Safety and preliminary clinical activity of REGN1979, an anti-CD20 × anti-CD3 bispecific antibody, in patients with B-NHL previously treated with CD20-directed antibody therapy

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Introduction

- REGN1979 is a bispecific, human anti-CD20 × anti-CD3 mAb based on an IgG4 isotype.
  - REGN1979 is designed to cross-link CD3-expressing T-cells and CD20+ B-cells, thereby mediating localized cytotoxicity independent of T-cell receptor recognition.[1,2]
- Here we provide updated information for the patients with B-NHL from an ongoing Phase 1 study[3] (NCT02290951) of REGN1979 monotherapy in patients with CD20+ B-NHL or chronic lymphocytic leukemia (CLL).

Study Objectives

- The primary study objective is to assess safety, tolerability, and dose-limiting toxicities (DLTs) of REGN1979 in patients with B-lymphoid malignancies.
- Secondary objectives are to:
  - Characterize the pharmacokinetic (PK) profile
  - Assess immunogenicity
  - Study preliminary antitumor activity.
- Objectives include evaluation of pharmacodynamic biomarkers, including cytokine levels.

Methods

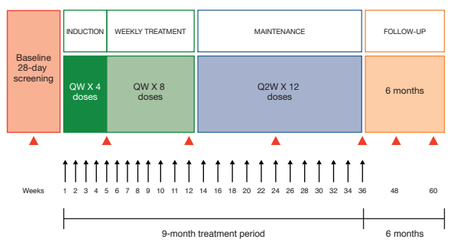
Study design

- This is an ongoing, Phase 1, open-label, multicenter, dose-escalation study of REGN1979 in patients with B-cell malignancies.
- Patients with CD20+ B-NHL after treatment failure with anti-CD20 therapy(ies) were included.
- Severity of adverse events (AEs) are graded according to the CTCAE (v4.03), with cytokine release syndrome (CRS) graded by Lee criteria.[4]
- B-NHL disease status and response assessment are conducted by Cheson (2007)[5] criteria (based on CT assessment), and metabolic response by Cheson (2014)[6] criteria (based on metabolic assessment).
- Dose-escalation follows a Simon 3 + 3 protocol.
- The DLT observation period is 28 days.

Treatment plan

- The treatment and follow-up schedule can be seen in **Figure 1.**

Figure 1. Overall REGN1979 treatment and follow-up schedule



Results

- Data are presented for REGN1979 dose groups <5 mg and ≥5 mg. At 5 mg, the dosing schedule was intensified for the entire cohort, contributing to significantly increased exposure.
- Demographics, safety and PK/exposure data are presented through the 12 mg dose level based on data available as of September 2017 (for ≥5mg, n=17).
- Efficacy data are presented through the 8 mg dose level based on data available as of November 2017 (for ≥5 mg, n=14).

Baseline characteristics and demographics

- Baseline characteristics and patient demographics are summarized in **Table 1**.

Patient disposition and treatment exposure

- In total, 11 patients (25.0%) were still on treatment, 7 (15.9%) had completed the treatment phase, and 26 (59.1%) had discontinued, most commonly due to disease recurrence or progression.

Table 1. Patient demographics and baseline characteristics

	REGN1979 dose group		
	<5 mg (n=27)	≥5 mg (n=17)	Total (n=44)
Mean (standard deviation) age, years	61.0 (13.44)	66.8 (11.55)	**63.3 (12.92)**
Male, n (%)	23 (85.2)	14 (82.4)	**37 (84.1)**
White, n (%)	20 (74.1)	17 (100)	**37 (84.1)**
NHL diagnosis by subtype, n (%)			
DLBCL	15 (55.6)	10 (58.8)	**25 (56.8)**
FL	8 (29.6)	5 (29.4)	**13 (29.5)**
MCL	3 (11.1)	1 (5.9)	**4 (9.1)**
MZL	1 (3.7)	1 (5.9)	**2 (4.5)**
ECOG performance status, n (%)			
0	12 (44.4)	7 (41.2)	**19 (43.2)**
1	15 (55.6)	10 (58.8)	**25 (56.8)**
Median (range) prior lines of cancer-related therapy	3.0 (1–6)	4.0 (1–11)	**3.5 (1–11)**
Median (range) duration from end of prior anti-CD20 treatment to starting REGN1979, months	3.3 (1–100)	6.6 (1–60)	**4.7 (1–100)**

DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

- Treatment exposure is summarized in **Table 2**.

