

# New molecular and immunotherapeutic approaches in biliary cancer



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## ABSTRACT

Biliary tract carcinoma is a collective term for a group of rare gastrointestinal cancers. This overview outlines the key pathways and specialised therapeutics in biliary cancer and the emerging role of immunotherapy by highlighting the rationale and selected examples of studies in each area.

This overview outlines the key pathways and specialised therapeutics in biliary cancer and the emerging role of immunotherapy by highlighting the rationale and selected examples of studies in each area.

Biliary tract carcinoma (BTC) is a collective term for a group of rare gastrointestinal cancers. The intrahepatic cholangiocarcinomas (IHCC) arise from the small ducts within the liver. The more common extrahepatic cholangiocarcinomas (EHCC) include hilar and perihilar carcinomas, more distal tract tumours, and gall bladder carcinomas (GBCs). The incidence of cholangiocarcinomas is rising in the Western world, with reports of up to 2/100 000. By contrast, in Asian countries the incidence is much higher and reflects the endemic liver fluke infection as a key risk factor, as opposed to chronic inflammation from hepatitis C and primary sclerosing cholangitis in the West. GBC also has an incidence of 2/100 000, but its aetiology is primarily related to cholecystitis and cholelithiasis, as well as some chronic infections, and is much more prevalent in parts of South America. Collectively these cancers present late in the majority of patients. Long-term outcomes for resectable patients are poor (about 30% 5-year survival) and survival in the advanced setting is short with a median survival of less than 1 year.<sup>1–4</sup>

Historically for unresectable disease, radiation and systemic chemotherapy have been the mainstay of treatment. Drug regimens with activity include gemcitabine and oxaliplatin, gemcitabine and cisplatin, 5-fluorouracil and oxaliplatin, and single agent options including gemcitabine and capecitabine.<sup>5</sup> Although the outlook has been dismal for these diseases, the molecular genomics revolution, which has

changed the paradigm of treatment in many cancers, has also led to novel approaches in biliary cancer [Table 1](#). A number of clinical trials with targeted therapies have been completed in recent years ([table 1](#)). A key problem that has emerged, however, is the breadth of driver mutations with small patient subsets for each target and key differences across IHCC, EHCC and GBC. This combined with the rarity of the disease creates challenges with testing novel therapies.<sup>4</sup> The development of international networks for rare cancers such as the International Rare Cancers Initiative, a consortium involving the USA, Canada, Europe and Australasia,<sup>6</sup> is key to translating the identification of targets into trials to test and validate efficacy. Additionally the concept of basket trials accepting multiple anatomical sites with shared genetic changes has the potential to accelerate identification of active targeted agents.<sup>7</sup>

Whole genomic tumour profiling studies have identified a wide range of mutations, amplifications and deletions, many of which have targetable options.<sup>2</sup> Important driver mutations reported in other tumours have also been documented, including the epidermal growth factor (EGF) pathway with EGF receptor (EGFR), *kras* and *braf* mutations or overexpression, as well as alteration in the mitogen-activated protein kinase and PI3K/mammalian target of rapamycin pathways, as well as TP53. Mutations in chromatin-remodelling genes *BAP1* (encoding a nuclear deubiquitinase), *ARID1A* (encoding a subunit of the SWI/SNF chromatin-remodelling complexes) and *PBRM1* (encoding a subunit of the ATP-dependent SWI/SNF chromatin-remodelling complexes) have been reported in frequencies of 10%–25%. Mutations in the metabolic pathway involving isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) are also seen. Amplifications in *c-MET*, FGF 19, cyclin-dependent kinase 6 and cyclin d1, as well as deletions in cyclin-dependent kinase inhibitors 2A and 2B, are all documented.<sup>2,8</sup>

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**Table 1** Incidence of molecular mutations in biliary tract cancer as determined by genomic sequencing<sup>10</sup>

Mutation	Intrahepatic cholangiocarcinoma (%)	Extrahepatic cholangiocarcinoma (%)	Gall bladder cancer (%)
<i>ERBB2</i> amplification	3	11	16
<i>BRAF</i> substitution	5	3	1
<i>KRAS</i>	15–22	42–47	11–19.2
<i>PI3KCA</i> substitution	5	7	14
<i>FGFR1-3</i> fusion	11–12.5	0	3
<i>CDKN2A/B</i> loss	18	17	19
<i>IDH1/2</i> substitution	15–23	3–4	0
<i>ARID1A</i> alteration	11–20	12	11–13
<i>MET</i>	4	0	0
<i>BAP1</i>	9–25	0	4–13

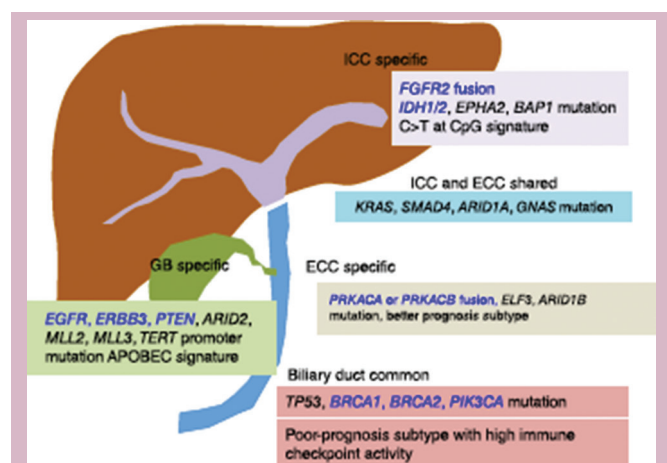
Overall Nakamura *et al*<sup>8</sup> identified five molecular modules, with alterations varying according to anatomical location (figure 1). They uncovered potentially targetable genetic alterations in 38.9% of BTC cases (93/239). These potential targets included kinases (*FGFR1*, *FGFR2*, *FGFR3*, *PIK3CA*, *ALK*, *EGFR*, *ERBB2*, *BRAF* and *AKT3*), other oncogenes (*IDH1*, *IDH2*, *CCND1*, *CCND3* and *MDM2*) and tumour suppressor genes (*BRCA1* and *BRCA2*). They also identified four molecular subgroups of gene expression which clustered with clinical prognosis. Of particular interest, in one group they identified positive enrichment for genes involved in the immune system, in cytokine activity and in antiapoptotic genes. In addition there were cases where a high mutation load created abundant tumour-specific neoantigens, which were also significantly enriched in this group.

