

GENETIC AND MOLECULAR BIOLOGY IN PANCREATOBILIARY CANCERS: TESTING FOR PANCREATOBILIARY CANCER IN THE CONTEXT OF THE BELGIAN NGS CONVENTION

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Acknowledgements: The authors would like to acknowledge all the ComPerMed experts

Keywords: Molecular tests, NGS, oncology, personalised medicine

Abstract

Pancreatobiliary cancers (PBC) group pancreatic and biliary tract cancers and are among the cancers with the lowest survival rate. Emerging data suggest that novel biomarker-specific targeted therapies can be proposed for selected populations with survival benefit. This review summarises the scientific evidence to test for these biomarkers in order to optimise the management of pancreatobiliary cancers, within the context of the Belgian NGS convention.

INTRODUCTION

Pancreatobiliary cancers (PBC) group pancreatic and biliary tract cancers. Pancreatic cancers (PC) are mostly subdivided in exocrine carcinomas and neuroendocrine tumours. Biliary tract cancers (BTC) include intrahepatic/extrahepatic (both Klatskin and distal) cholangiocarcinoma (CCA), gallbladder cancer (GBC), and cancer of the ampulla of Vater.¹ It is estimated that 707 new cases of gallbladder and other BTCs and 2,024 pancreatic cancers were diagnosed in 2018 in Belgium. Altogether, pancreatobiliary cancers represent 3.9% of all invasive tumours (excl. non-melanoma skin cancer) and 19% of all cancers of the digestive tract in Belgium. The incidence is increasing, mainly for pancreatic cancers.^{2,3} Pancreatobiliary cancers are among the cancers with the lowest survival rate. The five-year relative survival (2014-2018) is 17.2% for BTC and 11.6% for PC. Pancreatobiliary cancers remain challenging to treat due to their aggressive biology and heterogeneous molecular patterns. The prognosis remains poor and palliative chemotherapy is the treatment of choice for advanced disease. Based on rapid advances in biotechnology, including next generation sequencing (NGS), novel biomarker-specific targeted therapies are in development and emerging data suggest that these targeted therapies can be proposed for selected populations with some survival benefit. This review summarises the scientific evidence to test for these biomarkers in order to select therapies for pancreatobiliary cancers, within the framework of the Belgian NGS convention.

METHODOLOGY

To provide access to NGS technology for routine diagnostics in oncology, the Belgian federal government has financed an implementation project entitled *“Roadbook Personalized medicine: the introduction of next-generation in routine diagnostics in oncology and hemato-oncology (2016-2020)”*. The Belgian Commission of Personalised Medicine (ComPerMed) was created in 2015 and includes experts with different backgrounds (molecular biologists, clinical biologists, pathologists, geneticists and oncologists). The objective of the ComPerMed is to act as a national advisory board on new developments in personalised medicine by advising the Platform Companion Diagnostics from the INAMI/RIZIV, to reinforce the link between the reimbursement of a molecular test and corresponding targeted therapy and more generally, to install coherent reimbursement decisions. In July 2019, the reimbursement of NGS tests has been broadened in Belgium through the NGS convention, a contract

between networks of hospitals/laboratories and the INAMI/RIZIV. In this NGS convention, tumour types and genes of interest per tumour type for which an NGS test is reimbursed are listed, as advised by the ComPerMed. With the purpose of harmonising molecular testing in Belgium for healthcare decisions, the experts of the ComPerMed have selected the OncoKB test levels and have adapted it to the Belgian situation (Figure 1), as described previously.^{3,4} Three test levels were determined, with level 1 representing the biomarkers with the most scientific and medical evidence, which have the highest priority for test reimbursement by the policy makers. Only biomarkers with a test level 1 and 2A are included in the NGS convention. These test levels 1 and 2A are linked to standard of care biomarkers and to reimbursed treatments in Belgium. A subgroup of ComPerMed experts performed this exercise for biomarkers in pancreatobiliary cancers. Recommendations together with scientific evidence are formulated in the section below.

