SESSIONE IV

SCLC: dalla pratica clinica attuale alle prospettive future

Il ruolo dell'immunoterapia

Dott. Alberto Pavan

alberto.pavan1@aulss3.veneto.it

Oncologia Medica

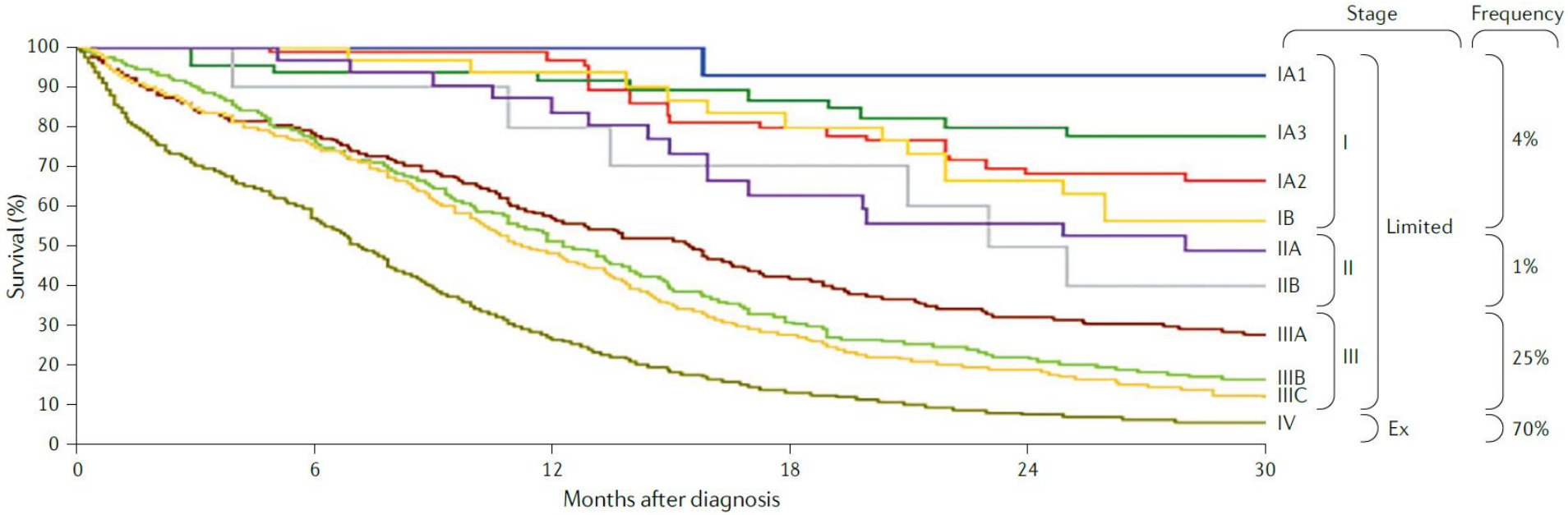
AULSS 3 - Venezia/Mestre

Disclosures

- Consultation: MSD, Roche, Lilly, BMS and AstraZeneca

SCLC - Premises

- High grade neuroendocrine cancer
- 13-15% of lung malignancies
- Initial sensitivity to treatment -> ≈ 100% recurrence
- Associated with smoking exposure (over 98%)
- High symptoms' burden / early spread potential
- Particularly dismal prognosis



Rudin, Nature 2021; Bray, CA Cancer J Clin 2018; Francisci, EJC 2015

SCLC – Premises (back in 2018)

- Standard SCLC treatment

Limited Stage SCLC (30%)

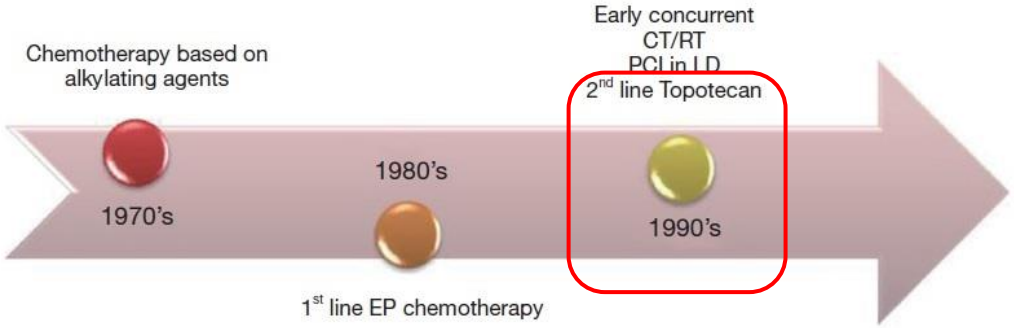
- CT (platinum and etoposide) + Concurrent thoracic RT
- PCI if response

Extended Stage SCLC (70%)

- CT (platinum and etoposide)

- No changes

RECALCITRANT CANCER RESEARCH ACT

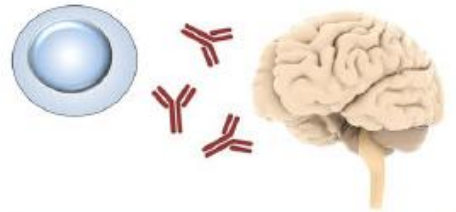


Pavan ELCC 2018; Sabari, Nature 2017

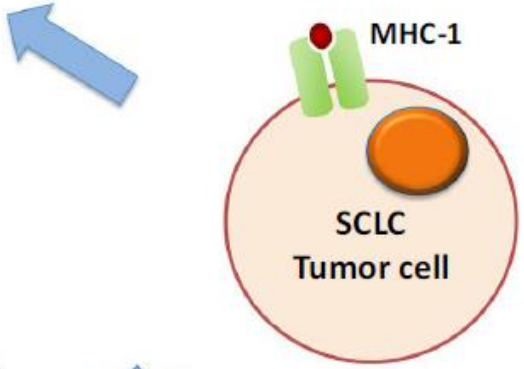
SCLC – Promises (for ICI efficacy)

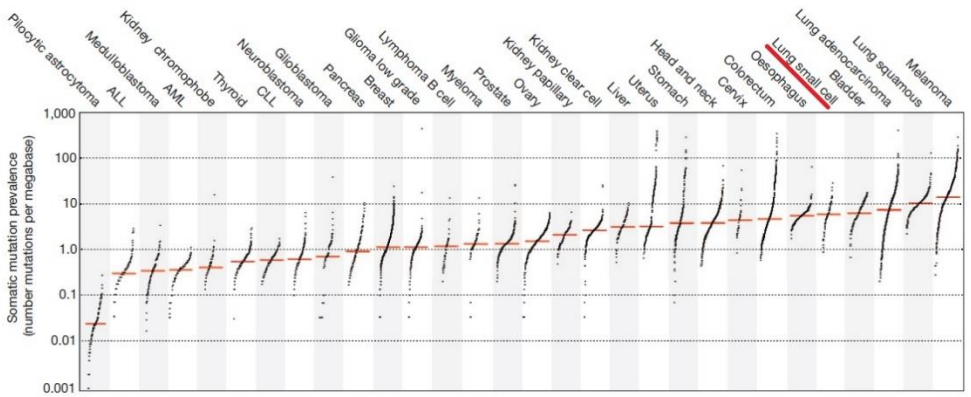
Smoking signature

- DNA mutations
- Inflammation

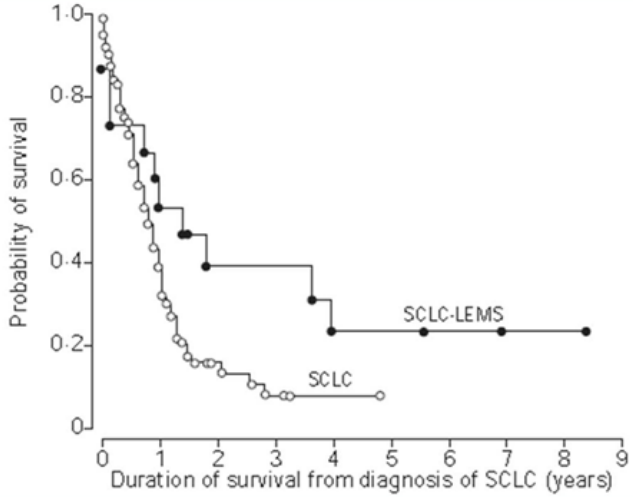


Autoimmune disorders





Neo-Antigen production



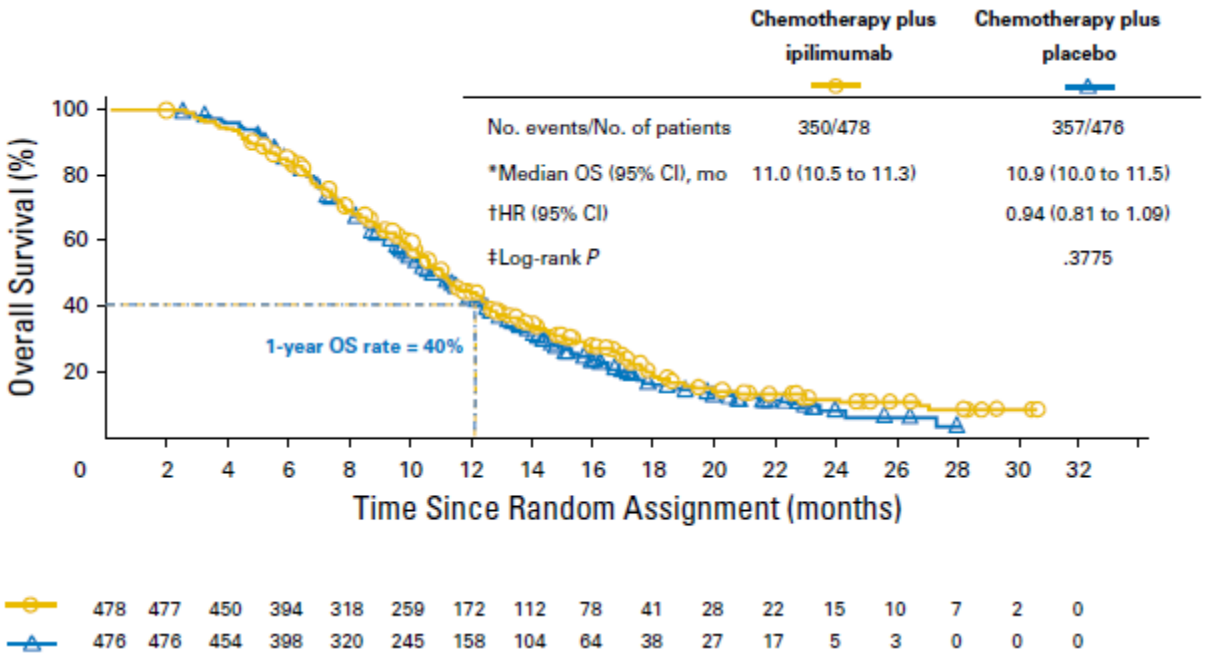
Modified from Calles, Clin Trans Onc 2019; Bunn, JTO 2016; Madison, Lancet 1999

