EMERGING CLINICAL ACTIVITY OF REGN1979, AN ANTI-CD20 X ANTI-CD3 BISPECIFIC ANTIBODY, IN PATIENTS WITH RELAPSED/REFRACTORY B-CELL NON-HODGKIN LYMPHOMA

Rajat Bannerji, M.D., Ph.D.,[1] Jon Arnason, M.D.,[2] Ranjana Advani, M.D.,[3] Jennifer R. Brown, M.D., PhD.,[4] John Allan, M.D.,[5] Stephen Ansell, M.D., Ph.D.,[6] Susan O'Brien, M.D.,[7] Julio Chavez, M.D.,[8] Johannes Duell, M.D.,[9] Andreas Rosenwald, M.D.,[9] Robert Charnas. Ph.D.,[10] Srikanth R. Ambati, M.B.B.S., M.D.,[10] Lieve Adriaens, Pharm.D.,[11] Melanie Ufkin, Ph.D.,[10] Min Zhu, Ph.D.[10] Jingjin Li, Ph.D.,[11] Peter Gasparini, M.S,[10] Vladimir Jankovic, M.D.,[10] Nathalie Fiaschi, Ph.D.,[10] Wen Zhang, Ph.D.,[10] Raquel P. Deering, Ph.D., [10] Sara Hamon, Ph.D.,[10] Gavin Thurston, Ph.D.,[10] Andrew J. Murphy, Ph.D.,[10] George D. Yancopoulos, M.D., Ph.D.,[10] Israel Lowy, M.D., Ph.D.,[10] David Sternberg, M.D., Ph.D.,[10] Max S. Topp, M.D.[9]

[1]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [2]Beth Israel Deaconess Medical Center, Boston, MA, USA; [3]Stanford University, Stanford, CA, USA; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Weill Cornell Medicine, New York, NY, USA; [6]Mayo Clinic, Rochester, MN, USA; [7]University of California, Irvine, Orange, CA, USA; [8]Moffitt Cancer Center, Tampa, FL, USA; [9]Universitätsklinikum Würzburg, Würzburg, Germany; [10]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [11]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA

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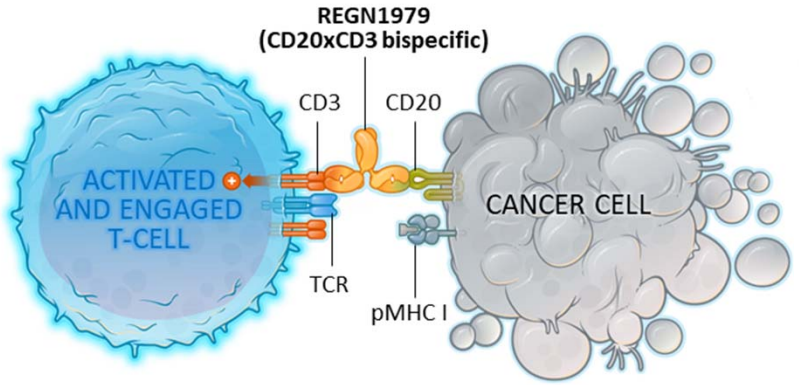
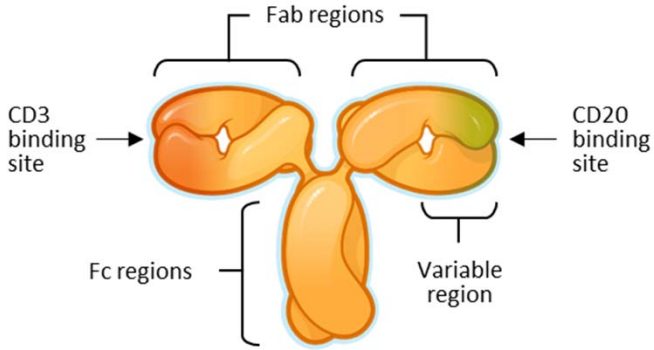
Background

- REGN1979 is an anti-CD20 x anti-CD3 bispecific IgG4 Ab, modified to have reduced effector function, and designed to cross-link and activate CD3 expressing T-cells upon contact with CD20+ B-cells, thus killing CD20+ tumour cells independent of T-cell receptor recognition[1,2]
- Preclinical studies support the potent antitumour activity of REGN1979
- Here, we provide updated data on the safety, PK, and efficacy of REGN1979 in patients with heavily pre-treated B-NHL, including patients who have progressive disease after CAR T-cell therapy

REGN1979 mode of action



REGN1979 molecular structure



B-NHL, B-cell non-Hodgkin lymphoma; TCR, T-cell receptor; CAR, chimeric antigen receptor; Fab, fragment antigen-binding; Fc, fragment crystallizable; PK, pharmacokinetics; pMHC I: peptide-bound major histocompatibility complex class I. 1. Smith EJ et al. *Sci Rep*. 2015;5:17943. 2. Choi BD et al. *Expert Opin Biol Ther*. 2011; 11:843-853.

