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Dexamethasone is associated with reduced frequency and intensity of cytokine release syndrome compared with alternative corticosteroid regimens as premedication for glofitamab in patients with relapsed / refractory large B-cell lymphoma

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Running head: Dex/non-Dex glofitamab premedication for R/R LBCL (49/50 characters including spaces)

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Data-sharing statement

For eligible studies, qualified researchers may request access to individual patient-level clinical data through the clinical study data request platform. At the time of writing this request, the platform is Vivli (https://vivli.org/ourmember/roche/). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

Trial registration: ClinicalTrials.gov (NCT03075696)

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Contributions

LF, MH, and EB were responsible for conception and design. LF, MH, GC, NLB, AS, SL and EB were responsible for provision of study materials or patients. NLB was responsible for collection and assembly of data. LF, MH, NLB, SL and EB were responsible for data analysis and interpretation. LF, MH, CC-S, FM, MD, GC, CK, MT, JM-L, NLB, AS, JDB, SL, AB, MK, JR, FBT, LL and EB were responsible for manuscript writing and final approval of the manuscript. LF, MH, GC, NLB, SL and EB were accountable for all aspects of the work.

Over the last decade, T-cell based immunotherapies, including chimeric antigen receptor T-cells and T-cell-engaging single-chain antibody constructs, have profoundly reshaped the treatment landscape of non-Hodgkin lymphoma. Cytokine release syndrome (CRS) is a potentially serious adverse event (AE) related to this specific treatment modality.[1]

Glofitamab is unique in the emerging class of CD20×CD3 bispecific antibodies, due to its innovative 2:1 tumor T-cell binding arrangement.[2,3] This structure provides dual binding capability for CD20 (on B cells) and single binding ability for CD3 (on T cells).[2] As a result, glofitamab activates and redirects the patient's T cells to target and eliminate malignant B cells.[2,3] With a fixed treatment duration and off-the-shelf accessibility, glofitamab demonstrated frequent and durable complete responses (CRs) with a manageable safety profile in pivotal expansion cohorts of an ongoing Phase I/II study (NCT03075696) in patients with relapsed/refractory (R/R) large B cell lymphoma (LBCL).[2,3] In one expansion cohort (D5) dexamethasone (Dex) was mandated as premedication to assess whether this corticosteroid could reduce the rate and severity of CRS versus other corticosteroids.[2] This retrospective study reports data from the dose-escalation and expansion cohorts in patients with R/R LBCL treated with glofitamab, who received Dex only versus non-Dex pretreatment.

This was a Phase I/II, multicenter, open-label, dose-escalation study and the methods have been previously published.[2] This study fully conformed to the Good Clinical Practice guidelines of the International Council for Harmonisation, the Declaration of Helsinki and local laws and regulations. Briefly, patients aged ≥18 years who had histologically confirmed diffuse LBCL (DLBCL; not otherwise specified [NOS]), high-grade B-cell lymphoma (HGBCL), transformed follicular

lymphoma (trFL) or primary mediastinal large B-cell lymphoma (PMBCL), and an Eastern Cooperative Oncology Group performance status score of 0 or 1, were included. All patients had disease that had either relapsed following treatment or was unresponsive to at least two prior lines of therapy, including at least one anti-CD20 antibody-containing regimen and one anthracycline-containing regimen. The primary endpoint was Independent Review Committee-assessed CR rate as measured by positron emission tomography-computed tomography using Lugano criteria.[4] The secondary endpoints focused on efficacy, including duration of CR, overall response rate (ORR), duration of response, progression-free survival (PFS), overall survival, and safety. CRS events were assessed using the American Society for Transplantation and Cellular Therapy criteria.[5]

Glofitamab was preceded by a single 1000 mg dose of obinutuzumab pretreatment (Cycle 1, Day 1) and was administered intravenously using step-up dosing in Cycle 1 (Day 8, 2.5 mg; Day 15, 10 mg), followed by 30 mg on Day 1 of Cycles 2-12, in 21-day cycles.[2,6] Patients were hospitalized for the first dose of glofitamab. Subsequent doses were administered in the outpatient setting unless Grade ≥2 CRS was reported after the first dose. Patients were treated for up to 12 cycles, or until disease progression, or unacceptable side effects, whichever came first.

To prevent hypersensitivity or infusion-related reactions to obinutuzumab or glofitamab, premedication with oral acetaminophen or paracetamol (500-1000 mg) and an antihistamine, such as intravenous or oral diphenhydramine (50-100 mg), was administered at least 30 minutes prior to each study medication infusion (unless contraindicated). Corticosteroid premedication (80 mg intravenous methylprednisolone, 100 mg prednisone, 100 mg prednisolone, or 20 mg intravenous Dex) was given at least 60 minutes prior to obinutuzumab and

glofitamab administration during Cycles 1-3. Corticosteroids were optional in later cycles for patients who tolerated glofitamab step-up dosing and two target doses without experiencing CRS.

