Advances in Small Cell Lung Cancer & Mesothelioma/Thymic Malignancies

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Small Cell Lung Cancer

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*	

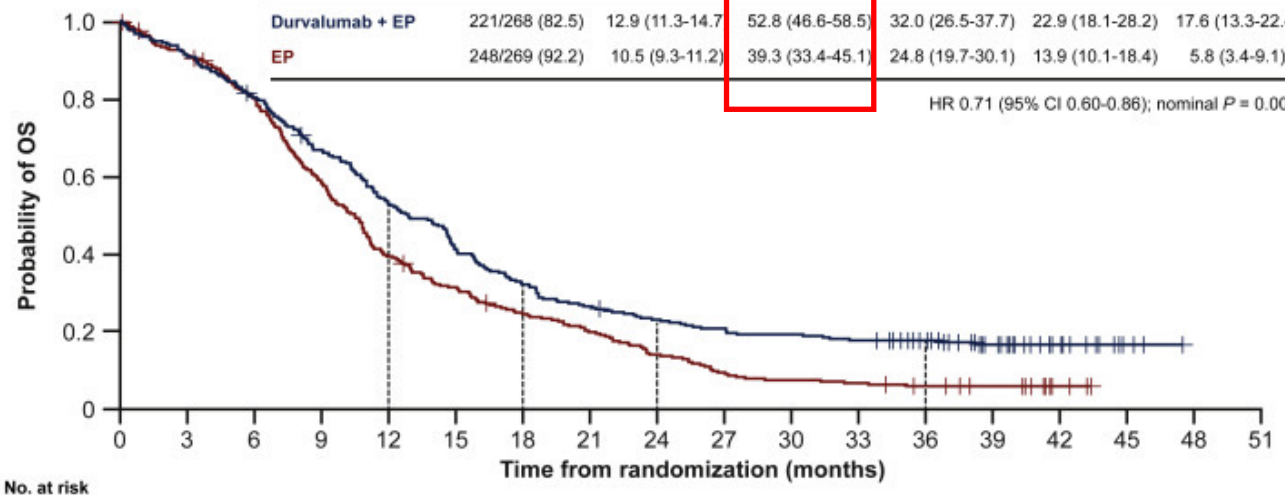
PD(L)1 maintenance trials ongoing:

- NRG LU005
- ADRIATIC
- KEYLYNK-013

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



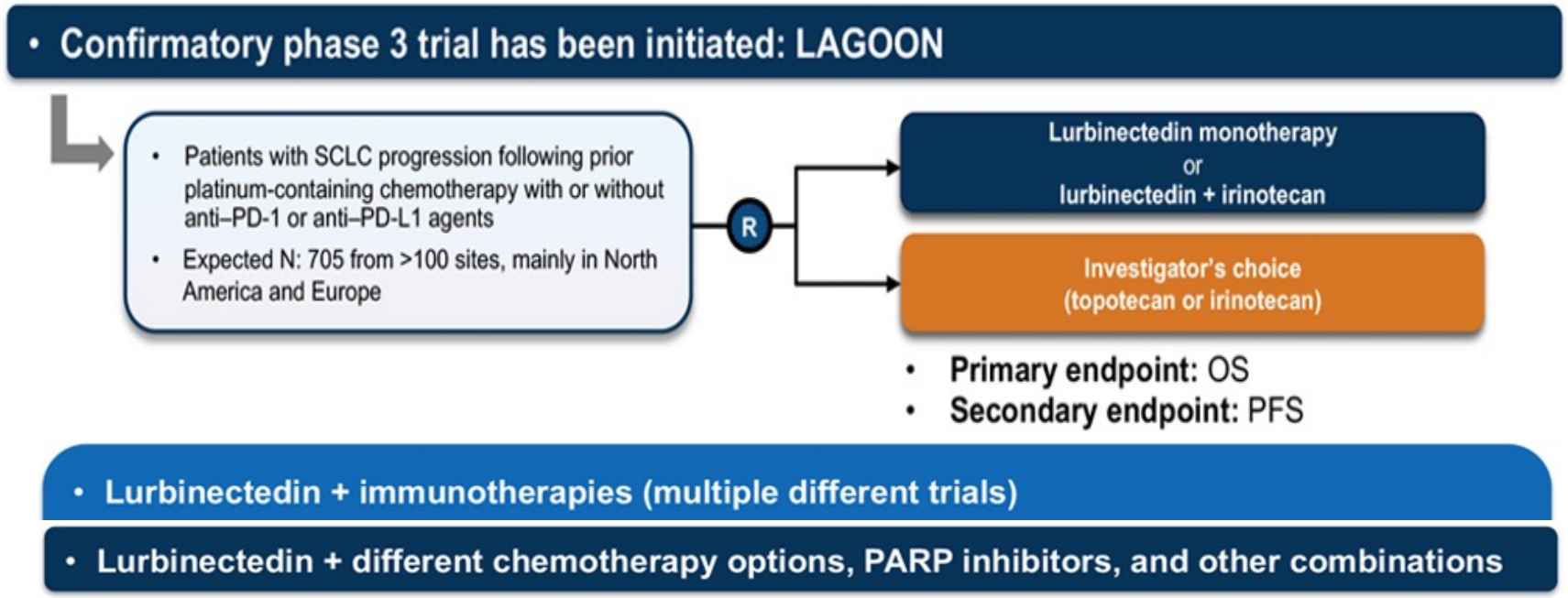
Limited options in 2nd line

Drug	Median PFS	Approval
Topotecan	13.3 weeks	1998
Lurbinectedin	3.5 months	2020

Paz-Ares et al, ESMO Open 2022
von Pawel et al, JCO 1999.
Trigo et al, Lancet Oncol 2020.

Lurbinectedin

- Selective inhibitor of oncogenic transcription
- In SCLC cohort of phase 2 basket trial, ORR 35.2%, DCR 68.6%
- ATLANTIS trial: did not meet OS endpoint (doxorubicin + Lurbinectedin vs topotecan/physician choice)



Trigo et al, Lancet Oncol 2020.
Laz-pres et al, WCLC 2021.
Figure courtesy: Jacob Sands

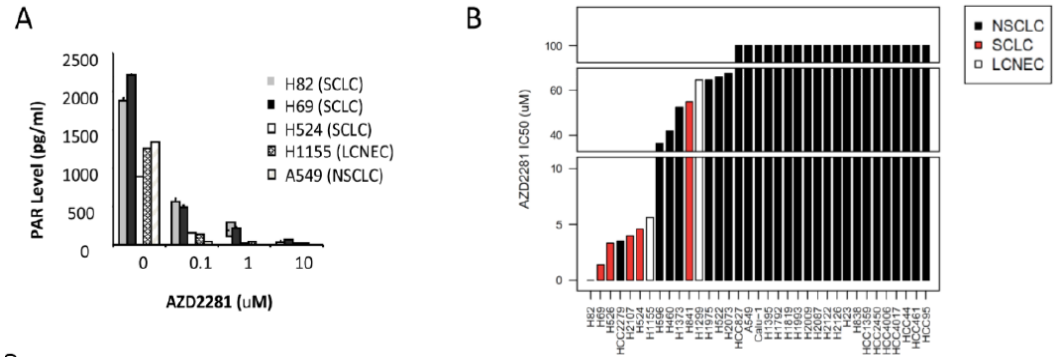
Recent maintenance trials in first-line ES-SCLC

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**

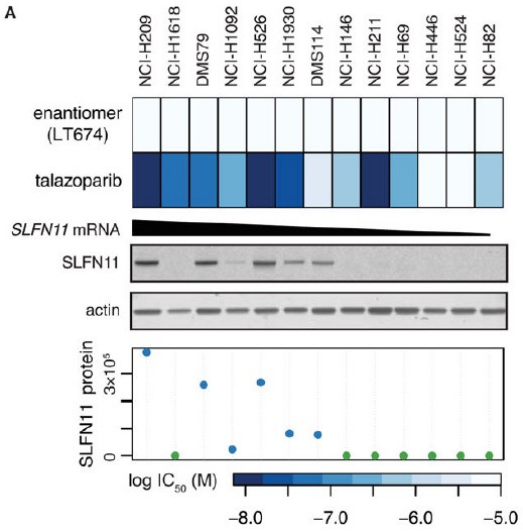
Owonikoko et al, JCO 2021
Rudin et al, JCO 2022
Karim et al, ASCO annual meeting 2023

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



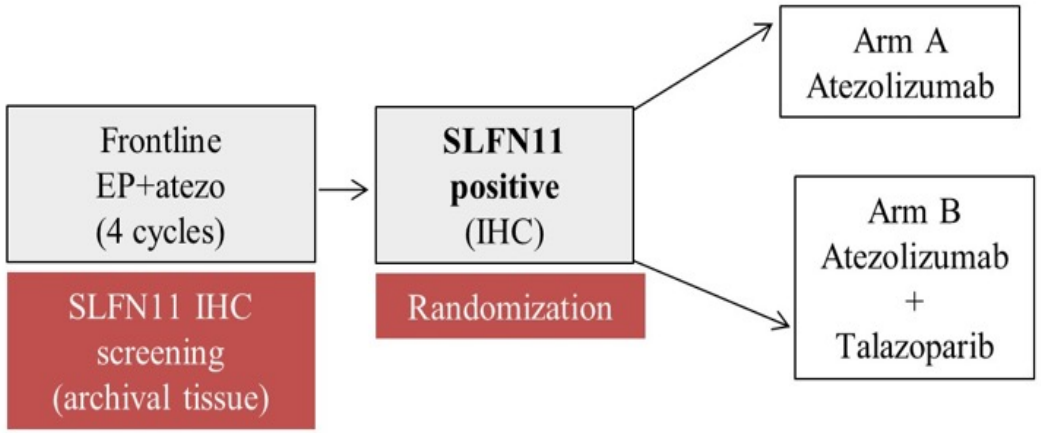
SLFN11 expressed in about 50% of SCLC as measured by IHC

