mRNA Expression in DLBCL Patients who are CD20 Dim With an Eye Towards More Thoughtful Design of R/R Trials, Possibly Incorporating BCMA Bite Therapy

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Clinical Lymphoma, Myeloma and Leukemia, Vol. 000, No.xxx, 1–3 © 2025 Published by Elsevier Inc.
Keywords: CD19 dim, Diffuse large b-cell lymphoma, Relapsed/Refractory, Bispecific T-cell engagers, Third line

Introduction

Diffuse Large B-cell Lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma with an estimated 80,620 new case in the US in 2024.[1] While most patients are cured with the current standard of care treatment, a combination of the drugs rituximab, Cytoxan, doxorubicin, vincristine and prednisone (R-CHOP),[2] 25%-30% of patients have either primary refractory disease or have a relapse of their disease.

Those patients who are either primary refractory or have a DLBCL recurrence (R/R) have a relatively poor outcome, as seen recently in a series of patients from the Netherlands.[3] In that trial, 50% of 455 patients did not receive subsequent treatment at the first instance of R/R disease. The median OS from subsequent treatment initiation was only 3.6 months with a 2 year OS rate of 13%. New strategies and therapies are desperately needed in this vulnerable subset of patients.

Patients who are CD20 "dim" at the time of diagnosis have inferior outcomes.[4] In a series by Johnson et al.,[4] those patients who were deemed to be "dim" by flow cytometry had statistically significant worse outcomes with RCHOP compared to patients who were not CD20 dim. In that trial, an arbitrary distinction was made between dim and bright by defining the lowest 16% on flow cytometry as being dim.

The traditional second line therapy for patients who relapse or are refractory to front line treatment of DLBCL is CAR-T therapy, following the success of the Zuma-7 trial comparing CAR-T to the previous standard of care, autologous HCT. In Zuma-7, evaluating CD19 expression by immunohistochemistry or flow cytometry was not a requirement for enrollment.[5] Conceptually, it is possible that some patients in that trial would be considered "CD19 dim", or perhaps could have even been CD19 negative by IHC.

There is clear data showing negative selective pressure and clonal explansion of CD20 negative clones following rituximab therapy.[6] A similar mechanism occurs with CD19 in patients with DLBCL treated with the anti-CD19 CART product axicabtagene ciloleucel.[7]

On July 31st, 2020, the FDA has approved a naked anti-CD19 monoclonal antibody in combination with lenalidomide for use in patients who have relapsed or refractory DLBCL and who are not eligible for autologous stem cell transplant, the standard of care at the time of approval. This approval was based on the L-MIND trial, a phase II showing an overall response rate of 43% and a complete response rate of 18%.[8] This regimen is currently in use as the backbone for the SWOG 2207 trial comparing tafasitamab/lenalidomide alone or in combination with either zanubrutinib or tazemetostat. This trial is currently ongoing. It is being stratified by cell or origin (GCB vs. non-GCB), but does not require testing of CD19 expression for enrollment.

In another B-cell malignancy, multiple myeloma, marked improvements have been seen with the use of anti-BCMA bispecific T-cell engager (BITE) therapy. The FDA approved teclistamab on October 25th, 2022 in light of the overall response rate of 61.8% in the MajesTEC-1 trial.[9] The patients in the MajesTEC-1 trial were all heavily pretreated including triple class exposure to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody.

Anti-CD38 antibodies have been evaluated in patients with relapsed/refractory DLBCL, however use of single agent daratumumab in the R/R DLBCL setting has been disappointing with only single agent repsonse rates.[10]

New Data Presentation

In this 398-patient dataset from Genomic Testing Cooperative, LCA, patient tissue was evaluated for mRNA expression of multiple genes including MS4A1 (the gene that codes forCD20), CD19 and BCMA. De-identified data was analyzed using SAS 9.4 and sorted by mysql on a protected University server. Using an mRNA cutoff of 10% (which is more conservative than the 16% cutoff found in Johnson's flow study) yielded a population of 39 patients that would likely be considered CD20 "dim" (see Table 1 below). In those CD20 dim patients, the majority (25/39 = 64%) expressed BCMA. Some of those patients had markedly BCMA elevated expression (see graph 1 below) suggesting sensitivity to a BCMA treatment. This population of CD20 dim, BCMA positive patients is higher

Abbreviations: DLBCL, diffuse large b-cell lymphoma; NHL, non-Hodgkin's lymphoma; BCMA, b-cell maturation antigen; R-CHOP, Rituximab, cytoxan, doxorubicin, vincristine, and prednisone; CAR-T, chimeric antigen receptor T-cell therapy; GCB, germinal center B; mRNA, messenger ribonucleic acid.

