Management of the elderly unfit CLL patient treated with Venetoclax Obinutuzumab

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REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Roma, 11 aprile 2024
UNAHOTELS Decò

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					x		x
AstraZeneca					x		x
Beigene							x
Johnson & Johnson					x		x

Clinical presentation

Female, **79 years**, CLL stage A/I at diagnosis in 2010 → wait and watch

Comorbidities: thalassaemia trait, AF undergoing treatment, hypertension under control with 2 antiipertensive drugs, osteoporosis with vertebral fractures, total thyroidectomy for thyroid nodules, appendectomy, tonisillectomy, benign gastric polyp removal, allergy to NSAIDs, penicillins and cephalosporins
→ **CIRS 9**

February 2022

CBC: WBC 40.360/mmc, ANC 5.000/mmc, ALC 34.100/mmc, Hb 10,1 g/dl, MCV 69, fl, Plts 144.000/mmc

Abdominal ultrasound: Splenomegaly 15 cm. Hepatic steatosis. Renal cyst 10 x 6.7 cm.

August 2022

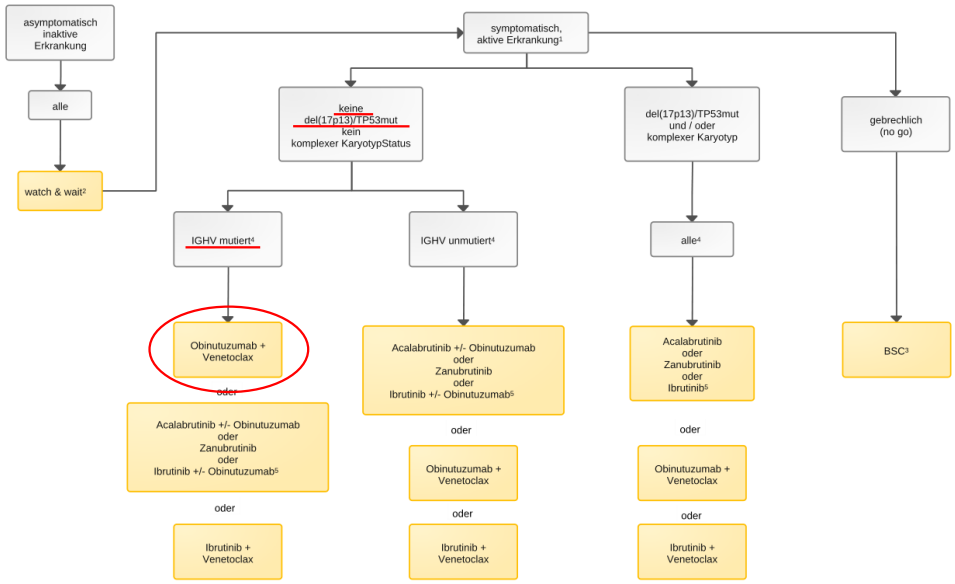
CBC: WBC 55.630/mmc, ANC 5.500/mmc, ALC 49.300/mmc, Hb 9,9 g/dl, MCV 69,6 fl, Plts 96.000/mmc

Abdominal ultrasound: Splenomegaly 20 cm. Hepatic steatosis. Renal cyst 10 x 6.7 cm.

IGHV mutated 3-07, TP53 wild type, BIRC3 mutated, FISH positive for del13q, negative for del17p, del11q, tris12

