

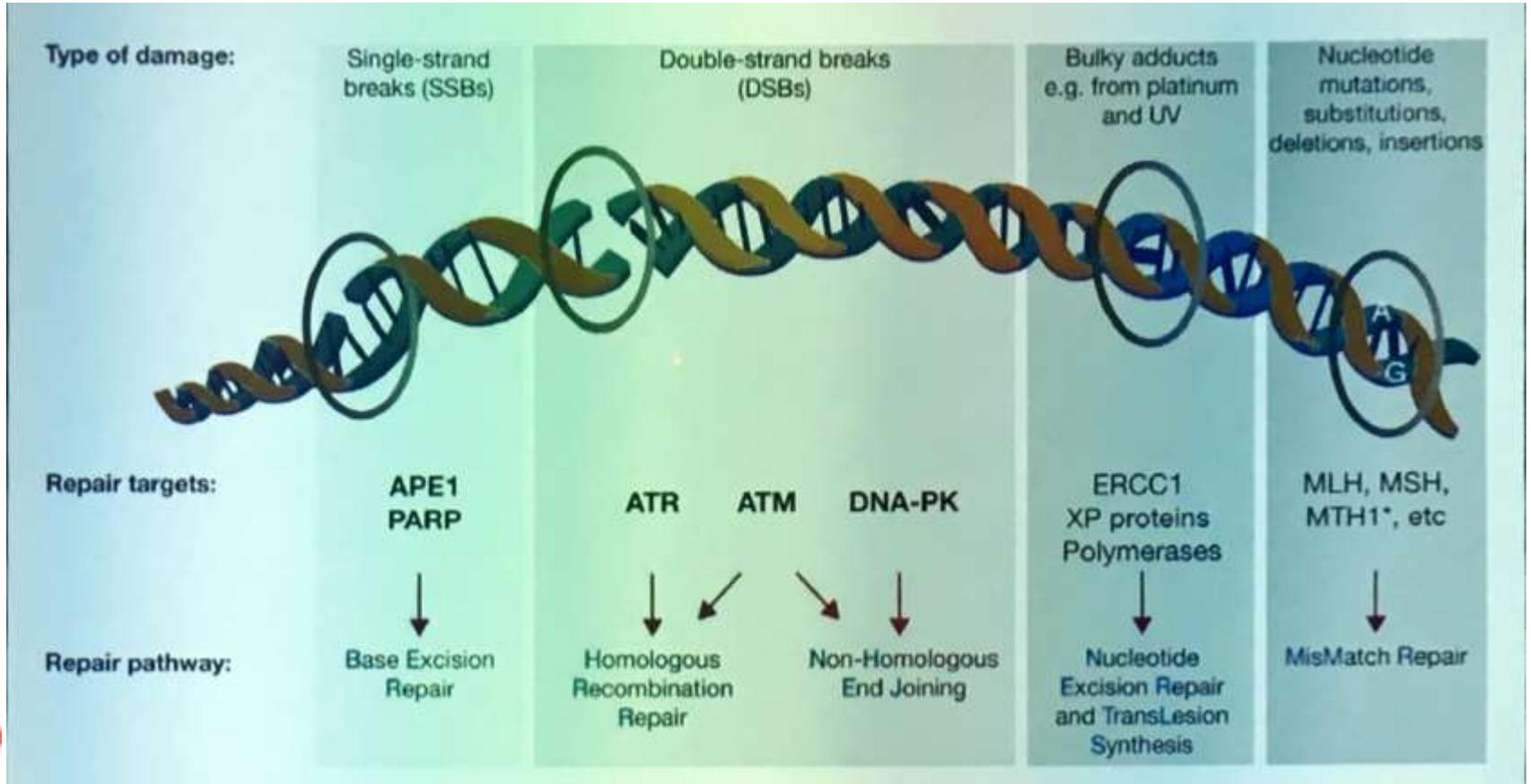


A Beneficência
Portuguesa
de São Paulo

Trato Gastrointestinal Baixo

Dr Fabio Kater

Mecanismos de lesão e reparo de DNA



Formação dos microssatélites

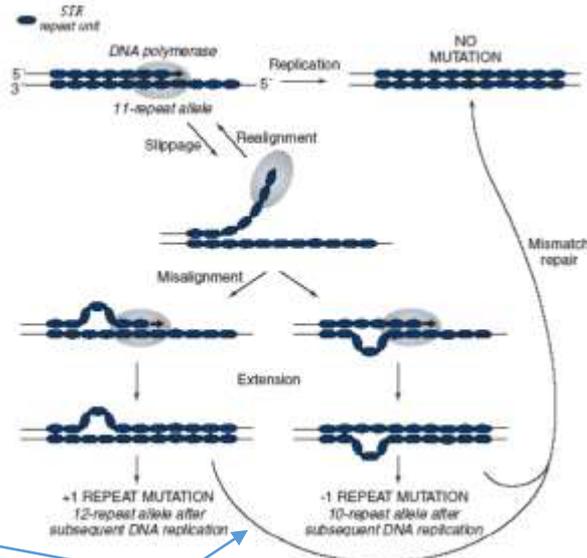
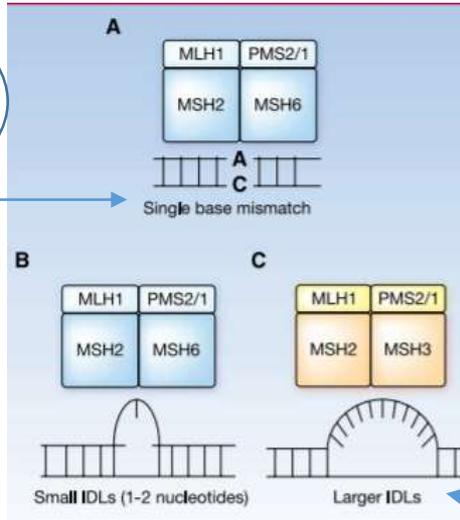
- Microssatélites são pequenas sequencias repetidas de pares de base encontradas ao longo do DNA – sequencias hipervariáveis
- Esses locais são mais susceptíveis a erros no processo de duplicação do DNA
- DNA polimerase – responsável pela replicação da dupla fita – pode deixar passar áreas de DNA errado
- Essas áreas são facilmente corrigidas pelas enzimas de reparo



Formação dos microssatélites

Durante a replicação do DNA pode acontecer erros de **base-base** ou **inserção / deleção** de alças de DNA

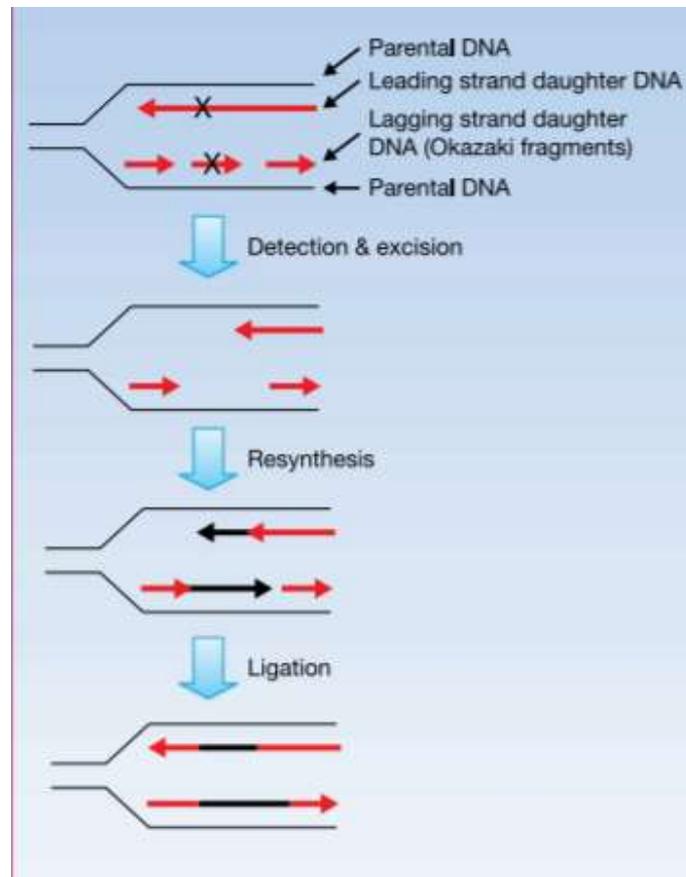
Defeito de 1 par de base



Inserção ou deleção de alças

Formação dos microssatélites

- Proteínas de reparo → Mecanismo molecular de reparo de erros gerados no momento da replicação de DNA
 - Reparo pós replicativo
- Falta dessas enzimas faz acumular esses erros - falhas das enzimas de reparo de DNA (Mismatch Repair Deficiency ou MMR)

