Chimeric antigen receptor (CAR) T-cell therapy induces durable, curative responses in patients with hematologic malignancies, but efforts to treat solid tumors with this approach have so far had limited success. In a phase I study, using interventional radiologic techniques, Adusumilli and colleagues administered mesothelin-targeted CAR T cells in the pleural cavity in patients with therapy-refractory pleural cancers. Regional delivery was feasible and safe (no on-target, off-tumor toxicities) and established long-lasting systemic circulation, with evidence of antitumor efficacy. For patients subsequently treated with pembrolizumab to rescue exhausted CAR T cells, combination immunotherapy was safe and further enhanced CAR T-cell functional persistence.

See article, p. 2748.

Malignant peritoneal mesothelioma is a rare and lethal cancer with no approved treatment options beyond first-line platinum-pemetrexed chemotherapy. Raghav and colleagues conducted a phase II clinical trial of the combination of atezolizumab (anti–PD-L1) and bevacizumab (anti-VEGF) in patients with advanced malignant peritoneal mesothelioma previously treated with platinum-pemetrexed chemotherapy. Among 20 evaluable patients, treatment was well tolerated, and the confirmed objective response rate was 40% with a median duration of response of 12.8 months. Progression-free and overall survival at 1 year were 61% and 85%. An epithelial–mesenchymal transition gene-expression phenotype correlated with response and resistance to therapy.

See article, p. 2738.

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See article, p. 2748.

The long-term benefit of precision oncology studies in a real-world clinical setting is largely unknown for pediatric oncology. Van Tilburg and colleagues applied comprehensive molecular profiling in the multinational INFORM registry and prospectively tested a target prioritization algorithm. Of the 519 analyzed patients, 20 patients received matched targeted treatment for targets with the highest priority level and showed a significantly improved progression-free survival of 204 days compared with 117 days in all other patients. Furthermore, hereditary cancer predisposition syndromes were identified in 7.5% of patients, and integrated molecular analyses resulted in a change or refinement of diagnoses in 8.2% of cases.

See article, p. 2764.
Patients with advanced rare cancers often lack treatment options, and the relevance of comprehensive molecular analyses for clinical decision-making in this setting is largely unknown. Horak, Heining, Kreutzfeldt, Hutter, and colleagues analyzed the molecular profiles and clinical outcomes of 1,310 patients enrolled in a multicenter observational precision oncology trial. Based on whole-genome/whole-exome and RNA sequencing, evidence-based management recommendations were provided, including diagnostic reevaluation, genetic counseling, and experimental treatment. Recommended therapies were associated with improved overall response/disease control rates, and progression-free survival compared with previous regimens. This study demonstrates the utility of molecular stratification for many patients with advanced rare cancers.

See article, p. 2780.

A Prospective Longitudinal Study Provides Insights into Metastatic Breast Cancer

Genomic characterization of metastatic breast cancer has, to date, largely focused on samples after heavy pretreatment, capturing genomic alterations driven by therapy. AURORA is the largest initiative to date performing genomic and transcriptomic analyses on paired primary tumors and early-course metastases, as well as collecting blood for cell-free DNA every 6 months and longitudinal clinical information to identify alterations causing metastatic relapse. Analyzing samples from AURORA, Aftimos and colleagues uncovered genomic alterations enriched in metastases as well as frequent intrinsic subtype switching and immune permissive microenvironments. More than half of the patients had actionable alterations, and high tumor mutational burden was identified as an independent prognostic biomarker in luminal tumors.

See article, p. 2796.

Specific DNA Repair Defects Predict Olaparib Benefit in Prostate Cancer

The phase II TOPARP-B trial evaluated the response to the PARP inhibitor olaparib in patients with metastatic castration-resistant prostate cancer with DNA damage response gene aberrations. Carreira, Porta, and colleagues analyzed patient samples from TOPARP-B with targeted, whole-exome, and low-pass whole-genome sequencing, immunohistochemistry, and a functional RAD51 foci immunofluorescence assay to elucidate biomarkers identifying prostate cancers sensitive to PARP inhibition. Advanced prostate cancers with homozygous loss of BRCA2 responded the longest, with BRCA2-altered prostate cancers being most sensitive to PARP inhibition. Unlike BRCA2 alterations, deleterious alterations in other DNA damage repair genes including PALB2 and ATM were not commonly biallelic, although when biallelic loss was present these tumors could also be sensitive to PARP inhibition.

See article, p. 2812.

