

Shah, et al. ZUMA-3 2-year follow-up treatment subgroup manuscript – *JITC*

SUPPLEMENTARY APPENDIX

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Supplementary Methods

Eligibility criteria

Full eligibility requirements were previously reported.^{1,2}

Procedures

Disease and adverse event monitoring and toxicity management were previously described.^{1,2}

Outcomes

Definitions for duration of remission (DOR), overall survival (OS), and relapse-free survival (RFS) were previously reported.^{1,2} Briefly, DOR was defined as the time from reaching complete remission (CR) or CR with incomplete hematological recovery (CRi) (central assessment) to relapse or death without documented relapse. The calculation of DOR did not include disease assessments occurring after new anticancer therapies, including alloSCT. RFS was defined as the time from infusion of KTE-X19 to the date of relapse or death from any cause. Patients were evaluated as having an RFS event at Day 0 if they did not achieve CR or CRi as of the data cutoff date; as such, patients in the intention-to-treat population who were not infused would also have been considered to have an event at Day 0. For DOR and RFS, sensitivity analyses were performed in which disease assessments obtained after alloSCT were included in the derivation of DOR and RFS.

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Supplementary Tables

Table S1. Summary of subsequent anticancer therapies received by Phase 1 and 2 patients with response to brexu-cel who proceeded to subsequent therapies, by number of prior therapies

Reported therapies	Patients with 1 prior therapy (n=4)	Patients with ≥2 prior therapies (n=4)
Dexamethasone	3 (75)	1 (25)
Inotuzumab	3 (75)	0
Vincristine	3 (75)	0
Cyclophosphamide	2 (50)	2 (50)
Blinatumomab	1 (25)	0
Blinatumomab ^a	1 (25)	0
Ponatinib	1 (25)	0
Rituximab	1 (25)	0
Inotuzumab Ozogamicin	0	2 (50)
Antithymocyte Immunoglobulin (rabbit)	0	1 (25)
Cytarabine	0	1 (25)
Etoposide	0	1 (25)
Fludarabine	0	1 (25)
Fludarabine Phosphate	0	1 (25)
Haploid Allo Tx ^a	0	1 (25)
Hydrocortisone	0	1 (25)
Inotuzumab Ozogamicin (CMC-544) ^a	0	1 (25)
Investigational antineoplastic drugs	0	1 (25)
Melphalan	0	1 (25)
Methotrexate	0	1 (25)
Ponatinib Hydrochloride	0	1 (25)
Thiotepa	0	1 (25)
Tisagenlecleucel-T	0	1 (25)

Subsequent anticancer therapies are coded using WHO-Drug Dictionary March 2021 version.

Therapies taken during the retreatment period are excluded.

^a Indicates reported name of therapy.

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Table S2. Baseline disease and patient characteristics in Phase 2 treated patients (N=55) by prior therapies

	Phase 2 patients (N=55)	Prior number of therapies		Prior blinatumomab		Prior inotuzumab		Prior alloSCT	
		1 (n=10)	≥2 (n=45)	Yes (n=25)	No (n=30)	Yes (n=12)	No (n=43)	Yes (n=23)	No (n=32)
Age, median (range), years	40 (19-84)	38.5 (21-65)	41 (19-84)	38 (19-84)	42.5 (19-73)	45 (19-84)	39 (19-73)	38 (19-68)	45.5 (19-84)
≥65 years, n (%)	9 (16)	1 (10)	7 (16)	3 (12)	5 (17)	2 (17)	6 (14)	2 (9)	6 (19)
Male, n (%)	33 (60)	6 (60)	27 (60)	16 (64)	17 (57)	10 (83)	23 (53)	12 (52)	21 (66)
ECOG PS of 1, n (%)	39 (71)	6 (60)	33 (73)	18 (72)	21 (70)	8 (67)	31 (72)	16 (70)	23 (72)
Philadelphia chromosome-positive, n (%)	15 (27)	2 (20)	13 (29)	5 (20)	10 (33)	4 (33)	11 (26)	8 (35)	7 (22)
Extramedullary disease at screening, n (%)	6 (11)	0	6 (13)	4 (16)	2 (7)	1 (8)	5 (12)	2 (9)	4 (13)
CNS-1 disease at baseline, n (%)	55 (100)	10 (100)	45 (100)	25 (100)	30 (100)	12 (100)	43 (100)	23 (100)	32 (100)
Bone marrow blasts at baseline, median (range) %	60 (0-98)	47 (0-73)	65 (2-98)	70 (2-98)	50 (0-96)	74 (2-98)	50 (0-97)	72 (2-96)	50 (0-98)
>25%, n (%)	40 (73)	7 (70)	33 (73)	18 (72)	22 (73)	10 (83)	30 (70)	17 (74)	23 (72)
CD19 lymphoblast baseline category per central lab, %									
≥95	41 (75)	8 (80)	33 (73)	18 (72)	23 (77)	9 (75)	32 (74)	17 (74)	24 (75)
<95	12 (22)	2 (20)	10 (22)	5 (20)	7 (23)	3 (25)	9 (21)	5 (22)	7 (22)
Missing	2 (4)	0	2 (4)	2 (8)	0	0	2 (5)	1 (4)	1 (3)
Number of prior therapies, median (range)	2 (1-8)	1 (1-1)	3 (2-8)	3 (1-8)	2 (1-5)	3.5 (2-5)	2 (1-8)	3 (1-8)	2 (1-4)
≥3 prior lines of therapy, n (%)	26 (47)	0	26 (58)	15 (60)	11 (37)	11 (92)	15 (35)	16 (70)	10 (31)
Prior blinatumomab, n (%)	25 (45)	1 (10)	24 (53)	25 (100)	0	6 (50)	19 (44)	11 (48)	14 (44)
Prior inotuzumab, n (%)	12 (22)	0	12 (27)	6 (24)	6 (20)	12 (100)	0	5 (22)	7 (22)
Prior alloSCT, n (%)	23 (42)	1 (10)	22 (49)	11 (44)	12 (40)	5 (42)	18 (42)	23 (100)	0
Prior radiotherapy, n (%)	13 (24)	2 (20)	11 (24)	8 (32)	5 (17)	3 (25)	10 (23)	9 (39)	4 (13)
Primary refractory, n (%)	18 (33)	4 (40)	14 (31)	8 (32)	10 (33)	2 (17)	16 (37)	6 (26)	12 (38)
Relapsed or refractory to second or greater line of therapy ^a , n (%)	43 (78)	0	43 (96)	23 (92)	20 (67)	12 (100)	31 (72)	12 (91)	22 (69)
First relapse with remission ≤12.0 months, n (%)	16 (29)	5 (50)	11 (24)	5 (20)	11 (37)	0	16 (37)	5 (22)	11 (34)

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Relapsed or refractory post-alloSCT^b, n (%)	24 (44)	2 (20)	22 (49)	11 (44)	13 (43)	5 (42)	19 (44)	23 (100)	1 (3) ^b
Response to the last prior therapy, n (%)									
CR	16 (29)	5 (50)	11 (24)	7 (28)	9 (30)	1 (8)	15 (35)	9 (39)	7 (22)
Cri	1 (2)	1 (10)	0	0	1 (3)	0	1 (2)	0	1 (3)
PR	2 (4)	0	2 (4)	1 (4)	1 (3)	0	2 (5)	1 (4)	1 (3)
NR	20 (36)	3 (30)	17 (38)	7 (28)	13 (43)	5 (42)	15 (35)	4 (17)	16 (50)
PD	10 (18)	1 (10)	9 (20)	7 (28)	3 (10)	2 (17)	8 (19)	4 (17)	6 (19)
Not evaluated	6 (11)	0	6 (13)	3 (12)	3 (10)	4 (33)	2 (5)	5 (22)	1 (3)

^a Two patients with relapsed or refractory disease to second or greater lines of therapy were erroneously not marked in the eCRF as such. ^b One patient had prior autologous transplantation but was erroneously marked in the eCRF as relapsed/refractory disease after alloSCT.

alloSCT, allogeneic stem cell transplantation; CNS, central nervous system; CR, complete remission; CRi, complete remission with incomplete hematological recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, no response; PD, progressive disease; PR, partial response.

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Table S3. Summary of cytokine release syndrome and neurological events in Phase 2 treated patients (N=55)

	Prior number of therapies		Prior blinatumomab		Prior inotuzumab		Prior alloSCT	
	1 (n=10)	≥2 (n=45)	Yes (n=25)	No (n=30)	Yes (n=12)	No (n=43)	Yes (n=23)	No (n=32)
Cytokine release syndrome, n (%)	9 (90)	40 (89)	21 (84)	28 (93)	11 (92)	38 (88)	20 (87)	29 (91)
Grade 1	4 (40)	7 (16)	2 (8)	9 (30)	2 (17)	9 (21)	5 (22)	6 (19)
Grade 2	4 (40)	21 (47)	13 (52)	12 (40)	6 (50)	19 (44)	11 (48)	14 (44)
Grade ≥3	1 (10)	12 (27)	6 (24)	7 (23)	3 (25)	10 (23)	4 (17)	9 (28)
Neurological events, n (%)	6 (60)	27 (60)	14 (56)	19 (63)	9 (75)	24 (56)	12 (52)	21 (66)
Grade 1	2 (20)	4 (9)	2 (8)	4 (13)	3 (25)	3 (7)	2 (9)	4 (13)
Grade 2	1 (10)	12 (27)	7 (28)	6 (20)	3 (25)	10 (23)	4 (17)	9 (28)
Grade ≥3	3 (30)	11 (24)	5 (20)	9 (30)	3 (25)	11 (26)	6 (26)	8 (25)

^a Cytokine release syndrome is graded per the revised grading system proposed by Lee et al (2014).³ ^b Neurological events are identified based on a modification of criteria proposed by Topp and colleagues (Topp et al 2015).⁴

alloSCT, allogeneic stem cell transplantation.

