# Futibatinib (LYTGOBI)
# Mini-Monograph
# Nov 2023

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

Abbreviations: MOA=mechanism of action; TBD=to be determined; VANF=VA National Formulary; NF = non-formulary; PADR-F = Prior Authorization Drug Review, facility level

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| **FDA Approval** | **Description/MOA** | Futibatinib (LYTGOBI) is a small-molecule, fibroblast growth factor receptor (FGFR) kinase inhibitor. Futibatinib non-competitively binds FGFR 1,2,3 and 4 inhibiting FGFR phosphorylation and downstream signaling and decreased viability in cancer cell lines with FGFR alterations.[1] |
| | **Indication(s) Under Review** | Futibatinib received FDA accelerated approval for the treatment of adults with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene fusions or other rearrangements[1] |
| | **Dosage Form(s)** | Futibatinib is available in 4mg tablets. Starting dose is 20mg/day (5 tablets) once daily until disease progression or unacceptable toxicity occurs.[1]<br>NOTE: *LYTGOBI is packaged as 7-day, blister-packed dose cards available in:*<br>**20mg per day (5 tablets/day #35 ), *16mg per day (4 tablets/day #28), or*<br>**12mg per day (3 tablets/day #21)* |

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| **Clinical Evidence** | **Study/Design** | Open-label, single-arm, phase 2 trial conducted in 47 sites. Trial sponsored by Taiho Oncology and Taiho Pharmaceuticals.[2] |
| | **Population** | Total of 103 adult patients with unresectable or metastatic iCCA harboring an FGFR2 fusion or rearrangement which was prospectively identified by DNA testing. All patients had disease progression after >/= 1 prior regimen including gemcitabine plus platinum-based chemotherapy and with radiographically measurable disease (i.e. RECIST v 1.1) |
| | **Demographics** | **Age**<br>Average age =58<br>Range 22-79<br><br>**ECOG**<br>0 = 48 (47%)<br>1 = 55 (53%)<br><br>**Ethnicity**<br>White-50%, Asian-30%,<br>Black-8%, Other-13%<br><br>**FGFR Alteration**<br>Fusion = 78%<br>Rearrangement = 22%<br><br>**Prior Treatment**<br>ChemoTx = 100%<br>Radiation Tx = 27%<br>Surgery = 40%<br><br>**# Prior Lines of Systemic Treatment**<br>1 = 48 (47%)<br>2 = 31 (30%)<br>3 or more = 24 (23%) |
| | **Intervention** | Futibatinib 20mg/day administered in 21-day cycles with no days off. Treatment interruptions and/or dose reduction for any grade 3 or grade 4 laboratory related events.[3] |
| | **Results** | Primary endpoint in the FOENIX-CCA trial was overall response rate (ORR) and was 42 percent. Secondary endpoints included (median values with 95% confidence interval):<br>**Progression Free Survival**: 9.0 months (6.9 - 13.1)<br>**Overall Survival**: 21.7 months (14.5 - Not reached)<br>**12 Month Survival Rate**: 72 percent (62%-90%)<br>**Time to Response**: 2.5 months (0.7 – 7.4)<br>**Duration of Response**: 9.7 months (7.6 – 17.0)<br>**Median Cycles Received**: 13.0 (range 1-36) |
| | **Limitations** | Open-label trial with no comparator arm. FGFR2 alterations only present in 10-15% of iCCA so generalizability/applicability is limited. |
| | **Summary** | In an open label, single arm study of 103 patients with metastatic or unresectable, treatment refractory iCCA with FGFR2 alterations treatment with futibatinib 20mg/day yielded an ORR of 43%, OS of 21.7 months and a 12-month survival rate of 72%. Although side effects are common with |



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| | | futibatinib, adverse effects leading to treatment discontinuation were not common (2%). See safety section below for additional safety information |

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| **SAFETY:** | **Boxed Warnings / Contraindications** | None | |
| | **Warnings/ Precautions** | *Hyperphosphatemia occurred in 85% of receiving futibatinib. Initiation of phosphate lowering therapy is likely. Median onset was day 5 of treatment. Monitor serum phosphate and adjust dose based on severity<br>*LYTGOBI can cause retinal pigment epithelial detachment (RPED). Perform a comprehensive ophthalmologic examination including optical coherence tomography (OCT) prior to initiation of therapy, every 2 months for first 6 months, and every 3 months thereafter, and urgently at any time for visual symptoms<br>*Can cause fetal harm. Advise patients of reproductive potential the possible risk to the fetus and to use effective contraception. | |
| | **Adverse reactions (AE)** | **Treatment Related Adverse Events (TREAs) – Any Grade >15%**<br>Hyperphosphatemia 85% Alopecia 33%<br>Dry Mouth 30% Diarrhea 28% Dry Skin 27%<br>Fatigue 25% Palmar-Plantar Syndrome 21%<br>Stomatitis 20% Dysgeusia 18% ↑AST 18%<br>Dry Eye 17% Constipation 17%<br>Nail disorder 16% Onycholysis 16% | **Grade3 or 4 TREAs >1%***<br>Hyperphosphatemia 30%<br>Increased AST 7% Stomatitis 6% Fatigue 6%<br>Palmar-Plantar Syndrome 5%<br>Increased ALT 4% Nausea 2%<br><br>**No grade 5 TREAs were reported. Two patients permanently discontinued treatment due to TREAs (1 pt stomatitis, 1 pt esophagitis)* |
| | **Drug Interactions** | *Futibatinib (LYTGOBI) is a substrate of CYP3A and P-glycoprotein P-gp)<br>*Avoid use of drugs that are dual P-gp and strong CYP3A inhibitors (e.g., itraconoazole) which may increase futibatinib exposure and increase incidence and severity of adverse effects<br>*Avoid use of drugs that are dual P-gp and strong CYP3a inducers (e.g., rifampin) which may decrease futibatinib exposure and reduce efficacy | |



