IV Simpósio Internacional de
IMUNO-ONCOLOGIA
O FUTURO DA ONCOLOGIA
27 E 28 DE JULHO – HOTEL PULLMAN VILA OLÍMPIA

Estratégias de Seleção - MSI

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FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release May 23, 2017

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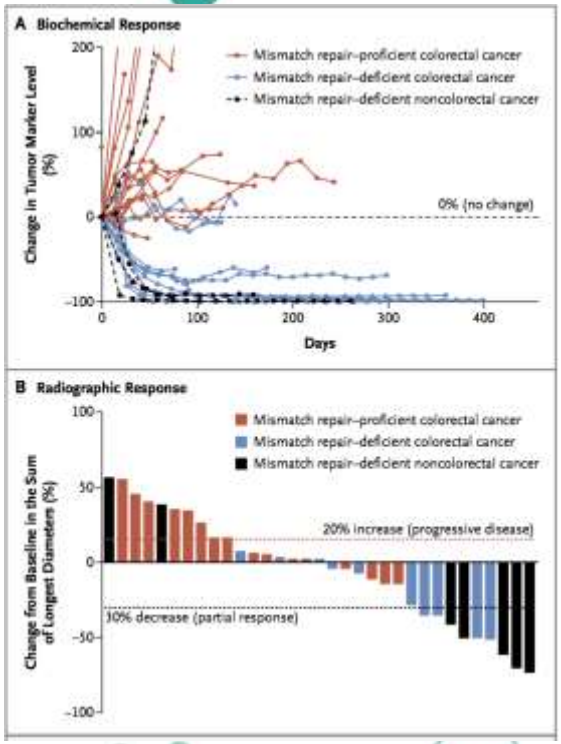
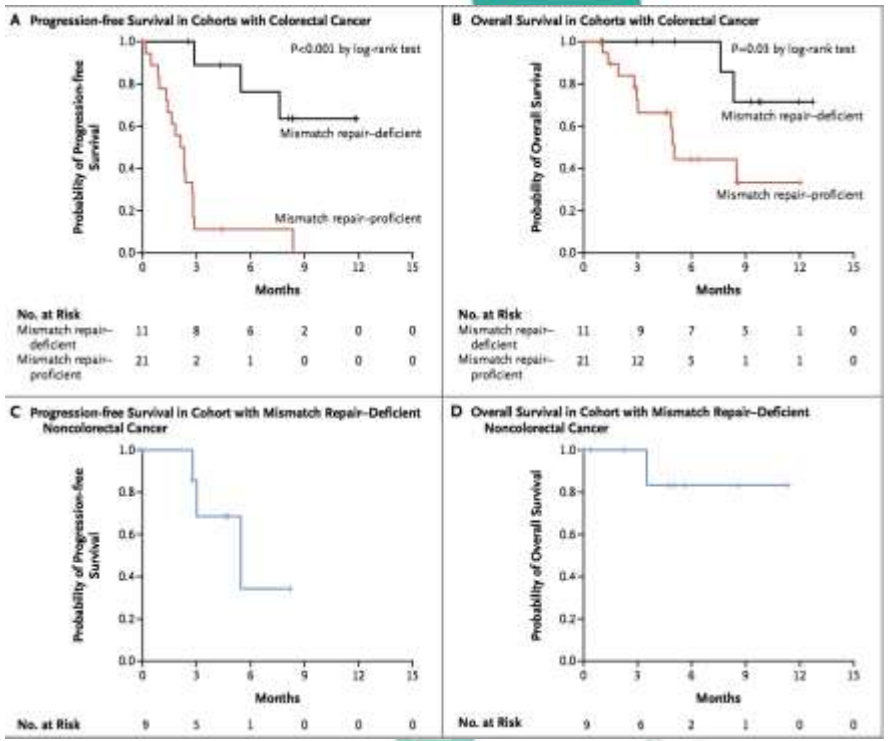
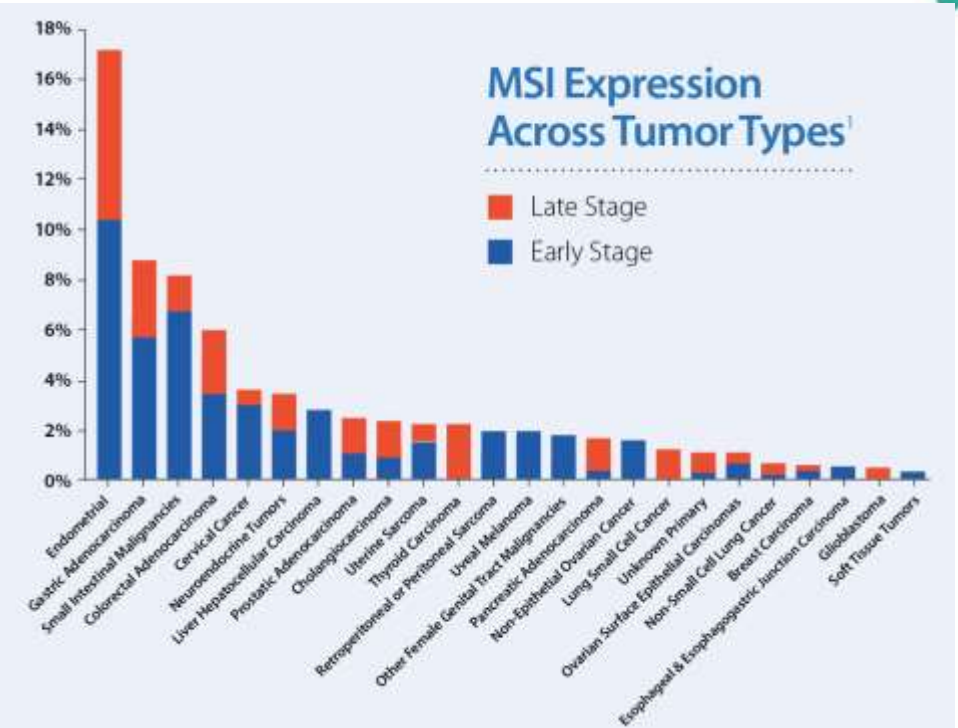
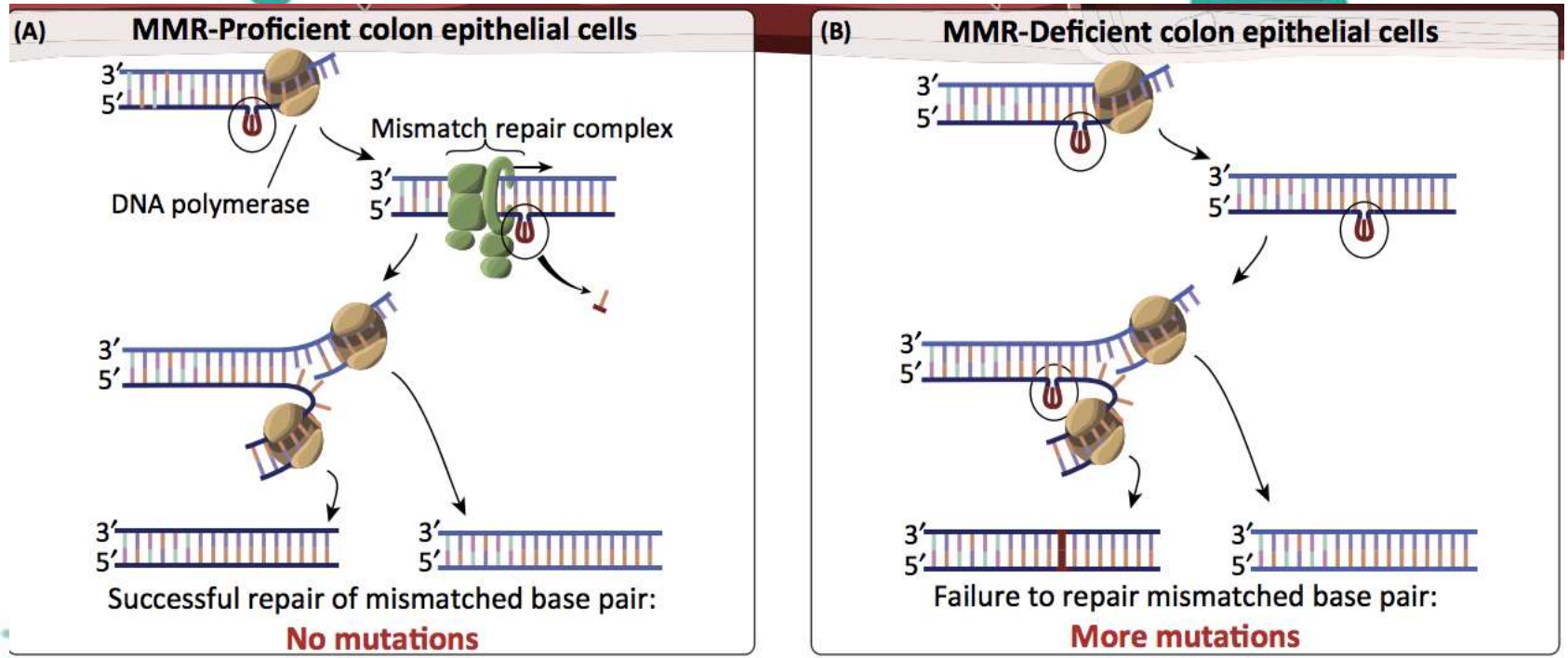




