Mantle Cell Lymphoma: Currently Available and Emerging Novel Approaches

ASH 2020 Satellite Symposium

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UVA Health

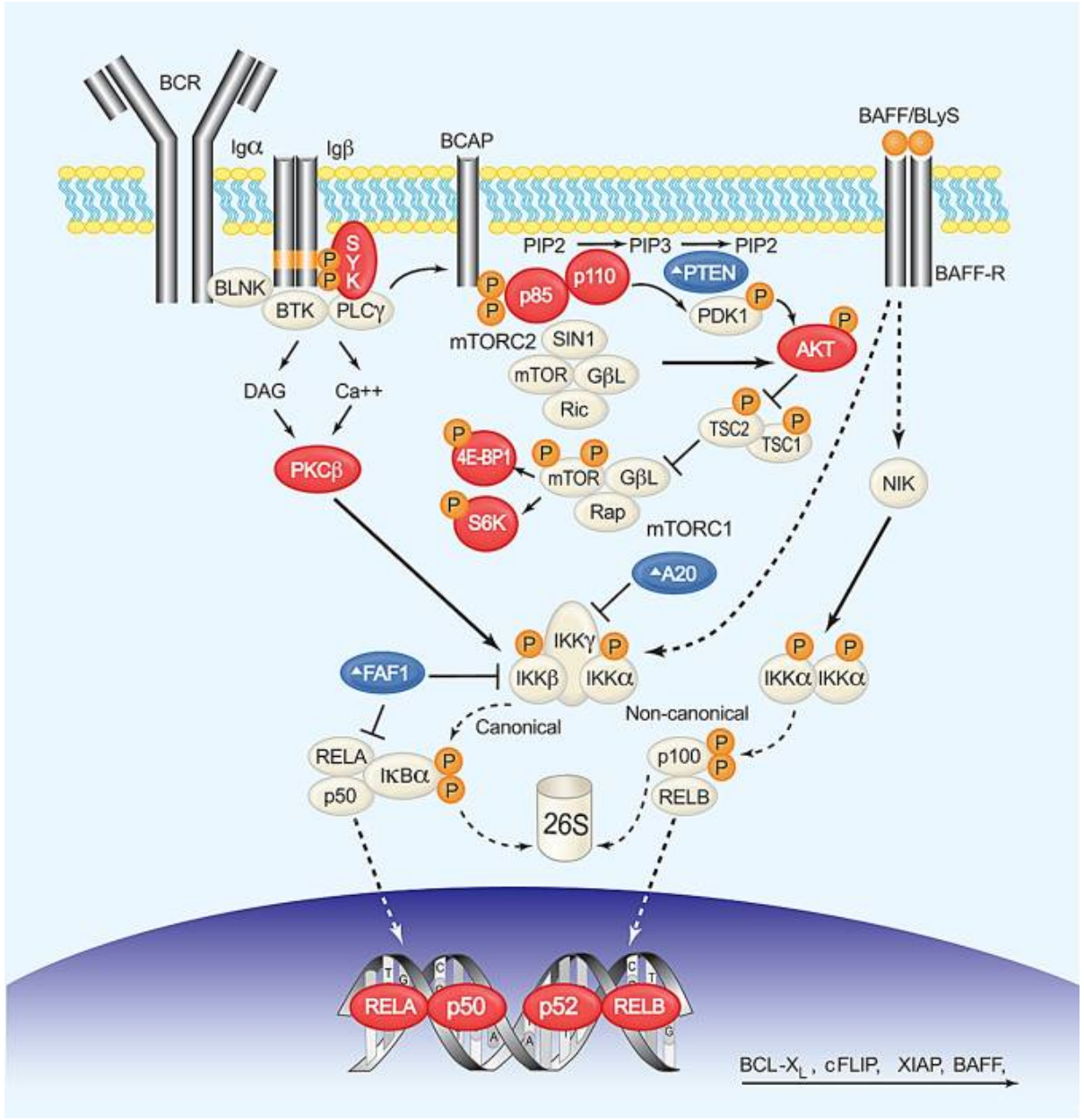
MCL Challenges and Opportunities

- Biologic and clinical heterogeneity
  - Many subtypes → complex Rx decisions
- Better treatment endpoints
  - Emerging role for MRD-directed therapy
- Optimize use of targeted agents
  - Chemotherapy-free regimens
- Post-induction SCT vs Maintenance therapy
  - MRD-driven approaches
- Cure

