Cedazuridine/decitabine (Inaqovi®) for the treatment of newly diagnosed acute myeloid leukaemia (AML)

General information

Drug description [1]

Inaqovi® (ASTX727) will be available as a 35 mg/100 mg film-coated tablet containing a fixed combination of the active substances decitabine and cedazuridine. Decitabine is a nucleoside metabolic inhibitor that inhibits the action of DNA methyltransferases, leading to hypomethylation of DNA and subsequent cellular differentiation and/or apoptosis. Cedazuridine is a cytidine deaminase inhibitor that increases systemic exposure to decitabine.

Indication [1]

Cedazuridine/decitabine (Inaqovi®) is indicated as monotherapy for the treatment of adult patients with newly diagnosed AML who are ineligible for standard induction chemotherapy.

Incidence [2]

The incidence of AML is approximately 3.7 cases per 100,000 population per year and increases with age with age-specific incidences exceeding 100 cases per 100,000 population in patients older than 70 years.

Current treatment [2]

- 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 quality of life.
- 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 prolong 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 that an efficacy assessment is not recommended until 3-4 months. Therapy should be administered every 4 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.
- In two randomised placebo-controlled trials, the combination of 5-azacitidine or (low-dose Ara-C) LDAC with the bcl2 inhibitor venetoclax resulted in a significant increase in remission rates (CR/CRi) from 28.3% to 66.4% with azacitidine and from 13% to 48% with LDAC, respectively. Venetoclax significantly prolonged OS in combination with azacitidine from 9.6 to 14.7 months. This beneficial effect was demonstrated in all genetic subgroups. The predefined primary endpoint analysis in the combination study with venetoclax and LDAC after 12 months of median follow-up showed a survival difference of 7.2 vs. 4.1 months, which did not reach statistical significance. Only after an additional 6 months and a difference in OS of 8.4 vs. 4.1 was statistical significance achieved. On the basis of the above data, the EMA did not grant approval to the combination of LDAC plus venetoclax.
- Approval for the combination of venetoclax with a hypomethylating agent was granted by the EMA in 2021. Based on data, this combination is recommended as the first priority treatment standard in first-line therapy of patients ineligible for intensive chemotherapy. The evidence is more robust for azacitidine, but similar efficacy can be assumed for decitabine as a combination partner.
- 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, 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. We recommend:
    - Cycle 1 should be started under inpatient 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.

- ❖ As another option for combination with LDAC in unresectable patients, the hegdehog inhibitor glasdegib was approved in June 2020, resulting in an increase in CR/CRi rates from 5.3% to 24.3% and a median significant increase in survival from 4.3 to 8.3 months compared with LDAC monotherapy in a randomised non-placebo-controlled trial. To date, there is no direct comparison of this combination 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 for assessment of the optimal treatment strategy.

Regulatory status

EMA [1]	FDA [2, 3]
Approval status for this indication: On 20 July 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for **Inaqovi®**. The full indication is: ❖ Inaqovi® is indicated as monotherapy for the treatment of adult patients with newly diagnosed AML who are ineligible for standard induction chemotherapy. **Other indications**: none ✓ **Medicine is under additional monitoring**	**Approval status for this indication**: not approved Other indications: On 7 July 2020, the FDA approved an oral combination of decitabine and cedazuridine (**Inqovi®**) for adult patients with myelodysplastic syndromes (MDS[1]) including the following: ❖ previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anaemia, refractory anaemia with ringed sideroblasts, refractory anaemia with excess blasts, and CMML) and ❖ intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. ✓ This application was granted priority review.

Manufacturer

Inaqovi® is manufactured by Otsuka Pharmaceutical Netherlands B.V.

Costs

Currently, there is no cost information available.

Posology

- ❖ Treatment must be initiated and supervised by a physician experienced in the use of anticancer therapies.
- ❖ The recommended dose of Inaqovi is 1 tablet once daily on Days 1 through 5 of each 28-day cycle.
- ❖ Cycles are to be repeated every 28 days. Treatment is to be continued for a minimum of 4 cycles until disease progression or unacceptable toxicity. A complete or partial response may take longer than 4 cycles.
- ❖ Substitution with an intravenous decitabine product within a cycle is not recommended.
- ❖ Premedication with standard antiemetic therapy prior to each dose to minimise nausea and vomiting is to be considered.

A delay or reduction in the dose per cycle is to be considered for patients who experience haematologic and non-haematologic toxicities.

[1] AML is not infrequently associated with myelodysplastic syndromes (MDS), such as a history of MDS or MDS-typical morphology or typical cytogenetics. In particular, patients in the genetically defined subgroups with chromatin spliceosome mutations are more likely to have a history of MDS or typical morphological changes.

