Therapeutic Update: NMSC

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RELEVANT DISCLOSURES

Investigator and/or Consultant: AbbVie, Almirall, Apogee, Arcutis Biotherapeutics, Benev, Biofrontera, Bristol Myers Squibb, Crown Aesthetics, Eli Lilly, Flint Clinical, Genentech, Janssen, LEO Pharma, Oruka, Pfizer, Regeneron Pharmaceuticals, Sun Pharma, Verrica, and UCB; has served as an investigator for AbbVie, Allergan, Almirall, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Biofrontera, Bristol Myers Squibb, Boehringer Ingelheim, Cara Therapeutics, Castle Biosciences, Concert Pharmaceuticals (acquired by Sun Pharma), Cutanea Life Sciences, Dermavant Sciences, Eli Lilly, Galderma, HighlightII, Incyte, Janssen, Nimbus Therapeutics, Medicus, Novartis, Processa, Prolacta, Regeneron Pharmaceuticals, Sanofi, SkinCure Oncology, Takeda, Trevi Pharmaceuticals, and Verrica

Shareholder of Bristol Myers Squibb, Chronicle Medical Software, Eli Lilly, and Remedly

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Dr. Bhatia's Disclosures:

- Affiliations with Abbvie, Advanced Derm Solutions, Almirall, Alumis, Apogee, Arcutis, Avene, Biofrontera, Blueprint, Celldex, Galderma, Highlight, InCyte, J&J, Journey, LaRoche-Posay, LEO, Lilly, NAOS, Novartis, Ortho, Oruka, Pelthos, Pfizer, Regeneron, Sagimet, Sanofi, SkinFix, Soligenix, SunPharma, Takeda, Veradermics, and Verrica

- Copies of pdf or questions: bhatiaharbor@gmail.com

- Acknowledgments:
  - Scott Dinehart, MD
  - Laura Ferris, MD, PhD

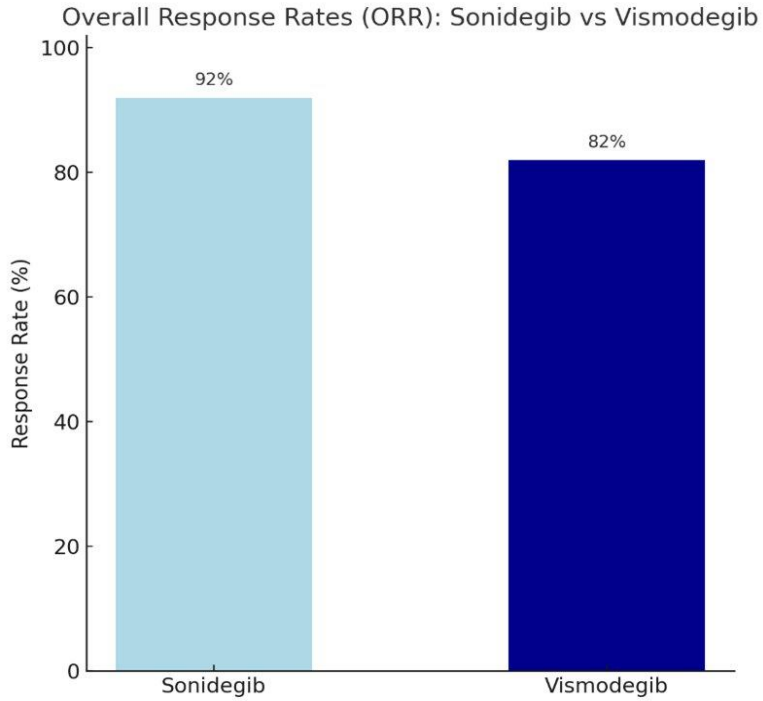
Outline

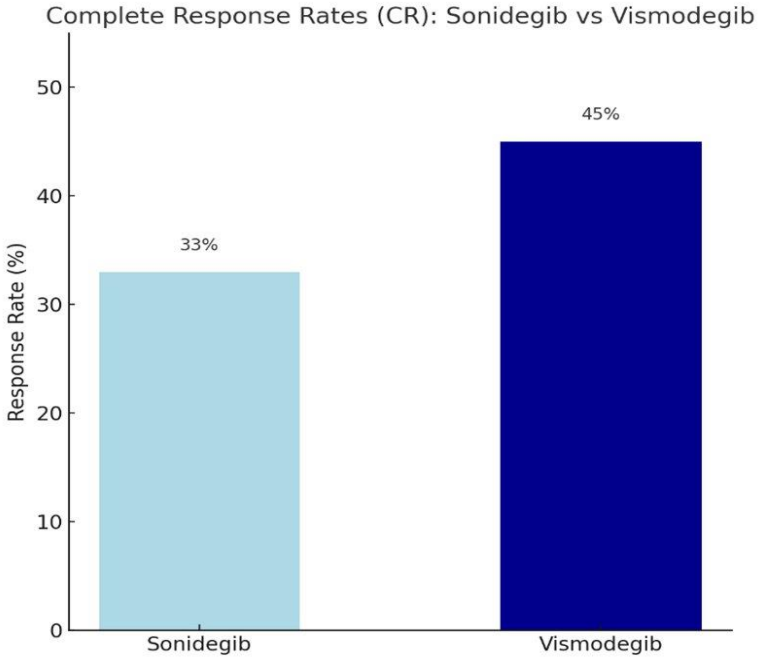
- Pharmaceuticals
- IV Immunotherapy
- Intralesional Therapy
- Topicals
- Pipeline
- Light/Energy Therapy

Hedgehog Inhibitor Therapy

- **Overall Response Rate (ORR):** 87% (20/23 patients) saw tumor shrinkage
- **Overall Complete Response (CR):** 39% (9/23 patients) had clearance
- **Sonidegib:** Works well for most patients, but full clearance ~1/3
- **Vismodegib:** Slightly lower response overall, but more patients saw complete clearance

- **Adjunctive therapies** post-HHI
  - **RFR** was higher for MMS (87%) and surgery (86%) compared to radiation therapy (67%).
  - *Take home:* Following HHI with surgery offers best chance at long-term control





Comparing Vismodegib and Sonidegib

	Vismodegib (ERIVANCE study)[19]	Sonidegib (BOLT study)[27]
Indication	Locally advanced BCC that has recurred following surgery, metastatic BCC, and patients who are not candidates for surgery or radiation	Locally advanced BCC that has recurred following surgery, and patients who are not candidates for surgery or radiation
Dose	150 mg once daily	200 mg once daily
Objective response rate (complete or partial response)	43% in locally advanced 30% in metastatic BCC	56% in locally advanced
Median duration of response	7.6 months	26.1 months
Progression-free survival	9.5 months	22.1 months
Common side effects	Muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, decreased appetite, and diarrhea	

- **Half-life vismodegib is 4-12 days / sonidegib is 28 days**
  - Critical for post-therapy washout period
- **Volume of distribution (vD) for vismodegib is 16.4-26.6L and 9,166L for sonidegib** (lipophilic - probably more tissue distribution)
- **What is the vD of human blood?** About 5 liters. Vd ≤40 is likely mostly confined to blood and some tissue

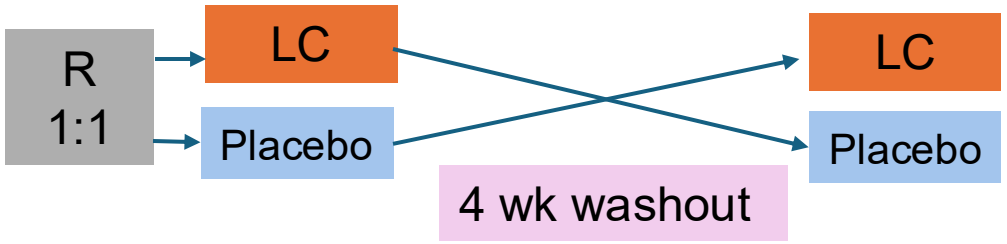
Wilson et al. *J Am Acad Dermatol*. 2022 Jun;86(6S):S14-S24.

Key Clinical Adverse Events in Patients With Advanced Basal Cell Carcinoma Treated With Sonidegib or Vismodegib: A Post Hoc Analysis

L-carnitine 1000-2000 mg daily *decreased* muscle cramps

Gutzmer R, Loquai C, Robert C, Dréno B, Guminski A, Lewis K, Arntz R, Martelli S, Squittieri N, Kheterpal M. *Dermatol Ther (Heidelb)*. 2021 Oct;11(5):1839-1849.

Levocarnitine (LC) for treatment of muscle spasms in BCC patients taking vismodegib



Dose : Levocarnitine 495 mg PO BID

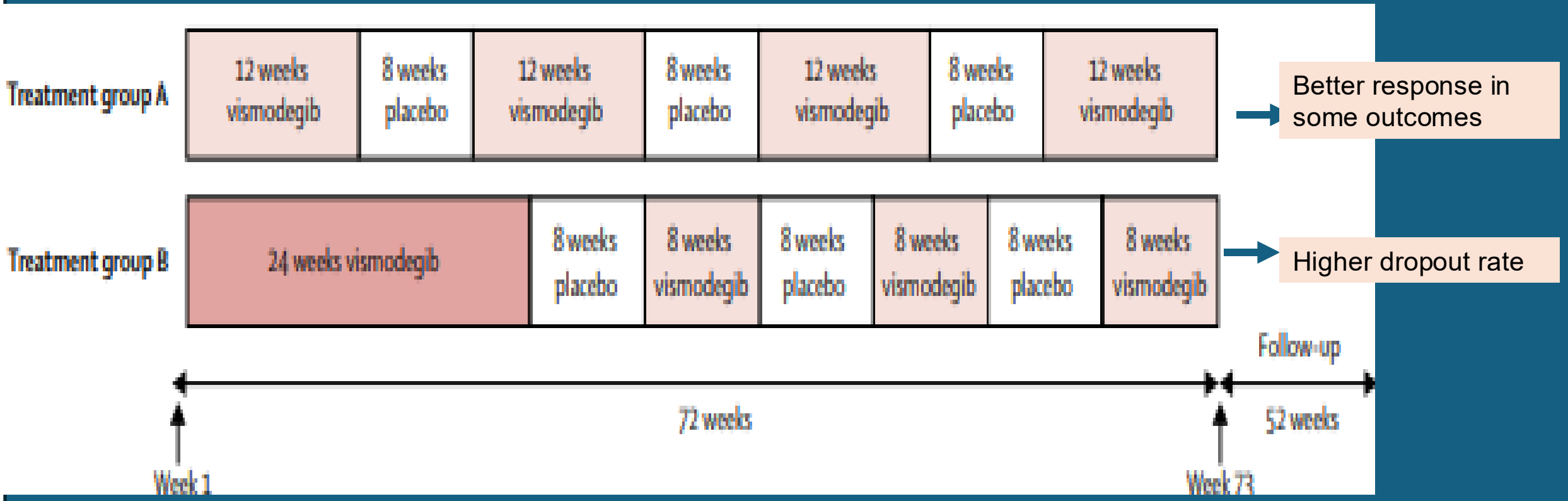
Endpoint	LC (*N* = 8)	Placebo (*N* = 8)	*P*-value	Effect size (95% CI)
Median per cent change in muscle spasm frequency	−48.1%	+54.1	0.02	−137% (−278.8%, −25%)
Median change in number of body locations affected by spasms	−1	0	0.04	−1 (−3, −0.5)

Levocarnitine (LC) period led to a large median per cent reduction in muscle spasm frequency and decreased the median number of body locations affected by spasms. Placebo period did not reduce median per cent change in muscle spasm frequency, nor the median number of body locations affected by spasms. CI, confidence interval.

J Eur Acad Dermatol Venereol. 2018 Jul;32(7):e298-e299.

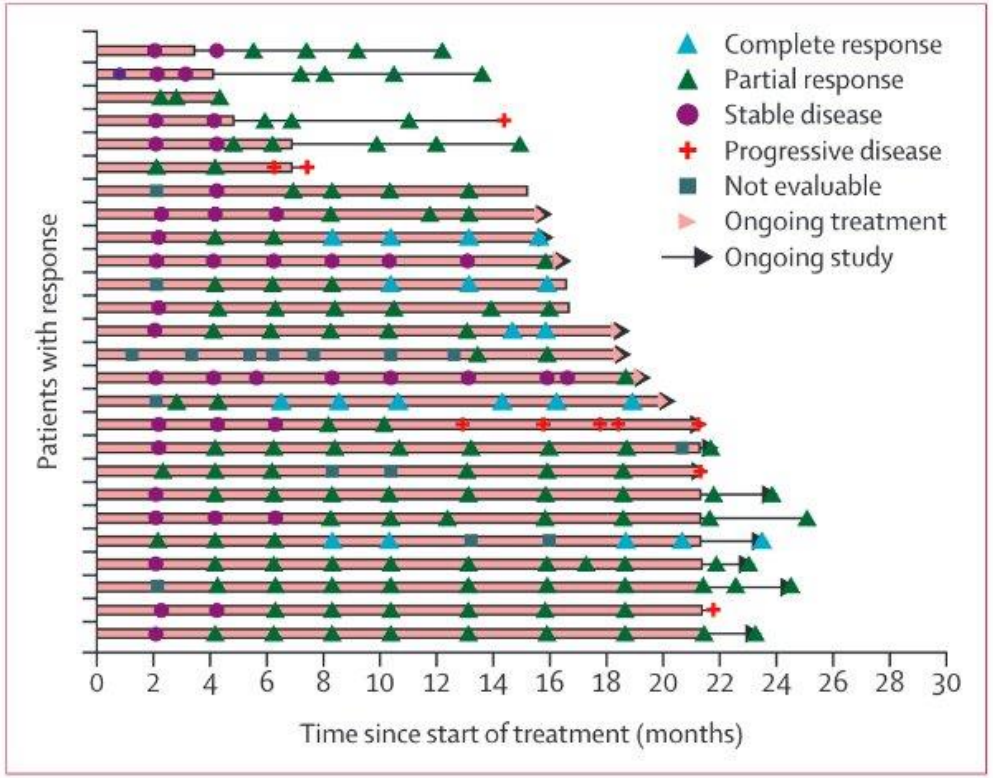
Treatment interruption may improve HHI tolerability

MIKIE study: 2 dosing regimens in people with multiple BCCs



IV Immunotherapy for BCC

- **Cemiplimab**
  - For patients with locally advanced BCC who did not respond to HHI
- **Brand Name**: Libtayo
- **Features:** Immune checkpoint inhibitor targeting PD-1[1]
- **Clinical Trial**: 2021 Phase II EMPOWER-BCC-1
  - 84 patients received cemiplimab 350 mg IV infusion every 3 weeks.
  - 31% of patients saw tumor shrinkage
  - Acceptable safety profile[2,3]

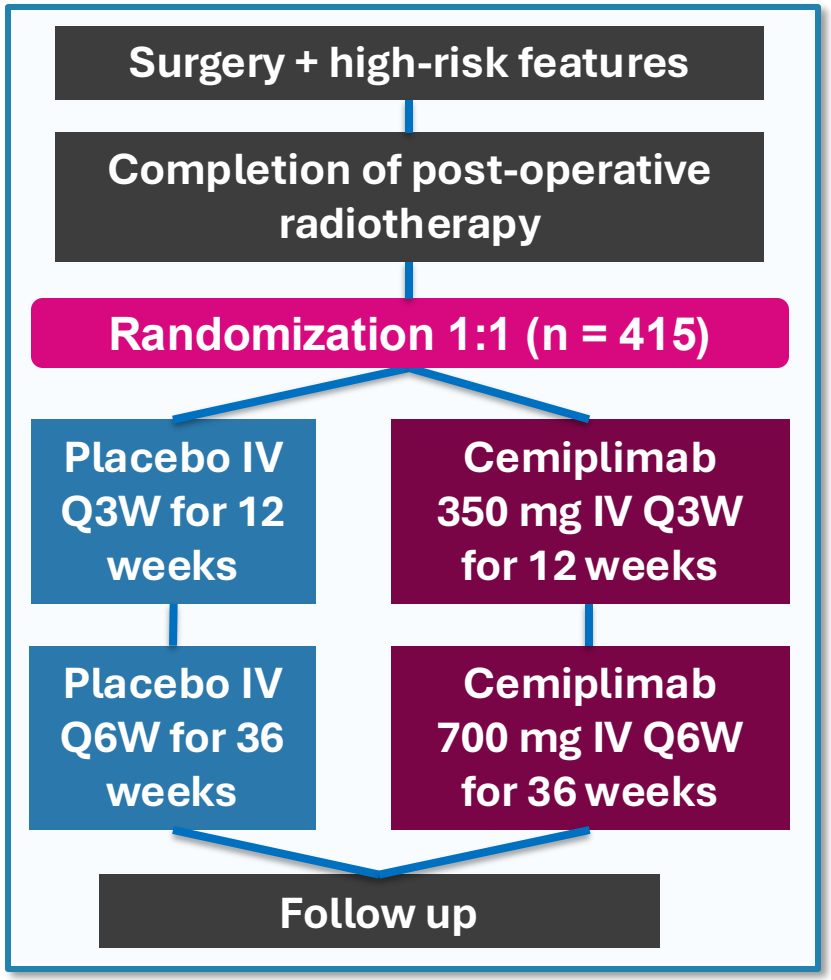


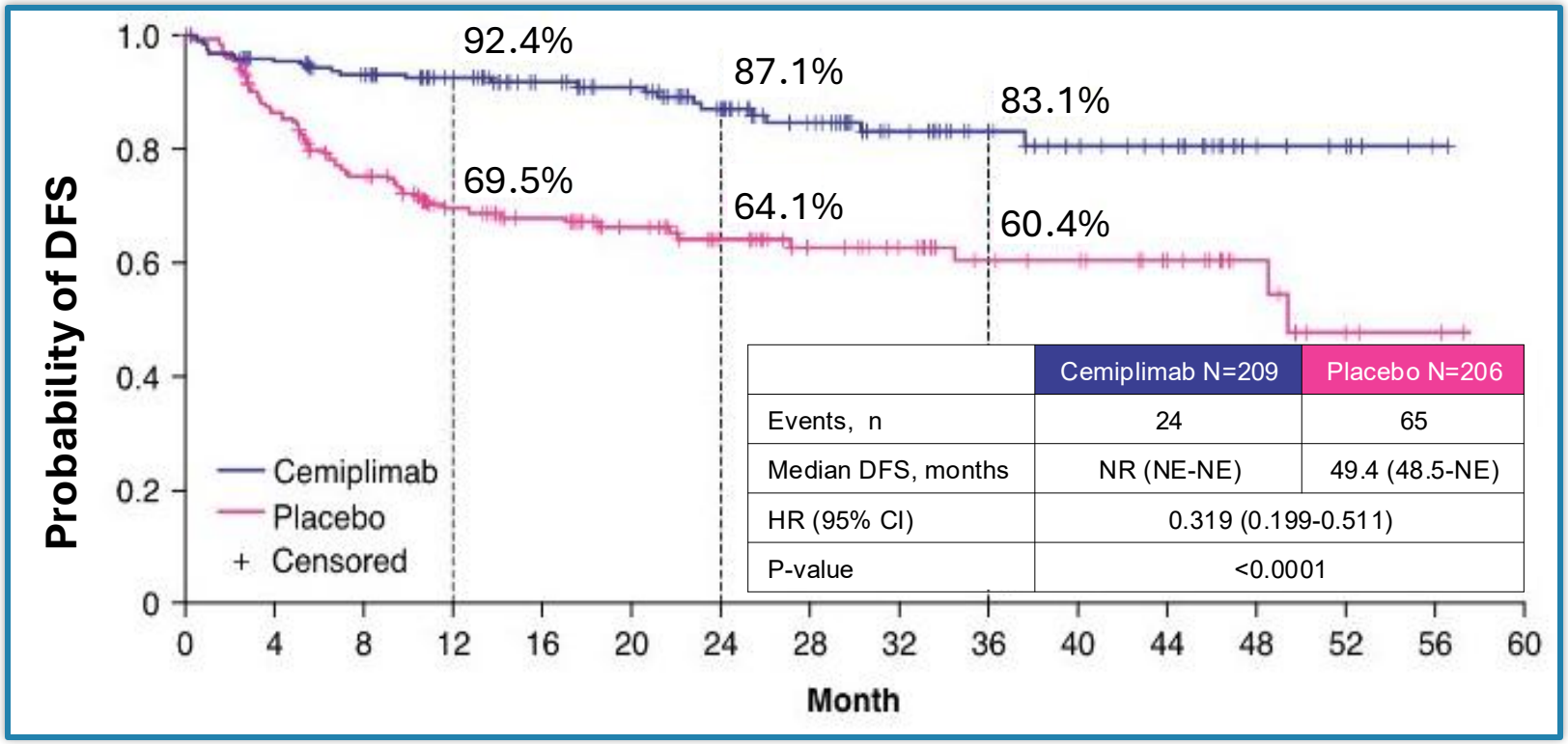
Tumor response N = 56 for laBCC

- Estimated proportion of patients alive and w/o disease progression:
  - 6 mos: 76%
  - 12 mos: 57%
- Median OS
  - Estimated proportion of patients alive at 2 yrs: 80%

1. Bapna M, Ruiz E. Future Oncol Lond Engl. Published online May 27, 2025:1-7. doi:10.1080/14796694.2025.2511568
2. Stratigos AJ, Sekulic A, Peris K, et al. Lancet Oncol. 2021;22(6):848-857. doi:10.1016/S1470-2045(21)00126-1
3. Lewis KD, Peris K, Sekulic A, et al. Ann Oncol Off J Eur Soc Med Oncol. 2024;35(2):221-228.

