

Non-Melanoma Skin Cancers: Advances in Immunotherapy

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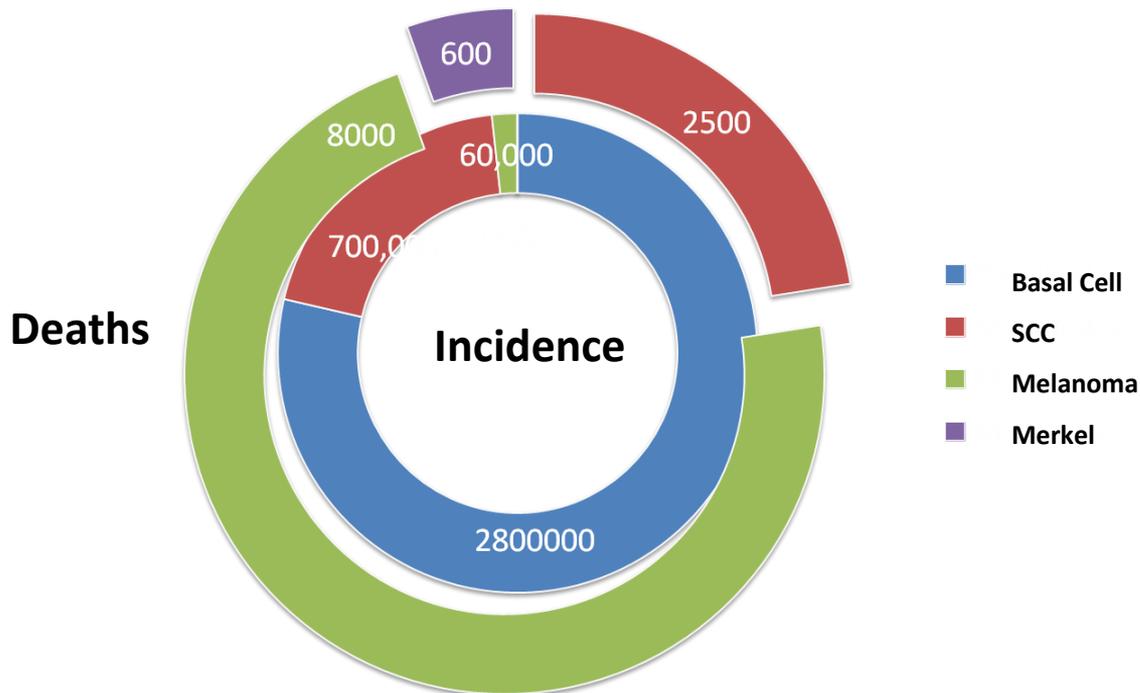
November 9th, 2019



Disclosures

- ◆ **Research Support (to the institution):** EMD-Serono, BMS, Merck, Oncosec, ImmuneDesign, NantKwest, Novartis.
- ◆ **Advisory Board:** Genentech, EMD-Serono, BMS (received honoraria)
- ◆ **Speaker:** None

Skin, the largest organ, is also the most vulnerable to cancer development



NOTE: The numbers listed in this figure do not reflect the most up-to-date statistics.

Non-melanoma Skin cancers (NMSCs)

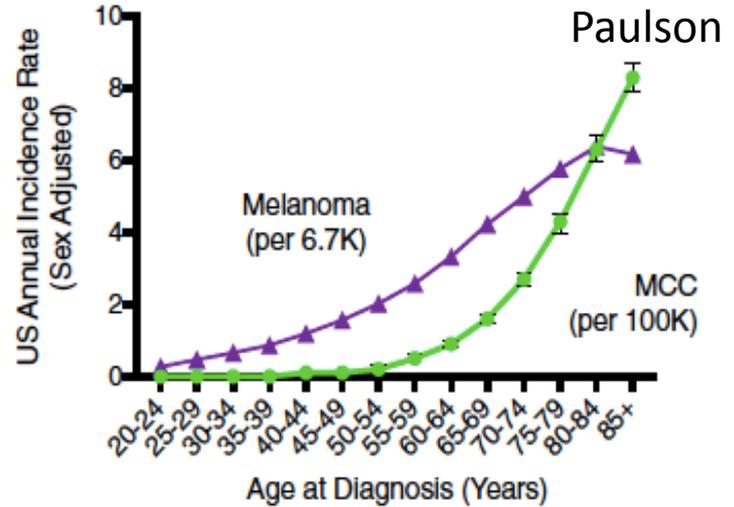
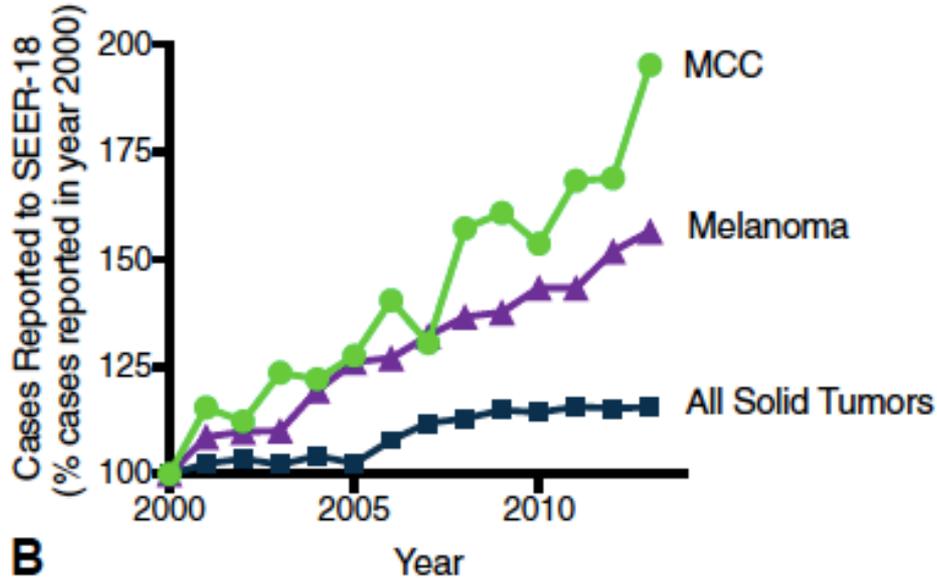
- 5.4 Million diagnosed in 2012
- 3.3 Million treated
 - 80% BCCs
 - 20% cSCC
 - <1% others (including MCC)