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Table S4. Summary of best overall responses for patients with blinatumomab as last prior therapy in ZUMA-3

	N	Best response to brexu-cel				
		Overall CR/CRI rate, n (%)	CR, n (%)	CRI, n (%)	BFBM, n (%)	NR, n (%)
Phase 1 and 2 patients with blinatumomab as last prior therapy	17	12 (71)	10 (59)	2 (12)	3 (18)	2 (12)
Best response to prior blinatumomab^a						
CR	6	3 (50)	3 (50)	0	1 (17)	2 (33)
PR	1	1 (100)	0	1 (100)	0	0
NR	3	3 (100)	2 (67)	1 (33)	0	0
PD	7	5 (71)	5 (71)	0	2 (29)	0

^a Data regarding duration of blinatumomab therapy received is not available.

BFBM, blast-free hypoplastic or aplastic bone marrow; brexu-cel, brexucabtagene autoleucel; CR, complete remission; CRI, CR with incomplete hematologic recovery; NR, no response; PD, progressive disease; PR, partial response.

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Table S5. Baseline disease and patient characteristics in Phase 1 and 2 responders by subsequent alloSCT

	Responders with subsequent alloSCT (n=14)	Responders without subsequent alloSCT (n=43)
ECOG PS of 1, n (%)	8 (57)	30 (70)
Philadelphia chromosome-positive, n (%)	2 (14)	12 (28)
Extramedullary disease at screening, n (%)	1 (7)	4 (9)
CNS-1 disease at baseline, n (%)	14 (100)	43 (100)
Bone marrow blasts at baseline, median (range) %	37 (2-88)	60 (0-97)
>25%, n (%)	9 (64)	30 (70)
Number of prior therapies, median (range)	2 (1-5)	3 (1-8)
Prior blinatumomab, n (%)	5 (36)	19 (44)
Prior inotuzumab, n (%)	1 (7)	9 (21)
Prior alloSCT, n (%)	1 (7)	21 (49)
Prior radiotherapy, n (%)	2 (14)	14 (33)
Primary refractory, n (%)	6 (43)	12 (28)
Relapsed or refractory to second or greater line of therapy ^a , n (%)	11 (79)	30 (70)
First relapse with remission ≤12.0 months, n (%)	4 (29)	11 (26)
Relapsed or refractory post-alloSCT ^b , n (%)	1 (7)	22 (51)
Response to the last prior therapy, n (%)		
CR	2 (14)	16 (37)
CRi	1 (7)	1 (2)
PR	1 (7)	0
NR	9 (64)	11 (26)
PD	1 (7)	11 (26)
Not evaluated	0	4 (9)

^a Two patients with relapsed or refractory disease to second or greater lines of therapy were

erroneously not marked in the eCRF as such. ^b One patient had prior autologous transplantation but was erroneously marked in the eCRF as relapsed/refractory disease after alloSCT.

alloSCT, allogeneic stem cell transplantation; CNS, central nervous system; CR, complete remission; CRi, complete remission with incomplete hematological recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, no response; PD, progressive disease; PR, partial response.

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Table S6. Peak and AUC₀₋₂₈ CAR T-cell levels in pooled Phase 1 and 2 treated patients by bone marrow blast levels at baseline in patients with and without prior blinatumomab

Baseline BM blast %	Prior blinatumomab (Yes)			Prior blinatumomab (No)		
	N	Median peak CAR T cells/ul	Median AUC ₀₋₂₈ CAR T cells/ul × days	N	Median peak CAR T cells/ul	Median AUC ₀₋₂₈ CAR T cells/ul × days
Total	31	18.805	199.830	35	34.791	329.811
≤25%	9	37.003	485.627	11	40.473	424.962
>25% to ≤50%	4	41.896	388.809	7	76.696	831.701
>50% to ≤75%	6	20.345	269.104	5	13.111	137.668
>75%	12	4.025	48.706	12	19.138	213.441

AUC₀₋₂₈, area under the curve from time of dose to 28 days; BM, bone marrow; CAR, chimeric antigen receptor.

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Table S7. Peak and AUC₀₋₂₈ CAR T-cell levels in pooled Phase 1 and 2 treated patients by BM blast levels at baseline in patients with and without prior inotuzumab

Baseline BM blast %	Prior inotuzumab (Yes)			Prior inotuzumab (No)		
	N	Median peak CAR T cells/ul	Median AUC ₀₋₂₈ CAR T cells/ul × days	N	Median peak CAR T cells/ul	Median AUC ₀₋₂₈ CAR T cells/ul × days
Total	12	21.034	240.834	38	19.933	197.987
≤25%	2	43.115	480.634	12	37.632	436.092
>25% to ≤50%	1	183.501	642.252	9	59.750	831.701
>50% to ≤75%	3	31.004	329.811	6	2.941	46.696
>75%	6	3.139	41.781	11	5.689	60.698

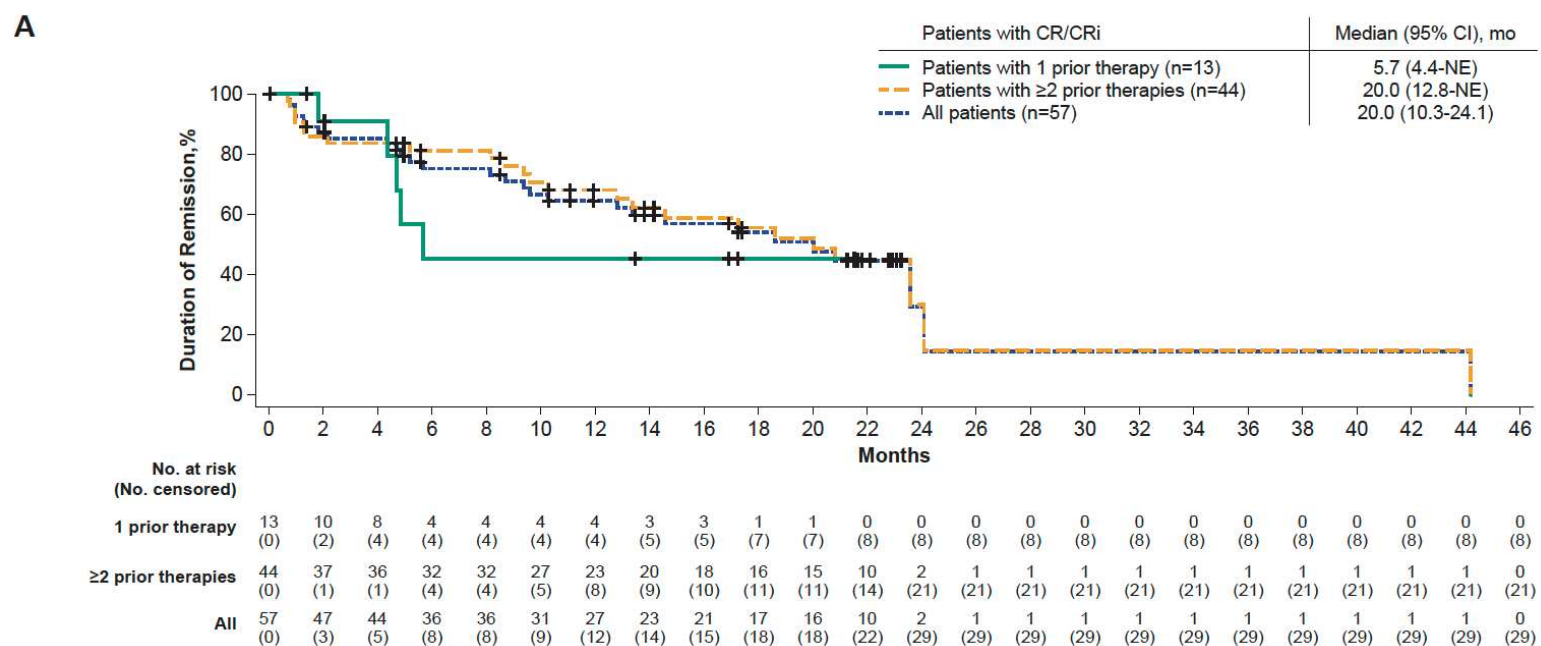
AUC₀₋₂₈, area under the curve from time of dose to 28 days; BM, bone marrow; CAR, chimeric antigen receptor.

