



THE UNIVERSITY *of* EDINBURGH
Centre for Inflammation Research

Cholangiocarcinoma – recent advances and personalised pathology

Dr Tim Kendall

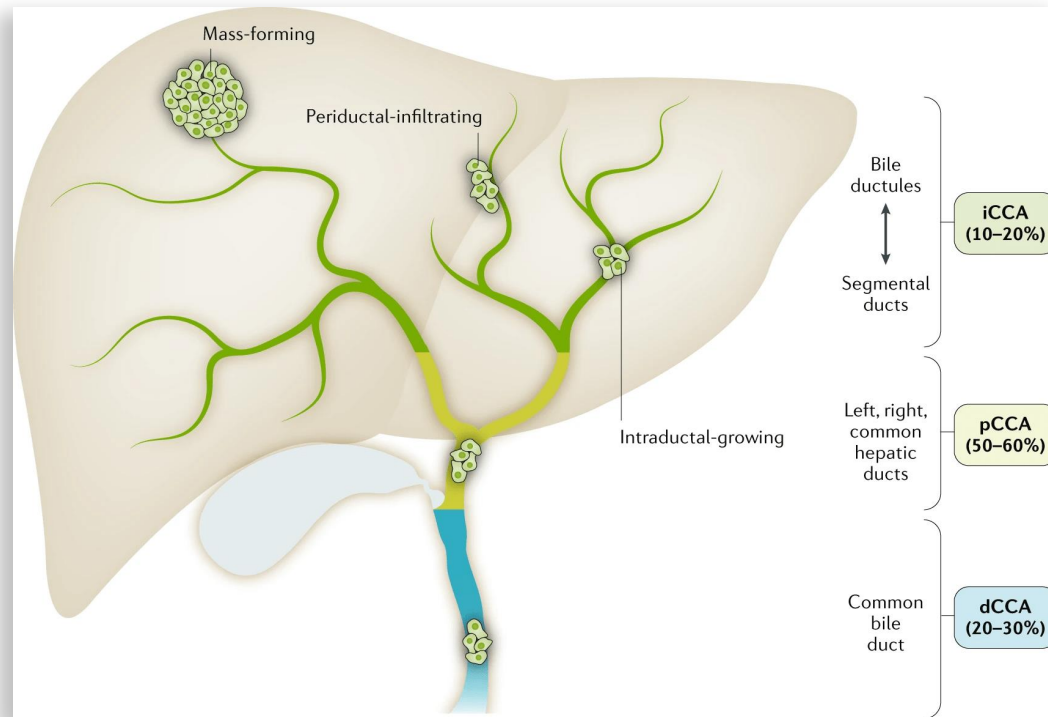
Centre for Inflammation Research

UKLPG Annual Liver Update meeting, 9th December 2021

Relevant disclosures

Speaker's fee – Incyte Corp

Introduction



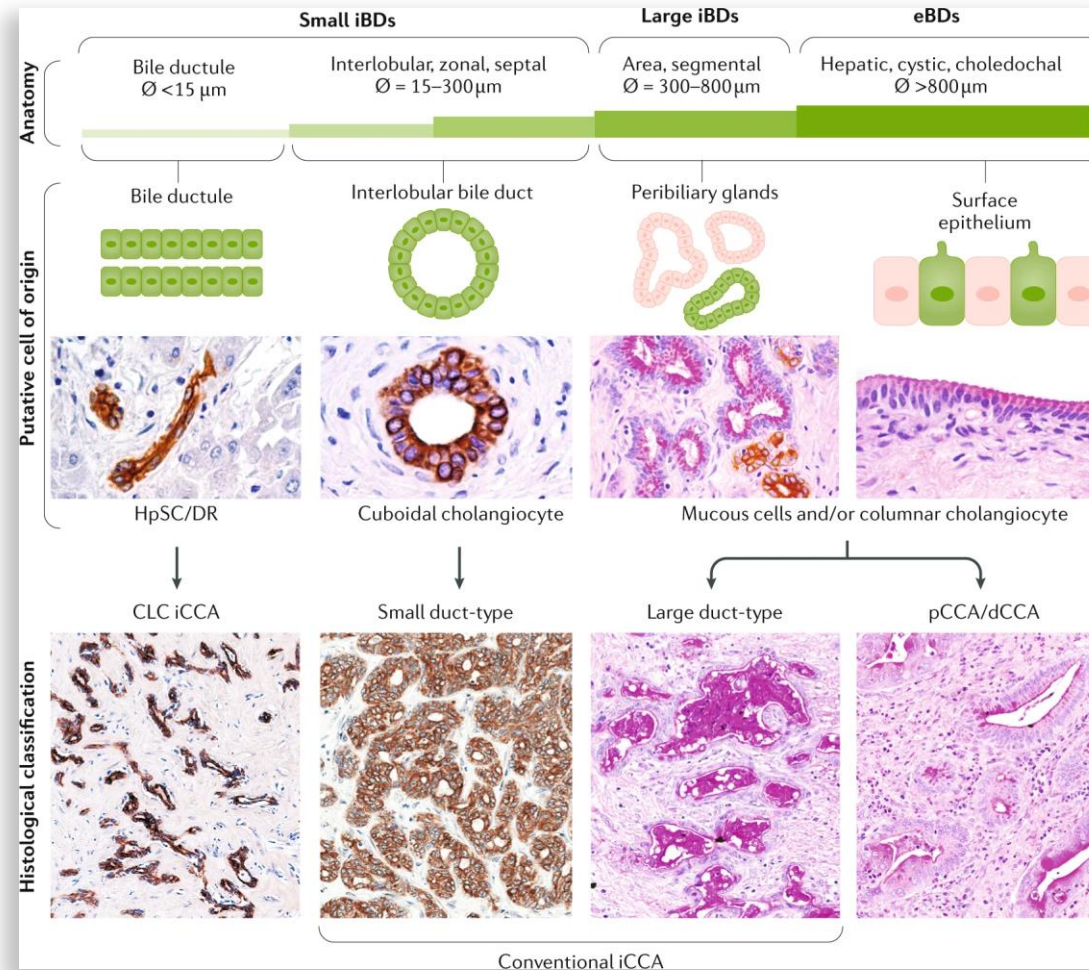
Bañales et al. NRGH, 2020. PMID: 32606456

