Indication	Untreated adult acute myeloid leukaemia (AML) instead of standard induction chemotherapy with daunorubicin and cytarabine and falls into one of the following categories: • The patient does not have core binding factor AML [i.e. t(8;21) or inv(16)] and is aged >60 years and is deemed fit for intensive chemotherapy. • The patient has mutated NPM1 or IDH1/2 AML and is either aged >50 years and deemed fit for intensive chemotherapy or has significant comorbidity (but is still deemed fit for intensive chemotherapy). • The patient has the NPM1mutFLT3 ITDneg genotype AML and is deemed fit for intensive chemotherapy (regardless of age). NB This protocol has been made available as part of the response to the COVID-19 pandemic.
Treatment Intent	Disease Modification
Frequency and number of cycles	Repeat every 28 days. Continue until progressive disease or unacceptable toxicity or patients' choice (ideally treat for a minimum of 6 cycles) NB: formal medical review as to whether treatment with venetoclax should continue will occur at least by the end of the second cycle of treatment. Patients not achieving CR by this stage should be discussed at the haematology oncology/AML MDT.
Monitoring Parameters pre-treatment	• Monitor FBC, U&Es and LFTs every day for the first week, then every week for the first 6 weeks, and then at the beginning of each cycle or as clinically indicated. See section below on haematological and non-haematological toxicities. Patients should be admitted for at least 5 days with the first cycle. • Consider a bone marrow aspiration on day 21 of first cycle. If blast clearance is confirmed then stop venetoclax before day 28 of cycle 1. Restart venetoclax at cycle 2 (and subsequent cycles), but in the case of haematological toxicity, reduce duration of venetoclax to 14-21 days if in remission. • U&Es (in particular potassium, uric acid, phosphorous, calcium and creatinine) should be assessed prior to the initial dose to evaluate kidney function and correct pre-existing abnormalities. • **Tumour Lysis Syndrome (TLS)** is a particular risk in patients receiving Venetoclax. • Changes in electrolytes consistent with TLS can occur as early as 6 to 8 hours following the first dose and at each dose increase. Patients with a high tumour burden and reduced renal function (CrCl <80ml/min) are at greatest risk of TLS. All patients should have white cell count less than 25×10^9/L prior to initiation of venetoclax. Cytoreduction prior to treatment may be required. • Blood chemistries should be monitored pre-dose, and at 6 to 8 hours and at 24 hours after each new dose. Electrolyte abnormalities should be corrected promptly. The next dose should not be administered until the 24 hour blood chemistry results have been evaluated. The same monitoring schedule should be followed for patients who continue to be at risk. Blood chemistries should be reassessed prior to each cycle. • Anti-hyperuricaemic agents should be administered 2 to 3 days prior to starting treatment with venetoclax and be continued through the titration phase and beyond as clinically appropriate. Rasburicase, if required, should be initiated by a consultant. Review and amend as necessary allopurinol prescription. • All patients should be adequately hydrated during the dose titration phase to reduce the risk of TLS. Patients should be particularly instructed to drink 1.5 - 2 litres of water daily, 2 days prior to and the days of dosing at initiation and each subsequent dose increase. Intravenous fluids should be administered as indicated based on overall risk of TLS or for those who

cannot maintain an adequate level of oral hydration.

- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pre-treatment lactate dehydrogenase (LDH) levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing venetoclax starting dose.

- **Renal impairment:**
- Venetoclax: No dose adjustment for mild to moderate (CrCl >/=30ml/min and <90ml/min). Patients with severe renal impairment (CrCl<30ml/min) should only be administered venetoclax if the benefits outweigh the risks and they should be monitored more closely for signs of toxicity and TLS at initiation and titration phase.
- Azacitidine: No recommendations regarding dose reduction for starting treatment. If serum Creatinine rises >/= 2 x baseline value 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%.
- **Hepatic impairment:**
  Venetoclax: No dose adjustment for mild to moderate but close monitoring required for moderate impairment for signs of toxicity at initiation and during titration. A dose reduction of at least 50% throughout treatment is recommended for patients with severe hepatic impairment, with close monitoring for toxicity.
  Azacitidine: Clinical decision to treat in hepatic impairment.
- **Dose modifications and toxicities**:
- **Haematological toxicities:**
- Venetoclax should not be interrupted for haematological toxicity prior to documentation of marrow response on D21-28.
- If blast clearance confirmed and the patient has grade 4 neutropenia, G-CSF may be commenced until neutrophil recovery.
- Commence next cycle when neutrophil count > $1x10^9$/L and platelet count >75 $x10^9$/L
- If counts have not recovered above these levels by D42 please do a bone marrow aspirate
- Once in complete remission, if grade 4 neutropenia or thrombocytopenia develops, cease venetoclax and commence G-CSF until resolution of grade 4 neutropenia.
- If grade 4 toxicity persists beyond day 42 of the previous cycle, the duration of venetoclax may be reduced to 14-21 days.
- If prolonged treatment-related grade 4 neutropenia or thrombocytopenia occurs in subsequent cycles, azacitidine treatment could also be reduced to 5 days.
- In patients who have not yet been confirmed to be in complete remission, the length of treatment cycles should not be altered.
- Patients who do not achieve CR after cycle 2 should be discussed at an MDT
- **Non-Haematological toxicities**
- In patients with grade 3-4 abnormal liver function tests (i.e. alanine aminotransferase [ALT] aspartate aminotransferase [AST] and bilirubin), venetoclax and any potentially hepatotoxic drugs (including azole antifungals) should be withheld until these have resolved to grade 2 or below and then venetoclax (and the azole antifungal if applicable) should be restarted at the original dose.
- Venetoclax should not be interrupted for any other non-haematological toxicity for patients who are not in complete remission.
- In patients in complete remission with grade 3 or 4 non-haematological toxicity thought to be related to venetoclax, this should be withheld until the toxicity has resolved to grade 2 or below and then restarted at the original dose.
- Azacitidine - Monitor for skin and subcutaneous tissue adverse reactions.

