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Glofitamab plus polatuzumab vedotin: a novel safe, and highly effective chemotherapy-free regimen for pediatric relapsed/ refractory B-cell non-Hodgkin lymphoma

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Running heads: Efficient Glofit-Pola in pediatric R/R B-NHL

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Mature B-cell non-Hodgkin lymphomas (B-NHLs) constitute approximately 60% of all pediatric NHL, characterized by rapid proliferation and aggression. The most common pediatric B-NHL subtypes are Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), and primary mediastinal B-cell lymphoma (PMBCL), with BL predominating in children aged 0–14 years and DLBCL incidence rising markedly in adolescents[1]. Although front-line therapy for B-NHL is highly effective, the prognosis for pediatric patients with relapsed/refractory (R/R) B-NHL remains dismal and often fatal, with a survival rate of less than 20%[2]. The current optimal treatment strategy is achieving a second complete remission (CR) through salvage therapy followed by consolidative hematopoietic stem cell transplantation (HSCT). Commonly used salvage chemotherapy regimens, such as rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) and rituximab, cytarabine, and etoposide (R-CYVE), are associated with a markedly high incidence of grade III/IV infection, hematologic toxicities, and mucositis, yet their CR rates remain below 50%[3-5]. Strikingly, a recent report showed a CR rate of only 24.3%[5]. Although CAR T-cell therapy has shown promise, there are still various limitations for children: a lack of approval and access; a lengthy and costly manufacturing process; severe treatment-related toxicities; and suboptimal efficacy in BL, the most common pediatric B-NHL subtype[6]. Moreover, salvage therapy must balance efficacy with toxicity, because the interval from initial treatment to relapse is commonly short, and patients still have cumulative bone marrow suppression and organ toxicity at relapse, which limits tolerance to further intensive chemotherapy and increases transplant-related mortality. To date, achieving CR in R/R B-NHL remains an

unresolved challenge[7], and effective yet low-toxicity therapies are urgently needed.

Glofitamab (a CD20×CD3 bispecific antibody) has been established as a standard treatment option for adult patients with R/R diffuse large B-cell lymphoma (DLBCL). Emerging clinical data have shown that polatuzumab vedotin (a CD79b-targeted antibody-drug conjugate), when combined with glofitamab, demonstrates robust efficacy with durable responses and manageable safety in heavily pretreated adult patients with R/R DLBCL[8]. However, evidence in R/R BL remains limited. A recent study reported that three R/R adult BL patients who received the glofitamab plus polatuzumab vedotin (Glofit-Pola) regimen achieved complete responses[9]. Given that BL represents the majority of pediatric B-NHL, this chemotherapy-free regimen holds transformative clinical promise for pediatric patients: it could not only overcome the historically dire prognosis of R/R B-NHL, but also prevent severe toxicities. More importantly, while neither glofitamab nor polatuzumab vedotin monotherapy induced tumor regression, their combination resulted in rapid and profound tumor shrinkage in preclinical models[10], which strongly suggested synergistic efficacy. This finding underscores the Glofit-Pola regimen as a novel, highly active, and well-tolerated therapeutic strategy. Here, we present the first report of Glofit-Pola as salvage therapy in two pediatric patients with R/R B-NHL (one with LBCL and one with BL), with a detailed assessment of early efficacy and safety. This study received full ethical approval from the Institutional Review Board of Guangzhou Women and Children's Medical Center (Approval number: 2025-18) and was conducted in strict accordance with the principles of the Declaration of Helsinki. Written informed consent was

obtained from the legal guardians of both pediatric patients before enrollment.

