Safety and Preliminary Antitumor Activity of the Anti-PD-1 Monoclonal Antibody Cemiplimab (REGN2810) Alone or in Combination with REGN1979, an Anti-CD20 x Anti-CD3 Bispecific Antibody, in Patients with B-Lymphoid Malignancies

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Introduction

- REGN1979 is a bispecific, human anti-CD20 × anti-CD3 monoclonal antibody based on an IgG4 isotype.[1]
- REGN1979 is designed to cross-link CD20+ B-cells and CD3-expressing T-cells, thereby mediating localized cytotoxicity independent of T-cell receptor recognition. This mechanism of action is distinct from that of currently approved anti-CD20 antibodies.[1,2]
- Cemiplimab (REGN2810) is a human IgG4 monoclonal antibody directed against PD-1 blocking PD-1/PD-L1-driven inhibitory T-cell signaling.[3]
- The combination of cemiplimab and REGN1979 provides an attractive therapeutic opportunity for augmenting antitumor immunity in previously treated B-cell non-Hodgkin lymphoma (B-NHL).

Objectives

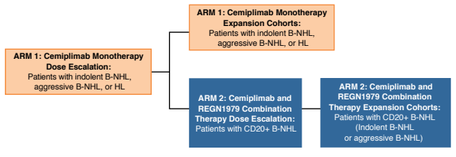
- The primary objective is to assess safety, tolerability, and dose-limiting toxicity (DLT) of cemiplimab as a monotherapy in patients with lymphoma (B-NHL and Hodgkin lymphoma [HL]), or in combination with REGN1979, in patients with B-NHL.
- Secondary objectives include:
  - Determination of recommended doses of cemiplimab as a monotherapy, or in combination with REGN1979
  - Assessment of pharmacokinetics, immunogenicity, and preliminary antitumor activity of cemiplimab as a monotherapy, or in combination with REGN1979.
- Exploratory objectives include cytokine profiling and immunophenotyping of peripheral blood mononuclear cells (PBMCs).

Methods

Patients and overall study design

- This is an ongoing, Phase 1, open-label, multicenter, two-arm, dose escalation study (NCT02651662) of patients with B-lymphoid malignancies (B-NHL and HL).
- Dose escalation rules followed a traditional 3 + 3 dose escalation design.
- Combination therapy opened after dose escalation of cemiplimab monotherapy.

Figure 1. Overall study design



- Severity of adverse events (AEs) were graded according to the CTCAE (v4.03), with cytokine release syndrome (CRS) graded by Lee criteria.[4]
- The DLT monitoring period is 28 days for both arms.
- CT-based responses are assessed by the Cheson criteria (Cheson 2007)[5] and metabolic responses (PET) by Lugano criteria (Cheson 2014).[6]

Cemiplimab monotherapy

- Patients with indolent B-NHL, aggressive B-NHL, or HL receive cemiplimab intravenously (IV) every 2 weeks (Q2W) for a minimum of 12 and maximum of 24 doses.

Cemiplimab and REGN1979 combination therapy

- Patients with indolent or aggressive B-NHL receive cemiplimab IV Q2W in combination with REGN1979.
  - Patients receive cemiplimab Q2W for a minimum of 12 and maximum of 24 doses.
  - REGN1979 is administered IV weekly for 11 doses, followed by Q2W dosing from Week 13, for 11 additional doses.
  - REGN1979 is administered at an initial dose followed by a step-up dose if the initial starting dose is tolerated.

Results (data as of 18SEP17)

Patient demographics and baseline characteristics

- Sixty-two patients with B-NHL (n=36) or HL (n=26) received treatment with cemiplimab monotherapy (**Table 1**).
  - Twelve patients were in the dose escalation arm; six (B-NHL, n=5 and HL, n=1) received cemiplimab 1 mg/kg Q2W and six (B-NHL, n=1 and HL, n=5) received cemiplimab 3 mg/kg Q2W.
    - Both cemiplimab 1 and 3 mg/kg Q2W dose levels were generally well tolerated (no DLTs in the dose escalation cohort); cemiplimab 3 mg/kg Q2W was selected for combination therapy with REGN1979.
  - Fifty patients enrolled in the dose expansion cohorts with cemiplimab 3 mg/kg Q2W monotherapy; 20 with HL, 21 with aggressive B-NHL, and 9 with indolent B-NHL.

