Ivosidenib (Tibsovo®, Tidhesco®[1]) in combination with azacitidine for the treatment of newly diagnosed acute myeloid leukaemia (AML)

General information [1, 2]

Drug description	Indication
Ivosidenib (Tibsovo®, Tidhesco®) is an antineoplastic agent. Ivosidenib inhibits the mutant isocitrate dehydrogenase 1 (IDH1) enzyme, which converts alpha-ketoglutarate to 2-hydroxyglutarate. This blocks cellular differentiation and promotes tumorigenesis. The mechanism of action of ivosidenib is not fully understood beyond its ability to reduce 2-HG and restore cellular differentiation is not fully understood across indications.	Ivosidenib (Tibsovo®, Tidhesco®) in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy.

Incidence

- The incidence of AML is approximately 3.7 cases/100,000 population per year and increases with age-specific incidences exceeding 100 cases per 100,000 in patients older than 70 years [3].
- AML is most frequently diagnosed among people aged 65–74; the median age at diagnosis is 68 years [4].
- A mutation in the IDH1 or IDH2 gene is found in 10-20% of AML patients at initial diagnosis [3].

Current treatment [3]

- For the therapy of elderly patients without intensive therapy options, **DGHO recommends** the following:
  - In patients with a biological age over 75 years or with significant comorbidities such as late-stage diabetic syndrome, liver or kidney disease, congestive heart failure (EF <30%), ECOG ≥3 or low chances of cure due to unfavourable cytogenetics (unfit, fragile or frail), the therapeutic goal is to prolong life while maximising QoL.
  - In addition to BSC, these patients should be offered cytoreductive outpatient chemotherapy.
  - In addition to a purely symptomatic administration of hydroxyurea to lower the leukocyte count, the hypomethylating agents (HMA) 5-azacitidine and decitabine are recommended because they can induce higher response rates and prolonged survival compared to the historical standard of low-dose cytarabine.
  - Due to the mechanism of action of HMA, there may be a delayed response with HMA monotherapy, so an efficacy assessment is not recommended until 3-4 months.
  - Therapy should be administered every four weeks until progression, as relapses occur rapidly after discontinuation.
  - Although randomised direct comparisons of the two agents are lacking, their efficacy can be considered equivalent. Thus, their use is also guided by practical considerations.
  - Combining venetoclax with a hypomethylating agent is recommended as the priority treatment standard in first-line therapy of patients ineligible for intensive chemotherapy.
  - Clinical management for combination therapy with venetoclax differs significantly from that for monotherapy with HMA:
    - To reduce the risk of tumour lysis, venetoclax combination should be started only when the leukocyte count is less than 25,000/µl, a dose ramp-up should be performed over 4 days, and supportive measures should be taken to prevent tumour lysis. In addition, drug interactions have to be considered.
    - The DGHO recommends:
      - Cycle 1 should be started under in-patient conditions.
      - Venetoclax dosing must be adjusted when co-medicating with CYP3A inhibitors.
      - The more pronounced cytopenia compared with HMA monotherapy, combined with a higher likelihood of infectious complications, requires close monitoring, including bone marrow diagnostics already after cycle 1 (between days 21 and 28) and prompt dose adjustments depending on remission status and blood count. After achieving blast clearance, G-CSF can be used if regeneration is delayed, although there is no firm evidence of benefit from the growth factor.
      - Dose adjustment of venetoclax with concomitant administration of ciprofloxacin or macrolides.
      - Reduction of venetoclax dose by 75% with concomitant administration of Posaconazole.

[1] Tidhesco® is a duplicate of Tibsovo®.

