GECP lung cancer research

New hope in SCLC?

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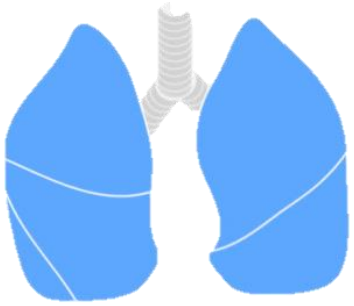
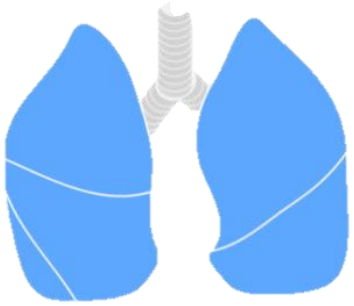


Small Cell Lung Cancer, new hope ?

- Epidemiology
- New drugs, relevant new data?
- Future

SMALL CELL LUNG CANCER

Background & Current Situation



Small Cell Lung Cancer, new hope ?

- 15% of all lung cancer subtypes
- Most related to tobacco
- Radon

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Original

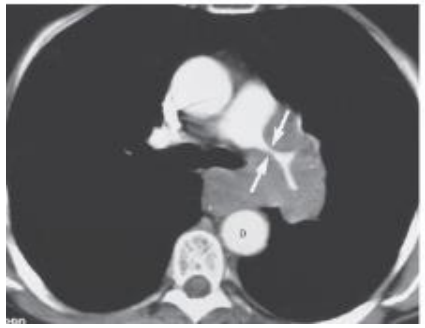
Cáncer de pulmón microcítico. Metodología y resultados preliminares del estudio SMALL CELL☆

Ángeles Rodríguez-Martínez[a,b], Alberto Ruano-Ravina[b,c,*], María Torres-Durán[d], Iria Vidal-García[e], Virginia Leiro-Fernández[d], Jesús Hernández-Hernández[f], Silvia García-García[g], Mariano Provencio[h], Olalla Castro-Añón[i], Isaura Parente-Lamelas[j], Ihab Abdulkader[k], José Abal-Arca[j], Carmen Montero-Martínez[e], Margarita Amenedo[l], Rosirys Guzmán-Taveras[m], Alberto Fernández-Villar[d] y Juan Miguel Barros-Dios[b,c]

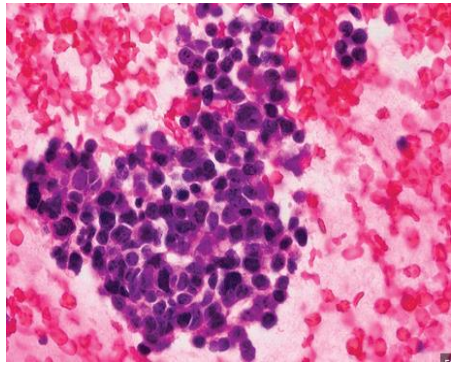
- More than two-thirds are diagnosed with extensive stage
- Historic treatments still present
- Poor prognosis *(“historic”)*

SMALL CELL LUNG CANCER

Background & Diagnosis

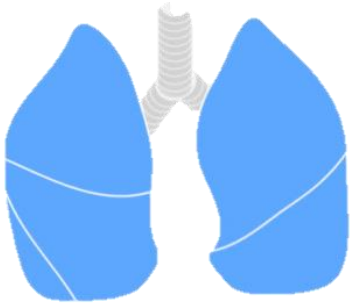


- A defined precursor lesion for SCLC has not been identified in humans
- SCLC: typically occurs as a large perihiliar mass, necrotic cut surface.
- **Diagnosis criteria**:
  - Essential:
    - Tumor composed of small cells(less than the size of lymphocytes), with scant cytoplasm, oval to spindle shape and high mitotic count (>10 mitoses/2 mm2)
    - Tumor cells have finely granular nuclear chromatin
    - Nucleoli are absent or inconspicuous
  - Desirable
    - Positive immunohistochemistry for low-molecular-weight cytokeratin
    - Frequent expression of neuroendocrine markers (90%)
    - Lack of diffuse p40 expression, unless in areas of SCC in a combined SCLC



	Nodule	Peripheral mass	Cavity	Infiltrate	Pleural thickening	Central mass	Atelectasis	Pleural effusion
Localization	Peripheral					Central		Central or peripheral
Schematic diagram								
Adenocarcinoma	++	++	(+)	+	(+)	(+)	(+)	++
Squamous cell carcinoma	+	+	+	–	–	++	++	+
Large-cell carcinoma	+	++	–	–	–	+	(+)	+
Small-cell carcinoma	(+)	(+)	–	–	–	+++	+	+

Fig. 9.11 Radiologic appearance of peripheral and central lung cancers. Incidence of occurrence in different histologic types.



Small Cell Lung Cancer, new hope ?
Pathologic and Genomic Profiles

HE: characteristic appearance of small round uniform cells, distinctive nuclear features *(fine granular chromatin lacking prominent nucleoli)*

Ki 67: proliferation index is consistently high (50-100%)

Immunohistochemistry results show expression of epitelial markers such as keratin and neuroendocrine markers including synaptophysn, chromogranin A and insulinoma-associated protein 1 (INSM1)

Key genomic profiling studies of SCLC including whole exome and whole genomic genome analyses published

Rudin C.M. et al. *Nat. Genet.* 2012;44:1111–1116; George J, el at. *Nature.* 2015;524:47–53

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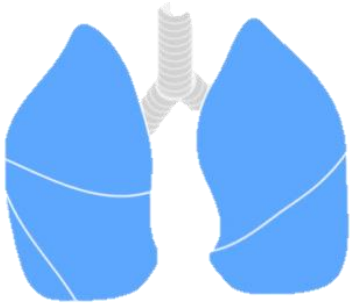
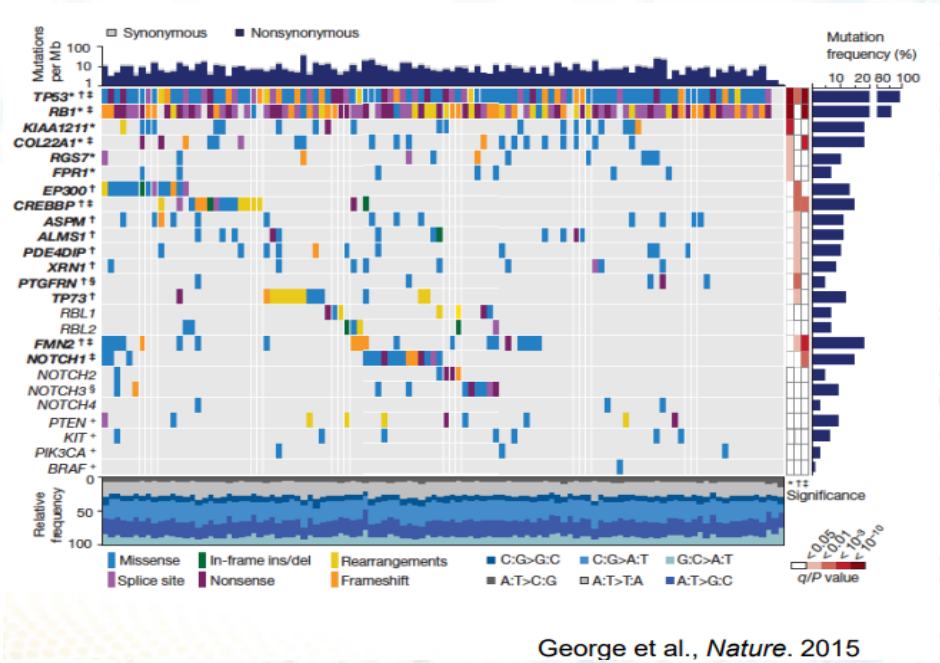
Genomic Profiles





George et al., *Nature*. 2015

SCLC exhibited an extremely **high mutation rate of 8.62** nonsynonymous mutations per million base pairs

There was nearly universal functional **loss of two key tumor** suppressor genes: **TP53** and **RB1**

Targetable mutations in known oncogenes, including BRAF, PTEN, PIK3CA only found in **rare cases**

High frequency of mutations affecting known **epigenetic regulators** including histone-modifying genes and inactivating mutations in **NOCTH family members**

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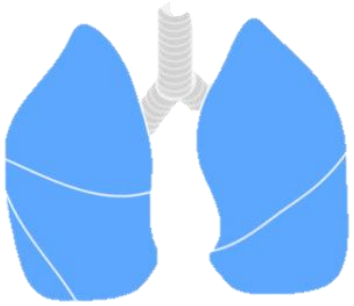
Genomic Profiles



Using gene expression data, four subtypes with distinct transcriptional characteristics were defined

Further study is needed to elucidate how this might translate to disease management.

SCLC Subtype Classification as described by Gay et al. 2021 [9].

Subtype (Key Gene; % of Sample [1])	Key Characteristics	Potential Therapeutic Vulnerabilities
SCLC-A (ASCL1; 51%)	Neuroendocrine, epithelial subtype; TTF1 expression	BCL2 inhibitors
SCLC-N (NEUROD1; 23%)	Neuroendocrine, lacks TTF1 expression, cMYC expression	Aurora kinase inhibitors (AURKi)
SCLC-P (POU2F3; 7%)	Less neuroendocrine (NE) expression	PARP inhibitors, antimetabolites, AURKi
SCLC-I (inflamed; 17%) [2]	Less NE expression, mesenchymal type	Immune checkpoint inhibitors

[1] Based on the Impower133 dataset; [2] SCLC-I expressed no clear transcriptional signature, but numerous immune checkpoints.

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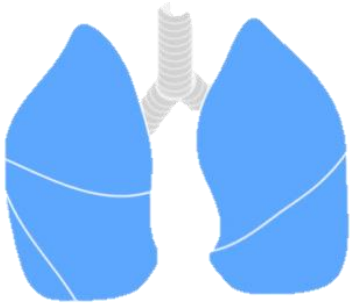
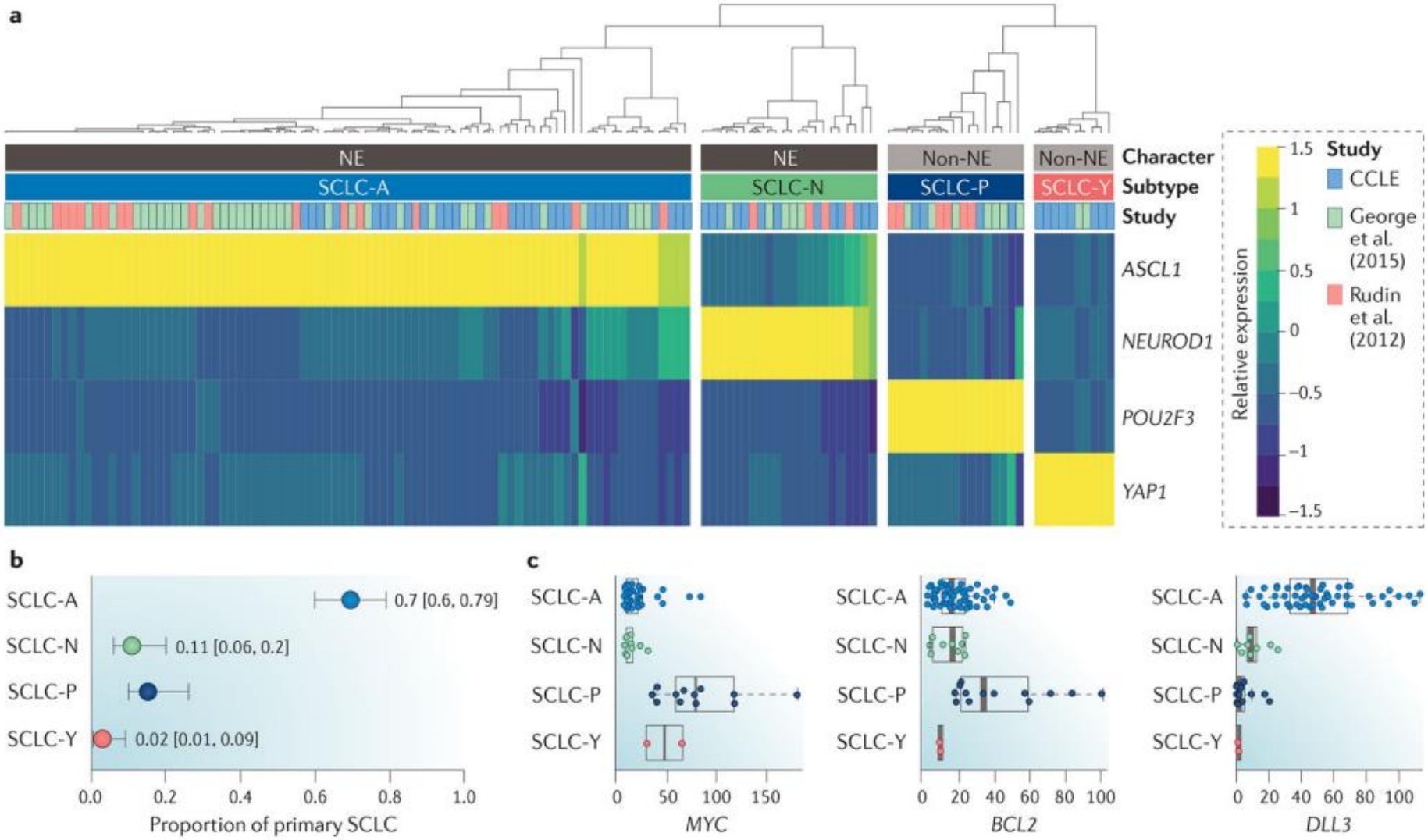
Genomic Profiles

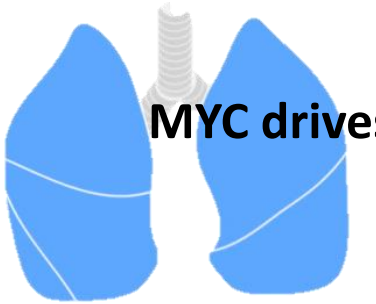
Rudin C et al. Nat Rev Cancer 2019, 289–297



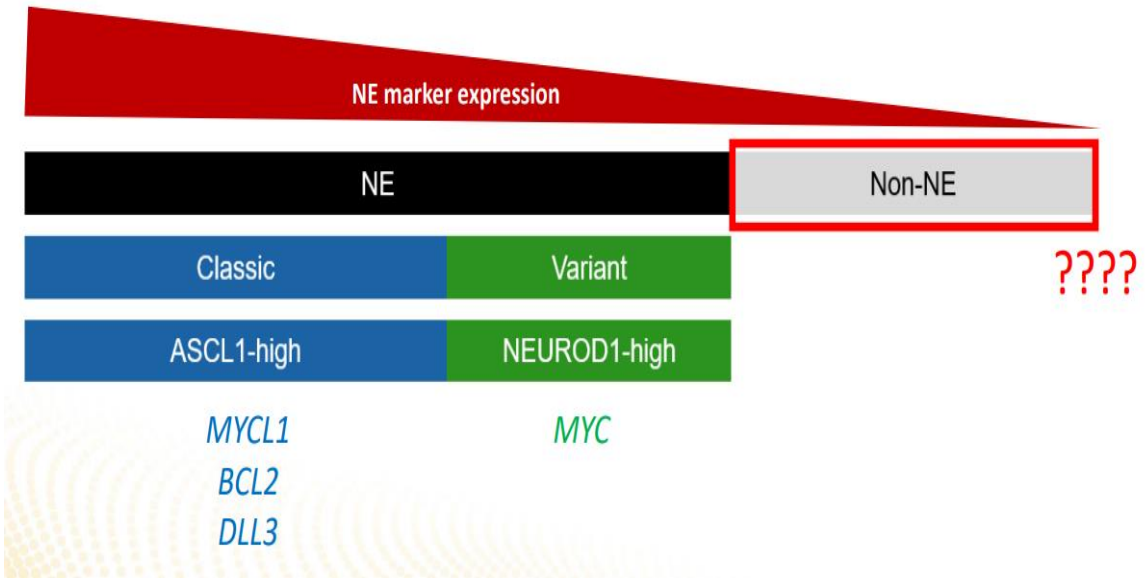


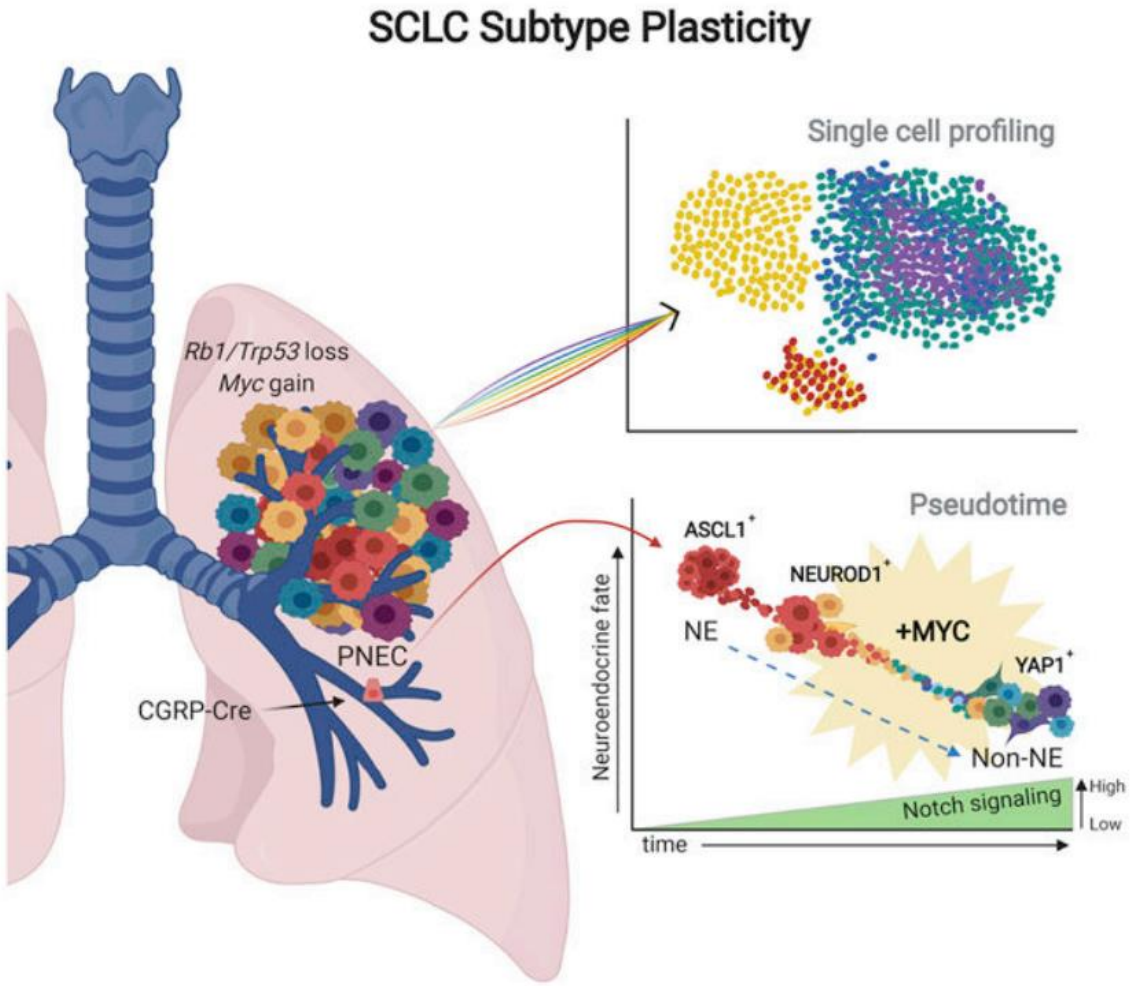
SMALL CELL LUNG CANCER

Background & Current Situation



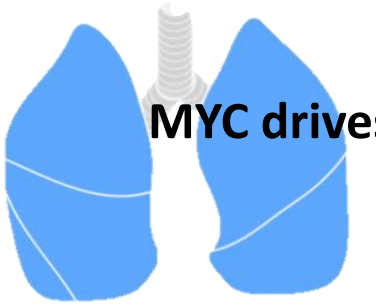
MYC drives dynamic evolution of SCLC subtypes



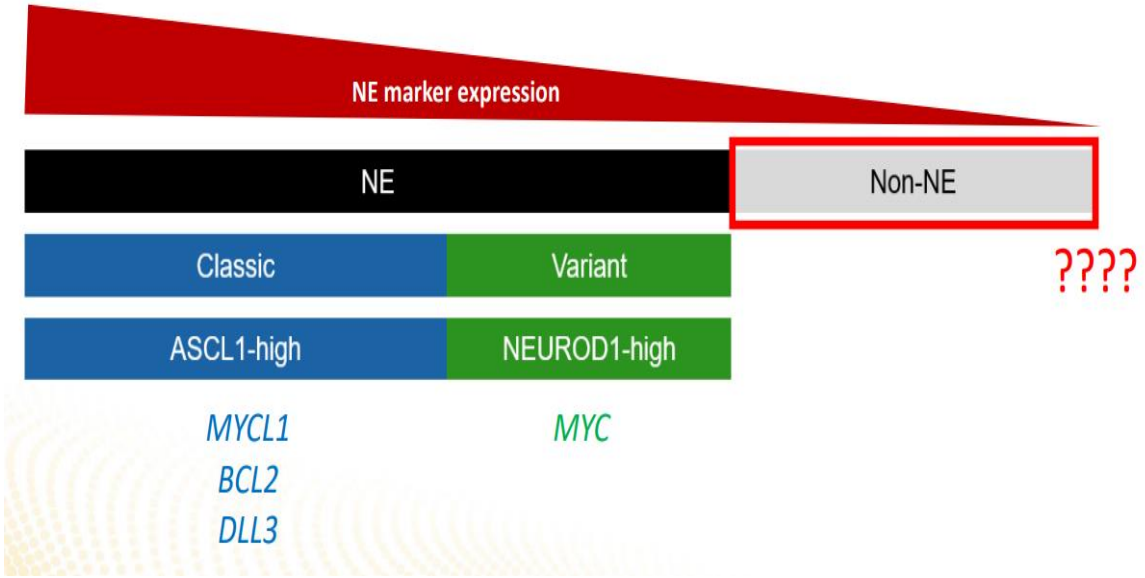


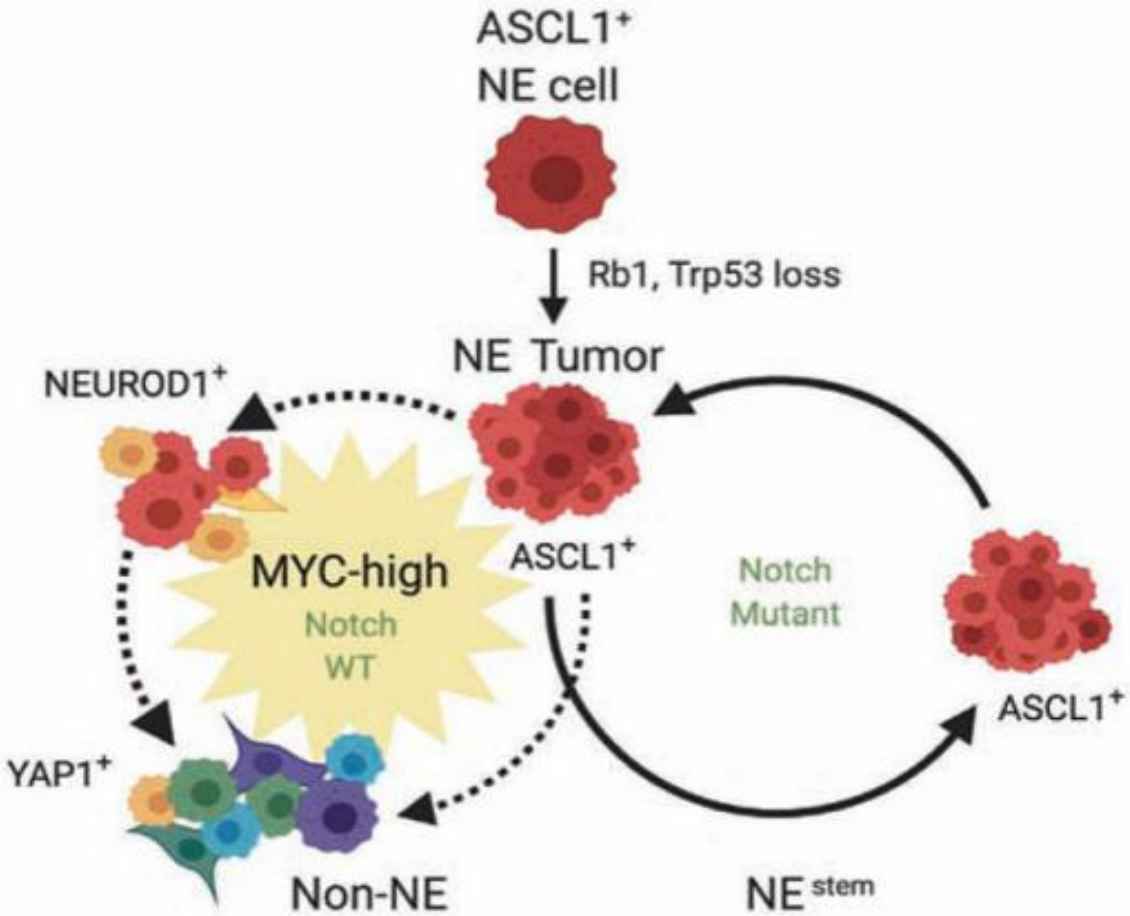
Ireland A et al. Cancer Cell 2020

Background & Current Situation



MYC drives dynamic evolution of SCLC subtypes





Ireland A et al. Cancer Cell 2020

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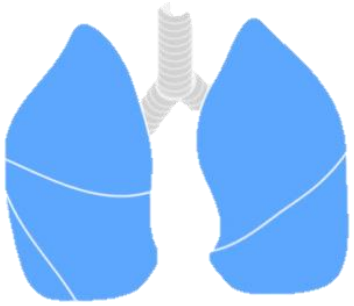
Staging

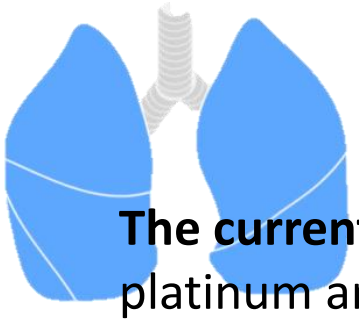


AJCC and IASLC recommended the using of TNM system for SCLC as well as NSCLC

In clinical practice, however, patients are typically divided into limited versus extensive disease using Veteran´s staging system (VALSG)

SMALL CELL LUNG CANCER

Current treatment- limited stage



The current standard treatment is concurrent thoracic radiotherapy and chemotherapy with platinum and etoposide

- Based:
  - meta-analysis of 13 trials that showed a 14% reduction in the mortality
  - Carbo vs cisplatin has shown equivalent efficacy in a randomised trial in limited stage
- Surgery
  - Small fraction of patients limited stage disease may be candidates for up-front surgical resection
  - Based only on retrospective data

Pignon, J.-P. et al. *N. Engl. J. Med.* **1992**, *327*, 1618–162. Kosmidis, *Lung Cancer* **1995**, *12*, 146–147. Wakeam, E. et al. *Lung Cancer* **2017**, *109*, 78–88.

