Disclosures

- **Dr. Kyriakos Papadopoulos has received research support from Abbvie, MedImmune, Daiichi Sankyo, GlaxoSmithKline, Regeneron, Sanofi, ARMO BioSciences, ArQule, Amgen, Calithera Biosciences, Curagenix, Incyte, Merck, Peloton Therapeutics, 3D Medicines, Formation Biologics, EMD Serona**

REGN2810, A Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy

Kyriakos Papadopoulos,[1] Taofeek Owonikoko,[2] Melissa Johnson,[3] Irene Braña,[4] Marta Gil Martin,[5] Raymond Perez,[6] Victor Moreno,[7] April Salama,[8] Emiliano Calvo,[9] Nelson Yee,[10] Howard Safran,[11] Antonio Gonzalez Martin,[12] Raid Aljumaily,[13] Daruka Mahadevan,[14] Kosalai Mohan,[15] Chetachi Emeremni,[15] Elizabeth Stankevich,[15] Israel Lowy,[15] Matthew Fury,[15] Jade Homsi[16]

[1]South Texas Accelerated Research Therapeutics, San Antonio, TX, USA; [2]Emory Winship Cancer Institute, Atlanta, GA, USA; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]Vall D'Hebron Institute of Oncology, Barcelona, Spain; [5]Institut Català d'Oncologia, Barcelona, Spain; [6]Unversity of Kansas, Fairway, KS, USA; [7]START Madrid Fundacion Jimenez Diaz, Madrid, Spain; [8]Duke University Medical Center, Durham, NC, USA; [9]START Madrid, Hospital Madrid Norte Sanchinarro, Madrid, Spain; [10]Penn State Cancer Institute, Hershey, PA, USA; [11]Miriam Hospital, Providence, RI, USA; [12]MD Anderson Cancer Center, Madrid, Spain; [13]University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [14]University of Arizona Cancer Center, Tucson, AZ, USA; [15]Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA; [16]Banner MD Anderson Cancer, Gilbert, AZ, USA.

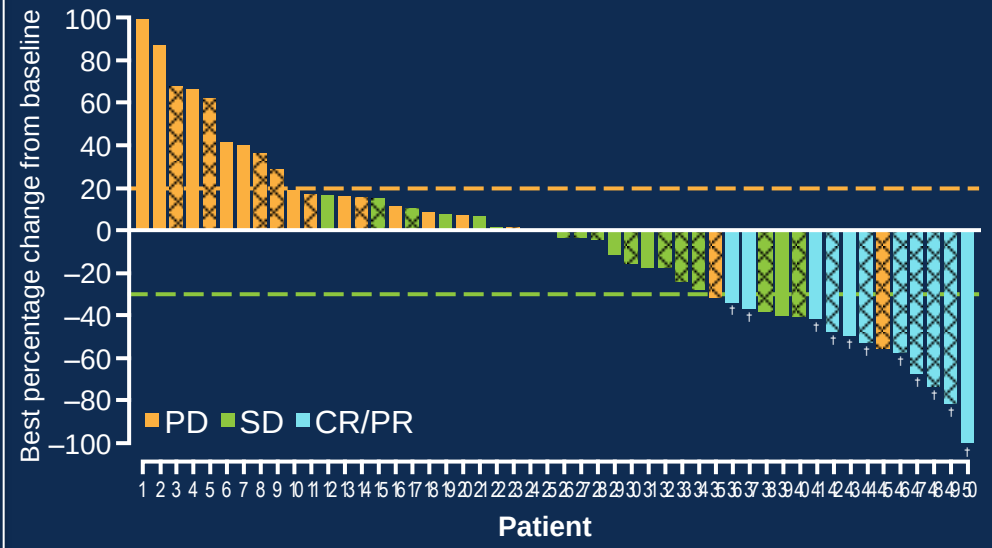
PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented by: Kyri Papadopoulos

REGN2810 (Anti-PD-1): Phase 1 Dose Escalation

- REGN2810 is a human IgG4 mAb directed against PD-1[1]
- Phase 1 results from first 60 patients with advanced solid tumors:[1]
  - No DLTs; most common treatment-related AEs: fatigue (28%), arthralgia (12%), and nausea (12%)
  - Overall response rate: 18%
- 3 mg/kg REGN2810 Q2W selected for further study in Expansion Cohorts
- As of 27 April 2017, 392 patients have been enrolled in the Phase 1 study

Best percentage reduction from baseline in tumor burden during study period: all treatment groups[1]



†Patients with confirmed CR or PR. Unhatched boxes represent patients who did not receive hfRT, hatched boxes represent patients who received hfRT.
AEs, adverse events; CR, complete response; DLTs, dose-limiting toxicities; hfRT, hypofractionated radiation therapy; IgG4, immunoglobulin G4; PR, partial response; Q2W, every two weeks; PD-1, programmed cell death 1.