Phase 3 C-POST Study: Response to Adjuvant Cemiplimab in High-risk cSCC





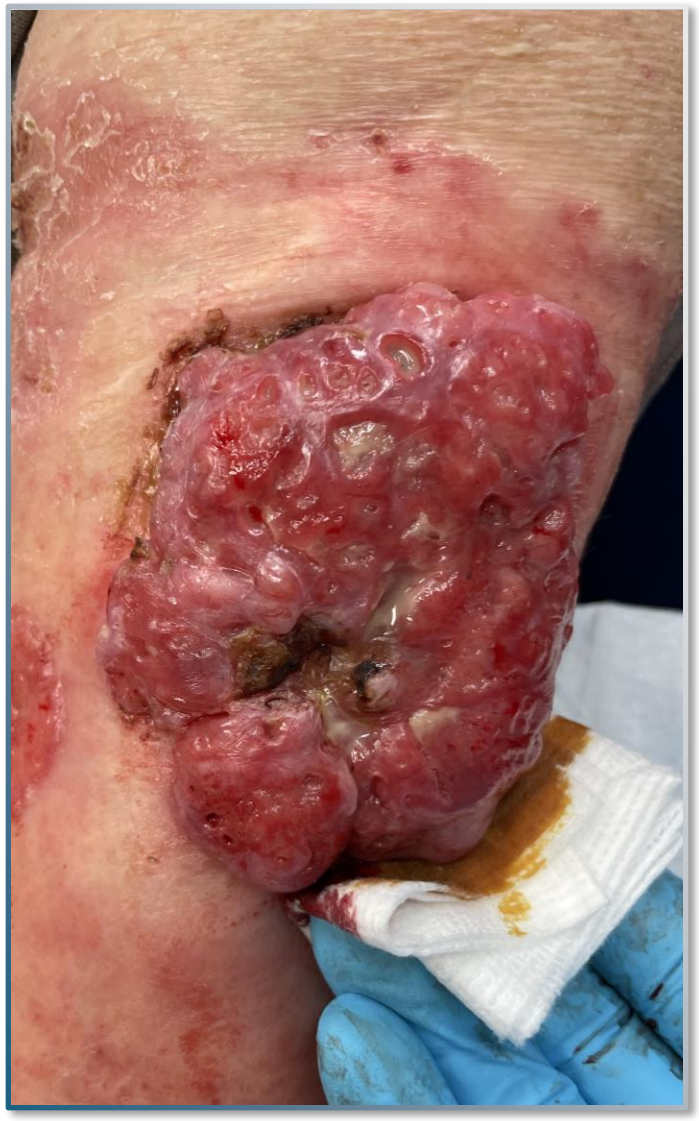
- **DFS: 87.1% with cemiplimab versus 64.1% with placebo**
- **Recurrence Risk Reduction:**
  - **Local recurrence: ↓ 80%**
  - **Distant recurrence: ↓ 65%**

CI, confidence interval; cSCC, cutaneous squamous cell carcinoma; DFS, disease free survival; HR, hazard ratio; IV, intravenous; NE, not estimable; NR, not reached; Q3W, every 3 weeks; Q6W, every 6 weeks.

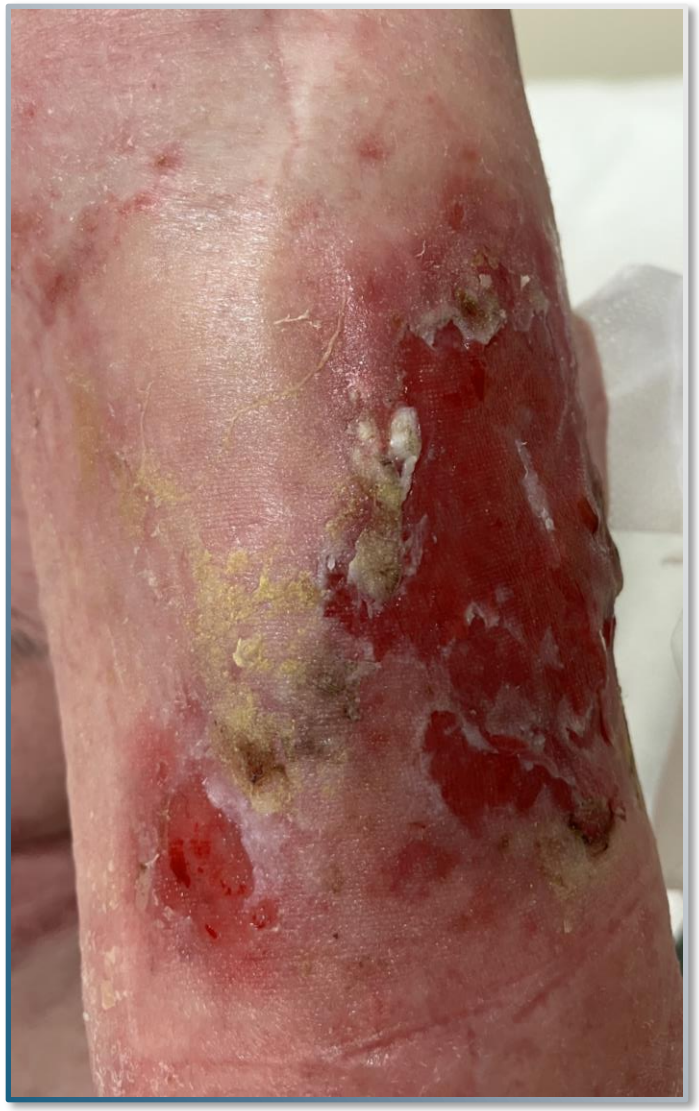
Rischin D, et al. Presented at the ASCO Annual Meeting. May 31, 2025. Chicago, IL.

Case: ~50-Year-Old Male With laBCC treated with Cemiplimab

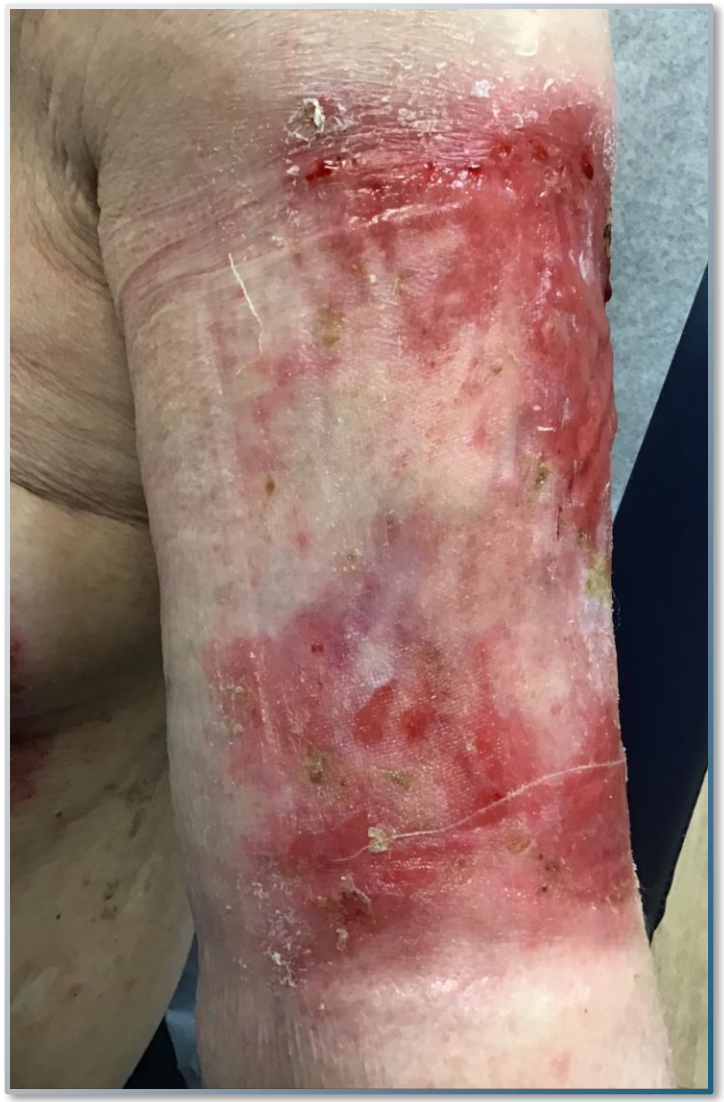
Individual patient response may vary.
laBCC, locally advanced basal cell carcinoma.
Case and patient images provided by Dr. Todd Schlesinger, MD, FAAD



Baseline



After 3 cycles of cemiplimab

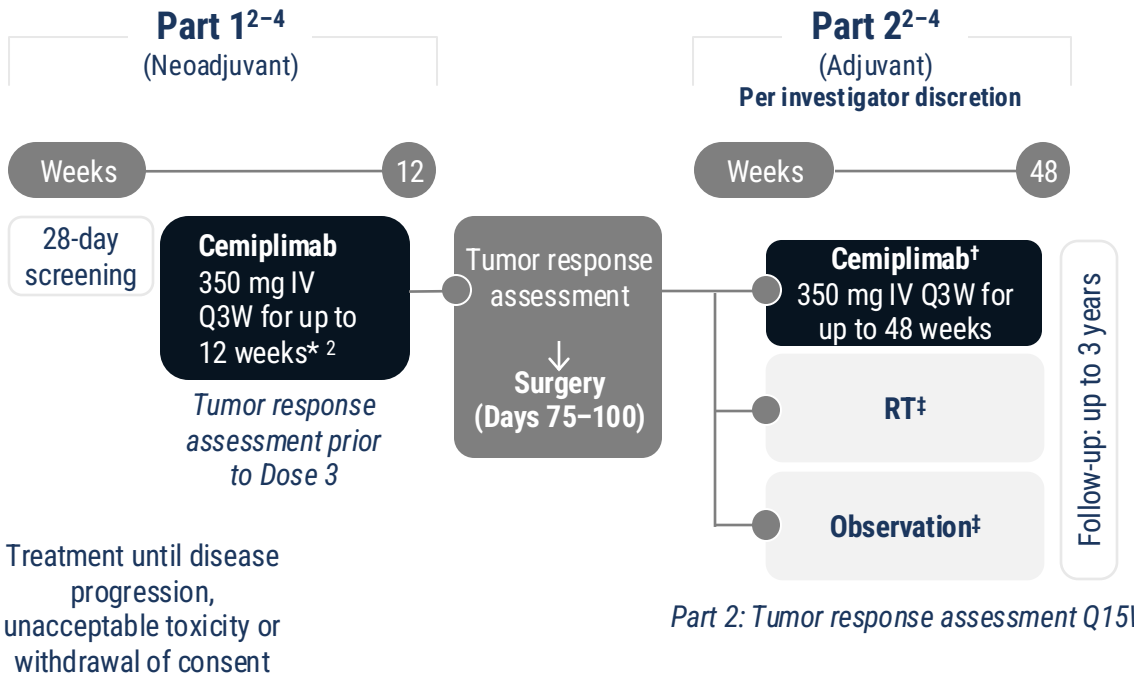


After 6 cycles of cemiplimab

Phase 2 Study of Neoadjuvant Cemiplimab (PD-1) in Stage II–IV CSCC (R2810-ONC-1901) – NCT04154943

Key Inclusion Criteria[1]
- Stage II–IV (M0) CSCC for which surgery would be recommended
- ≥1 measurable lesion by RECIST 1.1; for Stage II patients, lesion must be ≥3 cm at the longest diameter
- ECOG PS ≤1

Key Exclusion Criteria[1]
- Prior RT for CSCC
- Distant metastatic disease (M1), visceral and/or distant nodal



Primary Endpoint[1]
- pCR§

Secondary Endpoints[1]
- MPR§‖, pCR‖, ORR (prior to surgery)¶, EFS, DFS, OS, safety and tolerability and patients with planned and actual surgery and post-surgical management

*If a patient meets criteria to discontinue cemiplimab during the neoadjuvant period, the treating physician may divert the patient to surgery at an earlier time. †First dose will occur Q3W (±3 days) after end of treatment in Part 1. ‡Recurrence imaging Q15W. §Per ICPR. ‖Per local pathology review. ¶According to local assessment based on RECIST 1.1.

CSCC, cutaneous squamous cell carcinoma; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; ICPR, independent central pathology review; IV, intravenous; MPR, major pathologic response; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PD-1, programmed death receptor 1; Q3W, every 3 weeks; Q15W, every 15 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy.

1. ClinicalTrials.gov. NCT04154943. Accessed March 18, 2024. **2.** Gross ND, et al. *N Engl J Med*. 2022;387(17):1557-68. **3.** Gross ND, et al. *N Engl J Med*. 2022;387(suppl):1557-68. **4.** Gross ND, et al. *N Engl J Med*. 2022;387(17):1557-68. R2810-ONC-1901 Protocol.

Neoadjuvant Cemiplimab (Study 1901) – Follow-Up 2-Years Post-Surgery Analysis (N=79): Tumor Response

Median EFS (95% CI)	All Patients (N=79)	pCR (N=40)	MPR (N=10)	pPR (N=7)	Nonresponders/ NE* (N=22)
	NR (NE–NE)	NR (NE–NE)	NR (8.3–NE)	NR (NE–NE)	NR (8.1–NE)
Estimated 24-month EFS, % (95% CI)	86 (75–92)	92 (78–97)	89 (43–98)	100 (100–100)	64 (35–83)
Events, n (%)	11 (14)	3 (8)	1 (10)	0	7 (32)
PD that precludes surgery	2 (3)	—	—	—	2 (9)
Disease recurrence	3 (4)	0	1 (10)	0	2 (9)
Death	6 (8)	3 (8)†	0	0	3 (14)

- Estimated 24-month DFS was 90% (95% CI, 80–96) for patients who underwent surgery (n=70)
- Estimated 24-month OS was 86% (95% CI, 76–92) for all patients (n=79)

Data cut-off date: December 1, 2023.

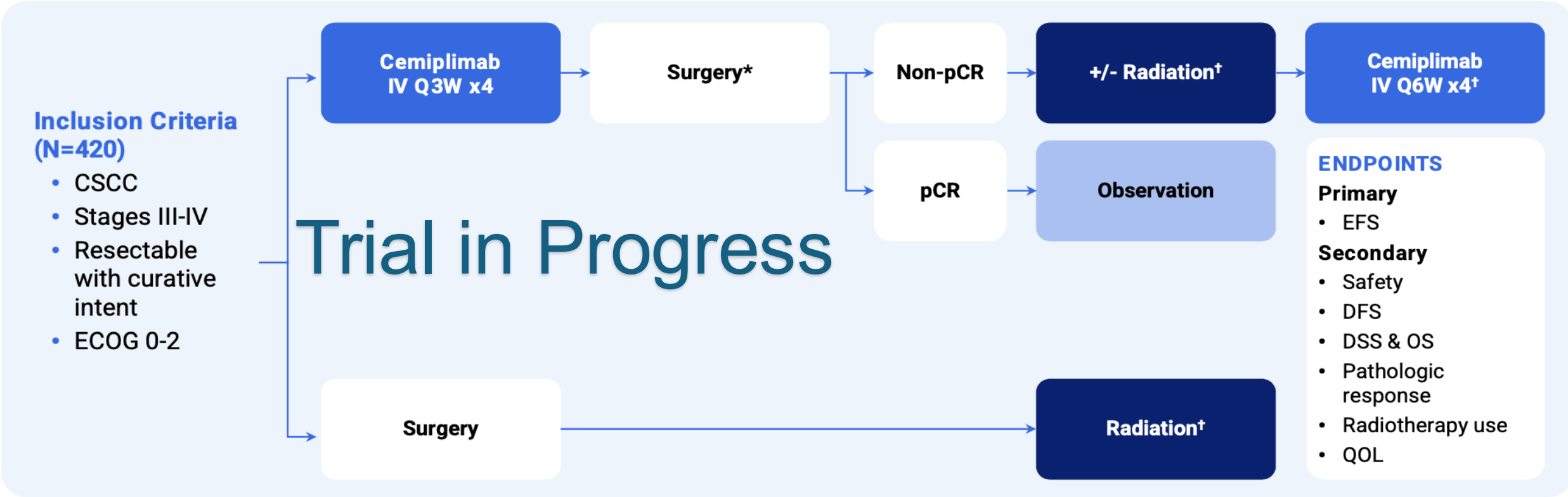
(–) Data are not available. Median duration of follow-up: 29.4 months (range, 1.3–41.1). ICPR categories: pCR (0% RVT); MPR (>0–≤10% RVT); pPR (>10–≤50% RVT); nonresponder (>50% RVT).

*Nine patients did not have surgery and 13 surgical patients were nonresponders. †One death due to COVID-19, 1 death due to complications of cardiac valve repair surgery in Year 2, and 1 death approximately 3 months after surgery in a patient who had multiple post-operative AEs including myocardial infarction.

AE, adverse event; CI, confidence interval; DFS, disease-free survival; EFS, event-free survival; ICPR, independent central pathology review; MPR, major pathologic response; NE, not evaluable; NR, not reached; OS, overall survival; pCR, pathologic complete response; PD, progressive disease; pPR, pathologic partial response; RVT, residual visible tumor.

Rischin D, et al. ESMO; 2024; Poster FPN1091P.

