THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

The unifying principle: Give immunotherapy for ALL advanced skin cancers

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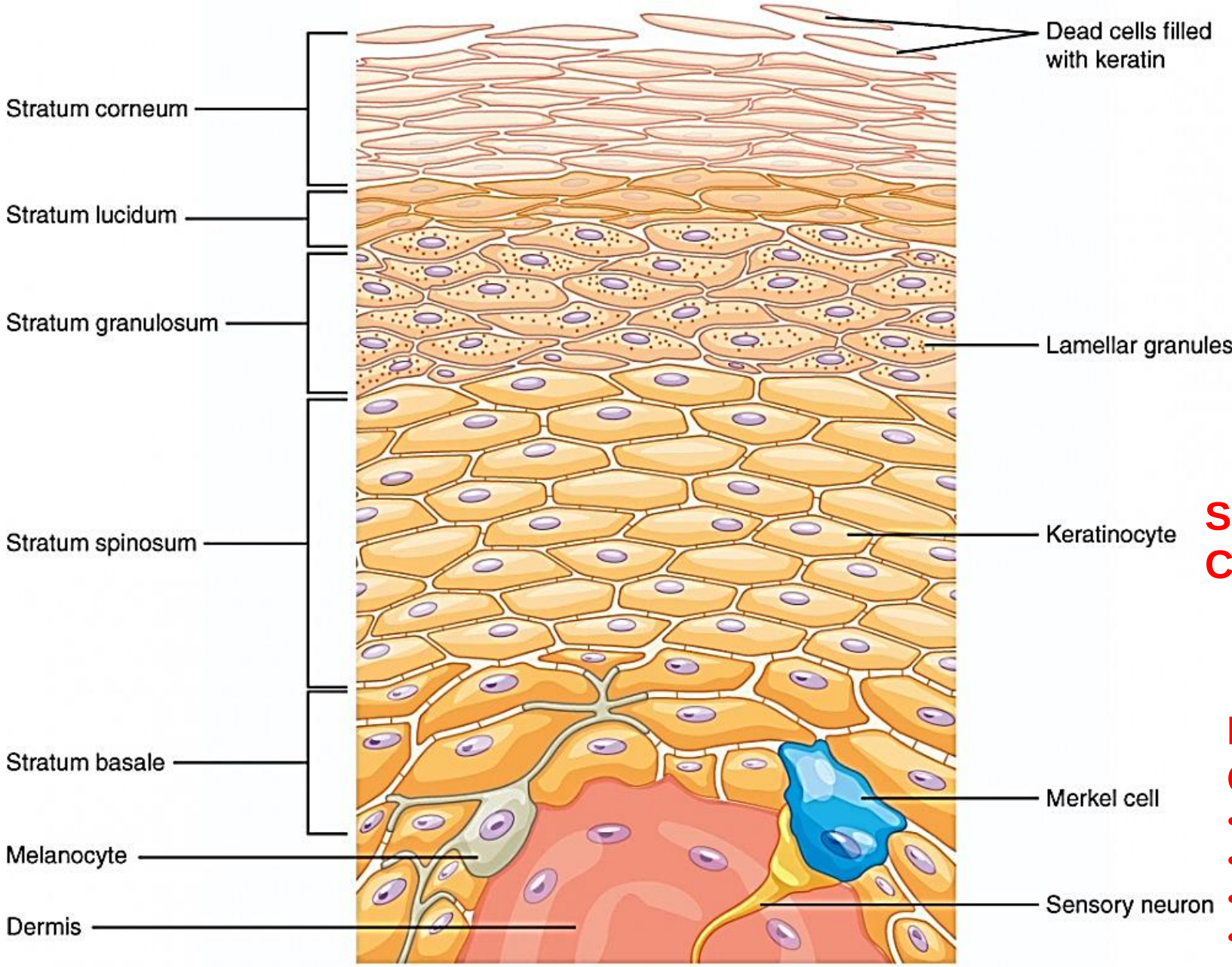
Disclosures

- Advisory Board Participation

  Merck , Pfizer, Bristol Myers Squibb, Regeneron, EMD-Serono, ExiCure, Castle Biosciences, Adagene

Agenda

- Skin : The elements of skin that can become cancerous.
  - Melanoma
  - Cutaneous Squamous Cell Carcinoma
  - Basal Cell Carcinomas
  - Merkel Cell Carcinomas
- Hot Button topics/areas for the use of immunotherapy in each cancer.
- “Wrinkles” in using immunotherapy for individual nonmelanoma skin cancers.



Squamous Cell Carcinoma

Basal Cell Carcinoma

Merkel Cell Carcinoma ??

- Keratinocytes
- Dermal Fibroblasts
- B Cells
- Epithelial progenitor cells

Adapted from: Figure 4 Layers of the Epidermis , https://courses.lumenlearning.com/cuny-csi-ap-1/chapter/layers-of-the-skin/

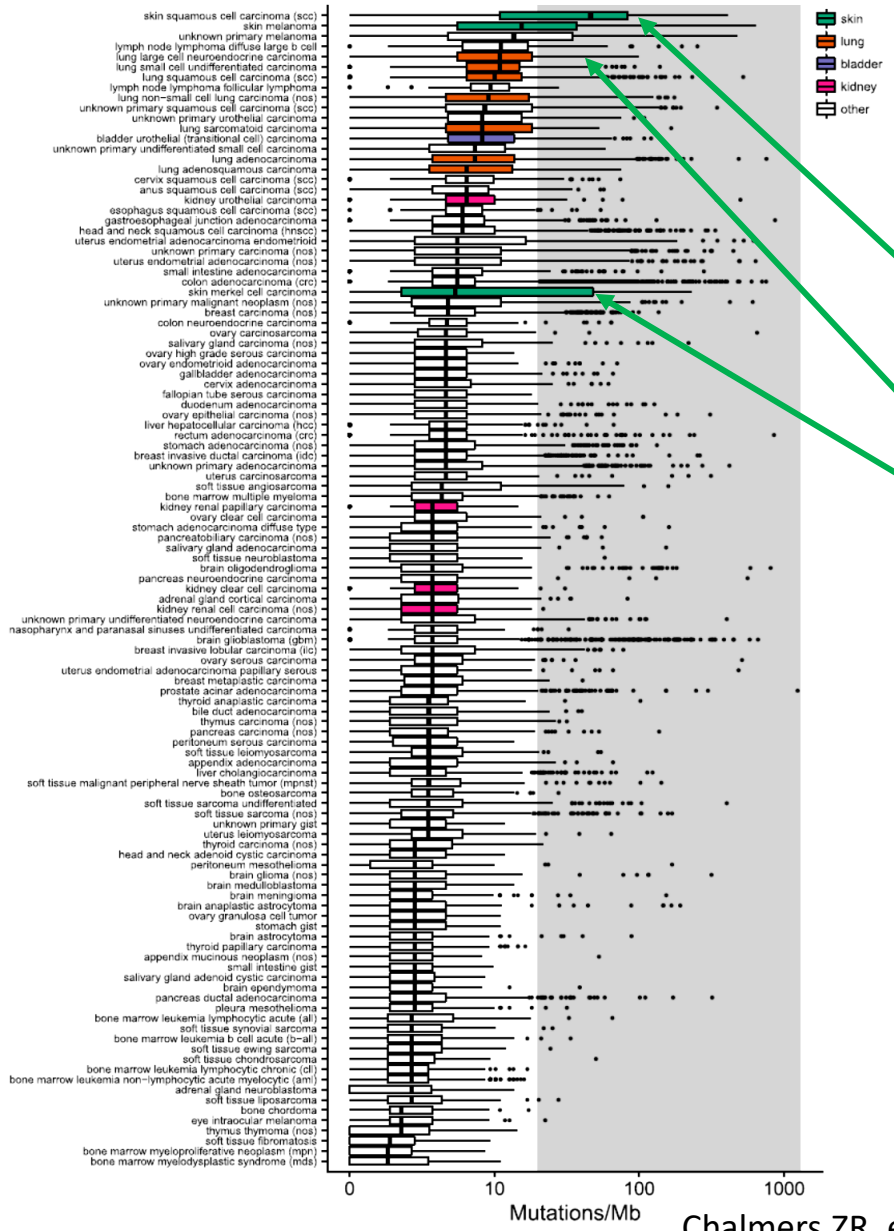
Skin Cancer	Indication	“Wrinkle”
Melanoma		
Cutaneous Squamous Cell Carcinoma		
Basal Cell Carcinoma		
Merkel Cell Carcinoma		

Skin Cancers Cluster Together

Shared risk factors

- Age
- UV Exposure
- Immunosuppression
- However, each have different ‘drivers’, biologic behavior, and prognostic factors.

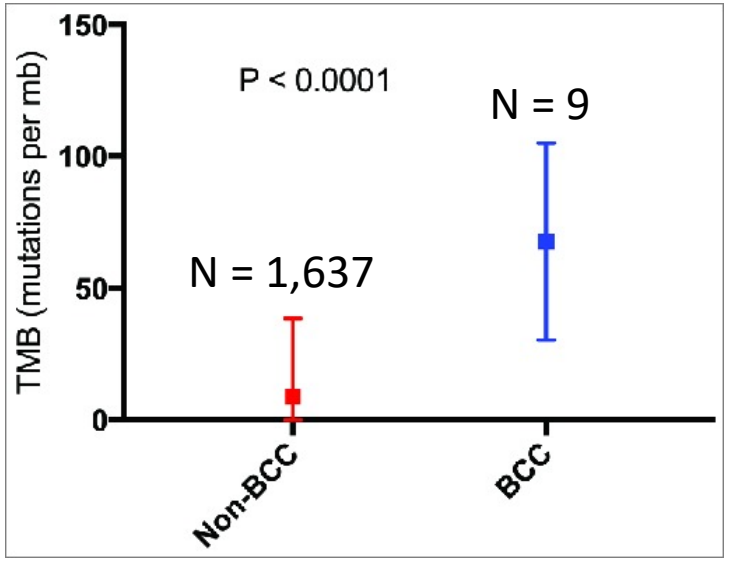
High Tumor Mutation is associated with Response to Immunotherapy



Analysis of 100,000 Human Cancer Genomes Reveals the Landscape of Tumor Mutational Burden

skin malignancies are, on average, HIGH in mutational burden.