1. Papadopoulos KP et al. *J Clin Oncol.* 2016:34 (suppl; abstr 3024).

Cutaneous Squamous Cell Carcinoma (CSCC)

- 2nd most common skin cancer in US[1]
- Risk factors: UV exposure, advanced age, immunosuppression[2]
  - Male predominance; median age: 71 years[3]
- Surgical cure rate >95% in early stage disease
- Small percentage of patients develop unresectable locally advanced or metastatic CSCC
  - US Mortality: 3,900–8,800/year[1]

CSCC, cutaneous squamous cell carcinoma; UV, ultraviolet.

1. Karia PS et al. *J Am Acad Dermatol*. 2013;68:957–66; 2. Stratigos A et al. *Eur J Cancer.* 2015;51:1989–2007;
3. Karia PS et al. *J Clin Oncol*. 2014;32:327–34.

Rationale for PD-1 inhibition with REGN2810 in CSCC

- No widely accepted standard of care systemic therapy for locally advanced or metastatic CSCC[1]
  - Conventional cytotoxic chemotherapy can induce tumor responses, but often is poorly tolerated among older patients with CSCC
  - Cetuximab: single arm trial (n=36) → median OS was 8.1 months[2]

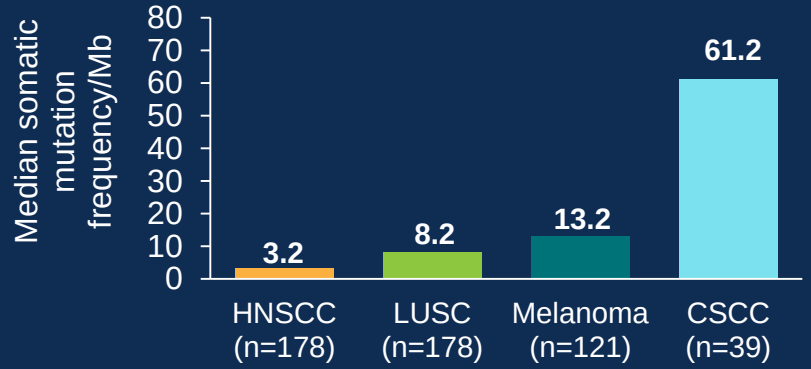
- In phase I dose escalation study of REGN2810, a durable radiologic complete response to REGN2810 was achieved in a CSCC patient[3,4]

CSCC, cutaneous squamous cell carcinoma; OS, overall survival; PD-1, programmed cell death 1.

1. Cranmer LD et al. *The Oncologist*, 2010;15:1320–8; 2. Maubec E et al. *J Clin Oncol,* 2011;29:3419–26;
3. Falchook GS et al. *J Immunother Cancer*, 2016:4:50; 4. Papadopoulos KP et al. *J Clin Oncol.* 2016:34 (suppl; abstr 3024).

Immunologic Rationale for REGN2810 in CSCC

- Higher mutation burden than any tumor type in The Cancer Genome Atlas (TCGA)[1]



