Cemiplimab (REGN2810), A Fully Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy from Expansion Cohorts of Phase 1 Study

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Background

- Cemiplimab (REGN2810) is a human immunoglobulin G4 monoclonal antibody directed against PD-1.[1]
- Phase 1 results from the first 60 patients with advanced solid tumors showed no dose-limiting toxicities:[1]
  - The most common treatment-related adverse events were fatigue (28%), arthralgia (12%), and nausea (12%).
  - The overall response rate was 18%.
- Cemiplimab 3 mg/kg every 2 weeks (Q2W) was selected for further study in Expansion Cohorts.
- As of April 27, 2017, 392 patients have been enrolled in the Phase 1 study.
- Cutaneous squamous cell carcinoma (CSCC) is the 2nd most common skin cancer in US.[2]
- Risk factors for CSCC include ultraviolet exposure, advanced age, immunosuppression.[3]
  - There is a predominance of males and a median age of 71 years at diagnosis.[4]
- CSCC has a surgical cure rate of >95% in early stage disease; however, a small percentage of patients develop unresectable locally advanced or metastatic CSCC[4]
  - US mortality: 3,900–8,800/year.[4]
- There is no widely accepted standard of care systemic therapy for locally advanced or metastatic CSCC (mCSCC).[5]
  - Conventional cytotoxic chemotherapy can induce tumor responses, but often is poorly tolerated among older patients with CSCC.
  - In a single arm trial with cetuximab (n=36), median overall survival was 8.1 months.[6]
- In Phase 1 dose escalation study of cemiplimab, a durable radiologic complete response to cemiplimab was achieved in a CSCC patient.[1,7]
- There is a higher mutation burden in CSCC than any tumor type in The Cancer Genome Atlas (TCGA).[8]
- Immunosuppression is a well-described risk factor for CSCC (especially in solid organ transplant patients).[9]
- Programmed death-ligand 1 (PD-L1) expression has been associated with high-risk disease[10]; CSCC tumors may therefore be responsive to PD-1 checkpoint blockade.

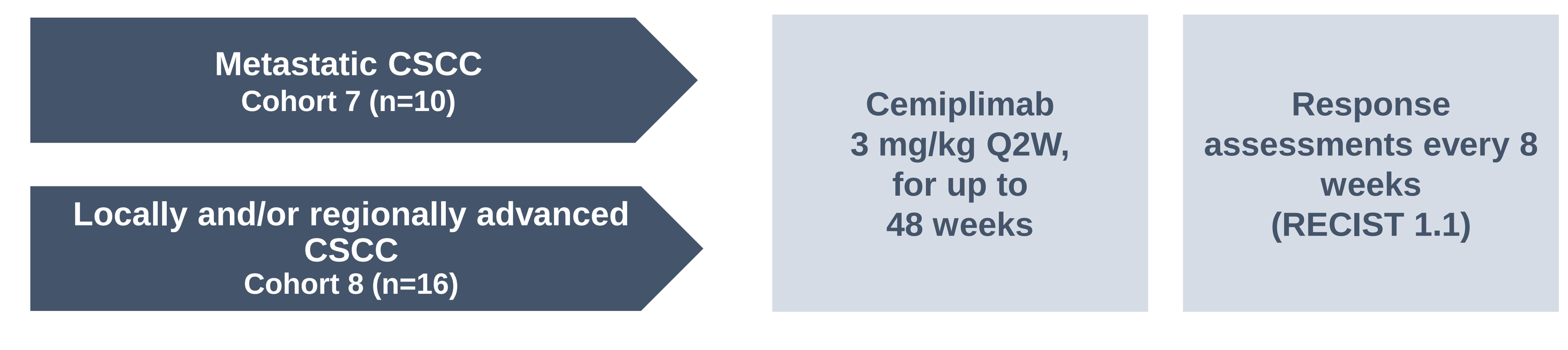
Objectives

- The co-primary objectives of the CSCC Expansion Cohorts of this Phase 1 open label study were to:
  - Characterize the safety and tolerability of intravenous cemiplimab 3 mg/kg.
  - Evaluate the efficacy of cemiplimab by measuring overall response rate (ORR).

Methods

Study design: CSCC Expansion Cohorts (NCT02383212)

- Cohort 7 enrolled 10 patients with mCSCC and Cohort 8 enrolled 16 patients with unresectable locally and/or regionally advanced CSCC **(Figure 1)**.



