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## Disease-specific outcomes after CAR T-cell therapy

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## **Abstract**

We compared outcomes of patients with B-cell malignancies treated in clinical trials with the same CD19 CAR T-cells across different indications, including B-cell acute lymphoblastic leukemia (B-ALL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and follicular lymphoma (FL). We found that, for a given CAR T-cell, efficacy and toxicity varied depending on the disease. Overall, we found a low rate of primary resistance in FL, MCL and B-ALL compared to DLBCL. Acute toxicities (CRS and ICANS) appeared to be significantly less severe in FL compared to more aggressive diseases such as B-ALL, DLBCL and MCL. These observations suggest that each B-cell malignancy harbors specific biology which may interact differently with CAR T-cell therapy. Thus, CAR T-cells may be tailored differently depending on the type of B-cell malignancy to optimize their efficacy and safety.

**Keywords:** (CAR) T-cells, B-cell, lymphoma

## **Introduction**

To date, four different CD19 chimeric antigen receptor (CAR) T-cells (tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel, brexucabtagene autoleucel) have been approved by the food and drug administration (FDA) for the treatment of four different B-cell malignancies: B-cell acute lymphoblastic leukemia (B-ALL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and follicular lymphoma (FL). Interestingly, each of these CAR T-cells has been evaluated in several diseases. Thus, for a given CAR T-cell, differences in outcome (efficacy and toxicity) for each indication are expected to be related to the disease rather than to the CAR T-cells themselves. In this review, we aimed to compare outcomes in studies which evaluated the same CAR T-cell across different B-cell malignancies. We found that the efficacy and toxicity varied according to the disease. These observations suggest that each B-cell malignancy harbors specific biology which may interact differently with CAR T-cell therapy.

## **Results and discussion**

### *Tisagenlecleucel in B-ALL vs DLBCL vs FL*

Tisagenlecleucel (tisa-cel) is a CD19 CAR T-cell with a 4-1BB costimulatory domain. Tisa-cel has been evaluated for the treatment of B-ALL in the ELIANA trial [1,2], DLBCL in the JULIET trial [3] and FL in the ELARA trial [4] (Table 1).

When comparing Tisa-cel efficacy across indications, the overall response (OR) and complete response (CR) rates appeared significantly higher in B-ALL (81% and 61%, respectively) and FL (86% and 66%, respectively) compared to DLBCL (52% and 40%, respectively), with less primary resistance (19% and 14% vs 48%, respectively) (Table 2A). Efficacy correlated with expansion and persistence of CAR T-cells in B-ALL but not in DLBCL nor FL. Although the efficacy in FL appeared similar to B-ALL and superior to DLBCL, the safety was significantly better in FL with fewer severe cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Conversely, toxicity was the most important in B-

ALL with 46% and 13% grade 3 or higher CRS and ICANS, respectively.

These differences may be related to the intrinsic biology of each of these malignancies.

However, other factors may also have contributed to the differences observed in efficacy and toxicity, including age (the ELARA trial was restricted to children and young adults), prior therapies (including prior allogeneic stem cell transplantation (SCT) in B-ALL vs prior autologous SCT in DLBCL and FL), bridging therapy (fewer bridges in ELARA), lymphodepleting regimens (more intensive in ELIANA), and CAR T-cell doses.

#### *Axicabtagene ciloleucel in DLBCL vs FL*

Axicabtagene ciloleucel (axi-cel) is a CD19 CAR T-cell with a CD28 costimulatory domain. Axi-cel has been evaluated for the treatment of large B-cell lymphomas, including DLBCL, primary mediastinal B-cell lymphoma and transformed FL (tFL) in the ZUMA-1 trial [5,6], and indolent B-cell lymphomas (iNHL), including FL and Marginal Zone Lymphoma (MZL) in the ZUMA-5 trial [7] (Table 1).

When comparing Axi-cel efficacy across indications, the OR and CR rates appeared significantly higher in iNHL (92% and 76%, respectively) compared to DLBCL (83% and 58%, respectively), with less primary resistance (8% vs 17%, respectively) (Table 2B).

Although the efficacy in iNHL appeared superior to DLBCL, the safety was significantly better in FL with fewer severe CRS (7% vs 13%, respectively) and ICANS (19% vs 28%, respectively), and less treatment-related mortality (TRM) (0.6% vs 2%, respectively).

