Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2615

ivosidenib film-coated tablet (Tibsovo®)

Servier Laboratories

09 February 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan medicine process

ivosidenib (Tibsovo®) is accepted for use within NHSScotland.

Indication under review: in combination with azacitidine for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.

Addition of ivosidenib to azacitidine improved event-free and overall survival in untreated adults with newly diagnosed AML and IDH1 R132 mutation who were ineligible for intensive induction chemotherapy.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Ivosidenib is an inhibitor of mutant IDH1 enzyme. The mutant IDH1 enzyme converts alpha-ketoglutarate to 2-hydroxyglutarate (2-HG), which impairs differentiation of haematopoietic stem cells into mature blood cells, thereby increasing the production of cancer cells. By inhibiting the mutant IDH1 enzyme, ivosidenib reduces 2-HG overproduction and restores cell differentiation. However, its mechanism of action is not fully understood.[1, 2] It is administered orally once daily in combination with intravenous or subcutaneous azacitidine, which is administered once daily on days 1 to 7 of each 28-day cycle.

1.2. Disease background

Acute myeloid leukaemia (AML) is an aggressive, rapidly progressing malignancy characterised by clonal proliferation of myeloid blast cells in the bone marrow and often in the peripheral blood and other tissues. IDH1 mutations are associated with poor prognosis. Patients with AML usually present with symptoms of impaired blood cell production: neutropenia, anaemia and thrombocytopenia. They may experience fatigue, weakness, palpitations, dyspnoea and, if untreated, patients will die from infection or bleeding complications in a short time. Other complications may include hepatomegaly, splenomegaly, skin problems, swollen gums, hyperuricaemia and renal failure.[2]

1.3. Treatment pathway and relevant comparators

Standard first-line treatment for AML comprises intensive induction chemotherapy followed by consolidation for those who achieve complete remission (CR), which may include chemotherapy or haematopoietic stem cell transplant (HSCT). Some patients, who are generally older or have poor prognostic factors, cannot tolerate these intensive, potentially curative therapies. They receive non-intensive therapies, with guidelines recommending first-line treatment with hypomethylating agents (HMA), such as azacitidine and decitabine, in combination with venetoclax.[2, 3] In the absence of a submission, SMC issued advice that decitabine is not accepted for use in NHS Scotland. Clinical experts consulted by SMC advised that venetoclax plus azacitidine is currently given to most of these patients.

1.4. Category for decision-making

Eligibility for a PACE meeting
Ivosidenib meets SMC end of life and orphan criteria in this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence is from the AGILE study, detailed in Table 2.1 below.[2, 4]

Table 2.1. Overview of relevant studies

Criteria	AGILE study[2, 4]
Study design	Double-blind phase III
Eligible patients	Untreated newly diagnosed adults with AML and IDH1 mutation resulting in R132C, R132G, R132H, R132L, or R132S substitution. ECOG performance status 0 to 2; not had HMA for MDS; not had IDH1 inhibitor. Ineligible for intensive induction chemotherapy due to one of the following: age ≥75 years; ECOG performance status of 2; severe cardiac disorder; severe pulmonary disorder; creatinine clearance < 45 mL/minute; or bilirubin >1.5 times ULN.
Treatments	Ivosidenib 500mg orally once daily or placebo, per randomisation. All received azacitidine 75mg/m^2 IV or SC daily on days 1 to 7 of 28-day cycles for at least six cycles. Treatment continued until disease relapse or progression, unacceptable toxicity, death or end of study.
Randomisation	Stratified according to geographic region and disease status (primary versus secondary AML). Equally randomised to ivosidenib or placebo.
Primary outcome	Event-free survival, where event was defined as treatment failure (no complete remission by week 24), relapse from remission, or death from any cause assessed by the investigator using modified International Working Group response criteria for AML and the European LeukemiaNet guidelines. This was assessed in the intention-to-treat population, which comprised all randomised patients.
Secondary outcomes	CR; OS; CR+CRh; and ORR.
Statistical analysis	Planned to test secondary outcomes in hierarchy above if primary significant

AML = acute myeloid leukaemia; CR = complete remission; CRh = complete remission with partial hematologic recovery; ECOG = Eastern Cooperative Oncology Group; HMA = hypomethylating agents; IDH1 = isocitrate dehydrogenase-1; IV = intravenous; MDS = myelodysplatic syndrome; ORR = objective response rate; OS = overall survival; SC = subcutaneous; ULN = upper limit of normal.

