Clinical Activity of REGN1979, a Bispecific Human, Anti-CD20 x Anti-CD3 Antibody, in Patients with Relapsed/Refractory (R/R) B-cell Non-Hodgkin Lymphoma (B-NHL)

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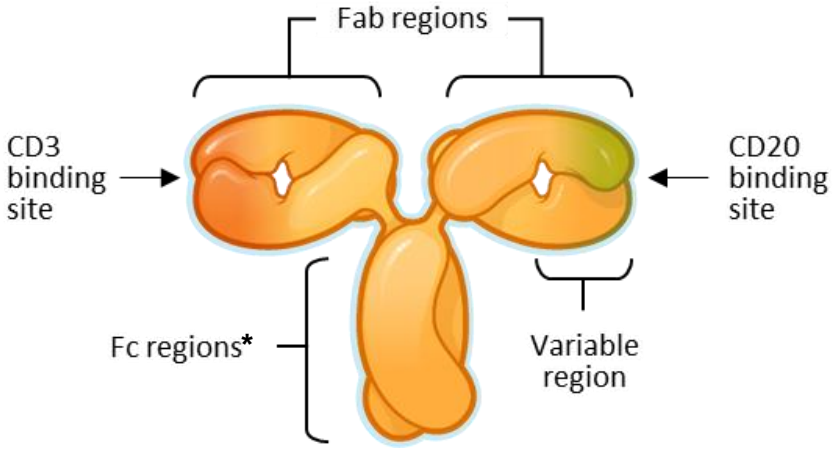
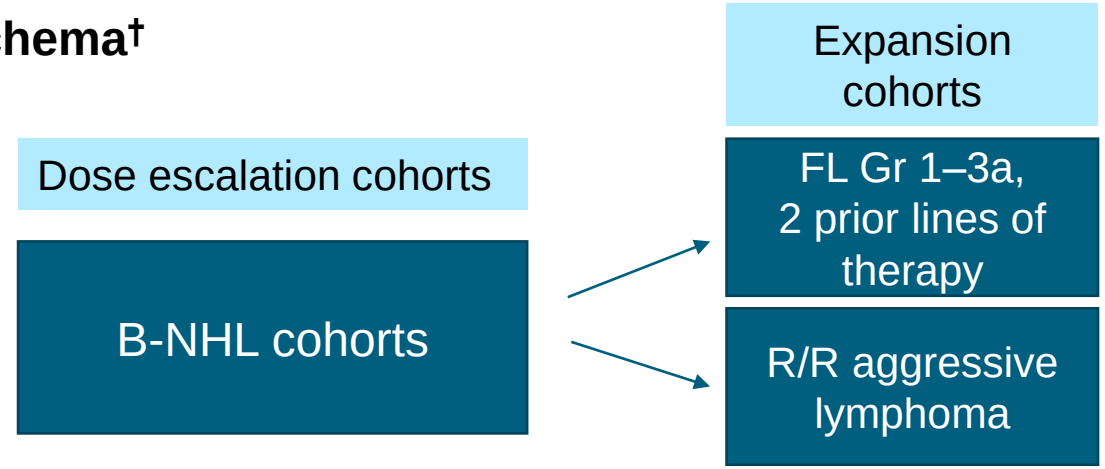
Abstract #626

REGN1979, anti-CD20 x anti-CD3 bispecific antibody: structure and first-in-human study design

REGN1979 molecular structure



Study schema†



- REGN1979 is an anti-CD20 x anti-CD3 bispecific IgG4 Ab
- Designed to cross-link and activate CD3 expressing T-cells upon contact with CD20+ B-cells, thereby killing CD20+ tumor cells independent of T-cell receptor recognition[1,2]

- Primary objectives:
  - Safety
  - Tolerability
  - DLTs
- Secondary objectives:
  - Antitumor activity
  - Pharmacokinetics
  - Immunogenicity
- REGN1979 was administered using an escalating dose schedule consisting of initial, intermediate, and step-up dose

*IgG3 substitution on fragment crystalizable (Fc) regions is associated with the CD3 arm; †CLL arm of study not shown.
Ab, antibody; B-NHL, B-cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLT, dose-limiting toxicity; FL, follicular lymphoma; Gr, grade; R/R, relapsed/refractory.
1. Smith EJ et al. *Sci Rep*. 2015;5:17943. 2. Choi BD et al. *Expert Opin Biol Ther*. 2011;11:843–853.

Patient demographics and baseline characteristics: heavily pre-treated and refractory population

Patient and disease characteristics	Total N=110
Median age, years (range)	67.0 (30–88)
Male, **n** (%)	**77** (70.0)
ECOG Performance Status, **n** (%)	
0	**47** (42.7)
1	**63** (57.3)
Ann Arbor stage at study entry, **n** (%)	
I–II	**16** (14.5)
III–IV	**94** (85.5)
B-NHL diagnosis, **n** (%)	
DLBCL	**61** (55.5)
FL Gr 1–3a	**31** (28.2)
MCL	**9** (8.2)
MZL	**6** (5.5)
Other*	**3** (2.7)

