Poster #: PS1865

First-in-human, open-label, phase 1 study of CD30-directed antibody drug conjugate, PF-08046044 (35C), in patients with relapsed/refractory lymphomas: dose escalation safety and preliminary efficacy

Christina Poh,[1]* Carlo Visco,[2] Michael Spinner,[3] Kendan Jones-Isaac,[4] Mina Nayeri,[4] Erika Rudnicki,[4] Maria Delioukina,[4] Swetha Thiruvengadam[5]

[1]University of Washington School of Medicine, Fred Hutchinson Cancer Center, Seattle, USA, [2]University of Verona, Department of Engineering for Innovative Medicine, Verona, Italy, [3]University of California San Francisco, San Francisco, USA, [4]Pfizer Inc., New York, USA, [5]City of Hope National Medical Center, Lymphoma Division, Department of Hematology & Hematopoietic Cell Transplantation, Duarte, USA

Objective

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

Conclusions

- 35C was well tolerated at the evaluated dose levels 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 prior BV and PD-1 inhibitors, as well as in patients with R/R PTCL and DLBCL.
- These preliminary data suggest 35C could be a potential option for R/R lymphomas that do not respond to standard of care or progress on standard of care, both as a monotherapy and potentially in combination therapies.

Presenter: Christina Poh

Email for more information: cpoh10@uw.edu

Electronic Poster and Supplementary Material

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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.** Ji Y et al. *Clin Trials*. 2010;7:653-663. **5.** Cheson BD et al. *J Clin Oncol* 2014;32:3059-68. **6.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Antiemesis. V2.2025. May 12, 2025. National Comprehensive Cancer Network, Inc. 2025.

Abbreviations: acCPT, antibody conjugated drug; AE, adverse event; ALCL, anaplastic large cell lymphoma; ASCT, autologous stem cell transplant; AMDCPT, 7-aminomethyl-10, 11-methenedioxycamptothecin; 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; MEC, moderately emetogenic chemotherapy; 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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Introduction

- 35C is a novel, investigational antibody-drug conjugate of an anti-CD30 monoclonal antibody (cAC10) and a camptothecin-derived TOP1 inhibitor payload conjugated with a glucuronide linker (See **Supplementary Figure 1**. 35C phase 1 proposed MOA).[1]
- The antibody backbone of 35C is shared with BV, allowing 35C to bind CD30 on the cell surface, internalize, and subsequently release the TOP1 inhibitor payload into the cell to induce cytotoxicity.[2,3]
- Preclinical data have demonstrated that 35C induces cytotoxicity in Hodgkin lymphoma, ALCL, and BV-resistant cell lines and i nhibits tumor growth in animal models of lymphoma, including BV-resistant lymphoma.[3]
- This FIH study was designed to evaluate safety, tolerability, PK, and preliminary antitumor activity of 35C in patients with R/R lymphomas.

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 (See **Supplementary Figure 2**. 35C phase 1 study schema and inclusion/exclusion criteria).
- Dose escalation is being conducted using the modified toxicity probability interval (mTPI) method.[4]
- Here, we report the preliminary analysis of the ongoing part A dose escalation with a data cutoff of March 4, 2025.

TREATMENT

- All patients receive 35C as an IV infusion Q3W.
- Dose escalations begin with an initial dose of 0.6 mg/kg that are incrementally increased to 1.2, 2.0, and 2.5 mg/kg.
- Dose escalations are ongoing.

OUTCOMES 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.
- Antitumor activity is assessed by investigators using Lugano response criteria (2014).[5]

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 (0.6 mg/kg, n = 2; 1.2 mg/kg, n = 12; 2.0 mg/kg, n = 15; 2.5 mg/kg, n = 6).
- 2 patients with an initial dose of 1.2 mg/kg escalated to 2.0 mg/kg at Cycle 6 and Cycle 10.
- Patient demographics and disease characteristics at baseline are reported in **Table 1**.
- Nearly all patients had received prior BV (n = 32, 91.4%).
- A majority of patients with cHL had received a prior PD-1 inhibitor (n = 21, 95.5%).
  - 16 (72.7%) had received prior nivolumab; 17 (77.3%) prior pembrolizumab
- 16 patients (45.7%) had received any SCT; 2 patients (5.7%) had received an allogeneic SCT.
- Median duration of treatment across all dose cohorts was 2.6 months (range: 0.0–7.5) with median number of cycles administered = 4.0 (range: 1–11). The short treatment duration is due to the limited follow-up period (median: 3.0 months; range: 0.0–7.9).
- The relative dose intensity across all dose cohorts was 99.2%.

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[a] (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)	1 (20.0)	1 (100)	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,[b] 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)

[a]2 patients with an initial dose of 1.2 mg/kg escalated to 2.0 mg/kg at Cycle 6 and Cycle 10. [b]Prior treatment lines may include prior systemic therapies and/or procedures.

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%).
  - Primary antiemetic prophylaxis was introduced at 35C dose level 2.5 mg/kg based on NCCN guidance for MEC[6] and institutional guidelines. GI toxicity is an expected on-target effect based on 35C MOA.
- 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 (8.6%) had a dose interruption (full dose received) due to nausea (grade 2) and 2 events of infusion-related reaction (grade 2), and 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).

- The most common TRAEs were nausea (n = 17, 48.6%), anemia (n = 6, 17.1%), alopecia (n = 5, 14.3%), and fatigue (n = 5, 14.3%); most patients (16 of 25) had grade 1–2 TRAEs (**Table 3**).

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

- Preliminary PK analysis indicates 35C PK for acCPT is approximately dose-proportional for doses evaluated ranging from 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	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

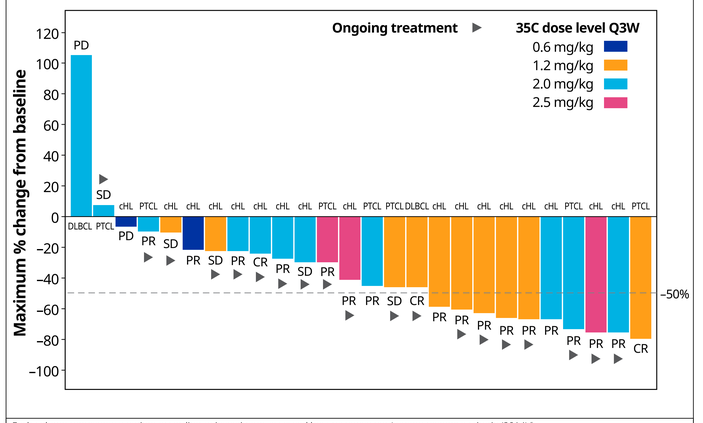
- Among 27 response-evaluable patients across all dose cohorts, ORR was 70.4% (19/27), including 3 CRs (1 patient with cHL, 1 with PTCL, and 1 with DLBCL) and 16 PRs. 5 patients had SD as best response.
  - Objective responses were observed across all dose cohorts.
- Among the 17 response-evaluable patients with cHL, there has been 1 CR and 12 PRs.
- The ORR details per 35C dose level are provided in **Table 5 and Figure 1**.
  - Among 8 response-evaluable patients with PTCL, 1 CR (sALCL) and 4 PRs were observed; 2 patients had SD.
  - Among 2 response-evaluable patients with DLBCL, 1 patient had CR.
- 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)
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)
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]
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)**
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)
Not available,[d] n (%)	0	0	0	0	0
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]

[a]According to investigator-assessed best response per Lugano response criteria (2014)[5]. [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 computing 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 diameter 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).[5]
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.