The study was stopped early on the advice of an independent data monitoring committee (IDMC) who had requested unplanned efficacy analyses (at data cut-off 18 March 2021). Subsequently, these became the primary analysis, with median follow-up for event-free survival (EFS) of 12.4 months and for overall survival (OS) of 15.1 months. As they had inadequate control of type 1 error, their p-values have not been reported. The primary and key secondary outcomes appear improved with ivosidenib-azacitidine compared with placebo-azacitidine. Table 2.2 details the results.[2]

Table 2.2: Primary and key secondary outcomes of AGILE study.[2]

	Ivosidenib-azacitidine (n=72)	Placebo-azacitidine (n=74)
Event-free survival (EFS)[a]		
Events	46	62
Median event-free survival, months	0.03	0.03
Hazard ratio (95% CI)	0.33 (0.16 to 0.69)	
KM 1-year event-free survival	37%	12%
Complete remission (CR)		
Events (%)	34 (47%)	11 (15%)
Odds ratio (95% CI)	4.76 (2.15 to 10.50)	
Overall survival (OS)		
Deaths	28	46
Median overall survival, months	24.0	7.9
Hazard ratio (95% CI)	0.44 (0.27 to 0.73)	
KM 2-year overall survival	45%	20%

Complete remission + complete remission with partial hematologic recovery (CR+CRh)		
Events (%)	38 (53%)	13 (18%)
Odds ratio (95% CI)	5.01 (2.32 to 10.81)	
Objective response rate (ORR)[b]		
Events (%)	45 (62%)	14 (19%)
Odds ratio (95% CI)	7.15 (3.31 to 15.44)	

a = primary outcome; b = objective response was defined as complete remission, complete remission with incomplete hematologic recovery (including complete remission with incomplete platelet recovery), partial remission, and morphologic leukemia-free state; CI = confidence interval; KM = Kaplan-Meier estimated.

In an updated analysis of OS (data cut-off 30 June 2022), at median follow-up of 28.6 months, when 64% of patients had died, there was no adjustment for five placebo patients who crossed over to ivosidenib after March 2021. Within the ivosidenib and placebo groups, median OS was 29.3 versus 7.9 months, respectively, with a hazard ratio (HR) of 0.42 (95% confidence interval [CI]: 0.27 to 0.65). Estimated OS rates were 63% versus 38% at 12 months; and 53% versus 17% at 24 months in the respective groups.[1,5]

2.2. Health-related quality of life outcomes

Over the course of the study, mean scores for European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status and Fatigue appeared generally better in the ivosidenib group compared with placebo group in analyses that were not adjusted for multiplicity.[2, 4]

2.3. Supportive studies

An open-label phase Ib study (AG-221-AML-005) included 23 newly diagnosed adults with AML and IDH1 mutations who were not eligible to have intensive chemotherapy and who received the licensed dose of ivosidenib plus azacitidine. The objective response rate (ORR) was 78% (18/23), which included 13 patients (56%) with complete remission and 2 patients (8.7%) with complete remission but partial haematological recovery. Estimated one-year EFS was 69% and OS was 82%.[2]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

A network meta-analysis (NMA) comparing ivosidenib-azacitidine versus venetoclax-azacitidine was presented and is detailed in Table 2.3. This supported the economic analysis.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Network meta-analysis
Population	Treatment-naïve adults with newly diagnosed AML ineligible for intensive chemotherapy
Comparators	Venetoclax plus azacitidine
Studies included	AGILE;[4] VIALE-A[6]
Outcomes	Overall survival and event-free survival
Results	For ivosidenib plus azacitidine versus venetoclax plus azacitidine:* EFS HR and OS HR

AML = acute myeloid leukaemia EFS = event-free survival; HR = hazard ratio; OS = overall survival. *Results considered confidential by company.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

The addition of ivosidenib to azacitidine in newly diagnosed AML is characterised by increased rates of common haematological and gastrointestinal adverse events and by adverse events of special interest including, QT prolongation, leucocytosis and differentiation syndrome.[2]

