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The Basic Principles of Chimeric Antigen Receptor Design... 388
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RESEARCH BRIEF

Biallelic Deleterious BRCA1 Mutations in a Woman with Early-Onset Ovarian Cancer... 399

Précis: The presence of a dysfunctional BRCA1 BRCT domain variant in trans with a known deleterious BRCA1 mutation was documented in a woman with early-onset ovarian carcinoma.
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RESEARCH ARTICLES

First-in-Humans Trial of an RNA Interference Therapeutic Targeting VEGF and KSP in Cancer Patients with Liver Involvement... 406

Précis: A lipid nanoparticle multitarget siRNA formulation is deliverable to tumors and shows evidence of on-target activity in patients with advanced cancers enrolled in a phase I trial.
Multifunctional T-cell Analyses to Study Response and Progression in Adoptive Cell Transfer Immunotherapy .......................... 418
Précis: Single-cell immune monitoring of patients receiving adoptive cell transfer therapy reveals time-dependent changes in adoptively transferred and endogenous T-cell functionality.

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Targeted Inhibition of the Molecular Chaperone Hsp90 Overcomes ALK Inhibitor Resistance in Non-Small Cell Lung Cancer .......................... 430
Précis: Inhibition of HSP90 with ganetespib may represent an alternative or complementary therapeutic strategy for treatment of ALK-positive non-small cell lung cancer.

Primary Melanoma of the CNS in Children Is Driven by Congenital Expression of Oncogenic NRAS in Melanocytes ...... 458
Précis: Early embryonic NRAS mutation promotes melanocyte proliferation and induces early-onset primary melanoma of the central nervous system but not cutaneous melanoma.

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Tabernero and colleagues report the results of a phase I dose-escalation and expansion study assessing the safety, activity, and pharmacodynamics of ALN-VSP, a lipid nanoparticle containing siRNAs against vascular endothelial growth factor A (VEGFA) and kinesin spindle protein (KSP), in patients with advanced solid tumors with liver involvement. One patient with metastatic endometrial cancer had a complete response and 3 patients (2 with metastatic renal cell carcinoma and 1 with metastatic pancreatic neuroendocrine tumor) experienced disease stabilization. Post-treatment tumor biopsies showed evidence of intratumoral delivery, increased VEGFA mRNA cleavage, and decreased VEGFA and KSP mRNA levels compared with pre-treatment biopsy samples, consistent with an on-target response and an RNAi mechanism of action. For details, please see the article by Tabernero and colleagues on page 406.