Novel therapies for Waldenström macroglobulinemia

Jorge J. Castillo, MD
Associate Professor of Medicine
Harvard Medical School
JorgeJ_Castillo@dfci.harvard.edu

Dana-Farber
Cancer Institute

Clinical trials

- Pinnacle of medical research
- Patients become participants
- Physicians become investigators
- Every current standard of care was a past clinical trial

Clinical trials

- Phase I – safety
- Phase II – efficacy
- Phase III – comparative efficacy
- Phase IV – post-marketing

Ongoing studies

Rituximab and Ibrutinib (RI) Versus Dexamethasone, Rituximab and Cyclophosphamide (DRC) as Initial Therapy for Waldenström Macroglobulinemia (RAINBOW)

- UK
- 148 participants (TN) randomized 1:1

www.clinicaltrials.gov: NCT04061512

Experimental Arm
Ibrutinib
Rituximab

Comparator Arm
Cyclophosphamide
Dexamethasone
Rituximab

Primary outcomes
Response at 24 weeks
PFS at 2 years

Secondary Outcomes
Safety and tolerability
Overall response rate
Time to next treatment
Duration of response
Overall survival (OS)
Quality of Life

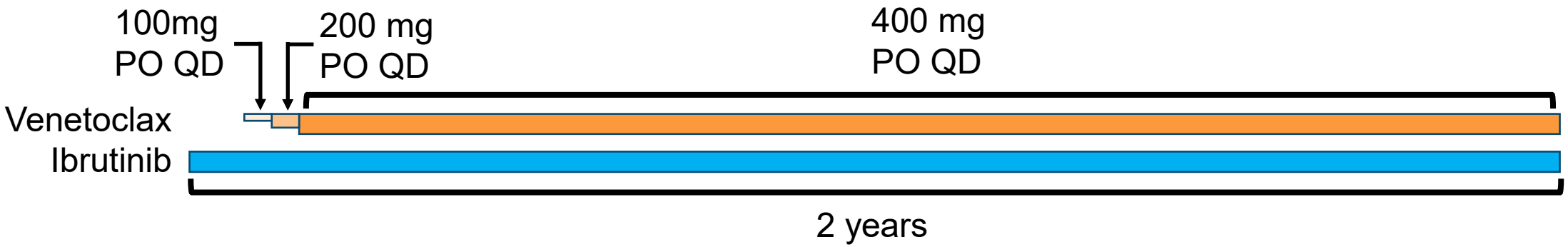
Ibrutinib and venetoclax for patients with previously untreated Waldenström macroglobulinemia

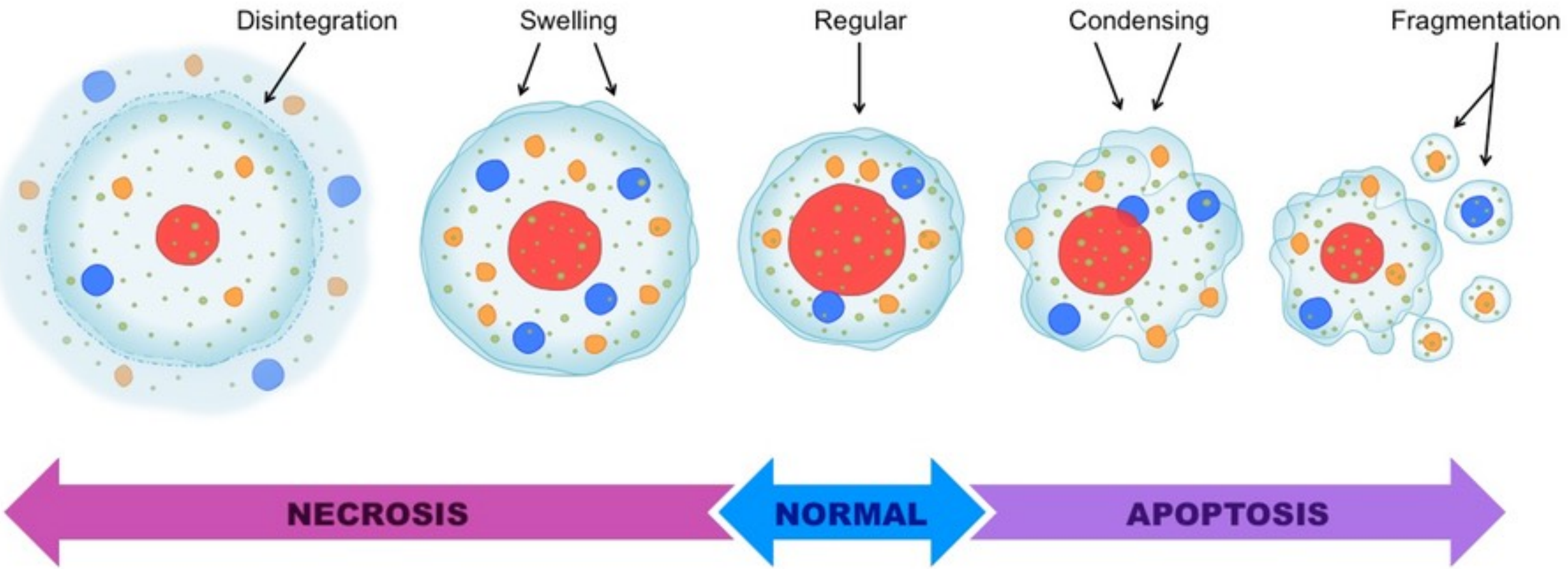
Sample size
50 participants (TN)