In the AGILE study, at the latest cut-off for safety (1 October 2021), within the ivosidenib and placebo group (before any crossover), median duration of treatment was 227.5 and 95.5 days, respectively. In the respective groups, rates of adverse events were 99% (71/72) and 100% (74/74) and these were considered to be related to treatment with ivosidenib or placebo only in 39% and 30% of patients; with azacitidine only in 58% and 51% of patients; and with ivosidenib or placebo plus azacitidine in 60% and 50% of patients, respectively. Serious adverse events were reported by 68% and 84% of patients, respectively and were considered related to treatment with ivosidenib or placebo only in 6.9% and 4.1% of patients; with azacitidine only in 6.9% and 6.8% of patients; and with ivosidenib or placebo plus azacitidine in 22% and 14% of patients. In the respective groups, adverse events led to discontinuation of treatment with ivosidenib or placebo only in 4.2% and 4.1%; with azacitidine alone in 2.8% and 1.4%; and with ivosidenib or placebo plus azacitidine in 26% and 26% of patients.[2]

In the AGILE study (at the 1 October 2021 data cut-off), in the ivosidenib and placebo groups, haematological adverse events were common, including anaemia (32% and 31%); thrombocytopenia (28% and 20%); neutropenia (31% and 22%); and febrile neutropenia (28% and 34%). Gastrointestinal adverse events were frequently reported, including nausea (44% and 39%); vomiting (40% and 27%); diarrhoea (35% and 39%) and constipation (31% and 53%). Other common adverse events included pyrexia (35% and 43%); pneumonia (24% and 32%) and asthenia (15% and 34%), respectively. Adverse events of special interest were reported more often in the ivosidenib group compared with placebo and included QT-interval prolongation (21% and 6.8%); leucocytosis, (11% and 2.7%); and differentiation syndrome, (14% and 8.1%), respectively.[2]

As differentiation syndrome is a potentially life-threatening event and can induce non-specific symptoms, a patient alert card is necessary for all AML patients to inform them about the symptoms of this condition and the importance of seeking medical advice. To mitigate the risks of QT prolongation, patients have an electrocardiogram (ECG) prior to initiating treatment, weekly for the first three weeks and monthly thereafter to detect abnormalities and allow prompt action.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the AGILE study, more than half of the patients in the ivosidenib-azacitidine and placebo-azacitidine groups did not have complete remission by week 24, and the median EFS was therefore the same in each (0.03 months). However, the estimated probability that a patient would remain event-free was 37% and 12% at 12 months in the ivosidenib-azacitidine and placebo-azacitidine groups respectively.[2, 4]
- In the double-blind phase III study, addition of ivosidenib to azacitidine improved EFS and OS, with an increase in median OS of approximately 21 months at the latest analysis.

Response rates appear higher with ivosidenib, with ORR increased by 43% which included 32% higher CR rate.[2, 5]

- Ivosidenib is the first IDH1 inhibitor licensed for treatment of AML and it is the first medicine specifically targeting the mutant enzyme that characterises AML with IDH1 mutations.

4.2. Key uncertainties

- The AGILE study was stopped early (data cut-off 18 March 2021) due to efficacy after an unplanned early analysis by the IDMC. There was inadequate control for type 1 error in this analysis, therefore, the regulatory authority specified that p-values should not be reported.[2] There were concerns that the integrity of the study could be compromised by this and a mid-study protocol amendment, which changed the primary endpoint from OS to EFS, reduced the sample size from 392 to 200 and increased the number of study centres. However, reassurance was provided through additional analysis submitted to the regulator; the strong results were supported by several sensitivity analyses; and acknowledgement that amendments were made prior to unblinding.[2]
- The change in size of the study and early discontinuation may have an impact on the estimates of OS benefit at the primary analysis and crossover may confound subsequent OS analysis.
- Except for azacitidine, there is no direct comparison with alternative treatment options. Relative efficacy compared with the current standard of care, venetoclax-azacitidine, was estimated from an NMA.
- The NMA has several limitations. The results do not support a conclusion of superiority for ivosidenib-azacitidine, compared with venetoclax-azacitidine for both EFS and OS. There were significant differences in the proportion of patients with IDH1 mutations, which were present in all ivosidenib-treated patients but only in 7.9% of patients who received venetoclax. Although conclusions cannot be supported by preclinical studies and subgroup analyses, these suggest a possible increased response to venetoclax in patients with IDH1 mutations. Therefore, as it cannot be assumed that IDH1 mutation status is not a treatment effect modifier, its heterogeneity is a limitation. There was heterogeneity in other disease characteristics and in study methodology. Statistical weaknesses were also noted in the NMA. Due to these limitations, the company's conclusions are uncertain.

