Treatment algorithm

IWCLL treatment criteria met — *No* → Continue W&W

Yes

- Screen for TP53 disruptions & *IGHV* mutational status
- Consider co-morbidities/concurrent medication/patient preference
- Consider clinical trials at all lines of treatment

Patient group (s):	**TP53 intact, no Co-Morbidities, IGHV-M** *and potentially suitable for FCR*	**TP53 disrupted** *(preferred option)*	**TP53 disrupted** *(alternative option)*
		Any IGHV status & unsuitable for FCR/BR	
		TP53 intact & unsuitable for FCR/BR	
Frontline Therapy	Historical CIT Ven-O§ FCR	Acalabrutinib +/- Obinutuzumab@ Ibrutinib	Ven-O Ven-Mono¶
		Consider AlloSCT for suitable high risk patients (TP53 disrupted) after failure of first line BTKi or BCL2i, start 2nd line therapy	
Choice of 2L agent	BTKi (Acalabrutinib /Ibrutinib) Ven-R	BTKi (Acalabrutinib /Ibrutinib) Ven-R or Ven-Mono+	Ven-R Alternate BTKi if intolerance*	BTKi (Acalabrutinib /Ibrutinib) Ven-R Or Ven-Mono (see +below)
	Consider AlloSCT for suitable patients with failure to 2 of CIT, BTKi and/or BCL2i irrespective of TP53 status, start 3rd line therapy		
3rd line exemplar sequencing scenarios by prior treatments	Ven +/- R (If BCL2i naïve) or BTKi (if BTKi naïve) Venetoclax Re-Treatment can be offered even if previous Venetoclax (see +below) Alternate BTKi if intolerance* PI3Ki (Idelalisib-Rituximab)		

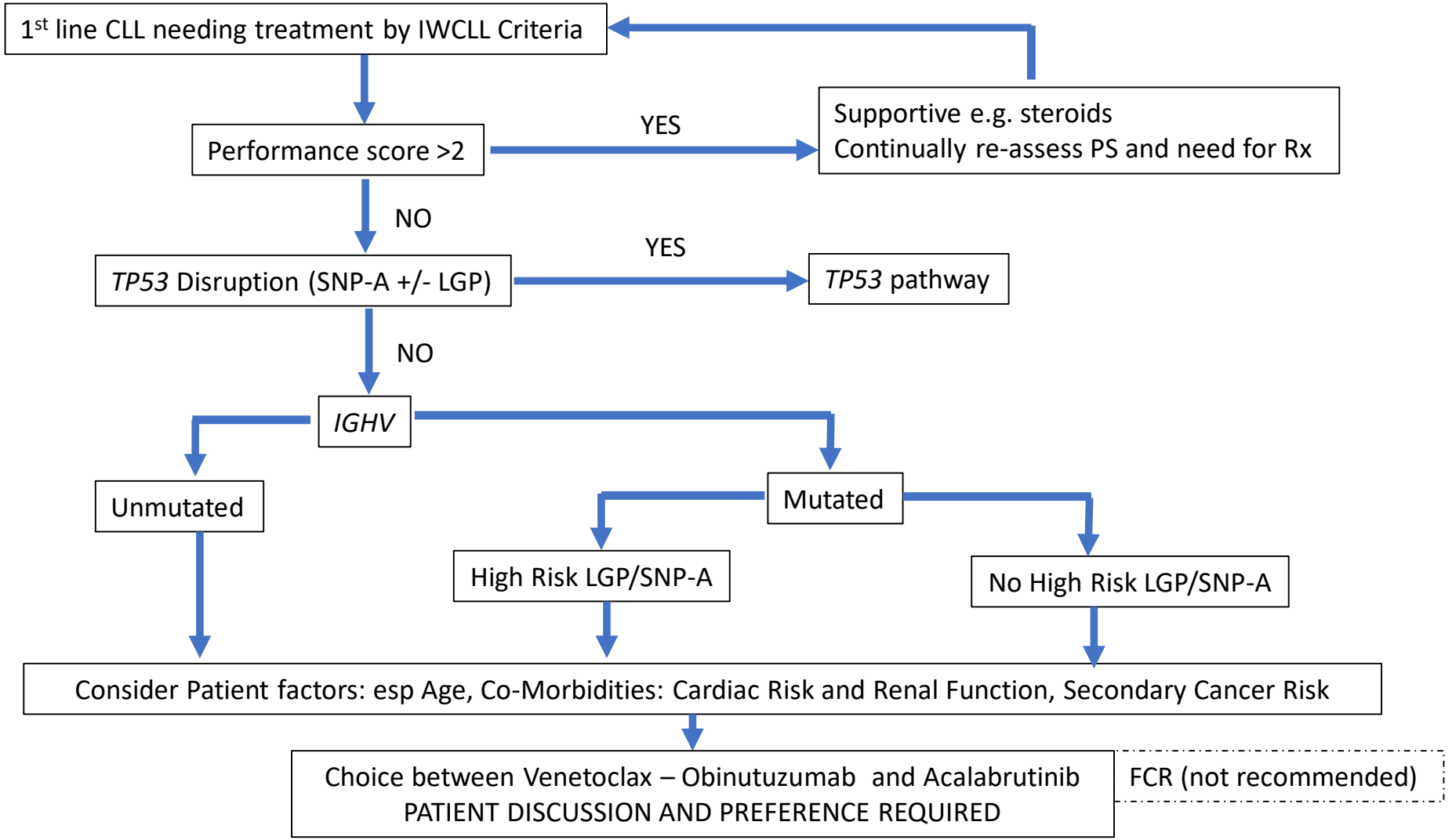
Br J Haematol. 2022;00:1–14.