In another analysis restricted to IHCC, profiling identified two different molecular-defined subclasses with distinctive clinical behaviour.<sup>9</sup> An ‘inflammation’ class

(38% of patients) characterised by activation of inflammatory signalling pathways, overexpression of cytokines and *STAT3* activation, and a ‘proliferation’ class (62% of patients) were characterised by activation of oncogenic signalling pathways (eg, (RAS-Kirsten rat sarcoma viral oncogene homolog and MET-mesenchymal-epithelial transition factor (MET) receptor tyrosine kinase gene)), DNA amplifications at 11q13.2, deletions at 14q22.1, and mutations in *KRAS* and *BRAF*.

A significant feature of these genetic changes is the variation in targets by anatomic site. Bridgewater *et al*<sup>10</sup> have summarised these in table 2, showing that apart from *CDK 2A/B* deletions and *ARID1A*, there is quite a distinct variation between IHCC, EHCC and GBC. To add to this complexity, significant differences in frequency of mutations are reported in liver fluke-related cholangiocarcinomas compared with non-liver fluke in Asians and compared with Western studies.<sup>2</sup> Some of these may be related to anatomic site variations as well as aetiology.

Overall the ability of genomic sequencing to appropriately segment patients into groups for which targeted treatments would be most likely to improve outcomes has been supported by the work of Javle *et al*.<sup>11</sup> They showed a similar spread of genetic changes in a large cohort of patients, but in particular in a subgroup of 321 with clinical annotation. A multivariate analysis showed that TP53 and *kras* mutations were indicators of inferior survival and *FGFR2* of improved survival. In an analysis restricted to intrahepatic cholangiocarcinoma (IHCC), they showed that patients receiving experimental targeted therapies had a numerically better outcome than those on standard therapy (241 vs 186 weeks,  $p=0.07$ ). They also showed that targeting a specific genomic association can have a major impact. They identified a number of fibroblast growth factor receptor (FGFR) aberrant expression in 54 patients. Twenty of those patients received appropriate targeted therapy and the overall survival exceeded those receiving non-FGFR-targeted therapy (25 vs 80 months,  $p=0.006$ ).



**Figure 1** Molecular spectra of BTC. In addition to subtype-specific characteristics, alterations were identified that were common to ICC, intrahepatic cholangiocarcinoma and ECC or common to all three subtypes. Blue symbols indicate genes.

**Table 2** Completed clinical trials with targeted therapies, alone or in combination with chemotherapy, in biliary tract cancers

Therapeutic regimen (target)	Authors	Patients (n)	End points		
<b>EGFR</b>					
Cetuximab			RR	PFS	OS
GEM and cetuximab First-line ph2	Borbath <i>et al</i> <sup>34</sup>	44	20.4	6mPFS 47	13.5
GEMOX and cetuximab First-line, single-arm ph2	Gruenberger <i>et al</i> <sup>35</sup>	30	63%	8.8	15.2
First-line versus GEMOX ph2	Malka <i>et al</i> <sup>36</sup>	150	23 vs 29	6 vs 5.3	11 vs 12.4
First-line versus GEMOX ph2	Chen <i>et al</i> <sup>37</sup>	122	27 vs 15	6.7 vs 4.1	10.6 vs 9.8
Second-line ph2	Paule <i>et al</i> <sup>38</sup>	9	33%	EGFR low: 4 vs high: 7	EGFR low: 7 vs high: 9
GEMCAP versus cetuximab Anyline ph2	Rubovszky <i>et al</i> <sup>39</sup>	34	17.6	8.6	15.7
<b>Panitumumab</b>					
GEMOX and panitumumab First-line ph2 KRAS WT	Hezel <i>et al</i> <sup>40</sup>	31	45%	10.6	20.3
GEMOX-CAP and panitumumab Anyline ph2	Jensen <i>et al</i> <sup>41</sup>	46	33	8.3	10
GEM-IRINO and panitumumab First-line ph2	Sohal <i>et al</i> <sup>42</sup>	35	39	9.7	12.9
GEMCIS and panitumumab versus GEMCIS in KRAS WT First-line ph2	Vogel <i>et al</i> <sup>43</sup>	93	45 vs 39, pNS	6.7 vs 8.2, pNS	12.8 vs 21.4, pNS
<b>Erlotinib</b>					
GEMOX and erlotinib versus GEMOX First-line ph3	Lee <i>et al</i> <sup>44</sup>	268	30 vs 16	5.8 vs 4.2	9.5 vs 9.5
Docetaxel and erlotinib Ph2	Chiorean <i>et al</i> <sup>45</sup>	11	0		5.7
Erlotinib First-/Second-line ph2	Philip <i>et al</i> <sup>46</sup>	42	8	2.6	7.5
<b>HER2</b>					
Lapatinib First-/Second-line ph2	Ramanathan <i>et al</i> <sup>47</sup>	17	0	1.8	5.2
Trastuzumab Second-line ph2	Kaseb <sup>48</sup>	4	50	NR	NR
GEMCIS and afatinib First-line ph1b	Moehler <i>et al</i> <sup>49</sup>	9	NR	158 days	235 days
<b>VEGF and multitarget</b>					
<b>Bevacizumab</b>					
GEMOX and bevacizumab First/Second ph2	Zhu <i>et al</i> <sup>50</sup>	35	40	7	12.7
GEMCAP and bevacizumab First-line ph2	Iyer <i>et al</i> <sup>51</sup>	50	72	8.1	11.3
<b>Sorafenib</b>					
First-line ph2	El-Khoueiry <i>et al</i> <sup>52</sup>	31	0	3	9
Anyline ph2	Bengala <i>et al</i> <sup>53</sup>	46	2	2.3	4.4
GEM-sorafenib versus GEM First-line ph2	Moehler <i>et al</i> <sup>54</sup>	102	8 vs 6	3 vs 4.9	8.4 vs 11.2
GEMCIS and sorafenib First-line ph2	Lee <i>et al</i> <sup>55</sup>	39	NR	6.5	14.4
<b>Sunitinib</b>					
Second-line ph1	Yi <i>et al</i> <sup>56</sup>	56	9	1.7	4.8
Second-line ph2	Neuzillet <i>et al</i> <sup>57</sup>	53	15 DCR: 85	5.2	9.6

