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Comprehensive Cancer Center

Advances in SCLC Therapy

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Disclosures

Ticiana A. Leal, MD (past 12 months)

- **Advisory Board:**
  - Blueprint, Merck, AstraZeneca, Jazz, Boehringer-Ingelheim, Bayer, Mirati
- **Consulting:**
  - Jazz, Boehringer-Ingelheim, Genentech, Lilly, Janssen

Serplulimab + Chemotherapy in 1L SCLC

A randomized, double-blind, multicenter, placebo-controlled, phase 3 trial (NCT04063163)

Main inclusion criteria

- Histologically/cytologically diagnosed with ES-SCLC
- No prior systemic therapy for ES-SCLC
- At least one measurable lesion
- ECOG PS 0/1

Stratification factors

- PD-L1 expression levels (negative: TPS <1%, positive: TPS ≥1%, or NA)
- Brain metastases (yes or no)
- Age (<65 vs ≥65)

R 2:1

	IV, Q3W, up to 4 cycles	IV, Q3W
Serplulimab arm	**Serplulimab** 4.5 mg/kg, D1 + **carboplatin** (AUC 5, D1) + **etoposide** (100 mg/m^2, D1-3)	**Serplulimab** (4.5 mg/kg, D1)
Placebo arm	**Placebo** (4.5 mg/kg, D1) + **carboplatin** (AUC 5, D1) + **etoposide** (100 mg/m^2, D1-3)	**Placebo** (4.5 mg/kg, D1)

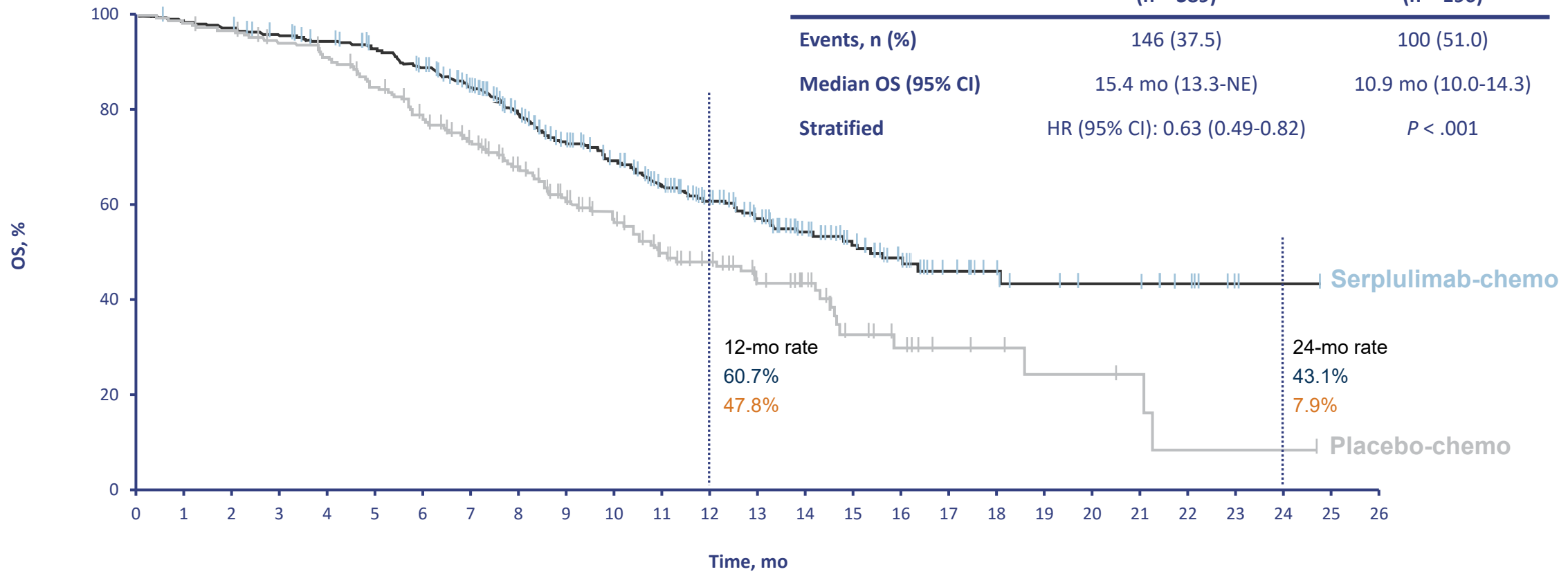
- **Primary endpoint:** OS
- **Key secondary endpoints:** PFS, ORR, DOR, safety, and immunogenicity

1. Cheng Y et al. ASCO 2022. Abstract 8505.

Serplulimab + Chemotherapy vs Chemotherapy as 1L Treatment for ES-SCLC: OS

Rates of never smokers was very high in this study—was it representative of the global, real-world SCLC population?

	Serplulimab-Chemo (n = 389)	Placebo-Chemo (n = 196)
Events, n (%)	146 (37.5)	100 (51.0)
Median OS (95% CI)	15.4 mo (13.3-NE)	10.9 mo (10.0-14.3)
Stratified	HR (95% CI): 0.63 (0.49-0.82)	*P* < .001



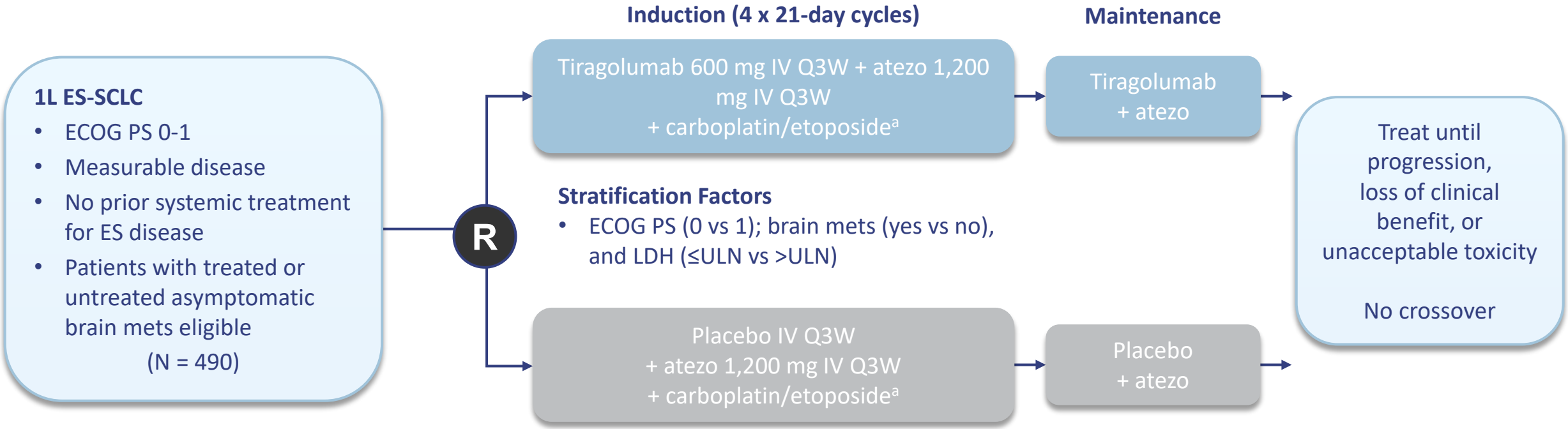
No. at Risk

389	383	378	368	359	346	328	288	248	212	186	158	124	100	76	59	40	23	17	13	11	11	7	3	1	0	0
196	193	189	181	174	160	144	123	106	85	72	56	48	35	29	15	11	7	6	4	4	3	1	1	1	0	0

1. Cheng Y et al. ASCO 2022. Abstract 8505.

SKYSCRAPER-02: Phase 3 Study of Tiragolumab + Atezolizumab + Chemotherapy in Untreated ES-SCLC

TIGIT is an investigational immune checkpoint pathway, and tiragolumab is a human IgG1/kappa anti-TIGIT mAb



Coprimary endpoints

- OS and investigator-assessed PFS in primary set analysis set (all randomized patients without presence or history of brain mets at BL)

Secondary endpoints

- PFS and OS in full analysis set (all randomized patients); confirmed ORR, DOR, safety, pharmacokinetics, PROs

Primary analysis

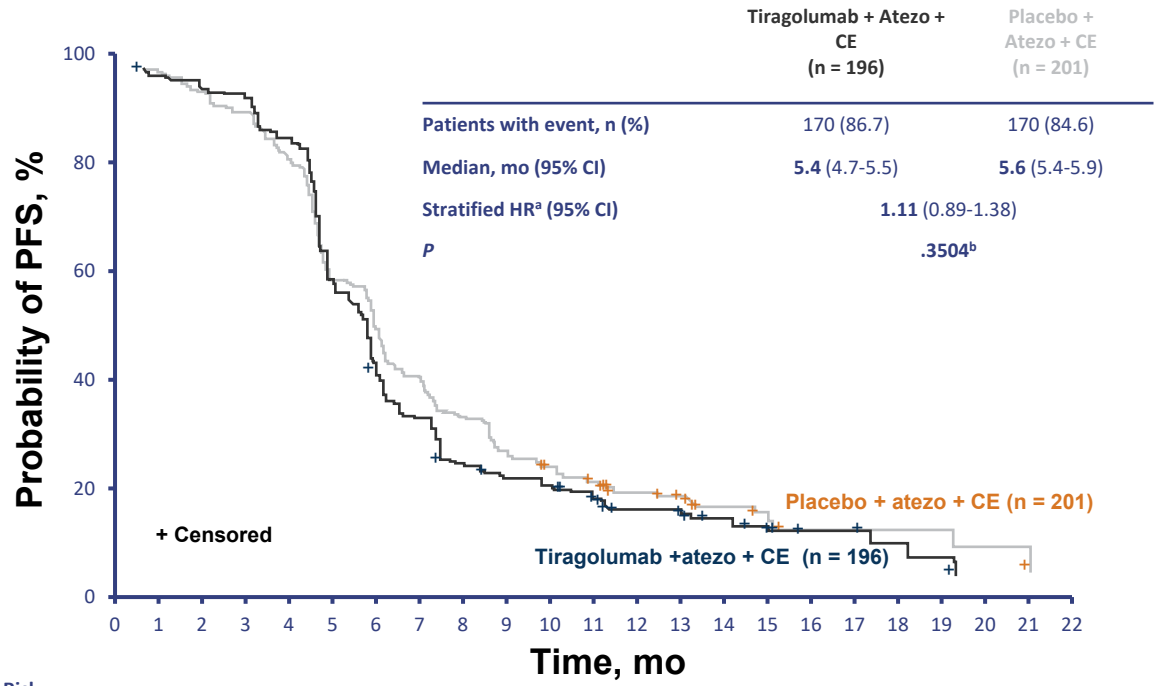
- Cutoff date: Feb 6 2022; median follow-up: 14.3 months (primary analysis set)

[a] Carboplatin IV AUC 5 mg/mL/min Q3W and etoposide IV 100 mg/m^2 body surface area days 1-3 Q3W.

