University of Colorado Cancer Center

University of Colorado Hospital

University of Colorado Health Sciences Center

SCLC: What's next After 1st Line immunotherapy?

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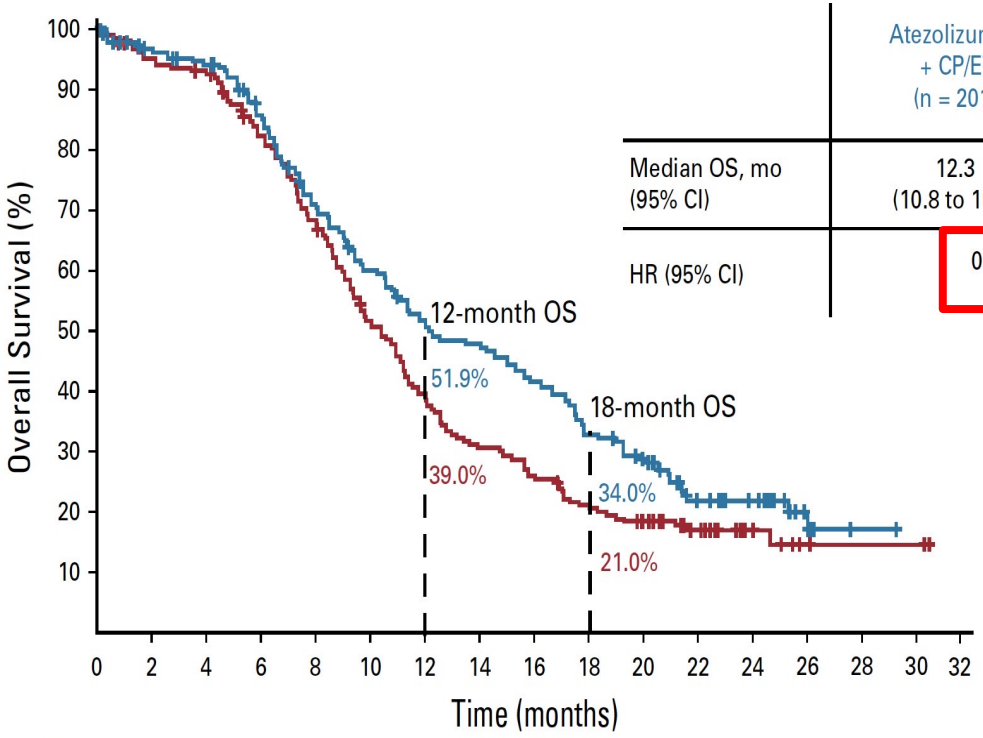
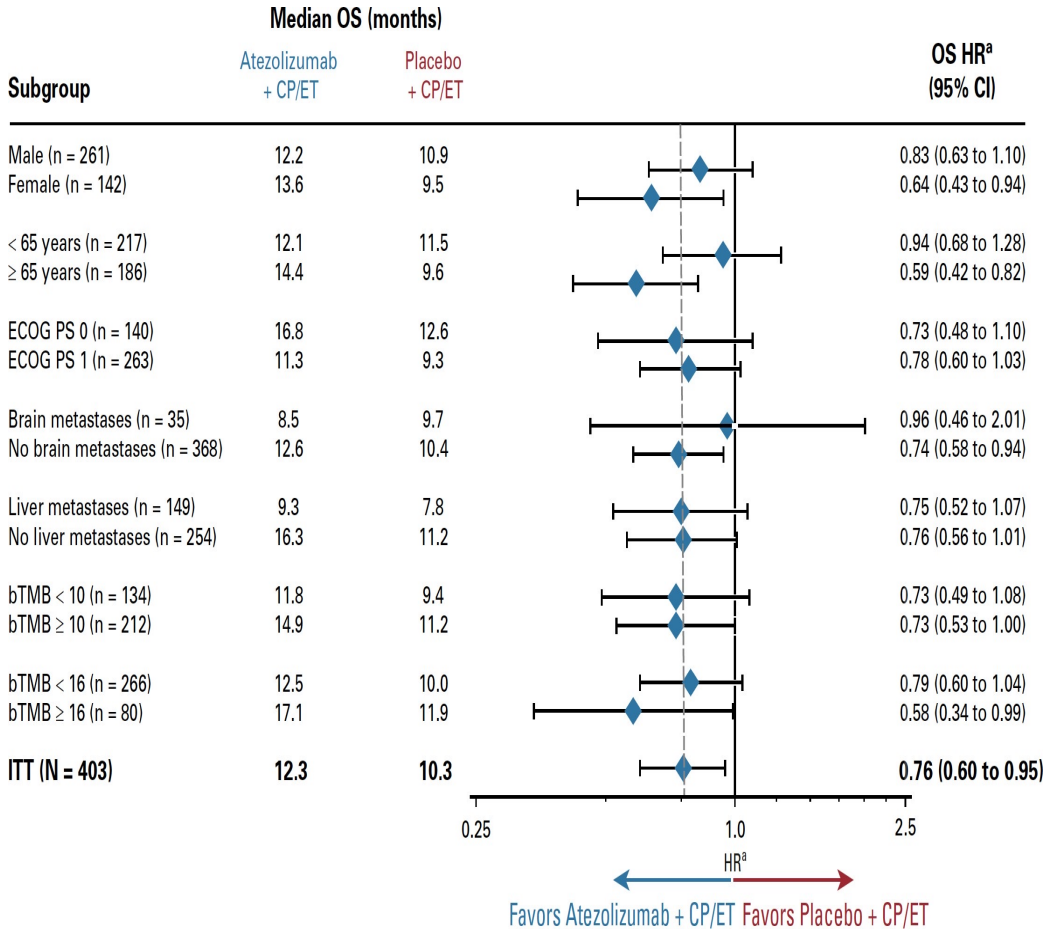
IMpower 133: Chemo +/- Atezolizumab



	Atezolizumab + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8 to 15.8)	10.3 (9.3 to 11.3)
HR (95% CI)	0.76 (0.60 to 0.95) *P* = .0154*	

No. of Patients at Risk

Atezolizumab + CP/ET	201	187	180	159	130	109	93	86	75	61	51	28	21	8	1
Placebo + CP/ET	202	189	183	160	131	97	74	58	49	39	33	20	8	3	2	2

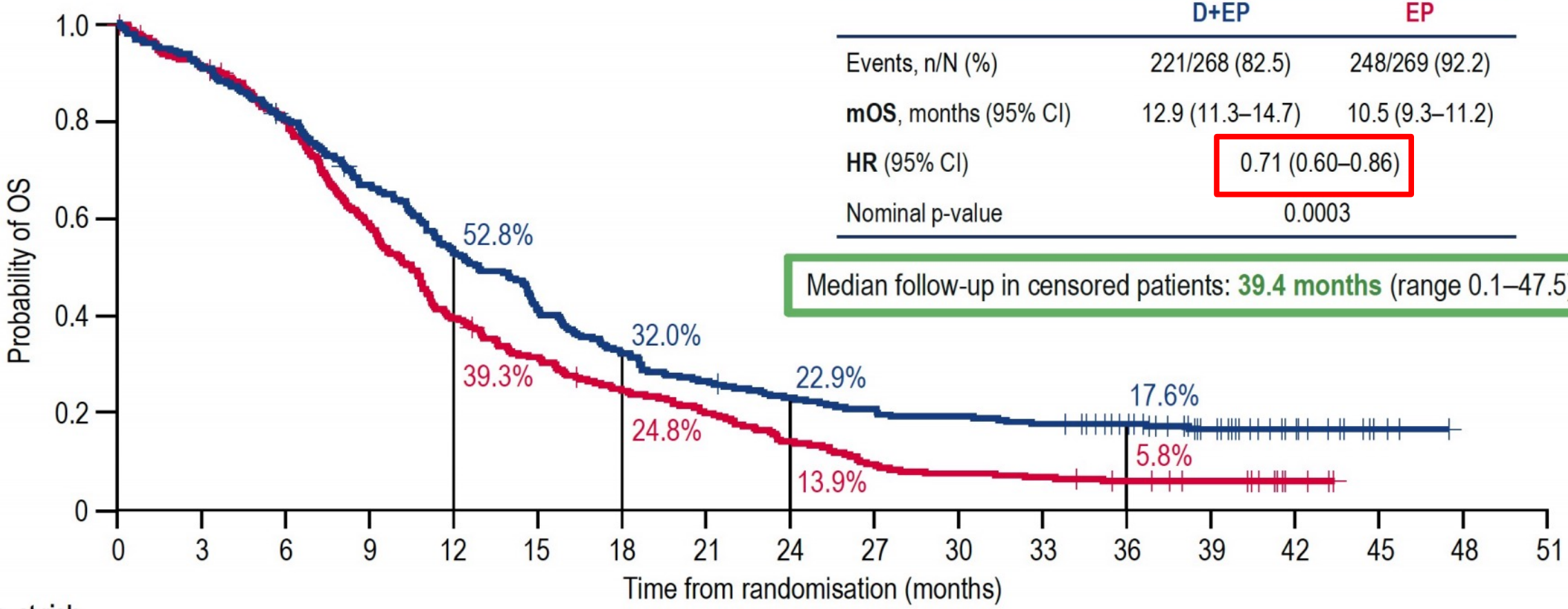


Liu et al, JCO 2021

CASPIAN 3-Year OS Update: Durvalumab + EP vs EP[1]

	D+EP	EP
Events, n/N (%)	221/268 (82.5)	248/269 (92.2)
mOS, months (95% CI)	12.9 (11.3–14.7)	10.5 (9.3–11.2)
HR (95% CI)	0.71 (0.60–0.86)	
Nominal p-value	0.0003	

Median follow-up in censored patients: **39.4 months** (range 0.1–47.5)



No. at risk

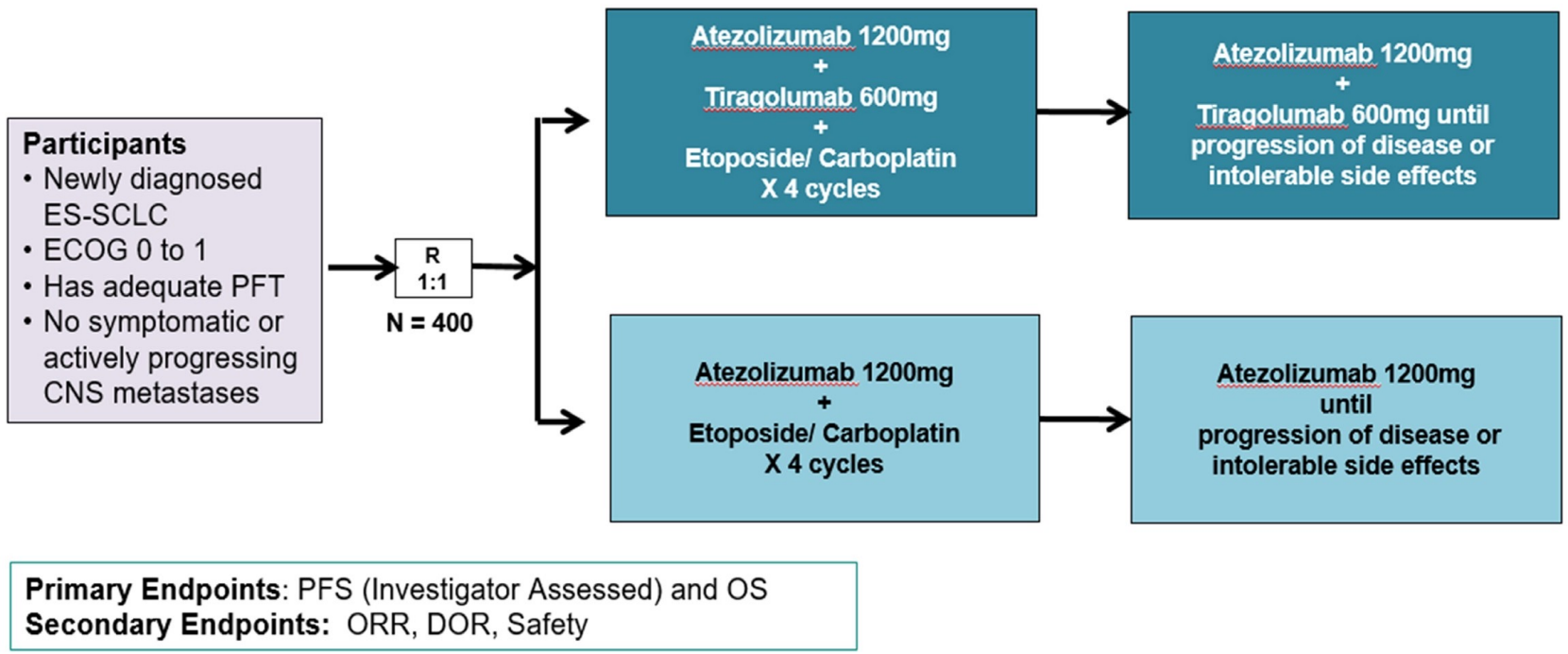
D+EP	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
EP	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	0

Data cutoff: March 22, 2021. Size of circle is proportional to the number of events across both treatment groups.