Research tumor biopsies were taken at screening and Day 29±3.
RECIST, Response Evaluation Criteria In Solid Tumors.

Figure 1. Study design: CSCC expansion cohorts

- All patients received cemiplimab 3 mg/kg Q2W for up to 48 weeks (if no progression or intolerance), followed by post-treatment follow-up.
  - There is an option for re-treatment for patients who experienced disease progression during post-treatment follow-up, but no CSCC patients have required this re-treatment option at this time.
- All patients underwent tumor imaging every 8 weeks, and response assessments are per RECIST 1.1.
- Research biopsies were performed at baseline and at Day 29.
- Selected inclusion criteria include:
  - Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
  - Measureable disease by RECIST 1.1.
  - Adequate organ function (bone marrow, kidney, liver).
  - mCSCC (M1): Expansion Cohort 7.
  - Unresectable locally and/or regionally advanced CSCC (M0): Expansion Cohort 8:
    - Acceptable reasons for surgery to be deemed inappropriate are:
      - Recurrence of CSCC after 2 or more surgical procedures and an expectation that curative resection would be unlikely, and/or;
      - Substantial morbidity or deformity anticipated from surgery.
- Selected exclusion criteria:
  - Autoimmune disease within 5 years.
  - Active brain metastases.
  - Other invasive malignancy within 5 years (no exclusion for tumors considered cured by localized treatment).
  - Immunosuppressive doses of steroids (>10 mg prednisone daily or equivalent).
  - Systemic antitumor treatment within 4 weeks of initial dose of cemiplimab.
  - History of solid organ transplant.
  - Tumors of lip or eyelid not eligible for CSCC cohorts.

Results

Patient characteristics

- As of April 27, 2017 (data cut-off date), 26 patients (median age, 73 years) from the CSCC expansions cohorts have been treated with cemiplimab.
- Patient characteristics and exposure to cemiplimab are summarized in **Table 1**.

Table 1. Patient characteristics and exposure to cemiplimab

	mCSCC (n=10)	Locally advanced CSCC (n=16)	Overall (N=26)
Median age, years (min–max)	71 (56–86)	73 (56–88)	73 (56–88)
Males, n (%)	8 (80.0)	13 (81.3)	21 (80.8)
ECOG performance status, n (%)			
0	4 (40.0)	6 (37.5)	10 (38.5)
1	6 (60.0)	10 (62.5)	16 (61.5)
Primary CSCC site, n (%)			
Head/neck	5 (50.0)	13 (81.3)	18 (69.2)
Extremity	3 (30.0)	2 (12.5)	5 (19.2)
Trunk	1 (10.0)	1 (6.3)	2 (7.7)
Genital	1 (10.0)	0	1 (3.8)
Any prior systemic therapy, n (%)	9 (90.0)	6 (37.5)	15 (57.7)
Any prior radiation therapy, n (%)	6 (60.0)	14 (87.5)	20 (76.9)
Number of doses of cemiplimab, median, (min–max)	12.5 (3–23)	10.0 (2–24)	11.0 (2–24)
Months of follow up, median, (min–max)	7.3 (1.6–13.8)	6.6 (1.1–13.3)	6.9 (1.1–13.8)

Treatment-emergent adverse events (TEAEs)

- Treatment-related TEAEs occurring in ≥2 patients overall, or ≥Grade 3 in any patient are summarized in **Table 2**.

Table 2. Summary of treatment-related TEAEs (N=26)

Treatment-related TEAEs of any grade occurring in ≥2 patients, or ≥Grade 3 in any patient	Number of patients (%)	
	Any grade	≥Grade 3
Fatigue	6 (23.1)	0
Arthralgia	2 (7.7)	1 (3.8)
Rash, maculopapular	2 (7.7)	1 (3.8)
Diarrhea	2 (7.7)	0
Nausea	2 (7.7)	0
Hypothyroidism	2 (7.7)	0
Asthenia	1 (3.8)	1 (3.8)
Aspartate aminotransferase elevation	1 (3.8)	1 (3.8)
Alanine aminotransferase elevation	1 (3.8)	1 (3.8)

- Two patients discontinued study treatment after treatment-related TEAEs
  - 86-year old female developed Grade 3 rash after 3 doses; she continues post-treatment follow-up
  - 88-year old male withdrew consent following Grade 3 transaminase elevation and Grade 2 fatigue after 6 doses.
- There were 2 deaths within 30 days of last dose of study drug, both considered unrelated to study drug.

