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Michael E. Williams, MD, ScM, FACP

Byrd S. Leavell Professor of Medicine and Professor of Pathology
Physician Lead, Oncology Service Line, UVA Health
Associate Director for Clinical Affairs,
UVA Comprehensive Cancer Center
University of Virginia School of Medicine, Charlottesville

Dr. Williams received his MD from the University of Cincinnati College of Medicine and Master of Science from the Harvard School of Public Health. Following Medicine residency, Chief Residency and Fellowship at UVA Health he joined the Department of Medicine faculty and the NCI-designated Cancer Center. He serves in several leadership roles including past Chief of the Hematology/Oncology Division.

Dr. Williams' patient care and research interests include clinical trials and translational science for mantle cell lymphoma, other non-Hodgkin lymphomas and CLL, with a focus on targeted agents and immuno-therapeutics.

He is an Emeritus member of the Scientific Advisory Board and was the inaugural Chair of the Mantle Cell Consortium of the Lymphoma Research Foundation. He was awarded the inaugural LRF Mantle Cell Lymphoma Leadership Award in 2021 and honored by establishment of the Dr. Michael Williams Abstract Achievement Award for MCL Research. He is a member of the Eastern Cooperative Oncology Group Lymphoma Core Committee and of the European Mantle Cell Lymphoma Network.

Dr. Williams is past Chair of the Hematology Subspecialty Board of the American Board of Internal Medicine, a past member of the ABIM Council, and currently serves on ABIM's Hematology Longitudinal Assessment Committee. He serves on the editorial board of the Journal of Clinical Oncology, and is Associate Editor for Hematologic Malignancies for the NEJM Group Journal Watch Oncology and Hematology. He participates regularly in national and international programs devoted to research and education in lymphoma and CLL.

Most Important Advances in Lymphoid Cancers

LPP Excel Meeting

October 15, 2022

Michael E. Williams, MD, ScM, FACP

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University of Virginia Cancer Center

UVA Cancer Center

An NCI Comprehensive Cancer Center

UVA Health

Presentation Outline

- Update in MCL
  - A paradigm for targeted therapeutics
- CAR-T cell therapy
  - MCL
  - DLBCL
  - Follicular lymphoma
- Waldenstrom macroglobulinemia/LPL

MCL Initial Therapy

- Over the past 15 y, survival has improved from < 3 y to >10 y
- Watch/Wait patients
  - indolent subtype or low tumor burden, asymptomatic (~20% of patients)
- Younger, fit patients, < 70 y
  - Rituximab plus high-dose cytarabine-based regimen (e.g.,R-DHAX) → Auto SCT→ Maint R *(LeGouill et al, NEJM 2017)*
  - Is ASCT needed if MRD negative after induction therapy? *(ECOG 4151)*
  - Non-HiDAC regimen pre-ASCT? *(ECOG 4181)*

Mantle Cell Lymphoma: Prognostic Factors at Diagnosis

Biomarker	Favorable	Unfavorable
MIPI or MIPI-c Score	Low	High
Ki-67 Score	< 30%	>/= 30%
Chromosome 17p	Intact	Deleted
TP53	Wild type	Mutated
Clinical/Morphologic	Leukemic/Non-nodal subtype	Blastoid or Pleomorphic MCL
Post-induction Measurable Residual Disease (MRD)	Negative	Positive
MCL35 Proliferation Assay	Low-risk	High-risk
Anti-LRPAP1 seropositive *(Proposed)*	Present	

Williams ME. *Blood* 2021; 137:3158-60

Mantle Cell Lymphoma: Prognostic Factors at Diagnosis

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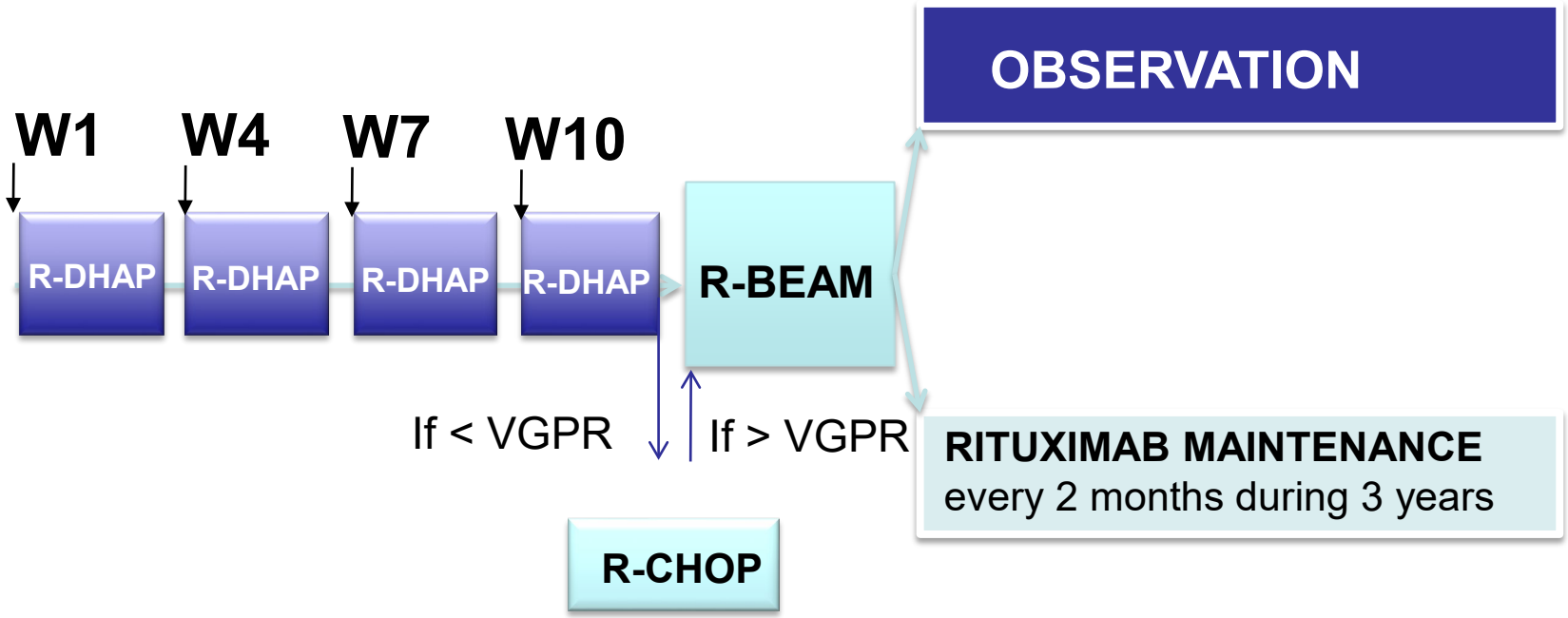
Clinica		
Post-in Measur Disease		
MCL35 Proliferation Assay	Low-risk	High-risk
Anti-LRPAP1 seropositive *(Proposed)*	Present	

None of these factors are currently utilized to guide choice of initial therapy, although blastoid morphology and TP53 mutated are very high risk and may benefit from addition of a targeted agent.

Williams ME. *Blood* 2021; 137:3158-60

LyMa trial

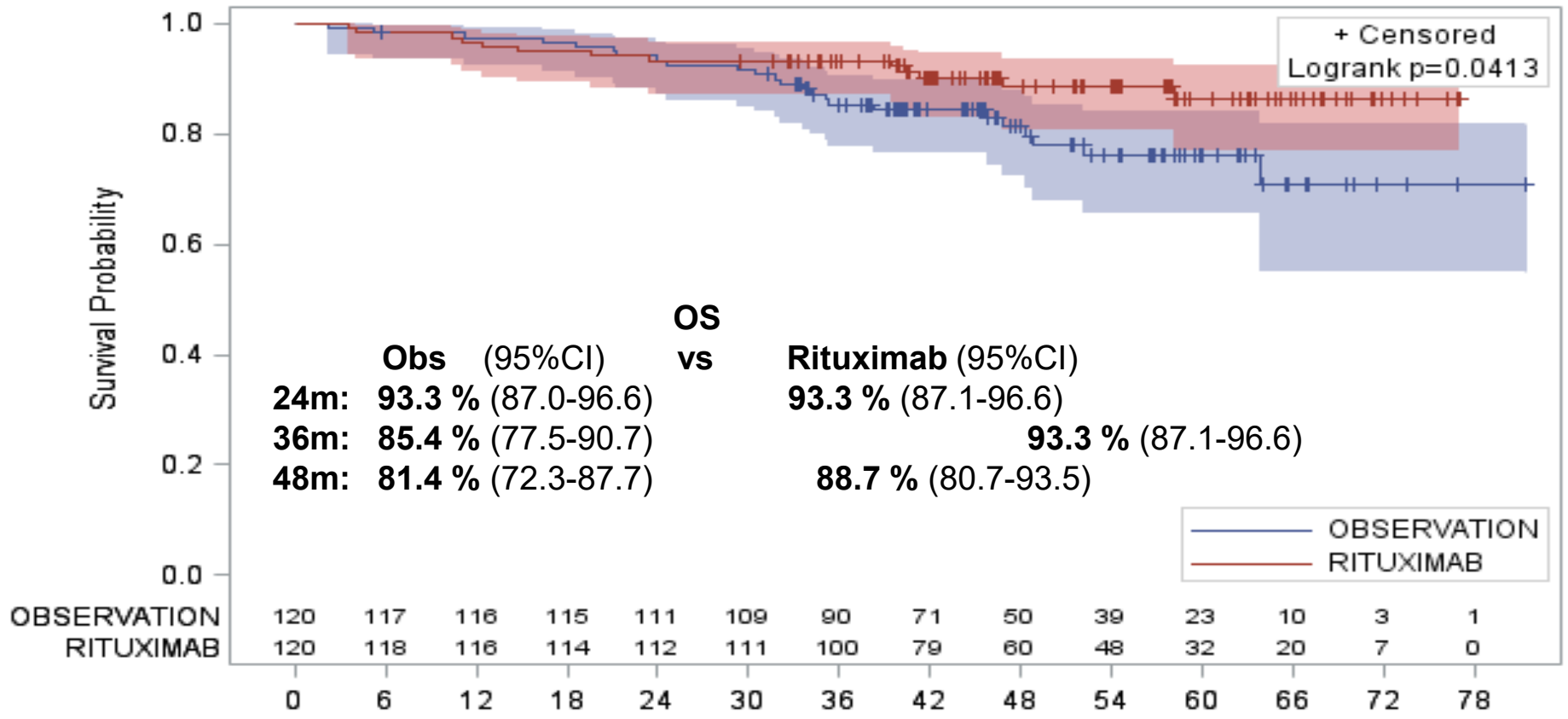


R-DHAP: Rituximab 375mg/m^2; cytarabine 2g/m^2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m^2 d1 (or **oxaliplatin** or carboplatin)

R-BEAM: Rituximab 500mg/m^2 d-8; BCNU 300mg/m^2 d-7; Etoposide 400mg/m^2/d d-6 to -3; cytarabine 400mg/m^2/d d-6 to d-3; melphalan 140mg/m^2 d-2

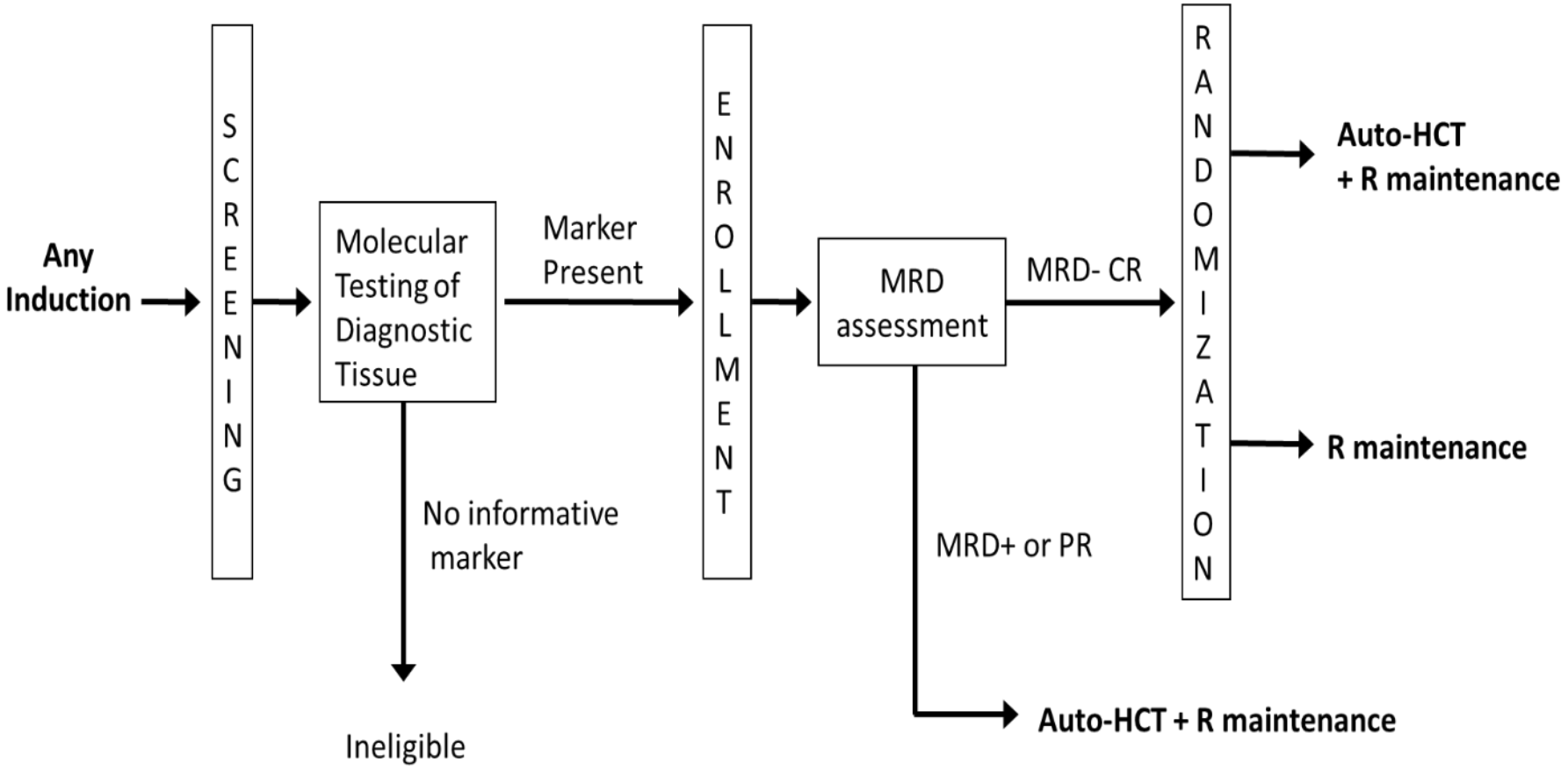
OS from Randomization

mFU: 50.2m (46.4-54.2)



