Clinical Cancer Research

Highlights

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Selected Articles from This Issue

	Dose level (mg/kg)				
	0.05	0.06	0.07	0.075	0.085
N	5	3	3	8	4
F14512 AUClast (h*ng/mL)					
Min	38.7	52.7	62.5	36.2	73.7
Median	45.2	83.4	115	142	126
Max	73.8	102	261	224	152
F16490 AUClast (h*ng/mL)					
Min	8.89	27	21.4	13.9	27.7
Median	12.6	28.3	25.2	36.2	35.2
Max	20.5	29.9	38.5	42.7	40.6

F14512 Dose-Escalation Trial in Spontaneous Canine Lymphoma

Tierny *et al.* Page 5314

Although preclinical mice models often fail to accurately predict the antitumor activity and toxicity of new therapies, comparative oncology has revealed that spontaneous lymphomas in dogs share many similarities with their human counterparts. Tierny and colleagues designed a dose escalation and biomarkers trial in dogs with naturally occurring lymphoma and demonstrated that F14512, a new vectorized anticancer drug currently in Phase I/II clinical trial in patients, can be safely administered to dogs resulting in strong therapeutic efficacy. This study has translational relevance for both the treatment of lymphomas in humans and the ongoing clinical development of F14512.

BRAF Inhibitors and GI Polyps

Amaravadi *et al.* Page 5215

BRAF inhibitors (BRAFi) can promote the growth of cutaneous squamous cell carcinomas with MAPK pathway mutations. Amaravadi and colleagues report that in a series of BRAF mutant melanoma patients treated for >2 years with a BRAFi, multiple gastrointestinal polyps, including tubular colonic adenomas and hyperplastic gastric polyps, were observed. Genotyping identified no MAPK pathway mutations, but tubular adenomas had *APC* mutations. Treatment of *APC Min* +/− mice with BRAFi significantly increased polyp number compared to control, suggesting BRAFi can promote the growth of gastrointestinal polyps. Adenocarcinoma was not identified even in rechallenged patients, so the potential for accelerated polyposis should not preclude using BRAFi in BRAF mutant melanoma.

Activation of PIK3CA in Latin American Cervical Cancer

Lou *et al.* Page 5360

Invasive cervical cancer patients in Guatemala and Venezuela have an average age at diagnosis of 50 years and 5.6 children each. Although HPV16 and HPV18 are the predominant types in tumors, there is considerable viral diversity in Guatemala. Sequencing of tumors from these countries and Mexico reveals frequent mutations in the helical domain of the PIK3CA gene; however, the E542K and E545K mutations do not activate AKT. Therefore therapies targeting PIK3CA directly or the as-yet-undescribed downstream targets are required.

Transcriptomic Profiles of Metastatic Breast Cancer

McBryan *et al.* Page 5371

Distant metastases are frequently drug resistant and are heavily implicated in breast cancer mortality. McBryan and colleagues sought to characterise the global expression changes occurring with metastatic disease progression in the endocrine-resistant setting. Using RNAsequencing technology, the transcriptomes of sequential primary, nodal and liver metastatic tumors were profiled from tamoxifen-treated patients. Patient heterogeneity was evident as was a common need for tumor cells to adapt their cell-cell communications to facilitate successful colonisation of distant host organs. These findings emphasise the need for re-evaluation of tumor biology and ongoing personalized medicine throughout disease management.

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