Systemic Therapies for cSCC

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Disclosures

- Consulting: Bicara Therapeutics, PDS Biotechnology, EMD Serono

- Research support as PI: Aveo, Ascendis, Bicara Therapeutics, EMD Serono, Gilead, Merck, Naveris, Natera, PDS Biotechnology, Regeneron, Replimune

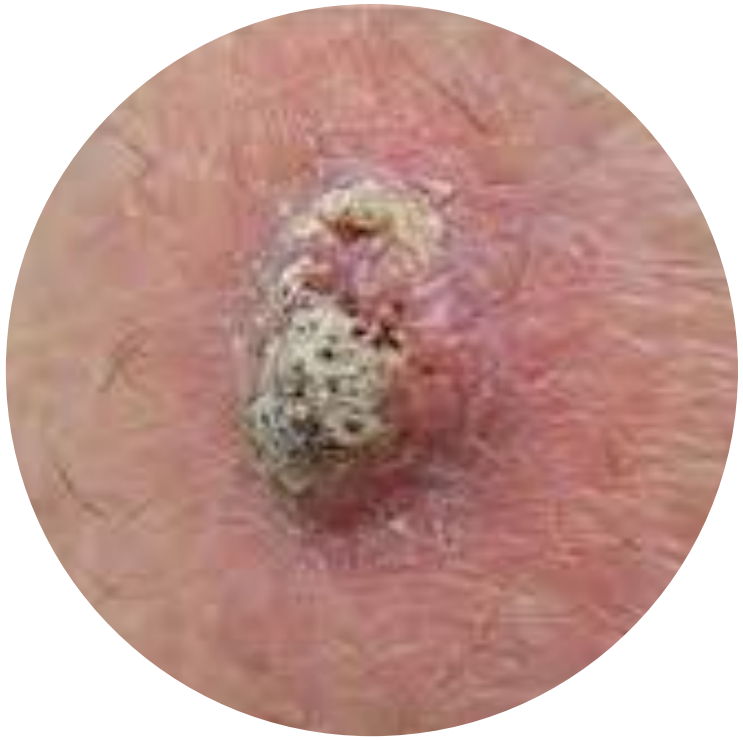
I will discuss investigational therapies for cSCC

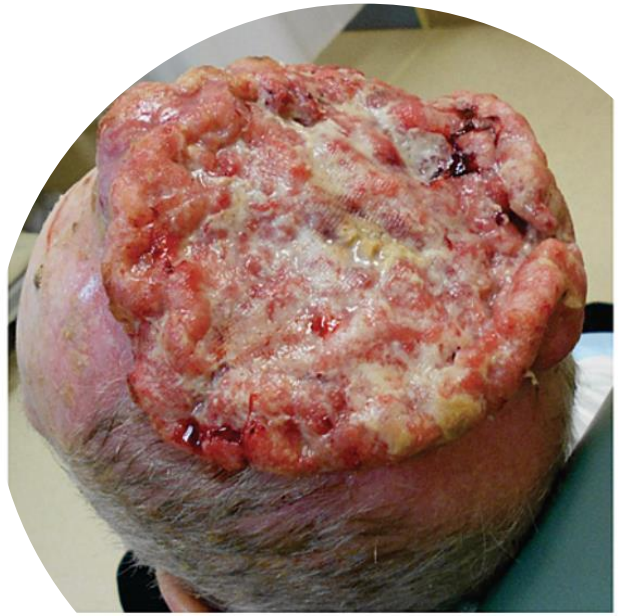
Learning Objectives

- Systemic Therapy in the Adjuvant Phase
- Immunotherapy for cSCC
- Neoadjuvant therapy
- Systemic Therapy in Unresectable/Metastatic disease

Cutaneous Squamous Cell Carcinoma (cSCC)

- 2nd most common skin cancer (1.8 million cases per year)
- Management usual driven by a dermatologist
- Rarely manifests in a more advanced state
  - Locally invasive
  - Regional metastasis
  - Distant metastasis





Adjuvant therapy

- Potential indications for adjuvant radiation
  - Peri-neural invasion (PNI)
  - Nodal involvement
  - Large tumor
  - Recurrent tumor
  - Immunosuppressed patient
- Should you ever add chemotherapy?
  - Extrapolate from RTOG 9501 & EORTC22931?
    - Adjuvant radiation + cisplatin if high risk features (extracapsular and/or +margin)
  - Is there any data in cSCC?

TROG 05.01 study

- Primary endpoint, freedom from locoregional relapse
- Radiation (60-66 Gy) vs. Radiation (60-66 Gy) + carboplatin AUC 2
- Inclusion
  - “high risk nodal disease”
    - Intraparotid node
    - Cervical nodal disease (2+, ENE, >3 cm size)
  - “advanced primary disease”
    - >5 cm or invasion of bone/skeletal muscle/cartilage

Patient Characteristics

Table 1. Patient, Tumor, and Treatment Characteristics

Characteristic	RT Arm (n = 157)	CRT Arm (n = 153)
Median age, years (range)	65 (37-83)	63 (32-85)
Sex		
Male	147 (94)	140 (92)
Female	10 (6)	13 (8)
ECOG PS		
0	144 (92)	133 (87)
1	12 (8)	20 (13)
2	1 (1)	0 (0)
High-risk feature		
High-risk nodal	122 (78)	116 (76)
Advanced primary/in transit	29 (18)	30 (20)
T3	3	1
T4	17	24
In transit	9	4
In transit/T4	0	1
High-risk nodal and advanced primary/ in transit	6 (4)	7 (5)
T3	1	1
T4	4	6
In transit	1	0
Extracapsular extension		
Absent	58 (40)	57 (42)
Present	86 (60)	79 (58)
Advanced primary (T3-4) margin status with or without high risk nodal disease	25 (16)	33 (22)
Positive	10	16
≤ 5 mm	7	12
> 5 mm/clear	3	2
Missing	5	3

Porceddu et al. JCO 2018

- Nodal status drove inclusion
- Significantly older than in HNSCC adjuvant studies

Results

- No benefit to radiosensitizing chemotherapy
- How applicable are these results to our patients?
- Survival was rather high
  - Are these patients truly at the highest risk?