ECOG EA 4151: ASCT in MCL

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



T. Fenske, Study PI: study open, accruing

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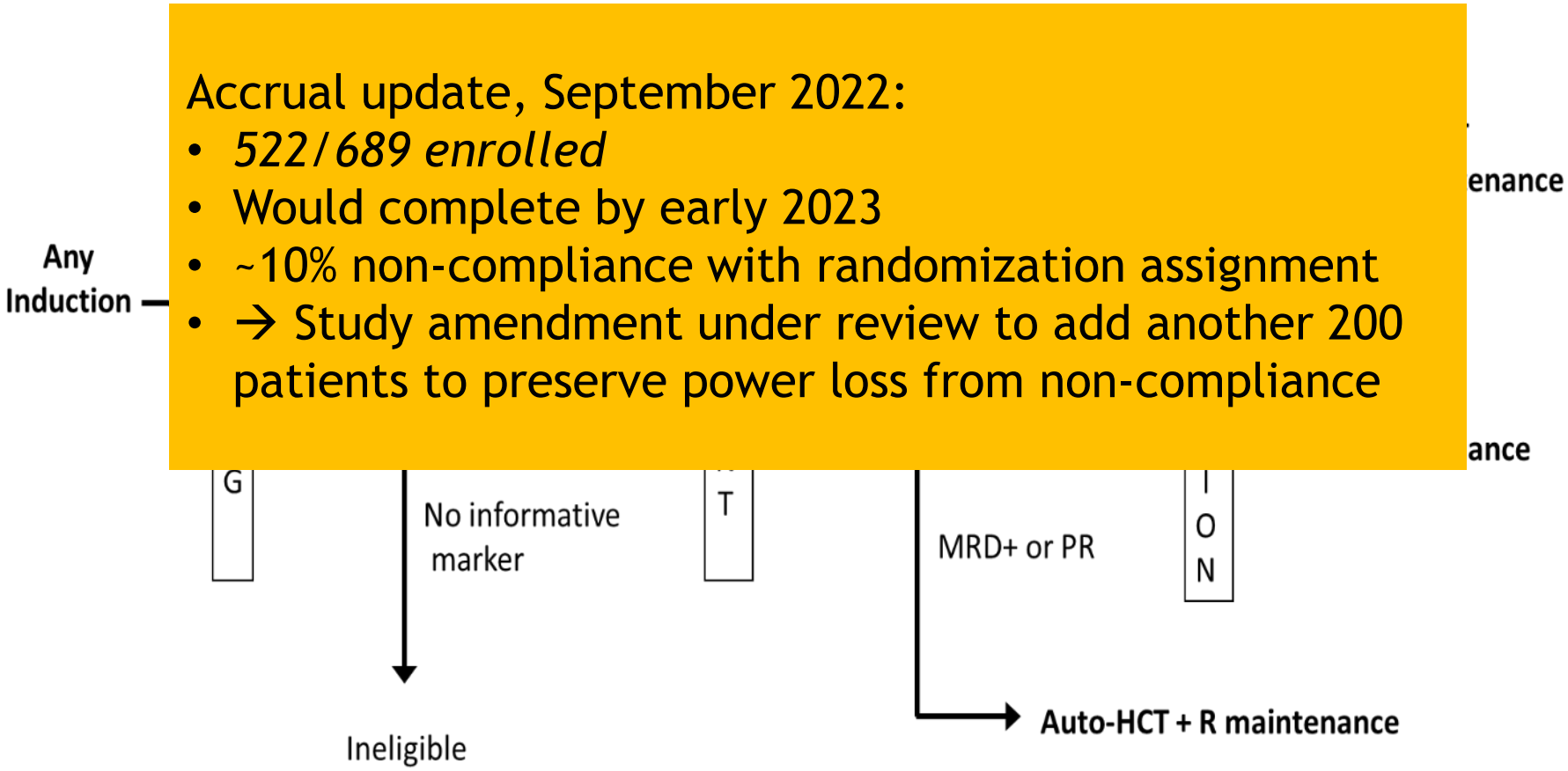
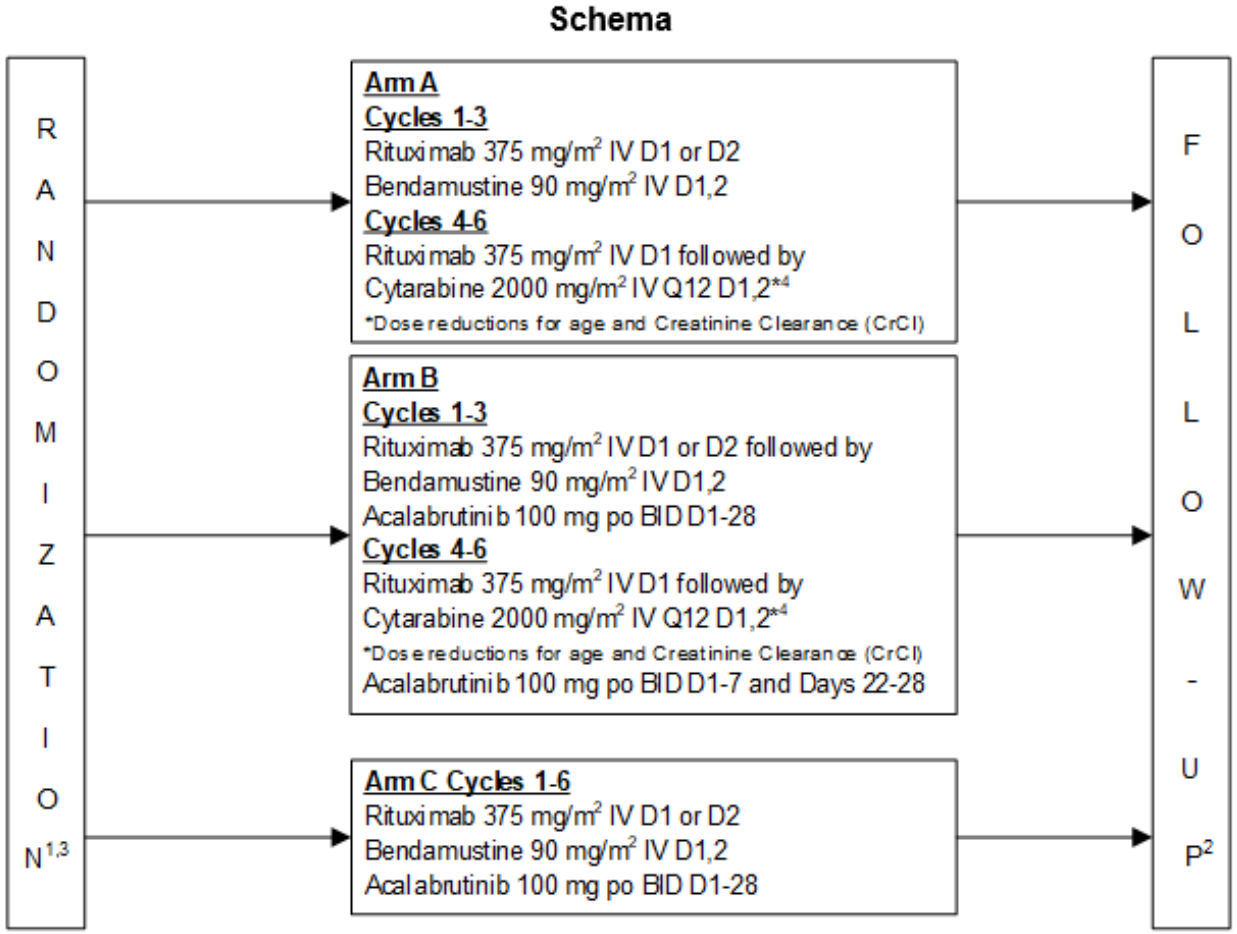


Accrual update, September 2022:

- *522/689 enrolled*
- Would complete by early 2023
- ~10% non-compliance with randomization assignment
- → Study amendment under review to add another 200 patients to preserve power loss from non-compliance

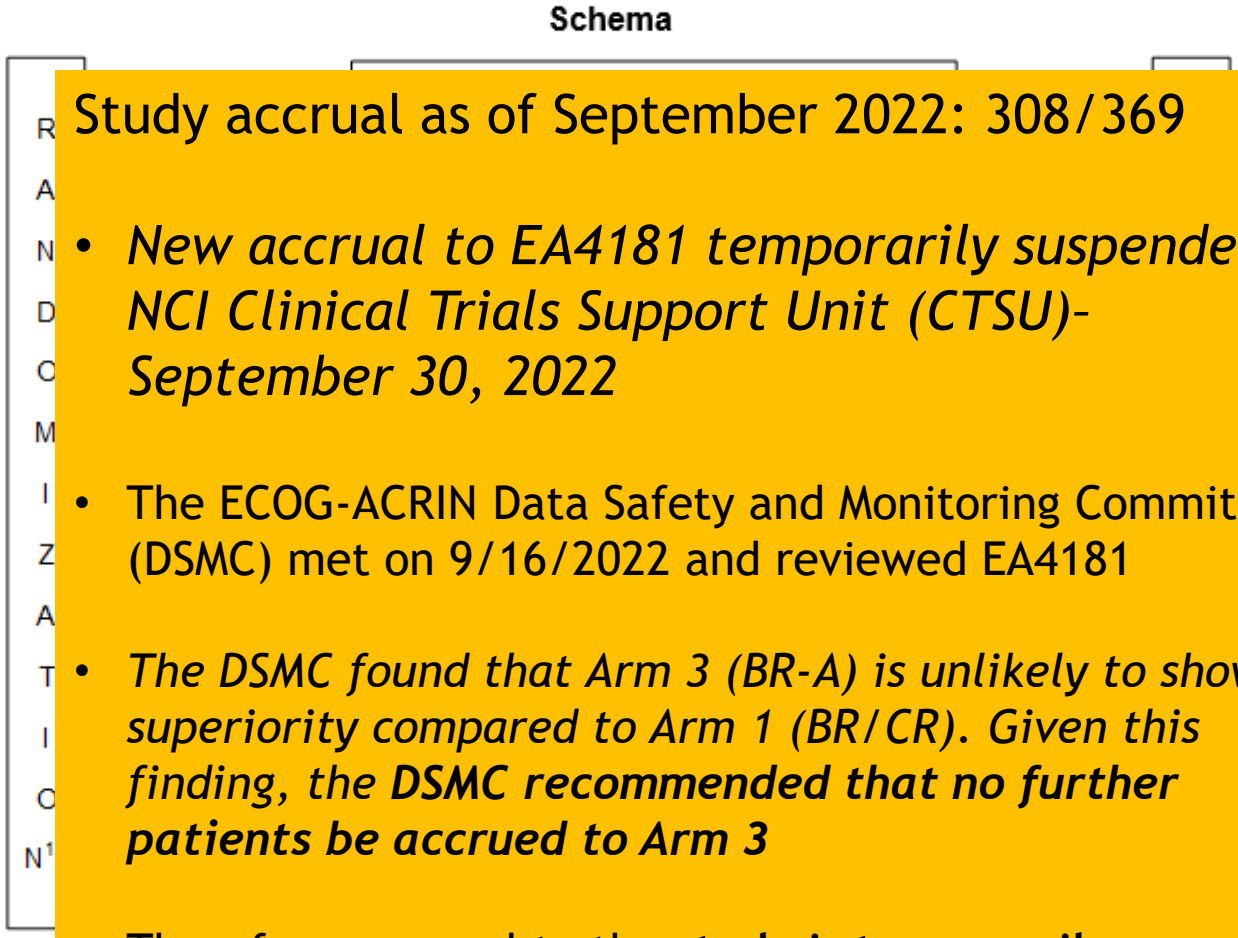
T. Fenske, Study PI: study open, accruing

ECOG EA4181: Front-line MCL (age </=70 y)



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

ECOG EA4181: Front-line MCL (age </=70 y)



Study accrual as of September 2022: 308/369

- *New accrual to EA4181 temporarily suspended by NCI Clinical Trials Support Unit (CTSU)- September 30, 2022*
- The ECOG-ACRIN Data Safety and Monitoring Committee (DSMC) met on 9/16/2022 and reviewed EA4181
- *The DSMC found that Arm 3 (BR-A) is unlikely to show superiority compared to Arm 1 (BR/CR). Given this finding, the **DSMC recommended that no further patients be accrued to Arm 3***
- Therefore, accrual to the **study is temporarily suspended** until an addendum to the protocol can be processed to modify the consent form with this information

Initial therapy: Older or transplant-ineligible MCL patients

1. BR *(Bendamustine-rituximab)*
2. R-CHOP
3. VR-CAP *(Bortezomib plus R-CHP)*
4. R-BAC$_{500}$ *(BR plus cytarabine 500 mg/m^2)*
5. R^2 *(Lenalidomide-rituximab)*
6. Clinical trial *(e.g., BTKi, or BTKi combined with an anti-CD20 or venetoclax)*

Rituximab-Lenalidomide vs Rituximab Maintenance after First-line R-Chemo in Mantle Cell Lymphoma: MCL R2 Elderly Clinical Trial

Ribrag et al. European Mantle Cell Network. ASH 2021, Abstract 379

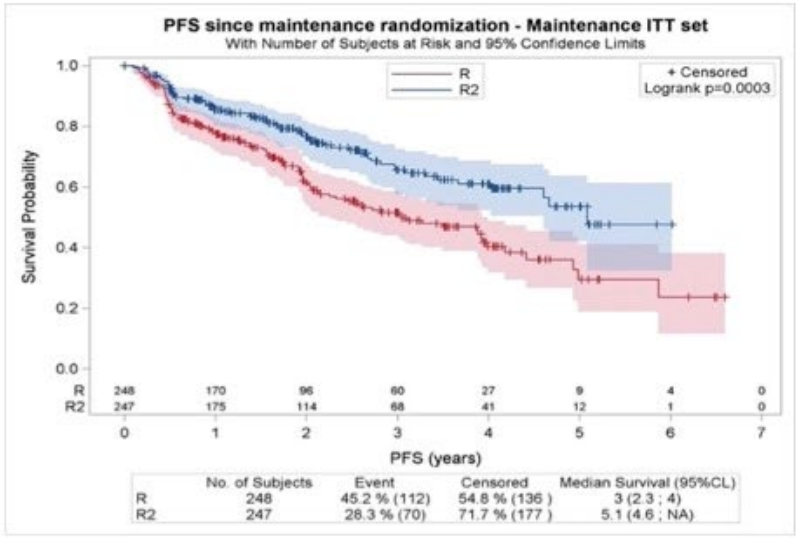
- Untreated MCL, age > 60y, not eligible for auto SCT consolidation
- Regimens:
  - **R-CHOP x 6 cycles, vs**
  - **R-CHOP x 3 cycles alternating with R-HAD (AraC, Dex) x 3 cycles**
- Patients with PR or CR randomized to maintenance:
  - **R q2mo x 2 yr, vs**
  - **Len 10 or 15 mg/d x 21d on 28d cycles, plus R q2mo x 2 yr**
- Induction results: 514/620 (87%) responded, CR 41%
- 495 randomized to maintenance therapy
- **2 yr PFS: R^2 76.6% vs R 60.8% (p=0.0003)**
- OS: no difference
- Toxicity: higher in R^2, 46% needed Len dose reductions

R^2 vs R Maintenance in MCL

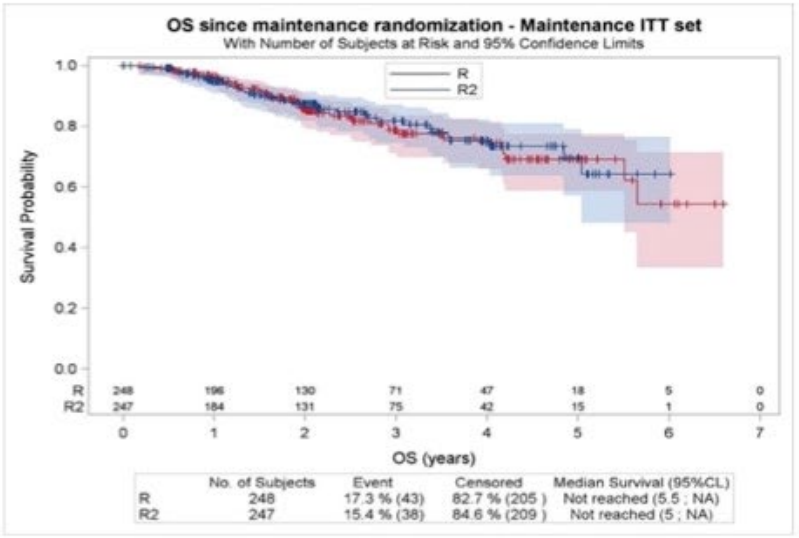
ASH 2021, Abstract 379

Figure 1: PFS (A) and OS (B) by maintenance with rituximab (R) or rituximab-lenalidomide (R2).

