



# Os outros tumores de pele a serem tratados com imunoterapia

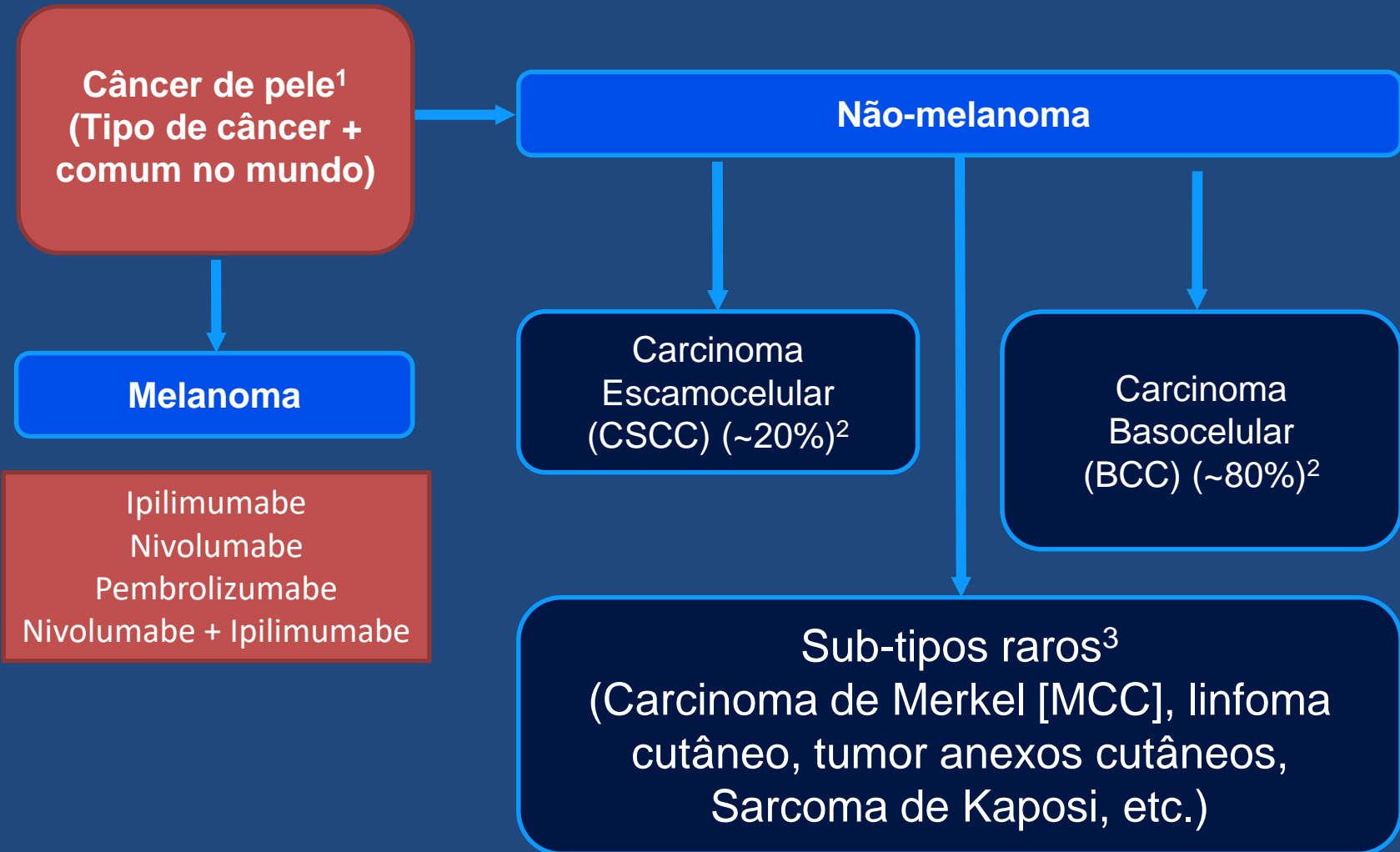
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Oncologia Clínica  
Salvador, Bahia





- Declaração de potenciais conflitos de interesse:
  - Não possuo conflitos de interesse para esta apresentação

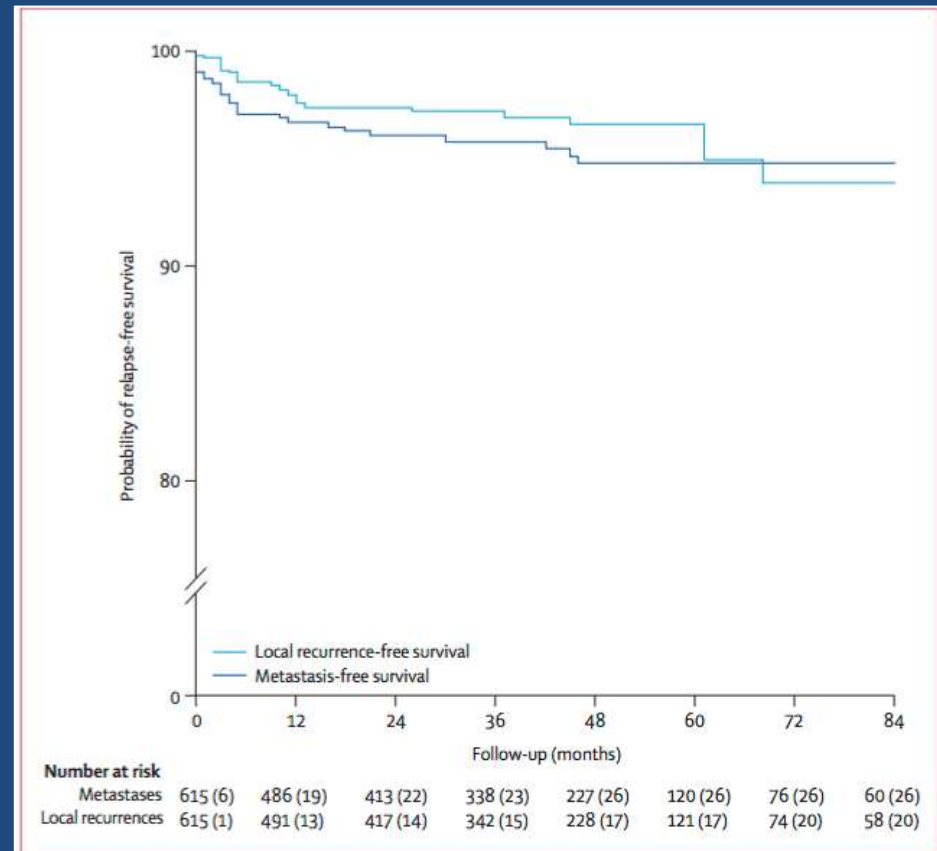
# Câncer de pele



1. Rogers et al., 2015;
2. Karia PS, et al. J Am Acad Dermatol 2013;68:957-66.
3. ACS, 2016

# Carcinoma escamocelular de pele

- 263% aumento incidência EUA:
  - Exposição solar
  - Envelhecimento da população
- 95% obtém cura com cirurgia
- 2-5% metastases linfonodais e a distância
- Fatores de risco de metástases:
  - Espessura do tumor (>6mm)
  - Imunossupressão
  - Localização na orelha
  - Invasão perineural
  - Histologia pouco diferenciada

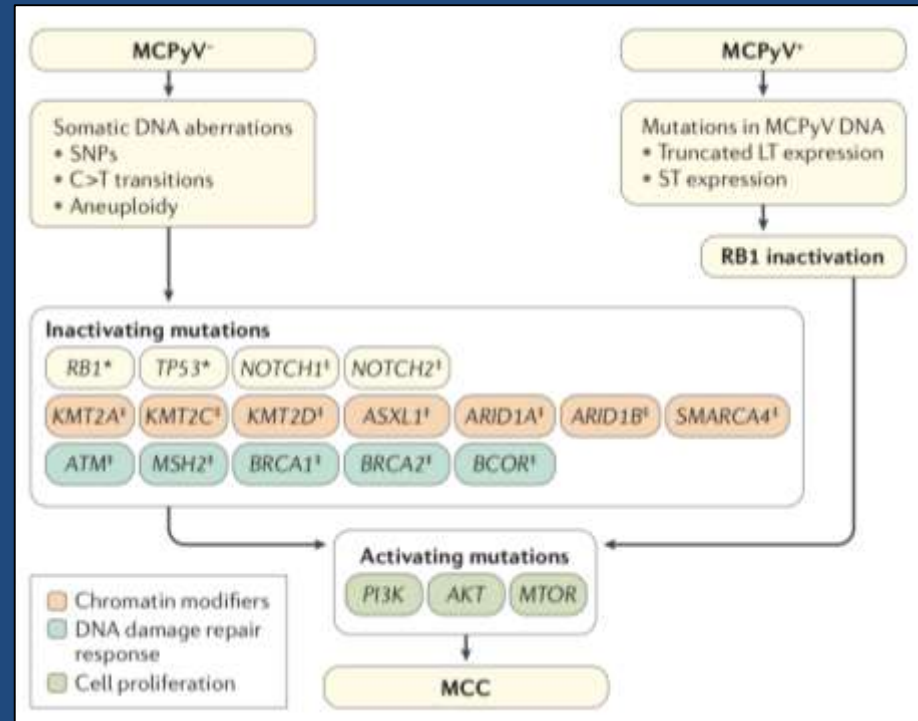
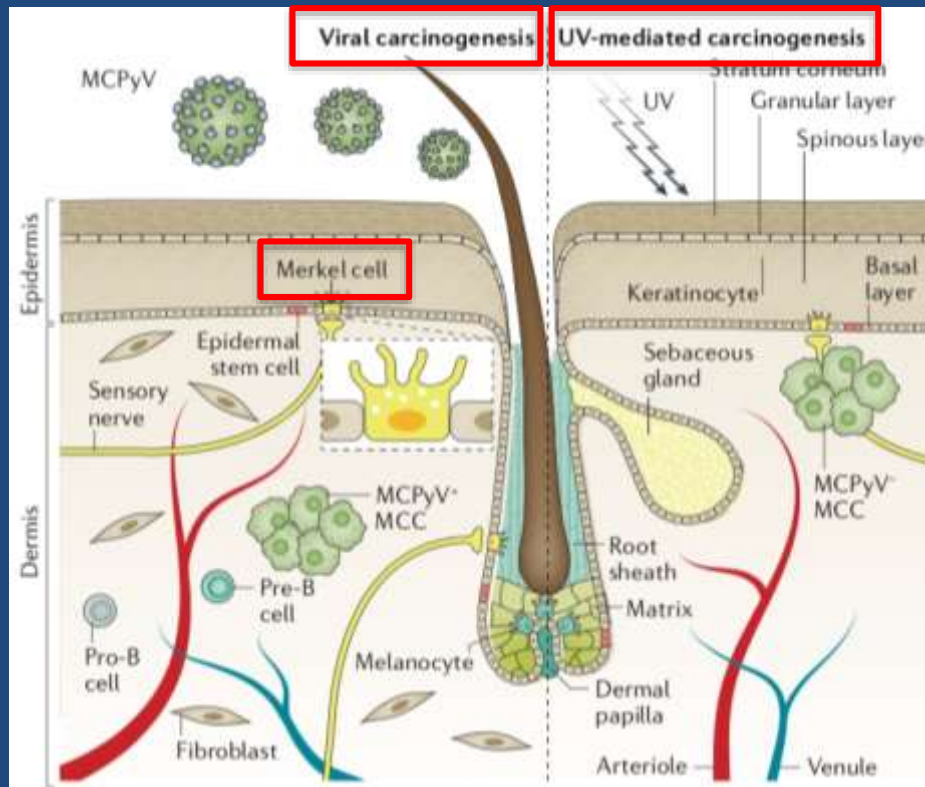


**Figure 1:** Kaplan-Meier estimates of metastasis-free and local recurrence-free survival after resection of the primary squamous-cell carcinoma in 615 patients  
Numbers in parentheses are sum of all patients with metastases or local recurrence. Y-axis shortened.

