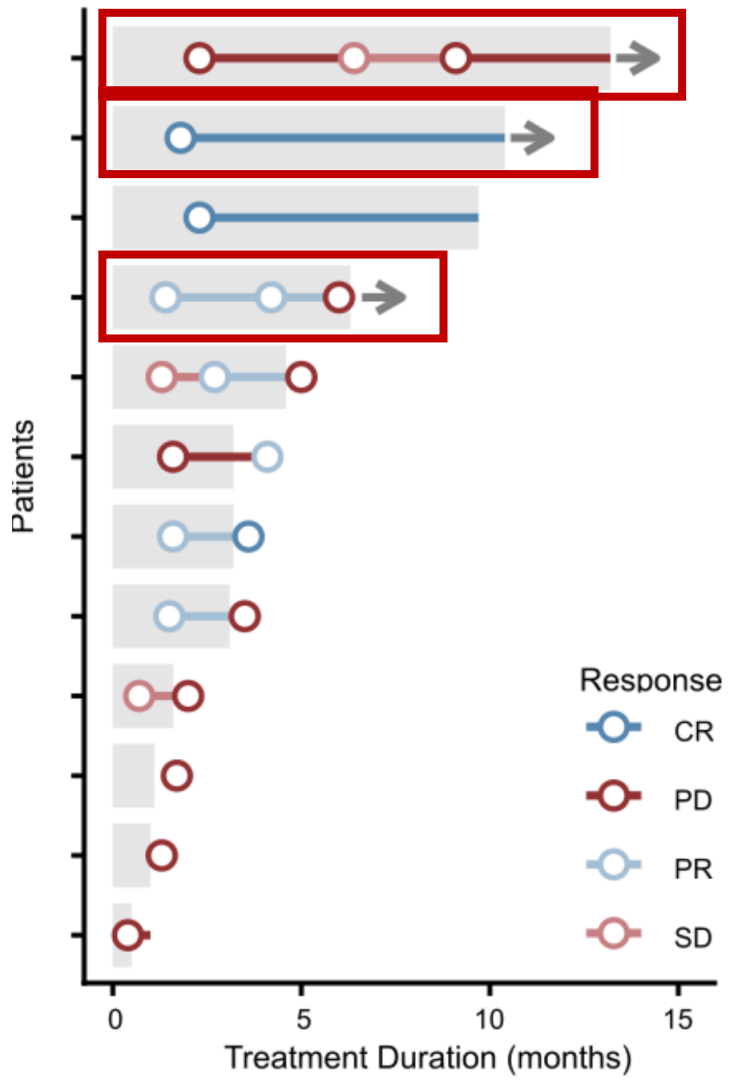
Patient Characteristics

- **3** patients with ongoing therapy



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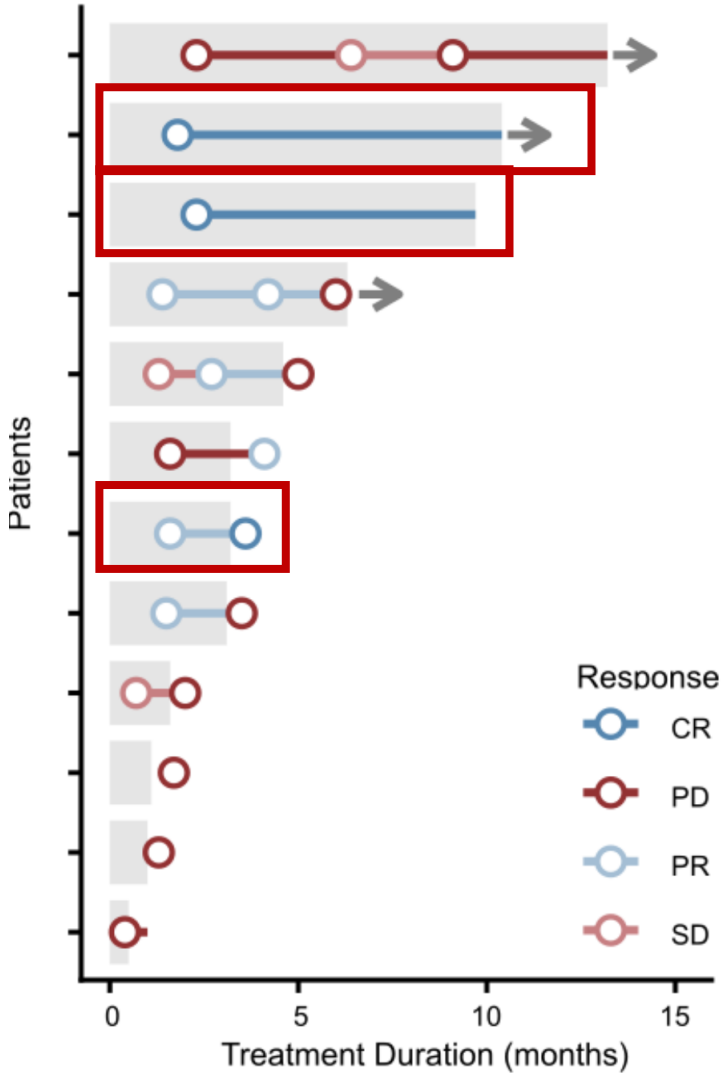
Patient Characteristics

- **3** patients with complete response



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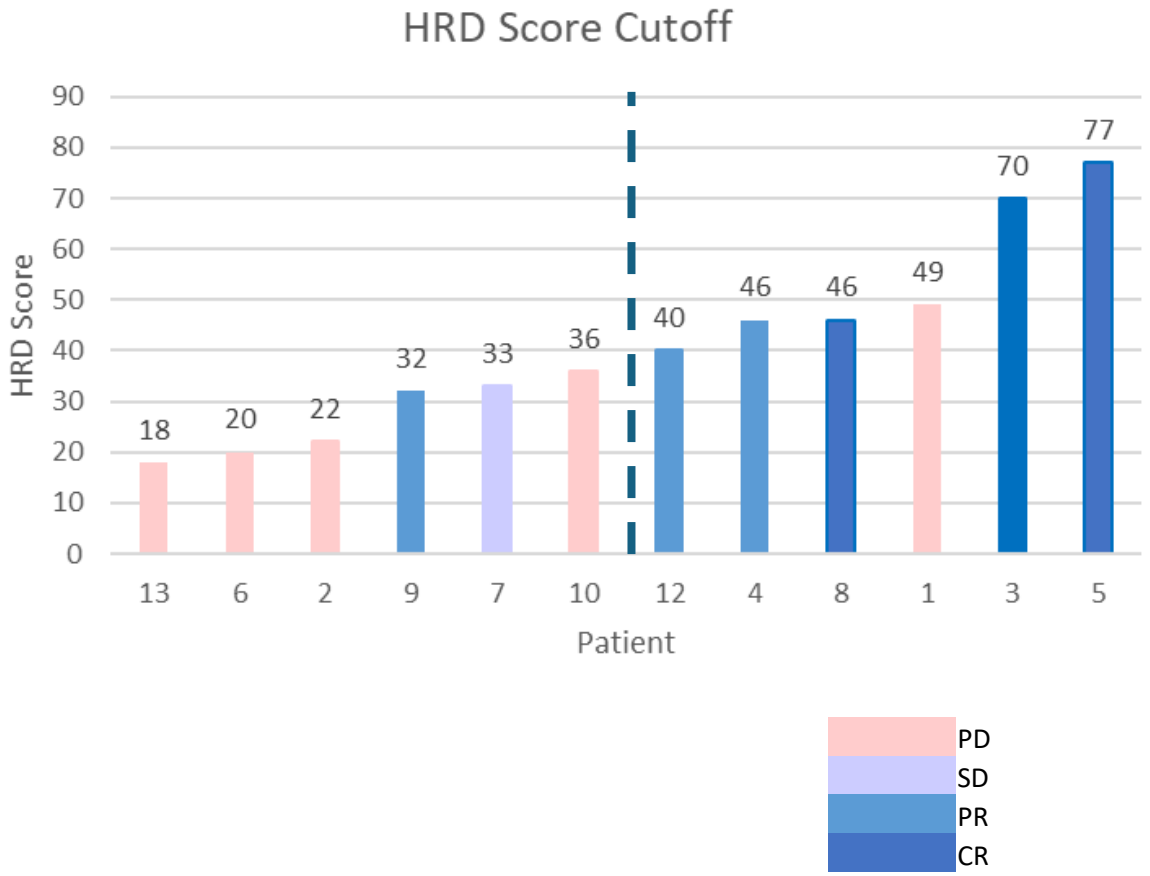
Homologous Recombination Deficiency (HRD) Score

