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Mantle Cell Lymphoma

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Disclosures

Advisory Committee and Consulting Agreements	Celgene Corporation, Gilead Sciences Inc, Takeda Oncology, TG Therapeutics Inc
Contracted Research	Allos Therapeutics, Celgene Corporation, Gilead Sciences Inc, Novartis, TG Therapeutics Inc

Case presentation: Dr Johl

65-year-old woman with MCL

- Presented with left neck adenopathy
- Biopsy: Stage IV MCL with marrow, splenic and nodal involvement
- R-CHOP x 3 cycles alternating with R-DHAP x 3 cycles → complete response → ASCT → R maintenance
- Disease progression 8 months later

Additional questions regarding the management of MCL

Dr Sinha

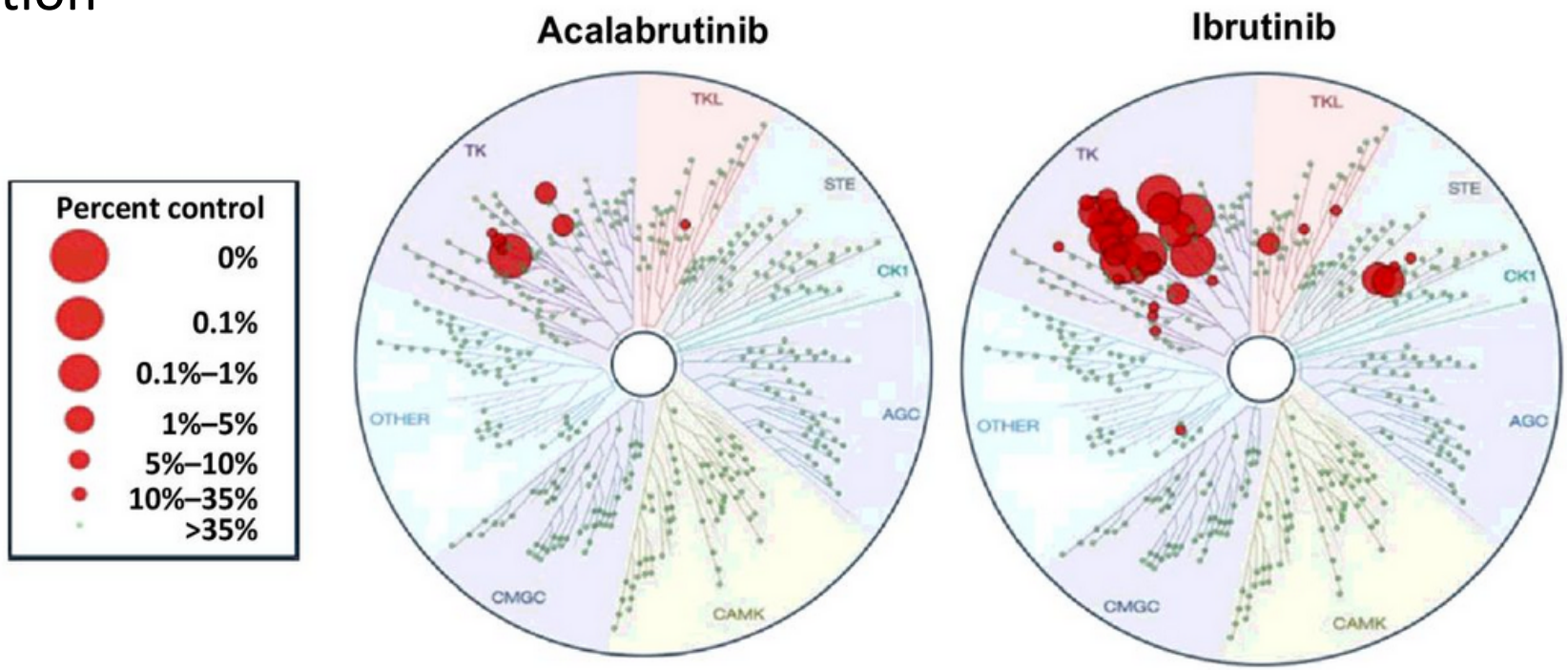
Novel Approaches to R/R MCL

Agent	N	Response Rate	mDOR
Bortezomib	155	33%	9.2 months
Temsirolimus	54	22%	7.1 months
Lenalidomide	134	28%	16.6 months
Lenalidomide-rituximab (R^2)	52	57%	18.9 months
Idelalisib	40	40%	4 months
Ibrutinib	111	68%	17.5 months
Acalabrutinib	124	81%	72% at 12 months
Venetoclax (ABT-199)	28	75%	?

