CANCER DISCOVERY
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Précis: In a phase II basket trial, the BRAF inhibitor vemurafenib showed preliminary evidence of efficacy in 13 BRAF-mutant non-melanoma tumor types, including some typically considered treatment refractory.
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Plasma DNA End-Motif Profiling as a Fragmentomic Marker in Cancer, Pregnancy and Transplantation .................. 664
Précis: Short sequences at the ends of cell-free DNA fragments in plasma can be used to detect and assess pathophysiologic states, including cancer.

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Précis: Combining trastuzumab emtansine with irreversible pan-HER inhibitors—increasing HER2 ubiquitination and internalization—or switching to trastuzumab deruxtecan improves responses of ERBB2-mutant or -amplified lung tumors.
See commentary, p. 643

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Targeting HER2 with Trastuzumab Deruxtecan: A Dose-Expansion, Phase I Study in Multiple Advanced Solid Tumors. .......................... 688


Précis: In a phase I trial, the antibody–drug conjugate trastuzumab deruxtecan had a manageable safety profile and showed promising preliminary evidence of efficacy in non-small cell lung cancer.

See commentary, p. 643

Tuning the Antigen Density Requirement for CAR T-cell Activity .......................... 702


Précis: The costimulatory and hinge–transmembrane domains of CAR-T cells can be manipulated to enhance their sensitivity to target cells expressing low levels of surface antigens.

Correction

Correction: Senescence Sensitivity of Breast Cancer Cells Is Defined by Positive Feedback Loop between CIP2A and E2F1 .......................... 746


Précis: Integrative analyses revealed functional noncoding variants connecting enhancer dysregulation with nuclear-receptor signaling to modulate gene programs in leukemogenesis.

See commentary, p. 646

ON THE COVER  Resistance to CAR-T cells can result from low expression of target antigens on cancer cells. In B-cell cancers, Majzner and colleagues found a high degree of intra- and interpatient heterogeneity in the expression of CAR-T cell target antigens. Importantly, though, the sensitivity of CAR-T cells to target-antigen level was tunable: CAR-T cells could be made more or less sensitive by altering their costimulatory and hinge–transmembrane (H/T) domains. Specifically, CD28 costimulatory and H/T domains (both as in axicabtagene ciloleucel) conferred more sensitivity than 4-1BB costimulatory domains and CDB H/T domains (both as in tisagenlecleucel). For details, please see the article by Majzner and colleagues on page 702.