MANAGING RELAPSE FOR ADVANCED SCLC

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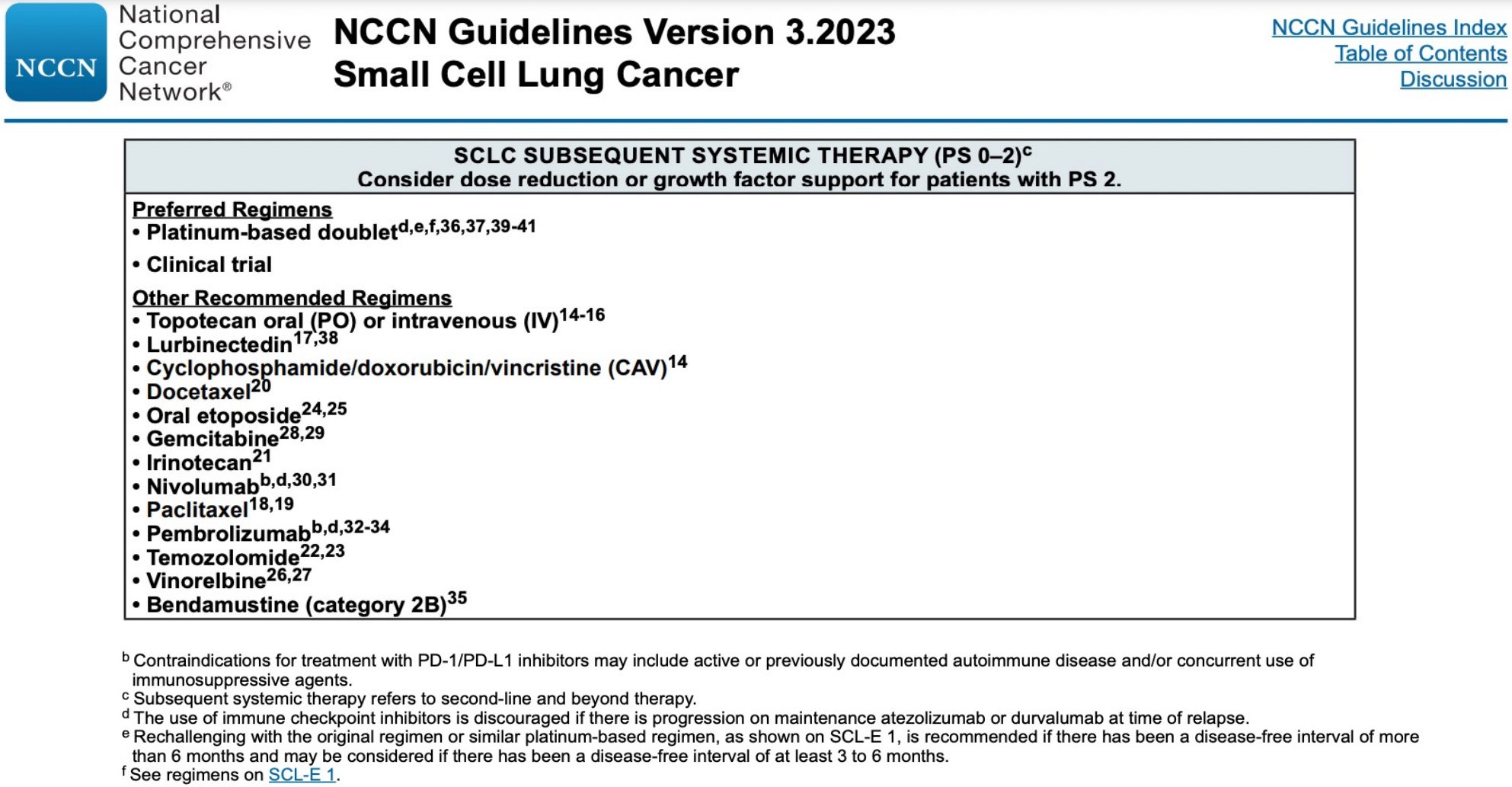
Introduction

- 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.

Relapsed SCLC



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Small Cell Lung Cancer

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Discussion

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

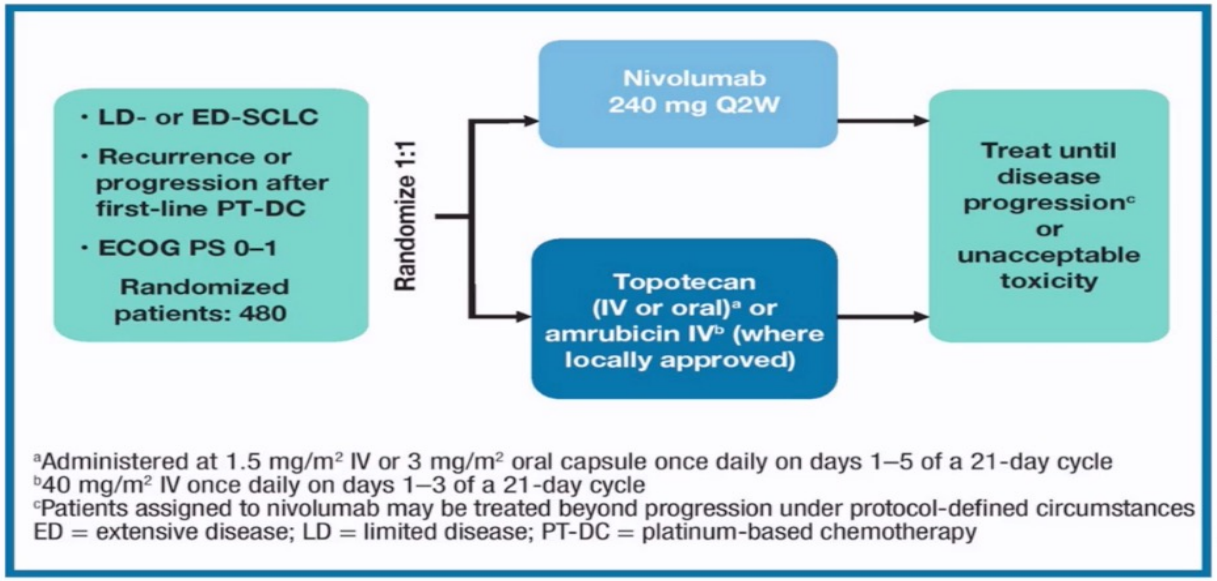
Preferred Regimens
- **Platinum-based doublet**[d,e,f,36,37,39-41]
- **Clinical trial**

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]

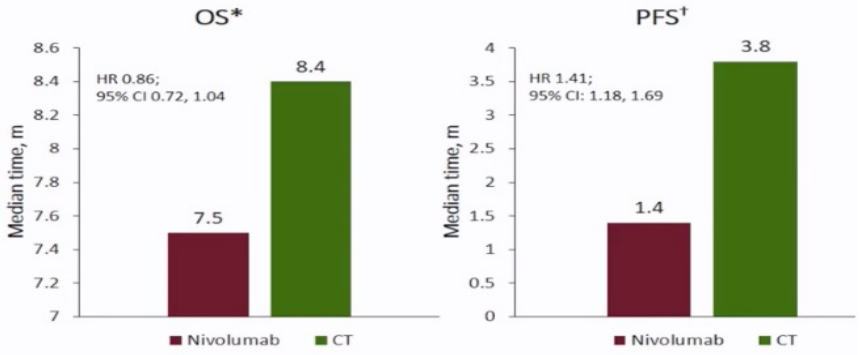
[b] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents.
[c] Subsequent systemic therapy refers to second-line and beyond therapy.
[d] The use of immune checkpoint inhibitors is discouraged 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.

Topotecan is still an option

CHECKMATE331 - Relapsed SCLC



[a]Administered at 1.5 mg/m² IV or 3 mg/m² oral capsule once daily on days 1–5 of a 21-day cycle
[b]40 mg/m² IV once daily on days 1–3 of a 21-day cycle
[c]Patients assigned to nivolumab may be treated beyond progression under protocol-defined circumstances
ED = extensive disease; LD = limited disease; PT-DC = platinum-based chemotherapy



*1-year OS rates were 37% nivolumab vs 34% CT.
†1-year PFS rates were 11% nivolumab vs 10% CT.
Reck M, et al. *Ann Oncol.* 2018;29(suppl 10):LBA5.