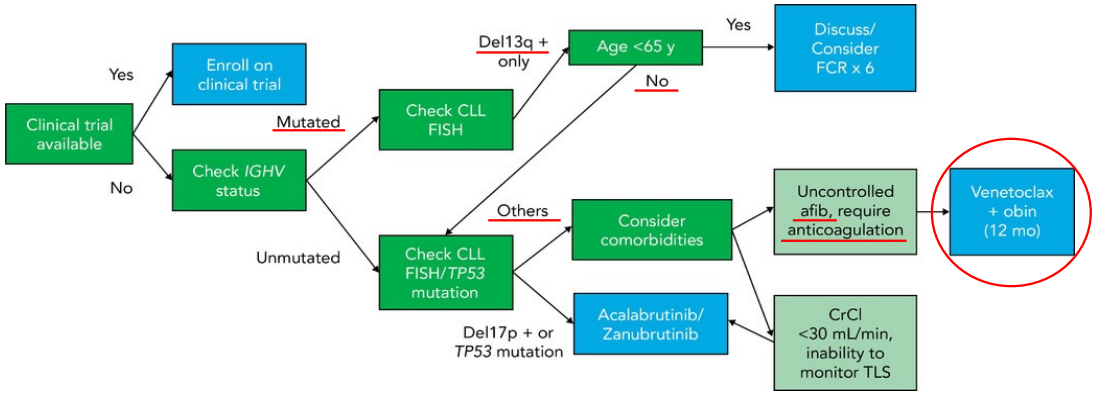
Treatment choice

ONKOPEDIA 2023



Onkopedia guidelines update: Clemens-Martin Wendtner, Othman Al-Sawaf, Mascha Binder, et al. Chronische Lymphatische Leukämie (CLL).

NCCN 2023



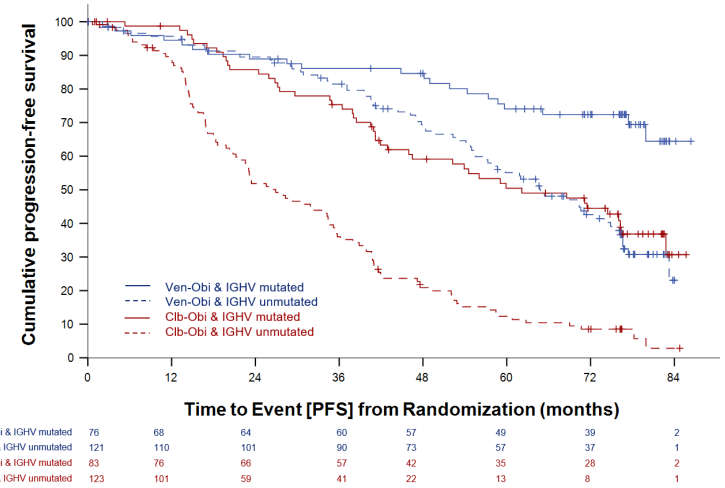
NCCN Guidelines Update: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. J Natl Compr Canc Netw. 2023;21(5.5):563-566

Treatment choice

CLL14 6-year update

PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months

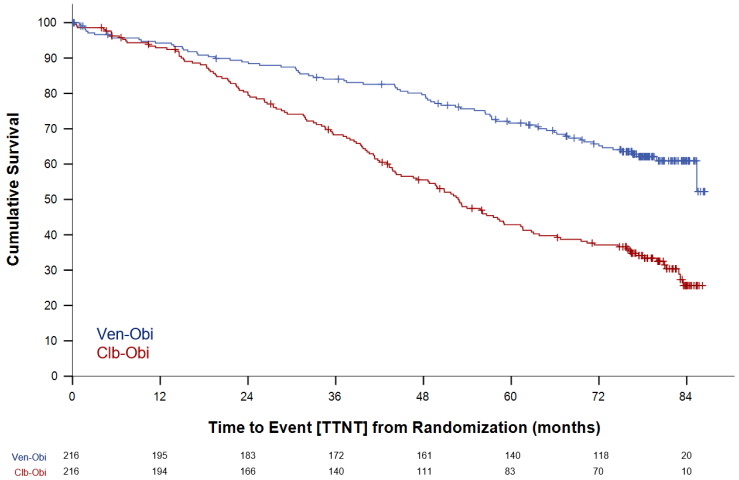


Median PFS
Ven-Obi & IGHVmut: NR
Ven-Obi & IGHVunmut: 64.8 m
HR 0.38, 95%CI [0.23-0.61], p<0.001

Clb-Obi & IGHVmut: 62.2 m
Clb-Obi & IGHVunmut: 26.9 m
HR 0.33, 95% CI [0.23-0.47], p<0.001