NCI-2023-03425/NRG-HN014: Randomized Phase 3 Trial of Neoadjuvant Cemiplimab in Resectable, Stage III-IV CSCC (NCT06568172)

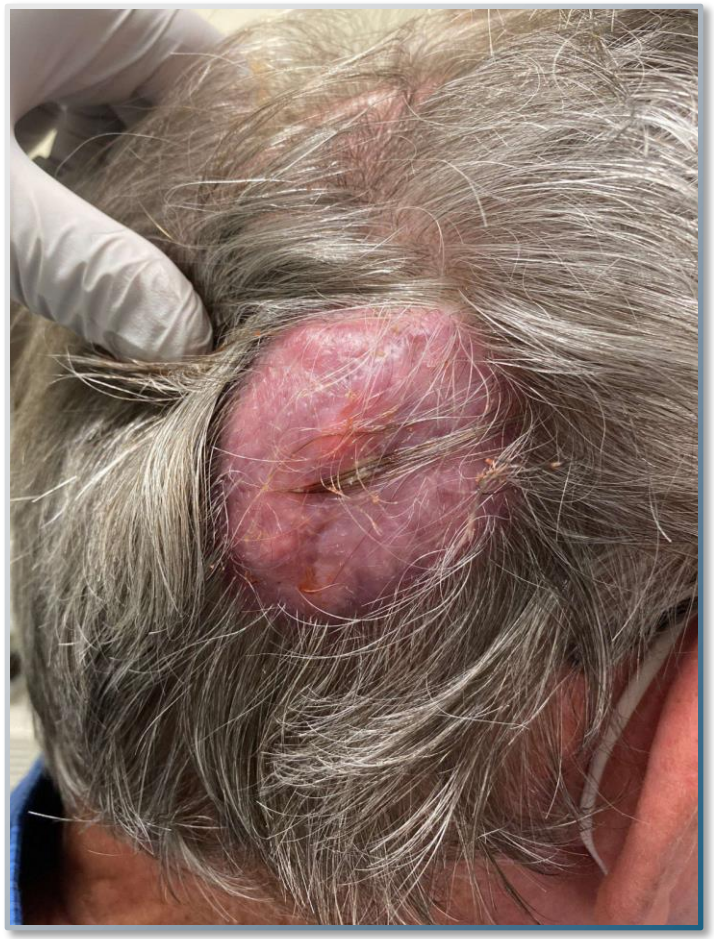


*Response-adapted oncologic surgery. †As indicated per protocol.
CSCC, cutaneous squamous cell carcinoma; DFS, disease-free survival; DSS, disease-specific survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; OS, overall survival; pCR, pathologic complete response; QOL, quality of life; RT, radiation therapy; SOC, standard of care.
Clinical trials identifier: NCT06568172. Accessed September 6, 2024.

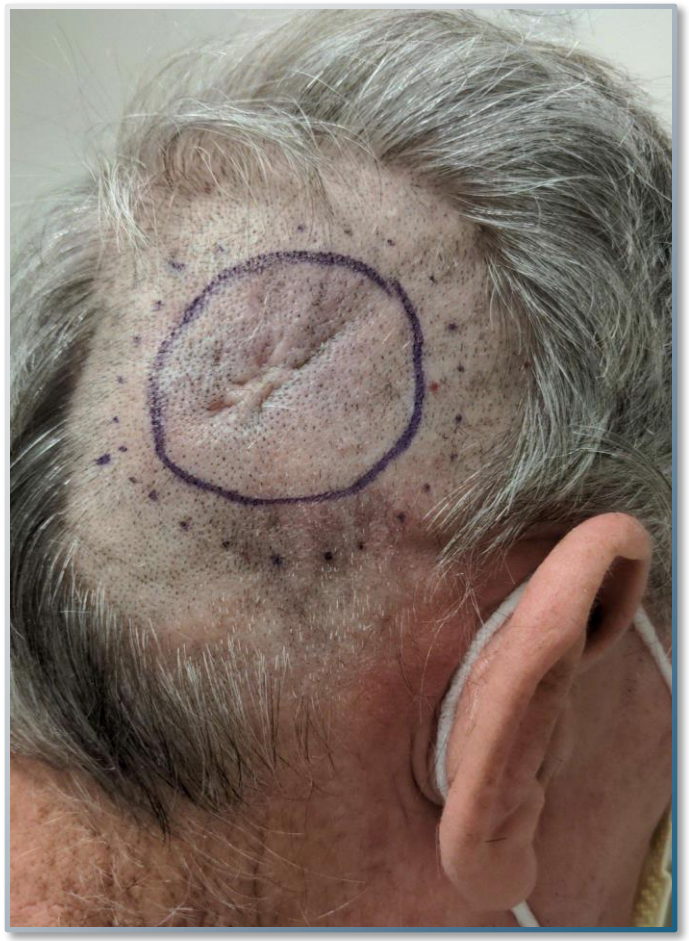
National Cancer Institute (NCI)-sponsored trial led by NRG Oncology. Cemiplimab provided under collaborative agreement with NCI.

Regeneron Medical Affairs. Phase 3 Study of Intralesional Cemiplimab (PD-1) vs Primary Surgery in Early Stage CSCC (CLEAR CSCC; R2810-ONC-2251) – NCT06585410.

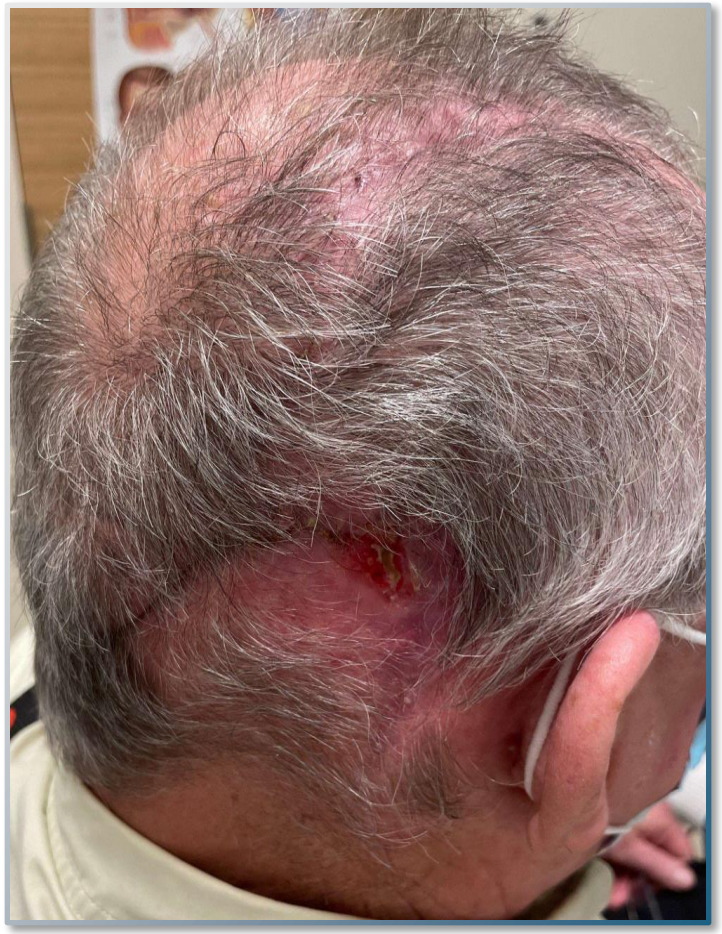
Case: Neoadjuvant Cemiplimab and Surgery for Stages II–IV CSCC (NCT04154943)



78-year-old immunocompetent male with large primary tumor and NM



S/p 4 cycles of cemiplimab



S/p Mohs + lymphadenectomy

Individual patient response may vary.
CSCC, cutaneous squamous cell carcinoma, NM, nodal metastasis; S/p, status post.
Case and patient images have been provided by Dr. Emily Ruiz.

NEW KID ON THE BLOCK

REVIEW

Cosibelimab: A Novel Therapeutic for Advanced Cutaneous Squamous Cell Carcinoma

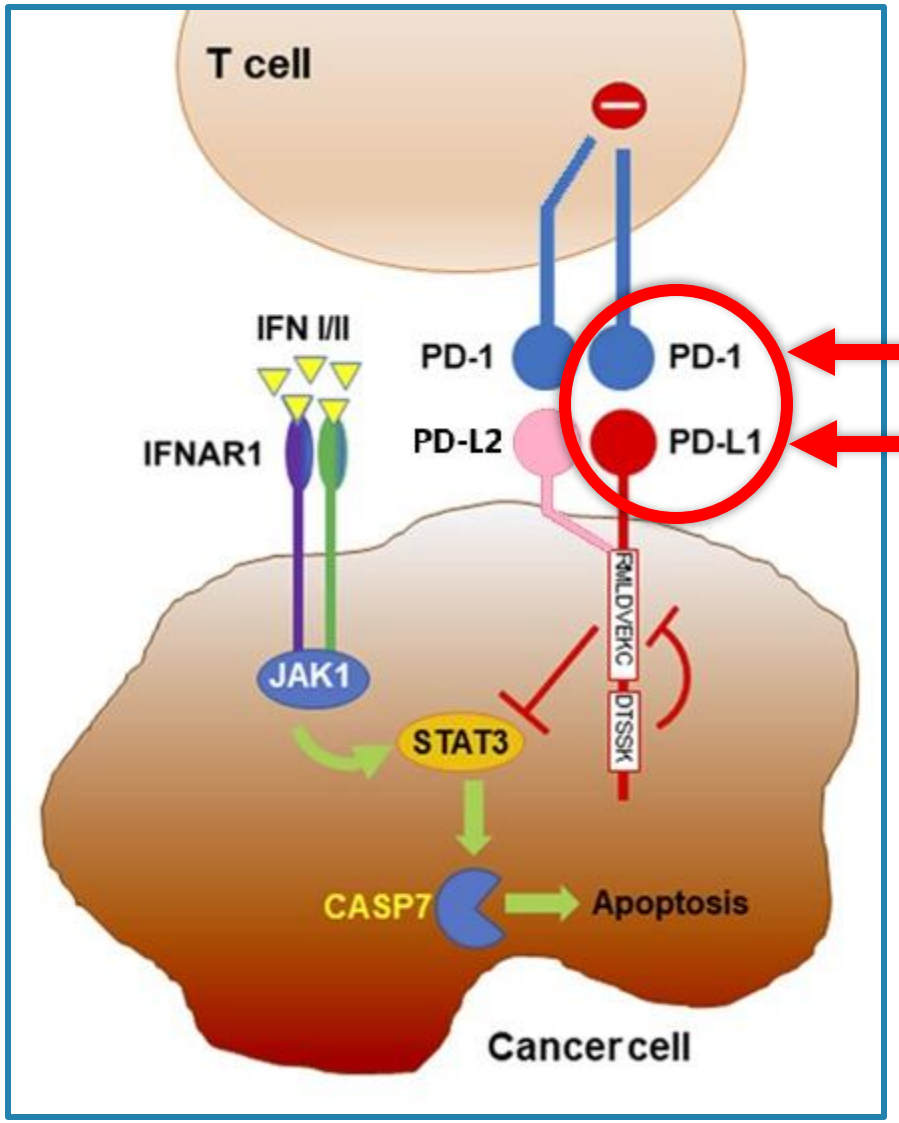
by JOSHUA BURSHTEIN, MD, and TODD SCHLESINGER, MD

Dr. Burshtein is with the Department of Dermatology at the University of Illinois-Chicago in Chicago, Illinois. Dr. Schlesinger is with the Clinical Research Center of the Carolinas in Charleston, South Carolina, and the Department of Dermatology at George Washington University School of Medicine and Health Sciences in Washington, District of Columbia.

J Clin Aesthet Dermatol. 2025;18(11):21–23.

Selected Cell Surface Ligands in Advanced cSCC

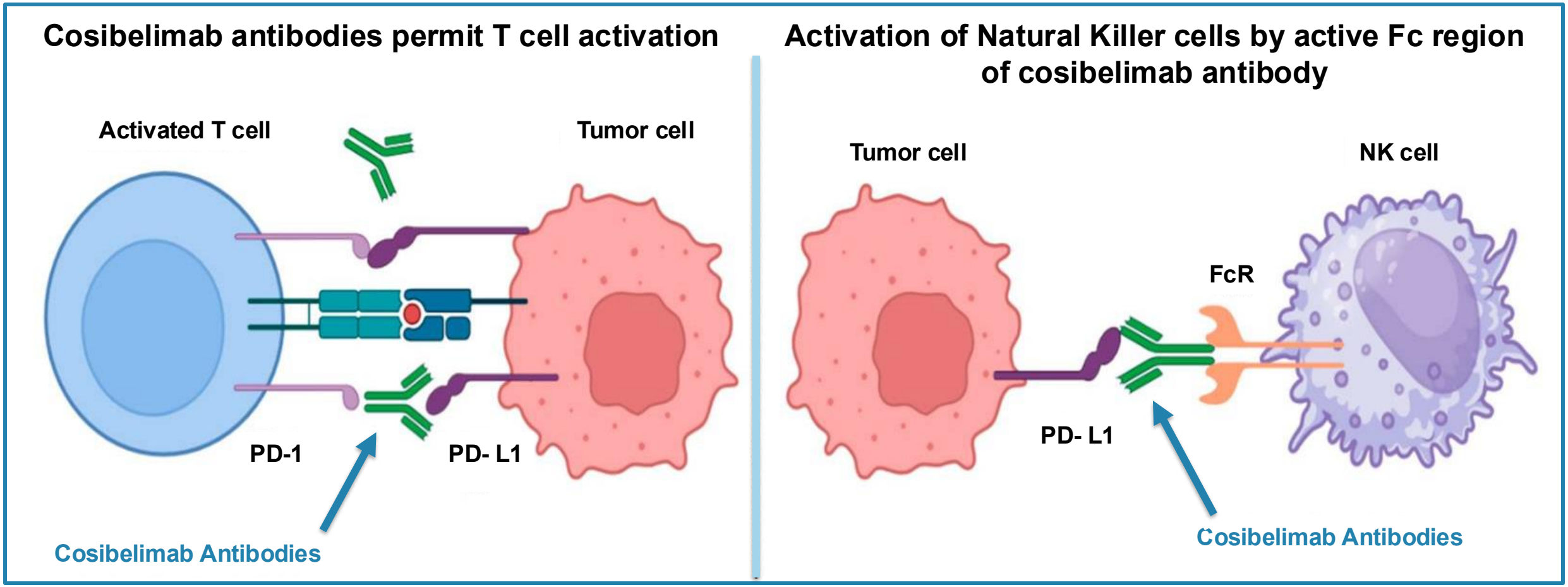
- Programmed Death-1 (PD-1) is an inhibitory receptor induced in activated T cells.
- PD-1 engagement by its ligand, PD-L1, maintains peripheral tolerance but also compromises anti-tumor immunity.
- Over expression of PD-L1 ligand helps protect the tumor cell from T cell activation.
- PD-1 and PD-L1 inhibitors block the interactions and allow the T cells to neutralize tumor cells.
- Adverse events are related to a loss of T cell inhibition.
- Blocking antibodies against PD-1 or its ligands have revolutionized cancer immunotherapy.



cSCC, cutaneous squamous cell carcinoma; IFN, interferon; IFNAR1, interferon alpha/beta receptor alpha chain; JAK, janus kinase; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1.

Patsoukis, et al. *Sci. Adv.* 2020;6(38):eabd2712.

Cosibelimab Dual Mechanism of Action



Idris OA, et al. *Biomedicines*. 2025;13(4):889.

Efficacy of Immunotherapies for Advanced cSCC

Immunotherapy	Mechanism	Efficacy Endpoints	
Cosibelimab - 1,200 mg IV q3w	• PD-L1 antibody • Induces antibody-dependent cellular cytotoxicity	**mCSCC** • ORR: 47.4% • CR: 8% • PR: 40%	**laCSCC** • ORR: 48% • CR: 10% • PR: 39%
Cemiplimab - 350 mg IV q3w	• PD-1 antibody	**mCSCC** • ORR: 41.1% • CR: 5.4% • PR: 35.7%	**laCSCC** • ORR: 44.0% • CR: 13% • PR: 31%
Pembrolizumab - 200 mg IV q3w - 400 mg IV q6w	• PD-1 antibody	**mCSCC** • ORR: 35.2% • CR: 10.5% • PR: 24.8%	**laCSCC** • ORR: 50.0% • CR: 16.7% • PR: 33.3%

CR, complete response; cSCC, cutaneous squamous cell carcinoma; IV, intravenous; laCSCC, locally advanced cSCC; mCSCC, metastatic cSCC; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; PR, partial response; q3w, every 3 weeks; q6w, every 6 weeks;
Burshtein J and Schlesinger T. *J Clin Aesthet Dermatol*. 2025;18(11):21–23.; Cosibelimab (UNLOXCYT) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761297s001lbl.pdf. Accessed 12/10/25.; Cemiplimab (LIBTAYO) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761097s032lbl.pdf. Accessed 12/10/25.; Pembrolizumab (KEYTRUDA) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s188lbl.pdf. Accessed 12/10/25.

Safety of Immunotherapies for Advanced cSCC

Immunotherapy	Mechanism	Safety	
Cosibelimab - 1,200 mg IV q3w	• PD-L1 antibody • Induces antibody-dependent cellular cytotoxicity	**Common TRAEs:** • Fatigue, rash, anemia • Grade 3 TRAEs: 10.3% • Grade 4/5 TRAEs: none	• irAEs: 23.1% • Grade 3: 2.6% • **Grade 4/5: none**
Cemiplimab - 350 mg IV q3w	• PD-1 antibody	**Common TRAEs:** • Fatigue, diarrhea, nausea, pruritus • Grade ≥3: 45.5%-49.2%	• irAEs: 57.1% • Grade ≥3: 12.5%
Pembrolizumab - 200 mg IV q3w - 400 mg IV q6w	• PD-1 antibody	**Common TRAEs:** • Pruritus, fatigue, asthenia, rash, diarrhea • Grade ≥3: 11.9%	• irAEs: 22.6% • Grade ≥3: 8.2%

cSCC, cutaneous squamous cell carcinoma; IV, intravenous; irAE, immune-related adverse event; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; q3w, every 3 weeks; q6w, every 6 weeks; TRAE, treatment related adverse event.

Burshtein J and Schlesinger T. *J Clin Aesthet Dermatol*. 2025;18(11):21–23.; Cosibelimab (UNLOXCYT) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761297s001lbl.pdf. Accessed 12/10/25.; Cemiplimab (LIBTAYO) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761097s032lbl.pdf. Accessed 12/10/25.; Pembrolizumab (KEYTRUDA) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s188lbl.pdf. Accessed 12/10/25.