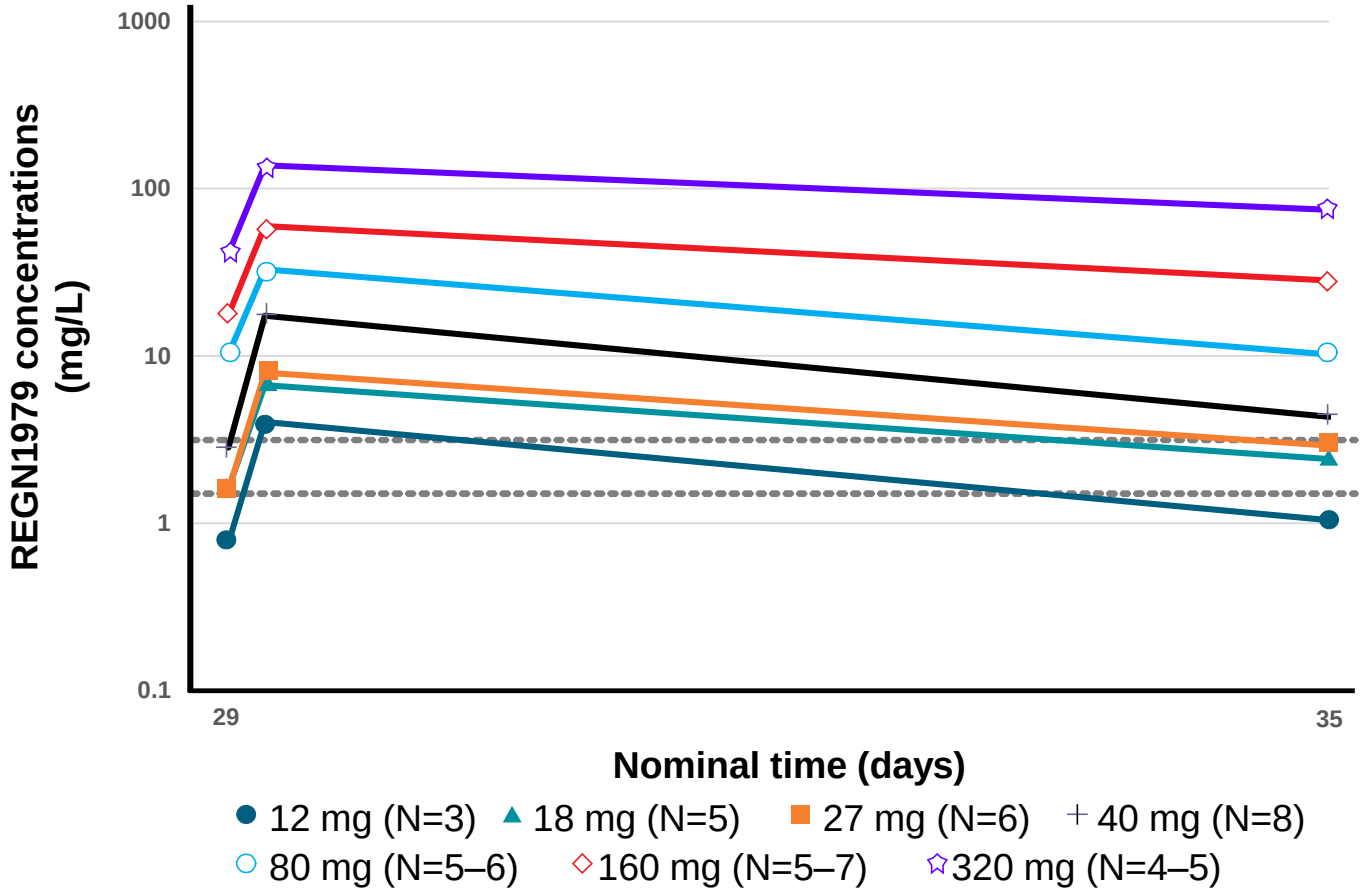
Prior treatment	Total N=110
Median prior lines of cancer-related systemic therapy, n (range)	3 (1–11)
R/R to last treatment†, **n** (%)	
Refractory	**88** (80.0)
Relapsed	**17** (15.5)
Missing	**5** (4.5)

Patient disposition	Total N=110
Patients continuing on study, **n** (%)	**31** (28.2)
Patients who completed study, **n** (%)	**10** (9.1)
Patients who discontinued study, **n** (%)	**69** (62.7)
Progression/recurrence of disease	**35** (31.8)
Death	**13** (11.8)
Other	**9** (8.2)
Physician decision	**6** (5.5)
Subject decision	**5** (4.5)
Adverse event	**1** (0.9)

Data cut-off date: September 03, 2019

*Other includes FL Gr 3b or Gr unknown, Waldenström macroglobulinemia; †Refractory defined as no response or relapse within ≤6 months, relapsed defined as recurrence >6 months after response to last therapy. B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; Gr, grade; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory.

Mean REGN1979 PK profiles during Week 5 for patients with B-NHL: linear PK, $t_{1/2}$ ~ > 1 week at effective doses



Efficacious C_{max} and C_{trough} concentrations in mice

C_{max}: 3.7 mg/L in mice

C_{trough}: 2 mg/L in mice

- REGN1979 exposure increased with dose approximately linearly
- At ≥40 mg, REGN1979 exposure in humans was higher than the efficacious exposures in mice at which growth of established B-cell (Raji) tumors was inhibited

B-NHL, B-cell non-Hodgkin lymphoma; C_{max}, maximum concentration; C_{trough}, minimum concentration; PK, pharmacokinetics.

Data cut-off date: September 03, 2019

Safety and summary of adverse events in 110 patients: Gr 3 CRS was 6.4%; no seizures

TEAE (any Gr)*	Total (N=110) n (%)
Pyrexia	88 (80.0)
CRS	65 (59.1)
Chills	56 (50.9)
Infections and infestations†	55 (50.0)
Fatigue	40 (36.4)
Anemia	39 (35.5)
Increased C-reactive protein	34 (30.9)
Hypotension	33 (30.0)
Hypophosphatemia‡	33 (30.0)
Thrombocytopenia‡	31 (28.2)
Nausea	30 (27.3)
Cough	28 (25.5)
IRR	27 (24.5)
Tachycardia	27 (24.5)
Headache	27 (24.5)
Peripheral edema	25 (22.7)
Neutropenia‡	25 (22.7)
Dyspnea	24 (21.8)
Lymphopenia‡	23 (20.9)
Vomiting	23 (20.9)
Decreased appetite	23 (20.9)