TIME TO NEXT TREATMENT

Defined as time to death or next-antileukemic treatment



Median TTNT
Ven-Obi: not reached
Clb-Obi: 52.9 m

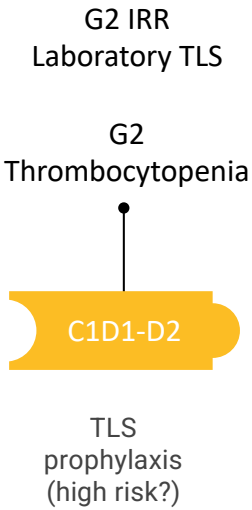
6-year TTNT rate
Ven-Obi: 65.2%
Clb-Obi: 37.1%

Next anti-leukemic therapy:
Ven-Obi: 67 PDs – 39 NLT
Clb-Obi: 141 PDs – 103 NLT

HR 0.44, 95% CI [0.33-0.58]
P<0.0001

Al-Sawaf O, et al. EHA 2023. Abstract S145 (Oral).

Treatment journey



❖ Infusion related reaction (IRR) on C1D1 and C1D2

Fever, chills and hypotension resolved with steroids and IV fluids

❖ Laboratory tumor lysis syndrome (TLS risk: intermediate)

ALC before treatment 49500/mmc, no lymphadenopathies >5 cm, BUT splenomegaly 20cm
Hyperuricemia and hypocalcemia treated with rasburicase and calcium supplementation

❖ G2 Thrombocytopenia

Drop in platelet count 54000/mmc, BUT only transient and self-resolved by C1D8
Absence of non-overt disseminated intravascular coagulation
No need to withhold anticoagulant therapy

Safety concerns

Table S6. Overview of adverse events with an incidence rate of ≥10% of patients in either treatment group (safety population).

Adverse events	Venetoclax–obinutuzumab (N=212)	Chlorambucil–obinutuzumab (N=214)
At least one adverse event – no. of patients (%)	200 (94.3)	213 (99.5)
Adverse events with an incidence rate of ≥10% in any treatment group – no. of patients (%)		
Blood and lymphatic system disorders	145 (68.4)	137 (64.0)
Neutropenia*	122 (57.5)	122 (57.0)
Thrombocytopenia	51 (24.1)	50 (23.4)
Anemia	35 (16.5)	40 (18.7)
Injury, poisoning, and procedural complications	95 (44.8)	110 (51.4)
Infusion-related reaction	95 (44.8)	110 (51.4)
Gastrointestinal disorders	89 (42.0)	74 (34.6)
Diarrhea	59 (27.8)	32 (15.0)
Nausea	40 (18.9)	46 (21.5)
Constipation	28 (13.2)	19 (8.9)
General disorders and administration site conditions	68 (32.1)	60 (28.0)
Pyrexia	48 (22.6)	33 (15.4)
Fatigue	32 (15.1)	30 (14.0)
Respiratory, thoracic, and mediastinal disorders	34 (16.0)	25 (11.7)
Cough	34 (16.0)	25 (11.7)
Nervous system disorders	24 (11.3)	21 (9.8)
Headache	24 (11.3)	21 (9.8)

Adverse events are reported by *Medical Dictionary for Regulatory Activities* (MedDRA) superclass and preferred terms and NCI CTCAE grade.

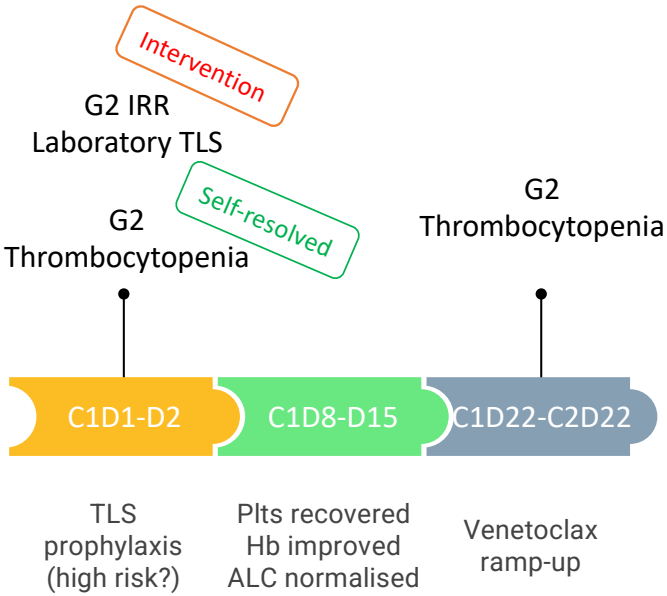
* GCSF could be administered at the discretion of the treating physician according to local practice