2nd most common hepatobiliary malignancy
intrahepatic (iCCA) and extrahepatic

extrahepatic subdivided into perihilar (pCCA) and distal (dCCA) – reportedly in iCCA but ICD/ICD-O coding issues mean pCCA underestimated

combined 5-year survival 5–15%

Site and morphology



Bañales et al. NRGH, 2020. PMID: 32606456

Current treatments – surgery

surgery only curative treatment

only a minority of patients suitable for surgery at presentation

after surgery, high risk of relapse

Current treatment – pre-personalisation

adjuvant treatment –

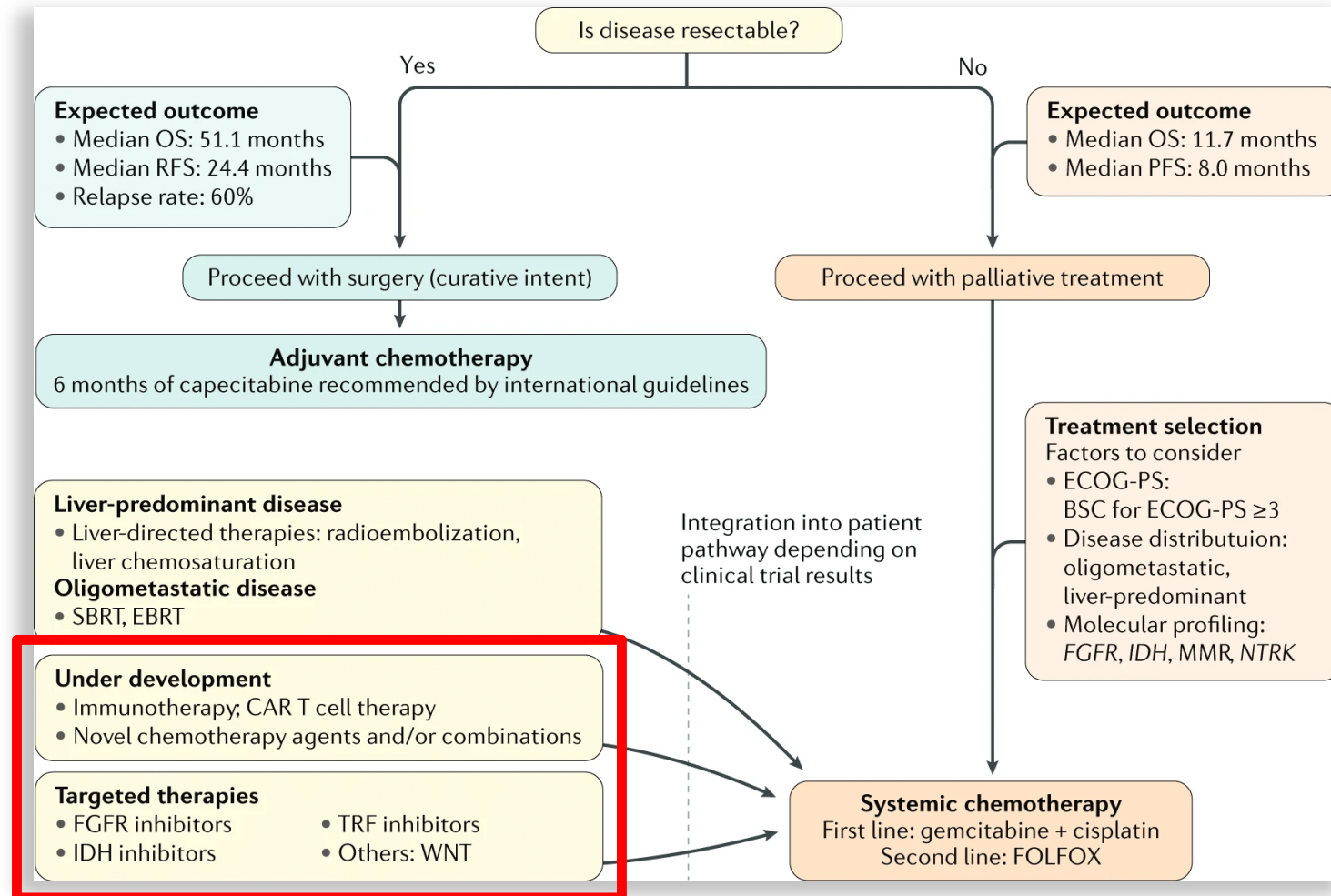
capecitabine following curative resection (BILCAP, PMID: 30922733)

advanced disease (palliative) therapies –

1st line: cisplatin/gemcitabine (ABC-02, PMID: 20375404)