Study Design and Objectives

Phase 1, open-label study with 3+3 dose escalation design*

Key eligibility criteria:

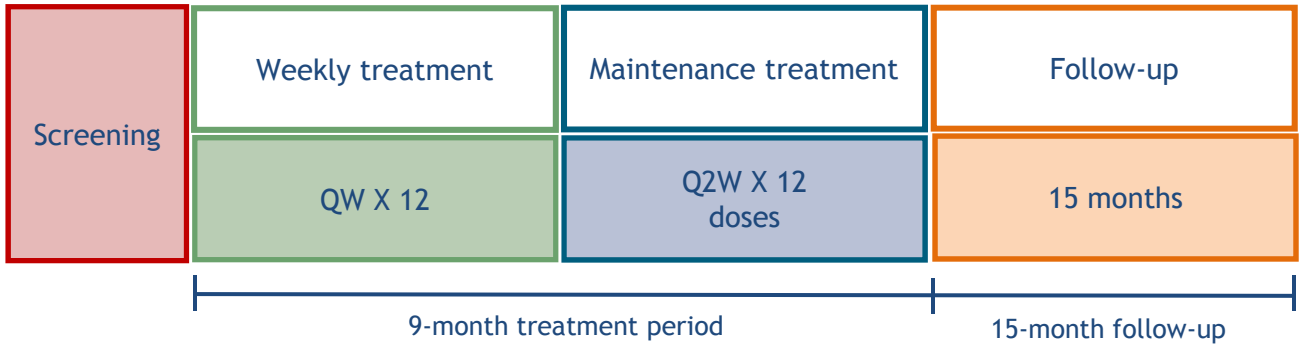
- CD20+ B-NHL
- Prior treatment with an anti-CD20 antibody
- ECOG performance status ≤1
- Adequate bone marrow and organ function

Primary objective:

Assess safety, tolerability, and dose-limiting toxicities

Secondary objectives:

- Characterize PK profile
- Assess immunogenicity
- Study antitumour activity



*Trial includes dose escalation and expansion cohorts in CLL, not shown.

B-NHL, B-cell non-Hodgkin lymphoma; ECOG, Eastern Cooperative Oncology Group; PK, pharmacokinetics; QW, weekly; Q2W, every two weeks

B-NHL patient demographics and disease characteristics at study entry

EUROPEAN HEMATOLOGY ASSOCIATION

Data as of 15 March 2019; includes efficacy data to 160 mg and safety data to 320 mg

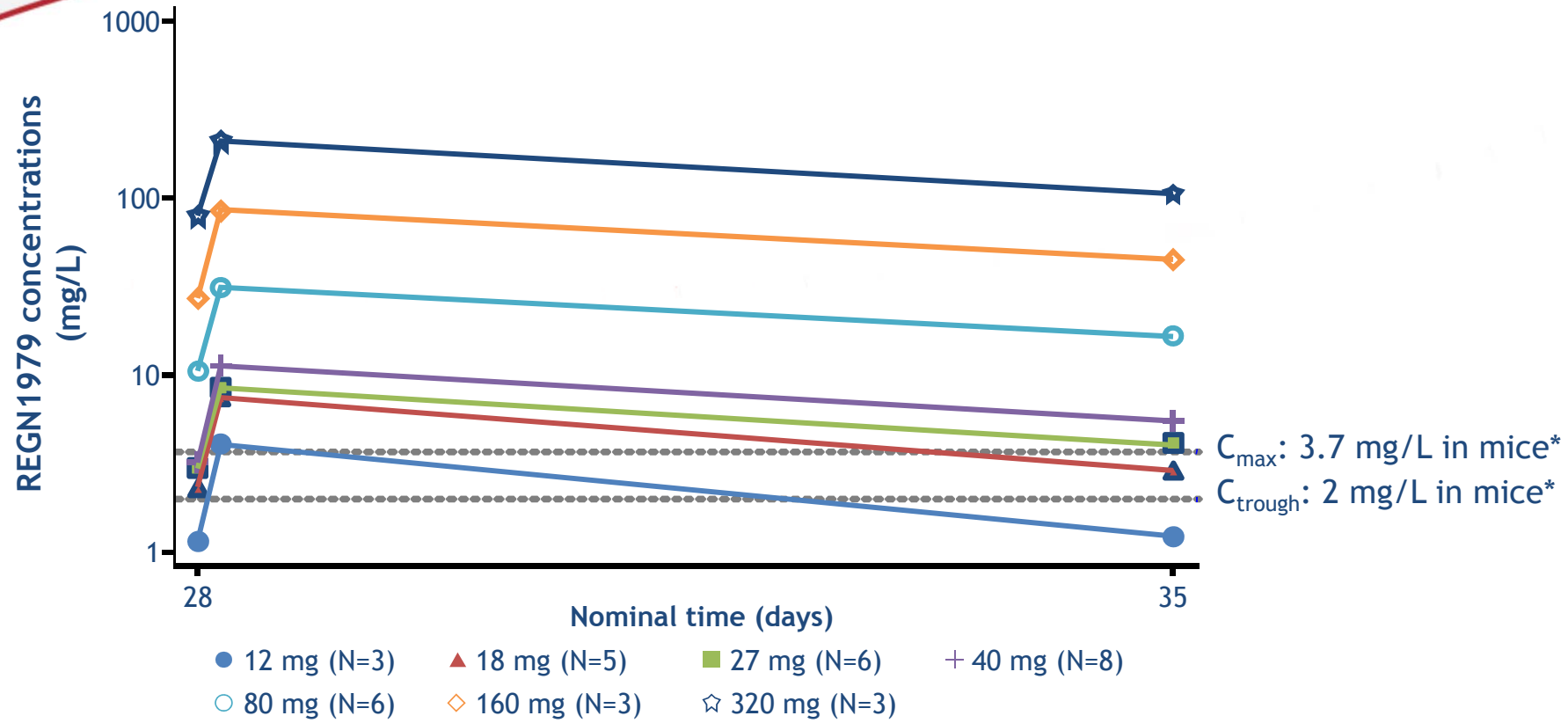
	Total (N=81)
Median age, years (range)	67.0 (30-85)
Male, n (%)	58 (71.6)
B-NHL diagnosis, n (%)	
FL Gr 1-3a	21 (25.9)
DLBCL[ǂ]	45 (55.6)
MCL	6 (7.4)
MZL	6 (7.4)
Other*	3 (3.7)
Ann Arbor stage at study entry	
I-II	13 (16.0)
III-IV	68 (84.0)
Patients with bulky disease, n (%)	
Yes	23 (28.4)
No	58 (71.6)