1. Cutaneous SCC the highest mutation burdens in all malignant diseases
2. Melanoma is #2 and 3
3. Merkel cell carcinoma

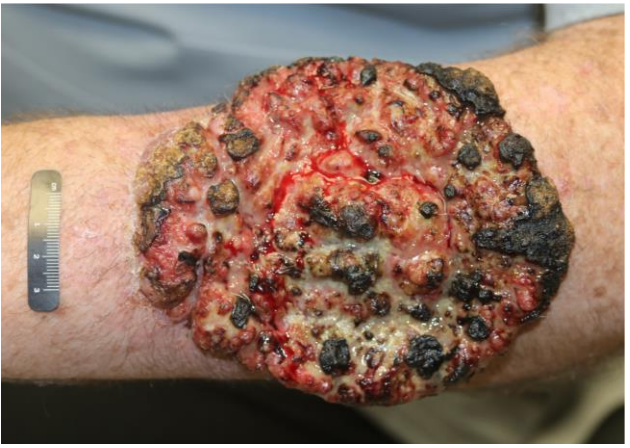


Chalmers ZR, et al. Genome Med. 2017 Apr 19;9(1):34.; Goodman, Aaron M., et al. *Oncoimmunology* 7.3 (2018):

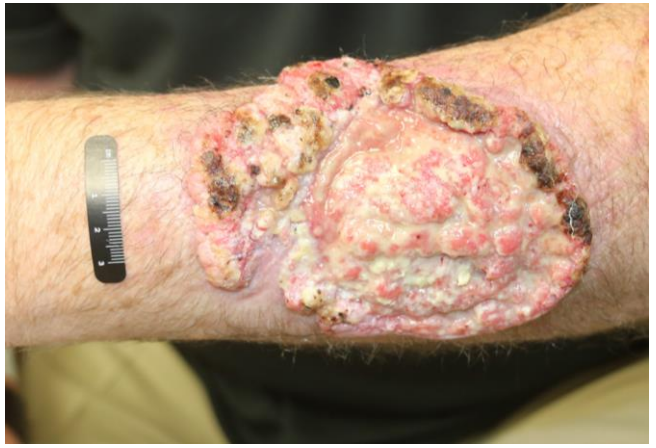
Skin Cancer	Indication	"Wrinkle"
Melanoma	Pembrolizumab, Nivolumab, TVEC, Atezolizumab, IL-2, (Relatlimab) • Stage III, IV melanoma. • Unresectable melanoma • Adjuvant therapy	• Ipi+nivo, vs nivo monotherapy • Stage IIB, C ? • Neoadjuvant therapy • Sequence with immunoRx and Targeted Therapy.
Cutaneous Squamous Cell Carcinoma		
Basal Cell Carcinoma		
Merkel Cell Carcinoma		

Cemiplimab Therapy : LA cSCC , Lt Forearm

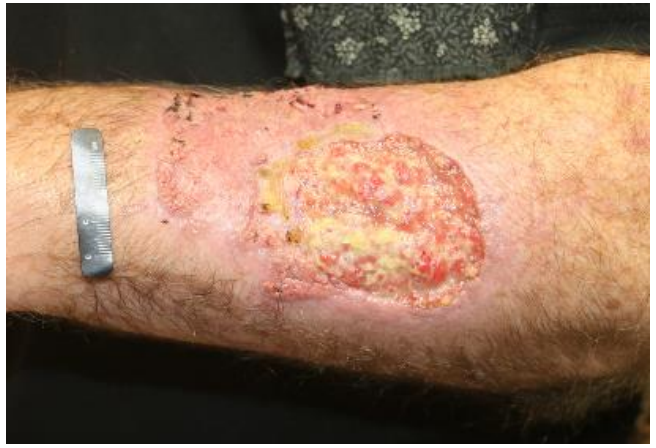
10/08/2019
Pre treatment



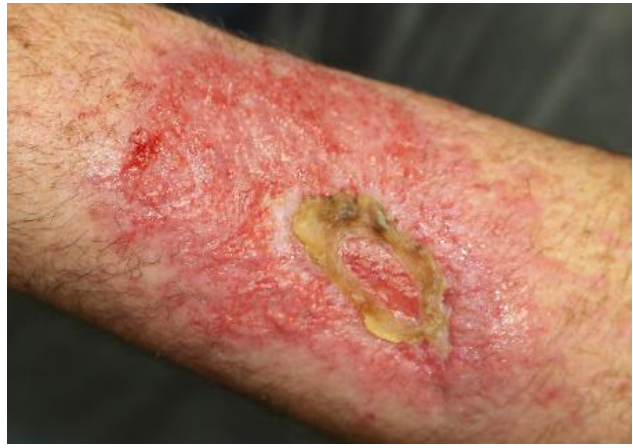
10/29/2019
Post Cycle 1



11/19/2019
Post Cycle 3



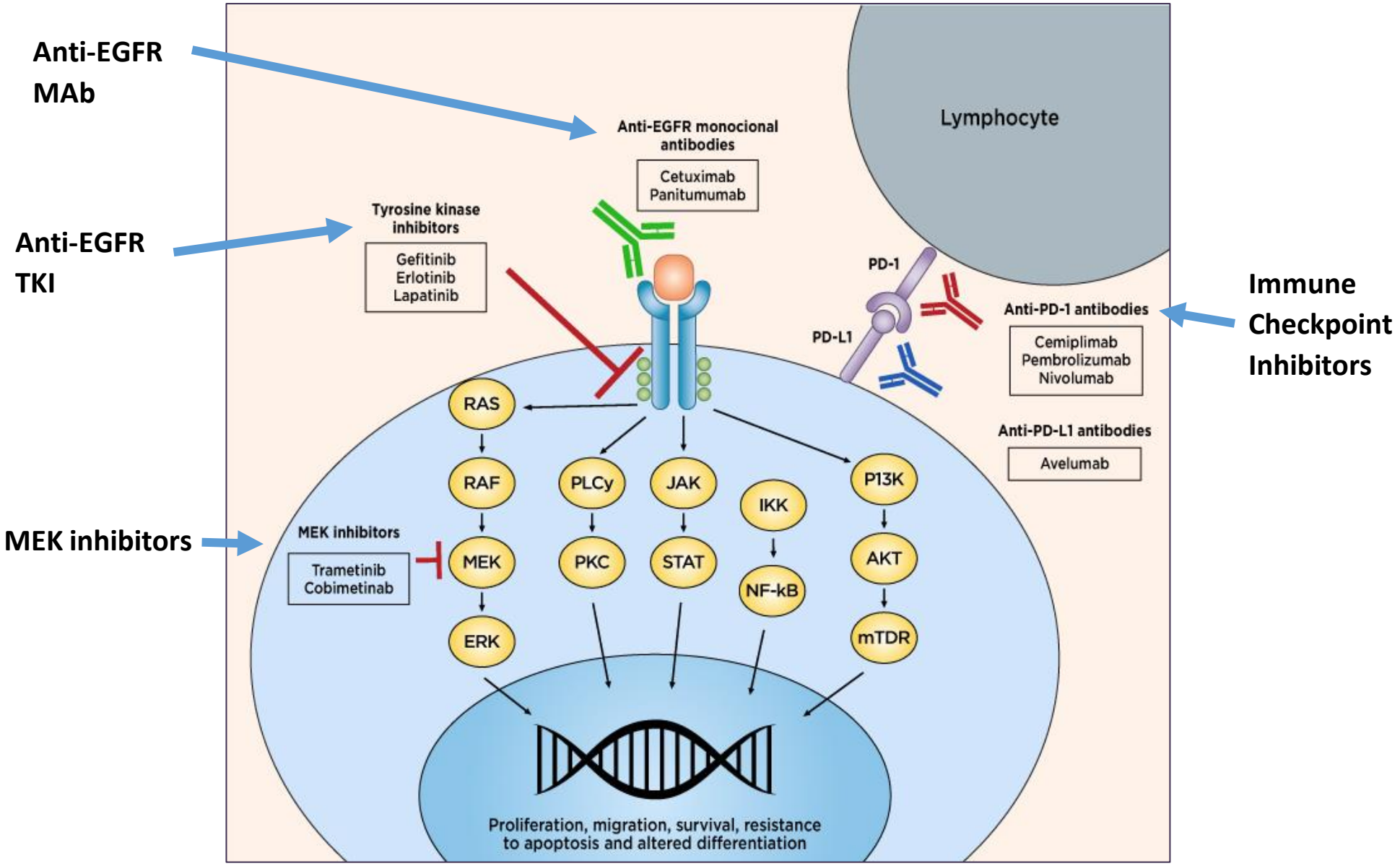
1/07/2020
Post Cycle 5 , Pre-resection



Histologic diagnosis of resection material:

"LEFT POSTERIOR UPPER ARM, SKIN ELLIPSE:
SKIN AND SUBCUTIS WITH FOCAL SCAR AND SQUAMOUS CELL CARCINOMA IN SITU
Margins of resection appear free of squamous cell carcinoma in situ."

Mechanistic Approach to the Therapy of Cutaneous Squamous Cell Carcinoma



Adapted from Corchado-Cobos R, et al. *Int J Mol Sci.* 2020;21(8):2956.

