Health-Related Quality of Life (HRQL) in Patients with Advanced Cutaneous Squamous Cell Carcinoma (CSCC) Treated with Cemiplimab: Post Hoc Exploratory Analysis of a Phase 2 Clinical Trial

Michael R. Migden,[1] Danny Rischin,[2] Medha Sasane,[3] Vera Mastey,[4] Anna Pavlick,[5] Chrysalyne D. Schmults,[6] Zhen Chen,[4] Alexander Guminski,[7] Axel Hauschild,[8] Denise Bury,[9] Anne Lynn S. Chang,[10] Guilherme Rabinowits,[11] Sherrif Ibrahim,[12] Israel Lowy,[4] Matthew G. Fury,[4] Siyu Li,[13] Chieh-I Chen[4]

[1]Departments of Dermatology and Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [3]Sanofi, Bridgewater, NJ, USA; [4]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [5]Department of Medical Oncology, New York University Langone Medical Center, New York, NY, USA; [6]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [7]Department of Medical Oncology, Royal North Shore Hospital, St Leonards, Australia; [8]Department of Dermatology, University Hospital (UKSH), Kiel, Germany; [9]Sanofi, Cambridge, MA, USA [10]Department of Dermatology, Stanford University School of Medicine, CA, USA; [11]Department of Hematology/Oncology, Miami Cancer Institute/Baptist Health South Florida, Miami, FL, USA; [12]Department of Dermatology, Rochester Medical Center, Rochester, NY, USA; [13]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA

Synopsis

- Cutaneous squamous cell carcinoma (CSCC) is considered the second most common malignancy in the US, although its exclusion from national cancer registries has presented a barrier to epidemiologic characterization.[1]
  - Estimates suggest an incidence of around 1.5 million cases per year in the US.[2]
  - The incidence of CSCC is increasing yearly in the US.[3]
- Most CSCC patients have a favorable prognosis, but for the patients who are not amenable to curative surgery, palliative systemic therapy has been administered.[1]
- Cemiplimab is a programmed cell death (PD)-1 inhibitor that is indicated for treatment of CSCC in patients with metastatic (mCSCC) or locally advanced (laCSCC) disease not amenable to curative surgery or curative radiation.[4]
  - Cemiplimab demonstrated a robust durable clinical response and a safety profile consistent with other checkpoint inhibitors in a recent Phase 2 study (NCT02760498).[5–8]
  - Longer follow-up data from the Phase 2 study of cemiplimab in patients with advanced CSCC is presented in the poster titled "**Phase 2 Study of Cemiplimab in Patients with Advanced Cutaneous Squamous Cell Carcinoma (CSCC): Longer Follow-Up**", also available on the 2020 Fall Clinical Dermatology Conference platform.
  - No new safety signals emerged with longer follow-up. The most common treatment-emergent adverse events of any grade were fatigue (n=67, 34.7%), diarrhea (n=53, 27.5%), and nausea (n=46, 23.8%).
- The Phase 2 trial included the European Organisation for Research and Treatment of Cancer (EORTC) cancer-specific 30-item questionnaire (QLQ-C30)[9] as a measure of patient-reported health-related quality of life (HRQL).
- Pain is an important and bothersome symptom in the diagnosis and treatment of CSCC from the patient and clinical perspectives.[10]

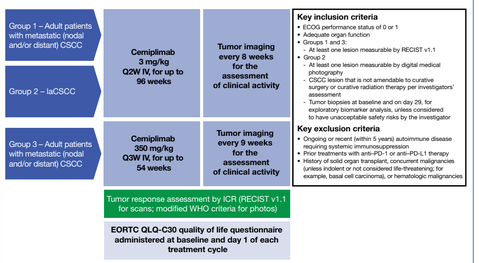
Objective

- This post hoc exploratory analysis examined the QLQ-C30 data from a Phase 2 clinical trial (NCT02760498) to determine the effects of cemiplimab treatment on HRQL and pain.