- DeLLphi-301 clinical trial has **40%** response rate
- Data suggests HRD cutoff value of **39** has a response prediction of **83%**



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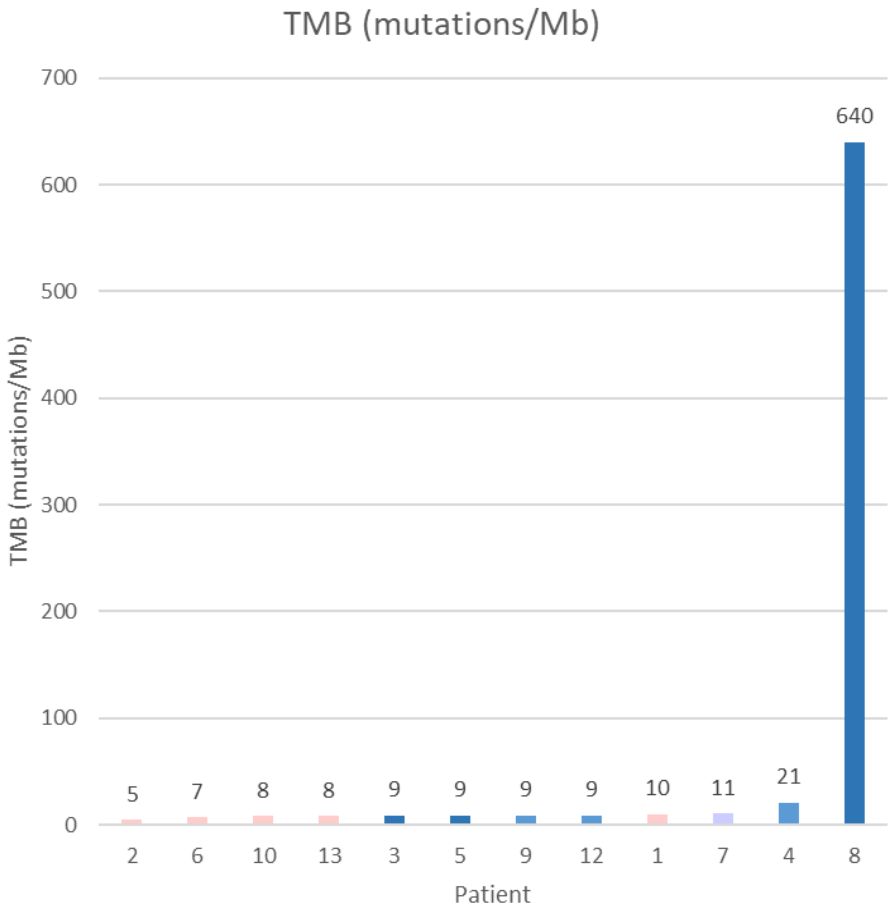
Tumor Mutational Burden (TMB)

- Median TMB: **9**
- One “exceptional responder” had TMB **71x** higher than median



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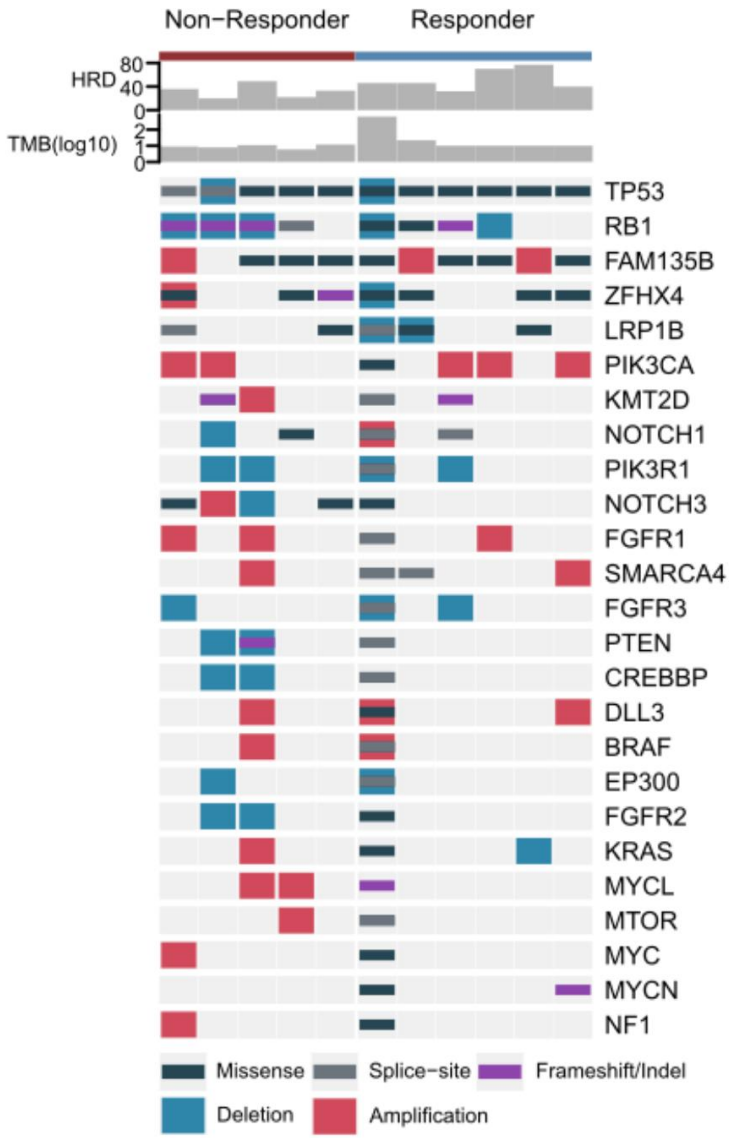
Mutational Profiling

- Mutational profiles between responders and non-responders are not statistically significant likely due to small sample size.



