Zotiraciclib and TMZ in Recurrent High-Grade Astrocytoma

Wu et al. | Page 3298

Zotiraciclib, a cyclin-dependent kinase 9 (CDK9) inhibitor, was previously shown to synergize with temozolomide (TMZ) in preclinical studies. To translate this finding to the clinic, Wu and colleagues performed a clinical trial of zotiraciclib plus TMZ in recurrent high-grade astrocytoma. This two-stage phase I trial simultaneously optimized the dosing and schedule of the combination of zotiraciclib and temozolomide using a BOIN dose-finding design. In addition to establishing the optimal dosing schedule for zotiraciclib and temozolomide, in-depth analyses of zotiraciclib-induced neutropenia, PK/PG and longitudinal symptom burden analysis were performed. The comprehensive information from this multifaceted early-stage investigation supports further clinical trials of this agent.

Selinexor + R-CHOP in Non-Hodgkin Lymphomas

Seymour et al. | Page 3307

Nuclear exporter protein exportin1/XPO1 overexpression in hematological malignancies leads to cytoplasmic mislocalization and functional inactivation of tumor suppressors. Specific inhibitor of nuclear export (SINE) compounds block XPO1-mediated protein transport, retaining tumor suppressors in the nucleus. Seymour and colleagues demonstrate preclinical efficacy and clinical validation of XPO1 inhibitor selinexor in non-Hodgkin lymphoma with a phase I study of R-CHOP plus weekly selinexor as frontline treatment of NHL. This combination was well tolerated, and an MTD was not reached. An ORR of 100% and a CR rate of 90% were observed. Further study of this combination in lymphoma is warranted.

Neoadjuvant PD-L1 Inhibition for Resectable EAC

van den Ende et al. | Page 3351

While neoadjuvant chemoradiation (nCRT) has improved the survival of patients with resectable esophageal adenocarcinoma (rEAC), nearly half of patients succumb to their disease within 5 years. To assess improving this treatment strategy, van den Ende and colleagues assessed the combination of nCRT with PD-L1 inhibition in patients with rEAC. The pathological complete response rate was 25%, but there was no significant improvement in survival compared with nCRT alone. However, potential biomarkers of response were identified. An IFNγ signature was associated with response, while low levels of cytotoxic lymphocytes or the presence of checkpoint inhibition correlated with lack of response. Further study is necessary to clarify the therapeutic potential of this combination in rEAC.

IL-15R Agonist Plus Rituximab for Relapsed/Refractory Indolent Non-Hodgkin’s Lymphoma

Foltz et al. | Page 3339

IL-15 is an important cytokine for the function of NK cells, and IL-15 activation has been proposed as a strategy for immunotherapy. Foltz and colleagues conducted a clinical trial of N-803, an IL-15 receptor superagonist complex, with rituximab in patients with relapsed/refractory non-Hodgkin’s lymphoma. This combination was well tolerated and led to prolonged responses in a subset of patients. N-803 treatment led to the activation of NK cells, CD8+ T cells, and monocytes. Further clinical study of N-803 is needed to identify patient populations for whom this agent will be beneficial, as well as appropriate combination treatments.