{Rogers HW et al. *JAMA Dermatol.* 2015}

Alarming increase in MCC incidence



Kelly Paulson



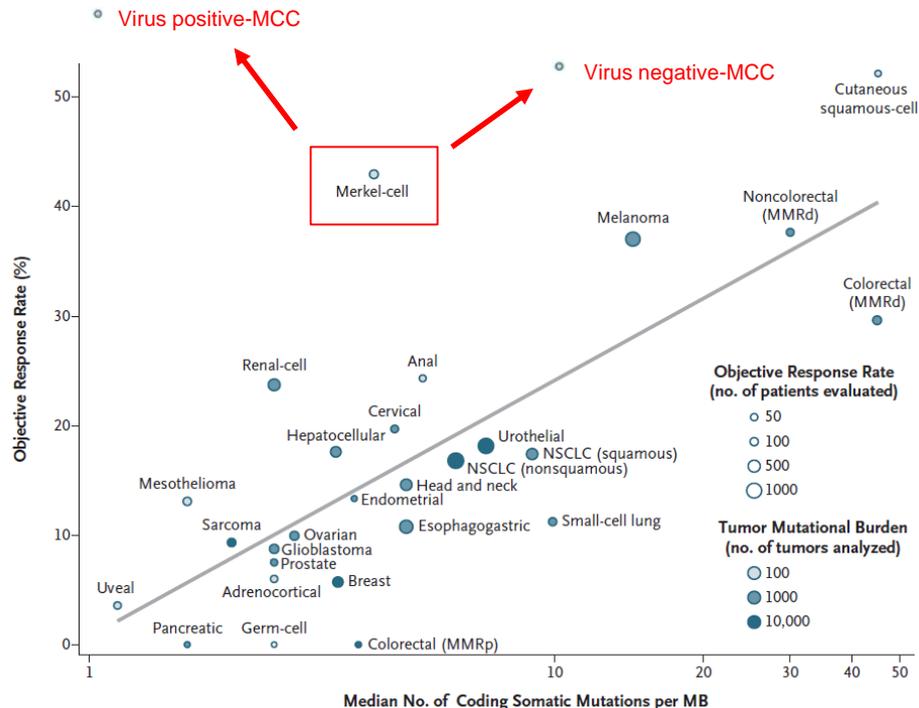
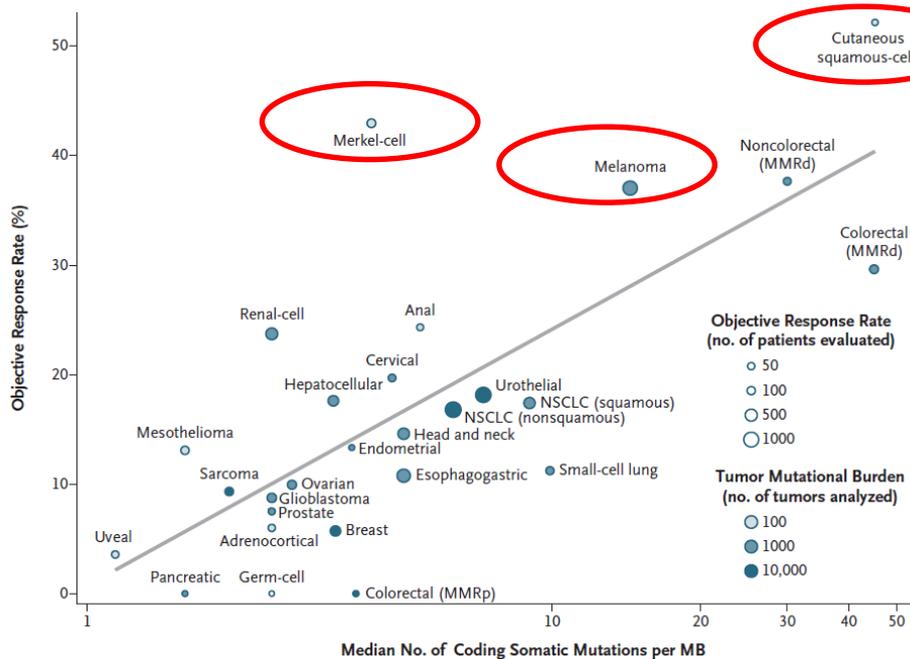
Incidence rate by Age

2500 new MCC cases in 2013; estimated ~3300 by the year 2025

{Paulson K et al. *J Am Acad Dermatol.* 2017}

Tumor Mutational Burden (TMB) is generally high in NMSCs: Rationale for immunotherapy

BCC's 75/MB



Yarchoan, et al, NEJM 2017
 Harms, et al, CA Res, 2015
 Jayaraman SS JID 2014

Paulson, et al, unpublished

Remarkable success of PD-1/PD-L1 blockade in MCC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Paul T. Nghiem, M.D., Ph.D., Shailender Bhatia, M.D., Evan J. Lipson, M.D., Ragini R. Kudchadkar, M.D., Natalie J. Miller, B.A., Lakshmanan Annamalai, D.V.M., Ph.D., Sneha Berry, M.S., Elliot K. Chartash, M.D., Adil Daud, M.B., B.S., Steven P. Fling, Ph.D., Philip A. Friedlander, M.D., Harriet M. Kluger, M.D., Holbrook E. Kohrt, M.D., Ph.D.,* Lisa Lundgren, M.S., Kim Margolin, M.D., Alan Mitchell, M.Sc., Thomas Olencki, D.O., Drew M. Pardoll, M.D., Ph.D., Sunil A. Reddy, M.D., Erica M. Shantha, M.D., William H. Sharfman, M.D., Elad Sharon, M.D., M.P.H., Lynn R. Shemanski, Ph.D., Michi M. Shinohara, M.D., Joel C. Sunshine, M.D., Ph.D., Janis M. Taube, M.D., John A. Thompson, M.D., Steven M. Townson, Ph.D., Jennifer H. Yearley, D.V.M., Ph.D., Suzanne L. Topalian, M.D., and Martin A. Cheever, M.D.

Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

Howard L Kaufman, Jeffery Russell, Omid Hamid, Shailender Bhatia, Patrick Terheyden, Sandra P D'Angelo, Kent C Shih, Michele Milella, Isaac Brownell, Karl D Lewis, Jochen H Lorch, Kevin Chin, Lisa Mahnke, Anja von Heydebreck, Jean-Marie

Lancet Oncol 2016

Published Online

September 1, 2016

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S1470-2045(16)30364-3)

[S1470-2045\(16\)30364-3](http://dx.doi.org/10.1016/S1470-2045(16)30364-3)

See Online/Comment

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S1470-2045(16)30441-7)

[S1470-2045\(16\)30441-7](http://dx.doi.org/10.1016/S1470-2045(16)30441-7)

2018 Nobel Prize in Medicine report mentions MCC:

The tumors that show the highest frequency of responses (50-90%) are Hodgkin's lymphoma especially in patients with overexpression of PD-L1 and PD-L2 caused by gene amplification (Ansell et al., 2015), **Merkel cell carcinoma of the skin, being of viral origin** (Nghiem et al., 2016), in microsatellite-instability cancers of any origin having high mutational load from mismatch-repair deficiency (Le et al., 2017) and in desmoplastic melanoma carrying numerous, UV-induced mutations (Eroglu et al., 2018).

ORIGINAL ARTICLE

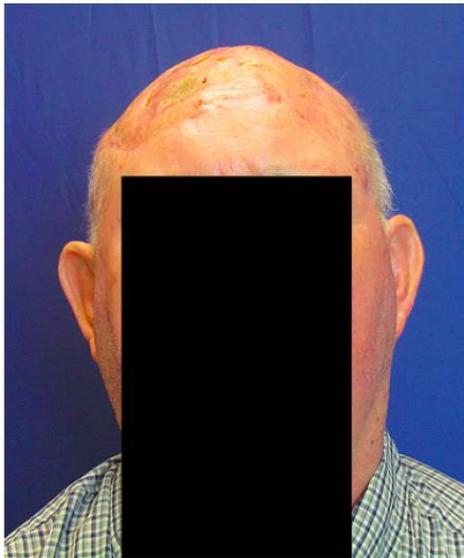
PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsí, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

