DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

Treatments around the corner for Waldenström macroglobulinemia

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Disclosures

Consulting

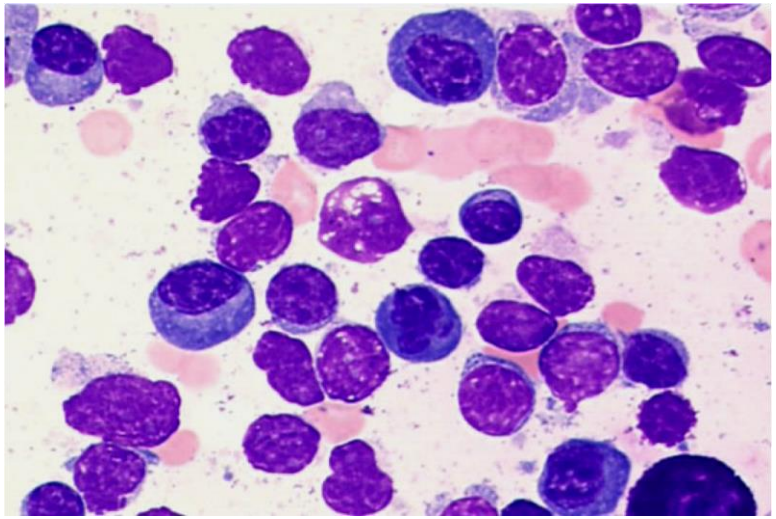
- Janssen Pharmaceuticals
- Merck Co.
- Pharmacyclics Inc
- Roche

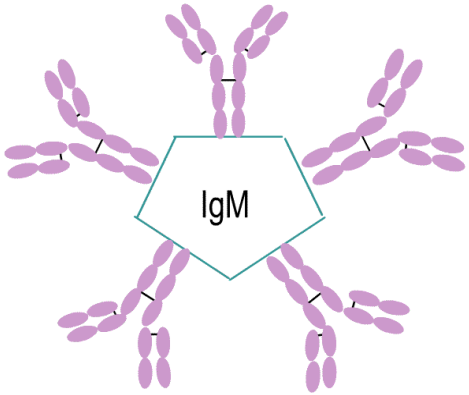
Research Funding

- Abbvie Inc
- Beigene
- Gilead Sciences
- Janssen Pharmaceuticals
- Millennium Pharmaceuticals
- Pharmacyclics Inc

Diagnostic criteria

1. Lymphoplasmacytic lymphoma in the bone marrow
2. IgM monoclonal protein is serum protein electrophoresis
3. MYD88 L265P gene mutation

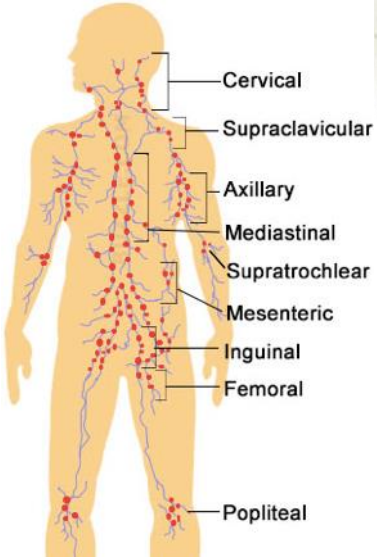




WHO Classification 2018

Manifestations of WM

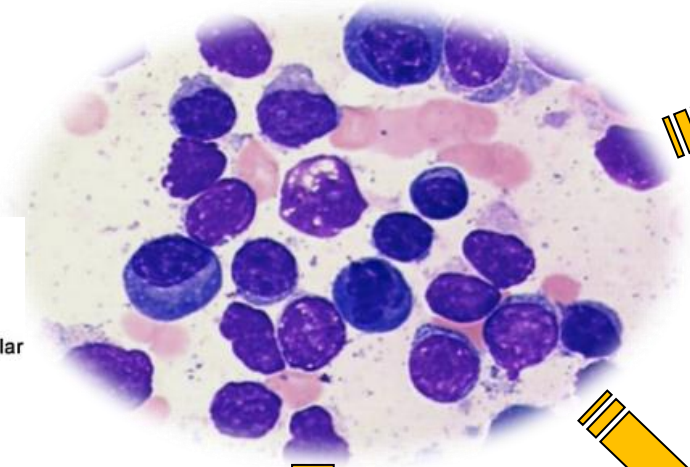
Bing Neel Syndrome



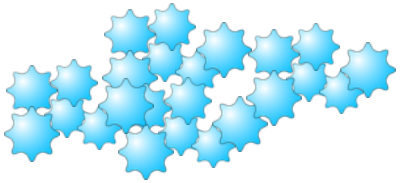
≤20% at diagnosis;
50-60% at relapse.

Bone Marrow

↓HB>>> ↓PLT> ↓WBC



Hepcidin
↓Fe Anemia

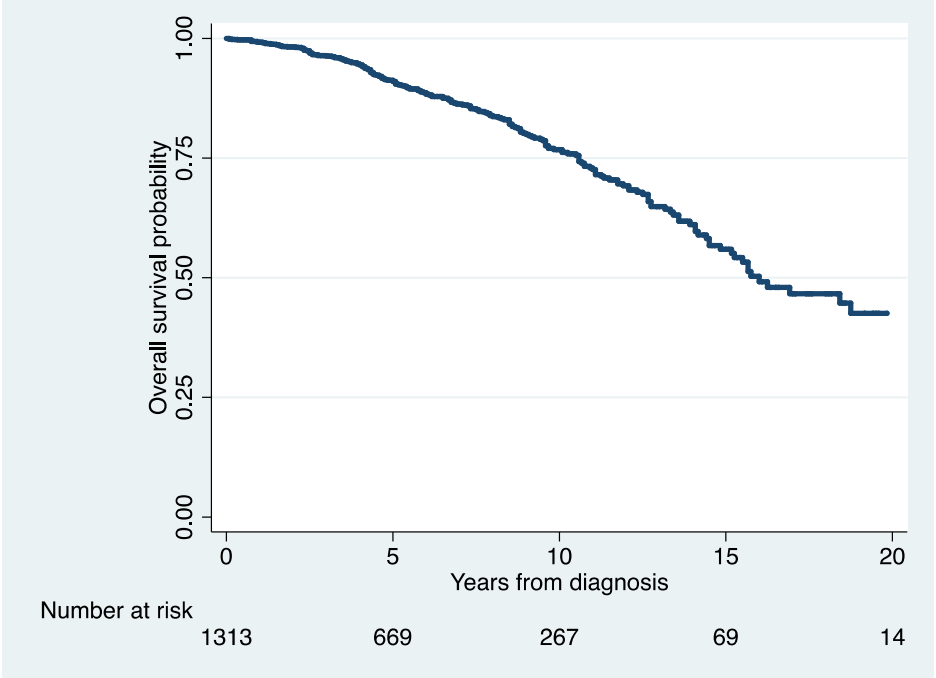


Hyperviscosity Syndrome:
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP

Cold Agglutinemia (5%)
Cryoglobulinemia (10%)
IgM Neuropathy (20%)
Amyloidosis (5-10%)

Why not treat everybody at diagnosis?

- WM is incurable
- WM patients enjoy decades of life
- Treatment promotes resistance