Methods

- For inclusion in the Phase 2, non-randomized, global, pivotal trial of cemiplimab (**Figure 1**), adults with invasive CSCC not amenable to curative surgery or curative radiotherapy according to the investigator were also required to have ≥1 lesion, Eastern Cooperative Oncology Group (ECOG) performance status ≤1, and life expectancy >12 weeks.
  - Adult patients (N=193) received intravenous (IV) cemiplimab 3 mg/kg every 2 weeks (Q2W; mCSCC n=59; laCSCC n=78) for 12 treatment cycles or 350 mg every 3 weeks (Q3W; mCSCC n=56) for six treatment cycles.
  - Treatment cycle length was 8 weeks for Groups 1 and 2 and 9 weeks for Group 3.
  - The primary efficacy endpoint was objective response rate, defined as the proportion of patients with complete or partial response.
- At baseline and day 1 of each treatment cycle until progression, patients were administered the QLQ-C30.[9]

Figure 1. Study design



ICR, independent central review; PD-L1, PD-ligand 1; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization.

- The QLQ-C30 assesses HRQL over the past week among cancer patient populations using a global health status/HRQL scale, five functional scales, and nine symptom scales/items.
  - Functional scales include physical, role, cognitive, emotional, and social functioning.
  - Symptom scales/items include fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.
  - Scores range from 0 to 100; high scores on functional scales and low scores on symptom scales reflect better outcomes.
  - A change ≥10 points from baseline is considered clinically meaningful.[11]
- The full analysis set included patients who had baseline and at least one post-baseline assessment for any QLQ-C30 scale.
- Descriptive statistics were used to summarize HRQL scores over time (only pain and global health status/HRQL scores are shown).
- Mixed effects repeated measures models (MMRM) were used to estimate the mean treatment effect (change from baseline while accounting for missing data) for all QLQ-C30 scales.
  - The model included fixed effects of treatment, visit, treatment-by-visit interaction, and baseline value of the specified individual item.
  - Results are expressed as the least squares (LS) mean and standard error (SE).
- A responder analysis was also conducted at cycle 6 and cycle 12 based on evaluation of average change from baseline among patients who had baseline scores that allowed a ≥10-point change.
  - A responder was defined as a patient who achieved an average 10-point increase in functional scale scores and 10-point decline in symptom scale scores.

Results

Patient population and baseline scores

- A total of 193 adult patients were enrolled in the study, and demographic characteristics were generally similar across the treatment groups (**Table 1**).

Table 1. Demographic and clinical characteristics of the full analysis set

Variable	Total (N=193)	mCSCC 350 mg Q3W (n=56)	mCSCC 3 mg/kg Q2W (n=59)	laCSCC 3 mg/kg Q2W (n=78)
Age, mean ± SD, years	71.1 ± 11.4	69.7 ± 12.8	70.4 ± 10.1	72.5 ± 11.2
≥65 years, n (%)	144 (74.6)	42 (75.0)	43 (72.9)	59 (75.6)
Male, n (%)	161 (83.4)	48 (85.7)	54 (91.5)	59 (75.6)
ECOG performance status, n (%)				
0	86 (44.6)	25 (44.6)	23 (39.0)	38 (48.7)
1	107 (55.4)	31 (55.4)	36 (61.0)	40 (51.3)
Primary site, n (%)				
Head and neck	131 (67.9)	31 (55.4)	38 (64.4)	62 (79.5)
Other	62 (32.1)	25 (44.6)	21 (35.6)	16 (20.5)
Prior cancer-related systemic therapy, n (%)	65 (33.7)	20 (35.7)	33 (55.9)	12 (15.4)
Prior cancer-related radiotherapy, n (%)	131 (67.9)	38 (67.9)	50 (84.7)	43 (55.1)

SD, standard deviation.

