Advances in Limited and Extensive Stage Small Cell Lung Cancer

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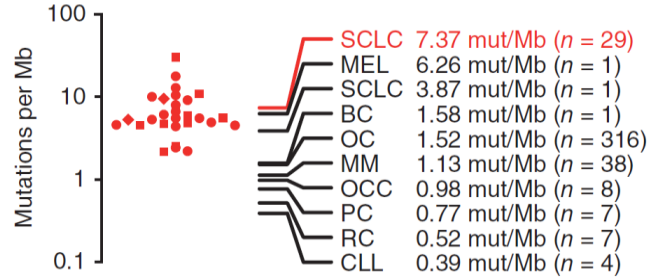
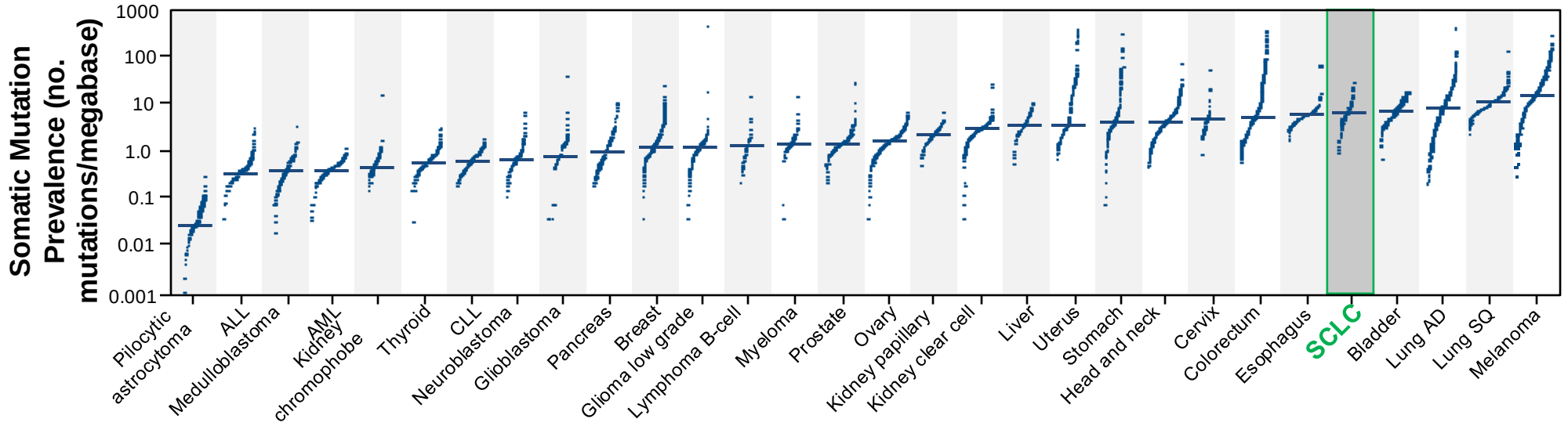
Outline

- Immunotherapy for SCLC
- Maintenance therapy for ES-SCLC
- Second-line and beyond for recurrent/refractory SCLC
- Emerging therapies in development
- Molecular sub-classification of SCLC

Immunotherapy for SCLC

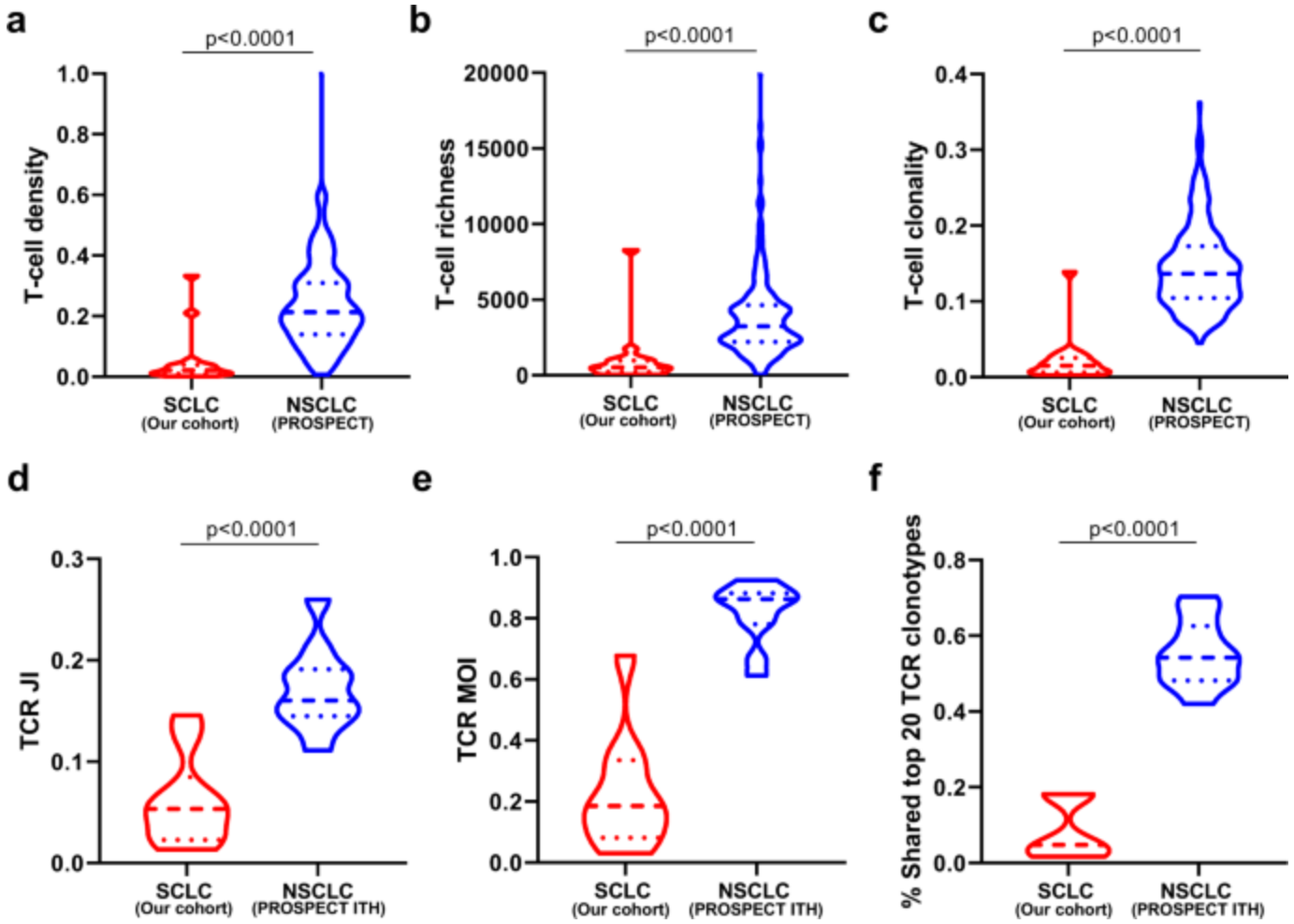
High mutational burden seen in SCLC





Peifer et al. Nat Genet 2012.
Alexandrov et al, Nature 2013.

SCLC is an Immune Cold tumor

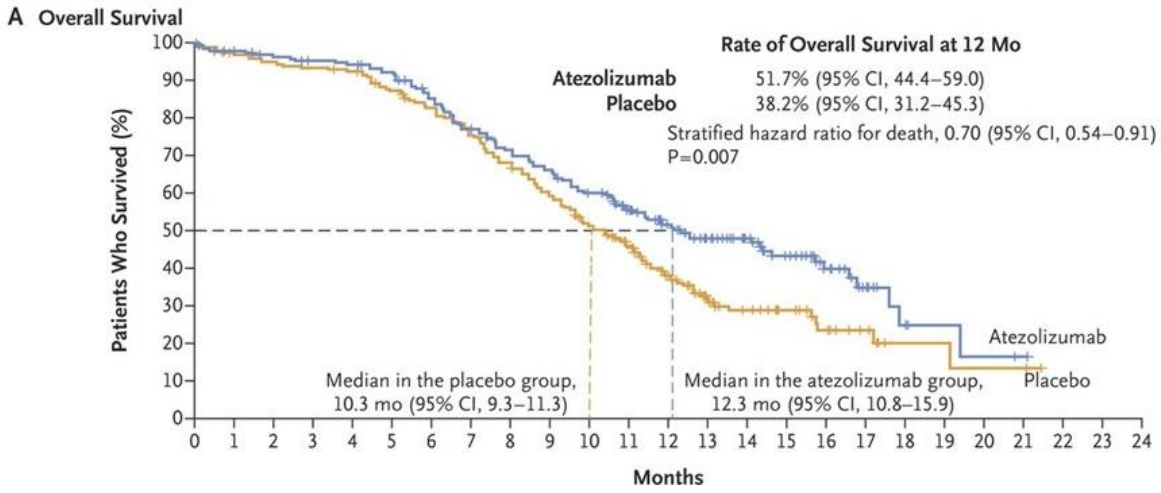


- Low T cell infiltration
- Increased immunosuppressive monocytes and macrophages

Chen et al, Nature 2021

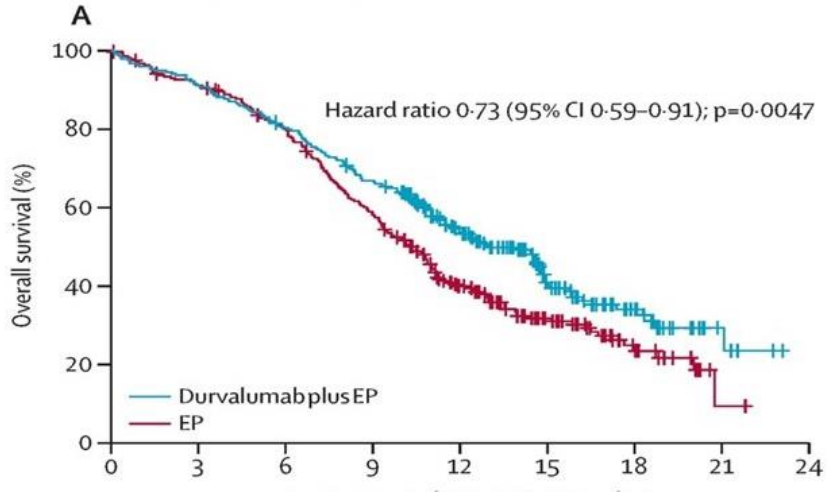
First-line PD(L)1 inhibitors for ES-SCLC

- The **IMpower133** study was a phase 3 study comparing **atezolizumab** and chemotherapy to chemotherapy alone in treatment naïve patients with SCLC.
- **OS (12.3 vs 10.3 months; HR 0.70)** was **significantly improved** with atezolizumab (p=0.007).



Horn et al., NEJM 2018.

- The **CASPIAN** study was a similarly designed phase 3 study comparing **durvalumab** and chemotherapy to chemotherapy alone.
- **OS** was also significantly improved (**13.0 vs 10.3 months**; HR 0.73; p=0.005).



Paz-Ares et al., Lancet Oncol 2019.

