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A Phase 2 Study of REGN1979, an Anti-CD20 x Anti-CD3 Bispecific Antibody (Ab), in Patients with Relapsed/Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL)

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Introduction

B-Cell Non-Hodgkin Lymphoma (B-NHL)

- Anti-CD20 Ab in combination with chemotherapy is the standard of care for the treatment of B-NHLs; however, despite initial responses, many patients relapse, often with progressively shorter response durations in subsequent lines of therapy and poor outcomes.[1,2]
  - Phosphatidylinositol 3-kinase inhibitors, including idelalisib, copanlisib and duvelisib, were approved in the US as third-line treatment for follicular lymphoma (FL). However, they are associated with considerable toxicities, and their clinical activity and safety are being evaluated in confirmatory studies.[3]
  - Patients with R/R diffuse large B-cell lymphoma (DLBCL) who have chemotherapy-insensitive disease or are deemed to be ineligible for autologous stem cell transplant have a dismal prognosis, with a median overall survival (OS) of only 4 months.[4]
  - High unmet need also exists for treatment of R/R mantle cell lymphoma (MCL) after Bruton's tyrosine kinase inhibitor (BTKi) failure. The median OS of patients after cessation of ibrutinib is brief at 2.9 months.[5]
  - Patients with R/R marginal zone lymphoma (MZL) lack effective salvage therapies. Patients treated with ibrutinib have a median progression-free survival (PFS) of only 14.2 months and a complete response (CR) rate of 3.2%.[6]

REGN1979

- REGN1979 is a human IgG4-based bispecific Ab that binds to CD3+ T-cells and CD20+ B-cells, targeting CD20+ tumor cells via T-cell-mediated cytotoxicity.[7]
- Data from the ongoing Phase 1 study of REGN1979 (NCT02290951) in heavily pretreated R/R B-NHL patients, including some with progression after prior chimeric antigen receptor T (CAR T)-cell therapy, show broad antitumor activity and an acceptable safety profile at doses up to 320 mg weekly, with no dose-limiting toxicities (DLTs) observed during dose escalation.

Methods

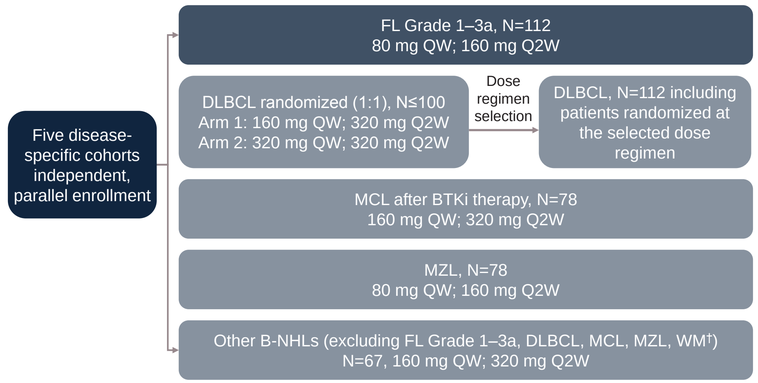
Study design

- This Phase 2, open-label, multi-cohort, multi-center study (NCT03888105) is designed to assess the antitumor activity and safety of REGN1979 in patients with B-NHL subtypes at approximately 130 sites across the US, Canada, Europe, and Asia Pacific regions.
- Five disease-specific cohorts are included, each with independent parallel enrollment **(Figure 1**; **Table 1**).
  - The study opened with FL Grade 1–3a cohort.
  - The other disease-specific cohorts have been included subsequently based on efficacy observations of the Phase 1 study.
- REGN1979 monotherapy is administered as an intravenous infusion at an initial dose of 1 mg, an intermediate dose of 20 mg, an assigned weekly (QW) nominal dose, and an assigned every 2 weeks (Q2W) nominal dose (**Figure 1**).
- Patient flow diagram is shown in **Figure 2**.
- **Primary endpoint**: Objective response rate (ORR) according to the Lugano Classification of response in malignant lymphoma (Cheson, 2014) by independent central review.[8]
- **Secondary endpoints**: ORR by investigator, CR rate, PFS, duration of response, disease control rate (DCR), duration of disease control, OS; incidence and severity of treatment-emergent adverse events; patient-reported outcomes; pharmacokinetics; and immunogenicity responses.

Statistical analysis

- ORR (primary endpoint), CR rate and DCR (secondary endpoints): summarized along with a two-sided 95% confidence interval (CI).
- Time to event endpoints: summarized, where appropriate, by median and the corresponding 95% CI using the Kaplan–Meier method.
- Cohort sizes: determined by analyses of the primary endpoint, ORR, of each cohort.

