The COVID 19 outbreak has caused major capacity pressures within the NHS and emerging evidence suggests a high mortality rate in patients with AML, particularly those undergoing intensive therapy. The NCRI AML working group has consulted widely in order to identify strategies to safely reduce duration and intensity of therapy whilst preserving long-term patient outcomes, in order to minimise both NHS resource use and short-term risk to patients.

This document takes into account guidance already issued by NICE, NHS England and other relevant organisations. Since the last version of this document, NHS England has granted emergency approval of venetoclax and gilteritinib for specific patient groups as described below. In the devolved nations, individual funding requests are still required for these therapies. Further information is available from medinfo.gb@astellas.com (for gilteritinib) / ukmedinfo@abbvie.com (for venetoclax).

The dynamics of the epidemic have shown marked local variation. In those areas which have been relatively spared, it may now be feasible to revert to standard-of-care treatment subject to staffing, bed and pharmacy capacity. Nonetheless, many areas continue to experience unprecedented demand on the healthcare resources needed to safely deliver intensive therapy, therefore these recommendations should be interpreted in the context of the local situation and guidance.

Mindful of the pace of change, these recommendations will undergo regular review and should be considered valid until 31st May 2020. Separate guidelines for stem cell transplantation are available at nice.org.uk (NG164) and bsbmtct.org. AML-specific guidance is provided in this document (section 6).

1. General points
   - All patients receiving intensive therapy should, where possible, be barrier nursed in a single room and ideally in a designated COVID-negative ward with enhanced screening and protection measures if available.
   - All patients should be screened for COVID-19 before initiation of induction or consolidation chemotherapy. If positive, therapy should be delayed if possible until resolution of symptoms (if present) and PCR negativity.
   - We recommend waiting for cytogenetics and NPM1/FLT3 status before treatment where possible.
   - MRD monitoring may be particularly helpful during this outbreak. Flow MRD monitoring may be performed without a baseline sample, however this is needed for molecular MRD. To allow quick turnaround of molecular MRD status please ensure a baseline cDNA sample is sent from the local diagnostic lab to Guy’s as soon as a molecular marker is identified (any fusion gene or NPM1 mutation).
   - The PACE study is collecting outcome data for AML patients during COVID-19. Please contact justin.loke@nhs.net and s.fox.2@bham.ac.uk if your site has not yet registered. Additionally, please consider reporting to the ASH COVID registry https://www.ashresearchcollaborative.org/covid-19-registry.

2. Intensive treatment for adults aged <60y
   - Patients with favourable (i.e. t(8;21) and inv(16) – CBF AML) or intermediate risk cytogenetics:
     - These patients should receive DA with a single dose of Mylotarg with their first course of induction chemotherapy. The exception to this is patients with a FLT3 mutation receiving midostaurin during induction who should not receive Mylotarg at all.
     - Mylotarg should be given to all CBF-AML patients. They should not receive midostaurin with induction even if FLT3 mutated. If Mylotarg supplies run low it may be necessary to restrict Mylotarg to CBF-AML patients.
     - Mylotarg is not recommended in cycle 2 or subsequent cycles of chemotherapy since it can delay count recovery and is of uncertain benefit.
     - In patients who are MRD negative in the bone marrow after the second cycle of treatment (by flow or molecular methods), consideration should be given to omitting the 4th cycle. In this case post course 3 samples for MRD evaluation are mandatory and, for patients with a molecular marker, sequential monitoring is recommended.
     - The dose of cytarabine in consolidation chemotherapy should be reduced to 1.5g/m² for all patients. This is associated with faster count recovery than the standard dose with no effect on overall survival.
     - These measures, which reduce exposure to cytarabine during consolidation, may modestly reduce relapse free survival but are not predicted to decrease overall survival if effective salvage strategies are deployed. Therefore, careful molecular monitoring should be adopted in all eligible patients with an informative marker, with pre-emptive intervention in patients with molecular relapse.
   - Patients with a NPM1mut/FLT3 ITDzero genotype:
     - These patients have a high rate of durable CR with venetoclax (VEN) based treatment (see page 4). VEN + LDAC or AZA should therefore be considered as an alternative to induction chemotherapy for these patients, and this approach is approved and funded by NHSE. Stringent MRD molecular monitoring for NPM1mut transcripts is mandatory in this setting.
Patients with an $NPM1^{mut}/FLT3^{ITD^{pos}}$ or $NPM1^{neg}/IDH1^{mut}$ or $NPM1^{neg}/IDH2^{mut}$ genotype:
- These patients have a high rate of complete remission with VEN based treatment but data on long-term outcomes are less robust. Consider the use of VEN-based treatment as a bridging strategy for patients aged >50y or those with significant comorbidity who would be considered eligible for intensive treatment.
- These patients could then receive intensive chemotherapy or transplantation after the epidemic if needed based on MRD response, individualised risk assessment and clinical status.
- MRD monitoring is mandatory for patients with an $NPM1$ mutation if treated with a VEN based protocol.

