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Pemigatinib for Cholangiocarcinoma– A Novel Drug

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Abstract: Cholangiocarcinoma(CLCA) is a cancer that develops in the narrow tubes known as bile ducts, which transport the digesting fluid bile. This disease, also recognized as Hepatic-duct cancer, is a form of tumor that is extremely difficult to cure with standard chemotherapy. iCLCA refers to cancers that develop within the gastrointestinal tract of the Hepatic-ducts inside the liver and are usually instigated by mutations in the Fibroblast Growth Factor Receptor2 (FiGFR2) gene. Pemigatinib(Pg) is a distinctive, powerful medication that specifically inhibits the action of mutated FGFR2 and is now identified being a viable therapy option for individuals with intrahepatic CLCA. Cholangiocarcinoma (CLCA) is a diverse category of cancers with few therapeutic options. Considering the latest developments in health oncology, CLCA individuals with metastasizing cancer have a terrible prognosis, with an overall median lifespan of barely an entire year. The CLCA health community has made substantial efforts in the recent decade to enhance distinct clinical results by introducing molecularly embattled treatments in this environment. Among some of these therapies, the FiGFR 2 inhibitor Pg has been granted rapid authorization by the USA-Food and Drug Administration (FDA) in CLCA individuals who have FiGFR2 gene combinations or additional rearrangements founded on the outcomes of the FIGHT-202 trial, making it the initial molecularly specific rehabilitation to be endorsed as a remedy of CLCA.This review seeks to present a concise review of pemigatinib's latest advancement, with a precise emphasis on the FIGHT-202 study, the endorsement of this FiGFR inhibitor, and the impending problems related to the routine of FiGFR-directed medicines in CLCA individuals.

Keywords: Cholangiocarcinoma, Pemigatinib**,** Fibroblast Growth Factor Receptor, Bile duct cancer, Intrahepatic cholangiocarcinoma, and PEMAZYRE TM

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1. INTRODUCTION

Hepatobiliary system malignancies are diverse tumors that fluctuate physically and genetically. Intrahepatic cholangiocarcinoma (iCLCA), which arises beyond the second-order Hepatic-duct, perihilar and distal cholangiocarcinoma (extrahepatic), gallbladder cancer, and ampulla of Vater cancer are the conventional classifications[1]. The intrahepatic disease is the second largest liver tumor after hepatocellular carcinoma, accounting for around 10% of cholangiocarcinoma cases. In Australia, Japan, North America, and Europe, the prevalence of iCLCA has increased in recent decades[2]. This rising prevalence may be partly attributed to innovative procedures, which improved diagnostic accuracy. It was recently proposed that it is linked to an upsurge in risk features such as chronic viral hepatitis, cirrhosis, and obesity. Cholangiocarcinomas (CLCAs) is a type of malignancy that arises from various components of the biliary tree, including intrahepatic cholangiocarcinoma (iCLCA) and extrahepatic cholangiocarcinoma (eCLCA), with the latter supplementary subdivided into perihilarcholangiocarcinoma (pCLCA) and distal cholangiocarcinoma (dCLCA). Pemigatinib (PEMAZYRE TM) is an orally given small molecule inhibitor of FiGFR1, FiGFR2, and FiGFR3 developed by Incyte Establishment[3,4]. It is the initial personalized medicine to be authorized for the administration of CLCA in the USA (in April 2020), where it is suggested in adults with earlier treated, locally progressive,unresectable, or metastatic CLCA and a FiGFR2 combining or other reorganization, as identified by a USA FDA-approved test.

2. PEMIGATINIB(PG)

Pemigatinib (INCB054828, Pemazyre) is an oral FiGFR1, 2, and 3 inhibitors that is both powerful and selective. This drug's chemical formula is 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4- ylmethyl)-1,3,4,7-tetrahydro-2H-pyrrolo [3_,2_:5,6] pyrido[4,3d] pyrimidin-2-one. $C_{24}H_{27}F_2N_5O_4$ is the chemical formula, and the molecular weight is 487.50(Figure-01) [5]. INCB054828 is currently in medical practice for treating CLCA and other solid tumors. It works by blocking the bustle of the FiGFR, which is complicated in cell growth and proliferation. The situation is also being studied to treat other forms of cancer. $C_{24}H_{27}F_2N_5O_4$ is the chemical structure of INCB054828, a small molecule that binds to and blocks the pharmacology of FiGFR[6]. By blocking this receptor, it prevents the cancer cells from growing and increasing, potentially leading to a reduction in tumor size or even complete remission of cancer. This could offer an exciting alternative to existing cancer treatments, as it can potentially stop cancer growth and provide cancer remission without the procedure of other treatments[7].