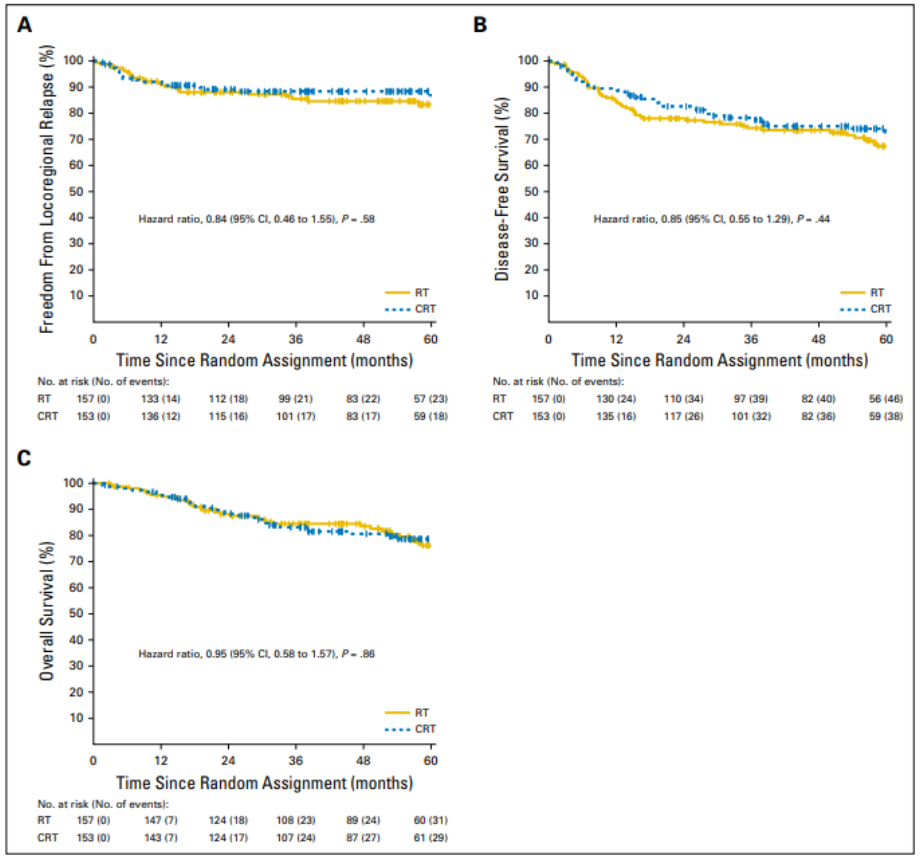


Fig 2. Kaplan-Meier estimates of (A) freedom from locoregional relapse, (B) disease-free survival, and (C) overall survival by treatment arm. CRT, chemoradiotherapy;

Porceddu et al. JCO 2018

Guideline recommendations

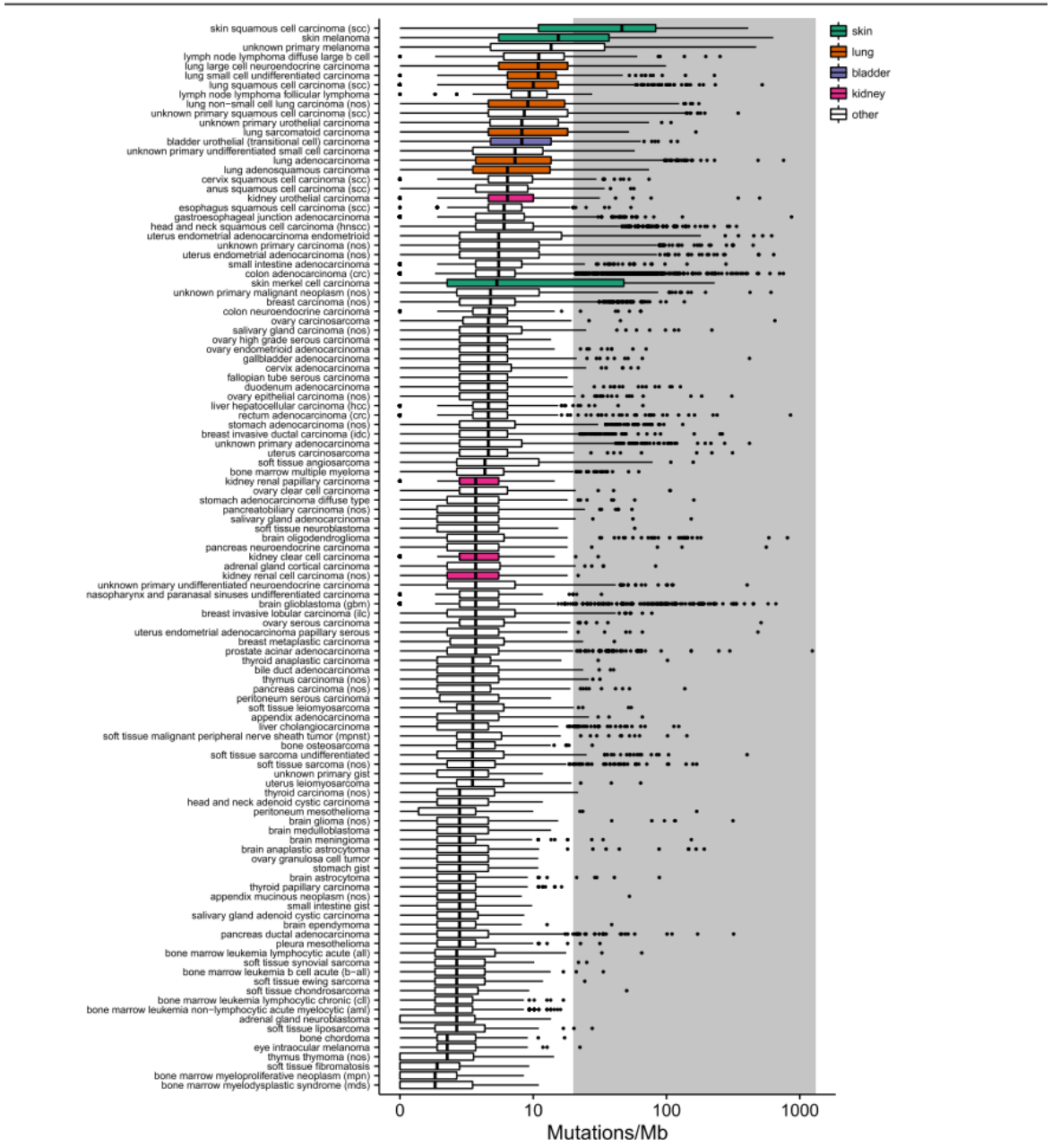
- Adjuvant RT is guideline concordant
- Consideration of chemotherapy (not carboplatin) if ENE, positive margins that cannot be cleared, ideally in the context of a clinical trial
- My practice

Immunotherapy in cSCC

Prior to 2018 no approved therapies available for cSCC

Combination of Phase 1&2 cohorts of cempilimab in cSCC

FDA approved cemiplimab 9/2018



Chalmers et al. Genome Medicine 2017

Tumor mutational Burden

- Predicts response to immunotherapy (Keynote-158)
- Look what's on top

Symmetry with melanoma

Checkmate 067

Table 1. Response to Treatment.*

Variable	Nivolumab plus Ipilimumab (N=314)	Nivolumab (N=316)	Ipilimumab (N=315)
Best overall response — no. (%)†			
Complete response	69 (22)	60 (19)	18 (6)
Partial response	114 (36)	81 (26)	42 (13)
Stable disease	38 (12)	30 (9)	69 (22)
Progressive disease	74 (24)	121 (38)	159 (50)
Unable to determine	19 (6)	24 (8)	27 (9)
Objective response‡			
Patients with response			
No.	183	141	60
% (95% CI)	58 (53–64)	45 (39–50)	19 (15–24)
Estimated odds ratio (95% CI)§	6.35 (4.38–9.22)	3.54 (2.46–5.10)	—
P value§	<0.001	<0.001	—

Larkin et al. NEJM 2019

Keynote 001

Table 1. Best overall responses based on irRC (investigator review) [ ] in all patients and treatment-naive patients[a]

Response	Total, % (95% CI) N = 655	Treatment-naive, % (95% CI) n = 151
ORR	41 (37–45)	52 (43–60)
DCR	65 (61–68)	72 (64–79)
Best response		
CR	16 (13–19)	25 (19–33)
PR	25 (22–28)	27 (20–34)
SD	24 (21–27)	20 (14–27)
PD	25 (22–29)	21 (15–29)
No assessment	10 (8–13)	7 (4–13)

[a]Only confirmed responses.
CR, complete response; DCR, disease control rate; irRC, immune-related response criteria; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Hamid et al. Annals of Oncology 2019