1. https://clinicaltrials.gov/ct2/show/NCT04256421. 2. Rudin CM et al. ASCO 2022. Abstract LBA8507.

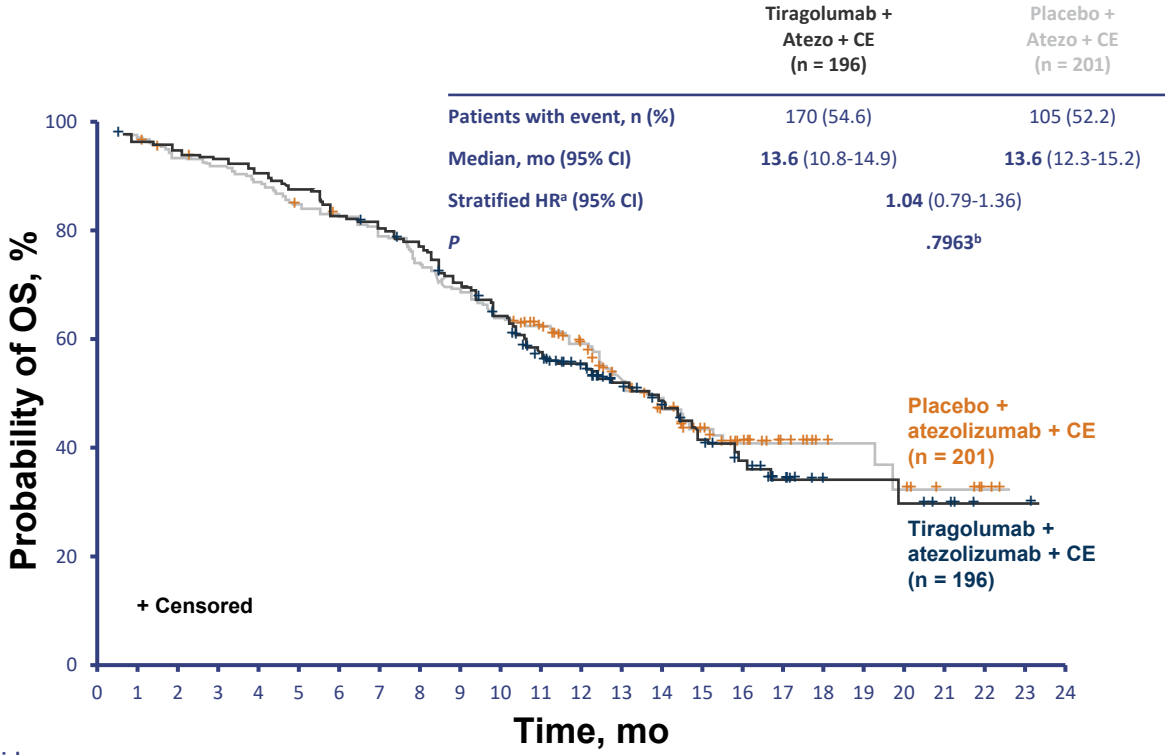
SKYSCRAPER-02: PFS and OS

PFS: Primary Analysis Set



No. at Risk																						
Placebo + atezo + CE	201	192	184	171	152	115	84	68	62	46	39	34	26	20	11	8	3	3	3	3	2	2	NE
Tiragolumab + atezo + CE	196	189	183	170	154	105	67	54	41	37	33	25	17	17	11	8	5	5	3	2	NE	NE	NE

OS: Primary Analysis Set

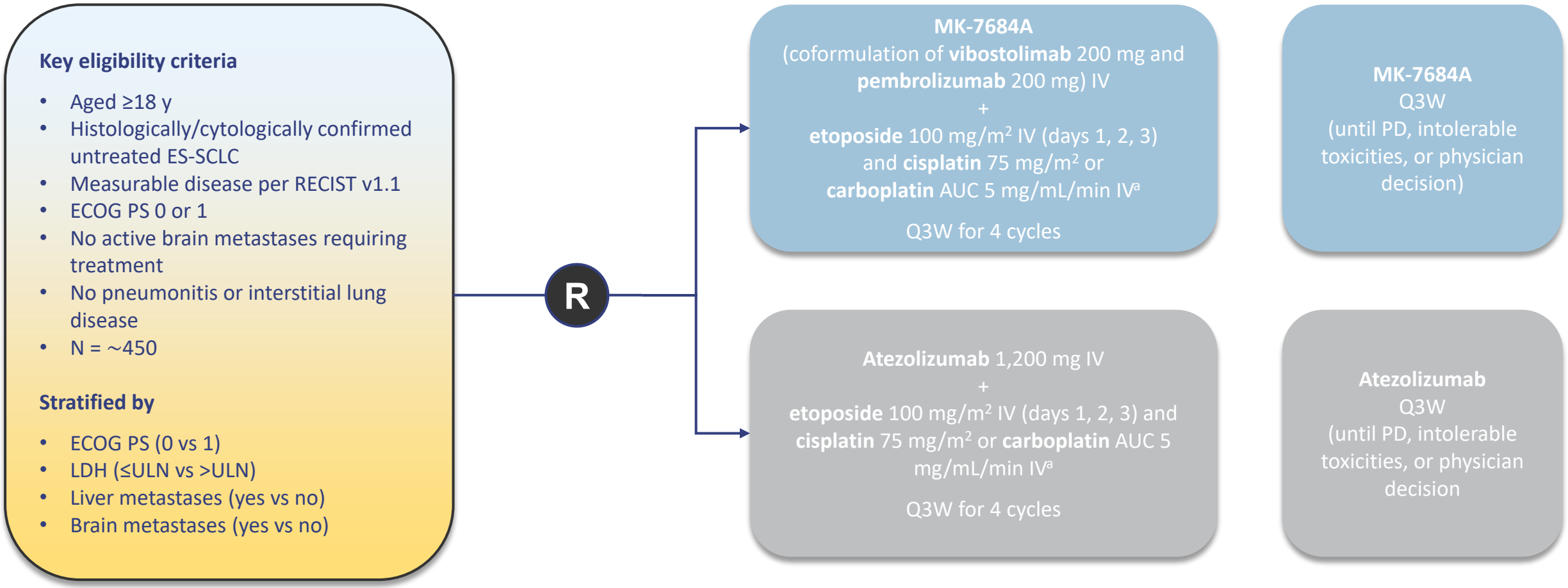


No. at Risk																										
Placebo + atezo + CE	201	195	188	183	175	168	164	156	144	134	125	115	97	70	47	36	26	19	12	9	7	5	4	NE	NE
Tiragolumab + atezo + CE	196	191	186	184	177	172	162	154	146	133	116	93	80	62	51	32	21	14	9	7	7	5	2	1	NE

[a] Stratification factors are: ECOG, LDH. [b] Statistical boundary: 0.001.

1. Rudin CM et al. ASCO 2022. Abstract LBA8507.

KEYVIBE-008: Phase 3 Study of First-Line Vibostolimab + Pembrolizumab + Chemotherapy in ES-SCLC

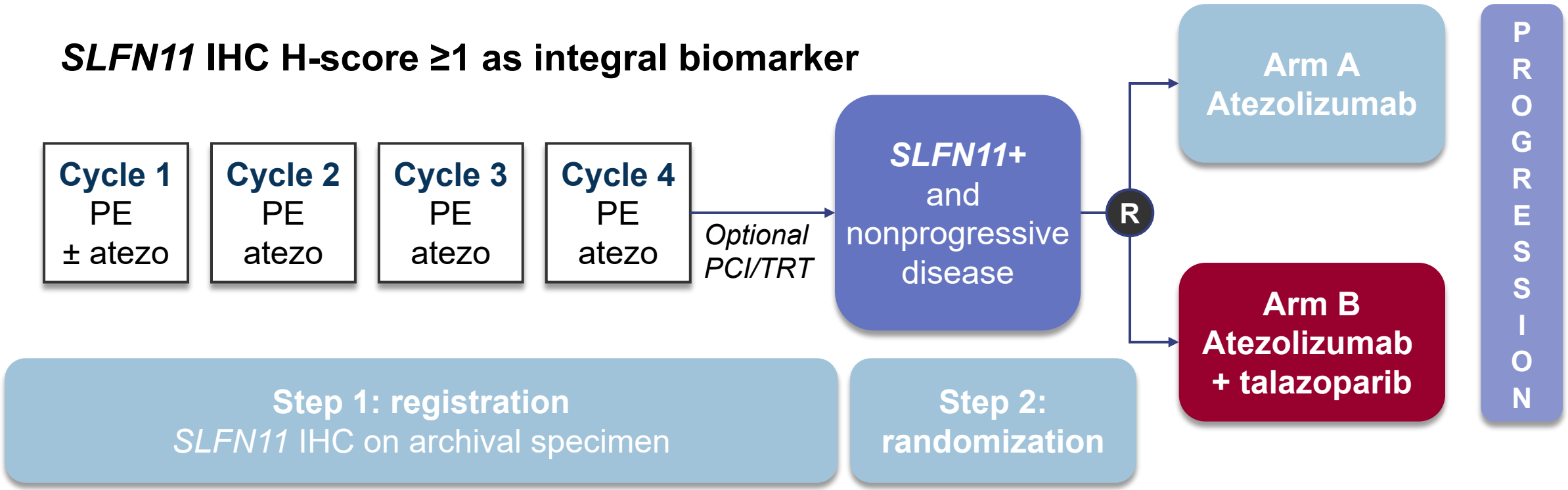


1. https://clinicaltrials.gov/ct2/show/NCT05224141. 2. Sands J et al. ASCO 2022. Abstract TPS8606.

