Small Cell Lung Cancer

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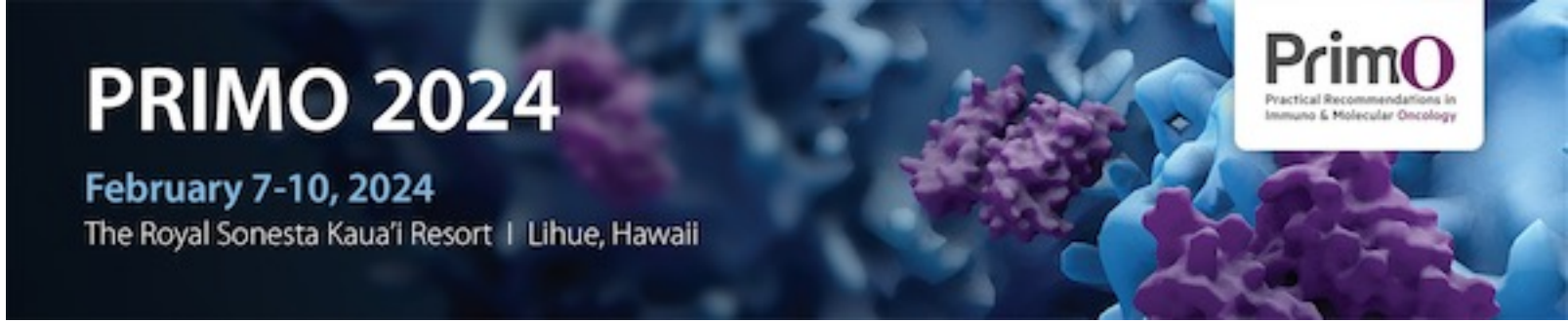
PrimO
Practical Recommendations in Immuno & Molecular Oncology



Outlines

- Epidemiology
- Biomarkers
- Limited stage SCLC (L-SCLC)
- Extensive disease SCLC (E-SCLC)
- Future Directions

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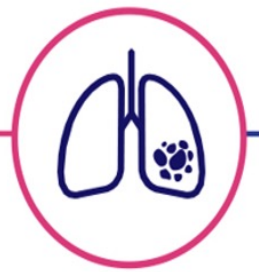
Epidemiology

SCLC accounts for ~15% of lung cancers and is characterized by a poor survival.

Lung Cancer Epidemiology



Lung cancer is the third most common cancer in both men and women[3]

- **~236,000** people will be diagnosed with lung cancer in 2021[3]
- **~35,000** new diagnoses with SCLC[3]
- ~15% of cases are SCLC[1]
- ~85% of cases are NSCLC[1]

Extensive Stage	Limited Stage
~23,000	~12,000

The majority of patients are diagnosed with ES-SCLC[4]

Poor Survival in SCLC

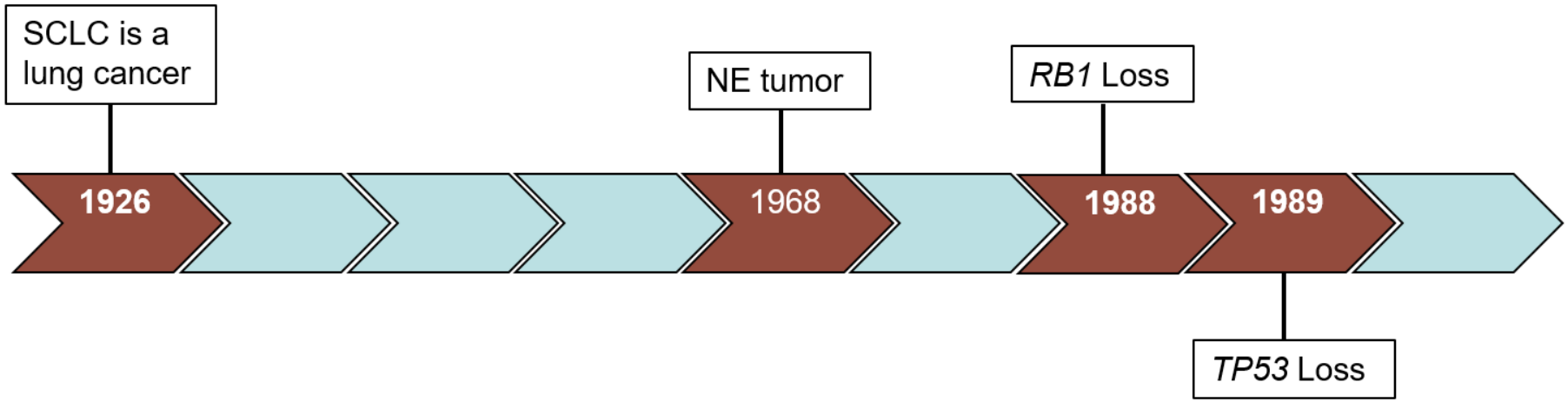
5-year SCLC survival rate[2]

With treatment, **median survival is 6-24 months**, depending on stage[5]

- **27%** for **localized** SCLC that has not spread beyond the lung
- **16%** for **regional metastases** that have spread beyond the lung
- **3%** for **distant metastases**

References: 1. Chen Y, et al. *Cancer Commun*. 2019;39(1):53. 2. American Cancer Society. Lung Cancer Survival Rates. https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survival-rates.html. Accessed August 24, 2021. **3.** SEER. Cancer Stat Facts: Cancer of Any Site. https://seer.cancer.gov/statfacts/html/all.html. Accessed August 23, 2021. **4.** American Cancer Society. Small cell lung cancer stages. https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/staging-sclc.html. Accessed September 19, 2021. **5.** National Cancer Institute. Small Cell Lung Cancer Treatment (PDQ)-Health Professional Version. https://www.cancer.gov/types/lung/hp/small-cell-lung-treatment-pdq. Accessed August 23, 2021.

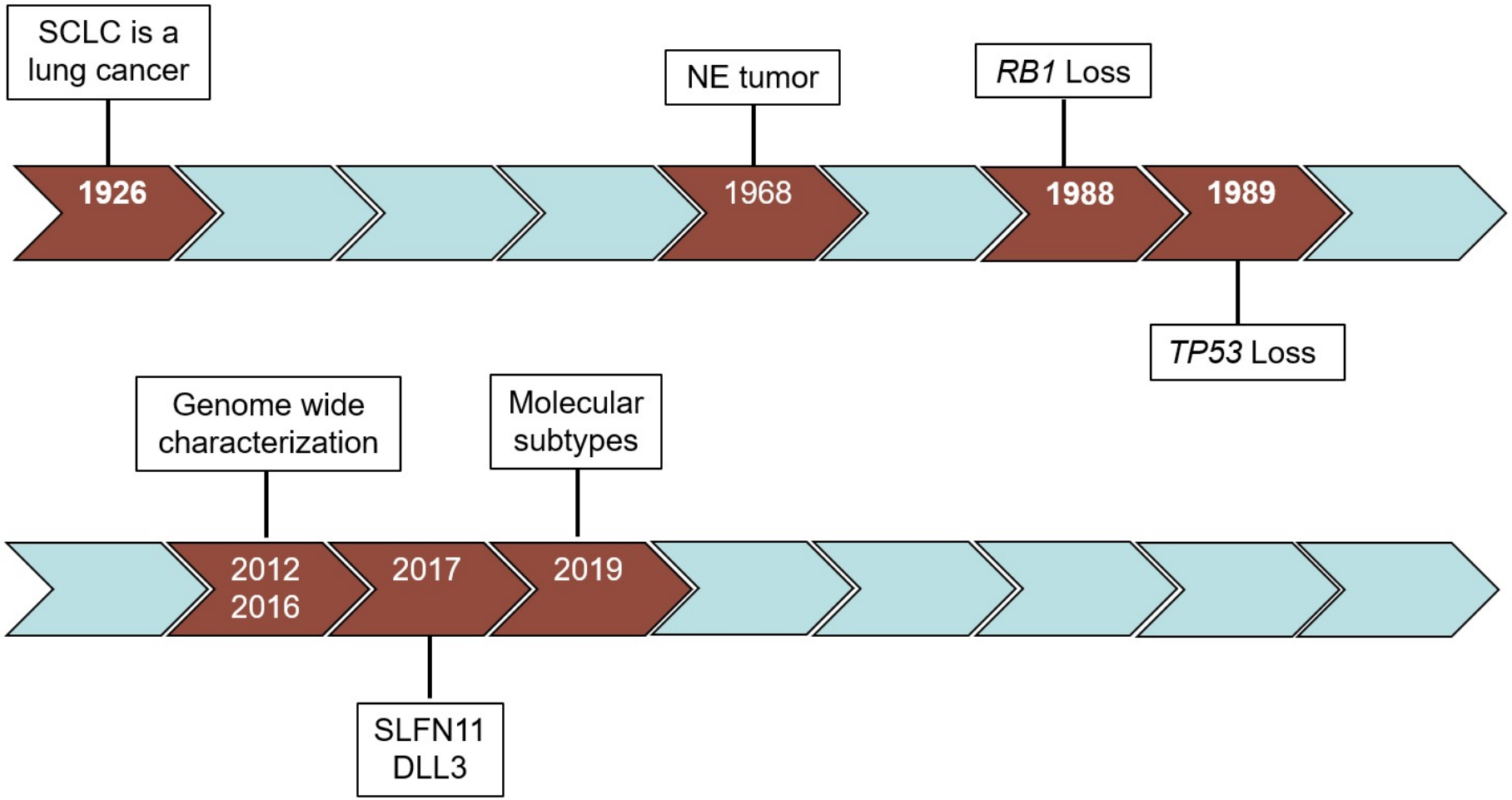
Small Cell Lung Cancer



- Poorly differentiated neuroendocrine tumor characterized by lack of actionable driver mutations.
- Express at least 1 NE marker – Chromogranin A, synaptophysin, CD56 & INSM1 on IHC
- Near universal loss of *TP53* & *RB1*

Barnard. J Pathol Bacteriol 1926
Bensch Cancer 1968
Takahashi. Science 1989
Harbour, Science 1988

Small Cell Lung Cancer



Barnard. J Pathol Bacteriol 1926
Bensch Cancer 1968
Takahashi. Science 1989
Harbour, Science 1988

George. Nature 2014
Rudin Nat Genet 2012
Fernandez-Cuesta. Nat Genet 2012
Gardner. Cancer Cell 2017

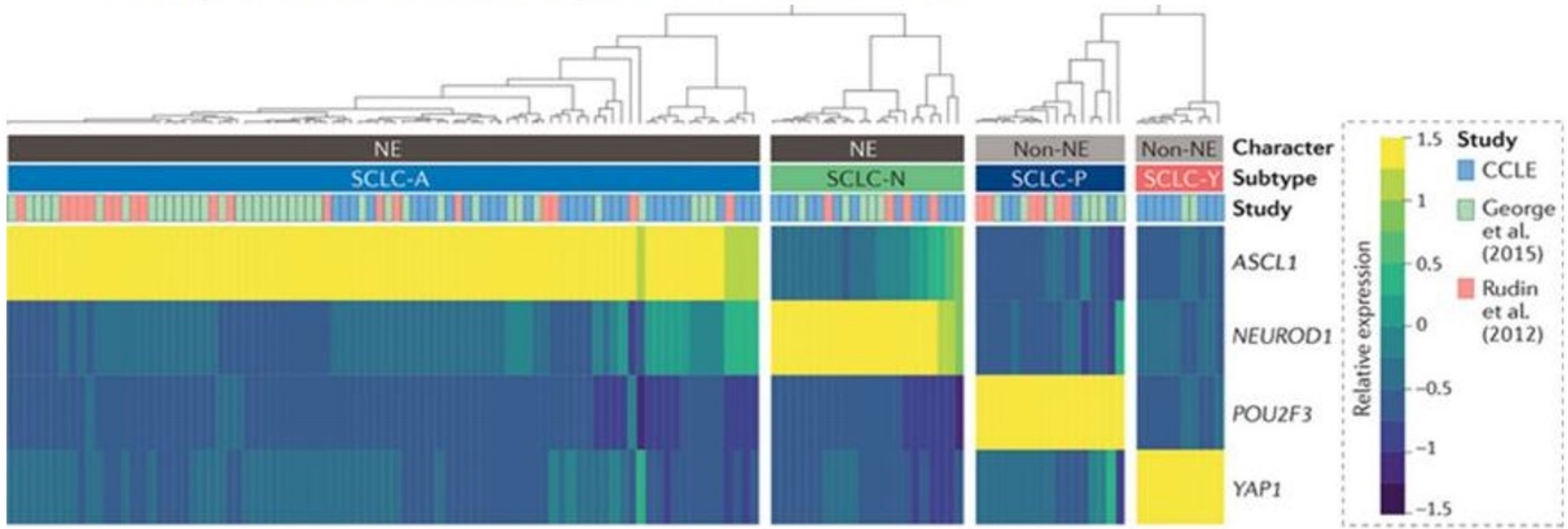
Stewart. Oncotarget
Rudin. Lancet Oncol. 2017
Rudin. Nat Rev Cancer 2019

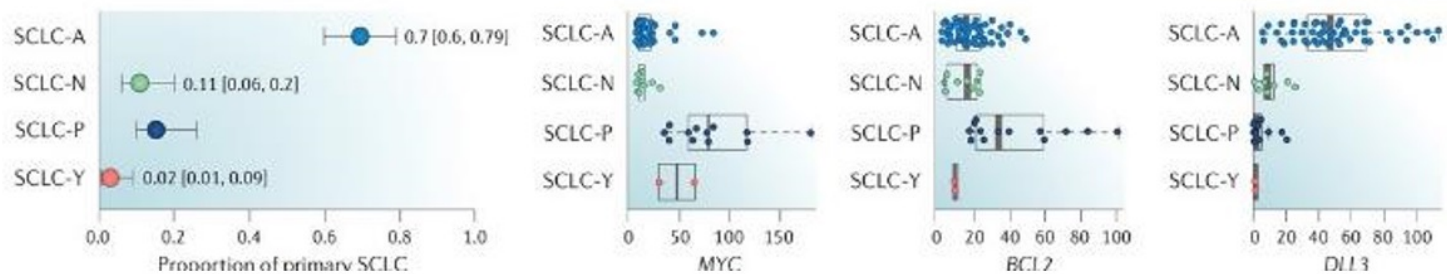
SCLC subtypes defined by dominant transcriptional regulator

Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data

Charles M. Rudin[1,*], John T. Poirier[1,*], Lauren Averett Byers[2], Caroline Dive[3], Afshin Dowlati[4], Julie George[5], John V. Heymach[2], Jane E. Johnson[6], Jonathan M. Lehman[7], David MacPherson[8], Pierre P. Massion[7], John D. Minna[6], Trudy G. Oliver[9], Vito Quaranta[7] Julien Sage[10], Roman K. Thomas[5], Christopher R. Vakoc[11], and Adi F. Gazdar[6,12]

- 4 subtypes – SCLC-A, SCLC-P, SCLC-N & SCLC-Y!





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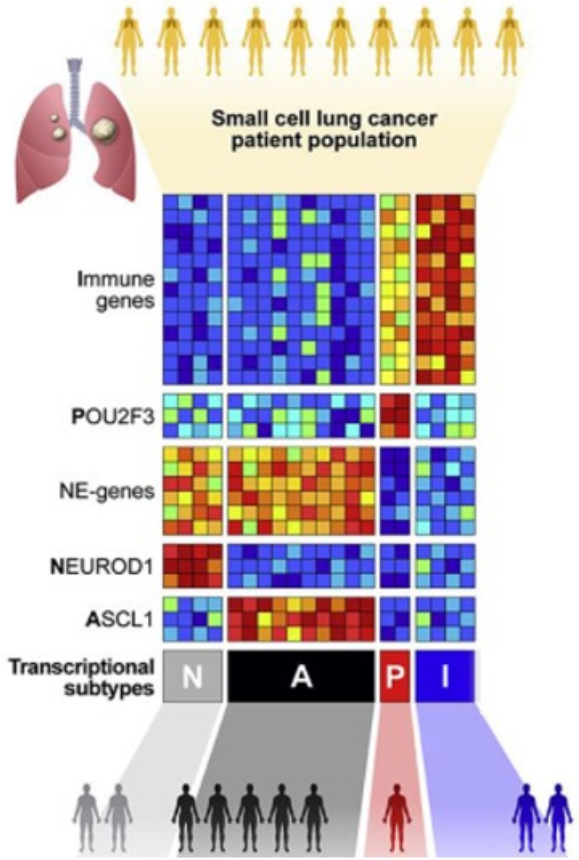
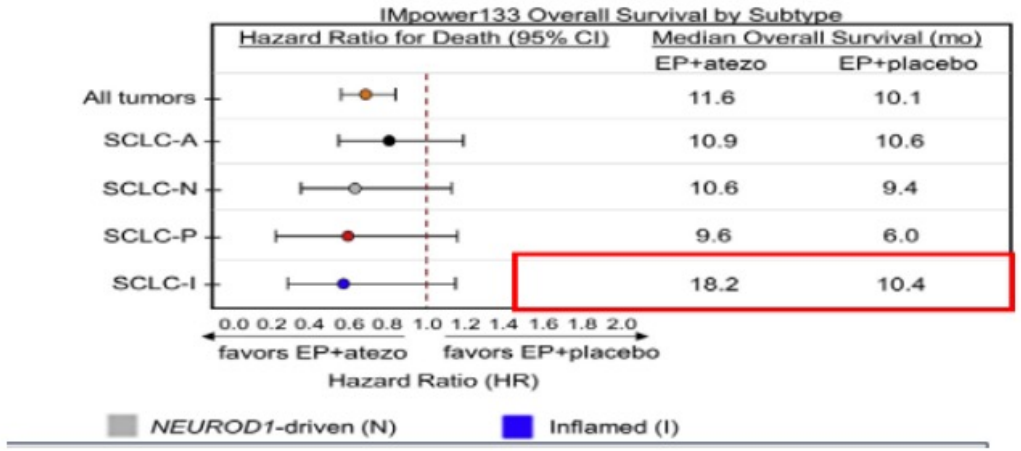
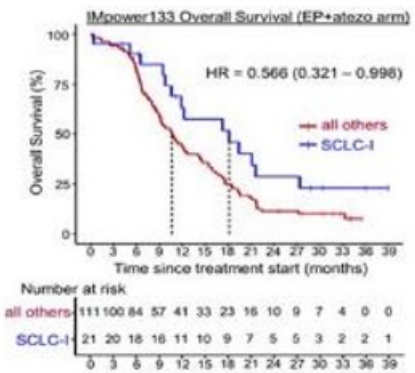
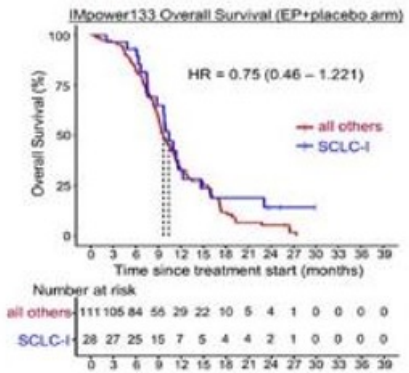
Clinical Impact: SCLC-I subtype may predict response to immunotherapy