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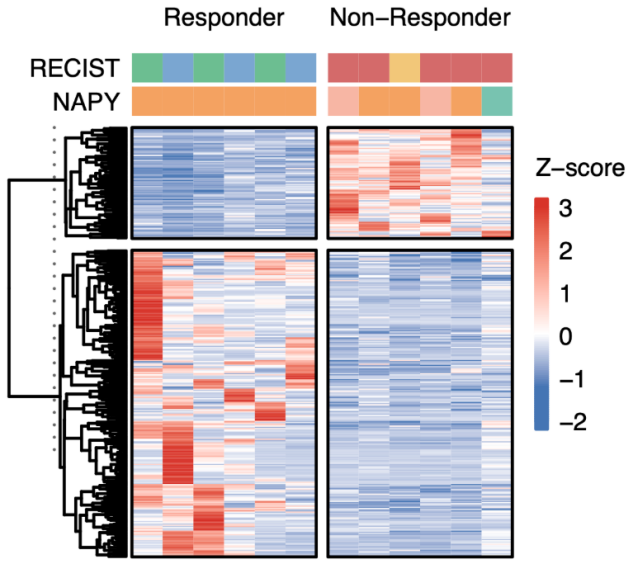
Whole Transcriptome Analysis



Differential expression of **genes**

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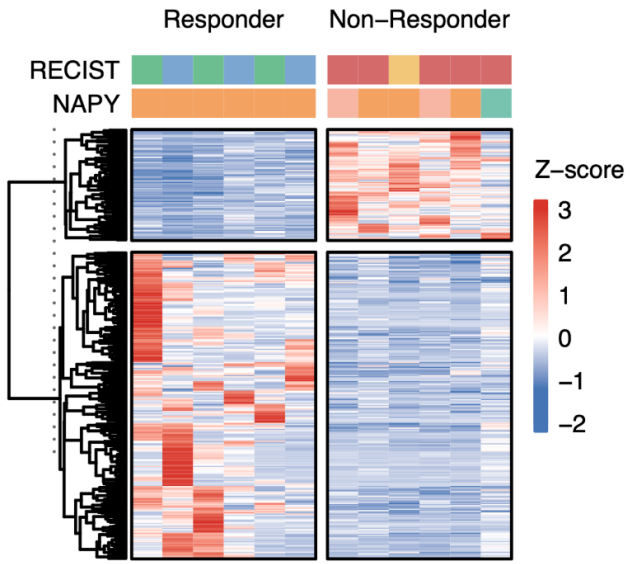

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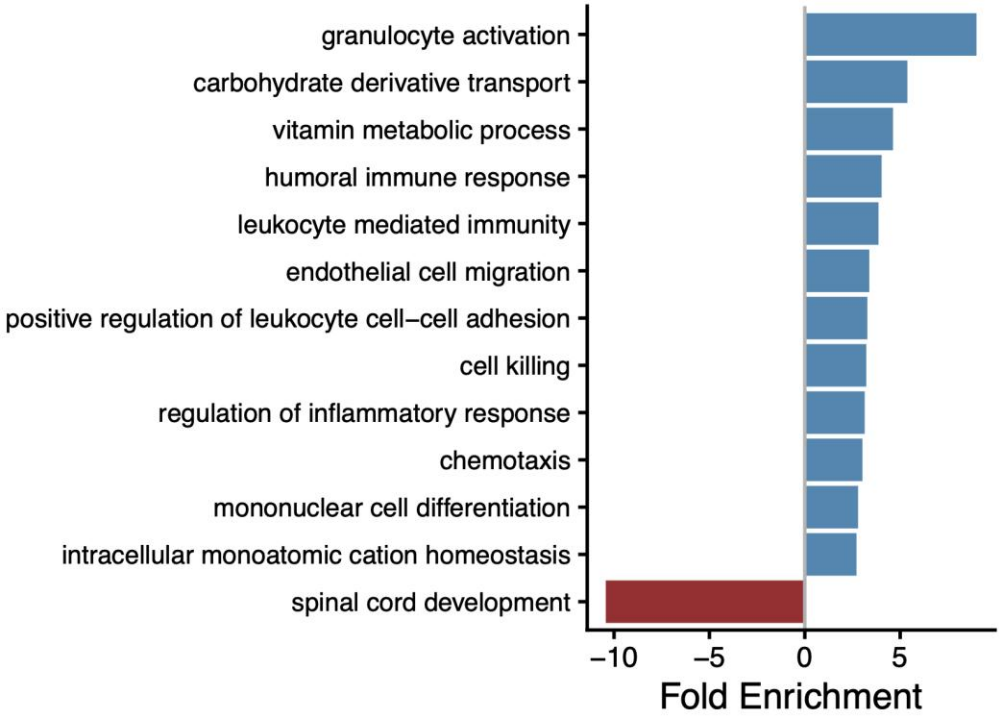

Differential expression of **GO enriched pathways** in responders compared to non-responders

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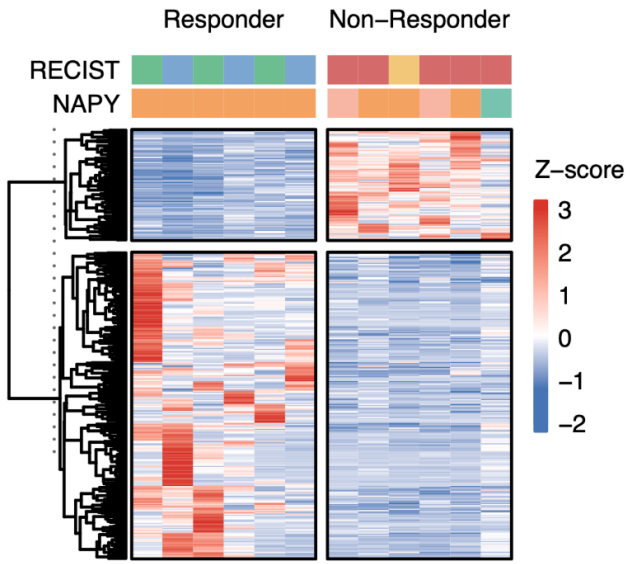

