Poster #: HL-998

First-in-Human, Open-Label, Phase 1 Study of a CD30-Directed Antibody-Drug Conjugate (ADC) With a Topoisomerase 1 Inhibitor Payload, PF-08046044 (35C), in Patients With Relapsed/Refractory Lymphomas

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Objective

- To report the safety and tolerability, PK, and preliminary efficacy data from an ongoing FIH phase 1 study (NCT06254495) of 35C (PF-08046044) in patients with R/R lymphoma.

Conclusions

- 35C was well tolerated with a manageable safety profile in patients with R/R lymphomas.
- 35C demonstrated promising emerging antitumor activity in heavily pretreated patients with R/R cHL that progressed after BV and PD-1 inhibitors, as well as in patients with R/R PTCL and DLBCL.
  - ORR was 70.4% in the overall population and 76.5% in cHL.
  - Additionally, median time to response was short at 1.3 months.
- Dose escalation is ongoing. Future plans may include disease-specific (cHL, PTCL, DLBCL) monotherapy dose expansion cohorts and combination therapy.

Introduction

- 35C is an ADC comprised of an anti-CD30 monoclonal antibody and a camptothecin-derived TOP1 inhibitor payload that is conjugated with a glucuronide linker.[1]
- The antibody backbone of 35C is identical to that of brentuximab vedotin. This enables 35C to bind to CD30 on the cell surface, internalize into the cell, and release its TOP1 inhibitor payload.[2,3]
- The payload differentiates 35C from BV in terms of safety profile, eliminating risk of peripheral neuropathy.

Methods

STUDY DESIGN

- This phase 1, open-label, multicenter study has 3 parts, a dose escalation (part A), an optional dose/schedule optimization (part B), and a dose expansion (part C), with an optional biology cohort.

TREATMENT

- All patients receive 35C as an IV infusion Q3W; study part A dose escalation began at an initial dose of 0.6 mg/kg and has been incrementally increased to 1.2, 2.0, and 2.5 mg/kg as of the data cutoff of March 4, 2025.

OBJECTIVES AND ASSESSMENTS

- The primary objectives are to characterize 35C safety and tolerability and identify the maximum tolerated dose and recommended dose of 35C.
- Secondary objectives include assessment of 35C PK and preliminary antitumor activity; exploratory objectives include selective biomarkers analyses.

Please scan the QR code to view the supplementary material, including 35C proposed MOA and phase 1 study schema and inclusion/exclusion criteria.

Results

PATIENTS

- At the data cutoff of March 4, 2025, 35 patients had received ≥ 1 dose of 35C (**Table 1**).
- 2 patients with an initial dose of 1.2 mg/kg escalated to 2.0 mg/kg at Cycle 6 and Cycle 10.
- Patients had received prior BV (22/22 with cHL, 8/9 with PTCL, and 2/4 with DLBCL).
- Most patients with cHL had received a prior PD-1 inhibitor (21/22, 95.5%).
  - 16 (72.7%) had received prior nivolumab; 17 (77.3%) prior pembrolizumab
- Median duration of treatment across all dose cohorts was 2.6 months (range: 0.0–7.5) with median number of cycles administered = 4 (range: 1–11). The short treatment duration is due to the limited follow-up period.

Table 1. Baseline demographics and disease characteristics of patients with R/R lymphomas

	35C Q3W dosing				
	0.6 mg/kg (n = 2)	1.2 mg/kg (n = 12)	2.0 mg/kg (n = 15)	2.5 mg/kg (n = 6)	Total (N = 35)
Age, years, median (min, max)	41.5 (41, 42)	34.0 (28, 87)	63.0 (24, 81)	47.0 (27, 78)	42.0 (24, 87)
Male sex, n (%)	1 (50.0)	8 (66.7)	9 (60.0)	4 (66.7)	22 (62.9)
Disease diagnosis, n (%)					
cHL	2 (100.0)	7 (58.3)	9 (60.0)	4 (66.7)	22 (62.9)
PTCL	0	3 (25.0)	5 (33.3)	1 (16.7)	9 (25.7)
sALCL	0	3 (100.0)	1 (20.0)	1 (100.0)	5 (55.6)
PTCL (NOS)	0	0	4 (80.0)	0	4 (44.4)
DLBCL	0	2 (16.7)	1 (6.7)	1 (16.7)	4 (11.4)
ECOG performance status, n (%)					
0	0	7 (58.3)	8 (53.3)	4 (66.7)	19 (54.3)
1	2 (100.0)	5 (41.7)	7 (46.7)	2 (33.3)	16 (45.7)
Ann Arbor staging at study entry, n (%)					
Stage II	0	0	2 (13.3)	0	2 (5.7)
Stage III	0	3 (25.0)	3 (20.0)	0	6 (17.1)
Stage IV	2 (100.0)	9 (75.0)	10 (66.7)	6 (100.0)	27 (77.1)
Prior treatment lines, median (min, max)	8.5 (4, 13)	6.5 (2, 10)	4.0 (2, 14)	5.0 (3, 7)	5.0 (2, 14)
Prior treatment with BV, n (%)	2 (100.0)	11 (91.7)	13 (86.7)	6 (100.0)	32 (91.4)
Prior treatment with a PD-1 inhibitor, n (%)	2 (100.0)	8 (66.7)	10 (66.7)	6 (100.0)	26 (74.3)
Prior any SCT, n (%)	1 (50.0)	5 (41.7)	7 (46.7)	3 (50.0)	16 (45.7)
Prior allogeneic SCT, n (%)	0	1 (8.3)	1 (6.7)	0	2 (5.7)