- SCLC-I subtype responsive to ICI
- But gene expression based-signatures may not be viable in clinic

Gay. Cancer Cell 2021

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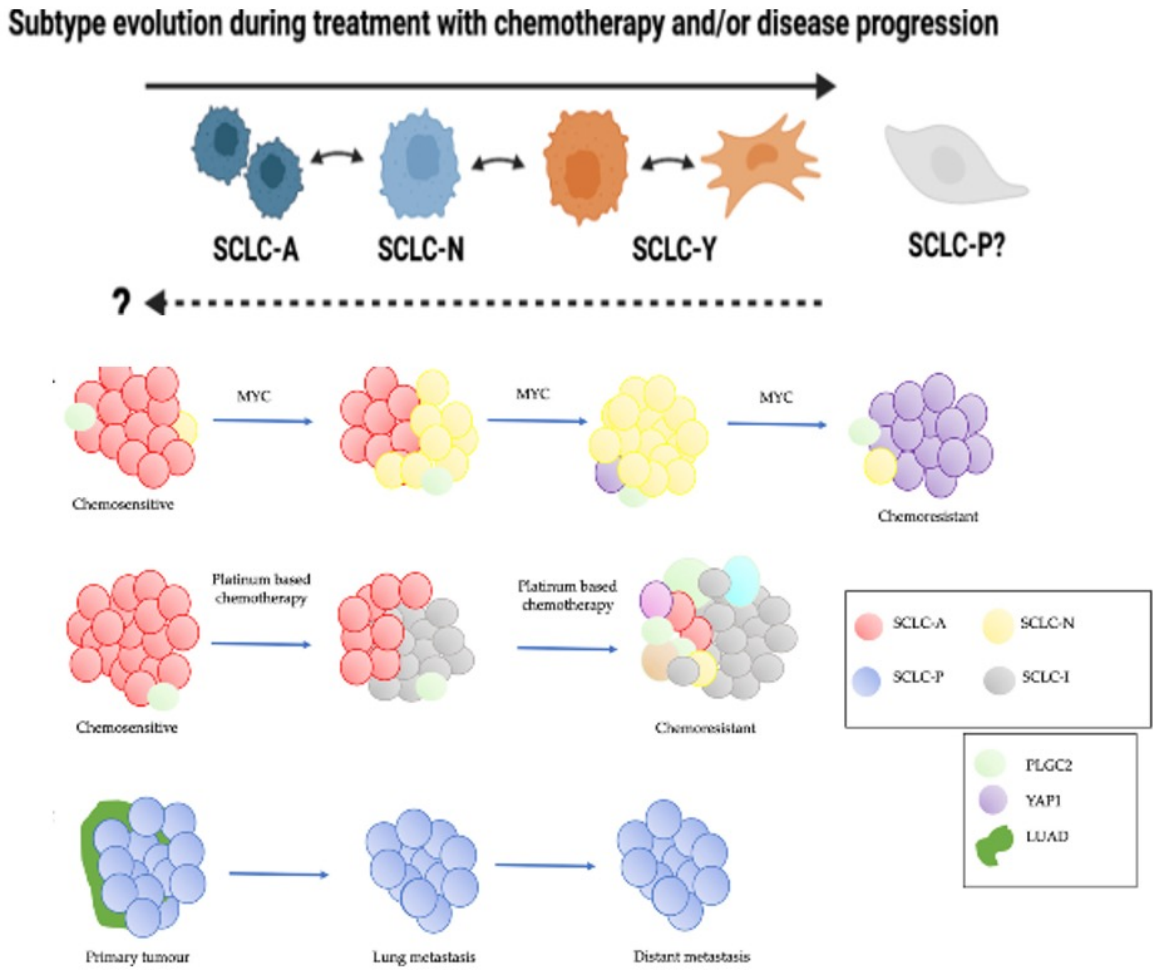
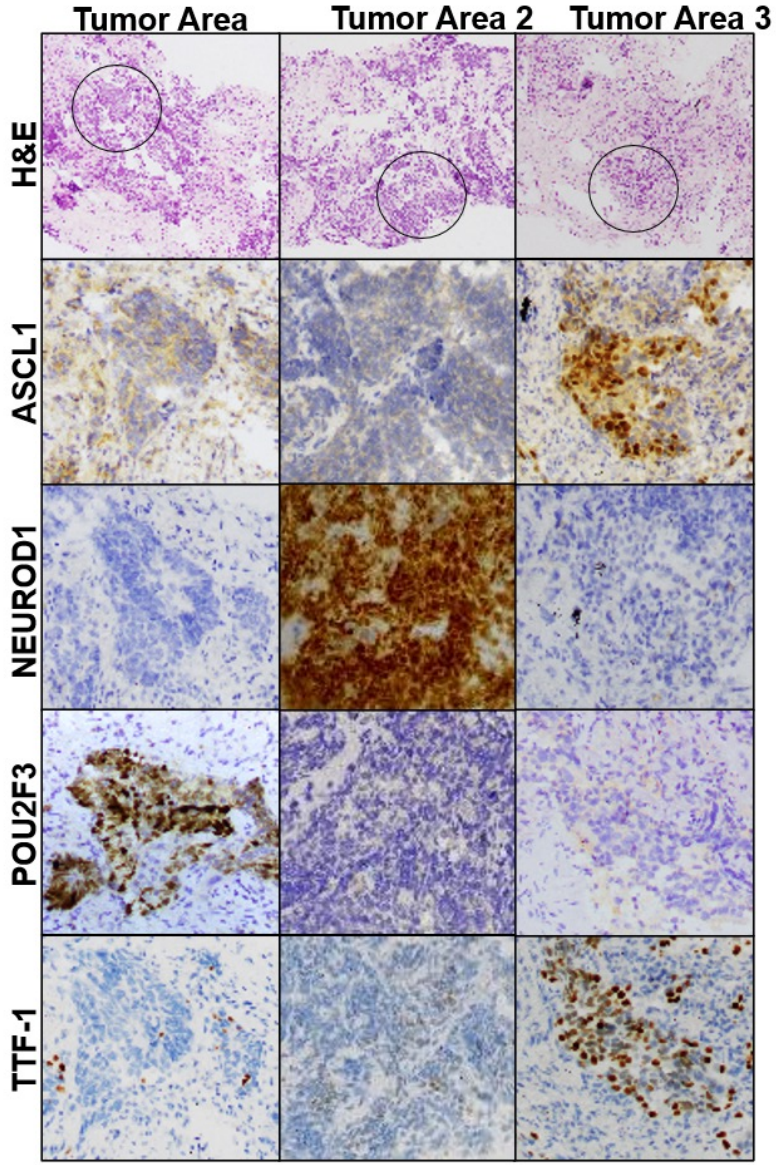
There is more!… SCLC exhibits plasticity enhanced by treatment & tumor evolution



Keogh Cancers 2022
Ireland Cancer Cell 2020
Baine. JTO 2020

Sutherland. Genes Dev 2022



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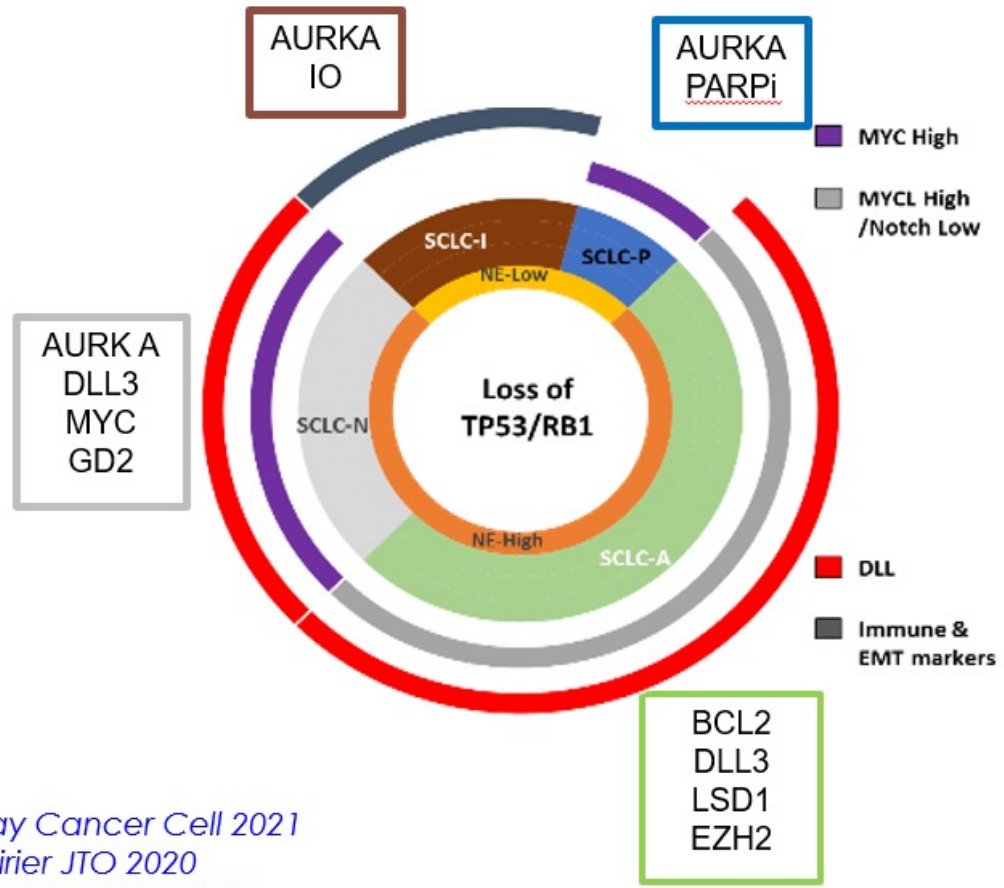
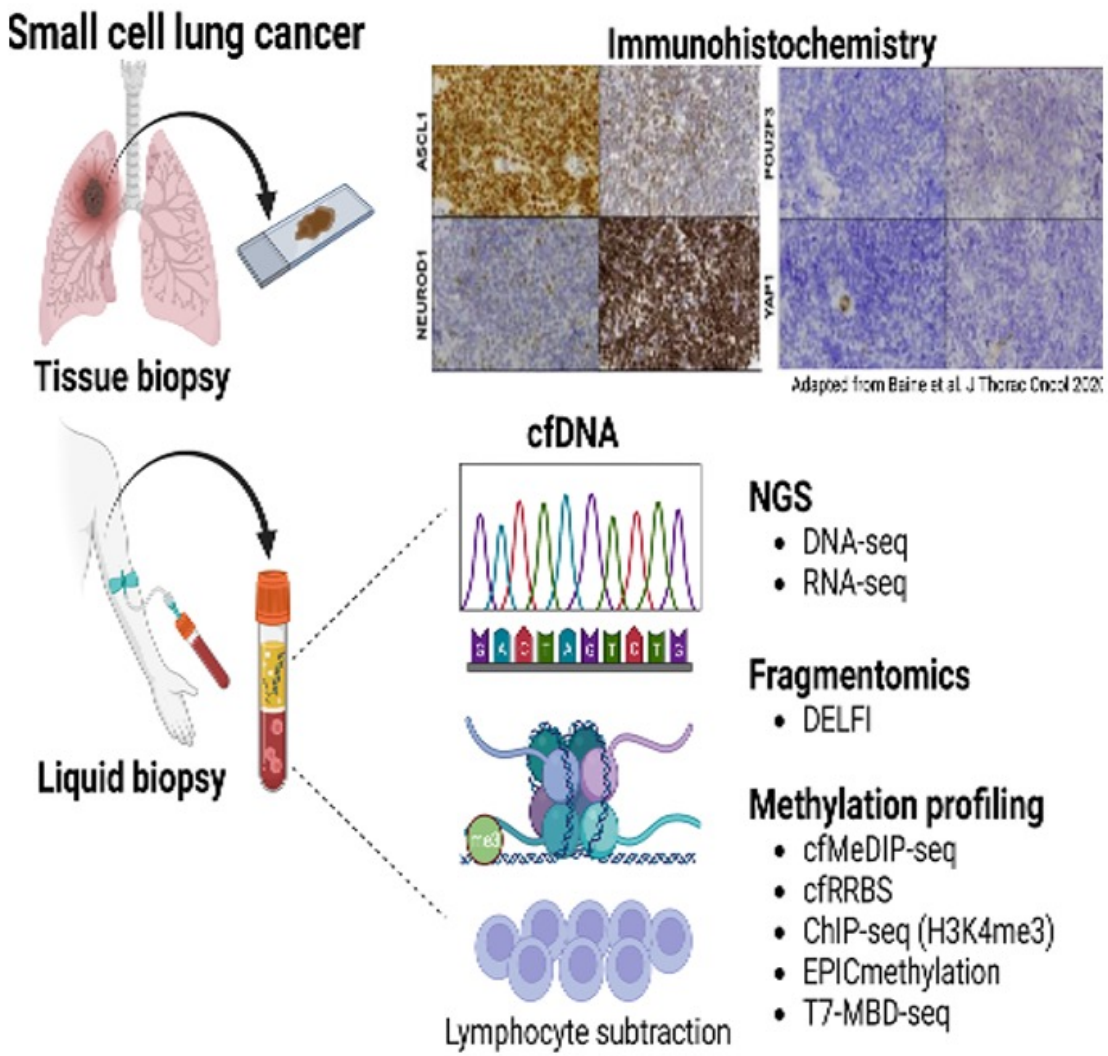
Clinical implications for SCLC subtypes



Gay Cancer Cell 2021
Poirier JTO 2020
Shields ASCO 2023

SCLC subtype ID by tissue or blood



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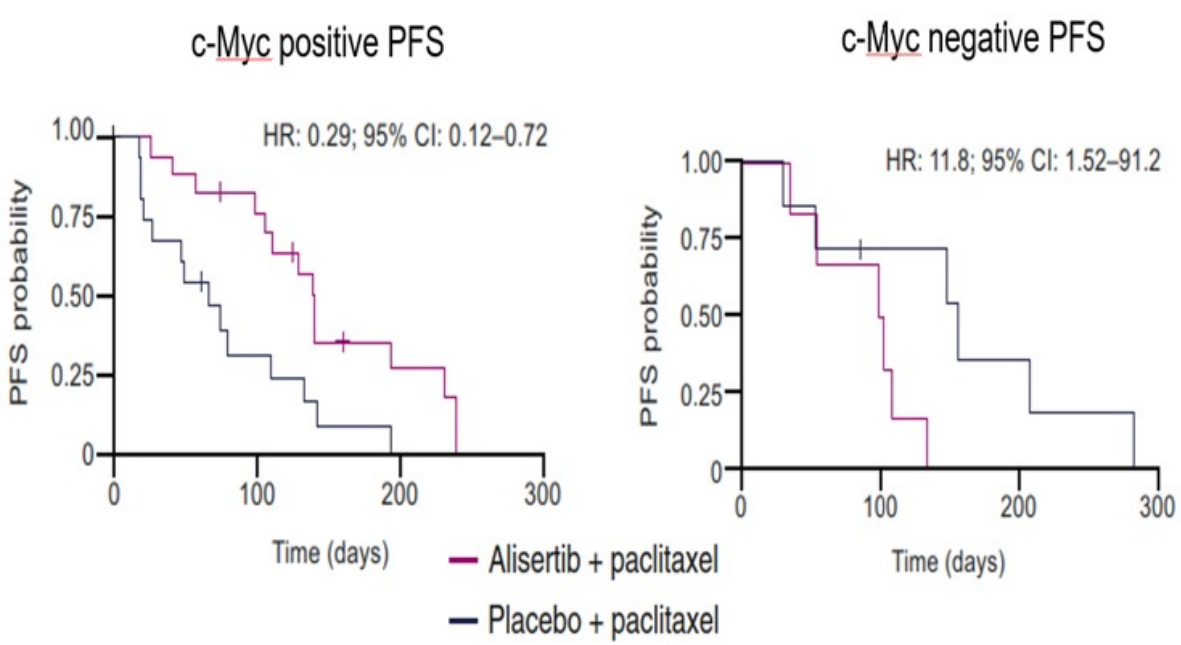
Targeting MYC in SCLC

ORIGINAL ARTICLE

IASLC

Randomized Phase II Study of Paclitaxel plus Alisertib versus Paclitaxel plus Placebo as Second-Line Therapy for SCLC: Primary and Correlative Biomarker Analyses

Taofeek K. Owonikoko, MD,[a,*] Huifeng Niu, PhD,[b] Kristiaan Nackaerts, MD, PhD,[c] Tibor Csoszi, MD,[d] Gyula Ostoros, MD,[e] Zsuzsanna Mark, MD,[f] Christina Baik, MD, MPH,[g] Anil Abraham Joy, MD,[h] Christos Chouaid, MD,[i] Jesus Corral Jaime, MD,[j] Vitezslav Kolek, MD, PhD,[k] Margarita Majem, MD, PhD,[l]

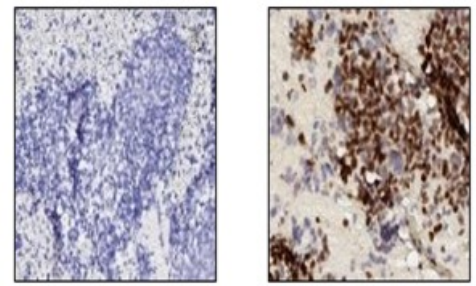


Targeting SLFN11 in SCLC

SLFN11 predicted improved PFS and OS in Veliparib (PARPi) - Temozolomide (TMZ) combination cohort

