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Pemigatinib: Hot topics behind the first approval of a targeted therapy in cholangiocarcinoma

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ABSTRACT

Cholangiocarcinoma (CCA) includes a heterogeneous group of malignancies with limited treatment options. Despite recent advances in medical oncology, the prognosis of CCA patients with metastatic disease remains poor, with a median overall survival of less than a year. In the last decade, notable efforts have been made by the CCA medical community in an attempt to improve clinical outcomes of patients, with the development of molecularly targeted therapies in this setting. Among these treatments, the fibroblast growth factor receptor (FGFR) 2 inhibitor pemigatinib has received accelerated approval in April 2020 by the US Food and Drug Administration (FDA) in CCA patients harboring FGFR2 gene fusions or other rearrangements, on the basis of the results of the FIGHT-202 trial, and thus, representing the first molecularly targeted therapy to be approved for the treatment of CCA. However, several issues remain, including the emergence of polyclonal mutations determining resistance to pemigatinib, the identification of biomarkers predictive of response, and the knowledge gaps regarding the role of other FGFR gene aberrations.

This review aims to provide an overview of recent development of pemigatinib, especially focusing on the results of the pivotal FIGHT-202 trial, the approval of this FGFR inhibitor, and the future challenges concerning the use of FGFR-directed treatments in CCA patients.

Introduction

Cholangiocarcinomas (CCAs) represent a group of aggressive and relatively rare malignancies arising from different locations of the biliary tree and including intrahepatic cholangiocarcinoma (iCCA) and extrahepatic cholangiocarcinoma (eCCA) – with the latter further subclassified into perihilar cholangiocarcinoma (pCCA) and distal cholangiocarcinoma (pCCA) [1-3]. Classically, iCCA originates from the biliary tree within the liver parenchyma, while pCCA and dCCA arise outside the liver [4-6]. Notably enough, despite CCAs have been historically considered rare tumors reporting wide epidemiological differences, according to the presence of well-known risk factors such as liver flukes in Asian countries, the last decades have witnessed a marked increase in most western countries [7-10].

Although radical surgery remains the mainstay of treatment for resectable disease, resection is beneficial for only a small proportion of CCA patients [11]; in addition, even following curative resection and despite aggressive approaches, recurrence rates are high [12,13]. On the basis of these premises, adjuvant treatments have been explored in resected CCA, and despite the recent BILCAP study has raised several controversies, the results of this trial have provided evidence supporting the use of adjuvant capecitabine following CCA resection, based on a median overall survival (OS) benefit (53 months versus 36 months in the observational arm, Hazard Ratio [HR] 0.75, 95% Confidence Intervals [CI] 0.58–0.97, $p = 0.028$) [14-17].

In patients with metastatic disease, ten years after the publication of the ABC-02 and the BT22 trials, the combination of cisplatin plus gemcitabine (CisGem) remains the standard of care first-line therapy [18-20]. However, the overall moderate survival benefit provided by CisGem, with most of patients reporting a median survival of less than one year, has led to huge efforts aimed at identifying more effective treatments in this setting [21,22]. Notably enough, the last decade has witnessed the advent of genomic sequencing, an epochal change which has provided an unprecedented amount of information regarding the processes of cancer pathogenesis in human malignancies [23-26]. As regards CCA, molecular profiling has become increasingly important, with a wide range of studies describing genetic aberrations which are exclusive to specific subtypes of these hepatobiliary tumors [27-33];

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these findings have paved the way towards the development of molecularly targeted therapies in CCA, whose role has been explored and is currently under investigation as monotherapy or in combination with other anticancer agents in several phase I to III clinical trials [34-41] (Fig. 1). However, a large proportion of CCA patients (approximately the 50%) does not harbor potentially actionable aberrations, and the vast majority of data regarding targeted therapies are limited to a highly specific population [42-44]. In fact, "Precision Oncology" is primarily limited to iCCA patients so far, where isocitrate dehydrogenase (IDH) and fibroblast growth factor receptor (FGFR)2 represent the most promising therapeutic targets, as witnessed by several recently published or presented studies [45, 46]. Among these trials, the open-label, multicenter, phase II FIGHT-202 study investigated the role of the FGFR1, FGFR2, and FGFR3 inhibitor pemigatinib in previously treated CCAs, providing an objective response rate (ORR) of 35.5% and median progression-free survival (PFS) of 6.9 months in patients harboring FGFR2 gene fusion or other rearrangements [47]. Following these results, on 17 April 2020, the United States (US) Food and Drug Administration (FDA) granted accelerated approval of this molecule [48]. Nonetheless, the use of pemigatinib has raised important issues, including the emergence of genetic alterations driving acquired resistance, the identification of biomarkers able to predict response to this molecule, and the application of liquid biopsies and circulating tumor DNA (ctDNA) in an attempt to optimize FGFR-directed treatments [49, 50].

In this paper, we provide an overview of the development of pemigatinib as novel therapeutic option in CCA, especially focusing on the results of the FIGHT-202 clinical trial, together with current and future controversies and challenges in this setting.

FGFR2 aberrations in cholangiocarcinoma

The FGFR receptors family is composed of FGFR1, FGFR2, FGFR3, FGFR4, and FGFR5 [51]; from a structural point of view, the first four receptors contain intracellular tyrosine kinase domains, while FGFR5 lacks the tyrosine kinase domain, and thus, the fifth receptor does not seem to be involved in carcinogenetic processes [52]. Notably enough, the FGF/FGFR signaling is implicated in cell proliferation, differentiation, angiogenesis, and intracellular survival, and it is readily apparent that FGFR aberrations have been described in several solid tumors [53]. More specifically, the interaction between FGF ligands to FGFRs causes the dimerization the receptor and the transphosphorylation of the tyrosine kinase domains [54]; subsequently, this process leads to the activation of several intracellular signaling cascades, including JAK/-STAT, phospholipase Cγ (PLCγ), RAS-dependent mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K-CA)/Akt/mTOR (Fig. 2) [55].

As previously stated, FGFR alterations have been observed in a wide range of malignancies, including ovarian cancer, glioma, breast cancer, endometrial cancer, and especially urothelial carcinoma and iCCA [56-59]. With regard to the latter, the predominance of FGFR aberrations have been highlighted in the gene encoding for FGFR2, and in particular, a majority of gene fusions or rearrangements have been identified, with amplifications and mutations reported as less frequent events [60].