Table 2. Duration of exposure and number of doses of REGN1979 by dose group

	REGN1979 dose group		
	<5 mg (n=27)	≥5 mg (n=17)	Total (n=44)
Duration of exposure (weeks)			
Median	9.14	10.14	**9.21**
Range	3.0–39.0	1.0–37.0	**1.0–39.0**
Number of doses administered			
Median	5.0	8.0	**5.5**
Range	2–21	1–24	**1–24**

Safety

- Treatment-related treatment emergent adverse events (TEAEs) are summarized in **Table 3**.

Table 3. Summary of treatment-related TEAEs by dose group

	REGN1979 dose group		
	<5 mg (n=27)	≥5 mg (n=17)	Total (n=44)
Patients with any Gr ≥3 treatment-related TEAE, n (%)	9 (33.3)	11 (64.7)	**20 (45.5)**
Patients with any treatment-related TEAE, n (%)	24 (88.9)	15 (88.2)	**39 (88.6)**
Patients with treatment-related TEAEs with overall incidence ≥10%, n (%)			
Pyrexia	18 (66.7)	11 (64.7)	**29 (65.9)**
Chills	13 (48.1)	7 (41.2)	**20 (45.5)**
CRS	11 (40.7)	8 (47.1)	**19 (43.2)**
Fatigue	9 (33.3)	2 (11.8)	**11 (25.0)**
Hypotension	8 (29.6)	2 (11.8)	**10 (22.7)**
Nausea	8 (29.6)	1 (5.9)	**9 (20.5)**
Elevated CRP	3 (11.1)	5 (29.4)	**8 (18.2)**
IRR	8 (29.6)	0	**8 (18.2)**
Hypophosphatemia	4 (14.8)	3 (17.6)	**7 (15.9)**
Anemia	4 (14.8)	2 (11.8)	**6 (13.6)**
Elevated AST	3 (11.1)	3 (17.6)	**6 (13.6)**
Dizziness	5 (18.5)	1 (5.9)	**6 (13.6)**
Headache	3 (11.1)	3 (17.6)	**6 (13.6)**
Tachycardia	6 (22.2)	0	**6 (13.6)**
Thrombocytopenia	1 (3.7)	5 (29.4)	**6 (13.6)**
Elevated ALT	2 (7.4)	3 (17.6)	**5 (11.4)**

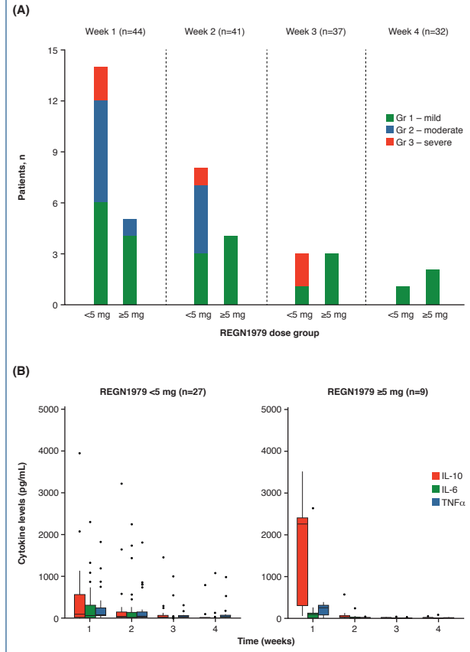
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; Gr, Grade; IRR, infusion-related reaction.
Adverse events were coded using MedDRA Dictionary 17.0.