Courtesy of Michael E Williams, MD, ScM

The B-cell receptor pathway is activated in most B-cell malignancies

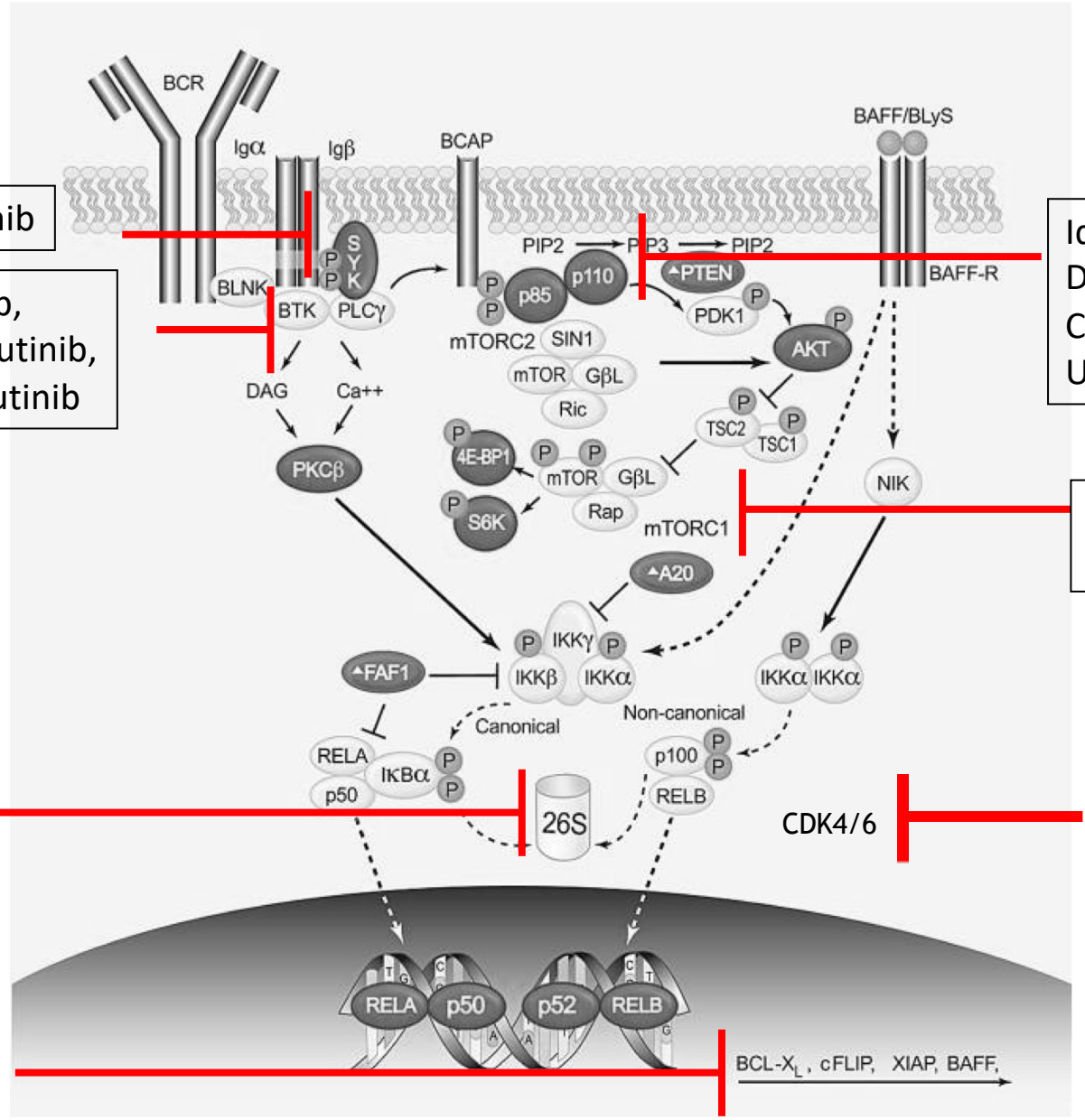
Overexpressed
Down-regulated



Courtesy of Michael E Williams, MD, ScM

P. Perez-Galan et al. Blood. 2011

The B-cell receptor pathway: Selected Inhibitors



Courtesy of Michael E Williams, MD, ScM

Modified and updated from P. Perez-Galan et al. Blood. 2011

Targeted, non-Chemotherapy Approaches for Relapsed/Refractory MCL

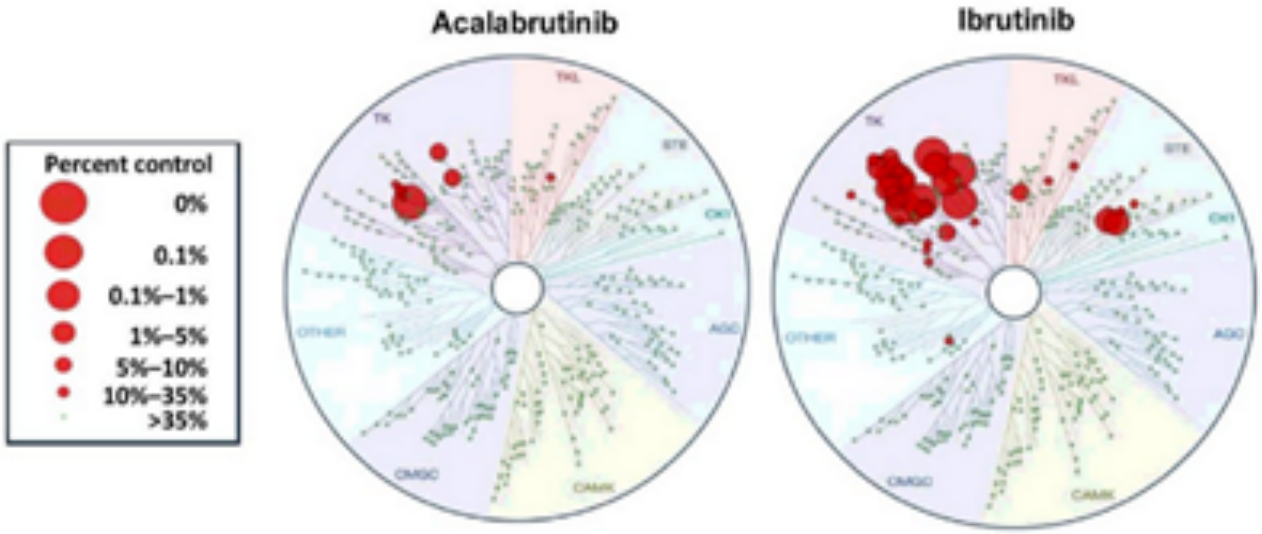
Agent	N	Response Rate	mDOR (mo.)
Bortezomib	155	33%	9.2 m
Temsirolimus	54	22%	7.1 m
Lenalidomide	134	28%	16.6 m
Lenalidomide-rituximab	52	57%	18.9 m
Idelalisib	40	40%	4 m
Ibrutinib	111	68%	17.5 m
Acalabrutinib	124	81%	72% at 12 m
Zanubrutinib	86	84%	16.7 m
Venetoclax	28	75%	12 m
Ibrutinib-Venetoclax	24	71% (all CR)	80% at 12 m

Courtesy of Michael E Williams, MD, ScM

Overview of FDA-approved BTKi for MCL:

Ibrutinib, Acalabrutinib and Zanubrutinib

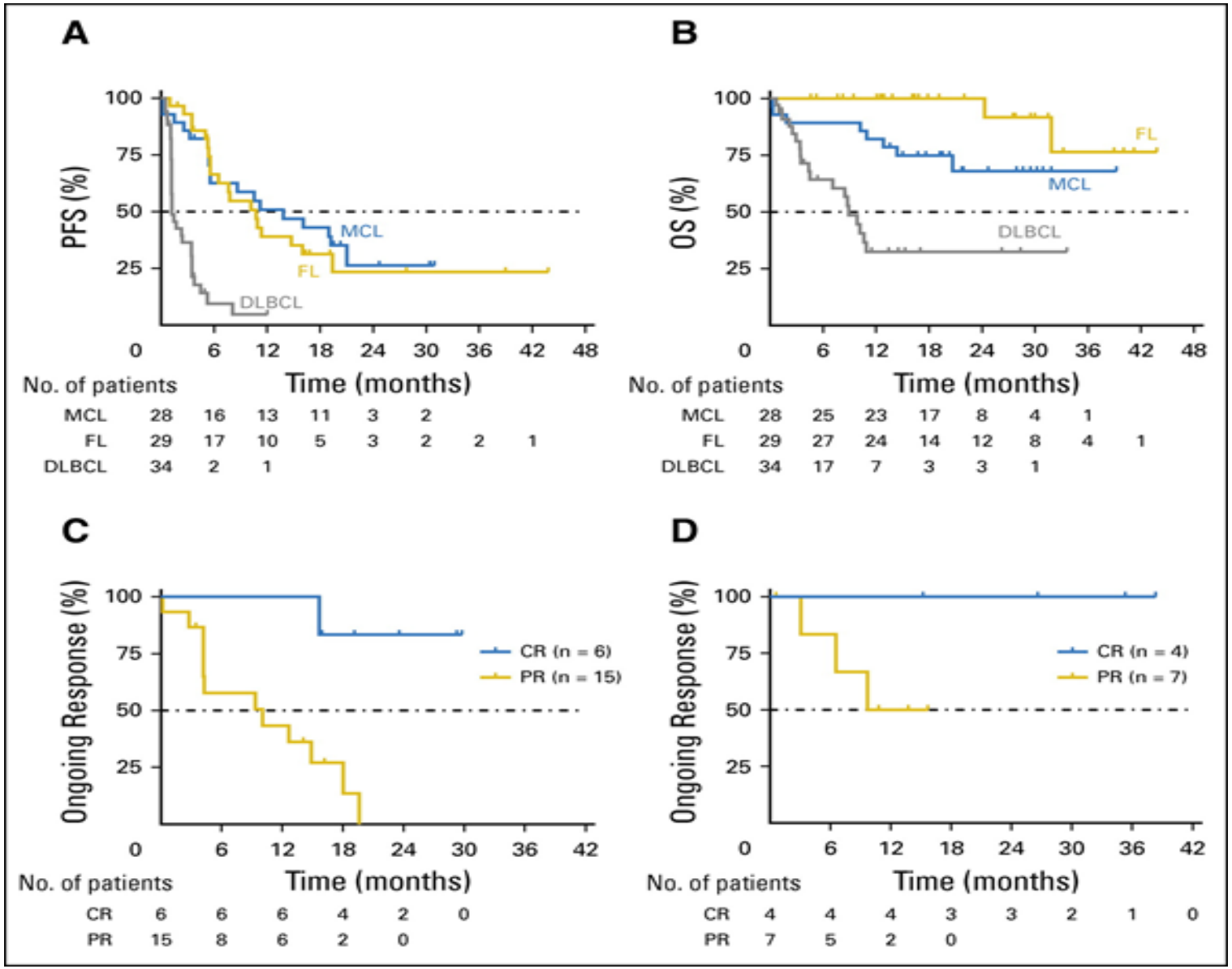
- Similar overall response rates, ~70-80%
  - Better when used earlier (2nd or 3rd line)
- Improved toxicity profile for acala and zanu
  - More specific BTKi inhibition (Zanu similar to Acala)
  - Less Afib, bruising/bleeding, arthralgia
  - Prefer over ibrutinib if concurrent anticoagulation and/or anti-platelet therapy



Courtesy of Michael E Williams, MD, ScM

Herman et al, Clin Ca Res 2017

Venetoclax: A potent oral inhibitor of bcl-2 that induces apoptosis in B-cell lymphomas *(M Davids et al, JCO 2017)*



Courtesy of Michael E Williams, MD, ScM

Venetoclax after BTKi failure in MCL

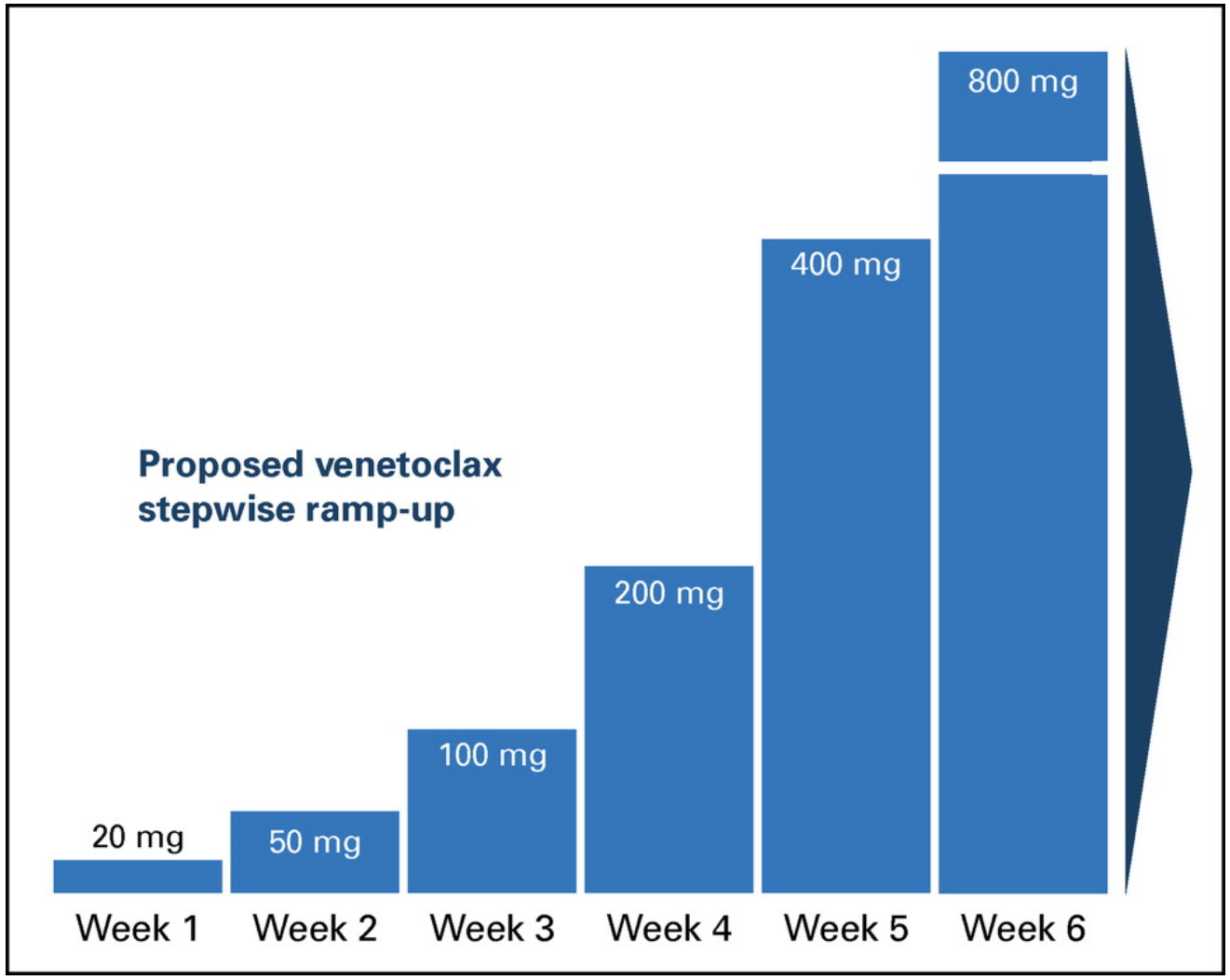
- Single-agent Ven (n=20; median 2-5 prior Rx, ASCT 30%)
  - ORR 53%, CR 18%
  - Median PFS 3.2 m, DOR 8.1 m
  - Median OS 9.4 months
- Venetoclax plus anti-CD20 mAb
  - Increases ORR
  - May “rescue” otherwise suboptimal responses to single-agent Veneto

