Phase I Trial of Cemiplimab, Radiotherapy, Cyclophosphamide, and Granulocyte Macrophage Colony-Stimulating Factor in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier**: NCT02383212
- **Sponsor**: Regeneron Pharmaceuticals and Sanofi
- **Principal Investigator**: Hani Babiker
- **IRB Approved**: Yes

LESSONS LEARNED

- Cemiplimab in combination with radiation therapy, cyclophosphamide, and granulocyte macrophage colony-stimulating factor did not demonstrate efficacy above what can be achieved with other PD-1 inhibitor monotherapies in patients with refractory and metastatic head and neck squamous cell carcinoma.
- The safety profile of cemiplimab combination therapy was consistent with previously reported safety profiles of cemiplimab monotherapy. No new safety signal was observed.

ABSTRACT

Background. Refractory and metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) generally does not respond to PD-1 inhibitor monotherapy. Cemiplimab is a human anti–PD-1 monoclonal antibody. An expansion cohort enrolled patients with R/M HNSCC in a phase I study combining cemiplimab plus radiation therapy (RT), cyclophosphamide, and granulocyte macrophage colony-stimulating factor (GM-CSF).

Methods. Patients with R/M HNSCC refractory to at least first-line therapy and for whom palliative RT is clinically indicated received cemiplimab plus RT, cyclophosphamide, and GM-CSF. The co-primary objectives were the safety, tolerability, and efficacy of cemiplimab plus RT, cyclophosphamide, and GM-CSF in 15 patients with R/M HNSCC.

Results. Fifteen patients were enrolled. Patients discontinued treatment due to progression of disease. The most common treatment-emergent adverse events (TEAEs) of any grade were fatigue (40.0%), constipation (26.7%), and asthenia, dyspnea, maculo-papular rash, and pneumonia (each 20%). The only grade ≥3 TEAE that
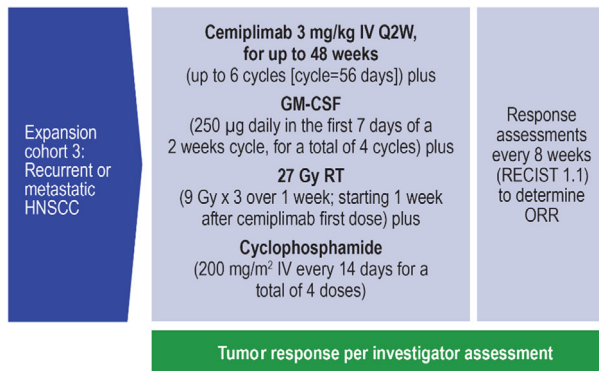
Figure 1. Study design: HNSCC expansion cohort.
Abbreviations: HNSCC, head and neck squamous cell carcinoma; ORR, overall response rate; Q2W, every 2 weeks; RT, radiation therapy.
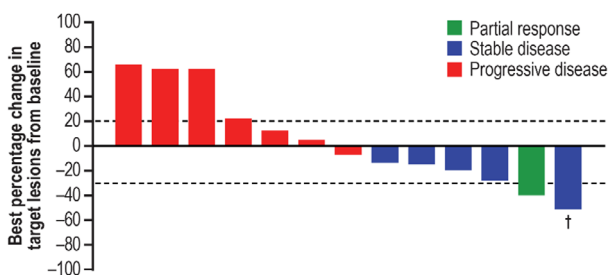

Figure 2. Clinical activity of tumor response to cemiplimab combination therapy per investigator assessment. Plot shows the best percentage change in the sum of target lesion diameters from baseline for the 13 patients who had at least one response evaluation. Lesion measurements after progression were excluded. The horizontal lines indicate criteria for partial response (≥30% decrease in the sum of target lesion diameters) and progressive disease (≥20% increase in the target lesion diameters), respectively. †, Partial response was not confirmed in this patient; therefore, the tumor response was downgraded to stable disease.

