IV Simpósio Internacional de

IMUNO-ONCOLOGIA

O FUTURO DA ONCOLOGIA

27 E 28 DE JULHO – HOTEL PULLMAN VILA OLÍMPIA

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Tumor Mutation Burden

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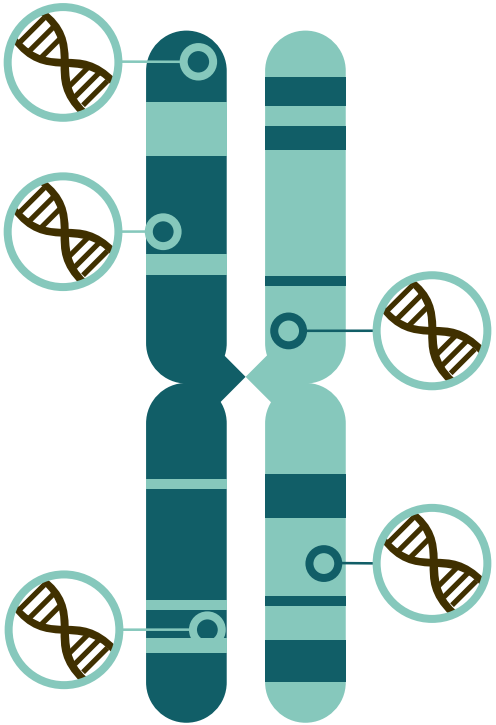
Disclosures

- Consultoria: BMS, United Medical

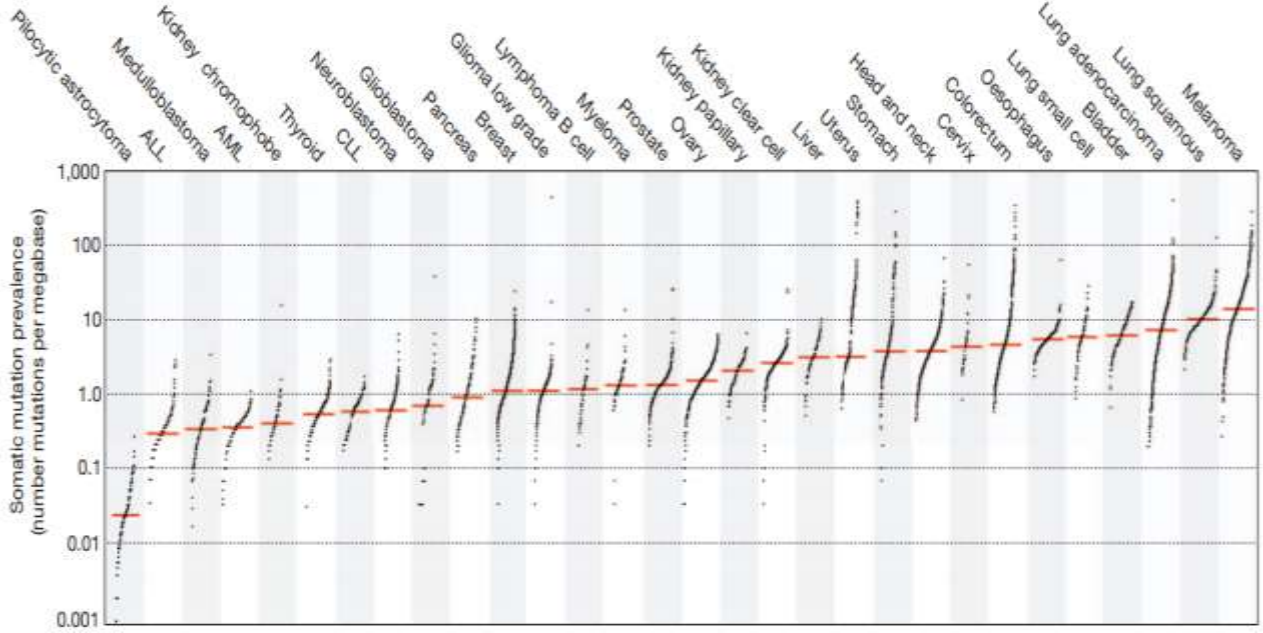
TMB: Número de mutações somáticas por área do genoma[1]

- **Mutações somáticas se acumulam, diferentemente de mutações germinativas[3]**
  - Fatores exógenos mutagênicos: Radiação UV, tabagismo
  - Mutações em genes de reparo de DNA (BRCA1, BRCA2, MMR) podem aumentar o número de mutações somáticas



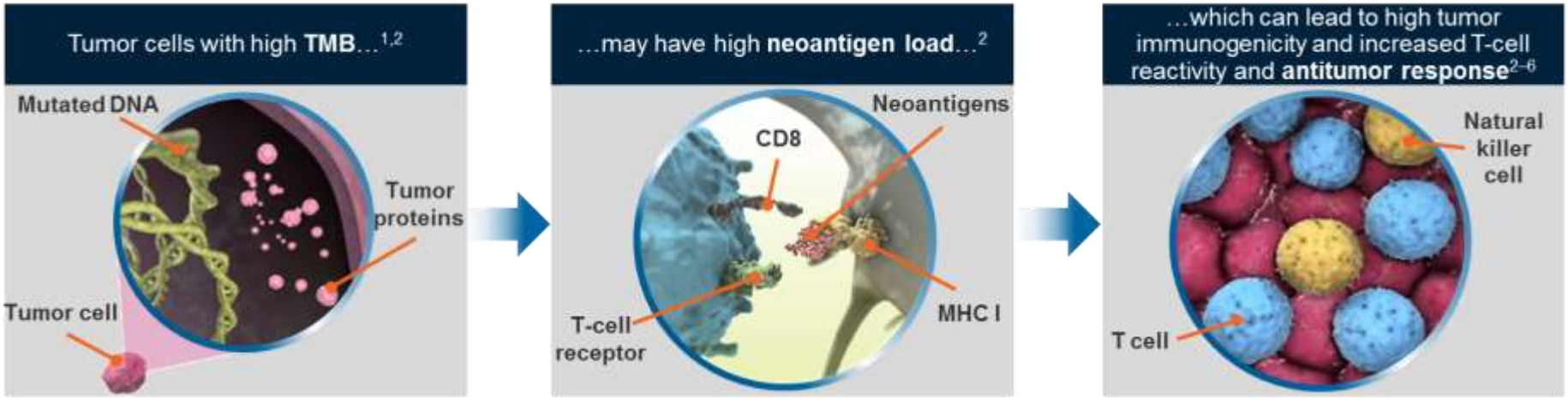
1. Schumacher TN, Schreiber RD. *Science*. 2015;348(6230):69-74.
2. Stratton MR et al. *Nature.* 2009;458(7239):719-724.