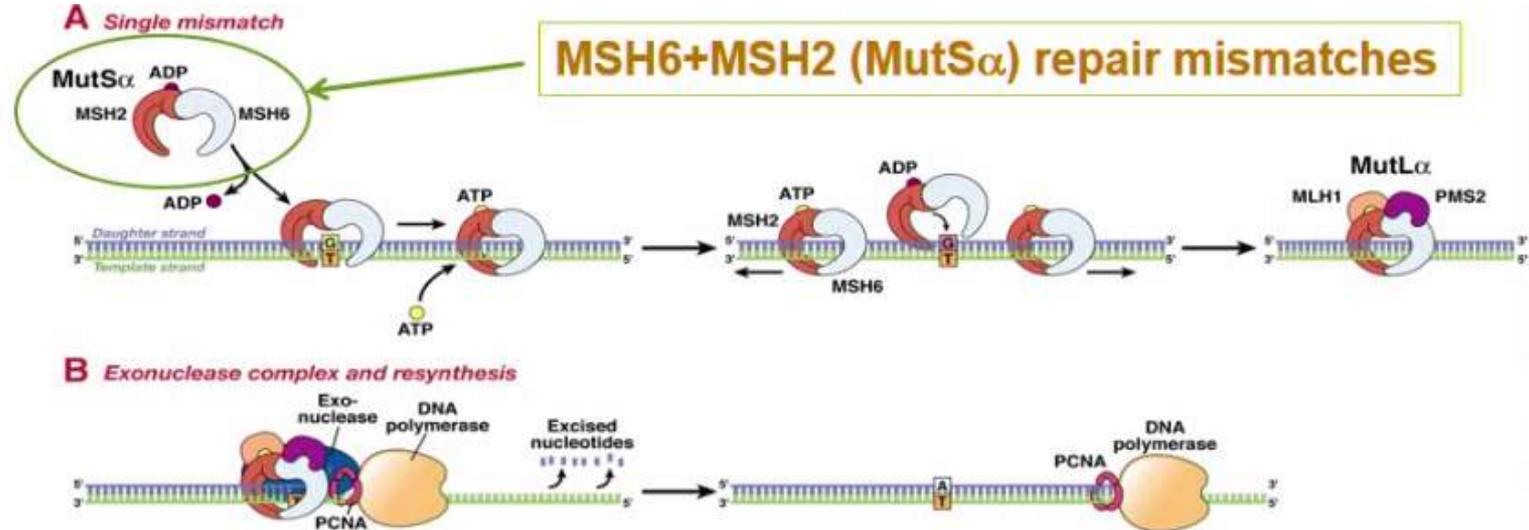


Martin, Clin Can Res 2010, 16 (21): 5107

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Enzimas de reparo



Alta taxa de instabilidade de microssatélite

MSI – high

- Tumores com defeito de reparo guardam centenas a milhares de mutações somáticas – nas regiões de acúmulo de sequências de DNA (microssatélites)
 - Acúmulo de mutação nessas regiões do genoma é chamado de instabilidade do microssatélite

Deficiência das enzimas de reparo

- Defeito nos genes que controlam o reparo, tais como
 - MLH1
 - MSH2
 - PMS2
 - MLH6

Perda do alelo promotor do gene – herdado : Síndrome de Lynch

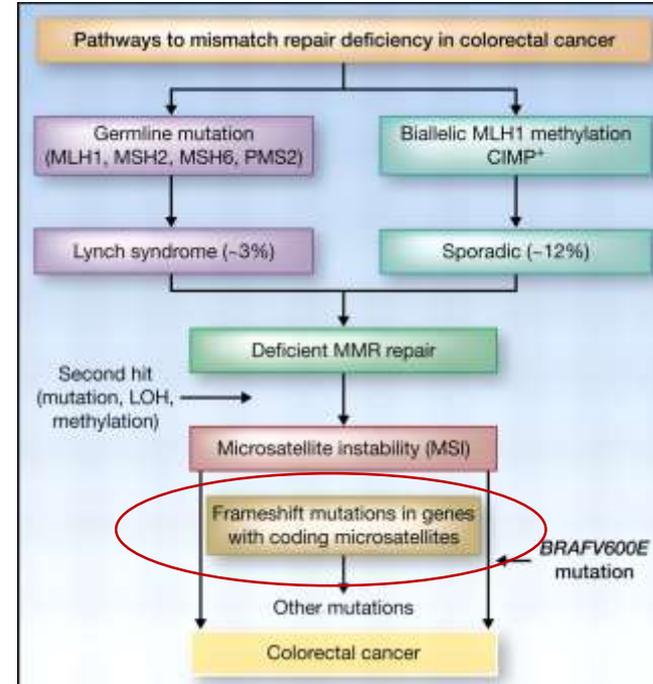
Metilação do promotor – adquirido : esporádico



Imunogenicidade da instabilidade

- Instabilidade determina células com mutações frameshift

→ não reconhecidas como self : **imunogênico**



Cenário

- Aproximadamente 15% dos tumores colorretais apresentam defeito no mecanismo de reparo de DNA
- Resultado das inativação dos genes das proteínas de reparo
 - MSH2 e MLH1 (genes maiores)
 - MSH6 e PMS2 (genes menores)
- A avaliação da presença da instabilidade do microssatélite
 - PCR para sequencias mutadas de microssatélite a partir de DNA extraído de tumor
 - Ou imuno-histoquímica detecta ausência da expressão das proteínas de reparo
- Teste da instabilidade é mais sensível que Imunohistoquímica (99% vs 90-95%)
 - Imunohistoquímica muito mais fácil de obter

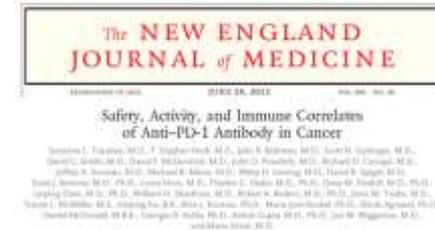


Câncer Colorretal

Estudo de fase Ib com nivolumabe incluindo 296 pts (19 com mCRC)

- Nenhum pt com mCRC respondeu

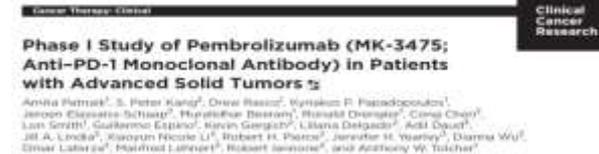
N Engl J Med 2012;366:2443–54



Estudo de fase I com pembrolizumabe em 32 pts (3 com mCRC)

- Nenhum pt com mCRC respondeu
- Todos com PD < 10 semanas

Clin Cancer Res 2015 Oct 1;21(19):4286-93



Estudo de fase I com 207 pts avaliando BMS-936559 (anti-PD-L1) em múltiplos tumores sólidos (18 pts com mCRC)

- Nenhum pt com mCRC respondeu

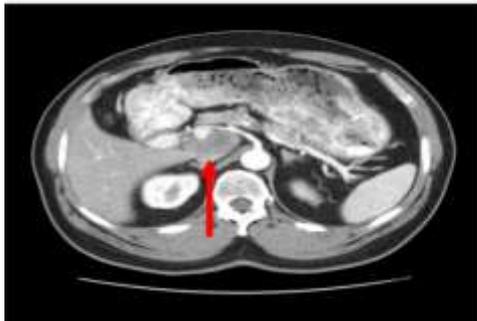
N Engl J Med 2012;366:2455–65



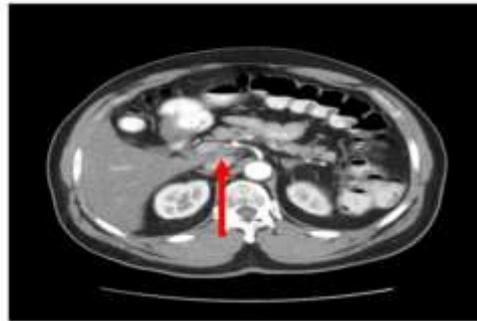
Câncer Colorretal

- Estudo de fase I com nivolumabe em 39 pts com múltiplos tumores sólidos refratários (14 pts com mCRC)
- Um paciente com mCRC e MSI recebeu 5 doses de nivolumabe (3 mg/kg)
- Obteve **RC duradoura** (4 anos depois)
- Inicialmente RP mas obteve RC em 7 meses

