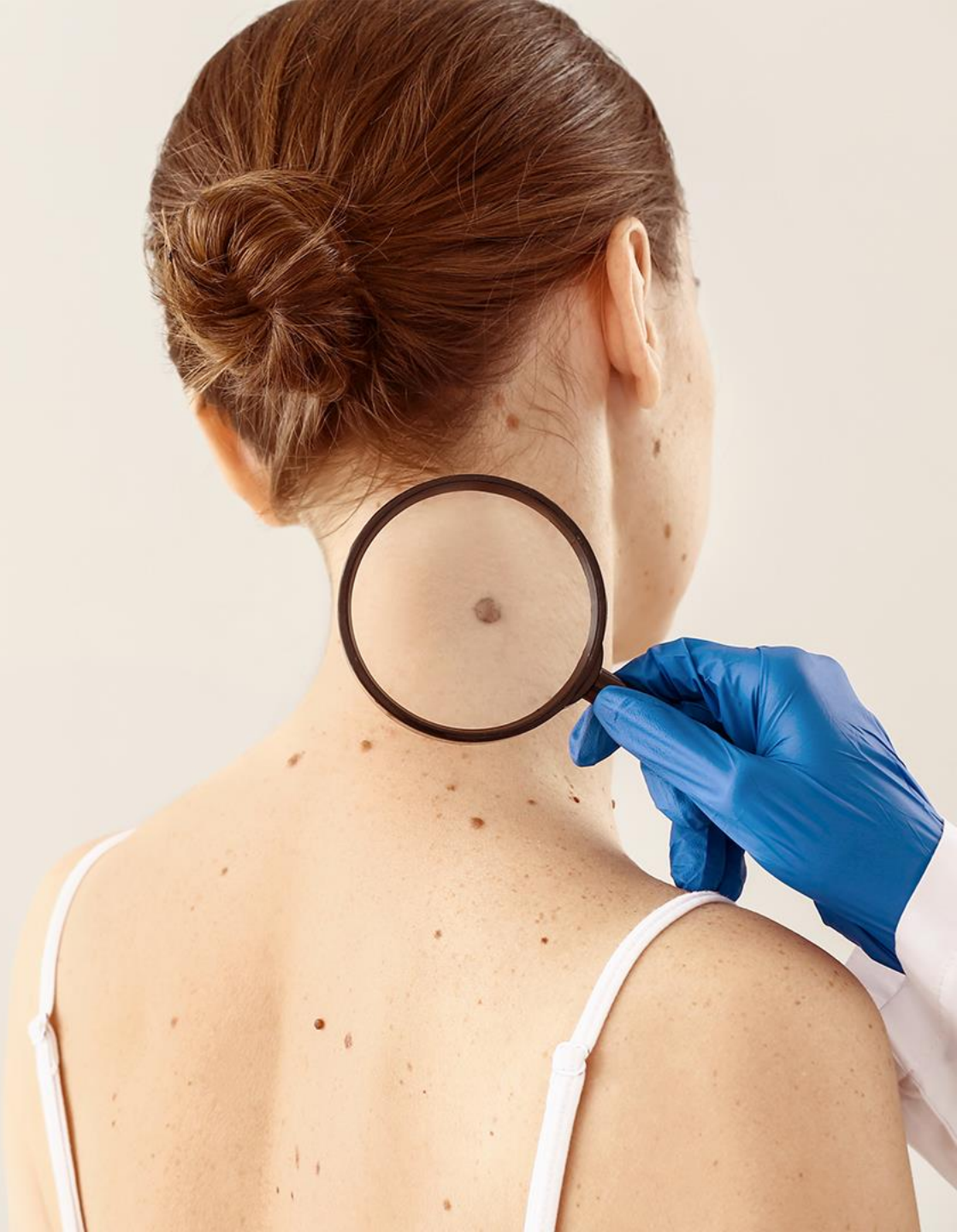
VII SIMPÓSIO INTERNACIONAL DE Melanoma

HOTEL PULLMAN VILA OLÍMPIA

29 E 30 DE NOVEMBRO 2019



VII SIMPÓSIO INTERNACIONAL DE Melanoma
HOTEL PULLMAN VILA OLÍMPIA
29 E 30 DE NOVEMBRO 2019

Carcinoma de Merkel: de onde viemos e onde chegamos

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Passo Fundo-RS

Instituto do Câncer
Hospital São Vicente

HSVP
Hospital São Vicente de Paulo

Declaração de Conflito de Interesses

VII SIMPÓSIO INTERNACIONAL DE Melanoma
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29 E 30 DE NOVEMBRO 2019

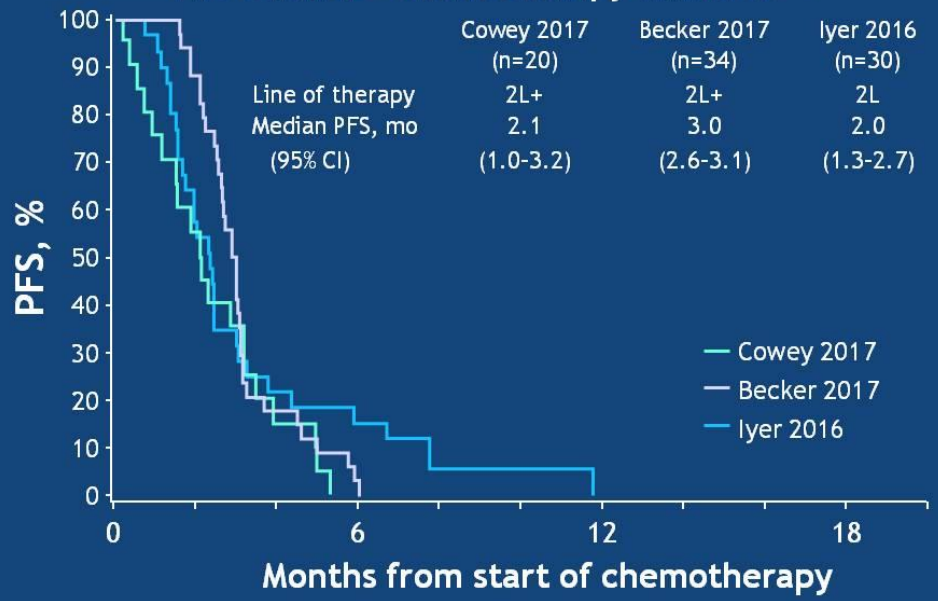
De acordo com a resolução do **Conselho Federal de Medicina nº 1595/2000** e **Resolução da Diretoria Colegiada da ANVISA nº 96/2008**, eu declaro que:

- Pesquisa Clínica – Como investigador: **Novartis, Roche, Astellas, Merck, Bayer**
- Apresentações Científicas – Como palestrante: **MSD**, **BMS**, **Novartis, Janssen**
- Atividades de Consultoria – Como membro de Advisory Boards: **Novartis, BMS, MSD**

Merkel cell carcinoma

- Rare, aggressive skin cancer associated with poor survival[1]
  - MCPyV+ in ≈80%[2]
  - Risk factors: UV light, advanced age, and immunosuppression[1,3]
- MCC is a chemo-sensitive disease, but responses are seldom durable[4-6]

PFS with 2L+ chemotherapy in mMCC[4-6,*]



2L+, second line or later; **MCPyV**, Merkel cell polyomavirus; **mMCC**, metastatic Merkel cell carcinoma; **PFS**, progression-free survival
* Includes both immunocompetent and immunocompromised patients

1. Lebbé C, et al. *Eur J Cancer*. 2015;51(16):2396-403. 2. Feng H, et al. *Science*. 2008;319(5866):1096-100. 3. NCCN Clinical Practice Guidelines. Merkel cell carcinoma. V1.2018. 4. Cowey CL, et al. *Future Oncol*. 2017;13(19):1699-1710. 5. Becker J, et al. *Oncotarget*. 2017;8(45):79731-41. 6. Iyer JG, et al. *Cancer Med*. 2016;5(9):2294-301.

