PERSPECTIVAS
EM ONCOLOGIA VIII

13, 14 e 15 FEV 2020
SHERATON PORTO

Biomarcadores em Imunoterapia

Porto, 13 de Fevereiro 2020

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SÃO JOÃO HOSPITAL

IBMC INSTITUTO DE BIOLOGIA MOLECULAR E CELULAR
INSTITUTE FOR MOLECULAR AND CELL BIOLOGY

3S INSTITUTO DE INVESTIGAÇÃO E INOVAÇÃO EM SAÚDE
UNIVERSIDADE DO PORTO

A função do biomarcador

Doente → Amostra de sangue ou de tecido → Estudo molecular → Análise → Identificação do **biomarcador** → Terapia personalizada

Medicina clássica

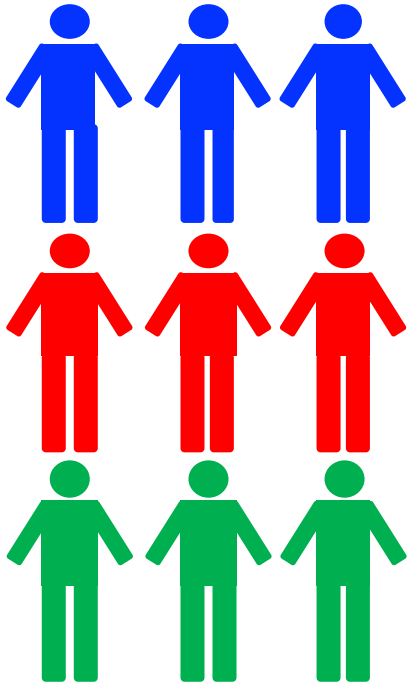
One size fits all?

Estratificação

Doentes agrupados por
- perfis clínicos
- subtipos imagiológicos
- subtipos histológicos

Medicina moderna

Categorização de doentes

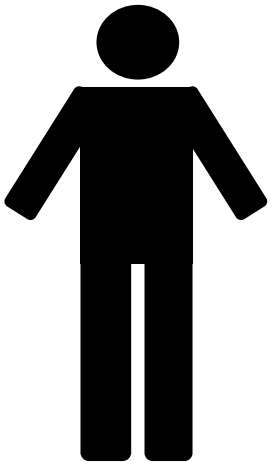


Personalização

Doente individualizado
- perfil histológico
- perfil genético
- biomarcadores

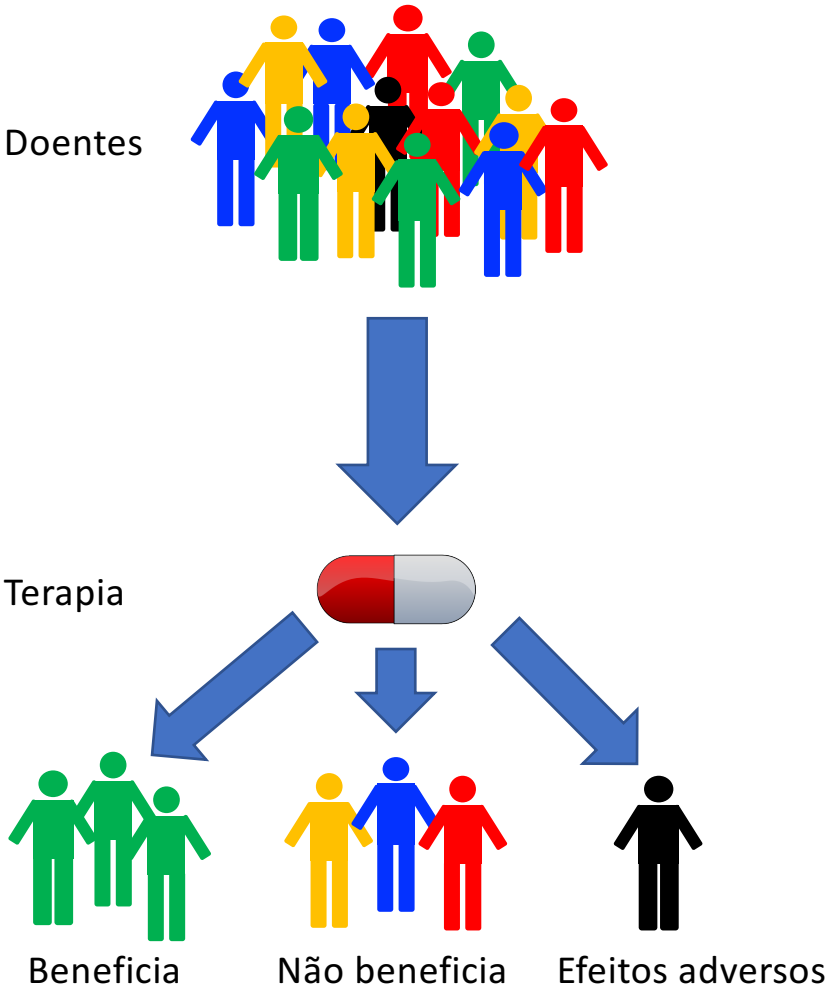
Medicina de futuro

Medicina de precisão

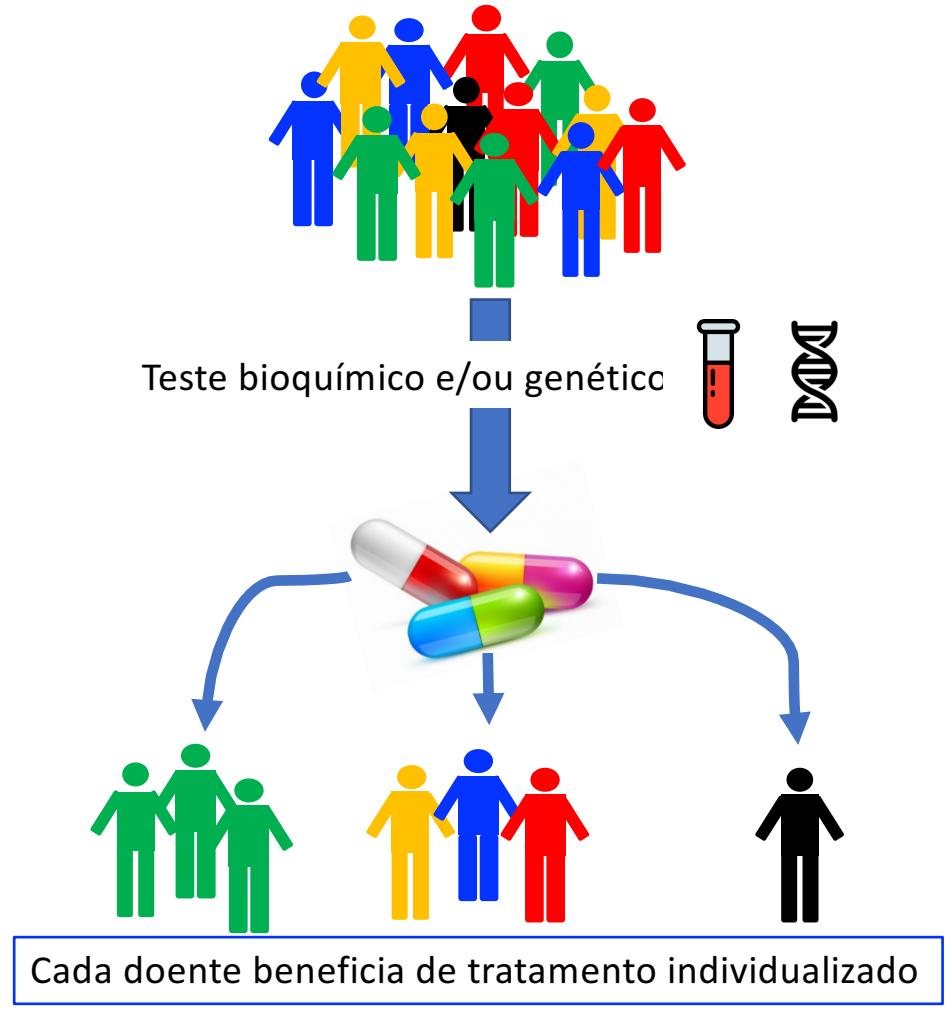


Personalização da medicina no Cancro

Medicina convencional

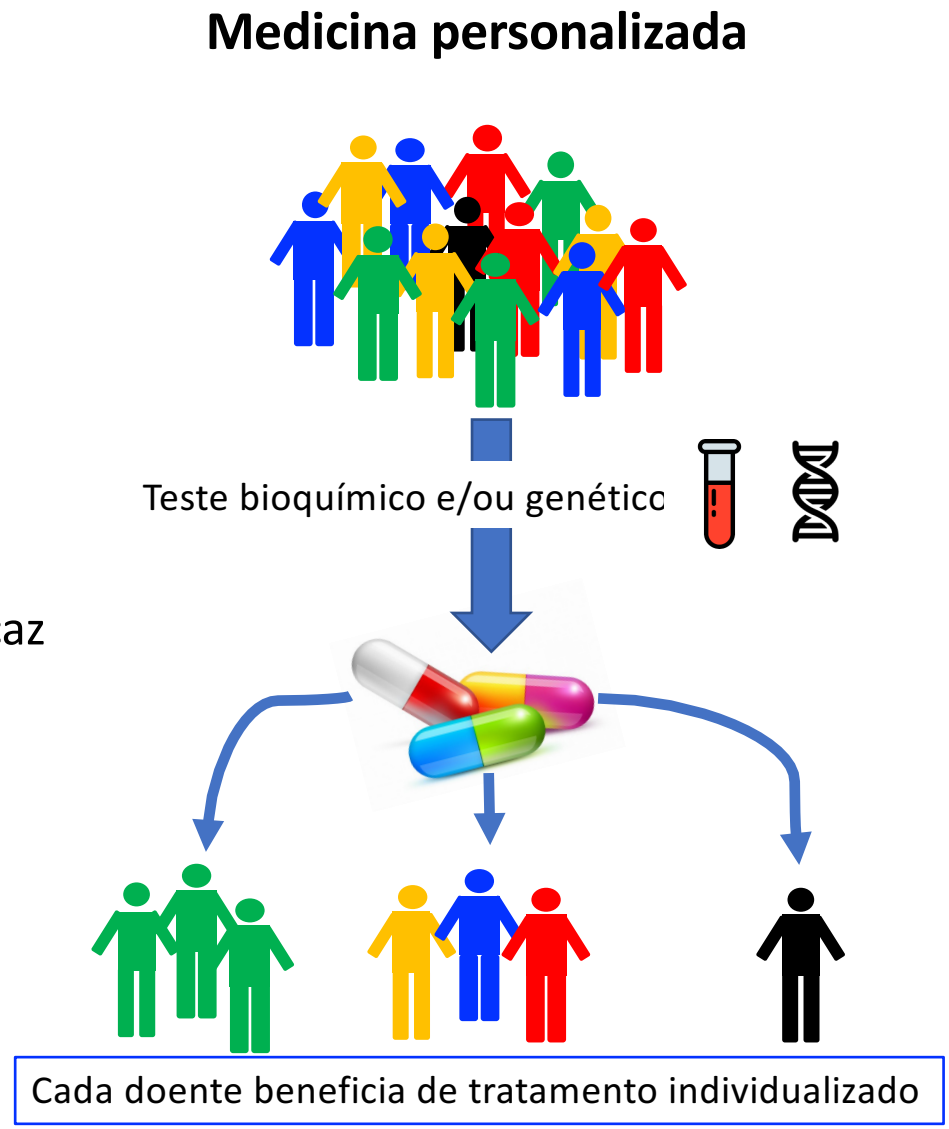


Medicina personalizada



Vantagens da medicina personalizada

- Melhor resultado clínico
- Menor frequência de efeitos adversos
- Previne exposição desnecessária a terapia ineficaz
- Tratamento mais custo-efectivo