A Patient in Phase 1 Study



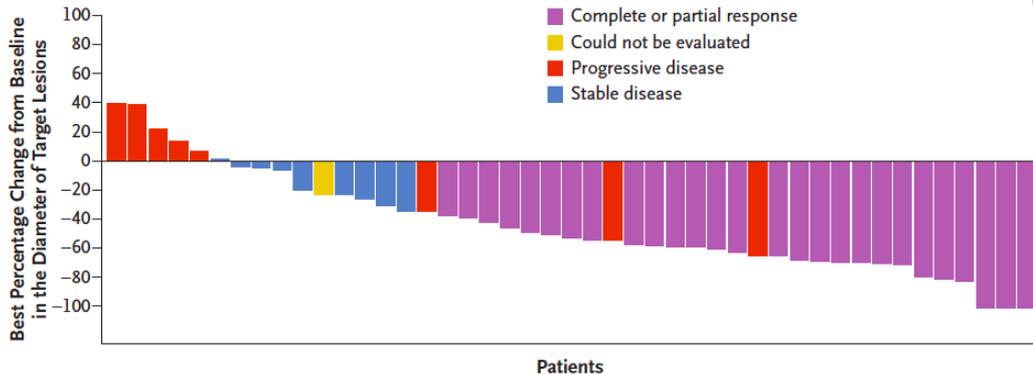
Baseline



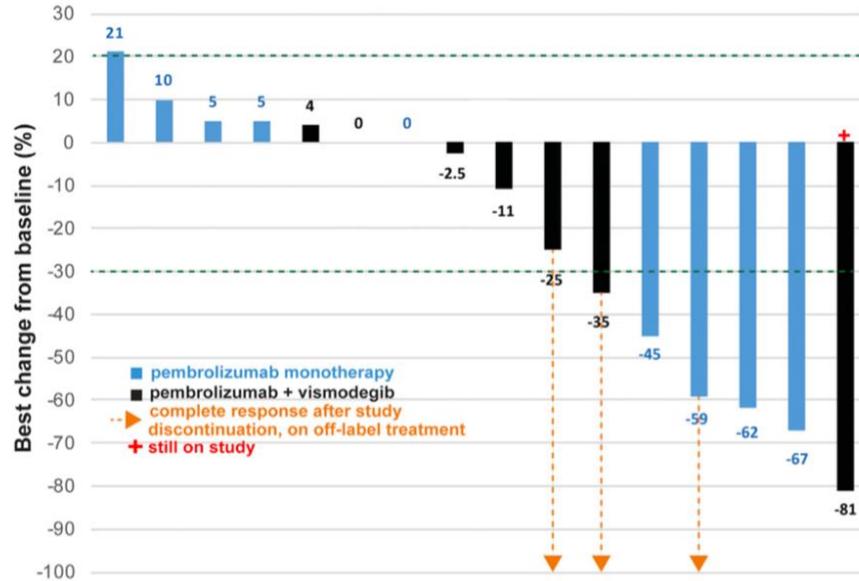
Week 6

On September 28, 2018, the US Food and Drug Administration (FDA) **approved cemiplimab-rwlc** (Libtayo; Regeneron/Sanofi US) for the treatment of patients with locally advanced or metastatic CSCC who are not candidates for curative surgery or curative radiation.

A Best Tumor Response for 45 Patients in the Phase 2 Study



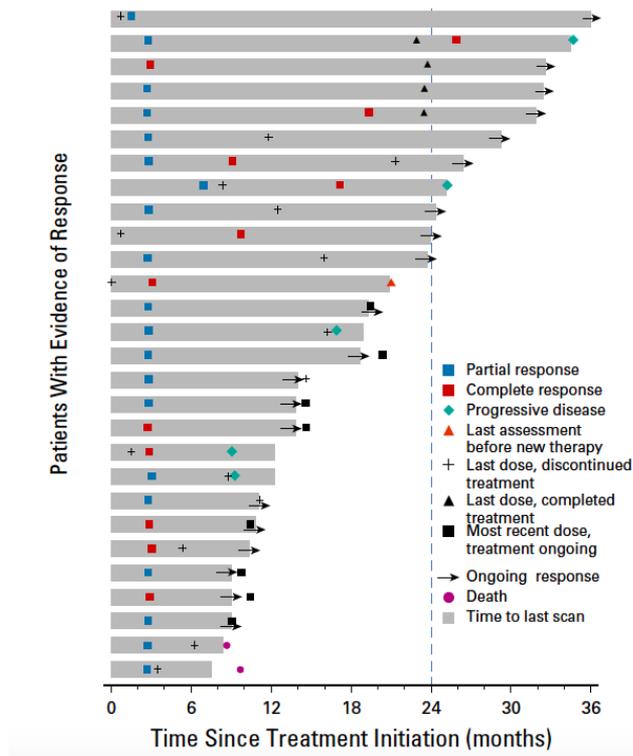
Pembrolizumab for advanced basal cell carcinoma: An investigator-initiated, proof-of-concept study



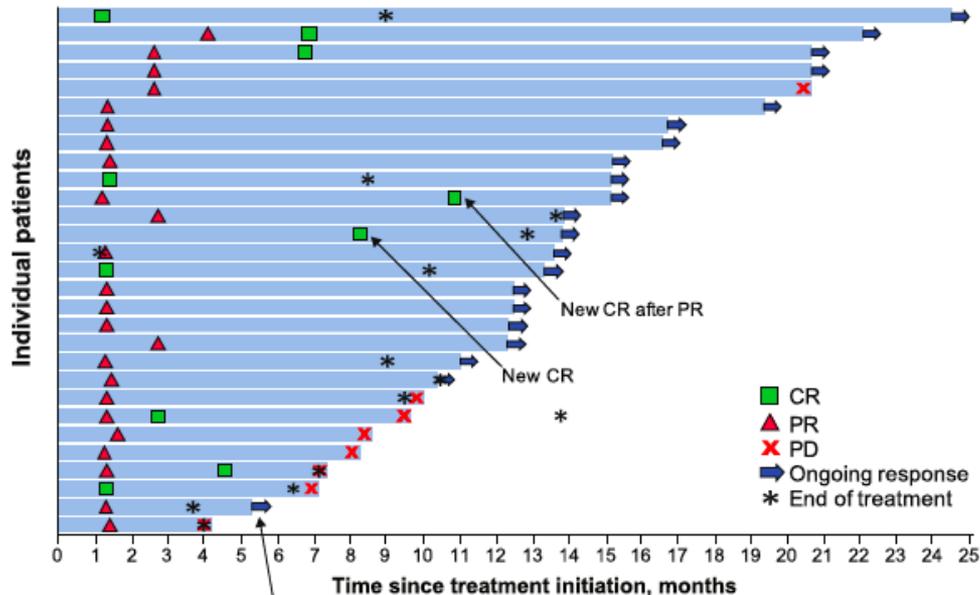
{Chang ALS JAAD 2019}

Emerging Data in Merkel cell carcinoma (MCC): Lessons for NMSCs (and even Melanoma)

