Check for updates

ELSEVIER

Blood 142 (2023) 851–852

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

A CD5 Gene Signature Identifies Diffuse Large B-Cell Lymphomas Sensitive to Bruton's Tyrosine Kinase Inhibition

Alan Cooper[1], *Sravya Tumuluru*[2], *Kyle Kissick*[3], *Girish Venkataraman*[3], *Joo Y Song, MD*[4], *Andrew Lytle*[5], *Gerben Duns, PhD*[6], *Jovian Yu, MDMS*[7], *Nikita Kotlov*[8], *Alexander Bagaev, PhD*[8], *Brendan Paul Hodkinson, PhD BS*[9], *Srimathi Srinivasan*[10], *Sonali M. Smith*[7], *David W. Scott, PhDMD,FRACP,FRCPA*[6], *Christian Steidl, MD PhD*[11], *James Godfrey, MD*[12], *Justin Kline, MD*[7,2]

[1] Department of Medicine, Section of Hematology/Oncology, University of Chicago, Old Westbury, NY
[2] Committee on Cancer Biology, University of Chicago, Chicago, IL
[3] Department of Pathology, University of Chicago, Chicago, IL
[4] Department of Pathology, City of Hope National Medical Center, Duarte, CA
[5] Department of Pathology and Laboratory Medicine, The University of British Columbia, Vancouver, Canada
[6] BC Cancer, Vancouver, Canada
[7] Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL
[8] BostonGene, Corp., Waltham, MA
[9] Oncology Translational Research, Janssen Research & Development, Spring House, PA
[10] Oncology Translational Research, Janssen Research & Development, Lower Gwynedd Township, PA
[11] Centre for Lymphoid Cancer, BC Cancer, Vancouver, Canada
[12] Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, CA

Introduction:
Diffuse large B-cell lymphomas (DLBCLs) with a non-germinal center B cell-like (non-GCB) cell-of-origin are frequently driven by genetic alterations that culminate in constitutive B-cell receptor (BCR) signaling, which has inspired the exploration of Bruton's tyrosine kinase inhibitors (BTKi) in these lymphomas. However, the phase III PHOENIX study that randomized untreated, non-GCB DLBCL patients to R-CHOP plus placebo or ibrutinib failed to meet its primary endpoint of event-free survival (Younes et al. 2019), which suggests that cell-of-origin alone is an insufficient biomarker to predict BTKi sensitivity in DLBCL. More recently, a DLBCL genetic classifier termed LymphGen has identified distinct subtypes (MCD and N1) of non-GCB DLBCL that benefit from the addition of BTKi to R-CHOP (Wilson et al. 2021). However, genetic classifiers are complex and difficult to implement in routine clinical settings and may fail to capture all DLBCLs that benefit from BTKi. Therefore, we sought to identify a straightforward biomarker of BTKi responsiveness in DLBCL with greater precision than cell-of-origin but with broader inclusivity than current genomic platforms, such as LymphGen. We hypothesized that CD5 - a surrogate marker of BCR activation - may effectively identify BCR-driven, non-GCB DLBCLs that are sensitive to BTKi therapy, and evaluated the extent to which CD5 protein expression and a transcriptionally defined CD5 gene signature could accurately identify BCR-activated DLBCLs with potential susceptibility to BTKi-based therapies.

Methods:
CD5 immunohistochemistry (IHC) was performed on a cohort of 406 diagnostic DLBCL samples, which were considered CD5+ if >=30% of lymphoma cells exhibited unequivocal membranous staining. A majority of DLBCL samples had available RNA-sequencing and targeted mutational sequencing data. A comparison of differentially expressed genes between CD5+ and CD5- DLBCLs was performed in order to construct a 60-gene CD5 signature (CD5sig), which was applied to large genomic DLBCL datasets, including pre-treatment biopsies from patients enrolled on PHOENIX (n = 584) to evaluate the utility of the CD5sig in identifying DLBCLs that benefitted from the addition of ibrutinib to R-CHOP.

Results:
Twenty-six of 406 DLBCLs were identified as CD5+ by IHC (6% of all DLBCLs; 12% of non-GCB DLBCLs). CD5 IHC+ DLBCLs were majority non-GCB cell-of-origin and were associated with inferior progression-free survival (PFS) to R-CHOP (50% 3-year PFS), compared with CD5 IHC- DLBCLs, consistent with previous reports. Gene set enrichment analysis revealed that CD5 IHC+ DLBCLs exhibited transcriptional features of BCR activation, and mutational analysis demonstrated that CD5 IHC+ DLBCLs were enriched for *CD79B* BCR-activating mutations known to correlate with BTKi sensitivity. Many CD5 IHC+ DLBCLs,

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/851/2195828/blood-5455-main.pdf by guest on 18 May 2024

© 2023 by The American Society of Hematology

however, lacked canonical BCR-activating mutations or were classified as "Other" by LymphGen. A CD5 gene signature (CD5sig; **Figure 1A**) was developed that recapitulated these findings in independent DLBCL datasets (NCI, Duke), where ~13% of non-GCB DLBCLs were classified as CD5sig+. Together, these results suggest that CD5 signature expression captures DLBCLs with both a genetic and non-genetic basis for BCR dependence. Supporting this notion, CD5sig+ DLBCL patients (< 60 years) derived a selective and striking event-free and overall survival advantage from the addition of ibrutinib to R-CHOP in the PHOENIX study (**Figure 1B)**, independent of LymphGen classification.