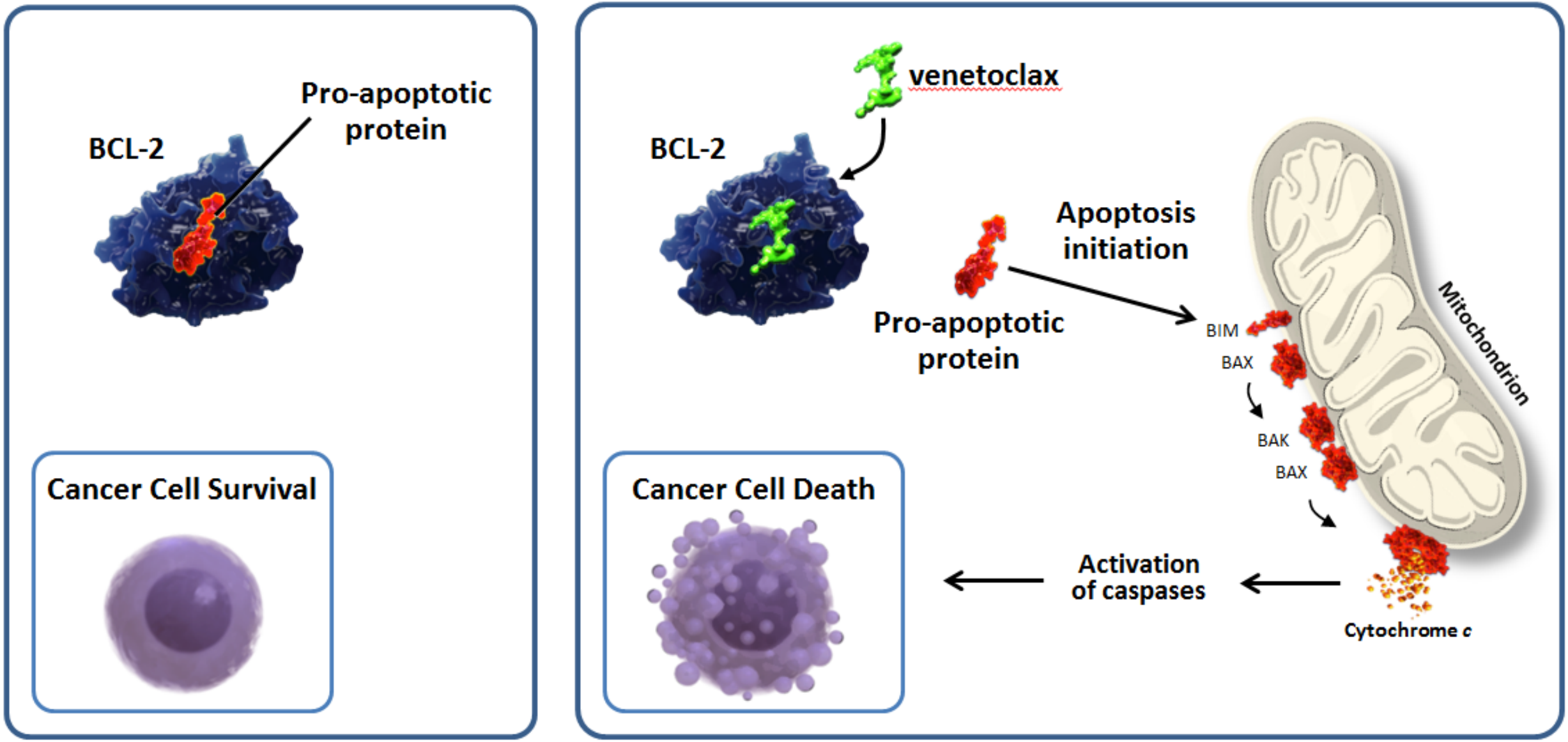
Primary outcome
VGPR ≥40%

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

www.clinicaltrials.gov: NCT04273139

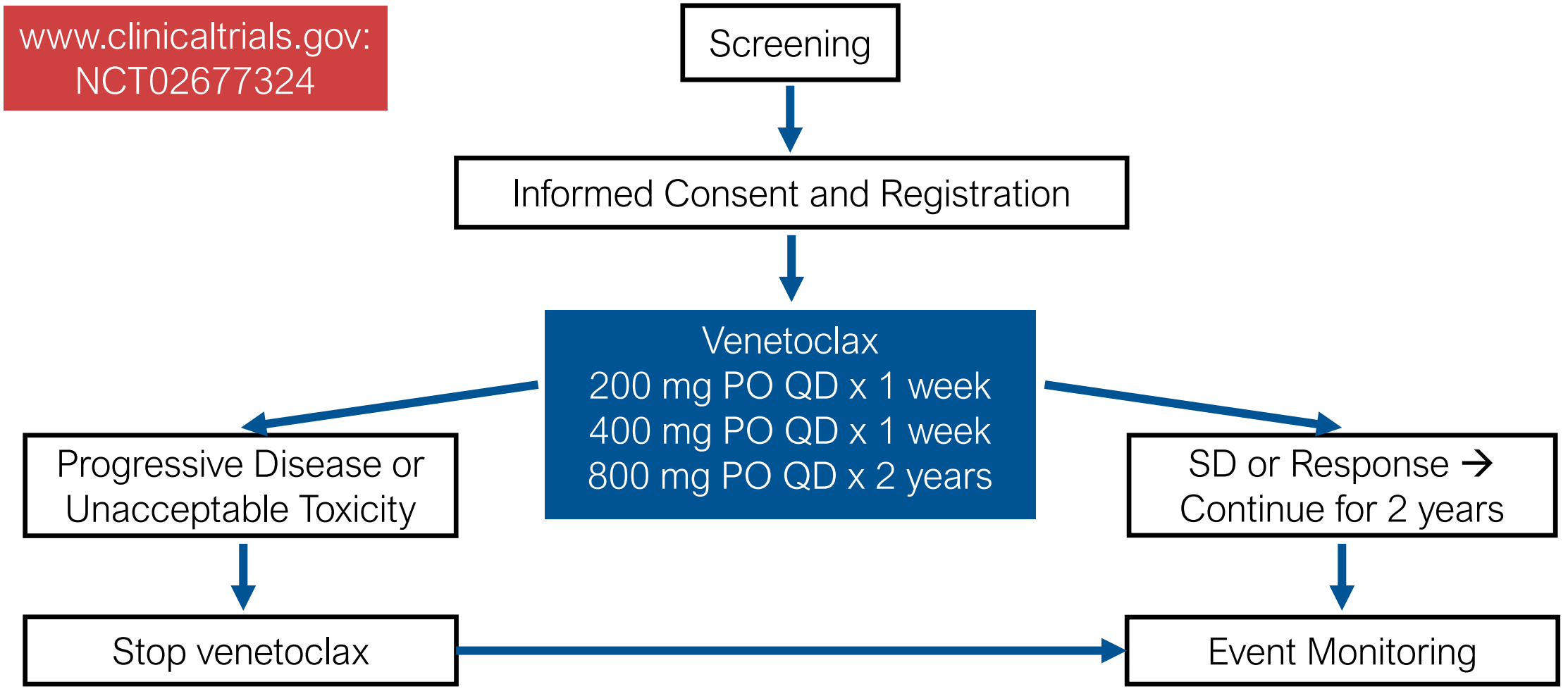



Disintegration
Swelling
Regular
Condensing
Fragmentation
NECROSIS
NORMAL
APOPTOSIS

