

Royal Cornwall NHS Trust Haematology Department Lymphoma Treatment Pathways

Pathway for front line treatment of DLBCL

Reference: Chaganti et al. BSH Guidelines May 2016

If available consider clinical trial

New diagnosis DLBCL
 Excluding:

- PMBCL
- PCNSL

Baseline Special Ix

- FBC
- UEs
- LFTs
- Bone profile
- LDH
- HIV/Hep B/Hep C serology
- CSF for cytospin and flow cytometry with IT MTX if CNS disease suspected
- PET-CT preferentially or CT TAP + BMAT
- Calculate:
 - R-IPI
 - CNS-IPI
- Echo (>70yrs or Ischaemic heart disease)

Stage I (nodal and <7.5cm bulk)
 R-CHOP x 3 or 4
 RCHOP x6 if ISRT contra-indicated
 If >80yrs: R-GCVP / miniCHOP / RCE

Stage II-IV
 R-CHOP x6

- (Consider CT-NTAP after #4*)

If unfit for RCHOP: R-GCVP / R-mini-CHOP x 6

- >80yrs,
- PS >2
- Significant comorbidities
- Ejection fraction <50% or cardiac risk factors (R-GCVP only)

Consider DA-EPOCH-R or R-CODOX-M-R-IVAC for double / triple hit (MYC + BCL2 and/or BCL6 rearranged)

Consider FISH for MYC rearrangement (and if positive for *BCL2* + *BCL6*) in cases where Ki67 >40% *and* eligible for intensified approach

CNS Prophylaxis:
 Consider for:

- CNS-IPI 4-5
- High risk sites: testis, kidney, adrenal, breast, epidural
- Double hit lymphoma

Consider ISRT to sites of initial bulk (>7.5cm in any dimension)

End of treatment response assessment with PET-CT 6 weeks post chemotherapy, 12 weeks post radiotherapy (or CT-TAP after final course).

PET +ve – consider:

- Rpt biopsy
- Interval PET-CT at 3mths if low clinical suspicion
- ISRT
- Salvage

PET –ve: Follow up 2yrs:
 3 monthly 1yr, 4 monthly 1yr then discharge with end-of-treatment summary to GP if in stable clinical remission. No bloods required at follow up unless specifically indicated

CNS Prophylaxis Options (for discussion):

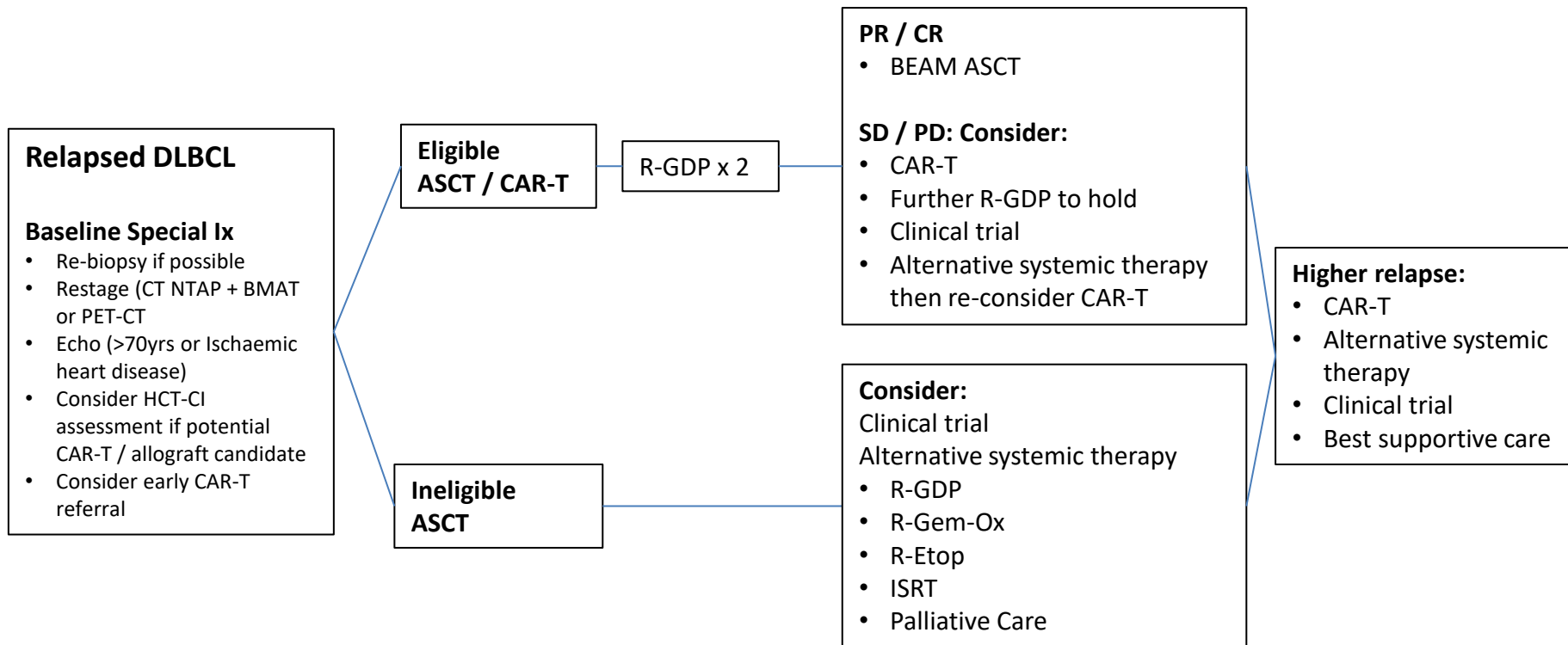
1. IV HDMTX day 10 #2, #3 & #6 with GCSF
2. 2-4 IT MTX early on in treatment if not fit for HDMTX (consider HDMTX after RCHOP)

* Not required if disease easily clinically assessable

Pathway for treatment of Relapsed DLBCL

Reference: BSH Guidelines 2016; Locke et al. Lancet Oncol. Vol 20, Jan 2019; NICE / CDF for CAR-T

If available consider clinical trial



Axicabtagene ciloleucel (Yescarta) (CDF) for DLBCL (Autologous CAR-T)