Patient 1 was initially evaluated at an outside hospital for pancreatitis with PET-CT showing extensive systemic metastases. He was diagnosed with DLBCL (R4 group) according to the Berlin-Frankfurt-Münster 95 (NHL-BFM-95) protocol[11]. The patient underwent the BFM-95-based chemotherapy regimen[11] combined with rituximab (v, R-AA, R-BB, R-CC, R-AA, R-BB, R-CC; details in Supplemental Table 2). The clinical characteristics of the patient were summarized in Table 1. After the second cycle, the patient achieved a partial response (PR). However, end-of-treatment PET evaluation was not performed due to personal reasons. Two months later, tumor recurrence was noted with involvement of multiple organs, including the central nervous system (CNS). Despite receiving R-EPOCH regimen as salvage therapy at an outside hospital, the disease continued to progress. Upon transfer to our center, the Glofit-Pola regimen (Supplemental Table 3) was applied. PET MRI demonstrated a partial metabolic response (PMR) after three cycles, with significant tumor shrinkage and extensive necrosis, and only a subcentimeter focus of residual activity remained in the mediastinum. All other sites demonstrated complete metabolic response (CMR). Following three additional cycles of Glofit-Pola, PET MRI confirmed CMR (Figure 1A) and contrast-enhanced MRI also showed complete resolution of all CNS lesions (Figure 1B), with clearance of all detectable circulating tumor DNA (ctDNA) (Figure 1E).

Patient 2 presented with facial swelling and hemophagocytic lymphohistiocytosis, and pathologic biopsy confirmed BL. Baseline evaluation revealed extensive multi-focal bone involvement with bone marrow and CNS infiltration, and he was classified as R4

group. His clinical characteristics were summarized in Table 1. He achieved a CMR on PET-MRI after two cycles of chemotherapy, and MRI showed complete resolution of previously detected CNS lesions. Clinical CR was maintained through six cycles of BFM-95-based chemotherapy regimen[11] combined with rituximab (Supplemental Table 2), but cerebrospinal fluid (CSF) ctDNA remained positive. One month after the completion of therapy, a systemic relapse with CNS involvement was diagnosed based on symptoms of headache and vomiting. Imaging confirmed multifocal bone and cerebral white matter involvement (Figure 1C, D). Thus, salvage therapy with Glofit-Pola was initiated. After three cycles, the patient achieved a CMR of all lesions (Figure 1C, D), accompanied by complete clearance of ctDNA in CSF and plasma after only two cycles (Figure 1F).

To date, both patients have achieved CMR and have been successfully bridged to autologous HSCT. A glofitamab monotherapy maintenance regimen[8] was administered after transplantation to sustain remission and prevent relapse. The maintenance regimen was given on day 1 of each 21-day cycle for up to 6 cycles, at doses of 30 mg for patient 1 and 15 mg for patient 2. Currently, both patients remain in CR, with durations of 4 months for patient 1 and 3 months for patient 2. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) and were summarized in Supplemental Table 1. Only patient 1 experienced grade 1 cytokine release syndrome (CRS) during the first cycle. No myelosuppression, organ toxicity, grade >1 CRS, or immune effector cell-associated neurotoxicity syndrome (ICANS) were observed, despite both patients presenting with

high tumor burden and CNS involvement at relapse.

Lymphoma with CNS involvement remains a challenging clinical problem of poor performance status and unfavorable prognosis[12]. As part of front-line therapy, high-dose methotrexate and intrathecal injections pose a non-negligible toxicity risk[13]. Meanwhile, the repeated sedation procedures required for intrathecal chemotherapy, specifically higher cumulative anesthesia exposure, may contribute to late neurocognitive impairment in pediatric long-term survivors[14]. Notably, our salvage regimen did not include high-dose methotrexate, intrathecal injections, or repeated sedations. Encouragingly, complete radiological resolution of the CNS lesions was observed on MRI after only two cycles of Glofit-Pola for patient 1. For patient 2, despite the persistence of CSF ctDNA throughout front-line therapy, clearance was achieved after only two cycles of Glofit-Pola. These results highlight the powerful CNS-directed efficacy of the Glofit-Pola regimen against CNS-positive B-NHL. This outcome aligns with the emerging evidence supporting the efficacy of CNS-penetrant bispecific antibodies[15]. We speculate that Polatuzumab vedotin may potentiate the effect of Glofitamab by enhancing immune cell infiltration into CNS tumor lesions, a hypothesis that warrants further investigation in future studies. The above findings indicate that this chemotherapy-free regimen warrants further clinical investigation, not only in the relapsed/refractory setting but also as a potential frontline alternative to conventional chemotherapy, which could reduce treatment-related toxicity and improve the quality of life for pediatric patients.