FGFR2 gene fusions are estimated to range between 10 and 20% of iCCAs, presenting a mutual exclusivity with KRAS/BRAF mutations and observed as more frequent in non-Opistorchis Viverrini-related malignancies [61]. Notably enough, FGFR2 gene fusions have been reported

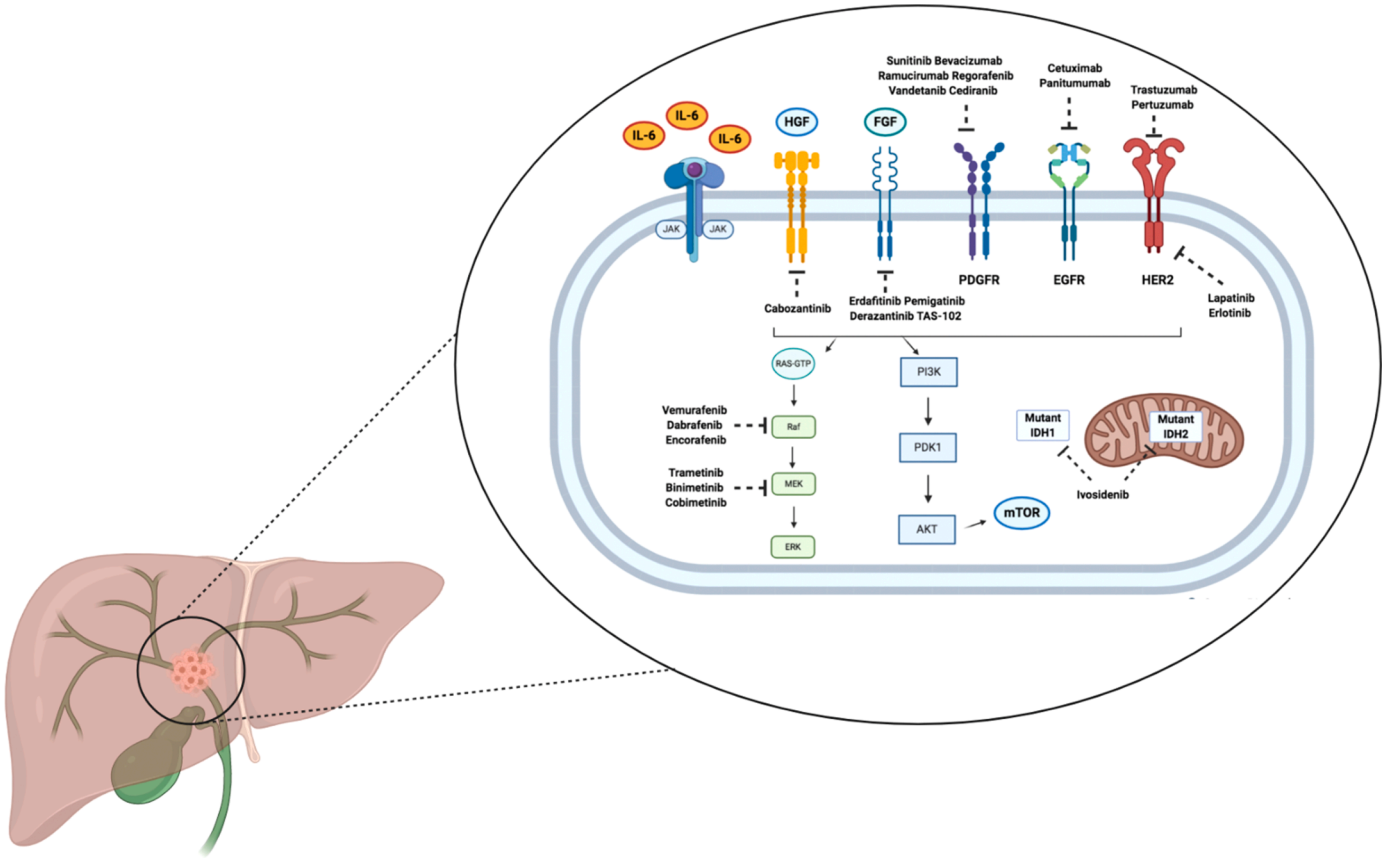

Fig. 1. Schematic representation of therapeutically relevant signaling pathways and selected targeted therapies currently under evaluation in biliary tract cancer. AKT: protein kinase B; EGFR: epidermal growth factor receptor; FGF: fibroblast growth factor; HER2: epidermal growth factor receptor 2; HGF: hepatocyte growth factor; IL-6: interleukin 6; IDH: isocitrate dehydrogenase; JAK: Janus kinase; mTOR: mammalian target of rapamycin; PDGFR: platelet derived growth factor receptor;; PDK1: phosphoinositide-dependent kinase-1; PI3K: phosphoinositide 3-kinase.