SWOG 1929

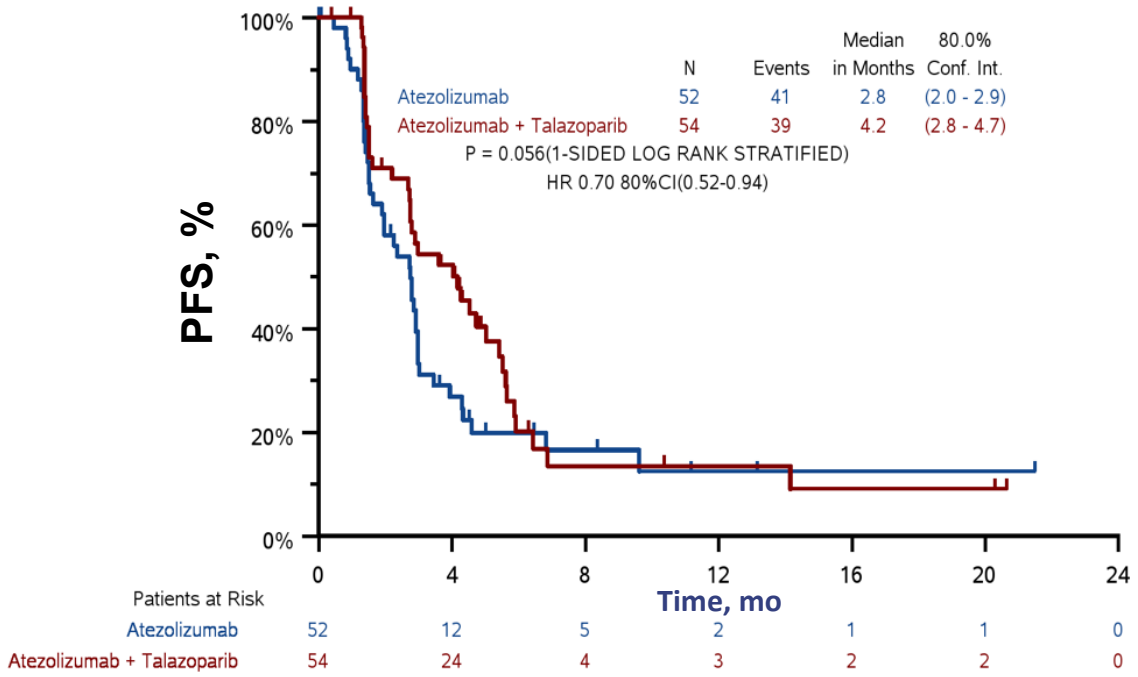
Atezolizumab + Talazoparib Maintenance

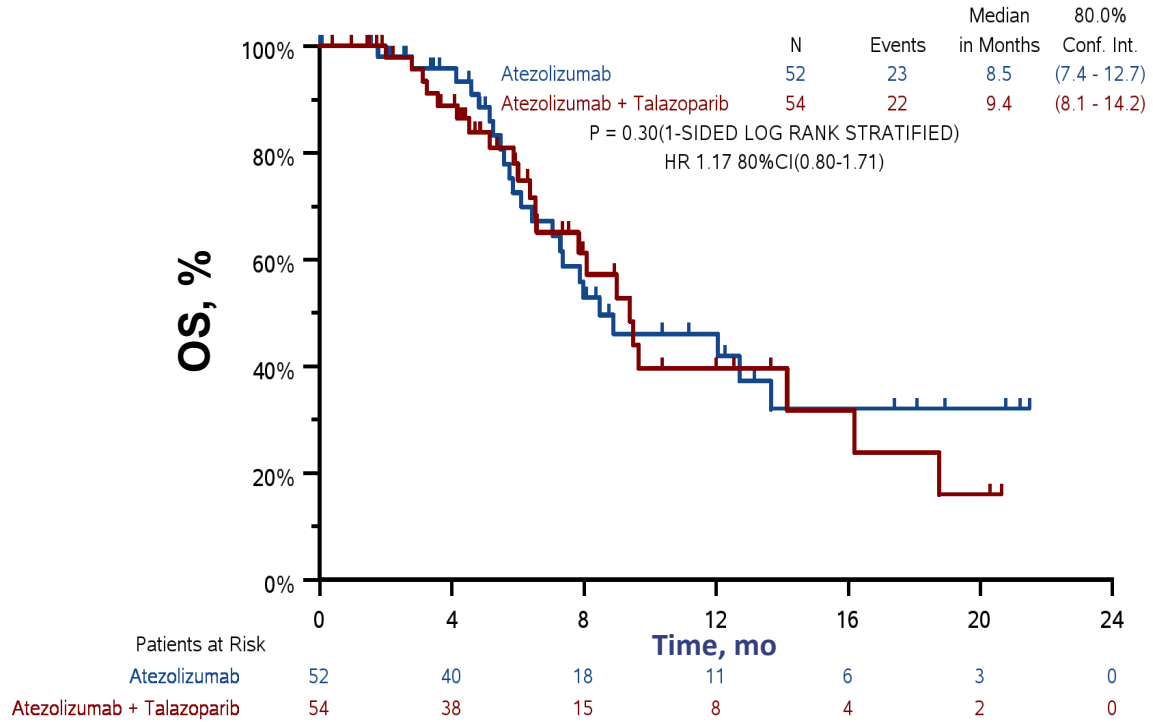
SCLC 1L, SLFN11+ disease



1. https://clinicaltrials.gov/ct2/show/NCT04334941.

SWOG 1929: PFS and OS





1. Karim NFA et al. ASCO 2023. Abstract 8504.

Trials underway testing thoracic RT and RT to metastatic sites with maintenance immunotherapy

Relapsed SCLC

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Small Cell Lung Cancer

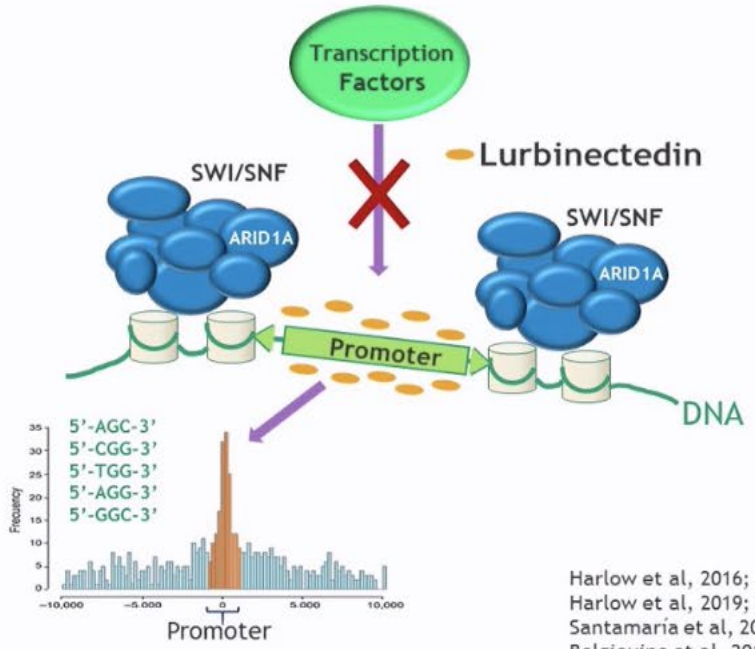
NCCN Guidelines Index
Table of Contents
Discussion

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[c] Consider dose reduction or growth factor support for patients with PS 2.
Preferred Regimens
• Platinum-based doublet[d,e,f,36,37,39-41]
• Clinical trial
Other Recommended Regimens
• Topotecan oral (PO) or intravenous (IV)[14-16]
• Lurbinectedin[17,38]
• Cyclophosphamide/doxorubicin/vincristine (CAV)[14]
• Docetaxel[20]
• Oral etoposide[24,25]
• Gemcitabine[28,29]
• Irinotecan[21]
• Nivolumab[b,d,30,31]
• Paclitaxel[18,19]
• Pembrolizumab[b,d,32-34]
• Temozolomide[22,23]
• Vinorelbine[26,27]
• Bendamustine (category 2B)[35]

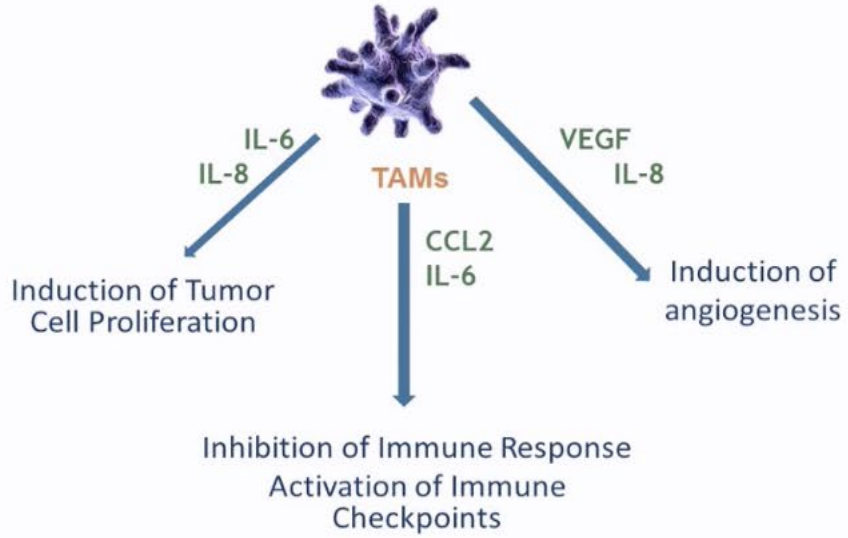
[b] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents.
[c] Subsequent systemic therapy refers to second-line and beyond therapy.
[d] The use of immune checkpoint inhibitors is discouraged if there is progression on maintenance atezolizumab or durvalumab at time of relapse.
[e] Rechallenging with the original regimen or similar platinum-based regimen, as shown on SCL-E 1, is recommended if there has been a disease-free interval of more than 6 months and may be considered if there has been a disease-free interval of at least 3 to 6 months.
[f] See regimens on SCL-E 1.

Lurbinectedin - a Selective Inhibitor of Oncogenic Transcription

CANCER IS FREQUENTLY A TRANSCRIPTIONAL DISEASE CAUSED BY DEREGULATED ONCOGENIC TRANSCRIPTION FACTORS



BY INHIBITING ACTIVE TRANSCRIPTION IN TUMOR ASSOCIATED MACROPHAGES (TAMS), LURBINECTEDIN DOWNREGULATES IL-6, IL-8, CCL2 AND VEGF



Harlow et al, 2016; Cancer Res 72: 6657-68
Harlow et al, 2019; Clin Cancer Res doi: 10.1158/1078-0432.CCR-18-3511
Santamaría et al, 2016. Mol Cancer Ther 15:2399-412
Belgiovine et al, 2017 Br J Cancer 117:628-38

Lurbinectedin as Single Agent in Second Line SCLC: Phase II BASKET Trial

PRIMARY OBJECTIVE : ORR by RECIST V.1.1

(Investigator assessed)

SCLC patients

- PS 0-2
- One prior chemotherapy line
- Prior immunotherapy was allowed
- Adequate organ function
- CNS mets excluded

➢ **Lurbinectedin 3.2 mg/m², 1h iv, q3wk**

≥ 2 responses in first 15 patients*

Enroll up to 100 patients

* 5 confirmed responses observed in the first 15 treated patients

Statistical assumptions for SCLC cohort

Null hypothesis :
≤15% get a response
(p ≤ 0.15)

Alternative hypothesis:
≥30% get a response
(p ≥ 0.30)

Statistical power 95%

≥ 23% of confirmed responses needed to reject the null hypothesis

Data cut-off: January 15th 2019

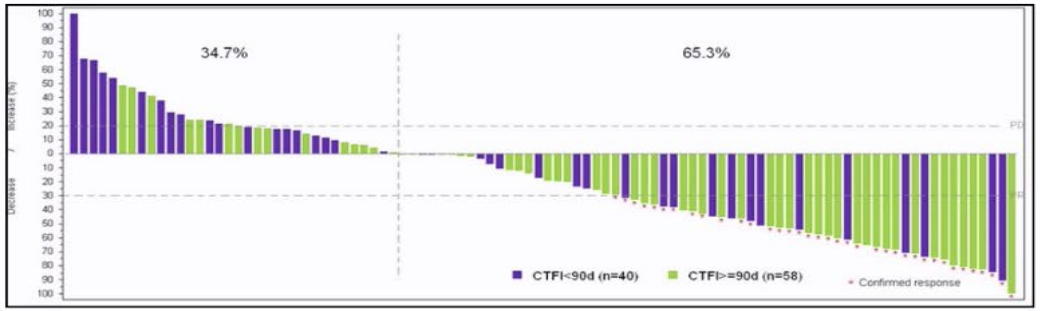
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Dr. Luis Paz Ares

