A Look into the Future: Treatments on the Horizon

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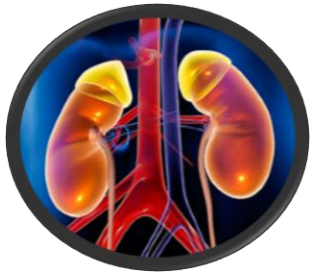
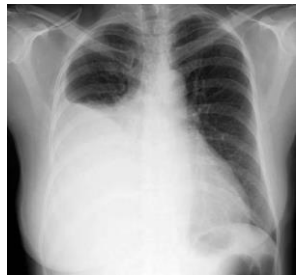
Manifestations of Waldenstrom Macroglobulinemia

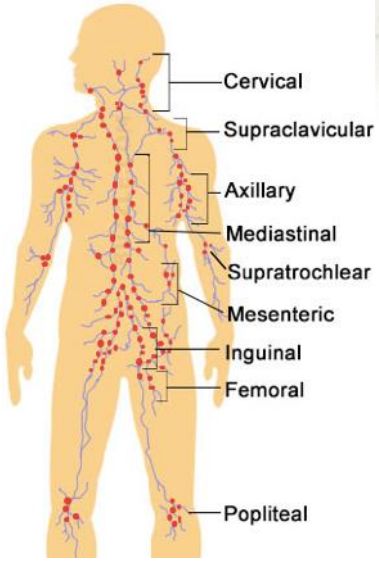


Renal involvement
(2-3%)

Bing Neel
Syndrome (1%)



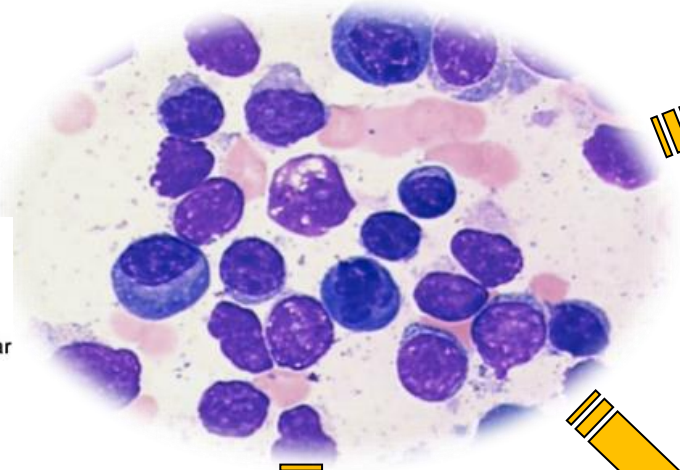
Pleural effusions
(1-2%)

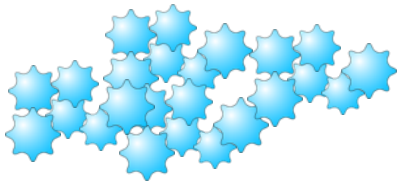


≤20% at diagnosis
50-60% at relapse

Bone Marrow

↓HB>>> ↓PLT> ↓WBC



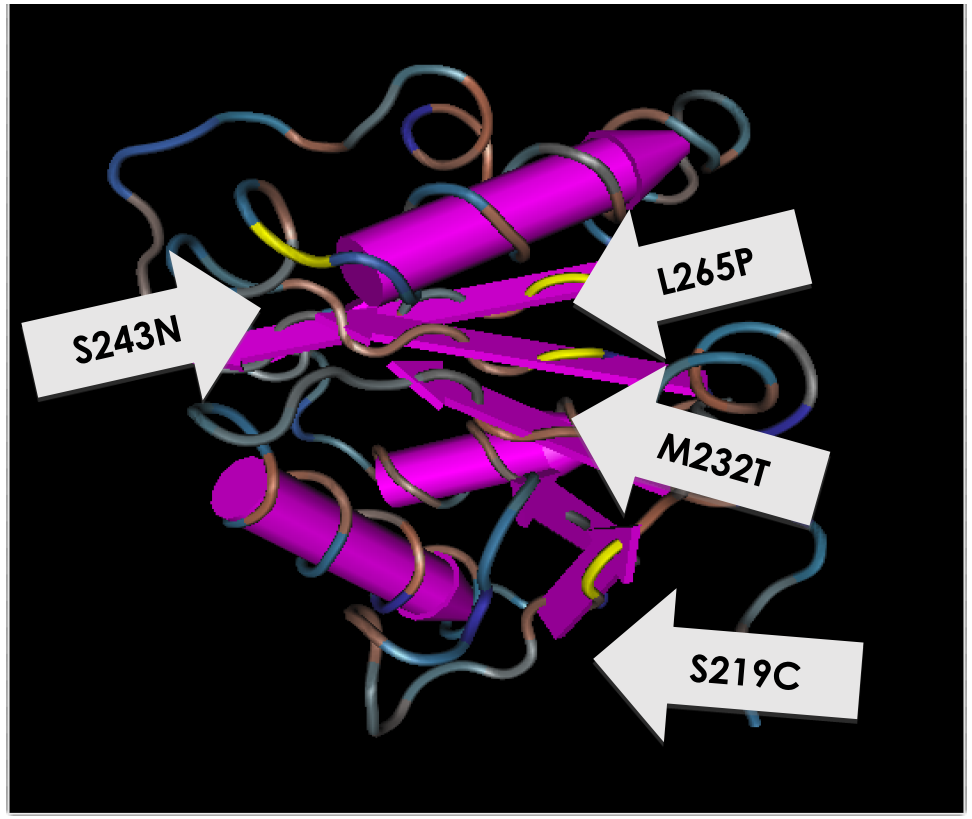


Hyperviscosity Syndrome (15%)
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP

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

Hepcidin
↓Fe Anemia

MYD88 mutations

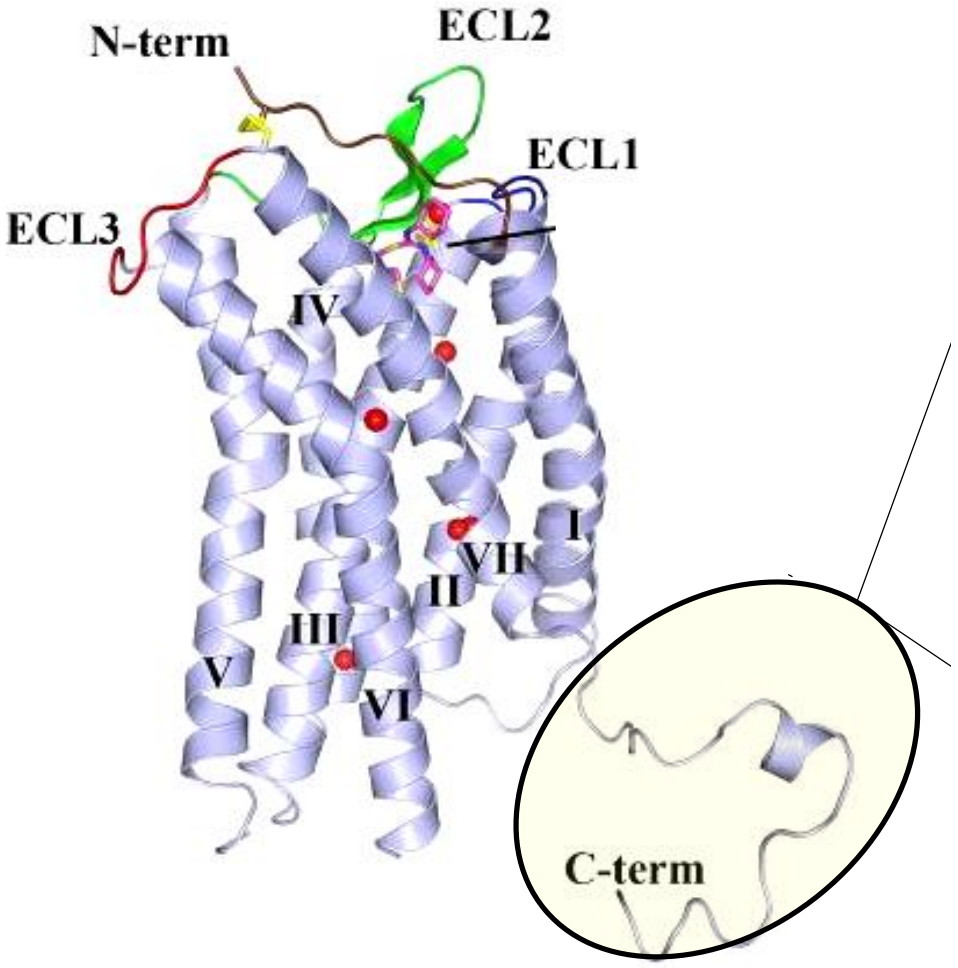


2% non-L265P MYD88 mutations

Treon et al. N Engl J Med 2012
Xu et al. Blood 2013

Study	Method	%
Xu	AS-PCR	93%
Gachard	PCR	70%
Varettoni	AS-PCR	100%
Landgren	Sanger	90%
Jimenez	AS-PCR	86%
Poulain	PCR	80%
Argentou	PCR-RFLP	92%
Willenbacher	Sanger	86%
Mori	AS-PCR	80%
Ondrejka	AS-PCR	100%
Ansell	WES/AS-PCR	97%
Patkar	AS-PCR	85%
Cao	AS-PCR	92%