- As another option for combination with LDAC in unresectable patients, the hedgehog inhibitor glasdegib was approved in June 2020, resulting in an increase in CR/CRi rates from 5.3% to 24.3% and a significant median increase in survival from 4.3 to 8.3 months compared with low-dose cytarabine (LDAC) monotherapy in a randomised non-placebo-controlled trial. To date, this combination has not been directly compared to the efficacy of LDAC plus venetoclax.
- Alternatively, LDAC can be used in case of contraindications to HMA or progressive disease. LDAC has a higher efficacy than hydroxyurea in this situation.
- A small proportion of newly diagnosed patients may be so impaired by leukaemia-related organ impairment (e.g., leukemic infiltration of the liver), neutropenic infectious complications, or B symptoms that intensive therapy is not possible or justifiable at initial diagnosis. Successful treatment of AML with HMA or LDAC, possibly in combination with venetoclax, may improve the condition such that SCT appears feasible and can be successfully performed.
- Due to the far-reaching prognostic consequences for or against intensive curative or palliative cytoreductive therapy, newly diagnosed AML patients should be presented to an experienced therapy centre to assess the optimal treatment strategy.

Regulatory status

EMA [1, 2]

Ivosidenib (Tibsovo®)

Approval status for this indication: On 23 February 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Tibsovo® for the following indication:

- ❖ Tibsovo®, in combination with azacitidine, is indicated for the treatment of adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy.

Other indications:

- ❖ Tibsovo® monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

✓ **Orphan status**

Ivosidenib (Tidhesco®)

Approval status for this indication: On 23 February 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Tidhesco® for the following indication:

- ❖ Tidhesco®, in combination with azacitidine, is indicated for the treatment of adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy.

UPDATE as of 26 April 2023 [2]:
The applicant **withdrew** the marketing authorisation application for Tidhesco® on 27 March 2023. This application was a duplicate of the application for the medicine Tibsovo, for which the CHMP adopted a positive opinion on 23 February 2023. The application was withdrawn after CHMP had adopted a positive opinion recommending the granting of a marketing authorisation. At the time of withdrawal, the European Commission had not yet granted marketing authorisation for this product.

Other indications: none

FDA [5, 6]

Approval status for this indication: On 25 May 2022, the FDA approved ivosidenib (Tibsovo®) in combination with azacitidine (azacitidine for injection) for newly diagnosed AML with a susceptible IDH1 mutation, as detected by an FDA-approved test in adults 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy.

- ✓ Priority review
- ✓ Breakthrough designation

Other indications: Tibsovo® is indicated for patients with a susceptible IDH1 mutation as detected by an FDA-approved test with:

- ❖ Relapsed or refractory AML
  - For the treatment of adult patients with relapsed or refractory AML.
- ❖ Locally advanced or metastatic cholangiocarcinoma
  - To treat adult patients with locally advanced or metastatic cholangiocarcinoma who have been previously treated.

✓ **Orphan status**	

Manufacturer

The manufacturer of Tibsovo® and Tidhesco® is Les Laboratoires Servier.

Costs

Currently, there is no cost information available.

Warnings and precautions [6]

- **Differentiation syndrome**
  - Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal.
  - Symptoms of differentiation syndrome in patients treated with Tibsovo® included non-infectious leukocytosis, peripheral oedema, pyrexia, dyspnoea, pleural effusion, hypotension, hypoxia, pulmonary oedema, pneumonitis, pericardial effusion, rash, fluid overload, tumour lysis syndrome and creatinine increased.
  - Patients treated with Tibsovo® have experienced symptoms of differentiation syndrome. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.
- **QTc interval prolongation**
  - Monitor electrocardiograms and electrolytes. If QTc interval prolongation occurs, the dose reduces or withheld, then resume dose or permanently discontinue Tibsovo®.
- **Guillain-Barré syndrome**
  - Monitor patients for signs and symptoms of new motor and/or sensory findings. Permanently discontinue Tibsovo® in patients who are diagnosed with Guillain-Barré syndrome.