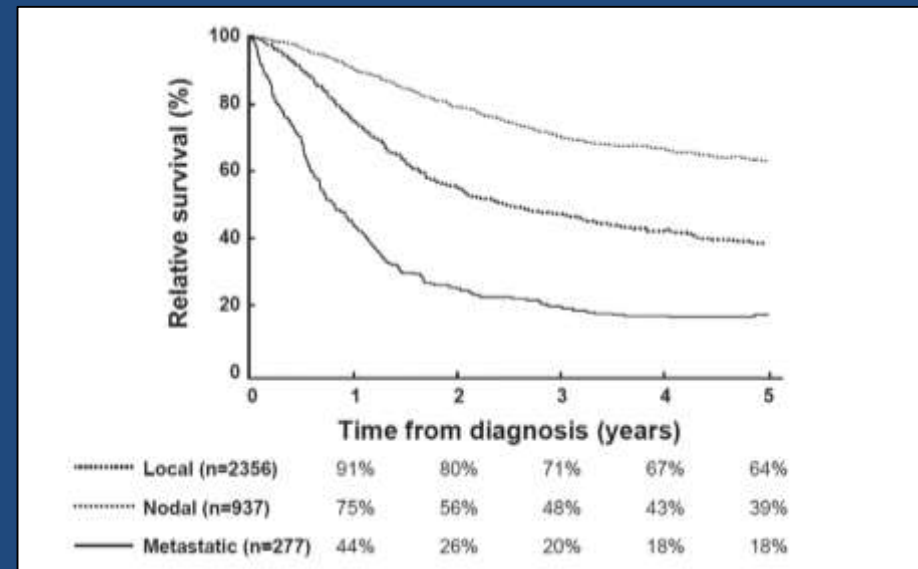
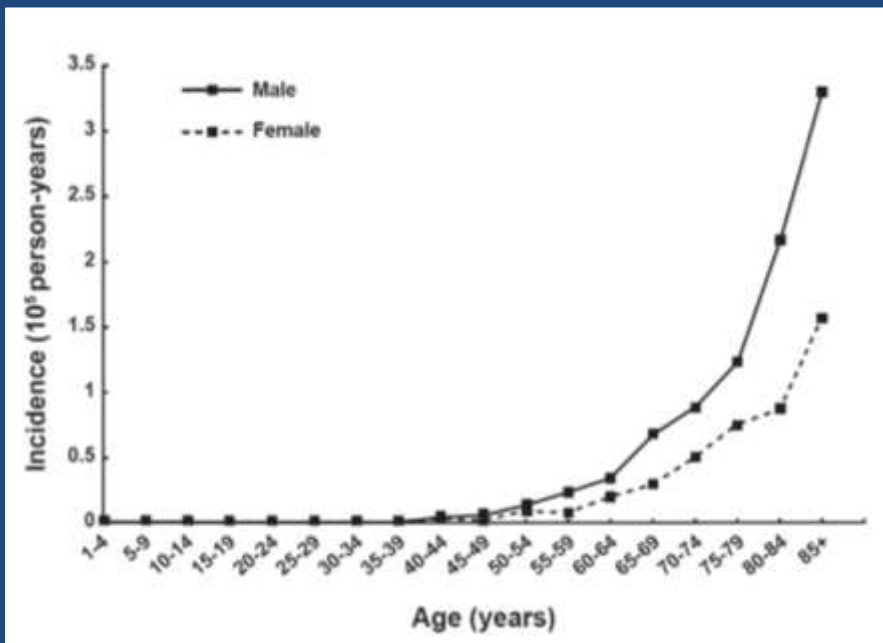
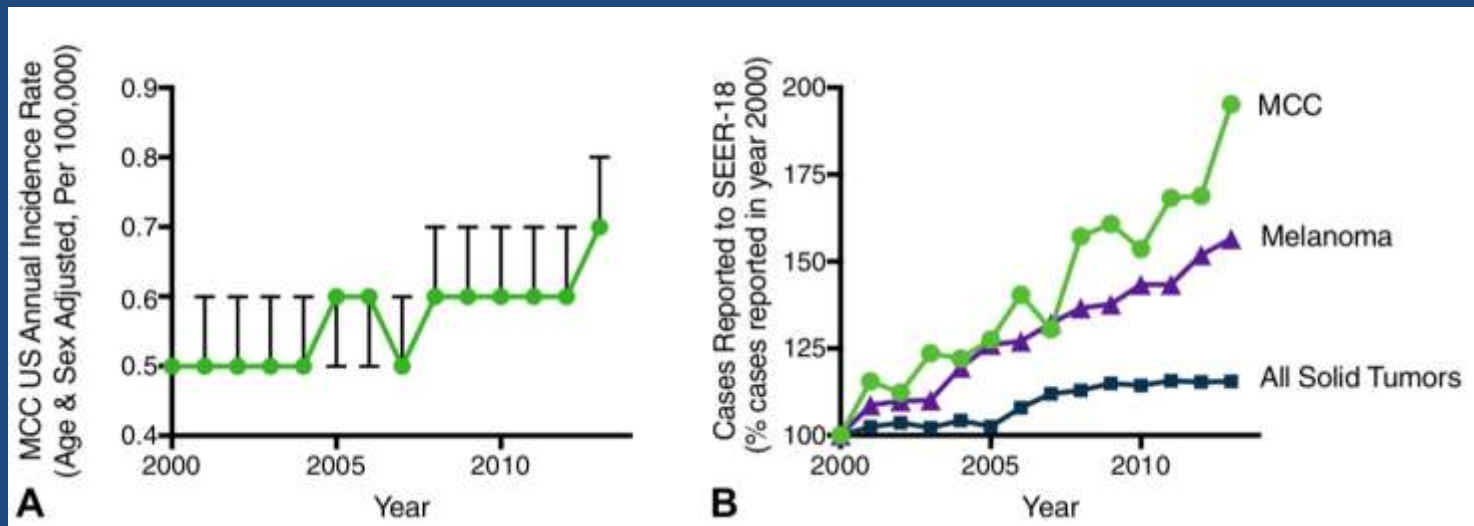
# Carcinoma de Merkel: Carcinoma neuroendócrino agressivo

## Dano DNA pelos raios UV *versus*

## Integração clonal do MCPyV no genoma



# Carcinoma de Merkel: Aumento da incidência





# CEC pele e Carcinoma de Merkel: Fatores de risco

## CEC pele

- Idade média 71 anos
- Mais comum cabeça e pescoço
- Exposição raios UV
- Imunossupressão
- Tipo pele clara

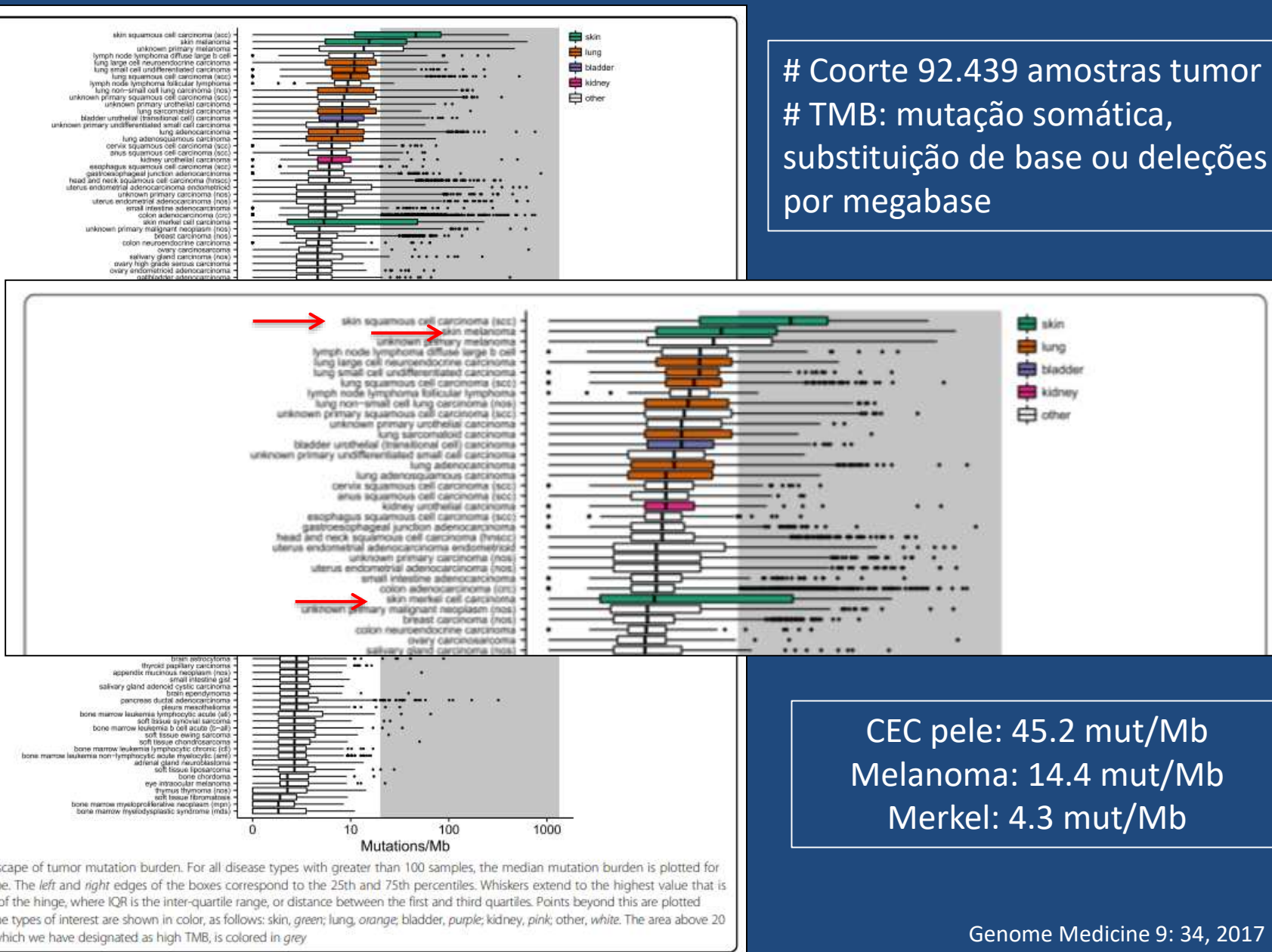
## Carcinoma de Merkel

- Idade média 76 anos
- Mais comum cabeça e pescoço
- Exposição raios UV
- Imunossupressão
- Tipo pele clara
- Infecção poliovírus (MCPyV+ 60-80% casos)

Qual o racional da imunoterapia no tratamento destas neoplasias?