Figure 1

1	Standard of care biomarker for diagnosis and/or prognosis *	
	Biomarker predictive of response or resistance to a reimbursed drug in Belgium for this indication	
2A	Recommended standard of care biomarker for diagnosis and/or prognosis +	
	Biomarker predictive of response or resistance to an EMA-approved drug for this indication	
2B	Biomarker predictive of response or resistance to an EMA-approved drug for another indication or to a drug for which a clinical trial is available for this indication	
3	Preliminary clinical evidence supporting the biomarker for diagnosis and/or prognosis °	
	Biomarker predictive of response or resistance to (1) a drug for which a clinical trial is not available in this indication or to (2) a compassionate use of drug	
* Standard of care: Included in guidelines (WHO...) AND consensus from ComPerMed experts. + Recommended standard of care: Clinical evidence AND consensus from ComPerMed experts. ° Preliminary evidence and no consensus from ComPerMed experts.		

At the moment, only GNAS NGS testing is reimbursed for diagnostic work-up of pancreatic cysts. BRCA1 and BRCA2 NGS testing is also in the process of being reimbursed for advanced pancreatic adenocarcinomas.

RECOMMENDATIONS AND SCIENTIFIC EVIDENCE

For each biomarker and for each clinical utility (therapy, diagnosis and prognosis) a test level was assigned. This information is summarised in *Table 1*.

BILIARY TRACT CANCERS (CHOLANGIOCARCINOMAS)

The distribution of the molecular alterations found in BTCs is different in the specific localisations, emphasising that precision therapy will be different for intrahepatic vs. extrahepatic cholangiocarcinomas vs. gallbladder cancers.

Table 1

Biliary tract cancers	test level	Clinical utility (T/D/P)	predilection site
NTRK	Level 1	T	
FGFR2	Level 2B	T	intrahepatic cholangiocarcinoma
	Level 2B	P	
IDH1	Level 2B	T	intrahepatic cholangiocarcinoma
BRAF	Level 2B	T	
	Level 2B	P	
MSI	Level 2B	T	extrahepatic cholangiocarcinoma
BRCA1/2	Level 2B	T	extrahepatic cholangiocarcinoma and gallbladder carcinoma
HER2	Level 2B	T	extrahepatic cholangiocarcinoma
PIK3CA	Level 2B	T	
ROS1	Level 2B	T	
ALK	Level 2B	T	
MET	Level 2B	T	
Pancreatic cancers			
GNAS	Level 2A	D	
NTRK	Level 2A	T	
BRCA1/2	Level 2A	T	
	Level 2B	P	
other HRR genes	Level 2B	T	
MSI	Level 2B	T	
HER2	Level 2B	T	
KRAS	Level 2B	T	pancreatic ductal adenocarcinoma
PIK3CA	Level 2B	T	
BRAF	Level 2B	T	
MDM2	Level 2B	T	
HER2	Level 2B	T	
NRG1	Level 2B	T	
ALK	Level 2B	T	
RET	Level 2B	T	
ROS1	Level 2B	T	
<i>T: therapy; D: diagnosis; P: prognosis.</i>			

BIOMARKERS WITH A TEST LEVEL OF 1 OR 2A:

Gene fusions involving one of the three neurotrophic tyrosine receptor kinases (*NTRK*) are very rare in BTC (<1%). However, inhibitors of TRK (*e.g.* larotrectinib, entrectinib) have been shown to have durable anti-tumour activity. So testing of *NTRK* fusions in BTC is of high interest even if the incidence of those fusions is low. Larotrectinib is EMA-approved and reimbursed in Belgium.^{1,5,6}

BIOMARKERS WITH A TEST LEVEL OF 2B OR 3:

Fibroblast growth factor receptor *FGFR2* fusions/translocations are reported in 10–16% of cholangiocarcinomas, and are especially observed in intrahepatic cholangiocarcinoma. *FGFR2* fusions are associated with a better prognosis.^{1,6,7} Early results of the use of *FGFR2* inhibitors in cholangiocarcinoma are very promising, with durable partial responses and prolonged progression-free survival in target-positive populations. For example, pemigatinib has been investigated in the phase II FIGHT-202 trial where previously treated patients were separated in three cohorts based on their FGF/FGFR status (*FGFR2* fusions/rearrangements, other FGF/FGFR genetic alterations, and no *FGF/FGFR* genetic alterations). FGFR2 rearranged patients are the best responders.^{8,9} Pemigatinib is not yet reimbursed in Belgium and no medical need program is available, but this treatment is currently investigated in a first-line trial and an EMA approval is coming. Two other *FGFR2* inhibitors, derazantinib and infigratinib, are currently under investigation in clinical trials.

Isocitrate dehydrogenase *IDH1* and *IDH2* mutations occur in about 25% of patients with intrahepatic cholangiocarcinoma.¹⁰ Targeting cell metabolism through IDH1 inhibition has been under investigation in several clinical trials and might offer a well-tolerated treatment option for patients with *IDH1*-mutated cholangiocarcinoma.^{7,10} For example, ivosidenib has been investigated in the ClarIDHy phase III clinical trial and has shown a significant benefit in progression-free survival (PFS) compared to placebo for advanced, *IDH1*-mutated cholangiocarcinoma. Unfortunately, ivosidenib is not yet available in Belgium, not even in a clinical trial.^{1,6,11,12}

Within the group of biliary tract cancers, *BRAF* variants are limited to intrahepatic cholangiocarcinoma, with an incidence of 3–5%, and are more likely to be associated with a more aggressive phenotype and a poor outcome.¹³ Trials with single-agent therapies targeting *BRAF* have demonstrated effectiveness, but were associated with significant toxicity and side effects, including secondary malignancies. In addition, the combination of these agents with MEK inhibitors has proven to be effective.¹³

For example, the ROAR phase II clinical trial that enrolled patients with different types of rare cancers carrying the *BRAF*^{V600E} variant showed promising results as nearly half of *BRAF*^{V600E} mutated cholangiocarcinoma patients responded to a combination of two targeted drugs – Tafinlar® (dabrafenib – *BRAF* inhibitor) and Mekinist® (trametinib – MEK inhibitor).¹⁴

An estimated 1% of CCA have a microsatellite instable (MSI-H) phenotype. MSI-H tumours may respond to immunotherapy. Twenty-two patients with MSI-H cholangiocarcinoma were enrolled in the phase II KEYNOTE-158 study, evaluating pembrolizumab in previously treated patients with non-colorectal MSI-H/dMMR cancer. The response rate was 40.9%, mPFS was 4.2 months and mOS 24.3 months.¹⁵ Clinical trials with PD-L1 inhibitors for patients with MSI-H cancer are ongoing in Belgium. *BRCA1/BRCA2* variants are more frequently observed in extrahepatic cholangiocarcinoma. The identification of DNA damage repair aberrations has been associated with better response to platinum-based chemotherapy strategies. On this basis, a PRECISION2 clinical trial with olaparib is ongoing in Belgium.

HER2 amplifications are observed in biliary tract adenocarcinomas with a frequency around 3% in distal extrahepatic cholangiocarcinomas and 10% in gallbladder carcinomas. A PRECISION2 clinical trial with afatinib is ongoing in Belgium for *HER2* variants.^{1,6,7,10,12,13,16}

PIK3CA variants are frequently observed in extrahepatic cholangiocarcinomas.^{1,17} A phase II trial using a PI3K inhibitor, copanlisib (BAY 80-6946), in first-line in combination with gemcitabine and cisplatin is ongoing in advanced cholangiocarcinomas (NCT02631590).