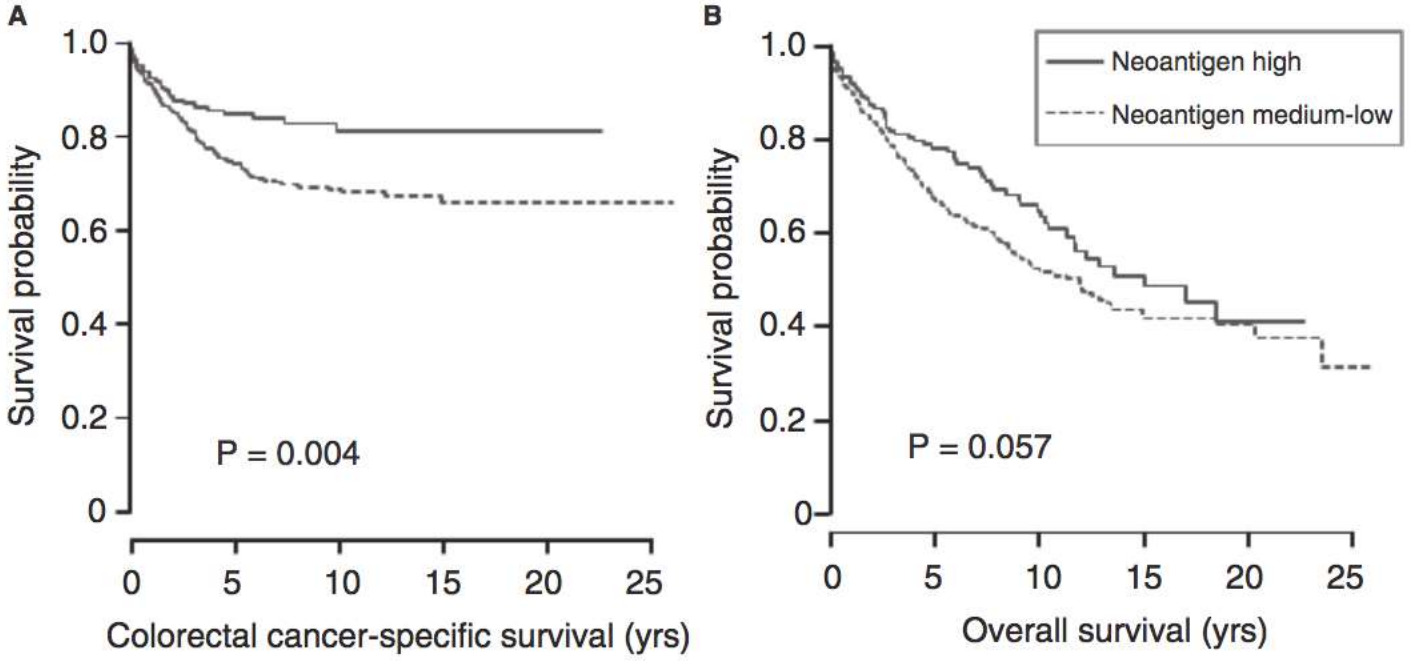
N Engl J Med 2015; 372:2509-2520



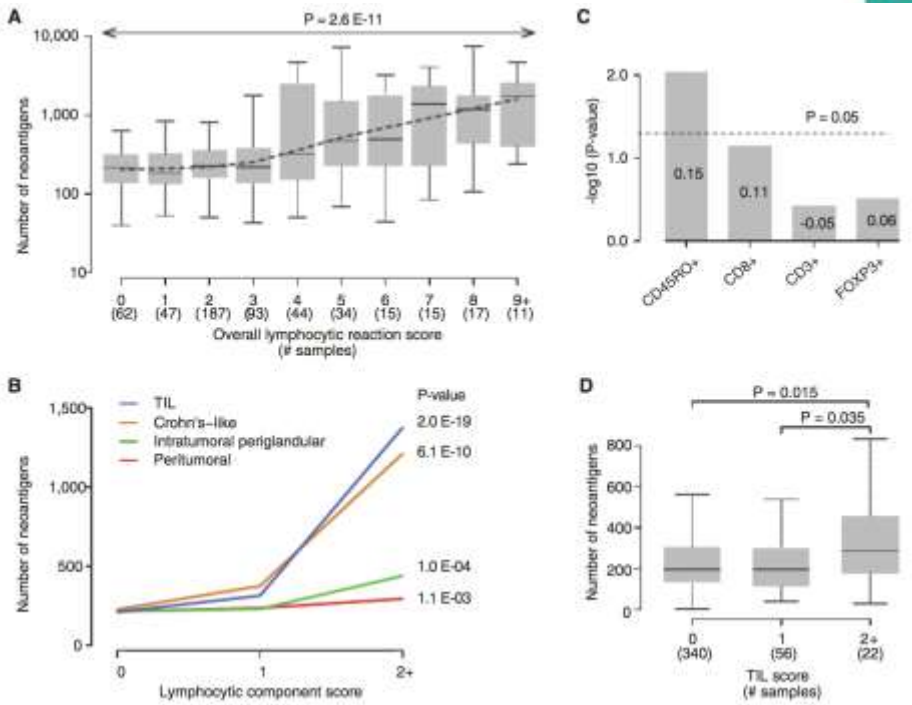
Science. 2017 Jul 28;357(6349):409-413



Trends Mol Med. 2016 Apr;22(4):274-289



Giannakis et al., 2016, Cell Reports 15, 857–865



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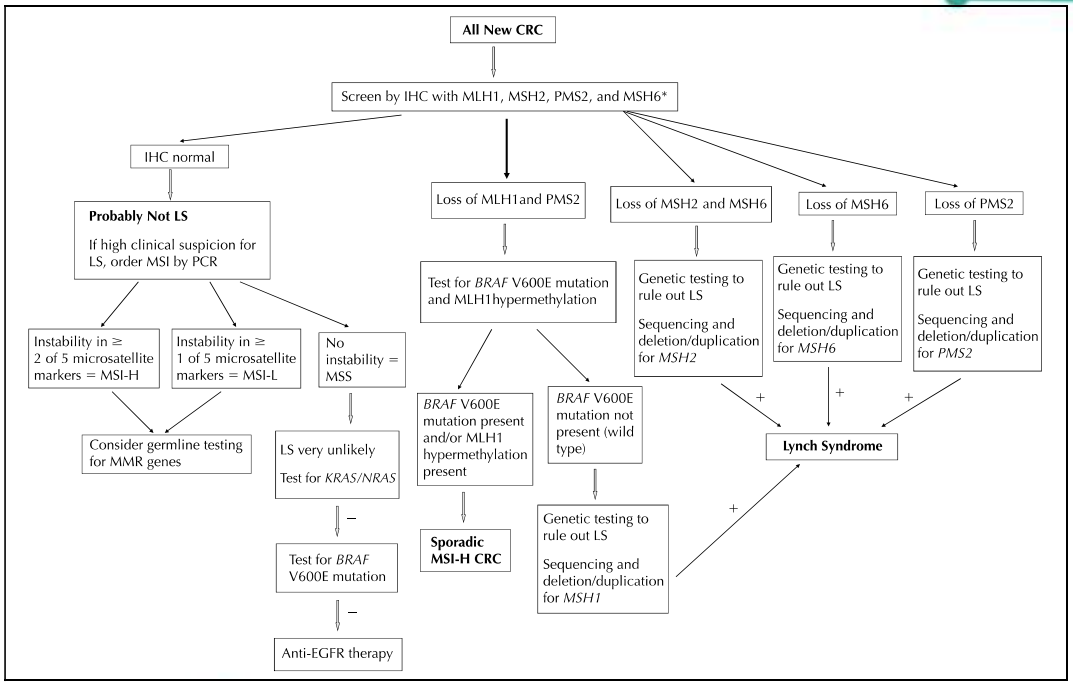
