GALGOTIAS UNIVERSITY

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AN INSIGHT ON CHOLANGINOCARCINOMA AND ITS RECENT ADVANCES IN TREATMENT

IN

BACHELOR OF PHARMACY

Submitted By

PRAVEEN SHARMA
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UNIVERSITY

SCHOOL OF MEDICAL ALLIED SCIENCE

Under the Supervision of

MR. RAKESH SAHU
Assistant Professor

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DEPARTMENT OF PHARMACY

GALGOTIAS UNIVERSITY, GREATER NOIDA, G.B. NAGAR (U.P)

CERTIFICATE

This is to certified that the work contained in this project on Sources of **AN INSIGHT ON CHOLANGINOCARCINOMA AND ITS RECENT ADVANCES IN TREATMENT** Submitted in partial fulfillment for the academic requirement in the degree of Bachelor of Pharmacy is the original work carries out by **PRAVEEN SHARMA** during the academic year 2020-21, under the guidance of **MR. RAKESH SAHU** (Assistant Professor) the work is completed and the ready for evaluation in partial fulfillment for the award of bachelor of pharmacy under Galgotias university greater Noida during the academic year 2020-21.

Date:
Place:

Prof**. PRAMOD KUMAR SHARMA**
DEAN SCHOOL OF MEDICAL
AND
ALLIED SCIENCE

CERTIFICATE

This to certify that the project work entitled **"AN INSIGHT ON CHOLANGINOCARCINOMA AND ITS RECENT ADVANCES IN TREATMENT"** by "**PRAVEEN SHARMA"** for the award of **"Bachelor of Pharmacy"** degree, comprises of the bonafide research work done by him/her at Department of Pharmacy, School of Medical & Allied Sciences, Galgotias University, Greater Noida under my guidance and supervision and to my full satisfaction.

MR. RAKESH SAHU
Associate Professor
School of Medical and Allied Sciences
Galgotias University
Greater Noida (U.P.)
(Guide)

DECLARATION

The project report
AN INSIGHT ON CHOLANGINOCARCINOMA AND ITS RECENT ADVANCES IN T REATMENT, entitled is the compilation work of **PRAVEEN SHARMA** under supervision of **MR.RAKESH SAHU** (Assistant Professor) **Department of Pharmacy**, **GALGOTIAS UNIVERSITY Greater Noida U.P. India**. All structures, tables and information used in project are taken from various sources are true and best of my knowledge.

Name and signature of candidate
(PRAVEEN SHARMA)
ENROLLMENT No. 1712102060

DEDICATION

I dedicate this to my guider teacher **MR.RAKESH SAHU** (Assistant Professor) who taught me everything about this project and taught me the basics rules of life that are very useful and important for a person to live a healthy life. Sir taught that never too late to start a thing and achieve your goals. Sir you and your thoughts really motivates me in my life and my carrier so sir thank you for guiding me.
I also dedicate this thesis to my parents, Thank you for supporting me.

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Lastly, I wish to express my gratitude to my colleagues and friends for encouragement and support.

PRAVEEN SHARMA

ABSTRACT

Cholangiocarcinoma (CCA) is a malignant disease of the epithelial cells of the intra- and extrahepatic bile ducts. Although, it remains a rare malignancy and is the second most common primary malignancy of the liver. The incidence is increasing; especially the incidence of intrahepatic CCA. Due to its rarity and complexity, surgery remains the preferred treatment in respectable patients. However, recently reported targeted drugs may have the potential to become an alternative option for the treatment of CCA and related complications. This review provides an overview of the current scenario of targeted therapies for CCA, which were tabulated with their current status. These reviews will certainly benefit the community and the researcher for further investigation.

Keywords: Cholangiocarcinoma (CCA), Primary biliary cholangitis, Liver Cancer, Treatment. Novel drug

1.Introduction

Cholangiocarcinoma (CCA) is a disease entity comprising several tumors arising from the epithelial lining of the bile ducts [1], in other words, cholangiocarcinoma is a cancer that forms in the thin ducts (bile ducts) that carry bile from the digestive fluid. CCA is the second most common primary liver cancer after hepatocellular carcinoma and accounts for approximately 10-15% of all hepatobiliary cancers worldwide [2]. It is currently subclassified into three subtypes according to anatomical locations: intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) cholangiocarcinoma. The intrahepatic subtype develops from malignant cholangiocytes within the liver parenchyma located proximal to the second-degree bile ducts[3],pCCA is limited to the area between the second-degree bile ducts and the insertion of the cystic duct into the common bile duct; and dCCA is located between the origin of the cystic duct and the ampulla of Vater[4].More than 90% of cholangiocarcinomas are adenocarcinomas, with rare occurrences of other histologic subtypes such as signet ring and lymphoepithelial carcinomas[5]. The incidence of CCA is geographically different, although rare in western countries, the incidence is increasing markedly globally[6].