Slide courtesy: Sally Lau, MD

Standard of care: first-line SCLC

Extensive-stage		Limited-stage
Carboplatin/etoposide + Atezolizumab (+Atezolizumab maintenance)	Platinum/etoposide + Durvalumab (+Durvalumab maintenance)	Platinum/etoposide + Radiation Therapy
IMpower 133	*CASPIAN*	

PD(L)1 maintenance trials ongoing:

- ADRIATIC
- NRG LU005
- KEYLYNK-013

Standard of care: first-line SCLC

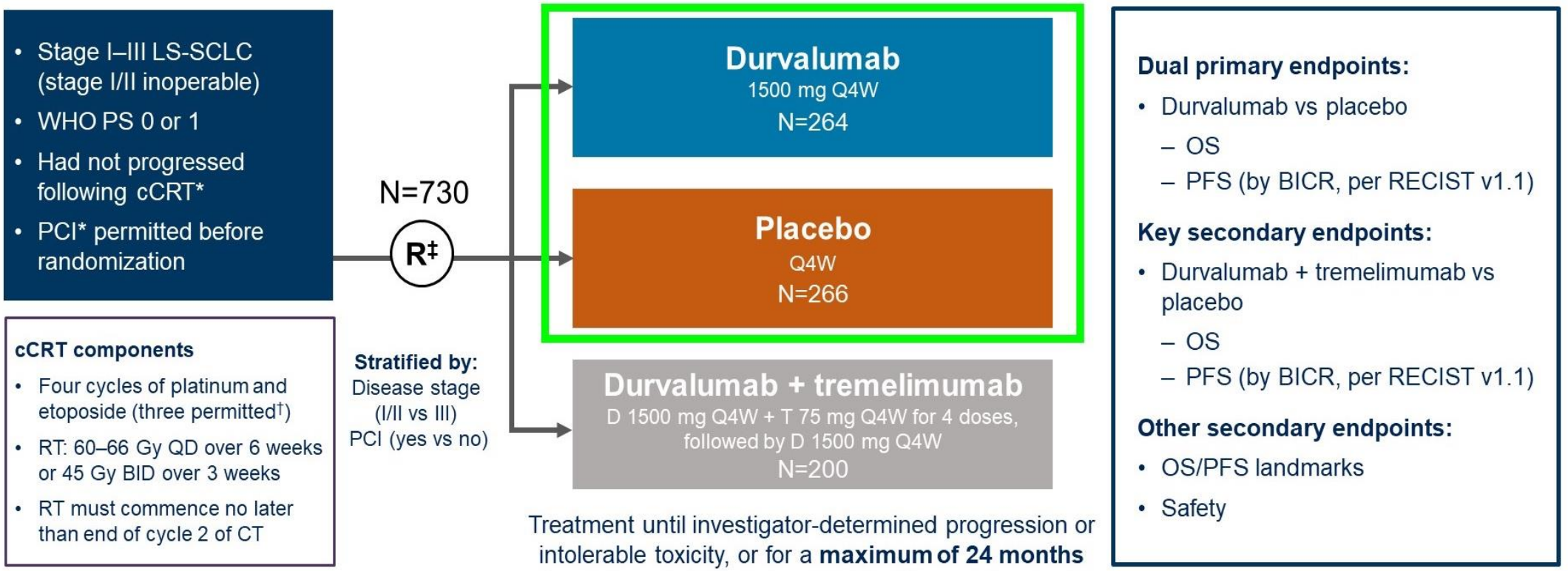
Extensive-stage	
Carboplatin/etoposide + Atezolizumab (+Atezolizumab maintenance)	Platinum/etoposide + Durvalumab (+Durvalumab maintenance)
IMpower 133	*CASPIAN*

Limited-stage
Platinum/etoposide + Radiation Therapy

PD(L)1 maintenance trials ongoing:

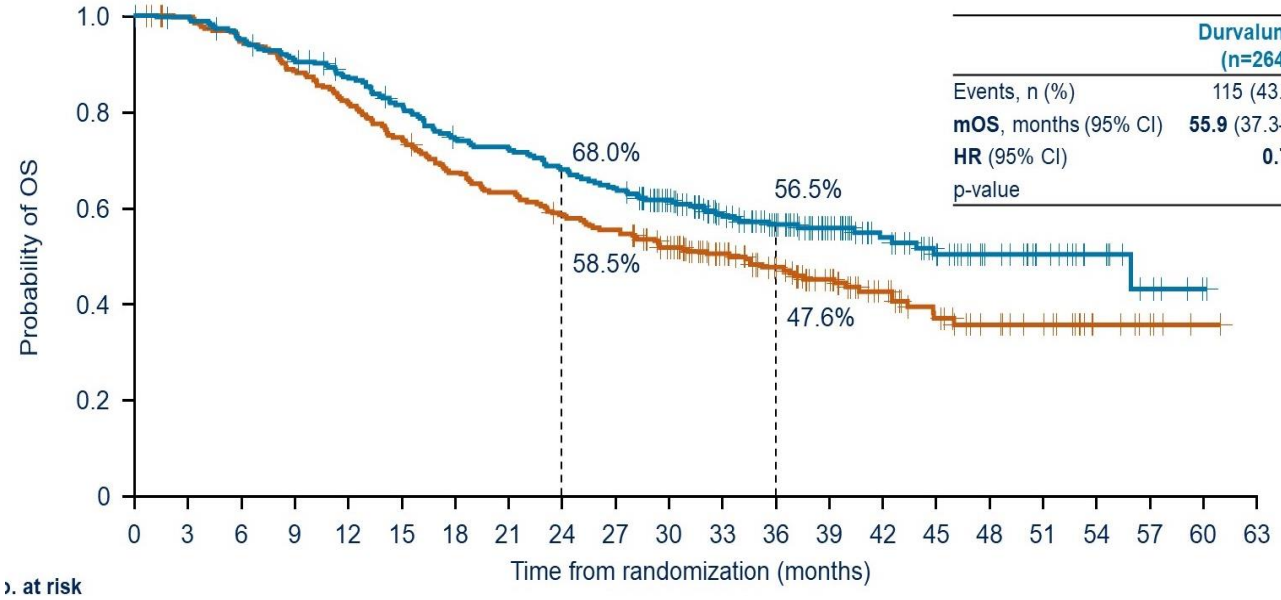
- ADRIATIC
- NRG LU005
- KEYLYNK-013

ADRIATIC: Durvalumab as consolidation treatment for LS-SCLC

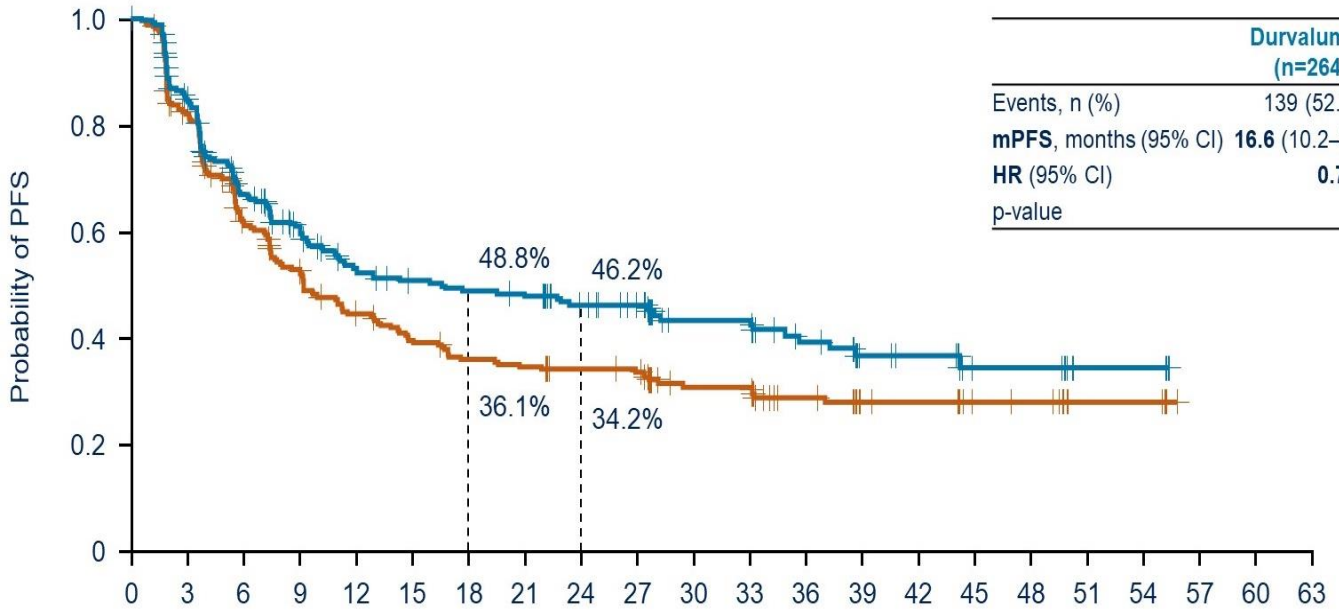


Spigel et al, ASCO 2024.

ADRIATIC



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

Spigel et al, ASCO 2024.

ADRIATIC

Pneumonitis or radiation pneumonitis (grouped terms*), n (%)	Durvalumab (n=262)	Placebo (n=265)
Any grade	100 (38.2)	80 (30.2)
Maximum grade 3/4	8 (3.1)	7 (2.6)
Leading to death	1 (0.4)	0
Leading to treatment discontinuation	23 (8.8)	8 (3.0)

- Durvalumab consolidation → significant improvement in OS and PFS
- Well tolerated and no new safety signals
- New SOC!

Spigel et al, ASCO 2024.

Maintenance therapy for ES-SCLC

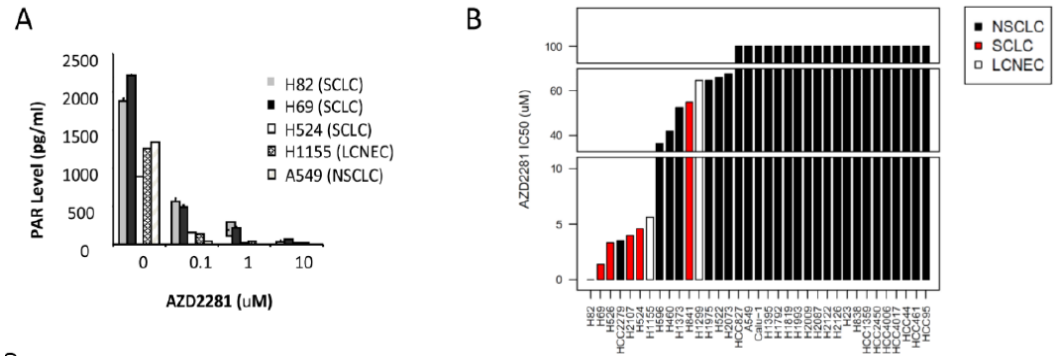
Recent maintenance trials in first-line ES-SCLC

Trial	Phase	Maintenance agent	Efficacy
CheckMate 451	III	PD-1/CTLA4	No OS benefit
SKYSCRAPER-02	III	PDL-1/anti-TIGIT	No OS and PFS benefit
SWOG S1929	II	PD1/PARPi (only in SLFN11+)	**PFS benefit, but no OS benefit**