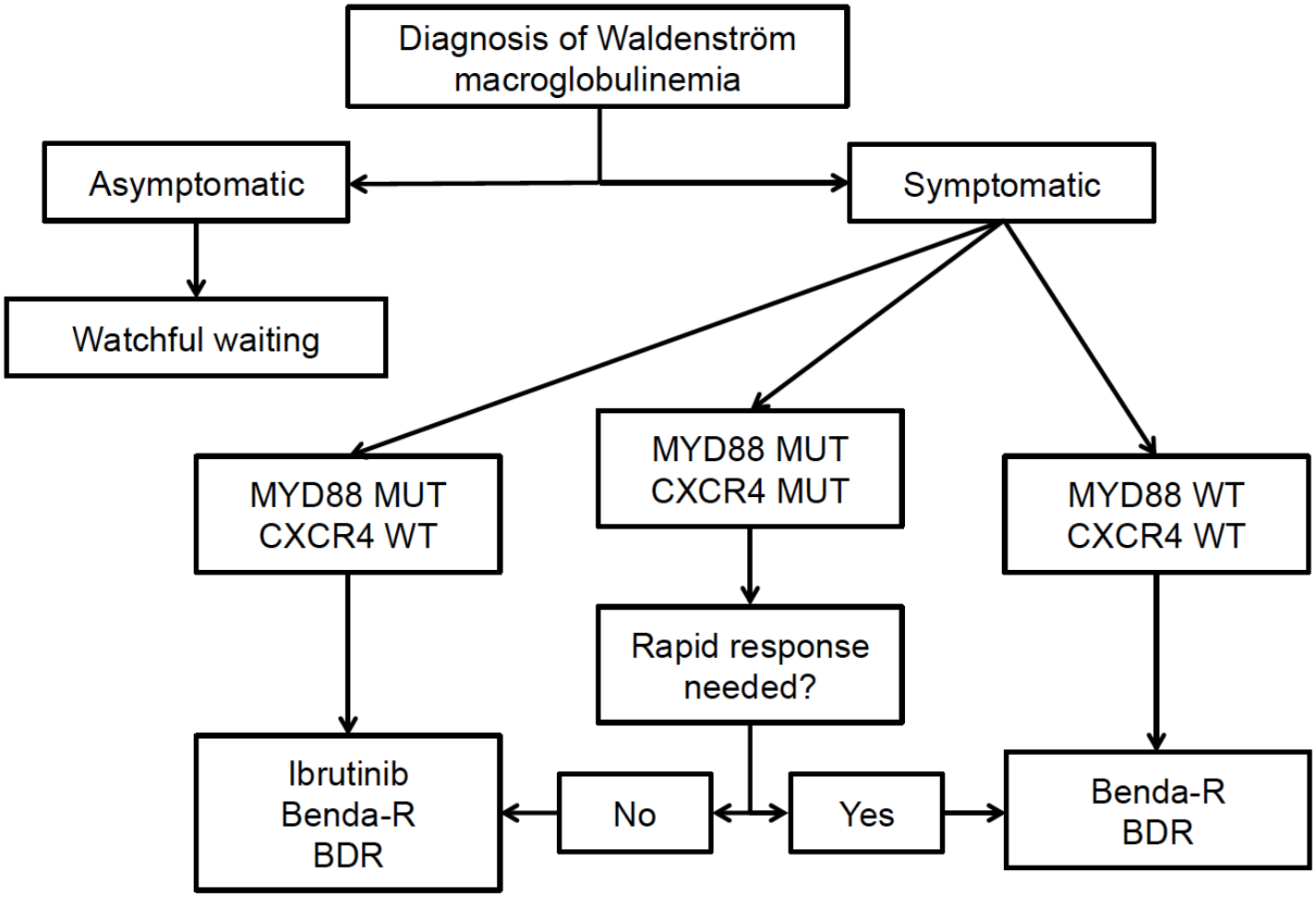


Guidelines for Initiation of Therapy

- Hemoglobin ≤10 g/dL on basis of disease
- Platelet <100,000 mm^3 on basis of disease
- Symptomatic hyperviscosity
- Moderate/severe peripheral neuropathy
- Symptomatic extramedullary disease (e.g. lymphadenopathy, hepatosplenomegaly, renal involvement, pleural effusions, Bing-Neel syndrome, etc.)
- Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloidosis.

Kyle et al. Semin Oncol 2003
Castillo et al. Br J Haematol 2016

BCWM treatment algorithm



NEW TREATMENTS

Proteasome inhibitors

Regimen	N	Overall response	Major response	PFS
BDR	23	88%	65%	66 months
BDR weekly	59	85%	68%	42 months
BR	71	80%	75%	NR
CaRD	31	87%	68%	46 months

Treon JCO 2009
Dimopoulos Blood 2013
Ghobrial AJH 2010
Treon Blood 2014

Clinical Cancer Research

Prospective Clinical Trial of Ixazomib, Dexamethasone, and Rituximab as Primary Therapy in Waldenström Macroglobulinemia

Jorge J. Castillo[1,2], Kirsten Meid[1], Joshua N. Gustine[1], Toni Dubeau[1], Patricia Severns[1], Zachary R. Hunter[1], Guang Yang[1,2], Lian Xu[1], and Steven P. Treon[1,2]

Table 1. Baseline characteristics of 26 patients who received protocol therapy

Characteristics	Median or number	Range or %
Age at WM diagnosis (years)	62.5	46–81
Age at enrollment (years)	65	46–82
Male sex	21/26	81%
Serum IgM (mg/dL)	4,528	653–7,650
Serum IgA (mg/dL)	61.5	8–140
Serum IgG (mg/dL)	609	160–4,677
Hemoglobin (g/dL)	10.2	6.9–13.2
Platelet count (K/μL)	211.5	77–420
Beta-2-microglobulin (mg/L)	4.0	1.8–10.8
Low IPSSWM score	5/26	19%
Intermediate IPSSWM score	11/26	42%
High IPSSWM score	10/26	38%
Adenopathy	14/26	54%
Splenomegaly	3/26	12%
BM involvement (%)	55%	5–95%
MYD88 L265P mutation	26/26	100%
CXCR4 mutation	15/26	58%

Clinical Trial Brief Report

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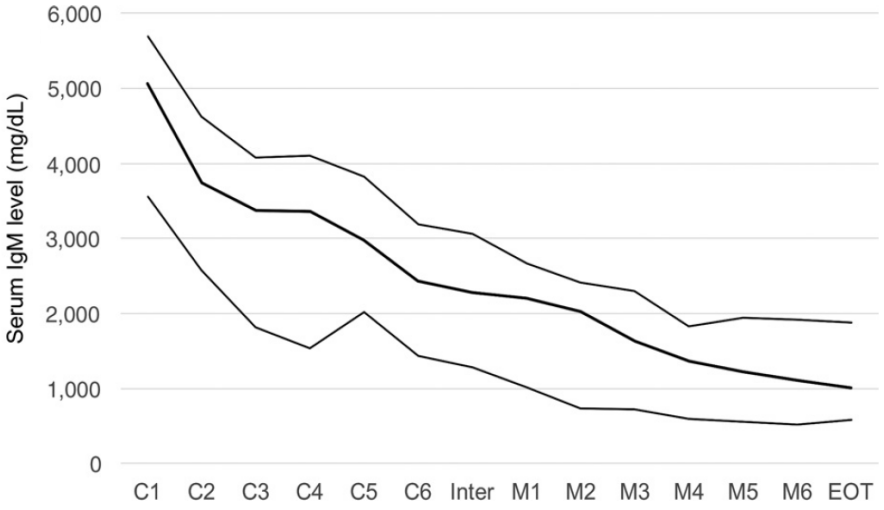

