Immune Checkpoint Inhibitors in Advanced Keratinocytic Carcinomas (SCC & BCC)

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Financial Disclosures

- Consultant for Kadmon, Merck, Regeneron, and Sanofi Genzyme.
- On the Speakers Bureau for Regeneron, and Sanofi Genzyme.

Skin cancers are highly responsive to immunotherapy

- Melanoma: 3-year survival has improved from 12% to 58% since immunotherapy
- Merkel cell carcinoma: > 40% ORR in advanced MCC for multiple immune checkpoint inhibitors

- Squamous cell carcinoma ?
- Basal cell carcinoma ?

Paulson, K et al. “Immuntherapy for skin cancer.” International Immunology. 2019.

Epidemiology of CSCC and BCC

- Neither tumor is required to be reported to the national cancer database, therefore incidence is extrapolated from smaller cohort studies

Estimated health burden of cSCC in Caucasians, 2012		Melanoma, 2020	Oral & pharyngeal Cancer, 2020
Number of new diagnoses	186,157–419,843	100,350	53,260
Tumor related deaths	3,932–8,791	6,850	10,750

- Estimated BCC incidence approaches 2 million annually

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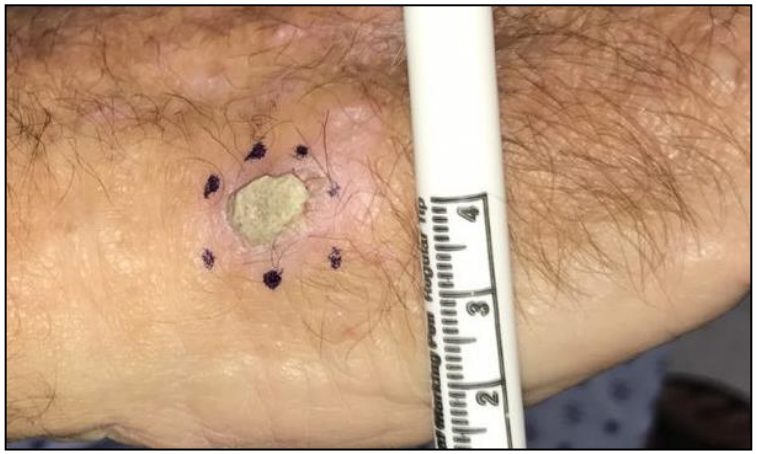
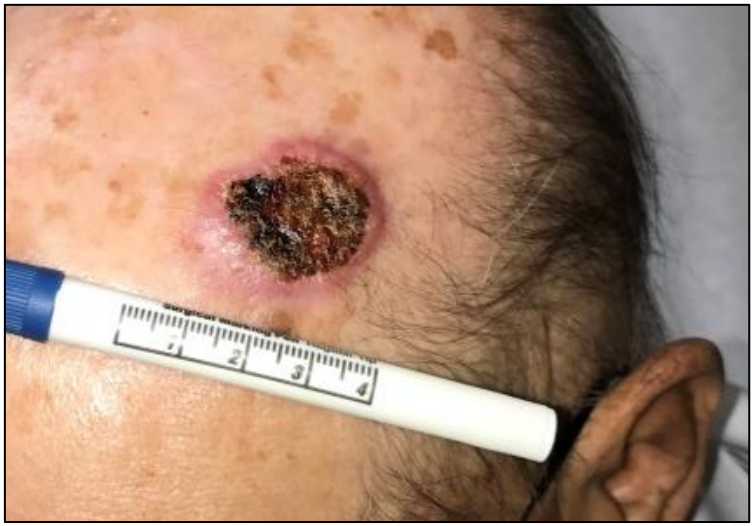
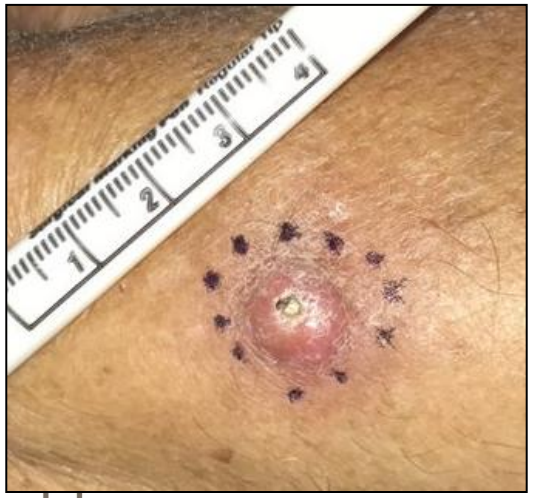
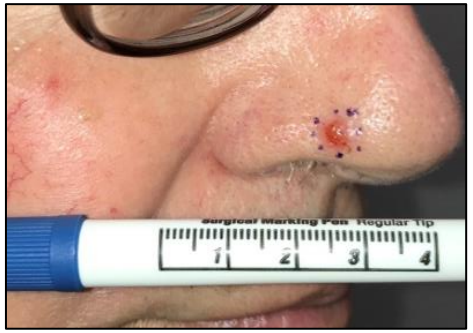
American Cancer Society, Cancer Facts and Figures, 2020.
Karia, et al. “Cutaneous squamous cell carcinoma….” JAAD. 2013.
Rogers, et al. “Incidence estimate of nonmelanoma….” JAMA Derm. 2015.

Vast majority of CSCCs and BCCs should be treated with surgery or other local modality









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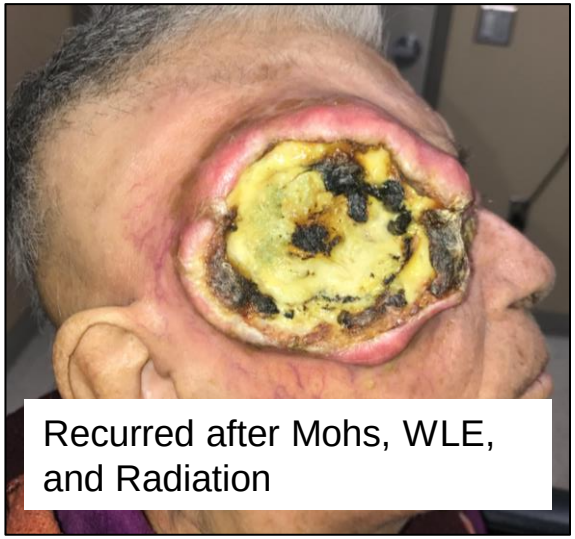
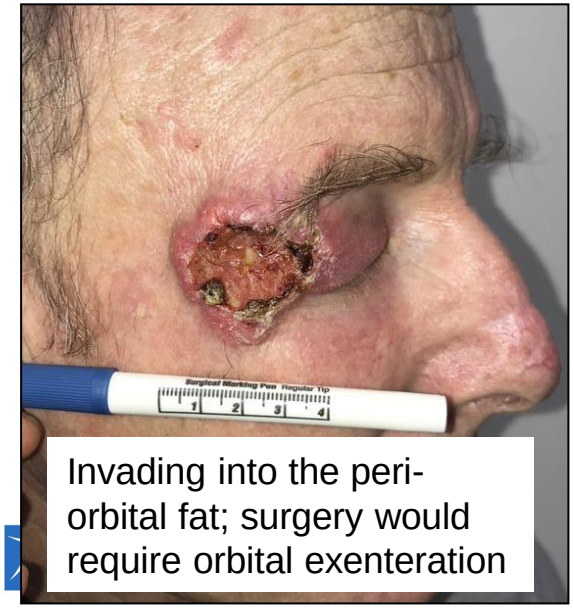
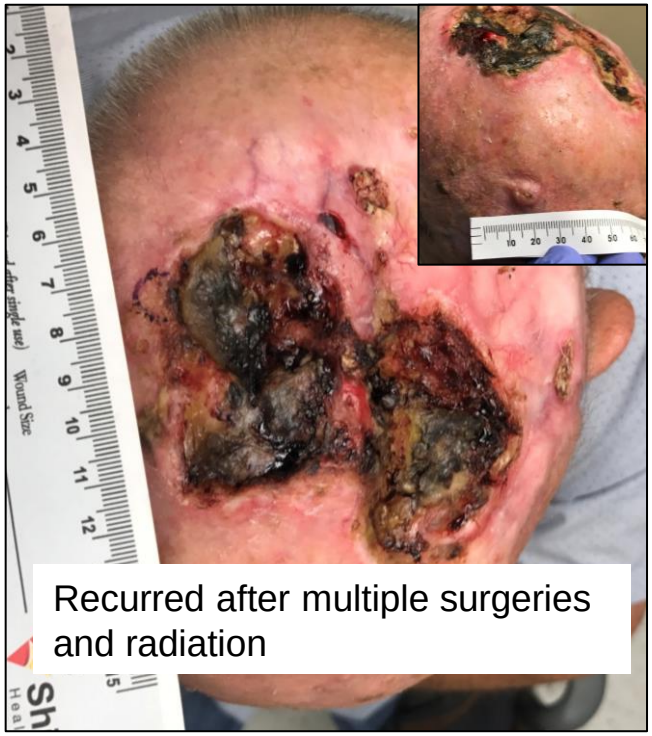
Some keratinocytic carcinomas require systemic therapy