Expressão PD-L1

Teff (effector T-cell) gene signature

Tumor Mutational Burden

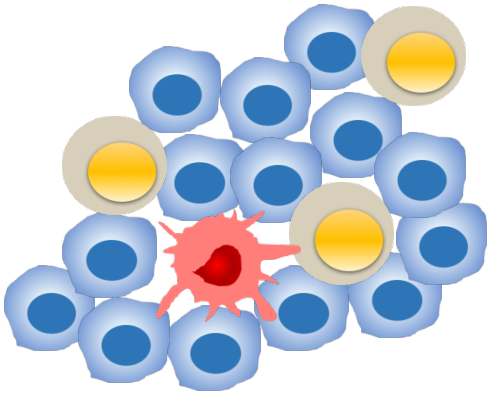
Perspectivas futuras

Expressão PD-L1

Teff (effector T-cell) gene signature

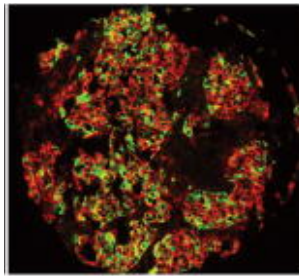
Tumor Mutational Burden

Perspectivas futuras



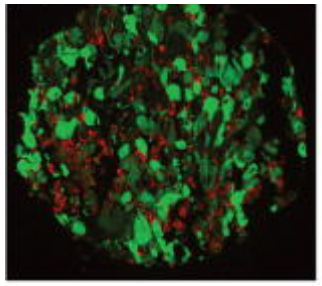
Microambiente tumoral

Cancro do pulmão

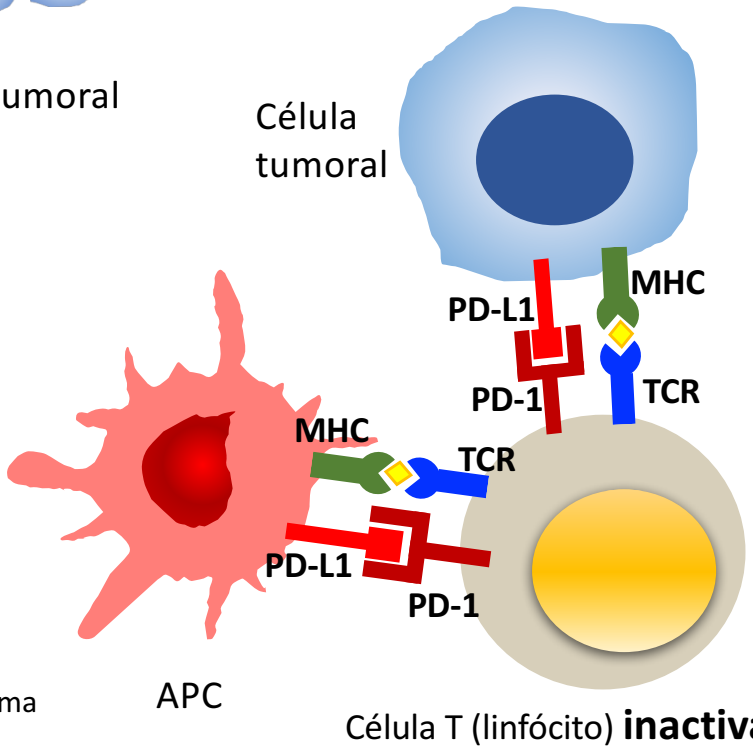


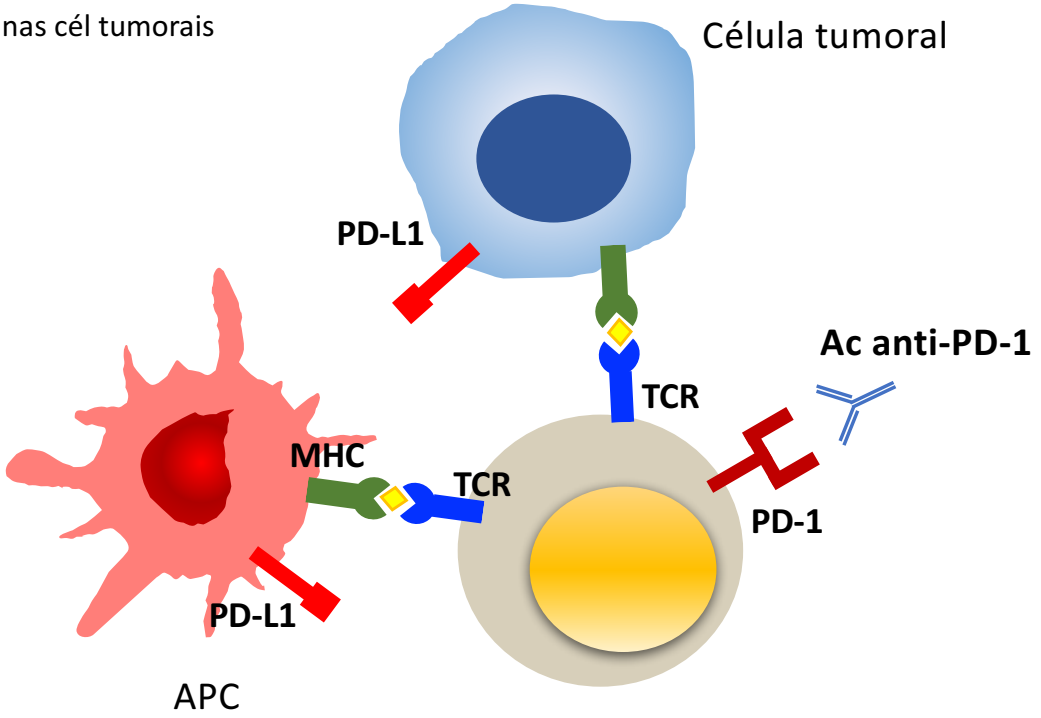
Verde = células tumorais
Laranja = PD-L1 nas cél tumorais

Melanoma



Verde = células tumorais
Vermelho = PD-L1 no estroma



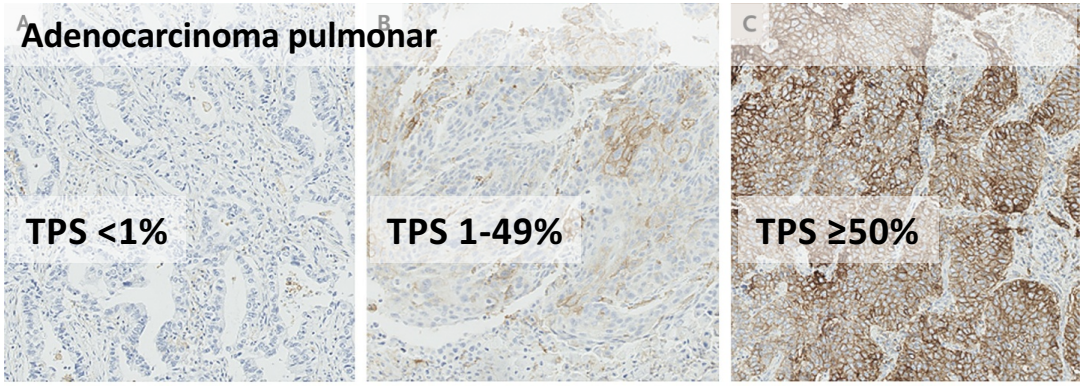


- Proliferação, diferenciação e sobrevivência de cél. T
- Função efectora anti-tumoral

Vasaturo A et al. Frontiers Immunol 2013; Kluger HM et al. Clin Cancer Res 2017

A importância do biomarcador revelada no KEYNOTE-001

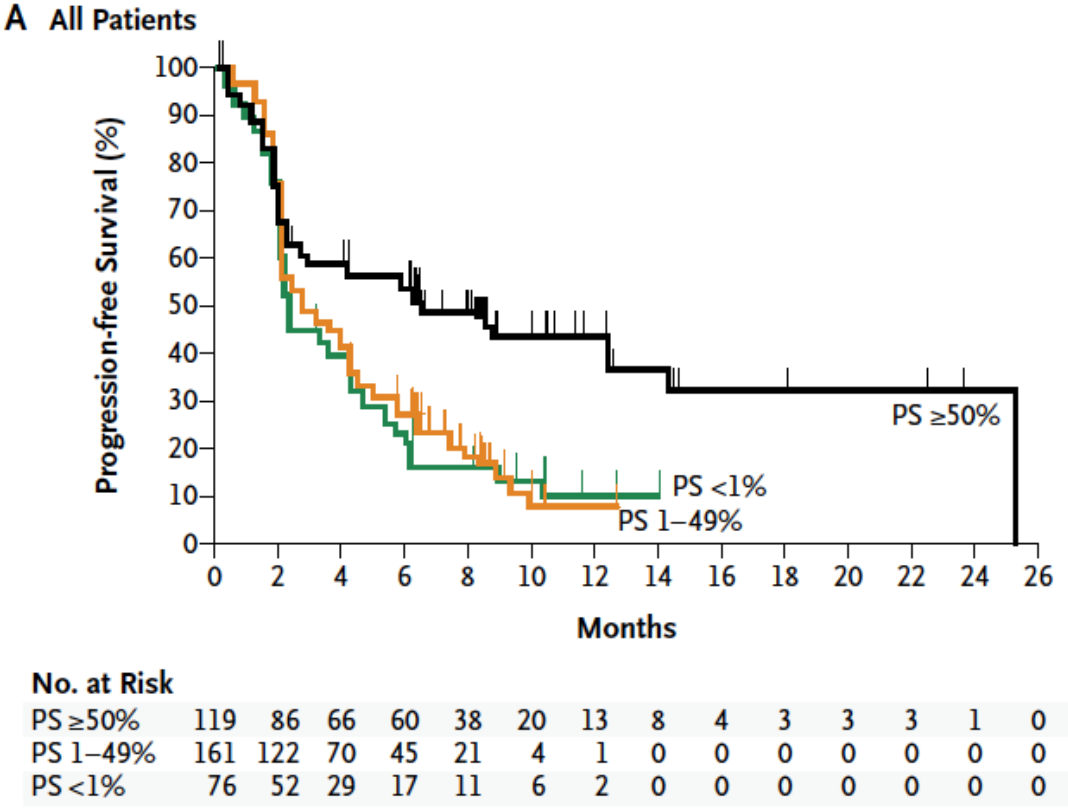
Expressão PD-L1 testada através de ensaio de imuno-histoquímica pharmDx (**PD-L1 IHC 22C3**; Dako/Agilent)



$$\text{TPS}(\%) = \frac{\text{No. PD-L1–stained tumor cells}}{\text{Total No. of viable tumor cells}} \times 100$$

Pembrolizumab provado no CPCNP

- 2ª linha monoterapia: TPS ≥1 %
- 1ª linha monoterapia: TPS ≥50 %

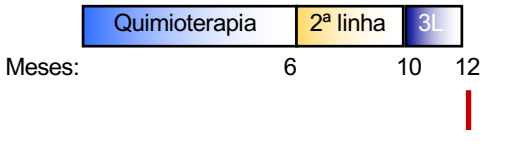


No. at Risk														
PS ≥50%	119	86	66	60	38	20	13	8	4	3	3	3	1	0
PS 1–49%	161	122	70	45	21	4	1	0	0	0	0	0	0	0
PS <1%	76	52	29	17	11	6	2	0	0	0	0	0	0	0

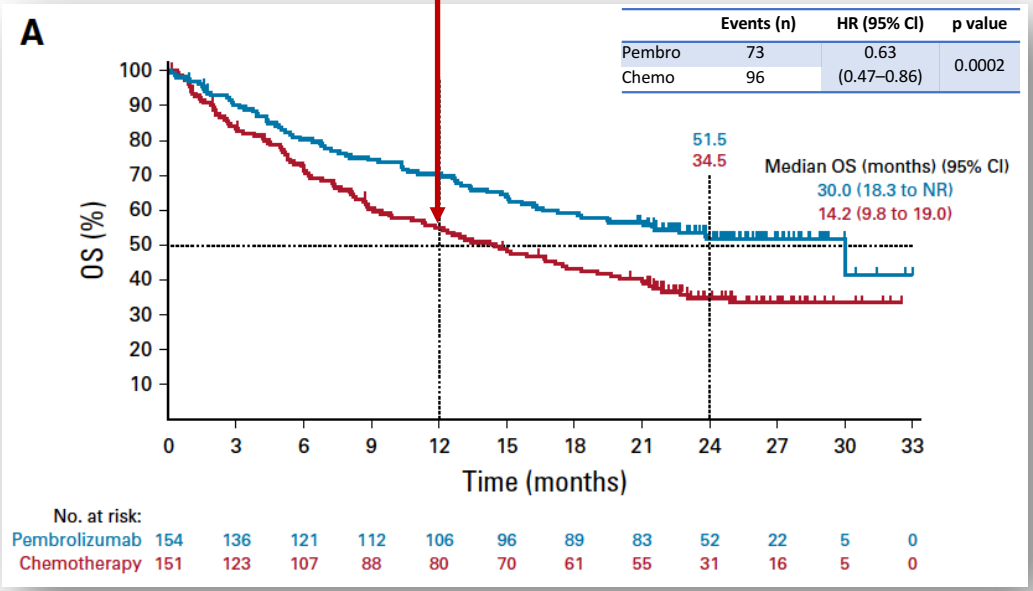
Garon EB et al. NEJM 2015

Impacto do PD-L1 como biomarcador de resposta a Pembrolizumab (1L)