SAFETY AND TOLERABILITY

- Overall, 29 patients (82.9%) experienced a TEAE, with 25 (71.4%) having experienced a TRAE (**Table 2**).
  - The most common TEAEs were nausea (n = 19, 54.3%), constipation (n = 7, 20.0%), fatigue (n = 7, 20.0%), and anemia (n = 6, 17.1%).
  - The most common TRAEs were nausea, anemia, alopecia, and fatigue (**Table 3**).
  - GI TEAEs are a class-effect of camptothecin-based payloads and antiemetic prophylaxis was instituted at 2.0 mg/kg.
- Serious AEs were experienced by 2 patients (5.7%); both events (anemia and catheter site infection) were considered treatment related.
- No patients discontinued treatment due to a TEAE and there were no TEAEs leading to death.
- 9 patients (25.7%) experienced a TEAE that resulted in dose modification:
  - 2 patients (5.7%) had a dose reduction due to nausea (grade 2) and decreased neutrophil count (grade 2).
  - 3 patients (8.6%) had a dose interruption (full dose received) due to nausea (grade 2) and infusion-related reaction (grade 2).
  - 5 patients (14.3%) required a dose delay (only 2 were due to a TRAE; catheter site infection [grade 2] and decreased neutrophil count [grade 2]).
- One DLT was observed in the 2.0 mg/kg dose cohort (grade 3 decreased platelet count lasting > 7 days).

Table 2. Summary of TEAEs and TRAEs[a]

	35C Q3W dosing				
n (%)	0.6 mg/kg (n = 2)	1.2 mg/kg (n = 12)	2.0 mg/kg (n = 15)	2.5 mg/kg (n = 6)	Total (N = 35)
Any TEAE	2 (100.0)	10 (83.3)	12 (80.0)	5 (83.3)	29 (82.9)
Any TRAE	0	9 (75.0)	11 (73.3)	5 (83.3)	25 (71.4)
Any TEAE leading to dose modification	0	5 (41.7)	2 (13.3)	2 (33.3)	9 (25.7)
Treatment discontinuation	0	0	0	0	0
Dose delay[b]	0	2 (16.7)	1 (6.7)	2 (33.3)	5 (14.3)
Dose reduction	0	1 (8.3)	0	1 (16.7)	2 (5.7)
Dose interruption[c]	0	2 (16.7)	1 (6.7)	0	3 (8.6)
Any grade ≥ 3 TEAE	0	4 (33.3)	4 (26.7)	2 (33.3)	10 (28.6)
Any grade ≥ 3 TRAE	0	4 (33.3)	3 (20.0)	2 (33.3)	9 (25.7)
Any serious TEAE	0	1 (8.3)	0	1 (16.7)	2 (5.7)
Any serious TRAE	0	1 (8.3)	0	1 (16.7)	2 (5.7)
Any TEAE leading to death	0	0	0	0	0

[a]Treatment relatedness was assessed by the investigator. [b]Dose did not occur within the protocol-specified window due to a TEAE. [c]Infusion was interrupted (full dose received) or stopped early (full dose not received).