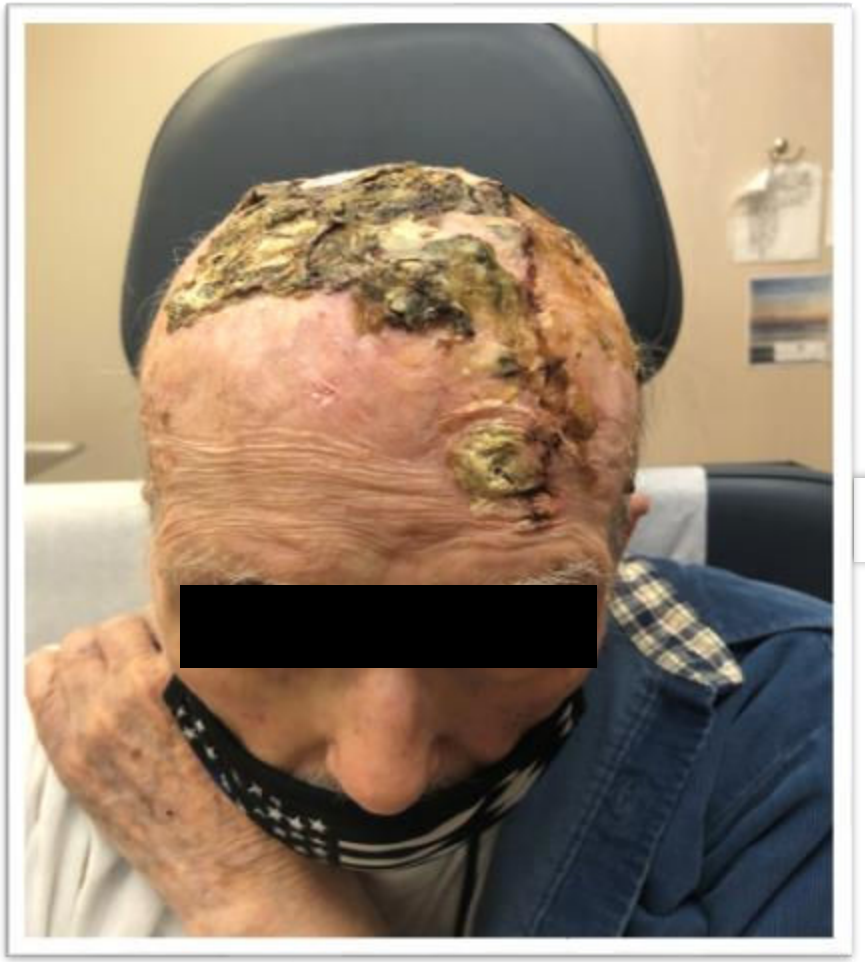
Checkpoint Inhibitor Onset of Action

	Studies	Indication	Response	Time to Response
Pembrolizumab (PD-1)	**KEYNOTE-629**	**R/M cSCC**	**34.3%**	**1.5 months (range 1.2–5.7)**
Cemiplimab (PD-1)	**EMPOWER-CSCC-1 (phase 2, pooled analysis)**	**laCSCC + mCSCC**	**~46% overall**	**2.0-2.3 months (range 1.7–7.3)**
Cosibelimab (PD-L1)	**CK-301-101 (metastatic cohort)**	**mCSCC**	**47–50% (follow-up dependent)**	**1.9 months (range 1.6–16.9)**

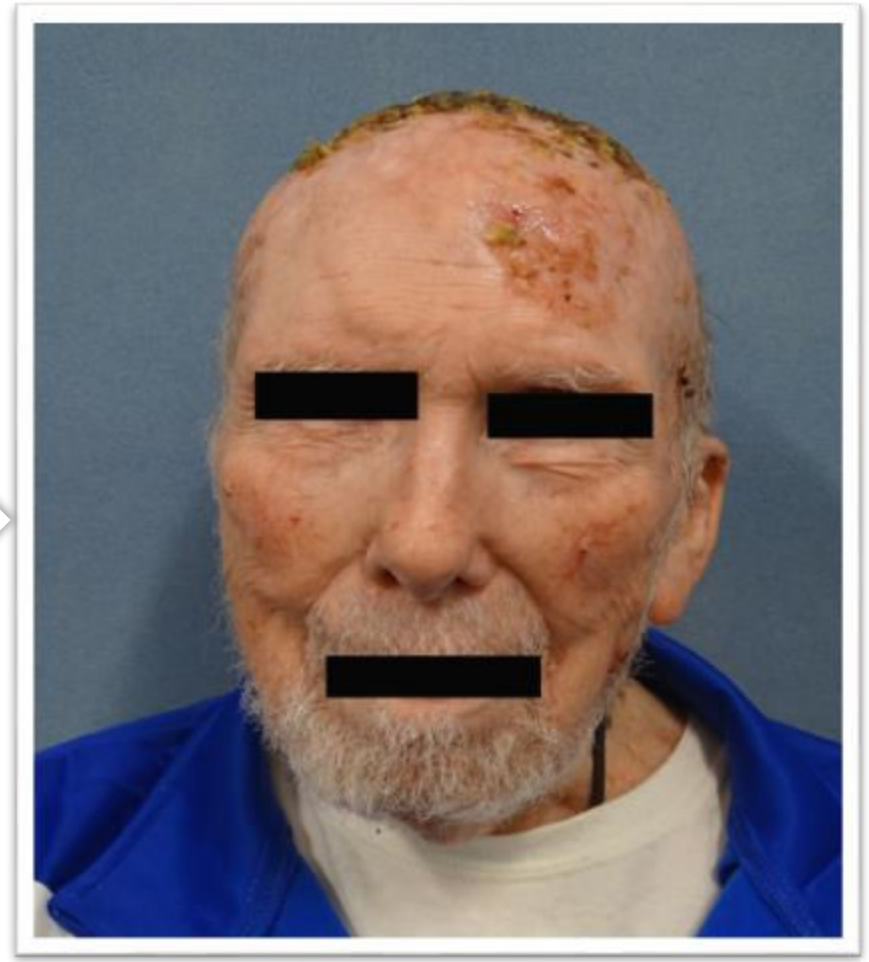
cSCC, cutaneous squamous cell carcinoma; laCSCC, locally advanced cSCC; mCSCC, metastatic cSCC; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; R/M, recurrent and/or metastatic.

Grob JJ, et al. *J Clin Oncol*. 2020;38(25):2916-2925.; Migden MR, et al. *NEJM*. 2018;379(4):341-351.; Clingan P, et al. *J Immunother Cancer*. 2023 Oct;11(10):e007637.

Case: cSCC With Cortical Bone Invasion on CT



5 Cycles Immunotherapy with Cemiplimab



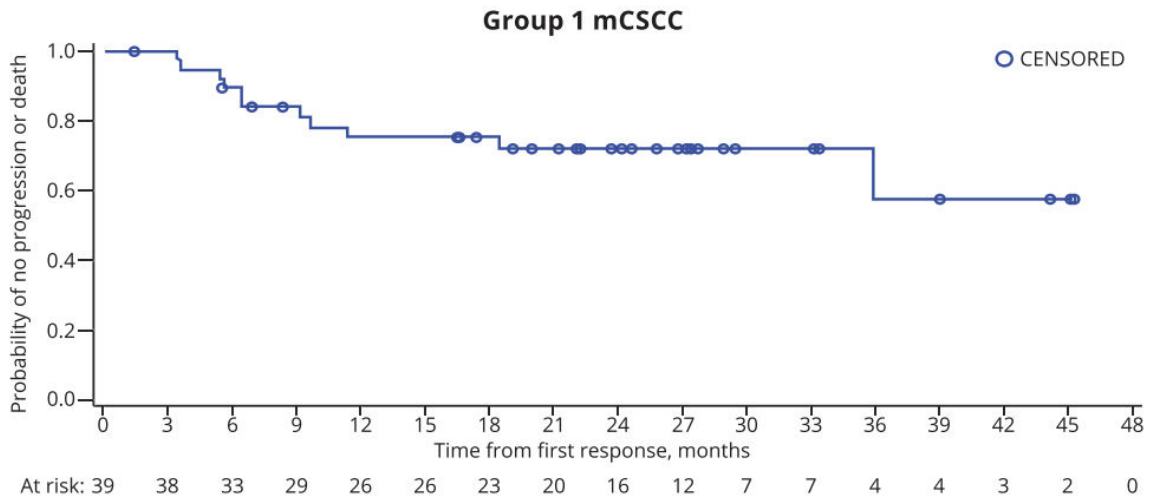
Images courtesy of Todd Schlesinger, MD

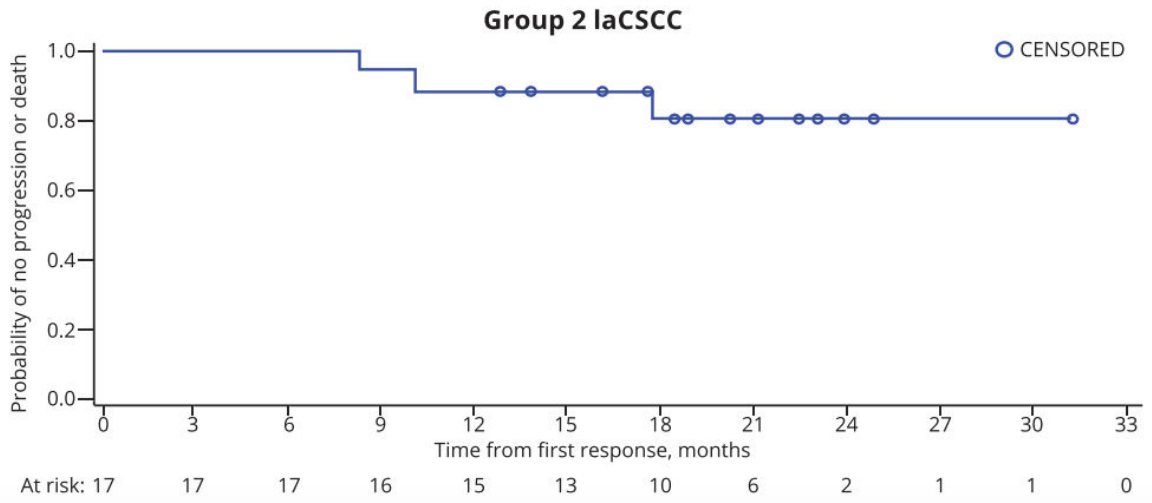
DERMATOLOGY & laser center OF CHARLESTON

cSCC, cutaneous squamous cell carcinoma; CT, computed tomography scan.

Long-term efficacy and safety outcomes of Cosibelimab

- mCSCC cohort:
  - ~89.5% of responders remained in response at 6 months
  - ~75.4% at 12 months
  - ~72.1% at 24 months
- laCSCC cohort:
  - ~100% of responders remained in response at 6 months
  - ~88.2% at 12 months
  - ~80.2% at 24 months

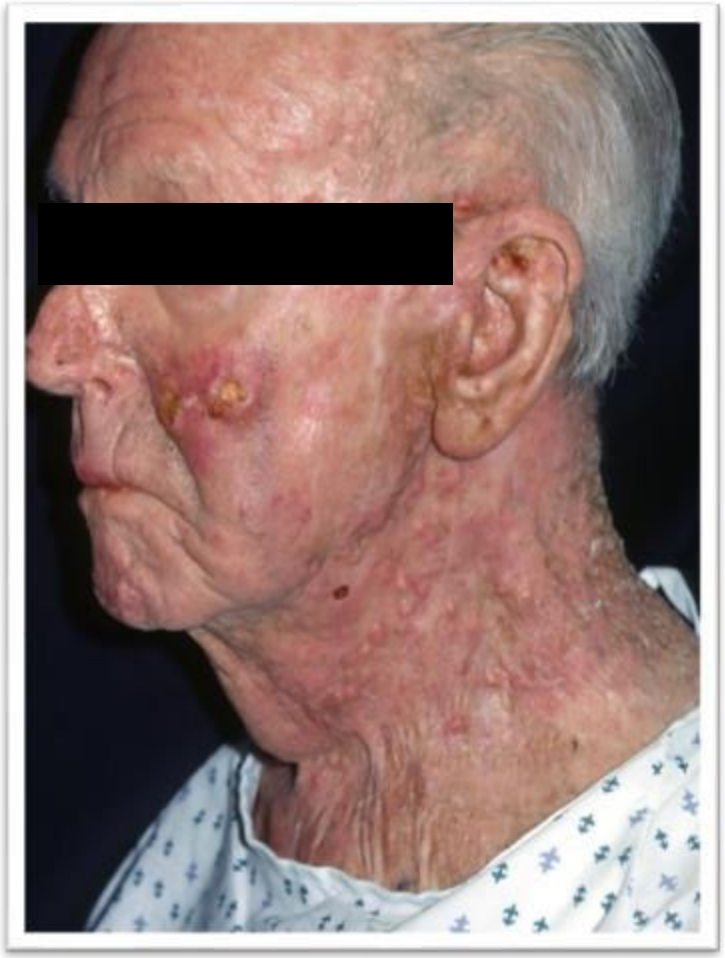


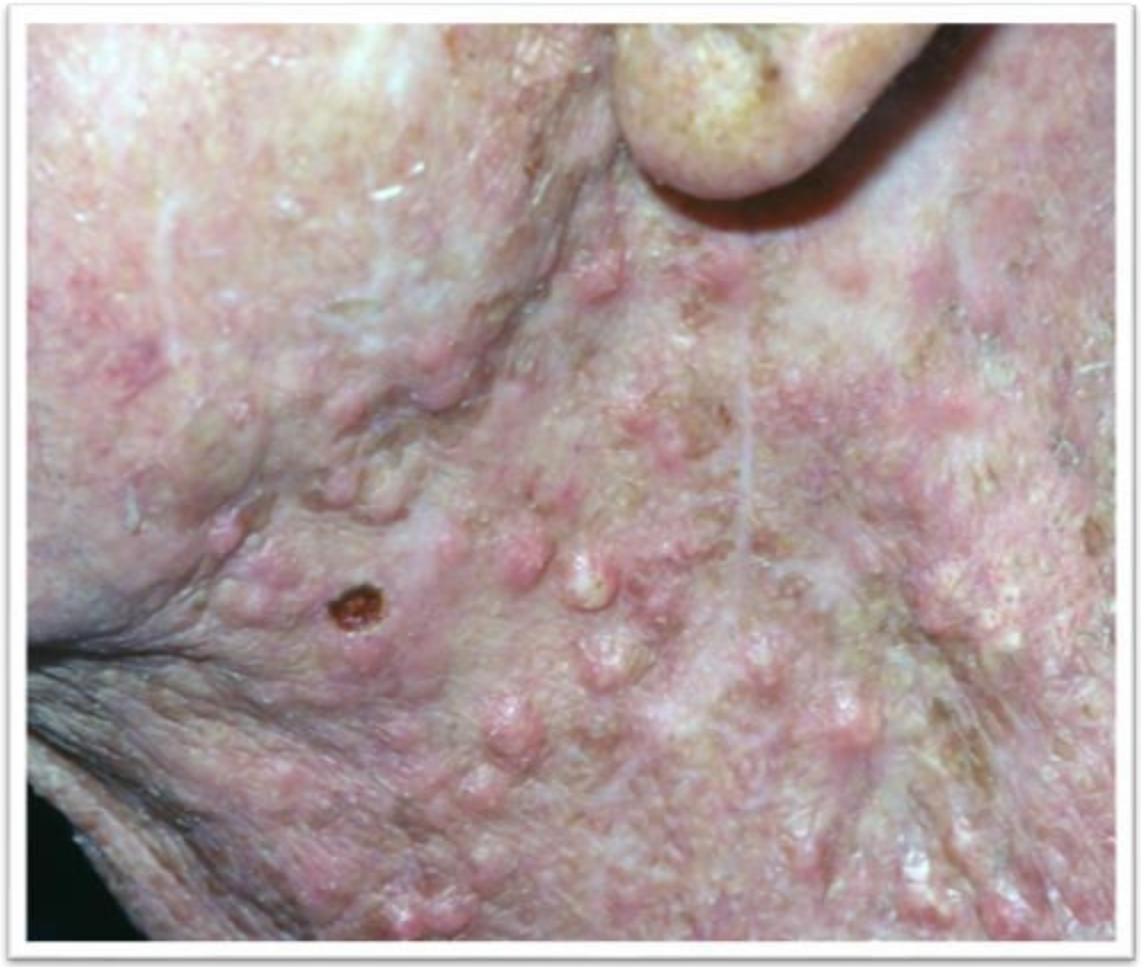


Ruiz ES, et al. Efficacy and safety of cosibelimab in advanced cutaneous squamous cell carcinoma: Results from a Pivotal Open-label Study with a median follow-up of ≥2 years. J Am Acad Dermatol. 2025 Sep 29

Case: Patient With Miliary Metastasis Squamous Cell Carcinoma - Wary of Adverse Events

Cosibelimab

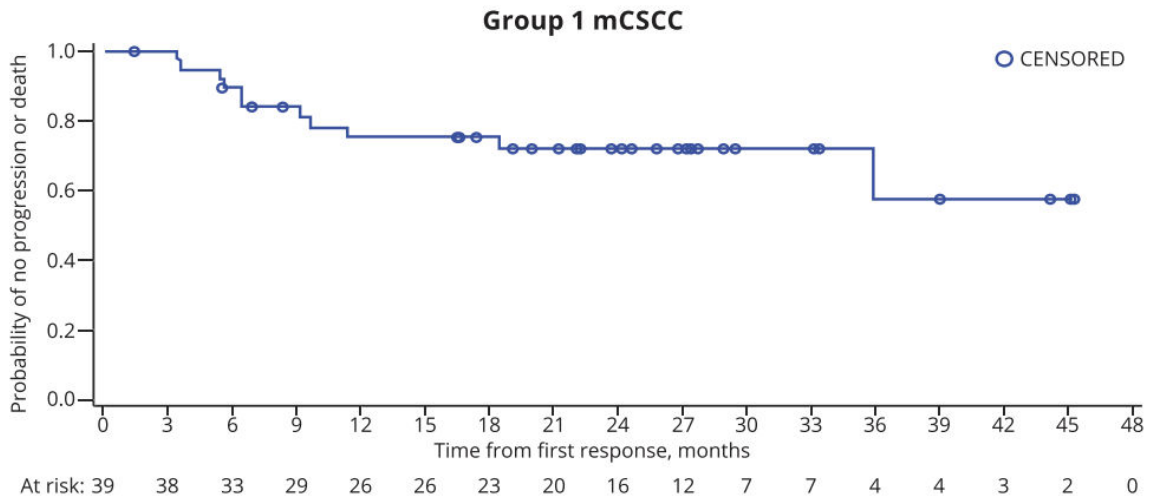


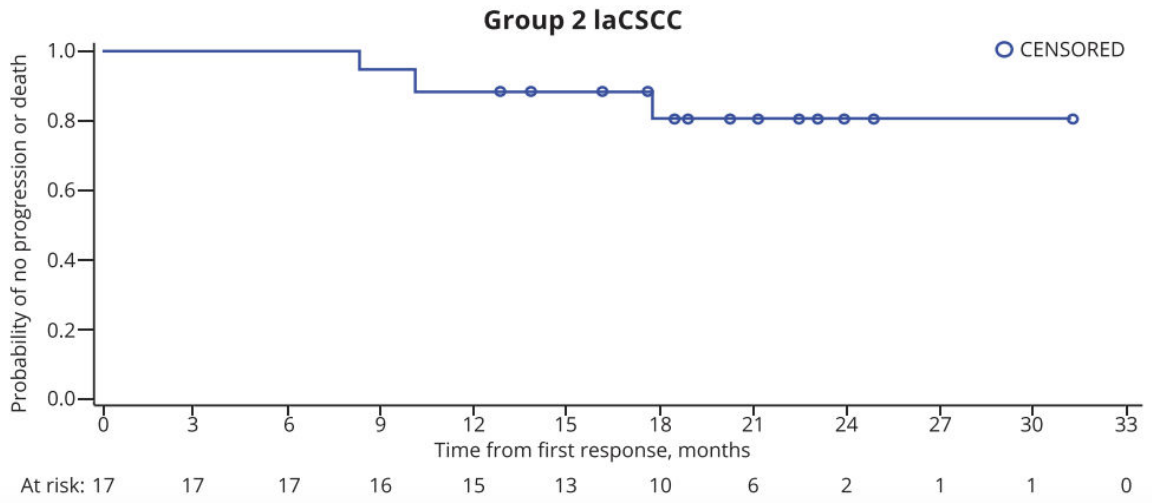


Images courtesy of Scott Dinehart, MD

Long-term efficacy and safety outcomes of Cosibelimab

- mCSCC cohort:
  - ~89.5% of responders remained in response at 6 months
  - ~75.4% at 12 months
  - ~72.1% at 24 months
- laCSCC cohort:
  - ~100% of responders remained in response at 6 months
  - ~88.2% at 12 months
  - ~80.2% at 24 months





Ruiz ES, et al. Efficacy and safety of cosibelimab in advanced cutaneous squamous cell carcinoma: Results from a Pivotal Open-label Study with a median follow-up of ≥2 years. J Am Acad Dermatol. 2025 Sep 29

KEYNOTE-629: Pembrolizumab in cSCC

- Single-arm, phase II study of 105 patients with recurrent/metastatic cSCC who received pembrolizumab 200 mg Q3W for up to 35 infusions
- ORR was 34.3% (3.8% achieved CR, 30.5% achieved PR)
- Median PFS was 6.9 months
- Disease control rate was 52.4%
- 12-month PFS rate of 32.4%
- Treatment-related AEs occurred in 66.7% of patients
  - 5.7% of patients experienced grade 3-5 AEs
  - 1 patient died of treatment-related cranial nerve neuropathy
  - Most common AEs were pruritus (14.3%), asthenia (13.3%), and fatigue (12.4%)

Grob JJ, et al. *Ann Oncol*. 2019;30(5):LBA72.