SMALL CELL LUNG CANCER

Limited stage-Timing of RT

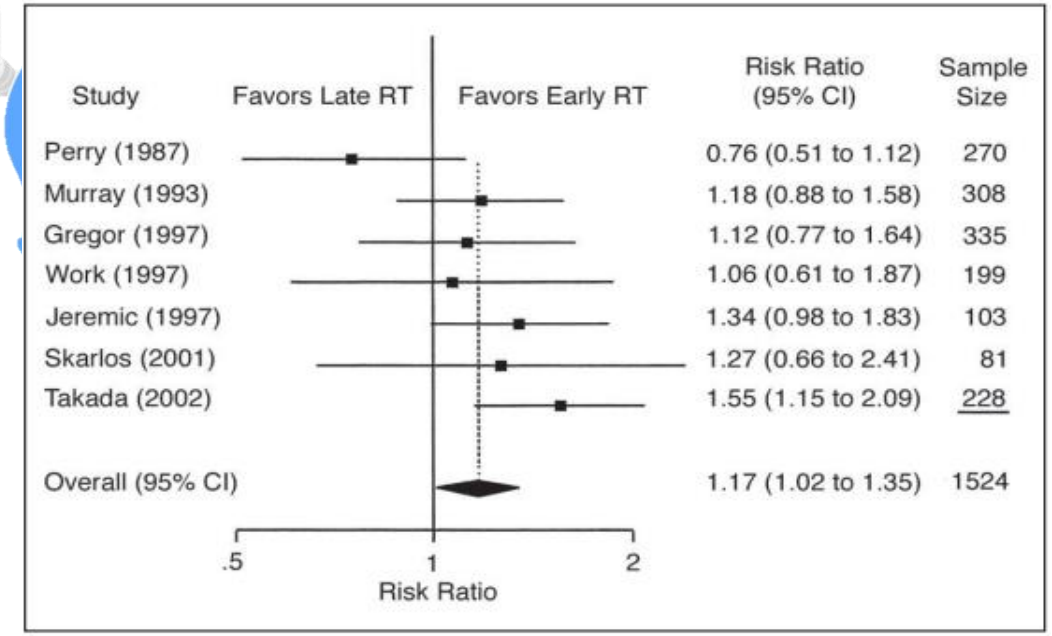


Fig 1. Two-year overall survival risk ratio forest plot for early *v* late thoracic radiation therapy (RT).

Definitions

ERT was defined as beginning before 9 weeks after the initiation of chemotherapy and before the third cycle of chemotherapy. LRT was defined as beginning 9 weeks or more after the initiation of chemotherapy or after the beginning of the third cycle of chemotherapy. This definition was modified from our a priori

Systematic Review Evaluating the Timing of Thoracic Radiation Therapy in Combined Modality Therapy for Limited-Stage Small-Cell Lung Cancer

Daniel B. Fried, David E. Morris, Charles Poole, Julian G. Rosenman, Jan S. Halle, Frank C. Detterbeck, Thomas A. Hensing, and Mark A. Socinski

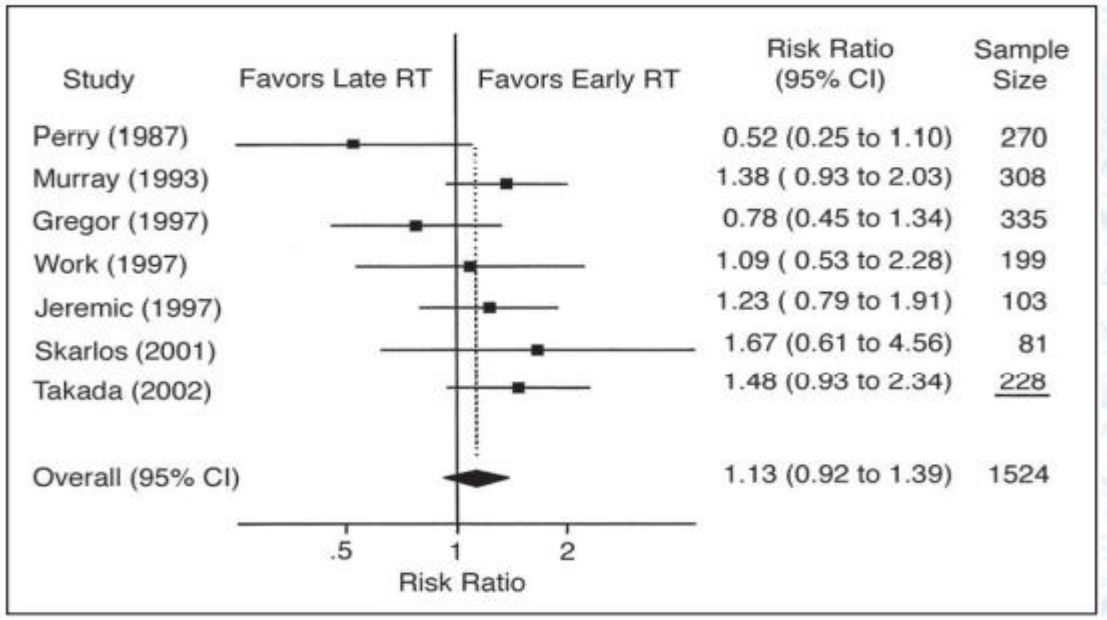
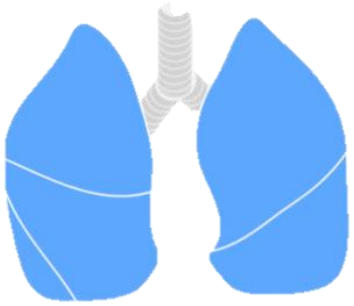


Fig 2. Three-year overall survival risk ratio forest plot for early *v* late thoracic radiation therapy (RT).

SMALL CELL LUNG CANCER

Current treatment- limited stage

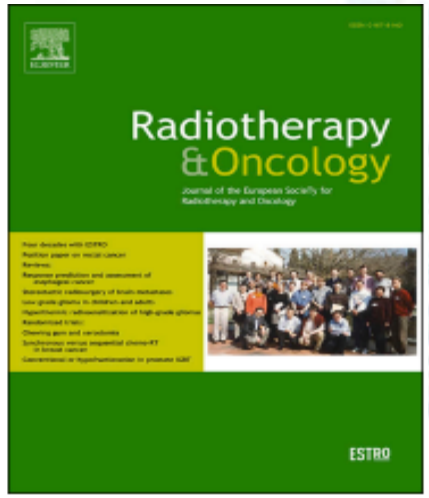


Journal Pre-proofs

Original Article

ESTRO ACROP guidelines for Target Volume Definition in the thoracic radiation treatment of Small cell lung cancer

Cecile Le Pechoux, Corinne Faivre-Finn, Sara Ramella, Fiona McDonald, Farkhad Manapov, Paul Martin Putora, Ben Slotman, Dirk De Ruysscher, Umberto Ricardi, Xavier Geets, José Belderbos, Christoph Pöttgen, Rafal Dziadiuszko, Stephanie Peeters, Yolande Lievens, Coen Hurkmans, Paul Van Houtte, Ursula Nestle



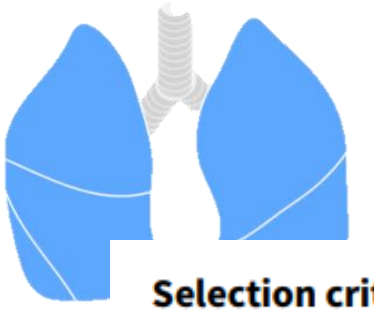
The current state-of-the-art treatment for patients with stage I-III disease amenable to curative RT, involves platinum-etoposide based chemotherapy (4-6 cycles), administered concomitantly with thoracic RT [6-9]. RT should be initiated as early as possible, ideally concomitant to the first or second cycle of chemotherapy in fit patients [10-14]. A prospective randomised phase III study from Korea has shown that thoracic RT starting concomitantly with the third cycle of chemotherapy appeared to be non-inferior to thoracic RT initiated concomitantly with the first cycle [15].

SMALL CELL LUNG CANCER

Current treatment- limited stage

Cochrane Library

Cochrane Database of Systematic Reviews



Early versus late chest radiotherapy in patients with limited-stage small cell lung cancer (Review)

Pijls-Johannesma M, De Ruysscher DKM, Lambin P, Houben R, Rutten I, Vansteenkiste JF

Selection criteria

Randomised controlled clinical trials comparing different timing of chest radiotherapy in patients with limited-stage small cell lung cancer.

Data collection and analysis

Seven randomised trials were included. There were differences in the timing and overall treatment time of chest radiotherapy, and the type of chemotherapy used.

Main results

We found no significant differences in overall survival, whether chest radiotherapy was delivered within 30 days after the start of chemotherapy or later, even after exclusion of the only study that delivered chest radiotherapy during cycles of non-platinum chemotherapy (HR 0.86 in favour of early radiation, P = 0.11). The same was observed for studies having early chest radiotherapy delivered in an overall treatment time of less than 30 days compared to a longer treatment time (HR 0.82, P = 0.13). These results should be interpreted with caution because the largest trial has follow-up data up to three years only. The outcome of longer follow up for overall survival remains to be seen. Local tumour control was not significantly different between early and late chest radiotherapy, nor the incidence of severe pneumonitis or severe oesophagitis. However, we observed a trend towards a higher chance of developing oesophagitis and pneumonitis

2010

SMALL CELL LUNG CANCER

Current treatment- limited stage

Cochrane Library
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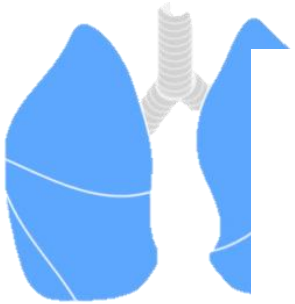
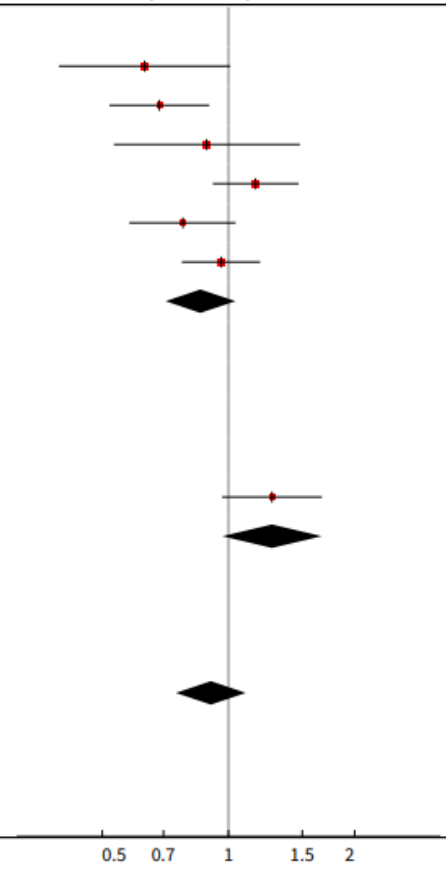


Analysis 1.1. Comparison 1 Early versus late chest RT, Outcome 1 Overall survival.

Study or subgroup	Early N	Late N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 Platinum-based CT						
Jeremic 1997	0	0	-0.5 (0.24)		9.7%	0.63[0.39,1.01]
Murray 1993	0	0	-0.4 (0.14)		15.71%	0.68[0.52,0.9]
Skarlos 2001	0	0	-0.1 (0.26)		8.81%	0.89[0.53,1.48]
Spiro 2006	0	0	0.2 (0.12)		17.17%	1.16[0.92,1.47]
Takada 2002	0	0	-0.2 (0.15)		15%	0.78[0.58,1.04]
Work 1997	0	0	-0 (0.11)		17.9%	0.96[0.77,1.19]
Subtotal (95% CI)					**84.29%**	**0.86[0.71,1.04]**
Heterogeneity: Tau^2=0.03; Chi^2=11.8, df=5(P=0.04); I^2=57.62%						
Test for overall effect: Z=1.58(P=0.11)						
1.1.2 Non-platinum based CT						
Perry 1998	0	0	0.2 (0.14)		15.71%	1.27[0.97,1.67]
Subtotal (95% CI)					**15.71%**	**1.27[0.97,1.67]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=1.71(P=0.09)						
Total (95% CI)					**100%**	**0.91[0.75,1.1]**
Heterogeneity: Tau^2=0.04; Chi^2=17.34, df=6(P=0.01); I^2=65.41%						
Test for overall effect: Z=0.98(P=0.33)						
Test for subgroup differences: Chi^2=5.55, df=1 (P=0.02), I^2=81.97%						



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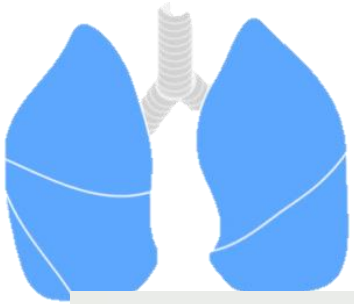
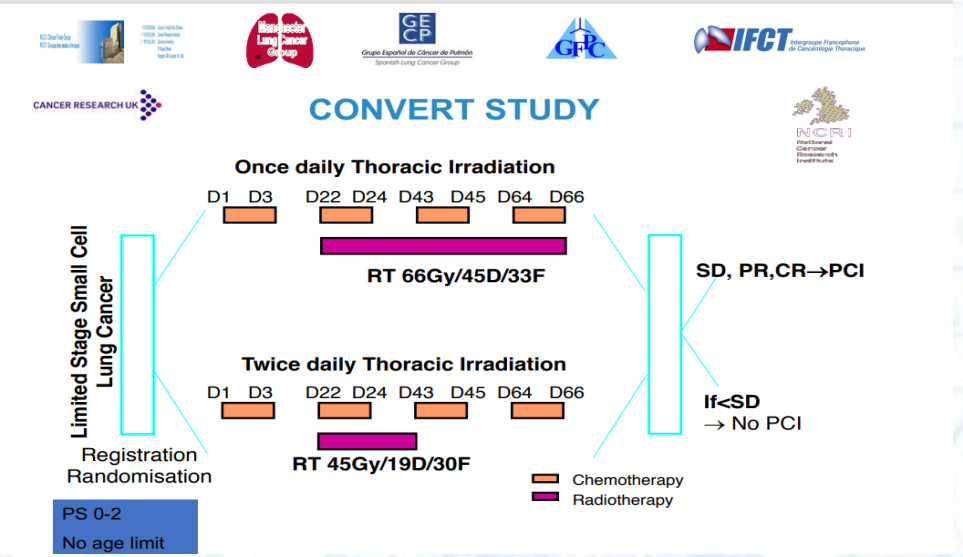
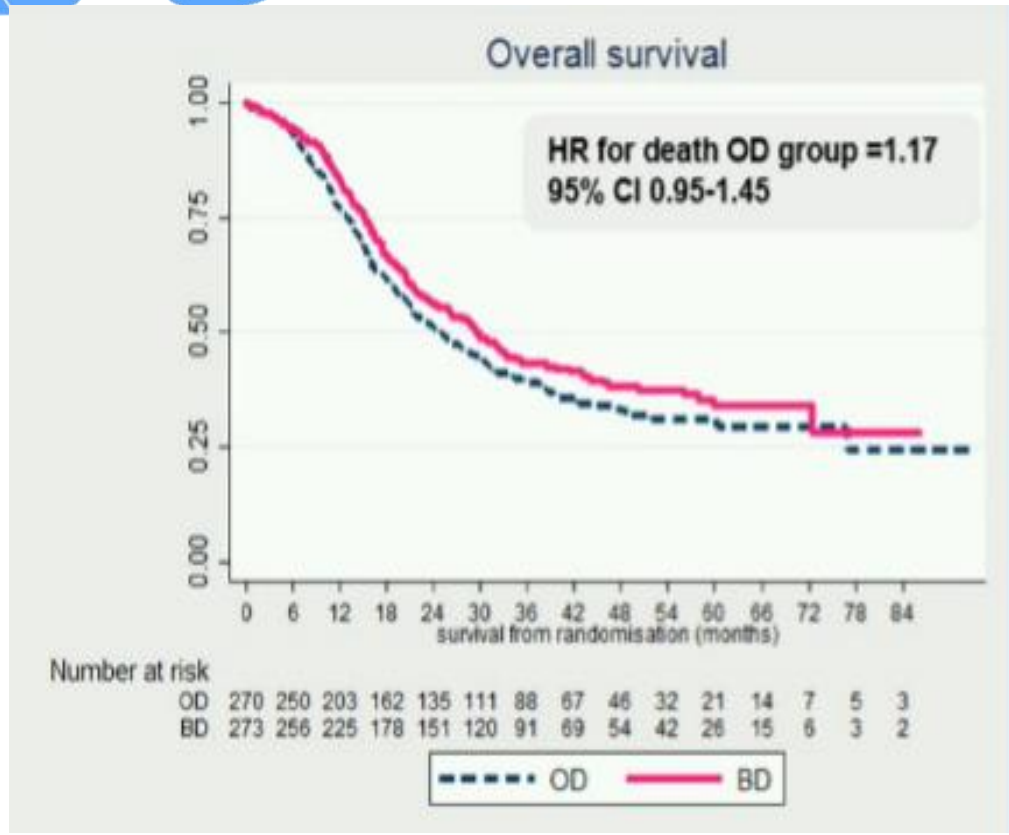
Current treatment- limited stage







Primary objective-survival at 2 years
Trial hypothesis

- Expected survival BD arm 44%
- Projected survival OD arm 56%

Median follow-up: 45 months

Overall survival (n=543)	BD	OD	Log-rank
Median (months)	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)	

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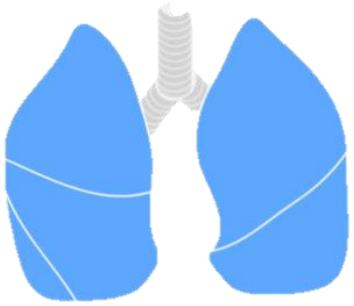
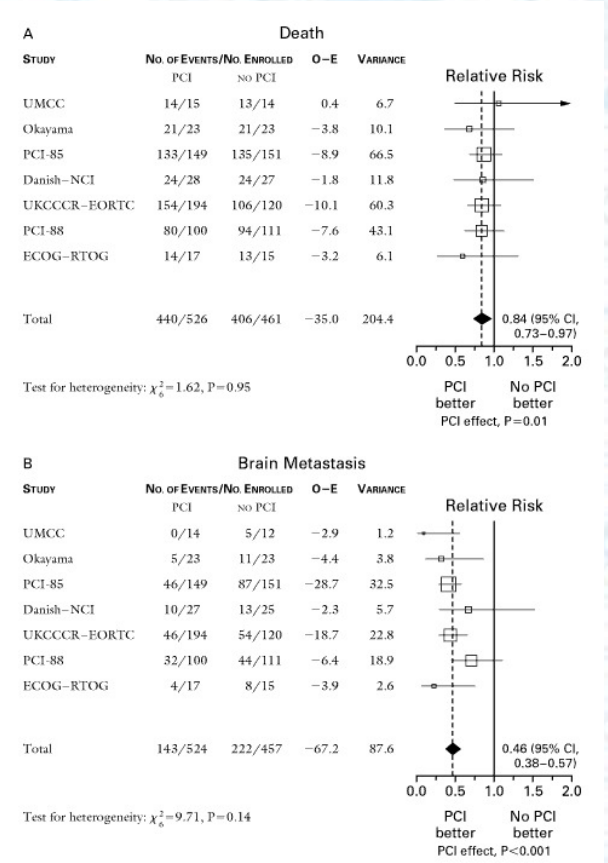


Prophylactic Cranial Irradiation (PCI)



5 Meta-analyses (Auperin 1999; Meert 2001; Zhang 2014;Ge 2018; Yin 2019; Wen 2020)

- Decreases brain metastases incidence: RR. 0.46 (95% CI; 0.38-0.57)
- Improves overall survival: 0.84 (95% CI; 0.73-0.97) ≈ 5.4% OS at 3-years

- Dose of 25 Gy standard of care.
  - PCI 25 Gy vs 36 Gy : not more effective, more toxic (Le Pechoux 2009)

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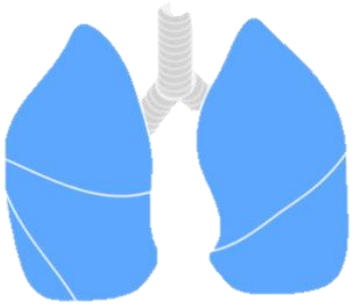
SMALL CELL LUNG CANCER

Current treatment- extensive stage



About 85% of patients with SCLC have extensive stage disease at the time of diagnosis

Until recently, the standard of care treatment had been platinum—based chemotherapy

- *Outcomes: Overall response rate: 66%, Overal Survival: 9.4 months*

The addition of immune checkpoint inhibitors has been the only improvemnet in SCLC for many years

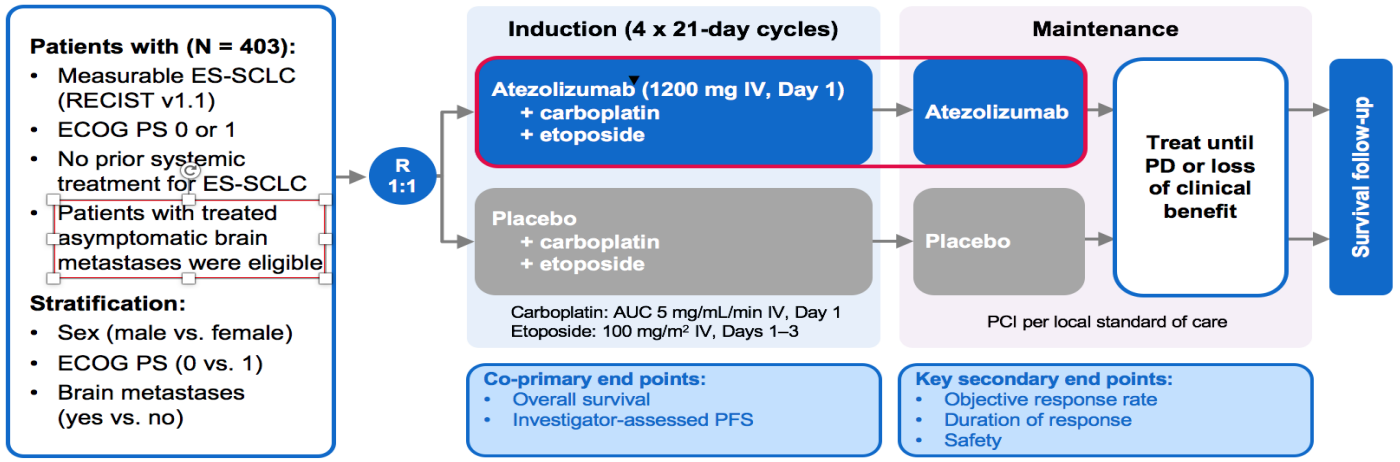
Study	Year	Agents	Phase; Line (n)	Key Results
First Line Treatment				
IMpower133 [5]	2018	EP +/− atezolizumab	III; 1 (403)	EP + atezolizumab: mOS 12.3 mo EP + placebo: mOS 10.3 mo ($p = 0.0154$)
CASPIAN [22]	2019	EP + durvalumab + tremelimumab or EP + durvalumab or EP alone	III; 1 (805)	EP + durva + trem: mOS 10.4 mo EP + durva: mOS 12.9 mo EP alone: mOS 10.5 mo
KEYNOTE-604 [23]	2020	EP +/− pembrolizumab	III; 1 (453)	EP + pembrolizumab: mOS 10.8 mo EP + placebo: 9.7 mo ($p = 0.0164$ [1])