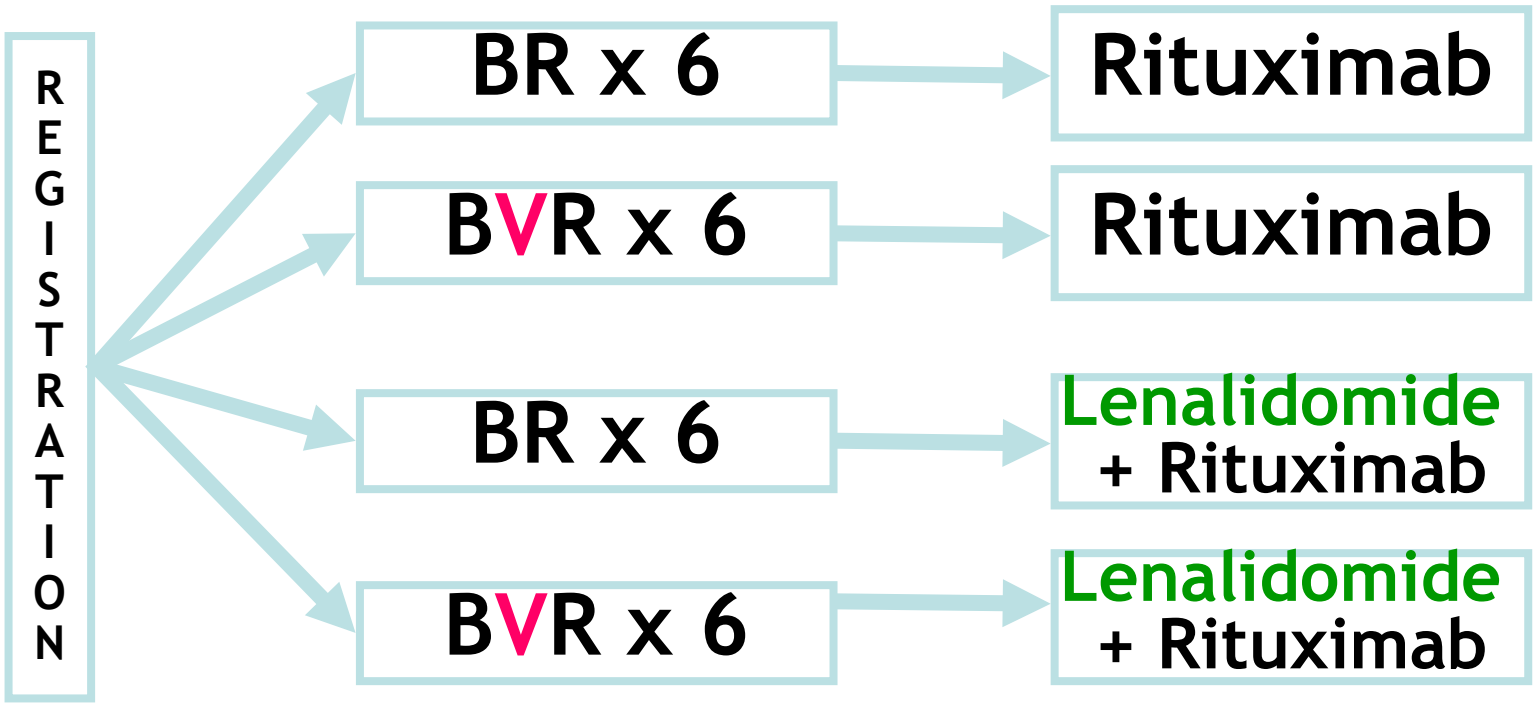
A



B



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

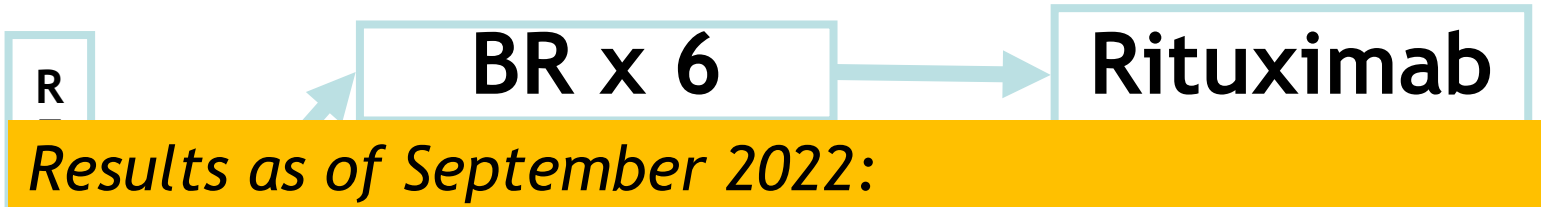


BR = Bendamustine, Rituximab

V= Bortezomib

M. Smith, Study PI; *accrual completed September 2012-16*

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



Results as of September 2022:

- **Front-line:** no benefit for adding bortezomib to BR in ORR or PFS @ median f/u 51 mo *(Smith et al, ASCO 2021)*
- **MRD:** > 90% MRD negative at end of induction in both arms *(Smith et al, ASH 2019)*
  - MRD+ after cycle 3 → high relapse risk
- **Maintenance:** submitted to ASH 2022

BR = Bendamustine, Rituximab

V= Bortezomib

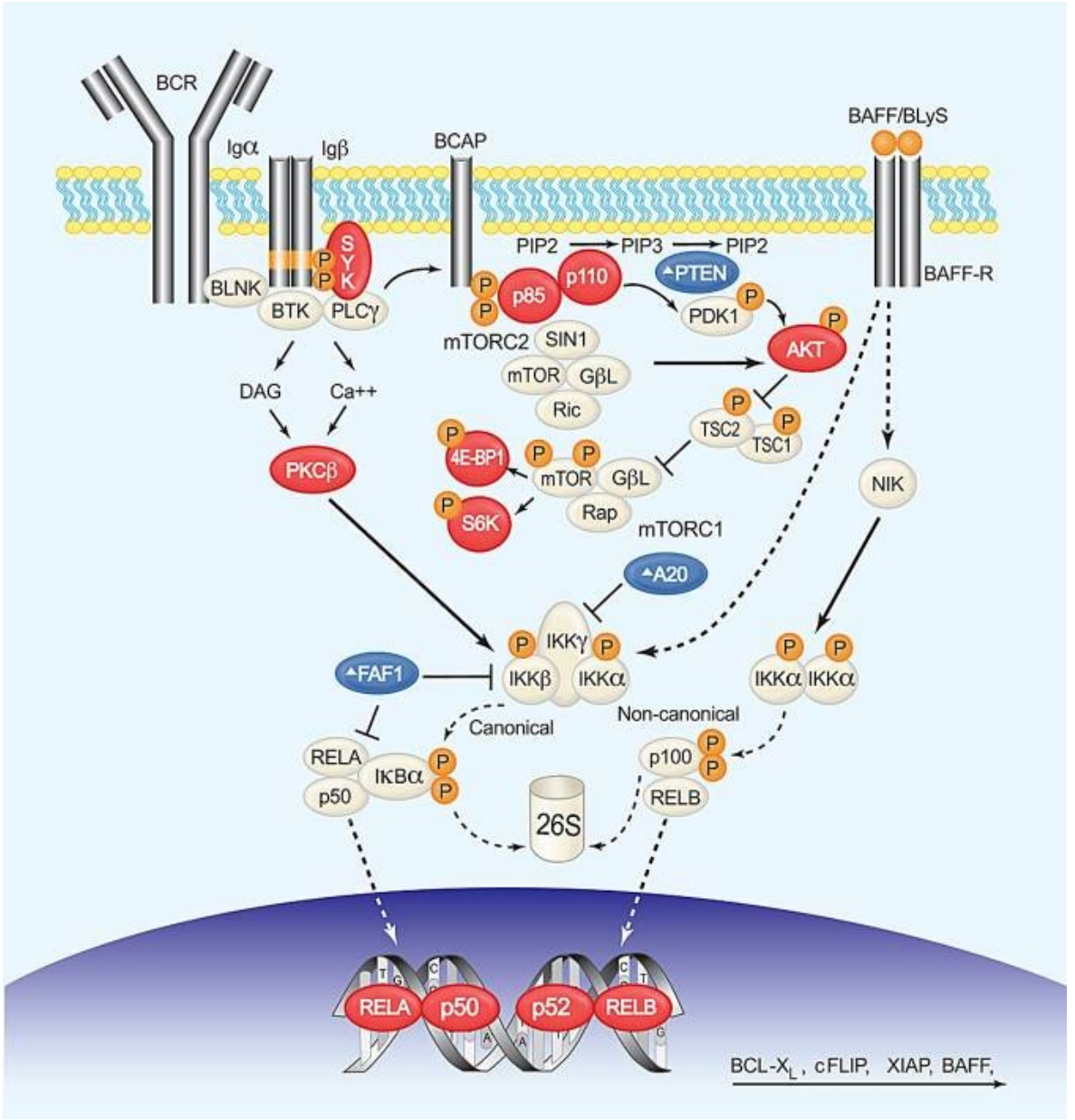
M. Smith, Study PI; ***accrual completed September 2012-16***

Targeted Therapeutics

Moving beyond traditional
cytotoxic chemotherapy regimens

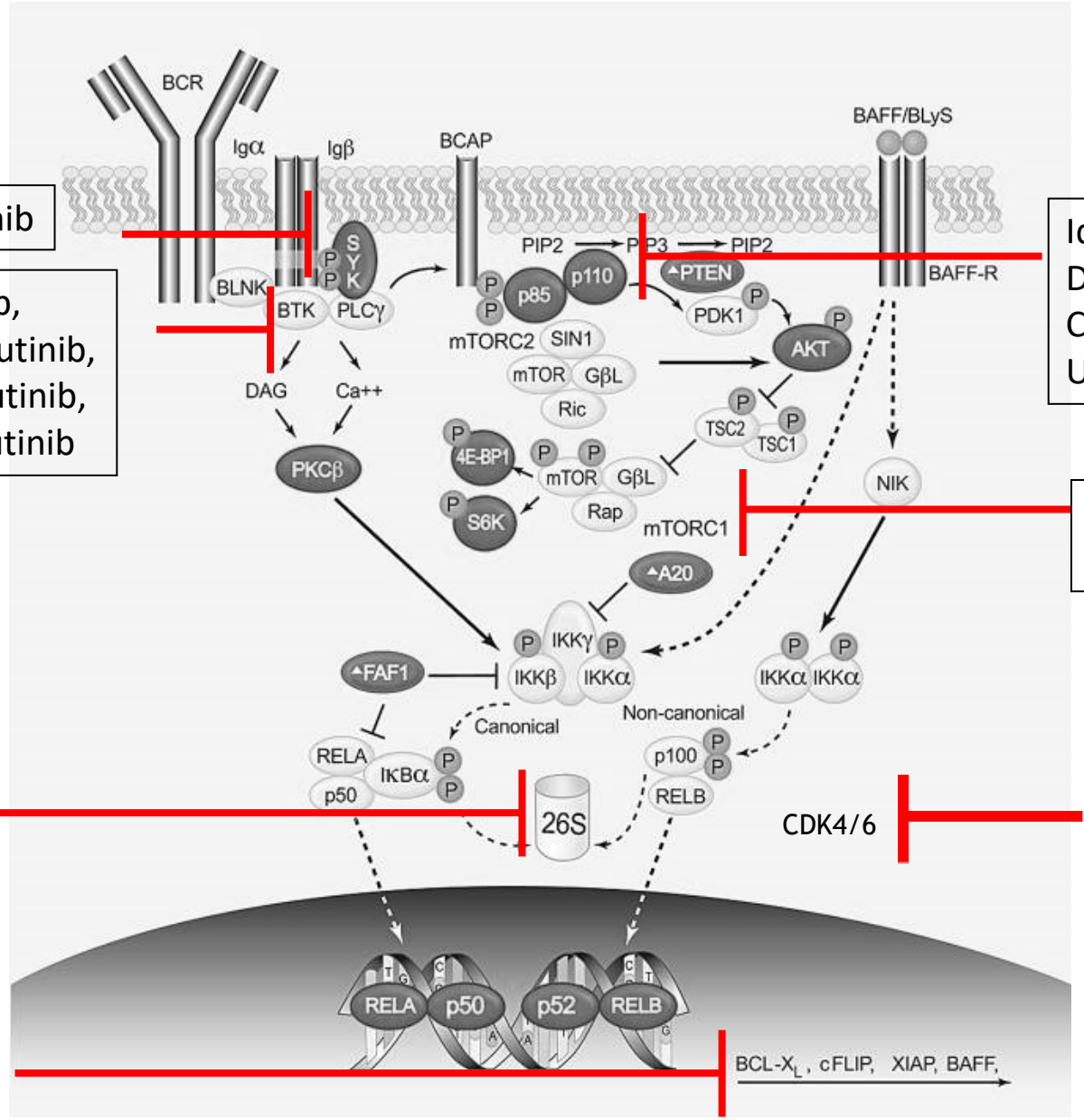
The B-cell receptor pathway is activated in most B-cell malignancies

Overexpressed
Down-regulated



P. Perez-Galan et al. Blood. 2011

The B-cell receptor pathway : Selected Inhibitors



Fostamatinib

Ibrutinib,
Acalabrutinib,
Zanabrutinib,
Pirtabrutinib

Idelalisib,
Duvelisib,
Copanlisib,
Umbralisib

Everolimus,
Temsirolimus

Bortezomib,
Carfilzomib,
Ixazomib

Palbociclib,
Ribociclib,
Abemaciclib

Venetoclax

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
Zanabrutinib	86	84%	16.7 m
Venetoclax	28	75%	12 m
Pirtabrutinib*(non-covalent BTKi)	20	65%	Too early
Ibrutinib-Venetoclax	24	71% (all CR)	80% at 12 m

*=LOXO-305; 7 CR, 6 PR; ~90% of patients had prior BTKi (Wang et al, ASH 2020)

FDA-approved BTKi for R/R MCL:
Ibrutinib, Acalabrutinib and Zanubrutinib

- Similar overall response rates, ~70-80%
- Improved toxicity profile for Acala and Zanu
  - More specific BTKi inhibition with 2nd generation BTKi
  - Less Afib, bruising/bleeding, arthralgia vs Ibrutinib
  - Prefer over Ibrutinib if patient receiving concurrent anticoagulation and/or anti-platelet therapy