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

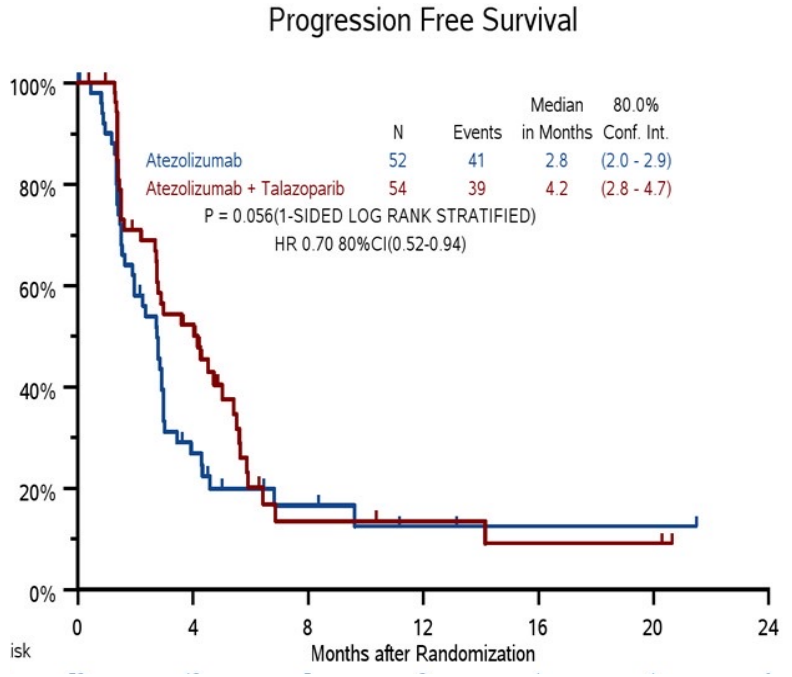
PIs: Karim, Reckcamp

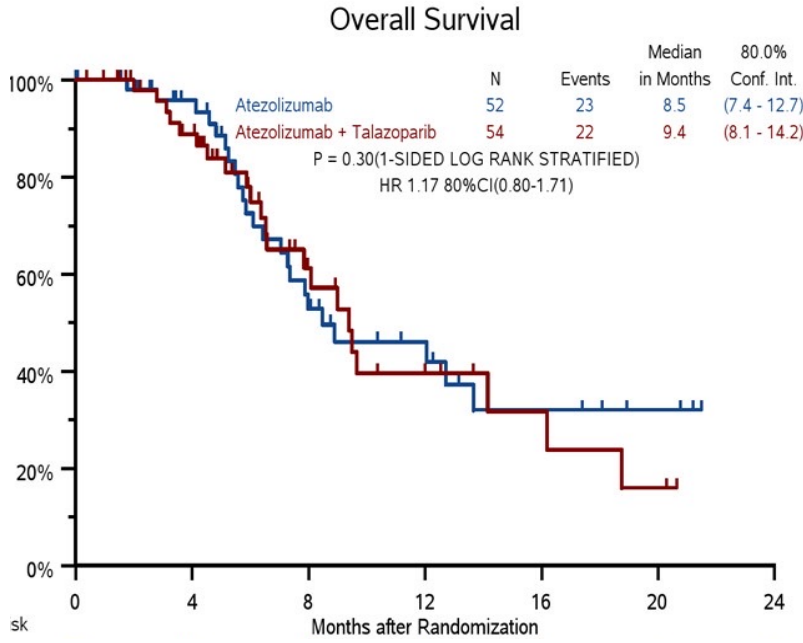
Translational PIs: Gay, Byers



Primary Objective: PFS

Secondary: OS, ORR, AE



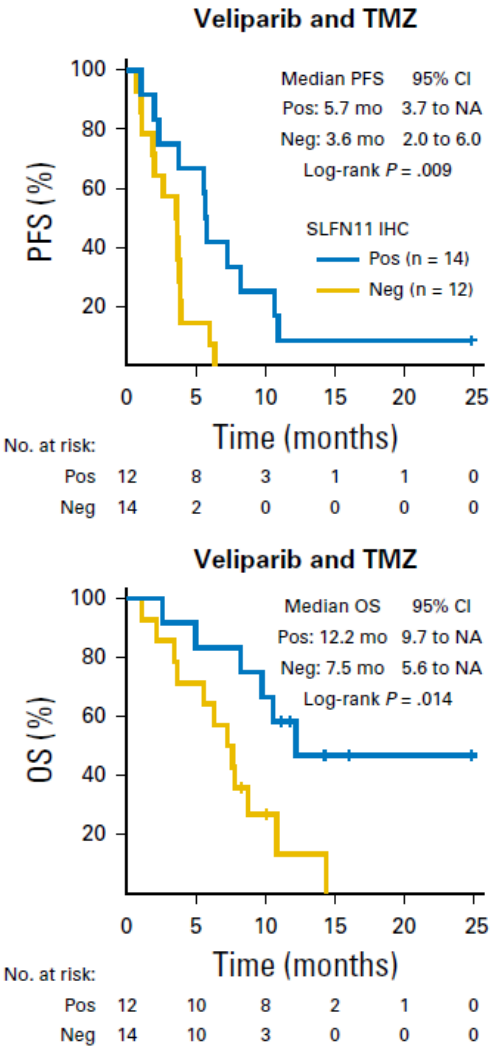


Karim et al, ASCO annual meeting 2023

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%

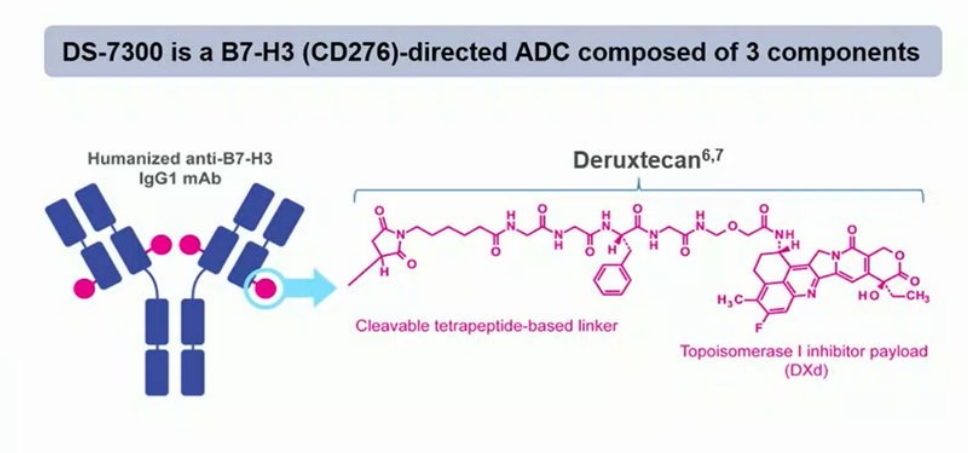
SLFN11 IHC predicts improved survival



Emerging biomarker driven therapies for second-line SCLC

	Targeted	MAb	ADC	BiTE	TriTE	CAR-T
B7-H3			DS-7300, HS-20093			
DLL3			Rova-T	Tarlatamab, BI764532	HPN328	AMG 119, LB102
Fucosyl-GM1		BMS-986012				
SEZ6			ABBV-011, ABBV-706			
SLFN11	PARPi, ATRi					

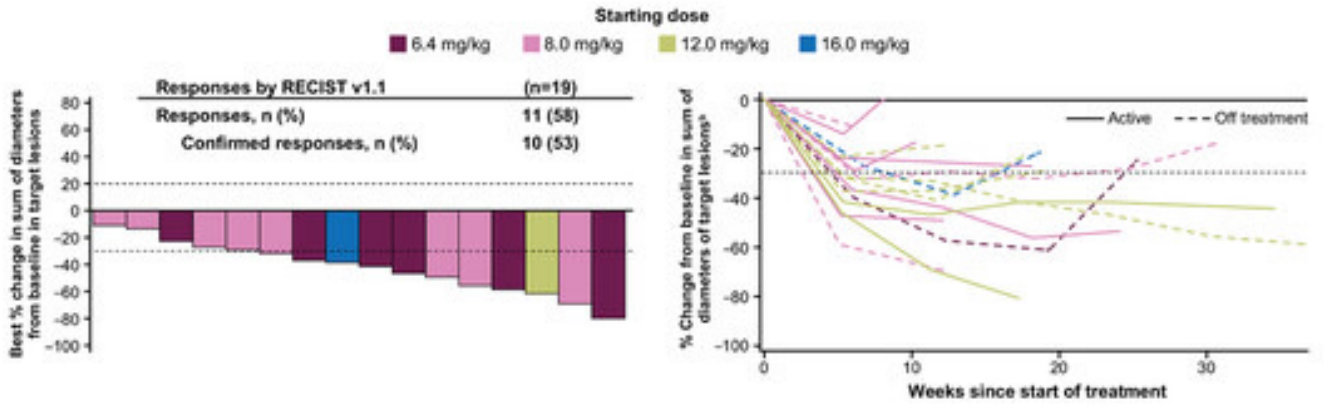
B7-H3: member of the B7 superfamily, highly expressed in various solid tumors, but limited expression in normal tissues.