Mutações somáticas por megabase



Alexandrov et al. Nature, 2013

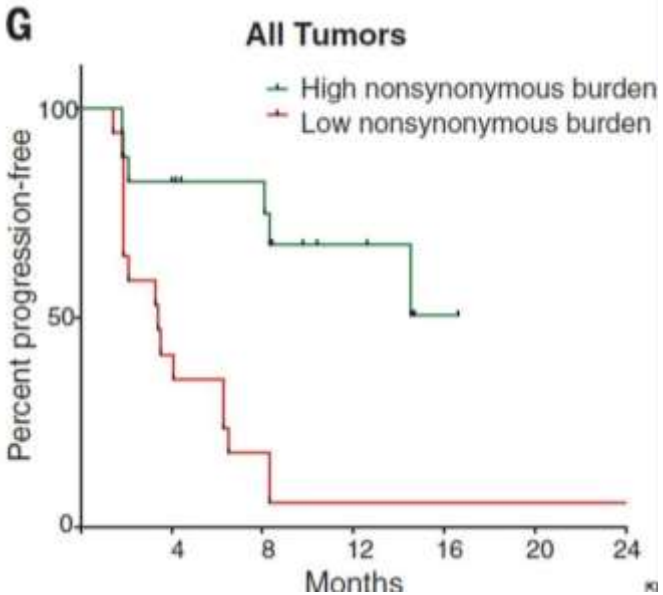
Racional para imunoterapia em tumores TBM-high

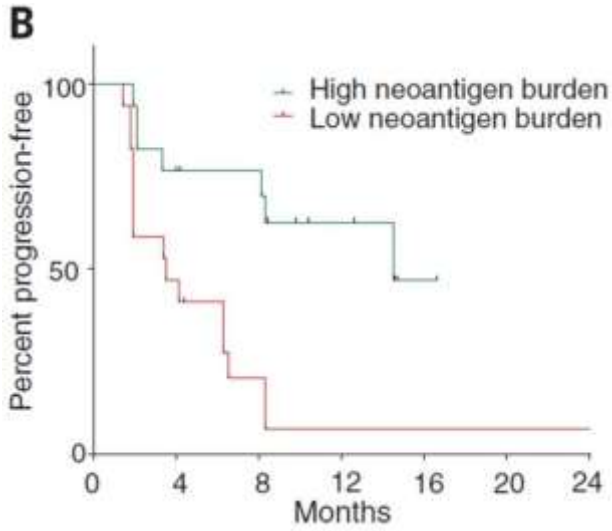


CD8 = cluster of differentiation 8; DNA = deoxyribonucleic acid; I-O = immuno-oncology; MHC = major histocompatibility complex; TMB = tumor mutational burden.

1. Stratton MR, et al. *Nature* 2009;458:719–724. 2. Schumacher TN, et al. *Science* 2015;348:69–74. 3. Chalmers ZR, et al. *Genome Med* 2017;9:34.
4. Chabanon RM, et al. *Clin Cancer Res* 2016;22:4309–4321. 5. Kim JM, et al. *Ann Oncol* 2016;27:1492–1504. 6. Giannakis M, et al. *Cell Rep* 2016;15:857–865. .