Patients with adverse risk cytogenetics:
- These patients should not receive Mylotarg.
- Many such patients may be eligible for treatment with CPX351 (as are patients with secondary AML).

3. Intensive treatment for adults aged >60y

Patients with favourable risk cytogenetics (i.e. $t(8;21)$ and inv(16) – CBF AML):
- These patients should receive intensive therapy with a single dose of Mylotarg in induction.
- They should not receive midostaurin even if FLT3 mutated.
- They should receive 1.5g/m² cytarabine in consolidation and could omit the fourth cycle of consolidation if MRD negative by RT-qPCR in a sample affording adequate sensitivity after cycle 2 as described above, they should receive careful sequential molecular MRD monitoring after completion of treatment.

Patients with intermediate risk cytogenetics
- These patients may still enter AML18 if your hospital allows this. AML18 allows access to CPX351 for 66% of patients. Of note trial capacity across the NHS has been significantly reduced at the present time.
- Although standard of care would be DA+GO, consider omitting Mylotarg altogether for these patients currently. If patients are later found to have favourable risk cytogenetics then a single dose can be given with cycle 2.
- Treatment with a VEN based regimen should be considered for these patients either as an alternative to induction chemotherapy or as a bridging strategy and this is endorsed and funded by NHS England.
- Where a bridging strategy is chosen, plans for chemotherapy or transplant after the epidemic should be made by a multidisciplinary team and consider age, molecular and cytogenetic features, remission and MRD status.
- VEN+AZA is the preferred regimen for patients without $NPM1$ or $IDH$ mutations but VEN+LDAC may sometimes be preferable on practical grounds for example the need to minimise visits to hospital.
- VEN based regimens can be considered for patients with $NPM1$ or $IDH1/2$ mutations. Stringent molecular monitoring is mandatory for patients with $NPM1^{mut}$ but is of uncertain value for $IDH1/2^{mut}$.
- VEN+LDAC and VEN+AZA both appear effective for these patients on the basis of available data and the choice should be made on emerging data and practical grounds.

Patients with adverse risk cytogenetics
- These patients should not receive Mylotarg.
- Many such patients may be eligible for treatment with CPX351 (as are patients with secondary AML).
- There is a good clinical rationale for considering a VEN+AZA in these patients especially if access to the in-patient facilities required for the safe delivery of induction chemotherapy is challenging. Although data are sparse and immature, CR rates may be comparable to intensive chemotherapy and this may allow patients to receive outpatient therapy. VEN+AZA is approved and funded by NHSE for these patients.

4. Patients with APL

Patients with non-high-risk APL (presenting white blood cell count <10x10⁹/L) should continue to receive ATO+ATRA as frontline therapy. We recommend the AML17 schedule which requires fewer hospital visits.
- If these patients are MRD negative after the second cycle, consideration should be given to omission of the final (5th) cycle of treatment. These patients would need to have ongoing MRD monitoring.

Patients with high-risk APL should continue to receive AIDA as induction, but could switch to ATO+ATRA for consolidation and should receive all four consolidation cycles with ongoing MRD monitoring.

