The impact of alterations in cancer driver genes and other potentially targetable mutations on progression and overall survival in patients with intrahepatic cholangiocarcinoma (iCCA) treated on the randomised phase III multicentre BILCAP clinical trial.

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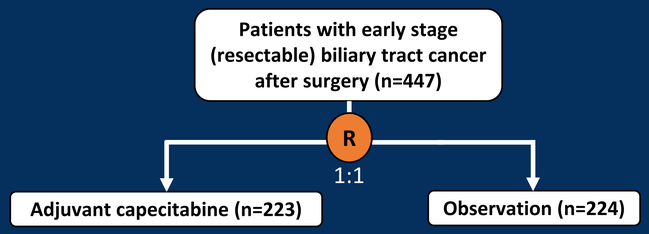
Introduction

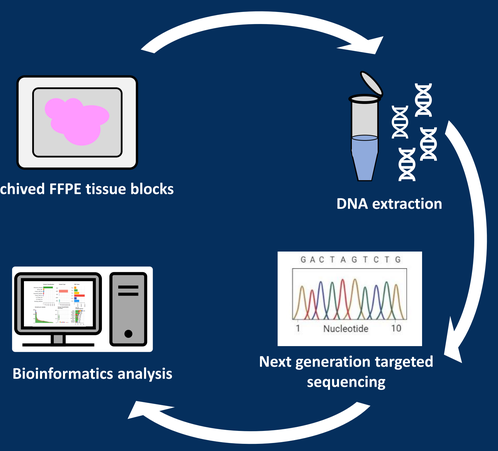
The BILCAP clinical trial established adjuvant capecitabine as standard of care after biliary tract cancer resection.



We aimed to investigated the link between cancer driver genes and other potentially targetable mutations in patients with intrahepatic cholangiocarcinoma enrolled on BILCAP and progression free and overall survival.

Methods

Archived fixed formalin (FFPE) tissue samples were collected from consented BILCAP patients.



These samples underwent DNA and RNA extraction followed by low-pass whole genome sequencing (lp-WGS), targeted gene sequencing (TGS) and RNA sequencing (RNAseq) for copy number (CN) analysis, mutation analysis and gene fusion analysis.

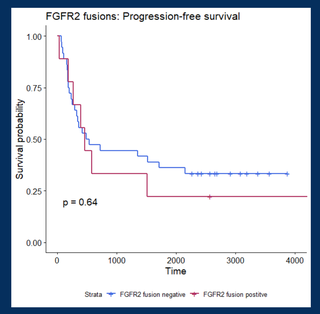
Results

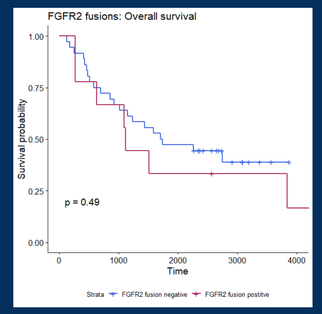
So far, 45 patients with intrahepatic cholangiocarcinoma have undergone low-pass whole-genome sequencing and RNA sequencing, of whom 36 also have also undergone targeted gene sequencing. Pathogenic mutations in FGFR2 included F276C and pathogenic IDH1 mutations included 2 R132G mutations, and one mutation each in R132S and R132L.

Alteration	Total number	Percentage altered (%)
FGFR2 gene fusions	9	20.0
NTRK1 fusions	3	6.7
FGFR1 fusions	3	6.7
FGFR3 fusions	2	4.4
ROS1 mutations	12	33.3
MET mutations	10	27.8
ALK mutations	7	19.4
IDH1 pathogenic mutations	4	11.1
FGFR2 pathogenic mutations	1	2.7
NTRK1 amplification	9	20.0
ERBB2 amplification	8	17.8
MET amplification	7	15.6
Regulatory T-cell fraction > 0.2	3	6.7
CD4 T-cell fraction > 0.2	3	6.7

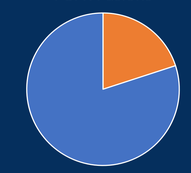
Most of the alterations investigated did not significantly affect overall survival or progression-free survival.

In particular, FGFR2 fusions did not significant affect overall survival or progression-free survival.

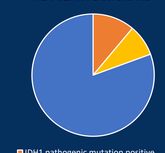




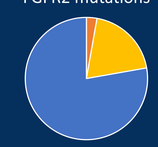
FGFR Fusions



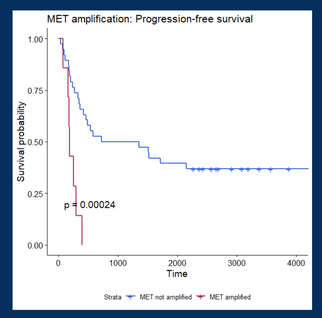
IDH1 mutations

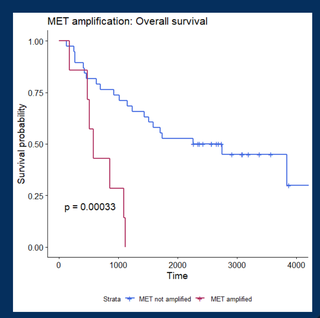


FGFR2 mutations



However, FGFR3 fusions significant decreased overall survival (although n was only 2 in this cohort) and amplification of MET (where there were > 4 copies regardless of ploidy) significantly reduced both progression-free survival and overall survival.





Conclusions

The BILCAP cohort shows a wide variety of driver and potentially targetable mutations in unselected iCCA patients, comparable to similar datasets.

Patients with MET amplification had significantly shorter OS, and MET amplification had significantly reduced OS and PFS.

MET amplification and FGFR3 fusions may be important indicators in determining prognosis and could provide attractive targets for future targeted anti-cancer therapy in iCCA.