In conclusion, Glofit-Pola regimen showed compelling efficacy and favorable toxicity

profile for pediatric patients with R/R B-NHL, particularly those with CNS involvement. Our findings suggest that Glofit-Pola may represent a novel, well-tolerated, and chemotherapy-free salvage strategy capable of redefining the management of pediatric R/R B-NHL. Further prospective investigations are warranted to explore its potential, which may enable a paradigm shift in the treatment of pediatric R/R B-NHL.

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Table 1. Baseline Demographic and Clinical Characteristics of the Two Patients

Clinical Characteristics	Patient 1	Patient 2
Age（years）	17	8
Sex	Male	Male
Sites of initial presentation	Meninges, lungs, mediastinum, lymph nodes, liver, pancreas, kidneys, and bones	Multi-focal bone lesions, bone marrow and pancreas
Histological Subtype	DLBCL	BL
Molecular characteristics	Missense mutations in *BTG1*, *FAT1*, *INPP5D*, *IRF4*, *ITPKB*, *JAK3*, *MFHAS1*, *P2RY8*, *STAT6*, *TLE1*, and *TNFAIP3*	Missense mutations in *FAT3*, *FOXA1*, *GNA13*, *ID3*, *MYC* and *RHOA*
Stage at diagnosis	IV	IV
Risk group*	R4	R4
No of prior lines of therapy	2	1
Prior treatment†	1. v, R-AA, R-BB, R-CC, R-AA, R-BB, R-CC 2. R-EPOCH	1.v, R-AA, R-BB, R-CC, R-AA, R-BB, R-CC
Sites of recurrence	Meninges, lungs, mediastinum, lymph nodes, kidneys and bones	Multi-focal bone lesions and malignant cells present in CSF
Cycles of Glofit-Pola administered‡	6	5
Response to Glofit-Pola	CMR (after 6 cycles)	CMR (after 3 cycles)

* R4: Stage III/IV or B-cell acute lymphoblastic leukemia with serum lactate dehydrogenase (LDH) >1,000 IU/L, or/and central nervous system disease.

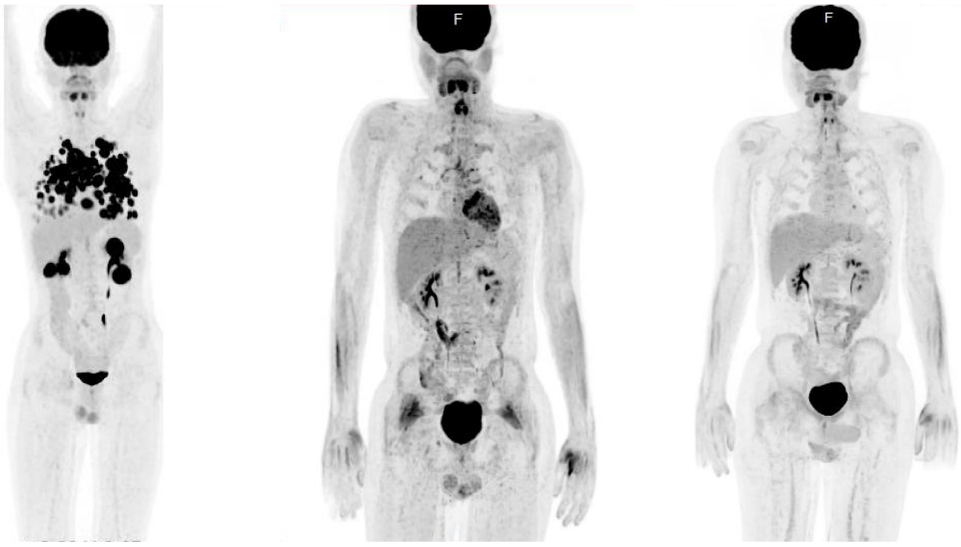
† The "R" in the regimen stands for rituximab. The v, AA, BB, and CC regimens refer to the NHL-BFM-95 protocol[11]. v: prednisone, cyclophosphamide; R-AA: rituximab, dexamethasone, ifosfamide, vincristine, methotrexate, cytarabine, etoposide; R-BB: rituximab, dexamethasone, vincristine, methotrexate, cyclophosphamide, adriamycin; R-CC: rituximab, dexamethasone, vindesine, cytarabine, etoposide; The detailed regimens of v, R-AA, R-BB, and R-CC are shown in Supplemental Table 2. R-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and adriamycin.

