FOR mIDH1 CCA

TREAT PATIENTS IN THE 2ND LINE WITH A TARGETED THERAPY[1]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend ivosidenib (TIBSOVO®) as an NCCN category 1, subsequent-line, systemic treatment option[2,a]

TIBSOVO delivered significant improvements in PFS in m*IDH1* CCA[1]

63% **reduction in the risk of disease progression or death**
(HR, 0.37 [95% CI, 0.25-0.54]; *P*<0.0001)[1]

32% **6-month PFS rate**[3]

22% **12-month PFS rate**[3]

[a]For patients with unresectable or metastatic progressive CCA with *IDH1* mutations.[2]

CCA, cholangiocarcinoma; CI, confidence interval; HR, hazard ratio; m*IDH1*, mutated isocitrate dehydrogenase-1; PFS, progression-free survival.

INDICATION

TIBSOVO is indicated for patients with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma who have been previously treated.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

QTc Interval Prolongation: Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (eg, anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes. In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.
Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

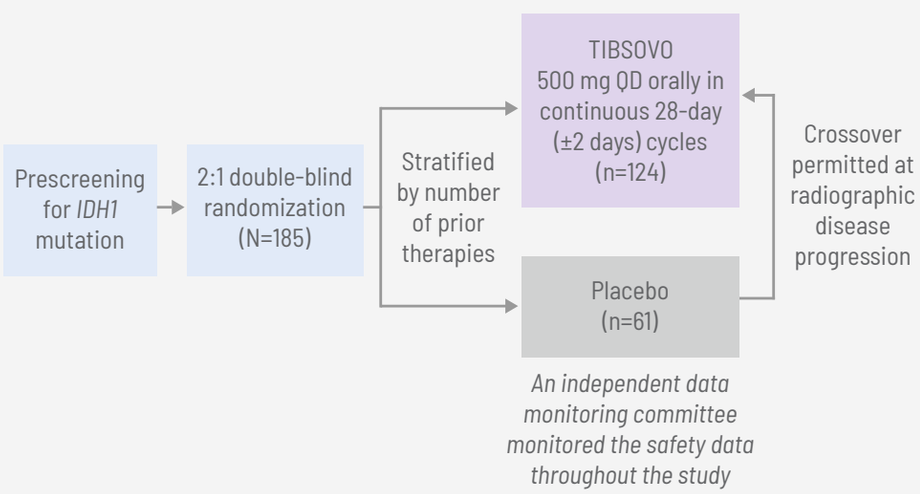
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ClarIDHy IS A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY[1,3]

Key Eligibility Criteria

- ≥18 years of age
- Histologically confirmed diagnosis of CCA
- Centrally confirmed m*IDH1* status by NGS
- ECOG PS score of 0 or 1
- 1-2 prior therapies (at least 1 gemcitabine- or 5-FU-containing regimen)
- Adequate hematologic, hepatic, and renal function



- Primary endpoint: PFS by blinded independent radiology center[3]
- Key secondary endpoints: OS; ORR; PFS by local review; HRQoL; safety and tolerability[3]
- 53% of patients received 1 prior line of therapy and 47% received 2 prior lines of therapy[3]
- The majority of patients had intrahepatic CCA (91%) and metastatic disease (92%) at screening[3]

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRQoL, health-related quality of life; NGS, next-generation sequencing; OD, once a day; OS, overall survival; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