Eyer et al, Haematologica 2019

Courtesy of Michael E Williams, MD, ScM

Dose Ramp-Up to Mitigate the Risk of Tumor Lysis Syndrome When Initiating Venetoclax in Patients With Mantle Cell Lymphoma

MS Davids, G von Keudell, CA Portell, JB Cohen, et al
J Clin Oncol 2018; 36: 3525-7



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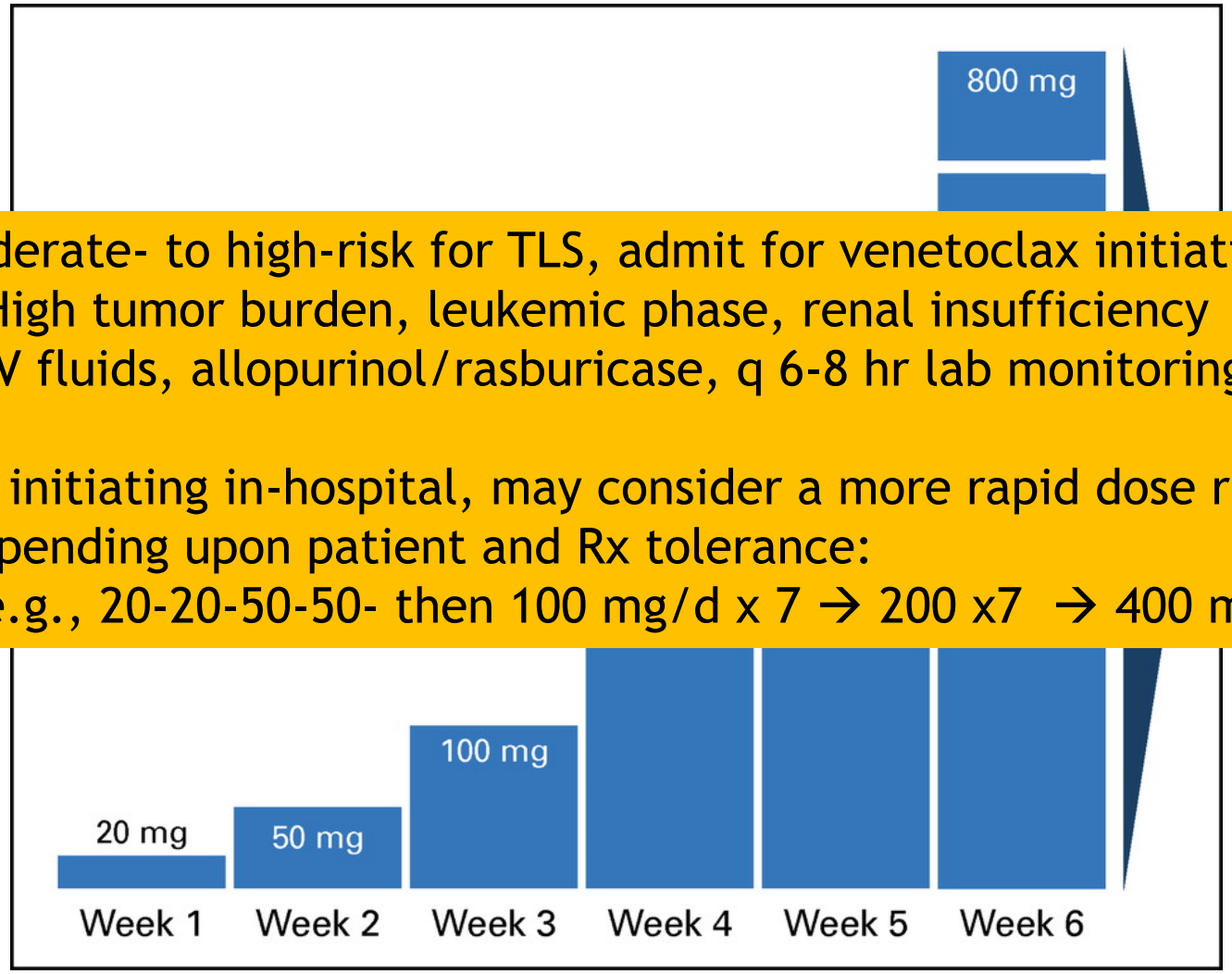


If moderate- to high-risk for TLS, admit for venetoclax initiation:

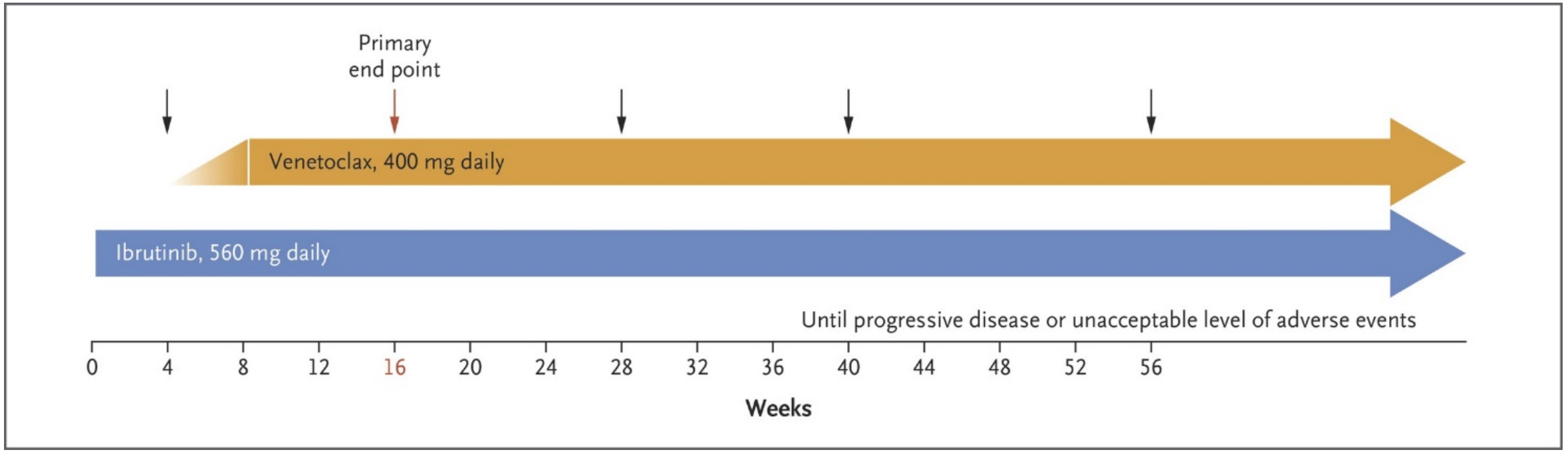
- High tumor burden, leukemic phase, renal insufficiency
- IV fluids, allopurinol/rasburicase, q 6-8 hr lab monitoring

When initiating in-hospital, may consider a more rapid dose ramp-up depending upon patient and Rx tolerance:

- e.g., 20-20-50-50- then 100 mg/d x 7 → 200 x7 → 400 mg/d

Courtesy of Michael E Williams, MD, ScM

Ibrutinib plus venetoclax in MCL: Study Schema



24 MCL patients; 23 relapsed or refractory
Most had very poor-risk features, including TP53 del or mutation

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

Courtesy of Michael E Williams, MD, ScM

The NEW ENGLAND JOURNAL of MEDICINE

Update: Ibrutinib/Venetoclax in R/R MCL, median 37.5 m f/u *(ASH 2019, #756)*

Figure 1. Progression free survival (Dashed lines represent 95% confidence interval)

