The KRAS\textsuperscript{G12C} Inhibitor MRTX849 Elicits Anti-Tumor Immunity

Briere et al. | Page 975

MRTX849 represented an exciting advancement in KRAS\textsuperscript{G12C} inhibitors. Contrarily, immune checkpoint monotherapy remains limited for most patients of non-small cell lung cancers (NSCLC). Since KRAS\textsuperscript{G12C} mutations are smoking-induced transversion mutations in a high mutation burden setting, Briere and colleagues tested MRTX849’s potential to augment immune checkpoint therapy. Treatment with MRTX849 and anti-PD1 generated durable complete responses in the CT26 Kras\textsuperscript{G12C} model that rejected re-challenge. MRTX849 increased M1-polarized macrophages and reduced intratumoral myeloid-derived suppressor cells in human tumor xenograft, syngeneic, and genetically engineered mouse (GEM) models. Their research demonstrates MRTX849 may enable the durable response of checkpoint inhibitors for a greater number of KRAS\textsuperscript{G12C}-mutant NSCLC patients.

TEAD Inhibitors as Anti-Cancer Therapeutics

Tang et al. | Page 986

Malignant pleural mesothelioma remains a deadly disease with unmet therapeutic needs. Due to the high occurrence of NF2 mutations, the Hippo pathway may be one avenue to meet this need. As YAP and TAZ have no known catalytic activity to inhibit, the focus has been placed on upstream factors such as TEAD. In this study, Tang and colleagues outline potent TEAD inhibitors with excellent pharmacokinetics that inhibited the growth of subcutaneous tumor xenografts. The TEAD inhibitors blocked YAP/TAZ-TEAD promoted gene transcription, TEAD auto-palmitoylation, and the interaction between YAP/TAZ and TEAD. Their work highlights a viable strategy for targeting the Hippo-YAP pathway in malignant mesothelioma and suggests their use in other YAP-driven cancers.

ABBV-167 Converts to Venetoclax in Healthy Volunteers

Salem et al. | Page 999

Venetoclax has categorically low aqueous solubility and permeability. Due to its food effects, it also requires patients to take venetoclax with a meal. In this study, Salem and colleagues characterize the bioavailability and pharmacokinetics of ABBV-167, a phosphate prodrug of venetoclax with significantly increased solubility. Twelve healthy adult female subjects were dosed with ABBV-167 in fasting and fed conditions with either a 100 mg single dose of venetoclax or 100 mg equivalent of ABBV-167. ABV-167 tablets showed increased venetoclax Cmax and AUC\textsubscript{¥} than the venetoclax tablet with a < 0.01% systemic ABV-167 exposure. Therefore, ABV-167 can decrease venetoclax pill burden and improve the quality of life of patients.

TGF-\(\beta\) and PD-L1 Inhibition in the 4-NQO Oral Carcinogenesis

Ludwig et al. | Page 1102

Transforming growth factor-\(\beta\) (TGF-\(\beta\)) is a key regulator in the progression of oral squamous cell carcinoma. Historically, inhibition of TGF-\(\beta\) has shown variable success in clinical trials. Ludwig and colleagues utilize the 4-nitroquinoline 1-oxide (4-NQO) model in immunocompetent C57BL/6 mice to characterize two TGF-\(\beta\) inhibitors. The first, mRER, utilizes the murine sequence of the trivalent TGF-\(\beta\) ligand trap RER. The second (mmTGF-\(\beta\)2-7m) is an engineered TGF-\(\beta\) monomer that lacks the heel helix essential for binding the TGF-\(\beta\) type 1 receptor. Both inhibitors promoted CD8\textsuperscript{+} T cell infiltration into the tumors and enhanced immune checkpoint therapy.
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