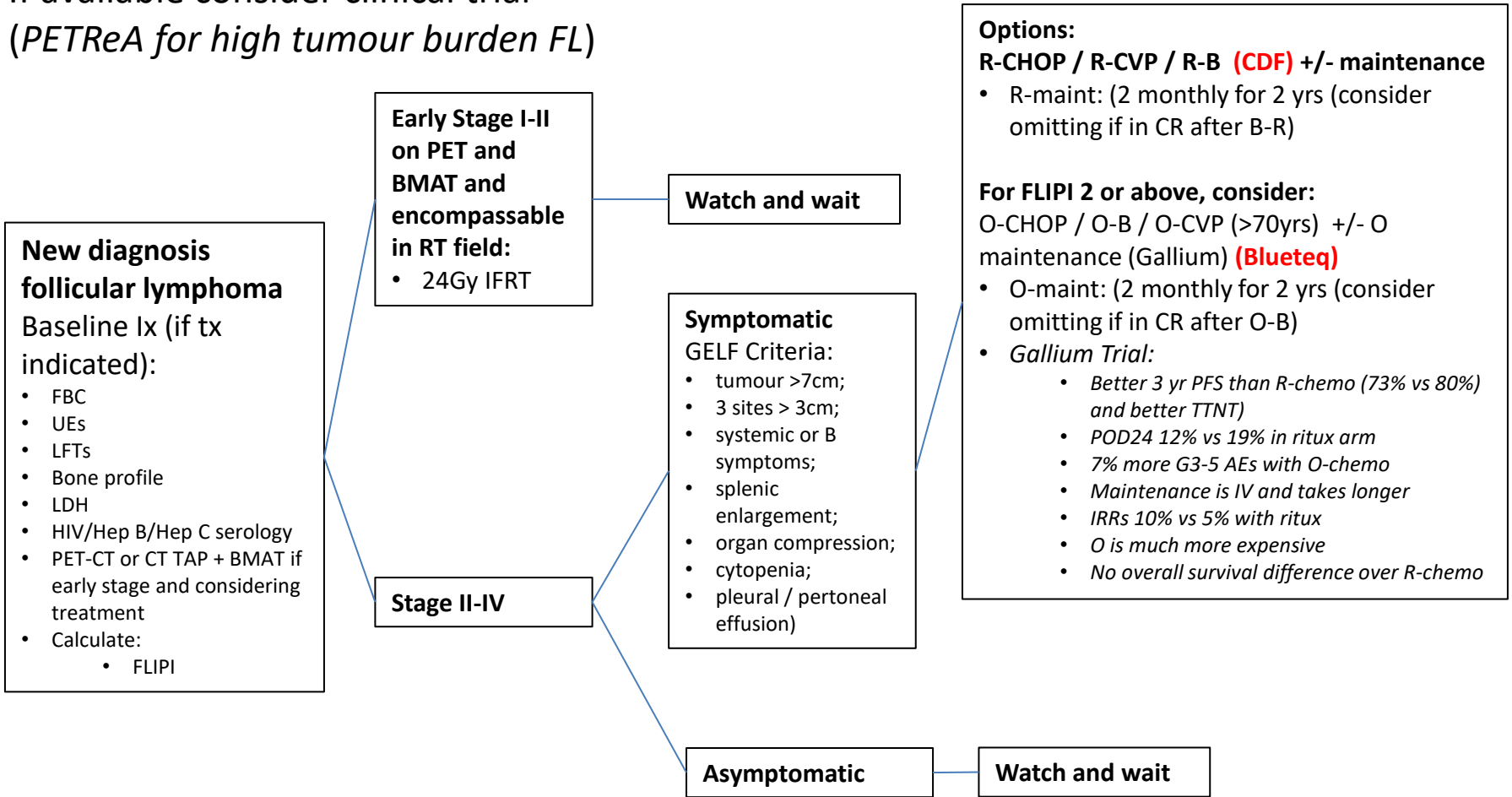
- DLBCL / PMBCL / HGTFCL after 2 or more systemic therapies (inc. salvage not responding prior ASCT)
- (ZUMA-1: mean age 58yrs, ECOG 1, 83% ORR (not ITT) 58% CR, PFS 50% 6/12, median DOR 11.1months, median OS not reached) G3 AEs in 48% (CRS 11%, 32% neurological), TRM 2%, B-cell aplasia 20%.

Pathway for front line treatment of Follicular NHL

Reference:; Marcus et al. NEJM 2017;377:1331-44; Hill et al. BJH 2019, 184, 524-535; Thames Valley SCN: T. Eyre, G. Collins, May 2018)

If available consider clinical trial

(PETReA for high tumour burden FL)

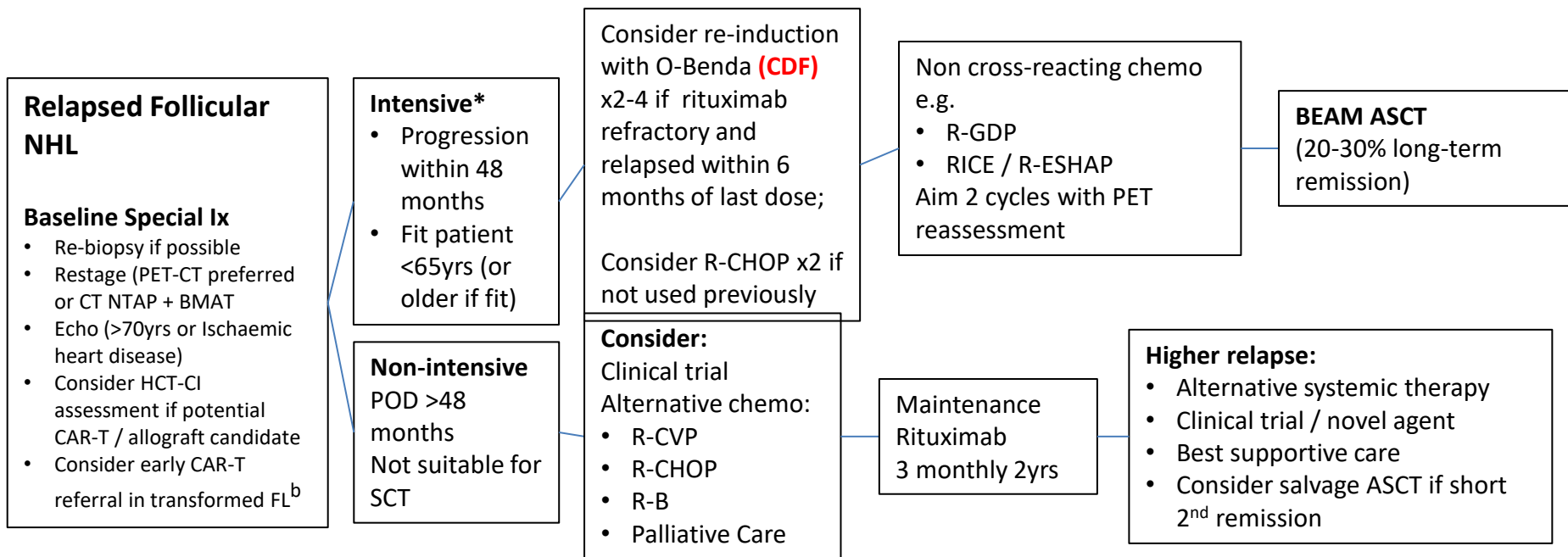


Follow Up:
Evaluate on a case by case basis. Consider 3 monthly 1yr, 4 monthly 1yr, then 6-12 monthly or with patient-led follow up in place it may be appropriate to discharge patients to a patient-led follow up plan after 2-3 years.

Pathway for treatment of Relapsed Follicular Lymphoma

Reference: T. Eyre, G. Collins Thames Valley Strategic Clinical Network May 2018; NICE guidelines on CAR-T

If available consider clinical trial



^bHigh Grade Transformation

- Treatment naïve – treat as de-novo DLBCL and consider CART after 2 systemic therapies;
- Pre-treated FL – consider salvage and ASCT then CAR-T.