Special warnings and precautions for use [4]

- ❖ **Myelosuppression**
  - Fatal and serious myelosuppression can occur with treatment.
  - Complete blood cell counts must be obtained prior to the initiation of treatment, prior to each cycle, and as clinically indicated to monitor response and toxicity. Growth factors and anti-infective therapies must be administered for treatment or prophylaxis as appropriate. The next cycle must be delayed and resumed at the same or reduced dose as recommended. Patients must be monitored for signs and symptoms of infection and treated promptly.
- ❖ **Neutropenia**
  - Supportive treatments include, administration of prophylactic antibiotics and/or growth factor support(e.g., G-CSF) for neutropenia according to institutional guidelines. For situations where administration must be delayed.
- ❖ **Respiratory, thoracic and mediastinal disorders**
  - Cases of interstitial lung disease (ILD) (including pulmonary infiltrates, organising pneumonia and pulmonary fibrosis) without signs of infectious aetiology have been reported in patients receiving intravenous decitabine.
  - Patients with an acute onset or unexplained worsening of pulmonary symptoms must be carefully assessed to exclude ILD. If ILD is confirmed, appropriate treatment must be initiated
- ❖ **Hepatic impairment**
  - Use in patients with hepatic impairment has not been established. Caution must be exercised in the administration of medicinal product to patients with hepatic impairment and in patients who develop signs or symptoms of hepatic impairment.
  - Liver function tests must be performed prior to the initiation of therapy, prior to each treatment cycle, and as clinically indicated.
- ❖ **Renal impairment**
  - Use in patients with severe renal impairment has not been studied. Caution must be exercised in the administration of the medicinal product to patients with severe renal impairment (CrCl < 30 mL/min).
  - Renal function tests must be performed prior to the initiation of therapy, prior to each treatment cycle, and as clinically indicated.
- ❖ **Cardiac disease**
  - Patients with a history of severe congestive heart failure or clinically unstable cardiac disease were excluded from clinical studies and therefore, the safety and efficacy of the medicinal product in these patients has not been established.
  - Cases of cardiomyopathy with cardiac decompensation, in some cases reversible after treatment discontinuation, dose reduction or corrective treatment, have been reported in the postmarketing setting with intravenous decitabine. Patients, especially those with a history of cardiac disease, must be monitored for signs and symptoms of heart failure.
- ❖ **Differentiation syndrome**
  - Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported during the post-marketing period with intravenous decitabine. Differentiation syndrome may be fatal.
  - Treatment with high-dose intravenous corticosteroids and haemodynamic monitoring must be considered at first onset of symptoms or signs suggestive of differentiation syndrome.
  - Treatment must be temporarily discontinued until symptoms resolve, and if resumed, caution is advised.
- ❖ **Administration of antiemetics**
  - Nausea and vomiting may occur during treatment. Administration of standard antiemetic therapy prior to each dose should be considered to minimise nausea and vomiting.
- ❖ **Excipients**
  - Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Study characteristics [5-7]

