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CHRONIC LYMPHOCYTIC LEUKEMIA

Venetoclax–Obinutuzumab Dosing Regimen

This is a medical resource for scientific information and is intended for healthcare providers practicing in the United States

Current as of December 2024

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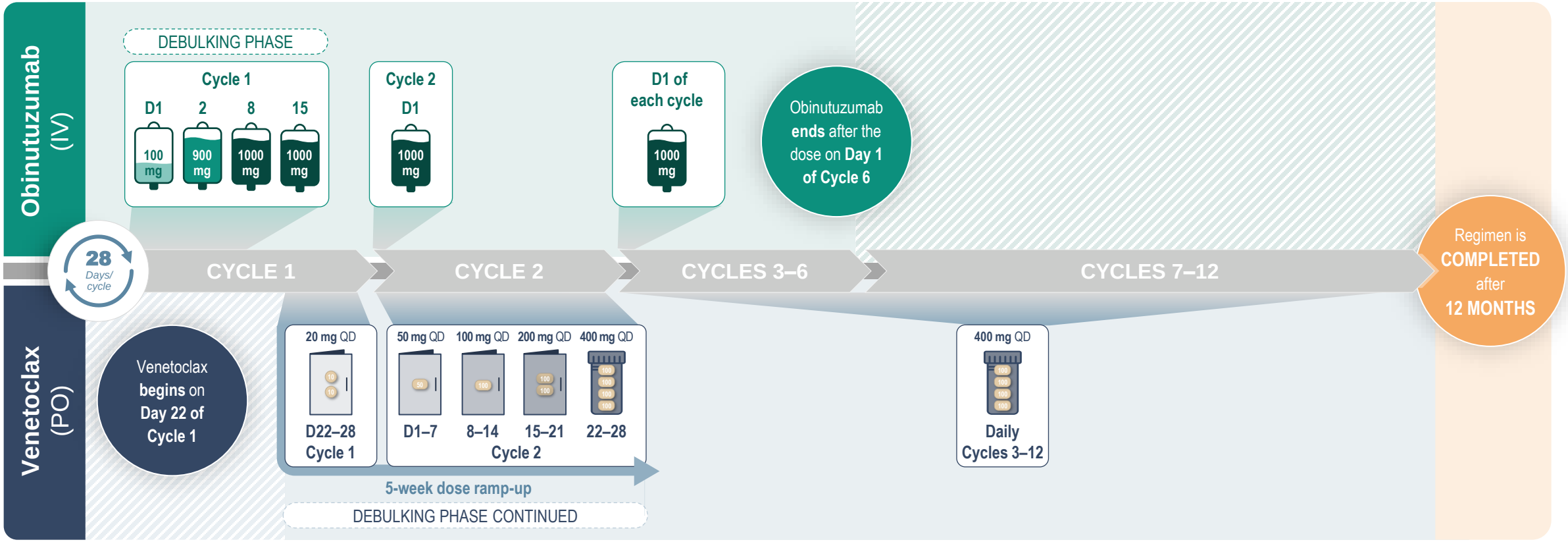
VENETOCLAX–OBINUTUZUMAB FIRST-LINE DOSING SCHEDULE OVERVIEW



Graphic is not to scale. Each cycle is 28 days.
D=day; IV=intravenous; PO=oral; QD=once daily.
1. VENCLEXTA [prescribing information]. South San Francisco, CA: Genentech, Inc. 2. Fischer K, et al. *N Engl J Med*. 2019;380:2225–2236 (protocol).

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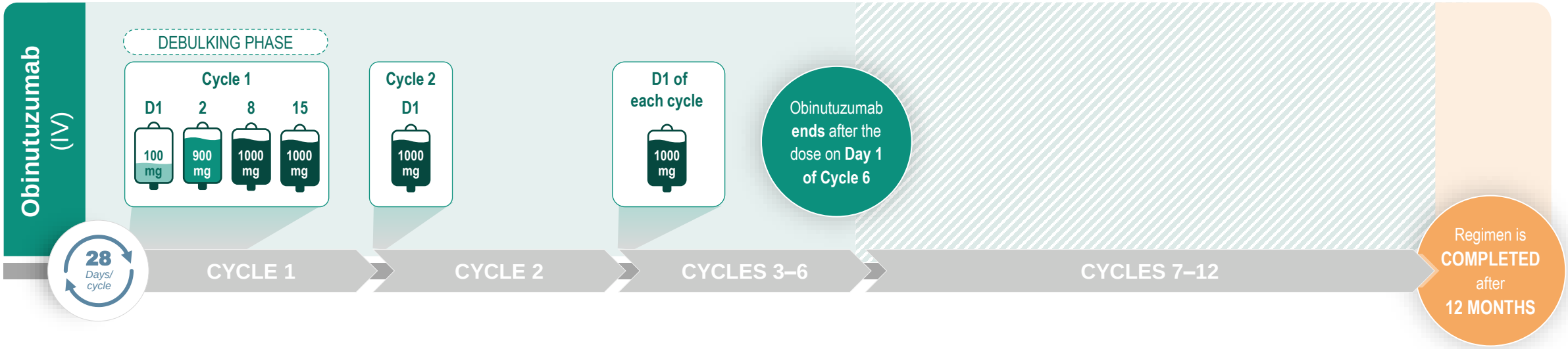
Obinutuzumab Infusions