5. Patients with relapsed or refractory AML
- Carefully assess the risks and benefits of pursuing a curative approach on a case-by-case basis.
- Gilteritinib monotherapy is an effective salvage therapy and is now funded by NHSE for patients with relapsed or refractory FLT3 mutated AML. We recommend testing for both ITD and TKD mutations in all adults with relapsed AML. Gilteritinib is active against both TKD and ITD mutations and is effective in the context of molecular relapse.
- Standard diagnostic tests may be unable to detect FLT3 mutations in the setting of molecular relapse and specialist assays may be required – these can be performed at Guy’s Hospital (email richarddillon@nhs.net).
- For FLT3 unmutated patients, if using the FLAG-IDA regimen, consider omission of fludarabine.
- Venetoclax based regimens may be suitable for relapsed patients with $NPM1^{mut}/FLT3^{ITD^{pos}}$ genotype.
6. Stem cell transplantation

The clinical and capacity implications of the current COVID-19 pandemic mandate a fundamental re-evaluation of transplant activity in AML. It is important to stress that all decisions concerning the appropriateness of stem cell transplantation are patient specific and the result of careful discussion between the transplant consultant, patient and their family. Valuable guidelines have recently been published by NICE, in consultation with the BSBMT and NHS England BMT Clinical Reference Group https://www.nice.org.uk/guidance/ng164. Specifically, it is imperative that any patient in whom a transplant procedure is planned must have confirmation of the availability of cryopreserved stem before the patient admitted to commence their conditioning regimen. It is also important when counselling patients about the benefits and risks of stem cell transplantation to specifically highlight both the possible, and largely undetermined impact of COVID-19 infection on patient outcome as well as possible challenges in terms of accessing ITU capacity should this be required depending upon the local circumstances of the specific transplant unit.

Allogeneic stem cell transplantation:

- Consistent with the recent NHSE clinical guide for the management of cancer patients during the coronavirus pandemic (17 March 2020 Version 1) patients with a high likelihood of disease progression without transplantation should still be considered candidates for allograft according to normal clinical practice.
- Such patients include fit adults with a suitable donor who are in CR1 and have:
  - secondary or treatment related AML
  - disease refractory to one cycle of induction therapy (defined as >15% blasts with <50% blast reduction)
  - greater than 40% risk of disease relapse on the basis of diagnostic cytogenetic or molecular characteristics according to the ELN risk stratification (Dohner et al Blood et al 2017 129: 424-447) but see below (*)
  - NPM1 mutation and MRD positivity in peripheral blood after two courses of induction therapy
  - rising or re-emergent MRD after completion of treatment, in the absence of a suitable alternative therapy
  - fit adults with a suitable donor with AML in CR2 but see below (*)
- Clinicians may wish to restrict allogeneic transplants to patients with a HCT-CI score of less than 3 although such decisions are patient specific given the lack of precision of the HCT-CI scoring system
(*) Carefully assess the risks and benefits of allograft for patients with a very high risk of relapse after transplant

Autologous stem cell transplantation:

- It would be reasonable to defer or avoid transplant for patients with first relapse of APL who received AIDA as first line therapy, provided they did not have CNS disease at relapse and they achieve molecular complete remission. Such patients should receive a total of 5 cycles of ATO-ATRA salvage and have careful MRD monitoring. This recommendation is based on data from AML17 (Russell N et al, Blood 2018 132:1452-1454).

7. Non-intensive therapy

Patients considered unfit for intensive chemotherapy due to a combination of age, co-morbidity and disease characteristics should generally be managed with supportive care +/- hydroxycarbamide. Selected patients may benefit from disease modifying therapy such as azacitidine or low dose cytarabine within their licensed indications. Such patients can be difficult to predict at diagnosis- again evaluation of cytogenetic and molecular features should be undertaken prior to initiation of such therapy. Consideration should be given to deferring azacitidine / low dose cytarabine where the disease is non-proliferative and blood counts reasonably preserved.

8. Writing group membership and contacts for clinical and MRD advice

These recommendations represent the opinions of a subgroup of the NCRI AML Working Party (Chair Charles Craddock) and have been coordinated by Richard Dillon working with Paul Cahalin, Jamie Cavenagh, Charles Craddock, Mike Dennis, Sylvie Freeman, Asim Khwaja, Steven Knapper, Tony Pagliuca, Nigel Russell, David Taussig, Paresh Vyas and David Bowen.

