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The impact of alterations in cancer driver genes and other potentially targetable mutations on progression and overall survival in patients with biliary tract cancer treated on the randomised phase III multicentre BILCAP clinical trial

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Background

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

Methods

Translational work from this clinical trial involved collecting archived fixed formalin tissue from consented BILCAP patients and carrying out low-pass whole genome (lp-WGS), targeted gene (TGS) and RNA sequencing (RNAseq) for copy number (CN), mutation and gene-fusion analysis. In total, 98 patients underwent RNAseq, 95 of 98 underwent lp-WGS and 39 of 98 underwent TGS.

Results

47 patients had intrahepatic cholangiocarcinoma, 47 patients had gallbladder cancer, 2 patients had perihilar cholangiocarcinoma, and 2 patients had distal cholangiocarcinoma. 62 (63.3%) patients were female, and 48 (49.0%) received adjuvant capecitabine. FGFR2 gene fusions were present in 24 patients (24.5%), as were fusions in NTRK1 (n=4, 4.1%), FGFR1 (n=4, 4.1%), FGFR3 (n=2, 2.0%) and FGFR4 (n=2, 2.0%). Known pathogenic mutations were seen in IDH1 (n=4, 10.3%, total number of mutations=8, 20.5%), IDH2 (n=1, 2.6%, total n=6, 15.4%), and FGFR2 (n=1, 2.6%, total n=7, 17.9%). Commonly amplified (CN ≥ 4) genes included NTRK1 (n=28, 29.5%), ERBB2 (n=27, 28.4%) and MDM2 (n=20, 21.1%) with MYC (n=19, 20.0%), EGFR (n=16, 16.8%) and MET (n=15, 15.8%) also amplified. Nearly all the alterations investigated did not significantly affect recurrence risk (PFS) or overall survival (OS), including FGFR2 fusions (OS hazard ratio (HR) 1.11 p=0.762, PFS HR 1.10 p=0.763). However, the presence of amplified EGFR (CN ≥ 4) significantly decreased both OS (HR 5.40 p=0.01) and PFS (HR 3.44 p=0.04).

Conclusions

The BILCAP cohort shows a wide variety of driver and potentially targetable mutations in unselected biliary tract cancer patients, comparable to similar datasets. Of note, patients with EGFR amplification had significantly reduced OS and PFS. This indicates that EGFR amplification may be an important indicator in determining prognosis and could provide an attractive target for future targeted anti-cancer therapy in biliary tract cancer.

Clinical trial identification

EudraCT 2005-003318-13.

Legal entity responsible for the study

The authors.

Funding

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Disclosure

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