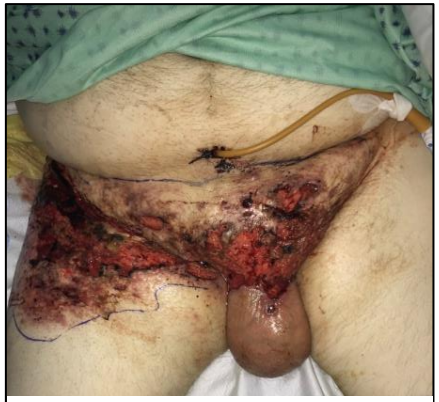
Recurred after Mohs, WLE, and Radiation



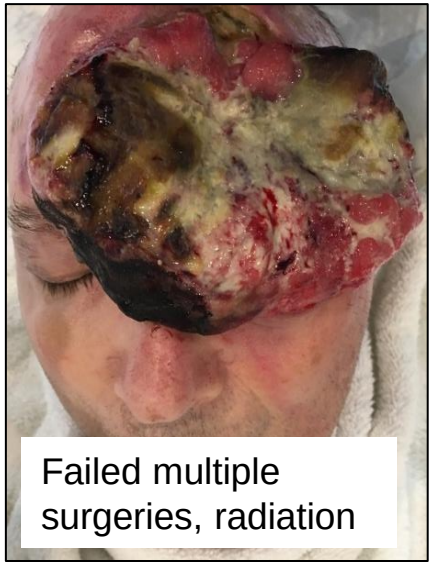
Invading into the peri-orbital fat; surgery would require orbital exenteration



Recurred after multiple surgeries and radiation



Metastatic disease from penile CSCC, despite WLE & penectomy

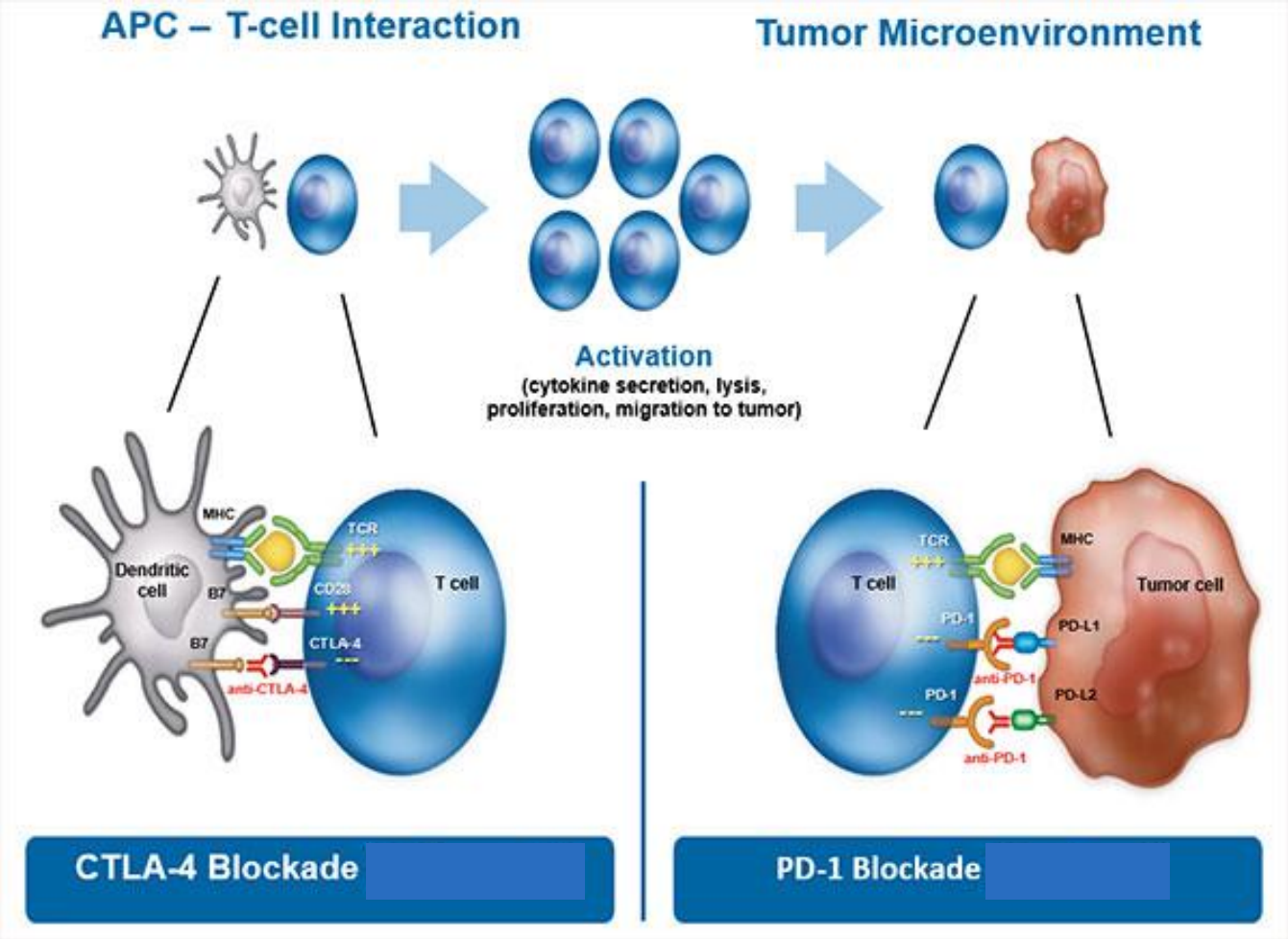


Failed multiple surgeries, radiation

Systemic therapy for keratinocytic carcinomas

- Prior to Sept 2018, there was no FDA-approved therapy for advanced CSCC. Historically, off-label treatment options included
  - Cytotoxic chemotherapy (platinum based drugs)
  - Biologic response modifiers including systemic retinoids and interferon-alpha
  - Epidermal Growth Factor Receptor (EGFR) inhibitors
  - Recent role for PD1 blockade
- Hedgehog inhibitors are 1st line systemic therapy advanced BCC, approved in 2012
  - Recent role for PD1 blockade

Checkpoint blockade: mechanism of action



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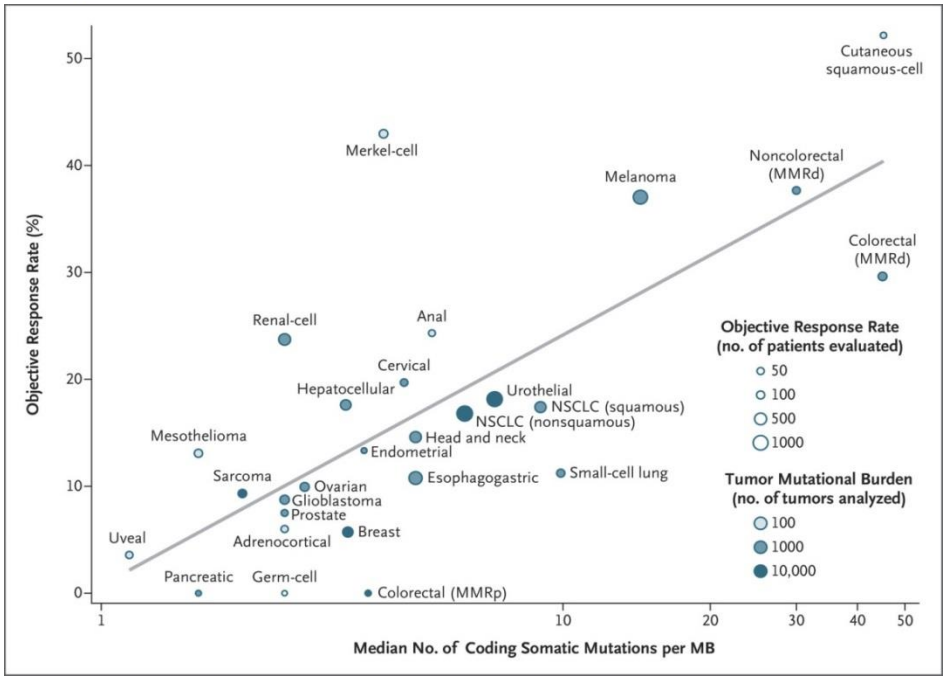
Why might immunotherapy be effective in keratinocytic carcinomas?