TMB e carga de neoantígenos: NSCLC

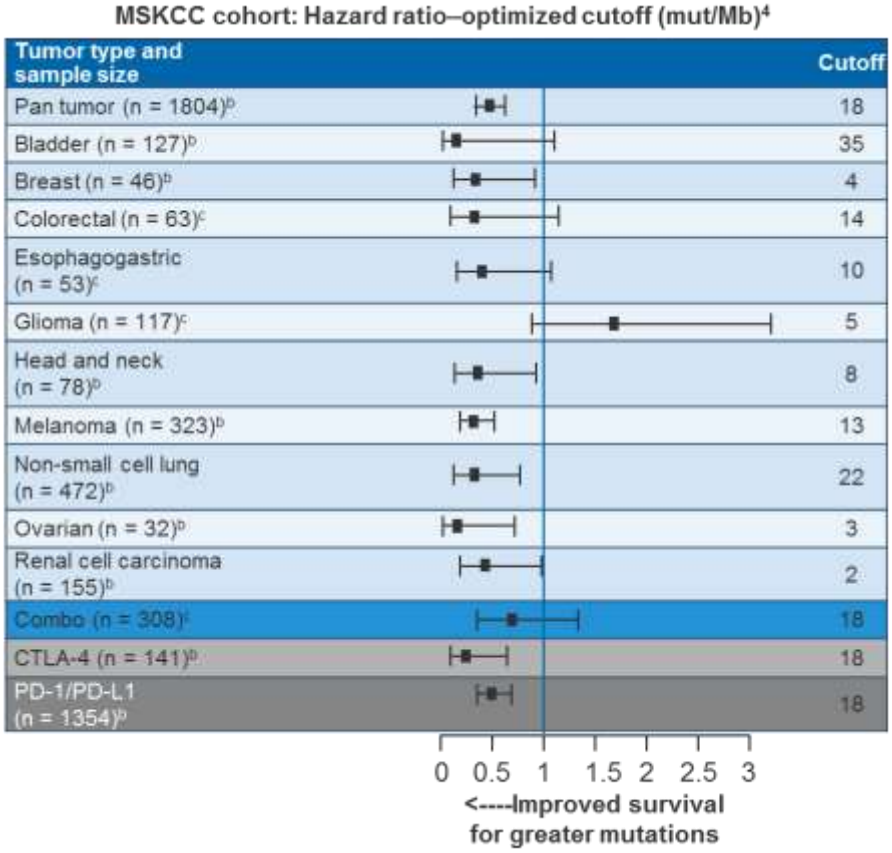




Rizvi et al. Nature, 2015

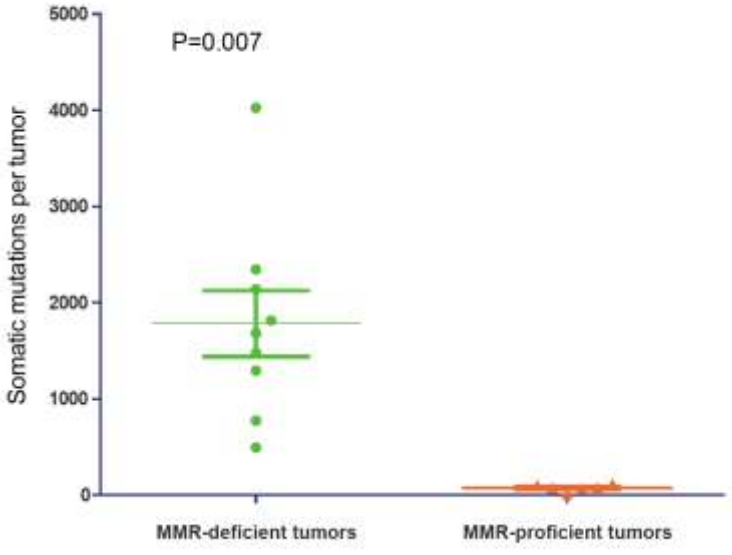
TMB: outros tumores

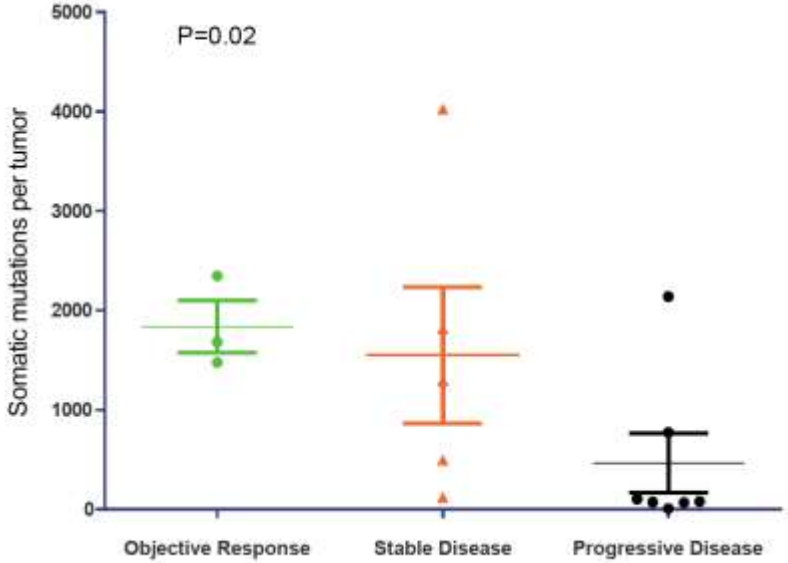
TMB por MSK-IMPACT (NGS) e sobrevida em diversos tumores recebendo imunoterapia



Chan T, et al. Oral presentation at ASCO-SITC; February 23–25, 2017; Orlando, FL.

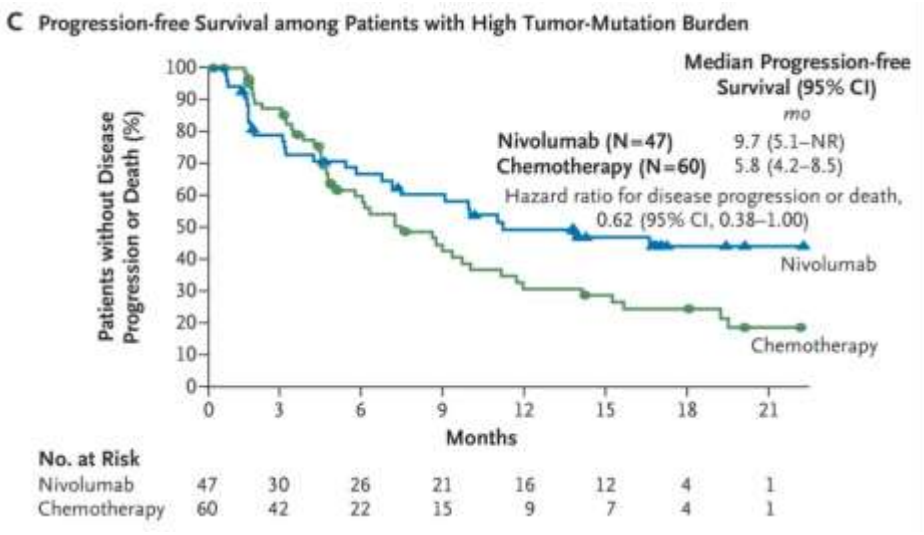
TMB e MMR: Correlação e resposta a Anti-PD1