CYCLES 1 THROUGH 6: OBINUTUZUMAB INFUSIONS



Premedications to Reduce IRRs | Dosing Schedule and Infusion Rates | IRR Management | Tumor Lysis Syndrome Prophylaxis | Neutropenia Management

ALC=absolute lymphocyte count; IRR=infusion-related reaction.

1. GAZYVA [prescribing information]. South San Francisco, CA: Genentech, Inc. 2. Fischer K, et al. *N Engl J Med*. 2019;380:2225–2236 (protocol).

OBINUTUZUMAB PREMEDICATIONS TO REDUCE IRRs

ANTIPYRETIC

DOSAGE
Acetaminophen **650 mg to 1000 mg PO**

ADMINISTRATION
At least **30 minutes before infusion**

30 MIN

Cycles 1–6: All patients

ANTIHISTAMINE

DOSAGE
Diphenhydramine **50 mg PO/IV** or equivalent

ADMINISTRATION
At least **30 minutes before infusion**

30 MIN

Cycle 1, Days 1 and 2: All patients

Cycle 1, Days 8 and 15; Cycles 2–6:

Patients with a Grade 1–3 IRR with the previous infusion *OR* with a lymphocyte count >25×10^9/L prior to next treatment.

CORTICOSTEROID

DOSAGE
Dexamethasone **20 mg IV** *or* methylprednisolone **80 mg IV**[a]

ADMINISTRATION
Completed at least **1 hr prior to infusion**

1 HR

Cycle 1, Days 1 and 2: All patients

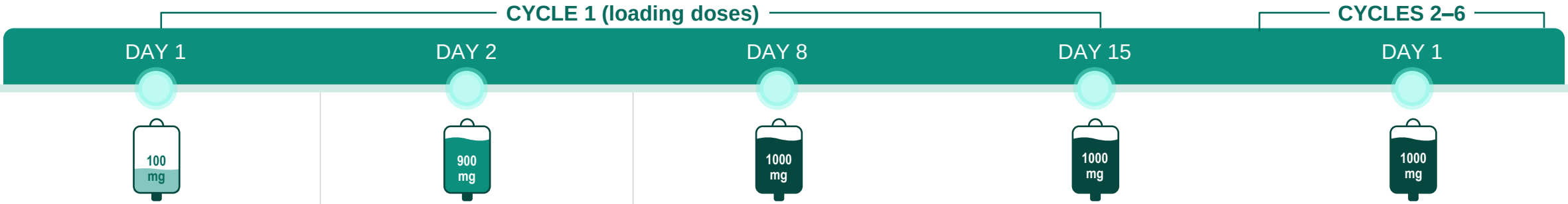
Cycle 1, Days 8 and 15; Cycles 2–6:

Patients with a Grade 3 IRR with the previous infusion *OR* with a lymphocyte count >25×10^9/L prior to next treatment.

Hypotension may occur during infusions. Consider withholding antihypertensive treatments for 12 hrs prior to and throughout each infusion and for the first hr after administration.

[a]Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions.
hr=hour.
1. Goede V, et al. *N Engl J Med*. 2014;370:1101–1110. 2. GAZYVA [prescribing information]. South San Francisco, CA: Genentech, Inc.