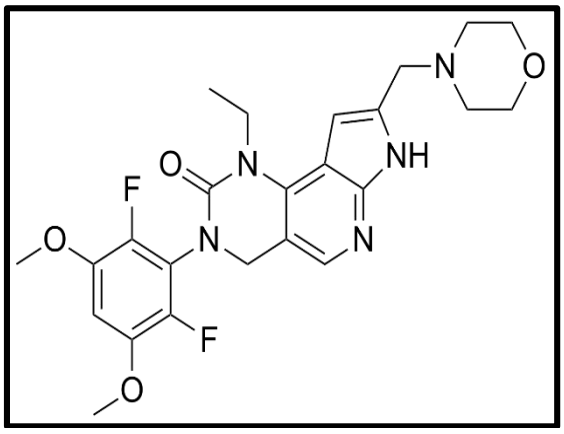

Fig-01: Pemigatinib(Pg) – Molecular Structure

3. PHARMACOLOGY & PHARMACOKINETICS

Pemigatinib is an ATP-competitive FiGFR tyrosine kinase domain inhibitor. Pemigatinib inhibits FiGFR1, FiGFR2, and FiGFR3 with half maximum inhibitory concentration (IC_{50}) values of 0.4, 0.5, and 1 nmol/l, respectively, but had a lesser effect on FiGFR4. Pemigatinibactivity was evaluated utilizing a panel of 56 distinct tyrosine and serine-threonine kinases with a constant ATP dosage of 1 mM[8].Pemigatinib was highly selective for FiGFRs, with IC_{50} values less than 1 nMonly for VEGFR2/KDR and c-KIT. Pemigatinib did not affect the other kinases tested, with IC_{50} values greater than 10 nM. Furthermore, pemigatinib was also initiated to be efficacious in FiGFR-driven cell line multiplyingevaluates[9]. These outcomes validate that pemigatinib is highly discerning for FiGFRs, with minimal activity on other kinases tested, and is also effective in blocking FiGFR-driven cell proliferation. This suggests that pemigatinib could be an encouraging therapeutic option for treating FiGFR-related diseases[10]. Moreover, pemigatinib showed encouraging results in cell proliferation assays, indicating that it may be an effective therapy for FiGFR-related diseases.

4. PEMIGATINIB IS CLINICALLY INVESTIGATED IN STRONG CARCINOMAS.

FIGHT-101 (INCB54828-101, ClinicalTrials.gov: NCT02393248) is a three-part, open-label, dose-escalation trial for individuals with advanced previously treated solid tumors with (parts 2 and 3) or without (parts 1 and 3) FGF/FiGFR modifications receiving pemigatinib alone[11]. Absence of dose-limiting toxicities were detected with monotherapy, and the highest tolerable dosage was not achieved. The pharmacologically active dosage was 9 mg QD, with an appropriate safe intake of 20 mg[12]. Several research in various phases of urothelial carcinoma are now underway. FIGHT-201 (NCT02872714) is a Phase II, open-label, multicenter study that is currently enrolling individuals with metastatic or unresectable urothelial carcinoma mutations/fusions (cohort A) or other FGF/FiGFR alterations

(cohort B) who have given up at least a single course of therapy or are platinum ineligible[13]. In cohort A, which included individuals with unconfirmed PRs, interim data showed an ORR of 25%. FIGHT-203 is a Phase II trial that looks at the effectiveness and safety of pemigatinib in individuals with myeloid or lymphoid neoplasms that have FiGFR1 rearrangements. According to preliminary findings, 80% of the individuals showed a significant cytogenetic reaction. Pemigatinib is being tested in two tumor-agnostic trials in solid tumors with FiGFR mutations. FIGHT-207 (NCT03822117) is a Phase II, open-label, single-arm study designed to evaluate the efficacy and safety of pemigatinib in individuals with advanced solid tumor malignancies with activating FiGFR mutations, fusions, or rearrangements who have progressed on a minimum of one prior line of therapy and have no other viable options for treatment[14].