Unlike chemotherapy, ICI responses are impressively durable

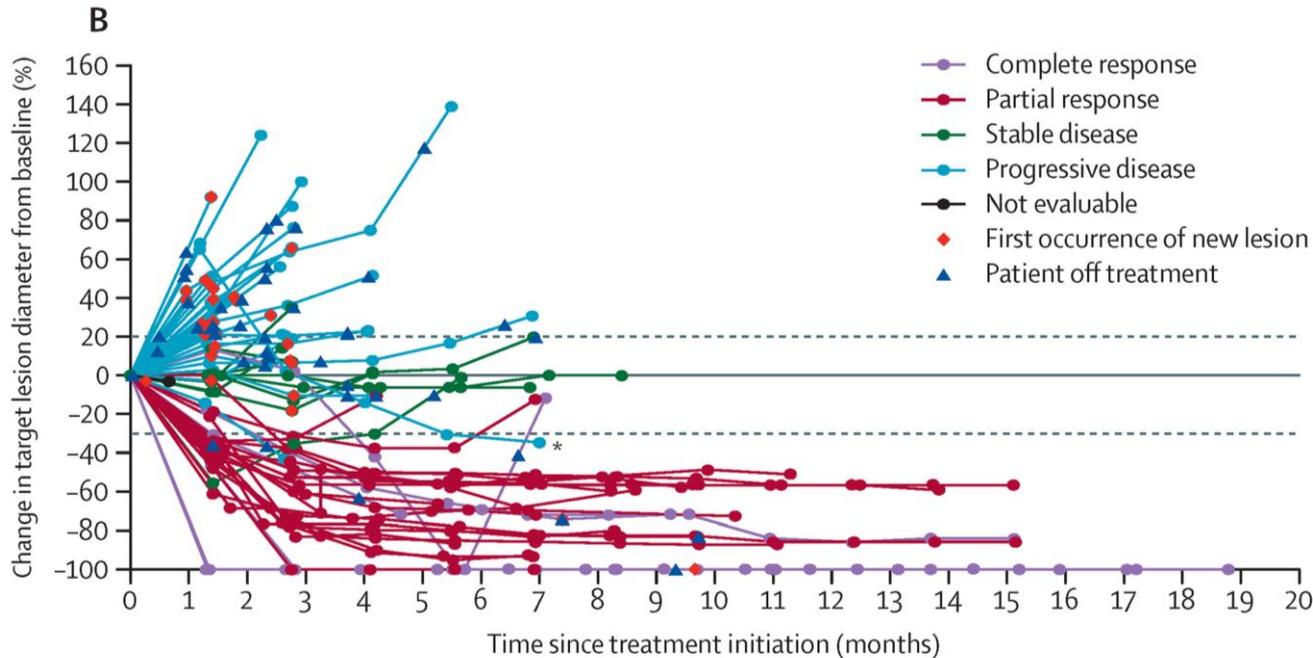


{Nghiem P, Bhatia S et al. 2019 *JCO*}



{Kaufman H et al. *JITC* 2018}

Responses to ICIs are generally rapid-onset



Median time to respond was 6 weeks (time of 1st scan)

{Kaufman H et al. *The Lancet Oncology* 2016}

Rapid response to Pembrolizumab



Baseline



3 Wk

- 69 years old female
- MCPyV+ve tumors
- Chemotherapy-naive



Baseline

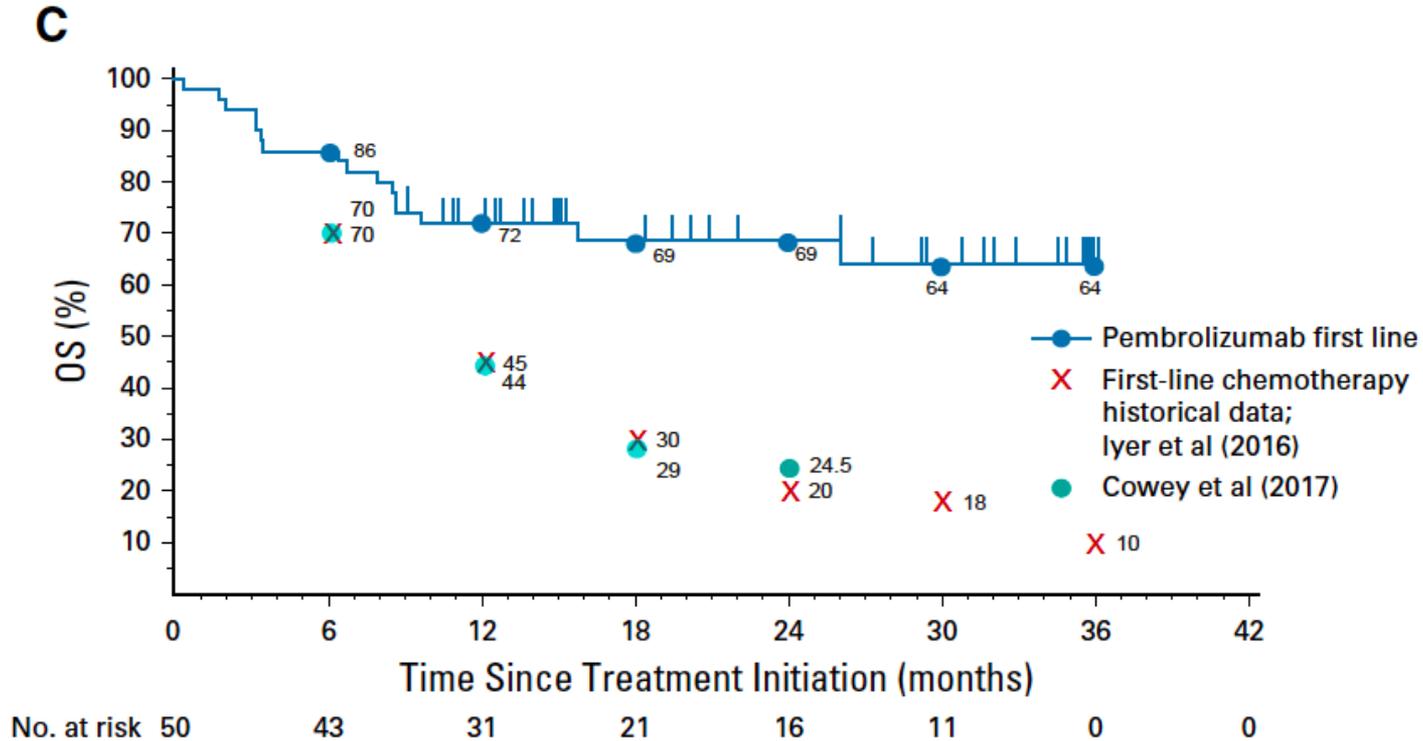


12 Wk

Are we meeting our goals for advanced MCC pts with ICIs?

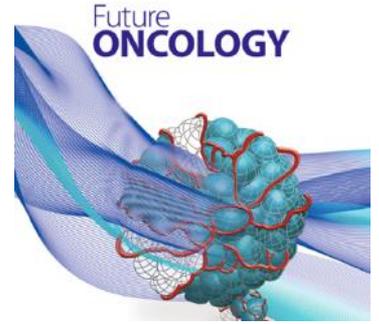
- **CURE**
- Improve overall survival (OS)
- Improve/preserve Quality of life (QoL)

Impact of ICIs on OS in MCC patients



Nonprogression with avelumab treatment associated with gains in quality of life in metastatic Merkel cell carcinoma

Howard L Kaufman¹, Matthias Hunger², Meliessa Hennessy³, Michael Schlichting⁴ & Murtuza Bharmal^{*.4}

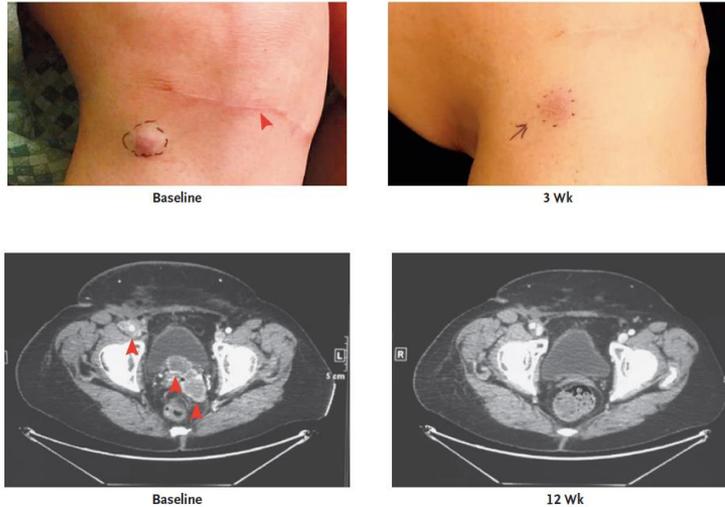


mated. **Results:** Tumor shrinkage correlated positively with patients' change from baseline in the FACT-M total (0.364 [95% CI: 0.050–0.607]) and subscale scores. Differences in HRQoL and utility between nonprogressive disease and progressive disease were clinically relevant. **Conclusion:** In patients with metastatic Merkel cell carcinoma, nonprogression during treatment with avelumab correlated with gains in HRQoL.