# Carga mutacional: marcador de resposta a imunoterapia

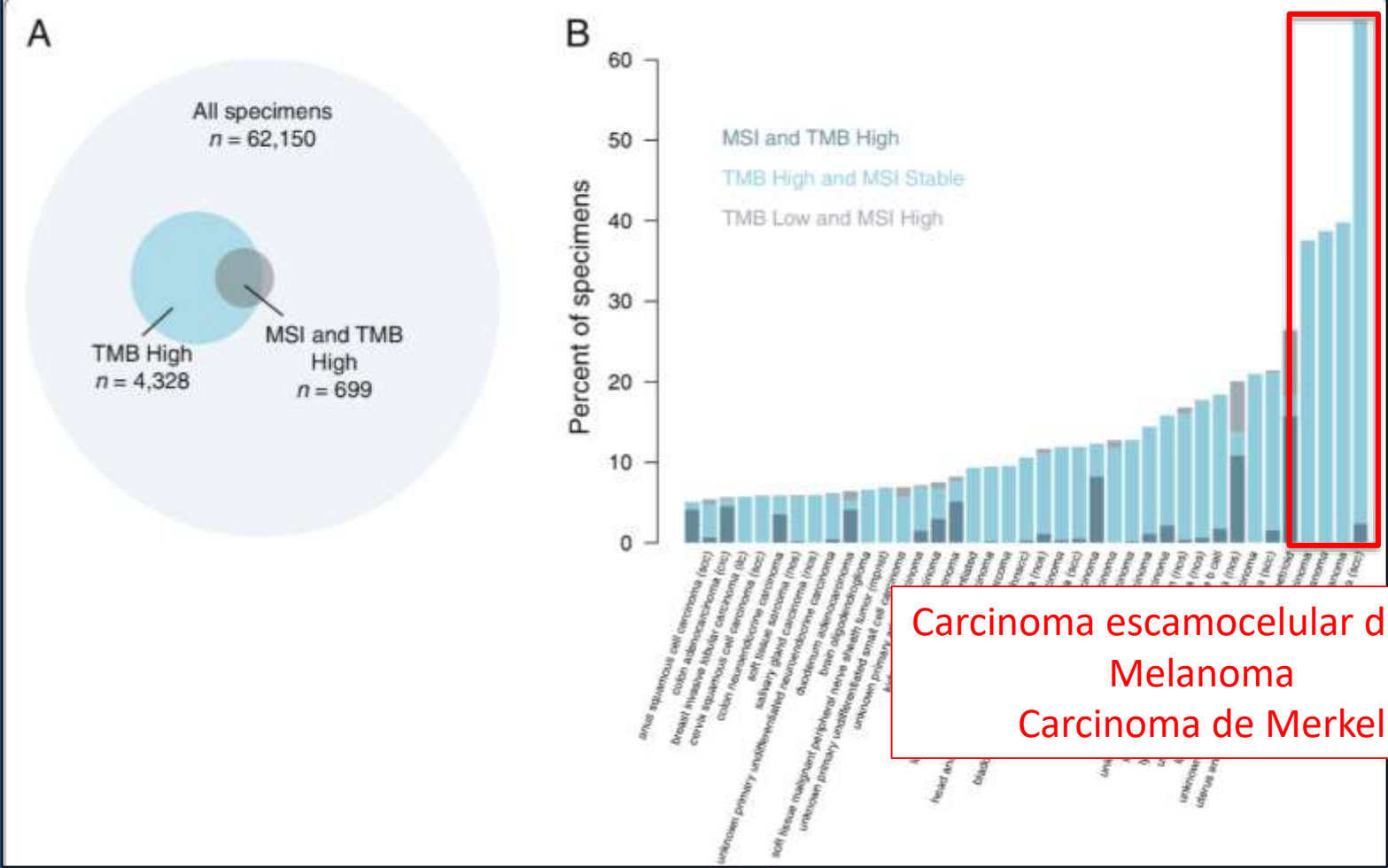
# Coorte 92.439 amostras tumor  
 # TMB: mutação somática, substituição de base ou deleções por megabase



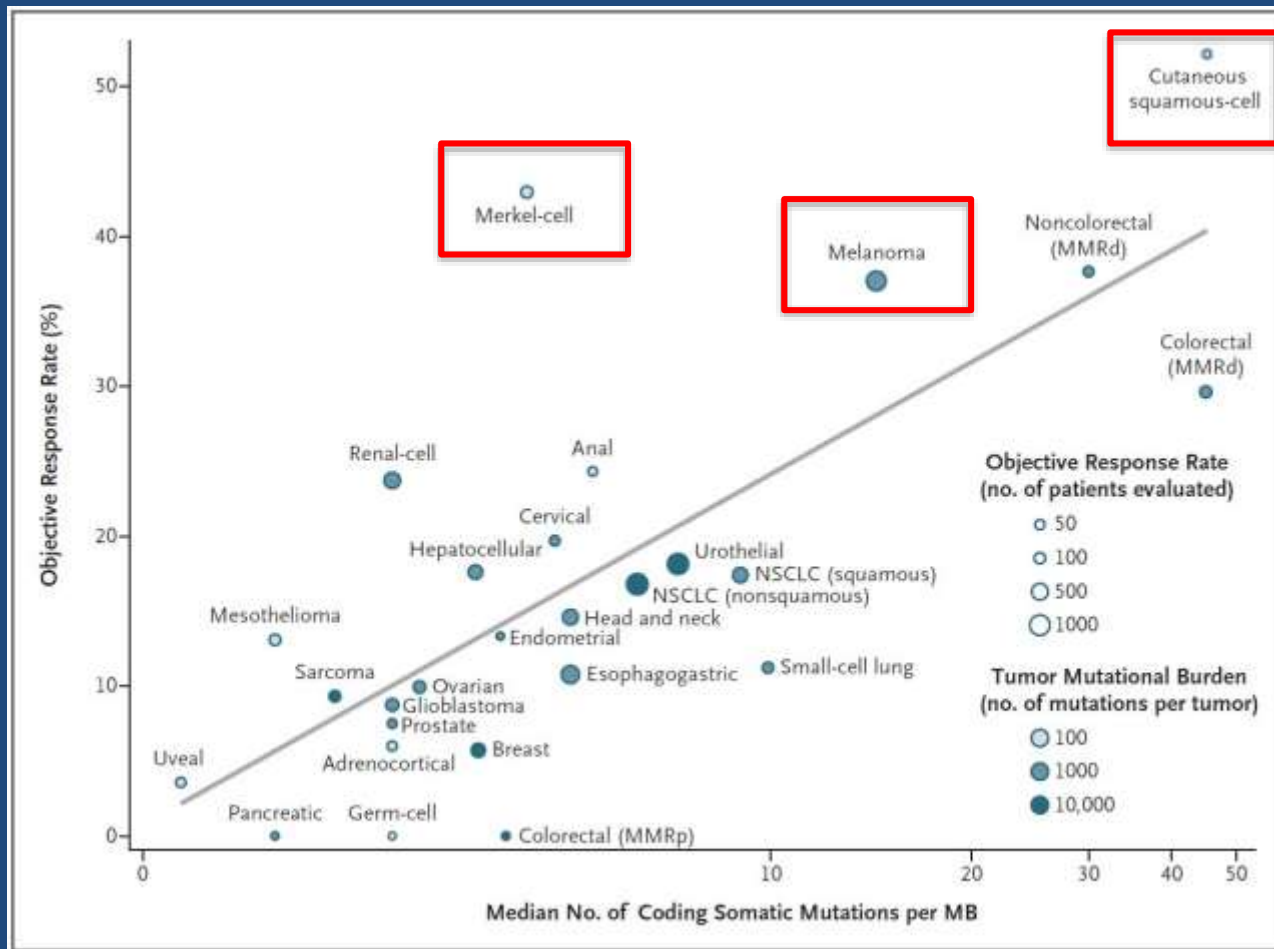
CEC pele: 45.2 mut/Mb  
 Melanoma: 14.4 mut/Mb  
 Merkel: 4.3 mut/Mb



# Câncer de pele: Carga mutacional não depende de instabilidade de microssatélites



# Carga mutacional e resposta ao anti PD-1



# Carcinoma de Merkel avançado: Pembrolizumabe na 1ª linha

50 pacientes MCC avançado  
1ª linha  
N: 26 pacientes (1/15 a 12/15)  
N: 24 pacientes (3/16 a 5/17)

Características da população:

- Idade mediana: 70 anos
- 80% > 65 anos
- 86% metástase a distância
- 14% localmente avançado
- 64% status viral positivo

Pembrolizumabe  
2 mg/kg q3w

Até 2 anos de  
tratamento ou PD  
ou toxicidade  
limitante

Objetivo primário: ORR (CR + PR por RECIST 1.1)  
Objetivos secundários: PFS, DOR e OS  
Análise exploratória: Status viral, status expressão PD-L1

# Pembrolizumabe na 1ª linha: ORR

## Treatment response

(per independent central review, RECIST 1.1)

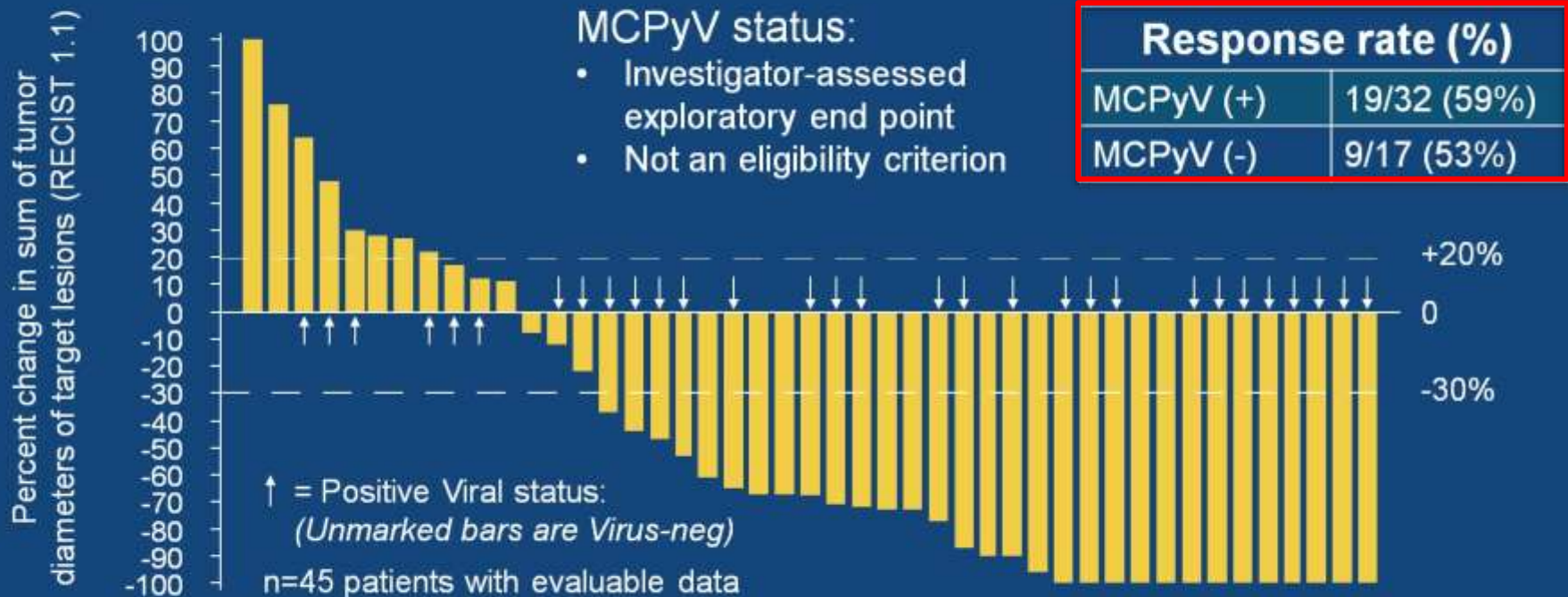
- 50 patients received  $\geq 1$  dose of pembrolizumab
  - Median follow-up 14.9 mos (range 0.4-36 mos as of 06 Feb 2018 database)