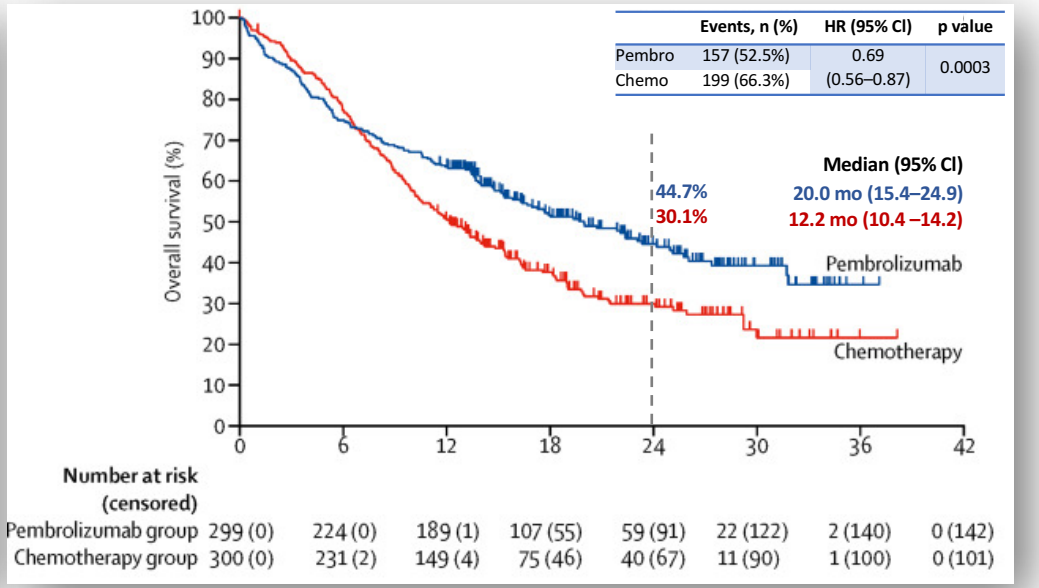
Tratamento de doente com tumor PD-L1+ e sem alvo mutacional até em 2016:



KEYNOTE-024



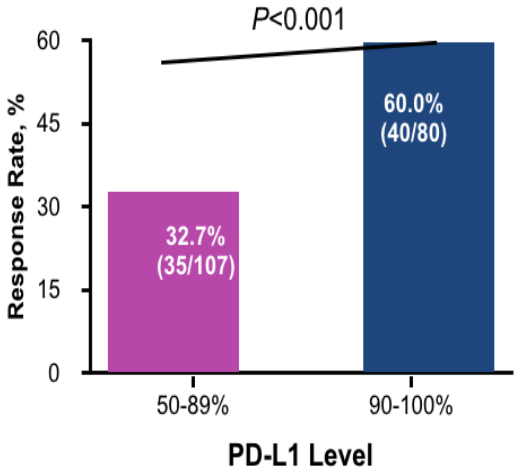
KEYNOTE-042



Reck M et al. NEJM 2016; Lopes G, et al. J Clin Oncol. 2018; Reck M et al. J Clin Oncol 2019; Mok T et al. Lancet 2019

Pembrolizumab monoterapia 1L CPCNP: PD-L1 ≥90% vs 50-89%

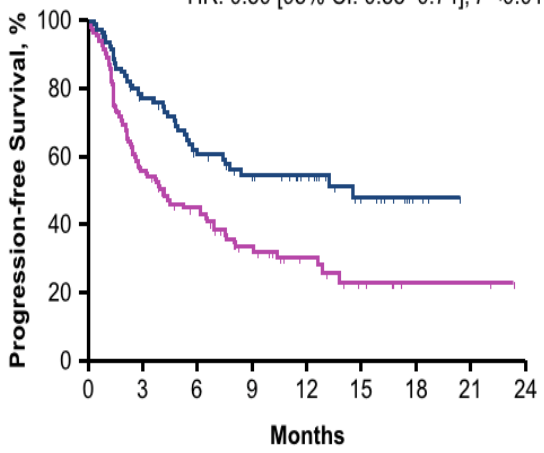
ORR



PFS

	N	mPFS (95% CI)
PD-L1 90–100%	80	14.5 mo (6.0–NR)
PD-L1 50–89%	107	4.1 mo (1.7–6.6)

HR: 0.50 [95% CI: 0.33–0.74], *P*<0.01

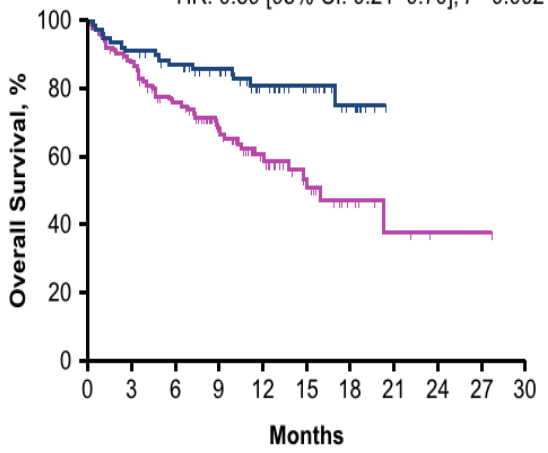


No. at risk									
PD-L1 90-100%	80	58	44	34	27	12	3	0	0
PD-L1 50-89%	107	59	42	25	13	6	2	2	0

OS

	N	mOS (95% CI)
PD-L1 90–100%	80	NR (NR–NR)
PD-L1 50–89%	107	15.9 mo (11.2–20.7)

HR: 0.39 [95% CI: 0.21–0.70], *P*=0.002



No. at risk											
PD-L1 90-100%	80	73	66	57	38	22	10	0	0	0	0
PD-L1 50-89%	107	92	75	51	33	18	8	4	1	1	0

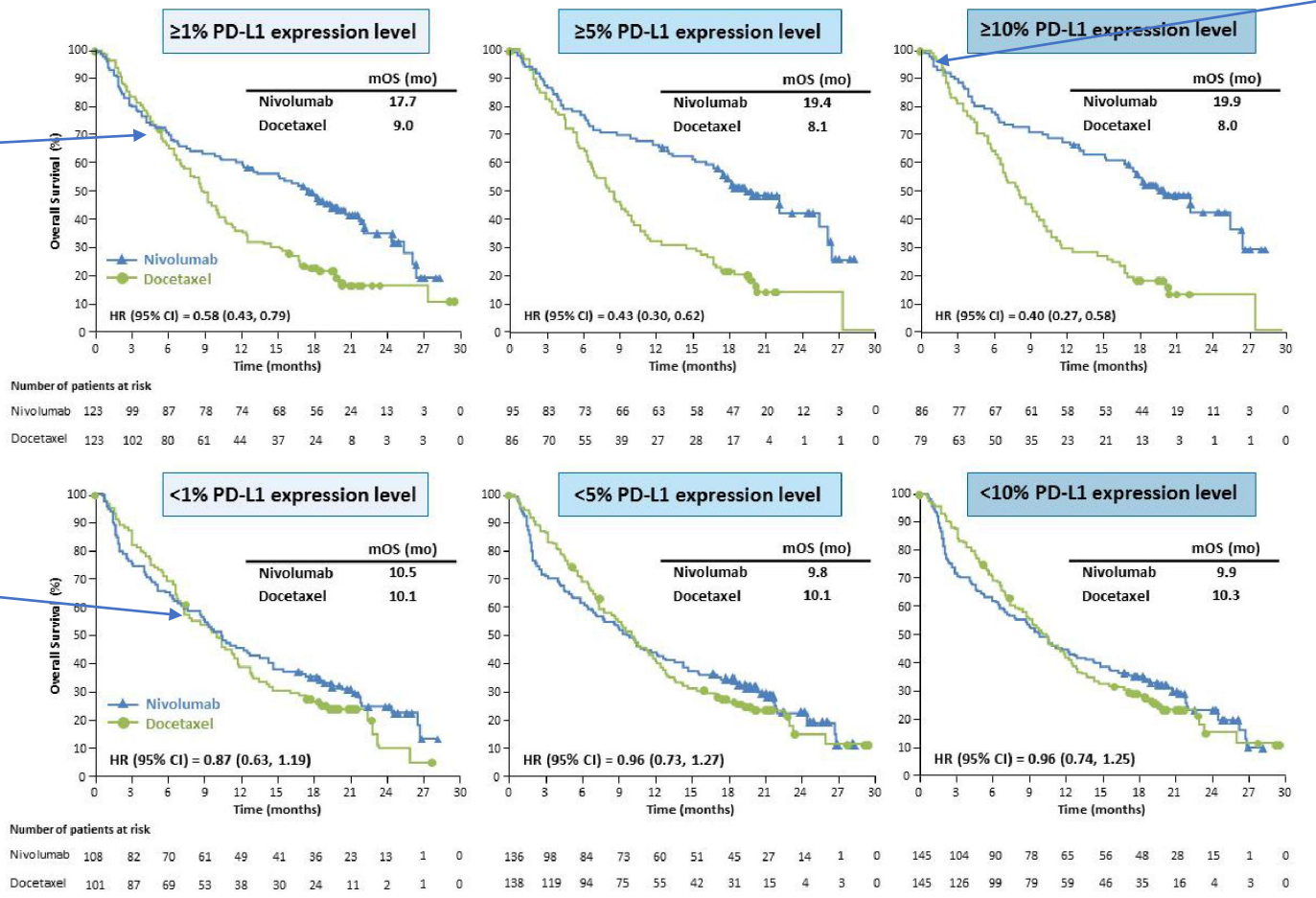
Aguilar EJ et al. Ann Oncol. 2019

Impacto da expressão PD-L1 na OS por Nivolumab (2L): CheckMate 057 trial

Efeito tardio do tratamento

Efeito precoce do tratamento

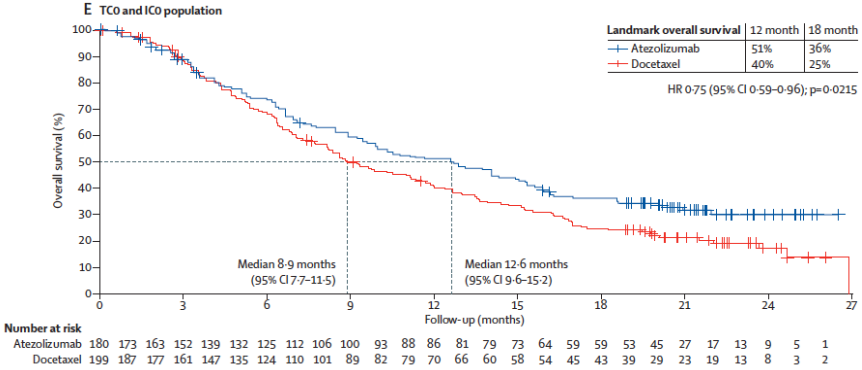
Efeito reverso do tratamento com o tempo



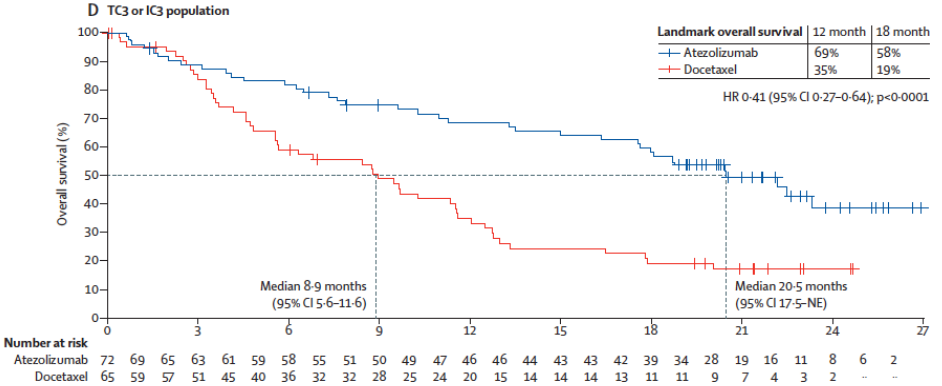
Borgaei H et al. NEJM 2015

PD-L1 NÃO tem impacto na OS por Atezolizumab (2L): OAK trial

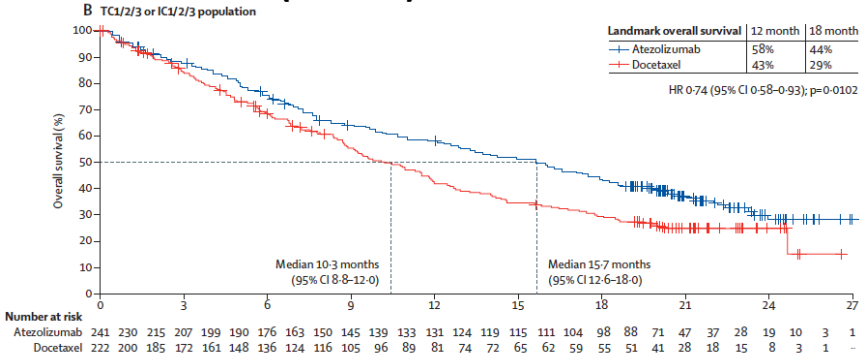
PD-L1 <1% (TC e IC)