Conclusions:

We demonstrate that CD5 IHC and a novel CD5 gene signature identify high-risk, BCR-driven DLBCLs. Importantly, the CD5 signature also identifies DLBCL patients with a selective survival advantage to BTK inhibitor-based therapy, independent of LymphGen classification. In conclusion, the CD5 signature expands upon LymphGen classification as a biomarker of BTKi response by accurately identifying DLBCLs with both genetic and non-genetic bases for BTKi response. The CD5 signature and/or CD5 IHC should be prospectively evaluated in BTKi-based clinical trials for non-GCB DLBCLs.

Disclosures Kotlov: *BostonGene, Corp.:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company, Patents & Royalties. **Bagaev:** *BostonGene:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company, Patents & Royalties: patents. **Hodkinson:** *Janssen Research & Development:* Current Employment. **Srinivasan:** *Janssen Research & Development:* Current Employment. **Smith:** *Bristol-Myers Squibb, Gilead, Ono Pharmaceutical:* Consultancy, Speakers Bureau. **Scott:** *Janssen and Roche:* Research Funding; *Abbvie, AstraZeneca, Incyte:* Consultancy. **Steidl:** *Seattle Genetics, AbbVie, and Bayer:* Consultancy; *Bristol Myers Squibb, Epizyme and Trillium Therapeutics Inc.:* Research Funding. **Godfrey:** *Merck, Secura Bio:* Research Funding; *Verastem:* Research Funding. **Kline:** *iTeos, Secura Bio:* Research Funding; *Merck:* Consultancy, Research Funding; *Verastem:* Consultancy, Research Funding; *Karyopharm:* Consultancy; *Kite/Gilead:* Consultancy; *MorphoSys:* Consultancy; *Seagen:* Consultancy.

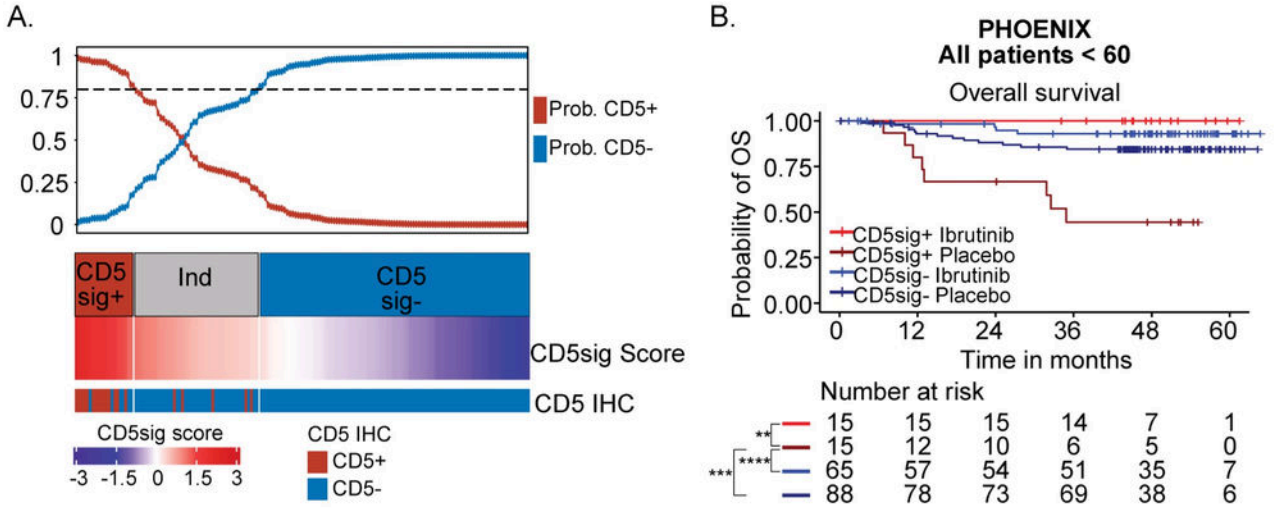

Figure 1. A. The CD5 signature (CD5sig) was devised based on the weighted expression score of genes differentially expressed between CD5+ and CD5- non-GCB DLBCLs. The probability of DLBCL cases belonging to CD5+ or CD5- subgroups, based on a probability cutoff of 80% (dashed line), is shown at the top. Middle track shows corresponding CD5sig score for DLBCLs in CD5sig+, indeterminate, or CD5sig- groups. Bottom track shows CD5 IHC status (positive- red, negative- blue) for each DLBCL. **B.** Kaplan-Meier survival curve of overall survival (OS) in all younger DLBCL patients (age < 60 years) classified as CD5sig+ or CD5sig- and treated with placebo + R-CHOP or ibrutinib + R-CHOP in PHOENIX. P-values were calculated using a log-rank test and adjusted for multiple comparisons. Adjusted p values are shown (* adj p < 0.05, ** adj p < 0.01, *** adj p<0.001, **** adj p < 0.0001).

Figure 1

https://doi.org/10.1182/blood-2023-182390

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/851/2195828/blood-5455-main.pdf by guest on 18 May 2024