Figure 1. Study cohorts*



*Cohort in dark blue was included in the original study design; cohorts in light gray were added to the amended study design.
†WM, Waldenström macroglobulinemia.

Table 1. Patient eligibility

Key inclusion criteria

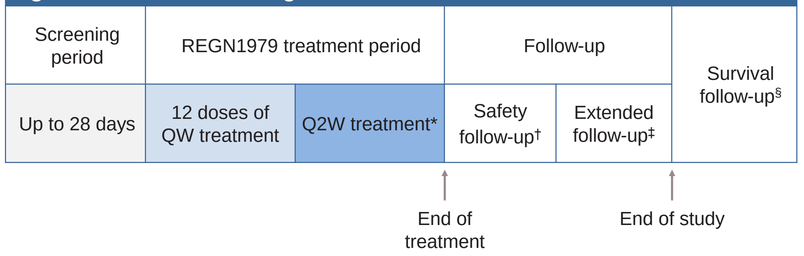
- ≥18 years of age
- ≥1 bi-dimensionally measurable nodal lesion of ≥1.5 cm by CT or MRI
- ECOG performance status 0 or 1
- **Adequate bone marrow function**: Platelet count ≥50×10^9/L; hemoglobin ≥9.0 g/dL; absolute neutrophil count ≥1.0×10^9/L
- **Adequate hepatic function:** Total bilirubin ≤1.5×ULN; alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase ≤2.5×ULN (≤5×ULN if attributed to lymphoma infiltration of liver)
- Serum creatinine ≤1.5×ULN, or calculated creatinine clearance by Cockcroft-Gault formula ≥50 mL/min
- **FL Grade 1–3a cohort:**
  - Central histopathologic confirmation of FL Grade 1–3a diagnosis based on WHO classification[9]
  - R/R to ≥2 prior lines of systemic therapy, including an anti-CD20 Ab and an alkylating agent
- **DLBCL cohort:**
  - R/R to ≥2 prior lines of systemic therapy, including an anti-CD20 Ab and an alkylating agent
- **MCL after BTKi therapy cohort:**
  - R/R to BTKi or intolerant of BTKi and progressed on other systemic therapy
- **MZL cohort:**
  - R/R to ≥1 prior line of systemic therapy
- **Other B-NHL cohort:**
  - With B-NHL other than FL Grade 1–3a, DLBCL, MCL, MZL, or WM
  - R/R to ≥1 prior line of systemic therapy

Key exclusion criteria

- Primary CNS lymphoma or involvement of non-primary CNS NHL
- Treatment with any systemic anti-lymphoma therapy within five half-lives or 28 days prior to first administration of REGN1979, whichever is shorter
- History of allogeneic stem cell transplantation
- Prior treatment with any CAR T-cell therapy
- Continuous systemic corticosteroid treatment with ≥10 mg/day prednisone or equivalent within 72 hours of start of study drug
- History of neurodegenerative condition or CNS movement disorder
- Known hypersensitivity to both allopurinol and rasburicase

CNS, central nervous system; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; ULN, upper limits of normal; WHO, World Health Organization.

Figure 2. Patient flow diagram



*Study treatment will continue until disease progression or other protocol-defined reason for treatment discontinuation. If a patient has achieved CR and durable response of ≥9 months after CR, the investigator may choose to change the assigned dosing from Q2W to every 4 weeks (Q4W) thereafter.

†Safety follow-up consists of three Q4W visits starting from 4 weeks following last dose.

‡Extended follow-up starts after safety follow-up Visit 3 for patients who discontinue study drug for any reason other than disease progression, start of non-protocol anti-lymphoma therapy, or withdrawal of consent, or death. Treatment response will be assessed until disease progression, start of non-protocol anti-lymphoma therapy, or withdrawal of consent, or death.

§Survival follow-up will be conducted for patients who discontinue from extended follow-up until death, loss to follow-up, withdrawal of consent, or study termination by sponsor.

Summary

- **This Phase 2, open-label, multi-cohort, multi-center study (NCT03888105) will further assess the antitumor activity of REGN1979, a fully human, CD20 x CD3 bispecific IgG4 Ab, in five disease-specific cohorts of patients with B-NHL subtypes, each with independent parallel enrollment.**
- **This study will include approximately 130 sites across the US, Canada, Europe, and Asia Pacific regions. Recruitment is open for the FL Grade 1–3a cohort and planned for the other cohorts.**

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