IN THIS ISSUE
Highlighted research articles 920

NEWS IN BRIEF
Important news stories affecting the community 924

NEWS IN DEPTH
Why First-Line Nivolumab Is No Better than Chemo 927
Taking the Guesswork Out of Stopping TKIs 928

RESEARCH WATCH
Selected highlights of recent articles of exceptional significance from the cancer literature 929

ONLINE
For more News and Research Watch, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.

REVIEW
New Horizons for Precision Medicine in Biliary Tract Cancers 943
J.W. Valle, A. Lamarca, L. Goyal, J. Barriuso, and A.X. Zhu

RESEARCH BRIEFS
A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion–Positive Solid Tumors 963

Précis: Parallel development of the first-generation TRK TKI larotrectinib with the next-generation TKI LOXO-195 allowed for rapid use of LOXO-195 to treat patients with acquired larotrectinib resistance.
See commentary, p. 934

Exome Sequencing of African-American Prostate Cancer Reveals Loss-of-Function ERF Mutations 973

Précis: Sequencing of an African-American prostate cancer cohort identified ERF as a tumor suppressor in prostate cancer and shows that increasing ethnic diversity enhances the discovery of potential cancer drivers.

In The Spotlight
Fast-TRKing Drug Development for Rare Molecular Targets 934
A.R. Parikh and R.B. Corcoran
See article, p. 963

Reversion Mutations with Clinical Use of PARP Inhibitors: Many Genes, Many Versions 937
S.M. Domchek
See article, p. 984
See article, p. 999
See article, p. 1006

Spotlight on Ibrutinib in PCNSL: Adding Another Feather to Its Cap 940
A. Lakshmanan and J.C. Byrd
See article, p. 1018
Secondary Somatic Mutations Restoring RAD51C and RAD51D Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma


Précis: In patients with high-grade ovarian carcinoma treated with a PARP inhibitor rucaparib, secondary reversion mutations in HR genes restore the open reading frame and HR activity to confer resistance. See commentary, p. 937

Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of BRCA2 Reversion Mutations Associated with Resistance to PARP Inhibitors


Précis: Multiclonal BRCA2 reversion mutations were detected in circulating cell-free DNA from two patients with metastatic prostate cancer after PARP inhibitor treatment, suggesting a mechanism of resistance. See commentary, p. 937

Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma


Précis: The BTK inhibitor ibrutinib has activity in patients with relapsed or refractory B-cell lymphomas of the CNS, and dual treatment with PI3K/mTOR inhibitors may enhance ibrutinib efficacy in patients with CD79B-mutant tumors. See commentary, p. 940

Discovery and Optimization of HKT288, a Cadherin-6–Targeting ADC for the Treatment of Ovarian and Renal Cancers


PARP inhibitors (PARPi) have demonstrated activity in patients with mutations in homologous recombination (HR) genes such as BRCA1 and BRCA2. Three related studies identified HR gene reversion mutations that confer resistance to PARPi. Kondrashova and colleagues discovered secondary reversion mutations in BRCA1, RAD51C, and RAD51D in patients with PARPi-resistant ovarian cancer. Similarly, Quigley, Alumkal, and colleagues identified BRCA2 reversion mutations associated with PARPi resistance in circulating cell-free DNA (cfDNA) from two patients with prostate cancer. Finally, Goodall, Mateo, and colleagues found secondary reversion mutations in BRCA2 and PALB2 in cfDNA from patients with PARPi-resistant metastatic prostate cancer. Together, these studies demonstrate that HR gene reversion mutations can promote resistance to PARPi. For details, please see the article by Kondrashova and colleagues on page 984, the article by Quigley, Alumkal, and colleagues on page 999, and the article by Goodall, Mateo, and colleagues on page 1006.