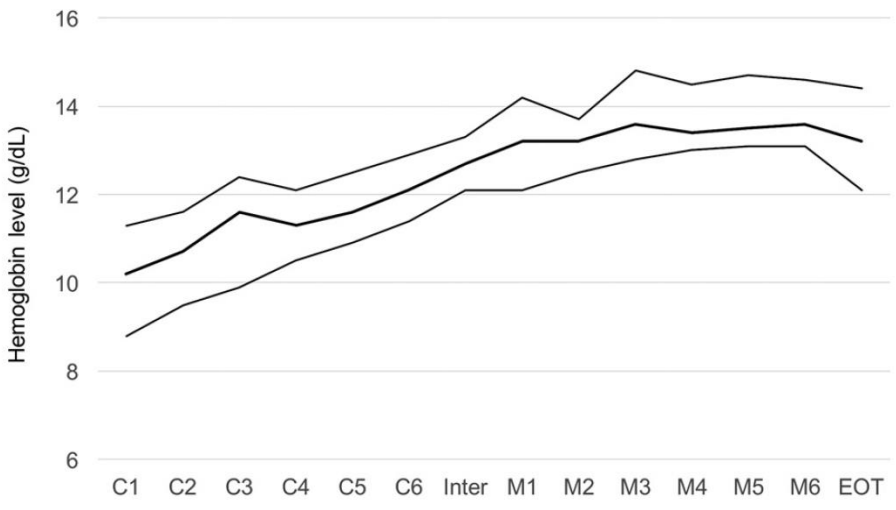

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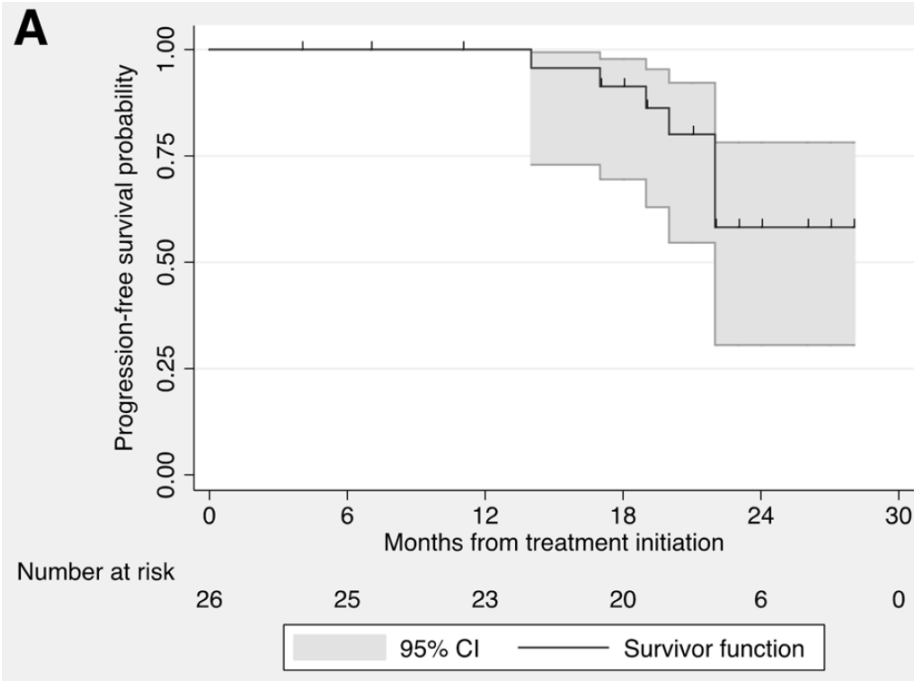

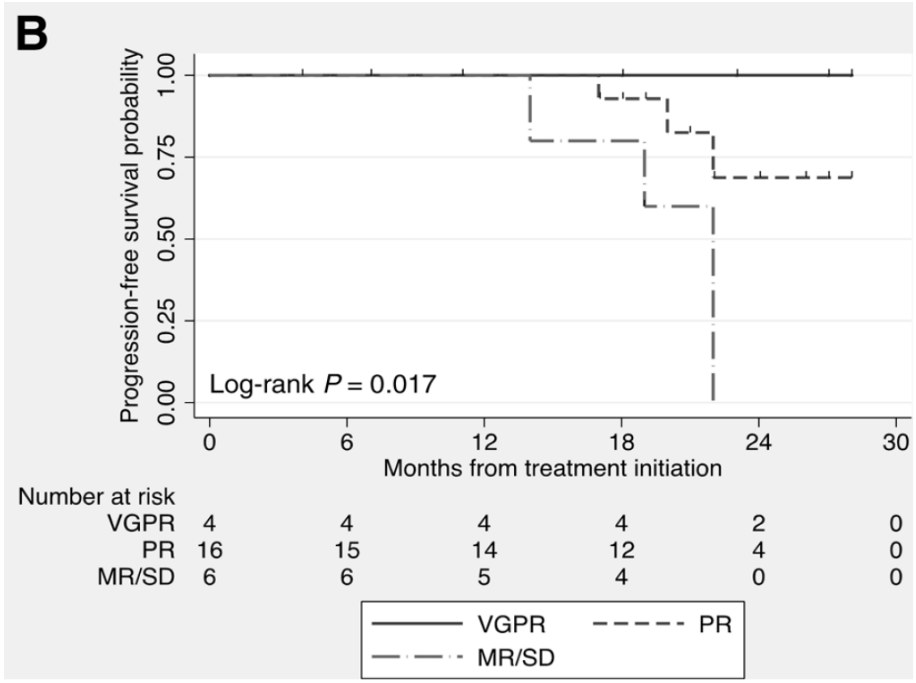

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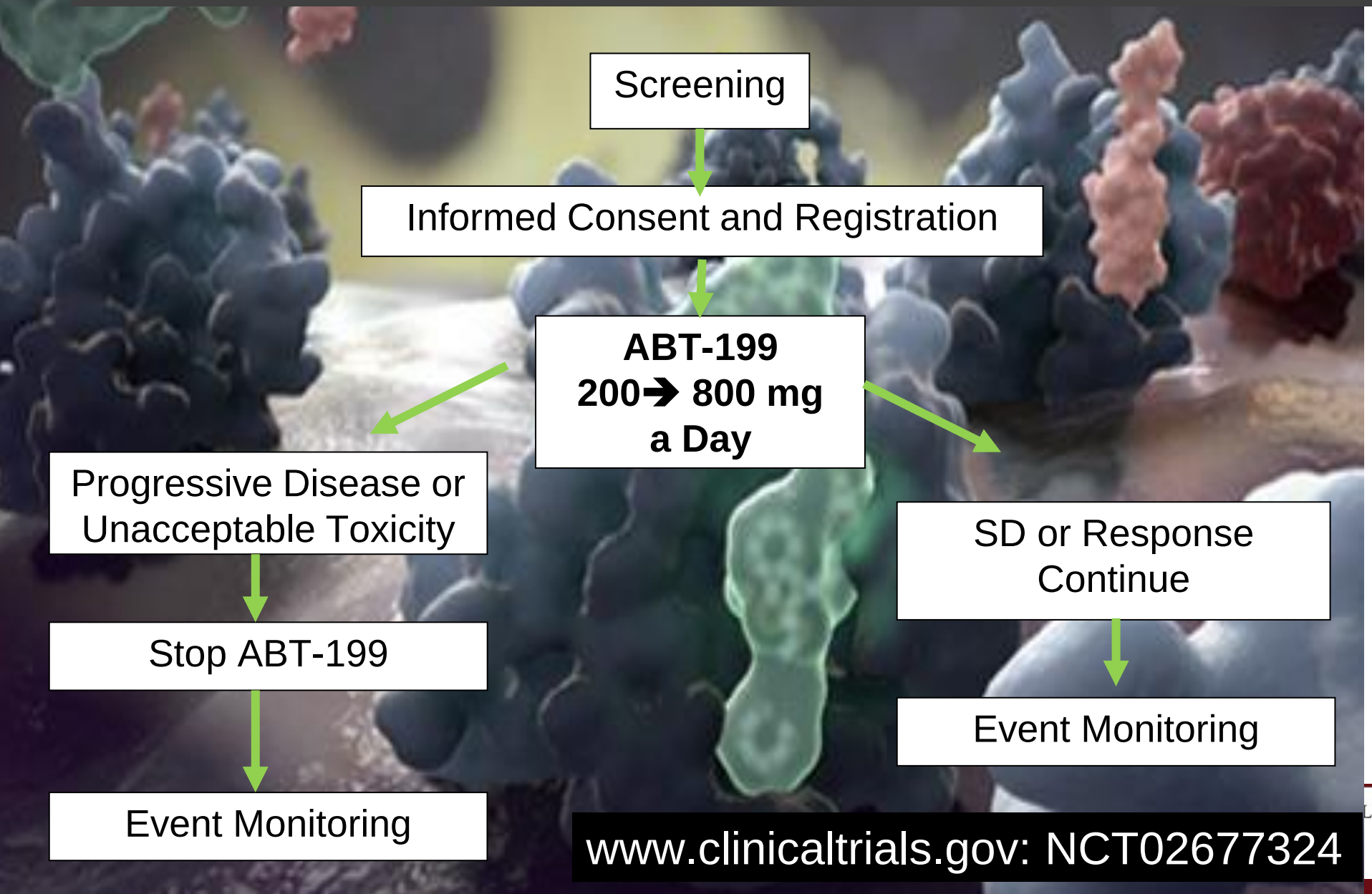
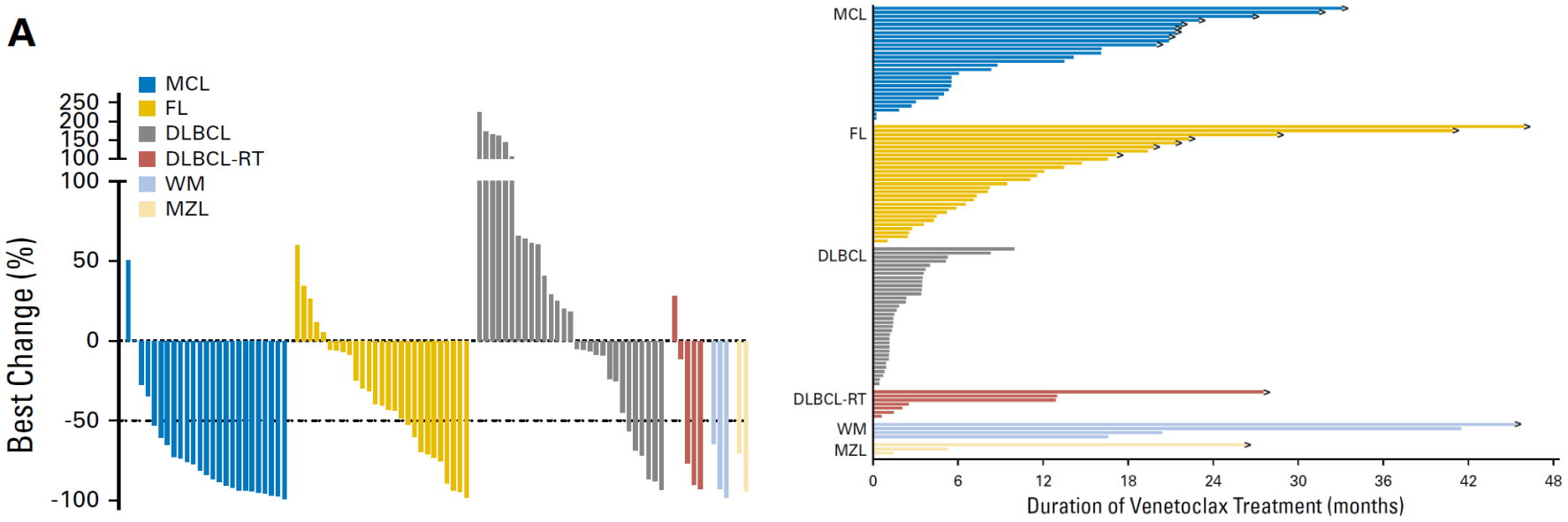
Toxicity	Any grade	Grade 2	Grade 3
Infusion reactions	10 (39%)	5 (19%)	0 (0%)
Neuropathy	6 (23%)	5 (19%)	1 (4%)
Rash	7 (27%)	2 (8%)	0 (0%)
Insomnia	7 (27%)	2 (8%)	0 (0%)
Pneumonia	1 (4%)	0 (0%)	1 (4%)
Sepsis	1 (4%)	0 (0%)	1 (4%)