Courtesy, B. Kahl, July 2018

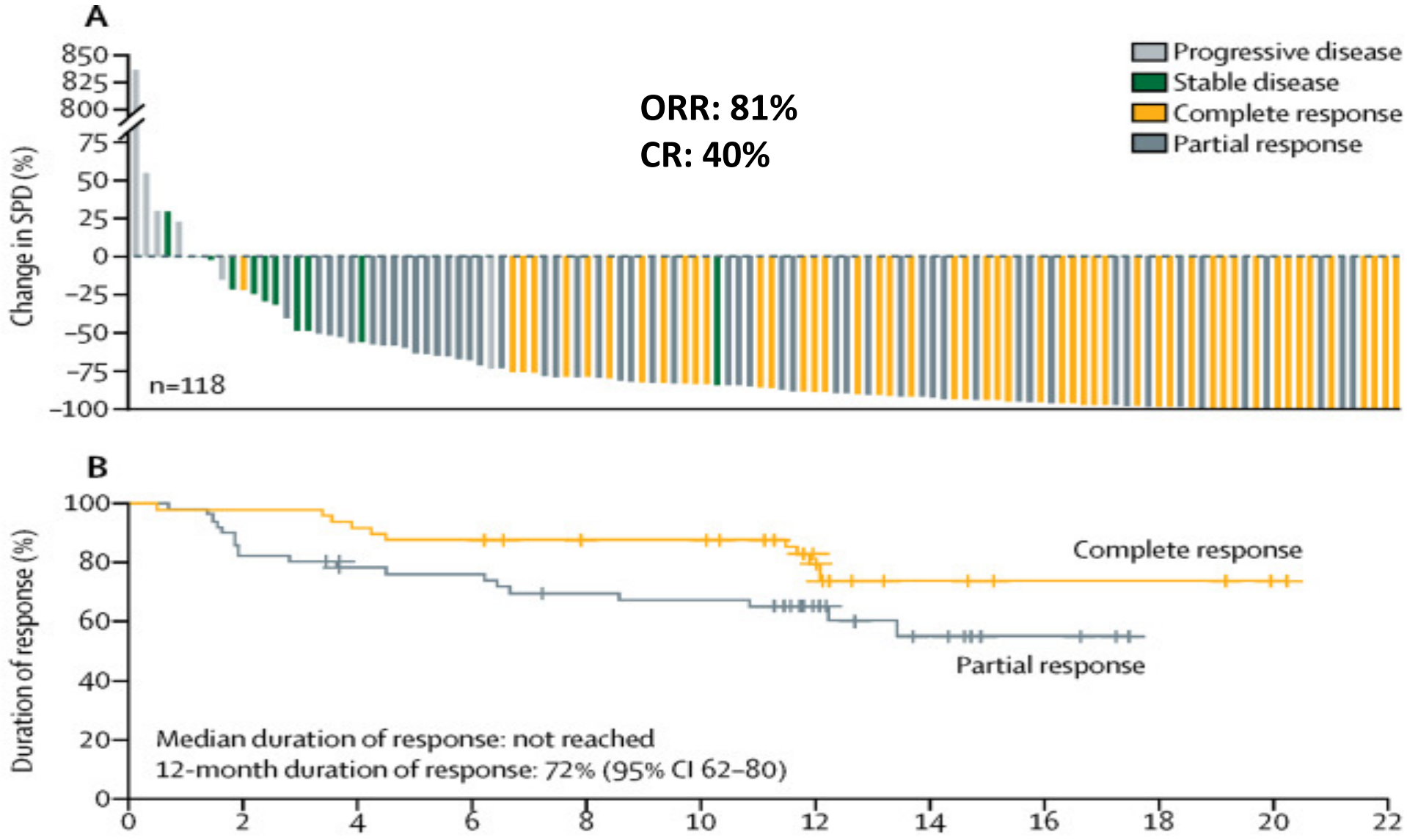
Acalabrutinib

- Second-generation BTK inhibitor
  - FDA-approved in mantle cell lymphoma with at least one prior therapy
  - Dose: 100 mg twice daily until unacceptable toxicity or progression
- More specific for BTK, fewer off-target effects than ibrutinib
  - Less TEK kinase inhibition



Herman S, CCR 2017

Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): A single-arm, phase 2 trial