	Total (N=81)
Median time from end of last prior anti-CD20 antibody containing regimen to first dose of REGN1979, months (range)	6.9 (0.1-100)
Refractory/relapsed[†], n (%)	
Refractory	67 (82.7)
Relapsed	14 (17.3)
Median prior lines of therapy, n (range)	3.0 (1-11)

	Total (N=81)
Patients off study, n (%)	60 (74.1)
Patients who discontinued study, n (%)	52 (64.2)
Progression/recurrence of disease	27 (33.3)
Death	10 (12.3)
Other	7 (8.6)
Subject decision	5 (6.2)
Physician decision	2 (2.5)
AE	1 (1.2)

[ǂ]Includes both primary and transformed *Includes FL Gr 3b, unknown, Waldenstrom macroglobulinemia subtypes; [†]Refractory defined as no response or relapse within ≤6 months, relapsed defined as recurrence >6 months after response to last therapy. AE, adverse event; B-NHL, B-cell non-Hodgkin lymphoma; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

Mean REGN1979 PK Profiles in Week 5 in Patients with B-NHL



*C_{max} and C_{trough} concentrations associated with an effective dose in mice at which the growth of established B-cell (Raji) tumours was inhibited

B-NHL, B-cell non-Hodgkin lymphoma.

Summary of Adverse Events

TEAEs (all grade)*	Total (N=81) n (%)
Pyrexia	67 (82.7)
Cytokine release syndrome	46 (56.8)
Chills	44 (54.3)
Infections and infestations[Ŧ]	40 (49.4)
Increased C-reactive protein	31 (38.3)
Fatigue	31 (38.3)
Anaemia	29 (35.8)
Thrombocytopenia[†]	24 (29.6)
Infusion-related reaction	22 (27.2)
Hypotension	21 (25.9)
Nausea	21 (25.9)
Peripheral oedema	20 (24.7)
Headache	18 (22.2)
Hypophosphatemia	18 (22.2)
Neutropenia	18 (22.2)
Cough	17 (21.0)
Dyspnoea	17 (21.0)
Lymphopenia[†]	17 (21.0)
Vomiting	17 (21.0)

TEAEs Grade 3-4[§]	Total (N=81) n (%)
Anaemia	17 (21.0)
Lymphopenia[†]	16 (19.8)
Neutropenia[†]	14 (17.3)
Infections and infestations[Ŧ]	12 (14.8)
Thrombocytopenia[†]	11 (13.6)
Hypophosphatemia	9 (11.1)
Cytokine release syndrome	6 (7.4)
Fatigue	6 (7.4)
Leukopenia	6 (7.4)
Hypotension	5 (6.2)

TEAEs Grade 5	Total (N=81) n (%)
Cardiac arrest (not-related)	1 (1.2)
Gastric perforation (related)	1 (1.2)
Lung infection (related)	1 (1.2)
Multi-organ failure (not-related)	1 (1.2)
Pneumonia (related)	1 (1.2)

Data as of 15 March 2019; includes data to 320 mg

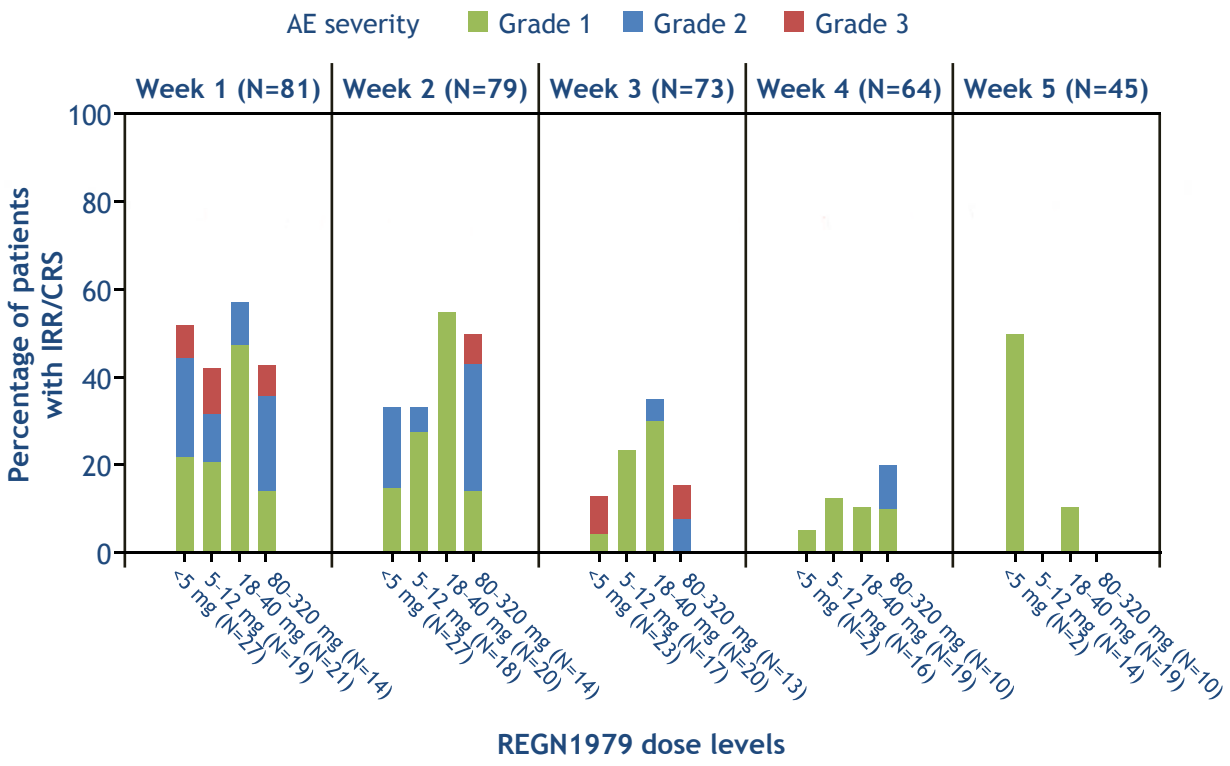
*In ≥20% of patients; [†]Composite terms; thrombocytopenia, lymphopenia, and neutropenia include decrease in platelet count, lymphocytes, and neutrophils, respectively; [Ŧ]SOC term; [§] in >4 patients. TEAEs, treatment-emergent adverse events.