TEAE (Gr 3–4)§	Total (N=110) n (%)
Anemia	24 (21.8)
Hypophosphatemia‡	21 (19.1)
Neutropenia‡	21 (19.1)
Lymphopenia‡	21 (19.1)
Thrombocytopenia‡	15 (13.6)
Leukopenia‡	11 (10.0)
Increased aspartate aminotransferase	9 (8.2)
Hypotension	9 (8.2)
Increased alanine aminotransferase	7 (6.4)
CRS	7 (6.4)
Fatigue	6 (5.5)
Dyspnea	6 (5.5)
Hyperglycemia	6 (5.5)

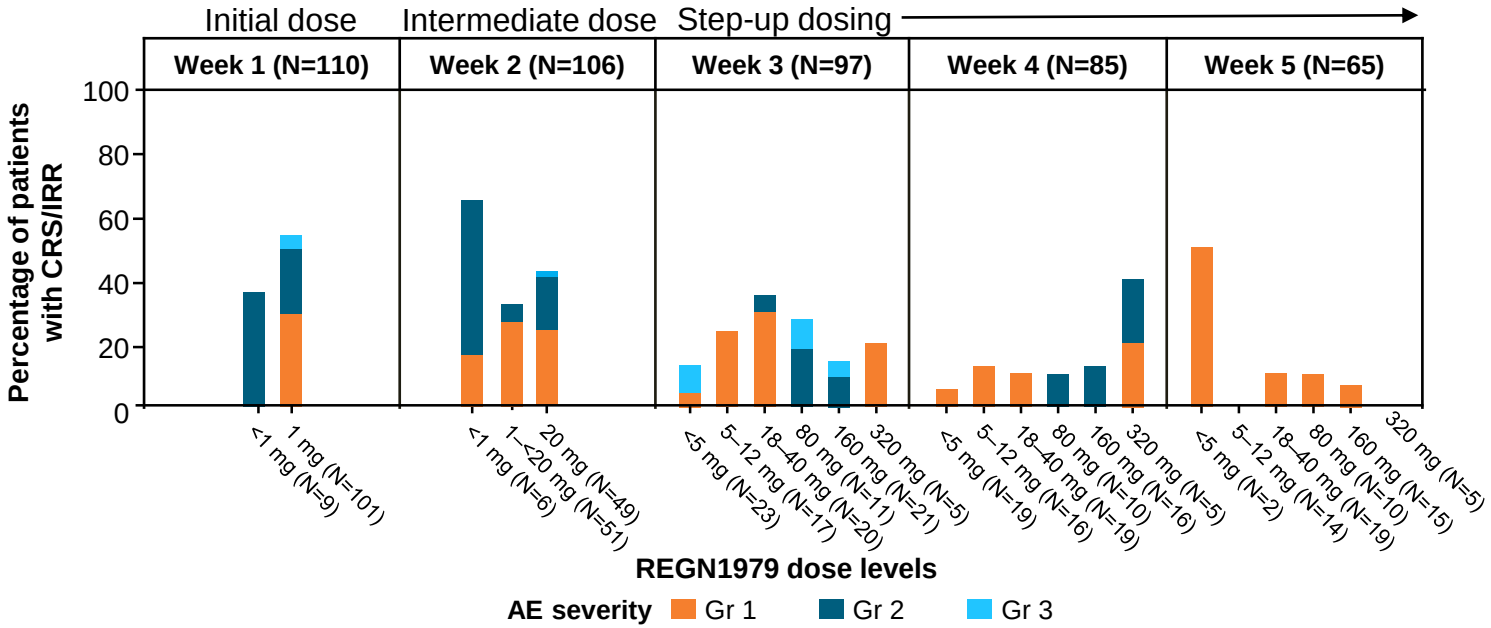
TEAE (Gr 5)	Total (N=110) n (%)
Cardiac arrest (unrelated)	1 (0.9)
Gastric perforation	1 (0.9)
Lung infection	1 (0.9)
Multi-organ failure (unrelated)	1 (0.9)
Acute renal failure (unrelated)	1 (0.9)
Pneumonia	1 (0.9)

*Occurred in ≥20% of patients; †Comprises SOC terms infections and infestations; ‡Composite terms; thrombocytopenia, lymphopenia, neutropenia, leukopenia, and hypophosphataemia include decrease in platelet count, lymphocytes, neutrophils, white blood cells, and blood phosphorus, respectively; §Occurred in >5 patients. CRS, cytokine release syndrome; Gr, grade; IRR, infusion-related reaction; SOC, system organ class; TEAE, treatment-emergent adverse event.