1. Paz-Ares LG et al. ESMO 2021. Abstract LBA61.

SKYSCRAPER-02: Phase III Study of Atezolizumab plus Carboplatin and Etoposide with/without Tiragolumab in ED-SCLC

- TIGIT is an important immune checkpoint pathway
- Tiragolumab: human IgG1/kappa anti-TIGIT mAb with an intact Fc region that blocks the binding of TIGIT to its receptor PVR

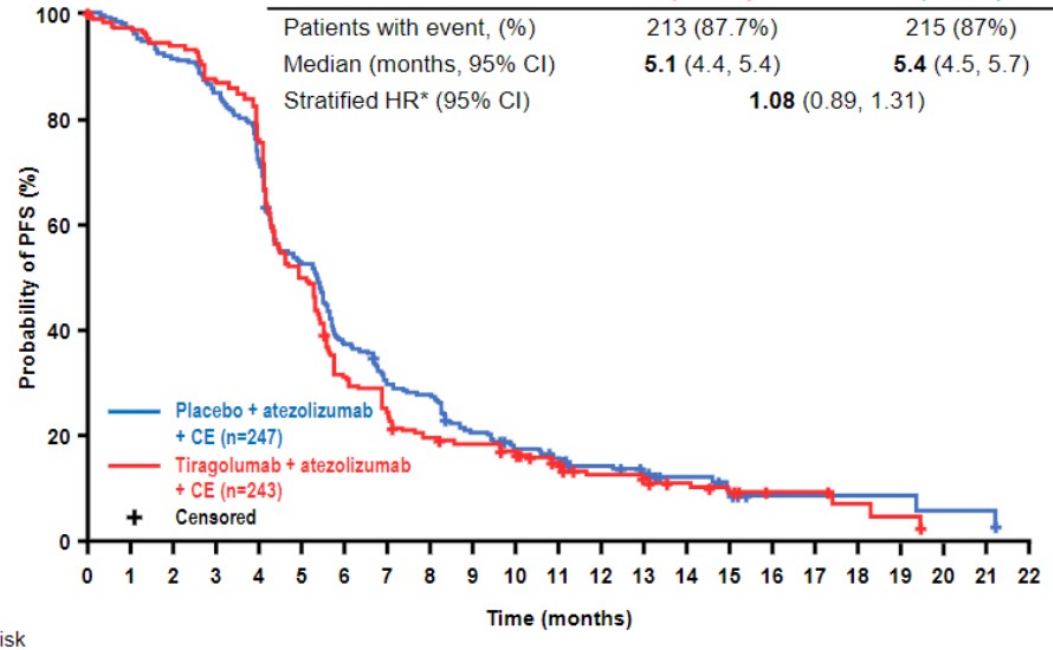


ClinicalTrials.gov. NCT04256421

PFS and OS: Full Analysis Set

PFS in the Full Analysis Set

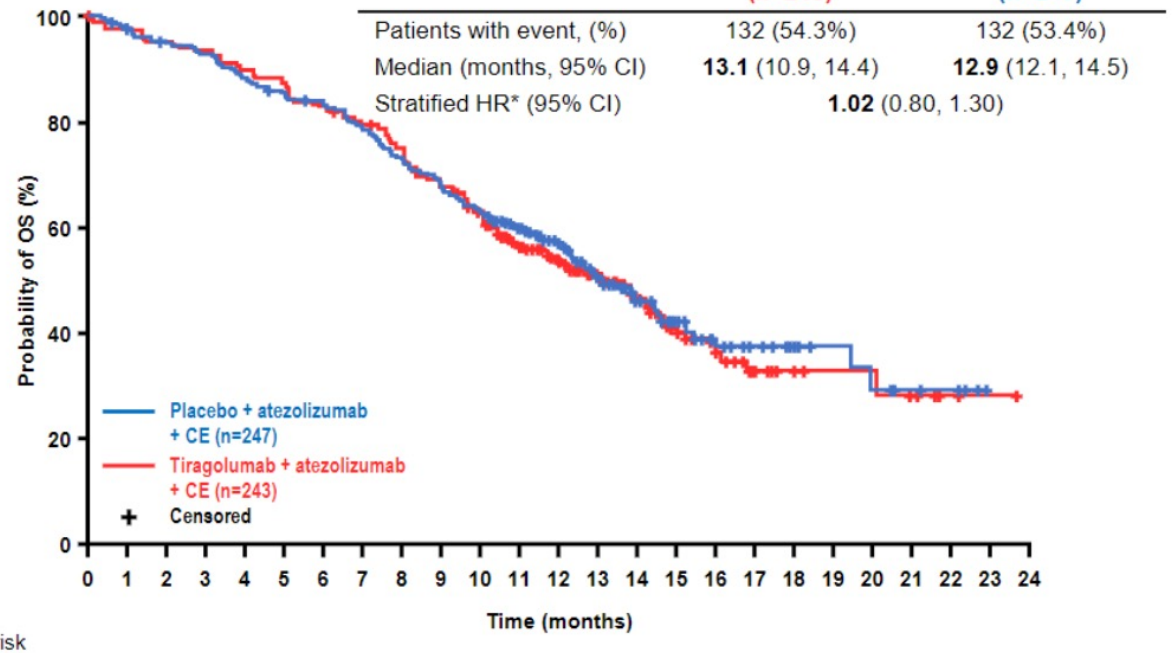
	Tiragolumab + atezolizumab + CE (n=243)	Placebo + atezolizumab + CE (n=247)
Patients with event, (%)	213 (87.7%)	215 (87%)
Median (months, 95% CI)	**5.1** (4.4, 5.4)	**5.4** (4.5, 5.7)
Stratified HR* (95% CI)	**1.08** (0.89, 1.31)	



No. at risk																						
Placebo + atezo + CE	247	237	224	207	185	128	92	73	66	49	40	34	26	20	11	8	3	3	3	3	2	2	NE
Tiragolumab + atezo + CE	243	232	224	209	188	120	74	59	45	41	35	27	18	18	12	9	5	5	3	2	NE	NE	NE

Interim OS in the Full Analysis Set

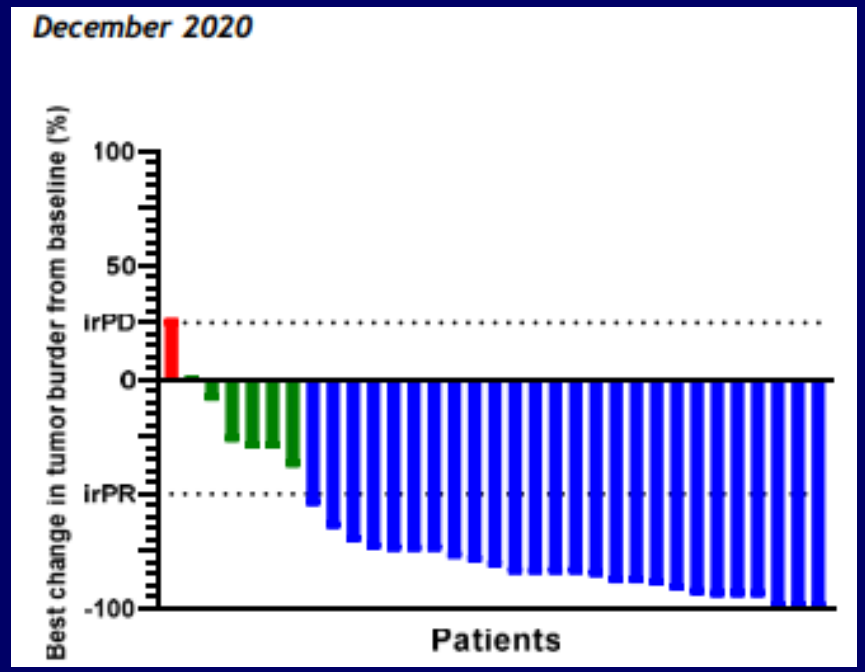
	Tiragolumab + atezolizumab + CE (n=243)	Placebo + atezolizumab + CE (n=247)
Patients with event, (%)	132 (54.3%)	132 (53.4%)
Median (months, 95% CI)	**13.1** (10.9, 14.4)	**12.9** (12.1, 14.5)
Stratified HR* (95% CI)	**1.02** (0.80, 1.30)	

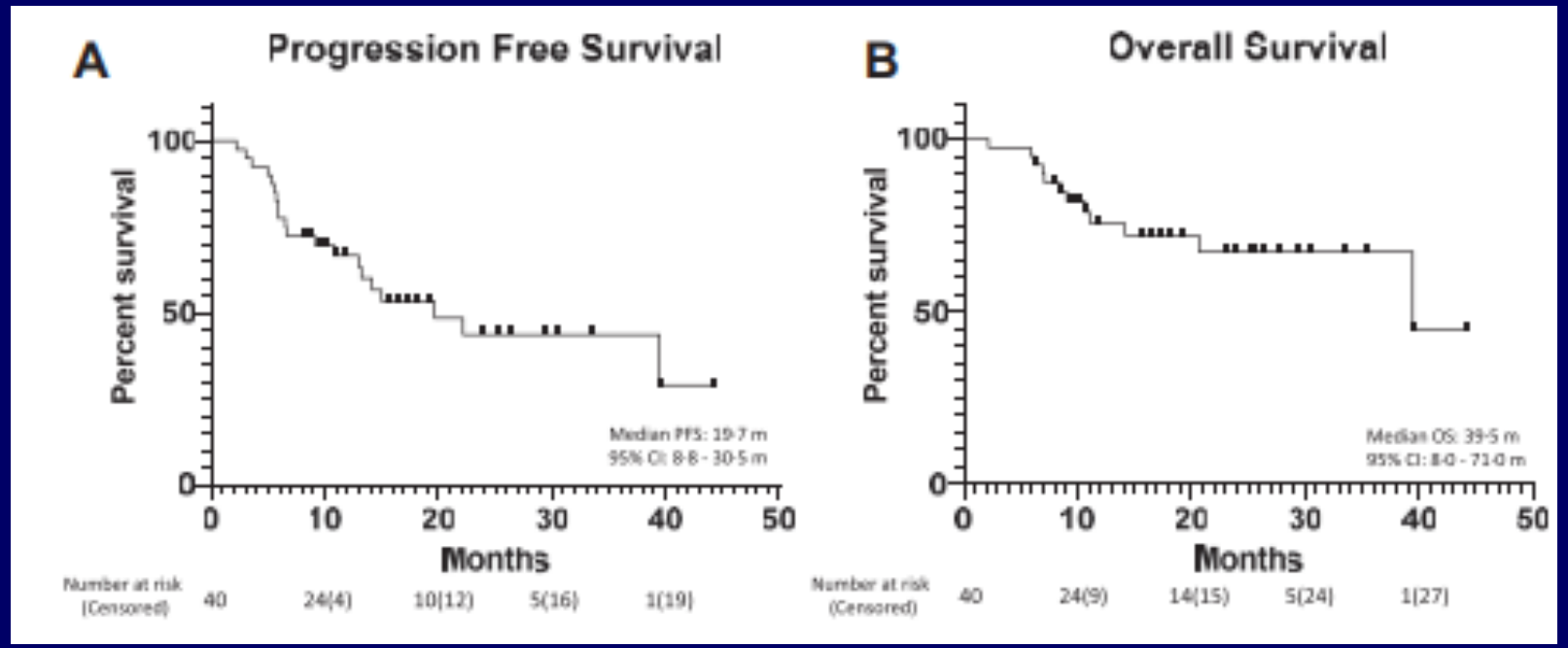


No. at risk																									
Placebo + atezo + CE	247	240	232	226	215	207	202	190	176	165	152	134	109	80	52	40	26	19	12	9	7	5	4	NE	NE
Tiragolumab + atezo + CE	243	235	228	225	216	210	199	190	176	161	141	114	90	70	56	36	24	14	9	7	7	5	2	1	NE

*Stratification factors are: ECOG, LDH
Data cut-off: 6 February 2022 (median follow-up:13.9 months)