Study characteristics [7-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up for PE	Characteristics	Biomarker	Funding	Publication(s)
AGILE, AG120-C-009 NCT03173248	146[2] (1:1)	ivosidenib (500 mg) orally, once daily, + azacitidine 75 mg/m² of BSA subcutaneously or IV for 7 days in 28-day cycles	matched placebo + azacitidine 75 mg/m2 of BSA subcutaneously or IV for 7 days in 28-day cycles	event-free survival (EFS)[3,4]	12.4 months	**ongoing**[5], global, double-blind, randomised, placebo-controlled, phase 3 trial	IDH1	Agios Pharmaceuticals and Servier Pharmaceuticals	AGILE trial [9]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (ITT-population, n=72 vs. n=74)
❖ Patients ≥18 years with a centrally confirmed diagnosis of previously untreated IDH1-mutated AML (determined with the FDA–approved Abbott Real-Time IDH1PCR assay) ❖ No previous treatment with an IDH1 inhibitor or HMA for MDS	❖ Patients ≥75 years or at least one of the following medical conditions: • ECOG PS score of 2	❖ Median age: 76.0 vs. 75.5 years ❖ Male patients: 58% vs. 51% ❖ ECOG PS 0: 19% vs. 14% ❖ ECOG PS 1: 44% vs. 54%

[2] On the basis of the recommendation of the data monitoring committee, whose members noted a difference in the number of deaths favouring ivosidenib and azacitidine, the sponsor and former sponsor **discontinued trial recruitment** on May 27, 2021. To account for this unplanned analysis, an individual set of groups-sequential boundaries was applied separately to the primary and key secondary efficacy endpoints.

[3] Defined as the time from randomisation until treatment failure (i.e., the patient did not have complete remission by week 24), relapse from remission, or death from any cause, whichever occurred first.

[4] **PE change from OS to EFS**: Sample size estimation showed that the change of PE from OS to EFS allowed for a smaller (200 vs. 398) and more feasible trial in this rare patient population. Furthermore, EFS more accurately describes the contribution of a novel therapy to clinical benefit by removing the potentially confounding effects of post-trial therapies and by capturing treatment failure as an event. Collectively, these considerations supported the amendment of the protocol to include a PE of EFS as a meaningful and direct measure of clinical benefit for the treatment of patients with AML who are ineligible for intensive induction chemotherapy. OS was kept as a secondary endpoint, and it was met together with the primary EFS endpoint.

[5] The AGILE trial is ongoing until 06/2024.

❖ ECOG PS 0-2 ❖ Adequate hepatic and renal function	• Severe cardiac disorder (e.g., CHF resulting in treatment, a LVEF of ≤50%, or chronic stable angina) • Severe pulmonary disorder (e.g., a diffusing capacity of the lungs for carbon monoxide of ≤65% or a forced expiratory volume in 1 second of ≤65%) • Creatinine clearance <45 ml/min • Bilirubin level >1.5 times the upper limit of the normal range	❖ ECOG PS 2: 36% vs. 32% ❖ Disease history according to investigator/ primary AML: 75% vs. 72% ❖ IDH1 mutation type R132C: 62% vs. 69%