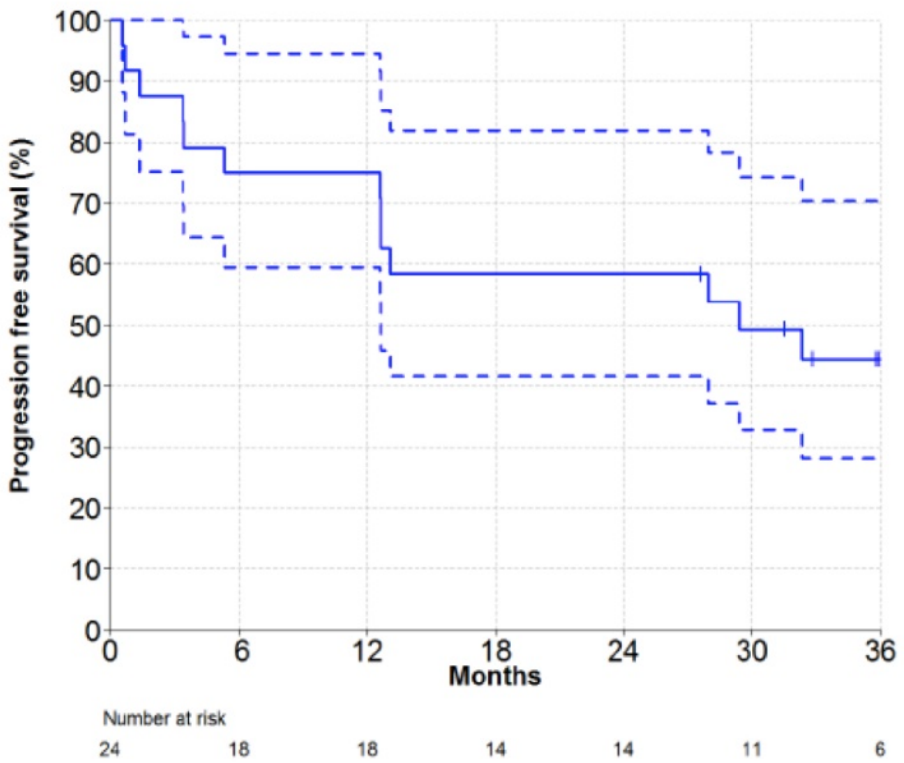
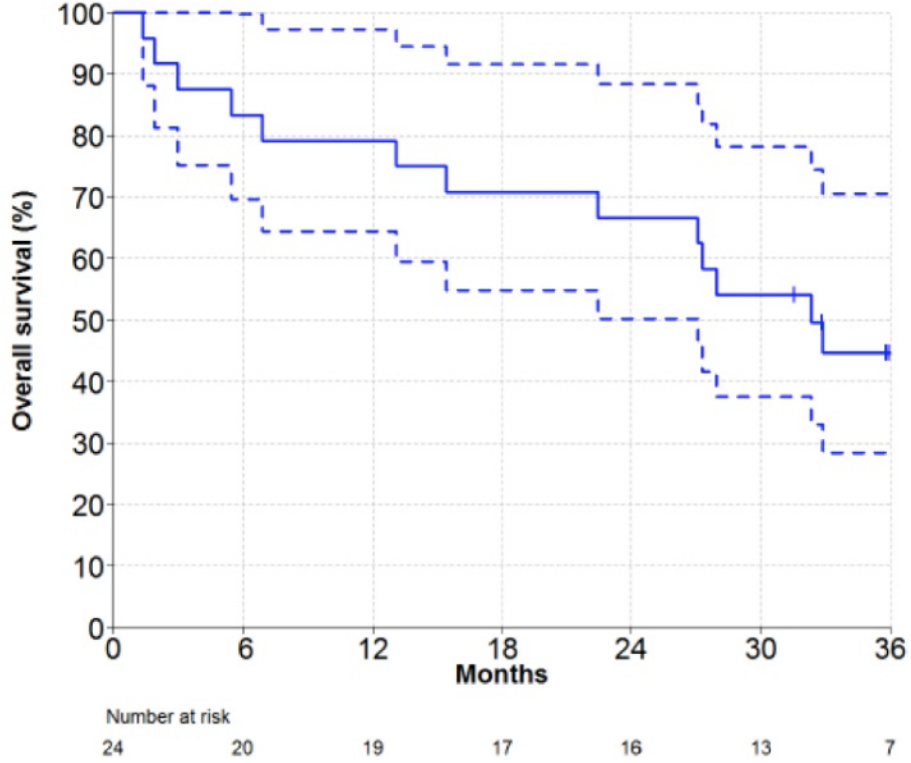


Figure 2. Overall survival (Dashed lines represent 95% confidence interval)



- MRD-negative by flow in 67%, and by ASO-PCR in 38%
- 5 MRD-negative patients discontinued Rx at median of18.5 mo

→4 remained MRD-neg after 6, 13, 17 and 18 months off Rx

Courtesy of Michael E Williams, MD, ScM

Ibrutinib Combined With Venetoclax in R/R Mantle Cell Lymphoma (SYMPATICO)

- Initiated May 2017
- Phase 3 multinational, randomized, double-blind study to compare the efficacy and safety of the combination of **ibrutinib/venetoclax vs. ibrutinib/placebo**
- R/R MCL, 1-5 prior treatments
- Study revised to include front-line MCL therapy

Courtesy of Michael E Williams, MD, ScM

Ibrutinib plus venetoclax in R/R MCL:
SYMPATICO safety run-in period

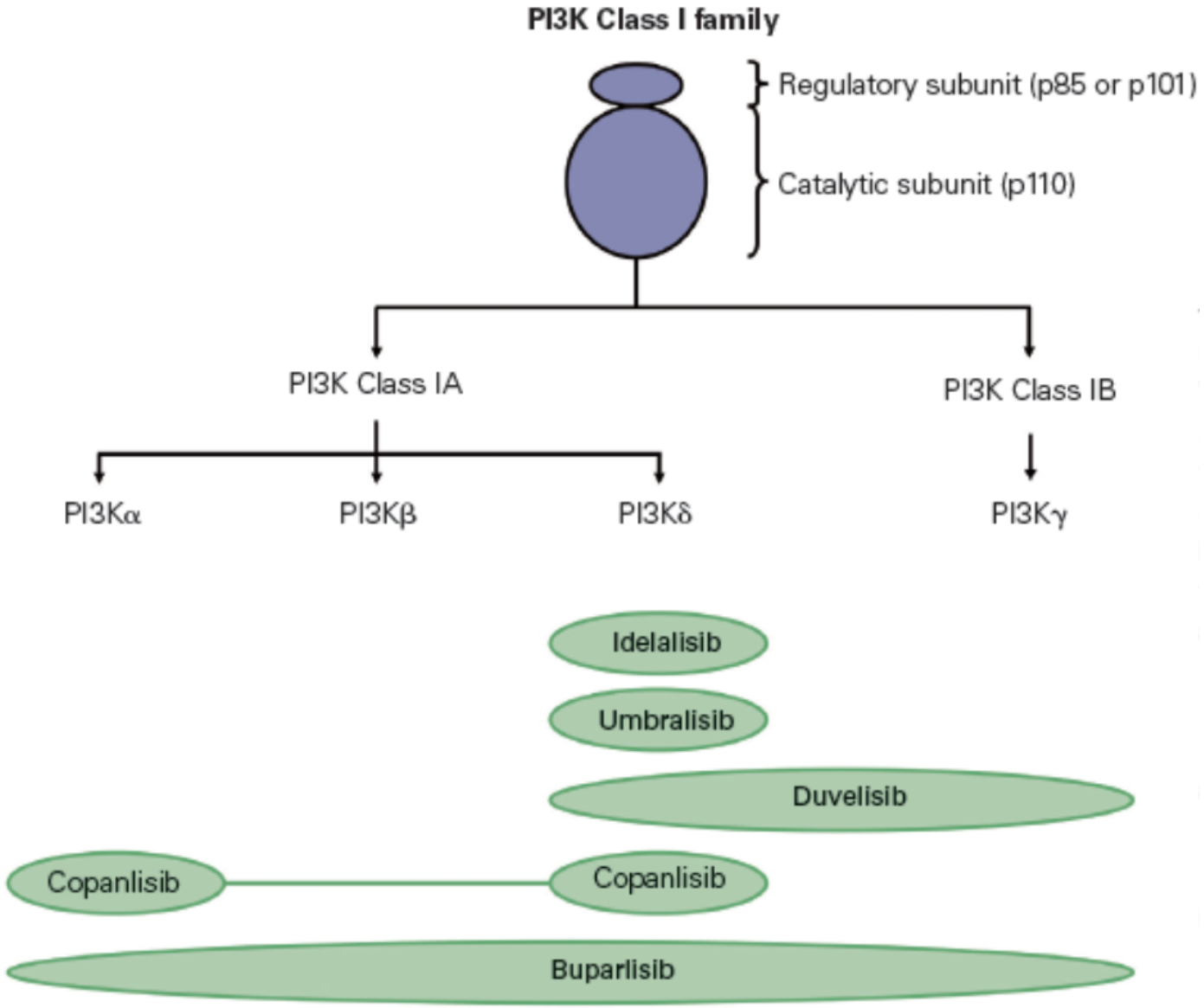
- **Schema:** IBR 560 mg/d plus stepped-up Ven (or placebo) 20 mg → 400 mg/d over 5 weeks
  - At 24 mo, Ven/placebo discontinued, IBR continued
- N = 21, TLS low-risk in 6, high-risk in 15
- Lab TLS in 1 high-risk patient (leukemic MCL)
  - No clinical TLS observed
- DLTs in 3 patients
- **Recommendation from safety run-in analysis:**

  Continue concurrent initiation of IBR + Ven in low- and high-risk patients

Wang M et al. Int'l Conf Malig Lymphoma, Lugano, June 2019

Courtesy of Michael E Williams, MD, ScM

PI3Ki (Phosphatidylinositol 3-kinase inhibitors)