SCLC and ICI: a story of highs and lows

ED-SCLC and ICI: not the best start

- May 2012: phase II trial Ipi 10mg/kg (phased/concurrent) / placebo + CT (carbo-paclitaxel)
- November 2016: phase III trial Ipi 10mg/kg (phased) / placebo + CT (Cis/Carbo-VP16)

	Adverse Events (%)		
	Any grade	Led to Discontinuation	Grade ≥ 3 (5)
Experimental	82	18	48 (1)
Standard	76	2	45 (0.4)



"It is unclear why ipilimumab did not confer additional benefit over etoposide and platinum"

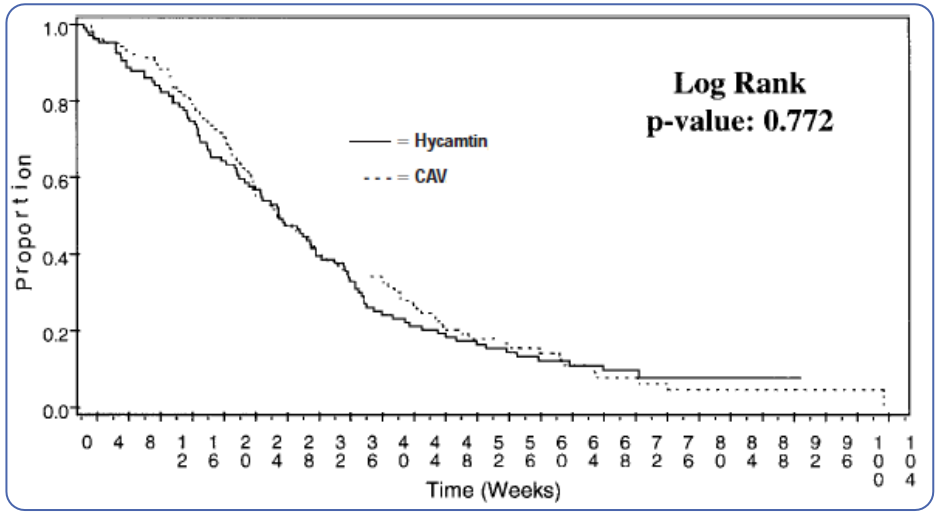
Reck, Ann Onc 2012; Reck, JCO 2016

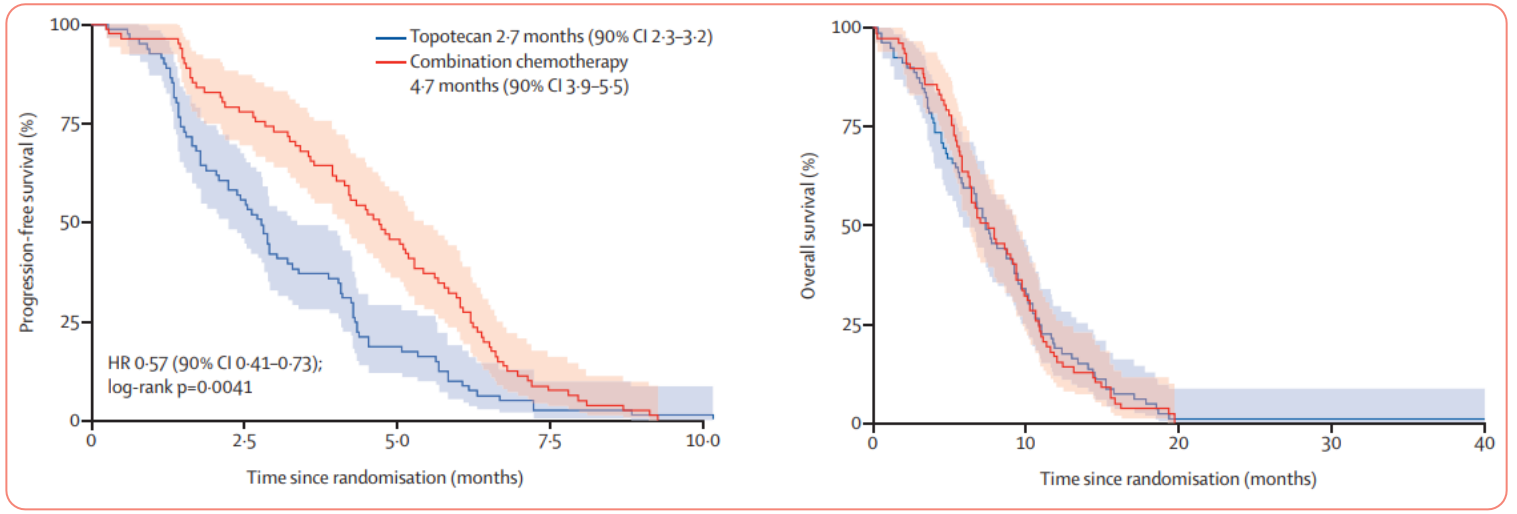
ED-SCLC and ICI: second line first

- Topotecan or CAV as mainstay after first line failure

- PFS benefit for Carbo-Etoposide rechallenge
  - Surely when TFI > 90 days
  - Especially when TFI > 180 days

	REGIMEN	RR (%)	PFS (m)	OS (m)
	Topotecan	24.3	3.3	6.2
	CAV	18.3	3.1	6.2
TFI ≥ 90 days	**CarboVP16 rechallenge**	39	4.7	7.5
	Topotecan	19	2.7	7.4





Von Pawel, JCO 1999; Baize, Lancet 2020

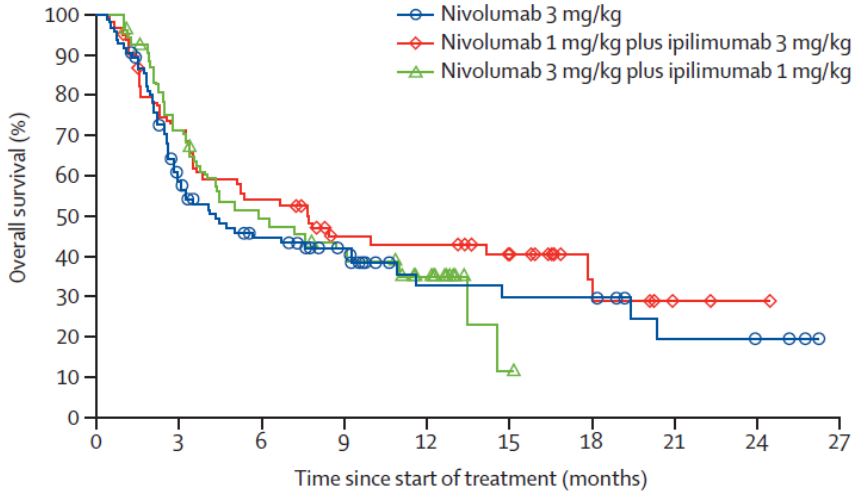
ED-SCLC and ICI: second line first

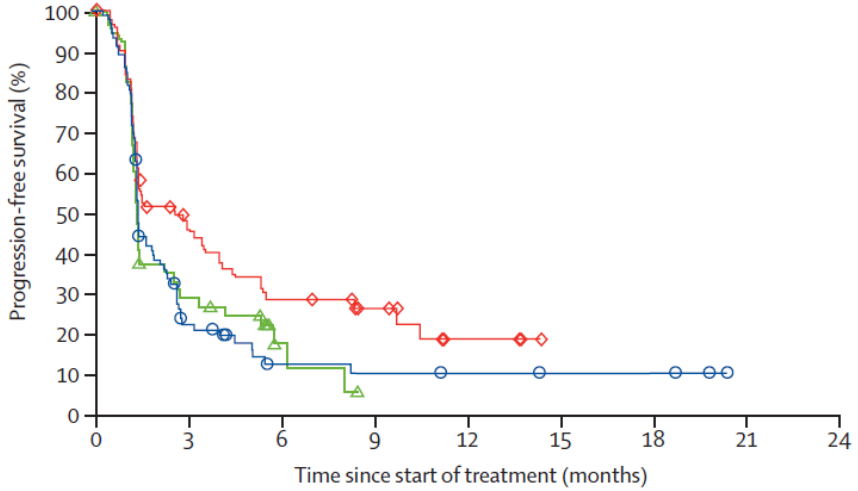
- **CheckMate 032**

Patients with SCLC

REGIMEN	RR (%)	PFS (m)	OS (m)	TrAE (%) G>3 (5)	STOP TrAE
Nivo 3	10	1.4	4.4	13 (0)	6
Nivo 1 + Ipi 3	23	2.6	7.7	30 (3)	11
Nivo 3 + Ipi 1	19	1.4	6	19 (2)	7
Topotecan	*24.3*	*3.3*	*6.2*	*50-60 (5)*	-
CAV	*18.3*	*3.1*	*6.2*	*50-60 (4)*	-

