

CANCER DISCOVERY CONTENTS

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S.M. Domchek, J. Tang, J. Stopfer, D.R. Lilli, N. Hamel, M. Tischkowitz, A.N.A. Monteiro, T.E. Messick, J. Powers, A. Yonker, F.J. Couch, D.E. Goldgar, H.R. Davidson, K.L. Nathanson, W.D. Foulkes, and R.A. Greenberg

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.

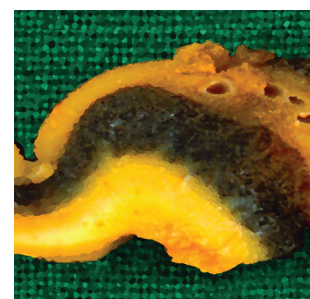
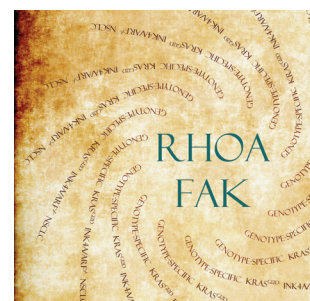
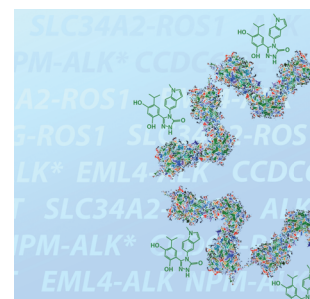
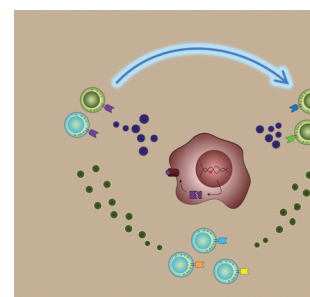
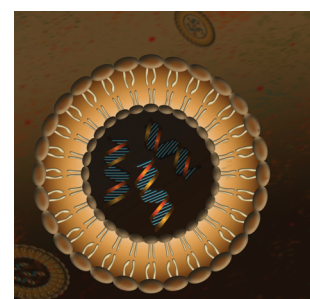
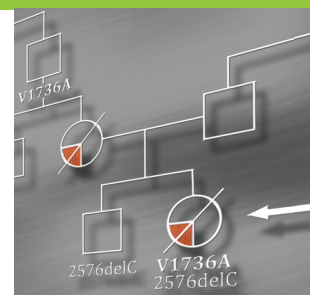
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J. Tabernero, G.I. Shapiro, P.M. LoRusso, A. Cervantes, G.K. Schwartz, G.J. Weiss, L. Paz-Ares, D.C. Cho, J.R. Infante, M. Alsina, M.M. Gounder, R. Falzone, J. Harrop, A.C.S. White, I. Toudjarska, D. Bumcrot, R.E. Meyers, G. Hinkle, N. Svrzikapa, R.M. Hutabarat, V.A. Clausen, J. Cehelsky, S.V. Nochur, C. Gamba-Vitalo, A.K. Vaishnav, D.W.Y. Sah, J.A. Gollob, and H.A. Burris III

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

C. Ma, A.F. Cheung, T. Chodon, R.C. Koya, Z. Wu, C. Ng, E. Avramis, A.J. Cochran, O.N. Witte, D. Baltimore, B. Chmielowski, J.S. Economou, B. Comin-Anduix, A. Ribas, and J.R. Heath

Précis: Single-cell immune monitoring of patients receiving adoptive cell transfer therapy reveals time-dependent changes in adoptively transferred and endogenous T-cell functionality.

See commentary, p. 379

Targeted Inhibition of the Molecular Chaperone Hsp90 Overcomes ALK Inhibitor Resistance in Non-Small Cell Lung Cancer..... 430

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Précis: Inhibition of HSP90 with ganetespib may represent an alternative or complementary therapeutic strategy for treatment of ALK-positive non-small cell lung cancer.

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Précis: RHOA-FAK signaling is a genotype-specific therapeutic target in aggressive KRAS-mutant, *INK4A/ARF*-deficient non-small cell lung cancers.

Primary Melanoma of the CNS in Children Is Driven by Congenital Expression of Oncogenic *NRAS* in Melanocytes..... 458

M. Pedersen, H.V.N. Küsters-Vandeveld, A. Viros, P.J.T.A. Groenen, B. Sanchez-Laorden, J.H. Gilhuis, I.A. van Engen-van Grunsven, W. Renier, J. Schieving, I. Niculescu-Duvaz, C.J. Springer, B. Küsters, P. Wesseling, W.A.M. Blokx, and R. Marais

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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For more News and Research Watch, visit *Cancer Discovery* online at <http://CDnews.aacrjournals.org>. Online-only News stories include the following:

- Drug Combo Effective Against Pancreatic Cancer
- 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.