occurred in two patients was pneumonia (13.3%). By investigator assessment, there was one partial response (6.7%); disease control rate was 40.0% (95% confidence interval [CI], 16.3–67.7; five patients with stable disease); seven patients had progressive disease, and two were not evaluable. Median progression-free survival by investigator assessment was 1.8 months (95% CI, 1.7–4.7).
Conclusion. The regimen demonstrated tolerability but not efficacy above that which can be achieved with anti–PD-1 inhibitor monotherapy for R/M HNSCC. *The Oncologist* 2021;26:e1508–e1513

DISCUSSION

Treatment with anti–PD-1 inhibitor in R/M HNSCC has demonstrated modest efficacy with only a slight improvement in median overall survival and overall response rate (ORR) when compared with chemotherapy alone [1]. Hence, combinations with adjunct immunostimulatory drugs and RT to achieve higher responses are strategies currently under investigation. We sought to investigate the combination of cemiplimab plus RT, cyclophosphamide, and GM-CSF in this cohort of patients. This was one expansion cohort of a dose-escalation phase I trial of REGN2810 (cemiplimab) in patients with advanced malignancies (Figs. 1 and 2). There was a total of 26 cohorts. RT augments immunotherapy drugs via the release of soluble tumor cell antigens from killed cells, increases tumor cell surface expression of antigens that mediate T-cell recognition, and increases the efficiency of antigen-presenting cells [2, 3]. However, regulatory T cell–mediated immunosuppression caused by RT can be an obstacle for a proimmune tumor microenvironment. Thus cyclophosphamide, which has been shown to abrogate this effect, might improve the efficacy of the anti–PD-1 plus RT combination [4]. The addition of GM-CSF improves dendritic cell maturation and antigen presentation of released cancer antigens and has demonstrated efficacy in advanced refractory solid tumors [5, 6]. These observations generated the hypothesis for the combination outlined in this clinical trial. Our trial demonstrated the tolerability and the safety of the combination with the most common adverse events being fatigue, constipation, and grade 3 pneumonia and dehydration. The ORR was 6.7%, and the DCR was 40%, which is similar to what is achieved with single agent anti–PD-1 monotherapy [1]. One explanation for the failure of this combination to exceed single agent data may be the enrollment of patients who were heavily pretreated, with 100% of patients receiving platinum-based chemotherapy, 60% monoclonal antibodies, 60% pyrimidine analogue, 53% taxanes, and 93.3% prior radiotherapy. This can lead to a general immunosuppressive state, potentially abrogating the immunostimulatory effect of the regimen. Moreover, patients received only 7 days of radiation as opposed to longer courses of radiation administered in previous trials demonstrating some efficacy [6]. A future potential avenue to consider is studying this regimen in earlier lines of therapy with a longer duration of RT as opposed to a shorter duration aimed at palliative treatment and potentially using a different schedule of the drugs.

TRIAL INFORMATION	
Disease	Head and neck cancers
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	One prior regimen
Type of Study	Phase I, expansion cohort
Primary Endpoint	Safety
Additional Details of Endpoints or Study Design	Co-primary objectives of the HNSCC expansion cohort were to (a) characterize the safety, tolerability, and dose-limiting toxicities (DLTs) of cemiplimab in combination with RT, cyclophosphamide, and GM-CSF and (b) evaluate the efficacy of cemiplimab in combination with RT, cyclophosphamide, and GM-CSF by measuring ORR.
Investigator's Analysis	Level of activity did not meet planned endpoint

DRUG INFORMATION

Cemiplimab

Generic Name	Cemiplimab
Trade Name	Libtayo
Company Name	Cemiplimab (REGN2810)
Drug Type	Immunotherapy (PD-1 inhibitor)
Drug Class	Immune therapy
Dose	3 milligrams (mg) per kilogram (kg)
Route	i.v.
Schedule of Administration	Every 2 weeks for up to 48 weeks (up to six cycles [cycle = 56 days]).

GM-CSF

Generic Name	GM-CSF
Company Name	GM-CSF
Drug Type	Immunostimulatory
Drug Class	Immune therapy
Dose	250 mcg per m^2
Route	i.v.
Schedule of Administration	Daily in the first 7 days of a 2-week cycle, for a total of four cycles.