Continued



Table 2 Continued

Therapeutic regimen (target)	Authors	Patients (n)	End points		
<b>Cediranib</b>					
GEMCIS and cediranib versus GEMCIS First-line ph2/3	Valle <i>et al</i> <sup>58</sup>	124	44 vs 19	8 vs 7.4	14.1 vs 11.9
Vandetanib First-line ph2	Santoro <i>et al</i> <sup>59</sup>	173	4	105 days	228 days
<b>FGFR</b>					
BGJ398 in CC with FGFR2 ≥Second-line phase 2	Javle <i>et al</i> <sup>60</sup>	26	14 DCR: 82	NR	NR 50% pts on study for >120 days
ODM-203	Ahnert <i>et al</i> <sup>61</sup>	24 (1 CC with FGFR fusion)	8	NR	NR (>40 weeks for CC pt)
<b>MAPK pathway</b>					
Selumetinib First-/Second-line ph2	Bekaii-Saab <i>et al</i> <sup>62</sup>	28	12	3.7	9.8
GEMCIS and selumetinib First-line ph1	Bridgewater <i>et al</i> <sup>63</sup>	12	37.5	6.4	NR
Trametinib	Ioka <i>et al</i> <sup>64</sup>	20	5	10.6 weeks	NR 1 pt>9m
Binimetinib and GEMCIS First-line ph1	Lowery <i>et al</i> <sup>65</sup>	12	50	6.4	9.1
MK-2206 ≥Second-line, ph2	Ahn <i>et al</i> <sup>66</sup>	8	NR	1.7	3.5
<b>c-MET</b>					
Tivantinib + gemcitabine Anyline ph1	Pant <i>et al</i> <sup>67</sup>	20	20	NR	NR
Cabozantinib ≥Second-line ph2	Goyal <i>et al</i> <sup>68</sup>	19	0	1.8	5.2
<b>Multiagent/Other</b>					
Bevacizumab and erlotinib First-line ph2	Lubner <i>et al</i> <sup>69</sup>	49	12	4.4	9.9
Sorafenib and erlotinib First-line ph2	El-Khoueiry <i>et al</i> <sup>70</sup>	34	7	2	6
Bortezomib Second-/Third-line ph2	Denlinger <i>et al</i> <sup>71</sup>	20	5	1.6	9.5
Pazopanib and trametinib ≥Second-line ph1b	Shroff <i>et al</i> <sup>72</sup>	25	5 DCR: 75	4.3	6.7
GEMOX-CAP and panitumumab versus bev First-line with crossover at PD	Jensen <i>et al</i> <sup>73</sup>	88	46 vs 18	6.1 vs 8.2	9.5 vs 12.3
<b>IDH1</b>					
AG-120	Burris <i>et al</i> <sup>74</sup>	20	5 DCR: 60	NR	5 SD>6 months
<b>WNT pathway</b>					
DKN-01 First-line ph1	Eads <i>et al</i> <sup>75</sup>	22 ongoing abstract	33% (3 from 9 evaluable)	NR	NR
<b>Solid tumour studies</b>					
GDC-0919 (IDO1)	Nayak <i>et al</i> <sup>76</sup>	19 (1 CC)	NR	NR	1 CC SD>225 days

CAP, capecitabine; CIS, cisplatin; DCR, disease control rate; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GEM, gemcitabine; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase; IRINO, irinotecan; KRAS, Kirsten rat sarcoma viral oncogene homologue; MAPK, mitogen-activated protein kinase; OS, overall survival; OX, oxaliplatin; PD, progressive disease; PFS, progression-free survival; ph, phase; RR, response rate; VEGF, vascular endothelial growth factor; WT, wild-type.



## KEY PATHWAYS AND SELECTED STUDIES

### Epidermal growth factor receptor

A number of key targets have been identified, including EGFR mutation and amplification, BRAF mutation, and HER2/neu amplification. EGFR blockade has been less successful in four randomised trials, with erlotinib, cetuximab and panitumumab not showing a survival gain (table 1) despite promising progression-free survival.<sup>12</sup> However, a study in a more molecularly defined all RAS wild-type population may still be indicated. Identification of HER2/neu in 13% of Gb and 8% of EHCC and some retrospective data provide an impetus for more defined study.<sup>13</sup> BRAF mutations occur in a small number of BTC cases [2], and given the significant survival advantage that BRAF inhibition gives in the melanoma setting,<sup>14</sup> dual blockade with BRAF and MEK inhibitors merits evaluation in this subset. Further trials with such targets are outlined in table 3.