Trigo et al. Lancet Oncol 2020

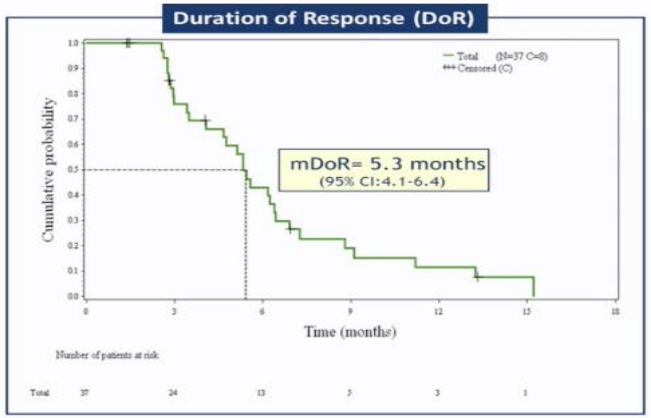
Lurbinectedin: Efficacy in SCLC

The study met its primary end point, ORR



	n	OS mo median (95% CI)	OS at 12 mo % (95% CI)
All	105	9.3 (6.3-11.8)	34.2 (23.2-45.1)
Resistant CTFI< 90d	45	5.0 (4.1-6.3)	15.9 (3.6-28.2)
Sensitive CTFI≥ 90d	60	11.9 (9.7-16.2)	48.3 (32.5-64.1)

- Single arm Phase 2 study
- Immature OS data
- Shifting standards for first-line therapy: chemo/IO
- Active CNS metastases excluded

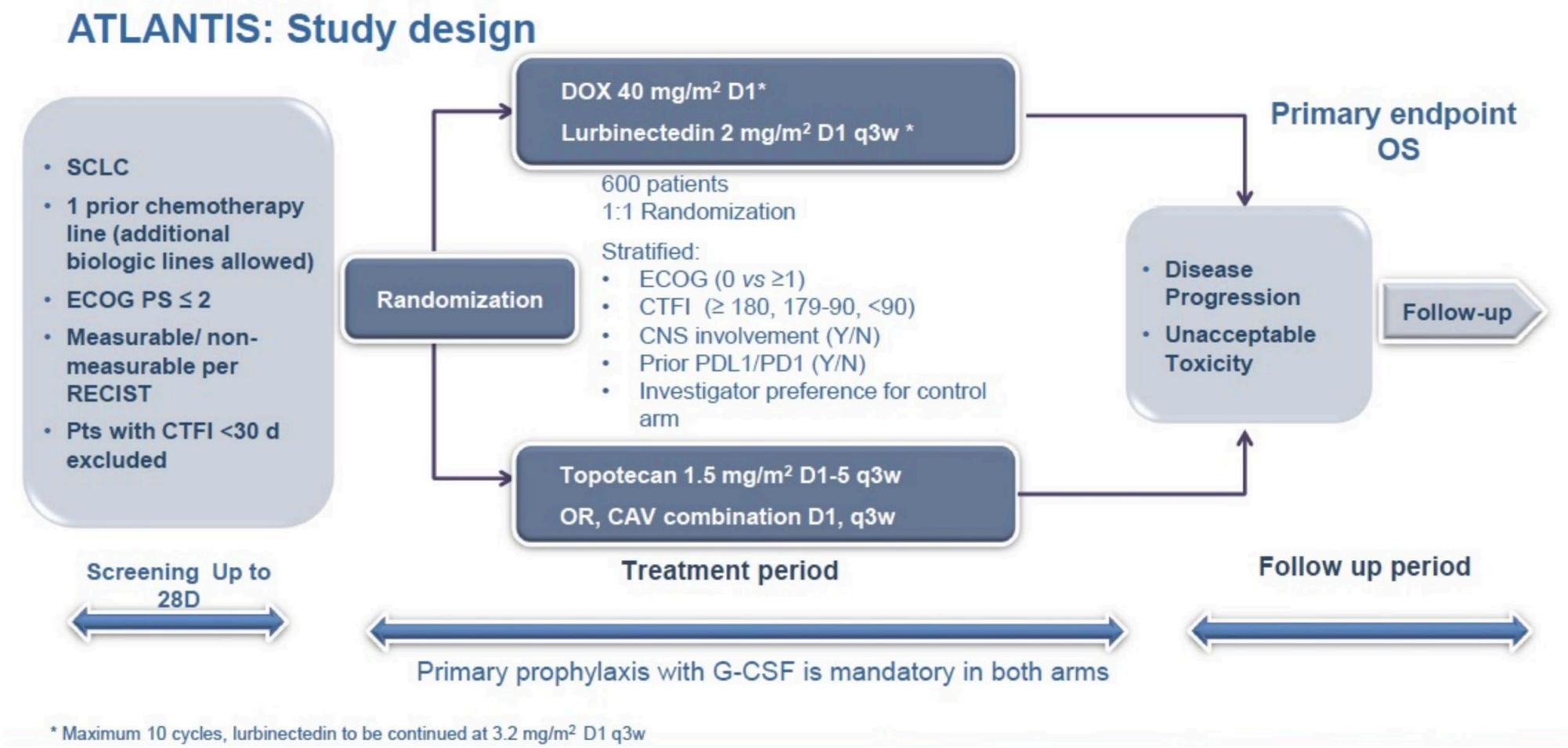


	Lurbinectedin (n=105)	Von Pawel 2014: Topotecan (n=213)[1]	Von Pawel 2014: Amrubicin (n=424)[1]	CheckMate 331: Chemotherapy (n=285)[2]	CheckMate 331: Nivolumab (n=284)[2]
ORR (%)	35.2	16.9	31.1	16.5	13.7
ORR sens (%)	45.0	23.1	40.9		
ORR res (%)	22.2	9.4	20.1		
mPFS	3.9 m	3.5 m	4.1 m	3.8 m	1.4 m
mPFS sens	4.6 m	4.3 m	5.5 m		
mPFS res	2.6 m	2.6 m	2.8 m		
mOS	9.3 m 95% CI 6.3-11.8	7.8 m 95% CI 6.6-8.5	7.5 m 95% CI 6.8-8.5	8.4 m 95% CI 7.0-10.0	7.5 m 95% CI 5.6-9.2
mOS sens	11.9 m	9.9 m	9.2 m	11.1 m	7.6 m
mOS res	5.0 m	6.2 m	5.7 m	5.7 m	7.0 m

Lurbinectedin: Safety[1]

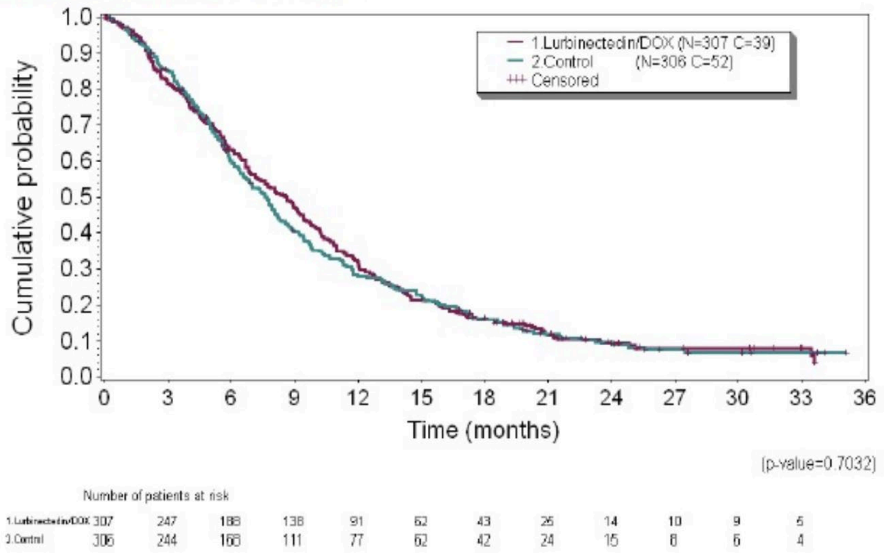
	Grade 1/2	Grade 3	Grade 4
Hematological abnormalities (regardless of relation to study drug), n (%)[a]			
Anemia	91 (87)	9 (9)	0
Leukopenia	53 (50)	20 (19)	10 (10)
Neutropenia	27 (26)	22 (21)	26 (25)
Thrombocytopenia	39 (37)	3 (3)	4 (4)
Biochemical abnormalities (regardless of relation to study drug), n/N (%)[a]			
Creatinine[b]	86/104 (83)	0	0
Alanine aminotransferase	69/103 (67)	5/103 (5)	0
Aspartate aminotransferase	52/103 (50)	13/103 (13)	2/103 (2)
γ-glutamyltransferase	44/103 (43)	2/103 (2)	0
Alkaline phosphatase	31/103 (30)	3/103 (3)	0
Treatment-related adverse events, n (%)			
Fatigue	54 (51)	7 (7)	0
Nausea	34 (32)	0	0
Decreased appetite	22 (21)	0	0
Vomiting	19 (18)	0	0
Diarrhea	13 (14)	1 (1)	0
Febrile neutropenia	0	2 (2)	3 (3)
Pneumonia	0	2 (2)	0
Skin ulcer	0	1 (1)	0

Relapsed SCLC: Atlantis



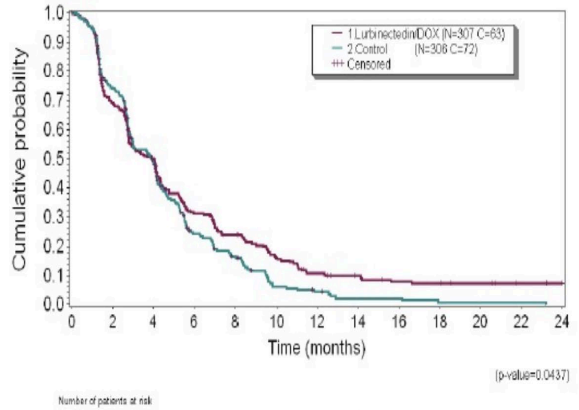
Relapsed SCLC: Atlantis

Overall Survival (ITT population)



	Lurbinectedin+DOX (N=307)	Control (N=306)	Parameter	p-value
Events, n (%)	268 (87.3)	254 (83.0)		
Censored, n (%)	39 (12.7)	52 (17.0)		
Median OS (95% CI), months	8.6 (7.1, 9.4)	7.6 (6.6, 8.2)	HR : 0.967 (0.815, 1.148)	0.7032
Mean OS, months	10.6	9.9		