Interestingly, patients' characteristics (age, PS, prior therapies) and treatments (bridging, conditioning regimen, CAR T-cell dose) were rather similar between the DLBCL and iNHL cohorts (Table 2B). Thus, differences in efficacy and toxicity are likely due to differences in the intrinsic biology of DLBCL vs iNHL.

#### *Brexucabtagene autoleucel in B-ALL vs MCL*

Brexucabtagene autoleucel (brexu-cel) is a CD19 CAR T-cell with a CD28 costimulatory domain. Brexu-cel has been evaluated for the treatment of B-ALL in the ZUMA-3 trial [9] and

MCL in the ZUMA-2 trial [10] (Table 1).

When comparing Brexu-cel efficacy across indications, the OR and CR rates appeared higher in MCL (93% and 67%, respectively) compared to B-ALL (71% and 56%, respectively), with less primary resistance (7% vs 29%, respectively) (Table 2C). Toxicity (CRS and ICANS) appeared rather comparable between the B-ALL and MCL cohorts.

Several factors may have contributed to the differences in efficacy between B-ALL and MCL including the intrinsic biology of the disease, age (younger patients in ZUMA-3), prior therapies (prior allo-SCT in B-ALL vs prior auto-SCT in MCL), bridging therapy (more frequent in ZUMA-3), lymphodepleting regimens, and CAR T-cell doses (twice as many CAR T-cells in ZUMA-3 vs ZUMA-2).

#### *Lisocabtagene maraleucel in DLBCL vs MCL*

Lisocabtagene maraleucel (liso-cel) is a CD19 CAR T-cell with a 4-1BB costimulatory domain. Liso-cel has been evaluated for the treatment of DLBCL and MCL in the TRANSCEND NHL001 trial [11], which included a specific MCL cohort [12] (Table 1).

When comparing Liso-cel efficacy across indications, the OR and CR rates appeared higher in MCL (84% and 66%, respectively) compared to DLBCL (73% and 53%, respectively), with less primary resistance (16% vs 27%, respectively) (Table 2D). Toxicity (CRS and ICANS) appeared comparable between the DLBCL and MCL cohorts.

Interestingly, patients' characteristics (age, prior therapies) and treatments (bridging therapy, conditioning regimen) were rather similar between the DLBCL and MCL cohorts (Table 2D). Thus, differences in efficacy are likely due to differences in the intrinsic biology of DLBCL vs MCL.

#### **Conclusion**

Intrinsic differences exist between CD19 CAR T-cells which result from different manufacturing processes, specific constructs, and product composition. To get rid of this

variable, we aimed to compare outcomes of patients treated with the same CD19 CAR T-cells across different indications. These comparisons were then integrated in a semi-quantitative way to identify trends in efficacy and toxicity between diseases, independently of CAR T-cells (Table 3).

Overall, we found a low rate of primary resistance in FL, MCL and B-ALL compared to DLBCL. CAR T-cells' efficacy correlated with CAR T-cells expansion in B-ALL. At relapse, loss of CD19 target Ag was more frequent in B-ALL and DLBCL compared to MCL and FL. Acute toxicities (CRS and ICANS) appeared to be significantly less severe in FL compared to more aggressive diseases such as B-ALL, DLBCL and MCL.

In some cases, other factors may also have contributed to the differences observed in efficacy and toxicity, which may be related to differences in patients (age, performance status, prior therapies), tumor burden, and treatment procedures (bridging therapy, lymphodepleting regimens, CAR T-cell doses, and toxicity management). These differences have been highlighted for each study except for tumor burden which was not available (Table 2).

Despite these limitations, our observations suggest that each B-cell malignancy harbors specific biology which may interact differently with CAR T-cell therapy. Thus, CAR T-cells may be tailored differently depending on the type of B-cell malignancy to optimize their efficacy and safety.

These results should be confirmed after adjusting for potentially confounding factors in larger cohorts of patients to further define differences in outcomes specifically related to the disease after CAR T-cell therapy.