- CSCC occurs 65 to 250 times more frequently in solid organ transplant population compared to general population
- Tumor mutational burden (TMB) is highest in CSCC amongst all studied human cancers
- TMB correlates with response to immunotherapy



Mutation → Neo-Antigen → New target for the immune system

Euvard, et al. *NEJM.* 2003.
Pickering, et al. *Clin Cancer Research*. 2014.
Chalmers, et al. *Genome Med*. 2017.
Yarchoan, et al. *NEJM*. 2017.

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Immunotherapy trials for keratinocytic carcinomas

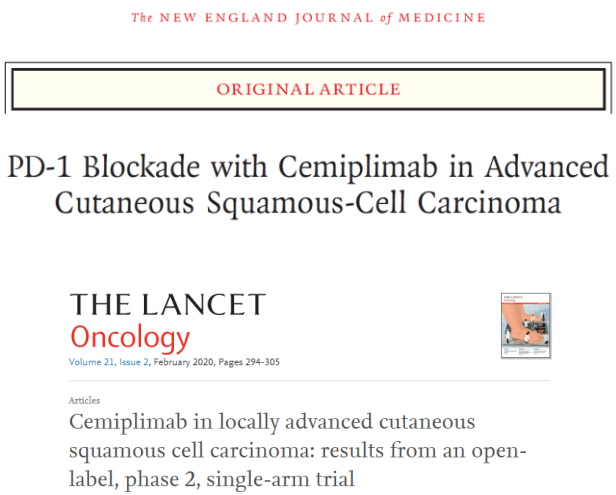
Metastatic and locally advanced CSCC
- Cemiplimab –NCT 02760498 (Regeneron / Sanofi)
- Pembrolizumab – NCT 03284424 (Merck)

Locally advanced BCC that failed hedgehog inhibitor
- Cemiplimab – NCT 03132636 (Regeneron / Sanofi)

- Phase 2 studies, no control group
- All 3 studies are industry sponsored
- There are no head-to-head studies that compare cemiplimab to pembrolizumab, or other immune checkpoint inhibitors.

Cemiplimab, CSCC: Clinical studies

- Study 1423: Phase 1
- Study 1540: Phase 2


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

THE LANCET Oncology

Volume 21, Issue 2, February 2020, Pages 294-305

Articles

Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial

Publications:

- Migden, et al. NEJM. 2018.
- Rischin, et al. JITC. 2020.

} Metastatic CSCC cohorts

- Migden, et al. Lancet. 2020.

} Locally advanced cohort

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Cemiplimab, CSCC: Trial design

EMPOWER-CSCC1

*industry sponsored, phase 2, multicenter, international

Group 1	Metastatic: 59	Cemiplimab 3mg/kg q2w up to 96wks Response assessment q8wk
Group 2	Locally advanced: 78	
Group 3	Metastatic: 56	Cemiplimab 350mg q3w up to 54wks Response assessment q9w

Primary endpoint: confirmed objective response rate (ORR) by independent central review

Secondary endpoint:
- Duration of response
- Complete response rate

Inclusion Criteria
- ECOG 0 or 1
- Groups 1, 3:
  - At least 1 lesion measurable by RECIST 1.1
- Group 2:
  - At least 1 lesion measurable by digital photography
  - CSCC lesion that is not amenable to curative surgery or radiation

Exclusion Criteria
- Ongoing or recent autoimmune disease requiring immunosuppressives (within past 5 years)
- Prior treatment with anti-PD1 or -PDL1
- History of solid organ transplant, concurrent malignancy), or hematologic malignancy
- Infection with HIV, Hepatitis B, or Hepatitis C

Rischin, et al., presented at ASCO 2020. Interim analysis of NCT 02760498.

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Cemiplimab, CSCC: Demographics

Table 1. Baseline demographics

	Advanced CSCC (n=193)
Median age, years (range)	72.0 (38–96)
Male, n (%)	161 (83.4)
ECOG performance status, n (%)	
0	86 (44.6)
1	107 (55.4)
Primary CSCC site: head and neck, n (%)	131 (67.9)
mCSCC, n (%)	115 (59.6)
laCSCC, n (%)	78 (40.4)
Patients with cemiplimab as first-line therapy, n (%)	128 (66.3)
Patients with prior systemic therapy, n (%)†	65 (33.7)
Median duration of exposure to cemiplimab, weeks (range)	51.1 (2.0–109.3)
Median number of doses of cemiplimab administered (range)	18.0 (1–48)

†Settings for prior lines of therapy included metastatic disease, adjuvant, chemotherapy with concurrent radiation, or other and the most common types of prior systemic therapy were platinum compounds (n=46/65 [70.8%]) and monoclonal antibodies (n=18/65 [27.7%]).

Rischin, et al., presented at ASCO 2020. Interim analysis of NCT 02760498.

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Cemiplimab, CSCC: Results

Table 2. Duration of follow-up and tumor response to cemiplimab per ICR

	Group 1 (mCSCC) 3 mg/kg Q2W (n=59)	Group 2 (laCSCC) 3 mg/kg Q2W (n=78)	Group 3 (mCSCC) 350 mg Q3W (n=56)	Total (n=193)
Median duration of follow-up, months (range)	18.5 (1.1–36.1)	15.5 (0.8–35.6)	17.3 (0.6–26.3)	15.7 (0.6–36.1)
ORR, % (95% CI)	50.8 (37.5–64.1)	44.9 (33.6–56.6)	42.9 (29.7–56.8)	46.1 (38.9–53.4)
Complete response, n (%)	12 (20.3)	10 (12.8)	9 (16.1)	31 (16.1)
Partial response, n (%)	18 (30.5)	25 (32.1)	15 (26.8)	58 (30.1)
Stable disease, n (%)	9 (15.3)	27 (34.6)	10 (17.9)	46 (23.8)
Non-complete response/non-progressive disease, n (%)	3 (5.1)	0	2 (3.6)	5 (2.6)
Progressive disease, n (%)	10 (16.9)	10 (12.8)	14 (25.0)	34 (17.6)
Not evaluable, n (%)	7 (11.9)	6 (7.7)	6 (10.7)	19 (9.8)
Disease control rate, % (95% CI)	71.2 (57.9–82.2)	79.5 (68.8–87.8)	64.3 (50.4–76.6)	72.5 (65.7–78.7)
Durable disease control rate,† % (95% CI)	61.0 (47.4–73.5)	62.8 (51.1–73.5)	57.1 (43.2–70.3)	60.6 (53.3–67.6)
Median observed time to response, months (IQR)‡	1.9 (1.8–2.0)	2.1 (1.9–3.8)	2.1 (2.1–4.2)	2.1 (1.9–3.7)
Median observed time to complete response, months (IQR)	11.1 (7.5–18.4)	10.5 (7.4–12.9)	12.4 (8.2–16.6)	11.2 (7.4–14.8)
Median DOR, months (range)‡	NR (20.7, NE)	NR (18.4, NE)	NR (NE, NE)	NR (28.8, NE)
Kaplan–Meier 12-month estimate of patients with ongoing response, % (95% CI)	89.5 (70.9–96.5)	83.2 (64.1–92.7)	91.7 (70.6–97.8)	87.8 (78.5–93.3)
Kaplan–Meier 24-month estimate of patients with ongoing response, % (95% CI)	68.8 (46.9–83.2)	62.5 (38.4–79.4)	NE (NE, NE)	69.4 (55.6–79.6)

†Defined as the proportion of patients without progressive disease for at least 105 days.
‡Based on number of patients with confirmed complete or partial response.
ORR per INV was 54.4% (95% CI: 47.1–61.6) for all patients; 50.8% (95% CI: 37.5–64.1) for Group 1, 56.4% (95% CI: 44.7–67.6) for Group 2, and 55.4% (95% CI: 41.5–68.7) for Group 3. ORR per INV was 57.8% (95% CI: 48.8–66.5) among treatment-naïve patients and 47.7% (95% CI: 35.1–60.5) among previously treated patients.
CI, confidence interval; NE, not evaluable; NR, not reached.

