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Progress in Biomarkers for SCLC – Are We Ready for Implementation into Routine Clinical Practice?

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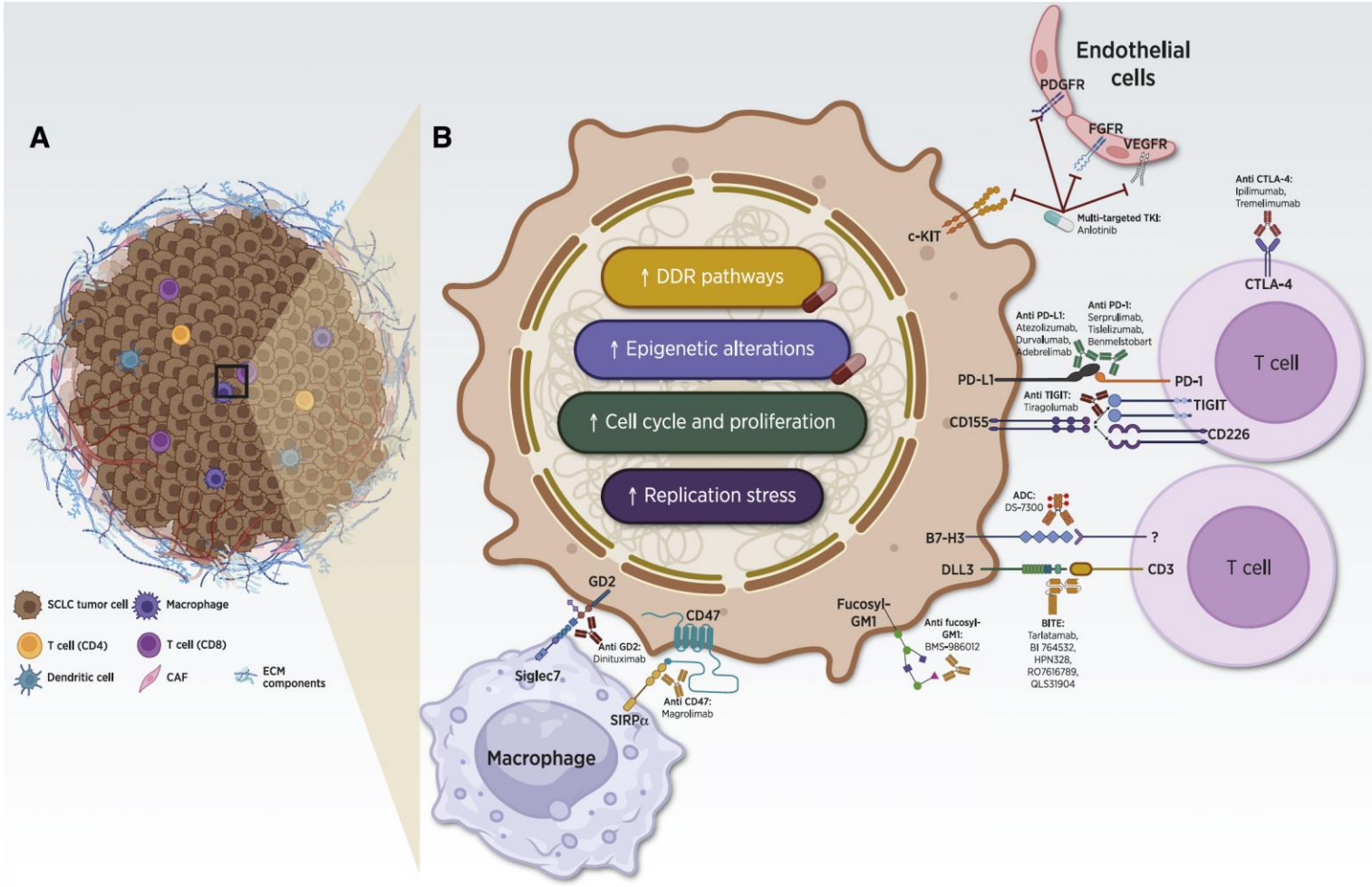
1L chemoimmunotherapy for ES-SCLC

Study	Agent	Sample Size	mPFS / HR	mOS / HR	1y OS Rate
IMpower 133 *Liu, JCO 2021*	Atezolizumab	403 pts	5.2m HR 0.77	12.3m HR 0.76	52%
CASPIAN *Paz-Ares, ESMO Open 2022*	Durvalumab	805 pts	5.1m HR 0.80	12.9m HR 0.71	53%
EA5161 (phase II) *Leal, ASCO 2020*	Nivolumab	160 pts	5.5m HR 0.68	11.3m HR 0.73	50%
KEYNOTE 604 *Rudin, WCLC 2022*	Pembrolizumab	453 pts	4.8m HR 0.70	10.8m HR 0.76	45%
ASTRUM 005 *Cheng, JAMA 2022*	Serplulimab	585 pts	5.7m HR 0.48	15.4m HR 0.63	61%
CAPSTONE-1 *Wang, Lancet Oncol 2022*	Adebrelimab	462 pts	5.8m HR 0.67	15.3m HR 0.72	63%
RATIONALE-312 *Cheng, WCLC 2023*	Tislelizumab	457 pts	4.8m HR 0.63	15.5m HR 0.75	63%

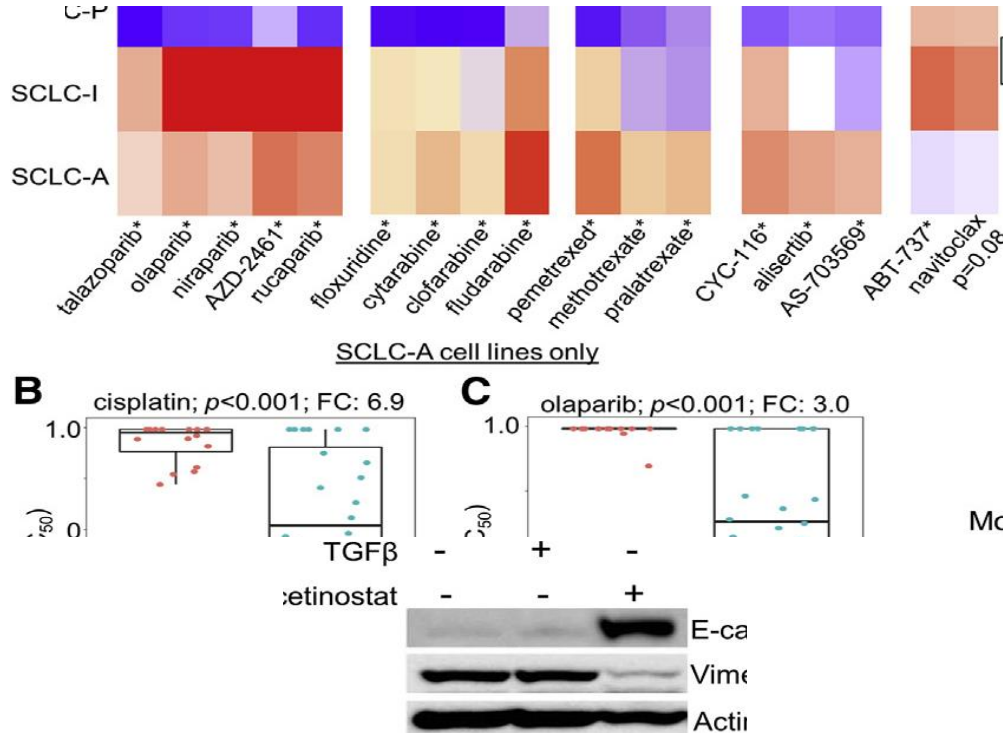
Liu S, ESMO 2024.

