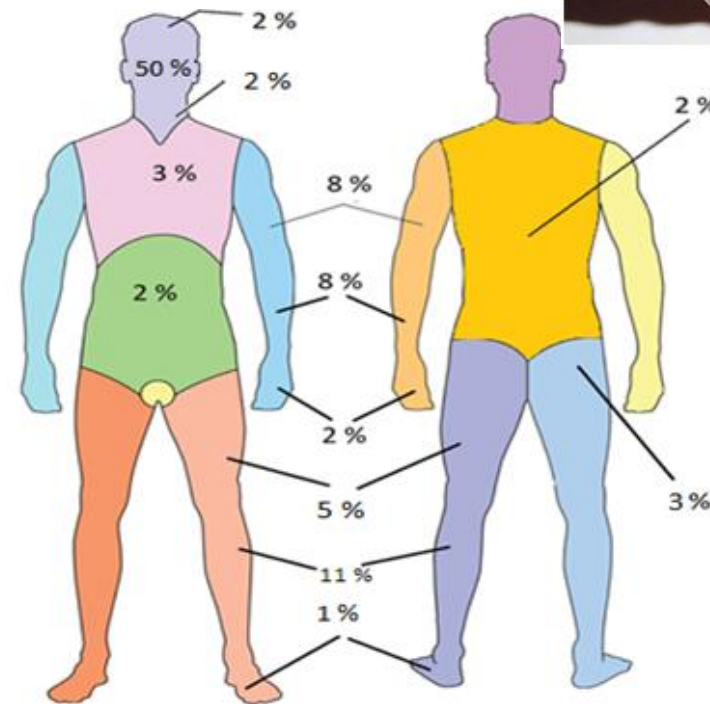


Medical Treatment of Merkel Cell Carcinoma

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October 8, 2020

Merkel cell carcinoma

- Rare and highly aggressive neuroendocrine malignancy of the skin
- Sunexposed areas in elderly patients
- 50% located in the head and neck region and 35% on extremities



Merkel cell carcinoma

- Highly aggressive tumor – mortality twice that of melanoma
- 37% present with regional metastatic disease
- 10% present with distant metastatic disease
- At Risk population
 - Elderly people
 - Immunosuppressed patients
 - HIV infected patients
- Incidence rates vary across the world
 - Europe: 0.13 per 100.000
 - USA: 0.79 per 100.000
 - Queensland, Australia: 1.6 per 100.000

Merkel cell carcinoma – treatment strategy

- Surgery for localized disease
 - Excision margin: 2-3 cm to ensure local control, or
 - Narrower excision and adjuvant radiotherapy
- Definitive radiotherapy for pts not candidates for primary resection
- Stage III patients
 - SLNB indicated in most patients
 - Will CLND impact OS?
 - Adjuvant medical treatment?
- Metastatic MCC
 - 25% of all pts – corresponding to app 1.2 patient per 1.000.000 per year

Metastatic Merkel cell carcinoma

- Cytotoxic chemotherapy
 - Platinum based regimens
 - 45% response – sensitive tumor
 - CRR: 5%
 - Median PFS: 4-6 mths – shortlived effect
 - Median OS: 14.6 mths – long term survivors?
 - Toxicity significant to elderly pts

Metastatic Merkel cell carcinoma

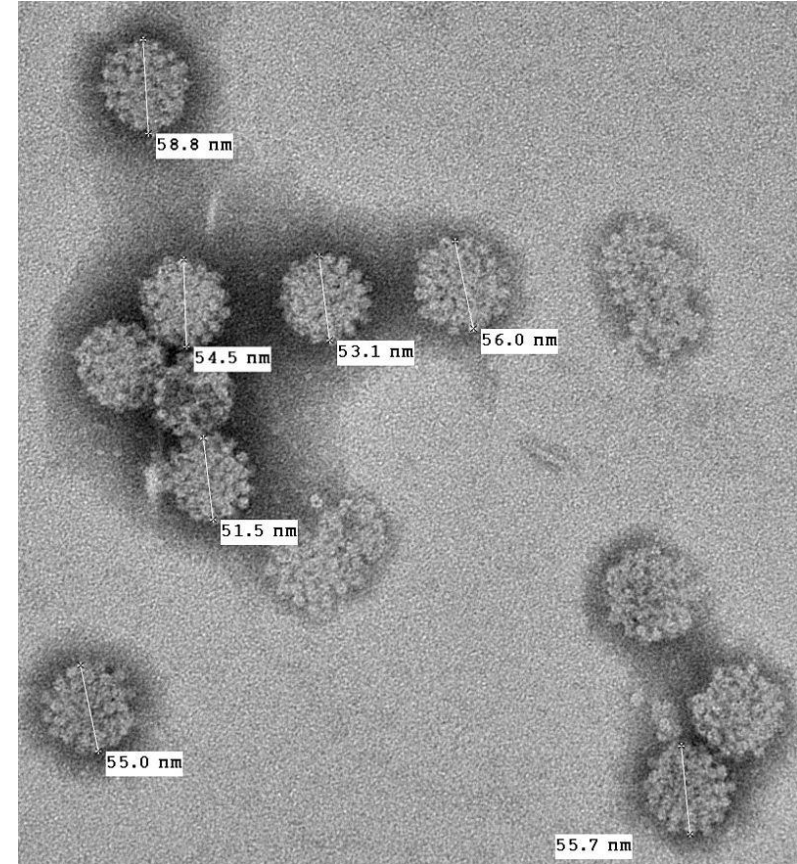
Efficacy data

	Chemotherapy ^{1,2,3}	Avelumab (2nd L)	Avelumab (1st L)	Pembrolizumab
ORR	45%			
CRR	5%			
Median DoR	3-6 m			
Median PFS	4-6 m			
PFS-12m	50%			
PFS-24m	31%			
PFS-36				
Median OS	14.6 m			
OS-6m	77.5%			
OS-12m	38%			
OS-42m	-			