Pretreatment



Day 85



Antitumor Activity

One patient with CRC (3 mg/kg) achieved a CR, and two patients with RCC (10 mg/kg) and melanoma (10 mg/kg) experienced PRs to therapy. A 67-year-old male with CRC metastatic to intra-abdominal lymph nodes received five doses of MDX-1106 and experienced a CR persisting 21+ months. A 72-year-old male with multiorgan meta-

Câncer Colorretal

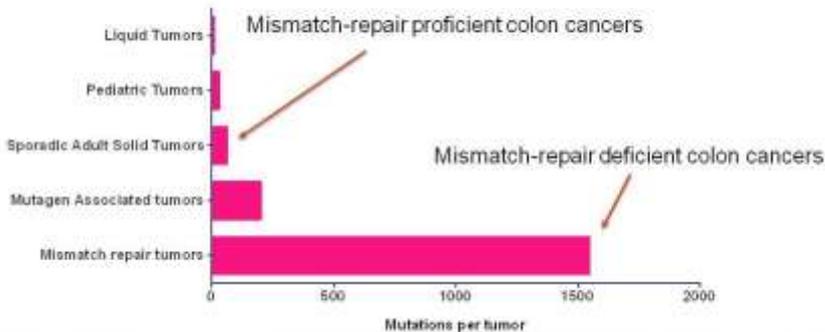
THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

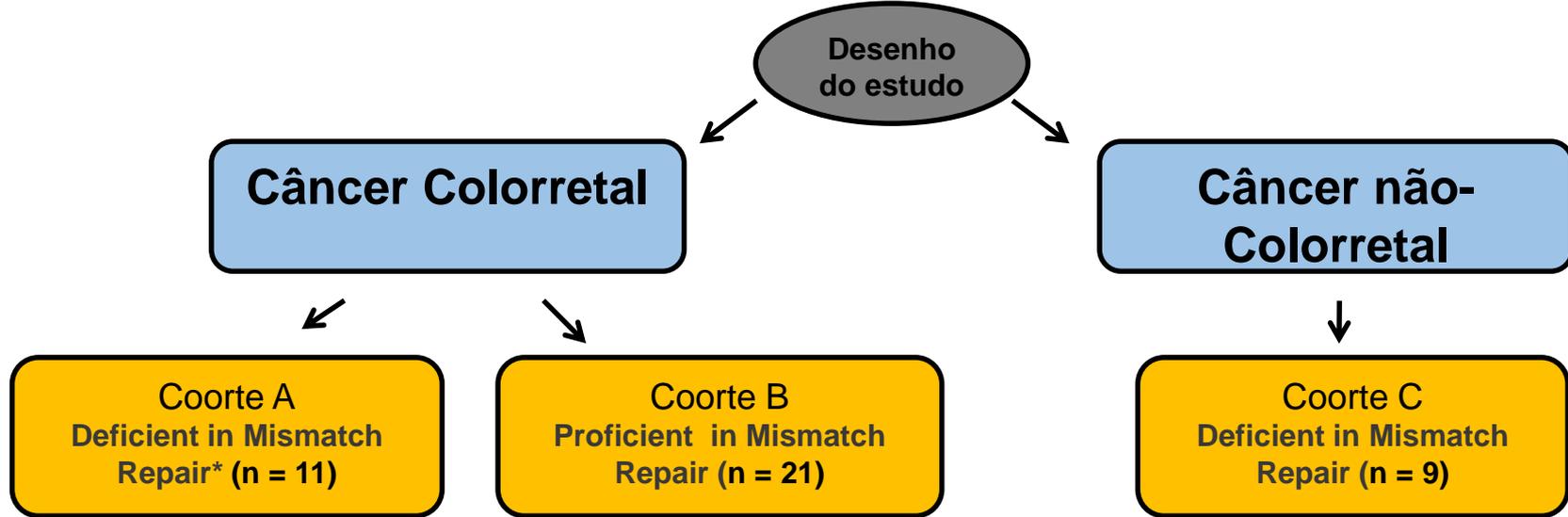
D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donohower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhajee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

Mutations per tumor



- Mutações somáticas levam à proteínas mutantes que são reconhecidas como antígenos imunogênicos “não-próprios”
- Tumores com deficiência MMR tem 10 – 100 mais mutações somáticas que os proficientes
- Infiltração linfocitária proeminente
- Postulou-se que tumores deficientes em MMR teriam maior suscetibilidade à bloqueio imunológico de checkpoint

Câncer Colorretal



- Anti-PD1 (Pembrolizumabe) 10 mg/kg a cada 2 semanas
- *Endpoint* primário: SLP imune e taxa de resposta

*avaliação por PCR

Câncer Colorretal – Características da população

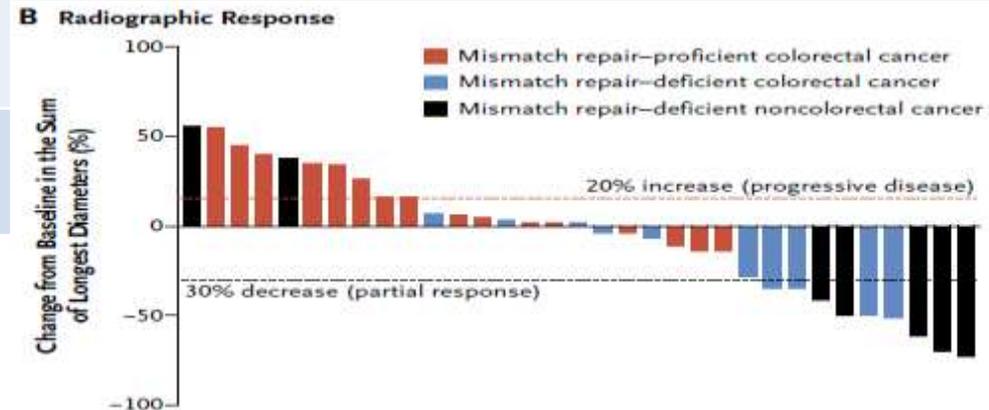
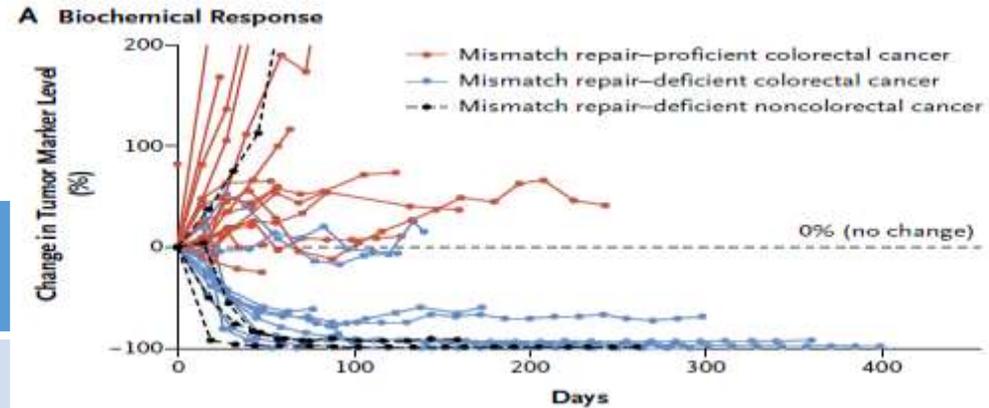
Tipo de câncer (%)	CCR dMMR (N = 11)	CCR pMMR (N = 21)	Não-CCR dMMR (N = 9)	Valor de P > 0,99
Cólon	9 (82%)	18 (86%)	0	
Reto	2 (18%)	3 (14%)	0	
Colangiocarcinoma ou ampular	0	NA	4 (44%)	
Endometrial	0	NA	2 (22%)	
Intestino delgado	0	NA	2 (22%)	
Gástrico	0	NA	1 (11%)	

Nº de terapias prévias	CCR dMMR (N = 11)	CCR pMMR (N = 21)	Não CCR dMMR (N = 9)	Valor de P 0,89
1	0	0	1 (11%)	
2	3 (27%)	4 (19%)	5 (56%)	
3	3 (27%)	5 (24%)	1 (11%)	
> 4	5 (45%)	12 (57%)	2 (22%)	

Câncer Colorretal

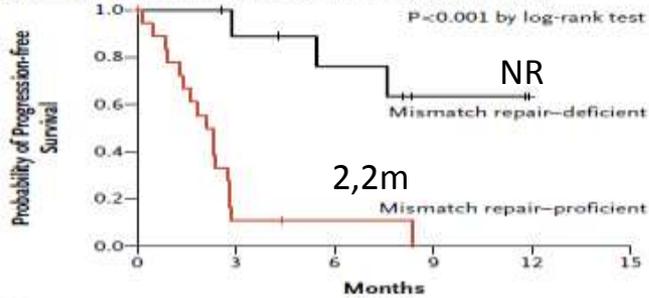
Resultados

	MMR-deficiente CRC	MMR-proficiente CRC	MMR-deficiente non-CRC
N	10	18	7
ORR	40%	0%	71%
DCR	90%	11%	71%



