LymphomaHub

DLBCL

EBMT Debate Session | How to treat R/R DLBCL in 2019? | Part 3 – CAR-T

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A Keynote Debate Session on how to treat patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) took place on Tuesday 26 March 2019, during the 45th Annual Meeting of the European Society of Blood and Marrow Transplantation (EBMT), Frankfurt, DE.

During this Lymphoma Working Party (LWP) session (LWP-7), arguments in favour of the use of autologous stem cell transplantation (ASCT), allogeneic stem cell transplantation (allo-SCT) or chimeric antigen receptor T cell (CAR-T) therapy for the treatment of R/R DLBCL, were presented by the following experts, respectively:

- Prof Christian Gisselbrecht from Hospital Saint Louis, Paris Diderot VII University, Paris, FR
  - Presented evidence in favour of ASCT
- Dr Stephen Robinson from University Hospitals Bristol NHS Foundation Trust, Bristol, UK
  - Presented evidence in favour of allo-SCT
- Prof Marie José Kersten from the University of Amsterdam, Amsterdam, NL
  - Presented evidence in favour or CAR-T therapy

All the experts clarified that with the lack of prospective trials comparing each of these three regimens with one another, it is not possible to accurately compare these treatments. Nevertheless, they sought to present results from phase II and III trials that have provided favourable evidence for each treatment strategy.

CAR-T[3]

In the third part of the debate, Prof Kersten debated in favour of CAR-T therapy for R/R DLBCL. She started her presentation by explaining that based on various trials and especially the SCHOLAR-1 there is no cure for approximately 30% of R/R DLBCL patients, creating an unmet medical need for this population. She clarified that at this stage CAR-T therapy is targeted to the DLBCL population that is transplantation-ineligible, does not respond to salvage chemotherapy or relapses after ASCT and/or allo-SCT.

She continued by presenting the three main multicenter CD19 CAR-T trials in aggressive NHL:

- ZUMA-1 (Kite/Gilead)
- JULIET (Novartis)
- TRANSCEND (Juno/Celgene)

The study design, baseline characteristics and the response rates from each trial were highlighted (see Tables 1 and 2 below which have been adapted from the presentation).

Study/Sponsor	**ZUMA-1 (Kite/Gilead)[4]**	**JULIET (Novartis)[5–7]**	**TRANSCEND (Juno/Celgene)[8,9]**
CAR-T dose	2 x 10^6/kg	0.1–6 x 10^8 (median 3 x 10^8)	Dose level (DL)1: 5 x 10^7 DL2: 1 x 10^8
Conditioning	Cy/Flu	73% pts Cy/Flu; 20% pts bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL, PMBCL, TFL	DLBCL, TFL	DLBCL, TFL, FL Grade 3B, tMZL, tCLL, PMBCL
R/R	Refractory	R/R	R/R
Relapse after ASCT	21%	47%	42%
Bridging therapy	Not allowed	Allowed (92%)	Allowed
Manufacturing success	99%	97%	98%
Treated/Enrolled	101/111 (91%)	111/165 (67%)	108/140 (77%)

Table 1. Adapted from Professor Kersten's presentation. Study design & key baseline characteristics of the three main multicenter CAR-T trials in aggressive NHL. Cy, cyclophosphamide; FL, follicular lymphoma; Flu, fludarabine; PMBCL, primary mediastinal large B-cell lymphoma; TFL, transformed follicular lymphoma. The data shown in this table are Prof Kersten's interpretation of the CAR-T trials.

Study/Sponsor	Product	N	Best ORR	Best CR rate	Follow-up (months)
ZUMA 1[10] **Kite/Gilead**	CD19/ CD3ζ/ CD28 (axi-cel)	101	83%	58%	27
JULIET[5] **Novartis**	CD19/ CD3ζ/ 4-1BB (kymriah)	93	52%	40%	14
TRANSCEND[9] **Juno/Celgene**	CD19/ CD3ζ/ 4-1BB (JCAR017)	65	80%	55%	6

Table 2. Adapted from Professor Kersten's presentation. Available CAR-T product characteristics and response rates. The data shown in this table are Prof Kersten's interpretation of the CAR-T trials.