DS-7300

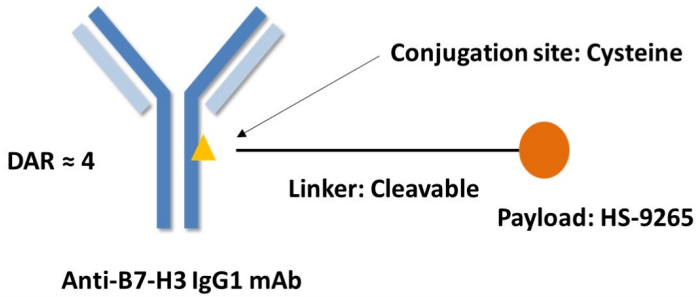
- phase I/II dose-finding study of DS-7300 (4.8 to 16.0 mg/kg)
- 147 patients with advanced solid tumors unselected for B7-H3 expression
- In 19 patients with SCLC, 58% ORR, with a median duration of response of 5.5 months.

Antitumour activity: SCLC subset[a]



Doi et al, ASCO Annual meeting 2023

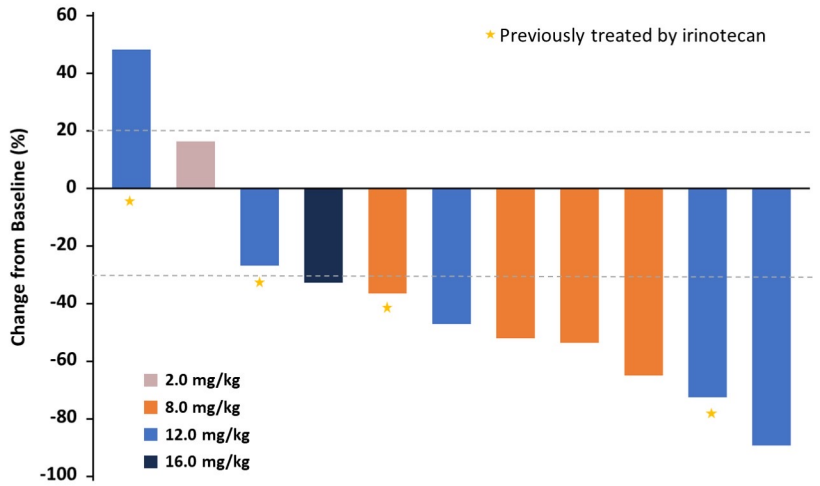
B7-H3



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

HS-20093

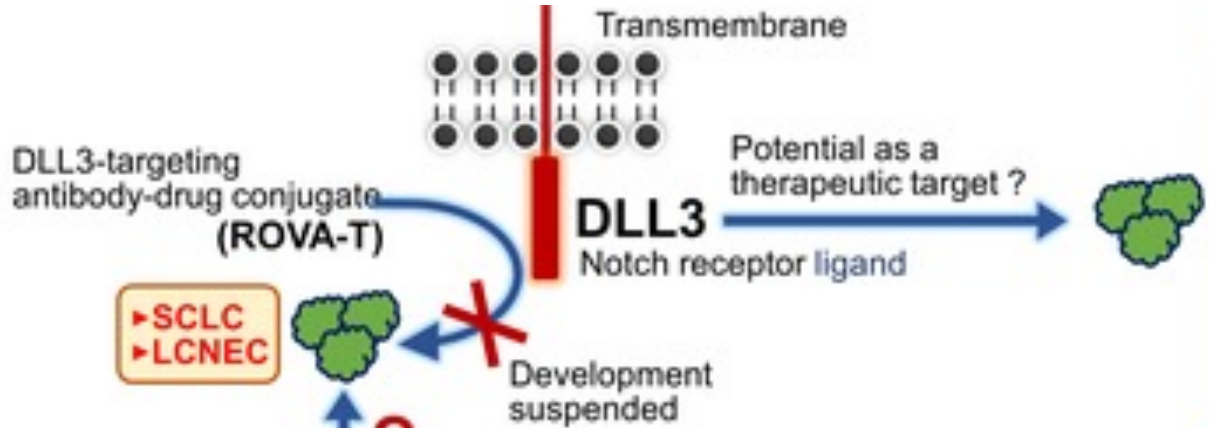
- ARTEMIS-001: phase I dose-finding study of HS-20093 (1 to 16.0 mg/kg)
- 53 patients with advanced solid tumors unselected for B7-H3 expression
- In 11 patients with SCLC, 64% ORR, with a median PFS of 4.6months.
- Toxicity: mainly hematological



Wang et al, ASCO Annual meeting 2023

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

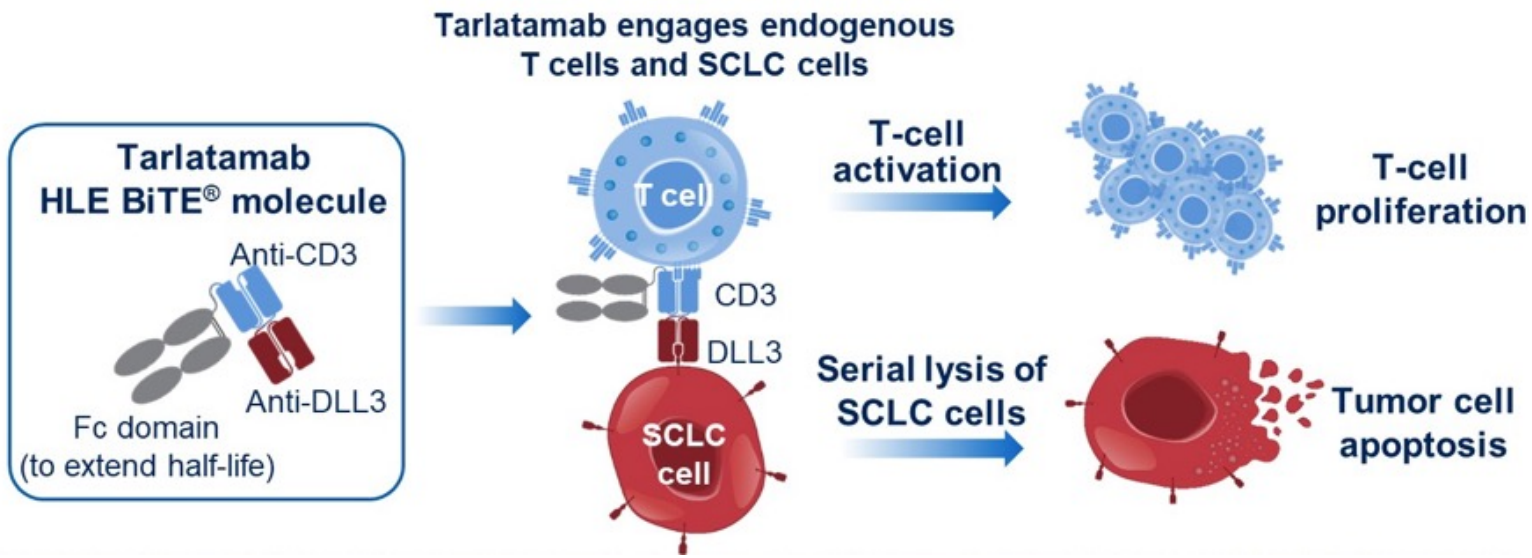


DLL3 ADC Rovalpituzumab Tesirine (Rova-T) program discontinued in 2019: promising results in phase 1 but no clinical benefit and increased toxicity in phase III trials (TAHOE, MERU)

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

DLL3: BiTE

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



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

DLL3: BiTE

Tarlatamab: FIH phase 1 dose-escalation and expansion (107 patients)

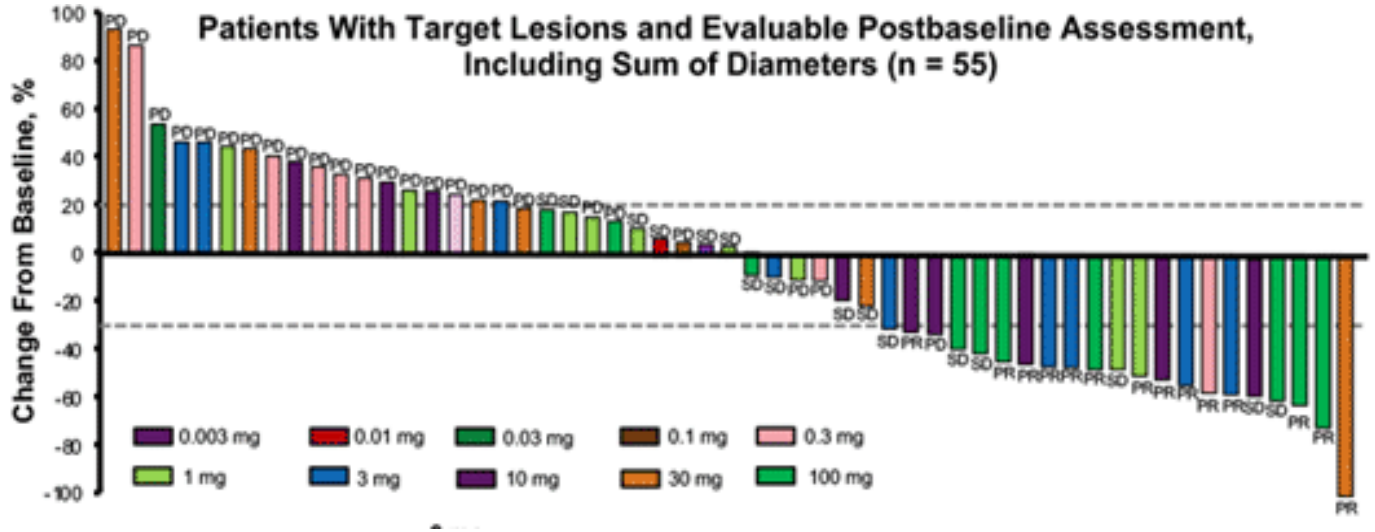
Toxicity: mostly CRS (52% all grade; 1 grade 3)