SLFN11 Negative

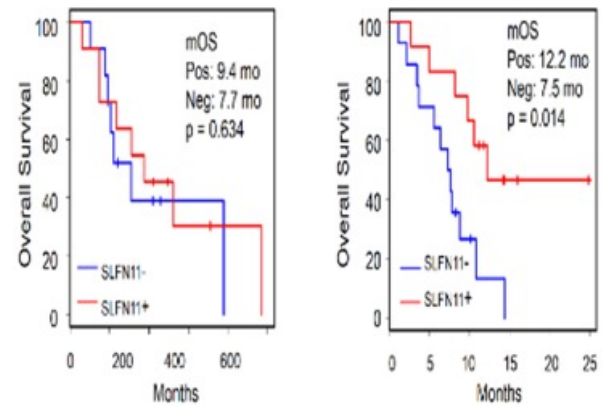
SLFN11 Positive



- FFPE sections from archival (diagnostic) tumors stained for SLFN11 (>1% = positive)
- **High SLFN11 (IHC) predicts improved outcome in Veliparib/TMZ arm (PFS, OS)** *(Interaction p-value 0.009)*

Placebo/TMZ

Veliparib/TMZ



OS 12.2 months in SLFN11+ Patients vs SLFN11- (7.5mo)

Pietanza et al, JCO, 2018

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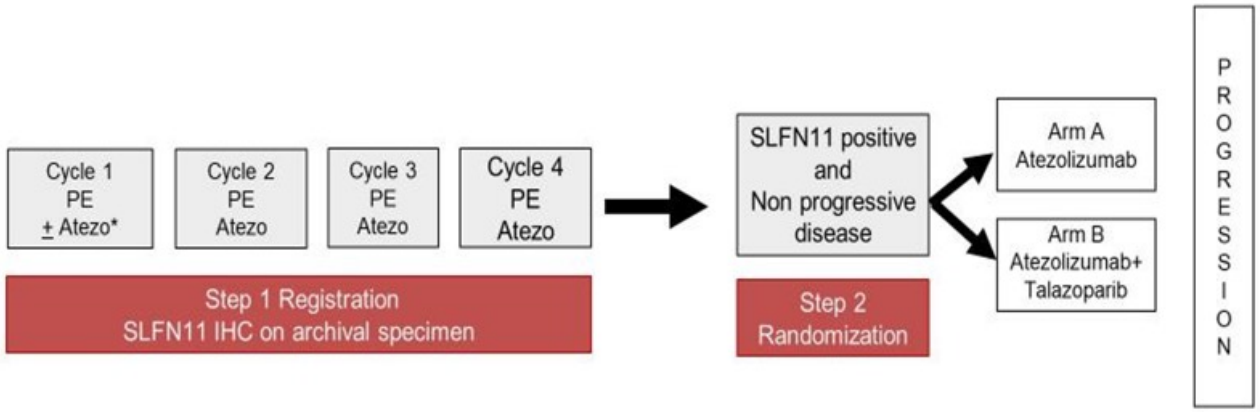
Targeting SLFN11 in SCLC- *Selected Population*

PRIMO 2024
February 7-10, 2024
The Royal Sonesta Kaua'i Resort | Lihue, Hawaii
PrimO Practical Recommendations in Immuno & Molecular Oncology

S1929: Phase II Study of Maintenance Atezolizumab Versus Atezolizumab in Combination with Talazoparib in Patients with SLFN11 Positive Extensive Stage Small Cell Lung Cancer (ES-SCLC) NCT04334941

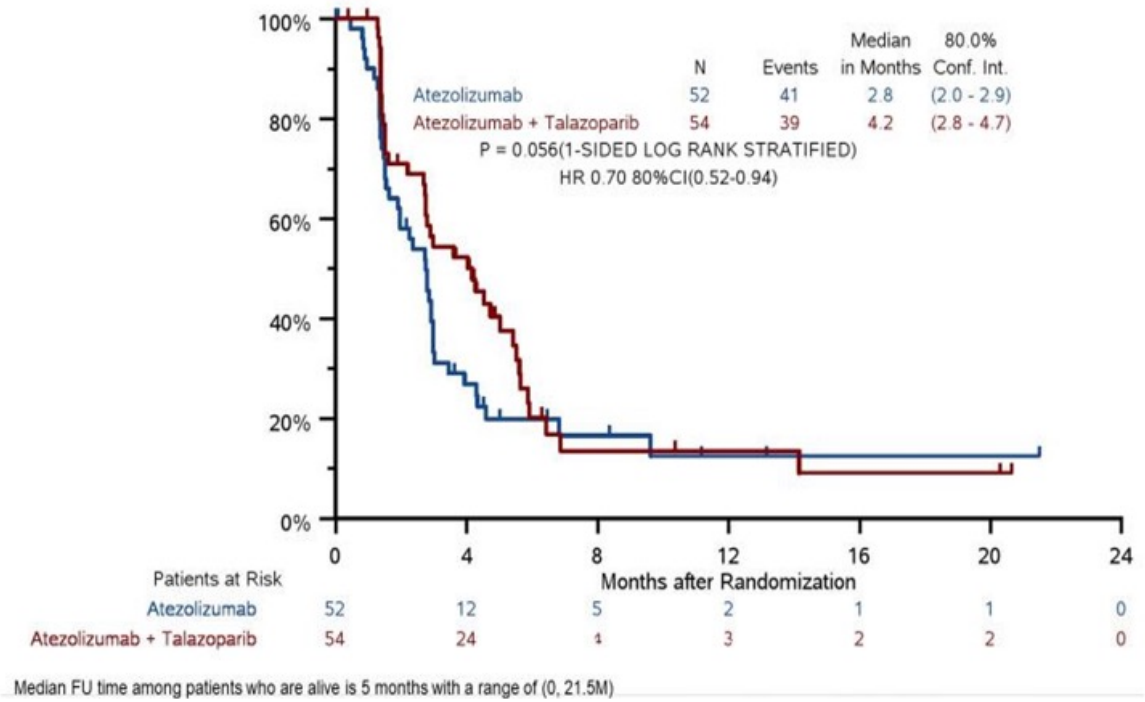


Hypothesis: The addition of talazoparib to maintenance atezolizumab will improve PFS in SLFN11+ SCLC.

Primary Endpoint: PFS
Secondary endpoints: OS, ORR, AE.
TM Objective: To bank specimens for future correlative studies.

**Atezolizumab was optional if the patient is hospitalized for cycle 1*
A maximum of 9 weeks after the end of cycle 4 was allowed prior to randomization

Progression Free Survival



Median FU time among patients who are alive is 5 months with a range of (0, 21.5M)

2023 ASCO Annual Meeting. Nagla Abdel Karim, MD

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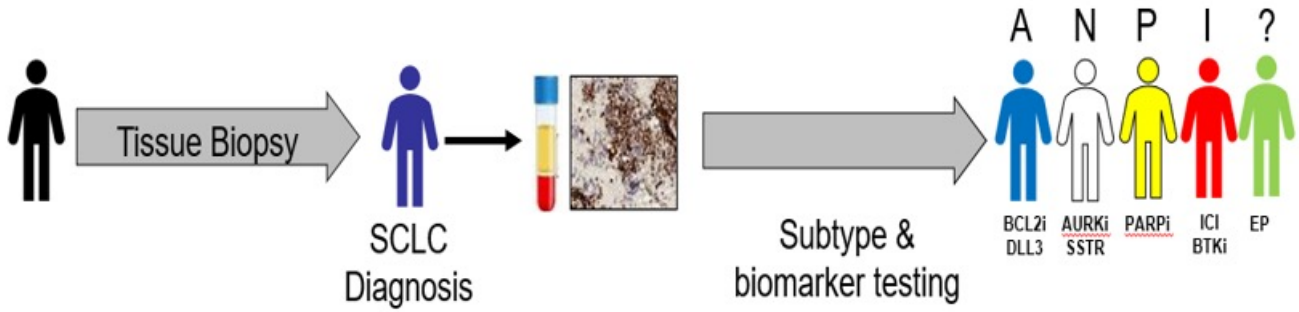
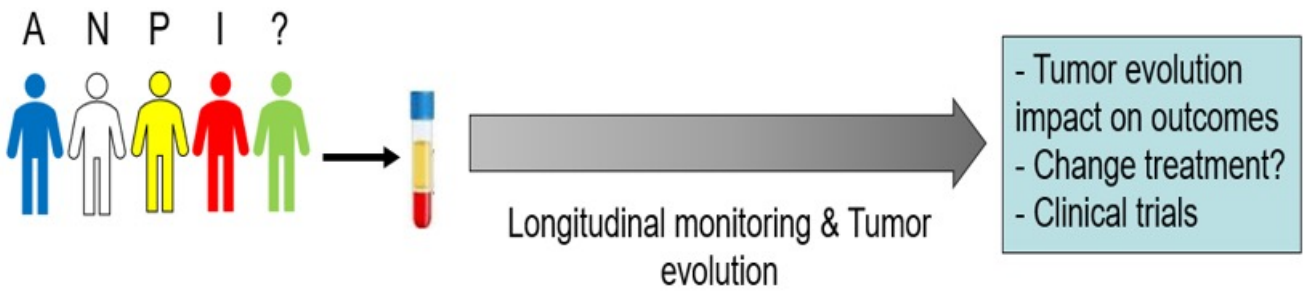
Personalizing SCLC Treatment→





Biomarker	Status
PD-L1	
tTMB	
ecDNA	
CD8/MHC-I	
MYC	
SCLC subtypes	
SLFN11	
DLL3	

SCLC Biomarker Scorecard- Conclusions:

- At present biomarker testing in SCLC has minimal impact in clinic
- Transcriptional subtypes:
  - Need simple & robust test platforms
    - ✓ IHC or blood-based testing
  - Guide selection of patients for clinical trials
- Continued surveillance during treatment
- BiTEs targeting DLL3 are promising
- Other targets – SLFN11, c-Myc and LSD1

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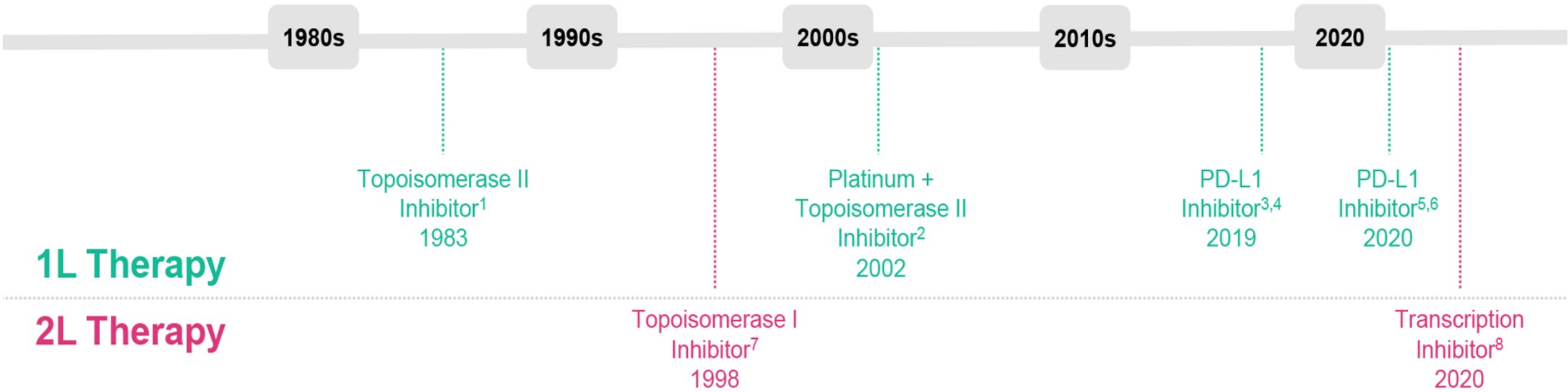
Timeline of FDA-approved Therapies for SCLC



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Limited-Small Cell Lung Cancer

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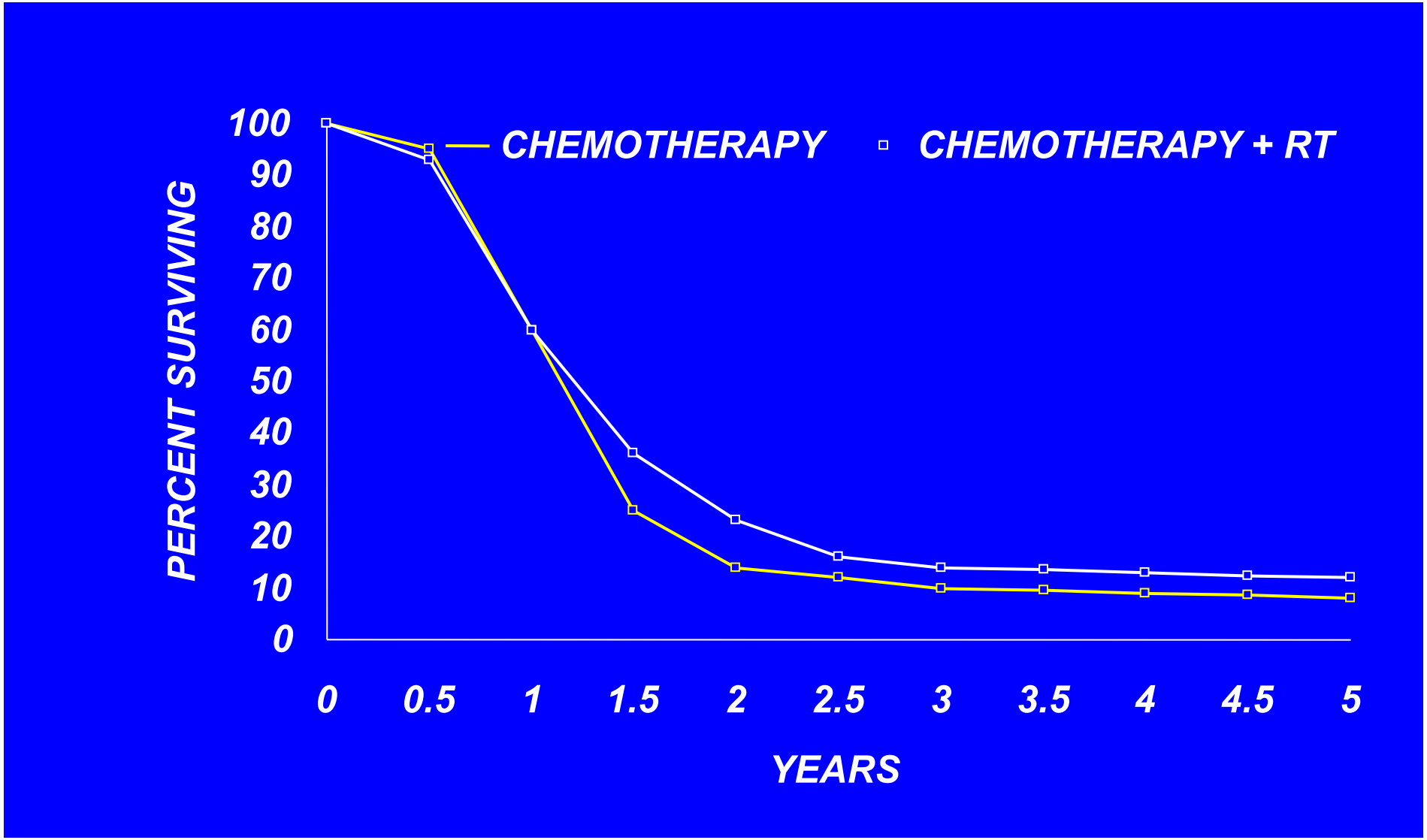
Limited Stage Small Cell Lung Cancer

Chemotherapy vs Chemotherapy + RT (N = 2103)

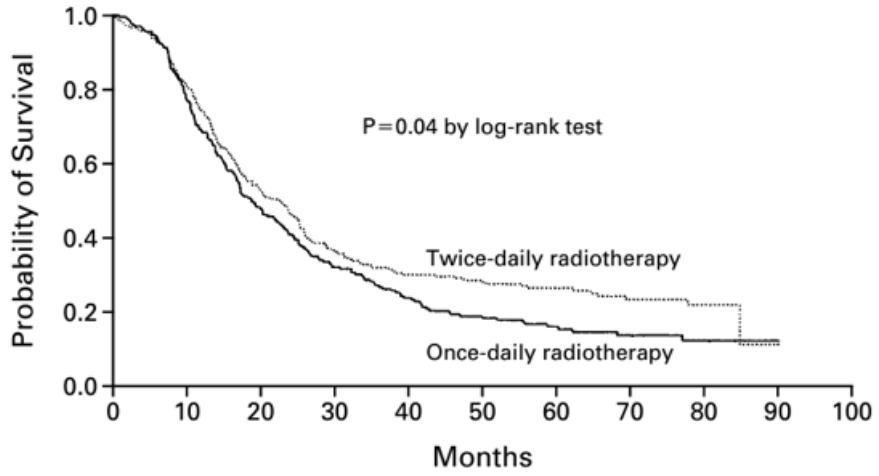


Chemotherapy with Chest Radiotherapy in L-SCLC

Modality	Schedule
First-line chemotherapy	Cisplatin 60 mg/m^2 IV day 1; etoposide 120 mg/m^2/d IV days 1-3; repeat every 3 weeks
	Cisplatin 80 mg/m^2 IV day 1; etoposide 100 mg/m^2/d IV days 1-3; repeat every 3-4 weeks
	Cisplatin 80 mg/m^2 IV day 1; etoposide 80 mg/m^2/d IV days 1-3; repeat every 3 weeks
	Cisplatin 25 mg/m^2 IV days 1-3; etoposide 80 mg/m^2/d IV days 1-3; repeat every 3-4 weeks
	Cisplatin 60 mg/m^2 IV day 1; etoposide 120 mg/m^2/d IV days 1-3; repeat every 3 weeks
	Carboplatin AUC 5 IV day 1; etoposide 100 mg/m^2/d IV days 1-3; repeat every 4 weeks
	Carboplatin AUC 5 IV day 1; etoposide 80 mg/m^2/d IV days 1-3; repeat every 3-4 weeks
Thoracic radiotherapy	1.5 Gy twice daily (at least 6 hours apart) in 3 weeks for total dose of 45 Gy
	1.8 Gy daily over 6.5 weeks to total dose of at least 60 Gy
Prophylactic cranial irradiation	25 Gy in 10 daily fractions
	30 Gy in 10-15 daily fractions

L-SCLC: QD or BID RT

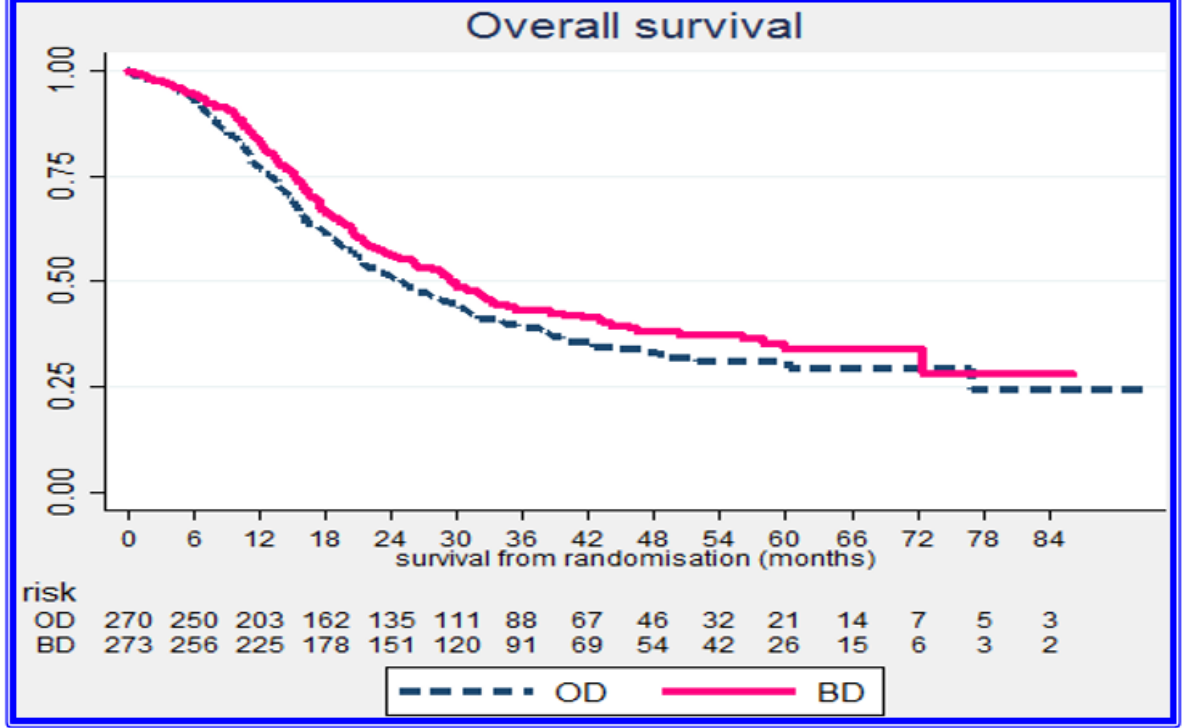
Intergroup 45 Gy QD vs BID



Treatment Group	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

Figure 1. Kaplan–Meier Estimates of Overall Survival for All 417 Patients Assigned to Treatment Groups.

