Molecular driver alterations and their clinical relevance in cancer of unknown primary site.

Abstract:
Cancer of unknown primary (CUP) is defined as metastatic solid malignancy where no primary tumor is detected despite appropriate staging. About 90% of CUP represent adenocarcinoma or undifferentiated carcinoma. Since therapy regimens are only modestly effective, identification of the molecular landscape of these neoplasms might be a promising approach to direct CUP therapy and aid in tumor classification. We screened a cohort of 128 patients with adenocarcinoma or undifferentiated carcinoma meeting the definition of CUP. Massive parallel multigene sequencing of 50 genes, which had been selected due to their relevance as oncogenic drivers or druggable molecular targets could ultimately be performed on samples from 55 patients for whom complete clinical datasets were also available. Overall, 60 tumor-specific mutations and 29 amplifications/deletions, as revealed by coverage analysis, were detected in 46 cases (84%). The most frequently mutated genes were TP53 (30 cases, 55%), KRAS (9 cases, 16%), CDKN2A (5 cases, 9%), and SMAD4 (5 cases, 9%). The most frequently deleted gene was CDKN2A (8 cases, 15%). KRAS and CDKN2A mutations significantly correlated with poor progression-free survival (PFS) and, in case of KRAS, overall survival (OS). Wildtype TP53 and female sex
defined a relatively favorable category, with favorable PFS and OS. 8 cases (15%) harbored mutations that may be targetable by currently approved drugs. Taken together, Mutations of relevant driver genes are present in the vast majority of CUP tumors. Some of them impact on prognosis and a subset is putatively druggable.