PRACTICAL INSIGHTS FOR EARLY DIAGNOSIS AND MANAGEMENT OF BILIARY TRACT CANCERS

Tailoring Treatment Strategies: The Importance of Early and Comprehensive Molecular Testing

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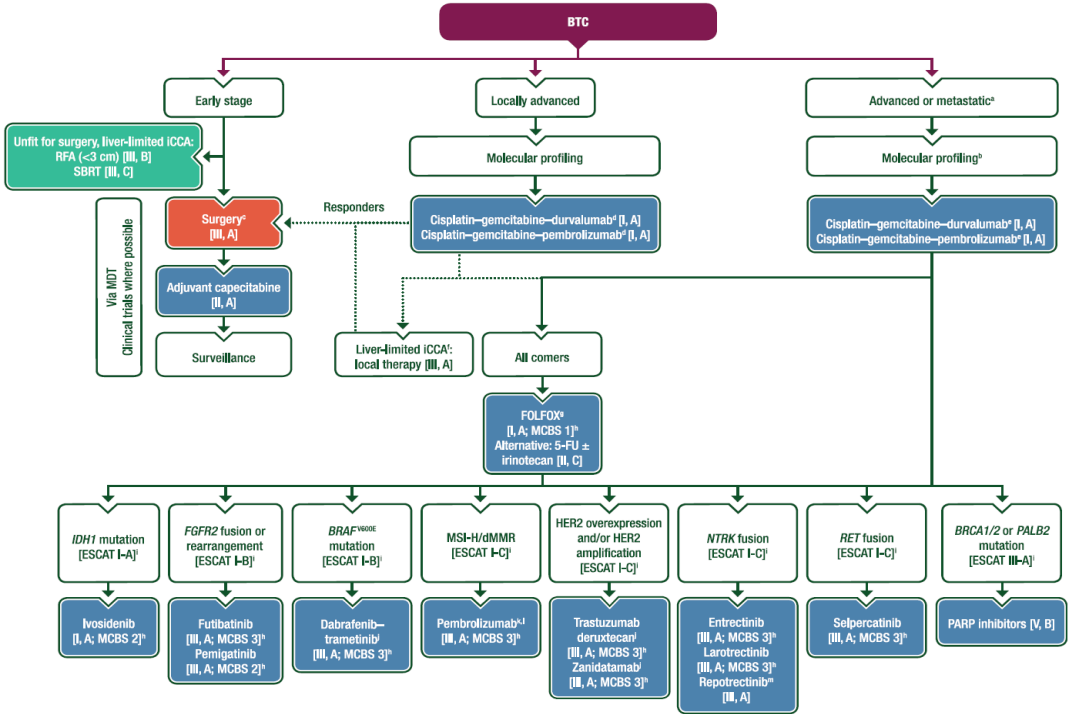
ESMO Guidelines on Molecular Testing in BTC



BTC: Biliary Tract Cancer; **IDH1**: Isocitrate Dehygrogenase 1; FGFR2: Fibroblast Growth Factor Receptor 2; **HER2**: Human Epidermal Growth Factor Receptor 2; **iCCA**: intrahepatic cholangiocarcinoma; **MSI**: Microsatellite Instability; **NTRK**: Neurotrophic Tyrosine Receptor Kinas; **RET:** Rearranged during Transfection; **BRCA 1/2:** BReast Cancer gene 1/2; **PALP2:** Partner And Localizer of BRCA2 **MCBS:** Magnitude of Clinical Benefit Scale ; **PARP**: Poly (ADP-Ribose) Polymerase.

Molecular testing should take place before or during first-line therapy.

Adapted from Vogel A, Ducreux M; ESMO Guidelines Committee. ESMO Clinical Practice Guideline interim update on the management of biliary tract cancer. ESMO Open. 2025 Jan;10(1):104003.

What is the Frequency of these Alterations in BTC?

Mutation	Frequency in CCA
IDH-1 mutation	1-18 % · iCCA: 8-18 %
FGFR2 fusion/rearrangement	<10 % · iCCA: 5-15 %
HER2 overexpression/amplification	5-10 % · pCCA/dCCA/GBC: 10-20 %
MSI/dMMR	<1 %
BRAFV 600E	1-5 %
NRTK fusion	<1 %
KRAS mutation	<1 %
RET fusion	1 %

BTC: Biliary Tract Cancer; **IDH1**: Isocitrate Dehygrogenase 1; **FGFR2**: Fibroblast Growth Factor Receptor 2; **HER2**: Human Epidermal Growth Factor Receptor 2; **pCCA**: perihilar cholangiocarcinoma; **dCCA**: distal cholangiocarcinoma; **GBC**: gallbladder carcinoma; **iCCA**: intrahepatic cholangiocarcinoma; **MSI**: Microsatellite Instability; **dMMR**: Mismatch Repair deficient; **NTRK**: Neurotrophic Tyrosine Receptor Kinas; **KRAS**: Kirsten Rat Sarcoma virus; **RET**: Rearranged during Transfection.