SMALL CELL LUNG CANCER

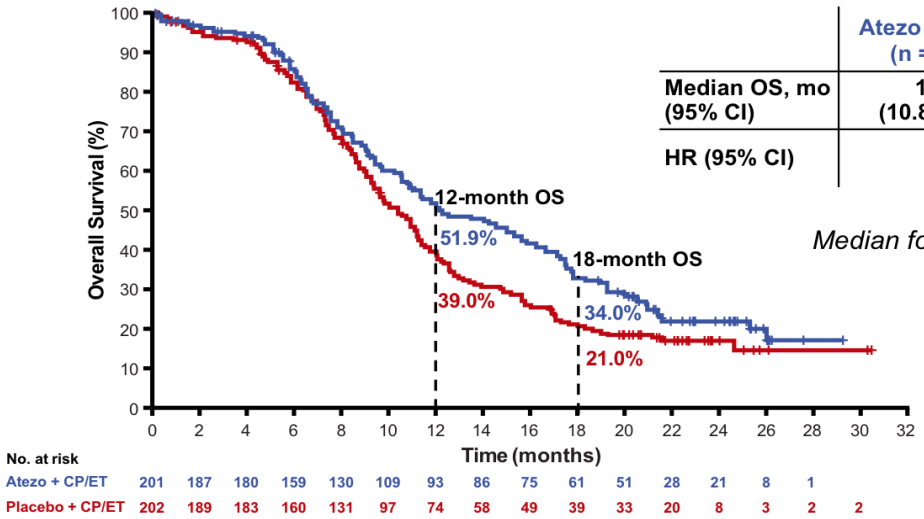
Current treatment- extensive stage

Study	Year	Agents	Phase; Line (n)	Key Results
First Line Treatment				
IMpower133 [5]	2018	EP +/− atezolizumab	III; 1 (403)	EP + atezolizumab: mOS 12.3 mo EP + placebo: mOS 10.3 mo ($p = 0.0154$)
CASPIAN [22]	2019	EP + durvalumab + tremelimumab or EP + durvalumab or EP alone	III; 1 (805)	EP + durva + trem: mOS 10.4 mo EP + durva: mOS 12.9 mo EP alone: mOS 10.5 mo
KEYNOTE-604 [23]	2020	EP +/− pembrolizumab	III; 1 (453)	EP + pembrolizumab: mOS 10.8 mo EP + placebo: 9.7 mo ($p = 0.0164$ [1])
CheckMate 451 [24]	2021	EP -> ipilimumab + nivolumab followed by nivolumab, or EP -> nivolumab, or EP -> placebo	III; 1 (849)	EP -> ipi/nivo: mOS 9.2 mo EP -> nivo: mOS 10.4 mo EP -> placebo: 9.6 mo
CAPSTONE-1 [25]	2022	EP +/− adebrelimab	III; 1 (462)	EP + adebrelimab: mOS 15.3 mo EP + placebo: mOS 12.8 mo ($p = 0.0017$)
ASTRUM-005 [26]	2022	EP +/− serplulimab	III; 1 (585)	EP + serplulimab: mOS 15.4 mo EP + placebo: mOS 10.9 mo ($p < 0.001$)

1st line ES-SCLC: IMpower133 phase I/III placebo-controlled trial atezolizumab + carboplatin + etoposide



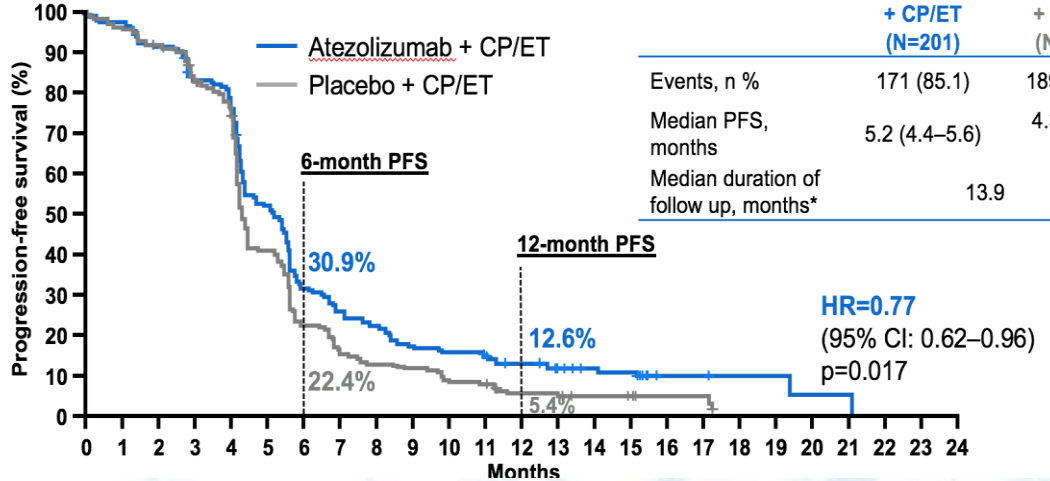
IMpower 133 Updated Survival



	Atezo + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)
HR (95% CI)	0.76 (0.60, 0.95) p = 0.0154[a]	

Median follow-up, 22.9 months

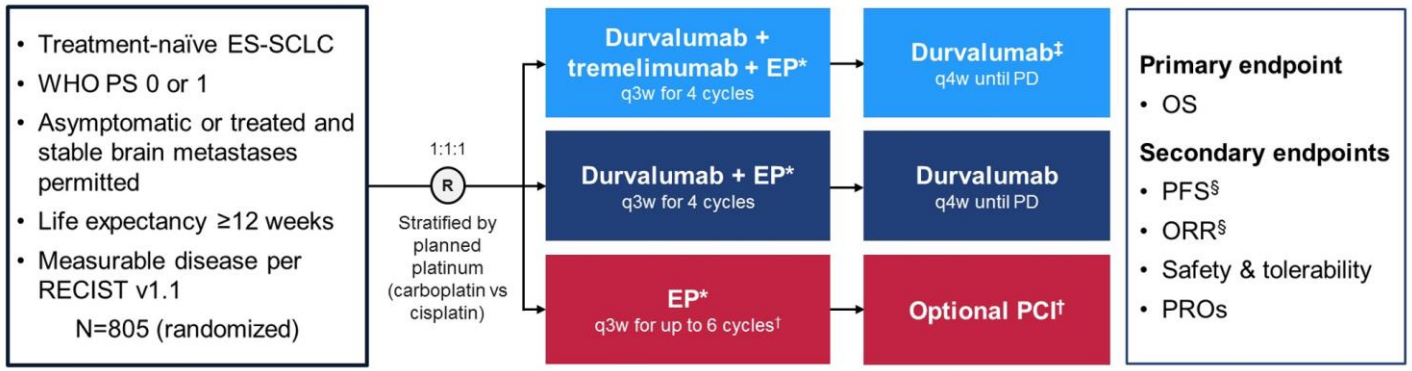
IMpower133: INV-assessed progression-free survival



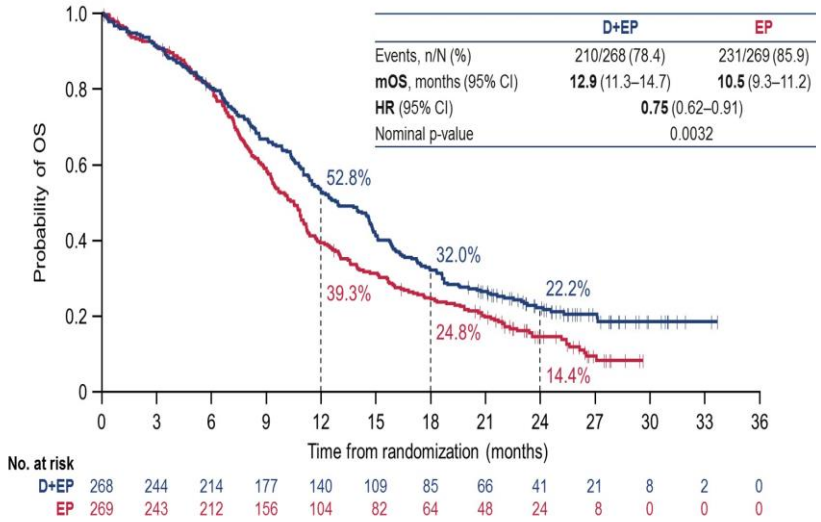
	Atezolizumab + CP/ET (N=201)	Placebo + CP/ET (N=202)
Events, n %	171 (85.1)	189 (93.6)
Median PFS, months	5.2 (4.4–5.6)	4.3 (4.2–5.6)
Median duration of follow up, months*	13.9	

Liu, et al. WCLC 2018 (Abs PL02.07); Horn, et al. N Engl J Med 2018;Reck, et al ESMO 2019

1st line ES-SCLC: CASPIAN phase IIII study Durvalumab ± tremelimumab + platinum-etoposide.

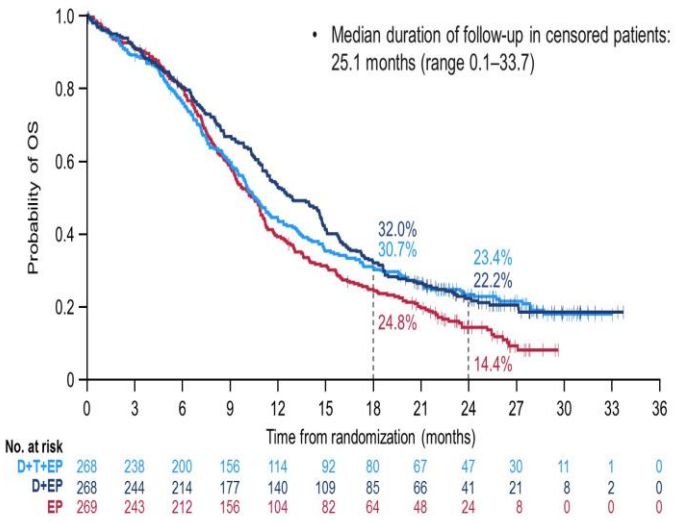


Updated Overall Survival: D+EP vs EP

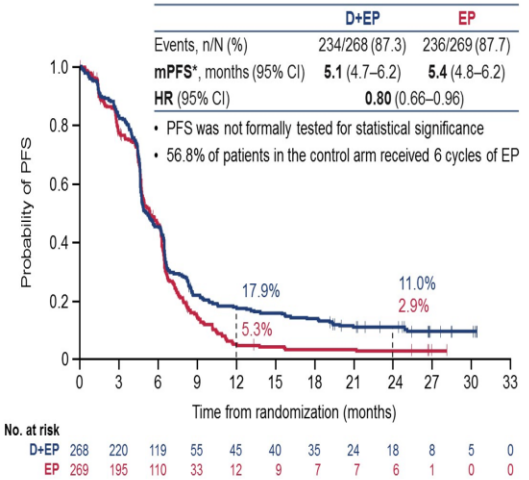


	D+EP	EP
Events, n/N (%)	210/268 (78.4)	231/269 (85.9)
mOS, months (95% CI)	**12.9** (11.3–14.7)	**10.5** (9.3–11.2)
HR (95% CI)	**0.75** (0.62–0.91)	
Nominal p-value	0.0032	

Overall Survival: All Arms



Updated Progression-free Survival: D+EP vs EP



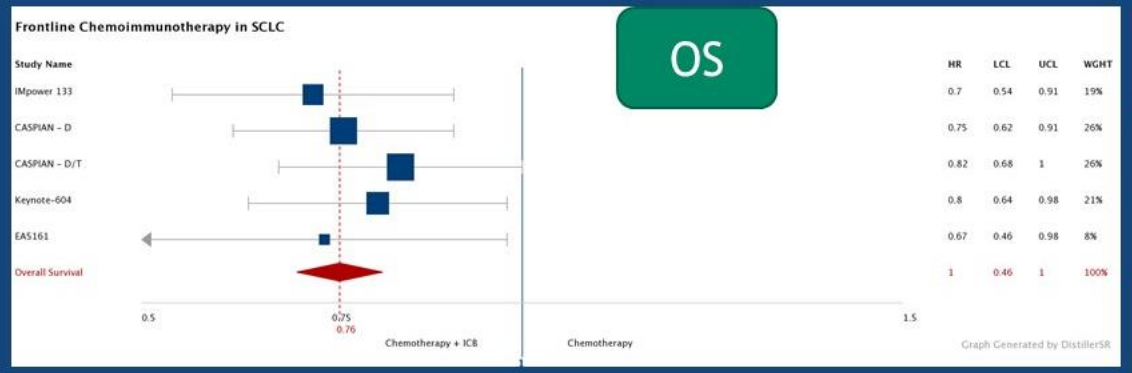
	D+EP	EP
Events, n/N (%)	234/268 (87.3)	236/269 (87.7)
mPFS*, months (95% CI)	**5.1** (4.7–6.2)	**5.4** (4.8–6.2)
HR (95% CI)	**0.80** (0.66–0.96)	

- PFS was not formally tested for statistical significance
- 56.8% of patients in the control arm received 6 cycles of EP

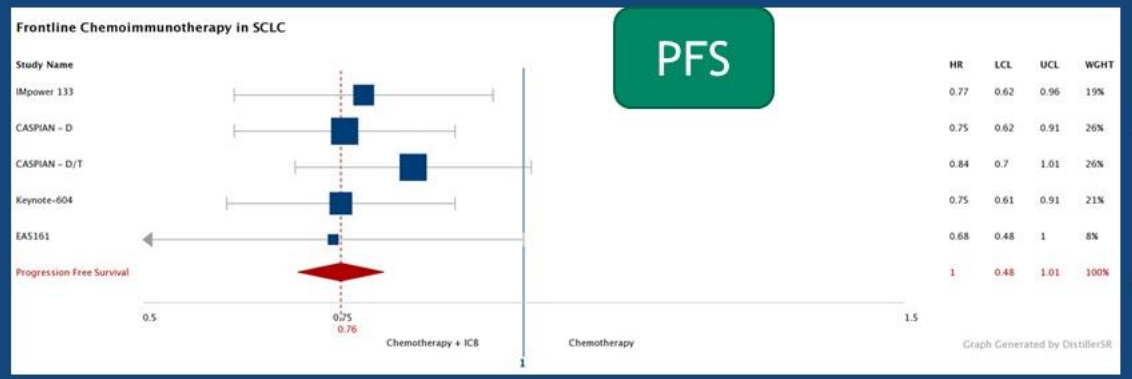
Landmark PFS, %	D+EP (n=268)	EP (n=269)
6 months	45.4	45.8
12 months	17.9	5.3
18 months	13.9	3.4
24 months	11.0	2.9

Paz Ares, et al. Lancet 2019; Paz Ares, et al. ASCO 20.

Summary: Chemo-Immunotherapy in SCLC



OS

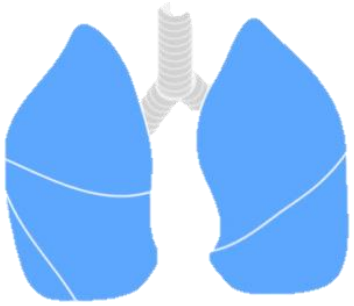


PFS

	IMpower133	Caspian D	Caspian D/T	KN-604	EA5161
Median PFS	5.2	5.1	4.9	4.5	5.5
Median OS	12.3	13	10.4	10.8	11.3
12-month OS	**51.7**	**52.8**	**43.8**	**45.1**	**≈48**
24-month OS	**≈22**	**22.2**	**23.4**	**22.5**	**NR**
HR PFS 95% CI	0.77 0.62-0.96	0.78 0·65-0·94	0.84 0.70-1.01	0.75 0.61-0.91	0.68 0.48-1.0
HR OS 95% CI	0.70 0.54-0.91	0·73 0·59-0·91	0.82 0.68-1.00	0.80 0.64-0.98	0.67 0.46-0.98

- Owonikoko TK presentation at ASCO 2020.

Current treatment- extensive stage



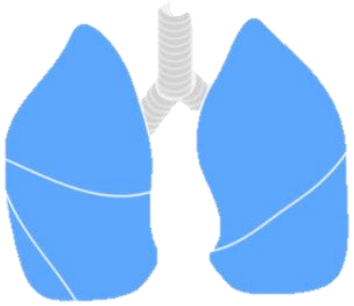
CASPIAN vs IMpower133

CASPIAN	IMpower133
• Free choice for platinum	• Only carboplatin
• Up to 6 cycles of CT	• Up to 4 cycles of CT
• Maintenance every 4 wks	• Maintenance every 3 wk
• PCI not allowed in ICI group	• PCI allowed
• 10% BM - untreated	• 9% BM - treated
• OS as primary endpoints	• OS and PFS co-primary
• Median OS 13 months	• Median OS 12.3 months
• Median PFS 5.1 months	• Median PFS 5.2 months
• AE grade ≥ 3: 62%	• AE grade ≥ 3: 58.1%

Paz-Ares L, et al. Lancet. 2019; 394: 1929-39.
Horn L, et al. N Engl J Med. 2018; 379: 2220-9.

SMALL CELL LUNG CANCER

Current treatment- extensive stage



Taking these pivotal immunotherapy trials together

-There is clearly benefit from the addition of checkpoint inhibitors to platinum- based chemotherapy

- The long tails of K-M curves suggest that there is a small subset of patients, whom we are still ill-equipped to identfy
- There has not been any reliable or robust prognostic biomarkers identified
- PDL-1 expression was not predictive of efficacy and likewise tumor mutational burden

McNamee N. et al. IN J Molecular Sciences 2023.

SMALL CELL LUNG CANCER

RTT: Small Cell Lung Cancer

SCLC: 1,658 p -12.9% total patients registered in the RTT database

Ranges 13.5% and 19%

- Choi CM et al. Report of the Korean Association of Lung Cancer Registry (KALC-R) 2014. *Cancer Res Treat* 2019
- Sun A et al. A systematic review. *Curr Oncol* 2019; 26 (3): e372-84.

SEER Database

1,037 patients were **extensive-stage**: **956** completed data (62.6%)

606 patients **limited-stage** (36.6%)

Table 1. Patient characteristics

Characteristic	Patients (N = 26,221)
Male, n (%)	13,306 (50.7)
>65 years old, n (%)	14,498 (55.7)
Caucasian, n (%)	21,489 (82)
Stage IV, n (%)	18,574 (70.8)

SMALL CELL LUNG CANCER

RTT: Small Cell Lung Cancer

Characteristic	n	%
Sex		
Male	751	78.6
Female	205	21.4
Age at diagnosis		
Mean (SD), years	64.7 (9.1)	
Median [min-max], years	65 [37-88]	
Distribution		
<55 years	117	12.2
55-64 years	355	37.1
65-74 years	335	35
≥75 years	149	15.6
Race		
Caucasian	929	97.2
Other	27	2.8
Patient cancer history*	110	11.5
Head and neck	21	2.2
Bladder/urinary tract	21	2.2
Prostate	14	1.5
Non-melanoma skin	10	1.0
Smoking habit		
Never smoker	14	1.5
Former smoker	357	37.3
Smoker	579	60.6
ECOG at diagnosis		
0	221	23.1
1	507	53.0
≥2	228	23.8

CASPIAN
63 (35-82)
IMP 133
64 (28-90)

CASPIAN/IMP 133
PS 0/1
100%

Datos del Registro de Tumores Torácicos del Grupo Español de Cáncer de Pulmón

EXTENSIVE DISEASE

SCLC: 1,658 p -12.9% total patients registered in the RTT database
1,037 patients were **extensive-stage**: **956** completed data
606 patients limited-stage

Characteristic	n	%
Symptoms at diagnosis		
Asymptomatic	**54**	**5.6**
Symptomatic	**882**	**92.3**
Unknown	**23**	**2.4**
Metastasis at diagnosis	924	96.7
Liver	422	44.1
Bone	333	34.8
Thoracic lymphadenopathy	299	31.3
Lung	237	24.8
Extrathorax- lymphaden	206	21.5
Adrenal	203	21.2
CNS	189	19.8
Comorbidities*	826	86.4
Hypertension	460	48.1
Dyslipidemia	330	34.5
COPD	248	25.9
Diabetes mellitus	248	25.9
Heart disease	180	18.8

CASPIAN
40%
IMP 133
38.3%

CASPIAN
Untreated 10%
IMP 133
9% treated

SMALL CELL LUNG CANCER

RTT: Small Cell Lung Cancer

FIRST LINE: 91.9%

Carboplatin+ etoposide: 61.8%

Cisplatin+ etoposide: 31.7%

	First line (n=879)
Number of cycles	
Mean (sd)	4.3 (1.9)
Median [min-max]	4 (1-12)
Duration of treatment (months)	
Mean (SD)	2.86 (1.78)
Median [min-max]	3.0 [0-16.1]
Best response, n (%)	
CR	24 (2.7%)
PR	449 (51.5%)
SD	72 (8.2%)
PD	108 (12.3%)
NE	87 (9.9%)
ND	50 (5.7%)

Datos del Registro de Tumores Torácicos del Grupo Español de Cáncer de Pulmón

CASPIAN/CONTROL

Median 4 (both IPM 133)

Carbo-Etop: 78% vs 61.8%

Cisp – Etop: 25% vs 31.7%

n.s.

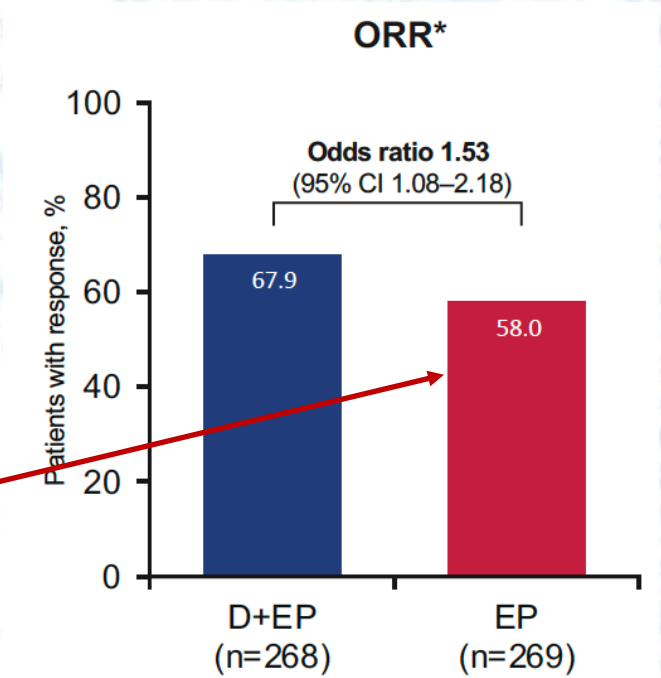
ORR-RTT

54.2%

Table 2. Response Rate, Duration of Response, and Disease Progression.*

Variable	Atezolizumab Group (N=201)	Placebo Group (N=202)
Objective confirmed response†	121 (60.2 [53.1–67.0])	130 (64.4 [57.3–71.0])
Complete response — no. (% [95% CI])	5 (2.5 [0.8–5.7])	2 (1.0 [0.1–3.5])
Partial response — no. (% [95% CI])	116 (57.7 [50.6–64.6])	128 (63.4 [56.3–70.0])
Median duration of response (range) — mo‡	4.2 (1.4§–19.5)	3.9 (2.0–16.1§)
Ongoing response at data cutoff — no./total no. (%)	18/121 (14.9)	7/130 (5.4)
Stable disease — no. (% [95% CI])	42 (20.9 [15.5–27.2])	43 (21.3 [15.9–27.6])
Progressive disease — no. (% [95% CI])	22 (10.9 [7.0–16.1])	14 (6.9 [3.8–11.4])

Horn L NEJM 2018



Paz-Ares L ASCO 2020

SMALL CELL LUNG CANCER

RTT: Small Cell Lung Cancer

FIRST LINE: 91.9%
Carboplatin+ etoposide: 61.8%
Cisplatin+ etoposide: 31.7%

SECOND LINE: 36%

CASPIAN
42%

IMP 133
50.2%

THIRD LINE: 13.8%

CASPIAN
12 %-14%

IMP 133
14.4%

	First line (n=879)	Second line (n=344)	Third line (n=132)
Number of cycles			
Mean (sd)	4.3 (1.9)	3.7 (3.3)	3.4 (2.7)
Median [min-max]	4 (1-12)	3 (1-31)	3 [1-16]
Duration of treatment (months)			
Mean (SD)	2.86 (1.78)	2.39 (2.67)	1.96 (2.11)
Median [min-max]	3.0 [0-16.1]	1.8 [0-18.9]	1.4 [0-15.2]
Best response, n (%)			
CR	24 (2.7%)	9 (2.6%)	1 (0.8%)
PR	449 (51.5%)	64 (18.7%)	17 (12.9%)
SD	72 (8.2%)	55 (16.0%)	22 (16.7%)
PD	108 (12.3%)	128 (37.3%)	49 (37.1%)
NE	87 (9.9%)	48 (14.0%)	24 (18.2%)
ND	50 (5.7%)	18 (5.2%)	4 (3.0%)

Datos del Registro de Tumores Torácicos del Grupo Español de Cáncer de Pulmón

EXTENSIVE DISEASE

Higher mortality rates were significantly associated with male sex, older age, smoking habit and ECOG

	Event (progression)	Censored	HR	CI 95%	p-value
Total	745 (77.9%)	211 (22.1%)			
Sex					**0.016**
Male	598 (79.6%)	153 (20.4%)	-		
Female	147 (71.7%)	58 (28.3%)	0.802	0.669-0.960	
Age			1.016	1.007-1.024	**<0.001**
Mean (SD)	64.9 (9.3)	64.0 (8.4)			
Median [min-max]	65 (37-88)	64 (42-87)			
Smoking habit					0.006
Smoker	460 (79.4%)	119 (20.6%)	-		
Former smoker	275 (76.4%)	85 (23.6%)	0.877	0.754-1.019	0.086
Never smoker	8 (57.1%)	6 (42.9%)	0.363	0.180-0.732	0.005
Asbestos exposure					0.247
No	234 (70.5%)	98 (29.5%)	-		
Yes	26 (81.3%)	6 (18.8%)	1.271	0.847-1.908	
CNS metastasis					0.484
No	603 (78.6%)	164 (21.4%)	-		
Yes	142 (75.1%)	47 (24.9%)	1.068	0.889-1.908	
ECOG					**<0.001**
0	167 (75.6%)	54 (24.4%)	-		
1	389 (76.7%)	118 (23.3%)	1.212	1.011-1.453	0.038
≥2	189 (82.9%)	39 (17.1%)	2.229	1.807-2.749	**<0.001**

SMALL CELL LUNG CANCER

Current treatment- extensive stage

A multinational, multicenter, randomized, double-blind, Phase III trial comparing the efficacy of ipilimumab plus etoposide/platinum vs etoposide/platinum in newly diagnosed ED-SCLC[1]