Tumor microenvironment of human SCLC and potential targets for therapies



SCLC subtypes defined by a dominant transcriptional regulator

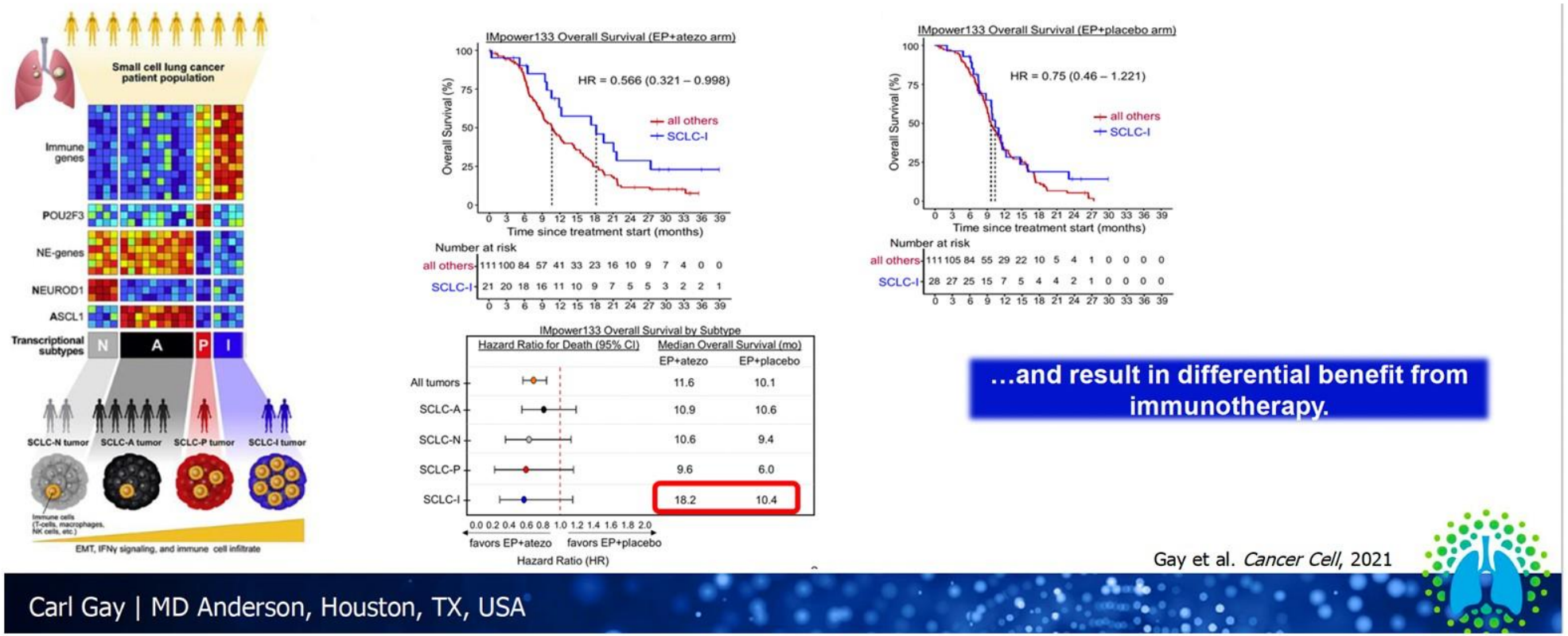
	Neuroendocrine		Non-Neuroendocrine	
Subtype	SCLC-A (36-51%)	SCLC-N (23-31%)	SCLC-P (7-17%)	SCLC-Inflamed (16-18%)
Targets	DLL3 BCL2 CD56 EZH1 LSD1	AURKA DLL3 MYC GD2	PARP1	AXL CD274 CD38 CTLA4 PD1/PDL1 BTKi



Poirier et al. JTO 2020

Gay et al. Cancer Cell 2021

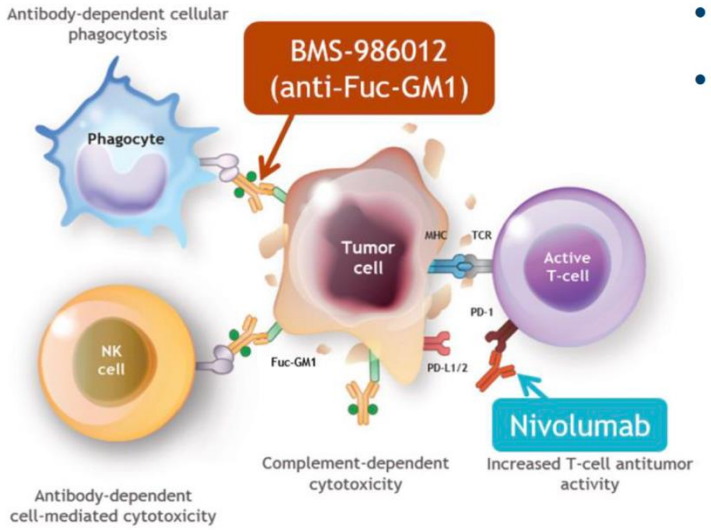
SCLC-I with differential benefit from immunotherapy



Gay, Hot Topics SCLC 2023

Targeting the surface glycome

- BMS-986012 is an anti-fucosyl-monosialoganglioside-1 monoclonal antibody

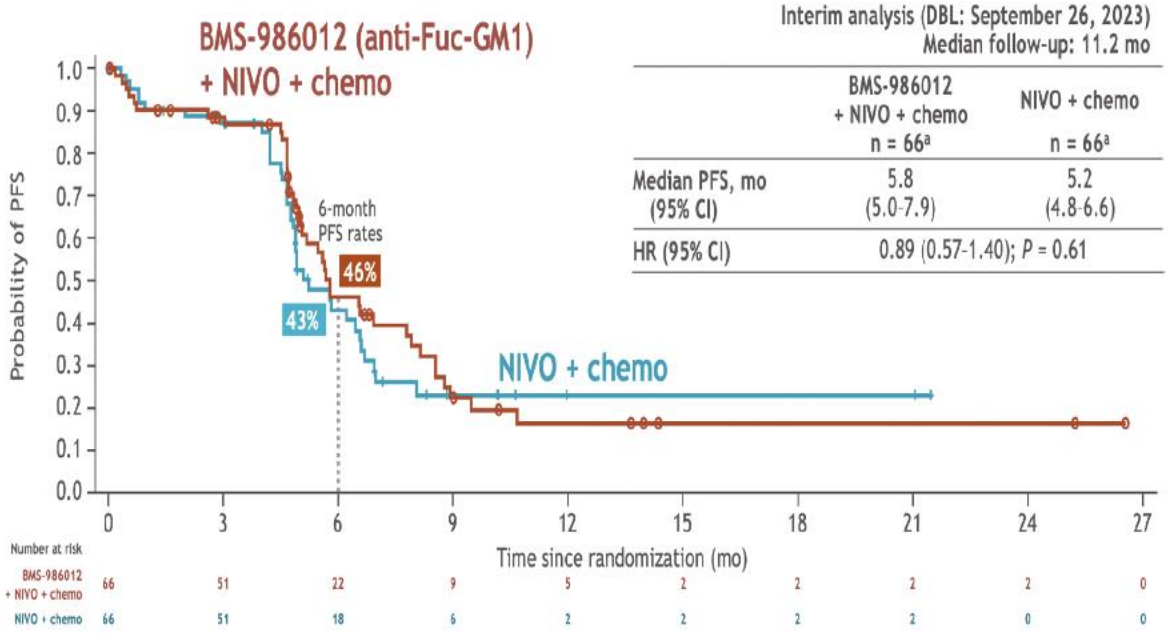


- Fuc-GM1 is highly expressed in SCLC
- Preclinically, BMS-986012 bound to CD16:
  - Enhances antibody-dependent cellular cytotoxicity (ADCC)
  - Enhances complement-dependent cytotoxicity (CDC)
  - Enhances antibody-dependent cellular phagocytosis (ADCP)
  - Exerted far greater effect with anti-PD-1 antibody than as monotherapy

