North of Scotland Clinical Management Guideline (CMG): Chronic Lymphocytic Leukaemia (CLL) Last Updated 27/04/2023

Document Control

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Approved: 7th October 2020

Published: 12th November 2020

File Reference: NCA-CMG-CLL19

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Clinical Staging (Binet)

Stage A - <3 lymphoid areas
Stage B - >/=3 lymphoid areas
Stage C – Hb <100g/L or Plts <100x10^9/L

Exclude immune cytopenias when ascertaining clinical stage.

For symptoms of suspected Haematological Cancer, please refer to the Scottish Referral Guidelines for Suspected Cancer

The majority of patients have Binet stage A disease at diagnosis and are asymptomatic. Management will be observation and the median time to therapy is over 10 years. Some will never require specific CLL therapy.

Supportive Care

Infective complications account for up to 50% of CLL related deaths. The risk of infection is exacerbated by the use of purine analogues and steroids.

- Recommend annual influenza vaccine.
- Recommend pneumococcal and haemophilus vaccines at diagnosis. Repeat vaccination can be guided by assessment of specific antibody levels.
- Vaccination should be generally avoided immediately prior to and following chemoimmunotherapy.
- Live vaccines, including varicella-zoster vaccine, are absolutely contraindicated
- Consider prophylactic antibiotics or Immunoglobulin replacement therapy for patients with recurrent bacterial infection and hypogammaglobulinaemia. See Scottish guidance on secondary antibody deficiency.
- Patients with HBV require prophylaxis against reactivation during CLL therapy and should be managed in conjunction with a Hepatologist.

General Principles

- Where available, clinical trials should always be considered as the preferred option for all eligible patients.
- Auto-immune complications (autoimmune phenomena) can present at any time during the pathway and require separate management (see page 6).
- If clinical suspicion of Richter's transformation, a PET CT scan and biopsy is recommended to confirm. Treatment is as per histology which is typically Diffuse Large B Cell Lymphoma but may be Hodgkin Lymphoma.

Diagnostic Tests

Baseline Investigations

- FBC, Reticulocyte Count, DAT, Film, immunophenotyping
- U+E, LFT, glucose, LDH, Igs, PEP
- Calculated creatinine clearance (Cockcroft Gault)
- HBV, HCV and HIV serology
- FISH or other studies for del(17p), del(11q) and trisomy 12 (prior to considering treatment)
- TP53 gene sequencing (if treatment required)
- CT neck, thorax, abdomen & pelvis is recommended prior to initiation of therapy
- If clinical suspicion of high grade (Richter) transformation, PET-CT and biopsy and the most PET-avid area is required
- Bone marrow examination not routinely necessary but can be informative in the following circumstances:
  - -Suspected immune thrombocytopenia and neutropenia
  - -Suspected red cell aplasia
  - -Immunophenotype not typical for CLL
  - -Prolonged cytopenias post therapy
  - -Prior to therapy where the diagnosis in not certain
- Lymph node biopsy, preferably excision of a complete lymph node, may be helpful where the diagnosis is unclear

Diagnosis

The diagnosis of CLL is made by peripheral blood phenotyping when a clonal B cell population with a typical CLL phenotype is identified and this accounts for more than $5x10^9$ cells per litre.

If the clonal B cell population is less than $5x10^9$ cells per litre (and tiny clones are present in up to 3% of the hospital patient population), the diagnosis may be monoclonal B cell lymphocytosis (MBL) which is a precursor stage of CLL. In order to make this diagnosis, these patients must also satisfy the following criteria:

- B symptoms should be absent
- Lymphadenopathy and splenomegaly should be absent
- Bone marrow biopsy (if performed) should not show a significant B cell infiltrate

MBL can be diagnosed by careful history and examination in addition to blood testing without the need for more extensive investigation. MBL does not require treatment and some of these patients will never progress to CLL. If any of the above features are present then the diagnosis is small lymphocytic lymphoma, which should be managed in accordance with this guideline.

Indications for Treatment

As per iwCLL guidelines:
B symptoms
Bulky symptomatic lymphadenopathy
Massive splenomegaly
Bone marrow failure
Immune complications not responding to immunosuppressive therapy
Lymphocyte doubling time <6 months

TP53 Testing

There should be screening for TP53 deletion by FISH and for TP53 mutation by sequencing.

Clinical Staging (Binet)

Stage A - <3 lymphoid areas
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Exclude immune cytopenias when ascertaining clinical stage.