Table 2. Grade 3 or 4 Adverse Events (Safety Population).*

Adverse Event	Venetoclax–Obinutuzumab (N=212)†			Chlorambucil–Obinutuzumab (N=214)		
	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4
	number of patients (percent)					
Adverse event of grade 3 or 4	81 (38.2)	86 (40.6)	167 (78.8)	93 (43.5)	71 (33.2)	164 (76.6)
Adverse events of grade 3 or 4 that occurred in ≥3% of the patients in either treatment group‡						
Blood and lymphatic system disorders	59 (27.8)	69 (32.5)	128 (60.4)	61 (28.5)	57 (26.6)	118 (55.1)
Neutropenia	52 (24.5)	60 (28.3)	112 (52.8)	56 (26.2)	47 (22.0)	103 (48.1)
Thrombocytopenia	20 (9.4)	9 (4.2)	29 (13.7)	19 (8.9)	13 (6.1)	32 (15.0)
Anemia	16 (7.5)	1 (0.5)	17 (8.0)	13 (6.1)	1 (0.5)	14 (6.5)
Febrile neutropenia	7 (3.3)	4 (1.9)	11 (5.2)	4 (1.9)	4 (1.9)	8 (3.7)
Leukopenia	5 (2.4)	0	5 (2.4)	9 (4.2)	1 (0.5)	10 (4.7)
Infections and infestations	31 (14.6)	6 (2.8)	37 (17.5)	31 (14.5)	1 (0.5)	32 (15.0)
Pneumonia	8 (3.8)	1 (0.5)	9 (4.2)	8 (3.7)	0	8 (3.7)
Injury, poisoning, and procedural complications	21 (9.9)	5 (2.4)	26 (12.3)	29 (13.6)	1 (0.5)	30 (14.0)
Infusion-related reaction	16 (7.5)	3 (1.4)	19 (9.0)	21 (9.8)	1 (0.5)	22 (10.3)
Investigations	26 (12.3)	6 (2.8)	32 (15.1)	16 (7.5)	7 (3.3)	23 (10.7)
Neutrophil count decreased	7 (3.3)	2 (0.9)	9 (4.2)	4 (1.9)	6 (2.8)	10 (4.7)
Aspartate aminotransferase increased	5 (2.4)	0	5 (2.4)	7 (3.3)	0	7 (3.3)
Alanine aminotransferase increased	4 (1.9)	0	4 (1.9)	7 (3.3)	0	7 (3.3)
Metabolism and nutrition disorders§	19 (9.0)	6 (2.8)	25 (11.8)	11 (5.1)	1 (0.5)	12 (5.6)
Hyperglycemia	6 (2.8)	2 (0.9)	8 (3.8)	2 (0.9)	1 (0.5)	3 (1.4)
Gastrointestinal disorders ¶	16 (7.5)	1 (0.5)	17 (8.0)	6 (2.8)	1 (0.5)	7 (3.3)
Diarrhea‖	9 (4.2)	0	9 (4.2)	1 (0.5)	0	1 (0.5)
Cardiac disorders	9 (4.2)	1 (0.5)	10 (4.7)	10 (4.7)	2 (0.9)	12 (5.6)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	10 (4.7)	3 (1.4)	13 (6.1)	7 (3.3)	1 (0.5)	8 (3.7)
Vascular disorders**	12 (5.7)	2 (0.9)	14 (6.6)	7 (3.3)	0	7 (3.3)
General disorders and administration-site conditions ††	14 (6.6)	0	14 (6.6)	6 (2.8)	0	6 (2.8)

