Small Cell Lung Cancer

2 New IO Regimens as Standard of Care

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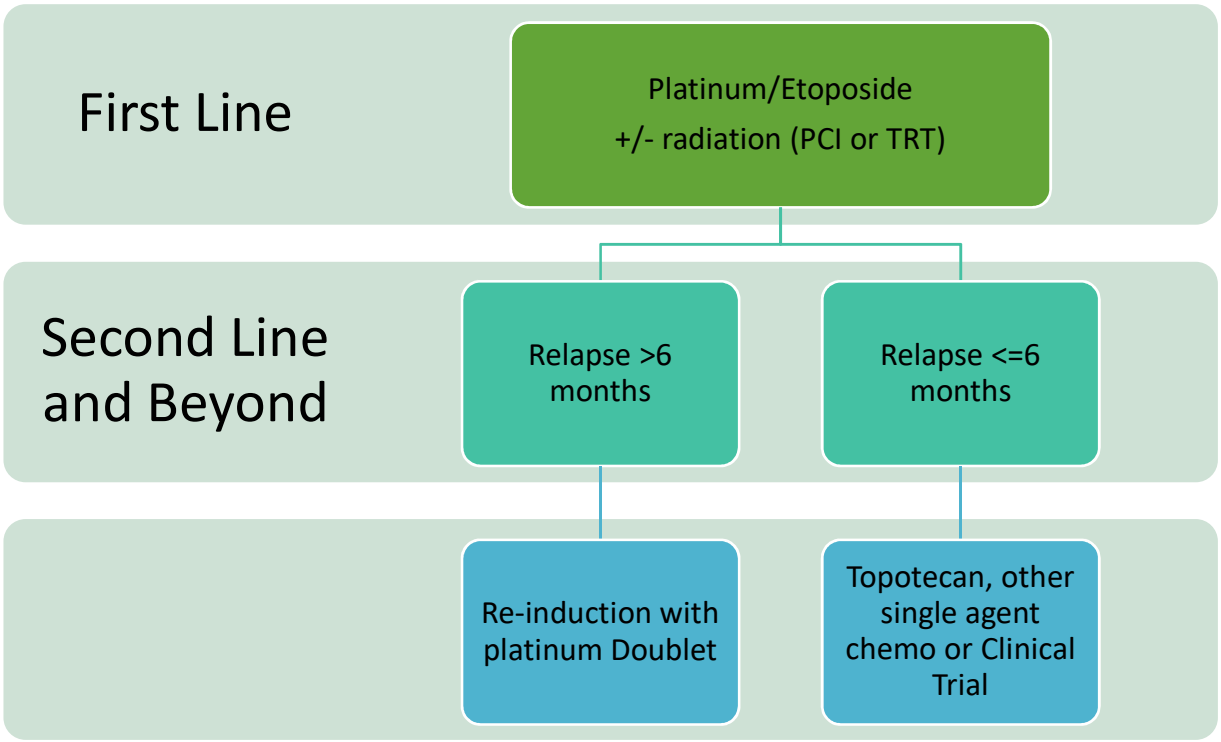
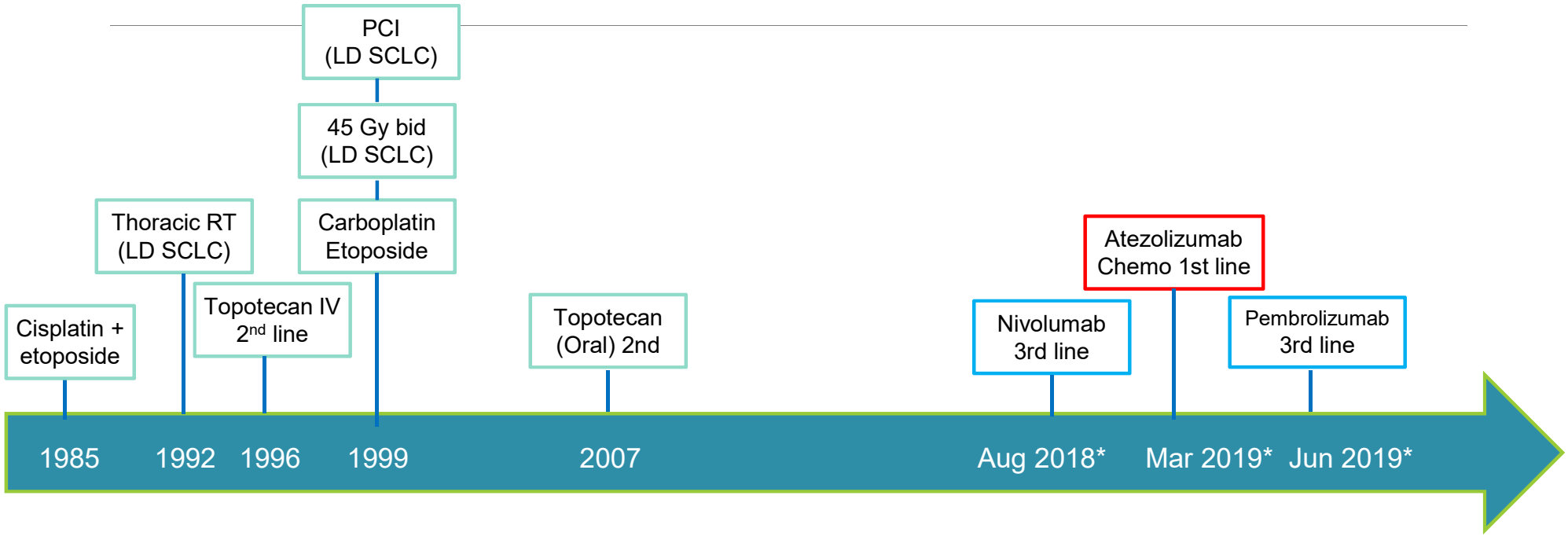
ES-SCLC Management (pre-IO era)



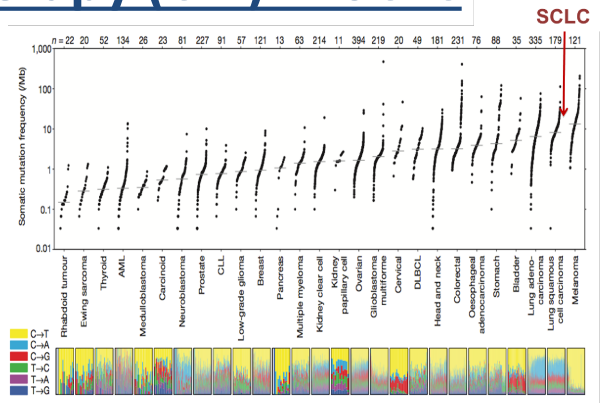
Small Cell Lung Cancer: Immunotherapy Age



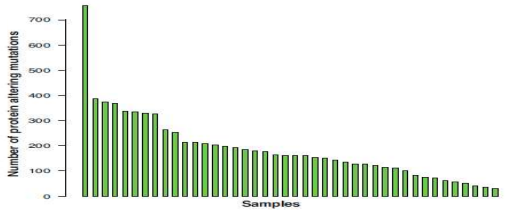
* FDA approval

Rationale for Checkpoint Immunotherapy (CPI) in SCLC

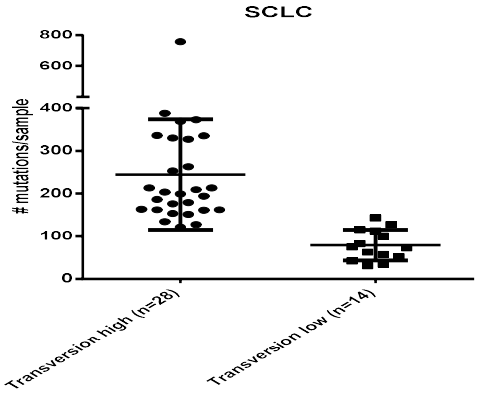
- SCLC ranks among the highest of all tumor types in terms of # of mutations/Mb of DNA



- Extraordinarily high numbers of somatic mutations in some SCLC patients



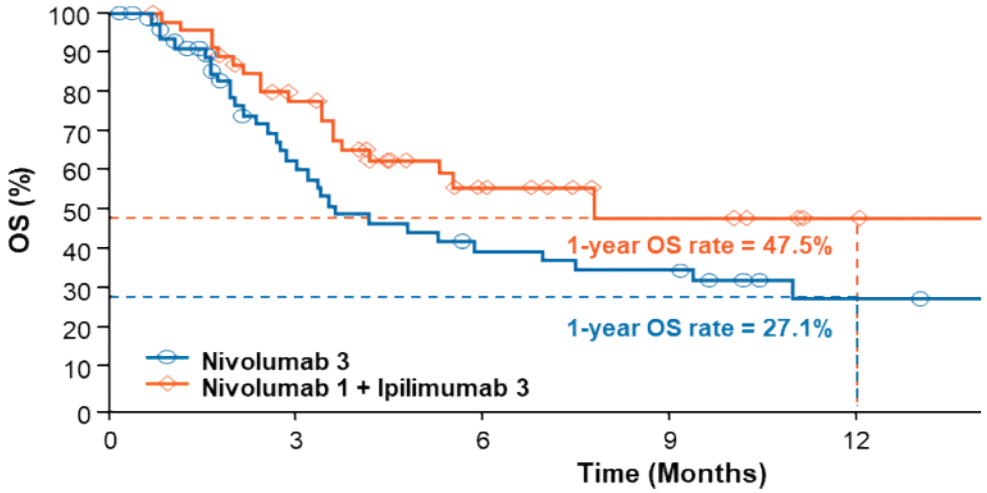
- Mutations are most commonly G to T transversions
  - Reflective of DNA-damaging tobacco carcinogens
  - Strongly neoantigenic



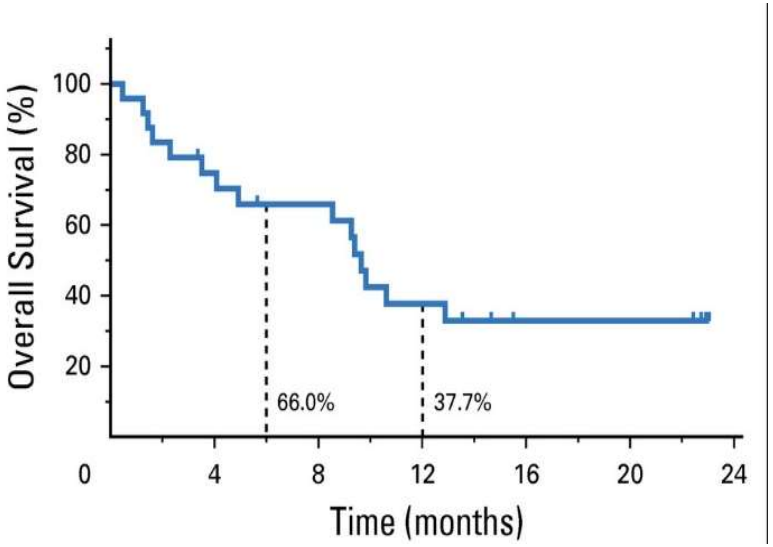
Rudin C, et al. *Nature Genetics*. 2012; Peifer M, et al. *Nature Genetics.* 2012; George J, et al. *Nature*. 2015;524:47.