2nd line: 5-fluorouracil and oxaliplatin (ABC-06, PMID: 33798493)

Current treatment summary flow chart

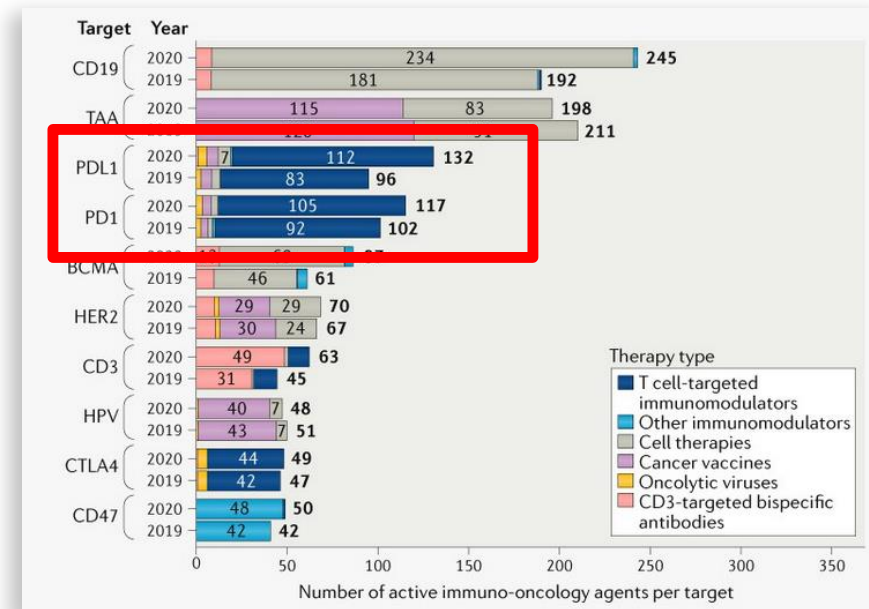


Bañales et al. NRGH, 2020. PMID: 32606456

Immuno-oncology treatments



Pan et al, JHO, 2020. PMID: 32245497



Upadhaya et al, NRDD, 2020. PMID: 32948858

IO in cholangiocarcinoma

currently immunotherapy (pembrolizumab) only for patients with MMR and MSI

TOPAZ-1 –

phase III trial of durvalumab (mAb binding PD-L1) or placebo with CisGem as 1st line in advanced disease

improvement in OS, PFS and overall response rate, results announced late October 2021