- Baseline scores for QLQ-C30 indicated generally moderate to high levels of functioning and moderate to low symptom burden (**Table 2**).
  - Pain is of importance as a symptom in patients with advanced CSCC, and the baseline pain score of patients with advanced CSCC receiving cemiplimab (29.8 ± 30.4) was worse than that reported by patients with advanced head and neck cancer (24.9 ± 26.3; n=1722) and the general population (20.9 ± 27.6; n=7802) in the literature[12]; comparisons with both groups were significant, $P<0.05$ and $P<0.0001$, respectively.

Table 2. Baseline scores and change from baseline (MMRM) in patients in the full analysis set who had baseline and post-baseline assessments on each QLQ-C30 scale or item

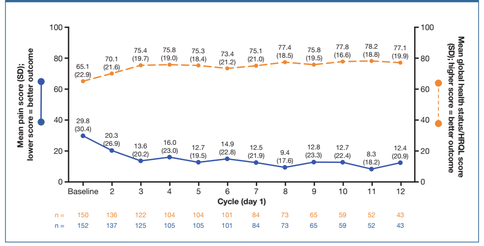
QLQ-C30 scale/item	Baseline, mean ± SD (n)	LS mean change ± SE (n)	
		Cycle 3	Cycle 12
Global health status/HRQL	65.1 ± 22.9 (150)	7.8 ± 1.6 (122)**	11.1 ± 2.6 (43)**
Functional scales†			
Physical function	80.1 ± 22.8 (151)	1.1 ± 1.3 (124)	4.0 ± 2.1 (43)
Role function	75.8 ± 30.0 (151)	0.4 ± 2.1 (123)	5.6 ± 3.4 (43)
Emotional function	80.2 ± 21.2 (151)	4.2 ± 1.3 (123)*	5.3 ± 2.2 (43)*
Cognitive function	83.4 ± 22.2 (151)	1.7 ± 1.4 (123)	2.5 ± 2.3 (43)
Social function	74.4 ± 31.8 (150)	5.3 ± 1.8 (122)*	8.6 ± 3.0 (43)*
Symptoms‡			
Fatigue	30.2 ± 24.6 (152)	−2.8 ± 1.7 (125)	−4.8 ± 2.8 (43)
Nausea/vomiting	4.6 ± 12.2 (152)	−1.6 ± 0.8 (125)*	−2.9 ± 1.3 (43)*
Pain	29.8 ± 30.4 (152)	−11.5 ± 1.9 (125)**	−14.3 ± 3.1 (43)**
Dyspnea	12.9 ± 23.4 (152)	0.7 ± 1.7 (125)	1.5 ± 2.9 (43)
Insomnia	27.4 ± 28.0 (151)	−9.1 ± 2.0 (123)**	−17.4 ± 3.3 (43)**
Appetite loss	19.5 ± 29.3 (152)	−8.4 ± 1.6 (124)**	−13.7 ± 2.7 (43)**
Constipation	13.6 ± 24.1 (152)	−4.5 ± 1.5 (125)*	−11.2 ± 2.5 (43)**
Diarrhea	4.9 ± 13.6 (150)	3.6 ± 1.4 (121)*	0.6 ± 2.3 (43)
Financial difficulty	19.1 ± 30.7 (150)	0.5 ± 2.0 (122)	−3.4 ± 3.3 (43)

**$P<0.001$ and *$P<0.05$ versus baseline. †Higher scores reflect better outcomes. ‡Lower scores reflect better outcomes.