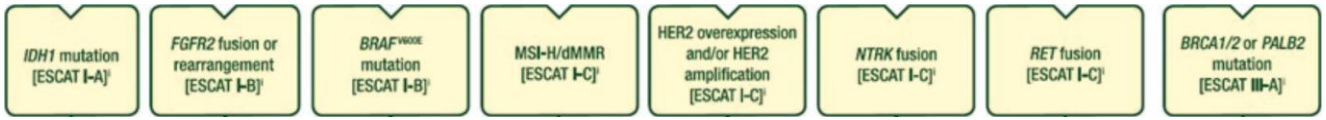
Many actionable alterations occur at low frequency.

Taken together, 40-50 % of BTC will harbor a target!

Table from Ros-Buxó M, Mauro E, Sauri T, Iserte G, Fuster-Anglada C, Díaz A, et al. Integrating molecular insights into biliary tract cancer management: A review of personalized therapeutic strategies. Curr Oncol [Internet]. 2024;31(7):3615–29. Available from: http://dx.doi.org/10.3390/curroncol31070266.

How to Test

Low-frequency alterations → NGS as a 'one stop shopping' method.



NGS analysis for:

- SNV
- Fusions
- MSI
- Copy number variation (amplification)

IHC for HER2 expression

If NGS not possible, single gene analysis/FISH can be performed.

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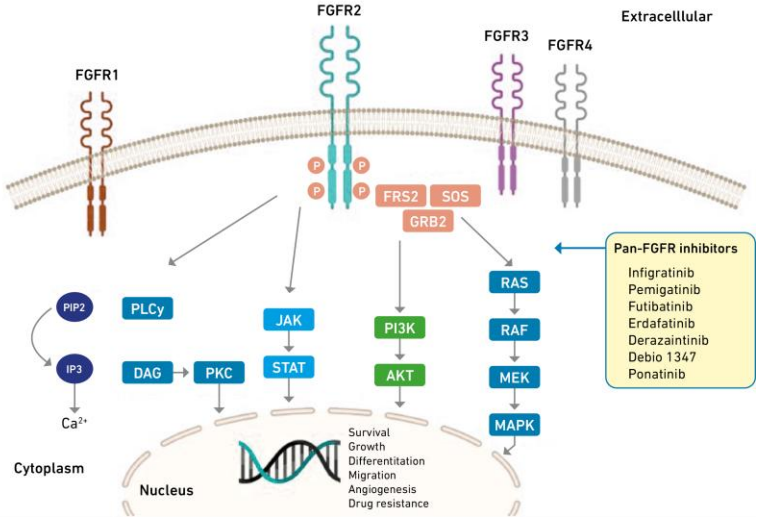
Special Considerations: FGFR

2 ways of ligand independent FGFR activation:

- Loss of c-terminal region by fusion (regardless of reading frame) deletion, splice site mutation.
- Gain of domains enhancing dimerization (in frame fusion).