JAVELIN Merkel 200 (NCT02155647)
Phase II, prospective, open-label, international, multicentre trial
Part A cohort, mMCC 2L+ N=88

Patients: key eligibility criteria
• Histologically confirmed stage IV MCC • Immune-competent status • Unselected for PD-L1 expression or MCPyV status • ECOG PS 0–1 and adequate end-organ function

→

Treatment
Avelumab 10 mg/kg IV Q2W until confirmed PD*

→

Part	Key assessments
A 2L+	Primary endpoint: BOR by RECIST v1.1 per IRC
	Secondary endpoints: DOR; PFS; OS; safety and tolerability

1. Kaufman HL et al. Lancet Oncol. 2016;17:1374–1385; 2. Kaufman HL AACR 2017. Abstract CT079 (presentation);.

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)

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

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

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

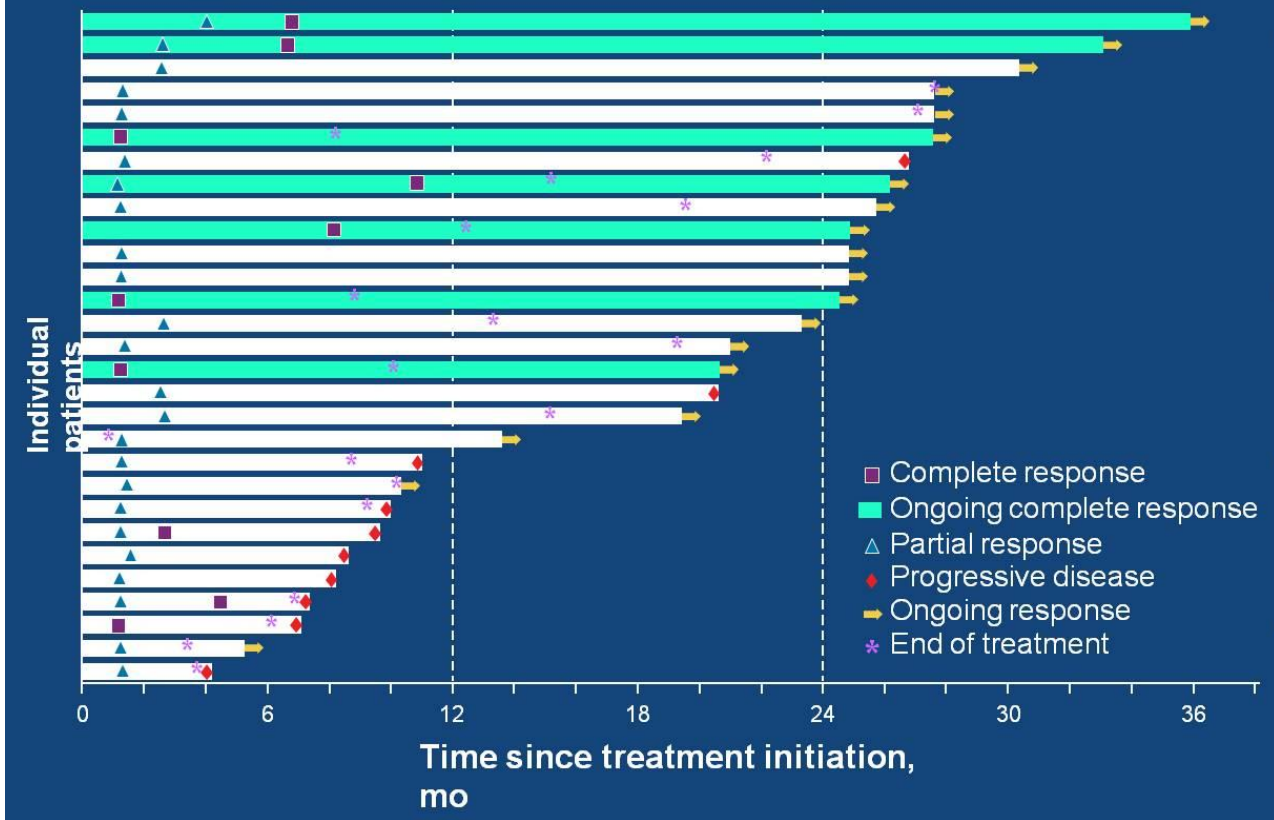
Patient responses remain unchanged from the 1-y analysis[1]

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.

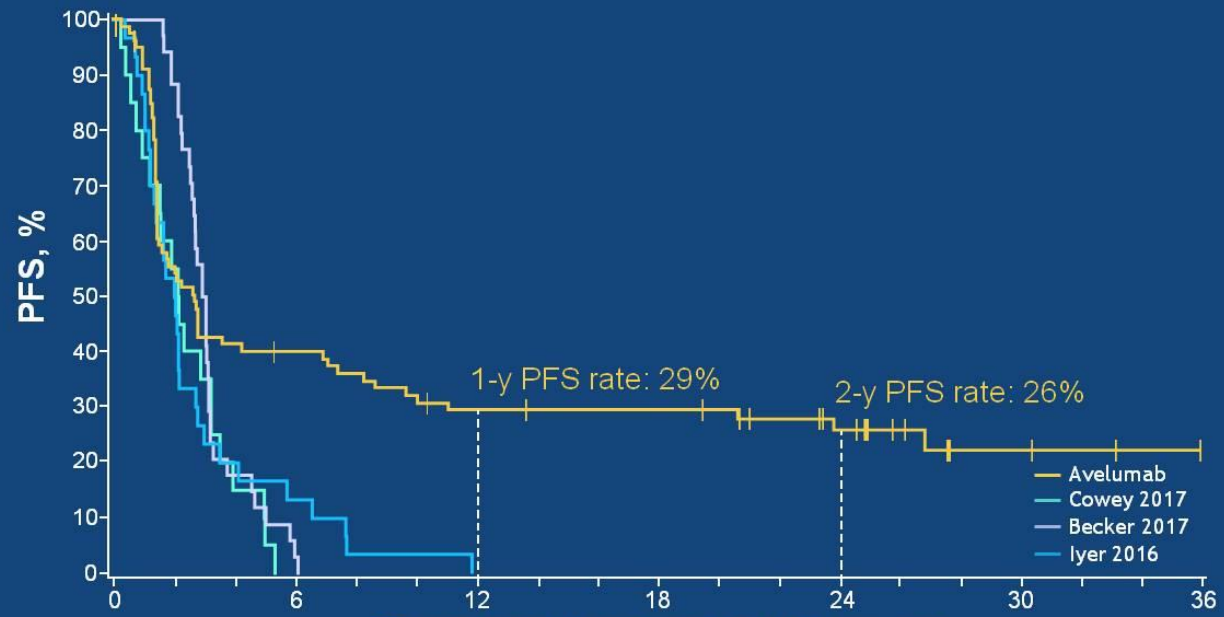
Time to and duration of response (n=29)



- 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 ≥2 y (95% CI, 46%-81%)*
- PD in 10 responders (most between 6-12 mo; no predictors)

*Based on Kaplan-Meier estimate

Progression-free survival with avelumab and retrospective chemotherapy data[1-3,*]

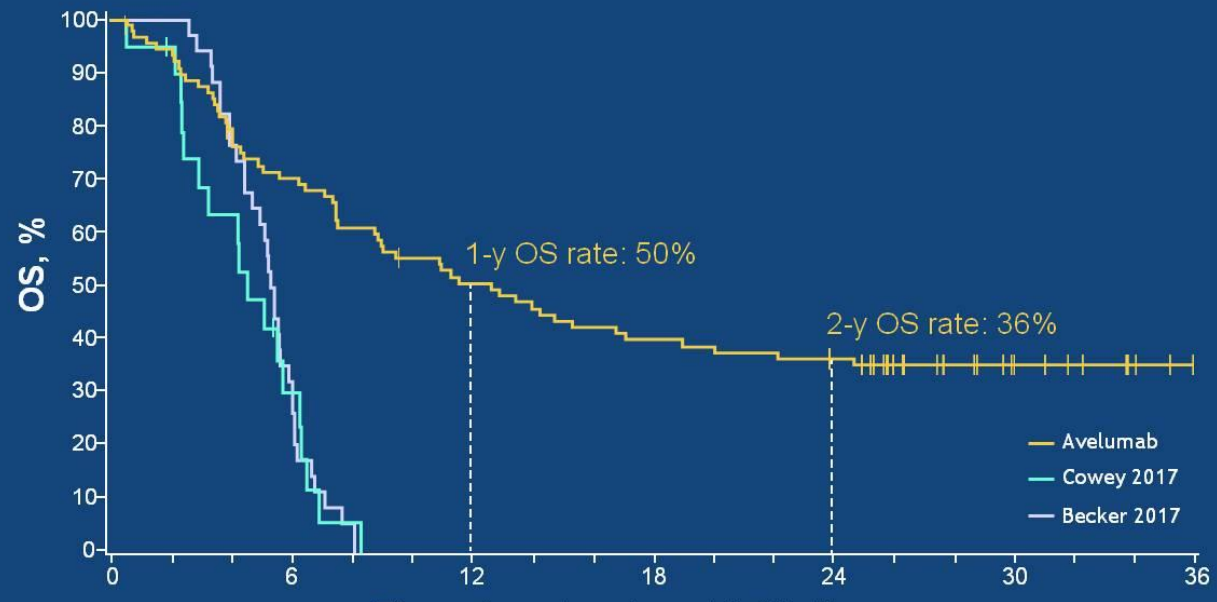


Number at risk																			
Avelumab	88	43	32	30	27	24	21	20	20	20	19	16	13	8	3	3	2	1	0
Cowey 2017	20	11	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Becker 2017	34	30	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Iyer 2016	30	15	6	4	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0