	• **<u>Common drug interactions</u>: (for comprehensive list refer to BNF/SPC)**
	  ◦ Concomitant use with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS. Concomitant use of strong CYP3A inhibitors at <u>initiation and during dose escalation</u> is contraindicated.
	  Dose modification of venetoclax is required when given concomitantly with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole, posaconazole) and moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil) NB this dose adjustment has been applied to the protocol in line with the prescribing criteria in the covid-19 interim treatment Blueteq form where the prescribing of antifungal prophylaxis is mandatory.
	  If a moderate CYP3A inhibitor must be used, <u>the initiation and titration doses</u> of venetoclax should be reduced by at least 50%. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. In the event that a CYP3A inhibitor (eg posaconazole) is stopped, the dose of venetoclax should be reviewed.
	  Concomitant use of venetoclax with strong (e.g., carbamazepine, phenytoin, rifampicin) or moderate (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) CYP3A4 inducers should be avoided. Concomitant use of preparations containing St John's Wort is contraindicated.
	  • Inhibitors of P-gp or BCRP may increase venetoclax exposure; these should be avoided at initiation of treatment and during the titration phase. If concomitant use of P-gp inhibitors is unavoidable, administration should be at least 6 hours before venetoclax dose and the initiation and titration doses of venetoclax should be reduced by at least 50%.
	  • Co-administration of bile acid sequestrants with venetoclax is not recommended.
	  • It is recommended that the international normalized ratio (INR) be monitored closely in patients receiving warfarin.
	  • Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g., digoxin, dabigatran, everolimus, sirolimus) with venetoclax should be avoided.
	  • If statins are given concomitantly with venetoclax monitor for statin toxicity.
	  • Avoid grapefruit products, Seville oranges and starfruit.
	• Live vaccines should not be administered during treatment and thereafter until B-cell recovery.
	• Azacitidine is contraindicated in patients with an allergy to mannitol & in advanced hepatic tumours.
	• **Missed dose:** If a patient misses a dose of venetoclax within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the following day.
	• If a patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.
	• Fatigue has been reported with the use of azacitidine caution is recommended when driving or operating machines.
	• For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.

References	KMCC protocol HAEM-AML-031v1 SPC accessed online 01/06/20

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

Cycle 1 - 28 day cycle titration of venetoclax

***Where it is considered clinically appropriate, the dosing schedule of azacitidine may be changed to 100mg/ m² once a day for 5 days (maximum single dose = 200mg)**

Day	Drug	Dose	Route	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	(Doses greater than 100mg will be split into two syringes and injected at two sites)
TTO	Drug	Dose	Route	Administration
Day 1	**Venetoclax** (available as 10mg, 50mg and 100mg tablets)	**See administration details For escalation schedule.**	PO	**100mg** OM day 1 **200 mg** OM day 2, **300mg** OM day 3 **100mg** OM day 4 and continue at this dose until day 28. NB A dose adjustment has been applied to the protocol in line with the prescribing criteria in the covid-19 interim treatment Blueteq form where the prescribing of antifungal prophylaxis is mandatory. Swallow whole with water at approximately the same time each day and with a meal. Do not crush, chew or break the tablets before swallowing. During dose titration the dose should be taken in the morning to facilitate laboratory monitoring.
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD
	Allopurinol	300mg	PO	Start 2 to 3 days before treatment with venetoclax. od for the first 2 – 3 cycles based on clinical judgement of tumour burden eg WBC count, extent of lymphadenopathy Review if alternative anti-hyperuricaemic agent required. If Rasburicase is needed, then hold Allopurinol. Re-start allopurinol after uric acid levels have settled and Rasburicase has been stopped.
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays
	Loperamide	2mg-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.
	Posaconazole	300mg	PO	BD on **day 4** OD on **day 5-28**

Cycle 2 onwards repeat every 28 days

***Where it is considered clinically appropriate, the dosing schedule of azacitidine may be changed to 100mg/ m² once a day for 5 days (maximum single dose = 200mg)**

Day	Drug	Dose	Route	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	(Doses greater than 100mg will be split into two syringes and injected at two sites)
TTO	Drug	Dose	Route	Administration
Day 1	**Venetoclax** (available as 10mg, 50mg and 100mg tablets)	**100mg**	PO	OM for 28 days. Swallow whole with water at approximately the same time each day and with a meal. Do not crush, chew or break the tablets before swallowing. NB A dose adjustment has been applied to the protocol in line with the prescribing criteria in the covid-19 interim treatment Blueteq form where the prescribing of antifungal prophylaxis is mandatory.
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD
	Allopurinol	300mg	PO	Start 2 to 3 days before treatment with venetoclax. od for the first 2 – 3 cycles based on clinical judgement of tumour burden eg WBC count, extent of lymphadenopathy
	Co-trimoxazole	480mg	PO	BD on Mondays, Wednesdays and Fridays
	Loperamide	2mg-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.
	Posaconazole	300mg	PO	OD