Subcutaneous Epcoritamab in Combination With Rituximab and Lenalidomide in Relapsed or Refractory Follicular Lymphoma: Preliminary Phase 1/2 Results

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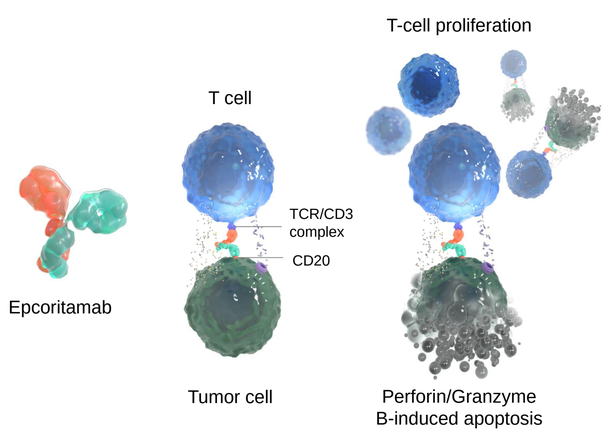
Background

Relapsed/Refractory Follicular Lymphoma

- Patients with relapsed or refractory (R/R) follicular lymphoma (FL) develop increasingly aggressive disease with each line of therapy and, as a result, are at increased risk for earlier relapse, histologic transformation, and/or death[1,2]
- Despite high overall response rates (ORRs) with the combination of rituximab and lenalidomide (R^2) in R/R FL, 2-year progression-free survival is only 53%–58%,[3] and FL remains incurable
- Response rates and duration of response decrease in later lines of treatment as patients become less sensitive to available options[4]; better treatment options are needed

Epcoritamab

- Epcoritamab (DuoBody®-CD3xCD20) is a subcutaneously administered IgG1 bispecific antibody that kills $CD20^+$ malignant B cells by binding to CD20 and CD3, which activates T cells and directs them toward $CD20^+$ B cells[5,6]
- Epcoritamab had substantial antitumor activity when administered as a single agent in patients with heavily pretreated B-cell non-Hodgkin lymphoma (NHL) in the first-in-human phase 1/2 trial[7]
  - Among patients with R/R FL (median of 5 prior lines of therapy), epcoritamab treatment (dose: 0.76–48 mg; n=10) was associated with an ORR of 90% (9/10) and a complete response (CR) rate of 50% (5/10)[7]



EPCORE NHL-2 Arm 2

- R^2 has immunomodulatory properties that may potentiate the activity of epcoritamab, suggesting that combining R^2 with epcoritamab may be beneficial
  - In preclinical studies, potent inhibition of tumor growth was observed in the presence of an Fc-silenced rituximab analogue at the tested concentrations[5]
  - Preclinical data suggest that lenalidomide may enhance epcoritamab-induced T-cell–mediated killing[8]
- The EPCORE NHL-2 phase 1/2 trial (NCT04663347) is evaluating epcoritamab in combination with different standard of care therapies in patients with B-cell NHL
- Here we present initial data from EPCORE NHL-2 arm 2, which is evaluating epcoritamab in combination with R^2 in patients with R/R FL

Study Design: EPCORE NHL-2 Arm 2

Arm 2 of EPCORE NHL-2, a phase 1b/2, open-label, multicenter trial, is evaluating the safety and antitumor activity of SC epcoritamab + standard R^2 for 12 cycles of 28 days, followed by epcoritamab monotherapy for a total of 2 years, in adults with R/R FL[a]

Key inclusion criteria

- R/R $CD20^+$ FL
  - Grade 1, 2, or 3A
  - Stage II–IV
- Need for treatment based on symptoms or disease burden, as determined by GELF criteria[9]
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Dose escalation → **Expansion**

Dose escalation		Expansion	
Dose level 1: Epcoritamab 24 mg QW C1–3, Q2W C4–9, Q4W C10+ **+ R^2** C1–12	**Dose level 2: Epcoritamab 48 mg** QW C1–3, Q2W C4–9, Q4W C10+ **+ R^2** C1–12	**Cohort 2a: Epcoritamab 48 mg** QW C1–3, Q2W C4–9, Q4W C10+ **+ R^2** C1–12	**Cohort 2b: Epcoritamab 48 mg** QW C1–2, Q4W C3–26 **+ R^2** C1–12
n=3 enrolled	n=3 enrolled	n=23 enrolled	n≈80 planned
Primary objectives: DLT/Safety and tolerability **Key secondary objective:** Antitumor activity[b]		**Primary objective:** Antitumor activity[b]	

Data cutoff: September 16, 2021

[a]Patients received SC epcoritamab with step-up dosing (ie, priming and intermediate doses before first full dose) and corticosteroid prophylaxis as previously described[7] to mitigate CRS. Epcoritamab was administered in 28-d cycles as shown. Rituximab regimen: 375 mg/m² IV QW in C1 and Q4W in C2–5; lenalidomide regimen: 20 mg QD (oral administration) for 21 d in C1–12. [b]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression. Lugano criteria and LYRIC were used to assess response.
AEs were graded by CTCAE v5.0; CRS was evaluated by Lee et al[10] criteria.
ClinicalTrials.gov Identifier: NCT04663347.