  The study excluded patients who had previously received a hypomethylating agents (HMA), such as azacitidine, for myelodysplatic syndrome (MDS).

*Other data were also assessed but remain confidential.**

4.3. Clinical expert input

Clinical experts consulted by SMC note that ivosidenib plus azacitidine may be used in practice as an alternative to venetoclax plus azacitidine.

4.4. Service implications

Clinical experts consulted by SMC noted a variety of timeframes for the return of IDH1 mutation test results. They advised that current arrangements for testing of IDH1 mutations in newly diagnosed AML patients require development to facilitate the provision of results within a timeframe that would permit initiation of treatment with ivosidenib. This may have service implications. Ivosidenib is associated with regular ECG monitoring, which may have service implications. However, patient numbers are expected to be small.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ivosidenib, as an orphan and end of life medicine, in the context of treatments currently available in NHSScotland. The key points expressed by the group were:

- Acute myeloid leukaemia (AML) is an aggressive (rapidly-progressing) blood cancer that is incurable in patients who are not able to receive intensive chemotherapy followed by stem cell transplant. Their prognosis with the currently available treatments is poor (estimated 5-year survival of 15%).
- Patients suffer debilitating symptoms and may require help from family and friends with self-care and attending numerous hospital appointments. These practical challenges and the poor prognosis have a substantial psychological impact on the patient and their family, with many reporting symptoms of depression. There is an unmet need for more effective therapies with acceptable tolerability. The ivosidenib regimen can provide a prolonged period when the patient's disease is controlled (in remission). During this time, their quality of life may be greatly improved and they may not need to attend hospital for blood transfusion and treatment of infection or bleeding complications as frequently. They may feel generally well and be able to spend time with their family and friends, which may alleviate some of the psychological impact of AML.
- Compared to alternatives, the ivosidenib regimen is considered to have fewer side-effects, particularly cytopenias, which can require hospital admission. Availability of this medicine would increase the range of options available for patients who are not able to receive intensive chemotherapy and it may be particularly useful for those who are also not able to tolerate the venetoclax plus azacitidine regimen or who have contra-indications to it. Ivosidenib is convenient to take as it is taken orally.
- Clinical experts advised that ivosidenib is associated with differentiation syndrome, but this can be effectively managed in practice. It was noted that patients are generally happy with the additional monitoring (such as ECG) and the risk of adverse effects (such as differentiation syndrome) to achieve the good outcomes that are associated with ivosidenib.
- Clinical experts noted that the speed of IDH1 mutation testing within NHS Scotland needs to increase to facilitate the use of ivosidenib in the first-line setting. However, they considered that this is feasible.

Additional Patient and Carer Involvement

We received patient group submissions from Blood Cancer UK and Leukaemia Care, both organisations are registered charities. Blood Cancer UK has received 5.41% pharmaceutical company funding in the past two years, with none from the submitting company. Leukaemia Care has received 18.82% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Leukaemia Care participated in the PACE meeting. The key points of the submissions from both organisations have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic case is described in Table 6.1.