¹Becker: Oncotarget 2017; 8: 79731, ²Iyer: Cancer Med 2016; 5:2294, ³Cowey: ESMO 2020; poster 1090,

Merkel cell carcinoma – Polyoma virus

- Majority (>80%) of cases associated with Merkel cell Polyoma virus
- Rest is triggered by UV-mediated mutations



Merkel cell carcinoma

THE LATEST ADVANCES IN ONCOLOGY

2020

Anti-PD-1/L1 approved indications and suspected mechanism of action

Group	Indication	ORR	Agents approved*	Main driver of response
High response rate	Hodgkin's disease	87%	Nivolumab, pembrolizumab	PDJ amplicon
	Desmoplastic melanoma	70%	Nivolumab, pembrolizumab	Mutations from chronic sun exposure
	Merkel cell carcinoma	56%	Avelumab, pembrolizumab	Merkel cell virus and sun exposure
	MSI-h cancers	53%	Nivolumab, pembrolizumab	Mutations from mismatch repair deficiency
Intermediate response rate	Skin melanoma	35-40%	Nivolumab, pembrolizumab	Mutations from intermittent sun exposure
	Lung cancer	20%	Atezolizumab, nivolumab, pembrolizumab	Mutations from cigarette smoking
	Head and neck cancers	15%	Nivolumab, pembrolizumab	Mutations from cigarette smoking
	Gastro-esophageal cancer	15%	pembrolizumab	Mutations from cigarette smoking
	Bladder/urinary tract cancers	15%	Atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab	Mutations from cigarette smoking
	Renal cell carcinoma	25%	Nivolumab, pembrolizumab	Insertion/deletions (indels)
	Hepatocellular carcinoma	20%	nivolumab	Hepatitis virus

Ribas and Wolchok, Science 2018

Drugs approved

- FDA:
 - Avelumab (anti PD-L1) – Mar 2017
 - Pembrolizumab (anti-PD1) – Dec 2018
- EMA
 - Avelumab (anti-PD-L1) – Jul 2017
 - Pembrolizumab (anti-PD1) - ?
- Other candidates
 - Nivolumab (anti-PD1)
 - Retinfanlimab (anti-PD1)

Two-year efficacy and safety update from JAVELIN Merkel 200 part A: a registrational study of avelumab in metastatic Merkel cell carcinoma progressed on chemotherapy

Paul Nghiem¹, Shailender Bhatia², Andrew S. Brohl³, Omid Hamid⁴, Janice M. Mehnert⁵, Patrick Terheyden⁶, Kent C. Shih⁷, Isaac Brownell⁸, Celeste Lebbé⁹, Karl D. Lewis¹⁰, Gerald P. Linette¹¹, Michele Milella¹², Meliessa Hennessy¹³, Marcis Bajars¹³, Christine Hicking¹⁴, Sandra P. D'Angelo¹⁵

¹University of Washington Medical Center at South Lake Union, Seattle, WA, USA; ²University of Washington Medical Center, Seattle, WA, USA; ³Moffitt Cancer Center, Tampa, FL, USA; ⁴The Angeles Clinic and Research Institute, Los Angeles, CA, USA; ⁵Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; ⁶University of Lübeck, Lübeck, Germany; ⁷Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; ⁸National Cancer Institute, Bethesda, MD, USA; ⁹CIC and Dermatology, Saint-Louis Hospital, Paris, France; ¹⁰University of Colorado Denver, School of Medicine, Aurora, CO, USA; ¹¹University of Pennsylvania, Philadelphia, PA, USA; ¹²IRCCS Regina Elena National Cancer Institute, Rome, Italy; ¹³EMD Serono, Inc, Billerica, MA, USA; ¹⁴Merck KGaA, Darmstadt, Germany; ¹⁵Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA

Abstract No. 9507

Metastatic Merkel cell Carcinoma: 2nd-line avelumab: JAVELIN Merkel 200, part A

- 88 patients with mMCC
- Median follow-up: > 44 mths
- ECOG PS: 0-1
- 78% PD-L1 positive
- 60% MCPyV positive

Response to Avelumab

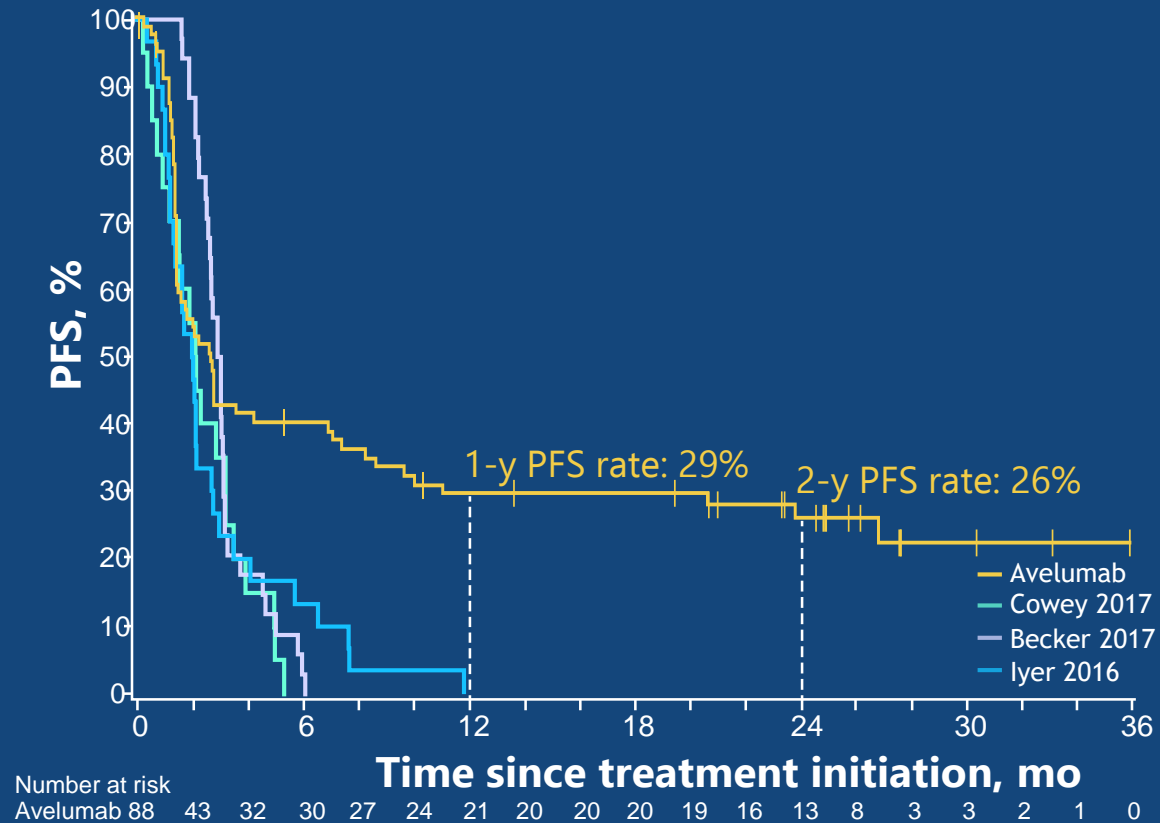
Response parameter	N=88
ORR (95% CI), %	33.0 (23.3-43.8)
Confirmed BOR, n (%)	
CR	10 (11.4)
PR	19 (21.6)
SD	9 (10.2)
PD	32 (36.4)
Not evaluable*	18 (20.5)
DCR, %	43.2