CONVERT 45 Gy BID vs 60 GY QD



OS(n=543)	BD	OD	Log-rank
Median Mo.	30 (24-34)	25 (21-31)	p=0.15
1-year	83% (78-87)	76% (71-81)	
2-year	56% (50-61)	51% (45-57)	
3-year	43% (37-49)	39% (33-45)	

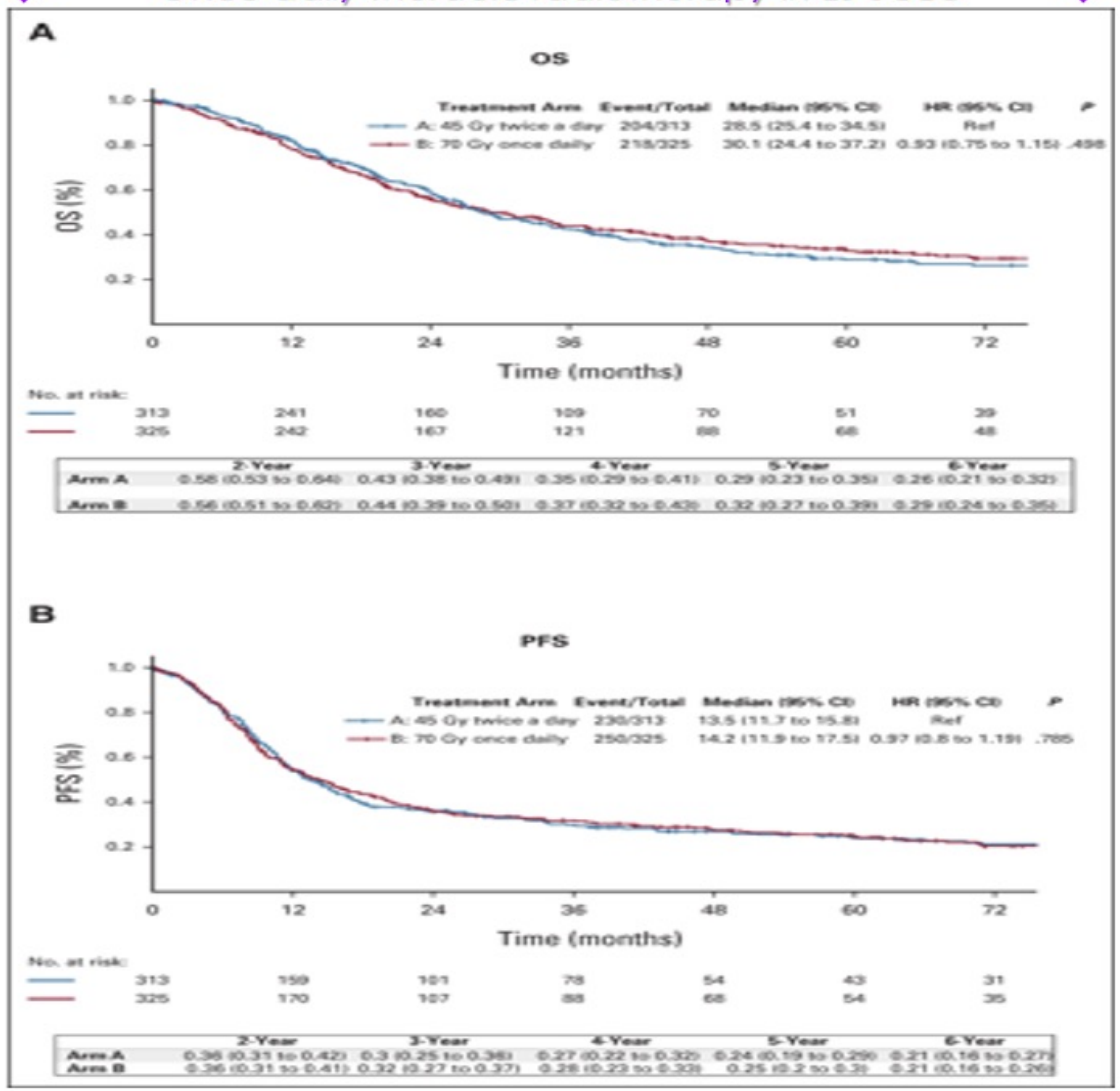
Other Studies comparing RT Twice vs Once Daily in Combination with Chemotherapy

Phase III trials of once-daily thoracic radiation therapy compared towith twice daily in combination with cisplatin and etoposide

First author [reference no.]	#No. of patients	Chemotherapy	Thoracic radiation therapy	Median overall survival (months)	Hazard ratio or *p* value	5-year overall survival rate
Turrisi [22]	206	Cisplatin and etoposide, 4 cycles	45 Gy once daily starting cycle 1	19	$p = .04$	16%
	211	Cisplatin and etoposide, 4 cycles	45 Gy twice daily starting cycle 1	23		26%
Schild [23]	131	Cisplatin and etoposide, 6 cycles	50.4 Gy daily starting cycle 4	20.6	$p = .68$	21%
	130	Cisplatin and etoposide, 6 cycles	Split course: 24 Gy, a 2.5 week break, and 24 Gy starting cycle 4	20.6		22%
Faivre-Finn [24]	274	Cisplatin and etoposide, 4–6 cycles	45 Gy twice daily starting cycle 2	30	HR: 1.18, $p = .14$	34%
	273	Cisplatin and etoposide, 4–6 cycles	66 Gy once daily starting cycle 2	25		31%

Abbreviation: HR, hazard ratio.

CALGB 30610(Alliance)/RTOG0538
Once daily thoracic radiotherapy in LS SCLC



No advantage of 70 Gy QD vs 45 Gy BID; *Jeffrey Bogart, et al; J Clin Oncol. 2023, 41(13):2394-402.*

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Ongoing Phase II and Phase III Trials in L- SCLC

Agent	Mechanism of Action	Phase	Sample Size	Primary End Point	NCT
Concurrent with chemoradiation and as consolidation					
Durvalumab	Anti–PD-L1	2	51	PFS	NCT03585998
Durvalumab (DOLPHIN)	Anti–PD-L1	2	105	PFS	NCT04602533
Pembrolizumab concurrent followed by pembrolizumab ± olaparib (KEYLYNK-013)	Anti–PD-1 and PARP inhibitor	3	672	PFS, OS	NCT04624204
Atezolizumab (NRG LU-005)	Anti–PD-L1	2 or 3	506	PFS or OS	NCT03811002
Sintilimab induction plus platinum-etoposide, followed by chemoradiation and sintilimab consolidation	Anti–PD-1	2	140	PFS	NCT04189094
Consolidation following chemoradiation					
Toripalimab	Anti–PD-1	2	170	PFS	NCT04418648
SHR-1316	Anti–PD-1	2	60	PFS	NCT04647357
Atezolizumab (ACHILES)	Anti–PD-L1	2	212	2 year OS	NCT03540420
Ipilimumab and nivolumab (STIMULI)	Anti–CTLA-4 and anti–PD-1	2	174	OS, PFS	NCT02046733
Durvalumab plus or minus tremelimumab (ADRIATIC)	Anti–PD-L1 and anti–CTLA-4	3	724	PFS, OS	NCT03703297
Atezolizumab ± tiragolumab	Anti–PD-L1 and anti–TIGIT	2	150	PFS	NCT04308785

Abbreviations: CTLA-4, cytotoxic T-cell lymphocyte-4; ICI, immune checkpoint inhibitor; LS-SCLC, limited-stage small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

Bogart J. et al; J Clin Oncol. 2023, 41(13):2394-402.

Extensive-Small Cell Lung Cancer

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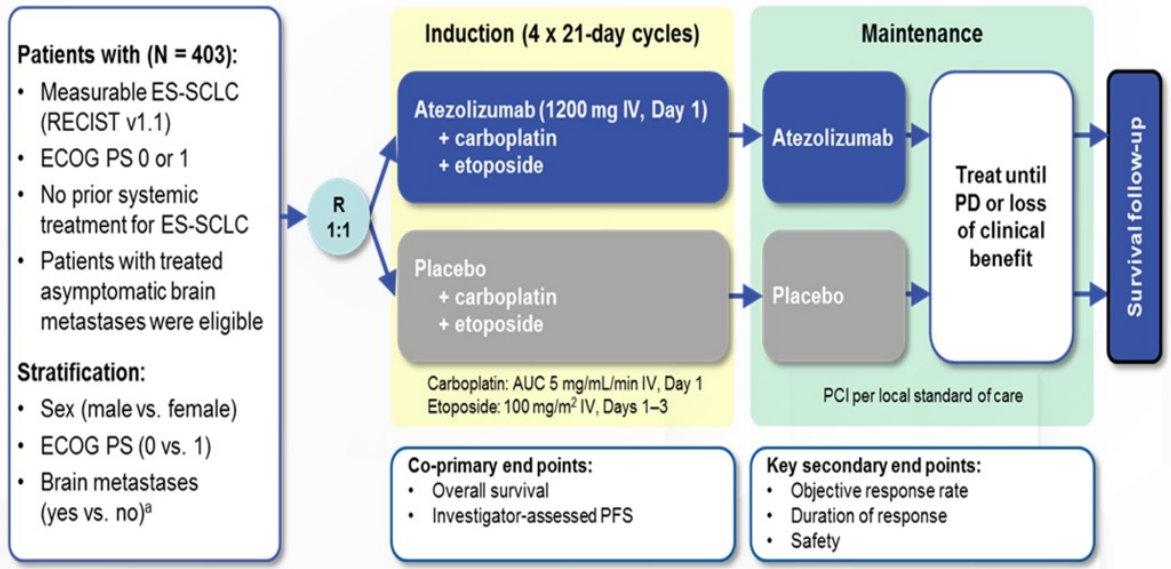
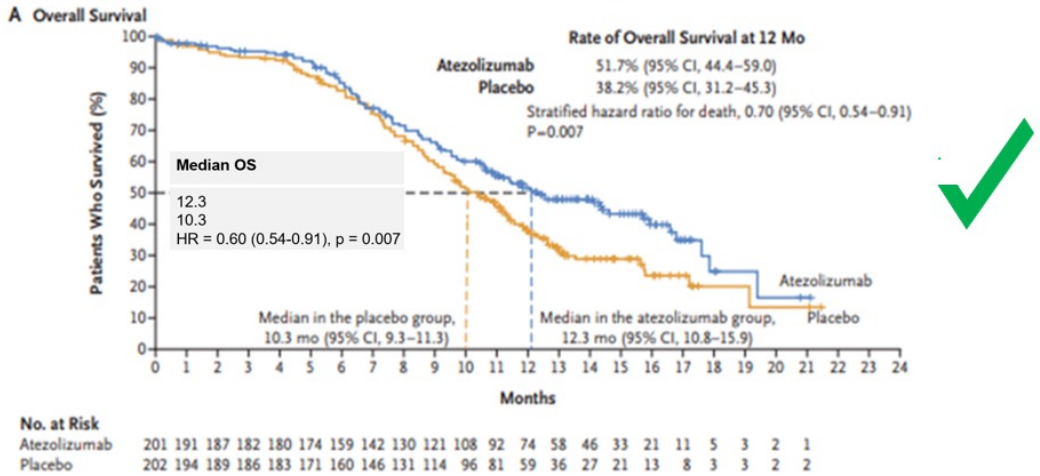
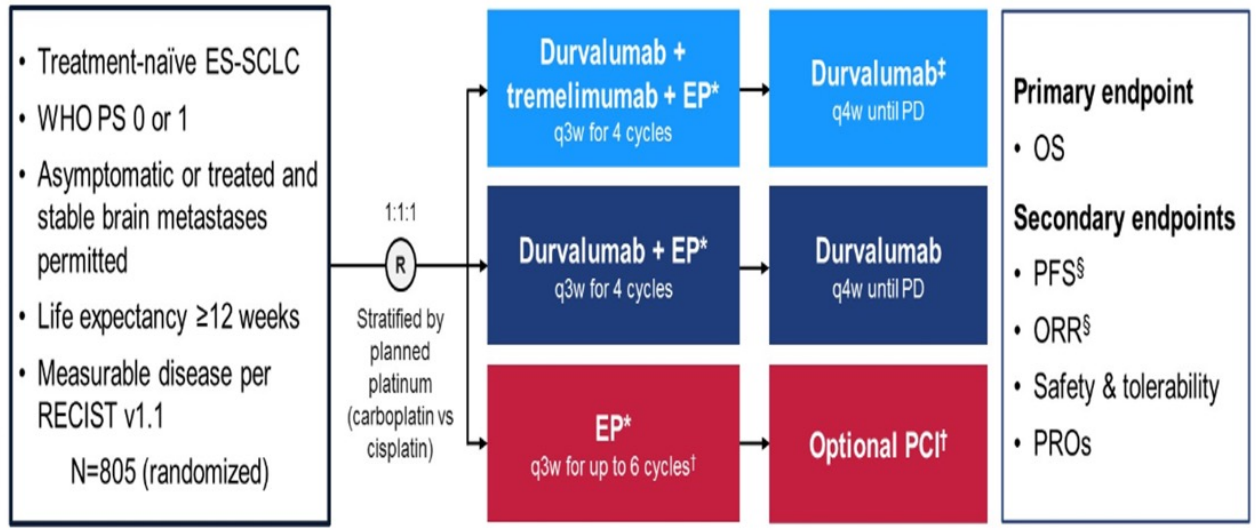
First Line Therapy for SCLC is well defined (for now).