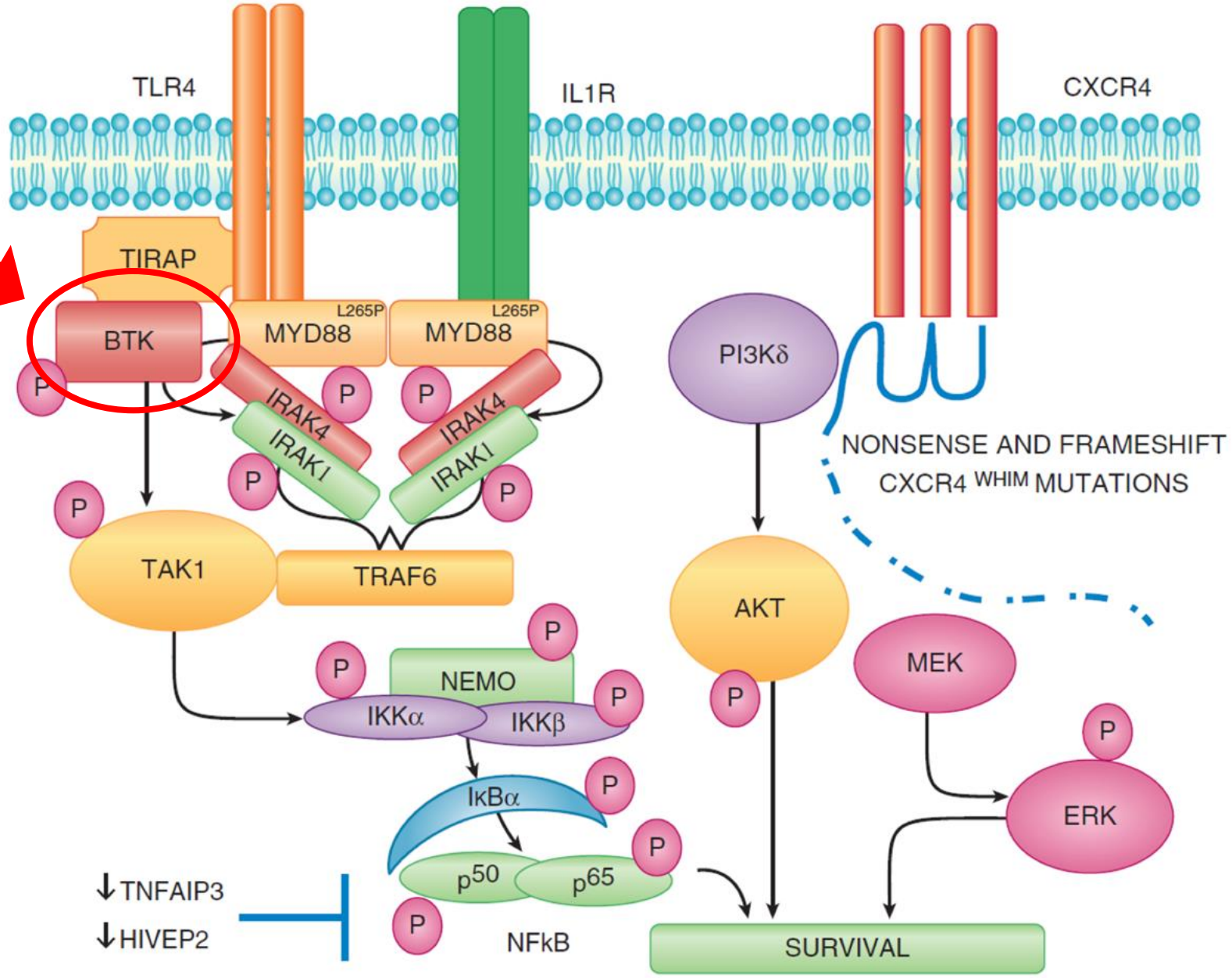
CXCR4 mutations



Study		Method	%
Hunter		WGS	27%
Roccaro		AS-PCR	28%
Poulain		NGS/Sanger	25%
Schmidt		Sanger	36%
Xu		AS-PCR/Sanger	40%
Ballester		Sanger	25%
Cao		Sanger	24%
Shin		Target capture	19%

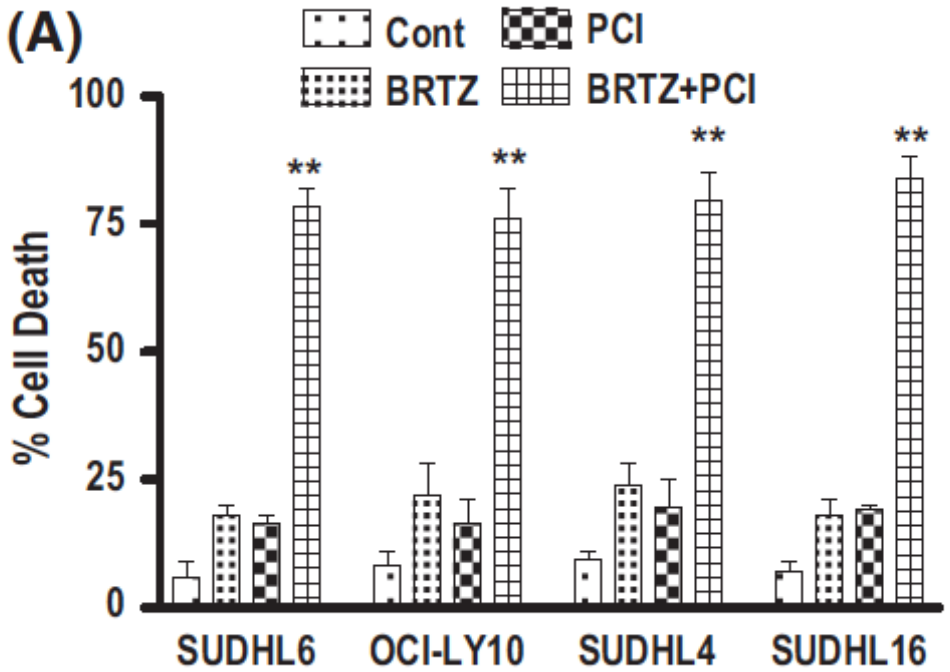
Hunter et al. Blood 2014
Xu et al. Br J Haematol 2017

BTK is an important component of the activation pathway of MYD88 L265P

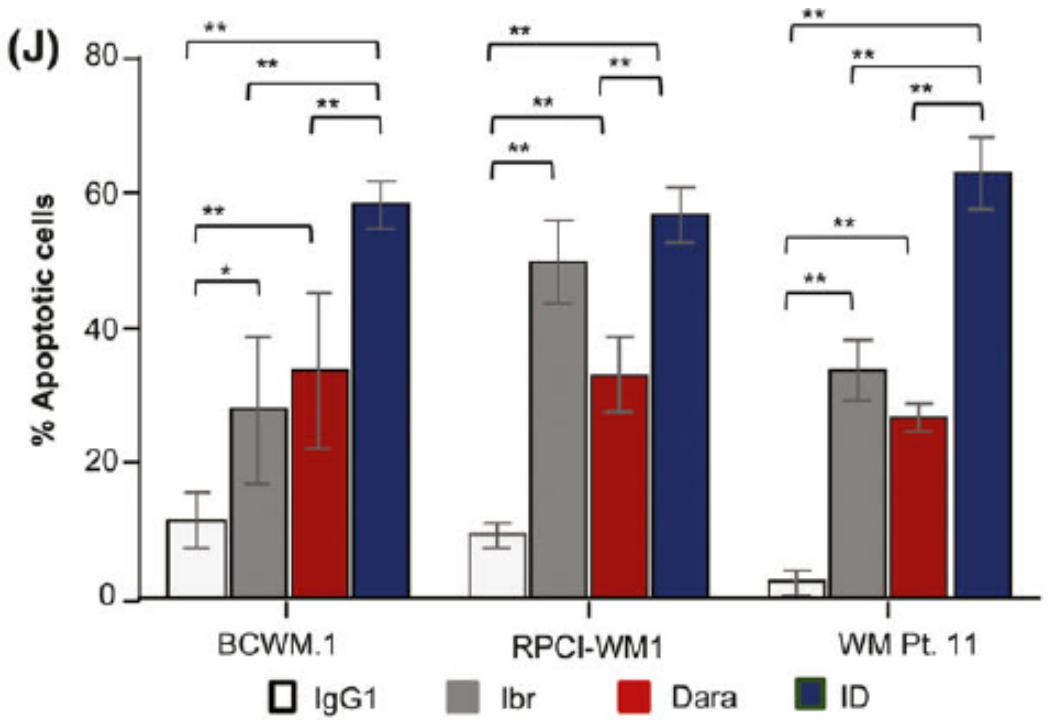


Ibrutinib combinations

The Bruton tyrosine kinase (BTK) inhibitor PCI-32765 synergistically increases proteasome inhibitor activity in diffuse large-B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) cells sensitive or resistant to bortezomib

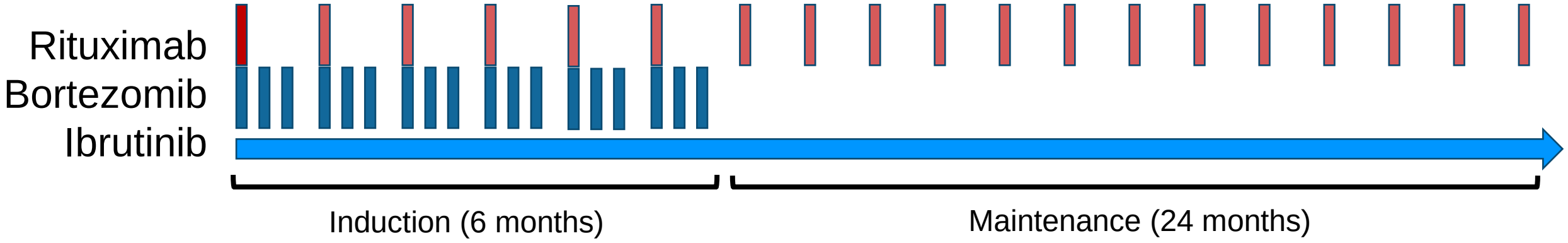


Targeting CD38 with daratumumab is lethal to Waldenström macroglobulinaemia cells