Cemiplimab in advanced cSCC

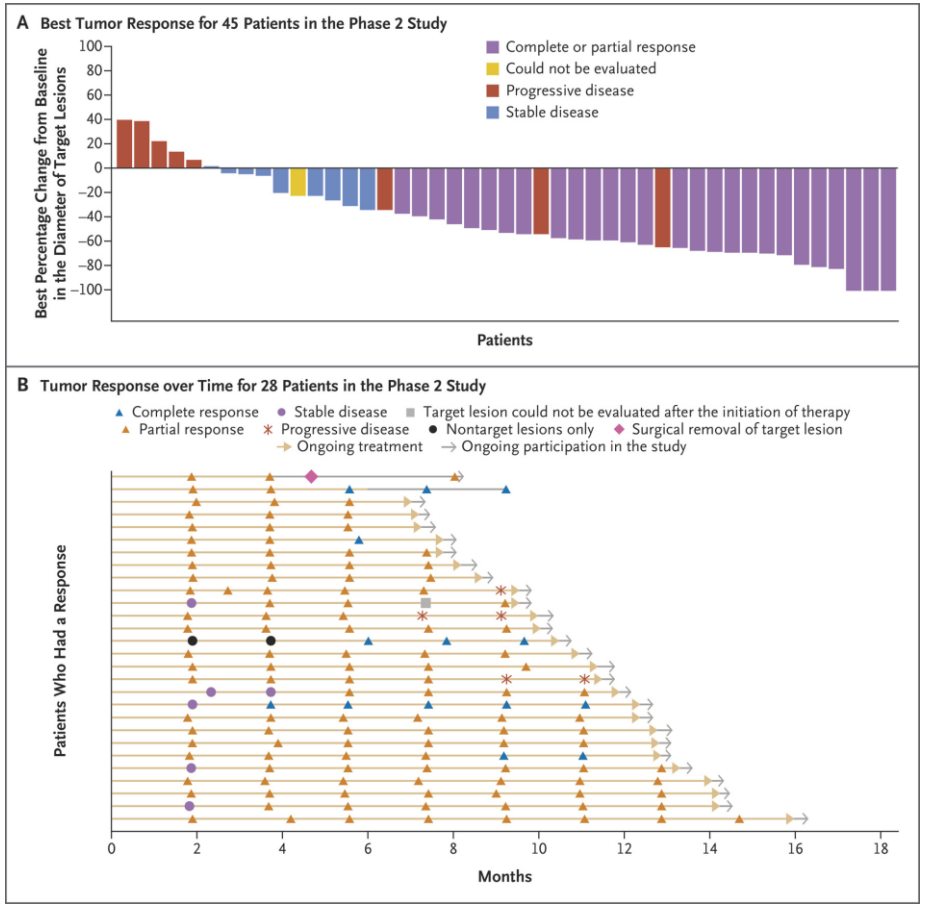
- Patients are relatively elderly
- Head & Neck (H&N) subsite predominates
- Who was included?
  - Disease recurrence after two or more surgical procedures and the treating clinicians expected that curative resection would be unlikely
  - Anticipation that surgery would result in substantial complications or deformity
  - Metastatic disease

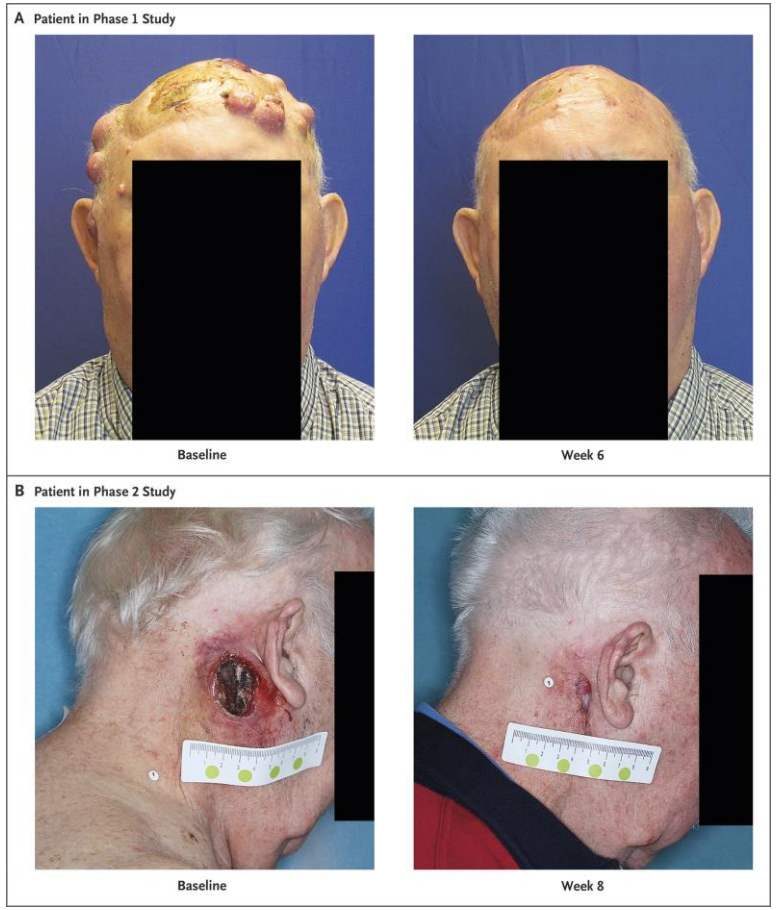
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Expansion Cohorts of the Phase 1 Study (N=26)	Metastatic-Disease Cohort of the Phase 2 Study (N=59)
Age		
Median (range) — yr	73 (55–88)	71 (38–93)
≥65 yr — no. (%)	21 (81)	43 (73)
Male sex — no. (%)	21 (81)	54 (92)
ECOG performance status score — no. (%)†		
0	10 (38)	23 (39)
1	16 (62)	36 (61)
Primary site of cutaneous squamous-cell carcinoma — no. (%)		
Head or neck	18 (69)	38 (64)
Arm or leg	5 (19)	12 (20)
Trunk	2 (8)	9 (15)
Penis	1 (4)	0
Previous systemic therapy for cutaneous squamous-cell carcinoma — no. of patients (%)‡		
No regimens	8 (31)	26 (44)
Any regimen	15 (58)	33 (56)
1 regimen	15 (58)	22 (37)
≥2 regimens	0	11 (19)
Previous radiotherapy for cutaneous squamous-cell carcinoma — no. (%)	20 (77)	50 (85)
Extent of cutaneous squamous-cell carcinoma — no. (%)		
Distant metastasis	8 (31)	45 (76)
Regional metastasis only	8 (31)	14 (24)
Locally advanced progression only	10 (38)	0