Results

Baseline Demographics and Characteristics

Characteristic	Total N=29
Median age, y (range)	67 (42–80)
Female, n (%)	17 (59)
ECOG PS, n (%)	
0	22 (76)
1	7 (24)
Stage, n (%)	
II	3 (10)
III	6 (21)
IV	20 (69)
Histologic grade, n (%)	
1	4 (14)
2	18 (62)
3A	5 (17)
Unknown[a]	2 (7)
Median time from diagnosis to first dose, mo (range)	92 (6–281)
FLIPI score, n (%)	
0–2	8 (28)
3–5	18 (62)
Unknown[b]	3 (10)

Data cutoff: September 16, 2021. [a]Unknown histologic grade was confirmed low grade, not grade 3B. [b]FLIPI scores were calculated based on baseline data. Unknown FLIPI scores were due to missing baseline laboratory values.

Prior Therapies and Timing

Characteristic	Total N=29
Median number of prior lines of therapy, n (range)	1 (1–5)
Prior lines of therapy, n (%)	
1	19 (66)
2	4 (14)
≥3	6 (21)
Prior lines of anti-CD20–containing therapy, n (%)	
1	23 (79)
2	3 (10)
≥3	3 (10)
Primary refractory disease, n (%)	5 (17)
Refractory to last line of therapy, n (%)	5 (17)
Progressed within 24 mo of initial therapy, n (%)	11 (38)
Progressed within 24 mo of first immunochemotherapy, n (%)	8 (28)
Median time from end of last line of therapy to first dose, mo (range)	30 (1–182)
Median time from end of last anti-CD20–containing therapy, mo (range)	35 (1–182)
Prior radiotherapy, n (%)	5 (17)
Prior stem cell transplant, n (%)	5 (17)

Data cutoff: September 16, 2021.

Follow-Up, Disposition, and Treatment Exposure

- Median (range) follow-up was 2.8 (0.2–8.5) mo
- 2 patients (7%) discontinued treatment. Reasons for discontinuation were patient request (in the setting of CMR and lenalidomide-related hypothyroidism) and an AE (corticosteroid-induced mania; confirmed not consistent with immune effector cell–associated neurotoxicity syndrome [ICANS]); no patients discontinued due to CRS
- Median (range) number of cycles initiated was 7 (6–8) for 24 mg, 3 (1–6) for 48 mg, and 3 (1–8) overall
- 6 TEAEs, 3 of which were CRS, led to epcoritamab dose delays

Treatment-Emergent Adverse Events

TEAE ≥15%, n (%)	Total N=29			
	Grade 1–2	Grade 3	Grade 4	Any grade
CRS	12 (41)	2 (7)	0	14 (48)
Injection-site reaction[a]	12 (41)	0	0	12 (41)
All infections[b]	9 (31)	2 (7)	0	11 (38)
Constipation	8 (28)	0	0	8 (28)
Cough	8 (28)	0	0	8 (28)
Fatigue	6 (21)	1 (3)	0	7 (24)
Nausea	7 (24)	0	0	7 (24)
Muscle spasms	6 (21)	0	0	6 (21)
Neutropenia[c]	1 (3)	4 (14)	1 (3)	6 (21)
Tremor	5 (17)	0	0	5 (17)

Data cutoff: September 16, 2021. [a]Combined term includes injection-site reaction, erythema, pain, and rash. [b]Includes all events under the System Organ Class of infections and infestations: cellulitis, conjunctivitis, device-related infection, infection, mucosal infection, nasopharyngitis, neuroborreliosis, oral fungal infection, oral herpes, pneumonia, rhinovirus infection, sinusitis, staphylococcal infection, tinea pedis, and urinary tract infection (each n=1 [3%]). Three grade 3 infections were observed in a total of 2 patients overall: cellulitis, neuroborreliosis, and pneumonia. [c]Combined term includes neutropenia and neutrophil count decreased; 1 patient (3%) had febrile neutropenia.

- No DLTs were reported for epcoritamab
- No ICANS or clinical tumor lysis syndrome events were reported
- No fatal TEAEs were observed

CRS Graded by Lee et al[10] Criteria

	Total N=29
CRS, n (%)	14 (48)
Grade 1	8 (28)
Grade 2	4 (14)
Grade 3	2 (7)

Data cutoff: September 16, 2021.