Yamagiwa was the scientist who first recognized liver cancer in 1911, he divided primary liver cancer into two groups, "hepatoma" and "cholangioma": names that denote the cellular origin of the cancer [7].In his proposal, he did not emphasize that the two terms were only for carcinoma. Due to the ambiguity of these terms, Goldzieher and von Bokay suggested the use of "hepatocellular carcinoma" and "cholangiocellular carcinoma" for malignant tumors[8].Cholangiocarcinoma accounts for 10% to 20% of deaths related to primary liver carcinoma [9]. Currently, the only treatment for cholangiocarcinoma is surgical resection of the tumor, and traditional chemotherapy and radiation therapy have little effect in improving long-term survival of patients[10]. However, therapeutic surgery is only available for early-stage patients, but not for advanced-stage patients, and the 5-year survival rates of patients are still below 20% -40%, despite the combinationsurgery and chemotherapy [11]. Molecularly targeted therapy shows the obvious advantage of controlling cancer cell proliferation, as well as preventing or delaying recurrence and metastasis[12].

1.1. Types of cholangiocarcinoma

Cancers can form anywhere in the bile ducts. They are divided into two broad categories based on the origin of the tumor growth;

1.1.1. Intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma (iCCA) is the second most common type of primary liver cancer. It arises from tumors that grow in the small ducts of the liver. The incidence of ICC represents 10-15% of primary liver cancers. [13-15].Data from the WHO database indicated that overall ICC morbidity and mortality rates have shown a clear upward trend in recent years [15]. Globally, morbidity rates increased from approximately 0.14 to 1.47 per 100,000 people in 1993 to 0.29 to 2.19 per 100,000 people in 2012 [16,17].

1.1.1.1 Stages of intrahepatic cholangiocarcinoma

1. Table 1 AJCC 8th edition, classification of bile duct cancer with it's stages and criteria

Classification	**Criteria**	**Stages**	**Extend of tumor spread**	**Ref.**
Primary tumour(T)				
T0	No evidence of primary tumour	IA	Not verified	[18,19]
T1	Solitary tumour without vascular invasion	I	Bile duct mucosa	[18,19]
T2a	Solitary tumour with vascular invasion	II	Periductal connective tissue	[18,19]
T3	Tumour perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion	III	Vessel or organ invasion	[18,19]
T4	Tumour with periductal invasion	IV		[18,19]
Regional lymph node (N)				
N0	No regional lymph node metastasis	IA,IB, II, IIIA,	No region found	[18,19]
N1	Regional lymph node metastasis present	IIIB	Lymph node involvenment: hepatic, cystic, common duct and hepatoduodenal	[18,19]

			ligament	
Distant metastases (M)				
M0	No distant metastasis	IA,IB, II,IIIA	No region found	[18,19]
M1	Distant metastasis present	IV	Distant metastases	[18,19]

AJCC:American Joint Committee on Cancer; Ref: reference

1.1.2. Extrahepatic cholangiocarcinoma

Extrahepatic cholangiocarcinoma (eCCA), on the other hand, arises from tumors that grow in the bile ducts outside the liver. While intrahepatic cholangiocarcinoma produce similar symptoms, their risk factors, response to therapies, and origins are different[13]. Surgical resection for eCCA, including perihilar and distal cholangiocarcinoma, offers only the possibility of cure. However, the survival outcomes of patients with eCCA remain poor due to prognostic factors such as lymph node metastases [13,20-23] or positive resection margins[24]. The regional lymph node metastasis (LNM) rate in eCCA was reported to be 40-53% [20–22, 24].

1.2. CAUSES ASSOCIATED WITH CHOLANGIOCARCINOMA

Perihilar disease represents about 50%, distal disease 40%, and intrahepatic disease less than 10% of cholangiocarcinoma cases [23]. Mixed hepatocellular cholangiocellular carcinomas, also called combined hepatocellular-cholangiocellular carcinomas according to the WHO classification, were only recently acknowledged as a distinct subtype of cholangiocarcinoma[25-27]. According to scarce reports [26,28], mixed hepatocellular-cholangiocellular carcinomas represent less than 1% of all liver cancers. The incidence of intrahepatic cholangiocarcinoma seems to be increasing in many countries[29,30].