Pembro with concurrent CT/RT in Lim SCLC

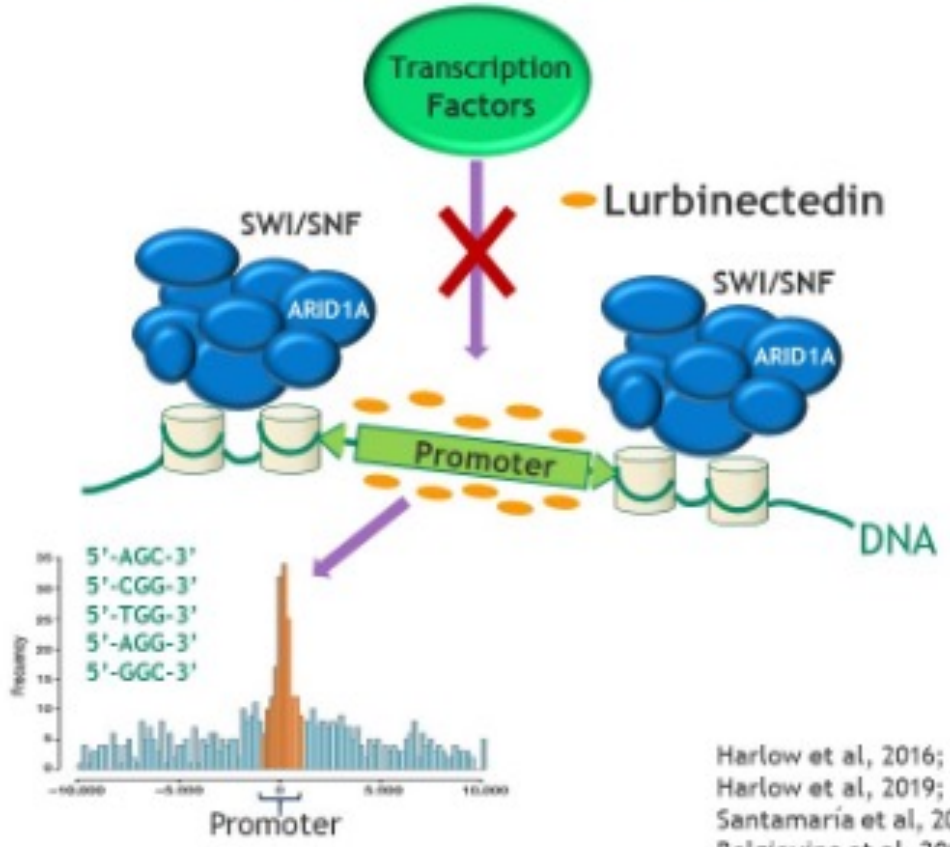




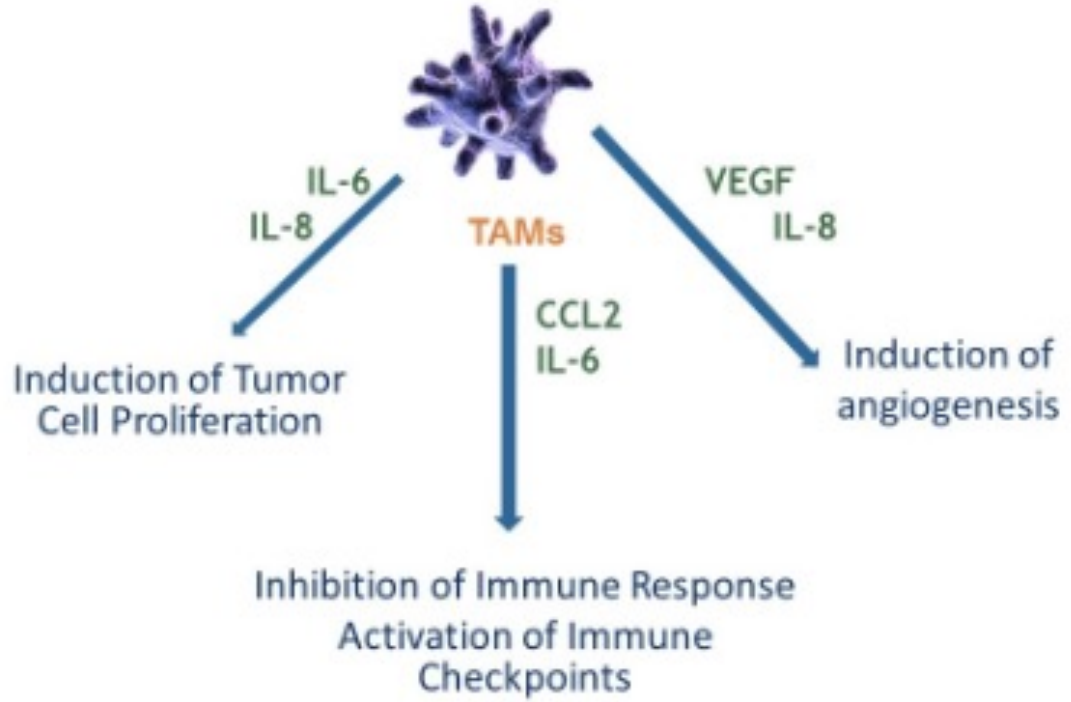
Welsh j etal JTO 15:1919-27, 2020

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
Santamaria 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
($p \leq 0.15$)

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

Statistical power 95%

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

Data cut-off: January 15th 2019

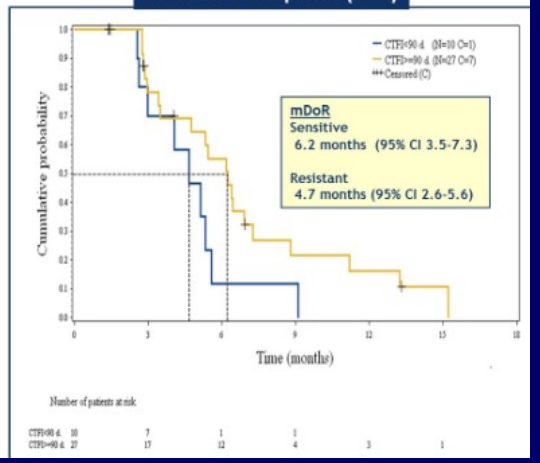
Lurbinectidin Phase II Results

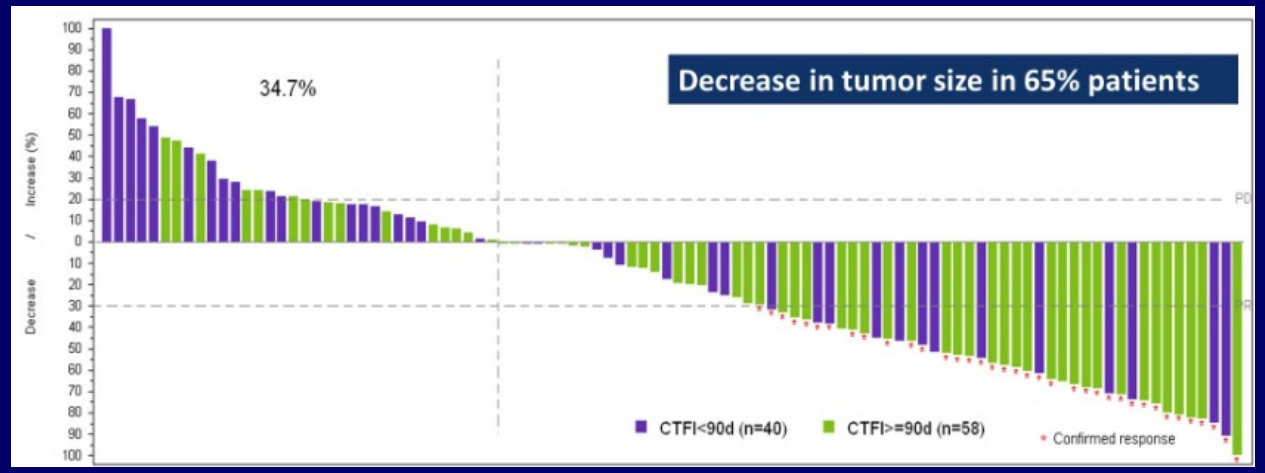
Antitumor Activity According to Sensitive or Resistant Population

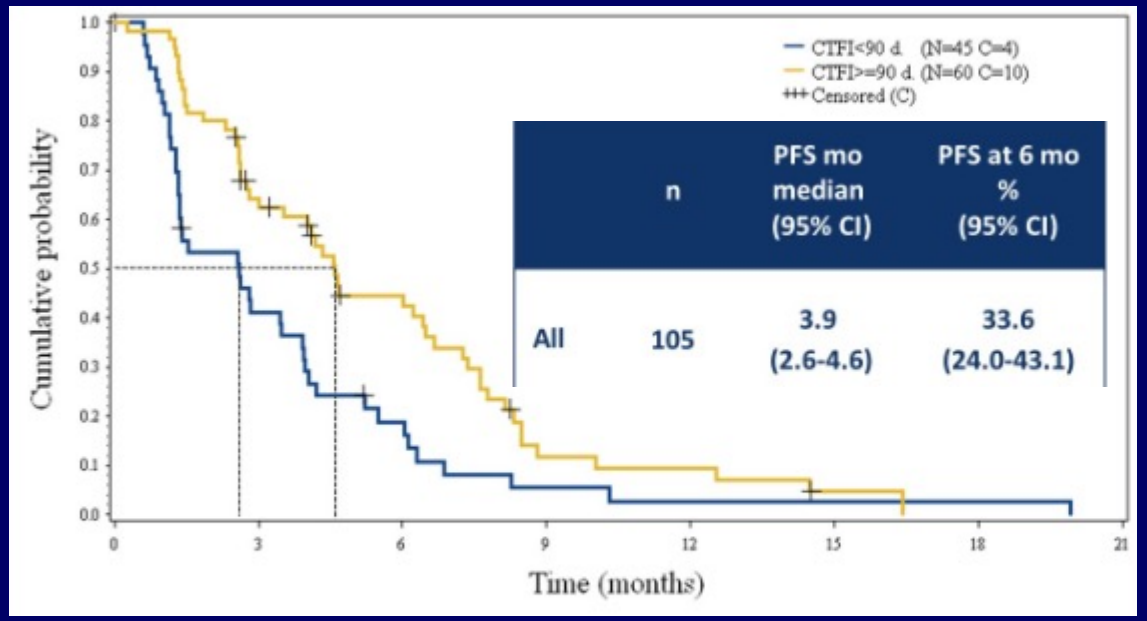
	Resistant CTFI< 90 days (n=45)	Sensitive CTFI ≥ 90 days (n=60)
ORR, % (95% CI)	22.2 (11.2-37.1)	45.0 (32.1-58.4)
Best response (confirmed)	n (%)	n (%)
- PR	10 (22.2) #	27 (45.0) #
- SD	13 (28.9)	22 (36.7)
- PD	18 (40.0)	10 (16.7)
- NE* (non- evaluable)	4 (8.9)	1 (1.7)
Disease Control Rate), % (95% CI)	51.1 (35.8-66.3)	81.7 (69.6-90.5)

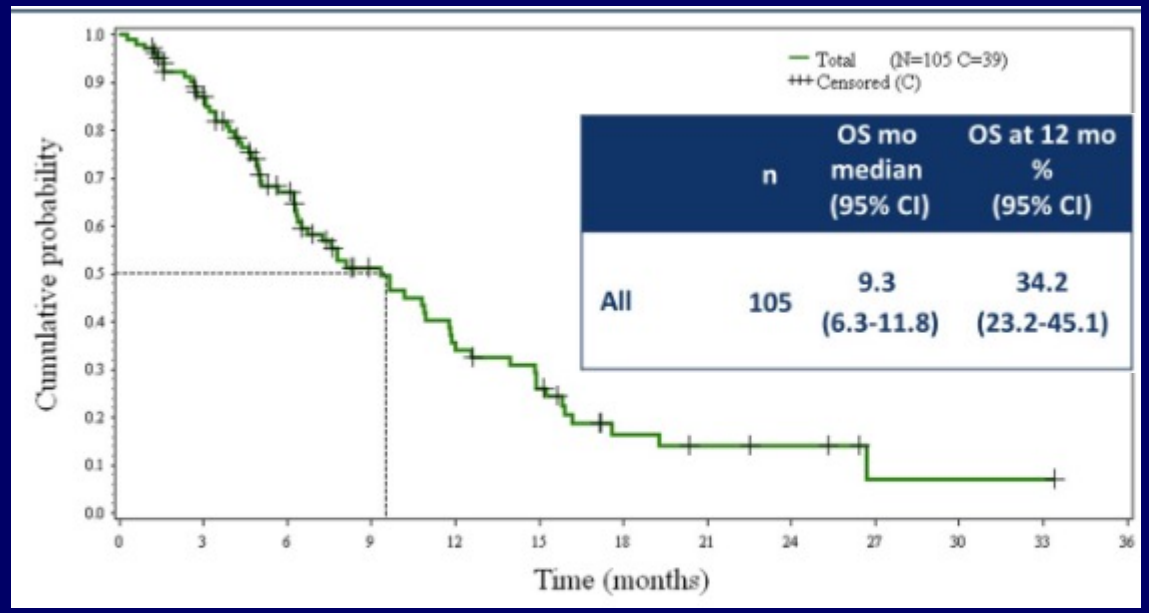
3 of 5 patients with resistant disease and 2 of 3 patients with sensitive disease who failed prior immunotherapy had confirmed response