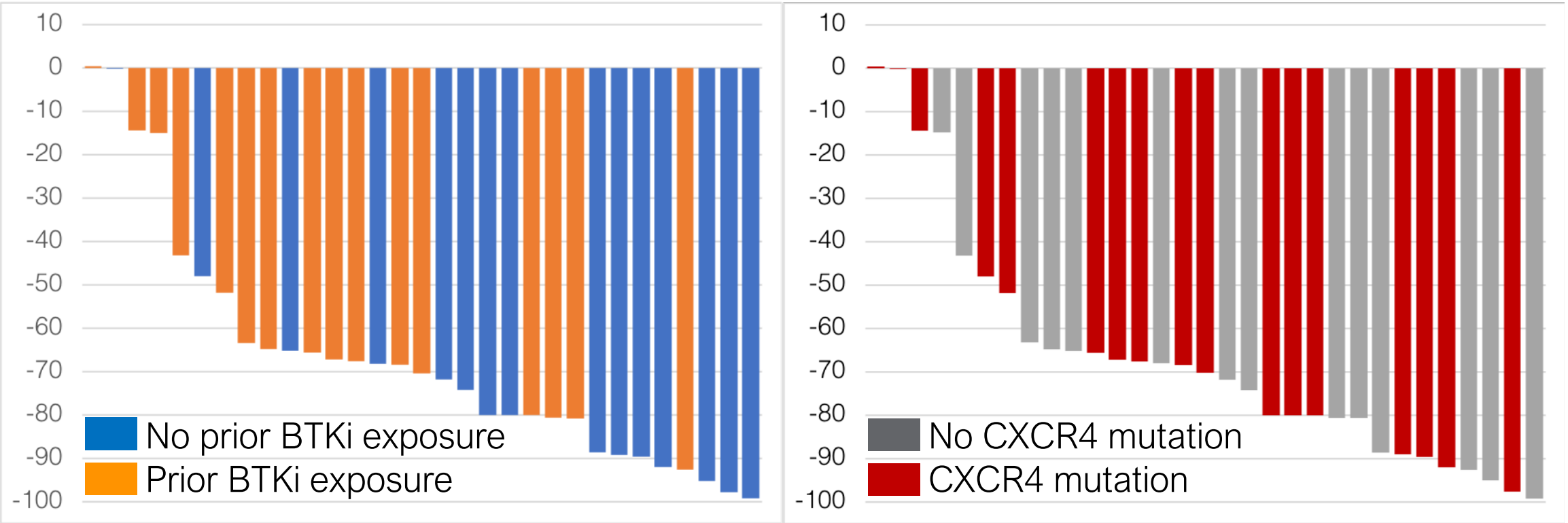

Pro-apoptotic protein
BCL-2
Cancer Cell Survival
venetoclax
BCL-2
Apoptosis initiation
Pro-apoptotic protein
BIM
BAX
BAK
BAX
Mitochondrion
Cytochrome c
Activation of caspases
Cancer Cell Death

Study design

www.clinicaltrials.gov:
NCT02677324

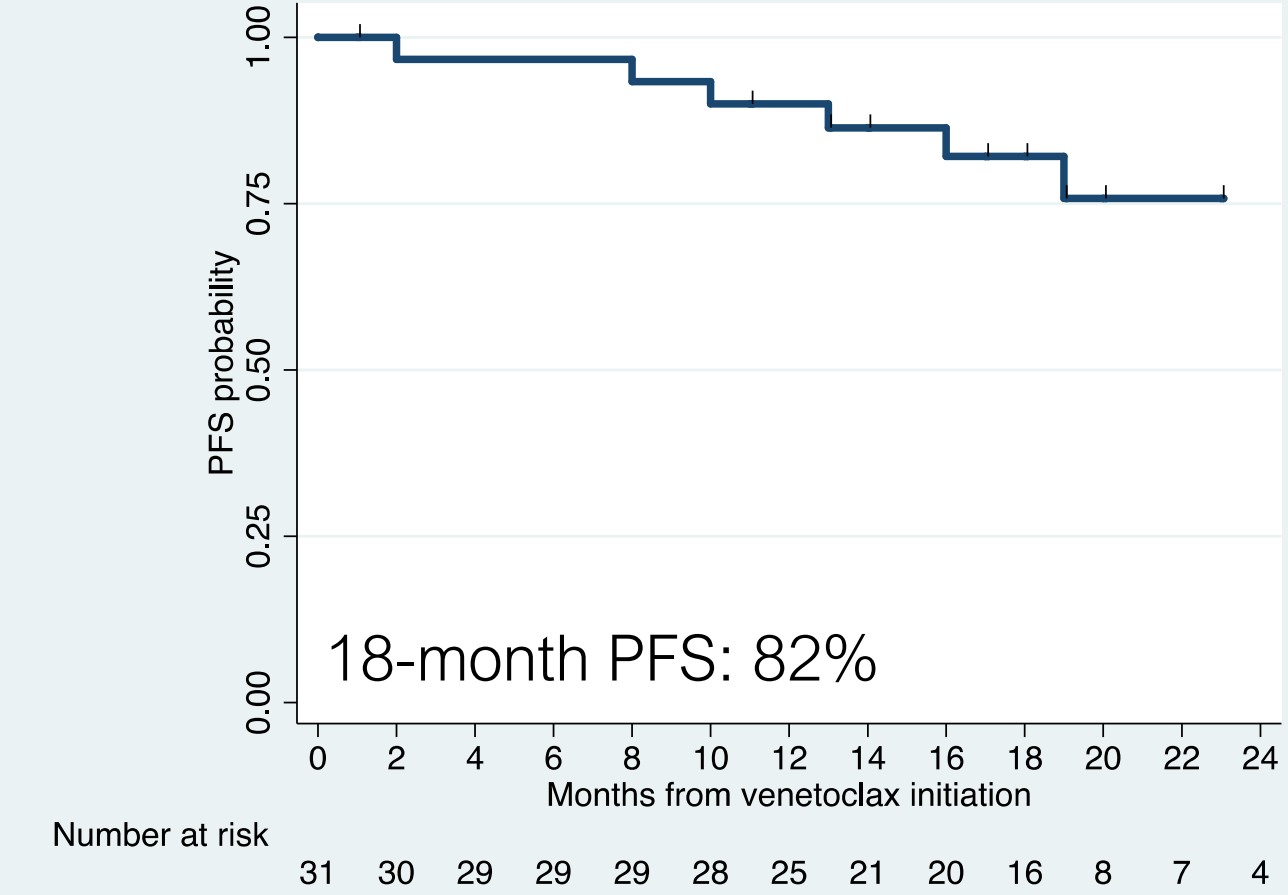


Multicenter prospective phase II study of venetoclax in previously treated Waldenström macroglobulinemia