Clinical Studies with EGFR Inhibitors

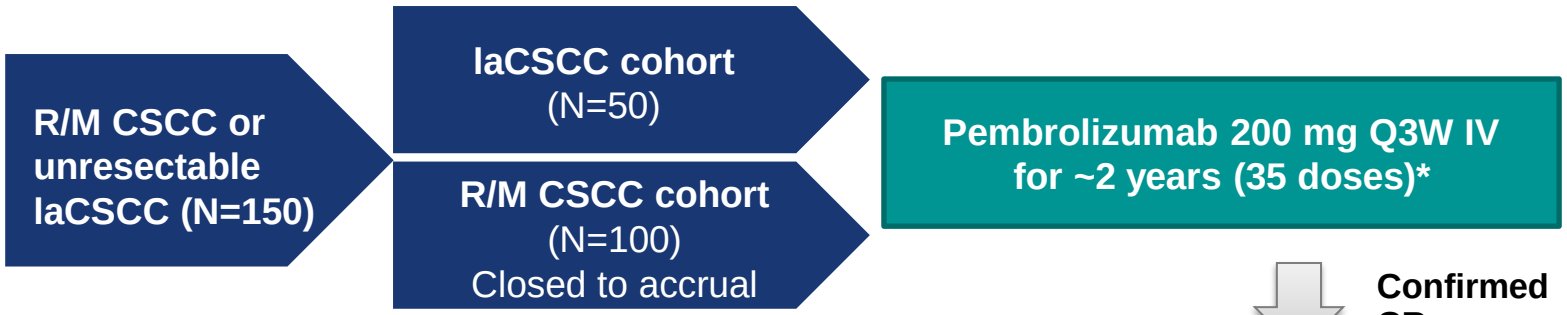
Therapy	Line of therapy	Number of evaluable patients	Overall response rate (ORR)	Duration of response (DOR)	Complete remission (CR)
Cetuximab[14]	First-line	36	28%	6.8 months	6%
Panitumumab[15]	First-line/second-line	16	31%	8 months	12%
Gefitinib[16]	Neoadjuvant	22	45%	64% **(2-year-PFS)**	18%
Erlotinib[17]	First-line/second-line	29	10%	4.7 months **(PFS)**	0%
Erlotinib andradiation [18]	T4 primary tumours	15	–	60% **(2-year-PFS)**	–
Lapatinib[19]	Neoadjuvant	10	25%	–	0%

Table adapted from : Gellrich, F. F., et al. "Medical treatment of advanced cutaneous squamous-cell carcinoma." Journal of the European Academy of Dermatology and Venereology 33 (2019): 38-43.

14. Maubec, Eve, et al. "Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin." J Clin Oncol 29.25 (2011): 3419-3426.
15. Foote, M. C., et al. "Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma." *Annals of oncology* 25.10 (2014): 2047-2052.
16. Lewis, Carol M., et al. "A phase II study of gefitinib for aggressive cutaneous squamous cell carcinoma of the head and neck." *Clinical Cancer Research* 18.5 (2012): 1435-1446.
17. Gold, Kathryn A., et al. "Erlotinib in the treatment of recurrent or metastatic cutaneous squamous cell carcinoma: a single-arm phase 2 clinical trial." *Cancer* 124.10 (2018): 2169-2173.
18. Heath, C. Hope, et al. "Phase 1 study of erlotinib plus radiation therapy in patients with advanced cutaneous squamous cell carcinoma." *International Journal of Radiation Oncology* Biology* Physics* 85.5 (2013): 1275-1281.
19. Jenni, D., et al. "A prospective clinical trial to assess lapatinib effects on cutaneous squamous cell carcinoma and actinic keratosis." *ESMO open* 1.1 (2016): e000003.

Phase 2 KEYNOTE-629 R/M CSCC or laCSCC Study

Open-label, single-arm, phase 2 multicenter study (NCT03284424)[1–2]



Primary endpoint:
ORR†

Key secondary endpoints:
DOR†, DCR†, PFS†, OS, safety and tolerability

Exploratory endpoints:
PK, biomarkers, and HRQoL

Key inclusion criteria:
- ✓ Aged ≥18 years
- ✓ Histologically-confirmed CSCC as primary site of malignancy
- ✓ Metastatic disease and/or locally recurrent disease not curable by surgery, radiation, or systemic therapy
- ✓ Measurable disease
- ✓ ECOG PS 0–1

Active, not recruiting

Start date: Oct 2017
Primary completion date: Jan 2021

*Or until disease progression, unacceptable toxicity, intercurrent illness, noncompliance, or investigator or patient decision to withdraw; †According to blinded independent central review.
‡Patients who discontinue treatment after achieving CR may be eligible to receive an additional 17 cycles of pembrolizumab if PD occurs.
CSCC, cutaneous squamous cell carcinoma; CR, complete response; DCR, disease control rate; DOR, duration of response; EGOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; laCSCC, locally advanced cutaneous squamous cell carcinoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; R/M, recurrent/metastatic; Q3W, every 3 weeks.

1. ClinicalTrials.gov. NCT03284424. https://clinicaltrials.gov/ct2/show/NCT03284424. Accessed June 10, 2020. 2. Grob JJ et al. Poster presented at AACR Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA. Abstract CT170.

Phase 2 EMPOWER-CSCC-1 Study

Ongoing pivotal phase 2 EMPOWER-CSCC-1 study (NCT02760498)[1–5]

Group 1: Metastatic (nodal or distant) CSCC (N=59)	**Cemiplimab 3 mg/kg IV Q2W for up to 96 weeks**	**Response assessments Q8W***
Group 2: Patients with laCSCC who were not candidates for surgery or radiation therapy (N=78)		
Group 3: Metastatic (nodal or distant) CSCC (N=56)	**Cemiplimab 350 mg IV Q3W for up to 54 weeks**	**Response assessments Q9W***
Group 4: Metastatic (nodal or distant) or laCSCC (planned N=63)	**Cemiplimab 600 mg Q4W IV for up to 48 weeks**	**Response assessments Q8W***

Primary endpoint:
ORR by ICR

Key secondary endpoints:
ORR by INV, PFS, OS, CR rate, DOR, safety and tolerability, QoL

Key inclusion criteria:
- ✓ Adults (≥18 years) with histologically confirmed invasive CSCC
- ✓ ECOG PS 0–1
- ✓ At least 1 measurable lesion by RECIST version 1.1 or digital medical photography
- ✓ Adequate organ function

*RECIST 1.1 for scans; modified WHO criteria for photos

CR, complete response; CSCC, cutaneous squamous cell carcinoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ICR, independent central review, INV, investigator; IV, intravenous; laCSCC, locally advanced cutaneous squamous cell carcinoma; ORR, objective response rate; OS, overall survival, PFS, progression-free survival; QnW, every n weeks; QoL, quality of life; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization.

1.ClinicalTrials.gov. NCT02760498. https://clinicaltrials.gov/ct2/show/NCT02760498. Accessed June 10, 2020. 2. R2810-ONC-1540 Clinical Study Protocol. 3. Migden MR et al. *N Engl J Med* 2018;379:341–351. 4. Migden MR et al. *J Clin Oncol* 2019;37 (suppl). Abstract 6015. [poster presentation]. 5. Guminski AD et al. *J Clin Oncol* 2019;37 (suppl). Abstract 9526 [poster presentation].

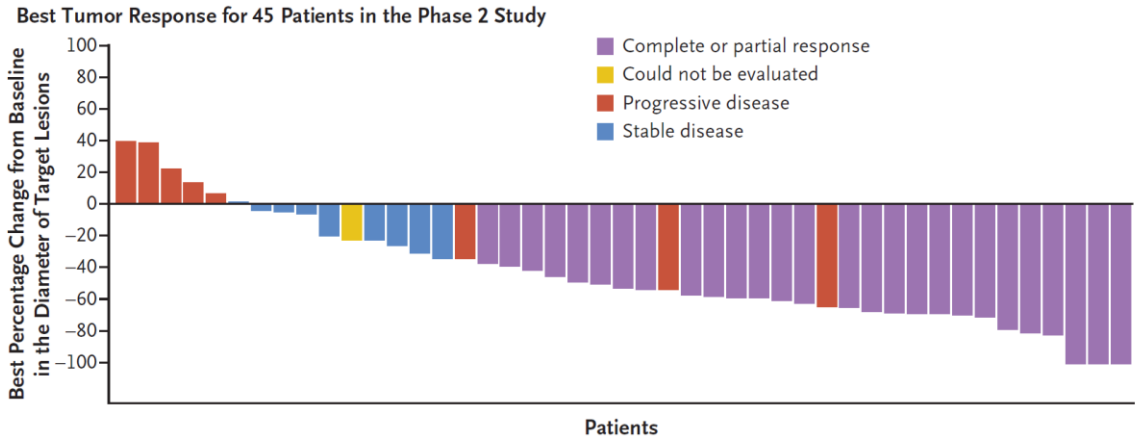
Cemiplimab and Pembrolizumab Trial Data (Multiple Trials)