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Tables

**Table 1. Studies comparing the same CAR T-cells across different histologies**

<b>Comparison</b>	<b>CAR-T</b>	<b>B-ALL</b>	<b>DLBCL</b>	<b>MCL</b>	<b>iNHL</b>
<b>1</b>	<b>Tisa-cel</b>	ELIANA [1,2]	JULIET [3]	-	ELARA [4]
<b>2</b>	<b>Axi-cel</b>	-	ZUMA-1[5,6]		ZUMA-5 [7]
<b>3</b>	<b>Brexu-cel</b>	ZUMA-3 [9]	-	ZUMA-2 [10]	-
<b>4</b>	<b>Liso-cel</b>	-	TRANSCEND NHL 001 [11]	TRANSCEND NHL-001[12]	-

*Tisa-cel, Tisagenlecleucel ; Axi-cel, Axicabtagene ciloleucel ; Brexu-cel, Brexucabtagene autoleucel ; Liso-cel, Lisocabtagene maraleucel*



**Table 2. Characteristics and outcomes between histologies treated with the same CAR T- cells**

NA, not available; Flu, Fludarabine, Cy, Cyclophosphamide, Benda, Bendamustine; CTAE v4.03 National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03; ICU, intensive care unit; TRM, treatment related mortality.

Table 2A. Tisa-ce l		B-ALL	DLBCL	FL
<b>Study</b>	CAR T-cell	Tisa-cel	Tisa-cel	Tisa-cel
	Costimulatory domain	4-1BB	4-1BB	4-1BB
	Study name	ELIANA	JULIET	ELARA
	Reference	[1,2]	[3]	[4]
	Median FU (months)	13.1	14	10.6
<b>Patients</b>	Infused (N)	75	111	97
	Median age (min-max)	11 (3-23)	56 (22-76)	57 (29-73)
	PS	0-1	0-1 0 (55%); 1 (45%)	0-1
	Prior lines (median, min-max)	3 (1-8)	3 (1-6)	4 (2-13)
	Prior auto-SCT (%)	0	49	36
	Prior allo-SCT (%)	61	0	0
<b>Treatment</b>	Manufacturing success (%)	92	93	100
	Median time from enrollment to infusion (days)	45	54	45
	Bridging therapy (%)	87	92	44
	Type of lymphodepleting chemotherapy	Flu/Cy	Flu/Cy or Benda	Flu/Cy or Benda
	Doses of lymphodepleting chemotherapy	Flu 30 mg/m <sup>2</sup> /d (4d) + Cy 500 mg/m <sup>2</sup> /d (2d)	Flu 25 mg/m <sup>2</sup> /d + Cy 250 mg/m <sup>2</sup> /d (3d) ; Benda 90 mg/m <sup>2</sup> /d (2d)	Flu 25 mg/m <sup>2</sup> /d + Cy 250 mg/m <sup>2</sup> /d (3d) ; Benda 90 mg/m <sup>2</sup> /d (2d)
	Target dose of CAR T-cells	NA	NA	NA
	Actual dose of infused CAR T-cells, median (range)	(0.76 – 20.6) x10 <sup>6</sup> cells/kg	3.0 (0.1 – 6.0) x10 <sup>8</sup> cells	2.06 (0.6 – 6) x10 <sup>8</sup> cells
	Consolidation with allo-SCT (%)	11	0	NA
<b>Efficacy</b>	Best OR (%)	81	52	86
	Best CR (%)	61	40	66
	Primary resistance (%)	19	48	14
	Secondary resistance (%)	29	22	36
	CD19-negative relapse (% of relapses)	68	NA	NA
	Median DOR (months)	Not reached	Not reached	Not reached
	DOR (%)	59% at 12 months	65% at 12 months	79% at 6 months
	Median PFS (months)	12	3	Not reached
	PFS (%)	50% at 12 months	35% at 12 months	76% at 6 months
	Median OS (months)	19.1	12	Not reached

	OS (%)	76% at 12 months	49% at 12 months	97% at 12 months
	Correlation with expansion (Y/N)	Y	N	N
	Correlation with persistence (Y/N)	Y	N	N
<b>Toxicity</b>	CRS grading	Penn scale	Penn scale	Lee scale
	CRS grade 1-2 (%)	31	36	48.5
	CRS grade 3-4 (%)	46	22	0
	ICANS grading	NA	CTCAE v4.03	CTCAE v4.03
	ICANS grade 1-2 (%)	27	9	8.3
	ICANS grade 3-4 (%)	13	12	1
	Tocilizumab (%)	48	14	15
	Corticosteroids (%)	NA	10	6.4
	ICU (%)	47	24	8.5
	TRM (%)	4	0	0