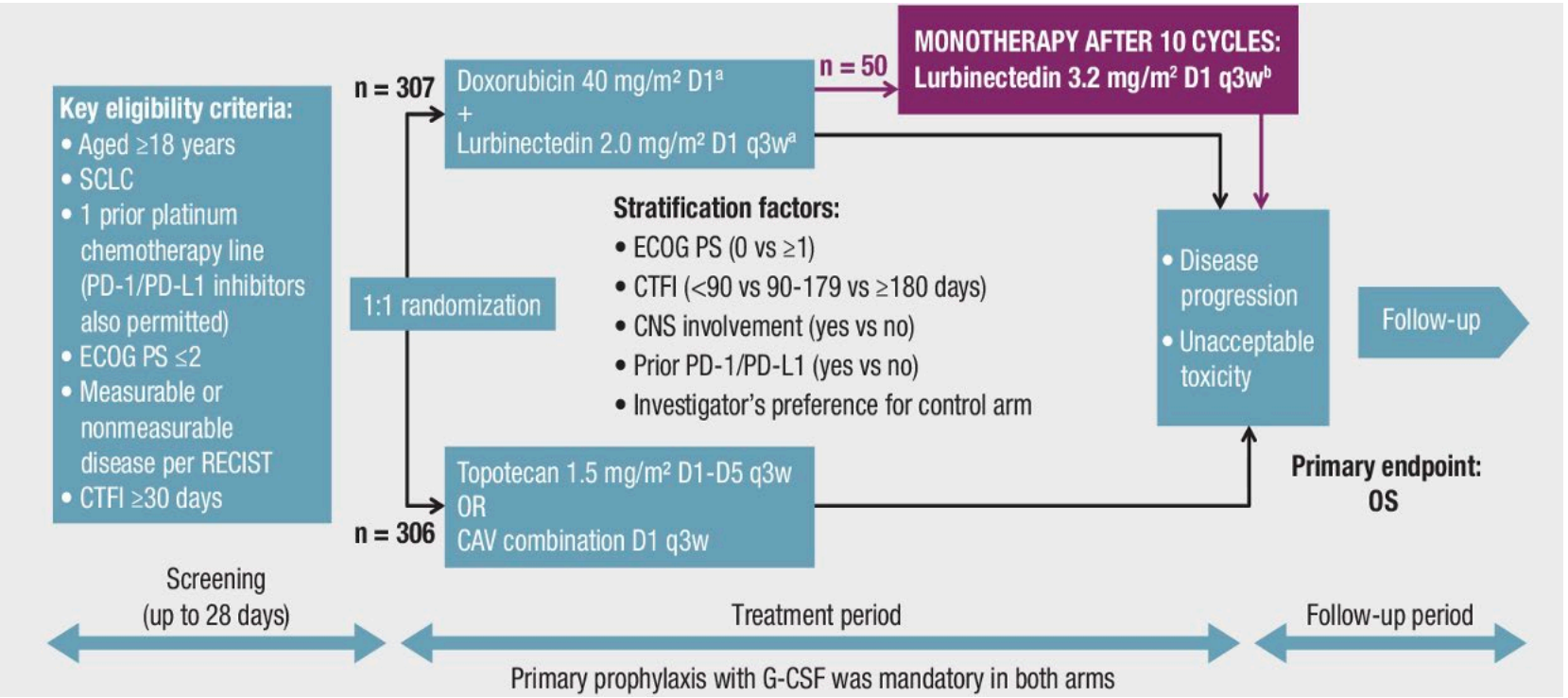
PFS by Independent Review Committee: Lurbinectedin/Doxo vs Control



	Lurbinectedin+DOX (N=307)	Control (N=306)	Parameter	p-value
Events, n (%)	244 (79.5)	234 (76.5)		
Censored, n (%)	63 (20.5)	72 (23.5)		
Median PFS (95% CI), months	4.0 (2.8, 4.2)	4.0 (3.0, 4.1)	HR: 0.831 (0.693, 0.996)	0.0437
Mean PFS, months	5.9	4.6		
PFS (%) at 6 months (95% CI)	31.3 (25.8, 36.9)	24.4 (19.1, 30.1)		0.0851
PFS (%) at 12 months (95% CI)	10.8 (7.1, 15.3)	4.4 (2.1, 8.1)		0.0129

Paz-Ares et al. WCLC 2021; Aix et al. Respiratory Medicine 2023

Analysis of patients with relapsed SCLC receiving lurbinectedin in the phase 3 ATLANTIS trial



Baseline characteristics

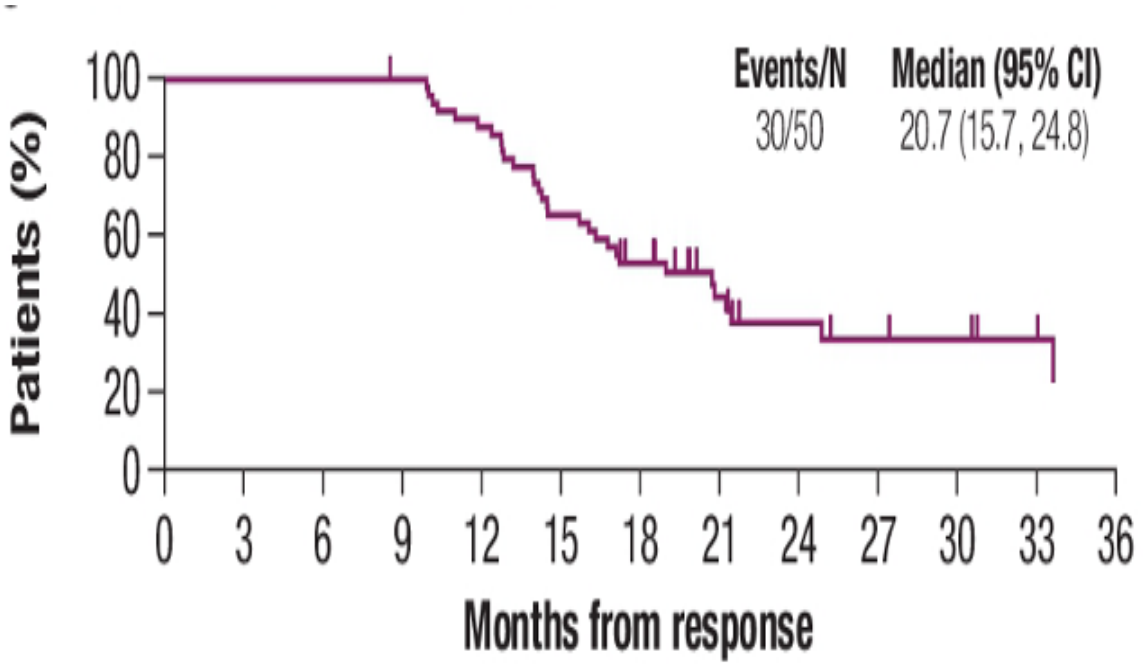
	n = 50
Median (range) age, years	61.5 (43, 77)
Age group, n (%)	
18 to 49 years	1 (2)
50 to 65 years	31 (62)
>65 years	18 (36)
Male, n (%)	31 (62)
Race, n (%)	
White	40 (80)
Not available	10 (20)
ECOG PS, n (%)	
0	21 (42)
1	29 (58)
Smoking status, n (%)	
Former	31 (62)
Current	16 (32)
Never	3 (6)
Disease stage at baseline, n (%)	
Extensive	40 (80)
Limited	10 (20)
Baseline CNS involvement, n (%)	3 (6)
Best response to first-line therapy, n (%)	
CR	9 (18)
PR	32 (64)
SD	6 (12)
PD	1 (2)
Unknown	2 (4)
CTFI, n (%)	
<90 days	2 (4)
≥90 days	48 (96)
<180 days	18 (36)
≥180 days	32 (64)

Navarro et al. ASCO 2022.

Analysis of patients with relapsed SCLC receiving lurbinectedin in the phase 3 ATLANTIS trial

Best response to lurbinectedin + doxorubicin	Best response on lurbinectedin monotherapy 3.2 mg/m²			
	CR	PR	SD	PD
CR (n = 3)	3			
PR (n = 26)	3	15		8
SD (n = 19)	1	2	8	8

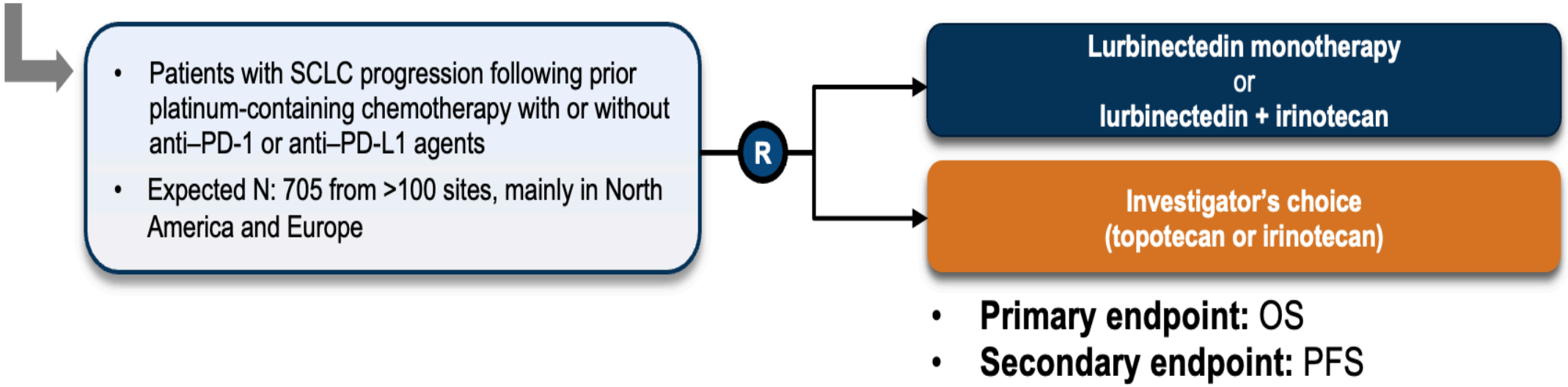
Improving response ⟷ Declining response



Navarro et al. ASCO 2022.