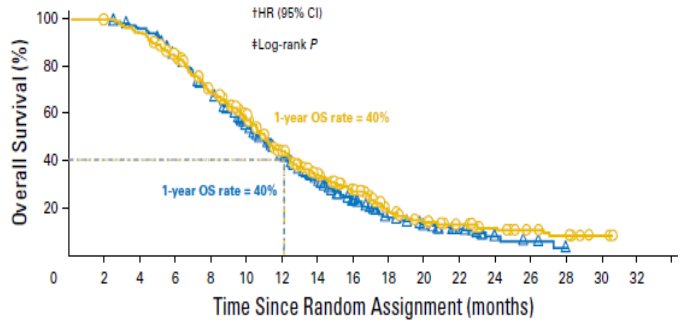
Key Inclusion Criteria
- ≥18 years of age
- ED-SCLC
- ECOG PS ≤1
- No prior systemic therapy for lung cancer
- No symptomatic CNS metastases or autoimmune disease

R → Ipilimumab + Pt/Etoposide; Placebo + Pt/Etoposide

- **Primary outcome measure: OS**
- **Secondary outcome measure: PFS**

A

	Chemotherapy plus ipilimumab	Chemotherapy plus placebo
No. events/No. of patients	350/478	357/476
*Median OS (95% CI), mo	11.0 (10.5 to 11.3)	10.9 (10.0 to 11.5)
†HR (95% CI)		0.94 (0.81 to 1.09)
‡Log-rank *P*		.3775



No. of patients at risk																
Chemotherapy plus ipilimumab	478	477	450	394	318	259	172	112	78	41	28	22	15	10	7	2	0
Chemotherapy plus placebo	476	476	454	398	320	245	158	104	64	38	27	17	5	3	0	0	0

Reck M, et al. JCO 2016

CheckMate 451 Study Design

Key eligibility criteria
- ED-SCLC at diagnosis
- No symptomatic CNS metastases
- ECOG PS 0 or 1
- Ongoing response of CR, PR or SD following 4 cycles of platinum-based 1L chemotherapy[b,c]

Stratified by ECOG PS (0 vs 1), prior PCI (yes vs no), sex

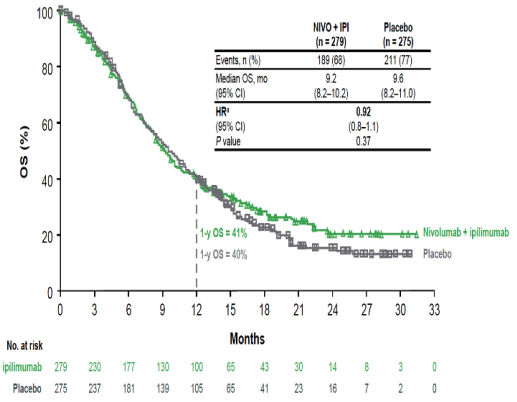
R 1:1:1 N = 834

- Nivolumab 1 mg/kg Q3W + Ipilimumab 3 mg/kg Q3W (max 4 doses) n = 279
- Nivolumab 240 mg Q2W
- Nivolumab 240 mg Q2W n = 280
- Placebo n = 275

Treat until disease progression[d] or unacceptable toxicity, for a maximum of 2 years

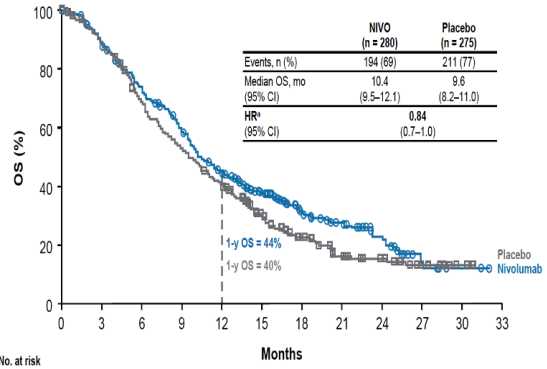
- **Primary endpoint:**
  - OS: nivolumab + ipilimumab vs placebo
- **Secondary endpoints:**[e]
  - OS: nivolumab vs placebo
  - PFS: nivolumab + ipilimumab vs placebo[f]
  - PFS: nivolumab vs placebo[f]
- **Exploratory endpoints:**
  - ORR and DOR
  - Safety and tolerability

OS for Nivolumab Plus Ipilimumab Versus Placebo (Primary Endpoint)



No. at risk													
Nivolumab + ipilimumab	279	230	177	130	100	65	43	30	14	8	3	0	
Placebo	275	237	181	139	105	65	41	23	16	7	2	0	

OS for Nivolumab Versus Placebo



No. at risk													
Nivolumab	280	242	195	155	114	81	49	37	21	6	2	0	
Placebo	275	237	181	139	105	65	41	23	16	7	2	0	

Owonikoko T, et al. JCO 2021

SMALL CELL LUNG CANCER

Current treatment- extensive stage

Tuesday, Mar 29, 2022

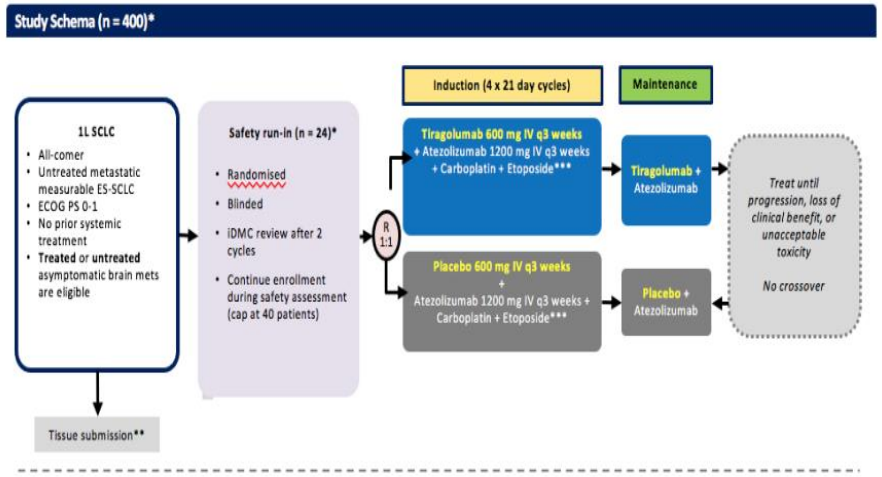
Genentech Provides Update on Phase III SKYSCRAPER-02 Study in Extensive-Stage Small Cell Lung Cancer

SKYSCRAPER-02, the first randomized study of tiragolumab in extensive-stage small cell lung cancer (ES-SCLC), did not meet its co-primary endpoint of progression-free survival

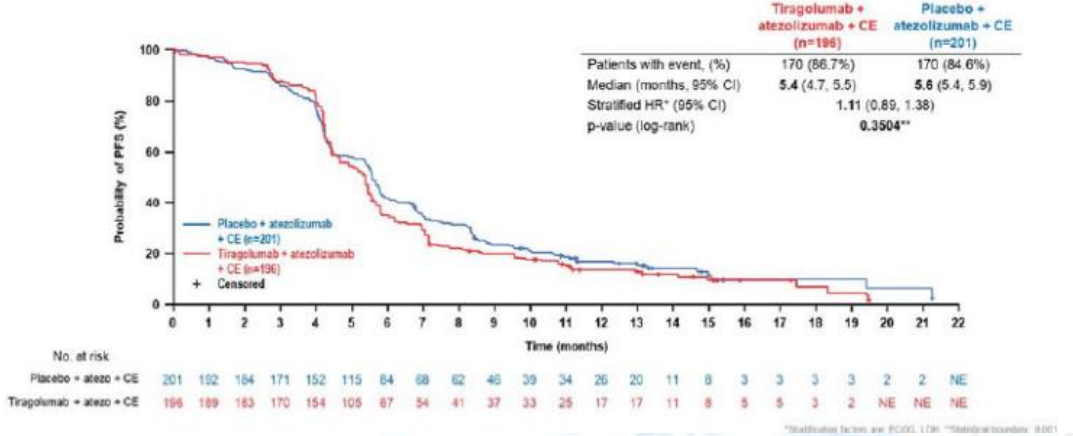
ES-SCLC is a hard-to-treat disease and Tecentriq plus chemotherapy remains a standard of care

Tiragolumab continues to be evaluated in non-small cell lung cancer and other cancer types through additional Phase III trials as planned

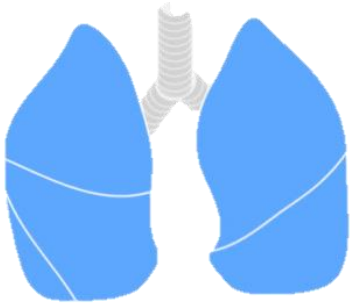
SKYSCRAPER-02: atezolizumab + tiragolumab (Anti Tigit) + EP in 1L EE-SCLC



PFS: Primary Analysis Set



SMALL CELL LUNG CANCER



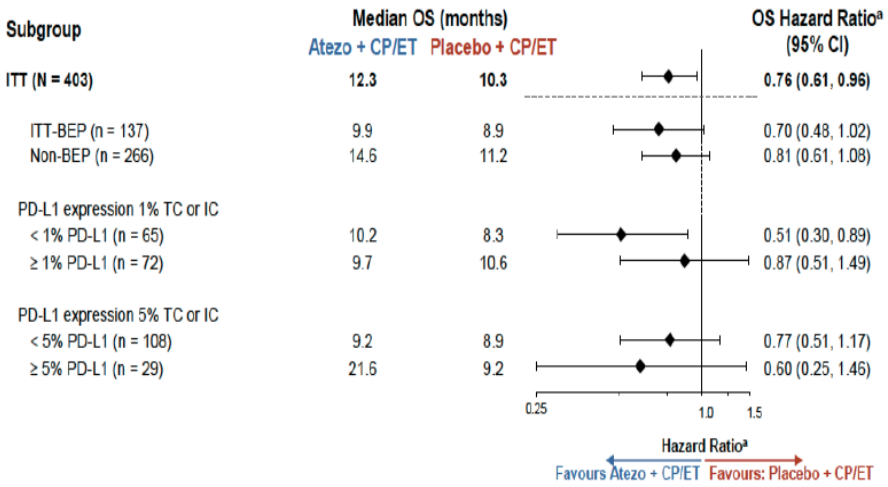
Small Cell Lung Cancer, new hope ?

- RWE small cell lung cancer in our country
- New drugs, relevant new data?
- Biomarkers?
- Future

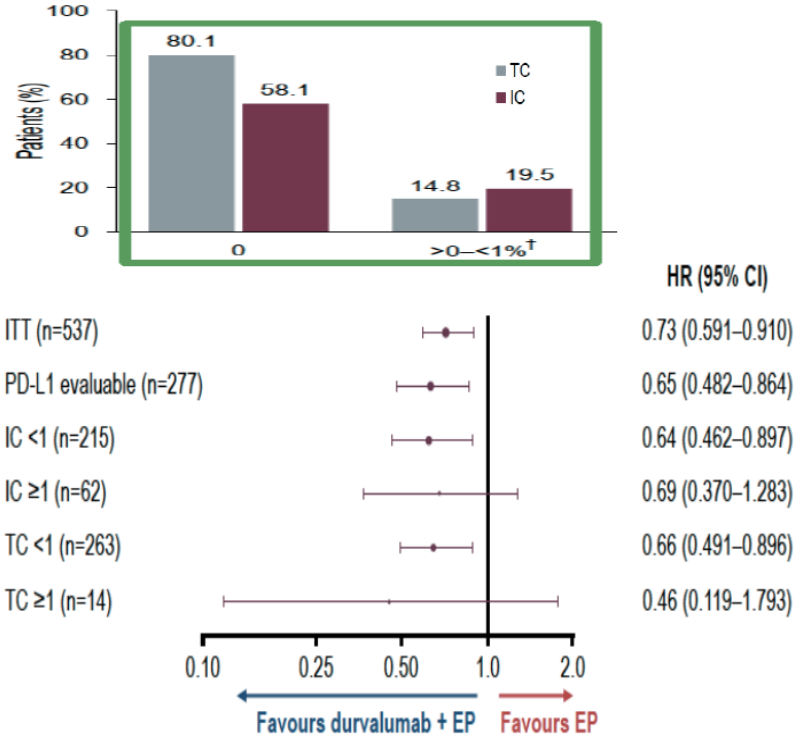
PD-L1 expression and outcome

IMpower133 PD-L1 (SP263) evaluable in 34% of ITT

PD-L1 IHC expression in ES-SCLC (n = 137)			
IC	**% BEP (n)**	**TC**	**% BEP (n)**
< 1%	49.6% (68)	< 1%	94.2% (129)
≥ 1%	50.4% (69)	≥ 1%	5.8% (8)



CASPIAN PD-L1 (SP263) evaluable in 59% of pts. in 3 arms



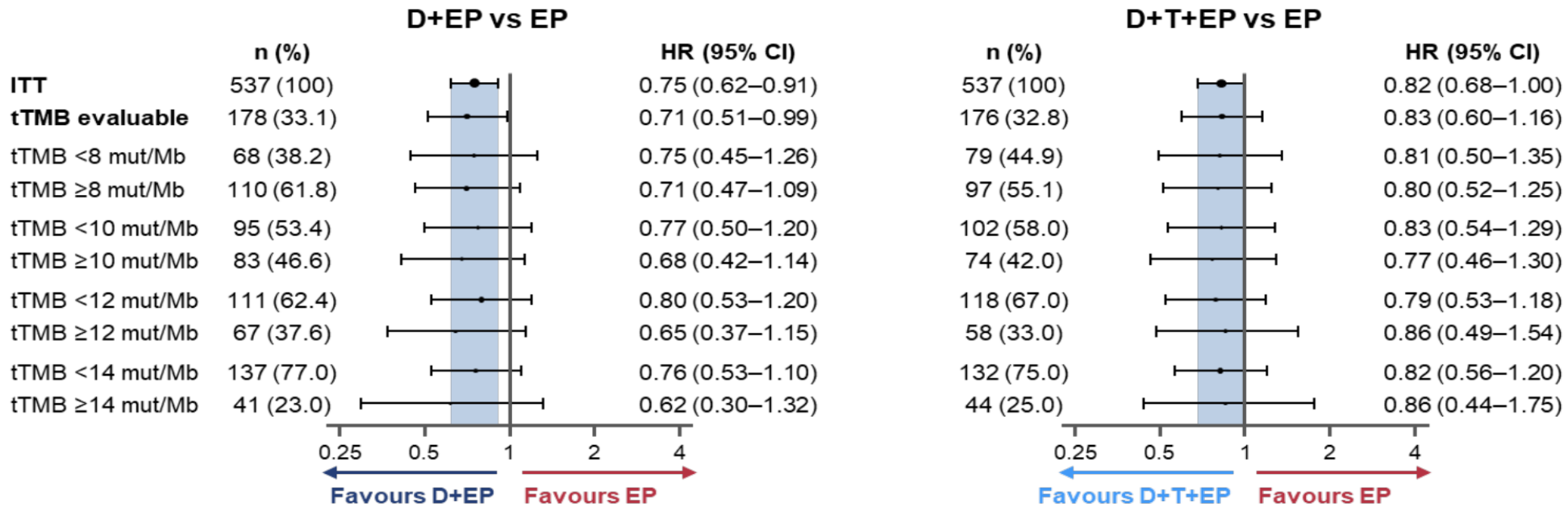
PD-L1 expression in TC is low and no significant interaction PD-L1 and outcome

BEP, biomarker evaluable population; IC, immune cells; TC, tumor cells.

Reck M, et al. Presented at: ESMO 2019; Abstract 2374. Paz-Ares, et al. Presented at: ESMO 2019; Abstract 3837.

CASPIAN: Overall survival based on tTMB

tTMB was not predictive of an improvement in OS for durvalumab ± tremelimumab + EP vs EP

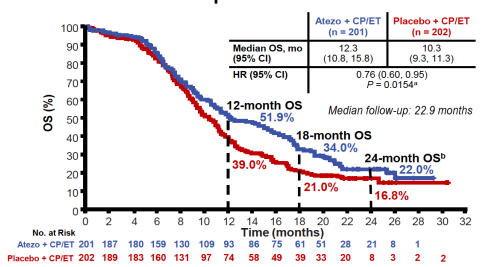


CI, confidence interval; D, durvalumab; EP, platinum-etoposide; HR, hazard ratio; ITT, intent-to-treat; T, tremelimumab; tTMB, tissue tumour mutational burden.

IMpower133 LTS: background and aim

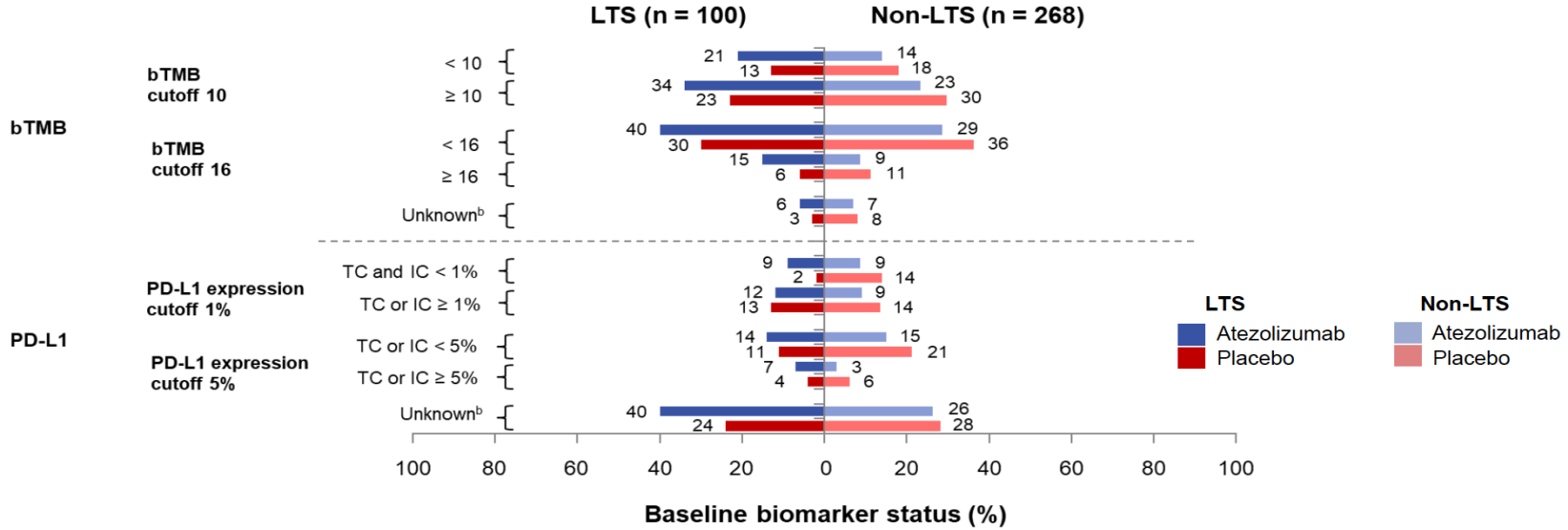
- In IMpower133, atezolizumab + CP/ET for first-line treatment of ES-SCLC led to improved OS and PFS vs placebo + CP/ET[1]
- Additional follow-up showed persistent OS benefit with the atezolizumab + CP/ET regimen[2]
- Limited data exist regarding the characteristics of patients with ES-SCLC who experience long-term survival with CIT and chemotherapy
- Exploratory analyses to characterise long-term survivors (LTS) in IMpower133 are presented here

Updated OS in ITT



Atezo, atezolizumab; CIT, cancer immunotherapy; CP/ET, carboplatin + etoposide; ES-SCLC, extensiv
ITT, intent-to-treat. [a] Provided for descriptive purposes only. [b] With a median follow-up of 22.9 months,
are still unstable. 1. Horn L, et al. *N Engl J Med*. 2018;379:2220-2229. 2. Reck M, et al. *Ann Oncol* 201
Data cutoff, 24 Jan 2019.

IMpower133 LTS: baseline bTMB status and PD-L1 expression[a]

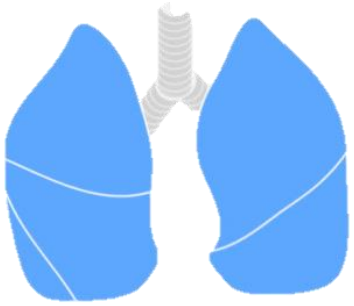


- Percentages are calculated for each subgroup within LTS and non-LTS, respectively

bTMB, blood tumour mutational burden; IC, tumour-infiltrating immune cell; TC, tumour cell. [a] Among patients evaluable for long-term survival, 87% were evaluable for bTMB (n = 323 of 373), and 43% were evaluable for PD-L1 (n = 160 of 373). The VENTANA SP263 assay was used to determine PD-L1 status on slide sections (regardless of age at the time of staining). [b] Unknown biomarker status irrespective of cutoff level. Data cutoff, 24 Jan 2019.

Liu et al. IMpower133 LTS. https://bit.ly/2Ywu0bI

SMALL CELL LUNG CANCER



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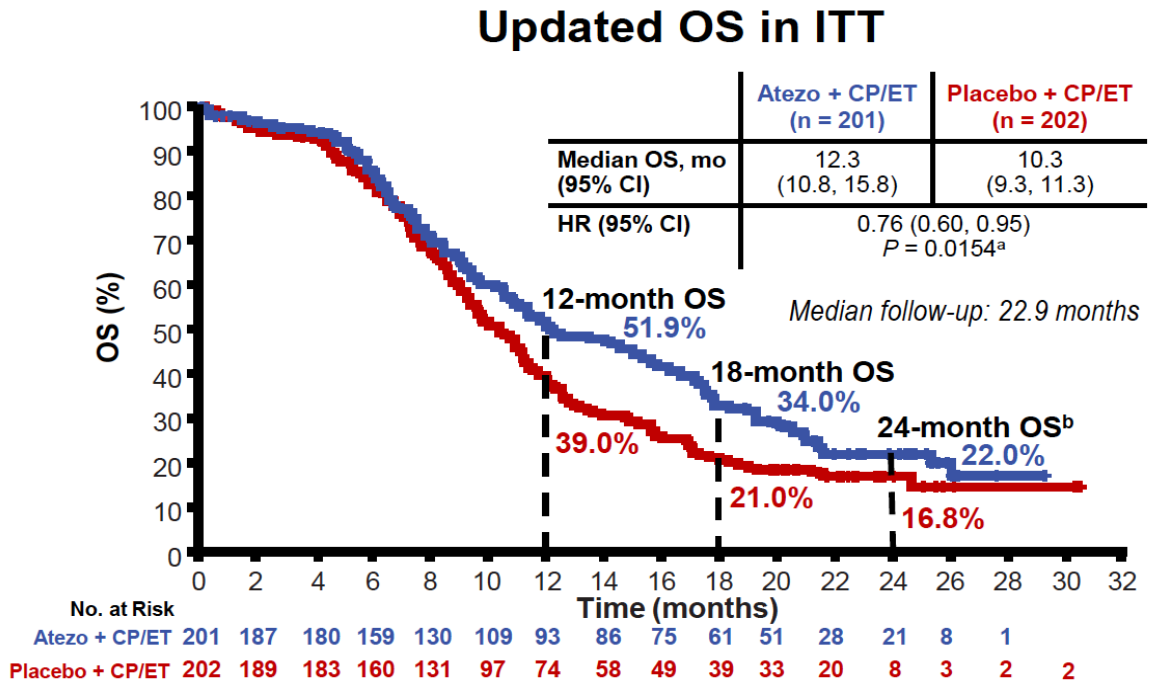


Atezo, atezolizumab; CIT, cancer immunotherapy; CP/ET, carboplatin + etoposide; ES-SCLC, extensive-stage small cell lung cancer; ITT, intent-to-treat. [a] Provided for descriptive purposes only. [b] With a median follow-up of 22.9 months, 24-month landmark estimates are still unstable. 1. Horn L, et al. *N Engl J Med*. 2018;379:2220-2229. 2. Reck M, et al. *Ann Oncol* 2019;30(suppl 5):v710-v717. Data cutoff, 24 Jan 2019.

Liu et al. IMpower133 LTS. https://bit.ly/2Ywu0bl

IMpower133 LTS: univariate and multivariate Cox regression analysis (ITT population)[a]

Covariate	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment arm (ref: atezolizumab)	0.76 (0.61, 0.96)	0.02	0.71 (0.56, 0.90)	< 0.01
Sex (ref: male)	1.11 (0.88, 1.41)	0.38	1.21 (0.94, 1.54)	0.13
Age (ref: ≥ 65 y)	1.17 (0.93, 1.47)	0.17	1.18 (0.93, 1.50)	0.17
ECOG PS (ref: 1)	1.64 (1.29, 2.10)	< 0.01	1.43 (1.11, 1.85)	0.01
Metastatic sites (ref: ≥ 3)	1.53 (1.18, 1.97)	< 0.01	1.22 (0.93, 1.61)	0.15
LDH (ref: > ULN)	1.53 (1.21, 1.94)	< 0.01	1.30 (1.01, 1.66)	0.04
SLD (ref: ≥ 111 mm)	1.69 (1.34, 2.12)	< 0.01	1.56 (1.22, 2.00)	< 0.01

- Treatment by covariate interactions were tested, but no significant interactions were observed at the 5% level

[a] Regression models were tested independent of LTS/non-LTS.
Data cutoff, 24 Jan 2019.

