1454 MULTIOMICS AND MULTIMODAL ANALYSIS APPROACH TO CONSTRUCT A DIFFUSE LARGE B CELL LYMPHOMA ATLAS OF TUMOR MICROENVIRONMENT FOR PREDICTIVE MODELING

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Background Expansion of therapeutic strategies against diffuse large B-cell lymphoma (DLBCL) offers new opportunities to fight aggressive non-Hodgkin's lymphoma. To unveil mechanisms driving cancer evolution and tumor immune contexture from a personalized medicine and diagnostic assay perspective, we sought to build a first-in-class reference database. Using a high-quality testing and innovative multimodal and integrative approach, the first Veracyte Biopharma Atlas for DLBCL evaluated thousands of parameters across more than 150 pre-treatment DLBCL lesions and enabled us to precisely map the spectrum of tumor microenvironments across samples and to establish a robust unsupervised descriptive model. By projecting new specimens associated to relevant clinical information and sample data onto the referential map, Atlas analysis provides a detailed description of the tumor microenvironment and facilitates the development of predictive and prognostic tools.

Methods Veracyte Biopharma Atlas characterizes the tumor microenvironment by analyzing information from 3 different modalities: (i) proteomics (Brightplex® panels), (ii) transcriptomics (RNA sequencing and hybridization using Nanostring technology), (iii) genomics (somatic mutations by exome sequencing and/or the rearrangement of the V(D)J regions of the CDR3 receptor of T cells). The specificity, complexity and volume of the information generated required the development of mathematical and bioinformatics processing to extract relevant biological information. The Veracyte Biopharma Atlas innovative approach combines linear (multimodal factor analysis) and non-linear (self-organizing map) approaches with graphical representation of the data. Finally, the incorporation of clinical annotation, either from samples used to generate the map or from clinical specimens projected onto the Atlas, made it possible to identify specific patterns predictive of a clinical parameter of interest (eg, response or toxicity).

Results Gene expression profiling, genomic analysis and proteomics by multiplex spatial technology were performed on more than 150 DLBCL samples collected at diagnosis. Using a centralized multi-omics integrative approach, data were analyzed to capture DLBCL immune contexture. Multimodal analysis allowing multifactor integration was used to derive a unique Atlas map and identify key features. Baseline and screening samples from axicabtagene ciloleucel (axi-cel) anti-CD19 chimeric antigen receptor (CAR) T-cell treated patients from the pivotal ZUMA-1 trial were analyzed with the same multi-omics integrative approach. Projection of ZUMA-1 immune contexture data onto the Atlas map revealed actionable information related to patients receiving CAR-T-cell treatment.

Conclusions Projection of CAR-T clinical trial data highlighted the Veracyte Biopharma Atlas as a powerful tool to stratify patients and identify key immune biomarkers linked to response to CAR T-cell therapy.

Ethics Approval The study protocol for the single-arm, multicenter, registrational ZUMA-1 study of axi-cel in patients with relapsed LBCL was previously described.[1] [2] Each study site's institutional review board reviewed and approved the study protocol and amendments, and all patients provided written informed consent. The study was done according to the International Conference on Harmonisation Good Clinical Practice guidelines. Patients in the ZUMA-1 study did not receive compensation for their participation in the study.

REFERENCES

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