* This figure is for illustrative purposes only and is not a direct head-to-head comparison; it incorporates multiple different data sets and is not from a randomized clinical trial

1. Cowey CL, et al. *Future Oncol*. 2017;13(19):1699-1710. 2. Becker J, et al. *Oncotarget*. 2017;8(45):79731-41. 3. Iyer JG, et al. *Cancer Med*. 2016;5(9):2294-301.

Overall survival with avelumab and retrospective chemotherapy data[1,2,*]



Number at risk																			
Avelumab	88	82	68	60	52	46	42	38	35	33	32	31	29	19	13	8	6	3	0
Cowey 2017	20	17	12	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Becker 2017	34	34	26	9	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0

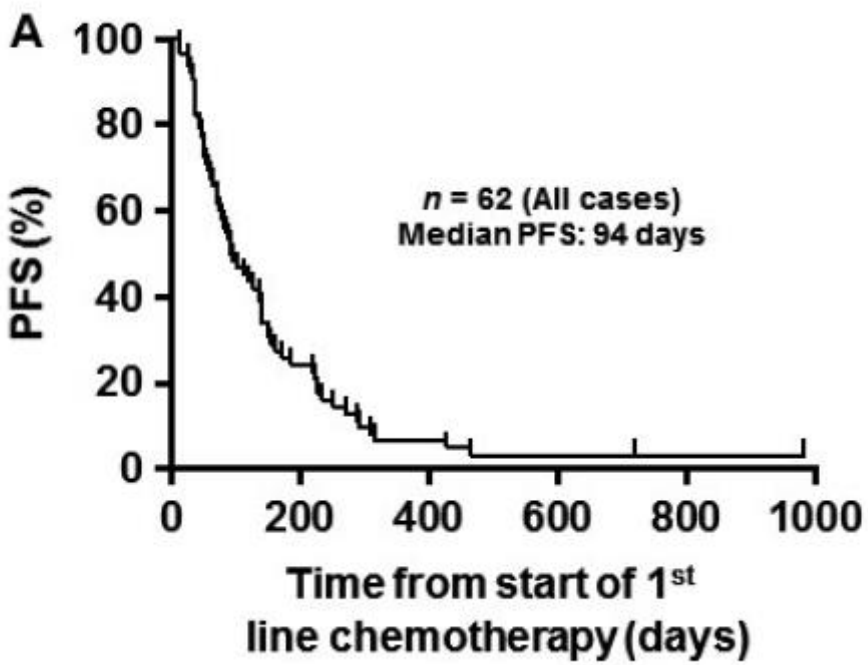
OS, overall survival

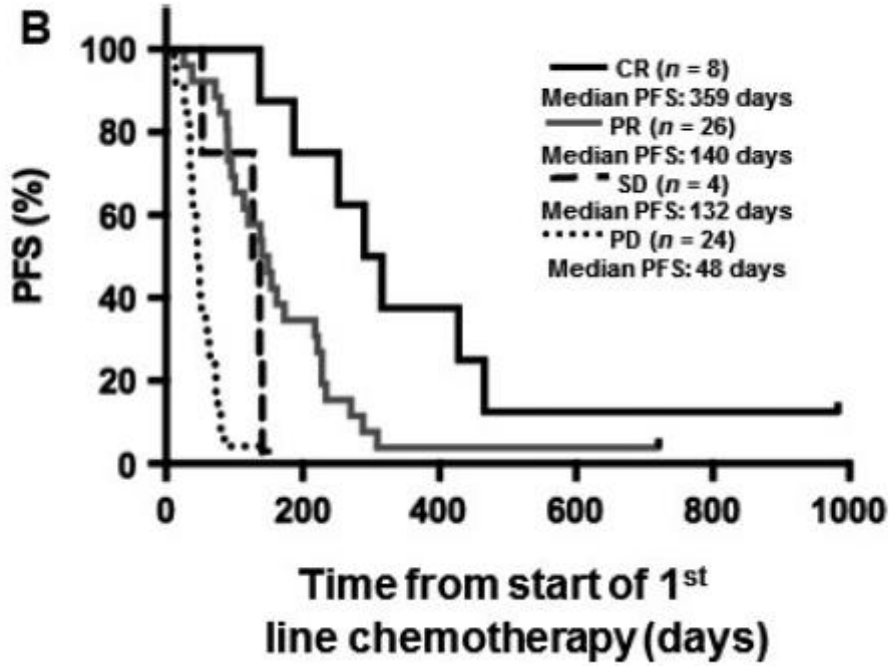
* This figure is for illustrative purposes only and is not a direct head-to-head comparison; it incorporates multiple different data sets and is not from a randomized clinical trial

1. Cowey CL, et al. *Future Oncol*. 2017;13(19):1699-1710. 2. Becker J, et al. *Oncotarget*. 2017;8(45):79731-41.

QT em 1ª linha

RR 55%





Iyer JG et al. Cancer Med 2016; published online July 19

JAVELIN Merkel 200 (NCT02155647)
Phase II, prospective, open-label, international, multicentre trial
Part A cohort, mMCC 2L+ N=88
Part B cohort, mMCC 1L N=112

Patients: key eligibility criteria

- Histologically confirmed stage IV MCC
- Immune-competent status
- Unselected for PD-L1 expression or MCPyV status
- ECOG PS 0–1 and adequate end-organ function

Treatment

Avelumab 10 mg/kg IV Q2W until confirmed PD*

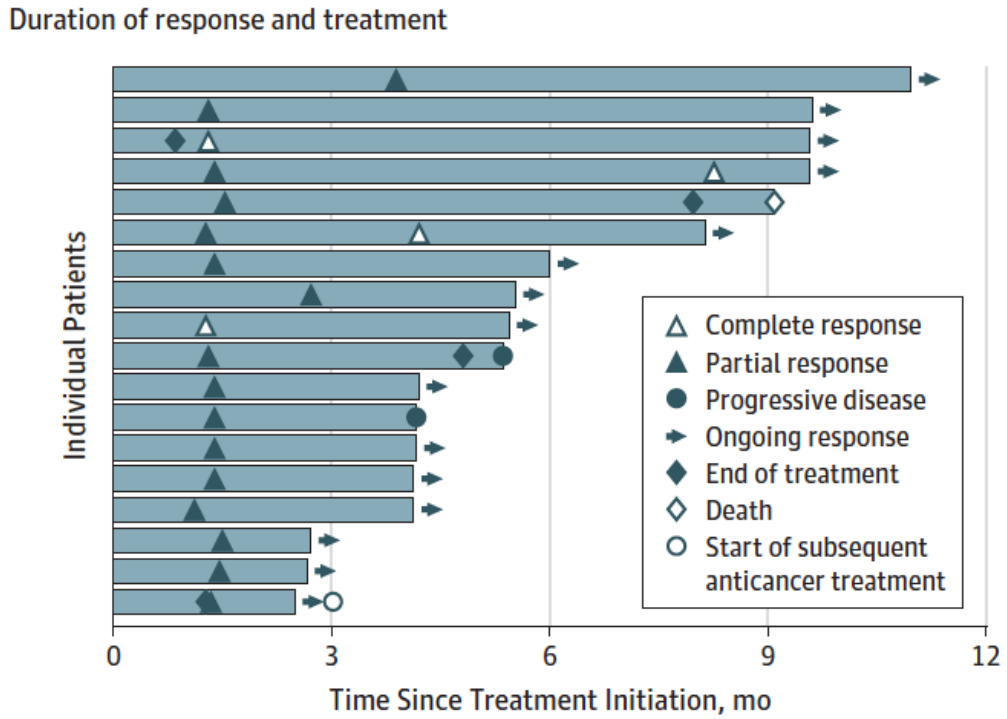
Part	Key assessments
A 2L+	Primary endpoint: BOR by RECIST v1.1 per IRC
	Secondary endpoints: DOR; PFS; OS; safety and tolerability
B 1L	Primary endpoint: durable response†
	Secondary endpoints: BOR; DOR; PFS; OS; safety