Table 3. Summary of TRAEs[a] by preferred term occurring in ≥ 5% of patients

	35C Q3W dosing				
n (%)	0.6 mg/kg (n = 2)	1.2 mg/kg (n = 12)	2.0 mg/kg (n = 15)	2.5 mg/kg (n = 6)	Total (N = 35)
Any TRAE	0	9 (75.0)	11 (73.3)	5 (83.3)	25 (71.4)
Nausea	0	7 (58.3)	7 (46.7)	3 (50.0)	17 (48.6)
Anemia	0	4 (33.3)	0	2 (33.3)	6 (17.1)
Alopecia	0	0	4 (26.7)	1 (16.7)	5 (14.3)
Fatigue	0	2 (16.7)	1 (6.7)	2 (33.3)	5 (14.3)
Constipation	0	2 (16.7)	0	2 (33.3)	4 (11.4)
Headache	0	2 (16.7)	2 (13.3)	0	4 (11.4)
Rash maculopapular	0	1 (8.3)	3 (20.0)	0	4 (11.4)
Diarrhea	0	2 (16.7)	1 (6.7)	0	3 (8.6)
Neutropenia	0	0	2 (13.3)	1 (16.7)	3 (8.6)
Infusion-related reaction	0	1 (8.3)	1 (6.7)	0	2 (5.7)
Myalgia	0	1 (8.3)	1 (6.7)	0	2 (5.7)
Night sweats	0	1 (8.3)	0	1 (16.7)	2 (5.7)
Paresthesia	0	1 (8.3)	1 (6.7)	0	2 (5.7)
Platelet count decreased	0	0	1 (6.7)	1 (16.7)	2 (5.7)

[a]Treatment relatedness was assessed by the investigator.

PHARMACOKINETICS

- The preliminary PK analysis indicated that the PK of the antibody conjugated drug was approximately dose-proportional for the evaluated doses (0.6–2.0 mg/kg Q3W); estimated terminal half-life is ~6–7 days. (**Table 4**).

Table 4. Dose-normalized PK parameters of acCPT in plasma up to cycle 1 post infusion

Dose (mg/kg)	n	$AUC_{0\text{-}21d}$ (ng/ml*d)	C_{max} (ng/ml)	C_{trough} (ng/ml)	Half-life (days)
		Mean (stdev)	Mean (stdev)	Mean (stdev)	Median (min–max)
0.6	2	2153 (NA)	513 (NA)	20.8 (NA)	NA (6.6–6.9)
1.2	12	2464 (577)	503 (130)	24.2 (6.1)	5.7 (5.0–12.6)
2.0	11	2657 (808)	473 (121)	43.3 (28.5)	7.2 (4.9–10.5)

Stdev and median have been reported when ≥ 3 observations are available for a dose and schedule. Total patient number (n) at each dose level is based on number of patients with ≥ 1 measured concentration of acCPT; NA in table represents "not available/not analyzed due to limited information."

ANTITUMOR ACTIVITY

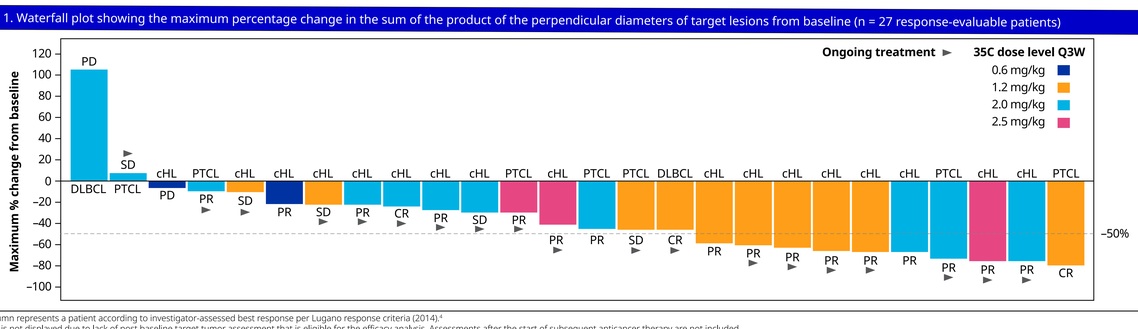
- Among 27 response-evaluable patients across all dose cohorts, ORR was 70.4% (19/27), including 3 CRs (1 patient with cHL, 1 with PTCL, and 1 with DLBCL) and 16 PRs (**Table 5**, **Figure 1**).
  - Objective responses were observed across all dose cohorts.
- Among 17 response-evaluable patients with cHL, ORR was 76.5% (13/17), including 1 CR and 12 PRs.
- Among 8 response-evaluable patients with PTCL, ORR was 62.5% (5/8) with 1 CR (sALCL) and 4 PRs.
- Among 2 response-evaluable patients with DLBCL, 1 patient had CR (ORR: 50.0%).
- As of March 4, 2025, 77.1% (27/35) patients remained on study treatment with ongoing follow-up; median follow-up of 3.0 months (range: 0.0–7.9); 22.9% (8/35) discontinued treatment (7 due to PD and 1 proceeded to allogeneic SCT).