- Overall 20 (45.5%) patients experienced one or more Grade ≥3 treatment-related TEAE:
  - Three (6.8%) experienced lymphocytopenia
  - Two (4.5%) each experienced CRS, hypotension, IRR, hypophosphatemia, anemia, elevated AST, thrombocytopenia, and neutropenia
  - One (2.3%) each experienced a pulmonary embolism, skin infection, pyrexia, fatigue, tachycardia, elevated ALT, dyspnea, hyperglycemia, leukopenia, dehydration, hypoxia, leukocytosis, febrile neutropenia, hemolysis, elevated hepatic enzymes, hypertension, lymphopenia, muscular weakness, tachypnea, and tumor pain.
- No patient died as a result of a treatment-related TEAE, nor did anyone develop severe neurologic toxicity.
- Overall five patients died during the study, all resulting from progressive disease, one while on treatment and four after discontinuing.
- No DLTs have been observed thus far in this study.

Pharmacodynamics and IRR/CRS events

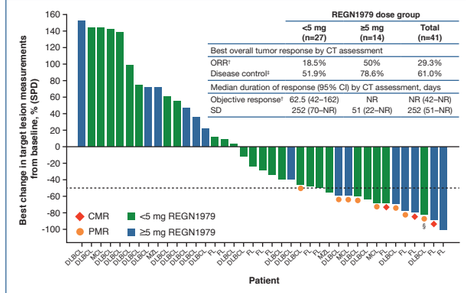
- Interim analysis (n=36) indicates cytokine levels trending towards a correlation with REGN1979 dose administered, as expected with REGN1979 mechanism of action.
- Overall, 25 patients (56.8%) experienced an IRR/CRS event(s) while on treatment (**Figure 2A**).
  - After observations of IRR/CRS in the initial cohorts, the protocol was amended to require pre-medication (including dexamethasone) and dosing modifications. With these additional measures in place, no patient in the REGN1979 ≥5 mg dose group developed a severe IRR/CRS event.
- Increases in IL-6, IL-10, TNF-α, and to a lesser extent IFNγ and IL-2 were observed, associated for the majority of patients with the initial 2–3 doses of REGN1979 (**Figure 2B**).
  - Occurrence of a cytokine response was consistent with an IRR/CRS event.

Figure 2. (A) Number of IRR/CRS events and (B) median peak cytokine levels in patients treated with REGN1979



Patients received a lower initial dose of REGN1979 in Week 1 prior to the indicated step-up dose in subsequent weeks.

Figure 3. Best change in target lesion measurements from baseline



CMR, complete metabolic response; CR, complete response; NR, not reached; ORR, objective response rate; PMR, partial metabolic response; PR, partial response; SD, stable disease; SPD, sum of the product of the diameters.
[1]ORR/objective response by CT assessment, CR/PR.
[2]Disease control by CT assessment, CR/PR/SD.
[3]Patient considered to have SD due to an increase in size of one node.

Tumor response

- In total, 41 of 44 patients had the opportunity to be evaluated for tumor response through 12 weeks (efficacy assessments for the 12 mg cohorts were not as mature).
- Best overall tumor response identified by CT assessment and best change in target lesion measurements are summarized in **Figure 3**.
  - ORR was 7 of 14 (50.0%) patients treated with REGN1979 ≥5 mg and 5 of 27 (18.5%) treated with <5 mg
  - Disease control was achieved in 11 of 14 (78.6%) patients treated with REGN1979 ≥5 mg and 14 of 27 (51.9%) treated with <5 mg.
- For patient tumor response identified by Cheson 2014 metabolic criteria (not all patients had PET scans; a composite ORR was not calculated):
  - 10 of 14 (71.4%) patients treated with REGN1979 ≥5 mg and 19 of 27 (70.4%) treated with <5 mg were assessed
  - ORR was 6 of 14 (42.9%) patients treated with REGN1979 ≥5 mg, compared with 5 of 27 (18.5%) treated with <5 mg
  - Disease control (CMR/PMR/no metabolic response [NMR]) was achieved by 8 of 14 (57.1%) patients treated with REGN1979 ≥5 mg, compared with 9 of 27 (33.3%) treated with <5 mg.
- Best overall tumor response by NHL subtype can be seen in **Table 4**.
  - Patient tumor response in those treated with REGN1979 ≥5 mg, identified by CT assessment, are as follows:
    - ORR was 2 of 8 (25.0%) in patients with DLBCL and 6 of 8 (75.0%) achieved disease control
    - ORR was 4 of 4 (100.0%) in patients with FL, two (50.0%) with a CR and 2 (50.0%) with a PR.