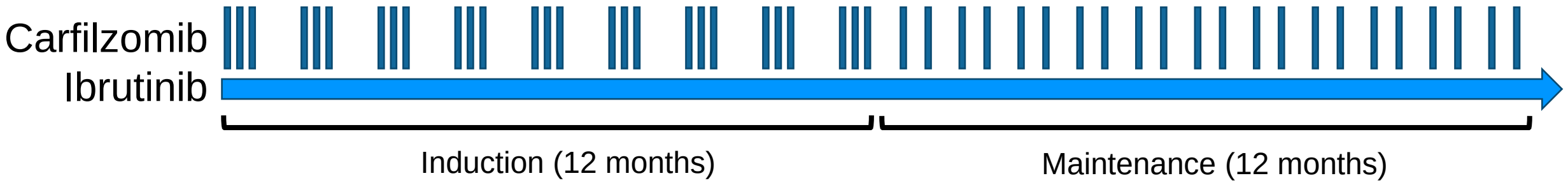
Efficacy of First Line B-RI for Treatment Naive Waldenström Macroglobulinemia

- Germany
- 53 patients
- SQ bortezomib, SQ rituximab, ibrutinib



Efficacy of Carfilzomib in Combination With Ibrutinib in Waldenström Macroglobulinemia

- Germany
- 184 patients (TN and RR)
- Ibrutinib vs. carfilzomib-ibrutinib

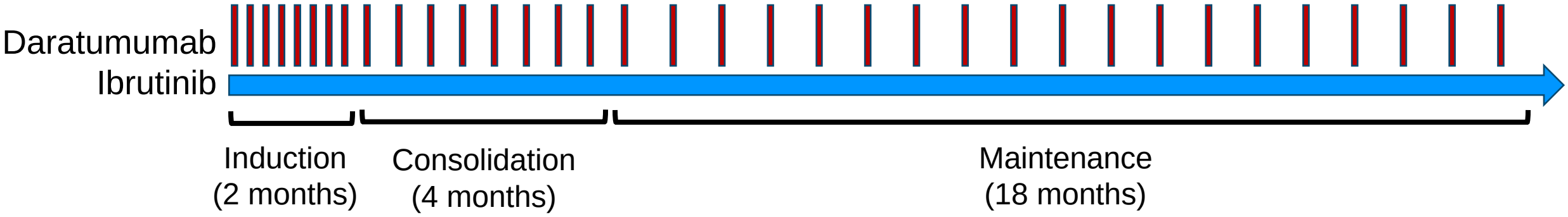


Ibrutinib and Ixazomib Citrate in Treating Relapsed or Refractory Waldenstrom Macroglobulinemia

- Mayo Clinic and NCI
- 47 patients

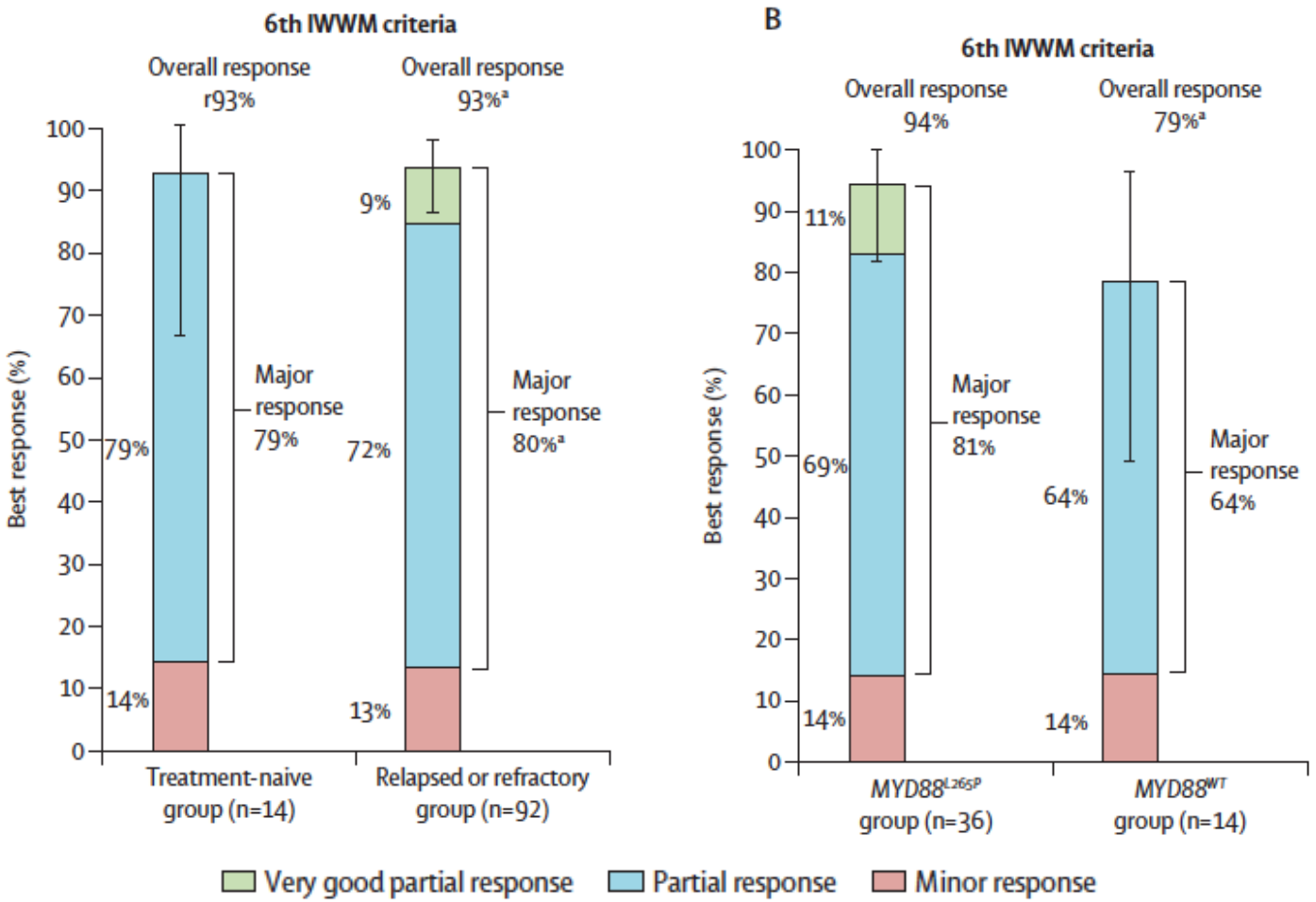
Daratumumab Plus Ibrutinib in Patients With Waldenström Macroglobulinemia

- Weill Cornell and Mayo Clinic
- 24 participants
  - Ibrutinib naïve
  - Ibrutinib plateau



NEW BTK INHIBITORS

Acalabrutinib monotherapy in patients with Waldenström macroglobulinemia: a single-arm, multicentre, phase 2 study



Owen et al. Lancet Haematol 2020

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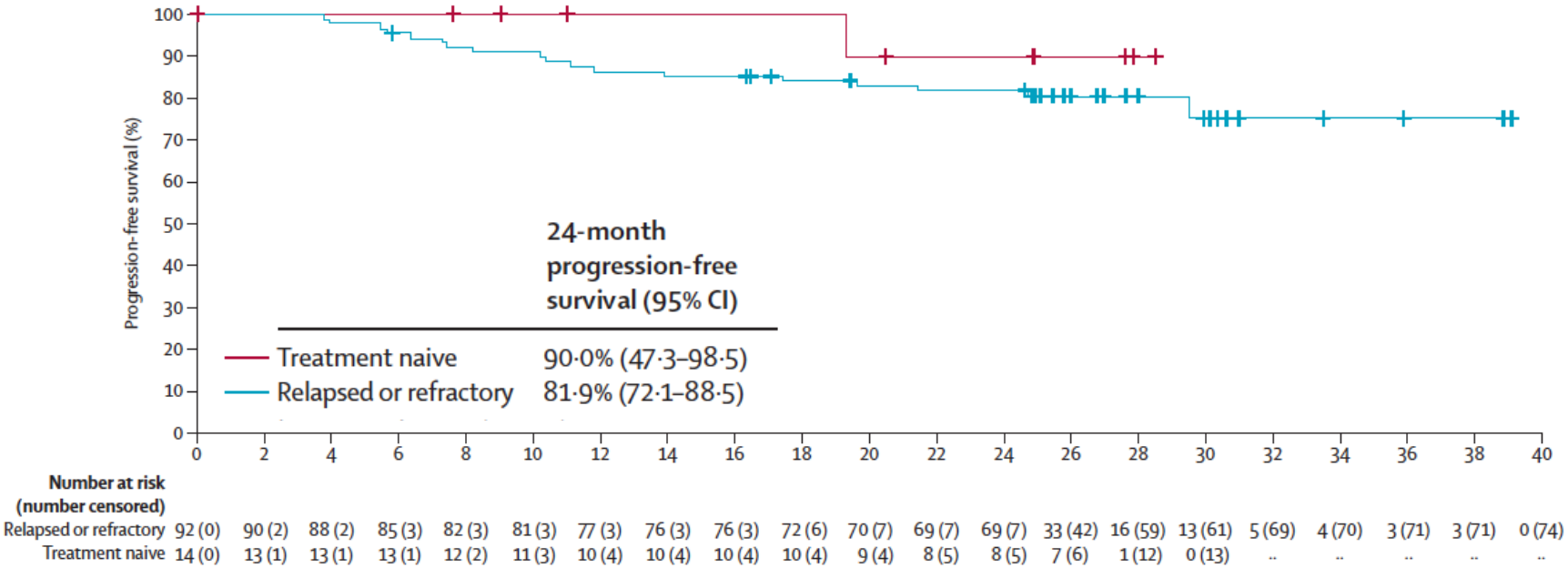
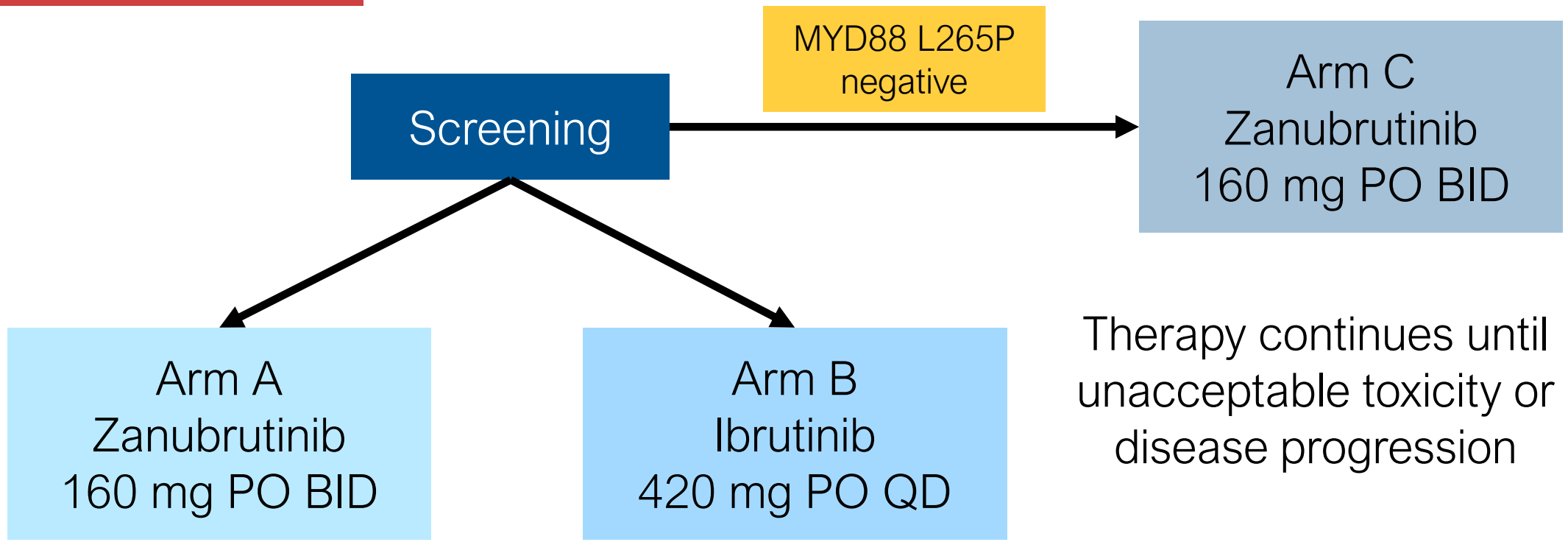