‡ The treatment regimen of glofitamab plus polatuzumab vedotin is shown in Supplemental Table 3.

Figure legends

Figure 1. Radiographic responses and ctDNA to the Glofit-Pola regimen of two pediatric patients with R/R B-NHL. **(A)** Serial PET/MRI in Patient 1 shows metabolic response. Images obtained at baseline (relapse; left panel), after 3 cycles (middle panel), and after 6 cycles (right panel). **(B)** Resolution of CNS disease in Patient 1. Brain MRI shows complete resolution of left frontal meningeal enhancement (arrow) compared to compared with baseline. (**C**) Treatment response in Patient 2 by PET/MRI. Baseline at relapse (left) and after 3 cycles (right), demonstrating CMR. (**D)** Resolution of bone lesions in Patient 2. Post-treatment MRI demonstrates complete disappearance of the previous lesions in the right pterygoid process and left ilium following 3 treatment cycles, as indicated by arrow markers. (**E)** CtDNA clearance in Patient 1. Longitudinal plasma monitoring showed clearance of tumor-specific mutant ctDNA after 6 cycles compared with baseline. (**F)** CtDNA clearance in Patient 2. Longitudinal monitoring of plasma and CSF demonstrated clearance of tumor-specific mutant ctDNA after 2 cycles compared with baseline. In plasma from Patient 2, the longitudinal ctDNA profiles of GNA13 p.T365dup, ID3 p.L80P, and TBL1XR1 c.1122+2T>A coincided, with their curves superimposed in the figure.