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.

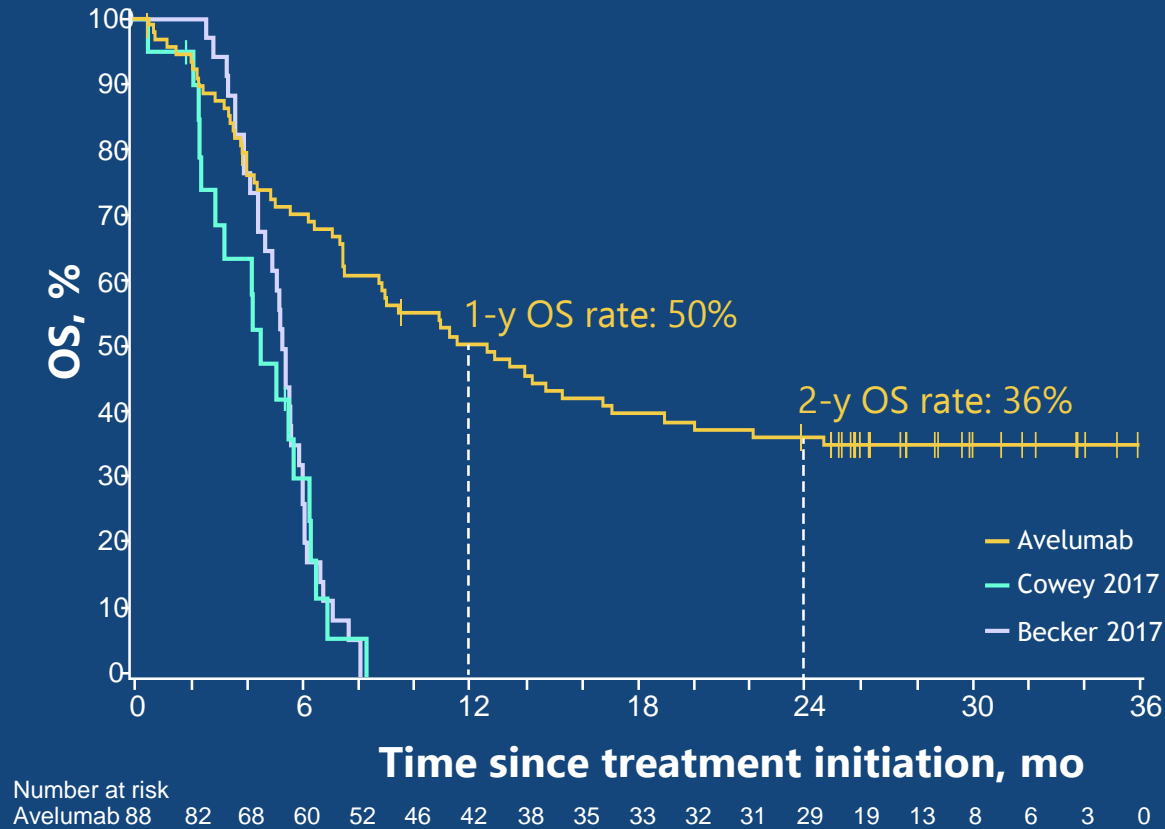
Progression-free survival with avelumab and retrospective chemotherapy data^{1-3,*}