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Submitted: Jan 9, 2025; Accepted: Jan 26, 2025; Epub: xxx

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2152-2650/$ - see front matter © 2025 Published by Elsevier Inc.
https://doi.org/10.1016/j.clml.2025.01.016

Please cite this article as: Bruce Hough, Maher Albitar, mRNA Expression in DLBCL Patients who are CD20 Dim With an Eye Towards More Thoughtful Design of R/R Trials, Possibly Incorporating BCMA Bite Therapy, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2025.01.016

Table 1 Percent of patients by mRNA expression.

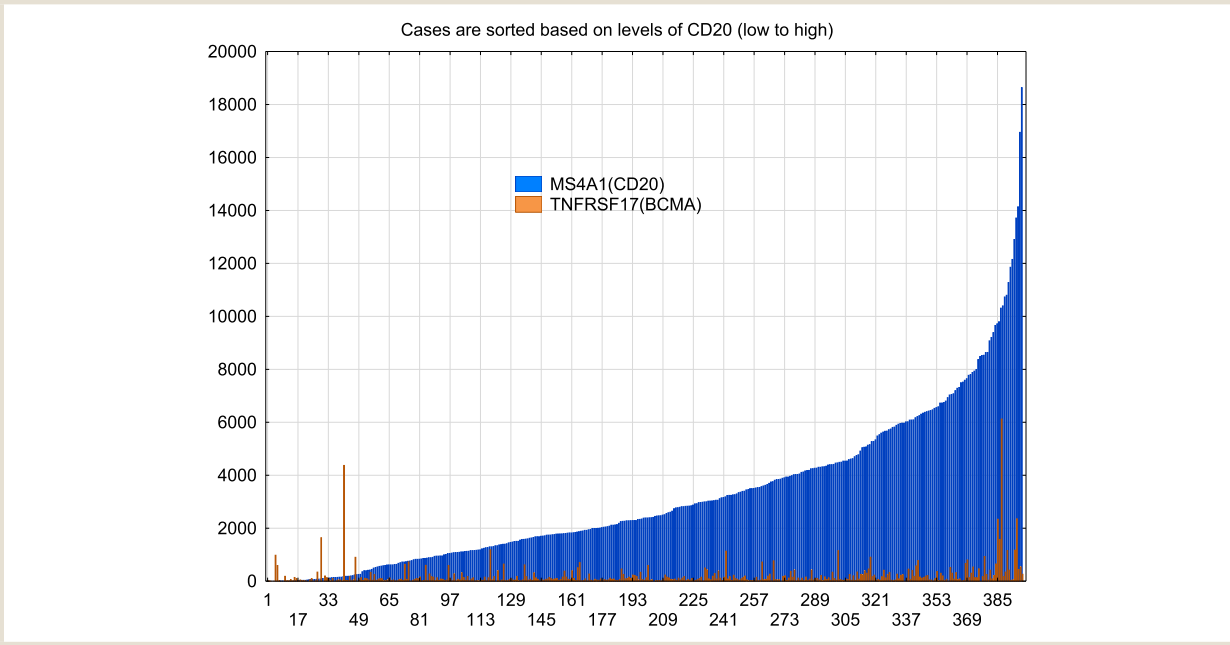
		CD20 < 10%	CD20 > 10%
CD 19	< 10%	22	17
	> 10%	17	342
		39	**359**

		CD19 < 10%	CD19 > 10%
BCMA	< 10%	13	27
	> 10%	26	332
		39	**359**

		CD20 < 10%	CD20 > 10%
BCMA	< 10%	14	26
	> 10%	25	333
		39	**359**

	CD 19 and CD20 Both < 10%
BCMA < 10%	13
BCMA > 10%	11
	24

Figure 1 mRNA expression for CD20 and BCMA, ordered by ascending CD20 expression.



than the population of CD20 dim, CD19 positive (17/39 = 43%) (Figure 1).

Instead of opening third line DLBCL trials that offfers the same therapy to all patients, it stands to reason that given the great diversity between different DLBCL patients and the selective pressure that prior treatments exert on clonal evoluation, a strategy of focusing on targets with available therapies may be more beneficial than focusing on new drugs as a "one-size fits all" third line strategy. One of the most simplest strategies would be to offer BCMA Bite therapy to those patients who are CD20 and CD19 dim, but who express BCMA using those products that are already FDA approved for multiple myeloma-teclistamab and elranatamab.

A small pilot study showing proof of concept and toxicity evaluation would require only a handful of patients and a positive signal may pave the way for a larger multi-institutional phase II trial.

Data Statement

Complete dataset in SQL or CSV format is available upon request.

Disclosure

Bruce Hough, MD: BMS-advisory board, Beigene-research grant.

Maher Albitar, MD: financial interest in Genomic Testing Cooperative.

CRediT authorship contribution statement

Bruce Hough: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project

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administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Maher Albitar:** Data curation, Validation, Conceptualization.

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