Efficacy (I vs. C)	**Safety** (I vs. C)
Data cut-off date, 18 March 2021, median follow-up 12.4 months: **EFS significantly** longer in I vs. C; HR for treatment failure, relapse from remission, or death, 0.33; 95% CI, 0.16-0.69; p= 0.002 **Median EFS**: 0.03 months (95% CI, 0.03-11.01) vs. 0.03 months (95% CI, could not be estimated) **Estimated probability that a patient would remain event-free at 6 months:** 40% vs. 20% **Estimated probability that a patient would remain event-free at 12 months**: 37% vs. 12% **Patients with complete remission by 24 weeks**: 38% vs. 11% **Median EFS**: 22.9 months (95% CI, 7.5-could not be estimated) vs. 4.1 months (95% CI, 2.7-6.8) **Median OS**: 24.0 months (95% CI, 11.3-34.1) vs. 7.9 months (95% CI, 4.1-11.3), HR for death, 0.44; 95% CI, 0.27 to 0.73; p=0.001 **Complete remission**: 47% (95% CI, 35-59) vs. 15% (95% CI, 8-25); p<0.001 **Median duration of complete remission**: NR vs. 11.2 months (95% CI, 3.2-could not be estimated) **Estimated probability that a patient would remain in complete remission at 12 months**: 88% vs. 36% **Median time to complete remission**: 4.3 months (range, 1.7-9.2) vs. 3.8 months (range, 1.9-8.5) **Complete remission or complete remission with partial hematologic recovery**: 53% (95% CI, 41-65) vs. 18% (95% CI, 10-28); p<0.001 **Objective response**: 62% (95% CI, 50-74) vs. 19% (95% CI, 11-30); p<0.001 **Median duration of response**: 22.1 months (95% CI, 13.0-could not be estimated) vs. 9.2 months (95% CI, 6.6-14.1) **Median duration of treatment**: 6.0 months (range, 0.1-33.5) vs. 2.8 months (range, 0.1-19.8) **Patients who converted to transfusion independence**: 46% vs. 18%; p=0.006 **Median variant allele frequency of IDH1 mutations in bone marrow aspirates at baseline**: 36.8% vs. 35.5% Among patients with available samples who had CR or CR with partial hematologic recovery, 52% vs. 30% had **IDH1 mutation clearance**. Among all patients with data on IDH1 mutation clearance from bone marrow mononuclear cells, 33% vs. 6% had CR with IDH1 mutation clearance; p=0.009.	**AE grade ≥3:** n=66/71 (93%) vs. n=69/73 (95%) **Infections of any grade**: 28% vs. 49% **Bleeding events**: 41% vs. 29% **Differentiation syndrome of any grade[6]:** 14% (no grade ≥4 events) vs. 8% **AEs leading to discontinuation[7]**: n=19/71 vs. n=19/73 **Death from AEs**: n=10/71 (14%) vs. 21/73 (29%)

Patient-reported outcomes
❖ Baseline EORTC QLQ-C30 scores were available for 69 patients (96%) receiving ivosidenib and azacitidine and 66 (89%) receiving placebo and azacitidine. ❖ No assessments of HRQoL in the placebo-and-azacitidine group were available after cycle 19. ❖ Adherence was generally more than 70%. Results favoured ivosidenib and azacitidine across all EORTC QLQ-C30 subscales. ❖ After an initial decline in both groups consistent with the time to response, HRQoL with ivosidenib and azacitidine was similar to or improved from baseline for most subscales from cycle 5 through cycle 19 when applied a 10-point threshold for clinically meaningful change. ❖ Improvements from baseline did not occur for any subscale with placebo and azacitidine.

[6] The median time to onset of investigator-reported differentiation syndrome of any grade in the ivosidenib-and-azacitidine group was 19.5 days (range, 3.0 to 33.0). No deaths due to differentiation syndrome were noted in either group.

[7] The most common was pulmonary embolism in the ivosidenib-and-azacitidine group (n=2; 3%) and pneumonia in the placebo and azacitidine group (n=4; 5%).

ESMO-MCBS version 1.1 [11]

Disclaimer: Though not finally validated, feasibility was tested in [12], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, ESMO assessments were also carried out for haematological indications in new fact sheets and updates.

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	<12 months	OS: + 16.7 months	0.44 (0.27 to 0.73)	HR ≤ 0.65 AND gain ≥3 months	4	-	improved	+1	5

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	unclear[8]	yes[9]	unclear

Ongoing RCTs [14]

NCT number/trial name	Description	Estimated study completion date
NCT03173248/AGILE	Please see above.	06/2024
NCT03839771/ HOVON150AML	A phase 3, multi-centre, double-blind, randomised, placebo-controlled study of ivosidenib or enasidenib in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed AML or MDS with excess blasts-2, with an IDH1 or IDH2 Mutation, respectively, eligible for intensive chemotherapy.	03/2033
NCT02677922	A phase 1b/2 open-label, randomised study of 2 combinations of IDH mutant targeted therapies plus azacitidine: oral AG-120 plus subcutaneous azacitidine and oral AG-221 plus SC azacitidine in subjects with newly diagnosed AML harbouring an IDH1 or an IDH2 mutation, respectively, who are not candidates to receive intensive induction chemotherapy.	10/2024
NCT05401097/ I-DATA Study	Randomised, sequential, open-label study to evaluate the efficacy of IDH targeted/non-targeted vs. non-targeted/IDH-targeted approaches in treating newly diagnosed IDH mutated AML patients not candidates for intensive induction therapy.	12/2024