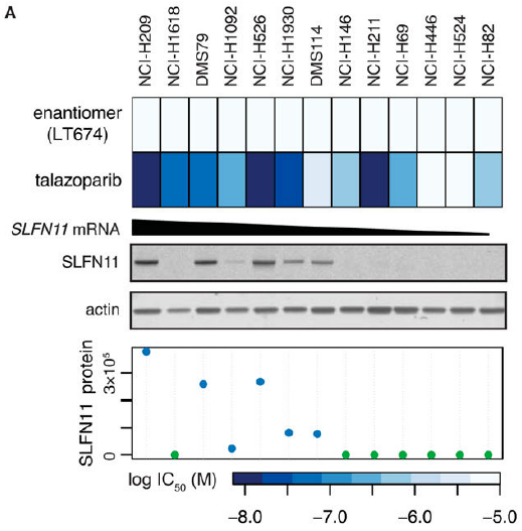
Owonikoko et al, JCO 2021
Rudin et al, JCO 2022
Karim et al, ASCO annual meeting 2023

Activity of PARP-inhibitors in SCLC

- PARP1 mRNA expression and protein levels significantly elevated in SCLC cell lines
- PARPi→ significant activity in SCLC lines
- SCLC sensitive to PARPi even though BRCA-neg/HRD-neg



SLFN11 is the dominant mechanism of response to PARPi in SCLC



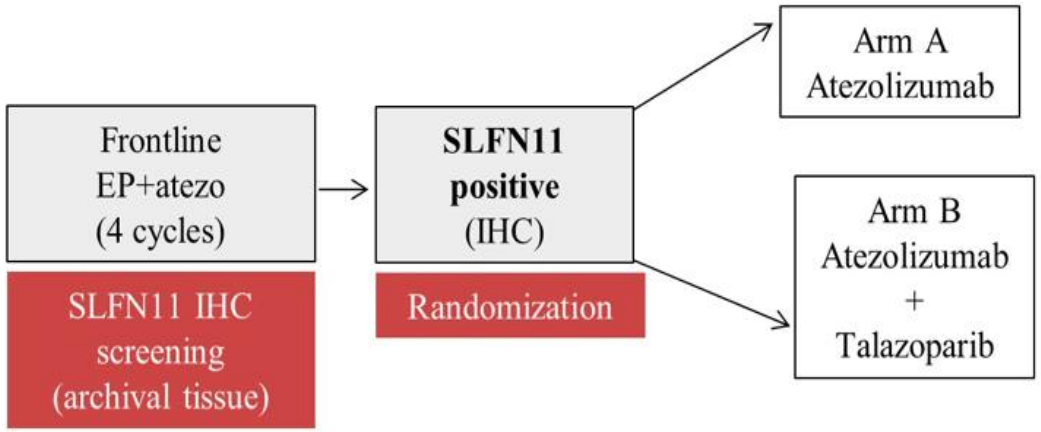
SLFN11 expressed in about 50% of SCLC as measured by IHC

Zoppoli et al, Proc Natl Acad Sci USA, 2012
Zhang et al, Br J Cancer, 2022
Byers et al, Cancer Discovery 2012
Lok et al, Clinical Cancer res 2017

SWOG1929: Phase 2 EP+Atezo followed by Atezo vs Atezo+Talazoparib in **SLFN11-Positive** ES-SCLC

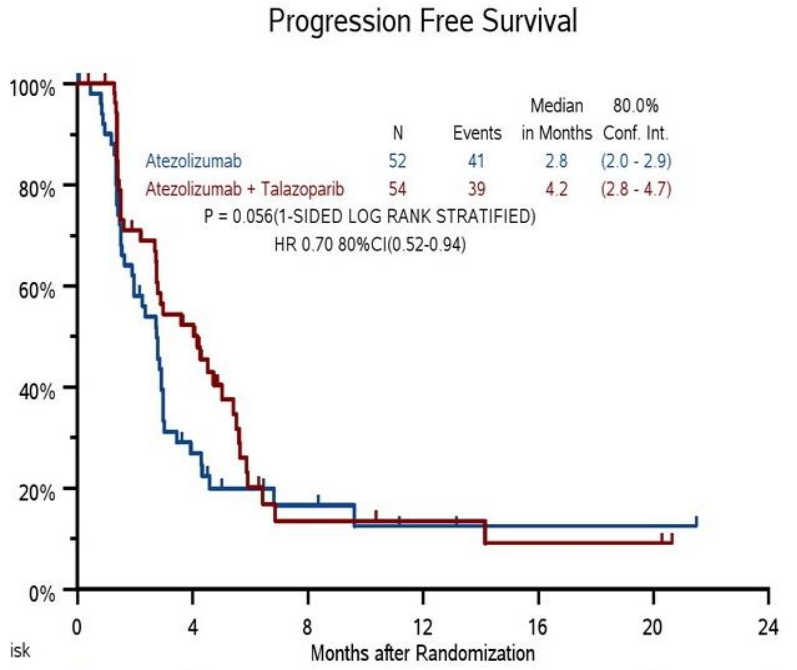
PIs: Karim, Reckcamp

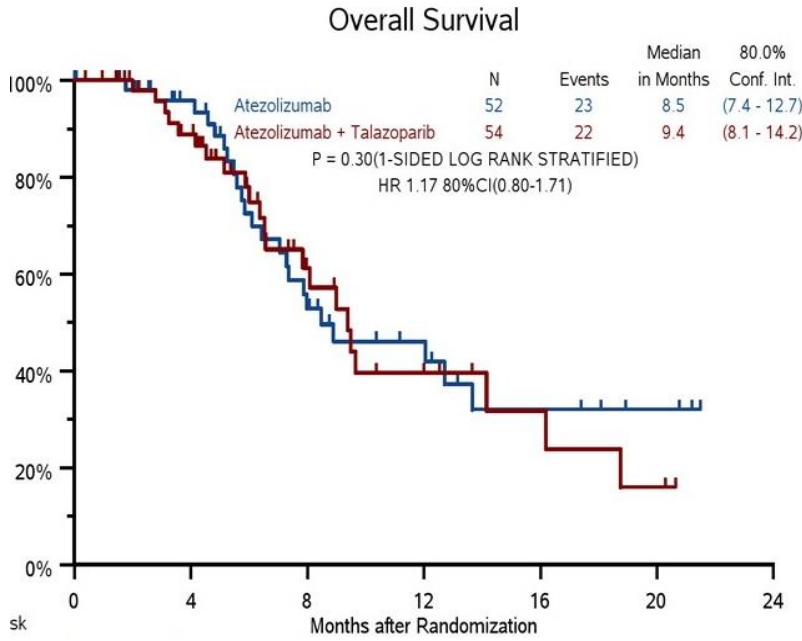
Translational PIs: Gay, Byers



Primary Objective: PFS

Secondary: OS, ORR, AE



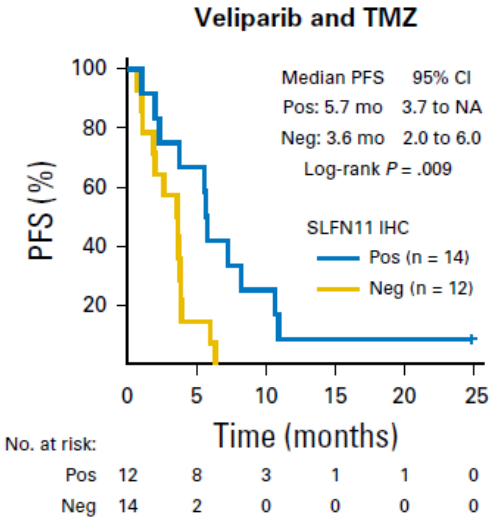


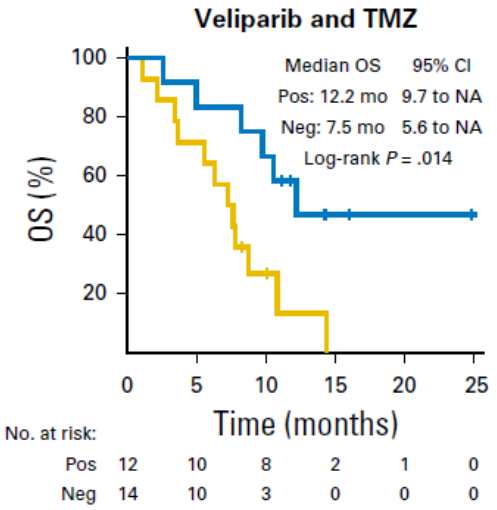
Karim et al, ASCO 2023

PARPi + Temozolomide in 2nd line and beyond

Trial	Agents	ORR
Pietanza et al, J Clin Oncol. 2018	TMZ + veliparib	39%
Farago et al, Cancer Discov. 2019	Low-dose TMZ + olaparib	41.7%
Goldman et al, ASCO 2022	Low-dose TMZ + talazoparib	39.3%

SLFN11 IHC predicts improved survival



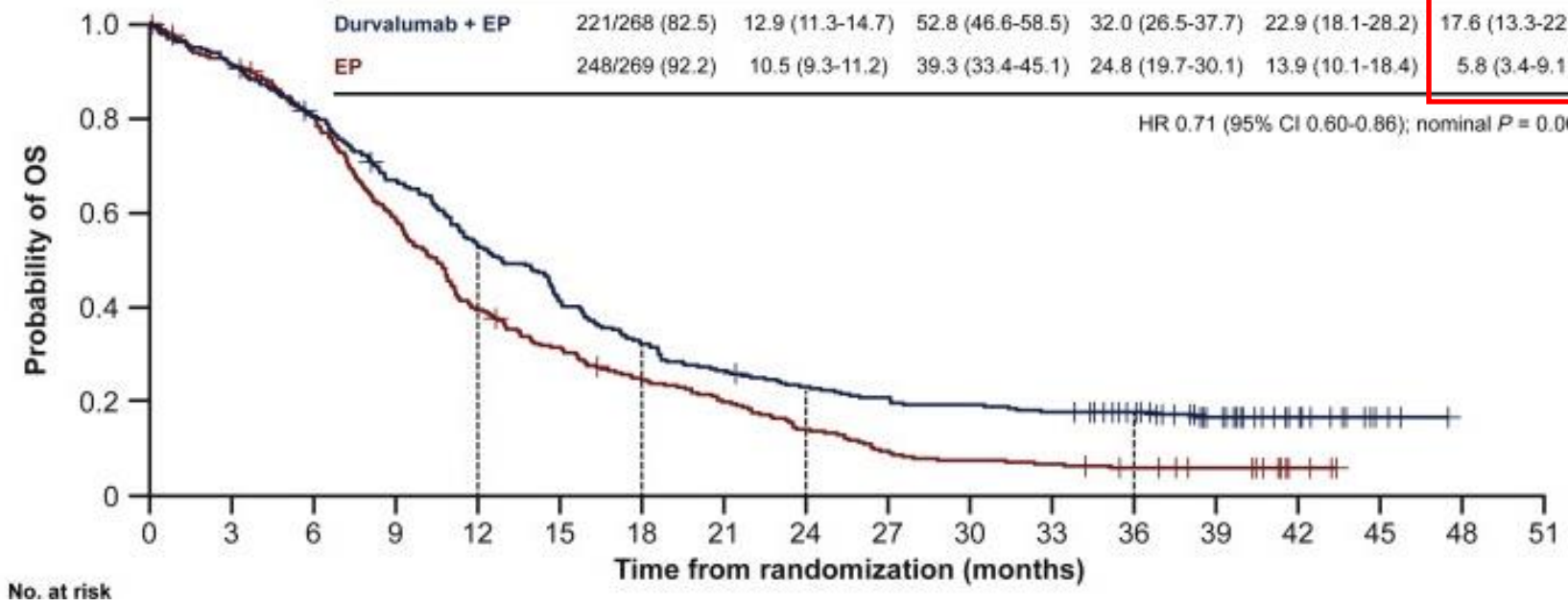


Second-line and beyond for recurrent/refractory SCLC

Updated survival analysis from CASPIAN

	Events/ patients, *n* (%)	Median OS (95% CI), months	12-month OS rate (95% CI), %	18-month OS rate (95% CI), %	24-month OS rate (95% CI), %	36-month OS rate (95% CI), %
Durvalumab + EP	221/268 (82.5)	12.9 (11.3-14.7)	52.8 (46.6-58.5)	32.0 (26.5-37.7)	22.9 (18.1-28.2)	17.6 (13.3-22.4)
EP	248/269 (92.2)	10.5 (9.3-11.2)	39.3 (33.4-45.1)	24.8 (19.7-30.1)	13.9 (10.1-18.4)	5.8 (3.4-9.1)