1. Kaufman HL et al. Lancet Oncol. 2016;17:1374–1385; 2. Kaufman HL AACR 2017. Abstract CT079 (presentation);.

JAVELIN Merkel 200 parte B: análise interina

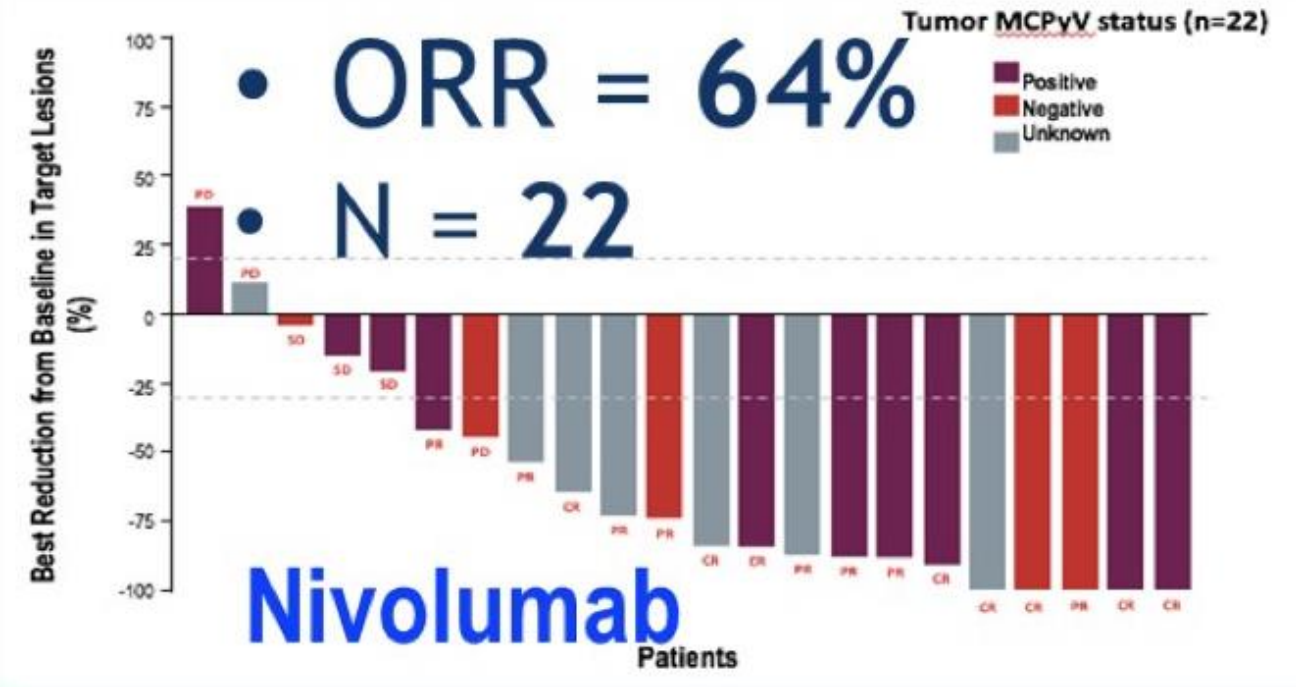
N=39
mFU 5.1m

Outcome	Patient Follow-up Group ≥3 mo	≥6 mo
Response[a]		
Confirmed ORR, % (95% CI)	62.1 (42.3-79.3)	71.4 (41.9-91.6)
Confirmed BOR, No. (%)		
Complete response	4 (13.8)	4 (28.6)
Partial response	14 (48.3)	6 (42.9)
Stable disease	3 (10.3)	1 (7.1)
Progressive disease	7 (24.1)	2 (14.3)
Nonevaluable[b]	1 (3.4)	1 (7.1)
Response durability[c]		
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)



JAMA Oncol. Published online March 22, 2018

Nivolumabe em 1ª linha



Topalian S et al. AACR 2017

Trial design (NCT02267603)

Multi-center (12 sites in US), single arm, open label, Phase II trial

Patients: key eligibility criteria

- 1st systemic therapy
- Metastatic or recurrent locally advanced MCC

Treatment

Pembro (anti-PD1, IgG4 mAb, humanized)
2 mg/kg IV every three weeks for up to 2 years

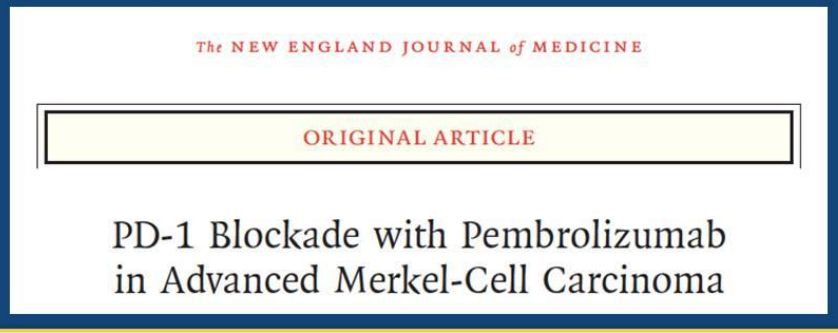
Key assessments

Primary endpoint: ORR (CR + PR, RECIST v1.1)

- Tumor evaluation q 9 or 12 wks

Secondary endpoints:
PFS, DOR, OS
Exploratory endpoints:
MCPyV, PD-1, and PD-L1 status

Early results from 26 pts with 33 weeks median follow-up
(Nghiem, et al NEJM 2016)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma

+ Reporting on completed enrollment of 50 patients with long-term follow-up (2 extra years)

Patient characteristics

50 patients enrolled: 1/2015 to 5/2017

(First 26 patients 01/2015 - 12/2015, expansion cohort of 24 patients 03/2016 - 05/2017)

- Median age: 70 years (range, 46–91, 80% of patients were ≥ 65 yrs of age)
- 43 patients (86%) had distant metastatic MCC
- 7 patients (14%) had recurrent locally advanced MCC

- Tumor viral status (N=50): 64% positive; 36% negative

Treatment-related adverse events (TRAEs)