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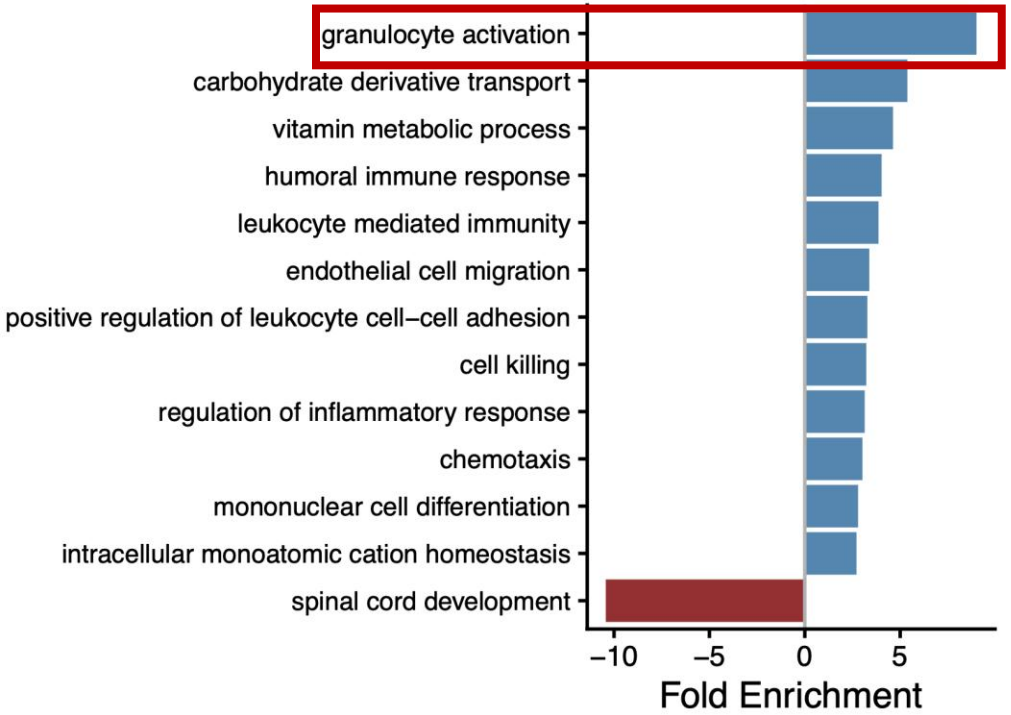

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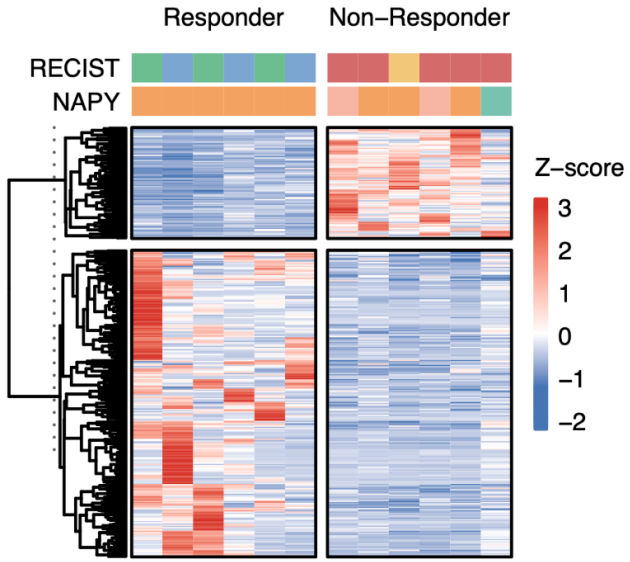

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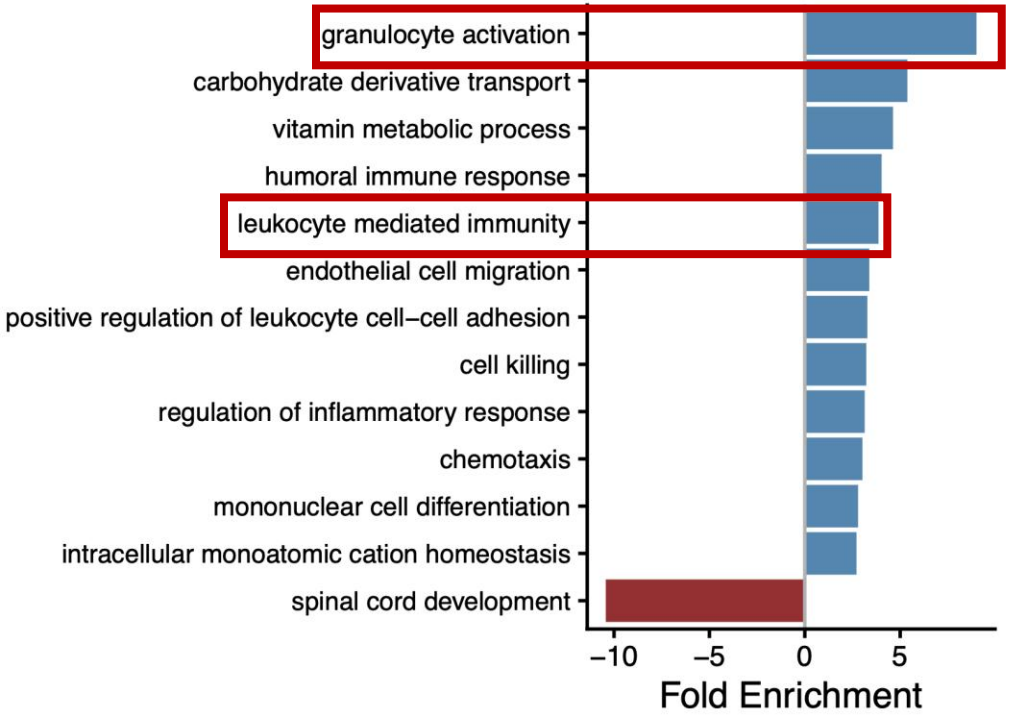

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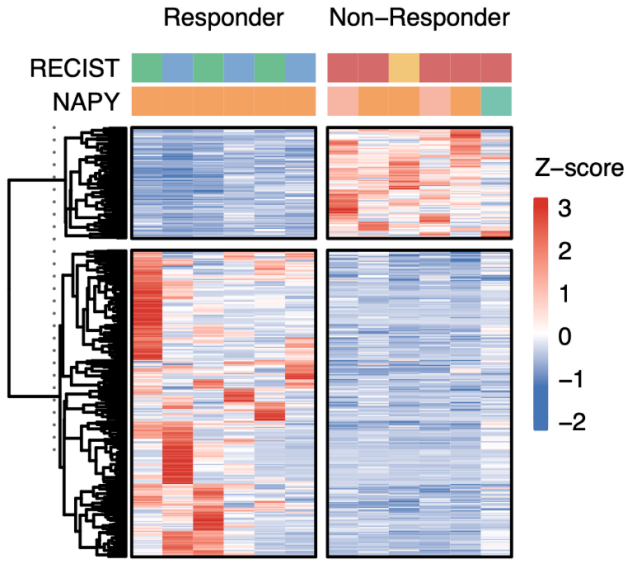

