PERSPECTIVAS EM ONCOLOGIA IX

18, 19 e 20 FEVEREIRO 2021

EDIÇÃO VIRTUAL

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18, 19 e 20 FEVEREIRO 2021 EDIÇÃO VIRTUAL

Imunoterapia no tratamento do mesotelioma pleural e no cancro de pequenas células do pulmão

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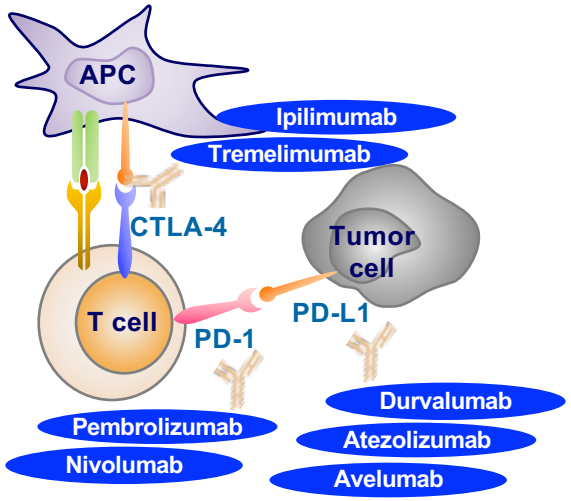
18 de Fevereiro de 2021

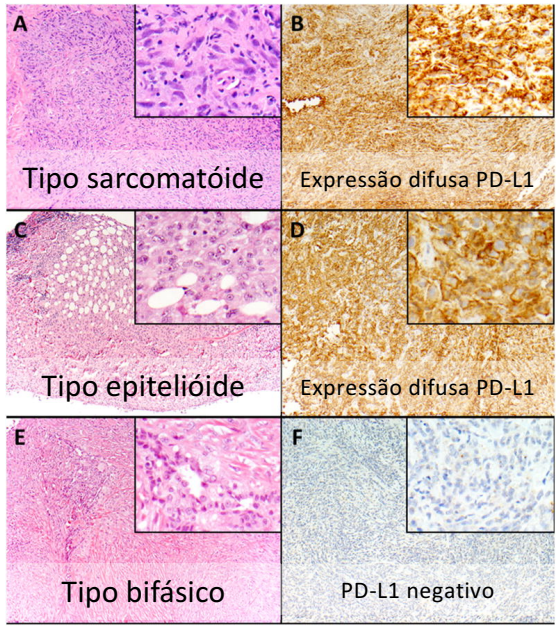


Inibição da proliferação e função das células T

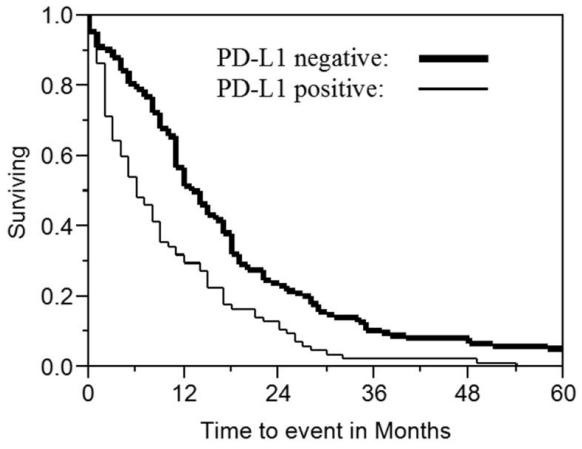
Adaptado de Pardoll DM, *Nat Rev Cancer*, 2012

Mesotelioma

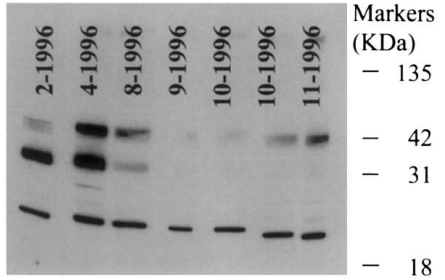
Pistas para o sucesso da imunoterapia no Mesotelioma

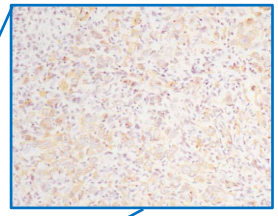


Mansfield et al. J Thorac Oncol. 2014 Jul;9(7):1036-1040

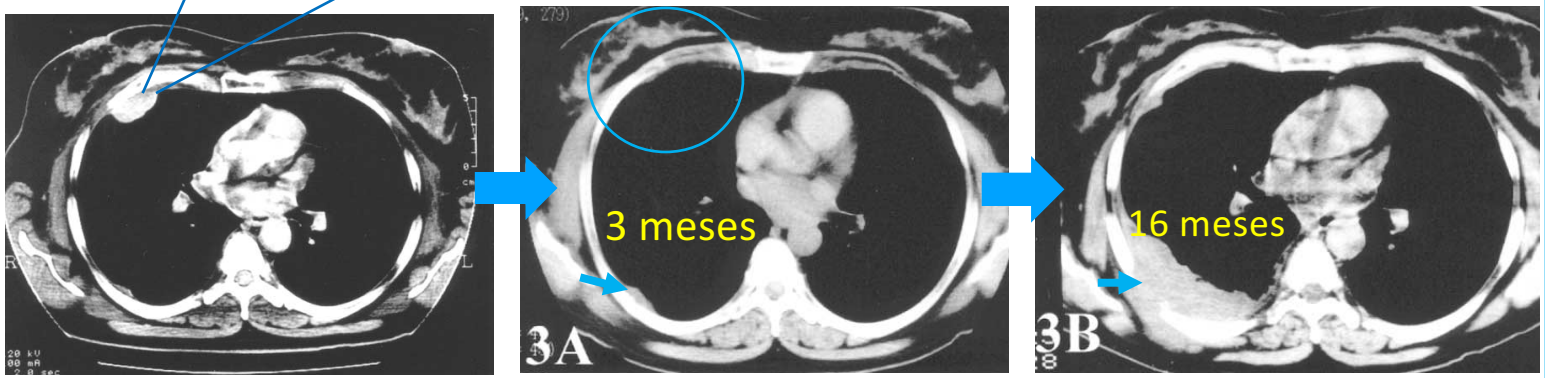


Perda de resposta serológica





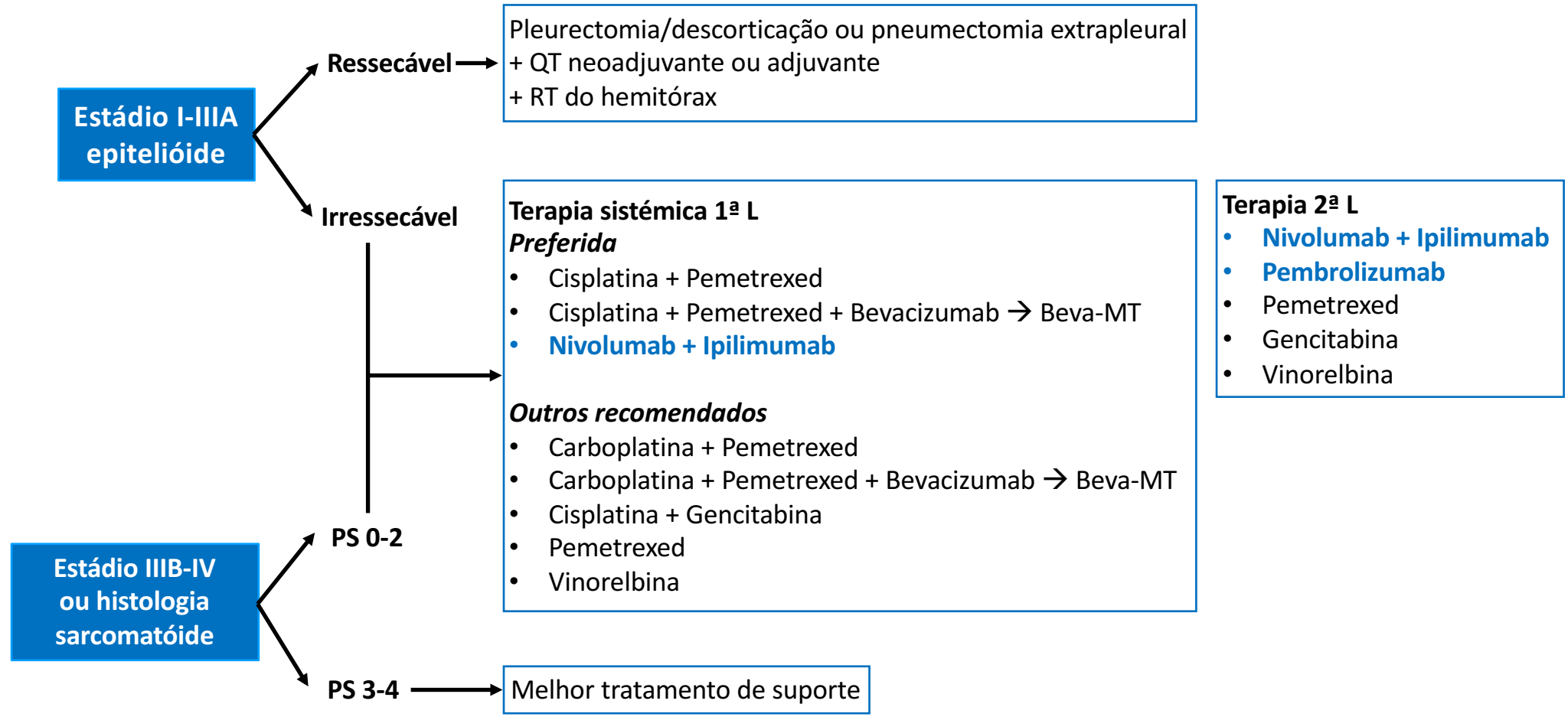
Células tumorais (castanho) e infiltrado mononuclear



Robinson et al. Lung Cancer 32 (2001) 197–201

- Expressão PD-L1 em ~40% dos mesoteliomas
- Expressão PD-L1 associa-se ao tipo sarcomatóide e a mau prognóstico
- A infiltração linfocitária associa-se a melhor prognóstico

NCCN Guidelines Version 1.2021
Malignant Pleural Mesothelioma



Sinergia entre Nivolumab e Ipilimumab

Ipilimumab (anti–CTLA-4)

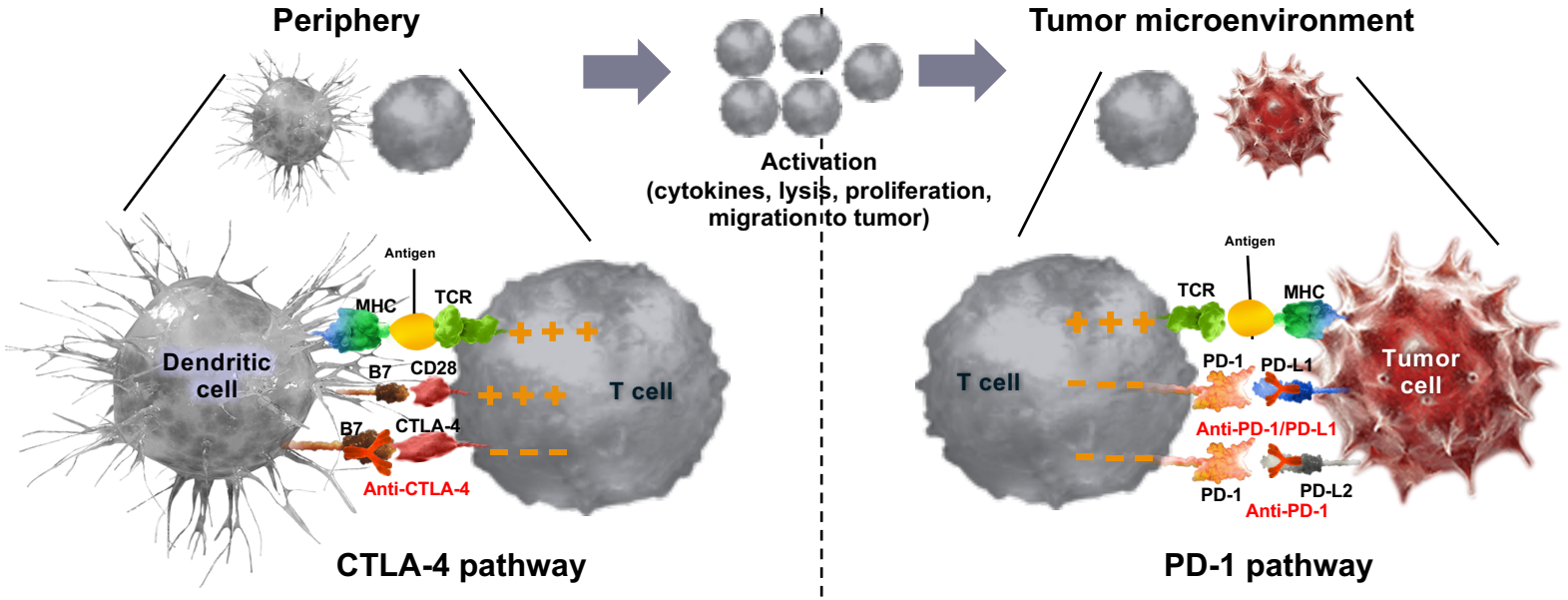
Induz resposta anti-tumoral de céls T *de novo*

- Possibilita adaptação ao tumor em evolução
- Promove a emergência de céls T de memória
- Provoca o aumento compensatório de PD-L1 tumoral

Nivolumab (anti–PD-1)

Restaura função anti-tumoral das céls T

- Aumenta a resposta de céls T pré-existente
- Aumenta a produção de citocinas



Adapted from Weber J. *J Cancer Immunol Immunother*. 2009;58:823-830.