Herman et al, Clin Ca Res 2017

Venetoclax after BTKi failure in MCL

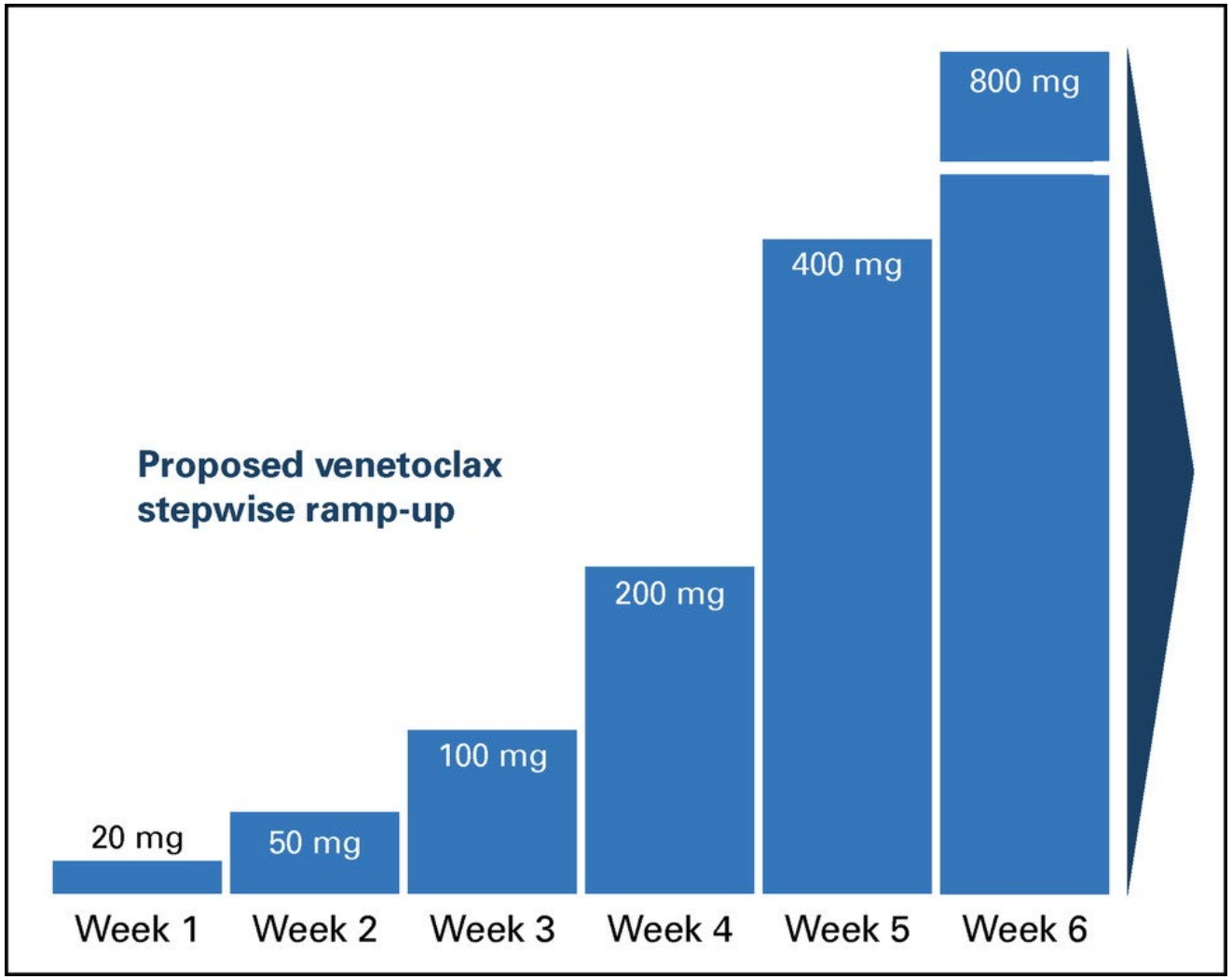
- **Single-agent Ven (n=20; median 2-5 prior Rx, ASCT 30%)**
  - Overall response rate 53%
    - Complete remission 18%
  - Median PFS 3.2 m, DOR 8.1 m
  - Median OS 9.4 months
- **Venetoclax plus anti-CD20 mAb**
  - Increases overall response and CR rate
  - May “rescue” otherwise suboptimal responses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

Eyer et al, Haematologica 2019

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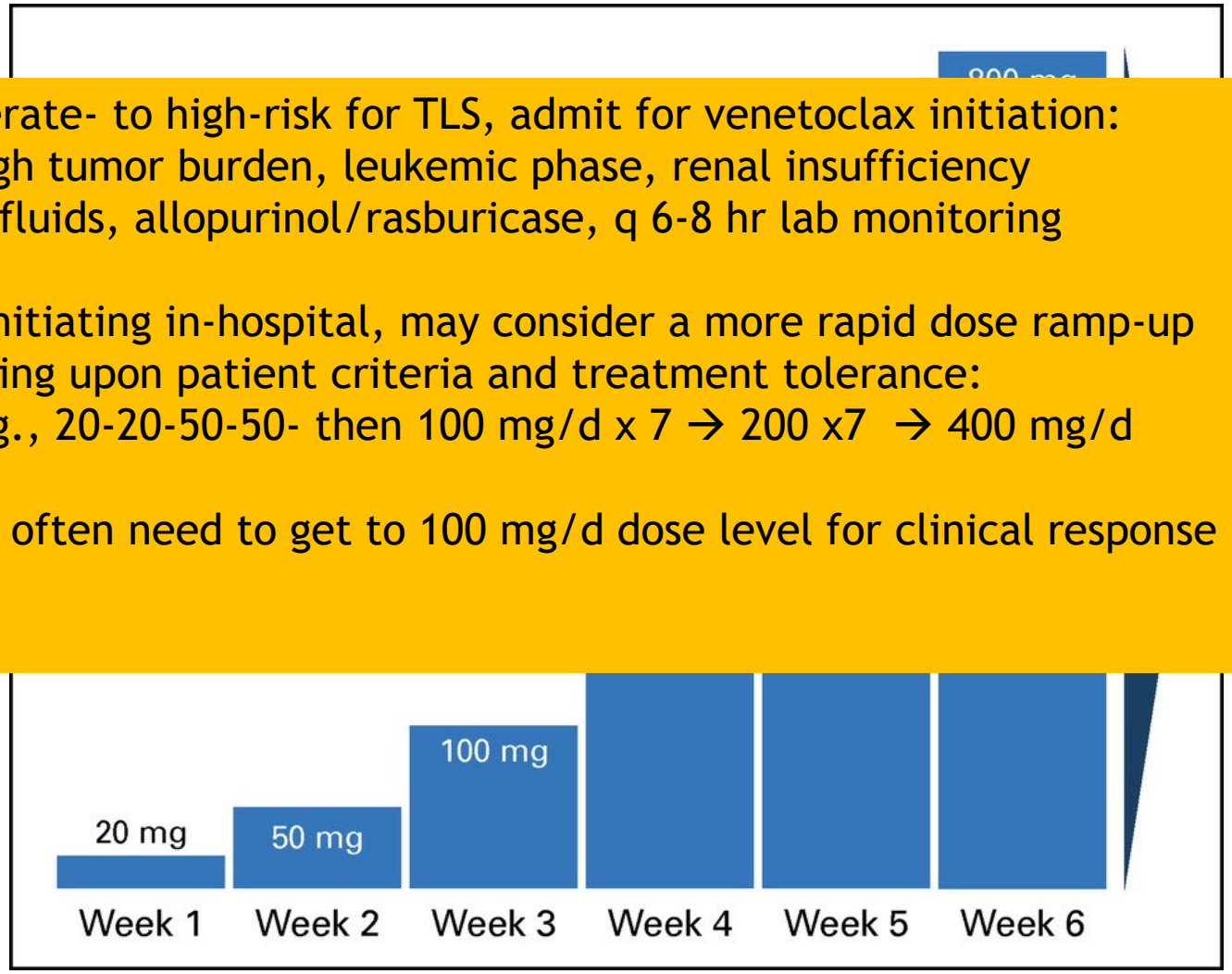
MS Davids, G von Keudell, CA Portell, JB Cohen, et al
J Clin Oncol 2018; 36: 3525-7

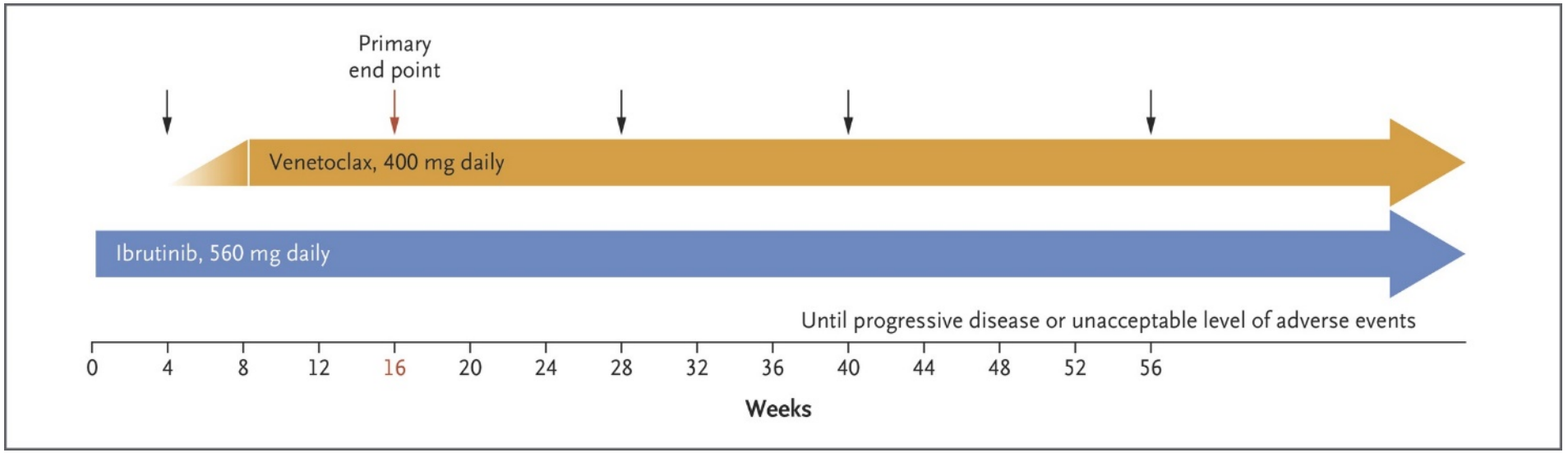
If moderate- to high-risk for TLS, admit for venetoclax initiation:
- High tumor burden, leukemic phase, renal insufficiency
- IV fluids, allopurinol/rasburicase, q 6-8 hr lab monitoring

When initiating in-hospital, may consider a more rapid dose ramp-up depending upon patient criteria and treatment tolerance:
- e.g., 20-20-50-50- then 100 mg/d x 7 → 200 x7 → 400 mg/d

In MCL, often need to get to 100 mg/d dose level for clinical response



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

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)

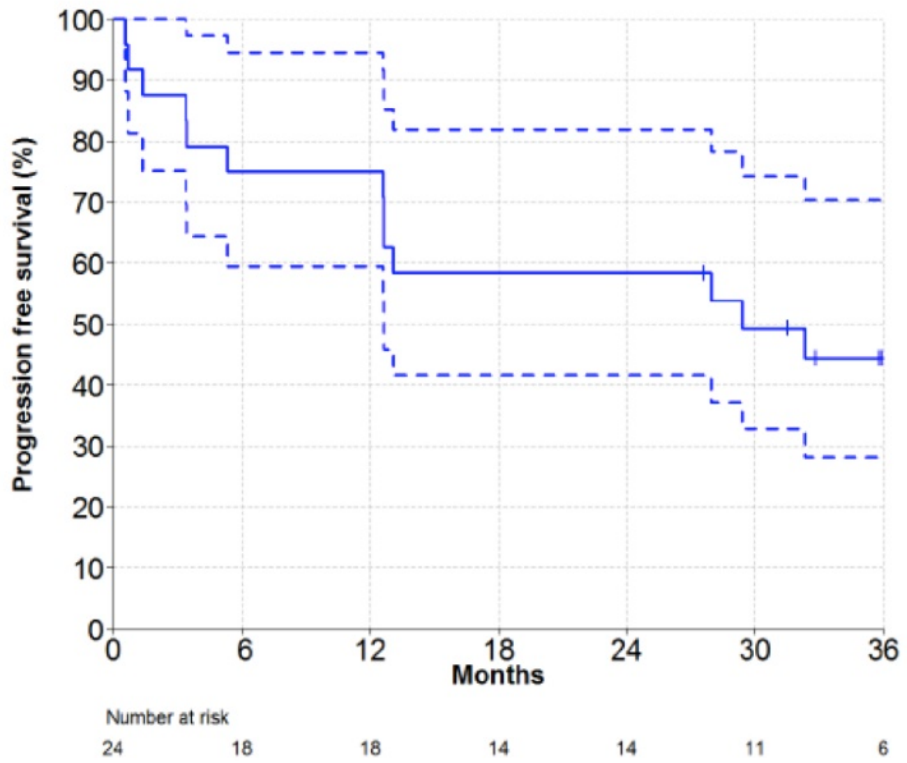
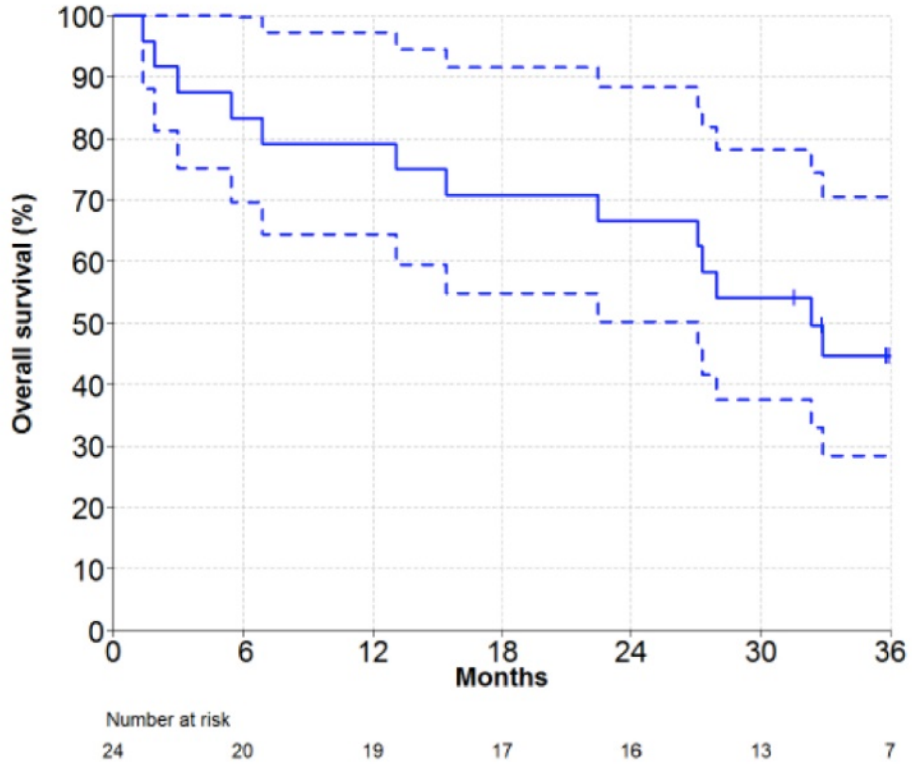