As of September 4, 2023, of the previously reported patients evaluable for safety (N=154)[2], 145 patients with R/R DLBCL NOS, trFL, HGBCL, or PMBCL received ≥1 dose of glofitamab. Thirty-three patients received premedication with Dex only (Dex group), and 112 patients received premedication with other corticosteroid regimens (non-Dex group; **Supplementary Figure 1**). Nine patients in the non-Dex group received some Dex; however, none of these patients received only Dex during Cycles 1-3. At data cut-off, 10 patients (30.3%) had completed glofitamab treatment in the Dex group and 29 patients (25.9%) in the non-Dex group. Baseline characteristics between the two groups were comparable and are summarized in **Table 1**. The median age for the Dex and non-Dex groups was 73 (range: 27-86) and 66 (range: 21-90) years, respectively. Twenty patients in the Dex group had an Eastern Cooperative Oncology Group performance status of 1 (60.6%) compared with 57 patients in the non-Dex group (50.9%); most patients had advanced disease (Ann Arbor stage III/IV: Dex, 78.7%; non-Dex, 74.2%). A five-parameter model (also known as CRS risk score[7,8]) was applied retrospectively to predict the risk of Grade ≥2 CRS after the first glofitamab dose; the proportion of patients classified at baseline as “high risk” for developing a Grade ≥2 CRS event was comparable amongst the Dex and non-Dex groups (**Table 1**).

The median number of prior therapies was three for the Dex (range: 2-5) and non-Dex (range: 2-7) groups; 51.6% and 61.7% of patients received ≥3 prior lines of therapy in the Dex and non-Dex groups, respectively. In both groups, the median

number of cycles of glofitamab received was five (Dex range: 1-12; non-Dex range: 1–13) and the median dose intensity of glofitamab was 100%.

The number of patients who discontinued treatment in the Dex and non-Dex groups was 21 (63.6%) and 80 (71.4%), respectively. Discontinuations in the Dex group occurred due to: progressive disease (n=12 [36.4%]), death (n=3 [9.1%]), AE (n=2 [6.1%;]), and lack of efficacy, physician decision, symptomatic deterioration and other (n=1 [3.0%] each); in the non-Dex group, discontinuations occurred due to: progressive disease (n=52 [46.4%]), physician decision (n=7 [6.3%]), death and AE (n=6 [5.4%] each), withdrawal by subject (n=3 [2.7%]), lack of efficacy and symptomatic deterioration (n=2 [1.8%] each), and protocol deviation and other (n=1 [0.9%] each).

CRS events occurred in 48.5% of patients in the Dex group and 73.2% of patients in the non-Dex group (**Figure 1A**). Grade 3/4 CRS events occurred in one patient (3.0%) in the Dex group compared with five patients (4.5%) in the non-Dex group (**Supplementary Table 1**). Five patients in the Dex group experienced serious CRS (15.2%) compared with 27 patients in the non-Dex group (24.1%). Median time to CRS onset was one day (range: 1–21) for the Dex group and two days (range: 1–17) for the non-Dex group. Tocilizumab was used to treat CRS in fewer patients in the Dex group (n=4 [12.1%]) compared with the non-Dex group (n=28 [25.0%]; **Figure 1B**). CRS was treated with corticosteroids in eight patients (24.2%) in the Dex group and 21 patients (18.8%) in the non-Dex group.

At the Cycle 1 Day 8 dose of glofitamab (2.5 mg), 15 patients (15/33; 45.5%) in the Dex group and 64 patients (64/112; 57.1%) in the non-Dex group experienced CRS. The median duration of CRS was 2 days for both the Dex (range: 1-14) and non-Dex

(range: 1-8) groups. Among the patients dosed at Cycle 1 Day 15 (10 mg), five patients (5/30; 16.7%) in the Dex group and 40 patients (40/105; 38.1%) in the non-Dex group experienced CRS. For the patients dosed from Cycle 2 onwards, Grade 1 CRS events were reported in one (1/28; 3.6%) patient in the Dex group (**Figure 2A**) and 35 (35/99; 35.4%) patients in the non-Dex group (Grade 2 CRS in one patient [1.0%]; **Figure 2B**).

Overall, Grade ≥3 AEs occurred in over 60% of patients in both groups; of these, 48.5% and 47.3% were deemed glofitamab-related in the Dex and non-Dex groups, respectively (**Supplementary Table 1**). AEs leading to withdrawal/discontinuation of glofitamab treatment occurred in two (6.1%) patients in the Dex group and eight (7.1%) patients in the non-Dex group. AEs consistent with immune effector cell-associated neurotoxicity syndrome were infrequent (Dex group: 6.1% [n=2]; non-Dex group: 3.6% [n=4]). In the Dex group, both cases were Grade 1, while in the non-Dex group two were Grade 1, one was Grade 3 somnolence, and one was Grade 5 delirium (considered multifactorial in the context of progressive disease).