Adapted from Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Checkmate 743 Phase 3 RCT: Nivo+ipilimumab vs Platino/Pemetrexed 1L em mesotelioma pleural maligno irresecável

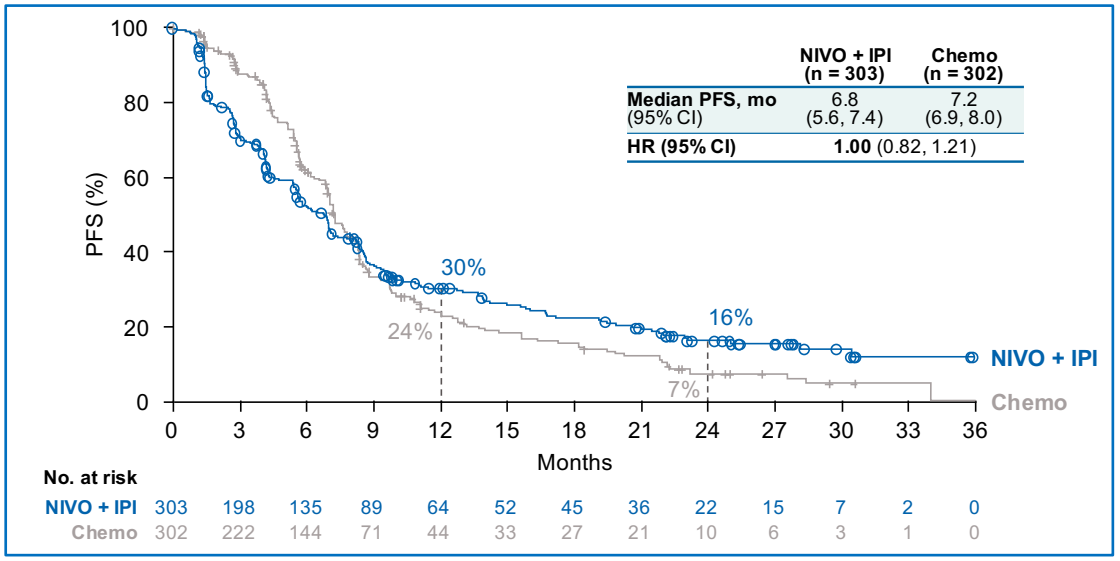
Key Eligibility Criteria
- Unresectable pleural mesothelioma
- No prior systemic therapy
- ECOG performance status 0–1

N=605 → R 1:1

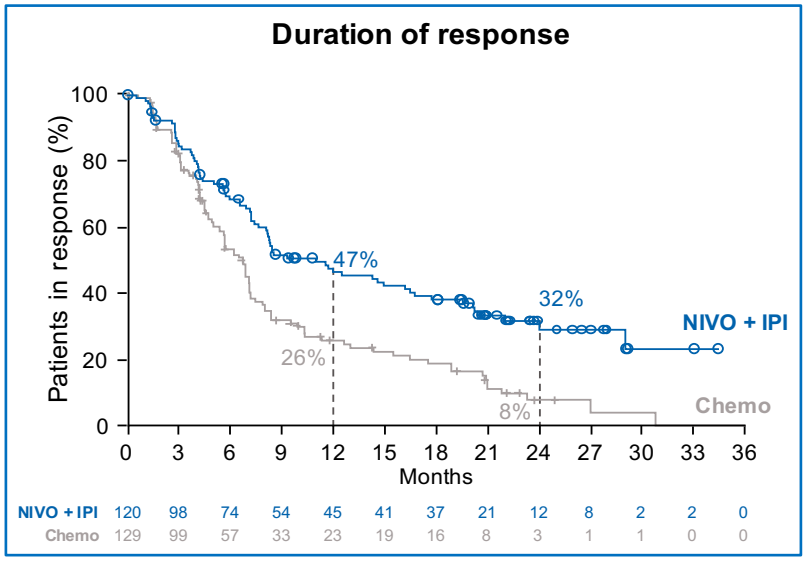
n=303: **Nivolumab** 3 mg/kg q2w + **Ipilimumab** 1 mg/kg q6w **(for up to 2 years)**

n=302: **cisplatin/carboplatin + pemetrexed Q3W (6 cycles)**

	NIVO+IPI	Platino+Pem
DCR	76.6%	85.1%
ORR	40%	43%

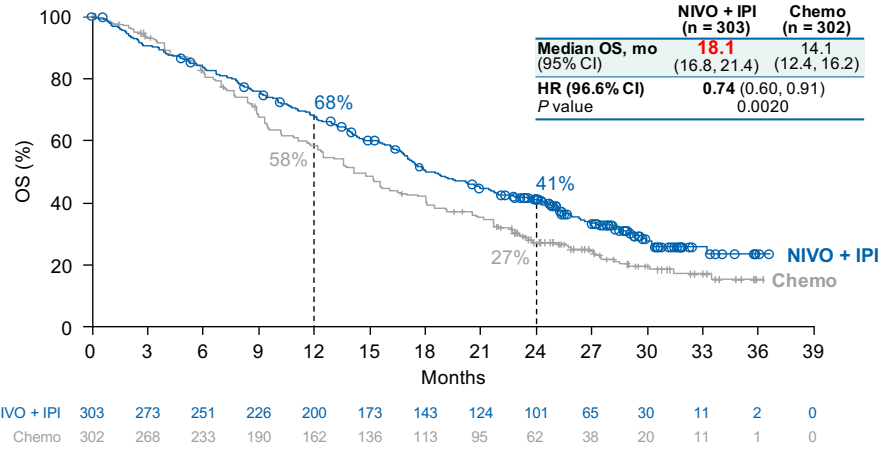


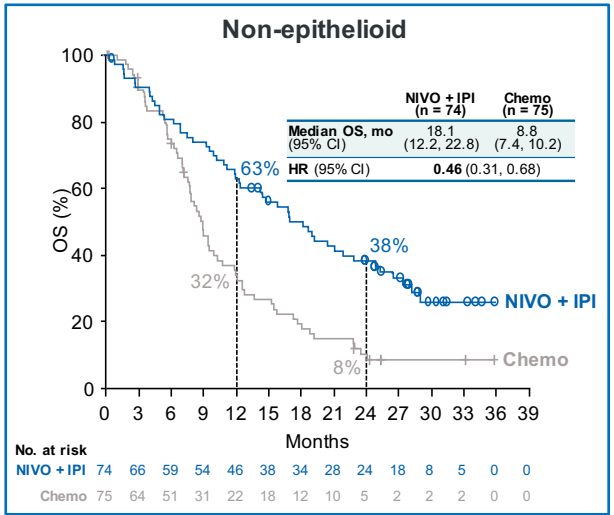
	NIVO + IPI (n = 303)	Chemo (n = 302)
Median PFS, mo (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.0)
HR (95% CI)	**1.00** (0.82, 1.21)	

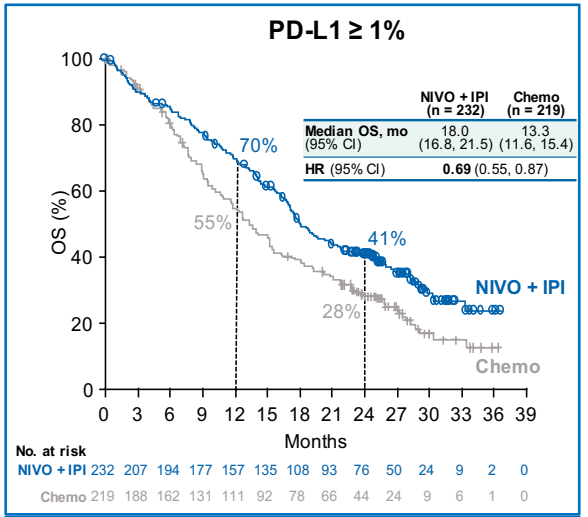


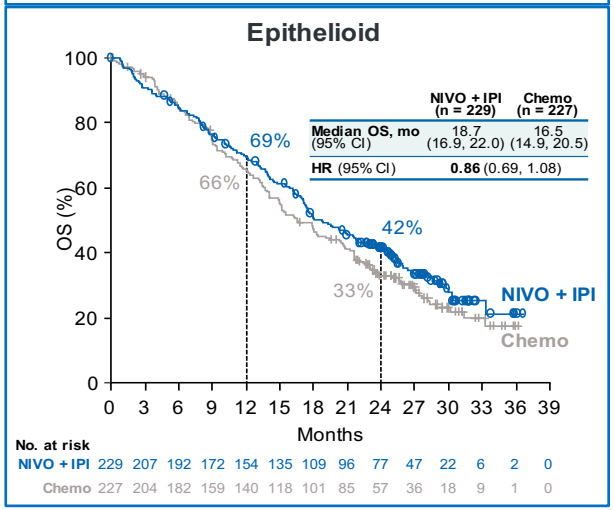
Baas et al. Lancet. 2021 Jan 30;397(10272):375-386

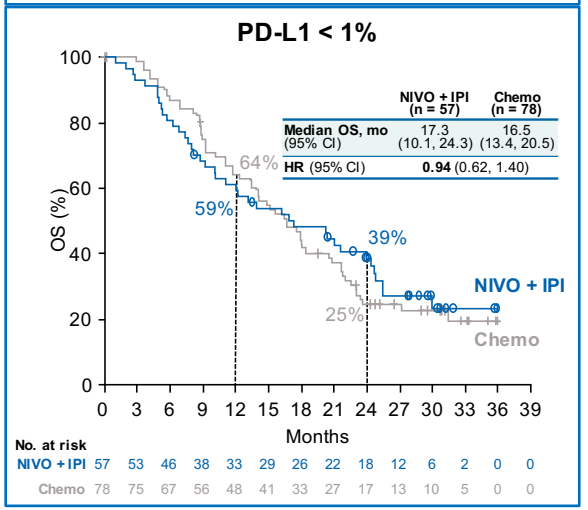
Checkmate 743 Phase 3 RCT: Nivo+ipilimumab vs Platino/Pemetrexed 1L em mesotelioma pleural maligno irresecável











Baas et al. Lancet. 2021 Jan 30;397(10272):375-386

Checkmate 743 Phase 3 RCT: Nivo+ipilimumab vs Platino/Pemetrexed 1L em mesotelioma pleural maligno irresecável

TRAE, %	NIVO + IPI (n = 300)		Chemo (n = 284)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any TRAE	80	30	82	32
TRAEs leading to discontinuation of any component of the regimen	23	15	16	7
Serious TRAEs	21	15	8	6
Treatment-related deaths	1 Pneumonitis, encephalitis, acute HF		0.4 myelosuppression	

- Duração mediana (IQR) de tratamento foi 5.6 (2.0–11.4) meses no braço NIVO + IPI e 3.5 (2.7–3.7) meses no braço QT
- O TRAEs mais comuns (≥15%) foram diarreia e prurido com NIVO + IPI; náuseas, anemia, neutropenia, fadiga, anorexia e astenia com QT

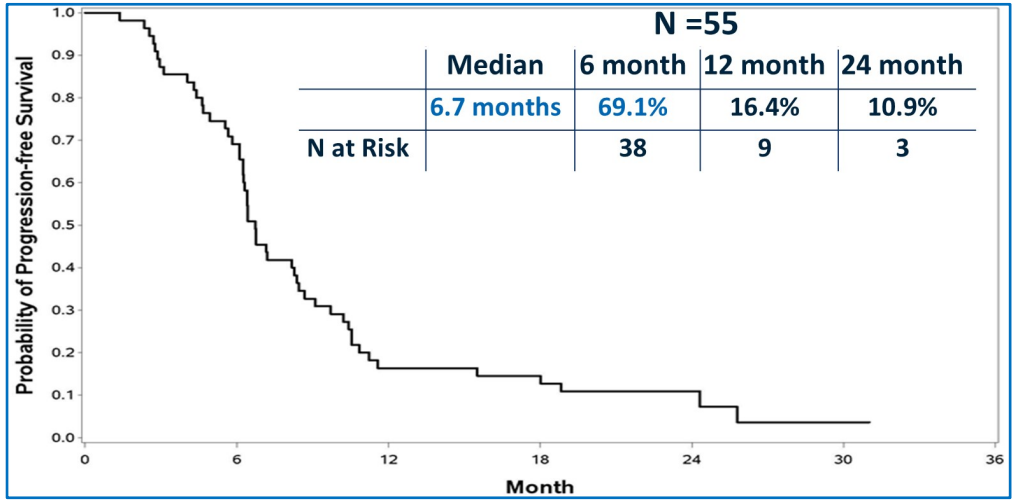
Baas et al. Lancet. 2021 Jan 30;397(10272):375-386

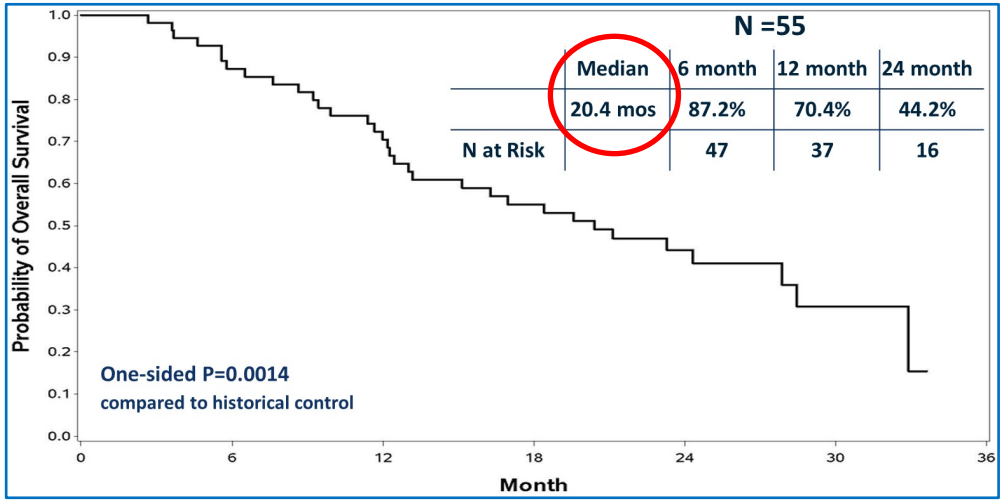
PrE0505 Phase II trial: Durvalumab em combinação com Cisplatina e Pemetrexed 1L para mesotelioma pleural maligno irressecável

- Unresectable MPM
- No prior therapy
- ECOG 0-1
- Baseline tumor specimen

→ Durvalumab 1120 mg + Pemetrexed 500 mg/m² + Cisplatin* 75 mg/m² every 3 weeks x 6 cycles → SD or PR → Durvalumab 1120 mg every 3 weeks until PD**