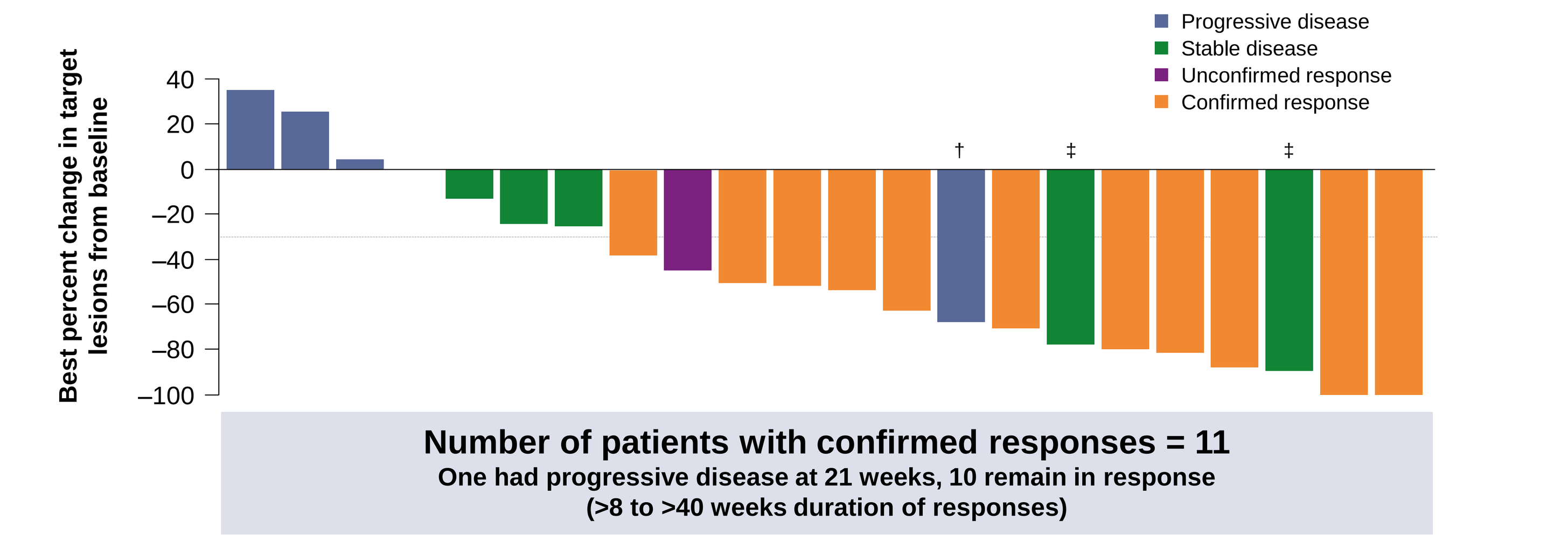
Tumor response

- Tumor response by cohort are summarized in **Table 3**.
- Investigator assessed preliminary ORR (complete response [CR] + partial response [PR] + one unconfirmed PR) by RECIST 1.1 was 46.2% (12/26 patients; 95% CI: 26.6–66.6; intention-to-treat population).
- Disease control rate (DCR = ORR + stable disease [SD]) was 69.2% (18/26 patients; 95% CI: 48.2–85.7).
- Clinical activity in all patients with at least 1 response evaluation of target lesions are shown in **Figure 2**.
- Cemiplimab also produced rapid, deep and durable tumor reductions in target lesions in both cohorts **(Figure 3)**.

Table 3. Best overall tumor response rate by cohorts

Investigator assessment	mCSCC (n=10), n (%)	Locally advanced CSCC (n=16), n (%)	Overall (N=26), n (%)
Complete response	0	2 (12.5)	2 (7.7)
Partial response	6 (60.0)†	4 (25.0)	10 (38.5)
Stable disease	1 (10.0)	5 (31.3)	6 (23.1)
Progressive disease	2 (20.0)	4 (25.0)	6 (23.1)
Not evaluated	1 (10.0)	1 (6.3)	2 (7.7)