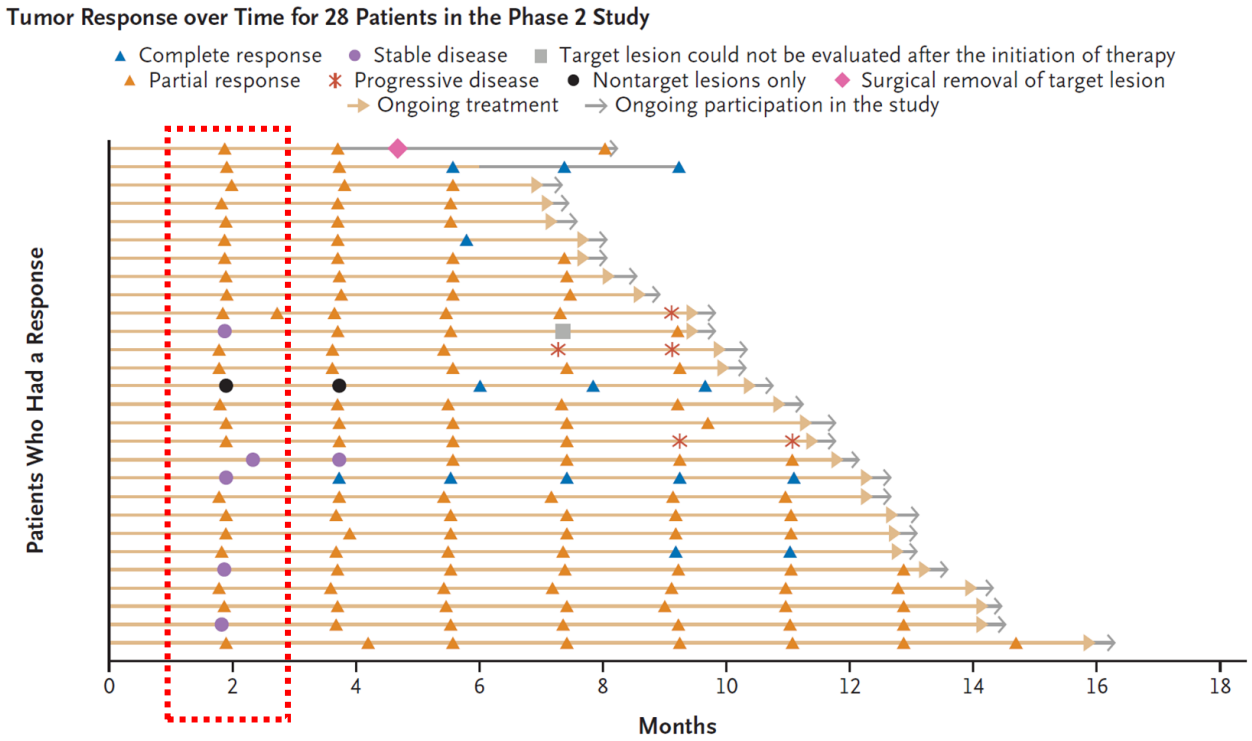
	Cemiplimab[1-3, 5]				Pembrolizumab[4]
Study	EMPOWER-CSCC-1 (Study 1540; pivotal phase 2)				KN-629
Source	September/October 2018 Data Cut[1-3]				ESMO 2019
Patients	Cohort 1: Met[1,3]	Cohort 2: LA[2,3]	Cohort 3: Met[3]	Cohorts 1 and 3: Met	Recurrent/Metastatic CSCC
Dose	Q2W Weight	Q2W Weight	Q3W Fixed	Q2W weight and Q3week fixed	Q3W Fixed
N	59	78	56	115	105
Prior Surgery	—	—	—		80%
Prior RT	85%	55%	—	76.5%	74.3%
Prior Systemic Tx	56%	15%	—	46.1%	100%
Median age	71	74	—	71	72
ECOG PS 0	39%	49%	—	42%	34.3%
Median f/u (mo)	16.5	9.3	8.1	71	9.5
ORR	**49.2%**	**43.6%**	**39.3%**	**44.3%**	**34.4%**
CR	16.9%	12.8%	3.6%	10.4%	3.8%
PR	32.2%	30.8%	35.7%	34%	32%
SD	15.3%	35.9%	14.3%	15%	29.5%
PD	16.9%	11.5%	26.8%	22%	35.9%
Disc. due to TRAE	—	—	—	—	—
Median PFS	*18.4 mo*	*Not Reached*	—	*18.4 mos*	6.9 mos
PFS (6 mo est.)	66%	72%	59%	—	50.4%
PFS (12 mo est.)	53%	58%	45%	—	*32.4%*
Median OS	*Not Reached*	*Not Reached*	—	*Not reached*	*Not Reached*
OS (6 mo est.)	—	—	—		79%
OS (12 mo est.)	81%	93%	76%		

CR, complete response; disc, discontinuation; est, estimated; f/u, follow-up; LA, locally advanced; mo, months; ORR, objective response rate; OS, overall survival; Met, metastatic; PD, progressive disease; PFS, median progression-free survival; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; RT, radiotherapy; SD, stable disease; TRAE, treatment-related adverse event; Tx, treatment.

1. Guminski AD et al. *J Clin Oncol* 2019;37(suppl) Abstract 9526. 2. Migden MR et al. *J Clin Oncol* 2019;37(suppl) Abstract 6015. 3. Libtayo [summary of product characteristics]. Dublin, Ireland: Regeneron; June 2019. 4. Grobb JJ et al. Ann Oncol 2019;30 (suppl_5):v851-v934. Abstract 3622. 5. Rischin D et al. Poster presented at ESMO 2019. Poster 1318P.

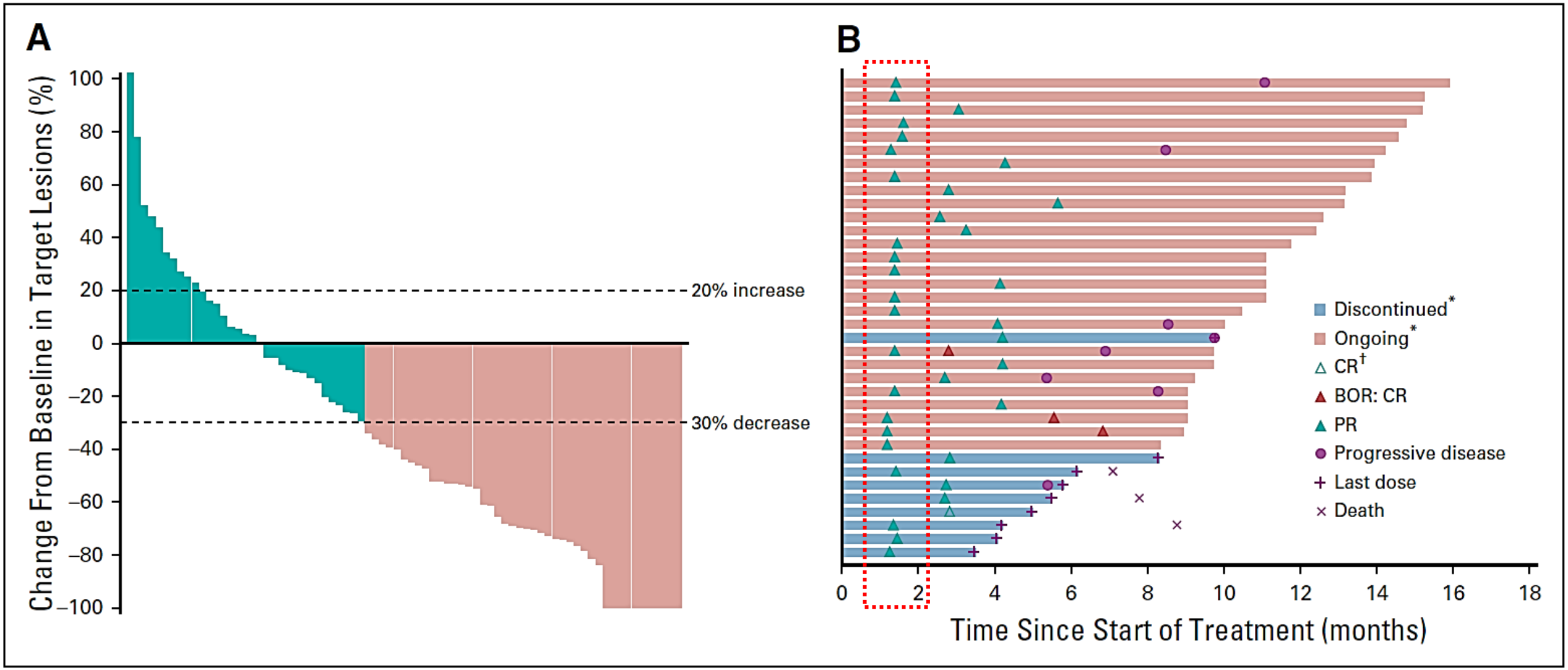
Cemiplimab Phase 2 EMPOWER-CSCC-1





Migden, Michael R., et al. "PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma." New England Journal of Medicine 379.4 (2018): 341-351.

Pembrolizumab Activity in cSCC



Grob, Jean-Jacques, et al. "Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: a single-arm phase II trial (KEYNOTE-629)." Journal of Clinical Oncology 38.25 (2020): 2916.

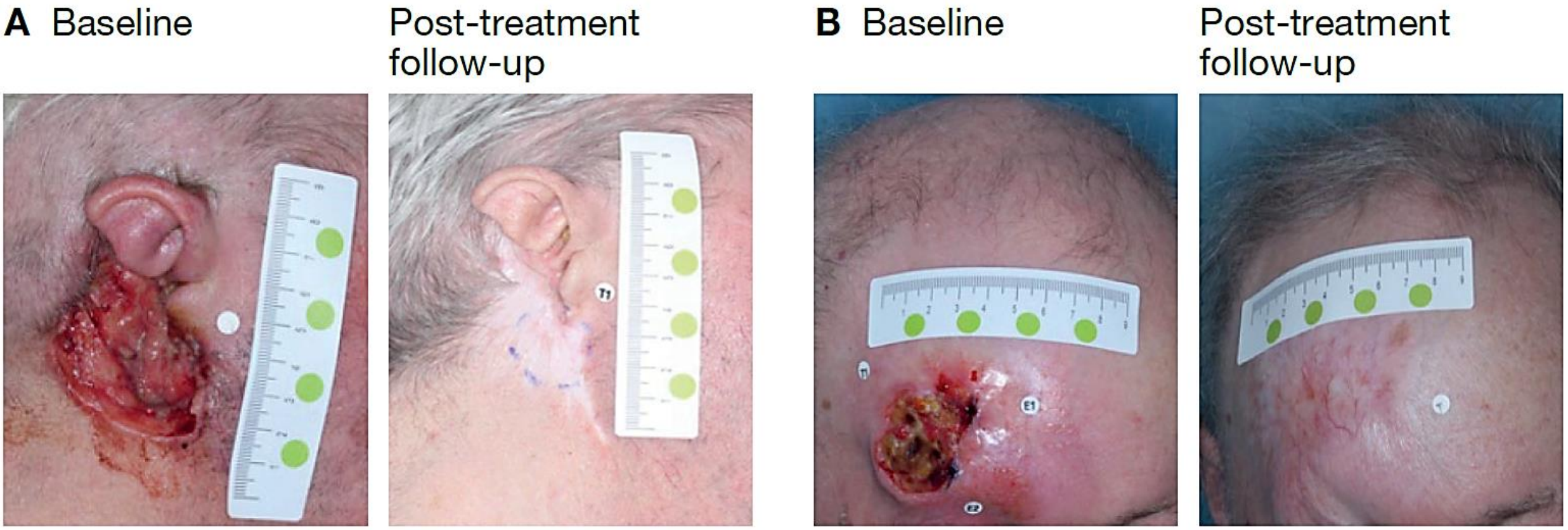
Skin Cancer	Indication	"Wrinkle"
Melanoma	Pembrolizumab, Nivolumab, TVEC, Atezolizumab, IL-2, (Relatlimab) • Stage III, IV melanoma. • Unresectable melanoma • Adjuvant therapy	• Ipi+nivo, vs nivo monotherapy • Stage IIB, C ? • Neoadjuvant therapy • Sequence with immunoRx and Targeted Therapy.
Cutaneous Squamous Cell Carcinoma	Cemiplimab, Pembrolizumab • Locally advanced, metastatic cSCC • "not candidates for curative surgery or radiation"	• Resection is in the eye of the surgeon • Problem of 'squam factory' unsolved • Confused w Lichen planus , topical effects. • Adjuvant benefit unknown • Neoadjuvant benefit unknown