likely to become new standard of care

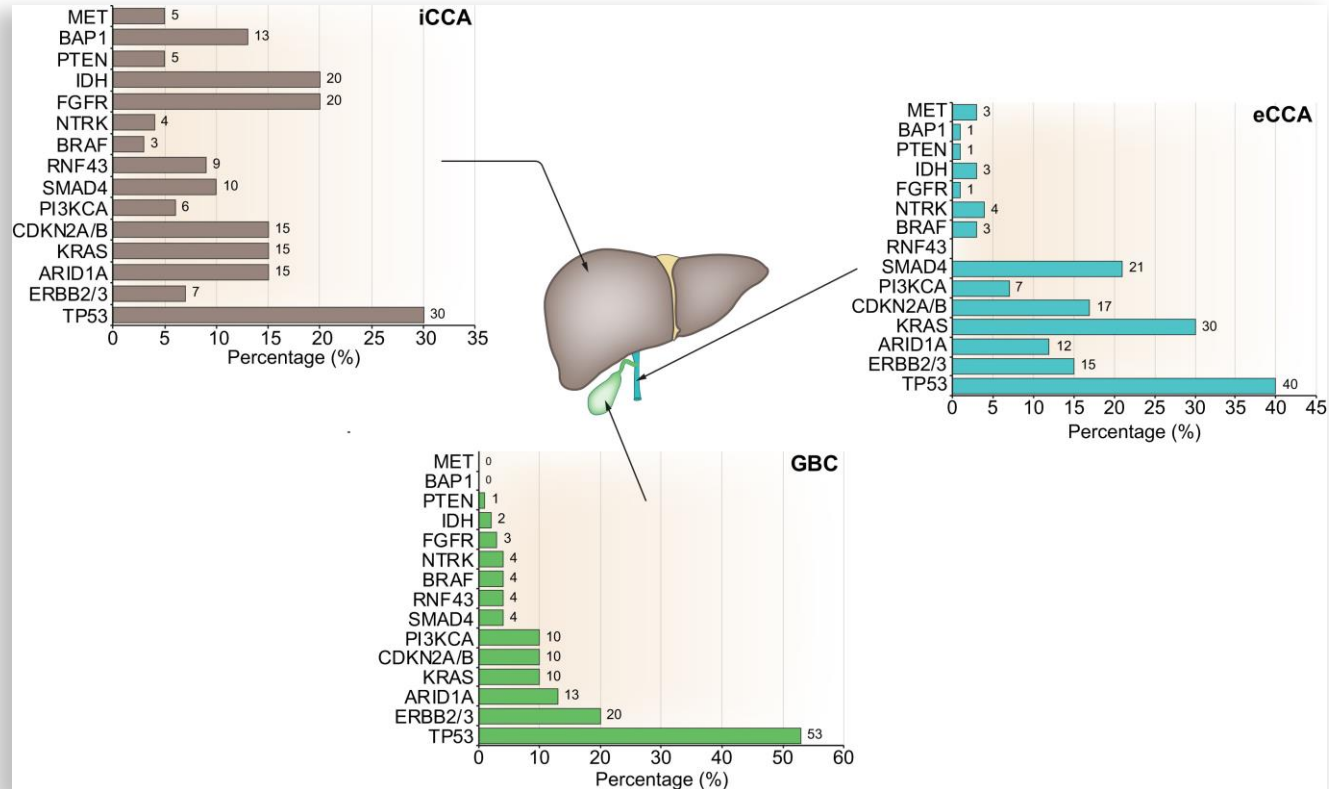
Precision and actionable mutations

studies on unselected populations manipulating multiple pathways showed minimal benefit

more recent understanding of the role of mutations in pathogenesis has informed development of targeted therapies

identification of mutations defining targetable aberrant pathways allows personalisation, increasing chance of trial and treatment success