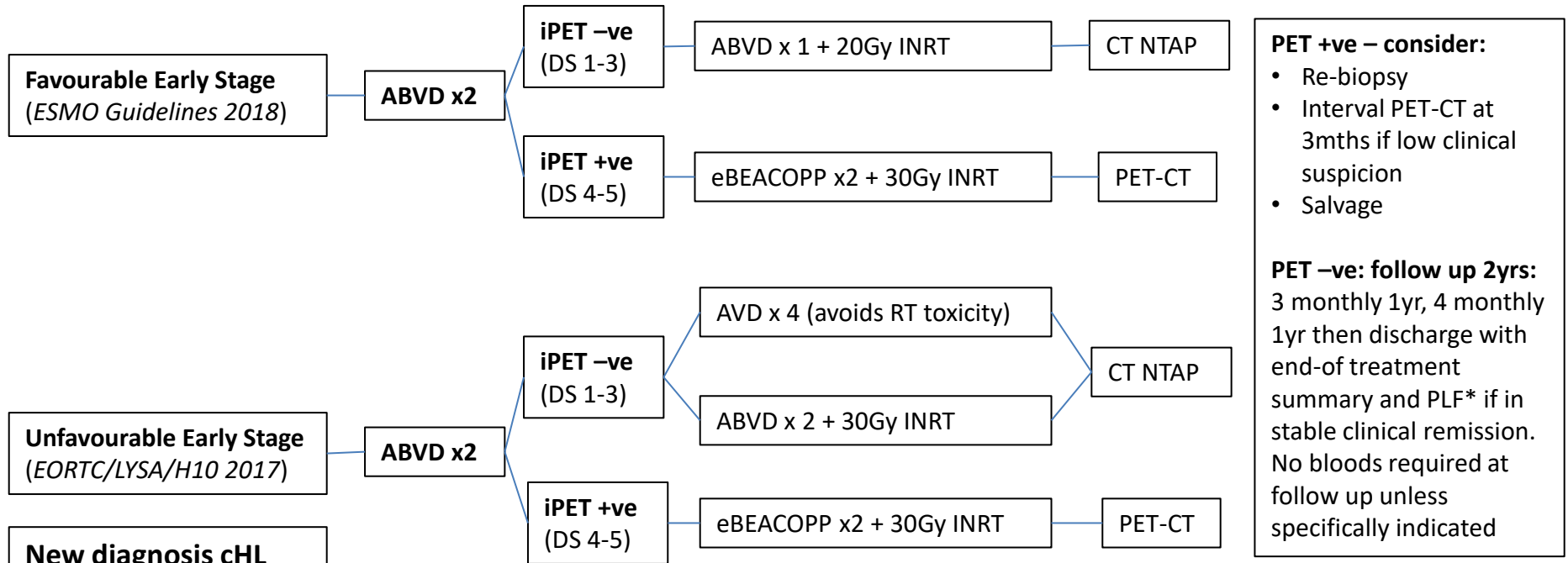
***Axicabtagene ciloleucel (Yescarta) (CDF) for tFL (Autologous CAR-T)**

- HG Transformation FL after 2 or more systemic therapies (inc. salvage not responding prior ASCT)
- (ZUMA-1: mean age 58yrs, ECOG 1, 83% ORR (not ITT) 58% CR, PFS 50% 6/12, median DOR 11.1months, median OS not reached) G3 AEs in 48% (CRS 11%, 32% neurological), TRM 2%, B-cell aplasia 20%.

Pathway for front line treatment of Early Stage (I-IIA) classical

Hodgkins Lymphoma *(Hodgkin Lymphoma Updates BJH Jan 2019 Vol 184 No1)*

If available consider clinical trial



PET +ve – consider:

- Re-biopsy
- Interval PET-CT at 3mths if low clinical suspicion
- Salvage

PET –ve: follow up 2yrs:

3 monthly 1yr, 4 monthly 1yr then discharge with end-of treatment summary and PLF* if in stable clinical remission. No bloods required at follow up unless specifically indicated

New diagnosis cHL

Baseline Ix:

- FBC
- UEs
- LFTs
- Bone profile
- ESR
- HIV/Hep B/Hep C serology
- PET-CT
- Echo (>70yrs or Ischaemic heart disease)
- **Discuss fertility preservation if appropriate**

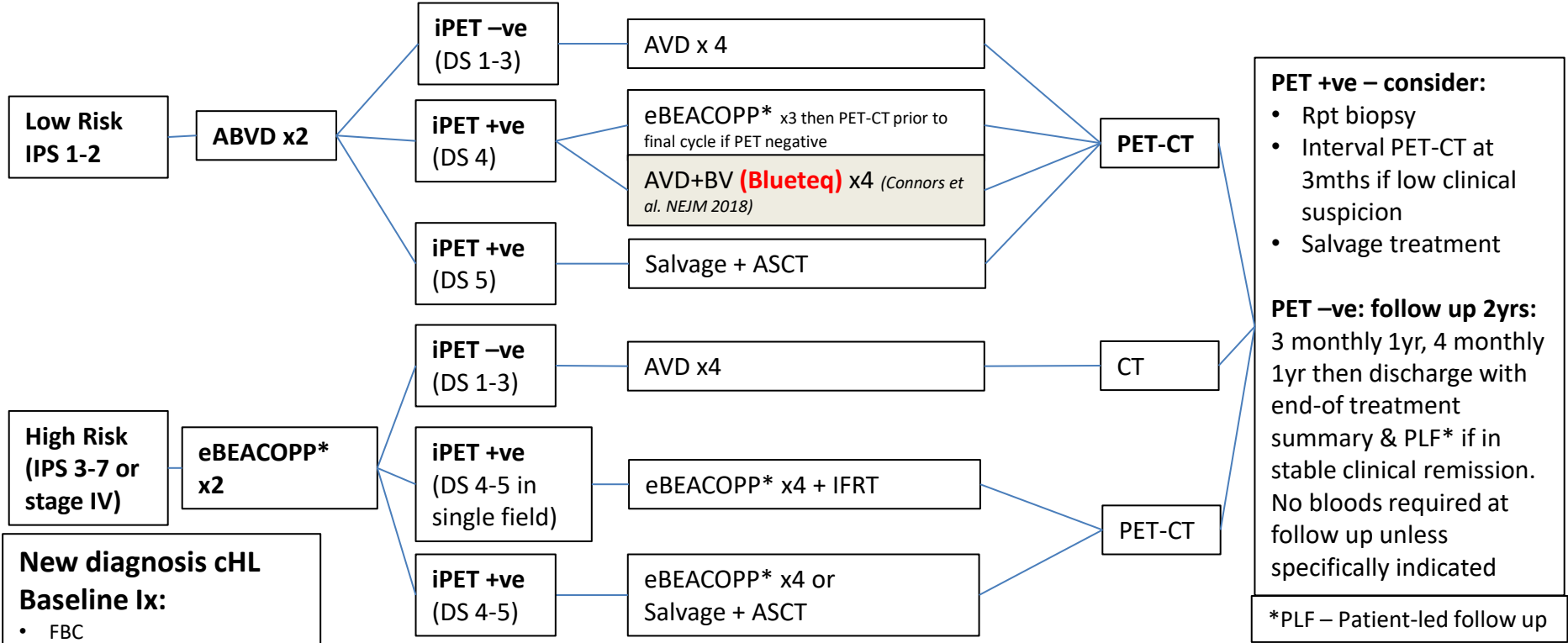
Unfavourable EORTC/LYSA (Unfavourable if any of below present):
Mediastinal mass (mediastinal:thoracic ratio >0.35)
Age greater than 50yrs
ESR greater than 50 or greater than 30 + B symptoms
More than 4 nodal areas

*PLF – Patient-led follow up

Intensive front line treatment of advanced (stage IIB – IV) classical Hodgkins lymphoma

