Molecular Cancer Therapeutics

Highlights

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Selected Articles from This Issue

Molecular Profiling Advanced Thyroid Carcinomas

Chen *et al.* Page 1575

Chen and colleagues analyzed next generation sequencing of 216 advanced thyroid carcinomas identifying prevalent targetable MAPK pathway activating mutations. Secondary mutations in PIK3CA which may confer resistant to single agent targeted therapy were 8x more frequent compared to the thyroid TCGA. In this retrospective analysis, when targeted therapy to actionable pathway mutations was used, an improved survival was noted in patients with poorly differentiated thyroid carcinomas compared to similar tumors lacking mutations or showing only tumor suppressor mutations. The combined findings lend support for mutational testing across targetable pathways to ultimately benefit patients with advanced thyroid carcinoma through targeted therapy.

Mechanisms of Resistance to Trastuzumab Emtansine (T-DM1)

Breed *et al.* Page 1441

Resistance to T-DM1 poses a challenge in therapy for HER2-positive breast cancer. A better understanding of the molecular mechanisms of primary and acquired resistance to T-DM1 is particularly important for the development of new therapeutic strategies. Breed and colleagues established resistant cells and identified different features of T-DM1 resistant cells. Their findings show the complexities of T-DM1 resistance in that the 2 models they studied showed little overlap in identified resistance mechanisms. The data also suggest possible therapeutic strategies using combinations with inhibitors that target signal transduction resistance pathways for overcoming T-DM1 resistance.

Induced Telomere Damage to Treat Pediatric Brain Tumors

Sengupta *et al.* Page 1504

Brain tumors are the leading cause of cancer-related deaths in children. Hence, there is an unmet need to develop novel therapies to improve outcome. Telomerase-dependent incorporation of 6-thio-dG into telomeres leads to telomere damage and cell death of primary stem-like cells derived from pediatric patients with high-risk brain tumors. The effect of 6-thio-dG is persistent after drug withdrawal. *In vivo*, 6-thio-dG delays tumor growth, crosses the blood-brain barrier and specifically targets tumor cells in the mouse brain. These findings suggest that 6-thio-dG is a promising novel approach to treat therapy-resistant pediatric brain tumors.

Chemotherapy-mediated Enhanced Lung Metastasis of Breast Cancer

Sasaki *et al.* Page 1515

5-fluorouracil (5-FU) is often given to breast cancer patients, after curative surgery of primary tumor to prevent tumor recurrence. However, 5-FU accelerated lung metastasis, when it was administered upon the complete resection of the tumors arising from the orthotopic injection of a mouse breast cancer cell line. The acceleration was associated with enhanced intrapulmonary infiltration of neutrophils, which were attracted by tumor cell-derived chemokines and expressed abundantly prokineticin-2 with a capacity to support the proliferation of prokinectin-2 receptor-expressing breast cancer cells. Thus, adjuvant chemotherapy with 5-FU may have adverse effects on some breast cancer patients.

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