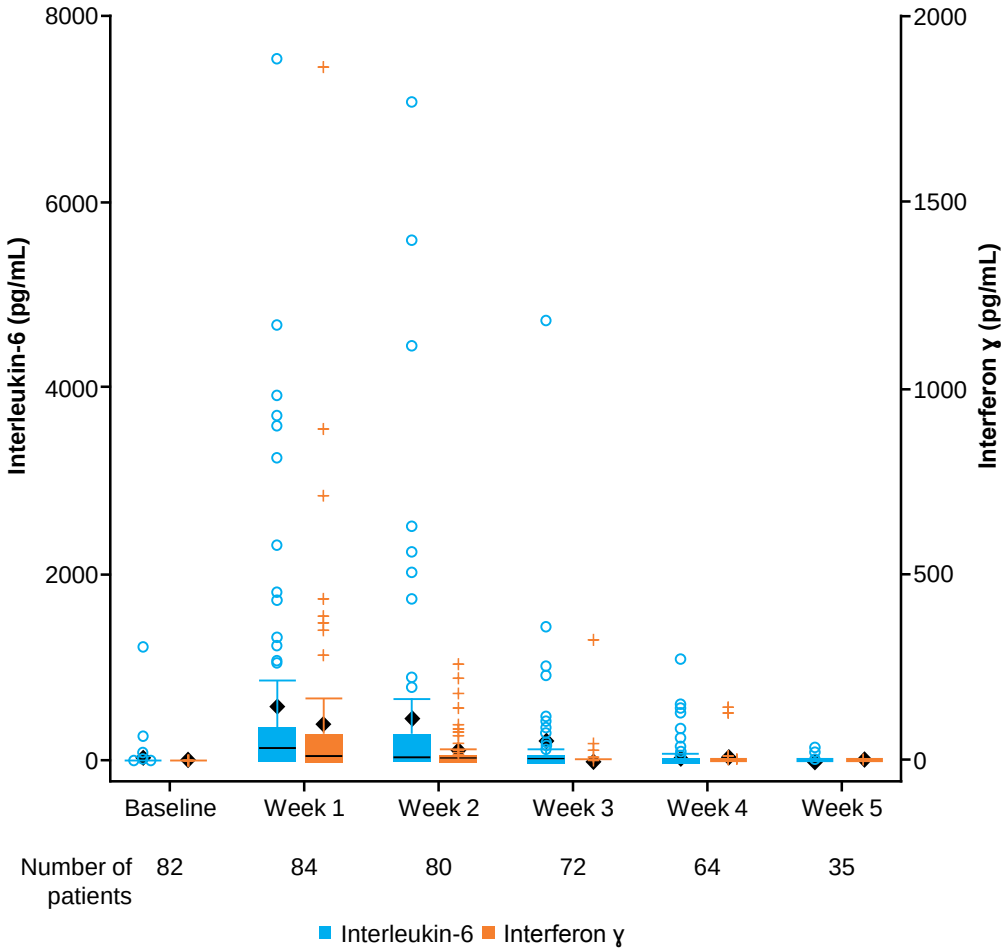
Data cut-off date: September 03, 2019

Step-up dosing mitigates IRR/CRS events and allows subsequent dosing up to 320 mg

- IRR/CRS events occurred predominantly during Weeks 1–3 and declined thereafter, without dose-dependent increase in incidence or severity
- At data cut-off, eight patients experienced Gr 3 IRR/CRS*, without reported Gr 4 or 5 IRR/CRS events†
  - After data cut-off, one patient with aggressive MCL blastoid variant, with bone marrow involvement and bulky disease, experienced Gr 4 CRS (and TLS)
- No patient discontinued due to IRR/CRS



Transient increase in cytokine levels following REGN1979 dosing



*IRR, infusion-related reaction according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03; CRS, cytokine release syndrome according to adapted Lee DW et al. *Blood* 2014;124:188–195.; †For patients who experienced both IRR and CRS during the same week, the maximum Gr of either was used. AE, adverse event; Gr, grade; MCL, mantle cell lymphoma; TLS, tumor lysis syndrome.

Data cut-off date: September 03, 2019

Safety and summary of adverse events

- No patients with B-NHL experienced a DLT during dose escalation; MTD not reached
- The most common TEAEs were pyrexia (n=88), CRS (n=65), chills (n=56), fatigue (n=40), and anemia (n=39)
- The most common Gr 3 or 4 AEs were anemia (n=24), hypophosphatemia (n=21), lymphopenia (n=21), and neutropenia (n=21)
- Neurologic AEs were transient, and none required treatment discontinuation. There were no seizures or Gr 4 or 5 neurologic AEs.
- Six patients discontinued study drug due to treatment-related AEs: Gr 1: CMV infection (n=1); Gr 3: hemolysis (n=1); fatigue (n=1); pneumonia (n=2); toxoplasmosis* (n=1). Two patients discontinued due to AEs unrelated to treatment (both Gr 3): neck abscess (n=1); worsening cytopenia (n=1).
- Infections and infestations† were reported in 50% of patients [20% Gr 3–4, with two deaths (1.8%)]
- 15 patients died during the study: progressive disease (n=10, one with Gr 5 multi-organ failure and one with Gr 5 renal failure acute); gastric perforation, cardiac arrest, lung infection, pneumonia (n=1 each); one patient died of fungal pneumonia 7 months after treatment discontinuation
- After data cut-off, one patient in an expansion cohort died of tumor lysis syndrome (TLS); this was a patient with MCL blastoid variant with bone marrow involvement and bulky disease

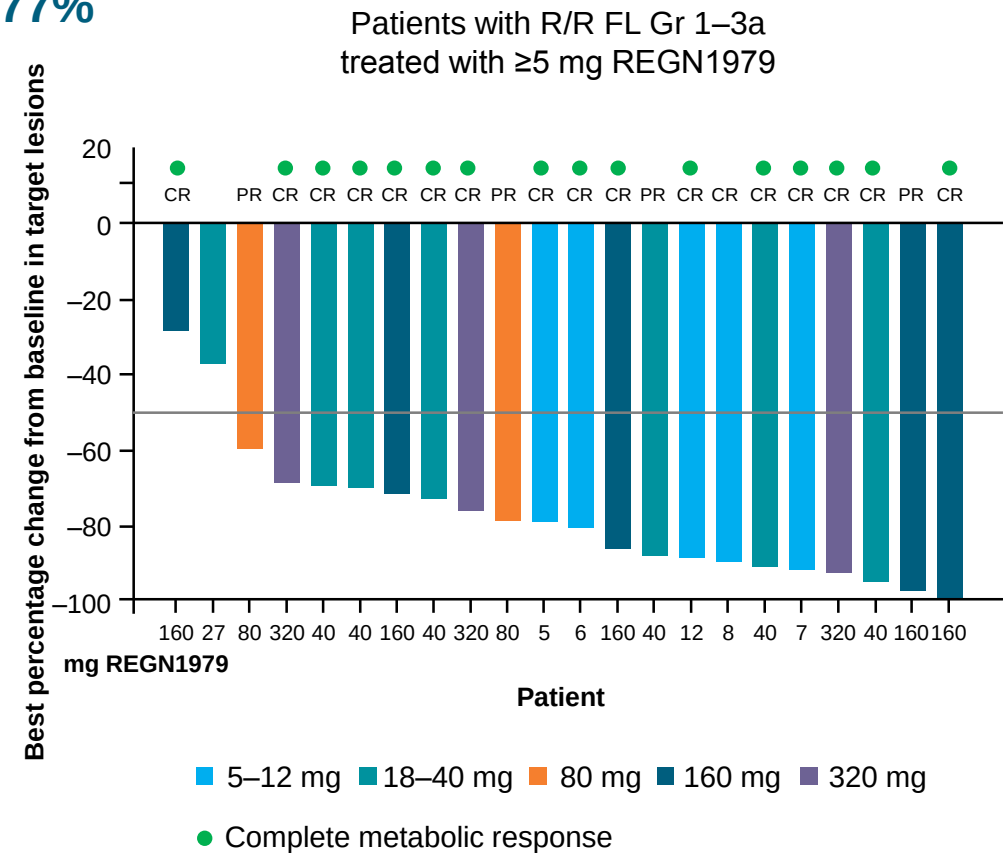
*Corrected from encephalopathy after data cut; †Comprises SOC terms infections and infestations.
AE, adverse event; B-NHL, B-cell non-Hodgkin lymphoma; CMV, cytomegalovirus; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; Gr, grade; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; SOC, system organ class; TEAE, treatment-emergent AE.