Patients (ITT, N = 401)[e] received either nivolumab monotherapy (n =





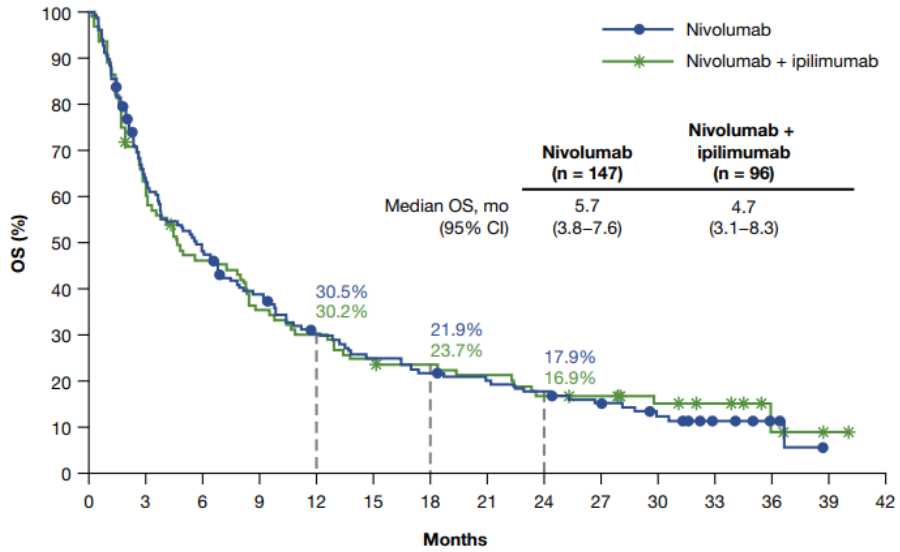
Antonia, Lancet 2016

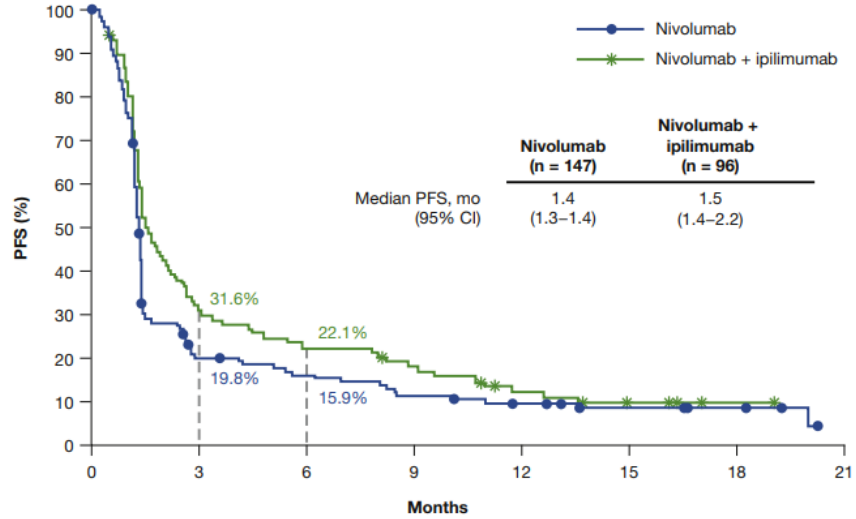
ED-SCLC and ICI: second line first

- **CheckMate 032**

  -> expansion Cohort Nivo 3 *vs* Nivo 1 + Ipi 3
  benefit NOT influenced by 1st line TFI

REGIMEN	RR (%)	PFS (m)	OS (m)	TrAE (%) G>3 (5)	STOP TrAE
Nivo 3	11.6	1.4	5.7	12.9 (0.6)	2.7
Nivo 1 + Ipi 3	21.9	1.5	4.7	37.5 (3)	13.5





Ready, JTO 2020

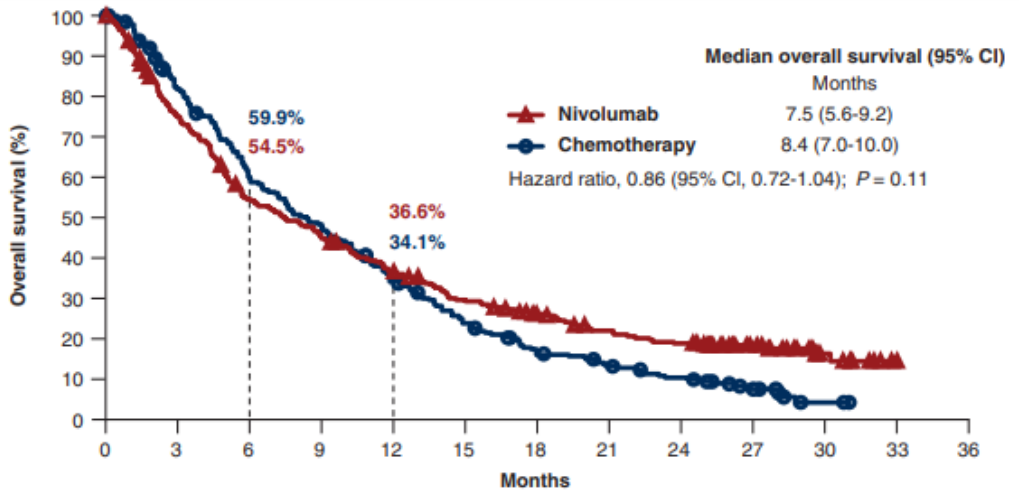
ED-SCLC and ICI: second line crashes

- **CheckMate 032**

  -> **THIRD+** line -> cohort expansion Nivo 3

  benefit NOT influenced by 1st line TFI

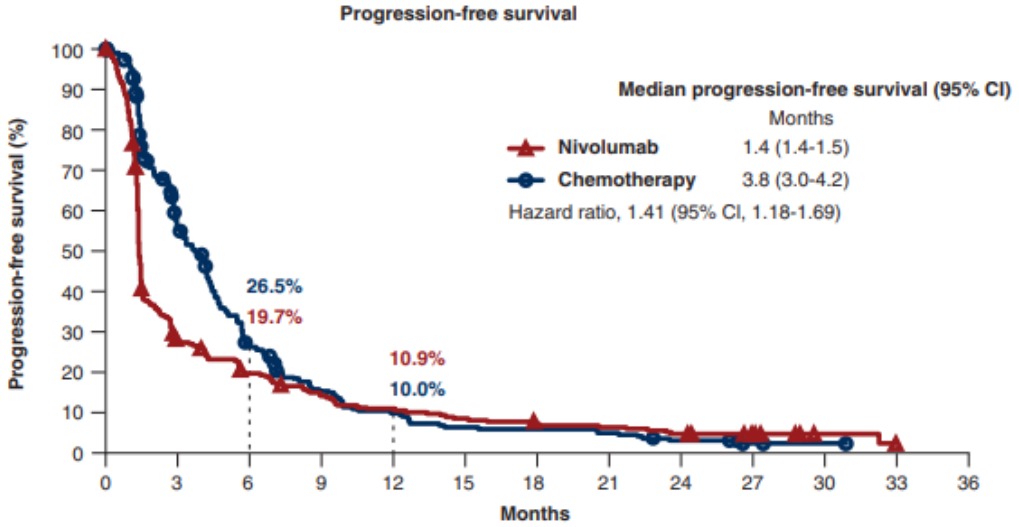
REGIMEN	RR (%)	PFS (m)	OS (m)	TrAE (%) G>3 (5)	STOP TrAE
Nivo 3	11.9	1.4	5.6	11.9 (0.9)	2.8



CheckMate 331

-> **SECOND** line: Nivo 240 *versus* topotecan / amrubicin

REGIMEN	RR (%)	PFS (m)	OS (m)	TrAE (%) G>3 (5)	STOP TrAE
Nivo 240	13.7	1.4	7.5	13.8 (0.7)	4.3
Chemo	16.5	3.8	8.4	73.2 (1.1)	9.4



Ready, JTO 2019; Spigel, Ann Oncol 2021

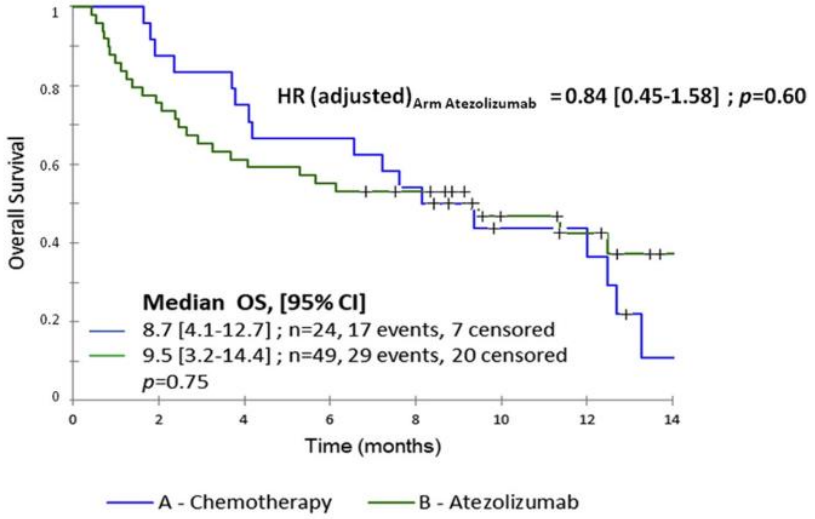
ED-SCLC and ICI: second line crashes

- **Keynote 028** and **158**

-> **THIRD+** line

benefit NOT influenced by 1st line TFI

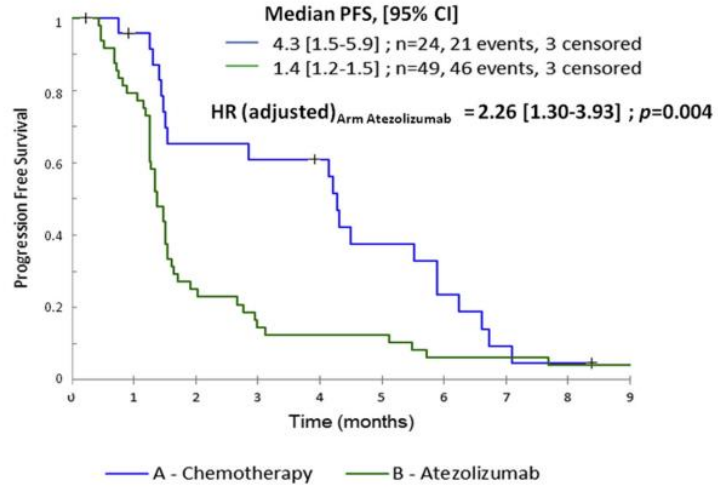
REGIMEN	RR (%)	PFS (m)	OS (m)	TrAE (%) G>3 (5)	STOP TrAE
Pembrolizumab	19.3	2.0	7.7	9.6 (2.4)	3.6
Nivo 3	*11.9*	*1.4*	*5.6*	*11.9 (0.9)*	*2.8*



