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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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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.
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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.

RHOA-FAK Is a Required Signaling Axis for the Maintenance of KRAS-Driven Lung Adenocarcinomas ................. 444
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Primary Melanoma of the CNS in Children Is Driven by Congenital Expression of Oncogenic NRAS in Melanocytes ..... 458
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- Reprioritizing Cancer Clinical Studies
- Glycoengineered Antibodies Show Promise
- FDA Approves Stivarga for GIST
- Analyses Suggest Risks with mTOR Inhibitors
- Ramucirumab Aids Gastric Cancer Survival

ON THE COVER
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.
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