### Fibroblast growth factor receptor

FGF mutations and fusions predominate in IHCCs in about 16% of cases.<sup>2 12</sup> There are now FGFR-targeted therapies undergoing clinical evaluation. These include multitargeted tyrosine kinase inhibitor (TKIs) that also inhibit FGFR (such as ponatinib, nintedanib, dovitinib and brivanib), as well as specific FGFR-directed small molecule TKI (eg, BGJ398), FGFR antibodies and FGFR trap molecules.<sup>2</sup> A recent phase II interim report was presented of BGJ398. Fifty patients with BTC having FGFR genetic alterations were enrolled, the majority being intrahepatic cholangio carcinoma (IHCC). The overall response rate was 15% and the disease control rate was 95% with progression-free survival of 6 months, supporting further development of FGFR-directed therapy for FGFR mutated cholangiocarcinoma.<sup>15</sup>

### IDH1 and IDH2 mutations in BTC

Mutations in IDH1 and IDH2 have been identified in cholangiocarcinoma. In IHCC, an estimated 20% have IDH1, whereas 5% have IDH2 mutations.<sup>2</sup> These mutations are not seen in EHCC or GBC.<sup>2 12</sup> The mutated IDH1 and IDH2 proteins have a gain-of-function activity, catalysing the reduction of  $\alpha$ -ketoglutarate to 2-hydroxyglutarate (2HG) by NADPH. Cancer-associated IDH mutations block normal cellular differentiation and promote tumorigenesis via the abnormal production of the oncometabolite 2HG,<sup>16</sup> although their prognostic significance is controversial.<sup>2 12</sup> Preliminary results from phase I clinical trials with IDH inhibitors in patients with advanced haematological malignancies have demonstrated an objective response rate ranging from 31% to 40% with durable responses (>1 year) observed.<sup>16</sup> Furthermore, the IDH inhibitors have demonstrated early signals of activity in solid tumours with IDH mutations, including cholangiocarcinomas and low-grade gliomas. Recently, Burris *et al*<sup>17</sup> reported the findings of a dose escalation study of AG-120 in various cancer types having these mutations. Of

the 20 cholangiocarcinoma patients enrolled, response or stability was noted in 12 patients, with disease stability seen beyond 6 months.

### Mutations in chromatin remodelling genes

Chromatin remodelling allows genomic DNA to access regulatory transcriptional proteins and thereby controls gene expression. Inactivating genetic alterations in ARID, BAPI, PBRM and MLL that are responsible for chromatin remodelling have been implicated in the development of BTC. Jiao *et al*<sup>18</sup> observed that mutations in at least one of these genes occurred in almost half of the BTCs sequenced in their study. The prognostic role of mutations in chromatin remodelling genes is currently unknown, although BAPI mutations were associated with aggressive disease resulting in bony metastases.<sup>2</sup> It is hypothesised that histone deacetylase inhibitors such as vorinostat and panobinostat may offer therapeutic value in this setting.<sup>2 12</sup>

### Vascular endothelial growth factor (VEGF)

VEGF expression is increased in many biliary tract cancers, and its expression is associated with metastasis and poor survival. In one retrospective study of 239 cholangiocarcinomas, VEGF was overexpressed in 53.8% and 59.2% of intrahepatic and EHCC, respectively.<sup>19</sup> On this basis, the multitargeted kinase inhibitors of VEGF receptors, such as sorafenib and sunitinib, have been studied without encouraging results.<sup>12 20</sup> Similarly, a recent randomised study with cediranib<sup>21</sup> and a study with the multitargeted kinase vandetanib<sup>22</sup> have also failed to demonstrate a survival advantage, also outlined in table 1. The major stumbling block remains the absence of a reliable biomarker of efficacy for VEGF inhibitors.

### DNA repair mutations in BTC

DNA repair mechanisms are essential for maintaining genomic stability and defects in these occur in BTC. Gene mutations leading to defective DNA mismatch repair (MMR) are commonly seen in several solid tumours like colorectal cancer, endometrial and gastric cancer.<sup>2</sup> Report on 321 BTCs who underwent mutational profiling, and DNA repair mutations (MSH6, BRCA1, BRCA2, ATM, MLH1 or MSH2 genes) occurred in 13% IHCCA, 26% in EHCCA and 6% of GBC cases.<sup>11</sup> The subset of cancers with MMR system defects is very sensitive to programmed cell death protein 1 (PD-1) blockade using checkpoint inhibitor agents like pembrolizumab.<sup>23</sup> BTC patients with mutations in the DNA repair pathways can represent a subset where specific DNA repair inhibitors in addition to immunotherapy may be effective.

### Immunotherapy

Biliary tract cancers represent a potentially attractive target for immune-based therapies given the background association with chronic inflammation<sup>24</sup> and conditions such as cholecystitis, sclerosing cholangitis and primary biliary cirrhosis.<sup>25</sup>