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Supplementary Figures

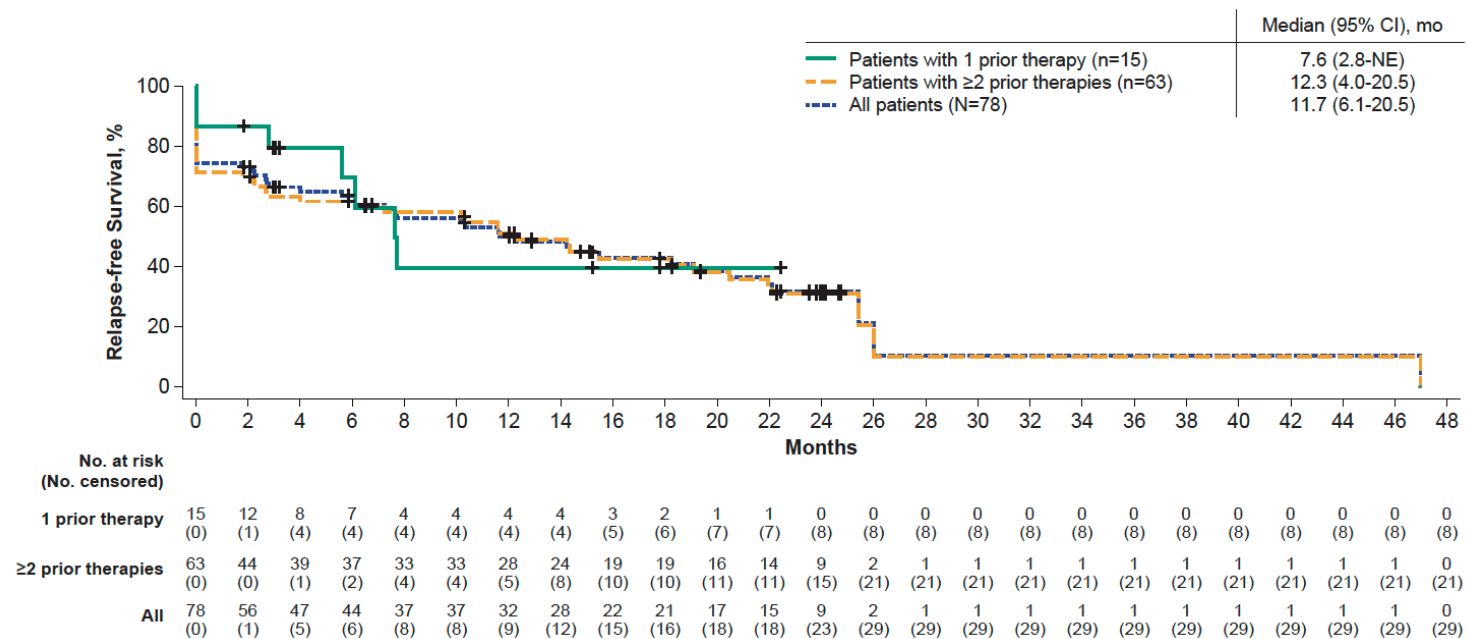
Figure S1: Duration of remission (not censored at subsequent alloSCT; A) and relapse-free survival (not censored at subsequent alloSCT; B) in pooled Phase 1 and 2 treated patients by prior number of therapy lines

alloSCT, allogeneic stem cell transplantation; CR, complete remission; CRi, complete remission with incomplete hematological recovery; mo, month; NE, not estimable; NR, not reached.