Liu et al. IMpower133 LTS.
https://bit.ly/2Ywu0bI

Long-term survival

63/956 (6.6%) patients (44 men and 19 women) were alive after 2-year follow-up

Multivariate analysis of 2-year OS
Better ECOG, smoking habit,
Absence of liver, bone mts

Most (95.2%) were smokers/former
ECOG PS 0 (31.7%) or 1 (58.7%)

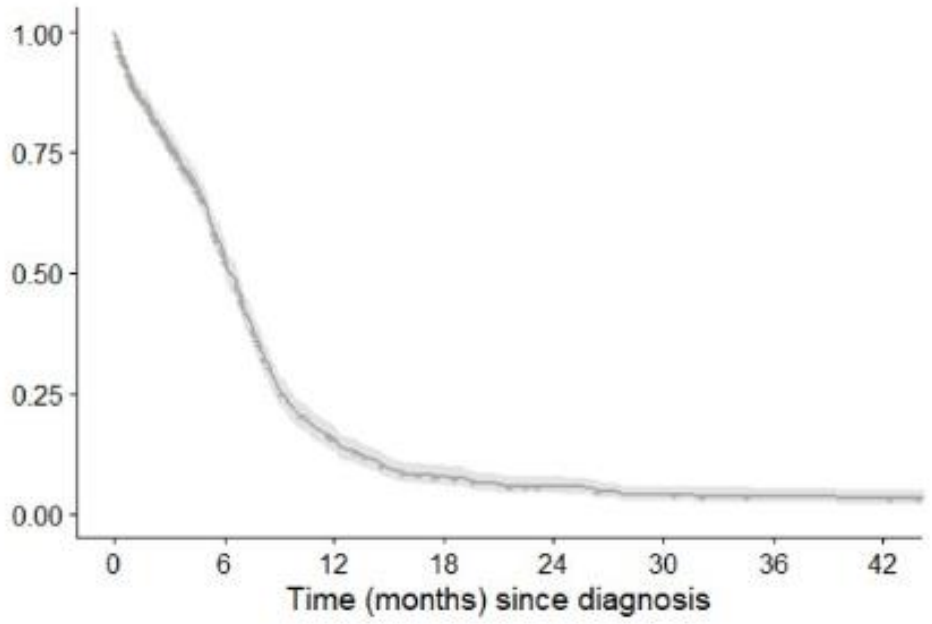
Higher proportion received Carbo-E
than Cis-E (63.5% vs 31.7%)

	2-year OS rate (%)	95% CI	p-value
Sex			0.077
Male	13.4	10.5-17.1	
Female	20.3	14.1-29.0	
Age			0.117
<65 years	17.2	12.9-21.9	
≥65 years	12.4	8.8-16.6	
ECOG			**0.001**
0	23.0	15.9-30.9	
1	14.9	11.1-19.2	
≥2	6.7	3.3-11.8	
Smoking habit			**0.004**
Never/former smoker	20.7	15.6-26.3	
Smoker	11.5	8.3-15.2	
Metastasis			
Liver	9.2	5.9-13.3	**0.001**
Bone	9.7	6.1-14.4	**0.012**
Thoracic adenopathy	9.6	5.5-15.1	**0.031**
Lung	14.3	8.8-21.0	0.850
Extrathoracic adenopathy	13.3	7.9-20.0	0.594
Adrenal	10.6	6.1-16.5	0.117
CNS	11.9	6.4-19.3	0.367
Pleural effusion	11.8	6.2-19.3	0.360
Treatment			0.078
Carboplatin + Etoposide VP16	14.3	10.8-18.4	
Cisplatin + Etoposide VP16	21.0	14.8-28.0	

SMALL CELL LUNG CANCER

RTT: Small Cell Lung Cancer

RTT: Long-term survival
63/956 (6.6%) patients (44 men and 19 women) were alive after 2-year follow-up

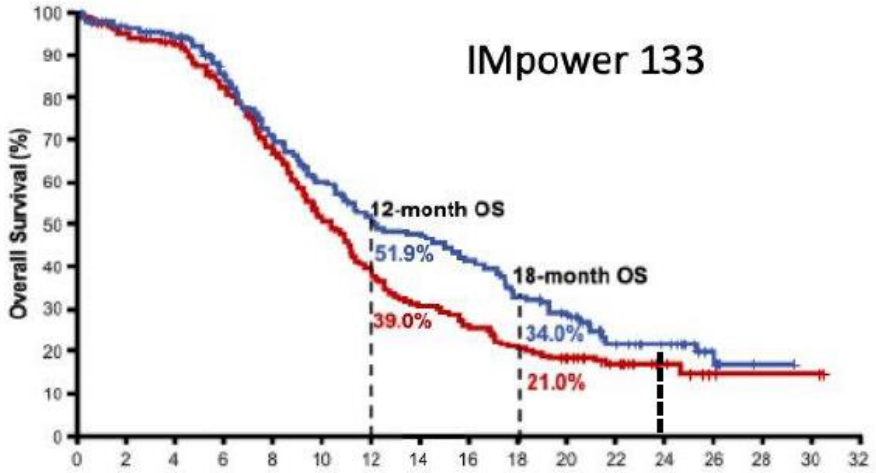


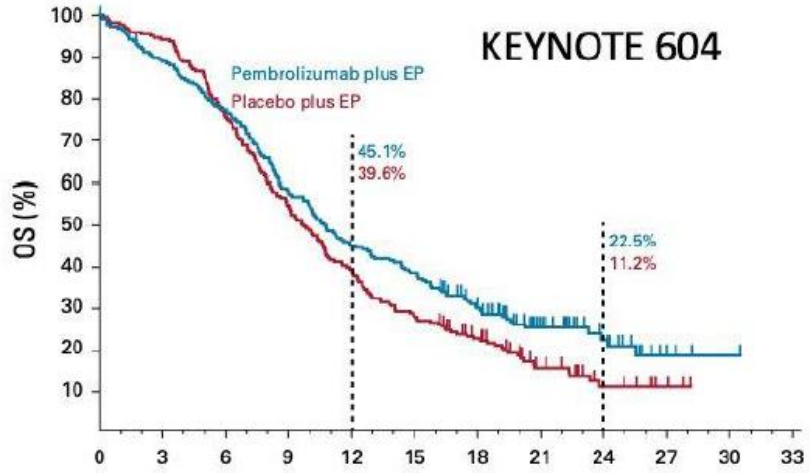
% Survival	Subgroups		
	LD and ED SCLC	LD-SCLC	ED-SCLC
6 months	68.09%	88.70%	**65.36%**
12 months	30.92%	57.98%	**29.37%**
24 months	8.08%	21.09%	**6.93%**

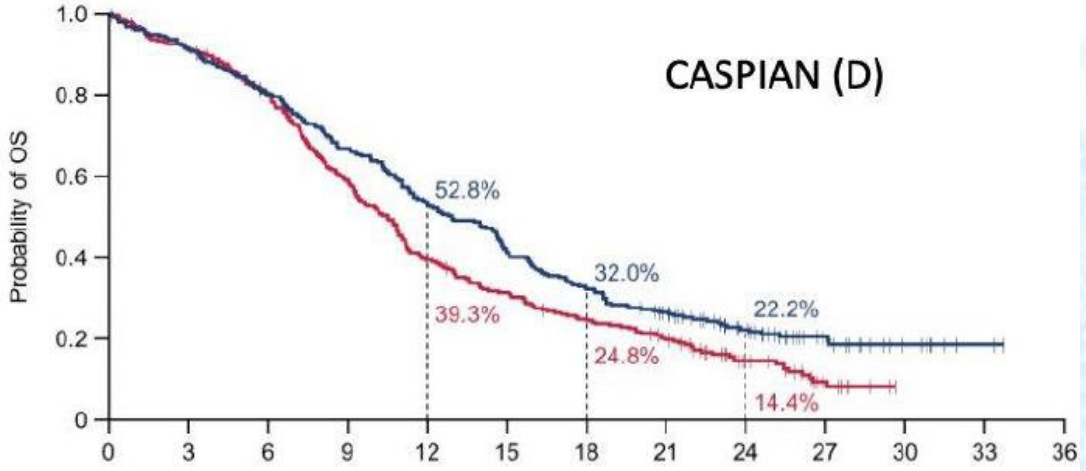
Survival data from 32 randomized studies analyzed 6075 SCLC patients; 3036 treated with platinum-based chemotherapy and 3039 with non-platinum-based chemotherapy.

Amarasena IU, Chatterjee S, Walters JAE, Wood-Baker R, Fong KM. Cochrane Database of Systematic Reviews 2015, 8. Art. No.: CD006849. DOI: http://dx.doi.org/10.1002/14651858.CD006849.pub3

Phase III trials 1st line ES-SCLC: Comparison of Overall Survival







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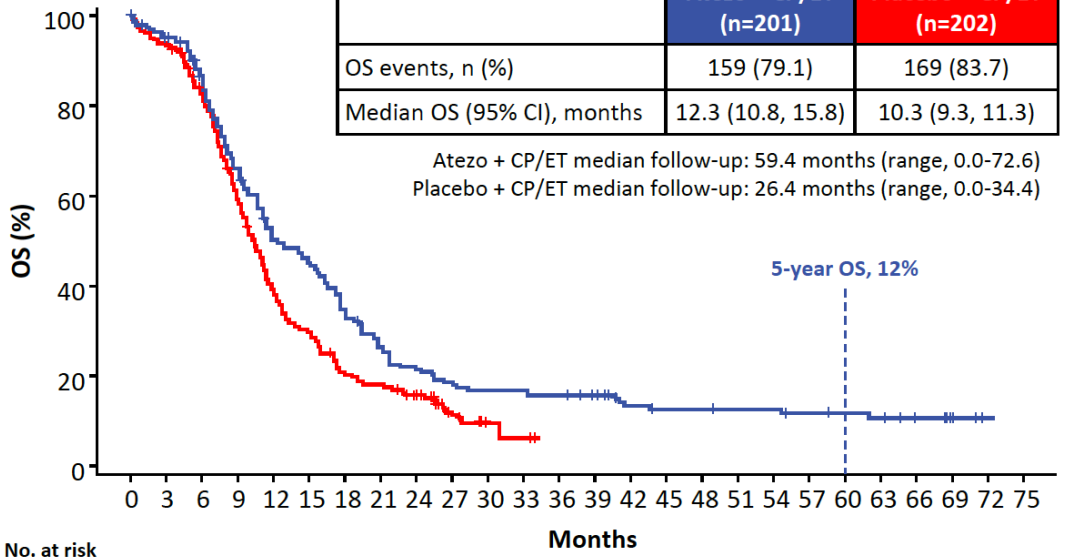
Probability of OS

Amarasena IU, Chatterjee S, Walters JAE, Wood-Baker R, Fong KM. Cochrane Database of Systematic Reviews 2015, 8. Art. No.: CD006849. DOI: http://dx.doi.org/10.1002/14651858.CD006849.pub3

IMpower133 and IMbrella A: long-term OS

	Atezo + CP/ET (n=201)	Placebo + CP/ET (n=202)
OS events, n (%)	159 (79.1)	169 (83.7)
Median OS (95% CI), months	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)

Atezo + CP/ET median follow-up: 59.4 months (range, 0.0-72.6)
Placebo + CP/ET median follow-up: 26.4 months (range, 0.0-34.4)



OS rate (95% CI), %	IMpower133 and IMbrella A Atezo + CP/ET (n=201)	IMpower133 only Placebo + CP/ET (n=202)
1-year	52% (45-59)	39% (32-46)
2-year	22% (16-28)	16% (11-21)
3-year	16% (11-21)	NE[a]
4-year	13% (8-18)	NE[a]
5-year	12% (7-17)	NE[a]

Clinical cutoff date: 16 March 2023. NE, not estimable. [a] OS rates were NE in the control arm as rollover to IMbrella A was not permitted.

% Survival	Subgroups		
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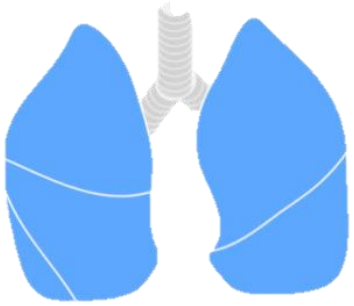


Patients who experience progression > 90 days: platinum-sensitive

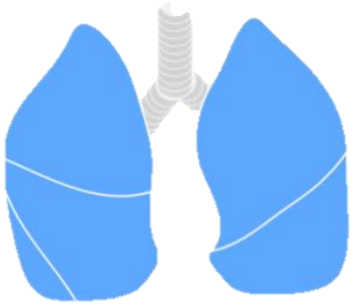
- PFS 4.7 m (platinum) vs 2.7 m (topetecan); ORR: 49% vs 25%. Not difference OS

Baize N et al. Lancet Oncol 2020

Author	n	cycle	D1=	ORR	OS	
O'Brien	141	TOPO PO 2,3 X 5	D21	7%	25,9 w	p=0,010
		Best supportive care	-----	--	13,9 w	
Eckradt	309	TOPO IV 1,5 X 5	D21	21.9%	35 w	p=0,98
		TOPO PO 2,3 X 5	D21	18.3%	33 w	
V.Pawel	311	**TOPO IV** 1,5 X 5	D21	24%	25 w	p=0,79
		CAV	D21	18%	24,7 w	

SMALL CELL LUNG CANCER

Recurrent disease



CNS mets excluded, one prior chemotherapy

Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial

José Trigo*, Vivek Subbiah*, Benjamin Besse, Victor Moreno, Rafael López, María Angeles Sala, Solange Peters, Santiago Ponce, Cristian Fernández, Vicente Alfaro, Javier Gómez, Carmen Kahatt, Ali Zeaiter, Khalil Zaman, Valentina Boni, Jennifer Arrondeau, Maite Martínez, Jean-Pierre Delord, Ahmad Awada, Rebecca Kristeleit, María Eugenia Olmedo, Luciano Wannesson, Javier Valdivia, María Jesús Rubio, Antonio Anton, John Sarantopoulos, Sant P Chawla, Joaquín Mosquera-Martínez, Manolo D'Arcangelo, Armando Santoro, Victor M Villalobos, Jacob Sands, Luis Paz-Ares

Summary

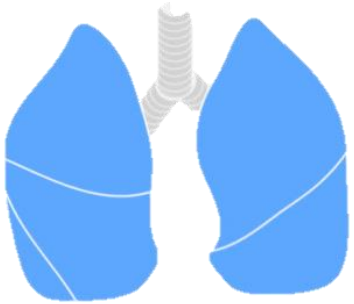
Background Few options exist for treatment of patients with small-cell lung cancer (SCLC) after failure of first-line Lancet Oncol 2020; 21: 645-54

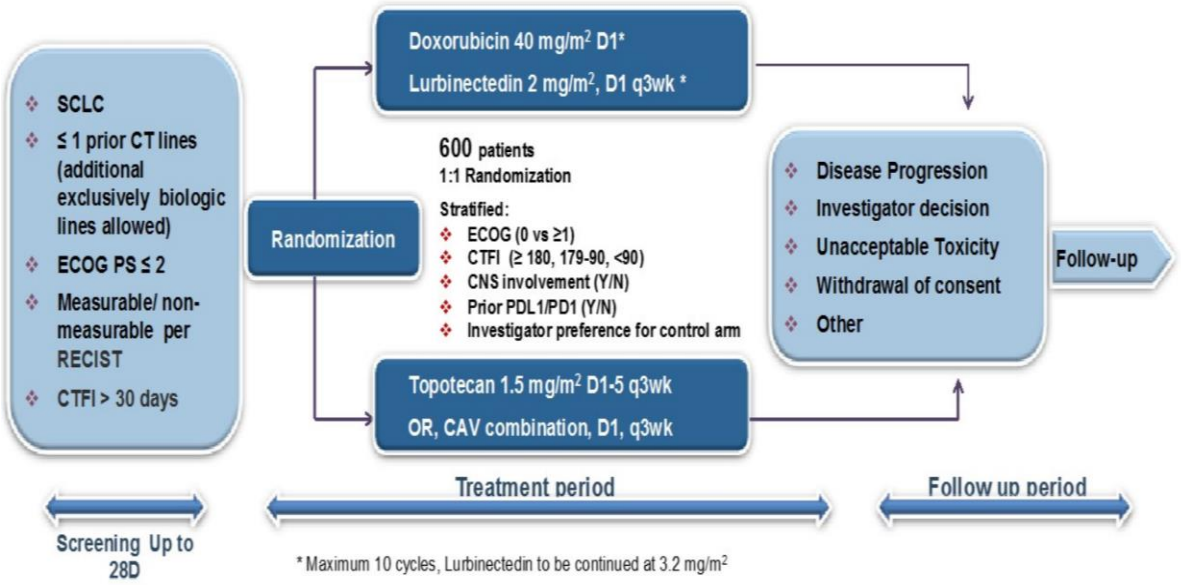
	All patients (n=105)	Chemotherapy-free interval <90 days (n=45)	Chemotherapy-free interval ≥90 days (n=60)
RECIST responses			
Complete response	0	0	0
Partial response	37 (35%)	10 (22%)	27 (45%)
Stable disease*	35 (33%)	13 (29%)	22 (37%)
Progressive disease	28 (27%)	18 (40%)	10 (17%)
Not evaluable†	5 (5%)	4 (9%)	1 (2%)
Overall response, % (95% CI)	35·2% (26·2–45·2)	22·2% (11·2–37·1)	45·0% (32·1–58·4)
Disease control, % (95% CI)‡	68·6% (58·8–77·3)	51·1% (35·8–66·3)	81·7% (69·6–90·5)
Duration of response			
Disease progression, relapse, or death events in responding patients, n/N (%)	29/37 (78%)	9/10 (90%)	20/27 (74%)
Median duration of response, months	5·3 (4·1–6·4)	4·7 (2·6–5·6)	6·2 (3·5–7·3)
Patients still responding at 6 months	43·0% (25·6–60·5)	11·7% (0·0–33·1)	55·3% (34·5–76·0)
Progression-free survival			
Progression-free survival events, n (%)	90 (86%)	41 (91%)	49 (82%)
Median progression-free survival, months (95% CI)	3·5 (2·6–4·3)	2·6 (1·3–3·9)	4·6 (2·8–6·5)
4-month progression-free survival (95%CI)	46·6% (36·7–56·5)	29·1% (15·3–42·8)	59·9% (47·1–72·7)
6-month progression-free survival (95% CI)	32·9% (23·3–42·5)	18·8% (6·8–30·9)	43·5% (30·1–56·9)
Overall survival			
Deaths	66 (63%)	37 (82%)	29 (48%)
Median overall survival, months (95% CI)	9·3 (6·3–11·8)	5·0 (4·1–6·3)	11·9 (9·7–16·2)
6-month overall survival (95%CI)	67·1% (57·6–76·7)	45·8% (30·4–61·3)	83·6% (73·7–93·5)
12-month overall survival (95% CI)	34·2% (23·2–45·1)	15·9% (3·6–28·2)	48·3% (32·5–64·1)

FDA approval as second-line**….**confirmatory study**: LAGOON Trial**: Lurbi vs Topo vs Lurbi+ Irino…..¿?

SMALL CELL LUNG CANCER

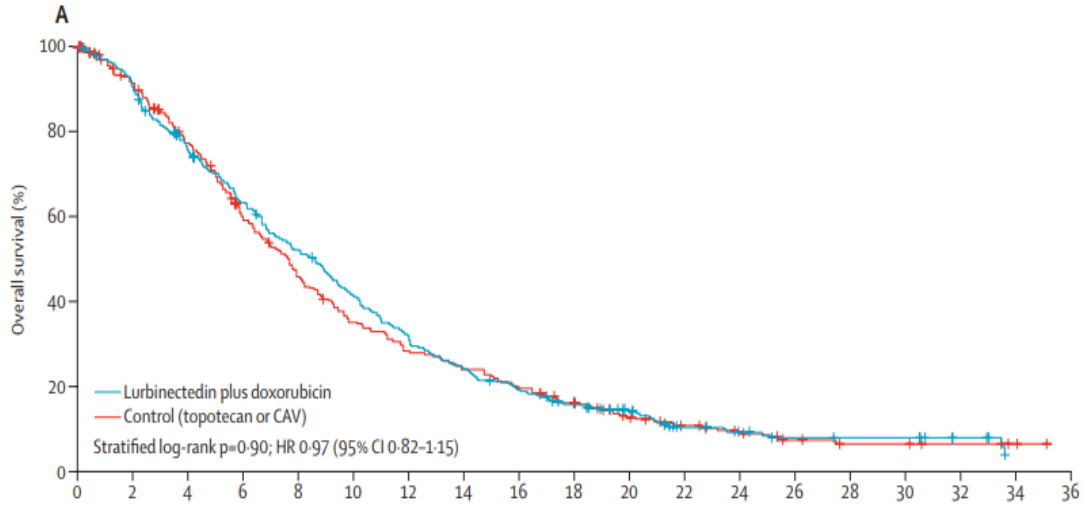
Recurrent disease



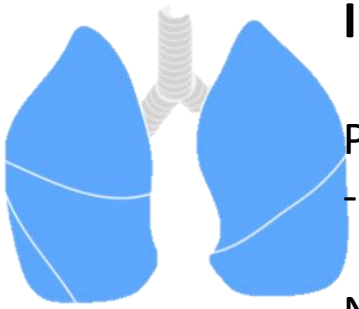


Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): a multicentre, randomised, open-label, phase 3 trial

Santiago Ponce Aix, Tudor Eliade Ciuleanu, Alejandro Navarro, Sophie Cousin, Laura Bonanno, Egbert F Smit, Alberto Chiappori,



Number at risk (number censored)																			
Lurbinectedin plus doxorubicin	307 (0)	277 (2)	227 (6)	188 (8)	155 (9)	122 (10)	91 (10)	71 (10)	56 (11)	43 (14)	32 (21)	18 (27)	14 (29)	10 (31)	9 (32)	9 (32)	6 (35)	0 (39)	0 (39)
Control (topotecan or CAV)	306 (0)	266 (15)	221 (19)	168 (23)	129 (24)	97 (25)	77 (25)	66 (25)	55 (25)	42 (28)	28 (34)	20 (38)	15 (41)	9 (44)	6 (46)	6 (46)	4 (48)	2 (50)	0 (52)



Immunotherapy

Pembro KN 028 Ott JCO 2017.

- ORR: 33.3%; mOS: 9.7 m; 37.7% OS 1-y

Nivolumab CM 032

- mOS: 4.4m; 27% OS 1-y; Antonia S Lancet oncol 2016

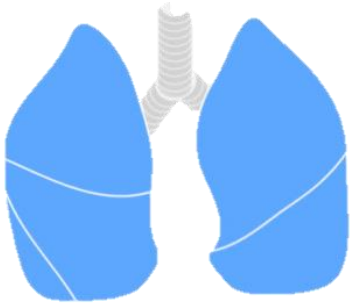
FDA (but not EMA) initially approved nivolumab in 2018 and pembrolizumab in 2019 as third-line treatments

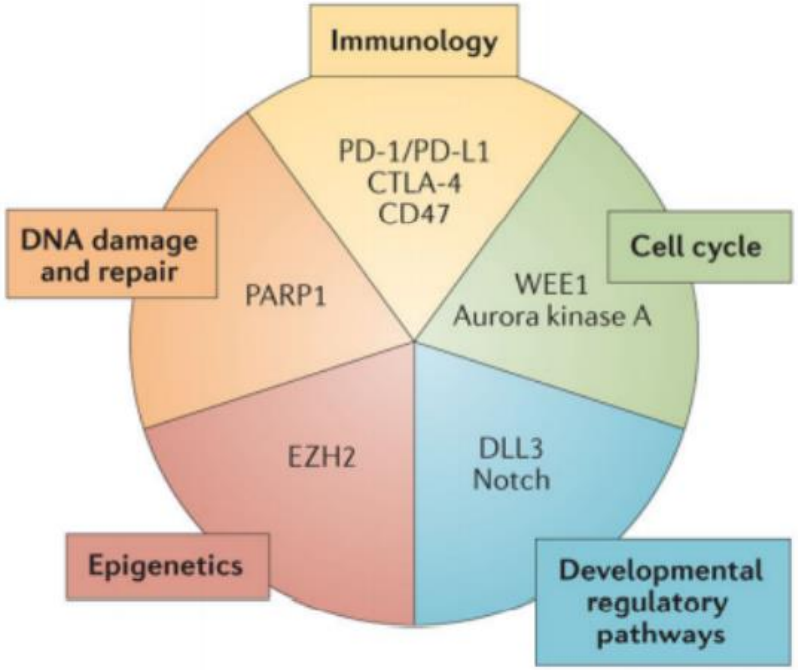
- Phase III confirmatory: did not show any survival benefit CM 331 (indication withdrawn)
  - Nivo vs Topotecan or amrubicin: mOS: 7.5 vs 8.4; OS 1-y: 37% vs 34% Spigel Ann Oncol 2021

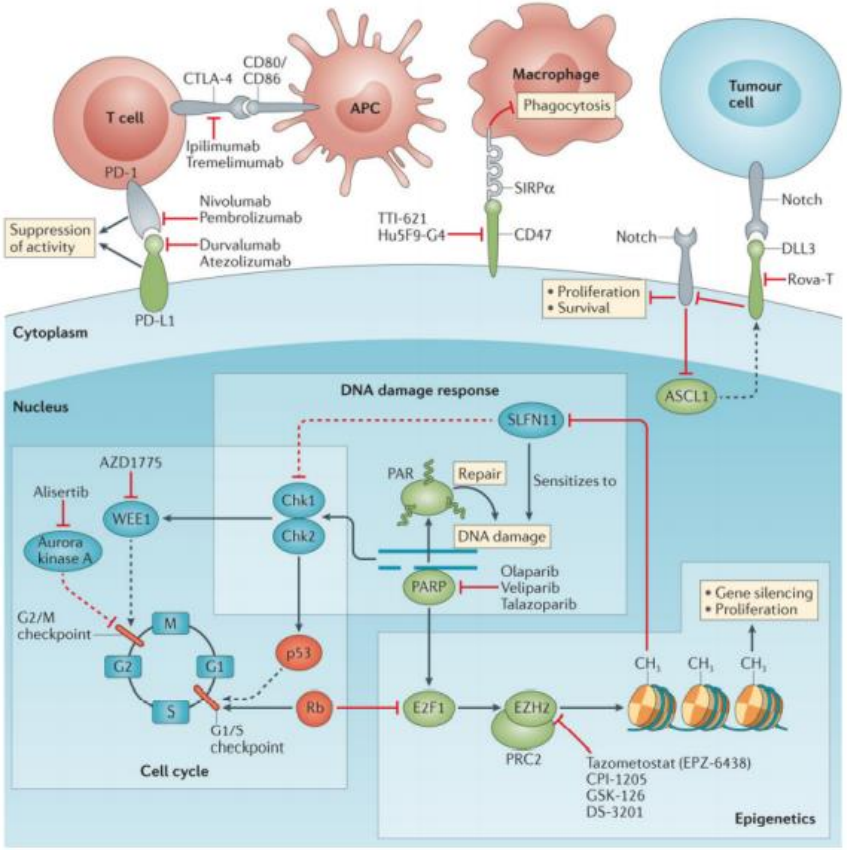
- Pembrolizumab remains an approved option