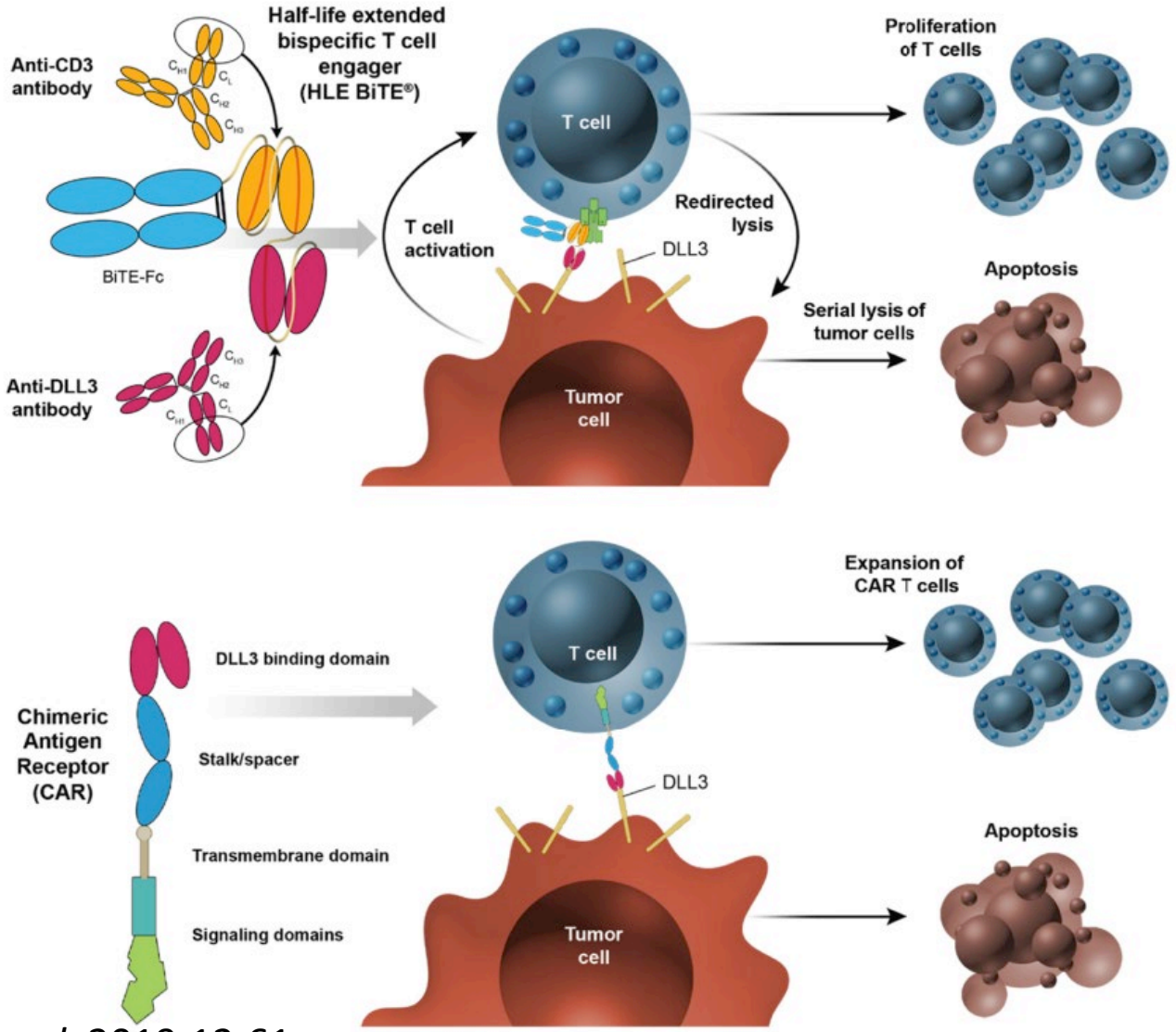
Phase 3 LAGOON trial ongoing

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



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

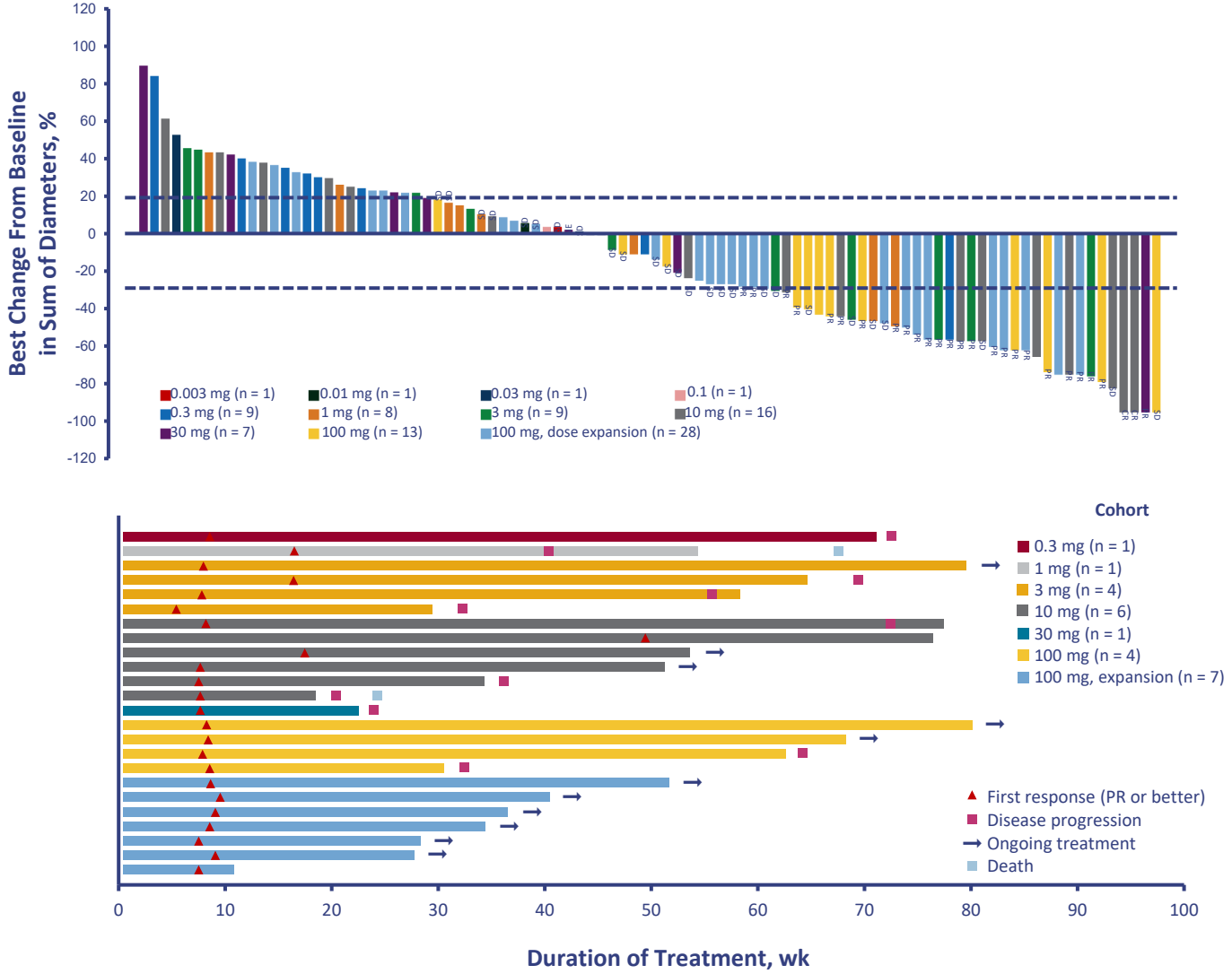
BiTEs and CARs: Immune Engagers to DLL3[1]



1. Owen DF et al. *J Hematol Oncol.* 2019;12:61.

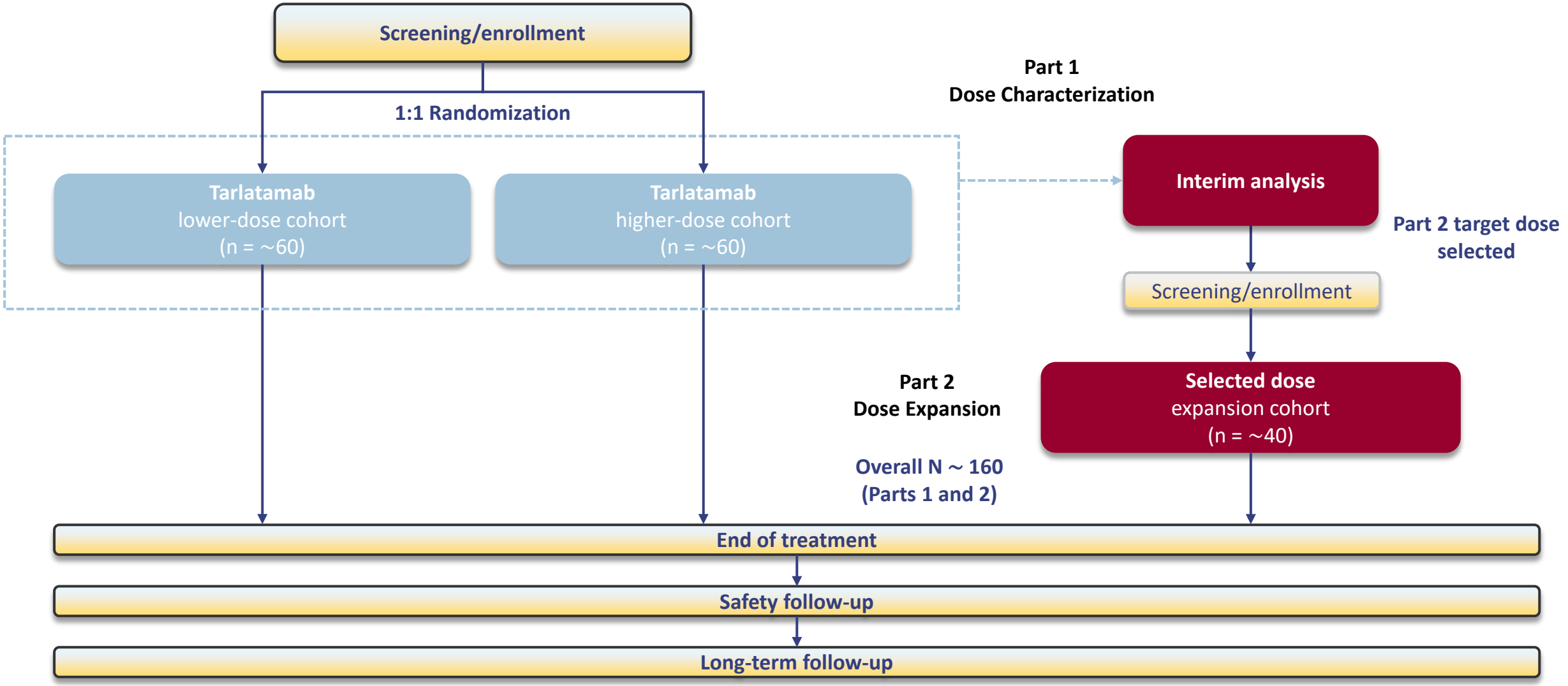
DeLLphi-300 Study: Tarlatamab (AMG 757) in SCLC[1]

- Promising antitumor activity with encouraging response durability in heavily pretreated SCLC: confirmed ORR 23%, median DOR 13 mo, median OS 13.2 mo
- Acceptable safety profile: CRS primarily grade 1 and reversible; treatment discontinuation because of TRAEs low (4%)



1. Borghaei H et al. WCLC 2022. Abstract OA12.05.

DeLLphi-301 Study: Phase 2 Registrational Study of Tarlatamab in ≥3L SCLC[1]



1. https://clinicaltrials.gov/ct2/show/NCT05060016.