DLTs: G5 pneumonitis (1)

RR: 23.4%; DCR 51.4%

mPFS: 3.7 months

mDOR: 12.3 months



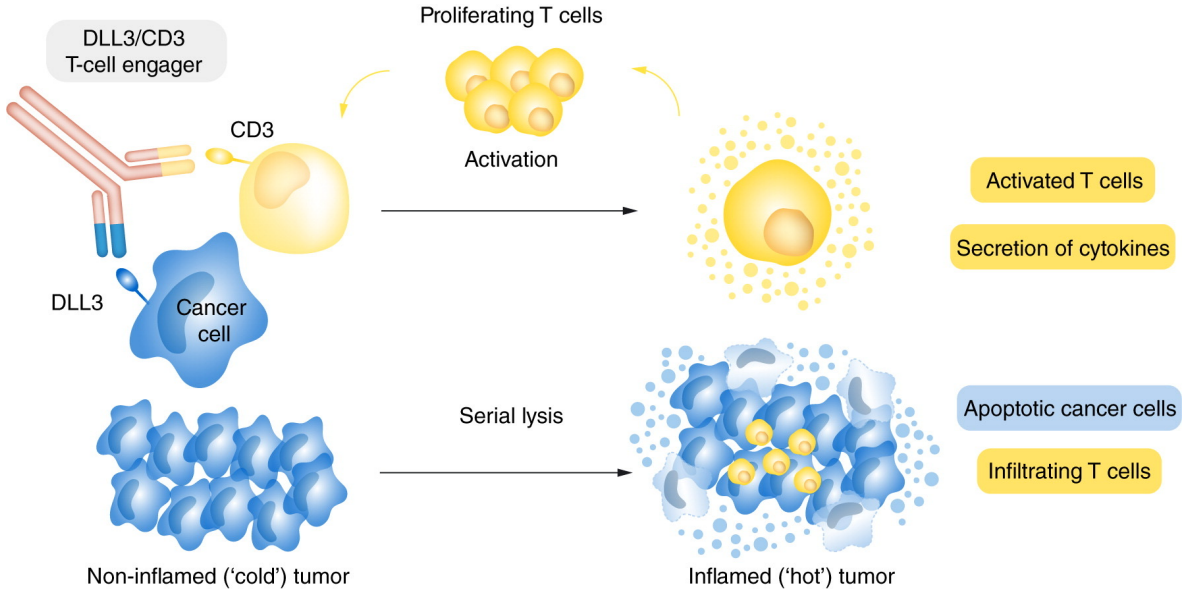
Phase III in 2nd line and phase I in first-line ongoing

Paz-Ares et al, JCO 2023

DLL3: BiTE

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

- phase I FIH, dose-escalation trial (ongoing) in SCLC, NEC or small cell carcinoma of any other origin
- Regimen (R) A (fixed iv dose q3w); RB1 (fixed iv dose qw); RB2 (step-in doses followed by a fixed dose)
- CRS 58% (≥G3 2%)

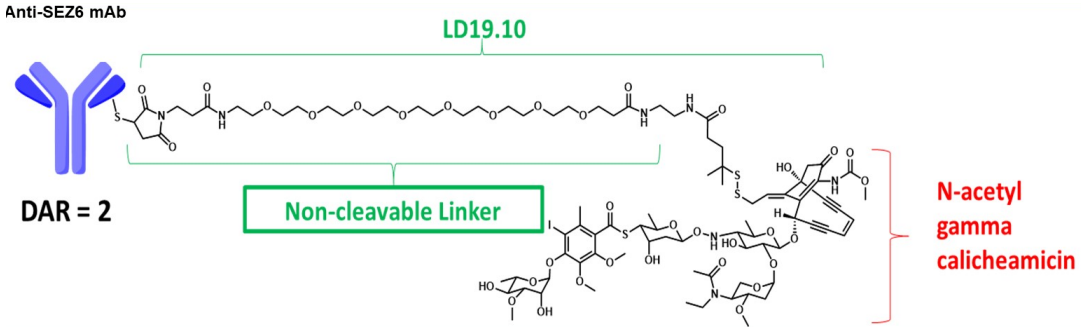


n, (%)	SCLC (n=39; 100%)*	epNEC (n=27; 100%)*	LCNEC (n=5; 100%)*
PR	10 (26)	5 (19)	3 (60)
SD	10 (26)	7 (26)	2 (40)
PD	12 (31)	13 (48)	0
DCR	20 (51)	12 (44)	5 (100)
NE†	7 (18)	2 (7)	0

Wermke et al, ASCO Annual meeting 2023
Wermke et al, Future Oncol 2022

Seizure-related Homolog Protein 6 (SEZ6)

ABBV-011 is an ADC targeting SEZ6 with a calicheamicin payload



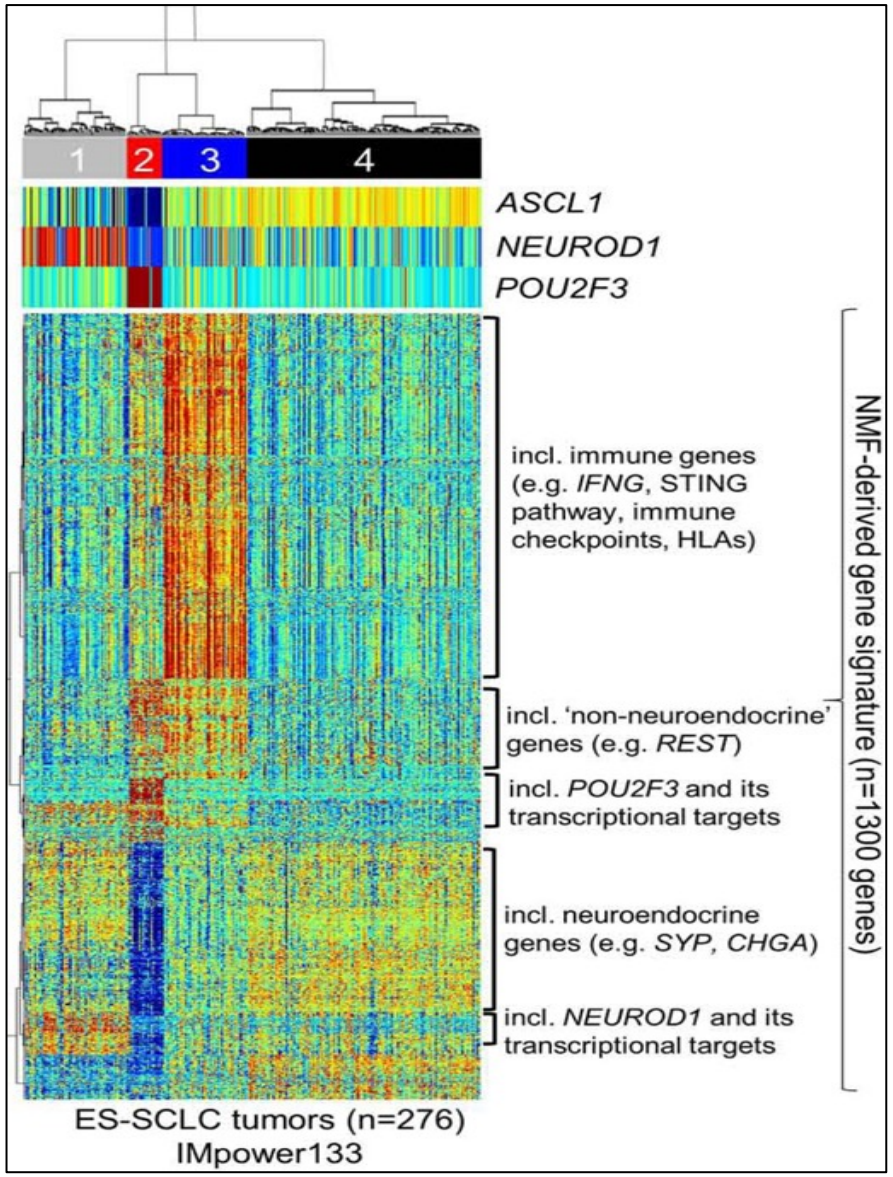
SEZ6 IHC expression cutoff	% positivity in study tissue samples (N=445)
≥1% tumor cells at 1+ or above	86%
≥25% tumor cells at 1+ or above (enrollment cutoff for dose expansion)	55%

- Phase I trial of ABBV-011 +/- budigalimab (anti-PD1)
- 99 patients were treated; 1 DLT of G3 fatigue
- 1 mg/kg MTD

