CANCER DISCOVERY

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Précis: In a phase II clinical trial, treatment with atezolizumab plus bevacizumab (PD-L1 + VEGF blockade) produced objective responses in 40% of previously treated patients with advanced malignant peritoneal mesothelioma, with a median response duration of 12.8 months.

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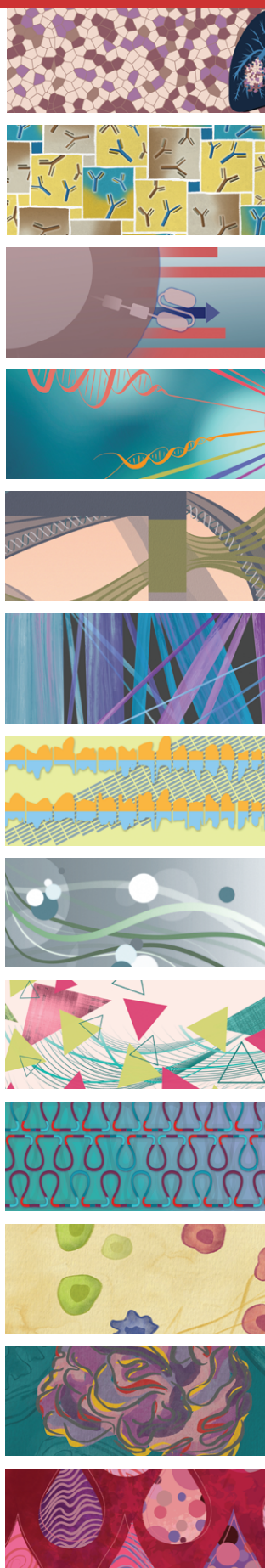

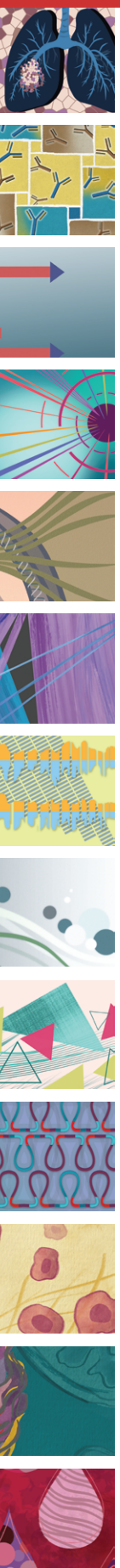

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Précis: For patients with cancers in the pleural cavity, regional delivery of mesothelin-targeted CAR T-cell therapy followed by administration of pembrolizumab is feasible and safe and demonstrates antitumor efficacy.

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Précis: A prospective observational study showed that a precision oncology approach based on comprehensive molecular profiling provides clinical benefit to patients with advanced rare cancers.

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Précis: DNA and RNA sequencing of paired primary tumor/metastases from 381 patients with metastatic breast cancer shed light on enriched genomic alterations, subtype switching, and immune cell composition, and identified new candidate biomarkers of premature lethality.

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Précis: Prostate cancers that benefit most from PARP inhibition have *BRCA2* alterations, with *BRCA2* homozygous loss associating with the longest benefit; biallelic loss of *PALB2* and *ATM* can also sensitize to PARP inhibition.

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Précis: Loss-of-function *STK11* mutations confer resistance to anti–PD-L1 or dual anti–PD-L1/anti-CTLA4 immunotherapy in nonsquamous non–small cell lung cancer, with preclinical data indicating that inhibition of STAT3-mediated immunosuppression can overcome the effects of STK11 loss.

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Précis: Integrated genomic and epigenomic analyses identifies structural variants juxtaposing hematopoietic stem cell enhancers to the T lineage transcription factor gene *BCL11B* as the driving alteration of a subset of lineage-ambiguous acute leukemia.

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Précis: A *GATA2* enhancer hijacked by the *EVI1* oncogene in leukemia is selectively bound by the MYB transcription factor, which makes the translocated enhancer and consequently *EVI1* transcription responsive to MYB inhibitors.

Proteomic Screens for Suppressors of Anoikis Identify IL1RAP as a Promising Surface Target in Ewing Sarcoma . . . 2884

H.-F. Zhang, C.S. Hughes, W. Li, J.-Z. He, D. Surdez, A.M. El-Naggar, H. Cheng, A. Prudova, A. Delaidelli, G.L. Negri, X. Li, M.S. Ørum-Madsen, M.M. Lizardo, H.Z. Oo, S. Colborne, T. Shyp, R. Scopim-Ribeiro, C.A. Hammond, A.-C. Dhez, S. Langman, J.K.M. Lim, S.H.Y. Kung, A. Li, A. Steino, M. Daugaard, S.J. Parker, R.I. Klein Geltink, R.J. Orentas, L.-Y. Xu, G.B. Morin, O. Delattre, D.S. Dimitrov, and P.H. Sorensen

Précis: Surface IL1RAP maintains cyst(e)ine and glutathione pools to block anoikis and facilitate metastatic dissemination in Ewing sarcoma, and minimal expression in normal tissues nominates IL1RAP as a promising immunotherapy target.