Phase II Study of Venetoclax (ABT-199) in Previously Treated WM



Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma



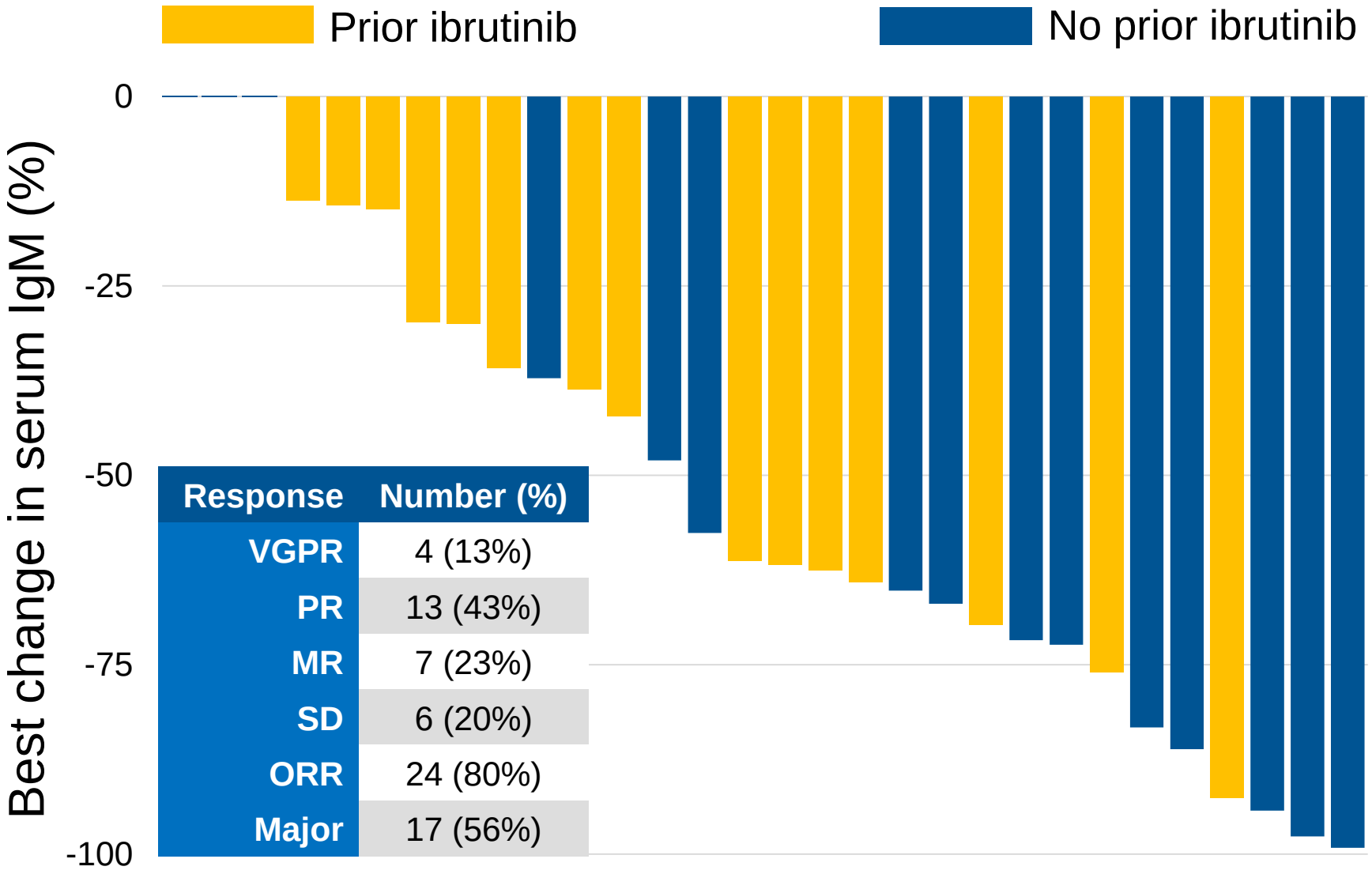
Davids JCO 2016

Phase II Study of Venetoclax in Previously Treated WM

- 30 patients enrolled
  - Enrollment complete
- Patients 1-6
  - Venetoclax 200 mg PO QD for 1 week
  - Venetoclax 400 mg PO QD for 1 week
  - Venetoclax 800 mg PO QD for 2 years
- Patients 7-30
  - Dropped 200 mg step
- Median follow-up
  - 8 months

Characteristic	Number (%)
Age	66 (39-80)
Male sex	17 (57%)
Previous treatments	2 (1-10)
Prior BTK inhibitors	15 (50%)
MYD88 L265P	30 (100%)
CXCR4 mutations	16 (53%)
Serum IgM level	3543 (642-7970)
Hemoglobin level	10.6 (6.4-13.5)
Lymphadenopathy	9 (30%)
Splenomegaly	6 (20%)