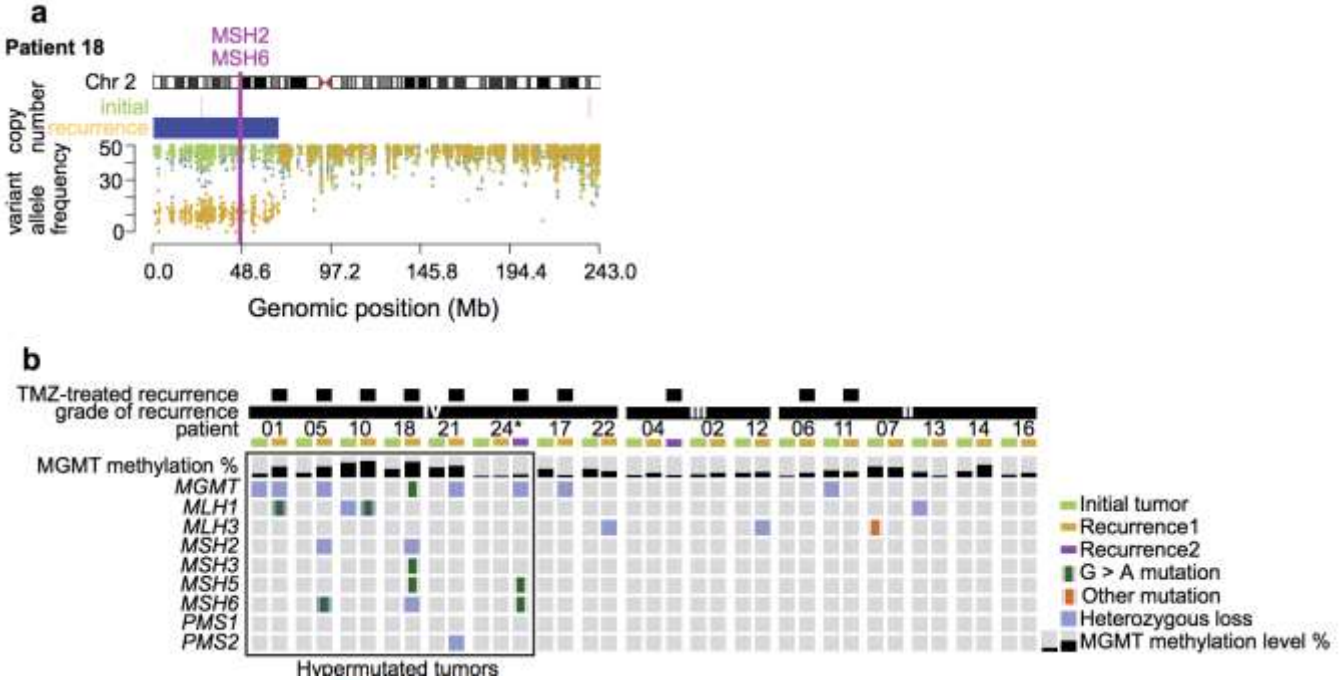


Figure 3. *Proposed testing algorithm for microsatellite instability testing. Abbreviations: CRC, colorectal cancer; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; LS, Lynch syndrome; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability–high; MSI-L, microsatellite instability–low; MSS, microsatellite stable; PCR, polymerase chain reaction. *Screening with IHC can be done at the same time as* MLH1 *methylation testing and* BRAF *testing, according to institution preferences and resources.*

Table 1
Molecular distinction between sporadic and Lynch-like tumours.