Trial name	n	Sequence A[2]	Sequence B	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
ASCERTAIN, ASTX727-02 NCT03306264	133 (1:1)	decitabine 35 mg/ cedazuridine 100 mg in cycle 1 followed by IV decitabine at 20 mg/ m^2 in cycle 2	IV decitabine in cycle 1 followed by oral decitabine/cedazuridine in cycle 2	total 5 day decitabine AUC equivalence (oral/IV 90% CI between 80% and 125%)	approx. 32 months	randomised, open-label, crossover, phase 3 study	-	Astex Pharmaceuticals, Inc.	ASCERTAIN (Abstracts) [5, 6]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (n=133)
❖ Men or women ≥18 years who are candidates to receive IV decitabine according to FDA or EMA approved indications: • In North America: Participants with MDS previously treated or untreated with de novo or secondary MDS, including all French-American-British subtypes (refractory anaemia, refractory anaemia with ringed sideroblasts, refractory anaemia with excess blasts, refractory anaemia with excess blasts in transformation, and chronic myelomonocytic leukaemia), and subjects with MDS IPSS int-1, -2, or high-risk MDS. • In Europe: Participants with de novo or secondary AML, as defined by the WHO criteria, who are not candidates for standard induction chemotherapy. ❖ ECOG PS of 0-1 ❖ Adequate organ function defined as follows: • Hepatic: Total or direct bilirubin ≤2 × ULN; aspartate transaminase/serum glutamic oxaloacetic transaminase and alanine transaminase/serum glutamic pyruvic transaminase ≤2.5 × ULN. • Renal: serum creatinine ≤1.5 × ULN or calculated creatinine clearance or glomerular filtration rate >50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal. ❖ No major surgery within 30 days of first study treatment. ❖ Life expectancy of at least 3 months. ❖ Women of child-bearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of non-childbearing potential are those who have had a hysterectomy or bilateral oophorectomy, or who have completed menopause, defined as no menses for at least 1 year AND either age ≥65 years or follicle-stimulating hormone levels in the menopausal range. Subjects and their partners with reproductive potential must agree to use effective contraceptive measures	❖ Prior treatment with more than 1 cycle of azacitidine or decitabine. Prior cytotoxic chemotherapy for AML except for hydroxyurea to control high white blood cell counts. ❖ Hospitalisation for more than 2 days for documented febrile neutropenia, pneumonia, sepsis, or systemic infection in the 30 days before screening. ❖ Treatment with any investigational drug or therapy within 2 weeks of study treatment, or 5 half-lives, whichever is longer, before the first dose of study treatment, or ongoing clinically significant AEs from previous treatment. ❖ Cytotoxic chemotherapy or prior azacitidine or decitabine within 4 weeks of first dose of study treatment. ❖ Concurrent MDS therapies, including lenalidomide, erythropoietin, cyclosporine/tacrolimus, granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor, etc. ❖ Poor medical risk because of other conditions such as uncontrolled systemic diseases, active uncontrolled infections, or comorbidities that may put the patient at risk of not being able to complete at least 2 cycles of treatment. ❖ Known significant mental illness or other condition, such as active alcohol or other substance abuse or addiction, that in the opinion of the investigator predisposes the subject to high risk of noncompliance with the protocol. ❖ Rapidly progressive or highly proliferative disease (total white blood cell count of >15 × 10^9/L) or other criteria that render the subject at high risk of requiring intensive cytotoxic chemotherapy within the next 3 months. ❖ Life-threatening illness or severe organ system dysfunction, such as uncontrolled congestive heart failure or chronic obstructive pulmonary disease, or other reasons including laboratory	❖ Median age: 71 years (range 44-88) ❖ Male sex: 65% ❖ Median weight: 83 kg ❖ Median BSA: 2 m^2 ❖ CMML: 12% ❖ MDS, IPSS classification: • High risk: 16% • Int 1 and 2: 68% • Low risk: 5% ❖ Transfusion dependent: • RBCs: 40% • Platelets: 9% ❖ ECOG PS: • 0: 41% • 1: 59%

[2] In ASCERTAIN trial, a randomised cross over design where patients were randomised in the first 2 cycles 1:1 to either sequence A or sequence B was used to do an intra-patient comparison of decitabine PK. Cycles were repeated every 28 days. All patients received oral decitabine/ cedazuridine in all subsequent cycles from cycle 3 onwards until disease progression or unacceptable toxicity.

during the study and for 3 months after the last dose of study treatment. Effective contraception includes methods such as oral contraceptives or double-barrier method.	abnormalities, which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ASTX727, or compromise completion of the study or integrity of the study outcomes. ❖ Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, prostate cancer or breast cancer under control with hormone therapy, or other cancer from which the subject has been disease free for at least 2 years.	

Efficacy (I vs. C)

Pharmacokinetics and Pharmacodynamics

- ❖ Compared to baseline, the median maximum LINE-1 methylation decrease (demethylation) in cycle 1 was 13.7%.
- ❖ The change in LINE-1 demethylation between oral vs. IV decitabine was less than 1% for both cycles 1 and 2 with overlapping 95% CIs suggesting similar biologic effect.
- ❖ Individual decitabine exposures from oral fixed dose decitabine/cedazuridine dosing overlapped with IV decitabine BSA based dosing.
- ❖ The study met its primary endpoint with high confidence: Oral/IV 5 day decitabine AUC ~99% with 90% CI of ~93 106% (n=123).
- ❖ All sensitivity (n=131) and secondary PK AUC analyses confirmed findings from primary analysis.

Responses

- ❖ Median follow up: approx. 32 months
- ❖ mOS for the 133 patients: 31.7 months (95% CI, 28.0-NE)
- ❖ Leukaemia-free survival: 29.1 months (95% CI, 22.1-NE)
- ❖ Median CR duration: 14.0 months (range, 2-29 months)
- ❖ Median duration of best response: 12.7 months (range, 1-33 months)
- ❖ 34 (26%) of subjects proceeded to HCT
- ❖ No survival difference was seen between subjects proceeding to HCT vs. others
- ❖ Subjects received median 9 cycles of treatment
- ❖ Complete response: 22% (95% CI 15.1-29.8)
- ❖ Partial response: 0
- ❖ Marrow CR (mCR): 32.3% (95% CI, 24.5-41.0)
- ❖ mCR with hematologic improvement: 16.5% (95% CI,10.7-24.0)
- ❖ Hematologic improvement (HI): 7.5% (95% CI, 3.7-13.4)
- ❖ HI erythroid: 1.5% (95% CI, 0.2-5.3)
- ❖ HI neutrophils: 0.8% (95% CI, 0.0-4.1)
- ❖ HI platelet: 5.3% (95% CI, 2.1-10.5)
- ❖ Overall response (CR + PR + mCR + HI): 61.7% (95% CI, 52.8-69.9)
- ❖ Progressive Disease: 4.5% (95% CI,1.7-9.6)
- ❖ No Response: 21.1% (95% CI,14.5-29.0)
- ❖ Non-evaluable: 12.8% (95%CI, 7.6-19.7)