Results - study did not meet its primary endpoint of overall survival (OS) with nivolumab versus chemotherapy.

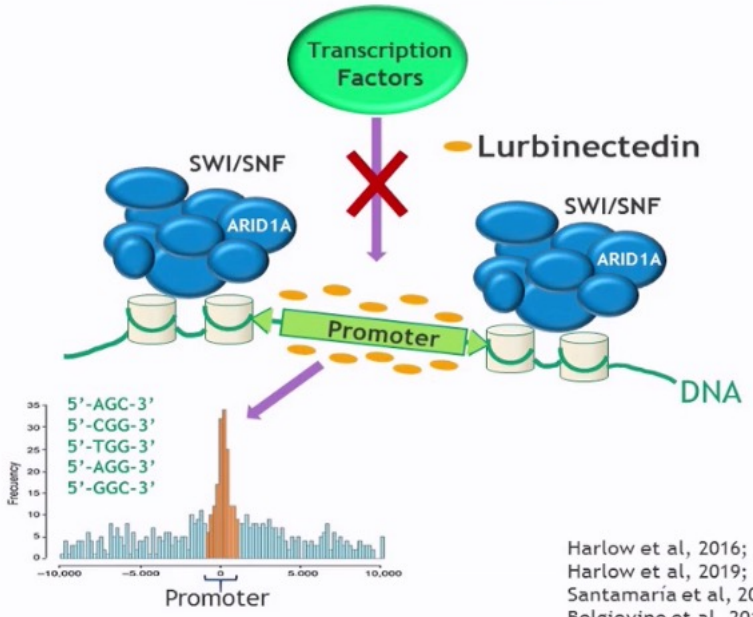
The safety profile of nivolumab was consistent with that observed in previously reported monotherapy studies on SCLC patients.

Horn L. et al. ASCO 2016, Abstract TPS8578

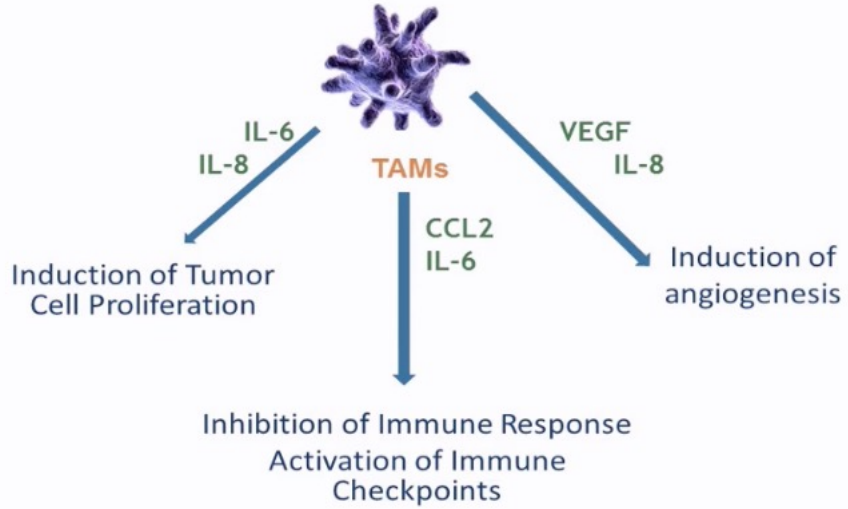
Spigel et al. 2021

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

Trigo et al. Lancet Oncol 2020

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

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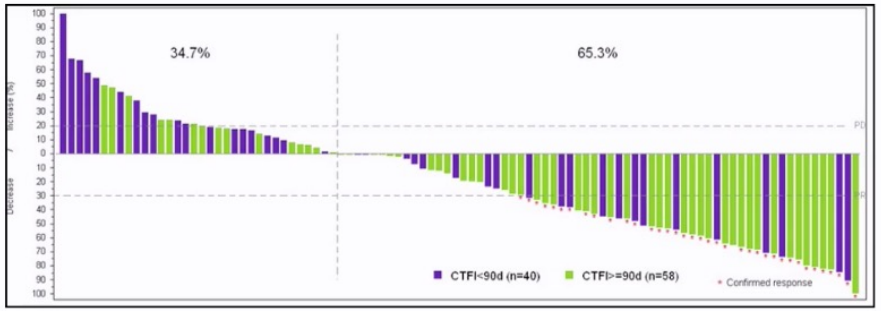
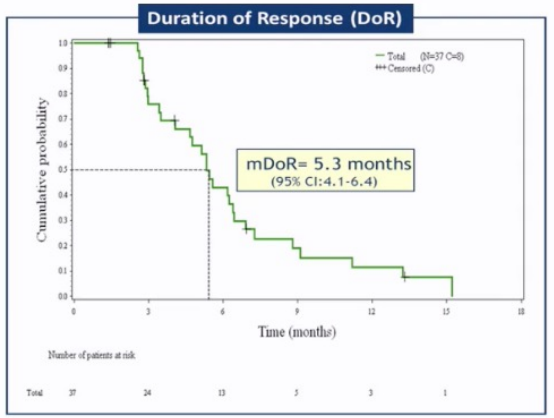
PRESENTED BY: Dr. Luis Paz Ares