Intralesional therapy for KCs

Most commonly for cutaneous SCCs and KAs

Methotrexate 25 mg/ml
- 12.5-25 mg IL q1-2 wks
- 1-4 doses

5FU 50 mg/ml
- 0.2-2 ml IL q1-2 wks
- 2-12 doses

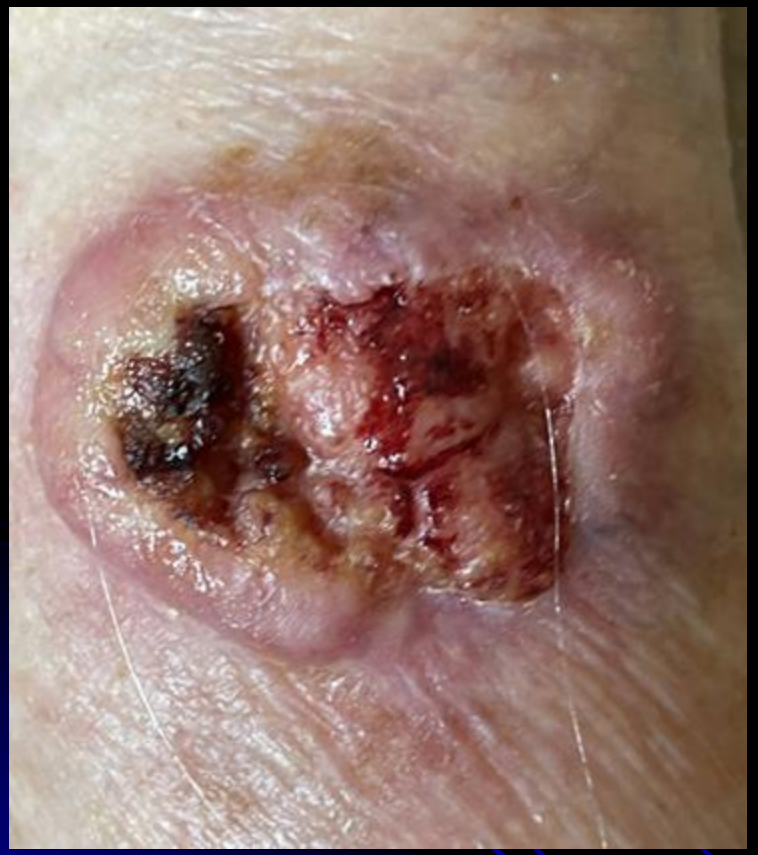
Benefits and Limitations:

- Resolution in 89-100% of lesions; most show size reduction → can be used as definitive therapy or pre-surgery (neoadjuvant)
- Best for smaller/ lower risk SCC, trunk/extremities
- Little prospective data, off label use, protocols vary

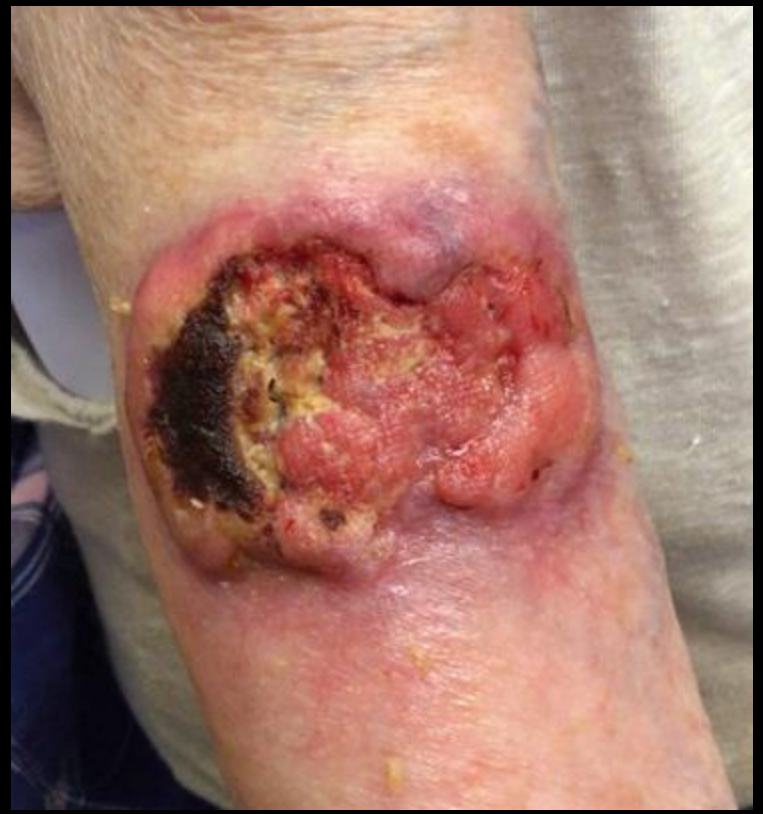
Caution: Methotrexate is contraindicated in patients with renal insufficiency: check labs!

Cancers (Basel). 2023 Dec 28;16(1):158.

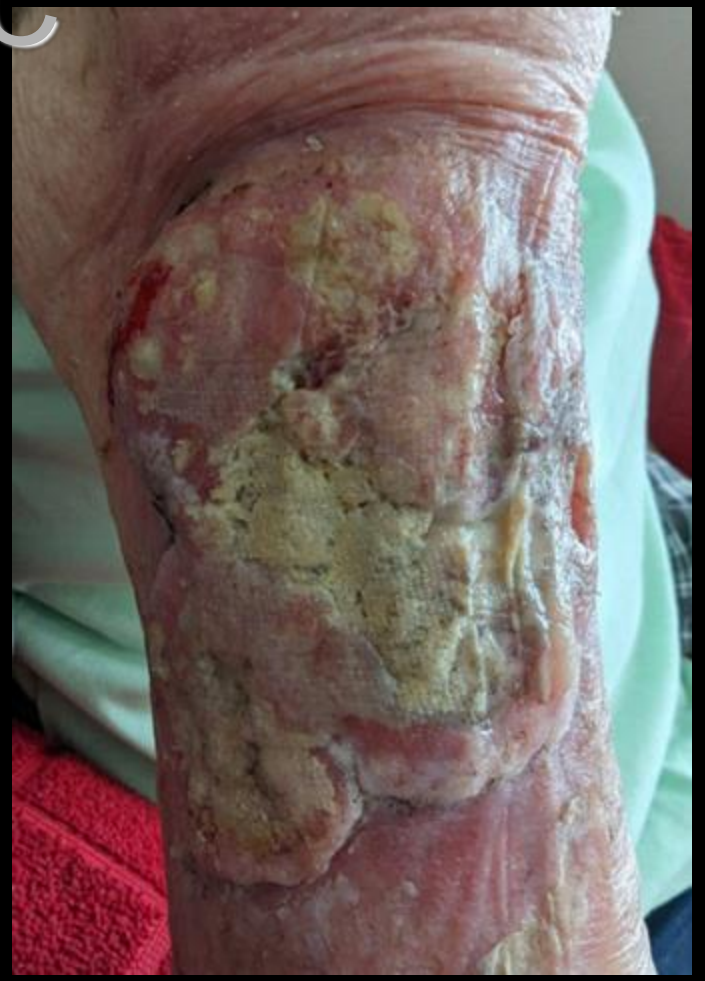
Not ideal for very advanced SCC



Initial presentation



/p IL MTX

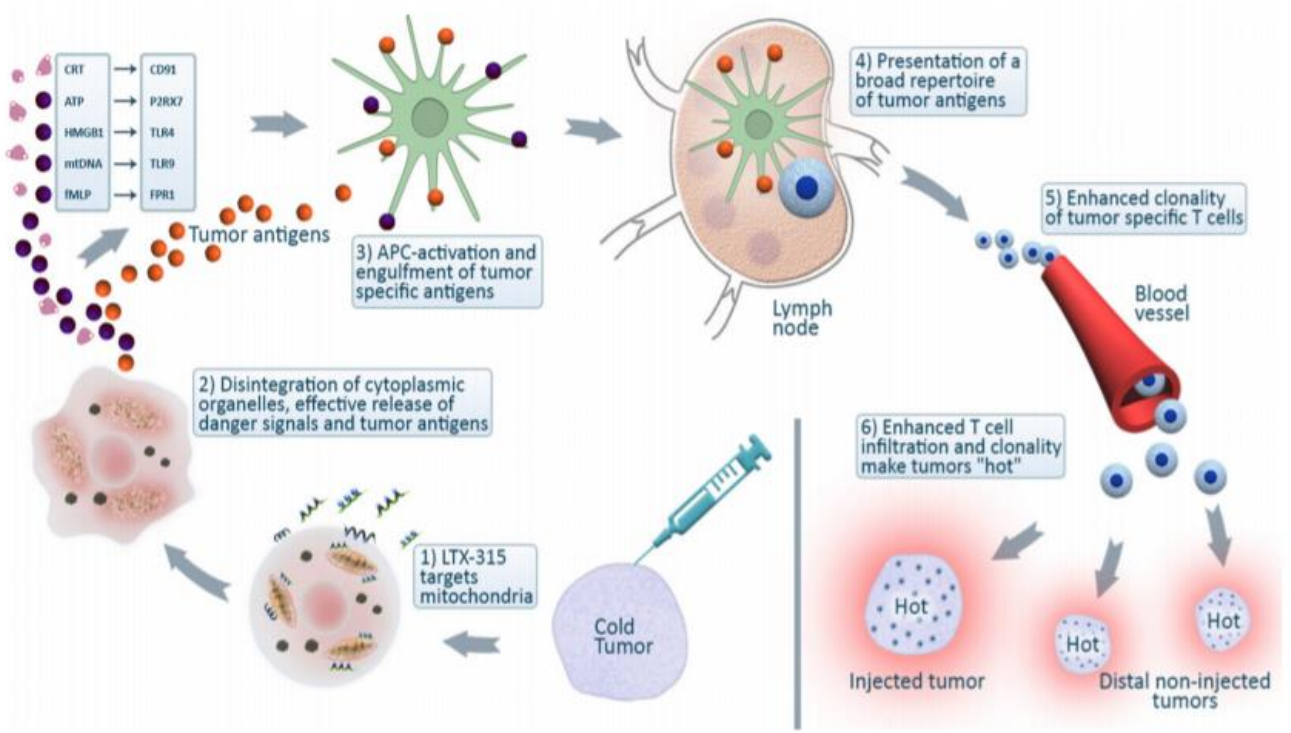


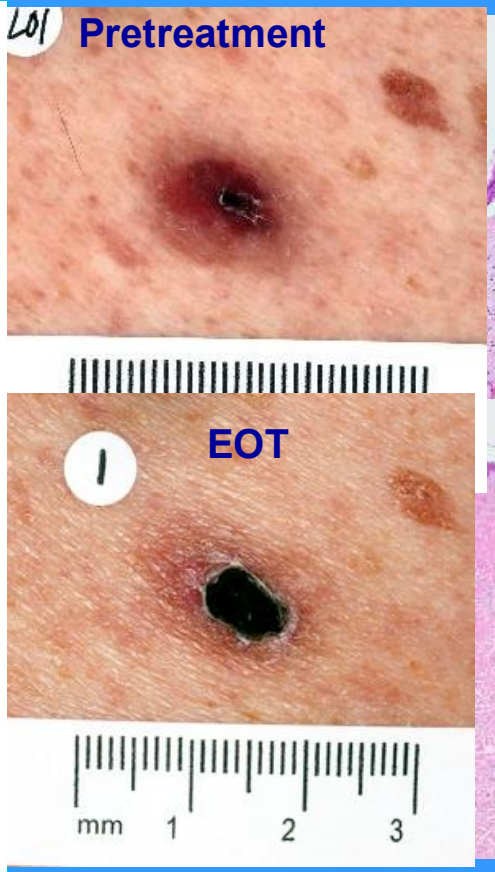
/p radiation

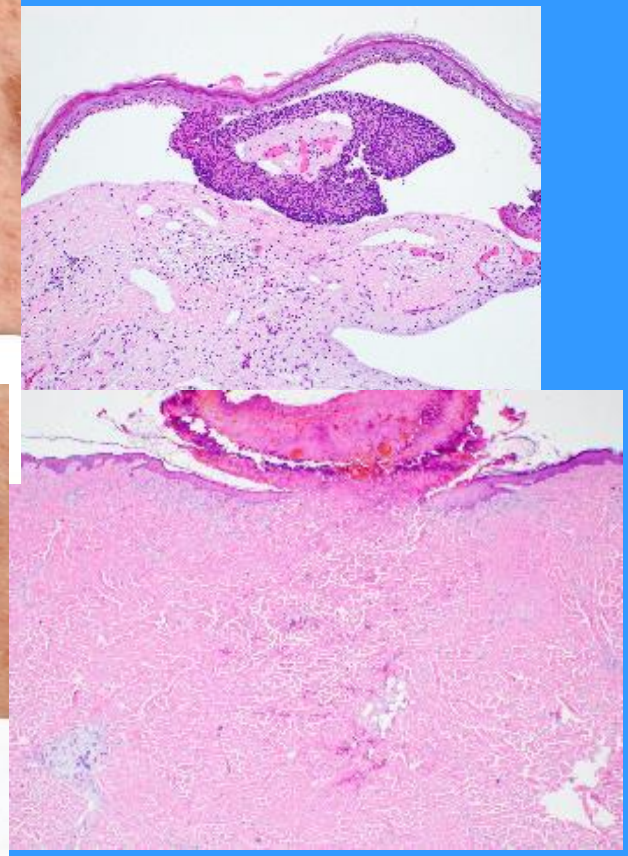
Courtesy Todd Schlessinger, MD FAAD

VP-315 Ruxotemitide

LTX-315's unique mode of action results in effective release of potent immunostimulants and antigens







Mean Percent Reduction in Tumor Clearance and Size

per Cohort	Complete Histologic Clearance by Tumor	Overall Percent Reduction of Tumor Size	Percent Reduction of Tumor Size with Remaining Tumor
Cohort 1 (n=7)	71%	98%	93%
Cohort 2 (n=3)	33%	88%	83%
Cohort 4 (n=38)	53%	87%	73%
Cohort 5 (n=44)	48%	83%	67%
Total (n=92)	51%	86%	71%

VP-315 Phase 2, Part 2 Study

ClinicalTrials.gov: NCT05188729

Emerging intralesional therapy: Intralesional Cemiplimab (anti-PD-1)

Phase 1 Study of Pre-Operative Intralesional Cemiplimab in Recurrent CSCC or BCC (R2810-ONC-1787) – NCT03889912[1–3]

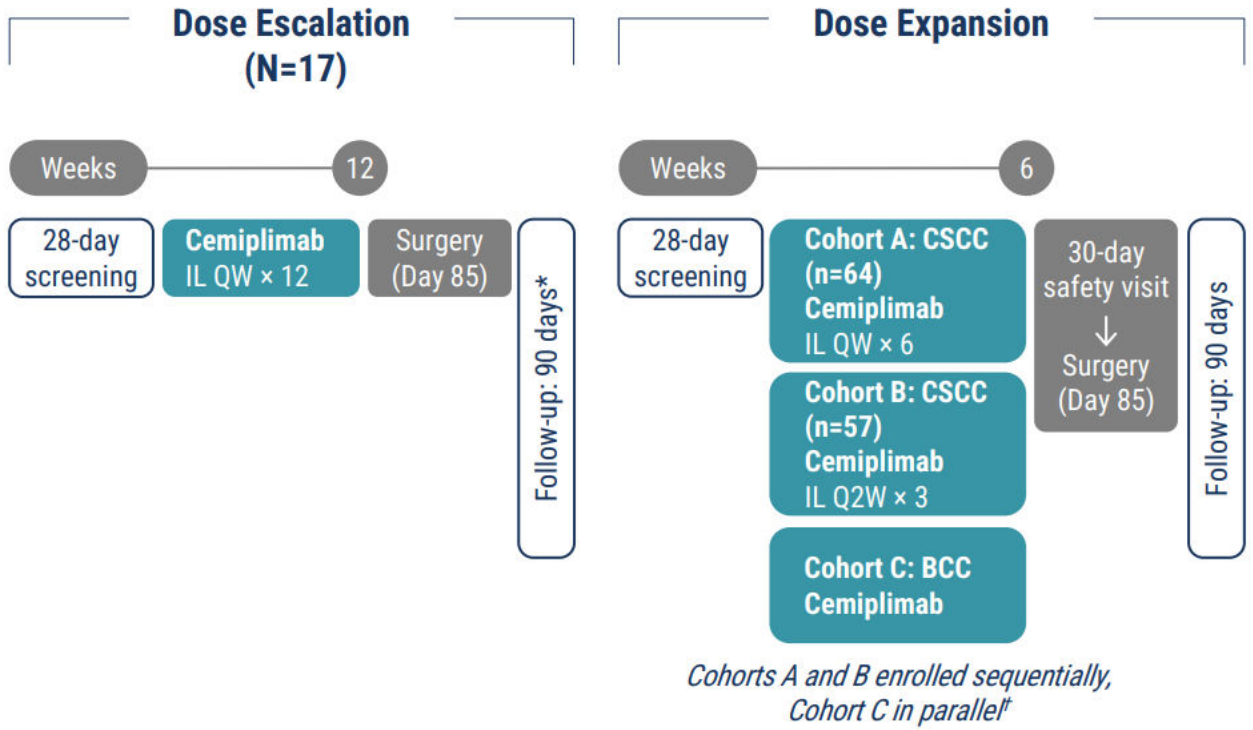
Open-label, single-arm cohort-expansion study

Key Inclusion Criteria

- Aged ≥18 years
- History of recurrent CSCC and ≥1 resectable lesion that is 1.0–2.0 cm
- Measurable disease in the index lesion, as per modified WHO criteria
- ECOG PS ≤1
- Meets all hepatic, renal and bone marrow function criteria

Key Exclusion Criteria

- Ongoing/recent (≤5 years) significant autoimmune disease requiring systemic immunosuppression
- Prior anti–PD-(L)1
- Concurrent malignancies, other than those with negligible risk of metastasis or death
- History of solid organ transplant or hematologic malignancies



Primary Endpoint

- Safety and tolerability

Key Secondary Endpoints

- ORR‡, pCR rate, MPR rate, PK and immunogenicity

Migden M, et al. ACMS; 2022; Oral Presentation.

Intralesional Cemiplimab (Study 1787) – Updated Analysis (N=17): Tumor Response by Modified WHO Criteria

Tumor Response by Modified WHO Criteria

n (%) Unless Stated Otherwise	Dose Level 1: 5 mg QW (N=8)	Dose Level 2: 15 mg QW (N=3)	Dose Level 3: 44 mg QW (N=6)	Total (N=17)
Index Lesion Response				
vCR*	6 (75.0)	2 (66.7)	5 (83.3)	13 (76.5)
vPR*	0	0	0	0
vSD	1 (12.5)	0	0	1 (5.9)
vPD	1 (12.5)	1 (33.3)	0	2 (11.8)
NE†	0	0	1 (16.7)	1 (5.9)
Response				
ORR (vCR + vPR)	6 (75.0)	2 (66.7)	5 (83.3)	13 (76.5)
95% CI for ORR‡	(34.9–96.8)	(9.4–99.2)	(35.9–99.6)	(50.1–93.2)

Pathologic Tumor Response

	Dose Level 1: 5 mg QW (n=8)	Dose Level 2: 15 mg QW (n=3)	Dose Level 3: 44 mg QW (n=6)	Total (N=17)
pCR, n (%) [95% CI]	6 (75.0) [34.9–96.8]	2 (66.7) [9.4–99.2]	5 (83.3) [35.9–99.6]	13 (76.5) [50.1–93.2]

- pCRs were seen at all dose levels

Reproduced with permission from Dr. Michael R. Migden, Migden MR, Phase 1 Study of Intralesional Cemiplimab in Patients with Recurrent Resectable Cutaneous Squamous Cell Carcinoma (CSCC). Presented at the American College of Mohs Surgery (ACMS) 2022.

Data cutoff date: July 12, 2021.

*Confirmation of CR/PR is not required. †NE response includes the missing and unknown tumor response. ‡Clopper-Person exact confidence interval.