Migden et al NEJM 2018

Immunotherapy for cSCC





Cemiplimab

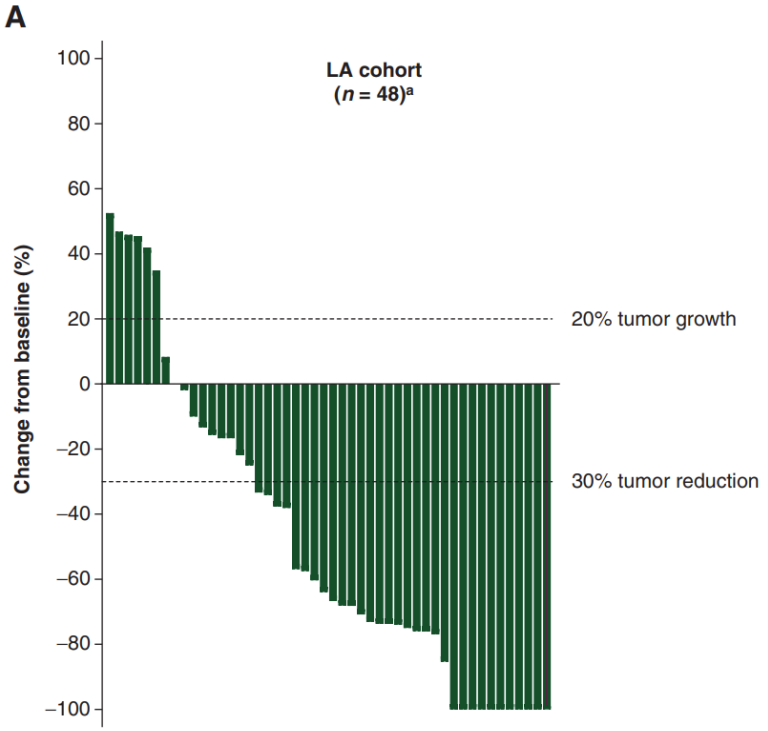
Table: 814P				
	Group 1 (mCSCC) 3 mg/kg Q2W (n=59)	**Group 2 (laCSCC) 3 mg/kg Q2W (n=78)**	**Group 3 (mCSCC) 350 mg Q3W (n=56)**	**Total (n=193)**
Median duration of follow-up, months, (range)	18.5 (1.1–41.0)	15.5 (0.8–43.2)	17.3 (0.6–43.4)	15.7 (0.6–43.4)
ORR, %, (95% CI)	50.8 (37.5–64.1)	44.9 (33.6–56.6)	46.4 (33.0–60.3)	47.2 (39.9–54.4)
Complete response, n (%)	12 (20.3)	10 (12.8)	11 (19.6)	33 (17.1)
Partial response, n (%)	18 (30.5)	25 (32.1)	15 (26.8)	58 (30.1)
Median DOR, months (95% CI)	NR (20.7–NE)	41.9 (20.5–54.6)	41.3 (40.8–46.3)	41.3 (38.8–46.3)
Median PFS, months (95% CI)	18.4 (7.3–53.2)	18.5 (11.1–43.8)	21.7 (3.8–43.3)	22.1 (10.4–32.3)
Median OS, months (95% CI)	57.7 (29.3–NE)	NR (58.3–NE)	48.4 (29.5–NE)	NR (56.0–NE)

CI, confidence interval; DOR, duration of response; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Migden et al Annals of Oncology 2022

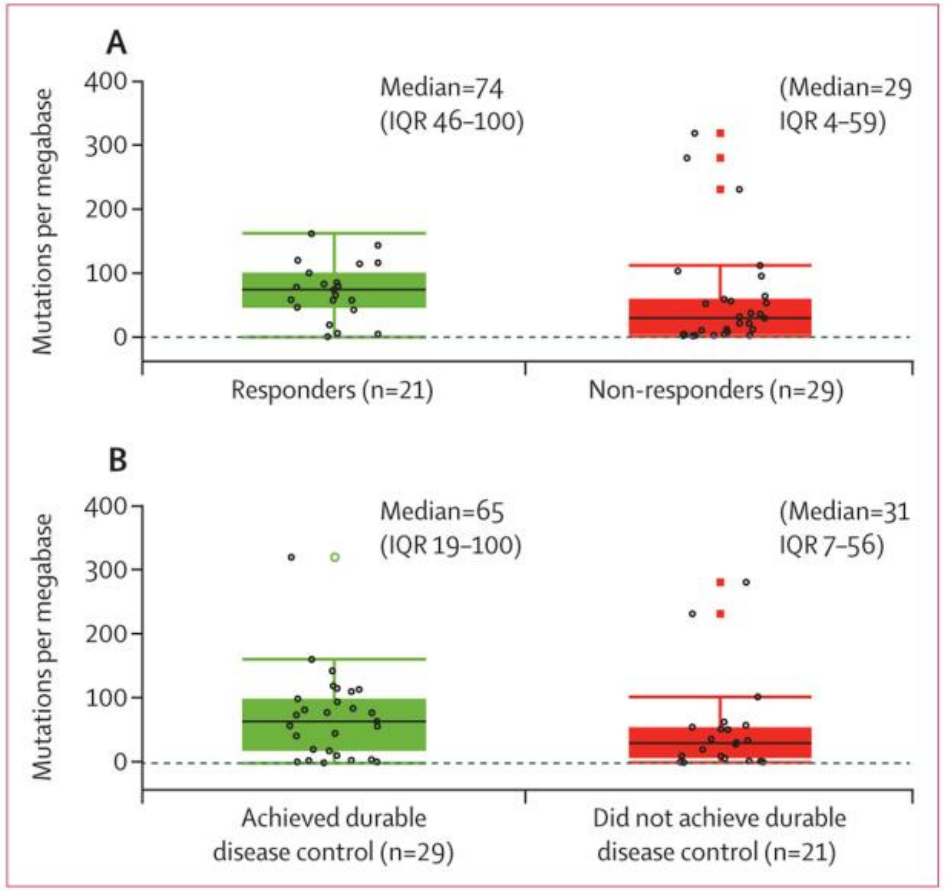
Pembrolizumab

- Keynote 629
  - Phase 2
  - 159 patients
    - 54 locally advanced
    - R/M 105
  - Objective Response rate (ORR) 50% in the locoregionally advanced group
  - ORR 35.2% in the Recurrent/Metastatic (R/M) group (86% had prior therapy)
    - Worse than cemiplimab? – cross trial comparison!! ~40% had no prior therapy
- FDA approved 2020



Hughes et al Annals of Oncology 2021

Predictors of Response?



Supplementary Table 5. Tumour response per independent central review by programmed death-ligand 1 status*

	PD-L1 <1% (n=17)	PD-L1 ≥1% (n=31)	PD-L1 ≥1–<5% (n=3)	PD-L1 ≥5–<50% (n=21)	PD-L1 ≥50% (n=7)	PD-L1 unknown* (n=30)
Objective response	6 (35%; 14–62%)	17 (55%; 36–73%)	2 (67%; 9–99%)	12 (57%; 34–78%)	3 (43%; 10–82%)	34 (44%; 32–55%)
Best overall response						
Complete response	1 (6%)	4 (13%)	0	4 (19%)	0	10 (13%)
Partial response	5 (29%)	13 (42%)	2 (67%)	8 (38%)	3 (43%)	24 (31%)
Stable disease	8 (47%)	7 (23%)	1 (33%)	4 (19%)	2 (29%)	28 (36%)
Progressive disease	2 (12%)	3 (10%)	0	1 (5%)	2 (29%)	9 (12%)
Not evaluable	1 (6%)	4 (13%)	0	4 (19%)	0	7 (9%)
Disease control	14 (82%; 57–96%)	24 (77%; 59–90%)	3 (100%; 29–100%)	16 (76%; 53–92%)	5 (71%; 29–96%)	62 (80%; 69–88%)
Durable disease control	10 (59%; 33–82%)	21 (68%; 49–83%)	3 (100%; 29–100%)	14 (67%; 43–85%)	4 (57%; 18–90%)	19 (63%; 51–74%)

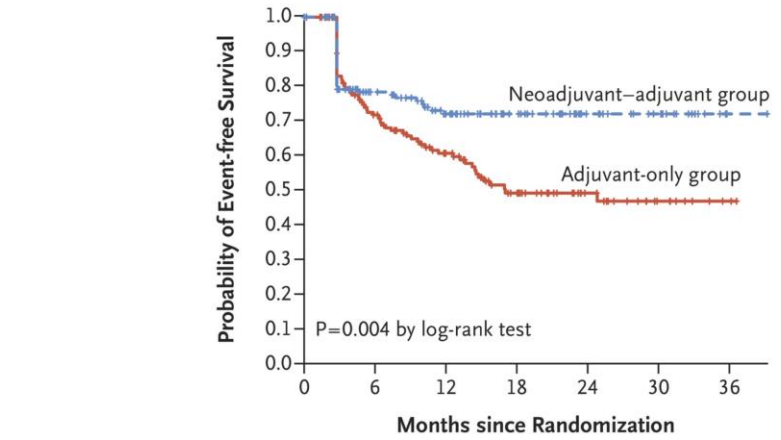
Data are % (95% CI) or n (%). *PD-L1 status unknown due to sample viability. Slides from 30 patients were excluded from PD-L1 IHC analysis because the slides were expired (>6 months since slide cut date) or because there were an insufficient number of cells (<100 viable cells) on the slide.