Summary of Adverse Events, Cont'd

- No protocol-defined dose-limiting toxicities among patients with B-NHL
- Four patients discontinued study treatment due to AEs:
  - Gr 3 haemolysis (1)
  - Gr 3 fatigue (1)
  - Gr 3 pneumonia (1)
  - Gr 3 neck abscess (1)
- Infections† were reported in 49.4% of patients [14.8% Grade 3-4, with two deaths (2.5%)]
- Neurologic safety experience:
  - Neurologic AE occurred in 49.5% (all Grade) and 3.7% (Grade 3: somnolence, depressed level of consciousness and syncope in one patient each) of patients. There were no Grade 4 or five neurologic AEs
  - Hallucinations were noted in one of 81 (1.2%) patients [Grade 2]. That patient had prior CAR T-cell therapy
  - No patient had seizures
  - Neurologic AEs were transient, and none required treatment discontinuation
- Ten patients died during the trial. Six due to progressive disease (one with an AE of Grade 5 multi-organ failure), and 1 each with cardiac arrest, gastric perforation, lung infection, and pneumonia

† Comprises SOC terms infections and infestations; AE, adverse event; B-NHL, B-cell non-Hodgkin lymphoma; CAR, chimeric antigen receptor; Gr, grade.

Incidence of IRR/CRS Events: Controlled with Management and Decreases with Time



Incidence of IRR/CRS events during initial treatment with REGN1979.

- Seven patients experienced Gr 3 IRR/CRS; no Gr 4 or 5 IRR/CRS reported
- The severity of IRR/CRS symptoms declined through optimised pre-medication even with REGN1979 dose escalation
- No patient discontinued due to IRR/CRS
- Elevated levels of serum cytokines were observed with dosing; however, no correlation was observed with clinical efficacy

AE, adverse event; Gr, grade; CRS, cytokine release syndrome; IRR, infusion related reaction

High Response Rate Consistent at ≥5 mg: BOR by IWG 2007 Criteria[1] in Patients with R/R FL Gr 1-3a and Opportunity for Assessment at Week 12

	R/R FL Gr 1-3a†			
REGN1979 dose	<5 mg	5-12 mg	18-40 mg	160 mg
	N=7	N=5	N=6	N=1
Overall response rate, n (%)	1 (14.3)	5 (100)	5 (83.4)	1 (100)
Complete response, n (%)	1 (14.3)	4 (80)	4 (66.7)	0
Partial response, n (%)	0	1 (20)	1 (16.7)	1 (100)
Stable disease, n (%)	4 (57.1)	0	1 (16.7)	0
Progressive disease, n (%)	2 (28.6)	0	0	0
Duration of response, median (95% CI), months‡	5.3	NR (5.7-NE)	11.8 (4.4-11.8)	NR

After data cut-off 2 additional evaluable patients*:

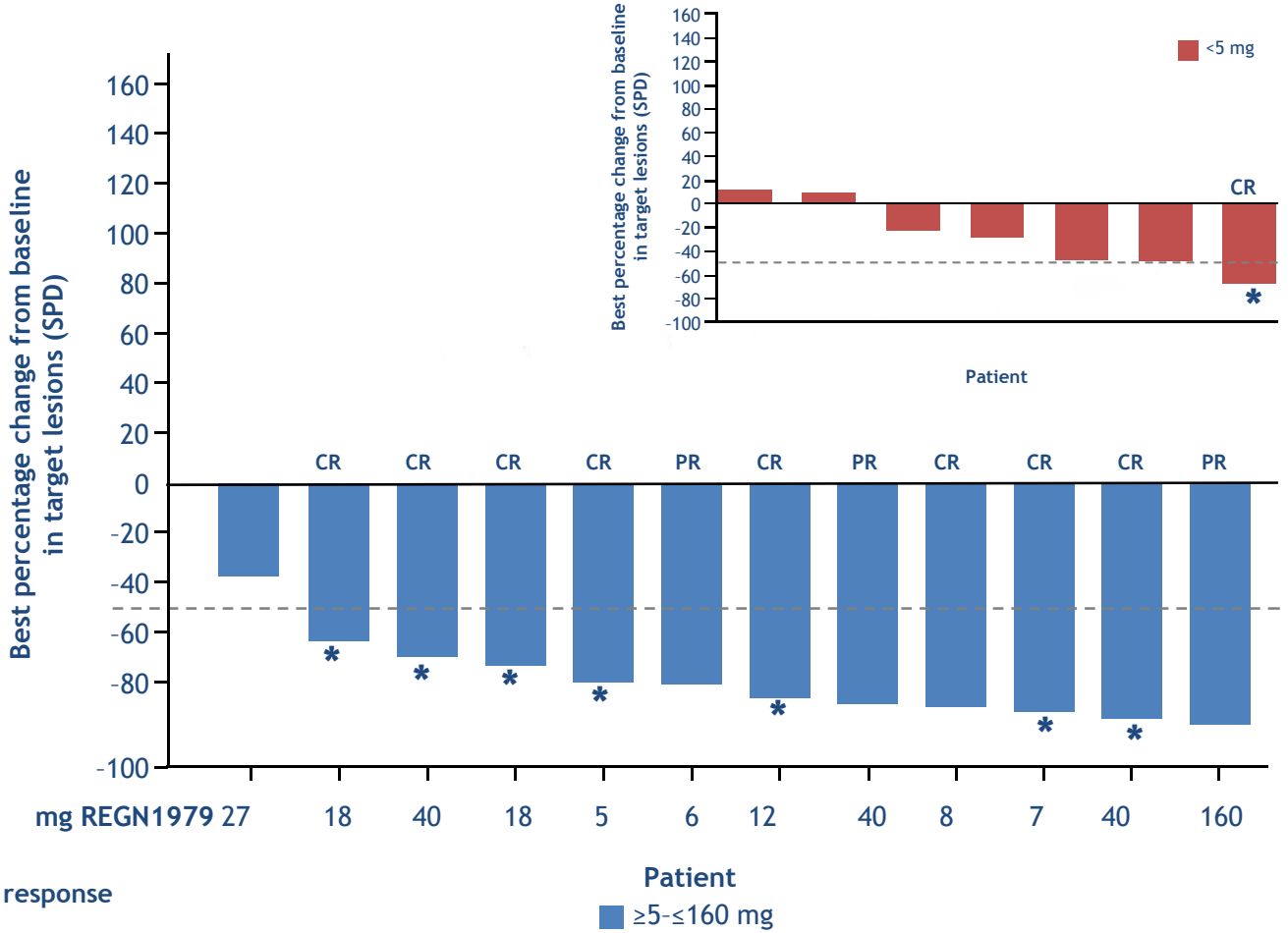
- 2 CRs:
  - 1 at 40 mg
  - 1 at 320 mg

- **Emerging data to date suggests similar response rate at doses ≥ 5 mg*:**
  - **At doses < 5 mg, ORR = 14% (1 of 7), CR = 14% (1 of 7)**
  - **At doses ≥ 5 mg, ORR = 93% (13 of 14), CR = 71% (10 of 14)**

†Data cut off 15 March 2019; no patients were treated with 80 mg dose in this subtype; ‡Kaplan-Meier estimate. *Data not fully monitored.
BOR, best overall response; CI, confidence interval; CR, complete response; FL, follicular lymphoma; Gr, grade; NE, not estimable; NR, not reached; ORR, overall response rate; R/R, relapsed/refractory.

1. Cheson BD. *J Clin Oncol*. 2007; 25:579-586.

High Response Rate Consistent at ≥5 mg: BOR by IWG 2007 Criteria[1] in Patients with R/R FL Gr 1-3a and Opportunity for Assessment at Week 12



***Complete metabolic response**

Data cut off as of 15 March 2019; includes data to 160 mg

[†]Patients were not treated with 80 mg dose in this subtype; BOR, best overall response; CR, complete response; FL, follicular lymphoma; Gr, grade; ORR, overall response rate; PR, partial response; SPD, sum of the product of two perpendicular dimensions; 1. Cheson BD. *J Clin Oncol.* 2007; 25:579-586.

Response Rate Increases at Doses of REGN1979 ≥18 mg: BOR by IWG 2007 Criteria[1] in Patients with R/R DLBCL and Opportunity for Assessment at Week 12

	R/R DLBCL*			
REGN1979 dose	<5 mg	5-12 mg	18-40 mg	80 mg
	N=15	N=11	N=11	N=2
Overall response rate, n (%)	2 (13.3)	2 (18.2)	6 (54.5)	2 (100)
Complete response, n (%)	0	1 (9.1)	2 (18.2)	2** (100)
Partial response, n (%)	2 (13.3)	1 (9.1)	4 (36.4)	0
Stable disease, n (%)	4 (26.7)	4 (36.4)	3 (27.3)	0
Progressive disease, n (%)	8 (53.3)	4 (36.4)	1 (9.1)	0
Missing/unable to evaluate, n (%)	1 (6.7)	1 (9.1)	1 (9.1)	0
Duration of response, median (95% CI), months[Ŧ]	2.1 (1.5-2.6)	NR	4.4 (2.5-NE)	NR

**1/2 of 80 mg patients with CR was CAR T-cell therapy failure

After data cut off[†]:

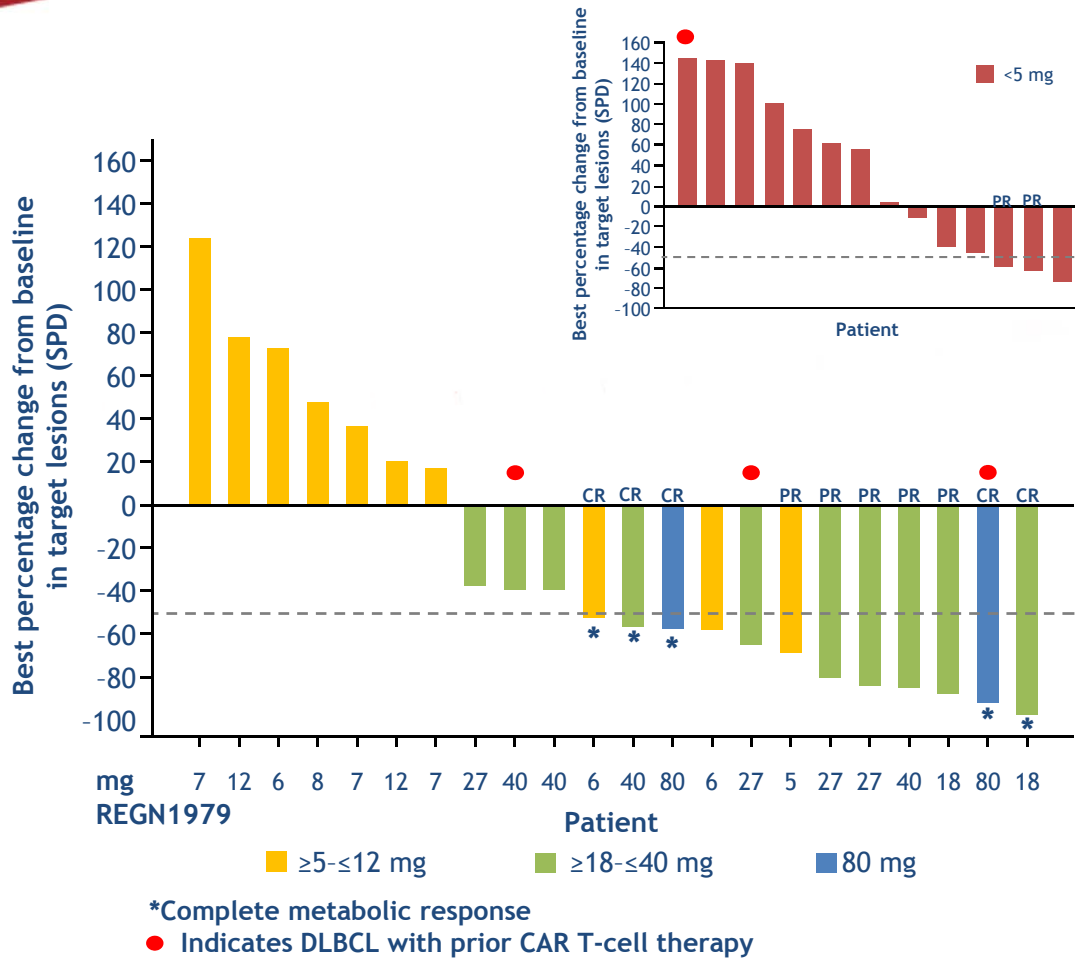
- 5 additional patients assessed (2/5 achieved CRs):
  - 80 mg patient CR at 9 weeks (post CAR T-cell therapy failure)
  - 80 mg patient who failed CAR T-cell therapy died with PD
  - 160 mg patient CR
  - 160 mg patient SD converted to PD prior to week 12
  - 160 mg patient had PD prior to reaching full dose

- **Emerging data to date suggests increasing efficacy with higher doses, with 4 of 7 treated at 80/160 mg achieving CR**
- **All CRs at 80/160 mg CRs are ongoing on study treatment**
- **2 of 4 CRs at 80/160 mg doses are in patients who failed CAR T-cell therapy**

*Data as of 15 March 2019; includes data to 80 mg
[Ŧ]Kaplan-Meier estimate. [†]Data not fully monitored. BOR, best overall response; CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; NE, not estimable; NR, not reached; R/R, relapsed/refractory.

1. Cheson BD. *J Clin Oncol.* 2007; 25:579-586.

Response Rate Increases at Doses of REGN1979 ≥18 mg: BOR by IWG 2007 Criteria[1] in Patients with R/R DLBCL and Opportunity for Assessment at Week 12