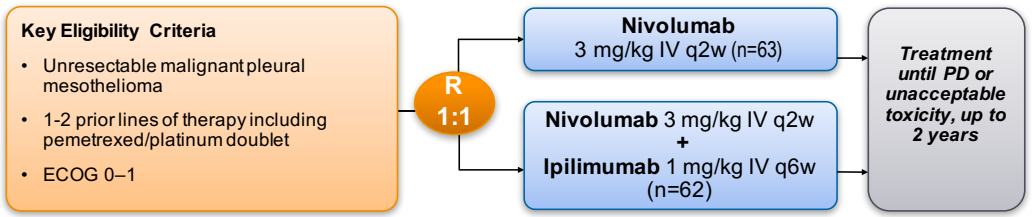
PR	56.4%
SD	40%
PD	1.8%

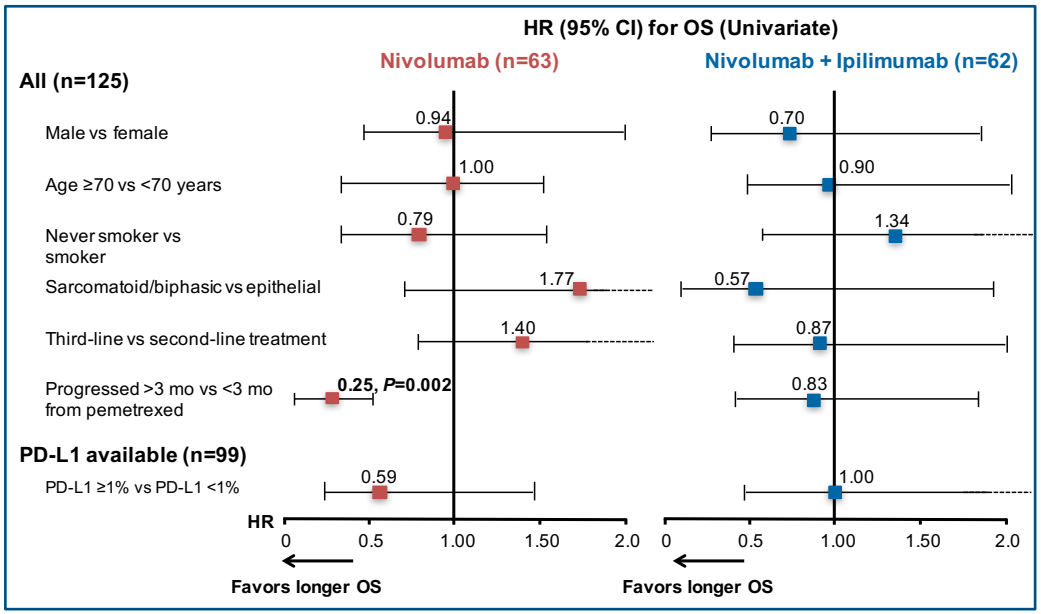


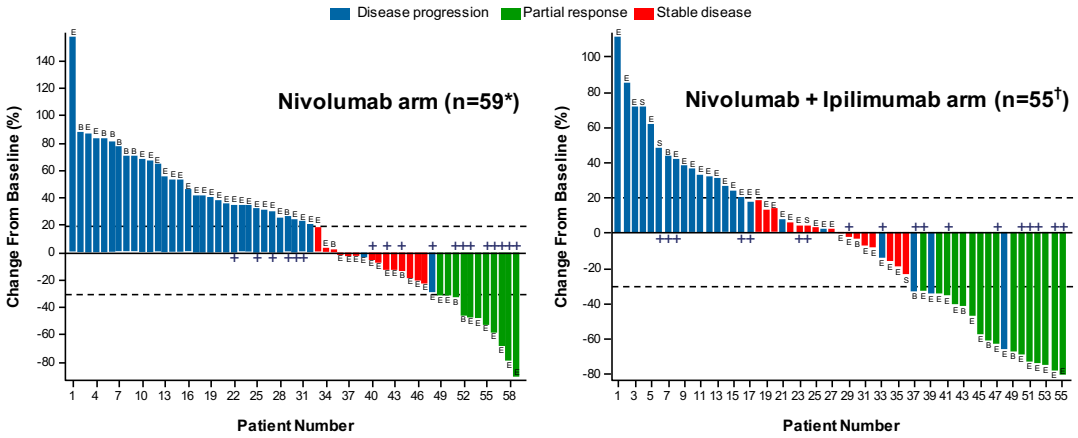


Apresentado na ASCO 2020. Forde et al. J Clin Oncol 38: 2020 (suppl; abstr 9003)

MAPS-2 Phase 2 trial: Nivolumab vs Nivo+ipilimumab em doentes previamente tratados (2L) com mesotelioma pleural maligno







Nivo (n=63)		Nivo + Ipi (n=62)
4 (2.8-5.7)	**PFS (95%CI), m**	5.6 (3.1-8.3)
11.9 (6.7-17.4)	**OS (95%CI), m**	15.9 (10.7-22.2)
25 (**40**)	**DCR, n (%)**	32 (**52**)
11 (**17.5**)	**ORR, n (%)**	16 (**25.8**)
14 (22.2)	**SD, n (%)**	16 (25.8)
34(54)	**PD, n (%)**	23 (37.1)

Scherpereel A et al. Lancet Oncol. 2019;20:239-53

ETOP 9-15 PROMISE-meso: Phase 3 Study of Pembrolizumab vs Chemotherapy in Previously Treated (2L) Patients With MPM

Key Eligibility Criteria

- Histologically confirmed MPM
- Progressing after/on previous platinum-based chemotherapy
- ECOG PS 0–1
- Life expectancy ≥3 months
- Measurable or evaluable disease according to RECIST v1.1 criteria

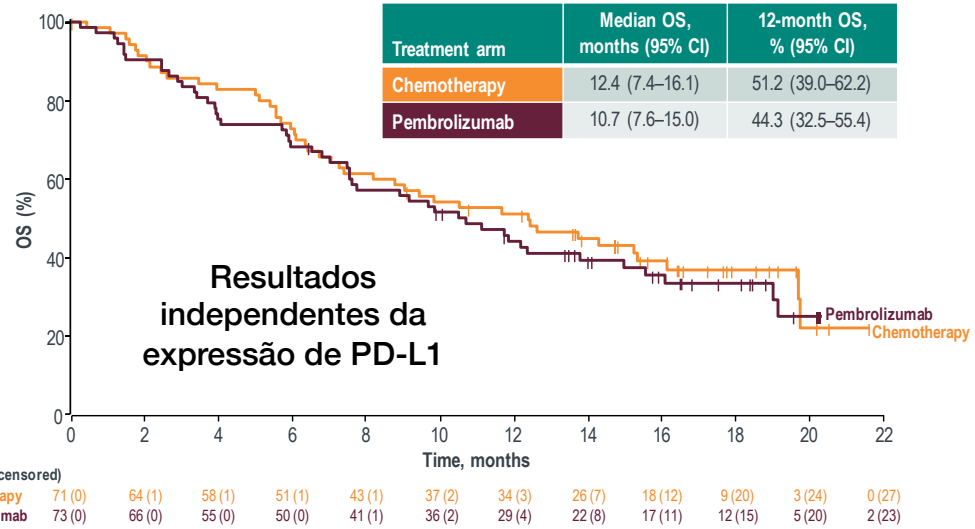
N=144 → R 1:1

- **Pembrolizumab 200 mg Q3W IV for 2 years[a] or until progression, lack of tolerability, or patient decision**
- **Chemotherapy by institutional choice**
  Gemcitabine 1000 mg/m² day 1 and day 8, Q3W IV OR
  Vinorelbine 30 mg/m² day 1 and day 8, Q3W IV OR
  Vinorelbine 60/80 mg/m² day 1 and day 8, Q3W PO

Crossover to pembrolizumab on progression permitted

	Pembrolizumab	Quimioterapia
PFS mediana	2.5 m	3.4 m
ORR	22%	6%*
DOR	4.6 m	7.2 m

*P=0.004



Popat et al. Annal Oncol 2020; 31(12):1734-45

1ª linha

Platino + Pemetrexed (6 ciclos)

ORR 43%
PFS 7.2 meses
OS 14.1 meses

+Bevacizumab

OS +2.7 meses
(Cis+Pem+Beva = 18.8m)

Nivolumab + Ipilimumab (até 2 anos)

ORR 40%
PFS 6.8 meses
OS 18.1 meses

Não epitelióide
PD-L1 ≥1%

Cis+Pem + Durva (6 ciclos) → Durva

ORR 56.4%
PFS 6.7 meses
OS 20.4 meses

2ª linha

Nivo + Ipilimumab

ORR 25.8%
PFS 5.6 meses
OS 15.9 meses

Gencitabina/VNR

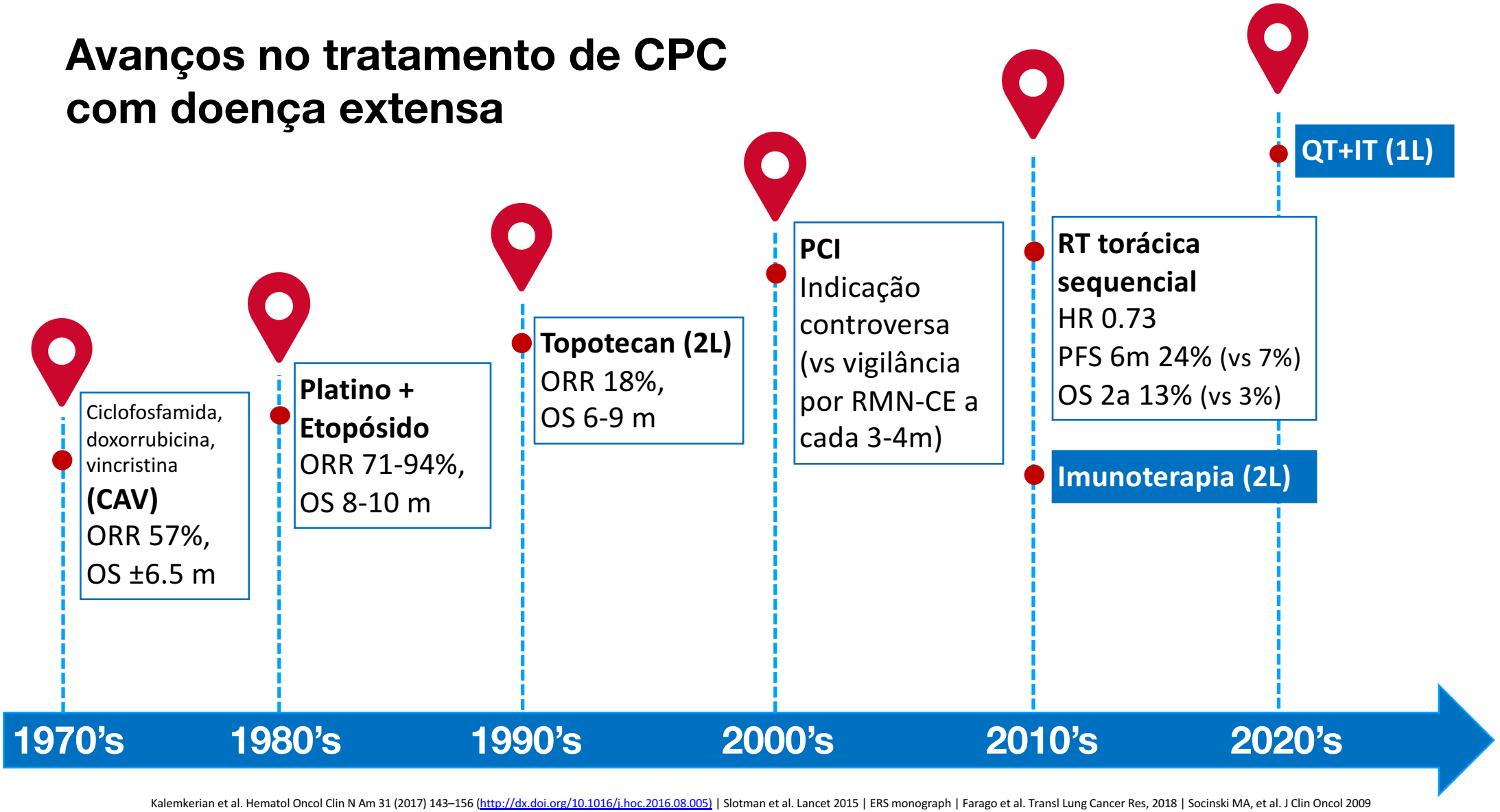
ORR 6%
PFS 3.4 meses
OS 12.4 meses (inclui *crossover* com Pembrolizumab)

Pembrolizumab

ORR 22%
PFS 2.5 meses
OS 10.7 meses

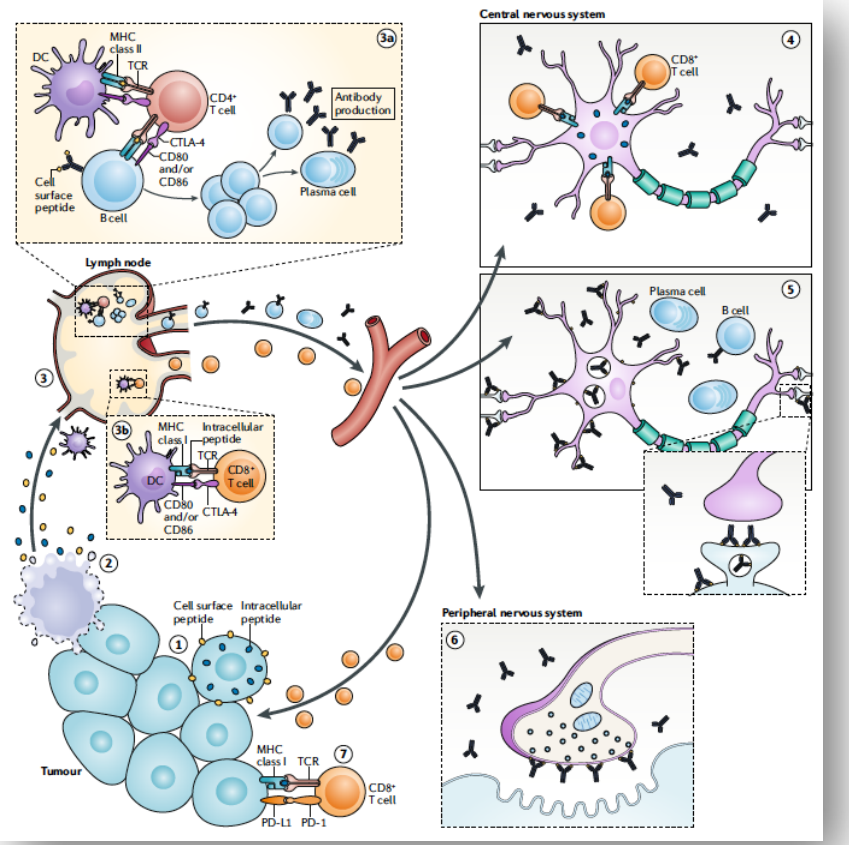
Cancro de pequenas células do pulmão

Avanços no tratamento de CPC com doença extensa



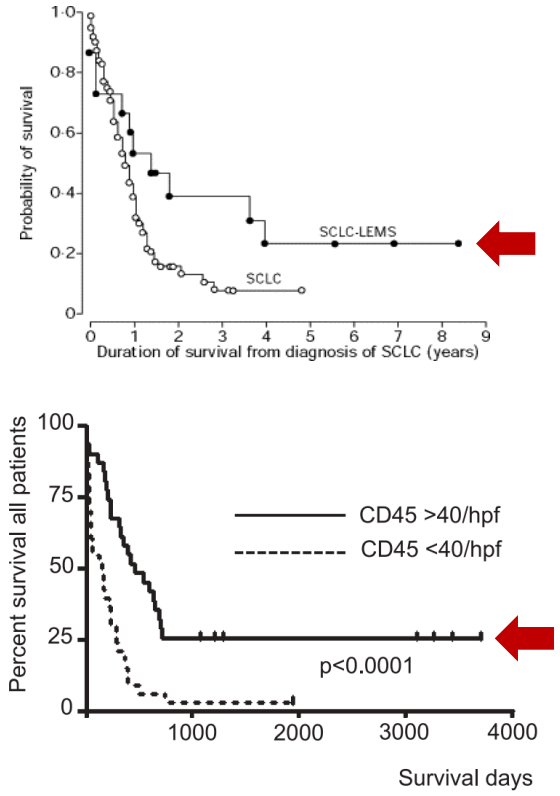
Kalemkerian et al. Hematol Oncol Clin N Am 31 (2017) 143–156 (http://dx.doi.org/10.1016/j.hoc.2016.08.005) | Slotman et al. Lancet 2015 | ERS monograph | Farago et al. Transl Lung Cancer Res, 2018 | Socinski MA, et al. J Clin Oncol 2009