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

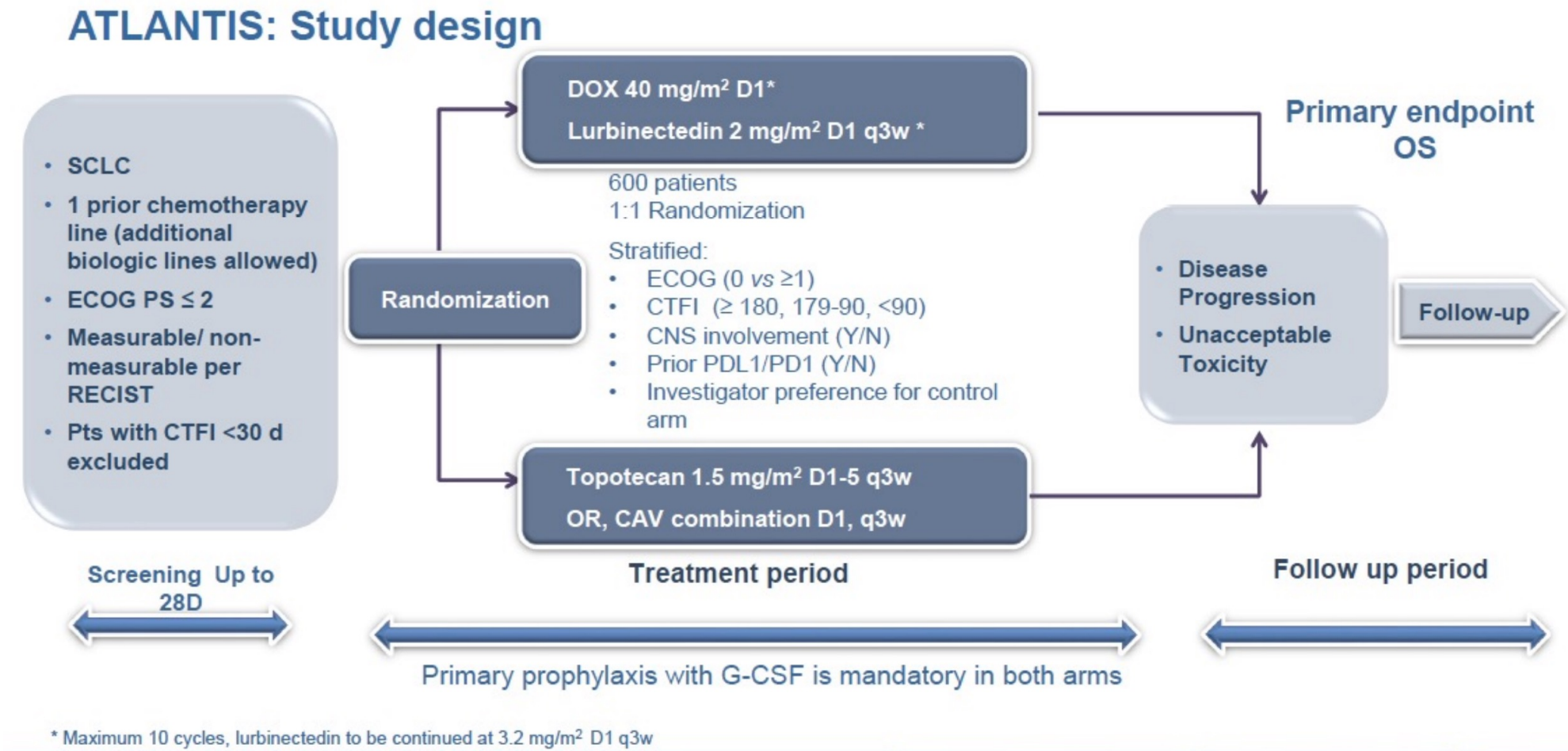
Trigo et al. Lancet Oncol 2020

Safety: Treatment-related Adverse Events

	Grade 1–2	Grade 3	Grade 4
Haematological abnormalities (regardless of relation to study drug)*			
Anaemia	91 (87%)	9 (9%)	0
Leucopenia	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)*			
Creatinine†	86/104 (83%)	0	0
Alanine aminotransferase	69/103 (67%)	5/103 (5%)	0
γ-glutamyl transferase	52/103 (50%)	13/103 (13%)	2/103 (2%)
Aspartate aminotransferase	44/103 (43%)	2/103 (2%)	0
Alkaline phosphatase	31/103 (30%)	3/103 (3%)	0
Treatment-related adverse events			
Fatigue	54 (51%)	7 (7%)	0
Nausea	34 (32%)	0	0
Decreased appetite	22 (21%)	0	0
Vomiting	19 (18%)	0	0
Diarrhoea	13 (14%)	1 (1%)	0
Febrile neutropenia	0	2 (2%)	3 (3%)
Pneumonia	0	2 (2%)	0
Skin ulcer	0	1 (1%)	0

Trigo et al. Lancet Oncol 2020

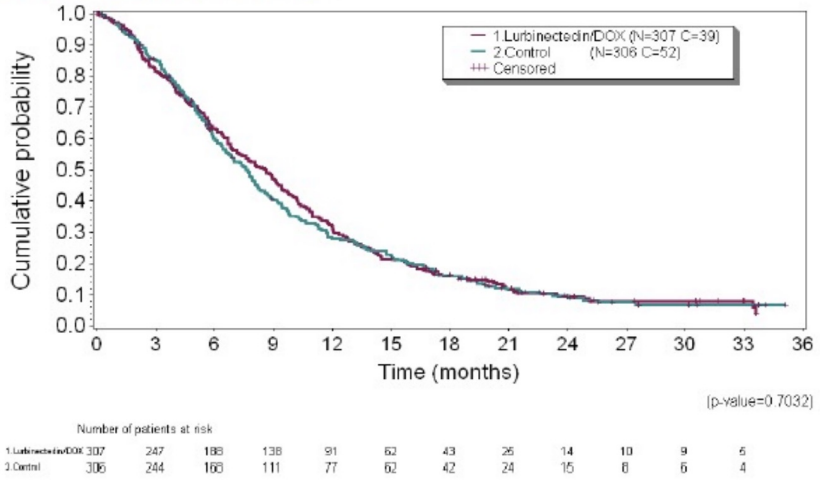
Relapsed SCLC: ATLANTIS



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

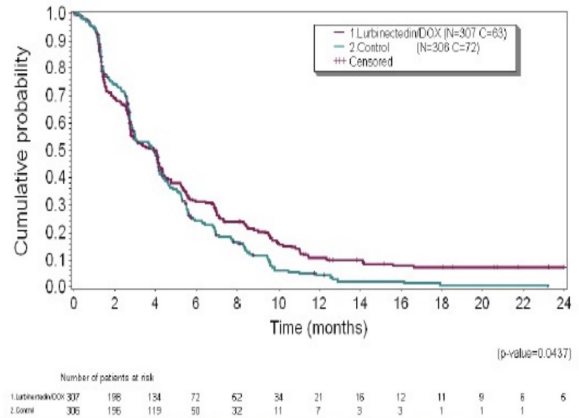
Relapsed SCLC: ATLANTIS

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		

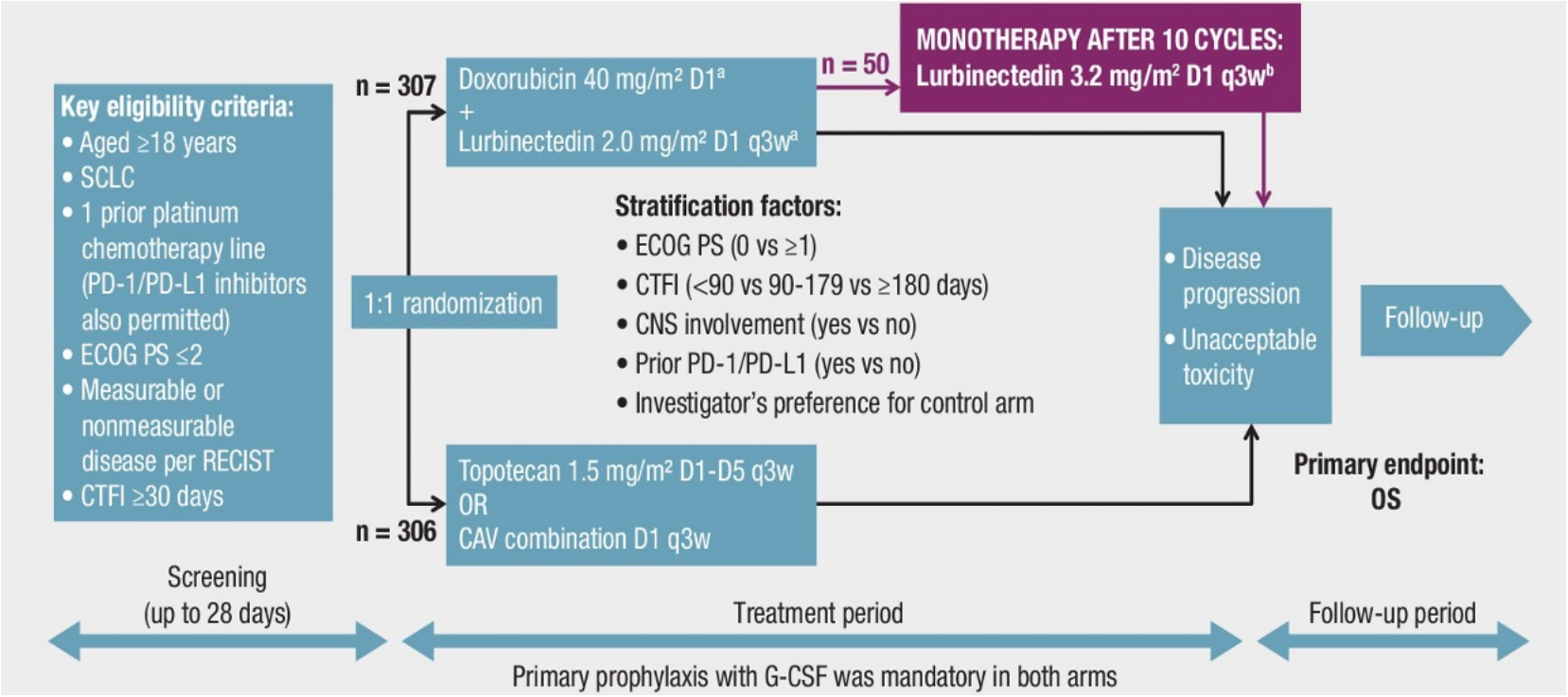
PFS by Independent Review Committee: Lurbinectedin/Doxo vs Control



	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)