North Cancer Alliance

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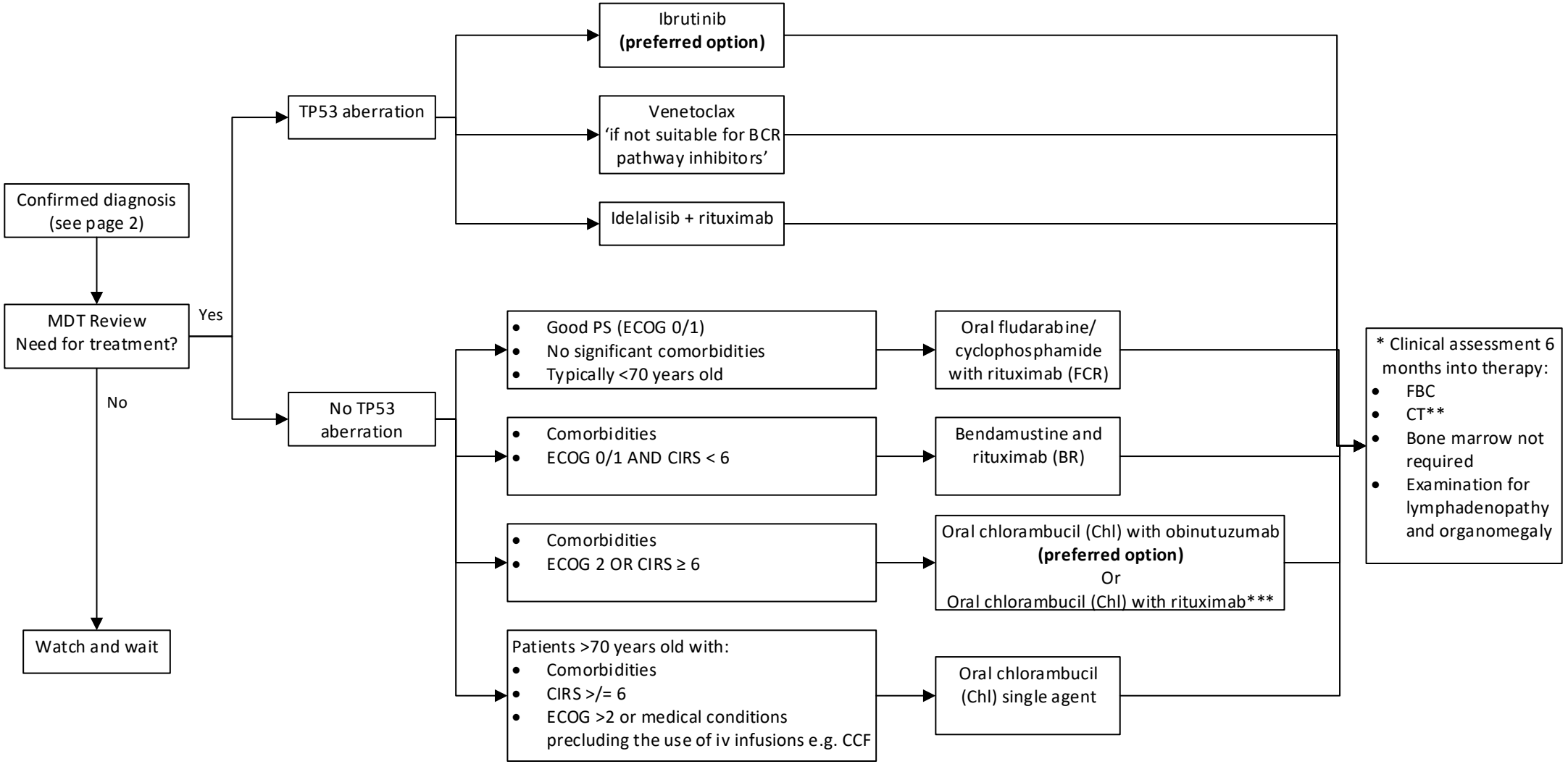
Initial Evaluation **Treatment**