	Overall population	Sporadic group	Lynch-like group
	N (%)	*N*	*N*
Number of patients	129 (100)	48	81
MLH1/PMS2 loss of expression	71 (55)	44	27
MLH1 constitutive mutation		–	12
$BRAF^{MT}$		27	–
$BRAF^{WT}$, hypermethylated		17	–
$BRAF^{WT}$ not hypermethylated		–	15
MSH2/MSH6 loss of expression	39 (30)	–	39
Loss of expression of MSH6 alone	9 (7)	–	9
Loss of expression of PMS2 alone	5 (4)	3[a]	2
pMMR MSI tumours	5 (4)	1[b]	4[c]

$BRAF^{MT}$: *BRAF*V600E mutated; $BRAF^{WT}$: *BRAF* wild-type.
[a] PMS2-negative $BRAF^{MT}$/hypermethylated tumours.
[b] 1 MMR-proficient MSI $BRAF^{MT}$ tumour.
[c] 2 MMR-proficient MSI tumours with known MMR gene constitutive mutation, 2 $BRAF^{WT}$ tumours without hypermethylation.



Acta Neuropathol. 2015 Apr;129(4):597-607

	Objective response	Disease control for ≥12 weeks
Tumour PD-L1 expression		
≥1% (n=21)	6 (29%)	11 (52%)
<1% (n=47)	13 (28%)	35 (75%)
Immune cell PD-L1 expression		
Rare (n=24)	5 (21%)	14 (58%)
Intermediate (n=21)	5 (24%)	17 (81%)
Numerous (n=23)	9 (39%)	15 (65%)
Mutation status		
BRAF mutant (n=12)	3 (25%)	9 (75%)
KRAS mutant (n=26)	7 (27%)	16 (62%)
Both *BRAF* and *KRAS* wild type (n=29)	12 (41%)	23 (79%)
Clinical history of Lynch syndrome*		
Yes (n=27)	9 (33%)	19 (70%)
No (n=28)	8 (29%)	21 (75%)

Data are n (%). dMMR/MSI-H=DNA mismatch repair deficient/microsatellite instability–high. *Lynch syndrome designation was based on the clinical records of the patients at sites in countries where this reporting was permitted (excluded Italy).

Table 3: **Investigator-assessed objective response and disease control in patients locally assessed as having dMMR/MSI-H (n=74)**

	dMMR/MSI-H per local assessment (n=74)		dMMR/MSI-H per central assessment (n=53)	
	Investigator	Blinded independent central review	Investigator	Blinded independent central review
Objective response	23 (31·1%, 20·8–42·9)	24 (32%, 22–44)	19 (36%, 23–50)	19 (36%, 23–50)
Best overall response				
Complete response	0	2 (3%)	0	1 (2%)
Partial response	23 (31%)	22 (30%)	19 (36%)	18 (34%)
Stable disease	28 (38%)	25 (34%)	20 (37%)	19 (36%)
Progressive disease	19 (26%)	21 (28%)	11 (21%)	12 (23%)
Not determined	4 (5%)	4 (5%)	3 (6%)	3 (6%)
Disease control for ≥12 weeks	51 (69%, 57–79)	47 (64%, 52–74)	39 (74%, 60–85)	37 (70%, 56–82)

Data are n (%, 95% CI) or n (%). dMMR/MSI-H=DNA mismatch repair deficient/microsatellite instability-high.