CI=confidence interval; IHC=immunohistochemistry; PD-L1=programmed death-ligand 1.

Migden et al. Lancet Oncology 2020

Symmetry with Melanoma cont.

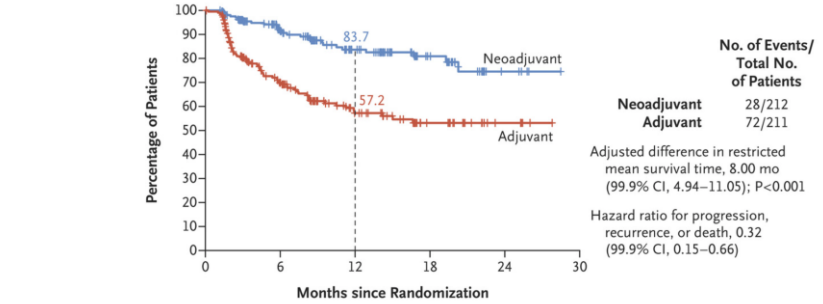
- Adjuvant melanoma with nivoumab (Checkmate 238) and pembrolizumab (Keynote 054 and Keynote 716
  - Have not shown OS benefit
  - Improved RFS
- Neoadjuvant in stage III
  - Pembrolizumab (SWOG 1801)
  - Ipilimumab/Nivolumab (NADINA)
    - 47.2% pathologic complete response (pCR)



No. at Risk

Neoadjuvant–adjuvant group	154	96	69	46	25	17	1
Adjuvant-only group	159	98	67	40	22	10	2

Patel et al NEJM 2023



No. at Risk (no. censored)

Neoadjuvant	212 (0)	126 (71)	77 (111)	34 (152)	5 (179)
Adjuvant	211 (0)	100 (57)	53 (89)	23 (116)	6 (133)

Blank et al NEJM 2024

Adjuvant immunotherapy

- Keynote 630 and C-POST studies ongoing
- Inclusion criteria differ somewhat but are relatively concordant
- Keynote 630
  - Extracapsular extension (ECE) in >2 cm node or 2+ nodes involved
  - Tumor with 2 or more high risk features (4 cm+ size, depth >6mm, poorly differentiated or sarcomatoid histology, recurrent disease, satellite lesion, LVI)
  - Cortical bone invasion or skull base invasion
- Awaiting results (primary endpoint is recurrence free survival and Disease free survival)

Neoadjuvant treatment

- Huge change in practice

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

N.D. Gross, D.M. Miller, N.I. Khushalani, V. Divi, E.S. Ruiz, E.J. Lipson, F. Meier, Y.B. Su, P.L. Swiecicki, J. Atlas, J.L. Geiger, A. Hauschild, J.H. Choe, B.G.M. Hughes, D. Schadendorf, V.A. Patel, J. Homsi, J.M. Taube, A.M. Lim, R. Ferrarotto, H.L. Kaufman, F. Seebach, I. Lowy, S.-Y. Yoo, M. Mathias, K. Fenech, H. Han, M.G. Fury, and D. Rischin

Neoadjuvant therapy

- Melanoma 21-47% pCR
- NSCLC chemo-immunotherapy ~25% pCR
- cSCC?

Neoadjuvant cemiplimab

- 79 patients phase 2 study
- 4 doses of cemiplimab followed by surgery and adjuvant therapy
- All patients had *resectable* stage II-IV cSCC

Table 1. Characteristics of the 79 Patients at Baseline.*

Characteristic	Value
Median age (range) — yr	73 (24–93)
Male sex — no. (%)	67 (85)
Race — no. (%)†	
White	69 (87)
Other	2 (3)
Not reported	8 (10)
Not Hispanic or Latinx — no. (%)†	74 (94)
Primary tumor site — no. (%)	
Head and neck	72 (91)
Trunk, arms, and legs	7 (9)
Stage group — no. (%)‡	
II	5 (6)
III	38 (48)
IV (M0)	36 (46)
Tumor stage at screening — no. (%)‡	
TX	23 (29)
Tis	1 (1)
T1	4 (5)
T2	10 (13)
T3	39 (49)
T4a	2 (3)
Node stage at screening — no. (%)‡	
NX	1 (1)
N0	31 (39)
N1	13 (16)
N2§	11 (14)
N2b	9 (11)
N2c	1 (1)
N3¶	1 (1)
N3a	1 (1)
N3b	11 (14)
ECOG performance-status score — no. (%)‖	
0	60 (76)
1	19 (24)

* Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the patient.
‡ Tumor–node–metastasis (TNM) staging of cutaneous squamous-cell carcinoma with involvement of the head and neck was based on the eighth edition of the *American Joint Committee on Cancer Staging Manual*, and TNM staging of cutaneous squamous-cell carcinoma without involvement of the head and neck was based on the ninth edition of the *Union for International Cancer Control Manual of Clinical Oncology*.
§ These values were not further specified as N2a, N2b, or N2c.
¶ These values were not further specified as N3a or N3b.
‖ Scores on the Eastern Cooperative Oncology Group (ECOG) performance-status scale range from 0 to 5, with higher scores indicating greater disability.