Kalinka, ESMO 2024; Ponath, Clin Cancer Res 2018

Phase II Nivolumab + Chemotherapy +/-BMS-986012: Efficacy

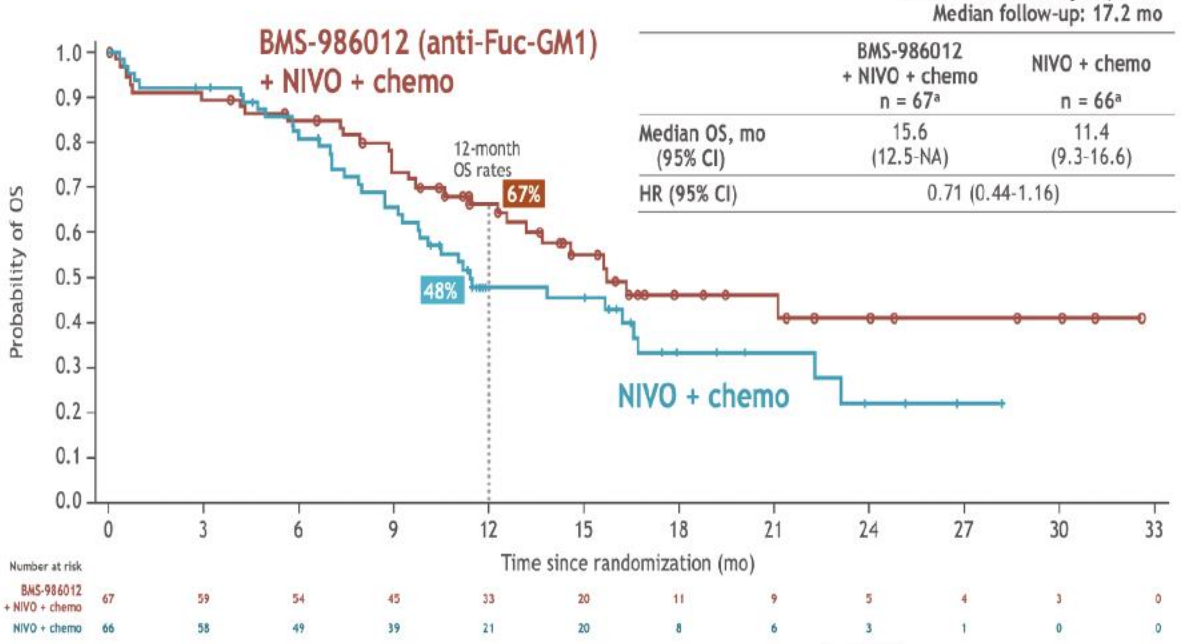
No difference in PFS



Interim analysis (DBL: September 26, 2023)
Median follow-up: 11.2 mo

	BMS-986012 + NIVO + chemo n = 66[a]	NIVO + chemo n = 66[a]
Median PFS, mo (95% CI)	5.8 (5.0-7.9)	5.2 (4.8-6.6)
HR (95% CI)	0.89 (0.57-1.40); *P* = 0.61	

No difference in OS



Data cutoff: February 26, 2024
Median follow-up: 17.2 mo

	BMS-986012 + NIVO + chemo n = 67[a]	NIVO + chemo n = 66[a]
Median OS, mo (95% CI)	15.6 (12.5-NA)	11.4 (9.3-16.6)
HR (95% CI)	0.71 (0.44-1.16)	

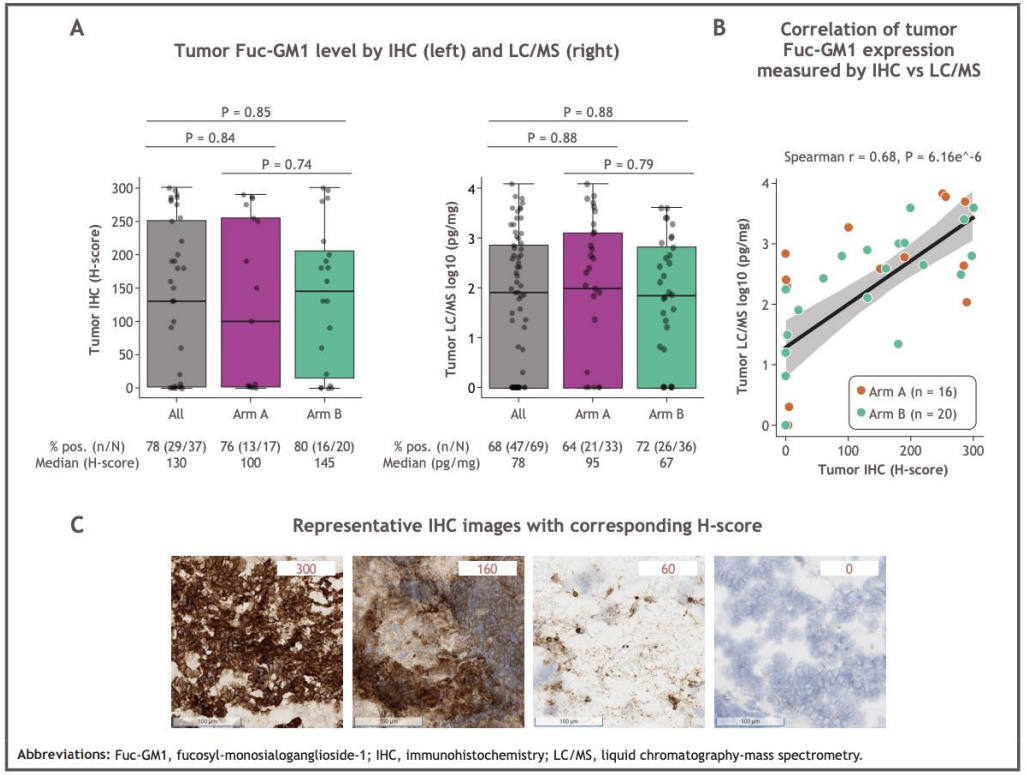
High prevalence of Fuc-GM1 expression in baseline tumor samples

- Preliminary analyses in a subset of patients from CA001-050 confirmed expression of baseline Fuc-GM1 in the majority of tumors as measured in frozen tumor tissue:

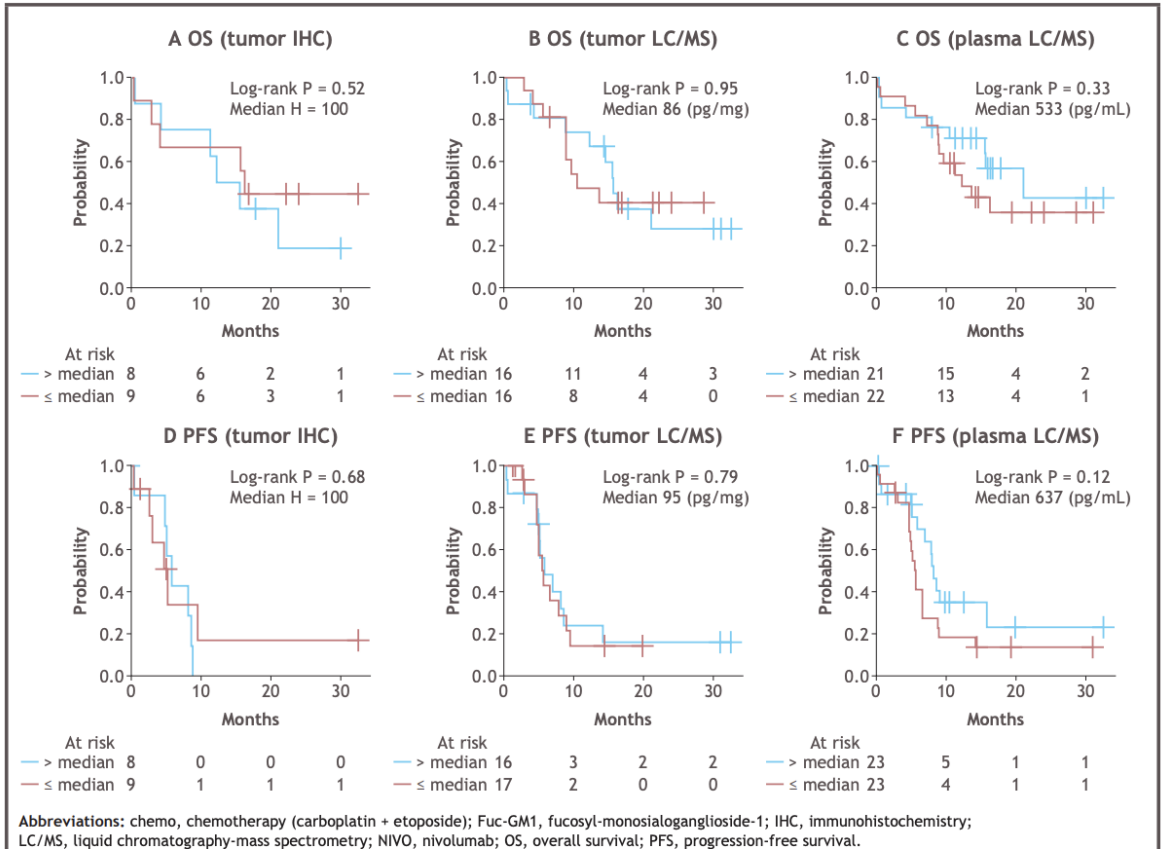
-78% with immunohistochemistry [IHC]

-68% with liquid chromatography-mass spectrometry [LC/MS])

-Moderate correlation between the two methodologies



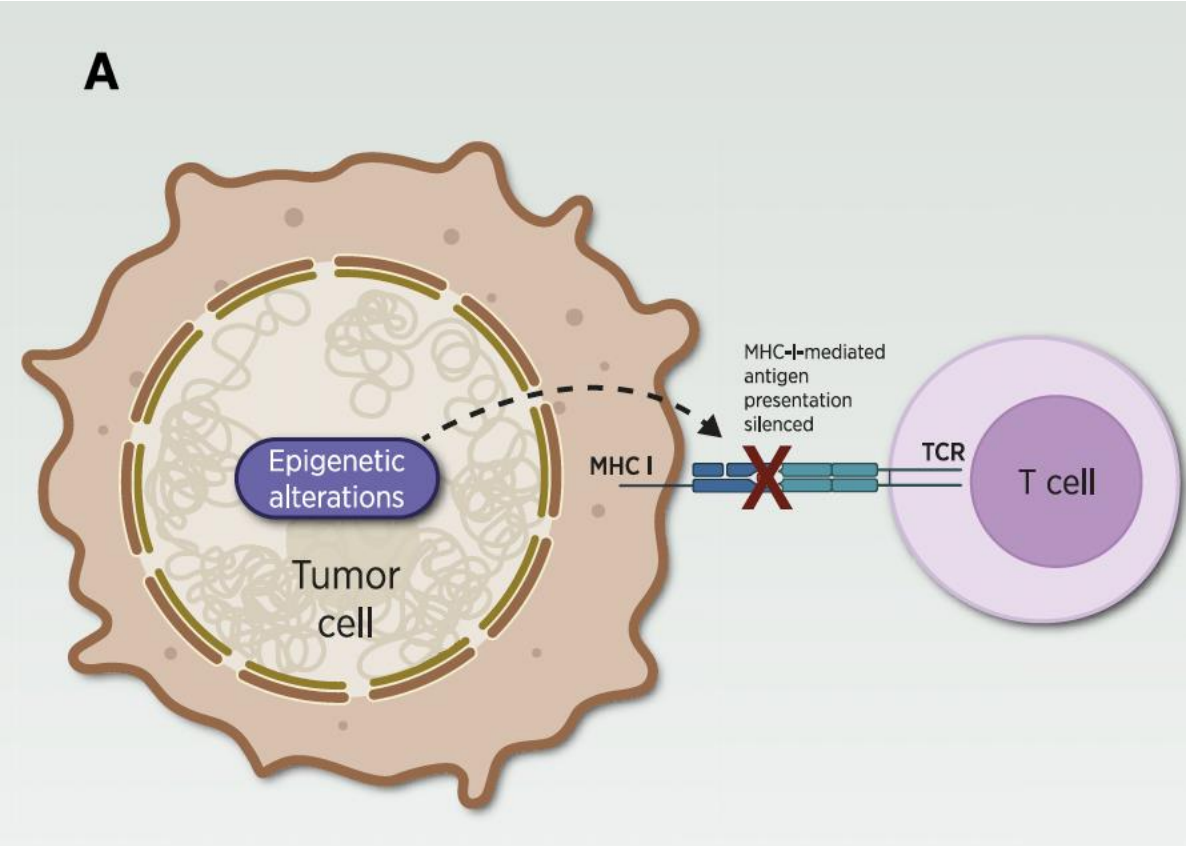
Baseline tumor/plasma level of Fuc-GM1 did not correlate with OS and PFS in a subset of patients from this study



Abbreviations: chemo, chemotherapy (carboplatin + etoposide); Fuc-GM1, fucosyl-monosialoganglioside-1; IHC, immunohistochemistry; LC/MS, liquid chromatography-mass spectrometry; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival.

O'Byrne et al. ESMO 2024

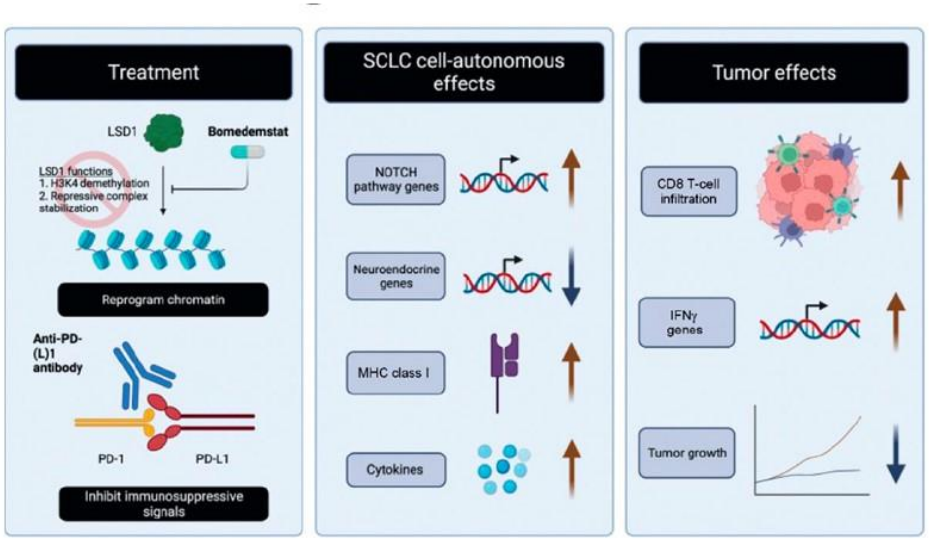
Targeting MHC I deficiency



- It has been shown that most human SCLCs (70%–80%) show loss of MHC class I expression at the protein level.
- This seems to be more prominent in neuroendocrine SCLC subtypes.
- Epigenetically driven downregulation or silencing of the MHC class I antigen processing and presentation machinery pathway is a prominent immune-suppressive feature