Table 6.1: Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	Lifetime (25 years, baseline start age of 75 years)
Population	Adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy.
Comparators	Venetoclax plus azacitidine
Model description	A partitioned survival model with health states of EFS, progressed disease or relapse (PD/RL), and death. Within EFS there were sub-states of complete response/ complete response incomplete count recovery (CR/CRi) or no CR/CRi. Model cycle length was 28 days.
Clinical data	Individual patient-level data (IPD) from the AGILE study for ivosidenib plus azacitidine versus azacitidine provided the EFS, CR/CRi, PD/RL, death, adverse event, time on treatment (ToT) and utility data for the economic model, whilst comparator data for assessing relative effectiveness and ToT was derived from the VIALE-A study for venetoclax plus azacitidine vs azacitidine.[4, 6] The relative effectiveness of ivosidenib plus azacitidine versus venetoclax plus azacitidine was assessed via a fixed effects NMA with the estimated hazard ratios for EFS and OS applied in the economic analysis. CR/CRi status within the EFS state can change over time, hence was modelled from the AGILE data for ivosidenib plus azacitidine, and relative CR/CRi estimates over time generated for venetoclax plus azacitidine using VIALE-A evidence.
Extrapolation	Extrapolation of EFS and OS for ivosidenib plus azacitidine was performed by fitting independent parametric functions to the Kaplan-Meier data. The base case function selected for EFS and for OS was the log-normal based on goodness of fit statistics and plausibility of the projections. Other functions had similar goodness of fit and were explored in scenario analysis. Extrapolation of EFS and OS for venetoclax plus azacitidine was based on the HRs from the NMA which were applied to the ivosidenib plus azacitidine extrapolated curves. The OS extrapolations were adjusted to take account of background mortality and the assumption that patients in the EFS state for 2 years would be assumed "cured" and become long-term survivors, with a general population mortality rate applied. ToT extrapolation was performed by fitting a best fitting Weibull function to the ivosidenib plus azacitidine data in AGILE, and estimated for venetoclax plus azacitidine

	using an exponential function based on mean treatment cycles in the VIALE-A study. Duration of treatment with either treatment was capped at 2 years maximum.
Quality of life	Health state utility values were informed via analysis of EQ-5D-5L data collected in the AGILE study, and mapped to the UK 3L value set. The estimated utilities were as follows: 0.769 for EFS-CR/CRi, 0.629 for EFS – no CR/Cri, and 0.594 for PD/RL. The LTS utility was assumed to be the same as EFS-CR/CRi. Adverse event disutilities were applied based on published estimates (not AML specific) and by assumption.
Costs and resource use	Medicine acquisition costs have been estimated for ivosidenib, venetoclax and azacitidine. Drug administration costs were estimated for subcutaneous or IV azacitidine. The dose of each combination were based on the SmPC but adjusted (reduced) to account for concomitant use of azoles, and a relative dose intensity estimate applied. Costs of subsequent therapies, consisting of gilteritinib for patients with both IDH1 and FLT-3 mutation, or hydroxycarbamide/hydroxyurea otherwise, were included. Other costs included days spent in hospital for initiation of treatment with either ivosidenib plus azacitidine or venetoclax plus azacitidine respectively based on AGILE data for the former and a published real world study[7] for the latter), resource use for routine monitoring (e.g. consultations/ appointments, tests and investigations, ICU stay) by health state derived from previous NICE appraisals (TA765 and TA765), red blood cell and platelet transfusions by health state based on AGILE data and assumption, management of adverse events, and end of life care. A further cost was applied to IVO+AZA for additional ECG monitoring for risk of QC prolongation.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price of ivosidenib. A PAS discount is in place for venetoclax and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

The base case results are presented in the table below.

Table 6.2 Base case results (list prices)

Technologies	ICER (£/QALY)
VEN + AZA	
IVO + AZA	£39,377

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

The key driver of cost-effectiveness for ivosidenib plus azacitidine was the incremental life years and QALYs associated with greater time in EFS and the proportion estimated to be long term survivors, and a larger proportion of patients with CR/CRi. Cost savings were driven by incremental medicine acquisition and administration costs for ivosidenib plus azacitidine being more than offset by lower medical resource use costs (lower initial treatment hospitalisation costs, blood transfusion costs and routine monitoring costs).

6.3. Sensitivity analyses

In one way sensitivity analysis the results were sensitive to applying the 95% CrIs for EFS and OS. Additional scenario analyses were also requested to fully explore uncertainty in key relative effectiveness, outcomes and cost/ resource use parameters. A key scenario was to set hospital duration for initiation of treatment with venetoclax plus azacitidine the same as ivosidenib plus azacitidine (scenario 8). Also a scenario including IDH1 mutation testing costs reduced the offsets associated with ivosidenib plus azacitidine (scenario 9).