Wang M, et al. Lancet 2018

Acalabrutinib in R/R MCL

Compared to ibrutinib (n=370, pooled data, 3 trials) more favorable patient population in the acalabrutinib trial (n=124)

	Ibrutinib 560 mg/day	Acalabrutinib 100 mg 2x/day
Median age	67.5	68 (61-75)
Median prior lines of therapy	2 (1-9)	2 (1-2)
sMIPI high	32%	17%
sMIPI int	45%	44%
sMIPI low	24%	39%
Blastoid	12%	NR
Prior SCT	34%	18%
Refractory	NR	24%

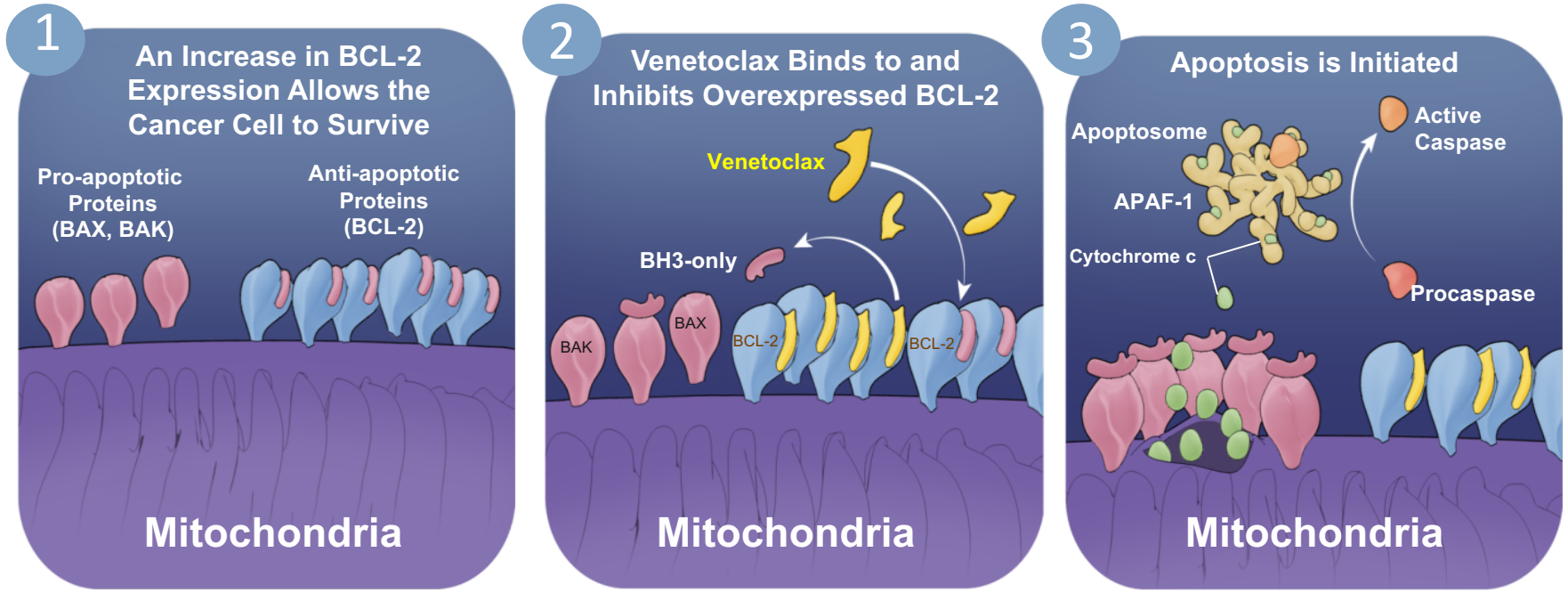
Rule S, et al. Brit J Haematol 2017;
Wang M, et al. Lancet 2018

Acalabrutinib vs. Ibrutinib in MCL

- Acalabrutinib appears to have better safety profile
  - Very infrequent atrial fibrillation and bleeding events
  - More headache with acalabrutinib
- Acalabrutinib was used in less heavily pre-treated patients
  - Can't say that it is more effective in MCL as yet
  - Head-to-head trial of ibrutinib vs acalabrutinib (ACE-CL-006) enrolled high-risk, relapsed CLL; results pending
- In MCL, both agents have efficacy, choose based on patient factors
- If a patient fails a BTK inhibitor, consider switch to venetoclax
- If a BTK inhibitor is stopped for toxicity, use the alternative BTK agent
- Acala plus BR, and other combinations, in current clinical trials