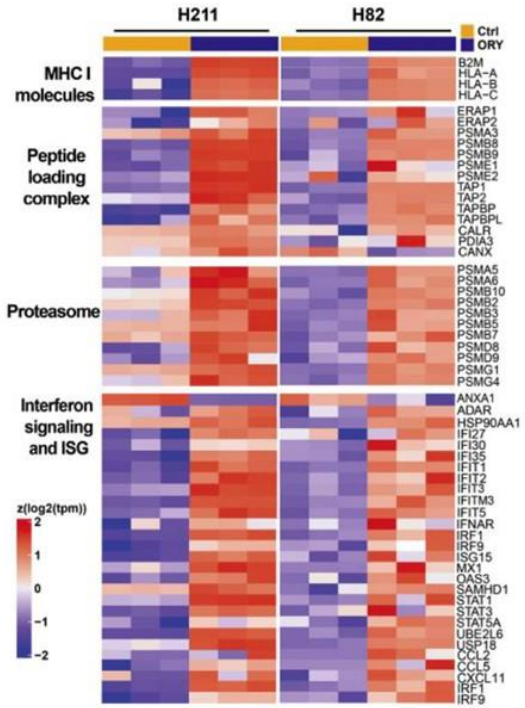
Zugazagoitia et al. Clin Cancer Res 2024;30:2872–83

Preclinical evidence that LSD1 inhibition increases MHC-I expression in vivo



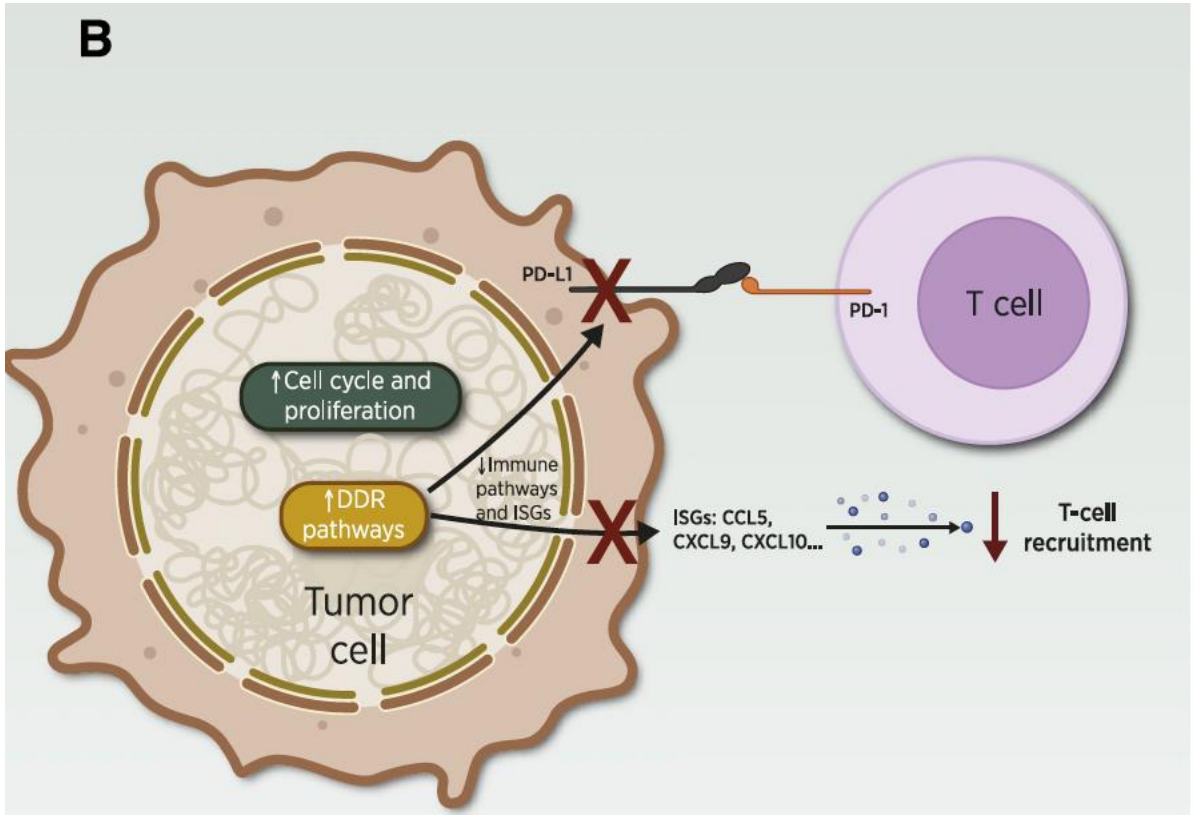
Hiatt et al. *Clinc Cancer Res*, 2022

LSD1 inhibition induces SCLC-I-like phenotype in otherwise uninflamed models.

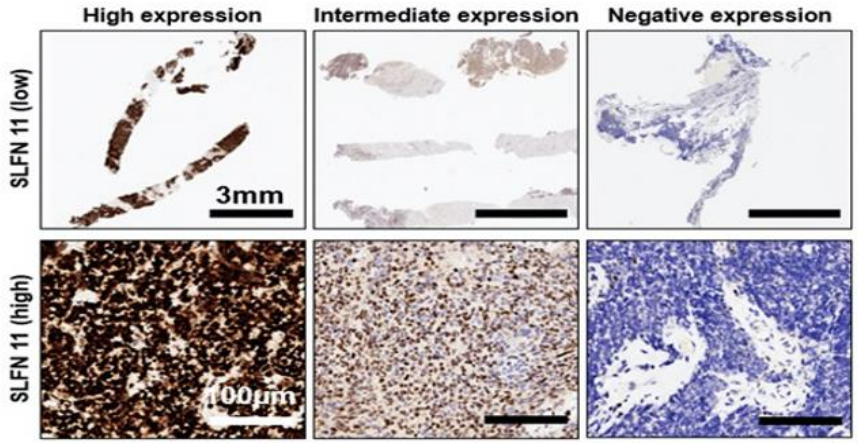


Nguyen et al. J Thorac Oncol, 2022

Targeting DDR



SLFN11 is frequently expressed, predicted PARP inhibitor benefit in retrospective analyses of SCLC pts



	Sample size	SLFN11+ % (n)
Phase II veliparib/TMZ *(Pietanza, JCO 2018)*	47	49% (23)
Phase II EP/veliparib *(Byers, CCR 2021)*	149	52% (77)