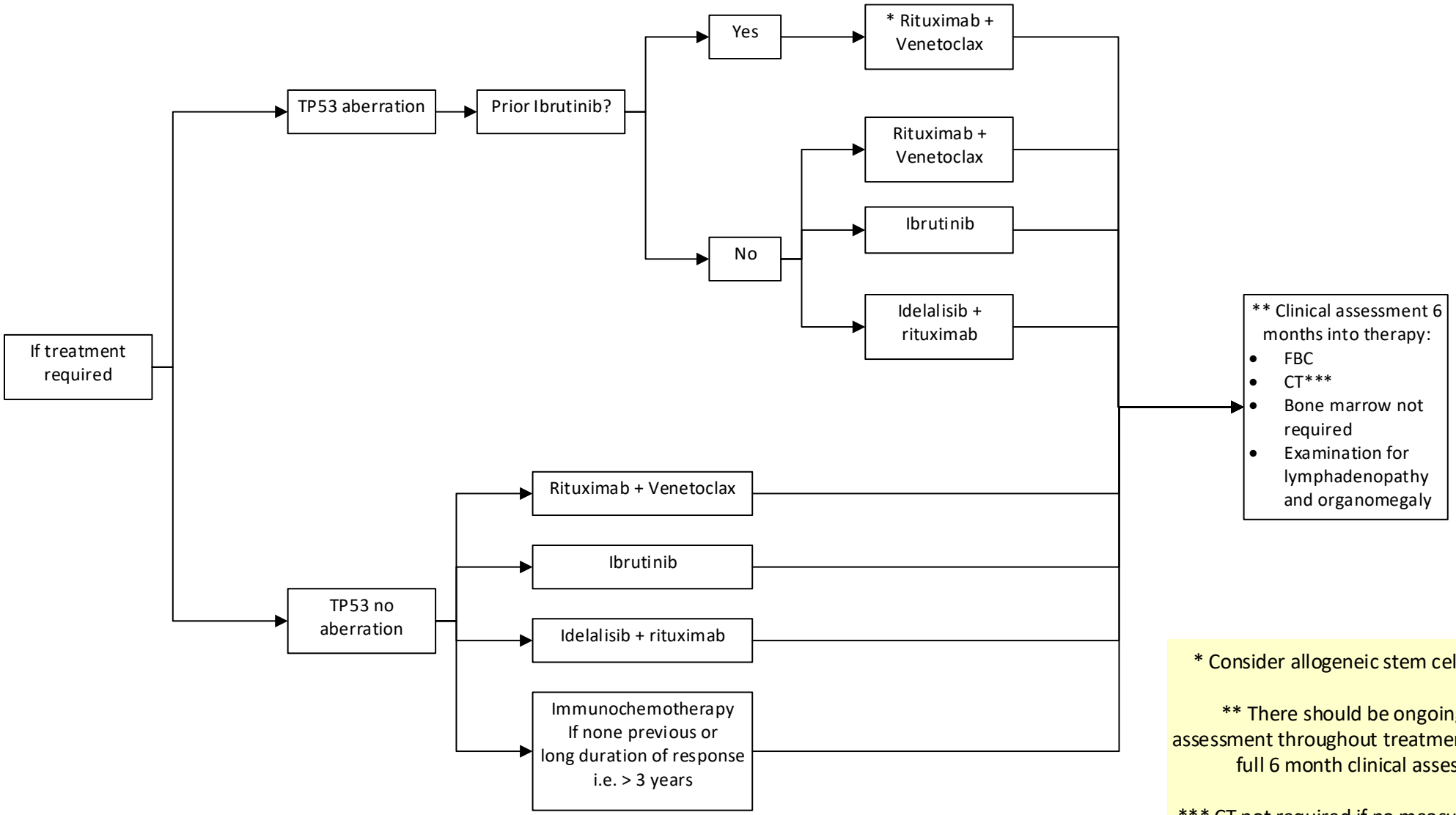
* There should be ongoing clinical assessment throughout treatment prior to the full 6 month clinical assessment

** CT not required if no measurable disease on baseline scan

*** Not recommended but may be used if patients chooses treatment in remote location where delivery of Obinutuzumab is not logistically possible such as the Islands.

In specific situations (typically palliative), consider low-dose cyclophosphamide