Clinical questions regarding all aspects of the AML 18 and 19 trials should be referred, as is normal practice, to the current AML 18 and 19 trial leadership team as outlined in the respective protocols.

For additional questions concerning non-trial management issues the following members of the AML Working Party are happy to be contacted for advice:

Richard Dillon (richarddillon@nhs.net), Charles Craddock (Charles.Craddock@uhs.nhs.uk), Mike Dennis (Mike.Dennis@christie.nhs.uk), Sylvie Freeman (s.freeman@bham.ac.uk), Steven Knapper (knappers@cardiff.ac.uk) Nigel Russell (Nigel.Russell@nottingham.ac.uk), and Paresh Vyas (paresh.vyas@immm.ox.ac.uk).
Use of Venetoclax based regimens in place of intensive therapy during the COVID19 outbreak

Venetoclax (VEN) based treatment protocols may lower treatment-related toxicity compared to intensive therapy. Treatment is largely delivered as an outpatient. Remission rates (CR+CRi) parallel those achieved with intensive therapy in older patients. The use of VEN based regimens is therefore attractive both to reduce pressure on the NHS and protect patients at especially high risk during the COVID19 outbreak.

Long-term follow up data are immature and in general the approach we recommend is to use VEN to bridge patients through the COVID19 epidemic with a view to delivering definitive therapy possibly including transplant later on. Decisions regarding subsequent treatment should be made on a case by case basis and MRD status will be particularly informative in this regard.

Venetoclax has been approved by NHS England for first line treatment during the epidemic, azacitidine is funded for use in conjunction. Based on the limited information available, we recommend the azacitidine schedule for most patients. However, VEN+LDAC appears equally effective for patients with NPM1 or IDH1/2 mutations and may be preferred for other patients on practical grounds.

- Any non-CBF patient aged >60y
- Patients with an NPM1 or IDH1/2 mutation aged >50y or with comorbidities
- Patients with the NPM1™ FL T3 ITD™ genotype of any age

The following treatment schedule is recommended (other schedules may be used according to established local practice)

Azacitidine schedule:
- Azacitidine 75mg/m² SC, once a day D1-7 (or D1-5 and D8-9)
- Venetoclax (cycle 1) 100mg D1, 200mg D2, 300mg D3 and 100mg* D4-D28 orally once daily
  *please note the dose drops on D4 to account for the azole loading*
- (cycle 2 onwards) 100mg D1-D28 orally (see below for guidance on changing number of days per cycle)
- Posaconazole (cycle 1) 300mg twice daily on D4 and once daily on D5-28
  (cycle 2 onwards) 300mg once daily on D1-D28
- or
- Voriconazole (cycle 1) 400mg twice daily on D4 and once daily on D5-28
  (cycle 2 onwards) 200mg twice daily on D1-D28

Cytarabine schedule:
- Cytarabine 20mg/m2 SC once a day on D1 to 10
- Venetoclax (cycle 1) 100mg D1, 200mg D2, 300mg D3 and 100mg* D4-D28 orally once daily
  *please note the dose drops on D4 to account for the azole loading*
- (cycle 2 onwards) 100mg D1-D28 orally (see below for guidance on changing number of days per cycle)
- Posaconazole (cycle 1) 300mg twice daily on D4 and once daily on D5-28
  (cycle 2 onwards) 300mg once daily on D1-D28
- or
- Voriconazole (cycle 1) 400mg twice daily on D4 and once daily on D5-28
  (cycle 2 onwards) 200mg twice daily on D1-D28

Dose adjustments for haematological toxicity:
- VEN based regimens are associated with significant haematological toxicity. We recommend admission to hospital for at least the first 5 days of cycle 1 and it may be safer in some cases that patients remain admitted until count recovery after cycle 1.
- 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 > 1x10⁹/L and platelet count >75x10⁹/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.

Dose adjustments for non-haematological toxicity:
- 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.