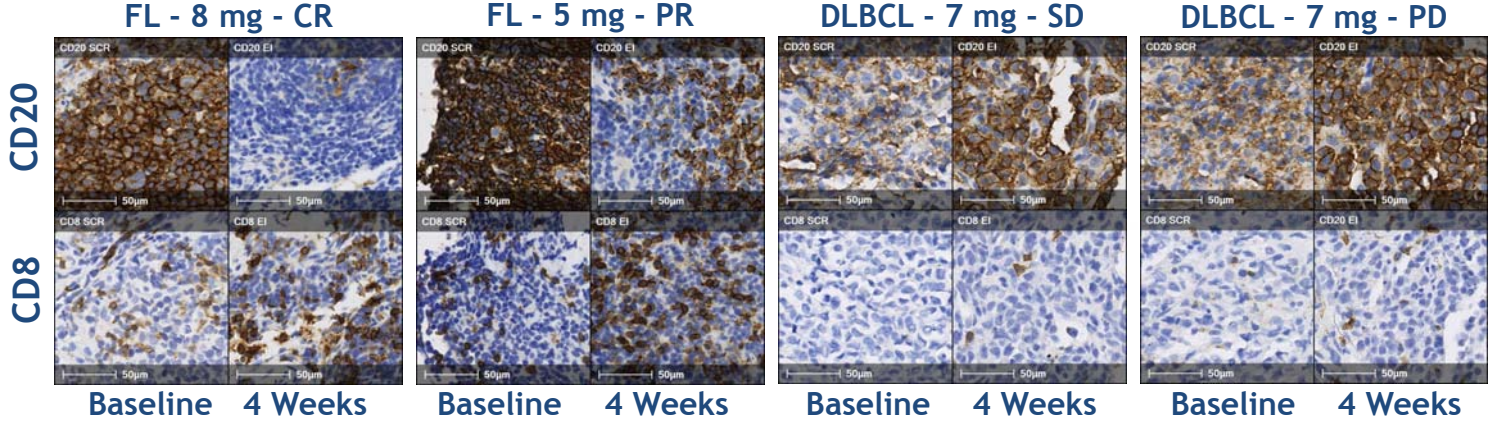


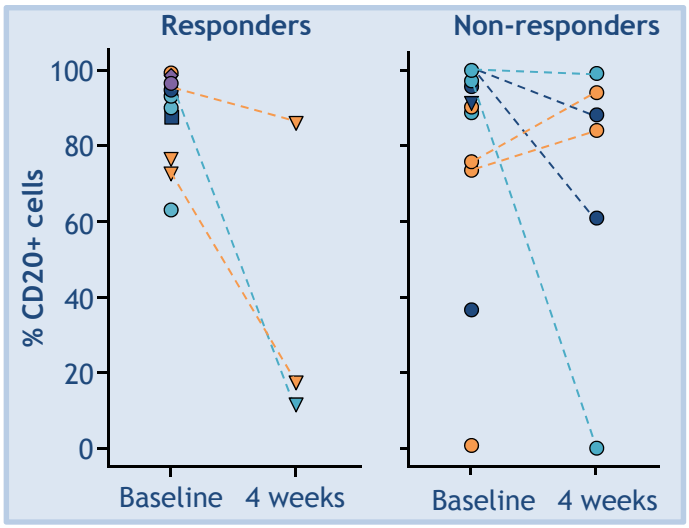
Data as of 15 March 2019

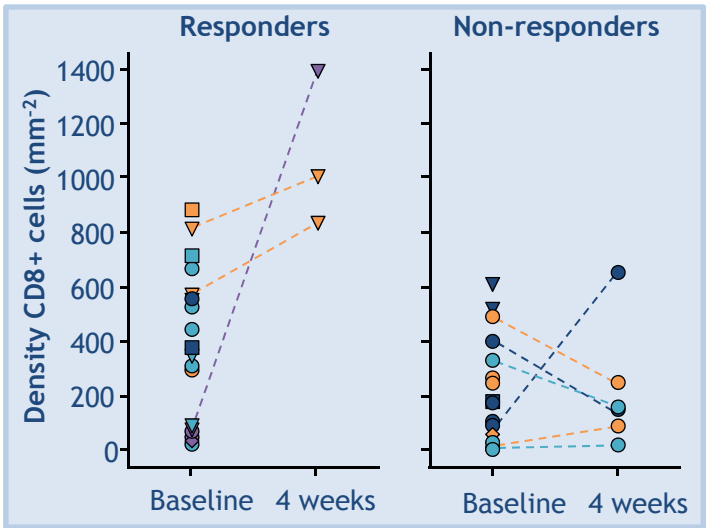
BOR, best overall response; CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; PR, partial response; SPD, sum of the product of two perpendicular dimensions 1. Cheson BD. *J Clin Oncol.* 2007; 25:579-586.

Immunohistological Analysis

Lymph node CD20 expression and CD8 T cell density at baseline and following initiation of REGN1979 treatment





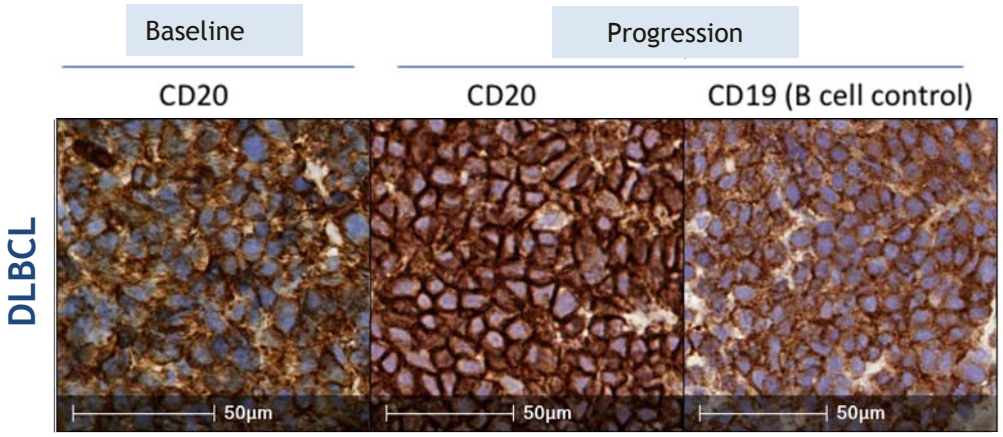


- DLBCL -<5 mg
- DLBCL - 5-12 mg
- DLBCL - 18-40 mg
- DLBCL - 80-160 mg
- FL - <5 mg
- FL - 5-12 mg
- FL - 18-40 mg
- FL - 80-160 mg
- MCL - <5 mg
- MCL - 5-12 mg
- MCL - 18-40 mg
- MCL - 80-160 mg
- MZL - <5 mg
- MZL - 5-12 mg
- MZL - 18-40 mg
- MZL - 80-160 mg

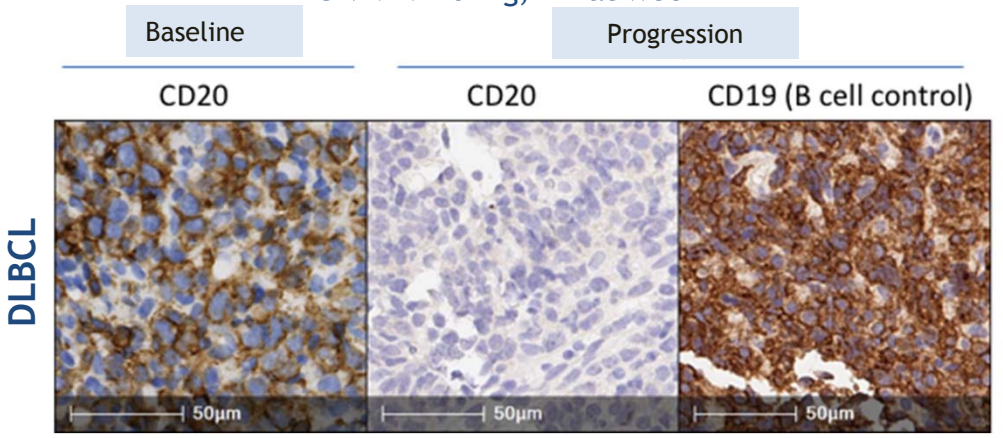
Immunohistological Analysis

DLBCL CD20 expression

- Eleven patients (one MCL, three FL, seven DLBCL) had paired samples at baseline and progression for CD20 IHC analysis
  - All cases positive for CD20 expression at baseline
  - CD20 antigen loss observed at disease progression in seven cases (64%)
    [five of seven had initial response]
  - Disease progression with preserved CD20 expression observed in four cases (36%)
    [two of four had initial response]



