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MUTATIONS IN KRAS AND DNMT3A ARE NOT RELATED TO DEPENDENCY IN ESTABLISHED TUMORS, IN PDX ACUTE LEUKEMIA MODEL IN VIVO

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The role of oncogenic mutations was not clear in patients' established tumors. We studied the dependency of frequently mutated genes in established AML in vivo using genetic engineered PDX models. A CRISPR/Cas9 library was tested in 2 PDX models in vivo. In hit validation experiments, knockout of NPM1 abrogated in vivo growth in all PDX models, reproducing the known common essential function. KRAS proved an essential function in PDX models with and without a KRAS mutation, suggesting that AML patients might beneﬁt from treatment inhibiting KRAS, no matter with or without KRAS mutation. DNMT3A were not essential in vitro in AML cell lines. But knockout DNMT3A vanished cells in certain PDX models in vivo and was unrelated to whether mutated or not. These data highlight the complementary use of PDX models to study gene dependencies. We conclude that both KRAS and DNMT3A harbor an essential function in certain patients' established AML in vivo, although independently from whether there is a mutation or not. Warranting veriﬁcation in additional patient samples, oncogenes and tumor entities, our data indicate re-consider basic principles of decision-making in Molecular Tumor Boards.