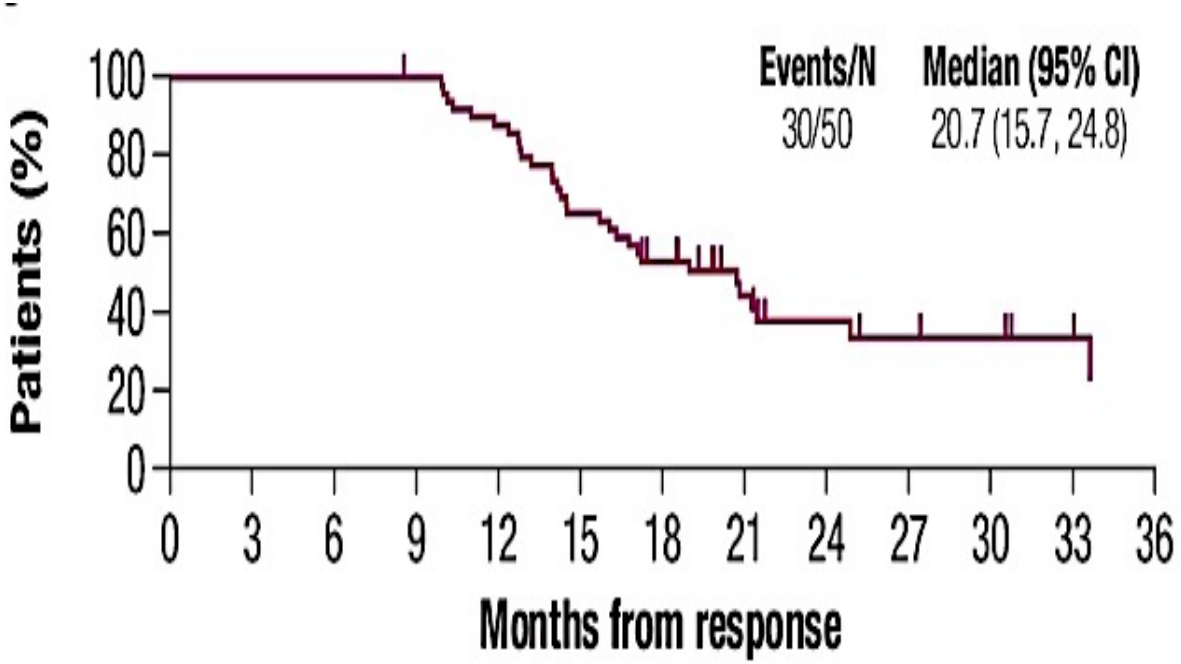
Navarro et al. ASCO 2022.

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

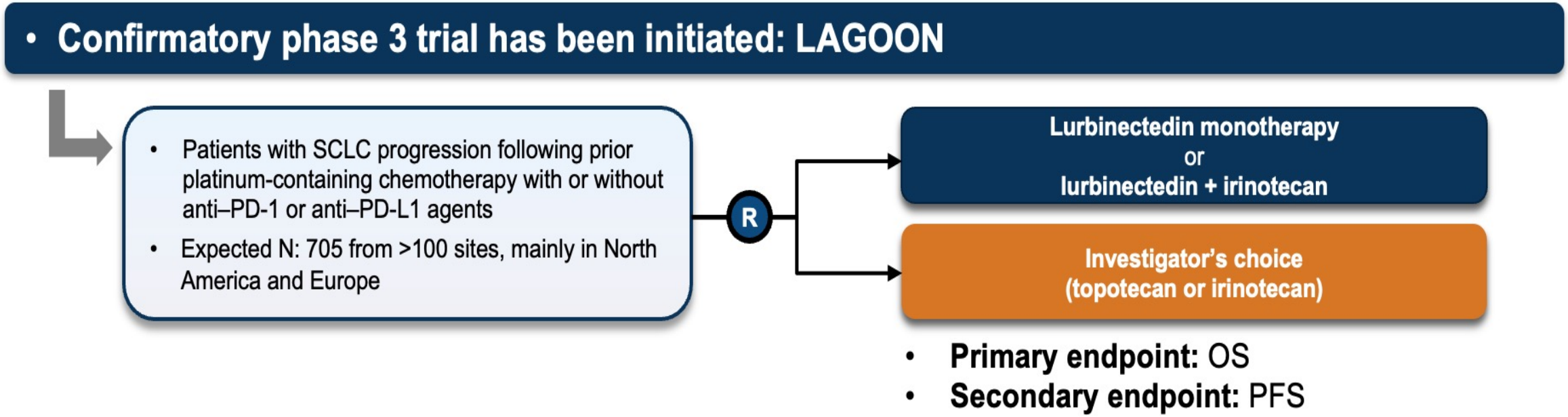
Improving response ⟷ Declining response

OS from Randomization

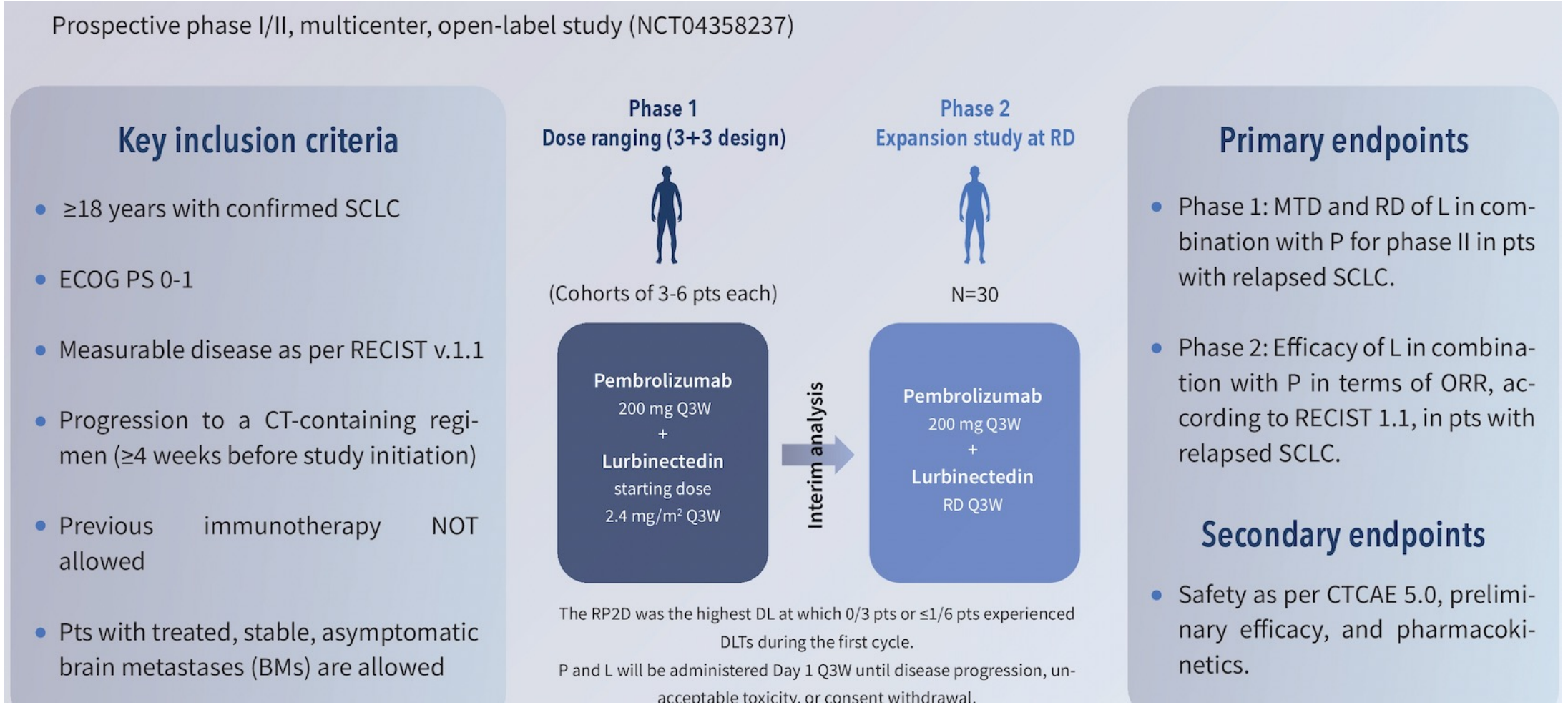


Navarro et al. ASCO 2022.