* 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,*}

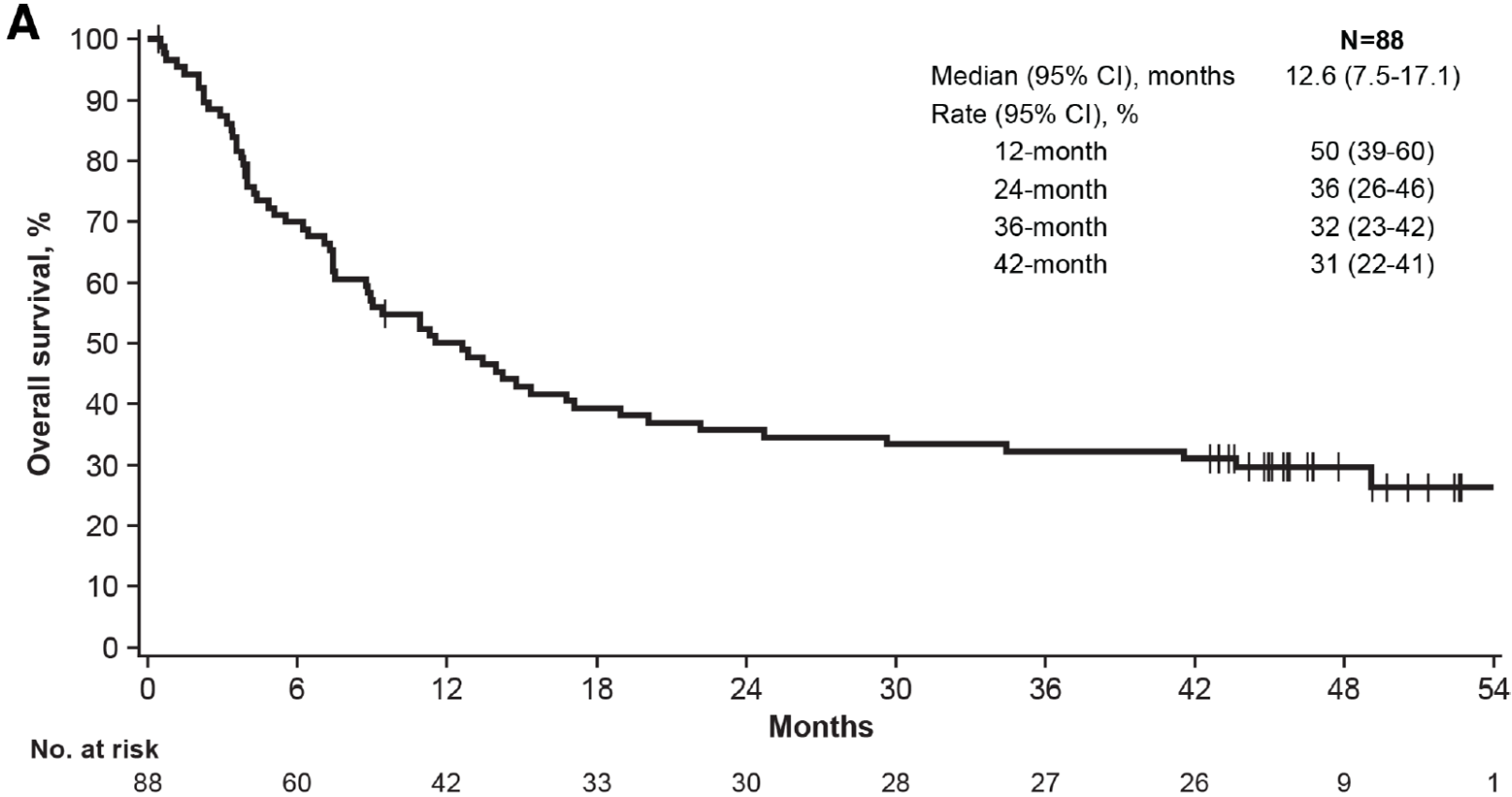


OS, overall survival

* 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.

Javelin 200, part A, 2020



Metastatic Merkel cell carcinoma

Efficacy data

	Chemotherapy ^{1,2,3}	Avelumab (2nd L) ⁴	Avelumab (1st L)	Pembrolizumab
ORR	45%	33%		
CRR	5%	11.4%		
Median DoR	3-6 m	40.5 m		
Median PFS	4-6 m	2.7		
PFS-12m	50%	29%		
PFS-24m	31%	26%		
PFS-36		21%		
Median OS	14.6 m	12.6		
OS-6m	77.5%	50%		
OS-12m	38%	36%		
OS-42m	-	31%		

¹Becker: Oncotarget 2017; 8: 79731, ²Iyer: Cancer Med 2016; 5:2294, ³Cowey: ESMO 2020; poster 1090, ⁴D'Angelo: J Immunother Cancer 2020; 8: 1-,

Metastatic Merkel cell Carcinoma: 1st-line avelumab: JAVELIN Merkel 200, part B

- 116 patients with mMCC, no prior therapy
- Median follow-up: 21.2 mths
- ECOG PS: 0-1
- 75% PD-L1 negative
- 60% MCPyV positive