Age-adjusted rates of cholangiocarcinoma are reported to be highest in Hispanic and Asian populations (2·8–3·3 per 100 000) and lowest in non-Hispanic white people and black people (both 2·1 per 100 000) [31-33]. The disease has a slight male predominance (1·2–1·5 per 100 000 vs one per 100 000 population),with the exception of the female Hispanic population in whom intrahepatic cholangiocarcinoma rates are increased (1·5 per 100 000) compared with the male population (0·9 per 100 000). Cholangiocarcinoma is unusual in children. Cumulative cholangiocarcinoma mortality rates have increased by39% because of increased disease incidence[33]. Mortality rates are higher in men and boys (1·9 per 100 000) than in women and girls (1·5 per 100 000). Mortality rates from intrahepatic cholangiocarcinoma are highest in American Indian and Alaska Native groups (1·3 per 100 000) and Asian populations (1·4 per 100 000) and lowest in white people (0·8 per 100 000) and black people (0·7 per 100 000).9 Both increased recognition and incidence have contributed to rising interest in this cancer [34].

Most cholangiocarcinomas arise de novo, and no risk factors are identified. Recently, cirrhosis and viral hepatitis C and B have been recognised as risk factors for cholangiocarcinoma, especially intrahepatic disease. In studies from the USA and Europe [35-38] hepatitis C was shown to be a risk factor for cholangiocarcinoma with the strongest association for intrahepatic cholangiocarcinoma. Studies from South Korea and China [39,40] have shown more consistently

hepatitis B as a risk factor for intrahepatic cholangiocarcinoma [41].

There is a well-established association between primary sclerosing cholangitis (PSC), marked by chronic inflammation with liver injury and likely proliferation of the progenitor cells, and cholangiocarcinoma, especially perihilar disease. The lifetime incidence of cholangiocarcinoma in this patient population ranges between 5% and 10% [42-44]. About 50% of patients with PSC who develop cholangiocarcinoma are diagnosed with cholangiocarcinoma within 24 months of diagnosis of PSC [42,45]. Although various risk factors for cholangiocarcinoma in primary sclerosing cholangitis have been reported, none are sufficient to guide risk stratification for disease surveillance. Guidelines for cholangiocarcinoma surveillance in patients with PSC have been published [43,46,47]

Early age at diagnosis is also noted in patients with bile duct cystic disorders, including Caroli's disease [31,35,48]. These patients develop cholangiocarcinoma at a mean age of 32 years with lifetime incidence ranging from 6% to 30% [39].Southeast Asia has a very high incidence (113 per 100 000) [31] of cholangiocarcinoma that is due to high prevalence of hepatobiliary flukes, Opisthorchis viverrini and Clonorchis sinensis, which are risk factors for cholangiocarcinoma [49,50]. Hepatolithiasis, in which 7% of patients develop intrahepatic cholangiocarcinoma [25,51] and biliary-enteric drainage,predisposing patients to enteric bacteria bile duct colonisation and infections [52], are additional risk factors for cholangiocarcinoma. Several genetic polymorphisms have been identified that increase risk of development of cholangiocarcinoma. The genes implicated as risk factors can be classified into those encoding proteins participating in cell DNA repair (MTHFR, TYMS, GSTO1, and XRCC1), cellular protection against toxins (ABCC2, CYP1A2, and NAT2), or immunological surveillance (KLRK1, MICA, and PTGS2).The results from studies on the role of alcohol and smoking exposure have been inconsistent [31,53]. The metabolic syndrome was associated with an increased risk of intra hepatic cholangiocarcinoma in the Surveillance and Epidemiology Results database analysis [53]. Consistent with these observations, the meta-analysis [53] of US and Danish studies identifi ed an association of intra hepatic cholangiocarcinoma with diabetes with an OR of 1·89 (95% CI 1·74–2·07) and obesity with an OR of 1·56 (1·26–1·94). Although obesity is a biologically plausible risk factor for cholangiocarcinoma development, too few data are available to definitely establish an association at this time [31,54].