Venetoclax

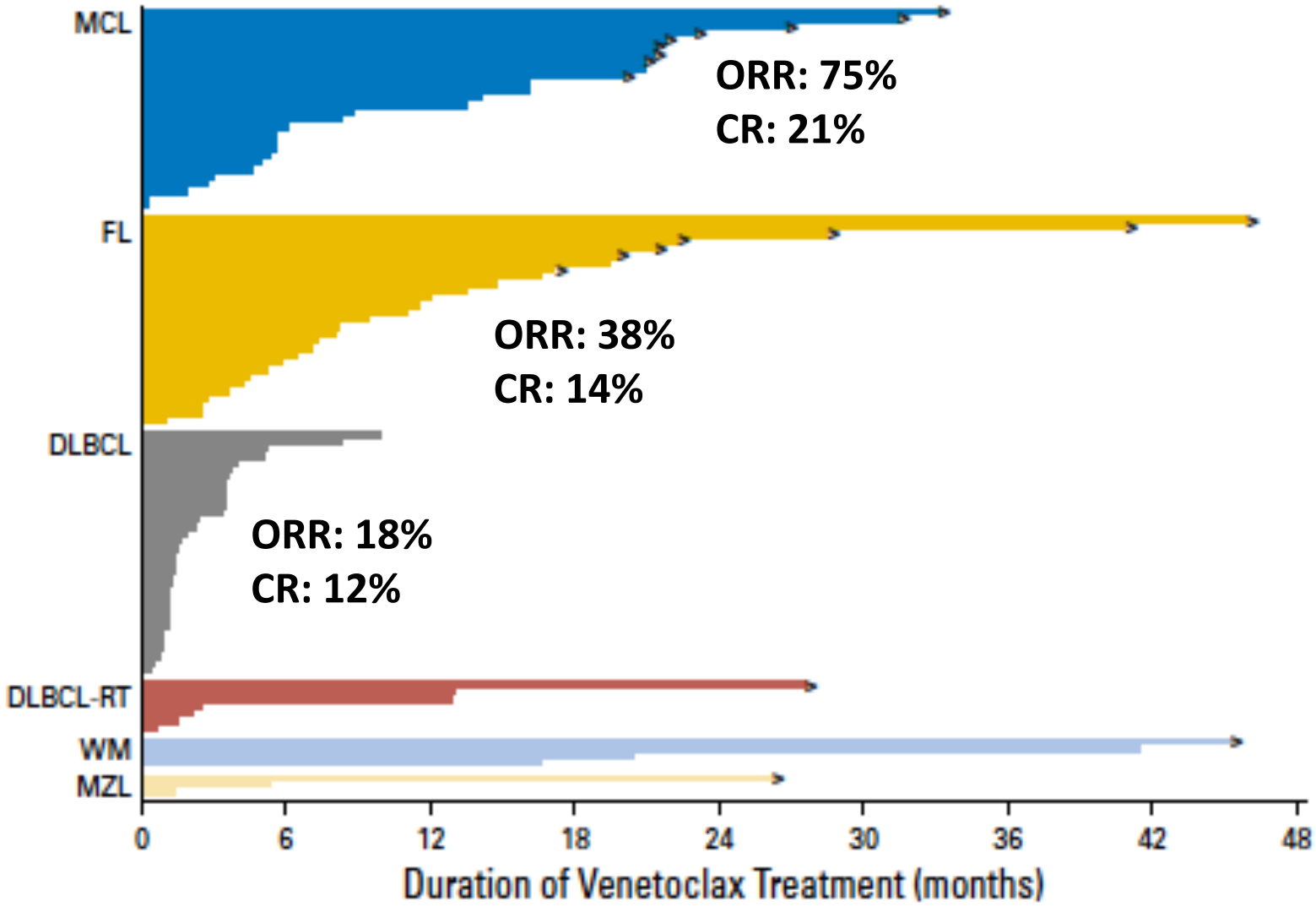
FDA-approved for CLL/SLL, with or without del 17p, with at least 1 prior therapy; approved Nov. 2018 for AML pts > 75y in combination with aza, decitabine or AraC