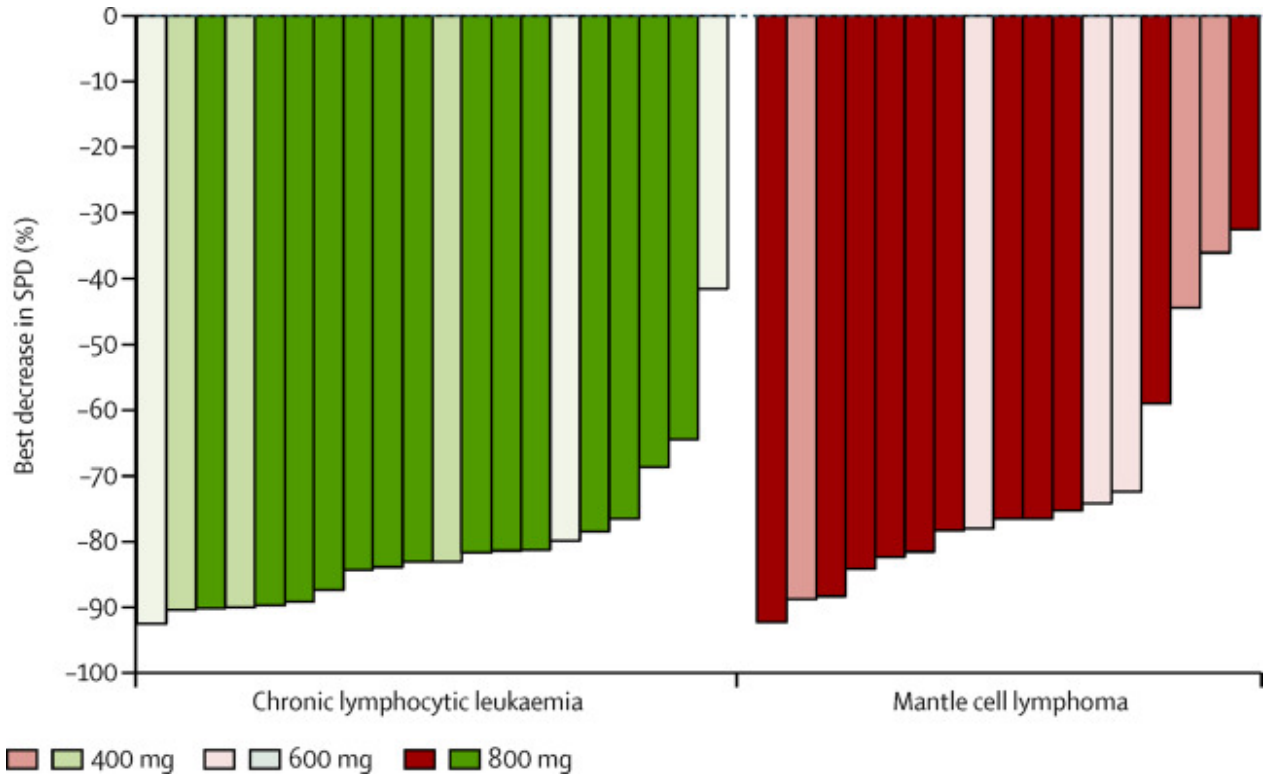


Courtesy of Michael E Williams, MD, ScM

(Greenwell IB et al. Oncology Journal 2017; 31)

Umbralisib in combination with ibrutinib in patients with relapsed or refractory **CLL** or **Mantle Cell Lymphoma**: a multicentre phase 1–1b study

M. Davids et al, Lancet Haematol 2019



MCL, n = 21

ORR 67% (CR = 4/21)

Median PFS 10.5 mo

Median OS 29.7 mo

Recommended phase 2 dose: Umbra 800 mg po qd plus Ibrutinib at standard dose (420 mg or 560 mg qd)

Umbralisib is investigational, not yet FDA approved

Courtesy of Michael E Williams, MD, ScM

Sustained remission with Lenalidomide plus Rituximab as **initial therapy** of MCL

*J Ruan et al, NEJM 2015; **JCO 2018***

- n=38, median f/u 64 mo. (21-78 mo.)
- **ORR 92%, CR 64%** **(by PET +/- BM; med. 11 mo. to reach CR)**
- **3 yr PFS 80%, OS 90%**
- **5 yr estimated PFS 64%, OS 77%**
  - *8/10 patients in CR @ 3 yr are MRD negative*
  - *No difference in ORR for Low- vs High-risk MIPI*
  - *No correlation with Ki-67 score*
- **Toxicity:**
  - Grade 3-4 neutropenia 50%, thrombocytopenia 13%
  - 1 pancreas cancer, 6 non-inv. skin cancer
  - Grade 3 infection in 3 pts
- Relapsing pts respond to second line Rx

Courtesy of Michael E Williams, MD, ScM

KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T Cell Therapy, in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Results of the Phase 2 ZUMA-2 Study

[*Presented at ASH 2019, published NEJM April 2020*]

Michael Wang,[1] Javier Munoz,[2] Andre Goy,[3] Frederick L. Locke,[4] Caron A. Jacobson,[5] Brian T. Hill,[6] John M. Timmerman,[7] Houston Holmes,[8] Samantha Jaglowski,[9] Ian W. Flinn,[10] Peter A. McSweeney,[11] David B. Miklos,[12] John M. Pagel,[13] Marie José Kersten,[14] Noel Milpied,[15] Henry Fung,[16] Max S. Topp,[17] Roch Houot,[18] Amer Beitinjaneh,[19] Weimin Peng,[20] Lianqing Zheng,[20] John M. Rossi,[20] Rajul K. Jain,[20] Arati V. Rao,[20] and Patrick M. Reagan[21]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Banner MD Anderson Cancer Center, Gilbert, AZ; [3]John Theurer Cancer Center, Hackensack, NJ; Moffitt Cancer Center, Tampa, FL; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Cleveland Clinic Foundation, Cleveland, OH; [7]David Geffen School of Medicine at UCLA, Los Angeles, CA; [8]Texas Oncology, Dallas, TX; [9]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [10]Sarah Cannon Research Institute, Nashville, TN; [11]Colorado Blood Cancer Institute, Denver, CO; [12]Stanford University School of Medicine, Stanford, CA; [13]Swedish Cancer Institute, Seattle, WA; [14]Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [15]CHU Bordeaux, Service D'hematologie et Therapie Cellulaire, F-33000 Bordeaux, France; [16]Fox Chase Cancer Center, Philadelphia, PA; [17]Universitatsklinikum Wurzburg, Wurzburg, Germany; [18]CHU Rennes, Univ Rennes, Inserm & EFS, Rennes, France; [19]University of Miami, Miami, FL, USA; [20]Kite, a Gilead Company, Santa Monica, CA; [21]University of Rochester Medical Center, Rochester, NY

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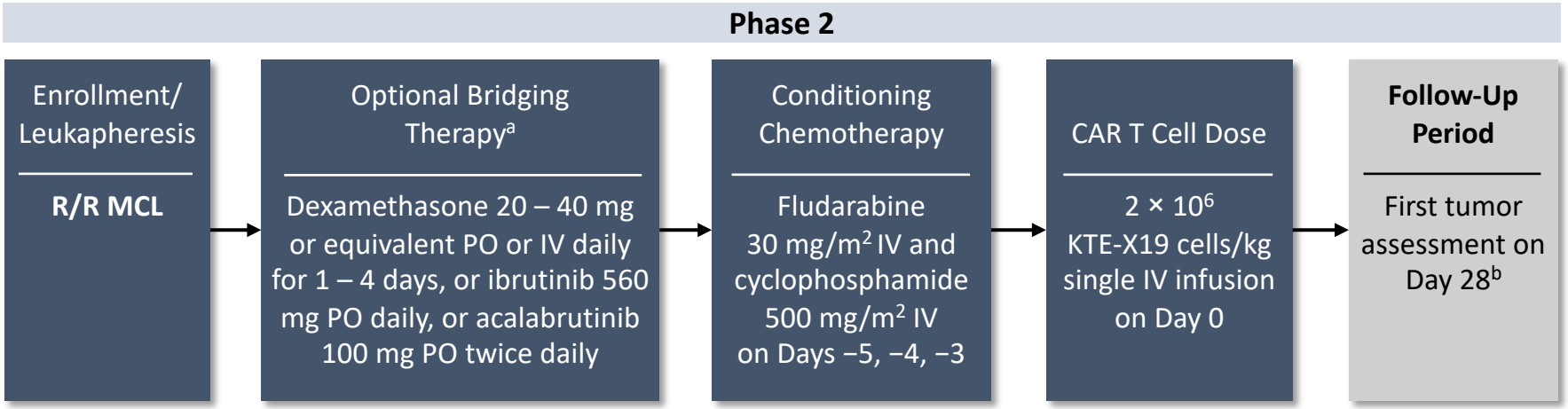
[1]The U... Cancer Cen... ion, Cle... ity Compr... Denver, CO; [12]S... iversity of Am... ance; [16]Fox C... serm & EFS, Rennes, France; [19]University of Miami, Miami, FL, USA; [20]Kite, a Gilead Company, Santa Monica, CA; [21]University of Rochester Medical Center, Rochester, NY

FDA approved CAR T-cell therapy for ***brexucabtagene autoleucel*** to treat relapsed or refractory mantle cell lymphoma. Jul 24, 2020

Courtesy of Michael E Williams, MD, ScM

ZUMA-2 Study Design

‡



Primary Endpoint

- ORR (IRRC-assessed per the Lugano classification[1])

Key Secondary Endpoints

- DOR
- PFS
- OS
- AEs
- ORR (Investigator-assessed per revised IWG criteria[2])
- EQ-5D
- Levels of CAR T cells in blood and cytokines in serum

[a] Administered after leukapheresis and completed ≤ 5 days before initiating conditioning chemotherapy; PET-CT was required post-bridging.
[b] Bone marrow biopsy was done at screening and if positive, not done, or indeterminate, a biopsy was needed to confirm CR.
AE, adverse event; CAR, chimeric antigen receptor, DOR, duration of response; EQ-5D, European Quality of Life-5 Dimensions; IRRC, Independent Radiology Review Committee; IWG, International Working Group;
MCL, mantle cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; R/R, relapsed/refractory.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068. 2. Cheson BD, et al. *J Clin Oncol*. 2007;25:579-586.