Castillo et al. IMW 2019

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

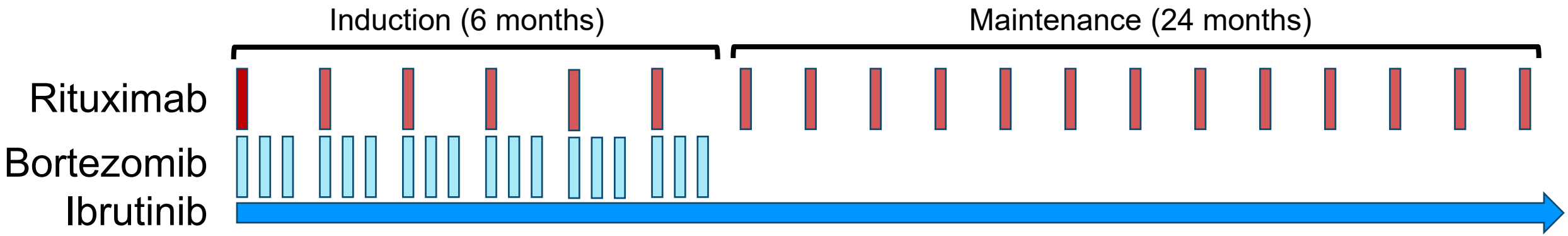


Castillo et al. IMW 2019

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

- Germany
- 53 participants
- SQ bortezomib, SQ rituximab, ibrutinib
- Enrolling

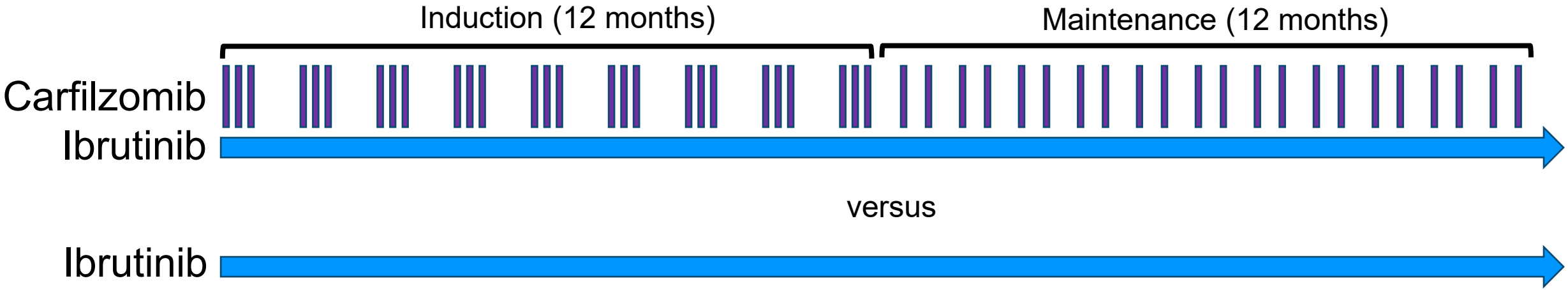
www.clinicaltrials.gov: NCT03620903



Efficacy of Carfilzomib in Combination With Ibrutinib in Waldenström Macroglobulinemia (CZAR-1)

- Germany
- 184 participants (TN and RR)
- Randomization 1:1
- Enrolling

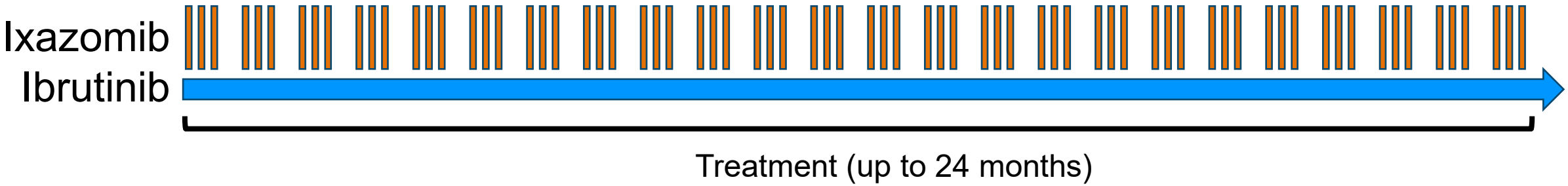
www.clinicaltrials.gov: NCT04263480



Ibrutinib and Ixazomib Citrate in Treating Relapsed or Refractory Waldenstrom Macroglobulinemia

