An Acquired HER2 T798I 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 T650I mutation who initially responded to neratinib acquired a HER2 T798I mutation that promoted neratinib resistance, but may retain sensitivity to afatinib.

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

See article, p. 586
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.