Table 6.3 Selected scenario analyses (list prices)

#	Scenario	ICER (£/QALY)
-	*Base-case analysis*	£39,377
1	Time horizon, 15 years	£43,626
2	Curve fit: IVO + AZA OS, Generalised gamma	£36,512
3	Curve fit: IVO + AZA EFS, Generalised gamma	£37,721
4	Curve fit: IVO + AZA ToT, Log-normal	£36,300
5	Long-term survival timepoint: 3 year(s)	£39,842
6	Long-term survival %: 80%	£41,725
7	Long-term survival SMR: 1.2	£44,865
8	Same hospital duration for treatment initiation	£54,515
9	Include IDH1 mutation test costs	£40,124

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

6.4. Key strengths

- Model structure is, in general, appropriate and baseline characteristics used from the AGILE study are reasonable.
- Although several comparators could be considered, based on SMC clinical expert feedback the choice of venetoclax plus azacitidine appears appropriate.
- Patient level data from AGILE study enabled good analysis of EFS, OS and ToT data and fitting of parametric functions to the data for extrapolation for ivosidenib plus azacitidine.

Good set of EQ 5D-5L data from the AGILE study enabling robust analysis, the resulting health state utilities have good face validity.

6.5. Key uncertainties

- No direct evidence is available for EFS, OS and CR/CRi for ivosidenib plus azacitidine vs venetoclax plus azacitidine, and given the uncertainties with the NMA there is no strong evidence of benefit for ivosidenib plus azacitidine. This is compounded by the small proportion of patients in the VIALE-A study with the IDH1 mutation, which may be a treatment modifier producing favourable relative efficacy results for ivosidenib plus azacitidine. To address these concerns with the clinical evidence base, a scenario was also explored which set the hazard ratios for EFS and OS equal to one.

- There is uncertainty regarding the criteria long term survivors, with patients having to be in the EFS state for 2 years based on assumption, clinical opinion and precedence (prior technology appraisals for venetoclax plus azacitidine). Several more pessimistic scenario analyses have been performed assuming a cure timepoint of 3 years, and 80% of patients achieving EFS at 2 years assumed to be long-term survivors. However, if the EFS HR is assumed to be one (see bullet above) there is then also no benefit in long term survival for ivosidenib plus azacitidine.
- Estimates of relative CR/CRi status (that impacts on utilities) over time are modelled and appear to represent a form of naïve comparison, meaning differences between treatments are uncertain. Further scenario analysis was requested assuming no difference in CR/CRi, however the company stated this was not possible to perform with the current model.
- The estimates of time in hospital for treatment initiation and monitoring are from separate non-UK based sources and estimated to be far longer for venetoclax plus azacitidine, hence a key potential cost offset for ivosidenib plus azacitidine. SMC clinical expert opinion has suggested the duration would be much shorter for venetoclax plus azacitidine in Scottish clinical practice, and scenario analysis setting the duration the same as ivosidenib plus azacitadine led to a higher ICER (scenario 8).
- The time horizon of 25 years based on trial data available and a starting age of 75 years in the model is long and scenario with a shorter time horizon of 15 years demonstrates a lower QALY gain (scenario 1).
- IDH1 mutation testing costs were not included in the original economic analysis submitted by the company. SMC clinical expert opinion has indicated that this testing is not routinely informing treatment eligibility management in current clinical practice. However, the company provided a scenario analysis including the costs of IDH1 mutation testing (scenario 9).

7. Conclusion

The Committee considered the benefits of ivosidenib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as ivosidenib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted ivosidenib for use in NHSScotland.

8. Guidelines and Protocols

In March 2020, the European Society for Medical Oncology (ESMO) published guidelines: Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[3]

9. Additional Information

9.1. Product availability date

5 July 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28-day cycle (£)
Ivosidenib **Azacitidine**	**500 mg orally once daily** **75 mg/m^2 IV or SC once daily on Days 1-7 of 28-day cycle**	**11,667** **980** **Total 12,647**

Costs from BNF online on 6 February 2024. Costs based on 1.8m^2 body surface area and calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 30 patients eligible for treatment with ivosidenib plus azacitidine in year 1, rising to 33 in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

References

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7. Rausch CR, DiNardo CD, Maiti A, Jammal NJ, Kadia TM, Marx KR*, et al.* Duration of cytopenias with concomitant venetoclax and azole antifungals in acute myeloid leukemia. Cancer. 2021;127(14):2489-99.

This assessment is based on data submitted by the applicant company up to and including 14 December 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.