Grade 3/4 Adverse events
Neutropenia 6%/10%
Thrombocytopenia 2%/2%
LFT increased 7%/1%
Pneumonia 15%
Anemia 5%

Owen et al. Lancet Haematol 2020

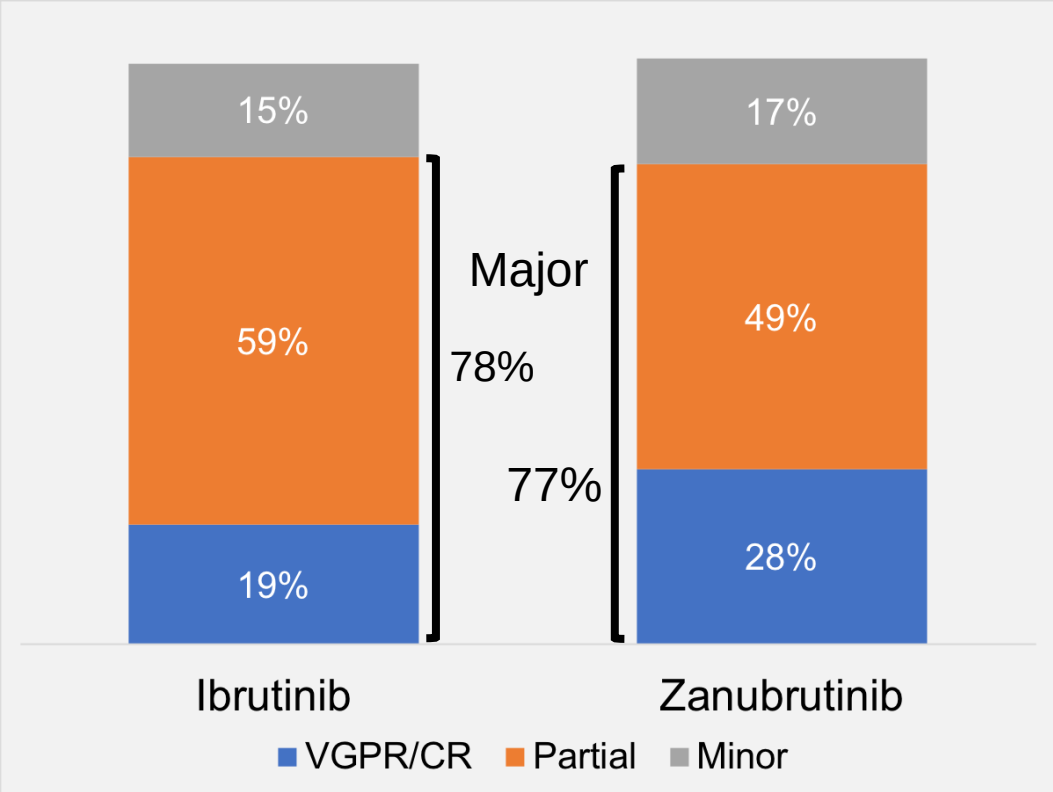
A Study Comparing Zanubrutinib and Ibrutinib in Subjects With Waldenström Macroglobulinemia

www.clinicaltrials.gov: NCT03053440



Therapy continues until unacceptable toxicity or disease progression

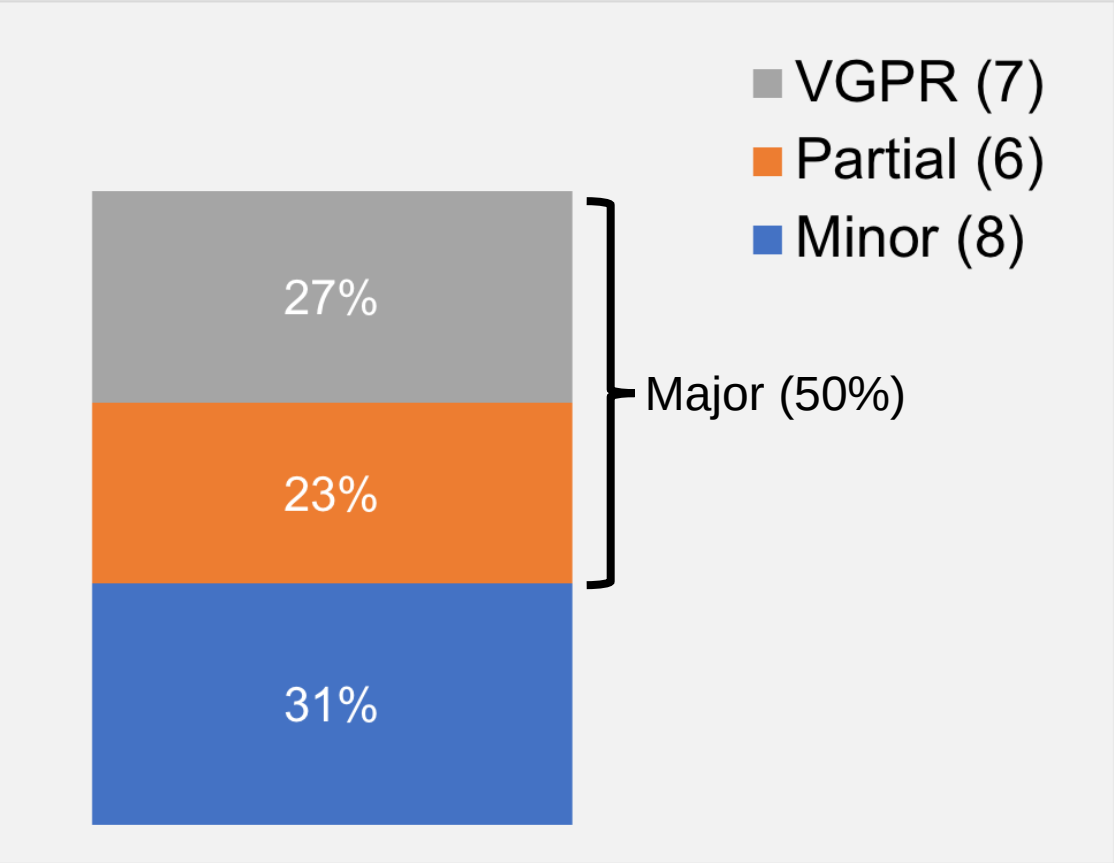
ASPEN: Phase III randomized trial of zanubrutinib versus ibrutinib for patients with Waldenström macroglobulinemia



Assessment, %	ZANU (n=102)	IBR (n=99)
CR+VGPR Rate	28.4	19.2
12-mo PFS/OS – overall population	89.7/97.0	87.2/93.9
12-mo PFS/OS – R/R population (n=83 vs 81)	92.4/98.8	85.9/92.5
AEs ≥Grade 3 / Grade 5	58.4 /1.0	63.3/4.1
AEs leading to discontinuation	4.0	9.2
Atrial fibrillation/flutter	2.0	15.3
Hypertension	10.9	17.3
Major bleeding[a]	5.9	9.2
Neutropenia	29.7	13.3

Tam et al. ASCO 2020

Updated results of the ASPEN trial from a cohort of patients with *MYD88* wild-type Waldenström macroglobulinemia