Difficult Categories: immunosuppressed (Transplant), autoimmune diseases, hematologic diseases (CLL, NHL)

Reductions of visible BCC lesions while on cemiplimab treatment

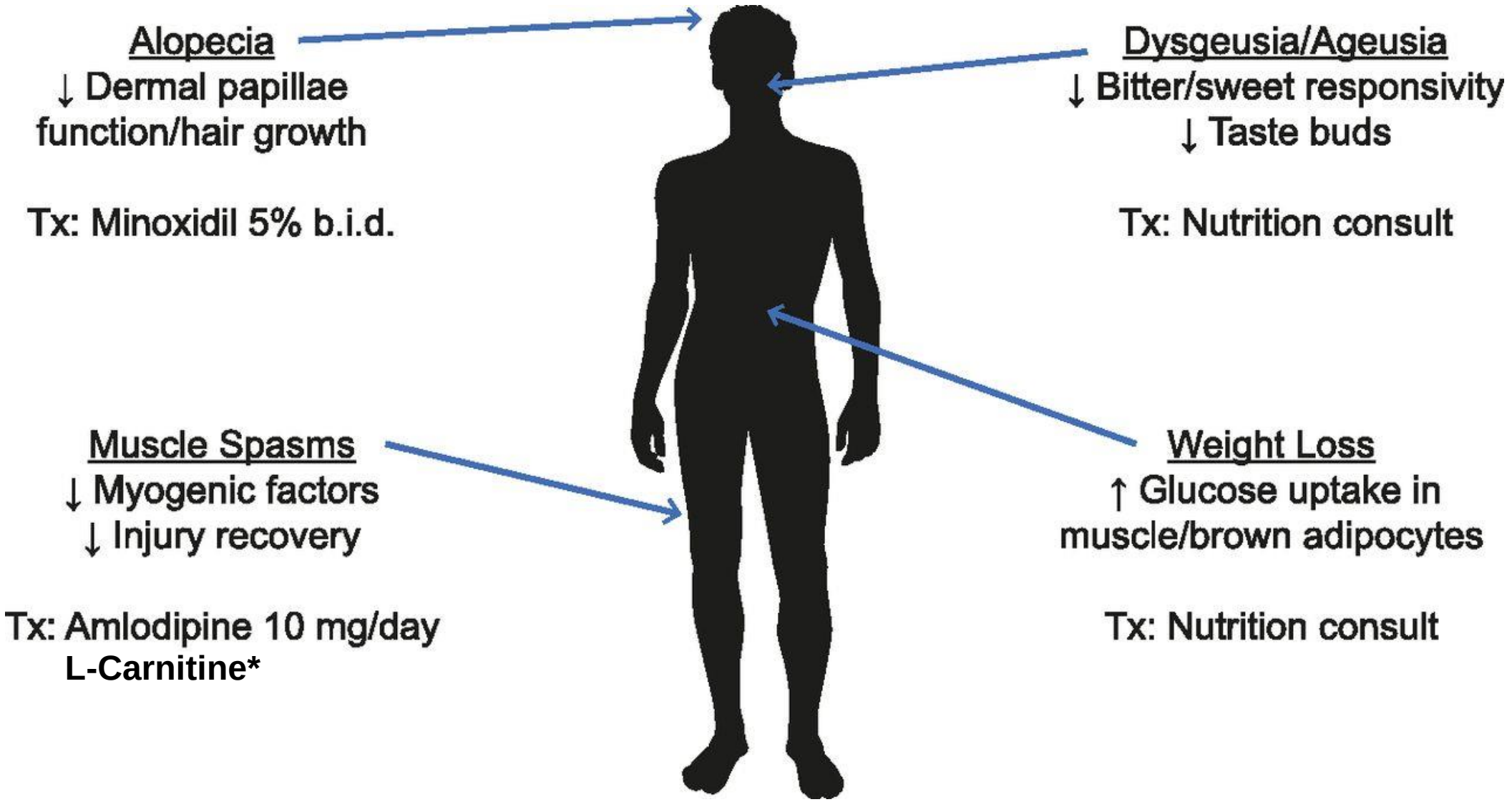
79-year-old man , progression on prior vismodegib.
Post-treatment follow-up (Study Day 726).

66-year-old man treated with radiotherapy and vismodegib
Post-treatment follow-up (Study Day 708).



Stratigos, A., et al. "Primary Analysis of Phase 2 Results for Cemiplimab in Patients (pts) with Locally Advanced Basal Cell Carcinoma (laBCC) who Progress on or are Intolerant to Hedgehog Inhibitors (HHIs)." Head and neck 89 (2021): 75.

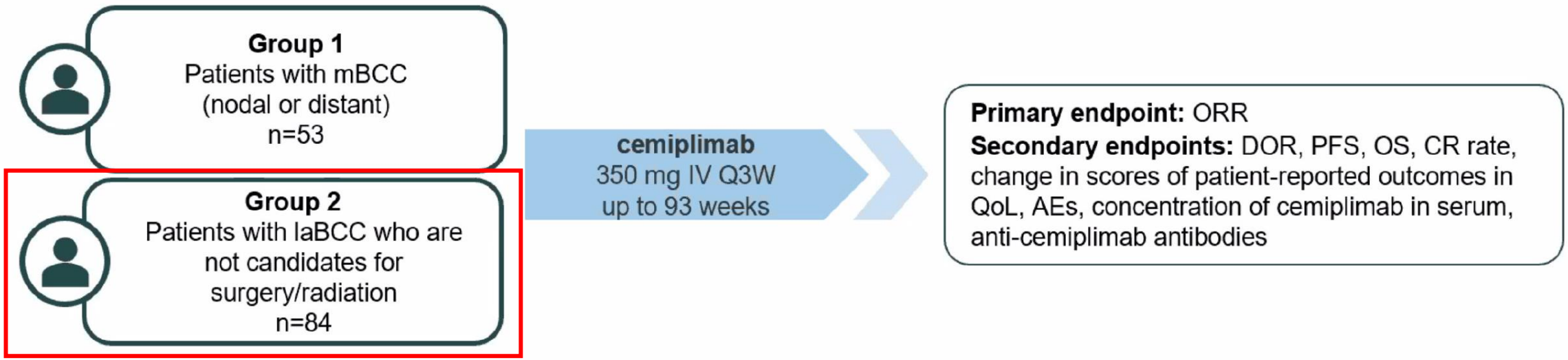
Hedgehog Pathway Inhibitor-Associated Adverse Events



Adapted from Lacouture ME, et al. *The Oncologist*. 2016;21:1218-1229, *Dinehart et al. SKIN The Journal of Cutaneous Medicine. 2018;2.2:90-95..

R2810-ONC-1620: EMPOWER BCC-1 DESIGN

A nonrandomized, two-group, phase 2 clinical trial of cemiplimab in patients with advanced BCC who experienced progression of disease following HHI therapy or were intolerant of prior HHI therapy (NCT03132636)[1,2]



- Tumor assessments are made at the end of each treatment cycle (9 weeks) by ICR
- Patients receive treatment until the end of the treatment period (93 weeks), or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed CR
- Patients will be followed for survival status until death, loss of follow-up, or study termination by the study sponsor

	Patients (n=84)
Median age, years	70 (61–79)
Age ≥65 years	53 (63%)
Sex	
Male	56 (67%)
Female	28 (33%)
Eastern Cooperative Oncology Group performance status score	
0	51 (61%)
1	33 (39%)
Patients with previous cancer-related radiotherapy	42 (50%)
Patients with previous HHI	
Vismodegib	79 (94%)
Sonidegib	14 (17%)
Vismodegib plus sonidegib	9 (11%)
Reason for discontinuation of previous HHI*	
Progression of disease on HHI	60 (71%)
Intolerant to previous HHI therapy	32 (38%)
Intolerant to vismodegib	32 (38%)
Intolerant to sonidegib	4 (5%)
No better than stable disease after 9 months on HHI therapy	7 (8%)
Primary basal cell carcinoma site	
Head and neck	75 (89%)
Trunk	7 (8%)
Arm or leg	2 (2%)

Data are median (IQR) or n (%). HHI=hedgehog inhibitor. *The sum is more than 84 because some patients had more than one reason for discontinuation.