Disposition and treatment exposure

- In the monotherapy arm, 11 of 62 patients continued study treatment with cemiplimab. The primary reason for discontinuation was disease progression (n=33).
- In the combination therapy arm, two patients remained on treatment and 10 were off treatment mainly due to disease progression (n=8).

Table 1. Demographics and baseline characteristics of patients receiving cemiplimab monotherapy or cemiplimab 3 mg/kg in combination with REGN1979

	Cemiplimab monotherapy			Cemiplimab and REGN1979 combination therapy
	1 mg/kg (n=6)	3 mg/kg (n=56)	Total (n=62)	Total (n=12)
Mean (standard deviation) age, years	68.0 (10.2)	55.1 (17.4)	**56.3 (17.2)**	**59.5 (12.5)**
Male, n (%)	3 (50.0)	37 (66.1)	**40 (64.5)**	**6 (50.0)**
White, n (%)	6 (100)	51 (91.1)	**57 (91.9)**	**12 (100)**
ECOG performance status[†]				
0	2 (33.3)	25 (44.6)	**27 (43.5)**	**6 (50.0)**
1	4 (66.7)	30 (53.6)	**34 (54.8)**	**6 (50.0)**
HL, n (%)	1 (16.7)	25 (44.6)	**26 (41.9)**	**–**
Nodular sclerosis	1 (16.7)	14 (25.0)	**15 (24.2)**	**–**
Mixed cellularity	0	5 (8.9)	**5 (8.1)**	**–**
Other[‡]	0	6 (10.7)	**6 (9.7)**	**–**
B-NHL, n (%)	5 (83.3)	31 (55.4)	**36 (58.1)**	**12 (100)**
DLBCL	2 (33.3)	16 (28.6)	**18 (29.0)**	**10 (83.3)**
FL	2 (33.3)	9 (16.1)	**11 (17.7)**	**1 (8.3)**
Other[¶]	1 (16.7)	6 (10.7)	**7 (11.3)**	**1 (8.3)**
Treatment history				
Median prior lines of cancer-related therapy (range)	3 (2–8)	3 (1–12)	**3 (1–12)**	**4 (1–9)**
Median time from initial diagnosis to first dose, months (range)	56.5 (24–160)	32.0 (6–280)	**33.0 (6–280)**	**20.7 (7–198)**

DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma. [†]One patient dosed with cemiplimab 3 mg/kg had an ECOG performance status of 2; [‡]includes lymphocyte-depleted, lymphocyte-rich classical, and nodular lymphocyte predominant subtypes; [¶]includes mantle cell lymphoma and marginal zone lymphoma for the monotherapy arm and only mantle cell lymphoma for the combination therapy arm.

Table 2. Overall duration of exposure and number of doses of cemiplimab and REGN1979 by study arm

	Cemiplimab monotherapy n=62	Cemiplimab and REGN1979 combination therapy	
		Cemiplimab n=12	REGN1979 n=12
Duration of exposure (weeks)			
Median	13.9	12.7	12.7
Range	2–55	2–33	3–33
Number of doses administered			
Median	7	6	11
Range	1–24	1–17	2–22

Safety

Treatment-related TEAEs with monotherapy cemiplimab

- A total of 46 patients (74.2%) reported at least one treatment-related treatment emergent adverse event (TEAE) (**Table 3**).
- There were no DLTs.

Table 3. Summary of treatment-related TEAEs with monotherapy cemiplimab in patients with B-NHL and HL

	Cemiplimab monotherapy		
Event, n (%)	1 mg/kg (n=6)	3 mg/kg (n=56)	Total (n=62)
Any treatment-related TEAE	2 (33.3)	44 (78.6)	**46 (74.2)**
Any grade ≥3 treatment-related TEAE	0	16 (28.6)	**16 (25.8)**
Any serious treatment-related TEAE	0	11 (19.6)	**11 (17.7)**
Treatment-related deaths	0	3 (5.4)	**3 (4.8)**
Treatment-related TEAEs occurring in ≥4% of patients, by preferred terms[†]			
Fatigue	1 (16.7)	7 (12.5)	**8 (12.9)**
Pyrexia	0	7 (12.5)	**7 (11.3)**
Chills	1 (16.7)	5 (8.9)	**6 (9.7)**
IRR	1 (16.7)	5 (8.9)	**6 (9.7)**
Nausea	0	5 (8.9)	**5 (8.1)**
Diarrhea	0	4 (7.1)	**4 (6.5)**
Neutropenia	0	4 (7.1)	**4 (6.5)**

IRR, infusion-related reaction. [†]AEs were coded using MedDRA Dictionary 20.0.