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UNMET NEED

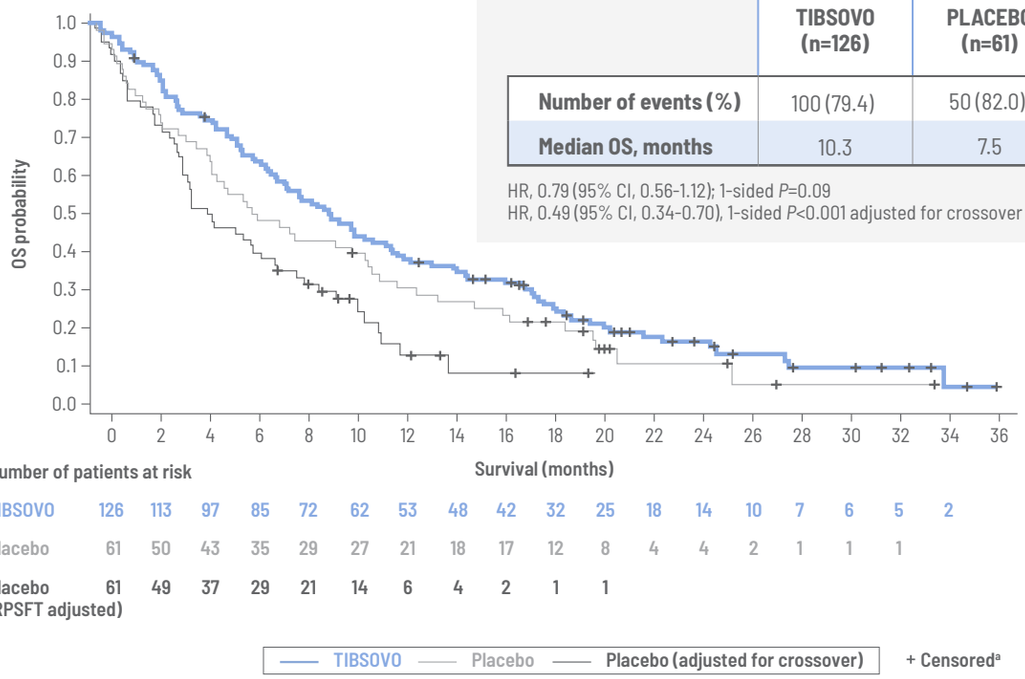
- The incidence of CCA is increasing, and the prognosis is poor[4]
- Chemotherapy is the primary first-line treatment option[4]
- Median survival among patients with advanced disease is typically less than 12 months[4]
- Five-year survival rate is 10% or less[4]

mIDH1 is an early driver mutation that occurs in up to 20% of intrahepatic CCA cases in the United States[4,5]

PFS AND OS OUTCOMES

- The improvement in PFS was statistically significant with TIBSOVO compared with placebo (HR, 0.37 [95% CI, 0.25-0.54]; 1-sided *P*<0.001)[1]
- Median OS was 10.3 months (95%CI, 7.8-12.4 months) with TIBSOVO vs 7.5 months (95% CI, 4.8-11.1 months) with placebo (HR, 0.79 [95%CI, 0.56-1.12]; 1-sided *P*=0.09)[1]
- The 12-month survival rate was 43% (95% CI, 34%-51%) in the TIBSOVO arm vs 36% (95% CI, 24%-48%) in the placebo arm (HR, 0.49 [95% CI, 0.34-0.70])[4]
- Among patients originally assigned to receive placebo, 70% crossed over to receive open-label TIBSOVO[1]
  - The primary analysis of OS followed the intent-to-treat principle, which does not account for the crossover effect[4]

OS[4]



	TIBSOVO (n=126)	PLACEBO (n=61)	PLACEBO (ADJUSTED FOR CROSSOVER) (n=61)
Number of events (%)	100 (79.4)	50 (82.0)	49 (80.3)
Median OS, months	10.3	7.5	5.1

HR, 0.79 (95% CI, 0.56-1.12); 1-sided *P*=0.09
HR, 0.49 (95% CI, 0.34-0.70), 1-sided *P*<0.001 adjusted for crossover

- A statistical model was used to recreate the placebo curve as if crossover had not occurred[6,b,c]
- **When adjusted for crossover, median OS for the placebo group was 5.1 months (95% CI, 3.8-7.6 months; HR, 0.49 [95% CI, 0.34-0.70])[4]**

[a]Subjects without documentation of death at the time of the data cutoff for analysis were censored at the date the subject was last known to be alive or the data cutoff date, whichever was earlier.[4]