OBINUTUZUMAB DOSING SCHEDULE AND INFUSION RATES



- Administer at 25 mg/hr over 4 hrs. Do not increase the infusion rate

- If no IRR occurred during the previous infusion, administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
- If an IRR occurred during the previous infusion, administer at 25 mg/hr. The rate of infusion can be escalated in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr

- If no IRR occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
- If an IRR occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr

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MANAGEMENT OF INFUSION-RELATED REACTIONS

Grade of IRRs[a]	Guidance
Grade 1–2 Mild to moderate	• Slow or hold infusion • Give supportive treatment • Upon symptom resolution, may continue or resume infusion **Note:** The Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hr but not increased further.
Grade 3 Severe	• Hold infusion • Give supportive treatment • Upon symptom resolution, may resume infusion at no more than half the previous rate (at the time the IRR occurred) • If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose **Note:** If the same adverse event recurs with the same severity, treatment must be permanently discontinued. The Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hr but not increased further.
Grade 4 Life-threatening	• Discontinue infusion immediately • Treat symptoms aggressively • Do not restart drug

In the event of an IgE-mediated anaphylactic reaction, obinutuzumab should be discontinued and no additional obinutuzumab should be administered.

[a]Refer to National Cancer Institute Common Terminology Criteria for Adverse Events for grading of symptoms. Ig=immunoglobulin.

1. Goede V, et al. *N Engl J Med*. 2014;370:1101–1110. 2. GAZYVA [prescribing information]. South San Francisco, CA: Genentech, Inc.

TUMOR LYSIS SYNDROME PROPHYLAXIS

Patients with high tumor burden, high circulating absolute lymphocyte counts (greater than 25 x 10^9/L), or renal impairment are **considered at risk of tumor lysis syndrome and should receive prophylaxis.**

PROPHYLAXIS

ADEQUATE HYDRATION

Hydration of ~3 liters per day, **1–2 days prior to first infusion**

ANTIHYPERURICEMICS

Start allopurinol or rasburicase **12–24 hrs prior to first infusion**

Continue prophylaxis prior to each subsequent infusion, as needed.

LABORATORY PARAMETERS

Monitor laboratory parameters of **patients considered at risk for TLS** during **initial days of treatment**

FOR PATIENTS WITH TLS

Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated

Please see **additional TLS prophylaxis considerations** for venetoclax administration.

TLS=tumor lysis syndrome.

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MANAGEMENT OF NEUTROPENIA

Grade of Neutropenia[a]	Guidance	
Grade 3–4 Severe to life-threatening	• Monitor patients frequently with regular laboratory tests until resolution • Anticipate, evaluate, and treat any symptoms or signs of developing infection • Consider dose delays • Consider administration of G-CSF	• Patients with Grade 3 or 4 neutropenia lasting more than 1 week are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2 • Consider antiviral and antifungal prophylaxis

[a]Refer to National Cancer Institute Common Terminology Criteria for Adverse Events for grading of symptoms. G-CSF=granulocyte colony-stimulating factors.
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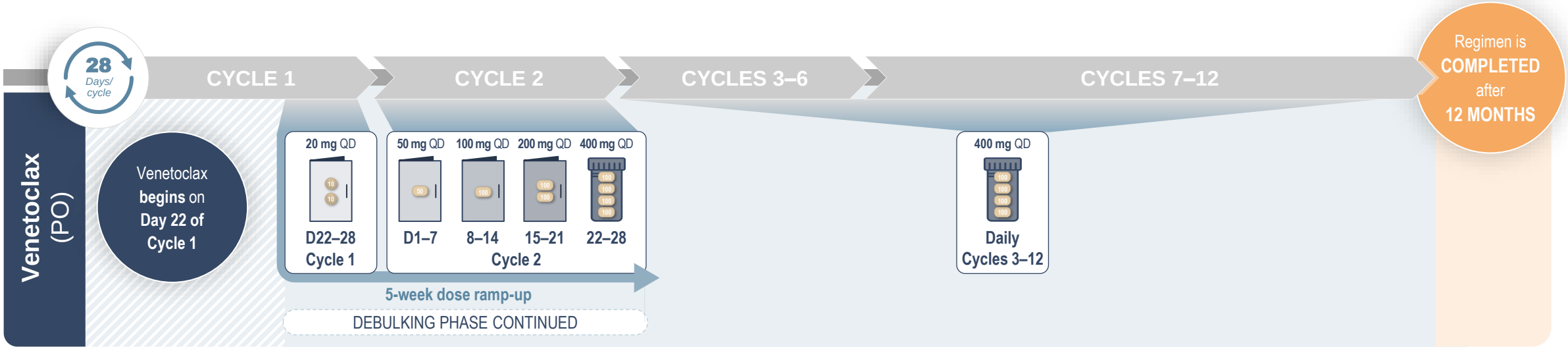
Venetoclax Ramp-Up

VENETOCLAX RAMP-UP



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PREPARING FOR VENETOCLAX RAMP-UP

All patients

TLS risk assessment

Reassess tumor burden (repeat ALC) and recategorize TLS risk as appropriate

Hydration

Ensure adequate hydration every day during venetoclax ramp-up and with resumption after an interruption

Blood chemistry

Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities

Drug interactions

Determine if the patient is taking any medications that interact with venetoclax, which may require an alternative medication or venetoclax dose modification

Patients with hepatic impairment (Child-Pugh class C)

Dose modification

Determine if venetoclax daily dose should be reduced by 50% for patients with hepatic impairment

Please see **additional TLS prophylaxis considerations** for obinutuzumab administration.