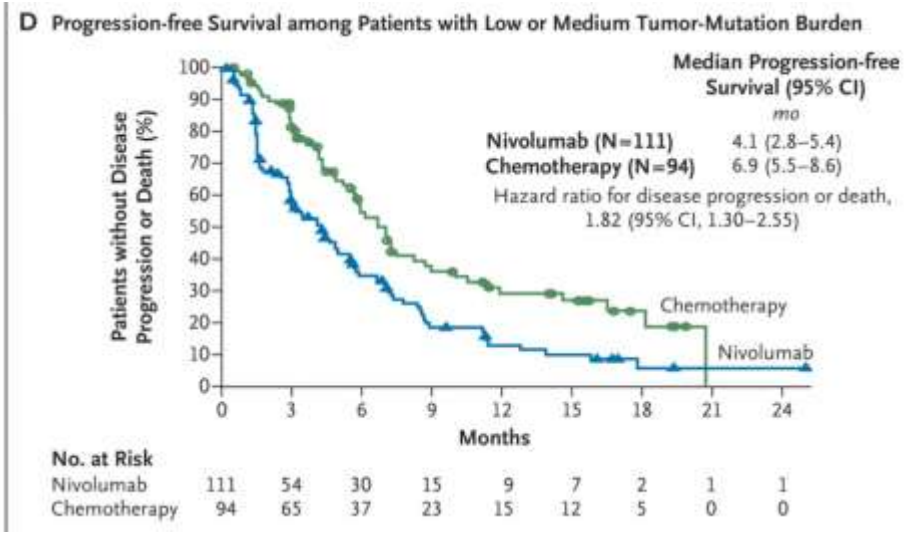




Le et al. NEJM, 2015

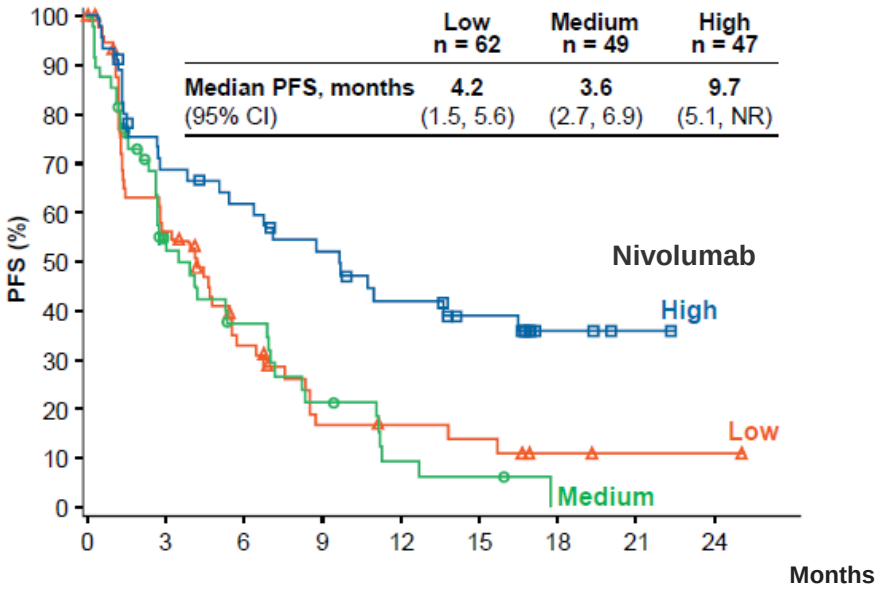
CheckMate-026: Nivolumab vs. QT em 1ª linha NSCLC com PD-L1 ≥ 1%

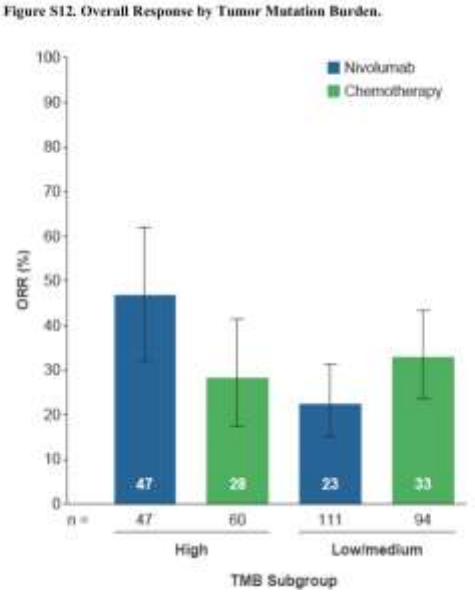




Carbone et al. NEJM, 2017

CheckMate-026: Nivolumab vs. QT em 1ª linha NSCLC com PD-L1 ≥ 1%





Carbone et al. NEJM, 2017

CheckMate 568 Study Design[a]

Key Eligibility Criteria
- Stage IV or recurrent stage IIIb NSCLC
- No prior systemic therapy
- No known sensitizing *EGFR/ALK* alterations
- ECOG PS 0–1
- PD-L1 all comers

→ **Nivolumab 3 mg/kg Q2W**
Ipilimumab 1 mg/kg Q6W
N = 288

→ **Until disease progression or unacceptable toxicity or maximum of 2 years**

Primary endpoints[b]:
- ORR[b] in PD-L1 ≥1% and <1% populations[c]

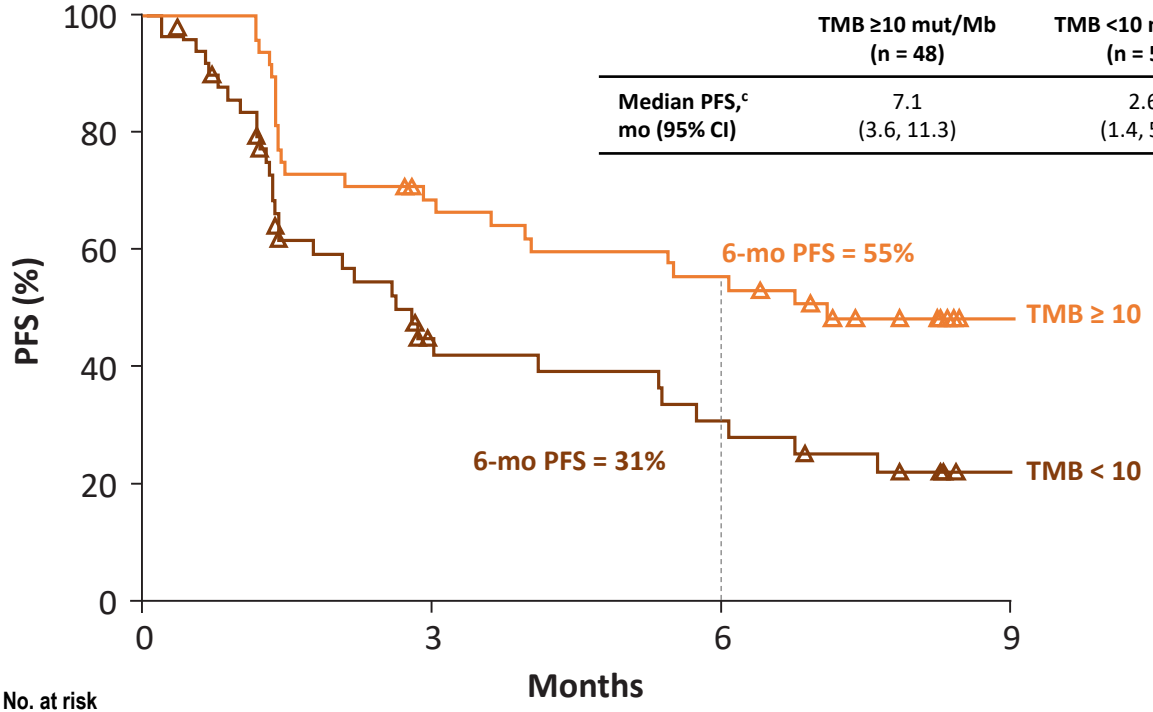
Select secondary endpoints[b]:
- PFS and OS
- ORR, PFS, and OS by TMB

Database lock: August 24, 2017; minimum follow-up: 6 months; median follow-up: 8.8 months

[a]NCT02659059; [b]Efficacy analyses by blinded independent central review (BICR); [c]PD-L1 status determined by Dako PD-L1 IHC 28-8 pharmDx immunohistochemical test

Ramalingam S et al. AACR Annual Meeting 2018.