2. Potential TARGET Treatment associated with cholangiocarcinoma

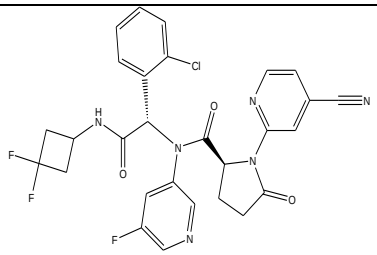
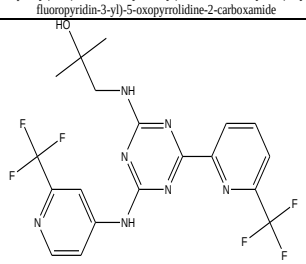
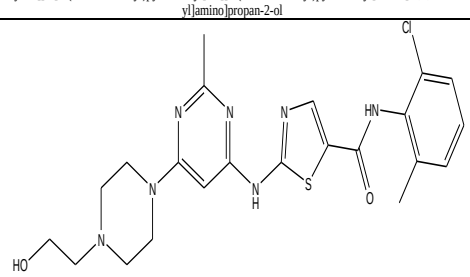
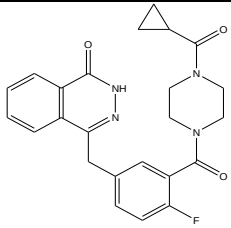
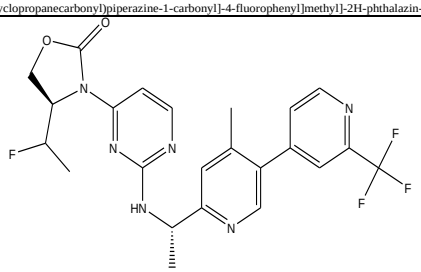
Although the only curative treatment for CCA presently is surgical resection, difficulties in diagnosing the disease in early stages, results in 10% to 30% of patients with CCA eligible for resection[55-57]. Furthermore, Patients with ICC who undergo curative-intent resection still have a high incidence of recurrence: Therefore, adjuvant therapy should be considered[55,58].Recent reported drugs with specific target for the treatment of cholangiocarcinoma. This drug may have 'potential to become an alternative option for the treatment of cholangiocarcinoma and its associated complications. Following are the primary sites of target with their recent drugs.

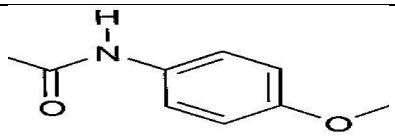
2.1 IDH

Isocitrate dehydrogenase promotes the conversion of isocitrate to α-ketoglutarate and is involved in the citric acid cycle and other metabolic processes [59-61]. When IDH is mutated, it increases the rate of metabolites that produce 2-hydroxyglutaric acid (2-HG), causing extensive epigenetic changes that affect the rates of cell differentiation, growth, and hypoxic signaling [62]. Of the cholangiocarcinomas, *IDH1*/*2* mutations are found in intrahepatic cholangiocarcinomas (iCCAs)

and rarely, if ever, in perihilar or extrahepatic cholangiocarcinomas [63,64].

Table 2 drugs affects IDH

S.no.	Name	Primary target	Development stage or fda approval	Chem. Str	Refer
1	Ivosidenib (AG-120	IDH1	Phase 3 [NCT02989857]	 (2S)-N-[(1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl]-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide	[65]
2	AG-221 (Enasidenib),	IDH2	Phase 1 [NCT02273739]	 2-methyl-1-[[4-[6-(trifluoromethyl)pyridin-2-yl]-6-[[2-(trifluoromethyl)pyridin-4-yl]amino]-1,3,5-triazin-2-yl]amino]propan-2-ol	[66]
3	Dasatinib	IDH1-2	Phase 2 [NCT02428855]	 N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl]amino]-1,3-thiazole-5-carboxamide	[67]
4	Olaparib	IDH1-2	Phase 2 NCT03212274	 4-[[3-[4-(cyclopropanecarbonyl)piperazine-1-carbonyl]-4-fluorophenyl]methyl]-2H-phthalazin-1-one	[68]
5	IDH305	IDH1	Phase 1 [NCT02381886]	 (4R)-4-[(1S)-1-fluoroethyl]-3-[2-[[(1S)-1-[4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl]ethyl]amino]pyrimidin-4-yl]-1,3-oxazolidin-2-one	[69]