Cyclophosphamide

Generic Name	Cyclophosphamide
Trade Name	Cyclophosphamide
Company Name	
Drug Type	Alkylating chemotherapy
Drug Class	Alkylating agent
Dose	200 milligrams (mg) per squared meter (m^2)
Route	i.v.
Schedule of Administration	Every 14 days for a total of four doses. In addition to cemiplimab, GM-CSF, and cyclophosphamide treatment included palliative radiation (27 Gy: 9 Gy × 3 over 1 week, starting 1 week after first dose of cemiplimab).

PATIENT CHARACTERISTICS

Number of Patients, Male	9	
Number of Patients, Female	6	
Stage	Refractory/advanced/metastatic	
Age	Median (range): 62 (45–78) years	
Performance Status: ECOG	0 — 20% 1 — 80% 2 — 0 3 — 0 Unknown — 0	
Other	Median age, years (range)	62.0 (45–78)
	Male, *n* (%)	9 (60.0)
	ECOG performance status score, *n* (%)	
	0	3 (20.0)
	1	12 (80.0)

Any prior cancer-related systemic therapy, n (%)	15 (100.0)
Antineoplastic agents	15 (100.0)
Platinum compounds	15 (100.0)
Monoclonal antibodies	9 (60.0)
Pyrimidine analogues	9 (60.0)
Taxanes	8 (53.3)
Combination of antineoplastic agents	1 (6.7)
Other	2 (13.3)
Immunosuppressants	2 (13.3)
Any prior cancer-related radiotherapy, n (%)	14 (93.3)

PRIMARY ASSESSMENT METHOD

Title	Efficacy
Number of Patients Screened	15
Number of Patients Enrolled	15
Number of Patients Evaluable for Toxicity	15
Number of Patients Evaluated for Efficacy	13
Evaluation Method	RECIST version 1.1
Response Assessment CR	n = 0 (0%)
Response Assessment PR	n = 1 (6.7%)
Response Assessment SD	n = 5 (33.3%)
Response Assessment PD	n = 7 (46.7%)
Response Assessment OTHER	n = 0 (0%)
(Median) Duration Assessments PFS	1.8 months; 95% CI, 1.7–4.7.

ADVERSE EVENTS

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
Fatigue	0	100	0	0	0	0	100
Constipation	0	100	0	0	0	0	100
Dyspnea	0	100	0	0	0	0	100
Rash maculo-papular	0	100	0	0	0	0	100
Lung infection	0	60	0	40	0	0	100
Arthralgia	0	100	0	0	0	0	100
Dehydration	0	67	0	33	0	0	100
Hypokalemia	0	100	0	0	0	0	100
Nausea	0	100	0	0	0	0	100
Weight loss	0	100	0	0	0	0	100

All cycles. TEAEs of any grade were reported in 14 patients (93.3%). TEAEs regardless of attribution are summarized. The most frequently experienced grade ≥ 3 TEAE was pneumonia (n = 2; 13.3%). One patient discontinued study treatment owing to a TEAE of community-acquired pneumonia. No DLTs were observed. No grade 4 or 5 events were reported.
Abbreviation: NC/NA, no change from baseline/no adverse event.

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion	Study completed
Investigator's Assessment	Level of activity did not meet planned endpoint

Head and neck squamous cell carcinoma (HNSCC) is associated with significant morbidity and mortality worldwide with more than 600,000 cases diagnosed annually [7]. Most patients present with locoregionally advanced disease, and