Rischin, et al., presented at ASCO 2020. Interim analysis of NCT 02760498.

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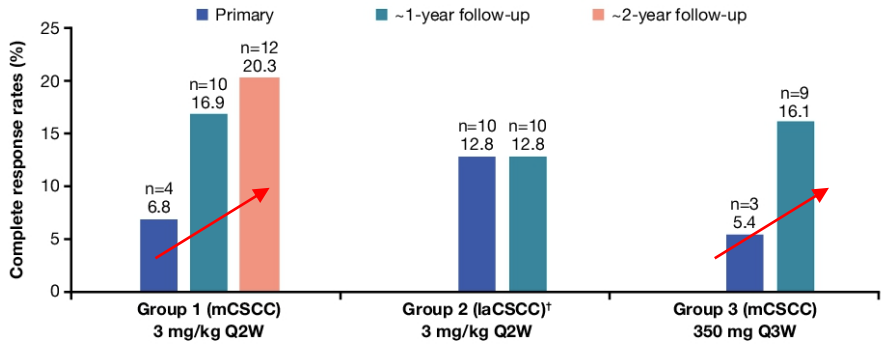
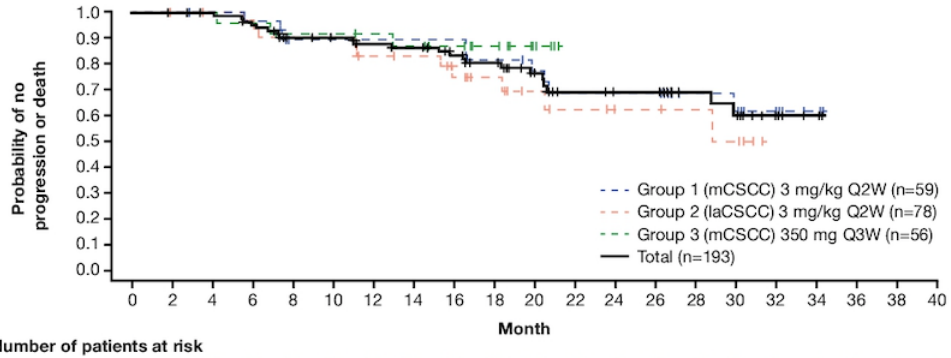
Cemiplimab, CSCC: Results

Figure 2. Complete response rates per ICR



†Among 23 laCSCC patients who were included in the pre-specified Group 2 interim analysis, there were no complete responses.

Figure 3. Kaplan–Meier curves of DOR per ICR



Number of patients at risk

Group 1 (n=59)	30	30	29	28	23	23	23	23	23	20	18	16	16	16	10	9	6	2	0	0	0
Group 2 (n=78)	35	33	32	30	27	25	22	21	17	14	10	8	6	6	5	4	0	0	0	0	0
Group 3 (n=56)	24	24	24	23	21	21	20	19	17	11	5	0	0	0	0	0	0	0	0	0	0
Total (n=193)	89	87	85	81	71	69	65	63	57	45	33	24	22	22	15	13	6	2	0	0	0

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Rischin, et al., presented at ASCO 2020. Interim analysis of NCT 02760498.

Cemiplimab, CSCC: Results

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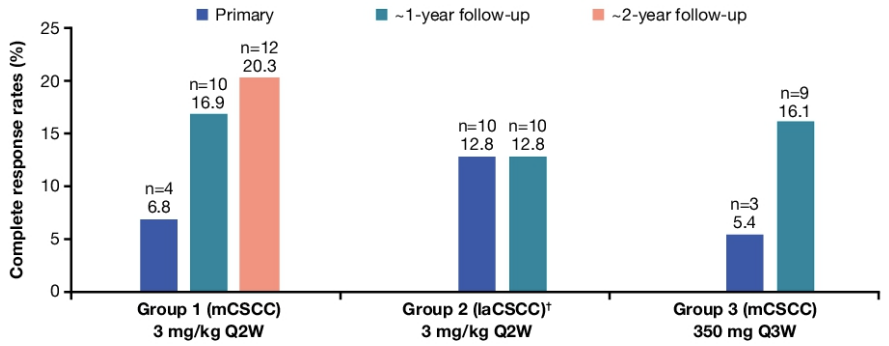

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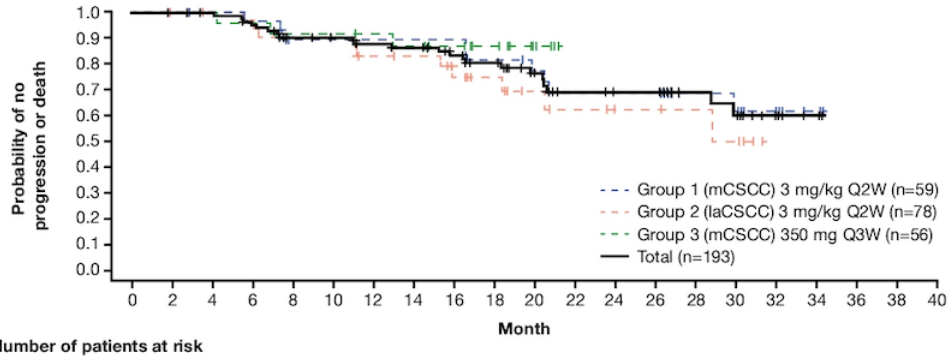

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Group 1 (n=59)	30	30	29	28	23	23	23	23	23	20	18	16	16	16	10	9	6	2	0	0	0
Group 2 (n=78)	35	33	32	30	27	25	22	21	17	14	10	8	6	6	5	4	0	0	0	0	0
Group 3 (n=56)	24	24	24	23	21	21	20	19	17	11	5	0	0	0	0	0	0	0	0	0	0
Total (n=193)	89	87	85	81	71	69	65	63	57	45	33	24	22	22	15	13	6	2	0	0	0

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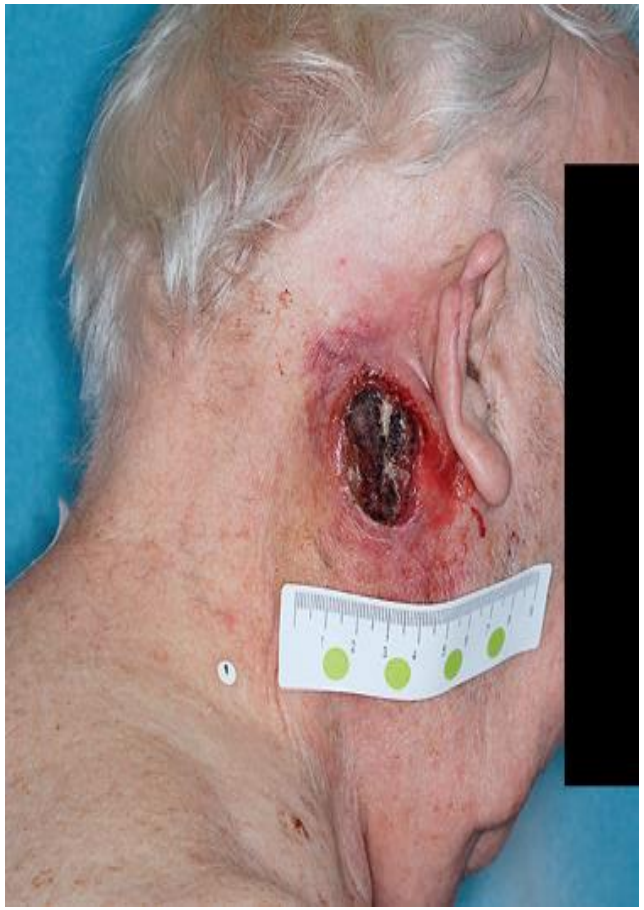
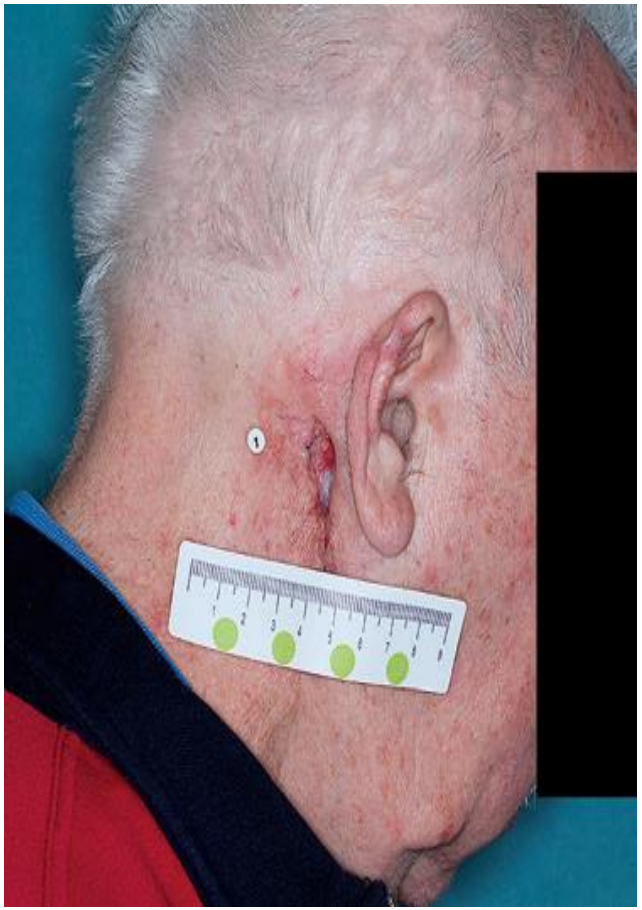
Rischin, et al., presented at ASCO 2020. Interim analysis of NCT 02760498.

