36P – The point mutation p.C382R in the transmembrane domain of FGFR2 is oncogenic and leads to a complete functional remission after treatment with pemigatinib in cholangiocarcinoma

A new promising oncogenic target (p.C382R) for treatment with pemigatinib in patients with cholangiocarcinoma

36 P

SCAN ME

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ABSTRACT

- The following report describes a patient with an intrahepatic cholangiocarcinoma (iCC) and detected FGFR 2 p.C382R mutation in liquid as well as tissue-based biopsies (no germline mutation detected).
- Treatment with pemigatinib results in a complete functional remission in FDG-PET/CT.
- This case illustrates that p.C382R is an oncogenic target and should be treated with pemigatinib.

KEYFINDINGS

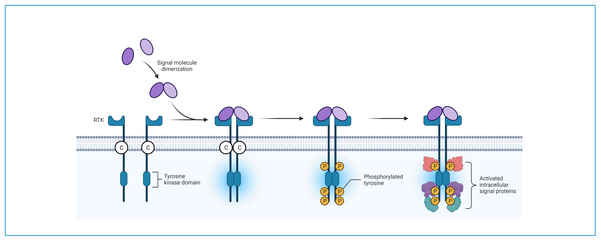
- p.C382R mutation of the FGFR2 receptor in iCC is sensitive to targeted therapy with pemigatinib and leads to a complete functional remission in a patient with a coincidental PTEN loss of function.
- Multigene sequencing should be performed in every patient with advanced iCC since not only FGFR fusions/rearrengements but also other gene alterations may have oncogenic potency and respond to a targeted treatment.

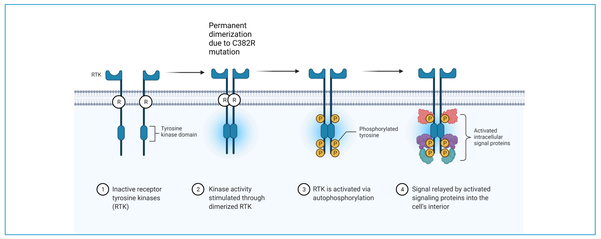
CLINICAL CASE

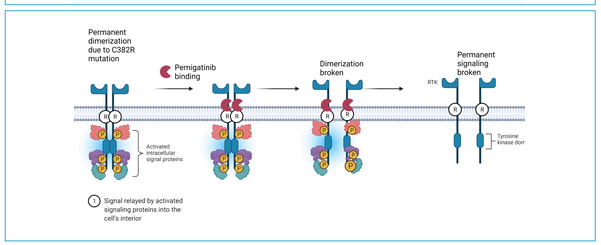
- 74-year-old male was diagnosed with iCCA in liver segments VII and VIII with infiltration of the hepatic veins and inferior vena cava.
- First-line chemotherapy with gemcitabine 800 mg/m2, cisplatin 25 mg/m2 and nab-paclitaxel 100 mg/m2 day one and eight qd22 was initiated.
- After the fifth treatment cycle, progressive disease (PD) was observed.
- Biopsies of the liver lesions as well as a liquid biopsy were taken and a hybrid capture-based NGS service platform (FoundationOne CDx, Penzberg, Germany) was performed for the tissue biopsies and FoundationOne Liquide CDx for the blood samples.

INTRODUCTION

- FGFR2 mutations may cause uncontrolled activation of the FGFR2 signaling pathway independent from ligand binding.
- Pemigatinib is approved for FGFR2 fusion and rearrangements[1].
- In vivo data suggest that FGFR2 point mutations might also be oncogenic[2,3].







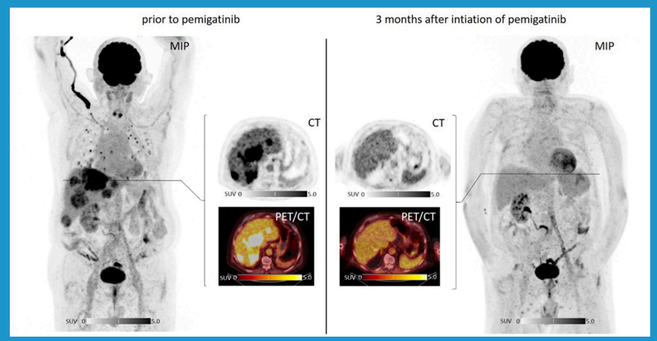


Fig. 1 Display of complete metabolic remission three months after initiation of pemigatinib. Given are maximum intensity projections (MIP; outer columns) as well as transaxial slices of computed tomography (CT, inner upper column) as well as fused positron emission tomography/computed tomography (PET/CT; inner lower column). While the patient initially presented with multiple pulmonary as well as hepatic metastases, follow-up imaging revealed complete metabolic resolution of all lesions.

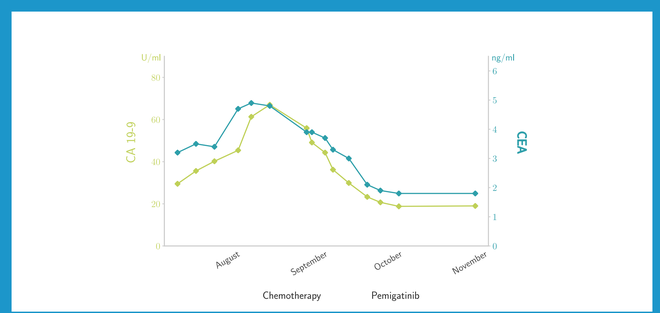


Fig 6: Shows the development of tumor markers during the clinical course and treatment. During therapy with pemigatinb, a significant decrease in the CA19-9 and CEA was observed resulting in a plateau representing complete remission.

DISCUSSION & CONCLUSION

- p.C382R mutation of the FGFR2 receptor is clinically relevant as it is sensitive to targeted therapy with pemigatinib and led to a complete functional remission.
- The report supports the importance of the transforming activity and drug sensitivity of in vitro assay as described by Nakamura for in vivo clinical application[3].
- Multigene sequencing should be performed in every patient with advanced iCC since not only FGFR fusions/rearrangements but also other gene alterations may respond to a targeted treatment.

HISTORIC PATIENT FINDING		ORD-308-01 VAF%
Blood Tumor Mutational Burden		3Muts/Mb
Microsatelite status		MSI-High Not Detected
Tumor Fraction		Cannot Be Determined
PIK3CA	H1047R	0.16%
ARIDA1A	A45fs*6	6.6%
FGFR2	C382R	8.1%
MTOR	S2013G	0.14%
PTEN	deletion exons 3-8	0.57%

GENE	PROTEIN EFFECT	CNA	VAF
FGFR2	C382R	_	76.48%
ARIDA1A	A45FS*6	_	67.81%
MYC	Amplification – equivocal	6	
PARP1	Amplification – equivocal	6	

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Acknowledgement

Disclosures: The authors declare no competing interests.

Ethical standards: All procedures performed in studies involving human particpAants or on human tissue werein accordance with the ethical standards of the institutional and/or national research committee andwith the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained the participant included in the study.

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