Longitudinal analysis

- Among the symptom scales and items, a marked improvement in pain score was observed as early as cycle 2 (**Figure 2**). The initial clinically meaningful improvement (≥10 points) in pain score at cycle 3 (LS mean [SE] change −11.5 [1.9]; $P<0.0001$) was maintained during study treatment to cycle 12 (LS mean [SE] change −14.3 [3.1]; $P<0.0001$) (**Table 2**).
  - At cycle 3, significant improvements from baseline were also observed for symptoms of insomnia, appetite loss, and constipation. At cycle 12, these improvements reached the clinically meaningful threshold (**Table 2**).
  - With the exception of a significant worsening of diarrhea at cycle 3 and a significant improvement of nausea/vomiting at cycle 12, all other domains/symptoms remained stable relative to baseline. By cycle 12, diarrhea remained stable relative to baseline.
- Among the functional scales, significant improvements were observed in emotional and social function at cycle 3 and cycle 12. All other functional scales remained stable relative to baseline (**Table 2**).
- For global health status/HRQL, significant improvement from baseline was observed at cycle 3. At cycle 12, this improvement reached the clinically meaningful threshold (LS mean [SE] change 11.1 [2.6]; $P<0.0001$) (**Table 2**).

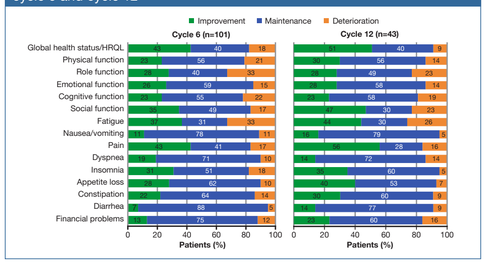
Figure 2. QLQ-C30 pain and global health status/HRQL scores by cycle



Responder analysis

- By cycle 6, the majority of patients experienced clinically meaningful (≥10 points) improvement or stability including pain (83%), nausea/vomiting (89%), diarrhea (95%), constipation (86%), and appetite loss (90%), as well as functional scales (77%–86%) (**Figure 3**).
  - These effects likely account for the clinically meaningful improvement or stability also reported on global health status/HRQL among the majority of patients (82%).
- At cycle 12, the majority of patients showed sustained improvement and stabilization across all symptoms and functional scales (74%–95%). Ninety-one percent of patients experienced clinically meaningful improvement or stability in global health status/HRQL scores at cycle 12 (**Figure 3**).
- The proportions of patients with clinically meaningful deterioration were generally low at both evaluated time points (**Figure 3**).
  - The highest rate of clinically relevant deterioration among the symptoms was observed for fatigue.

Figure 3. Proportion of patients reporting clinically meaningful change at cycle 6 and cycle 12



Study Limitations

- This was a non-randomized, single-arm, open-label study.
- The 10-point threshold considered indicative of a clinically meaningful change has not been validated for this specific patient population (i.e., advanced CSCC).

Summary and Conclusion

- In advanced CSCC patients, treatment with cemiplimab resulted in clinically meaningful reduction in pain as early as cycle 3 with maintenance of effect through cycle 12.
- Improvement in global health status/HRQL was observed as early as cycle 3 with clinically meaningful improvement seen by cycle 12.
- By cycle 6, the majority of patients experienced clinically meaningful improvement or stability in global health status/HRQL and functional status, while maintaining a low symptom burden.
- These results further support cemiplimab as a new standard of care option in the treatment of advanced CSCC.

References

1. Karia PS et al. *J Am Acad Dermatol*. 2013;68:957–966.
2. Rogers HW et al. *JAMA Dermatol*. 2015;151:1081–1086.
3. Que SK et al. *JAAD*. 2018;78:237–247.
4. Ahmed SR et al. *Expert Rev Clin Pharmacol*. 2019;12:947–951.
5. Migden MR et al. *N Engl J Med*. 2018;379:341–351.
6. Rischin D et al. *Ann Oncol*. 2019;30(suppl 5):v536–537.
7. Migden MR et al. *J Clin Oncol*. 2019;37(15 suppl):6015.
8. Migden MR et al. *Lancet Oncol*. 2020;21:294–305.
9. Aaronson NK et al. *J Natl Cancer Inst*. 1993;85:365–376.
10. Mills KC et al. *Arch Dermatol*. 2012;148:1422–1423.
11. Osoba D et al. *J Clin Oncol*. 1998;16:139–144.
12. Scott NW et al. EORTC QLQ-C30 Reference Values. 2nd ed. Brussels, Belgium: EORTC Quality of Life Group. 2008. Available at: www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf. [Accessed May 1, 2020].