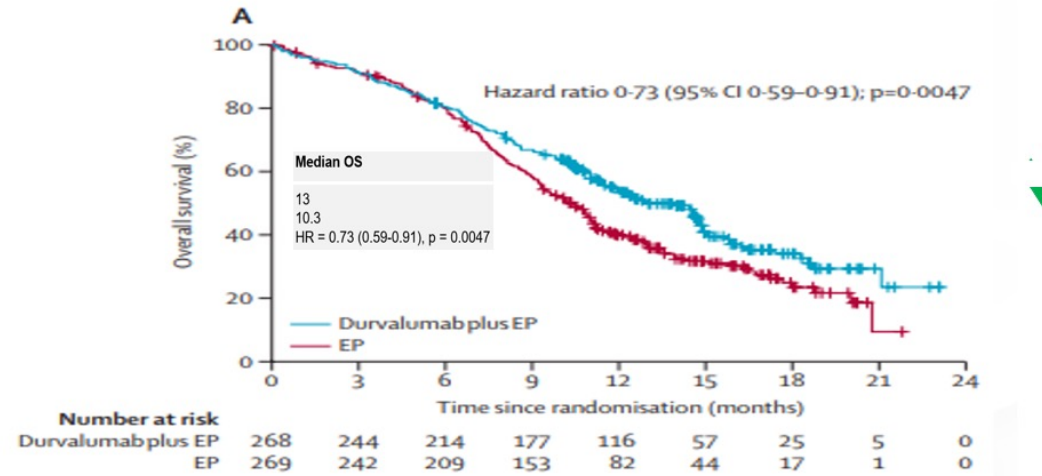
IMpower133: Study Design



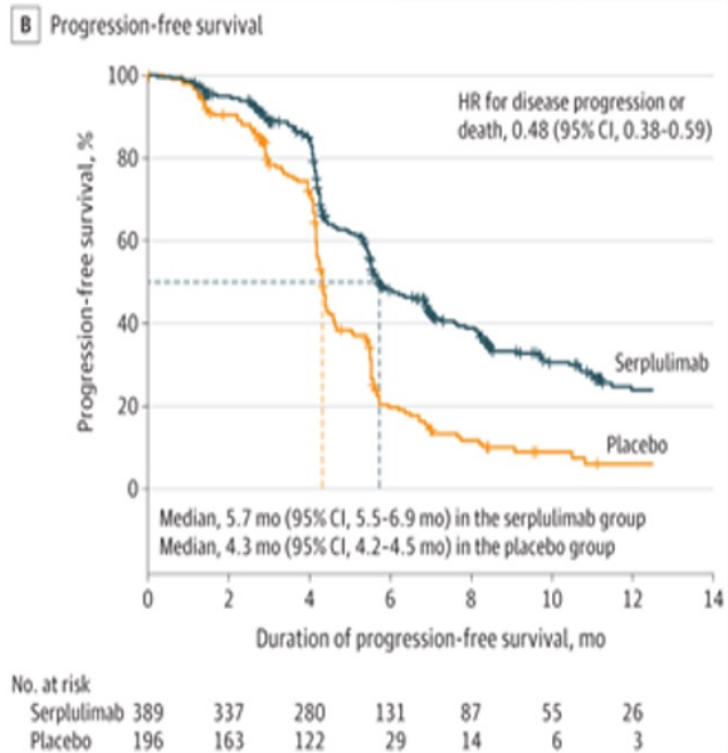


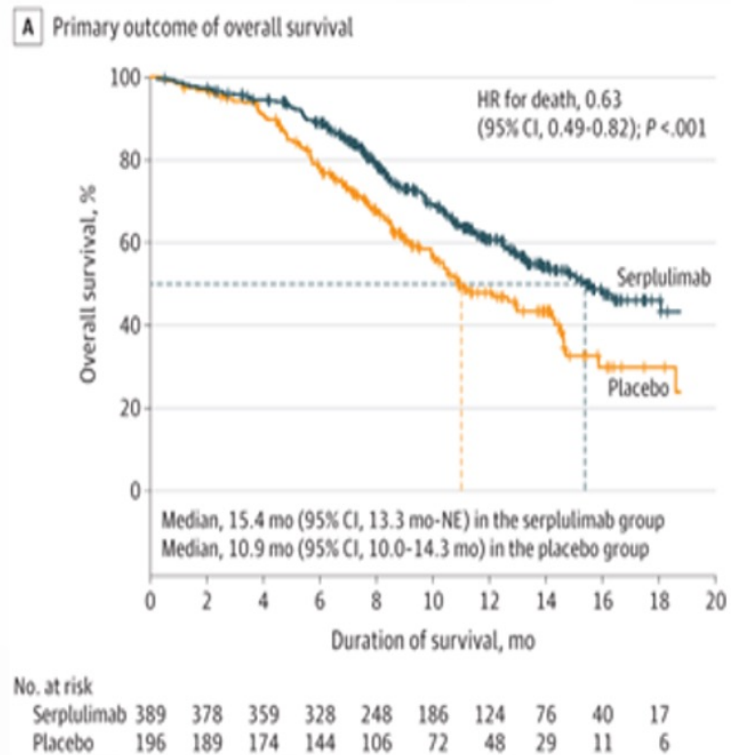
CASPIAN: Study Design





ASTRUM-005 (Serplimumab)





Median OS

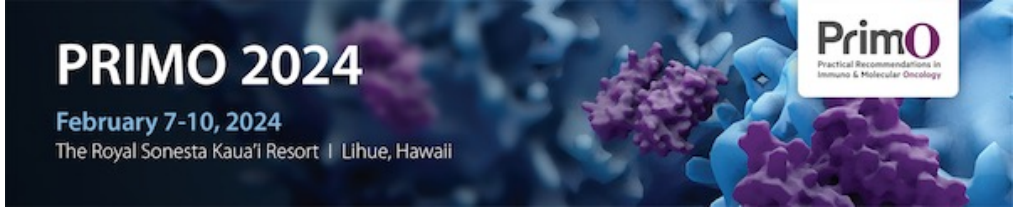
15.4

10.9

HR = 0.63 (0.49-0.82); p < 0.001

Cheng Y, et al. JAMA. 2022;328(12):1223-32.

Prior Efforts to Treat SCLC→



- SCLC is an aggressive disease with limited treatment options beyond first-line chemo-immune therapy and no approved third-line therapy

Trial	Phase	Drug	ORR	PFS	OS
von Pawel 1999	2	Topotecan IV	24%	~3.1 mo	--
von Pawel 1999	2	CAV	18%	~2.9 mo	--
Eckardt 2007	3	Topotecan PO	18%	~2.8 mo	~7.7 mo
Pietanza 2012	2	Temozolomide	20%	1.6 mo	5.8 mo
Pietanza 2018	2	Temozolomide + Veliparib	39%	3.8 mo	8.2 mo
Farago 2019	2	Temozolomide + Olaparib	41.7%	4.2 mo	8.5 mo
Checkmate 032, 2020	2	Nivolumab	11.6%	1.4 mo	5.7 mo
Checkmate 032, 2020	2	Nivolumab + Ipilimumab	21.9%	1.5 mo	4.7 mo
Trigo 2020	2	Lurbinectedin	34.7%	3.9 mo	9.3 mo
ATLANTIS, 2021	3	Dox + Lurbi 2mg/m2	31.6%	4.0 mo	8.6 mo
ATLANTIS, 2021	3	Topotecan or CAV	29.7%	4.0 mo	7.6 mo

Gentzler et al. ASCO 2022.

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What Are The Options as Second-line Therapy for Small Cell Lung Cancer?

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[f],
Consider dose reduction or growth factor support for patients with PS 2.

CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS

Preferred Regimens

- Clinical trial enrollment
- Re-treatment with platinum-based doublet[g,34,35,37-39]

Other Recommended Regimens

- Lurbinectedin[17,36]
- Topotecan oral (PO) or intravenous (IV)[14-16,28]
- Irinotecan[h,21,28]

CTFI ≤6 MONTHS

Preferred Regimens

- Clinical trial enrollment
- Lurbinectedin[17,36]
- Topotecan oral (PO) or intravenous (IV)[14-16,28,37]
- Irinotecan[h,21,28]
- Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[g,37,38,39]

Other Recommended Regimens

- Nivolumab or pembrolizumab (if not previously treated with an ICI)[b, 29,30,31,32,33]
- Paclitaxel[18,19]
- Temozolomide[22,23]
- Cyclophosphamide/doxorubicin/vincristine (CAV)[14]
- Docetaxel[20]
- Gemcitabine[26,27,40]
- Oral etoposide[24,25]

NCCN Guidelines- Version 2.2024, 11/21/23.

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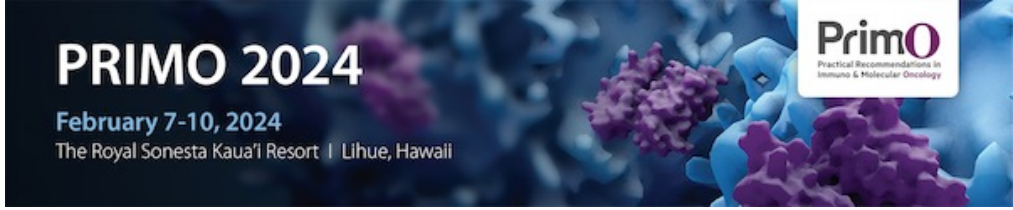
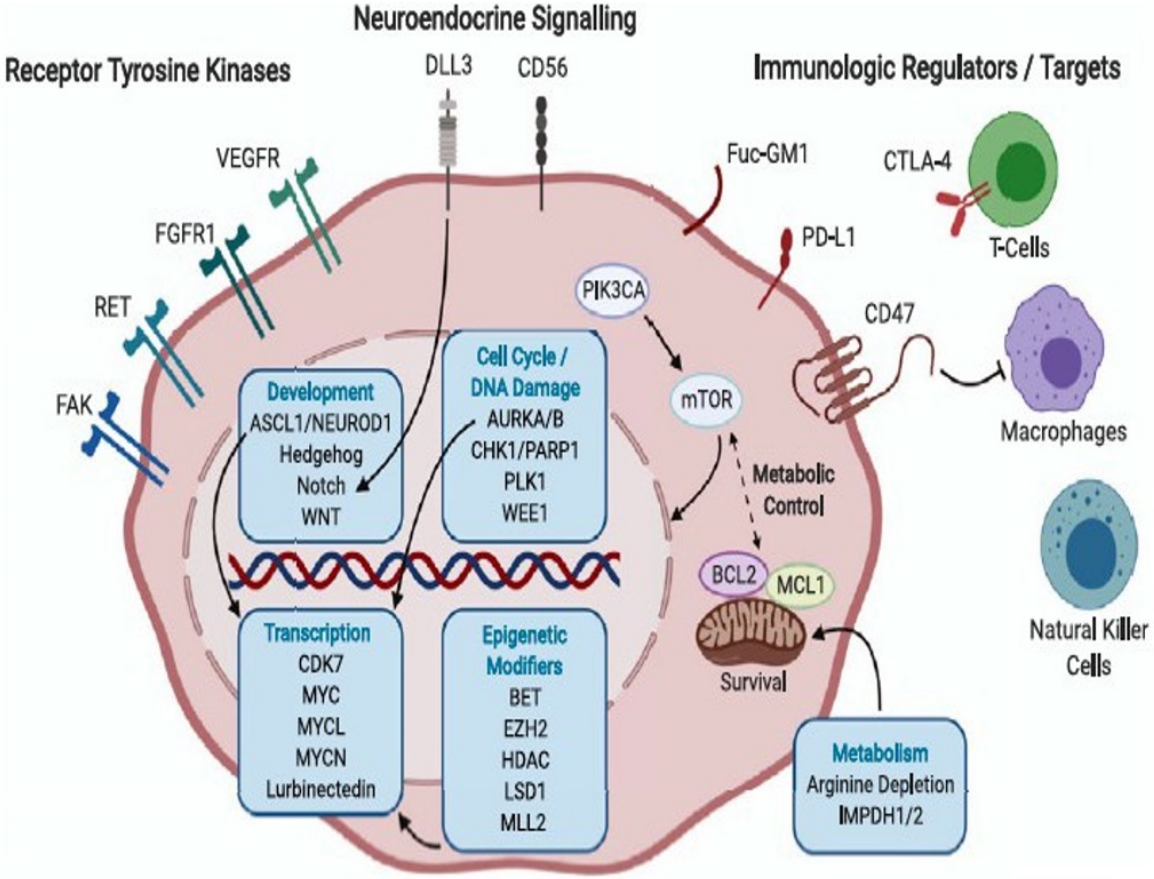
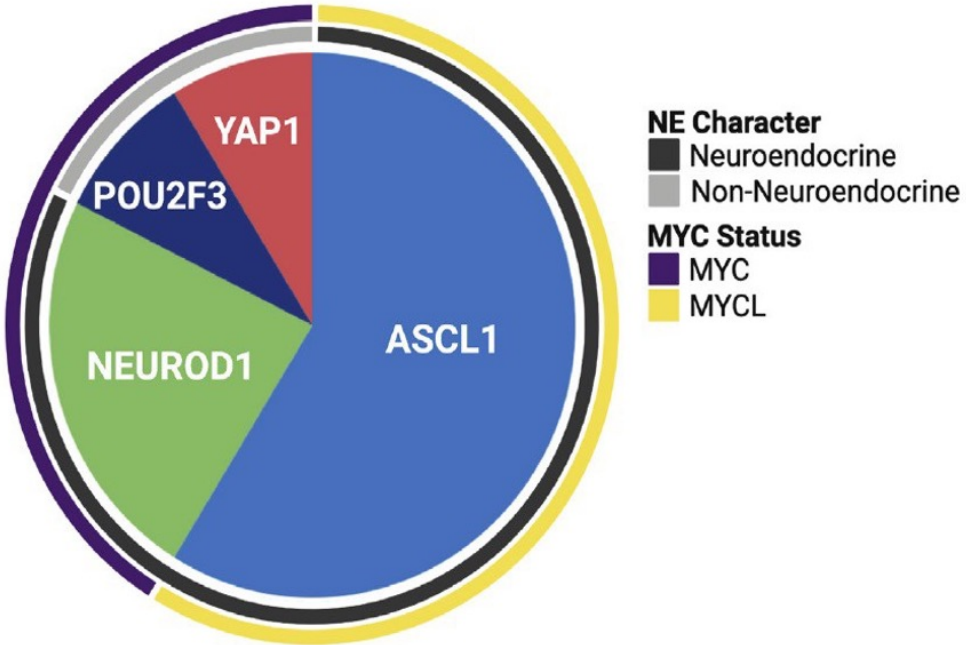
SCLC: Where do we go from here?



Future Directions





	ASCL1	NEUROD1	POU2F3	YAP1
Targeted Therapies	BCL2 CREBBP DLL3 LSD1	Arginine Deprivation AURKA/B CHK1 IMPDH LSD1	Arginine Deprivation AURKA/B CHK1 IGF-R1 IMPDH	Arginine Deprivation AURKA/B CHK1 IMPDH IO

Poirier et al, JTO 2020

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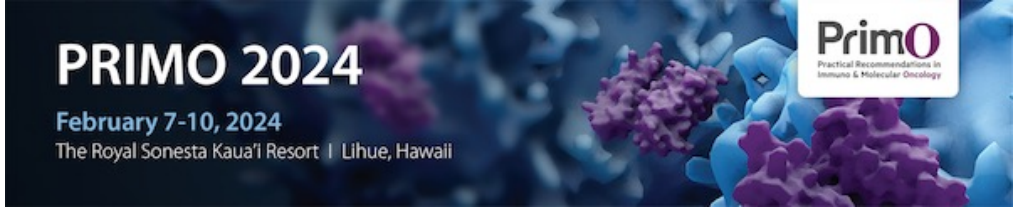

Future Directions

Ongoing clinical trials

Phase 3 LAGOON trial ongoing

- **Confirmatory phase 3 trial has been initiated: LAGOON**

- Patients with SCLC progression following prior platinum-containing chemotherapy with or without anti–PD-1 or anti–PD-L1 agents
- Expected N: 705 from >100 sites, mainly in North America and Europe

R

- **Lurbinectedin monotherapy**
  or
  lurbinectedin + irinotecan
- **Investigator's choice**
  (topotecan or irinotecan)

Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	705 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Multicenter, open-label, randomized, controlled
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Randomized, Multicenter, Open-label, Phase III Study of Lurbinectedin Single-Agent or Lurbinectedin in Combination With Irinotecan Versus Investigator's Choice (Topotecan or Irinotecan) in Relapsed Small Cell Lung Cancer Patients (LAGOON Trial)
Actual Study Start Date:	July 22, 2022
Estimated Primary Completion Date:	June 2025
Estimated Study Completion Date:	June 2025

- **Primary endpoint:** OS
- **Secondary endpoint:** PFS

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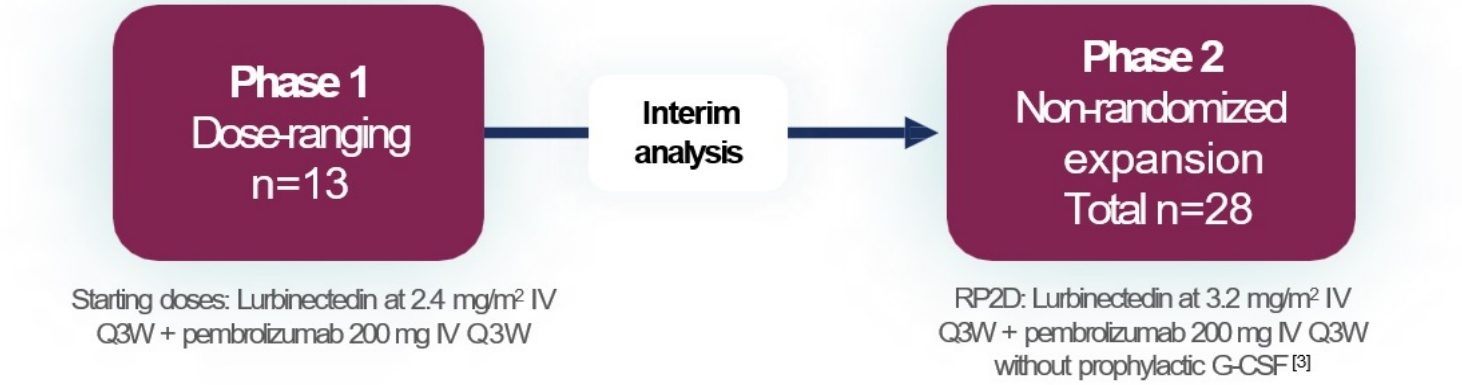
LUPER Study. Background and Study Design

- Patients with small-cell lung cancer (SCLC) who relapse have a very poor prognosis and very limited treatment options. [1]
- Lurbinectedin inhibits trans-activated transcription and modulates the tumor microenvironment and is FDA approved for metastatic SCLC patients with progressive disease on or after platinum-based chemotherapy.[2]
- LUPER is a prospective, phase I/II, multicenter, open-label, clinical and pharmacokinetic study of the combination of lurbinectedin + pembrolizumab in relapsed SCLC.
- The primary objective in the Phase II stage is to assess the efficacy of lurbinectedin with pembrolizumab in terms of ORR, according to RECIST v.1.1, in patients with relapsed SCLC.[3]
- Secondary endpoints include investigator-assessed DoR, PFS, OS, and safety per CTCAE 5.0.