Gross et al. NEJM 2022

Results

- CT scans not a great predictor of path response

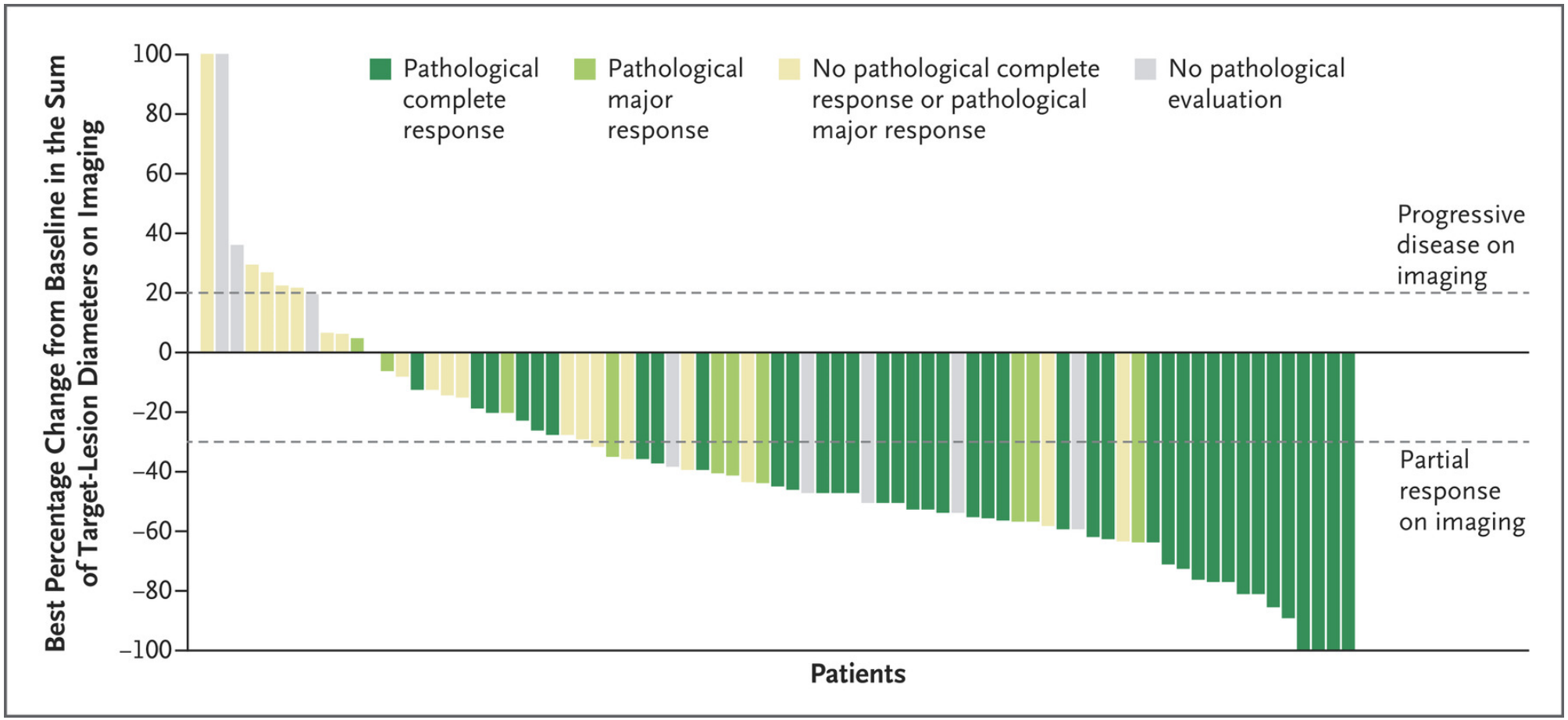


Table 2. Tumor Response to Neoadjuvant Cemiplimab in the 79 Patients According to Pathological and Imaging-Based Response Assessment.*

Tumor Response	Value			
	Independent Review		Investigator Assessment	
	no. (%)	*95% CI*	*no. (%)*	*95% CI*
Pathological response				
Pathological complete response: absence of viable tumor cells in surgical specimen	40 (51)	39–62	42 (53)	42–65
Pathological major response: presence of viable tumor cells that constitute ≤10% of surgical specimen	10 (13)	6–22	10 (13)	6–22
No pathological complete response or pathological major response: presence of viable tumor cells that constitute >10% of surgical specimen†	20 (25)†	—	NA	—
No pathological evaluation‡	9 (11)	—	9 (11)	—
Response on imaging§				
Objective response: complete or partial response	—	—	54 (68)	57–78
Best overall response¶				
Complete response	—	—	5 (6)	—
Partial response	—	—	49 (62)	—
Stable disease	—	—	16 (20)	—
Progressive disease	—	—	8 (10)	—
No imaging-based evaluation	—	—	1 (1)	—
Disease control‖	—	—	70 (89)	80–95

Results cont.

PDL1 in Neoadjuvant

Table S8. Pathological response per ICPR according to baseline PD-L1 tumor positive score

	Cemiplimab 350 mg Q3W (N=79)				
	PD-L1 <1% (n=15)	PD-L1 ≥1% (n=41)	Evaluable PD-L1 (n=56)	No evaluable PD-L1 (N=23)	All patients (N=79)
pCR (0% viable tumor)					
Patients, no.	3	22	25	15	40
% (95% CI)*	20 (4.3–48.1)	53.7 (37.4–69.3)	44.6 (31.3–58.5)	65.2 (42.7–83.6)	50.6 (39.1–62.1)
MPR (>0% and ≤10% viable tumor)					
Patients, no.	2	6	8	2	10
% (95% CI)*	13.3 (1.7–40.5)	14.6 (5.6–29.2)	14.3 (6.4–26.2)	8.7 (1.1– 28.0)	12.7 (6.2–22.0)
Non-pCR/MPR, no. (%)	8 (53.3)	10 (24.4)	18 (32.1)	2 (8.7)	20 (25.3)
NE, no. (%)†	2 (13.3)	3 (7.3)	5 (8.9)	4 (17.4)	9 (11.4)

*Clopper-Pearson exact CI.

†NE response includes the missing and unknown tumor response.

Table S9. Tumor response assessed by RECIST 1.1 per investigator assessment according to baseline PD-L1 tumor positive score

	Cemiplimab 350 mg Q3W (N=79)				
	PD-L1 <1% (n=15)	PD-L1 ≥1% (n=41)	Evaluable PD-L1 (n=56)	No evaluable PD-L1 (N=23)	All patients (N=79)
Objective response					
Patients, no.	7	31	38	16	54
% (95% CI)*	46.7 (21.3–73.4)	75.6 (59.7–87.6)	67.9 (54.0–79.7)	69.6 (47.1–86.8)	68.4 (56.9–78.4)
Best overall response, no. (%)					
CR†	1 (6.7)	3 (7.3)	4 (7.1)	1 (4.3)	5 (6.3)
PR†	6 (40.0)	28 (68.3)	34 (60.7)	15 (65.2)	49 (62.0)
SD	4 (26.7)	7 (17.1)	11 (19.6)	5 (21.7)	16 (20.3)
PD	4 (26.7)	3 (7.3)	7 (12.5)	1 (4.3)	8 (10.1)
NE‡	0	0	0	1 (4.3)	1 (1.3)
Disease control rate§					
Patients, no.	11	38	49	21	70
% (95% CI)*	73.3 (44.9–92.2)	92.7 (80.1–98.5)	87.5 (75.9–94.8)	91.3 (72.0–98.9)	88.6 (79.5–94.7)

*Clopper-Pearson exact CI.

- pCR and ORR higher in patients with TPS ≥1

TMB in Neoadjuvant

- pCR higher in patients with high TMB

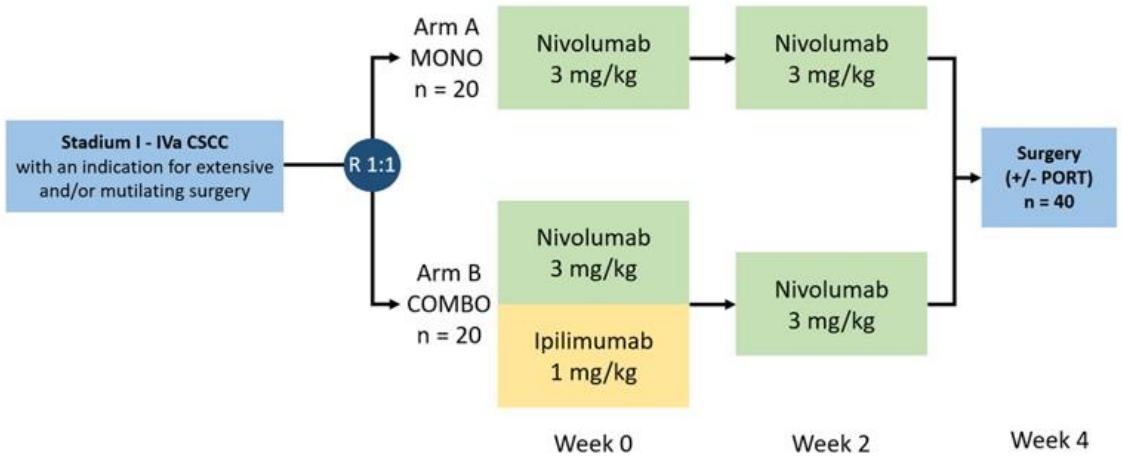
Table S11. Pathological response per ICPR according to baseline TMB

	Cemiplimab 350 mg Q3W (N=79)				
	Low TMB (n=25)	High TMB (n=25)	Evaluable TMB (n=50)	No evaluable TMB (N=29)	All patients (N=79)
pCR (0% viable tumor)					
Patients, no.	5	14	19	21	40
% (95% CI)*	20 (6.8–40.7)	56.0 (34.9–75.6)	38.0 (24.7–52.8)	72.4 (52.8–87.3)	50.6 (39.1–62.1)
MPR (>0% and ≤10% viable tumor)					
Patients, no.	6	3	9	1	10
% (95% CI)*	24.0 (9.4–45.1)	12.0 (2.5–31.2)	18.0 (8.6–31.4)	3.4 (0.1– 17.8)	12.7 (6.2–22.0)
Non-pCR/MPR, no. (%)	10 (40.0)	7 (28.0)	17 (34.0)	3 (10.3)	20 (25.3)
NE, no. (%)†	4 (16.0)	1 (4.0)	5 (10.0)	4 (13.8)	9 (11.4)

*Clopper-Pearson exact CI.