Figure 2. Overall survival (Dashed lines represent 95% confidence interval)

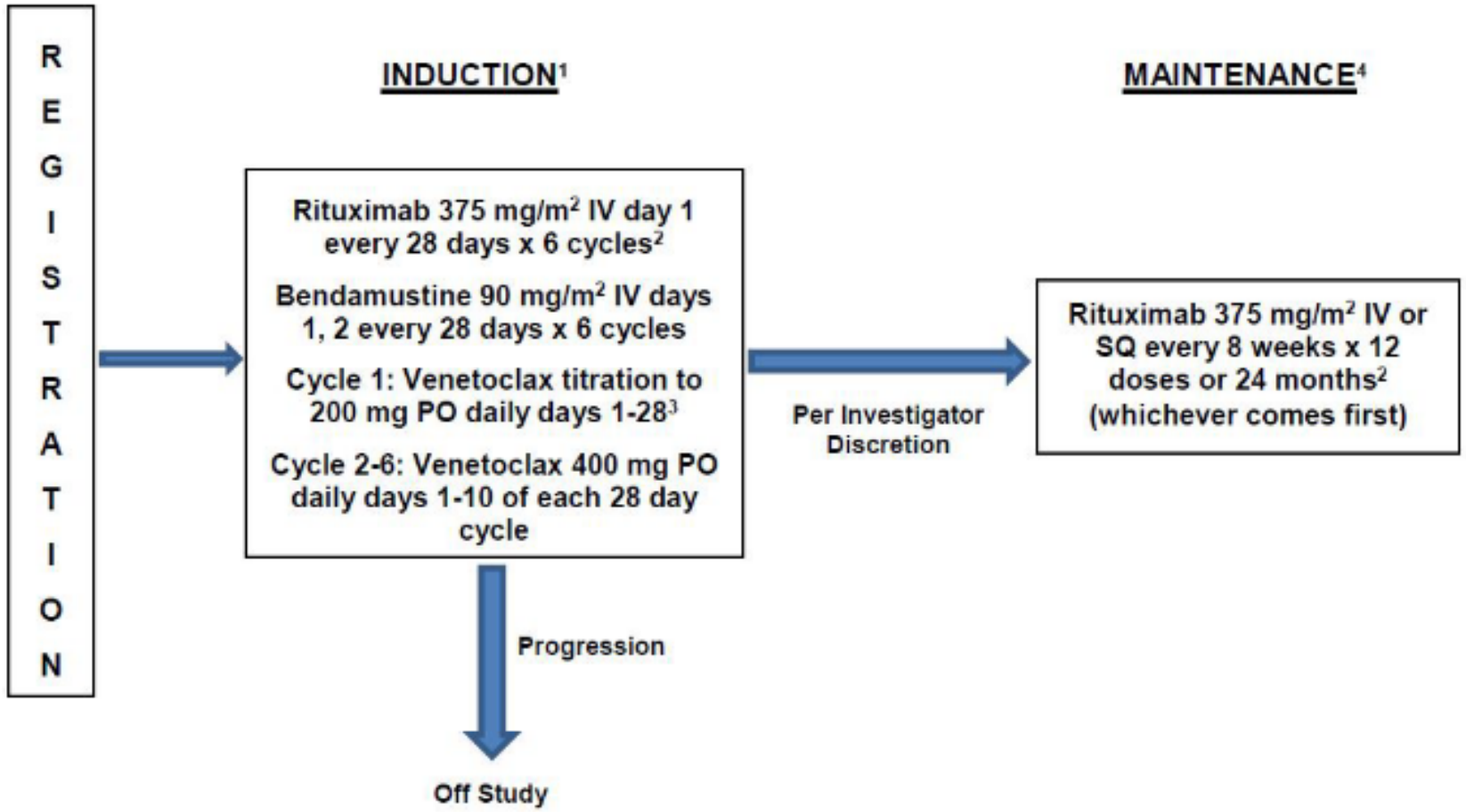


- MRD-negative by flow in 67%, and by ASO-PCR in 38%
- **5 MRD-negative patients discontinued Rx at median of18.5 mo**
  →4 remained MRD-neg at 6, 13, 17 and 18 months

Ibrutinib Combined With Venetoclax in Mantle Cell Lymphoma (SYMPATICO)

- Initiated May 2017 *(Sponsor: Pharmacyclics)*
- 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 later expanded to include front-line MCL therapy
- *Accrual complete, results pending as of July 2022*

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

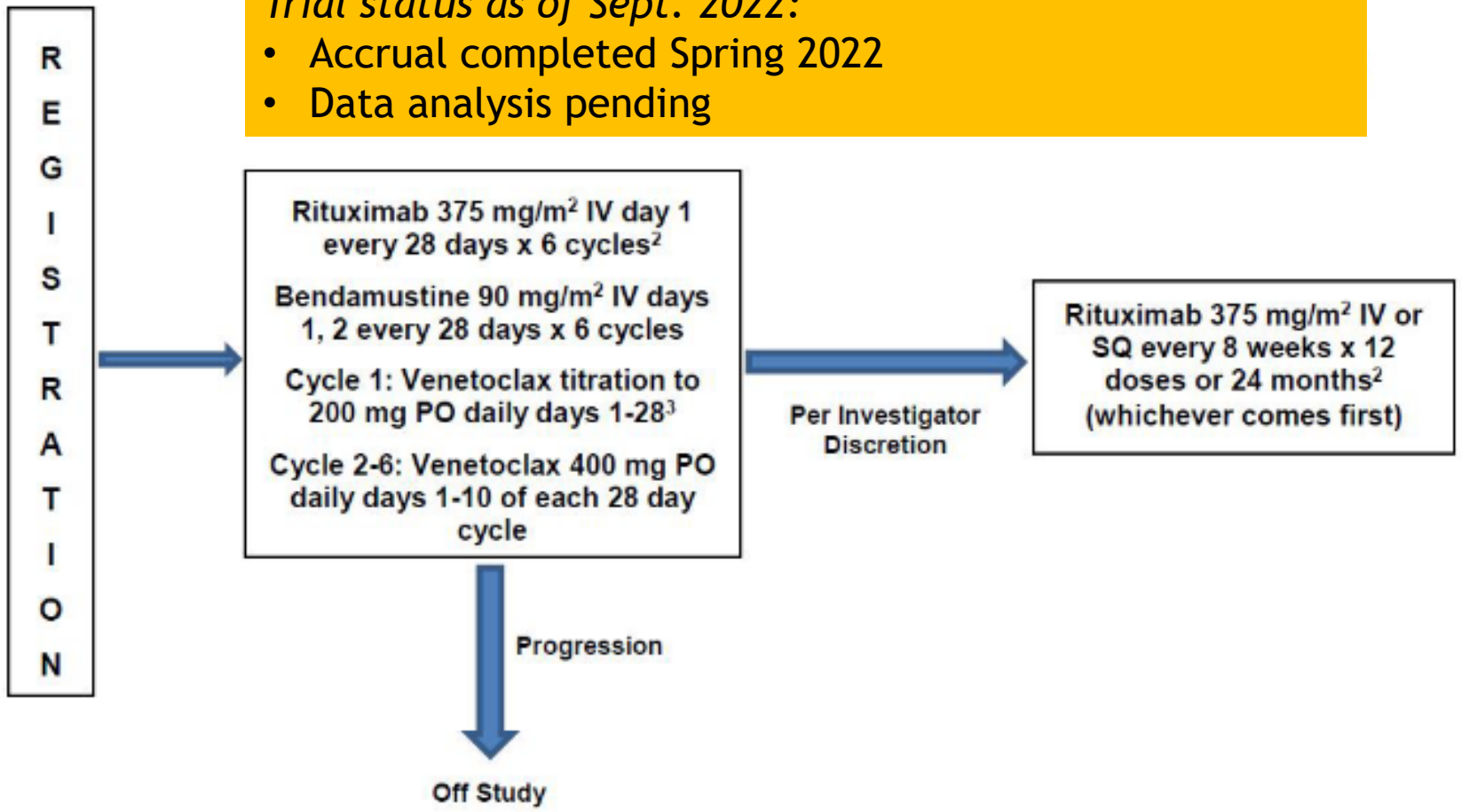


C. Portell, Study PI: Study opened 2020

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

Trial status as of Sept. 2022:

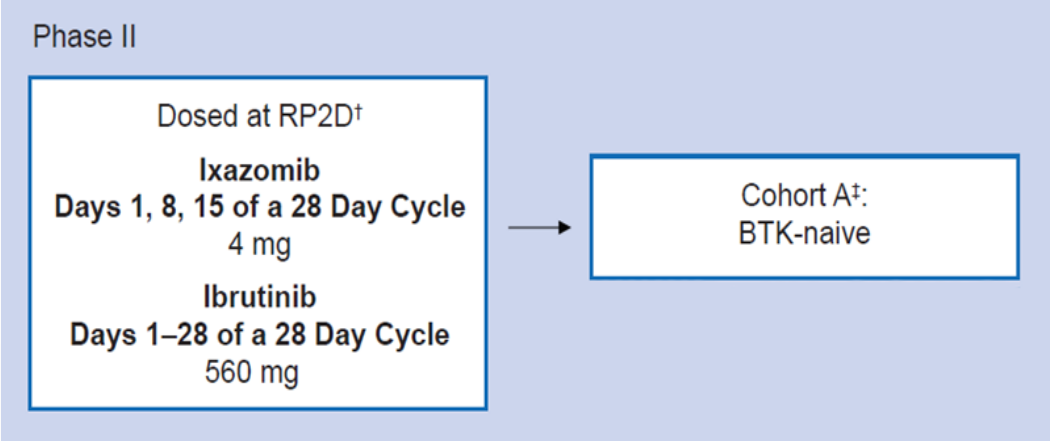
- Accrual completed Spring 2022
- Data analysis pending



C. Portell, Study PI: Study opened 2020

PrE0404: A Phase I/II Study of Ixazomib and Ibrutinib in Relapsed/Refractory Mantle Cell Lymphoma

as of August 2020



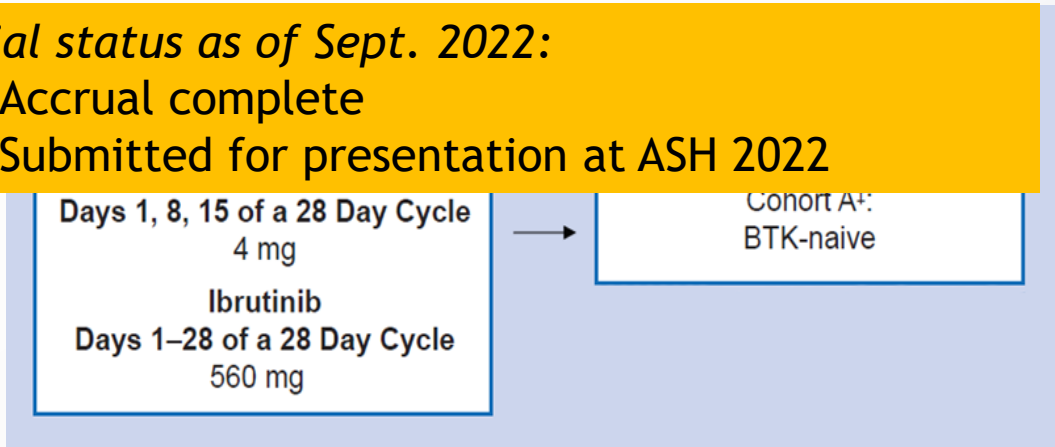
RP2D: Recommended Phase 2 Dose
BTK: Bruton's Tyrosine Kinase

PrE0404: A Phase I/II Study of Ixazomib and Ibrutinib in Relapsed/Refractory Mantle Cell Lymphoma

as of August 2020

Trial status as of Sept. 2022:

- Accrual complete
- Submitted for presentation at ASH 2022



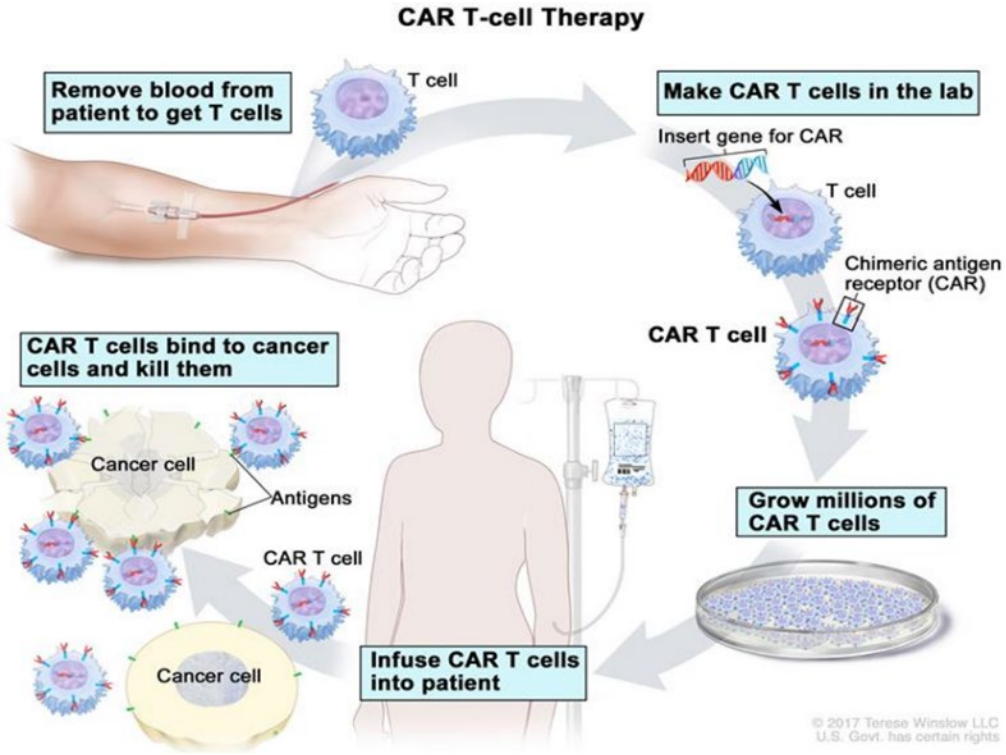
RP2D: Recommended Phase 2 Dose
BTK: Bruton's Tyrosine Kinase

Treatment approaches in **relapsed MCL**

- Younger, fit patient, including failed Auto SCT
  - Allogeneic SCT: the known curative option
  - CAR-T-cell therapy: durable remissions…. Cure?
- Older or less fit patients
  - Targeted agent or combination, usually BTKi
  - Clinical trial preferred
- Frail, elderly, or serious coexisting illness
  - BTKi, rituximab +/- lenalidomide