- Mayo Clinic and NCI
- 47 patients
- Enrollment suspended for interim analysis

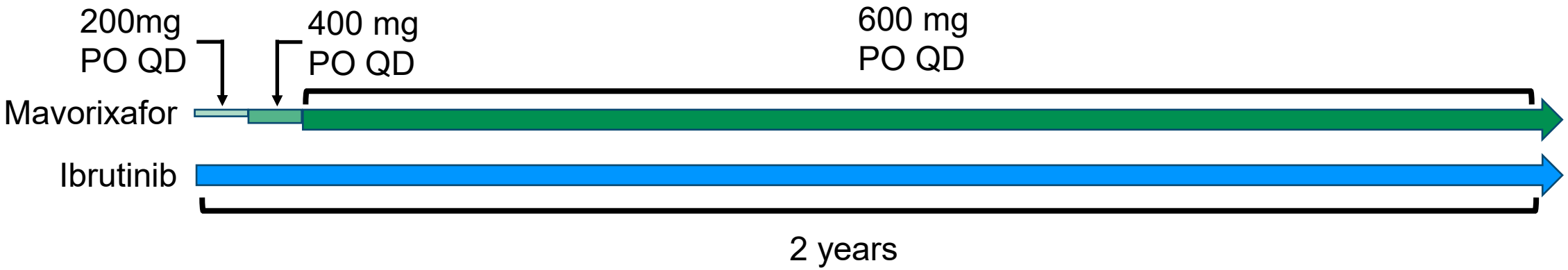
www.clinicaltrials.gov: NCT03506373



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

- Multicenter
- 20 participants (TN and RR)
- Enrolling

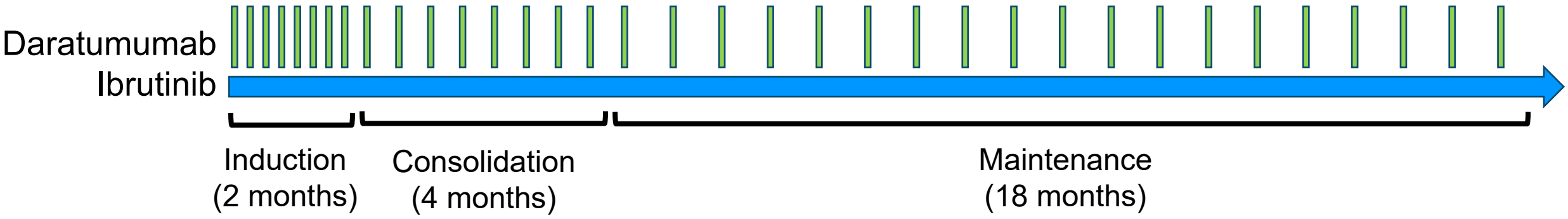
www.clinicaltrials.gov: NCT04274738



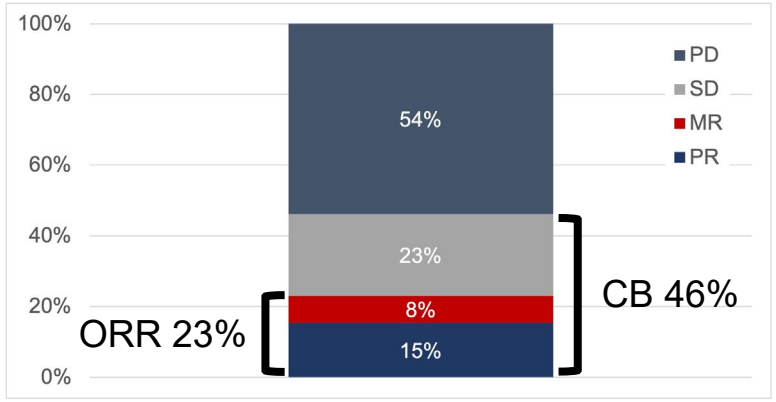
Daratumumab Plus Ibrutinib in Patients With Waldenström Macroglobulinemia

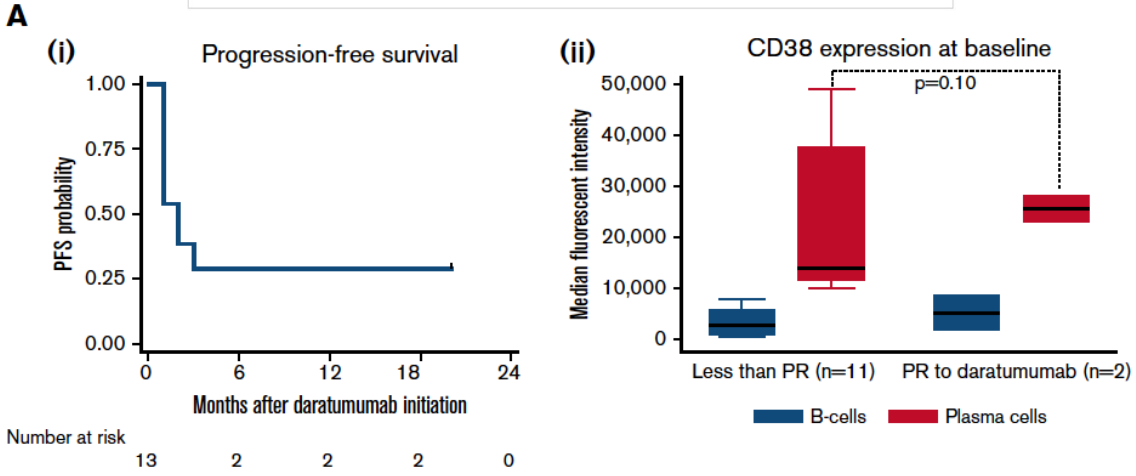
- Weill Cornell and Mayo Clinic
- 24 participants
  - Ibrutinib naïve and ibrutinib plateau
- Enrolling