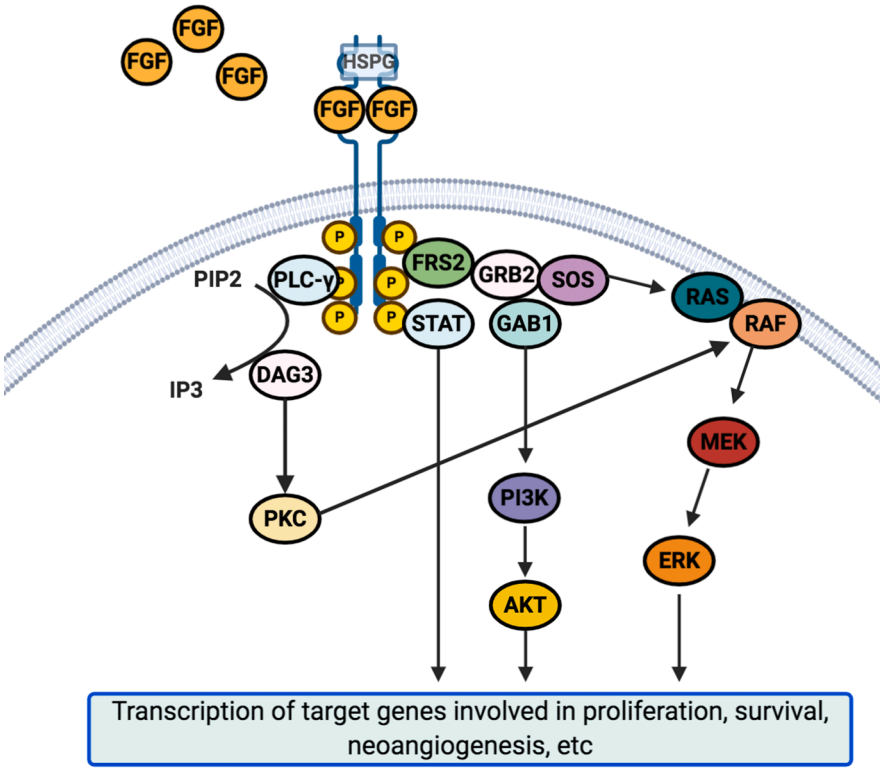

Fig. 2. Schematic figure representing Fibroblast Growth Factor Receptor (FGFR) structure, network, and alteration in tumors. As reported in the text, the FGFR family includes transmembrane receptors composed of three extracellular immunoglobulin-like domains and one intracellular split tyrosine kinase domain, with the exception of FGFR5. The complex of FGF, HSPG, and FGFR results in the receptor dimerization, and subsequent transphosphorylation of tyrosine kinase domains and activation of downstream signaling. Aberrations in FGFR (including mutation, amplification, translocation, etc.) causes a constitutive activation of the kinase domain. Abbreviations: FRS2: fibroblast growth factor receptor substrate 2; HSPG: heparan sulfate proteoglycan; PLC-γ: phospholipase gamma; PIP2: phosphatidylinositol 4,5-bisphosphate; IP3: phosphatidylinositol 3,4,5-triphosphate; DAG: diacylglycerol; PKC: protein kinase C; GRB2: growth factor receptor-bound protein 2; GAB1: GRB2-associated-binding protein; MEK: MAPK/ERK Kinase.

almost exclusively in iCCAs, and represent an extremely rare finding in pCCA, dCCA, and gallbladder cancer [62,63]. Over the years, FGFR2 fusion-positive iCCAs have been suggested to constitute a distinct and unique molecular subtype of CCA, due to the younger age at onset, the less aggressive clinical course, and the female predominance, compared to wild-type iCCA [64,65]. Additionally, patients harboring FGFR2 fusions frequently present concomitant BAP1 mutations and, despite these findings would deserve further evidence, bone metastases [66].

Genomic sequencing has made it possible to describe a wide range of FGFR2 fusion partners, including CREB5, TXLNA, KCTD1, PPHLN1, TACC3, MGEA5, AHCYL1, and BICC1 [67]. In particular, BICC1 has been the first partner to be identified in two cases of iCCA harboring FGFR2-BICC1 fusions in a pivotal report by Wu and colleagues [68]; more recently, several other studies have reported more than 150 fusions partners, with the same BICC1 resulting as the most frequent one [69, 70].

Non-selective and selective FGFR tyrosine-kinase inhibitors: a changing landscape

In recent years, the role of FGFR-directed therapies has been explored in phase I to III clinical trials, with various agents which have been evaluated or are currently being assessed [71]. Firstly, early studies on FGFR inhibition in CCA evaluated non-selective tyrosine kinase inhibitors (TKIs), including lucitanib, lenvatinib, pazopanib, dovitinib, and regorafenib [72-74]; of note, these agents inhibit a multitude of targets beyond the FGFR signaling, such as RET, FLT3, VEGFR, PDGFR, and KIT. However, these drugs reported low antitumor efficacy in FGFR2 fusion-positive iCCAs, and thus, have not entered into clinical practice [75].

On the basis of these premises, further efforts have been directed towards the development of selective FGFR inhibitors, with a wide range of these agents which have reported clinically meaningful activity in several phase II trials on pretreated FGFR2 fusion-positive iCCA patients [76]. As previously stated, pemigatinib represents the FGFR selective inhibitor furthest developed in CCA, and thus, this recently approved molecule will be discussed in detail in the following section.

Among selective FGFR inhibitors, infigratinib (BJG398) reported a median PFS of 5.8 months in previously treated iCCA patients harboring FGFR2 fusions, with an ORR of 18.8% and a disease control rate (DCR) of 83.3% in a phase II trial [77]. Most common all grade toxicities included hyperphosphatemia, fatigue, stomatitis, alopecia, and constipation, while grade 3–4 adverse events comprised hypophosphatemia, hyperphosphatemia, and hyponatremia. Similarly, the use of the orally bioavailable, multi-kinase inhibitor derazantinib (ARQ087) was associated to an ORR of 20.7% and a DCR of 82.8%, according to the results of a recent phase II clinical study [78].

Several other FGFR inhibitors have been assessed and are currently under investigation, including futibatinib, erdafitinib, and Debio 1347. With regard to the latter, the FUZE phase II trial has investigated the role of Debio 1347 not only in FGFR2 fusion-positive iCCAs, but also in patients harboring FGFR1 or FGFR3 gene fusions or rearrangements (NCT03834220). Of note, this study has finished recruitment, with results pending.

As witnessed by results presented by Goyal and colleagues at ESMO World Congress on Gastrointestinal Cancer 2020, the irreversible FGFR inhibitor futibatinib (TAS-120) has reported remarkable results in the FOENIX-CCA2 phase II trial [79]. In this open-label, multicenter study, 67 iCCA patients harboring FGFR2 gene fusions or other rearrangements were treated with futibatinib monotherapy; according to the results of this trial, ORR and a DCR were 34.3% and 76.1%, respectively. Not only that, the CCA medical community has shown growing attention towards this molecule, which has shown antitumor activity in patients previously treated with other FGFR inhibitors, and thus suggesting that futibatinib could play an important role in overcome acquired resistance in this setting [80,81].

Pemigatinib and FIGHT-202

Pemigatinib is a small molecule inhibitor of FGFR1, FGFR2, and FGFR3 (Table 1) [82]. Although the assessment of this molecule in CCA patients is recent, pemigatinib represents the first targeted treatment to be approved in CCA [48]. This US FDA approval has been based on the results of a phase II, open-label, multinational trial, the FIGHT-202, which explored the role of pemigatinib in previously treated metastatic CCA patients with FGFR2 fusions or rearrangements ($n = 107$), other FGF/FGFR aberrations ($n = 20$), or without FGFR alterations ($n = 18$) [47]. Pemigatinib was administered orally at the following starting dose: 13.5 mg once daily, on days 1–14 of 21-day cycles - 2 weeks on, 1 week off [47]. According to the study design of FIGHT-202, this phase II trial included patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0, 1, or 2, and whose disease had progressed following at least one treatment. Tumor response was evaluated by independent review according to RECIST 1.1 [47].