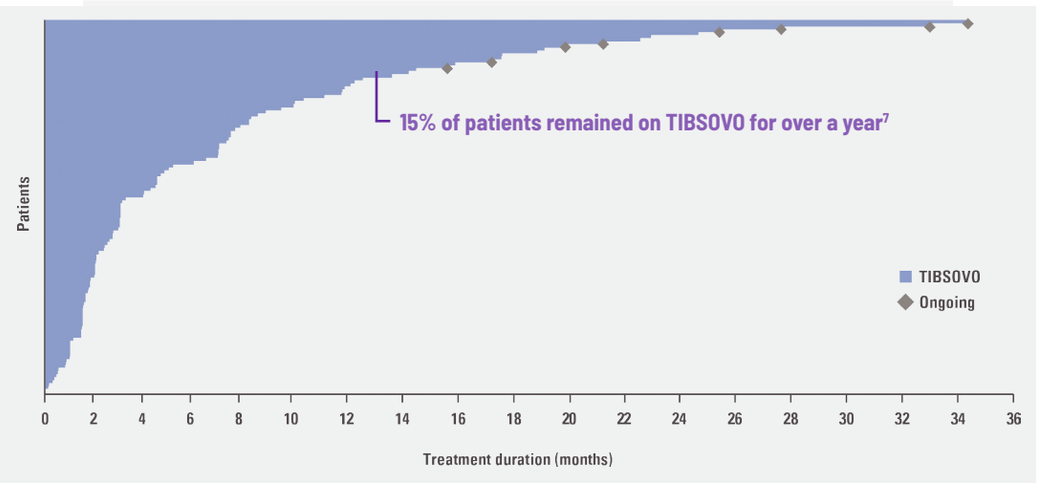
[b]This prespecified model, known as rank-preserving structural failure time (RPSFT), is one of the most commonly used statistical methods to adjust for treatment switching in oncology trials.[6]
This sensitivity analysis was exploratory, and appropriate multiplicity adjustments were not applied.

[c]The RPSFT model is based on the assumption that the treatment effect of TIBSOVO is the same for all individuals, regardless of when treatment is received.[4] This assumption was not verified.

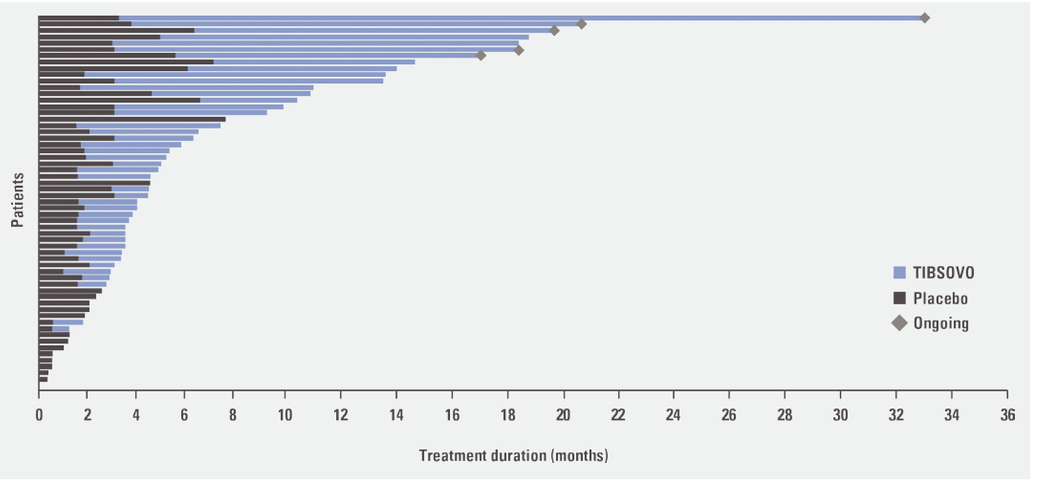
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TREATMENT DURATION

Treatment duration for all patients treated with TIBSOVO[4]
(n=123, range, 0.1-34.4 months)



Treatment duration for all patients treated with placebo, including those who crossed over to TIBSOVO[4]
(n=59, range, 0-6.9 months)



- Median treatment duration was 2.8 months (range, 0.1-34.4 months) for the TIBSOVO group (n=123) and 1.6 months (range, 0-6.9) for the placebo group (n=59)[4]
  - Median treatment duration for the TIBSOVO group after 43 patients crossed over from the placebo group was 2.7 months (range, 0.3-29.8 months)[4]
- Twenty-five of 166 patients (15%), including 6 patients who crossed over from placebo, remained on TIBSOVO for at least 1 year[7]

DISEASE CONTROL

Patients achieved better disease control on TIBSOVO[4]

Disease control rate[4,d]