**Table 3** New therapies under evaluation in biliary tract cancers

Therapeutic regimen	Target	Phase	ClinicalTrials.gov identifier	Status
<b>VEGF and multitarget</b>				
Ramucirumab	VEGFR2	2	NCT02520141	Recruiting
GEMCIS and ramucirumab or merestinib	VEGFR2 c-MET	2	NCT02711553	Recruiting
GEMOX and sorafenib	VEGFR-2/3, PDGFR- $\beta$ , B-Raf, C-Raf	1/2	NCT00955721	Completed (efficacy not reported)
GEM and sorafenib	VEGFR-2/3, PDGFR- $\beta$ , B-Raf, C-Raf			
FOLFOX and cediranib	VEGFR	2	NCT01229111	Not recruiting (no results)
Regorafenib	VEGFR1-3, c-KIT, TIE-2, PDGFR- $\beta$ , C-Raf, B-Raf, p38 MAPK, FGFR1-2, Ret	2 2	NCT02115542 NCT02053376	Recruiting Recruiting
<b>MAPK</b>				
Trametinib versus CAP/5FU	MEK 1/2	2	NCT02042443	Ongoing (not recruiting)
Binimetinib (MEK162) and GEMCIS	MEK 1/2	2	NCT01828034	Active (not recruiting)
Binimetinib and GEMOX	MEK 1/2	1	<b>NCT02105350</b>	Suspended (no results)
Binimetinib (MEK162) and capecitabine	MEK	1	NCT02773459	Recruiting
Selumetinib (at different doses) and GEMCIS	MEK 1/2	2	NCT02151084	Recruiting
MEK162 and capecitabine	MEK	1	NCT02773459	Recruiting
<b>mTOR</b>				
Everolimus	mTOR	2	NCT00973713	Unknown (not verified on ClinicalTrials.gov)
GEMCIS and everolimus	mTOR	1	NCT00949949	Not recruiting (no results)
<b>Other</b>				
ARG 087	FGFR	1/2	NCT01752920	Recruiting
Cabozantinib	c-MET, VEGFR2	2	NCT01954745	Active, not recruiting
AG-221	IDH2 mutation	1/2	NCT02273739	Completed (not reported)
GEMCIS and ADH1 (Exherin)	N-cadherin	1	NCT01825603	Recruiting
<b>Immunotherapy</b>				
Nivolumab	PD1	2	NCT02829918	Recruiting
Pembrolizumab and GM-CSF	PD1	2	NCT02703714	Recruiting
Ipilimumab and nivolumab	CTLA4 and PD1	2	NCT02923934	Not yet recruiting
Dendritic cell-precision T cells for neoantigen (DC-PNAT) and gemcitabine	Personalised neoantigens	2	NCT02632019	
<b>Multiagent</b>				
Multiple arms based on molecular profiling (cetuximab, trastuzumab, gefitinib, lapatinib, everolimus, sorafenib, crizotinib)	Multiple (EGFR, HER2, mTOR, VEGF/EGFR/ PDGFR, ALK/ROS1)	2	NCT02836847	Recruiting
Ramucirumab and pembrolizumab		1	NCT02443324	Recruiting

All cited from ClinicalTrials.gov on 21 November 2016.

5FU, 5-fluorouracil; ALK, anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homologue B; CAP, capecitabine; CIS, cisplatin; C-Raf, RAF proto-oncogene serine/threonine protein kinase; CTLA4, cytotoxic T-lymphocyte associated protein 4; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FOLFOX, 5-fluorouracil and oxaliplatin; GEM, gemcitabine; GM-CSF, granulocyte macrophage colony stimulating factor; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; OX, oxaliplatin; PDGFR, platelet-derived growth factor receptor; PD1, programmed cell death protein 1; ROS1, c-ros oncogene 1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.



Recognition that an activated tumour microenvironment exists in biliary cancers encourages a focus on adoptive therapy. There are identified tumour antigens, and the presence of both CD 4+, CD 8+ and Fox3+ T lymphocytes<sup>26</sup> and macrophages suggests both that response to antigen may occur in selected patients and that relevant cells can be isolated and stimulated *ex vivo*. The correlation of activated immune cell infiltration and better outcomes supports a focus on this area.<sup>27</sup>

Approaches to modulating the immune system include:

- ▶ vaccination with putative tumour antigens either as peptides or loaded within dendritic cells to enhance recognition;
- ▶ adoptive immunotherapy where patients' own T cells are expanded *ex vivo* and reinfused;
- ▶ reversing tumour cell-induced immune suppression.

Vaccination against tumour-associated antigens is attractive as a number of proteins that are overexpressed have been identified.<sup>28</sup> At least two tumour-related antigens have been identified with moderate to high expression in biliary cancers – Wilms tumour 1 (WT1) and mucin-1 (MUC-1).<sup>29</sup> Trials of both a dendritic-based cell vaccine against both antigens<sup>30</sup> as well as a randomised trial of chemotherapy and a WT1 vaccine in patients with advanced biliary cancer have been described,<sup>31</sup> as has a trial of combining a dendritic cell pulsed vaccine plus *ex vivo* activated T cells in the postoperative setting.<sup>32</sup> The future of antigen-based therapy may require more refinement as both the distribution of the antigens varies, as does the degree of immune response to them. An approach that identifies those most likely to be responded to in each patient is one such method.<sup>27</sup>

Recently the unpacking of the mechanisms behind tumour-induced immunosuppression has created optimism throughout the cancer community. Data on melanoma, non-small cell lung cancer and renal cancer have all sparked the search for identification of suitable patients for PD-1, PDL-1 and CTLA4 therapies, which can reverse immune suppression. The study by Nakamura *et al*<sup>8</sup> found that the worst prognosis for BTC patients was in those with relatively hypermutated tumours and elevated expression of checkpoint molecules such as CTLA-4 and PDL-1. In total, 45.2% of cases showed an increase in the expression of immune checkpoint molecules. In Keynote-026, a trial of pembrolizumab in advanced biliary tract patients, Bang *et al*<sup>33</sup> reported interim results, that of 89 screened patients 37 (42%) had PD-L1-positive tumours, of those 24 were studied. Eight patients (34%) had response or stable disease lasting 40+ weeks. The variation in immune predictors by anatomic site suggests a need for appropriate selection to trials.<sup>25</sup> In addition there is potential for augmenting tumour immunity with both chemotherapy and radiation. A number of immunotherapy studies are currently recruiting, some of which are outlined in [table 3](#). Ultimately combination studies that use all three approaches to immunotherapy in the context of standard therapy are the most likely to provide sustained benefit.