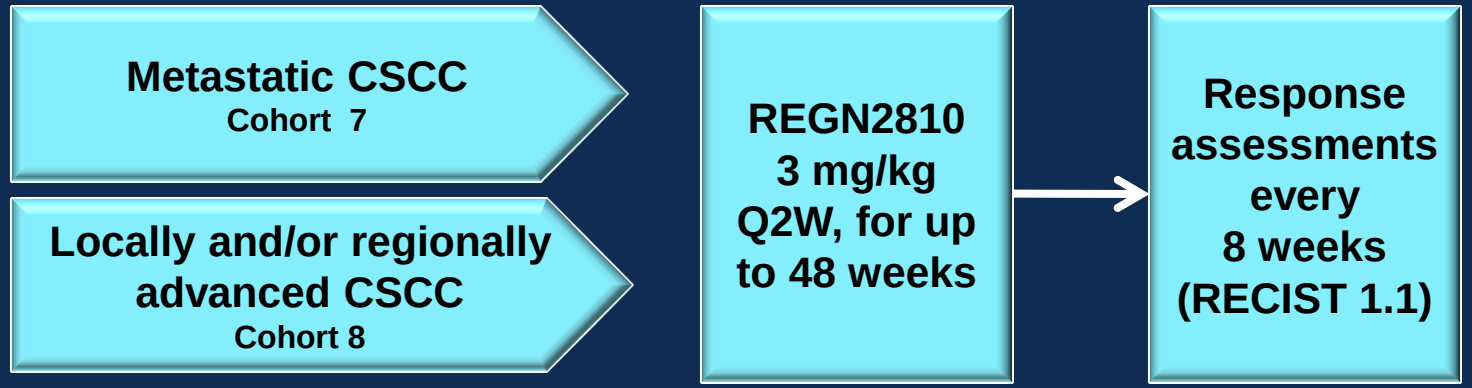
- Immunosuppression is a well-described risk factor for CSCC (especially in solid organ transplant patients)[2]
- PD-L1 expression has been associated with high risk disease[3]

CSCC tumors may therefore be responsive to PD-1 checkpoint blockade

CSCC, cutaneous squamous cell carcinoma; HNSCC, head and neck squamous cell cancer; LUSC; lung squamous carcinoma; PD-1, programmed death 1.

1. Pickering CR et al. *Clin Cancer Res*. 2014;15:6582–92; 2. Euvrard E et al. *New Engl J Med*. 2003;348:1681–91; 3. Slater NA, Googe PB *J Cutan Pathol* 2016;43:663–70.

Phase 1 Open-Label REGN2810 Study:
CSCC Expansion Cohorts (NCT02383212)



Co-primary objectives:

- To characterize the safety and tolerability of IV REGN2810, 3 mg/kg
- To evaluate the efficacy of REGN2810 by measuring ORR

Research tumor biopsies were taken at screening and Day 29±3.

CSCC, cutaneous squamous cell carcinoma; IV, intravenous; ORR, overall response rate; Q2W, every two weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

Selected Inclusion Criteria

- ECOG Performance Status of 0 or 1
- Measureable disease by RECIST 1.1
- Adequate organ function (bone marrow, kidney, liver)
- Metastatic CSCC (M1): Expansion Cohort 7
- Unresectable locally and/or regionally advanced CSCC (M0): Expansion Cohort 8:
  - Acceptable reasons for surgery to be deemed inappropriate:
    - 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

CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria In Solid Tumors.

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 (>10mg prednisone daily or equivalent)
- Systemic antitumor treatment within 4 weeks of initial dose of REGN2810
- History of solid organ transplant
- Tumors of lip or eyelid not eligible for CSCC cohorts

CSCC, cutaneous squamous cell carcinoma.

Patient Characteristics

	Metastatic CSCC (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 PS, 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)

CSCC, cutaneous squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Data cut-off date: 27 April 2017

Exposure to REGN2810

	Metastatic CSCC (N=10)	Locally advanced CSCC (N=16)	Overall (N=26)
Number of doses of study drug, 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)

CSCC, cutaneous squamous cell carcinoma.

Data cut-off date: 27 April 2017

TEAEs in Patients with Metastatic or Locally Advanced CSCC (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)
AST elevation	1 (3.8)	1 (3.8)
ALT 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
- Two deaths within 30 days of last dose of study drug, both considered unrelated to study drug

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAEs, treatment-emergent adverse events.

Data cut-off date: 27 April 2017

Investigator Assessed Preliminary Response Rate by RECIST 1.1 is 46.2% (ITT Population)

Investigator assessment	Metastatic (N=10), n (%)	Locally advanced (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)

ORR (CR + PR + one unconfirmed PR) = 46.2% (12/26 patients; 95% CI: 26.6–66.6)
DCR (ORR + SD) = 69.2% (18/26 patients; 95% CI: 48.2–85.7)

†Includes 5 confirmed partial responses and 1 unconfirmed partial response.
CR, complete response; DCR, disease control rate; ITT, intention-to-treat; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria In Solid Tumors.

