cabozantinib during the first 8 weeks (8W-DI; expressed a ratio between the cumulative dose actually received and the maximum theoretical dose). The 8W-DI was correlated with disease control at the first imaging, progression-free survival (PFS), and overall survival (OS). To assess the effects of dose reductions after the first 8 weeks on the OS, multivariable time-dependent Cox regressions were carried out.
Results: Disease control rate was 63%. The median PFS and OS were and 5.2 and 11.3 months, respectively. The majority of patients (n=45) received the full 60mg daily dose during the first 8 weeks (median 8W-DI 100%, IQR 70-100%). A 90% 8W-DI (equating to a mean 54 mg/daily dose) was chosen for further analysis. A high 8W-DI did not correlate with worse radiological response (OR 1.72, 95% CI 0.72-4.15), PFS (HR 1.39, 95% CI 0.87-2.22), or OS (HR 1.06, 95% CI 0.61-1.83). Sixty-one (63.5%) and 19 (19.8%) patients permanently reduced cabozantinib to 40 and 20 mg/day to manage AEs. In the time-dependent analyses, reduction to 40 mg and 20 mg were associated with increased OS (HR 0.47, 95% CI 0.29-0.76; HR 0.41 95% CI 0.21-0.80, respectively].
Conclusions: Our results underline the importance of tailored dosing of cabozantinib. Dose adjustements to manage AEs should not automatically induce fears of reduced efficacy, as higher 8W-DI were not related to better outcomes while dose reductions to manage AEs were associated with increased OS.

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F-06

Targeting the AAA+ ATPase RuvBL1 reduces mTOR-driven NASH-HCC development in mice

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Background and Aims: RuvBL1 is a highly conserved AAA+ ATPases. It is deregulated in various human cancers and its expression correlates with a worse prognosis in HCC patients. We previously found that liver haploinsufficiency of RuvBL1 impairs the PI3K/Akt/mTOR pathway. We thus hypothesized that genetic targeting of RuvBL1 could reduce mTOR driven hepatocarcinogenesis.
Method: $Pten^{hep-/-}$ and $Ruvbl1^{hep+/-}$ mice were crossed to generate $Pten^{hep-/-}Ruvbl1^{hep+/-}$ mice. NASH was assessed by histology at 12 weeks of age. Metabolic and inflammatory markers were evaluated by qPCR and IHC. mTOR pathway was analysed by WB of liver lysates. PPARalpha activity was evaluated by luciferase reporter assay. RuvBL1 interactome was evaluated by MS proteomics of RuvBL1-IP. HCC development was assessed by macroscopic tumour count and by histology. AML-12 PTEN KO cells were generated by CRISPR-Cas9 genome editing.
Results: $Pten^{hep-/-}Ruvbl1^{hep+/-}$ developed significantly less steatosis, fibrosis, and inflammation compared to $Pten^{hep-/-}$ mice. The mTOR-driven lipogenic targets were similarly expressed in the two mice models. However, Ppara and its target CPT1 was increased in $Pten^{hep-/-}Ruvbl1^{hep+/-}$. Inhibition of RuvBL1 activity by CB-6644 increased PPARalpha transcriptional activity in AML-12 hepatocytic cell line. Analysis of RuvBL1-IP in AML-12 and Hepa1-6 cells revealed that RuvBL1 interacts with members of the lysosomal AMPK complex. Furthermore, p-AMPK and p-RAPTOR were increased in $Pten^{hep-/-}Ruvbl1^{hep+/-}$ compared to $Pten^{hep-/-}$mice. The spontaneous and insulin-induced accumulation of lipid droplets in PTEN KO AML-12 cells was completely abrogated by RuvBL1 inhibition with CB-6644. Finally, $Pten^{hep-/-}Ruvbl1^{hep+/-}$mice aged to 15 months showed better survival than $Pten^{hep-/-}$ which developed significantly more HCC and of higher grade. qPCR analysis showed a significant upregulation of key lipolytic genes, such as Cpt1a, Acadl, Acadvl and Ppara, in $Pten^{hep-/-}Ruvbl1^{hep+/-}$ at 15 months of age.
Conclusion: RuvBL1 targeting reduces mTOR hyperactivation hampering NASH-HCC progression in $Pten^{hep-/-}$ mice, likely promoting the switch from mTOR-driven lipogenesis to AMPK-induced fatty acid catabolism.

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F-07

Altered fatty acid metabolism rewires cholangiocarcinoma stemness features

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Introduction: Metabolic reprogramming of cancer stem cells (CSC) has been intensively investigated in recent years. Nevertheless, the role of lipids in the control of tumor-stemness in intrahepatic cholangiocarcinoma (iCCA) remains to be elucidated.
Aim: Our study aimed to explore the contribution of fatty acids (FA) in the regulation of stem-like features in iCCA.
Materials and Methods: iCCA cells grown as 3D spheres (SPH) were used to enrich for stem-like cells. Parental cells grown as monolayer (MON) were used as control. Triglyceride (TG) composition and de novo synthesis products were quantified by LC-MS/QTOF and used for desaturation index calculation. NOD/SCID mice were injected with iCCA-SPH cells and treated with the fatty acid synthase (FASN) inhibitor orlistat. Five-year overall survival was analyzed in 68 patients with iCCA, sub-grouped based on FASN expression.
Results: In vitro exposure of iCCA-MON cells to oleic or palmitoleic monounsaturated FA (MUFA) enhanced stem-like features at both functional (resistance to antineoplastic drugs, spherogenicity) and molecular level (expression of stemness associated genes). Metabolically, iCCA-SPH retained superior unsaturated TG-content in accordance with upregulation of several genes involved in FA metabolism compared to MON. In patients with iCCA, tissue expression levels of FASN, a key gene involved in FA synthesis, correlated with overall survival. In vitro FASN inhibition by orlistat or its depletion by siRNA decreased sphere-forming ability and expression of stem-like markers. In a murine xenograft model