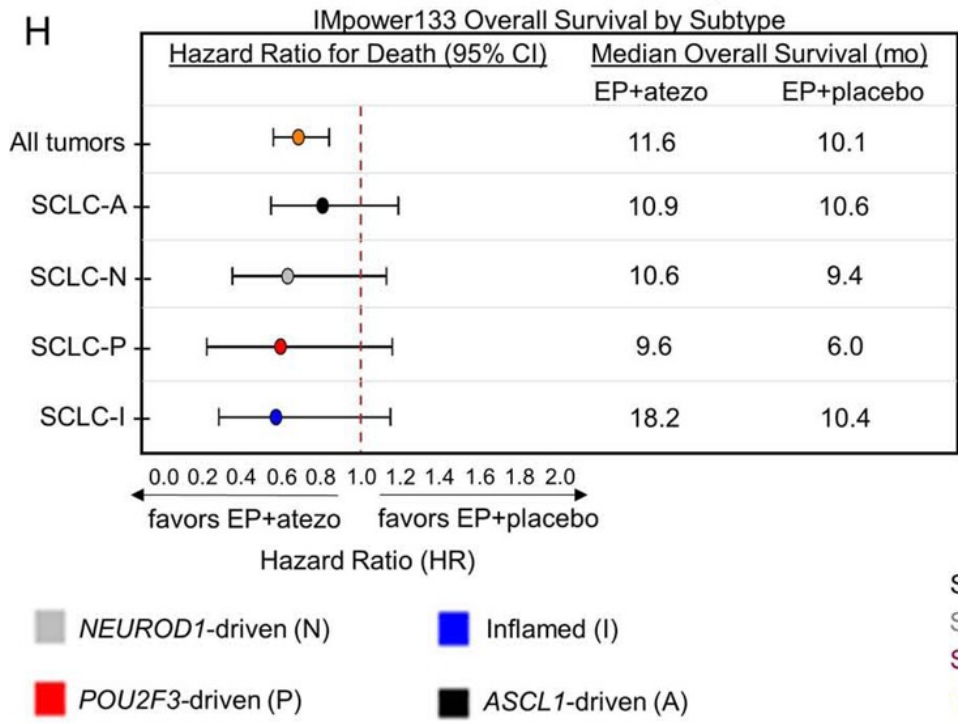
Efficacy Outcome	CTFI <90 days (n=12)	CTFI ≥90 days (n=26)
Confirmed ORR, n (%) *[95% CI]*	3 (25%) [5, 57]	7 (27%) [12, 48]
CBR, n (%) *[95% CI]*	7 (58%) [28, 85]	18 (69%) [48, 86]
CBR lasting >12 weeks, n (%) *[95% CI]*	4 (33%) [10, 65]	13 (50%) [30, 70]
Median PFS, months *[95% CI]*	3.0 [1.2, 3.9]	4.1 [1.5, 5.8]

Morgensztern et al, ASCO Annual meeting 2023

Molecular subtypes in SCLC



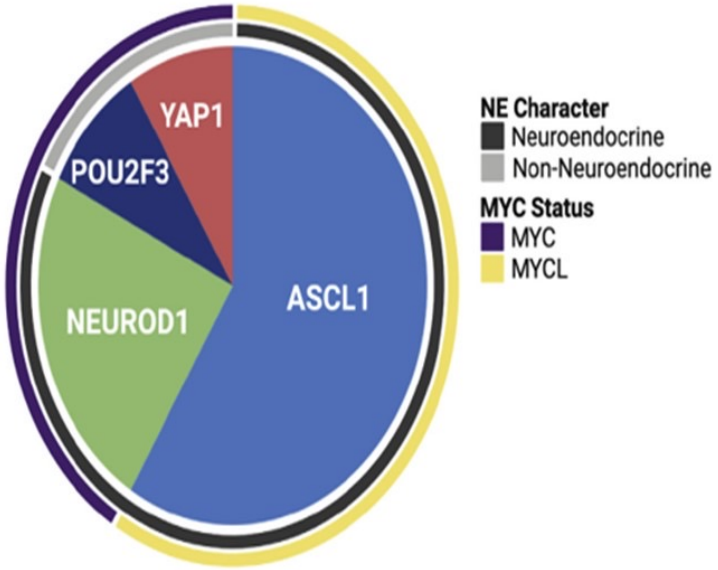
Based on expression of 4 key transcription regulators

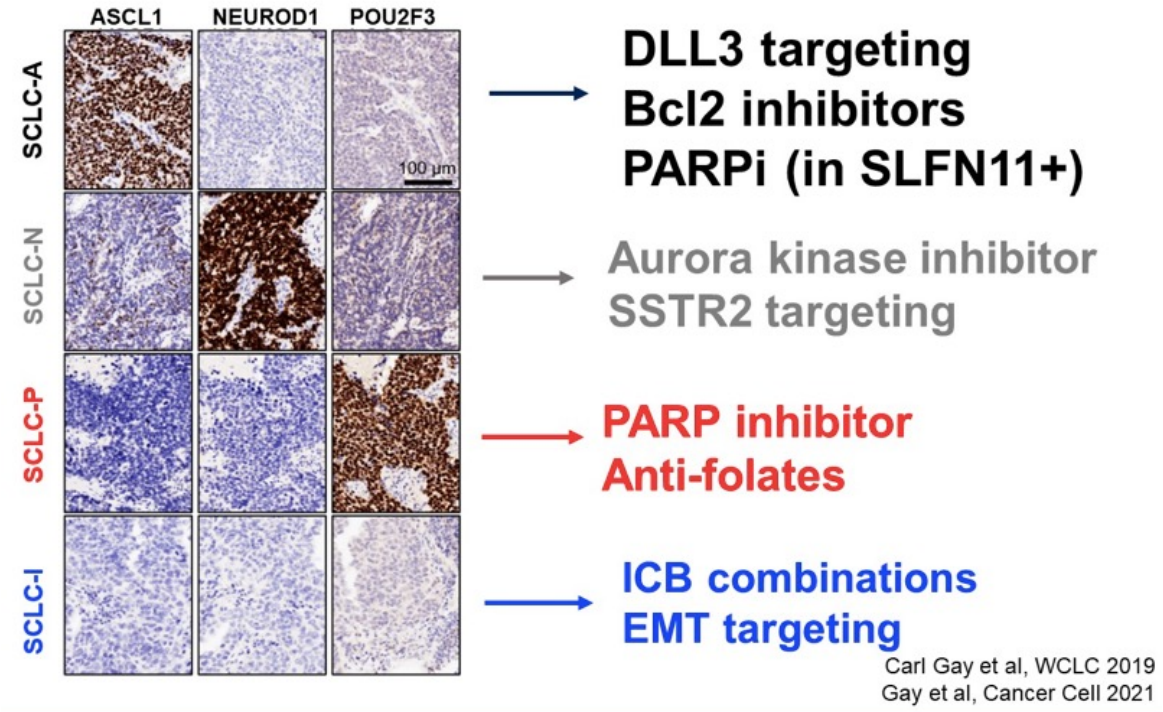


SCLC-inflamed (SCLC-I) subtype associated with greater benefit from immunotherapy