A



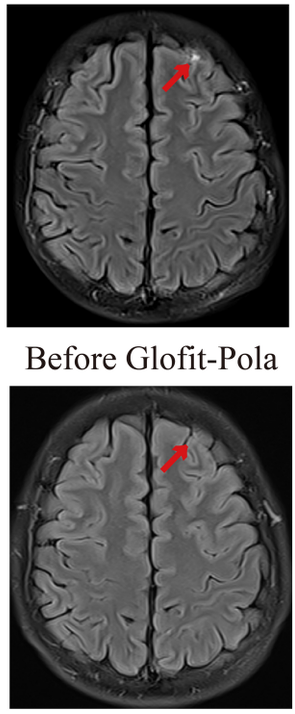
Before Glofit-Pola

After 3 cycles of Glofit-Pola

After 6 cycles of Glofit-Pola

Patient 1

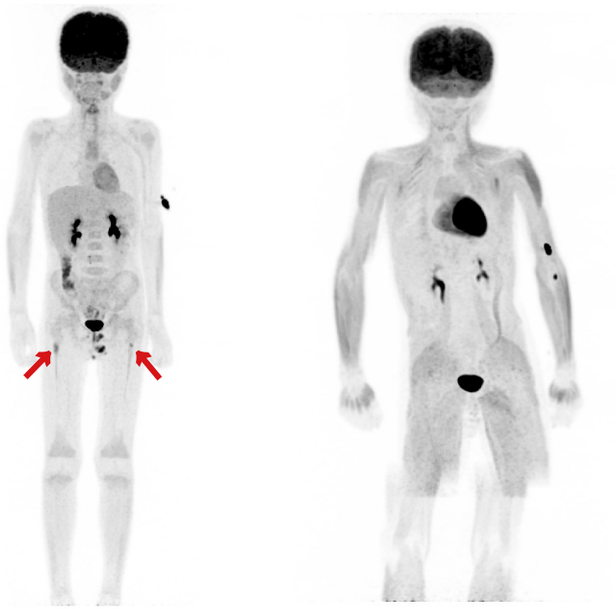
B



Before Glofit-Pola

After 3 cycles of Glofit-Pola

C

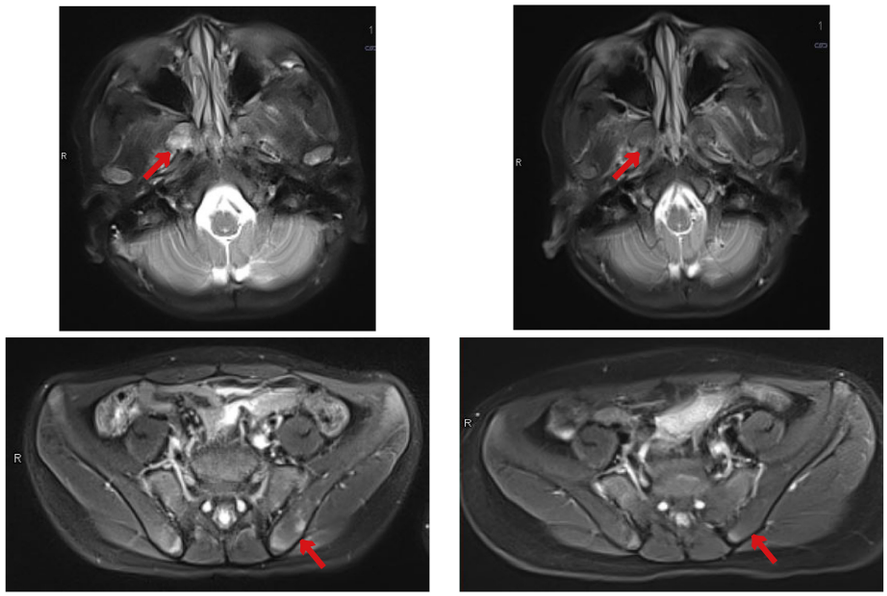


Before Glofit-Pola

After 3 cycles of Glofit-Pola

Patient 2

D

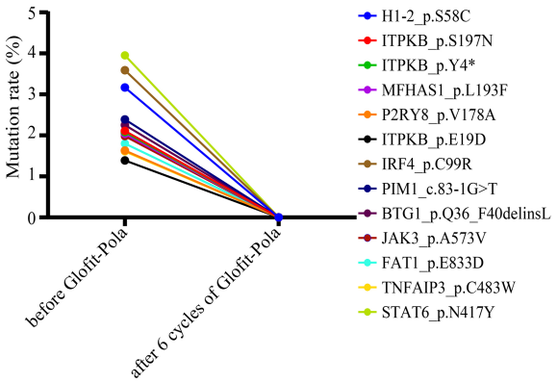


Before Glofit-Pola

After 3 cycles of Glofit-Pola

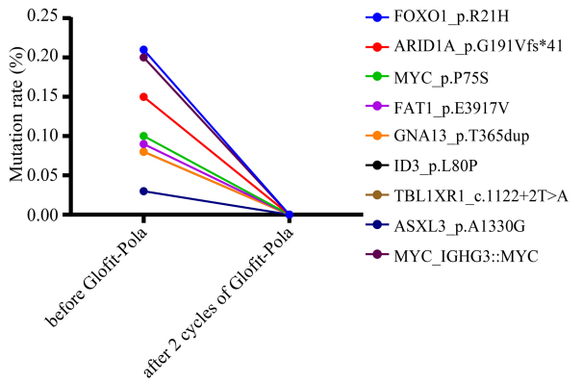
E

Plasma ctDNA

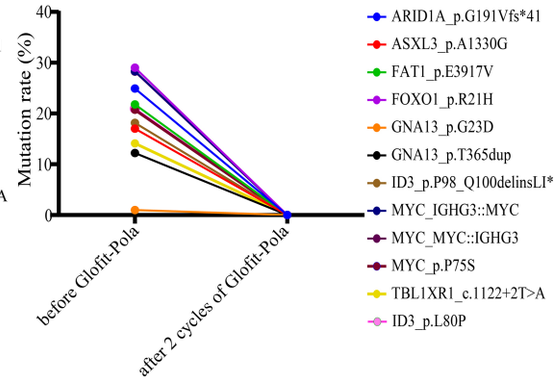


F

Plasma ctDNA



CSF ctDNA



Supplemental Table 1. Adverse Events in the Two Patients During Glofit-Pola therapy