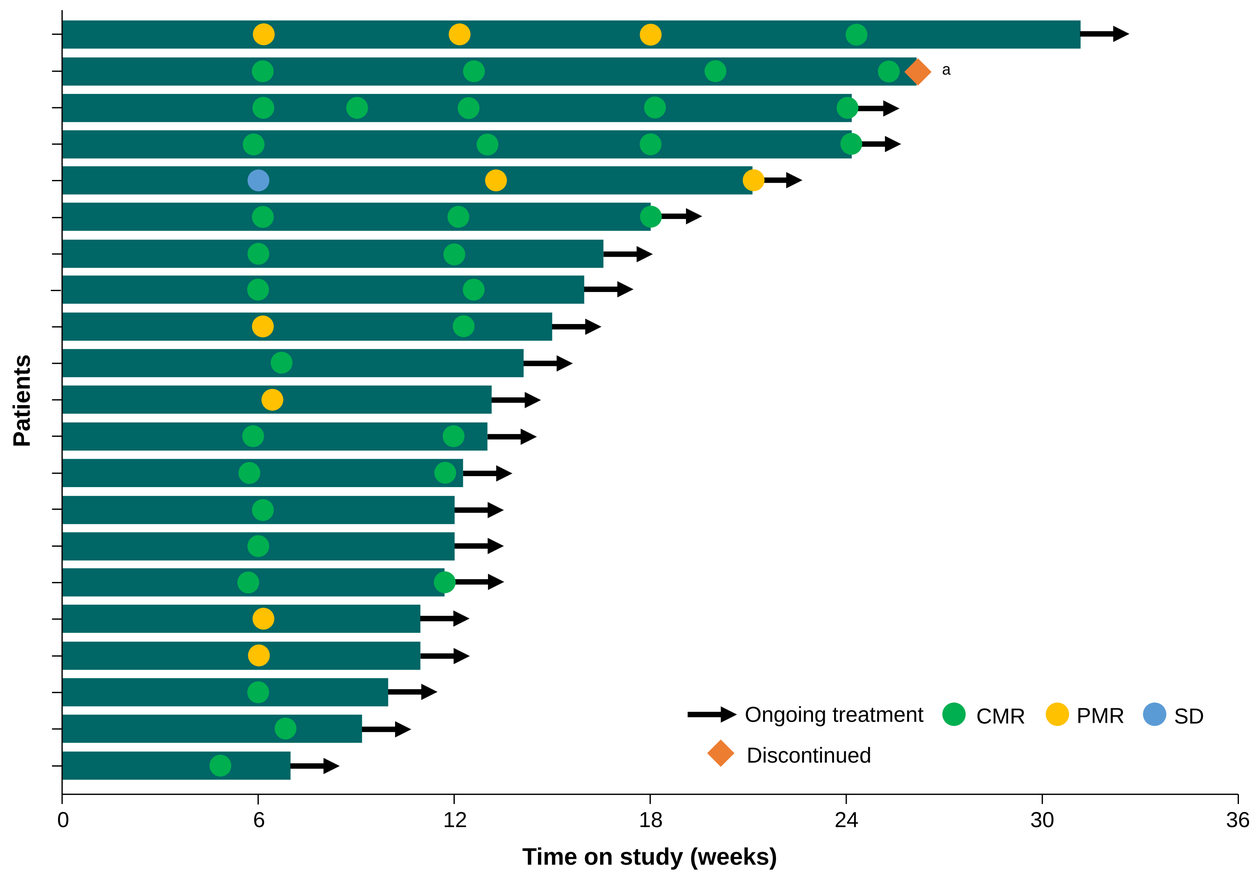
- Most CRS events occurred in cycle 1
- All CRS events resolved with standard management

Best Overall Responses

Response, n (%)[a]	Total n=21
Overall response	21 (100)
CMR	17 (81)
PMR	4 (19)[b]
Stable disease	0
Progressive disease	0

Data cutoff: September 16, 2021. [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and patients who died within 60 d of first dose. [b]All patients with PMR remained on therapy.

Response Profile



Data cutoff: September 16, 2021. [a]Responder discontinued all agents following lenalidomide-induced hypothyroidism. One patient discontinued treatment due to mania; 7 additional patients were receiving treatment but had not yet received their first scan (6 had not reached 6 wk of treatment). Patient with SD at first scan had a 6-wk delay between first and second epcoritamab doses due to pneumonia in the setting of underlying severe chronic obstructive pulmonary disease.

- 95% of responders (20/21) remained in response and continued to receive study treatment as of the September 16, 2021, data cutoff date
- As of an updated November 3, 2021, data cutoff date, ORR was 100% (24/24) and CMR rate was 92% (22/24); responses appear durable, although with short follow-up

Conclusions

- Preliminary data for subcutaneously administered epcoritamab in combination with R^2 in patients with R/R FL demonstrated:
  - No DLTs identified for epcoritamab
  - Manageable safety profile, with no new safety findings
  - No ICANS or tumor lysis syndrome events
- Response in 100% of patients, with nearly all achieving early CMR and no relapses observed
- No cases of progressive disease
- These data support further studies of epcoritamab + R^2 in this population; expansion cohort 2b will enroll up to approximately 80 additional patients

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Abbreviations

C, cycle; CMR, complete metabolic response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; Fc, fragment, crystallizable; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Étude des Lymphomes Folliculaires; IV, intravenous; LYRIC, Lymphoma Response to Immunomodulatory Therapy Criteria; ORR, overall response rate; PMR, partial metabolic response; TCR, T-cell receptor; TEAE, treatment-emergent adverse event.

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