Gay et al, Cancer Cell 2021

Molecular subtypes in SCLC





Slide Courtesy: Dr Lauren Byers, ASCO 2021

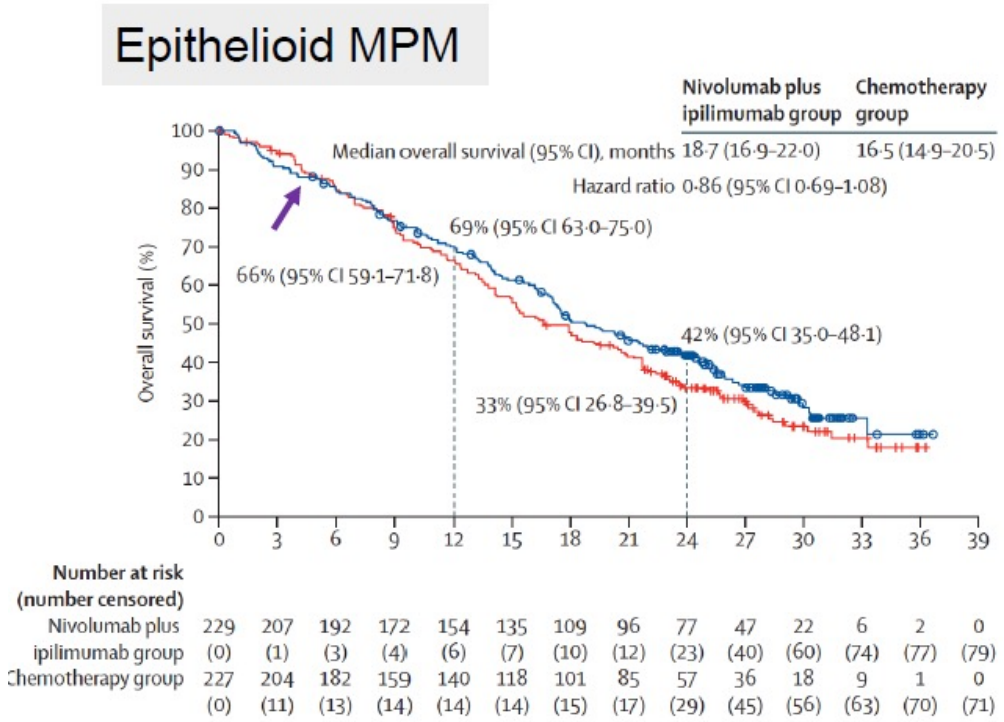
Conclusions

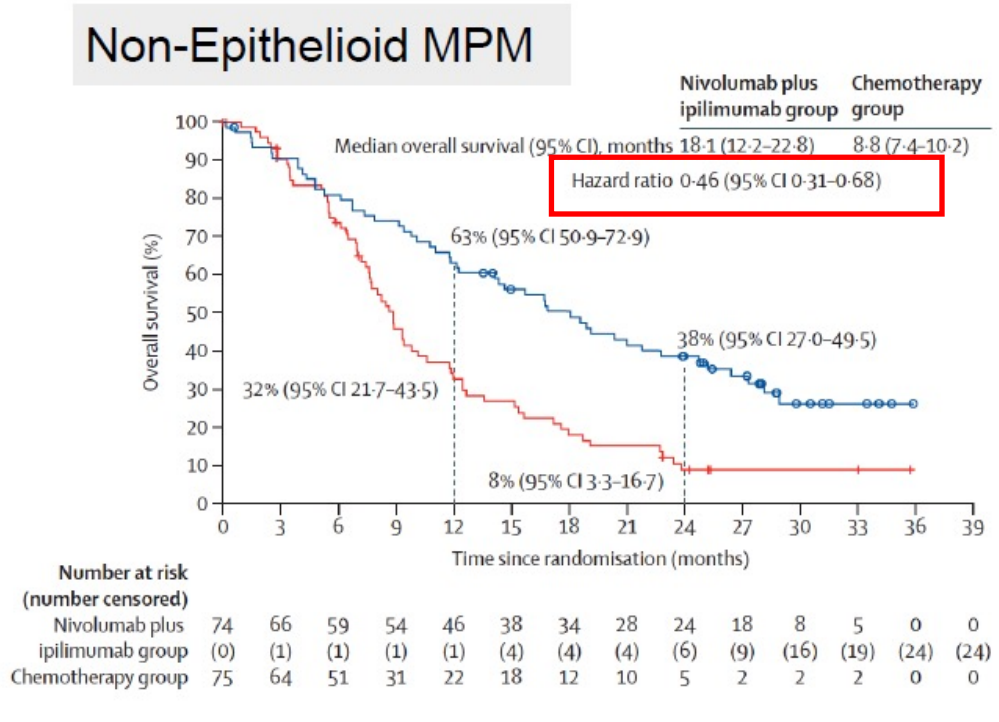
- Checkpoint inhibitors with chemotherapy SOC for 1st line ES-SCLC, trials ongoing for LS-SCLC
- Further biomarker-based therapies as monotherapy or in combination for 2nd line and beyond being explored

Pleural Mesothelioma

First-line: PD(L)1 + CTLA4

Checkmate 743: new SOC



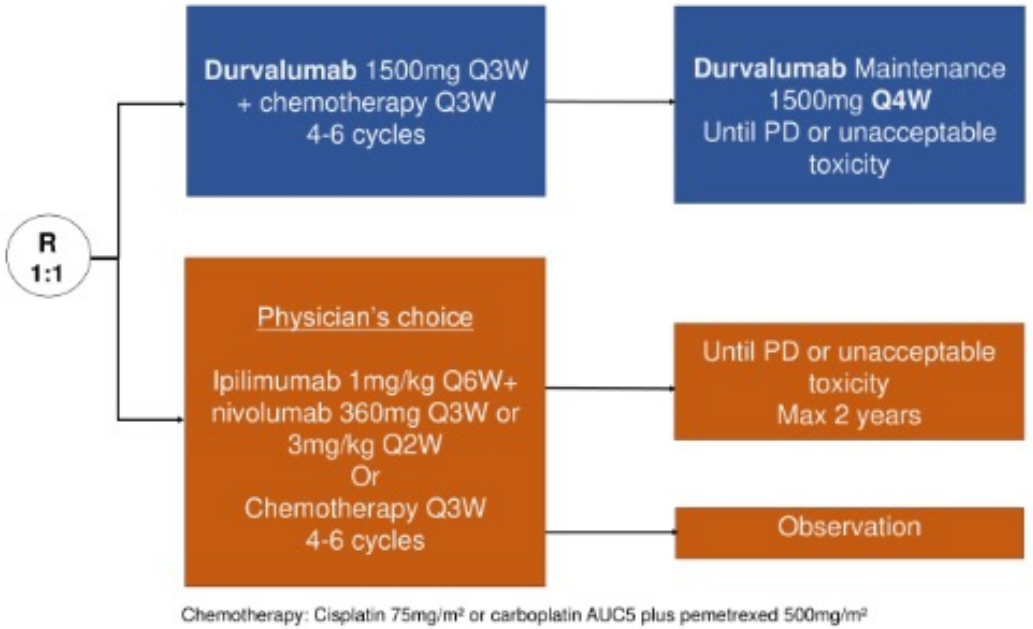


Baas et al. Lancet Oncol 2021

What's next in first-line

Study	Therapies	Phase	ORR	PFS, months	OS, months
DREAM[1], n=55	Cis/Pem + Durva	2	48%	6.9	18.4
PrE0505[2], n=55	Platinum/Pem + Durva	2	56.4%	6.7	20.4
IND 227	Chemo vs Chemo + Pembro	2/3	---	---	---
BEAT-Meso	Chemo/Bev vs Chemo/Bev/Atezo	3	---	---	---
DREAM3R	Chemo vs Chemo + Durva	3	---	---	---

DREAM 3R trial
Current enrollment: 170/480
USA and Australia

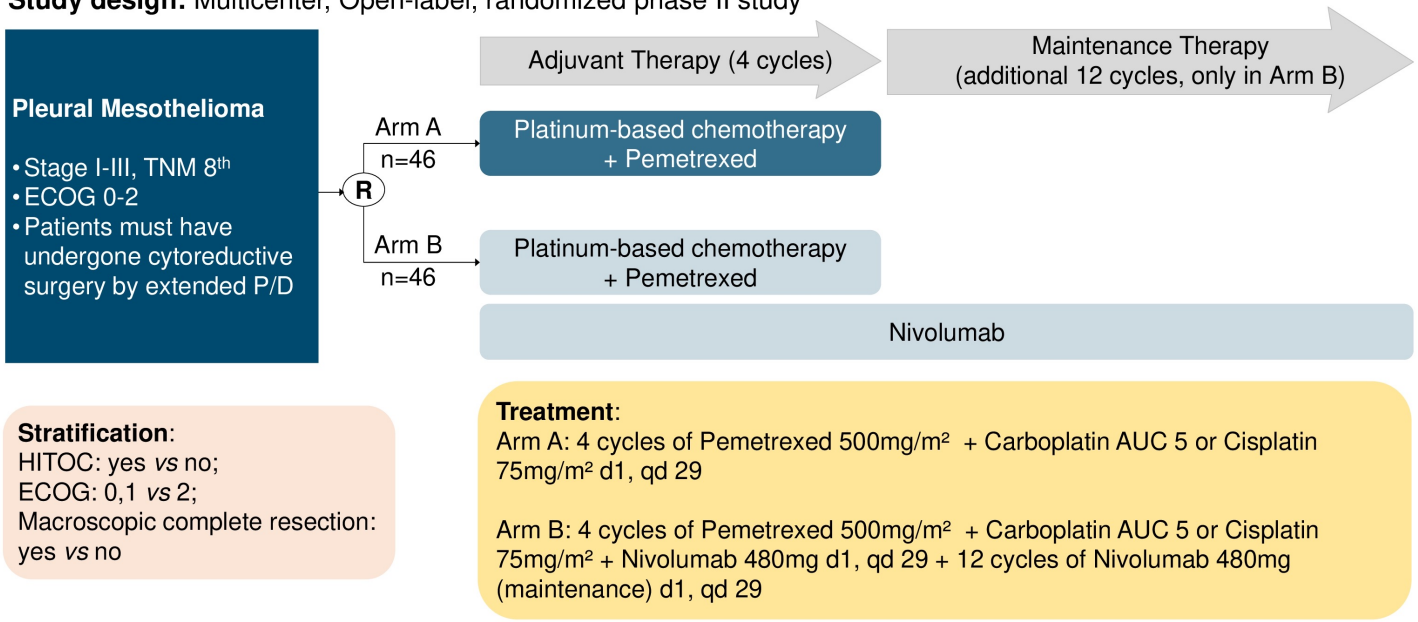


Forde et al, ASCO Annual meeting 2023
Dagogo-Jack et al, WCLC 2022

Neoadjuvant chemo-immunotherapy

- **NICITA trial:** Nivolumab with chemotherapy in pleural mesothelioma after surgery
- Primary endpoint: time to next treatment, safety

