IN THIS ISSUE
Highlighted research articles ................................. 539

NEWS BRIEF
An Acquired HER2<sup>T798I</sup> Gatekeeper Mutation Induces Resistance to Neratinib in a Patient with HER2 Mutant-Driven Breast Cancer ......................... 575
Précis: A patient with breast cancer with an activating HER2<sup>650R</sup> mutation who initially responded to neratinib acquired a HER2<sup>T798I</sup> mutation that promoted neratinib resistance, but may retain sensitivity to afatinib.

RESERCH ARTICLES
High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial ............ 586
Précis: In a prospective clinical trial of patients with advanced solid tumors, genomics analyses identified genomic alteration–matched therapies that extended progression-free survival in 33% of patients.
See commentary, p. 552

Prospective Comprehensive Molecular Characterization of Lung Adenocarcinomas for Efficient Patient Matching to Approved and Emerging Therapies .......... 596

NEWS IN BRIEF
Important news stories affecting the community .............. 542

NEWS IN DEPTH
Chromosome Instability Drives Tumor Evolution ............. 546

RESEARCH WATCH
Selected highlights of recent articles of exceptional significance from the cancer literature ...................... 547

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

IN THE SPOTLIGHT
Quantifying the Benefits of Genome-Driven Oncology .......... 552
A.M. Schram and D.M. Hyman
See article, p. 586

Toward Molecularly Driven Precision Medicine in Lung Adenocarcinoma ............ 555
D. Liu, N.I. Vokes, and E.M. Van Allen
See article, p. 596

Targeting BRAF-Mutant Colorectal Cancer: Progress in Combination Strategies ...................... 558
R. Sundar, D.S. Hong, S. Kopetz, and T.A. Yap
See article, p. 610

REVIEWS
Neoadjuvant Trials in ER<sup>+</sup> Breast Cancer: A Tool for Acceleration of Drug Development and Discovery .......... 561
A.L. Guerrero-Zotano and C.L. Arteaga

For more views, research, and reviews, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.
A Phase Ib Dose-Escalation Study of Encorafenib and Cetuximab with or without Alpelisib in Metastatic BRAF-Mutant Colorectal Cancer ...... 610


Précis: The RAF inhibitor encorafenib in combination with the EGFR inhibitor cetuximab is tolerable and achieves responses in patients with BRAF-mutant colorectal cancer with or without PI3Kα inhibition with alpelisib.

See commentary, p. 558

Phase I, Dose-Escalation, Two-Part Trial of the PARP Inhibitor Talazoparib in Patients with Advanced Germline BRCA1/2 Mutations and Selected Sporadic Cancers ................. 620


Précis: The PARP inhibitor talazoparib is well tolerated and has single-agent antitumor activity in patients with breast or ovarian cancer harboring germline BRCA1/2 mutations, and in patients with pancreatic or lung cancer.

Epigenomic Promoter Alterations Amplify Gene Isoform and Immunogenic Diversity in Gastric Adenocarcinoma .................. 630


Précis: Characterization of epigenetic promoter alterations in gastric cancer reveals that alternative promoters upregulate tumor-specific oncogenic isoforms and downregulate immunogenic peptides.

Qamra and colleagues characterized epigenetic promoter alterations in gastric cancer and identified unaltered promoters, somatic tumor-specific promoters gained in tumors, and normal-specific promoters lost in tumors. Overall, 18% of the gastric cancer somatic promoters were alternative promoters that resulted in overexpression of alternative transcript isoforms as well as proteins with altered N-terminal peptide sequences, which may allow for increased proteomic diversity in gastric cancer. Further, alternative somatic promoter usage was linked to decreased tumor immunity. The N-terminal peptides downregulated by gastric cancer somatic promoters elicited immune responses, suggesting that the tumor-specific promoters may decrease tumor immunogenicity. Altogether, these findings identify tumor-specific alternative promoters in gastric cancer that may produce tumor-specific isoforms to promote tumor immune evasion. For details, please see the article by Qamra and colleagues on page 630.