Table 4. Summary of best overall tumor response in patients treated with REGN1979 0.1–8 mg by NHL subtype

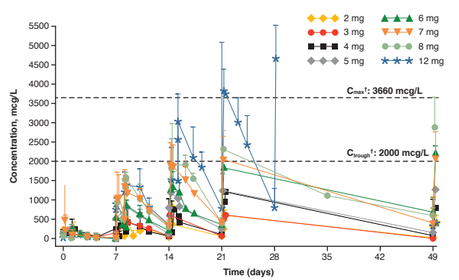
	NHL subtype				
	DLBCL (n=23)	FL (n=12)	MCL (n=4)	MZL (n=2)	Total (n=41)
Response by CT assessment, n (%)					
ORR	4 (17.4)	5 (41.7)	2 (50.0)	1 (50.0)	**12 (29.3)**
Disease control	12 (52.2)	10 (83.3)	2 (50.0)	1 (50.0)	**25 (61.0)**
CR	0	2 (16.7)	0	0	**2 (4.9)**
PR	4 (17.4)	3 (25.0)	2 (50.0)	1 (50.0)	**10 (24.4)**
SD	8 (34.8)	5 (41.7)	0	0	**13 (31.7)**
PD	11 (47.8)	2 (16.7)	1 (25.0)	1 (50.0)	**15 (36.6)**
Missing	0	0	1	0	**1**
Response by metabolic assessment, n (%)					
ORR[1]	5 (21.7)	4 (33.3)	2 (50.0)	0	**11 (26.8)**
Disease control[2]	7 (30.4)	8 (66.7)	2 (50.0)	0	**17 (41.5)**
CMR	0	3 (25.0)	0	0	**3 (7.3)**
PMR	5 (21.7)	1 (8.3)	2 (50.0)	0	**8 (19.5)**
NMR	2 (8.7)	4 (33.3)	0	0	**6 (14.6)**
PMD	8 (34.8)	2 (16.7)	1 (25.0)	0	**11 (26.8)**
UE	0	1 (8.3)	0	0	**1 (2.4)**
Missing	8	1	1	2	**12**

PD, progressive disease; PMD, progressive metabolic disease; UE, unable to evaluate.
[1]ORR by Cheson 2014 metabolic criteria, CMR/PMR.
[2]Disease control by Cheson 2014 metabolic criteria, CMR/PMR/NMR.

Pharmacokinetics

- REGN1979 exposure (C_{max}, C_{av}, and AUC) in patients treated with <5 mg QW was significantly lower than that measured in an *in vivo* efficacy model using Raji tumor-bearing NSG mice treated with and controlled by a single dose of 0.4 mg/kg. Only after reaching doses of 12 mg QW has the peak level of REGN1979 reached the trough level of 2000 mcg/L identified preclinically for activity (**Figure 4**).

Figure 4. Mean (standard deviation) concentration of REGN1979 versus time by cohort



[1]Raji mouse target exposure for tumor killing at 0.4 mg/kg single dose in 2 weeks.

- As expected, REGN1979 exposure decreased when switching from QW to Q2W dosing during the maintenance phase; C_{trough} remained above 100 mcg/L at doses above 5 mg.
- Exposure at REGN1979 doses <4 mg is consistent with target-mediated clearance by tumor.

Conclusions

- At dose levels investigated, REGN1979 has shown good tolerability in patients with B-NHL.
- Safety events observed were consistent with the mechanism of action of REGN1979, mainly comprising CRS and IRR.
  - With refined dose administration, severe IRR/CRS AEs decreased even with higher doses and augmented cytokine levels.
  - No severe neurological toxicity has been observed in this program.
- For patients treated with REGN1979 ≥5 mg, the ORR was 50% (investigator assessed), and disease control 78.6%, demonstrating clinical activity across a range of B-NHL subtypes.
- PK results as of the data cutoff have demonstrated a linear profile.
- Dose-escalation is ongoing, with REGN1979 exposure now reaching the levels required for optimal efficacy in pre-clinical models.
- Treatment with CD20xCD3 bispecific antibodies has the potential to provide meaningful clinical benefit for patients with advanced B-NHL.

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