Wei-Lien Wang, Junya Fujimoto, Ignacio Wistuba, MDACC

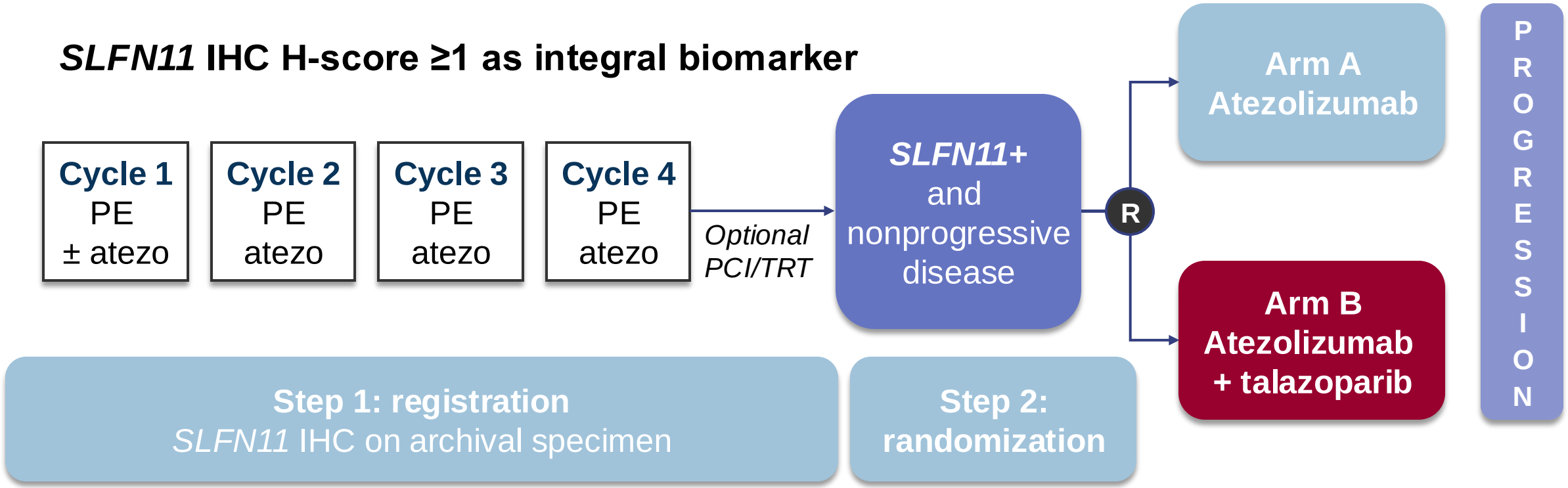
Zugazagoitia et al. Clin Cancer Res 2024;30:2872–83

Pietanza et al. *J Clin Oncol*. 2018;36(23):2386-2394. Byers LA et al. *Clin Cancer Res.* 2021;27(14):3884-3895.

SWOG 1929

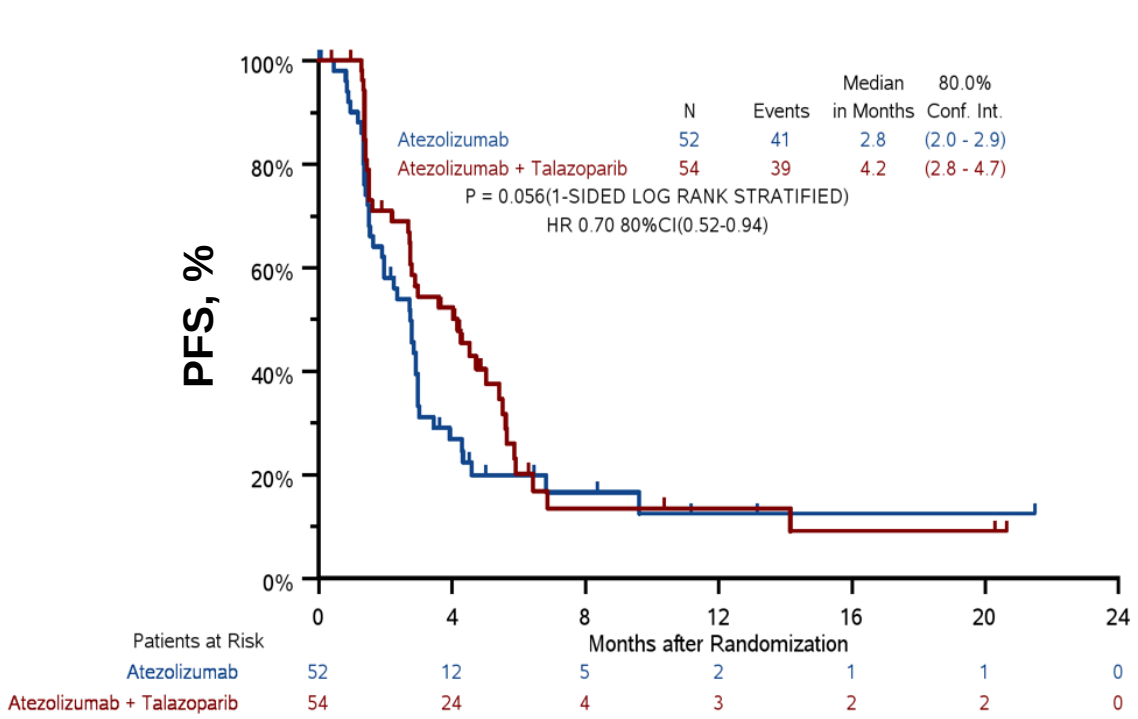
Atezolizumab + Talazoparib Maintenance

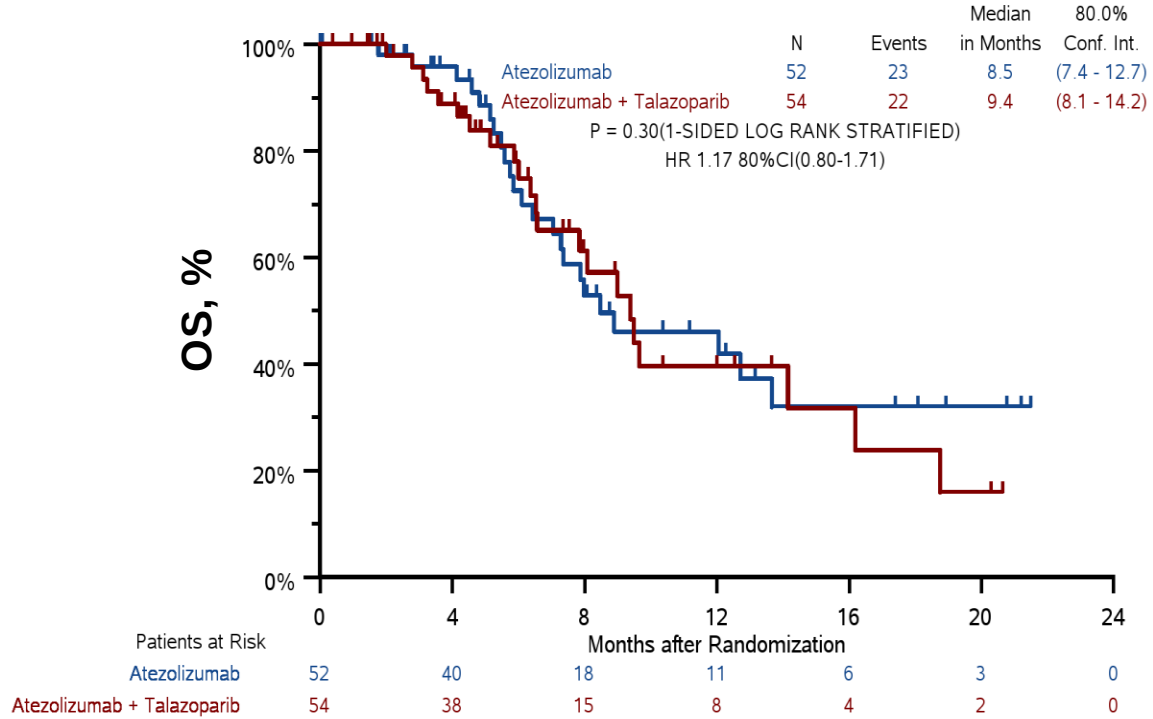
SCLC 1L, SLFN11+ disease



Karim NFA et al. JTO 2024

SWOG 1929: PFS and OS

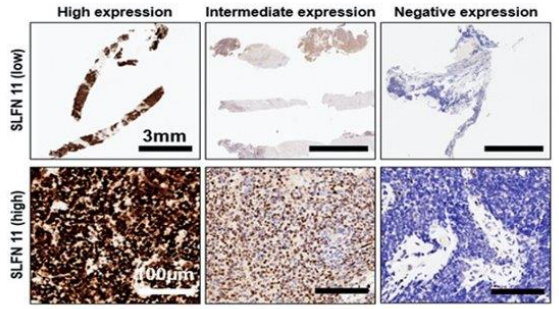




Karim NFA et al. JTO 2024

What is (are) the optimal biomarker (s)?