STAT3 Inhibition Overcomes STK11-Mediated Immunotherapy Resistance

Mutations that functionally inactivate the tumor suppressor STK11 (also known as LKB1) in non–small cell lung cancer (NSCLC) confer resistance to anti–PD-1 immunotherapy and standard-of-care chemotherapy. Pore, Wu, and colleagues found an association between STK11 mutations and resistance to anti–PD-L1 or dual anti–PD-L1 plus anti-CTLA4 immunotherapy in early-stage NSCLC clinical trials. Translational endpoints indicated a potential role for STAT3 signaling in establishing an immunosuppressive microenvironment. Using an antisense oligonucleotide approach in preclinical models to attenuate STAT3 activity in immune and stromal cells, checkpoint immunotherapy resistance was reversed when STAT3 knockdown reprogrammed the tumor microenvironment to be more immunostimulatory.

See article, p. 2828.
Acute leukemias with myeloid and T-lymphoid features are currently classified across multiple diagnostic entities. Montefiori, Bendig, Gu, Chen, and colleagues analyzed the transcriptomes of >2,700 leukemias and identified a new subtype spanning diagnostic classifications with a distinct gene expression profile, frequent FLT3 mutation, and structural variants deregulating BCL11B through enhancer hijacking or focal amplification resulting in neoenhancer formation. Coexpression of BCL11B and FLT3-ITD transformed and resulted in lineage aberrancy of hematopoietic progenitors. These findings describe a subtype of leukemia that transcends traditional immunophenotypic criteria, provides evidence for a hematopoietic stem cell as the cell of origin, and elucidates a new context-dependent oncogenic role for BCL11B.

See article, p. 2846.

In a subset of patients with acute myeloid leukemia, a distal enhancer of the GATA2 gene is translocated to the EVII oncogene to drive its expression. Smeenk and colleagues identified a MYB-binding element in the enhancer to be essential for EVII transcription. The same site at the nontranslocated allele is not essential for the activation of GATA2. Therefore, MYB knockout as well as MYB-peptidomimetic blockade resulted in downregulation of EVII but not of GATA2. Interference with MYB-driven EVII transcription provides a potential entry point to target leukemias with a translocated GATA2 enhancer.

See article, p. 2868.

Cancer cells must overcome anoikis, or detachment-induced cell death, to successfully metastasize. Zhang and colleagues integrated proteomic and acute translatomic screens in 3-D tumor cultures to identify regulators of anoikis, uncovering that distinct oncoproteins upregulate the surface protein IL1RAP. IL1RAP activates cysteine uptake by the xCT transporter and facilitates de novo cysteine synthesis by cystathionine-γ-lyase, thereby maintaining cyst(e)ine and glutathione pools for redox homeostasis and anoikis resistance. IL1RAP inactivation triggers anoikis and ferroptosis and impedes lung metastasis of Ewing sarcoma. IL1RAP is minimally expressed in normal tissues, and human anti-IL1RAP antibodies induce potent toxicity of Ewing sarcoma cells.

See article, p. 2884.

Using an in vivo loss-of-function screen in patient-derived glioblastoma (GBM) models, Puca and colleagues uncovered a novel metabolic dependency on medium-chain acyl CoA dehydrogenase (MCAD), which degrades medium-chain fatty acids in the mitochondria. MCAD loss potently abrogated cell proliferation and tumor growth in human GBM models. Beyond the expected impairment to energetics, which can be mitigated through metabolic shunt pathways, MCAD depletion in GBM models induced mitochondrial failure caused by the acute toxicity of hyperaccumulated fatty acids. Individuals with congenital MCAD deficiency thrive with simple dietary adjustments, and normal brain cells are unaffected by MCAD depletion, suggesting a therapeutically targetable tumor cell-specific dependency in GBM.

See article, p. 2904.
Acute leukemias are devastating blood cancers that excel at immune evasion and are frequently refractory to adaptive checkpoint therapy. Tirado-Gonzalez and colleagues discovered that leukemic cells effectively blunt the early steps of the immunity cycle by actively engaging the AXL receptor in leukemia-associated macrophages and skewing them toward a tumor-promoting phenotype. Consequently, genetic ablation of AXL in macrophages or its inhibition using a clinical-grade inhibitor leads to effective T and natural killer cell–mediated antileukemic immunity, including in treatment-resistant leukemia. AXL inhibition also synergizes with standard-of-care therapy and confers de novo sensitivity to adaptive checkpoint therapy.

See article, p. 2924.