- Grade ≥3 treatment-related TEAEs occurring in >1 patient were neutropenia (n=3; 4.8%); and anemia, pneumonia, pneumonitis, sepsis, and stomatitis (n=2; 3.2% each).
- Five patients had at least one TEAE that led to death; two patients died due to TEAEs unrelated to treatment (urosepsis and clostridial infection) and three died due to treatment-related TEAEs as follows:
  - Patient #1: acute liver failure associated with autoimmune hepatitis in the setting of rapidly progressing disease; there were no target lesions in the liver.
  - Patient #2: toxic epidermal necrolysis and stomatitis.
  - Patient #3: pneumonia in the setting of grade 4 stomatitis and grade 3 erythema multiforme.
- Among all study patients treated with cemiplimab (n=74), 10 patients experienced at least one severe immune-related AE (irAE) considered related to cemiplimab.
  - Of the 10 patients with at least one severe irAE, three were previously treated with idelalisib. Two of these three patients died due to treatment-related severe irAE (above noted patients #2 and #3), and the third patient experienced serious TEAEs of grade 3 dyspnea at rest, grade 3 myasthenia gravis, and grade 3 myositis that did not result in death.
    - Four additional patients with prior exposure to idelalisib and three patients with prior exposure to other phosphatidylinositol 3-kinase inhibitors did not show any severe irAE.
  - The study protocol was amended to exclude patients with prior exposure to idelalisib until more information becomes available regarding possible interactions of idelalisib and PD-1 blockade.

Treatment-related TEAEs with cemiplimab in combination with REGN1979

- All patients treated with cemiplimab in combination with REGN1979 reported at least one treatment-related TEAE (**Table 4**).

Table 4. Summary of treatment-related TEAEs with cemiplimab 3 mg/kg in combination with REGN1979 in patients with B-NHL

	Cemiplimab and REGN1979 combination therapy (by REGN1979 dose)				
Event, n (%)	2 mg (n=3)	3 mg (n=3)	4 mg (n=3)	5 mg (n=3)	Total (n=12)
Any treatment-related TEAE	3 (100)	3 (100)	3 (100)	3 (100)	**12 (100)**
Any grade ≥3 treatment-related TEAE	2 (66.7)	3 (100)	3 (100)	2 (66.7)	**10 (83.3)**
Any serious treatment-related TEAE	2 (66.7)	2 (66.7)	3 (100)	1 (33.3)	**8 (66.7)**
Treatment-related TEAEs occurring in ≥4 patients, by preferred term[†]					
CRS	3 (100)	2 (66.7)	3 (100)	3 (100)	**11 (91.7)**
Pyrexia	2 (66.7)	3 (100)	2 (66.7)	3 (100)	**10 (83.3)**
ALT increase	3 (100)	2 (66.7)	1 (33.3)	1 (33.3)	**7 (58.3)**
AST increase	2 (66.7)	2 (66.7)	1 (33.3)	1 (33.3)	**6 (50.0)**
Blood lactate dehydrogenase increase	3 (100)	1 (33.3)	1 (33.3)	1 (33.3)	**6 (50.0)**
Gamma-glutamyl transferase increase	3 (100)	1 (33.3)	1 (33.3)	1 (33.3)	**6 (50.0)**
Blood alkaline phosphatase increase	3 (100)	1 (33.3)	1 (33.3)	0	**5 (41.7)**
C-reactive protein increase	3 (100)	0	1 (33.3)	1 (33.3)	**5 (41.7)**
Anemia	0	2 (66.7)	1 (33.3)	1 (33.3)	**4 (33.3)**
Fibrin D-dimer increase	2 (66.7)	0	1 (33.3)	1 (33.3)	**4 (33.3)**
Lymphopenia	1 (33.3)	2 (66.7)	1 (33.3)	0	**4 (33.3)**

ALT, alanine aminotransferase; AST, aspartate aminotransaminase. [†]AEs were coded using MedDRA Dictionary.