6	LY3410738	IDH1	Phase 1 [NCT04521686]		[70]

Abbreviations:-IDH-Isocitrate dehydrogenase

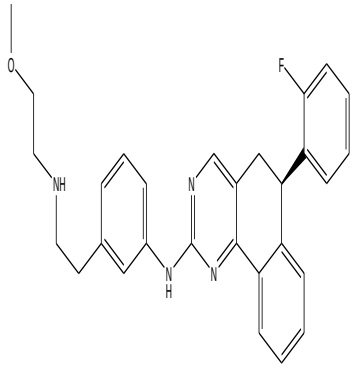
IDH1 is located in both the cytoplasm and peroxisomes, and catalyzes the reaction that leads to α-ketoglutarate (α-KG) production starting from oxidative decarboxylation of isocitrate (ICT). The reaction is reversible and dependent on nicotinamide adenine dinucleotide phosphate ($NADP^+$), Mg^{2+} or Mn^{2+}.[71]

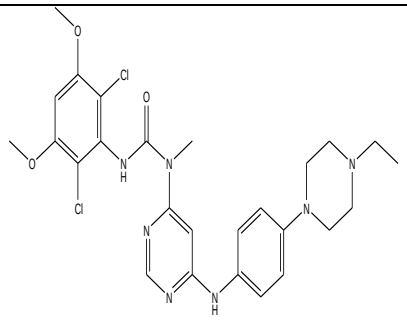
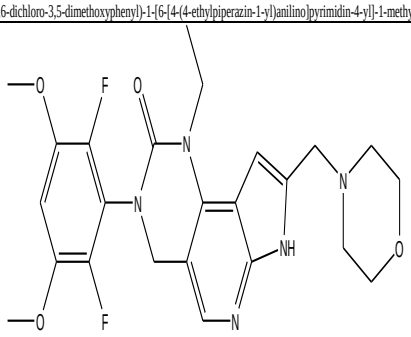
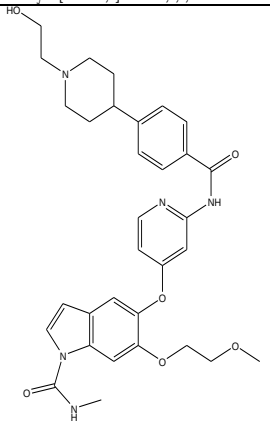
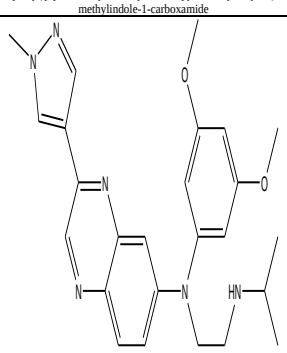
IDH2 is an enzyme of the citric acid cycle, and when mutated alters DNA methylation leading to impaired cellular differentiation

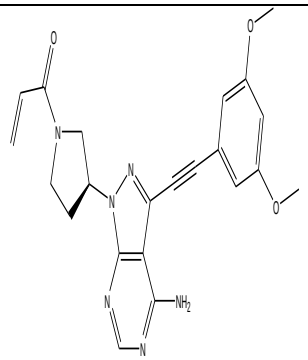
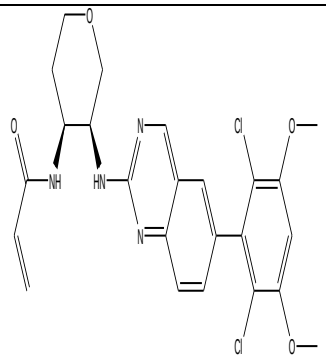
2.2. FGFR(fibroblast growth factor receptor)

Fibroblast growth factor receptors (FGFRs) are a family of four tyrosine kinase receptors (FGFR1–FGFR4) activated by extracellular signals, primarily fibroblast growth factors, that are involved in cell proliferation, differentiation, survival, migration, and angiogenesis [72]. The discovery of FGFR alterations in multiple tumor types has boosted scientific interest in the development of FGFR inhibitors. In iCCA recurrent FGFR2 fusions are found in 11% to 45% of patients [69,70]. FGFR2 fusions result in constitutive tyrosine kinase activity [75], which in turn led to downstream signaling pathways activation, such as RAS-RAF-MEK.