Full details of the response rates are provided in **Supplementary Table 2**. Independent Review Committee-assessed CR rates in the efficacy population (N=132; DLBCL NOS and trFL only; **Supplementary Table 2**) for the Dex and non-Dex groups were 45.2% (14/31; 95% confidence interval [CI]: 27.3-64.0) and 43.6% (44/101; 95% CI: 33.7-53.8), respectively. The ORR was 51.6% (16/31; 95% CI: 33.1-69.9) for the Dex group and 57.4% (58/101; 95% CI: 47.2-67.2) for the non-Dex group. Median duration of CR was not estimable (NE; 95% CI: 15.6-NE) for the Dex group and 28.3 months (95% CI: 19.8-NE) for the non-Dex group. The 18-month PFS rate for the Dex group was 31.8% (95% CI: 14.0-49.6) compared with 35.5% (95% CI: 25.7-45.4) in the non-Dex group.

Overall, in patients with R/R LBCL, the incidence and severity of CRS events after glofitamab administration was lower with Dex premedication versus other corticosteroids or a mixture of corticosteroids. The longer half-life of Dex compared with prednisone[10,11] as well as its greater cytotoxic effect,[12] may allow for a more prolonged anti-inflammatory effect, potentially reducing the need for frequent dosing and offering more stable symptom control, supporting its potential as a promising alternative.

The rate and durability of responses in this Phase I/II study were similar in both the Dex and non-Dex groups, suggesting that Dex premedication does not have a negative impact on glofitamab treatment efficacy. The results of this analysis suggest that premedication with Dex prior to glofitamab administration is effective in mitigating CRS in patients with R/R LBCL and should be considered as a preferred premedication corticosteroid for CRS prevention.

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Figures and tables:

Table 1. Summary of patient demographic and baseline characteristics.

	Dex group (n=33)	**Non-Dex group (n=112)**
Median age, years (range)	73.0 (27-86)	66.0 (21-90)
Age ≥65 years	19 (57.6)	60 (53.6)
Male, n (%)	20 (60.6)	75 (67.0)
ECOG PS, n (%)		
0	13 (39.4)	55 (49.1)
1	20 (60.6)	57 (50.9)
Ann Arbor stage, n (%)		
I/II	6 (18.2)	27 (24.1)
III/IV	26 (78.8)	83 (74.1)
Unknown	1 (3.0)	2 (1.8)
Bulky disease, n (%)		
>6 cm	13 (39.4)	46 (41.1)
>10 cm	3 (9.1)	14 (12.5)
NHL subtype, n (%)		
DLBCL	24 (72.7)	81 (72.3)
trFL	7 (21.2)	20 (17.9)
HGBCL	2 (6.1)	5 (4.5)
PMBCL	0 (0)	6 (5.4)
Median number of prior lines, n (range)	3 (2-5)	3 (2-7)
2 prior lines, n (%)	16 (48.5)	43 (38.4)
≥3 prior lines, n (%)	17 (51.5)	69 (61.6)
Prior CAR T-cell therapy, n (%)	10 (30.3)	37 (33.0)