2nd Line Treatments

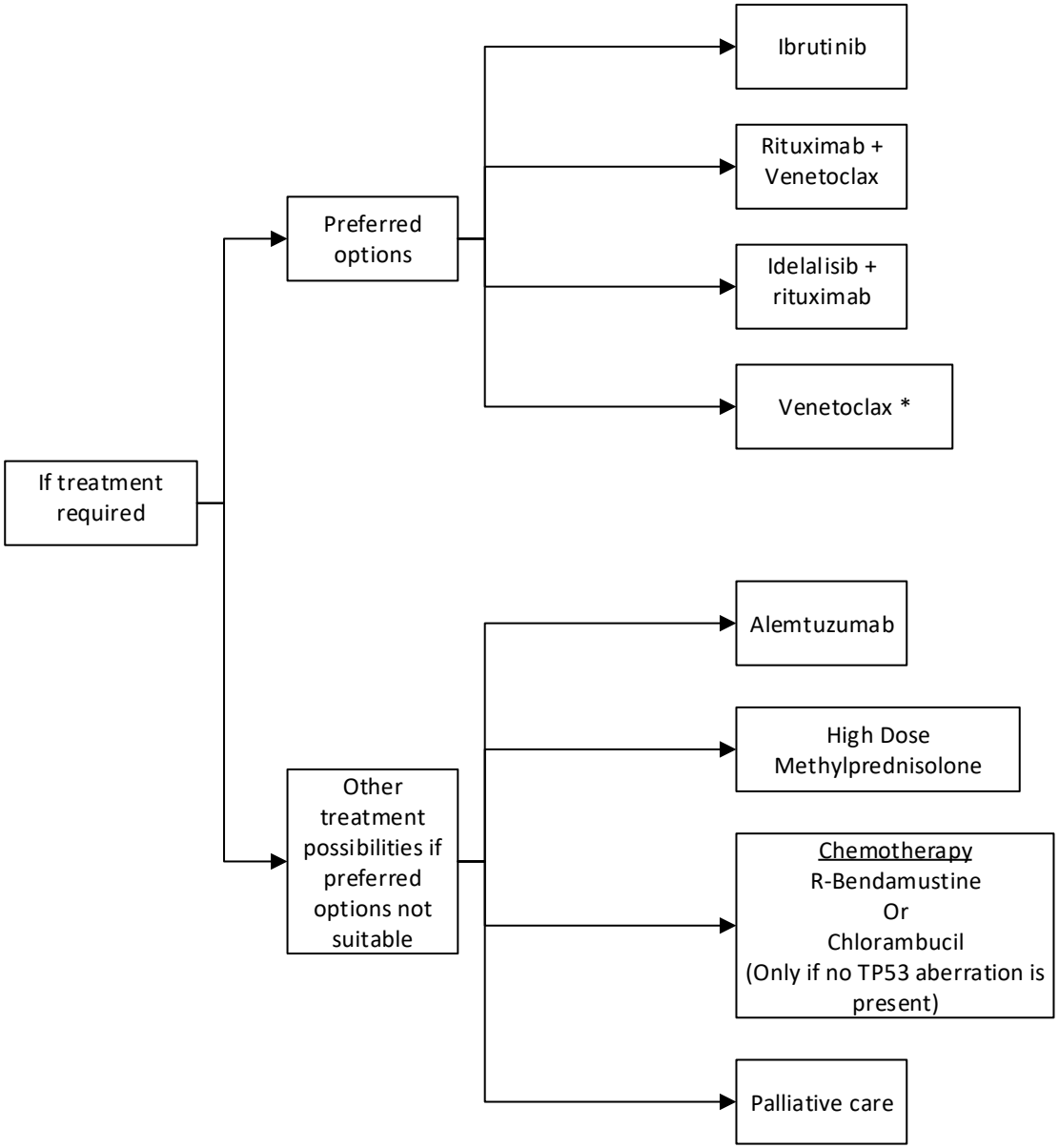


* Consider allogeneic stem cell transplant

** There should be ongoing clinical assessment throughout treatment prior to the full 6 month clinical assessment

*** CT not required if no measurable disease on baseline scan

3rd Line Treatments



Consider allogeneic stem cell transplant for all suitable patients responding to third line therapy. If available alternative cellular therapy may be preferred.

Treatment options at this stage will depend on prior therapy

* Re-treatment with Venetoclax may be used provided there was not disease progression whilst on Venetoclax therapy