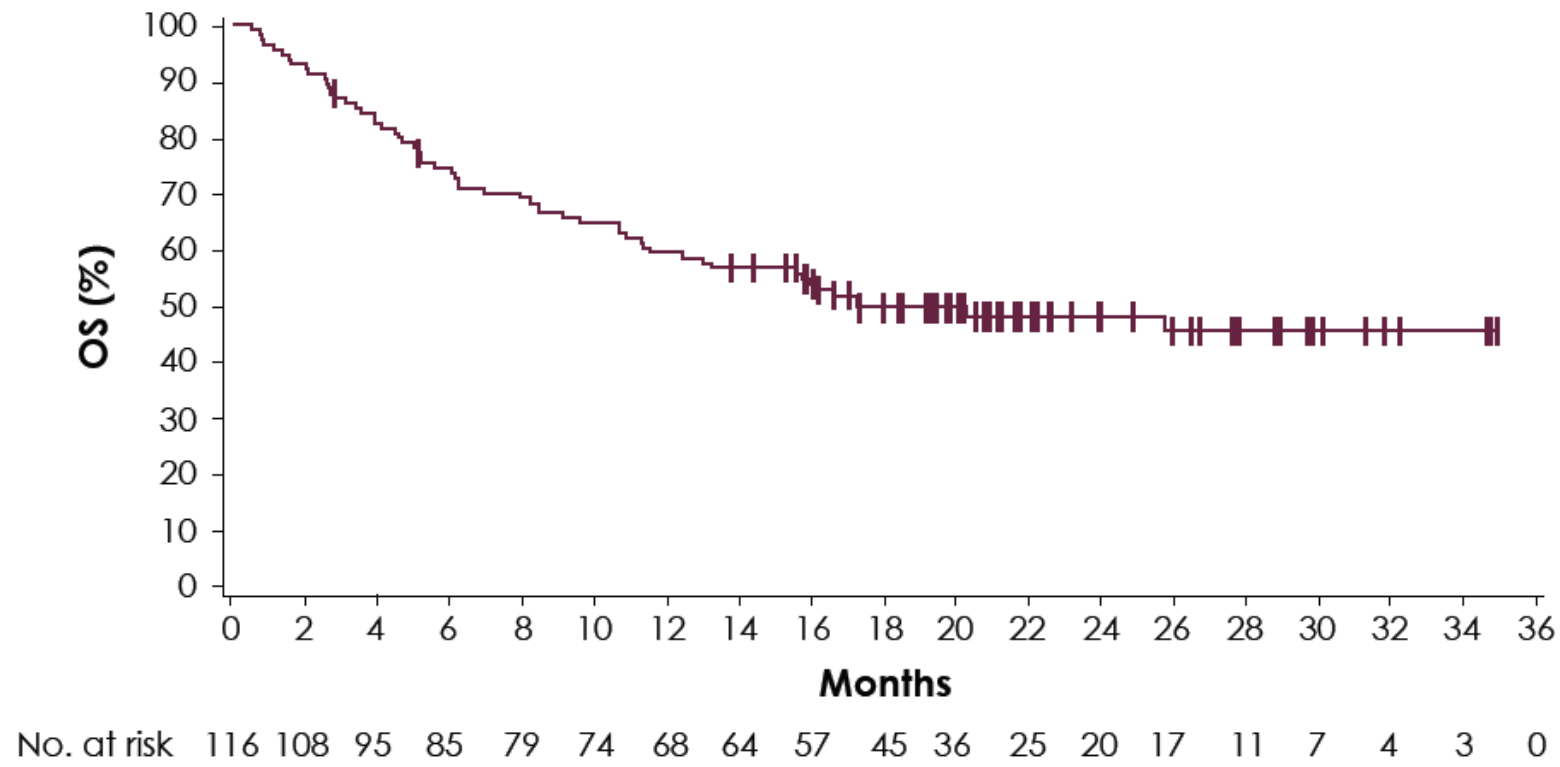
Metastatic Merkel cell carcinoma

Efficacy data

	Chemotherapy ^{1,2,3}	Avelumab (2nd L) ⁴	Avelumab (1st L) ⁵	Pembrolizumab ⁶
ORR	45%	33%	35%	
CRR	5%	11.4%	16.4%	
Median DoR	3-6 m	40.5 m	18.2 m	
Median PFS	4-6 m	2.7	4.1 m	
PFS-12m	50%	29%	31%	
PFS-24m	31%	26%	-	
PFS-36		21%	-	
Median OS	14.6 m	12.6	20.3	
OS-6m	77.5%	50%	-	
OS-12m	38%	36%	60%	
OS-42m	-	31%	-	

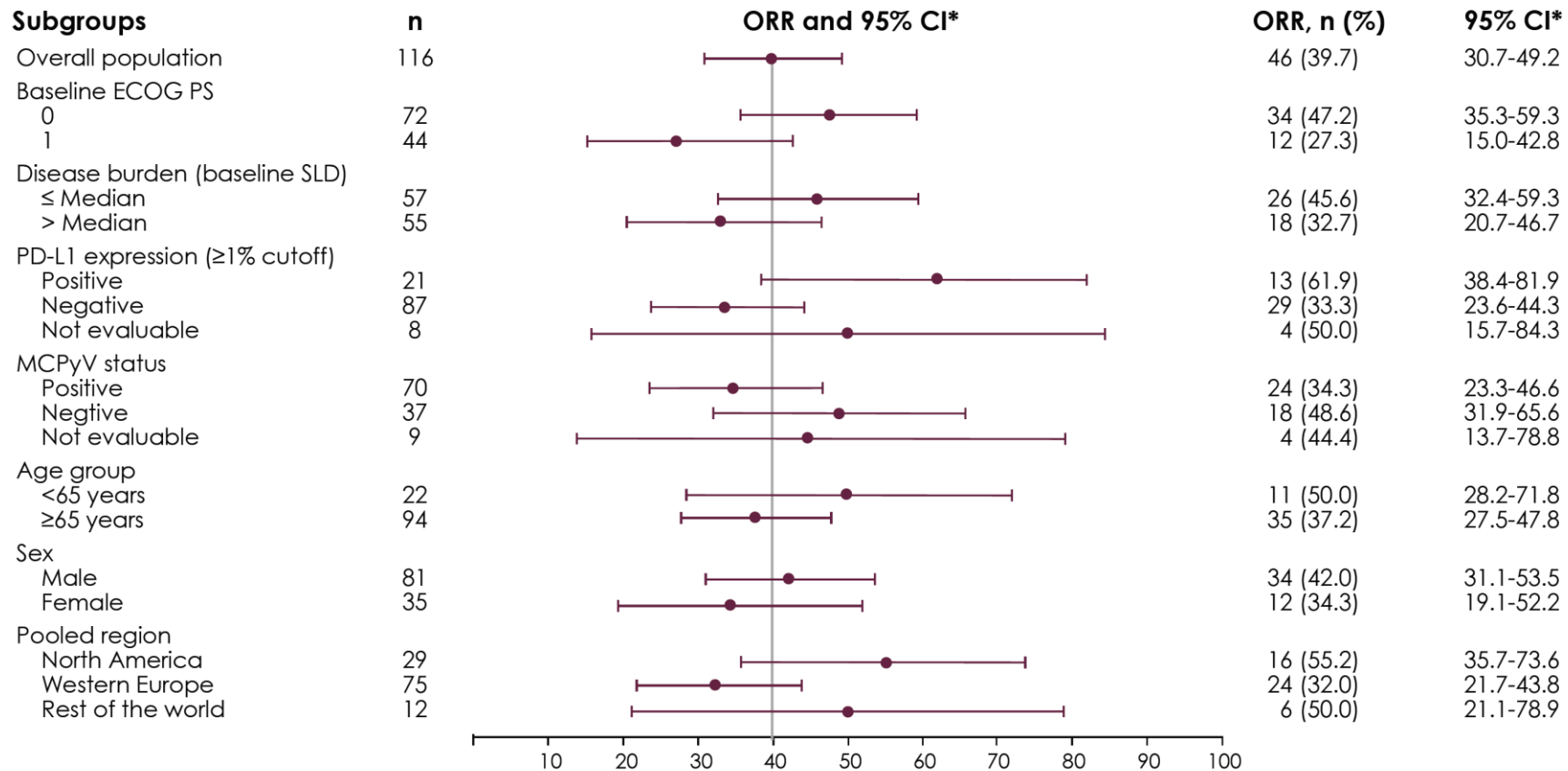
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⁵D'Angelo: Abst SITC 2019, P362, ⁶Nghiem: JCO 2019; 37:693-

