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A Phase I Study of PIT565, a First-in-Class, Anti-CD3, Anti-CD19, Anti-CD2 Trispecific Antibody in Patients With Relapsed and/or Refractory B-Cell Malignancies

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SUMMARY

- PIT565 is a first-in-class, CD19xCD3xCD2, IgG-like, trispecific antibody that targets CD19+ cells and at the same time engages CD3 and CD2 (a costimulatory receptor) on T cells, which leads to redirected T-cell cytotoxicity toward CD19-positive malignant B cells
- This Phase I, open-label study was designed to characterize the safety and tolerability of PIT565 in patients with R/R B-NHL and R/R B-ALL to determine recommended dose(s), schedule(s), and route(s) of administration for future studies, as well as to estimate the preliminary antitumor activity of PIT565

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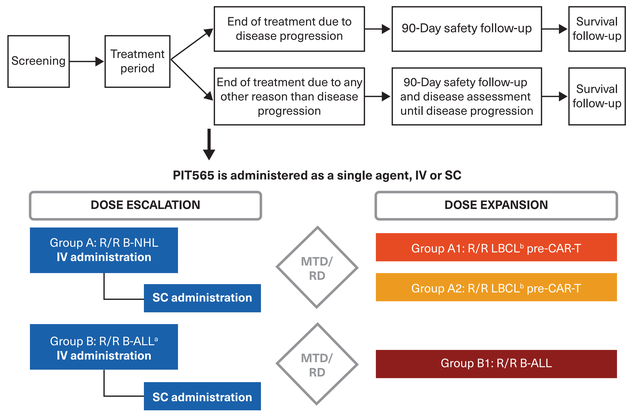
BACKGROUND AND OBJECTIVES

- There is an unmet therapeutic need for patients with R/R B-NHL and R/R B-ALL who failed multiple lines of therapy
- PIT565 is an investigational, first-in-class, immunoglobulin G–like, trispecific antibody that targets CD19 on malignant B cells while engaging CD3 and CD2 (a costimulatory receptor) on T cells, leading to redirected T-cell cytotoxicity toward CD19-positive malignant B cells
- CD2 signaling prevents transcriptional changes characterizing CD8 T-cell exhaustion, occurring during persistent T-cell receptor stimulation
- Furthermore, the loss of CD2 ligand, CD58, on tumor cells, has been shown to mediate resistance to the antitumor activity by T-cell–redirecting therapies, confirming the importance of CD2 activation in T cells
- Findings from preclinical studies suggest that PIT565 mediates more potent and sustained antitumor T-cell responses compared with CD3 bispecifics[1]
- The study design, along with endpoints of PIT565 trial in patients with R/R B-NHL and R/R CD19-positive B-ALL who failed to respond to ≥2 lines of prior therapy, is presented

STUDY DESIGN AND METHODS

- This is a first-in-human, open-label, phase I, multicenter study of PIT565 in patients with R/R B-NHL and R/R CD19-positive B-ALL who relapsed or failed to respond to ≥2 lines of prior therapy (including an anti-CD20 monoclonal antibody–containing chemotherapy combination regimen for patients with R/R B-NHL; NCT05397496)
- Key eligibility criteria are summarized in **Table 1**
- The primary objective is to assess the safety (including DLTs) and tolerability, and to identify MTD or RD, schedule, and route of administration for each indication (**Table 2**)
- The study comprises 2 parts: dose escalation and expansion
- The dose-escalation part will be initiated in NHL patients (Group A) to determine the MTD and/or RD. PIT565 will be administered in patients with R/R LBCL, previously treated (Group A1) or untreated (Group A2) with CAR-T cell therapy
- In B-ALL patients (Group B), the dose-escalation part will begin after MTD and/or RD determined in NHL patients
- The respective expansion part will be initiated once the MTD and/or RD of PIT565 are determined in corresponding dose-escalation parts (**Figure 1**)

Figure 1. Study design



[a]R/R ALL escalation will only start once MTD/RD of PIT565 has been determined for NHL patients
[b]DLBCL, HGBCL (double/triple hit), PMBCL, FL3B