Seguimento mediano 14.9 meses

	N = 50	
	n	%
ORR	28	56
Best overall response		
CR	12	24
PR	16	32
SD	5	10
PD	16	32
No assessment	1	2

# Pembrolizumabe na 1ª linha: Resposta de acordo com status MCPyV

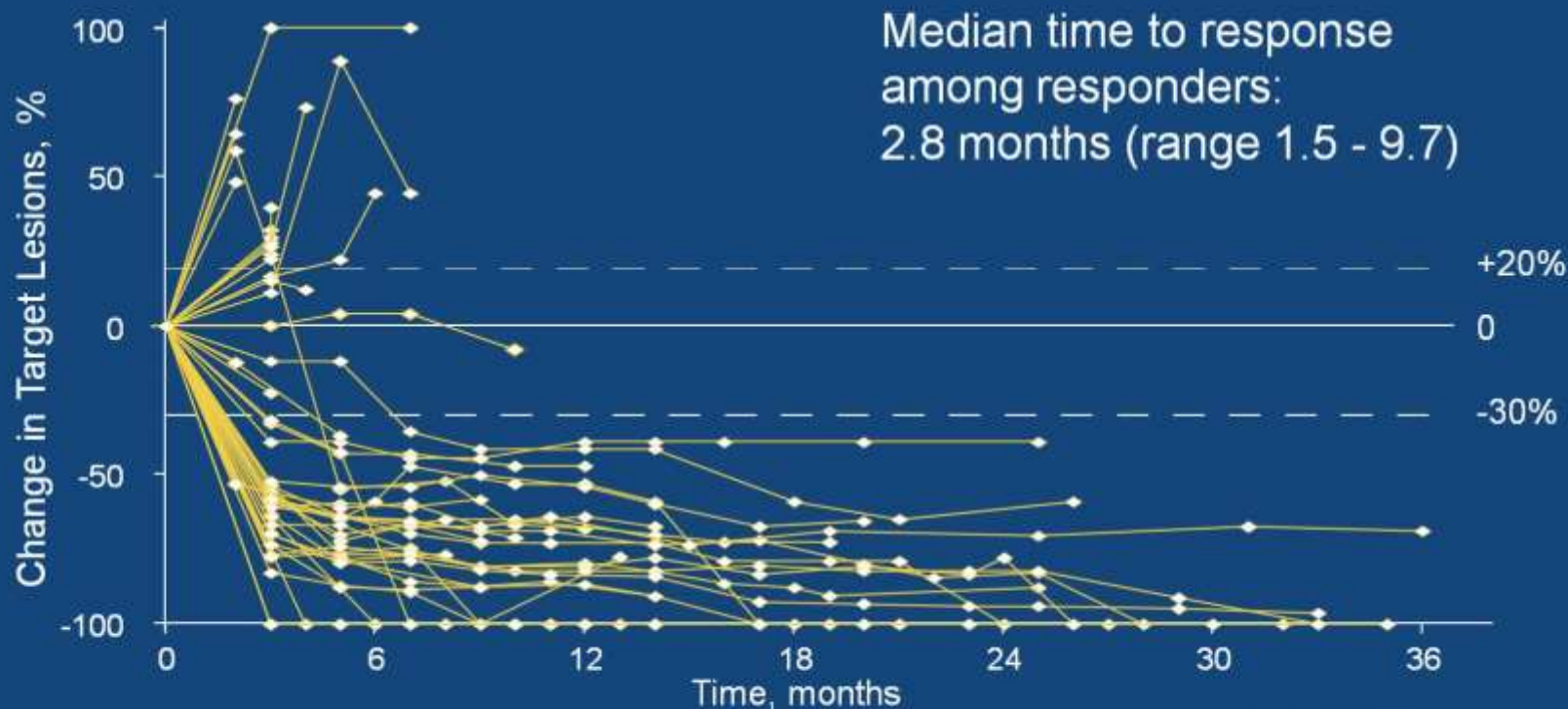
## Radiologic tumor response to pembrolizumab in patients per viral status





# Pembrolizumabe na 1ª linha: Cinética da resposta ao tratamento

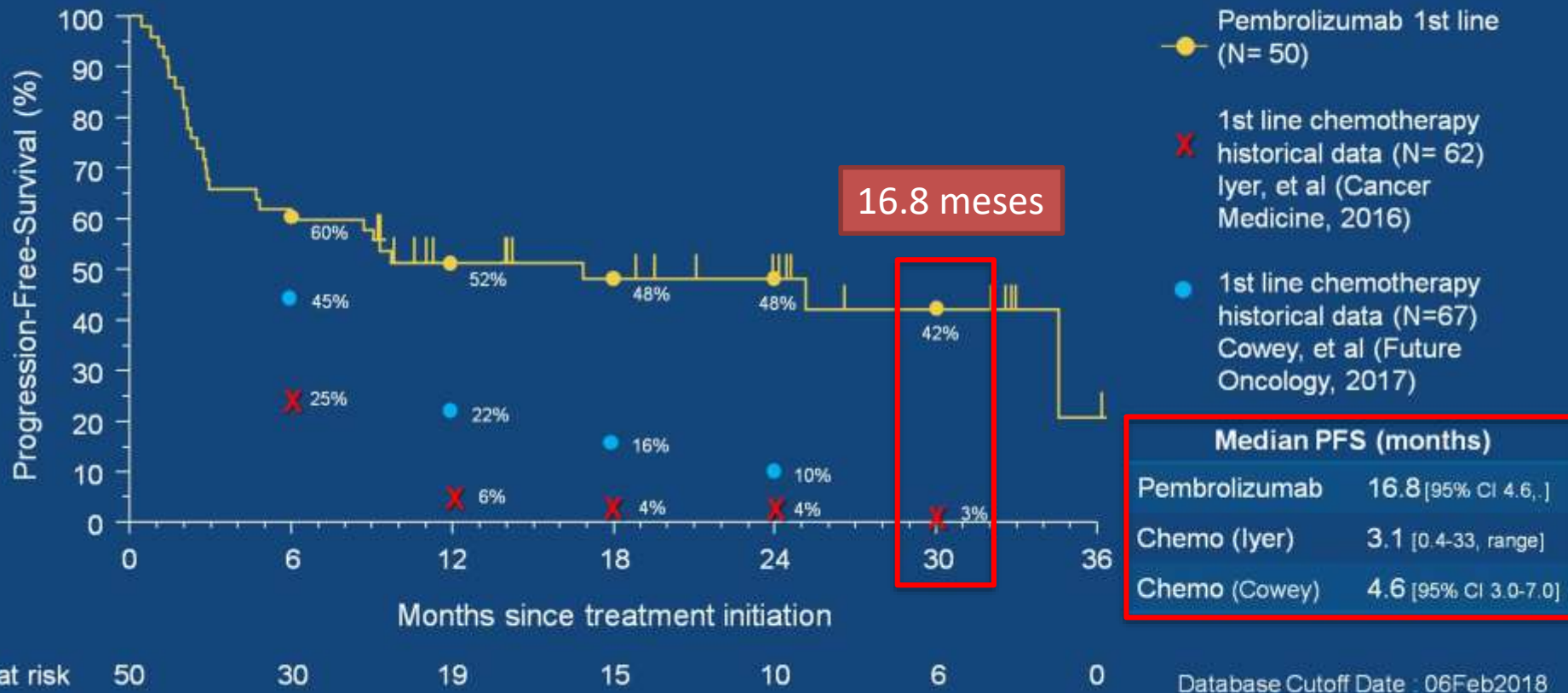
Response kinetics in patients with advanced MCC receiving pembrolizumab





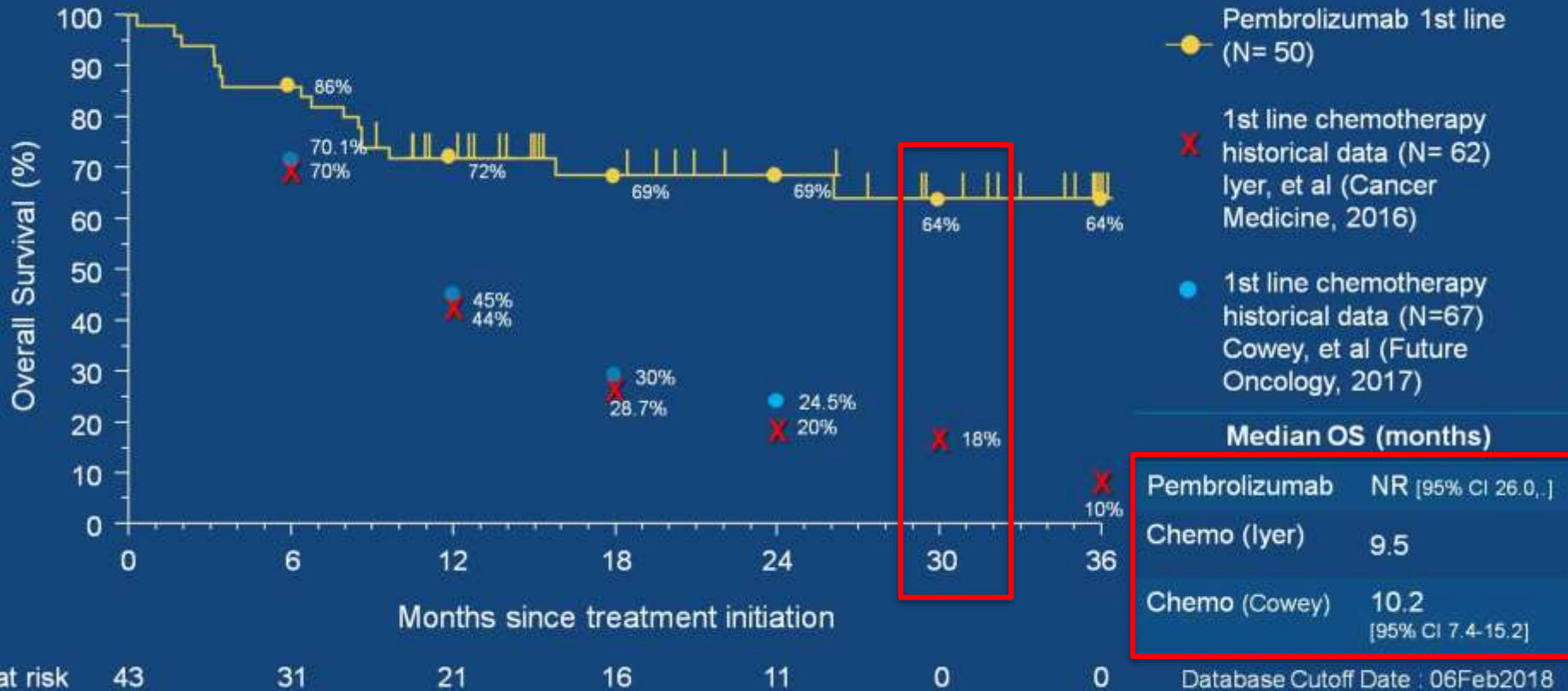
# Pembrolizumabe na 1ª linha: Sobrevida livre de progressão