Early response to cemiplimab in an 83-year-old-man with metastatic CSCC who had multiple prior surgeries for CSCC

Baseline



Week 8



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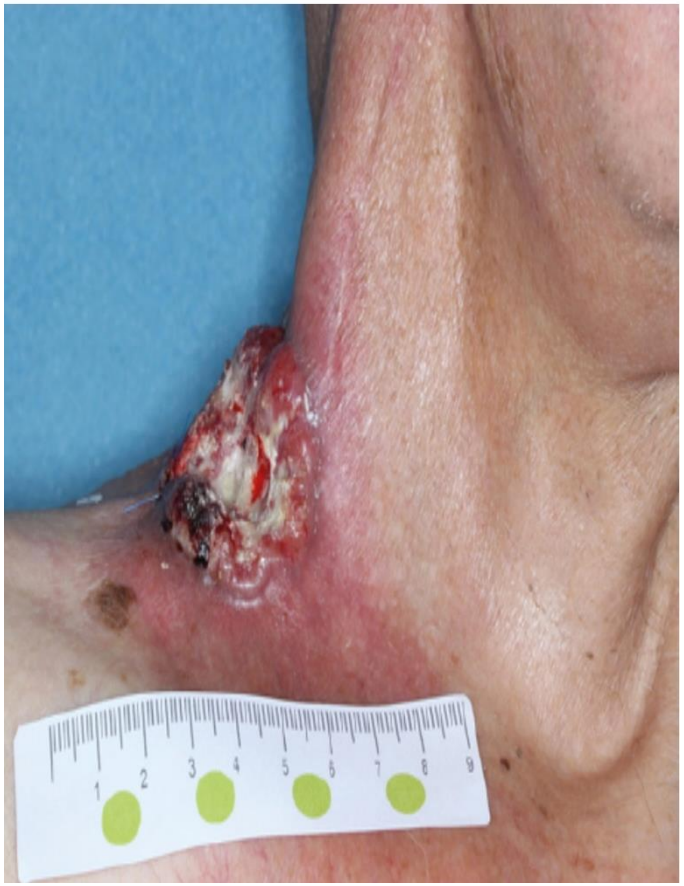
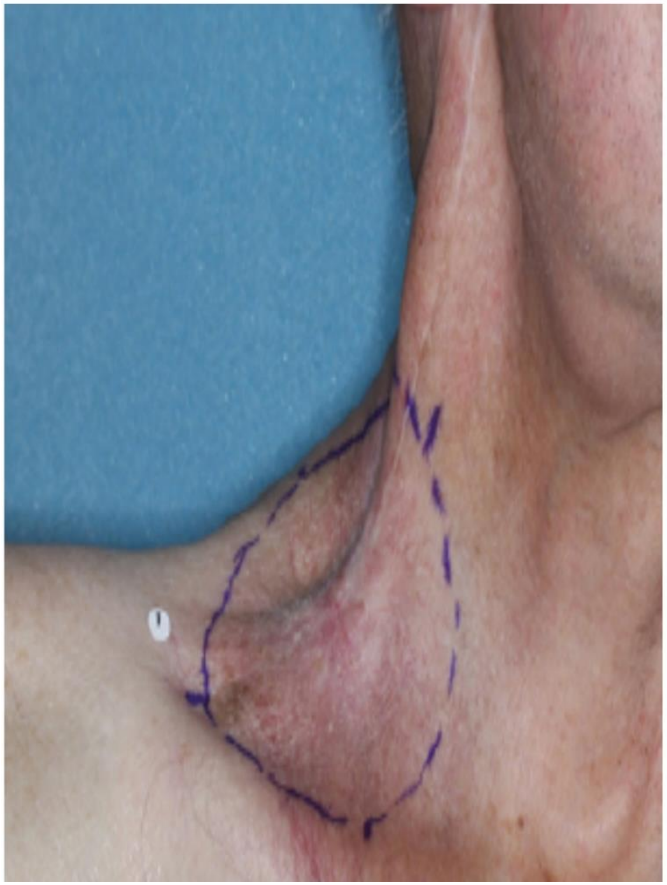
Migden and Rischin, et al. *NEJM.* 2018.

Response to cemiplimab in an 85-year-old man with metastatic CSCC with supraclavicular lesion who had received prior radiotherapy

Baseline



Week 32



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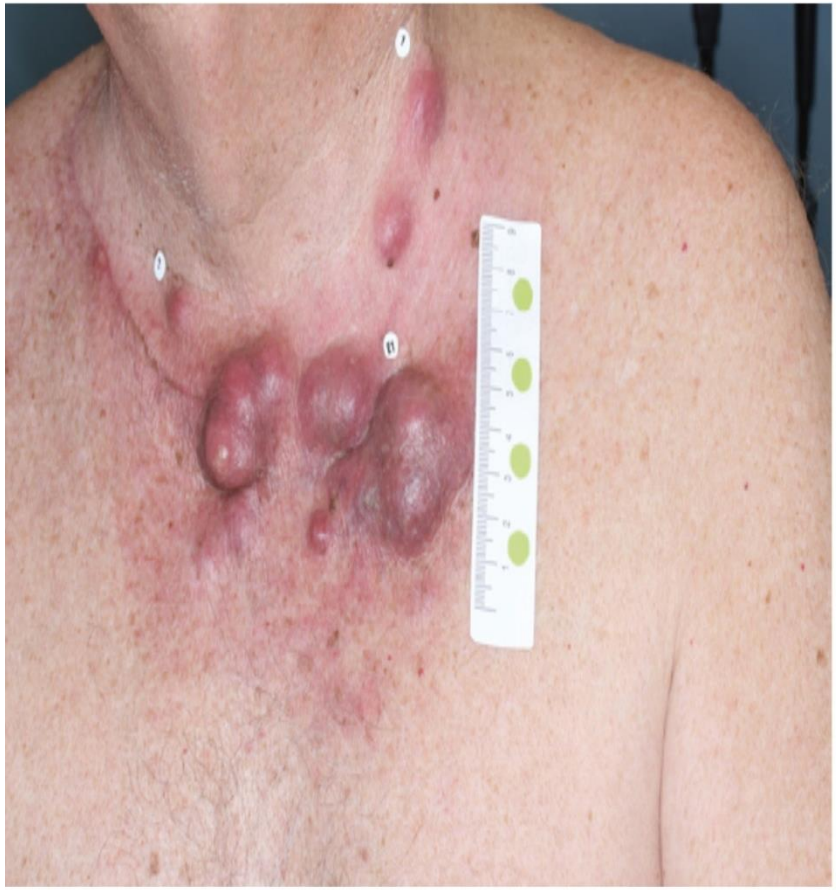
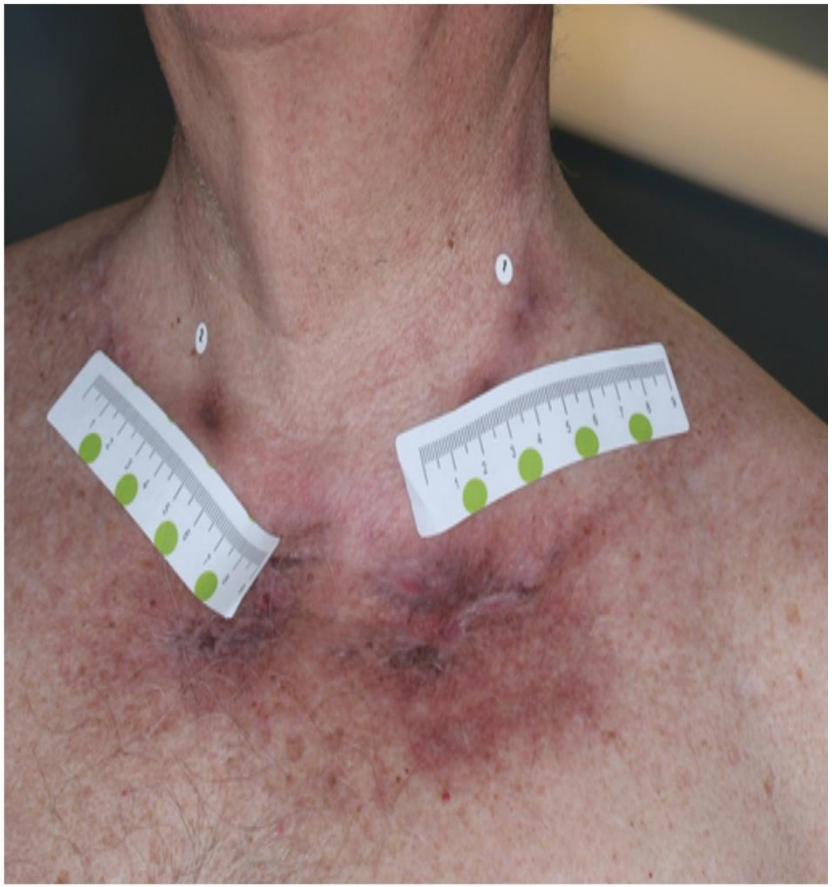
Migden and Rischin, et al. *NEJM.* 2018.