Notably enough, after a median follow-up of 17.8 months, the 35.5% (38/107) of patients harboring FGFR2 fusions or rearrangements showed an objective response, with 3 CCAs achieving complete responses and a median duration of treatment of 7.2 months [47]. Conversely, no responses were highlighted in the other two cohorts of CCA patients. With regards to other clinical outcomes, median PFS and median OS were 6.9 months and 21.1 months in patients with FGFR2 fusions or rearrangements. On the contrary, median PFS in the subgroup of patients with other FGF/FGFR alterations and in those without FGF/FGFR alterations was 2.1 months and 1.7 months, respectively; in the same patient populations, median OS was 6.7 months and 4.0 months, while median duration of treatment 1.4 months and 1.3 months, respectively [47].

In terms of side effects, the safety profile of pemigatinib was similar to what observed in previous trials on FGFR inhibitors in CCA and other malignancies, as well as in the FIGHT-101 on advanced solid tumors and the FIGHT-201 in metastatic urothelial carcinoma [24,56]. In FIGHT-202, hyperphosphatemia was recorded as the most frequent all-grade adverse event, which was observed in the 60% of enrolled subjects (88/146) [47]. In addition, 93 of 146 patients (64%) had grade 3 or worse toxicities, the most frequent of which were hypophosphatemia (12%), arthralgia (6%), abdominal pain (5%), stomatitis (5%), fatigue (5%), and hyponatremia (5%). Lastly, no grade 5 adverse events were deemed to be pemigatinib-related [47].

Based on these results, on April 17, 2020, the US FDA granted accelerated approval to pemigatinib for the medical treatment of previously treated patients with metastatic CCA harboring FGFR2 fusion or other rearrangement detected by the FoundationOne® CDX (Foundation Medicine, Inc.) test [48]. Of note, this approval has symbolically marked a new era, since pemigatinib represents the first targeted treatment approved for CCA in the USA.

Table 1
Drug summary of pemigatinib features.

Drug names	Pemigatinib; IBI-375; INCB-054,828; INCB-54,828; Pemazyre
Route of administration	Recommended dose: 13.5 mg once daily, on days 1–14 of a 21-day cycle until unacceptable toxicity or disease progression
Pharmacokinetics	Pemigatinib concentrations increase proportionally over a 1–20 mg dose range at steady state; the drug can be administered with or without food; median time to maximum plasma pemigatinib concentration is 1.13 h
Pharmacodynamics	Selective inhibitor of FGFR1, FGFR2, and FGFR3
Most common toxicities	Hyperphosphatemia, alopecia, diarrhea, fatigue, dysgeusia
Chemical name	3-(2,6-difluoro-3,5-dimethoxyphenyl)−1-ethyl-8-(morpholin-4-ylmethyl)−1,3,4,7-tetrahydro-2*H*-pyrrolo[3′,2′:5,6]pyrido[4,3-*d*]pyrimidin-2-one
Molecular formula	$C_{24}H_{27}F_2N_5O_4$

However, the results of the FIGHT-202 warrant further validation and more studies are warranted.

Pemigatinib and other FGFR inhibitors: open questions and new frontiers

Although the recently published results of the FIGHT-202 and the approval of pemigatinib represent a “breath of optimism” in a setting with traditionally limited treatment options and extremely disappointing prognosis, the efficacy of pemigatinib and other FGFR inhibitors is considerably limited by the emergence of acquired resistance [83]. In fact, secondary polyclonal mutations represent a notable challenge in FGFR-directed treatments in CCA, and further efforts are needed to optimize the use of these molecularly targeted therapies [83,84]. In 2017, a landmark report by Goyal and colleagues represented the first evidence of acquired resistance to FGFR inhibitors [83]; in this study, 3 iCCA patients with FGFR2 fusion received BGJ398 [83]. Notably enough, sequencing of cell-free DNA and biopsy samples collected at different stages (at baseline and post-progression) highlighted polyclonal mutations in the FGFR2 kinase domain [83]. In addition, a more recent report by the same author showed that futibatinib showed efficacy in 4 patients with FGFR2 fusions who previously experienced disease progression on FGFR inhibitors [81]. All things considered, in such a scenario a growing role will be played by liquid biopsy, which has the potential to track the emerging of acquired resistance, and thus to guide treatment selection [85]. In fact, strategic sequencing of FGFR inhibitors, oriented by serial biopsies and ctDNA could prolong the duration of benefit from these molecularly targeted treatments, and the coming years will probably tell us if this non-invasive strategy could become a fundamental tool in the everyday management of these patients.

In addition, since the therapeutic landscape of CCA is rapidly moving, novel strategies are currently under investigation and will be assessed. Among these, FGFR inhibitors are being explored as first-line treatment option in CCA patients with metastatic disease, as witnessed by the ongoing FIGHT-302 trial (NCT03656536). In fact, this study aims at comparing the reference doublet CisGem versus the FGFR inhibitor pemigatinib in treatment-naïve patients harboring FGFR2 rearrangements. Of note, the results of this phase III trial are awaited, and will provide important information regarding the superiority of pemigatinib or systemic chemotherapy as front-line treatment. The study has a planned enrollment of 432 participants, with an estimated primary completion date in October 2023.

Moreover, another potential approach includes the attempt to achieve more durable responses using the synergistic effect of combination therapies. In fact, despite only preclinical results have been observed so far, murine models have suggested that immune microenvironment of tumors can be altered by FGFR inhibition, and thus resulting in enhanced antitumor T cell responses [86]. Additionally, specific FGFR inhibitors have shown activity against other tyrosine kinases, with derazantinib which has been suggested to inhibit in vitro the Colony Stimulating Factor 1 Receptor (CSF1R), whose activity has been involved in the inhibition of immune checkpoints [87,88].

Lastly, another strategy under assessment involves the addition of a third drug to the reference doublet CisGem as first-line treatment, exploring the synergistic effect of combination therapies including pemigatinib plus systemic chemotherapy (NCT04088188).

Conclusions

The recent US FDA approval of pemigatinib in previously treated patients with locally advanced unresectable or metastatic CCA and FGFR2 gene fusions or rearrangements has symbolically marked a new era in CCA management, representing the first targeted therapy to be approved in this setting. However, several questions remain unanswered, including the development of secondary polyclonal mutations,

the proper use of liquid biopsy, and the identification of biomarkers predictive of response to FGFR inhibitors.