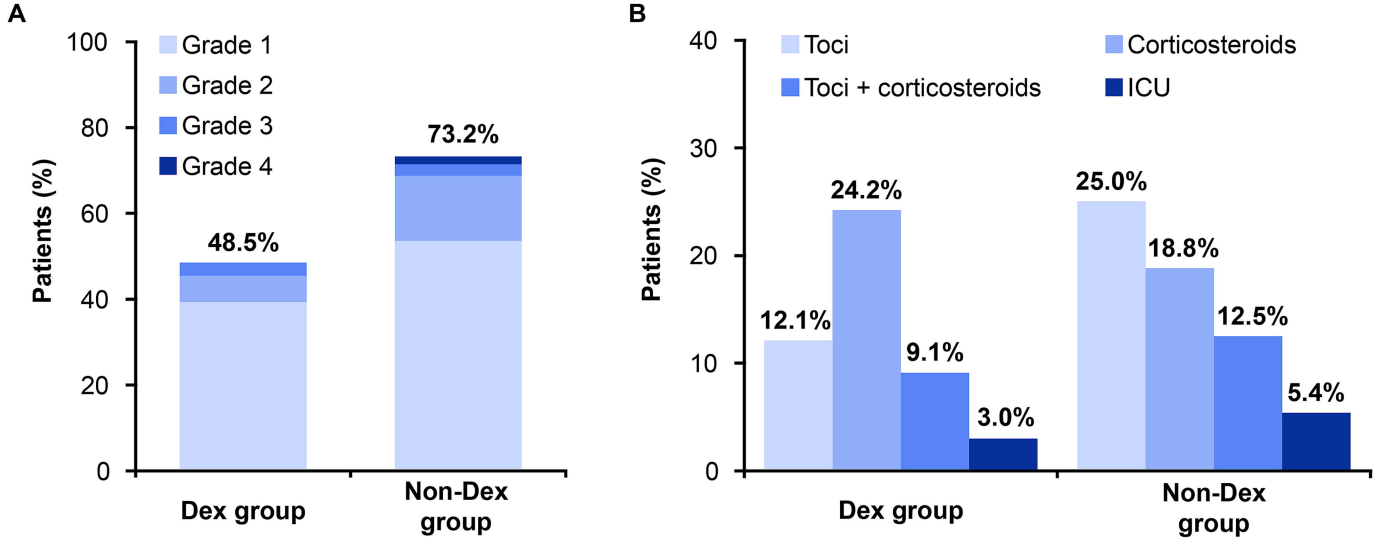
Refractory to any prior therapy, n (%)	29 (87.9)	100 (89.3)
Refractory to last prior therapy, n (%)	28 (84.8)	94 (83.9)
Elevated LDH >280 U/L, n (%)	13 (39.4)	68 (60.7)
WBC >4.5 × 10^9 cells/L, n (%)	23 (69.7)	78 (69.6)
CRS-RS.5p ≥4*, n (%)	15 (45.5)	55 (49.1)
Median number of treatment cycles of glofitamab, range	5.0 (1-12)	5.0 (1-13)
Median dose intensity of glofitamab, % (range)	100 (93.6-100)	100 (95.0-100)

*Five-parameter model used to predict the risk of Grade ≥2 CRS after the first glofitamab dose.[7] CAR, chimeric antigen receptor; CRS-RS.5p; cytokine release syndrome risk score 5-parameter model; Dex, dexamethasone; DLBCL, diffuse large B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBCL, high-grade B-cell lymphoma; LDH, lactate dehydrogenase; NHL, non-Hodgkin lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; trFL, transformed follicular lymphoma; WBC, white blood cell.

Figure Legends

Figure 1. Summary of A) CRS* events and B) CRS management† in the Dex (n=33) and non-Dex groups (n=112). *Graded by American Society for Transplantation and Cellular Therapy criteria.[5] †Other forms of CRS management used: single pressor (Dex group, n=1; non-Dex group, n=5), low flow oxygen (non-Dex group, n=10), high flow oxygen (Dex group, n=1), and mechanical ventilation (non-Dex group, n=2). CRS: cytokine release syndrome; Dex: dexamethasone; ICU: intensive care unit; Toci: tocilizumab.

Figure 2. Sunburst plots[9] of CRS events and tocilizumab usage by cycle of treatment in the A) Dex group (n=33), and B) non-Dex group (n=112). Each concentric circle represents consecutive dosing cycles of glofitamab, progressing outward from the center to the periphery. Within each circle, segments indicate the number of patients experiencing/not experiencing CRS events treated or not with tocilizumab. These events are sorted by severity from no CRS (green) to Grade 4 with tocilizumab (red) in a counterclockwise manner. Groups of patients initially recorded in a segment within the first circle are tracked through subsequent circles, enabling the observation of how CRS evolves over time. Segments are colored white when no dose of glofitamab was given (see **Supplementary Information** for more details). CRS: cytokine release syndrome; C: Cycle; D: Day; Dex: dexamethasone; Gr: grade; toci: tocilizumab.