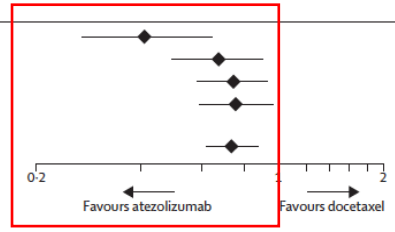
PD-L1 ≥50% TC ou ≥10% IC



PD-L1 ≥1% (TC e IC)



	n (%)	Median overall survival (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
TC3 or IC3	137 (16)	20·5	8·9	0·41 (0·27–0·64)
TC2/3 or IC2/3	265 (31)	16·3	10·8	0·67 (0·49–0·90)
TC1/2/3 or IC1/2/3	463 (54)	15·7	10·3	0·74 (0·58–0·93)
TC0 and IC0	379 (45)	12·6	8·9	0·75 (0·59–0·96)
ITT	850 (100)	13·8	9·6	0·73 (0·62–0·87)



TC: tumour cells; IC: tumour-infiltrating immune cells
PD-L1 Antibody: VENTANA **SP142** PD-L1 immunohistochemistry assay

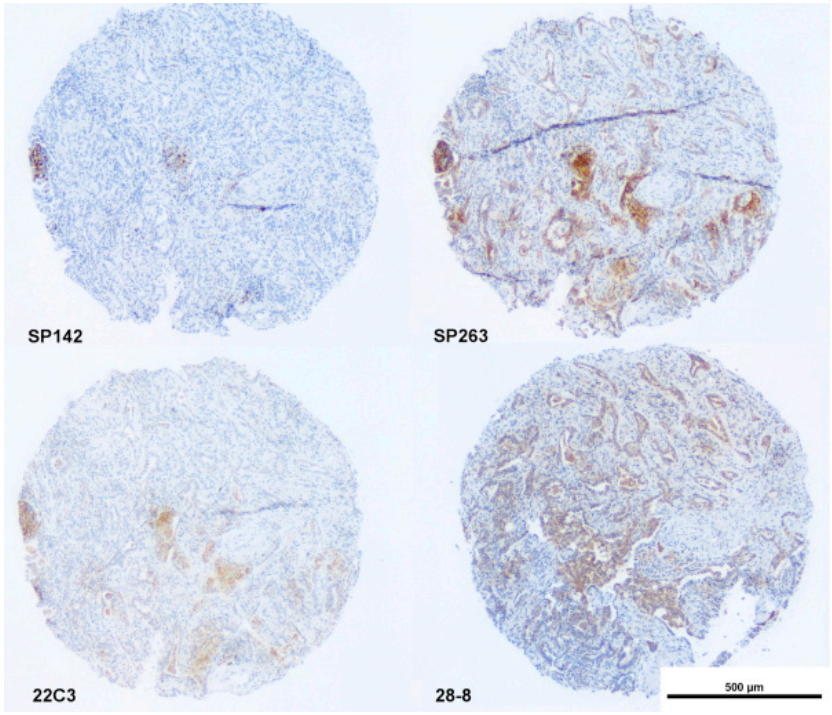
Rittmeyer A, et al. Lancet 2017

Desafios na utilização de PD-L1 como biomarcador

Variablidade inter-ensaio

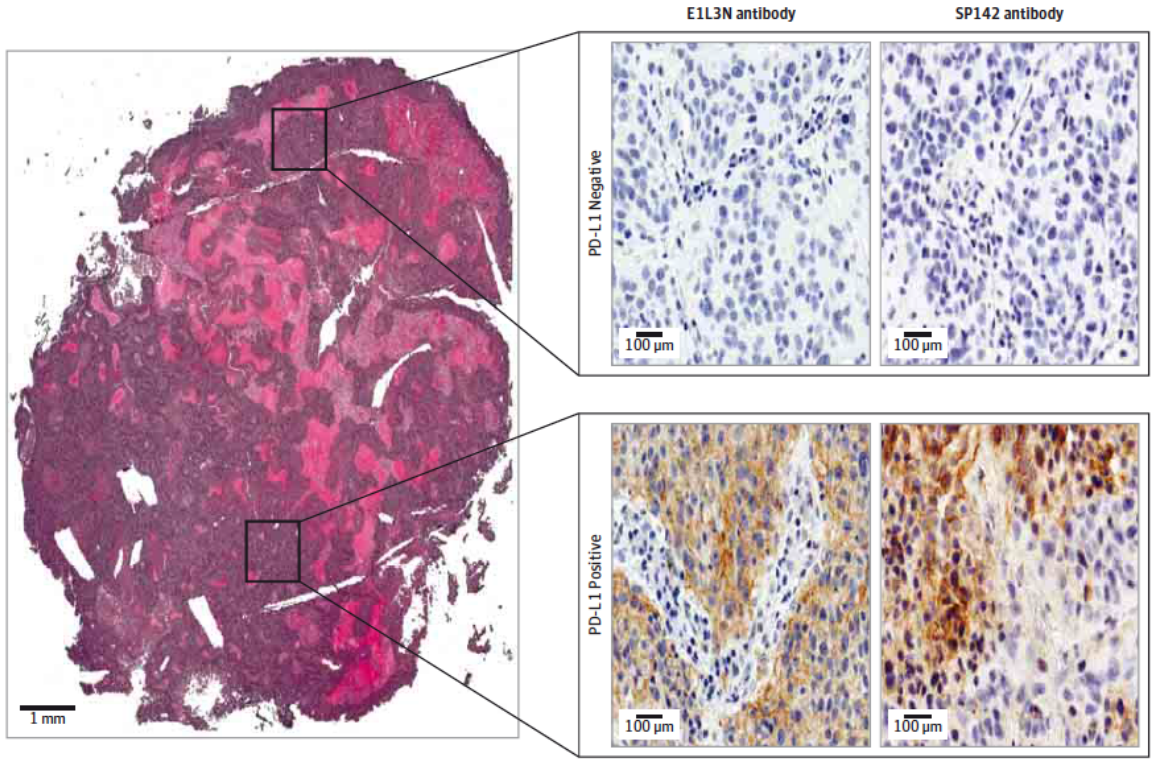
Clones de anticorpo usados nos estudos clínicos:

SP142 (Atezolizumab) **SP263** (Durvalumab)



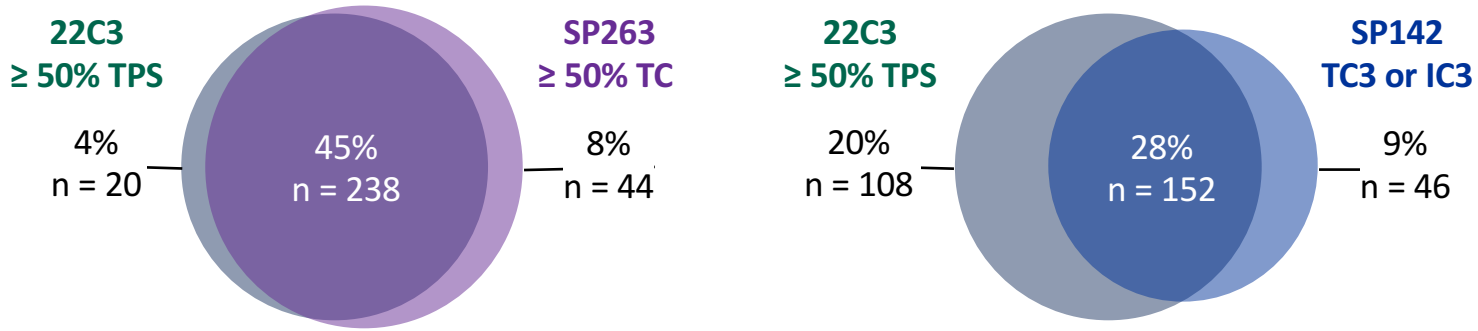
22C3 (Pembrolizumab) **Clone 28-8** (Nivolumab)

Heterogeneidade de expressão no mesmo tumor



Hendry S et al. J Thorac Oncol. 2018
McLaughlin J et al. JAMA Oncol. 2016

Sobreposição entre subgrupos de expressão PD-L1 alta (IMpower110)



- **Elevada sobreposição entre 22C3 e SP263** observada no subgrupo de expressão ≥ 50%
- Uma grande proporção do subgrupo SP142 TC3 /IC3 abrangeu também o subgrupo 22C3 ≥ 50% TPS.

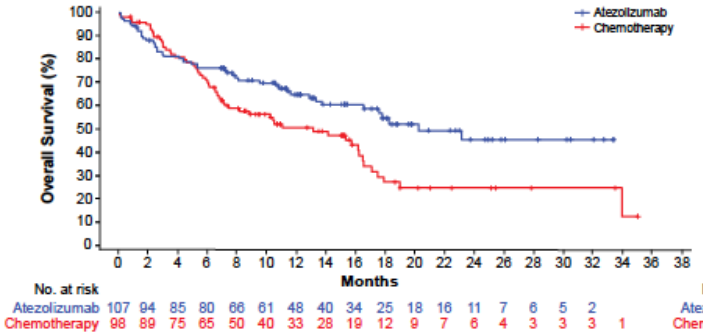
22C3 and SP263 overlap: BEP within the ITT-WT population, n = 530.
22C3 and SP142 overlap: BEP within the ITT-WT population, n = 534.

Clones de anticorpo usados nos estudos clínicos:
22C3 (Pembrolizumab)
SP263 (Durvalumab)
SP142 (Atezolizumab)

Herbst et al. ESMO-IO 2019

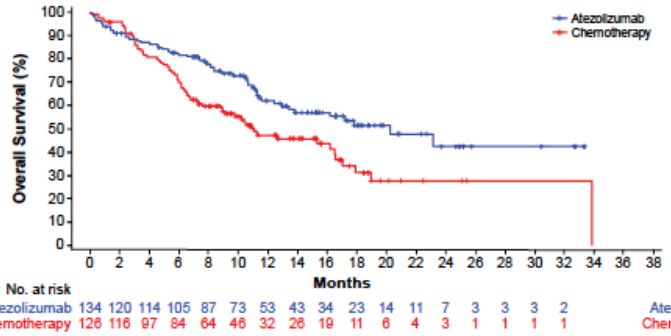
OS em subgrupos de expressão PD-L1 alta no IMpower110 (1L)

SP142 (TC3 or IC3-WT)[a]



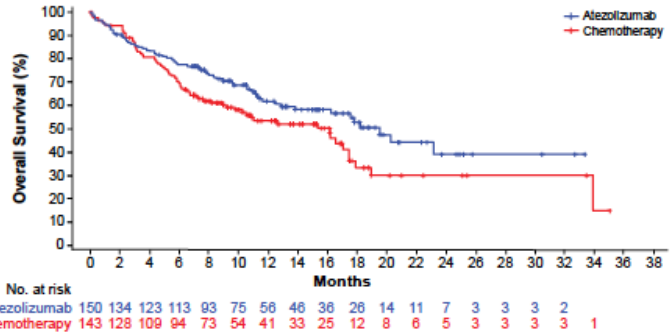
	Atezo (n = 107)	Chemo (n = 98)
mOS, mo	20.2	13.1
HR[b] (95% CI)	0.59 (0.40, 0.89)	

22C3 BEP-WT (TPS ≥ 50%)[a]



	Atezo (n = 134)	Chemo (n = 126)
mOS, mo	20.2	11.0
HR[c] (95% CI)	0.60 (0.41, 0.86)	

SP263 BEP-WT (TC ≥ 50%)[a]



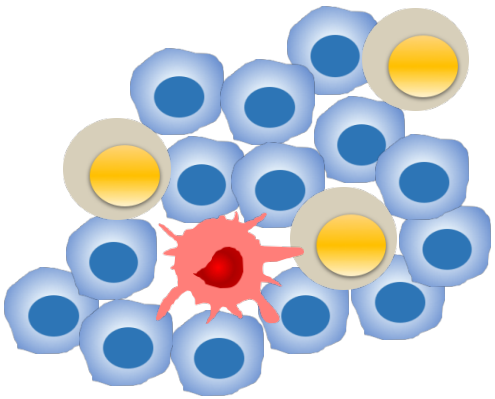
	Atezo (n = 150)	Chemo (n = 143)
mOS, mo	19.5	16.1
HR[c] (95% CI)	0.71 (0.50, 1.00)	

[a] SP142 TC1/2/3 or IC1/2/3-WT (n = 554); 22C3 BEP-WT (n = 534); SP263 BEP-WT (n = 546). [b] Stratified. [c] Unstratified.