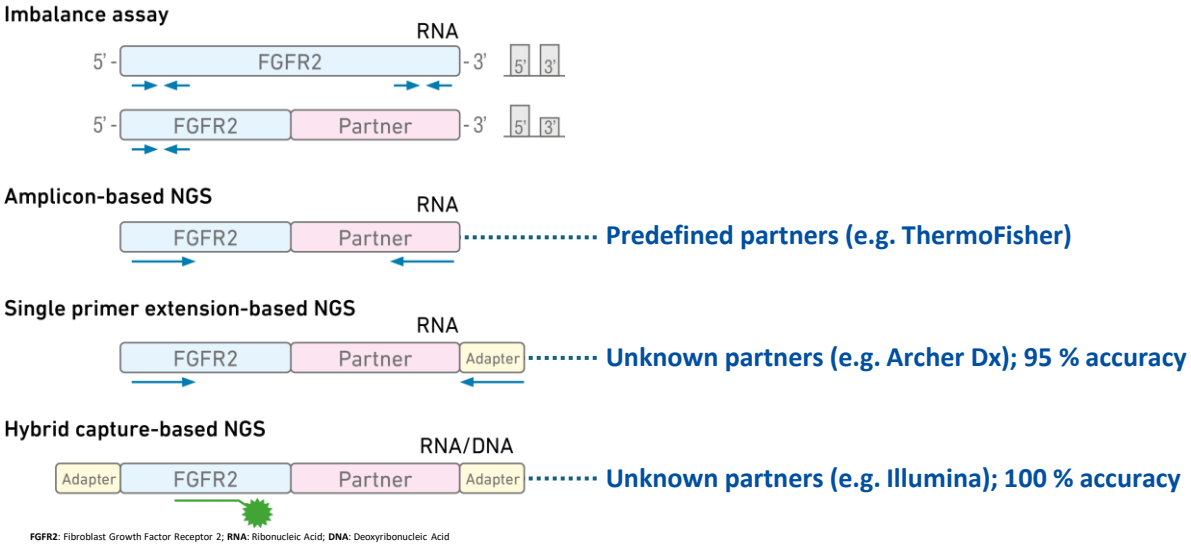


FGFR: Fibroblast Growth Factor Receptor; **PIP2**: Phosphatidylinositol Biphosphate; **IP3**: Inositol Trisphosphate; **PLCy**: Phospholipase C-gamma; **DAG**: Diacylglycerol; **JAK**: Janus Kinase; **PKC**: Protein Kinase C; **STAT**: Signal Transducers and Activators of Transcription; **FRS2**: Fibroblast Growth Factor Receptor Substrate 2; **SOS**: Son of Sevenless; **GRB2**: Growth factor Receptor-Bound protein 2; **PI3K**: Phosphoinositide 3-Kinase; **AKT**: Protein Kinase B; **RAS**: Rat Sarcoma; **RAF**: Rapidly Accelerated Fibrosarcoma; **MEK**: Mitogen-Activated Protein Kinase Kinase; **MAPK**: Mitogen-Activated Protein Kinase

1. Neumann O, Burn TC, Allgäuer M, Ball M, Kirchner M, Albrecht T, et al. Genomic architecture of FGFR2 fusions in cholangiocarcinoma and its implication for molecular testing. Br J Cancer 2022;127(8):1540–9. 2. Figure adapted from Zugman M, Botrus G, Pestana RC, Uson Junior PLS. Precision medicine targeting FGFR2 genomic alterations in advanced cholangiocarcinoma: Current state and future perspectives. Front Oncol. 2022.

Special Considerations: FGFR2 Testing

Over 100 fusion partners have been described for FGFR2!
Breakpoints can occur in large repetitive intronic sequences → RNA



FGFR2: Fibroblast Growth Factor Receptor 2; **RNA**: Ribonucleic Acid; **DNA**: Deoxyribonucleic Acid

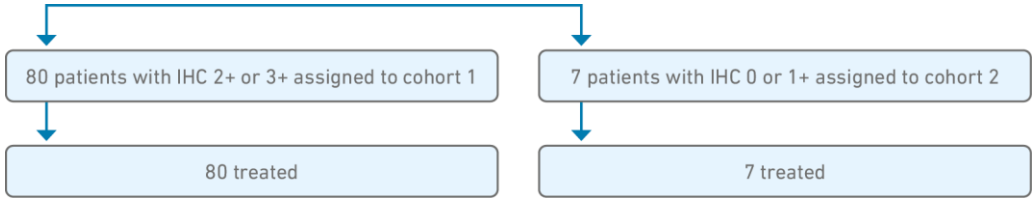
Figure adapted from Neumann O, Burn TC, Allgäuer M, Ball M, Kirchner M, Albrecht T, et al. Genomic architecture of FGFR2 fusions in cholangiocarcinoma and its implication for molecular testing. Br J Cancer 2022;127(8):1540–9. Available from: http://dx.doi.org/10.1038/s41416-022-01908-1.

Special Considerations: HER2 in BTC

Zanidatamab for *HER2*-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study

James J Harding, Jia Fan*, Do-Youn Oh, Hye Jin Choi, Jin Won Kim, Heung-Moon Chang, Lequn Bao, Hui-Chuan Sun, Teresa Macarulla, Feng Xie, Jean-Phillippe Metges, Jie'er Ying, John Bridgewater, Myung-Ah Lee, Mohamedtaki A Tejani, Emerson Y Chen, Dong Uk Kim, Harpreet Wasan, Michel Ducreux, Yuanyuan Bao, Lisa Boyken, Jiafang Ma, Phillip Garfin, Shubham Pant, on behalf of the HERIZON-BTC-01 study group†*

131 HER2 amplified tumors



Open questions: Guidelines for HER2 scoring in BTC accounting for specimen adequacy, heterogeneity, staining patterns etc.

BTC: Biliary Tract Cancer; **HER2**: Human Epidermal Growth Factor Receptor 2; **IHC**: Immunohistochemistry

Adapted from Harding JJ, Fan J, Oh D-Y, Choi HJ, Kim JW, Chang H-M, et al. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. Lancet Oncol. 2023;24(7):772–82.

Considerations: Coordination Between Disciplines

- Communicate with your pathology and molecular pathology team!
- Sometimes material for diagnosis can be very sparse → statement on specimen adequacy from diagnostic specimen is very useful.
- Establish turnaround times in your setting (in house/external); in house TAT typically 1-2 weeks.
- Timely results may become more important if targeted therapies move to first-line.

TAT: Turnaround Time

Summary

- The main actionable targets for BTC include IDH1, FGFR2, BRAF, MMR and HER2 overexpression.
- NGS is preferred as a one stop shopping method, especially since alterations can occur at low frequency.
- NGS cannot measure protein expression so HER2 IHC is an essential adjunct to NGS.
- For fusion analysis, RNA NGS using hybrid capture-based or single primer-extension based methods are preferred.
- Guidelines on HER2 IHC testing in BTC in analogy to gastric/colon cancer are needed.
- Interact with your pathology and molecular pathology to determine the best methods available to your healthcare setting and to get the timing right!

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