Key Inclusion Criteria

- ≥18 years old
- Histologically confirmed SCLC
- Progression after 1L platinum-based CT
- No prior exposure to immunotherapy
- ECOG PS of 0-1
- Measurable disease as per RECIST 1.1.
- Brain metastasis allowed if treated and asymptomatic



1 García-Campelo, R., et al. Clin Transl Oncol (2023) 25(9):2679-2691; 2. Singh, S., et al. Clin Cancer Res (2021) 27 (9): 2378–2382; 3. Calles, A., et al. ASCO (2022)

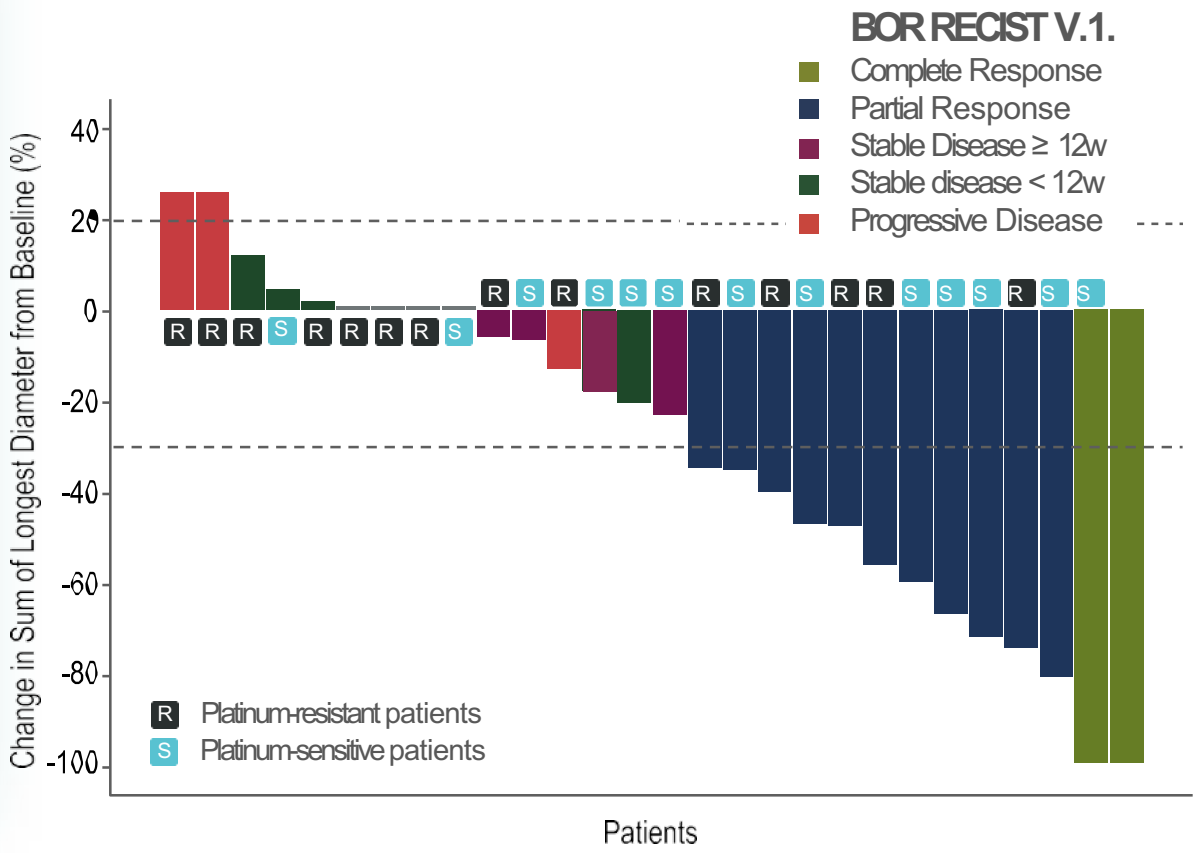
Antonio Calles MD. 2023 ESMO Congress, abstr 1989M0.

LUPER Study

Objective Response Rate (ORR) by RECIST v.1.1.

The primary objective has been achieved with 46.4% confirmed response rate assessed by investigator (95% CI: 29.5–64.2; p < 0.001)

Tumor response, n (%)	Platinum-free interval <90 days (n = 14)	Platinum-free interval ≥90 days (n = 13)	Overall (N = 28)
Best Overall Response			
CR*	0 (0%)	1 (7.7%)	2 (7.1%)
PR	5 (35.7%)	6 (46.2%)	11 (39.3%)
SD ≥ 12w	1 (7.1%)	3 (23.1%)	4 (14.3%)
SD < 12w	2 (14.3%)	2 (15.4%)	4 (14.3%)
PD	3 (21.4%)	0 (0%)	3 (10.7%)
NE	3 (21.4%)	1 (7.7%)	4 (14.3%)
Objective Response Rate			
Yes*	5 (35.7%)	7 (53.9%)	13 (46.4%)
No	9 (64.3%)	6 (46.1%)	15 (53.6%)
Clinical Benefit Rate			
Yes*	6 (42.9%)	10 (76.9%)	17 (60.7%)
No	8 (57.1%)	3 (23.1%)	11 (39.3%)

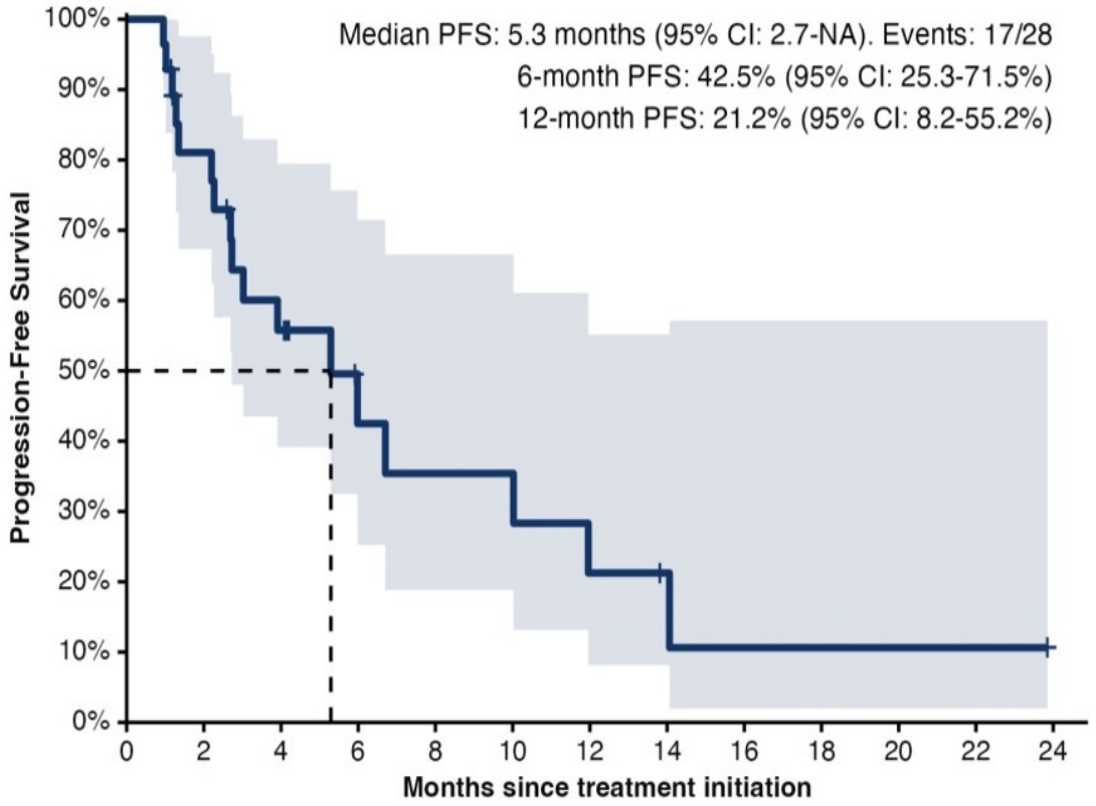


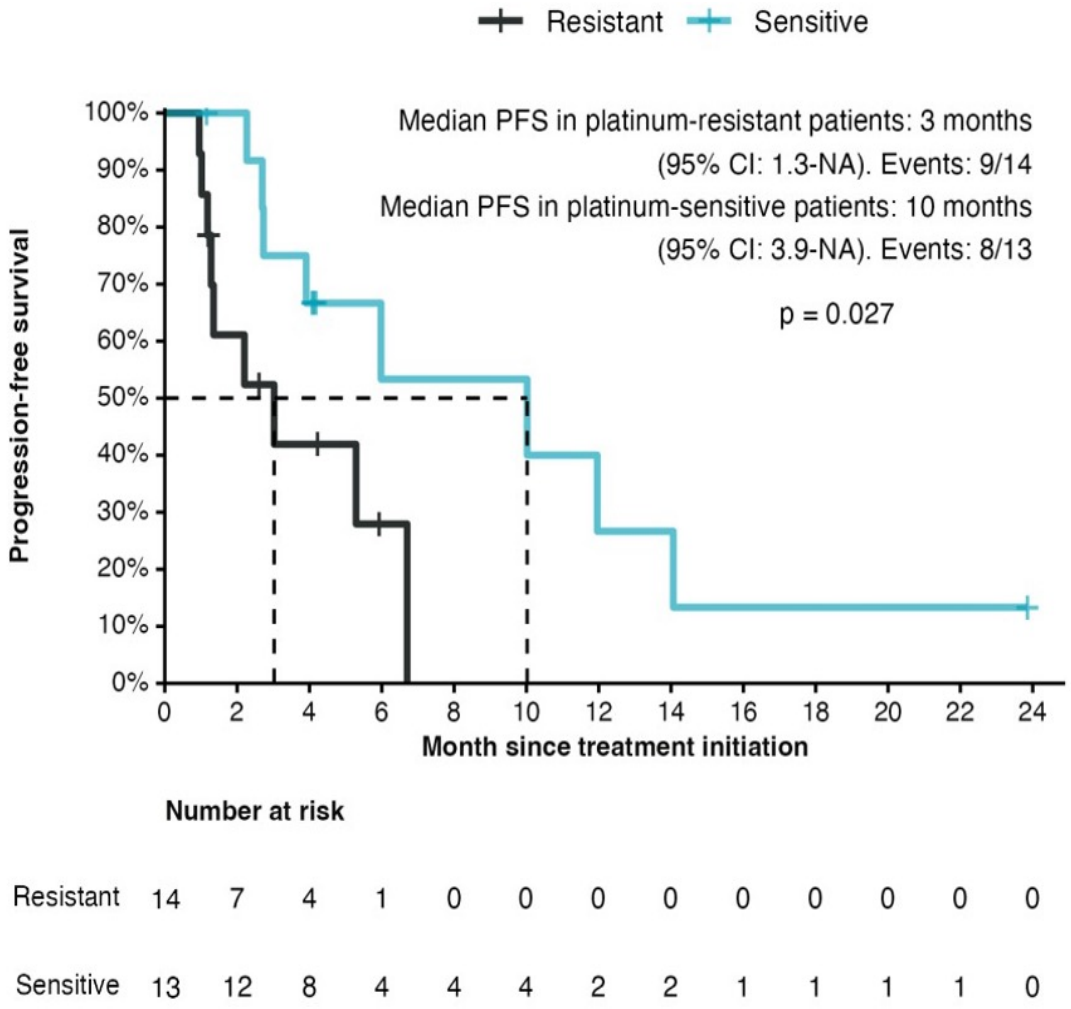
n (%), number of patients (percentage based on N); N, number of patients in the population; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NE: Not evaluated. *Information on the platinum-free interval of patient 0102-004 is missing. This patient had a BOR = CR.

Antonio Calles MD. 2023 ESMO Congress, abstr 1989M0.

LUPER Study

Results- Progression Free Survival

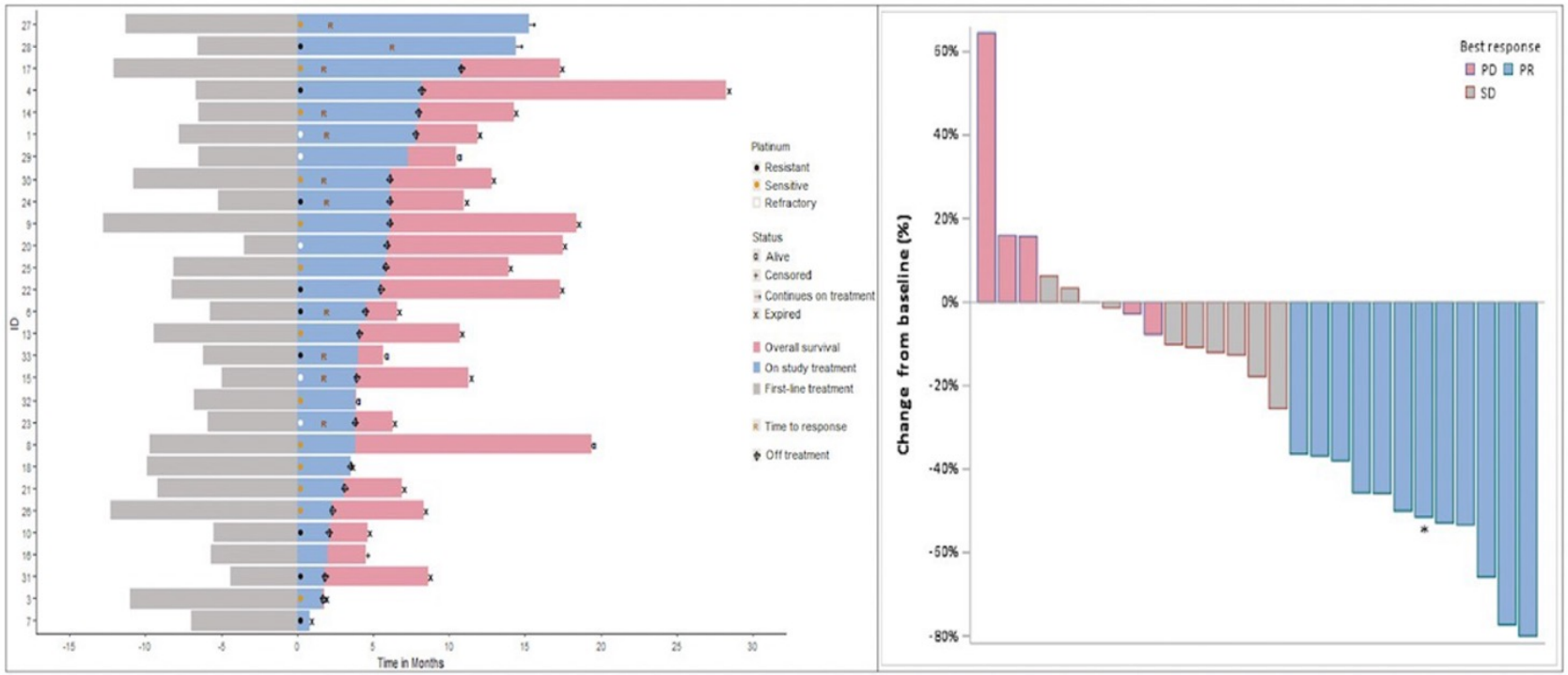




Antonio Calles MD. 2023 ESMO Congress, abstr 1989M0.

PARP inhibitors combos in Relapsed SCLC

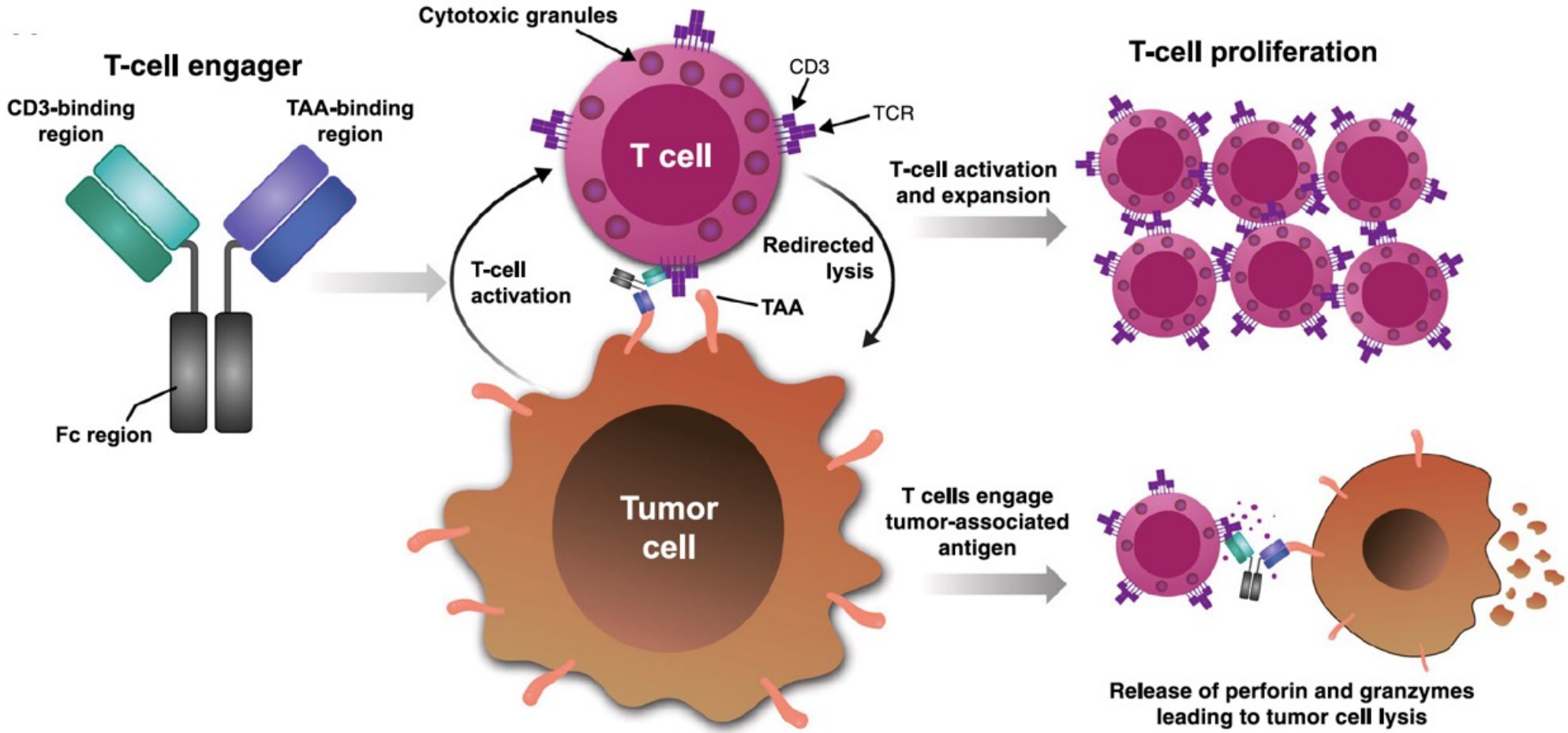
Phase II study of continuous talazoparib plus intermittent low-dose temozolomide



- **ORR 39.3%**
- **PFS 4.5 mo**
- **OS 11.9 mo**
- TRAEs ≥ 3: thrombocytopenia (61.3%), anemia (54.8%), neutropenia (41.9%), atypical pneumonia (3.2%)

Goldman et al. ASCO 2022.