Available assessments

- An evidence briefing, "Ivosidenib for acute myeloid leukaemia with IDH1 mutation ", published by the NHS, was identified [15].
- There are no assessments available from NICE, CADTH, ICER or G-BA.

Other aspects and conclusions

[8] On the basis of the recommendation of the data monitoring committee, whose members noted a difference in the number of deaths favouring ivosidenib and azacitidine, the sponsor and former sponsor discontinued trial recruitment on May 27, 2021. To account for this unplanned analysis, an individual set of group-sequential boundaries was applied separately to the primary and key secondary efficacy endpoints.

[9] This trial was designed by the former sponsor, Agios Pharmaceuticals (Servier Pharmaceuticals has acquired the Agios oncology business), in collaboration with the investigators. Data were collected by the investigators and their research staff. The authors analysed the data in collaboration with the sponsor. Drafts of the manuscript were written by the first two and last two authors and revised in collaboration with all the authors and the sponsor, all of whom vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. Assistance in manuscript preparation was provided by a professional medical writer paid by the sponsor.

- On 23 February 2023, the **CHMP adopted a positive opinion**, recommending granting marketing authorisation for **Tibsovo®** and its **duplicate Tidhesco®**, intended to treat adult patients with newly diagnosed AML. The **FDA approved** Tibsovo® in May 2022, in combination with azacitidine, for newly diagnosed AML with a susceptible IDH1 mutation.
- **AGILE (NCT03173248)**, an ongoing phase 3 trial, assessed the efficacy, safety and HRQoL of ivosidenib and azacitidine in IDH1-mutated AML. Patients ≥18 years with a centrally confirmed diagnosis of previously untreated IDH1-mutated AML, no previous treatment with an IDH1 inhibitor or hypomethylating agent for MDS, an ECOG PS 0-2 and adequate hepatic and renal function were included. Excluded were patients ≥75 years or at least one of the following medical conditions: ECOG PS score of 2, severe cardiac disorder, a severe pulmonary disorder, creatinine clearance <45 ml/min, and bilirubin level >1.5 times the upper limit of the normal range.
- Since the AGILE trial is currently **ongoing, no final analysis data** is available.
- Although the **risk of bias** of the AGILE trial is currently not evaluable due to the trial's ongoing status, it **increases** by the fact that the trial **recruitment was stopped by the sponsor and the primary endpoint changed from OS to EFS.**
- One phase 3 trial (NCT03839771/ HOVON150AML) evaluating ivosidenib or enasidenib in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed AML or MDS, and various phase 1/2 trials assessing ivosidenib treatment in different combinations, were identified.

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Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia, BSA=body surface area, BSC=best supportive care, C=comparator, CADTH=Canada's Drug and Health Technology Agency, CHF=congestive heart failure, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete remission, CRi=incomplete hematologic regeneration, DGHO=Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie, ECOG=Eastern Cooperative Oncology Group, EFS=event-free survival, EMA=European Medicines Agency, EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HMA=hypomethylating agents, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, ICER=Institute for Clinical and Economic Review, IDH1=isocitrate dehydrogenase 1, Int.=intention, LDAC=low-dose cytarabine, LVEF=left ventricular ejection fraction, MDS=myelodysplastic syndrome, MG=median gain, n=number of patients, NICE=National Institute for Health Care Excellence, NR=not reached, OS=overall survival, PCR= polymerase-chain-reaction, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SCT=stem cell transplantation, ST=standard treatment

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