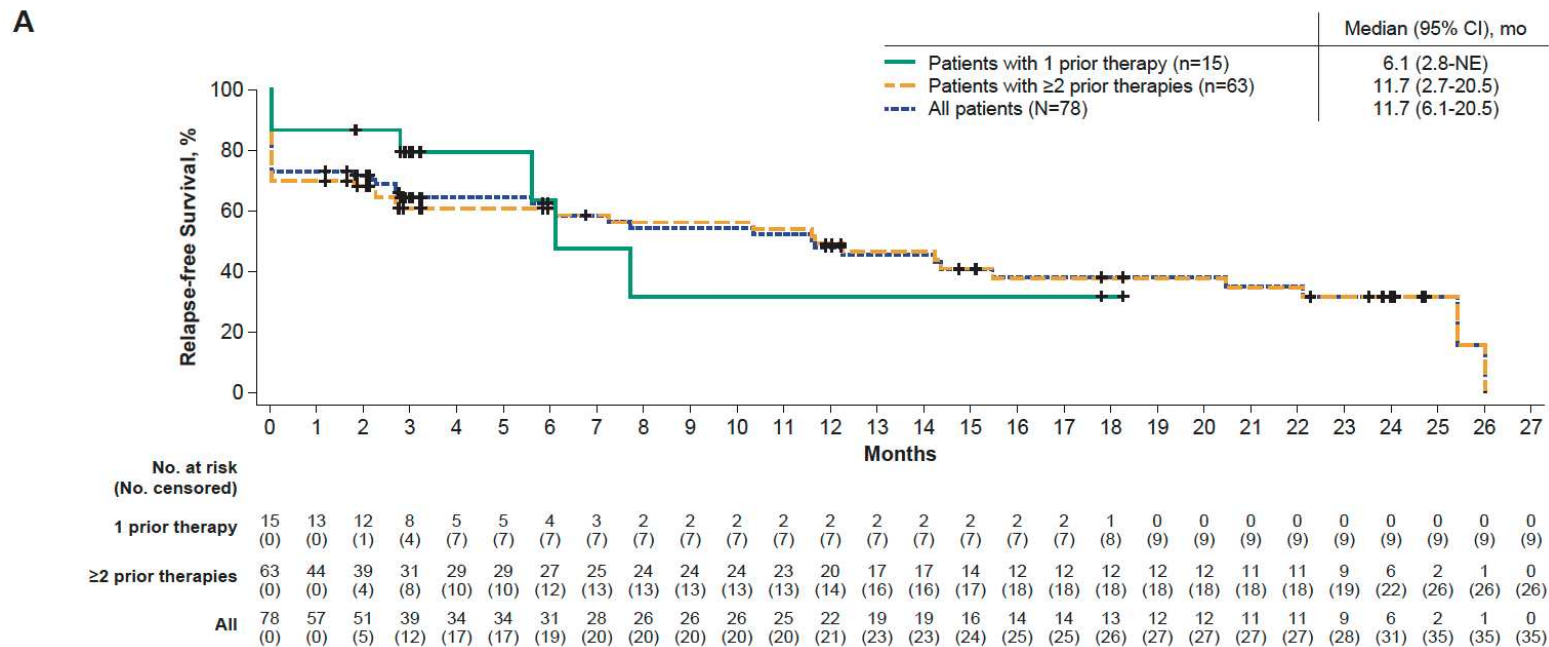
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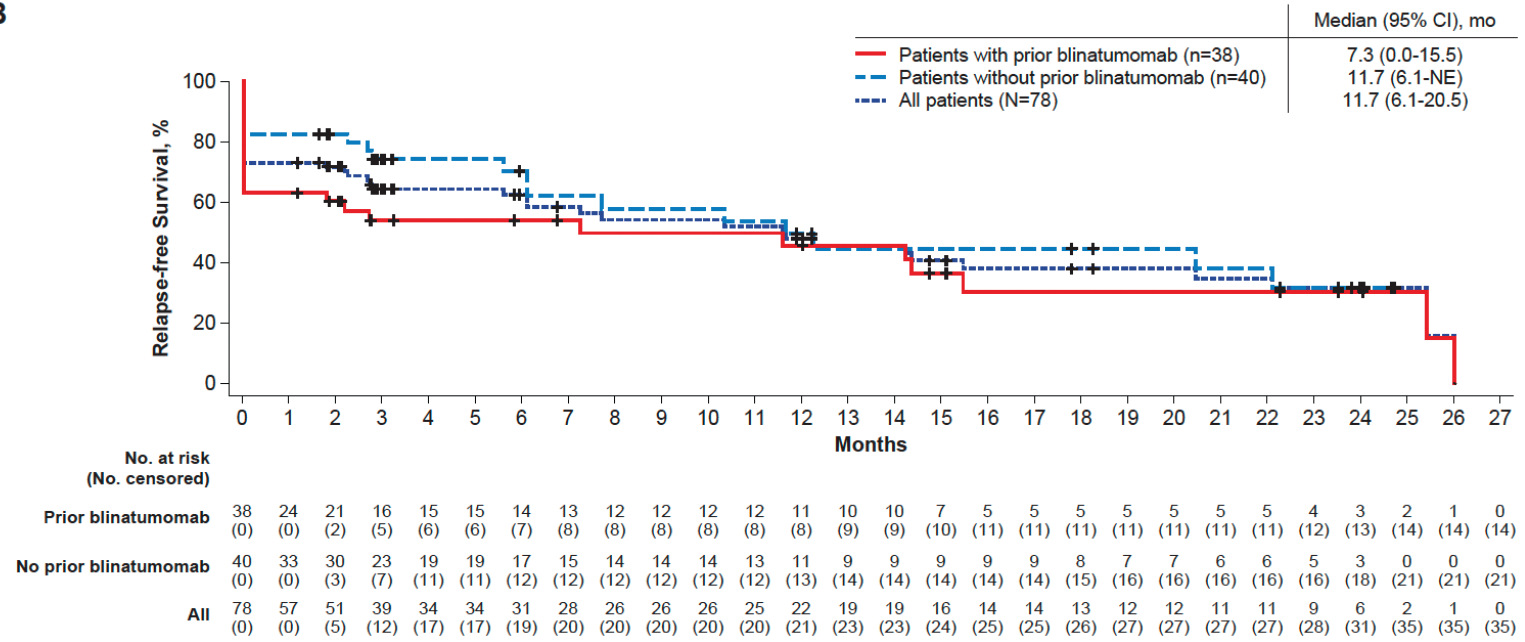
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Figure S2: Relapse-free survival (censored at subsequent alloSCT) in pooled Phase 1 and 2 treated patients by (A) prior number of therapy lines, (B) prior blinatumomab exposure, (C) prior inotuzumab exposure, and (D) prior alloSCT exposure
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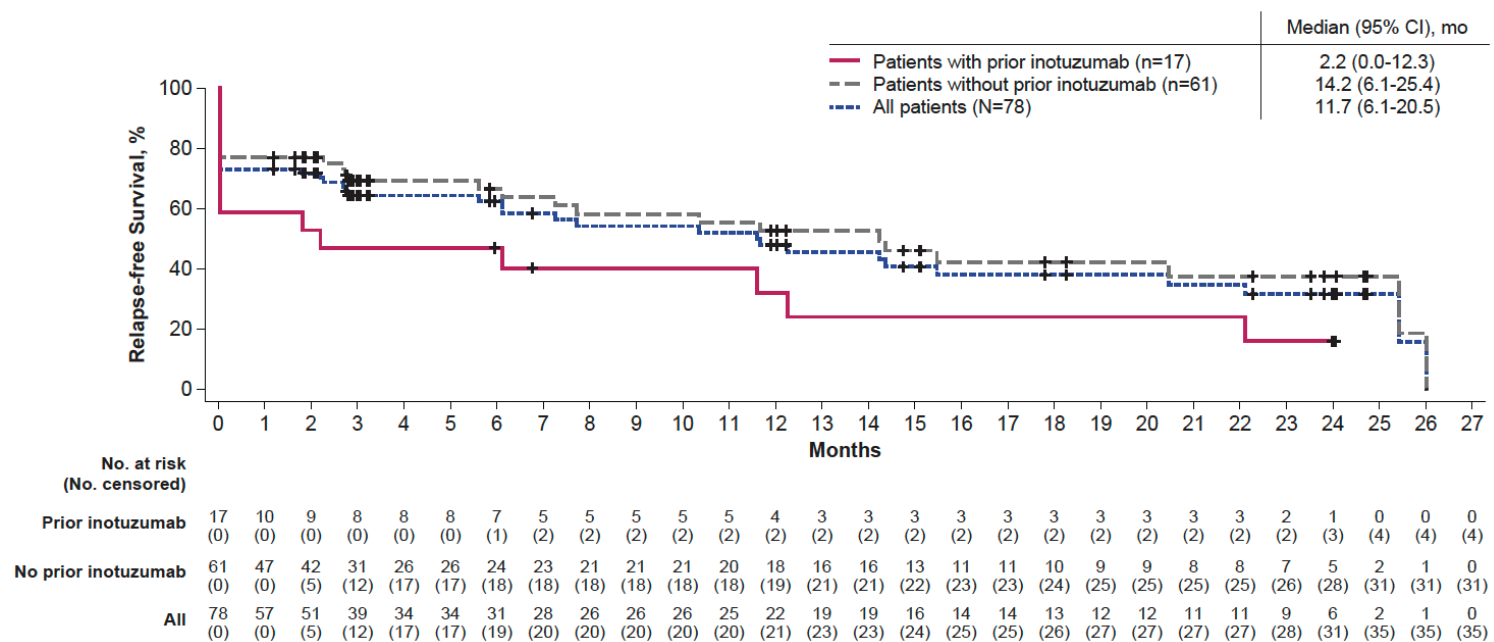
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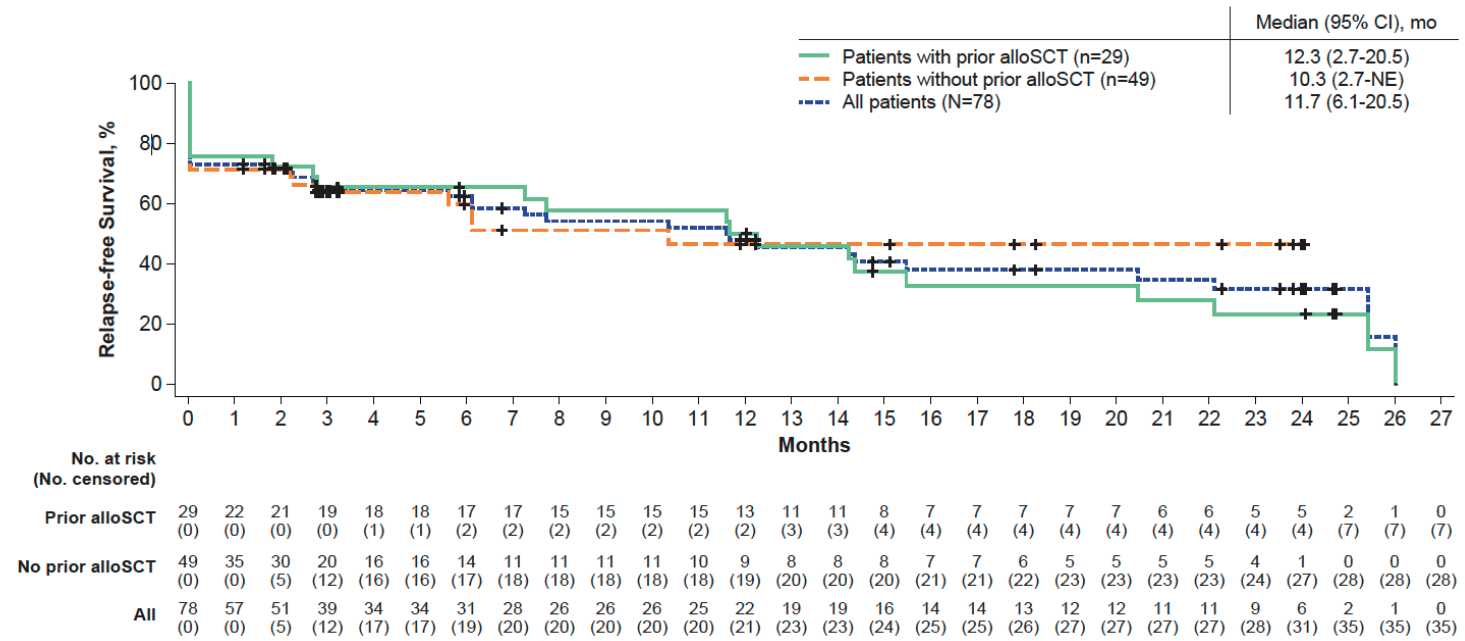
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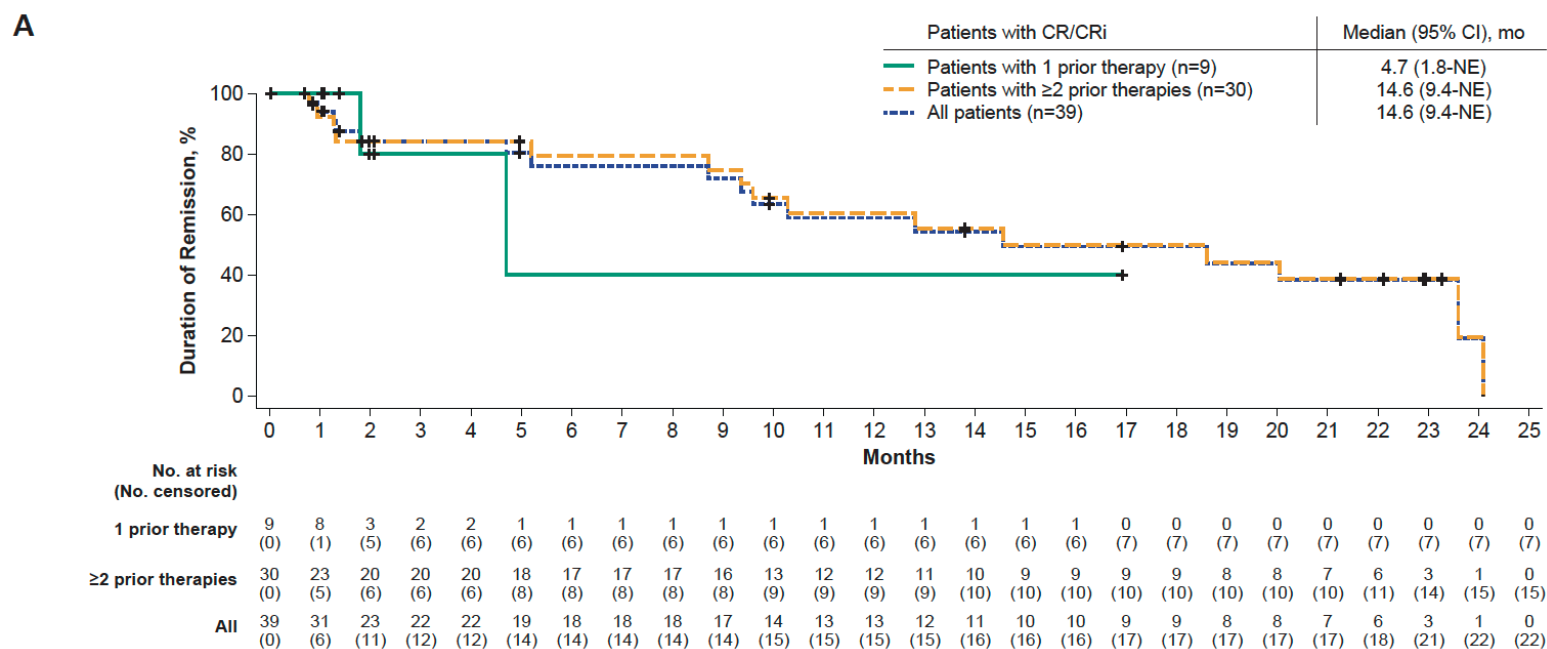
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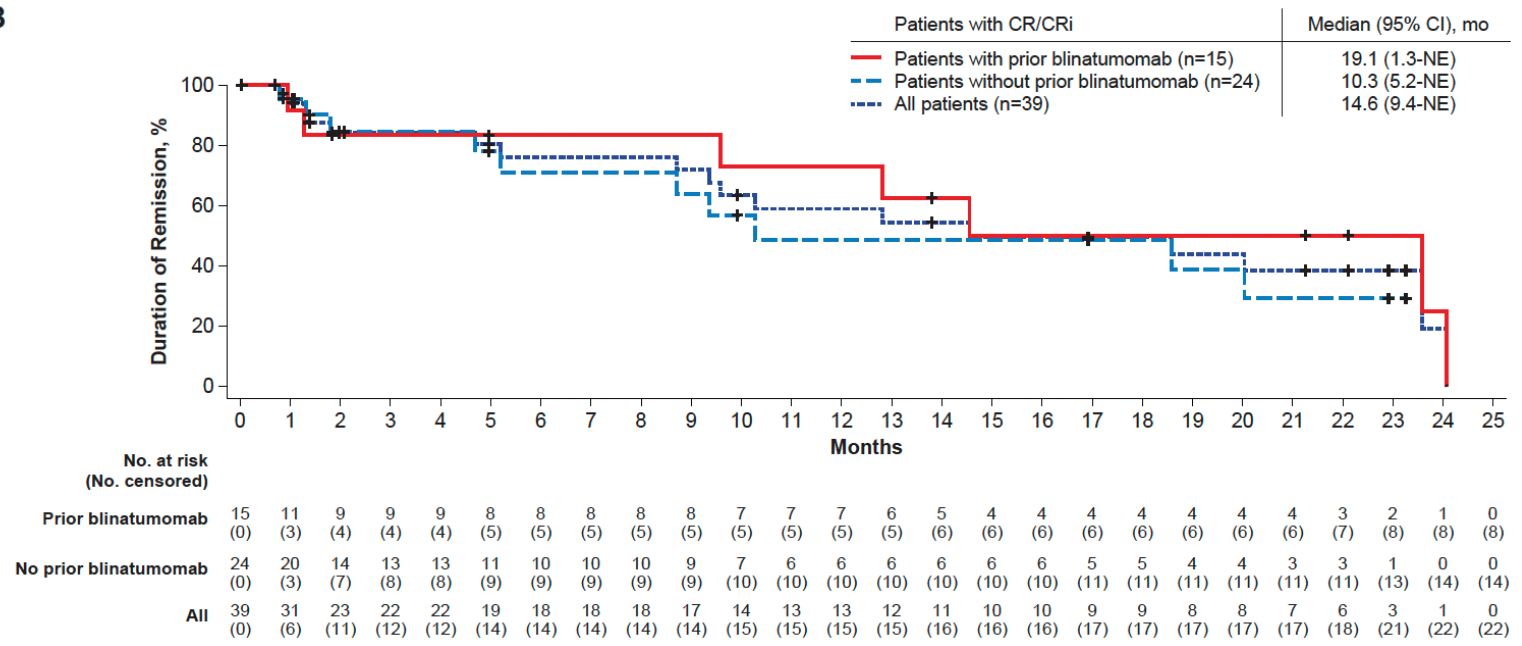
Figure S3: Duration of remission (censored at subsequent alloSCT) in Phase 2 treated patients by (A) prior number of therapy lines, (B) prior blinatumomab exposure, (C) prior inotuzumab exposure, and (D) prior alloSCT exposure