Checkmate 032 and Keynote 028 in previously treated ES-SCLC

Overall survival



Nivolumab and Nivo+Ipi



Pembrolizumab

Hellman et al: JCO 2017 & E. Calvo; ESMO, 2015

First Line Immunotherapy Landscape in SCLC

Study	Phase	Study Arms	N	Key Results
IMpower133	III	Carboplatin/Etoposide +/- Atezolizumab	403	mOS 12.3 m vs 10.3 m HR=0.76, p=0.015
CASPIAN	III	Platinum/Etoposide +/- Durvalumab +/- Tremelimumab	805	mOS 13 m vs 10.3 m HR=0.73, p=0.0047
KEYNOTE-604	III	Platinum/Etoposide +/- Pembrolizumab	453	Pending – press release only
EA 5161	II	Platinum/Etoposide +/- Nivolumab	150	pending

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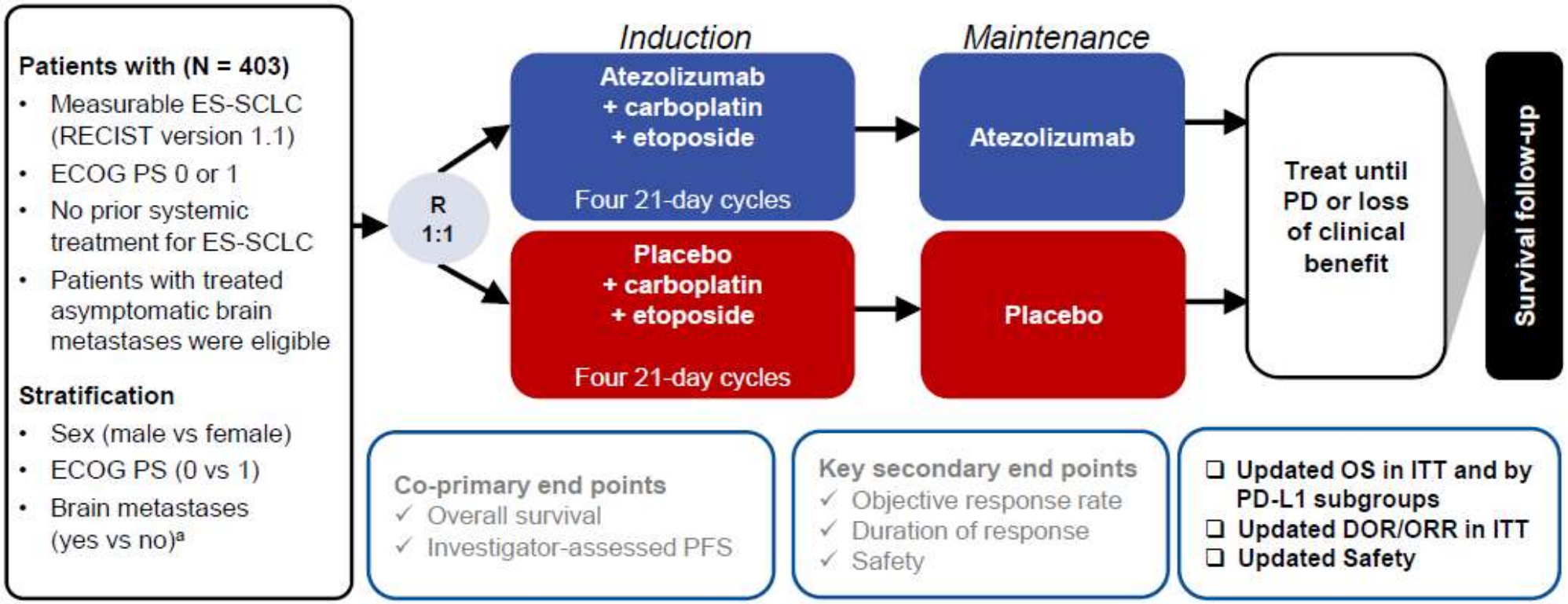
Phase 3 KEYNOTE-604 Study Did Not Meet Other Dual Primary Endpoint of Overall Survival; Results to be Presented at Upcoming Medical Meeting

IMpower133 study design

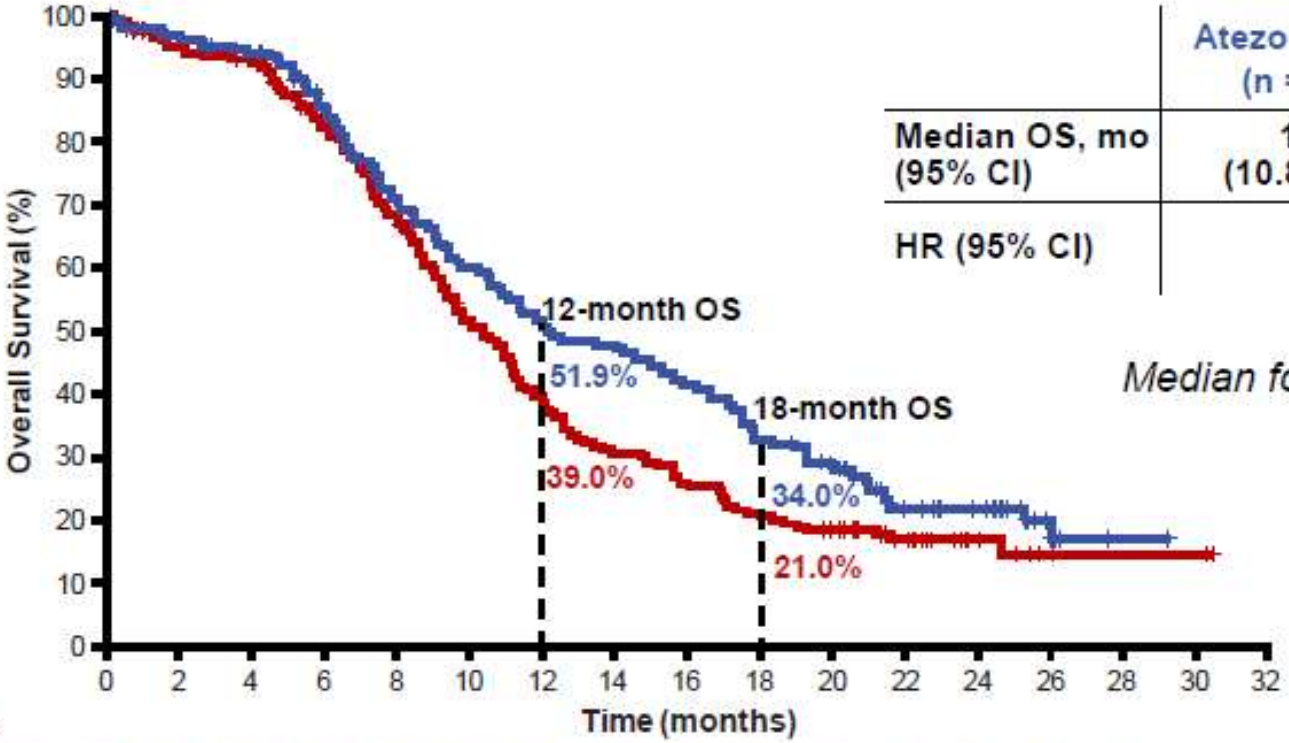


Atezolizumab, 1200 mg IV, Day 1; Carboplatin, AUC 5 mg/mL/min IV, Day 1; Etoposide, 100 mg/m^2 IV, Days 1–3.
[a] Only patients with treated brain metastases were eligible.

IMpower133 Updated OS Analysis: presented by Dr Martin Reck

http://bit.ly/2Z32WhW

Updated OS in ITT



	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

No. at risk															
Atezo + CP/ET	201	187	180	159	130	109	93	86	75	61	51	28	21	8	1
Placebo + CP/ET	202	189	183	160	131	97	74	58	49	39	33	20	8	3	2	2

[a]p-value is provided for descriptive purpose.
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Safety summary

Patients, n (%)	Atezo + CP/ET (n = 198)	Placebo + CP/ET (n = 196)
Patients with ≥ 1 AE	198 (100)	189 (96.4)
Grade 3–4 AEs	134 (67.7)	124 (63.3)
Treatment-related AEs	188 (94.9)	181 (92.3)
Serious AEs	77 (38.9)	69 (35.2)
Immune-related AEs	82 (41.4)	48 (24.5)
Treated with steroids or hormone replacement therapy[a]	40 (20.2)	11 (5.6)
AEs leading to withdrawal from any treatment[b]	24 (12.1)	6 (3.1)
AEs leading to withdrawal from atezolizumab/placebo	23 (11.6)	5 (2.6)
AEs leading to withdrawal from carboplatin	5 (2.5)	1 (0.5)
AEs leading to withdrawal from etoposide	8 (4.0)	2 (1.0)
Treatment-related Grade 5 AEs	3 (1.5)	3 (1.5)

- Median duration of treatment with atezolizumab was 4.7 months (range: 0 to 29)
- Median number of doses received:
  - Atezolizumab: 7 (range: 1 to 39)
  - Chemotherapy: 4 for carboplatin; 12 doses etoposide (for both arms)

[a] An event consistent with an immune-mediated mechanism of action requiring treatment with systemic corticosteroids or hormone replacement therapy.
[b] Incidence of treatment-related AEs and AEs leading to withdrawal from any treatment are for any treatment component.
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Adverse events of special interest

Immune-related AEs[a], n (%) > 1% in either treatment group	Atezo + CP/ET (n = 198)		Placebo + CP/ET (n = 196)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Rash	36 (18.2)	4 (2.0)	21 (10.7)	0
Hepatitis	12 (6.1)	3 (1.5)	9 (4.6)	0
Hypothyroidism	25 (12.6)	0	1 (0.5)	0
Hyperthyroidism	11 (5.6)	0	5 (2.6)	0
Infusion-related reaction	7 (3.5)	4 (2.0)	9 (4.6)	1 (0.5)
Pneumonitis	4 (2.0)	1 (0.5)	3 (1.5)	2 (1.0)
Colitis	1 (0.5)	2 (1.0)	0	0
Adrenal insufficiency	0	0	3 (1.5)	0