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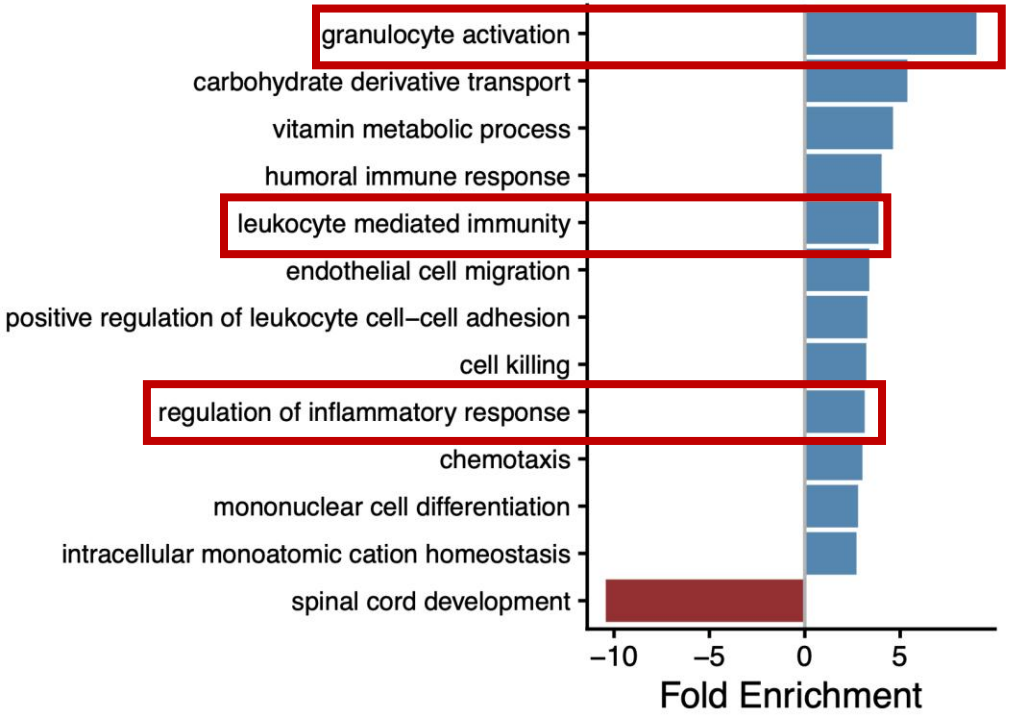

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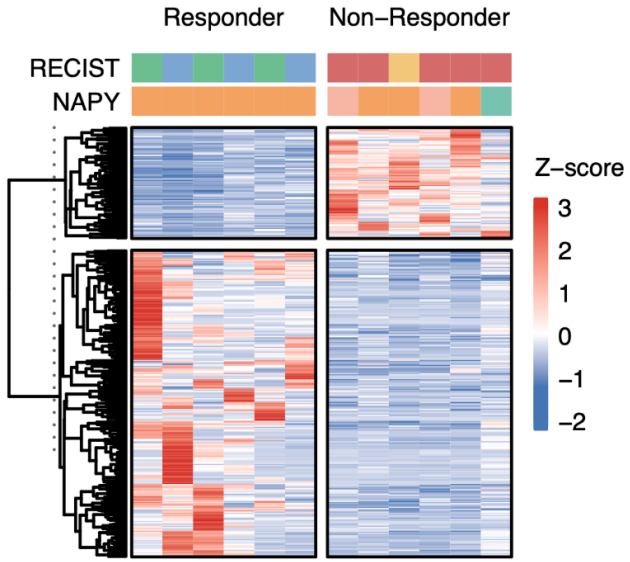

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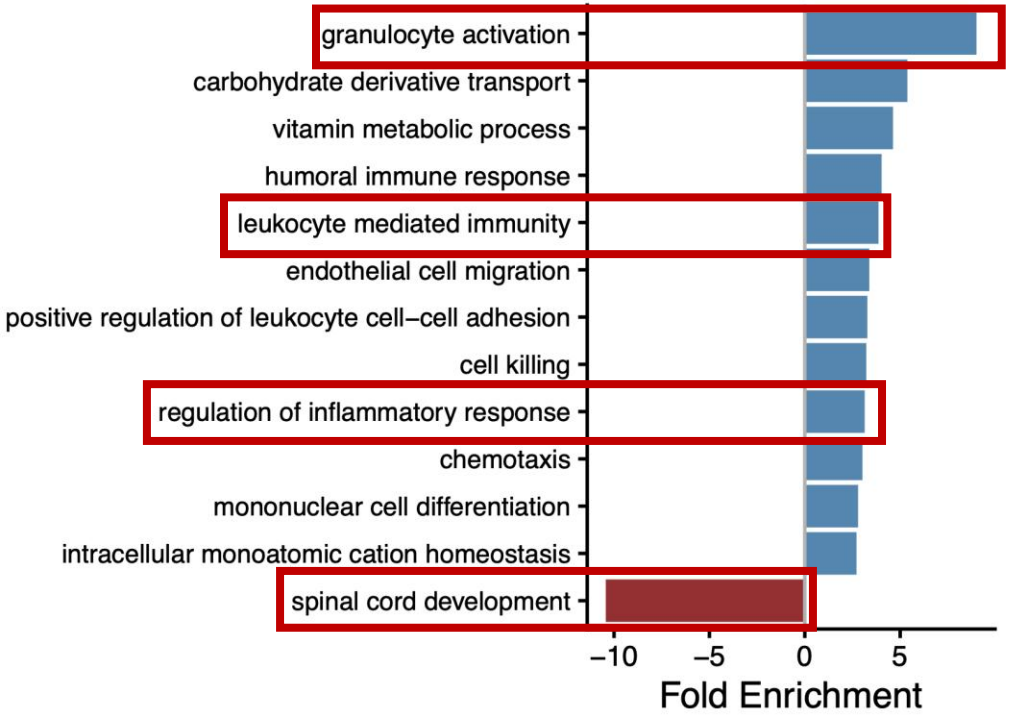

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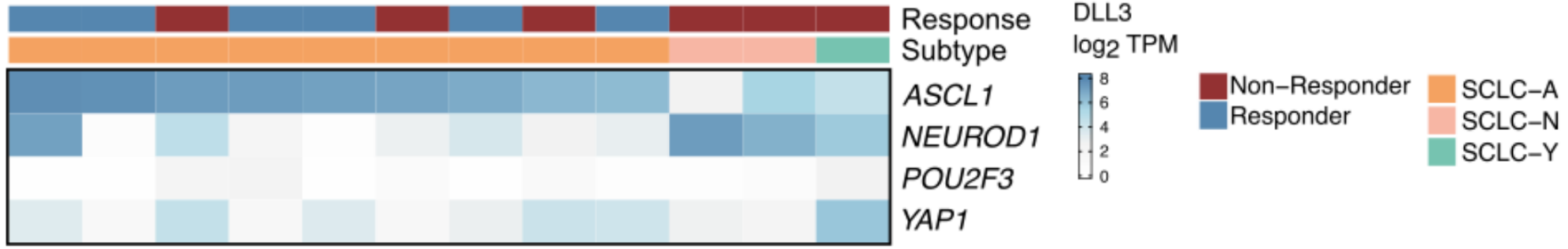
SCLC Subtypes From Gene Expression



- **9** ASCL1 , **2** NEUROD1, **1** YAP1
- All non-ASCL1 tumors had no response to tarlatamab
- **67%** of ASCL1 tumors were responsive and **33%** were unresponsive

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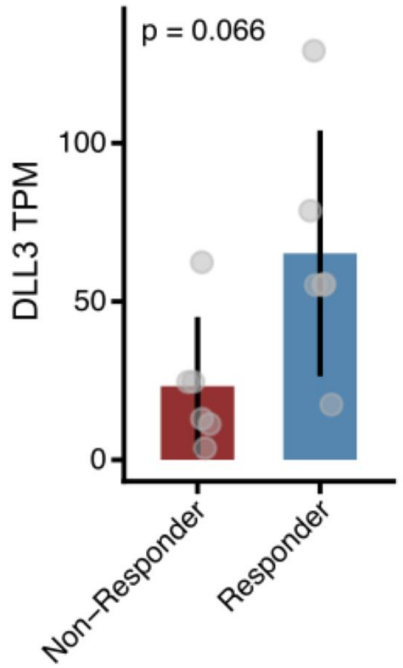
Gene Expression of DLL3

- Differential expression of DLL3 indicated a signal for response prediction.