IFCT - 1603

-> **SECOND** line: Atezo 1200 *versus* chemotherapy

REGIMEN	RR (%)	PFS (m)	OS (m)	TrAE (%) G>3 (5)	STOP TrAE
Atezo 1200	2.3	1.4	9.5	4.2	0
Chemo	10	4.3	8.7	75	NA



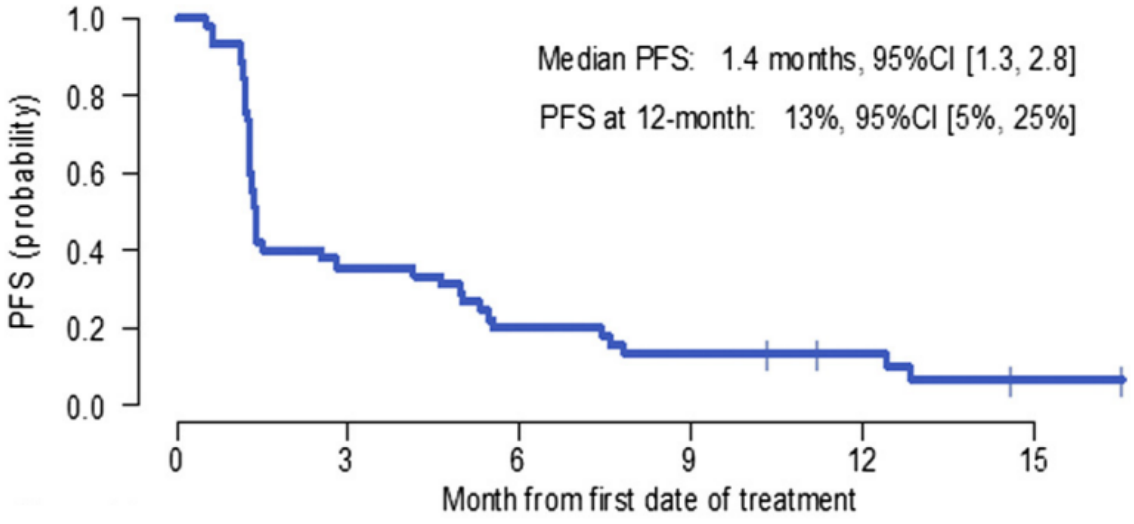
Chung, JTO 2019; Pujol, JTO 2019

ED-SCLC and ICI: a step closer to first line

Maintenance strategies (2 years of ICI) after 1st line chemo did not pay off as well

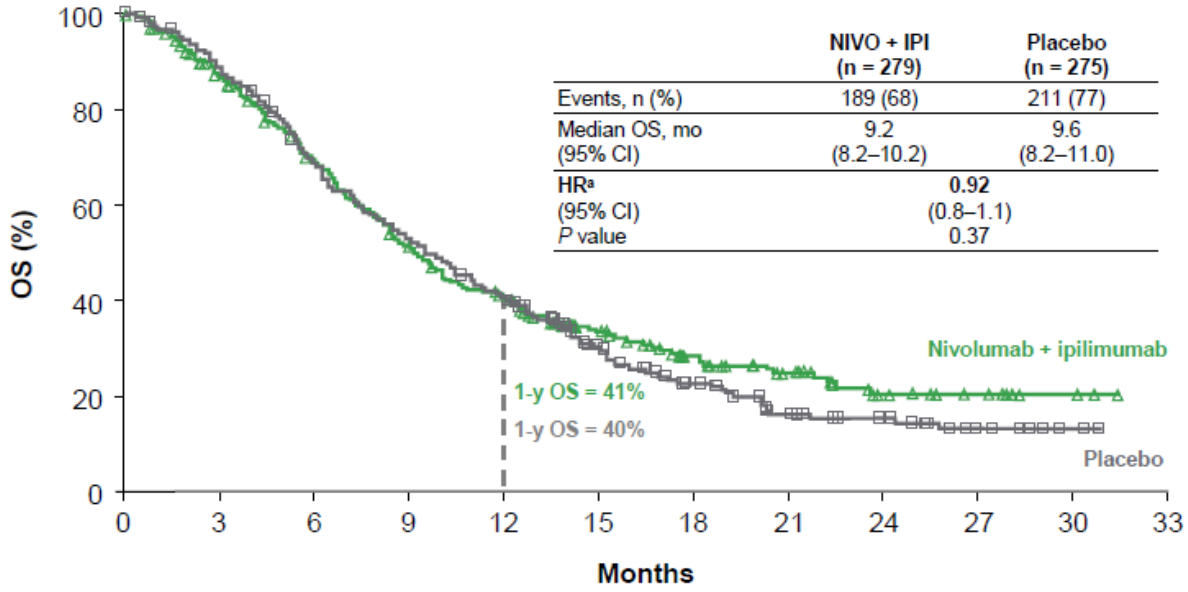
Pembrolizumab (ph II)

-> primary endpoint: expected improved PFS 3 months



CheckMate 451

-> primary endpoint OS: Nivo+Ipi vs placebo



Gadgeel, JTO 2018; Owonikoko, Ann Oncol 2019

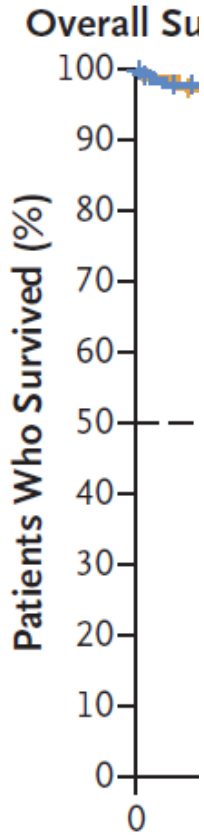
ED-SCLC and ICI: a new first line after 40 years

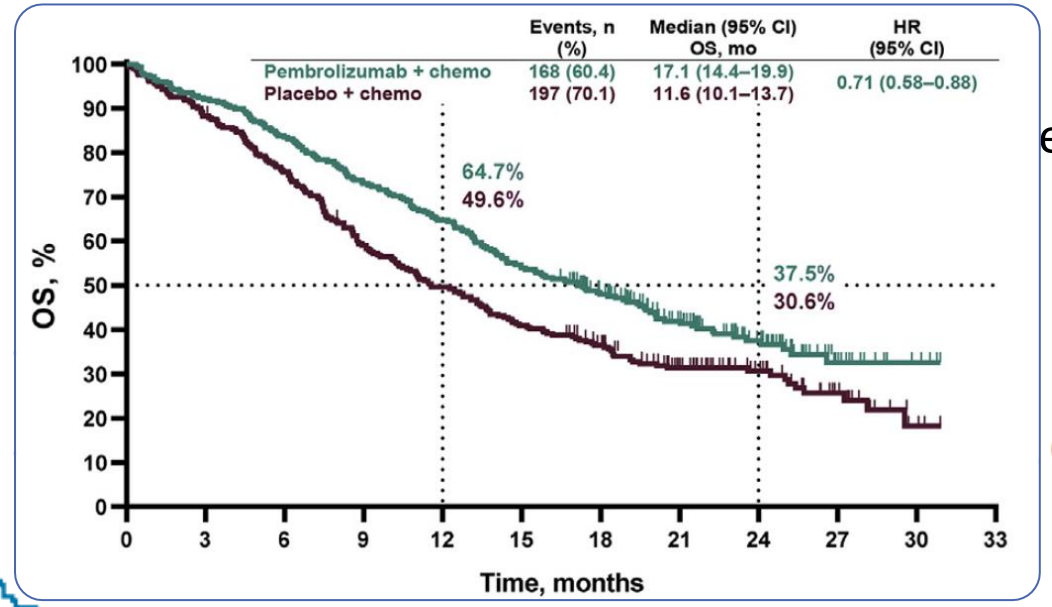
- **IMpower133**: Strangely enough, 1st line ew SOC