Courtesy of Michael E Williams, MD, ScM

Bridging Therapy

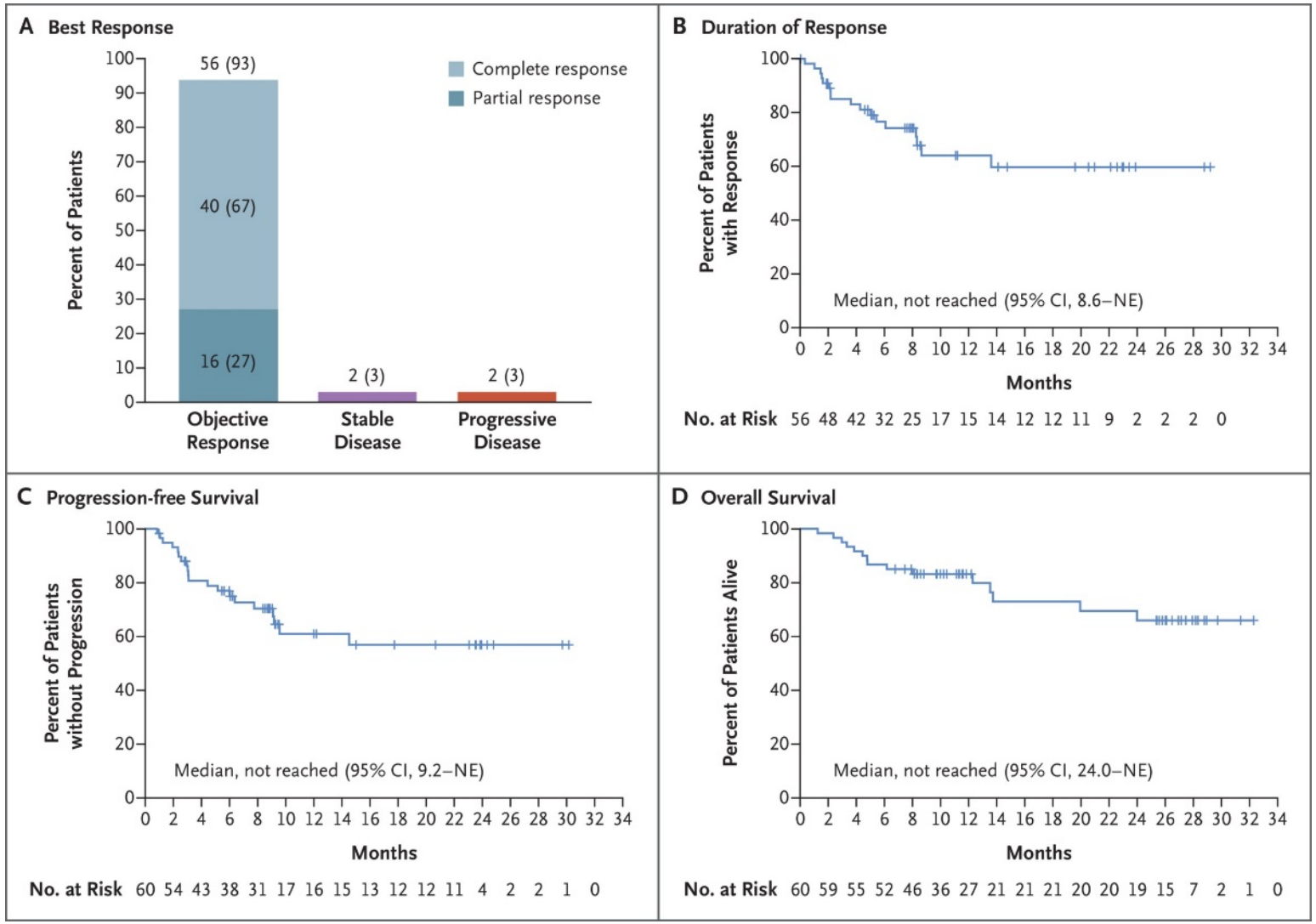
Characteristic	N = 68
Any bridging therapy, n (%)	25 (37)
Ibrutinib	14 (21)
Acalabrutinib	5 (7)
Dexamethasone	12 (18)
Methylprednisolone	2 (3)
Both BTKi and steroids, n (%)	6 (9)
Ibrutinib + steroid	4 (6)
Acalabrutinib + steroid	2 (3)

- Bridging therapy was administered for rapid PD at PI discretion
- No chemotherapy was allowed
- Not intended to be curative but to keep MCL stable during manufacturing
- 23/25 patients had post-bridging PET-CT scans and the majority had an increase in SPD mm^2 from screening

BTKi, Bruton tyrosine kinase inhibitor; MCL, mantle cell lymphoma; PET-CT, positron emission tomography-computed tomography; PD, progressive disease; PI, principal investigator; SPD, sum of product diameters.

Courtesy of Michael E Williams, MD, ScM

Results: *from Wang et al, NEJM 2020; 382:1331-1342*



Courtesy of Michael E Williams, MD, ScM

Authors' Conclusions (ASH 2019)

‡

- KTE-X19 [brexucabtagene autoleucel] demonstrates high rates of response in R/R MCL
  - 93% ORR, with a 67% CR rate
  - Of the initial 28 patients treated, 43% are in remission after ≥ 2 years of follow-up
- The safety profile is consistent with that reported in prior studies of anti-CD19 CAR T cell therapies in aggressive NHL
  - No deaths due to CRS or neurologic events; most symptoms occurred early and were generally reversible

Summary (NEJM 2020)

- KTE-X19 induced durable remissions in a majority of patients with relapsed or refractory mantle-cell lymphoma.
- The therapy led to serious and life-threatening toxic effects that were consistent with those reported with other CAR T-cell therapies.

MRC-00172 01/20

Courtesy of Michael E Williams, MD, ScM

Selected Ongoing Combinatorial MCL Trials

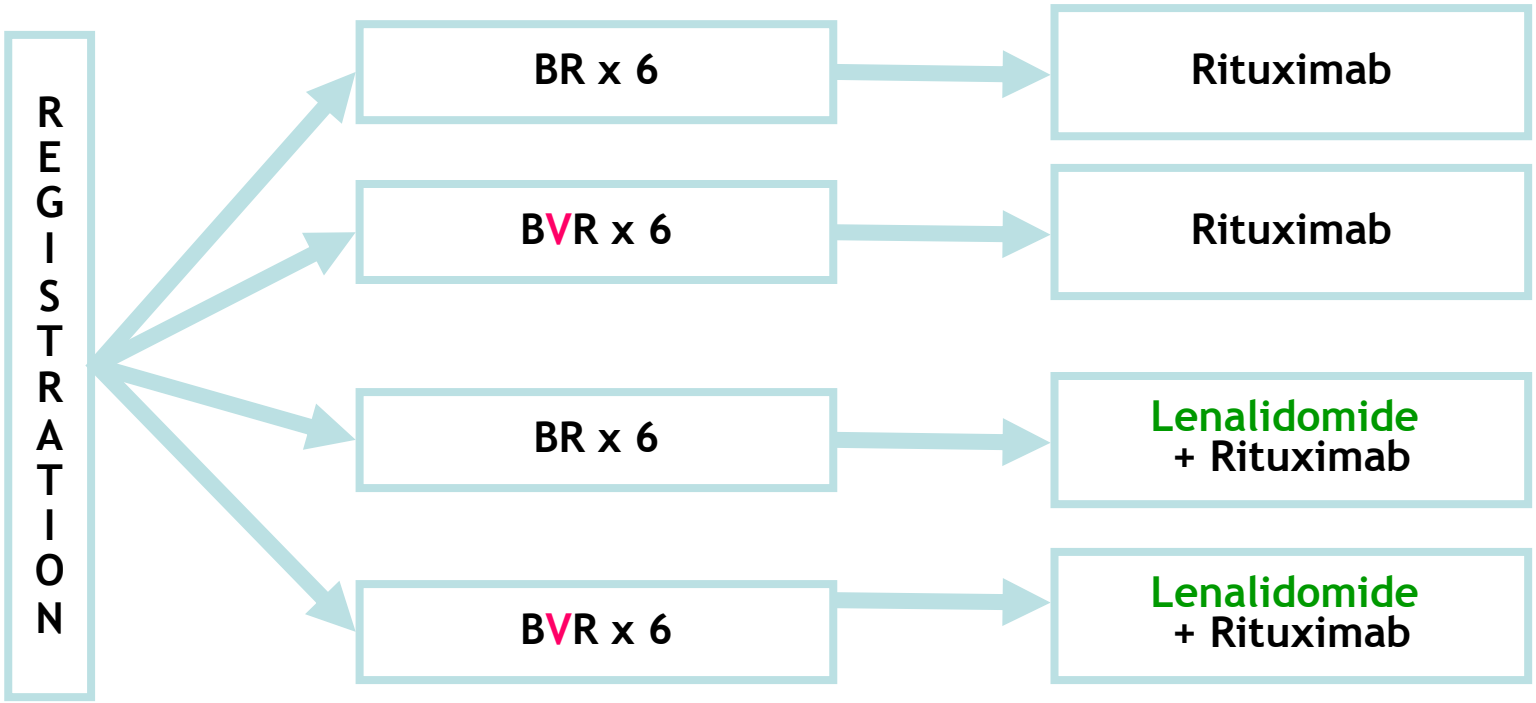
- **Front-line**
  - E4181: BR-HiDAC +/- Acalabrutinib vs BR + Acala
  - PrE0405: BR + Venetoclax (not ASCT eligible)
  - Ibrutinib + Veneto (SYMPATICO)
  - BR vs Zanubrutinib + R (Not ASCT eligible)
  - BR +/- Acalabrutinib
  - Acala + Veneto + R (MDACC)
  - Post-ASCT maintenance with acalabrutinib or ixazomib