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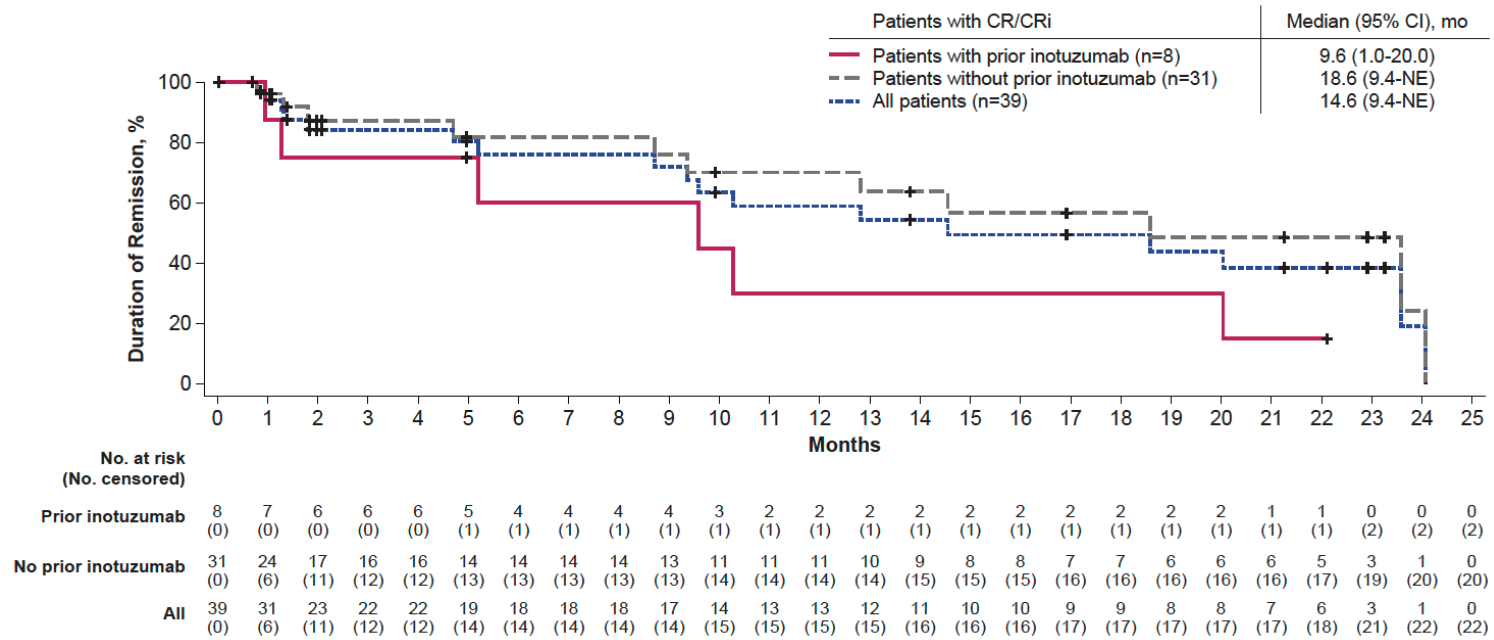
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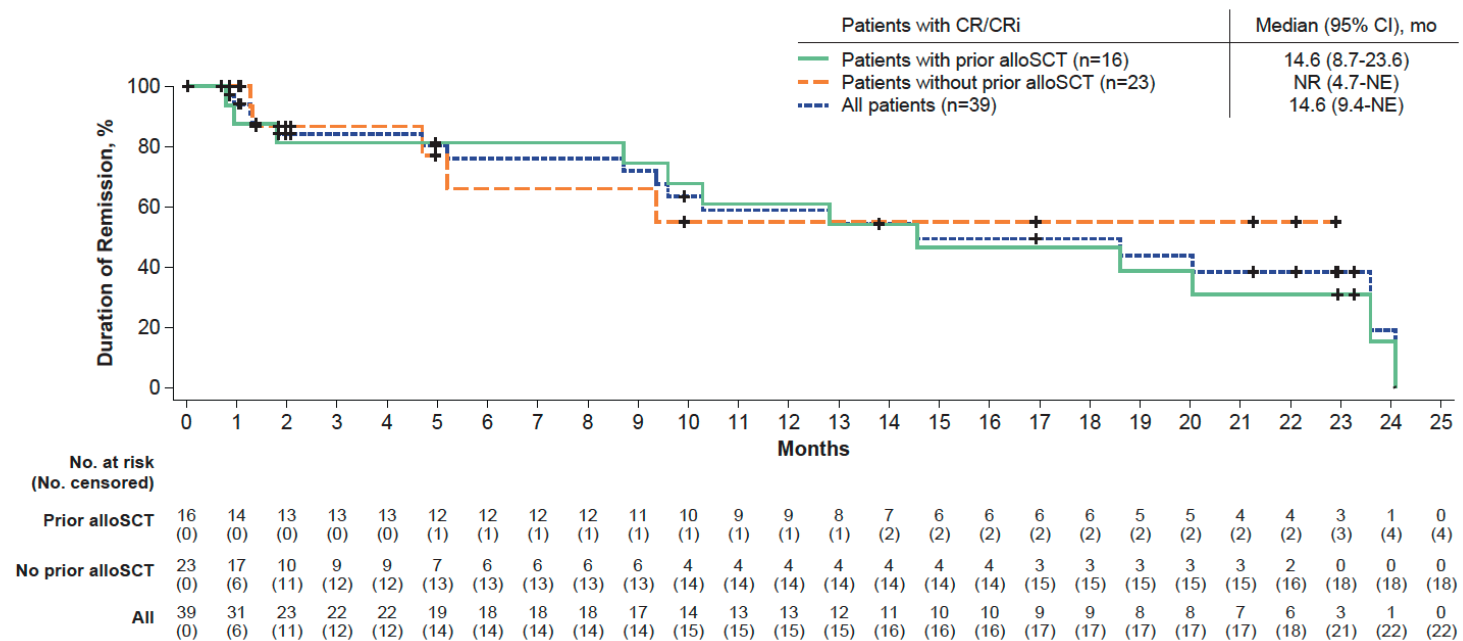
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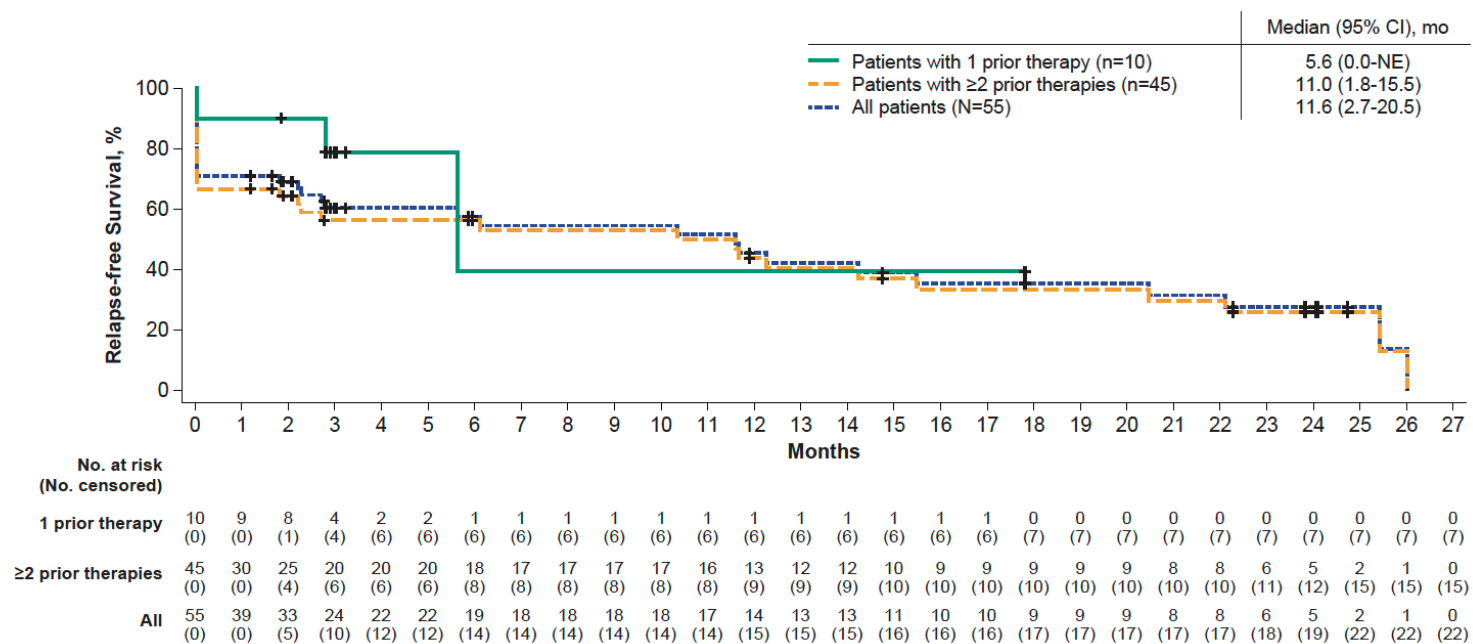