PFS by TMB[a]: 6-Month Minimum Follow-up[b]

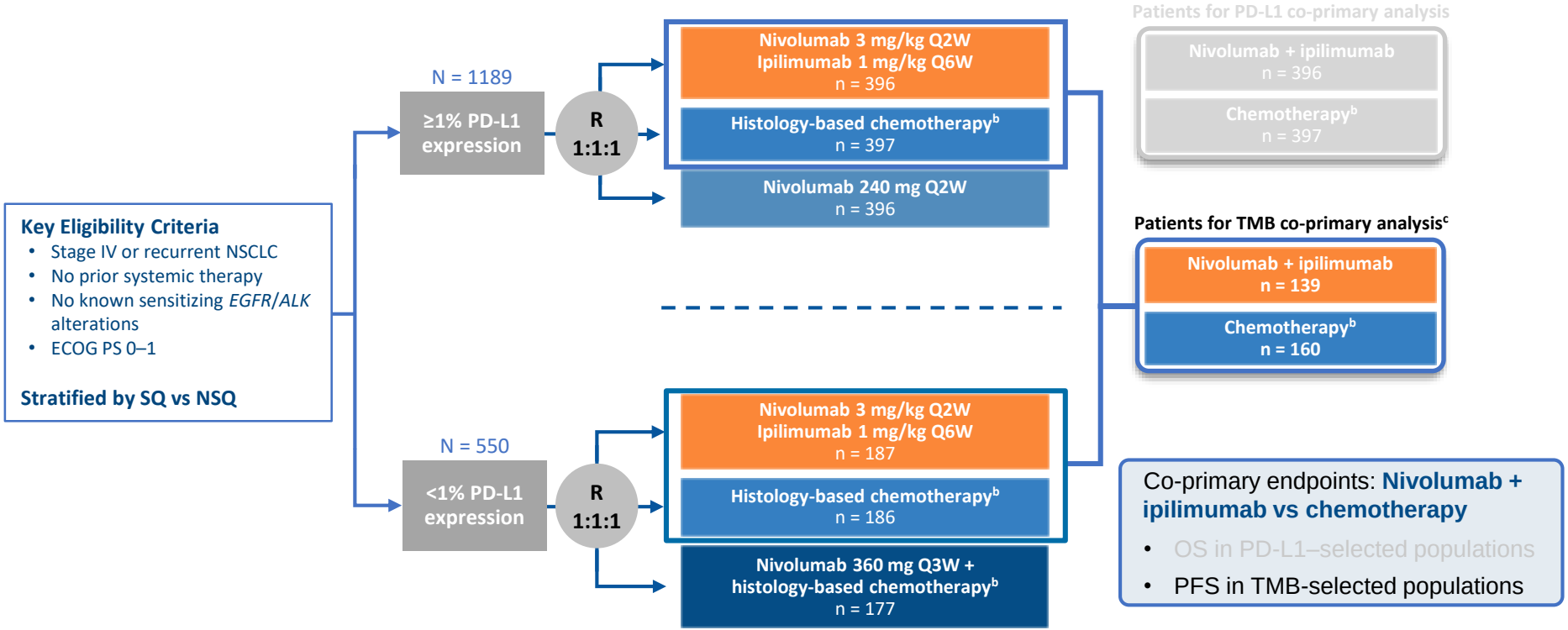


	TMB ≥10 mut/Mb (n = 48)	TMB <10 mut/Mb (n = 50)
Median PFS,[c] mo (95% CI)	7.1 (3.6, 11.3)	2.6 (1.4, 5.4)

[a]Irrespective of PD-L1 expression; [b]Median follow-up, 8.8 months; [c]In all treated patients (N = 288), median PFS (95% CI) was 4.2 (3.0, 5.7) months and the 6-month PFS rate was 43%

Ramalingam S et al. AACR Annual Meeting 2018.

CheckMate 227 Part 1 Study Design[a]

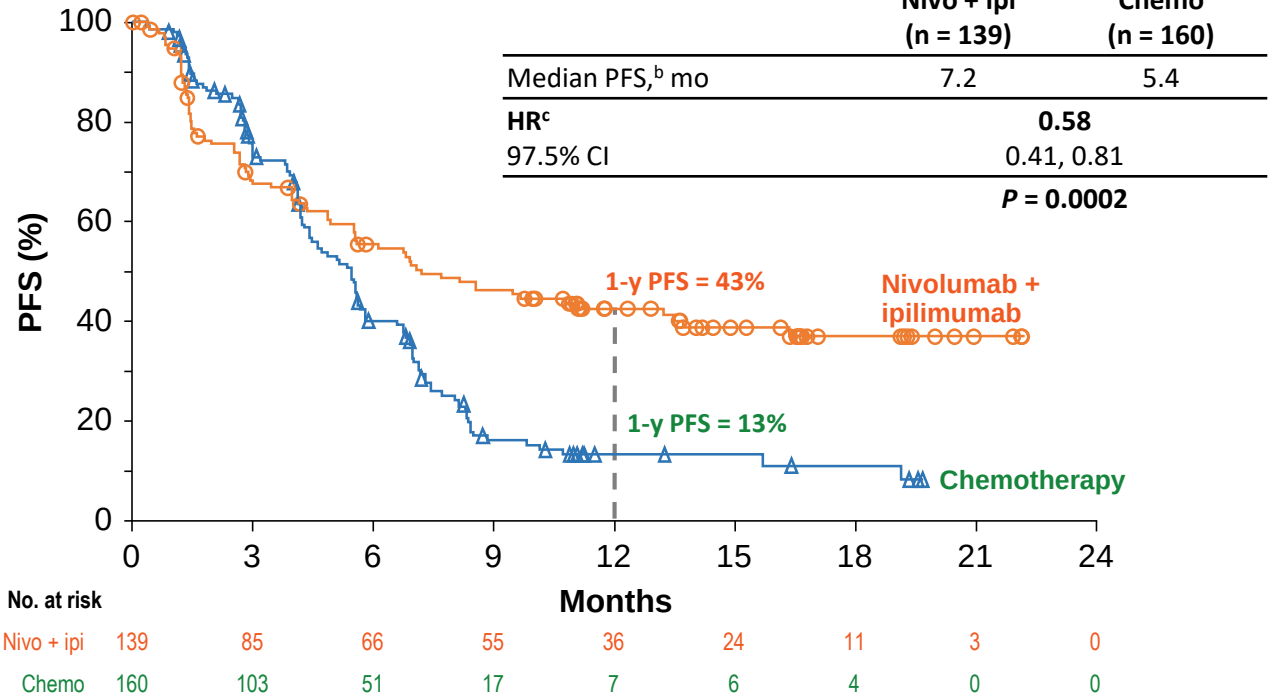


Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]NCT02477826 [b]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [c]The TMB co-primary analysis was conducted in the subset of patients randomized to nivolumab + ipilimumab or chemotherapy who had evaluable TMB ≥10 mut/Mb