Response to cemiplimab in a 66-year-old man with metastatic CSCC with anterior chest wall CSCC lesions who had received prior cisplatin

Baseline



Week 24



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Migden and Rischin, et al. *NEJM.* 2018.

Cemiplimab, CSCC: Adverse Events

Table 3. TEAEs regardless of attribution

n (%)	Advanced CSCC (n=193)	
	Any grade	Grade ≥3
Any	192 (99.5)	94 (48.7)
Led to discontinuation	19 (9.8)	14 (7.3)
Most common†		
Fatigue	67 (34.7)	5 (2.6)
Diarrhea	53 (27.5)	2 (1.0)
Nausea	46 (23.8)	0
Pruritus	41 (21.2)	0
Rash	32 (16.6)	1 (0.5)
Cough	32 (16.6)	0
Arthralgia	28 (14.5)	1 (0.5)
Constipation	26 (13.5)	1 (0.5)
Vomiting	24 (12.4)	1 (0.5)
Actinic keratosis	23 (11.9)	0
Maculopapular rash	23 (11.9)	1 (0.5)
Anemia	22 (11.4)	8 (4.1)
Hypothyroidism	22 (11.4)	0
Headache	21 (10.9)	0
Upper respiratory tract infection	20 (10.4)	0

†TEAEs reported in ≥10% of patients, ordered by frequency of any grade.

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Rischin, et al., presented at ASCO 2020. Interim analysis of NCT 02760498.

Pembrolizumab, CSCC: Study Design & Baseline Characteristics

KEYNOTE-629

*industry sponsored, phase 2, multicenter

Locally advanced: 54

Recurrent / Metastatic: 105

Pembrolizumab 200mg q3W
for up to 35 cycles

Primary endpoint: overall response rate (ORR)

Secondary endpoint:
- Duration of response
- Complete response rate
- Progression free survival
- Overall survival
- Safety / tolerability

Characteristics	Locally advanced (n=54)	Recurrent / metastatic (n= 105)	Total (n = 159)
Median age, years	75.5 (67-83)	72.0 (61-81)	74 (62-82)
Male	39 (72.2%)	80 (76.2%)	119 (74.8%)
ECOG PS1	32 (59.3%)	69 (65.7%)	101 (63.5%)
Prior systemic therapy for curative intent	12 (22.2%)	NA	12 (7.5%)
More than 1 prior systemic therapy	NA	91 (86.7%)	91 (57.2%)

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Hughes, B., et al. “Abstract CT006: Phase 2 study of pembrolizumab….” Cancer Res July 1 2021 (81) (13 Supplement) CT006; **DOI:** 10.1158/1538-7445.AM2021-CT006.

Pembrolizumab, CSCC: Results

	Locally advanced (n=54)	Recurrent / metastatic (n= 105)	Total (N=159)
Median duration of follow up	14.9 (10.1-19.4) mo	27.2 (24.6-32.0) mo	Not reported
Overall response rate	50%	35.2%	40.3%
Complete Response	9 (16.7%)	72.0 (61-81)	20 (12.6%)
Partial Response	18 (33.3%)	80 (76.2%)	44 (27.7%)
Duration of response, median months	Not reached	Not reached	Not reached
Grade 3-5 treatment related AEs			11.9%
Grade 3-5 immune related AEs			8.2%

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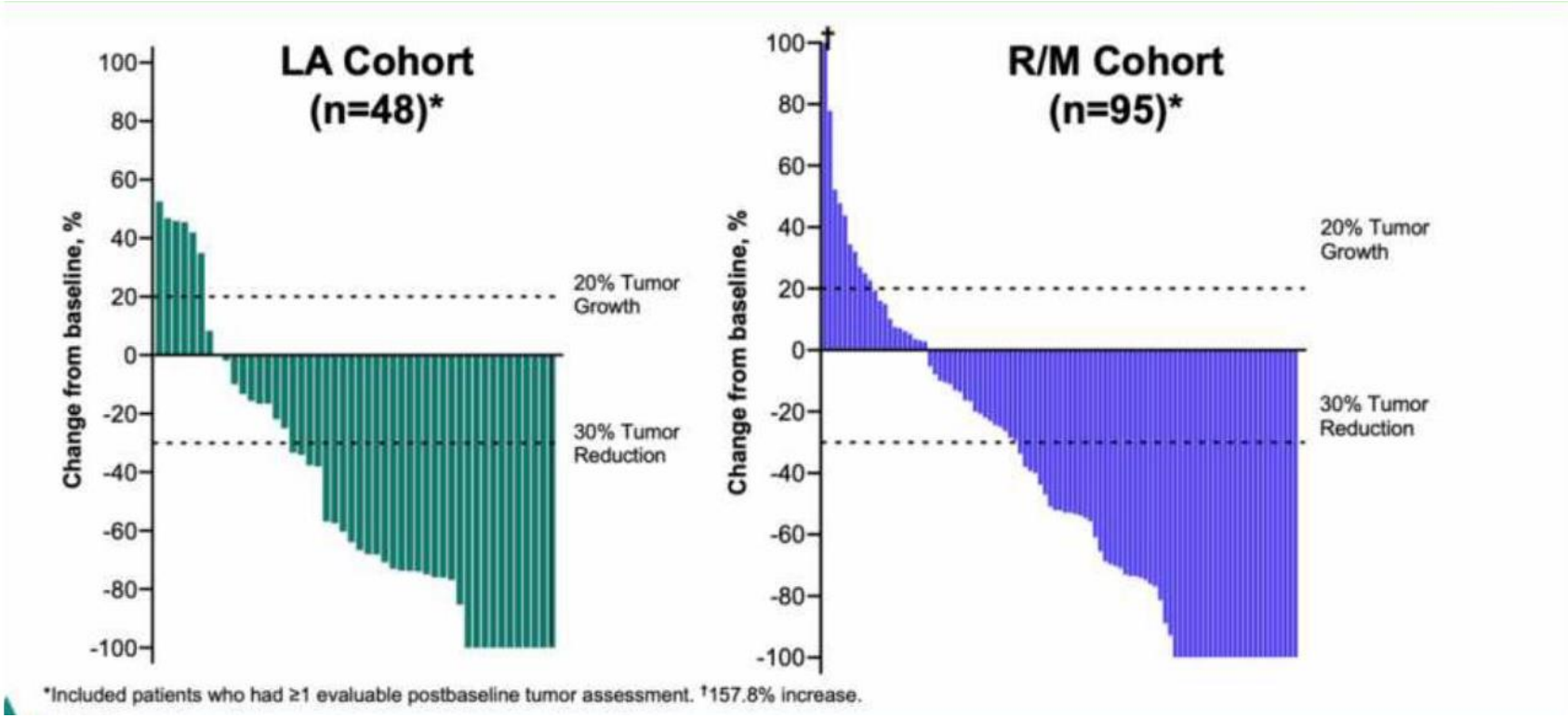
Hughes, B., et al. “Abstract CT006: Phase 2 study of pembrolizumab….” Cancer Res July 1 2021 (81) (13 Supplement) CT006; **DOI:** 10.1158/1538-7445.AM2021-CT006.