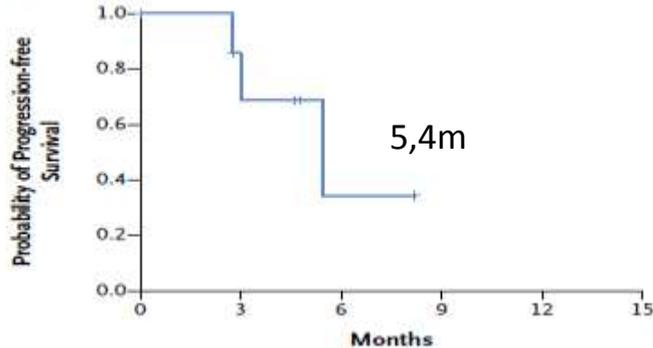
Câncer Colorretal

A Progression-free Survival in Cohorts with Colorectal Cancer



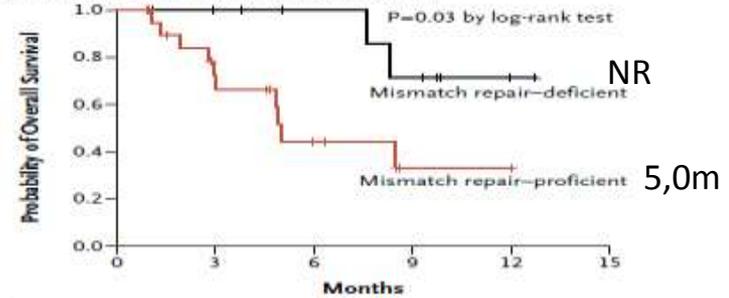
No. at Risk	0	3	6	9	12	15
Mismatch repair-deficient	11	8	6	2	0	0
Mismatch repair-proficient	21	2	1	0	0	0

C Progression-free Survival in Cohort with Mismatch Repair-Deficient Noncolorectal Cancer



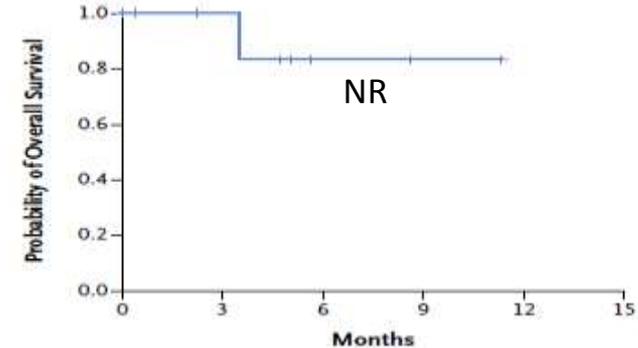
No. at Risk	0	3	6	9	12	15
	9	5	1	0	0	0

B Overall Survival in Cohorts with Colorectal Cancer



No. at Risk	0	3	6	9	12	15
Mismatch repair-deficient	11	9	7	5	1	0
Mismatch repair-proficient	21	12	5	1	1	0

D Overall Survival in Cohort with Mismatch Repair-Deficient Noncolorectal Cancer



No. at Risk	0	3	6	9	12	15
	9	6	2	1	0	0

Keynote 16

- Dados atualizados das cortes A (Colon MSI-H) e C (não Cólón MSI- H) em 2016

Study	Design and Patient Population	Number of patients	MSI-H/dMMR testing	Dose	Prior therapy
KEYNOTE-016 NCT01876511	<ul style="list-style-type: none">• prospective, investigator-initiated• 6 sites• patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	<ul style="list-style-type: none">• CRC: ≥ 2 prior regimens• Non-CRC: ≥1 prior regimen

Keynote 16 – características da população

Patient Baseline Characteristics

Characteristics	MMR Deficient CRC n=28	MMR Proficient CRC n=25
Age, median (range)	49 (26-75)	62 (32-79)
Sex, n (%)		
Female	13 (46)	9 (36)
ECOG, PS-zero	5 (18)	7 (28)
Liver metastases, n (%)	14 (50)	15 (60)
Median Prior Regimens	3	4
Detected Germline Mutation/Lynch Syndrome, n (%)		
Yes	15 (54)	0
No	2 (7)	25 (100)
Unknown	11 (39)	0

jovens

Predominante hepático

Politratado

Hereditário

Keynote 16 – Avaliação de resposta

Results Objective Responses

	MMR Deficient CRC n=28	MMR Proficient CRC n=25
Type of Response		
Complete response (CR), n (%)	3 (11)	0 (0)
Partial response (PR), n (%)	13 (46)	0 (0)
Stable disease (SD) at 12 weeks, n (%)	9 (32)	4 (16)
Progressive disease (PD), n (%)	1 (4)	11 (44)
Could not be evaluated, n (%) ^a	2 (7)	10 (40)
Objective response rate (ORR), % 95% CI	16 (57) 39-73	0 (0) 0-13
Disease Control rate, %	25 (89)	4 (16)

Keynote 16 – Eventos adversos

Adverse Events

Event, n (%)	All Grades N=53	Grade 3 or 4 N=53
Generalized Symptoms		
Fatigue	5 (9)	0 (0)
Arthralgias ←	8 (15)	0 (0)
Gastrointestinal		
Nausea/vomiting	4 (8)	0 (0)
Diarrhea/colitis ←	6 (11)	1 (2)
Endocrine Disorders		
Thyroiditis/hypothyroidism ←	6 (11)	0 (0)
Hepatobiliary		
Pancreatitis	4 (8)	2 (4)
Hyperbilirubinemia	2 (4)	0 (0)

Keynote 16 – Eventos adversos

Adverse Events

Event, n (%)	All Grades N=53	Grade 3 or 4 N=53
Rash/pruritus	13 (25)	1 (2)
Respiratory		
Pneumonitis ←	2 (4)	0 (0)
Other		
Anemia	2 (4)	1 (2)
Flu-like symptoms	2 (4)	0 (0)
Leukopenia	2 (4)	1 (2)
Thrombocytopenia	3 (6)	1 (2)

Toxicidade esperada e manejável

Nivolumab ± Ipilimumab in Treatment of Patients With Metastatic Colorectal Cancer With and Without High Microsatellite Instability: CheckMate 142 Interim Results

Michael Overman,¹ Scott Kopetz,¹ Ray McDermott,² Joseph Leach,³ Sara Lonardi,⁴ Heinz-Josef Lenz,⁵ Michael Morse,⁶ Jayesh Desai,⁷ Andrew Hill,⁸ Michael Axelson,⁹ Rebecca A. Moss,⁹ Chen-Sheng Lin,⁹ Monica Goldberg,⁹ Thierry Andre¹⁰

¹MD Anderson Cancer Center, Houston, TX, USA; ²St Vincent's University Hospital, Dublin, Ireland; ³Allina Health System, Minneapolis, MN, USA; ⁴Istituto Oncologico Veneto IOV-IRCSS, Padova, Italy; ⁵USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; ⁶Duke University Office of Research Administration, Durham, NC, USA; ⁷Royal Melbourne Hospital, Victoria, Australia; ⁸Tasman Oncology Research Pty Ltd, Southport, Queensland, Australia; ⁹Bristol-Myers Squibb, Princeton, NJ, USA; ¹⁰Hopital Saint Antoine, Paris, France

