Indication	For newly diagnosed and untreated acute myeloid leukaemia with an isocitrate dehydrogenease-1 (IDH1) R132 mutation in patients who are not eligible for standard induction chemotherapy.
Treatment Intent	Disease modification
Frequency and number of cycles	Repeat every 28 days. Continuous until disease progression or unacceptable toxicity or patient choice to stop treatment or an elective decision to discontinue treatment consequent to a sustained complete remission to therapy. If ivosidenib is stopped for any of the above reasons, no further ivosidenib can be prescribed. A formal medical review as to whether treatment with ivosidenib and azacitidine should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • An **ECG** must be performed prior to treatment initiation, QTc should be <450 msec, in the presence of an abnormal QT, consultant should thoroughly reassess the benefit/risk of initiating ivosidenib. If QTc interval prolongation is between 480 msec and 500 msec, initiation of treatment with ivosidenib should remain exceptional and be accompanied by close monitoring. • **ECG** must be performed at least weekly during the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains </= 480 msec and when clinically indicated. QTc interval abnormalities should be managed promptly (see management of adverse reactions and dose adjustments below). • FBCs, U&Es and LFTs should be assessed prior to initiation, at least once weekly for the first month of treatment, once every other week for the second month, and at each cycle. • Inform clinician if Hb is less than 8g/dl. • **Haematological toxicity: If platelets </= 50 x 10^9/l and/or absolute neutrophil count (ANC) </= 1 x 10^9/l.** o Patients without reduced baseline blood counts, WBC >/= 3.0 x10^9/l and ANC >/= 1.5 x 10^9/l and platelets >/= 75 x 10^9/l, prior to the first treatment: Delay azacitidine until recovery, if recovery is achieved within 14 days no dose adjustment required. If recovery is not within 14 days dose reduce as per table 1. o Patients with reduced baseline blood counts, WBC <3 .0 x 10^9/l, ANC <1.5 x 10^9/l and platelets <75 x 10^9/l, prior to the first treatment: If the decrease in WBC or ANC or platelets from that prior to treatment is </= 50%, or greater than 50% but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made. If the decrease in WBC or ANC or platelets is greater than 50% from that prior to treatment, with no improvement in cell line differentiation, the next cycle of azacitidine should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. If recovery is not within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is >50 %, no dose adjustments should be made. If bone marrow cellularity is </= 50 %, treatment should be delayed and the dose reduced according to table 2.

	• **Hepatic impairment:**
	  ○ **Ivosidenib:** No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). A recommended dose has not been determined for patients with moderate and severe hepatic impairment (Child-Pugh classes B and C).
	  Ivosidenib should be used with caution in patients with moderate and severe hepatic impairment with close monitoring.
	  ○ **Azacitidine:** Clinical decision to treat in hepatic impairment.
	• **Renal impairment:**
	  ○ **Ivosidenib:** No dose adjustment is required if CrCl >/=30ml/min.
	  No recommended dose for patients with severe renal impairment (CrCL <30ml/min), ivosidenib should be used with caution with close monitoring.
	  ○ **Azacitidine:** No recommendations regarding dose reduction for starting treatment.
	  If serum Creatinine rises >/= 2 x baseline value and above ULN or if unexplained reductions of serum bicarbonate (venous sample) to < 20 mmol/l then delay until values return to normal or baseline and reduce the dose by 50%.
	• **Management of adverse reactions and dose adjustments:**
	• **Cardiac Contraindications:**
	  ○ Congenital long QT syndrome.
	  ○ Familial history of sudden death or polymorphic ventricular arrhythmia.
	  ○ QT/QTc interval > 500 msec, regardless of the correction method.
	• **Cardiac monitoring:**
	  ○ QTc interval prolongation has been reported following treatment with ivosidenib. Any abnormalities should be managed promptly. In case of suggestive symptomatology, an ECG should be performed as clinically indicated.
	  In case of severe vomiting and/or diarrhoea, an assessment of serum electrolytes abnormalities, especially potassium and magnesium, must be performed.
	  ○ Patients should be informed of the risk of QT prolongation, the associated signs and symptoms (palpitation, dizziness, syncope or even cardiac arrest) and be advised to contact the oncology team immediately if any symptoms are experienced.
	  ○ Patients with congestive heart failure or electrolyte abnormalities should be closely monitored, with periodic monitoring of ECGs and electrolytes, during treatment with ivosidenib.
	  ○ Treatment should be permanently discontinued if patients develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.
	  ○ Concomitant administration of medicinal products known to prolong the QTc interval, or moderate or strong CYP3A4 inhibitors may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. ECG should be performed prior to co-administration, weekly monitoring for at least 3 weeks and then as clinically indicated.
	  If the use of moderate or strong CYP3A4 inhibitors cannot be avoided the recommended dose of ivosidenib should be reduced to 250mg once daily. This dose reduction has been applied to this protocol as posaconazole or voriconazole must be prescribed in line with commissioning criteria. If the moderate or strong CYP3A4 inhibitor is discontinued, the dose of ivosidenib should be increased to 500mg after at least 5 half-lives of the CYP3A4 inhibitor.
	• **Recommended dose modification of ivosidenib for QTc prolongation:**
	  ○ **QTc interval prolongation > 480 to 500 msec (Grade 2)**
	  Monitor and supplement electrolyte levels as clinically indicated, interrupt treatment until QTc interval returns to </=480 msec, then restart ivosidenib at 250mg once daily, unless dose prior to interruption had been increased to 500mg then restart at this dose.