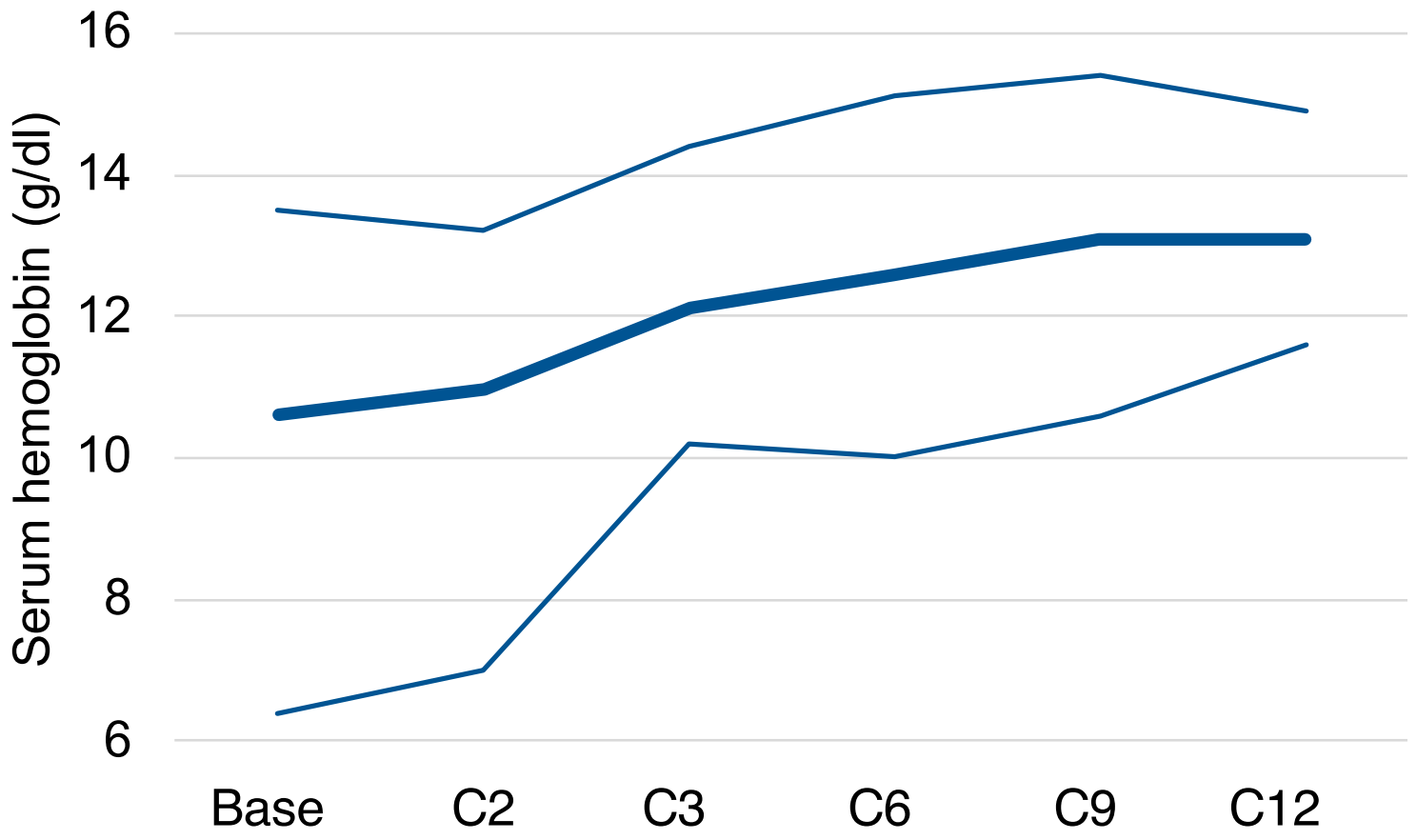
Castillo EHA 2018



Response	Number (%)
VGPR	4 (13%)
PR	13 (43%)
MR	7 (23%)
SD	6 (20%)
ORR	24 (80%)
Major	17 (56%)

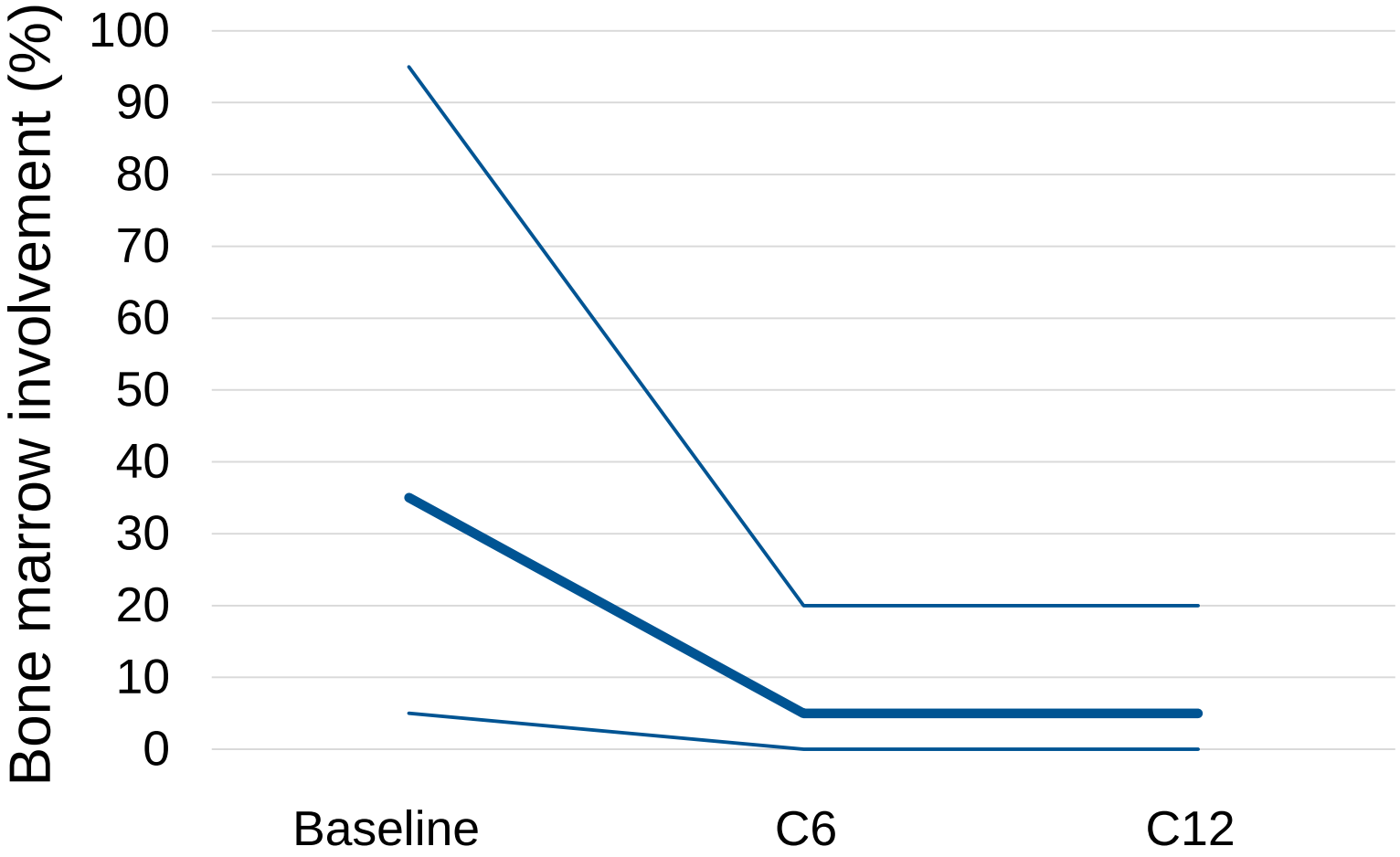
Castillo EHA 2018

Phase II Study of Venetoclax in Previously Treated WM



Castillo EHA 2018

Phase II Study of Venetoclax in Previously Treated WM



Castillo EHA 2018

Phase II Study of Venetoclax in Previously Treated WM

	Prior ibrutinib (n=10)	No prior ibrutinib (n=10)
VGPR	1 (10%)	1 (10%)
PR	2 (20%)	7 (70%)
MR	5 (50%)	2 (20%)
SD	2 (20%)	

	CXCR4 WHIM (n=9)	CXCR4 WT (n=11)
VGPR		2 (18%)
PR	4 (44%)	5 (45%)
MR	5 (56%)	2 (18%)
SD		2 (18%)

Castillo EHA 2018

Phase II Study of Venetoclax in Previously Treated WM

Adverse Event, N (%)	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Neutropenia	2 (7)	4 (14)	6 (21)	3 (10)	15 (52)
Anemia	1 (3)	5 (17)	2 (7)	0	8 (28)
URI	2 (7)	0	1 (3)	0	3 (10)
Nausea	9 (31)	4 (14)	0	0	13 (48)
Headache	2 (7)	3 (10)	0	0	5 (17)
diarrhea	4 (14)	1 (3)	0	0	5 (17)
Chills	2 (7)	1 (3)	0	0	3 (10)
Constipation	2 (7)	1 (3)	0	0	3 (10)
Mucositis oral	2 (7)	1 (3)	0	0	3 (10)
Muscle Cramps	1 (3)	1 (3)	0	0	2 (7)

Castillo EHA 2018

BTK inhibitors

Regimen	N	Overall response	Major response	PFS
Ibrutinib Relapsed	63	91%	73%	Not reached at 5 years
Ibrutinib R refractory	31	90%	71%	86% at 18 months
Ibrutinib Primary therapy	30	100%	83%	92% at 18 months

Treon NEJM 2015; Treon ASH 2017
Dimopoulos Lancet Oncology 2017
Treon ASH 2017

Randomized phase 3 trial of ibrutinib/rituximab vs. placebo/rituximab in Waldenström's macroglobulinemia

Characteristic	Ibrutinib+rituximab (n=75)	Placebo+rituximab (n=75)
Overall response	92%	47%
Major response	72%	32%
Hb improvement	73%	41%
Median PFS	Not reached	20 months
30-month PFS	82%	28%
30-month OS	94%	92%
IgM flare	8%	47%
Serious AE	43%	33%