Fischer K, et al. N Engl J Med 2019

Treatment journey



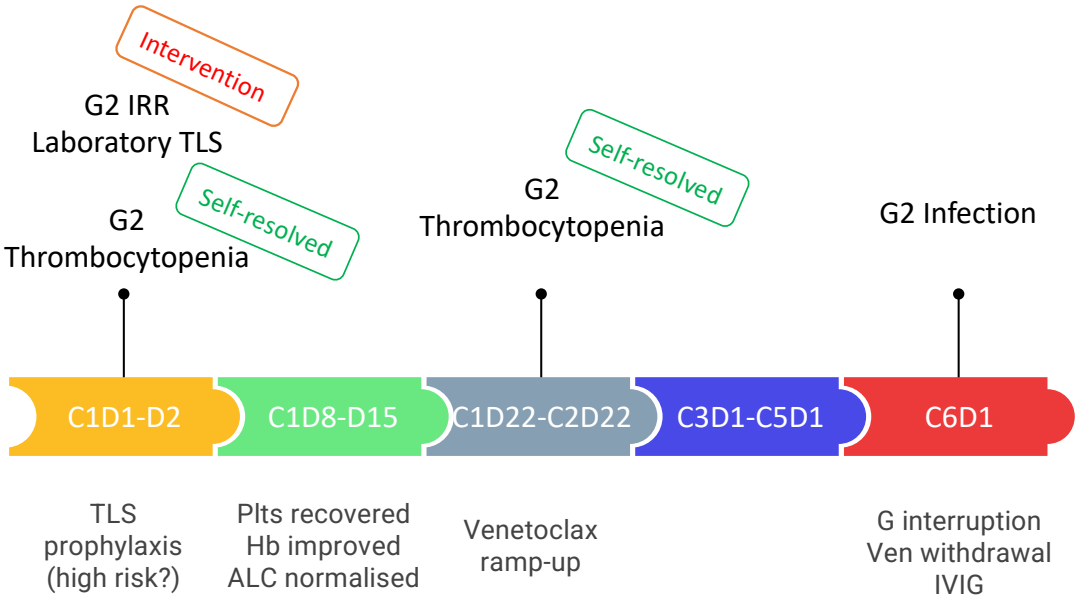
G2 Thrombocytopenia

During the ramp-up, we observed a decrease in platelet count to 58000/mmc, which was transient and self-resolved

C2D1 Plts 84000/mmc → ramp-up to ven 50 mg + Obinutuzumab administration
C2D8 Plts 58000/mmc → ramp-up to ven 100 mg
C2D15 Plts 91000/mmc → ramp-up to ven 200 mg
C2D22 Plts 116000/mmc → ramp-up to ven 400 mg
C3D1 Plts 112000/mmc

No need to withhold anticoagulant therapy

Treatment journey



G2 Infection

- **SARS-CoV2 infection** → Remdesivir → persistence of SARS CoV2 → Molnupinavir
- **Candida glabrata** on oral swab → Isavuconazole
- Evidence of pneumonia on **chest X-ray** → Azytromicin

The patient **omitted one administration of obinutuzumab** and **temporary suspended venetoclax** for about a month.

Since she had **hypogammaglobulinemia** (IgG <400 mg/dl) already before starting GV treatment, she started **IV immunoglobulins** once it was confirmed.