Duration of Response (DoR)



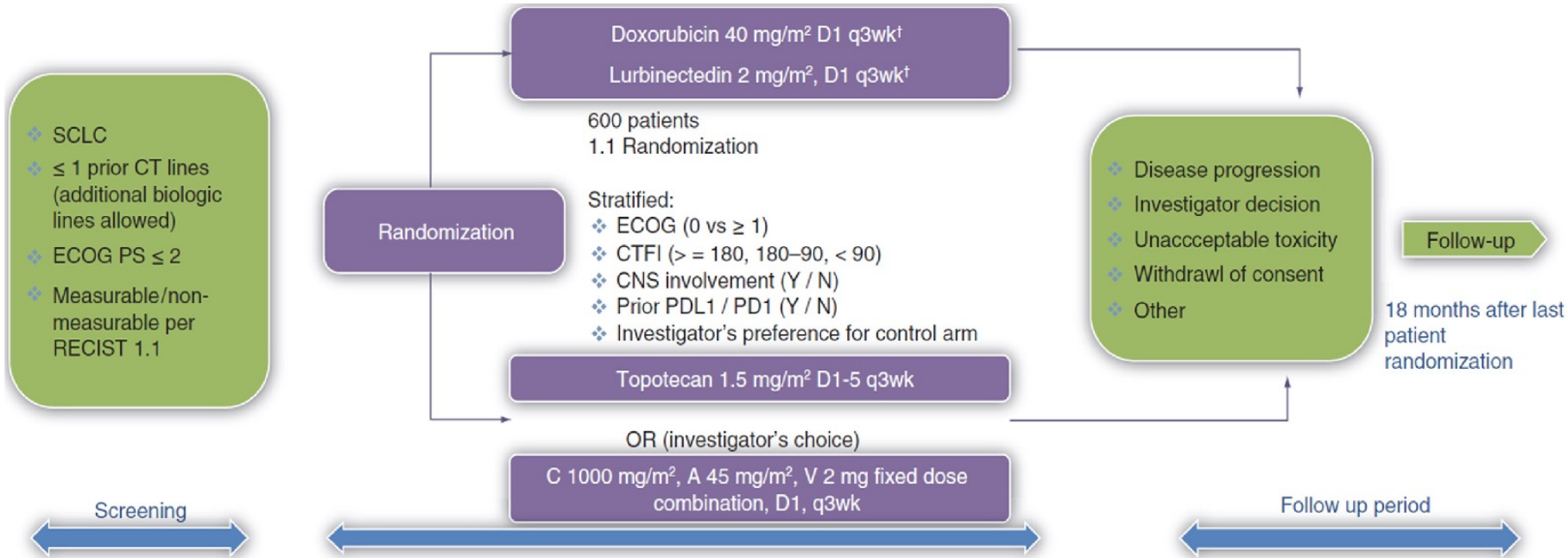






Lurbinectedin plus Doxorubicin: ATLANTIS

- Lurbinectedin is an RNA polymerase II inhibitor that targets active transcription
- Has direct cytotoxic effect inducing apoptosis and may impact TME targeting TAM
- Phase II basket study as single agent (n=105): ORR 35%. mPFS 3.5m, and mOS 9.3m
- Lurbinectedin plus doxorubicin has ORR of 92% with mPFS of 5.8m in platinum sensitive SCLC



Press | Press release: The primary endpoint was not met

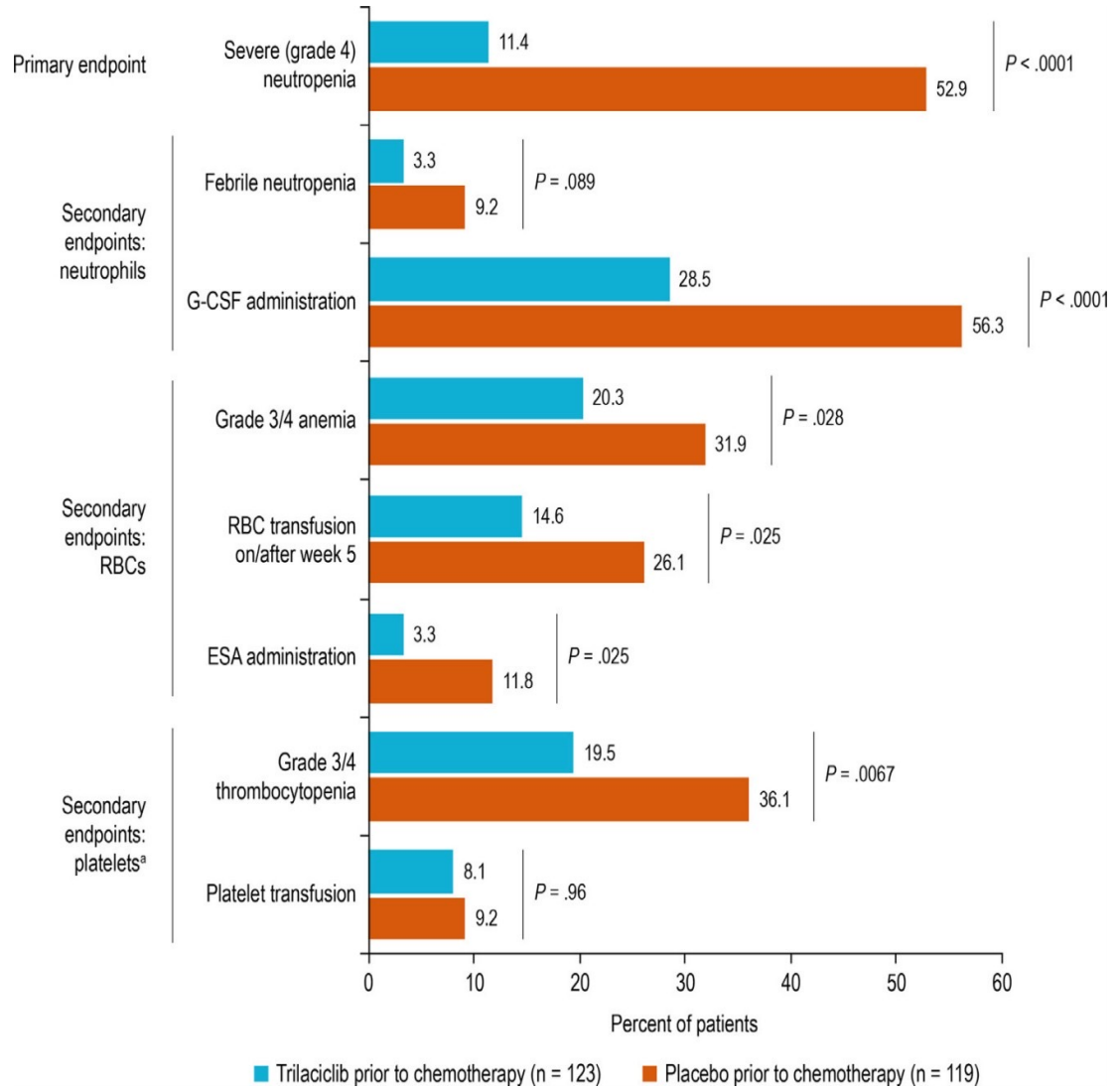
Trigo J et al, Lancet Oncol 2020;21:645-645
Farago AF et al Future Oncol 2019;15:231-9
Clinical Trial.gov.NCT02566993

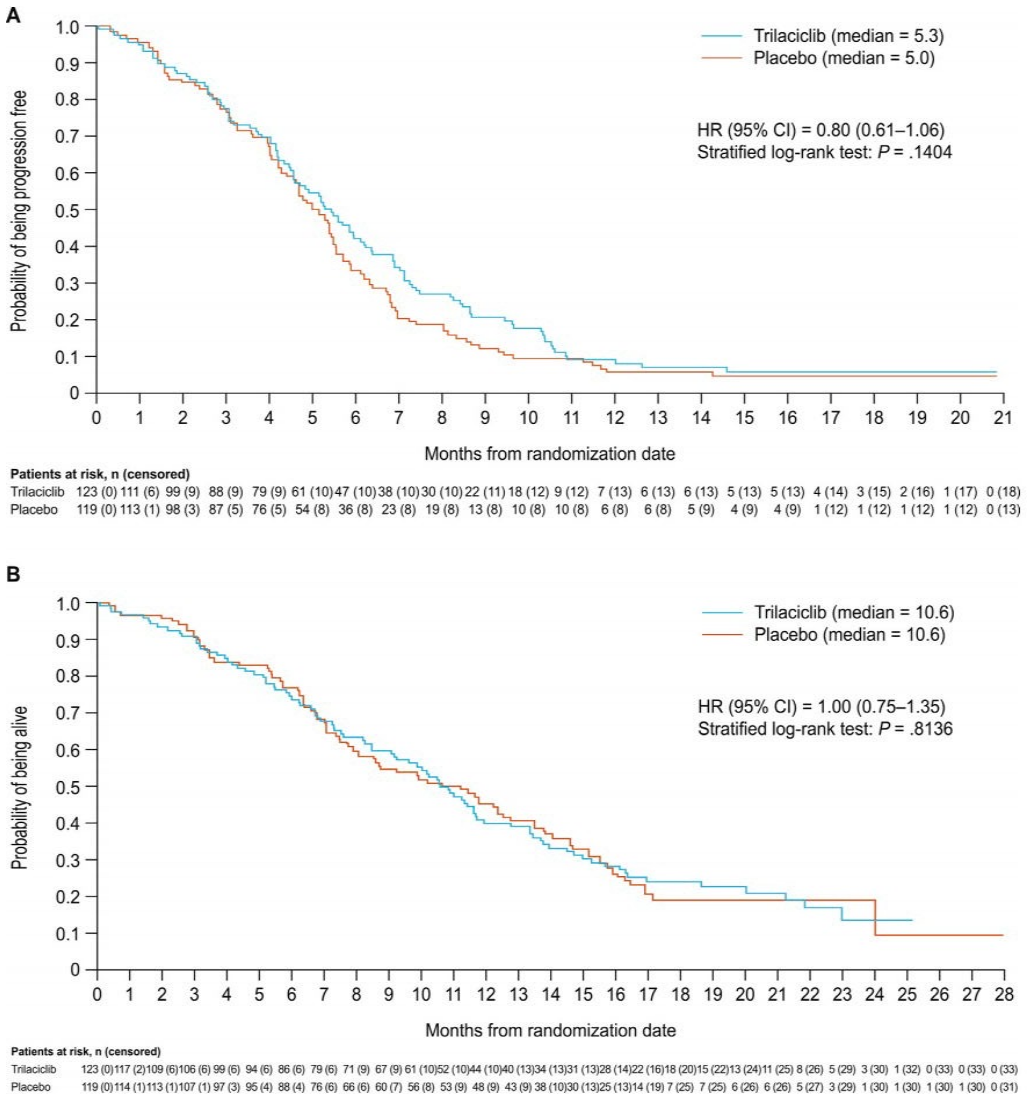
Trilaciclib CDK4/6 inhibitor: Pooled analysis

Study	Patient Population	Treatment Schedule
G1T28-05 (NCT03041311)	Newly diagnosed (first-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD prior to chemotherapy on days 1-3 of each 21-day E/P/A IV cycle[a] for up to four cycles followed by atezolizumab monotherapy (without trilaciclib) Q21D Placebo IV QD prior to chemotherapy on days 1-3 of each 21-day E/P/A IV cycle for up to four cycles followed by atezolizumab monotherapy (without placebo) Q21D
G1T28-02 (NCT02499770)	Newly diagnosed (first-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD prior to chemotherapy on days 1-3 of each 21-day E/P IV cycle[b] Placebo IV QD prior to chemotherapy on days 1-3 of each 21-day E/P IV cycle
G1T28-03 (NCT02514447)	Previously treated (second-/third-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD prior to topotecan 1.5 mg/m^2 IV QD on days 1-5 of each 21-day cycle Placebo IV QD prior to topotecan 1.5 mg/m^2 IV QD on days 1-5 of each 21-day cycle

Weiss et al, Clin Lung Cancer 2021

Trilaciclib: Pooled analysis

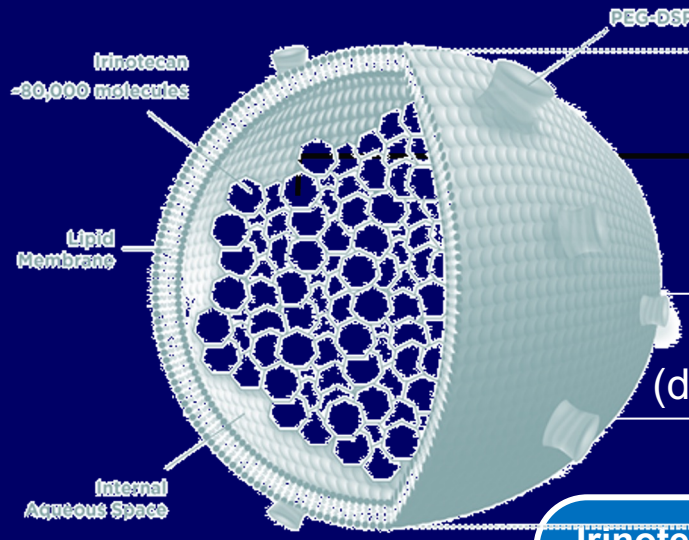




Weiss et al, Clin Lung Cancer 2021

RESILIENT: Study Design Overview

Study population: Patients with SCLC who have progressed on or after prior platinum-based therapy. Both platinum sensitive and platinum resistant/refractory patients are allowed. Prior immunotherapy is allowed.