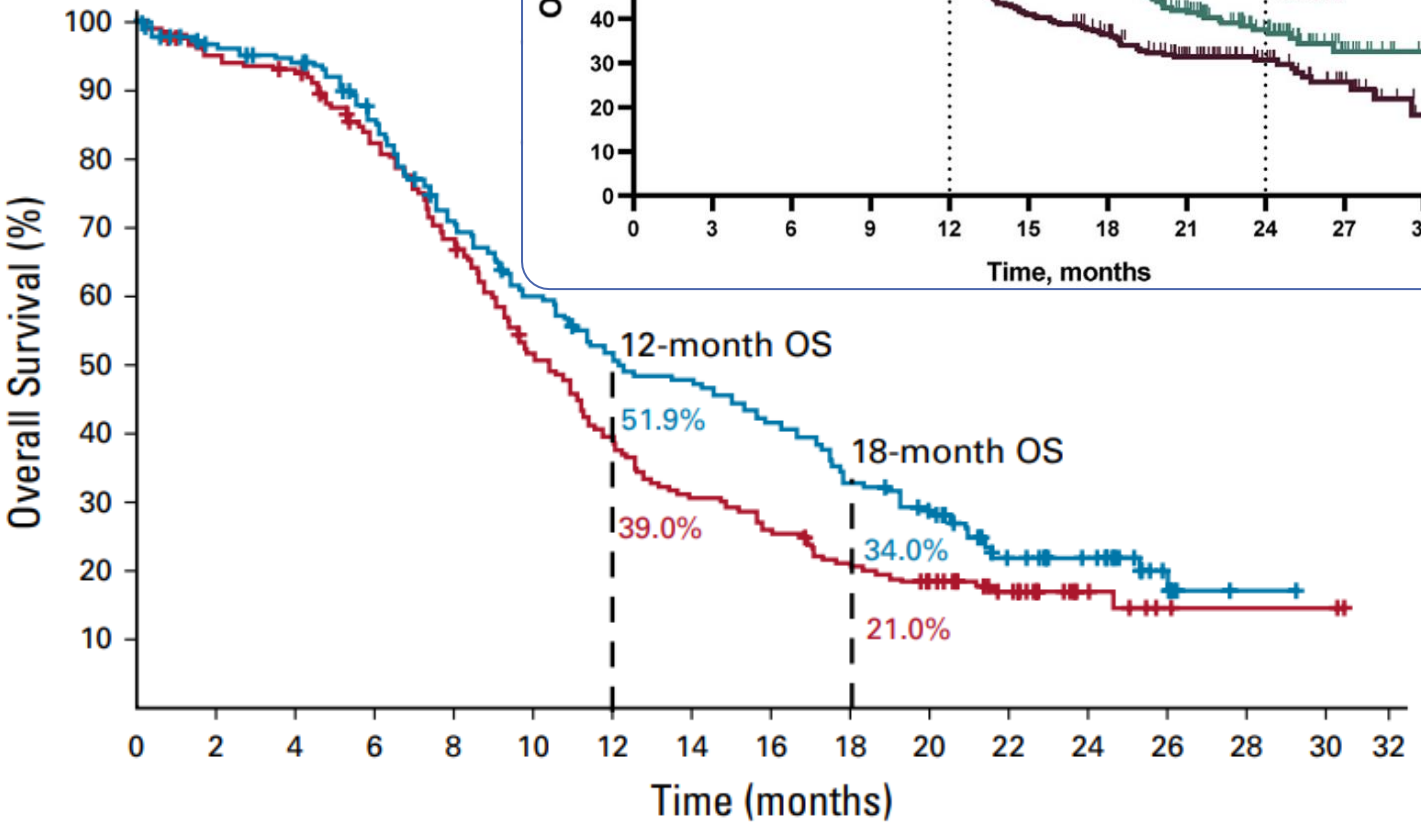
- Measu (per R
- ECOG
- No pri for ES
- Patien asymp metas

Stratific

- Sex (n
- ECOG
- Brain







0.54–0.91)

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acebo

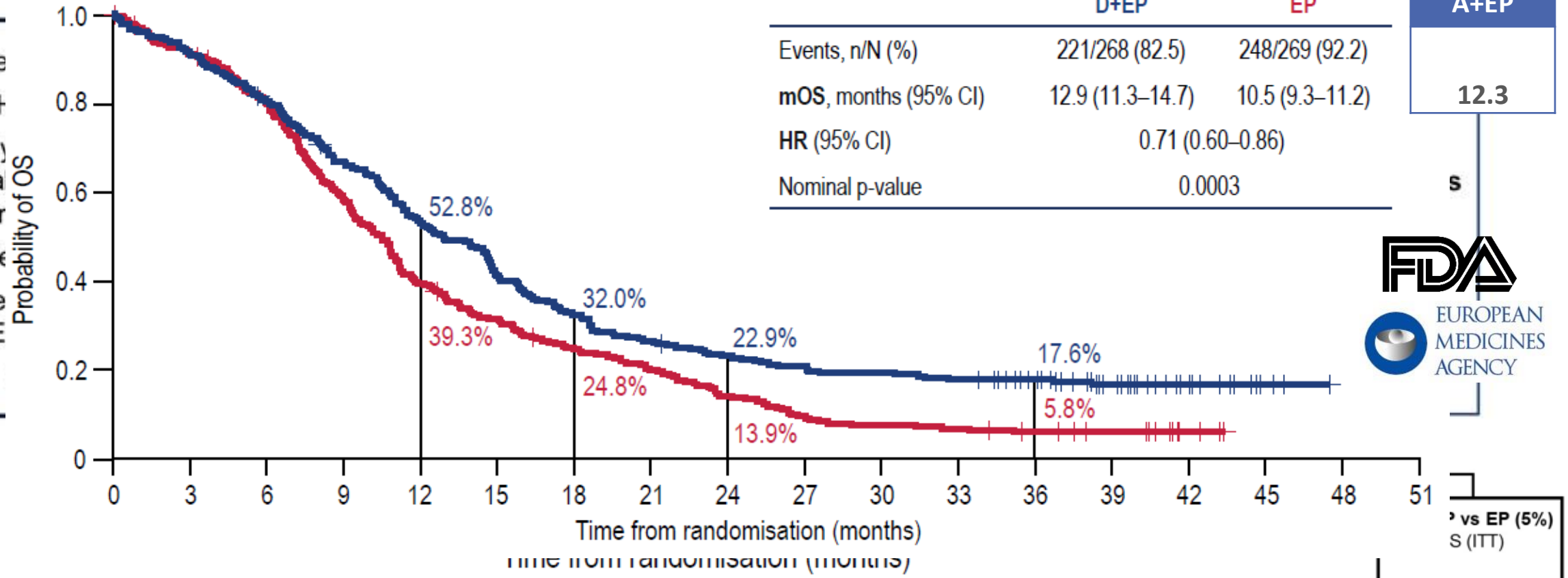
22 23 24

Survival follow-up

Horn, NEJM 2018; Liu, JCO 2021

ED-SCLC and ICI: another 1st line

- **CASPIAN**: again, 1st line combo EP + anti-PD-L1 did seem to pay off



	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	

A+EP
12.3

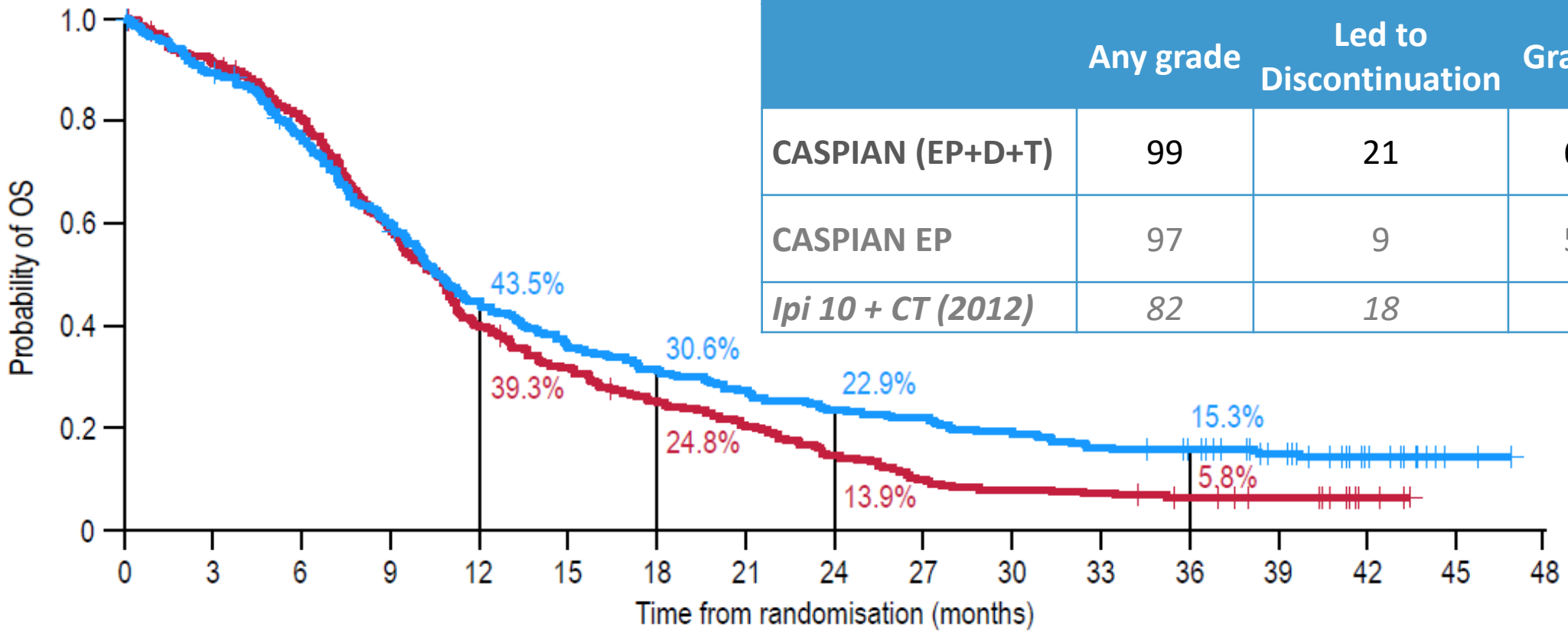
FDA

EUROPEAN MEDICINES AGENCY

Paz-Ares, ESMO 2019; Paz-Ares, ESMO 2021, Lancet 2021

ED-SCLC and ICI: the end of anti-CTLA-4?