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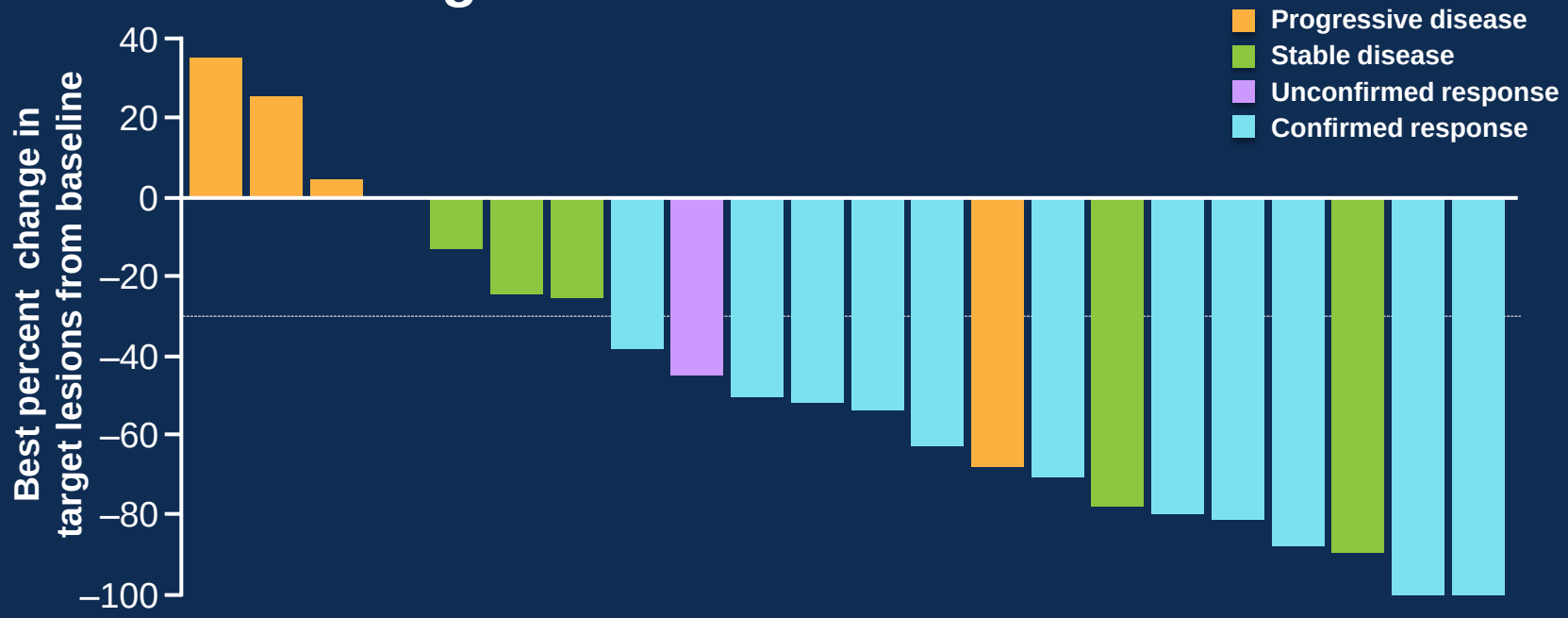
Data cut-off date: 27 April 2017