HR 0.71 (95% CI 0.60-0.86); nominal *P* = 0.0003



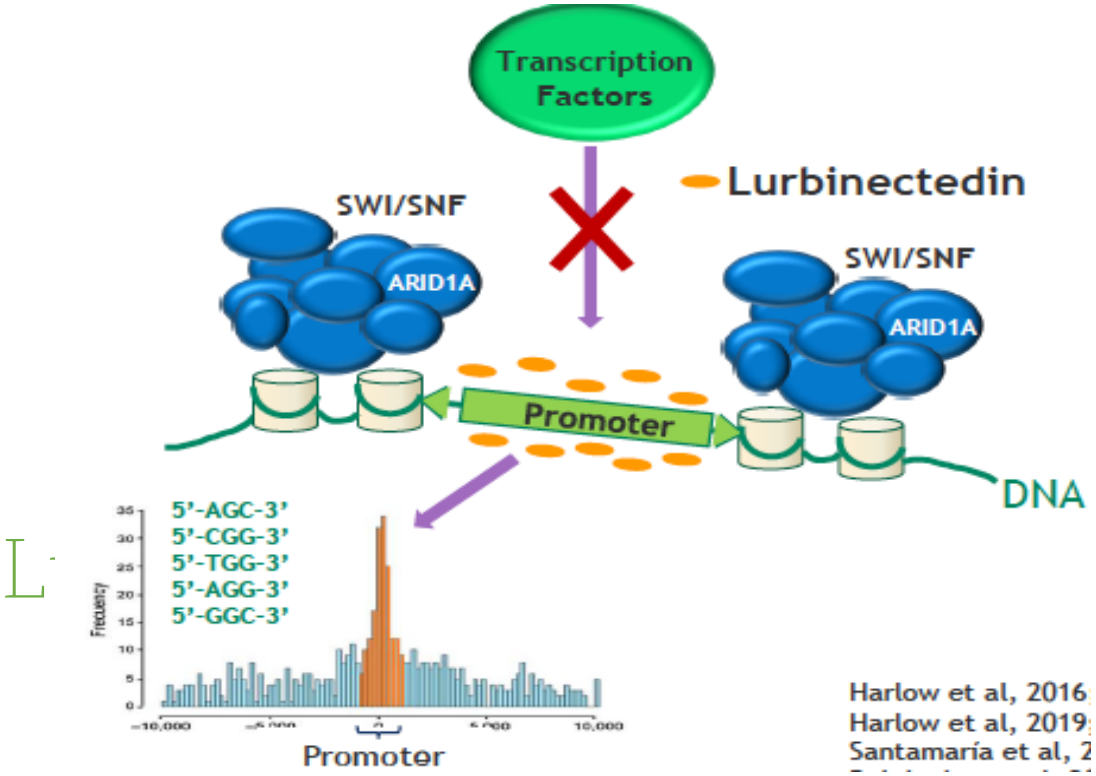
Paz-Ares et al, ESMO Open 2022

Approved for 2L+ SCLC

Drug	Median PFS	Approval
Topotecan	13.3 weeks	1998
Lurbinectedin	3.5 months	2020
Tarlatamab-dlle	4.9 months	2024

von Pawel et al, JCO 1999.
Trigo et al, Lancet Oncol 2020.

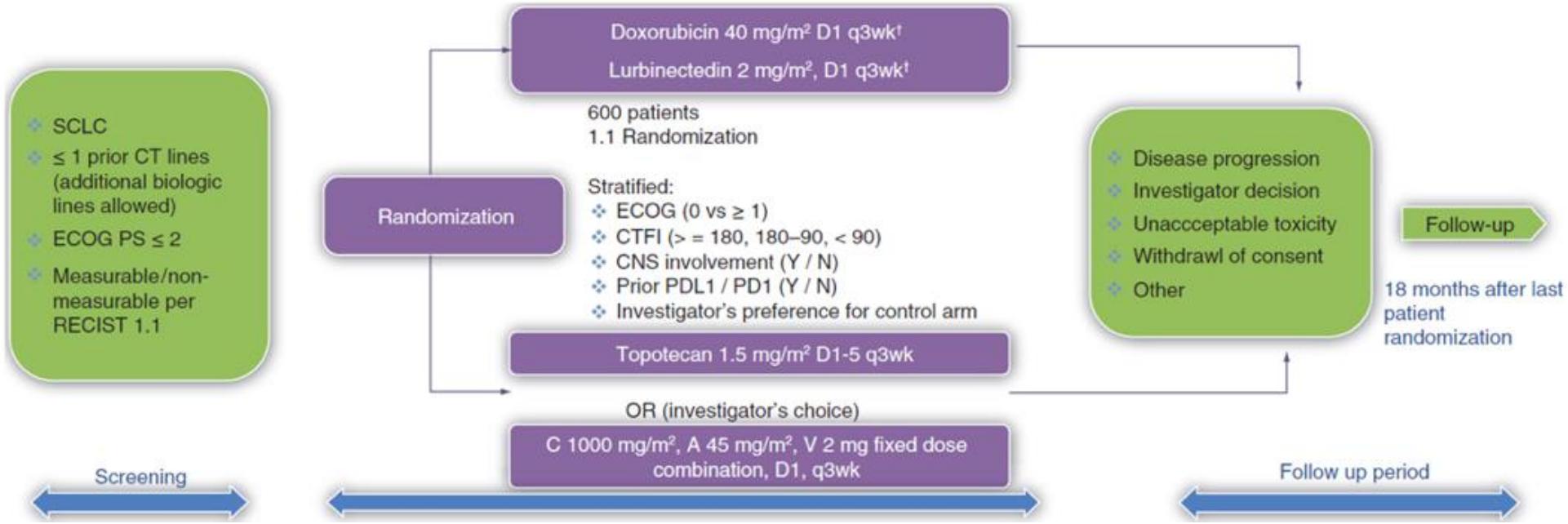
Lurbinectedin



- Selective inhibitor of oncogenic transcription
- In phase 2 basket trial, ORR 35.2%, DCR 68.6% (SCLC)

Harlow et al, Cancer Res, 2016
Harlow et al, Clinical Cancer Res 2019

ATLANTIS trial



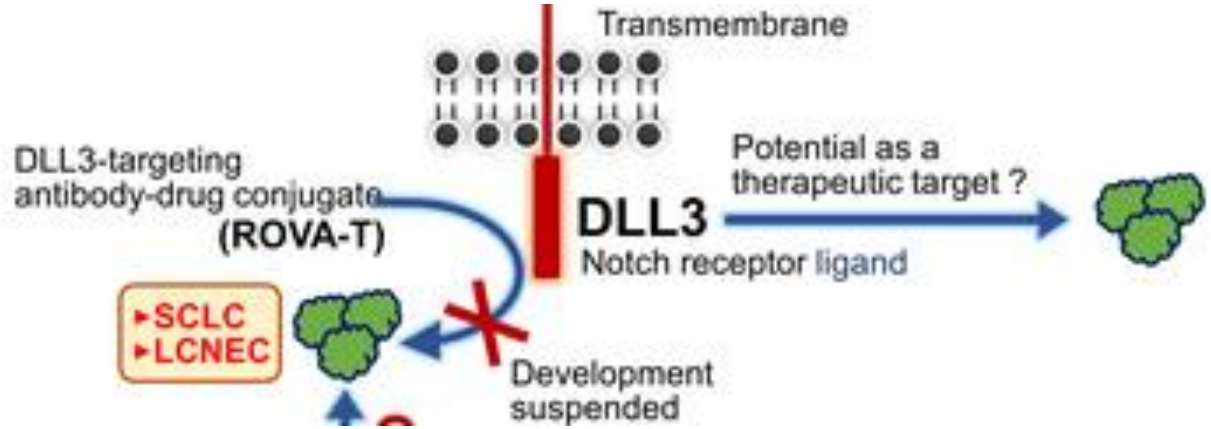
Did not meet primary endpoint of OS

LAGOON trial ongoing: phase III trial of lurbinectedin +/- irinotecan vs investigator's choice

Laz-pres et al, WCLC 2021

DLL3 (Delta Like Protein-3)

- Inhibitory ligand of Notch signaling pathway
- Expressed as cell surface marker
- Minimal expression in normal cells
- Related to transcription factor ASCL1
- Key regulator of neuroendocrine differentiation

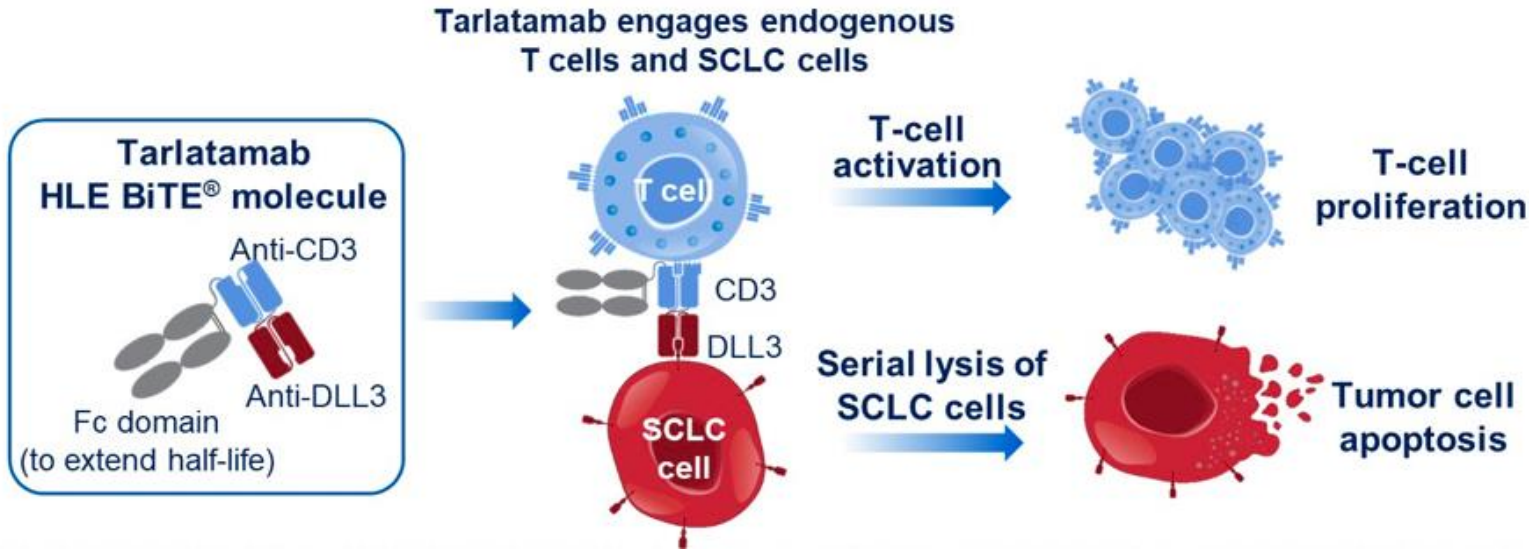


DLL3 ADC Rovalpituzumab Tesirine (Rova-T) program discontinued in 2019: promising results in phase 1 but no clinical benefit and increased toxicity in phase III trials (TAHOE, MERU)