Are we curing MCC patients with ICI?

Our work is not quite done, even in responders!!

Anecdotal reports of progression in ICI responders are emerging.

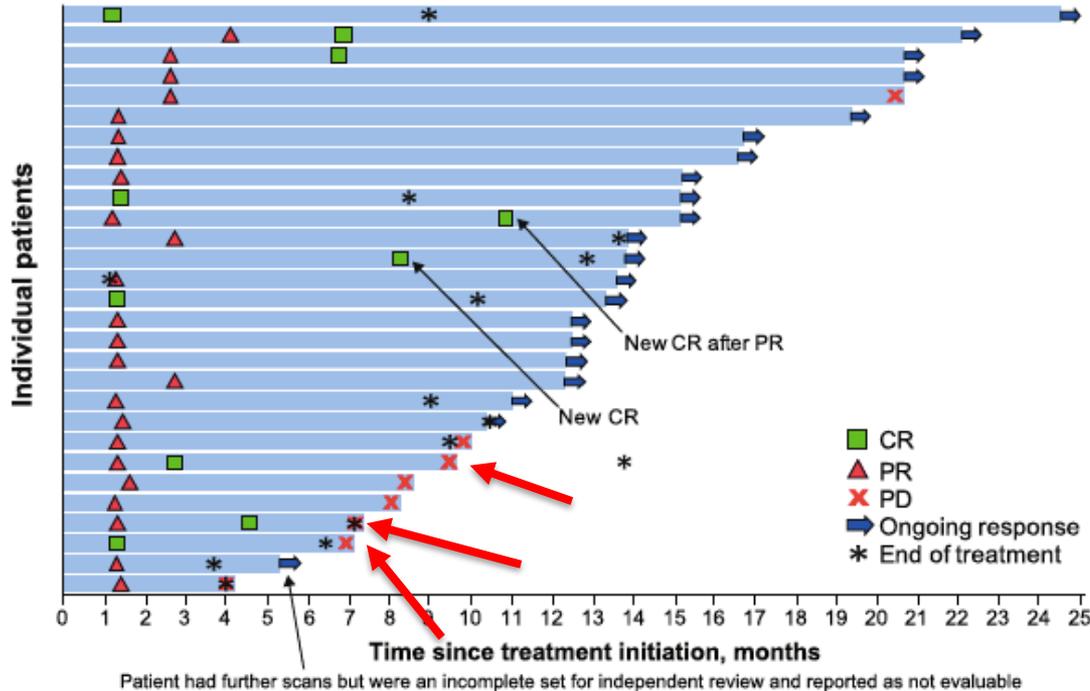


{Nghiem P, Bhatia S et al. 2016 *NEJM*}



3 years later (1 year after last pembrolizumab infusion)

Emerging LTFU data on avelumab trial



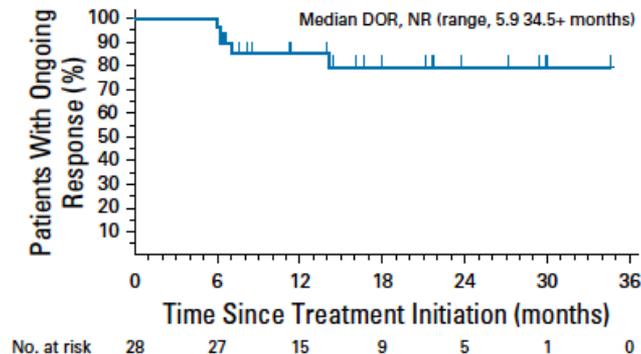
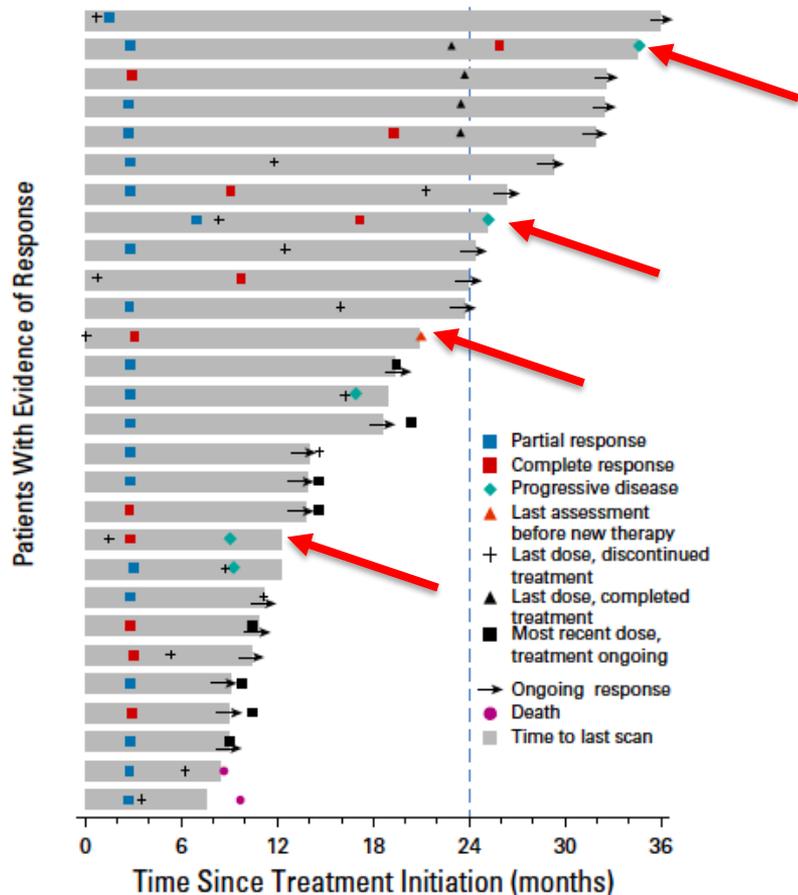
ORR only 33%

8/29 (**28%**) of responders have progressed

- Majority progressed while still receiving treatment
- Majority progressed in the first year, but delayed progression has also been seen