- **CASPIAN**: again, 1st line combo EP + anti-PD-L1 + anti-CTLA-1 did not pay off

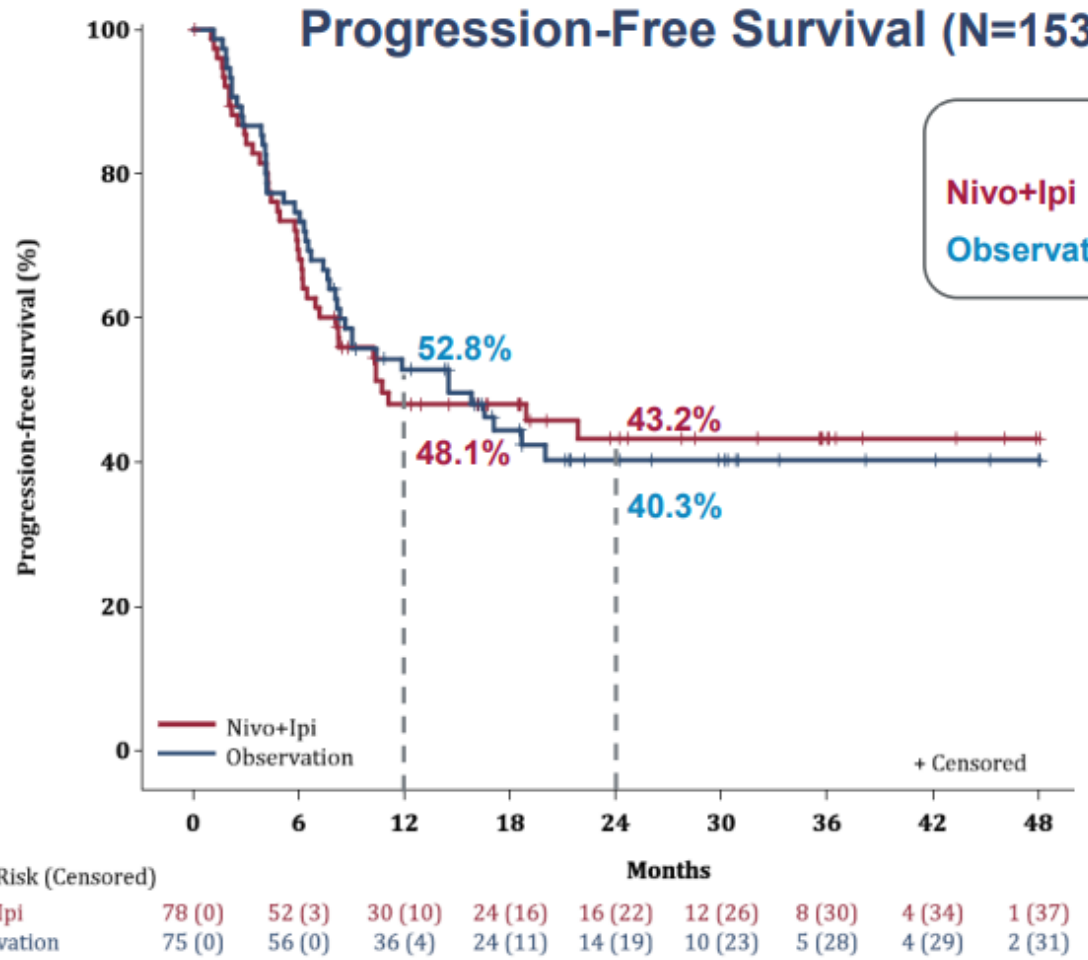


	Adverse Events (%)		
	Any grade	Led to Discontinuation	Grade ≥ 3 (5)
CASPIAN (EP+D+T)	99	21	63 (4.5)
CASPIAN EP	97	9	59 (0.8)
Ipi 10 + CT (2012)	*82*	*18*	*48 (1)*

Paz-Ares, ESMO 2019; Paz-Ares, ESMO 2021, Lancet 2021

LD-SCLC and ICI: the end of anti-CTLA-4?

STIMULI: “PACIFIC-like” consolidation strategy



	Events/N	Median PFS (95%CI)
Nivo+Ipi	40/78	10.7 (7.0 - NE)
Observation	42/75	14.5 (8.2 - NE)

NE: Not estimable

Stratified

HR (95%CI): 1.02 (0.66 - 1.58)
p = 0.93

Testing for non-proportionality: p=0.36

Attrition rate: 35%

Time to Nivo+Ipi discontinuation:
Median: 1.7 months (95%CI: 1.2-2.5)
25.6% on treatment by 6m
15.6% on treatment by 12m

Peters, ESMO 2020; Annal Onc 2022

SCLC and ICI: catching the tails

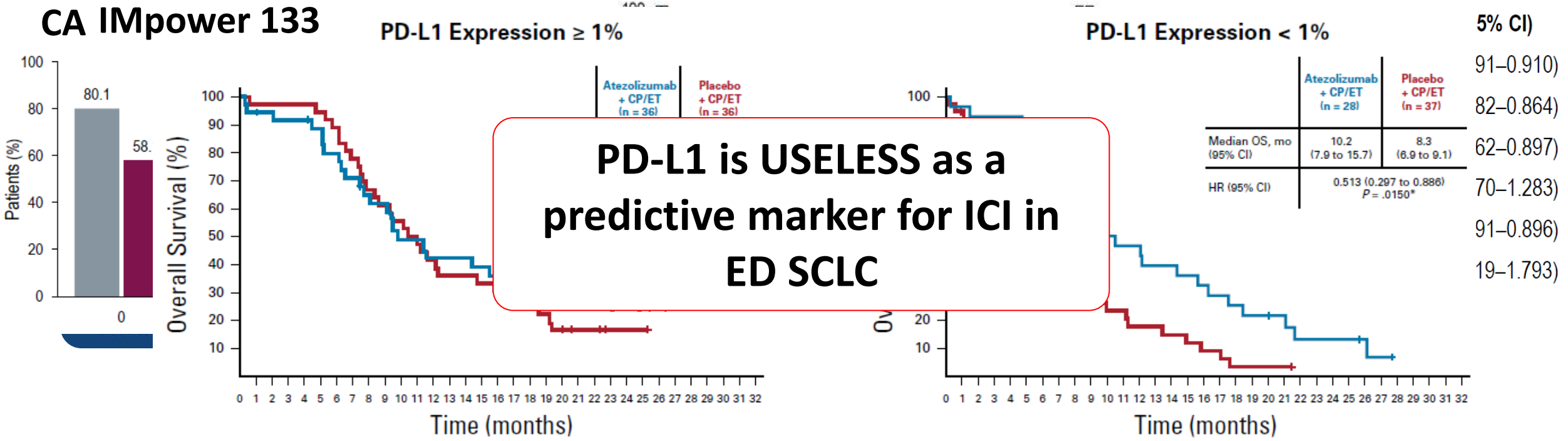
- Among trials (pretreated and 1st line), **13 to 20%** of patients gains a long term benefit from ICI

Ready, JTO 2020; Liu, JCO 2020; Goldman, ESMO 2020

SCLC and ICI: catching the tails

- Among trials (pretreated and 1st line), **13 to 20%** of patients gains a long term benefit from ICI

  → How to identify them? Good old **PD-L1 TPS or TC/IC**?



PD-L1 is USELESS as a predictive marker for ICI in ED SCLC

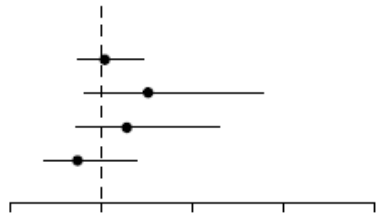
Ready, JTO 2020; Liu, JCO 2020; Goldman, ESMO 2020

SCLC and ICI: catching the tails

→ How to identify them? **TMB**?

CheckMate 032

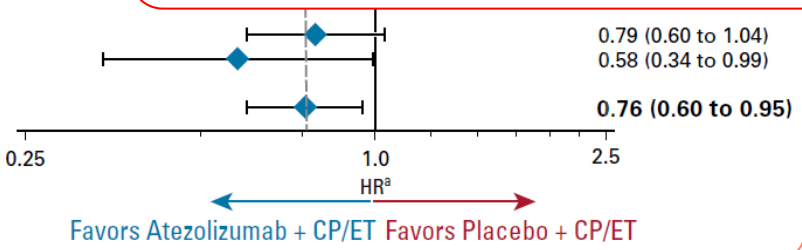
Baseline TMB		mOS N1+I3	mOS Nivo3	
All evaluable	164	4.5 (3.0–7.8)	5.5 (3.2–8.0)	1.05 (0.74–1.47)
TMB low	53	3.0 (1.9–7.3)	4.2 (2.4–14.6)	1.52 (0.83–2.78)
TMB medium	56	3.9 (1.8–7.0)	3.2 (2.4–6.8)	1.29 (0.73–2.30)
TMB high	55	10.7 (1.8–23.6)	6.6 (3.2–12.0)	0.74 (0.39–1.40)



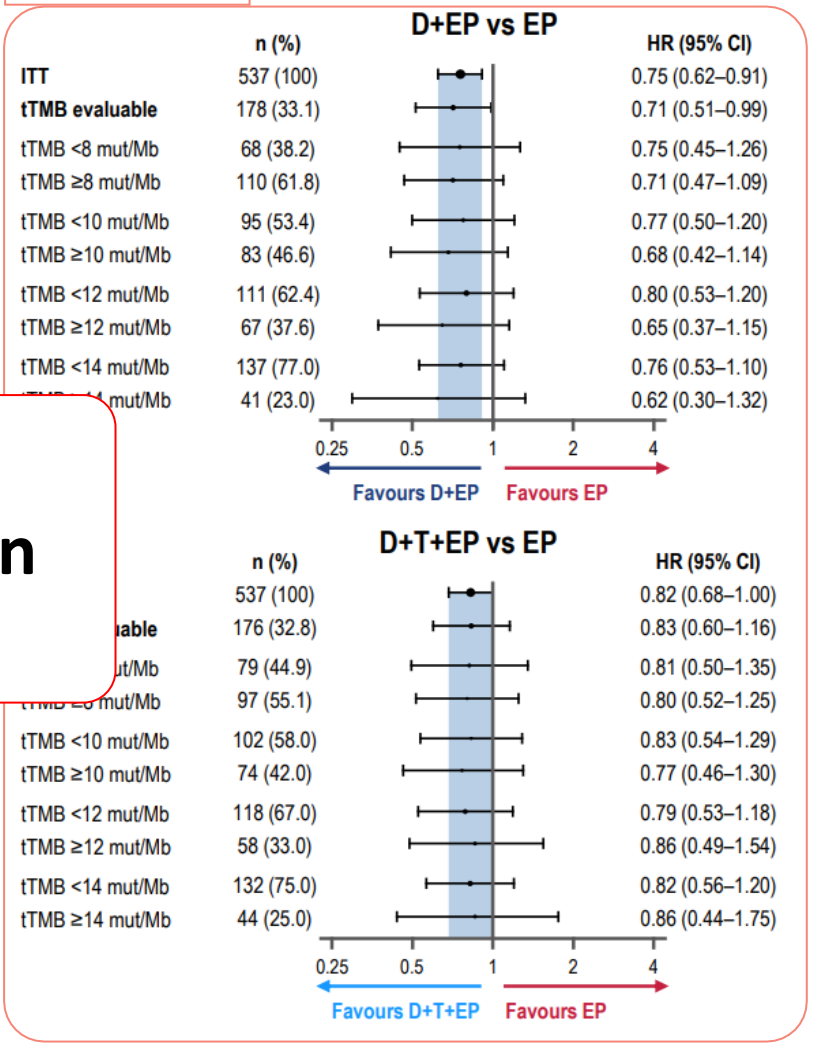
b/t TMB is USELESS as a predictive marker for ICI in ED SCLC