- No grade 5 immune-related AEs were observed in either treatment group

[a] An event consistent with an immune-mediated mechanism of action not taking into account whether treatment given for the event.
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IMpower133 Updated OS Analysis: presented by Dr Martin Reck *http://bit.ly/2Z32WhW*

CASPIAN Study Design

- Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1

N=805 (randomised)

1:1:1

R

Stratified by planned platinum agent (carboplatin vs cisplatin)

Durvalumab + EP*
Durvalumab 1500 mg + EP q3w for up to 4 cycles

→ **Durvalumab**
1500 mg q4w until disease progression

EP*
q3w for up to 6 cycles†

→ **Optional PCI†**

Durvalumab + tremelimumab + EP*
Durvalumab 1500 mg + tremelimumab 75 mg + EP q3w for up to 4 cycles

→ **Durvalumab‡**
1500 mg q4w until disease progression

Primary endpoint
- OS

Secondary endpoints
- PFS
- ORR
- Safety & tolerability
- Health-related QoL

The durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

*EP consists of etoposide 80–100 mg/m^2 with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m^2
†Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion
‡Patients received an additional dose of tremelimumab post-EP

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AUC, area under the curve; ORR, objective response rate; PCI, prophylactic cranial irradiation; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; WHO, World Health Organization

Treatment Exposure

	Durvalumab + EP (n=265)	EP (n=266)
Platinum agent received*, n (%)		
Carboplatin	208 (78.5)	208 (78.2)
Cisplatin	65 (24.5)	67 (25.2)
Median number of cycles of EP†, n (range)	4 (1–6)	6 (1–6)
Number of cycles of EP†, n (%)		
≥4 cycles	230 (86.8)	225 (84.6)
≥5 cycles	3 (1.1)	167 (62.8)
6 cycles	1 (0.4)	151 (56.8)
Median number of durvalumab doses, n (range)	7 (1–25)	–
Patients receiving ≥12 durvalumab doses, n (%)	64 (24.2)	–

*Patients were allowed to switch between carboplatin and cisplatin at the investigator's discretion
†Based on etoposide exposure

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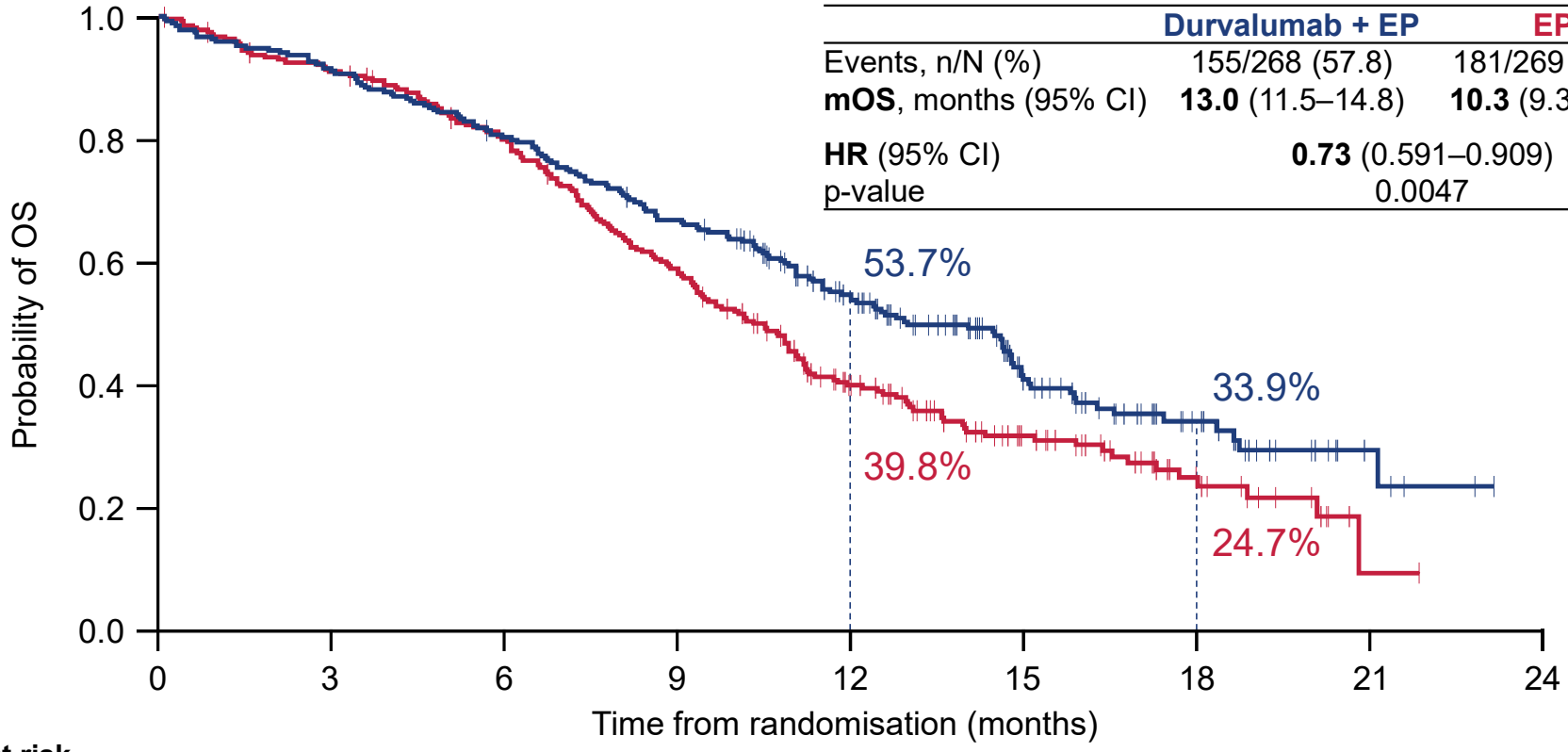
Overall Survival (Primary Endpoint)



	Durvalumab + EP	EP
Events, n/N (%)	155/268 (57.8)	181/269 (67.3)
mOS, months (95% CI)	**13.0** (11.5–14.8)	**10.3** (9.3–11.2)
HR (95% CI)	**0.73** (0.591–0.909)	
p-value	0.0047	

No. at risk									
Durvalumab + EP	268	244	214	177	116	57	25	5	0
EP	269	242	209	153	82	44	17	1	0

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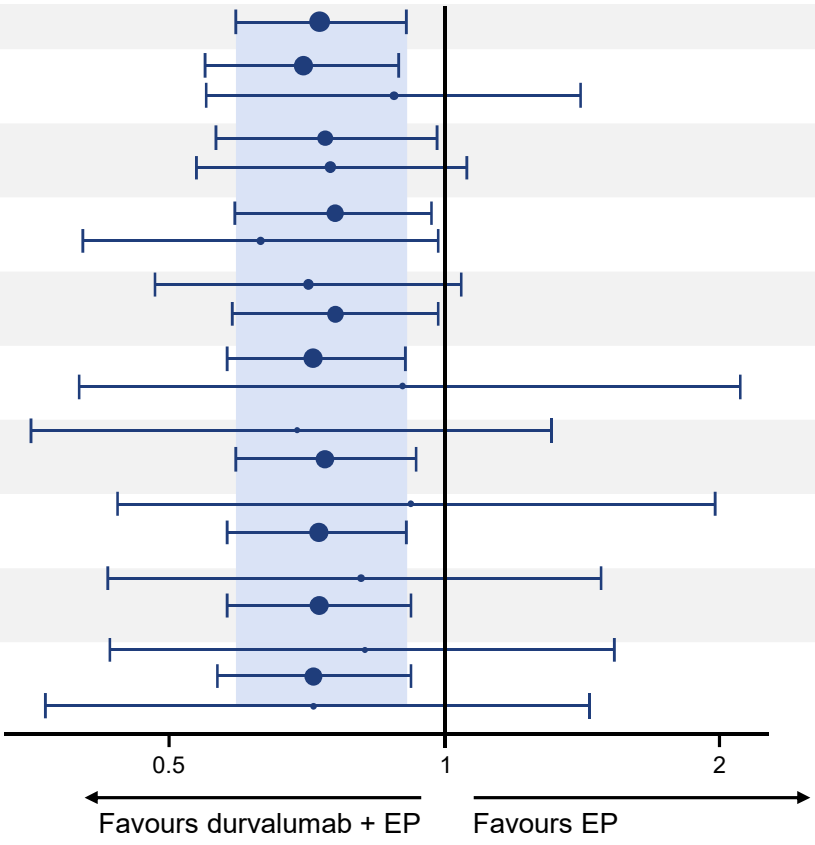
CI, confidence interval;
mOS, median overall survival

Overall Survival Subgroup Analysis

Pre-specified subgroup		HR (95% CI)
All patients (n=537)		0.73 (0.591–0.909)
Planned platinum agent	Carboplatin (n=402)	0.70 (0.548–0.890)
	Cisplatin (n=135)	0.88 (0.549–1.408)
Age	<65 years (n=324)	0.74 (0.562–0.982)
	≥65 years (n=213)	0.75 (0.536–1.058)
Sex	Male (n=374)	0.76 (0.590–0.968)
	Female (n=163)	0.63 (0.402–0.984)
Performance status	0 (n=189)	0.71 (0.483–1.043)
	1 (n=348)	0.76 (0.586–0.986)
Smoking status	Smoker (n=500)	0.72 (0.579–0.905)
	Non-smoker (n=37)	0.90 (0.399–2.107)
Brain/CNS metastases	Yes (n=55)	0.69 (0.354–1.312)
	No (n=482)	0.74 (0.591–0.933)
AJCC disease stage at diagnosis	Stage III (n=52)	0.92 (0.439–1.977)
	Stage IV (n=485)	0.73 (0.579–0.908)
Race	Asian (n=78)	0.81 (0.429–1.486)
	Non-Asian (n=458)	0.73 (0.580–0.919)
Region	Asia (n=76)	0.82 (0.430–1.536)
	Europe (n=405)	0.72 (0.564–0.919)
	Americas (n=56)	0.72 (0.366–1.438)