5. CLINICAL IMPROVEMENT OF PEMIGATINIB IN CLCA

The sophisticated Biliary Tract Cancer (ABC)-06 trial currently specified the current preferred strategy for second-line CLCA therapy, which demonstrated a significant improvement in median OS by using the chemotherapeutic regimen mFOLFOX (modified fluorouracil, leucovorin, and oxaliplatin) as opposed to engaged symptom control (6.2 vs. 5.3 months, HR: 0.69, p = 0.03) [15]. FIGHT-202 was an open-label, single-arm, multicenter Phase II study that assessed the protection and efficacy of pemigatinib for individuals with newly diagnosed or metastatic CLCA who were treated for at least one prior systemic cancer. Pemigatinib was given orally once daily at 13.5 mg in a 21-day cycle (2 weeks on, 1 week off) until disease progression or unacceptable toxicity occurred[16]. The study's primary end aim was the number of individuals in cohort A who obtained an objective responder. Although overall survival statistics were incomplete, and comparing data across studies is not officially acceptable, pemigatinib activity outcomes in the FIGHT-202 study were encouraging. Following the realization of the FIGHT-202 study, the Phase III FIGHT-302 (NCT03656536) experiment has already begun[17]. This is a multicenter, randomly selected open-label trial that will contrast pemigatinib to gemcitabine + cisplatin chemotherapy as first-line treatment for individuals with unresectable or metastatic cholangiocarcinoma with FiGFR2 combinations or rearrangements.

6. SAFETY &ACCEPTABILITY OF PEMIGATINIB

Hyperphosphatemia was the most dominant adverse effect when pemigatinib was provided as a solo drug on an intermittent regimen. (74%) and weariness (40%), respectively, for 9 and 13.5 mg dosages, and hyperphosphatemia (67%) and stomatitis (50%), respectively, for 20 mg dose[18]. Pneumonia (7%) and Hyponatremia (7%) were the utmost mutual grade 3 or higher adverse effects. When all three FIGHT-202 groups were combined, the most prevalent negative outcomes were hyperphosphatemia (60%), alopecia, diarrhea, exhaustion, dysgeusia, and nail toxicities (40% occurrence) [19]. The most collective problems were hypophosphatemia (12%), arthralgia (6%), hyponatremia (5%), weariness (5%), stomach discomfort (5%), and stomatitis (5%)[20]. Hyperphosphatemia is a predicted side effect of FiGFR inhibition, which blocks FiGF23-FiGFR1 gesturing in the renal tubule. A bell-shaped correlation is being discovered between changes in phosphate levels and individuals with an objective reaction, suggesting that 13.5 mg is an optimum beginning dosage. After day 15 of cycle 1, mean phosphate, 1,25(OH)2D3, and parathyroid hormone concentrations declined from baseline[21]. Similarly, individuals with low 1,25(OH)2D3 and parathyroid hormone levels rose from 15 and 11% at baseline to 79 and 22% on cycle 5, day 1[22]. Hypophosphatemia could have resulted from an overcorrection of hyperphosphatemia during the off-treatment week or from adverse reaction processes on phosphate homeostasis.