Funding sources

Funding was provided by Regeneron Pharmaceuticals, Inc. and Sanofi.

Acknowledgments

The authors would like to thank the patients, their families, all other investigators, and all investigational site members involved in this study. The study was funded by Regeneron Pharmaceuticals, Inc. and Sanofi. Medical writing support was provided by E. Jay Bienen, PhD, and typesetting was provided by Kate Carolan, PhD, of Prime, Knutsford, UK, funded by Regeneron Pharmaceuticals, Inc. and Sanofi.
For any questions or comments, please contact Dr Michael R Migden, mrmigden@mdanderson.org

Disclosures

M. R. Migden reports honoraria and travel expenses from Regeneron Pharmaceuticals, Inc., Sanofi, Novartis, Genentech, Eli Lilly, and Sun Pharma; and institutional research funding from Regeneron Pharmaceuticals, Inc., Novartis, Genentech, and Eli Lilly. **D. Rischin** reports institutional research grant and funding from Regeneron Pharmaceuticals, Inc., Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, and GlaxoSmithKline; uncompensated scientific committee and advisory board from Merck Sharp & Dohme, Regeneron Pharmaceuticals, Inc., Sanofi, GlaxoSmithKline, and Bristol-Myers Squibb; travel and accommodation from Merck Sharp & Dohme and GlaxoSmithKline. **A. Pavlick** reports honoraria and consulting or advisory roles at Bristol-Myers Squibb, Merck, Regeneron Pharmaceuticals, Inc., Array, Novartis, Seattle Genetics, and Amgen; research funding from Bristol-Myers Squibb, Merck, Regeneron Pharmaceuticals, Inc., Celldex, and Forance; travel, accommodation, and expenses from Regeneron Pharmaceuticals, Inc., Array, and Seattle Genetics. **C.D. Schmults** is a steering committee member for Castle Biosciences; a steering committee member and consultant for Regeneron Pharmaceuticals, Inc.; a consultant for Sanofi; has received research funding from Castle Biosciences, Regeneron Pharmaceuticals, Inc., Novartis, Genentech, and Merck, and is a chair for the National Comprehensive Cancer Network. **A. Guminski** reports personal fees and non-financial support (advisory board and travel support) from Bristol-Myers Squibb and Sun Pharma; personal fees (advisory board) from Merck KGaA, Eisai, and Pfizer; non-financial (travel) support from Astellas; and clinical trial unit support from PPD Australia. **A. Hauschild** reports institutional grants, speaker's honoraria, and consultancy fees from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme/Merck, Pierre Fabre, Provectus, Roche, and Novartis; institutional grants and consultancy fees from Merck Serono, Philogen, and Regeneron Pharmaceuticals, Inc.; and consultancy fees from OncoSec. **A.L.S. Chang** reports consulting and advisory roles at Regeneron Pharmaceuticals, Inc. and Merck; research funding from Regeneron Pharmaceuticals, Inc., Novartis, Galderma, and Merck. **G. Rabinowits** reports consulting and advisory roles for EMD Serono Pfizer, Sanofi, Regeneron Pharmaceuticals Inc., Merck and Castle, and stock/other ownership interests from Syros Pharmaceuticals and Regeneron Pharmaceuticals, Inc. **S. Ibrahim** reports research funding from Regeneron Pharmaceuticals, Inc. and Castle, speakers' bureau from Genentech, and travel and accommodation expenses from Regeneron Pharmaceuticals, Inc. and Genentech. **M. Sasane, V. Mastey, Z. Chen, D. Bury, I. Lowy, M.G. Fury, S. Li,** and **C-I Chen** are employees and shareholders of Regeneron Pharmaceuticals, Inc.

Presented at the 2020 Fall Clinical Dermatology Conference, October 29–November 1, Virtual Scientific Meeting (encore of ASCO 2020 poster presentation).