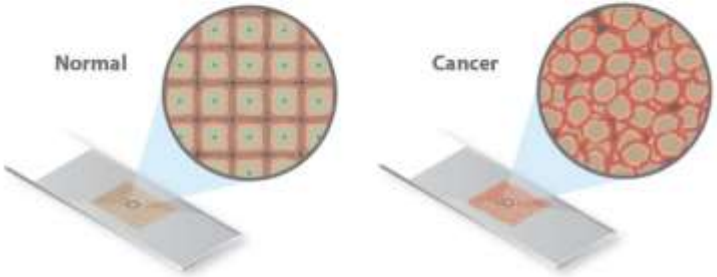
***Table 2*: Objective response, best overall response, and disease control per investigator and masked independent central review assessments**

21% respondeu ao tratamento

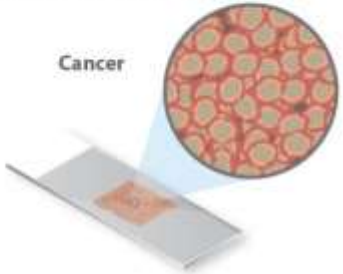
Concordance data: PCR vs NGS[2]

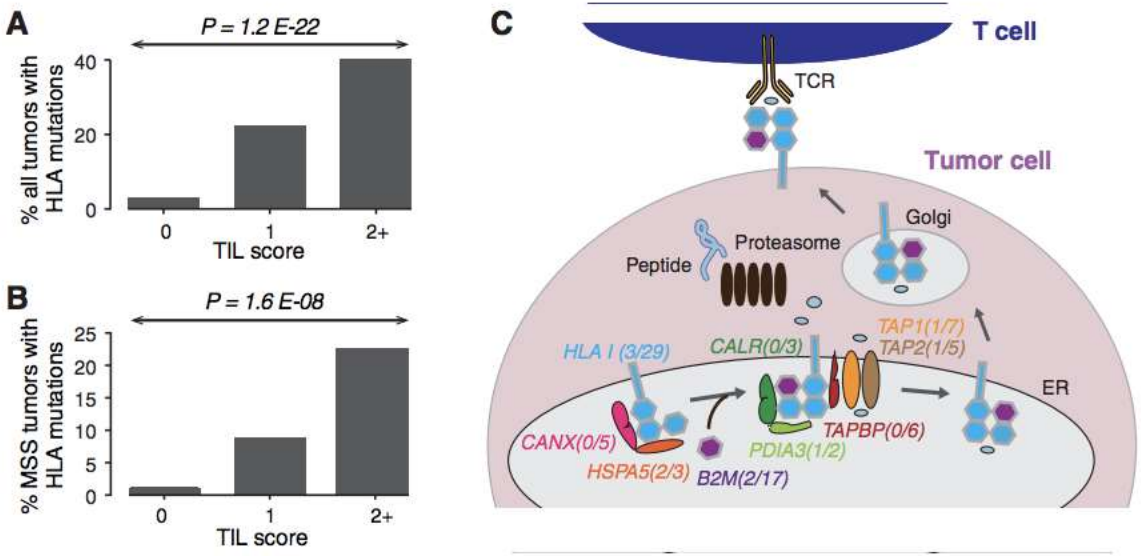
Lineage	Sensitivity	Specificity	PPV	NPV
All	95.8%	99.4%	94.5%	99.2%
CRC	100.0%	99.9%	98.7%	98.7%

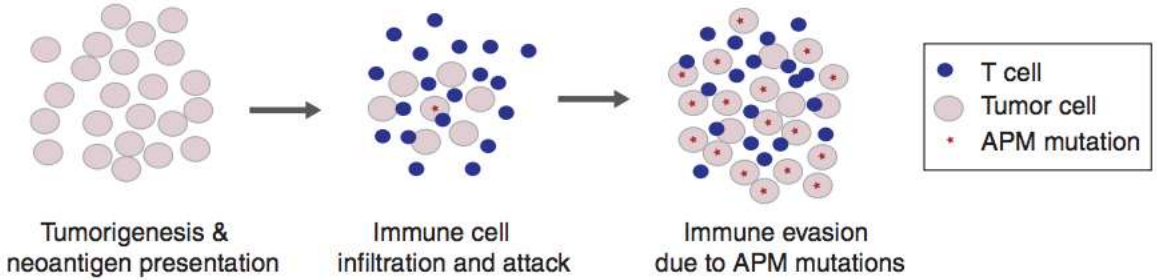
Traditional Approach: normal and cancer tissue required