Part 1a
(dose finding)

Part 1b
(signal seeking, randomized)

Go / No-go Criteria

Part 2
(phase 3, randomized)

Irinotecan liposome inj IV
70 mg/m², q2w (N=6)
If <2/6 DLTs, then
90 mg/m², q2w (N=6)

R 1:1

Irinotecan liposome inj IV (N=25)

Topotecan IV 1.5 mg/m², d1-5 q3w (N=25)

R 1:1

Irinotecan liposome inj IV Dose from Part 1a, q2w

N=420

Topotecan IV 1.5 mg/m², d1-5 q3w

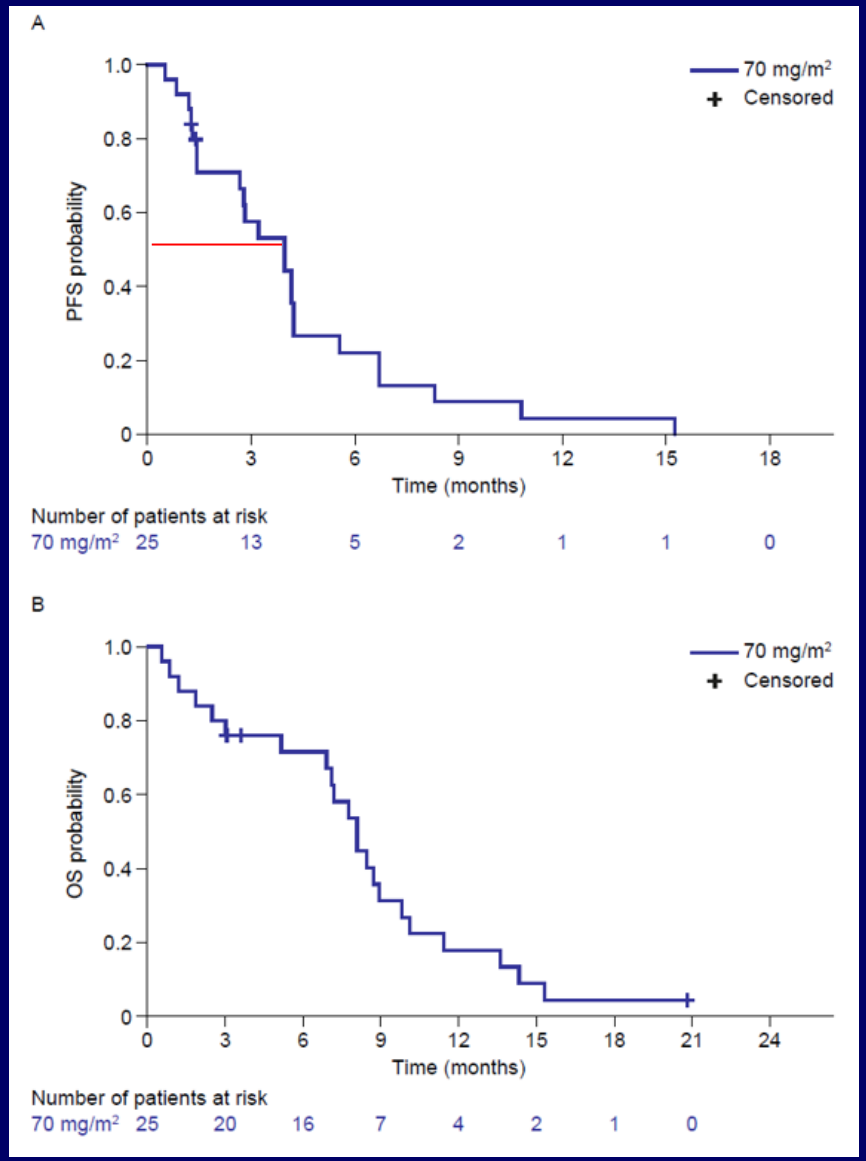
Primary endpoint
PFS rate @ 12 weeks

Primary endpoint
Overall Survival (OS)

Naliri (liposomal irinotecan) In SCLC Part 1

	Liposomal irinotecan		
	85 mg/m² (n = 5)	70 mg/m² (n = 25)	All patients (N = 30)
Best overall response, n (%)			
CR	0	1 (4.0)	1 (3.3)
PR	2 (40.0)	10 (40.0)	12 (40.0)
Stable disease	1 (20.0)	7 (28.0)	8 (26.7)
Progressive disease	1 (20.0)	5 (20.0)	6 (20.0)
Not evaluable	1 (20.0)	2 (8.0)	3 (10.0)
Objective response rate, % (95% CI)			
CR + PR	40.0 (5.27 to 85.34)	44.0 (24.40 to 65.07)	43.3 (25.46 to 62.57)
Duration of response			
Median, months (95% CI)	8.80 (4.11 to NE)	2.99 (2.37 to 7.03)	3.78 (2.43 to 7.03)

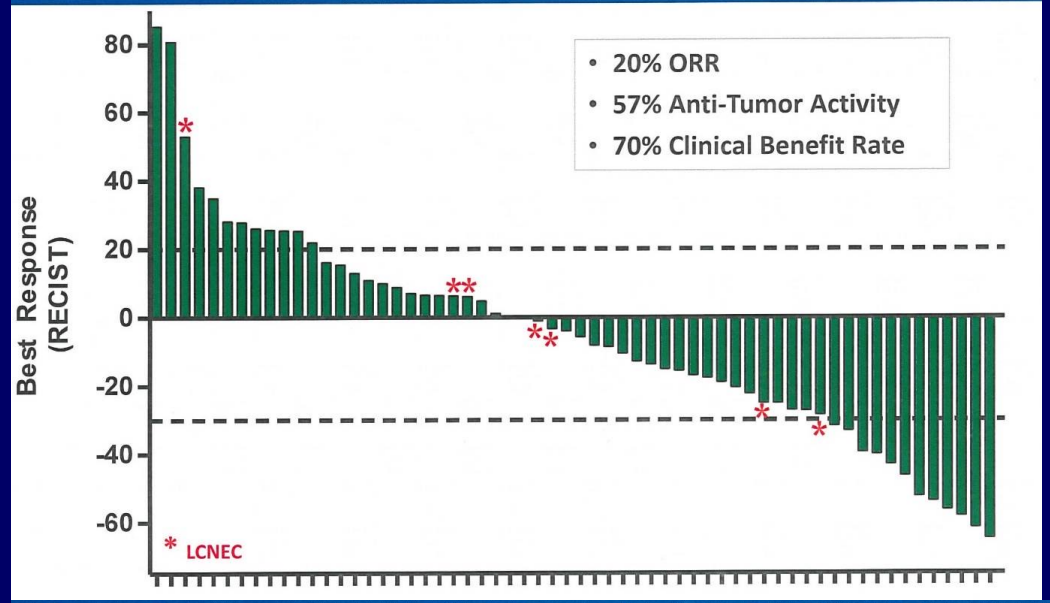
CI, confidence interval; CR, complete response; NE, not evaluable; PR, partial response.



Rova T Results and ongoing trials

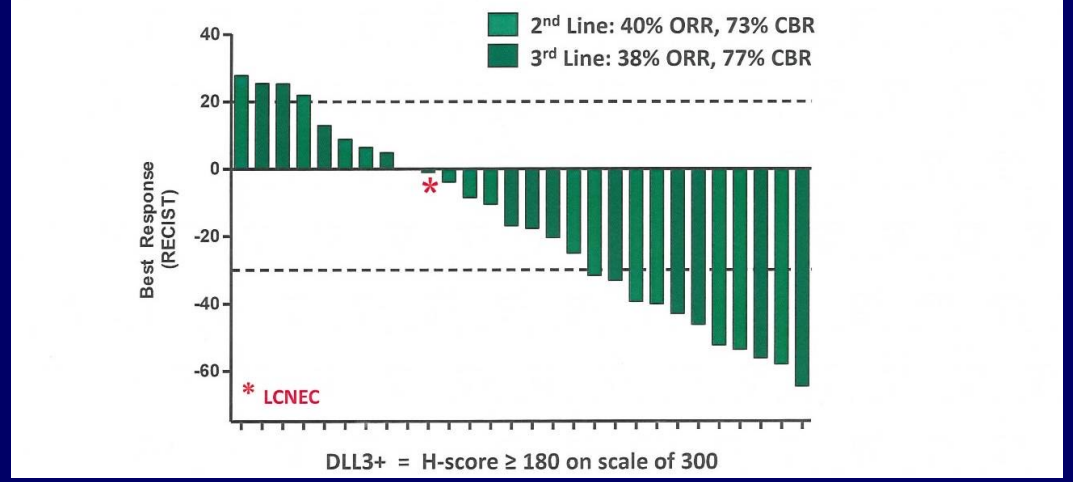
Rova-T: best response data in evaluable patients

0.2 mg/kg q3w and 0.3 mg/kg q6w cohorts (n=60)



Rova-T: best response data in evaluable DLL3+ patients

0.2 mg/kg q3w and 0.3 mg/kg q6w cohorts (n=28)

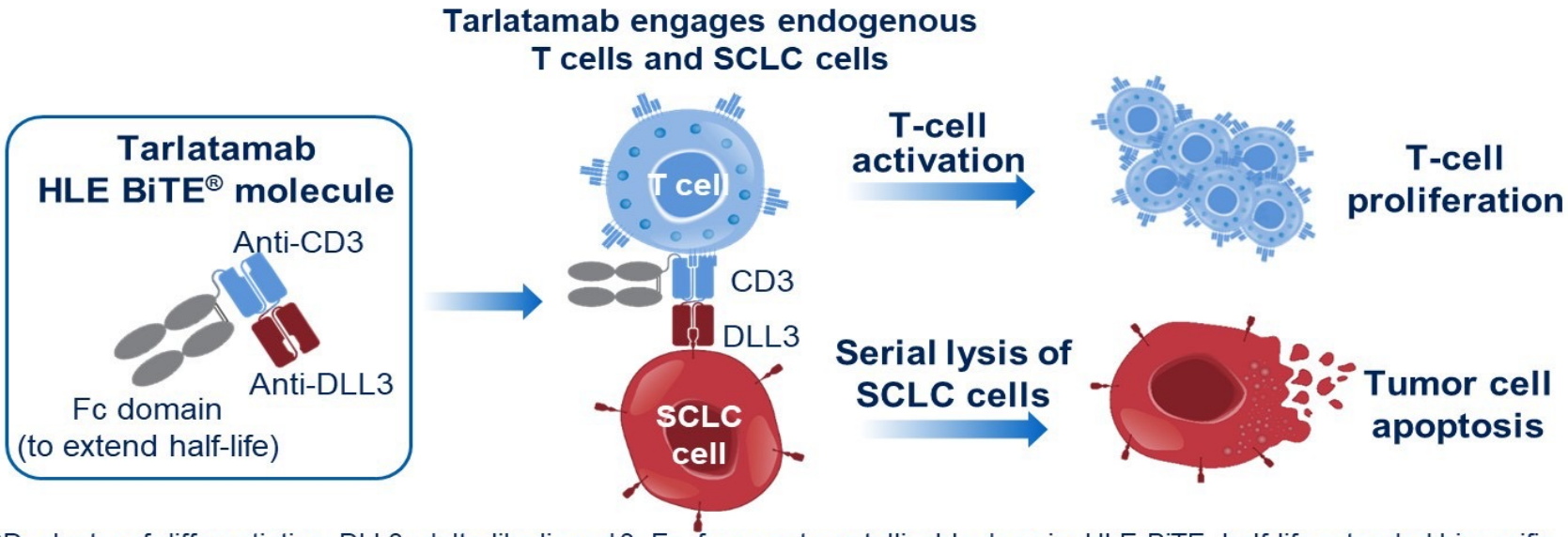


	Investigator-assessed			Central review		
	All patients (n=60)	DLL3 expression 0–49% (n=8)	DLL3 expression ≥50% (n=26)	All patients (n=56)	DLL3 expression 0–49% (n=6)	DLL3 expression ≥50% (n=26)
Confirmed objective response (complete response and partial response)	11 (18%)	0 (0%)	10 (38%)	9 (16%)	0 (0%)	8 (31%)
Confirmed disease control (complete response, partial response, and stable disease)	41 (68%)	4 (50%)	23 (88%)	36 (64%)	2 (33%)	22 (85%)
Duration of response (months)	5·6 (2·5–8·3)	0	4·3 (2·2–15)	4·4 (2·2–6·5)	0	4·6 (2·2–6·9)
Progression-free survival (months)	2·8 (2·5–4·0)	2·2 (1·3–2·5)	4·3 (2·8–5·6)	4·0 (2·6–4·8)	2·2 (1·1–3·7)	4·6 (4·0–5·7)

Ongoing phase III trials with 2 doses in 3rd line, in 1st line plus chemo and 1st line maintenance

Tarlatamab (AMG 757)

Tarlatamab: A Half-life Extended Bispecific T-cell Engager Targeting DLL3 for SCLC



CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable domain; HLE BiTE, half-life extended bispecific T-cell engager; SCLC, small cell lung cancer.