Pistas para o sucesso da imunoterapia no CPCP

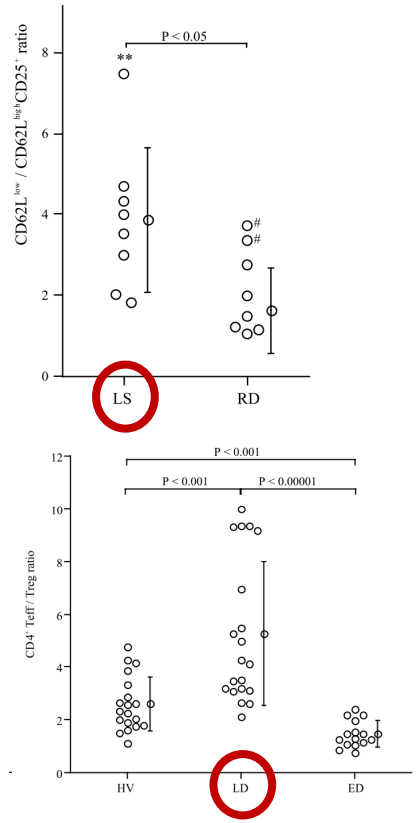


Síndromes paraneoplásicos imunomediados
como o Síndrome miasténico de Lambert-Eaton

Antigénios co-expressos por CPCP e neurónios saudáveis (HuD, HuC, Hel-N1, etc)



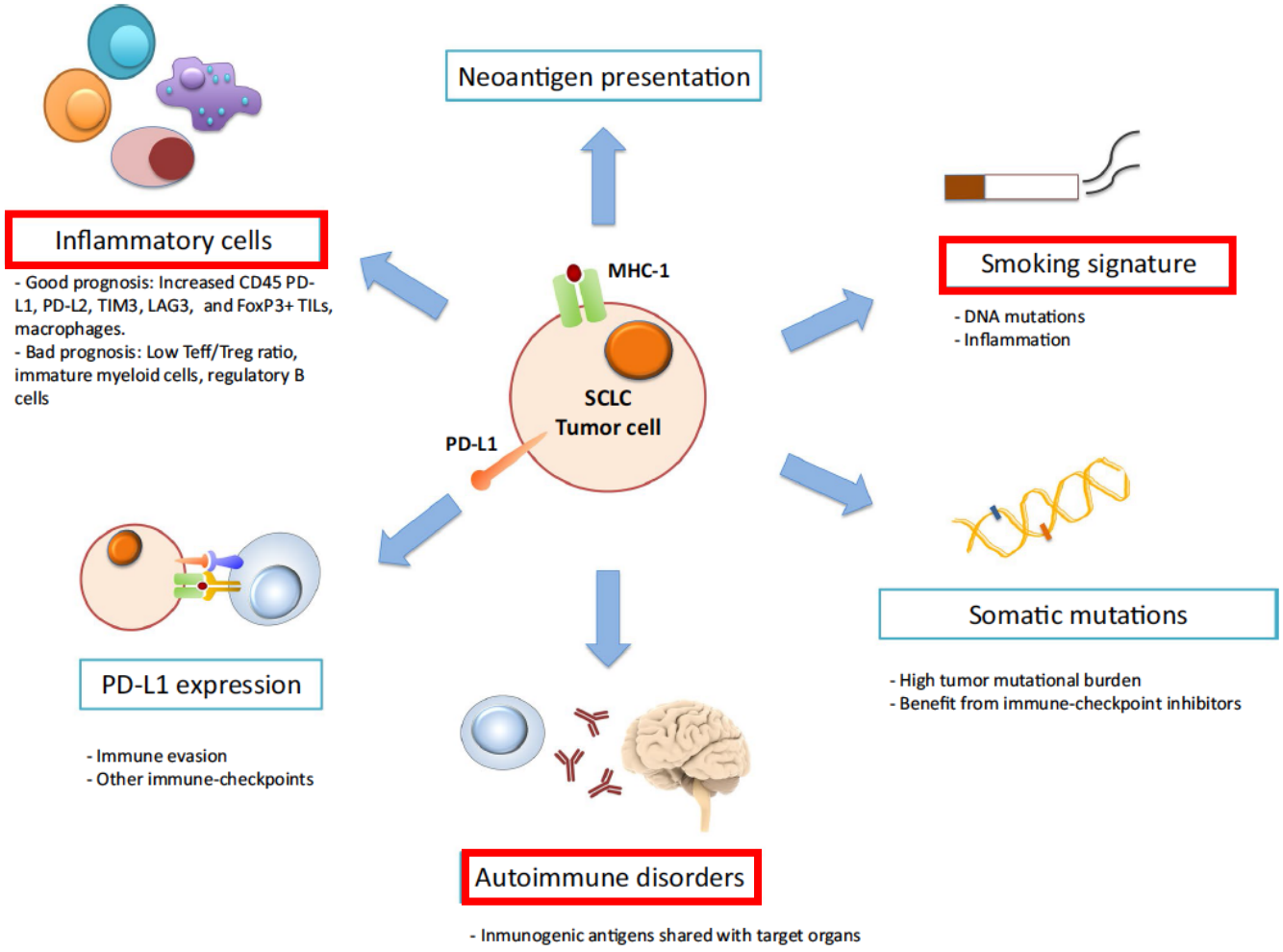
LEMS e tumores com maior grau de infiltração por céls T CD45+ são indicadores de melhor prognóstico



Maior proporção de céls T effectoras (vs. Treg) em sobreviventes >3 anos e doente com doença limitada

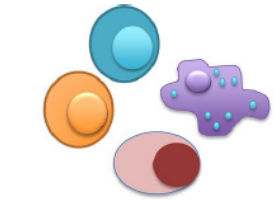
Graus & Dalmau. Nature Reviews Clinical Oncology (2019); Maddison et al. The Lancet (1999); Wang et al. Chest (2013); Koyama et al. Clin Cancer Res (2008)

Pistas para o sucesso da imunoterapia no CPCP



Cales et al. Clinical and Translational Oncology (2019)

Pistas para o sucesso da imunoterapia no CPCP



Inflammatory cells

- Good prognosis: Increased CD45 PD-L1, PD-L2, TIM3, LAG3, and FoxP3+ TILs, macrophages.
- Bad prognosis: Low Teff/Treg ratio, immature myeloid cells, regulatory B cells

Neoantigen presentation

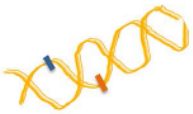
MHC-1

SCLC Tumor cell

PD-L1

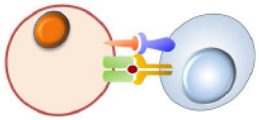
Smoking signature

- DNA mutations
- Inflammation



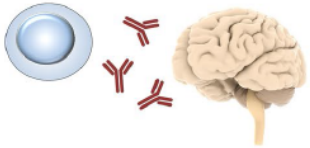
Somatic mutations

- High tumor mutational burden
- Benefit from immune-checkpoint inhibitors



PD-L1 expression

- Immune evasion
- Other immune-checkpoints

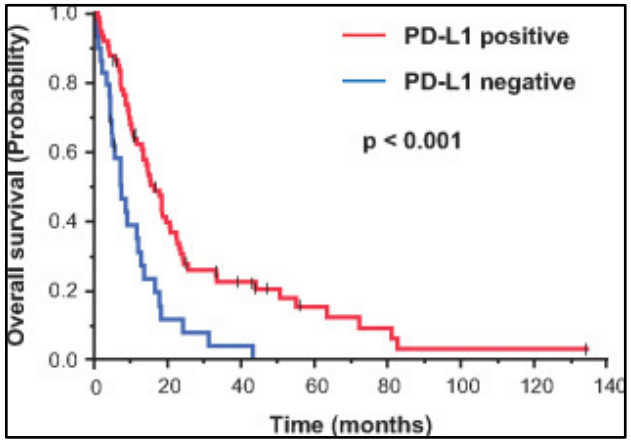


Autoimmune disorders

- Inmunogenic antigens shared with target organs

Cales et al. Clinical and Translational Oncology (2019)

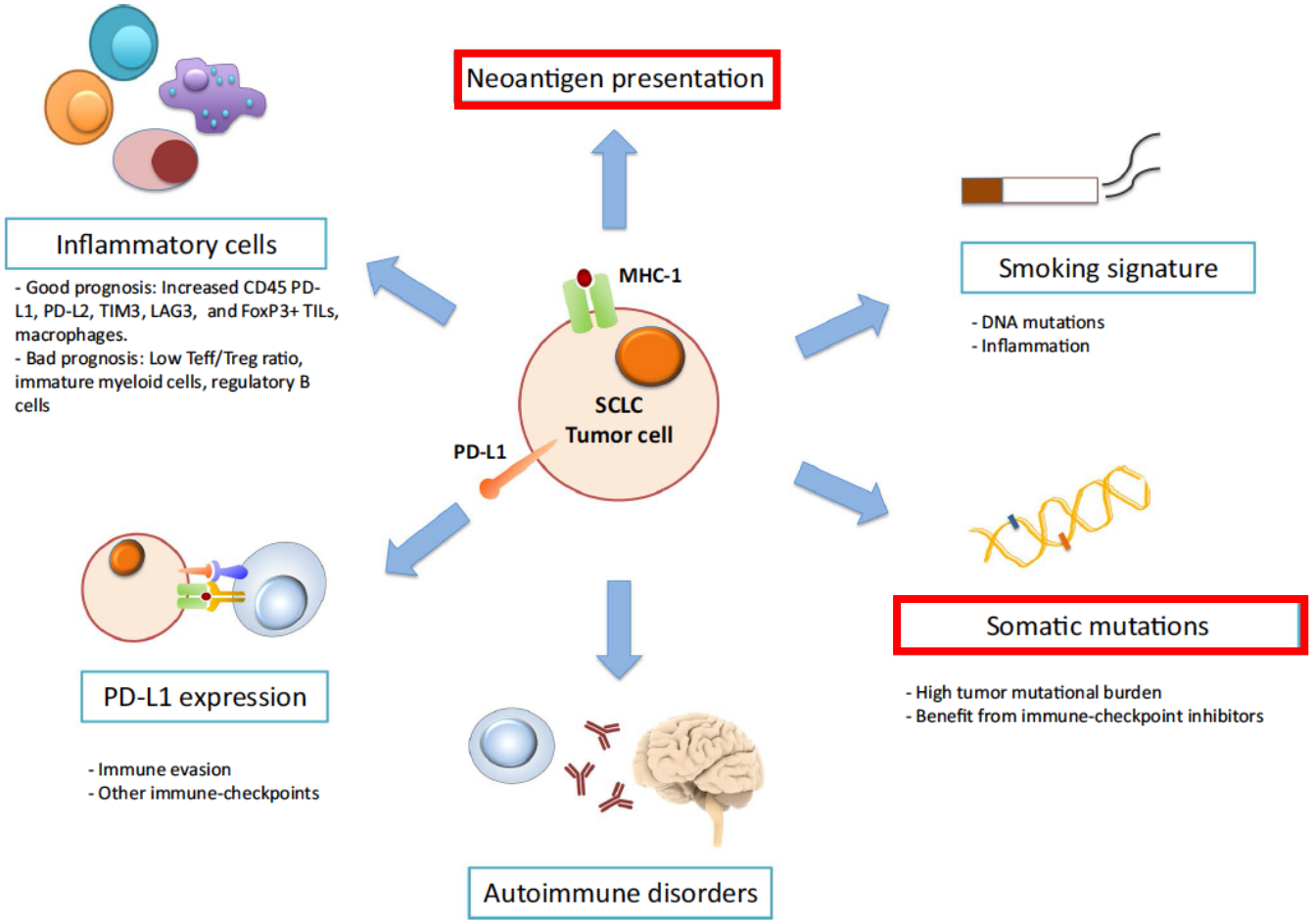
PD-L1 ≥1% em 30% dos CPCP
(vs. 60-70% em CPCNP)



Expressão PD-L1 correlaciona-se positivamente com doença limitada e é um preditor independente de prognóstico mais favorável

Ishii et al. Journal of Thoracic Oncology 2015

Pistas para o sucesso da imunoterapia no CPCP



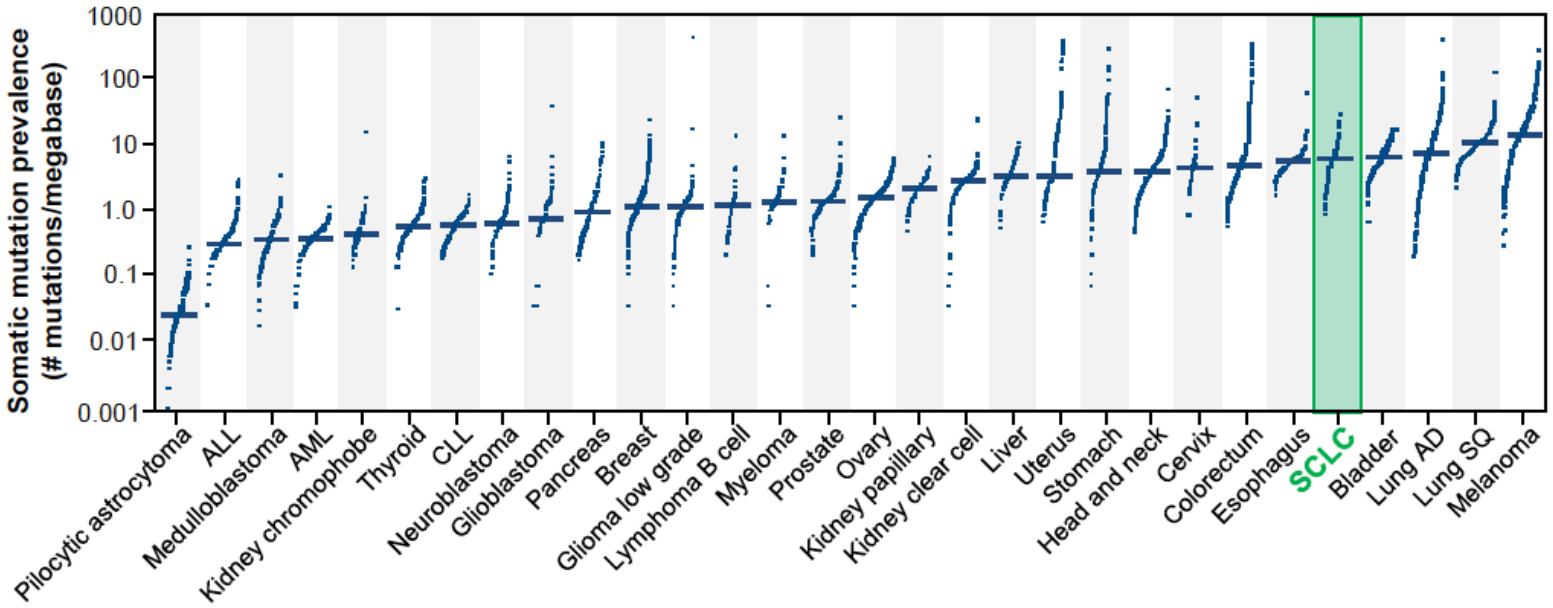
Cales et al. Clinical and Translational Oncology (2019)