Phase 3 LAGOON trial ongoing



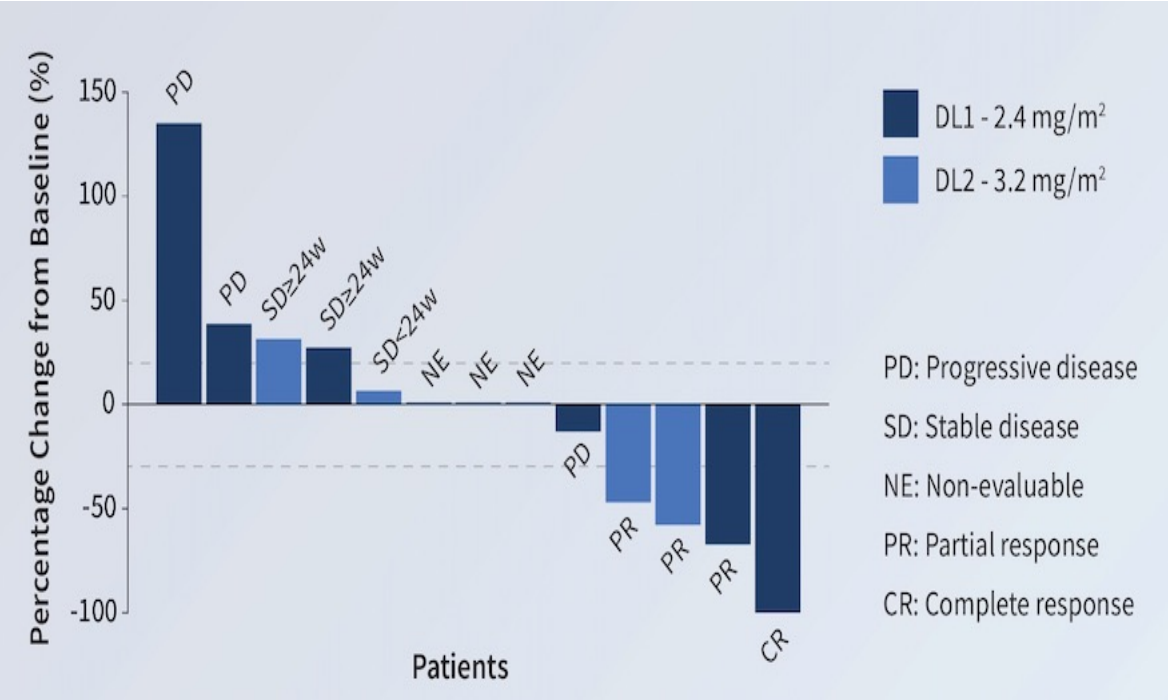
LUPER study



Calles et al. ASCO 2022

LUPER study

ORR =30%



Safety

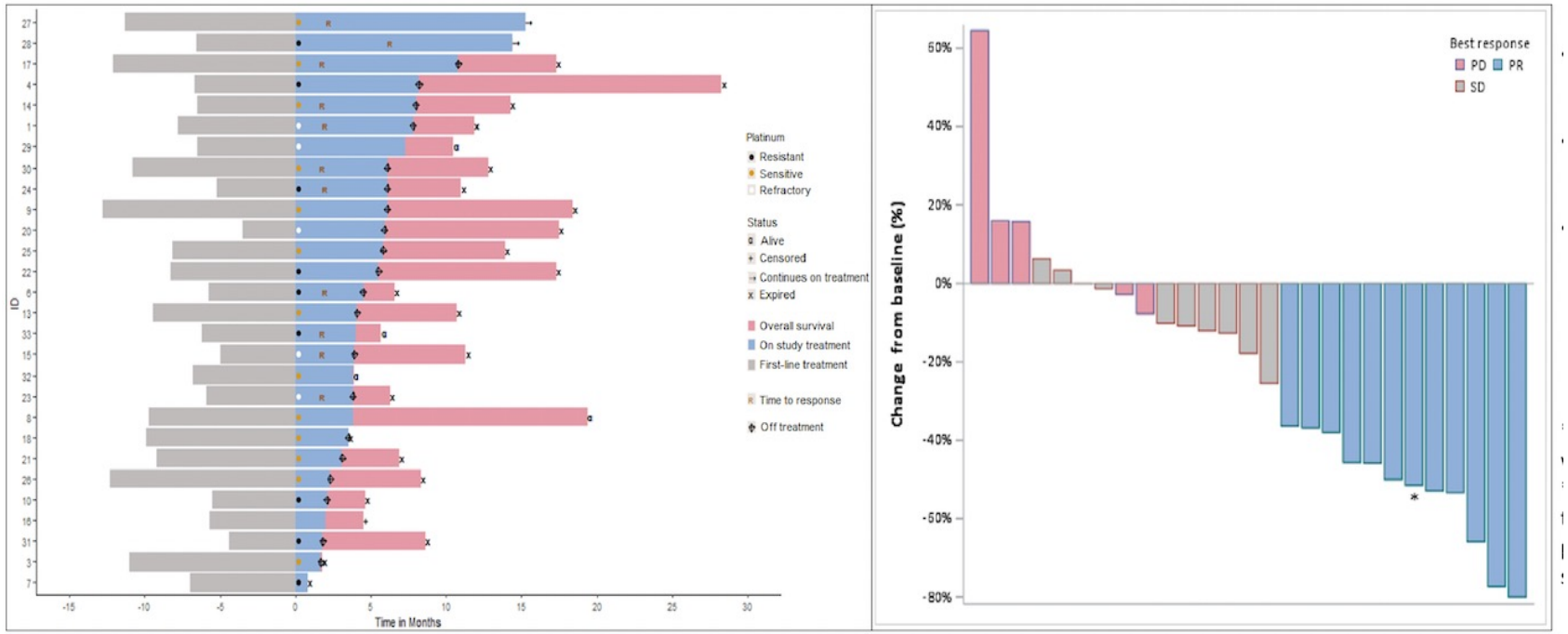
Overall (N=13)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
TEAEs*	11 (84.6)	7 (53.9)	2 (15.4)
Haematologic	8 (61.5)	3 (23.1)	2 (15.4)
Neutropenia	7 (53.9)	3 (23.1)	2 (15.4)
Thrombocytopenia	3 (23.1)	1 (7.7)	0 (0.0)
Anaemia	2 (15.4)	0 (0.0)	0 (0.0)
Non-haematologic**	11 (84.6)	4 (30.8)	0 (0.0)
Fatigue	10 (76.9)	1 (7.7)	0 (0.0)
Nausea	7 (53.9)	0 (0.0)	0 (0.0)
ALT increased	4 (30.8)	3 (23.1)	0 (0.0)
Decreased appetite	4 (30.8)	0 (0.0)	0 (0.0)
Vomiting	2 (15.4)	0 (0.0)	0 (0.0)
Constipation	2 (15.4)	0 (0.0)	0 (0.0)
AST increased	3 (23.1)	2 (15.4)	0 (0.0)
Dyspnoea	2 (15.4)	0 (0.0)	0 (0.0)

- DLTs: 1 G3 fatigue occurred in DL1; 1 G4 neutropenia in DL1 and DL2
- The RP2D was determined to be 3.2 mg/m2 L and 200 mg P IV Q3 weeks
- Further confirmation in the ongoing expansion phase 2 is warranted

Calles et al. ASCO 2022.

PARP inhibitors combos in Relapsed SCLC

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

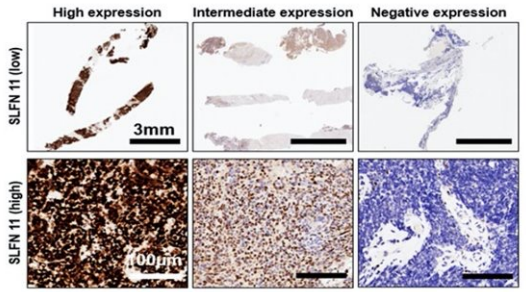


- ORR 39.3%
- PFS 4.5 mo
- OS 11.9 mo
- TRAEs ≥ 3: thrombocytopenia (61.3%), anemia (54.8%), neutropenia (41.9%), atypical pneumonia (3.2%)

Goldman et al. ASCO 2022.