SMALL CELL LUNG CANCER

Emerging therapies

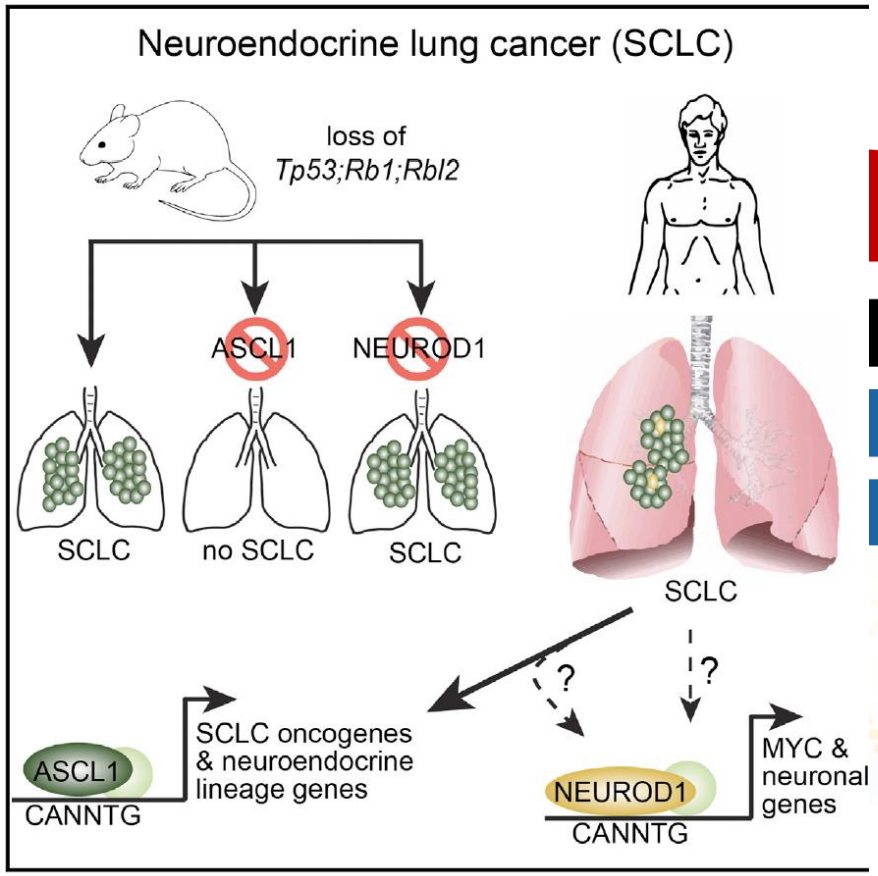


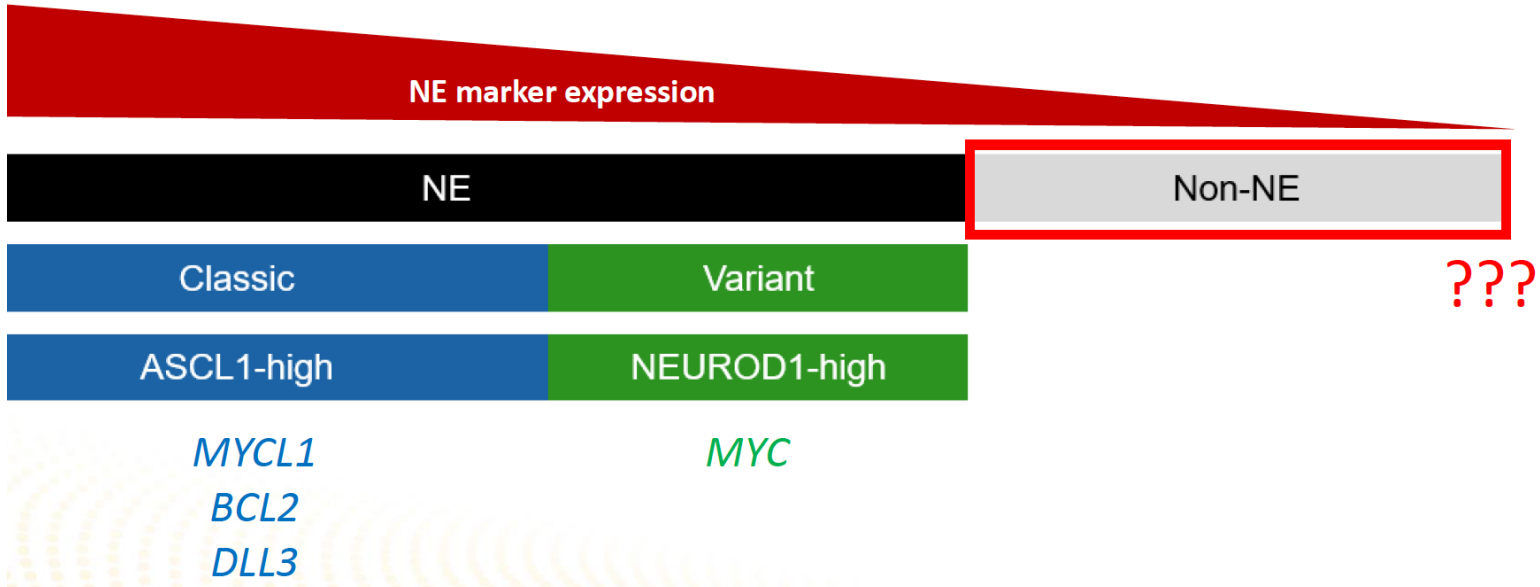




Sabari JK, et al. Nat Rev Clin Oncol 2017;14:549–61.

The treatment landscape for SCLC has remained largely unchanged since the introduction of chemotherapy

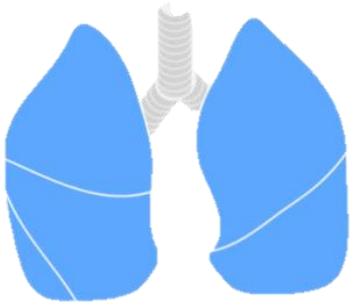


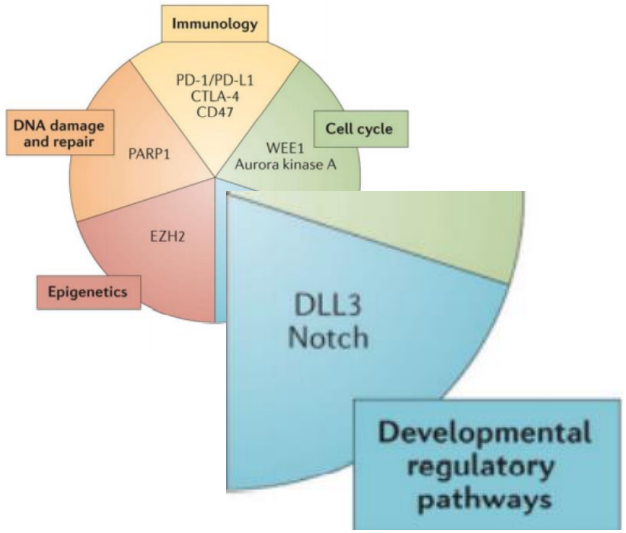


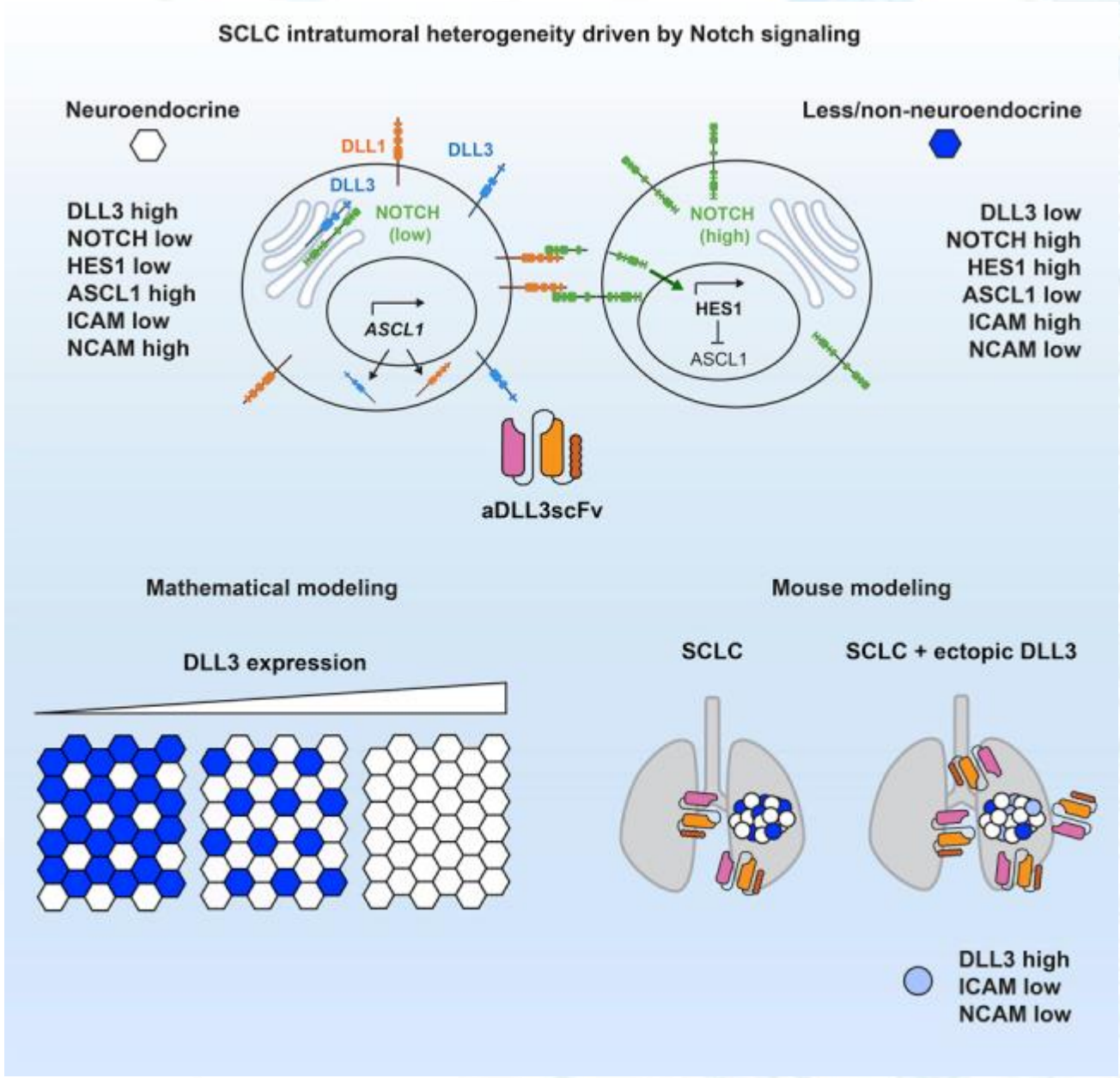
Rudin et al. Nat Rev Cancer 2019

SMALL CELL LUNG CANCER

Small Cell Lung Cancer, new hope ?



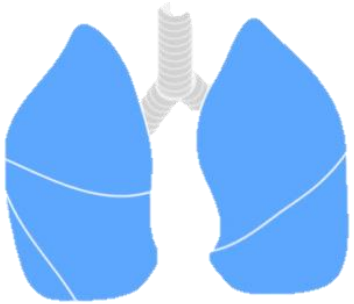




Kim Science 2022

SMALL CELL LUNG CANCER

Up to 85% of human SCLC tumors express the DLL3 protein on the cell surface



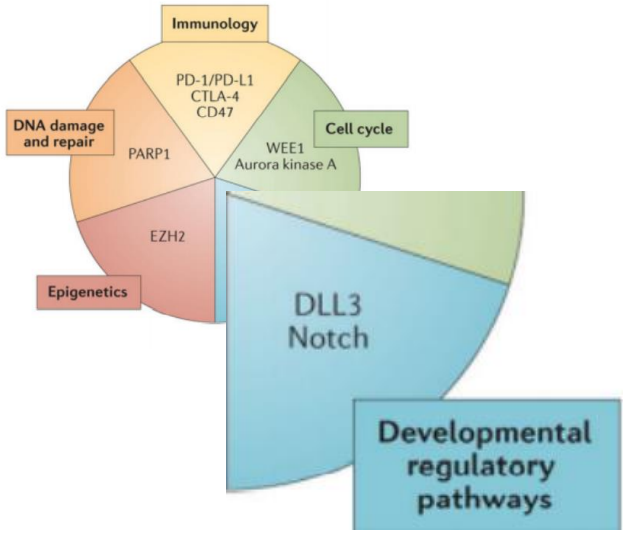


Table 1 Completed and ongoing clinical trials of DLL3-targeting therapies for SCLC[a]

Agent	Mechanism of action	Status[b]/trial identifier	Indications	Sponsor
ADCs				
Rovalpituzumab tesirine	ADC targeting DLL3	*Completed* NCT02674568 (phase 2) NCT01901653 (phase 1/2) NCT02874664 (phase 1) NCT03061812 (phase 3) NCT03086239 (phase 1) *Terminated or withdrawn* NCT02819999 (phase 1) NCT03026166 (phase 1/2) NCT03033511 (phase 3) NCT03334487 (phase 3) NCT02709889 (phase 1/2)	Relapsed/refractory/recurrent/extensive-stage/advanced/metastatic SCLC/delta-like protein 3–expressing advanced solid tumors	AbbVie/Stemcentrx
SC-002	ADC targeting DLL3	*Terminated* NCT02500914 (phase 1)	Relapsed SCLC or large cell NEC	Stemcentrx
CAR therapies				
DLL3-CAR-NK cells	Anti-DLL3–transduced NK cells	*Recruiting* NCT05507593 (phase 1)	Relapsed/refractory extensive-stage SCLC	Tianjin Medical University Cancer Institute and Hospital
AMG 119	Anti-DLL3–transduced autologous T cells	*Suspended* NCT03392064 (phase 1)	Relapsed/refractory SCLC	Amgen Inc
T-cell engagers				
Tarlatamab	Half-life–extended DLL3 x CD3 bispecific T-cell engager	*Recruiting* NCT03319940 (phase 1; DeLLphi-300) NCT05060016 (phase 2; DeLLphi-301) *Active, not recruiting* NCT04885998 (phase 1; DeLLphi-302) *Not yet recruiting* NCT05740566 (phase 3; Dellphi-304)	Relapsed/refractory SCLC	Amgen Inc
		Recruiting NCT05361395 (phase 1; DeLLphi-303)	First-line treatment for extensive-stage SCLC	
BI 764532	DLL3/CD3 T-cell–engaging bispecific antibody	*Recruiting* NCT04429087 (phase 1)	Refractory, DLL3-expressing SCLC and other neuroendocrine neoplasms	Boehringer Ingelheim
HPN328	Tri-specific recombinant protein construct	*Recruiting* NCT04471727 (phase 1/2)	Relapsed/refractory, advanced DLL3-expressing malignancies	Harpoon Therapeutics
RO7616789	DLL3 x CD3/CD137 multispecific antibody	*Recruiting* NCT05619744 (phase 1)	Relapsed extensive-stage SCLC or high-grade NEC of any other origin	Hoffmann-La Roche

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SMALL CELL LUNG CANCER

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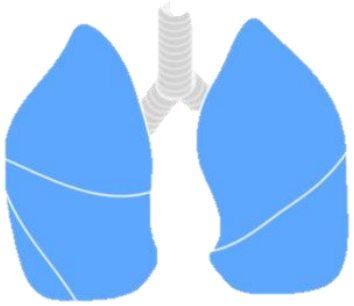

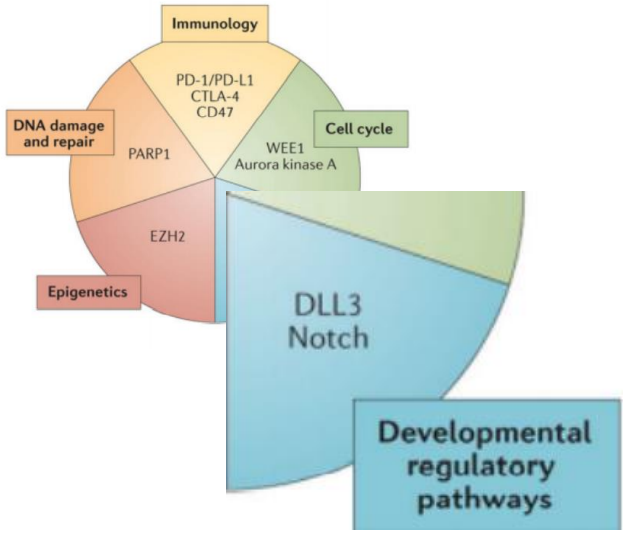

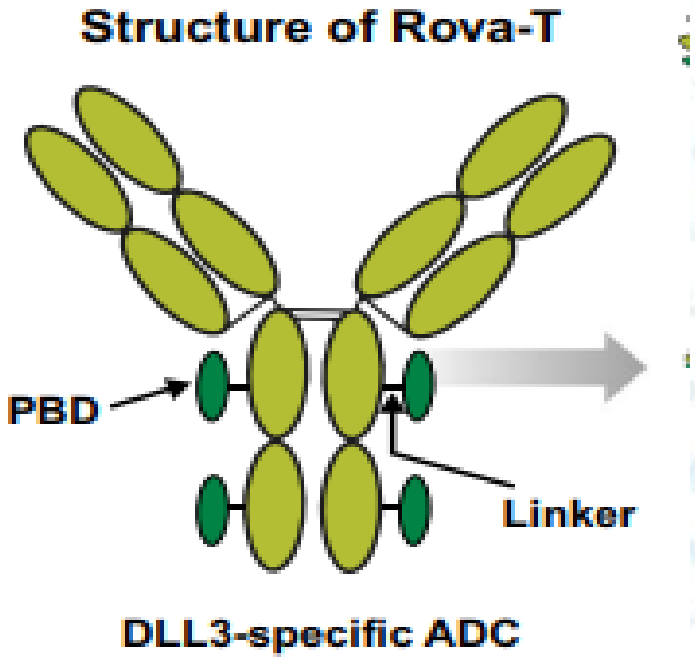

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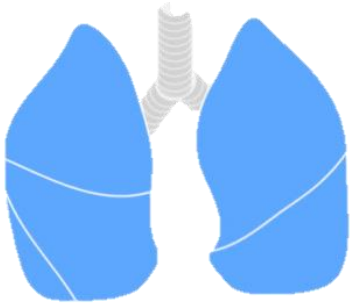

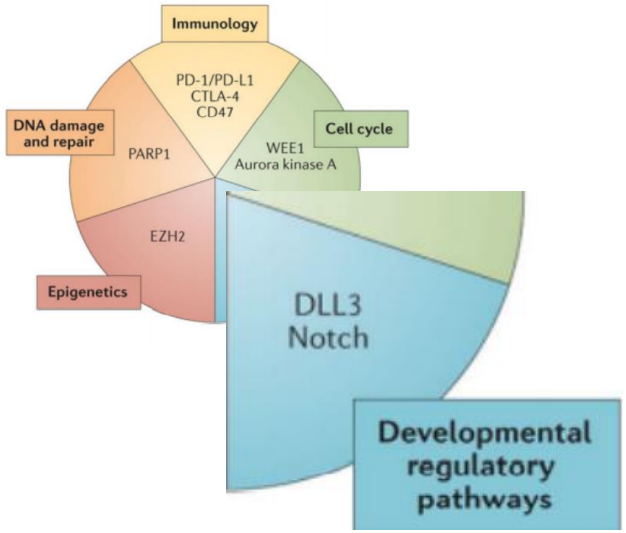

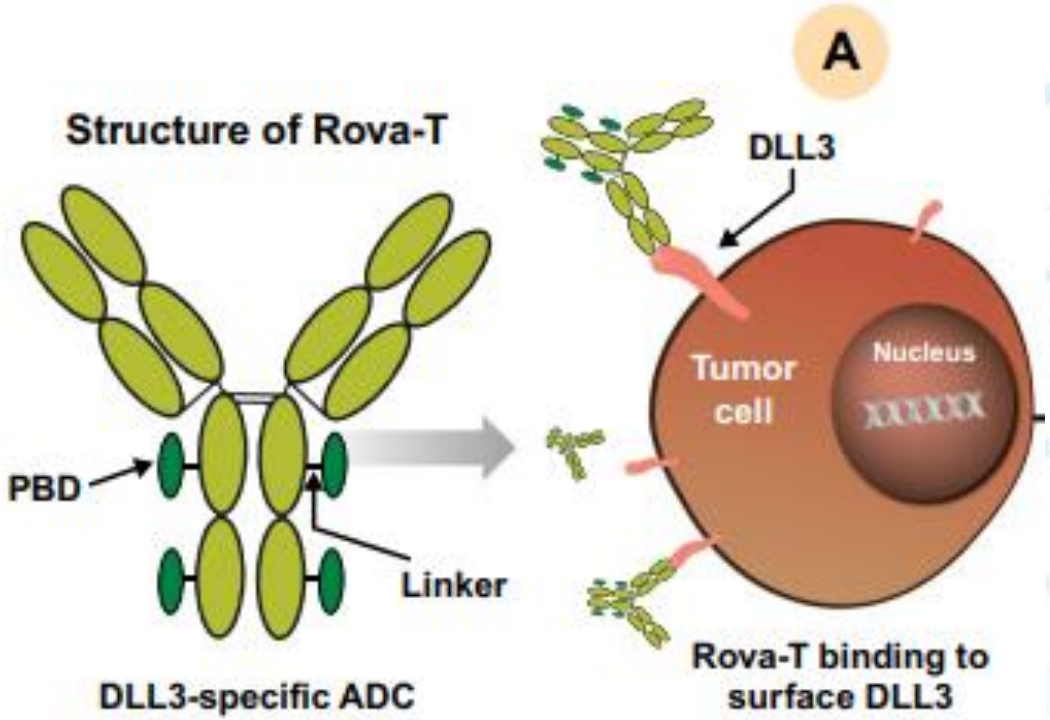

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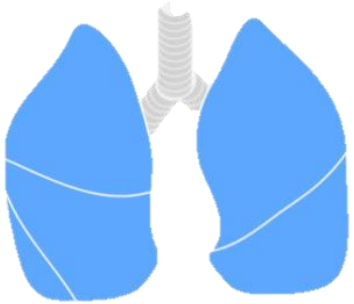

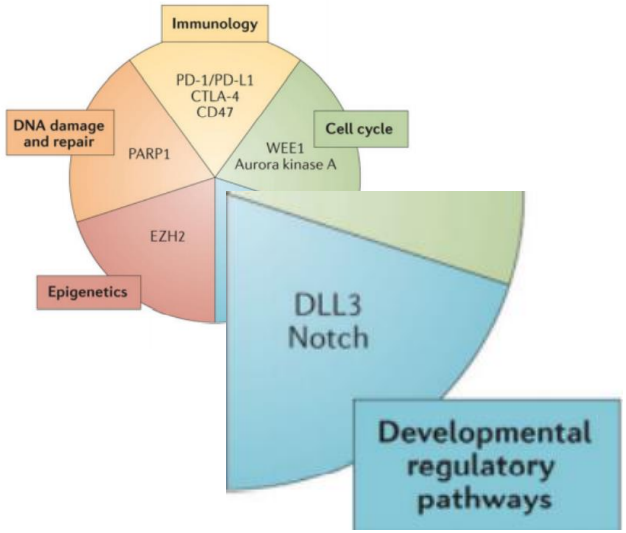

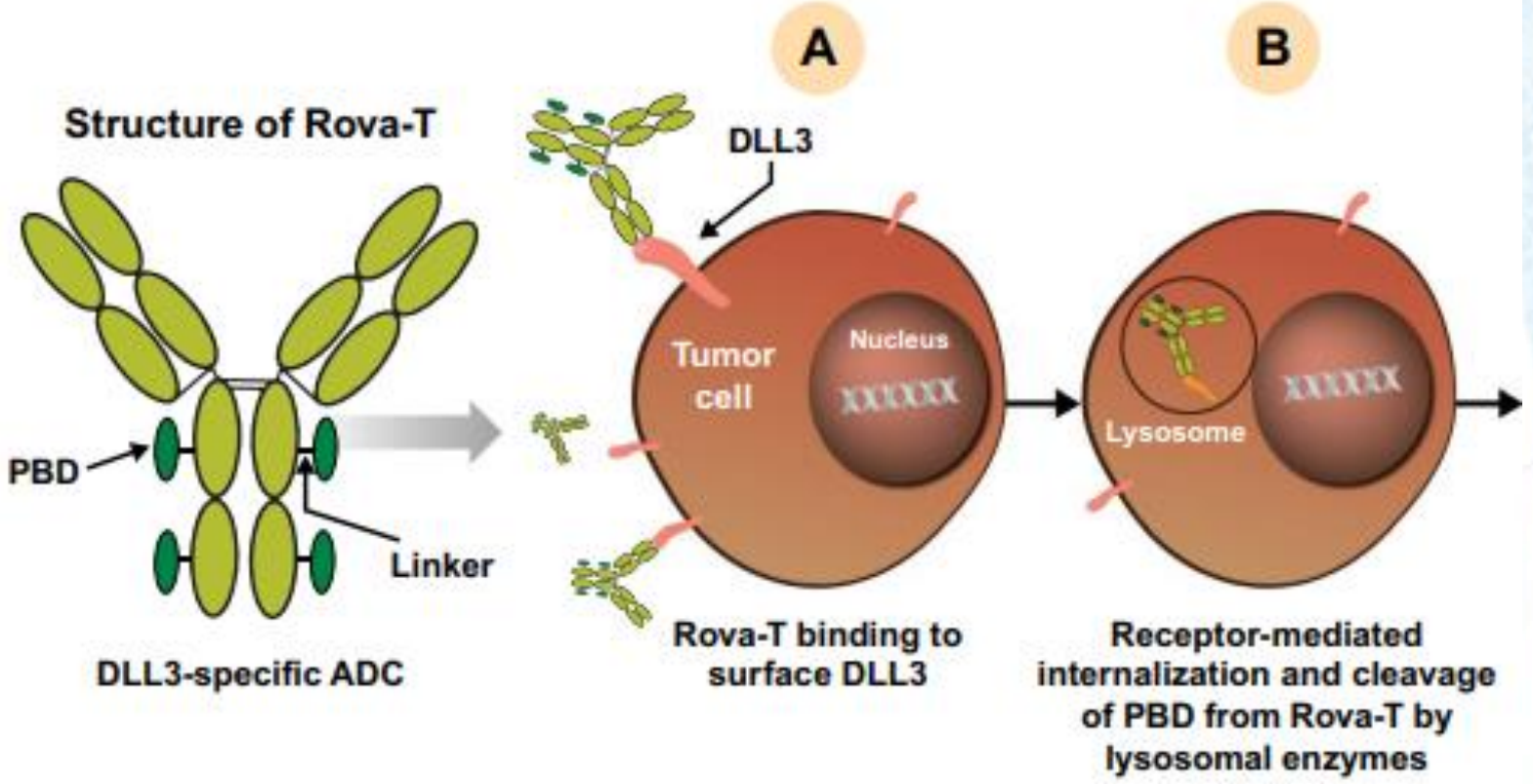

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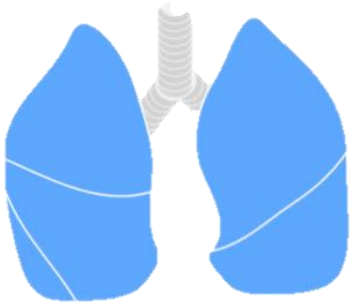