7. RESISTANCE MECHANISMS TO PEMIGATINIB IN CLCA

Numerous preclinical investigations have investigated resistance mechanisms for FiGFR inhibitors. A variability of mechanisms for evolved immunity to FiGFR inhibitors was identified. It can happen owing to the engagement of other receptor tyrosine kinases, such as MET, Ephrin 3B (Eph3B), or the EiGFR family[23]. Another resistance route to FiGFR inhibitors is through FGFR gatekeeper mutations that hinder drug binding. The first endeavor in a clinical environment to establish mechanisms causing acquired confrontation to FiGFR inhibitor treatment in CLCA individuals treated with infigratinib was described. Infigratinib trials with a median PFS of 5.8 months revealed rapid emergence of developed resistance[24]. All three individuals had the FiGFR2 V564F gatekeeper mutation, and two had supplementary FiGFR2 kinase domain mutations. As an outcome, intralesional heterogeneity poses a significant barrier in treating acquired resistance in patients using FiGFR inhibitors. FiGFR inhibitors that covalently engage the FiGFR ATP-binding pocket might be an exciting technique for overcoming resistance induced by FiGFR gatekeeper mutations. Futibatinib (TAS-120) is an irreversible third-generation FiGFR inhibitor that binds covalently to a highly conserved P-loop cysteine residue in the FiGFR ATP pocket[25].

8. PEMIGATINIB AND FIGHT-202

Pemigatinib is a single-molecule inhibitor of FiGFR1, FiGFR2, and FiGFR3. Even though this chemical has recently been evaluated in CLCA individuals, pemigatinib is the newest focused medication to be authorized in CLCA[26]. Based on the research design, this phase II trial comprised individuals with an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0, 1, or 2 and whose illness had advanced after at least one therapy. [27] Pemigatinib's safety profile was similar to prior trials on FiGFR inhibitors in CCA and other malignancies, FIGHT-101 on advanced solid tumors, and FIGHT-201 on metastatic urothelial carcinoma. The primary efficacy outcome measure was the overall response rate (ORR), the percentage of individuals who achieved either a complete or partial response[28]. Secondary efficacy outcomes included duration of response, progression-free survival, and complete survival. In addition, Pemigatinib demonstrated a manageable safety profile, with no unexpected or serious adverse events, and its primary efficacy outcome of ORR was positive, with promising results for secondary efficacy outcomes(Figure-02).

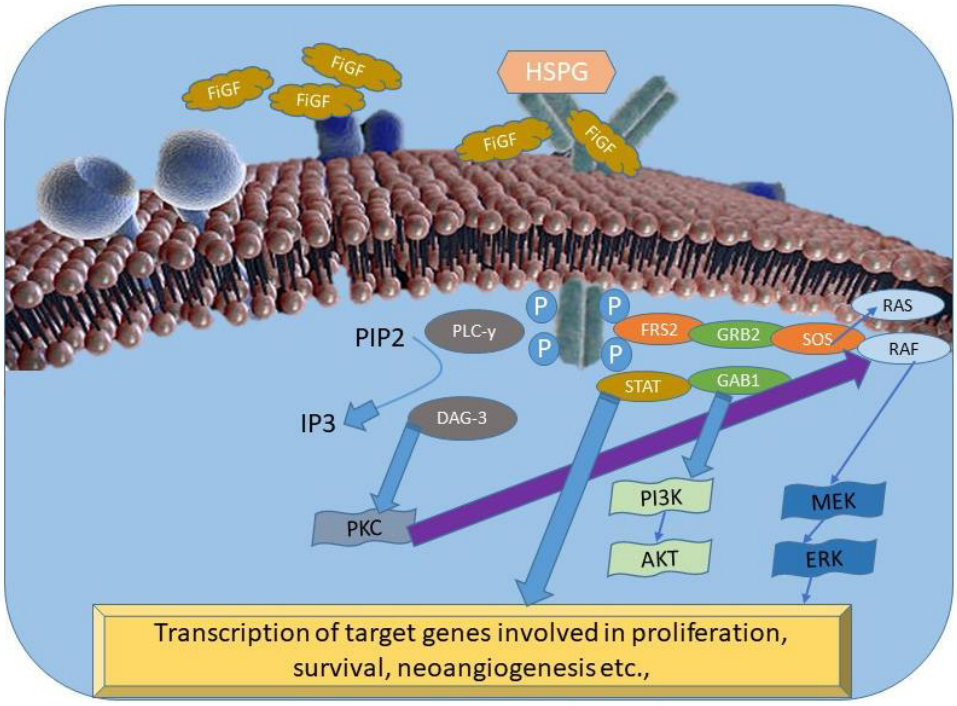

Fig-02: Image illustrations representing Fibroblast Growth Factor Receptor (FiGFR) structure, network, and tumor alteration. As reported in the text, the FiGFR family includes transmembrane receptors composed of three extracellular immunoglobulin-like domains and one intracellular split tyrosine kinase domain, except FiGFR5. FGF, HSPG, and FGFR complex results in receptor dimerization, subsequent transphosphorylation of tyrosine kinase domains, and activation of downstream signaling. Aberrations in FiGFR (including mutation, amplification, translocation, etc.) cause constitutive activation of the kinase domain.