CI, confidence interval; CR, complete response; NE, not evaluable; ORR, objective response rate; pCR, pathologic complete response; QW, weekly; vCR, complete response of externally visible disease; vPD, progression of visible disease; vPR, partial response of externally visible disease; vSD, stable externally visible disease; WHO, World Health Organization.

Migden MR. ACMS; 2022; Oral Presentation.

Migden M, et al. ACMS; 2022; Oral Presentation.

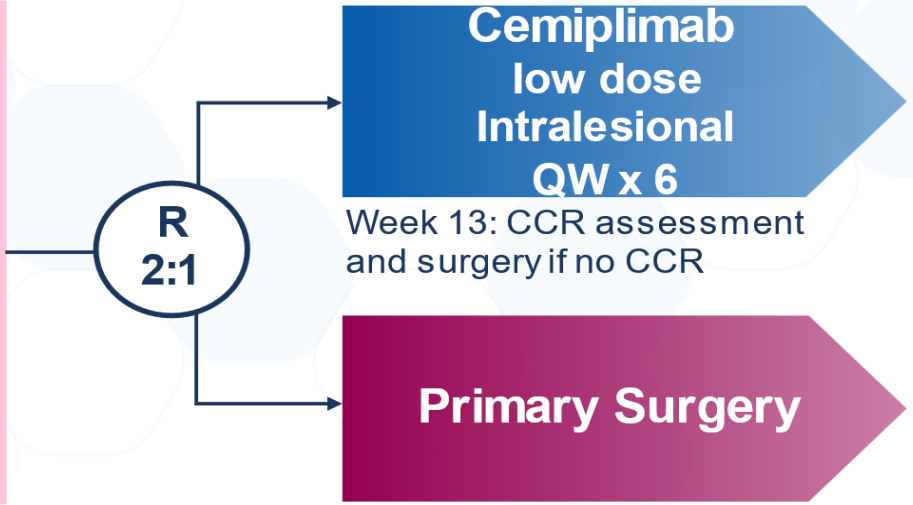
Phase 3 Trial of Intralesional Cemiplimab in Patients With Early-Stage CSCC (NCT06585410): Study Design

Randomized, Open-label Study

N=369 patients

Key Eligibility Criteria

- 1-2 cm maximum diameter
- HN, hand, pretibial surface
- Immunosuppressed, CLL, and transplant patients excluded



Primary Endpoints

- EFS (both arms): 1 year and 3 year from randomization, per investigator assessment

Secondary Endpoints

- CCR (experimental arm)
- Non-target lesions in region of TLs (experimental arm)
- Size of surgical defect
- Size of biopsy defect
- Safety and tolerability

CCR, composite complete response; CLL, chronic lymphocytic leukemia; CSCC, cutaneous squamous cell carcinoma; EFS, event-free survival; HN, head and neck; R, randomized; TL, target lesion.
ClinicalTrials.gov identifier: NCT06585410. Accessed September 5, 2024.

Trial in Progress

CLEAR CSCC (Intralesional Cemiplimab) Ongoing Phase III

Migden et al. Presented at Melanoma World Society (MWS) and European Association of Dermato-Oncology (EADO), 3–5 April 2025, Athens, Greece. Encore; originally presented at Maui Derm 2025, 20–24 January 2025, Maui, Hawaii, USA.

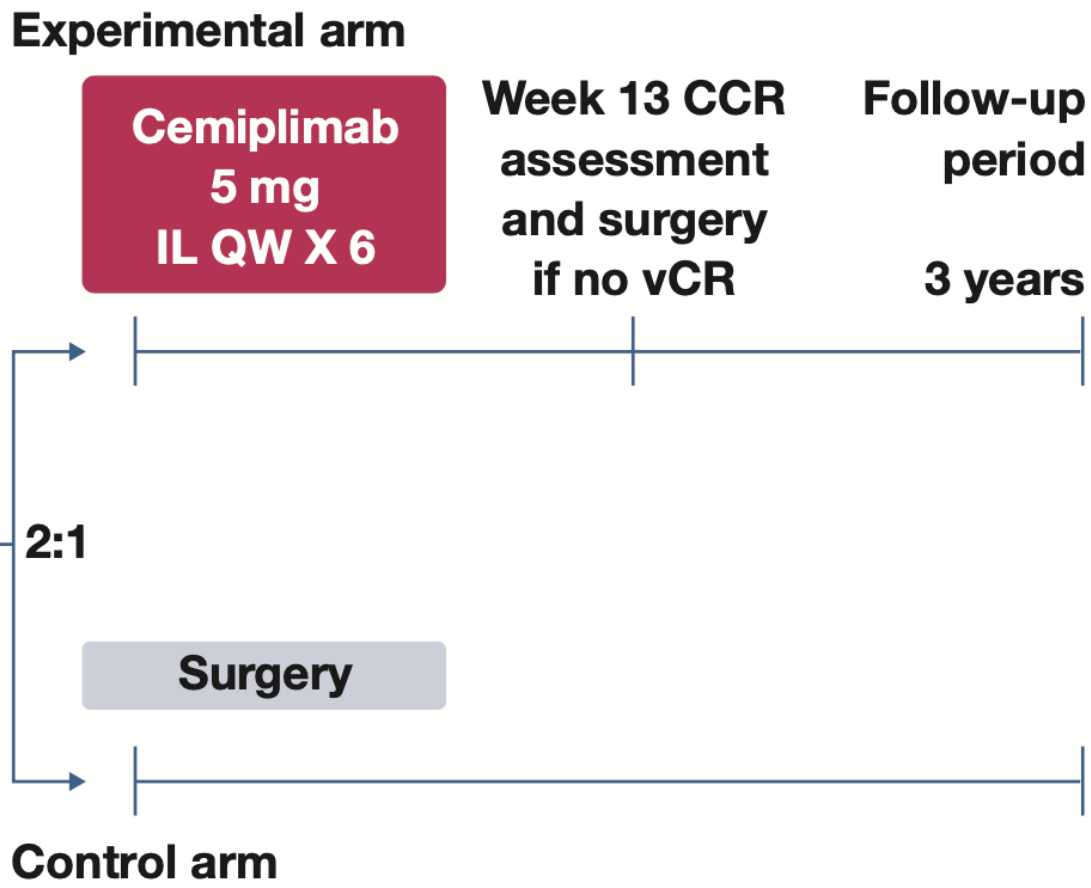
N=369

Key inclusion criteria

- CSCC TL (≥1 and ≤2 cm in longest diameter) located in the HN, hand or pre-tibial surface

At time of enrolment patients will be stratified as follows:

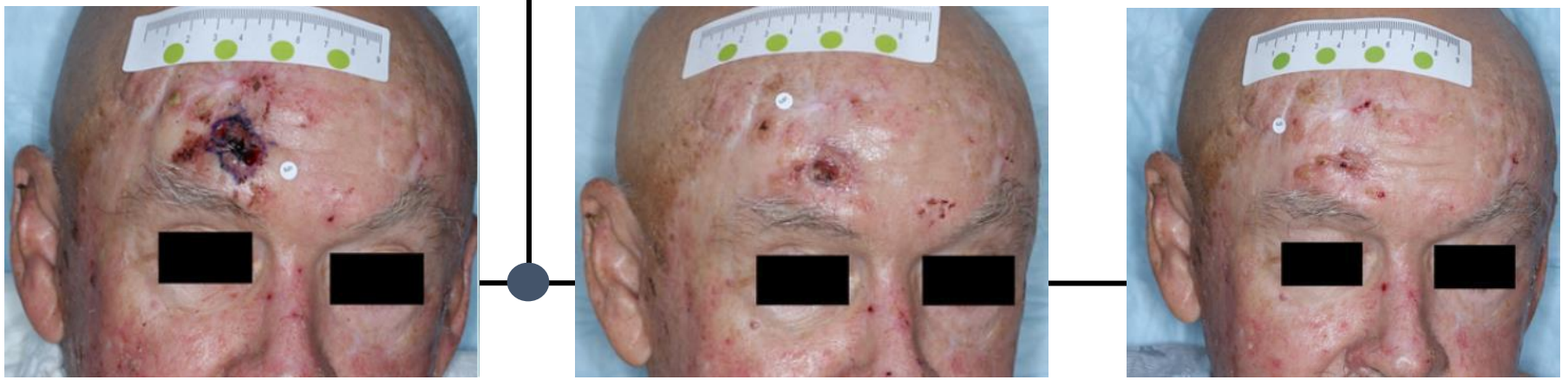
- TL location (HN vs non-HN)†
- Planned surgery (Mohs vs other CMA)†
- Degree of histologic differentiation of TL‡
- ECOG performance status (0 vs 1)‡



Case: Intralesional Cemiplimab in Patients With Recurrent Resectable CSCC

Effect of cemiplimab 5 mg QW (DL1) in a patient with recurrent CSCC

Started IL cemiplimab



CSCC, cutaneous squamous cell carcinoma; DL, dose level; QW, once weekly.
Migden MR. Presented at: ACMS; May 12-15, 2022; Philadelphia, PA. 814P.

March 2021 260 Volume 20 • Issue 3
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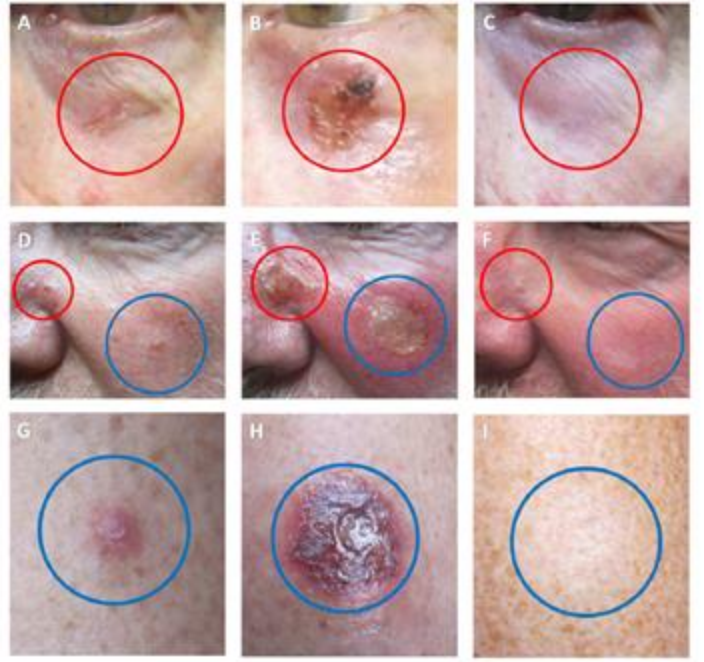
A Non-Surgical and Cost-Effective Treatment Approach Employing Topical Imiquimod, 5-Fluorouracil, and Tretinoin for Primary Non-Melanoma Skin Cancers

William J. Nahm BA,[a,b] John Shen MD,[c] Patrick M. Zito DO PharmD,[b,d] Adrianna M. Gonzalez MD,[b,e] Nicole Nagrani MD,[b,f] Kevin Moore MD MPH,[b,g] Evangelos V. Badiavas MD PhD,[b] Robert S. Kirsner MD PhD,[b,h] Anna J. Nichols MD PhD[b,h]



- Retrospective, 690 KCs
- 30 treatments, topical regimen + cryotherapy q2wks
- Clinical exam 3 yrs post treatment to evaluate for recurrence

Clearance Rates by Topical Therapy, Stratified by Type and Subtype of Skin Cancer†

Treatment Group	BCC				SCC			Overall
	Superficial	Nodular**	Morpheaform	Total	In Situ*	Invasive	Total	
IMI/TRET	100% (8/8)	97% (37/38)	60% (3/5)	94% (48/51)	92% (12/13)	96% (25/26)	95% (37/39)	94% (85/90)
5-FU/TRET	100% (2/2)	75% (6/8)	100% (3/3)	85% (11/13)	63% (5/8)	86% (6/7)	73% (11/15)	79% (22/28)
IMI/5-FU/TRET	100% (4/4)	100% (26/26)	67% (2/3)	97% (32/33)	100% (17/17)	100% (18/18)	100% (35/35)	99% (67/68)
Overall	100% (14/14)	96% (69/72)	73% (8/11)	94% (91/97)	89% (34/38)	96% (49/51)	93% (83/89)	94% (174/186)

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; IMI, imiquimod 5% cream; 5-FU, 5-fluorouracil 2% solution; TRET, tretinoin 0.1% cream.
†Clearance rates of each treatment group, stratified by skin cancer subtype, were compared using chi-square tests. *$P \leq .05$. **$P \leq .01$.

Tirbanibulin for SCC (Inhibits microtubule formation at mitosis)

- **Study Design**
  - **Tirbanibulin (tubulin inhibitor) 1% ointment to treat NMSCs**:
    - Applied once daily for 5 days
    - Followed by 2-week break
    - Combined with liquid nitrogen (LN2) each round
- **Patient Characteristics**
  - Most had extensive NMSC histories
  - Chose topical therapy before excision
- **Results**
  - 80% lesion resolution
  - No recurrence after 32 months
  - Local skin reactions (LSRs):
    - Mild or none in most cases
    - Stronger LSRs linked to faster response, but not required for efficacy

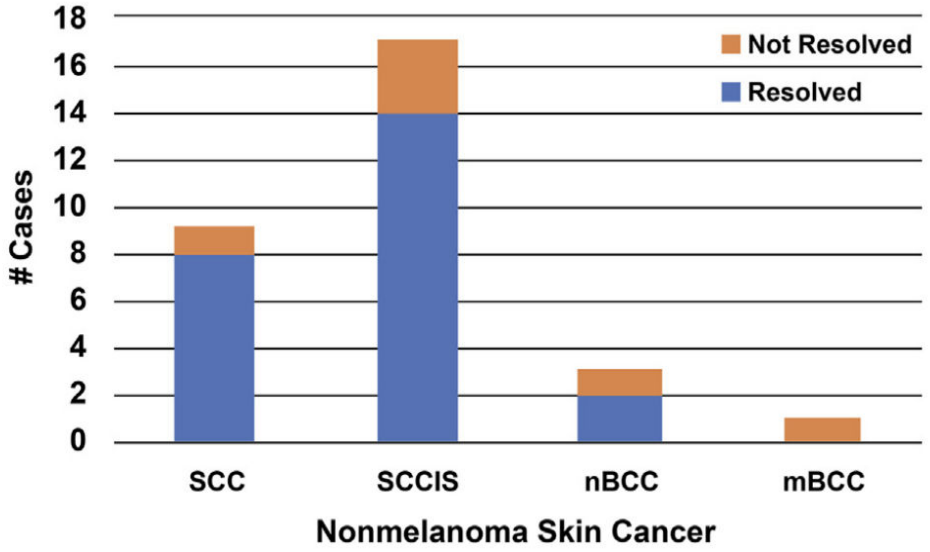


Figure: Nonmelanoma skin cancer response to tirbanibulin by subtype

1. DeTemple VK, Walter A, Bredemeier S, Gutzmer R, Schaper-Gerhardt K. Anti-tumor effects of tirbanibulin in squamous cell carcinoma cells are mediated via disruption of tubulin-polymerization. Arch Dermatol Res. 2024 Jun 7;316(7):341. doi: 10.1007/s00403-024-03032-x. PMID: 38847867; PMCID: PMC11161541.
2. Real-world experience with tirbanibulin 1% ointment for the treatment of nonmelanoma skin cancer following cryotherapy: A pilot study Moore, Angela et al. JAAD International, Volume 18, 168 – 170

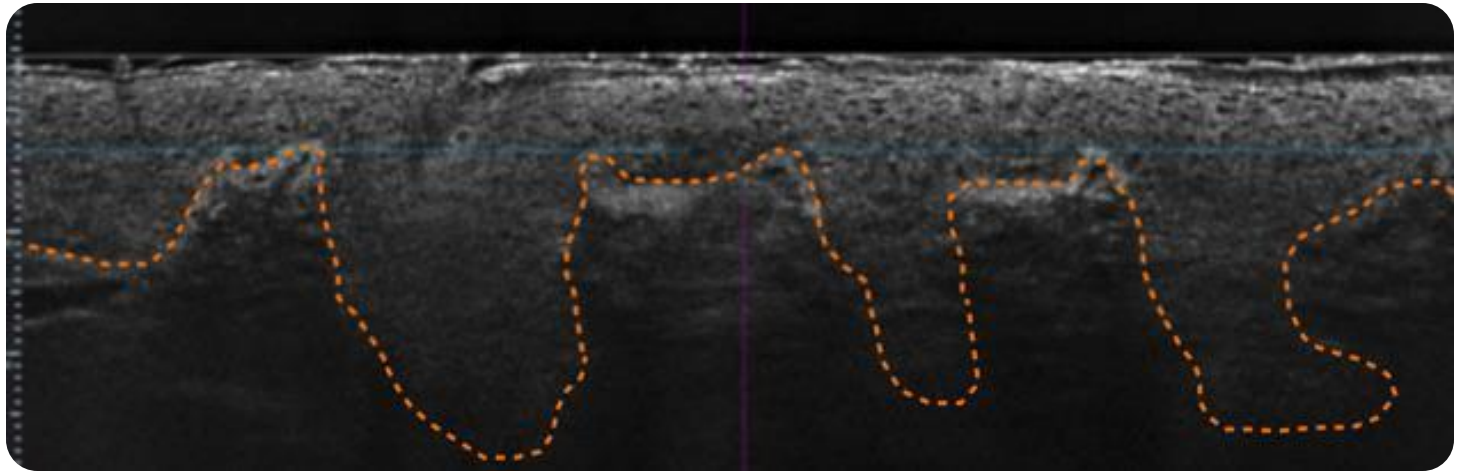
Tirbanibulin for sBCC

- Currently investigating safety and efficacy of tirbanibulin for sBCC

- Retrospective study of 24 total lesions showed 54.2% overall cure rate, 68.4% if nodular or micronodular subtypes excluded

https://www.clinicaltrials.gov/study/NCT06112522?term=TIRBANIBULIN&rank=1
Martin-Poch A, et al. Tirbanibulin 1% ointment for the treatment of superficial basal cell carcinoma: A retrospective study. J Eur Acad Dermatol Venereol. 2025 Jul 14. doi: 10.1111/jdv.20844. Epub ahead of print. PMID: 40657858.

Pre-treatment



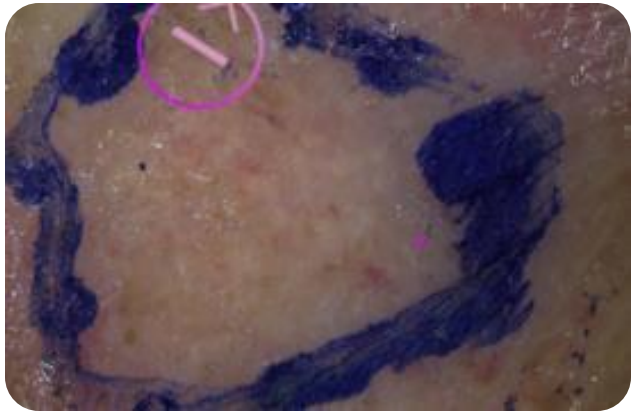


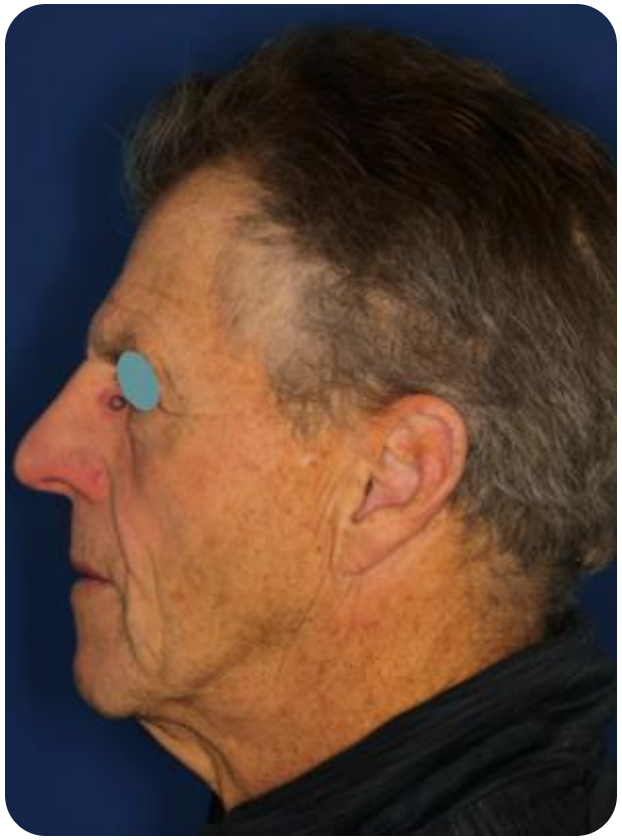
Fig. 2: A photograph of the AK (encircled) at the left side of the nose *(left picture)*.