Table 1: **Baseline patient characteristics**

	Patients (n=84)
Objective response	26 (31%; 21–42)*
Best overall response	
Complete response	5 (6%)
Partial response	21 (25%)
Stable disease	41 (49%)
Progressive disease	9 (11%)
Not evaluable†	8 (10%)
Disease control	67 (80%; 70–88)
Durable disease control	50 (60%; 48–70)
Median time to response, months‡	4·3 (4·2–7·2)
Observed duration of response‡	
Range, months	2–21
≥6 months	19 (79%)
≥12 months	11 (46%)
Kaplan-Meier estimation of duration response‡	
Median	Not reached
Remained in response at 6 months	91% (68–98)
Remained in response at 12 months	85% (61–95)

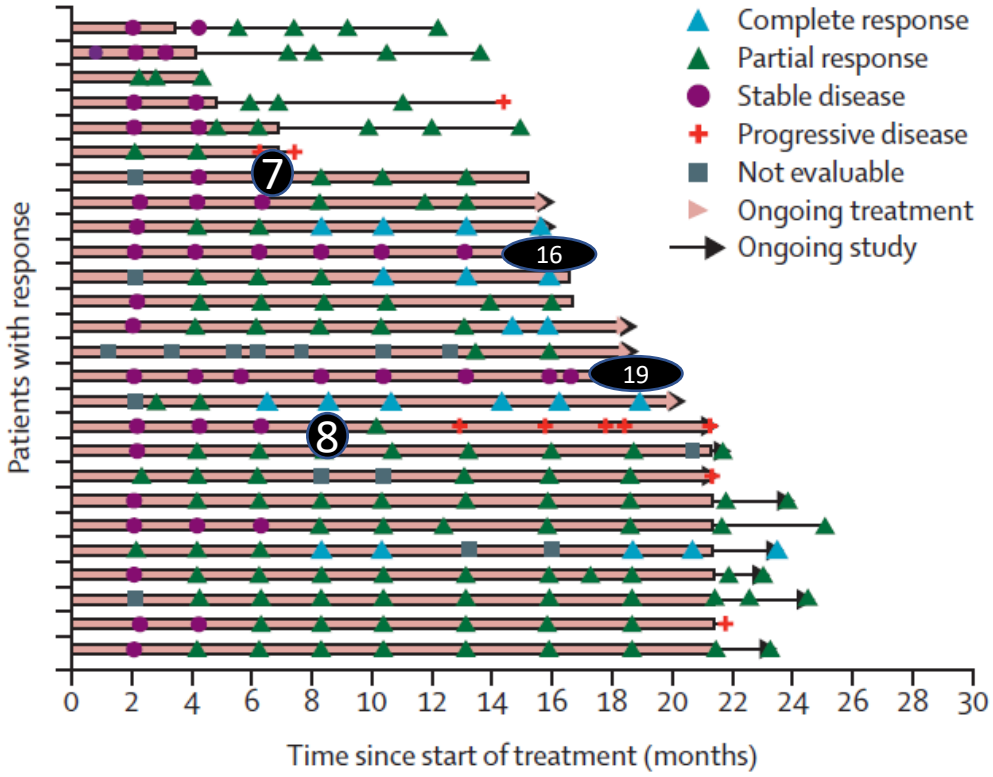
Data are n (%; 95% CI), n (%), median (IQR), or range (where specified). *Objective response per independent central review includes two partial responses that emerged at tumour assessments before the data cutoff and were confirmed by tumour assessments done subsequent to the data cutoff. †Of the eight patients who were not evaluable, four did not have any post-baseline tumour assessments, three patients were not considered to have evaluable lesions by either photographic or radiological assessment methods per the independent composite review committee, and one patient had a second target lesion not imaged after baseline. ‡Data shown are for patients with a confirmed complete response or partial response; duration of response was calculated for all patients with a confirmed response prior to the data cutoff.

Table 2: **Tumour response and duration of response by independent central review**

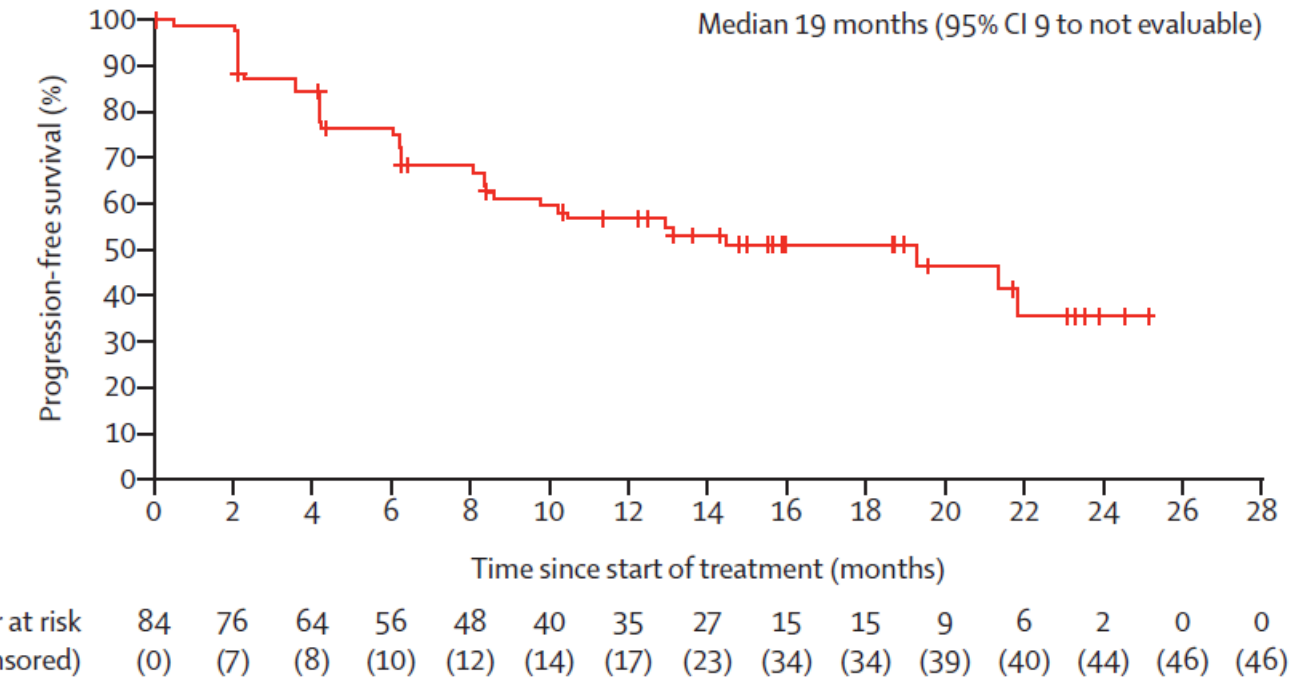
Stratigos, Alexander J., et al. "Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial." *The Lancet Oncology* 22.6 (2021): 848-857.

Cemiplimab post HHI therapy

Tumor Response (*)



Progressive Free Survival (*)



(*): by independent central review

Stratigos, Alexander J., et al. "Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial." *The Lancet Oncology* 22.6 (2021): 848-857.