REGN1979 40 mg; PD at week 7



REGN1979 18 mg; PR at week 4, 12; PD at week 23

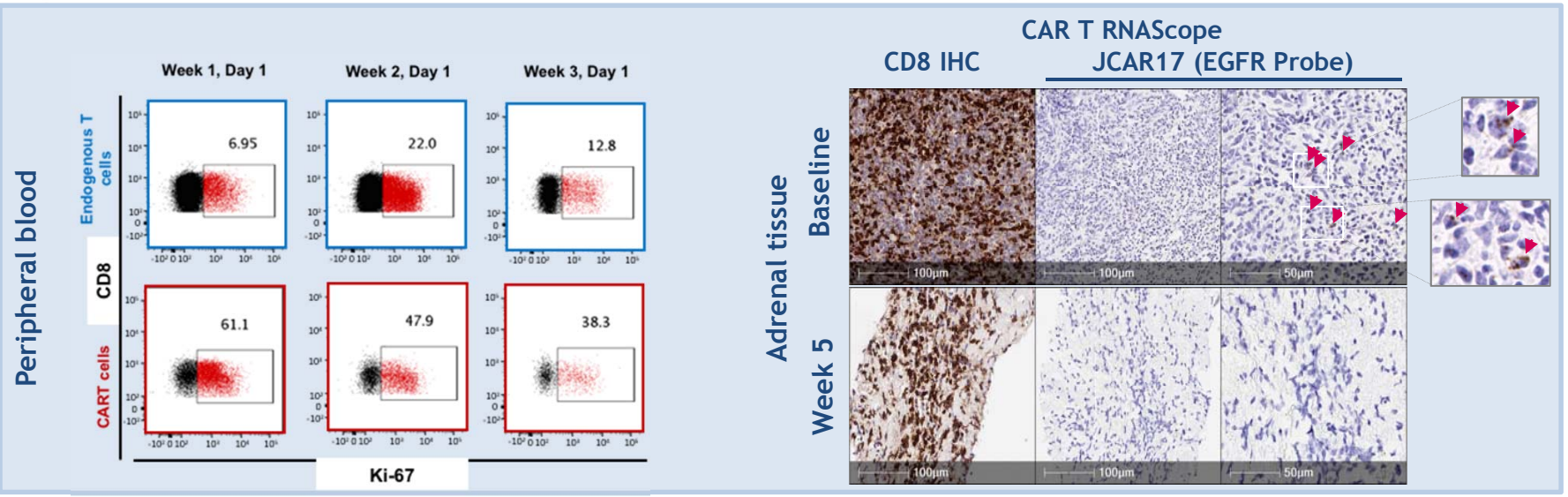
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IHC, ; MCL, mantle cell lymphoma; PD, progressive disease.

Efficacy of REGN1979 Monotherapy after CAR T-Cell Therapy Failure

EUROPEAN HEMATOLOGY ASSOCIATION

Patients with prior CAR T-cell therapy

- Seven DLBCL patients after prior CAR T-cell therapy
- REGN1979 doses ranged from 3 mg to 160 mg
  - One patient at 3 mg had PD, one patient at 27 mg had SD, one patient at 40 mg had PD, and 1 patient at 80 mg had PD
  - 2 patients treated at 80 mg REGN1979 achieved a CR
    - One patient had CR at week 5 (sustained CR at Week 24), continues on study treatment
    - One patient had CR at week 9, continues on study treatment
  - One patient at 160 mg had SD at week 5 but subsequently progressed



- DLBCL patient following CAR T failure treated with 80 mg REGN1979 evaluated for T-cell populations in adrenal tissue (baseline and week 5), and peripheral blood

→

- Induction of endogenous T-cell, but not CAR T proliferation in peripheral blood
- Loss of CAR T in tissue

CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; PD, progressive disease; SD, stable disease; EGFR, epidermal growth factor receptor

Conclusions

Activity observed broadly in heavily pretreated R/R B-NHL patients treated with REGN1979, including some with progression after prior CAR T-cell therapy:

- **FL Gr 1-3a**: 13/14 (93%) ORR [10/14 CR (71%)] at doses ≥5 mg
- **DLBCL:** 4/7 ORR [all CR] at doses of 80/160 mg, with two patients achieving CR after failure of CD19-directed CAR T-cell therapy
- **Mantle cell lymphoma**: 3/3 responses at doses ≥ 5 mg, including one CR (data not shown)
- **Marginal zone lymphoma**: 3/5 responses at doses ≥ 5 mg, including two CR (data not shown)

Tolerability in patients with B-NHL has been demonstrated at doses up to 320 mg weekly, with no observed DLTs in patients with B-NHL

- Majority of adverse events were mild-to-moderate in severity
- Infections were reported in 49.4% of patients (14.8% Grade 3-4), with two events leading to death (2.5%); 1 additional death related to study treatment was due to gastric perforation
- 4 of 81 patients discontinued treatment due to adverse event; no patient discontinued due to IRR/CRS or neurologic adverse event

Based on these data, a phase 2 study in R/R FL Gr 1-3a, DLBCL, and other B-NHL subtypes is planned

B-NHL, B-cell non-Hodgkin lymphoma; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DLTs, dose-limiting toxicities; FL, follicular lymphoma; Gr, grade; IRR, infusion related reaction; ORR, overall response rate

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