## Progression-free survival with pembrolizumab for MCC

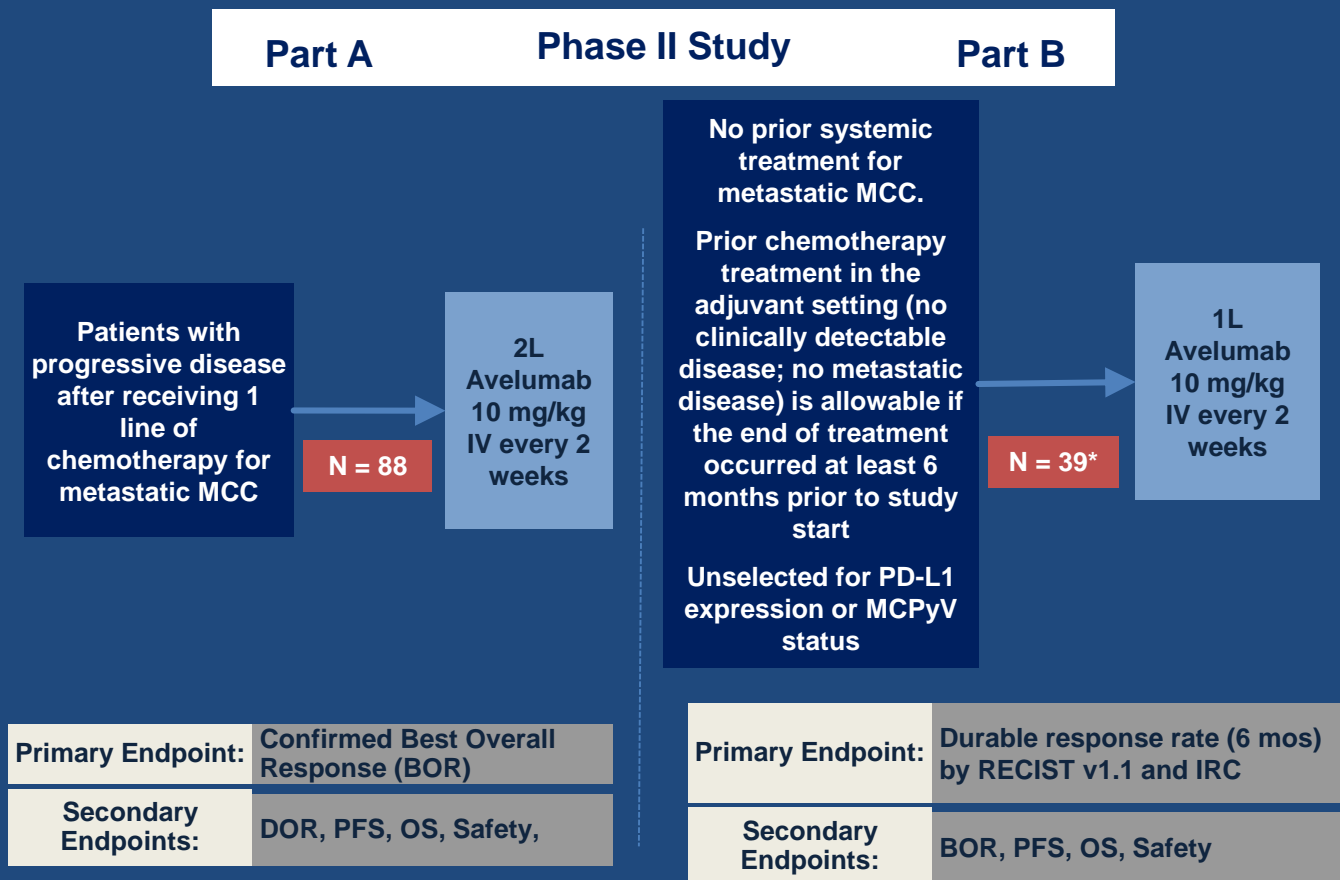


# Pembrolizumabe na 1ª linha: Sobrevida global

## Overall survival with pembrolizumab for MCC



# Carcinoma de Merkel avançado: *JAVELIN Merkel 200* Avelumabe na 1ª linha e 2ª linha



\* Análise interina pré-planejada já publicada, estudo em andamento

# Avelumabe na 2ª linha: *Update* 2 anos

## Características da população

### Baseline characteristics

Characteristic	N=88
Age, n (%)	
<65 y	22 (25.0)
≥65 y	66 (75.0)
Median (range), y	72.5 (33-88)
Sex, n (%)	
Male	65 (73.9)
Female	23 (26.1)
ECOG PS, n (%)	
0	49 (55.7)
1	39 (44.3)
Site of primary tumor, n (%)	
Skin	67 (76.1)
Lymph node	12 (13.6)
Other	2 (2.3)
Missing	7 (8.0)
Number of prior systemic anticancer treatments, n (%)	
1	52 (59.1)
2	26 (29.5)
≥3	10 (11.4)
Visceral disease at study entry, n (%)*	
Yes	47 (53.4)
No	41 (46.6)

79% PD-L1 +  
60% MCPyV +

~40% of patients received  
≥2 prior lines of therapy

\* Metastases not isolated to lymph nodes, skin, or soft tissue



# Avelumabe na 2ª linha: *Update* 2 anos

## Resposta objetiva

### Response to avelumab

Response parameter	N=88
ORR (95% CI), %	33.0 (23.3-43.8)
Confirmed BOR, n (%)	
CR	10 (11.4)
PR	19 (21.6)
SD	9 (10.2)
PD	32 (36.4)
Not evaluable*	18 (20.5)
DCR, %	43.2

**PD-L1 + : 34.5%**  
**PD-L1 - : 18.8%**  
**MCPyV + : 26.1%**  
**MCPyV - : 35.5%**

### *Patient responses remain unchanged from the 1-y analysis<sup>1</sup>*

DCR, disease control rate; ORR, objective response rate; PR, partial response; SD, stable disease

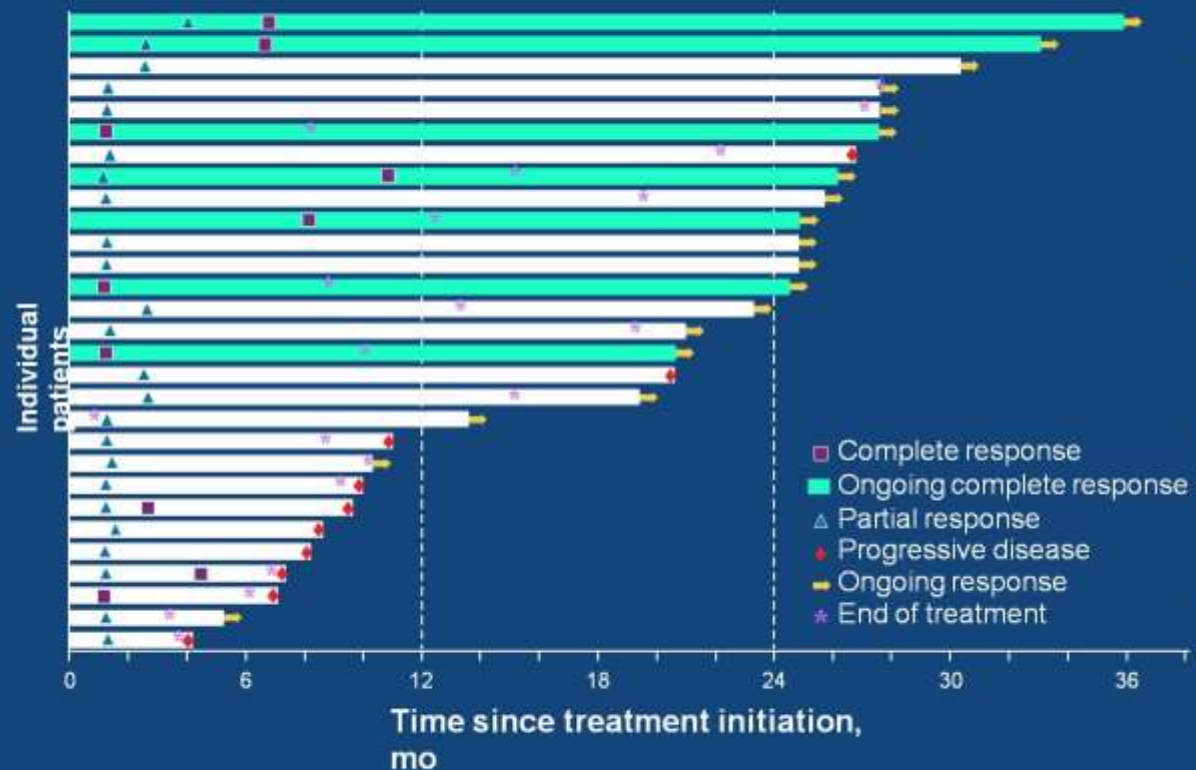
\* Patients not evaluable for a confirmed BOR had no baseline lesions identified by independent review (n=4), baseline but no postbaseline assessments (n=10), all nonassessable postbaseline assessments (n=2), no postbaseline tumor assessment before the start of new anticancer therapy (n=1), or SD of insufficient duration (n=1)

1. Kaufman HL, et al. *J Immunother Cancer*. 2018;6(1):7.

# Avelumabe na 2ª linha: *Update* 2 anos

## Duração de resposta prolongada

### Time to and duration of response (n=29)



- Median DOR not yet reached
  - Lower bound 95% CI: 18.0 mo
  - Range, 2.8 to 31.8+ mo