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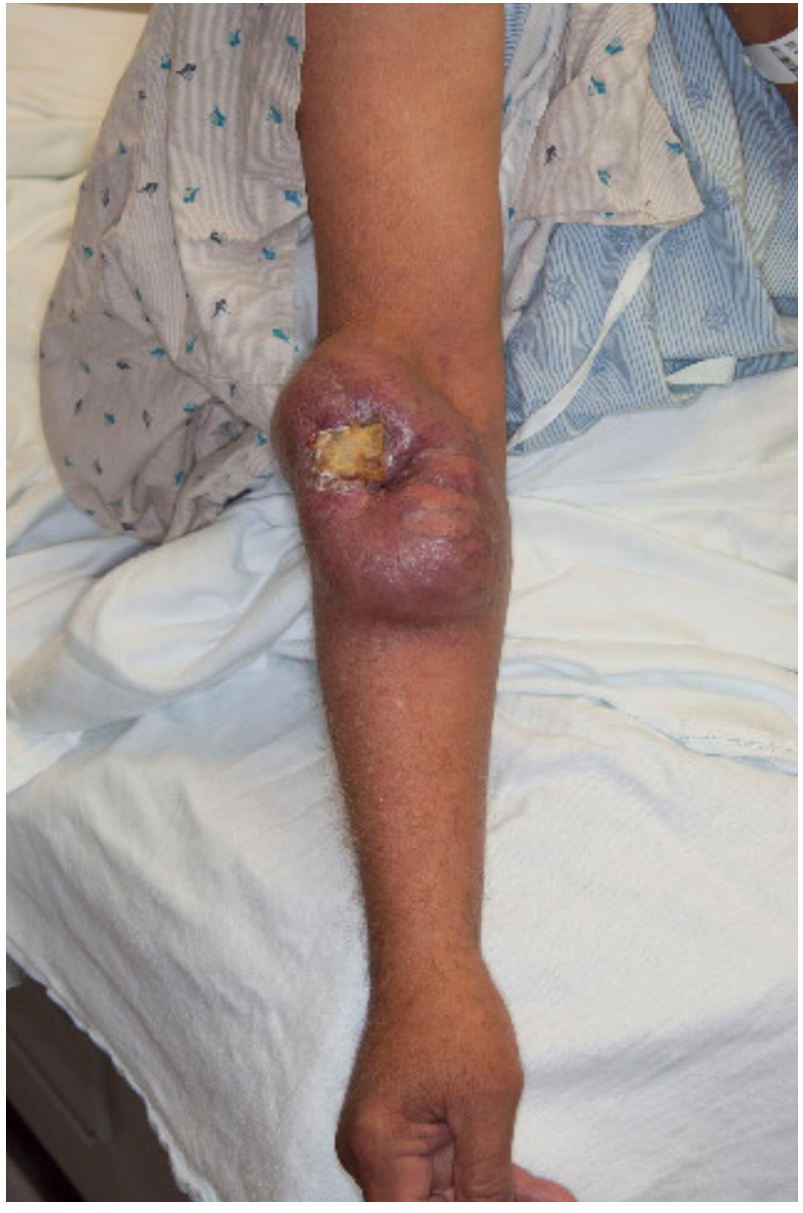
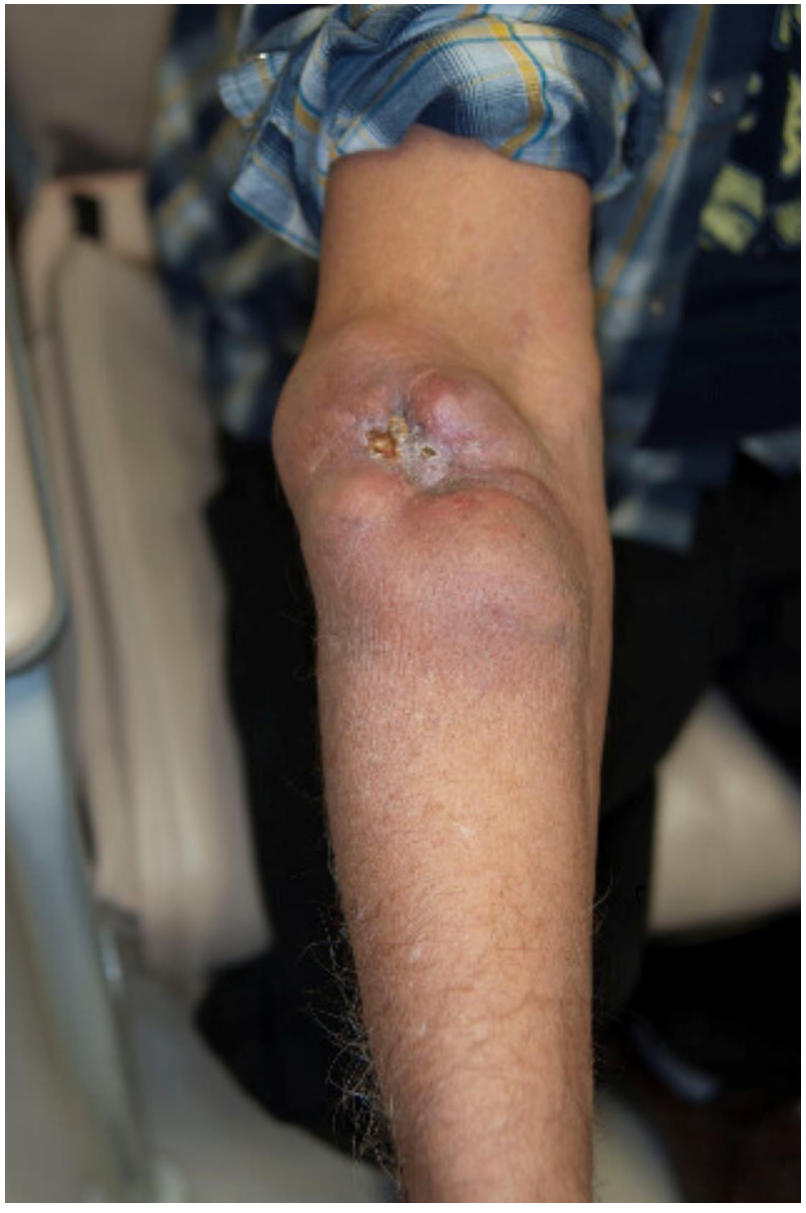
Cutaneous Squamous Cell Carcinoma	Cemiplimab, Pembrolizumab • Locally advanced, metastatic cSCC • "not candidates for curative surgery or radiation"	• Resection is in the eye of the surgeon • Problem of 'squam factories' • Confused w Lichen planus , topical effects. • Adjuvant benefit unknown
Basal Cell Carcinoma	Cemiplimab • Locally advanced basal cell carcinoma (laBCC) refractory to/intolerant of a hedgehog pathway inhibitor (HHI)	• BCC: Slow indolent in both groth and response to IO. • 'Sweet spot' for HHI use.
Merkel Cell Carcinoma		

Difficult Categories: immunosuppressed (Transplant), autoimmune diseases, hematologic diseases (CLL, NHL)

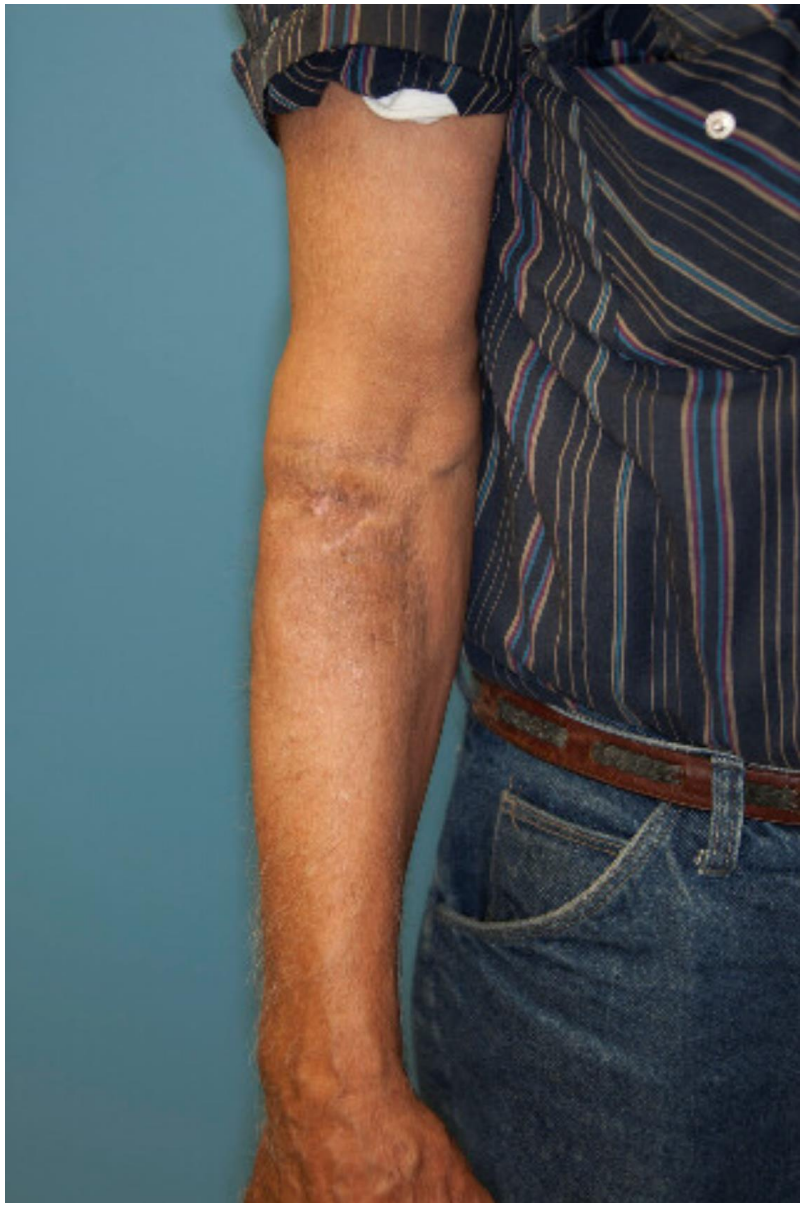
Pre-Therapy



Pre-Cycle 2
2 weeks after 1st infusion



Pre-Cycle 5
2 weeks after 4th infusion



Background

- An aggressive, but rare (**1/50th** of melanoma's incidence) primary cutaneous **neuroendocrine** tumor that has a high propensity for regional as well as distant metastasis
- First described in **1972** by Toker and was named "trabecular carcinoma" because of solid trabeculae arrangement of tumor cells
- The annual incidence of MCC in U.S. is increasing, with an estimated 1,600 new cases per year (**0.79 per 100,000**) [0.3 – 1.6] ;
- Most common primary sites (**sun exposed**): head, neck, extremities
- **Older** population: More than 9 out of 10 people diagnosed with MCC are older than age 50, and more than 2 out of 3 are older than 70.
- **White** race: More than 9 out of 10 cases of MCC in the United States develop in whites.

American Cancer Society, 2018

There are two variants of MCC

MCPyV -

- No presence of MCPyV DNA
- No expression of MCPyV LT and ST RNA or protein
- Inactivating mutations in *RB1* and *TP53*
- High frequency of DNA mutations induced by UV damage
- High degree of aneuploidy
- Inactivating mutations in genes involved in various signalling pathways, including DNA damage response and repair genes and chromatin-modifying genes

MCPyV +

- Clonal integration of MCPyV DNA into tumour genome
- Expression of MCPyV small T antigen (ST) and truncated large T antigen (LT)
- Wild-type *RB1* and *TP53*
- No UV mutational signature
- Predominantly diploid with minimal number of copy number alterations
- Minimal number of somatic nucleotide alterations

… but it does not matter clinically – at this time.

Becker, Jürgen C., et al. "Merkel cell carcinoma." Nature Reviews Disease Primers 3 (2017): 17077.

MCC is chemoresponsive initially

Reference	Study type	Sample size	Study conclusion
Cowey, 2016 [150]	Retrospective	20	Patients with distant metastatic MCC received little benefit from 2L+ chemotherapy • Objective response rate was 20% • Median progression-free survival was 2.1 months
Becker, 2016 [149]	Retrospective	34	2L+ chemotherapy demonstrated little benefit in patients with distant metastatic MCC • Objective response rate was 8.8% • Median progression-free survival was 3.0 months
Iyer, 2016 [144]	Retrospective	62	Responses to chemotherapy were frequent but of limited durability • Objective response rates to 1L chemotherapy and 2L chemotherapy were 55% and 23%, respectively • Median progression-free survival was 3.1 months
Satpute, 2014 [148]	Retrospective	13	Platinum-based combination chemotherapy shows clinical activity and adjuvant chemotherapy are recommended for patients with MCC who exhibits high-risk features • Seven of 13 patients who received chemotherapy achieved a complete response or partial response by RECIST • Median duration of remission was 4 months
Voog, 1999 [146]	Retrospective	72	MCC is a chemosensitive disease, but recurrence frequently occurred, and treatment was associated with a high incidence of toxic death • Overall response rate was 57% • Median overall survival was 9 months
Sharma, 1991 [142]	Case report/review	46	Complete and partial responses were achieved, although duration of responses were short • Response rates of 46–69% depending on the type of chemotherapy received
Tai, 2000 [147]	Case study/review	103	Chemotherapy provides benefit to patients with locally recurrent or advanced disease • 59% overall response rate in patients with distant metastases • In all patients (non-distant and distant), the 5-year overall survival rate was 17%

Schadendorf, Dirk, et al. "Merkel cell carcinoma: epidemiology, prognosis, therapy and unmet medical needs." European Journal of Cancer 71 (2017): 53-69.