IMpower 133

bTMB < 10 (n = 134)	11.8	9.4	
bTMB ≥ 10 (n = 212)	14.9	11.2	
bTMB < 16 (n = 266)	12.5	10.0	0.79 (0.60 to 1.04)
bTMB ≥ 16 (n = 80)	17.1	11.9	0.58 (0.34 to 0.99)
ITT (N = 403)	**12.3**	**10.3**	**0.76 (0.60 to 0.95)**



CASPIAN

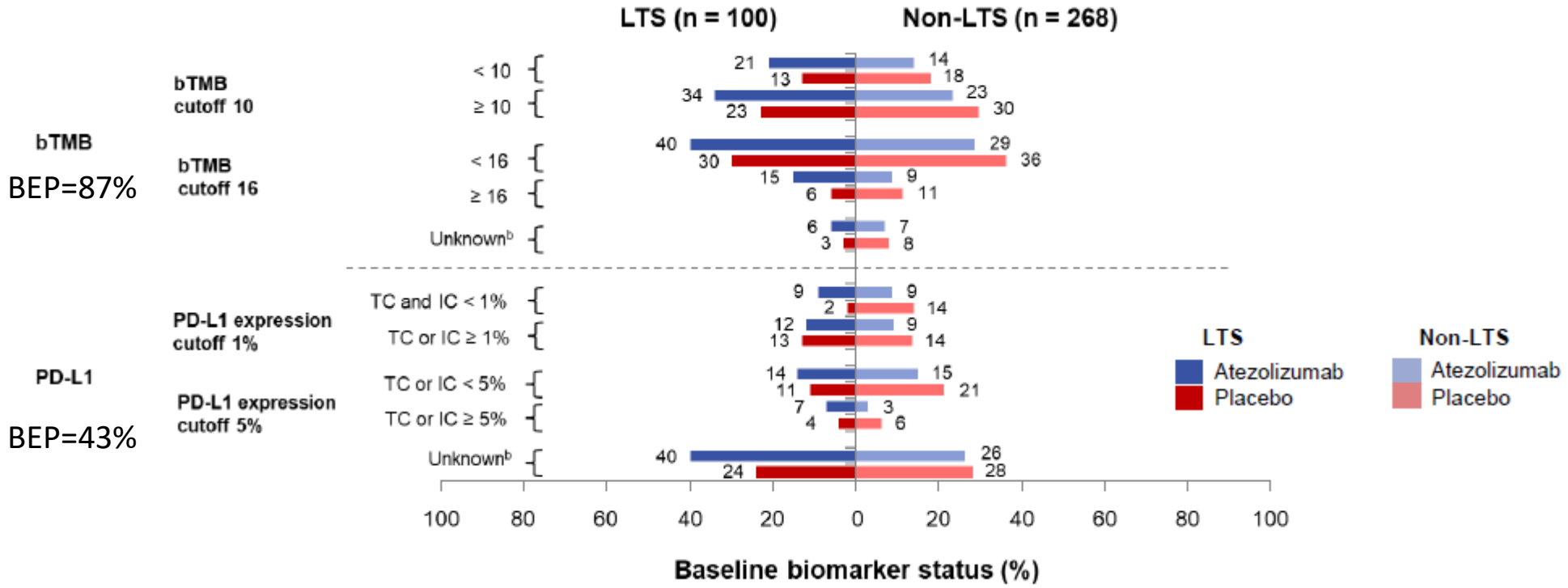


Ready, JTO 2020; Liu, JCO 2020; Goldman, ESMO 2020

SCLC and ICI: catching the tails

- Analyses on Long-Term Survivors (LTS) = pts alive ≥ 18 months after randomization

IMpower 133



SCLC and ICI: catching the tails

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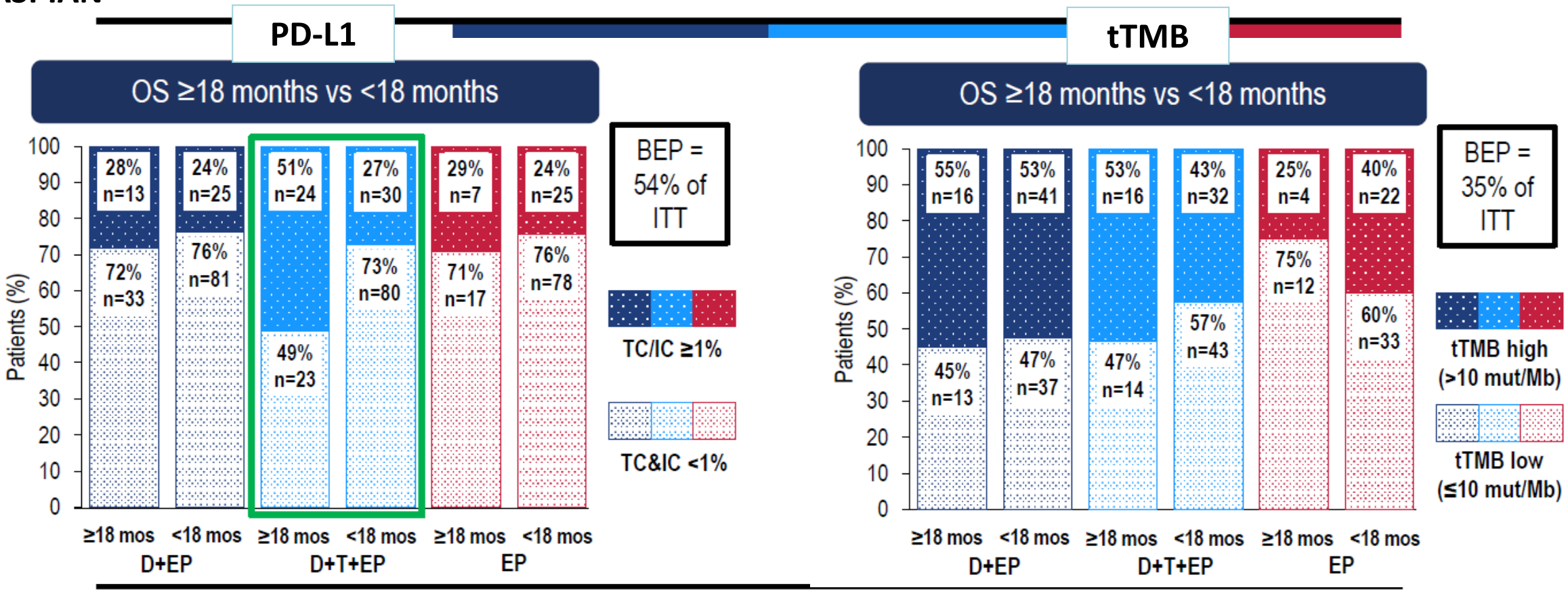
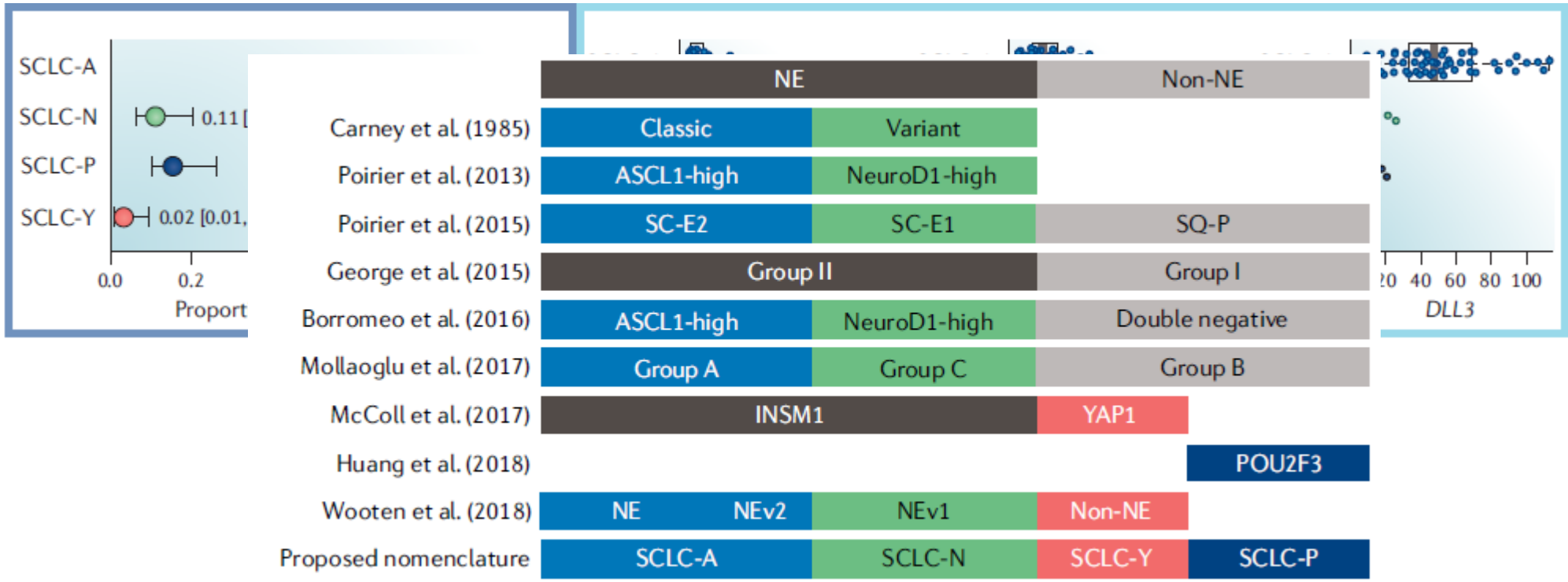
CASPIAN