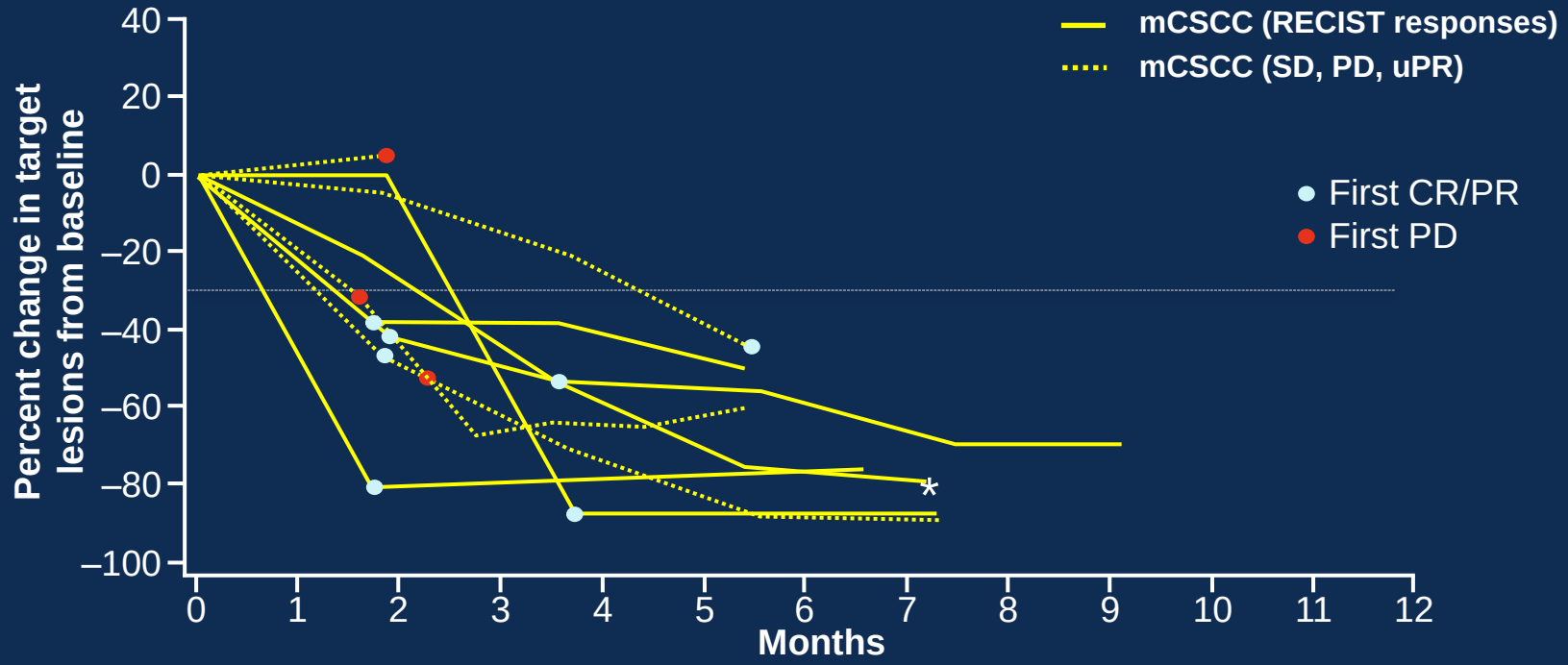
Clinical Activity in All Patients with At Least One Response Evaluation of Target Lesions



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)

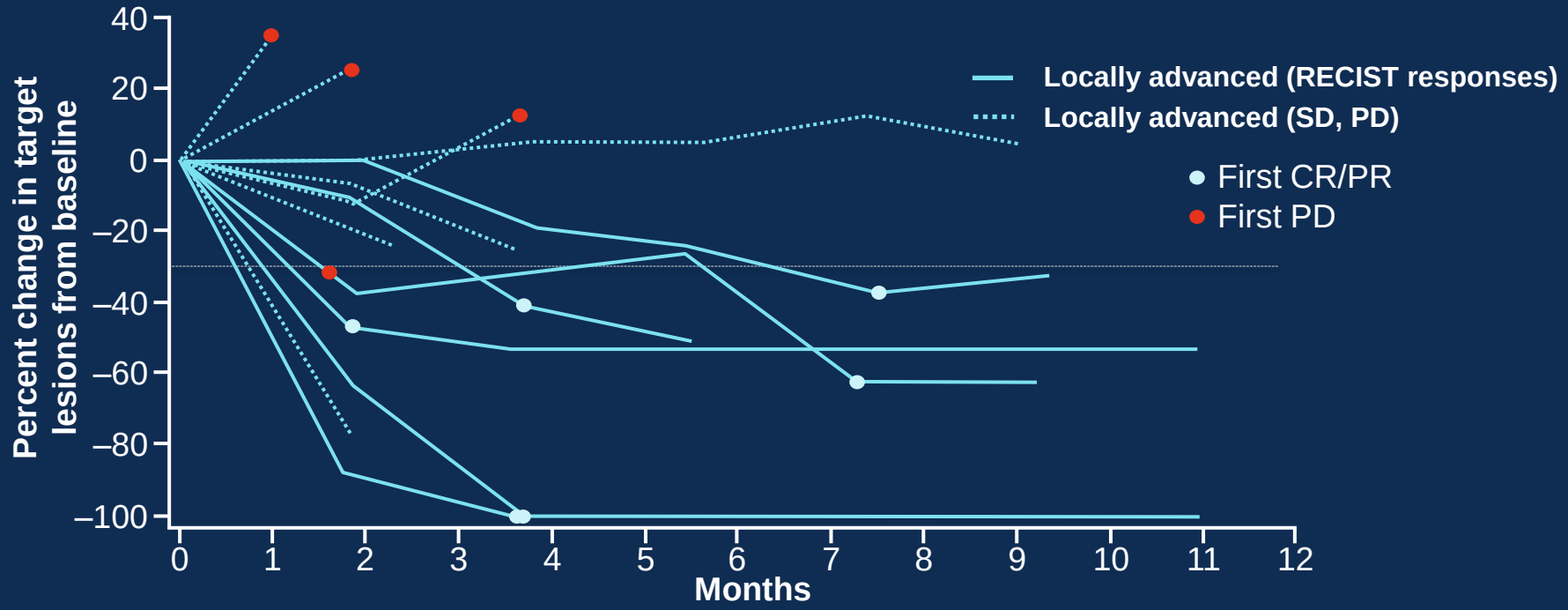
REGN2810 Produced Rapid, Deep and Durable Tumor Reductions in Target Lesions (Cohort 7)