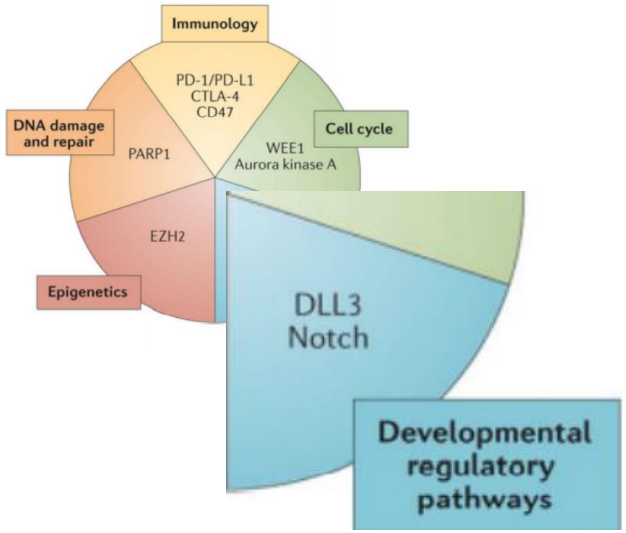

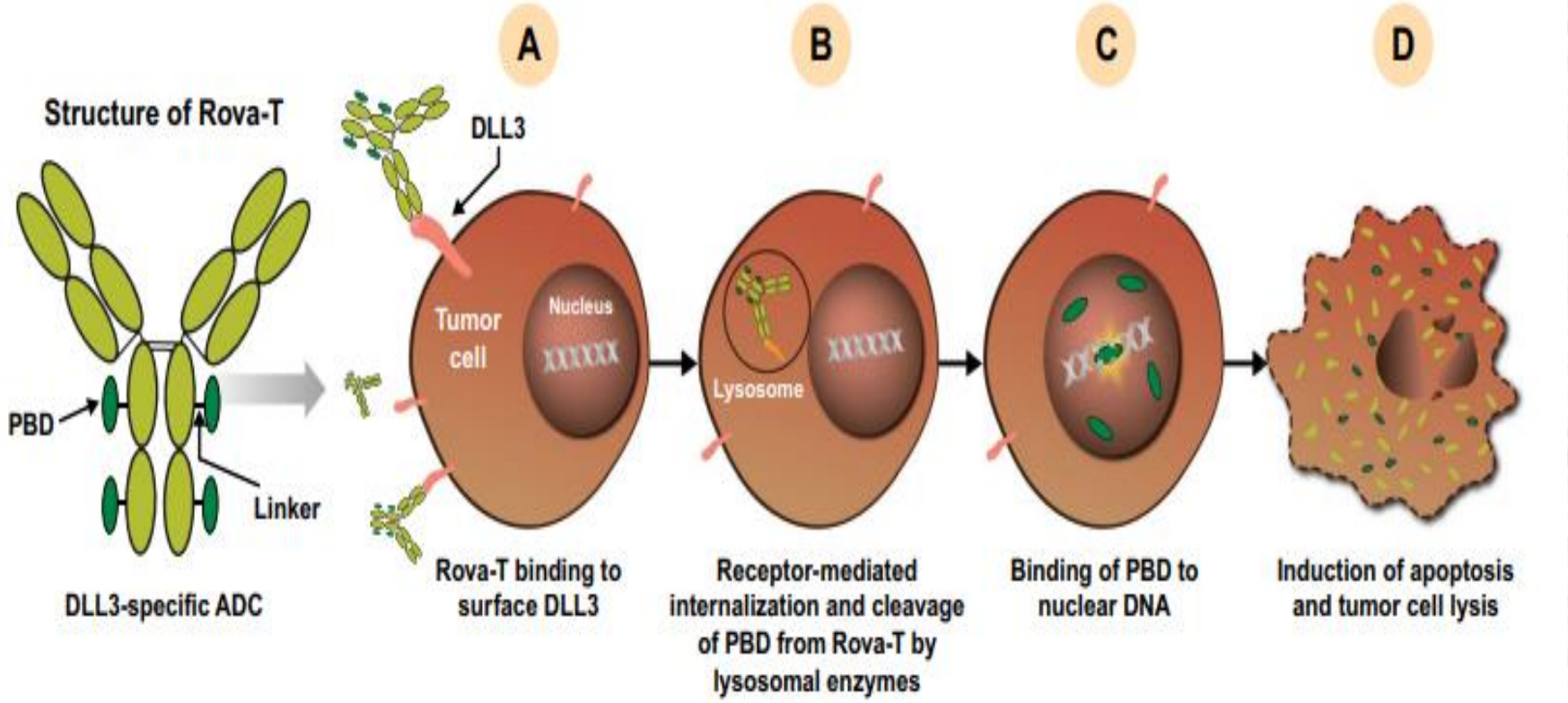

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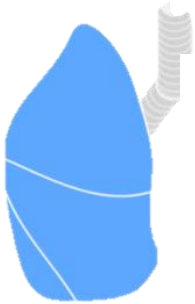
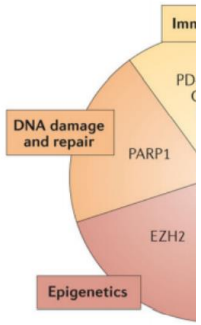
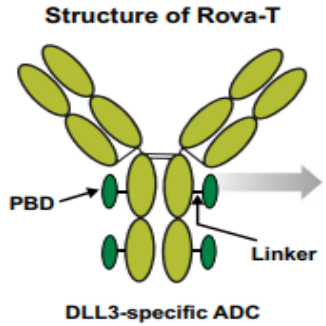
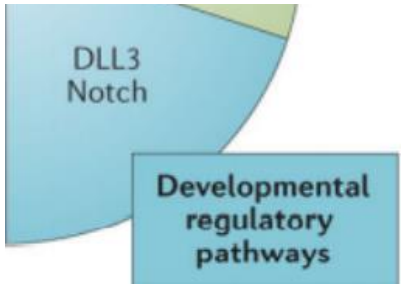




	Preclinical data	SCLC clinical program status[a]	Clinical safety	Clinical efficacy
Antibody-drug conjugates				
Rovalpituzumab tesirine (Rova-T)	In PDX models, mice treated with Rova-T demonstrated complete and durable responses against chemotherapy-resistant and recurrent tumors in contrast to mice treated with cisplatin and etoposide [17] In NHPs, Rova-T treatment was associated with reversible myelosuppression, mild kidney degeneration, and skin thickening and hyperpigmentation [17]	Administered to > 1000 patients across more than 10 studies, including two phase 3 studies Clinical development discontinued due to a lack of survival benefit in phase 3 studies	Results across multiple studies: Thrombocytopenia, pleural effusions, photosensitivity reactions, and anemia were the most frequently encountered TRAEs Toxicity attributed to the cytotoxic warhead—PBD Adverse events managed by dose reductions, treatment interruptions, treatment discontinuations, and symptom-specific management	Response rates of 12%–18% in the initial phase 1 and 2 studies [31, 33] Randomized phase 3 studies failed to show a benefit with Rova-T: Phase 3 TAHOE: Median OS: Rova-T (6.3 months) vs topotecan (8.6 months); ORR: Rova-T (15%) vs topotecan (21%) [6] Phase 3 MERU: OS: Rova-T (8.8 months) vs topotecan (9.9 months); ORR: Rova-T (9%) vs topotecan (4%) [35]





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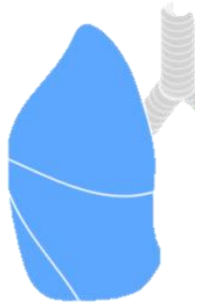
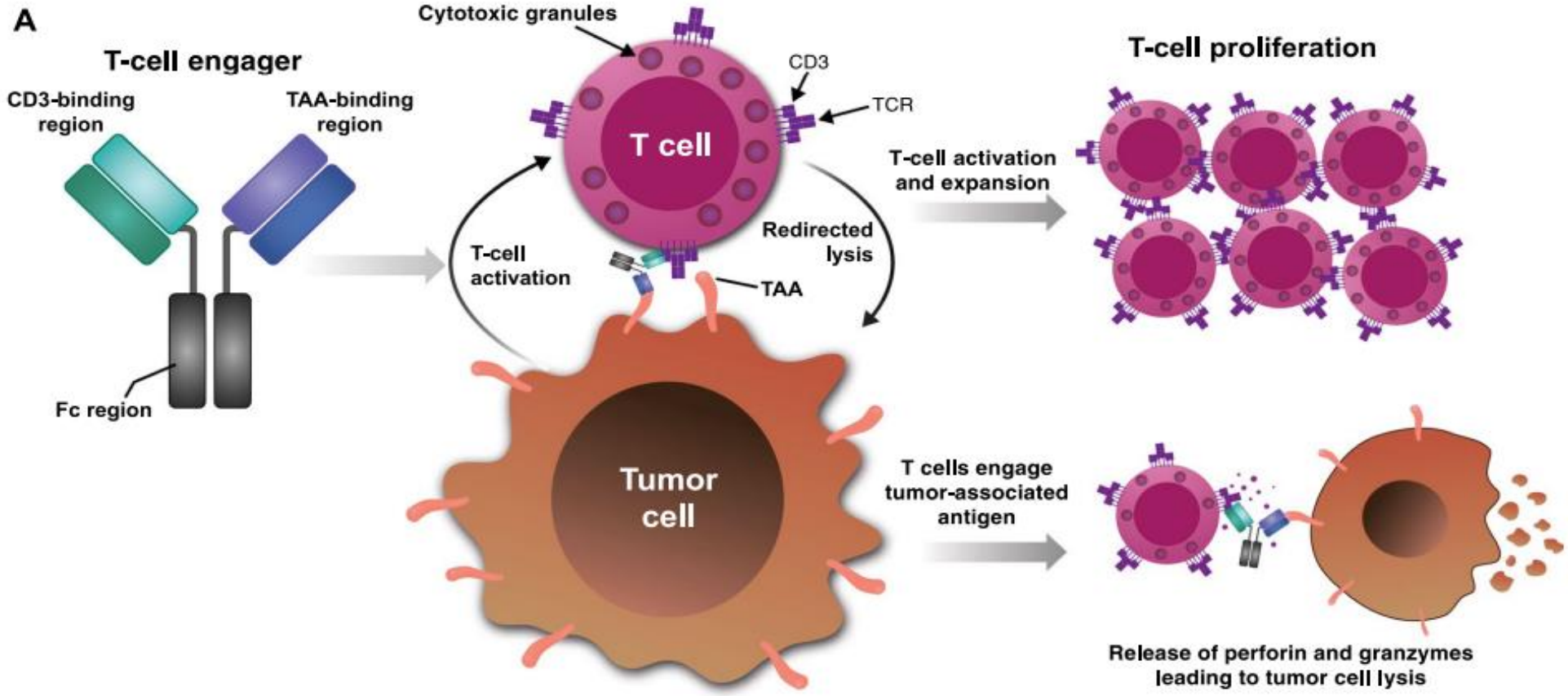
Rudin *et al. Journal of Hematology & Oncology* (2023) 16:66





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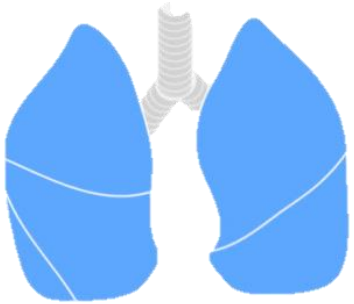

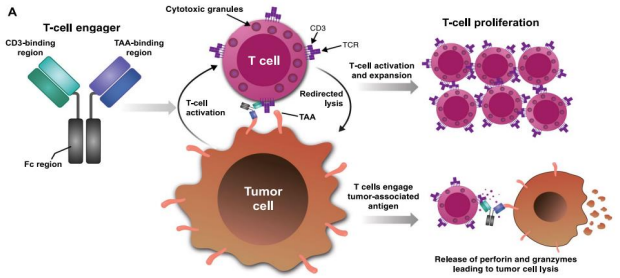

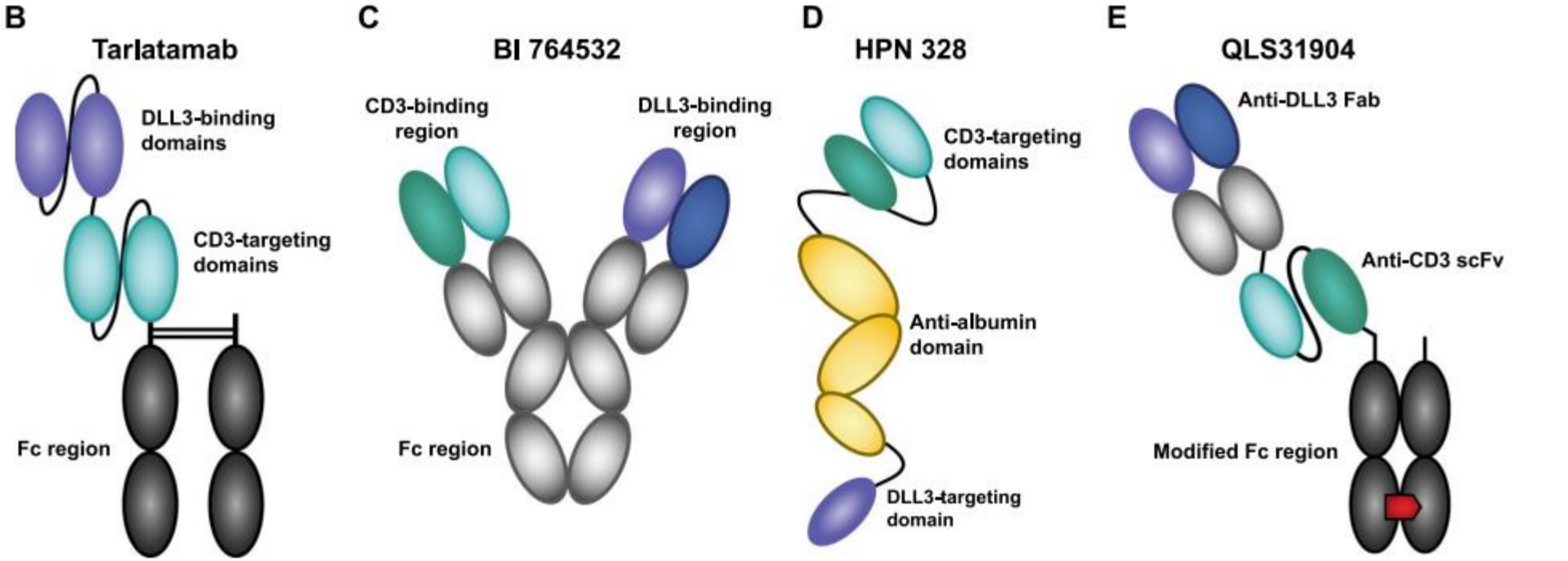

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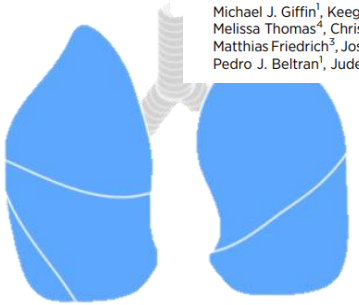
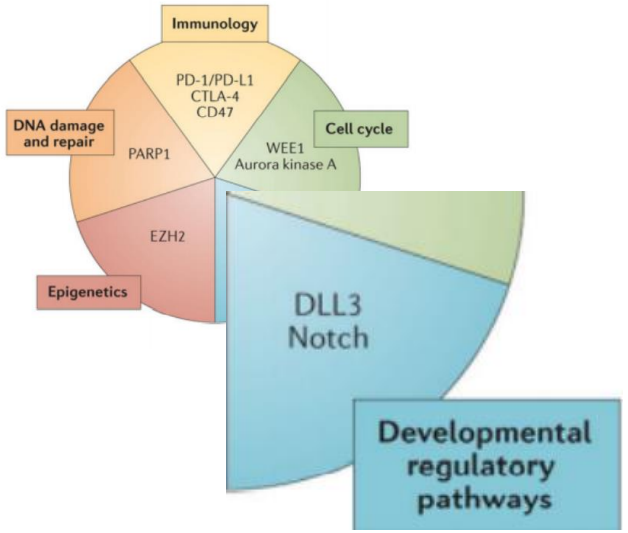
SMALL CELL LUNG CANCER

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

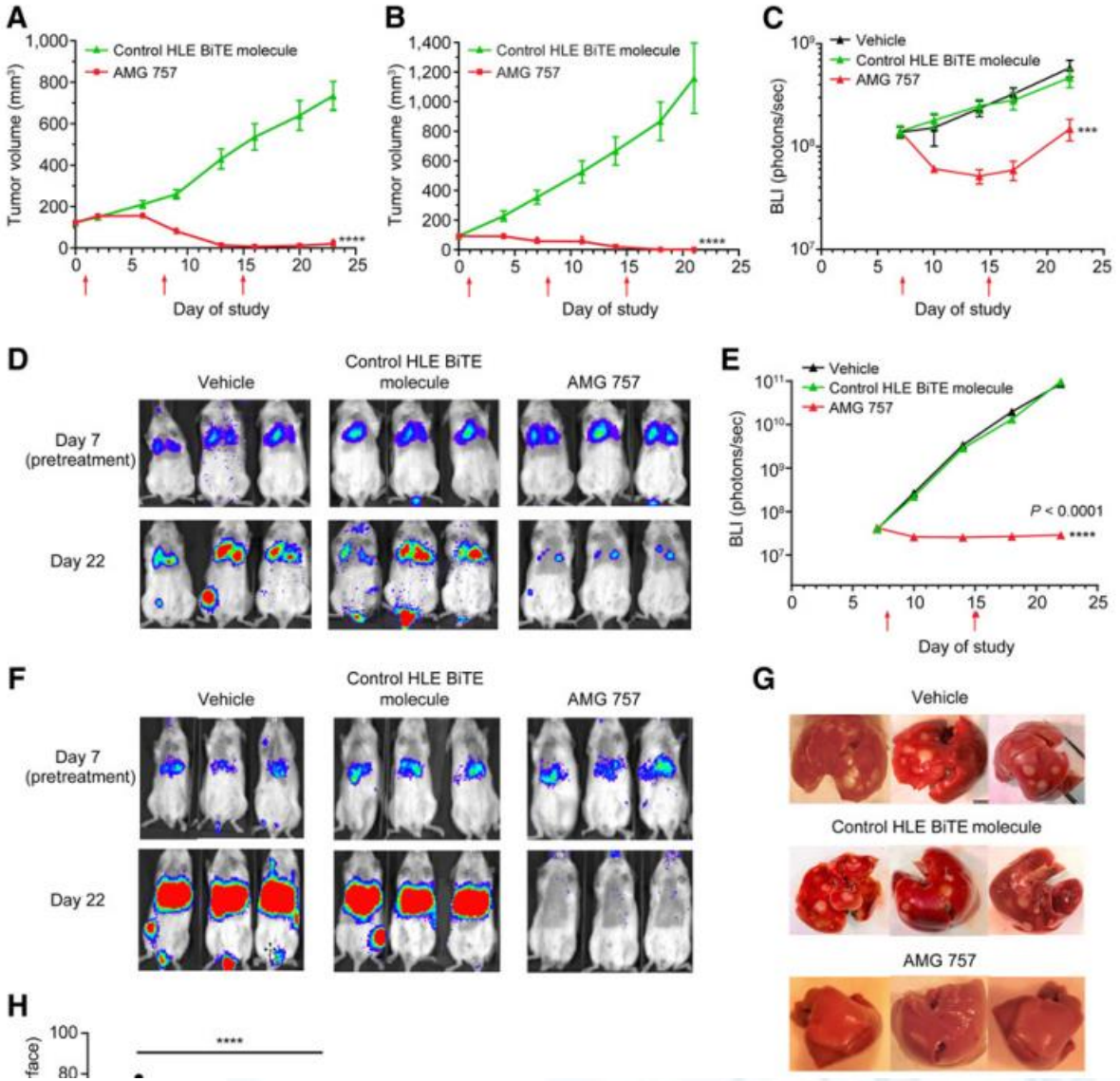
AMG 757, a Half-Life Extended, DLL3-Targeted Bispecific T-Cell Engager, Shows High Potency and Sensitivity in Preclinical Models of Small-Cell Lung Cancer

Michael J. Giffin[1], Keegan Cooke[1], Edward K. Lobenhofer[2], Juan Estrada[1], Jinghui Zhan[1], Petra Deegen[3], Melissa Thomas[4], Christopher M. Murawsky[5], Jonathan Werner[2], Siyuan Liu[1], Fei Lee[6], Oliver Homann[7], Matthias Friedrich[3], Joshua T. Pearson[8], Tobias Raum[9], Yajing Yang[1], Sean Caenepeel[1], Jennitte Stevens[10], Pedro J. Beltran[1], Jude Canon[1], Angela Coxon[1], Julie M. Bailis[6], and Paul E. Hughes[1]

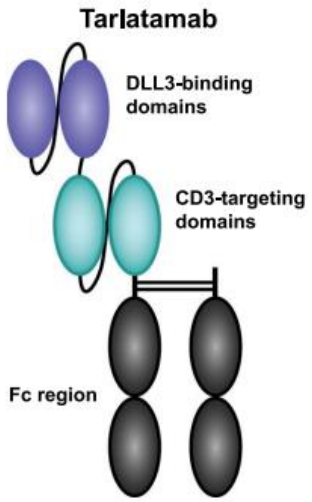




AMG 757 in Preclinical Models of Small-Cell Lung Cancer



SMALL CELL LUNG CANCER

	Preclinical data	SCLC clinical program status[a]	Clinical safety	Clinical efficacy
DLL3-targeting T-cell engagers				
Tarlatamab 	In PDX studies, tarlatamab caused significant tumor regression (83%–98%) and a significant reduction in tumor volume [59] In a disseminating orthotopic model of SCLC, tarlatamab-induced significant tumor growth inhibition at a low mg/kg weekly dose [59] In exploratory toxicology studies in NHPs, tarlatamab induced a transient increase in heart rate, a transient minor decrease in lymphocyte frequency, and a mild infiltration of lymphocytes and eosinophils into the pituitary [60]	Administered to > 100 patients in an ongoing FIH phase 1 study as second-line (and beyond) treatment for SCLC Phase 1 combination studies with anti–PD-1 and anti–PD-L1 (with or without platinum-etoposide) in ES-SCLC are ongoing Phase 2 study in SCLC is ongoing Phase 3 study comparing tarlatamab with SOC chemotherapy for patients with relapsed SCLC will begin patient recruitment shortly	Phase 1 (NCT03319940) results: TRAEs in 90.7%; grade ≥ 3 in 30.8% CRS (52.3%), pyrexia (37.4%), dysgeusia (22.4%), fatigue (21.5%), and nausea (19.6%) were the most commonly observed TRAEs Most CRS events occurred in the first treatment cycle and were managed with supportive care, corticosteroids, and tocilizumab when necessary Other adverse events of special interest (based on Amgen's MedDRA query narrow safety reporting definitions) included neurological events and neutropenia Treatment-related neurologic events, 49.5% (grade ≥ 3, 6.5%); treatment-related neutropenia, 15.9% (grade ≥ 3, 9.3%)	Results from the phase 1 study: Confirmed ORR of 23.4% (including two [1.9%] complete responses and 23 [21.5%] partial responses) Disease control rate of 51.4% Median duration of response of 12.3 months Median PFS of 3.7 months and median OS of 13.2 months

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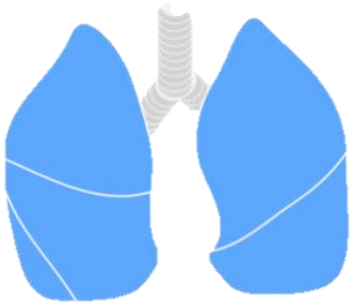
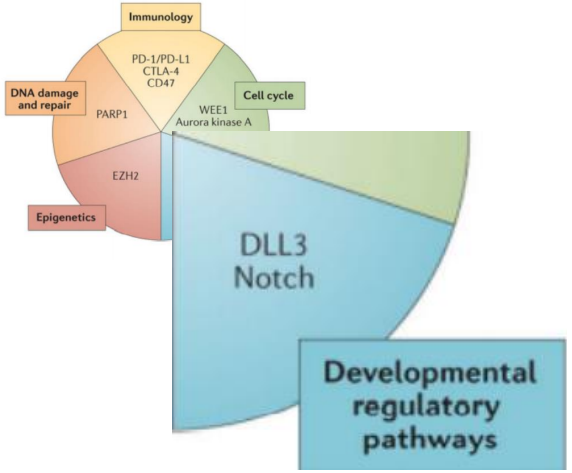
Tarlatamab: New Star on the Horizon for Small-Cell Lung Cancer?





rapid communications abstract

Tarlatamab, a First-in-Class DLL3-Targeted Bispecific T-Cell Engager, in Recurrent Small-Cell Lung Cancer: An Open-Label, Phase I Study

Luis Paz-Ares, MD, PhD[1]; Stephane Champiat, MD, PhD[2]; W. Victoria Lai, MD[3]; Hiroki Izumi, MD, PhD[4]; Ramaswamy Govindan, MD[5]; Michael Boyer, MB, BS, PhD[6]; Horst-Dieter Hummel, MD[7]; Hossein Borghaei, DO[8]; Melissa L. Johnson, MD[9]; Neeltje Steeghs, MD, PhD[10]; Fiona Blackhall, MD, PhD[11]; Afshin Dowlati, MD[12]; Noemi Reguart, MD, PhD[13]; Tatsuya Yoshida, MD, PhD[14]; Kai He, MD, PhD[15]; Shirish M. Gadgeel, MD[16]; Enriqueta Felip, MD, PhD[17]; Yiran Zhang, PhD[18]; Amrita Pati, PhD[18]; Mukul Minocha, PhD[18]; Sujoy Mukherjee, MD[18]; Amanda Goldrick, MD[18]; Dirk Nagorsen, MD, PhD[18]; Nooshin Hashemi Sadraei, MD[18]; and Taofeek K. Owonikoko, MD, PhD[19]

PURPOSE Small-cell lung cancer (SCLC) is an aggressive malignancy with limited treatments. Delta-like ligand 3 (DLL3) is aberrantly expressed in most SCLC. Tarlatamab (AMG 757), a bispecific T-cell engager molecule, binds both DLL3 and CD3 leading to T-cell–mediated tumor lysis. Herein, we report phase I results of tarlatamab in patients with SCLC.