Mutational landscape



differences in mutational profile between biliary tract cancers

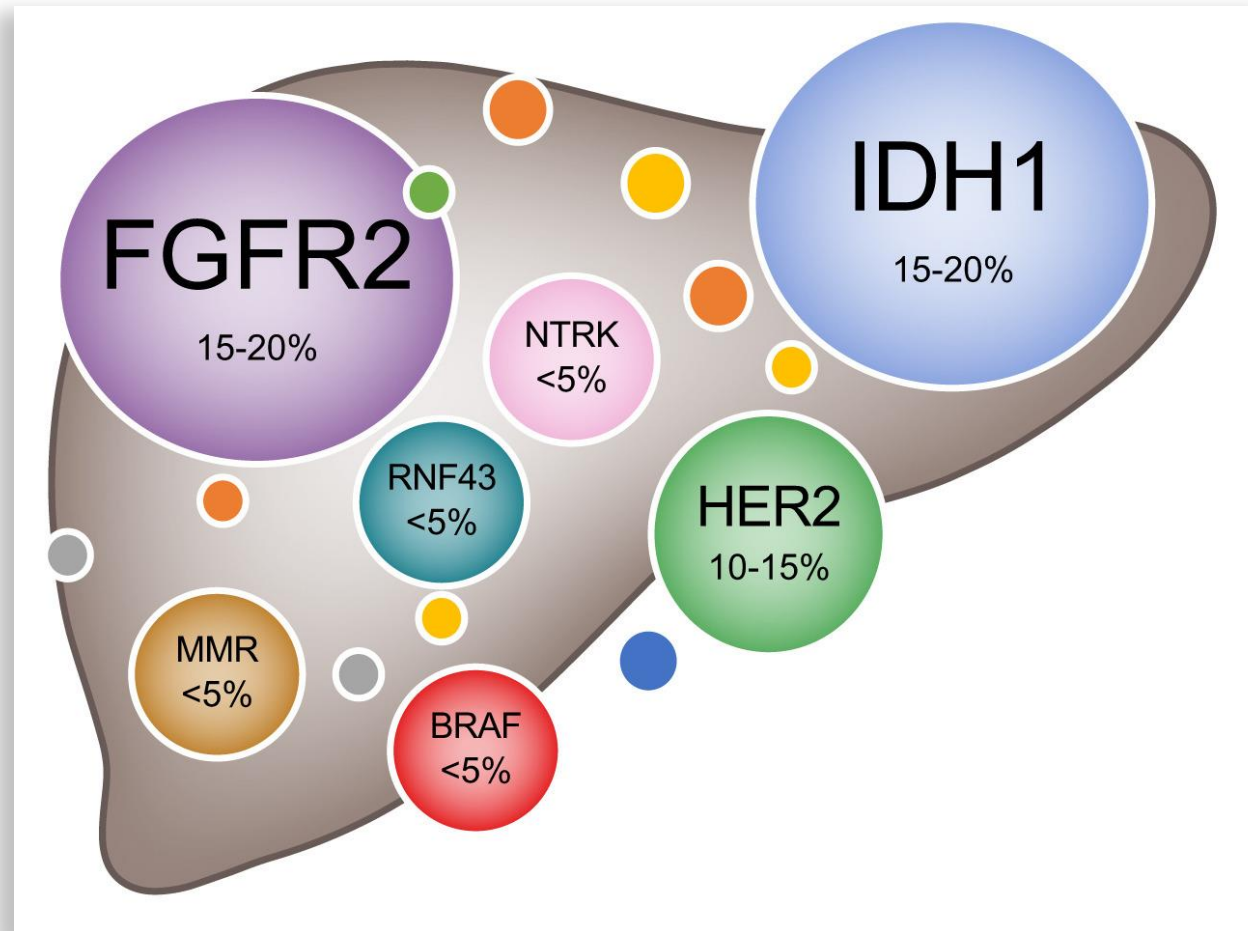
most targetable mutations in iCCA

profiles differ depending on aetiology, particularly in iCCA

PSC-related BTC (any site) have eCCa pattern

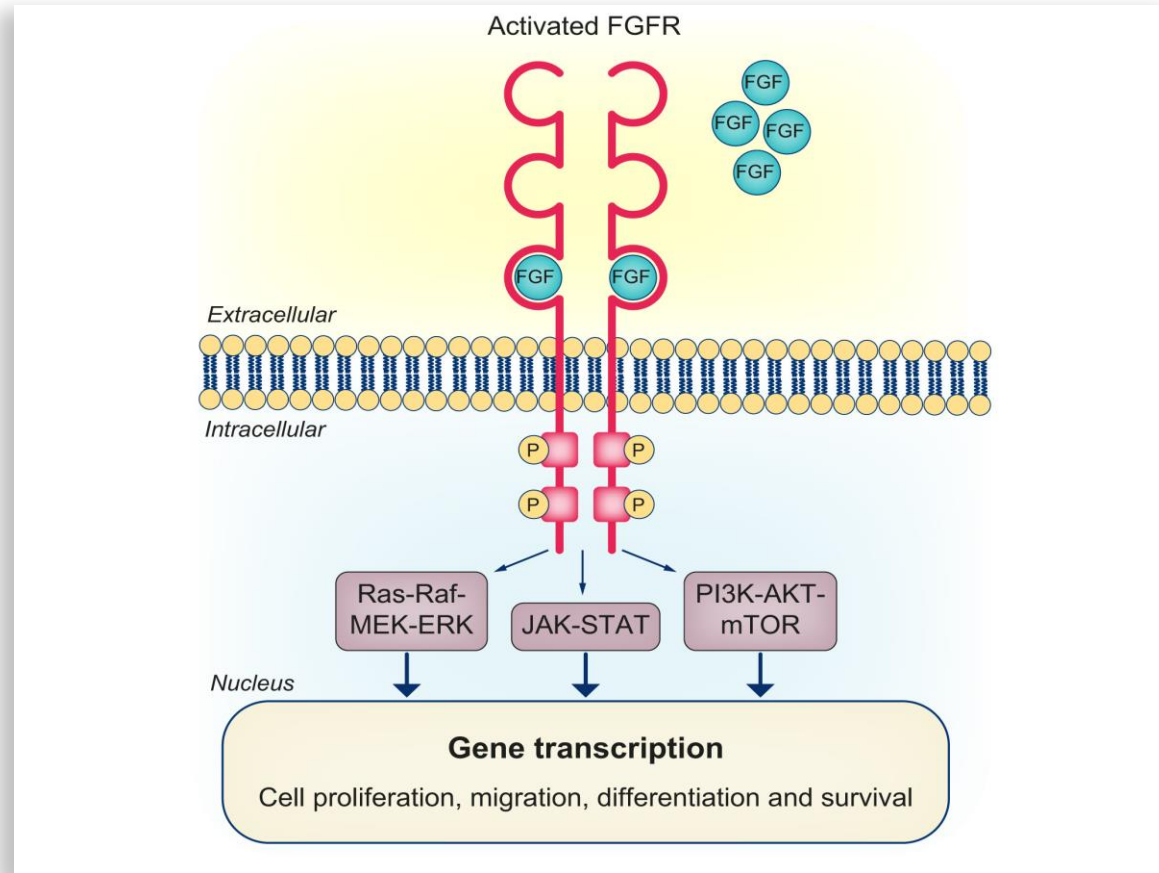
Lamarca et al, J Hep, 2021. PMID: 32171892