- Of 10 patients with CR, 7 are ongoing

- **Estimated 67% DOR  $\geq 2$  y (95% CI, 46%-81%)\***

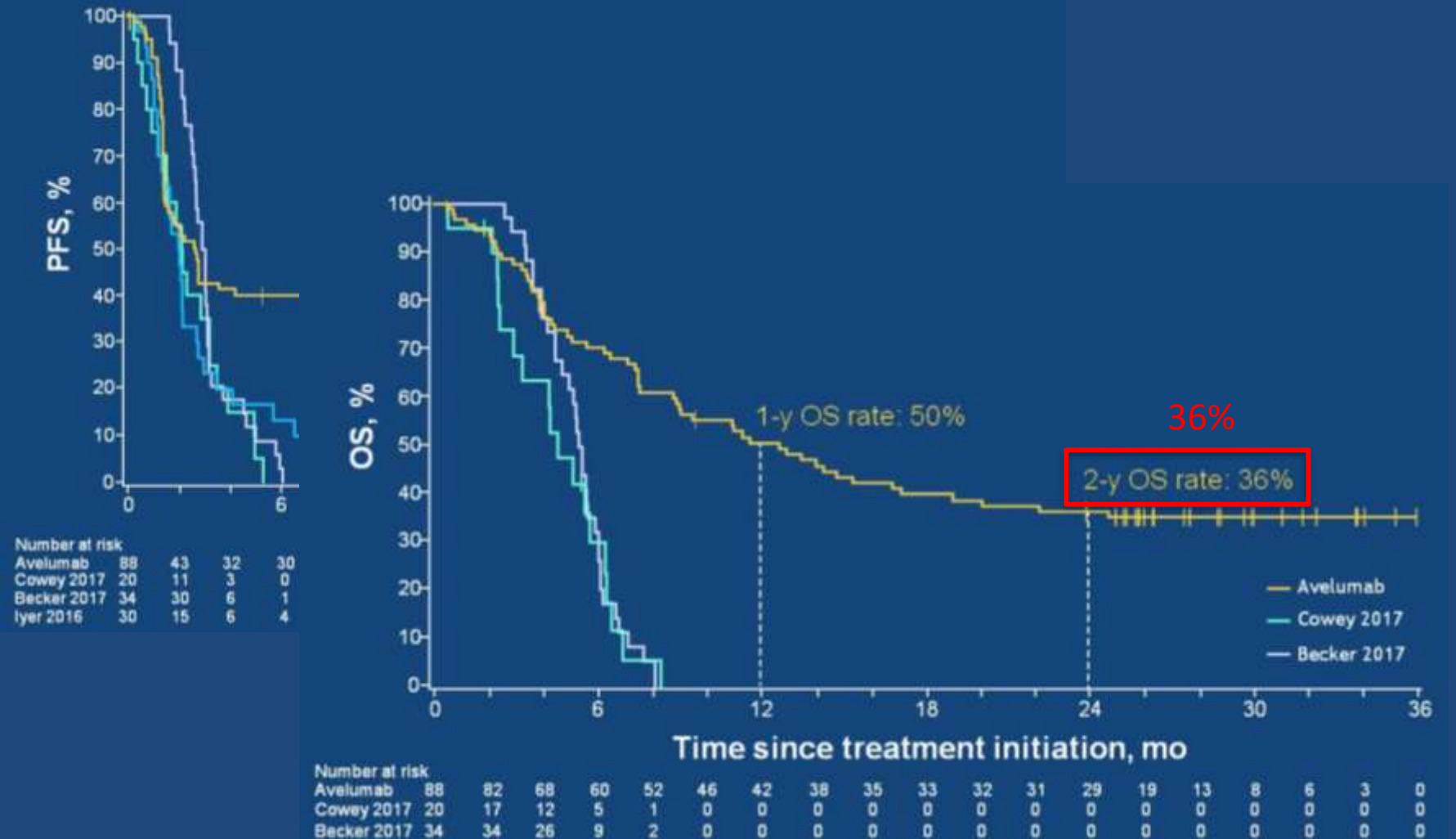
- PD in 10 responders (most between 6-12 mo; no predictors)

\* Based on Kaplan-Meier estimate



# Avelumabe na 2ª linha: *Update* 2 anos

## PFS e OS em comparação a dados históricos de QT



# Avelumabe na 1ª linha: Análise interina pré-planejada

29 pacientes  
Seguimento mediano: 5.1 meses

Table. Outcomes by RECIST Version 1.1, per Independent Review Committee Assessment

Outcome	Patient Follow-up Group	
	≥3 mo	≥6 mo
<b>Response<sup>a</sup></b>		
Confirmed ORR, % (95% CI)	62.1 (42.3-79.3)	71.4 (41.9-91.6)
Confirmed BOR, No. (%)		
Complete response	4 (13.8)	71.4%
Partial response	14 (48.3)	
Stable disease	3 (10.3)	1 (7.1)
Progressive disease	7 (24.1)	2 (14.3)
Nonevaluable <sup>b</sup>	1 (3.4)	1 (7.1)
<b>Response durability<sup>c</sup></b>		
Median DOR (95% CI), mo	NE (4.0 to NE)	NE (4.0 to NE)
Proportion of responses with duration ≥3 mo, % (95% CI)	93 (61-99)	100 (NE)
Proportion of responses with duration ≥6 mo, % (95% CI)	83 (46-96)	89 (43-98)

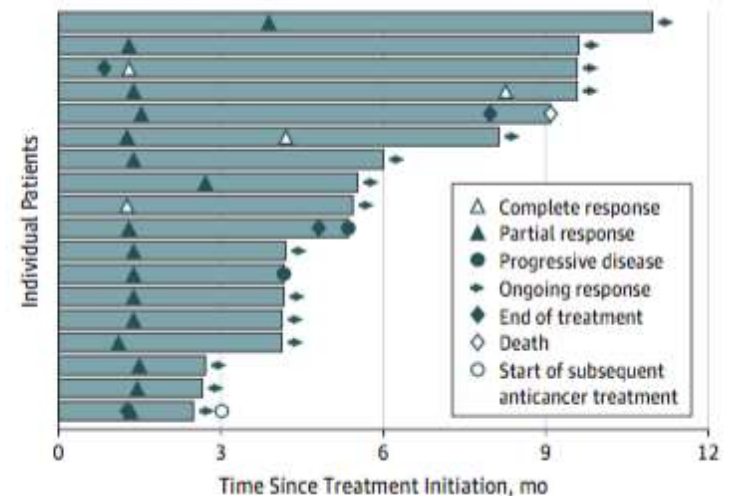
Abbreviations: BOR, best overall response; DOR, duration of response; NE, not estimable; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

<sup>a</sup> Includes 29 patients with at least 3 and 14 with at least 6 months of follow-up.

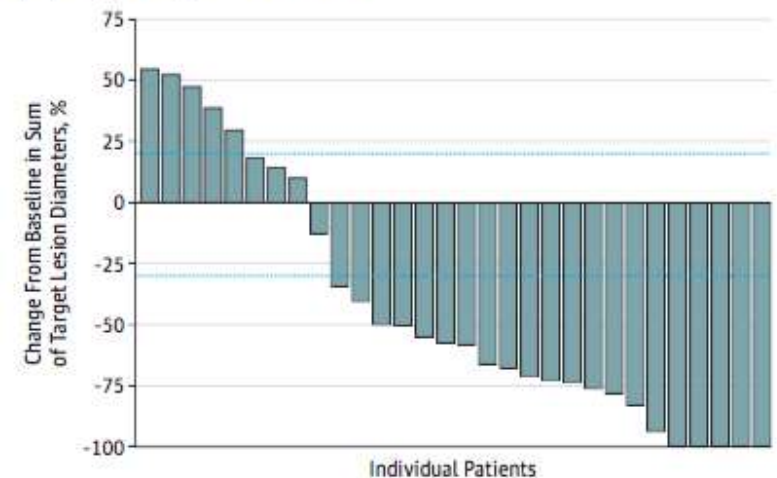
<sup>b</sup> Patient died before tumor assessment due to an adverse event unrelated to treatment with avelumab.

<sup>c</sup> Includes 18 patients with at least 3 and 10 with at least 6 months of follow-up.

A Duration of response and treatment



C Change in target lesion sum diameters



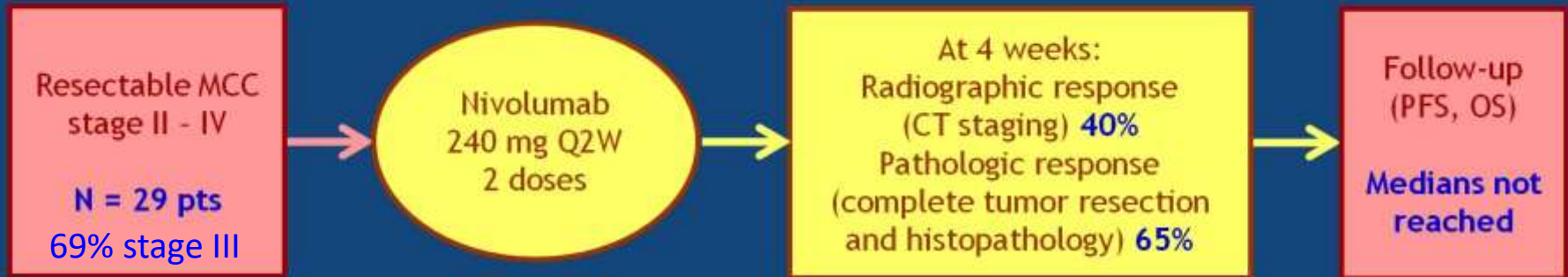
# Carcinoma de Merkel avançado: Nivolumabe – Checkmate 358 (fase 1/2)

- Múltiplas coortes
  - Pacientes com tumor associado a infecção viral
- MCC: 25 pacientes
  - Follow-up: 26 semanas
  - 67% vírus positivo
- Resultados 3 meses:
  - ORR: 71%
  - PFS: 82%
  - OS: 92%

Response to treatment	Response-evaluable pts (N=22)	Treatment-naive pts (n=14)	Pts with 1-2 prior therapies (n=8)
Best overall response – n (%)			
Complete response	3 (14)	3 (21)	0
Partial response	12 (55)	7 (50)	5 (63)
Stable disease	4 (18)	3 (21)	1 (13)
Progressive disease	3 (14)	1 (7)	2 (25)
ORR – % (95% CI)	68 (45–86)	71 (42–92)	63 (25–92)
Time to response, months; median (range)	2.0 (1.8–5.3)	–	–
Duration of response, months; median (range)	Not reached (0.0–5.6)	–	–

# Carcinoma de Merkel avançado: Nivolumabe neoadjuvante – Checkmate 358


## Neo-adjuvant nivolumab in resectable MCC CheckMate-358 (Topalian SL et al.: abstract 9505)




- Neo-adjuvant anti-PD-1 treatment resulted in high response rates after only 2 doses
- If this leads to a survival advantage versus surgery only has to be investigated in randomized comparative trials


# E no CEC de pele?

## Até 2018 apenas relatos de caso...


 **JAAD**  
Journal of the American Academy of Dermatology



### PD-1 inhibition for cutaneous squamous cell carcinoma: A study of six consecutive cases




 PlumX Metrics

DOI: <https://doi.org/10.1016/j.jaad.2017.04.751>

 Article Info

Importance: Currently there are no well-

JAMA Network

 JAMA Dermatology  

**Observation**

January 2016

### A Case Report of Unresectable Cutaneous Squamous Cell Carcinoma Responsive to Pembrolizumab, a Programmed Cell Death Protein 1 Inhibitor

Anne Lynn S. Chang, MD<sup>1</sup>; Jinah Kim, MD, PhD<sup>1,2</sup>;  
Richard Luciano, NP<sup>3</sup>; [et al](#)