Bi-specific T-cell engagers (BiTEs): Bringing the T-cell to the tumor



Rudin et al., J Hematol Oncol 2023

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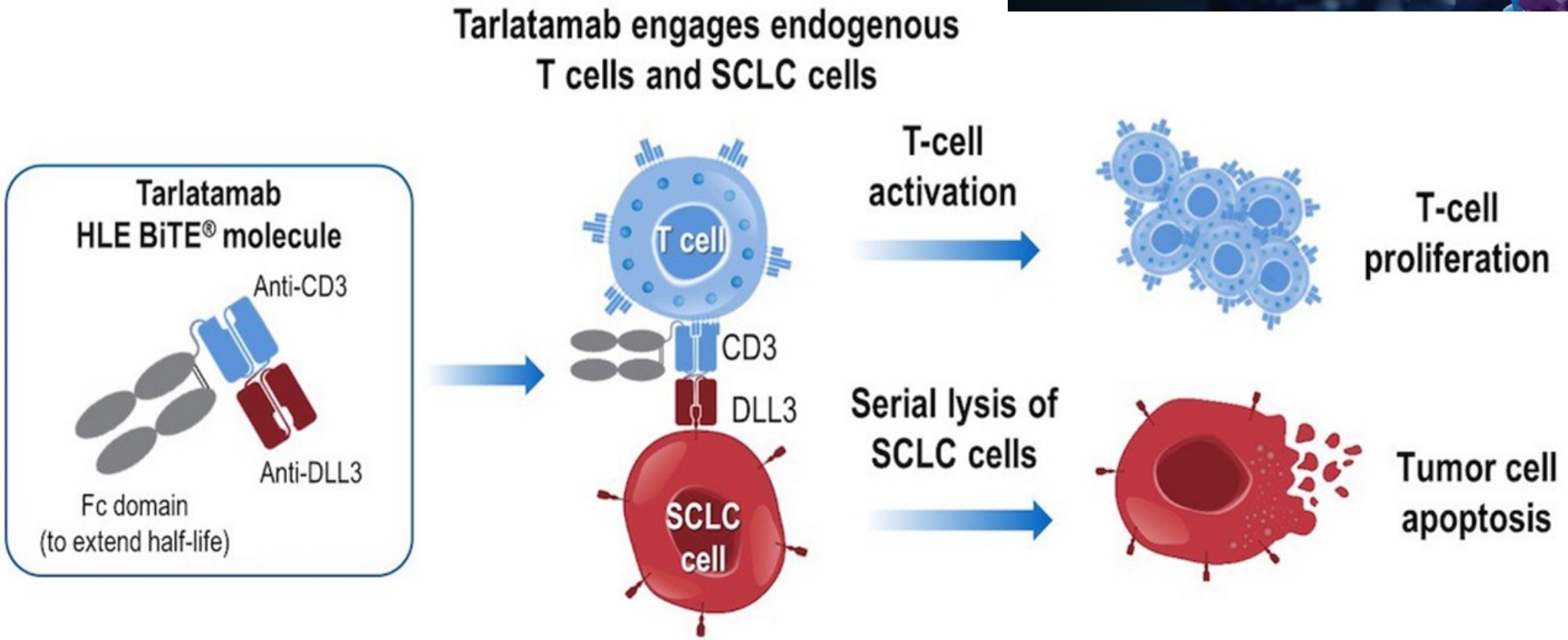
DLL3 targeting HLE BITE



- Tarlatamab, a half-life extended bispecific T-cell engager (HLE BiTE) molecule, binds both DLL3 on cancer cells and CD3 on T cells leading to T-cell–mediated tumor lysis.
- Tarlatamab promotes tumor regression in preclinical models of SCLC.

Owonikoko et al. ASCO 2022

Paz-Ares et al. JCO 2023

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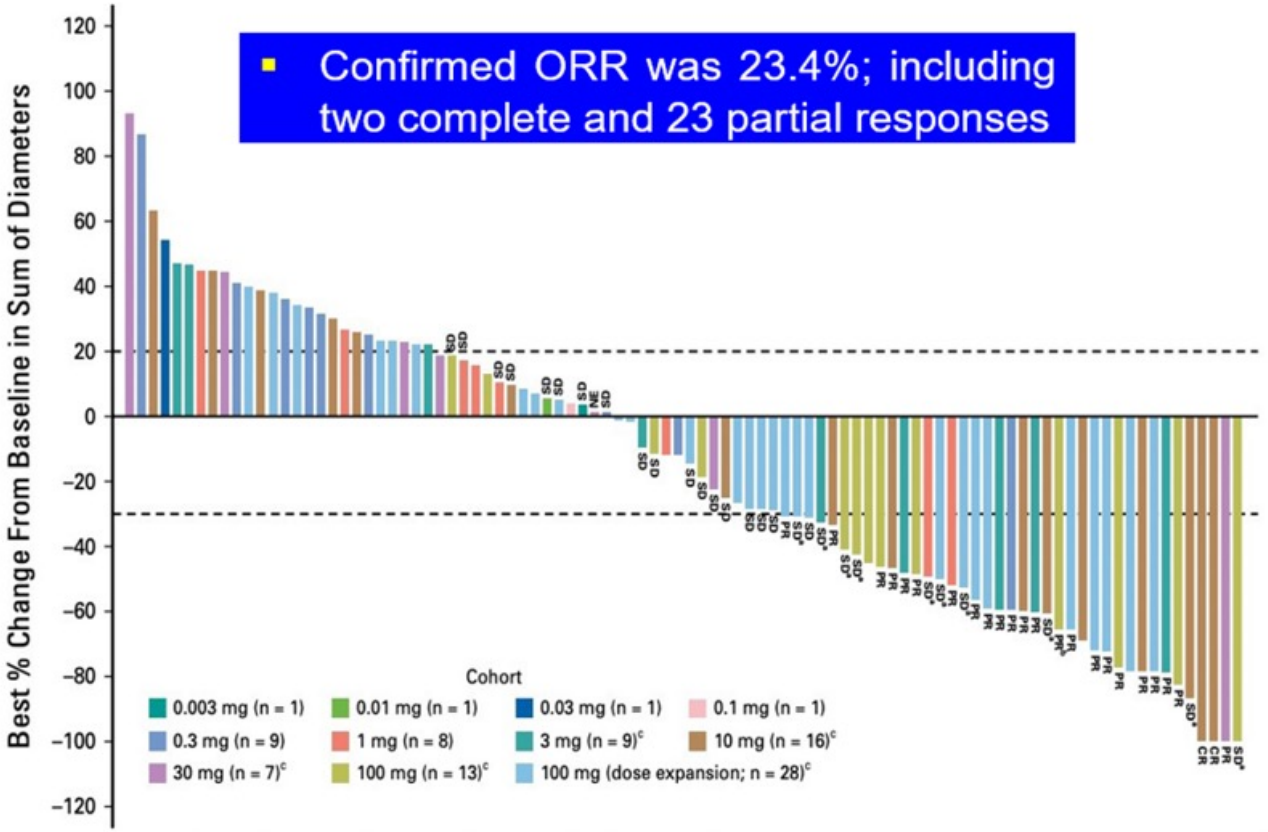
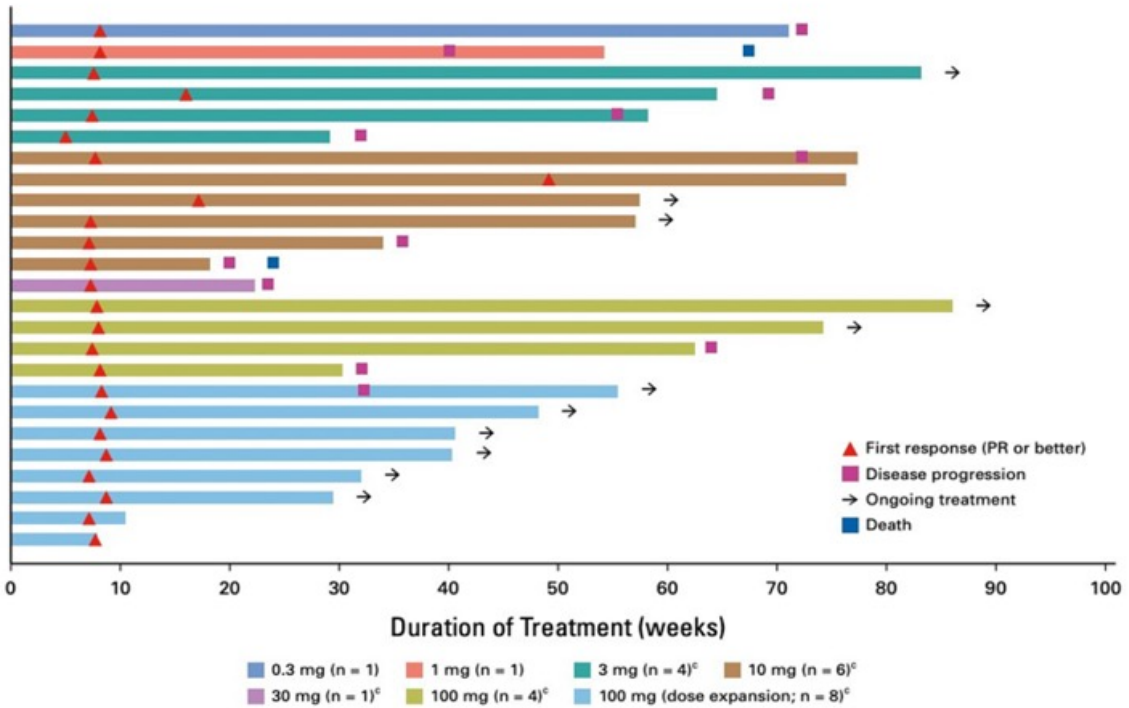
Phase I Tarlatamab: Efficacy

- Confirmed ORR was 23.4%; including two complete and 23 partial responses





Among confirmed responders, the median time to response was 1.8 months (range, 1.2-7.4) and the median DOR was 12.3 months (95% CI, 6.6 to 14.9; Fig 1B).

Owonikoko et al. ASCO 2022

Paz-Ares et al. JCO 2023

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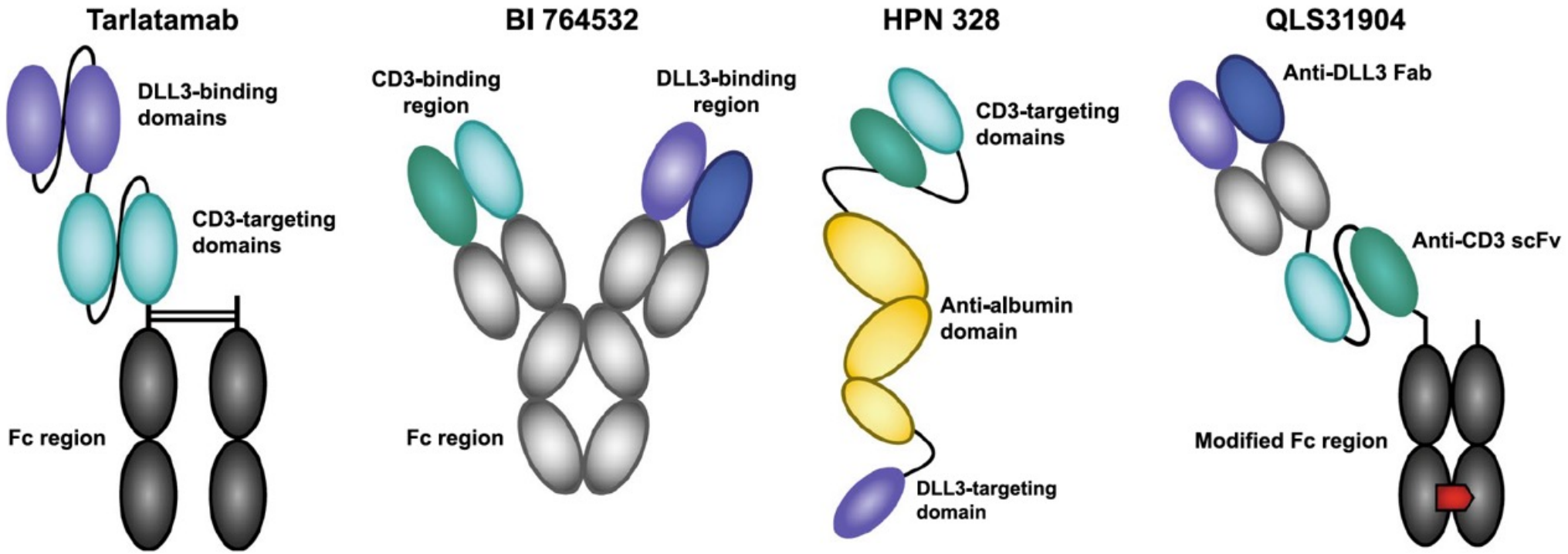
Many BiTEs, many flavors



Rudin et al., J Hematol Oncol 2023

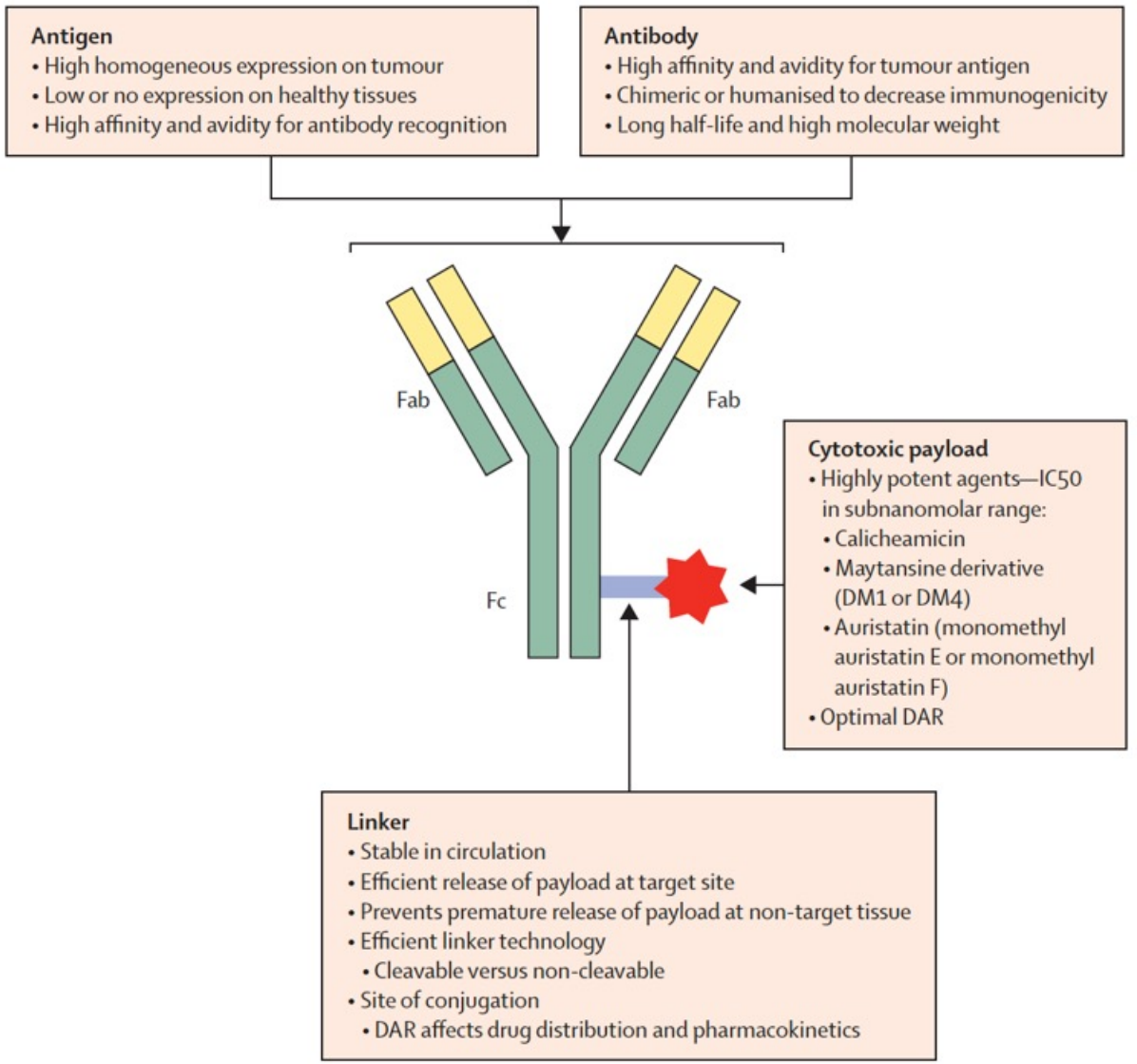
Antibody-based DLL3-targeted therapies in development for SCLC

AGENT	MECHANISM OF ACTION	STATUS
ANTIBODY-DRUG CONJUGATES (ADCs)		
Rovalpituzumab tesirine	ADC targeting DLL3	Terminated
SC-002	ADC targeting DLL3	Terminated
CHIMERIC ANTIGEN RECEPTORS		
DLL3-CAR-NK cells	Anti-DLL3-transduced natural killer cells	Recruiting (Phase 1)
AMG 119	Anti-DLL3 transduced autologous T cells	Suspended (Phase 1)
T-CELL ENGAGERS		
Tarlatamab	DLL3/CD3 BiTE	Recruiting (Phase 2)
BI 764532	DLL3/CD3 BiTE	Recruiting (Phase 1)
HPN328	DLL3/CD3/Albumin TriTAC	Recruiting (Phase 1/2)
RO7616789	DLL3/CD3/CD137 TriTAC	Recruiting (Phase 1)
PT217	DLL3/CD47 BiTE	Not yet recruiting
QLS31904	DLL3/CD3 BiTE	Not yet recruiting

Rudin et al. J Hematol Oncol 2023 (modified)