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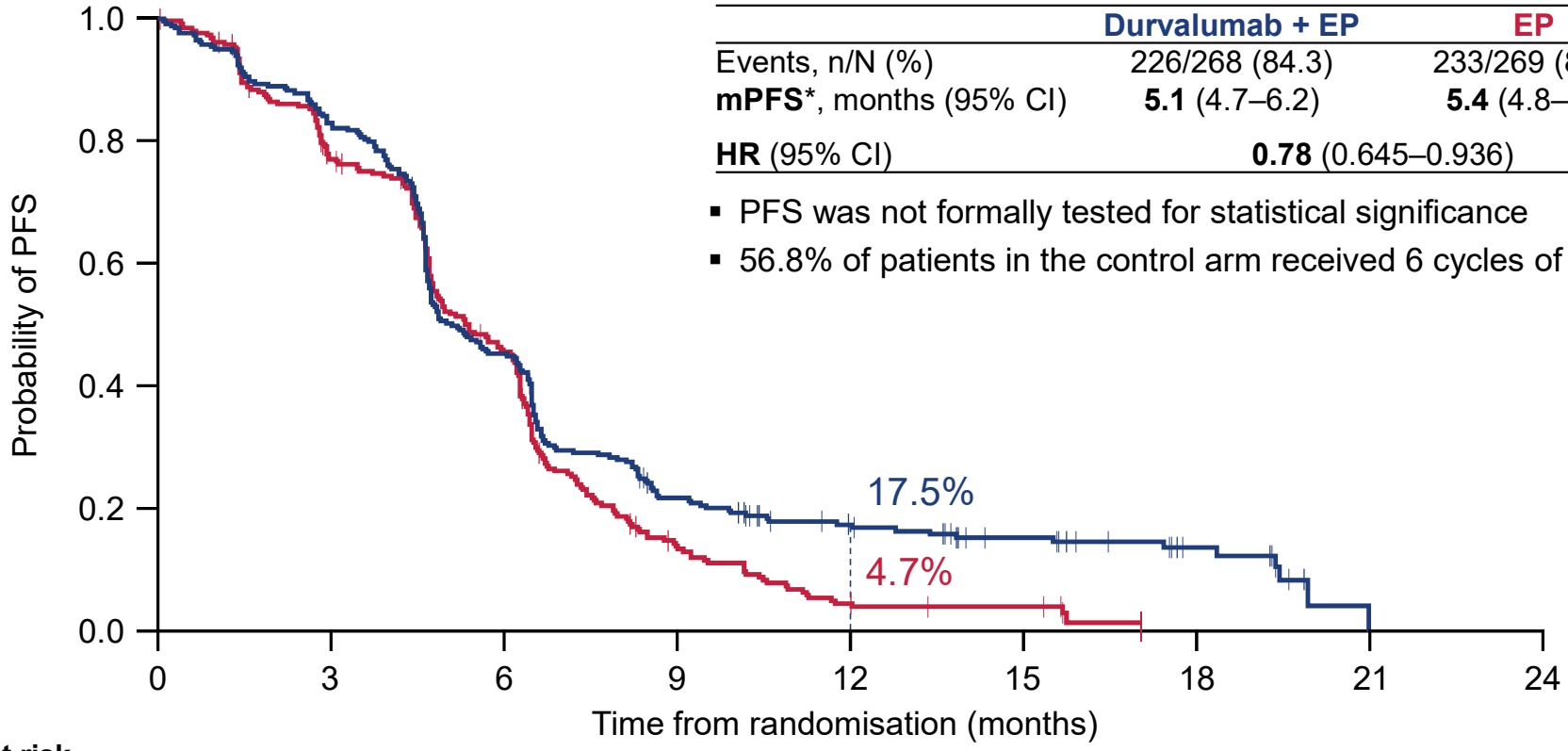
Progression-free Survival



	Durvalumab + EP	EP
Events, n/N (%)	226/268 (84.3)	233/269 (86.6)
mPFS*, months (95% CI)	**5.1** (4.7–6.2)	**5.4** (4.8–6.2)
HR (95% CI)	**0.78** (0.645–0.936)	

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

No. at risk									
Durvalumab + EP	268	220	119	54	34	22	10	0	0
EP	269	194	109	30	9	7	0	0	0

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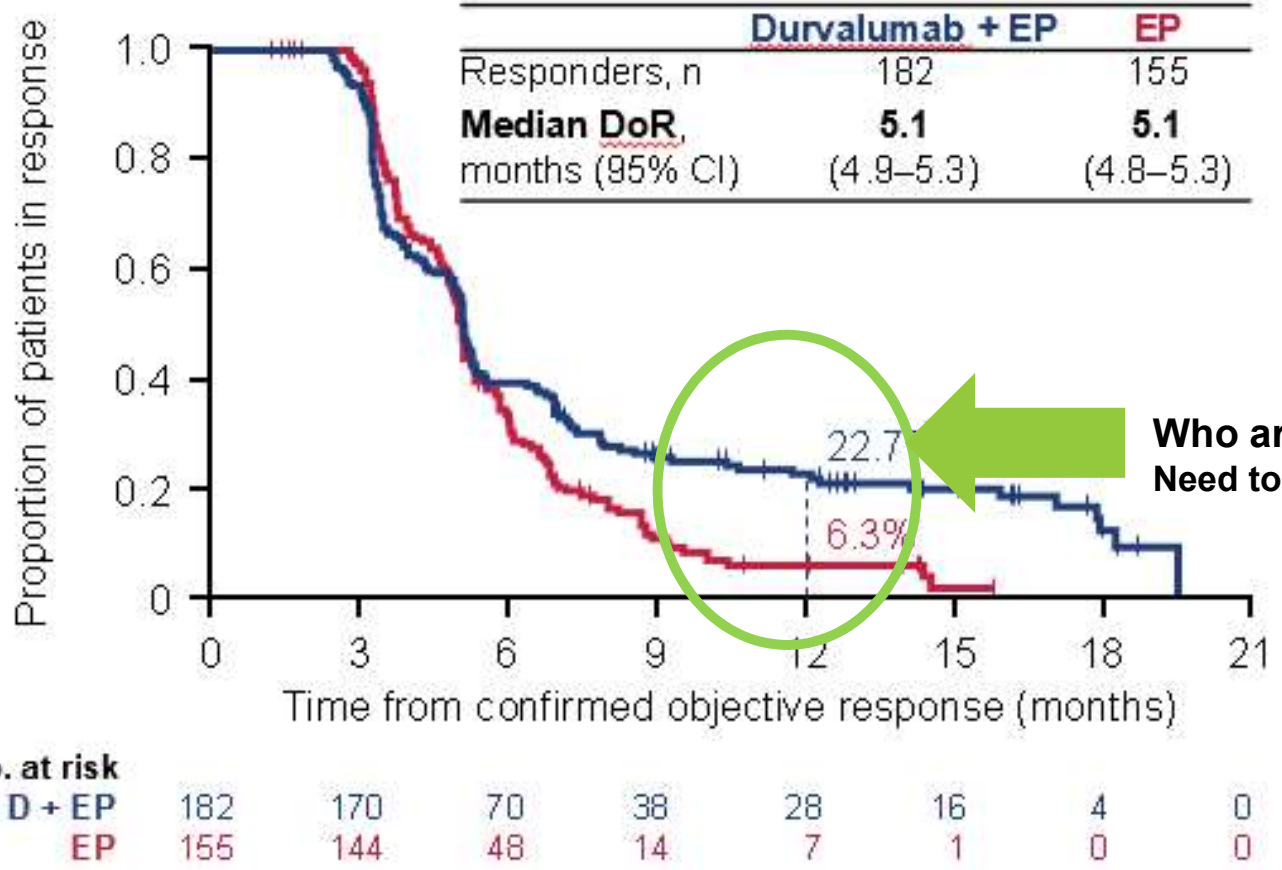
*Investigator assessed per RECIST v1.1

mPFS, median progression-free survival

Duration of Response



Who are these patients?
Need to find the right biomarkers

Paz-Ares WCLC 2019

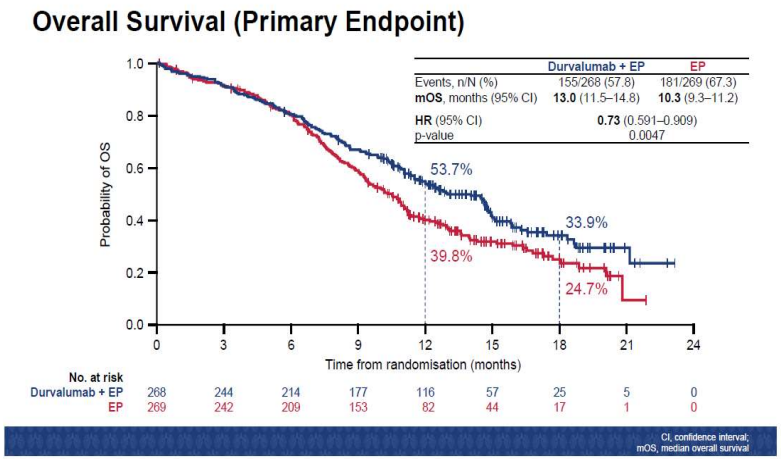
Safety Summary

	Durvalumab + EP (n=265)	EP (n=266)
Any-grade all-cause AEs, n (%)	260 (98.1)	258 (97.0)
Grade 3/4 AEs	163 (61.5)	166 (62.4)
Serious AEs	82 (30.9)	96 (36.1)
AEs leading to treatment discontinuation*	25 (9.4)	25 (9.4)
Immune-mediated AEs†	52 (19.6)	7 (2.6)
AEs leading to death	13 (4.9)	15 (5.6)
Treatment-related AEs leading to death‡	5 (1.9)	2 (0.8)

*Includes patients who permanently discontinued at least one study drug
†An event that is associated with drug exposure and consistent with an immune-mediated mechanism of action, where there is no clear alternate aetiology and the event required treatment with systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy; majority of immune-mediated AEs were low grade and thyroid related
‡AEs assessed by the investigator as possibly related to any study treatment. Causes of death were cardiac arrest, dehydration, hepatotoxicity, pancytopenia, and sepsis (one patient each) in the durvalumab + EP arm; pancytopenia and thrombocytopenia/haemorrhage (one patient each) in the EP arm