(>60yrs, PS 0-2) (Hodgkin Lymphoma Update BJH Jan 2019 Vol 184 No1 and Thames Valley SCN, May 2018 – G. Collins)

If available consider clinical trial



New diagnosis cHL
Baseline Ix:

- FBC
- UEs
- LFTs
- Bone profile
- ESR
- HIV/Hep B/Hep C serology
- PET-CT
- Echo (>70yrs or Ischaemic heart disease)

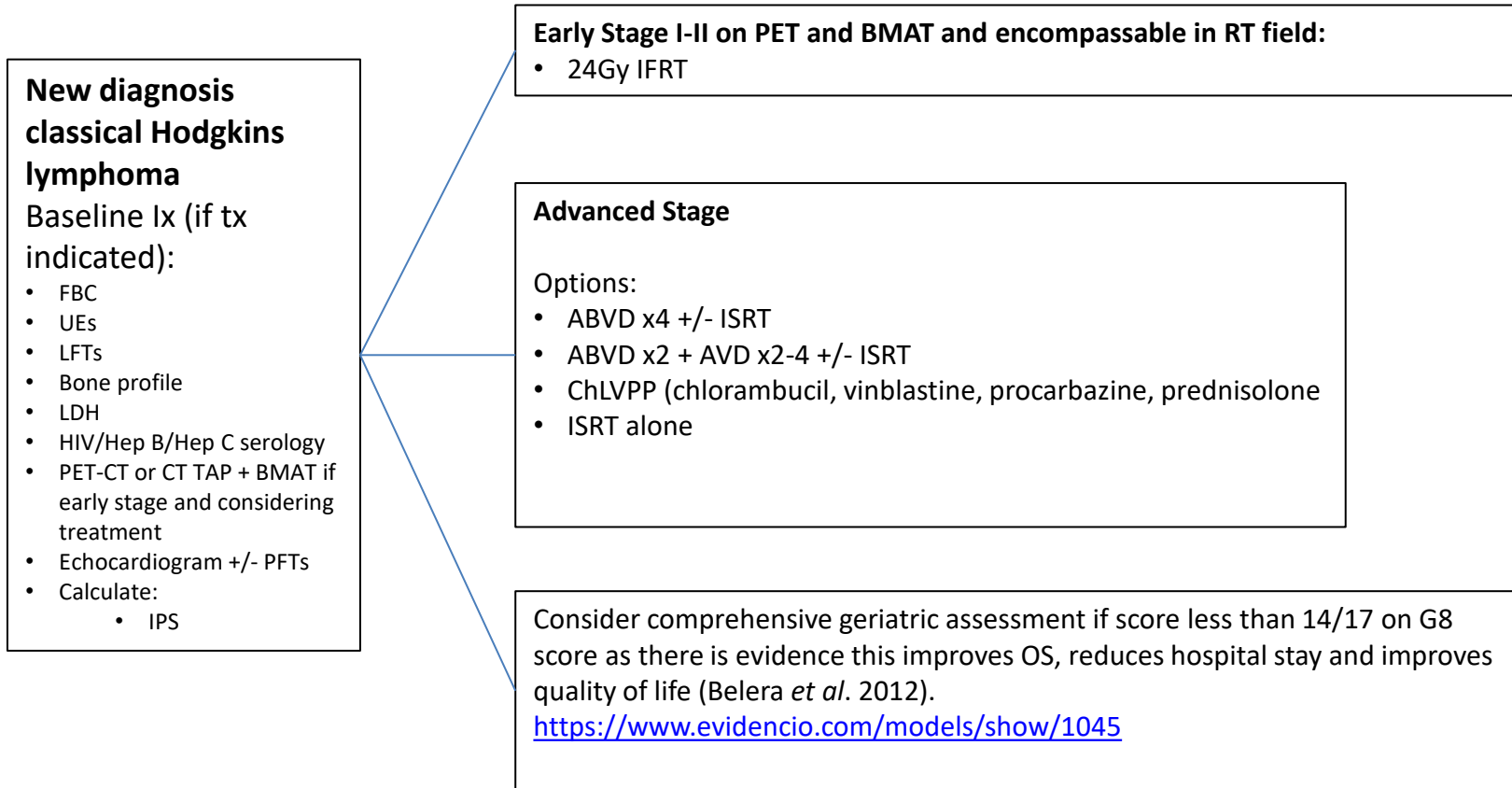
Calculate IPS
Discuss fertility preservation if appropriate

***Consider eBEACOPDac** to reduce phlebitis and nausea by spreading out dacarbazine dose. (21 day cycle): doxorubicin 35mg/m² IV o.d. day 1; cyclophosphamide 1250mg/m² IV over 30mins, o.d. day 1; mesna as per protocol; etoposide 200mg/m² IV o.d. d1-3, dacarbazine 250mg/m² o.d. d2-3, prednisolone 40mg/m² po o.d. d1-14, bleomycin 10,000 units/m² o.d. d8, vincristine 1.4mg/m² (2mg cap) d8, GCSF support.
NB. No direct comparison of eBEACOPDac vs eBEACOPP (modification option to discuss with patient)
NB. Only appropriate if WHO PS 0-2 and aged 60 or younger
 HD18 study – 10% relapse risk (vs 20% if start with ABVD). Borchmann *et al.* Lancet 2017

*PLF – Patient-led follow up

Pathway for front line treatment of classical Hodgkins in Older Patients (>60 / Comorbidities) (Boll et al. BJH Review 2019 184 pp82-92)