Clones de anticorpo usados nos estudos clínicos:
22C3 (Pembrolizumab)
SP263 (Durvalumab)
SP142 (Atezolizumab)

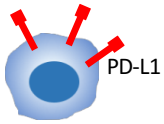
Herbst et al. ESMO-IO 2019

Quimioterapia
+
Inibidores PD-1/PD-L1



Microambiente tumoral

↑ Células apresentadoras de antigénio (APC)



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

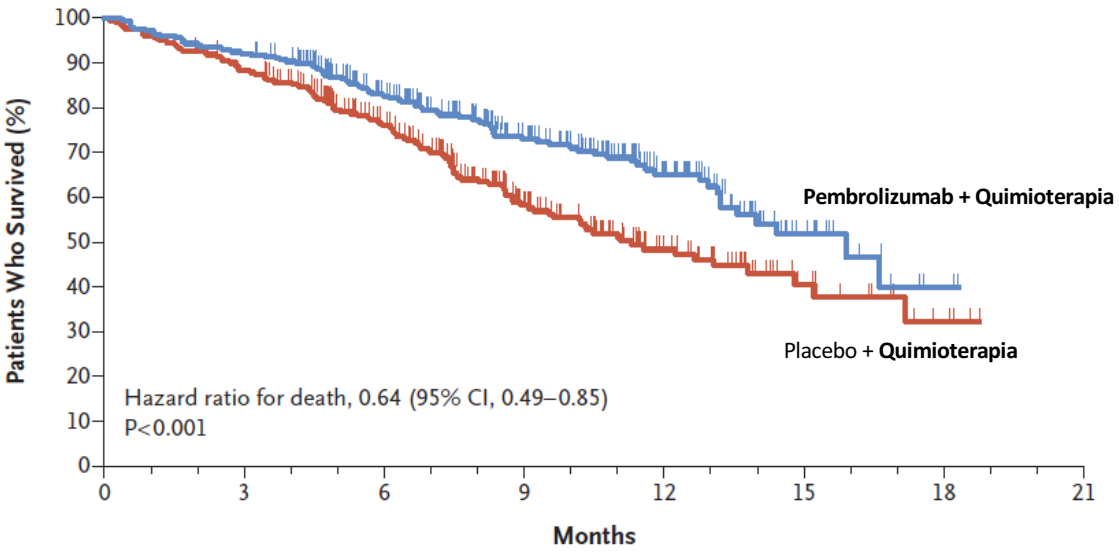
↑ Células T CD8+
↓ Células Treg ou MDSCs

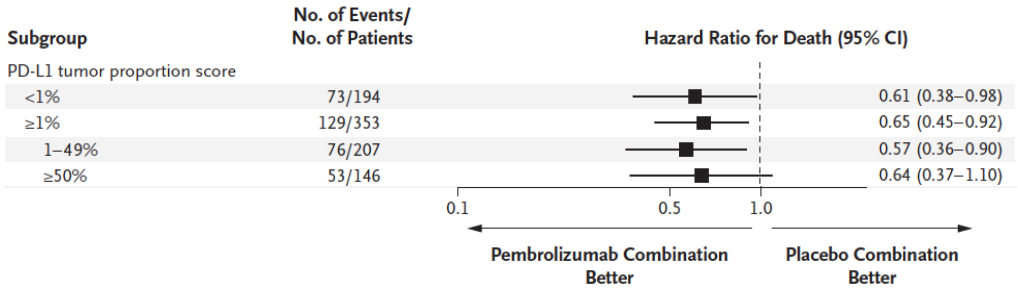
↑ Macrófagos

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

Combinações QT+IT

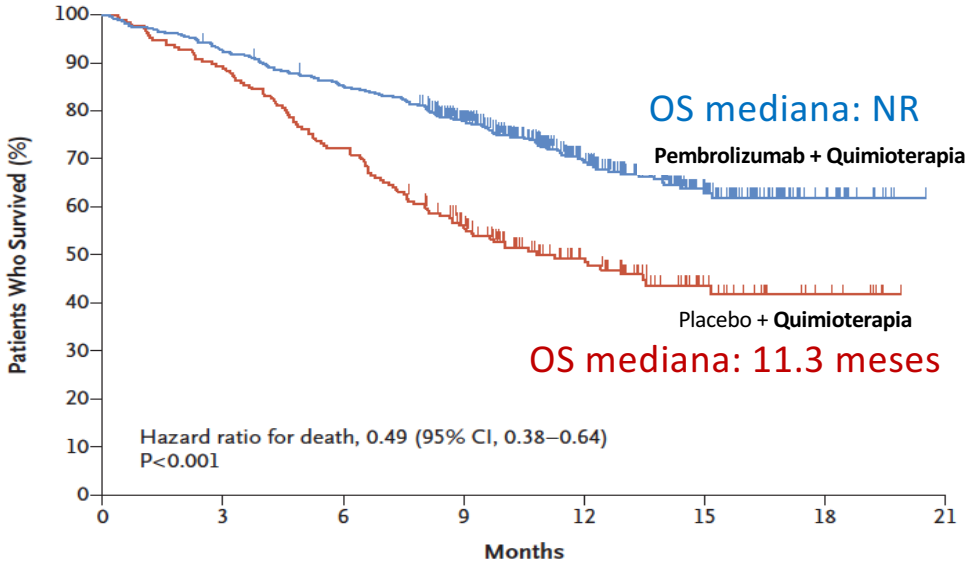
Squamous Non–Small-Cell Lung Cancer (KN-407)

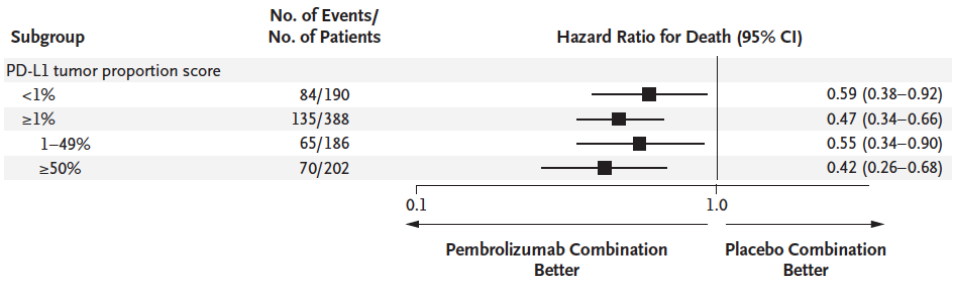




Paz-Ares L et al, NEJM 2018

Nonsquamous NSCLC EGFR/ALK negative (KN-189)