BH3-only family member proteins include BIM, BAD, PUMA, and NOXA

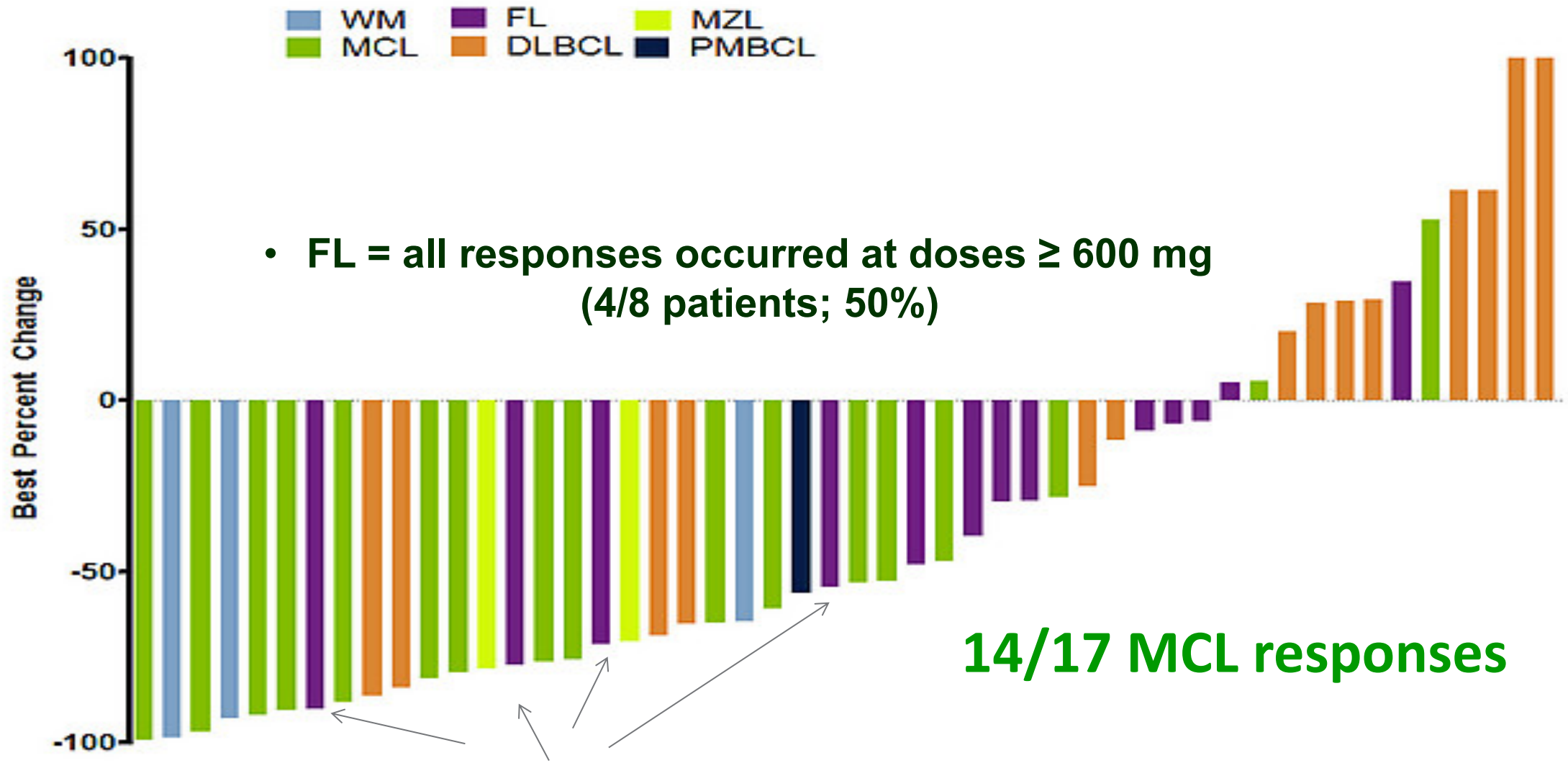
Courtesy of Dr. Sven de Vos, UCLA

Venetoclax in NHL



Davids M, JCO 2017

Venetoclax is BCL-2 specific: Surprisingly limited activity in FL, but high response rate in MCL



- FL = all responses occurred at doses ≥ 600 mg (4/8 patients; 50%)

14/17 MCL responses

4/13 FL responses

Davids et al, EHA, 2014

Venetoclax safety

- Tumor lysis syndrome
  - Must use dosing ramp-up for venetoclax initiation
  - Be very cautious in CLL and MCL, especially if coexisting renal insufficiency
  - Highest risk is with lymphocytosis and bulky disease, or rapidly progressing disease