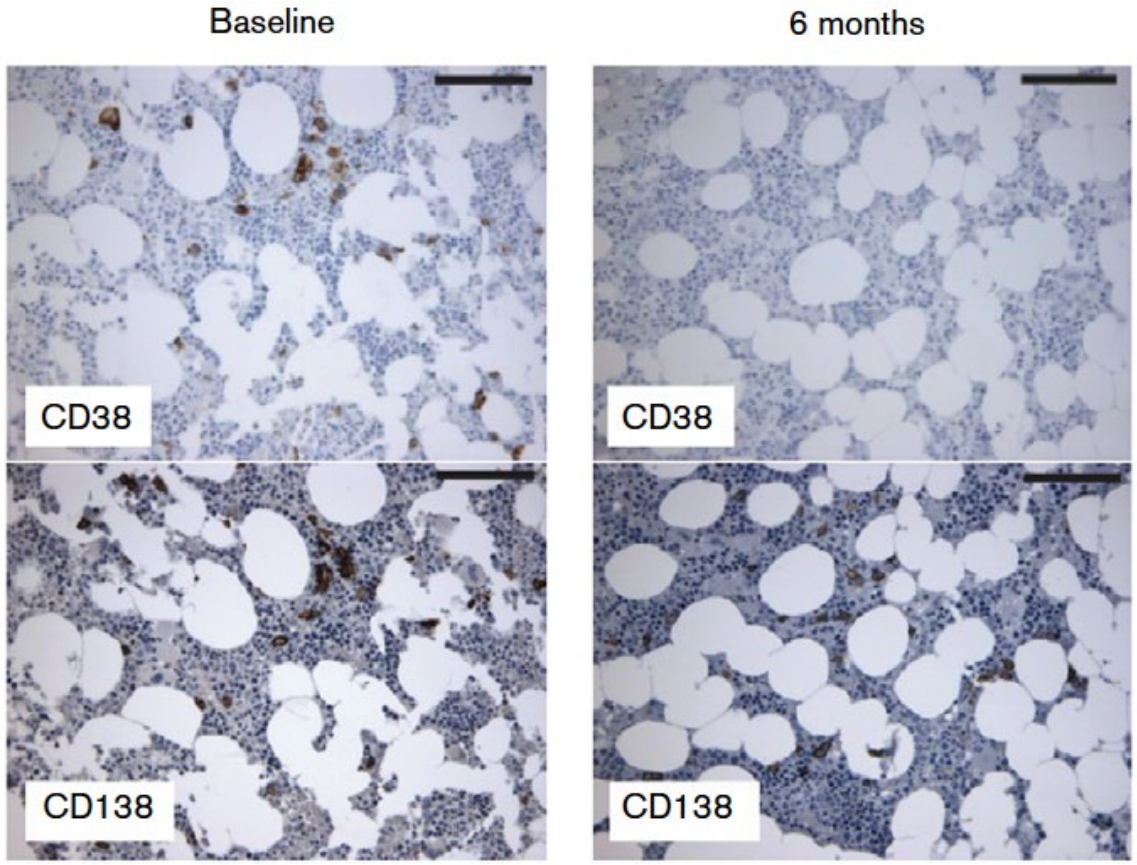
www.clinicaltrials.gov: NCT03679624



Multicenter phase 2 study of daratumumab monotherapy in patients with previously treated Waldenström macroglobulinemia





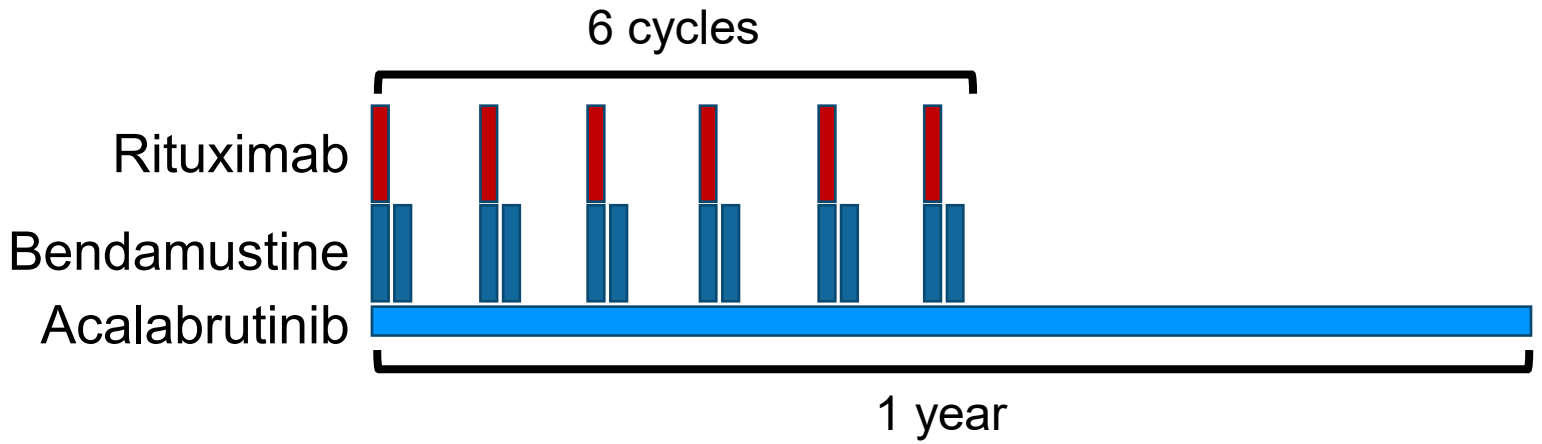


Castillo et al. Blood Adv 2020

Bendamustine, Rituximab and Acalabrutinib in Waldenström Macroglobulinemia (BRAWM)