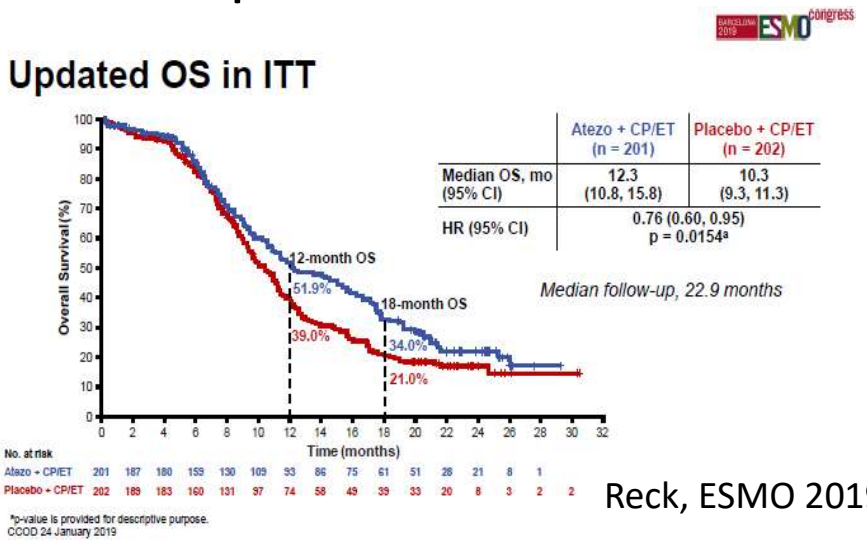
Paz-Ares WCLC 2019

CASPIAN



Paz-Ares, WCLC 2019

IMpower 133

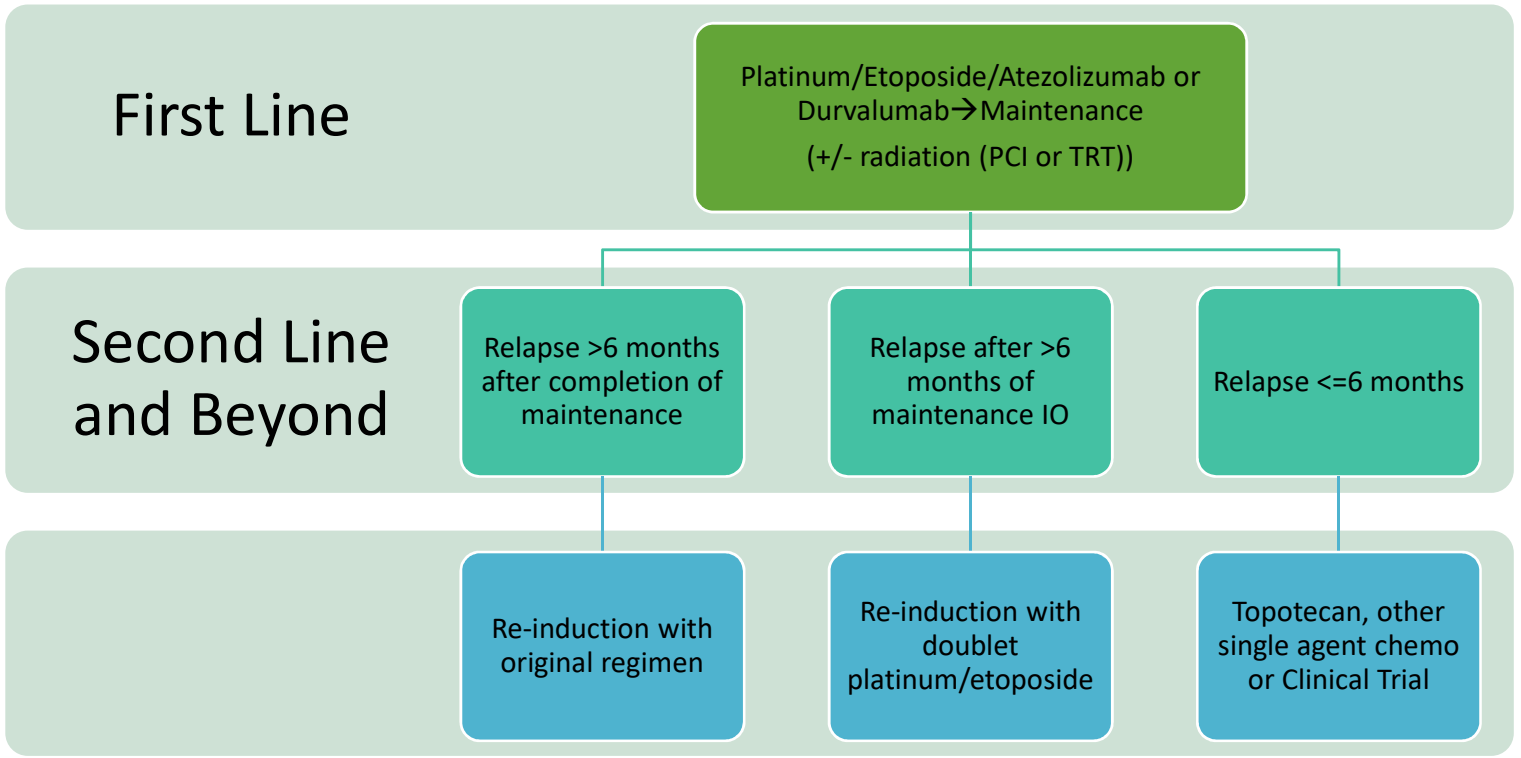


Reck, ESMO 2019

Caspian
• Open Label • PCI only in chemo group • Carbo or Cisplatin • Chemo alone received up to 6 cycles

IMpower 133
• Double Blinded • PCI allowed in both groups • Carboplatin only • Induction x 4 cycles in both arms

Current ES-SCLC Management



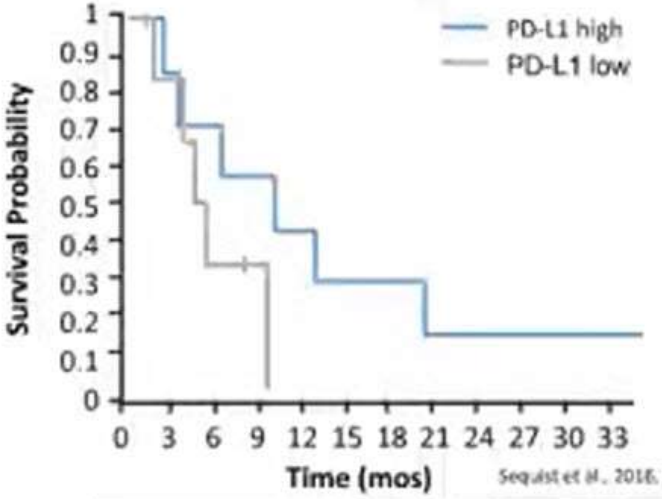
Based off NCCN guidelines v 2.2020

Biomarkers in SCLC

The role of PD-L1 status in SCLC

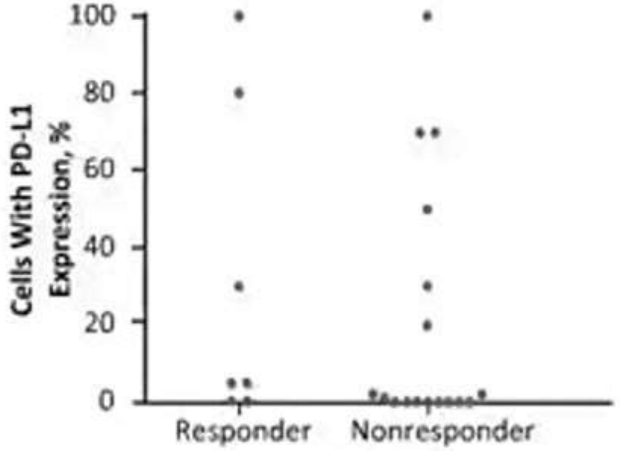
PCD4989g, SCLC cohort[1]	KEYNOTE-028, SCLC cohort[2]	Checkmate 032[3]
N=17	N=28*	N=216
53% of patients tested PD-L1+ (evaluated in tumor or immune cells)	29% of evaluable samples tested PD-L1+ (≥1% of tumor and immune cells or positive staining in stroma)	16% of evaluable samples tested PD-L1+ (≥1% of tumor cells)

PCD4989g[1]



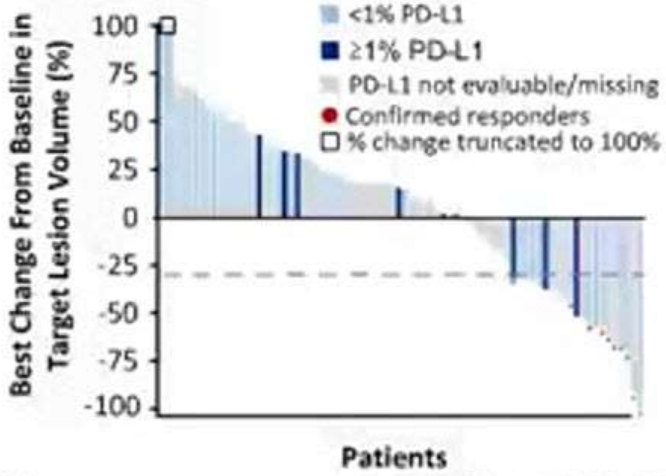
Sequist et al., 2016, ESMO.[1]

KEYNOTE-028[2]



Ott et al., 2015, WCLC.[2]

Checkmate 032 (nivo mono arm)[3]



Antonia et al., 2016, ASCO.[3]

Data thus far do not strongly support the ability of PD-L1 to predict response to I-O in SCLC

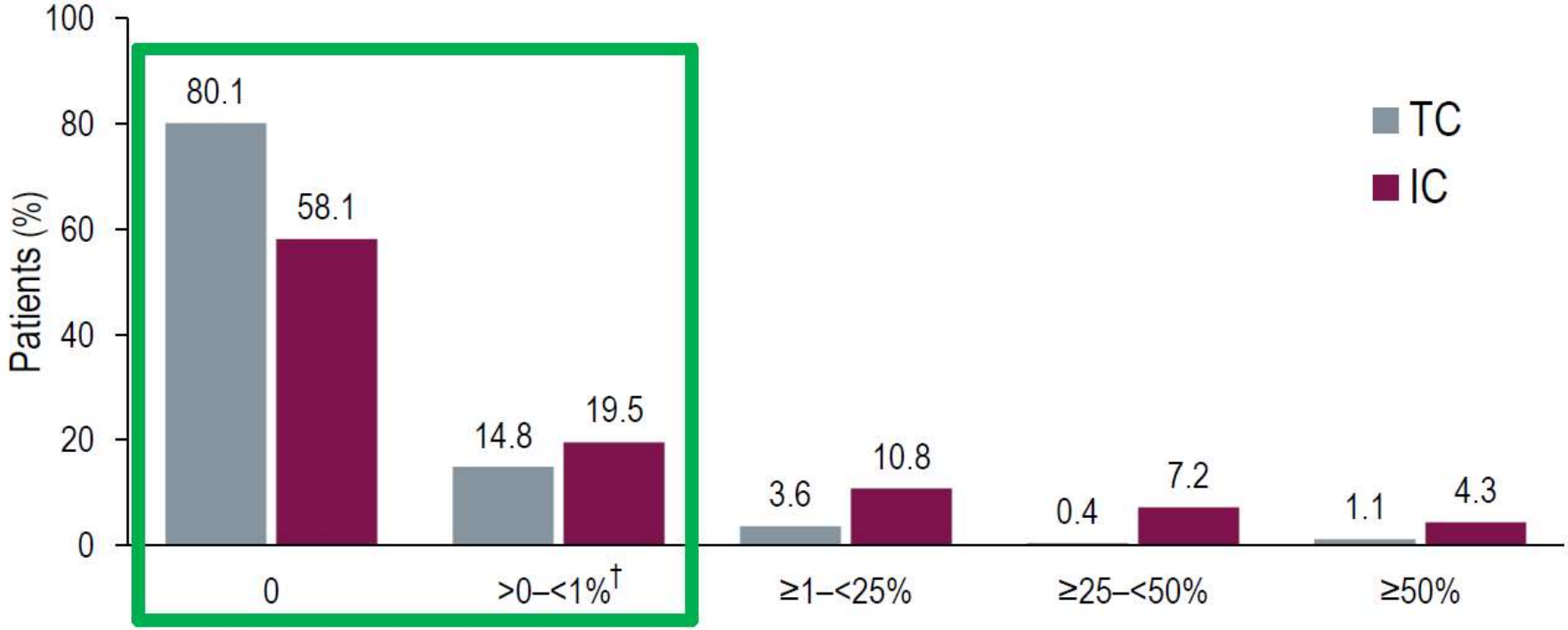
*Eligible patients had PD-L1 expression in ≥1% of tumor or immune cells in tumor nests or staining in the stroma.

