HOVON 140 tricks and tips

1. **Step 1:** Determine specific risks per arm (table 1)

Study arm	Study drugs	IRR risk*	TLS risk
1	FCR / BR	Unlikely	Unlikely
2	Ven+R	Unlikely	Likely if high risk category (see Table 2)
3	Ven+Obi	Likely	Likely if high risk category (see Table 2)
4	Ven+Obi+Ibrut	Likely	Likely if high risk category (see Table 2)

Table 1
IRR = Infusion related reaction
TLS = Tumor Lysis Syndrome

**Obinutuzumab-related IRR is very common, specifically at day 1 of the first gift. See Table 2 for dosing:*

Treatment day	dosage	Infusion rate
1	100 mg	Fixed infusion rate: 25 mg/h over approximately 4 hours. Infusion rate may not be increased.
2	900 mg	Starting infusion rate: 50 mg/h. Infusion rate can be escalated in increments of 50 mg/h approximately every 30 minutes to a maximum rate of 400 mg/hr.
All other	1000 mg	Starting infusion rate: 100 mg/h. Infusion rate can be escalated in increments of 100 mg/h approximately every 30 minutes to a maximum rate of 400 mg/h.

Table 2

Supportive treatment in case of IRR

In case of IRR, the following measures should be considered depending on the severity of the IRR:

- acetaminophen/paracetamol 1000 mg if not administered during the last 4 hrs.
- antihistamines including a H1- (e.g. dimetindene 4 mg i.v.) and a H2-antagonist (e.g. ranitidine 50mg i.v.) if not yet administered during the last 4 hrs.
- prednisolone or prednisone 100 mg i.v. in case of urticarial, bronchospasm and dyspnea
- intravenous fluids
- bronchodilators and oxygen in case of bronchospasm and dyspnea
- vasopressors in case of hypotension

2. **Step 2:** In case of arm 2-4 (venetoclax), determine TLS risk category **DIRECTLY PRIOR** to venetoclax intake (table 3)

TLS risk category	***Largest diameter of all measurable lymph nodes****		***Absolute lymphocyte count (ALC)*** **		
Low	<5 cm	AND	< 25 x 10^9/L		
Intermediate	≥ 5 and < 10 cm	OR	≥ 25 x 10^9/L		
High	≥ 5 and < 10 cm	AND	≥ 25 x 10^9/L		
	> 10 cm		Irrelevant		
	≥ 5 and < 10 cm	OR	≥ 25 x 10^9/L	AND	Creatinine clearance < 80 ml/min
	Irrelevant		Irrelevant		Signs of chemistry TLS
	Irrelevant		Irrelevant		Massive splenomegaly (≥20cm)

Table 3
*As measured by CT at baseline
** As measured minimum one day before first venetoclax gift

3. **Step 3:** Venetoclax guidance during ramp-up based on TLS risk profile (table 3)

Venetoclax ramp-up

Due to the risk of adverse events, especially tumor-lysis-syndromes (TLS), the dose of venetoclax will be increased slowly every week until the final dose of 400 mg is reached (ramp-up).

Venetoclax p.o.:

- Cycle 1: Days 22-28: venetoclax 20 mg (2 tabl. at 10 mg)
- Cycle 2 Days 1-7: venetoclax 50 mg (1 tabl. at 50 mg)
- Days 8-14: venetoclax 100 mg (1 tabl. at 100 mg)
- Days 15-21: venetoclax 200 mg (2 tabl. at 100 mg)
- Days 22-28: venetoclax 400 mg (4 tabl. at 100 mg)
- Cycles 3-12: Days 1-28: venetoclax 400 mg (4 tabl. at 100 mg)

All patients must receive the intended dose of venetoclax for at least 7 days before increasing to the next ramp-up dose.

Safety measures for TLS prophylaxis during venetoclax ramp-up (20 mg, 50 mg, 100 mg, 200 mg and 400 mg)

TLS risk	***Low-risk***	***Intermediate-risk***	***High-risk***
Hospitalization	No	No	Yes for first day 20mg and 50mg; continue at higher dose if TLS was present
TLS Laboratory assessments (K, phosphate, Calcium, Kreat, Uric acid, LDH)	Pre-dose, post-dose 6-8hrs, post-dose 24hrs Extra for pts at home: pre-dose 24hrs, post-dose 2hrs	Pre-dose, post-dose 6-8hrs, post-dose 24hrs Extra for pts at home: pre-dose 24hrs, post-dose 2hrs	Pre-dose, post-dose 6-8hrs, post-dose 24hrs
Hydration			
- Oral hydration (>2 l/24hrs)	Yes	Yes	No
- Intravenous (>2 l/24hrs)	No	No	Yes (20mg, 50mg)
Uric acid reducer			
- Allopurinol (start 2-3 days pre-dose)	Yes	Yes	Yes
- Rasburicase	No	No	Yes

