Niraparib for Advanced Breast Cancer with gBRCAm

Turner et al. | Page 5482

Breast cancers in women with germline BRCA1/2 mutations (gBRCAm) are sensitive to platinum-based chemotherapy and PARP inhibition. Niraparib is a potent oral selective PARP inhibitor that has shown clinical benefit in patients with ovarian and prostate cancers. To assess the potential of niraparib in breast cancer, Turner and colleagues conducted a clinical trial to compare the efficacy of niraparib monotherapy compared to chemotherapy monotherapy regimens in women with advanced gBRCAm, HER2-negative breast cancer. The trial was stopped early due to futility and informative censoring in the control arm at an interim analysis and was not able to assess its primary endpoint. However, the trial’s final analysis revealed an objective response rate of 35% in the niraparib arm and 31% in the control arm. Further clinical study of PARP inhibitors in women with gBRCAm breast cancer is warranted.

SBRT and Dual Immunotherapy for Advanced Solid Tumors

Foster et al. | Page 5510

In preclinical studies, CD137 agonism and CSF-1R blockade have each been shown to improve the efficacy of stereotactic body radiotherapy (SBRT) and checkpoint inhibition. To examine the clinical utility of this strategy, Foster and colleagues performed a clinical trial of SBRT with nivolumab combined with uralumab (a CD137 agonist) or cabiralizumab (a CSF-1R inhibitor) in patients with advanced solid tumors. These combinations were, generally, well tolerated. Of the patients evaluable for best overall response, 5% had a complete response, 17% had a partial response, 29% had stable disease, and 49% progressed; abscopal responses were limited. Interestingly, patients with elevated IL-8 prior to SBRT did not respond to treatment. Additional trials are necessary to further evaluate the relationship between IL-8 levels and response to these combinations.

Pexidartinib and Sirolimus to Target Macrophages in Sarcoma

Manji et al. | Page 5519

Pexidartinib is a novel inhibitor of colony-stimulating factor-1 receptor that promotes M1 polarization of tumor associated macrophages (TAMs). Preclinical studies in models of malignant peripheral nerve sheath tumors revealed potential efficacy of pexidartinib when combined with sirolimus. Therefore, Manji and colleagues conducted a first-in-human study to test this combination in heavily treated patients with soft tissue sarcomas. This combination led to acceptable safety and tolerability. Clinical benefit was observed in 12 out of 18 (67%) evaluable subjects, with three patients showing a partial response and nine showing stable disease. Analysis of pre-treatment and on-treatment tissue samples revealed a decrease in M2 TAMs over the course of treatment, without decreased levels of M1 TAMs or CD8+ T cells. A phase 2 study of this combination is underway to further assess the clinical benefit of this treatment strategy.

Copy Number Aberrations Predict pCR in HER2-Positive Breast Cancer

Venet et al. | Page 5607

Despite the identification of several potential biomarkers in HER2-positive breast cancer, response to neoadjuvant therapy is heterogeneous. To better understand the sensitivity and resistance to trastuzumab and lapatinib, Venet and colleagues investigated the role of copy number aberrations (CNAs) in predicting pathological complete response and survival in the NeoALTTO phase III clinical trial. ERBB2 copy number and chromosome 6q23-24 CNAs were identified as predictors of response to neoadjuvant HER2-targeting therapies. However, ERBB2 gene expression outperformed ERBB2 amplification. The role of 6q23-24 CNAs in predicting treatment response, particularly in estrogen receptor-positive and/or wild-type TP53 tumors, warrants further exploration.

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