Ibrutinib-R benefited CXCR4 WT and MUT patients

Dimopoulos ASCO 2018

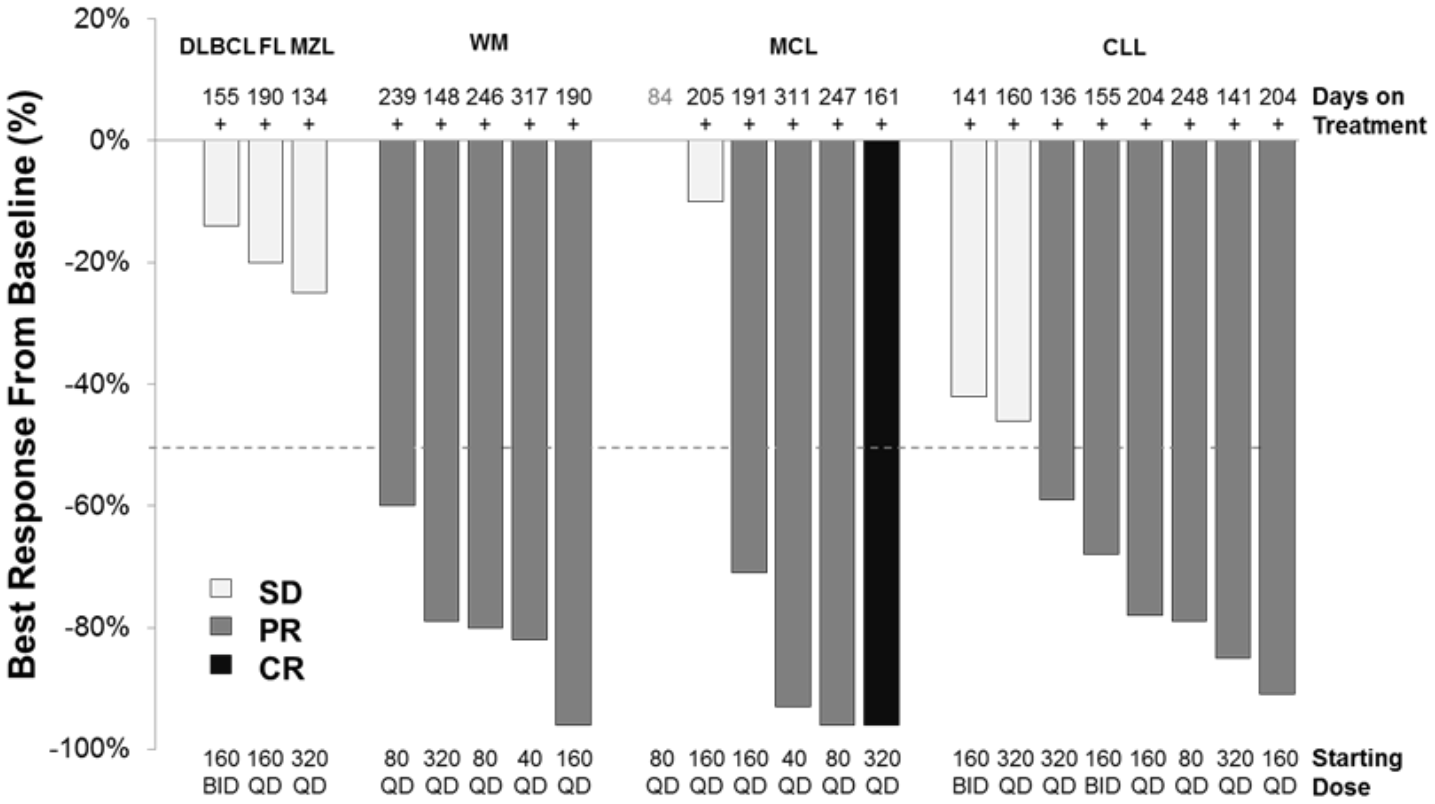
ACALABRUTINIB IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA

- 2nd generation BTK inhibitor
  - Recently approved for mantle cell lymphoma
- Dose
  - 100 mg PO BID
- Median follow-up
  - 2 years

Characteristic	N (%)
Median age	69 (36-90)
Median IgM level	3615 (291-9740)
Treatment naïve	14 (13%)
Previously treated	92 (88%)
Prior therapies	2 (1-7)
Atrial fibrillation	3 (3%)
Bleeding	59 (57%)
ORR	94%
Major response	78%
VGPR	32%

Owen EHA 2018

The BTK Inhibitor, Bgb-3111, Is Safe, Tolerable, and Highly Active in Patients with Relapsed/ Refractory B-Cell Malignancies: Initial Report of a Phase 1 First-in-Human Trial



Tam ASH 2017

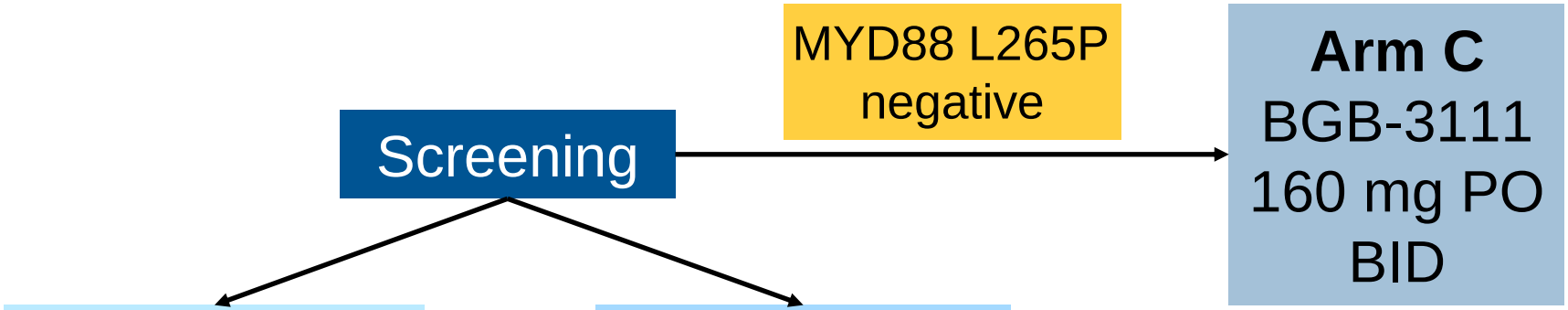
ZANUBRUTINIB IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA

- Phase I
- Date cutoff: 11/03/2017
- Dose: 40 mg QD - 160 mg BID
- 67 enrolled
  - 21 treatment naïve
  - 46 relapsed/refractory
- Median follow-up 15.5 months

Characteristic	N (%)
Median IgM level	3250 (530-8850)
Median hemoglobin	8.7 (6.3-9.8)
Prior therapies	NR (1-8)
Atrial fibrillation	4 (6%)
Bleeding	25 (37%)
ORR	92%
Major response	80%
VGPR	36%