Leonetti et al, Cell Oncol 2019
Matsuo et al, Cancer Science 2021

DLL3 BiTE: Tarlatamab

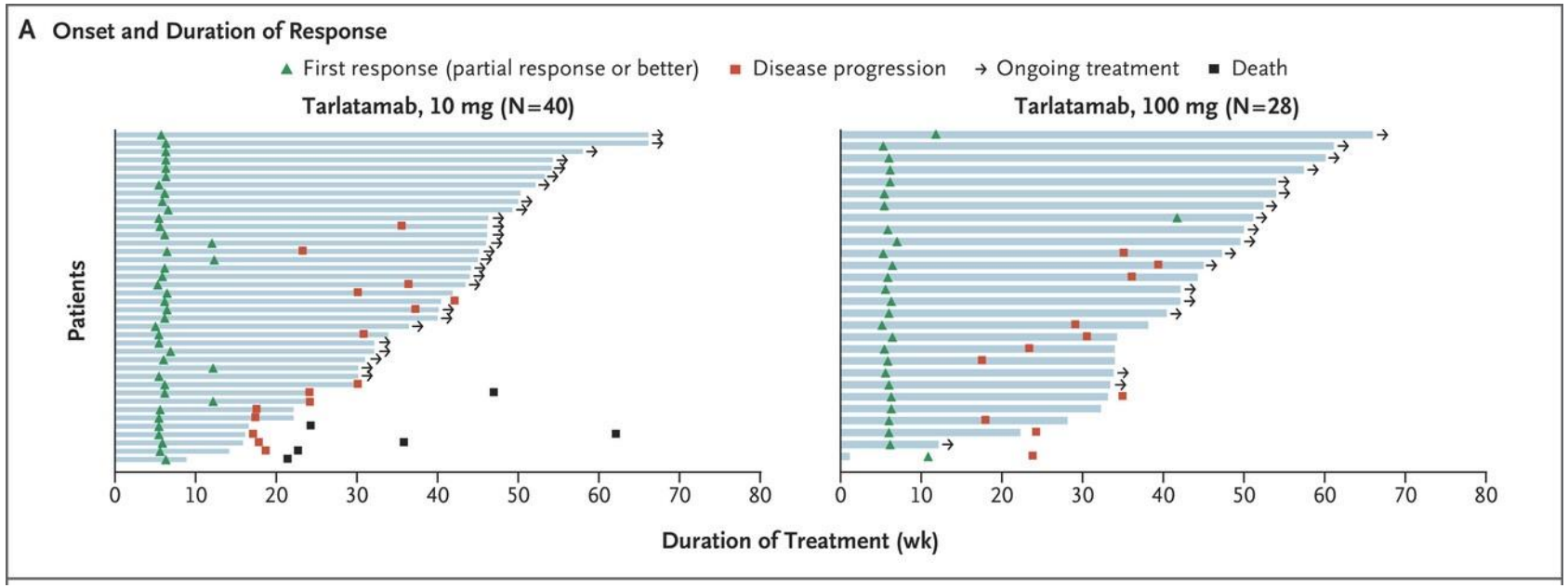
Tarlatamab-dlle (AMG 757): half-life extended Bispecific T-cell engager (BITE) targeting DLL3 and CD3



Einsele et al, Cancer 2020
Stieglmaier et al, Expert Opin Biol Ther, 2015

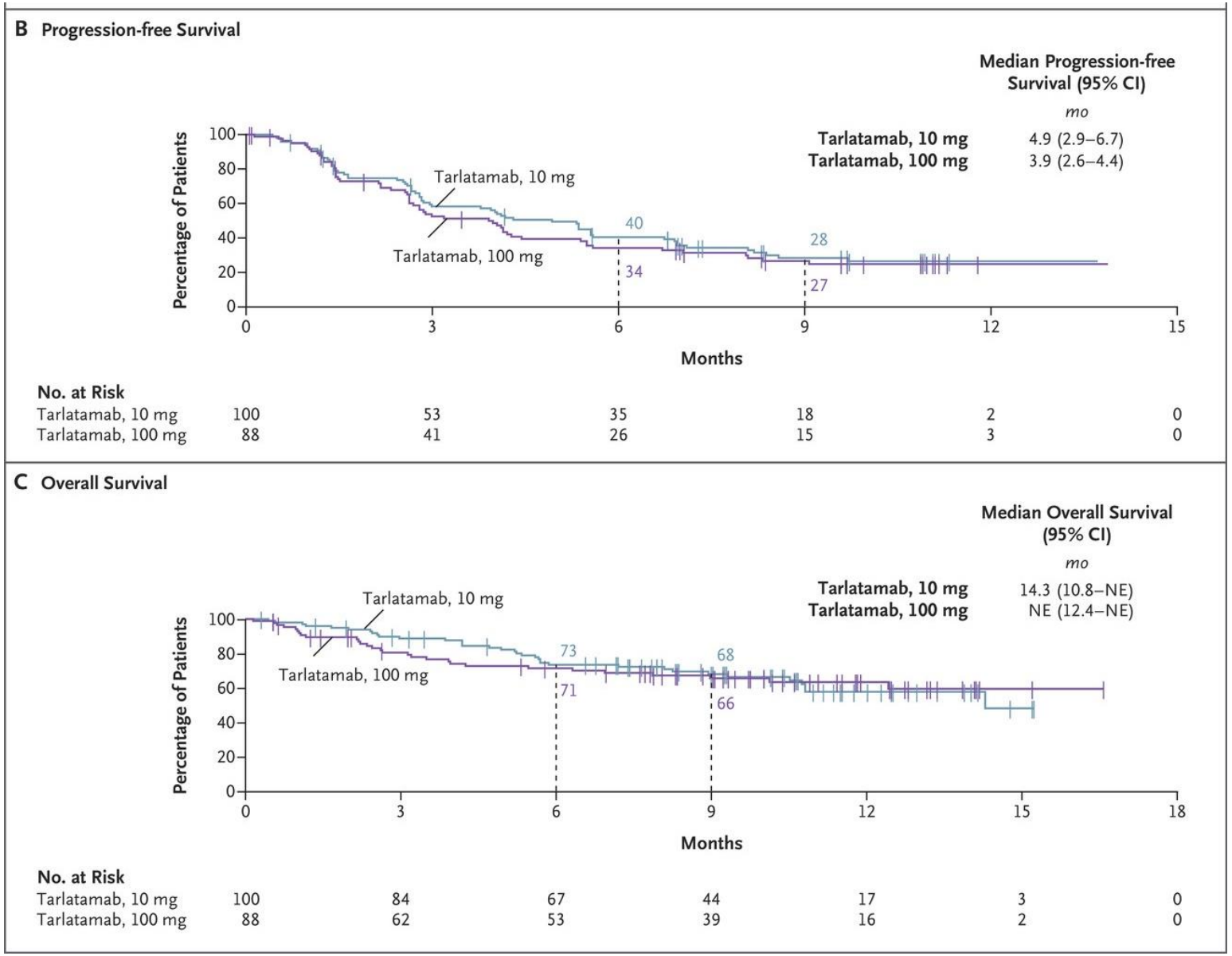
DeLLphi-301

- Phase II trial in pre-treated SCLC (10 mg or 100 mg iv every 2 weeks)
- N=220
- Primary end point: ORR
- **ORR:** 40% in 10 mg group



Ahn et al, NEJM 2023

DeLLphi-301



- **mPFS:** 4.9 months
- **mDOR:** 9.7 months

FDA approved in May 2024 at 10 mg dose

Ahn et al, NEJM 2023

Cytokine-release syndrome

- 51% (10 mg) and 61% (100 mg)
- Most at one of the first two doses (given on days 1 and 8 of cycle 1)
- Grade 3 in 1% (10 mg) and 6% (100 mg)
- Common symptoms: fever, hypoxia and hypotension

Immune effector cell–associated neurotoxicity syndrome (ICANS)

- 8% (10 mg) and 28% (100 mg)
- Most during cycle 1, with a median time to onset of 5 days
- Common symptoms: confusion, impaired attention, tremor, and motor findings, weakness

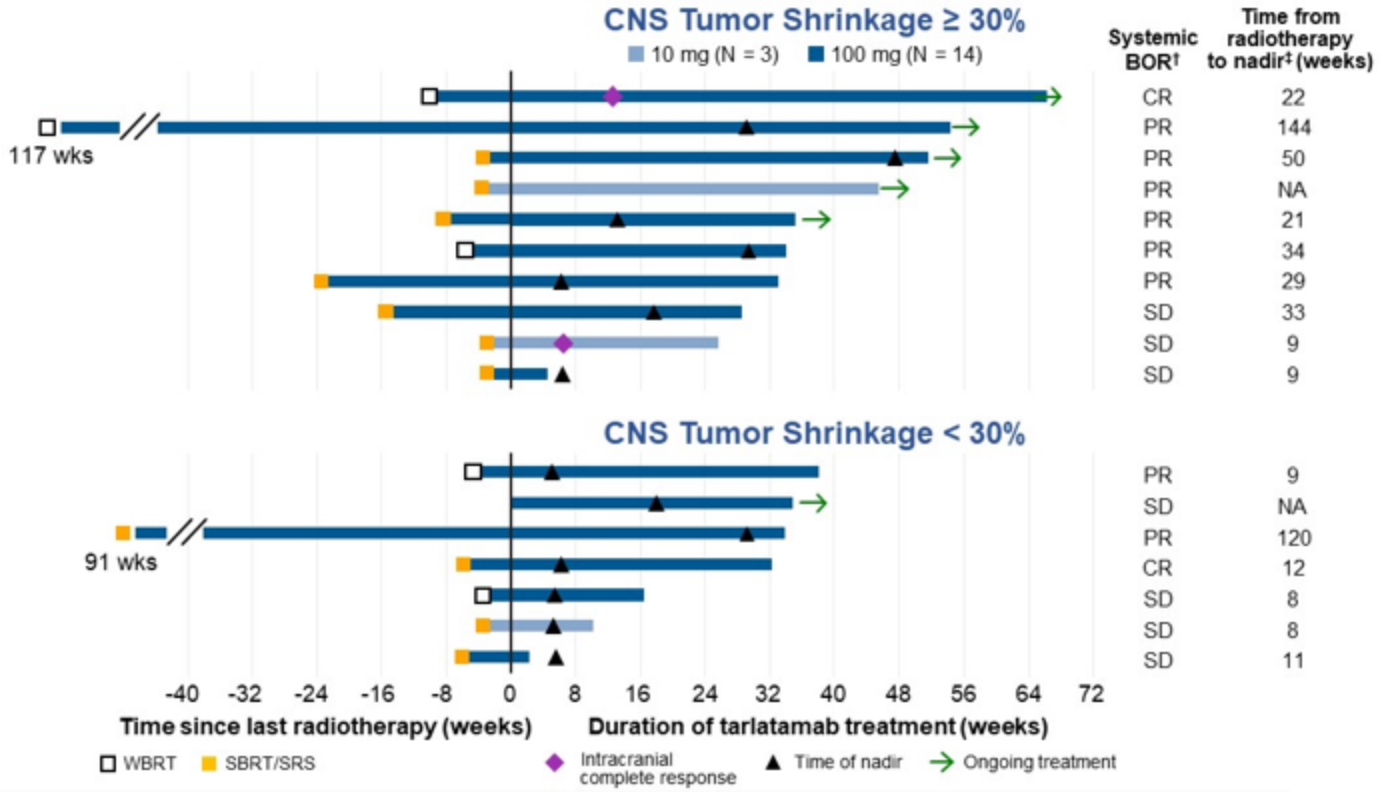
Treatment-discontinuation rate due to adverse events: 3%