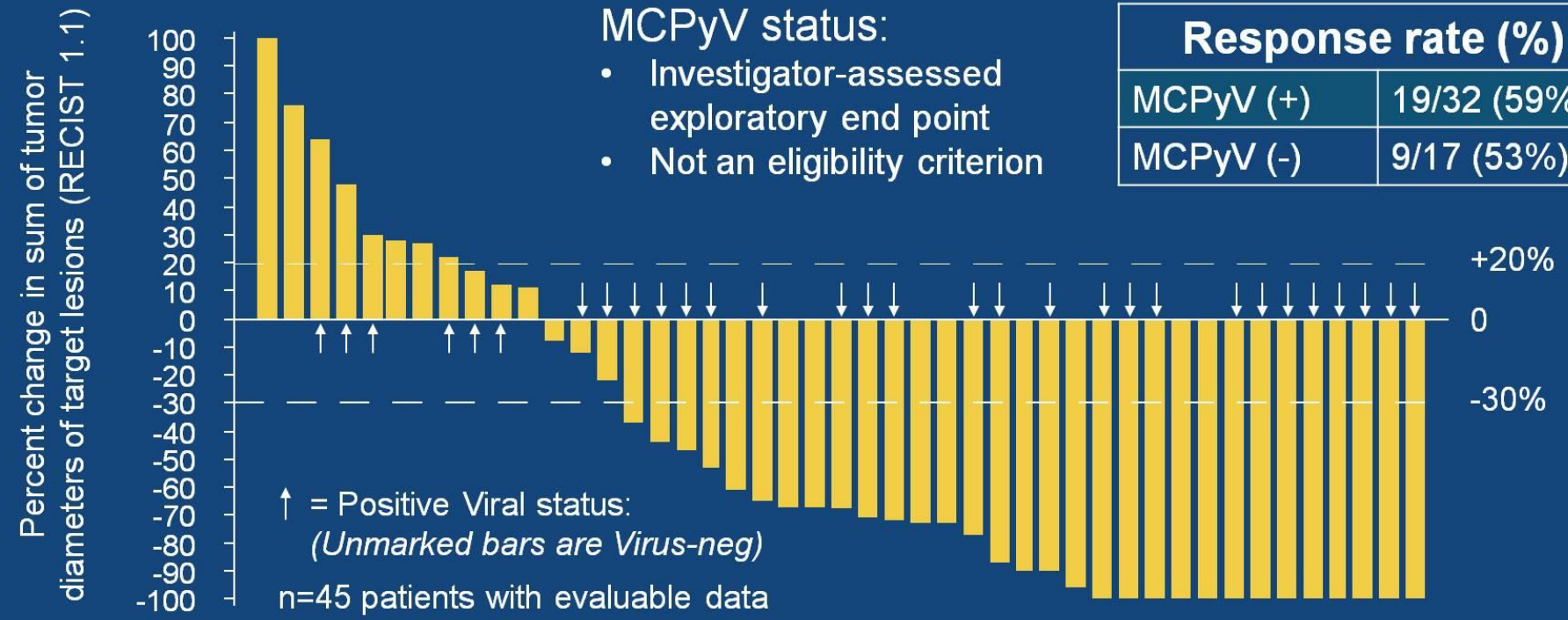
- TRAEs occurred in 48/50 (96%) patients (any grade)
- TRAEs led to discontinuation of pembrolizumab in 7/50 patients (14%)
- Grade ≥3 TRAEs in 14/50 patients (28%); 1 treatment-related death

Treatment response
(per independent central review, RECIST 1.1)

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

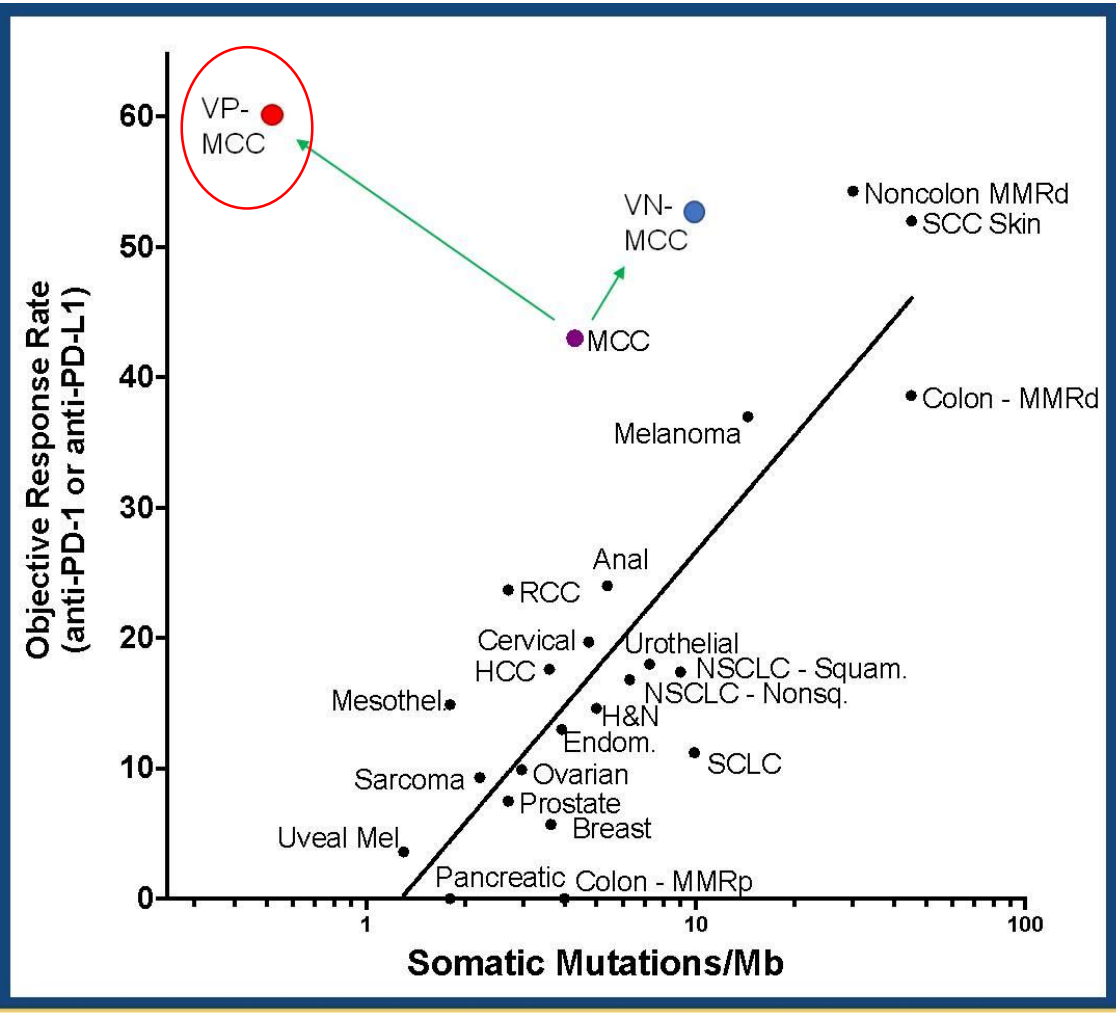
	N = 50	
	n	%
ORR	28	56
Best overall response		
CR	12	24
PR	16	32
SD	5	10
PD	16	32
No assessment	1	2

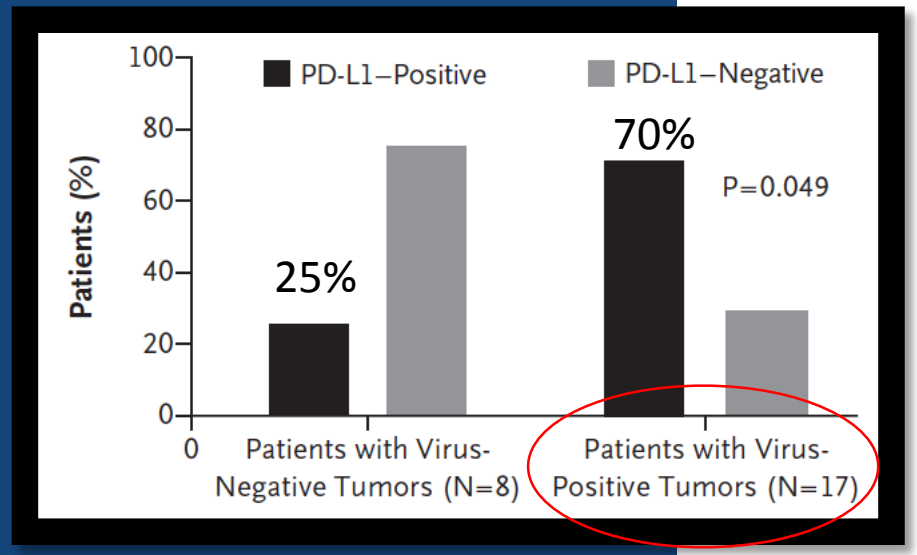
Radiologic tumor response to pembrolizumab in patients per viral status



Response rate (%)	
MCPyV (+)	19/32 (59%)
MCPyV (-)	9/17 (53%)