Table 1. Examples of molecular aberrations in lung cancer

	SCLC
Oncogenes	
RAS mutation	<1%
MYC amplification/overexpression	~15–30%
EGFR mutation	Rare
EML4/ALK fusion	
ROS1 fusion	
LKB1 mutation	
HER2 mutation/amplification	
PIK3CA mutation/amplification	
TTF1 amplification	
BRAF alterations	
MET mutation/amplification	? rare
FGFR1 amplification	
SOX2 amplification	
Autocrine loops	GRP/GRPR, SCF/KIT
Tumour suppressor genes	
CDKN2A mutation	<1%
TP53 mutation	~75–100%
17p LOH	~80–90%
Absent RB1 expression	~90%
13q LOH	~75%
3p allele loss	>90%
9p LOH	~20–50%

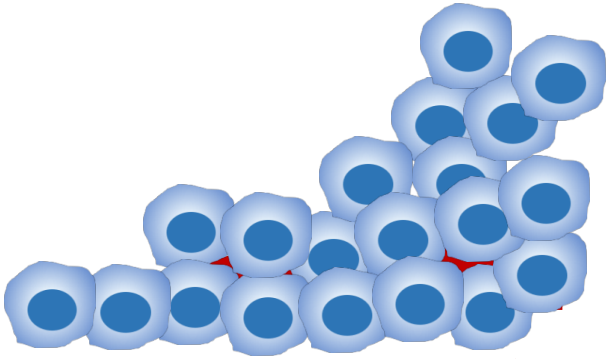
ERS monograph (2015)

Pistas para o sucesso da imunoterapia no CPCP

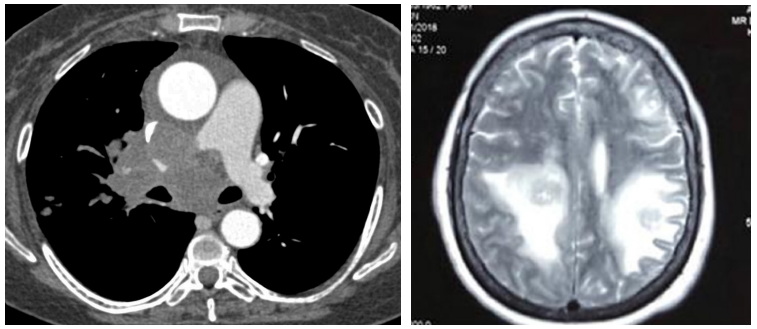


Alexandrov LB, et al. Nature 2013;500:415-421

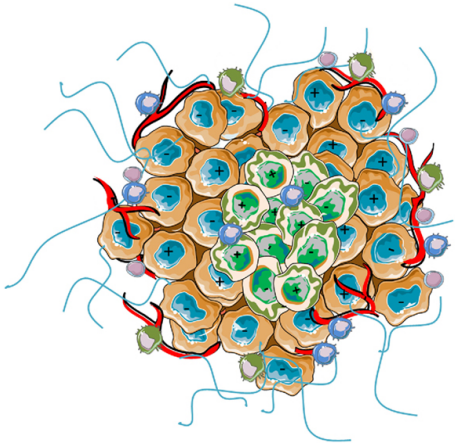
Pistas para o INSUCESSO da imunoterapia no CPCP



Rapidamente progressivo



Complicações debilitantes, com necessidade de corticoterapia (SVCS, Mets. cerebrais)

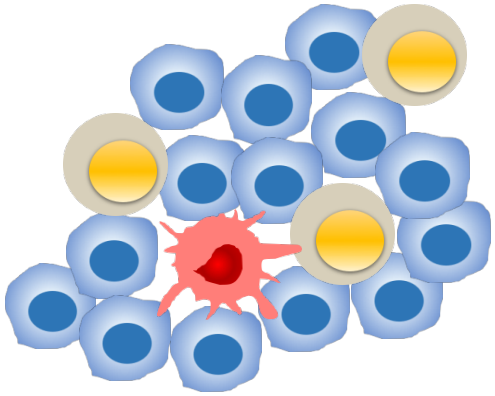


Microambiente tumoral

Fenótipo imunossupressivo:

- Baixa expressão MHC classe I (HLA-A, B, C e beta 2-microglobulina) (evasão da vigilância imunológica)
- Células tumorais e linfócitos infiltrados no tumor (TILs) não expressam MHC classe II
- O nível de TILs é baixo
- Baixa expressão PD-L1, TIM3, LAG3 nos tumores

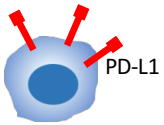
Quimioterapia
+
Inibidores PD-1/PD-L1



Microambiente tumoral

Efeito potencial de quimioterapia:

↑ Células apresentadoras de antigénio (APC)



↑ Expressão de PD-L1 nas células tumorais
↓ **Células tumorais**

↑ Células T CD8+
↓ Células Treg ou MDSCs

↑ Macrófagos

Lazzari et al. Ther Adv Med Oncol. 2018; 10: 1758835918762094.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021

1ª Linha

First-Line Therapy for Extensive-Stage SCLC

Carboplatin/etoposide/atezolizumab
Carboplatin/etoposide/durvalumab
Cisplatin/etoposide/durvalumab
Carboplatin/etoposide
Cisplatin (75 mg)/etoposide (100 mg)
Cisplatin (80 mg)/etoposide (80 mg)
Cisplatin (25 mg)/etoposide (100 mg)
Carboplatin/irinotecan
Cisplatin (60 mg)/irinotecan (60 mg)
Cisplatin (30 mg)/irinotecan (65 mg)

Maintenance Therapy

Atezolizumab†
Durvalumab‡

≥2ª Linha

SCLC SUBSEQUENT SYSTEMIC THERAPY:[c]

Relapse ≤6 months
PS 0–2

Preferred Regimens
- Topotecan PO or IV[14-16]
- Lurbinectedin[37]
- Clinical trial

Other Recommended Regimens
- Pembrolizumab[b,d,19,20,21]
- Paclitaxel[22,23]
- Docetaxel[24]
- Irinotecan[25]
- Temozolomide[26,27]
- Cyclophosphamide/doxorubicin/vincristine (CAV)[14]
- Oral etoposide[28,29]
- Vinorelbine[30,31]
- Gemcitabine[32,33]
- Bendamustine (category 2B)[34]
- Nivolumab (category 3)[b,d,17,18]

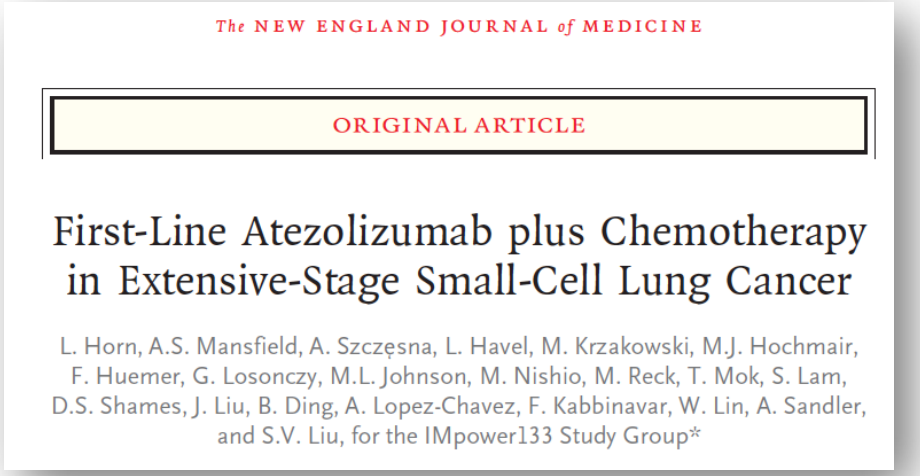
Relapse >6 months

Preferred Regimens
- Original regimen[d,35,36]

Other Recommended Regimen
- Lurbinectedin[37]

For patients who relapse after >6 months of atezolizumab or durvalumab maintenance therapy, recommend re-treatment with carboplatin + etoposide alone or cisplatin + etoposide alone.

IO em 1ª linha no tratamento de CPCP



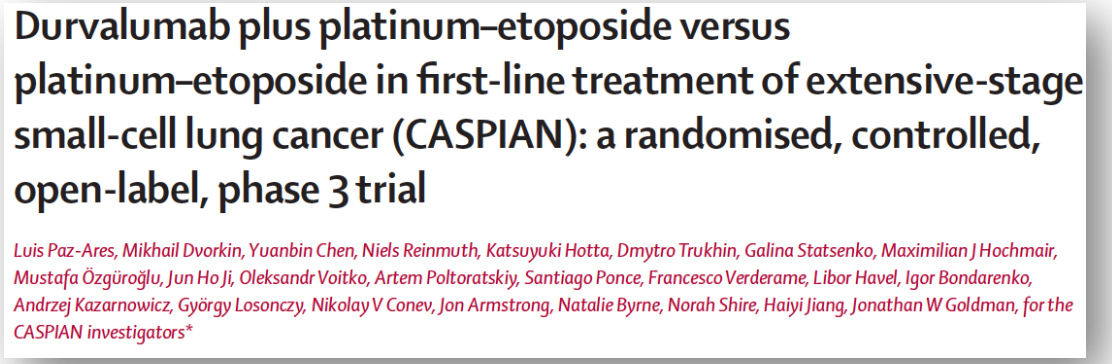
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

L. Horn, A.S. Mansfield, A. Szczęsna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D.S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinavar, W. Lin, A. Sandler, and S.V. Liu, for the IMpower133 Study Group*

N Engl J Med 2018



Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial

*Luis Paz-Ares, Mikhail Dvorkin, Yuanbin Chen, Niels Reinmuth, Katsuyuki Hotta, Dmytro Trukhin, Galina Statsenko, Maximilian J Hochmair, Mustafa Özgüroğlu, Jun Ho Ji, Oleksandr Voitko, Artem Poltoratskiy, Santiago Ponce, Francesco Verderame, Libor Havel, Igor Bondarenko, Andrzej Kazarnowicz, György Losonczy, Nikolay V Conev, Jon Armstrong, Natalie Byrne, Norah Shire, Haiyi Jiang, Jonathan W Goldman, for the CASPIAN investigators**

Lancet 2019

IMpower133: Atezolizumab + Carboplatino/Etoposido (1L) em CPCP (doença extensa)

Horn et al. NEJM 2018

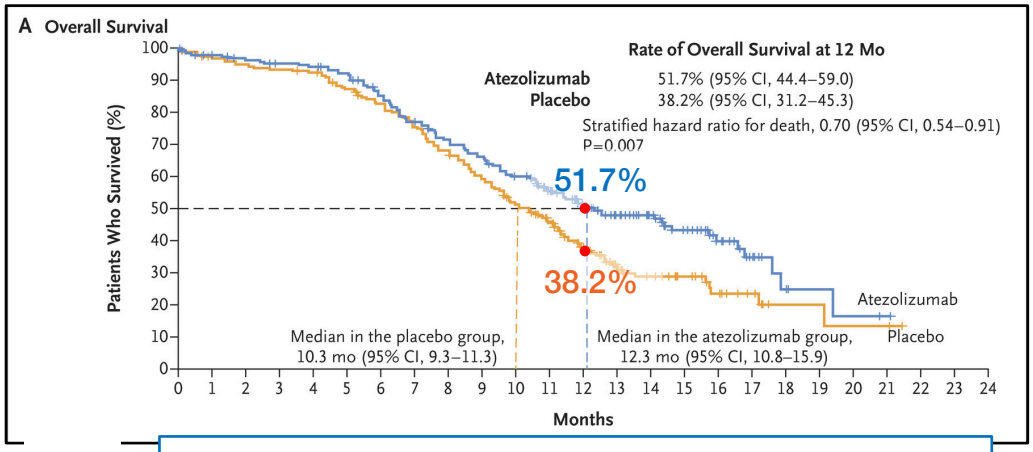
- SCLC doença extensa
- ECOG PS 0-1
- Metástases cerebrais estáveis, assintomáticas ou tratadas permitidas
- Sem QT prévia

(n=403)

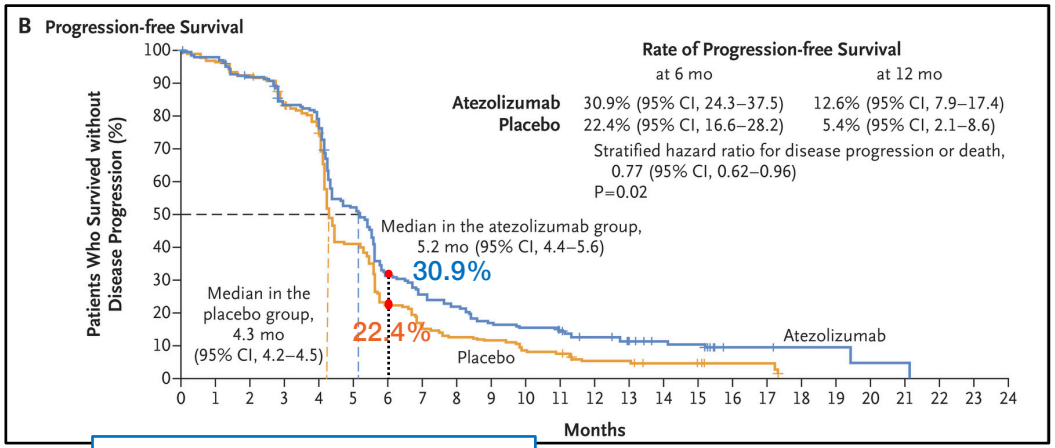
R 1:1

Tratamento de indução (4-6 ciclos q3w) → Tratamento de manutenção

- Carboplatina AUC 5 (D1) + Etoposido 100 mg/m^2 (D1-3) + Atezolizumab 1200 mg (D1) → Atezolizumab 1200 mg (q3w) → Perda de benefício clínico / toxicidade
- Carboplatina + Etoposido → Placebo → Perda de benefício clínico / toxicidade