A
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Patients (%)
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Dex group
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Patients (%)
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Corticosteroids
Toci + corticosteroids
ICU
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25.0%
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12.5%
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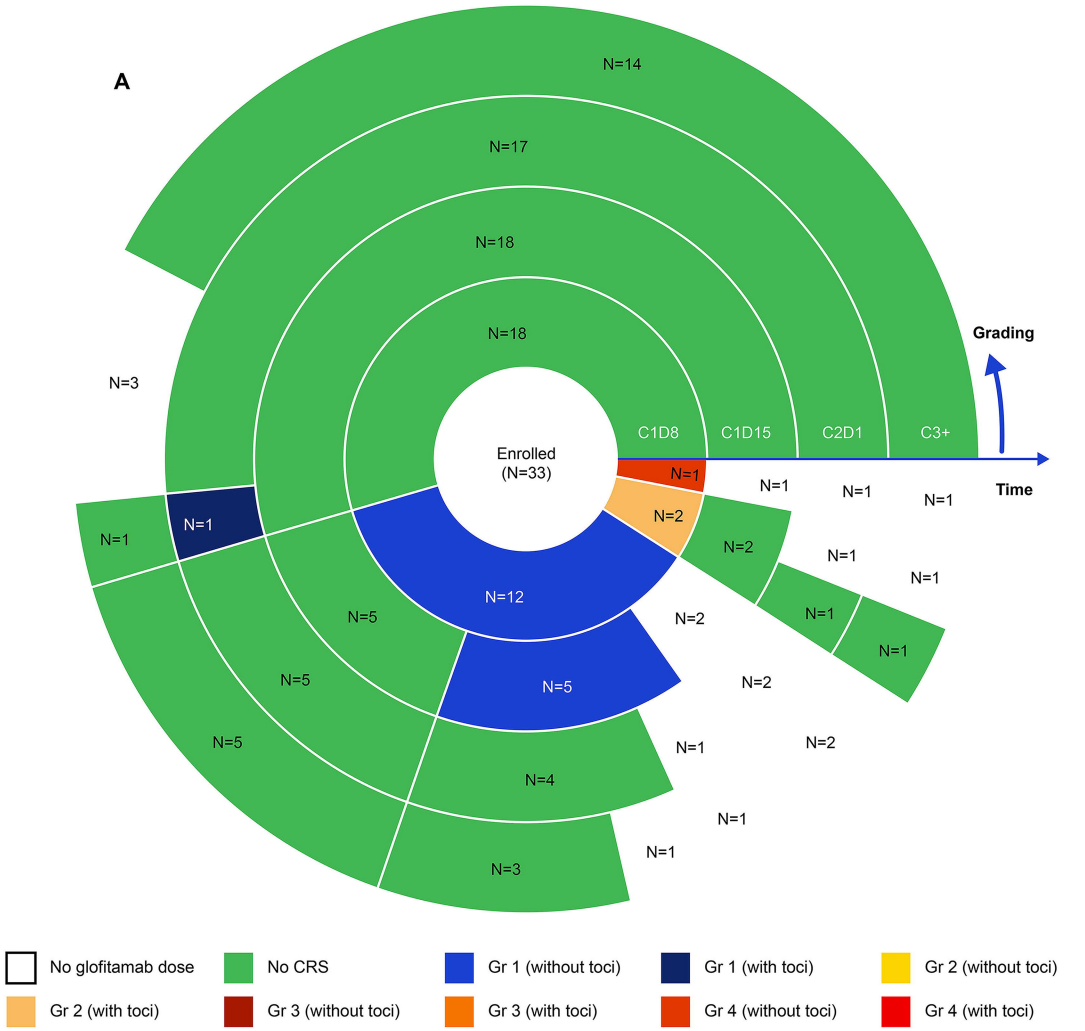