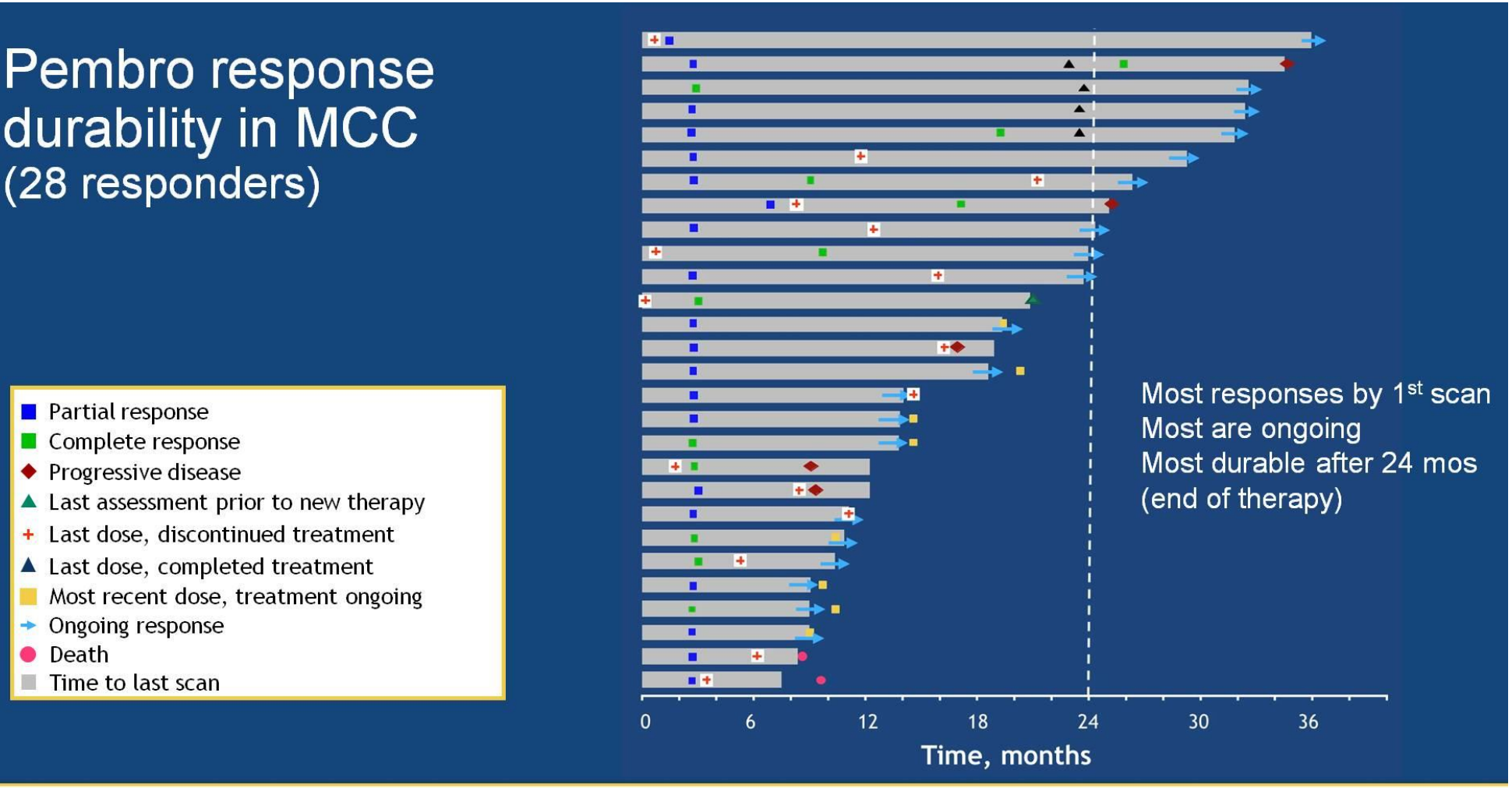
Correlation between Tumor Mutational Burden and ORR



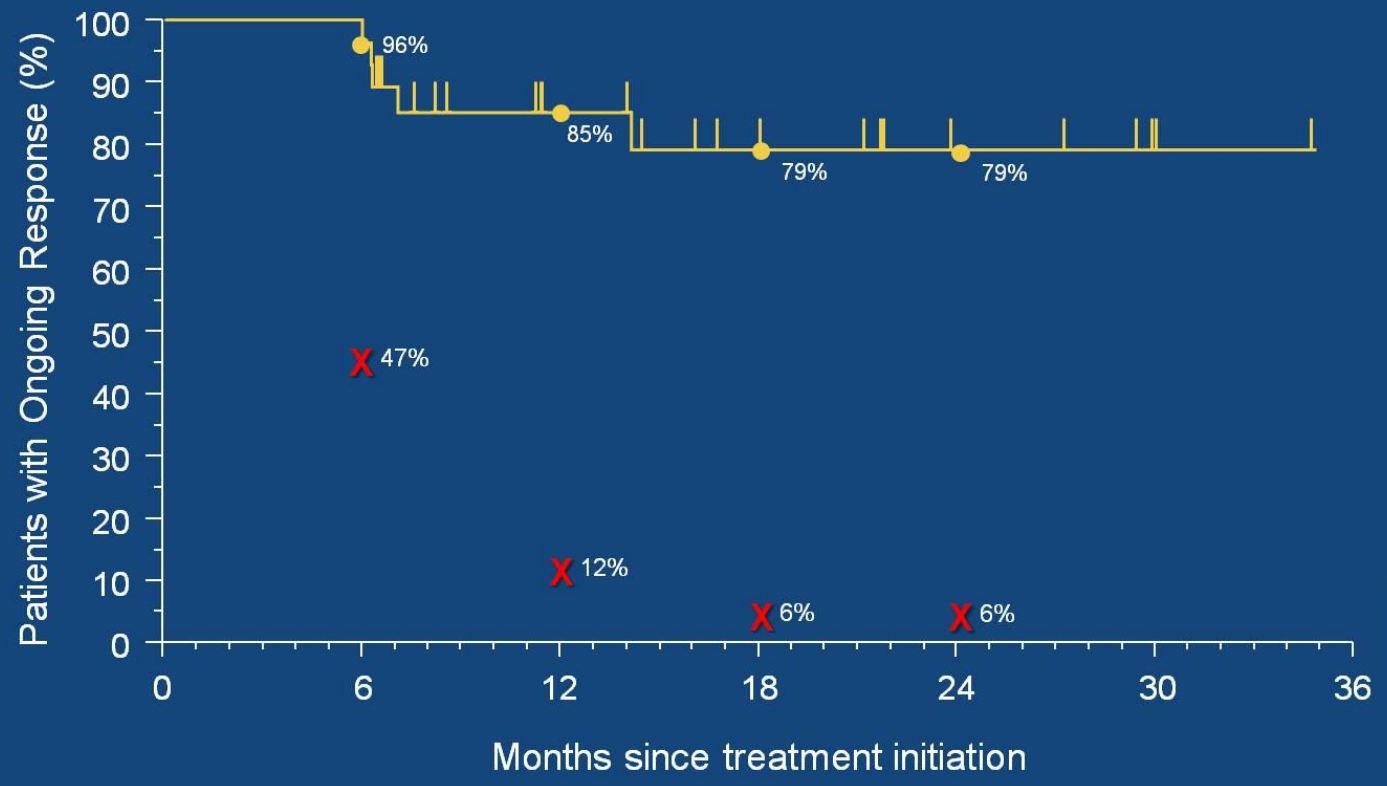


cancer immunotherapy trials network

Pembro response durability in MCC
(28 responders)



Responses are durable



Pembrolizumab 1st line trial (n= 28)