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F. Puca, F. Yu, C. Bartolacci, P. Pettazzoni, A. Carugo, E. Huang-Hobbs, J. Liu, C. Zanca, F. Carbone, E. Del Poggetto, J. Gumin, P. Dasgupta, S. Seth, S. Srinivasan, F.F. Lang, E.P. Sulman, P.L. Lorenzi, L. Tan, M. Shan, Z.P. Tolstyka, M. Kachman, L. Zhang, S. Gao, A.K. Deem, G. Genovese, P.P. Scaglioni, C.A. Lyssiotis, A. Viale, and G.F. Draetta

Précis: Genetic screening revealed a novel function for MCAD in glioblastoma, where in addition to its energetic role, it prevents toxic lipid accumulation, and targeting MCAD causes irreversible damage and cell death in glioblastoma cells, while sparing normal cells.

AXL Inhibition in Macrophages Stimulates Host-versus-Leukemia Immunity and Eradicates Naïve and Treatment-Resistant Leukemia 2924

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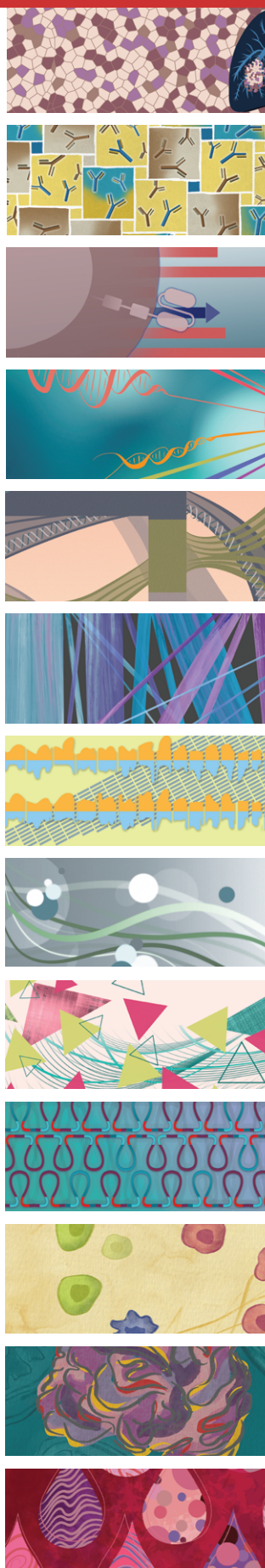
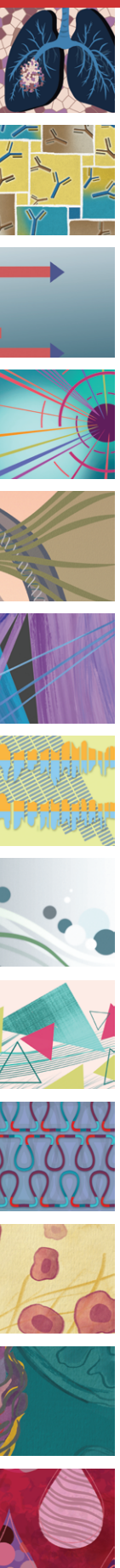
Précis: Leukemia cells evade immune control by engaging the AXL receptor tyrosine kinase in innate immune cells; targeting AXL lifts the innate immune barriers, triggers lymphocyte-mediated leukemic clearance, and elicits response to adaptive checkpoint therapy.





ON THE COVER Cancers within the pleural cavity such as malignant pleural mesothelioma (MPM) are aggressive and typically have poor response to therapies. Immune checkpoint inhibitors have been indicated for second-line use in this disease; however, low expression of PD-L1 has contributed to poor response in patients given monotherapy. Chimeric antigen receptor (CAR) T cells developed to target mesothelin and be delivered to the pleural cavity have shown promise in mouse models, but PD-1/PD-L1 signaling promoted functional exhaustion of these CAR T cells; administration of an anti–PD-1 therapy abrogated this effect. Adusumilli and colleagues therefore conducted a first-in-human phase I clinical trial combining pembrolizumab with intrapleural administration of CAR T cells targeting mesothelin. This trial indicated that this combination was not only feasible and safe but had antitumor efficacy, with two patients with MPM experiencing complete metabolic responses, and persistence of functional CAR T cells was observed. For more information, see the article by Adusumilli and colleagues on page 2748.

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