Ahn et al, NEJM 2023

DeLLphi-301: Intracranial activity

Tarlatamab 10 mg (n = 3) or 100 mg (n = 14) Q2W with baseline CNS lesion ≥ 10 mm

- **mRANO BM§ analyses (N = 17)**
  - CNS tumor shrinkage ≥ 30% in 10 of 17 patients (59%)
  - Intracranial disease control in 94% (16 of 17) patients (95% CI, 71.3–99.9)
  - Median duration of intracranial disease control was NE (range, 2.6–13.9+ months)
  - CNS disease progression per modified RANO-BM occurred in 3 of 17 patients (18%)



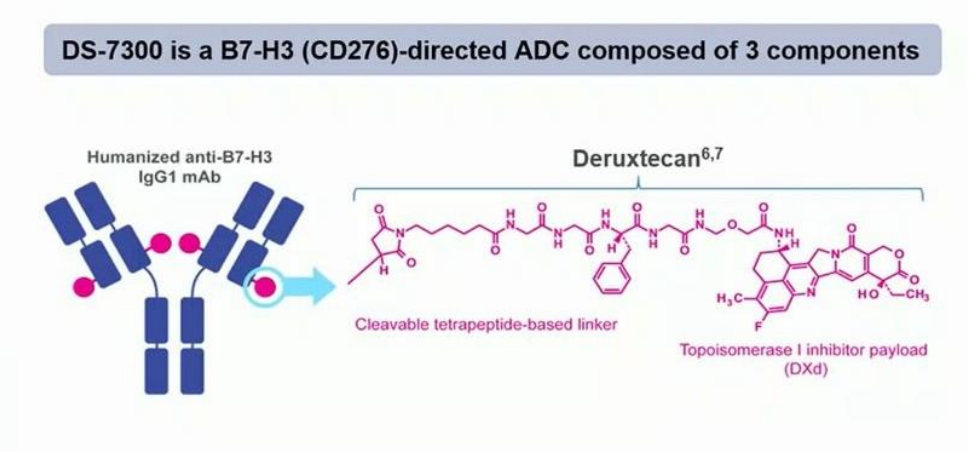
Dingemans et al, ASCO 2024

Emerging therapies for SCLC

Emerging biomarker driven therapies for second-line SCLC

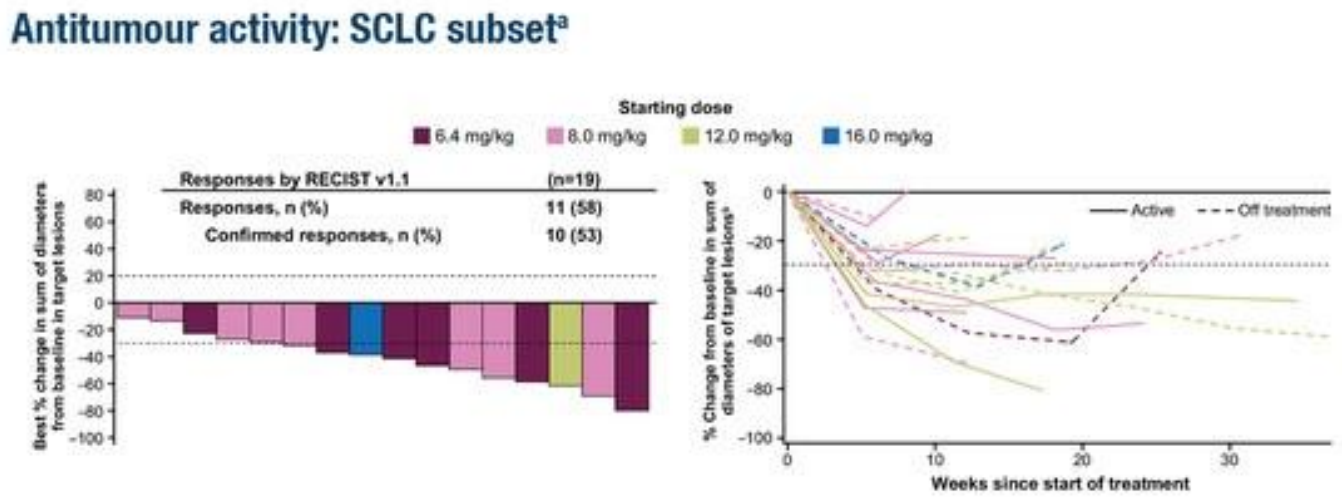
	Targeted	MAb	ADC	BiTE	TriTE	CAR-T
B7-H3			I-DXd, HS-20093			
DLL3			Rova-T	Tarlatamab, BI764532	HPN328	AMG 119, LB102
Fucosyl-GM1		BMS-986012				
SEZ6			ABBV-011, ABBV-706			
SLFN11	PARPi, ATRi					

B7-H3: member of the B7 superfamily, highly expressed in various solid tumors, but limited expression in normal tissues.



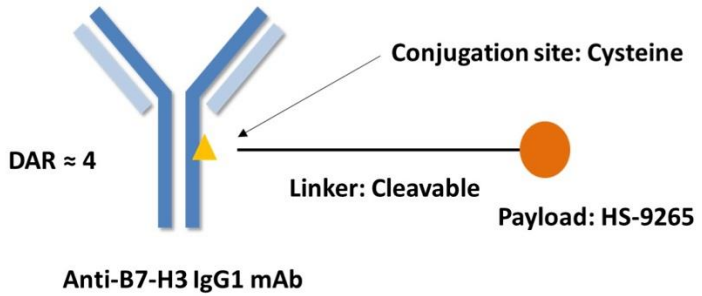
DS-7300 or Ifinatamab deruxtecan (I-DXd)

- phase I/II dose-finding study of DS-7300 (4.8 to 16.0 mg/kg)
- 147 patients with advanced solid tumors unselected for B7-H3 expression
- In 19 patients with SCLC, 58% ORR, with a median duration of response of 5.5 months.



Doi et al, ASCO 2023

B7-H3



HS-20093 is a B7-H3-targeted antibody-drug conjugate (payload: exatecan derivative)

HS-20093

- ARTEMIS-001: phase I dose-finding study of HS-20093 (1 to 16.0 mg/kg)
- 56 patients with ES-SCLC treated with doses at 8.0 mg/kg and 10.0 mg/kg randomly in dose expansion
- Responses were observed regardless of B7-H3 expression.
- Toxicity: mainly hematological

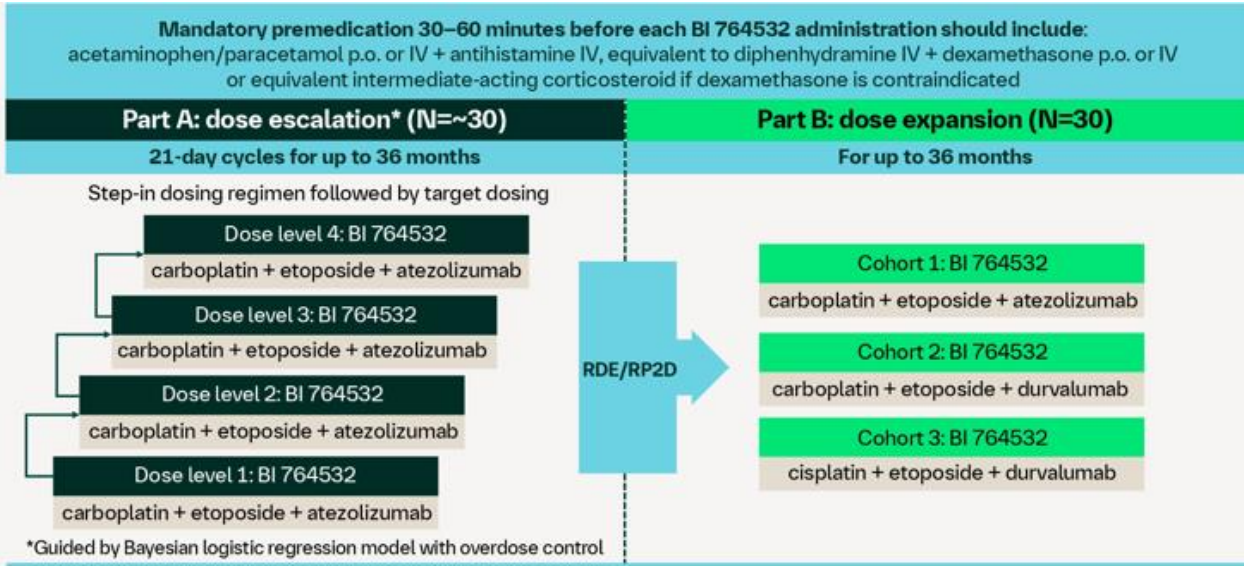
	8.0 mg/kg Q3W (n=31)	10.0 mg/kg Q3W (n=21)
ORR, n (%), (95% CI)	18 (58.1%)* (39.1, 75.5)	12 (57.1%)# (34.0, 78.2)
DCR, n (%), (95% CI)	25 (80.6%) (62.5, 92.5)	20 (95.2%) (76.2, 99.9)
Median DOR, month, (95% CI)	4.3 (3.3, NA)	NA (3.1, NA)
Median PFS, month, (95% CI)	5.6 (3.4, NA)	NA (4.4, NA)
Median follow-up time, month, (95% CI)	4.8 (3.6, 5.6)	4.9 (4.1, 5.6)

Wang et al, ASCO 2023
Wang et al, ASCO 2024

DLL3: BiTE

BI 764532, DLL3/CD3 IgG-like T-cell engager

- Phase I dose-escalation trial in SCLC, NEC or small cell carcinoma of other origin—>26% ORR in SCLC
- CRS 58% (≥G3 2%)
- DAREON-8, a Phase I open-label dose escalation/expansion trial of BI 764532 plus SoC for 1L ES-SCLC (ongoing)



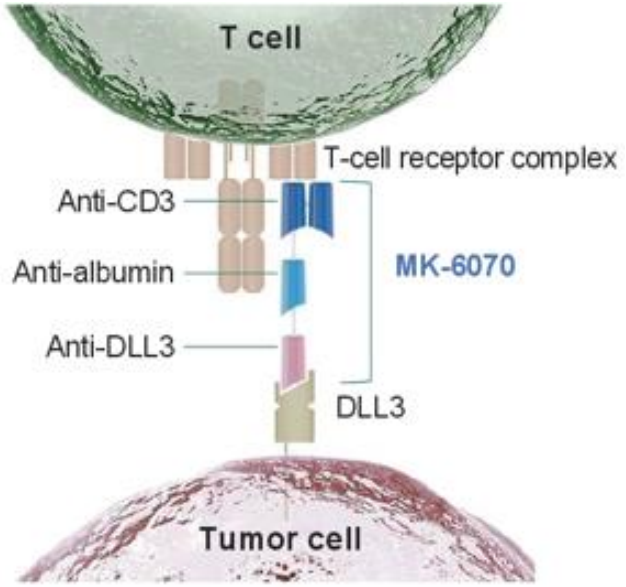
Peters et al, ASCO 2024.
Wermke et al, ASCO 2023
Wermke et al, Future Oncol 2022.