Table 3 drugs affect FGFR

S.no	Name of Drug	Primary target	Development stage or FDA approval	Chem. Structure	Refer
1	Derazantinib	FGFR 2	Phase 2 [NCT03230318]	 (6R)-6-(2-fluorophenyl)-N-[3-[2-(2-methoxyethylamino)ethyl]phenyl]-5,6-dihydrobenzo[h]quinazolin-2-amine	[76]

2	BGJ398 (infigratinib	FGFR 2	Phase 2 [NCT02150967]	 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-[6-[4-(4-ethylpiperazin-1-yl)anilino]pyrimidin-4-yl]-1-methylurea	[77]
3	(INCB054828) Pemigatinib	FGFR2	April 17, 2020,]	 11-(2,6-difluoro-3,5-dimethoxyphenyl)-13-ethyl-4-(morpholin-4-ylmethyl)-5,7,11,13-tetrazatricyclo[7.4.0.02,6]trideca-1,3,6,8-tetraen-12-one	[78,79]
4	E7090	FGFR2	Phase 2 NCT04238715	 5-[2-[[4-[1-(2-hydroxyethyl)piperidin-4-yl]benzoyl]amino]pyridin-4-yl]oxy-6-(2-methoxyethoxy)-N-methylindole-1-carboxamide	[80]
4	Erdafitinib	FGFR2 Or FGFR3	Active ,not recruiting [NCT02699606]	 N'-(3,5-dimethoxyphenyl)-N'-[3-(1-methylpyrazol-4-yl)quinoxalin-6-yl]-N-propan-2-ylethane-1,2-diamine	[81]

5	Futibatinib (TAS-120)	FGFR2	NCT04507503	 1-[(3S)-3-[4-amino-3-[2-(3,5-dimethoxyphenyl)ethynyl]pyrazolo[3,4-d]pyrimidin-1-yl]pyrrolidin-1-yl]prop-2-en-1-one	[82]
6	BLU-554 (Fisogatinib)	FGFR4	Phase 2 NCT04194801	 N-[(3S,4S)-3-[[6-(2,6-dichloro-3,5-dimethoxyphenyl]quinazolin-2-yl]amino]oxan-4-yl]prop-2-enamide	[83,84]

2.3. Tyrosine Kinase Inhibitors

The tyrosine kinase signaling pathways include some of the most important membrane machineries for cell communication, and mutations of their components are often involved in human cancer. Activating mutations of the *epidermal growth factor receptor* (*EGFR*) gene are well-characterized in non-small cell lung cancer (NSCLC), breast, colorectal, head and neck cancer, and other malignancies [85,86]

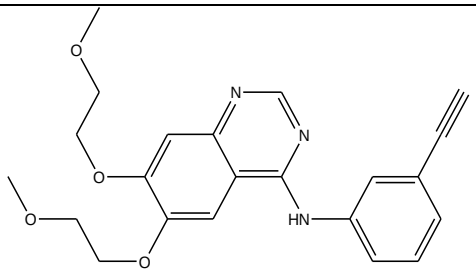
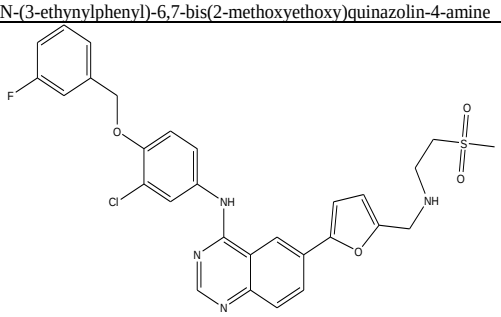
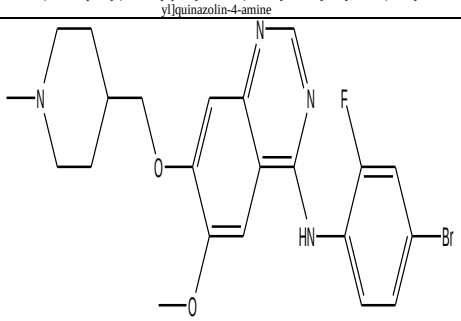
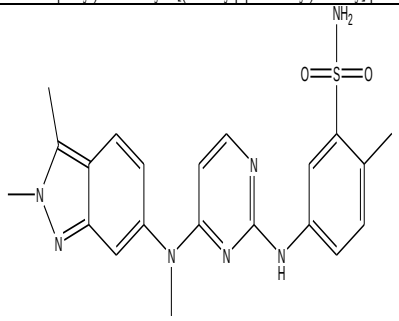
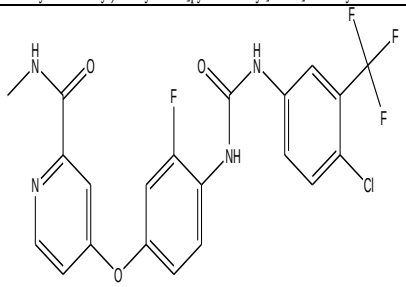
The tyrosine kinase family includes other members, including human epidermal growth factor receptor 2 (HER2/neu), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR2), which can be altered by activating critical pathways in tumorigenesis, cancer progression, survival, resistance to chemotherapy, and metastasis [87]