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Figure S4: Relapse-free survival (censored at subsequent alloSCT) in Phase 2 treated patients by (A) prior number of therapy lines, (B) prior blinatumomab exposure, (C) prior inotuzumab exposure, and (D) prior alloSCT exposure.

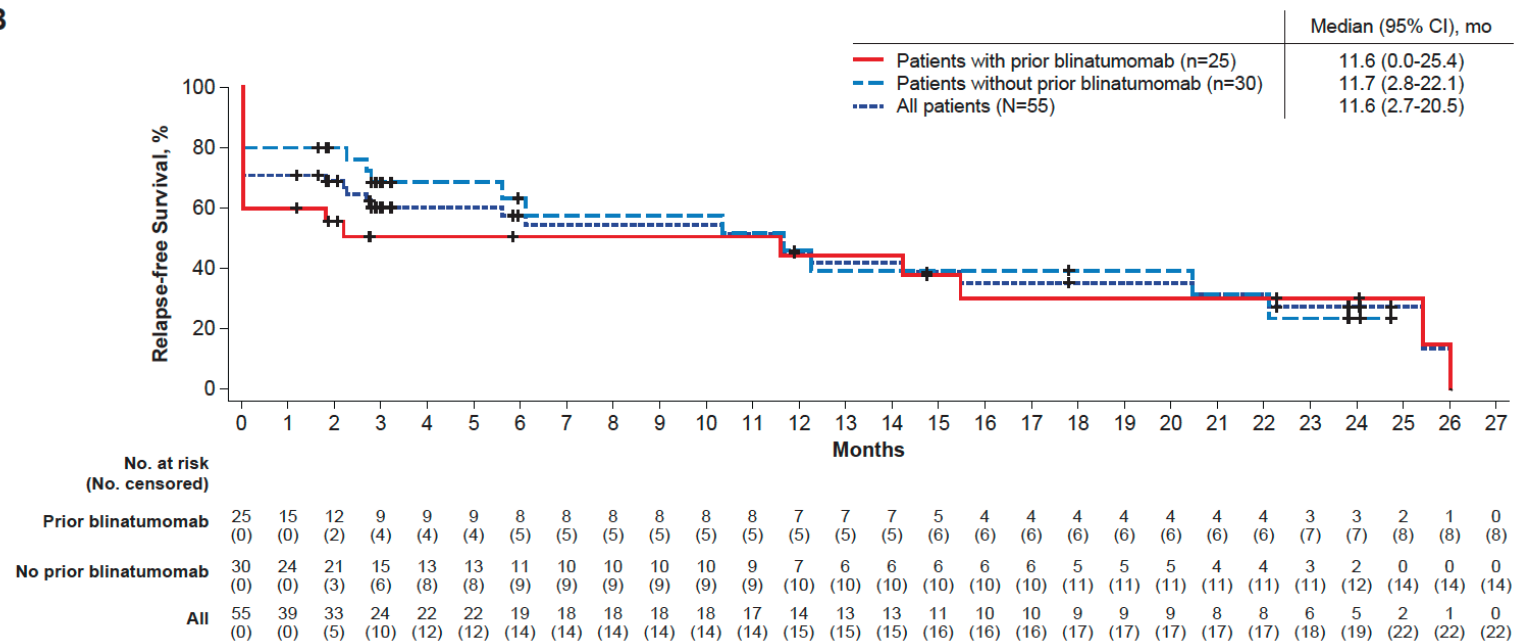
alloSCT, allogeneic stem cell transplantation; NE, not estimable.

A



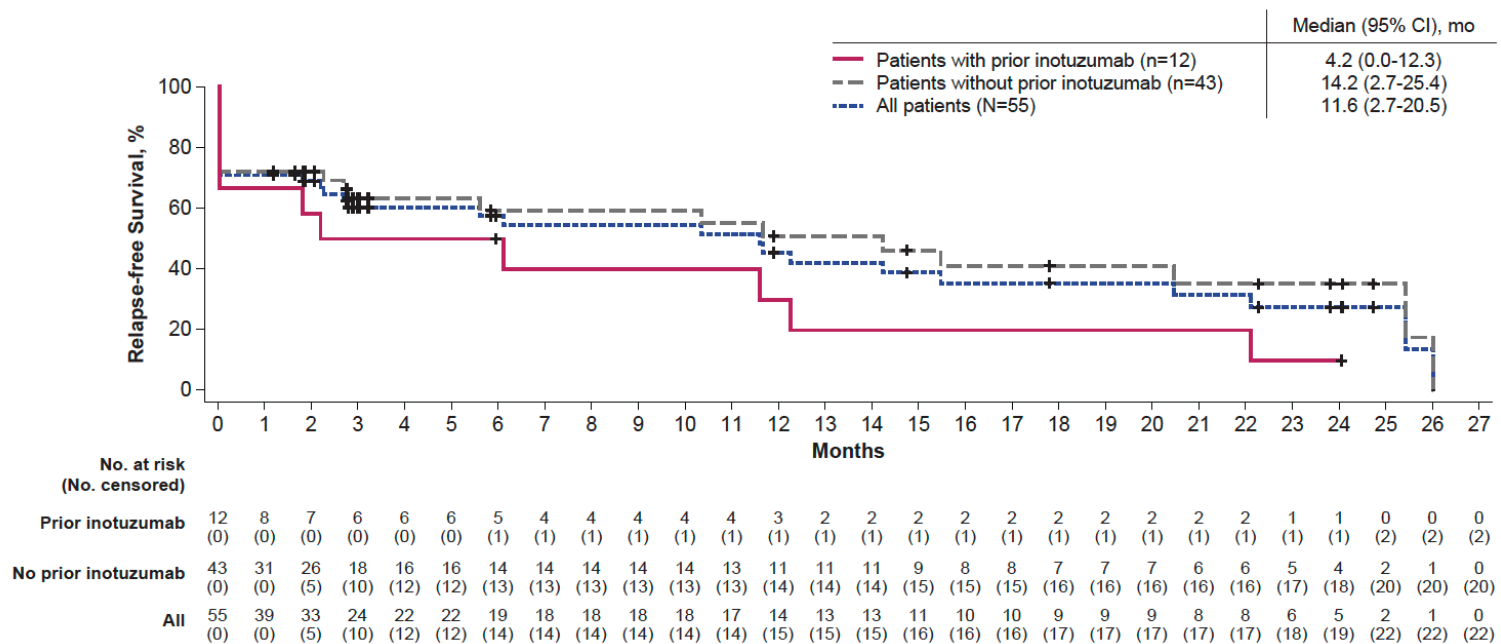
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B