many patients develop recurrence [8, 9]. Patients who develop disease progression within 6 months of platinum-based chemotherapy have a poor prognosis [10]. Nivolumab demonstrated improved clinical outcomes when compared with standard of care chemotherapy (SOC) in refractory and metastatic (R/M) HNSCC after platinum-based chemotherapy in a randomized phase III clinical [1]. This clinical trial demonstrated a median overall survival of 7.5 months versus 5.1 months, overall response rate (ORR) of 13.3% versus 5.8%, 6-month progression-free survival (PFS) rate of 19.7% versus 9.9%, and 1-year survival rate of 36% versus 16.6% favoring the anti–PD-1 inhibitor. However, PFS was 2 months for nivolumab compared with 2.3 months for SOC, hinting at late efficacy in this cohort of patients. Moreover, a large randomized clinical trial demonstrated an efficacy of the pembrolizumab plus chemotherapy and pembrolizumab alone (PD-L1–positive patients) in the frontline treatment of patients with HNSCC [11]. However, given the modest efficacy of single agent anti–PD-1 inhibitor in R/M HNSCC, a search for adjunct immunostimulatory regimens to improve efficacy is underway. Cyclophosphamide, when administered in low dose, has been shown to improve the immunologic and clinical responses of anticancer vaccines [12]. This immunologic reaction is achieved by increasing expression of class I human leukocyte antigen in the tumor microenvironment or on cancer cells as well as depleting regulatory T (Treg) cells, which can be increased after radiation treatment, as radiation therapy (RT) can increase Treg cells relative to cytotoxic T cells [13]. By reducing Treg cells, antitumor CD8+ cytotoxic effector T cells can be activated and expanded [12]. Low dose cyclophosphamide depleted Treg cells in patients treated with oncolytic viruses without compromising antitumor or antiviral T-cell responses in a clinical study [14]. Radiation therapy sensitizes cancer cells to immune-mediated attack via release of tumor antigens from killed cells, increasing tumor cell expression of antigens and receptor-mediated T-cell recognition and killing, and enhanced activity of antigen-presenting cells [2]. In addition, RT induces expression of chemokines needed for T-cell trafficking, and preclinical data demonstrated that tumor cells may counterbalance the aforementioned effect by upregulating the expression of PD-L1 [15]. Thus, these observations suggested a strong rationale for combining an anti–PD-1 inhibitor with RT and cyclophosphamide. Granulocyte macrophage colony-stimulating factor plays a role in dendritic cell maturation and proliferation in addition to activation of T cells [5]. Proliferation of dendritic cells enhances cancer cell antigen presentation produced by RT and thus can ameliorate the activity of the studied regimen and was thus studied in combination [16]. Our clinical trial demonstrated tolerability of the regimen with the most common treatment-emergent adverse events (TEAEs) of fatigue (40%) and constipation (26.7%) and asthenia, dyspnea, maculo-papular rash, and pneumonia (20% each). The most common grade 3 TEAE was pneumonia, which occurred in two patients (13.3%), and dehydration, which occurred in one patient (6.7%). One patient discontinued treatment due to TEAE of community acquired pneumonia. Serious TEAE of any grade occurred in 40% of patients, and serious TEAE of grade 3 occurred in 26.7% of patients. All patients discontinued therapy due to progression of disease. The median number of cemiplimab doses administered was 6 (range 1–19), and the median

duration of exposure was 12.3 weeks (range 2.0–41.7). The median duration of follow-up was 3.3 months (range 0.5–10.2). The median PFS was 1.8 months (95% confidence interval, 1.7–4.7). The ORR was 6.7% (RECIST version 1.1) with one patient achieving a partial response (PR) and a second patient with unconfirmed PR, who hence was downgraded to stable disease, and the stable disease rate was 33.3%. The data demonstrate that this regimen is similar to anti–PD-1 monotherapy treatment in patients with R/M HNSCC. This potentially may be secondary to the fact that enrolled patients received multiple lines of therapy including RT; hence it difficult to elicit an appropriate proimmune tumor microenvironment. In a small randomized trial of nivolumab with or without a similar radiation regimen, no benefit was seen with the addition of radiation [17]. The protocol allowed for the enrollment of patients regardless of PD-L1 expression or human papillomavirus positivity, and hence it is difficult to correlate responses with those biomarkers. The trial/cohort enrolled a low number of patients, and hence it is difficult to establish efficacy. This regimen can be further investigated in earlier lines of therapy; however, in patients with R/M HNSCC the combination failed to reveal higher efficacy compared with single agent anti–PD-1.

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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