Caris Approach: no normal tissue required; saving resources, costs and time




A
P = 1.2 E-22
% all tumors with HLA mutations
40
20
0
0
1
2+
TIL score
B
P = 1.6 E-08
% MSS tumors with HLA mutations
25
20
15
10
5
0
0
1
2+
TIL score
C
T cell
TCR
Tumor cell
Golgi
Proteasome
Peptide
TAP1(1/7)
TAP2(1/5)
HLA I (3/29)
CALR(0/3)
ER
CANX(0/5)
TAPBP(0/6)
PDIA3(1/2)
HSPA5(2/3)
B2M(2/17)


T cell
Tumor cell
APM mutation
Tumorigenesis &
neoantigen presentation
Immune cell
infiltration and attack
Immune evasion
due to APM mutations

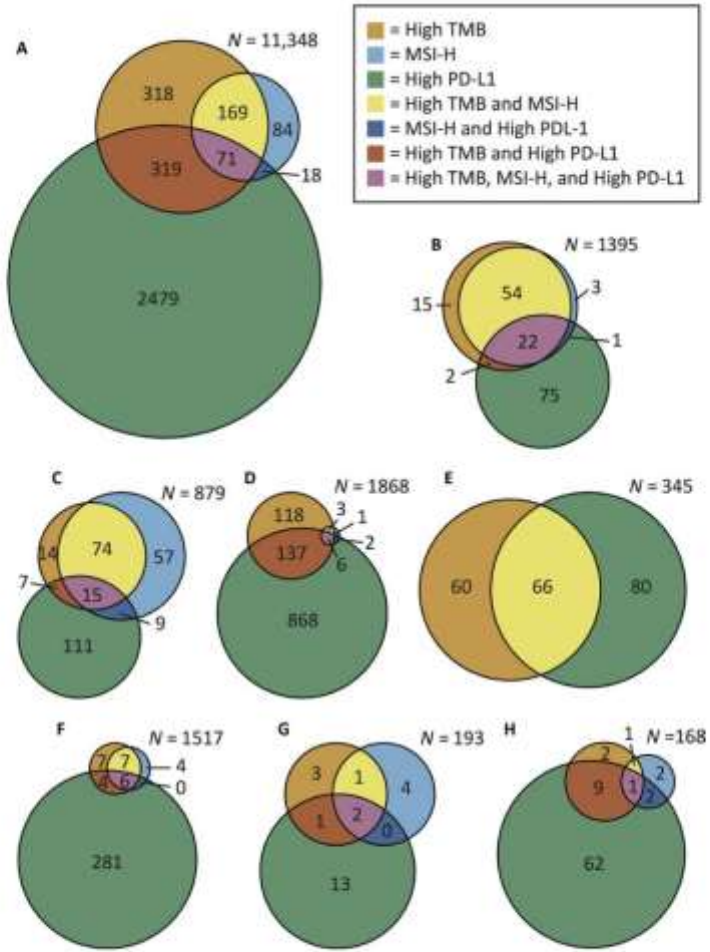


Figure 2. Venn diagrams of the relationships between high TMB, MSI-H, and high PD-L1 for (A) all cancer types, (B) CRC, (C) endometrial cancer, (D) NSCLC, (E) melanoma, (F) ovarian surface epithelial carcinomas, (G) neuroendocrine tumors, and (H) cervical cancer. Each *n* value indicates the total number of cases of that cancer type. Abbreviations: MSI-H, microsatellite high; TMB, tumor mutational burden; PD-L1, programmed death ligand 1.

- Conclusões
  - MSI marcador preditivo para imunoterapia
  - Hoje, não há como saber se mutações germinativas ou somáticas fazem diferença quanto a resposta/benefício
  - MSI, TMB e PD-L1 ainda todos importantes
  - Mutaçoes em HLA podem conferir resistência, mas específicas ou somadas