Dex group
Non-Dex group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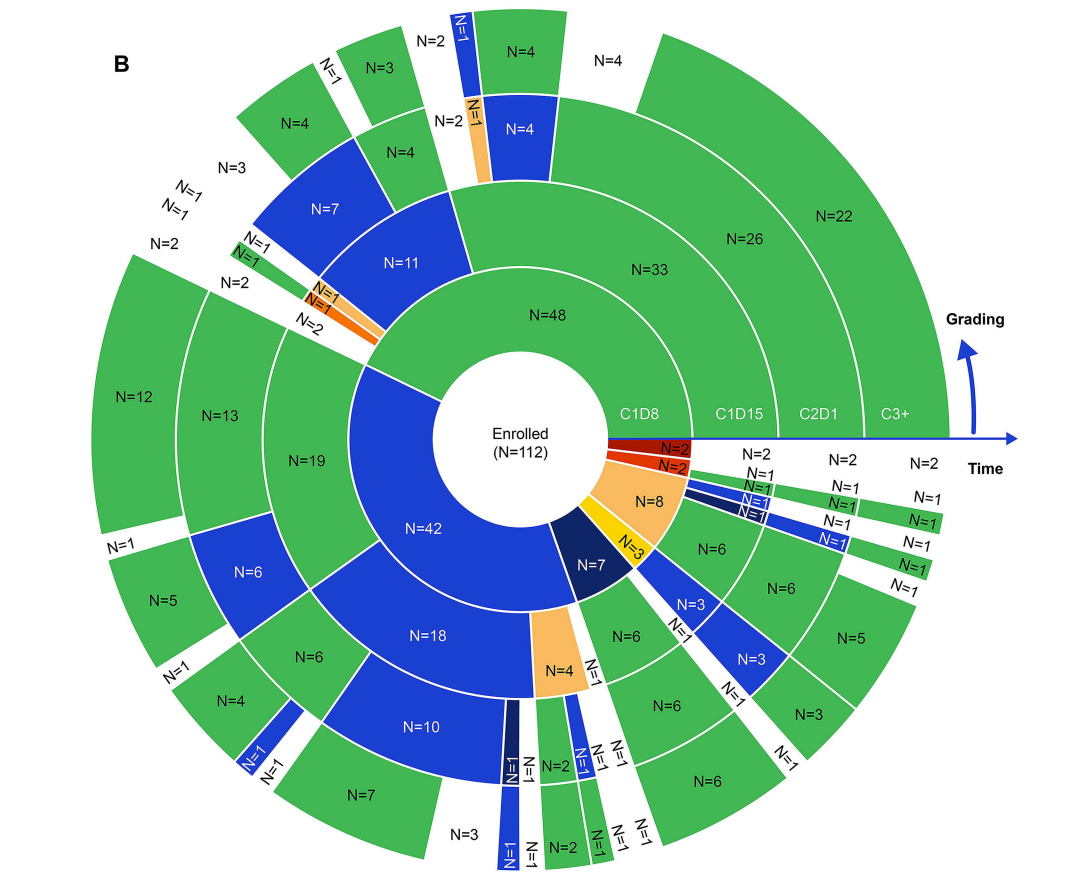
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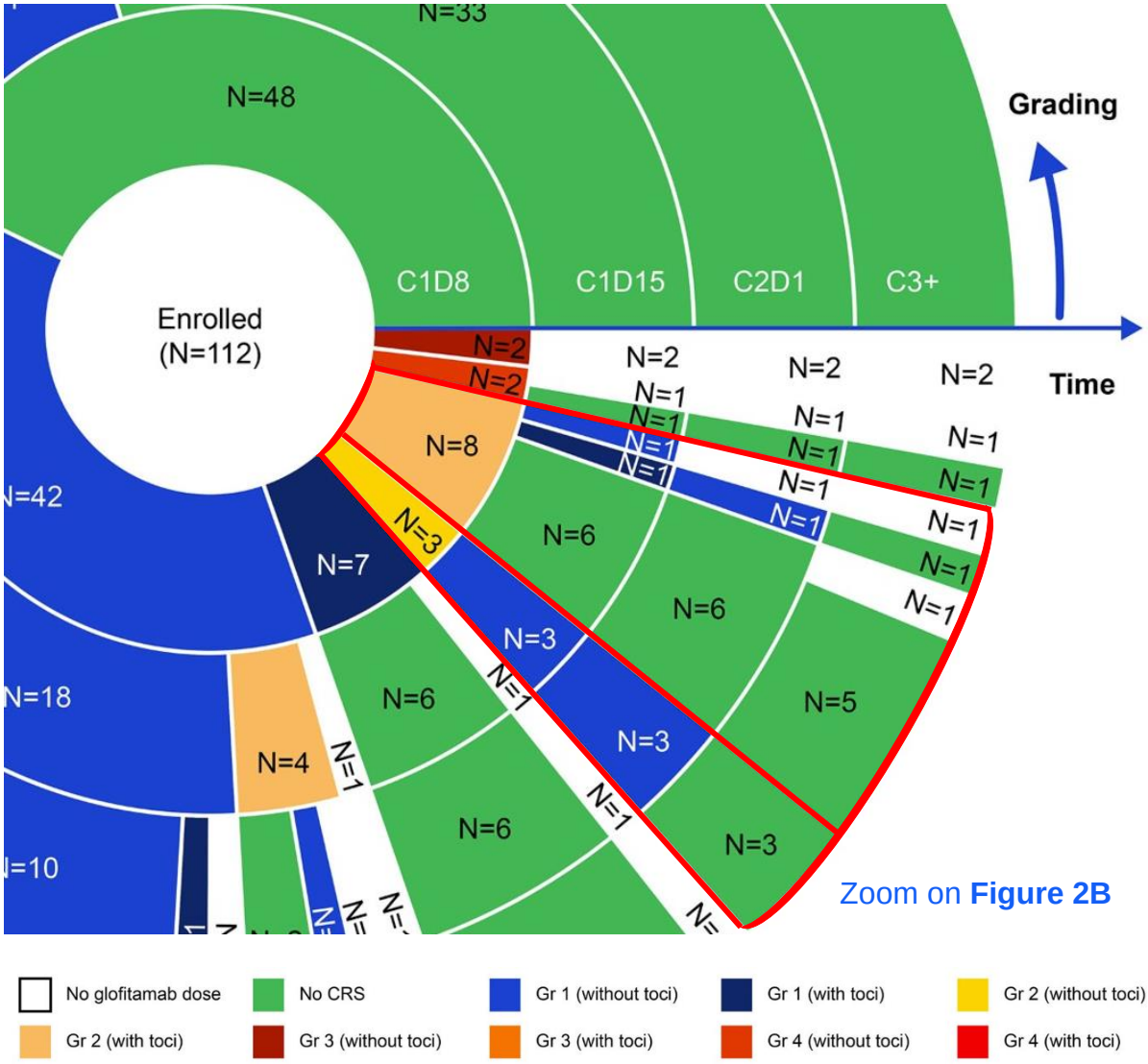
N=5
N=6
N=4
N=1
N=1
N=6
N=8
N=7
N=4
N=2
N=2
N=6
N=6
N=6
N=6
N=5
N=3
N=3
N=5
Enrolled
(N=112)
C1D8
C1D15
C2D1
C3+
Grading
Time
No glofitamab dose
No CRS
Gr 1 (without toci)
Gr 1 (with toci)
Gr 2 (without toci)
Gr 2 (with toci)
Gr 3 (without toci)
Gr 3 (with toci)
Gr 4 (without toci)
Gr 4 (with toci)

