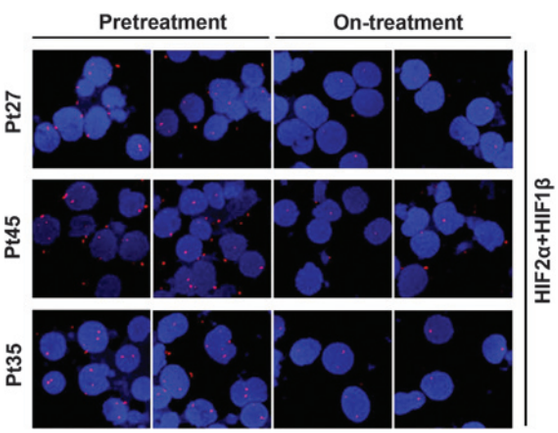
February 15, 2020 | Volume 26 | Number 4

CLINICAL CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Acquired Resistance to HIF-2 Inhibitor in ccRCC Patients



Courtney *et al.* | Page 793

HIF-2 is arguably the most important driver of renal cancer; however, as a transcription factor, HIF-2 has been regarded as undruggable. Courtney and colleagues report a translational companion study to a first-in-class, first-in-human clinical trial of a HIF-2a inhibitor (PT2385) in patients with clear cell renal cell carcinoma (ccRCC). PT2385 inhibited HIF-2 in nontumor as well as tumor tissues, leading to the dissociation of HIF-2 (but not HIF-1) complexes and the inhibition of target genes. A resistance gatekeeper mutation was identified in HIF-2a, which not only validates HIF-2a as the drug target, but also reveals a fundamental core dependency on HIF-2 for tumorigenesis.

Cabozantinib in Uveal Melanoma

Luke *et al.* | Page 804

Uveal melanoma (UM) is a rare subset of all melanomas with particularly poor outcomes in the metastatic setting. Primary UM overexpresses MET kinase, with preclinical studies suggesting potential efficacy of MET blockade. Cabozantinib is a MET/VEGFR2 kinase inhibitor and a randomized discontinuation phase I study of cabozantinib suggested a preliminary benefit in metastatic UM. Luke and colleagues performed a national, rare tumor, randomized phase II study comparing cabozantinib with chemotherapy. Surprisingly, in contrast to the prior phase I study, no confirmed objective responses or differences in progression-free or overall survival were observed between treatment arms. However, it is possible that the efficacy of cabozantinib in UM would be increased by combining this agent with immunotherapy.

Pembrolizumab and Vorinostat in Head and Neck Cancer

Rodriguez *et al.* | Page 837

The combination of epigenetic therapy with checkpoint blockade is seen as an intriguing option for many cancers as a strategy to activate silenced immune checkpoint proteins. Rodriguez and colleagues performed a phase II study combining pembrolizumab and the pan-HDAC inhibitor vorinostat in squamous cell carcinomas of the head and neck (HN) and salivary gland cancer (SGC). An overall response rate of 32% was observed in 25 HN patients, although the toxicity was higher than previously observed with pembrolizumab alone. Although a lower overall response rate of 16% was observed in 25 SGC patients, these responses remain ongoing. Overall, these results are encouraging for the continued study of epigenetic therapy combined with immunotherapy in head and neck cancer.

Therapeutic BRAFV600E Blockade in Neuroendocrine Tumors

Capdevila *et al.* | Page 902

Neuroendocrine cancers are highly heterogeneous and are rare; therefore, molecular profiling has been limited, especially in rare subtypes. Capdevila and colleagues performed a multiomic analysis of colon neuroendocrine carcinomas (co-NEC). A distinct mutational profile to colorectal cancer was observed. Notably, 28% of co-NEC harbored BRAF V600E mutations. Ecorafenib, a BRAF inhibitor, was effective at slowing growth of a co-NEC PDX harboring BRAF V600E, but not a CRC PDX harboring the same mutation. Furthermore, a separate patient harboring this mutation was treated with dabrafenib, another BRAF inhibitor; this patient showed a significant response to treatment. Additional epigenetic analysis revealed methylation and low expression of *EGFR*, the expression of which is a known resistance mechanism for BRAF inhibition. The combination of *BRAF* mutations and low EGFR expression makes patients with co-NEC good candidates for clinical BRAF inhibition.

Clinical Cancer Research

Selected Articles from This Issue

Clin Cancer Res 2020;26:759.