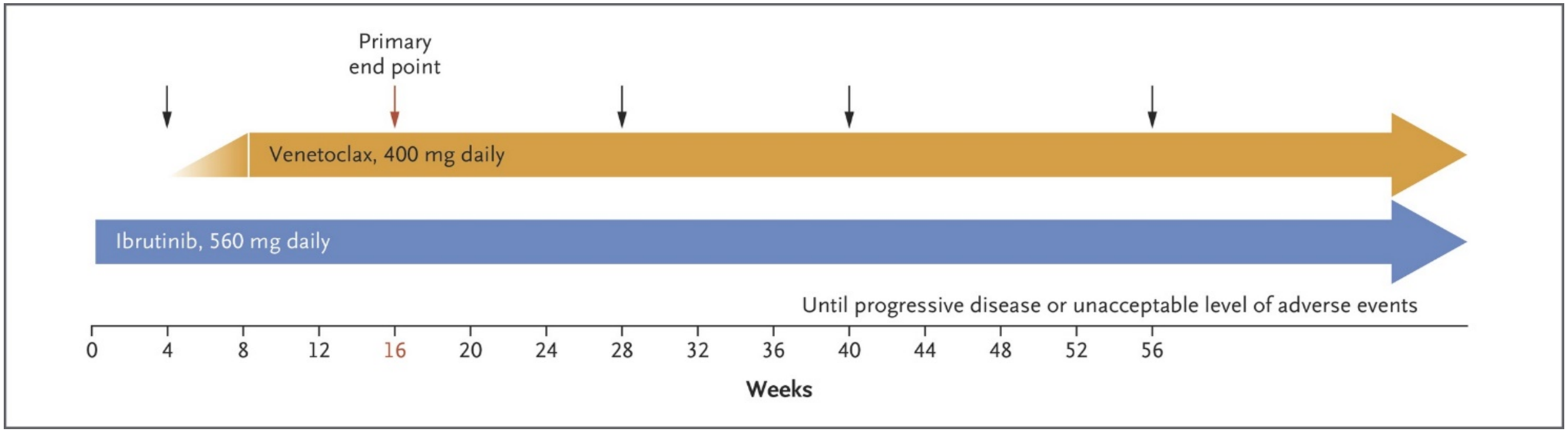
- Adverse events
  - GI: nausea/vomiting and diarrhea
  - Neutropenia and thrombocytopenia
  - Fatigue and headache

Davids M, et al. JCO 2017;
Davids M, et al. JCO 2018

Venetoclax combinations in MCL

- With chemotherapy, in relapse and front-line
  - Bendamustine/Rituximab + VEN study in MCL (PrECOG trial)
  - Preclinical evidence of enhancing chemosensitivity
- With other targeted agents or anti-CD20 mAbs
  - Multiple pre-clinical studies demonstrate synergy with BTK inhibitors
  - Caution with BTK inhibitors plus VEN: both metabolized via CYP4A
  - In R/R CLL, VEN can induce MRD-negative remissions, including del(17p), when given in combination with rituximab (Seymour J, et al, NEJM 2018)

Ibrutinib plus venetoclax in MCL: Study Schema



24 patients; 23 relapsed or refractory; most high-risk by MIPI score and TP53 mutations