Supplemental Digital Content

How to interpret the Sunburst Plots.[1]



By focusing on the 11 (3 and 8) patients who had cytokine release syndrome (CRS) Grade 2 at Cycle 1, Day 8, it can be observed that three did not receive tocilizumab after their CRS diagnosis and eight did. On Cycle 1, Day 15, 75% (6 out of 8) of the patients who received tocilizumab no longer exhibited CRS symptoms, while the three patients who did not receive tocilizumab still experienced CRS symptoms but at a lower grade (Grade 2 to Grade 1). The remaining two patients who experienced Grade 2 CRS events requiring tocilizumab at Cycle 1 Day 8, both went on to

experience CRS events at Cycle 1 Day 15; one a Grade 2 event requiring tocilizumab, and the other a Grade 1 event treated with tocilizumab. Overall, most of the patients who did not receive tocilizumab after their CRS diagnosis continued to experience CRS at subsequent glofitamab doses, albeit at a similar or lower grade. The sunburst plot effectively illustrates the benefit of tocilizumab in managing CRS events induced by glofitamab, by demonstrating its effectiveness in minimizing CRS events compared to scenarios without tocilizumab administration.

Supplementary Table 1. Summary of AEs and CRS.

	Dex group (n=33)	**Non-Dex group (n=112)**
Any AE, n (%)	33 (100)	110 (98.2)
Glofitamab related*	32 (97.0)	108 (96.4)
Serious AEs, n (%)	12 (36.4)	58 (51.8)
Glofitamab related*	6 (18.2)	40 (35.7)
Grade ≥3 AE, n (%)	21 (63.6)	74 (66.1)
Glofitamab related*	16 (48.5)	53 (47.3)
Grade 5 AE, n (%)	2 (6.1)	8 (7.1)
Glofitamab related*	0 (0)	0 (0)
AE leading to glofitamab withdrawal/discontinuation, n (%)	2 (6.1)	8 (7.1)
Glofitamab related*	1 (3.0)	4 (3.6)
Neurological AEs, n (%)	12 (36.4)	46 (41.1)
Grade ≥3	0 (0)	3 (2.7)
AEs consistent with ICANS, n (%)	2 (6.1)†	4 (3.6)‡
Infection, n (%)	11 (33.3)	48 (42.9)
Grade ≥3	3 (9.1)	19 (17.0)
Grade 3/4 CRS, n (%)	1 (3.0)	5 (4.5)
Serious CRS§, n (%)	5 (15.2)	27 (24.1)

Recurring CRS (any grade)¶, n (%)	6 (18.2)	41 (36.6)
Grade ≥2	0 (0)	6 (5.4)
Median time to CRS onset, days (range)	1 (1-21)	2 (1-17)
Duration of CRS after first glofitamab dose, days (range)	2 (1-14)	2 (1-8)
Median time to CRS onset from Cycle 1 Day 8 (2.5 mg) dose**, hours (range)	12.1 (5.2-34.6)	13.9 (5.7-50.8)
Median time to CRS resolution after Cycle 1 Day 8 (2.5 mg) dose, hours (range)	27.2 (5.7-316.7)	31.0 (0.0-167.9)

*As determined by the investigator. †Both Grade 1 events. ‡Grade 1, n=2; Grade 3, n=1 (somnolence); Grade 5, n=1 (delirium). §Including prolonged hospitalization. ¶Patients with more than one CRS event. **From the start of infusion. AE: adverse event; CRS: cytokine release syndrome; Dex: dexamethasone; ICANS: immune effector cell-associated neurotoxicity syndrome.