2.3.1. ErbB Inhibitors

Epidermal growth factor receptor (EGFR, ErbB1, HER1) is a transmembrane protein of the ErbB tyrosine kinase receptors family, which includes also ErbB2 or HER2/neu, ErbB3, and ErbB4. EGFR is activated by binding to its specific ligands, including epidermal growth factor (EGF) and transforming growth factor α (TGFα).[88]

Table 4 Drugs affect ErbB inhibitors

S.no.	Name of drug	Primary target	Development stage of FDA approval	Chem. Structure	Reference

1	Eriotinib	EGFR-1	Phase-1 [NCT00955149]	 N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine	[89]
2	Lapatinib	ErbB2	Phase 2 NCT00101036	 N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[(2-methylsulfonylethylamino)methyl]furan-2-yl]quinazolin-4-amine	[90,91]
3	Vandetenib	EGFR	Phase 2 [NCT00753675]	 N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine	[92]
4	Pazopanib	EGFR	Phase 2 NCT01855724	 5-[[4-[(2,3-dimethylindazol-6-yl)-methylamino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide	[93]
5	Regorafenib	EGFR 2	Phase 2 [NCT02053376]	 4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino]-3-fluorophenoxy]-N-methylpyridine-2-carboxamide	[94]

2.3.2. HER(human epidermal growth factor)

Two major classes of anti-epidermal growth factor receptor(ERBB) therapies are used in cancer, which are monoclonal antibodies,blocking ligand binding, and tyrosine kinase inhibitors (TKIs), which target the catalytic domain of the receptor.[95]

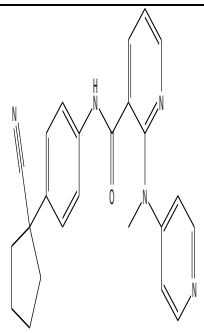
Table 5 Drugs affect HER

S.no.	Name of drug	Primary target	Development stage of FDA approval	Structure	Reference
1	Trastuzumab	HER2	Phase 2 [NCT03613168]	-	[96]
2	Pertuzumab	HER 2	20th December,2017	-	[97]

2.3.3. VEGFR inhibitor(vascular endothelial growth factor receptor)

VEGFR is a family of receptors characterized by an extracellular domain for ligand binding, a transmembrane domain, and a cytoplasmic domain, including a tyrosine kinase domain. VEGF was found to be overexpressed in 53.8% iCCAs and 59.2% extrahepatic CCAs, respectively, in a global cohort of 236 tumors; a statistically-significant association was found with intrahepatic metastases only in iCCAs [98,99]

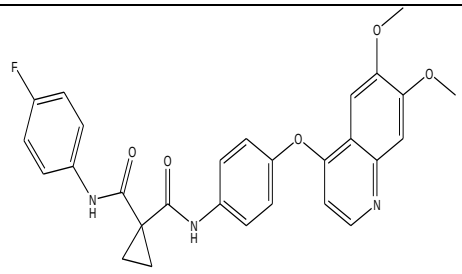
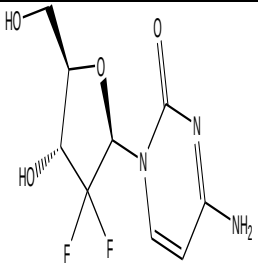
Table 6 Drugs affect VEGFR inhibitor

S no.	Name of drug	Primary target	Development stage of FDA approval	Chemical structure	Reference
1	Bevacizumab	VEGFR	Phase 1 [NCT03620292]	-	[100]
2	FOLFIRI(Bevacizumab +erlotinib) with cobnitations	VEGFR	Phase 1 NCT03872947	-	[101]
3	Ramucirumab	VEGFR1-2	Phase 2 NCT02520141	-	[102]
4	Apatinib	VEGFR-2	Phase 2 NCT03251443	 N-[4-[1-cyanocyclopentyl]phenyl]-2-(pyridin-4-ylmethylamino)pyridine-3-carboxamide	[103]

2.3.4. MET Inhibitors

Tyrosine kinase Met (c-MET) or hepatocyte growth factor receptor (HGFR), is encoded by the *MET* gene. Abnormal MET activation is frequent in several cancers and has been found in 12–58% of iCCAs [104]