Neoadjuvant Nivo +/- Ipi

MATISSE design: A randomized phase II trial

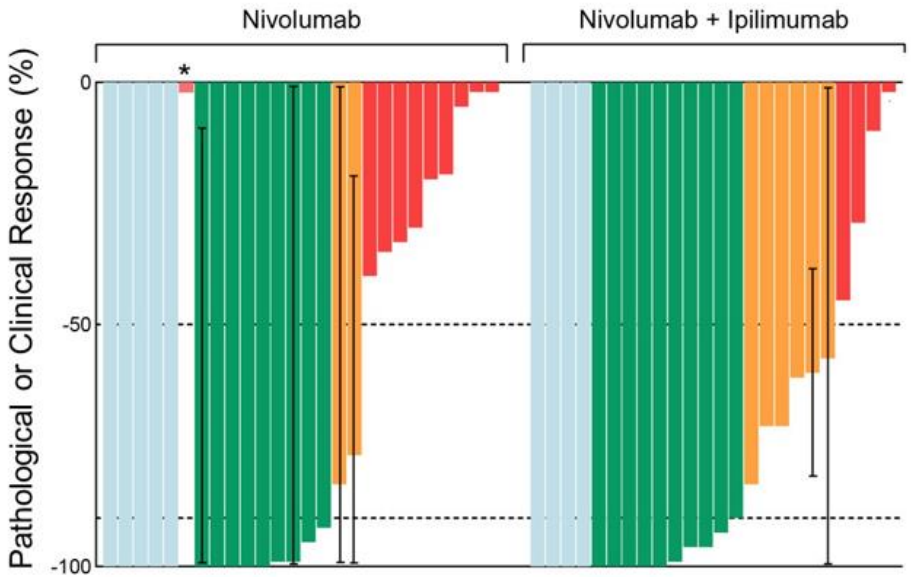


Primary objective:
Histopathological response upon neo-adjuvant immunotherapy at time of surgery

Zur et al. ASCO 2023

Results

MATISSE pathological and clinical responses



In total 10 patients withdrew consent to Surgery:
Clinical CR: 9 patients withdrew consent to surgery as they noticed clinical remission upon neoadjuvant immunotherapy in week 3-4 (pathological response not available) and reached a clinical CR during Follow-Up.
*CNR: Clinical Non-Response: 1 patient with clinically progressive disease withdrew consent to surgery (pathological response not available).

MPR: Major Pathological Response:
≤10% remaining vital tumor cells in the surgical resection specimen.
PPR: Partial Pathological Response:
<50% remaining vital tumor cells in the surgical resection specimen.
NPR: No Pathological Response:
≥50% remaining vital tumor cells in the surgical resection specimen.

High response rates (MPR & Clinical CR) were observed after 2 infusions of neoadjuvant NIVO (54%) and NIVO/IPI (58%).

Zur et al. ASCO 2023

- At 18 months of f/u the 9 withdrawn consents all remain in remission

What's next in Resectable cSCC?

- Phase 3 study upcoming NRG HN014 *Randomized Phase III Trial of Neoadjuvant Immunotherapy with Response-Adapted Treatment Versus Standard-Of-Care treatment For Resectable Stage III/IV Cutaneous Squamous Cell Carcinoma*
- Future direction anti-PD1 + X in neoadjuvant space
- Neoadjuvant is probably one size fits *most*.
  - Patient selection important!
  - Progression is possible

How is resectable cSCC best managed now?

- Rapidly changing with varying algorithms institutionally
- Surgery followed by radiation has reasonably good outcomes
- Phase 3 study upcoming, but many may not have equipoise
  - What kind of patients will be enrolled?

A little more about unresectable patients

- How does radiation fit in?
- A Phase II, Multicenter, Single-Arm Clnical Trial of Defintiive **R**adiotherapy **A**nd Ce**M**i**P**lim**A**b-wlc Immuno**T**Rherapy for locally Advanced, Unresectable Cutaneous Squamous cell Carcinoma
  - Primary endpoint disease free survival at 18 months
  - ORR is secondary endpoint

Study Phase:	*Screening*	*Neoadjuvant Treatment*	*Week 6 Response*	*Neoadjuvant Treatment*	*Concurrent Treatment*	*Adjuvant Treatment*
Time:	Weeks -6 - 0	Weeks 1 – 4	Progression →		Weeks 7 - 14 Weeks 13-20	Weeks 22 – 52
			Response/Stable disease →	Weeks 7-10		
Study Event:	Screening Procedures	Cemiplimab Immunotherapy		Cemiplimab Immunotherapy	Concurrent Radiotherapy & Cemiplimab Immunotherapy	Cemiplimab Immunotherapy

Systemic Therapy after anti-PD1

- Nothing approved
- How did we treat before anti-PD1?
  - Chemotherapy
  - Cetuximab