  - R/R MCL: PrE0404: Ibrutinib plus ixazomib

  - ***And many more……***

Courtesy of Michael E Williams, MD, ScM

ECOG Trial: E1411 - Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma



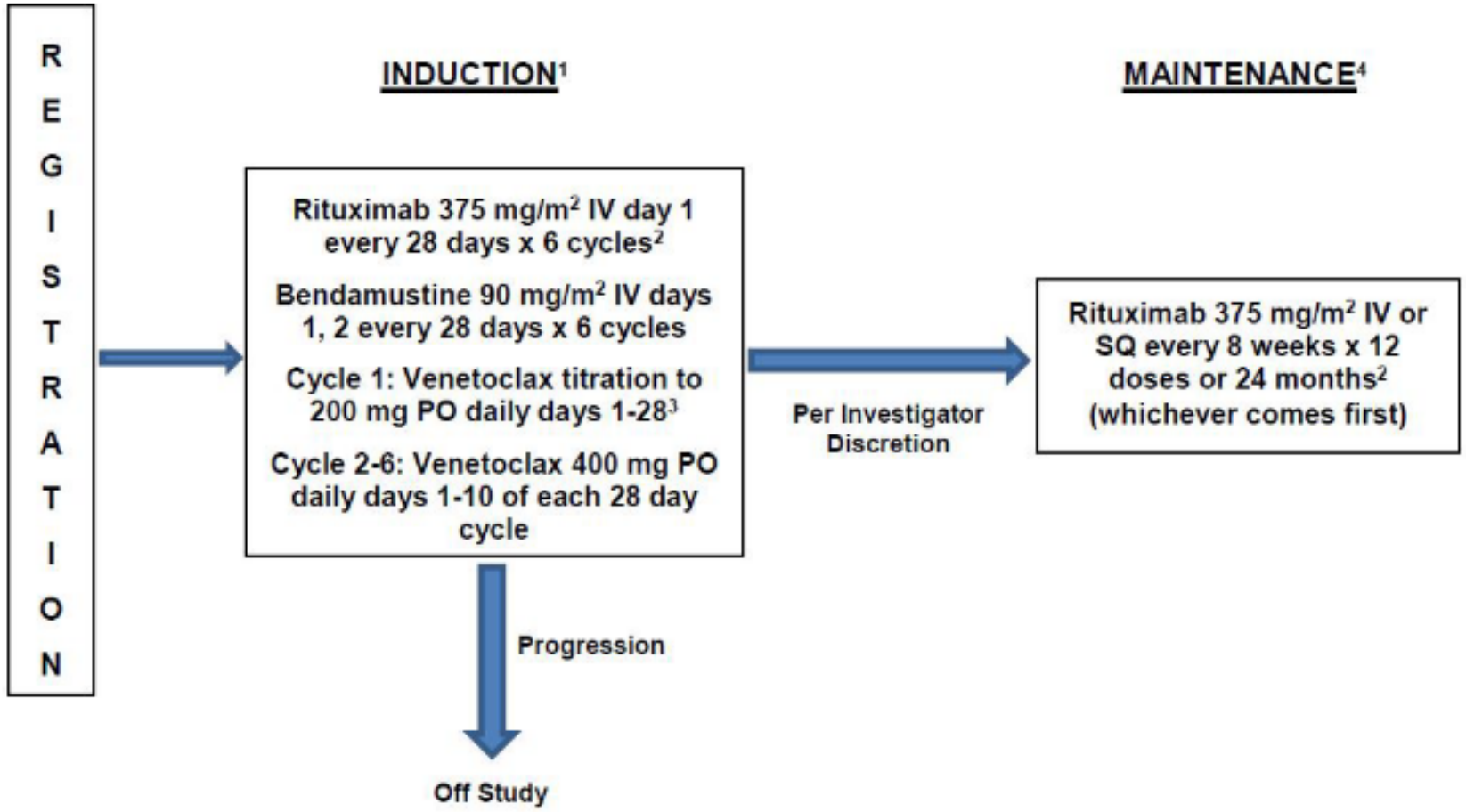
BR = Bendamustine, Rituximab

V= Bortezomib

M. Smith, Study PI; *accrual completed September 2016;*
Data analysis in progress as of Sept. 2020

Courtesy of Michael E Williams, MD, ScM

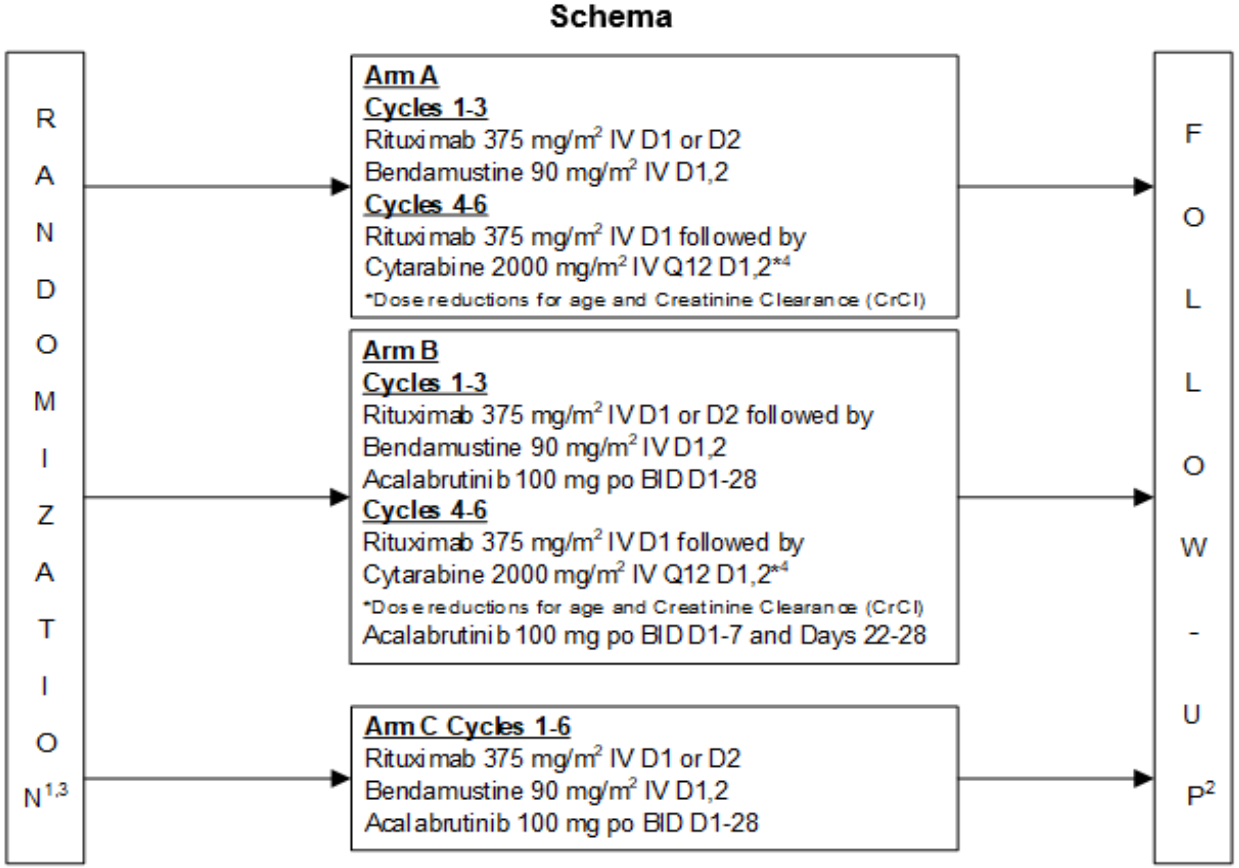
PrECOG0405: Bendamustine and Rituximab Plus Venetoclax in Untreated Mantle Cell Lymphoma over 60 Years of Age: A Phase II Study



C. Portell, Study PI: Study opened 2020, Accruing

Courtesy of Michael E Williams, MD, ScM

ECOG 4181: Front-line MCL (age </=70 y)