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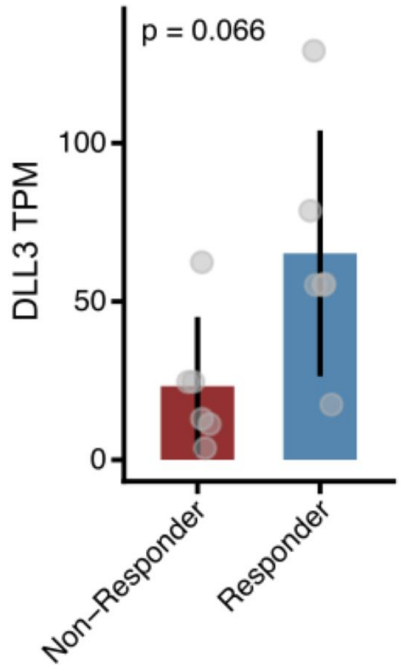
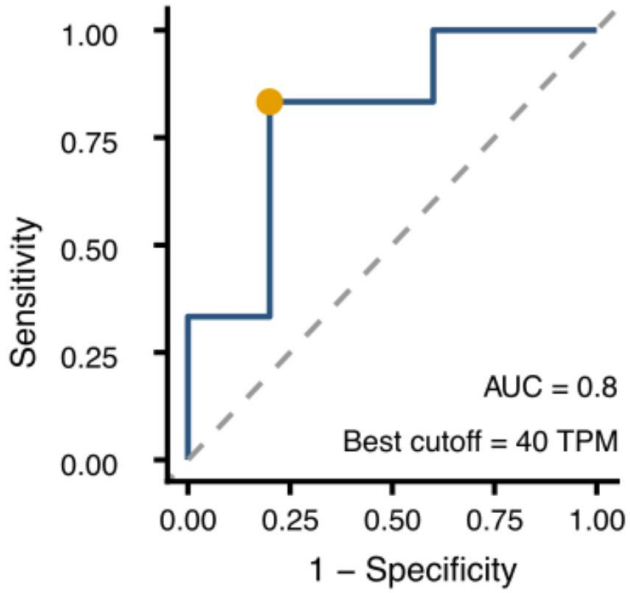
Gene Expression of DLL3

- Differential expression of DLL3 indicated a signal for response prediction.
- DLL3 TPM cutoff of 40 shows trend for differentiating by response





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Post-Treatment Cases

- 2 cases had pre and post treatment biopsies.
- Post treatment biopsies were obtained from progressive lesions.

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Post-Treatment Cases

Table 3: Pre and post tarlatamab patient and sample characteristics

	Patient 4		Patient 6	
Age	46		67	
Gender	F		M	
Line of therapy	3		2	
Smoking (pack years)	50		40	
Tmab response	Response		Response	
	Pre-tarlatamab	**Post-tarlatamab**	**Pre-tarlatamab**	**Post-tarlatamab**
Specimen type	FNA	Biopsy	Primary resection	Biopsy
Biopsy/cytology site	Primary lung tumor	Metastasis	Primary lung tumor	Metastasis
Metastatic site		Abdomen		Liver
SCLC type	ASCL1 →	ASCL1	ASCL1 →	YAP1
HRD Score	46	55	20	39
MSI %	0.96%	0.56%	1.47%	1.75%
TMB (mutations/Mb)	21	23	7	13

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Post-Treatment Cases

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HRD Score	46	55	20	39
MSI %	0.96%	0.56%	1.47%	1.75%
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ASCL1 to **YAP1** subtype switch.

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Conclusion

- Non ASCL1 tumors did not show response.
- DLL3 expression indicated a signal towards response.
- HRD cutoff can potentially help stratify response.
- Inflammatory and immune pathways appear to be significantly upregulated in responders.

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Limitations and Next Steps

- Small sample size → working to integrate public SCLC WES/WTS data
- Integrate other lines of multi-modal data (TF subtype IHC, immune TME, methylation)
- Collaborate?

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Thank You!

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Dr. Keisuke Shirai

Dr. Parth Shah

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Citations

- 1 Rudin CM, Poirier JT, Byers LA, et al. Update on the biology, management, and treatment of small cell lung cancer (SCLC) in 2020. J Thorac Oncol. 2020;15(11):e215-e226. doi:10.1016/j.jtho.2020.08.014
- 2 Li J, Chen J, Li P, et al. Small cell lung carcinoma: a comprehensive review of biology, molecular pathogenesis, and emerging therapies. Mol Cancer. 2021;20(1):143. doi:10.1186/s12943-021-01312-y
- 3 Wang H, Fang Y, Jiang J, et al. Genomic features and classification of small cell lung cancer: a comprehensive genomic analysis. BMC Med Genomics. 2022;15(1):106. doi:10.1186/s12920-022-01255-3
- 4 Yang Y, Li T, Zhang L, et al. Genomic landscape and prognostic factors in small cell lung cancer: a single-institution retrospective study. J Hematol Oncol. 2019;12(1):47. doi:10.1186/s13045-019-0736-3
- 5 Kelly G Paulson, Sally C M Lau, Myung-Ju Ahn, Mor Moskovitz, Michael Pogorzelski, Simon Häfliger, Amanda Parkes, Yuyang Zhang, Ali Hamidi, Corbin G Thompson, Martin Wermke, Safety and activity of tarlatamab in combination with a PD-L1 inhibitor as first-line maintenance therapy after chemo-immunotherapy in patients with extensive-stage small-cell lung cancer (DeLLphi-303): a multicentre, non-randomised, phase 1b study, The Lancet Oncology, Volume 26, Issue 10, 2025, Pages 1300-1311, ISSN 1470-2045, https://doi.org/10.1016/S1470-2045(25)00480-2.