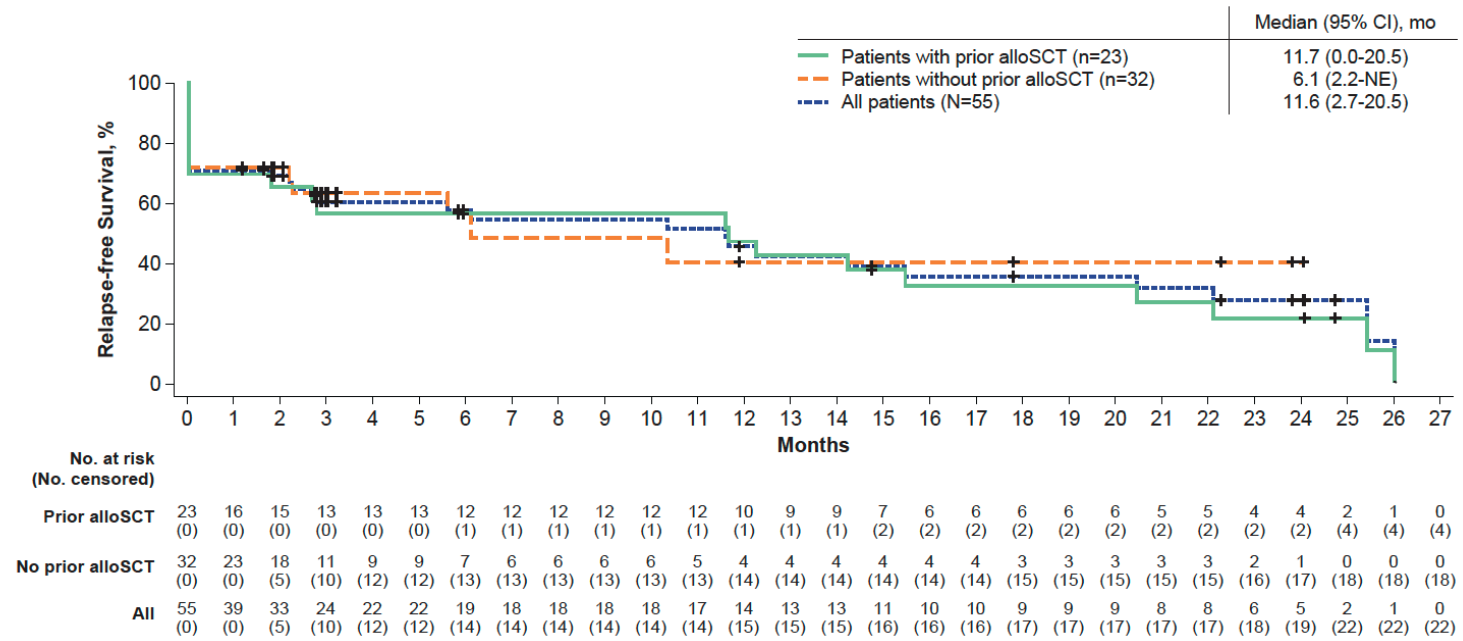
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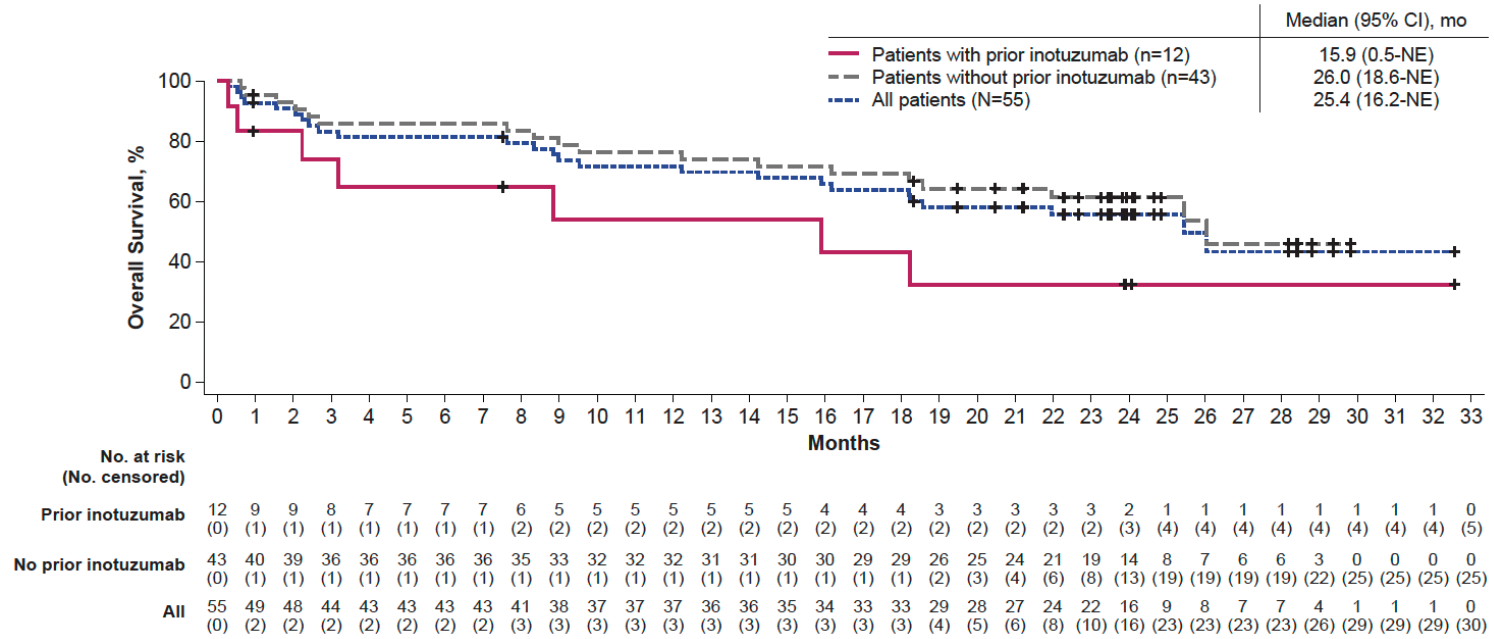
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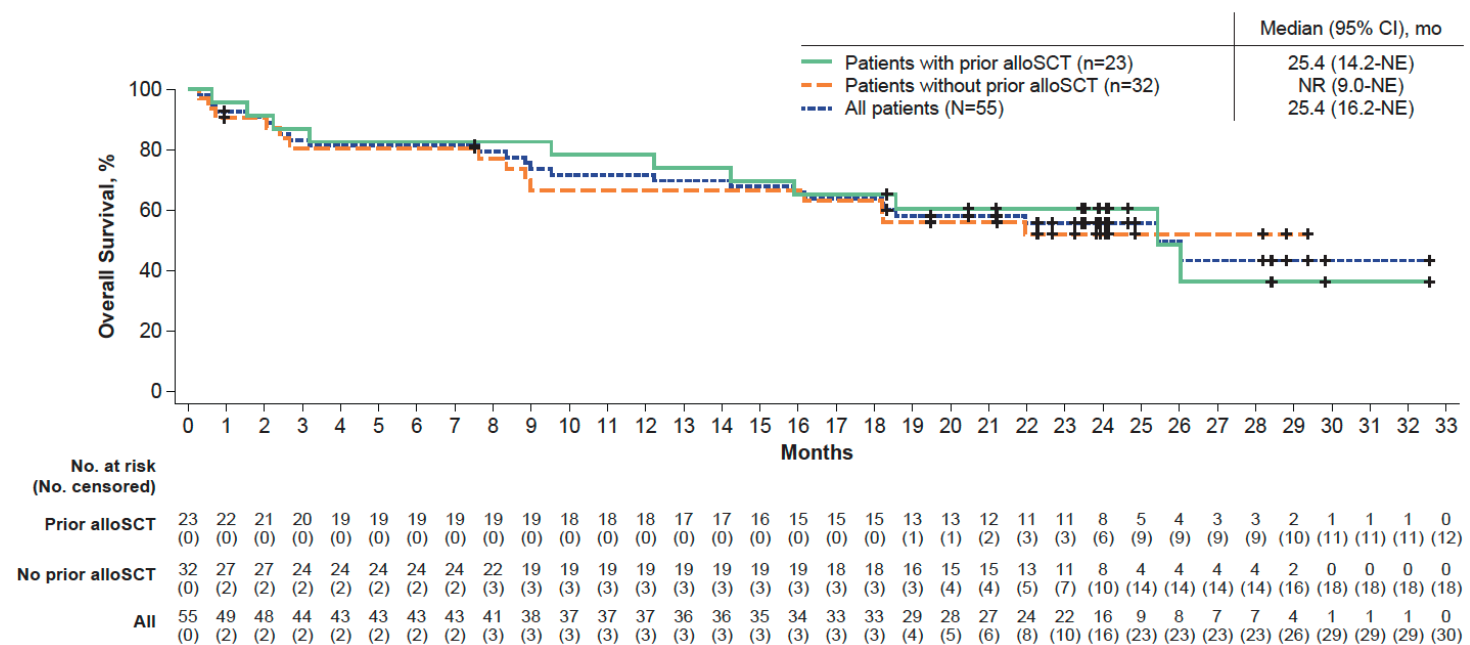
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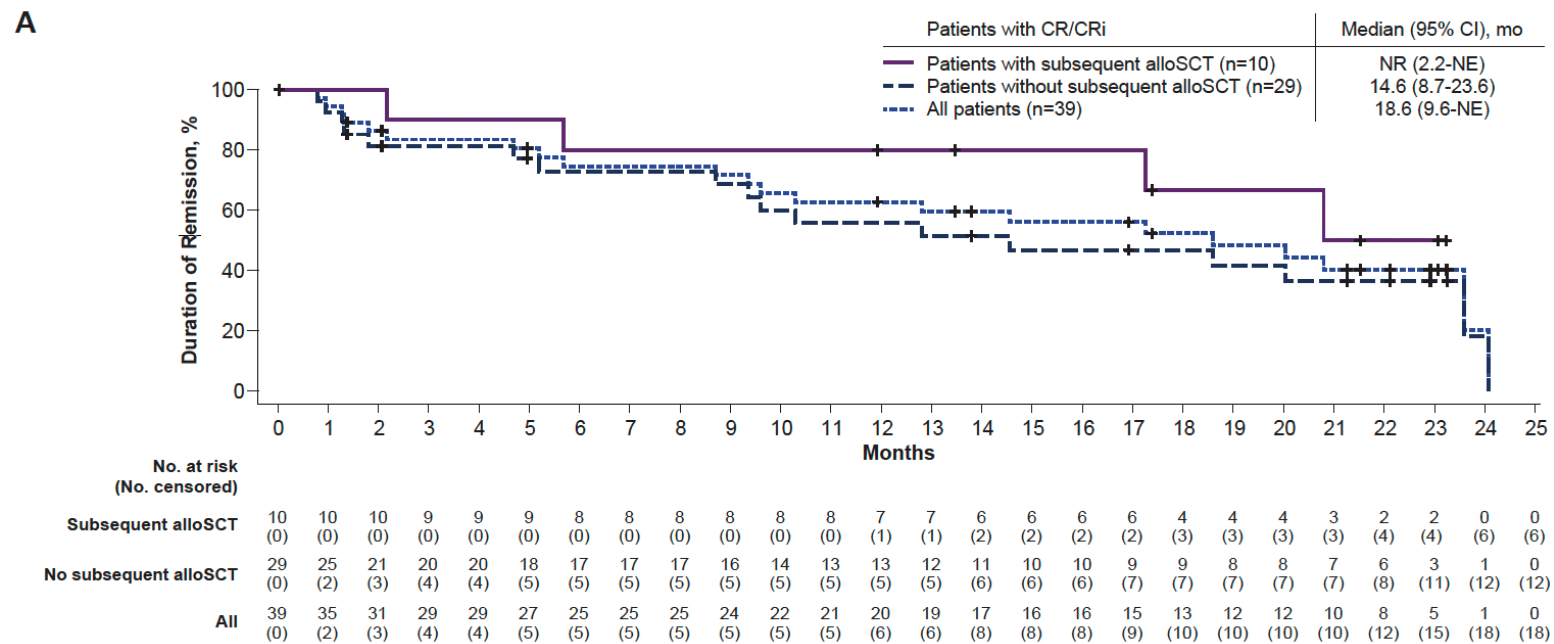
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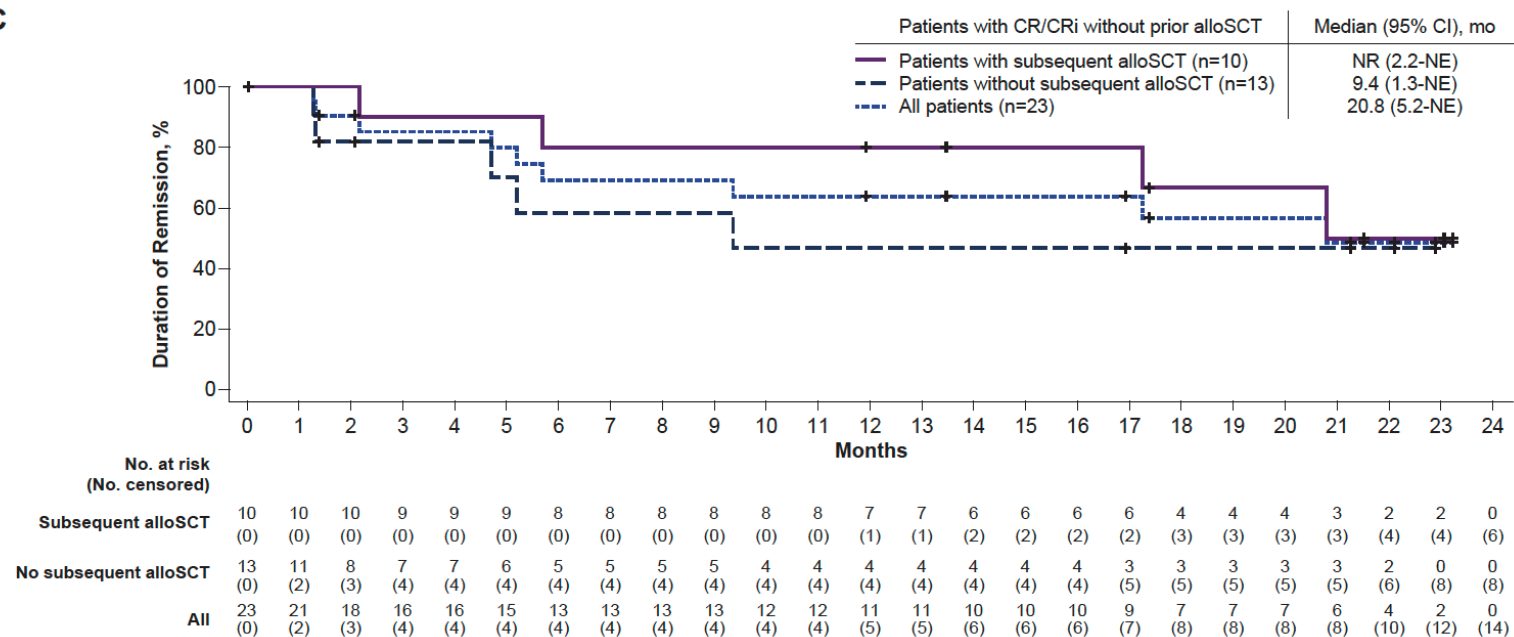