A more comprehensive definition of resistance mechanisms and the development of novel therapeutic strategies represent urgent needs, and results of ongoing clinical trials are highly awaited.

Financial & competing interests' disclosure

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] S. Rizvi, G.J Gores, Pathogenesis, diagnosis, and management of cholangiocarcinoma, Gastroenterology 145 (6) (2013) 1215–1229.
[2] D. Waseem, P Tushar, Intrahepatic, perihilar and distal cholangiocarcinoma: management and outcomes, Ann Hepatol 16 (1) (2017 Jan-Feb 2017) 133–139, https://doi.org/10.5604/16652681.1226927. PMID: 28051802PMCID: PMC5630455.
[3] A. Forner, G. Vidili, M. Rengo, L. Bujanda, et al., Clinical presentation, diagnosis and staging of cholangiocarcinoma, Liver Int 39 (Suppl 1) (2019) 98–107.
[4] J.M. Banales, J.J.G. Marin, A. Lamarca, et al., Cholangiocarcinoma 2020: the next horizon in mechanisms and management, Nat. Rev Gastroenterol Hepatol. (2020), https://doi.org/10.1038/s41575-020-0310-z.
[5] A. Rizzo, A.D. Ricci, G Brandi, Recent advances of immunotherapy for biliary tract cancer, Expert Rev. Gastroenterol. Hepatol (2021 Jan 8) 1–10.
[6] N. Razumilava, G.J Gores, Cholangiocarcinoma, Lancet 383 (9935) (2014) 2168–2179.
[7] S.K. Saha, A.X. Zhu, C.S. Fuchs, G.A. Brooks, Forty-year trends in cholangiocarcinoma incidence in the US: intrahepatic disease on the rise, Oncologist 21 (2016) 594–599.
[8] J.A. Bridgewater, K.A. Goodman, A. Kalyan, M.F Mulcahy, Biliary tract cancer: epidemiology, radiotherapy, and molecular profiling, Am Soc Clin Oncol Educ Book 35 (2016) e194–e203, https://doi.org/10.1200/EDBK_160831. PMID: 27249723.
[9] N. Schweitzer, M. Fischer, M.M. Kirstein, et al., Risk estimation for biliary tract cancer: development and validation of a prognostic score, Liver Int 37 (12) (2017 Dec) 1852–1860, https://doi.org/10.1111/liv.13517. Epub 2017 Jul 28PMID: 28695669.
[10] J.M. Banales, V. Cardinale, G. Carpino, et al., Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA), Nat. Rev. Gastroenterol Hepatol. 13 (5) (2016) 261–280.
[11] S. Matsukuma, Y. Tokumitsu, Y. Shindo, H. Matsui, H. Nagano, Essential updates to the surgical treatment of biliary tract cancer, Ann Gastroenterol. Surg 3 (4) (2019 May 22) 378–389, https://doi.org/10.1002/ags3.12266. PMID: 31346577PMCID: PMC6635684.
[12] M.L. DeOliveira, S.C. Cunningham, J.L. Cameron, F. Kamangar, J.M. Winter, K. D. Lillemoe, et al., Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution, Ann Surg. 245 (2007) 755–762.
[13] G.G. Kasumova, O. Tabatabaie, R.M. Najarian, et al., Surgical management of gallbladder cancer: simple versus extended cholecystectomy and the role of adjuvant therapy, Ann Surg 266 (4) (2017) 625–631.
[14] R.T. Shroff, E.B. Kennedy, M. Bachini, et al., Adjuvant therapy for resected biliary tract cancer: ASCO Clinical Practice Guideline, J Clin Oncol 37 (12) (2019) 1015–1027.
[15] J. Edeline, M. Benabdelghani, A. Bertaut, et al., Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): a Randomized Phase III Study, J Clin Oncol 37 (8) (2019 Mar 10) 658–667, https://doi.org/10.1200/JCO.18.00050. Epub 2019 Feb 1PMID: 30707660.
[16] A. Rizzo, G Brandi, BILCAP trial and adjuvant capecitabine in resectable biliary tract cancer: reflections on a standard of care, Expert Rev Gastroenterol Hepatol (2020 Dec 18) 1–3, https://doi.org/10.1080/17474124.2021.1864325. Epub ahead of printPMID: 33307876.
[17] J.N. Primrose, R.P. Fox, D.H. Palmer, et al., Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study, Lancet Oncol 20 (5) (2019) 663–673.
[18] J. Valle, H. Wasan, D.H. Palmer, et al., ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer, N Engl J. Med. 362 (2010) 1273–1281.
[19] J.W. Valle, J. Furuse, M. Jitlal, S. Beare, N. Mizuno, H. Wasan, J. Bridgewater, T Okusaka, Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials, Ann. Oncol 25 (2) (2014 Feb) 391–398, https://doi.org/10.1093/annonc/mdt540. Epub 2013 Dec 18PMID: 24351397.
[20] R.K. Kelley, J. Bridgewater, G.J. Gores, A.X Zhu, Systemic therapies for intrahepatic cholangiocarcinoma, J Hepatol 72 (2) (2020) 353–363.
[21] A. Rizzo, A.D. Ricci, G Brandi, PD-L1, TMB, MSI, and other predictors of response to immune checkpoint inhibitors in biliary tract cancer, Cancers (Basel) 13 (3) (2021 Feb 1) 558.
[22] D.P. Sohal, S. Shrotriya, M. Abazeed, M. Cruise, A Khorana, Molecular characteristics of biliary tract cancer, Crit Rev Oncol Hematol 107 (2016 Nov) 111–118, https://doi.org/10.1016/j.critrevonc.2016.08.013. Epub 2016 Sep 13PMID: 27823638.
[23] A. Lamarca, J. Barriuso, M.G. McNamara, J.W Valle, Molecular targeted therapies: ready for "prime time" in biliary tract cancer, J Hepatol. 73 (1) (2020) 170–185.
[24] G. Lamberti, E. Andrini, M. Sisi, et al., Beyond EGFR, ALK and ROS1: current evidence and future perspectives on newly targetable oncogenic drivers in lung adenocarcinoma, Crit Rev Oncol. Hematol 156 (2020 Dec), 103119.
[25] A. Massa, C. Varamo, F. Vita, et al., Evolution of the experimental models of cholangiocarcinoma, Cancers (Basel) 12 (2020) 2308.
[26] A. Astolfi, M. Nannini, V. Indio, et al., Genomic database analysis of uterine leiomyosarcoma mutational profile, Cancers (Basel) 12 (8) (2020 Jul 31) 2126, https://doi.org/10.3390/cancers12082126. PMID: 32751892PMCID: PMC7464219.
[27] J.W. Valle, A. Lamarca, L. Goyal, J. Barriuso, A.X Zhu, New Horizons for Precision Medicine in Biliary Tract Cancers, Cancer Discov 7 (9) (2017 Sep) 943–962, https://doi.org/10.1158/2159-8290.CD-17-0245. Epub 2017 Aug 17PMID: 28818953PMCID: PMC5586506.
[28] J.D. Mizrahi, R.T Shroff, New treatment options for advanced biliary tract cancer, Curr Treat Options Oncol. 21 (8) (2020) 63.
[29] M. Javle, H. Zhao, G.K Abou-Alfa, Systemic therapy for gallbladder cancer, Chin Clin Oncol 8 (4) (2019 Aug) 44, https://doi.org/10.21037/cco.2019.08.14. PMID: 31484490.
[30] I. Malenica, M. Donadon, A Lleo, Molecular and immunological characterization of biliary tract cancers: a paradigm shift towards a personalized medicine, Cancers (Basel) 12 (2020) 2190.
[31] B.A. Weinberg, J. Xiu, M.R. Lindberg, et al., Molecular profiling of biliary cancers reveals distinct molecular alterations and potential therapeutic targets, J Gastrointest Oncol. 10 (2019) 652–662.
[32] S. Rizvi, G.J Gores, Emerging molecular therapeutic targets for cholangiocarcinoma, J Hepatol 67 (3) (2017 Sep) 632–644, https://doi.org/10.1016/j.jhep.2017.03.026. Epub 2017 Apr 5PMID: 28389139PMCID: PMC5563275.
[33] H. Nakamura, Y. Arai, Y. Totoki, et al., Genomic spectra of biliary tract cancer, Nat Genet 47 (9) (2015 Sep) 1003–1010, https://doi.org/10.1038/ng.3375. Epub 2015 Aug 10PMID: 26258846.
[34] A. Athauda, C. Fong, D.K. Lau, et al., Broadening the therapeutic horizon of advanced biliary tract cancer through molecular characterisation, Cancer Treat Rev 86 (2020 Jun), 101998, https://doi.org/10.1016/j.ctrv.2020.101998. Epub 2020 Mar 12PMID: 32203843.
[35] G.K. Abou-Alfa, T. Macarulla, M.M. Javle, et al., Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study, Lancet Oncol 21 (6) (2020 Jun) 796–807, https://doi.org/10.1016/S1470-2045(20)30157-1. Epub 2020 May 13. Erratum in: Lancet Oncol. 2020 Oct;21(10):e462. PMID: 32416072; PMCID: PMC7523268.
[36] A.D. Ricci, A. Rizzo, G Brandi, Immunotherapy in biliary tract cancer: worthy of a second look, Cancer Control 27 (3) (2020 Jul-Aug), 1073274820948047, https://doi.org/10.1177/1073274820948047. PMID: 32806956.
[37] M. Javle, T. Bekaii-Saab, A. Jain, et al., Biliary cancer: utility of next-generation sequencing for clinical management, Cancer 122 (24) (2016 Dec 15) 3838–3847, https://doi.org/10.1002/cncr.30254. Epub 2016 Sep 13PMID: 27622582.
[38] A.D. Ricci, A. Rizzo, G Brandi, The DNA damage repair (DDR) pathway in biliary tract cancer (BTC): a new Pandora's box? ESMO Open 5 (5) (2020 Sep), e001042 https://doi.org/10.1136/esmoopen-2020-001042. PMID: 32994319PMCID: PMC7526276.
[39] E. Oneda, M. Abu Hilal, A Zaniboni, Biliary Tract Cancer: current Medical Treatment Strategies, Cancers (Basel) 12 (5) (2020) 1237.
[40] C. Morizane, M. Ueno, M. Ikeda, T. Okusaka, H. Ishii, J. Furuse, New developments in systemic therapy for advanced biliary tract cancer, Jpn J Clin Oncol 48 (8) (2018 Aug 1) 703–711, https://doi.org/10.1093/jjco/hyy082. PMID: 29893894.
[41] Y.S. Chun, M Javle, Systemic and adjuvant therapies for intrahepatic cholangiocarcinoma, Cancer Control 24 (3) (2017 Jul-Sep), https://doi.org/10.1177/1073274817729241, 1073274817729241PMID: 28975832PMCID: PMC5937242.
[42] A. Mahipal, A. Kommalapati, S.H. Tella, A. Lim, R Kim, Novel targeted treatment options for advanced cholangiocarcinoma, Expert Opin Investig Drugs 27 (9) (2018 Sep) 709–720.