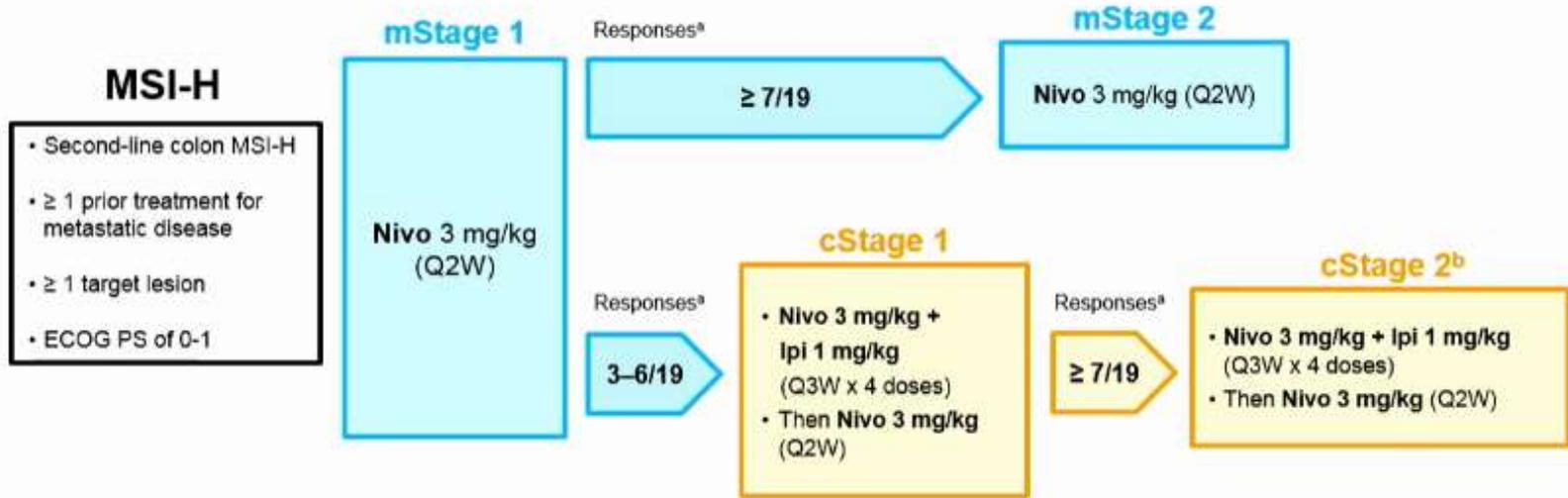
PRESENTED AT **ASCO ANNUAL MEETING '16**

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Desing do estudo CheckMate 142: MSI-H Cohort



^aIn patients with centrally confirmed MSI-H status

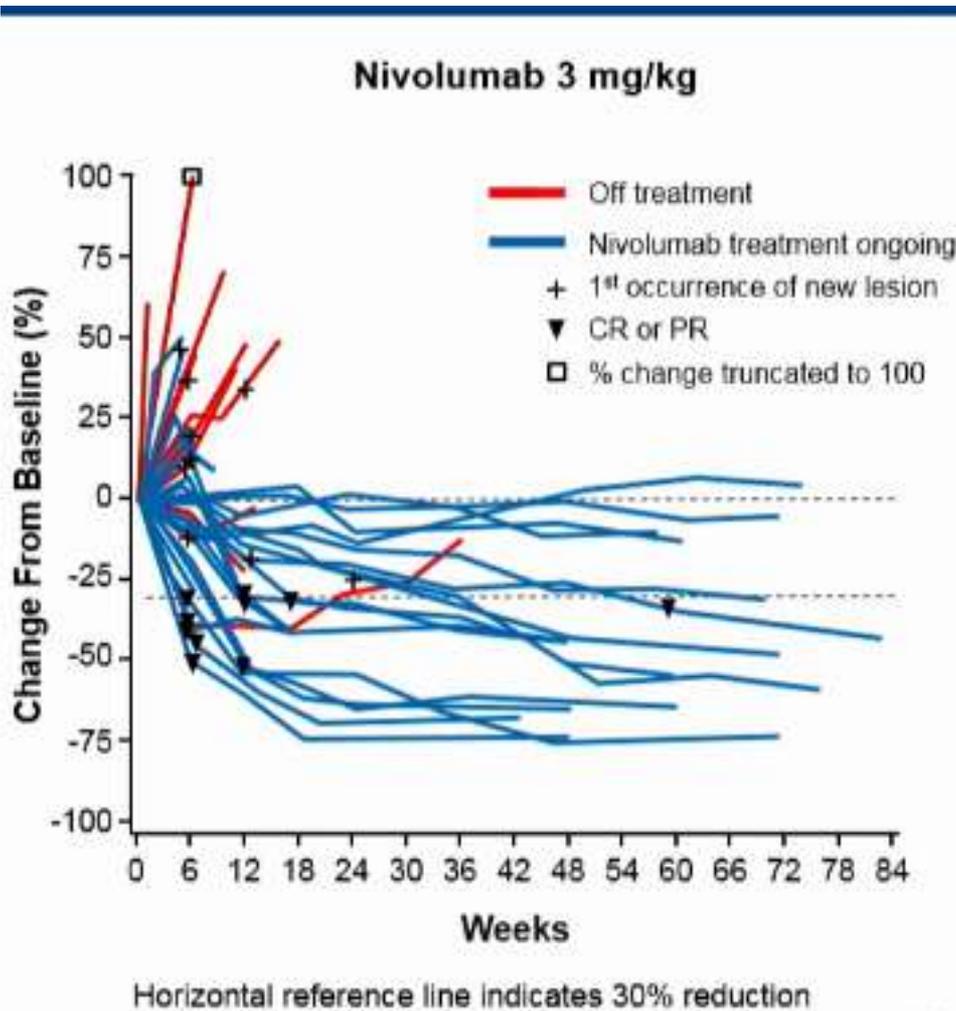
^bCurrently enrolling

cStage 1 = combination therapy stage 1; cStage 2 = combination therapy stage 2; Ipi = ipilimumab; mStage 1 = monotherapy stage 1; mStage 2 = monotherapy stage 2; Nivo = nivolumab; Q2W = every 2 weeks; Q3W = every 3 weeks

Checkmate 142

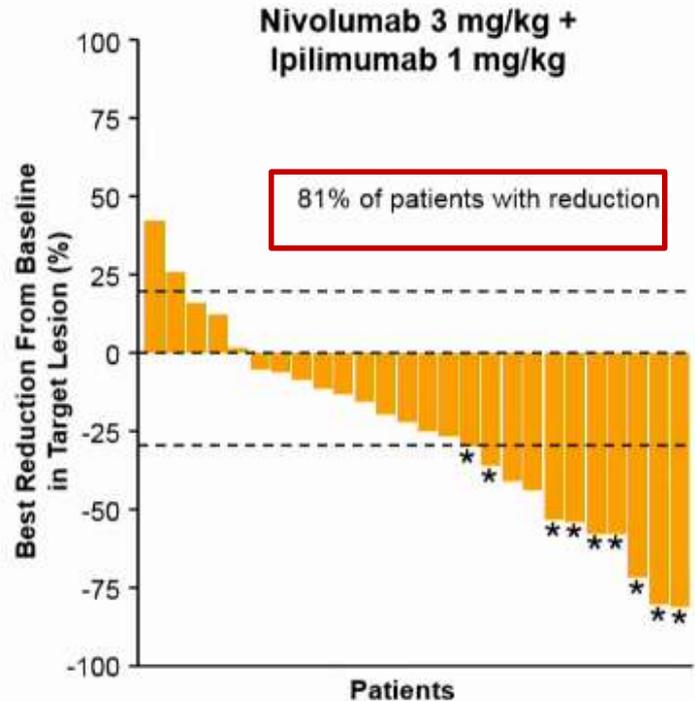
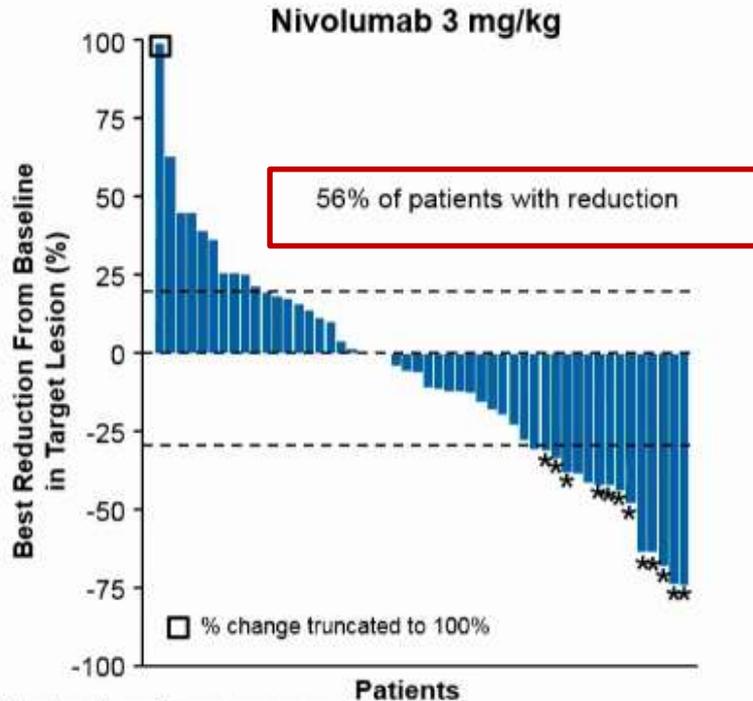
Nivolumab monoterapia