Therapies targeting *ROS1*, *ALK* and *MET* alterations are also currently evaluated in clinical trials in biliary tract carcinomas.¹² However, the prevalence of *ROS1* rearrangements seems to be very low.^{5,12,16}

Lastly, cancers arising from the biliary tree are technically challenging to biopsy, yielding insufficient tumour material for molecular profiling in approximately 25% of patients. Circulating tumour DNA (ctDNA)-based approaches, using liquid biopsies, may help to overcome this obstacle as its mutational profile has high concordance to that found in the tissue, especially when focusing on the main genes of interest, such as *IDH1* and *FGFR2*.⁷ In a diagnostic setting, testing should ideally include both DNA and RNA from the start, allowing the identification of gene variants and fusions/rearrangements, relevant to determine therapies.

PANCREATIC ADENOCARCINOMAS

Pancreatic neuroendocrine tumours (NET) will be not discussed in this article. Pancreatic ductal adenocarcinoma is the most common form of pancreatic cancer. Many gene alterations can be targeted but most of them have a low prevalence:

BIOMARKERS WITH A TEST LEVEL OF 1 OR 2A:

GNAS variant analysis within *exon 8* and *exon 9* is recommended for differential diagnosis between pancreatic IPMN and cystadenoma in FNA/FNB samples; *GNAS* variants have been described in 50 to 70% of IPMN and are absent in mucinous cystic neoplasms. A change in diagnosis will alter management.

A BRCAness mutational signature was found in 24% of analysed pancreatic of ductal adenocarcinoma (PDAC) patients, with 17% germline and 29% somatic pathogenic variants in *BRCA1/2*, *ATM* or *PALB2*.^{18,19} However, in daily clinical practice variant detection ratios may be lower. *BRCA1/2*, *ATM* or *PALB2* are involved in repair of DNA double strand breaks through homologous recombination repair (HRR). Inhibition of the PARP enzyme, involved in repair of DNA single strand breaks, with PARP inhibitors leads to death of cells with defective HRR genes (synthetic lethality). Platinum-based chemotherapy regimen (*e.g.* the combination of cisplatin and gemcitabine) are more effective in patients with pancreatic cancer with HRR damage. PARP inhibitors following platinum-based chemotherapy have shown early signs of efficacy in metastatic pancreatic cancer bearing a HRR mutant gene.^{20,21,22}

The randomised phase III POLO trial comparing olaparib treatment *vs.* placebo was conducted in patients with meta- static pancreatic cancer with *BRCA1/2* germline variants, who showed no

progression after an induction therapy with a platinum-containing regimen for sixteen weeks.²³ The response rate of somatically mutated *BRCA1/2* metastatic pancreatic cancers to PARP inhibitors is not yet clear and clinical studies are needed.^{5,21,24-27} Olaparib treatment in *BRCA1/2* mutated metastatic pancreatic cancer is currently being evaluated by EMA.^{20,21} A PRECISION2 clinical trial with olaparib is ongoing in Belgium.

BRCA1 and *BRCA2* variants identified by NGS in tumour samples of metastatic pancreatic cancer patients, may be of germline origin. Practically, in Belgium, germline testing of patients with mPDAC can be requested by the treating oncologist after preferentially signing an informed consent and results of the testing should be available within six weeks. Subsequently, patients with germline mutations should be referred to a genetic centre for genetic counselling to explain the impact of this finding, not only for the patient but also for their relatives.^{5,21,24-27}

The 2020 update of the American NCCN guidelines for pancreatic adenocarcinoma recommends that all patients with pancreatic cancer should be offered germline testing using comprehensive gene panels for hereditary cancer syndromes. Restriction of germline testing to patients with factors such as personal or family history of cancer, younger age, or ethnicity thought to be associated with *BRCA*-associated malignancies can result in underdiagnosis of pathogenic germline alterations.²⁴ ASCO guidelines have also been updated.²⁸ For Belgium, currently a consensus gene panel is being worked out in combination with guidelines for diagnosis and management of patients with hereditary pancreatic cancer. These will become available through the website of the College of Genetics (<https://www.college-genetics.be/>) and the FAPA (<https://belgianfapa.be/>). Furthermore, even if the prevalence is <1%, it is thought that the screening for *NTRK* fusions could add an additional layer of opportunity for selection of patients who may benefit from targeted therapies.^{5,28}