SCLC and ICI: know the enemy first

- Molecular knowledge, so far:
  - Near-universal loss of *TP53* and *RB1*
  - Different subsets based on expression of neuro-endocrine transcription factors



Rudin, Nature 2019

SCLC and ICI: know the enemy first

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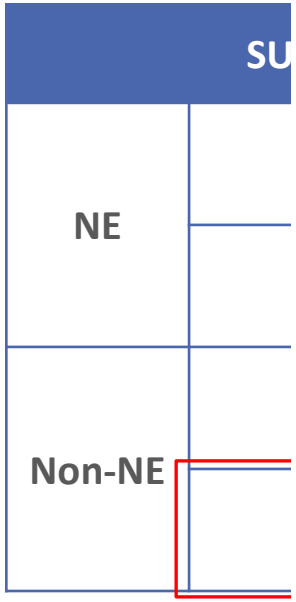
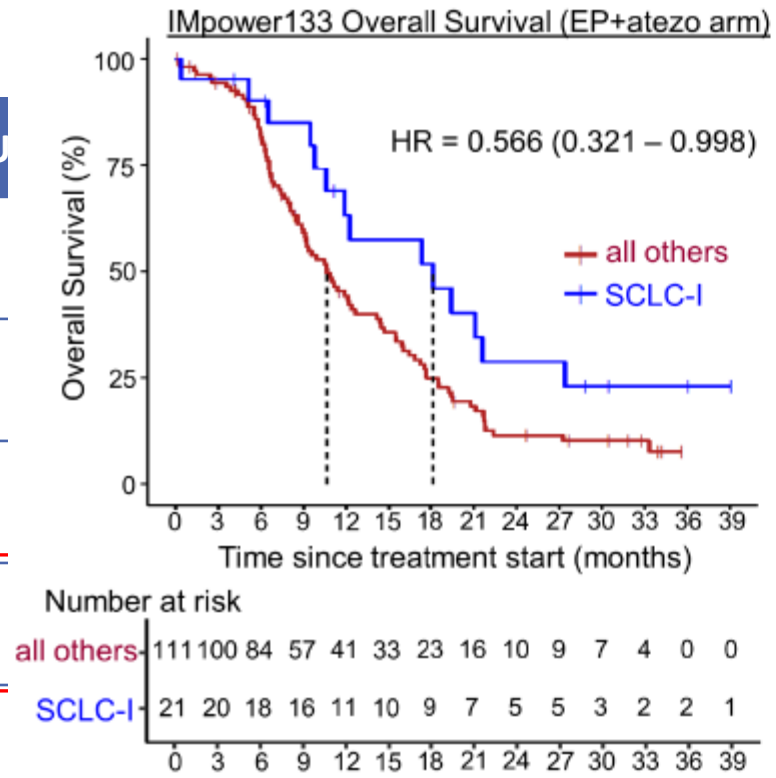
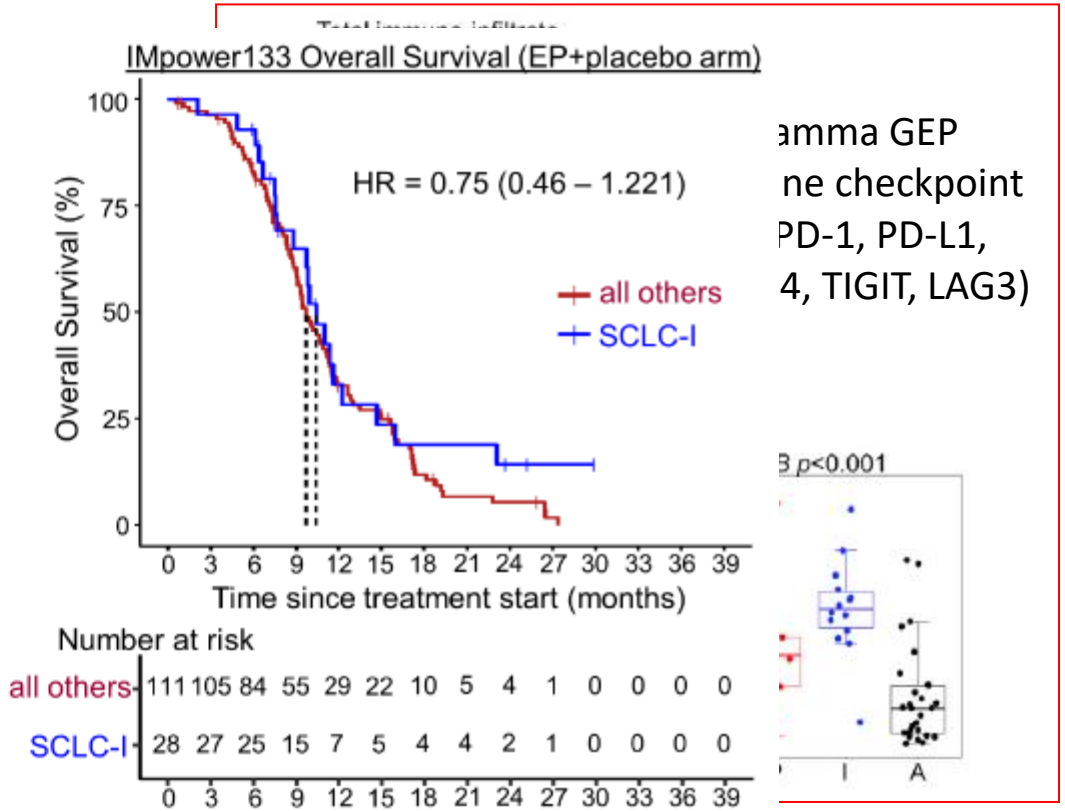
  → *2021 update:*





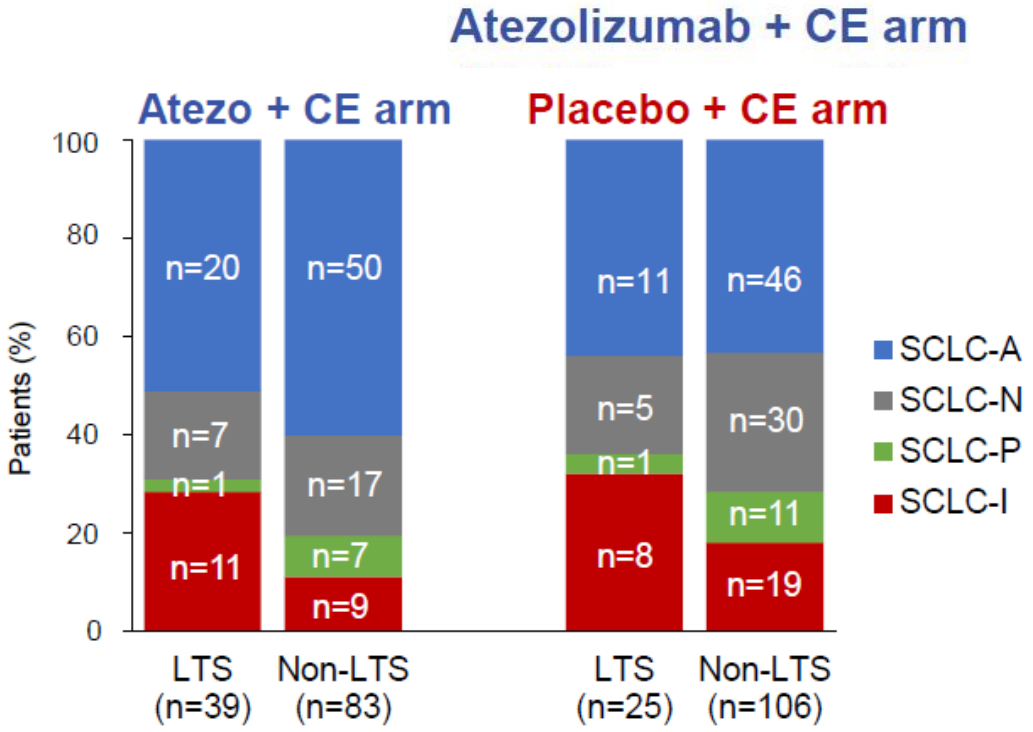


amma GEP
ne checkpoint
PD-1, PD-L1,
4, TIGIT, LAG3)

SCLC and ICI: know the enemy first

- Combined analyses:
  → **IMpower133** LTS population + RNA-sequ analysis (ANPI subtypes + T-cell GEP + B-cell GEP)
  - LTS pts in both treatment arms showed enriched T-cell GEP + B-cell GEP
  - LTS pts in both treatment arms showed enriched SCLC-inflamed

Prognostic



	Atezo + CE		Placebo + CE	
Subtype, n (%)	LTS n=39	Non-LTS n=83	LTS n=25	Non-LTS n=106
SCLC-A	20 (51%)	50 (60%)	11 (44%)	46 (43%)
SCLC-N	7 (18%)	17 (20%)	5 (20%)	30 (28%)
SCLC-P	1 (2%)	7 (8%)	1 (4%)	11 (10%)
SCLC-I	11 (28%)	9 (11%)	8 (32%)	19 (18%)

SCLC and ICI: conclusions

- New SOC after decades with ICI introduction

- Need of tools to identify patients who could benefit from ICI (or at least the ones who will get none)

- Further implement the molecular knowledge of the disease
  -> test targeted therapies or targeted combos