Data cut-off date: September 03, 2019

Overall response rate in patients with R/R FL Gr 1–3a and an opportunity for assessment at Week 12*

ORR/CR rate in patients treated with REGN1979 ≥5 mg was 95%/77%

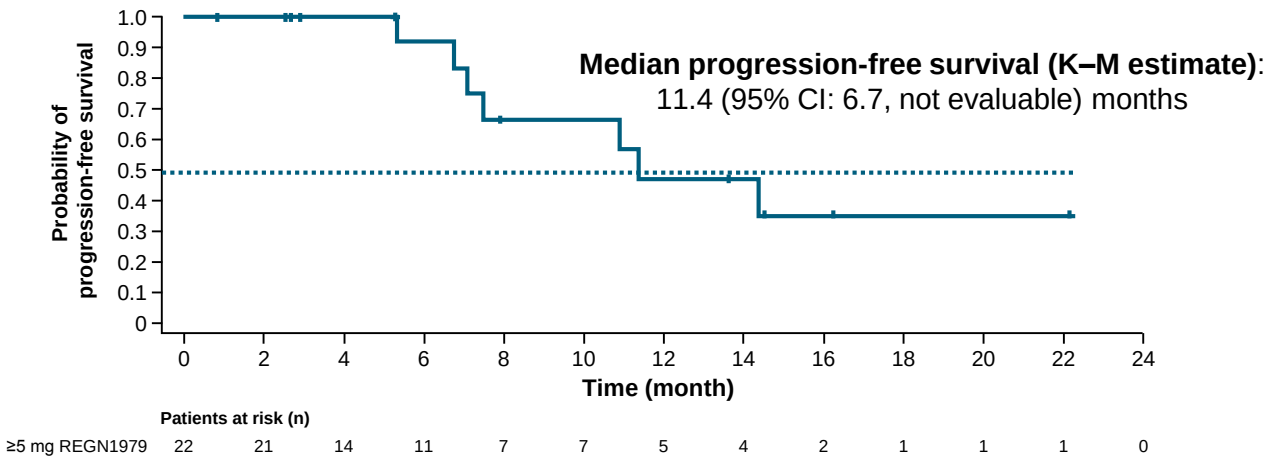
BOR by Lugano Criteria[1]	REGN1979 dose groups						
	<5 mg (N=7)	5–12 mg (N=5)	18–40 mg (N=7)	80 mg (N=2)	160 mg (N=5)	320 mg (N=3)	Total for ≥5 mg (N=22)
ORR (CR/PR), **n** (%)	**1** (14.3)	**5** (100)	**6** (85.7)	**2** (100)	**5** (100)	**3** (100)	**21** (95.5)
Complete response	**1** (14.3)	**5** (100)	**5** (71.4)	0	**4** (80.0)	**3** (100)	**17** (77.3)
Partial response	0	0	**1** (14.3)	**2** (100)	**1** (20.0)	0	**4** (18.2)
Stable disease	**4** (57.1)	0	**1** (14.3)	0	0	0	**1** (4.5)
Progressive disease	**2** (28.6)	0	0	0	0	0	0



*First dose at least 12 weeks before data cut-off. BOR, best overall response; CR, complete response; FL, follicular lymphoma; Gr, grade; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory. 1. Cheson BD et al. *J Clin Oncol.* 2014;32:3059–3067.

Data cut-off date: September 03, 2019

Median progression-free survival in patients with R/R FL Gr 1–3a and an opportunity for assessment at Week 12* was 11.4 months



Censored patients for current K–M estimates are mostly due to relatively short follow-up

In patients with FL Gr 1–3a treated with ≥5 mg REGN1979 (n=22)	
Median duration of follow-up (range), months	6.8 (1.0–22.1)
Number of patients with ongoing responses at the last tumor assessment†	14 of 21
Number of patients with ongoing CRs at the last tumor assessment†	12 of 17

*Includes patients treated with ≥5 mg REGN1979 and first dose at least 12 weeks before data cut-off. ; †Includes patients with responses that are ongoing or have completed the study without experiencing progressive disease or death at their last tumor assessment. CI, confidence interval; CR, complete response; FL, follicular lymphoma; Gr, grade; K–M, Kaplan–Meier; R/R, relapsed/refractory.