- Low/medium tumor burden/TLS risk
- High tumor burden/TLS risk

Click for details on prophylaxis and monitoring by tumor burden/TLS risk.

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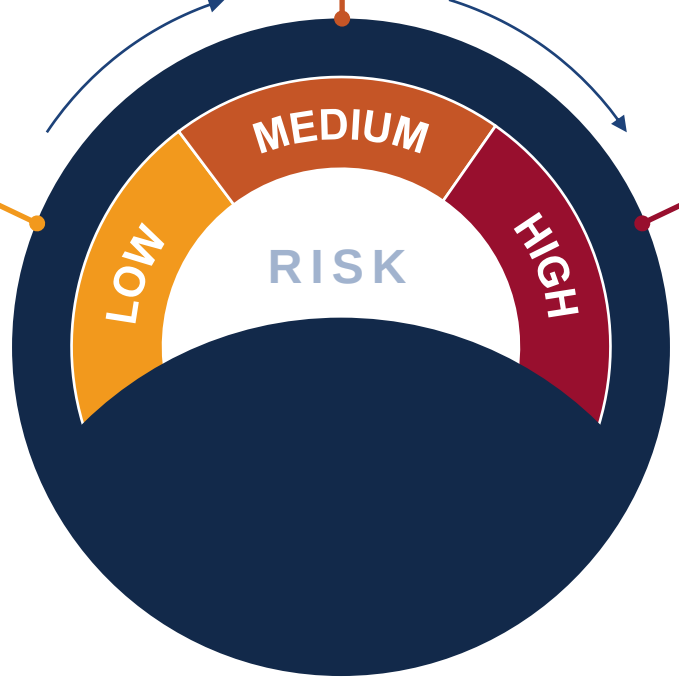
TUMOR BURDEN AND TLS RISK ASSESSMENT

Any lymph nodes 5 cm to <10 cm
OR
ALC ≥25×10^9/L



All lymph nodes <5 cm
AND
ALC <25×10^9/L

Any lymph node ≥10 cm
OR
Any lymph node ≥5 cm
AND **ALC ≥25×10^9/L**

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VENETOCLAX RAMP-UP: LOW OR MEDIUM TUMOR BURDEN/TLS RISK

CYCLE 1, DAY 22 THROUGH END OF CYCLE 2

	20 mg QD	50 mg QD	100 mg QD	200 mg QD	400 mg QD
	D22–28 *Cycle 1*	1–7 *Cycle 2*	8–14	15–21	22–28
TLS prophylaxis					
Hydration	1.5–2.0 L/day PO[a] throughout the ramp-up phase beginning **at least** 2 days prior to and continuing for at least 24 hrs after the first dose of each dose level. **For patients with medium tumor burden:** Consider IV hydration in addition to oral hydration during outpatient stay for the first doses of 20 mg and 50 mg.				
Antihyperuricemic	Allopurinol 300 mg/day beginning **at least** 2 days prior to initiation of venetoclax and continuing until ramp-up is completed (Cycle 3, Day 1).				
Laboratory monitoring on the first day of each dose level					
Setting	Outpatient **For patients with medium tumor burden and CrCl<80 mL/min:** Consider hospitalization for the first venetoclax doses of 20 mg and 50 mg. For these patients, follow the TLS prophylaxis and monitoring plan for high tumor burden.				
Blood chemistry tests	Pre-dose, 6−8 hrs, and 24 hrs	Pre-dose, 6−8 hrs, and 24 hrs	Pre-dose	Pre-dose	Pre-dose

[a]Administer IV hydration for any patient who cannot tolerate oral hydration.
CrCl=creatinine clearance.

1. VENCLEXTA [prescribing information]. South San Francisco, CA: Genentech, Inc. 2. Fischer K, et al. *N Engl J Med*. 2019;380:2225–2236 (protocol).