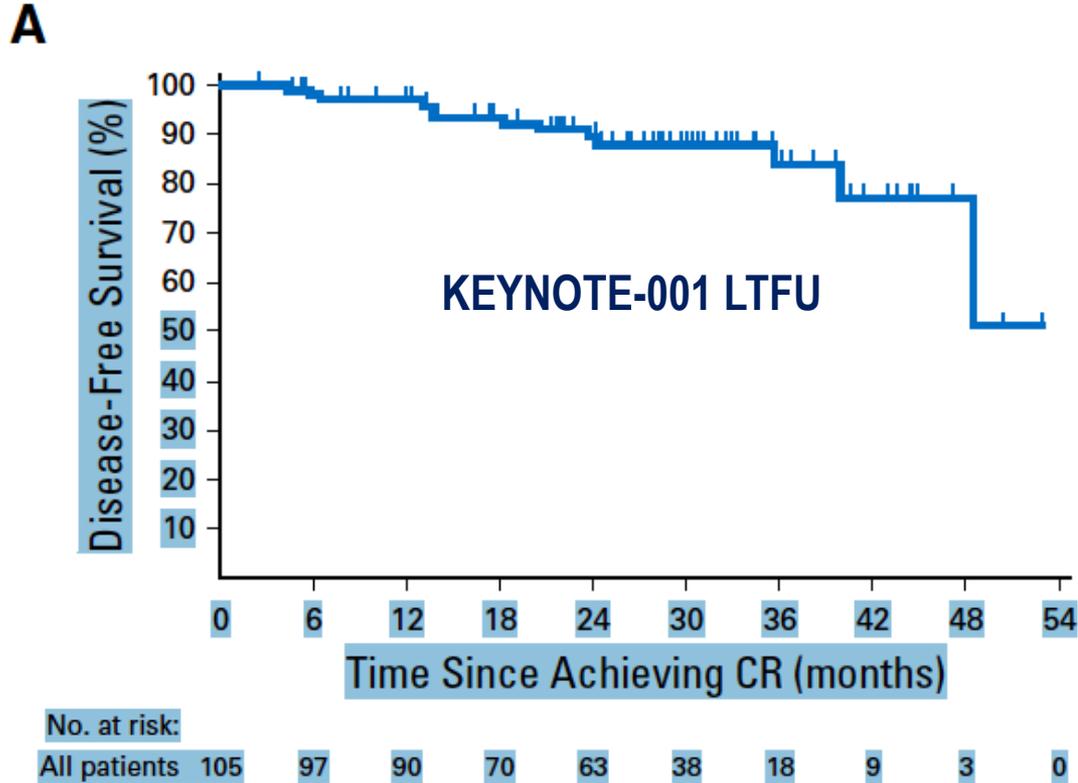
CR rate only 11%; 3 of 10 (30%) patients with CR progressed

LTFU data in pembrolizumab study



- ORR 56% (28/50)
- 20/28 (72.4%) responses ongoing; median F/U ~15 mos
- 12/50 (24%) patients with CR
 - 8/12 (66%) CRs ongoing at last F/U

How does this compare with melanoma experiences?



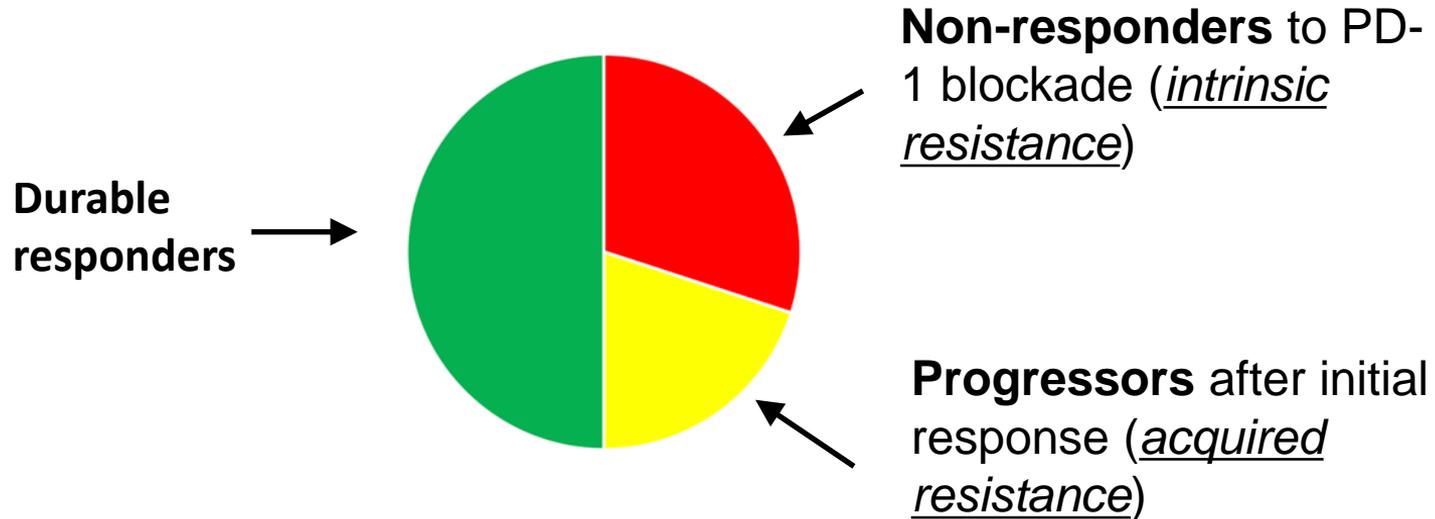
CR rate = 105/655 (**16%**)

Only 7 of 105 (**6.7%**) had PD at data cutoff

MCC experience so far:

- PD in 4/12 (**33%**)
pembro
- PD in 3/10 (**30%**) with
avelumab

3 distinct populations with unmet needs have emerged

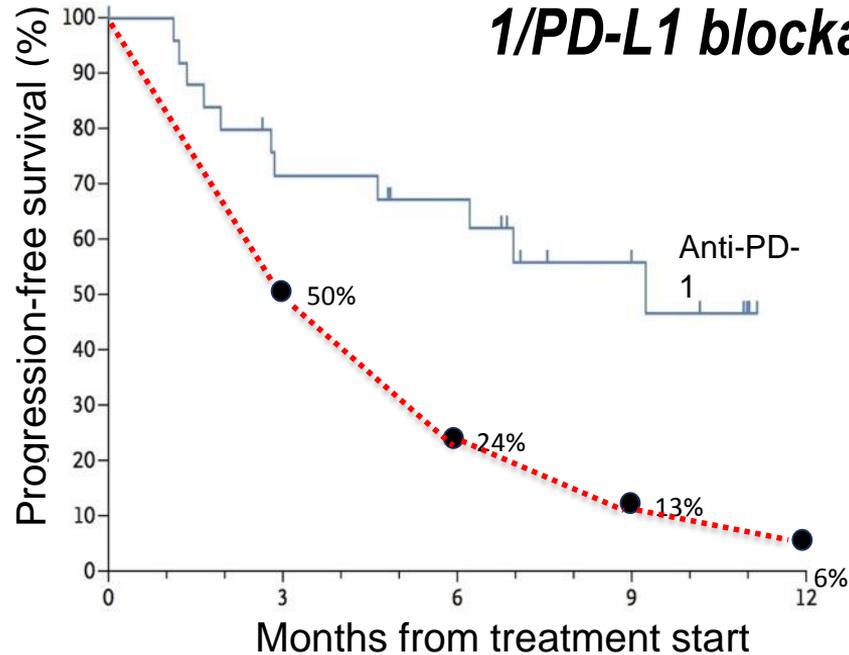


- **Ineligible** patients with contra-indications to PD-1 blockade: Immune-suppressed patients; Auto-immune conditions etc.

What can we do to help improve the chances of curing MCC patients?

I. Think critically before choosing chemotherapy over immunotherapy

Is there a reason to choose chemotherapy over PD-1/PD-L1 blockade in immune competent patients?