Safety (I vs. C)

TEAEs in >10% of patients (n=133, grade ≥3, events attributable to oral decitabine/cedazuridine):

- Neutropenia: 49%
- Thrombocytopenia: 47%
- Anaemia: 35%
- Leukopenia: 22%
- Febrile Neutropenia: 22%
- Fatigue: 2%
- Diarrhoea: 2%
- Nausea: 0%
- Decreased appetite: 0%
- Constipation: 0%

❖ Safety profile consistent with that of IV decitabine.

❖ No new safety concerns with longer follow-up.

Patient-reported outcomes

Patient reported outcomes are currently not available.

ESMO-MCBS for Haematological Malignancies [8]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS was not applicable because currently only abstract data is available.											

Risk of bias (RCT) [9]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
The risk of bias is currently not evaluable.					

Ongoing trials [10]

NCT number/trial name	Description	Estimated study completion date
NCT05883956/ PREFER	A phase 3b, randomised, open-label, double crossover study comparing treatment preference between oral decitabine/cedazuridine and azacitidine in adult patients with IPSS R intermediate myelodysplastic syndrome, low blast AML, IPSS intermediate-2 or high risk MDS or chronic myelomonocytic leukaemia.	04/2025

Available assessments

- In September 2021, CADTH published a pharmacoeconomic report [11] and a reimbursement review [11] for Inqovi®.
- NIHR published a Health Technology Briefing "ASTX727 for acute myeloid leukaemia" in April 2022 [12].
- No further assessment was identified via NICE, ICER and G-BA.

Other aspects and conclusions

- In July 2023, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for **Inaqovi®** indicated as monotherapy for the treatment of adult patients with newly diagnosed AML who are ineligible for standard induction chemotherapy. This indication is not approved by the FDA; However, in July 2020, the **FDA approved** an oral combination of decitabine and cedazuridine (**Inqovi®**) for adult patients with myelodysplastic syndromes (MDS) including the following: previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anaemia, refractory anaemia with ringed sideroblasts, refractory anaemia with excess blasts, and CMML) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.
- **ASCERTAIN** (ASTX727-02, NCT03306264) is a randomised, **open-label, crossover**, phase 3 study. Patients who are candidates for IV decitabine, had an ECOG PS of 0 or 1, a life expectancy of ≥3 months and adequate organ function were included. Detailed in- and exclusion criteria are listed above.
- Primary endpoint of the ASCERTAIN trial was the **total 5 day decitabine AUC equivalence** (oral/IV 90% CI between 80% and 125%), which the study **met** with high confidence: Oral/IV 5 day decitabine AUC ~99% with 90% CI of ~93 106% (n=123).
- Patient-reported outcomes are currently **not available**.
- Since currently **only abstract data is available**, the ESMO-MCBS for Haematological Malignancies is not applicable, as well as the risk of bias is not evaluable.
- One **ongoing** phase 3, a randomised, open-label, double crossover study comparing treatment preference between oral decitabine/cedazuridine and azacitidine in adult patients with IPSS R intermediate myelodysplastic syndrome, low blast AML, IPSS intermediate-2 or high risk MDS or chronic myelomonocytic leukaemia was identified.
- To finally determine the efficacy and safety of Inaqovi® for the treatment of AML patients, **robust phase 3 data including patient-reported outcome data is required**.

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Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia, AUC=area under the curve, BSA=body surface area, BSC=best supportive care, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CMML=chronic myelomonocytic leukaemia, CR=complete remission, CRi=complete remission with incomplete hematologic regeneration, DNA=deoxyribonucleic acid, ECOG PS=Eastern Cooperative Oncology Group performance status, EF=ejection fraction, EMA=European Medicines Agency, 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 Bundesauschuss, HI=hematologic improvement, HMA= Hypomethylating agent,

HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, IPSS=International Prognostic Scoring System, LDAC= low-dose cytarabine (low-dose Ara-c), mCR=marrow CR, MG=median gain, MDS=myelodysplastic syndromes, n=number of patients, NICE=National Institute for Health and Care Excellence, NIHR=National Institute for Health and Research, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial remission, QoL=quality of life, SAE=serious adverse event, SCT=stem cell transplantation, TEAE=treatment-emergent adverse event, ST=standard treatment, ULN=upper limit of normal, WHO=World Health Organization

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