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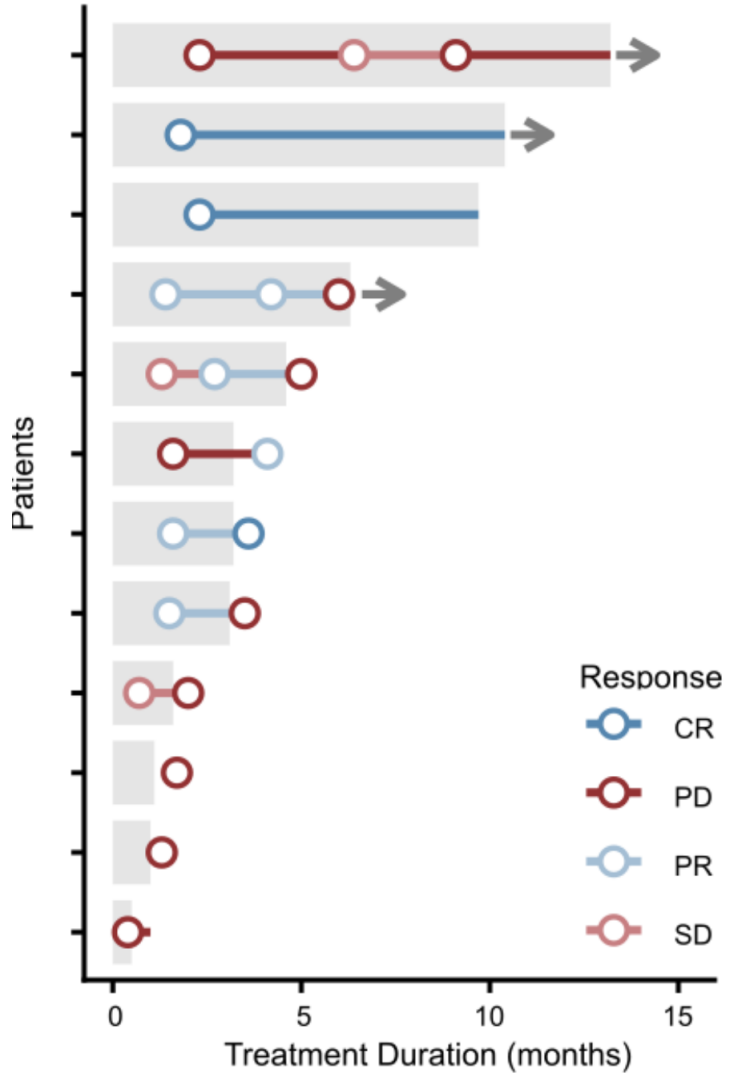
Patient Characteristics

- Treatment duration and timing of staging
- Overall survival: **8.6 ± 4.5 months** (mean ± SD)
- Progression free survival: **3.6 ± 2.5 months** (mean ± SD)



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Adverse effects

- Cytokine release syndrome (CRS): **31%**
  - Grade 2
- Immune effector cell-associated neurotoxicity syndrome (ICANS): **31%**
  - Grade 1

Table 2: Adverse effects

	(N=13)			
	Grade 1	Grade 2	Grade 3	Total
CRS	0	4	0	4
ICANS	3	0	1	4

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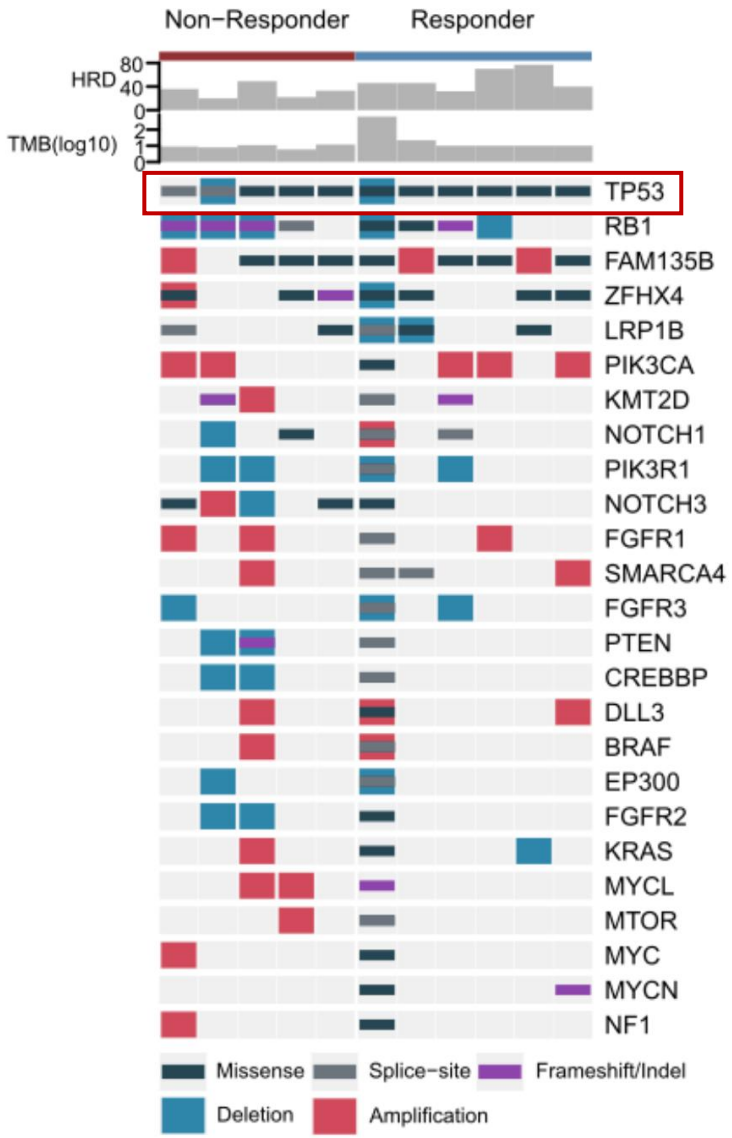
Mutational Profiling

- TP53 alterations in all , mostly missense mutations and deletions.



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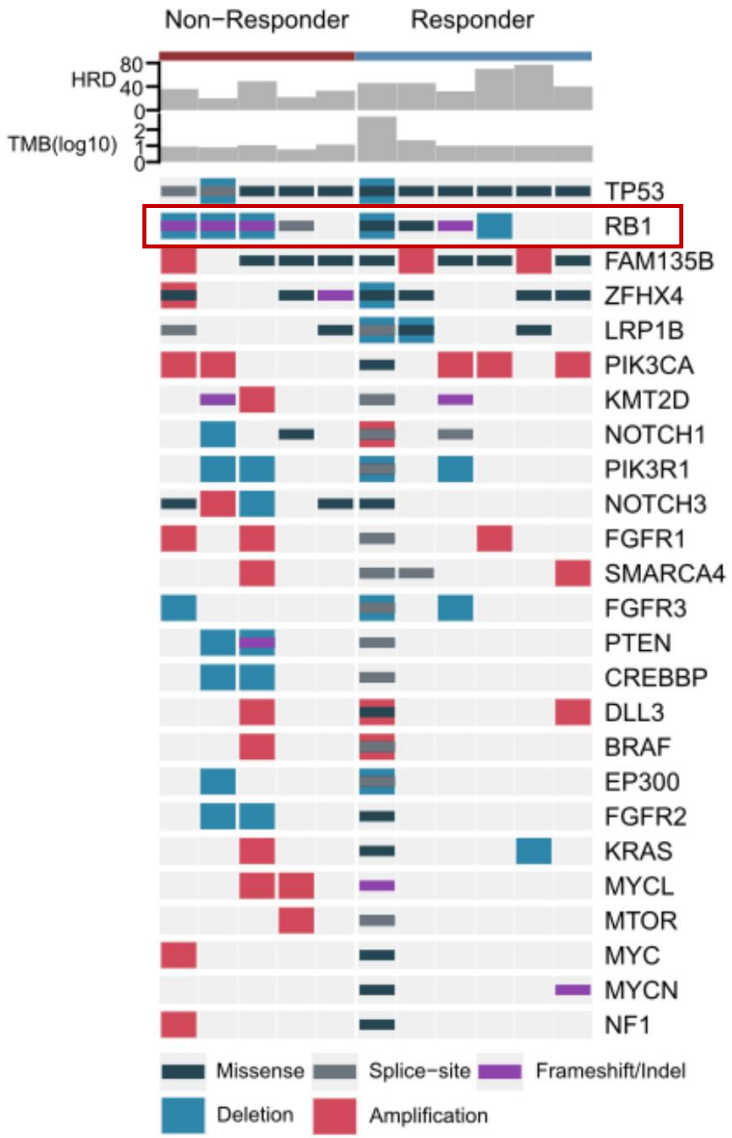
Genomics

- Frequent RB1 alterations, such as deletions and frameshift mutations/indels.