There are now TWO approved PD-1 agents

- **Avelumab** (Bavencio™): Anti-PD-1L, IgG1 (March 23, 2017) ,
- n=88; 35 centers

  “treatment of patients 12 years and older with metastatic Merkel cell carcinoma (MCC)”

Kaufman, Howard L., et al. "Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial." The Lancet Oncology 17.10 (2016): 1374-1385.

- **Pembrolizumab** (Keytruda ™) : Anti-PD1 IgG4 (December 19, 2018)
- n = 26 (50)

  “adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma ”

Nghiem, Paul T., et al. "PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma." New England Journal of Medicine 374.26 (2016): 2542-2552.

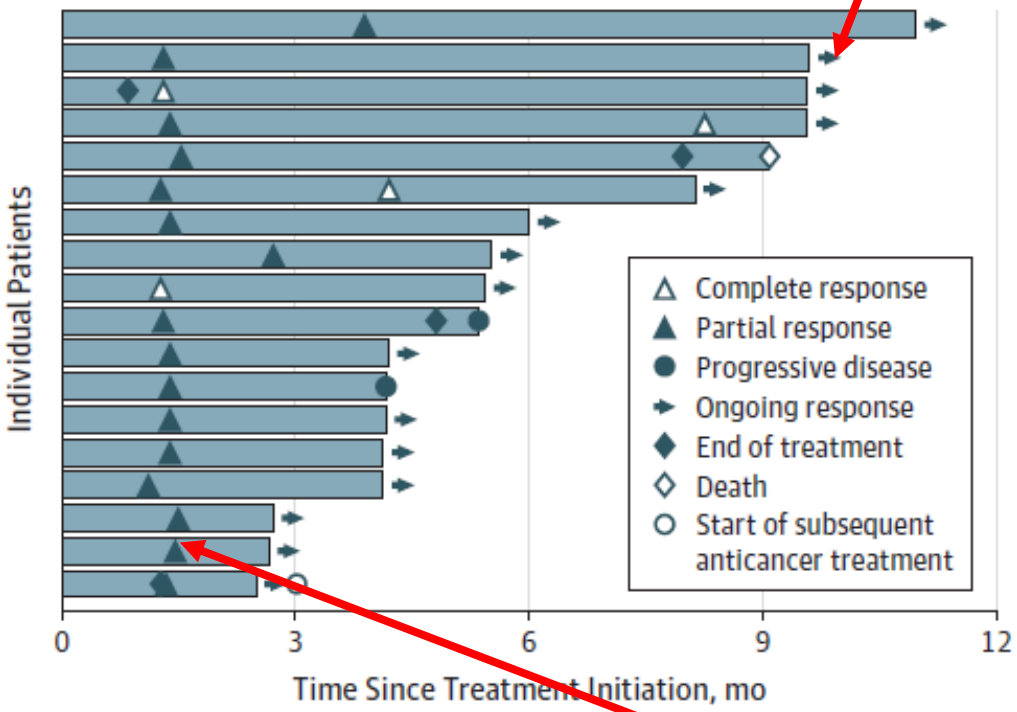
	Avelumab JAVELIN Merkel 200		Pembrolizumab KEYNOTE-017, First-Line[5,6]
	Part A[1-3] Second Line	Part B[4] First Line	
Overall response rate, (95% CI)			
ORR	33.0% (23.3, 43.8)	71.4% (41.9, 91.6)	56% (41, 70)
Complete response rate	11.4% (6.6, 19.9)	28.6%	24% (13, 38)
Partial response rate	21.6% (13.5, 31.7)	42.9%	32% (20, 47)
Stable disease	10.2%	7.1%	10% (3.3, 21.8)
Progressive disease	36.4%	14.3%	32% (19.5, 46.7)
Duration of response	**2-y update 2018** (n=29)	≥6 mo follow-up (n=10)	
Median DOR, mo (95% CI)	NR (18.0, NE)	NE (4.0, NE)	NR
Range in months	2.8, 23.3+	N/A	5.9, 34.5+
6-mo DRR, (95% CI)	30.6% (20.9, 40.3)	N/A	N/A
Patients with DOR ≥6 mo, (95% CI)	93% (74, 98)	89% (43, 98)	96%
Patients with DOR ≥1 y (95% CI)	74% (53, 87)	N/A	54%
Patients with DOR ≥2 y (95% CI)	67% (46, 81)	N/A	N/A
Median time to response (range)	6.1 wk (6, 36)	6.1 wk (5, 17)	2.8 mo (1.5, 9.7)

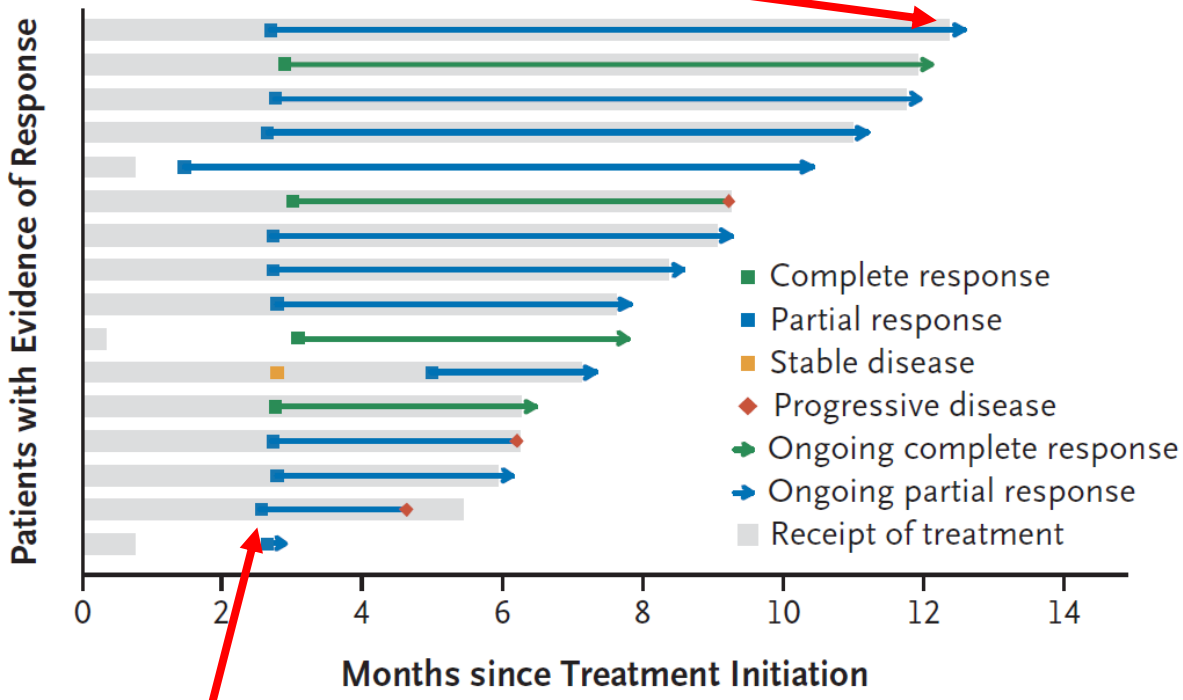
CI, confidence internal; DRR, durable response rate; NE, not estimable; NR, not reached.

[a] Data is from 39 patients included in the pre-planned interim analysis.[4]

1. Bavencio [prescribing information]. Rockland, MA: EMD Serono, Inc; New York, NY: Pfizer Inc. **2.** Kaufman HL, et al. *J Immunother Cancer.* 2018;6(1):7. doi:10.1186/s40425-017-0310-x. **3.** Nghiem P, et al. ASCO Annual Meeting. Chicago, IL; Abstract 9507. **4.** D'Angelo SP, et al. *JAMA Oncol.* 2018;4(9):3180077. doi:10.1001/jamaoncol.2018.0077. **5.** Keytruda [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; 2018. **6.** Nghiem P, et al. *J Clin Oncol.* 2019;37(9):693-702.

Majority of the responses are ongoing





Responses evident by the first restaging scans

Kaufman HL, et al. *J Immunother Cancer.* 2018;6(1):7. doi:10.1186/s40425-017-0310-x.; D'Angelo SP, et al. *JAMA Oncol.* 2018;4(9):3180077. doi:10.1001/jamaoncol.2018.0077. ; Nghiem P, et al. *J Clin Oncol.* 2019;37(9):693-702.

Skin Cancer	Indication	"Wrinkle"
Melanoma	Pembrolizumab, Nivolumab, TVEC, Atezolizumab, IL-2, (Relatlimab) • Stage III, IV melanoma. • Unresectable melanoma • Adjuvant therapy	• Ipi+nivo, vs nivo monotherapy • Stage IIB, C ? • Neoadjuvant therapy • Sequence with immunoRx and Targeted Therapy.
Cutaneous Squamous Cell Carcinoma	Cemiplimab, Pembrolizumab • Locally advanced, metastatic cSCC • "not candidates for curative surgery or radiation"	• Resection is in the eye of the surgeon • Problem of 'squam factories' • Confused w Lichen planus , topical effects. • Adjuvant benefit unknown
Basal Cell Carcinoma	Cemiplimab • Locally advanced basal cell carcinoma (laBCC) refractory to/intolerant of a hedgehog pathway inhibitor (HHI)	• BCC: Slow indolent in both groth and response to IO. • 'Sweet spot' for HHI use.
Merkel Cell Carcinoma	Avelumab, Pembrolizumab • adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.	• ImmunoRx: Polyoma virus agnostic • Role of XRT, cytotoxic chemoRx

Difficult Categories: immunosuppressed (Transplant), autoimmune diseases, hematologic diseases (CLL, NHL)

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