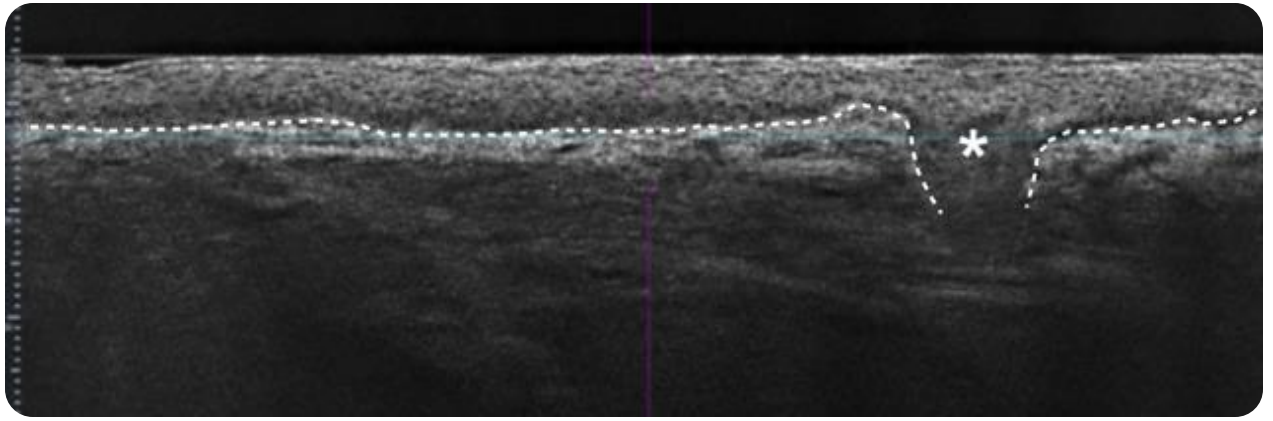
A dermatoscopic picture of the AK lesion for specific LC-OCT imaging *(bottom)*.

LC-OCT image representing the advanced basal proliferation stage of the AK – PRO III *(top)*.

Patient consented to disclose clinical information and pictures which has been supplied by Dr Dirschka.
AK, actinic keratosis; LC-OCT, line-field confocal optical coherence tomography; PRO, proliferation score system.
1. Dirschka T, et al. Poster P1-18, EADO 2025.

10 weeks post-treatment with tirbanibulin:





* = Hair follicle

-- = Dermo-epidermal junction

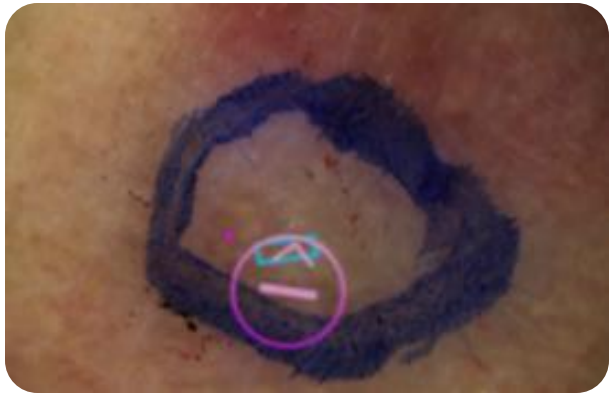


Fig. 4: Follow-up picture after 10 weeks post-treatment with tirbanibulin at the encircles area *(left picture).*

A dermatoscopic picture of the prior AK lesion for specific LC-OCT imaging *(bottom).*

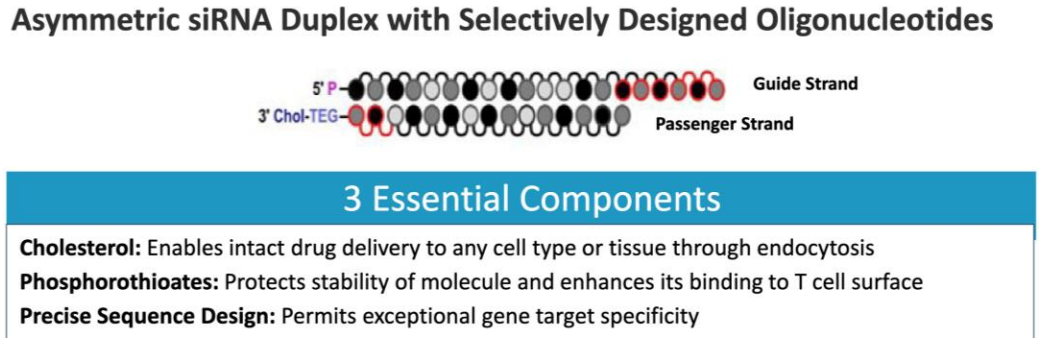
LC-OCT image, confirming the remission of the AK *(top)*.

Patient consented to disclose clinical information and pictures which has been supplied by Dr Dirschka.
AK, actinic keratosis; LC-OCT, line-field confocal optical coherence tomography;
1. Dirschka T, et al. Poster P1-18, EADO 2025.

Phio Pharmaceuticals – Pipeline & Technology

INTASYL® Technology

- Proprietary self-delivering siRNA platform
- Silences disease-driving genes without extra delivery systems
- Reactivates immune system's natural immunity to attack tumors



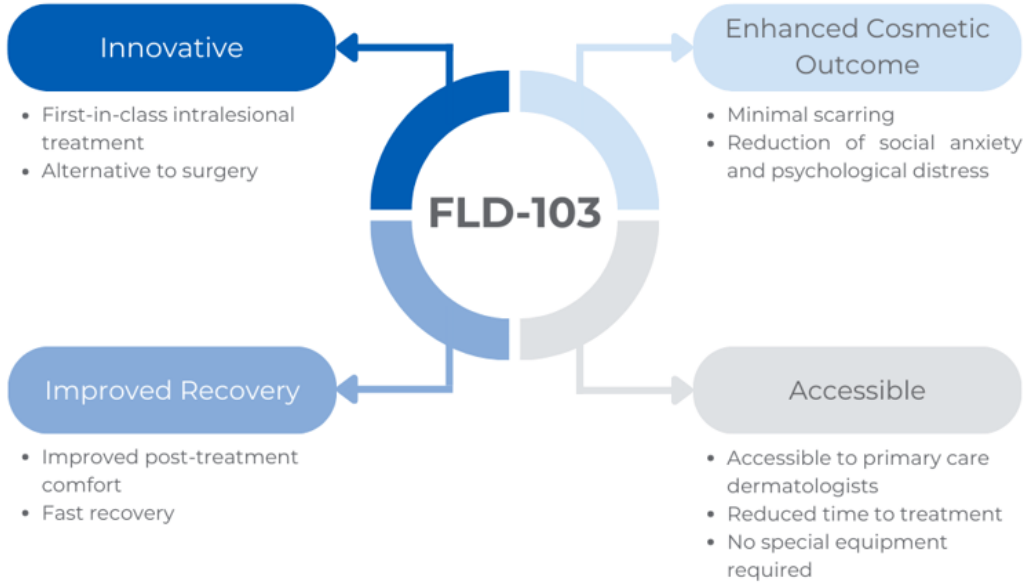
Pipeline

Candidate	Target	Stage	Indications
PH-762	PD-1 silencer	Phase 1b Clinical	Cutaneous SCC (Stages I–IV), Melanoma (Stage IV), Merkel Cell Carcinoma (Stage IV)
PH-894	BRD4 silencer	Preclinical	Cutaneous SCC (Stages I–IV), Melanoma (Stage IV), Merkel Cell Carcinoma (Stage IV)

Feldan Therapeutics

Feldan® Shuttle Technology

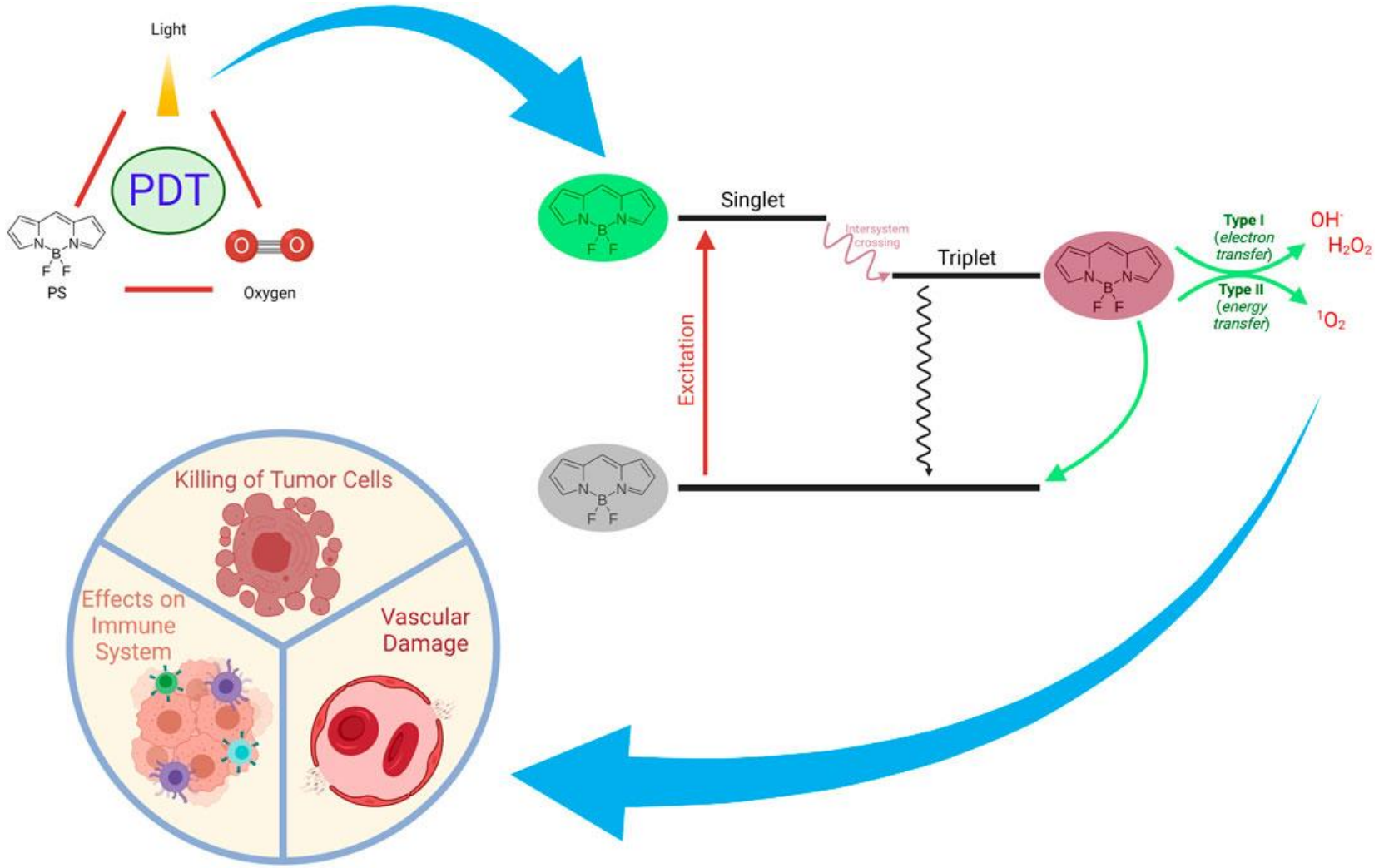
- Proprietary peptide-based delivery platform
- Breaks endosomal barriers for efficient intracellular delivery
- Has potential to become a non-surgical, injectable treatment option



Pipeline

	Therapeutic Cargo	Route of Administration	Research	Lead Optimization	IND-Enabling	Phase I/II	Phase III
Dermatology							
FLD-103 Basal Cell Carcinoma	ASO*	Intralesional					
Undisclosed	ASO	Local					

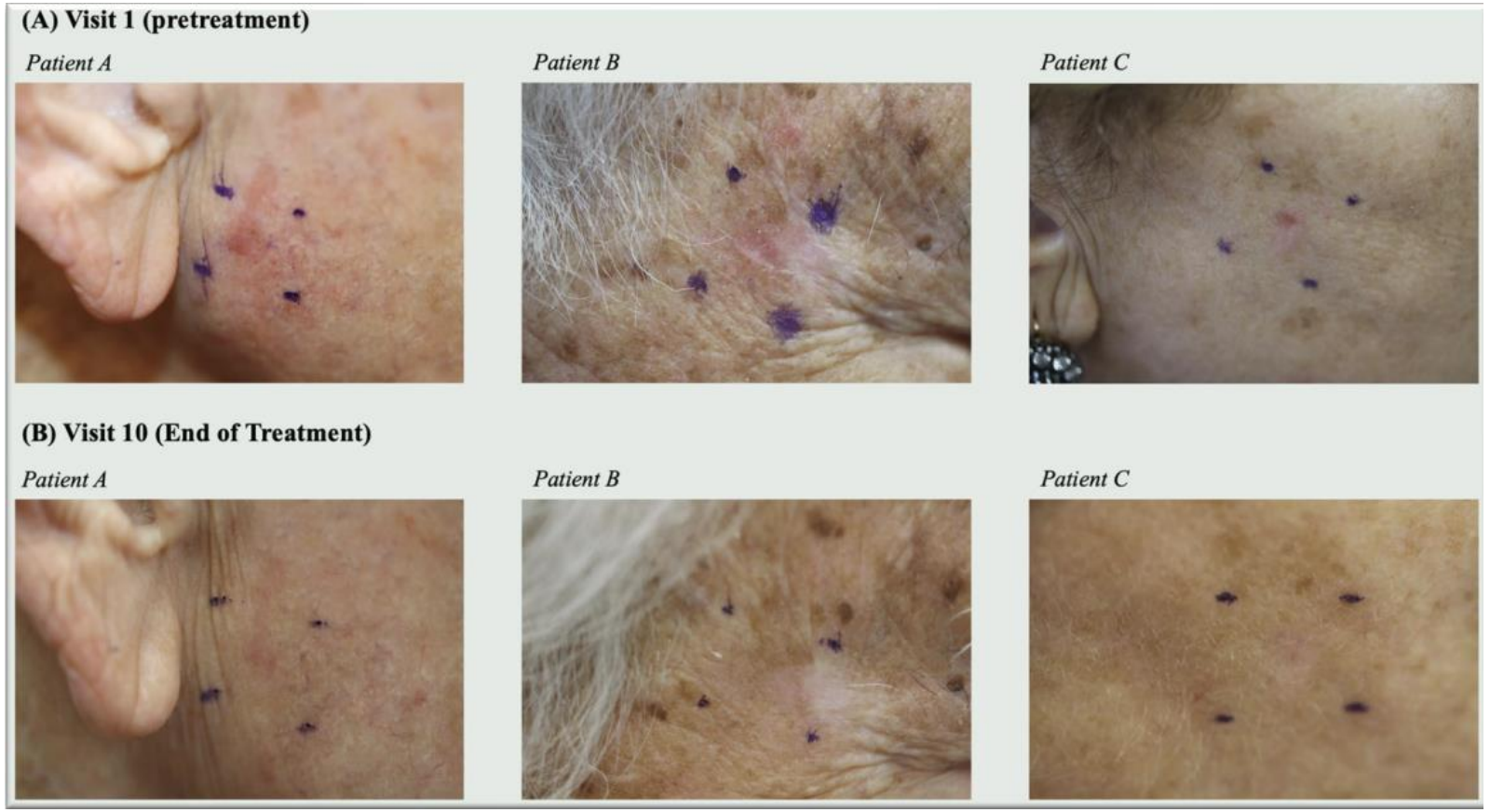
PDT Schema



Li, X., Lovell, J.F., Yoon, J. *et al.* Clinical development and potential of photothermal and photodynamic therapies for cancer. *Nat Rev Clin Oncol* **17**, 657–674 (2020).

Aminolevulinic Acid 20% Solution PDT For Facial Squamous Cell Carcinoma in situ (isSCC)

- Methods
  - 30/32 patients with biopsy-confirmed, 0.4–1.3 cm, facial isSCC completed the study
  - Lesion debrided with 4x4 gauze, ALA 20% topical solution applied & covered 18–24 hours, then blue light activation for 16 mins 40 secs at 10 J/cm2
  - PDT repeated after 28 +/- 3 days and area excised 8 weeks later for histopathology
- Primary efficacy endpoint: 30/30 complete absence histologically of isSCC - 100%
- Secondary efficacy endpoint: 30/30 clinical cure evaluation before excision - 100%
- Local skin reactions – well tolerated, erythema, erosion/scaling, flaking/scaling peaking 1 day and 2 weeks after treatment, respectively.
- Greater after treatment 1. VAS (0–10) Mean Pain score was 2.71 +SD 2.77, 15 minutes after light treatment



Evaluating the safety and efficacy of aminolevulinic acid 20% topical solution activated by pulsed dye laser and blue light in the treatment of facial cutaneous squamous cell carcinoma in situ

Mark S Nestor [1 2 3], Haowei Han [1], Francesca M Ceci [1], Alec Lawson [1], Anita Gade [1]

PDT, photodynamic therapy; ALA, aminolevulinic acid; VAS, visual analog scale; SD, standard deviation. || Nestor M et al. Fall Clinical Dermatology Conference 2024. Las Vegas, NV. October 24-27, 2024.