Review and adjust concomitant medicinal products with known QTc interval-prolonging effects.
Monitor ECGs at least weekly for 3 weeks and as clinically indicated following return of QTc interval to </= 480 msec.

- **QTc interval prolongation > 500 msec (Grade 3)**
  Monitor and supplement electrolyte levels as clinically indicated, interrupt treatment and monitor ECG every 24h until QTc interval returns to within 30 msec of baseline or </= 480 msec. If QTc interval prolongation > 550 msec, treatment should be interrupted and consider placing the patient under continuous electrocardiographic monitoring until QTc returns to values < 500 msec.
  After QTc interval returns to within 30 msec of baseline or </= 480 msec monitor ECGs at least weekly for 3 weeks and as clinically indicated.
  Restart ivosidenib at the following dose levels:
  500mg once daily prior to interruption give 250mg once daily.
  250mg once daily prior to interruption, discuss with consultant for alternative dose schedule.
  If alternative aetiology for QTc interval prolongation is identified, ivosidenib dose may be increased back to 500mg once daily or 250mg once daily (if dose reduced for interaction with CYP3A4 inhibitor).
  Review and adjust concomitant medicinal products with known QTc interval prolonging effects.
- **QTc interval prolongation with signs/symptoms of life-threatening ventricular arrhythmia (Grade 4)**
  Permanently discontinue treatment.

- **Differentiation syndrome** has been reported in patients receiving ivosidenib.
  Differentiation syndrome presents with respiratory distress, dyspnoea, hypoxia, radiological findings such as pleural, with or without, pericardial effusions, unexplained fever, creatinine increase and bone pain. IDH inhibition-associated differentiation syndrome is manageable by identifying risk factors, recognizing symptoms, and initiating treatment in a timely manner. Time to onset is from Day 1 till 3 months**.**
  Patients should be informed of the signs and symptoms of differentiation syndrome and inform the healthcare team immediately.
  If differentiation syndrome is suspected, administer systemic corticosteroids for a minimum of 3 days and taper only after symptom resolution (suggested dose 10 mg Dexamethasone IV every 12 hours) and initiate furosemide if clinically appropriate. Premature discontinuation may result in symptom recurrence.
  Initiate haemodynamic monitoring until symptom resolution and for a minimum of 3 days.
  Interrupt treatment if severe signs/symptoms persist for more than 48 hours after initiation of systemic corticosteroids.
  Resume treatment with ivosidenib once daily at the same dose prior to interruption when signs/symptoms are moderate or lower and upon improvement in clinical condition**.**
- **Leukocytosis,** white blood cell count > 25 x 10^9/L or an absolute increase in total white blood cell count > 15 x 10^9/L from baseline, can occur in association with differentiation syndrome.
  If leukocytosis occurs initiate treatment with hydroxycarbamide according to trust policy and leukapheresis as clinically indicated. Taper hydroxycarbamide only after leukocytosis improves or resolves. Premature discontinuation may result in recurrence.
  Interrupt ivosidenib if leukocytosis has not improved after initiation of hydroxycarbamide.
  Resume treatment with ivosidenib once daily at the same dose prior to interruption when leukocytosis has resolved**.**
- **Other Grade 3 or higher adverse reactions:**
  - Interrupt ivosidenib until toxicity resolves to Grade 1 or lower, or baseline, then resume at dose prior to interruption. For Grade 3 toxicity or for Grade 4 toxicity if patient was