SLFN11 is frequently expressed, predicted PARP inhibitor benefit in retrospective analyses of SCLC pts



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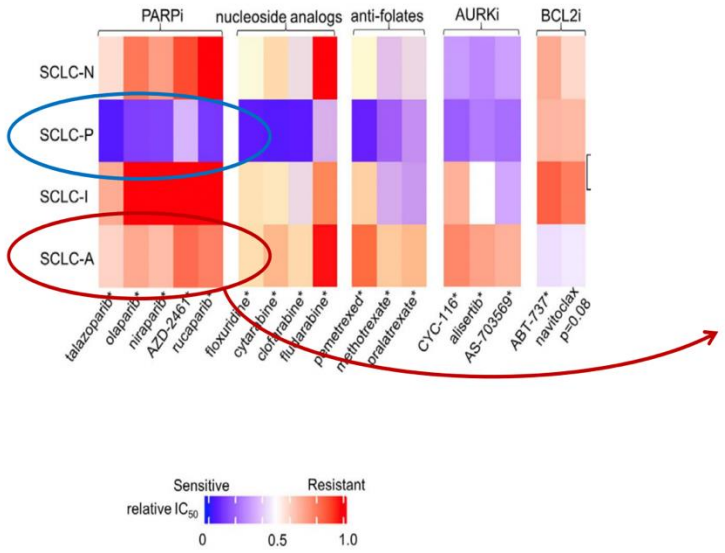
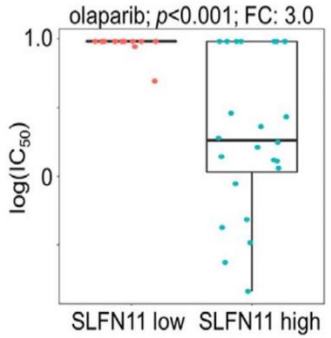
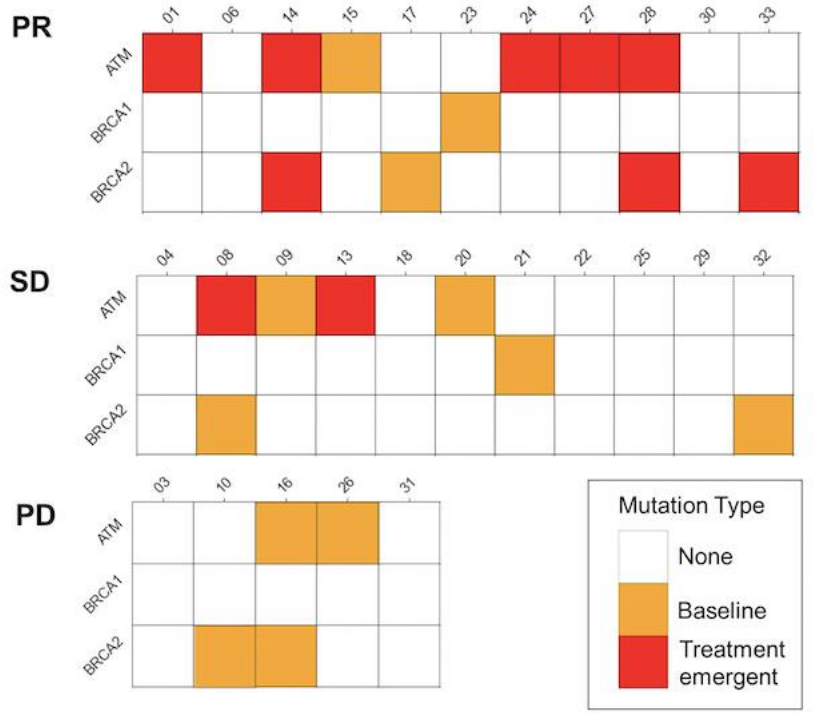
Wei-Lien Wang, Junya Fujimoto, Ignacio Wistuba, MDACC

SCLC subtypes as a predictor of benefit of PARPi



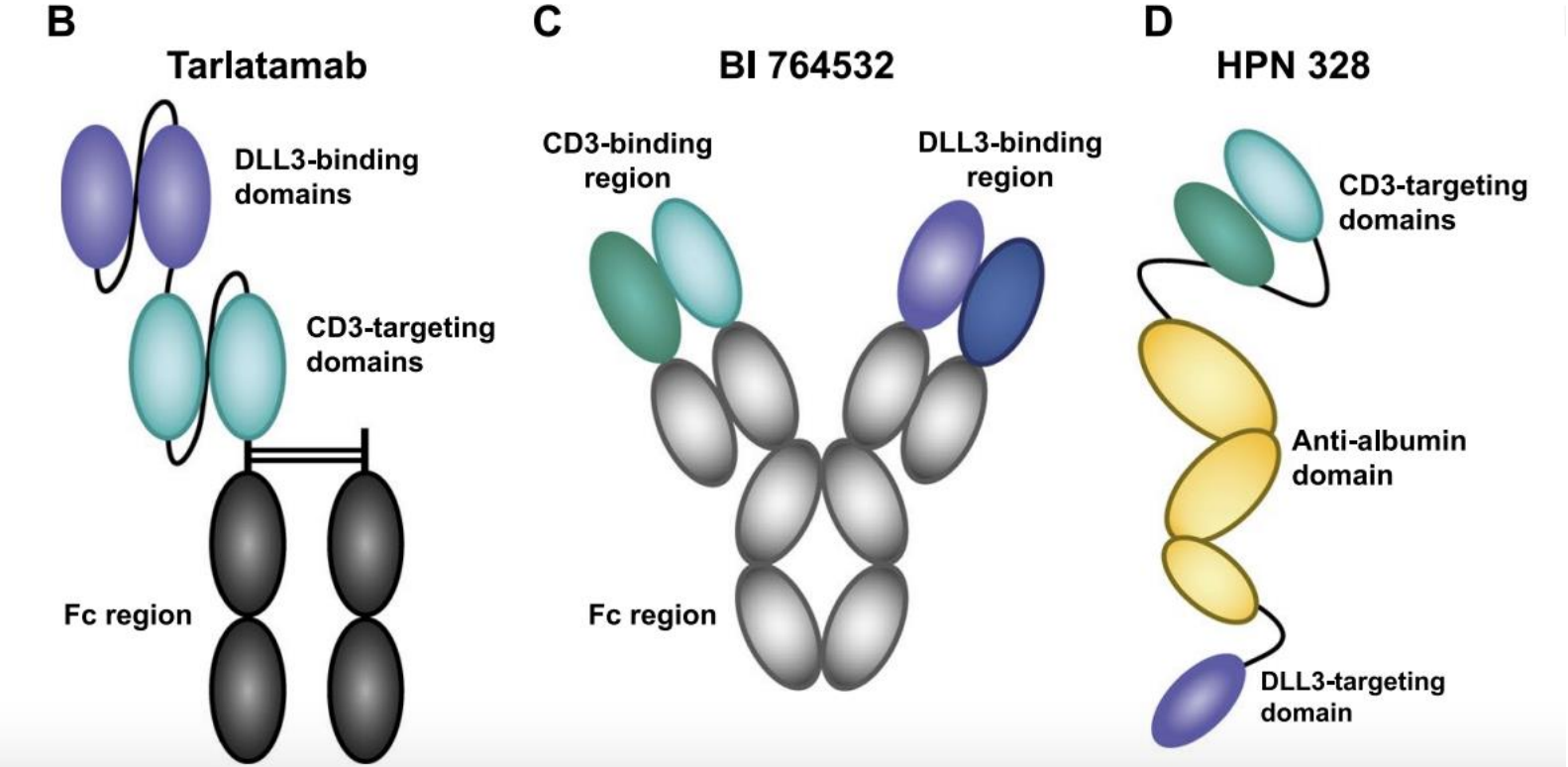


Mutations in DDR genes occur on treatment with tala and TMZ: association with DC.