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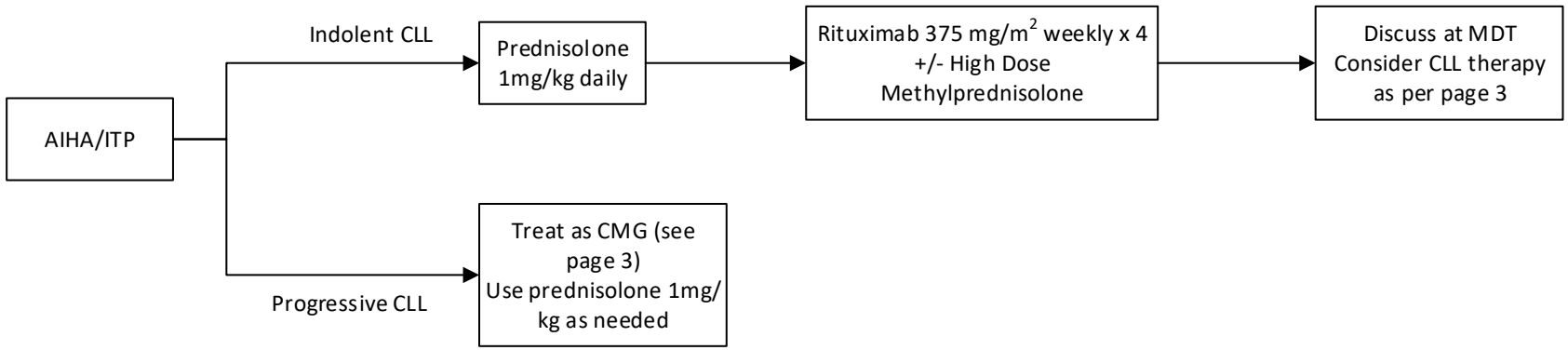
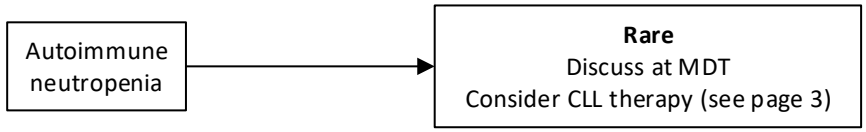
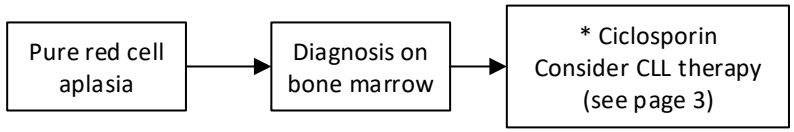
Auto-Immune Complications	1st Line	2nd Line	3rd Line





Immune-mediated complications may arise at any time during the treatment pathway

* Some patients may respond to other immunosuppressants such as prednisolone



SACT Protocols

In time these SACT Protocols will link from the table below. In the meantime, please visit the SACT Protocol section of the NCA website.

Alemtuzumab (SC)
Chlorambucil
FCR (fludarabine, cyclophosphamide, rituximab)
Ibrutinib
Obinutuzumab-Chlorambucil
Rituxumab +/- HDMP (high dose methylprednisolone)
R- bendamustine (rituximab/bendamustine)
R-chlorambucil (rituximab/chlorambucil)
R-idelalisib (rituximab/idelalisib)
Venetoclax
R-Venetoclax

Definitions

Definitions

AIHA	Auto-immune Haemolytic Anaemia
BCR	B-Cell Receptor
BCSH	British Society for Haematology
CCF	Congestive Cardiac Failure
CIRS	Cumulative Illness Rating Scale
CLL	Chronic Lymphocytic Leukaemia
CMG	Clinical Management Guideline
CT	Computed Tomography
DAT	Direct Antiglobulin Test
ECOG	The Eastern Cooperative Oncology Group
FBC	Full Blood Count
FISH	Flurorescent in-situ Hypridrisation
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
Igs	Immunoglobulins
ITP	Immune Thrombocytopenia Purpura
iwCLL	International Workshop on CLL
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
MBL	Monoclonal B Cell Lymphocytosis
MDT	Multidisciplinary Team
PEP	Protein Electrophoresis
PET	Positron Emission Tomography
PS	Performance Status
U+E	Urea + Electrolytes

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RESONATE 17 study (Ibrutinib in TP53 deleted CLL) - O'Brien S et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016 Oct;17(10):1409-1418. doi: 10.1016/S1470-2045(16)30212-1

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Secondary Antibody Deficiency Guidelines - https://www.nsd.scot.nhs.uk/Documents/clinimmumoMarch12.pdf

National Cancer Medicines Advisory Group (NCMAG)

COVID-19 NCMAG advice expired on 31/3/2023.

The following advice is no longer valid and has been withdrawn:-

- NCMAG017 - Ibrutinib, as a single agent for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
- NCMAG029 - Acalabrutinib, as monotherapy for the treatment of adult patients with previously untreated CLL without a del(17p) or TP53 mutation and who would otherwise be eligible for fludarabine-cyclophosphamide-rituximab (FCR).
- Requests for treatment for new patients must be made on an individual patient basis via local Board approval processes.

For further information, including access to a full list of expired advice, please see the section relating to the National Cancer Medicines Advisory Group (NCMAG) on the home page of the NCA website. https://www.nhsscotlandnorth.scot/nca