Antibody Drug Conjugates

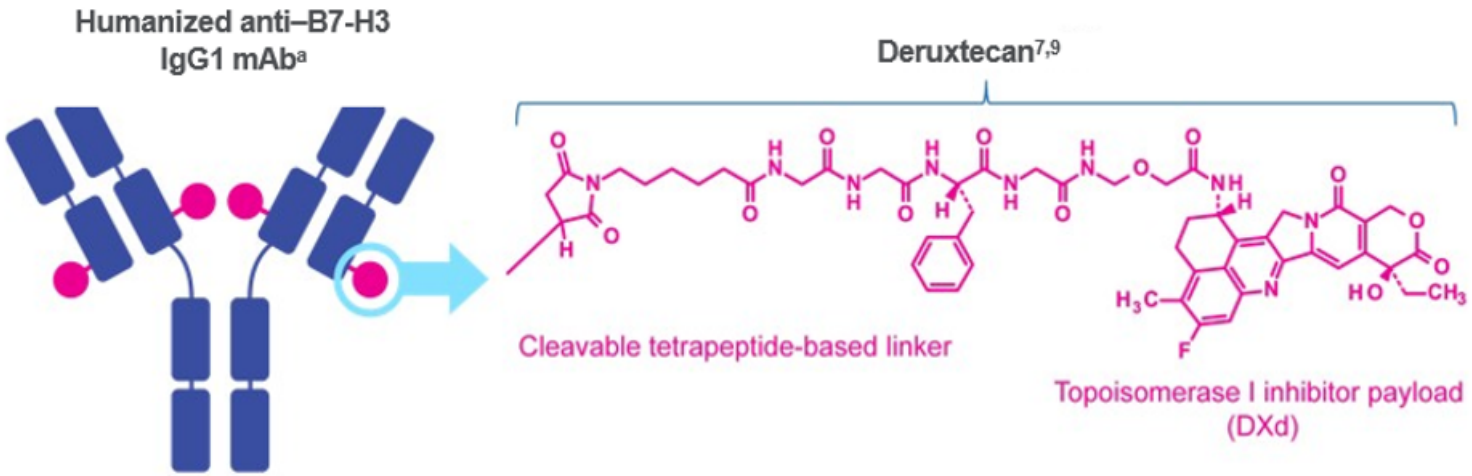
- Antibody drug conjugates assessed in SCLC:
  - Anti-DLL3
  - Anti-CD56
  - Anti-TROP2
  - Anti-CD276 **
  - Anti-SEZ6



Chau et al., Lancet 2019

Ifinatamab Deruxtecan (I-DXd; DS-7300) Was Designed With 7 Key Attributes

- B7-H3 is overexpressed in a wide range of cancer types and is associated with disease progression and lower survival[1–5]
- I-DXd is a B7-H3 **(CD276)-directed ADC** composed of 3 parts:[6–9,11]
  - A humanized anti–B7-H3 IgG1 monoclonal antibody[9,11]
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[9,11,b]
Optimized drug-to-antibody ratio ≈ 4[6–8,10,b]
Payload with short systemic half-life[9,11,b,c]
Stable linker-payload[9,11,b]
Tumor-selective cleavable linker[9,11,b]
Bystander antitumor effect[7,10,11,b]

[a]Image is for illustrative purposes only; actual drug positions may vary. [b]The clinical relevance of these features is under investigation. [c]Based on animal data.
ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; CD276, cluster of differentiation 276; DXd, deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
1. Yamato M, et al. AACR-NCI-EORTC 2020. Abstract 28. 2. Dong P, et al. *Front Oncol*. 2018;8:264. 3. Picarda E, et al. *Clin Cancer Res*. 2016;22(14):3425–3431. 4. Bendell JC, et al. *J Clin Oncol*. 2020;39(15 suppl 1). Abstract TPS3646.
5. Kontos F, et al. *Clin Cancer Res*. 2021;27(5):1227–1235. 6. Okajima D, et al. *Mol Cancer Ther*. 2021;20(12):2329–2340. 7. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173–185. 8. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097–5108.
9. Yamato M, et al. *Mol Cancer Ther*. 2022;21(4):635–646.10. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039–1046. 11. Daiichi Sankyo. Data on file.

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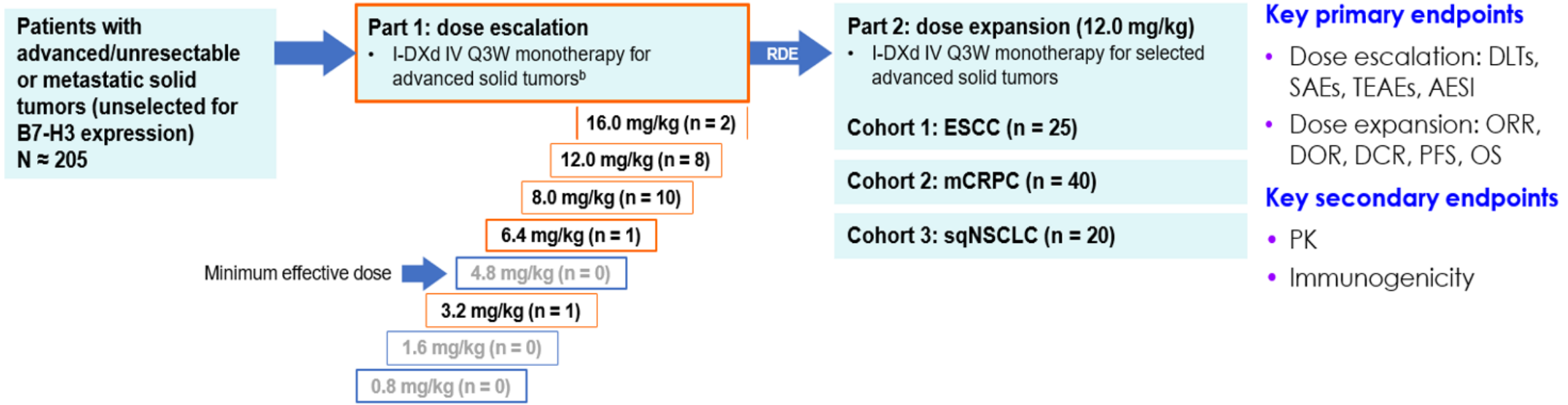
DS7300-A-J101 Study Design (NCT04145622)

- I-DXd is generally well tolerated with early signs of antitumor activity[1,2]
- **We present a subgroup analysis of patients with SCLC (N = 22[a]) from part 1 treated with I-DXd at all doses studied**
  - Patients dosed at ≥6.4 mg/kg (n = 21) were evaluable for efficacy
  - Baseline tumor biopsies were retrospectively examined for B7-H3 protein level by IHC and used for correlative analysis in biomarker-evaluable patients dosed at ≥6.4 mg/kg (n = 17)



Key primary endpoints

- Dose escalation: DLTs, SAEs, TEAEs, AESI
- Dose expansion: ORR, DOR, DCR, PFS, OS

Key secondary endpoints

- PK
- Immunogenicity

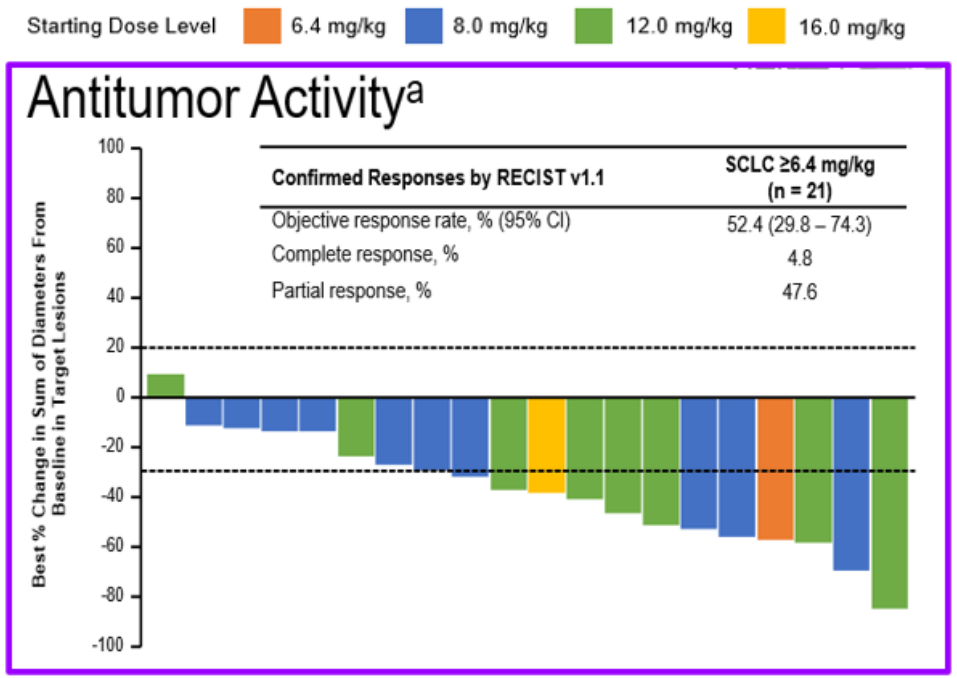
[a]Nu
event of special interest; B7-H3, B7 homolog 3; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ESCC, esophageal squamous cell carcinoma; IHC, immunohistochemistry; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RDE, recommended dose for expansion; SAE, serious adverse event;; SCLC, small cell lung cancer; sqNSCLC, squamous non-small cell lung cancer; TEAE, treatment-emergent adverse event. 1. Johnson ML, et al. ESMO. 2021. Abstract 513O. 2. Doi T, et al. ESMO. 2022. Abstract 453O.

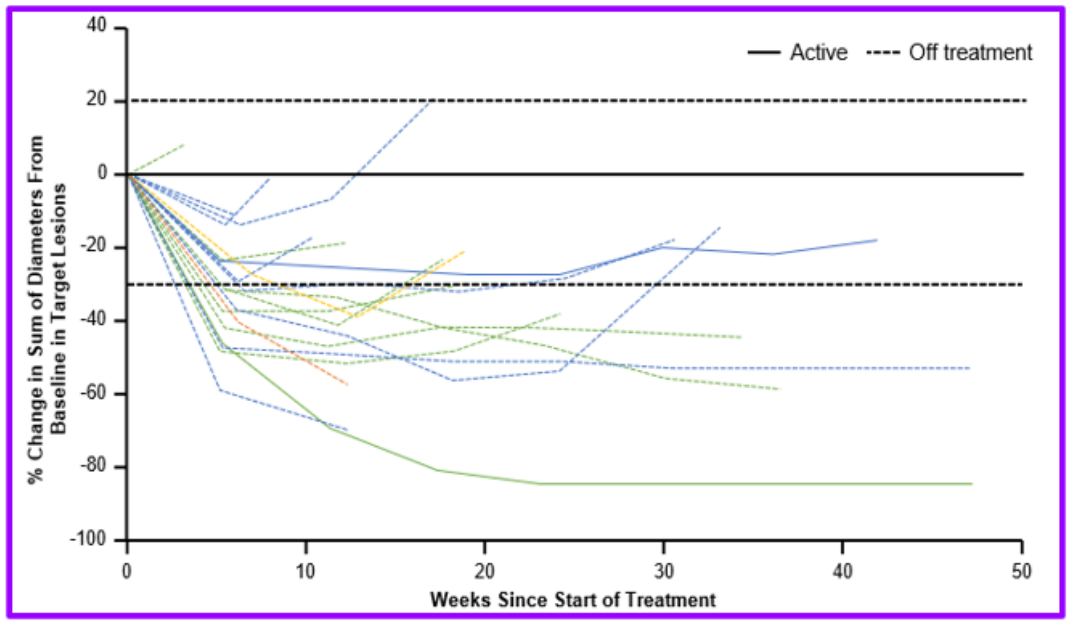
DS7300-A-J101 Study Design (NCT04145622)

- As of 31 January 2023, 22 patients with SCLC received I-DXd at doses of 3.2 mg/kg to 16.0 mg/kg

  - Nearly all patients with post-baseline scans had a reduction in target lesions
  - Median time to response was 1.2 months (95% CI, 1.2 – 1.4)
  - Median duration of response was 5.9 months (95% CI, 2.8 – 7.5); two patients remain on treatment
  - Median follow-up was 11.7 months (95% CI, 4.63 – 12.88)

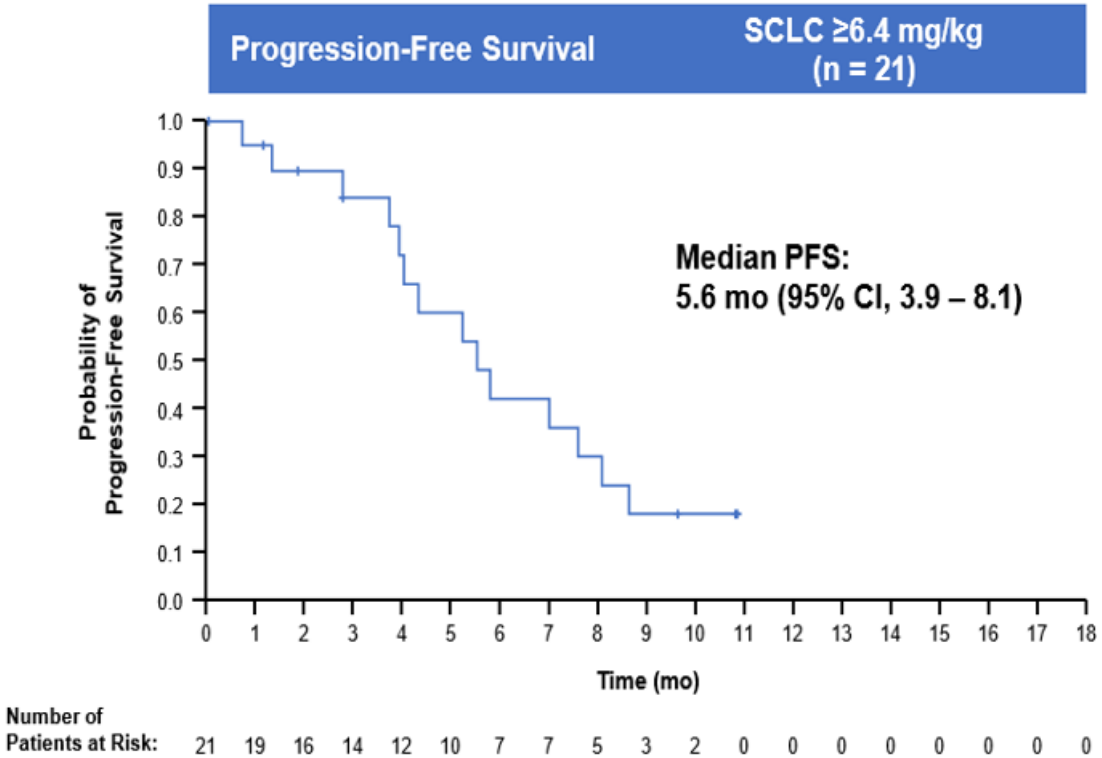
Patient or Disease Characteristic	SCLC (N = 22)
Age, median (range)	61 (40 – 84)
Male, n (%)	14 (63.6)
ECOG PS, n (%)	
0	7 (31.8)
1	15 (68.2)
Brain metastasis at baseline, n (%)	2 (9.1)
Number of prior systemic regimens, median (range)	2 (1 – 7)
Prior anticancer therapy received, n (%)	
Platinum-based chemotherapy	22 (100)
Immuno-oncology	18 (81.8)
Taxane	5 (22.7)
Irinotecan or topotecan	5 (22.7)[a]
Region of enrollment, n (%)	
United States	17 (77.3)
Japan	5 (22.7)

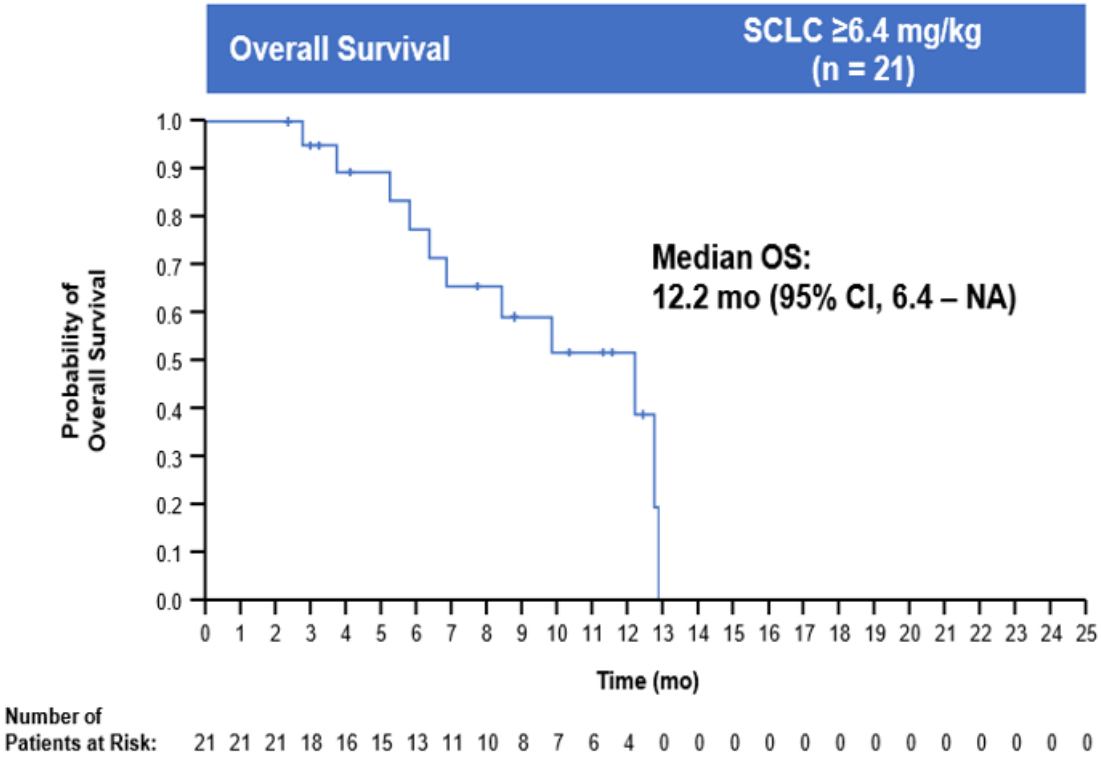




Johnson M et al. 2023 World Conference on Lung Cancer, Singapore, September 9-12, 2023

Progression-Free and Overall Survival





Data cutoff: January 31, 2023.
CI, confidence interval; NA, not applicable; mo, months; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer.

Johnson M et al. 2023 World Conference on Lung Cancer, Singapore, September 9-12, 2023

Conclusions

- At present biomarker testing in SCLC has minimal impact in clinic.
- Recent discoveries enable biomarker-driven clinical trials; molecular subtypes of SCLC (SCLC-**A**SCL1, **N**EUROD1, **P**OU2F3, **I**nflamed).
- Chemo-immunotherapy now the gold standard frontline treatment of E-SCLC (EP-atezolizumab or EP-durvalumab).
- More to do in second line; approval of Lurbinectedin (2020) occurred 22 years after topotecan approval.
- Multiple classes of antibody-based therapies are in the clinic, with more on the way: blocking antibodies, antibody-drug conjugates (ADCs), T-cell engagers (TCEs), CAR-T constructs and radioimmunoconjugates.
- ADCs and TCEs are showing promising activity in patients with recurrent SCLC (e.g., Ifinatamab deruxtecan, Tarlatamab)

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