I-O=immuno-oncology; mono=monotherapy; nivo=nivolumab; PD-L1=programmed death ligand 1; SCLC=small cell lung cancer.

1. Sequist LV et al. Poster presentation at ESMO 2016. 1425PD. 2. Ott PA et al. Presentation at WCLC 2015. 3285. 3. Antonia SJ et al. Oral presentation at ASCO 2016. 100.

PREVALENCE OF PD-L1 EXPRESSION ON TCs OR ICs*

CASPIAN



- 94.9% and 77.6% of patients had PD-L1 expression <1% on TCs and ICs, respectively
- Due to low PD-L1 expression, a 1% cut-off was used in post-hoc analyses

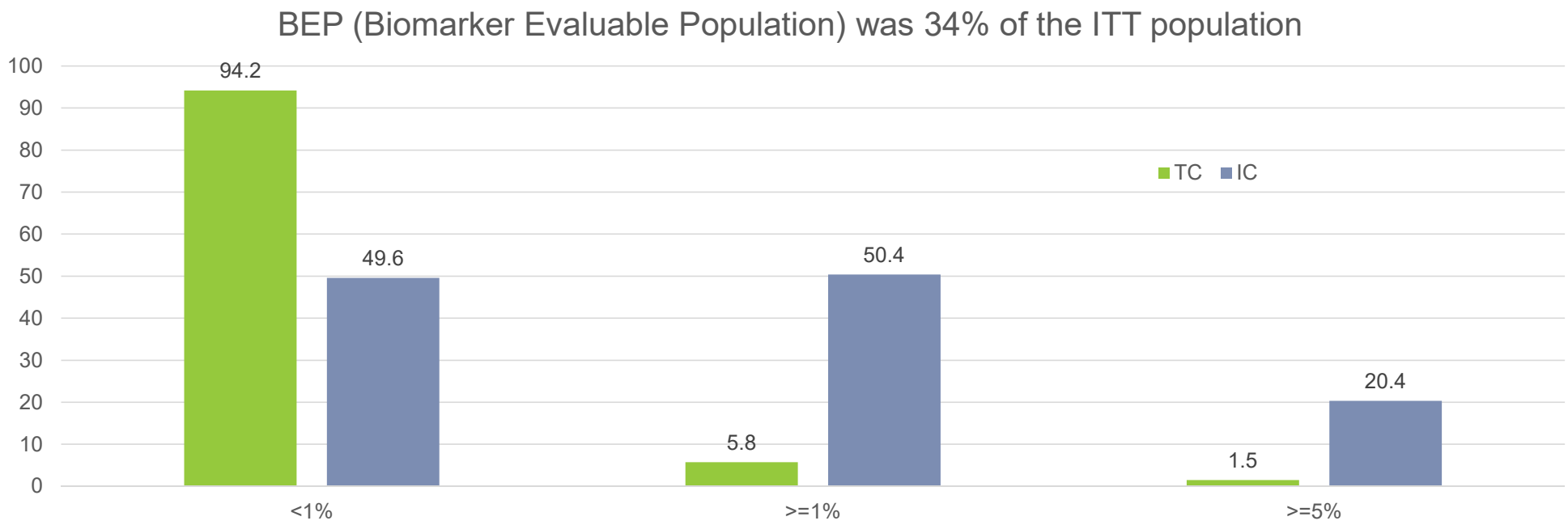
Paz-Ares ESMO 2019

BARCELONA 2019 ESMO congress

*Based on 277 PD-L1-evaluable patients in the durvalumab + EP and EP arms

†Includes patients whose tumours had <1% PD-L1 expression on TCs or ICs, but not absolute C

IMpower 133: Prevalence of PD-L1 Expression on TC/IC

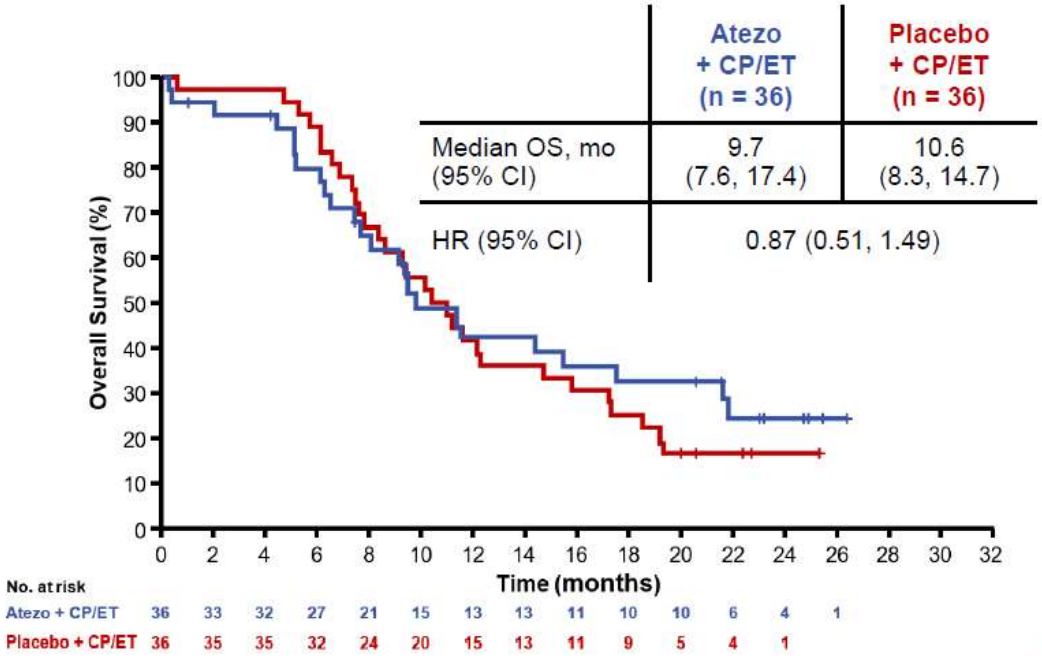


Reck, ESMO 2019

IMpower 133:
Updated OS in PD-L1 expression subgroups

BARCELONA 2019 ESMO congress

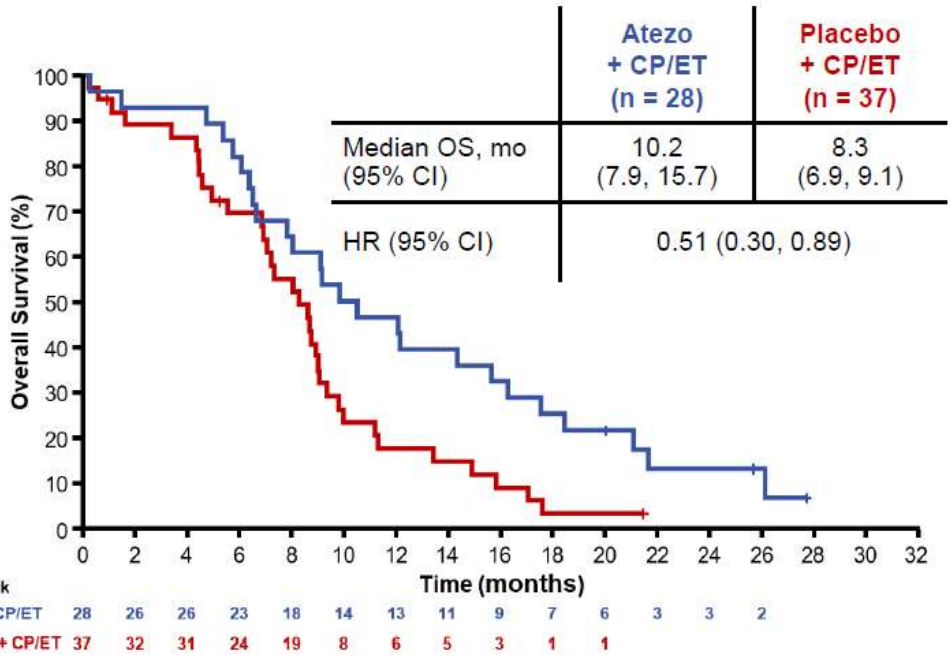
PD-L1 Expression ≥ 1% TC or IC



	Atezo + CP/ET (n = 36)	Placebo + CP/ET (n = 36)
Median OS, mo (95% CI)	9.7 (7.6, 17.4)	10.6 (8.3, 14.7)
HR (95% CI)	0.87 (0.51, 1.49)	

No. at risk														
Atezo + CP/ET	36	33	32	27	21	15	13	13	11	10	10	6	4	1
Placebo + CP/ET	36	35	35	32	24	20	15	13	11	9	5	4	1	

PD-L1 Expression < 1% TC or IC



	Atezo + CP/ET (n = 28)	Placebo + CP/ET (n = 37)
Median OS, mo (95% CI)	10.2 (7.9, 15.7)	8.3 (6.9, 9.1)
HR (95% CI)	0.51 (0.30, 0.89)	

No. at risk														
Atezo + CP/ET	28	26	26	23	18	14	13	11	9	7	6	3	3	2
Placebo + CP/ET	37	32	31	24	19	8	6	5	3	1	1			