Targeted Cellular Therapeutics: CAR-T cells

Chimeric Antigen Receptor T-Cell Therapy



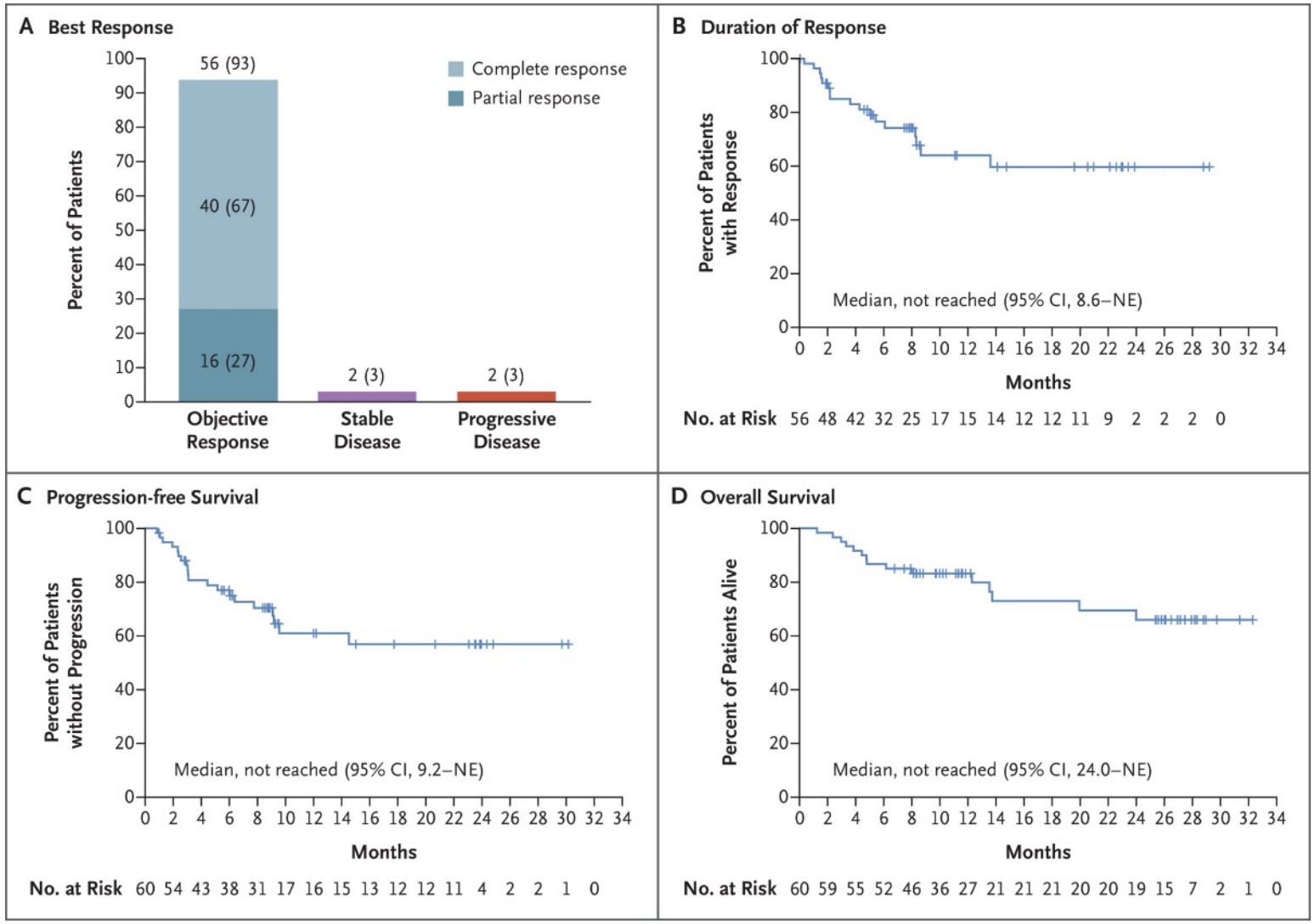
KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T Cell Therapy, in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Results of the Phase 2 ZUMA-2 Study

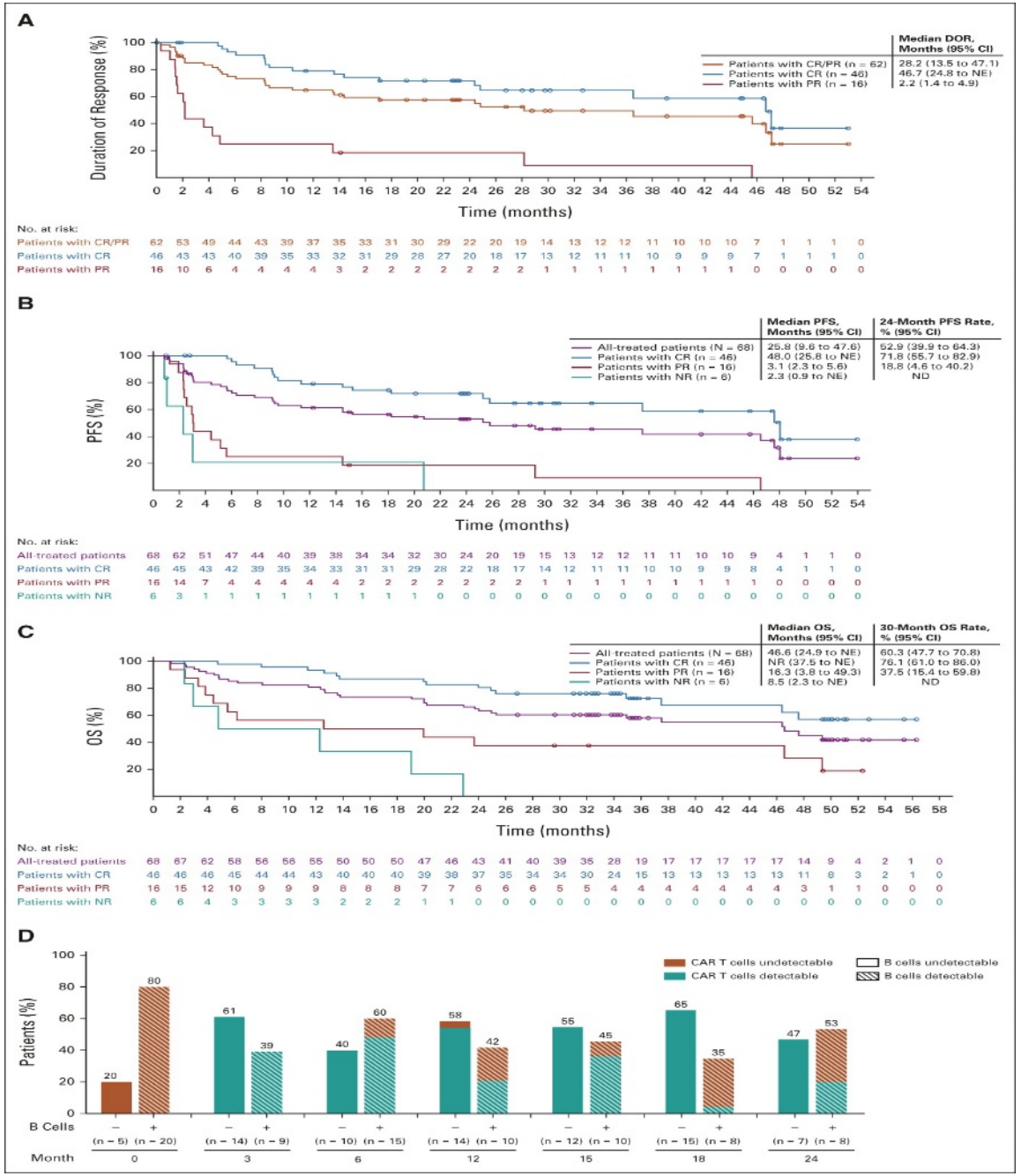
Michael Wang,[1] Javier Munoz,[2] Andre Goy,[3] Frederick L. Locke,[4] Caron A. Jacobson,[5] Brian T. Hill,[6] John M. Timmerman,[7] Houston Holmes,[8] Samantha Jaglowski,[9] Ian W. Flinn,[10] Peter A. McSweeney,[11] David B. Miklos,[12] John M. Pagel,[13] Marie José Kersten,[14] Noel Milpied,[15] Henry 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 U... Cancer Center, H... leveland, OH; [7]Dav... e Cancer Center, ... niversity School o... terdam, the N... nter, Philadelphia, PA; ...Universitätsklinikum Würzburg, Würzburg, Germany; ...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

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

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





ZUMA-2 Follow Up:
Median 36 mo
n = 68

Published in: Michael Wang; Javier Munoz; Andre Goy; Frederick L. Locke; Caron A. Jacobson; ……..Patrick M. Reagan; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.21.02370

Relapsed/Refractory DLBCL

- *CAR-T cell as 3rd line therapy*
- *CAR-T vs Auto SCT as 2nd line therapy*

CAR-T cell Products Approved in the U.S. for DLBCL: Targets, Signaling and Kinetics

	Tisagenlecleucel (Tisacel; Kymirah)	Axicabtagene ciloleucel (Axicel; Yescarta)	Lisocabtagene maraleucel (Lisocel)
B-cell target	CD-19	CD-19	CD-19
Indications	DLBCL ALL <\= 26 y of age	DLBCL Follicular Lymphoma	DLBCL
Signaling	41-BB	CD28	41-BB (defined CD8:CD4 ratio)
Manufacturer	Novartis	Kite/Gilead	JUNO/Celgene
Post-Infusion Kinetics	Later expansion	Early, rapid expansion	Later Expansion
Production Time	3-4 weeks	10-12 Days	Up to 3-4 weeks

Pivotal clinical trials of CAR-T for R/R DLBCL: Results

- Relapsed after 2 lines of chemotherapy
- CAR-T cells administered with curative intent, no transplant afterward

	Axi Cel (ZUMA1)	Tisa Cel (JULIET)	Liso Cel (TRANCEND)
Number treated	101	99	91
ORR % (CR %)	82 (54)	59 (43)	84 (61)
3 mo ORR (CR)	44 (39)	45 (37)	65 (53)
Med DOR	11.1	NR	9.2
CRS Grade >/= 3 (Cytokine release syndrome)	11%	23%	2%
CNS toxicity >/= 3	32%	11%	10%

Adapted from Chavez, Best Prac & Res-Clin Hem, 2018.
Abramson, Jeremy S., et al. "Lisocabtagene maraleucel (liso-cel) treatment of patients (pts) with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) and secondary CNS lymphoma: Initial results from TRANSCEND NHL 001." (2019): 7515-7515.

Preparing for CAR-T Treatment: Patient selection

- DLBCL with active progression during or following prior chemo-immunotherapy
- ECOG PS 0-2
- No severe organ dysfunction or active infections
- Heavily pre-treated patients may respond well, although the quality and collectability of T-cells may be impaired by prior treatments
- Anti-tumor activity may be achieved in secondary CNS involvement, without increased neurotoxicities
- High disease burden prior to CAR-T treatment is a risk factor for poor response and outcome, including more CRS and neurotoxicity

Amini et al, Nature Reviews 2022

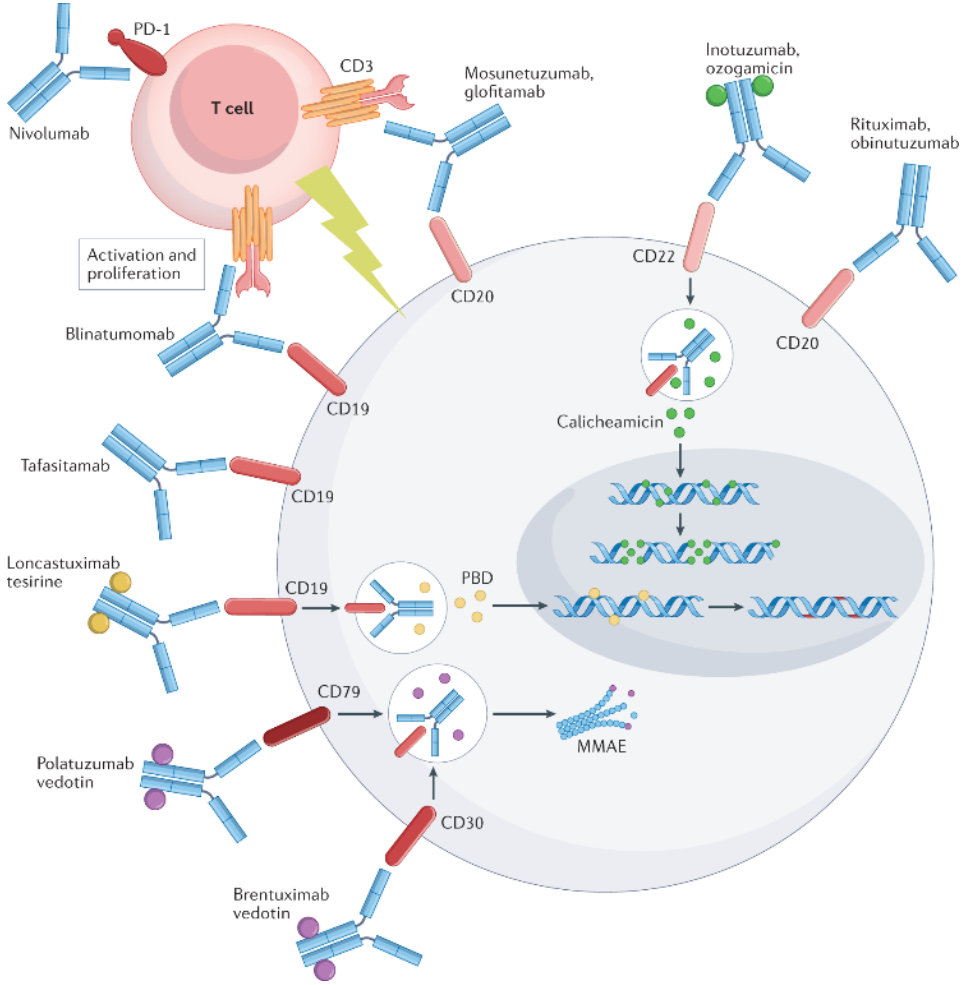
Preparing for CAR-T Treatment: Bridging Therapy

- R/R DLBCL progression is often rapid and must be controlled during the weeks of evaluation and CAR-T production
  - ~ 10% of patients die while awaiting CAR-T production
- Bridging therapy options:
  - Salvage chemo-immunotherapy: eg R-ICE, *apherese prior to chemo*
  - Brentuximab vedotin: *if the lymphoma expresses CD30*
  - Polatuzumab plus rituximab: *avoid bendamustine prior to apheresis*
  - Bispecific anti-CD20/CD3: *glofitamab, mosunetuzumab*
  - Radiation therapy: *may promote immune response*
- Unknown impact of using an anti-CD19 therapeutic agent on subsequent CAR-T response
  - Limited data indicates response in ~ 50% of patients, but best to avoid these agents prior to CAR-T infusion if possible