## CONCLUSIONS

Biliary tract cancers represent a key model of a rare cancer with complex genetic associations. Increasingly it is clear that this anatomic site is a collection of quite disparate genomically distinct neoplasms. Although easily viewed as an intractable problem with a multiplicity of small subgroups, a new approach agnostic to tissue of origin may represent a significant way forward. Instead of dedicated studies in each of intrahepatic, extrahepatic and gall bladder cancer, it may be possible to focus on the new basket trial designs, where a study of a particular targeted therapy directed at a specific mutation is identified and different histological subtypes with the right target are enrolled. If activity is shown, then an expansion study in that indication would follow. When patients are treated in a defined/personalised approach with the right target chosen, informed by their genomic landscape, we can expect to finally make some movement in dealing with this difficult group of diseases.

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## REFERENCES

1. GBD. Mortality and causes of death collaborators. global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the global burden of disease study 2013. *Lancet* 2013;2015:117–71.
2. Jain A, Javle M. Molecular profiling of biliary tract cancer: a target rich disease. *J Gastrointest Oncol* 2016;7:797–803.
3. Marcano-Bonilla L, Mohamed EA, Mounajjed T, *et al*. Biliary tract cancers: epidemiology, molecular pathogenesis and genetic risk associations. *Chin Clin Oncol* 2016;5:61. no 5.
4. Hezel AF, Deshpande V, Zhu AX. Genetics of biliary tract cancers and emerging targeted therapies. *J Clin Oncol* 2010;28:3531–40.
5. Jordan E, Abou-Alfa GK, Lowery MA. Systemic therapy for biliary cancers. *Chin Clin Oncol* 2016;5:65. no 5.
6. <http://www.irci.info/>
7. <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match>
8. Nakamura H, Arai Y, Totoki Y, *et al*. Genomic spectra of biliary tract cancer. *Nat Genet* 2015;47:1003–10.
9. Sia D. *Gastroenterology* 2013;144:829–40.
10. Bridgewater JA, Goodman KA, Kalyan A, *et al*. Biliary tract cancer: epidemiology, radiotherapy, and molecular profiling. *Am Soc Clin Oncol Educ Book* 2016;35:e194–202.
11. Javle M, Bekaii-Saab T, Jain A, *et al*. Biliary cancer: utility of next-generation sequencing for clinical management. *Cancer* 2016;122:3838–47.
12. Chong DQ, Ax Z. The landscape of targeted therapies for cholangiocarcinoma: current status and emerging targets. *Oncotargets Oncotarget* 2016;7:46750–67.
13. Javle M, Churi C2, Kang HC. HER2/neu-directed therapy for biliary tract cancer. *J Hematol Oncol* 2015;29:58.
14. Flaherty KT, Infante JR, Daud A, *et al*. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 2012;367:1694–703.