{Nghiem P, Bhatia S et al. 2016 *NEJM*}

Chemotherapy
historical data,
(n=62)
{Iyer, et al,
Cancer Med
2016}

**ORR by number of prior
Chemo regimens:**

0 ~ 60%

1 ~ 40%

≥2 ~ 20%

**Caution: Numbers are
rounded and from separate
trials**

{Kaufman H et al. *The Lancet Oncology* 2016}

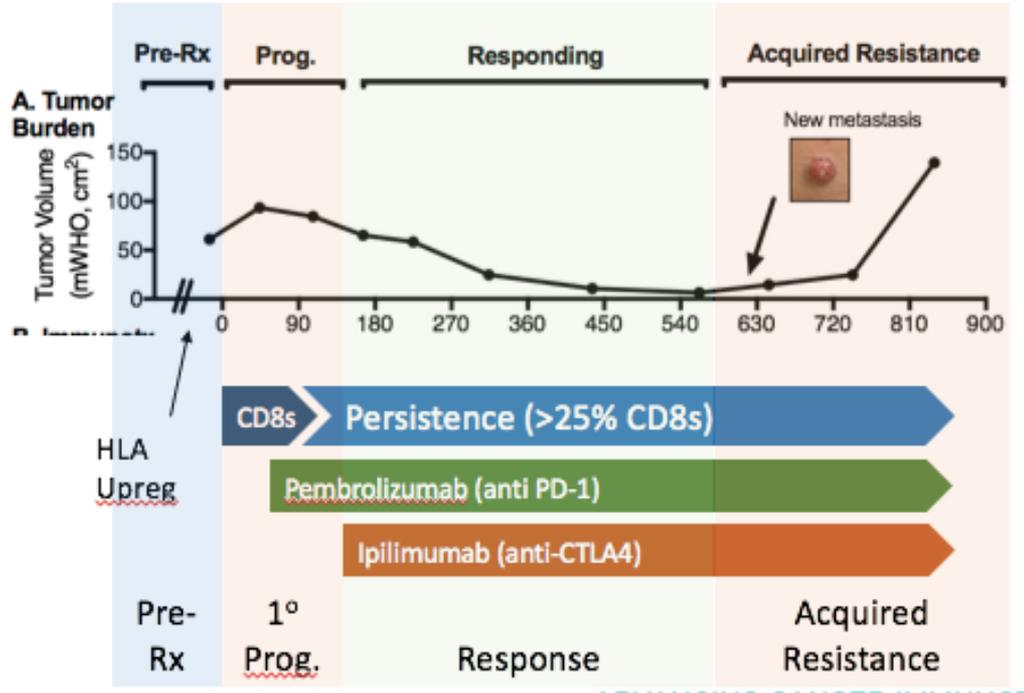
{Topalian S, Bhatia S et al. *AACR* 2017}

II. Uncover mechanisms of intrinsic and acquired resistance

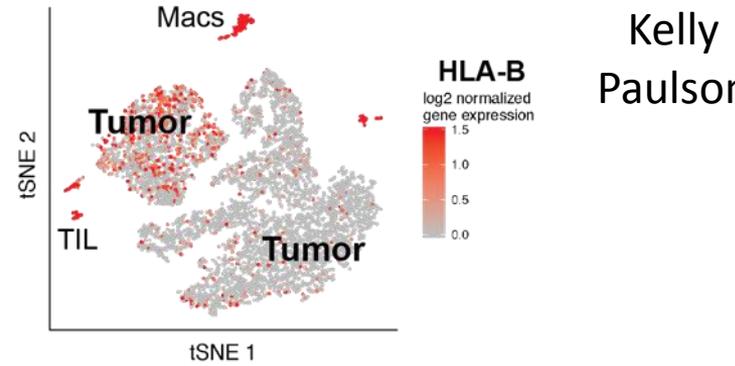
Patient had received **HLA-B*3502** restricted CD8s targeting MCPyV



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C. Tumor-specific HLA-B loss



{Paulson K, et al...Chapuis A. *SITC* 2017}

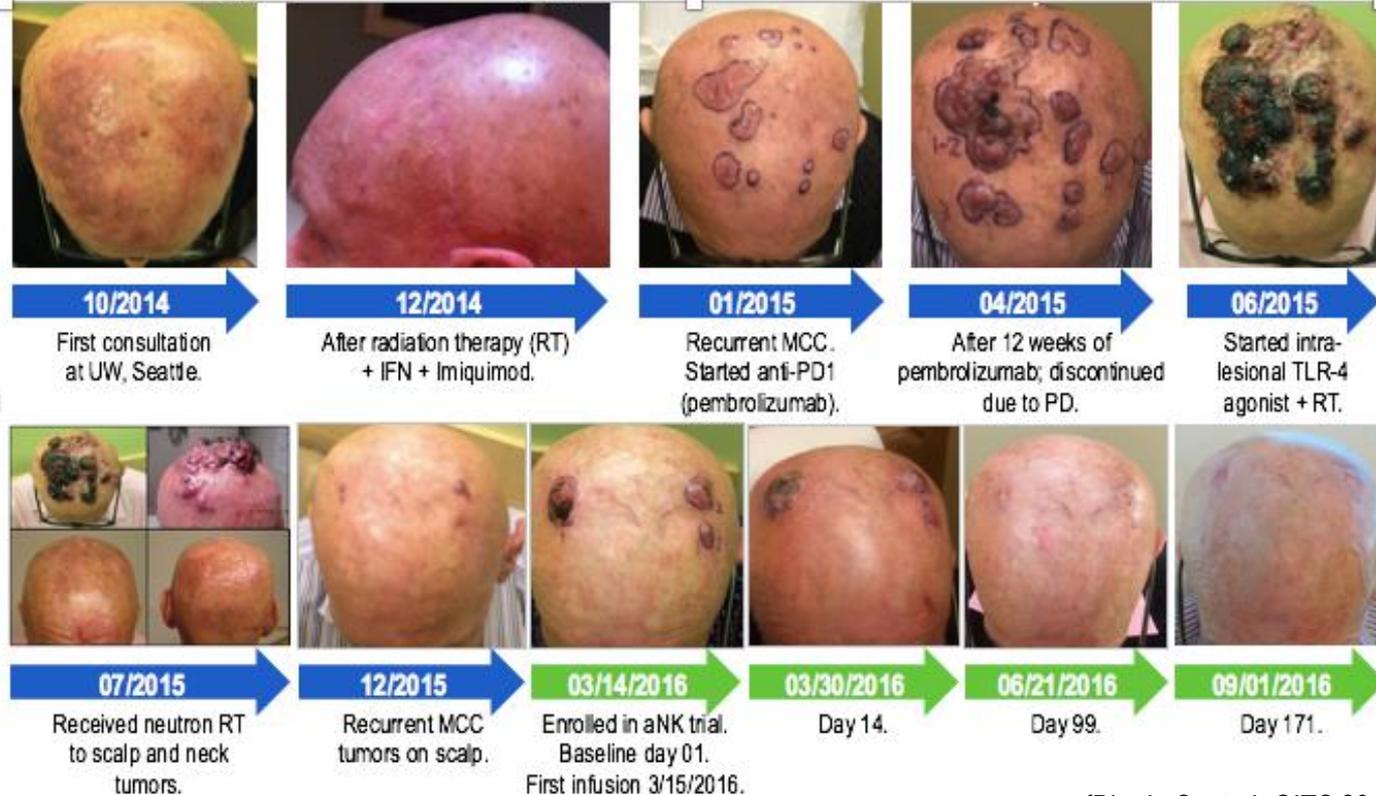
III. Prioritize **Clinical trials** for ICI-resistant MCC!!