Sobrevida global 10.3 vs 12.3 meses



PFS 4.3 vs 5.2 meses

- 5 (2.5%) no grupo Atezolizumab com resposta completa vs 2 (1%) no grupo placebo
- Expressão PD-L1 ou TMB não tiveram impacto nos resultados
- Sem aumento dos efeitos adversos relativamente ao expectável para cada agente utilizado isoladamente

CASPIAN: Durvalumab + Platino/Etoposido (1L) em CPCP (doença extensa)

Paz-Ares, L. et al., Lancet 2019

- Doentes com CPCP-DE (T3-4 ou M1) sem terapêutica sistémica prévia
- ECOG PS 0-1
- Metástases cerebrais estáveis, assintomáticas ou tratadas permitidas
- Esperança de vida ≥12 semanas
- Doença mesurável pelo RECIST v1.1
- N=805 (randomizados)

1:1:1

R

Estratificado de acordo com o agente de platina em planeamemto (carboplatina vs cisplatina)

Durvalumab + EP* Durvalumab 1500mg q3w até 4 ciclos	→ Durvalumab 1500mg q4w até progressão
EP* Q3w até 6 ciclos	→ Irradiação craniana opcional
Durvalumab + Tremelimumab + EP* Durvalumab 1500 mg + tremelimumab 75 mg + EP q3w até 4 ciclos	→ Durvalumab 1500mg q4w até progressão

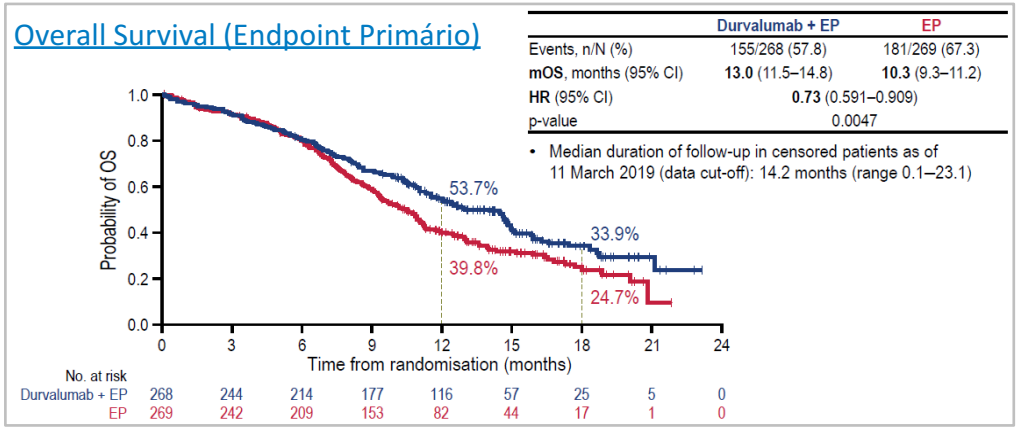
Endpoint Primário:
- OS

Endpoint Secundário:
- PFS
- ORR
- Segurança & Tolerabilidade
- HR QoL

Overall Survival (Endpoint Primário)

	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	

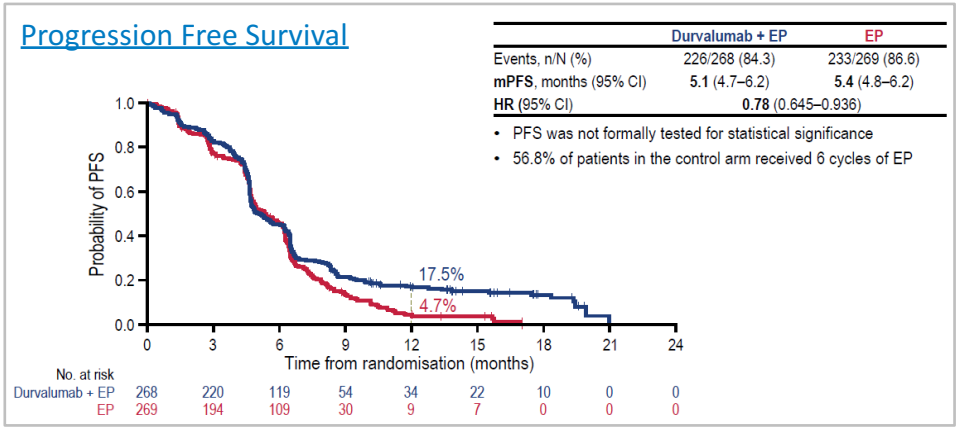
- Median duration of follow-up in censored patients as of 11 March 2019 (data cut-off): 14.2 months (range 0.1–23.1)



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



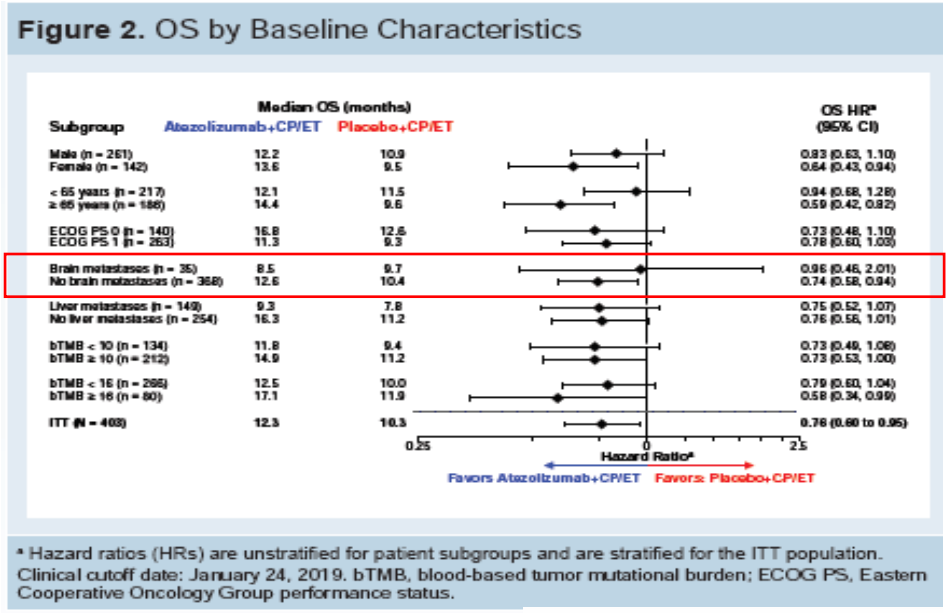
Sobrevida global 10.3 vs 13 meses

PFS 5.4 vs 5.1 meses

- Benefícios idênticos ao IMpower 133 (Atezo+EP)
- Não se verificou uma interação significativa entre a OS e a expressão de PD-L1 como variável contínua (TC, p=0.54; IC, p=0.23)
- Ocorrência de efeitos adversos foi idêntica entre grupos: 31% (22% grau 3-4) Durva+EP vs 36% (26% grau 3-4) EP

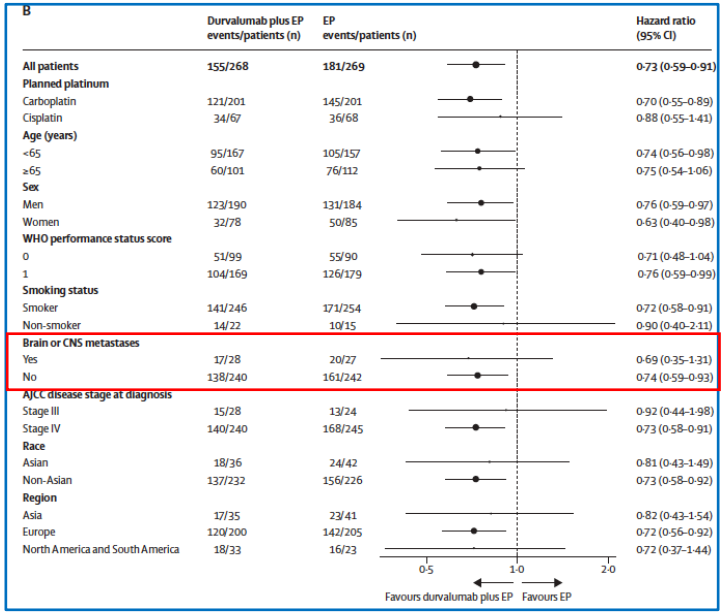
IMpower133 & CASPIAN

- O prognóstico de doentes com metastização cerebral não é significativamente melhorado com a imunoterapia
- Idade, ECOG-PS 0 (vs 1) e LDH ≤LSN (vs >LSN) foram identificados como factores de prognóstico preditores para alcançar a fase de manutenção com Atezolizumab (Impower133)



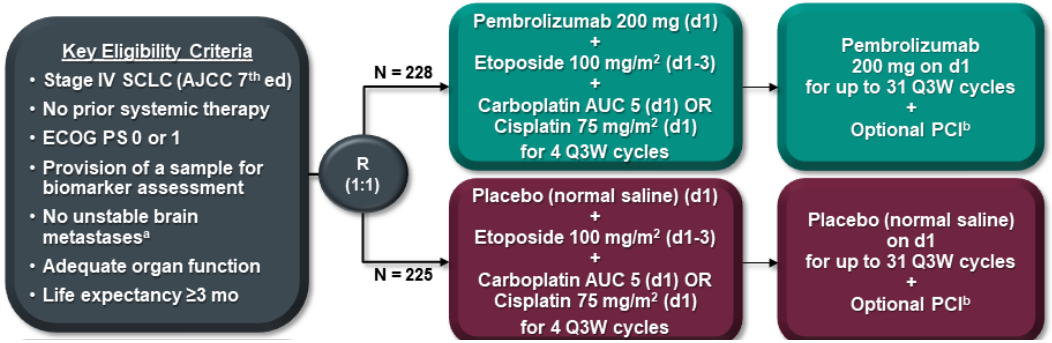
* Hazard ratios (HRs) are unstratified for patient subgroups and are stratified for the ITT population. Clinical cutoff date: January 24, 2019. bTMB, blood-based tumor mutational burden; ECOG PS, Eastern Cooperative Oncology Group performance status.

Abstract 1736O (Martin Reck, Germany)



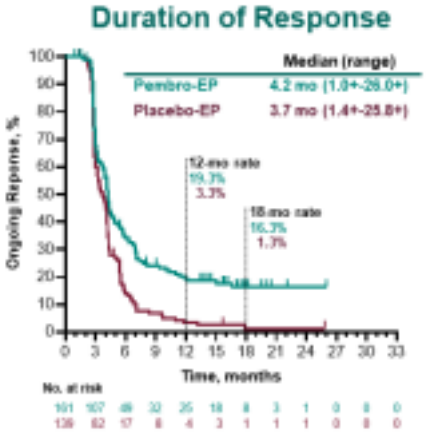
Paz-Ares, L. et al., Lancet 2019

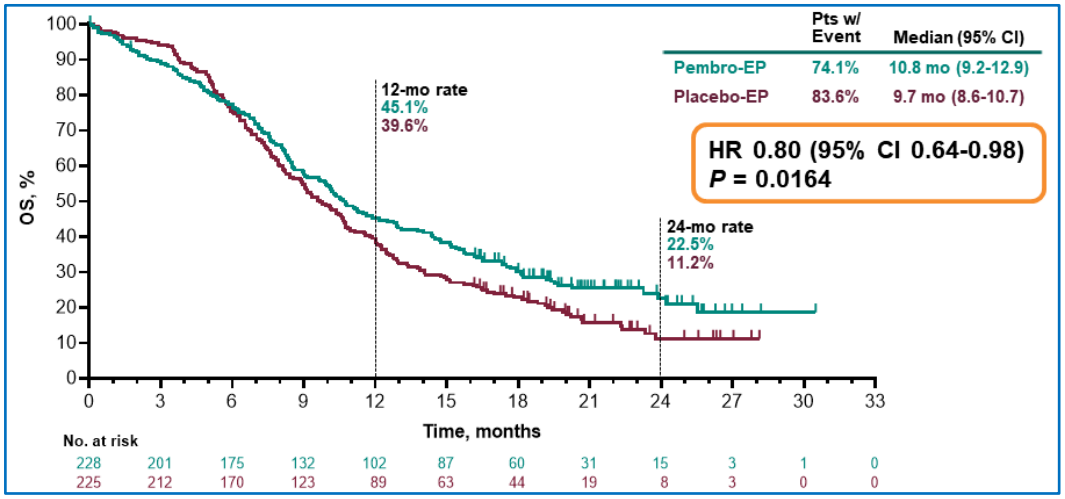
KN-604: Pembrolizumab + Platino/Etoposido (1L) em CPCP (doença extensa)

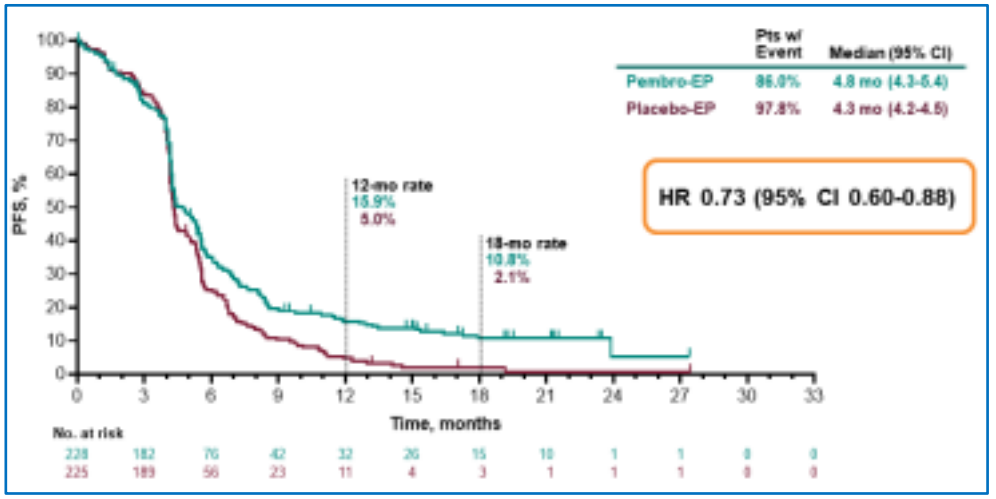


	Pembro-EP N = 228	Placebo-EP N = 225
ORR, % (95% CI)	70.6% (64.2-76.4)	61.8% (55.1-68.2)
Best response, n (%)		
CR	4 (1.8%)	2 (0.9%)
PR	157 (68.9%)	137 (60.9%)
SD	40 (17.5%)	56 (24.9%)
PD	8 (3.5%)	12 (5.3%)
NE[a]	6 (2.6%)	5 (2.2%)
NA[b]	13 (5.7%)	13 (5.8%)

[a]≥1 post-baseline imaging assessment, but none evaluable per RECIST v1.1 by BICR.
[b]No post-baseline imaging assessment.
Data cutoff date: Dec 2, 2019.