# Anti PD-1 no tratamento do CEC pele avançado

- 2 coortes (n = 85 pacientes):
  - Coorte de expansão do estudo fase I
  - Coorte estudo *pivotal* de fase II
- População:
  - CEC localmente avançado e/ou metastático não candidato a cirurgia por um dos motivos:
    - Recorrência de doença após 2 ou mais procedimentos cirúrgicos cuja expectativa de cura com nova cirurgia é baixa;
    - Cirurgia sujeita a complicações ou deformidades





# Cemiplimab no tratamento CEC pele avançado

## Características da população

Characteristic	Expansion Cohorts of the Phase 1 Study (N=26)	Metastatic-Disease Cohort of the Phase 2 Study (N=59)
<b>Age</b>		
Median (range) — yr	73 (55–88)	71 (38–93)
≥65 yr — no. (%)	21 (81)	43 (73)
<b>Male sex — no. (%)</b>		
	21 (81)	54 (92)
<b>ECOG performance status score — no. (%)<sup>†</sup></b>		
0	10 (38)	23 (39)
1	16 (62)	36 (61)
<b>Primary site of cutaneous squamous-cell carcinoma — no. (%)</b>		
Head or neck	18 (69)	38 (64)
Arm or leg	5 (19)	12 (20)
Trunk	2 (8)	9 (15)
Penis	1 (4)	0
<b>Previous systemic therapy for cutaneous squamous-cell carcinoma — no. of patients (%)<sup>‡</sup></b>		
No regimens	8 (31)	26 (44)
Any regimen	15 (58)	33 (56)
1 regimen	15 (58)	22 (37)
≥2 regimens	0	11 (19)
<b>Previous radiotherapy for cutaneous squamous-cell carcinoma — no. (%)</b>		
	20 (77)	50 (85)
<b>Extent of cutaneous squamous-cell carcinoma — no. (%)</b>		
Distant metastasis	8 (31)	45 (76)
Regional metastasis only	8 (31)	14 (24)
Locally advanced progression only	10 (38)	0

Idosos

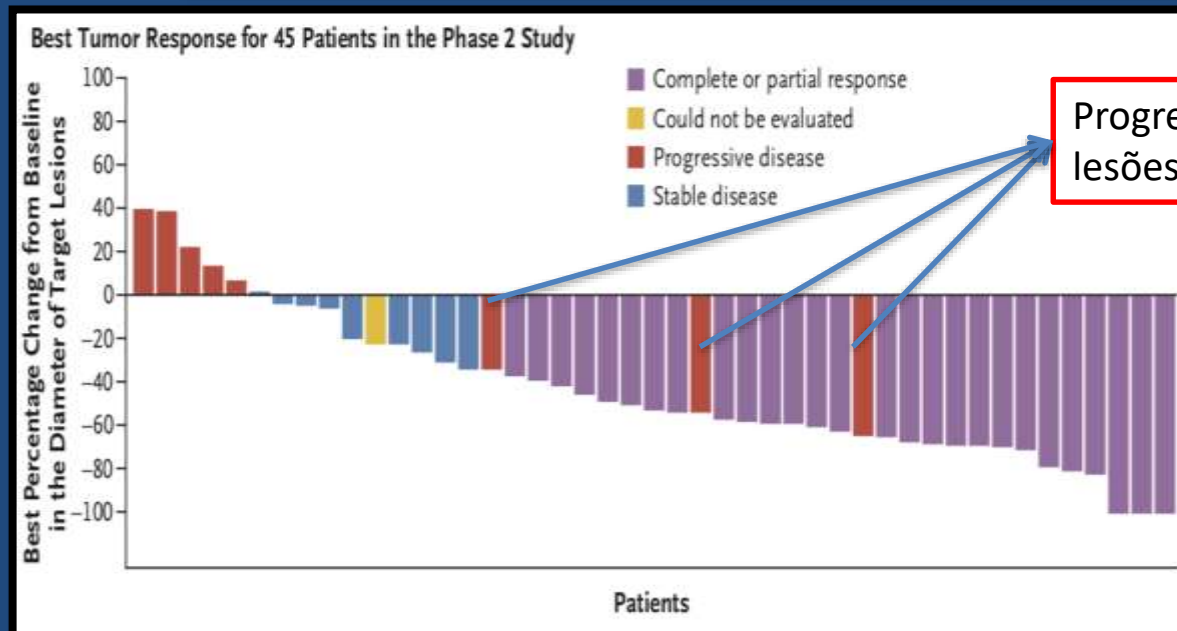
Cabeça e pescoço

Previamente tratado

# Cemiplimab: Taxa de resposta

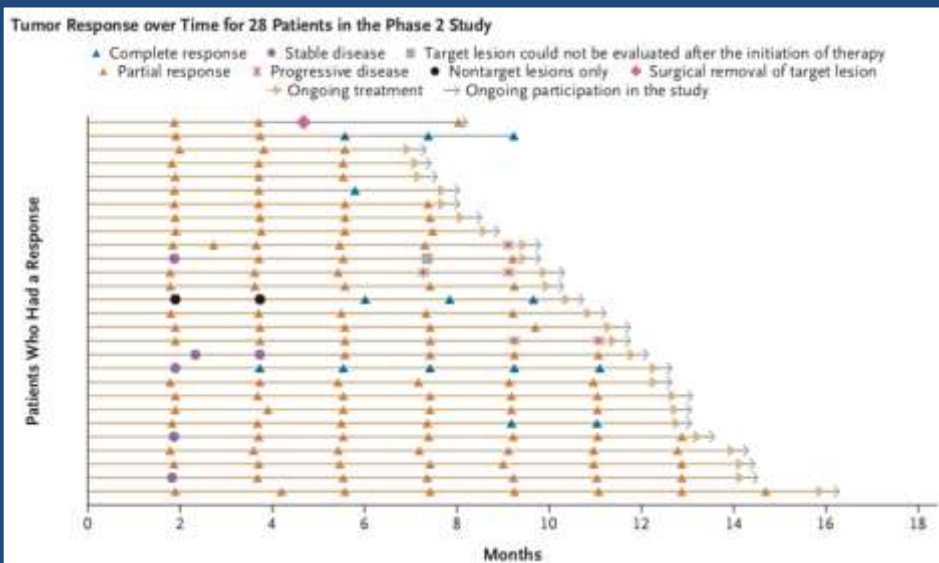
Outcome	Expansion Cohorts of the Phase 1 Study (N=26)	Metastatic-Disease Cohort of the Phase 2 Study (N=59)
Best overall response — no. (%)†		
Complete response	0	4 (7)
Partial response	13 (50)	24 (41)
Stable disease	6 (23)	9 (15)
Progressive disease	3 (12)	11 (19)
Could not be evaluated‡	3 (12)	7 (12)
Nontarget lesions only§	1 (4)	4 (7)
Objective response — % (95% CI)	50 (30–70)	47 (34–61)
Durable disease control — % (95% CI)	65 (44–83)	61 (47–74)
Median observed time to response (range) — mo¶	2.3 (1.7–7.3)	1.9 (1.7–6.0)