Median follow-up, 22.9 months

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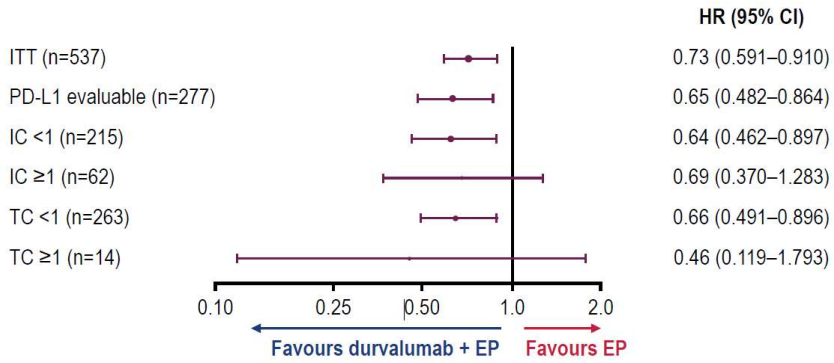
OVERALL SURVIVAL BASED ON PD-L1 EXPRESSION



CASPIAN

- Durvalumab + EP was associated with improved OS vs EP, regardless of PD-L1 expression with a 1% cut-off
- No significant interaction was observed with OS based on PD-L1 expression as a continuous variable (TC, p=0.54; IC, p=0.23); similar results were observed with PFS and ORR

Paz-Ares ESMO 2019

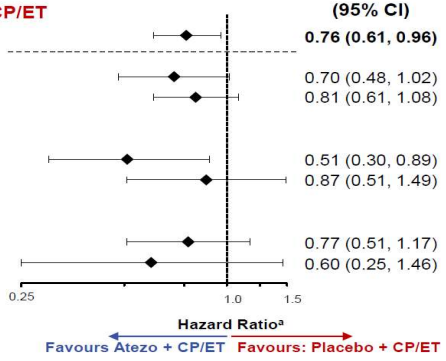
BARCELONA 2019 ESMO congress

The size of the HR dot represents th

IMpower 133

Updated OS in PD-L1 expression subgroups

Subgroup	Median OS (months) Atezo + CP/ET	Median OS (months) Placebo + CP/ET	OS Hazard Ratio[a] (95% CI)
ITT (N = 403)	**12.3**	**10.3**	**0.76 (0.61, 0.96)**
ITT-BEP (n = 137)	9.9	8.9	0.70 (0.48, 1.02)
Non-BEP (n = 266)	14.6	11.2	0.81 (0.61, 1.08)
PD-L1 expression 1% TC or IC			
< 1% PD-L1 (n = 65)	10.2	8.3	0.51 (0.30, 0.89)
≥ 1% PD-L1 (n = 72)	9.7	10.6	0.87 (0.51, 1.49)
PD-L1 expression 5% TC or IC			
< 5% PD-L1 (n = 108)	9.2	8.9	0.77 (0.51, 1.17)
≥ 5% PD-L1 (n = 29)	21.6	9.2	0.60 (0.25, 1.46)



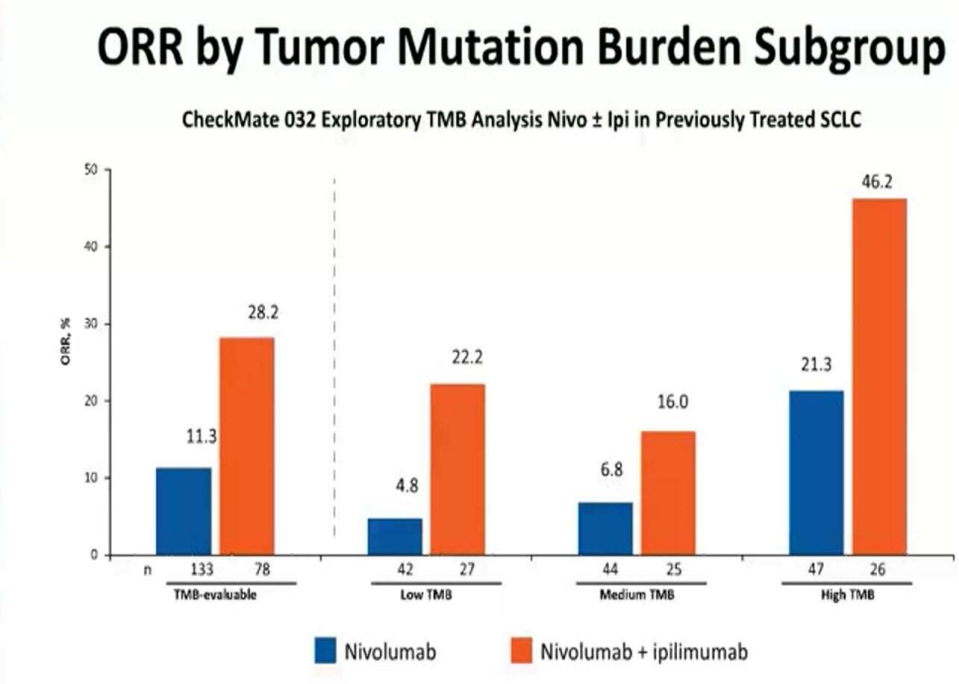
[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.
CCOD 24 January 2019