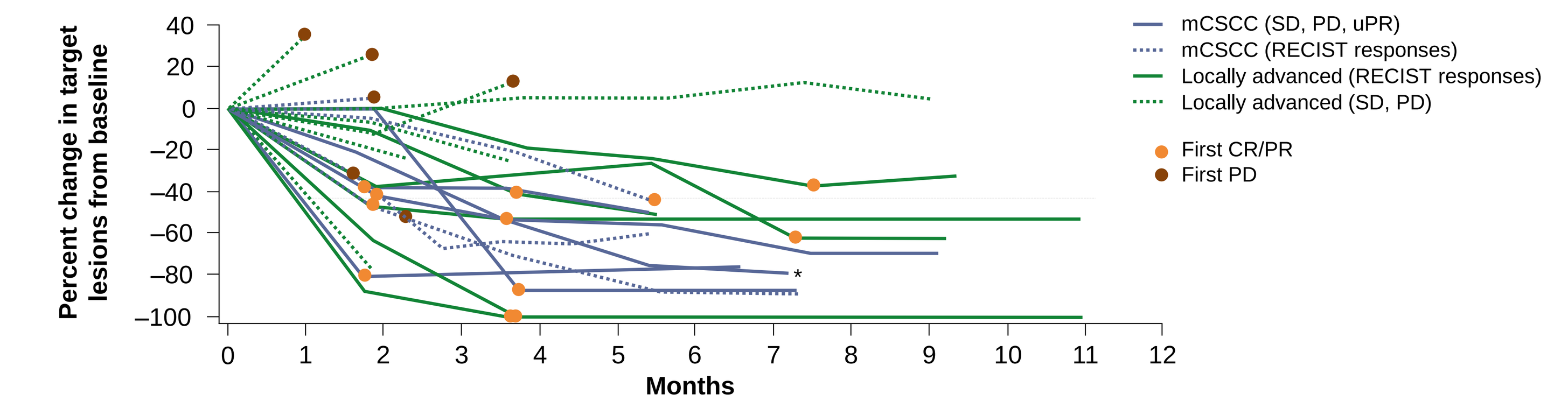
†Includes 5 confirmed partial responses and 1 unconfirmed partial response.



Progressive disease
Stable disease
Unconfirmed response
Confirmed response
Best percent change in target lesions from baseline
40
20
0
–20
–40
–60
–80
–100
†
‡
‡
Number of patients with confirmed responses = 11
One had progressive disease at 21 weeks, 10 remain in response
(>8 to >40 weeks duration of responses)

Plot shows 22 patients who had at least 1 response evaluation. Not listed are 4 enrolled patients who did not have at least 1 response evaluation due to death in cycle 1 (2 patients), early clinical progression but no scans (1 patient), and end-of-cycle 1 response assessment that showed new lesions but unevaluable target lesions (1 patient). †Patient had new lesions at end of cycle 1. ‡Patients had stable disease despite large decreases in target lesions: 1 patient discontinued treatment after cycle 1 due to arthralgia, so is stable disease by RECIST; 1 patient developed new lesions during cycle 2 so is stable disease by RECIST.

Figure 2. Clinical activity in all patients with at least 1 response evaluation of target lesions



*Patient progressed at subsequent assessment; however, the sum of target lesions are not evaluable.
PD, progressive disease; uPR, unconfirmed partial response.

Figure 3. Change in target lesion over time

- **Figure 4** shows a case example of a CSCC patient with early response.
- **Figure 5** shows a case example of a patient with CSCC of trunk, metastatic to bilateral axillary lymph nodes, with durable response to cemiplimab.
  - Cemiplimab was discontinued due to an adverse event (rash) after 3 doses; patient continued to maintain response >6 months after discontinuation.