Overall response rate in patients with R/R DLBCL and an opportunity for assessment at Week 12*

ORR/CR rate in patients treated with REGN1979 ≥80 mg: 58%/42%

Without prior CAR T-cell therapy† with REGN1979 ≥80 mg: 71%/71%

With prior CAR T-cell therapy† with REGN1979 ≥80 mg: 50%/25%

	REGN1979 dose groups						
BOR by Lugano Criteria[1]	<5 mg (N=15)	5 mg–12 mg (N=11)	18 mg–40 mg (N=11)	80 mg (N=6)	160 mg (N=11)	320 mg (N=2)	Total ≥80mg (N=19)
ORR (CR/PR), **n** (%)	**2** (13.3)	**2** (18.2)	**6** (54.5)	**5** (83.3)	**5** (45.5)	**1** (50.0)	**11** (57.9)
Complete response	0	**1** (9.1)	**2** (18.2)	**4** (66.7)	**3** (27.3)	**1** (50.0)	**8** (42.1)
Partial response	**2** (13.3)	**1** (9.1)	**4** (36.4)	**1** (16.7)	**2** (18.2)	0	**3** (15.8)
Stable disease	**4** (26.7)	**4** (36.4)	**3** (27.3)	0	**1** (9.1)	**1** (50.0)	**2** (10.5)
Progressive disease	**8** (53.3)	**4** (36.4)	**1** (9.1)	**1** (16.7)	**2** (18.2)	0	**3** (15.8)
Not available	**1** (6.7)	**1** (9.1)	**1** (9.1)	0	**3** (27.3)	0	**3** (15.8)

	Without prior CAR T at doses ≥80 mg	With prior CAR T at doses ≥80 mg
BOR by Lugano Criteria[1]	Total (N=7)	Total (N=12)
ORR (CR/PR), n (%)	**5** (71.4)	**6** (50.0)
Complete response	**5** (71.4)	**3** (25.0)
Partial response	0	**3** (25.0)
Stable disease	**1** (14.3)	**1** (8.3)
Progressive disease	**1** (14.3)	**2** (16.7)
Not available	0	**3** (25.0)

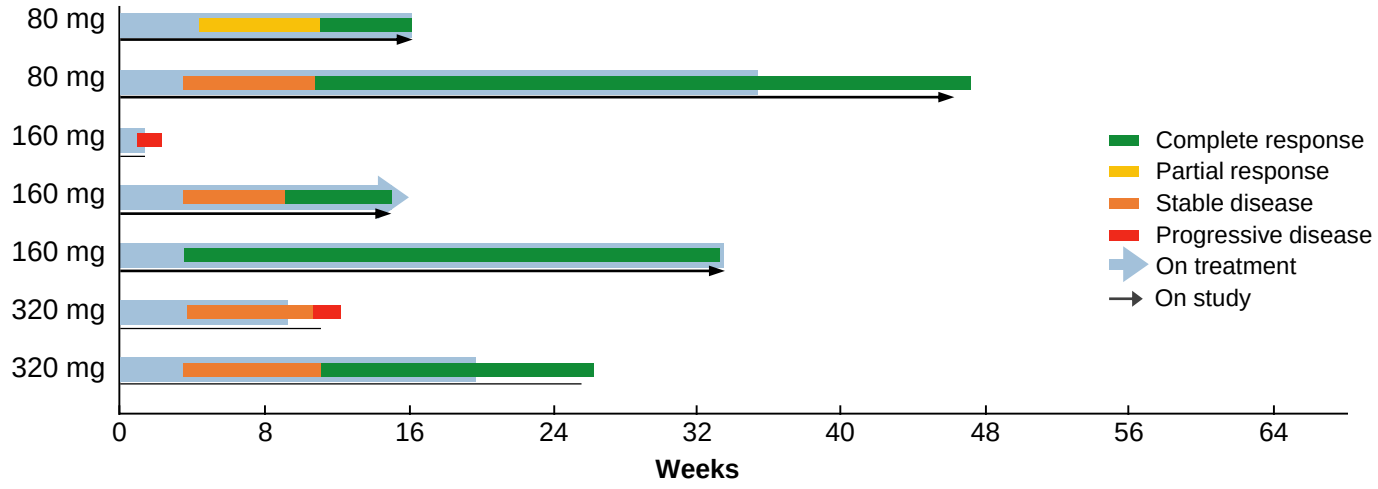
*First dose at least 12 weeks before data cut-off. †CD19-directed CAR T-cell therapy.
BOR, best overall response; CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory.

1. Cheson BD et al. *J Clin Oncol.* 2014;32:3059–3067.

Data cut-off date: September 03, 2019

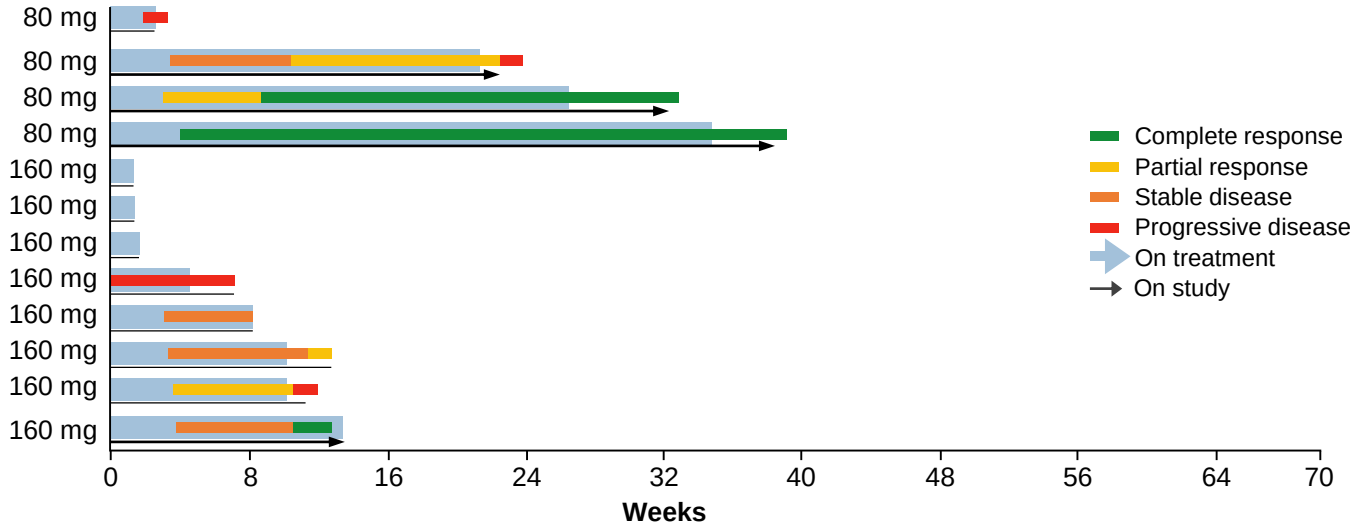
All CRs in patients with R/R DLBCL and an opportunity for assessment at Week 12 are ongoing