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**Indirect Comparison of FGFR2 inhibitors, as monotherapy in treatment refractory, non-resectable/metastatic iCCA**

| Drug/ VANF status | Dosing | Endpoint(s) in iCCA indication | Metabolism, dose adjustments, drug interactions | TREAs Grade 3 or 4 >1% | Dose adjustment or interruption due to AEs | NCCN v2.2023 per indication |
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| Futibatinib TBD | Once daily for 21 days on 21-day cycle | **Primary Endpoint** ORR = 42%<br><br>**Secondary Endpoints** PFS = 9 months OS = 21.7 months Duration of Response = 9.7 months Median treatment duration = 9.1 | • Primarily metabolized via CYP3A<br>• Metabolites primarily fecally excreted<br>• No dose adjustments for renal or hepatic failure<br>• Recommend avoid use with concurrent strong CYP3A inhibitors or inducers | *HYPERphosphatemia 30%<br>Increased AST 7%<br>Stomatitis 6%<br>Fatigue 6%<br>Hand-Foot syndrome 5%<br>Increased ALT 4%<br>Nausea 2% | **Dose Interruption** TRAEs = 50% **Dose Reduction** TRAEs = 54% | Cat 2A |
| Pemigatinib PA-F | Once daily for 14 days on a 21-day cycle | **Primary Endpoint** ORR = 35.5%<br><br>**Secondary Endpoints** PFS = 6.9 months OS = 21 months Duration of Response = 7.5 months Median treatment duration = 7.2 | • Primarily metabolized via CYP3A<br>• Metabolites primarily fecally excreted<br>• No dose adjustments for renal or hepatic failure<br>• Recommend avoid use with concurrent strong CYP3A inhibitors or inducers | *HYPOphosphatemia 7%<br>Stomatitis 5%<br>Arthrlagia 4%<br>Hand-Foot syndrome 4%<br>Diarrhea 3%<br>Hyponatremia 2% | **Dose Interruption** TRAEs = 43% **Dose Reduction** TRAEs = 14% | Cat 2A |

**NOTE -- Hyperphosphatemia of any grade was common with either pemigatinib or futibatinib (approaching 90%). Grade 3 HYPERphosphatemia was reported with futibatinib while grade 3 HYPOphosphatemia was reported with pemigatinib in each drug's key clinical trial (e.g., FOENIX-CCA2 and FIGHT-202 trials, respectively). FIGHT-202 authors reported that hypophosphatemia was likely due to excess phosphate lowering therapy especially in off week of 21-day treatment cycle.*[4]

AE=adverse event; Alk Phos=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate aminotransferase; ORR=Overall Response; OS=overall survival; Rate; PFS=Progression Free Survival; TRAEs=treatment related adverse events, UTI=urinary tract infection

## Conclusions/Projected Place in Therapy

- Futibatinib is the 3rd FGFR inhibitor that is FDA approved for non-resectable/metastatic, treatment refractory iCCA (Infigratinib, Pemigatinib, Futibatinib). However, only futibatinib and pemigatinib are still marketed.
- FGFR2 mutations occur in 10-15% of iCCA and all-time use of this class of agents has been low in VHA
- All 3 FGFR inhibitors were approved via FDA accelerated approval process with only single-arm studies, so drug-to-drug comparisons are difficult
- Futibatinib has an ongoing study as first-line treatment, vs. traditional chemotherapy,[5] but results are not published at time of monograph writing. Results may affect future futibatinib utilization
- Futibatinib has not been formally studied in patients previously treated with FGFR2 inhibitors. Low level evidence (i.e. single case report) suggest activity in settings of resistance with identification of new FGFR2 alterations.[6]

## References


1. LYTGOBI full prescribing information LYTGOBI_Prescribing_Information.pdf (amazonaws.com) Accessed September 2023
2. Goyal L, et al. (FOENIX-CCA2 Study Investigators). Futibatinib for *FGFR2*-Rearranged Intrahepatic Cholangiocarcinoma. N Engl J Med. 2023 Jan 19;388(3):228-239
3. FOENIX-CCA2 Supplementary Appendix nejmoa2206834_appendix.pdf Accessed September 2023




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4. Abou-Alfa GK, et al., Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020 May;21(5):671-684
5. Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients With Advanced Cholangiocarcinoma Harboring FGFR2 Gene Rearrangements - Full Text View - ClinicalTrials.gov Accessed September 2023
6. Rengan AK, Denlinger CS. Robust Response to Futibatinib in a Patient With Metastatic FGFR-Addicted Cholangiocarcinoma Previously Treated Using Pemigatinib. J Natl Compr Canc Netw. 2022 Apr 4;20(5):430-435



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