Hellmann MD, et al. AACR Annual Meeting 2018

Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)[a]



	Nivo + ipi (n = 139)	Chemo (n = 160)
Median PFS,[b] mo	7.2	5.4
HR[c]	**0.58**	
97.5% CI	0.41, 0.81	
	***P* = 0.0002**	

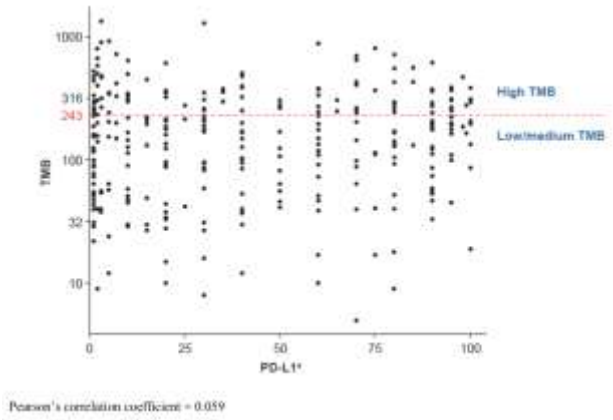
- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)[d]

[a]Per blinded independent central review (BICR); median (range) of follow-up in the co-primary analysis population was 13.6 mo (0.4, 25.1) for nivo + ipi and 13.2 mo (0.2, 26.0) for chemo; [b]95% CI: nivo + ipi (5.5, 13.2 mo), chemo (4.4, 5.8 mo); [c]95% CI: 0.43, 0.77 mo; [d]The *P*-value for the treatment interaction was 0.0018

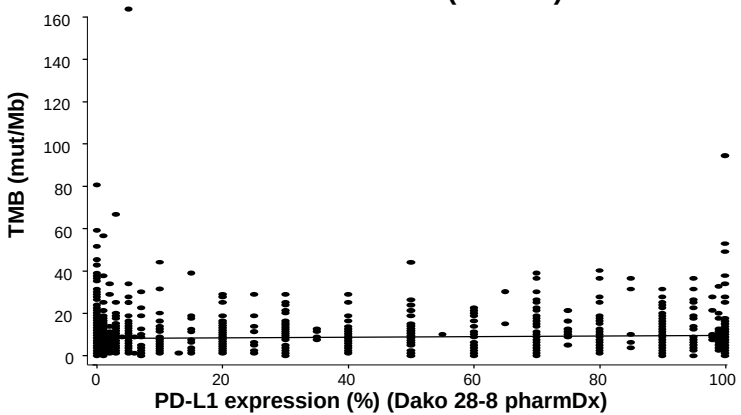
Hellmann MD, et al. AACR Annual Meeting 2018

- # Qual a frequência de TMB-high?
  - 30-50% dos casos
  - Correlacionado com tabagismo
  - Correlacionado com MMR deficiency
- # Sem correlação entre TMB e PD-L1

CheckMate 026 (NSCLC)



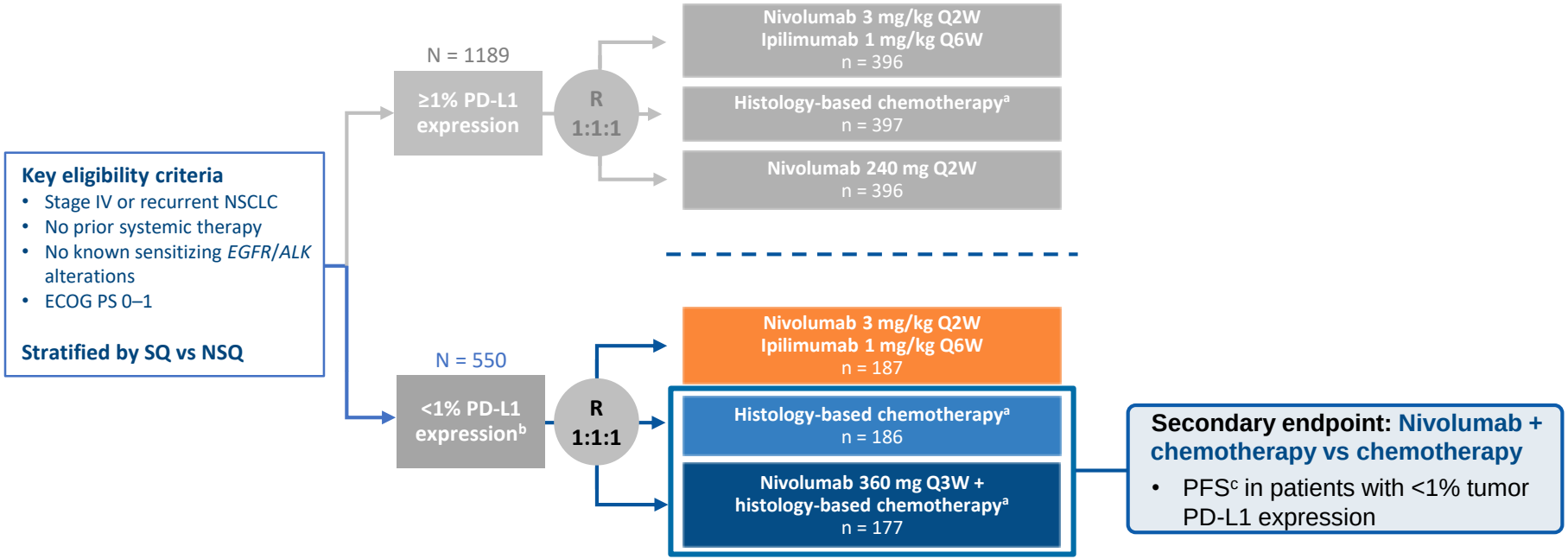
CheckMate 227 (NSCLC)