R/R: Relapsed/refractory; TP53mut: TP53 gene mutation; 2L: Second line; 3L: Third line; CIT: Chemoimmunotherapy; BTKi: Bruton tyrosine kinase inhibitors; FCR: Fludarabine Cyclophosphamide Rituximab; Ven O: Venetoclax Obinutuzumab 12 months; Ven-R: Venetoclax-Rituximab 24 months; Ven-Mono: Single agent continuous venetoclax, ; PI3Ki: Phosphatidylinositol-3 kinase inhibitor; AlloSCT: allogeneic Stem Cell Transplantation

§ Venetoclax-Obinutuzumab is available for NHSE patients for this patient population and is preferred; @Combination with Obinutuzumab is not licensed in the UK; *Alternate BTKi can be offered as an option if intolerant to initial BTKi choice and, when feasible, it is preferred over PI3Ki. ¶Only a first line option for TP53 disrupted patients who are ineligible for BTKi; +Venetoclax monotherapy can be offered to patients relapsing after fixed duration Venetoclax-based regimens, see text in addition.

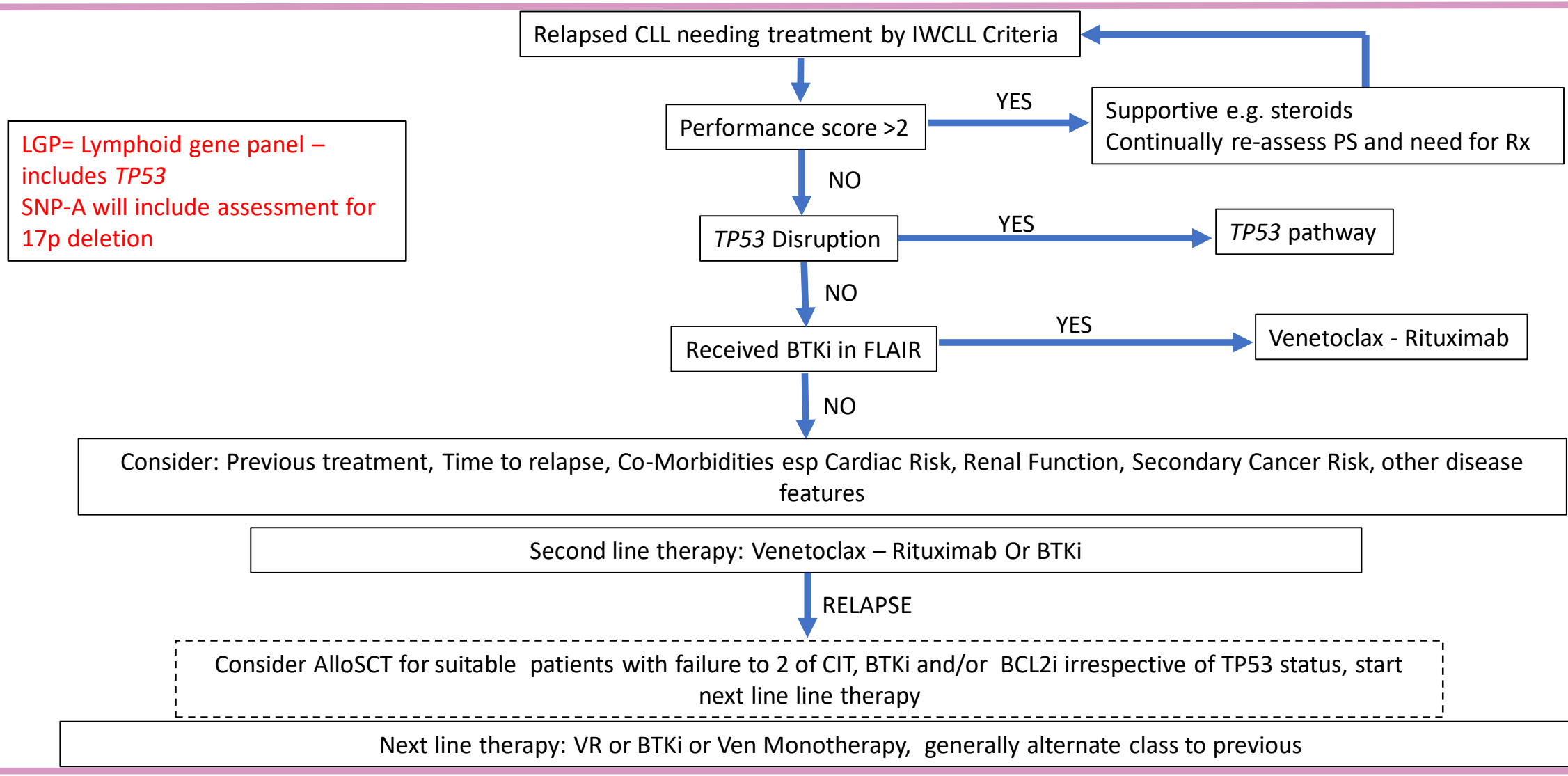
KHP CLL first-line management
(as per licence)

- LGP= Lymphoid gene panel – includes *TP53*
- SNP-A will include assessment for 17p deletion



Acalabrutinib: Only for "FCR/BR unsuitable"

RELAPSE Management: Second line and beyond



LGP= Lymphoid gene panel – includes *TP53*
SNP-A will include assessment for 17p deletion

NHSE currently funded treatments (this version November 2022)

TP53 Management

TP53 Disruption at first line of therapy

1st line de novo *TP53* disrupted CLL needing treatment by IWCLL Criteria

↓

BTKi (Preferred)
or
Venetoclax-O
or
Idelalisib-R
or
Venetoclax Monotherapy
(only if BCRi contra-indicated)

↓ RELAPSE

Consider AlloSCT after failure of first line BTKi or BCL2i, start 2nd line therapy

TP53 Disruption emerging during therapy

Relapsed *TP53* disrupted CLL needing treatment by IWCLL Criteria
(previously negative)

↓

BTKi (Preferred)
or
Venetoclax-R
or
Idelalisib-R
or
Venetoclax Monotherapy
(only if BCRi contra-indicated or progressed on either BTKi or PI3Ki)

↓ RELAPSE

Consider AlloSCT after failure of 2 of CIT, BTKi and/or BCL2i, start next line of therapy