<b>Table 2B. Axi-cel</b>		<b>DLBCL</b>	<b>iNHL ( FL/MZL)</b>
<b>Study</b>	CAR T-cell	Axi-cel	Axi-cel
	Costimulatory domain	CD28	CD28
	Study name	ZUMA-1	ZUMA-5
	Reference	[5,6]	[7]
	Median FU (months)	27.1	17.5
<b>Patients</b>	Infused (N)	101	146 124 FL; 22 MZL
	Median age (min-max)	58 (23-76)	61 (34-79)
	PS	0-1 0 (42%); 1 (58%)	0-1
	Prior lines (median, min-max)	3 (2-4)	3 (1-10)
	Prior auto-SCT (%)	21	23
	Prior allo-SCT (%)	0	0
<b>Treatment</b>	Manufacturing success (%)	99	100
	Median time from apheresis to infusion (days)	17	17
	Bridging therapy (%)	0	0
	Type of lymphodepleting chemotherapy	Flu/Cy	Flu /Cy
	Doses of Flu/Cy	Flu 30 mg/m <sup>2</sup> /d + Cy 500 mg/m <sup>2</sup> /d (3d)	Flu 30 mg/m <sup>2</sup> /d + Cy 500 mg/m <sup>2</sup> /d (3d)
	Target dose of CAR T-cells	2 x10 <sup>6</sup> cells/kg	2 x10 <sup>6</sup> cells/kg
	Dose of infused CAR-T cells	2 x 10 <sup>6</sup> cells/kg	2 x10 <sup>6</sup> cells/kg
	Consolidation with allo-SCT (%)	2	NA
<b>Efficacy</b>	Best OR (%)	83	92 FL (94); MZL (85)
	Best CR (%)	58	76 FL (80), MZL (60)
	Primary refractory (%)	17	8
	Secondary resistance (%)	43	30
	CD19-negative relapse (%)	27	0 ( /13)
	Median DOR (months)	11.1	Not reached
	DOR (%)	50% at 12 months	71.7% at 12 months
	Median PFS (months)	5.9	Not reached
	PFS (%)	42% at 12 months	73.7% at 12 months
	Median OS (months)	Not reached	Not reached
	OS (%)	60% at 12 months	92.9% at 12 months
	Correlation with expansion (Y/N)	Y	Y
Correlation with persistence (Y/N)	N	NA	
<b>Toxicity</b>	CRS grading	Lee scale	Lee scale
	CRS grade 1-2 (%)	80	75
	CRS grade 3-4 (%)	13	7 FL (6); MZL (9)
	ICANS grading	CTCAE v4.03	CTCAE v4.03
	ICANS grade 1-2 (%)	37	41
	ICANS grade 3-4 (%)	28	19 FL (15), MZL (41)
	Tocilizumab (%)	43	55
	Corticosteroids (%)	27	53
	ICU (%)	NA	NA
	TRM (%)	2	0.6

<b>Table 2C. Brexu-cel</b>		<b>B-ALL</b>	<b>MCL</b>
<b>Study</b>	CAR T-cell	Brexu-cel	Brexu-cel
	Costimulatory domain	CD28	CD28
	Study name	ZUMA-3	-2
	Reference	[9]	[10]
	Median FU (months)	16.4	12.3
<b>Patients</b>	Infused (N)	55	68
	Median age (min-max)	40 (28-52)	65 (38-79)
	PS	0-1 0 (29%); 1 (71%)	0-1
	Prior lines (median, min-max)	2 (2-5)	3 (1-5)
	Prior auto-SCT (%)	2	43
	Prior allo-SCT (%)	42	0
<b>Treatment</b>	Manufacturing success (%)	92	96
	Median time from apheresis to infusion (days)	13	16
	Bridging therapy (%)	93	37
	Type of lymphodepleting chemotherapy	Flu/Cy	Flu/Cy
	Doses of Flu/Cy	Flu 25 mg/m <sup>2</sup> /d (3d) + Cy 900 mg/m <sup>2</sup> /d (1d)	Flu 30 mg/m <sup>2</sup> /d + Cy 500 mg/m <sup>2</sup> /d (3d)
	Target dose of CAR T-cells	1 x10 <sup>6</sup> cells/kg	2 x10 <sup>6</sup> cells/kg
	Dose of infused CAR T-cells	1 x 10 <sup>6</sup> cells/kg	2 x10 <sup>6</sup> cells/kg
	Consolidation with allo-SCT (%)	18	1
<b>Efficacy</b>	Best OR (%)	71	93
	Best CR (%)	56	67
	Primary resistance (%)	29	7
	Secondary resistance (%)	22	35
	CD19-negative relapse (%)	33	7 (1/14)
	Median DOR (months)	12.8	Not reached
	DOR (%)	75% at 6 months	57% ; 12 months
	Median PFS (months)	11.6	Not reached
	PFS (%)	58% at 6 months	61% ; 12 months
	Median OS (months)	18.2	Not reached
	OS (%)	71% at 12 months	83% ; 12 months
	Correlation with expansion (Y/N)	Y	Y
	Correlation with persistence (Y/N)	N	N
<b>Toxicity</b>	CRS grading	Lee scale	Lee scale
	CRS grade 1-2 (%)	65	76
	CRS grade 3-4 (%)	24	15
	ICANS grading	CTCAE v4.03	CTCAE v4.03
	ICANS grade 1-2 (%)	35	32
	ICANS grade 3-4 (%)	24	31
	Tocilizumab (%)	80	70
	Corticosteroids (%)	75	58
	ICU (%)	NA	NA
	TRM (%)	3.6	3