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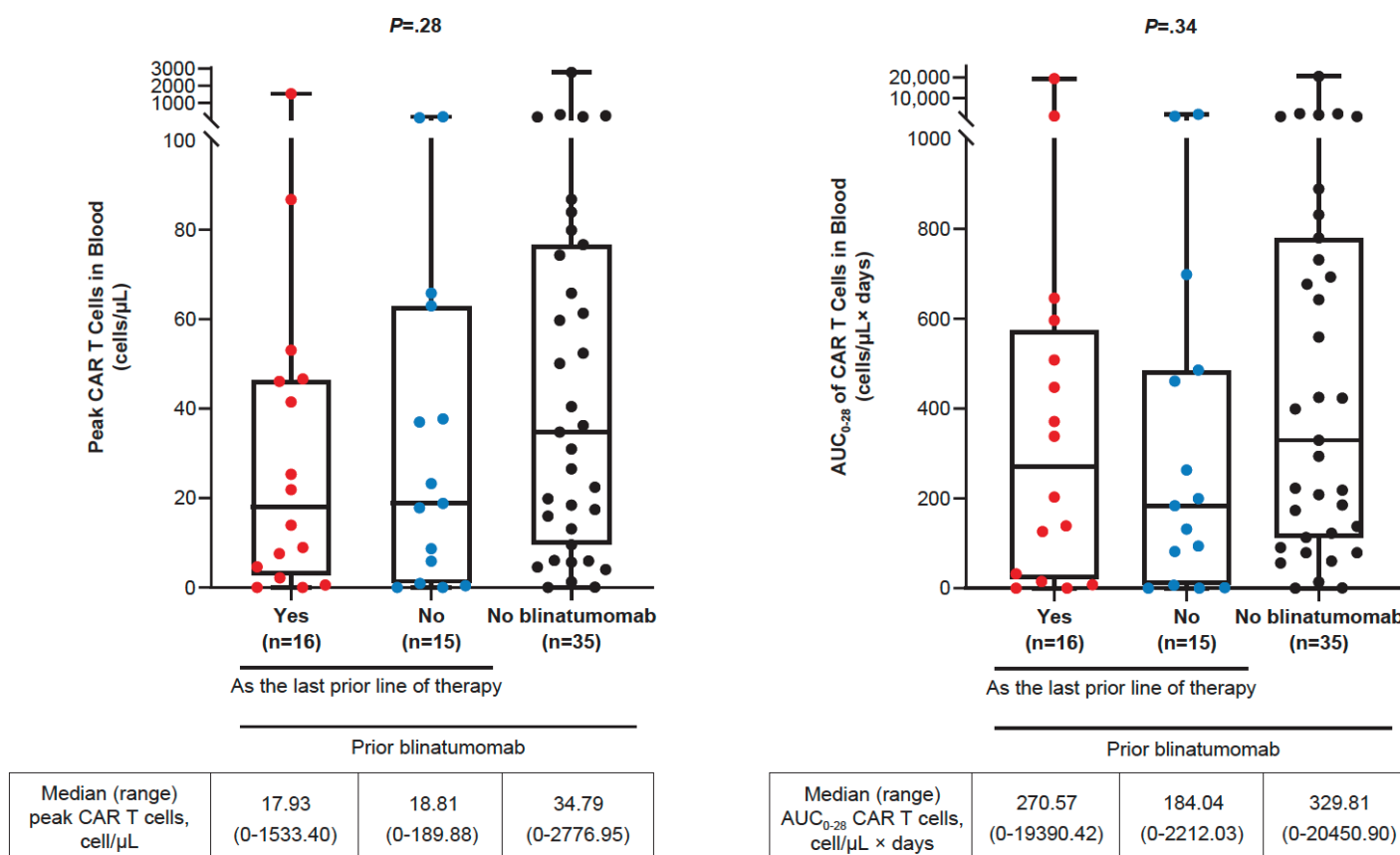
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Figure S7: Peak and AUC₀₋₂₈ CAR T-cell levels in pooled Phase 1 and 2 treated patients by blinatumomab as last prior therapy

AUC₀₋₂₈, area under the curve from time of dose to 28 days; CAR, chimeric antigen receptor.



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Supplementary References

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