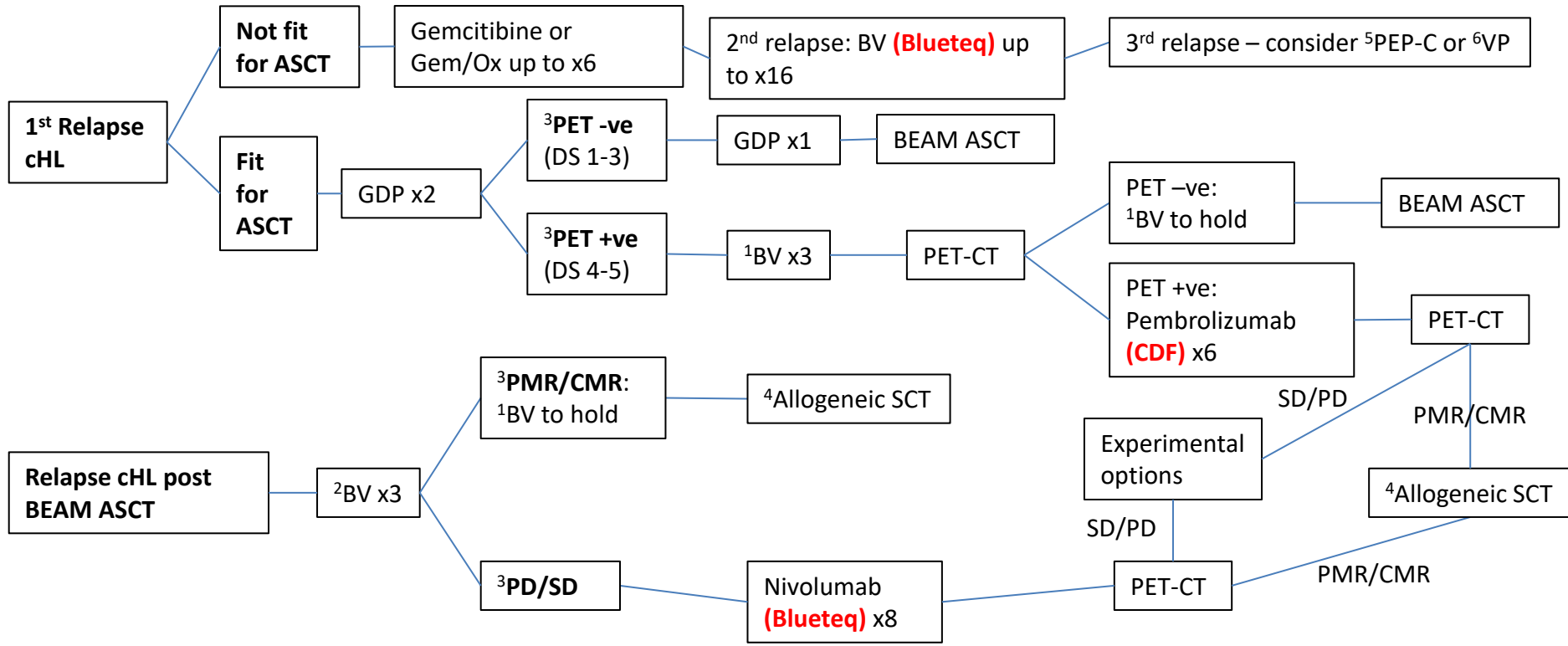
If available consider clinical trial



Pathway for treatment of relapsed classical Hodgkins Lymphoma

(Reference: BJH Jan 2019 Vol 184 No1 and Thames Valley SCN, May 2018 – G. Collins)

If available consider clinical trial



Very low risk relapse (early stage at first diagnosis and relapse; >1yr in remission; no radiotherapy given so far) may be treated with either RT alone or combination chemotherapy + RT – SCT may not be needed.

Radiotherapy recommended after systemic tx for bulk at relapse; localised relapse; residual PET avid areas

- 1 Aim for SCT promptly; keep administering BV until this is performed
- 2 If BV exposed re-treat if prior BV well tolerated and resulted in good remission; up to 16 cycles in total
- 3 PET interpretation can be hard; a very good PR but with residual uptake can be treated as negative – discuss at MDT
- 4 Allo SCT after PD1 inhibition should always be T-deplete with an 8 week washout
- 5 PEP-C – Prednisolone, cyclophosphamide, etoposide, procarbazine (Coleman *et al. Leuk. Lymph.* 2008)
- 6 VP – Vinblastine and prednisolone (UCLH protocol)

Pathway for front line treatment of Primary CNS Lymphoma

Reference: BSH Guidelines 2019

If available consider clinical trial

New diagnosis PCNSL
 Avoid or suspend steroids pre-diagnosis if possible

Baseline Special Ix

- Stereotactic brain bx
- Retinal bx if appropriate
- CSF for cytospin, flow cytometry and clonality (IGHV rearrangement by PCR to Jo Farrugia)
- FBC
- UE
- LFTs
- Bone profile
- LDH
- HIV/Hep B/Hep C serology
- Contrast MRI
- PET-CT or CT TAP + BMAT
- Calculate: Creatinine Cl.
- Echo (>70yrs or Ischaemic heart disease)

****Eligibility for HD MTX:**
 eGFR >50mls/min
 Ejection fraction >45%
 (Age and WHO PS are less good guides at diagnosis)

Eligible for ASCT

MATRix x2

≥ SD*

Thiotepa ASCT

***Assess response**
 Consider WBRT if residual disease

PD*

Consider options:

- RICE
- RIE
- HDMTX (if DOR >2yrs)
- Clinical trial

Eligible for HD-MTX** but not ASCT

MATRix x2

≥ SD*

MATRix x2

***Consider WBRT if residual disease on EoT MRI**

PD*

Consider options:

- RICE
- RIE
- HDMTX (if DOR >2yrs)
- Clinical trial

Ineligible for HD-MTX

Consider options:
 Oral temozolomide
 WBRT 20-30Gy +/- orbits
 Steroids
 IT chemotherapy

***Response Assessments are by contrast-enhanced MRI**
 SD = stable disease
 PD = progressive disease

Pathway for front line treatment of Primary Mediastinal B-cell

Lymphoma *(BSH Good Practice Paper 2019)*

If available consider clinical trial

New diagnosis PMBCL

Baseline Special Ix

- Biopsy
- FBC
- UEs
- LFTs
- Bone profile
- LDH
- HIV/Hep B/Hep C serology
- CSF for cytospin and flow cytometry with IT MTX if CNS disease suspected
- PET-CT or CT TAP + BMAT
- Echo (>70yrs or Ischaemic heart disease)
- **Discuss fertility preservation**

Options:

R-CHOP x 6 + ISRT
(mid treatment CT post #4)

DA-EPOCH-R x 6
(mid treatment CT post #4)

EoT PET-CT
2-3 months

EoT PET-CT
6 weeks

PET +ve – consider:

- Rpt biopsy
- Interval PET-CT at 3mths if low clinical suspicion
- ISRT if not had
- Salvage as relapsed DLBCL
- Clinical trial

PET –ve: Follow up 2yrs:
3 monthly 1yr, 4 monthly 1yr then discharge with end-of treatment summary and PLF if in stable clinical remission. No bloods required at follow up unless specifically indicated

Consider FISH for cMYC rearrangement (and if positive for BCL2 + BCL6 rearrangements) in cases where Ki67 >40% and eligible for DA-EPOCH-R

CNS Prophylaxis:
Consider for:

- CNS-IPI 4-5
- High risk sites: testis, kidney, adrenal, breast, epidural
- Double hit lymphoma

CNS Prophylaxis Options (for discussion):