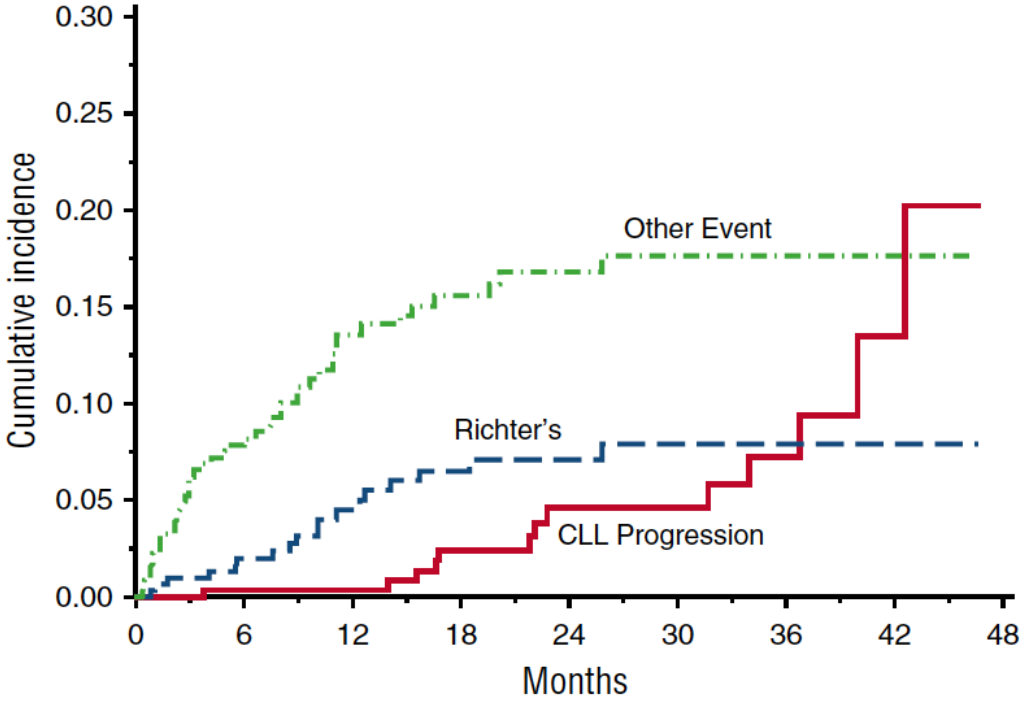


- 28 patients
- 5 TN, 23 RR
- NGS by NeoGenomics
- 12-month PFS 72%
- Adverse events:

Garcia-Sanz et al. ASCO 2020

NEW NEW BTK INHIBITORS

Resistance to covalent BTK inhibitors

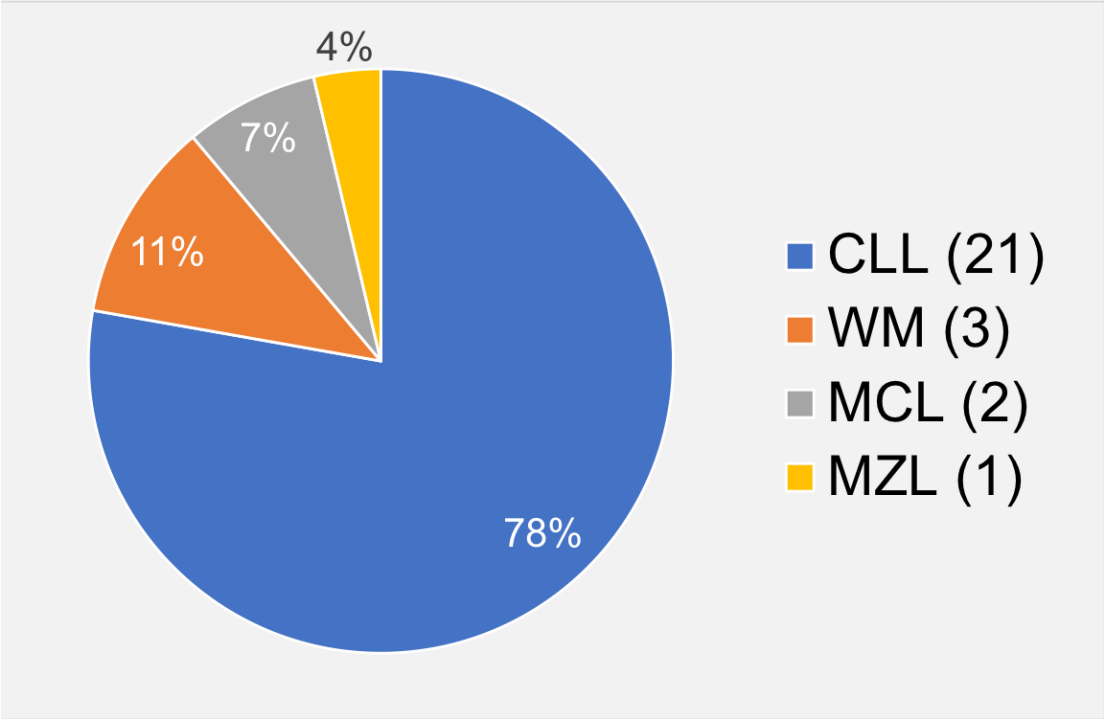


Woyach et al. Blood 2017

Mechanisms of resistance

- BTK mutations
  - BTK C481S
  - Reduces binding affinity
- PLCG2 mutations
  - Activates BCR with inactive BTK
- Present in 90% of patients at relapse on ibrutinib

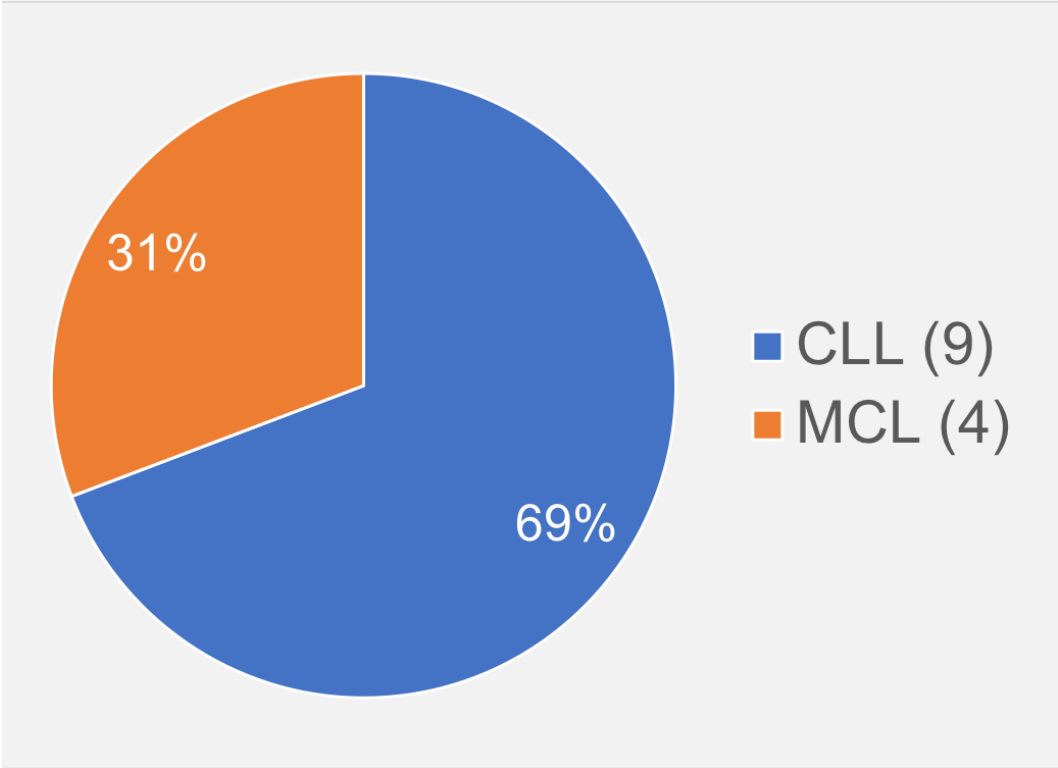
Phase 1B/2 Dose-Escalation and Cohort-Expansion Study of the Selective, Noncovalent, Reversible BTK Inhibitor, Vecabrutinib, in B-Cell Malignancies



Allan et al. ASH 2019

- 27 patients
- Prior lines 4 (2-9)
- Dose: 25-500 mg PO BID
- Enrolling at 300 mg PO BID
- Adverse events
  - Increased ALT
  - Neutropenia

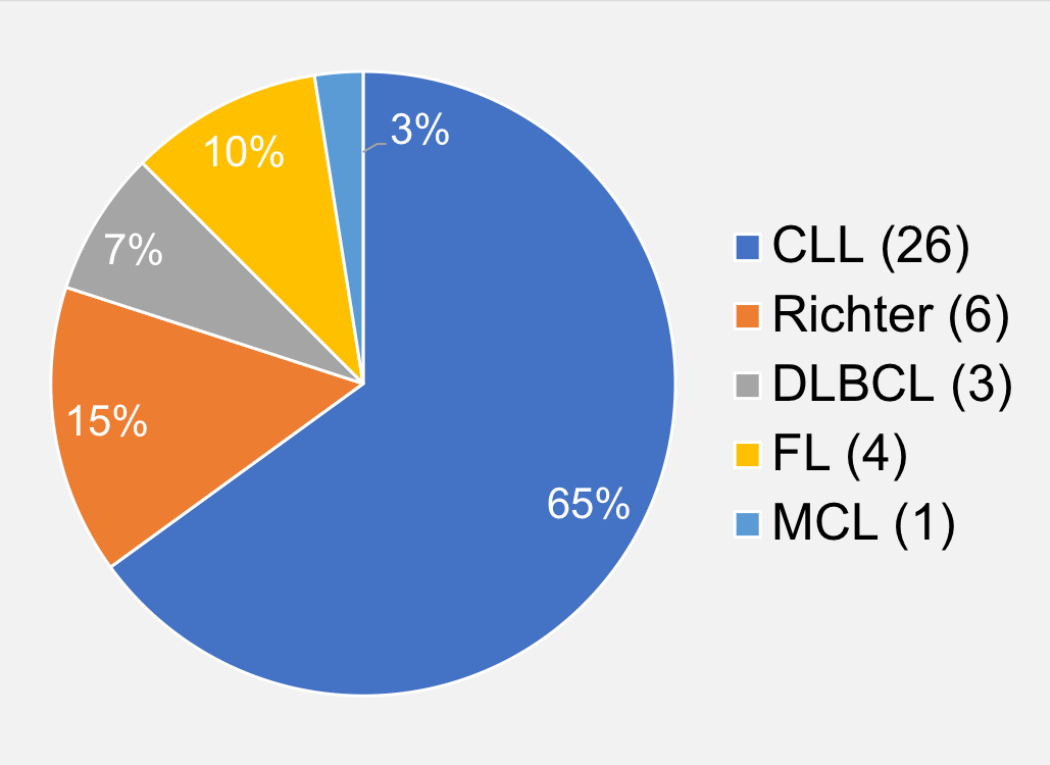
Phase 1 Trial in Pretreated B-Cell Malignancies for LOXO-305, a Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor



- 13 patients
- Prior lines 3 (2-6)
- Dose: 25-100 mg PO QD
- Responses in 7/8 patients
- No grade 3 side effects
- Enrolling WM patients intolerant or progressing on ibrutinib/acalabrutinib

Mato et al. ASH 2019

Phase 1, Dose Escalation Study Evaluating ARQ-531 in Patients with Relapsed or Refractory B-Cell Lymphoid Malignancies



Woyach et al. ASH 2019

- 40 patients
- Prior lines 4 (2-12)
- Dose: 5-75 mg PO QD
- Adverse events:
  - Neutropenia
  - Thrombocytopenia
  - Rash
- RP2D: 65 mg PO QD

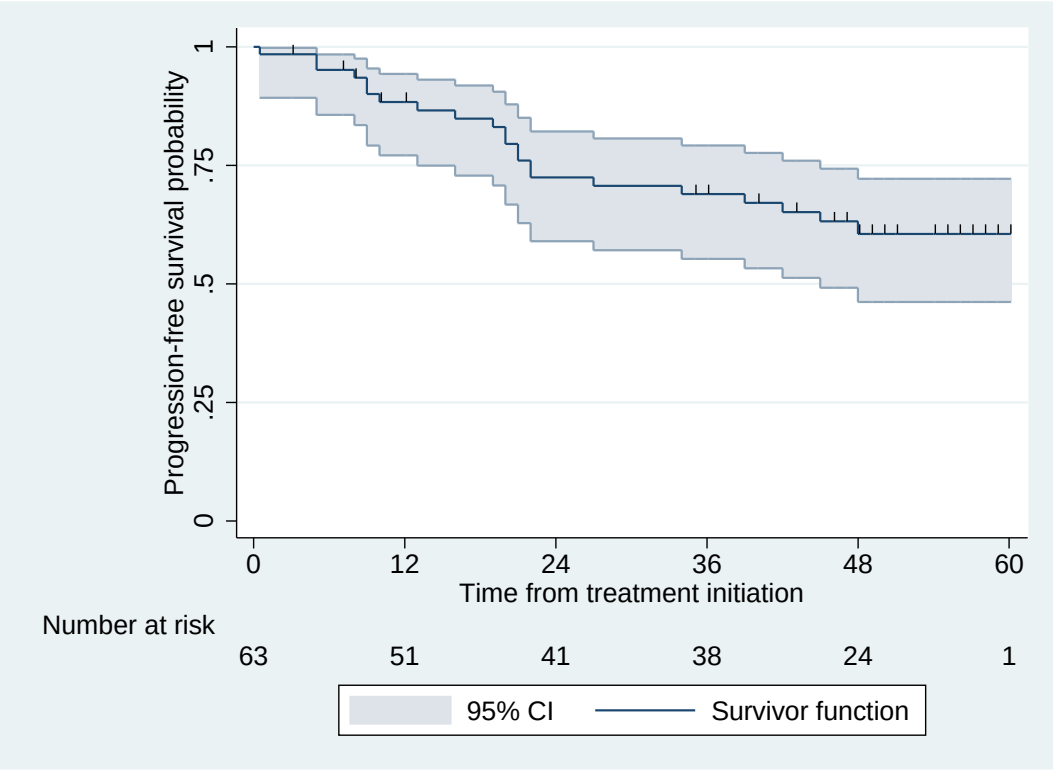
CXCR4 targeting agents

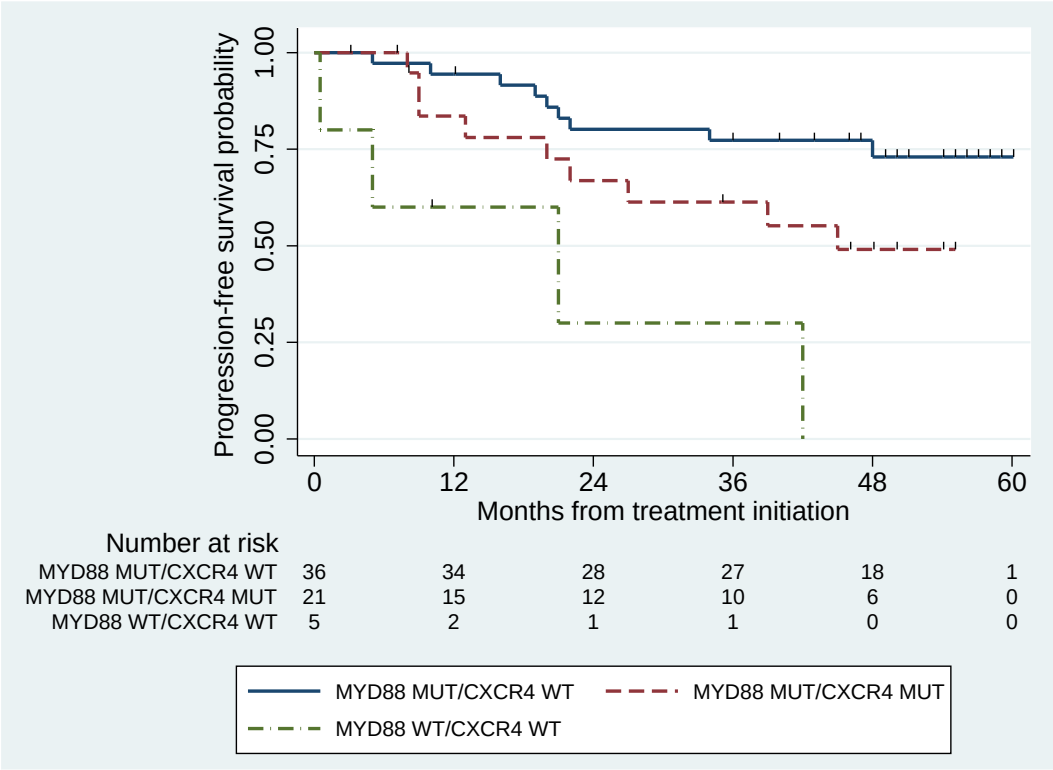
Responses to ibrutinib are impacted by MYD88 and CXCR4 mutational status

	ALL	$MYD88^{MUT}$ $CXCR4^{WT}$	$MYD88^{MUT}$ $CXCR4^{MUT}$	$MYD88^{WT}$ $CXCR4^{WT}$
N=	63	36	21	5
ORR	90%	100%	86%	60%
Major (>PR)	78%	97%	67%	0%
VGPR	27%	44%	10%	0%
TTR (mos.)	1.0	1.0	1.0	1.0
TTMR (mos.)	2.0	2.0	6.0	N/A

Treon et al. ASH 2017

Long-Term Follow-up of Previously Treated Patients Who Received Ibrutinib for Symptomatic Waldenström Macroglobulinemia: Update of Pivotal Clinical Trial