prescribed 500mg reduce to 250mg, if patient was prescribed 250mg discuss with consultant.
  - If Grade 3 toxicity recurs (a second time), if patient was on 500mg reduce to 250mg, if patient was on 250mg discuss with consultant for alternative dose schedule. Once toxicity resolves resume at original dose.
  - If Grade 3 toxicity recurs (a third time), or Grade 4 toxicity recurs, discontinue.
- Azacitidine - Monitor for skin and subcutaneous tissue adverse reactions.
- **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:**
  - **Ivosidenib:**
  - Concomitant administration of medicinal products known to prolong the QTc interval, (e.g. anti-arrhythmics, fluoroquinolones, 5-HT3 receptor antagonists, triazole antifungals) may increase the risk of QTc interval prolongation and should be avoided whenever possible. If use of a suitable alternative is not possible, patients should be treated with caution and closely monitored for QTc interval prolongation. An ECG should be performed prior to co-administration, weekly monitoring for at least 3 weeks and then as clinically indicated.
  - Concomitant administration of moderate (e.g. aprepitant, ciclosporin, diltiazem, erythromycin, fluconazole, grapefruit and grapefruit juice) or strong (e.g. clarithromycin, itraconazole, ketoconazole, posaconazole, ritonavir, voriconazole) CYP3A4 inhibitors increases plasma concentrations of ivosidenib. This may increase the risk of QTc interval prolongation and suitable alternatives that are not moderate or strong CYP3A4 inhibitors should be considered whenever possible during treatment (* see dose adjustment in cardiac monitoring section above).
  - Concomitant administration of strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort) is expected to decrease plasma concentrations of ivosidenib and is **contraindicated** during treatment.
  - Ivosidenib inhibits P-gp and has the potential to induce P-gp. Concomitant administration of dabigatran is **contraindicated**.
  - Concomitant administration of OAT3 substrates (e.g. benzylpenicillin, furosemide) or sensitive OATP1B1/1B3 substrates (e.g. atorvastatin, pravastatin, rosuvastatin) should be avoided whenever possible during treatment. Patients should be treated with caution if use of a suitable alternative is not possible. If administration of furosemide is clinically indicated to manage signs/symptoms of differentiation syndrome, patients should be closely monitored for electrolyte imbalances and QTc interval prolongation.
  - Ivosidenib induces CYP3A4, CYP2B6, CYP2C8, CYP2C9 and may induce CYP2C19. Therefore, it may decrease systemic exposure to substrates of these enzymes (such as itraconazole or ketoconazole). Suitable alternatives that are not CYP3A4, CYP2B6, CYP2C8 or CYP2C9 substrates with a narrow therapeutic index (e.g. alfentanil, ciclosporin, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, methadone, pioglitazone, repaglinide, phenytoin, warfarin), or CYP2C19 substrates (e.g. omeprazole) should be considered during treatment. Patients should be monitored for loss of substrate efficacy if use of such medicinal products cannot be avoided.
  - Ivosidenib has the potential to induce UGTs and it may, therefore, decrease systemic exposure to substrates of these enzymes (e.g. lamotrigine, raltegravir).
  - Ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended for at least 1 month after the last dose.
  - **Azacitidine:** No formal clinical drug interaction studies with azacitidine have been conducted.
- **Missed dose:** If a dose of ivosidenib is missed or not taken at the usual time, the dose should be taken as soon as possible within 12 hours after the missed dose. If longer than 12 hours the dose should be omitted and the dose taken at the next scheduled time, two doses

	should not be taken within 12 hours. If a dose is vomited, replacement tablets should not be taken. • **Driving:** Ivosidenib and azacitidine may cause fatigue and dizziness, patients who experience these symptoms should use caution when driving or operating machines. • **Oral Guidelines:** For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	SPC accessed online25.05.2024 Blueteq form accessed online 25.06.2024 KMCC protocol UGI-078 V1

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Dose modification of azacitidine in patients without reduced baseline bloods.

Cycle Nadir count		**Dose in the next cycle, if recovery* is not achieved within 14 days (%)**
ANC (x 10^9/l)	Platelets (x 10^9/l)	
</=1.0	</= 50.0	50 %
> 1.0	> 50.0	100 %

Table 2 Dose modification of azacitidine in patients with reduced baseline bloods.

Bone marrow cellularity	**Dose in the next cycle if recovery is not achieved within 14 days (%)**	
	Recovery* </= 21 days	Recovery* > 21 days
15-50 %	100 %	50 %
< 15 %	100 %	33 %

* Recovery = counts >/= nadir count + (0.5 x [baseline count – nadir count])

Repeat every 28 days:

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1 (Ideally starts on a Monday) 2, 3, 4, 5, 8 and 9	Ondansetron	8mg	PO		STAT
	Commence azacitidine at least 30 mins after anti-emetics				
	AZACITIDINE	**75mg/ m² once a day for 7 days**	SC		Once a day for 7 days. Inject into upper arm, thigh or abdomen. Injection sites should be rotated, and at least 2.5cm from previous site and never into areas where site is tender, bruised, red or hardened. (Doses greater than 100mg will be split into two syringes and injected at two sites)
TTO	Drug	Dose	Route	Directions	
Day 1	**IVOSIDENIB**	**250mg**	PO	OD, continuously. Patients should not eat anything for 2 hours before and until 1 hour after taking the tablets. Swallow whole with water. Avoid grapefruit/grapefruit juice. Available as 250mg tablets *Dose has been reduced due to interaction with posaconazole in line with SPC and commissioning criteria. If posaconazole is stopped dose should be reviewed. Dispense 60 x 250mg tablets **every other cycle.** Tablets must be kept in original container.	
	Posaconazole	300mg	PO	BD for 1 day then OD thereafter.	
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.	
	Metoclopramide	10mg	PO	TDS PRN Do not take for more than 5 days continuously. Dispense on Cycle 1 then only if specified.	
	* if an antifungal is prescribed that IS NOT a CYP3A4 inhibitor, such as Liposomal Amphotericin, then IVOSIDENIB should be administered at the standard licensed dose, as approved by NICE ,500mg (2 x250 mg) OD.				