In patients **without prior CAR T-cell therapy** with first dose at least 12 weeks before data cut-off†



In patients with DLBCL without prior CAR T-cell therapy treated with ≥80 mg REGN1979 (n=7)	
Median duration of follow-up (range), months	5.3 (1.2–11.8)
Number of patients with ongoing responses at the last tumor assessment*	5 of 5
Number of patients with ongoing CRs at the last tumor assessment*	5 of 5

In patients who **previously failed CAR T-cell therapy** with first dose at least 12 weeks before data cut-off†

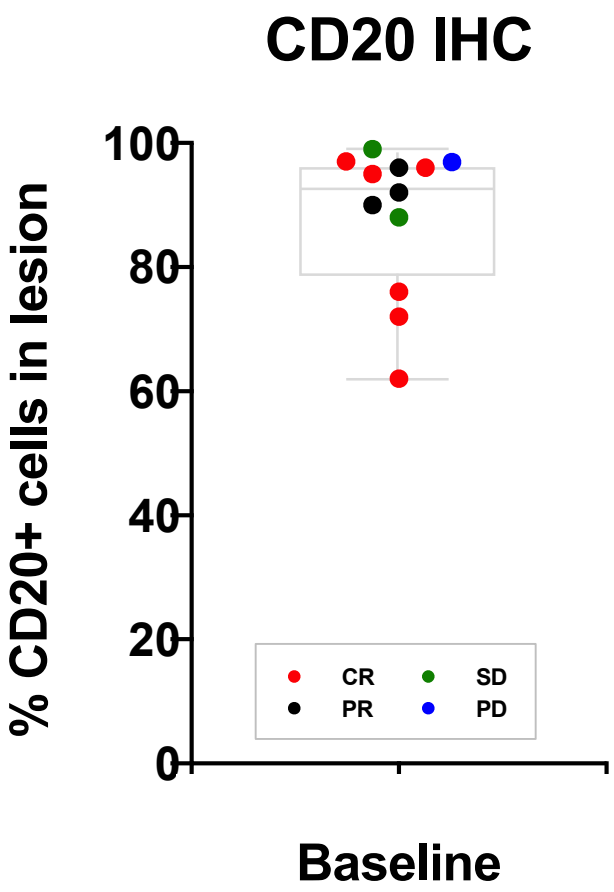


All CRs remain ongoing at the last tumor assessment; responses appear durable

In patients with DLBCL with prior CAR T-cell therapy treated with ≥80 mg REGN1979 (n=12)	
Median duration of follow-up (range), months	2.6 (0.4–9.9)
Number of patients with ongoing responses at the last tumor assessment*	4 of 6
Number of patients with ongoing CRs at the last tumor assessment*	3 of 3

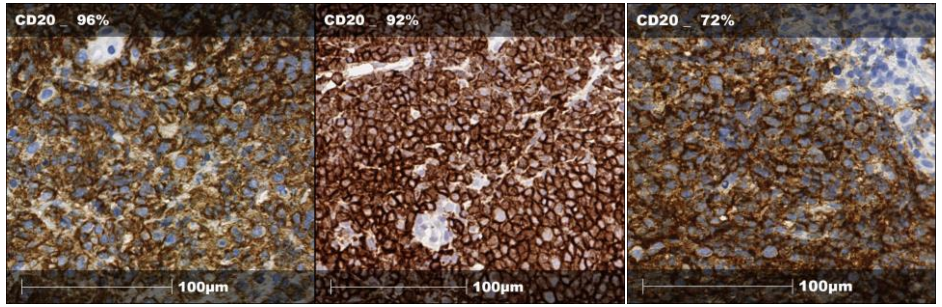
*Includes patients with responses that are ongoing or have completed the study without experiencing progressive disease or death at their last tumor assessment. †Includes patients treated with ≥80 mg REGN1979; CAR T-cell therapy refers to CD19-direct CAR T-cell therapy. CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; R/R, relapsed/refractory.

Baseline CD20 level does not predict response/non-response; some progression may be associated with loss of CD20