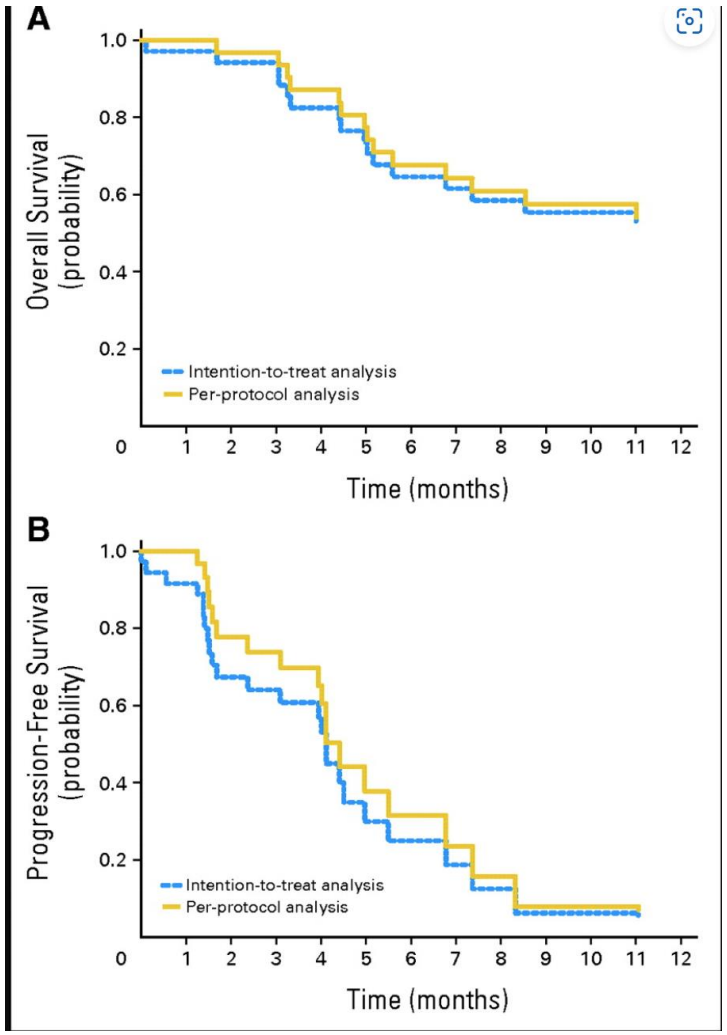
Systemic Therapy NCCN

Table 3: Options for Systemic Therapy Alone

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cemiplimab-rwlc[f,g] (if curative RT[d] or surgery is not feasible for locally advanced, recurrent, or metastatic disease)[8,9] • Pembrolizumab[f,g] (if curative RT[d] or surgery is not feasible for locally advanced, recurrent, or metastatic disease)[10] • Clinical trial	• If ineligible for or progressed on immune checkpoint inhibitors and clinical trials, consider: ▸ Carboplatin + paclitaxel ± cetuximab[14-18] ▸ EGFR inhibitors (eg, cetuximab)[e,13]	• Neoadjuvant cemiplimab-rwlc[g,8] • If ineligible for or progressed on immune checkpoint inhibitors and clinical trials, consider: ▸ Capecitabine[20,21] ▸ Cisplatin[e,7] ▸ Cisplatin + 5-FU[e,19]

[14] Ferrari D, Fiore J, Codecà C, et al. A phase II study of carboplatin and paclitaxel for recurrent or metastatic head and neck cancer. Anticancer Drugs 2009;20:185-190.
[15] Carinato H, Burgy M, Ferry R, et al. Weekly Paclitaxel, Carboplatin, and Cetuximab as First-Line Treatment of Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma for Patients Ineligible to Cisplatin-Based Chemotherapy: A Retrospective Monocentric Study in 60 Patients. Front Oncol 2021;11:714551.
[16] Botticelli A, Pomati G, Cirillo A, et al. Weekly chemotherapy as first line treatment in frail head and neck cancer patients in the immunotherapy era. J Transl Med 2021;19:303.
[17] Tahara M, Kiyota N, Yokota T, et al. Phase II trial of combination treatment with paclitaxel, carboplatin and cetuximab (PCE) as first-line treatment in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (CSPOR-HN02). Ann Oncol 2018;29:1004-1009.
[18] Geraghty L, Schultz TE, Hoffman SE, et al. Weekly vs. 3-weekly paclitaxel, carboplatin, and cetuximab (PCC) in recurrent/metastatic head and neck cancer. Mol Clin Oncol 2021;15:240.

- No quality studies of chemotherapy (couple small studies in the early 90s)
- Extrapolate from HNSCC
- Cetuximab has been studied more recently



Cetuximab for cSCC

- Phase 2 study, 36 patients
  - Median Age 79
  - 10/36 respond ~28% ORR
  - OS 8.1 months, PFS 4.1 months

Maubec et al. JCO 2011

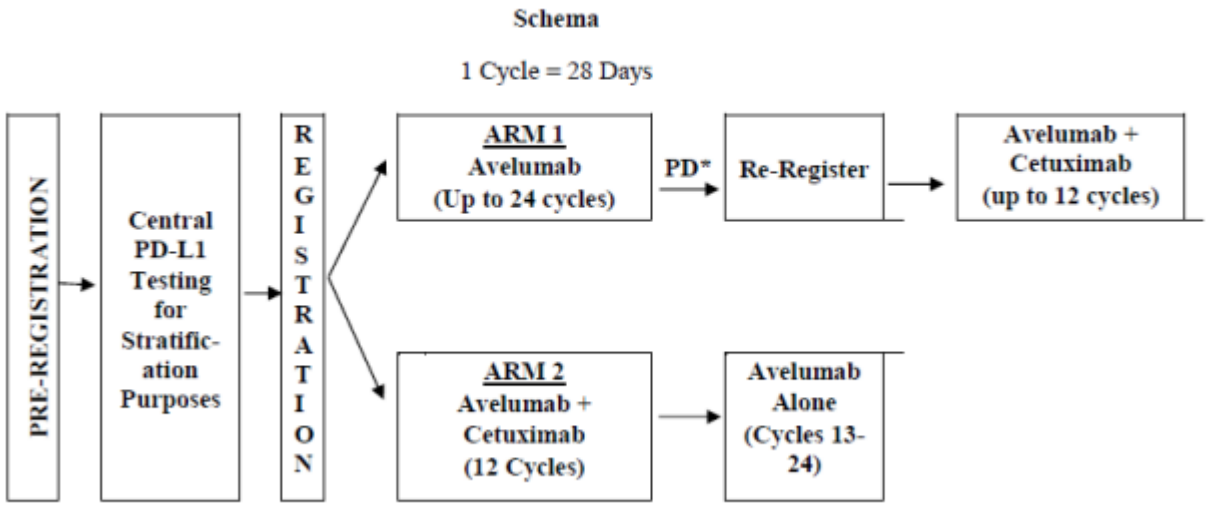
Cetuximab post immunotherapy

- Small retrospective study suggest higher response rate
  - 13 patient cohort post IO (10/13 metastatic)
    - 7/13 with response
    - 6 month disease control rate 77%
    - Complicated by fact half of patients also had definitive or palliative RT
    - Median OS not reached

Marin-Acevedo et al. Cancers (Basel) 2023

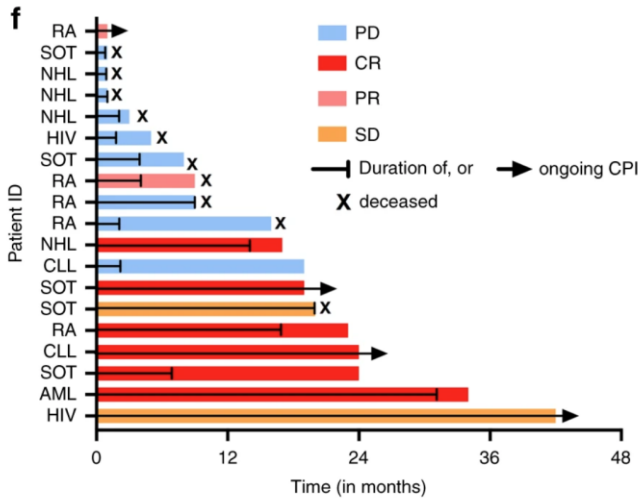
Cetuximab + immunotherapy

- Alliance A091802
  - Cetuximab + Avelumab vs. Avelumab
  - Accrual complete ~50 patients
  - Progression Free Survival is primary objective
  - Secondary endpoints of ORR, Overall Survival



cSCC in the immunocompromised

- CLL 5-10x increase in skin cancers
  - Anecdotally worse response to immuotherapy in patients with CLL and other conditions such as lupus that interfere with immune response or give rise to non-UV damage type cSCC
- What about transplant patients?
  - ~50% lifetime incidence of skin cancer
  - 65-250x more likely to develop cSCC
- Limited data suggests lower absolute lymphocyte count and certain immunosuppressed states may reduce response rates



Hanna et al. British Journal of Cancer 2020

Conclusion

- Systemic therapy in the adjuvant phase has scant supporting data
  - Immunotherapy data pending
- Immunotherapy has transformed management of locally advanced and metastatic patients
- The field is moving to immunotherapy upfront
  - Optimal treatment after immunotherapy needs to be defined
- Novel therapies and combinations remain an area of need for patients who are anti-PD1 refractory

Questions?