15. Javle MM, *et al*. Gastrointestinal cancer symposium. *J Clin Oncol* 2016;34(suppl 4S):335.
16. Fujii T, Khawaja MR, DiNardo CD, *et al*. Janku F targeting isocitrate dehydrogenase (IDH) in cancer. *Discov Med*. 2016;21:373–80.
17. Burris H, Mellinghoff I, Maher E, *et al*. Abstract PL04-05: the first reported results of AG-120, a first-in-class, potent inhibitor of the IDH1 mutant protein, in a phase I study of patients with advanced IDH1-mutant solid tumors, including gliomas. *Mol Cancer Ther* 2015;14(Suppl 2):PL04-05–5.
18. Jiao Y, Pawlik TM, Anders RA, *et al*. Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas. *Nat Genet* 2013;45:1470–3.
19. Yoshikawa D, Ojima H, Iwasaki M, *et al*. Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. *Br J Cancer* 2008;98:418–25.
20. Ciombor KK, Goff LW. Current therapy and future directions in biliary tract malignancies. *Curr Treat Options Oncol* 2013;14:337–49.
21. Valle JW, Wasan H, Lopes A, *et al*. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. *Lancet Oncol* 2015;16:967–78.
22. Santoro A, Gebbia V, Pressiani T, *et al*. A randomized, multicenter, phase II study of vandetanib monotherapy versus vandetanib in combination with gemcitabine versus gemcitabine plus placebo in subjects with advanced biliary tract cancer: the VanGogh study. *Ann Oncol* 2015;26:542–7.
23. Le DT, Uram JN, Wang H, *et al*. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372:2509–20.
24. Trinchieri G. Cancer and inflammation: an old intuition with rapidly evolving new concepts. *Annu Rev Immunol* 2012;30:677–706.
25. Duffy AG, Oxana V, Tim F. Makarova-RusherGreten the case for immune-based approaches in biliary tract carcinoma. *Hepatology*. 2016;64:1785–91. no. 5.
26. Goepfert B, Frauenschuh L, Zucknick M, *et al*. Prognostic impact of tumour-infiltrating immune cells on biliary tract cancer. *Br J Cancer* 2013;109:2665–74.
27. Marks IE, Yee NS. Immunotherapeutic approaches in biliary tract carcinoma world. *J Gastrointest Oncol*. 2015;7:338–46.
28. Cheever MA, Allison JP, Ferris AS, *et al*. The prioritization of cancer antigens: a National Cancer Institute pilot project for the acceleration of translational research. *Clin Cancer Res* 2009;15:5323–37.
29. Pauff JM, Goff LW. Current progress in immunotherapy for the treatment of biliary cancers. *J Gastrointest Cancer* 2016;47:351–7.
30. Kobayashi M, Sakabe T, Abe H, *et al*. Dendritic cell-based immunotherapy targeting synthesized peptides for advanced biliary tract cancer. DC-vaccine study group at the Japan Society of Innovative Cell Therapy (J-SICT). *J Gastrointest Surg* 2013;17:1609–17.
31. Okusaka T, Ueno M, Sato T, *et al*. Possibility of immunotherapy for biliary tract cancer: how do we prove efficacy? introduction to a current ongoing phase I and randomized phase II study to evaluate the efficacy and safety of adding Wilms tumor 1 peptide vaccine to gemcitabine and cisplatin for the treatment of advanced biliary tract cancer (WT-BT trial). *J Hepatobiliary Pancreat Sci* 2012;19:314–8.
32. Shimizu K, Kotera Y, Aruga A, *et al*. Clinical utilization of postoperative dendritic cell vaccine plus activated T-cell transfer in patients with intrahepatic cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2012;19:171–8.
33. Bang YJ, Do T, De Braud F, *et al*. Safety and efficacy of pembrolizumab in patients with advanced biliary tract cancers. *Eur J Cancer* 2015;51(suppl 3):S112.
34. Borbath I, Ceratti A, Verslype C, *et al*; Belgian Group of Digestive Oncology. Combination of gemcitabine and cetuximab in patients with advanced cholangiocarcinoma: a phase II study of the belgian group of digestive oncology. *Ann Oncol* 2013;24:2824–9.
35. Gruenberger B, Schueller J, Heubrandtner U, *et al*. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol* 2010;11:1142–8.
36. Malka D, Cervera P, Foulon S, *et al*; BINGO investigators. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. *Lancet Oncol* 2014;15:819–28.
37. Chen JS, Hsu C, Chiang NJ, *et al*; Taiwan Cooperative Oncology Group. A KRAS mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in combination with cetuximab in advanced biliary tract cancer. *Ann Oncol* 2015;26:943–9.
38. Paule B, Herelle MO, Rage E, *et al*. Cetuximab plus gemcitabine-oxaliplatin (GEMOX) in patients with refractory advanced intrahepatic cholangiocarcinomas. *Oncology* 2007;72(1-2):105–10.
39. Rubovszky G, Láng I, Ganofszy E, *et al*. Cetuximab, gemcitabine and capecitabine in patients with inoperable biliary tract cancer: a phase 2 study. *Eur J Cancer* 2013;49:3806–12.
40. Hezel AF, Noel MS, Allen JN, *et al*. Phase II study of gemcitabine, oxaliplatin in combination with panitumumab in KRAS wild-type unresectable or metastatic biliary tract and gallbladder cancer. *Br J Cancer* 2014;111:430–6.
41. Jensen LH, Lindebjerg J, Ploen J, *et al*. Phase II marker-driven trial of panitumumab and chemotherapy in KRAS wild-type biliary tract cancer. *Ann Oncol* 2012;23:2341–6.
42. Sohal DP, Mykulowycz K, Uehara T, *et al*. A phase II trial of gemcitabine, irinotecan and panitumumab in advanced cholangiocarcinoma. *Ann Oncol* 2013;24:3061–5.
43. Vogel A, Panitumumab in combination with gemcitabine/cisplatin (GemCis) for patients with advanced kRAS WT biliary tract cancer: a randomized phase II trial of the arbeitsgemeinschaft internistische onkologie (AIO). *Journal of Clinical Oncology* 2015;33;.
44. Lee J, Park SH, Chang HM, *et al*. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2012;13:181–8.
45. Chiorean EG, Ramasubbaiah R, Yu M, *et al*. Phase II trial of erlotinib and docetaxel in advanced and refractory hepatocellular and biliary cancers: hoosier oncology group GI06-101. *Oncologist* 2012;17:13–e23.
46. Philip PA, Mahoney MR, Allmer C, *et al*. Phase II study of erlotinib in patients with advanced biliary cancer. *J Clin Oncol* 2006;24:3069–74.
47. Ramanathan RK, Belani CP, Singh DA, *et al*. A phase II study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. *Cancer Chemother Pharmacol* 2009;64:777–83.
48. Kaseb AO. Trastuzumab in treating patients with locally advanced or metastatic gallbladder cancer or bile duct cancer that cannot be removed by surgery. 2014.
49. Moehler M, Ehrlich A, Ruckes C, *et al*. 2322 safety and efficacy of afatinib with gemcitabine/Cisplatin in chemo-naïve patients with metastatic biliary tract cancer: an open-label, uncontrolled phase Ib trial. *Eur J Cancer* 2015;51:S440.
50. Zhu AX, Meyerhardt JA, Blaszkowsky LS, *et al*. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: a phase 2 study. *Lancet Oncol* 2010;11:48–54.
51. Iyer RV, Pokuri VK, Groman A, *et al*. A multicenter phase II study of gemcitabine, capecitabine, and bevacizumab for locally advanced or metastatic biliary tract cancer. *Am J Clin Oncol* 2016:1.
52. El-Khoueiry AB, Rankin CJ, Ben-Josef E, *et al*. SWOG 0514: a phase II study of sorafenib in patients with unresectable or metastatic gallbladder carcinoma and cholangiocarcinoma. *Invest New Drugs* 2012;30:1646–51.
53. Bengala C, Bertolini F, Malavasi N, *et al*. Sorafenib in patients with advanced biliary tract carcinoma: a phase II trial. *Br J Cancer* 2010;102:68–72.
54. Moehler M, Maderer A, Schimanski C, *et al*; Working Group of Internal Oncology. Gemcitabine plus sorafenib versus gemcitabine alone in advanced biliary tract cancer: a double-blind placebo-controlled multicentre phase II AIO study with biomarker and serum programme. *Eur J Cancer* 2014;50:3125–35.
55. Lee JK, Capanu M, O'Reilly EM, *et al*. A phase II study of gemcitabine and cisplatin plus sorafenib in patients with advanced biliary adenocarcinomas. *Br J Cancer* 2013;109:915–9.
56. Yi JH, Thongprasert S, Lee J, *et al*. A phase II study of sunitinib as a second-line treatment in advanced biliary tract carcinoma: a multicentre, multinational study. *Eur J Cancer* 2012;48:196–201.
57. Neuzillet C, Seitz JF, Fartoux L, *et al*. Sunitinib as second-line treatment in patients with advanced intrahepatic cholangiocarcinoma (SUN-CK phase II trial): Safety, efficacy, and updated translational results. *Journal of Clinical Oncology* 2015;33;.
58. Valle JW, Wasan H, Lopes A, *et al*. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. *Lancet Oncol* 2015;16:967–78.
59. Santoro A, Gebbia V, Pressiani T, *et al*. A randomized, multicenter, phase II study of vandetanib monotherapy versus vandetanib in combination with gemcitabine versus gemcitabine plus placebo in subjects with advanced biliary tract cancer: the VanGogh study. *Ann Oncol* 2015;26:542–7.
60. Javle MM, Shroff RT, Zhu A, *et al*. A phase 2 study of BGJ398 in patients (pts) with advanced or metastatic FGFR-altered cholangiocarcinoma (CCA) who failed or are intolerant to platinum-based chemotherapy. *Journal of Clinical Oncology* 2016;34;.
61. Ahnert JR, Garratt C, Laapas K. Dose escalation study of ODM-203, a selective dual FGFR/VEGFR inhibitor, in patients with advanced solid tumors. *J Clin Oncol* 2016;34(suppl):2576.