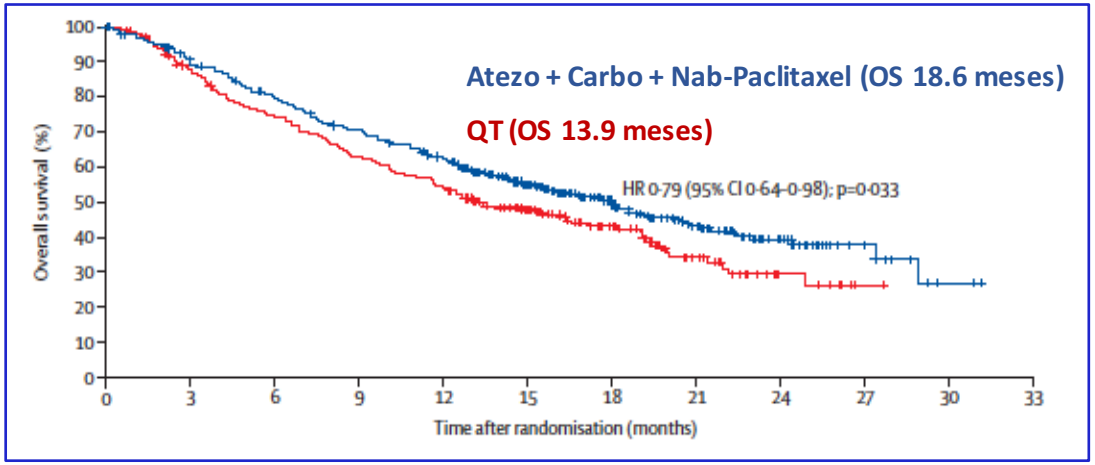


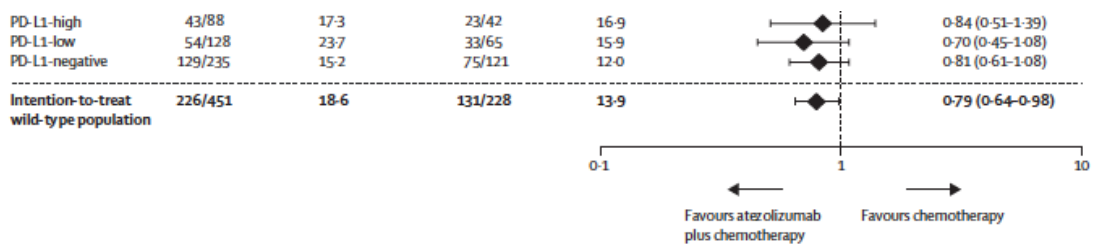


Gandhi L et al, NEJM 2018

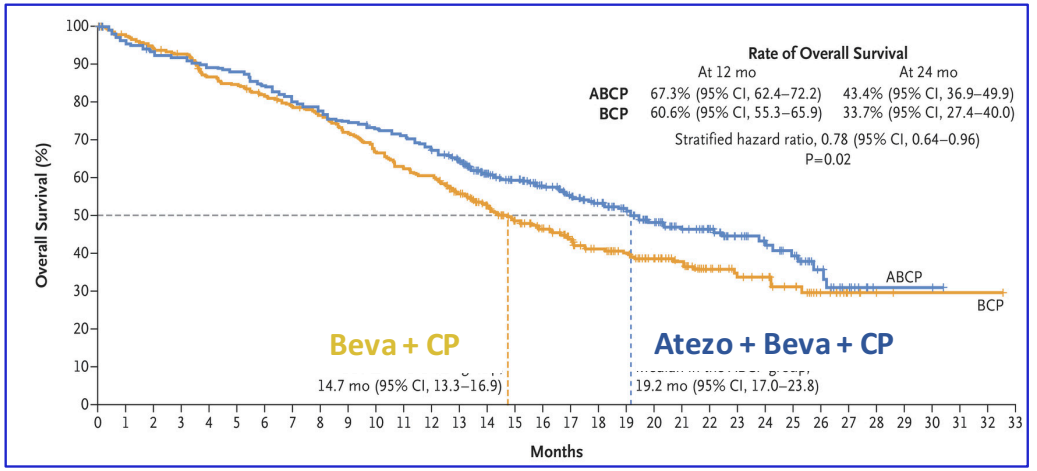
Combinações QT+IT

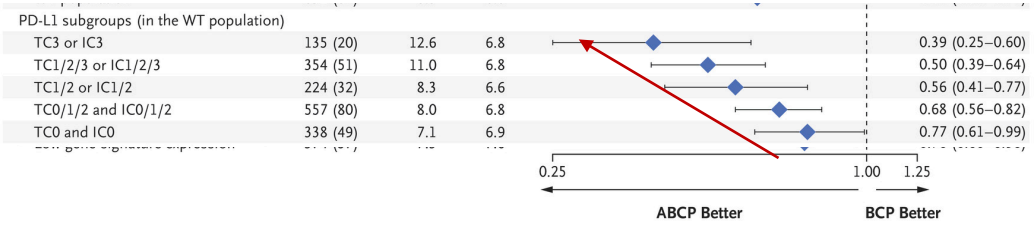
IMpower 130





IMpower 150





West et al. Lancet Oncol 2019; Socinski et al. NEJM 2018

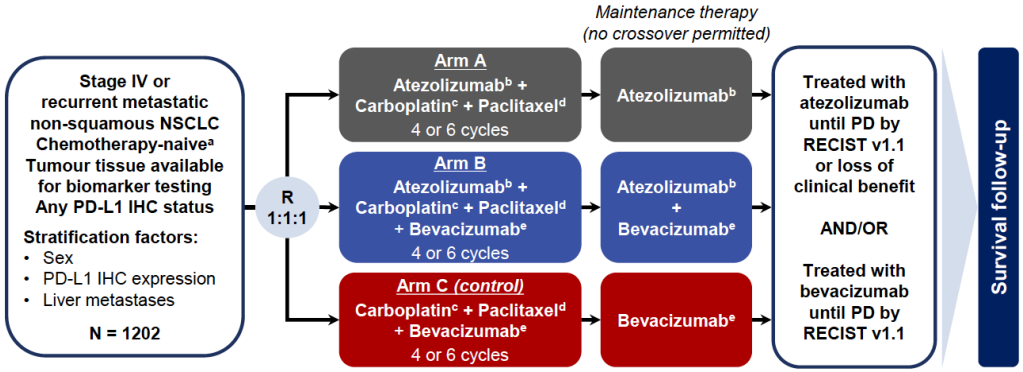
Expressão PD-L1

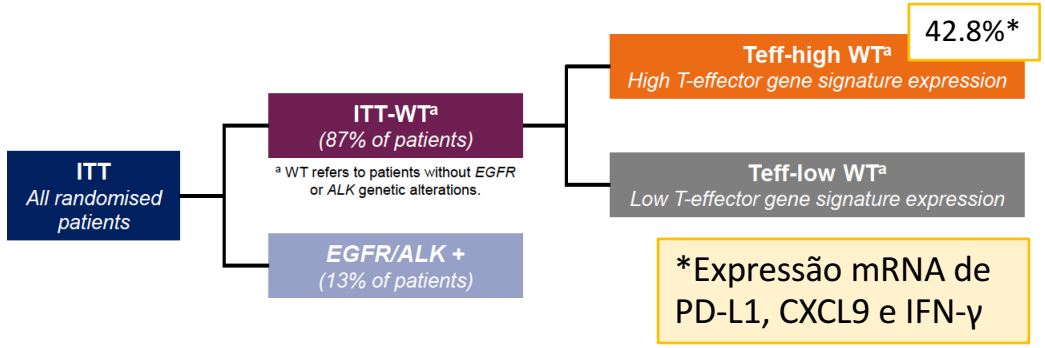
Teff (effector T-cell) gene signature

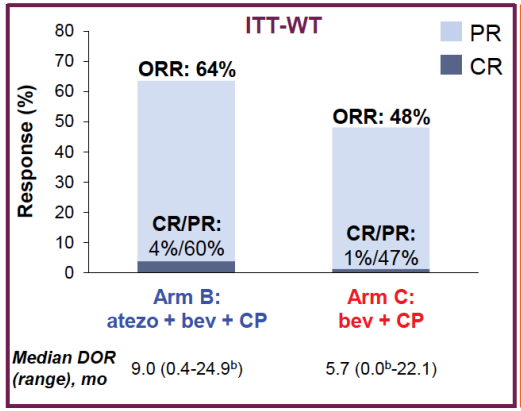
Tumor Mutational Burden

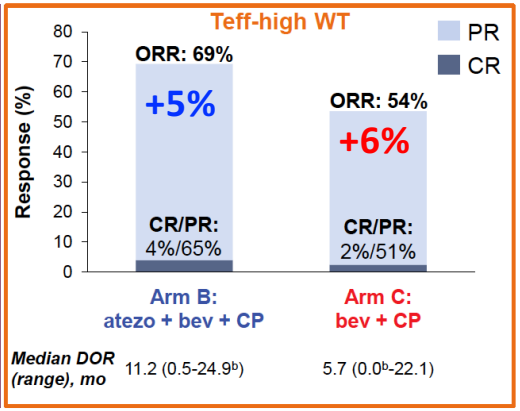
Perspectivas futuras

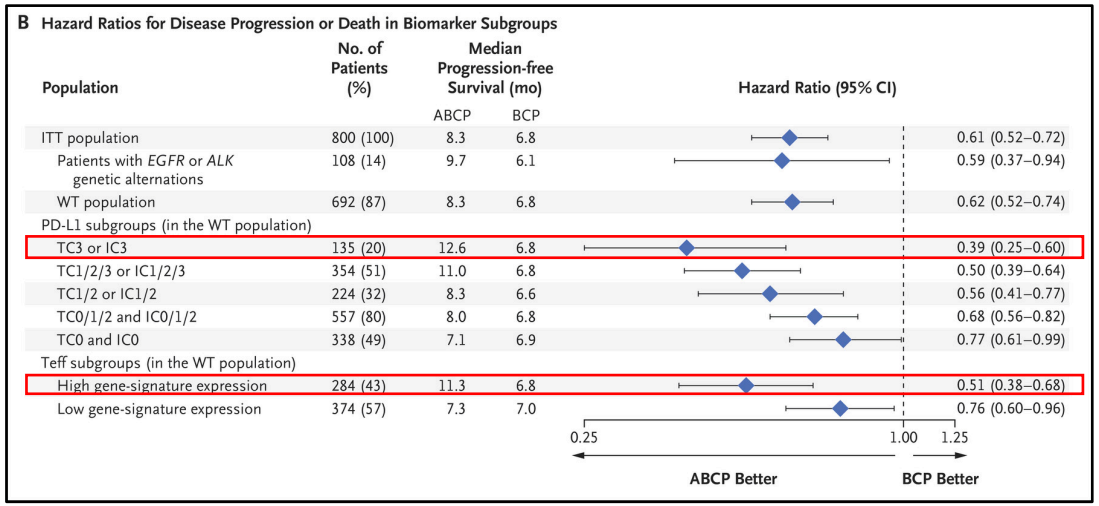
Teff (effector T-cell) gene signature - IMpower 150











B Hazard Ratios for Disease Progression or Death in Biomarker Subgroups

Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio (95% CI)
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61 (0.52–0.72)
Patients with *EGFR* or *ALK* genetic alternations	108 (14)	9.7	6.1	0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8	0.62 (0.52–0.74)
PD-L1 subgroups (in the WT population)				
TC3 or IC3	135 (20)	12.6	6.8	0.39 (0.25–0.60)
TC1/2/3 or IC1/2/3	354 (51)	11.0	6.8	0.50 (0.39–0.64)
TC1/2 or IC1/2	224 (32)	8.3	6.6	0.56 (0.41–0.77)
TC0/1/2 and IC0/1/2	557 (80)	8.0	6.8	0.68 (0.56–0.82)
TC0 and IC0	338 (49)	7.1	6.9	0.77 (0.61–0.99)
Teff subgroups (in the WT population)				
High gene-signature expression	284 (43)	11.3	6.8	0.51 (0.38–0.68)
Low gene-signature expression	374 (57)	7.3	7.0	0.76 (0.60–0.96)