[43] A. Jusakul, I. Cutcutache, C.H. Yong, et al., Whole-genome and epigenomic landscapes of etiologically distinct subtypes of cholangiocarcinoma, Cancer Discov 7 (10) (2017 Oct) 1116–1135, https://doi.org/10.1158/2159-8290.CD-17-0368. Epub 2017 Jun 30PMID: 28667006PMCID: PMC5628134.

[44] S. Chakrabarti, M. Kamgar, A Mahipal, Targeted therapies in advanced biliary tract cancer: an evolving paradigm, Cancers (Basel) 12 (8) (2020 Jul 24) 2039.

[45] R.M. Fostea, E. Fontana, G. Torga, H.T Arkenau, Recent progress in the systemic treatment of advanced/metastatic cholangiocarcinoma, Cancers (Basel) 12 (9) (2020 Sep 11) 2599, https://doi.org/10.3390/cancers12092599. PMID: 32932925PMCID: PMC7565778.

[46] Q.U.A.R. Sipra, R Shroff, The impact of molecular profiling on cholangiocarcinoma clinical trials and experimental drugs, Expert Opin Investig Drugs (2020 Nov 23) 1–4, https://doi.org/10.1080/13543784.2021.1849139. Epub ahead of printPMID: 33228417.

[47] G.K. Abou-Alfa, V. Sahai, A. Hollebecque, et al., Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study, Lancet Oncol (2020) pii: S1470-2045(20)30109-1.

[48] S.M Hoy, Pemigatinib: first approval, Drugs 80 (9) (2020 Jun) 923–929, https://doi.org/10.1007/s40265-020-01330-y. PMID: 32472305.