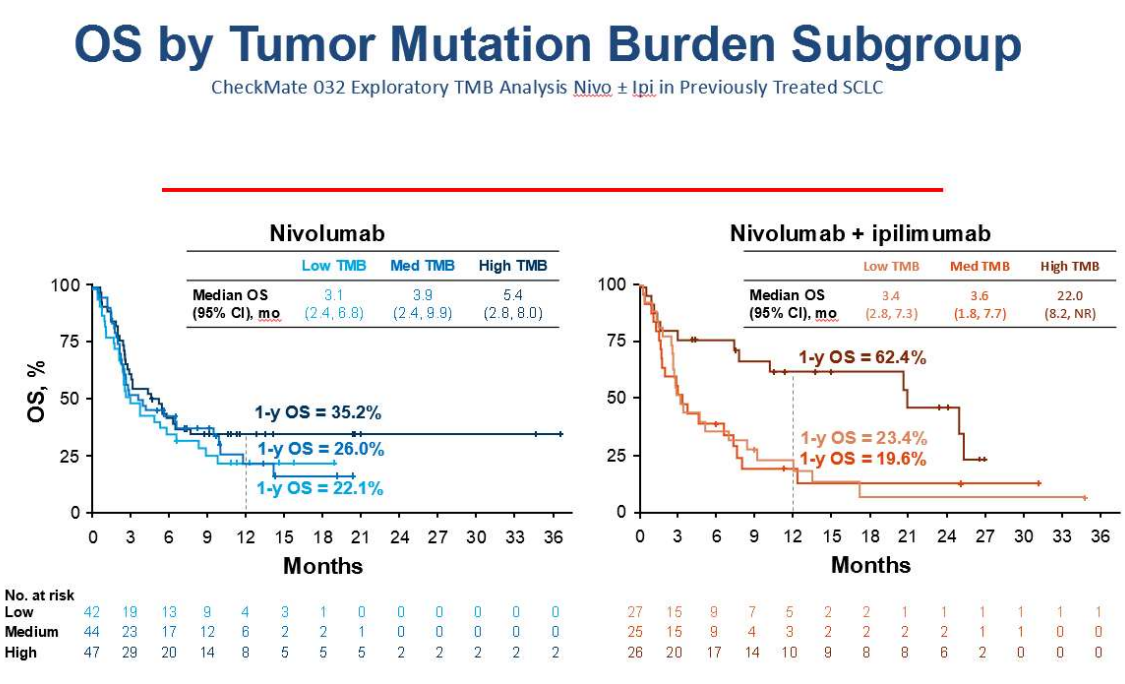
Reck, ESMO 2019

IMpower133 Updated OS Analysis: presented by Dr Martin Reck

http://bit.ly/2Z32WhW

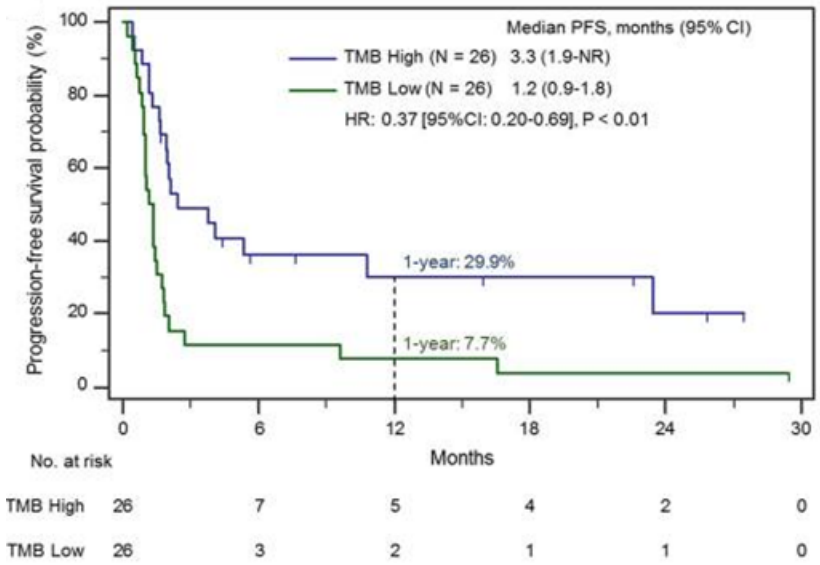
TMB (WES) as biomarker

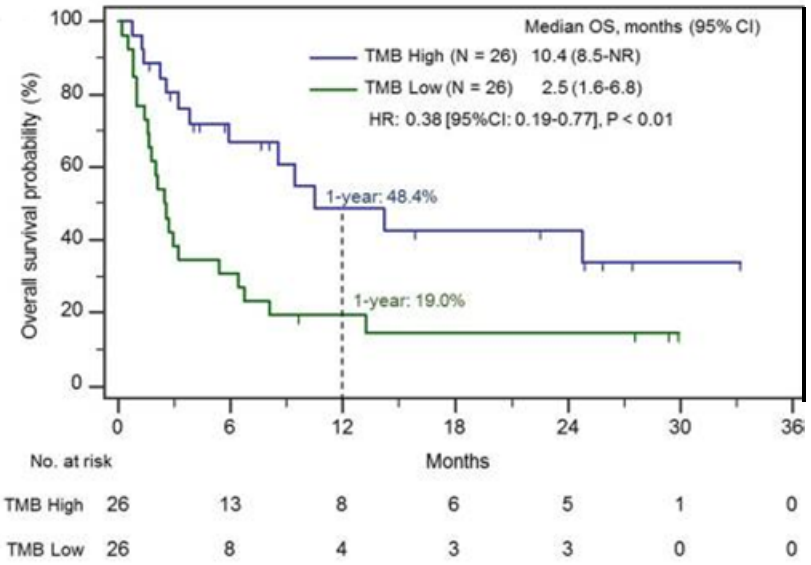




Hellmann, Cancer Cell 2018; 33 (5): 853-861

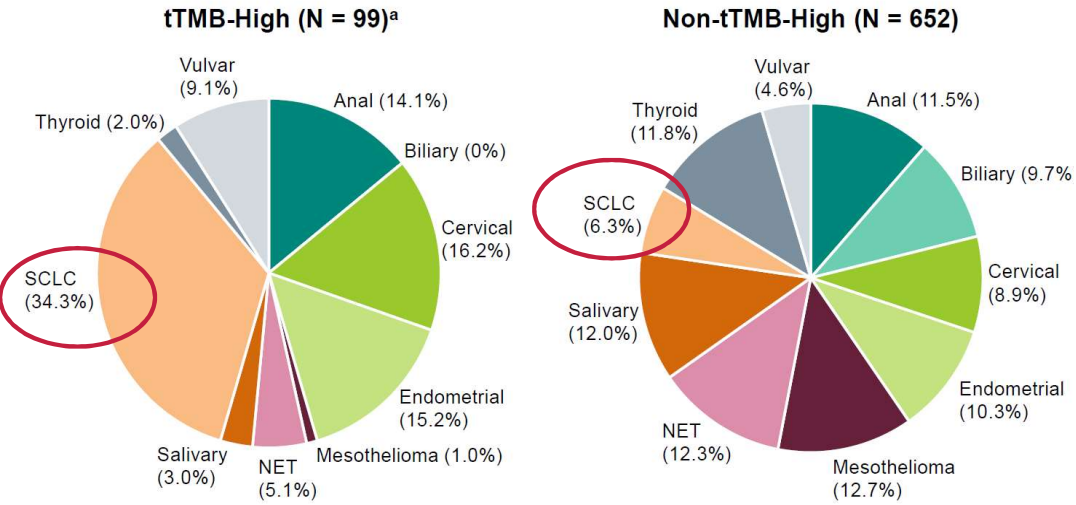
NGS testing and TMB in SCLC: retrospective review

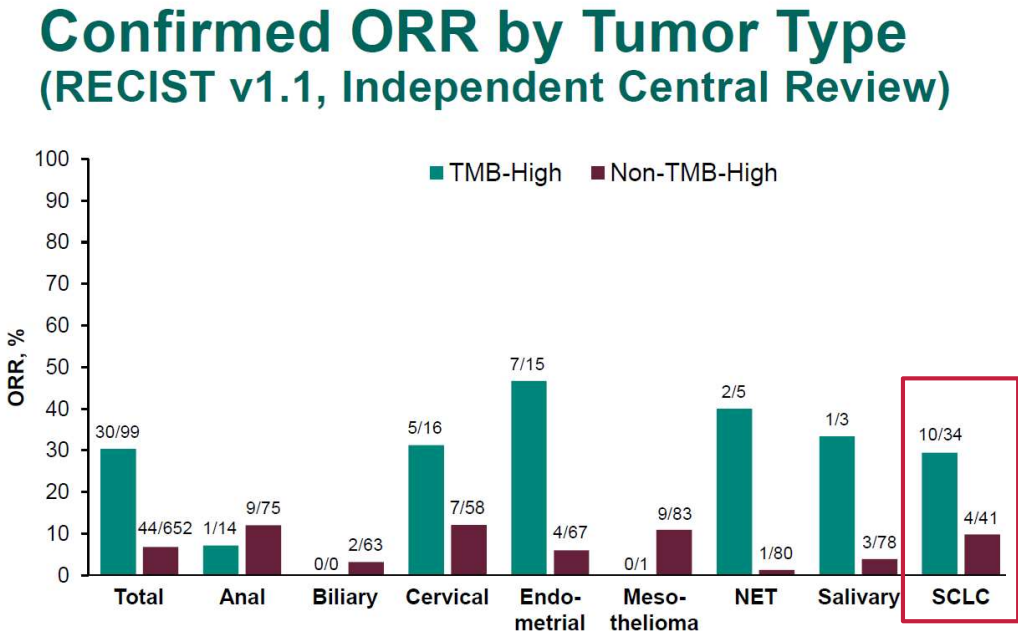




Ricciuti, et al. J Immuno Cancer 2019,7:87

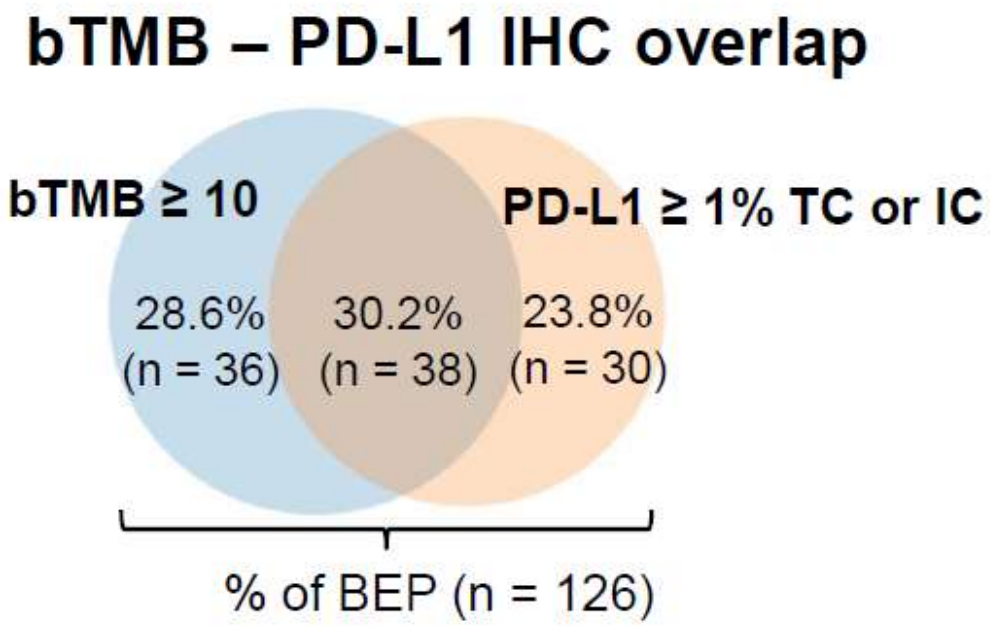
KEYNOTE-158:
Association of tTMB with outcomes





Marabelle ESMO, 2019

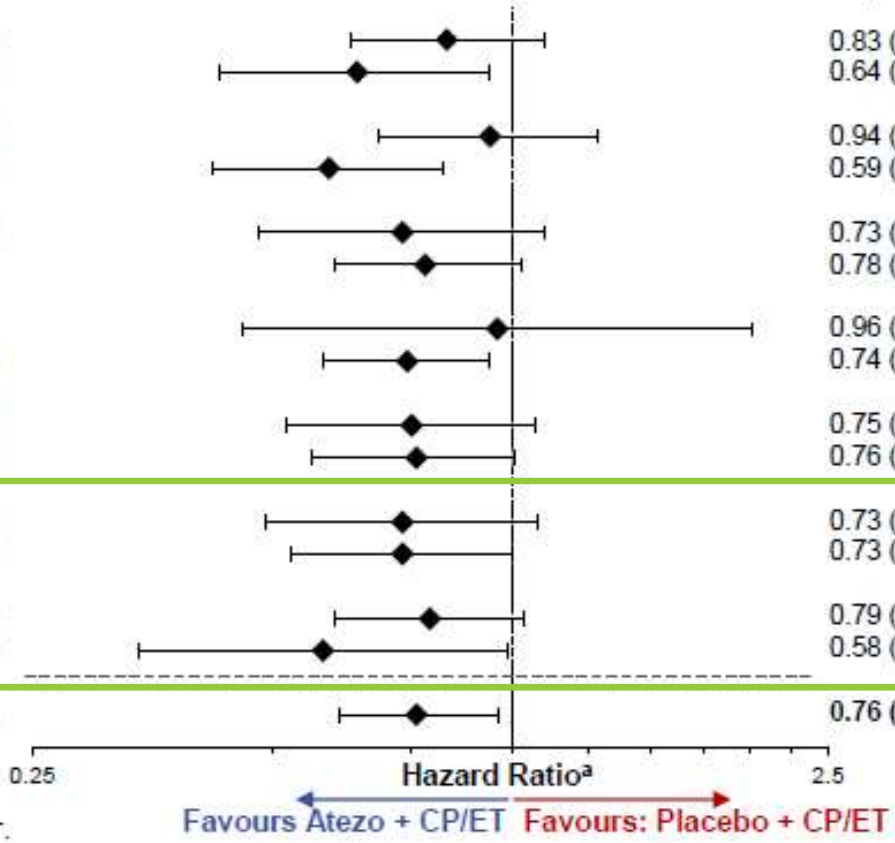
bTMB and PD-L1 identify distinct patient populations IMpower 133:



Reck, ESMO 2019

Updated OS in subgroups

Subgroup	Median OS (months) Atezo + CP/ET	Placebo + CP/ET	OS Hazard Ratio[a] (95% CI)
Male (n = 261)	12.2	10.9	0.83 (0.63, 1.10)
Female (n = 142)	13.6	9.5	0.64 (0.43, 0.94)
< 65 years (n = 217)	12.1	11.5	0.94 (0.68, 1.28)
≥ 65 years (n = 186)	14.4	9.6	0.59 (0.42, 0.82)
ECOG PS 0 (n = 140)	16.8	12.6	0.73 (0.48, 1.10)
ECOG PS 1 (n = 263)	11.3	9.3	0.78 (0.60, 1.03)
Brain metastases (n = 35)	8.5	9.7	0.96 (0.46, 2.01)
No brain metastases (n = 368)	12.6	10.4	0.74 (0.58, 0.94)
Liver metastases (n = 149)	9.3	7.8	0.75 (0.52, 1.07)
No liver metastases (n = 254)	16.3	11.2	0.76 (0.56, 1.01)
bTMB < 10 (n = 134)	11.8	9.4	0.73 (0.49, 1.08)
bTMB ≥ 10 (n = 212)	14.9	11.2	0.73 (0.53, 1.00)
bTMB < 16 (n = 266)	12.5	10.0	0.79 (0.60, 1.04)
bTMB ≥ 16 (n = 80)	17.1	11.9	0.58 (0.34, 0.99)
ITT (N = 403)	**12.3**	**10.3**	**0.76 (0.61, 0.96)**



A total of 57 patients had unknown bTMB score.
bTMB, blood tumour mutational burden.
[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.
CCOD 24 January 2019

Conclusion

First Line Chemotherapy + Immunotherapy should be considered SOC for Extensive Stage SCLC

- Carboplatin/Etoposide/Atezolizumab (FDA approved) –IMpower 133
- Cisplatin or Carboplatin/Etoposide/Durvalumab - CASPIAN

Further Biomarker Analysis crucial

- Tissue TMB appears to be most predictive for immunotherapy response
- Others being explored: bTMB, PD-L1
- Appropriate cut-points not standardized, need further confirmation