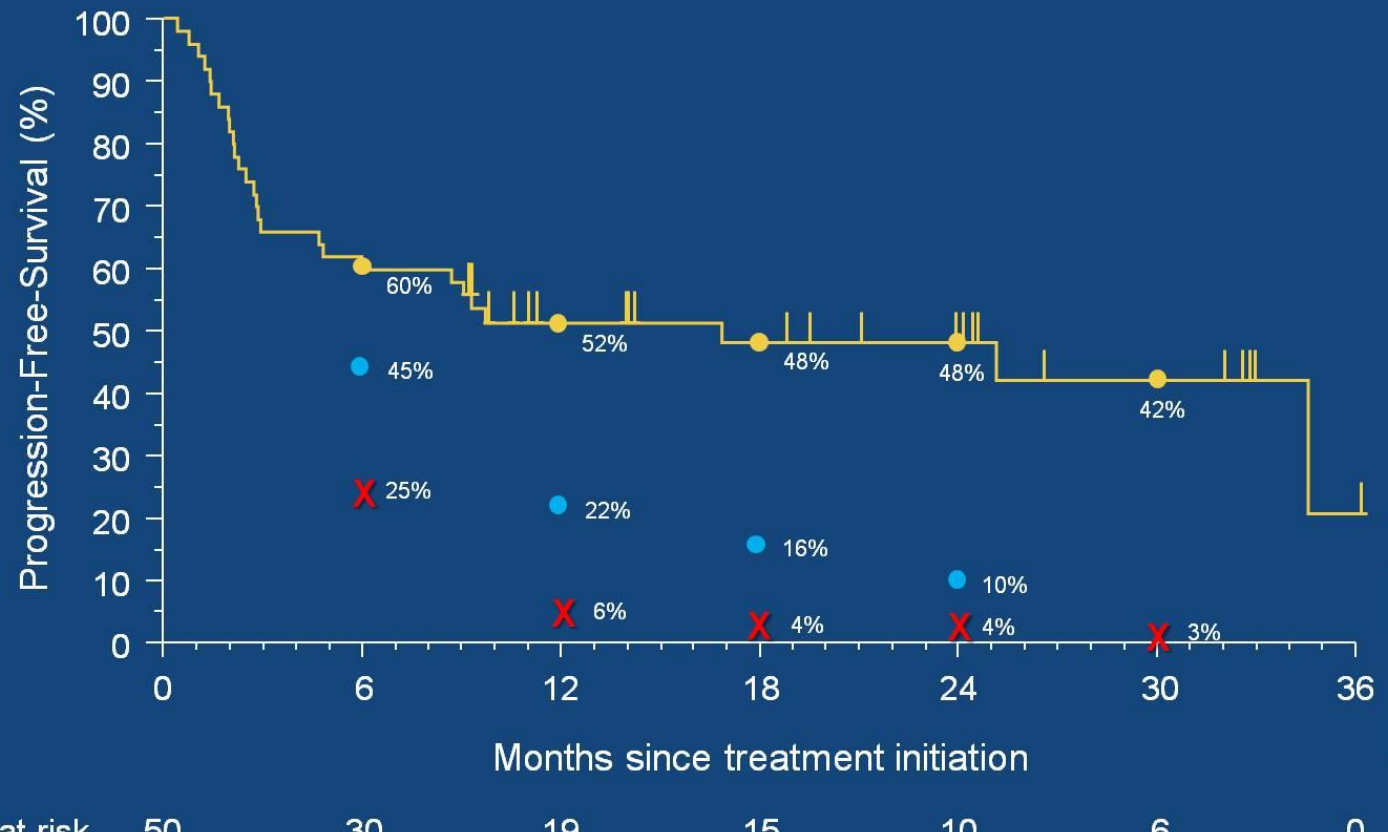
X 1st line chemotherapy historical data (n= 34) Iyer, et al (Cancer Medicine, 2016)

n= responder
(Best ORR : CR or PR)

Median response duration (months)	
Pembrolizumab	NR [5.9, 34.5+, range]
Chemo (Iyer)	5.6

Database Cutoff Date : 06Feb2018

Progression-free survival with pembrolizumab for MCC



Pembrolizumab 1st line (N= 50)

X 1st line chemotherapy historical data (N= 62) Iyer, et al (Cancer Medicine, 2016)

● 1st line chemotherapy historical data (N=67) Cowey, et al (Future Oncology, 2017)

Median PFS (months)	
Pembrolizumab	16.8 [95% CI 4.6,.]
Chemo (Iyer)	3.1 [0.4-33, range]
Chemo (Cowey)	4.6 [95% CI 3.0-7.0]

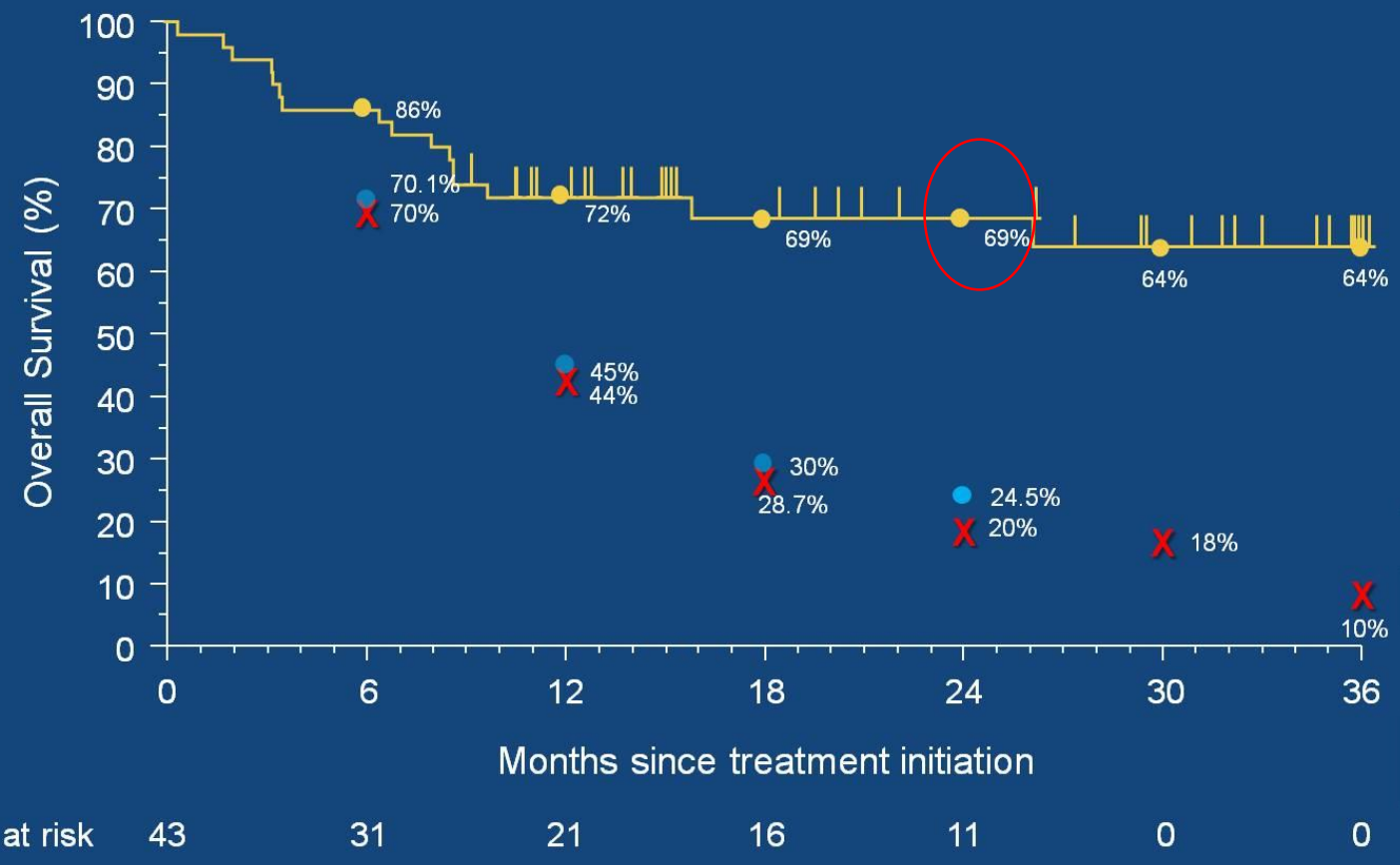
Database Cutoff Date : 06Feb2018

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Paul Nghiem, MD, PhD

cancer immunotherapy trials network

Overall survival with pembrolizumab for MCC



Pembrolizumab 1st line (N= 50)

1st line chemotherapy historical data (N= 62) Iyer, et al (Cancer Medicine, 2016)

1st line chemotherapy historical data (N=67) Cowey, et al (Future Oncology, 2017)

Median OS (months)	
Pembrolizumab	NR [95% CI 26.0,.]
Chemo (Iyer)	9.5
Chemo (Cowey)	10.2 [95% CI 7.4-15.2]

Database Cutoff Date : 06Feb2018

ADjuvant Avelumab in Merkel (ADAM)