Metastatic Merkel cell carcinoma OS – 1st line therapy



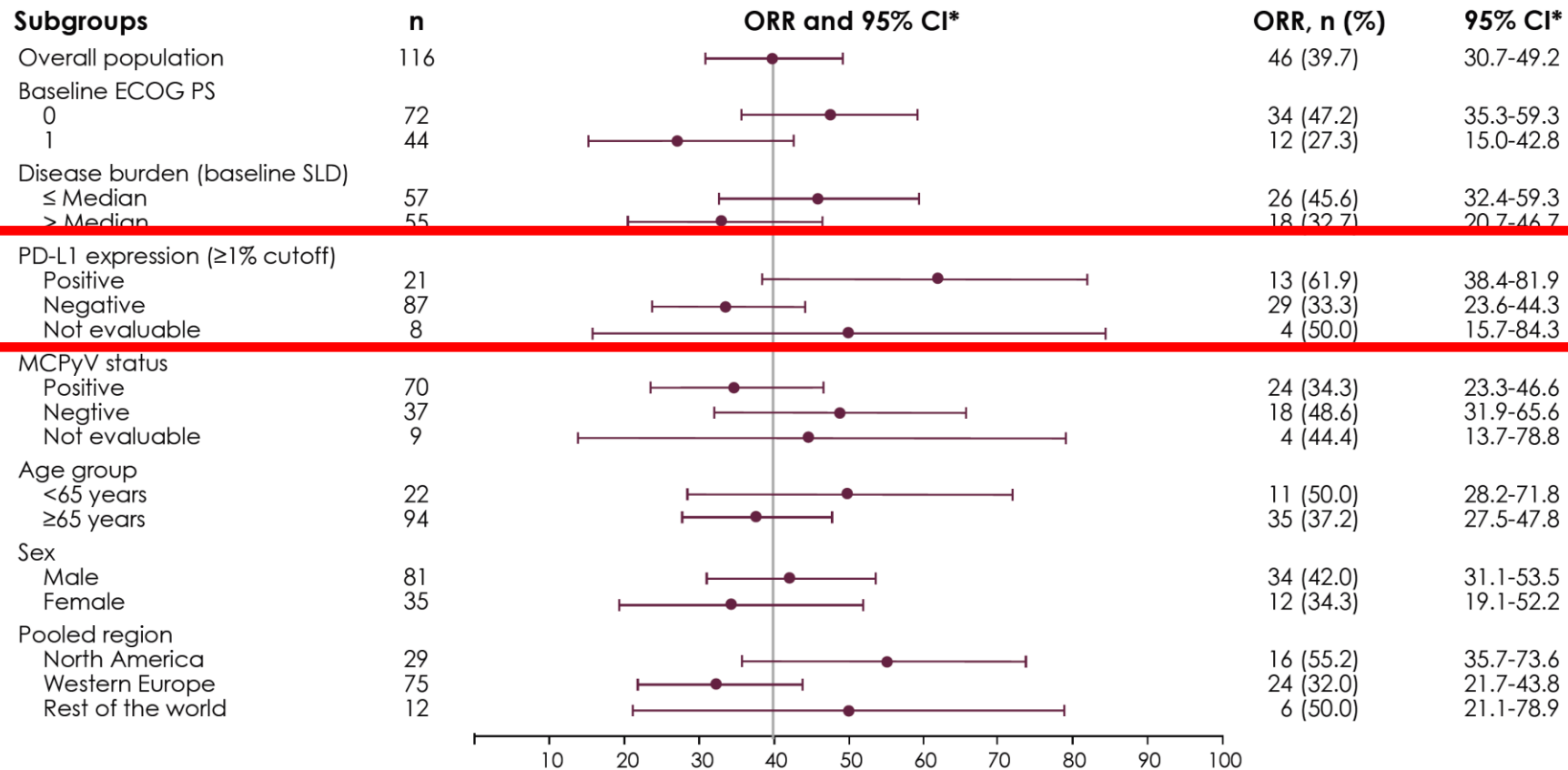
Metastatic Merkel cell carcinoma

ORR subgroup analyses – 1st line therapy



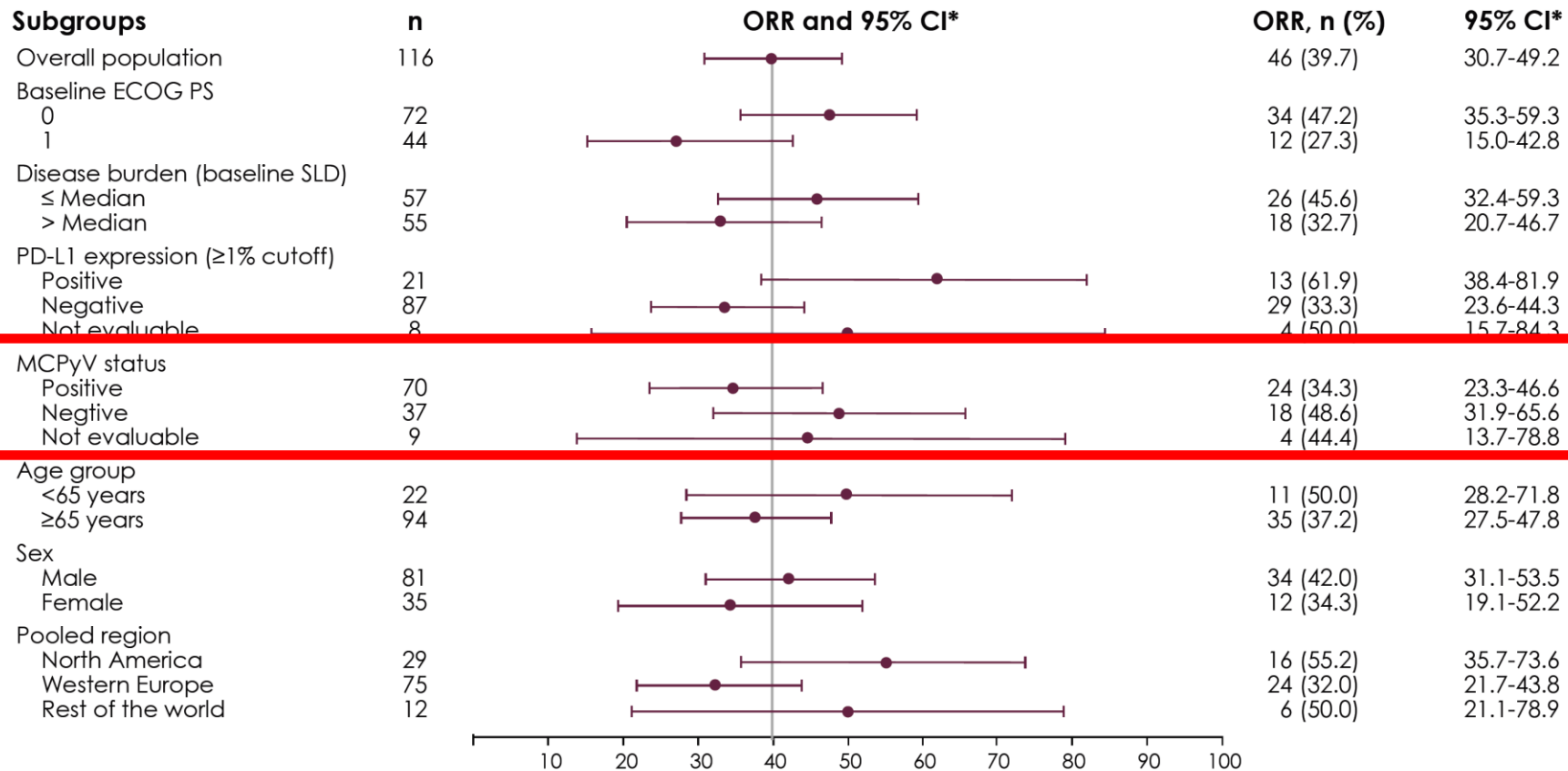
Metastatic Merkel cell carcinoma

ORR subgroup analyses – 1st line therapy



Metastatic Merkel cell carcinoma

ORR subgroup analyses – 1st line therapy



Metastatic Merkel cell Carcinoma: 1st-line pembrolizumab, phase II

- 50 patients with mMCC, no prior therapy
- Median follow-up: 14.9 mths
- ECOG PS: 0-1
- 51% PD-L1 negative
- 64% MCPyV positive