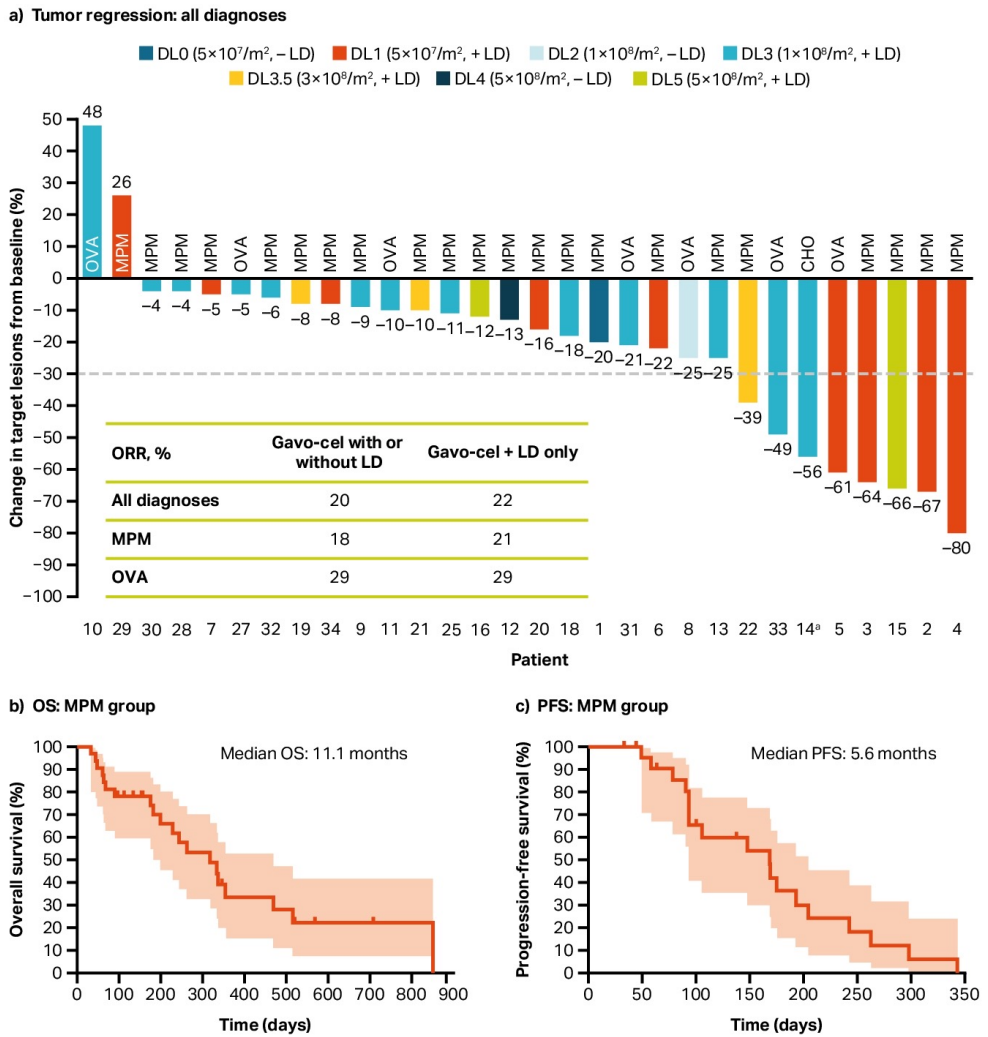
Study design: Multicenter, Open-label, randomized phase II study



Accrual: As of May 2nd 2023, all of fourteen sites are active and all of 92 planned patients have been enrolled.

T-cell therapy

- Phase 1 trial of gavo-cel, an autologous genetically engineered anti-mesothelin T cell receptor fusion construct (TRuC™) cell therapy in solid tumors
- Eligibility required 2+ or 3+ mesothelin expression by IHC in ≥50% of tumor cells.
- 32 pts (23 MPM); median no of prior therapies was 5 including ICI
- At the RP2D, 2/13 (15%) pts had reversible gr≥3 CRS.
- ORR 20% and DCR 77%

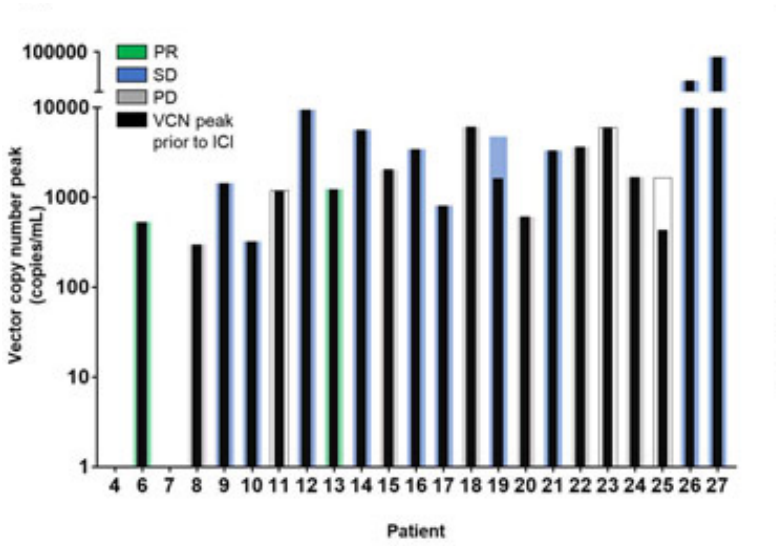


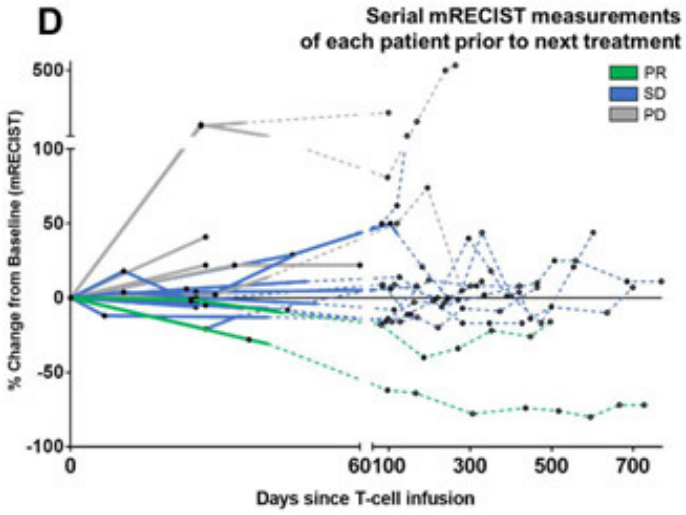
Change in tumor volume based on blinded independent central review unless otherwise noted. [a]Tumor volume decrease based on investigator assessment.

Hassan et al, ASCO Annual meeting 2023

CAR T-cell therapy

- FIH phase I study of regionally delivered, autologous, mesothelin-targeted CAR T-cell therapy
- Intrapleural administration of CAR T cells in 27 patients safe and well tolerated
- CAR T-cells were detected in peripheral blood for >100 days in 39% of patients
- 18 patients also received pembrolizumab safely
  - mOS 23.9 months; 2 patients with complete metabolic response on PET scan.





Adusumilli et al, Cancer Dis. 2021

Mesothelioma Stratified Therapy (MiST) study design

Trials.gov ID NCT03654833

Stage 1 Molecular Pre-Screening

Stage 2 Treatment Stratification

Stage 3 Genomic interrogation

Molecular/ Phenotypical Pre-screening*

- Inoperable mesothelioma
- Pleural, peritoneal mesothelioma
- Histologically confirmed
- ECOG 0-1
- Post 1st line therapy
- Consent for tissue

Arm		
1	BAP1/BRCA1-	PARP
2	p16INK4A-	CDK 4/6
3	N/A	AXL PD1
4	PDL1	VEGF PDL1
5	DNA damage sensitiive	PARP PD1

DNA and RNA sequencing (arms 1-5)

Molecular phenotyping

Gut microbiome (arms 3-5)

- Primary endpoint response
- Secondary endpoint DCR
- Rebiopsy, responders

Fennell et al

Conclusions

- PD1+CTLA4 vs platinum-pemetrexed standard of care for advanced MPM

- Emerging options for second line and beyond are:
    - Immunotherapy combinations with VEGFi, PARPi, AXLi
    - Targeted therapies such as CDKi
    - CAR-T therapies & anetumab targeting mesothelin expression
    - EZH2 inhibitors targeting BAP1
    - Tumor-treating fields

Thymic Malignancies

Systemic therapies

	Thymoma	Thymic carcinoma
First-line		
	Carboplatin/paclitaxel Cisplatin/doxorubicin/cyclophosphamide (CAP) Cisplatin/etoposide	
Second-line		
Chemotherapy	Etoposide, Paclitaxel, Pemetrexed, gemcitabine, capecitabine	
CPI		Pembrolizumab
Multi-target TKI		Sunitinib, Lenvatinib
MTOR inhibitor	Everolimus	

NCCN Guidelines, 2023

Small molecular targeted therapies for thymic cancer

First Author, Year	Drug	Patients (T/TC)	ORR % (T/TC)	DCR % (T/TC)	mPFS mo (T/TC)
Multi-targeted anti-angiogenic TKI, including c-Kit					
Thomas 2015	Sunitinib	40 (16/24)	6/**26***	81/91	8.5/7.2
Kim 2018	Sunitinib	25 (0/25)	**22***	92	15.2
Proto 2023	Sunitinib	44 (12/32)	0/**22***	92/89	7.7/8.8
Sato 2020	Lenvatinib	42 (0/42)	**38***	95	9.3
Perrino 2023	Regorafenib	19 (11/8)	10/14	96/100	**9.6/9.2***
mTOR, class I PI3K inhibitor					
Zucali 2018	Everolimus	51 (32/19)	9/17	**94/78***	16.6/5.6
Abu Zaid 2022	Buparlisib	14 (14/0)	7.1	50	11.1

- Multi-target anti-angiogenic TKI with efficacy in thymic cancer.
- mTOR inhibitors with efficacy in both thymoma and thymic cancer.

