Molecular Cancer Therapeutics

Highlights

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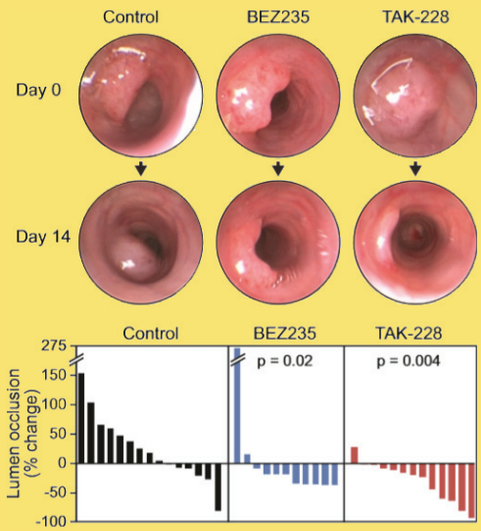
Selected Articles from This Issue



MTORC1/2 inhibition in PIK3CA mutant colorectal cancers

Fricke *et al.* **Page 346**

Molecular alterations activating the PI3K/AKT signaling pathway are common across cancers. The most efficacious means to target these cancers is yet to be established. Clinically MTORC1 inhibitors are often attempted with limited success. Prior work by Fricke and colleagues demonstrated significant benefit of dual PI3K and MTORC1/2 inhibition in this setting. Here they demonstrate using diverse models, including a novel colorectal cancer transgenic mouse model possessing the H1047R hotspot mutation of PIK3CA and organotypic cancer spheroids, that MTORC1/2 inhibition alone is sufficient to induce a treatment response in these cancers, while MTORC1 inhibition is not. These studies indicate the need for further clinical development of MTORC1/2 inhibitors in this setting.

Transcriptional regulation of KDM5B by AKT

Khan *et al.* **Page 356**

Understanding the therapeutic targeting of AKT on chromatin related events is important, as AKT kinase is known to affect chromatin. Khan and colleagues found that AKT inhibition in prostate specific PTEN knockout condition reduces expression of histone demethylases KDM5 family, especially KDM5B expression. Mechanistically, AKT inhibition increases miR-137 levels, which transcriptionally represses KDM5B expression. Overall, they observed that AKT transcriptionally regulates KDM5B mainly via repression of miR-137. Their data identified a novel mechanism by which AKT kinase modulates the cancer epigenome through regulating H3K4 methylation. Further studies will help in designing strategies to enhance the therapeutic efficacy of PI3K/AKT inhibitors.

CSC+/partial-EMT+ CTCs hold prognostic significance in breast cancer

Papadaki *et al.* **Page 437**

In the era of personalized medicine novel prognostic markers are needed to tailor therapy in metastatic breast cancer. Papadaki and colleagues therefore investigated the prognostic impact of different CTC subpopulations characterized according to the detection of stemness and EMT markers, before and after first-line chemotherapy. The detection of CSC+/partial-EMT+ CTCs before chemotherapy was independently associated with poor patient outcome. Their incidence increased post-chemotherapy among non-responders and in patients with HER2-negative tumors. These results highlight the importance of CTC characterization for the identification of aggressive CTC subsets that could be used for risk assessment, patient stratification and therapy monitoring to improve patients' outcome.

Sequencing cfDNA enables immunotherapy response monitoring

Jensen *et al.* **Page 448**

While treatment of cancer patients with immune checkpoint inhibitors has transformed clinical care and produced robust responses, the majority of patients do not respond; therefore, methods are needed help define clinical response. Jensen and colleagues performed low coverage, genome-wide sequencing on cell-free DNA (cfDNA) from a cohort of patients receiving immunotherapy. A new metric, termed the Genome Instability Number (GIN), was applied to the data and shown to differentiate the four major types of response to these treatments. Overall, these data demonstrate the feasibility of utilizing cfDNA as an analyte for noninvasively monitoring therapeutic response to immunotherapy.