Tam CS et al. N Engl J Med 2018;378:1211-1223

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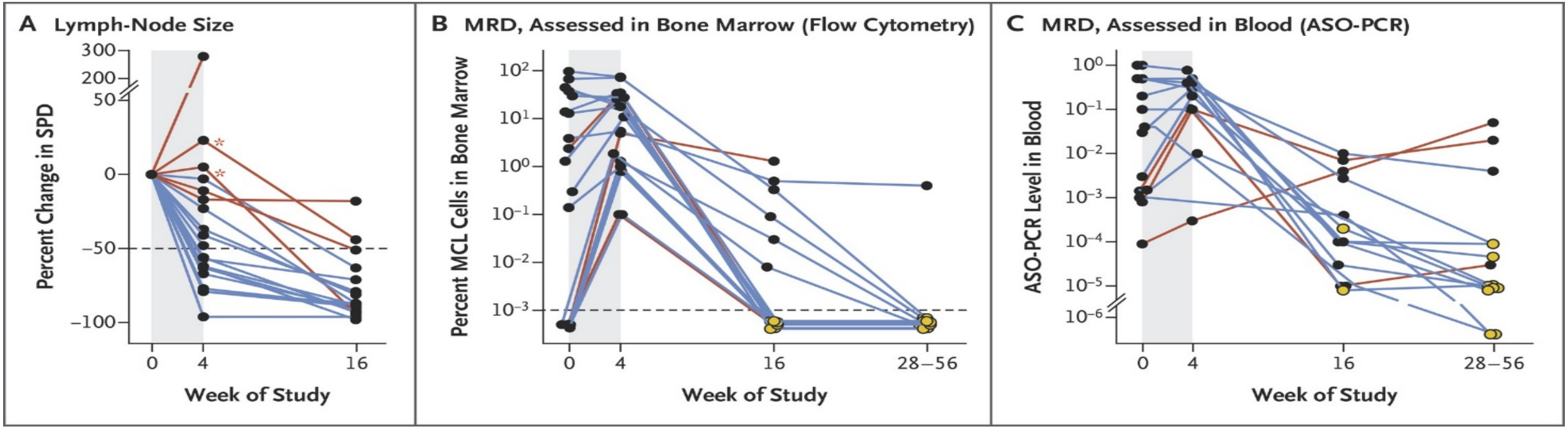
Kinetics of Response and Clearance of Minimal Residual Disease (MRD)