Sequencing of targeted inhibitors

RELAPSED THERAPY	SUGGESTED SEQUENCE
BTKi relapse	→BCL2i* or PI3Ki***
PI3Ki relapse	→BTKi or BCL2i
BCL2i/BTKi relapse	→PI3Ki or AlloSCT or clinical trial
BCL2i/BTKi/PI3Ki relapse	→ AlloSCT or clinical trial
Venetoclax Obinutuzumab	→BTKi or Venetoclax Rituximab**or PI3Ki***
Venetoclax mono relapse	→BTKi or PI3Ki***
Venetoclax Rituximab relapse**	→BTKi or Venetoclax monotherapy or PI3Ki***

*the only sequence with phase 3 clinical trial evidence
**as long as the patient have not relapsed whilst on Venetoclax combination treatment and had at least 12 months remission
*** BTKi or BCL2 are the preferred options in those naive to those classes
BTKi: Bruton tyrosine kinase inhibitors; Ven O: Venetoclax Obinutuzumab;
VenR: Venetoclax-Rituximab regimen; PI3K: Phosphatidylinositol-3 kinase inhibitor
AlloSCT, allogeneic Stem Cell Transplantation

Recommended TLS Prophylaxis based on tumour burden in patients with CLL when using venetoclax (SMPC)

Tumour burden		Prophylaxis		Blood chemistry monitoring[c,d]
		Hydration[a]	Anti-hyperuricaemics[b]	Setting and frequency of assessments
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent dose increases: Pre-dose
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent dose increases: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalisation for patients with CrCl <80ml/min; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 ml/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours Outpatient • For subsequent dose increases: Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; CrCl = creatinine clearance; LN = lymph node.

[a]Instruct patients to drink water daily starting 2 days before and throughout the dose-titration phase, specifically prior to and on the days of dosing at initiation and each subsequent dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.

[b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.

[c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.

[d]At subsequent dose increases, monitor blood chemistries at 6 to 8 hours and at 24 hours for patients who continue to be at risk of TLS.

https://www.medicines.org.uk/emc/product/10476/smpc

Venetoclax dose escalation algorithms at weekly ramp up

All LN <5 cm
AND
ALC <25 x10^9/L

Low Risk (Outpatient pathway)

D-1
- Bloods in Outpatient Department
- Checked by CNS

D1
- Venetoclax at home
- Oral fluids + allopurinol

D2
- 24hr bloods in Outpatient Department*
- Checked by CNS

*Mandatory at 20mg and 50mg dose

1. Venclyxto SmPC. https://www.medicines.org.uk/emc/product/10041/smpc#gref – Accessed November 2022

Any LN 5 cm to <10 cm
OR
ALC ≥25 x10^9/L

Medium Risk (Ambulatory pathway)

D-1
- Bloods in Outpatient Department/Ambulatory
- Bloods checked by Ambulatory team

D1
- Attend ambulatory
- Rasburicase (prescribed on Mosaiq) +/- IVI and venetoclax

D2
- 24 hr bloods in Ambulatory*

Use of single dose rasburicase +/- IVI in ambulatory setting is sufficient to mitigate TLS risk, with blood check at 24 hr only needed.

*Mandatory at 20mg and 50 mg dose

1. Venclyxto SmPC. https://www.medicines.org.uk/emc/product/10041/smpc#gref – Accessed November 2022

High Risk (Inpatient pathway)

Any LN ≥10 cm
OR
ALC ≥25 x10^9/L
AND
any LN ≥5 cm

D-1
- Bloods in Outpatient Department

D1
- Admit for IVI hydration o/n + rasburicase
- 12hr bloods

D2
- 24hr bloods +/- discharge

Audit revealed no TLS at 6 hrs, therefore suggest no need to assess TLS bloods prior to 12 hrs post 1st dose

*Re-assess risk before 100mg dose- ?appropriate for ambulatory pathway

1. Venclyxto SmPC. https://www.medicines.org.uk/emc/product/10041/smpc#gref – Accessed November 2022

High Risk Pts

Can downgrade if suitable

- At 100 mg and beyond re-assess risk
- If WCC <25 can downgrade;
  - Use Allopurinol
  - Oral fluids
  - Suggest bloods day before, patient take venetoclax at home at 6AM and attends for 6-8 hr bloods at midday
  - Can drop 24 hr blood assessments

Ven-O pathway at KCH

1. Obinutuzumab x 3 doses
2. CT NCAP
3. Risk stratify