

Leukemia

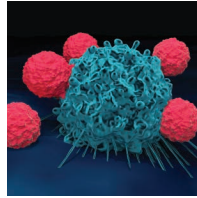
Major Finding: Blinatumomab nonresponders have worse CD19-CAR response than responders or blinatumomab-naïve patients.

Concept: Blinatumomab nonresponders are a high-risk population who may suboptimally respond to subsequent CD19-CAR.

Impact: This study reveals that blinatumomab does not directly preclude CD19-CAR treatment.

BLINATUMOMAB NONRESPONSE IS ASSOCIATED WITH POOR CD19-CAR OUTCOME IN B-ALL

Although CD19-directed chimeric antigen receptor T cells (CD19-CAR) and blinatumomab, a CD3-CD19 bispecific T-cell engager antibody, are both effective in inducing remission of B-cell acute lymphoblastic leukemia (B-ALL), how blinatumomab affects subsequent CD19-CAR outcomes is unknown. A critical concern is that the sequential targeting of CD19 by both treatments could increase the risk of antigen escape. To address this, Myers and colleagues conducted a retrospective multicenter study of 420 children and young adults who received CD19-CAR for relapsed or refractory B-ALL. Relapse-free survival (RFS) and event-free survival (EFS) were evaluated 6 months after CD19-CAR treatment, inclusive of patients who had and had not previously received blinatumomab. Complete remission (CR) rates, RFS, EFS, and overall survival (OS) were comparable in blinatumomab-naïve and blinatumomab-exposed patients who responded to blinatumomab, suggesting that blinatumomab does not directly preclude CD19-CAR response. However, RFS, EFS, and OS were reduced as was the CR rate in blinatumomab-exposed nonresponders or those who did not achieve CR, supporting that these blinatumomab-exposed nonresponding patients likely were a high-risk population inherently resistant to CD19-CAR. In addition, partial or



complete loss of CD19 was more common in blinatumomab-exposed than blinatumomab-naïve patients, but for patients who had normal CD19 expression pre-CAR, antigen escape was comparable for both blinatumomab-naïve and exposed patients. Furthermore, high disease burden amplified poor outcomes of blinatumomab-exposed nonresponders. Overall, this indicates that, while blinatumomab may lead to CD19 downregulation, there is likely an inherent risk factor other than CD19 escape responsible for the poor outcomes of blinatumomab-exposed, post-CD19-CAR patients. In summary, this study highlights blinatumomab-exposed nonresponse and high disease burden as risk factors for resistance to CD19-CAR and suggests further investigation into mechanisms of blinatumomab nonresponse and its impact on CD19-CAR response as well as serial CD19 expression monitoring pre- and post-blinatumomab to increase the understanding of its impact on future single or sequential antigen-targeted therapy. ■

Myers RM, Taraseviciute A, Steinberg SM, Lamble AJ, Sheppard J, Yates B, et al. Blinatumomab nonresponse and high-disease burden are associated with inferior outcomes after CD19-CAR for B-ALL. *J Clin Oncol* 2021 Nov 12 [Epub ahead of print].

doi: 10.1158/2159-8290.CD-RW2021-172

Oncogenes

Major Finding: Highly complex genomic amplification arises from chromothripsis followed by circular recombination.

Concept: Repetitive recombination in circular extrachromosomal DNA creates complex amplification patterns.

Impact: This stepwise process underlies oncogene amplification and overexpression in many human tumor types.

CHROMOTHRIPSIS AND CIRCULAR RECOMBINATION DRIVE ONCOGENE AMPLIFICATION

Genomic amplification contributes to tumor progression by increasing gene copy number (CN) and elevating oncogene expression. Although genomic amplification is prevalent in many tumor types, the events that give rise to complex amplification patterns are not well understood. To investigate mechanisms of amplification, Rosswog, Bartenhagen, and colleagues analyzed whole-genome sequencing (WGS) data of tumor samples from patients with neuroblastoma and identified a type of complex amplification referred to as “seismic amplification,” characterized by a pattern of multiple rearrangements and numerous genomic segments with distinct CN states, interrupted by non-amplified or deleted regions. Analysis of cytogenetic state via fluorescence *in situ* hybridization revealed that seismic amplification could present as extrachromosomal double minutes (DM), intrachromosomal homogeneously staining regions (HSR), or neochromosomes (NC). Extending these observations beyond neuroblastoma, seismic amplification was detected in WGS data of almost 10% of patient tumors representing 38 cancer types and was distinguishable from other types of amplifications by increased maximum CN and RNA expression of affected oncogenes. Further analysis found that chromothripsis, a catastrophic mutational event that leads to chromosome rearrangement of a

genomic region, was associated with seismic amplification in human tumors, suggesting that chromothripsis contributed in part to this process. Given that chromothripsis alone likely could not account for complex seismic amplicon structure, a progressive evolutionary model was proposed, in which seismic amplification is initiated by chromothripsis, producing DNA fragments which can undergo circularization, followed by cycles of circular recombination. After recombination, the amplicon can remain circular, integrate into a chromosome, or form an NC, stabilizing and presenting as DM, HSR, or NC, respectively. Read support of amplicon rearrangements supported this stepwise model, in addition to validation through computational simulations, as CN signatures observed in human tumors were similar to simulated amplifications in which chromothripsis was followed by circular recombination. In summary, this work describes a mechanism that gives rise to a highly complex type of genomic amplification that is pertinent to many tumor types. ■

Rosswog C, Bartenhagen C, Welte A, Kahlert Y, Hemstedt N, Lorenz W, et al. Chromothripsis followed by circular recombination drives oncogene amplification in human cancer. *Nat Genet* 2021;53:1673–85.

doi: 10.1158/2159-8290.CD-RW2021-173