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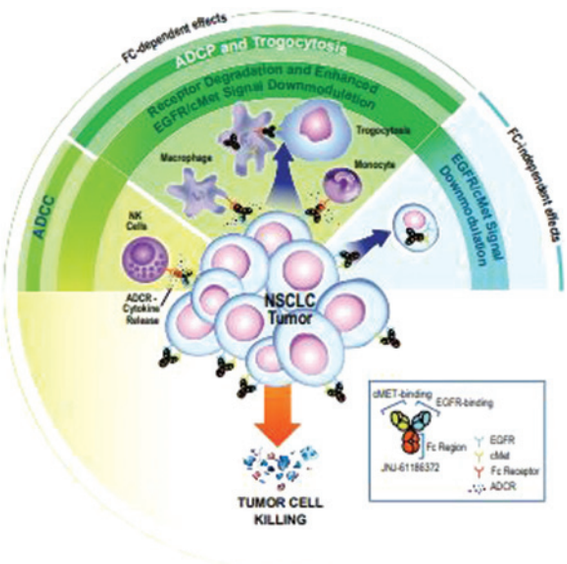
MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Selected Articles from This Issue

Amivantamab Induces EGFR/cMet Downmodulation By Trogocytosis



Vijayaraghavan *et al.* | Page 2044

Amivantamab (JNJ-61186372) is an EGFR/cMet bispecific low fucose antibody that recently received breakthrough therapy designation and is being testing clinically in NSLC patients. In this preclinical study, Vijayaraghavan and colleagues demonstrated that interaction of the Fc domain of amivantamab with monocytes or macrophages induces trogocytosis leading to EGFR and cMet receptor downmodulation and tumor cell death. In addition, they found that macrophages were required for amivantamab anti-tumor efficacy *in vivo*. Thus, this represents a novel Fc-dependent mechanism of action for amivantamab, and highlights trogocytosis as a key mechanism to exploit in designing new antibody-based cancer therapies.

Mechanisms of Antitumor Activity of Novel USP7 Inhibitors

Ohol *et al.* | Page 1970

The deubiquitinase USP7 stabilizes the expression of multiple substrates important in tumor progression, such as MDM2, PIM2 kinase, and MYCN. Therefore, potent inhibitors of USP7 are highly desired. Ohol and colleagues report selective inhibitors of USP7 which impede its binding to ubiquitin and tested the inhibitors on a panel of 430 cancer cell lines. Several TP53 wild-type and a subset of TP53 mutant cell lines were sensitive to USP7 inhibition. Inhibition led to increased levels of p53 in TP53 wild-type cells and upregulated genes repressed by the EZH2-containing PRC2 complex in TP53 mutant cells. In vivo, USP7 inhibition inhibited the growth of TP53 wild-type multiple myeloma tumors as well as TP53 mutant small cell lung cancer tumors. Their results demonstrate USP7 inhibitor candidates viable for continued mechanistic studies and clinical translation.

Antiandrogens Promote the Effects of Radiotherapy in GBM

Werner *et al.* | Page 2163

The androgen receptor (AR) is more highly expressed in glioblastoma (GBM) than in normal brain. Since AR signaling mediates radiation resistance in prostate cancer – as well as other cancers – and radiation resistance is a significant barrier to GBM treatment, we decided to utilize antiandrogens as a radiosensitizing strategy in GBM models. Antiandrogens inhibited the growth of and radiosensitized AR-positive cell lines and patient-derived xenografts. They also delayed repair of radiation-induced DNA damage and blocked adaptive transcriptional programs. Overall, the combination of blood-brain barrier permeable antiandrogens with radiation may represent a promising strategy for the treatment of AR-positive GBMs.

Tumor Mutational Burden and Overall Survival

Riviere *et al.* | Page 2139

High tumor mutational burden is correlated with positive responses to immune checkpoint blockade. Here, Riviere and colleagues determine if TMB serves as an independent prognostic marker in immunotherapy-naïve patients. They outline the parabolic nature of the TMB relationship to overall survival, wherein patients with low or high mutations trend higher survival times while those with intermediate TMB trend lower. As no patients had received immunotherapy, these results demonstrate TMB as a prognostic indicator that is independent of immunotherapy. Potential mediators of the lower overall survival in intermediate TMB patients are discussed and are a pertinent focus for future studies.

Molecular Cancer Therapeutics

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