We report updated safety, efficacy, and pharmacokinetic data from 10 cohorts from the open-label, multi-center phase 1 study of tarlatamab (0.003 mg to 100 mg IV every 2 weeks, with or without step dose: data cutoff, 22 March 2021) in relapsed/refractory SCLC (NCT03319940)

1. Stieglmaier J, et al. *Expert Opin Biol Ther.* 2015;15:1093-1099.
2. Einsele H, et al. *Cancer.* 2020;126:3192-3201.

Presented By: **Taofeek K. Owonikoko**
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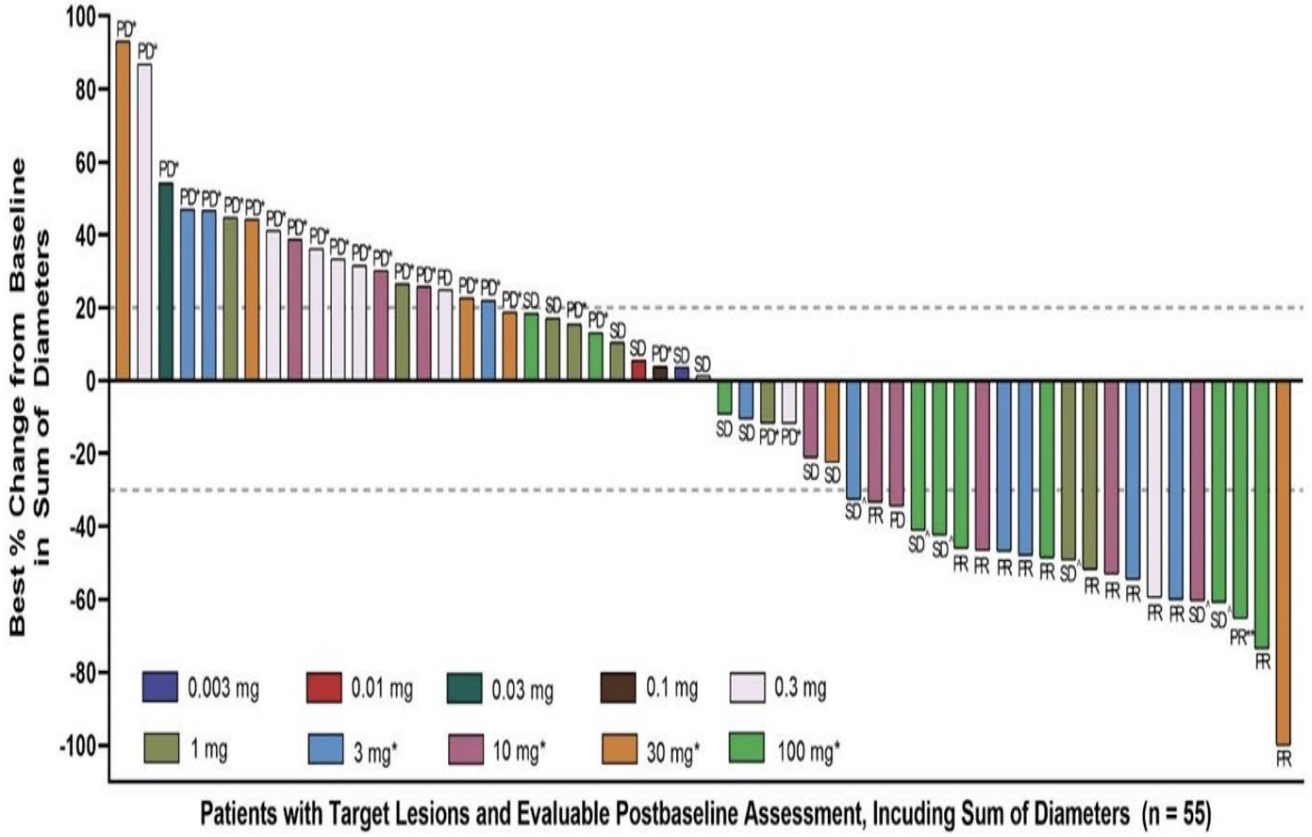
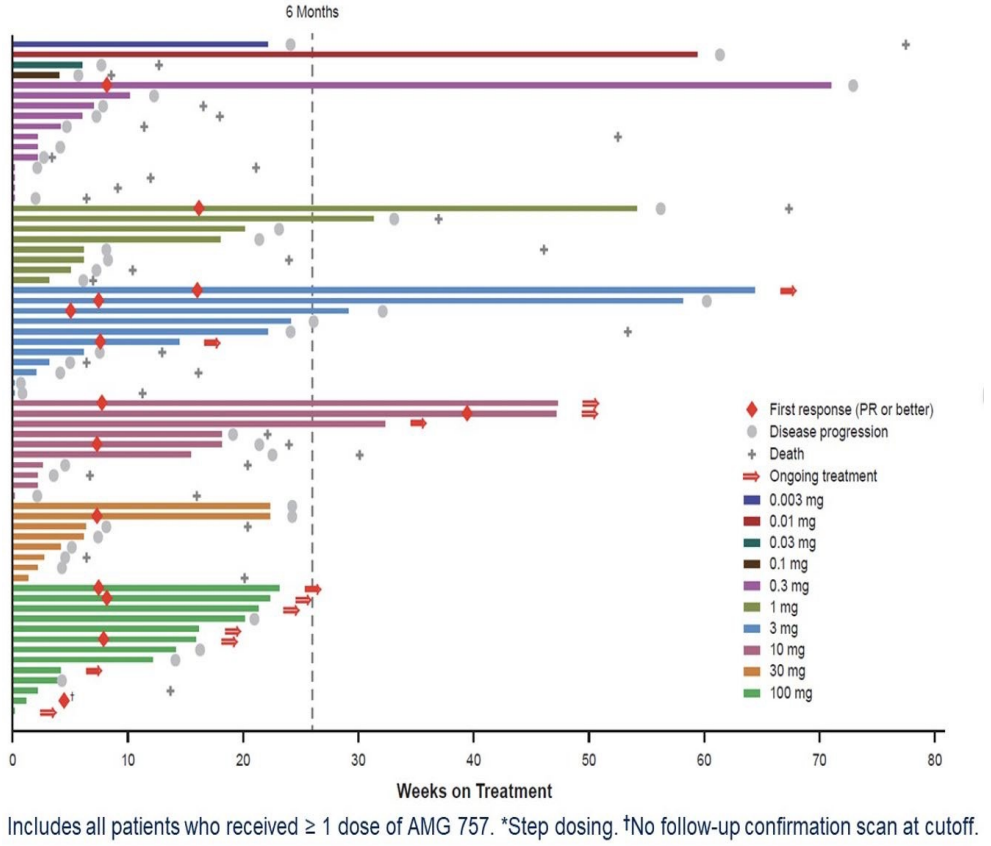
Tarlatamab (AMG 757) Efficacy





Includes all patients who received ≥ 1 dose of AMG 757. *Step dosing. †No follow-up confirmation scan at cutoff.

- Tox: Mostly CRS (44% all grade, 2% G3+)
- DLTs: G5 pneumonitis (1), G3 encephalopathy (1)
- ORR: 20%, but 30+% @ higher doses
- mDoR: 8.7m