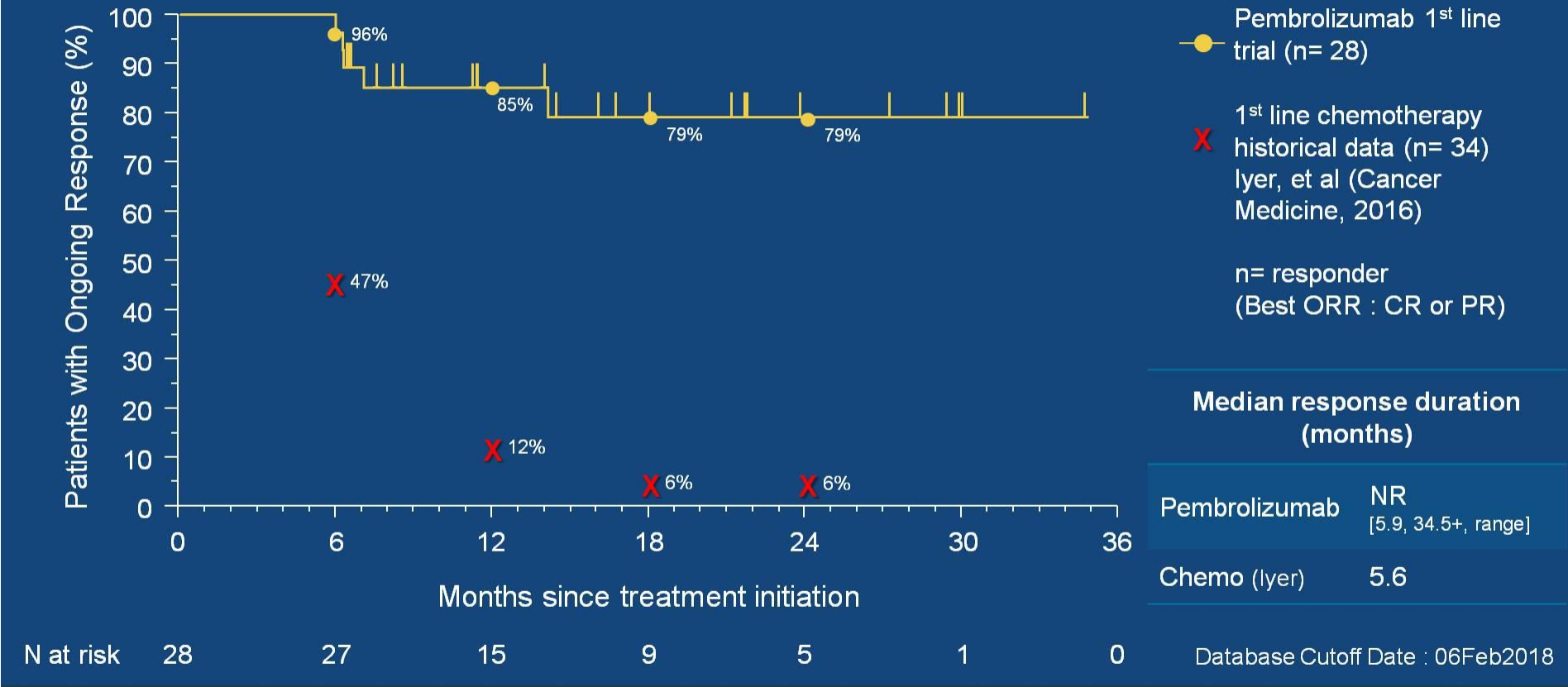
Metastatic Merkel cell carcinoma

Efficacy data

	Chemotherapy ^{1,2,3}	Avelumab (2nd L) ⁴	Avelumab (1st L) ⁵	Pembrolizumab ⁶
ORR	45%	33%	35%	56%
CRR	5%	11.4%	16.4%	24%
Median DoR	3-6 m	40.5 m	18.2 m	nr
Median PFS	4-6 m	2.7	4.1 m	16.8 m
PFS-12m	50%	29%	31%	-
PFS-24m	31%	26%	-	48.3%
PFS-36		21%	-	-
Median OS	14.6 m	12.6	20.3	nr
OS-6m	77.5%	50%	-	-
OS-12m	38%	36%	60%	-
OS-42m	-	31%	-	24 m: 68.7%

¹Becker: Oncotarget 2017; 8: 79731, ²Iyer: Cancer Med 2016; 5:2294, ³Cowey: ESMO 2020; poster 1090, ⁴D'Angelo: J Immunother Cancer 2020; 8: 1-,
⁵D'Angelo: Abst SITC 2019, P362, ⁶Nghiem: JCO 2019; 37:693-

Responses are durable



PRESENTED AT: 2018 ASCO ANNUAL MEETING

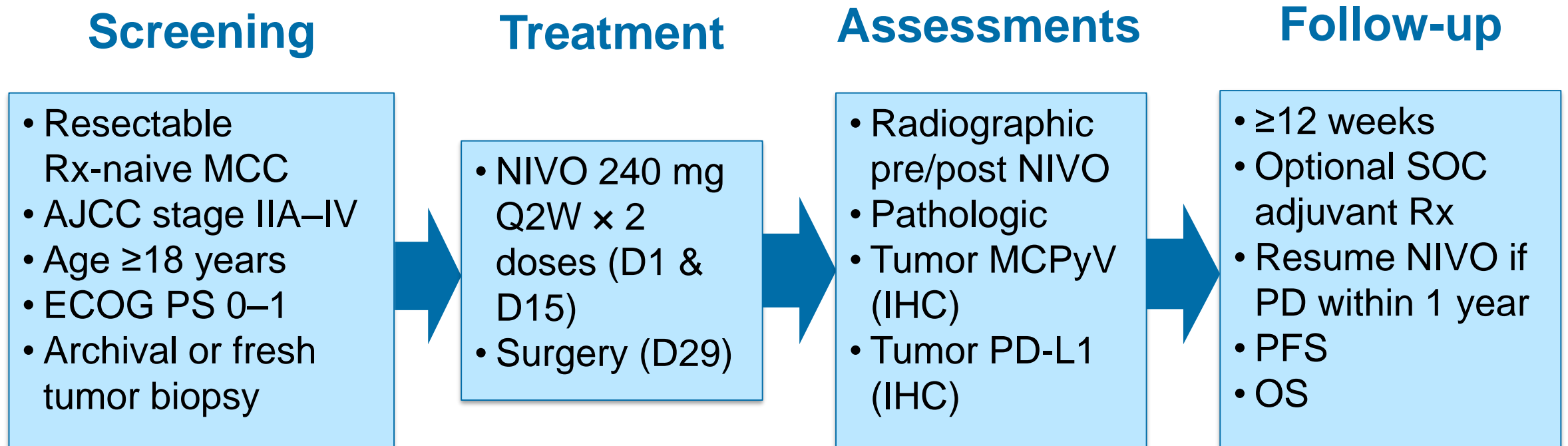
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PRESENTED BY: Paul Nghiem, MD, PhD



Resectable Merkel cell carcinoma

Neoadjuvant nivolumab – Checkmate 358



Resectable Merkel cell carcinoma

Neoadjuvant nivolumab – Checkmate 358

- 39 patients with stage IIA-IV resectable MCC
- Nivolumab 240 mg iv on d 1 and 15, with planned surgery d 30
- No unexpected toxicities
- 1 pt progressed and had no surgery
- 17 (47.2%) obtained a pCR

Ongoing adjuvant trials