- First ever Phase 3 RCT in MCC; NCT#03271372
- **N=100;** Avelumab versus **Placebo** (1:1)
- **Very high-risk MCC (clinically-detected LN mets)**
- RFS is the primary endpoint

Investigator-initiated (PI: Bhatia)
Funding Sponsor: EMD-Serono
Multi-center; 10 centers in the US

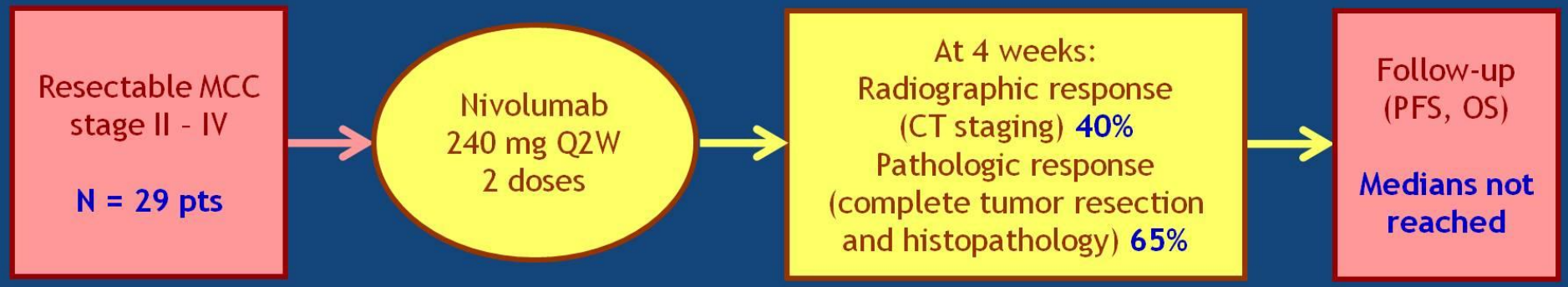
EA6174: An ECOG-ACRIN adjuvant MCC trial

- NCT03712605; activated in October 2018
- PI – Brian Gastman/Charles Hsu
- Stages I (no SLNB)-III
- Pembrolizumab vs observation
- N=500; Phase 3

Adjuvant Therapy of MCC with ICIs (ADMEC-O)

- Phase 2; NCT02196961
- N=177; Several centers in Germany (PI: Jürgen Becker, Dirk Schadendorf)
- Observation vs Nivolumab (1-year)
- Resected MCC; all stages
- DFS is the primary endpoint

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

PRESENTED BY: Selma Ugurel, MD
selma.ugurel@uk-essen.de

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29 E 30 DE NOVEMBRO 2019

Breaking avelumab resistance with combined ipilimumab and nivolumab in metastatic Merkel cell carcinoma?

Immune-checkpoint blockade (ICB) shows significant activity in metastatic Merkel cell carcinoma (MCC) but primary resistance remains a major clinical challenge [1, 2]. Here, we report a complete response to combined ipilimumab and nivolumab in a patient with metastatic MCC and primary resistance to the PD-L1 inhibitor avelumab.

A 60-year-old male with a known history of stage III MCC (UICC 2017, Merkel cell poliomavirus positive; Figure 1A) relapsed with limited retroperitoneal lymph node metastases and was treated with avelumab (10 mg/kg, q2w). He, however, experienced progressive disease (PD, RECIST 1.1; Figure 1B) after 3 months of treatment. Four months after salvage surgery of the retroperitoneal tumor mass, a CT scan showed a relapse again. A new adrenal metastasis was then treated with palliative radiation therapy. Unfortunately, the patient was hospitalized 4 months later with a painful new lymph node metastasis in the left axilla. A CT scan of chest and abdomen revealed new soft tissue, peritoneal, perihepatic, interenteric and retrosternal metastases (Figure 1C). At this point, a grand round recommended off-label combined immunotherapy with ipilimumab and nivolumab according to the ongoing CheckMate-358 study (NCT02488759). The patient received four applications of a combined immunotherapy (ipilimumab 1 mg/kg plus nivolumab 3 mg/kg, q3w). Apart from grade 1 fatigue (CTCAE 4.03) the patient did not experience any toxicity. A CT scan of chest and abdomen 4 weeks after the last dose of ipilimumab and nivolumab showed a complete remission (CR, RECIST 1.1; Figure 1C) without any signs of residual disease. Due to the complete response and the

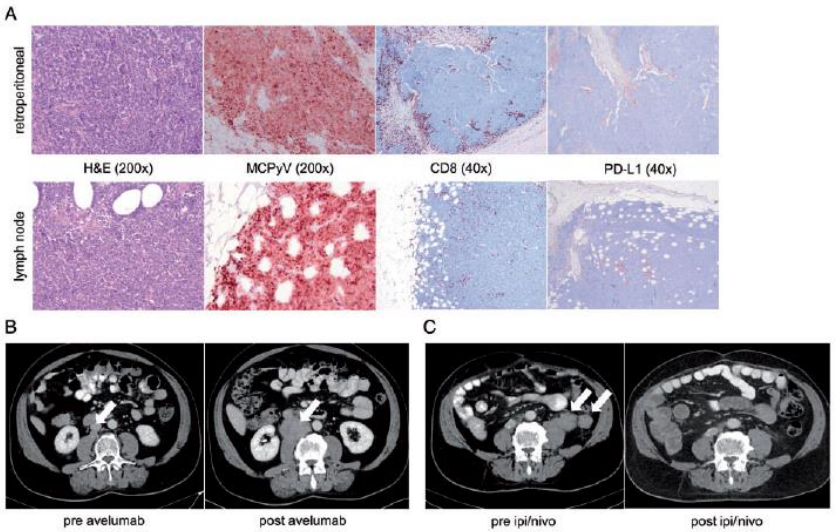

Figure 1. CT scans and tissue: (A) hematoxylin and eosin (H&E) staining as well as immunohistochemistry for Merkel cell poliomavirus, CD8 and PD-L1 (clone 22-8) of tissue obtained during salvage surgery after progression upon avelumab treatment (retroperitoneal, upper row) and of tissue (axillary lymph node metastasis, lower row) obtained before ipilimumab plus nivolumab. No significant differences in morphology or antigen expression could be observed. (B) CT scans carried out before and after seven cycles of avelumab illustrating primary resistance of the disease. (C) CT scans taken before and after four cycles of combined ipilimumab and nivolumab showing a complete remission of a representative abdominal tumor mass. White arrows indicate metastases.

A Phase 2, Randomized Study of Nivolumab (NIVO) and Ipilimumab (IPI) versus NIVO, IPI and Stereotactic Body Radiation Therapy (SBRT) for Metastatic Merkel Cell Carcinoma (MCC, NCT03071406) – a preliminary report.

Results

To date, 16 pts have been enrolled, including 4 treatment-naïve and 12 PD1/PDL1-refractory pts. 11 pts were male and 5 pts female. Median age at enrollment was 75.5. On Arm A, the RR was 80% (1 CR, 3 PR) in 4/5 evaluable pts. On Arm B, the RR was 17% (1 PR) among 6 evaluable pts. 4 pts are pending initial staging and 1 pt expired prior to first evaluation. Collectively, 2/8 (25%) PD1/PDL1refractory pts and 3/3 (100%) IT-naïve pts have achieved CR/PR. 7 pts experienced > G2 immune toxicity (1 G3 myocarditis, 1 G3 colitis, 1 G2 arthritis, 1 G2 cough, 3 G2 dermatitis, 1 G2 neurotoxicity, 1 G2 blurred vision, 1 G2 abdominal pain, 2 G2 hypothyroidism, 1 G2 renal insufficiency). 1 pt was taken off the trial due to toxicity.

Conclusões

- Tratamento com agentes anti-PD1/PD-L1 tem respostas duráveis e deve ser o tratamento de escolha em 1ª linha

- Tratamento em 1ª linha com imunoterapia tem melhor eficácia em comparação com 2ª linha (após QT)
  - TR: 60% x 30%
  - mSLP: 17m x 3m
  - mSG: NA x 12 m

- Várias questões pendentes:
  - Biomarcadores
  - Resistência primária e secundária
  - Duração ótima do tratamento nos respondedores
  - Retratamento para progressão após descontinuação
  - Adjuvância
  - Neoadjuvância