- Patients will receive PIT565 IV q1w over a 28-day cycle. Route of administration (IV or SC) and dose frequency (q1w or q2w) will be explored if supported by preliminary PK
- The dose-escalation part is guided by an adaptive Bayesian logistic regression model following the escalation with overdose control principle. The MTD and/or RD are further explored during the dose-expansion part
- The study is ongoing with plans to enroll approximately 140 patients in Belgium, France, Israel, Italy, Japan, Singapore, Spain, and the United States

Eligibility Criteria

Table 1. Key eligibility criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Eligible patients (age: ≥18 years) with R/R B-NHL and R/R CD19-positive B-ALL who had relapsed/failed to respond to ≥2 lines of prior therapy, including an αCD20 monoclonal antibody–containing chemotherapy combination regimen	• Patients receiving systemic treatment with any immunosuppressive medication with contraindication to tocilizumab
• ECOG ≤2	• Treatment with cytotoxic or small molecule targeted antineoplastics, or any experimental therapy, within 14 days or 5 half-lives whichever is shorter before the first dose of study treatment (patients received antibodies or immunotherapies the washout period is 4 weeks prior to study treatment)
• R/R B-NHL patients must have at least 1 bi-dimensionally measurable nodal lesion or 1 bi-dimensionally measurable extranodal lesion as measured on positron emission tomography-computed tomography scan	• History of malignant disease; active CNS involvement; autoimmune disease (other than patients with vitiligo, hypothyroidism only requiring hormone replacement, or psoriasis not requiring systemic treatment or conditions not expected to recur)
• For R/R B-ALL patients, conformed morphologic of BM (≥5% blasts)	

Table 2. Study objectives and endpoints

Objectives	Endpoints
Primary	
• Determine the safety and tolerability of PIT565 and to identify MTDs and/or RDs, schedule and route of administration, in R/R B-NHL and R/R B-ALL	• Safety: Incidence and severity of DLTs, AEs, SAEs, and change in laboratory parameters, vital signs, ECG, and assess CRS/ICANS
	• Tolerability: dose interruptions, reductions, and dose intensity
Secondary	
• Evaluate preliminary antitumor activity	• ORR, CR, BOR, DOR, OS, PFS for B-NHL, or EFS for B-ALL
• PK of PIT565	• Serum PIT565 concentration and derived PK parameters (C_{max}, AUC, and C_{trough})
• Immunogenicity of PIT565	• ADA prevalence at baseline and incidence on treatment
Main Exploratory	
• Assess CD19 protein expression in tumor cells	• Baseline levels and change in CD19 protein expression by immunohistochemistry (B-NHL) or flow cytometry (B-ALL) in tumor cells and their correlation with efficacy (e.g, ORR, CR, BOR)
• Assess MRD peripheral blood and in BM in B-ALL	• Percentage of patients with MRD-negative status by flow cytometry and IG sequencing in blood and BM
• Characterize gene expression and protein markers in the tumor microenvironment	• Changes in gene expression and immune cell protein markers in tumor biopsies (NHL)
• Characterize gene expression and protein markers in circulating malignant and immune cells	• Changes in gene expression and protein markers in malignant and immune-cell populations upon treatment in circulating tumor cells (ALL) and circulating immune cells
• Assess changes in cytokines and other soluble proteins with treatment	• Changes from baseline in circulating proteins
• Evaluate changes in T-cell clonalty following treatment	• Changes in T-cell clonalty in the circulation

Reference

1. Lu H, Oka A, Coulson M, et al. *Blood*. 2022;140:3148

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Abbreviations

ADAs, anti-drug antibodies; AEs, adverse events; AUC, area under curve; B-ALL, B-cell acute lymphoblastic leukemia; BM, bone marrow; B-NHL, B-cell non-Hodgkin lymphoma; BOR, best of response; CAR-T, chimeric antigen receptor T-Cell; CNS, central nervous system; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; DOR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; ICANS, immune-effector cell–associated neurotoxicity syndrome; IV, intravenous; LBCL, large B-cell lymphoma; MTD, maximally tolerated dose; MRD, minimal residual disease; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PMBCL, primary mediastinal large B-cell lymphoma; PS, progression survival; RD, recommended dose; R/R, relapsed and/or refractory; SAEs, serious AEs; SC, subcutaneous.

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