Slide courtesy: Sukhmani Padda

Checkpoint inhibitors

TET subtype	ICI type	Number of Patients	Response Rate (%)	Disease Stabilization (%)	Median PFS (months)
Thymic Carcinoma	Pembrolizumab[1,2]	40	22.5	52.5	4.2
	Pembrolizumab[3]	26	19.2	53.8	6.1
	Nivolumab[4]	15	0	73.3	3.8
	Avelumab[5]	1	0	100	Not reported
	Avelumab[6]	10	20.0	60.0	**14.7**
Thymoma	Avelumab[5]	7	57.1	28.6	Not reported
	Avelumab[6]	12	16.7	83.3	6.4
	Pembrolizumab[3]	7	28.6	71.4	6.1

1. Giaccone, G., *et al.*, *Lancet Oncol*, 2018
2. Giaccone, G. and C. Kim, *J Thorac Oncol*, 2021
3. Cho, J., *et al.*, *J Clin Oncol*, 2019
4. Katsuya, Y., *et al.*, *Eur J Cancer*, 2019
5. Rajan, A., *et al.*, *J Immunother Cancer*, 2019
6. Rajan, A, et al., SITC, 2019

Use limited by irAE

Grade 3-4 irAE

- 71% in thymoma
- 15-20% in thymic cancer

Chen Zhao, WCLC 2022

Ongoing Immunotherapy trials

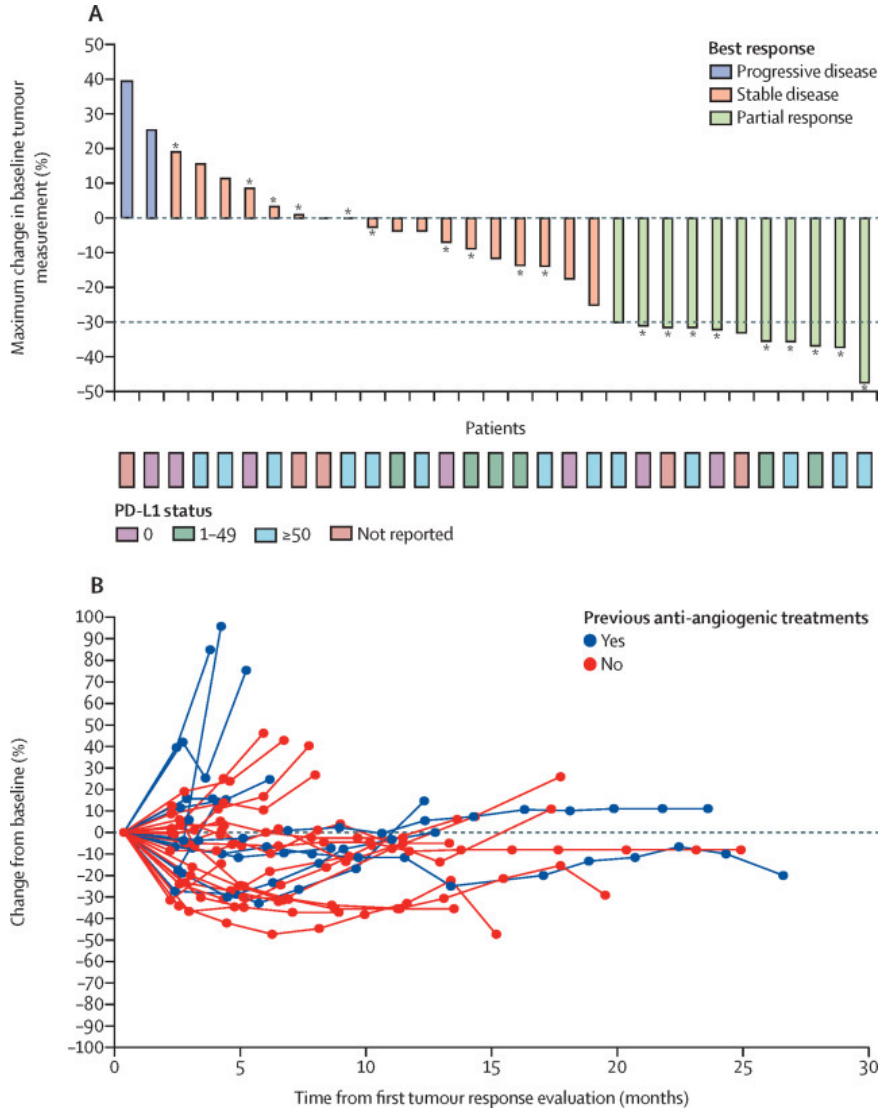
Intervention	Modality	Target	Patient Population	Trial
Nivolumab, Ipilimumab	Combinatory Immunotherapy	PD-1, CTLA-4	Thymic carcinoma, B3 thymoma	NCT03134118
Bintrafusp alfa	Combinatory Immunotherapy	PD-L1, TGF-β	Thymic carcinoma, thymoma	NCT04417660
Pembrolizumab, Epacadostat	Combinatory Immunotherapy	PD-1, IDO1	Thymic carcinoma	NCT02364076
Avelumab, Axitinib	Immunotherapy + Targeted Therapy	PD-L1, VEGFR	Thymic carcinoma, B3 thymoma	2017-004048-38
Nivolumab, Vorolanib	Immunotherapy + Targeted Therapy	PD-1, VEGFR, PDGFR	Thymic carcinoma	NCT03583086
Pembrolizumab, Sunitinib malate	Immunotherapy + Targeted Therapy	PD-1, VEGFR, PDGFR, CSFR	Thymic carcinoma	NCT03463460
Anetumab ravtansine	Cancer Antigen Targeting Therapy	Mesothelin	Thymic carcinoma	NCT03102320
Pembrolizumab	Neoadjuvant Immunotherapy	PD-1	Thymic carcinoma, thymoma	NCT03858582

- ICIs should only be offered as part of a clinical trial for patients with thymoma, require close monitoring for thymic carcinoma as well.
- Biomarkers needed for risk mitigation.

Chen Zhao, WCLC 2022

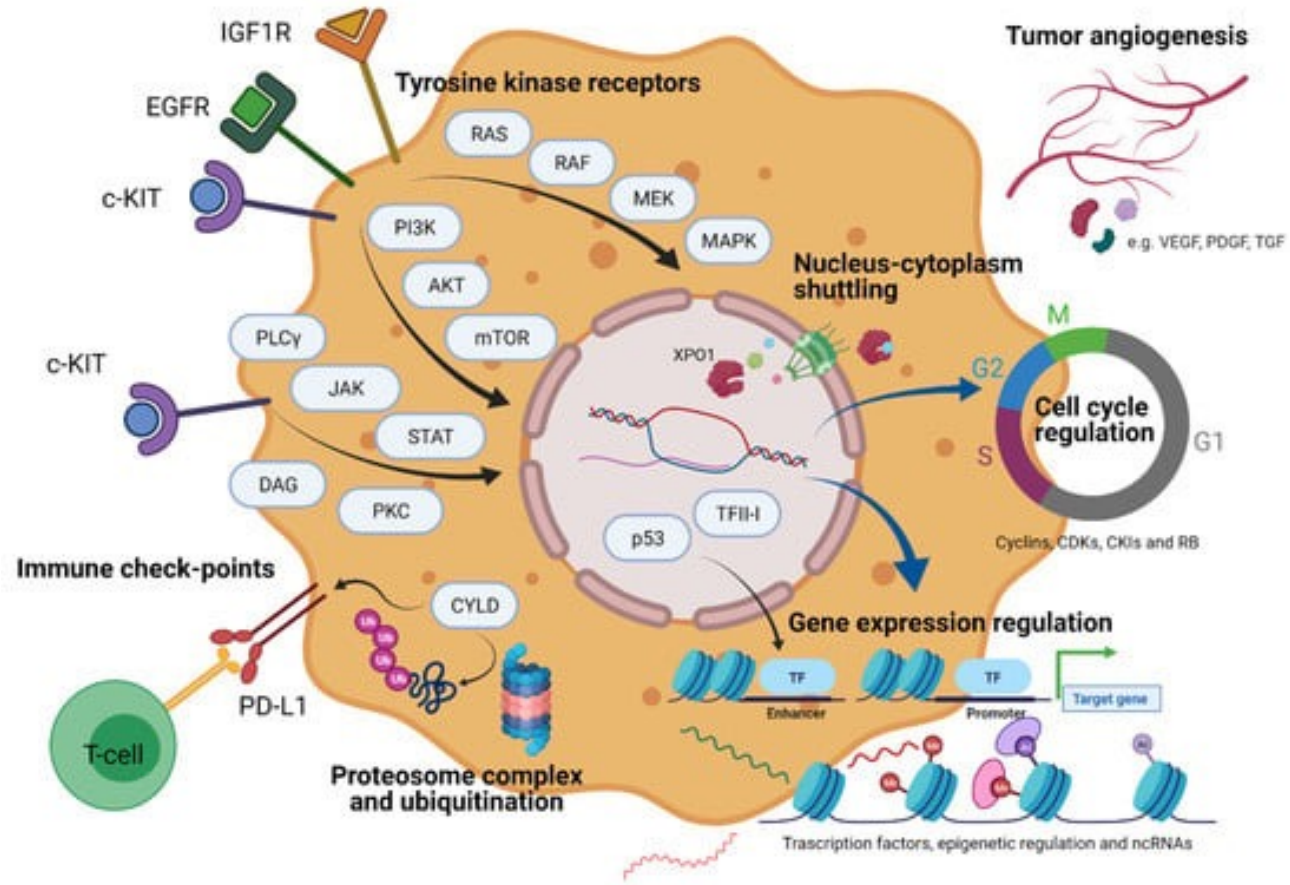
PD1 and multi-kinase TKI combination

- **CAVEATT:** single-arm, multicenter, phase II trial in Italy in patients with type B3 thymoma or thymic carcinoma pre-treated with chemotherapy
- Avelumab 10 mg/kg intravenously every 2 weeks and axitinib 5 mg orally twice
- 32 patients enrolled (27 thymic cancer)
- ORR 34%
- G3-4 irAEs 12%



Conforti et al, Lancet Oncol 2022

Molecular Change/Oncogene	Thymoma (%)	Thymic Carcinoma (%)
c-KIT		
Overexpression (IHC)	<5	73–86
HER2		
Overexpression (IHC)	6	53
EGFR		
Gene amplification (FISH)	20	25
Overexpression (IHC)	50–70	20–30
IGF-1R		
Overexpression	4	37



Kelly, JNCCN 2013
Tateo et al, Pharmaceuticals 2021

Thank you!