	Nivolumab 3mg/Kg (N=47) mais de 12sem F/U
ORR n (%)	12 (25.5) (15.4 – 38.1)
Resposta completa	0
Resposta parcial	12 (25.5)
Estável	14 (29.8)
PD	17 (36.2)
Não avaliável	4 (8.5)
Mediana de resposta	2.12 (1.3 -13.6)
Mediana de duração de resposta	NE (0-15)



Checkmate 142

Redução da lesão alvo em pacientes com MSI - H



Checkmate 142 - Atualização ESMO 2017

Característica dos pacientes

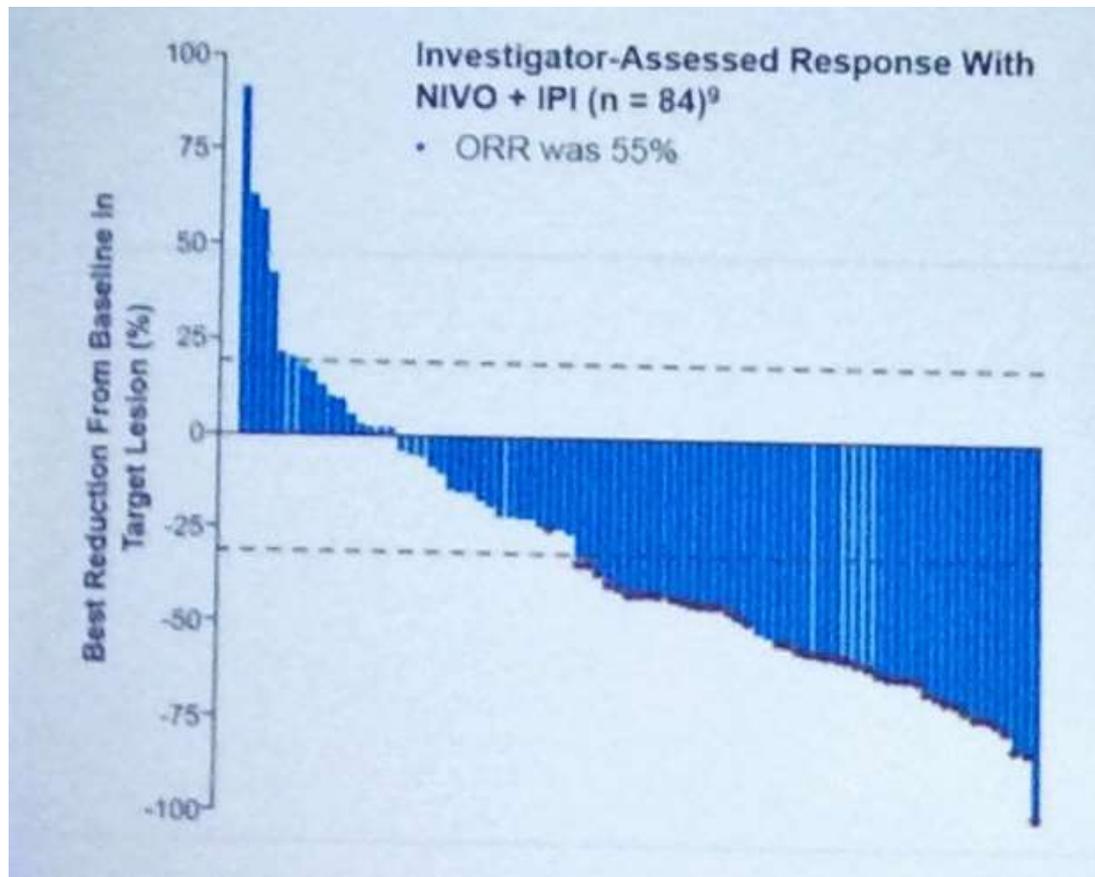
	dMMR/MSI – H (N 84)
Idade	
Mediana em anos	57 anos (21-61) jovens
Menores que 65 anos (%)	81 (73%)
Sexo masculino	48 (57%)
Raça branca	77 (92%)
ECOG 0	31 (37%)
ECOG 1	53 (63%)
Estadiamento da doença inicial	
I – II	9 (11%)
III	33 (39%)
IV	42 (50%)