Dados de atezolizumab (NSCLC e UC) ausência de/fraca correlação entre TMB e PD-L1

Carbone D, et al. N Engl J Med, 2017; Hellmann M, et al. Cancer Cell 2018; Kowanetz M, et al. Oral presentation at WCLC; 2016; Rosenberg J, et al. Lancet 2016; Rizvi et al. Nature, 2015

CheckMate 227 Part 1 Study Design



- Co-primary endpoints: OS in PD-L1–selected populations and PFS[c] in TMB-selected populations treated with nivolumab + ipilimumab vs chemotherapy

Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [b]One patient was randomized with <1% tumor PD-L1 expression in IVRS, but was subsequently found to have ≥1% tumor PD-L1 expression; [c]Per BICR

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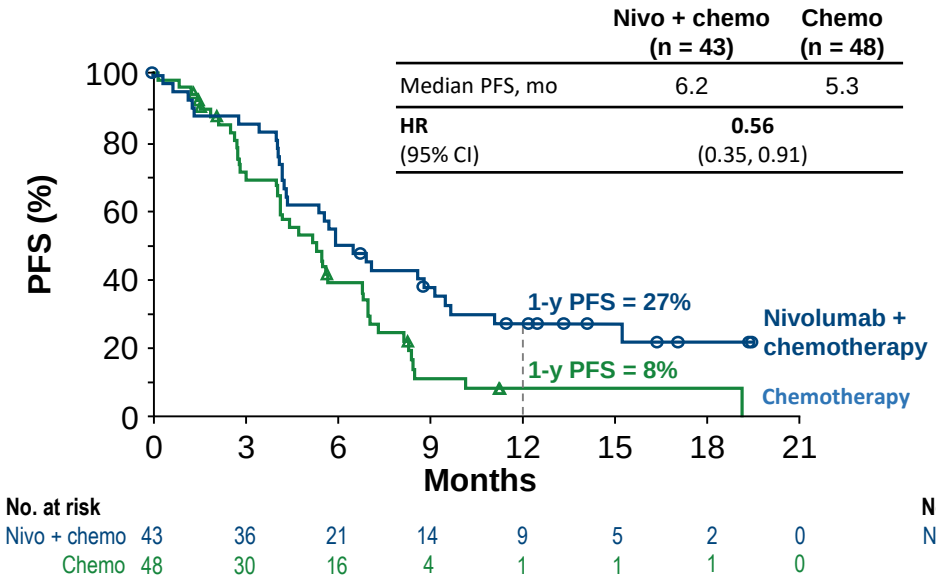
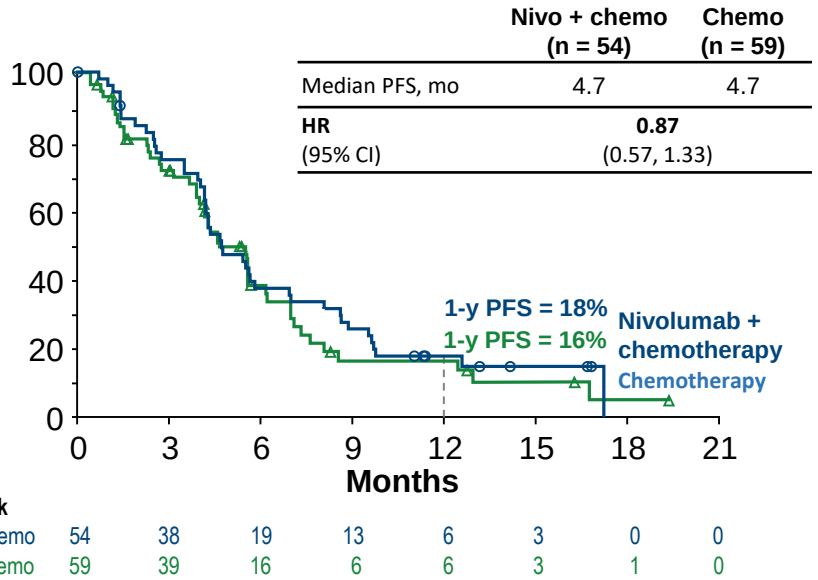
PFS: Nivolumab + Chemotherapy vs Chemotherapy By TMB

TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression



TMB <10 mut/Mb and <1% Tumor PD-L1 Expression



- TMB ≥10 mut/Mb: ORR was 60.5% with nivo + chemo and 20.8% with chemo
- TMB <10 mut/Mb: ORR was 27.8% with nivo + chemo and 22.0% with chemo

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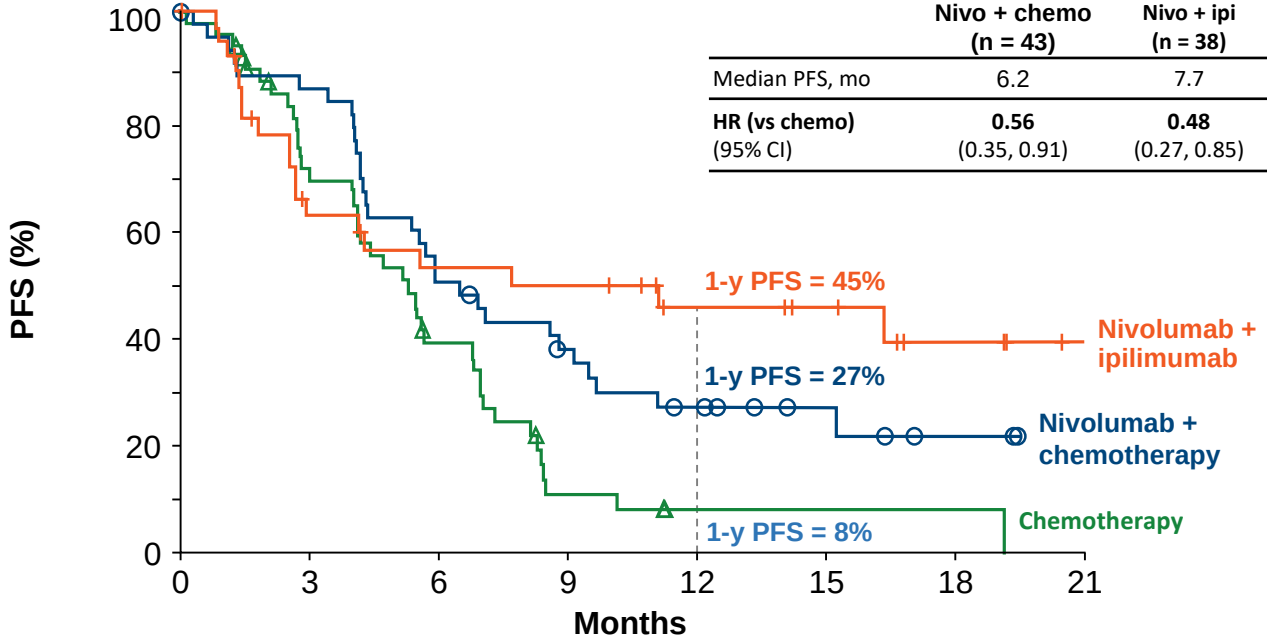
PFS: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab in Patients With TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 43)	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS, mo	6.2	7.7	5.3
HR (vs chemo) (95% CI)	**0.56** (0.35, 0.91)	**0.48** (0.27, 0.85)	