Pembrolizumab, CSCC: Results



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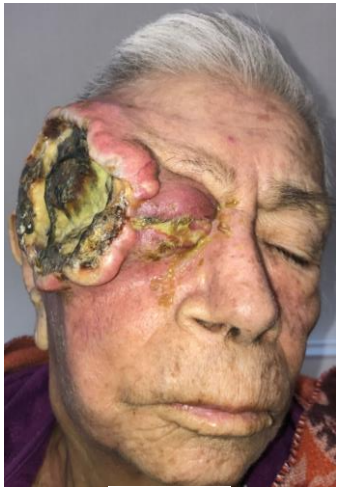
Pembrolizumab, CSCC: Case examples



Day 0

Failed Mohs Surgery,
wide local excision,
Radiation x 2 courses
in ~8 months

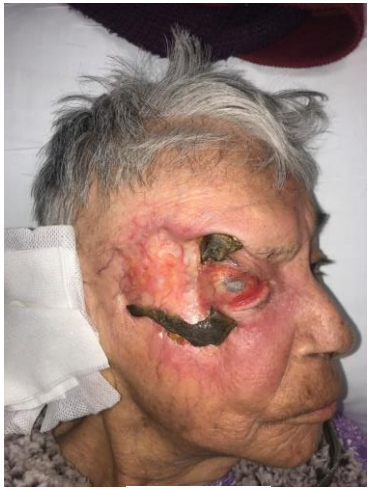
Invaded orbit
Facial nerve paulsy
Invaded optic canal
Dura enhancement
Invaded parotid
Invaded muscles

2 months

Pembrolizumab
200mg q3w offered
off-label at the time on
a compassionate care
basis

Pseudo-progression

5 months



2 years

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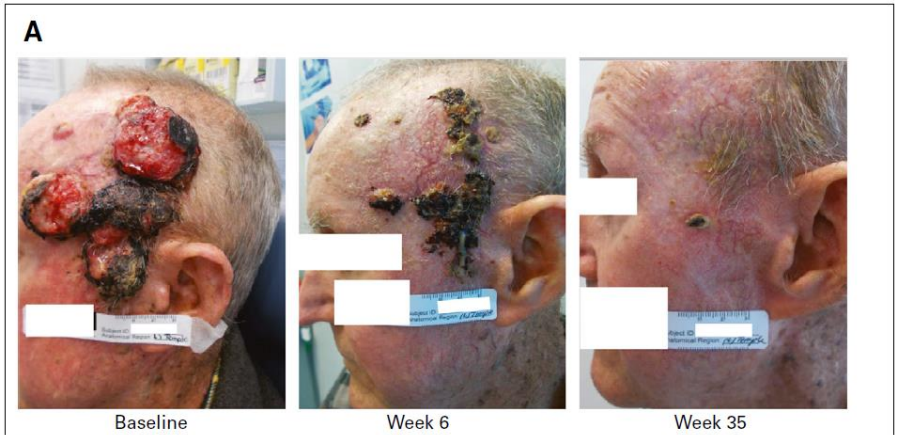
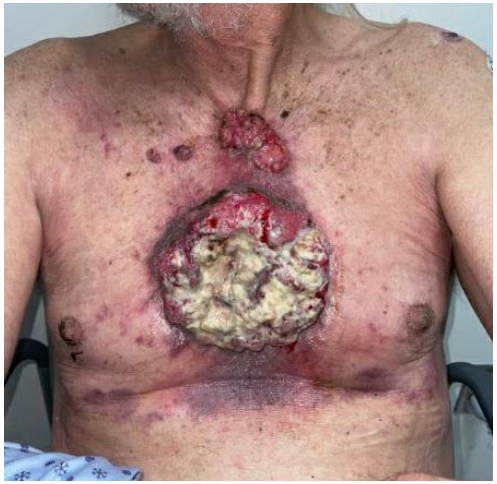
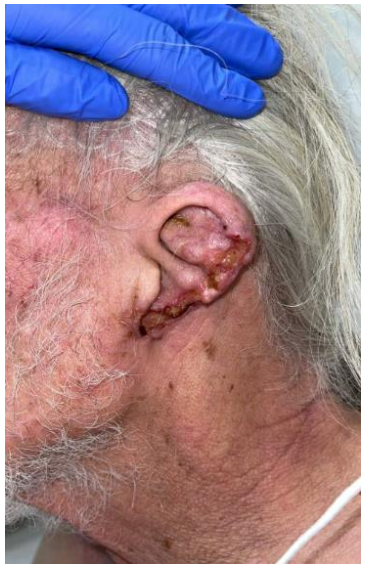
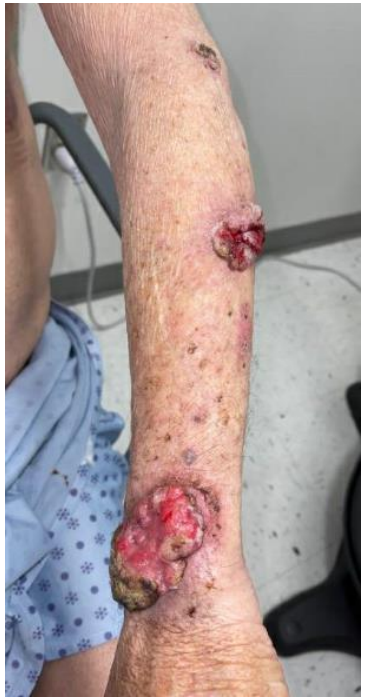
Pembrolizumab, CSCC: Case examples



Grob JJ, et al., JCO, 2020







Advanced Basal Cell Carcinoma

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Advanced Basal Cell Carcinoma

- More than 2 million BCCs diagnosed annually
  - More than 99% are treated with local treatments (surgery, ED&C, topicals, radiation)
  - A small percentage require systemic therapy, who are not amenable to surgery or radiation
- Hedgehog inhibitors (vismodegib, sonidegib) show an objective response rate of 30-60%, however more than 80% of patients discontinue HHI within 1 year
- Case for immunotherapy
  - BCCs have a high mutational burden
  - Risk of BCC is 10x in recipients of solid organ transplants

Cemiplimab, BCC: Study 1620 design

Phase 2, international (Canada, Europe, USA)
*industry sponsored

Locally advanced: n=84

Metastatic cohort, data not reported yet

→ Cemiplimab 350mg q3W
for up to 93 weeks, or until disease progression, unacceptable toxicity, or withdrawal of consent

Primary endpoint: confirmed objective response rate (ORR) by digital medical photography per modified WHO criteria or by radiological imaging as per RECIST criteria

Secondary endpoint:
- Duration of response
- Complete response rate

All patients were treated with prior hedgehog inhibitor (HHI) therapy
- Progressed on HHI
- No objective response to HHI after 9 months
- Intolerant of HHI therapy

Exclusion Criteria
- Ongoing or recent autoimmune disease requiring immunosuppressives (within past 5 years)
- Prior treatment with anti-PD1 or -PDL1
- History of solid organ transplant, concurrent malignancy), or hematologic malignancy
- Infection with HIV, Hepatitis B, or Hepatitis C

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Stratigos, et al. “Cemiplimab in locally advanced basal….” Lancet Oncol. May 2021.