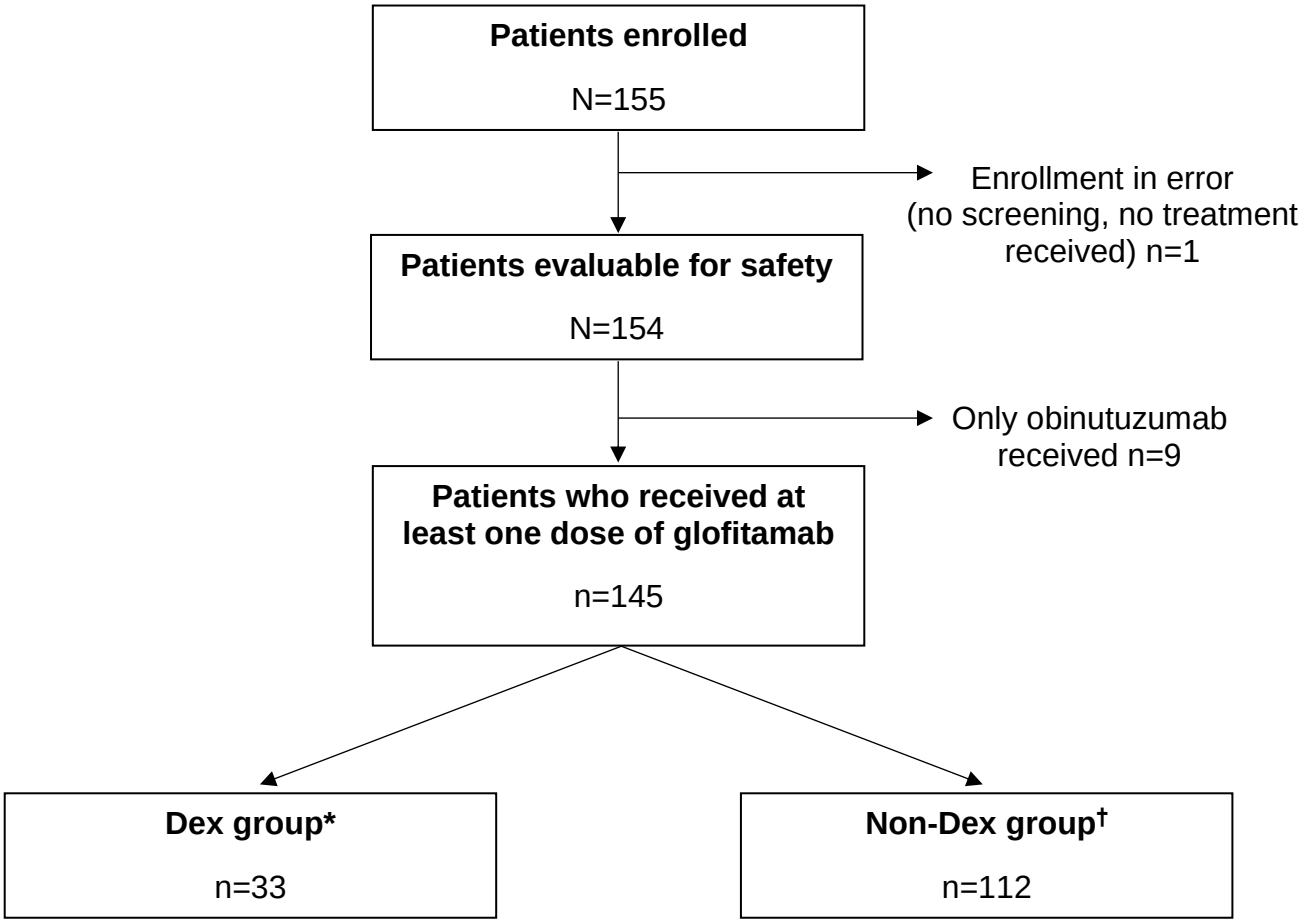
Supplementary Table 2. Responses in the Dex and non-Dex groups.

	Dex group (n=31)*	**Non-Dex group (n=101)***
CR rate, n (%) [95% CI]	**14 (45.2)** [27.3-64.0]	**44 (43.6)** [33.7-53.8]
ORR, n (%) [95% CI]	**16 (51.6)** [33.1-69.9]	**58 (57.4)** [47.2-67.2]
DOCR, months [95% CI]	**NE** [15.6-NE]	**28.3** [19.8-NE]
12-month DOCR rate, % [95% CI]	**83.1** [61.5-100]	**77.4** [64.4-90.4]
18-month DOCR rate, % [95% CI]	**72.7** [45.9-99.5]	**72.1** [58.0-86.1]
18-month PFS rate, % [95% CI]	**31.8** [14.0-49.6]	**35.5** [25.7-45.4]

*Patients with R/R DLBCL and trFL with ≥2 prior lines of therapy, only.

CI: confidence interval; CR: complete response; Dex: dexamethasone; DLBCL: diffuse large B cell lymphoma; DOCR: duration of complete response; ORR: overall response rate; PFS, progression-free survival; R/R: relapsed/refractory; trFL: transformed follicular lymphoma.

Supplementary Figure 1. Summary of study groups.[2,3,4]



*Patients who had received premedication with Dex only. †Patients who had received premedication with other corticosteroids or a mixture of corticosteroids including some Dex. Dex: dexamethasone.

References

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4. Columvi™ highlights of prescribing information. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf. Accessed March 21, 2024.