Borghaei et al. ASCO Annual Meeting 2018

Qual o melhor método?

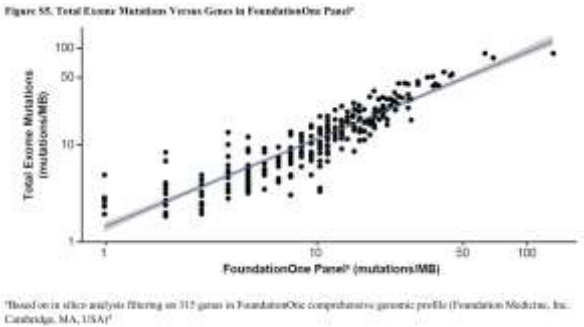
Whole-Exome Sequencing

- Todas as regiões codificantes (180.000 exons) > ~1% do genoma
- 85% das mutações que contribuem para doença

Targeted Gene Panel

- Painel de genes pré-estabelecido
- Testes comercialmente viáveis e validados disponíveis

Paineis utilizando NGS podem ser uma alternativa validada à WES, **inclusive para TMB**

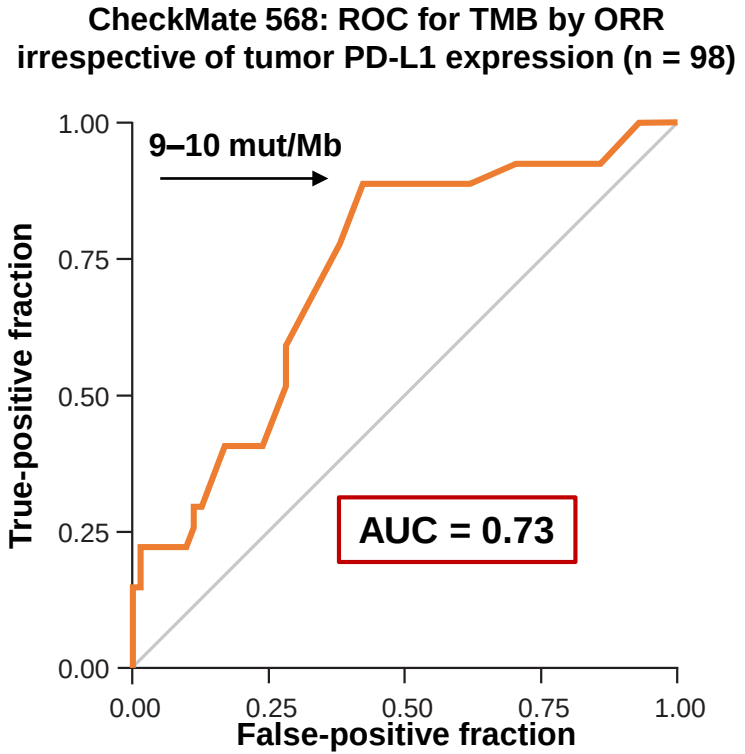


Ng SB et al. *Nature;* Choi M et al. *Proc Natl Acad Sci U.S.A.* 2009; Roszik J et al. *BMC Med.* 2016; Warner JL et al. *Genome Med.* 2016; Frampton GM et al. *Nat Biotechnol.* 2013; Veloso ZA et al. Presentation at AACR 2016. Kowanetz M et al. Oral Presentation at WCLC 2016. Choudary A et al. *BMC Med Genomics*. 2014. Carbone et al. NEJM, 2017

Qual o cutoff ideal?

FoundationOne

- NSCLC: 10 mut/mb (CheckMate 568)



Qual o cutoff ideal?

Assay	Tumor type	Cutoff	Study/trial
MSK-IMPACT™	Multiple solid tumors	High: median TMB + 2*IQR TMB	Zehir, et al.
	NSCLC	High: above vs below the 50th percentile of TMB	Rizvi, et al.
WES	1L NSCLC	Total missense mutations: low 0 to <100; medium 100 to 242; high ≥243	CheckMate 026
	1L NSCLC	Above and below median (158 mut) and quartiles	CheckMate 012
	2L+ SCLC	Total missense mutations: low 0 to <143; medium 143 to 247; high ≥248	CheckMate 032
	2L+ bladder	Total missense mutations: low 0 to <85; medium 85 to 166; high ≥167	CheckMate 275
	Melanoma	100 mut/tumor	Snyder, et al.
	1L or 2L+ melanoma	100 mut/tumor	CheckMate 038
	1L+ NSCLC	200 ns mut/tumor	KEYNOTE-001
	Advanced solid tumors	102 ns mut/tumor	KEYNOTE-012
FoundationOne®	1L or 2L+ NSCLC	9.9 mut/Mb (median) or 16.2 mut/Mb (75% quartile)	FIR/BIRCH/POPLAR
	1L bladder	0.9 to 62.2 mut/Mb (quartiles)	IMvigor 210
FoundationOne CDx™	1L NSCLC	≥10 mut/Mb	CheckMate 227 CheckMate 568
bTMB assays	1L NSCLC	9 and 14 mut/Mb	Fabrizio, et al.
	2L+ NSCLC	≥10 mut/Mb or ≥16 mut/Mb or ≥20 mut/Mb; ≥14 mut/Mb	POPLAR/OAK

Conclusões/Perspectivas para o Futuro

- TMB é um biomarcador independente de desfechos com imunoterapia
- Pode estar elevado mesmo em tumores PD-L1 negativo
- Necessita de dados de sobrevida global
- Necessita de validação e harmonização por diferentes plataformas e reduzir custos

Obrigado!

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