Tam CS et al. N Engl J Med 2018;378:1211-1223

The NEW ENGLAND JOURNAL of MEDICINE

MCL: Ibrutinib/venetoclax

n = 24

Complete response by PET/CT scan = 71%

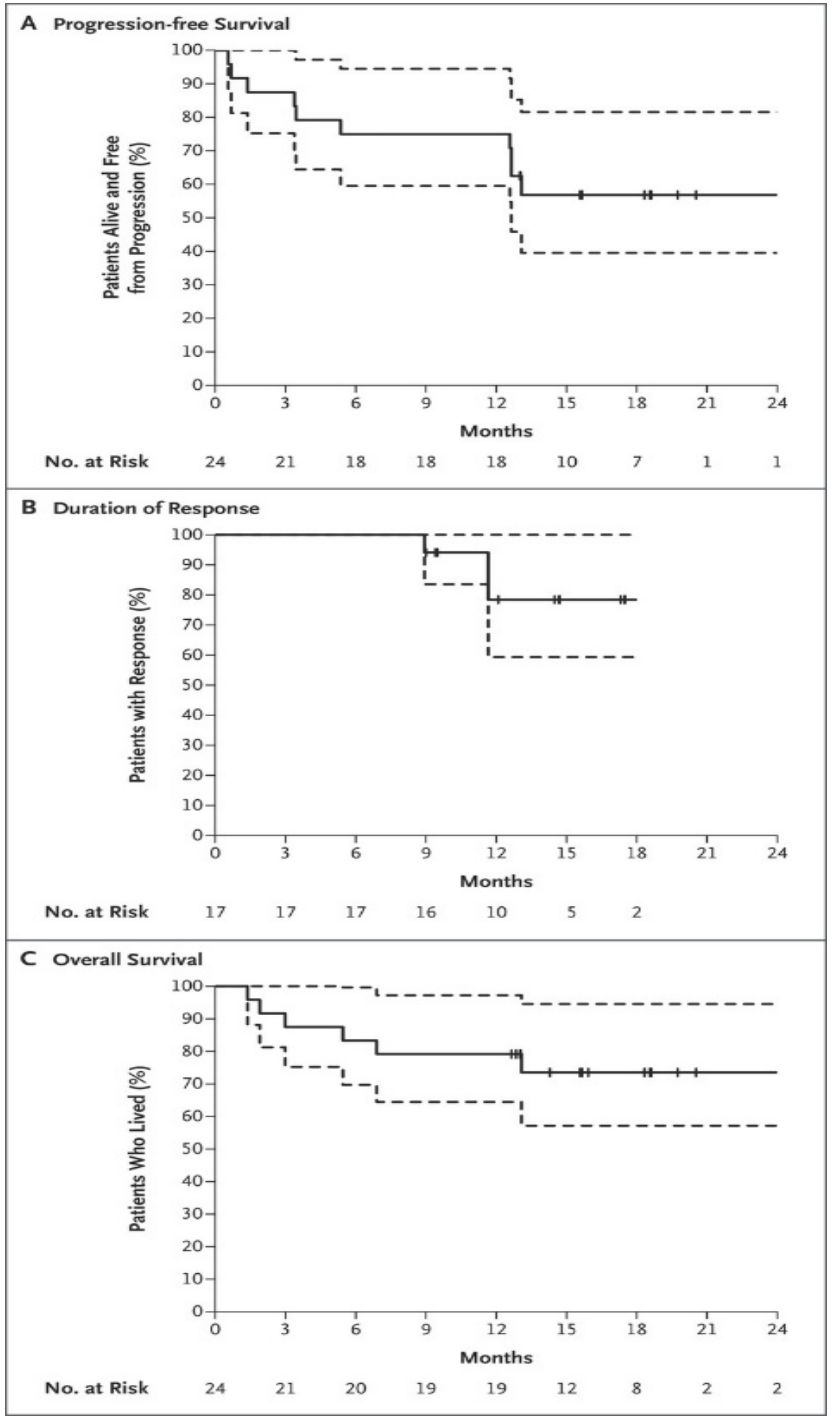
3 non-responders

Toxicity mostly Grade 1-2 diarrhea, fatigue

Grade 3-4:

33% neutropenia
12% diarrhea
4% bleeding
8% atrial fibrillation
8% tumor lysis

Tam CS et al, NEJM 2018



Progression-free survival

Median follow-up 16 mos

PFS at 12 mos: 75%
PFS at 18 mos: 57%

Duration of Response

Ongoing response at 12 mos: 78%

Overall survival

OS at 12 mos: 79%
OS at 18 mos: 74%

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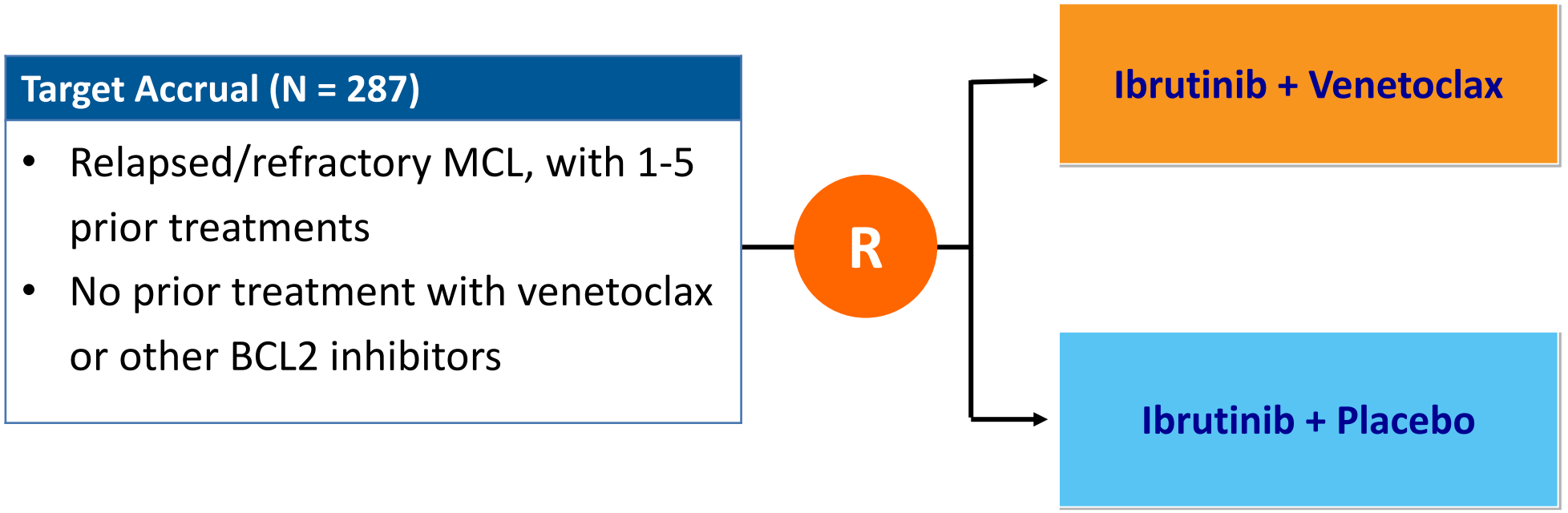
SYMPATICO Phase 3 Study Schema



Primary Endpoints: Occurrence of TLS and DLTs, PFS

Note: Subjects are enrolled into an open-label safety run-in period to evaluate the occurrence of TLS and DLTs with concurrent administration of ibrutinib and venetoclax

Clinicaltrials.gov, November 28, 2018 (NCT03112174)