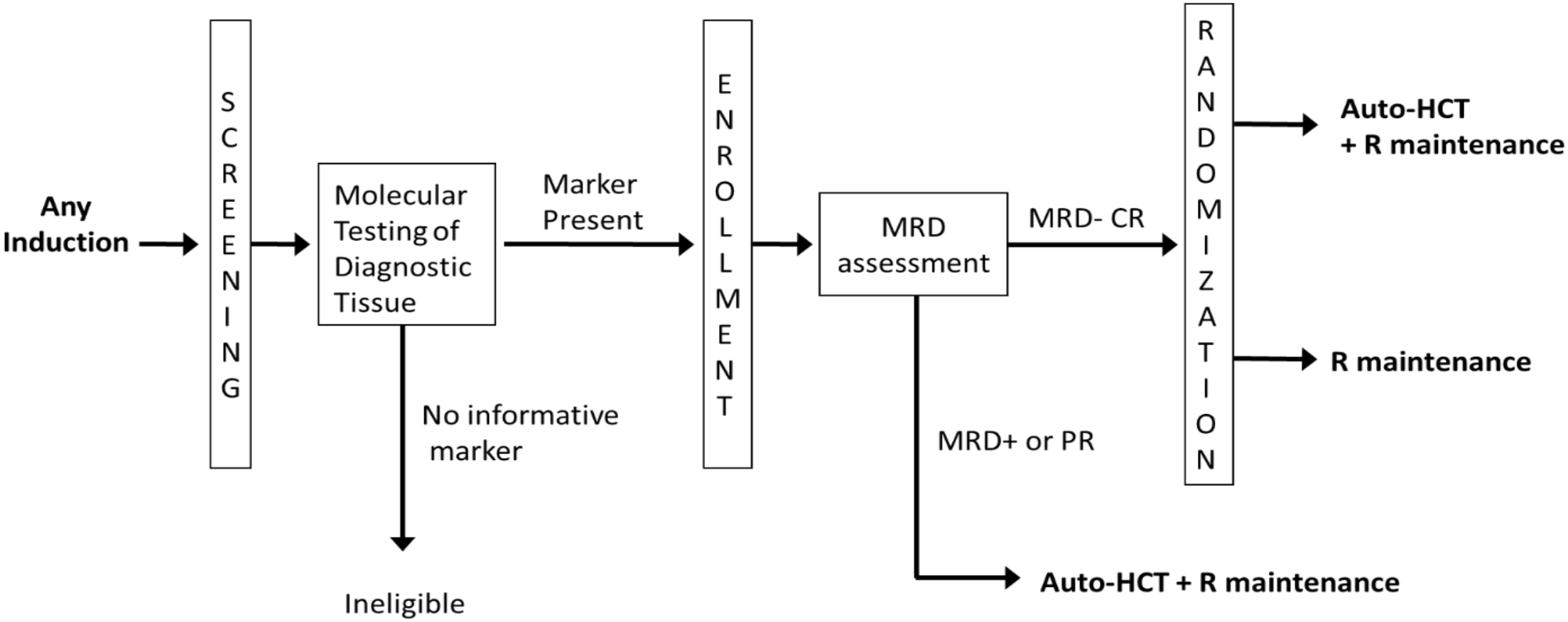


N. Wagner-Johnston, Study PI: Trial opened 2019, Accruing

Courtesy of Michael E Williams, MD, ScM

ECOG 5141: ASCT in MCL

ASCT → Maintenance Rituximab vs MR alone if MRD negative following Front-line induction therapy



T. Fenske, Study PI: study open, accruing

Courtesy of Michael E Williams, MD, ScM

MCL Case 1

- 72 yo physician referred July 2015 with fatigue, anemia and lymphocytosis 20k
  - Exam: diffuse adenopathy, splenomegaly to umbilicus
- PB flow c/w MCL, typical phenotype
- LN biopsy: MCL, mantle zone pattern, Ki67 30%
- He declined Rx with any cytotoxic agents
- Treated with rituximab weekly x 4 then maint. R → PR, cleared circulating cells
- 2 yr later, PD: orbital mass, diffuse adenopathy
  - → Ibrutinib 560/d → PR
  - Discontinued after 4 mo due to severe rash

Courtesy of Michael E Williams, MD, ScM

MCL: Case 1 (cont'd)

- Acalabrutinib 100 mg bid → transient decrease in adenopathy x 4 mo, then progressive adenopathy and splenomegaly. No recurrence of rash.
- Venetoclax stepped up dosing to 400 mg/d
  - Nodes and spleen decreased x 3 months, then progressed
  - Lymphocyte count remained normal
- Added obinutuzumab to Veneto, with goal of achieving synergy for apoptotic response
  - Obinu 100 mg IV, given IV fluids and he pushed po fluids, returned on day 2 for 900 mg dose. On allopurinol.
  - Patient asymptomatic, clear decrease in cervical and axillary node size, decreased splenomegaly on exam
  - Laboratory TLS: LDH 2000, phos 6.8, K 4.7, creat 1.1, uric acid 8.4 → resolved with IV and po fluids

Courtesy of Michael E Williams, MD, ScM

MCL: Case 1 (cont'd)

- Continued Veneto, gave dose 2 obinu 1 week later
  - No further TLS
- Completed obinu induction phase, then q2mo x 1 y
  - Achieved CR by imaging and exam at 3 months from initiation of obinu
- Obinu d/c due to pneumonia in Dec. 2019
- Continues Veneto 400 mg/d
- Oct. 2020: Remains in CR by exam and imaging

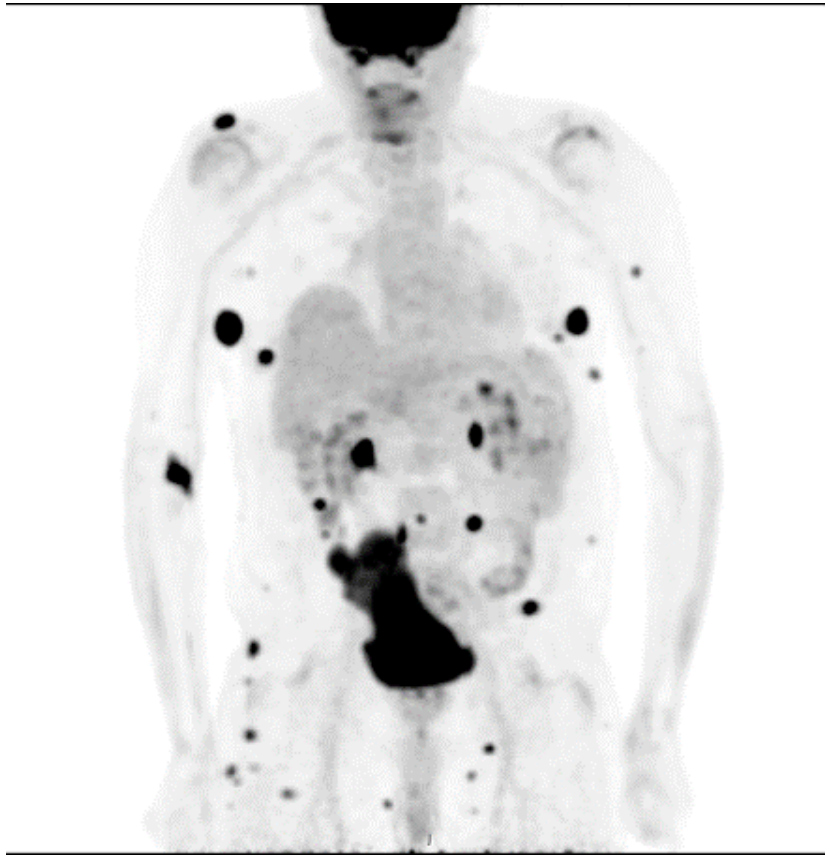
Courtesy of Michael E Williams, MD, ScM

MCL: Case 2

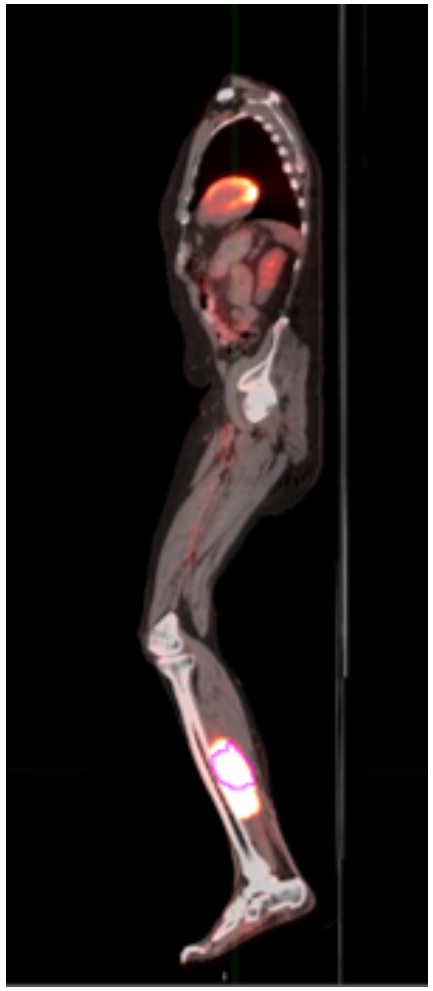
- 70 yo man presented with base of tongue mass
  - Biopsy: MCL, pleomorphic subtype, Ki67 50%
  - Marrow +, complex karyotype including t(11;14)
- Treated with Bendamustine/Rituximab x 6 cycles
  - Achieved CR by PET/CT
- Initiated maintenance Rituximab q2mo
- After 2nd dose, developed multiple subq skin lesions, largest 5x5 cm on R arm
  - Biopsy confirmed MCL
- Initiated phase 1b/2 Clinical trial: PrECOG 0404:
  - Ibrutinib 560 mg/d plus ixazomib 4 mg po on days 1, 8 and 15 of each 28-day cycle

Courtesy of Michael E Williams, MD, ScM

MCL: Case 2 (cont'd)



Multiple subcutaneous nodules, 1st relapse MCL → **achieved CR on Ibrutinib plus Ixazomib** by PET/CT



2nd relapse with 10x14 cm soft tissue mass L leg, 6 mo after CR on IBR/IXAZ; biopsy = pleomorphic MCL, Ki67 40%

Courtesy of Michael E Williams, MD, ScM

MCL: Case 2 (cont'd)

- Treatment of isolated LLE mass:
  - Clinical trial therapy discontinued
  - Patient continues Ibrutinib 560 mg daily to mitigate risk of near-term systemic progression
  - Completed radiation therapy to the leg mass
- Evaluating for CAR-T cell therapy with brexucabtagene autoleucel

Courtesy of Michael E Williams, MD, ScM