Abbreviations: FiRS2: 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[29].

9. PHARMACODYNAMICS

Food has no clinically effect on the pharmacokinetics of pemigatinib. The median time to a maximum plasma pemigatinib concentration was 1.13 h. A Steady-state was reached within 4 days of therapy with once-daily pemigatinib; at steady state, pemigatinib concentrations increased proportionally over a 1–20 mg dose range[30]. At concentrations ranging from 1–10 μ mol/L, pemigatinib was 90.6% bound to human plasma proteins in vitro. The binding was self-determining of drug concentration and was not altered by the co-administration of other medications. The in vivo binding of pemigatinib to plasma proteins was similar to the in vitro binding. There was no clinically confirmed effect of pemigatinib on the plasma protein binding with other drugs. This suggests that pemigatinib has a high affinity for plasma proteins, which is important for ensuring the drug's effectiveness. Additionally, this binding influenced drug concentration, suggesting that the drug will remain effective even if the concentration changes. Furthermore, there was no notable effect of pemigatinib on the plasma protein influence of other drugs, indicating that it does not interfere with the ability of other medications.

10. PHARMACOKINETICS[31]

Food has no clinically substantial influence on pemigatinib pharmacokinetics. The median time to a peak plasma pemigatinib concentration was 1.13 hours. With once-daily pemigatinib, a stable state was established in 4 days; at steady-state, pemigatinib concentrations rose proportionately throughout a 1-20 mg dosing range. Pemigatinib was 90.6% bound to human plasma proteins in vitro at doses ranging from 1 to 10 mol/L. Pemigatinib was primarily excreted in the feces (77.7%) and renal elimination (13.3%)[32]. The mean terminal elimination half-life of pemigatinib was approximately 24 hours. This shows that pemigatinib is a highly effective drug with a faster onset and a long duration of action, allowing it to be administered in once-daily doses. It is also highly bound to plasma proteins, meaning it will stay in the biological system longer. Furthermore, it is mainly excreted in the feces and renal elimination, meaning it is relatively safe for humans to take. This combination of features makes pemigatinib an ideal choice of drug for those seeking a highly effective and long-lasting treatment for their medical condition[33].

11. CONCLUSION

The latest FDA approval of pemigatinib in past-treated individuals who have locally progressing inoperable or metastatic CLCA and FiGFR2 gene mutations or rearrangements has figuratively heralded the beginning of a new era in CLCA care since it is the first targeted medication to be licensed in this context. Several problems, nevertheless, remain unsolved, particularly the emergence of additional polyclonal mutations, the appropriate use of liquid biopsy, and the finding of biomarkers predictive of the effect of FiGFR inhibitors.

12. FUTURE PERSPECTIVE

In cholangiocarcinoma, genomic sequencing revealed molecular changes in many intracellular pathways. Suppressing the FiGFR pathway was the initial focused treatment method authorized in cholangiocarcinoma. Many medications that target FiGFR fusions have shown favorable results, with substantial responses and significant disease control. Combining FiGFR inhibitors with chemotherapeutic drugs or checkpoint inhibitors may boost their effectiveness. The mutational backdrop of CLCA, on the other hand, implies that various medicines might address several distinct changed pathways. Soon, customized therapy may become a norm of care in cholangiocarcinoma individuals as the first line of treatment.

13. AUTHORS CONTRIBUTION STATEMENT

Kiruthika Balasubramanian, Dr. Bablee Jyoti, M. Thillainayagi contributed to this article by gathering the resources, and Vinoth Kumar S, Prof. Dr. Ammar A. Razzak Mahmood drafted the manuscript and revised it. All authors approved the manuscript's published form after they had read it.

14. CONFLICT OF INTEREST

Conflict of interest declared none.

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