Cemiplimab, BCC: Patient characteristics and results

	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**

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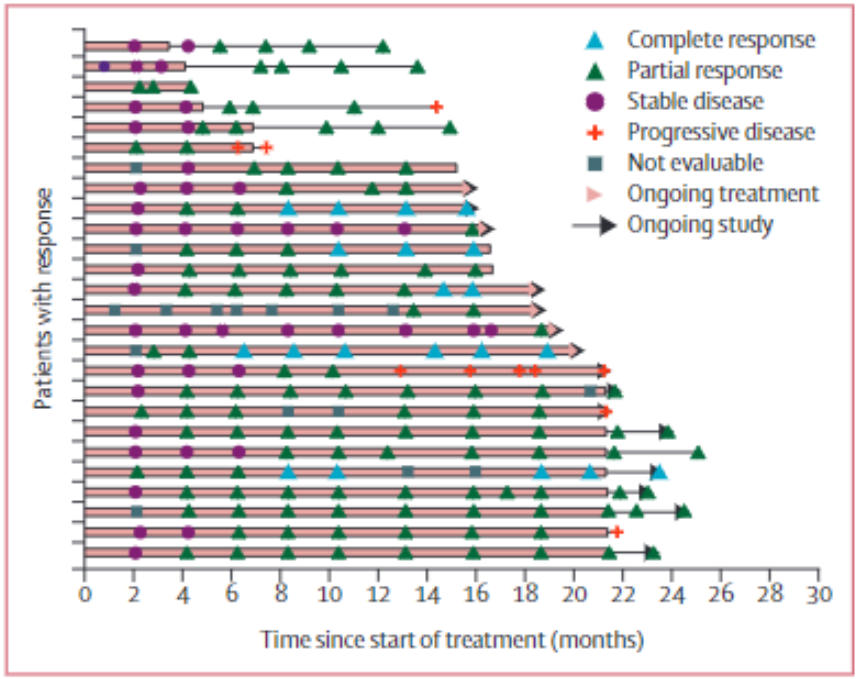
Stratigos, et al. "Cemiplimab in locally advanced basal…." Lancet Oncol. May 2021.

Cemiplimab, BCC: Results & adverse events



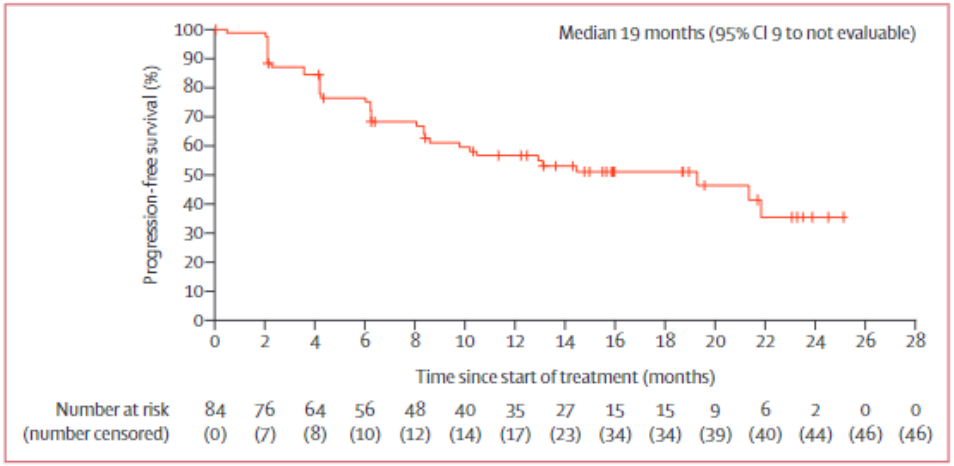


Figure 2: **Kaplan-Meier curve for progression-free survival per independent central review**
Crosses denote censored patients.

Adverse events:

- Grade 3-4 treatment emergent AEs occurred in 48% of patients
- Cemiplimab was discontinued in 11% of patients due to AEs due to the following reasons: adrenal insufficiency, asthenia, colitis, hypophysitis, immune-mediated hepatitis, acute kidney injury, hypothyroidism
- Most common side effects: colitis, hypertension, fatigue, UTI, visual impairment

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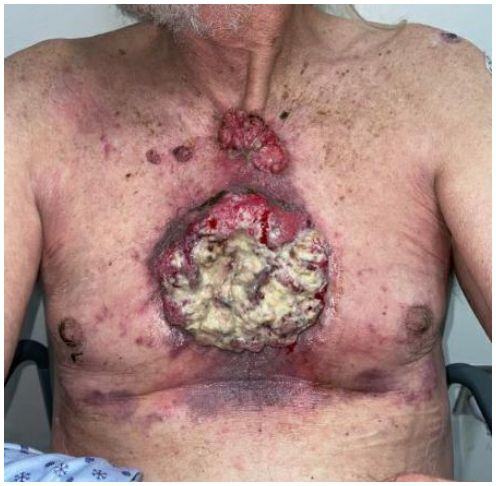
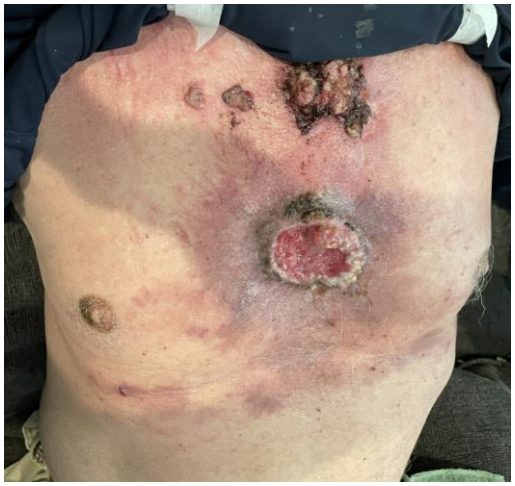
Stratigos, et al. "Cemiplimab in locally advanced basal…." Lancet Oncol. May 2021.

Cemiplimab, BCC: Case example

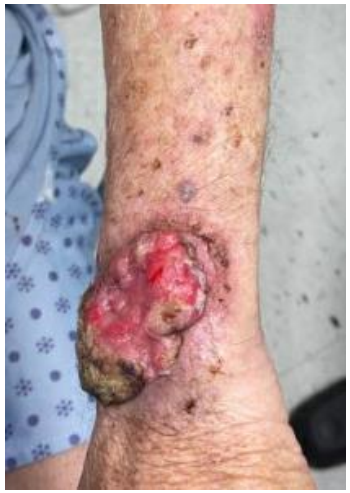


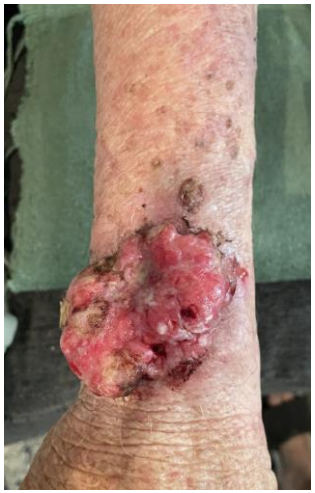
8 June 2021



17 August 2021

4 infusions of cemiplimab





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Stratigos, et al. “Cemiplimab in locally advanced basal….” Lancet Oncol. May 2021.

Summary of the combined data phase 2 studies in keratinocytic carcinoma

	CSCC, Cemiplimab	CSCC, Pembrolizumab	BCC, Cemiplimab
Overall response rate	46.1%	40.3%	31%
Median duration of follow up	15.7 months	Not reported in abstract	15 months
Median duration of response	Not reached	Not reached	Not reached
Time to response	2.1 months		4.3 months

Future directions for immunotherapy in keratinocytic carcinoma

	NCT #	Summary	Primary outcome	Estimated completion
Neoadjuvant	NCT04154943	Cemiplimab prior to surgery, stage 2-4 (M0)	Pathologic response	2024
	NCT04710498	Atezolizumab prior to surgery	Feasibility	2024
	NCT03889912	Intralesional cemiplimab prior to surgery	Safety (phase 1)	July 2021

Summary: Immunotherapy for keratinocytic carcinomas

- Local therapy remains standard of care for keratinocytic carcinoma when possible
- Major advances in systemic therapy for CSCC & BCC since approval of immune checkpoint inhibitors
- **CSCC**: Cemiplimab and pembrolizumab have been evaluated in separate phase 2 studies (no comparison group) and show clinical activity. Both now hold FDA approval and NCCN 2A recommendation for use when surgery & radiation are not an option.
  - No head-to-head studies to comment on one being better than the other
  - Cemiplimab has longer follow up data in CSCC
  - Pembrolizumab is approved in q6 week dosing and has larger overall experience due to widespread use in other tumor types
- **BCC**: Cemiplimab shows clinical activity in locally advanced BCC in 2nd line after hedgehog inhibitor. It now holds FDA approval in this setting. Cemiplimab for metastatic BCC is still being evaluated.
- Adverse events are an important concern with immune checkpoint blockade
  - 30-50% experience treatment related AEs in the clinical trials
  - Approximately 10% discontinue rate due to AEs
- Several clinical trials underway to further elucidate the role of immunotherapy in treatment of keratinocytic carcinomas

Thank you

- Questions?

- bamodi@coh.org

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