Rudin et al. J Clin Oncol 2020;38:2369-2379 (Presented at ASCO 2020)

1ª linha

Etopósido+Platino
(4-6 ciclos)

ORR 58-64.4%
PFS 4.3-5.4 meses
OS 9.6-10.3 meses

EP+Atezo (4-6 ciclos) → Atezo

ORR 60.2%
PFS 5.2 meses
OS 12.3 meses

EP+Durva (4 ciclos) → Durva

ORR 68%
PFS 5.1 meses
OS 13 meses

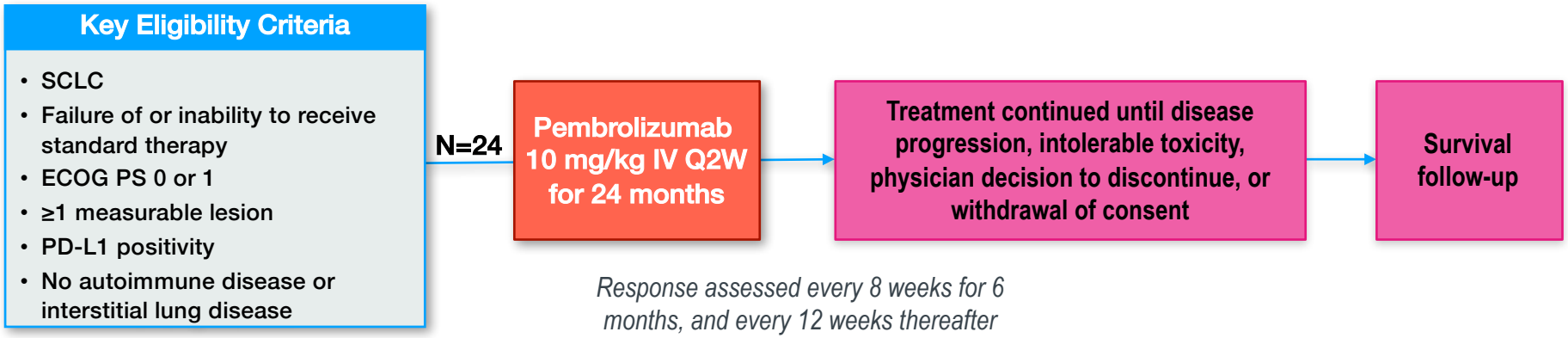
EP+Pembro (4 ciclos) → Pembro

ORR 70.6%
PFS 4.8 meses
OS 10.8 meses

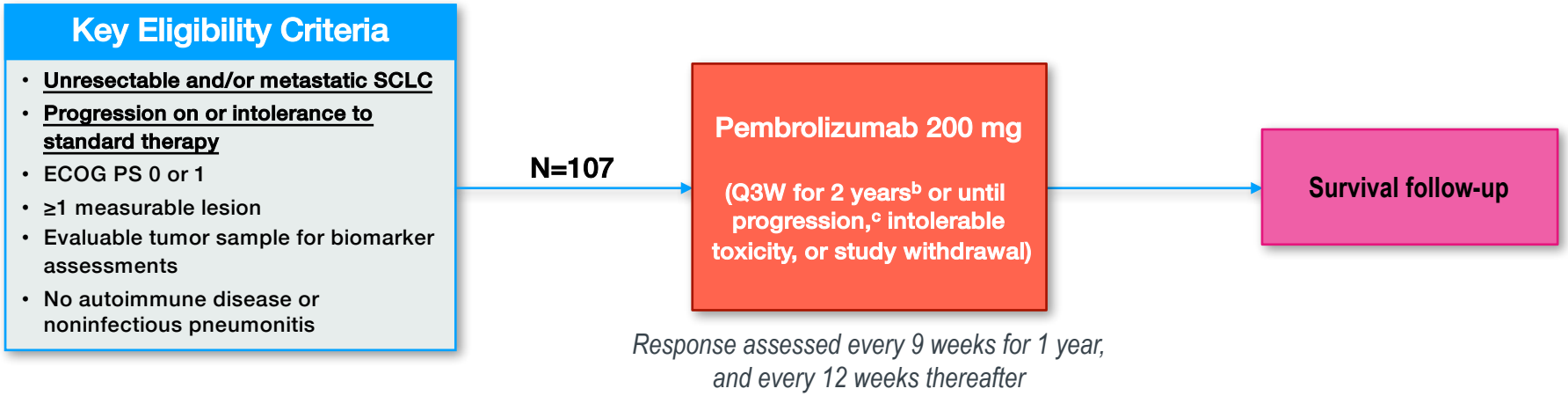
2ª linha?

- Combinação QT+IT com benefício modesto na OS
- Expressão PD-L1 e TMB **não** são preditores de resposta a IT
- Sem aumento dos efeitos adversos relativamente ao expectável para cada agente utilizado isoladamente

KEYNOTE-028: Phase 1b multicohort study of Pembrolizumab for PD-L1+ solid tumors (ES-SCLC)

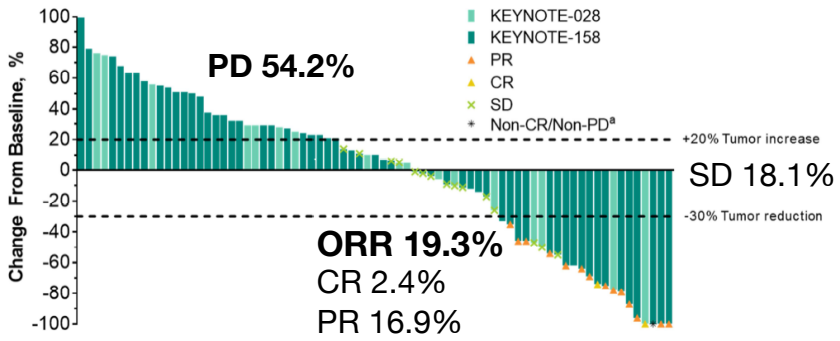


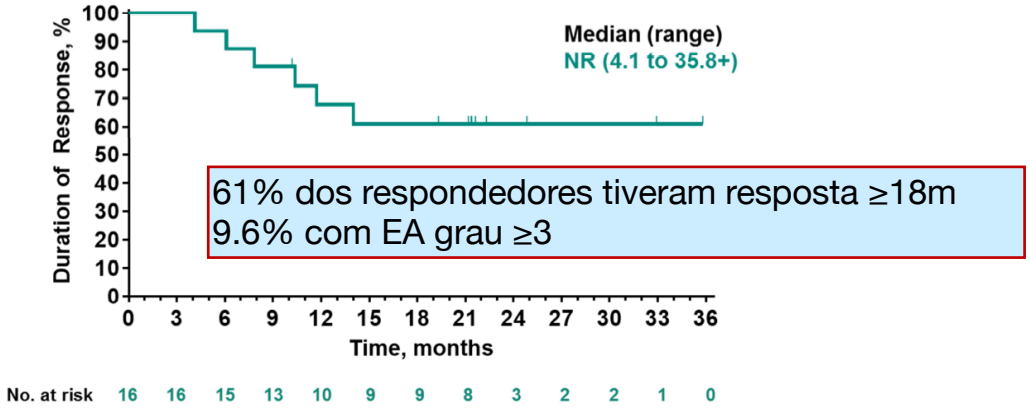
KEYNOTE-158: Phase 2 study of Pembrolizumab in patients with progressive SCLC



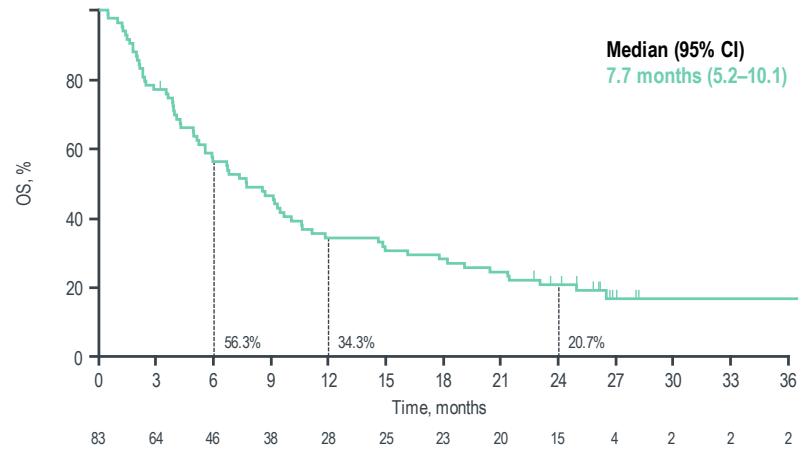
KEYNOTE-028/-158 combined analysis: Pembrolizumab após ≥2 linhas (3L)

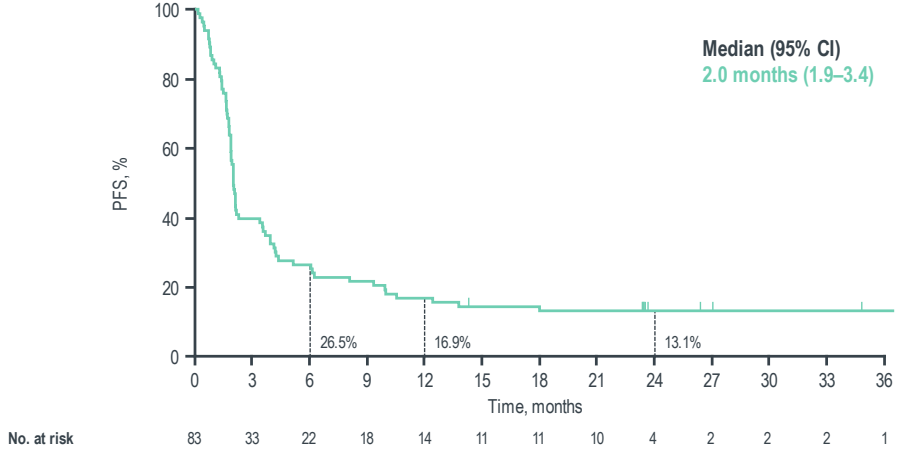
- 83 doentes (KN-028, n=19; KN-158, n=64)
- PD-L1–positive tumors 47 (57%)





61% dos respondedores tiveram resposta ≥18m
9.6% com EA grau ≥3





Chung et al. J Thorac Oncol. 2020 Apr;15(4):618-627

Pembrolizumab: expressão de PD-L1 como preditor de resposta

Clinical Study	ORR[a]	DOR	PFS	OS
KEYNOTE-028[1] (phase 1b; PD-L1+ only)	33.3% (95% CI, 15.6–55.3)	19.4 mo (3.6+ to 20.0+)	1.9 mo (95% CI, 1.7–5.9)	9.7 mo (4.1–NR)
KEYNOTE-158[2] (phase 2; any PD-L1 expression)	18.7% (95% CI, 11.8–27.4)	NR (2.1+ to 18.7+ mo)	2.0 mo (95% CI, 1.9–2.1)	8.7 mo (5.6–12.0)

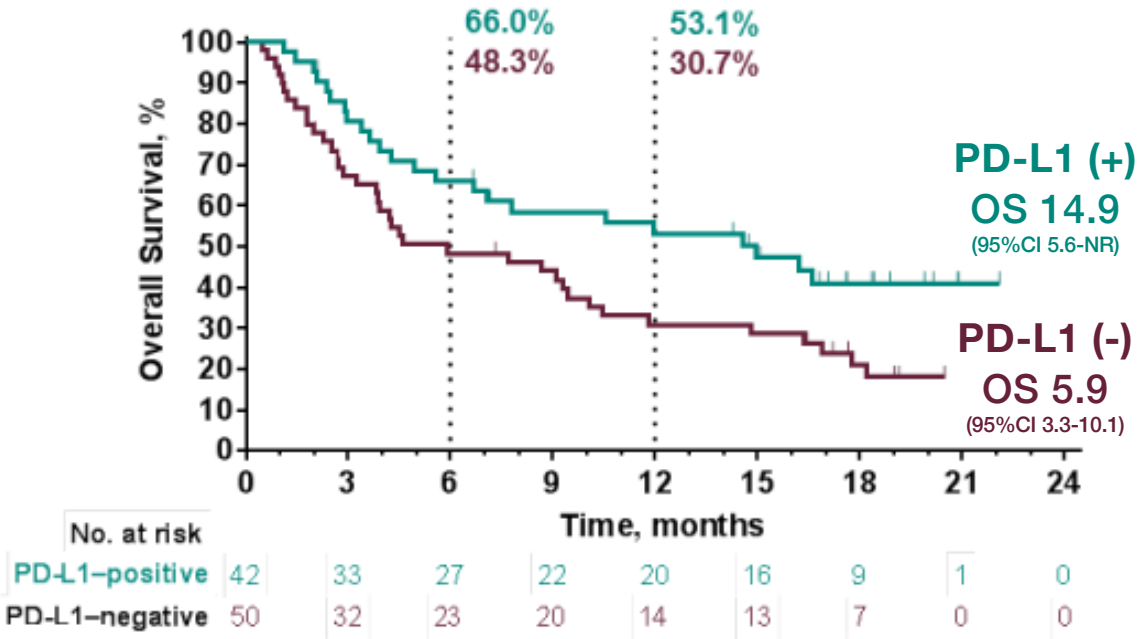
KEYNOTE-158 (n=107)

≥2 linhas QT prévia: 57%

39% PD-L1 positivos

47% PD-L1 negativos

14% não avaliável



1. Ott PA, et al. J Clin Oncol. 2017;35(34):3823-3829. Pembro 10 mg/Kg q2w
2. Chung HC, et al. J Clin Oncol. 2018;36(15S):8506. Pembro 200 mg q3w

CheckMate 331: Nivolumab vs Quimioterapia no CPCP recorrente (≥2L) — ensaio randomizado fase 3 sem ocultação

Key eligibility criteria
- LD- or ED-SCLC at diagnosis
- Relapse after platinum-based 1L chemotherapy[a]
- ECOG PS 0–1

Stratification factors
- Response to prior platinum-based treatment (sensitive vs resistant[b])
- Brain metastases at baseline (yes vs no)