Treon et al. ASH 2017

Phase I/II Study of Ibrutinib plus Ulocuplumab in CXCR4 mutated WM Patients

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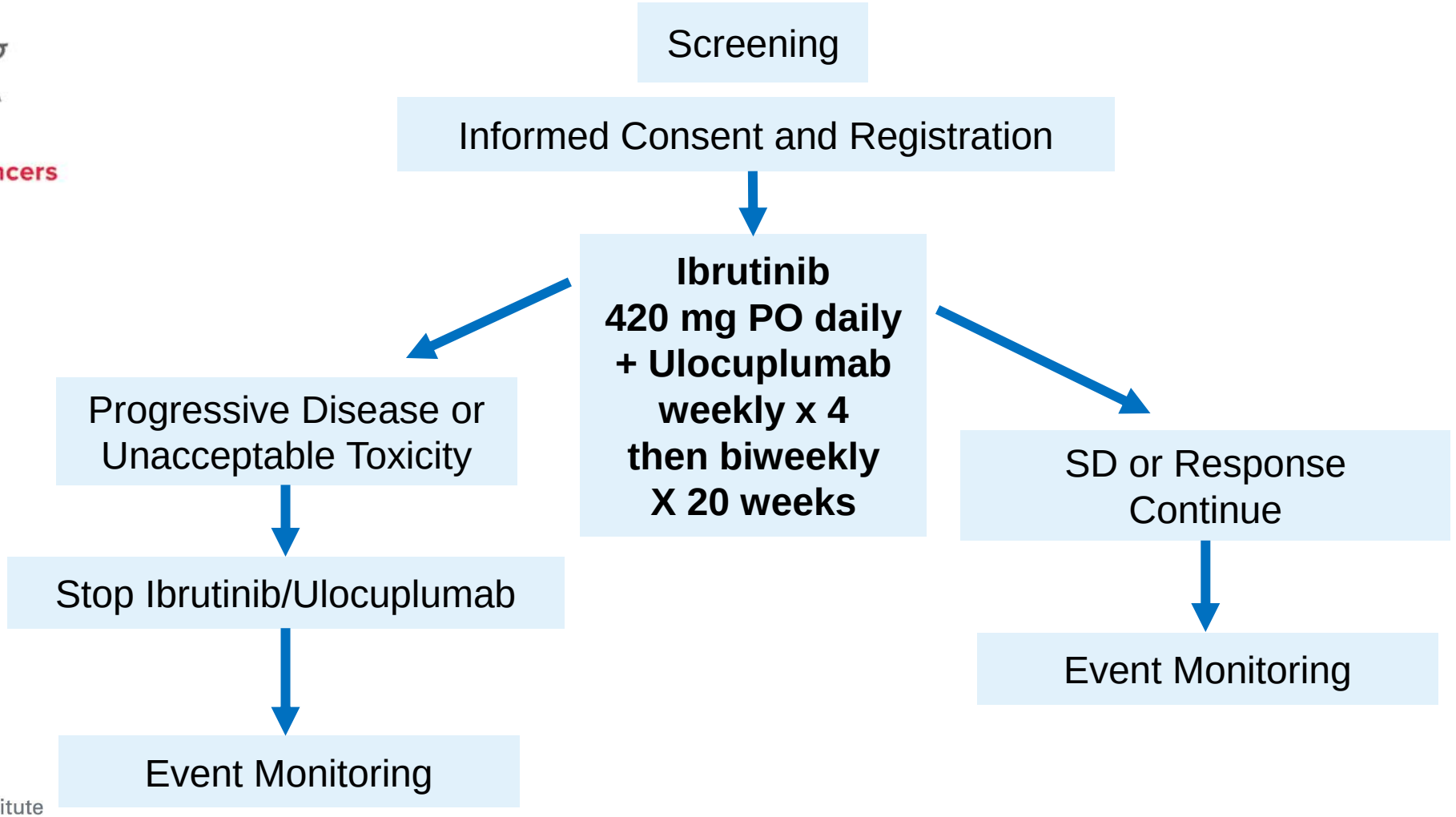
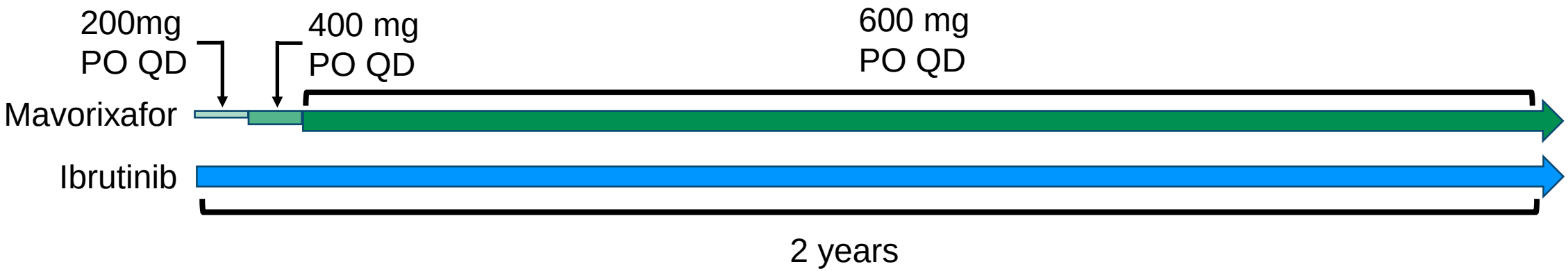
fighting blood cancers



A Study of Mavorixafor in Combination With Ibrutinib in Participants With Waldenstrom Macroglobulinemia Whose Tumors Express Mutations in MYD88 and CXCR4

- Multicenter
- 18 participants (TN and RR)



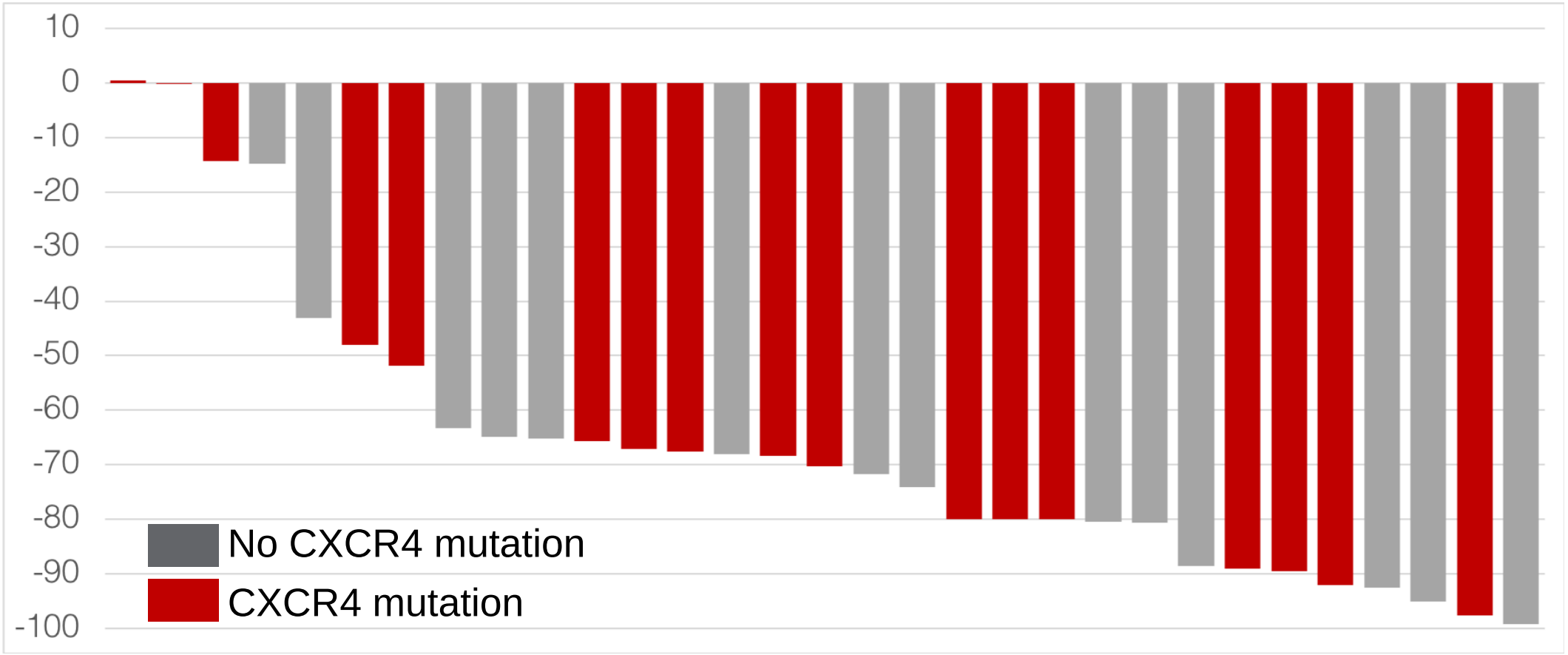
BCL2 inhibitors

Multicenter prospective phase II study of venetoclax in patients with previously treated Waldenström macroglobulinemia

Characteristic	Number (%)
Age (years)	66 (39-80)
Previous treatments	2 (1-10)
Prior BTK inhibitors	16 (52%)
MYD88 L265P	31 (100%)
CXCR4 mutations	17 (55%)
Serum IgM level (mg/dl)	3,543 (642-7,970)
Hemoglobin level (g/dl)	10.6 (6.4-13.5)
Platelet count (K/ul)	222 (7-445)
Lymphadenopathy	9 (29%)
Splenomegaly	6 (19%)

Castillo et al. IMW 2019

Multicenter prospective phase II study of venetoclax in patients with previously treated Waldenström macroglobulinemia



Castillo et al. IMW 2019

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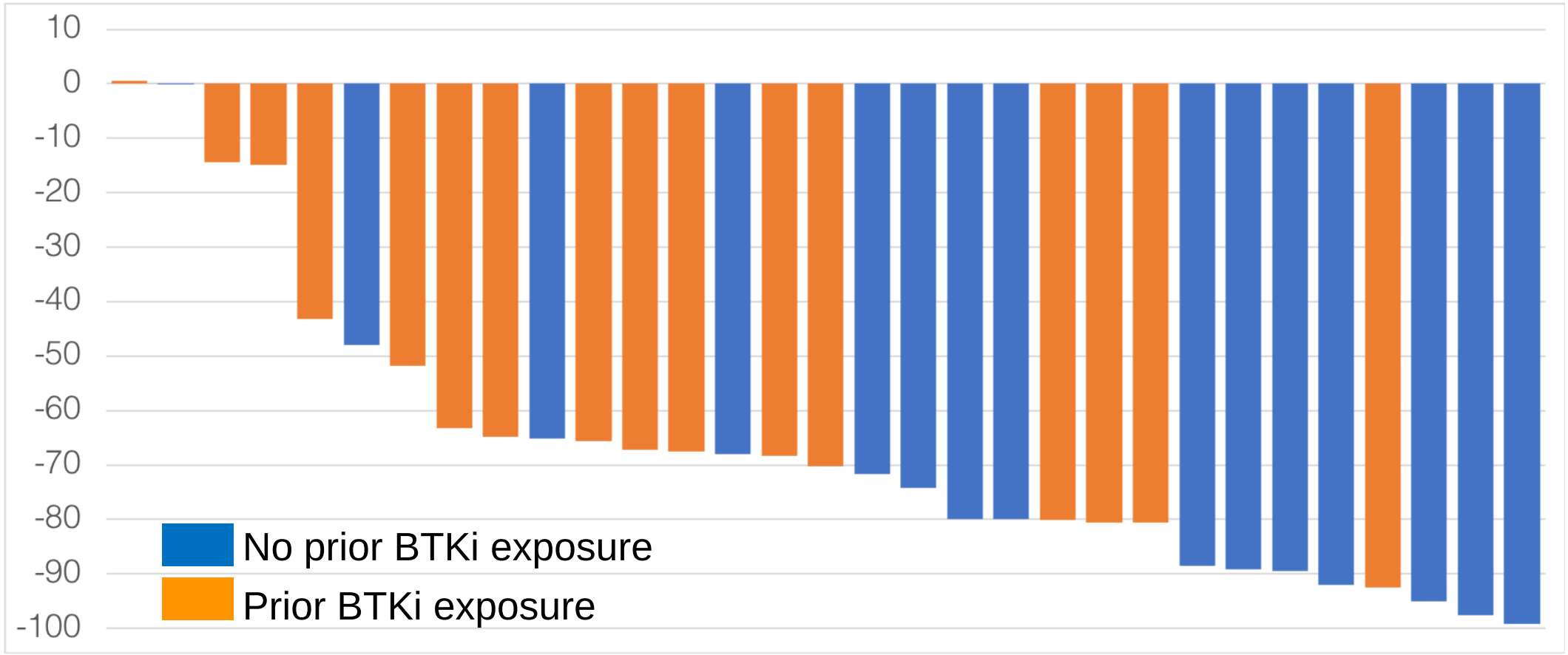