Reck M, et al. IMpower150 PFS analysis. ESMO 2019; Socinski et al. NEJM 2018

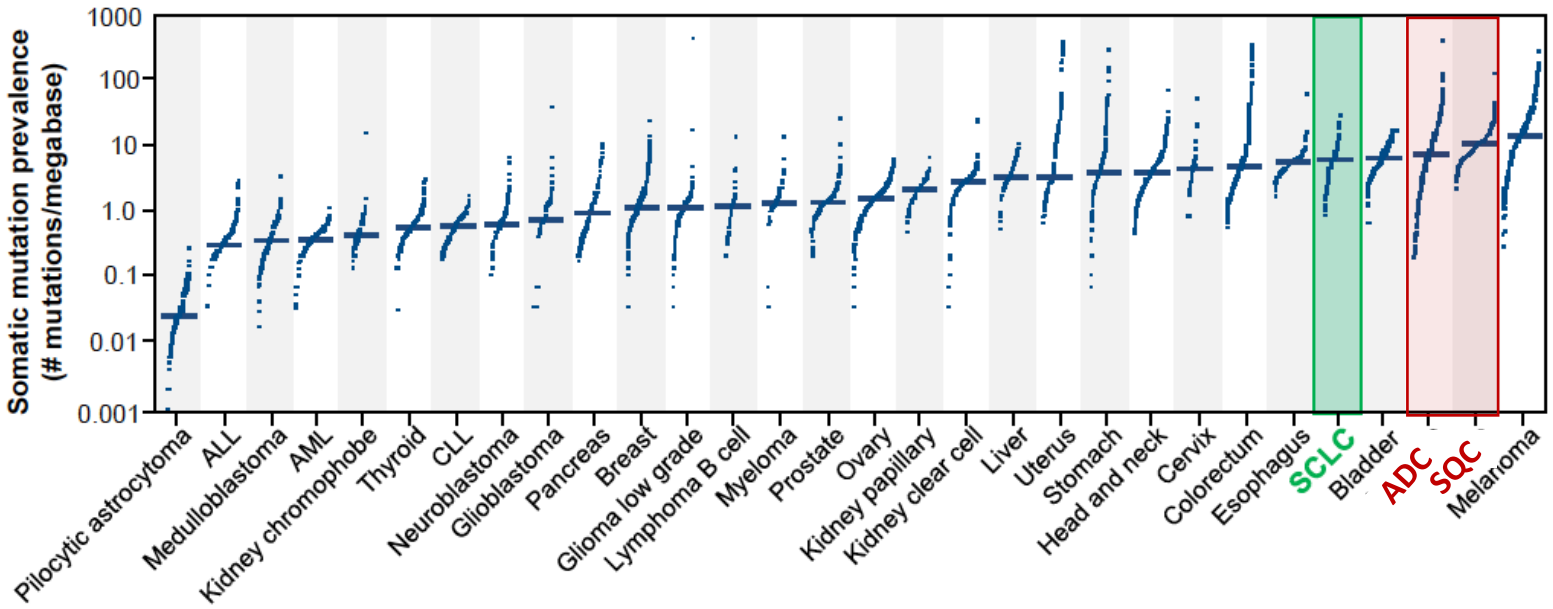
Expressão PD-L1

Teff (effector T-cell) gene signature

Tumor Mutational Burden

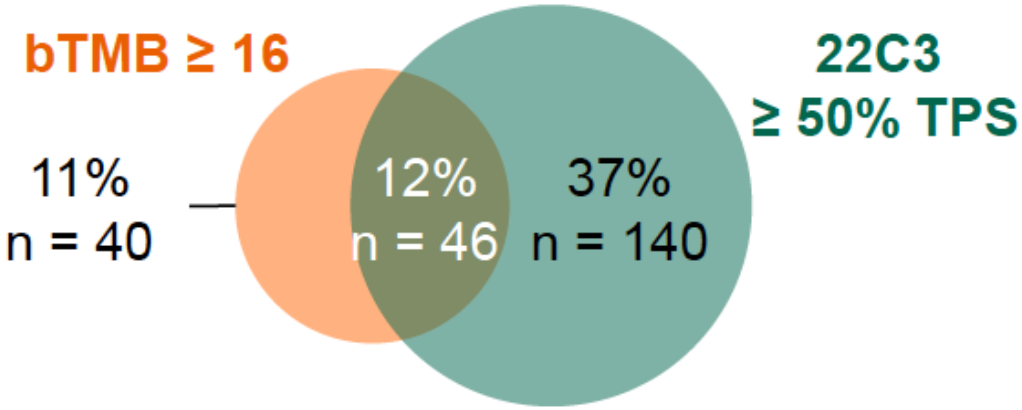
Perspectivas futuras

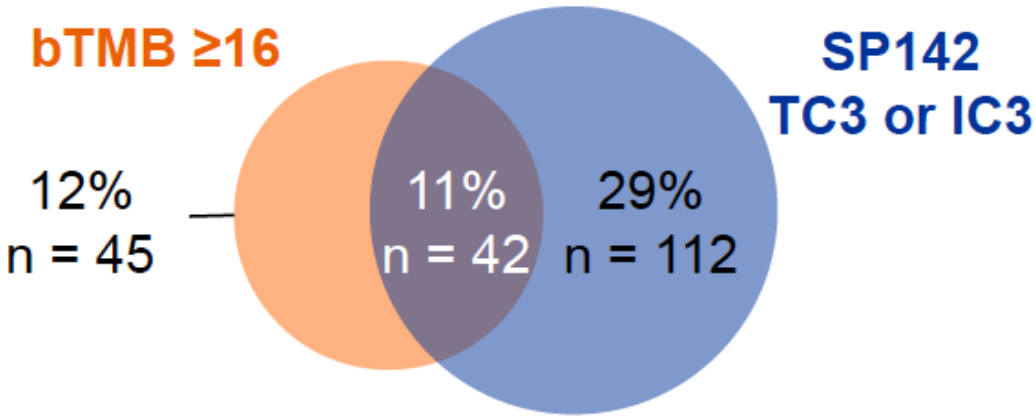
Tumor Mutational Burden



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

PD-L1 (SP142/22C3) e TMB identificaram populações distintas no IMpower110

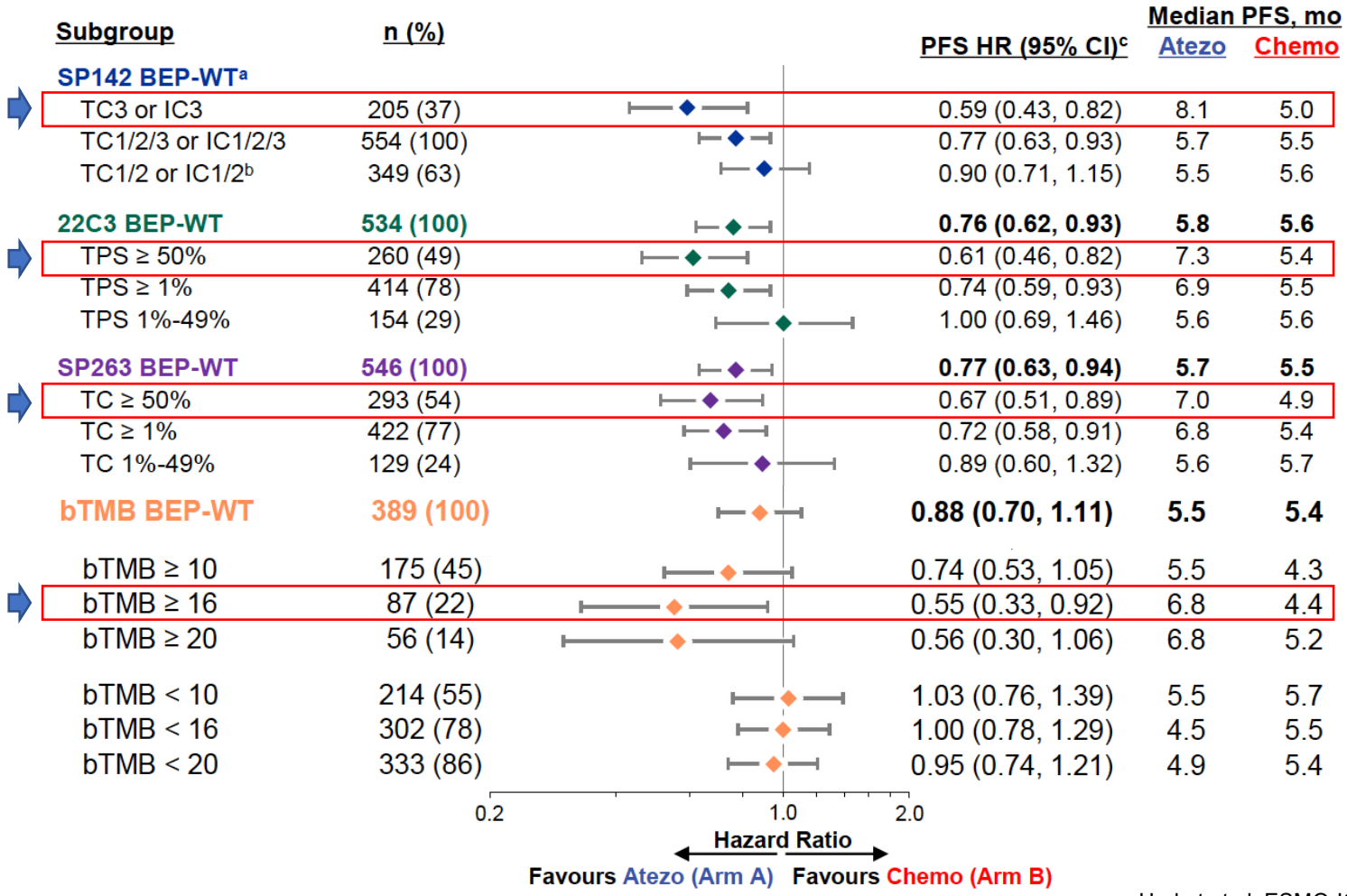




- No IMpower110, TMB foi avaliada usando *blood-based assay* da Foundation Medicine)
- bTMBscore de 16 é equivalente a 16 mutações/1.1 Mb, ou ≈14.5 mut/Mb

Herbst et al. ESMO-IO 2019

Benefício idêntico na OS e PFS com Atezo (1L) em PD-L1 alto ou TMB ≥16

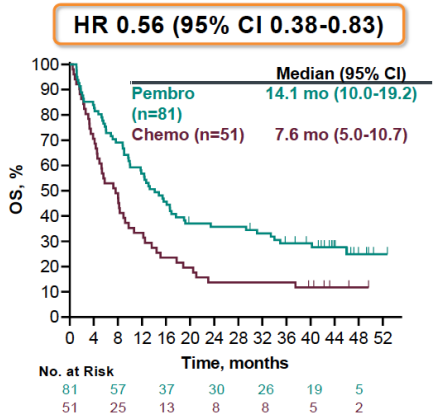


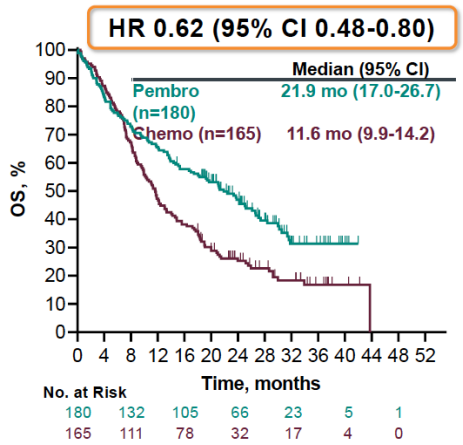
Herbst et al. ESMO-IO 2019

Benefício de Pembro (mono 1L) pode estar restrito a TMB ≥175 mut/exoma

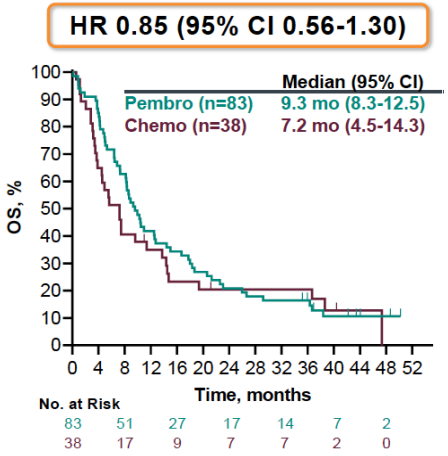
KEYNOTE-010 (PD-L1 ≥1%) **KEYNOTE-042 (PD-L1 ≥1%)**

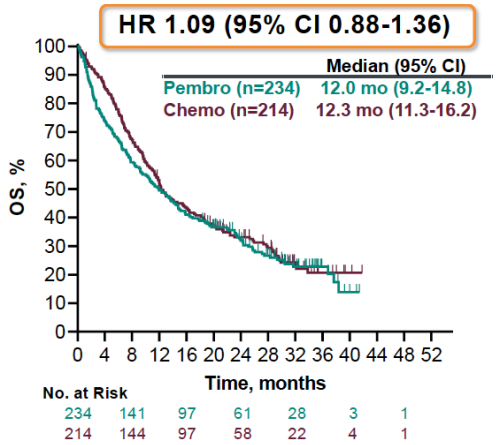
tTMB ≥175 mut/exome





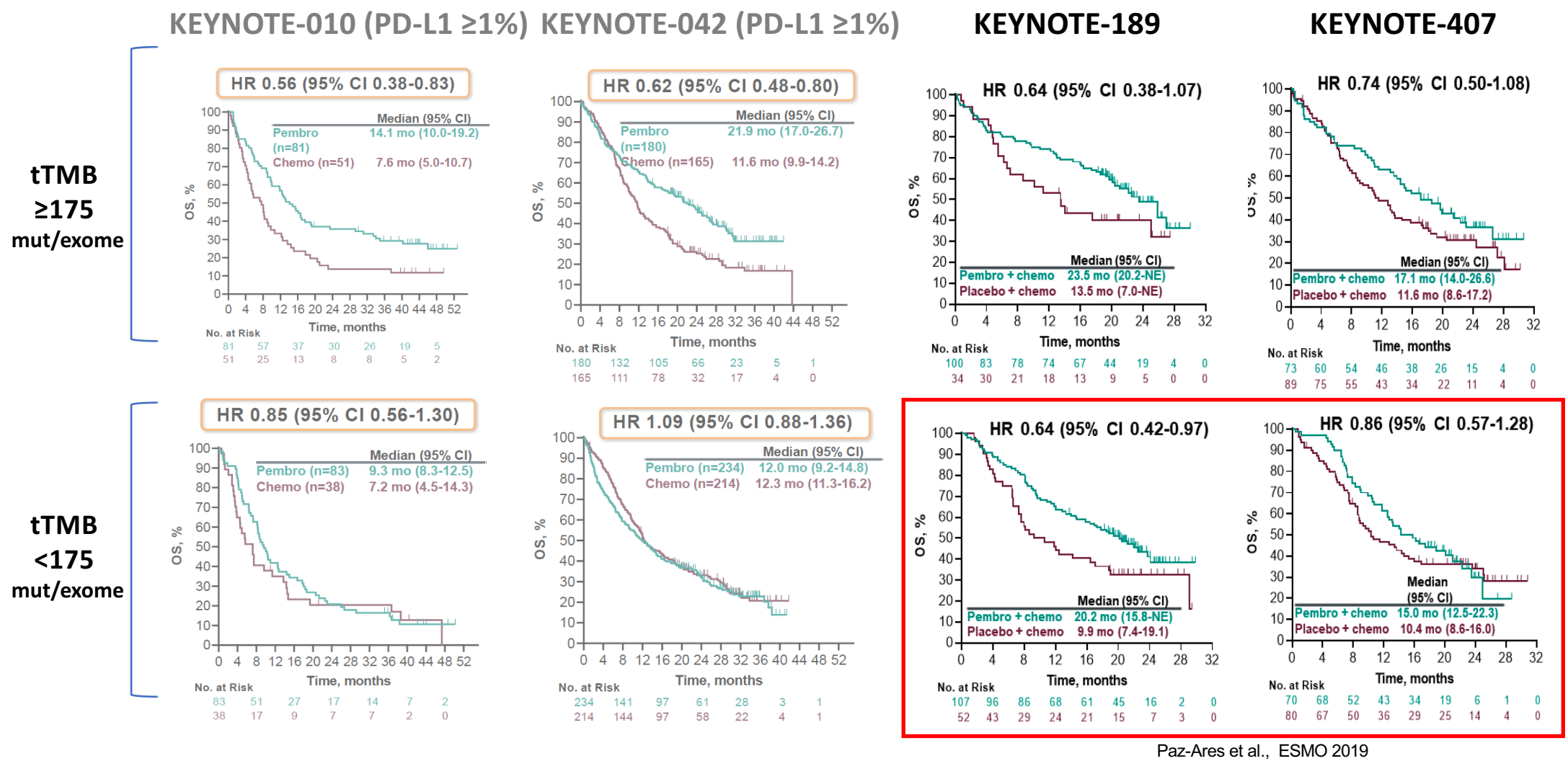
tTMB <175 mut/exome





Herbst et al. ESMO 2019

TMB pode não prever o resultado com QT+IT



Paz-Ares et al., ESMO 2019

CheckMate 227: Nivolumab + Ipilimumab vs Quimioterapia (1L)

Principais Critérios de Elegibilidade:
- CPCNP recorrente ou estádio IV
- Sem terapêutica sistémica prévia
- ECOG PS 0-1
- Ausência de metástases no SNC
- EGFR/ALK neg