Precision medicine/pathology in cholangiocarcinoma



Lamarca et al, J Hep, 2021. PMID: 32171892

Fibroblast growth factor receptor

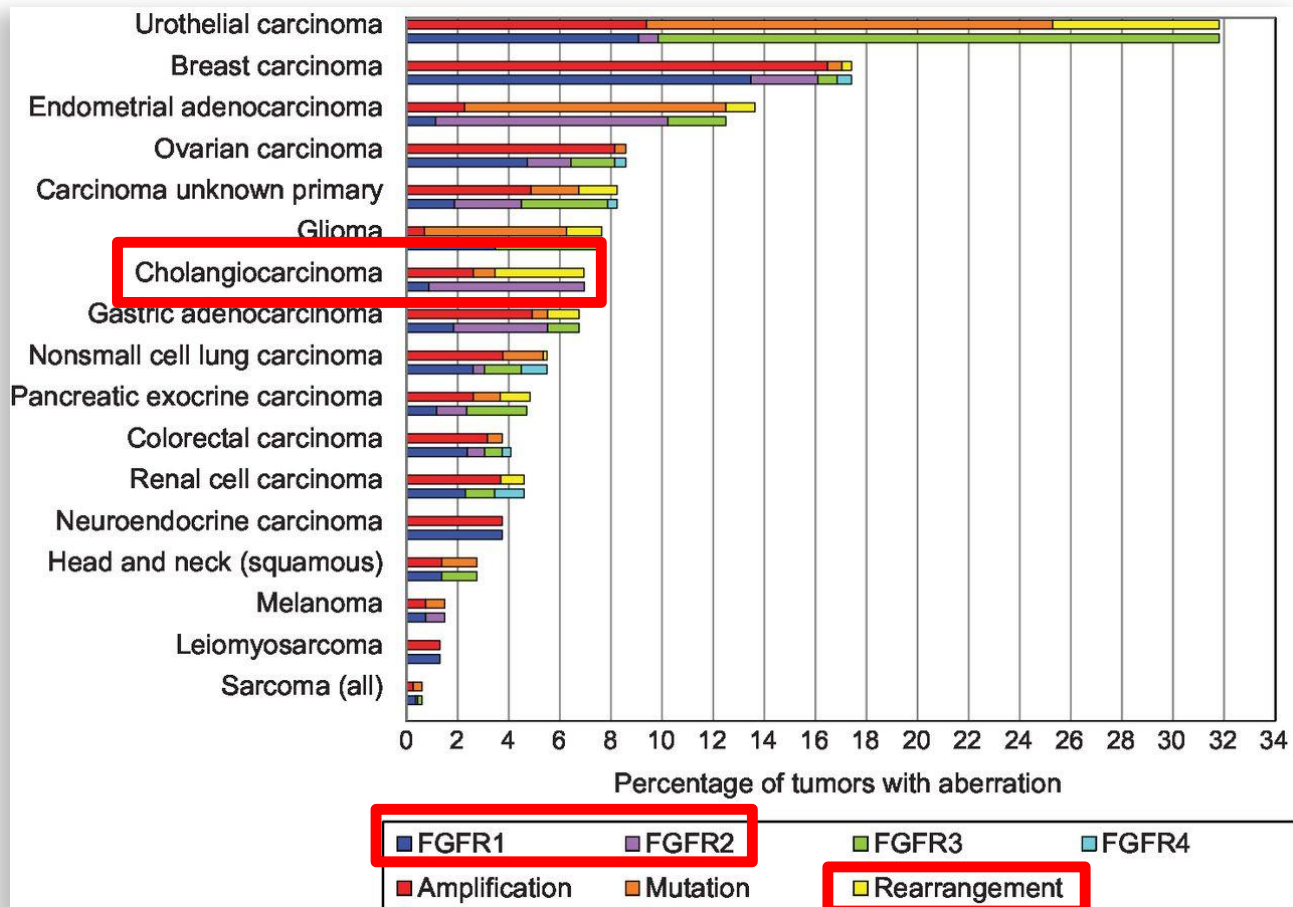


4 transmembrane receptors with intracellular tyrosine kinase domains (FGFR1-4)

abnormalities present in 7% of all cancers

Lamarca et al, J Hep, 2021. PMID: 32171892

FGFR in cholangiocarcinoma



10-20% of iCCa show FGFR2 fusions (mainly non-fluke)

multiple FGFR2 fusion partners, partner relevance unclear

concomitant *BAP1* mutations and younger age, possibly conferring better prognosis

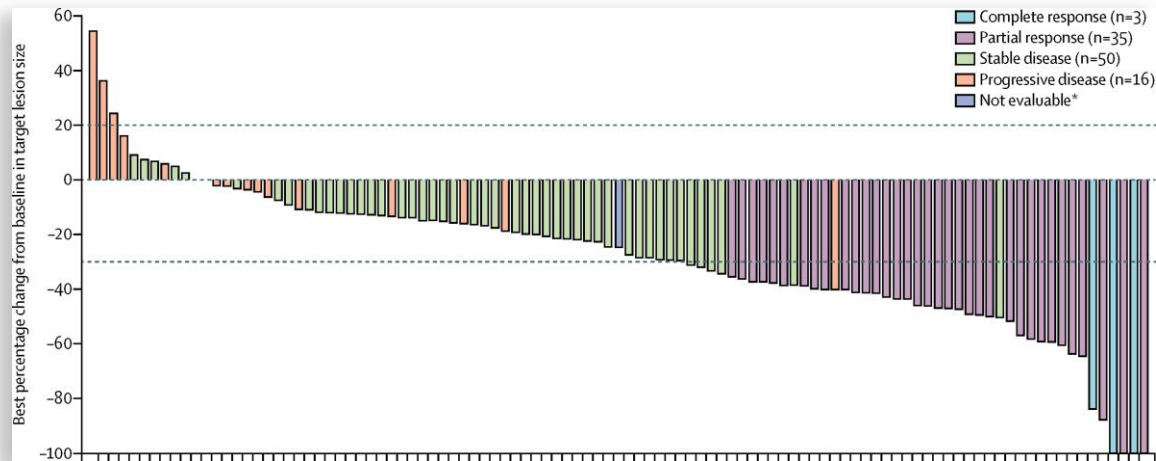
Helsten et al, Clin Cancer Res, 2016. PMID: 26373574

FGFR inhibitors in intrahepatic cholangiocarcinoma

non-selective tyrosine kinase inhibitors in FGFR2 fusion iCCa showed poor efficacy

many selective FGFR tyrosine kinase inhibitors under development

FGFR inhibitor - pemigatinib (1)