*Patient progressed at subsequent assessment; however, the sum of target lesions are not evaluable.
CR, complete response; mCSCC, metastatic cutaneous squamous cell carcinoma;
PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors;
uPR, unconfirmed partial response; SD, stable disease.

Data cut-off date: 27 April 2017

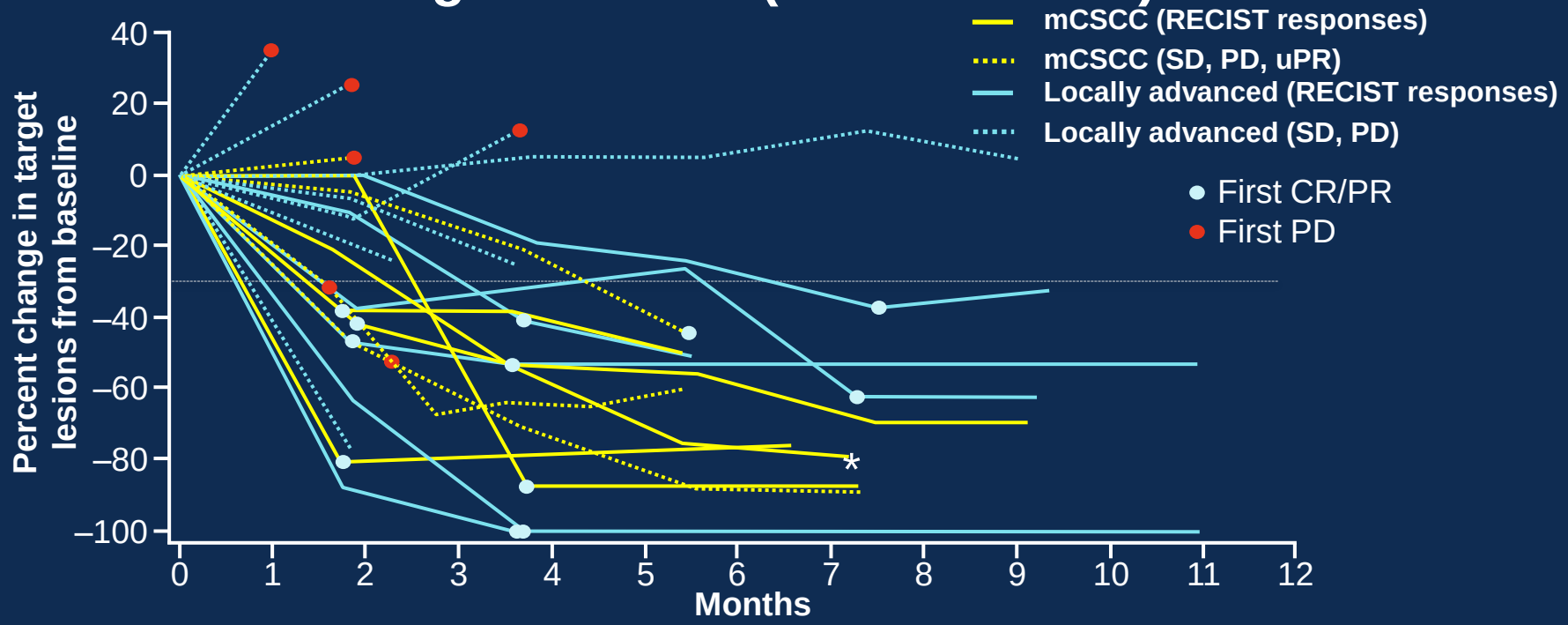
REGN2810 Produced Rapid, Deep and Durable Tumor Reductions in Target Lesions (Cohort 8)



CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Data cut-off date: 27 April 2017

REGN2810 Produced Rapid, Deep and Durable Tumor Reductions in Target Lesions (Both Cohorts)

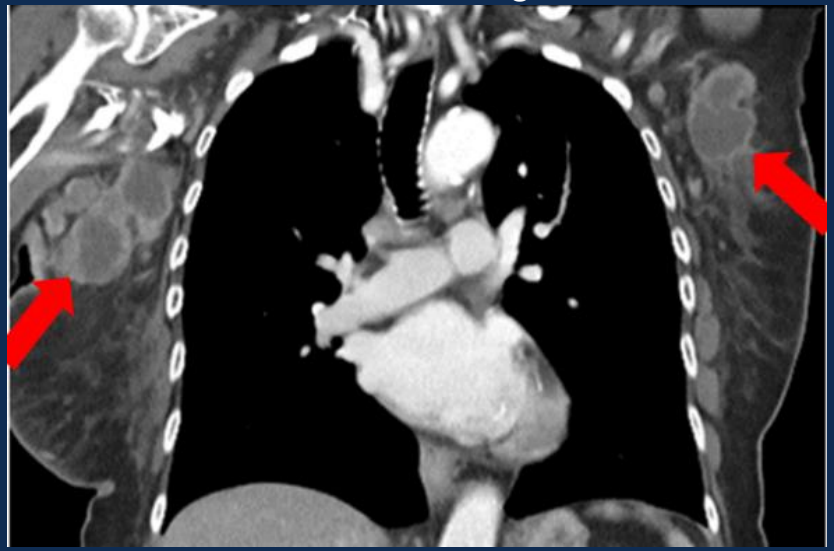


*Patient progressed at subsequent assessment; however, the sum of target lesions are not evaluable.
CR, complete response; mCSCC, metastatic cutaneous squamous cell carcinoma;
PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors;
uPR, unconfirmed partial response; SD, stable disease

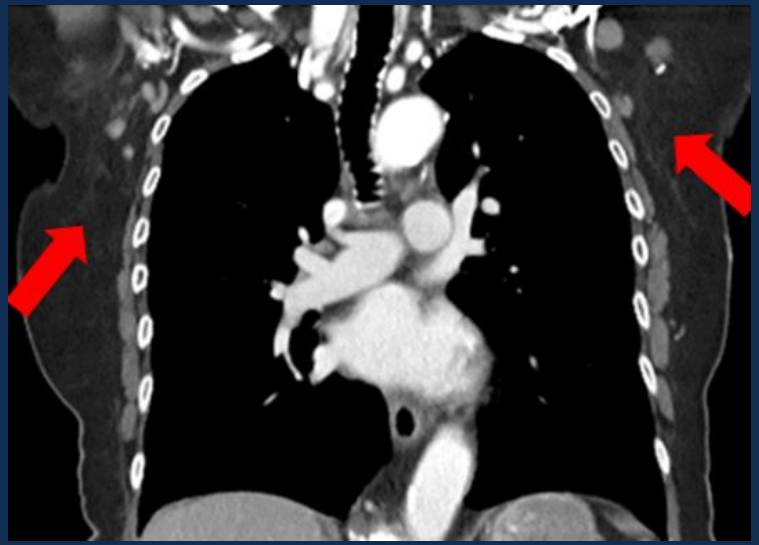
Data cut-off date: 27 April 2017

Durable Response with REGN2810 in an 86-Year Old with CSCC of Trunk, Metastatic to Bilateral Axillary Lymph Nodes

Screening



>6 months after treatment discontinuation



- REGN2810 discontinued due to AE (rash) after 3 doses
- Patient continues to maintain response >6 months after discontinuation

AE, adverse event; CSCC, cutaneous squamous cell carcinoma.