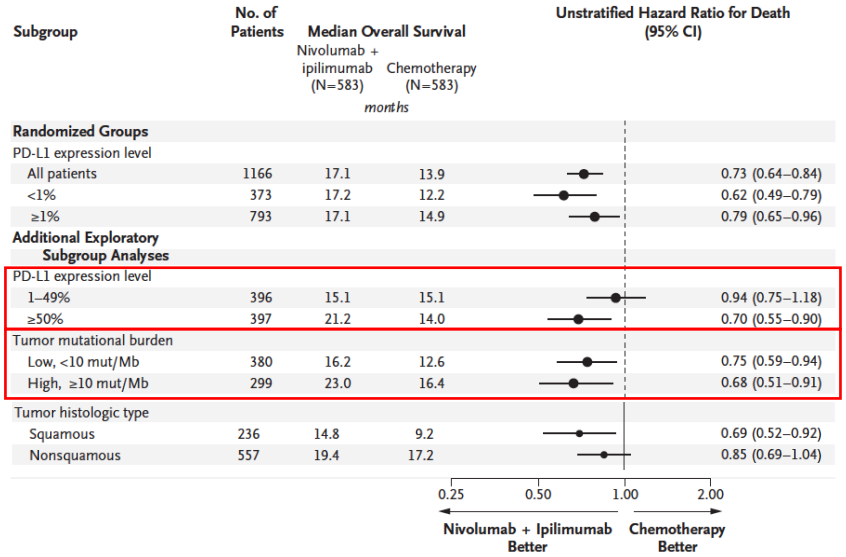
Estratificado por
Escamoso vs Não Escamoso

Part 1a
Expressão PD-L1≥1%
N = 1189
R 1:1:1
- NIVO + IPI (Dose baixa) N= 396
- Quimioterapia N= 397
- NIVO N= 396

Part 1b
Expressão PD-L1<1%
N = 550
R 1:1:1
- NIVO + IPI (Dose baixa) N= 187
- Quimioterapia N= 186
- NIVO + Quimioterapia N= 177

Endpoint Primário
- OS na pop PD-L1 ≥1%
- PFS na pop TMB ≥10mut/Mb

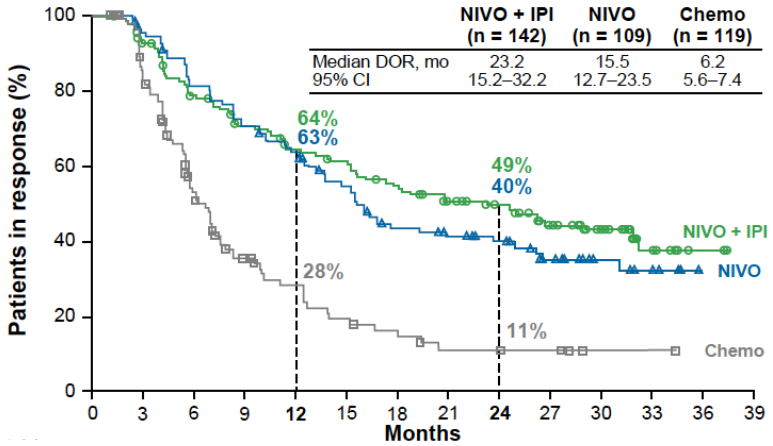
Tratamento até progressão, toxicidade inaceitável ou 2 anos de imunoterapia



Subgroup	No. of Patients	Median Overall Survival (months): Nivolumab + ipilimumab (N=583)	Median Overall Survival (months): Chemotherapy (N=583)	Unstratified Hazard Ratio for Death (95% CI)
Randomized Groups				
PD-L1 expression level				
All patients	1166	17.1	13.9	0.73 (0.64–0.84)
<1%	373	17.2	12.2	0.62 (0.49–0.79)
≥1%	793	17.1	14.9	0.79 (0.65–0.96)
Additional Exploratory Subgroup Analyses				
PD-L1 expression level				
1–49%	396	15.1	15.1	0.94 (0.75–1.18)
≥50%	397	21.2	14.0	0.70 (0.55–0.90)
Tumor mutational burden				
Low, <10 mut/Mb	380	16.2	12.6	0.75 (0.59–0.94)
High, ≥10 mut/Mb	299	23.0	16.4	0.68 (0.51–0.91)
Tumor histologic type				
Squamous	236	14.8	9.2	0.69 (0.52–0.92)
Nonsquamous	557	19.4	17.2	0.85 (0.69–1.04)

0.25 0.50 1.00 2.00
Nivolumab + Ipilimumab Better | Chemotherapy Better

DOR, meses (PD-L1 ≥1%)



Peters, S. et alNivolumab + Low -Dose Ipilimumab Versus Platinum -Doublet Chemotherapy as First -Line Treatment for Advanced Non -Small Cell Lung Cancer: CheckMate 227 Part 1 Final Analysis, presented at ESMO 2019
Hellmann et al. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. N Engl J Med. 2019 Sep 28. doi: 10.1056/NEJMoa1910231

Expressão PD-L1

Teff (effector T-cell) gene signature

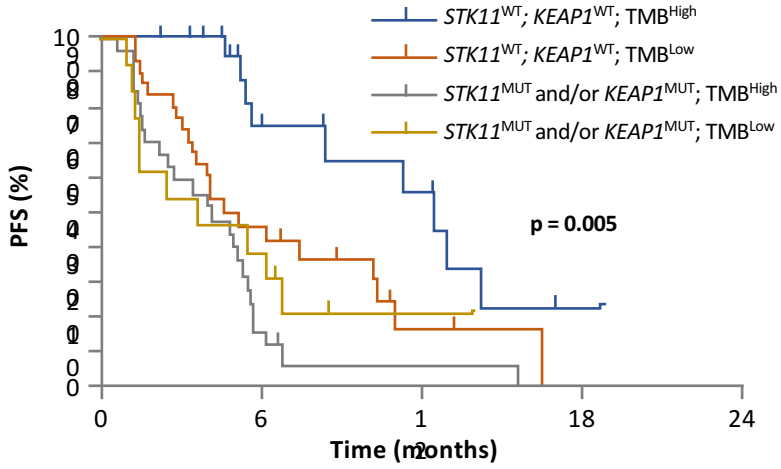
Tumor Mutational Burden

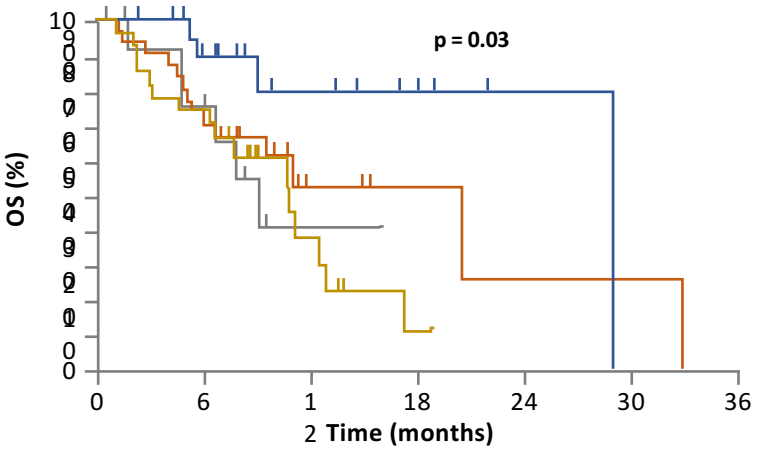
Perspectivas futuras

Integração de alterações genómicas *STK11* e *KEAP1* com TMB e outros biomarcadores: towards a composite panel?

Group	PFS, mo
STK11^{WT}; *KEAP1*^{WT}; TMB^{High}	12.4
STK11^{WT}; *KEAP1*^{WT}; TMB^{Low}	4.5
STK11^{MUT} and/or *KEAP1*^{MUT}; TMB^{High}	4.1
STK11^{MUT} and/or *KEAP1*^{MUT}; TMB^{Low}	3.6

Group	OS, mo
STK11^{WT}; *KEAP1*^{WT}; TMB^{High}	28.9
STK11^{WT}; *KEAP1*^{WT}; TMB^{Low}	20.4
STK11^{MUT} and/or *KEAP1*^{MUT}; TMB^{High}	10.7
STK11^{MUT} and/or *KEAP1*^{MUT}; TMB^{Low}	9.1



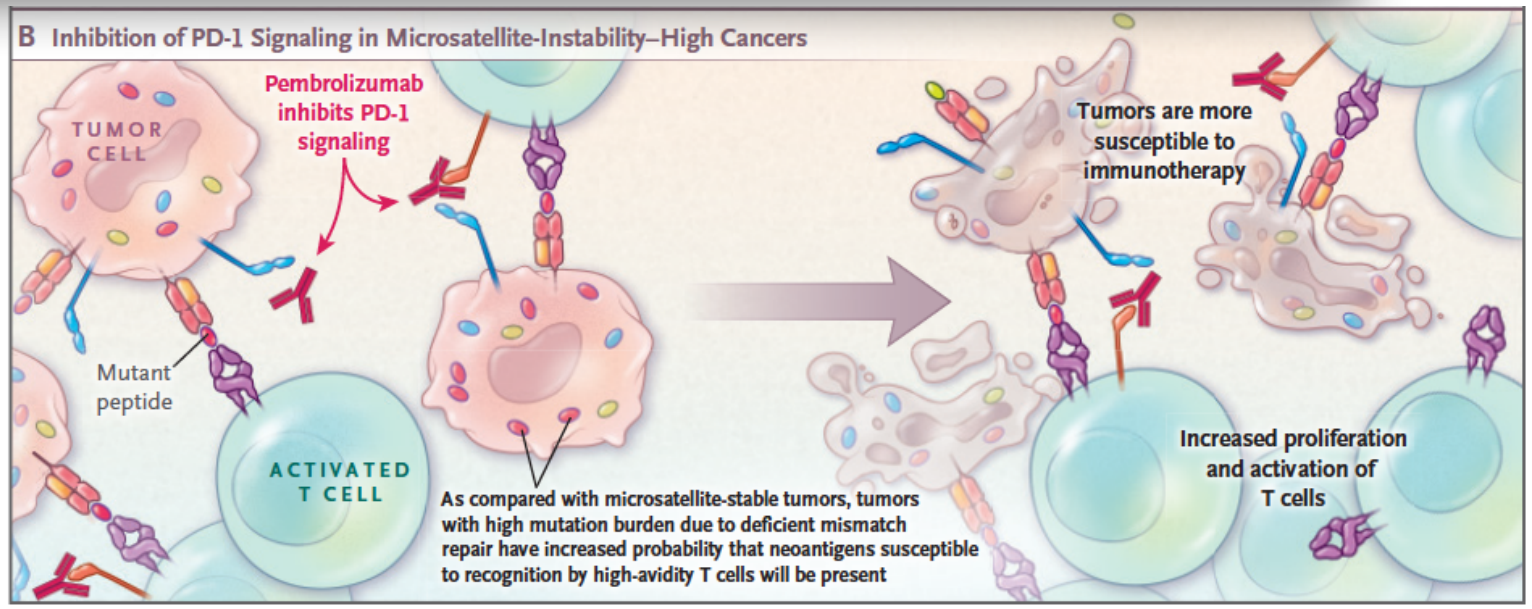


Skoulidis F, et al. J Clin Oncol. 2019;37 Suppl:abstr 102.

dMMR/MSI-H predicts the efficacy of anti-PD-1/ PD-L1 immunotherapy

First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication

Steven Lemery, M.D., M.H.S., Patricia Keegan, M.D., and Richard Pazdur, M.D.



Signaling Mechanism of PD-1 and PD-L1 and Inhibition of PD-1 Signaling in Microsatellite-Instability–High Cancers.
MHC1 denotes major histocompatibility complex 1.

N Engl J Med. 2017

Editorial

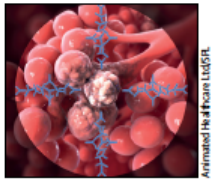
Lancet Respir Med 2018

Lung cancer immunotherapy biomarkers: refine not reject

Lung cancer is the leading cause of cancer-related mortality in the USA and UK, and for patients with metastatic non-small-cell lung cancer (NSCLC) 5-year survival is around 1%. The new era of immunotherapy drugs has given hope to millions, with impressive initial results for improving both progression-free and overall survival in these patients. The approval of immune checkpoint inhibitors has previously been tied to concentrations of the biomarker PD-L1, thought to predict treatment response. On April 16, 2018, two large

obtain a result, which can be 2 weeks or more. Another issue is the different assays and cutoffs available for PD-L1 testing that could lead to misclassification of PD-L1 status for some patients. These trials suggest that PD-L1 does still offer guidance as to who will respond better, and that for some indications PD-L1 status still plays a part. But if approval for use of pembrolizumab and other checkpoint inhibitors no longer always requires the determination of PD-L1 status, will physicians move away from testing?

With an increase in the patient group eligible for



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S2213-2600(18)30180-2