- Canada
- 59 participants (TN)
- Enrolling

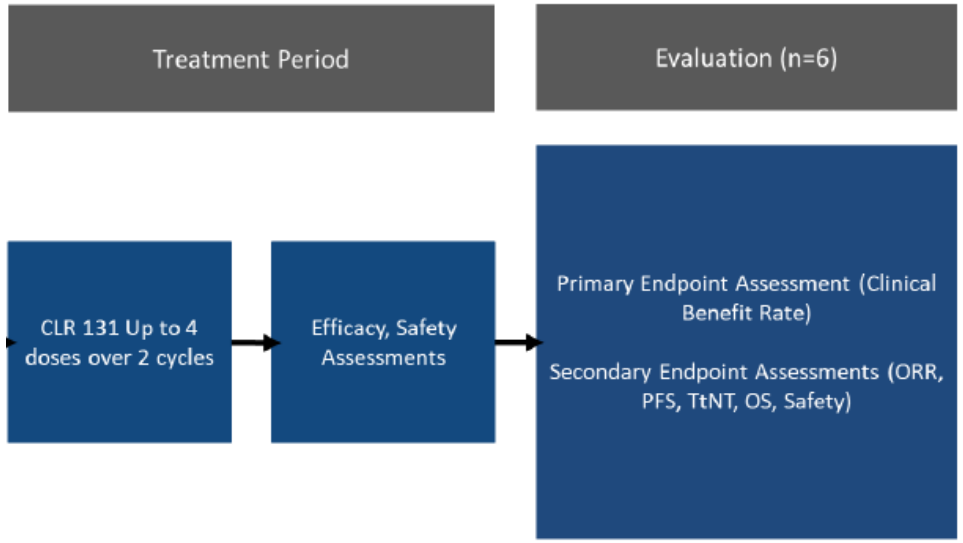
www.clinicaltrials.gov: NCT04624906

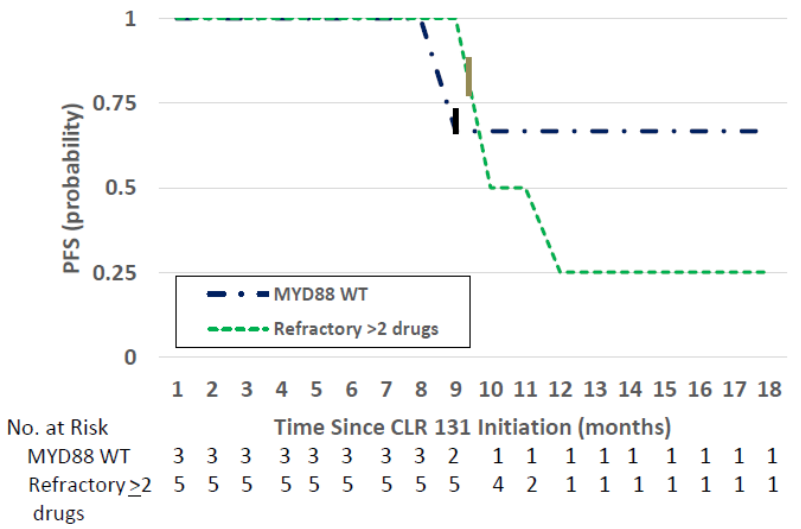


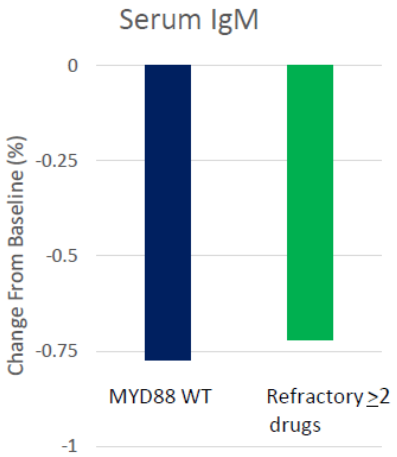
Study of CLR 131 in Select B-Cell Malignancies (CLOVER-1) and Pivotal Expansion in Waldenström Macroglobulinemia (CLOVER-WaM)

www.clinicaltrials.gov: NCT02952508

- 120 participants (RR)
- Includes myeloma, CNS lymphoma and WM
- Enrolling





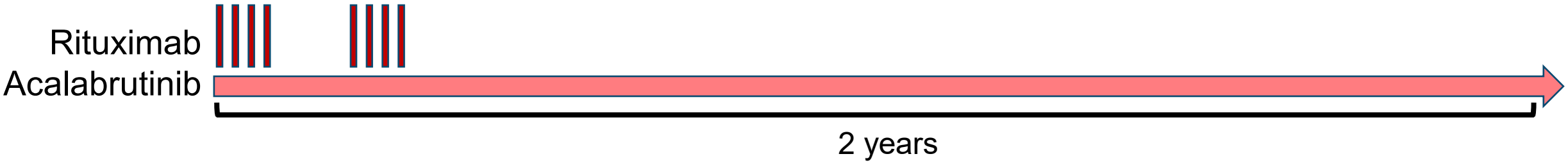


Ailawadhi et al. ASCO 2021

Acalabrutinib and Rituximab In Anti-MAG Mediated Neuropathy

- 33 participants
- Anti-MAG antibodies + neuropathy
- IgM MGUS and WM
- Not yet enrolling

www.clinicaltrials.gov: NCT05065554



Testing the Addition of a New Drug, Venetoclax, to the Usual Treatment (Ibrutinib and Rituximab) for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma

- 68 participants (TN)
- Randomized 1:1
- Suspended (FDA comments)

www.clinicaltrials.gov: NCT04840602

Experimental Arm
Ibrutinib
Rituximab
Venetoclax

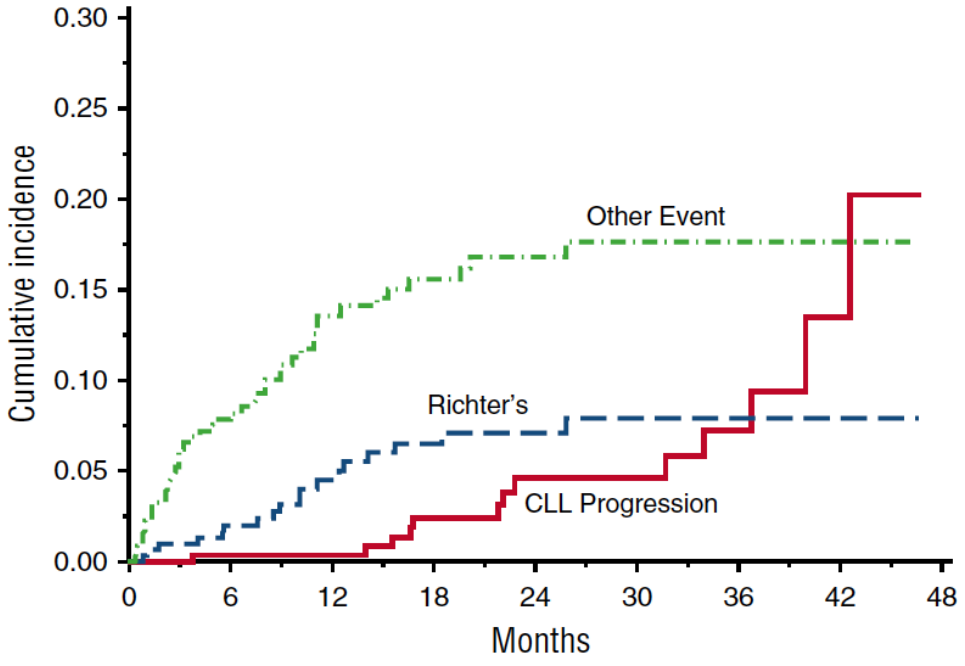
Comparator Arm
Ibrutinib
Rituximab

Primary outcome
Complete response rate

Secondary Outcomes
Time to complete response
Overall response rate
Progression-free survival
Overall survival
VGPR rate
Adverse events