REGN2810 is Active Across All PD-L1 Strata in CSCC

(Tumor PD-L1 expression by immunohistochemistry; Dako 22C3 clone)

81% (17/21) of evaluated tumors were positive (≥1%) for tumor expression of PD-L1 by IHC

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)

No apparent association between PD-L1 IHC results and objective responses

†5 patients not evaluated by IHC: 1 CR, 1 PR, 2 SD, 1 PD

‡Includes one unconfirmed PR

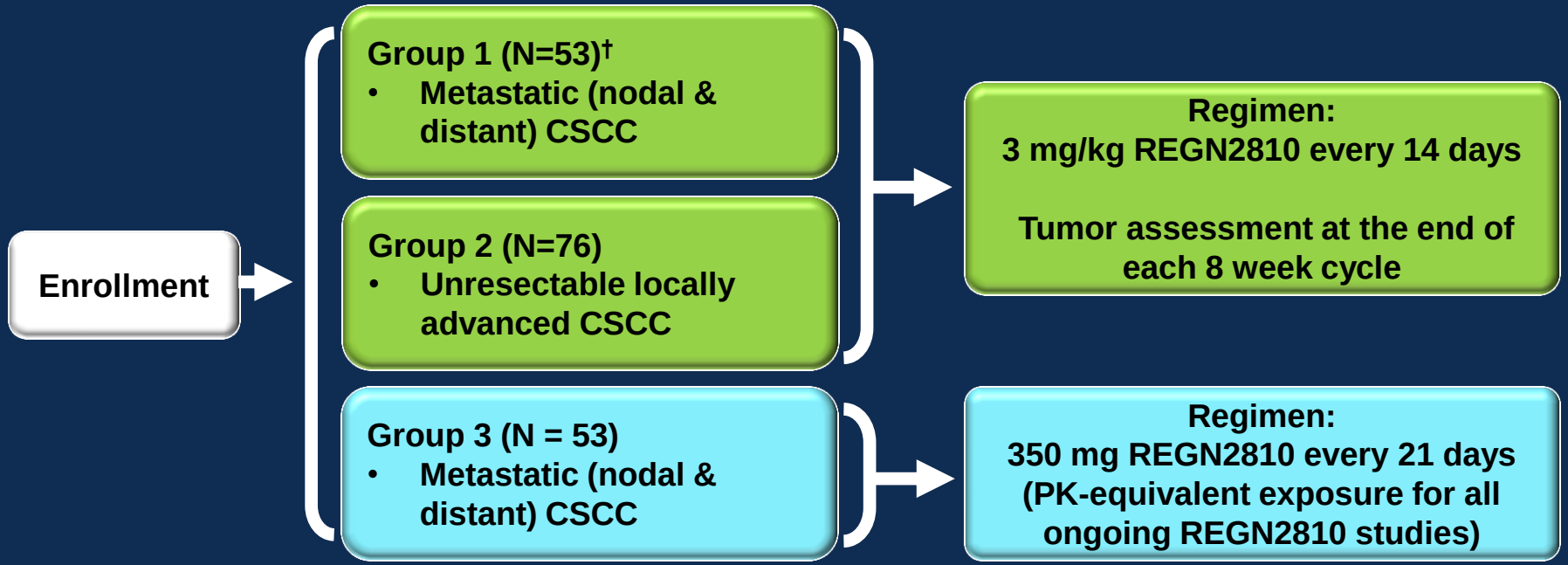
CR, complete response; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; uPR, unconfirmed partial response; ORR, overall response rate.

Summary and Conclusions

- This is the first prospective study of a PD-1 inhibitor in patients with advanced CSCC
- REGN2810 was generally well tolerated in CSCC in this predominantly older population
- Both locally advanced and metastatic CSCC are highly responsive to REGN2810 (combined ORR 46.2%), and durability is emerging
- 81% of pre-treatment tumor samples were PD-L1 positive
- A unifying characteristic of cutaneous malignancies appears to be responsiveness to immune checkpoint inhibition
- Phase 2 ongoing in patients with unresectable locally advanced and metastatic CSCC (NCT02760498)

CSCC, cutaneous squamous cell carcinoma; PD-1, programmed death 1; PD-L1, programmed death-ligand 1.

Ongoing Pivotal Phase 2 CSCC Study (NCT02760498)



Primary Endpoint: Objective Response Rate by Central Review in each Group

Study Sites Locations: US, Australia, Germany

†Fully enrolled.

CSCC, cutaneous squamous cell carcinoma; PK, pharmacokinetic.

Acknowledgments

- The patients and their families
- The investigators and study teams involved in this study
- The study was funded by Regeneron Pharmaceuticals, Inc and Sanofi
  - Thanks to Bo Gao, Frank Seebach, Laura Simpson, Ana Kostic, Usman Chaudhry, Wilson Caldwell, Minjie Feng, Dale LeSueur
- Medical writing support was funded by Regeneron