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

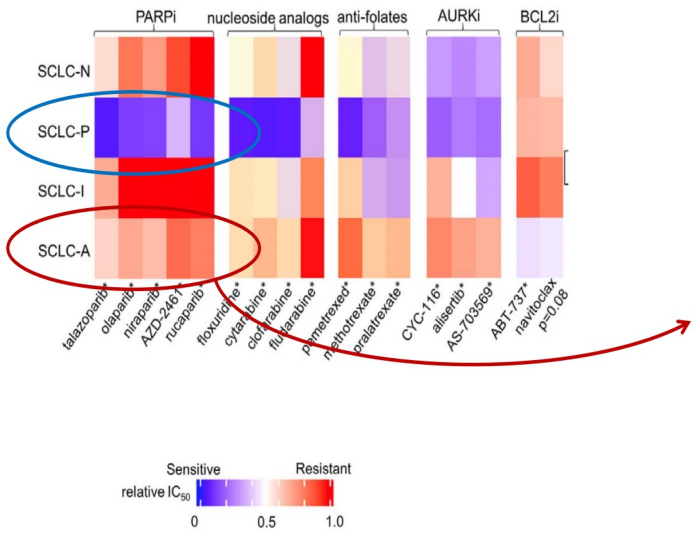
SLFN11 is frequently expressed, predicted PARP inhibitor benefit in retrospective analyses of SCLC pts

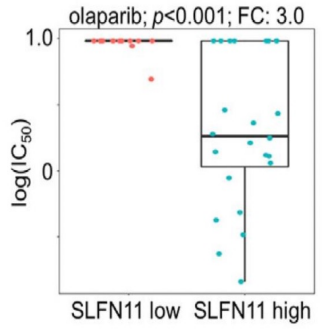


	Sample size	SLFN11+ % (n)
Phase II veliparib/TMZ *(Pietanza, JCO 2018)*	47	49% (23)
Phase II EP/veliparib *(Byers, CCR 2021)*	149	52% (77)

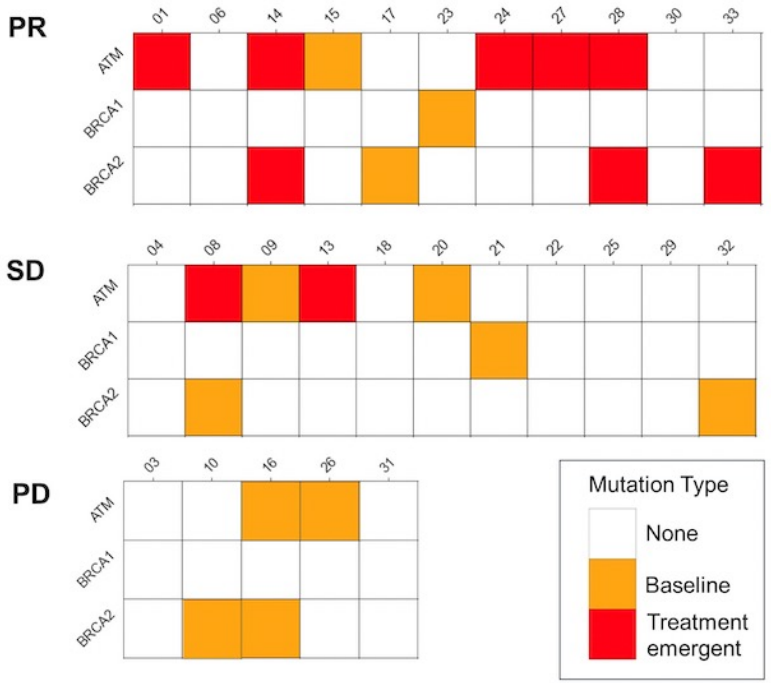
Wei-Lien Wang, Junya Fujimoto, Ignacio Wistuba, MDACC

SCLC subtypes as a predictor of benefit of PARPi



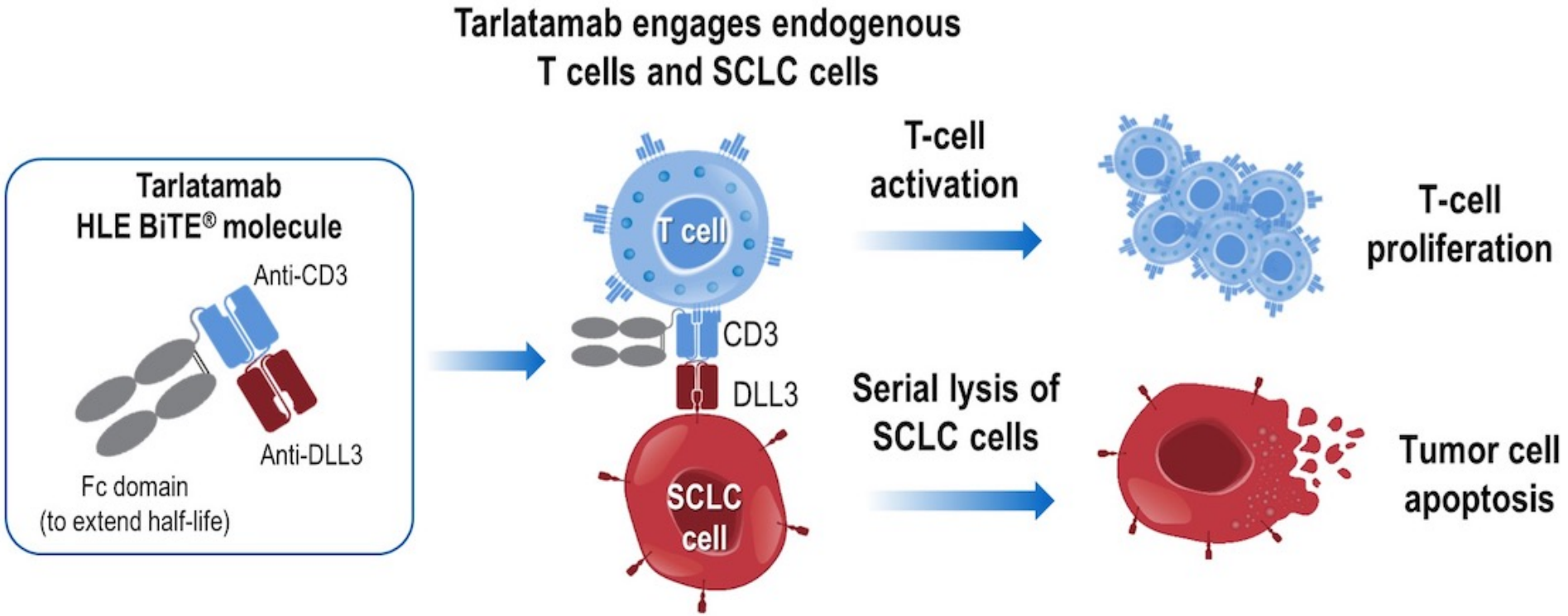


Mutations in DDR genes occur on treatment with tala and TMZ: association with DC.



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

DLL3 targeting HLE BITE



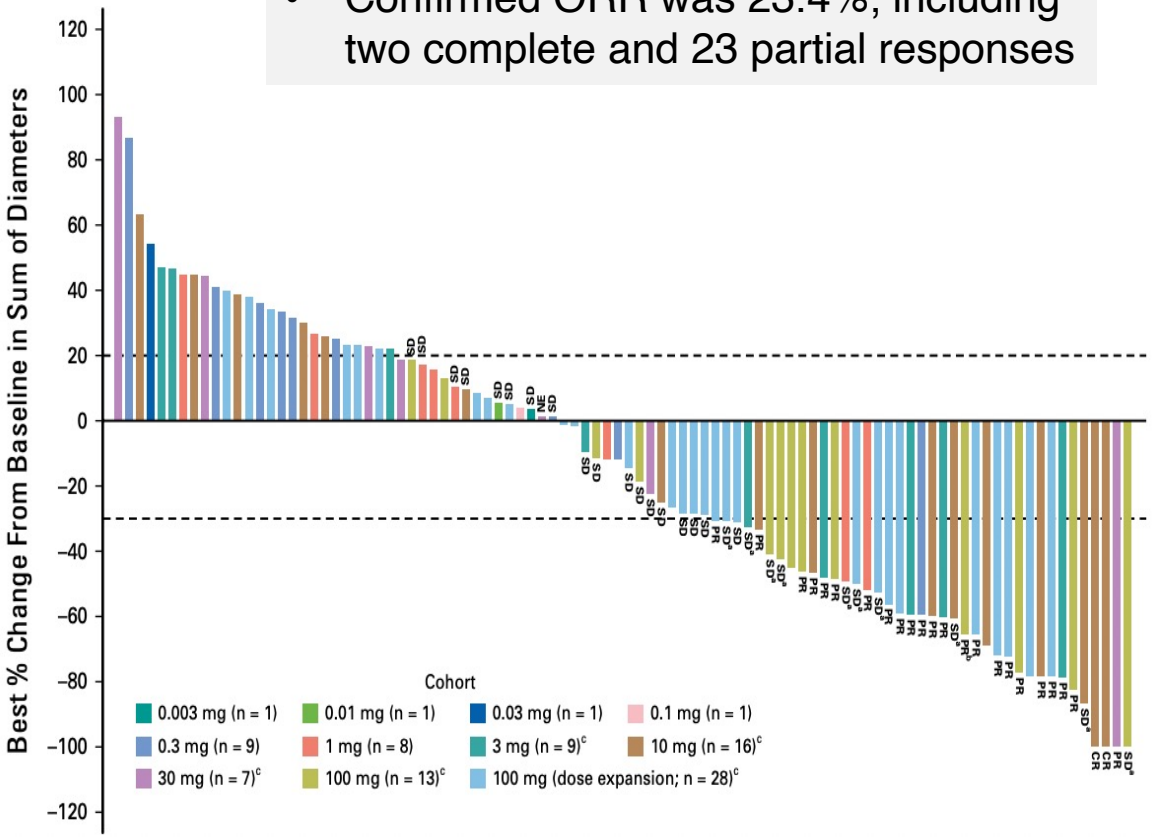
- Tarlatamab, a half-life extended bispecific T-cell engager (HLE BiTE) molecule, binds both DLL3 on cancer cells and CD3 on T cells leading to T-cell–mediated tumor lysis.
- Tarlatamab promotes tumor regression in preclinical models of SCLC.