53% with TIBSOVO **vs** **28%** with placebo

SAFETY

- Fatigue was the most common all-grade TEAE in both treatment groups before crossover[1]
  - TIBSOVO: 53 (43%) of 123 patients
  - Placebo: 18 (31%) of 59 patients
- Ascites was the most common grade 3 or higher TEAE reported in both treatment groups[1]
  - TIBSOVO: 11 (8.9%) of 123 patients
  - Placebo: 4 (7%) of 59 patients
- Other most common grade 3 or higher TEAEs (at least 5%) with TIBSOVO vs placebo were[1,3]:
  - Anemia (TIBSOVO: 8 [7%] of 123 patients vs 0 patients)
  - Increased blood bilirubin (36 [30%] of 123 patients vs 11 [19%] of 59 patients)
  - Decreased hemoglobin (48 [40%] of 123 patients vs 14 [25%] of 59 patients)
- Serious TEAEs were reported in 14 patients (24%) receiving placebo; none were related to treatment[4]

[d]The disease control rate (ORR + SD) was due mostly to the SD rate (an ORR of 2% [3 partial responses] and a SD rate of 51% with TIBSOVO vs an ORR of 0% and a SD rate of 28% with placebo).[4]

TEAE, treatment-emergent adverse event; SD, stable disease.

References: 1. Tibsovo. Package insert. Servier Pharmaceuticals LL; 2023. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Biliary Tract Cancers V.2.2025. © National Comprehensive Cancer Network, Inc., 2025. All rights reserved. Accessed January 28, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **3.** Data on file. Servier Pharmaceuticals, LLC. **4.** Zhu AX, Macarulla T, Javle MM, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. *JAMA Oncol.* 2021;7(11):1669-1677. doi:10.1001/jamaoncol.2021.3836 **5.** Boscoe A, Rolland C, Kelley RK. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. *J Gastrointest Oncol.* 2019;10(4):751-765. doi:10.21037/jgo.2019.03.10 **6.** Bennett I, Paracha N, Abrams K, et al. Accounting for Uncertainty in Decision Analytic Models Using Rank Preserving Structural Failure Time Modeling: Application to Parametric Survival Models. *Value in Health.* 2018;21(2):105–109. doi:10.1016/j.jval.2017.07.008 **7.** Zhu AX. Final results from ClarIDHy, a global, Phase III, randomised, double-blind study of ivosidenib versus placebo in patients with previously treated cholangiocarcinoma and an isocitrate dehydrogenase 1 (IDH1) mutation. *EMJ Oncology.* 2021;9(Suppl 2):2–5.

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TREAT 2ND-LINE PATIENTS WITH A TARGETED THERAPY OPTION IN ADVANCED CCA

TIBSOVO delivered a 63% reduction in the risk of disease progression or death

(HR, 0.37 [95% CI, 0.25-0.54]; *P*<0.0001)[1]

- Median **PFS** was nearly **twice as long** for patients assigned to TIBSOVO compared with placebo (2.7 months [95% CI, 1.6-4.2] versus 1.4 months [95% CI, 1.4-2.5])[3]
- **Meaningful improvements in PFS rates**[3]
  - 32% PFS rate at 6 months
  - 22% PFS rate at 12 months
- Median OS was 10.3 months for TIBSOVO (95% CI, 7.8-12.4 months), and without adjusting for crossover, median OS for the placebo group was 7.5 months (95% CI, 4.8-11.1 months; *P*=0.093)[1,a,b]

Please see inside for additional information on trial design and efficacy results.

NCCN Guidelines® recommend ivosidenib (TIBSOVO) as a category 1 subsequent-line systemic treatment option for patients with unresectable or metastatic progressive CCA with *IDH1* mutations.[2]

To view the most recent and complete version of the guidelines, visit NCCN.org.

[a]This prespecified model, known as rank-preserving structural failure time (RPSFT), is one the most commonly used statistical methods to adjust for treatment switching in oncology trials.[6] This sensitivity analysis was exploratory, and appropriate multiplicity adjustments were not applied.

[b]The RPSFT model is based on the assumption that the treatment effect of TIBSOVO is the same for all individuals, regardless of when treatment is received.[4] This assumption was not verified.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Guillain-Barré Syndrome: Guillain-Barré syndrome can develop in patients treated with TIBSOVO. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

ADVERSE REACTIONS

- **In patients with cholangiocarcinoma,** the most common adverse reactions (≥15%) were fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash. The most common laboratory abnormalities (≥10%) were hemoglobin decreased, aspartate aminotransferase increased, and bilirubin increased.

DRUG INTERACTIONS

Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation.

Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO.

Sensitive CYP3A4 Substrates: Avoid concomitant use with TIBSOVO.

QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation.

LACTATION

Advise women not to breastfeed.

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