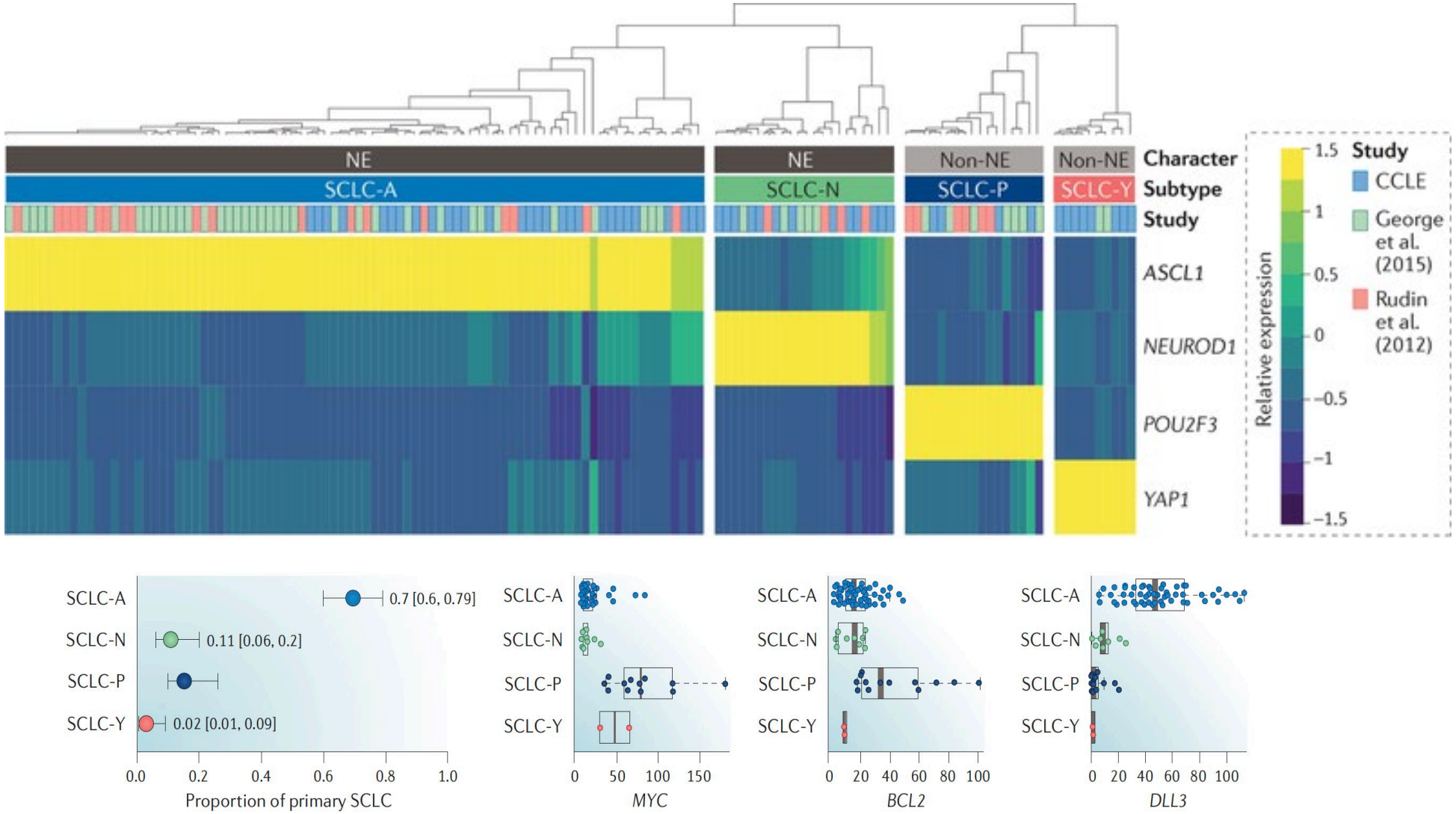
Other Investigational DLL3 T-Cell Engagers and DLL3 CAR-T

Clinical Trial Identifier	Treatment	Phase	Treatment Setting	Endpoint
DLL3 T-cell engagers				
NCT05060016	Tarlatamab	2	≥2L	ORR
NCT05361395	Tarlatamab, atezolizumab/durvalumab, chemotherapy	1b	1L	Safety
NCT05619744	RO7616789	1	≥2L	Safety
NCT04429087	BI764532	1	≥2L	Safety
NCT04471727	HPN328	1/2	≥2L	Safety
DLL3 CAR-T				
NCT05680922	LB2102	1	≥2L	Safety

ADCs in SCLC: Summary

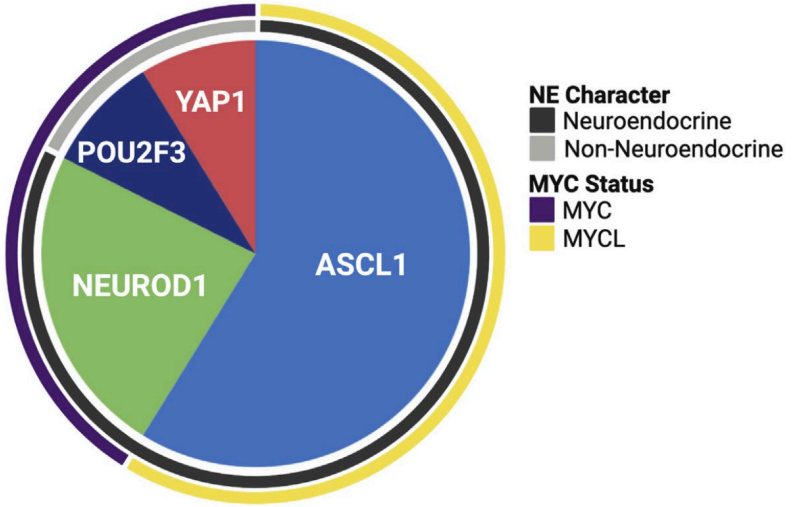
Target	Payload/MOA	Agent	DAR	SCLC Activity RR, DOR	Source
DLL3	Pyrrolobenzodiazepine	Rovalpituzumab tesirine	~2	–	–
TROP2	SN-38; topo I inhibitor Deruxtecan; topo I inhibitor	Sacituzumab govitecan Datopotamab deruxtecan	~7-8 ~4	N = 50, ORR 14%; DOR 5.7 mo	NCT01631552 (Gray et al. CCR 2017) NCT03401385
B7-H3	Deruxtecan; topo I inhibitor	Ifinatamab deruxtecan	~4	N = 19, ORR 58%; DOR 5.5 mo	NCT04145622
SEZ6	Calicheamicin; induces DS breaks	ABBV-011 ABBV-706	~2	–	NCT03639194 NCt05599984
CEACAM5	Maytansinoid DM4; MT inhibitor	Tusamitamab ravtansine	~3.8	–	NCT02187848
B7-H3	Clezutoclax; BCL-2/XL inhibitor	Mirzotamab clezutoclax	–	–	NCT03595059

SCLC subtypes defined by a dominant transcriptional regulator



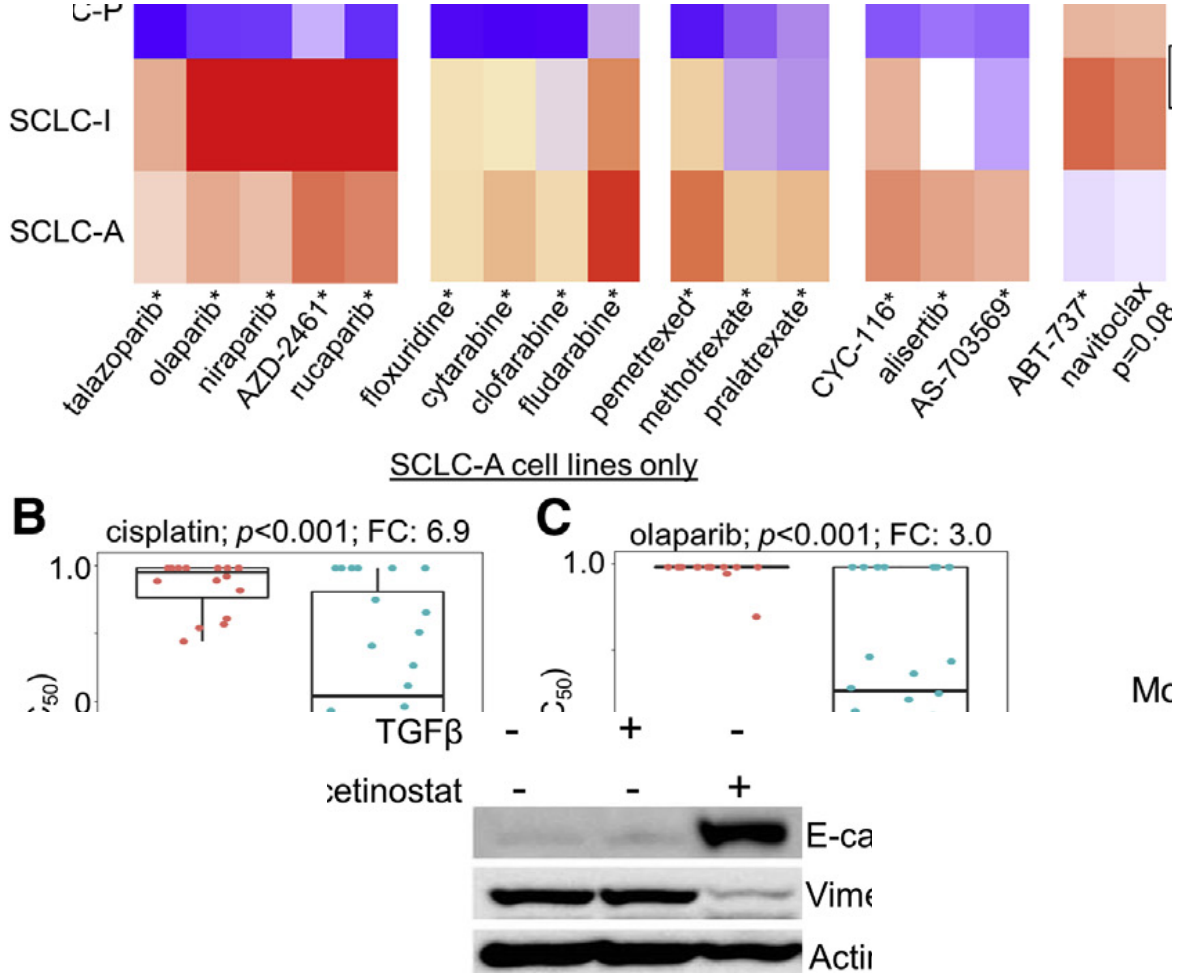
Rudin *et al. Nat Rev Cancer* 2019

SCLC molecular classification: therapeutic implications



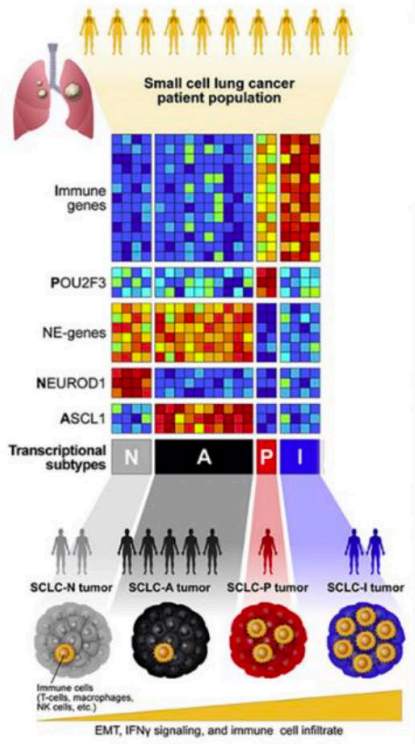
ASCL1	NEUROD1	POU2F3	YAP1
BCL2 CREBBP DLL3 LSD1	Arginine Deprivation AURKA/B CHK1 IMPDH LSD1	Arginine Deprivation AURKA/B CHK1 IGF-R1 IMPDH	Arginine Deprivation AURKA/B CHK1 IMPDH IO