VENETOCLAX RAMP-UP: HIGH TUMOR BURDEN/TLS RISK

CYCLE 1, DAY 22 THROUGH END OF CYCLE 2

	20 mg QD	50 mg QD	100 mg QD	200 mg QD	400 mg QD
	D22–28 *Cycle 1*	1–7 *Cycle 2*	8–14	15–21	22–28
TLS prophylaxis					
Hydration	1.5–2.0 L/day PO[a] throughout the ramp-up phase beginning **at least** 2 days prior to and continuing for at least 24 hrs after the first dose of each dose level. *AND* IV hydration 150−200 mL/hr as tolerated prior to the first dose of each dose level.				
Antihyperuricemic	Allopurinol 300 mg/day beginning **at least** 2 days prior to initiation of venetoclax and continuing until ramp-up is completed (Cycle 3, Day 1). Consider rasburicase for elevated uric acid (>8 mg/dL).				
Laboratory monitoring on the first day of each dose level					
Setting	Hospital	Hospital	Outpatient	Outpatient	Outpatient
Blood chemistry tests	Pre-dose, 4, 8, 12, and 24 hrs	Pre-dose, 4, 8, 12, and 24 hrs	Pre-dose, 8 hrs, and 24 hrs	Pre-dose, 8 hrs, and 24 hrs	Pre-dose, 8 hrs, and 24 hrs

[a]Administer IV hydration for any patient who cannot tolerate oral hydration.

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Dose Modifications for Drug Interactions and Adverse Reactions

VENETOCLAX DOSE MODIFICATIONS FOR DRUG INTERACTIONS

COADMINISTERED DRUG	INITIATION AND RAMP-UP PHASE	STEADY DAILY DOSE (post ramp-up phase)[a]
Posaconazole	Contraindicated	Reduce to 70 mg
Other strong CYP3A inhibitor	Contraindicated	Reduce to 100 mg
Moderate CYP3A inhibitor	Reduce by at least 50%	Reduce by at least 50% (to 200 mg or less)
P-gp inhibitor	Reduce by at least 50%	Reduce by at least 50% (to 200 mg or less)

[a]Consider alternative medications or reduce the venetoclax dose as described.
CYP3A=cytochrome P450, family 3, subfamily A; P-gp=P-glycoprotein.
VENCLEXTA [prescribing information]. South San Francisco, CA: Genentech, Inc.

DOSE MODIFICATIONS FOR ADVERSE REACTIONS (1 of 2)

Adverse reaction	Occurrence	Venetoclax dose modification	Obinutuzumab dose modification (Cycles 1–6)
Hematologic adverse reactions			
Grade 3 neutropenia with infection or fever OR **Grade 4 hematologic toxicities (except lymphopenia)**	1st occurrence	• Interrupt venetoclax • Upon resolution to Grade 1 or baseline level, resume venetoclax at the same dose	• Withhold obinutuzumab • Upon resolution, resume obinutuzumab at the same dose • See also Management of Neutropenia under Obinutuzumab Infusions section
	2nd and subsequent occurrences	• Interrupt venetoclax • Upon resolution, resume venetoclax at the reduced dose[a]	
Non-hematologic adverse reactions			
Grade 2 non-hematologic toxicities	Any occurrence	• Delay venetoclax and obinutuzumab • Upon resolution to Grade ≤1 or baseline, resume at same doses	
Grade 3 or 4 non-hematologic toxicities	1st occurrence	• Interrupt venetoclax • Upon resolution to Grade 1 or baseline level, resume venetoclax at the same dose	• Delay obinutuzumab • Upon resolution to Grade 1 or baseline, resume obinutuzumab at the same dose
	2nd and subsequent occurrences	• Interrupt venetoclax • Upon resolution, resume venetoclax at the reduced dose[a]	

[a]See next slide for dose reductions.

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DOSE MODIFICATIONS FOR ADVERSE REACTIONS (2 of 2)

Adverse reaction	Occurrence	Venetoclax dose modification
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	**Any occurrence**	• Withhold the next day's dose. If resolved within 24–48 hrs of last dose, resume at the same dose • For any blood chemistry changes requiring more than 48 hrs to resolve, resume at the reduced dose • For any events of clinical TLS, resume at the reduced dose following resolution

Consider discontinuing venetoclax for patients who require dose reductions to less than 100 mg for more than 2 weeks.

Venetoclax dose at interruption, mg	Venetoclax restart dose, mg[a,b]
400	300
300	200
200	100
100	50
50	20
20	10

[a]During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose. [b]If a dosage interruption lasts more than 1 week during the ramp-up phase or more than 2 weeks after completion of ramp-up, reassess the risk of TLS and determine if reinitiation at a reduced dosage is necessary.

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