Table 7 Drugs affect MET inhibitor

S. no.	Name of drug	Primary target	Development stage of FDA approval	Chemical structure	Reference
1	XL-184 Cabozantinib	MET	Phase 2 NCT01954745	 N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	[105]
3	Gemcitabine	MET	Phase 2 NCT01043172	 4-amino-1-[(2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one	[106]

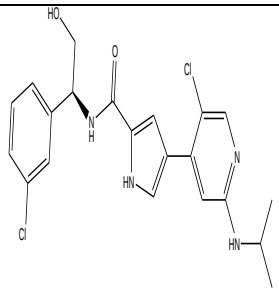
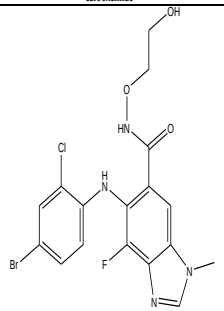
2.3.5.MAPK (Mitogen-Activated Protein Kinases) Pathway

Mitogen activated Protein Kinase(MAPK/MEK)proteins are mitogen activated protein kinase kinase, a dual specificity Tyr/Thr Protein Kinase that selectively phopholyrates serine/threionine and tyrosine residues in the activation loop of ERK1 and ERK2.The inhibition of MAPK could be an alternative strategy to target MAPK[107].

The inhibition of MEK could be an alternative strategy to target MAPK.

Table 8 Drugs affect MAPK Pathway

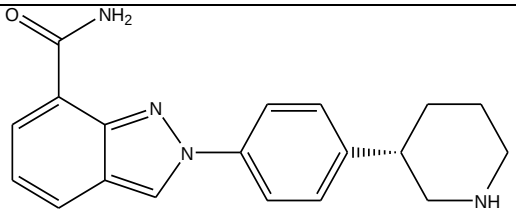
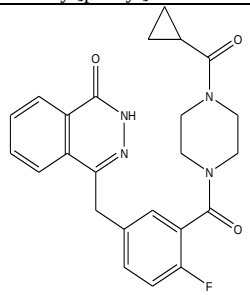
S. no.	Name of drug	Primary target	Development stage of FDA approval	Chemical structure	Reference

1	Ulixertinib (BVD-523)	MAPK	Phase 2 [NCT04566393]	 N-[(1S)-1-(3-chlorophenyl)-2-hydroxyethyl]-4-[5-chloro-2-(propan-2-ylamino)pyridin-4-yl]-1H-pyrrole-2-carboxamide	[108]
2	Selumetinib	MAPK	Phase 2 [NCT00553332] on April 10, 2020	 6-(4-bromo-2-chloroanilino)-7-fluoro-N-(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide	[109]

2.4. BRCA pathway

The presence of germline mutation of BRCA1 and BRCA2 confers an increased lifetime risk of developing CCA. The Breast Cancer Linkage Consortium reported an estimated relative risk for in BRCA2 mutation carriers of 4.97. Churi and colleagues [110] reported in a significant proportion of CCA alterations affecting genes involved in DNA repair pathways.

Table 9 Drugs affect BRCA pathway

S.no.	Name of drug	Primary target	Development stage of FDA approval	Chemical structure	Reference
1	Niraparib	BRCA 1	Phase 2 NCT03207347	 2-[4-[(3S)-piperidin-3-yl]phenyl]indazole-7-carboxamide	[111]
2	Olaparib	BRCA 2	Phase 2 NCT03212274	 4-[[3-[4-(cyclopropanecarbonyl)piperazine-1-carbonyl]-4-fluorophenyl]methyl]-2H-phthalazin-1-one	[112]

CONCLUSION

Cholangiocarcinoma (CCA) is a malignant disease of the epithelial cells of the intra- and extrahepatic bile ducts, the incidence is increasing; especially the incidence of intrahepatic CCA. Although, it remains a rare malignancy and is the second most common primary malignancy of the liver. The incidence is increasing; especially the incidence of intrahepatic CCA. Due to its rarity and complexity, surgery remains the preferred treatment in respectable patients due to the lack of effective medical treatment makes a radical surgical resection or hepatectomy the only therapeutic option. However, recently reported targeted drugs may have the potential to become an alternative option for the treatment of CCA and related complications. This review provides an overview of the current scenario of targeted therapies for CCA, some of which have already suggested interesting efficacy and adequate safety, these were tabulated with their current status. These reviews will certainly benefit the community and the researcher for further investigation.

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