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Titel des Beitrags:
Targeting Fibroblast Growth Factor Receptor 1 for Treatment of Soft-Tissue Sarcoma.

Abstract:
Purpose: Altered FGFR1 signaling has emerged as a therapeutic target in epithelial malignancies. In contrast, the role of FGFR1 in soft-tissue sarcoma (STS) has not been established. Prompted by the detection and subsequent therapeutic inhibition of amplified FGFR1 in a patient with metastatic leiomyosarcoma, we investigated the oncogenic properties of FGFR1 and its potential as a drug target in patients with STS.

Experimental Design: The frequency of FGFR1 amplification and overexpression, as assessed by FISH, microarray-based comparative genomic hybridization and mRNA expression profiling, SNP array profiling, and RNA sequencing, was determined in three patient cohorts. The sensitivity of STS cell lines with or without FGFR1 alterations to genetic and pharmacologic FGFR1 inhibition and the signaling pathways engaged by FGFR1 were investigated using viability assays, colony formation assays, and biochemical
Results: Increased FGFR1 copy number was detected in 74 of 190 (38.9%; cohort 1), 13 of 79 (16.5%; cohort 2), and 80 of 254 (31.5%; cohort 3) patients. FGFR1 overexpression occurred in 16 of 79 (20.2%, cohort 2) and 39 of 254 (15.4%; cohort 3) patients. Targeting of FGFR1 by RNA interference and small-molecule inhibitors (PD173074, AZD4547, BGJ398) revealed that the requirement for FGFR1 signaling in STS cells is dictated by FGFR1 expression levels, and identified the MAPK-ERK1/2 axis as critical FGFR1 effector pathway. Conclusions: These data identify FGFR1 as a driver gene in multiple STS subtypes and support FGFR1 inhibition, guided by patient selection according to the FGFR1 expression and monitoring of MAPK-ERK1/2 signaling, as a therapeutic option in this challenging group of diseases. Clin Cancer Res; 23(4); 962-73. ©2016 AACR.