Red light photodynamic therapy with 10% aminolevulinic acid gel showed efficacy for treatment of superficial basal cell carcinoma in a randomized, vehicle controlled, double-blind, multicenter phase III study

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First and Only Phase III RCT PDT sBCC Study in USA

U.S. Phase III Study for Treatment of sBCC with PDT

Double-blind, randomized, placebo-controlled, multi-center study evaluated safety and efficacy in 187 patients with one or more clinically and histologically confirmed superficial BCCs

Treatment Protocol

Histologically confirmed sBCC lesions (3mm Punch Biopsy)

↓

Degrease, remove scabs/crusts, roughen lesions

↓

Apply 10% ALA gel or Vehicle to lesions (1 mm thickness)

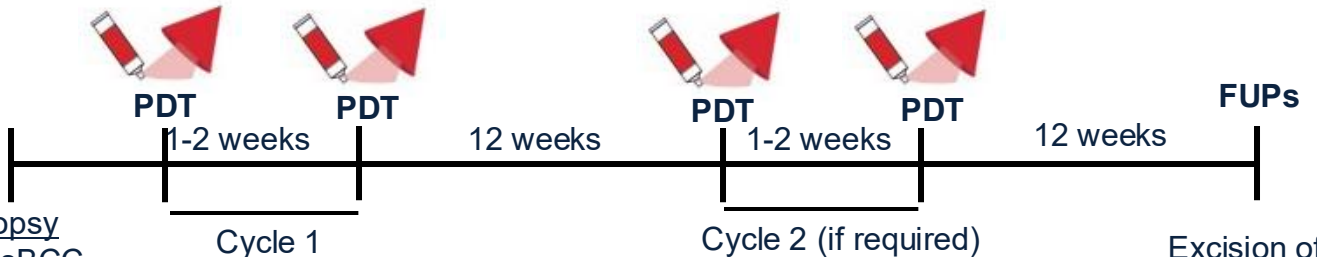
↓

3 hr incubation w/ occlusion

↓

Illumination with Red light

Course of Study



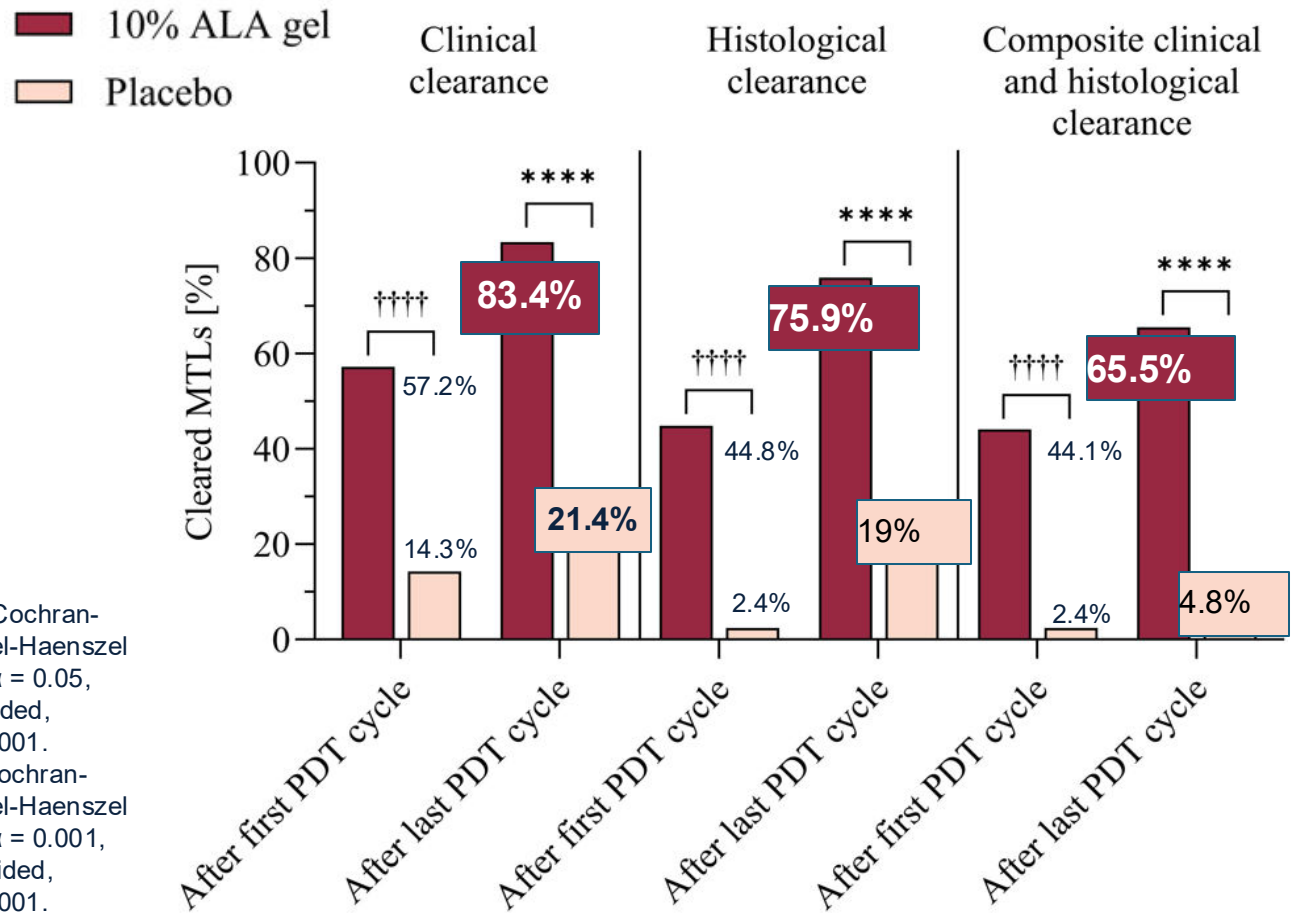
Enroll <u>biopsy confirmed</u> sBCC subject (1-3 lesions). **In case of multiple lesions, one lesion must be defined as the Main Target Lesion (MTL)**

Clinical Assessment, excision of cleared MTL for histological assessment. If any lesions remain → 2nd PDT cycle

Excision of cleared MTL for histological assessment & 5 year FUP

Schlesinger, T et al. Red light photodynamic therapy with 10% aminolevulinic acid gel showed efficacy for treatment of superficial basal cell carcinoma in a randomized, vehicle controlled, double-blind, multicenter phase III study. Journal of the American Academy of Dermatology, August 2025.

Main Target Lesions (MTLs) Clearance



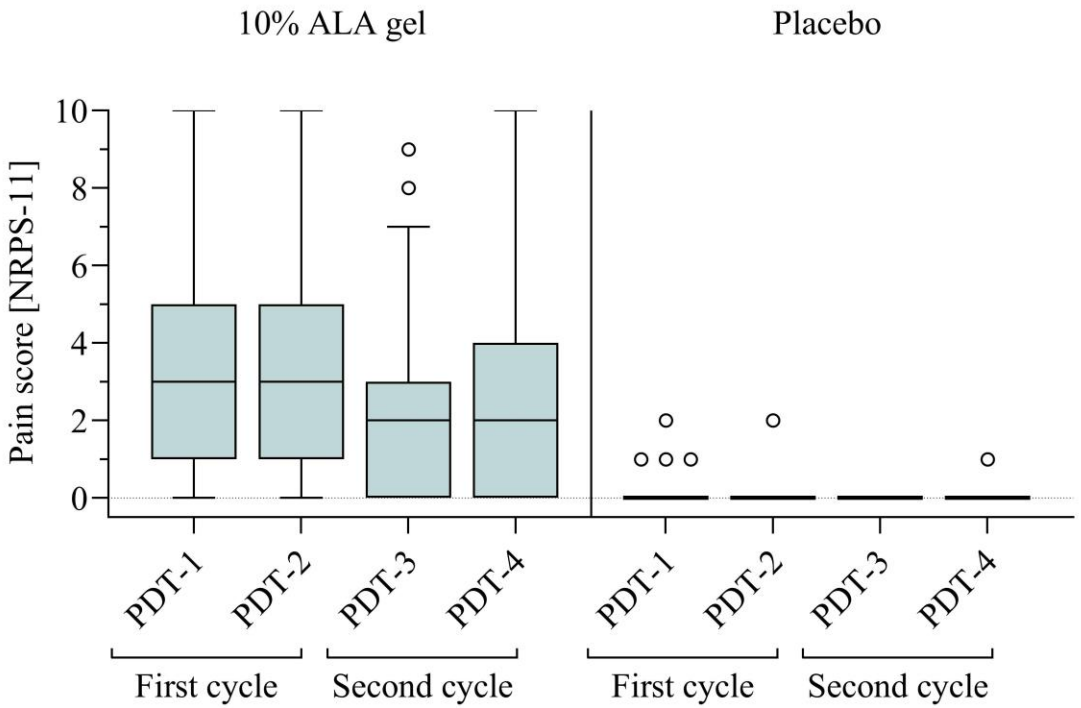
†††† Cochran-Mantel-Haenszel test, α = 0.05, two-sided, p<0.0001.
**** Cochran-Mantel-Haenszel test, α = 0.001, one-sided, p<0.0001.

65.5% (95/145) success with AMELUZ®-PDT vs. 4.8% (2/42) with placebo-PDT (p<0.0001)

- Each subject had one predefined MTL
- Clinically cleared MTLs were excised and histologically evaluated after each PDT cycle
- Non- or partially responding MTLs received a 2nd PDT cycle
- After last PDT cycle assessments reflect cumulative clearance

Schlesinger, T et al. Red light photodynamic therapy with 10% aminolevulinic acid gel showed efficacy for treatment of superficial basal cell carcinoma in a randomized, vehicle controlled, double-blind, multicenter phase III study. Journal of the American Academy of Dermatology, August 2025.

Pain Assessment



- Pain intensity recorded immediately post-illumination
- When evaluating each PDT session individually:
  - Pain decreased in the 2nd PDT cycle (median score: 3 → 2) (see figure)
- Highest pain scores across all PDT sessions (10% ALA gel vs. placebo)
  - 10% ALA: 4.5 (extremities), 4.3 (neck/trunk)
  - Placebo: 0.3 (extremities), 0.1 (neck/trunk)

Red light photodynamic therapy with 10% aminolevulinic acid gel showed efficacy for treatment of superficial basal cell carcinoma in a randomized, vehicle controlled, double-blind, multicenter phase III study. Schlesinger, Todd et al. Journal of the American Academy of Dermatology, Volume 0, Issue 0

Pulsed electrical energy for BCC

Multicenter, prospective feasibility study of Nano-Pulse Stimulation™ technology for the treatment of both nodular and superficial low-risk basal cell carcinoma

Amy S Ross [1], Todd Schlesinger [2], Christopher B Harmon [3], Ronald L Moy [4], Thomas E Rohrer [5], Darius R Mehregan [6], Richard Nuccitelli [7], Lauren Jauregui Johnston [7], William A Knape [7]

- **Results:** 92% complete histological clearance rate (34 of 37 lesions) after a single treatment with the CellFX System.
  - 3 lesions resulted in residual BCC due to minor errors in tip placement
  - Need for providing an improved tip placement guide

Ross AS, Schlesinger T, Harmon CB, et al. Multicenter, prospective feasibility study of Nano-Pulse StimulationTM technology for the treatment of both nodular and superficial low-risk basal cell carcinoma. Front Oncol. 2022;12:1044694. doi:10.3389/fonc.2022.1044694

Pulsed electrical energy for BCC

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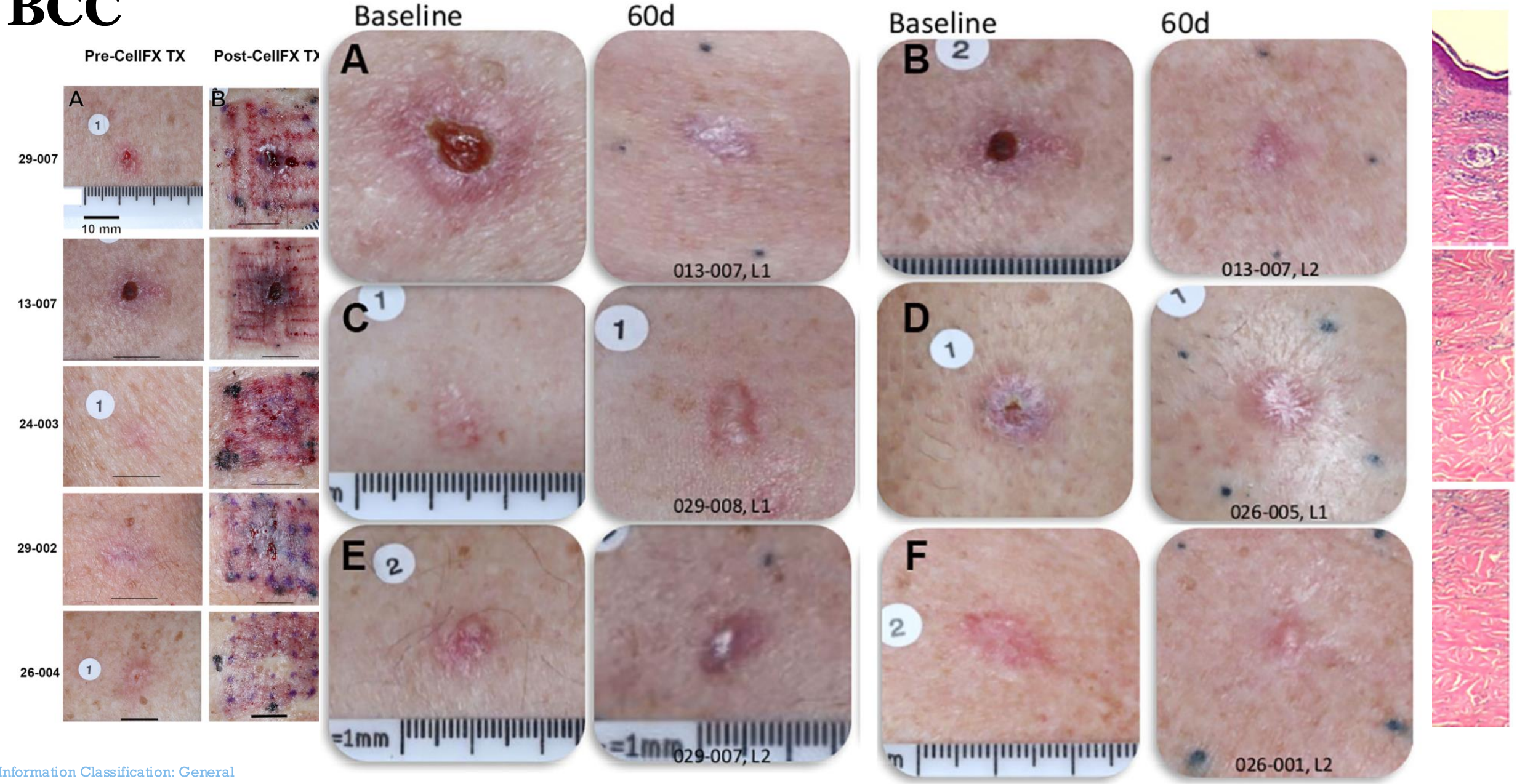
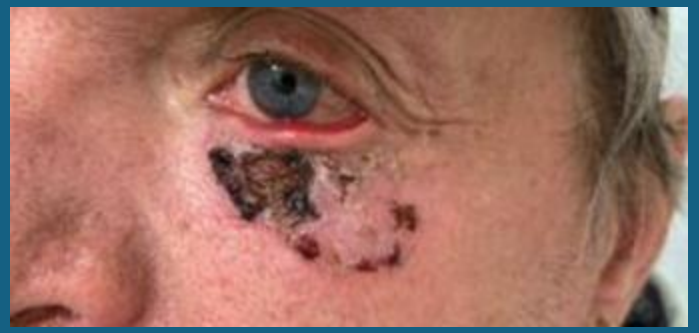


Key Takeaways – Skin Cancer Research

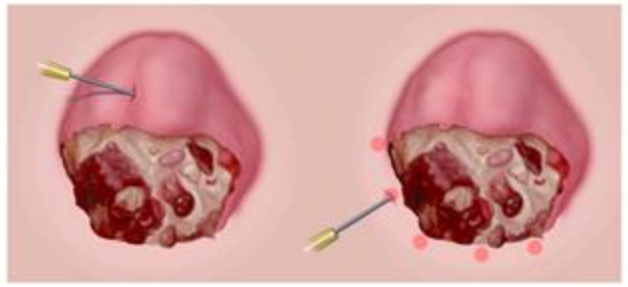
- Pharmaceuticals – HHI for aBCC – manage adverse effects
- Immunotherapy (IV) – cemiplimab for aCSCC and aBCC, cosibelimab for aSCC
  - Adjuvant (C-POST) and Neo-Adjuvant options
- Intralesional
  - Cemiplimab for early stage CSCC
  - VP-315 for BCC
- Topical tirbanibulin for SCC and maybe BCC
- Photodynamic therapy for SCC (early) and sBCC (big study)
- Pulsed electrical energy – any takers??

What is the role of the dermatologist?

1. We make the right diagnosis earlier



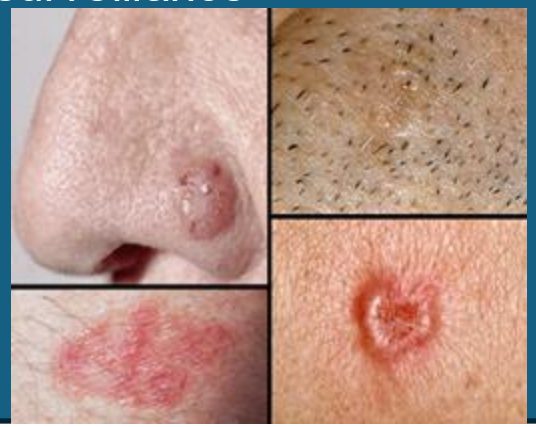
2. We are good at injections



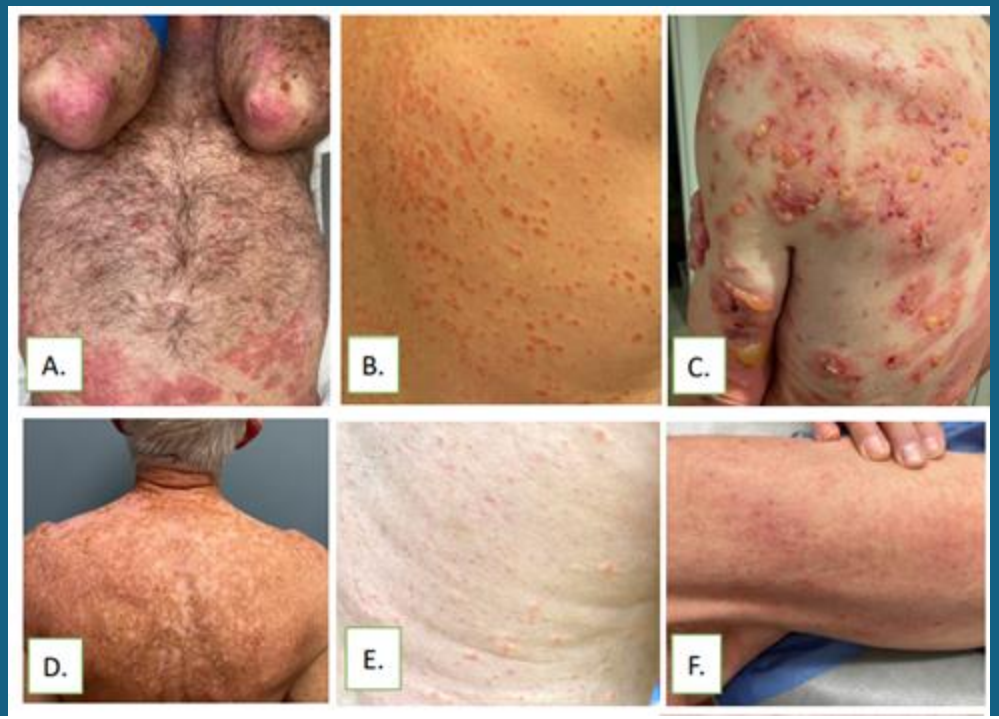
J Am Acad Dermatol. 2024 Jun 26

3. We are best at defining unresectable/ locally advanced disease

4. Patients are likely to get more KCs and need surveillance



5. We are best poised to diagnose and treat cutaneous toxicities of therapy



J Immunother Cancer. 2024 Apr 10;12(4):e007675.

Important Pearls for Dermatologists
Pearl #1: Get Known

- Oncologists still believe that dermatologists either pop pimples or make patients younger
- Skin cancer is our domain, we have to be visible even in the most advanced cases
- Systemic therapies also have cutaneous manifestations of concern
  - Checkpoint inhibitors always need a dermatologist's involvement
  - Hedgehog Inhibitors have many dose-limiting mucocutaneous AEs
- We may not operate the pump, but we still know the patients
- Many Oncologists dismiss the opinions if we dismiss the severity

Important Pearls for Dermatologists
Pearl #2: Get Shown

- Find a local tumor board and make an appearance
- Go to the hospital physician's lounge and introduce yourself
- Send business cards to Med Onc and Rad Onc clinics with an introductory letter to promote visibility
- Work with your Mohs' referral on how to position neoadjuvant therapy
- *Showing interest in medical dermatology is a lost art, so just do it…*

Important Pearls for Dermatologists
Pearl #3: Follow through

- Insist on active correspondence with the oncologists on the patient's progress, and provide the same during and after the course

- If possible, send someone from the office to visit the patient during an infusion cycle to check on the progress and tolerability…or have the patient come to the office if possible to catch up.

- The more we give these patients away, or don't get involved with their treatment, the more we will marginalize ourselves.

"Unfortunately it's inoperable. So I'm going to whack it with a hammer."

Thank You