BIOMARKERS WITH A TEST LEVEL OF 2B OR 3:

BRCA1/2 variants may indicate a more favourable disease behaviour in pancreatic cancer. Analysis of mismatch repair (MMR) protein expression and/or analysis of microsatellite instability (MSI) should be performed for all pancreatic cancers to screen for inherited cancer predisposition syndrome and/or for prediction of response to immunotherapy. Tumours characterised by an 'MSI-high' status, which is a very rare condition in PDAC (< 2%), can benefit from treatment with immunotherapy.¹⁵ However, the benefit of pembrolizumab (RR and OS) in these tumours seems to be limited and less pronounced than what is observed in other digestive cancers. *HER2* amplifications are observed in pancreatic cancers with an incidence of around 1-2%. A PRECISION2 clinical trial with afatinib is ongoing in Belgium for *HER2* variants. Several additional alterations classified with a high-test level in other tumours, have not yet shown a significant impact in pancreatic cancer, such as *KRAS*, *PIK3CA*, *BRAF*^{V600E} variants, *MDM2*, *HER2* amplifications and *NRG1*, *ALK*, *RET*, *ROS1* fusions. Some of these alterations are under evaluation in the framework of phase II clinical trials.^{5,20} New drugs targeting *KRAS* variants, in particular *KRAS*^{G12C} are currently being evaluated in a Belgian clinical trial with sotorasib (Amgen 510).²⁰

KEY MESSAGES FOR CLINICAL PRACTICE

Recommendations for optimal pancreatobiliary cancer management are:

1. Implementation of molecular/genetic testing of pancreatobiliary tumours in the algorithm of treatment is imperative, trying to identify selected targetable populations for precision treatments.
2. Chemotherapy remains the backbone therapy in advanced pancreatobiliary tract cancers.
3. Maintenance therapy is emerging in metastatic pancreatic ductal adenocarcinomas using olaparib in *gBRCA* mutated patients with prolonged PFS on platinum-based therapy (EMA approval is pending).
4. Current NCCN guidelines indicate that there is currently no indication for multigene NGS testing. However, it is recommended that clinical research centres perform multigene sequencing in the context of molecular screening programs in order to increase access to innovative drugs and to speed up clinical research.
5. Biliary tract cancers are heterogeneous tumours from the anatomical, molecular and therapeutic point of view.
6. *FGFR* inhibitors and *IDH-1* inhibitors have demonstrated interesting results in pre-treated patients and are further being tested, also in first-line phase III trials in intra-hepatic cholangiocarcinoma.
7. *HER2* amplification testing may offer specific and innovative targeted therapies in BTC (gallbladder) and PDAC.
8. MSI-High pancreatobiliary cancers are very rare (around 1%) but can respond to anti-PD-(L)1 therapy (BTC > PDAC).
9. Similarly, *NTRK1/2/3* fusions (2A) are also rare (1%) but targeting them shows durable response.
10. In a diagnostic setting, given the small amount of available tissue for these tumours, testing should ideally include both DNA and RNA from the start, allowing the identification of gene variants and fusions/rearrangements, relevant to determine therapies.
11. By somatic tumour testing, variants may be revealed that can be caused by germline mutation. Patients in whom potential germline variants are identified in cancer predisposition genes with clinical impact, should be referred for genetic counselling and germline testing.

CONCLUSIONS

In conclusion, targeting specific genes in pancreatobiliary cancers may significantly improve the patient management and is complementary to the conventional chemotherapies. It is then recommended in our treatable patients to perform NGS testing, searching for druggable targets.

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