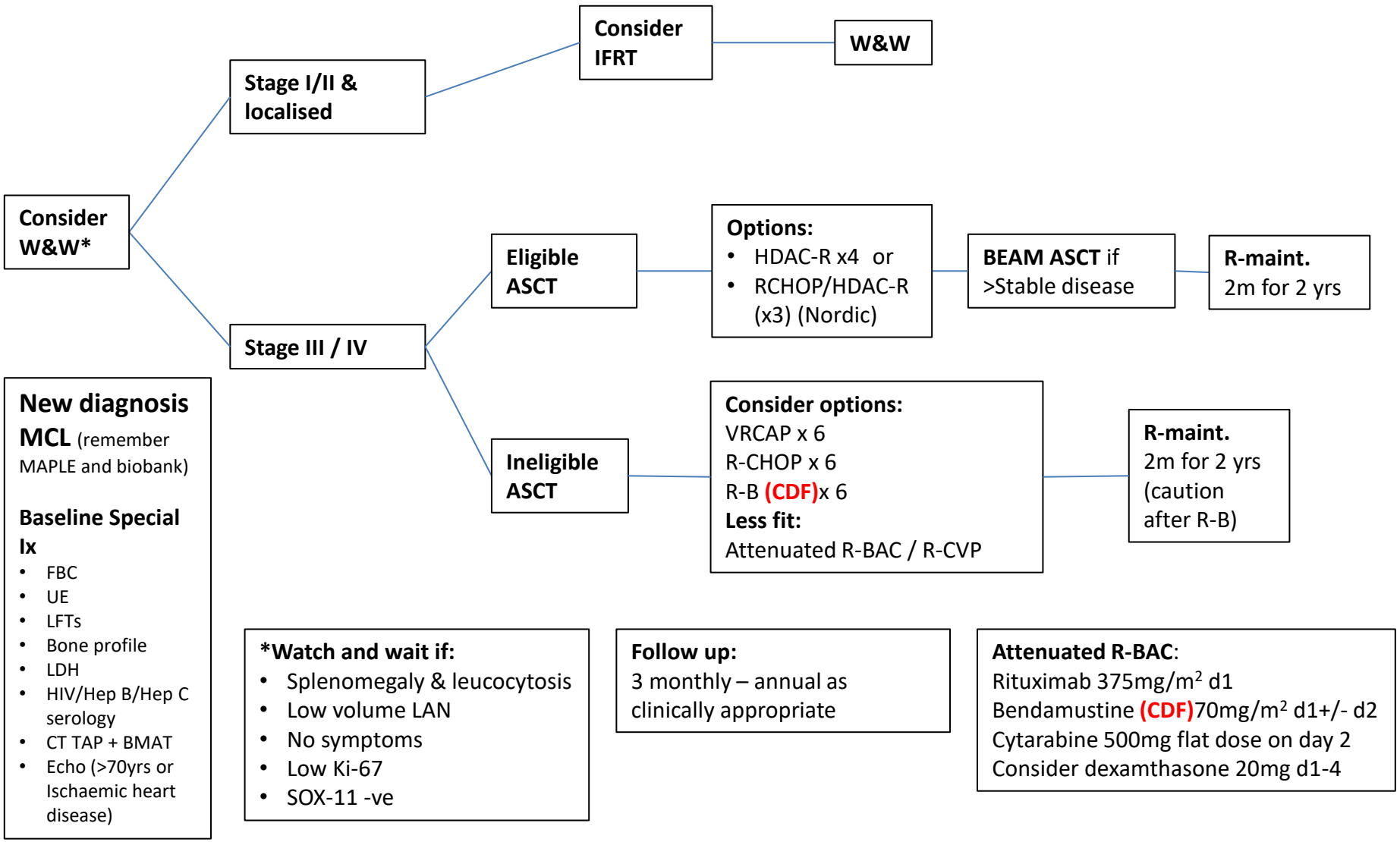
1. IV HDMTX day 10 #2, #3 and #6 with GCSF
2. 2-4 IT MTX early on in treatment if not fit for HDMTX