[49] A. Rizzo, A.D. Ricci, S. Tavolari, G Brandi, Circulating tumor DNA in biliary tract cancer: current evidence and future perspectives, Cancer Genomics Proteomics 17 (5) (2020) 441–452.

[50] A. Saborowski, U. Lehmann, A Vogel, FGFR inhibitors in cholangiocarcinoma: what's now and what's next? Ther Adv Med Oncol 12 (2020 Sep 16) https://doi.org/10.1177/1758835920953293, 1758835920953293PMID: 32983265PMCID: PMC7498964.

[51] M. Touat, E. Ileana, S. Postel-Vinay, F. André, J.C Soria, Targeting FGFR signaling in cancer, Clin Cancer Res 21 (12) (2015 Jun 15) 2684–2694, https://doi.org/10.1158/1078-0432.CCR-14-2329. PMID: 26078430.

[52] M. Presta, P. Chiodelli, A. Giacomini, M. Rusnati, R Ronca, Fibroblast growth factors (FGFs) in cancer: FGF traps as a new therapeutic approach, Pharmacol Ther 179 (2017 Nov) 171–187, https://doi.org/10.1016/j.pharmthera.2017.05.013. Epub 2017 May 28PMID: 28564583.

[53] T. Helsten, S. Elkin, E. Arthur, B.N. Tomson, J. Carter, R. Kurzrock, The FGFR landscape in cancer: analysis of 4,853 tumors by next-generation sequencing, Clin Cancer Res 22 (2016) 259–267.

[54] N. Hallinan, S. Finn, S. Cuffe, S. Rafee, K. O'Byrne, K Gately, Targeting the fibroblast growth factor receptor family in cancer, Cancer Treat Rev 46 (2016 May) 51–62, https://doi.org/10.1016/j.ctrv.2016.03.015. Epub 2016 Apr 12PMID: 27109926.

[55] I.S. Babina, N.C Turner, Advances and challenges in targeting FGFR signalling in cancer, Nat Rev Cancer 17 (5) (2017 May) 318–332, https://doi.org/10.1038/nrc.2017.8. Epub 2017 Mar 17PMID: 28303906.

[56] V. Mollica, A. Rizzo, R. Montironi, et al., Current strategies and novel therapeutic approaches for metastatic urothelial carcinoma, Cancers (Basel) 12 (6) (2020 Jun 2) 1449, https://doi.org/10.3390/cancers12061449. PMID: 32498352PMCID: PMC7352972.

[57] J. Perez-Garcia, E. Muñoz-Couselo, J. Soberino, F. Racca, J Cortes, Targeting FGFR pathway in breast cancer, Breast 37 (2018 Feb) 126–133, https://doi.org/10.1016/j.breast.2017.10.014. Epub 2017 Nov 20PMID: 29156384.

[58] S. Khalique, S Banerjee, Nintedanib in ovarian cancer, Expert Opin Investig Drugs 26 (9) (2017 Sep) 1073–1081, https://doi.org/10.1080/13543784.2017.1353599. PMID: 28721753.

[59] S. Rizvi, M.J Borad, The rise of the FGFR inhibitor in advanced biliary cancer: the next cover of time magazine? J Gastrointest Oncol 7 (5) (2016 Oct) 789–796, https://doi.org/10.21037/jgo.2016.08.12. PMID: 27747092PMCID: PMC5056253.

[60] A. Mahipal, S.H. Tella, A. Kommalapati, D. Anaya, R Kim, FGFR2 genomic aberrations: achilles heel in the management of advanced cholangiocarcinoma, Cancer Treat Rev 78 (2019 Aug) 1–7, https://doi.org/10.1016/j.ctrv.2019.06.003. Epub 2019 Jun 22PMID: 31255945.

[61] A. Jusakul, S. Kongpetch, B.T Teh, Genetics of Opisthorchis viverrini-related cholangiocarcinoma, Curr Opin Gastroenterol 31 (3) (2015 May) 258–263, https://doi.org/10.1097/MOG.0000000000000162. PMID: 25693006.

[62] D.Y. Zhao, K.H Lim, Current biologics for treatment of biliary tract cancers, J Gastrointest Oncol (2017), https://doi.org/10.21037/jgo.2017.05.04. Published online.

[63] S. Kongpetch, A. Jusakul, C.K. Ong, et al., Pathogenesis of cholangiocarcinoma: from genetics to signalling pathways, Best Pract Res Clin Gastroenterol 29 (2) (2015 Apr) 233–244, https://doi.org/10.1016/j.bpg.2015.02.002. Epub 2015 Feb 17PMID: 25966424.

[64] Y. Arai, Y. Totoki, F. Hosoda, et al., Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma, Hepatology 59 (4) (2014 Apr) 1427–1434, https://doi.org/10.1002/hep.26890. Epub 2014 Feb 18PMID: 24122810.

[65] C.R. Churi, R. Shroff, Y. Wang, et al., Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications, PLoS ONE 9 (12) (2014 Dec 23), e115383, https://doi.org/10.1371/journal.pone.0115383. PMID: 25536104PMCID: PMC4275227.

[66] Y. Jiao, T.M. Pawlik, R.A. Anders, et al., Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas, Nat Genet 45 (12) (2013 Dec) 1470–1473, https://doi.org/10.1038/ng.2813. Epub 2013 Nov 3PMID: 24185509PMCID: PMC4013720.

[67] M.J. Borad, M.D. Champion, J.B. Egan, et al., Integrated genomic characterization reveals novel, therapeutically relevant drug targets in FGFR and EGFR pathways in sporadic intrahepatic cholangiocarcinoma, PLoS Genet 10 (2) (2014 Feb 13), e1004135, https://doi.org/10.1371/journal.pgen.1004135. PMID: 24550739PMCID: PMC3923676.

[68] Y.M. Wu, F. Su, S. Kalyana-Sundaram, et al., Identification of targetable FGFR gene fusions in diverse cancers, Cancer Discov 3 (6) (2013 Jun) 636–647, https://doi.org/10.1158/2159-8290.CD-13-0050. Epub 2013 Apr 4PMID: 23558953PMCID: PMC3694764.

[69] J.S. Ross, K. Wang, L. Gay, et al., New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing, Oncologist 19 (3) (2014 Mar) 235–242, https://doi.org/10.1634/theoncologist.2013-0352. Epub 2014 Feb 21PMID: 24563076PMCID: PMC3958461.