Prof Kersten presented the current patient outcomes in ZUMA-1 and JULIET CAR-T trials. In the ZUMA-1, the median OS was not reached at 27 months, 72% of patients were progression-free at 24 months if they had achieved complete response (CR) at 3 months and 75% if the patients had achieved partial response (PR) at 3 months. The median duration of response (DoR) for complete responders was not reached.[10]

According to Prof Kersten, in the JULIET trial, the 12-month relapse-free survival was 65%, 54% of patients who achieved a PR converted to CR, and CAR-T cells were detectable for up to two years in responding patients.[5] In the ASH update of the JULIET trial, with a median follow-up of 19 months the median DoR was not reached, no relapses were observed beyond 11 months after CAR-T infusion and DoR was similar by age group and R/R status.[6]

She continued by mentioning the 'price tag' that comes with CAR-T therapy, the toxicity in the form of cytokine release syndrome (CRS) and neurotoxicity (NT). Grade 3–4 CRS was observed in 22% of patients in the JULIET trial and 11% in the ZUMA-1, while Grade 3–4 NT in 12% of patients in JULIET and in 32% of patients in ZUMA-1.[5,10] Further to the CAR-T-associated toxicity, Prof Kersten mentioned the 'financial toxicity' that also comes along with CAR-T therapy and that presents a key issue when trying to make CAR-T accessible to the real world. For that, Prof Kersten briefly presented the efficacy results of axi-cel in the real world *versus* the ZUMA-1 trial. Interestingly, both the best ORR, best CR rates and the toxicity were comparable to the ones observed in ZUMA-1, providing further evidence on the reality of the beneficial effect of CAR-T in R/R DLBCL.

Prof Kersten continued by presenting the benefits of CAR-T compared to allo-SCT, as shown below, and stated that NT presents the only disadvantage of CAR-T, when compared to allo-SCT:

	CAR-T cells	Allo-SCT

Need for a donor	No	Yes
Need to be in remission	No	Yes
Non-relapse mortality	< 5%	20–30%
Neurological toxicity	Yes	No
Long-term complications	Hypogammaglobulinemia	Graft-*versus*-host disease, opp. infections
Secondary malignancies	No	Yes

As far as the comparison between CAR-T and ASCT is concerned, Prof Kersten mentioned that the ongoing ZUMA-7 prospective comparative trial planned for axi-cel, as well as the respective ones for other CAR-T products against standard of care (SOC), will provide undisputable evidence over the potential superiority of CAR-T or ASCT. Prof Kersten agreed with the other two experts that there are still many unanswered questions with CAR-T therapy that should be answered in the long run and finished off by hoping that in the future the financial and logistical difficulties associated with CAR-T therapy will be minimised making CAR-T an approachable treatment plan for the many.

Summary of all three sessions

For the summaries of the ASCT and allo-SCT debate sessions follow these links respectively: https://lymphomahub.com/medical-information/ebmt-debate-session-how-to-treat-r-r-dlbcl-in-2019-part-1-asct and https://lymphomahub.com/medical-information/ebmt-debate-session-how-to-treat-r-r-dlbcl-in-2019-part-2-allo-sct

All three experts agreed that more long-term data are needed regarding CAR-T cells and large prospective comparative trials like ZUMA-7 to validate the potential superiority of ASCT, allo-SCT or CAR-T in R/R DLBCL. A summary of some of the above-mentioned advantages and drawbacks of ASCT, allo-SCT and CAR-T are shown in Table 1 below.

	SOC for R/R DLBCL	Can include non-responders to chemotherapy?	Long-term follow-up	Toxicity	Good prognostic markers	Risk of late MDS/AML	Graft contamination with malignant cells
ASCT	Yes	No	Yes (> 5 years)	Neutropenia Infections	Yes (low aaIPI and negative FDG-PET pre- and post-ASCT)	5–10% at 10 years follow-up	Yes
Allo-SCT	No	No	Yes	Acute and chronic GvHD	Yes	None	None
CAR-T	No	Yes	No (2 years currently)	CRS Neurotoxicity	No good prognostic group yet	N/A	N/A

Table 1. Advantages and disadvantages of allo-SCT, ASCT and CAR-T for R/R DLBCL[1,2,3]

References

1. Gisselbrecht C. LWP Keynote Debate: How should we treat R/R DLBCL in 2019? LWP-8 Session (ASCT): 45th Annual EBMT Meeting 2019, Frankfurt, DE

2. Robinson S. LWP Keynote Debate: How should we treat R/R DLBCL in 2019? LWP-9 Session (allo-SCT): 45th Annual EBMT Meeting 2019, Frankfurt, DE

3. Kersten M.J. LWP Keynote Debate: How should we treat R/R DLBCL in 2019? LWP-10 Session (CAR-T): 45th Annual EBMT Meeting 2019, Frankfurt, DE

4. Neelapu, S. S. *et al*. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N. Engl. J. Med.* 377, 2531–2544 (2017)

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7. Narasimhan, V. Novartis CTL019-JULIET data on DLBCL; Investor call Global Drug Development. (2017)

8. Abramson, J. S. *et al.* High Durable CR Rates in Relapsed/Refractory (R/R) Aggressive B-NHL Treated with the CD19-Directed CAR T Cell Product JCAR017 (TRANSCEND NHL 001): Defined Composition Allows for Dose-Finding and Definition of Pivotal Cohort. *Blood* 130, (2017)

9. Abramson, J. S. *et al*. Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. *J. Clin. Oncol*. 36, 7505–7505 (2018)

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