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Thrombocytopenia	20 (9.4)	9 (4.2)	29 (13.7)	19 (8.9)	13 (6.1)	32 (15.0)
Anemia	16 (7.5)	1 (0.5)	17 (8.0)	13 (6.1)	1 (0.5)	14 (6.5)
Febrile neutropenia	7 (3.3)	4 (1.9)	11 (5.2)	4 (1.9)	4 (1.9)	8 (3.7)
Leukopenia	5 (2.4)	0	5 (2.4)	9 (4.2)	1 (0.5)	10 (4.7)
Infections and infestations	31 (14.6)	6 (2.8)	37 (17.5)	31 (14.5)	1 (0.5)	32 (15.0)
Pneumonia	8 (3.8)	1 (0.5)	9 (4.2)	8 (3.7)	0	8 (3.7)
Injury, poisoning, and procedural complications	21 (9.9)	5 (2.4)	26 (12.3)	29 (13.6)	1 (0.5)	30 (14.0)
Infusion-related reaction	16 (7.5)	3 (1.4)	19 (9.0)	21 (9.8)	1 (0.5)	22 (10.3)
Investigations	26 (12.3)	6 (2.8)	32 (15.1)	16 (7.5)	7 (3.3)	23 (10.7)
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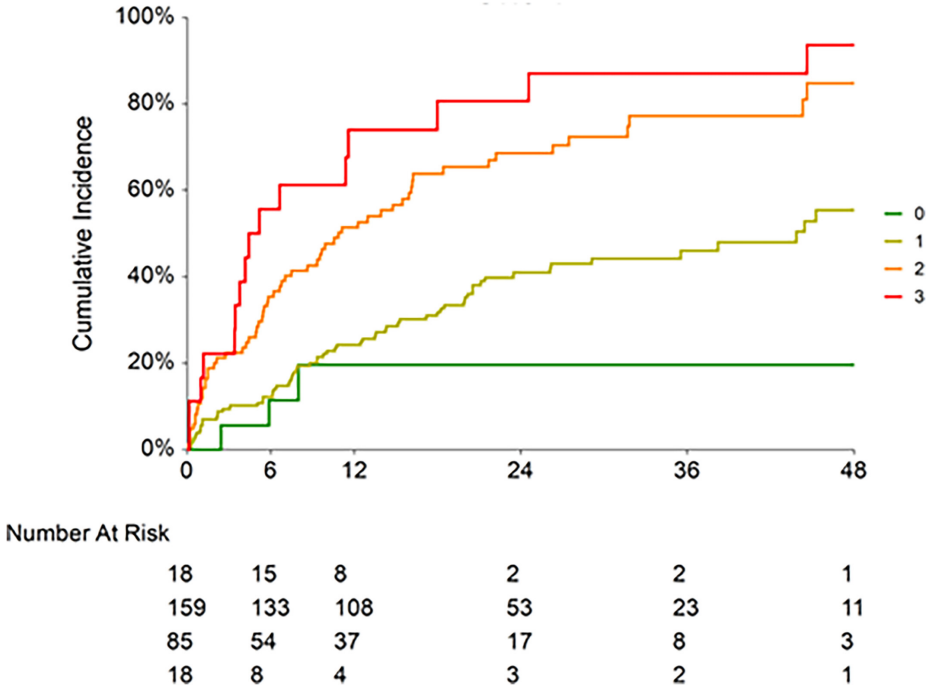
Gastrointestinal disorders ¶	16 (7.5)	1 (0.5)	17 (8.0)	6 (2.8)	1 (0.5)	7 (3.3)
Diarrhea‖	9 (4.2)	0	9 (4.2)	1 (0.5)	0	1 (0.5)
Cardiac disorders	9 (4.2)	1 (0.5)	10 (4.7)	10 (4.7)	2 (0.9)	12 (5.6)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	10 (4.7)	3 (1.4)	13 (6.1)	7 (3.3)	1 (0.5)	8 (3.7)
Vascular disorders**	12 (5.7)	2 (0.9)	14 (6.6)	7 (3.3)	0	7 (3.3)
General disorders and administration-site conditions ††	14 (6.6)	0	14 (6.6)	6 (2.8)	0	6 (2.8)