DLL3: TriTE

HPN328

→ DLL3-targeting T cell engager using TriTAC platform

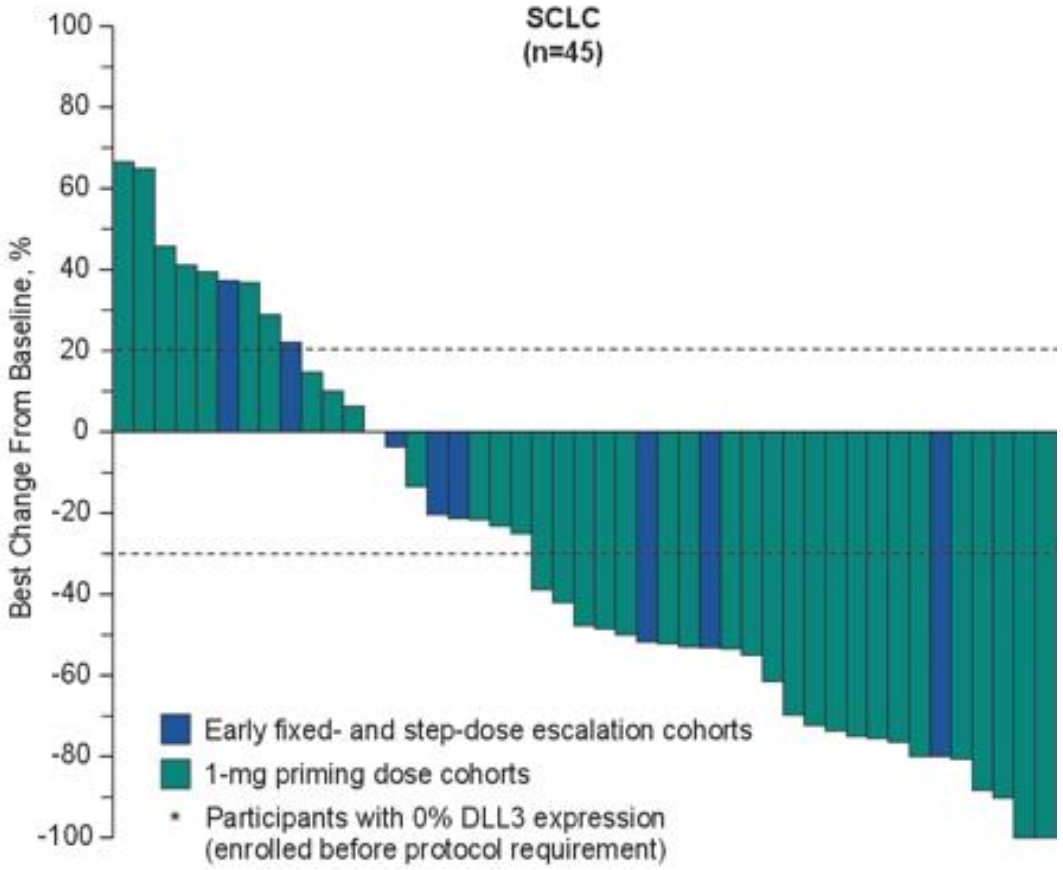
→Redirects T cells to kill DLL3 expressing cancer cells



NCT04471727 is a phase I study in SCLC & NEC.

26% grade 3 TrAE; CRS 63% (grade 3 ≥3%)

SCLC (n=28): ORR 39%, DCR 71%

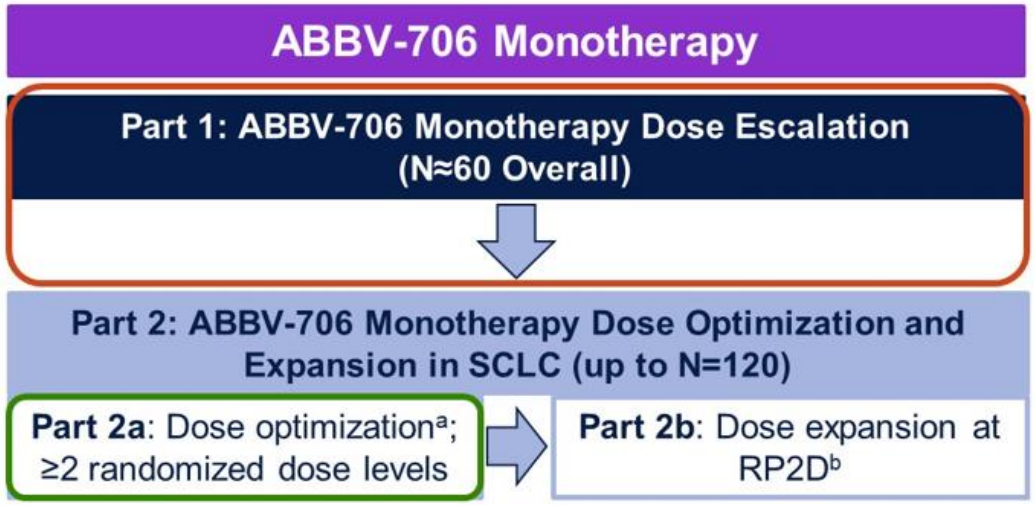


Beltran et al, ASCO 2024.

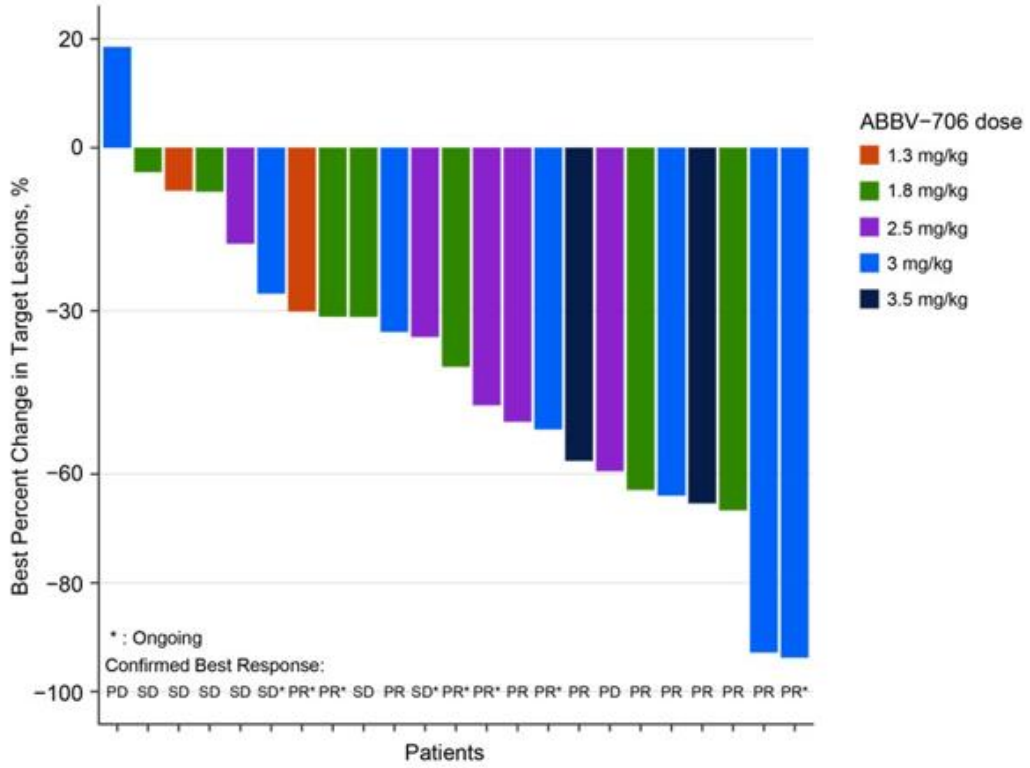
Seizure-related Homolog Protein 6 (SEZ6)

ABBV-706 is an ADC targeting SEZ6 with a Topoisomerase-1 inhibitor payload

SEZ6 expressed >80% SCLC



- Fatigue (66%) and anemia (60%) most common AEs
- ORR 61% in R/R SCLC (n=23)