- There were no DLTs.
- Grade ≥3 treatment-related TEAEs occurring in >1 patient were lymphopenia (n=4; 33.3%); leukopenia, ALT, and AST increase (n=3; 25.0% each); neutropenia, and neutrophil count decrease (n=2; 16.7% each).
- All CRS/IRR events were grade 1 or 2, with the majority occurring after the initial dose.
- One patient died due to TEAE of intracranial hemorrhage that was considered unrelated to study treatment.

Tumor response

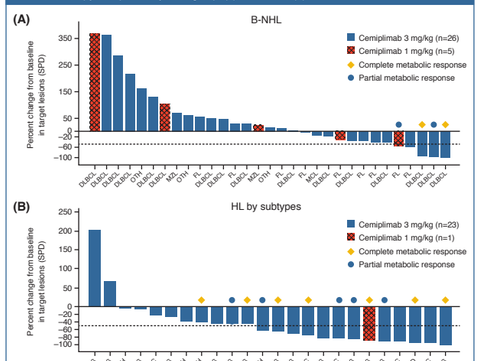
- In the monotherapy arm, overall response rates by both Cheson (Cheson 2007) and Lugano (Cheson 2014) criteria were 50.0% (13/26) for patients with HL and 11.1% (4/36) for patients with B-NHL (response by Cheson criteria shown in **Table 5**).

Table 5. Best overall response rate by study arm and lymphoma subtypes using Cheson 2007 criteria

	Cemiplimab monotherapy							Cemiplimab and REGN1979 combination therapy
	B-NHL subtypes				HL subtypes			B-NHL
n (%)	DLBCL (n=18)	FL[†] (n=11)	Other[‡] (n=6)	Total (n=36)	Nodular sclerosis (n=15)	Other[§] (n=11)	Total (n=26)	Total (n=12)
CR	3 (16.7)	0	0	**3 (8.3)**	5 (33.3)	2 (18.2)	**7 (26.9)**	**0**
PR	0	1 (9.1)	0	**1 (2.8)**	3 (20.0)	3 (27.3)	**6 (23.1)**	**1 (8.3)**
SD	2 (11.1)	5 (45.5)	1 (16.7)	**8 (22.2)**	5 (33.3)	3 (27.3)	**8 (30.8)**	**4 (33.3)**
PD	11 (61.1)	3 (27.3)	5 (83.3)	**19 (52.8)**	2 (13.3)	3 (27.3)	**5 (19.2)**	**5 (41.7)**
ORR[¶]	3 (16.7)	1 (9.1)	0	**4 (11.1)**	8 (53.3)	5 (45.5)	**13 (50.0)**	**1 (8.3)**
Disease control[#]	5 (27.8)	6 (54.5)	1 (16.7)	**12 (33.3)**	13 (86.7)	8 (72.7)	**21 (80.8)**	**5 (41.7)**

CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. [†]One patient was unevaluable; [‡]includes mantle cell lymphoma and marginal zone lymphoma subtypes; [§]includes lymphocyte-depleted, mixed-cellularity, lymphocyte-rich classical and nodular lymphocyte predominant subtypes; one patient was unevaluable; [¶]ORR = CR + PR; [#]Disease control = ORR + SD.

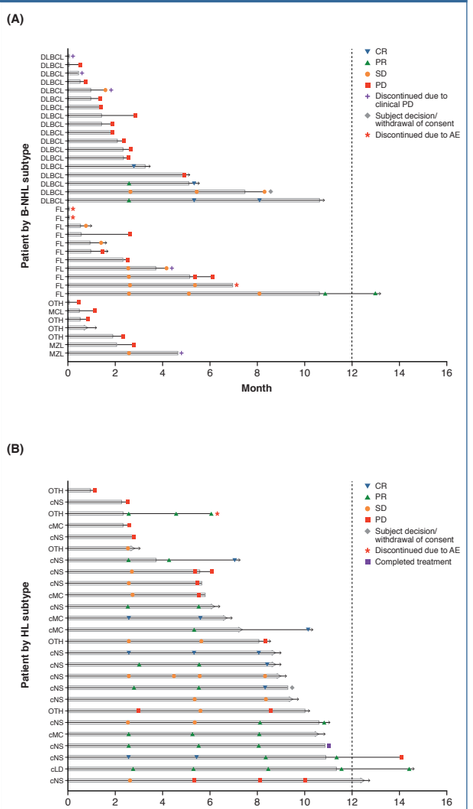
Figure 2. Best percentage change in target lesion measurements from baseline in patients treated with monotherapy cemiplimab by dose group: (A) B-NHL and (B) HL



cLD, classical lymphocyte depleted; cMC, classical mixed cellularity; cNS, classical nodular sclerosis; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; OTH, other; SPD, sum of the product diameters.