Numerous strategies being investigated in **refractory MCC** (too many to summarize in this talk)

- **Intra-lesional approaches** [TVEC; TTI-621; STING-agonist; several TLRs]
- **Cellular therapies** [aNK-cells; MCPyV-TCR (ATTAC-MCC)]
- **Immune-checkpoints and costimulatory agonists** [CTLA-4; 41bb]
- **Others** [MDM2i; cytokines (NKTR-214, ALT-803); SSTR-PRRT; Radiation]

Reversal of ICI-refractoriness with NK cells

Fig 1: Response with aNK Cell Therapy in a Patient With MCC Refractory to Chemotherapy, Radiation Therapy, and PD-1 Blockade



Abscopal response to Neutron RT in a patient with CLL and MCC progressing on pembrolizumab



Upendra
Parvathaneni
Rad Onc, UW

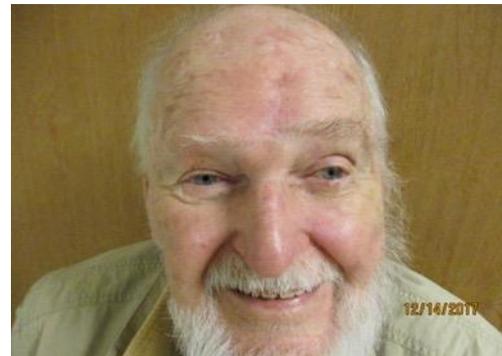


10/12/2017

Neutron RT



Continued
pembrolizumab



12/14/2017

IV. Use Adjuvant systemic therapy for high-risk NMSC

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 endpoint³²
- FPFV occurred in 12/2017



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

Pembrolizumab Versus Placebo Following Surgery and Radiation in Participants With Locally Advanced Cutaneous Squamous Cell Carcinoma (MK-3475-630/KEYNOTE-630)

- N=570
- Histologically confirmed LA cSCC with ≥ 1 high-risk feature(s) as the primary site of malignancy

V. Early detection of recurrences using surveillance

Serologic Surveillance for relapse (AMERK):

a validated, clinically available test listed in the NCCN guidelines

TESTING & DIAGNOSIS / SEROLOGY TEST

Serology test

A blood test for recurrence and disease status in Merkel cell carcinoma.

Purpose of the Merkel polyomavirus serology test

The **Merkel polyomavirus** serology test is a blood test that is helpful in managing MCC patients (whether they make these antibodies or not) so that possible disease recurrence can be detected early, when it can be most effectively treated. A

<https://merkelcell.org/testing-and-diagnosis/sero/>

Page 1

PT. NO.	CLINICAL LAB REQUEST UW MEDICINE CLINICAL IMMUNOLOGY LAB	UW LAB ACC. #																												
NAME (Last, First)	AMERK Requisition	LOGGED IN BY: _____ PROCESSED BY: _____																												
D.O.B.	University of Washington Medical Center 1959 NE Pacific St., NW 220 Seattle, WA, 98195	(206) 520-4600 How to Order/Send samples, Billing (206) 596-6149 Technical Questions																												
SSN: XXX-XX-XXXX	<input type="checkbox"/> M <input type="checkbox"/> F	NOTE: When ordering tests for which Medicare reimbursement will be sought, physicians should only order tests which are medically necessary for diagnosis or treatment of the patient. You should be aware that Medicare generally does not cover routine screening tests, and will only pay for tests that are covered by the program and are reasonable and necessary to treat or diagnose the patient.																												
ORDERING PHYSICIAN <small>REQUIRED</small>	NPI # <small>REQUIRED</small>	___ Anti-Merkel Cell Panel (Serum, 2 mL, min. 0.5 mL) AMERK																												
SPECIMEN TYPE <input type="checkbox"/> Serum		Merkel Virus Oncoprotein Serology: Oncoprotein antibodies are present in the blood of 50% of patients when they have clinically detectable MCC. In patients who make oncoprotein antibodies, titers are expected to decrease significantly within 3 months of successful treatment of MCC. Changes in oncoprotein titer of less than 25% may not be biologically significant. A significant rise in titer or stabilization of titer above 2000 STU may be associated with persistent or recurrent MCC. Questions? See www.merkelcell.org/sero																												
DATE & TIME COLLECTED <small>REQUIRED</small>	<input type="checkbox"/> AM <input type="checkbox"/> PM	ICD codes: ICD codes are provided only for informational or educational purposes. The decision as to which ICD code to use rests solely with the ordering health care provider. The ordering health care provider should assign the most accurate code possible whether included in the table of ICD codes or not.																												
SENDER SPECIMEN #		<table border="1"><tr><td>C4A Unspecified</td><td>MCC of the Trunk</td></tr><tr><td>MCC of the Face</td><td>C4A.5 Trunk, unspecified</td></tr><tr><td>C4A.0 Lip</td><td>C4A.51 Anal or perianal skin</td></tr><tr><td>C4A.1 Eyelid (incl. Canthus)</td><td>C4A.52 Skin of breast</td></tr><tr><td>C4A.10 Eyelid, unspecified</td><td>C4A.59 Trunk, other part</td></tr><tr><td>C4A.11 Eyelid, right</td><td>MCC of the Limb</td></tr><tr><td>C2A.12 Eyelid, left</td><td>C4A.6 Upper limb (incl. shoulder)</td></tr><tr><td>C4A.2 Ear (and ext. auricular canal)</td><td>C4A.60 Upper limb, unspecified</td></tr><tr><td>C4A.20 Ear, Unspecified</td><td>C4A.61 Upper limb, right</td></tr><tr><td>C4A.21 Ear, right</td><td>C4A.62 Upper limb, left</td></tr><tr><td>C4A.22 Ear, left</td><td>C4A.7 Lower limb, (incl hip)</td></tr><tr><td>C4A.3 Face, other parts</td><td>C4A.70 Lower limb, unspecified</td></tr><tr><td>C4A.30 Face, unspecified</td><td>C4A.71 Lower limb, right</td></tr><tr><td>C4A.31 Nose</td><td>C4A.72 Lower limb, left</td></tr></table>	C4A Unspecified	MCC of the Trunk	MCC of the Face	C4A.5 Trunk, unspecified	C4A.0 Lip	C4A.51 Anal or perianal skin	C4A.1 Eyelid (incl. Canthus)	C4A.52 Skin of breast	C4A.10 Eyelid, unspecified	C4A.59 Trunk, other part	C4A.11 Eyelid, right	MCC of the Limb	C2A.12 Eyelid, left	C4A.6 Upper limb (incl. shoulder)	C4A.2 Ear (and ext. auricular canal)	C4A.60 Upper limb, unspecified	C4A.20 Ear, Unspecified	C4A.61 Upper limb, right	C4A.21 Ear, right	C4A.62 Upper limb, left	C4A.22 Ear, left	C4A.7 Lower limb, (incl hip)	C4A.3 Face, other parts	C4A.70 Lower limb, unspecified	C4A.30 Face, unspecified	C4A.71 Lower limb, right	C4A.31 Nose	C4A.72 Lower limb, left
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SEND REPORT TO (Hospital, Clinic, Physician) <small>REQUIRED</small>																														
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CONCLUSIONS

- NMSCs are rising in incidence with a growing impact
- High-mutational burden and viral associations (MCC) contribute to immunogenicity
- Data with PD-1 blockade look highly promising, with frequent and durable responses
- Immunotherapy should be considered for front-line systemic therapy of NMSCs, when feasible and appropriate.

We still have lots of work to do!

Let us not celebrate too much too soon!

The New York Times

OP-ED CONTRIBUTOR

Clinical Trials Need Cancer Patients

By Stan Collender

June 19, 2015



Tuesday, September 3, 2019



Stan Collender

A TRIBUTE TO STAN COLLENDER: THE BUDGET GUY, IMMUNOTHERAPY PIONEER (PATIENT #1), COLLEAGUE AND FRIEND (1951-2019)

By Michael B. Atkins, MD