Amini et al, Nature Reviews 2022

Bridging therapy options: Schematic

Prefer to avoid anti-CD19-directed bridging agents prior to anti-CD19 CAR-T

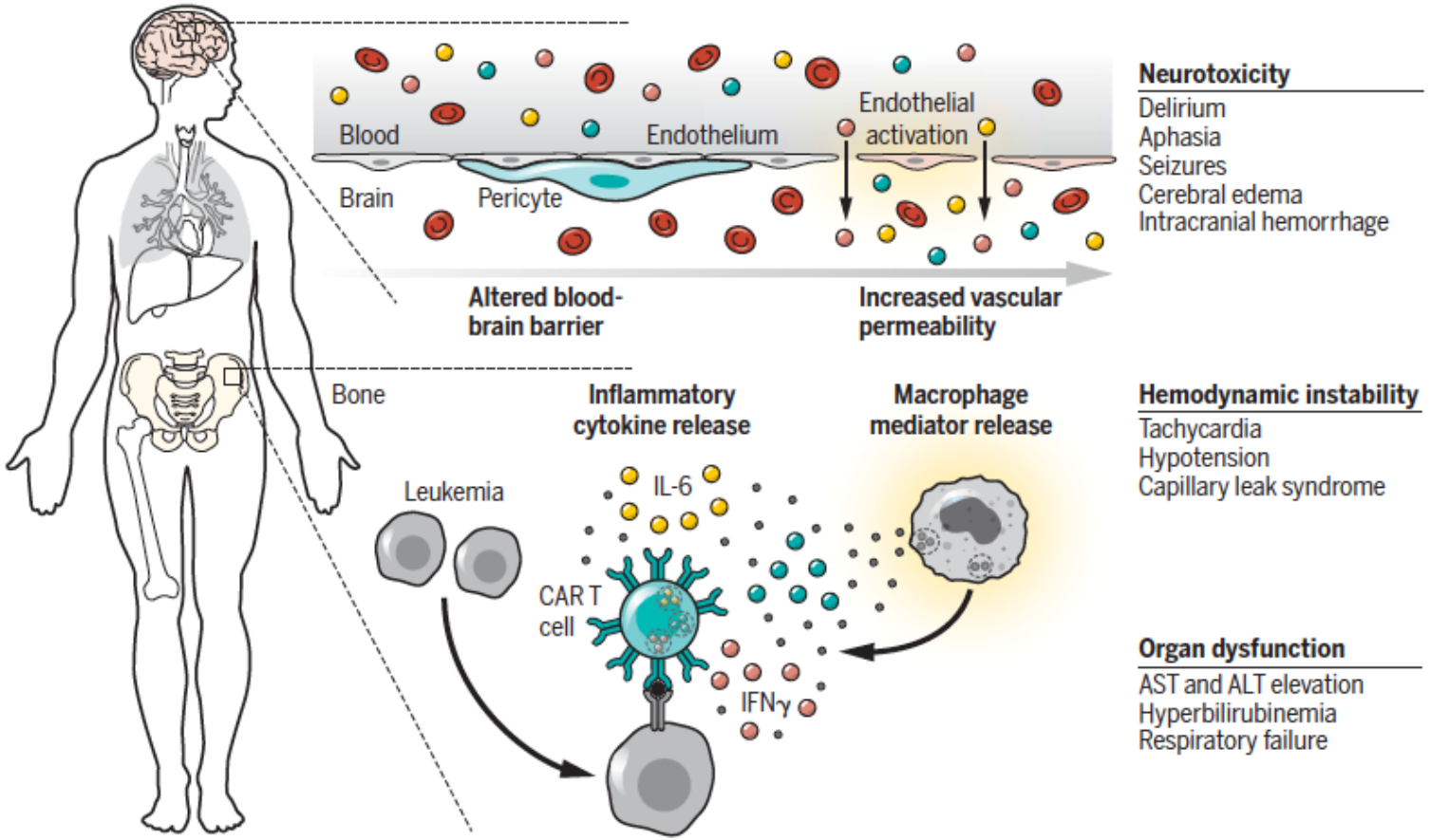


Amini et al, Nature Reviews 2022

CAR-T cell Toxicities: Overview

- Cytopenias related to lymphodepletion
  - Administered prior to CAR-T infusion
  - Usually fludarabine plus cyclophosphamide
- Cytokine release syndrome (CRS)
  - Hypotension, capillary leak
- Neurotoxicity

CAR-T cell Toxicities: Schematic



June C, Science 2018

Cytokine release syndrome (CRS)

- Systemic inflammatory response caused by supra-physiologic release of cytokines such as IL-6, INF-□, TNF-α, IL-2 and IL-10.
- Inflammatory response is primarily caused due to engagement of the CAR-T cells to the CD 19 positive cells.
- Occurs primarily with activation of large number of lymphocytes and myeloid cells like macrophages, dendritic cells and monocytes.
- IL-6 is the central mediator of toxicity in CRS

Cytokine release syndrome: Grading scale

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

- *Fever is defined as Temp > 38C.
- CRS Grade is determined by the more severe event
- Low flow nasal cannula – O2< 6L/min

Lee, D.W., et al, 2018. ASBMT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. *Biology of Blood and Marrow Transplantation*.

CAR-T-associated Neurotoxicity

- Defined as a “a disorder characterized by pathologic process involving the CNS following any immune therapy that results in the activation of the infused T cells”

- Clinical spectrum of presentation
  1. Progressive aphasia – most common and early onset feature
  2. Encephalopathy – Confusion, tremor, impairment of cognition, motor weakness
  3. Seizures
  4. Cerebral edema

- Pathophysiology : Undefined. Disruption of the blood brain barrier – CART cells have been found in the CSF

CAR-T-associated Neurotoxicity

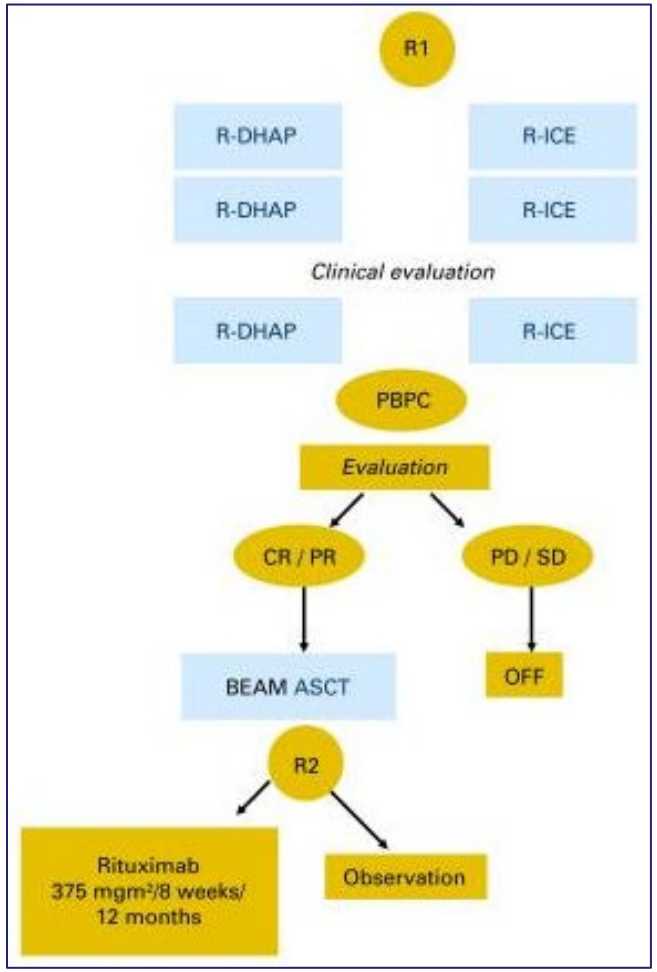
- All patients planning CAR-T therapy should have baseline neurological consult, including MMSE, MOCA testing
- Neurological Assessment includes the ICE score

ICE	Question	Points
Orientation	Year, Month, city, hospital	4
Naming	Ability to name 3 objects	3
Following commands	Follow 2 simple commands	2
Attention	Count backwards from 100 by 10	1
Writing	Write a simple sentence	1

CAR-T- associated Neurotoxicity: Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 – Unable to perform ICE
Depressed level of consciousness	Spontaneous awakening	Awakens to voice	Awakens only to tactile stimulus	Not arousable to tactile stimulus, Coma
Seizure	N/A	N/A	Any clinical or non convulsive seizures that resolve with Intvn	Prolonged seizure >5 mins. EEG activity –not resolving with Intvn
Motor Findings	N/A	N/A	N/A	Hemiparesis, paraperisis
Elevated ICP/Cerebral edema	N/A	N/A	Focal or Local edema on Neuro-image	Diffuse cerebral edema on imaging

Salvage chemotherapy with consolidative auto SCT in R/R DLBCL: CORAL Study

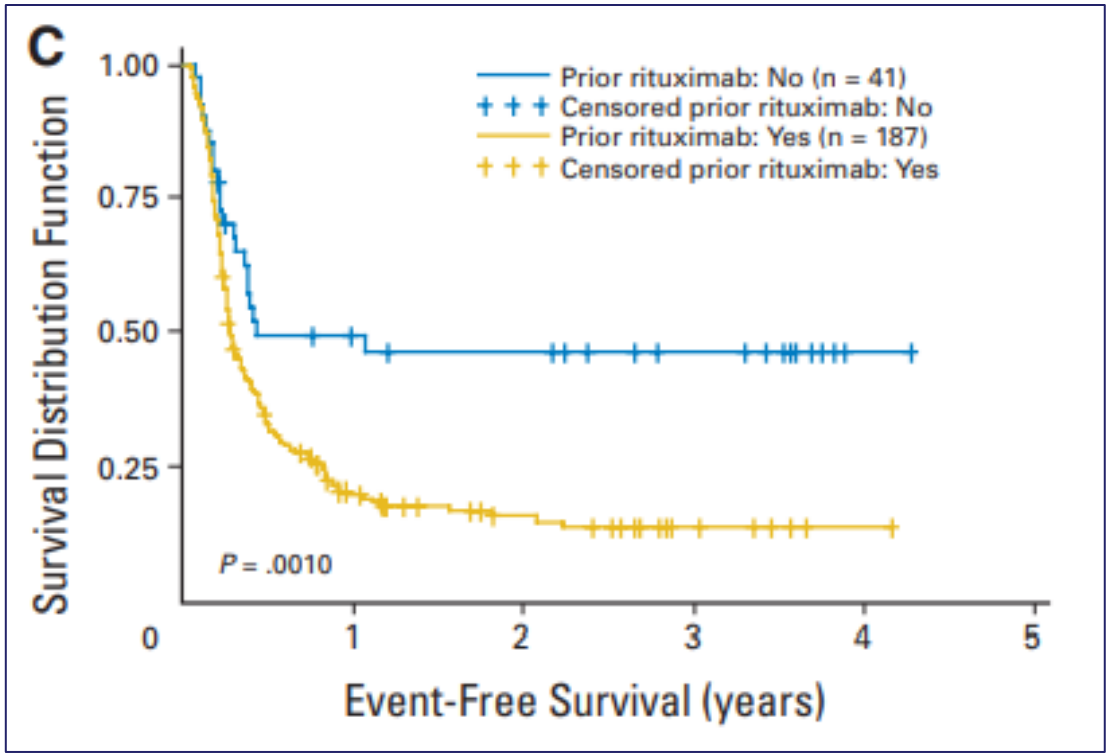


- Randomized Trial
- Transplant-eligible R/R DLBCL
- R-DHAP vs R-ICE
  - 2nd randomization to Observation vs R maintenance x 12 mo
- 398 patients
  - 62% with prior rituximab exposure
  - 60% relapsed <1 year from completing CHOP or R-CHOP induction therapy

J Clin Oncol 2010;28:4184-90

Salvage chemotherapy with consolidative auto SCT in R/R DLBCL:
CORAL Study

- No difference for R-DHAP vs R-ICE
- Prior rituximab exposure:
  - **3 year EFS 21%**
- Relapse within 12 m of 1st line Rx:
  - **3 year EFS 20%**



J Clin Oncol 2010; 28:4184-90

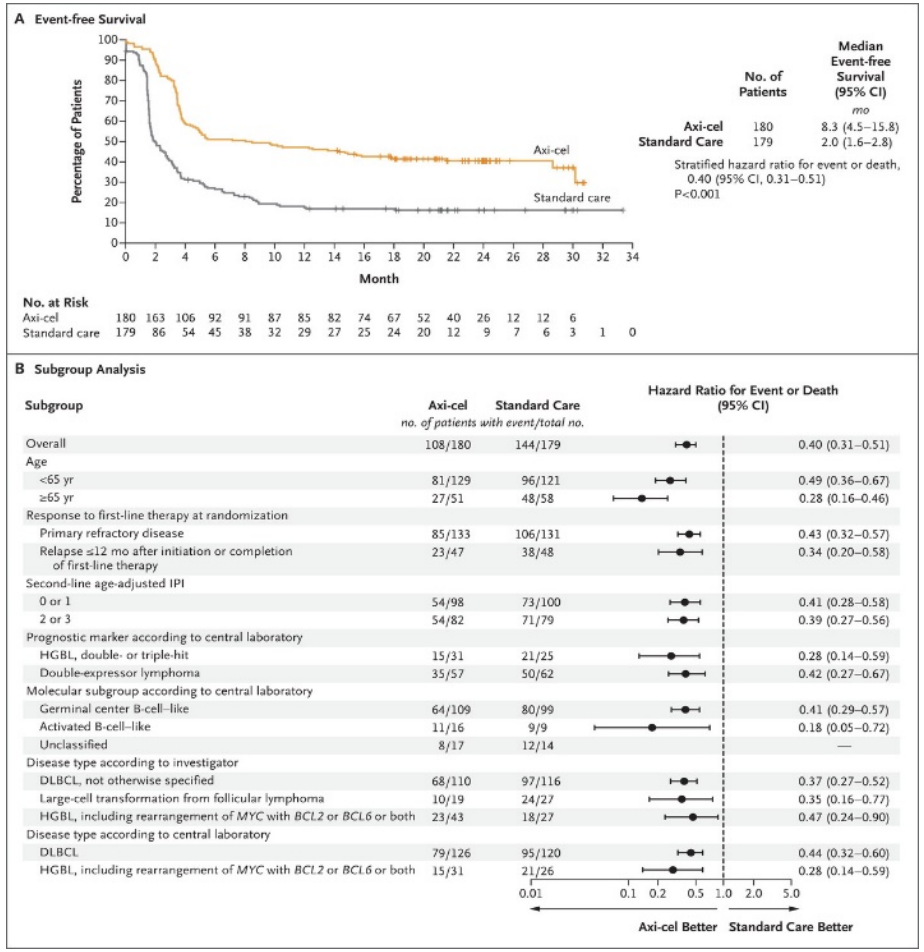
Axicabtagene Ciloleucel as Second-line Therapy for Large B-cell Lymphoma (ZUMA-7 Trial)

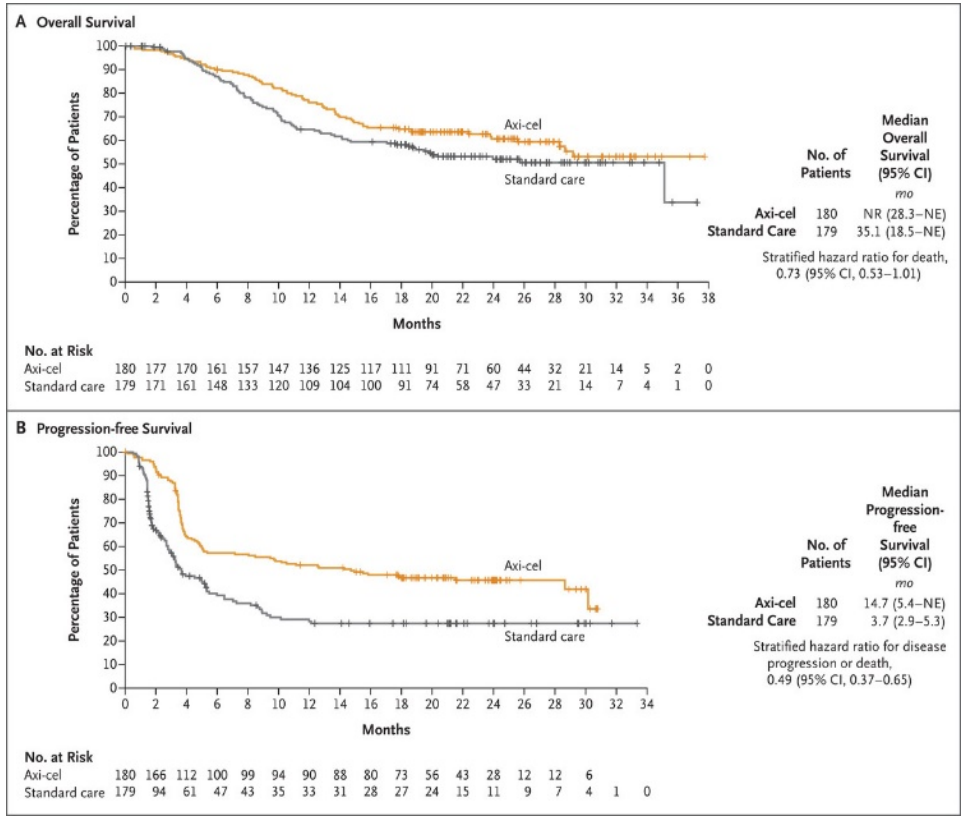
F. Locke et al, ASH 2021 Plenary, NEJM Dec. 2021