Fischer K, et al. N Engl J Med 2019

Infections during Venetoclax
Venetoclax Infectious Risk Score



Risk factors for any grade infections

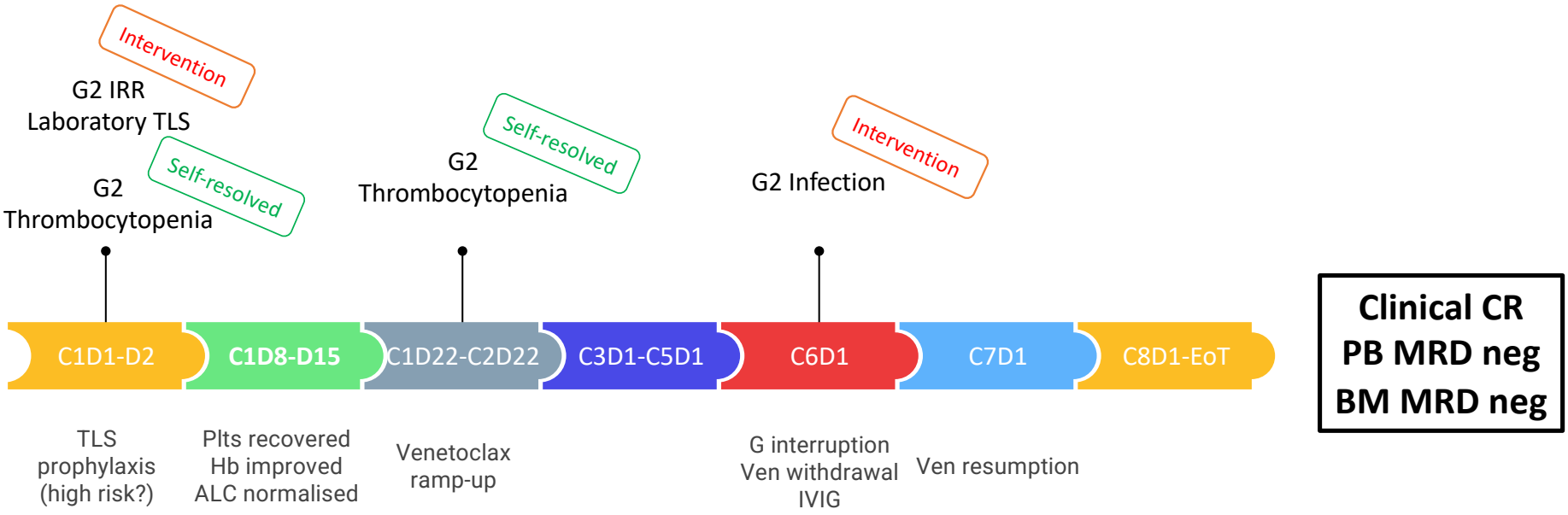
COPD [HR 2.04 (1.37–3.03)]
Previous treatments [HR 2.59 (1.14–5.89)]
Previous infections last 12 months [HR 1.99 (1.43 – 2.76)]

Risk factors for grade 3-5 infections

COPD [HR 2.21 (1.24-3.93)]

Autore F, et al. Am J Hematol 2024

Treatment journey



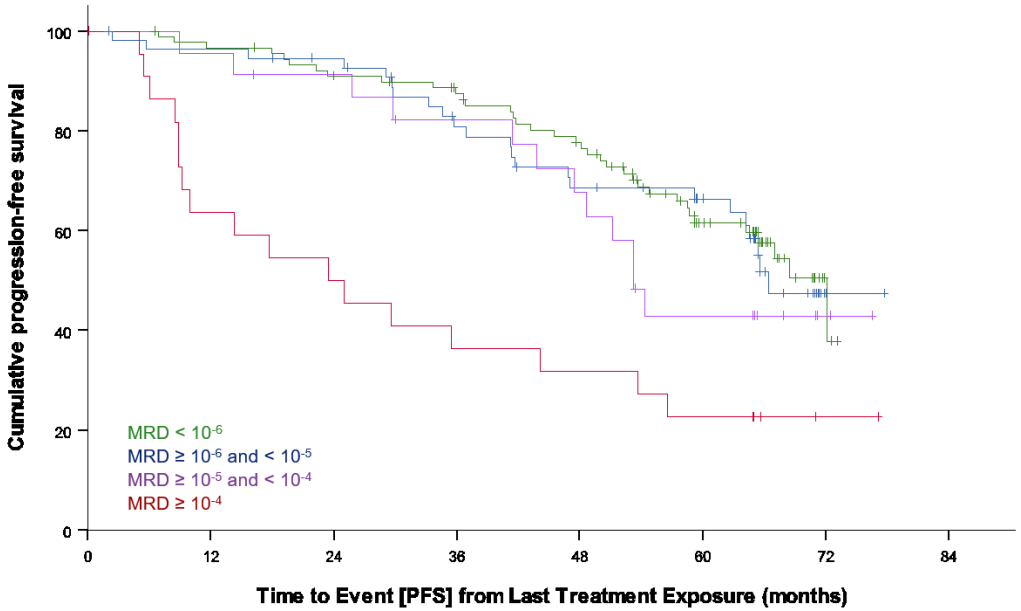
«If you know the enemy and know yourself, you need not fear the result of a hundred battles»