Planned studies

Resistance to covalent BTK inhibitors



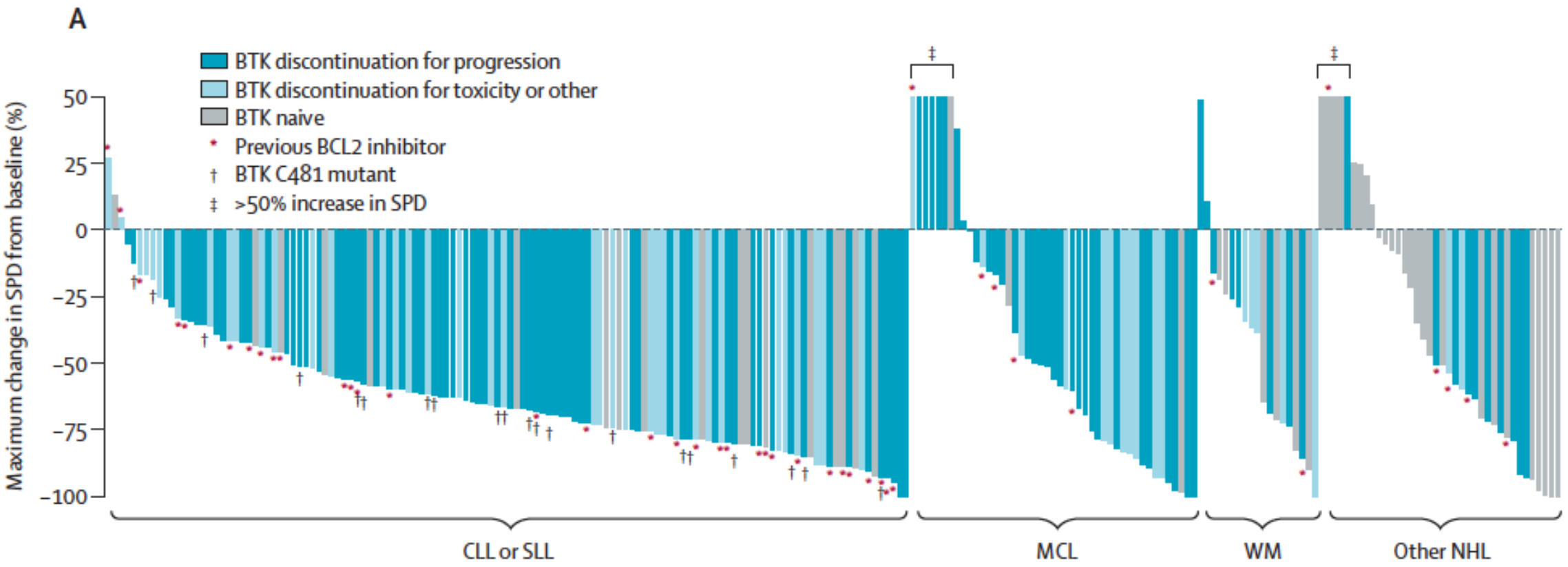
Cumulative Incidence Estimates (95% CI)	At 12 months	At 18 months
CLL Progression	0.3% (0% to 1.0%)	2.4% (0.3% to 4.6%)
Richter's	4.5% (2.0% to 7.0%)	6.5% (3.3% to 9.6%)
Other Event	13.5% (9.5% to 17.6%)	15.6% (11.1% to 20.0%)

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

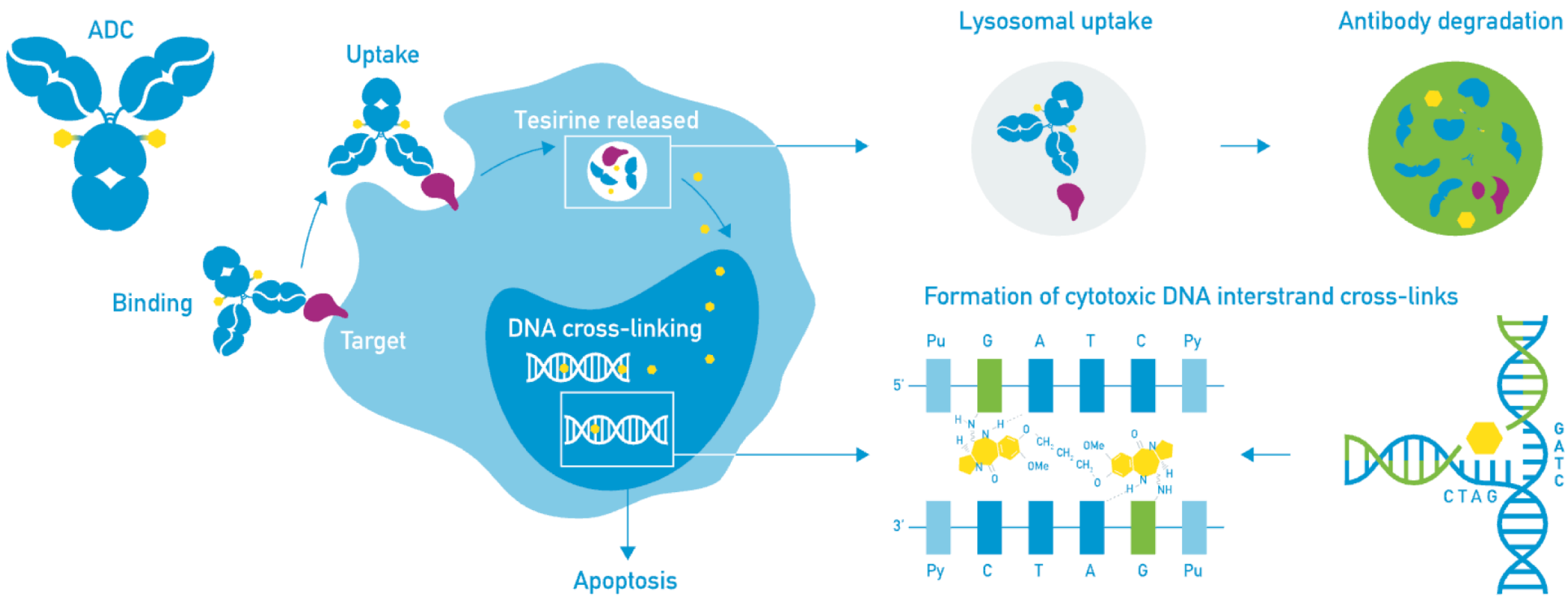
Woyach et al. Blood 2017

Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study



Mato et al. Lancet 2021

Loncastuximab – anti-CD19 ADC



Conclusions

- Several exciting clinical trials are ongoing
  - BTK inhibitor combinations: Doublets, triplets
  - Non-covalent BTK inhibitors
  - Immunotherapy
- Always consider participating in clinical trials
- Do your homework!

Novel therapies for Waldenström macroglobulinemia

Jorge J. Castillo, MD
Associate Professor of Medicine
Harvard Medical School
JorgeJ_Castillo@dfci.harvard.edu

Dana-Farber
Cancer Institute