PATIENTS AND METHODS This study evaluated tarlatamab in patients with relapsed/refractory SCLC. The primary end point was safety. Secondary end points included antitumor activity by modified RECIST 1.1, overall survival, and pharmacokinetics.

RESULTS By July 19, 2022, 107 patients received tarlatamab in dose exploration (0.003 to 100 mg; n = 73) and expansion (100 mg; n = 34) cohorts. Median prior lines of anticancer therapy were 2 (range, 1-6); 49.5% received antiprogrammed death-1/programmed death ligand-1 therapy. Any-grade treatment-related adverse events occurred in 97 patients (90.7%) and grade ≥ 3 in 33 patients (30.8%). One patient (1%) had grade 5 pneumonitis. Cytokine release syndrome was the most common treatment-related adverse event, occurring in 56 patients (52%) including grade 3 in one patient (1%). Maximum tolerated dose was not reached. Objective response rate was 23.4% (95% CI, 15.7 to 32.5) including two complete and 23 partial responses. The median duration of response was 12.3 months (95% CI, 6.6 to 14.9). The disease control rate was 51.4% (95% CI, 41.5 to 61.2). The median progression-free survival and overall survival were 3.7 months (95% CI, 2.1 to 5.4) and 13.2 months (95% CI, 10.5 to not reached), respectively. Exploratory analysis suggests that selecting for increased DLL3 expression can result in increased clinical benefit.

CONCLUSION In patients with heavily pretreated SCLC, tarlatamab demonstrated manageable safety with encouraging response durability. Further evaluation of this promising molecule is ongoing.

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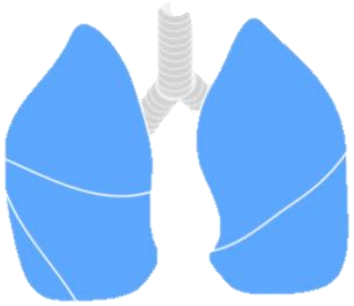
Prior lines of therapy	
Median (IQR)	2.0 (1.0-3.0)
1, No. (%)	30 (28)
2, No. (%)	45 (42)
≥ 3, No. (%)	32 (30)
Most recent line platinum-treated patients, No. (%)	
Platinum-sensitive	54 (50)
Platinum-resistant	22 (21)
Platinum-refractory	26 (24)
Not assessable/missing	4 (4)
Prior radiotherapy, No. (%)	
Yes	85 (79)
No	22 (21)
Prior anti–PD-1 or anti–PD-L1, No. (%)	
Yes	53 (50)
No	54 (50)

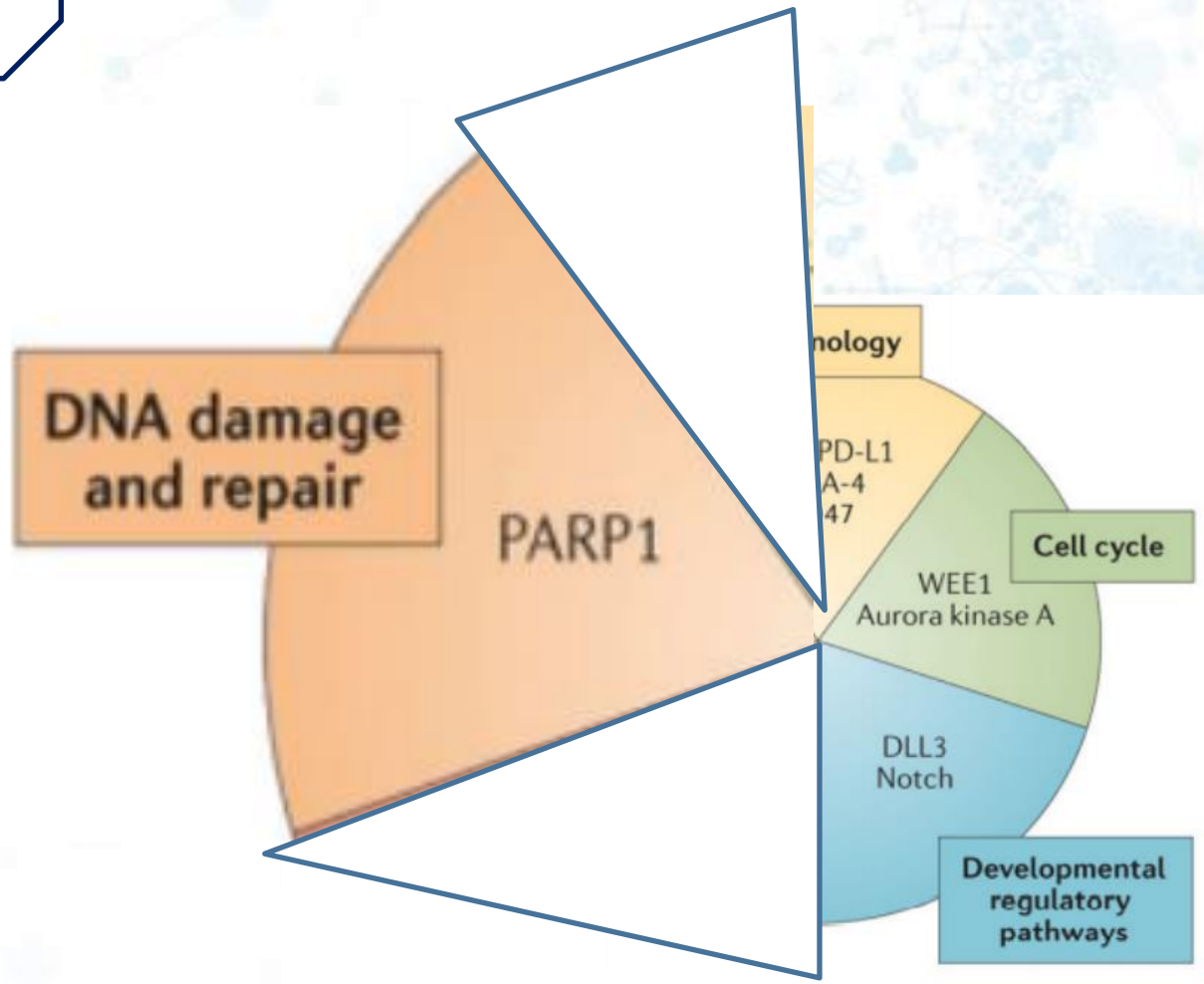
TABLE 3. Tumor Response to Tarlatamab According to Investigator Assessment

Response	Interim Efficacy Analysis Set[a] (N = 107)
ORR, % (95% CI)	
Confirmed	23 (15.7 to 32.5)
Confirmed and unconfirmed	25 (17.3 to 34.6)
Disease control rate, % (95% CI)	51 (41.5 to 61.2)
Best overall response, No. (%)	
Confirmed complete response	2 (2)
Confirmed partial response	23 (22)
Stable disease	30 (28)
Progressive disease	9 (8)
Could not be evaluated[b]	34 (32)
No assessment[c]	9 (8)
TTR, months, median (IQR)	1.81 (1.68-1.91)
Duration of objective response months, median (95% CI)	12.3 (6.6 to 14.9)

SMALL CELL LUNG CANCER

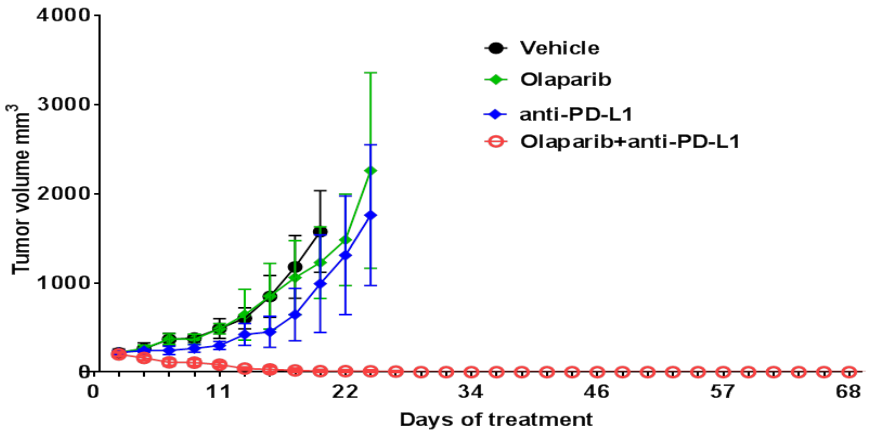
Emerging therapies

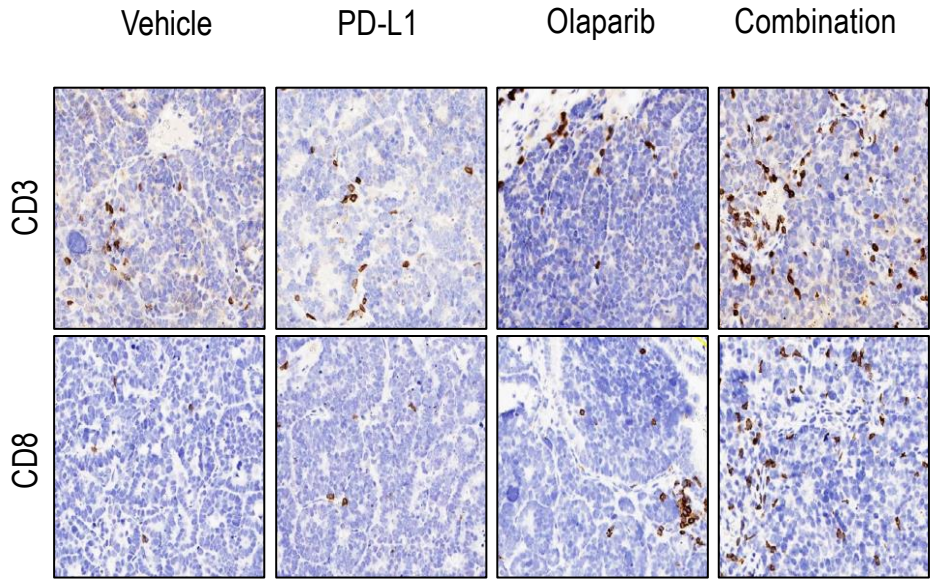




Targeting DNA damage response promotes anti-tumor immunity through STING- mediated T-cell activation in SCLC

- Despite having one of the highest TMB among solid tumors, SCLC paradoxically shows lower expression of PDL1 and relatively immunosuppressed phenotypes with low levels of infiltrating T-cells
- Targeting PARP and checkpoint kinase 1 (CHK1) significantly increased protein and surface expression of PDL1
  - ✓ Adding PARP or CHK1 inhibitors to ICI may enhance treatment efficacy in SCLC patients





Cytotoxic T cell infiltrates increased in SCLC tumors treated with PARPi plus PDL1i

Sen et al. Cancer Discov 2019

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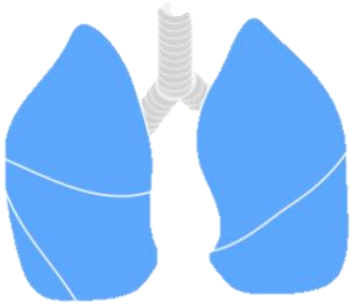
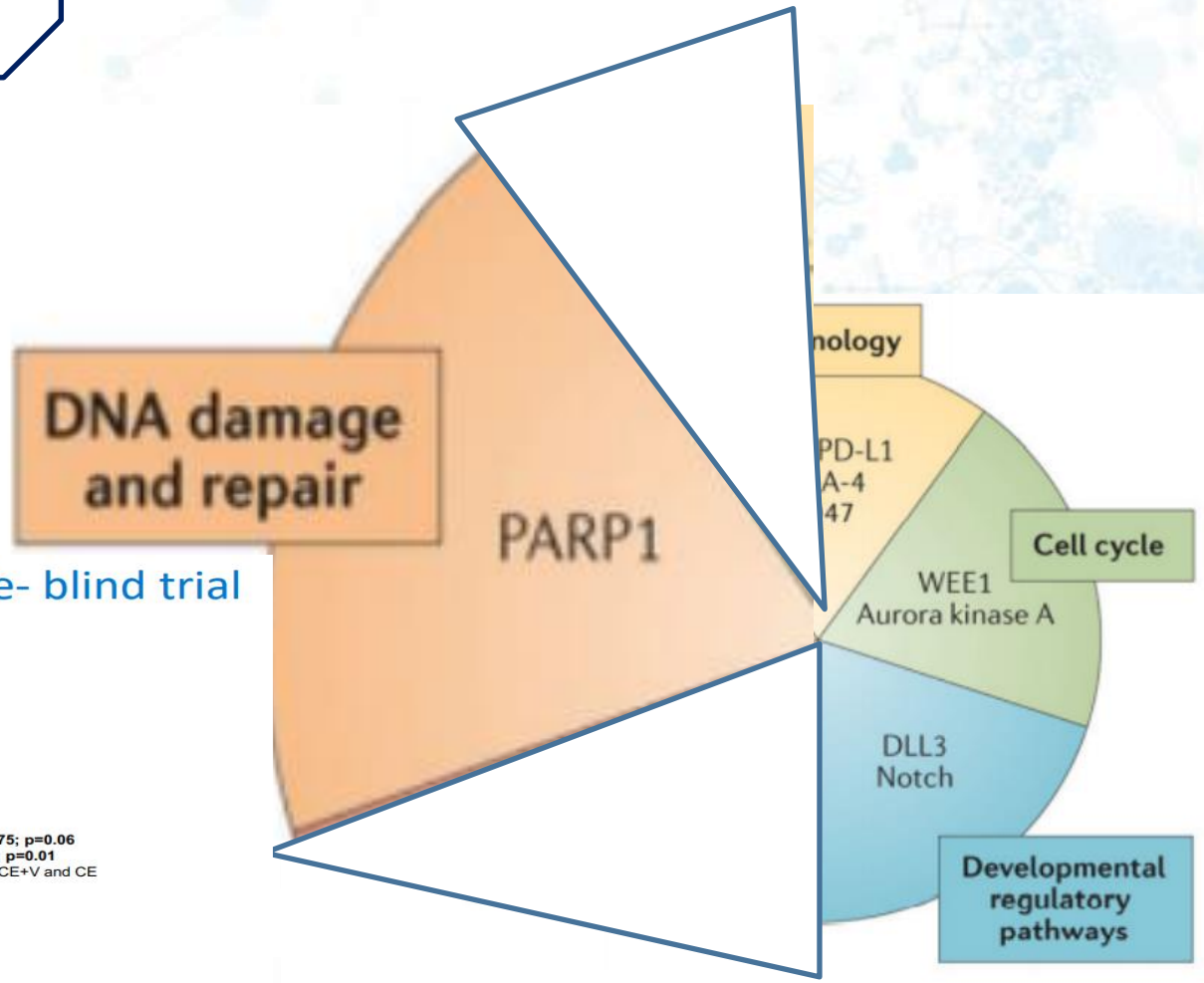
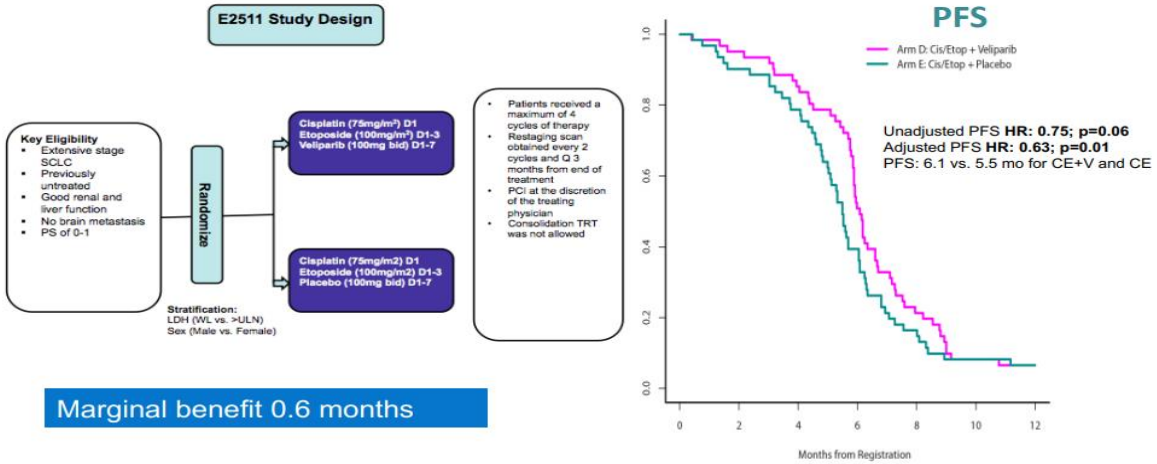
Emerging therapies





ECOG –ACRIN 2511 Phase I –II Randomized double- blind trial
Veliparib + EP VS Placebo + EP



Marginal benefit 0.6 months

Owonikoko TK, et al. JCO 2019; 37: 222-229

SMALL CELL LUNG CANCER

Emerging therapies

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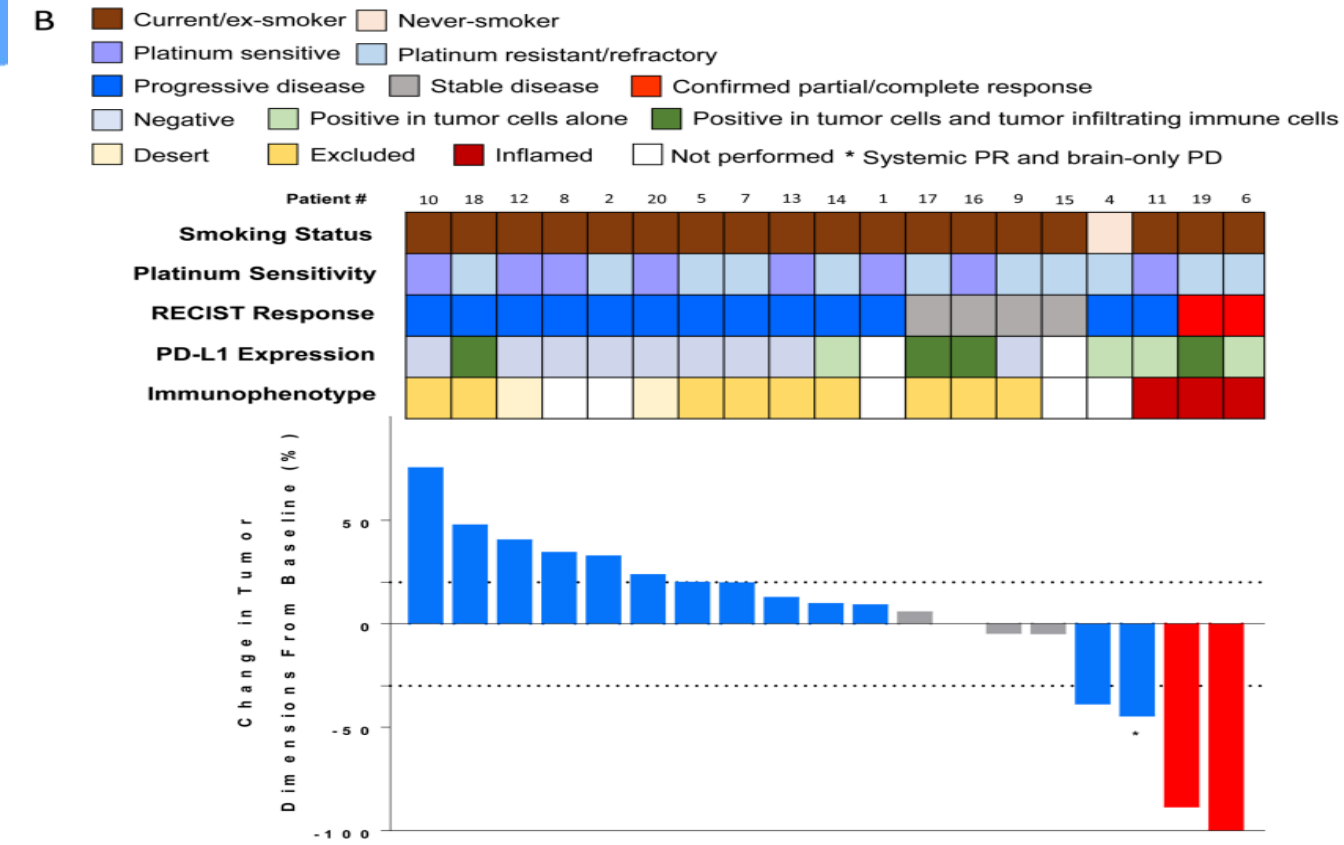
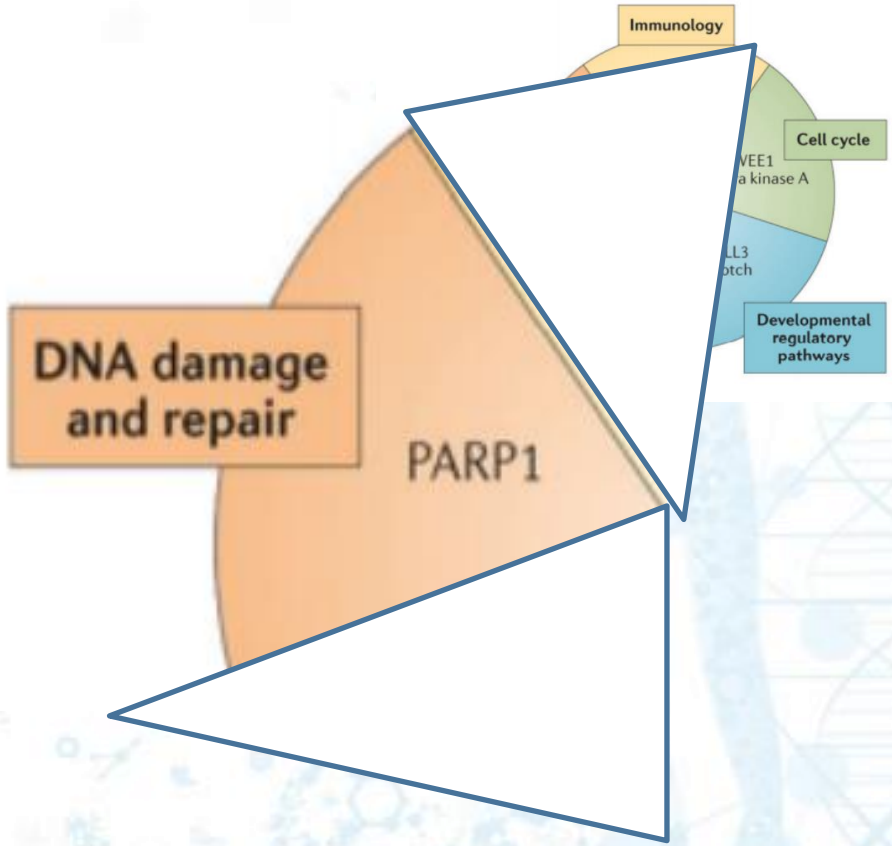
Durvalumab in Combination with Olaparib in Patients with Relapsed Small Cell Lung Cancer: Results from a Phase II Study

Anish Thomas, MD[a], Rasa Vilimas, BSN[a], Christopher Trindade, MD[b], Rebecca Erwin-





Conclusions

- **First-line IO + EP/Carbo demonstrated a statistically significant improvement in OS compared with a robust control arm**
  - 53.7% vs 39.8% of patients alive at 12 months; 33.9% vs 24.7% alive at 18 months **(Durva)**
  - 51.9% vs 39% of patients alive at 12 months; 34% vs 21% alive at 18 months **(Atezo)**
  - Benefit was consistent across all groups of patients
- **Clinical benefit was observed across all efficacy endpoints**
  - PFS rate at 12 months 17.5% vs 4.7%
  - PFS rate at 12 months 12.6% vs 5.4%
- **Safety findings were consistent with the known safety profiles of all agents received**
- **Ongoing exploration of novel strategies in SCLC include**
  - New chemotherapeutics (lurbenectidin) as single agent and in combination
  - Targeted agents (DDR agents, cell cycle modulators, AAG) particularly in combination schedules (Chemo, IO)
  - Novel IO agents (AMG 757,…) and combos