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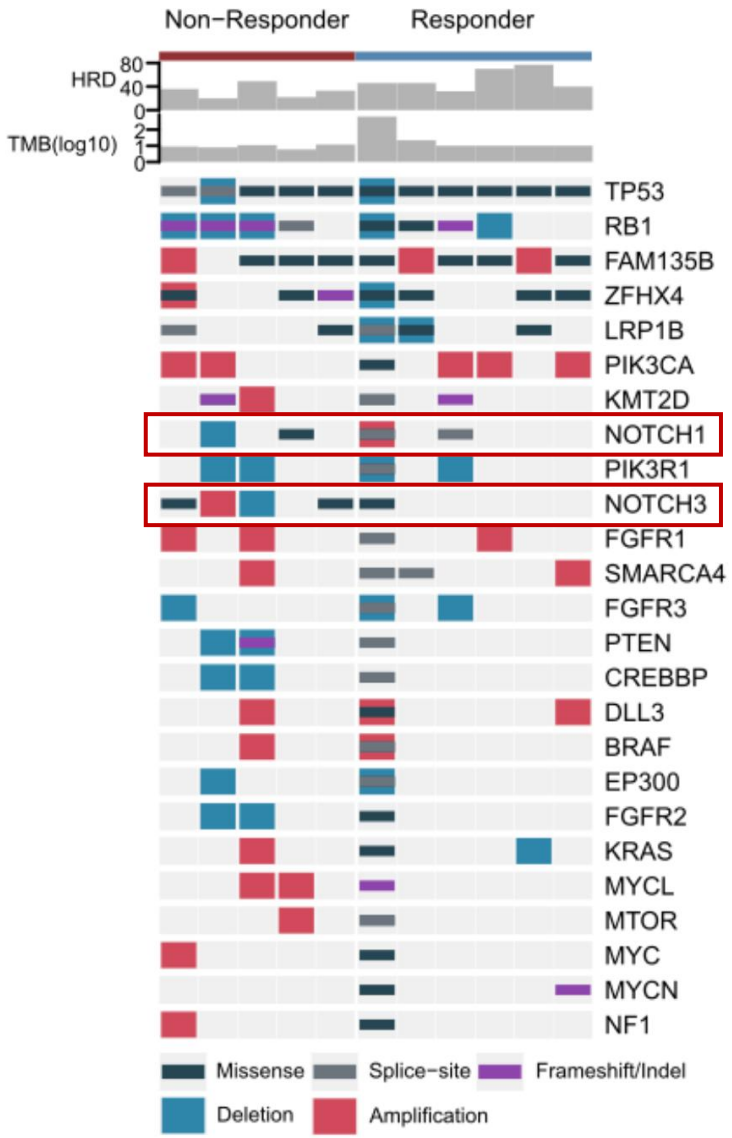
Genomics

- Alterations of NOTCH1 and NOTCH 3 of the Notch signaling pathway.



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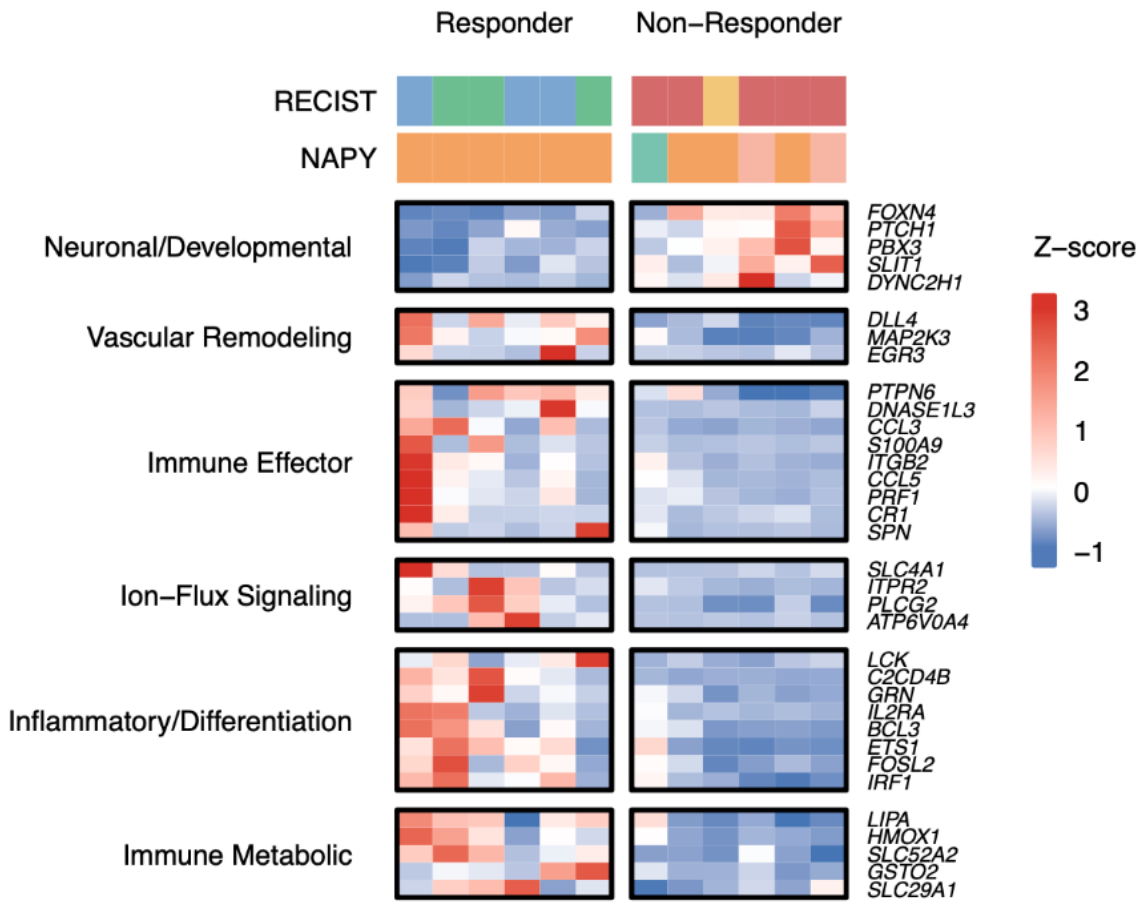
Whole transcriptome analysis



Differential expression of **GO enriched pathways with genes**

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