- NCT021196961 (Germany)
- **Adjuvant Therapy of Completely Resected Merkel Cell Carcinoma With Immune Checkpoint Blocking Antibodies vs Observation (ADMEC-O) – Nivolumab**
- NCT04291885 (Australia)
- **Immunotherapy Adjuvant Trial in Patients With Stage I-III Merkel Cell Carcinoma (I-MAT) - Avelumab**

Conclusions

- mMCCs are sensitive to chemotherapy, but responses are shortlived
- Immunotherapy with CPIs to mMCC is very effective and promising, with a chance of obtaining long-term survival.
- PD1 and PD-L1 targetting CPIs appears to be equally effective
- Toxicity profile comparable to what is known from other diseases
- CPIs are better tolerated in older patients with comorbidities compared with chemotherapy
- Neoadjuvant and Adjuvant trials are ongoing

Conclusions

- mMCCs are sensitive to chemo
- Immunotherapy with anti-PD1 and anti-CTLA4 with a chance of long-term survival
- PD1 and CTLA4 inhibitors are effective
- Toxicity is low compared to other diseases
- CPIs are effective in patients with comorbidities
- Neoadjuvant therapy trials are ongoing

**Paul Nghiem:
"Less Toxic, More Effective Treatment
A Win-Win for patients with
Metastatic Merkel Cell Carcinoma"
Viewpoint JAMA Dermatology 2019**