



Anti-HER2 x PRLR bispecific ADC improves upon the efficacy of HER2 ADC

Andreev *et al.* _____ Page 681

Because of poor lysosomal degradation, HER2-directed antibody-drug conjugate (ADC), T-DM1 is efficient only in patients with high HER2 overexpression. Thus, there is a need for HER2-directed ADCs effective in patients expressing low/moderate levels of HER2. Prolactin receptor (PRLR) is rapidly and constitutively degraded in lysosomes. Cross-linking HER2 to PRLR, using a HER2 x PRLR bispecific ADC, dramatically enhances lysosomal degradation of HER2. Accordingly, anti-HER2 x PRLR bispecific ADC significantly improves upon T-DM1 efficacy in cells expressing intermediate levels of HER2. These results demonstrate that coupling a tumor-specific ADC target to a rapidly internalizing protein may be a useful approach to enhance efficacy of ADCs.

Combining Oncolytic Adenovirus and PS-targeting Antibodies in Pancreatic Cancer

Dai *et al.* _____ Page 662

Delta-24-RGD is an oncolytic virus whose replication depends upon a defective p16/RB/E2F pathway, an alternation found in ~85% of pancreatic adenocarcinomas (PDAC). Dai and colleagues report that exposure of human PDAC cells to Delta-24-RGD induced dramatic cytotoxicity accompanied by robust exposure of phosphatidylserine (PS) on PDAC cell membranes. Sequential combination of Delta-24-RGD followed by a PS-targeting antibody, 1N11, enhanced anticancer activity and favorably altered the innate immune tumor microenvironment. These results suggest that combining these agents sequentially could achieve positive clinical results when used in a molecularly-defined subset of pancreatic cancer.

Anti-KIT treatment promotes antitumor efficacy of immune checkpoint inhibitors

Garton *et al.* _____ Page 671

The presence of mature mast cells within tumor tissue, expression of stem cell factor by many tumor cells and previous reports of interactions between mast cells and other innate immune cells suggest that KIT signaling within mast cells may influence tumor growth. Using a KIT-specific inhibitory antibody in syngeneic mouse tumor models, Garton and colleagues demonstrated that anti-KIT treatment enhanced the anti-tumor activity of immune checkpoint inhibitors (anti-CTLA-4 or anti-PD-1), and promoted immune responses by selectively reducing the immunosuppressive monocytic myeloid-derived suppressor cell (M-MDSC) population. These data provide a rationale for clinical investigation of a KIT-directed antibody in combination with checkpoint inhibitors.

Novel mechanism of action discovered with Chk1 inhibitors

Lee *et al.* _____ Page 694

Using high-throughput profiling of cancer cell lines with candidate anti-cancer agents, Lee and colleagues identified determinants of the response to inhibitors of the Chk1 kinase, a mediator of the DNA damage response. While sensitivity to Chk1 inhibition was previously linked to p53 mutation status, these new findings revealed an unexpected requirement for Chk1 in cells experiencing genotoxic stress after Ras-MEK pathway activation. Chk1 inhibition combined with DNA-targeted chemotherapeutics led to enhanced cell killing in some osteosarcoma, ovarian, and breast cancer cells. These findings provide insight on how to improve the efficacy of Chk1 inhibition in a subpopulation of patients.