* Not required if disease easily clinically assessable

Pathway for front line treatment of Mantle Cell Lymphoma

Reference: BSH Guidelines 2018 & Robak et al. Lancet Oncol. 2018;19:1449-58

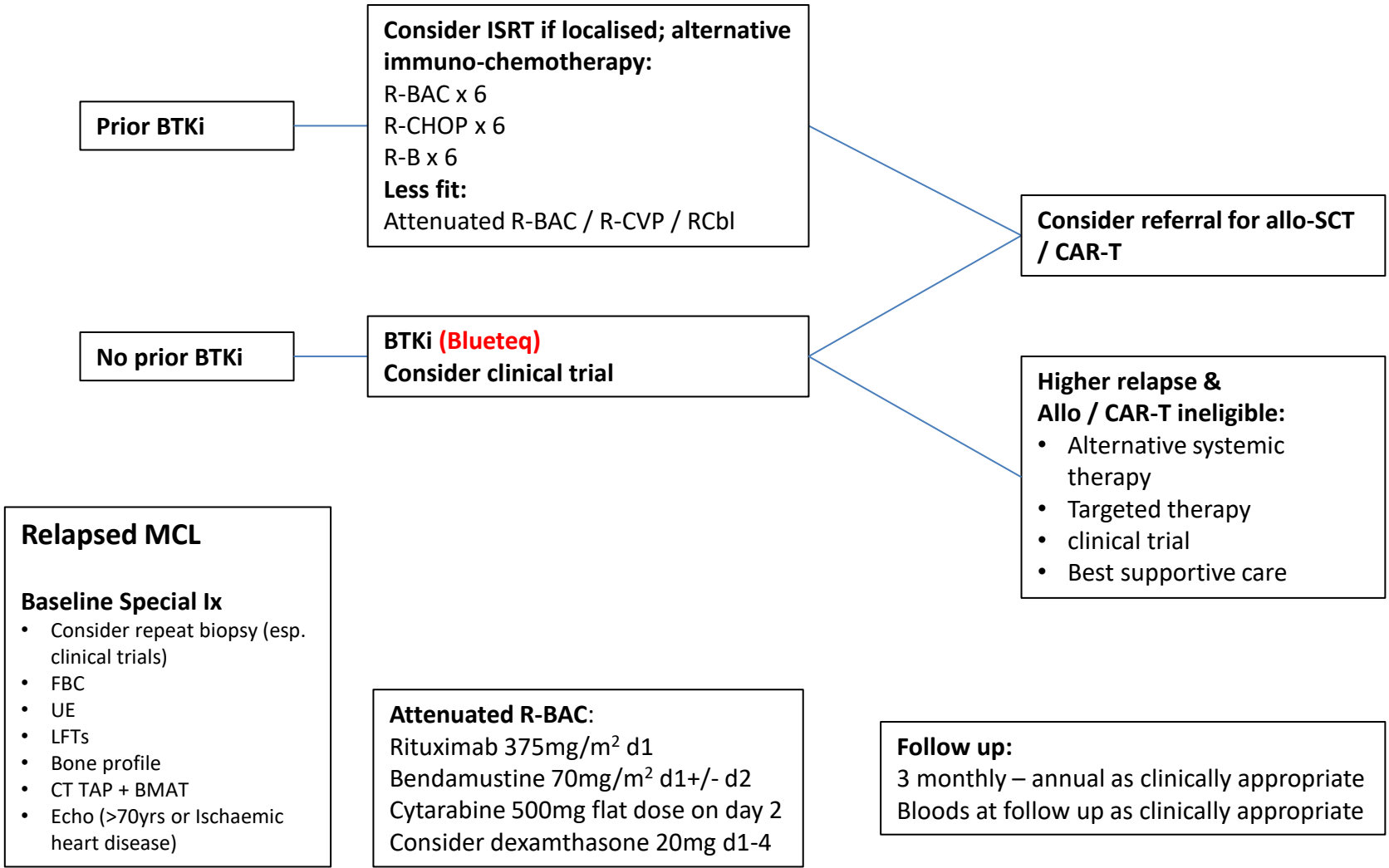
If available consider clinical trial



Pathway for treatment of Relapsed Mantle Cell Lymphoma

Reference: BSH Guidelines 2018

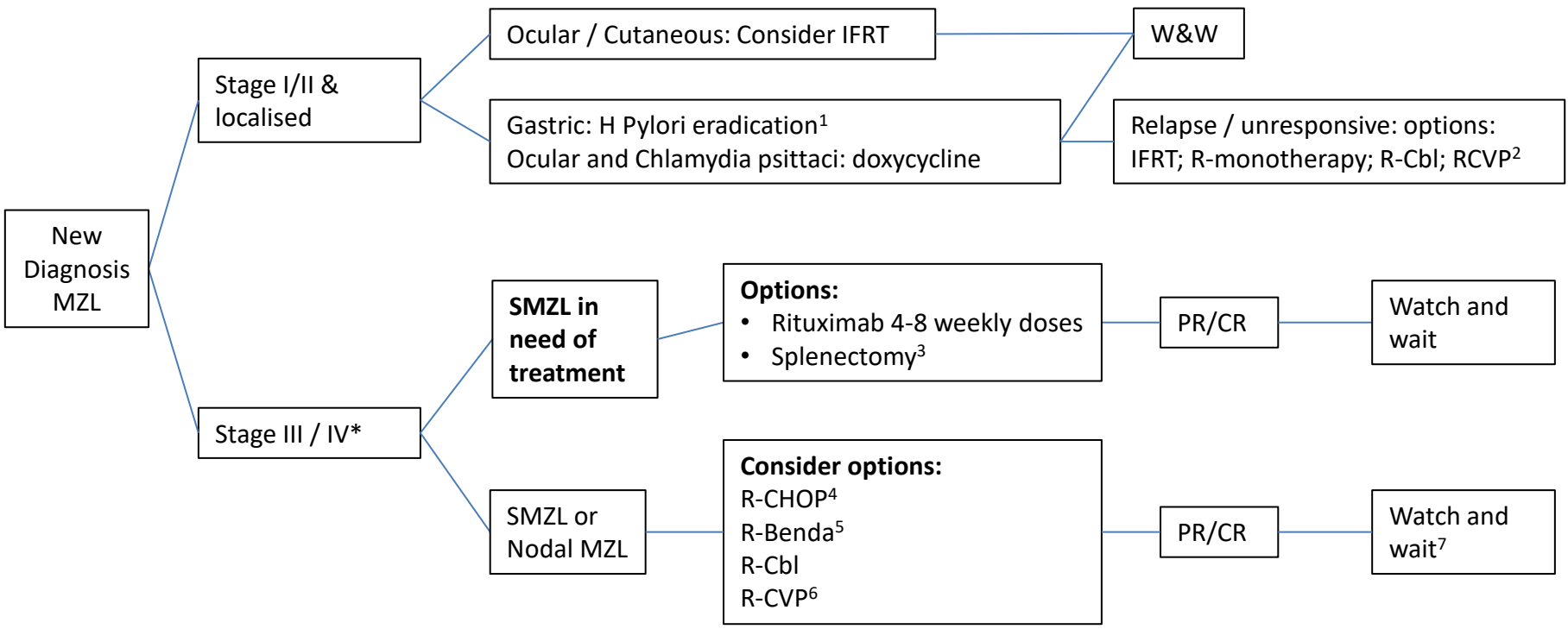
If available consider clinical trial



Pathway for front line treatment of Marginal Zone Lymphoma

Reference: Thames Valley SCN, G. Collins, 2019; NICE guidelines 2016

If available consider clinical trial



***Consider watch and wait if:**

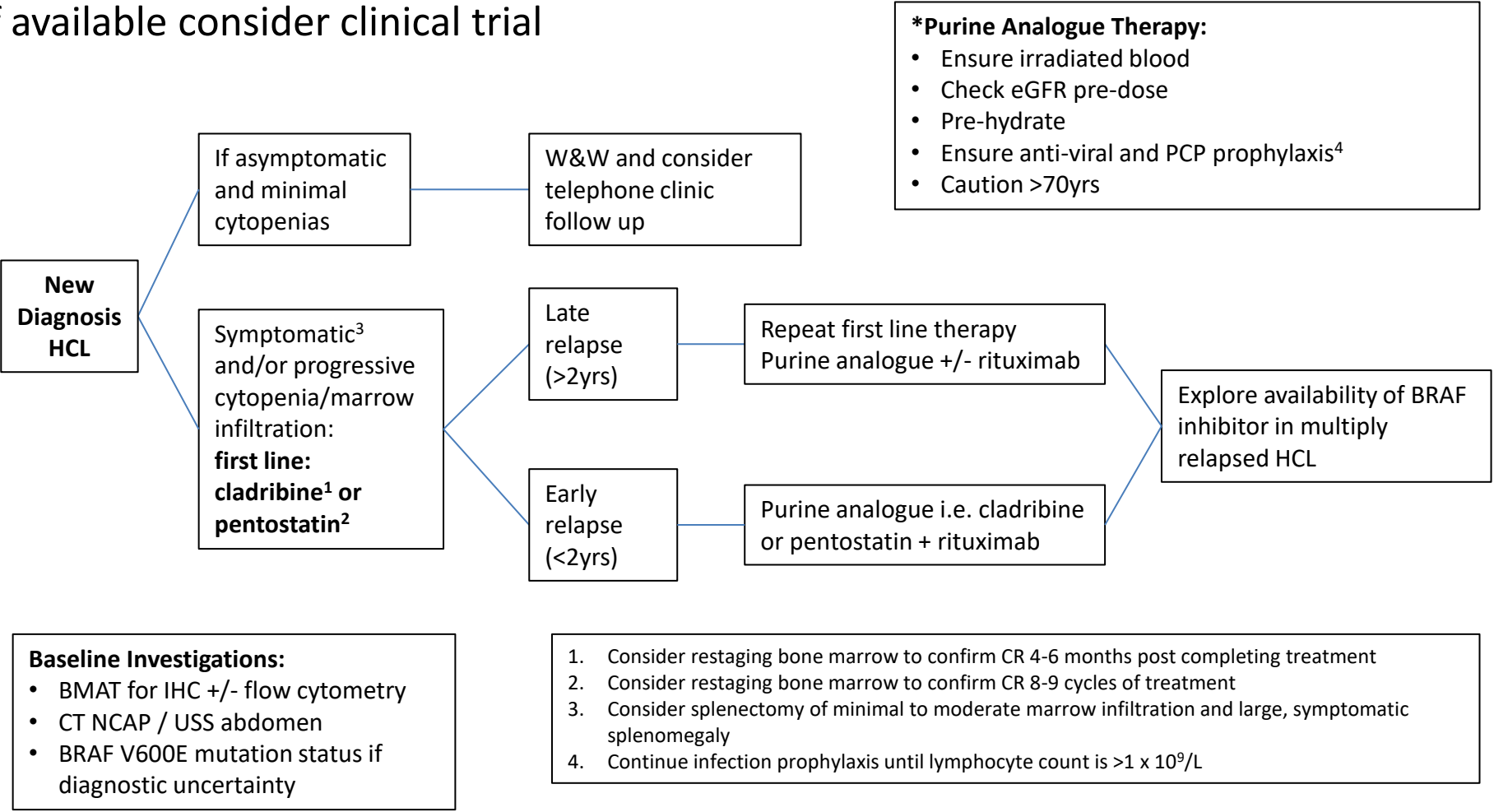
- Asymptomatic mild/moderate splenomegaly +/- leucocytosis with retained Hb and platelets;
- Low volume LAN or extranodal disease
- No symptoms

1. Repeat endoscopy at 3 months after H pylori eradication and subsequent therapy lines
2. Monitor 3-6 monthly endoscopy surveillance depending on clinical context
3. Can be appropriate if symptomatic, dominant splenomegaly with minimal marrow infiltration
4. Reserve for features concerning for high grade transformation
5. Typically age <70 with few comorbidities
6. Consider dose attenuation if significant comorbidities or >80yrs
7. Outcomes can be poor in early progression of disease, consider possible HGT and salvage / ASCT in selected patients under 70yrs

Pathway for front line treatment of Hairy Cell Leukaemia

Reference: BSH Guidelines: Jones et al. British Journal of Haematology, 2011; 156,186-195