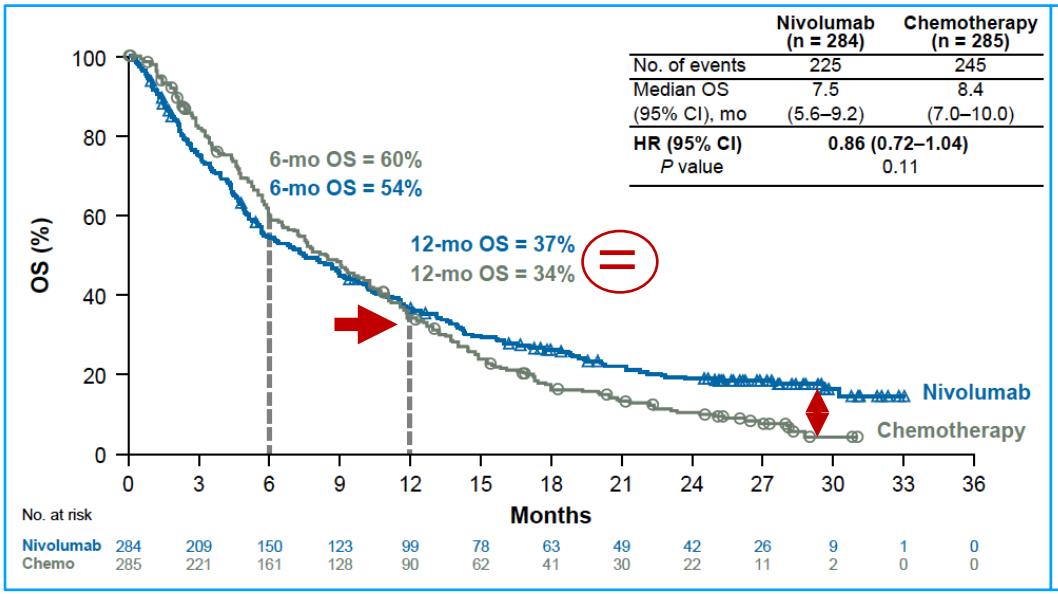
R[c] 1:1

- Nivolumab 240 mg Q2W n = 284
- Chemotherapy: topotecan (IV or oral)[d] or amrubicin IV[e,f] n = 285

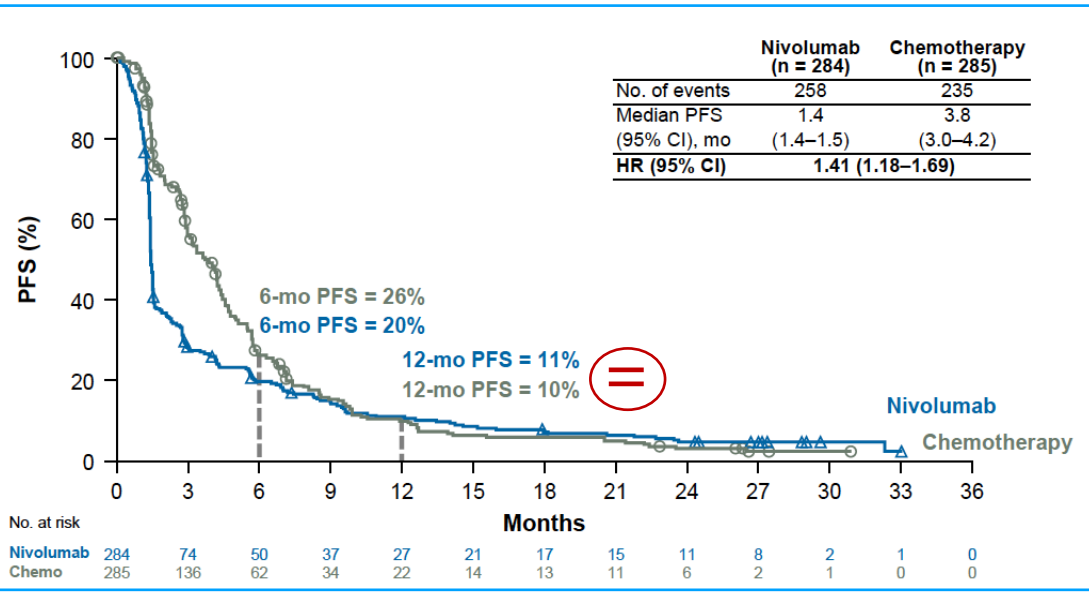
Treat until disease progression[g,h] or unacceptable toxicity

Endpoint Primário:
- OS

Endpoint Secundário:
- PFS
- ORR



	Nivolumab (n = 284)	Chemotherapy (n = 285)
No. of events	225	245
Median OS	7.5	8.4
(95% CI), mo	(5.6–9.2)	(7.0–10.0)
HR (95% CI)	**0.86 (0.72–1.04)**	
P value	0.11	

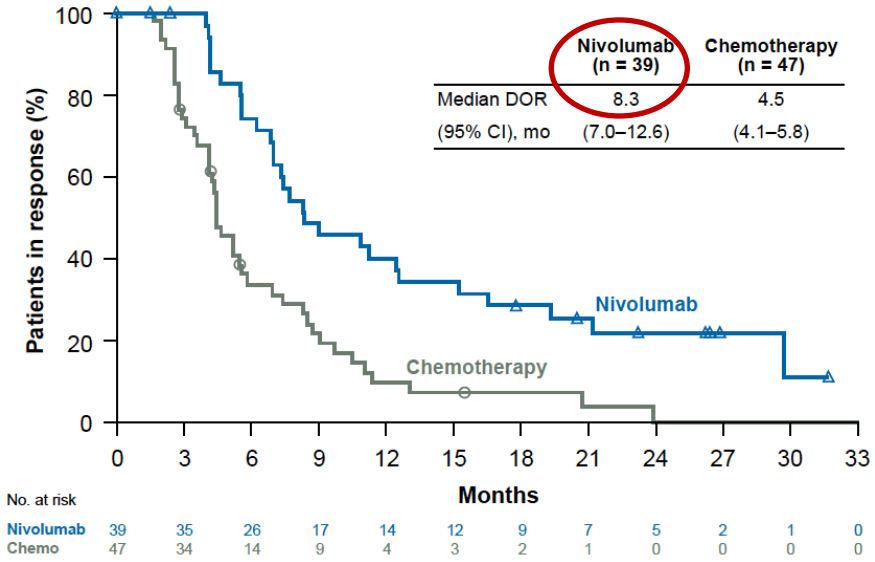


	Nivolumab (n = 284)	Chemotherapy (n = 285)
No. of events	258	235
Median PFS	1.4	3.8
(95% CI), mo	(1.4–1.5)	(3.0–4.2)
HR (95% CI)	**1.41 (1.18–1.69)**	

Reck M et al. Randomized Phase 3 Study of Nivolumab Monotherapy Versus Chemotherapy in Relapsed Small Cell Lung Cancer: Results From CheckMate 331. Abstract 489 (ESMO 2018)

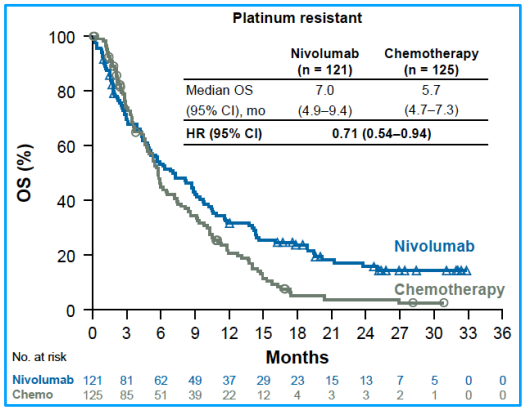
CheckMate 331: Nivolumab em ≥2L com menor ORR, mas maior DOR

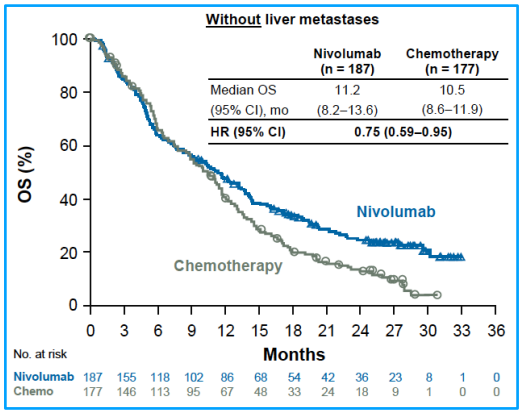
	PR/CR, %	ORR, %
Nivolumab	13.4/0.4	13.7%
Quimioterapia	16.1/0.4	16.5%



Análise de subgrupos

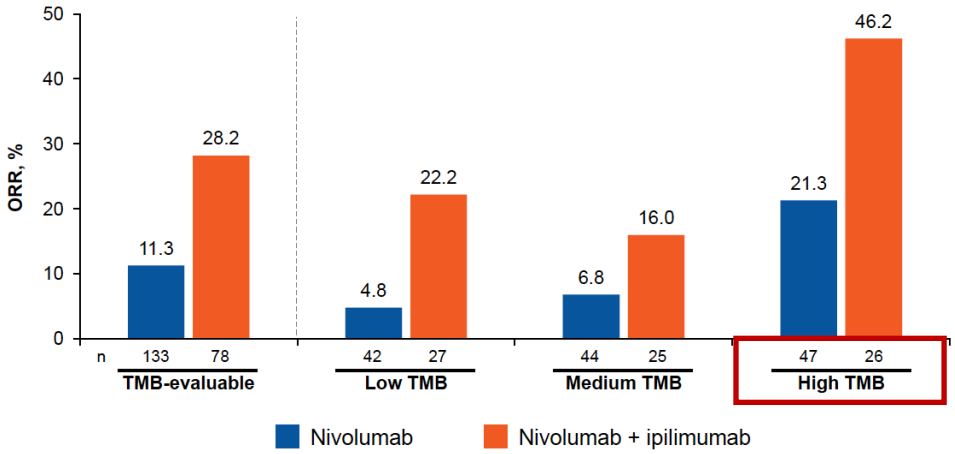
Subgrupo	OS mediana, m **Nivolumab**	OS mediana, m **Quimioterapia**	Unstratified HR
LDH ≤ ULN (n = 293)	13.6	11.6	0.70
Platino resistentes (n = 246)	**7.0**	5.7	0.71
Sem metástases hepáticas	11.2	10.5	0.75
Chineses	11.5	7.0	0.70

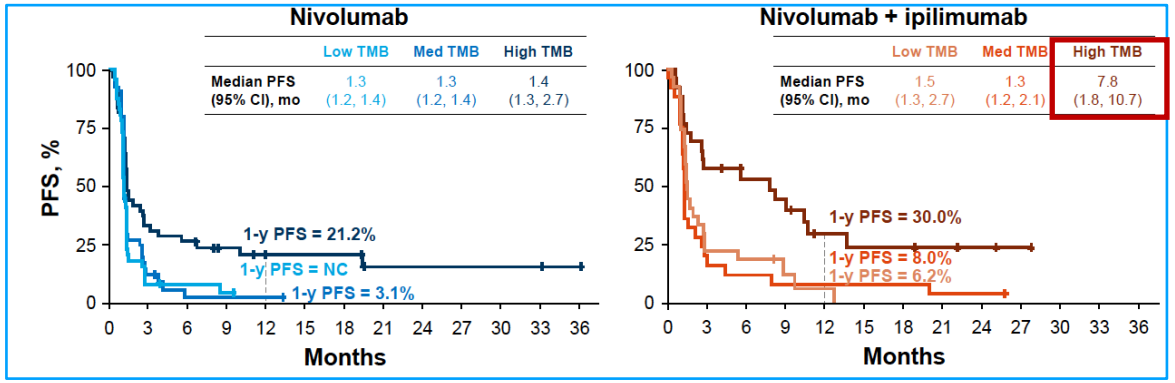


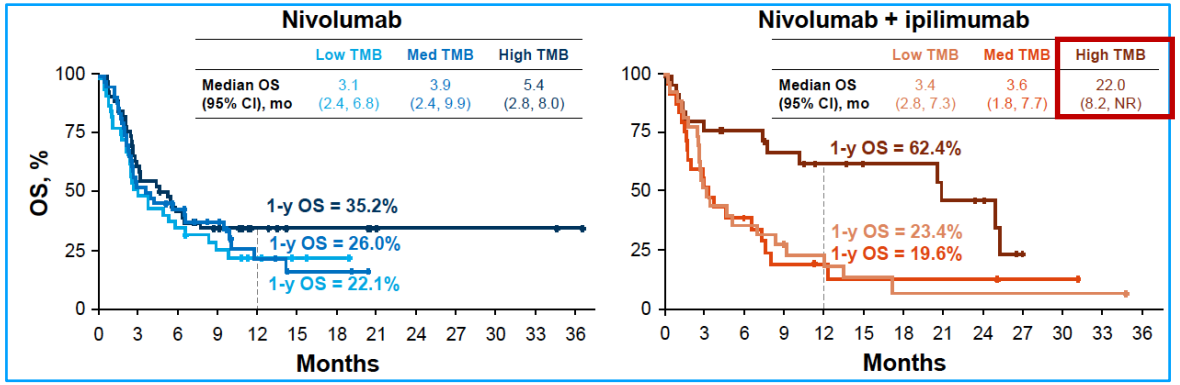


Reck M et al. Randomized Phase 3 Study of Nivolumab Monotherapy Versus Chemotherapy in Relapsed Small Cell Lung Cancer: Results From CheckMate 331. Abstract 489 (ESMO 2018)

CheckMate 032: TMB elevado como preditor de resposta ao Nivo+Ipilimumab







Antonia SJ, et al. Impact of Tumor Mutation Burden on the Efficacy of Nivolumab or Nivolumab+Ipilimumab in Small Cell Lung Cancer: An Exploratory Analysis of CheckMate 032. Abstract 1063 (IASLC 2017)

1ª linha

Etopósido+Platino
(4-6 ciclos)

ORR 58-64.4%
PFS 4.3-5.4 meses
OS 9.6-10.3 meses

EP+Atezo (4-6 ciclos) → Atezo

ORR 60.2%
PFS 5.2 meses
OS 12.3 meses

EP+Durva (4 ciclos) → Durva

ORR 68%
PFS 5.1 meses
OS 13 meses

EP+Pembro (4 ciclos) → Pembro

ORR 70.6%
PFS 4.8 meses
OS 10.8 meses

2ª linha

Pembrolizumab

ORR ±30% (PD-L1+)
PFS ±2 meses
OS 9-10 meses (±15 m se PD-L1+)

PD-L1+

Nivolumab

ORR ±14%
PFS ±1.4 meses
OS 7.5 meses

Recidiva precoce

Nivo+Ipil

ORR ±20%
PFS ±3 meses (7.8m se TMB alto)
OS 7.7 meses (22m se TMB alto)

TMB elevado

Topotecan/CAV

ORR ±20%
PFS ±3 meses
OS 5.6-7.8 meses

- Imunoterapia em ≥2ª linha com melhor perfil de segurança que QT
- Os respondedores a IT têm DOR mais longas
- Expressão PD-L1 pode ser preditor de resposta a Pembro
- Elevado TMB pode ser preditor de resposta a Nivo+Ipil


Ana Bastos, 2020