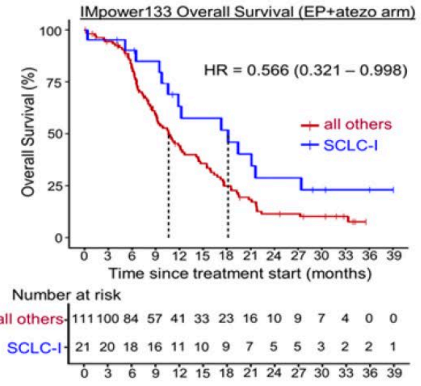
Poirier *et al. JTO* 2020

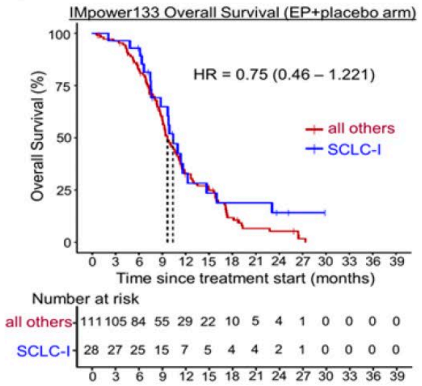


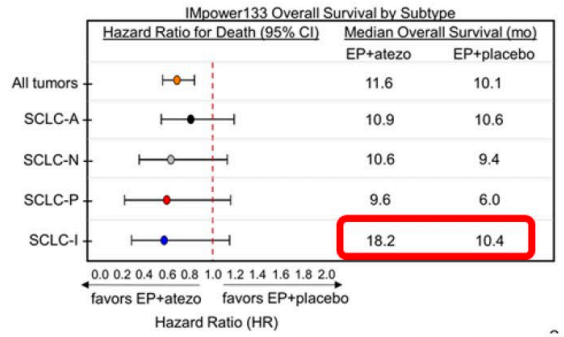
Gay *et al. Cancer Cell* 2021

SCLC-I with differential benefit from immunotherapy







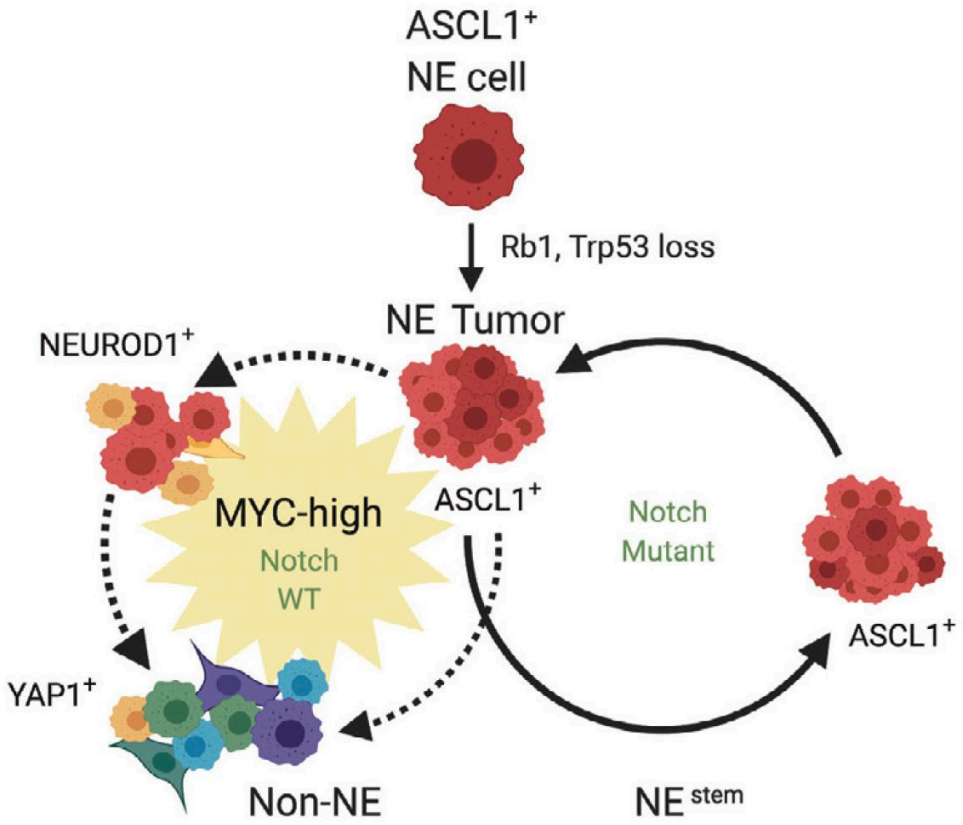


…and result in differential benefit from immunotherapy.

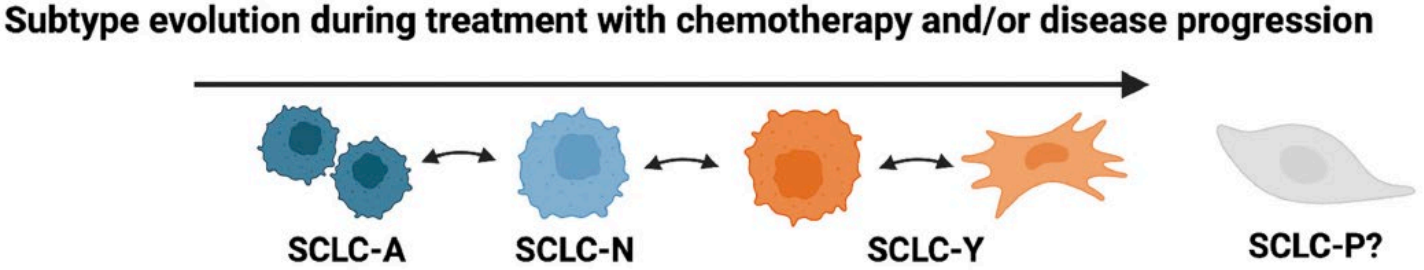
Gay et al. *Cancer Cell*, 2021

Gay, Hot Topics SCLC 2023

A *dynamic* classification

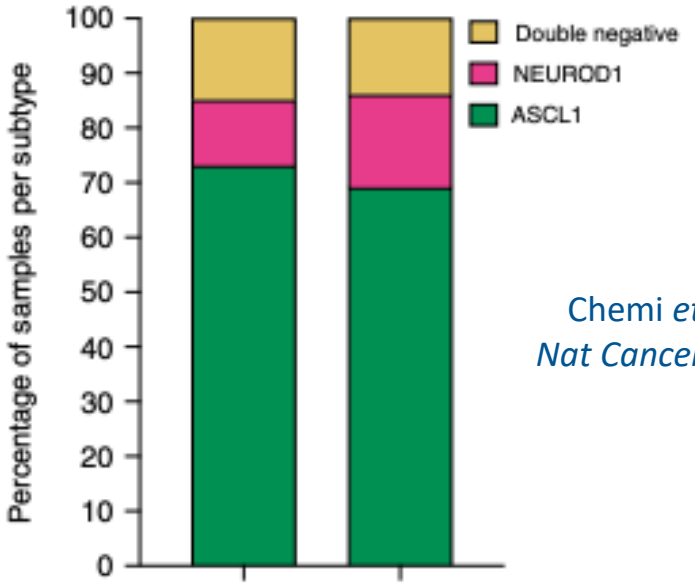


Ireland *et al. Cancer Cell* 2020

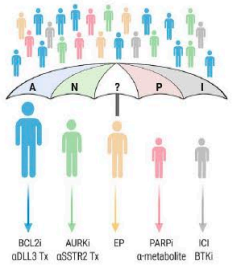


Gay *et al. Cancer Cell* 2021
Sutherland *et al. Genes Dev* 2022

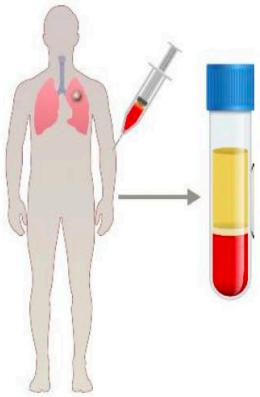
cfDNA methylome profiling



Chemi *et al.*
Nat Cancer 2022
(Baine *et al*)



Personalizing SCLC Treatment: *Clinical Trials*



Profile for SCLC subtype or drug specific biomarker and assign to treatment

(Repeat upon relapse)

Treatment Regimen 1
SCLC-A (**ASCL1**)

Treatment Regimen 2
SCLC-N (**NEUROD1**)

Treatment Regimen 3
SCLC-P (**POU2F3**)

Treatment Regimen 4
SCLC-I (**Inflamed**)

Treatment Regimen 5
Drug-specific biomarker

	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

Byers. TTLC 2023

Conclusions

- Despite recent advancements in first-line chemoimmunotherapy, effective treatments that provide greater magnitude of benefit are needed.
- The discovery of transcriptional subsets in SCLC is a major breakthrough in better understanding tumor heterogeneity and the potential therapeutic vulnerabilities.
- Blood-based biomarkers (e.g., ctDNA/methylation) are candidates that pave the way to better predict novel therapies.
- Prospective studies are needed to translate recent discoveries into personalized, biomarker-driven clinical trials.

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Spotlight on Small-Cell Lung Cancer and Other Lung Neuroendocrine Neoplasms

Lynnette Fernandez-Cuesta, PhD[1]; Alexandra Sexton-Oates, PhD[1]; Leyla Bayat, MD[2]; Matthieu Foll, PhD[1]; Sally C.M. Lau, MD, MPH[2]; and Ticiana Leal, MD[3]