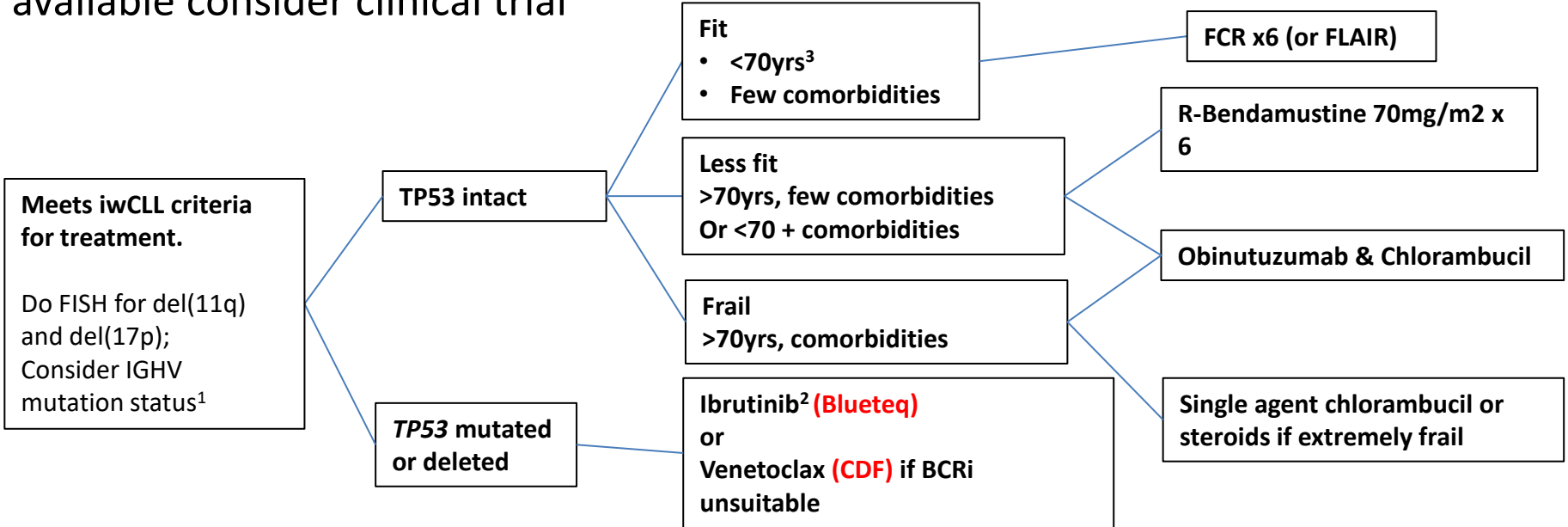
If available consider clinical trial



Pathway for front line treatment of CLL Reference: BSH Guidelines 2018; iwCLL

guidelines – Hallek et al. Blood 2018)

If available consider clinical trial



- ### iwCLL Criteria for Treatment
- B-symptoms
 - Hb <100, Plts <100
 - Massive (>6cm) or progressive or symptomatic splenomegaly
 - Massive nodes (>10cm) or progressive symptomatic LAN
 - Progressive lymphocytosis >50% increase over 2 months or doubling <6months excluding other factors (infections, steroids)
 - Autoimmune complications
 - Symptomatic or functional extranodal involvement
 - Disease related symptoms: fatigue (ECOG PS 2 or worse, cannot perform usual activities)

- ### Notes
1. IGHV mutation status can be helpful in counselling patients about expected duration of response post chemotherapy (unmutated IGHV do worse with FCR ([Hamblin et al. Blood 1999](#)))
 2. Consider idelalisib and rituximab for patients with significant cardiac comorbidity and or requirement for warfarin anti-coagulation
 3. Offer all seasonal flu vaccine; pneumococcal conjugate vaccine (Prevenar 13) followed by polysaccharide vaccine (Pneumovax) 2 months later with response assessment if hypogamma (ie. baseline pneumococcal *serotype* antibodies, followed by Prevenar, and repeat *serotypes* 4-6 weeks later (ie before Pneumovax)
 4. If IgG <5g/L and recurrent infections *and* failed 6 month trial of broad spec abx (e.g. azithromycin) with objective monitoring of infection rate, consider Immunoglobulins (0.4g/kg monthly with trough levels)
 5. Consider respiratory review if recurrent infections, to optimise chest physio/drainage, consideration of nebulised antibiotics etc.
 6. Avoid live vaccines
 7. Consider PJP prophylaxis + aciclovir.

Pathway for treatment of relapsed CLL Reference: BSH Guidelines 2018; iwCLL guidelines

– Hallek et al. Blood 2018)

If available consider clinical trial

Meets iwCLL criteria for treatment.

Do FISH for del(11q) and del(17p); Consider IGHV mutation status¹

- Options:**
- Ibrutinib (**Blueteq**) (if not had already)
 - R-Venetoclax (**CDF**) if had at least 1 previous therapy (inc. single agent venetoclax)
 - R-Idelalisib (**Blueteq**) (if relapsed within 24 months)⁷
 - Retreatment with immunochemotherapy

Notes on Abx Prophylaxis:
 doxy 100mg daily, amox 500mg BD, or azithro 250mg daily as a start) depending on sensitivities and other medication/potential interactions. If the azithro suggest check LFT and ECG a week or two after starting to exclude prolonged QTc.

- iwCLL Criteria for Treatment**
- B-symptoms
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 - Massive nodes (>10cm) or progressive symptomatic LAN
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 6. Avoid live vaccines
 7. Consider PJP prophylaxis + aciclovir.

CLL TLS Prophylaxis Pathway (Venetoclax SPC)

Venetoclax indicated:
 Risk assess tumour burden in clinic 2 weeks prior to starting*
 Check:
 • CT
 • Renal chemistry

low / medium risk

high risk

Friday	Monday	Tuesday	Weds	Thurs	Fri
Start Allopurinol 300mg od	Brisk hydration 3L/day to continue daily for 3 weeks	Confirm risk status against below criteria	0800 – Pt takes incremental dose with food at home	0930 – results reviewed and approved. Only then does patient takes next dose.	0930 – patient continues on current dose until next increment (following Wednesday).
		Urgent TLS bloods + check result on day	1200 – urgent TLS bloods and check result		
			1600 – urgent TLS bloods and check result		
			2000 – Pt attends MDU for urgent TLS bloods and check result		

Admit to ward for TLS monitoring

TLS Bloods:
 Na, K, Urea, Creatinine, Calcium, Phosphate and Uric acid
to be sent urgently and checked on the day by consultant, SpR or CNS

Tumour burden	Criteria
Low	All measurable lymph nodes with the largest diameter <5cm AND ALC <25.
Medium	Any node >5cm but <10cm (by CT) or ALC ≥ 25; or creatinine clearance <80ml/min.
High	Any node ≥10cm (by CT) OR ALC ≥25 AND any node ≥5 but <10cm (by CT)

If chemistry suggests TLS (refer to BSH Guidelines 2015):
 Withhold next dose of venetoclax – if resolves 24-48hrs – resume at same dose

- Consider ward admission for close monitoring
- Consider ICU / Renal input
- Maintain urine output >4ml/Kg/hr
- Rasburicase 0.2mg/kg/day as a 30min infusion
- Follow BSH TLS guidelines 2015.

Pathway for front line treatment of anaplastic large cell lymphoma (ALK positive / ALK negative)

If available consider clinical trial