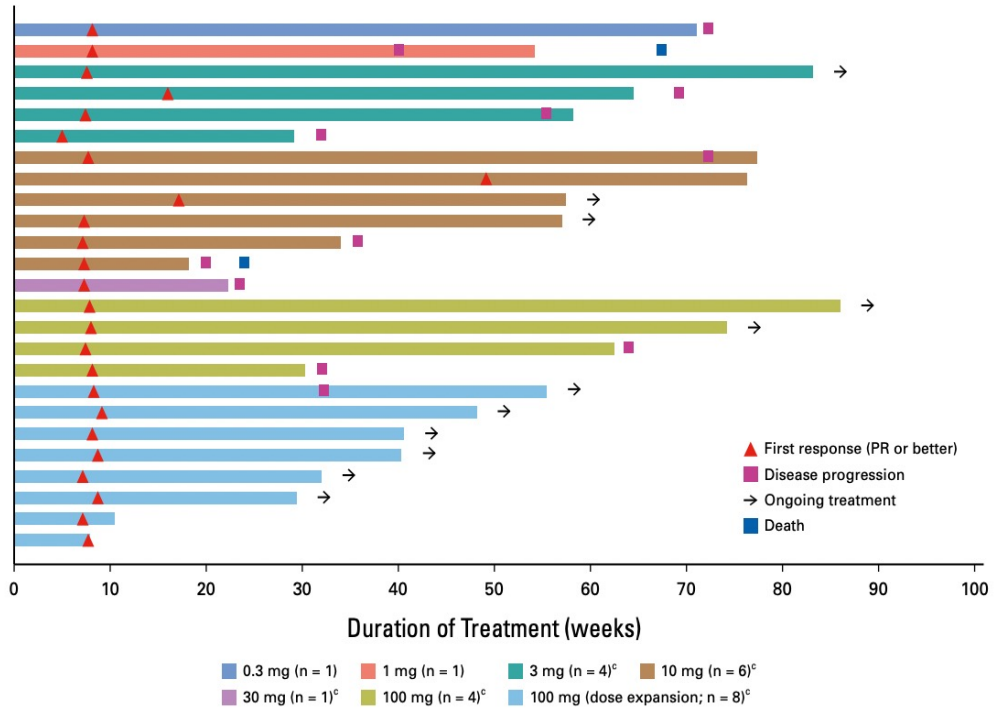
Owonikoko et al. ASCO 2022

Paz-Ares et al. JCO 2023

Phase I tarlatamab: Efficacy

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



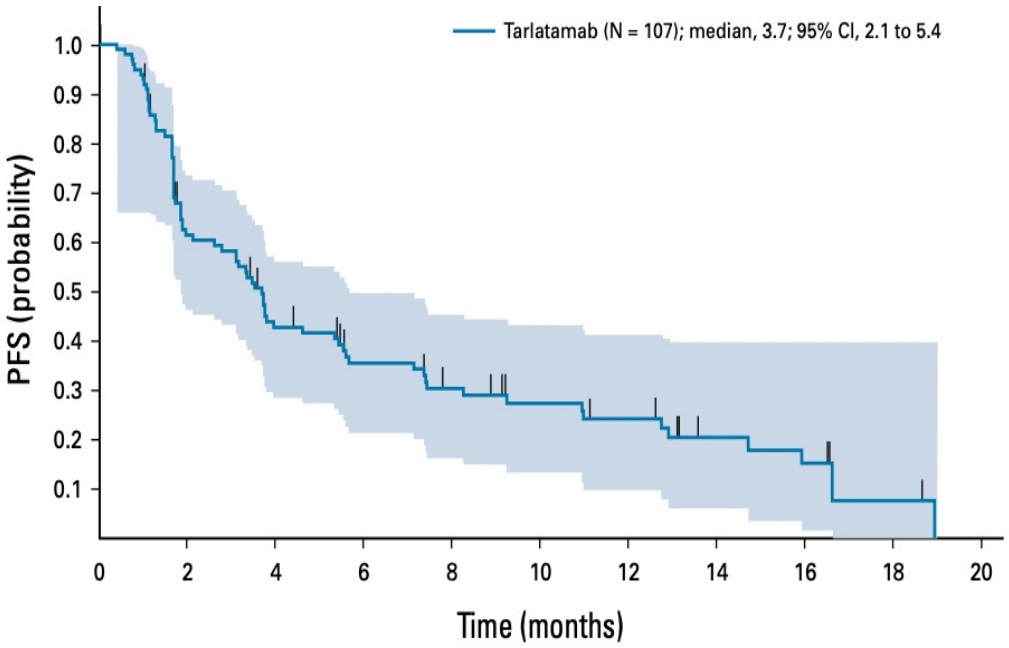


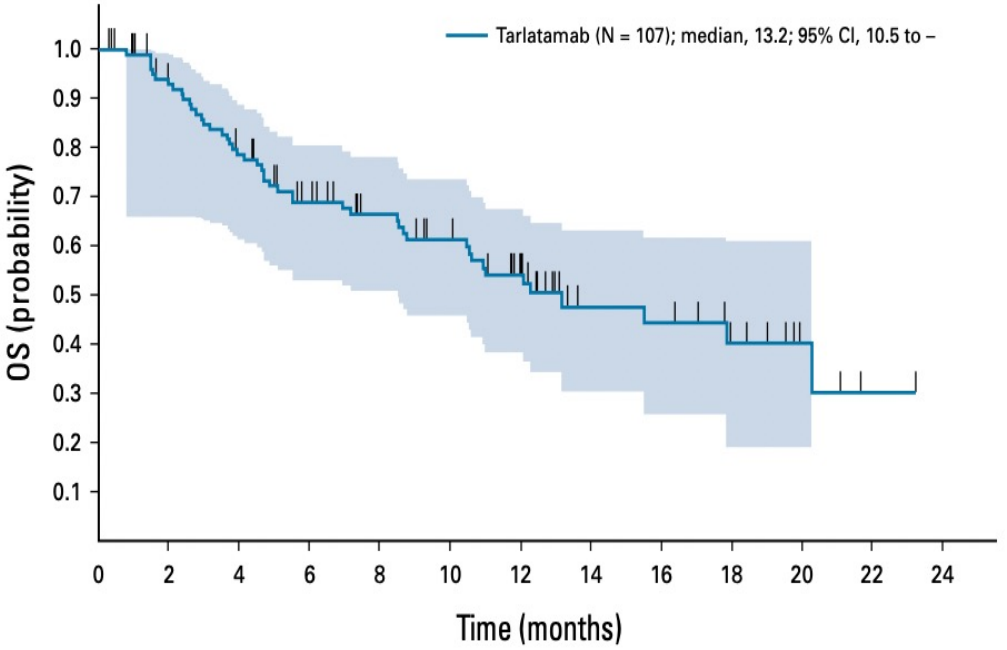
Among confirmed responders, the median time to response was 1.8 months (range, 1.2-7.4) and the median DOR was 12.3 months (95% CI, 6.6 to 14.9; Fig 1B).