<b>Table 2D. Liso-cel</b>		<b>DLBCL</b>	<b>MCL</b>
<b>Study</b>	CAR T-cell	Liso-cel	Liso-cel
	Costimulation domain	4-1BB	4-1BB
	Study name	TRANSCEND NHL 001	TRANSCEND NHL 001
	Reference	[11]	[12]
	Median FU (months)	18.8	3.1
<b>Patients</b>	Infused (N)	269	32
	Median age (min-max)	6: (18-86)	67 (36-80)
	PS	0-2 0 (41%); 1 (58%); 2 (1%)	0-1
	Prior lines (median, min-max)	3 (1-6)	3 (1-7)
	Prior auto-SCT (%)	33	31
	Prior allo-SCT (%)	3	9
<b>Treatment</b>	Manufacturing success (%)	99.4	NA
	Median time from apheresis to infusion (days)	37	NA
	Bridging therapy (%)	59	53
	Type of lymphodepleting chemotherapy	Flu/Cy	Flu/Cy
	Doses of Flu/Cy	Flu 30 mg/m <sup>2</sup> /d + Cy 300 mg/m <sup>2</sup> /d (3d)	Flu 30 mg/m <sup>2</sup> /d + Cy 300 mg/m <sup>2</sup> /d (3d)
	Target dose of CAR T-cells	100 x10 <sup>6</sup> cells 50 x10 <sup>6</sup> CD8; 50 x10 <sup>6</sup> CD4	100 x10 <sup>6</sup> cells 50 x10 <sup>6</sup> CD8; 50 x10 <sup>6</sup> CD4
	Dose of infused CAR-T cells, median (range)	91 (44-156) x10 <sup>6</sup> cells	100 (50-100) x10 <sup>6</sup> cells
	Consolidation with allo-SCT (%)	NA	NA
<b>Efficacy</b>	Best OR (%)	73	84
	Best CR (%)	53	66
	Primary resistance (%)	27	16
	Secondary resistance (%)	35	19
	CD19-negative relapse (%)	NA	NA
	Median DOR (months)	Not reached	Not reached
	DOR (%)	55 at 12 months	NA
	Median PFS (months)	6.8	NA
	PFS (%)	44 at 12 months	NA
	Median OS (months)	21.1	NA
	OS (%)	58 at 12 months	NA
	Correlation with expansion (Y/N)	Y	NA
Correlation with persistence (Y/N)	N	NA	
<b>Toxicity</b>	CRS grading	Lee scale	Lee scale
	CRS grade 1-2 (%)	40	47
	CRS grade 3-4 (%)	2	3
	ICANS grading	CTCAE v4.03	CTCAE v4.03
	ICANS grade 1-2 (%)	20	21.5
	ICANS grade 3-4 (%)	10	12.5
	Tocilizumab (%)	18	18.5
	Corticosteroids (%)	10	25
	ICU (%)	7	9
TRM (%)	3	6	

**Table 3. Summary of outcomes across histologies after CD19 CAR T-cell therapy**

		<b>B-ALL</b>	<b>DLBCL</b>	<b>MCL</b>	<b>FL</b>
<b>Efficacy</b>	OR (%)	++	+	+++	+++
	CR (%)	++	+	+++	+++
	Primary resistance (%)	++	+++	+	+
	CD19-negative relapse (%)	+++	++	+	-
	PFS	++	+	++	+++
	Correlation with expansion	++	+	++	+
	Correlation with persistence	+	-	NA	NA
<b>Toxicity</b>	Severe CRS (%)	+++	++	++	+
	Severe ICANS (%)	+++	+++	+++	+

-, +, ++, +++ denotes a semi-quantitative ascending scale. NA, not available.

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