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Précis: Mutations that result in loss of primary cilia promote resistance to SMO inhibitors by eliminating formation of the GLI2 repressor form, allowing persistent low-level activation of hedgehog signaling.

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Galectin-3, a Druggable Vulnerability for KRAS-Addicted Cancers

Neurologic adverse events induced by autologous transfer of CD19-targeted chimeric antigen receptor-modified T (CAR-T) cells were investigated in 133 patients with B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, or non-Hodgkin lymphoma who had received chemotherapy and CD19 CAR-T cell infusion. Cytokine release syndrome (CRS) preceded neurotoxicity in all 28 patients who developed grade 3+ neurotoxicity, and severe neurotoxicity was linked to endothelial activation and increased blood–brain barrier permeability. Signs of endothelial activation and vascular disruption were observed in the brain of a patient who died of CRS-induced neurotoxicity, and endothelial activation prior to treatment was linked to an increased risk of high-grade neurotoxicity. Altogether, these results identify risk factors for CD19 CAR-T cell therapy–induced neurotoxicity, and suggest that endothelial activation may serve as a biomarker for severe neurotoxicity. For details, please see the article by Gust, Hay, Hanafi, and colleagues on page 1404.

ON THE COVER Neurologic adverse events induced by autologous transfer of CD19-targeted chimeric antigen receptor-modified T (CAR-T) cells were investigated in 133 patients with B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, or non-Hodgkin lymphoma who had received chemotherapy and CD19 CAR-T cell infusion. Cytokine release syndrome (CRS) preceded neurotoxicity in all 28 patients who developed grade 3+ neurotoxicity, and severe neurotoxicity was linked to endothelial activation and increased blood–brain barrier permeability. Signs of endothelial activation and vascular disruption were observed in the brain of a patient who died of CRS-induced neurotoxicity, and endothelial activation prior to treatment was linked to an increased risk of high-grade neurotoxicity. Altogether, these results identify risk factors for CD19 CAR-T cell therapy–induced neurotoxicity, and suggest that endothelial activation may serve as a biomarker for severe neurotoxicity. For details, please see the article by Gust, Hay, Hanafi, and colleagues on page 1404.