Sun Tzu

Depth of remission

PFS AFTER VEN-OBI ACCORDING TO *MRD STATUS*

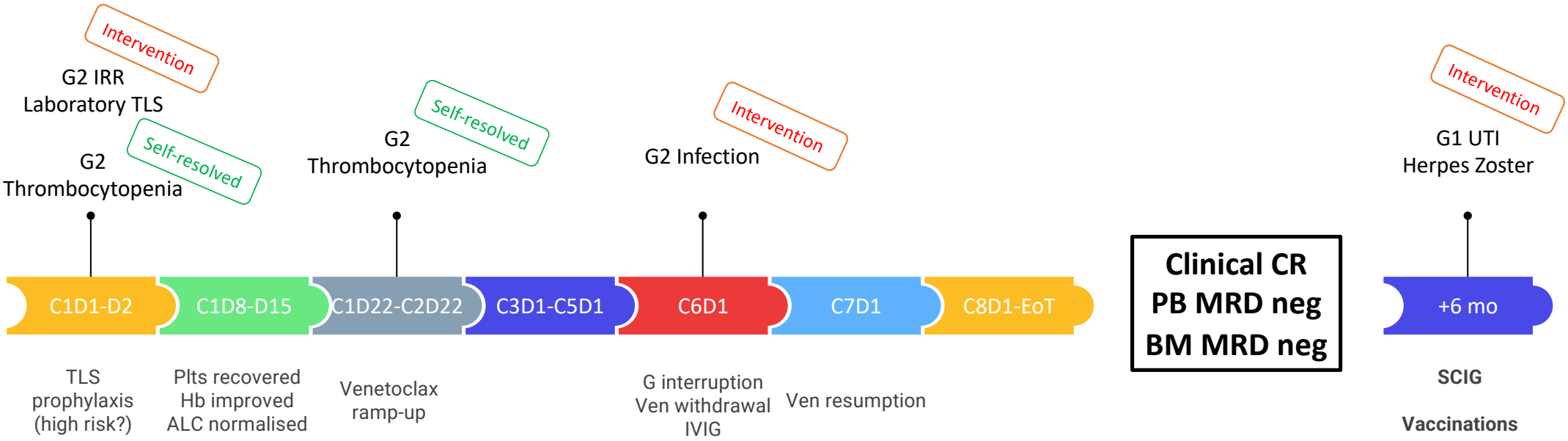
End-of-treatment MRD status in peripheral blood, by NGS



MRD < 10^{-6}	90	86	79	73	63	38	4	0
MRD ≥ 10^{-6} and < 10^{-5}	56	53	50	40	33	26	2	0
MRD ≥ 10^{-5} and < 10^{-4}	23	22	20	17	14	8	2	0
MRD ≥ 10^{-4}	23	14	11	8	7	5	1	0

Al-Sawaf O, et al. EHA 2023. Abstract S145 (Oral).

Treatment journey



Ig replacement for secondary immunodeficiency

- IgG <400 mg/dl AND history of recurrent, severe or unusual infections
- IgG <150 mg/dl

Recombinant Zoster Vaccine

- Patients aged 50 years and older.
- Patients aged 18 years and older who are or will be at increased risk of Zoster due to immunodeficiency or immunosuppression caused by known disease or therapy.

Otani IM, et al. J Allergy Clin Immunol. 2022

Kamboj M, et al. ASCO guidelines, JCO 2024

Thank you