Castillo et al. IMW 2019

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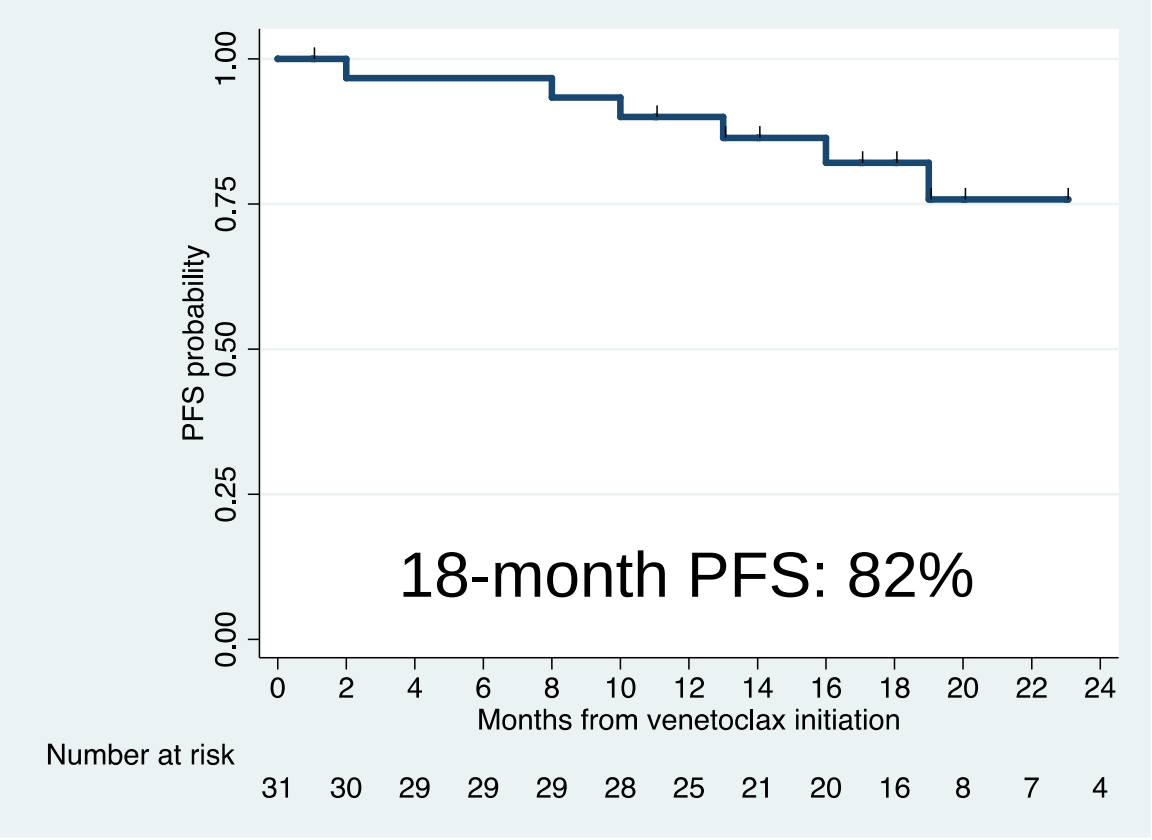


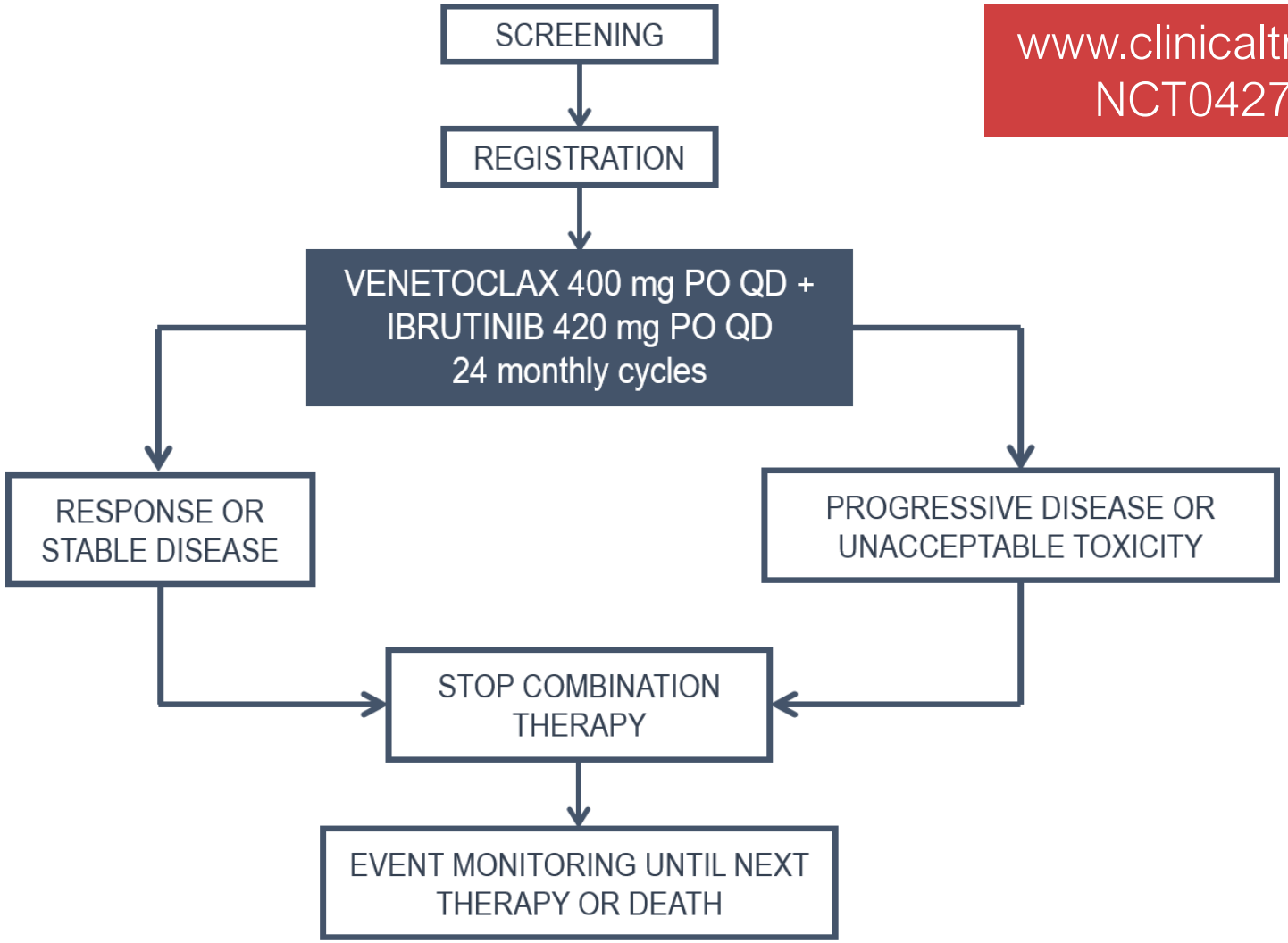
Castillo et al. IMW 2019

Adverse events

- Grade 4 events
  - Neutropenia (n=5)
- Grade 3 events
  - Neutropenia (n=15)
  - Anemia (n=4)
  - Diarrhea (n=4)

Ibrutinib and venetoclax for patients with previously untreated Waldenström macroglobulinemia

www.clinicaltrials.gov:
NCT04273139

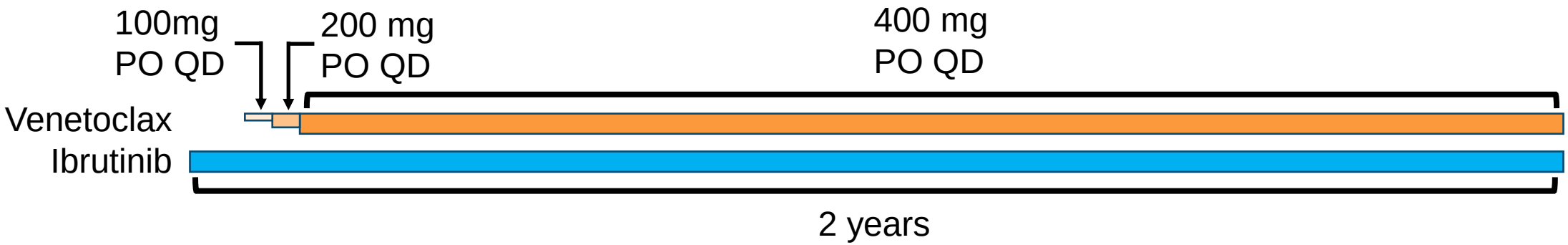


Ibrutinib and venetoclax for patients with previously untreated Waldenström macroglobulinemia

Sample size
50 patients (TN)

Primary outcome
VGPR ≥40%

Secondary outcomes
- Impact of genomic profiling
- Overall response rate
- Safety profile



A Look into the Future: Treatments on the Horizon

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