Checkmate 142

Nivo + Ipi

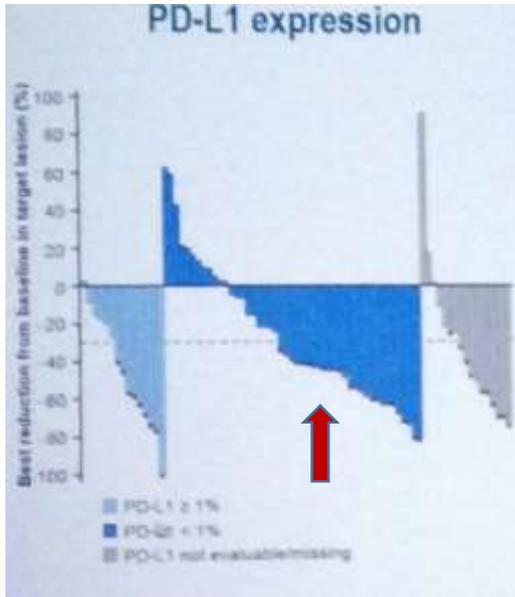
- Taxa de resposta global
 - 55%



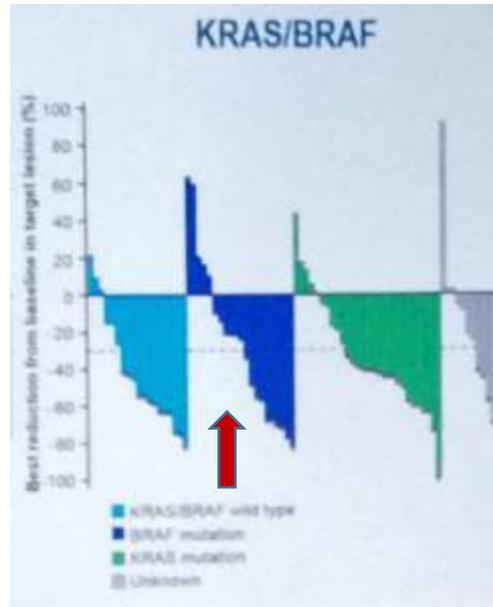
Checkmate 142

Taxa de resposta nos diferentes subtipos

Melhor resposta no PD-L1+

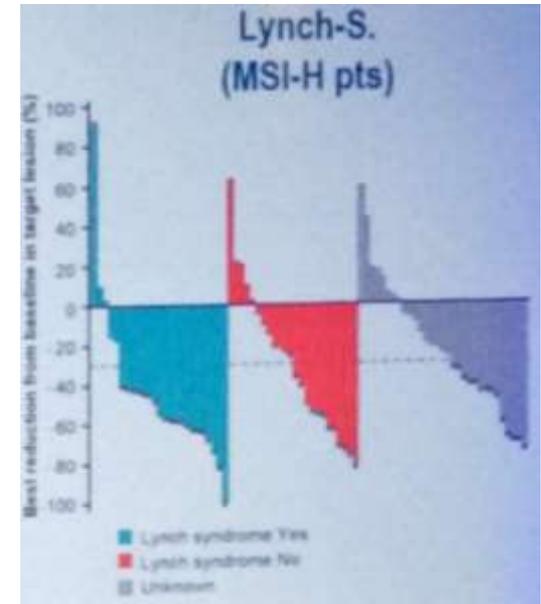


Resposta independente do BRAF



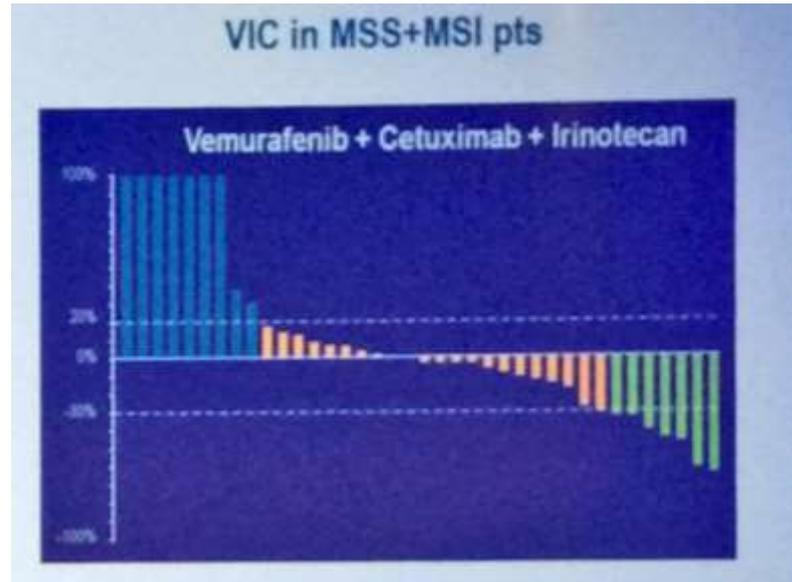
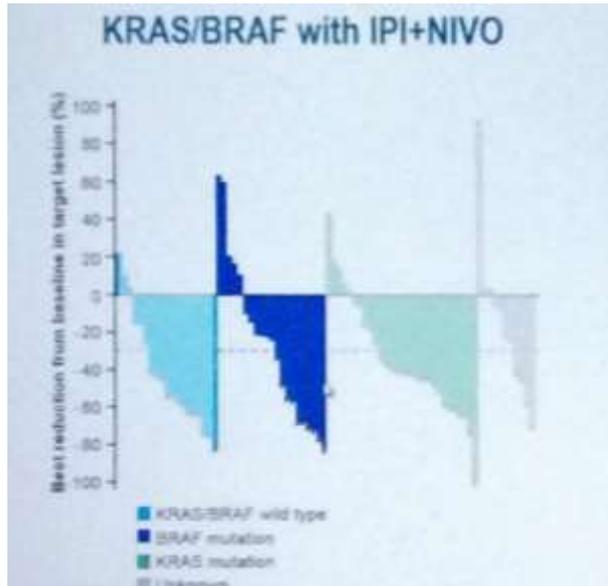
Taxa de resposta global: 55%

Resposta independente da síndrome genética



Checkmate 142

Avaliação na população BRAF mutada



ORR, n/N (%)	Investigator	BICR
BRAF mutation status		
Mutant	3/12 (25.0)	2/12 (16.7)
Wild type	12/28 (42.9)	9/27 (33.3)
KRAS mutation status		
Mutant	7/26 (26.9)	6/26 (23.1)
Wild type	12/28 (42.9)	9/27 (33.3)

Taxa de resposta:16%

Sugestão de melhor resposta de imunoterapia que terapia alvo + quimioterapia

Keynote 164

Fase II – ESMO 2017

KEYNOTE-164 NCT02460198	<ul style="list-style-type: none">• prospective international multi-center• CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
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Keynote 164

Característica dos pacientes

Baseline Characteristics and Demographics in Patients with MSI-H CRC

Characteristics	MSI-H CRC N=61
Age, years, median (range)	53 (21-84)
≥65 years, n (%)	17 (28)
Male, N (%)	36 (59)
ECOG PS, n (%)	
0	29 (48)
1	32 (52)
Stage, n (%)	
M1	61 (100)
Mutation status ^a , n (%)	
<i>KRAS</i> mutated	16 (26)
<i>BRAF</i> mutated	9 (15)
<i>NRAS</i> mutated	3 (5)
Tumor size, mm, median (range)	99 (11-408)
Prior (neo)adjuvant therapy, n (%)	22 (36)
Prior lines of therapy, n (%)	
0	—
1	6 (10)
2	28 (46)
≥3	9 (15)
Unknown	—

ECOG PS, Eastern Cooperative Oncology Group performance status.

^aMutation status was not assessed for MSI-H non-CRC tumors.

^bThese patients progressed <1 year after adjuvant therapy.



Keynote 164

Avaliação de resposta

Best Response (RECIST v1.1 per IRC) in Patients with MSI-H CRC

Best Response	MSI-H CRC N=61 ^a	
	n	% (95% CI)
ORR	17	28 (17-41)
Complete response	0	0
Partial response	17	28 (17-41)
Stable disease	14	23 (13-36)
Progressive disease	28	46 (33-59)
DCR (CR+PR+SD)	31	51 (38-64)
Median time to response, months (range)	4 (2-10)	



Keynote 164

Segurança

Events	MSI-H CRC N=61, n (%)		
Any grade	35 (57)		
Grade 3-4	9 (15)		
Led to death (grade 5)	0		
Led to discontinuation	1 (2)		
Events ≥10%	Any grade	Grade 3-4	Grade 5
Arthralgia	10 (16)	0	0
Nausea	9 (15)	0	0
Diarrhea	8 (13)	0	0
Asthenia	7 (12)	1 (2)	0
Pruritus	7 (12)	0	0
Fatigue	6 (10)	2 (3)	0

Immune-mediated^a Adverse Events in Patients with MSI-H CRC and MSI-H M

Events	MSI-H CRC N=61, n (%)
Any grade	11 (18)
Grade 3-4	3 (5)
Led to death (grade 5)	0
Led to discontinuation	1 (2)

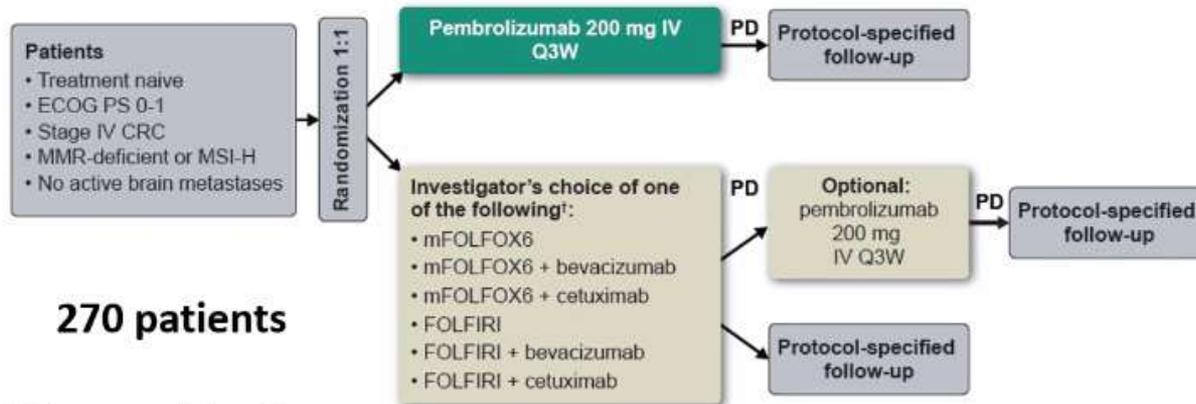
All events	Any grade	Grade 3-4	Grade 5
Hypothyroidism	5 (8)	0	0
Hyperthyroidism	3 (5)	0	0
Pancreatitis	3 (5)	3 (5)	0
Colitis	1 (2)	0	0
Hepatitis	1 (2)	1 (2)	0



KEYNOTE-177: Randomized phase III study of pembrolizumab versus investigator-choice chemotherapy for mismatch repair-deficient or microsatellite instability-high metastatic colorectal carcinoma.

Keynote 177 first line mCRC MSI-H

Recrutando



270 patients

Primary objective:
PFS



Conclusão

Estudos	Taxa de resposta
Keynote 16 (Pembro)	56%
Keynote 164 (Pembro)	57%
Checkmate 142 (Ipi + Nivo)	55%

- Em pacientes com alta taxa de instabilidade de microssatélite
- Após falha de quimio





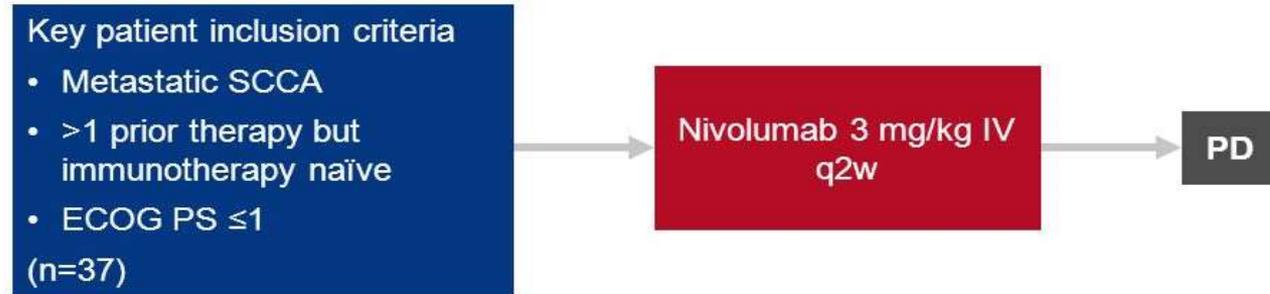
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de São Paulo

Canal Anal

Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study

Study objective

- To evaluate the efficacy and safety of nivolumab in patients with refractory metastatic SCCA