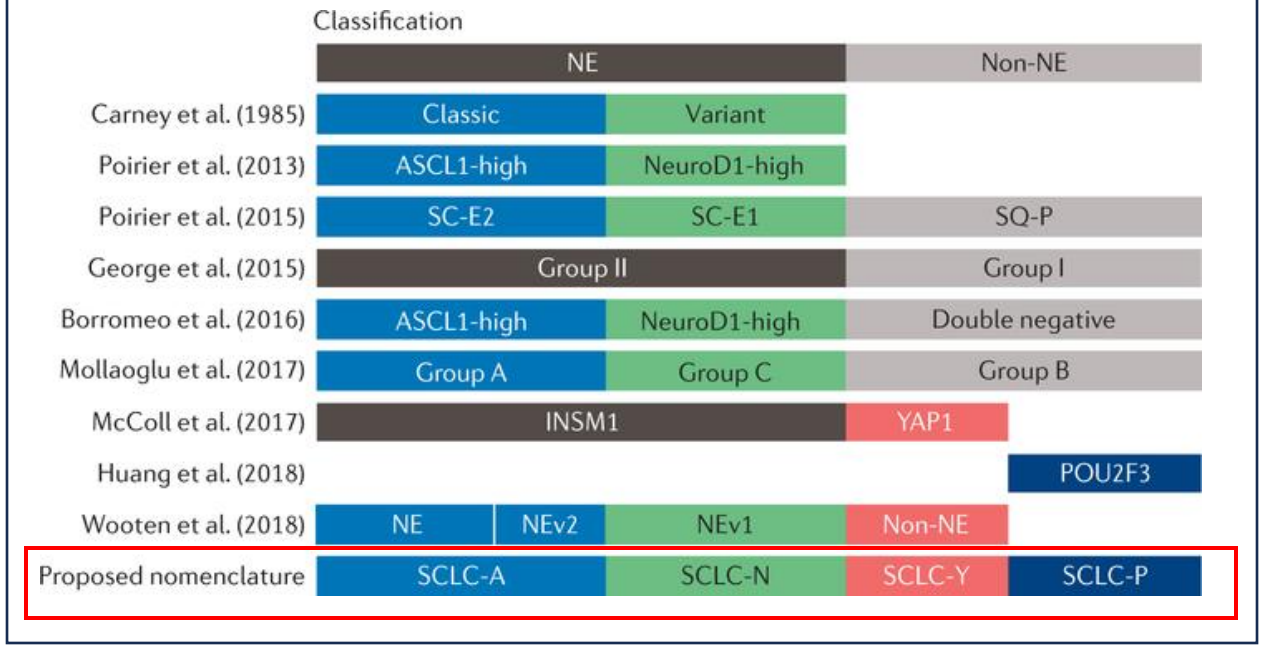
Chandana et al, ASCO 2024

Molecular subclassification of SCLC

SCLC subclassification

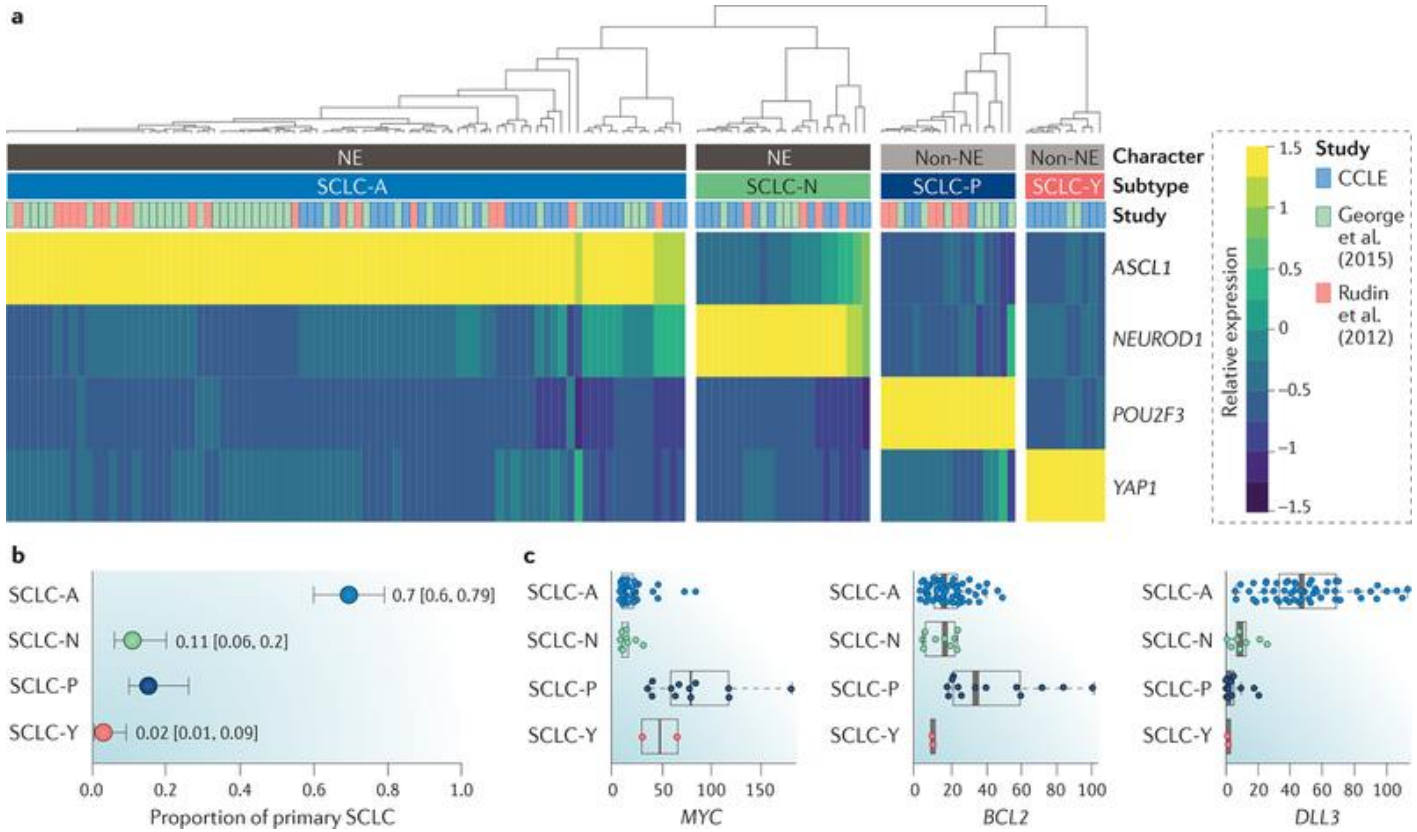
- SCLC genomic profiles are quite homogeneous (universal loss of the tumor suppressor genes TP53 and RB1)
- Epigenetic & gene expression studies report molecular diversity among SCLC cell lines and primary tumors.
- Differential expression of four key transcription regulators: ASCL1, NEUROD1, YAP1 and POU2F3 defines SCLC subtypes

Different nomenclature describing SCLC subtypes→ Key studies for SCLC subtypes based on differential gene expression



Rudin et al, Nat Rev Cancer 2019

Molecular subtypes of SCLC defined by expression of key transcription regulators

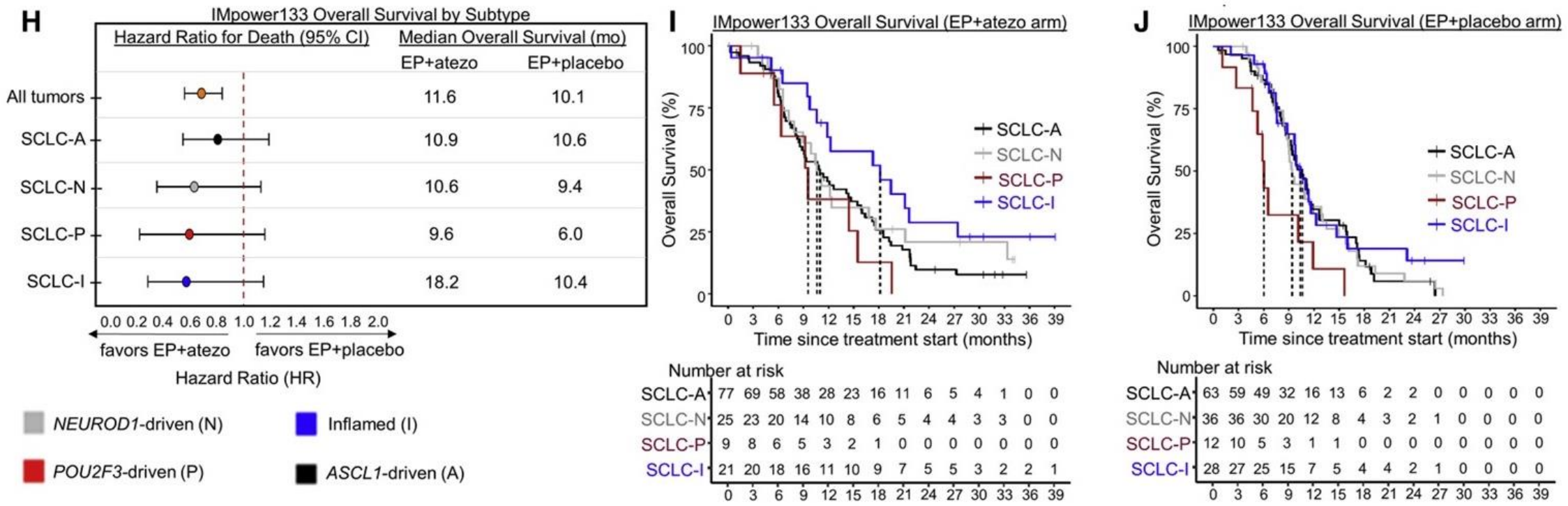


Hierarchical clustering of relative gene expression of four key transcription regulators:

- ❑ ASCL1 (SCLC-A)
- ❑ NEUROD1 (SCLC-N)
- ❑ POU2F3 (SCLC-P)
- ❑ YAP1 (SCLC-Y)

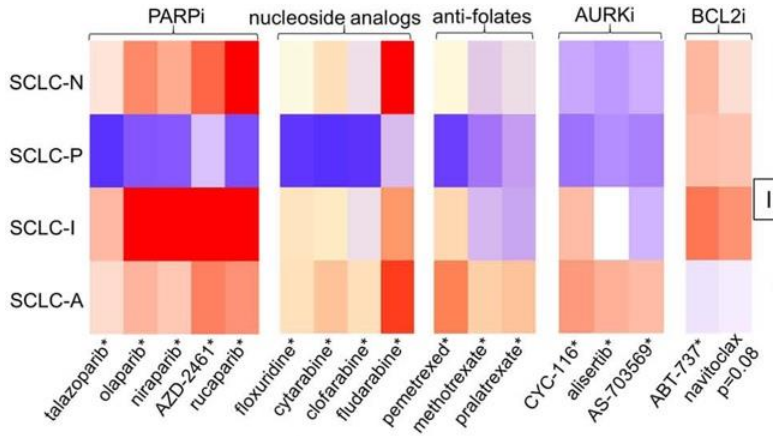
Rudin et al, Nat Rev Cancer 2019

SCLC-I associated with greater benefit from immunotherapy

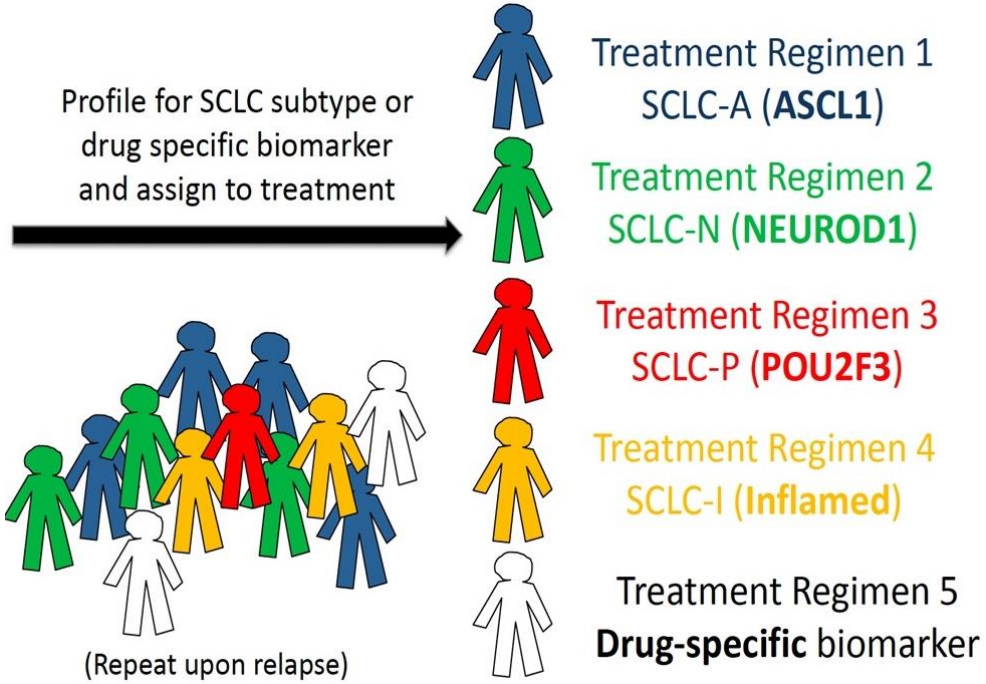


Gay et al, Cancer Cell 2021

Personalizing SCLC treatment: Trials



	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



Dr Lauren Byers, TTLC 2023

Conclusions

- Checkpoint inhibitors with chemotherapy SOC for 1st line ES-SCLC, and likely for LS-SCLC as consolidation therapy after chemoradiation
- Further biomarker-based therapies as monotherapy or in combination for 2nd line and beyond being explored
- Future research to better understand how to sequence and/or combine novel therapies in development

Thank you!