- In the combination therapy arm where the highest dose of REGN1979 administered was 5 mg (compared to 12 mg in the monotherapy study of REGN1979 [see poster number 1550]), 1/12 patients showed a PR, one had partial metabolic response, four had SD, and three had no metabolic response.
- The Kaplan–Meier estimation of median duration of CR/PR with cemiplimab 1 mg/kg Q2W was 351 days. The median duration of CR/PR or metabolic response for cemiplimab 3 mg/kg Q2W, and cemiplimab in combination with REGN1979, was not reached at the time of the data cutoff.

Figure 3. Swimmer plots for (A) B-NHL and (B) HL patients treated with monotherapy cemiplimab showing response as assessed by Cheson 2007 criteria



Dotted line indicates maximum treatment period of 12 months per protocol. Bar indicates treatment period until last dose. Arrow on bar indicates treatment ongoing. Arrow on line indicates study ongoing. Patients without arrow or box stopped treatment for reasons other than progressive disease as shown in the legend.

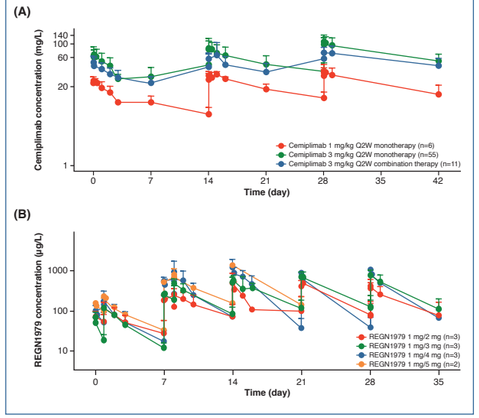
Pharmacokinetics

- Exposure of cemiplimab in serum was dose-proportional (**Figure 4A**). Cemiplimab pharmacokinetics at 3 mg/kg Q2W were similar as monotherapy and in combination with REGN1979. Cemiplimab exposure in combination therapy with REGN1979 appeared similar for the first 11 patients compared with monotherapy (n=55).
- REGN1979 exposure in serum increased slightly with dose (**Figure 4B**); the estimated half-life of REGN1979 ranged from 2.3 to 4.4 days.

Pharmacodynamics

- Interim analysis indicated that cemiplimab monotherapy (n=61) induced no or modest changes in cytokine levels, while combination therapy (n=8) induced a cytokine release specifically associated with the initial 2–3 doses of REGN1979.
- No augmented cytokine release was observed with combination therapy compared with REGN1979 monotherapy explored in the first in-human study.
- Immunophenotyping of PBMCs did not reveal any strong signals or trends in a limited preliminary data set.

Figure 4. Mean (standard deviation) concentration-time profiles by dose of (A) cemiplimab and (B) REGN1979



Conclusions

- In this ongoing study, cemiplimab monotherapy has been generally well tolerated with early evidence of clinical activity in patients with B-NHL and HL.
  - In HL (n=26), an ORR of 50% has been observed, including a CR in 26.9% of patients
  - In B-NHL (n=36), an ORR of 11.1% has been observed, including a CR in 8.3% of patients
  - These data are similar to those seen with other studies of PD-1 blockade, and the high proportion of CRs compared with other response measures is encouraging.
- Evaluation of cemiplimab monotherapy in patients with lymphoma is continuing.
- Preliminary results show that for patients (n=12) treated with a combination of cemiplimab and REGN1979 therapy has been generally well tolerated.
  - There was no evidence of increased CRS/IRR severity or increased cytokine levels compared with that observed in a single agent study of REGN1979 (see poster number 1550).
  - Preliminary results also show evidence of clinical activity for patients (n=10 of 12 that were evaluable) with B-NHL treated with cemiplimab and low-dose REGN1979.
  - In a separate study (see poster number 1550), REGN1979 has shown evidence of clinical activity as a single agent in patients with B-NHL, particularly at doses ≥5 mg.
- The dose of REGN1979 reached in combination with cemiplimab was 5 mg at the time of the data cutoff.
- Evaluation of the combination of cemiplimab with more effective doses of REGN1979 is underway.

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