Table 4

4. **Step 4:** How to handle in case of lab changes

Further actions need to be taken in case of:

- potassium increase by ≥0.5mmol/l from baseline and/or any potassium value >5.0 mmol/L
- phosphorus increase of >0.162 mmol/L and >1,454 mmol/L
- any other significant laboratory change, especially electrolyte imbalances

These actions should be according to the institutional practice and include but are not limited to:

- discontinuation of administration of venetoclax, no further dosage should be taken until resolution
- hospitalization for more aggressive monitoring (especially regular laboratory assessments, telemetry/ECG monitoring, observation for signs/symptoms of tumor lysis syndrome (e.g. fever, chills, tachycardia, nausea/vomiting, diarrhea, sweating, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures)
- administration of intravenous fluids at a rate of ≥1 ml/kg/h (≥50 ml/hr., target 150 to 200 ml/hr.; as clinically appropriate)
- in case the diagnosis of TLS is established, further measures, such as administration of rasburicase (Fasturtec®) as per institutional practice should be considered
- consultation of nephrology (or acute dialysis service) to ensure emergency dialysis is available

Please note: A rapidly rising serum potassium level is a medical emergency.

5. **Step 5:** when to apply dose venetoclax modification (Table 5)

Hematologic toxicity (unless directly attributable to the underlying CLL)	
Event	***Dose delay or dose modification***
Neutropenia (with or without fever and infection) CTC Grade 3 or 4	• If afebrile neutropenia occurs during ramp-up, G-CSF or growth factors should be administered andramp should continue if neutro-penia improves with growth factors • If neutropenia is occurring after ramp-up during the treatment with-hold of venetoclaxfor 7 days is due to the investigator´s discretion - Administer G-CSF or growth factors for neutropenia as indicated - When counts recover to ANC ≥ 1 x10^9/l resume venetoclax at one dose level reduction
Thrombocytopenia CTC Grade 4 and/or symptomatic bleeding	• If thrombocytopenia grade 4 occures during ramp-up consider platelet transfusion, but continue with ramp if clinically possible. • If thrombocytopenia grade 4 occurs after ramp-up withhold veneto-clax - Platelets may be transfused at the discretion of the investigator - When platelet level rises to > 50x10^9/l without transfusional support for 5 consecutive days, restart venetoclax at **previous dose** - Patients with thrombocytopenia due to CLL infiltration in bone mar-row prior to start of therapy should achieve at least baseline levels - When platelet level does not rise to > 50x10^9/l or to baseline level in patients with preexisting thrombocytopenia within 28 days, restart venetoclax at **one dose level reduction** *For a second episode*: o Withhold venetoclax o When platelet level rises to > 50 x10^9/l without transfusional support for 5 consecutive days, restart venetoclax at **one dose level reduction** *For subsequent episodes*: o Withhold venetoclax o When platelet level rises to > 50 x10^9/l without transfu-sional support for 5 consecutive days, restart veneto-clax at **one dose level reduction** For *recurrent episodes* please consult the GCLLSG study office.

Non-hematologic events (e.g. infections)	
CTC Grade	***Dose delay or dose modification***
Grade 3 or 4	• Delay venetoclax for a maximum of 28 days. • *First episode*: If improvement to Grade ≤ 1 or baseline, re-sume **previous doses** of venetoclax. • For *subsequent episodes*: If improvement to Grade ≤ 1 or baseline, restart venetoclax at **one dose level reduction**. *Certain treatment emergent non-hematologic adverse events (e.g., venous thromboembolic events) may be managed and become clinical-ly stable following medical intervention but may not improve to Grade ≤ 1 according to the NCI CTCAE definitions. In such cases resumption of study drug may be possible after consultation with the GCLLSG study office.*
Grade 2	• Delay venetoclax for a maximum of 28 days. • *First episode*: If improvement to Grade ≤ 1 or baseline, re-sume **previous doses** of venetoclax. • For *subsequent episodes*: If improvement to Grade ≤ 1 or baseline, restart venetoclax at **one dose level reduction**. • *Certain treatment emergent non-hematologic adverse events (e.g., venous*

	thromboembolic events) may be managed and become clin-ically stable following medical intervention but may not improve to Grade ≤ 1 according to the NCI CTCAE definitions. In such cases resumption of study drug may be possible after consultation with the GCLLSG study office.
Grade 1	• No dose reduction or delay

Table 5