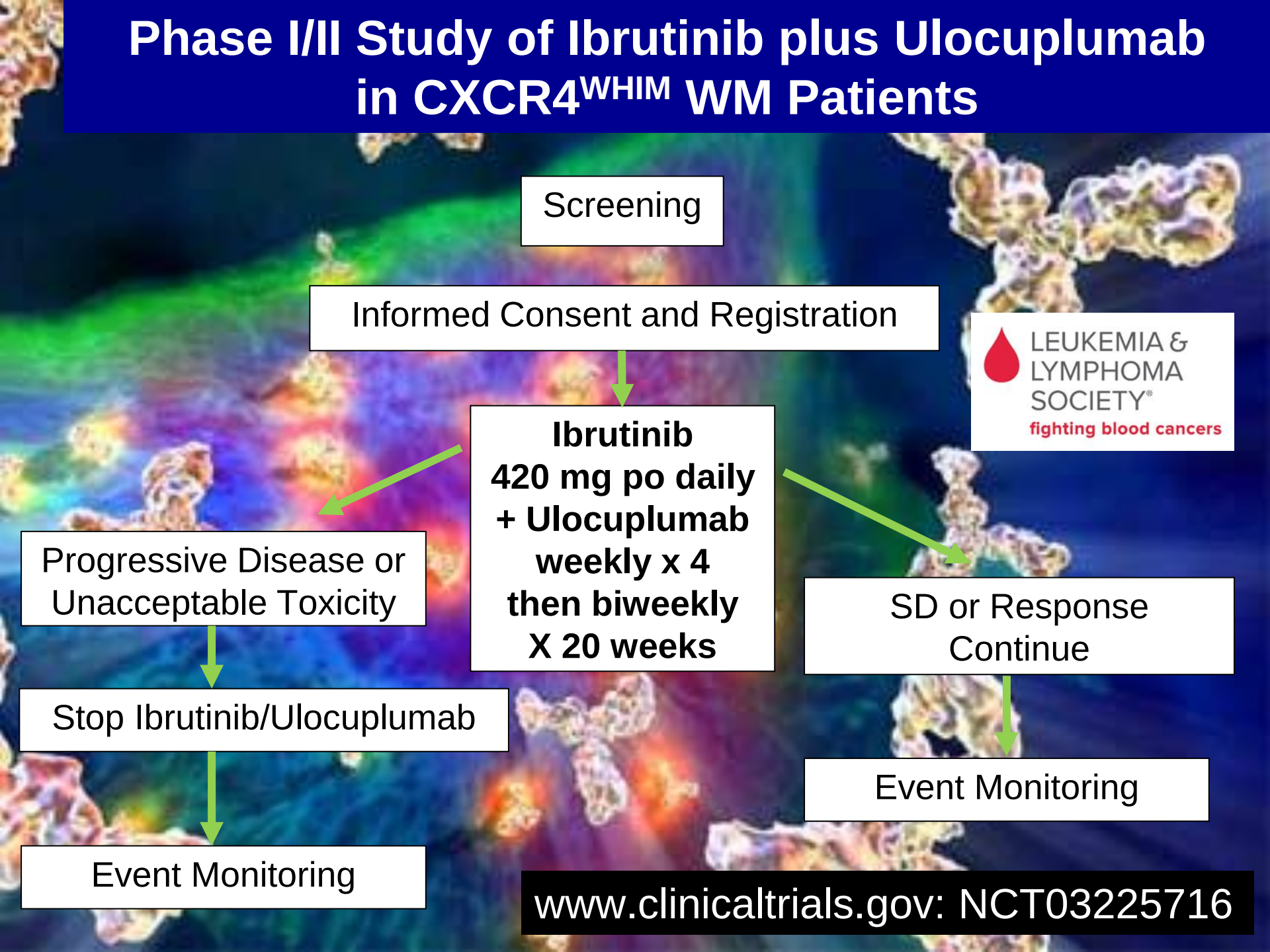
Trotman EHA 2018

A Study Comparing BGB-3111 and Ibrutinib in Subjects With Waldenström's Macroglobulinemia



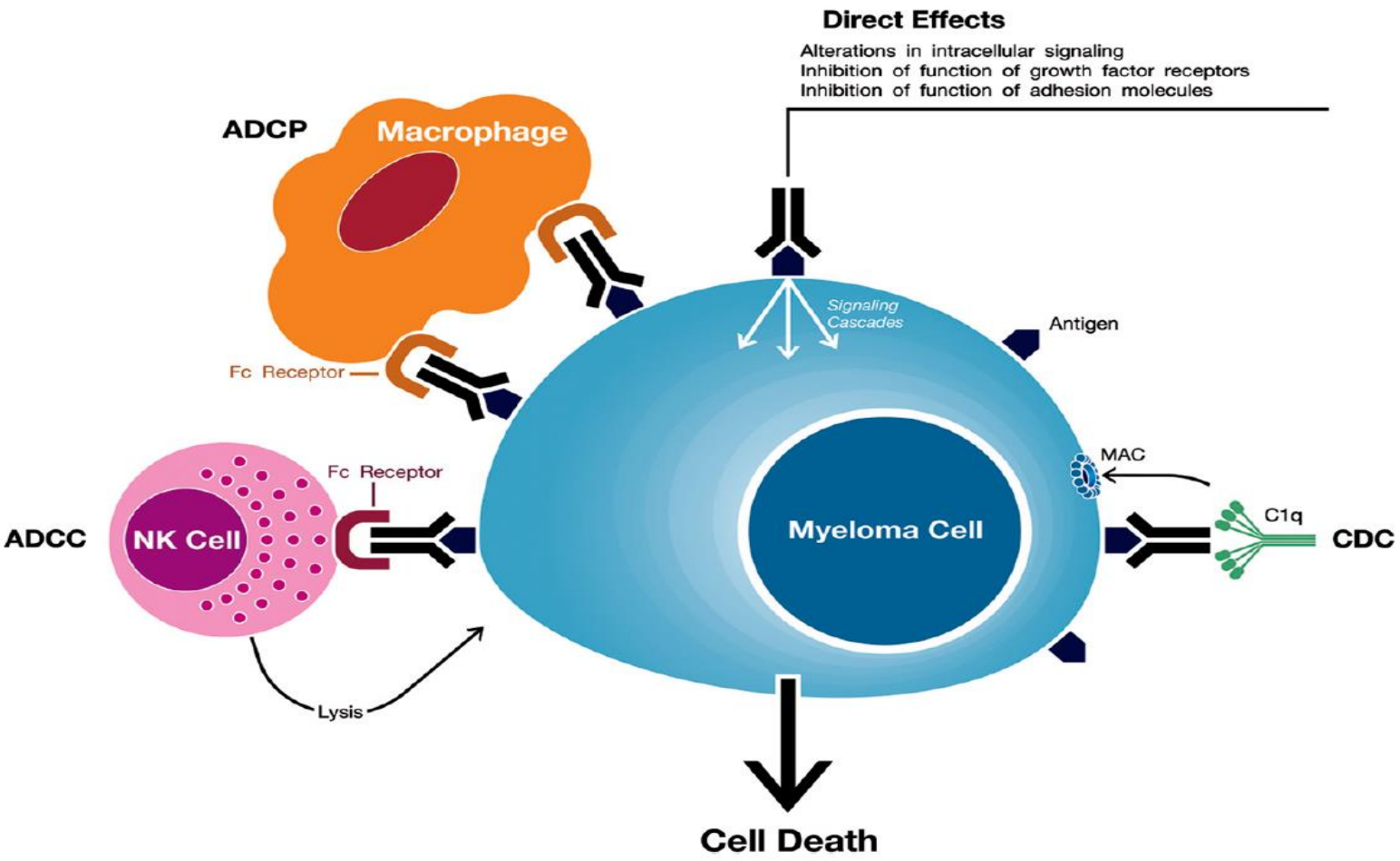
Therapy continues until unacceptable toxicity or disease progression