Abou-Alfa et al, Lancet Oncology, 2020. PMID: 32203698

pemigatinib (FIGHT-202; PMID: 32203698) –

small molecule inhibitor of FGFR1, 2 and 3

previously treated/metastatic disease

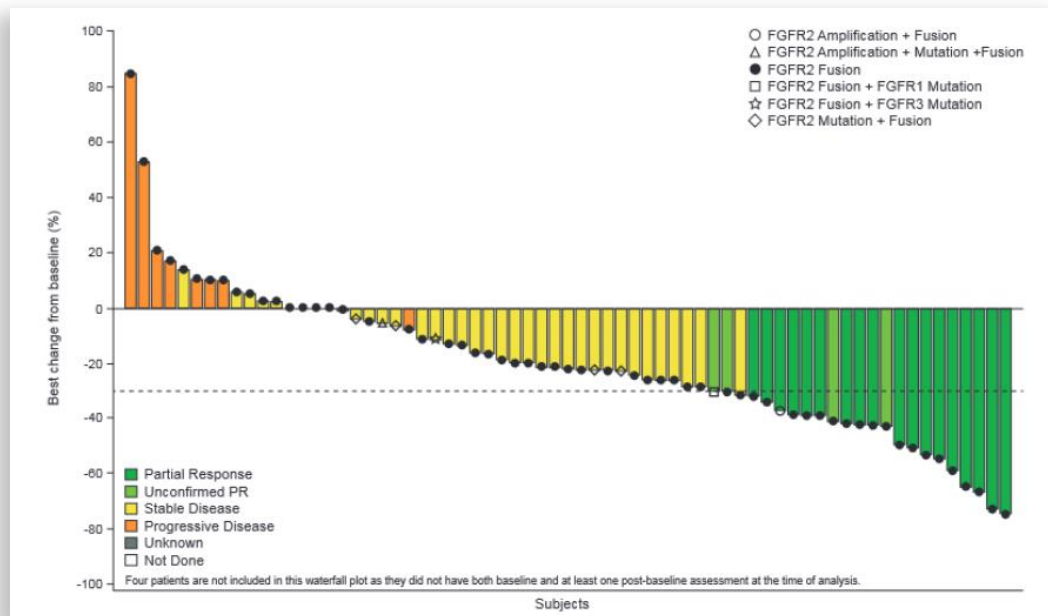
35.5% of patients with *FGFR2* fusions or rearrangements achieved an objective response (3 CR, 35 PR)

FGFR inhibitor – pemigatinib (2)

FDA accelerated approval in 2020

full NICE approval for advanced FGFR2 fusion/rearrangement iCCa July 2021

FGFR inhibitor – infigratinib



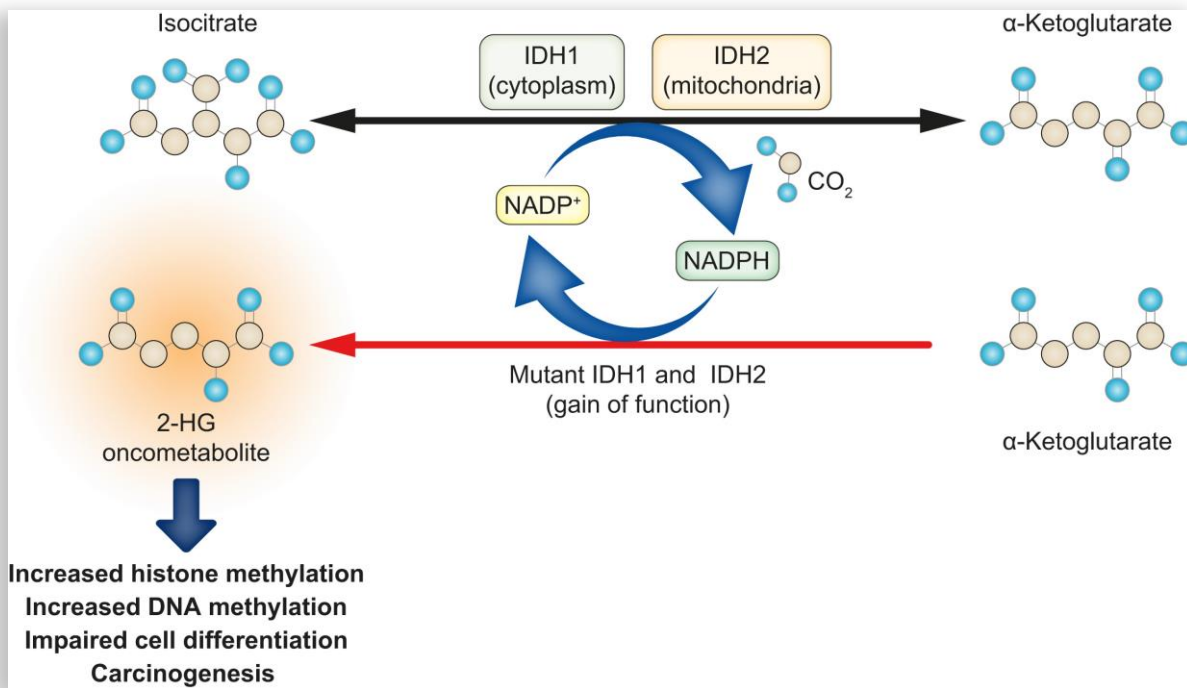
infigratinib –

alternative FGFR inhibitor

FDA accelerated approval August 2021

Javle et al, Lancet Gast Hep, 2021. PMID: 34358484

Isocitrate dehydrogenase in cholangiocarcinoma



IDH1 and 2 involved in cell metabolism

10-20% of iCCa have *IDH1* mutation; fewer *IDH2* mutation

gain-of-function, early event blocking normal differentiation and promoting carcinogenesis

multiple IDH-selective inhibitors developed to target tumours with IDH mutations

Lamarca et al, J Hep, 2021. PMID: 32171892

IDH inhibitors in cholangiocarcinoma

ivosidenib (ClarIDHy; PMID: 32416072, PMID: 34554208) –

oral, targeted mutant IDH1 inhibitor, approved for the treatment of *IDH1*-mutant AML

patients with *IDH1*-mutated CCa following progression on prior chemotherapy

primary endpoint of PFS met (median PFS 2.7 months v 1.4 month on placebo), improved OS