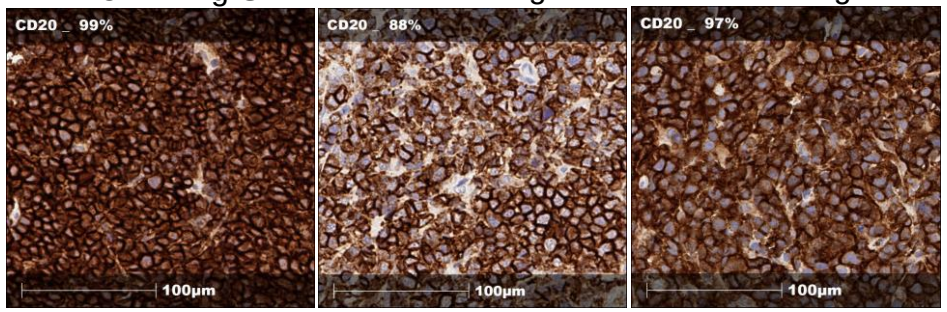


BASELINE

DLBCL-27mg-PR | DLBCL-27mg-PR | FL-8mg-CR



DLBCL-27mg-SD | DLBCL-27mg-SD | DLBCL-40mg-PD



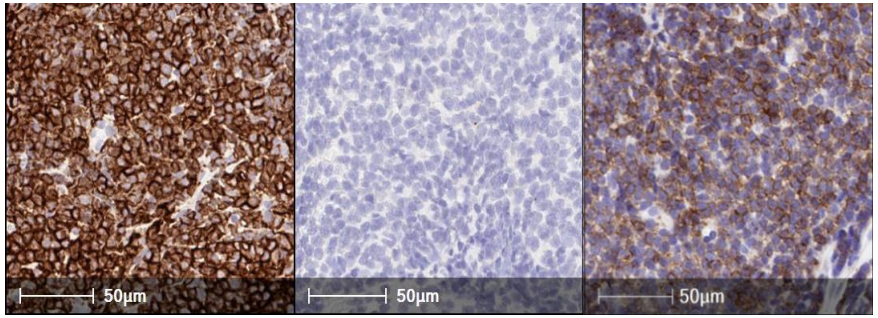
Responders

Non-responders

ON PROGRESSION

Baseline | Progression

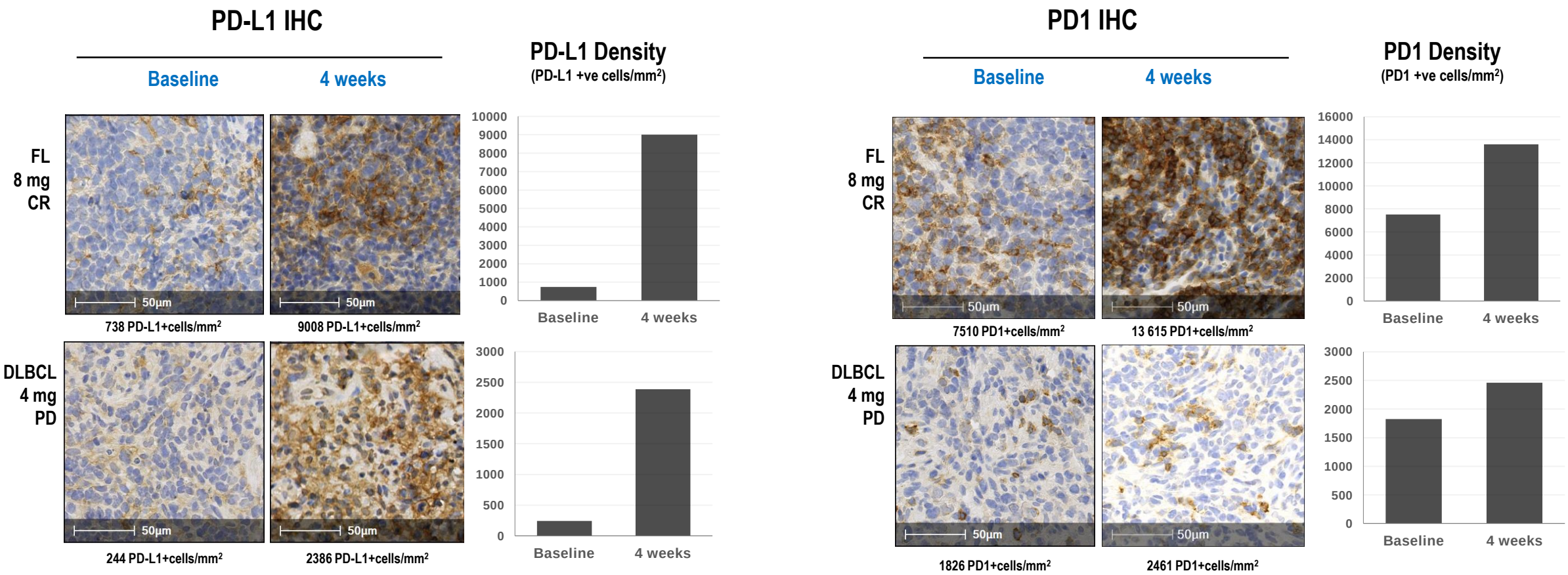
CD20 | CD20 | CD19 (B-cell control)



REGN1979 27 mg; PR at Week 4, 12; PD at Week 24

CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease.

Increases in PD-L1 expression and PD-1+ TIL density observed in malignant lymph node tissue following REGN1979 treatment



CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IHC, immunohistochemistry; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, PD ligand-1; TIL, tumor-infiltrating lymphocyte.

Conclusions

- REGN1979 is a human anti-CD20 x anti-CD3 bispecific IgG4 antibody with an acceptable safety profile at doses up to 320 mg weekly
  - No DLTs were observed during dose escalation in patients with R/R B-NHL
  - The majority of AEs were mild-to-moderate in severity; no significant neurotoxicity has been observed
  - Step-up dosing and supportive care measures mitigated IRR/CRS events; no B-NHL patient discontinued due to IRR/CRS
  - The most common AEs were pyrexia (n=88; 80.0%), CRS (n=65; 59.1%), and chills (n=56; 50.9%)
- REGN1979 has shown antitumor activity in heavily pre-treated patients with R/R B-NHL*; responses appear durable

B-NHL diagnosis	N	Dose level	ORR	CR
FL Gr 1–3a	**22**	**≥5 mg**	**95%**	**77%**
DLBCL without CAR T	**7**	**≥80 mg**	**71%**	**71%**
DLBCL with CAR T	**12**	**≥80 mg**	**50%**	**25%**
MCL	**6**	**Across all**	**67%**	**33%**
MZL	**6**	**Across all**	**67%**	**33%**

- Among patients with DLBCL treated with REGN1979 ≥80 mg, all CRs are ongoing as of data cut-off
- Dose escalation portion of this Phase 1 trial is complete, and expansion cohorts are enrolling
- A global multi-arm pivotal trial (NCT#03888105), as well as additional studies, are underway

*Includes patients with first dose at least 12 weeks before data cut-off. AE, adverse event; B-NHL, B-cell non-Hodgkin lymphoma; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; FL, follicular lymphoma; Gr, Grade; IRR, infusion-related reaction; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; R/R, relapsed/refractory.