System Organ Class / Preferred Term	Patient 1	Patient 2
Immune disorders		
CRS*	Grade 1	No
Blood and lymphatic system disorders		
Neutropenia	No	No
Anemia	No	No
Febrile neutropenia	No	No
Thrombocytopenia	No	No
Gastrointestinal disorders		
Nausea	No	No
Diarrhea	No	No
Vomiting	No	No
Abdominal pain	No	No
Constipation	No	No
Nervous system disorders		
Headache	No	Grade 1
Peripheral neuropathy	No	No
ICANS*	No	No
Skin and subcutaneous tissue disorders		
Rash	No	No
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	No	No
Hepatic function		
Alanine aminotransferase increased	No	No
Aspartate aminotransferase increased	No	No
Blood bilirubin increased	No	No
Gamma-glutamyl transferase increased	No	No
Renal function and electrolytes		
Blood creatinine increased	No	No
Hypokalemia	No	No
Hyponatremia	No	No
Adverse events leading to Glofit discontinuation	None	None
Glofit-related adverse events leading to discontinuation	None	None
Adverse events causing interruption of Glofit treatment	None	None

*The severity of CRS and ICANS occurring during Glofit-Pola therapy was assessed using the American Society for Transplantation and Cellular Therapy (ASTCT) criteria.

Supplemental Table 2. Chemotherapy Regimens

Course	Component	Usage	Dose	Day of administration
v	Prednisone	PO/IV	30 mg/m^2	d1-5
	CTX	IV	200 mg/m^2	d1-2
	MTX + Ara-C + Dex	IT	dose adjusted for age	d1
R-AA	Rituximab	IV	375 mg/m^2	d0
	MTX + Ara-C + Dex	IT	dose adjusted for age	d1
	Dexamethasone	PO/IV	10 mg/m^2	d1-5
	IFO	IV	800 mg/m^2	d1-5
	VCR	IV	1.5 mg/m^2 (maximal dose 2 mg)	d1
	MTX	IV 24h	5 g/m^2	d1
	Ara-C	IV	150 mg/m^2 q12h	d4-5
	VP16	IV	100 mg/m^2	d4-5
R-BB	Rituximab	IV	375 mg/m^2	d0
	MTX + Ara-C + Dex	IT	dose adjusted for age	d1
	Dexamethasone	PO/IV	10 mg/ m^2	d1-5
	VCR	IV	1.5 mg/ m^2 (maximal dose 2mg)	d1
	MTX	IV 24h	5 g/ m^2	d1
	CTX	IV	200 mg/m^2	d1-5
	ADR	IV	25 mg/m^2	d4-5
R-CC	Rituximab	IV	375 mg/m^2	d0
	Dexamethasone	PO/IV	20 mg/m^2	d1-5
	VDS	IV	3 mg/m^2 (maximal dose 5 mg)	d1
	Ara-C	IV	2 g/m^2 q12h	d1-2
	VP16	IV	150 mg/m^2	d3-5
	MTX + Ara-C + Dex	IT	dose adjusted for age	d5

CTX, cyclophosphamide; MTX, methotrexate; Ara-C, cytarabine; Dex, dexamethasone; IFO, ifosfamide; VCR, vincristine; VP16, etoposide; ADR, adriamycin; VDS, vindesine; IV, intravenous injection; PO, peros; IT, intrathecally.

Supplemental Table 3. Glofit-Pola Regimen for the Two Patients

Drug	Patient 1*	Patient 2†
Obinutuzumab‡ (pretreatment in cycle 1)	1000 mg IV	530mg IV
Glofitamab step-up dose (cycle 1)	Day 1: 2.5 mg IV	Day 1: 1 mg IV
	Day 8: 10 mg IV	Day 8: 4 mg IV
Polatuzumab vedotin (cycle 1)	Day 2: 1.8 mg/kg IV	Day 2: 1.8 mg/kg IV
Glofitamab (cycles 2–6)	Day 1: 30 mg IV	Day 1: 15 mg IV
Polatuzumab vedotin (cycle 2–6)	Day 1: 1.8 mg/kg IV	Day 1: 1.8 mg/kg IV

*Patient 1 (body weight: 60 kg) received all drugs at adult doses.

†Patient 2 (body weight: 23 kg) received all drugs at doses adjusted based on body weight, referencing standard adult doses.

‡Obinutuzumab is given as pretreatment in cycle 1, 7 days prior to the first glofitamab administration.