FDA advanced approval August 2021

Other precision targets in cholangiocarcinoma (1)

HER receptor family –

trials of inhibitors of HER pathways in HER-overexpressing CCa and GBC disappointing

? patient selection-related

NTRK (neurotropic tyrosine kinase receptor) fusions –

NTRK fusions in 3.5% of patients with iCCA

TKIs under development

Other precision targets in cholangiocarcinoma (2)

BRAF –

mutations in <5% BTC

patients with BTC V600E mutations included in the ROAR (PMID: 32818466) basket trial of dabrafenib, promising PFS

RNF43 –

RING domain E3 ubiquitin ligase suppresses P53-mediated apoptosis, inhibits Wnt signalling

RNF43 mutations, that may predict the sensitivity to porcupine inhibitors, found in <5% BTC.
Under development

Biopsy & precision oncology in cholangiocarcinoma

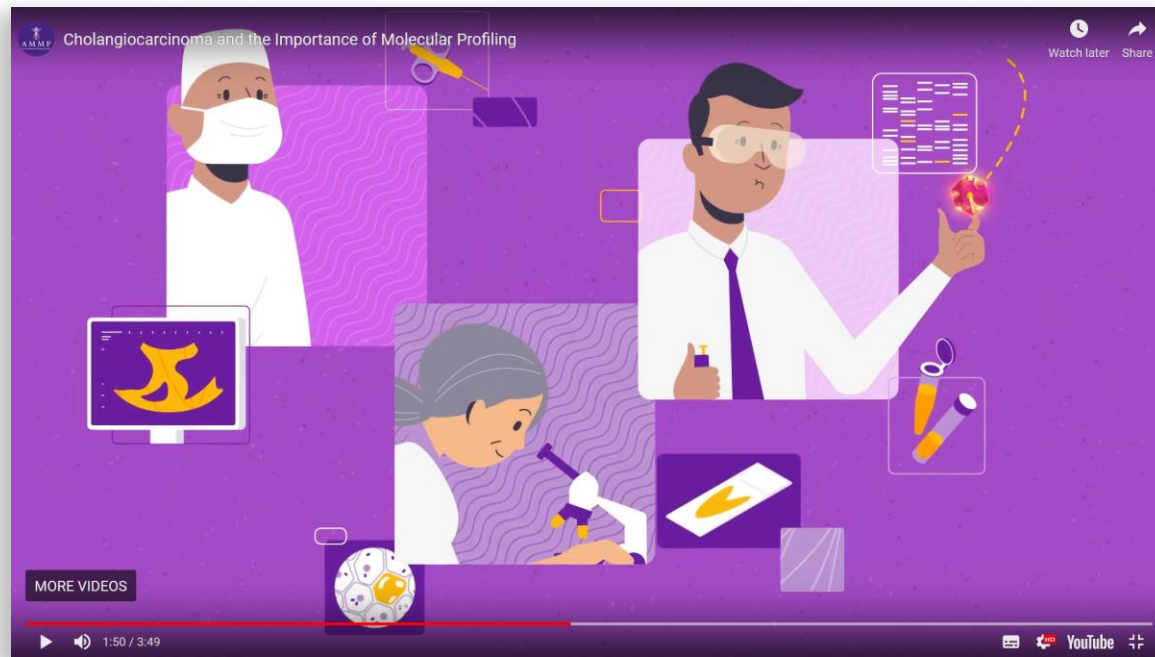
FGFR2 fusion testing pathway (NCRN/CG/HPS/signaling/precision)

sequencing or FISH should be available (with NTRK) through 7 NHS England Genomic Laboratory Hubs, Edinburgh

‘full’ mutational profiling for trial inclusion screening in research centres
 (outside of GLH service) e.g. Christie
 NHS England Genomic Test Directory for cancer 2021/2022 entry –

Cholangiocarcinoma	M220.1	Multi-target NGS panel - structural variant (NTRK1, NTRK2, NTRK3, FGFR2)	NTRK1, NTRK2, NTRK3, FGFR2	Structural variant detection	Panel	Patient's clinical status means they are eligible for an NTRK inhibitor in the event an NTRK rearrangement is detected. Patient's clinical status means they are eligible for a protein kinase inhibitor therapy in the event an FGFR2 fusion is detected
	M220.2	Multi-target NGS panel - small variant (DPYD)	DPYD	Small variant detection	Panel	Patient planned to receive fluoropyrimidine treatment
	M220.3	DPYD hotspot	DPYD	Small variant detection	Simple targeted mutation testing	Patient planned to receive fluoropyrimidine treatment Delivered via germline testing

tissue is now needed for diagnosis **and** therapeutic precision



‘although it is a great thing to be able to do a diagnosis, there’s enough left over for molecular testing’

AMMF YouTube channel

personal view – adenocarcinoma in the absence of an extrahepatic primary lesion (as documented in EHR) is cholangiocarcinoma

IHC is often non-contributory

‘being mindful of need for tissue suitable for molecular testing’ may be included as a recommendation in update to BSG guidelines (with Yoh Zen)



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