[70] S. Zou, J. Li, H. Zhou, et al., Mutational landscape of intrahepatic cholangiocarcinoma, Nat Commun 5 (2014 Dec 15) 5696, https://doi.org/10.1038/ncomms6696. PMID: 25526346.

[71] T. Yang, L. Liang, M.D. Wang, F Shen, FGFR inhibitors for advanced cholangiocarcinoma, Lancet Oncol 21 (5) (2020 May) 610–612, https://doi.org/10.1016/S1470-2045(20)30152-2. Epub 2020 Mar 20PMID: 32203699.

[72] R.T. Shroff, M. Yarchoan, A. O'Connor, et al., The oral VEGF receptor tyrosine kinase inhibitor pazopanib in combination with the MEK inhibitor trametinib in advanced cholangiocarcinoma, Br J Cancer 116 (11) (2017 May 23) 1402–1407, https://doi.org/10.1038/bjc.2017.119. Epub 2017 Apr 25. Erratum in: Br J Cancer. 2018 Jan 09: PMID: 28441383; PMCID: PMC5520097.

[73] M. Ueno, M. Ikeda, T. Sasaki, et al., Phase 2 study of lenvatinib monotherapy as second-line treatment in unresectable biliary tract cancer: primary analysis results, BMC Cancer 20 (1) (2020 Nov 16) 1105, https://doi.org/10.1186/s12885-020-07365-4. PMID: 33198671PMCID: PMC7667859.

[74] M.A. Krook, A. Lenyo, M. Wilberding, et al., Efficacy of FGFR inhibitors and combination therapies for acquired resistance in FGFR2-fusion cholangiocarcinoma, Mol Cancer Ther 19 (3) (2020 Mar) 847–857, https://doi.org/10.1158/1535-7163.MCT-19-0631. Epub 2020 Jan 7PMID: 31911531PMCID: PMC7359896.

[75] R. Plummer, A. Madi, M. Jeffels, et al., A Phase I study of pazopanib in combination with gemcitabine in patients with advanced solid tumors, Cancer Chemother Pharmacol 71 (1) (2013 Jan) 93–101, https://doi.org/10.1007/s00280-012-1982-z. Epub 2012 Oct 11PMID: 23064954PMCID: PMC3535414.

[76] A. Rizzo, A.D. Ricci, N. Tober, et al., Second-line treatment in advanced biliary tract cancer: today and tomorrow, Anticancer Res 40 (6) (2020 Jun) 3013–3030, https://doi.org/10.21873/anticanres.14282. PMID: 32487595.

[77] M. Javle, M. Lowery, R.T. Shroff, et al., Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma, J Clin Oncol 36 (3) (2018 Jan 20) 276–282, https://doi.org/10.1200/JCO.2017.75.5009. Epub 2017 Nov 28PMID: 29182496PMCID: PMC6075847.

[78] V. Mazzaferro, B.F. El-Rayes, M. Droz Dit Busset, et al., Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma, Br. J. Cancer 120 (2019) 165–171.

[79] L. Goyal, F. Meric-Bernstam, A. Hollebecque, et al., FOENIX-CCA2: a phase II, open-label, multicenter study of futibatinib in patients (pts) with intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene fusions or other rearrangements, J. Clin Oncol. 38 (15_suppl) (2020), 108-108.

[80] A. Rizzo, A.D. Ricci, G Brandi, Futibatinib, an investigational agent for the treatment of intrahepatic cholangiocarcinoma: evidence to date and future perspectives, Expert Opin Investig Drugs (2020 Oct 25) 1–8.

[81] L. Goyal, L. Shi, L.Y. Liu, et al., TAS-120 overcomes resistance to ATP-Competitive FGFR inhibitors in patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma, Cancer Discov 9 (8) (2019 Aug) 1064–1079, https://doi.org/10.1158/2159-8290.CD-19-0182. Epub 2019 May 20PMID: 31109923PMCID: PMC6677584.

[82] V. Merz, C. Zecchetto, D Melisi, Pemigatinib, a potent inhibitor of FGFRs for the treatment of cholangiocarcinoma, Future Oncol (2020 Oct 9), https://doi.org/10.2217/fon-2020-0726. Epub ahead of printPMID: 33034201.

[83] L. Goyal, S.K. Saha, L.Y. Liu, et al., Polyclonal secondary *FGFR2* mutations drive acquired resistance to FGFR inhibition in patients with FGFR2 fusion-positive cholangiocarcinoma, Cancer Discov 7 (3) (2017 Mar) 252–263, https://doi.org/10.1158/2159-8290.CD-16-1000. Epub 2016 Dec 29PMID: 28034880PMCID: PMC5433349.

[84] E.C. Smyth, I.S. Babina, N.C Turner, Gatekeeper mutations and intratumoral heterogeneity in *FGFR2*-translocated cholangiocarcinoma, Cancer Discov 7 (3) (2017 Mar) 248–249, https://doi.org/10.1158/2159-8290.CD-17-0057. PMID: 28264865.

[85] R.I.R. Macias, J.M. Banales, B. Sangro, et al., The search for novel diagnostic and prognostic biomarkers in cholangiocarcinoma, Biochim Biophys Acta Mol Basis Dis 1864 (4 Pt B) (2018 Apr) 1468–1477, https://doi.org/10.1016/j.bbadis.2017.08.002. Epub 2017 Aug 4PMID: 28782657.

[86] S. Palakurthi, M. Kuraguchi, S.J. Zacharek, et al., The combined effect of FGFR inhibition and PD-1 blockade promotes tumor-intrinsic induction of antitumor immunity, Cancer Immunol Res 7 (9) (2019 Sep) 1457–1471, https://doi.org/10.1158/2326-6066.CIR-18-0595. Epub 2019 Jul 22PMID: 31331945.

[87] P. McSheehy, F. Bachmann, N. Forster-Gross, et al., Derazantinib (DZB): a dual FGFR/CSF1R- inhibitor active in PDX-models of urothelial cancer, Mol Cancer Ther 18 (2019). Abstract LB-C12.

[88] X. Zheng, K. Turkowski, J. Mora, et al., Redirecting tumor-associated macrophages to become tumoricidal effectors as a novel strategy for cancer therapy, Oncotarget 8 (29) (2017 Jul 18) 48436–48452, https://doi.org/10.18632/oncotarget.17061. PMID: 28467800PMCID: PMC5564660.