Owonikoko et al. ASCO 2022

Paz-Ares et al. JCO 2023

Phase I tarlatamab



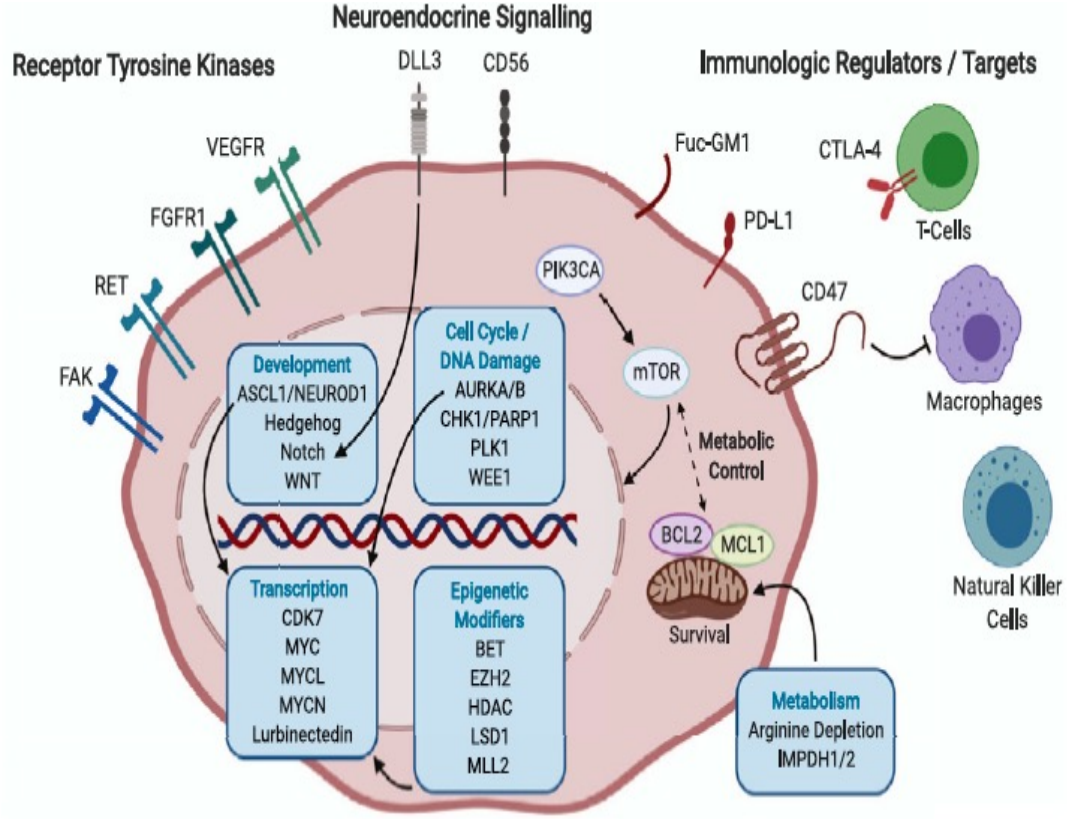


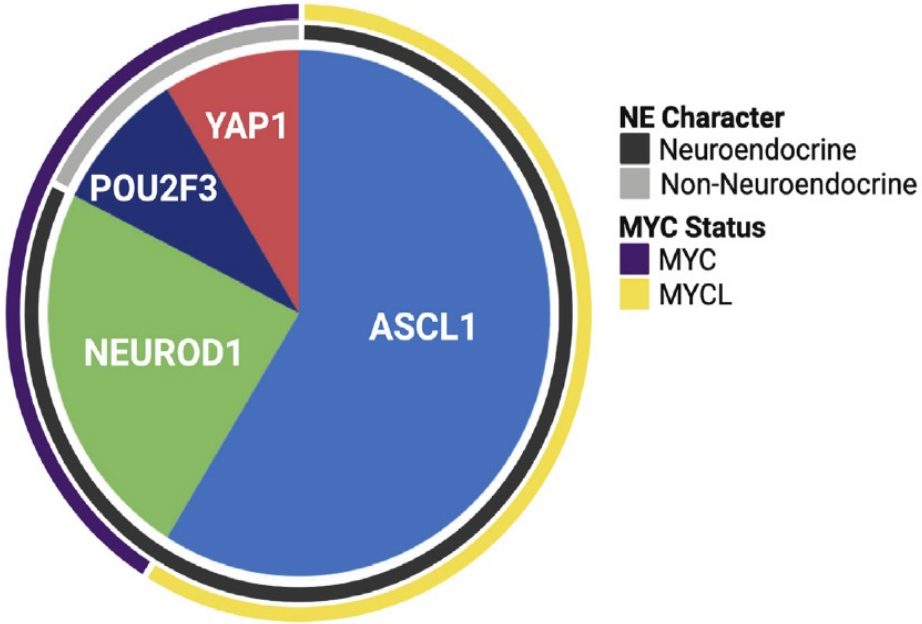
•The overall safety profile of tarlatamab was acceptable, with dose-limited toxicities occurring in 6 patients. Nearly half of the patients had grade 1 or 2 transient cytokine release syndrome; 1 patient had grade 3.

Owonikoko et al. ASCO 2022

Paz-Ares et al. JCO 2023

SCLC: Where do we go from here?





	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

Conclusions

- Treatment for patients with SCLC in the relapsed setting needs to be individualized.
- Lurbinectedin as single agent remains an option for salvage therapy preferably in platinum sensitive disease.
- Promising strategies are investigating novel therapies in subtypes of SCLC.
- PARP inhibitor combinations such as talazoparib plus temozolomide have shown encouraging response rates in pretreated SCLC.
- Tarlatamab shows promising response durability and acceptable safety profile in heavily pretreated SCLC.

Safety: Tarlatamab

TABLE 2. AEs (preferred term and AMQ for selected terms)

	All Patients (N = 107)				
AE	**Any Grade, No. (%)**	**Grade 1-2, No. (%)**	**Grade 3, No. (%)**	**Grade 4, No. (%)**	**Grade 5, No. (%)**
AEs of any cause that occurred during treatment[a]					
Any	107 (100)	46 (43)	48 (45)	12 (11)	1 (1)
Serious	55 (51)	25 (23)	23 (21)	6 (6)	1 (1)
Resulting in discontinuation	4 (4)	1 (1)	3 (3)	0 (0)	0 (0)
Treatment-related AEs	97 (91)	64 (60)	23 (21)	9 (8)	1 (1)
Treatment-related AEs occurring in > 10% of patients or grade ≥ 3 in > 1%)[a]					
CRS	56 (52)	55 (51)	1 (1)	0	0
Pyrexia	40 (37)	38 (36)	2 (2)	0	0
Dysgeusia	24 (22)	24 (22)	0	0	0
Fatigue	23 (22)	20 (19)	3 (3)	0	0
Nausea	21 (20)	21 (20)	0	0	0
Decreased appetite	14 (13)	14 (13)	0	0	0
Vomiting	13 (12)	13 (12)	0	0	0
Anemia	12 (11)	11 (10)	1 (1)	0	0
Asthenia	12 (11)	10 (9)	2 (2)	0	0
Neutropenia	12 (11)	4 (4)	5 (5)	3 (3)	0
Headache	11 (10)	11 (10)	0	0	0
Decreased white blood cell count	9 (8)	4 (4)	4 (4)	1 (1)	0
Decreased lymphocyte count	8 (8)	3 (3)	2 (2)	3 (3)	0
Confusional state	6 (6)	1 (1)	4 (4)	1 (1)	0
Decreased neutrophil count	6 (6)	3 (3)	2 (2)	1 (1)	0
Hyponatremia	6 (6)	4 (4)	2 (2)	0	0
Maculopapular rash	6 (6)	4 (4)	2 (2)	0	0
Pneumonitis	4 (4)	2 (2)	1 (1)	0	1 (1)
Lymphopenia	3 (3)	1 (1)	1 (1)	1 (1)	0
Encephalopathy	3 (3)	1 (1)	2 (2)	0	0
Hypertension	3 (3)	1 (1)	2 (2)	0	0
AEs of interest[b]					
CRS					
Any cause	56 (52)	55 (51)	1 (1)	0	0
Related	56 (52)	55 (51)	1 (1)	0	0
Neurologic events					
Any cause	75 (70)	63 (59)	11 (10)	1 (1)	0
Related	53 (50)	46 (43)	6 (6)	1 (1)	0
Neutropenia					
Any cause	17 (16)	6 (6)	7 (7)	4 (4)	0
Related	17 (16)	7 (7)	6 (6)	4 (4)	0