ORR: 50%  
DCR: 65%

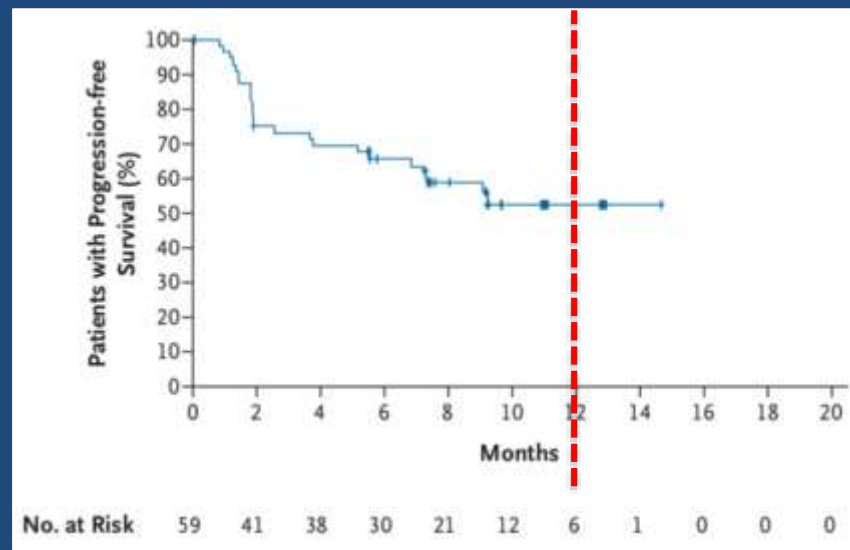


Progressão de doença devido novas lesões ou aumento lesões não-alvo

# Cemiplimab em CEC pele: Tempo duração resposta e SLP



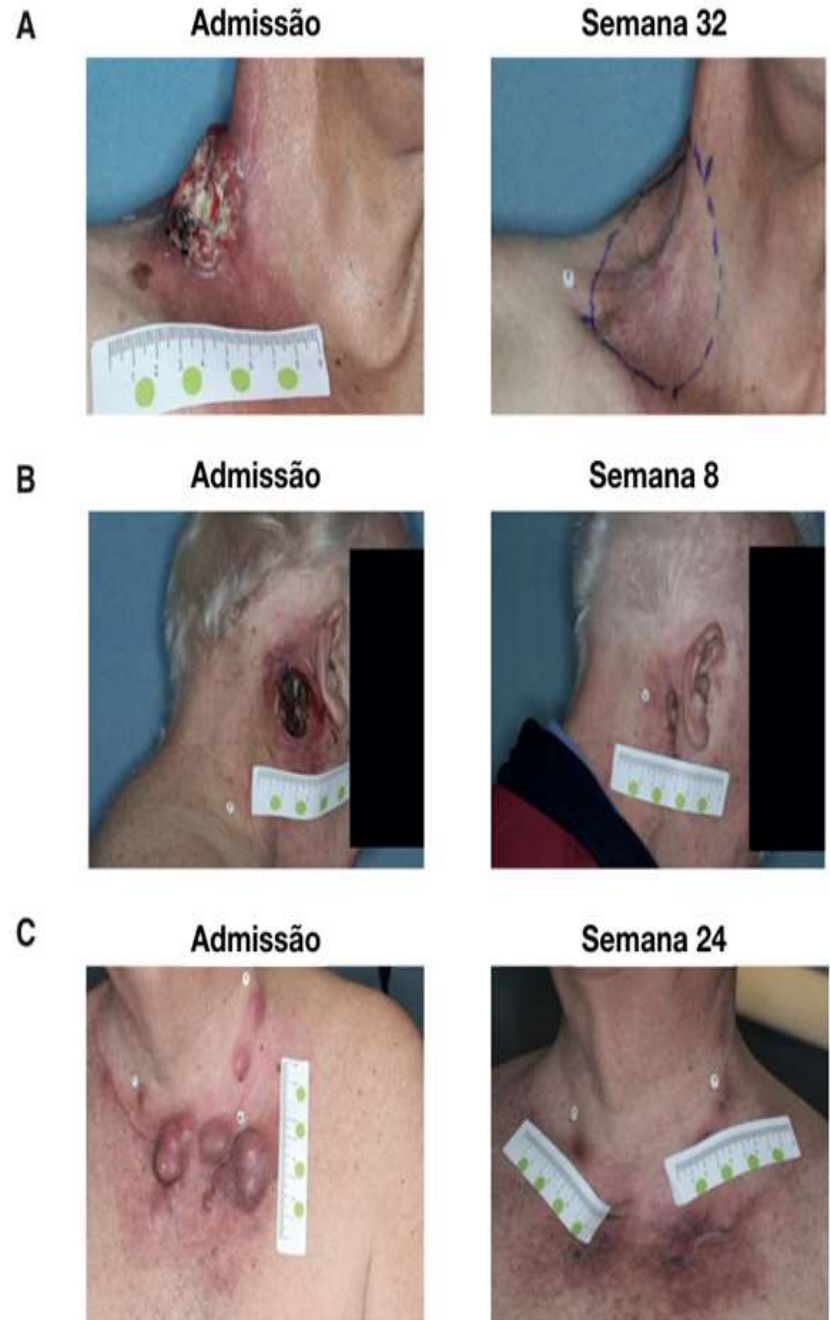
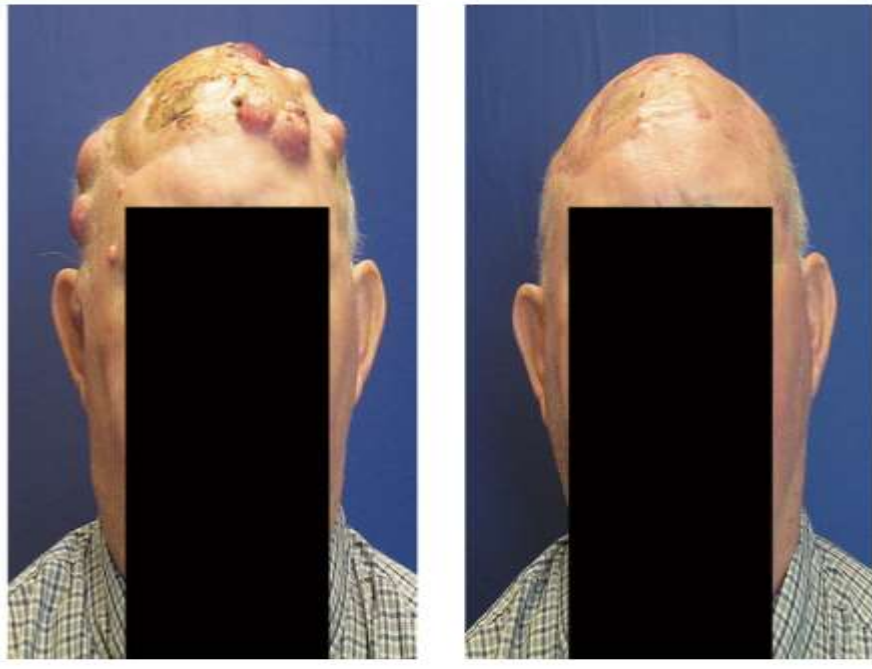
SLP em 12 meses: 53%



Rápido tempo para resposta  
23/26 resposta mantida após *cutoff*  
3 progressão de doença  
1 remoção cirúrgica

# Effect of Cemiplimab in Patients with Advanced Cutaneous Squamous-Cell Carcinoma

Patient in Phase 1 Study



# CEC pele avançado: Ex





09/05/17



15/06/17



01/08/17



22/09/17

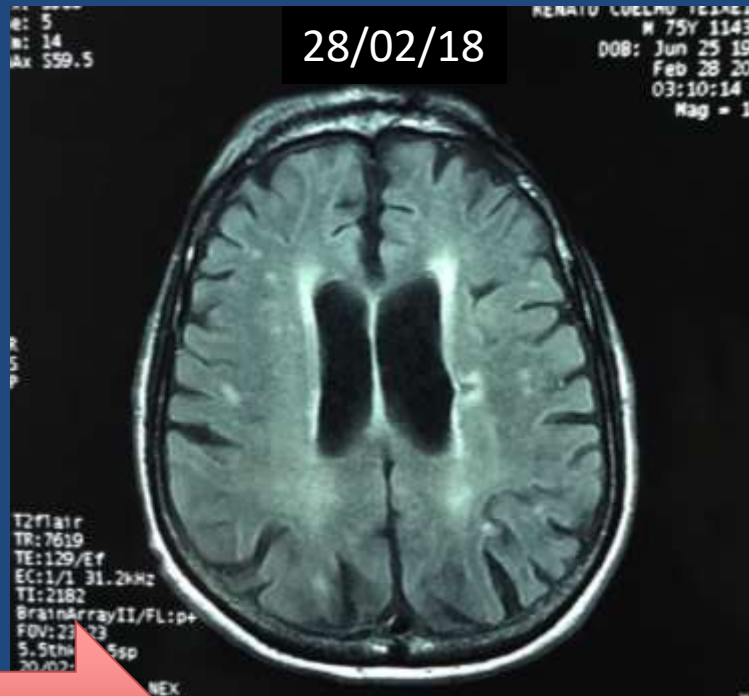
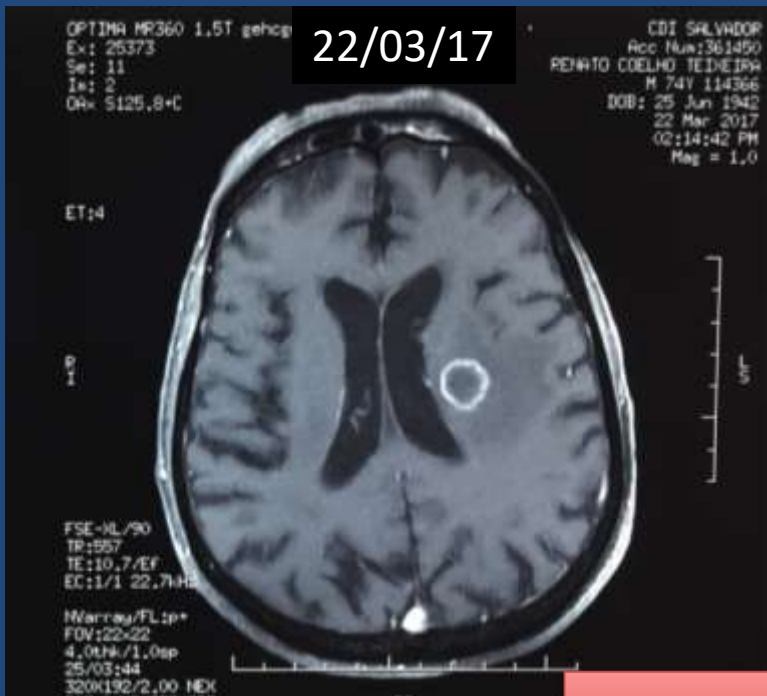


16/12/17



06/03/18



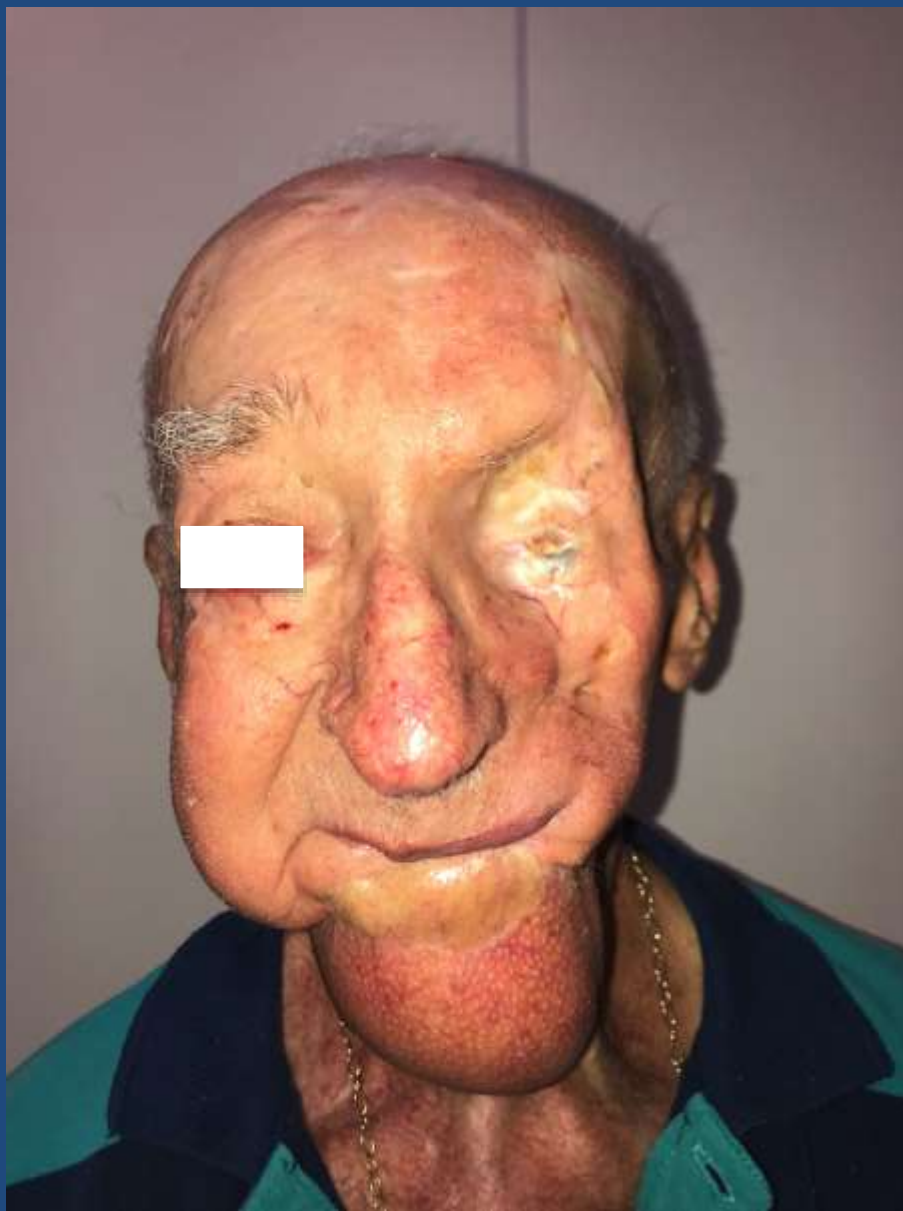


6 meses tratamento





# Baseline → Após 6 meses de Pembrolizumabe



# Os outros tumores de pele podem ser tratados com imunoterapia?

- Uso de anti PD-1/PD-L1 é nova realidade no CEC pele e MCC avançados:
  - Alta taxa de resposta na 1ª linha
  - Resposta durável
  - Toxicidade já conhecida, aceitável e manejável
- Raridade da doença permite avaliação de eficácia com estudo de fase II
- Aprovação no Brasil:
  - MCC avançado: Avelumabe
  - CEC avançado: Nenhum
- Neoadjuvância: Resultado preliminar é promissor
- Estudos na adjuvância já estão em andamento

# Novos desafios para a prática clínica

- Ausência de biomarcador de resposta
  - Sem associação status MCPyV ou expressão PD-L1
  - 30 - 40% resistência primária na 1ª linha
- Estudos não incluíram pacientes imunossuprimidos
  - HIV, malignidades hematológicas, transplantados, tto imunossupressor



**Obrigado!**

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