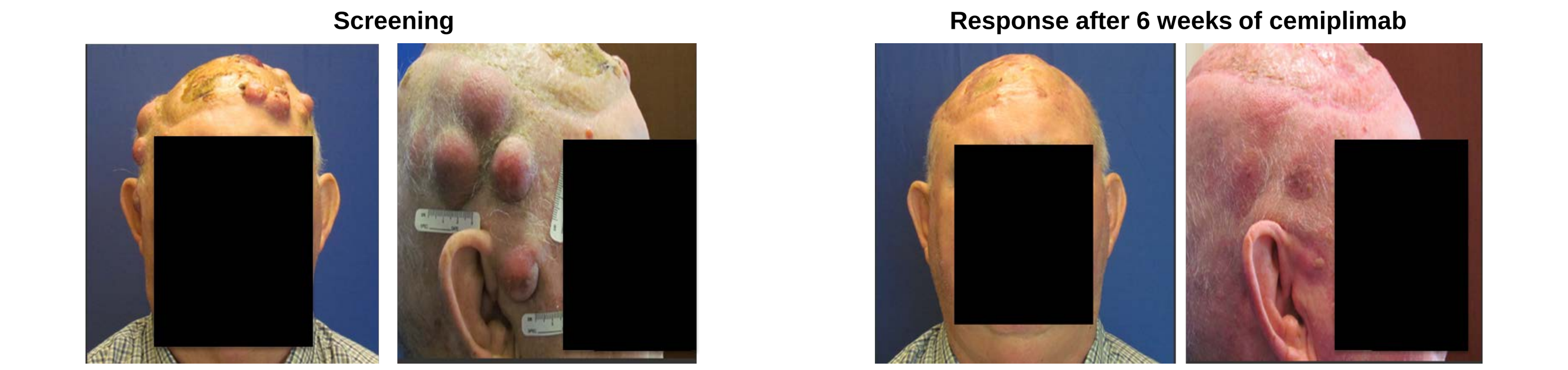


Figure 4. Early response to cemiplimab in a 62-year old male with locally advanced CSCC

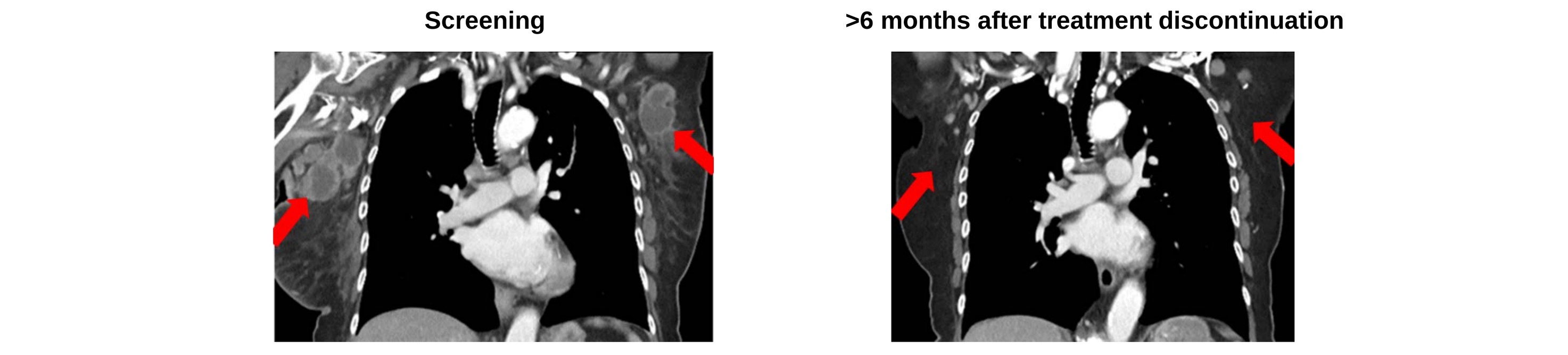


Figure 5. Durable response with cemiplimab in an 86-year old with CSCC of trunk, metastatic to bilateral axillary lymph nodes

Immunohistochemistry

- A total of 17 of 21 evaluated tumors (81%) were positive (≥1%) for tumor expression of PD-L1 by immunohistochemistry **(Table 4)**.
- There was no apparent association between PD-L1 immunohistochemistry results and objective responses.

Table 4. Tumor PD-L1 expression by immunohistochemistry using Dako 22C3 clone

Tumor PD-L1	Total	CR	PR	SD	PD	NE	ORR†
	Number of patients						
≥50%	8	0	3‡	3	2	0	38% (3/8)‡
≥1–49%	9	1	4	0	2	2	56% (5/9)
<1%	4	0	2	1	1	0	50% (2/4)

†5 patients not evaluated by immunohistochemistry: 1 CR, 1 PR, 2 SD, 1 PD; ‡Includes 1 unconfirmed PR. NE, not evaluable.

Conclusions

- This is the first prospective study of a PD-1 inhibitor in patients with advanced CSCC.
- Cemiplimab was generally well tolerated in CSCC in this predominantly older population.
- Both locally advanced and mCSCC are highly responsive to cemiplimab (combined ORR 46.2%), and durability is emerging.
- Eighty-one percent of pre-treatment tumor samples were PD-L1 positive.
- A unifying characteristic of cutaneous malignancies appears to be responsiveness to immune checkpoint inhibition.
- A phase 2 study is ongoing in patients with unresectable locally advanced and mCSCC (NCT02760498).

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