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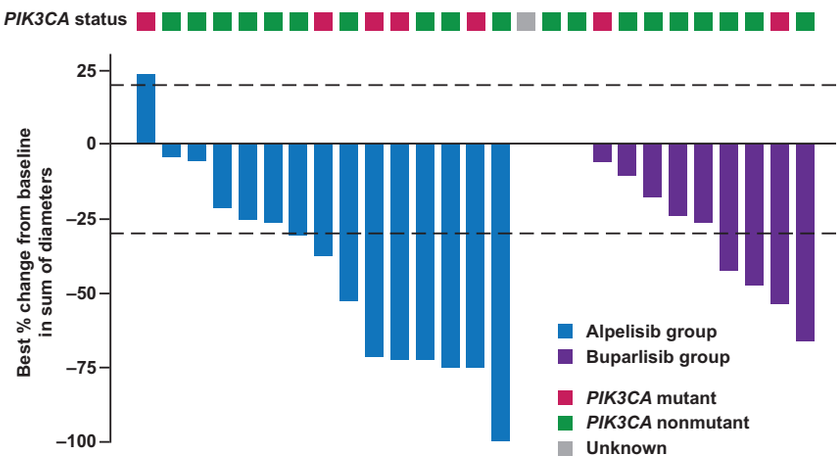
CLINICAL CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue



PI3K Inhibitors in Premenopausal Advanced Breast Cancer

Lu *et al.* | Page 408

HR$^+$, HER2$^-$ advanced breast cancer (ABC) can be challenging to treat in premenopausal women due to endocrine resistance, which can be mediated by the PI3K pathway. Treatment with a PI3K inhibitor (PI3Ki) may be a strategy to overcome endocrine resistance. In a phase Ib trial, Lu and colleagues evaluated alpelisib, a α-selective PI3Ki, or buparlisib, a pan-PI3Ki, plus tamoxifen, in premenopausal women with HR$^+$, HER2$^-$ ABC. With both combinations, the MTD was not exceeded, and safety was consistent with previous reports. Furthermore, improved efficacy was observed with alpelisib+tamoxifen, supporting this combination as a potential treatment option for premenopausal women with HR$^+$, HER2$^-$ ABC.

BMS-986178 in Patients with Advanced Solid Tumors

Gutierrez *et al.* | Page 460

Immune checkpoint inhibitors have aided the treatment of several cancer subtypes, but novel approaches are needed to expand this option to additional cancer subtypes and further improve response rates. In preclinical models, combining checkpoint inhibitors with a murine ligand-blocking OX40 agonist was an effective strategy. In a phase I/IIa study, Gutierrez and colleagues assessed BMS-986178, a fully human immunoglobulin G1 agonist monoclonal antibody, with or without nivolumab and/or ipilimumab in patients with advanced solid tumors. This combination exhibited an acceptable safety profile in this cohort. However, objective response rates were not improved compared with nivolumab with or without ipilimumab. These findings of this study do not support the combination BMS-986178 with nivolumab and/or ipilimumab.

Immunosenescence in NSCLC

Ferrara *et al.* | Page 492

The impact of immunosenescence on anti-PD(L)-1 (ICI) or platinum-based chemotherapy (PCT) in advanced NSCLC patients is unknown. To address this open question, Ferrara and colleagues assessed circulating T-lymphocytes with a senescent immune phenotype (SIP) in patients with advanced NSCLC. SIP was detected at baseline in 28% of advanced NSCLC patients and validated in an independent cohort. In patients treated with ICI, SIP was associated with poor overall response rate, progression-free survival, and overall survival, as well as the presence of hyperprogressive disease. These results may be due to altered circulating immunophenotypes in patients with SIP, including decreased CD8$^+$ T cell proliferation and increased TNF-α and IFNγ production. In contrast, SIP did not correlate with outcomes in patients treated with PCT. These results suggest that SIP may have utility as a circulating biomarker of progression in patients with NSCLC treated with single-agent ICI.

SADA-BsAb Platform for Curative 2-Step PRIT

Santich *et al.* | Page 532

Many cancer therapeutics currently in clinical development will fail, in part due to dose-limiting toxicities and insufficient therapeutic index (TI). Santich and colleagues developed a novel drug-delivery platform to address this need; the platform was designed as a fusion of a self-assembling and disassembling (SADA) domain to a tandem single-chain bispecific antibody (BsAb, anti-ganglioside GD2 x anti-DOTA). SADA-BsAbs were assessed with multiple *in vivo* tumor models using two-step pretargeted radioimmunotherapy (PRIT). SADA-BsAbs allowed for PET-mediated tumor detection and showed antitumor effects in models of small-cell lung cancer and neuroblastoma. Importantly, toxicity to the bone marrow, liver, and kidney was not observed. Based on these data, the SADA platform has entered development for first-in-human clinical trials.