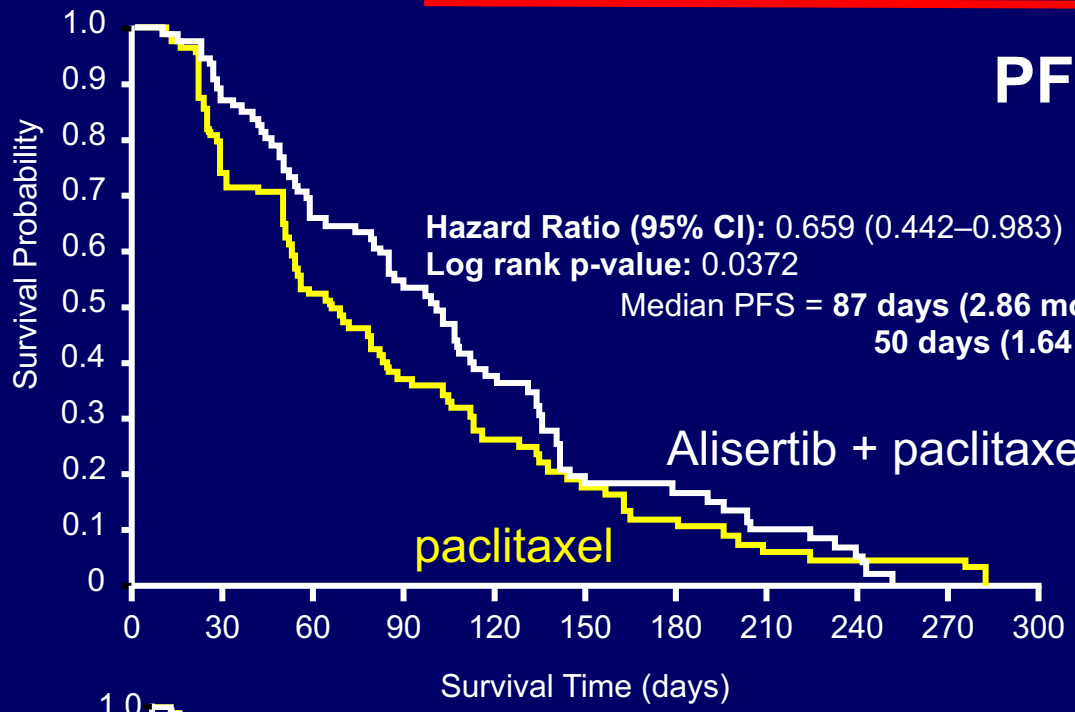
Owonikoko et al. ASCO 2021

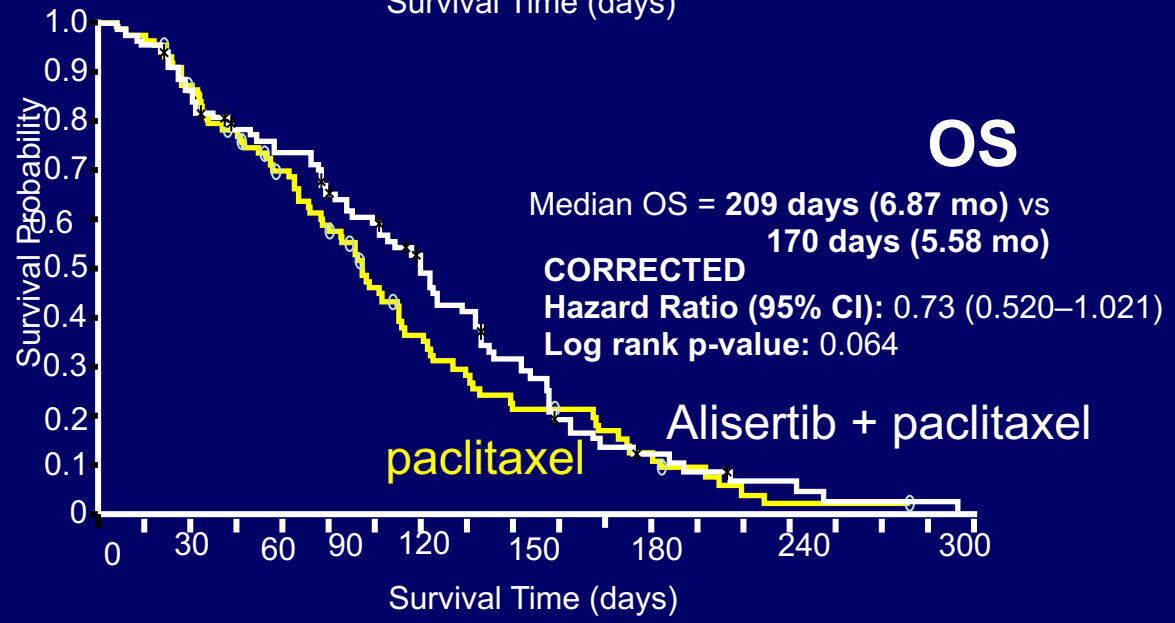
Tarlatamab Toxicity

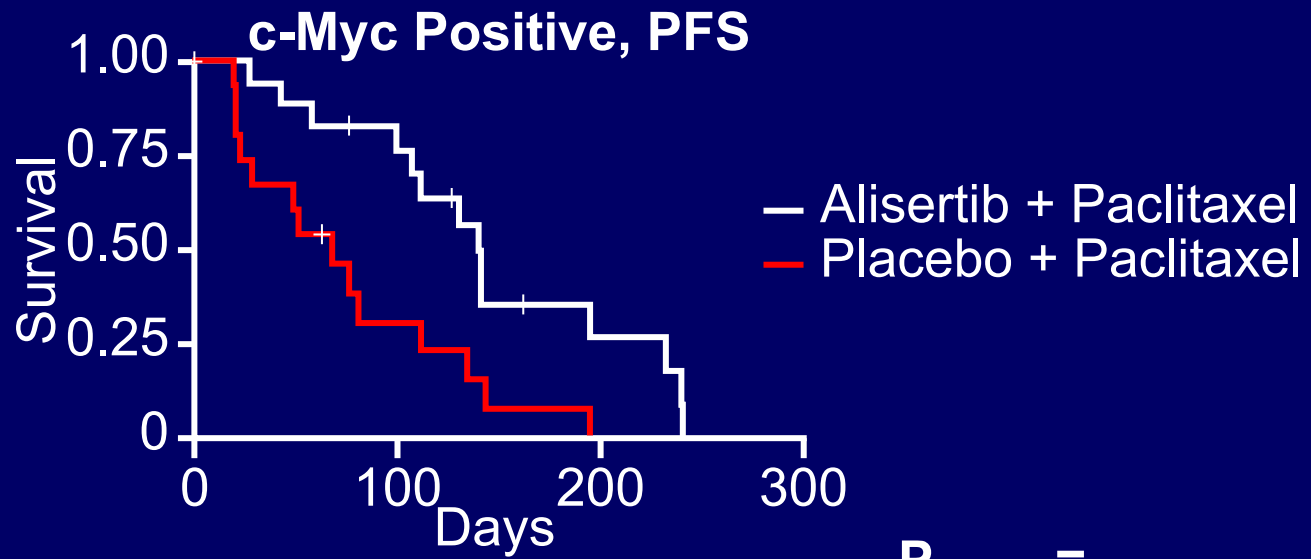
Treatment-related AEs	Patients (N = 66)	
	All Grades, n (%)	Grade ≥ 3, n (%)*
Any treatment-related AE	56 (85)	18 (27)
Treatment-related AEs in ≥ 10% of patients		
CRS	29† (44)	1 (2)
Pyrexia	17 (26)	2 (3)
Fatigue	11 (17)	0 (0)
Asthenia	7 (11)	1 (2)
Dysgeusia	7 (11)	0 (0)
Nausea	7 (11)	0 (0)

*Includes one patient with grade 5 pneumonitis. †Of the 29 patients, 21 had grade 1, 7 had grade 2, and 1 had grade 3 CRS. ‡Lee 2014 grading.
AE, adverse event; CRS, cytokine release syndrome; DLT, dose limiting toxicity.

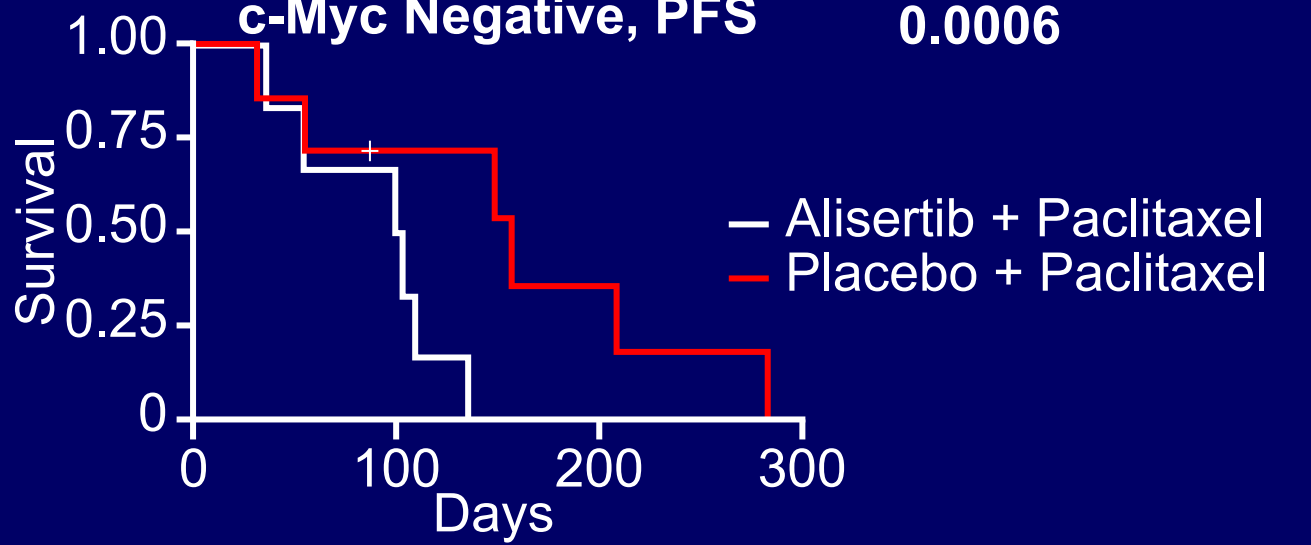
Alisertib vs paclitaxel+Alisertib 2nd Line SCLC





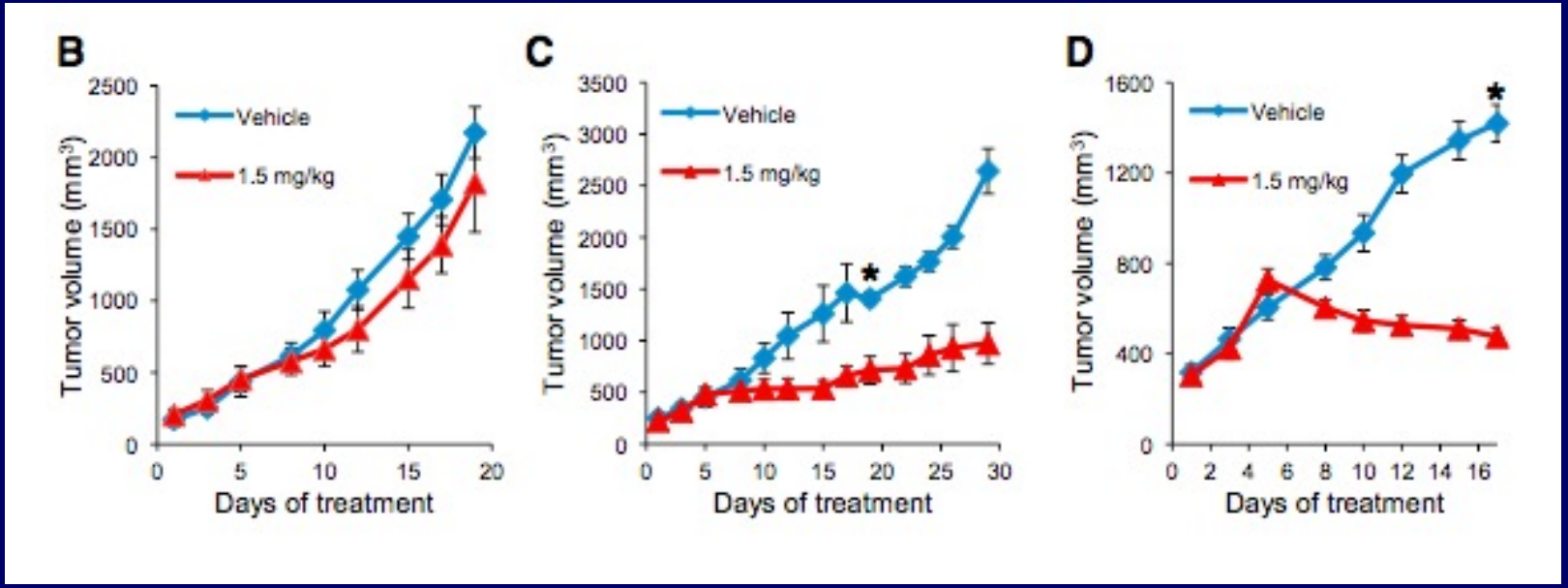


P_{binary} = 0.0006



LSD1 Inhibition

- LSD1 inhibitors are generally derivatives of tranylcypromine, an irreversible MAO inhibitor
- Animal studies predict that myelosuppression is an expected on target effect
- LSD1 inhibition is associated with therapeutic efficacy in animal models and PDX of AML and SCLC
  - In AML, leads to differentiation and potentiates impact of ATRA



Mohammad et al Cancer Cell 2015

PARP inhibitor Clinical Trials for SCLC

Phase 1/2 Cisplatin-Etoposide +/- Veliparib
(PI: T. Owonikoko)

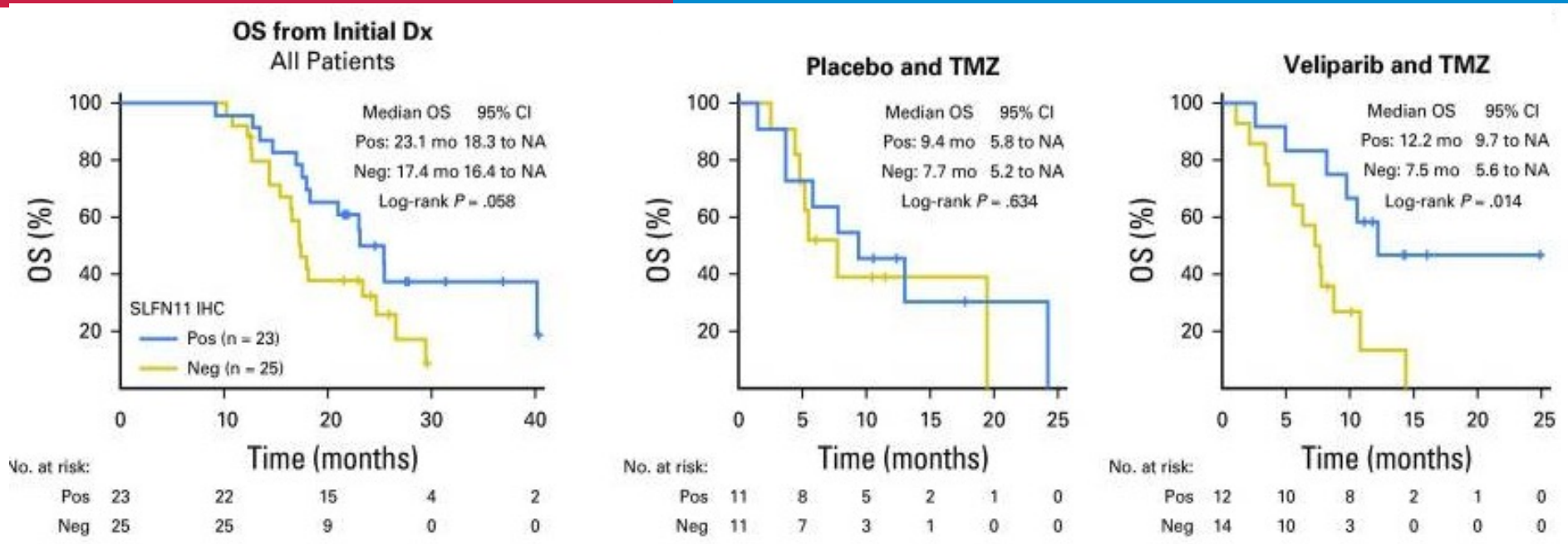
Phase 1/2 Carboplatin-Etoposide +/- Veliparib → Veliparib maintenance (ongoing)