PRIMARY ENDPOINT(S)

- ORR (RECIST 1.1)

SECONDARY ENDPOINTS

- PFS, OS
- Safety

Característica dos pacientes

n=37	
Median age (years)	56 (51-64)
Race	
White	33 (90%)
Black	2 (5%)
Asian	2 (5%)
Sex	
Male	10 (27%)
Female	27 (73%)
ECOG performance status	
0	10 (27%)
1	27 (73%)
HIV positive	2 (5%)

HPV positivo em 15/15 pacientes

Median number of prior lines of therapy	2 (1-7)
Distribution of unresectable disease	
Local recurrence	15 (41%)
Distant metastasis	37 (100%)
Sites of distant metastases	
Lung	19 (51%)
Liver	14 (38%)
Lymph node	10 (27%)
Soft tissue	5 (14%)

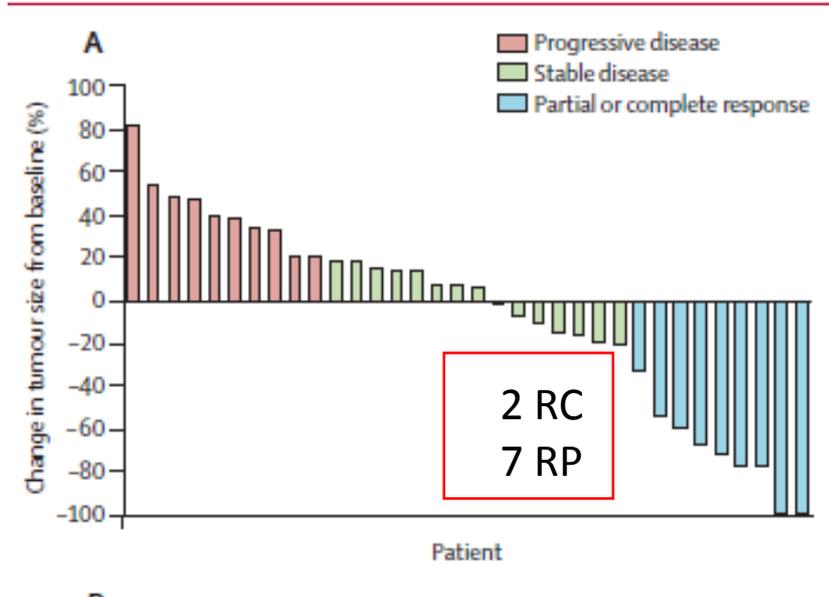
Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group.

Table 1: Baseline demographics



Resposta

Taxa resposta: 24% (9/37 pacientes)



Response rate, n (%)	
CR	2 (5.4)
PR	7 (18.9)
SD	17 (45.9)
PD	8 (21.6)
NE	3 (8.1)
ORR, ITT (n=37)	9 (24.3)
ORR, evaluable (n=34)	9 (26.5)



Resultados

Sobrevida livre de progressão

4,1 meses

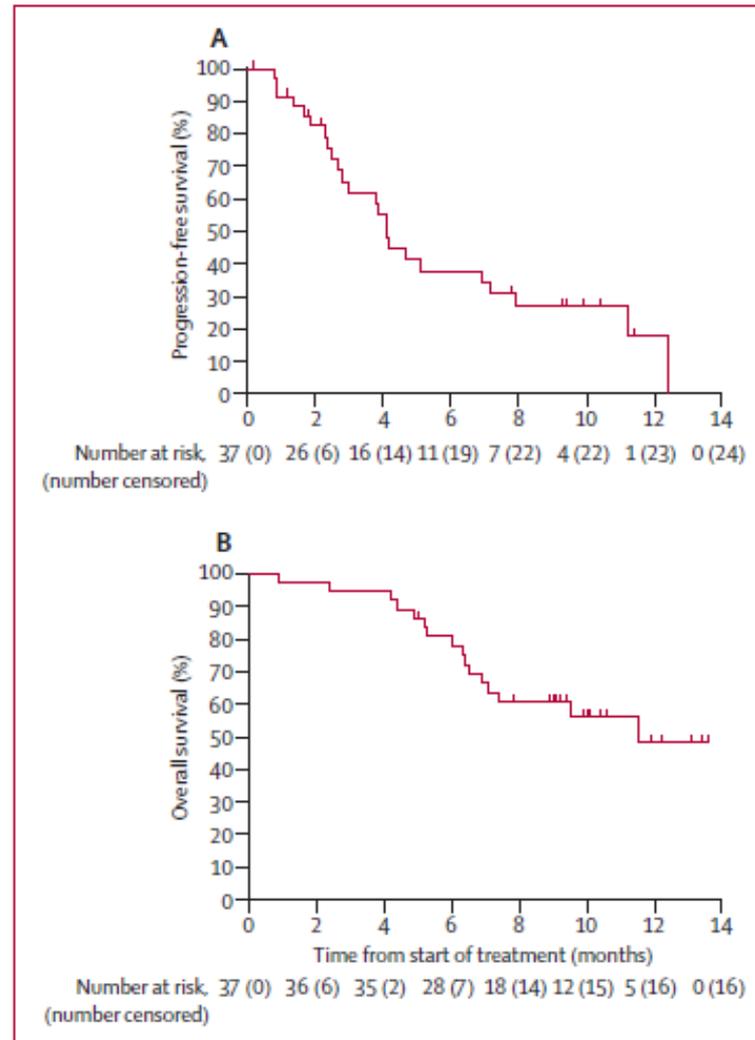
Sobrevida global

11,5 meses

SG1ano: 48%



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Resultados

Eventos adversos
Bem conhecidos e
tolerados

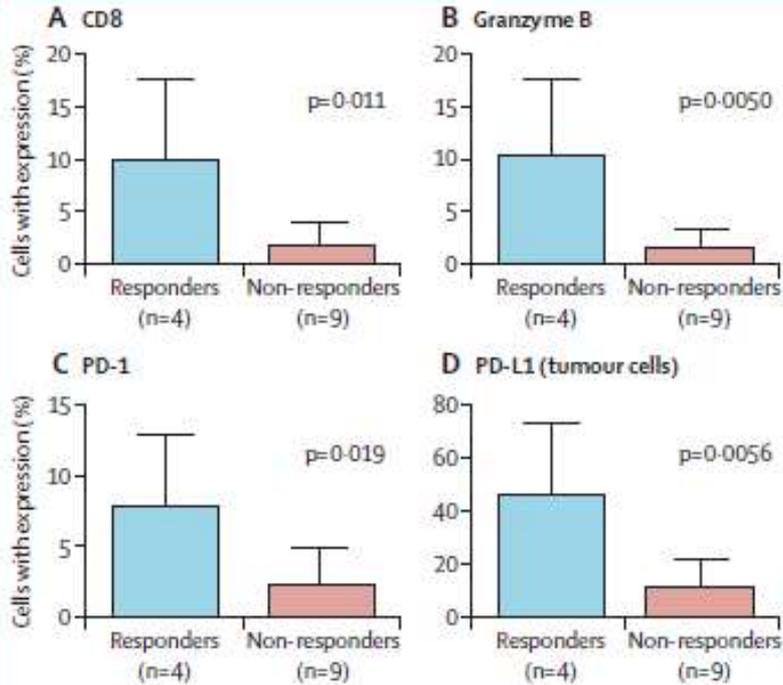
	Grade 1	Grade 2	Grade 3
Anaemia	13 (35%)	11 (30%)	2 (5%)
Fatigue	17 (46%)	7 (19%)	1 (3%)
Rash	8 (22%)	2 (5%)	1 (3%)
Constipation	8 (22%)	2 (5%)	0
Anorexia	5 (14%)	4 (11%)	0
Diarrhoea	8 (22%)	0	0
Weight loss	5 (14%)	1 (3%)	0
Arthralgia	3 (8%)	3 (8%)	0
Hyperglycaemia	3 (8%)	1 (3%)	0
Hypothyroidism	1 (3%)	1 (3%)	1 (3%)
Lymphoedema	1 (3%)	1 (3%)	0
Nausea	2 (5%)	0	0
Pneumonitis	0	1 (3%)	0

Data are n (%). n=37.

Table 2: All adverse events



Avaliação do microambiente



- Maior resposta com aumento do infiltrado inflamatório
- Resposta relacionada com a expressão de PD1 e PD-L1

Conclusão

Nivolumab para cancer de canal refratário

- Ativo
- Bem tolerado
- Relação com provável imunogenicidade conferida pela infecção do HPV

- Nivo + Ipilimumab em andamento





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Obrigado