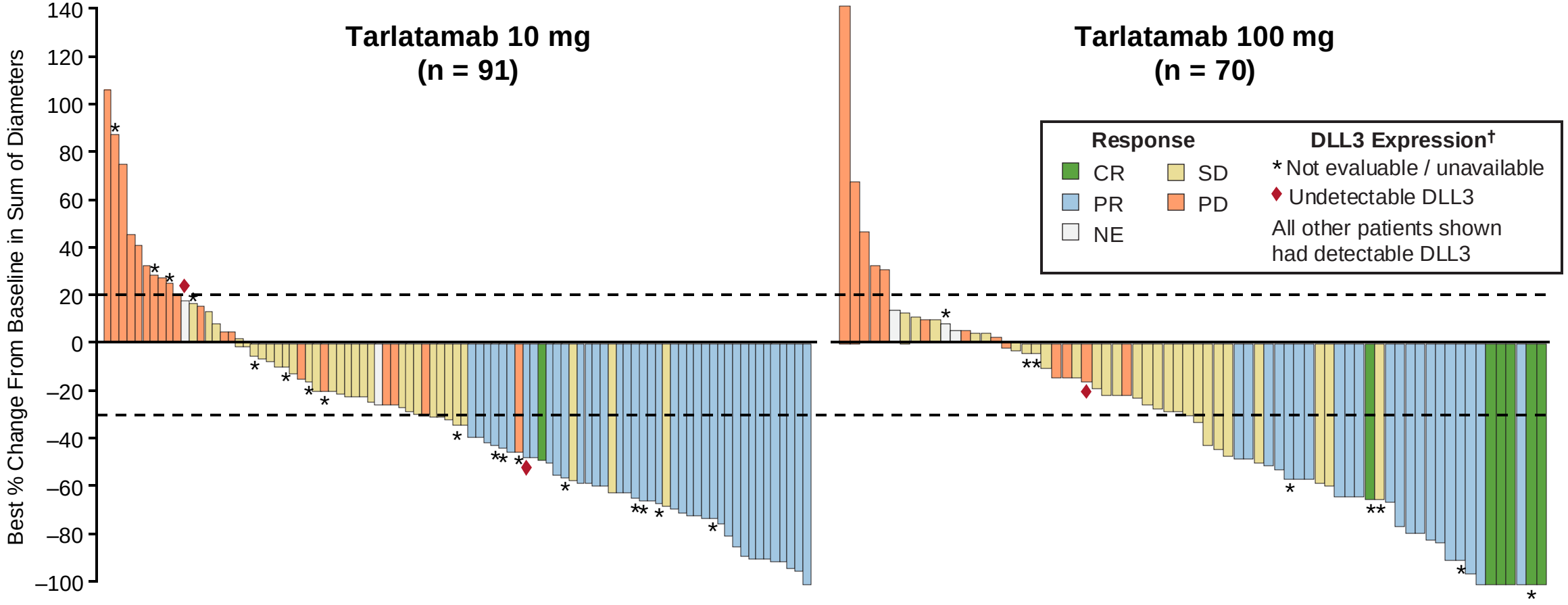


Pietanza et al. *J Clin Oncol*. 2018;36(23):2386-2394. Byers LA et al. *Clin Cancer Res*. 2021;27(14):3884-3895. Gay et al. Cancer Cell 2021. Goldman et al. ASCO 2022.

Structure of DLL3-targeting TCEs in development



Anti-tumor Activity



Responses were observed regardless of DLL3 expression, as well as in patients without evaluable tumor tissue

Shown are 91 of 100 patients (tarlatamab 10 mg) and 70 of 88 patients (tarlatamab 100 mg) who had available post-baseline measurements of target lesions.
†DLL3 expression was assessed by immunohistochemistry of tumor tissue samples.
CR, complete response; **DLL3,** delta-like ligand 3; **NE,** not evaluable; **PD,** progressive disease, **PR,** partial response; **SD,** stable disease.

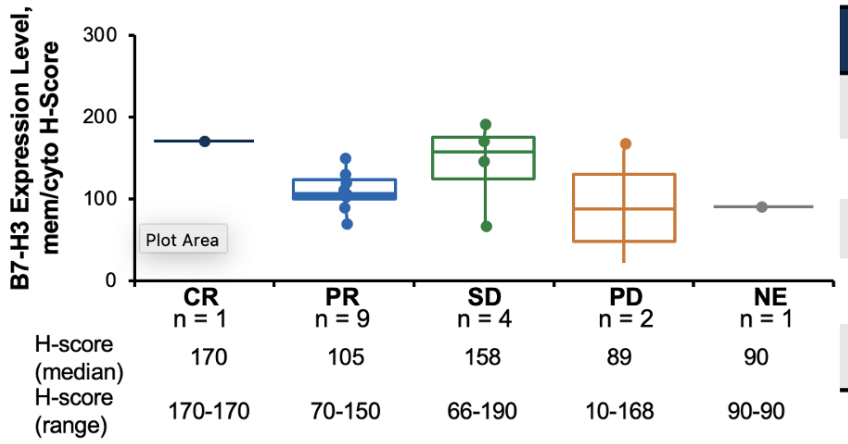
MADRID 2023 ESMO congress

Targeting B7H3

- B7H3 seems to play a predominant inhibitory role on adaptive immunity by suppressing T-cell activation and proliferation. In addition, it can promote tumorigenic properties in tumor cells themselves.

- No trend of correlation between B7-H3 expression and efficacy was observed in the SCLC subset

SCLC—B7-H3 Level by BOR Status for Evaluable Patients (n = 17)



	Low B7-H3[a] (n = 8)	High B7-H3[a] (n = 9)
B7-H3 mem/cyto H-score at baseline, median (range)	115 (10-190)	
H-score at baseline, range	10-105	115-190
Unconfirmed ORR, n (%)	5 (62.5)	5 (55.6)
Median PFS, mo (95% CI)	5.8 (0.7-NE)	5.3 (1.4-NE)
Median OS, mo (95% CI)	12.2 (5.8-NE)	6.9 (2.8-NE)

Conclusions

- There are currently no biomarkers to help tailor any systemic therapy, including immunotherapy, in SCLC.
- The discovery of transcriptional subsets in SCLC is an important breakthrough in better understanding tumor heterogeneity and the potential therapeutic vulnerabilities.
- Validated assays for DLL3 expression may be helpful in selecting patients with SCLC, LCNEC and extra-pulmonary NEC in clinical trials.
- Prospective studies are needed to translate recent discoveries into personalized, biomarker-driven clinical trials.