Phase I BMN 673 (talazoparib) -
SCLC expansion cohort

CTEP Phase 2 Veliparib vs placebo with Temozolomide
(PI: C. Pietanza)

Phase 1/2 Olaparib + temozolomide (ongoing)
(PI: A. Farago)

SNFL 11 may be a predictive biomarker for PARP Inhibitors

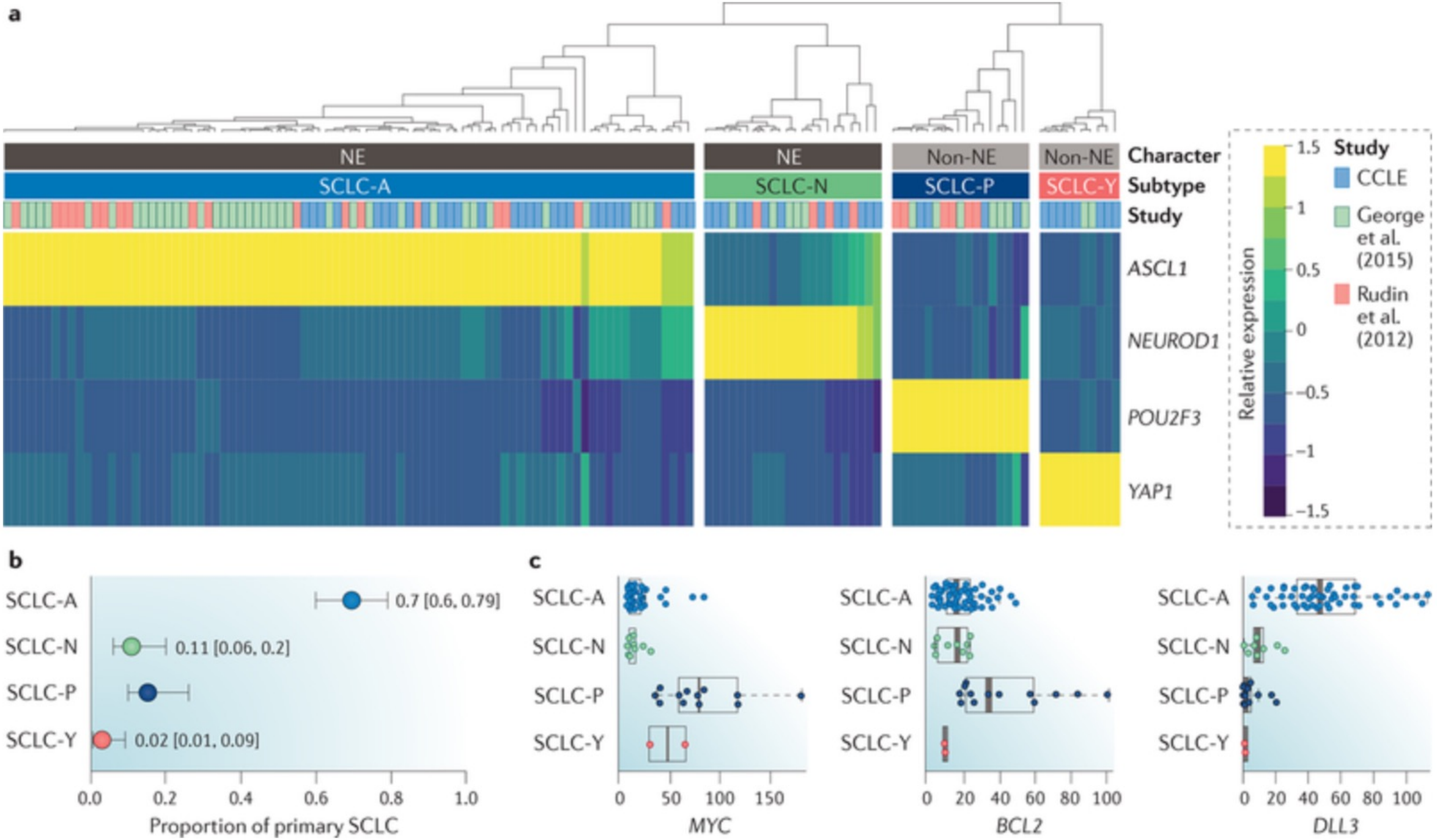


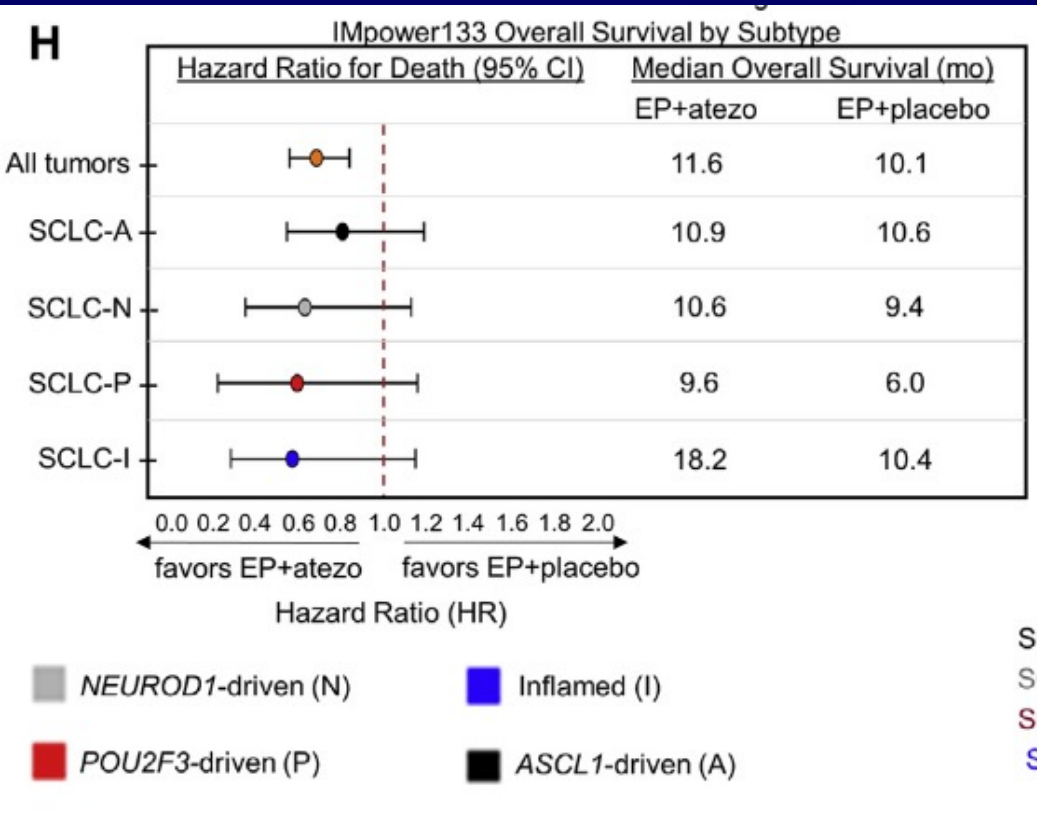
Pietanza et al, J Clin Oncol. 2018 Aug 10; 36(23): 2386–2394

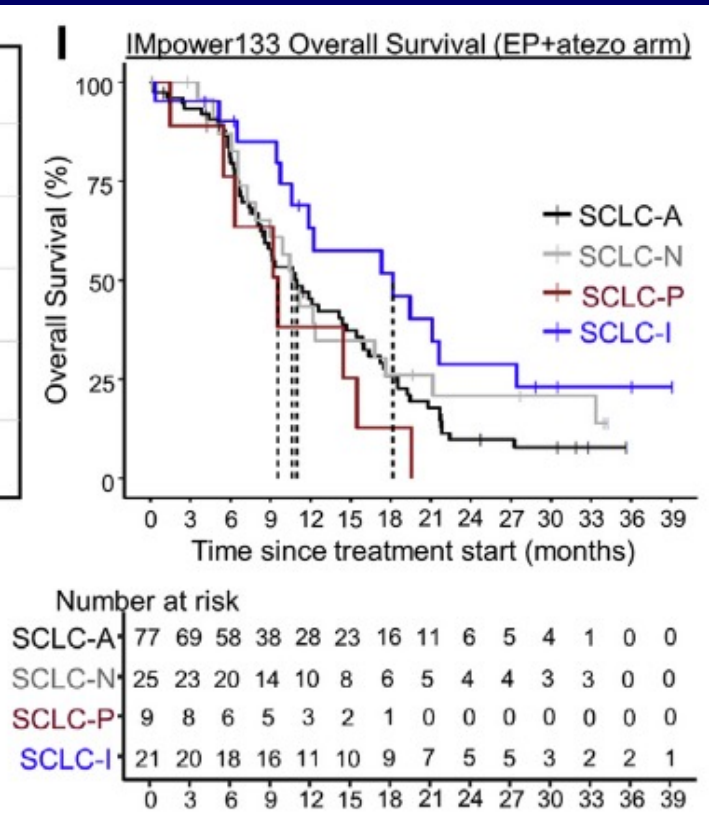
Many trials combining PARP inhibitors with checkpoint inhibitors are in progress

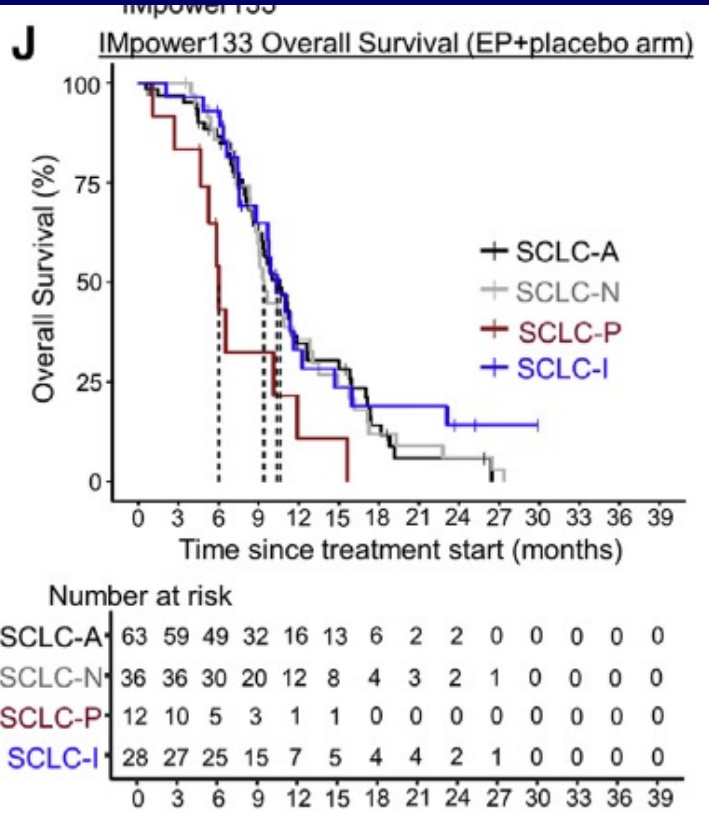
Schlafen 11 (SLFN11) as Potential Biomarker

- SLFN11
  - Putative DNA/RNA helicase
  - Recruited to stressed replication fork
  - Potantial biomarker for sensitivity to DNA damaging agents (including cytotoxic agents as well as potentially novel agents such as PARPi and others)
- SWOG 1929: Phase II Study of Maintenance Atezolizumab Versus Atezolizumab in Combination with Talazoparib in Patients with SLFN11 Positive Extensive Stage Small Cell Lung Cancer (SCLC)
  - Primary Objective: testing PFS in patients with SLFN11 positive SCLC randomized to Atezolizumab alone or Atezolizumab plus Talazoparib maintenance (after achieving a response to standard chemo-immunotherapy)
  - Secondary Objectives: OS, ORR, and Translational Correlatives (banked specimens)


a
NE
NE
Non-NE
Non-NE
SCLC-A
SCLC-N
SCLC-P
SCLC-Y
Character
Subtype
Study
ASCL1
NEUROD1
POU2F3
YAP1
Relative expression
1.5
1
0.5
0
−0.5
−1
−1.5
Study
CCLE
George et al. (2015)
Rudin et al. (2012)
b
SCLC-A
SCLC-N
SCLC-P
SCLC-Y
0.7 [0.6, 0.79]
0.11 [0.06, 0.2]
0.02 [0.01, 0.09]
0.0
0.2
0.4
0.6
0.8
1.0
Proportion of primary SCLC
c
SCLC-A
SCLC-N
SCLC-P
SCLC-Y
0
50
100
150
MYC
0
20
40
60
80
100
BCL2
0
20
40
60
80
100
DLL3







Gay et al., 2021, Cancer Cell39, 346–360.