Table 5. Best overall response[a] in response-evaluable[b] patients treated with 35C Q3W

Overall	0.6 mg/kg (n = 2)	1.2 mg/kg (n = 11)	2.0 mg/kg (n = 11)	2.5 mg/kg (n = 3)	Total (N = 27)
ORR (CR + PR), n (%)	1 (50.0)	7 (63.6)	8 (72.7)	3 (100.0)	19 (70.4)
[95% CI][c]	[1.3–98.7]	[30.8–89.1]	[39.0–94.0]	[29.2–100.0]	[49.8–86.2]
CR, n (%)	0	2 (18.2)	1 (9.1)	0	3 (11.1)
[95% CI][c]		[2.3–51.8]	[0.2–41.3]		[2.4–29.2]
PR, n (%)	1 (50.0)	5 (45.5)	7 (63.6)	3 (100.0)	16 (59.3)
SD, n (%)	0	3 (27.3)	2 (18.2)	0	5 (18.5)
PD, n (%)	1 (50.0)	0	1 (9.1)	0	2 (7.4)
Not available,[d] n (%)	0	1 (9.1)	0	0	1 (3.7)
cHL	**0.6 mg/kg (n = 2)**	**1.2 mg/kg (n = 7)**	**2.0 mg/kg (n = 6)**	**2.5 mg/kg (n = 2)**	**Total (n = 17)**
ORR (CR + PR), n (%)	1 (50.0)	5 (71.4)	5 (83.3)	2 (100.0)	13 (76.5)
[95% CI][c]	[1.3–98.7]	[29.0–96.3]	[35.9–99.6]	[15.8–100.0]	[50.1–93.2]
CR, n (%)	0	0	1 (16.7)	0	1 (5.9)
[95% CI][c]			[0.4–64.1]		[0.1–28.7]
PR, n (%)	1 (50.0)	5 (71.4)	4 (66.7)	2 (100.0)	12 (70.6)
SD, n (%)	0	2 (28.6)	1 (16.7)	0	3 (17.6)
PD, n (%)	1 (50.0)	0	0	0	1 (5.9)

[a]According to investigator-assessed best response per Lugano response criteria (2014).[4] [b]Patients who received ≥ 1 dose of 35C, had a baseline disease assessment and ≥ 1 post-baseline disease assessment, or had discontinued the study with no evaluable post-baseline disease assessment. [c]Two-sided 95% exact CI computed using the Clopper-Pearson method. [d]Patients without a post-baseline response assessment.

Figure 1. Waterfall plot showing the maximum percentage change in the sum of the product of the perpendicular diameters of target lesions from baseline (n = 27 response-evaluable patients)



Each column represents a patient according to investigator-assessed best response per Lugano response criteria (2014).[4]
1 patient is not displayed due to lack of post baseline target tumor assessment that is eligible for the efficacy analysis. Assessments after the start of subsequent anticancer therapy are not included.

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aPLS

References: 1. Herrera AF et al. *Blood* 2024;144:1674.1-1674.1. **2.** Pommier Y. *Nat Rev Cancer* 2006;6:789-802. **3.** Hamblett KJ et al. *Blood* 2023;142:1440-1440. **4.** Cheson BD et al. *J Clin Oncol* 2014;32:3059-68.

Abbreviations: acCPT, antibody conjugated drug to camptothecin-derived TOP1 inhibitor payload; AE, adverse event; ALCL, anaplastic large cell lymphoma; AMDCPT, 7-aminomethyl-10, 11-methenedioxycamptothecin; aPLS, abstract plain language summary; ASCT, autologous stem cell transplant; AUC, area under the curve; BV, brentuximab vedotin; CAR, chimeric antigen receptor; CD30, cluster of differentiation 30; cHL, classical Hodgkin lymphoma; CHP, cyclophosphamide, doxorubicin, and prednisone; CI, confidence interval; C_{max}, maximum plasma drug concentration; CR, complete response; C_{trough}, trough plasma concentration; d, day; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; dsDNA, double-stranded DNA; ECOG, Eastern Cooperative Oncology Group; FDG PET, fluorodeoxyglucose positron emission tomography; FIH, first-in-human; GI, gastrointestinal; GVHD, graft-versus-host disease; IV, intravenous; max, maximum; min, minimum; MOA, mechanism of action; NOS, not otherwise specified; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PK, pharmacokinetics; PR, partial response; PTCL, peripheral T-cell lymphoma; Q3W, once every 3 weeks; R/R, relapsed/refractory; sALCL, systemic anaplastic large cell lymphoma; SCT, stem cell transplant; SD, stable disease; ssDNA, single-stranded DNA; stdev, standard deviation; TEAE, treatment-emergent adverse event; TOP1, topoisomerase 1; TRAE, treatment-related adverse event.

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