Phase I/II Study of Ibrutinib plus Ulocuplumab in CXCR4^{WHIM} WM Patients



Daratumumab

An anti-CD38 monoclonal antibody



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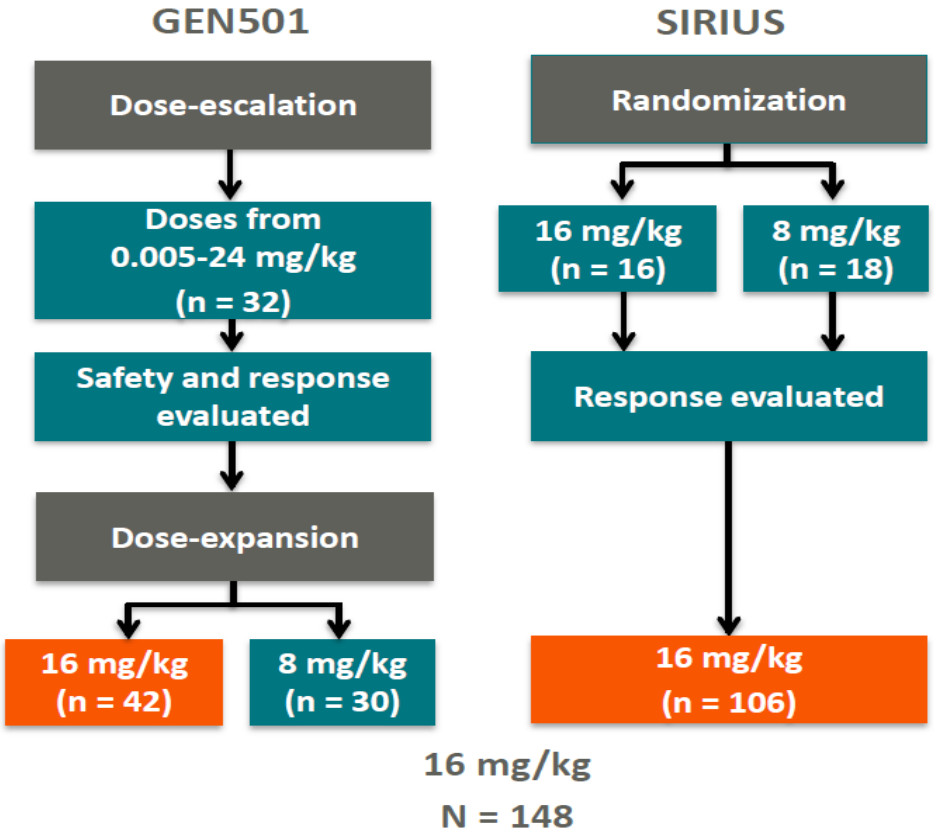
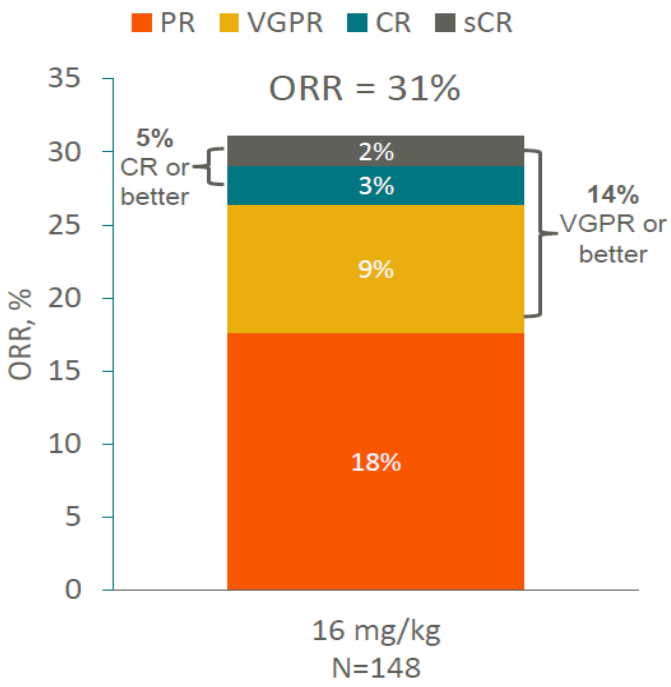
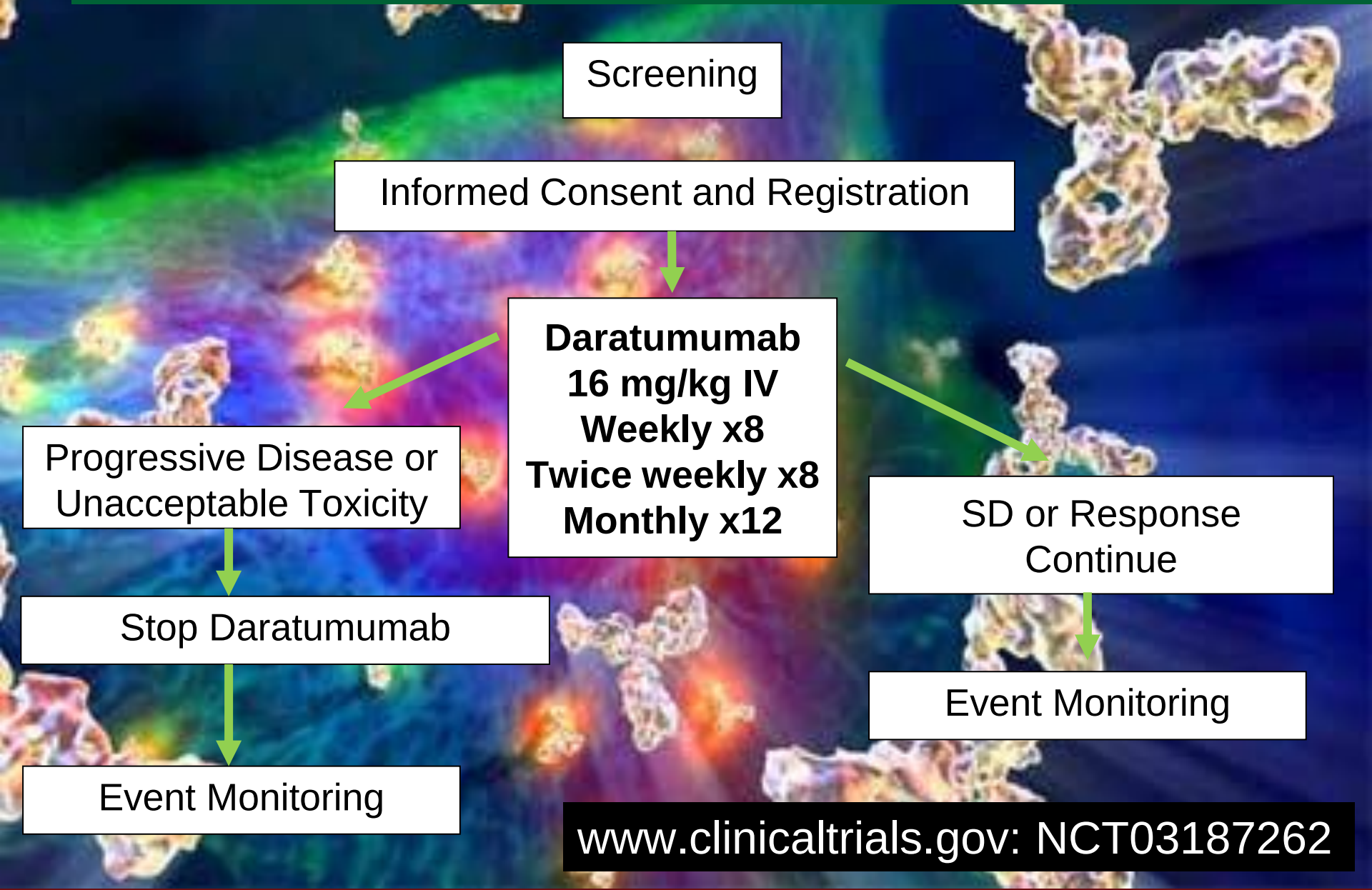


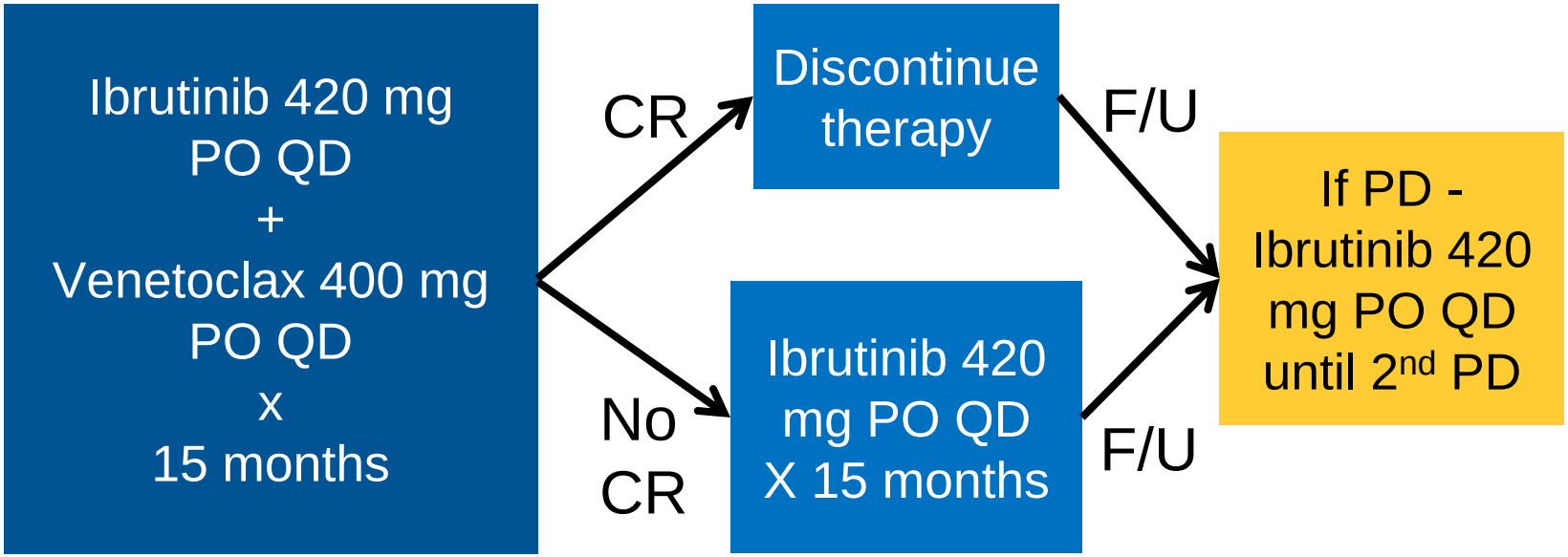


Usmani. Blood 2016

Phase II Study of Daratumumab in Previously Treated WM patients



Ibrutinib-venetoclax in previously untreated patients with Waldenström Macroglobulinemia



Primary Objective: To evaluate the rate of very good partial response or better to IVEN in patients with WM.
Sample size: 50 patients (20 CXCR4)

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