62. Bekaii-Saab T, Phelps MA, Li X, *et al.* Multi-institutional phase II study of selumetinib in patients with metastatic biliary cancers. *J Clin Oncol* 2011;29:2357–63.
63. Bridgewater J, Lopes A, Beare S, *et al.* A phase 1b study of selumetinib in combination with cisplatin and gemcitabine in advanced or metastatic biliary tract cancer: the ABC-04 study. *BMC Cancer* 2016;16:153.
64. Ioka T, Ikeda M, Fukutomi A, *et al.* 2382 A proof-of-concept study of MEK inhibitor trametinib monotherapy in patients with biliary tract cancers. *Eur J Cancer* 2015;51(suppl 3):S464.
65. Lowery MA, O'Reilly EM, Harding JJ, *et al.* A phase I trial of binimetinib in combination with gemcitabine (G) and cisplatin (C) patients (pts) with untreated advanced biliary cancer (ABC). *J Clin Oncol* 2015;33(suppl):e15125.
66. Ahn DH, Li J, Wei L, *et al.* Results of an abbreviated phase-II study with the akt inhibitor MK-2206 in patients with advanced biliary cancer. *Sci Rep* 2015;5:12122.
67. Pant S, Saleh M, Bendell J, *et al.* A phase I dose escalation study of oral c-MET inhibitor tivantinib (ARQ 197) in combination with gemcitabine in patients with solid tumors. *Ann Oncol* 2014;25:1416–21.
68. Goyal L YM, Abrams TA, *et al.* A phase II trial of cabozantinib (XL-184) in patients with advanced cholangiocarcinoma. *J Clin Oncol* 2015;33(Suppl 3):800.
69. Lubner SJ, Mahoney MR, Kolesar JL, *et al.* Report of a multicenter phase II trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: a phase II consortium study. *J Clin Oncol* 2010;28:3491–7.
70. El-Khoueiry AB, Rankin C, Siegel AB, *et al.* S0941: a phase 2 SWOG study of sorafenib and erlotinib in patients with advanced gallbladder carcinoma or cholangiocarcinoma. *Br J Cancer* 2014;110:882–7.
71. Denlinger CS, Meropol NJ, Li T, *et al.* A phase II trial of the proteasome inhibitor bortezomib in patients with advanced biliary tract cancers. *Clin Colorectal Cancer* 2014;13:81–6.
72. Shroff RT, O'Connor A, Gallagher D, *et al.* Pazopanib (P) and trametinib (T) in advanced cholangiocarcinoma (CC): a phase Ib study. *J Clin Oncol* 2015;33(suppl):4072.
73. Jensen LH, Fernebro E, Ploen J, *et al.* Randomized phase II crossover trial exploring the clinical benefit from targeting EGFR or VEGF with combination chemotherapy in patients with non-resectable biliary tract cancer. *J Clin Oncol* 2015;33(suppl):4071.
74. Burris H M.I, Maher E, *et al.* The first reported results of AG-120, a first-in-class, potent inhibitor of the IDH1 mutant protein, in a phase I study of patients with advanced IDH1-mutant solid tumours, including gliomas. *Molecular cancer therapeutics* 2016;14(suppl 2):PL04–5.
75. Eads JR, Goyal L, Stein S, *et al.* Phase I study of DKN-01, an anti-DKK1 antibody, in combination with gemcitabine (G) and cisplatin (C) in patients (pts) with advanced biliary cancer. *J Clin Oncol* 2016;34(suppl):e15603.
76. Nayak A, Hao Z, Sadek R, *et al.* 346 phase 1a study of the safety, pharmacokinetics, and pharmacodynamics of GDC-0919 in patients with recurrent/advanced solid tumors. *Eur J Cancer* 2015;51(suppl 3):S69.



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