- High-dose therapy → ASCT is the current SOC for relapsed DLBCL in transplant-eligible patients
  - Poor outcomes for primary refractory DLBCL, or relapse within 1 year of R-chemotherapy*
- Phase 3 trial of CAR-T vs HDT → ASCT in responders
- Primary endpoint: EFS
  - Secondary: ORR, OS, Safety
- *No bridging therapy* (only corticosteroids if needed) prior to CAR-T

*CORAL study. JCO 2010; 28:4184

CAR-T vs ASCT (ZUMA-7): **Results**





Locke et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2116133

Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma (BELINDA Trial)

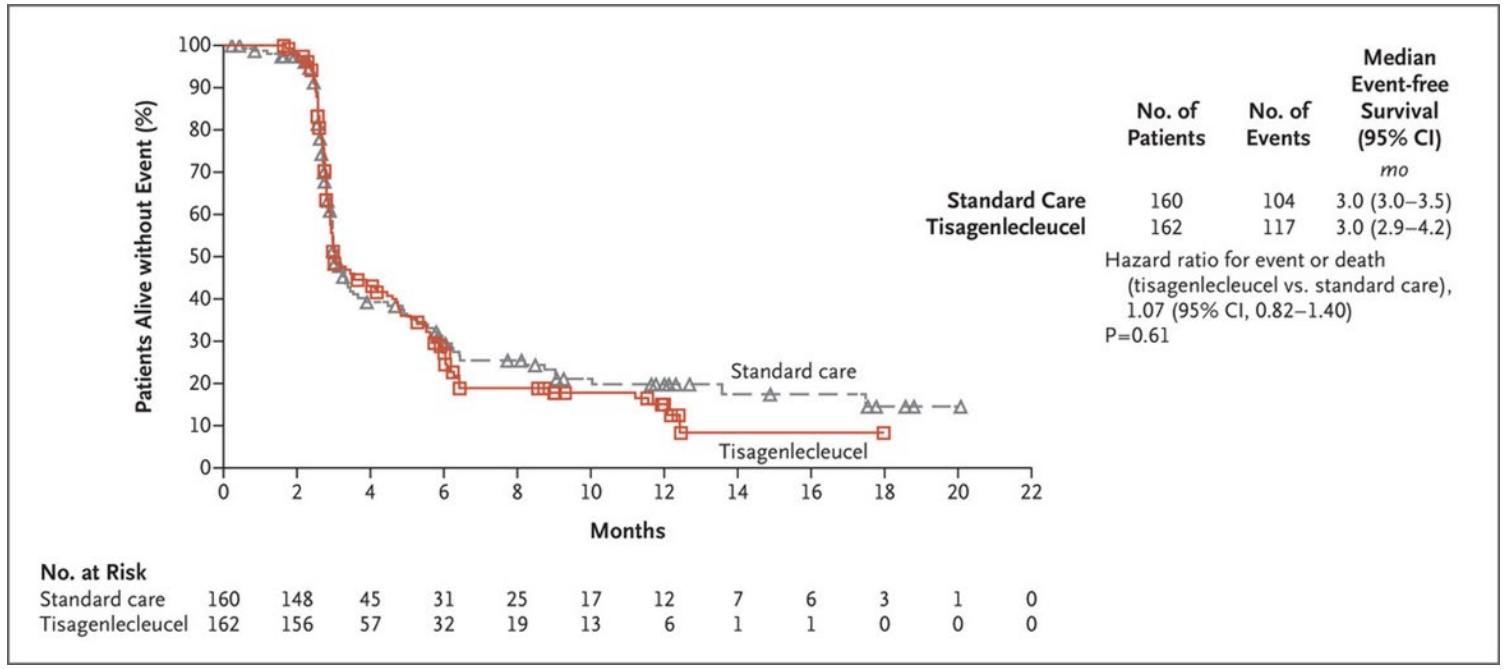
Bishop et al, ASH 2021 LBA-6; NEJM Dec 2021

- High-dose therapy → ASCT is the current SOC for relapsed DLBCL in transplant-eligible patients
- Poor outcomes for patients with primary refractory DLBCL, or relapsing within 1 year of R-chemotherapy*
- Phase 3 trial of CAR-T vs HDT → ASCT in responders
  - **Primary endpoint: EFS**
  - **Secondary: ORR, Safety**
- *Bridging chemotherapy allowed* prior to CAR-T
- *Crossover to Tisa-cel* if an event occurred at or after week 12 assessment in SOC arm

CORAL study. JCO 2010; 28:4184

Tisa-cel vs HDT-ASCT: Results

- Overall, 83% received bridging therapy
- Tisa-cell arm: 95.7% received infusion, *median time 52d from leukapheresis*
  - **42 (26%) progressed before CAR-T, allowed to get CAR-T, all included in the analysis**
- HDT-ASCT arm: 32.5% received ASCT



Bishop et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2116596

Lisocabtagene ciloleucel (Lisocel) vs ASCT in R/R DLBCL: TRANSFORM Study

- Adult patients with DLBCL either refractory to primary treatment or relapse within 12 months after completion of 1st line induction therapy
- 1:1 randomization to receive liso-cel or SOC
- Bridging therapy allowed with protocol-defined SOC regimen

Characteristic	Liso-cel arm n = 92	SOC arm n = 92
Male, n (%)	44 (48)	61 (66)
Age, years, n (%)		
Median (IQR)	60 (53.5–67.5)	58.0 (42–65)
< 65	56 (61)	67 (73)
≥ 65 to < 75	36 (39)	23 (25)
≥ 75	0	2 (2)
LBCL subtypes, n (%)		
DLBCL NOS	53 (58)	49 (53)
HGBCL with rearrangements in *MYC* and *BCL2*, *BCL6*, or both (DLBCL histology)	22 (24)	21 (23)
PMBCL	8 (9)	10 (11)
DLBCL transformed from any indolent lymphoma	7 (8)	8 (9)
THRBCL	1 (1)	4 (4)
FL3B	1 (1)	0
ECOG PS, n (%)		
0	48 (52)	57 (62)
1	44 (48)	35 (38)
sAAIPI, n (%)		
0 or 1	56 (61)	55 (60)
2 or 3	36 (39)	37 (40)
Prior response status, n (%)		
Refractory[a]	67 (73)	68 (74)
Relapsed[b]	25 (27)	24 (26)
Secondary CNS lymphoma, n (%)	1 (1)	3 (3)

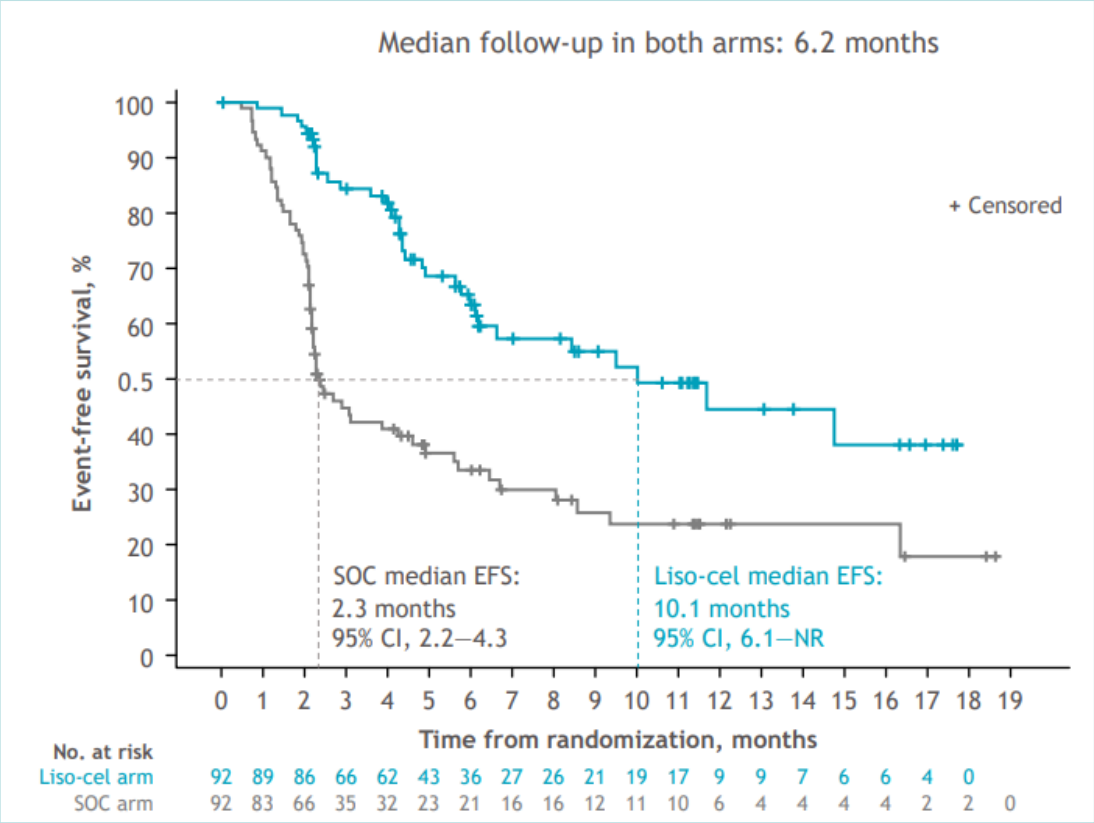
Patient population:

- 39% over 65
- 39% sAAIPI 2-3
- 73% primary refractory disease

Abramson et al. Lisocabtagene Maraleucel (liso-cel), **a CD19-Directed Chimeric Antigen Receptor (CAR) T Cell Therapy, Versus Standard of Care (SOC) with Salvage Chemotherapy (CT) Followed By Autologous Stem Cell Transplantation (ASCT) As Second-Line (2L) Treatment in Patients (Pts) with Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL): Results from the Randomized Phase 3 Transform Study**. Paper presented at Annual Meeting of the American Society of Hematology. 11 Dec 2021. Atlanta GA.

Kamdar et al, Lancet 2022;399:2294-2308

Liso-cel vs ASCT in R/R DLBCL: EFS Results



- 12 month EFS 44.5 % vs 23.7 %
- CR rate 66% vs 39% (p<0.0001)

et al. **Lisocabtagene Maraleucel (liso-cel), a CD19-Directed Chimeric Antigen Receptor (CAR) T Cell Therapy, Versus Standard of Care (SOC) with Salvage Chemotherapy (CT) Followed By Autologous Stem Cell Transplantation (ASCT) As Second-Line (2L) Treatment in Patients (Pts) with Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL): Results from the Randomized Phase 3 Transform Study**. Paper presented at Annual Meeting of the American Society of Hematology. 11 Dec 2021. Atlanta GA.

R/R DLBCL CAR-T 2nd line Trials: Summary

	Axicel ZUMA -7	Tisacel BELINDA	Lisocel TRANSFORM
# pts	359	322	184
Bridging therapy	NO	YES	YES
Cross Over	Not allowed	Allowed	Allowed
EFS* (mo.)	8.3	3	10.1
ORR	83%	46%	86%
CR	65%	28%	39%
OS (mo.) (Median)	25.7 (Favoring CAR-T therapy)	15.3 (No difference)	16.4 (Trend towards improvement)
% pts who proceeded to ASCT	36	32.5	45.6

1. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2021.
2. Bishop MR, Dickinson M, Purtill D, Barba P, Santoro A, Hamad N, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. N Engl J Med. 2021.
3. Kamdar M, Solomon SR, Arnason JE, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene Maraleucel (liso-cel), a CD19-Directed Chimeric Antigen Receptor (CAR) T Cell Therapy, Versus Standard of Care (SOC) with Salvage Chemotherapy (CT) Followed By Autologous Stem Cell Transplantation (ASCT) As Second-Line (2L) Treatment in Patients (Pts) with Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL): Results from the Randomized Phase 3 Transform Study. Blood. 2021;138(Supplement 1):91-.

CAR-T vs Salvage chemo/AutoSCT in second-line treatment of R/R DLBCL

Conclusions

- Axicabtagene ciloleucel and lisocabtagene maraleucel showed survival benefit over salvage chemotherapy and autoSCT for primary refractory disease or disease relapsing within 12 months of 1st line therapy
- Tisagenlecleucel did not demonstrate same benefit
    - Sicker patients on the Belinda trial?
    - Differences in study design (bridging vs not allowed on ZUMA-7)
    - Longer time to T-cell infusion on Belinda

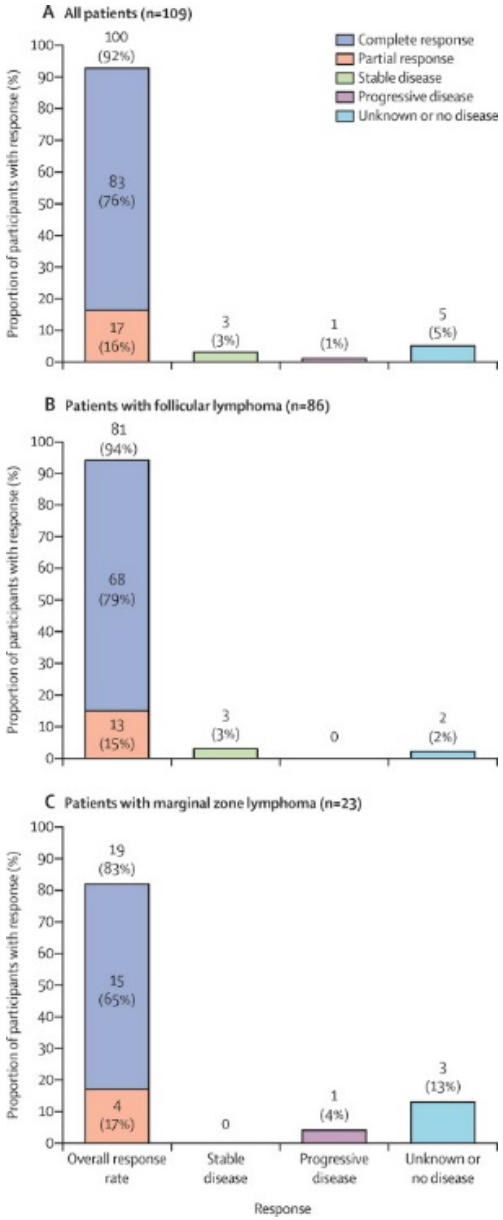
- CAR-T favored over high dose chemotherapy and autoSCT for primary refractory or early relapsing DLBCL (<1 yr from completing induction Rx)

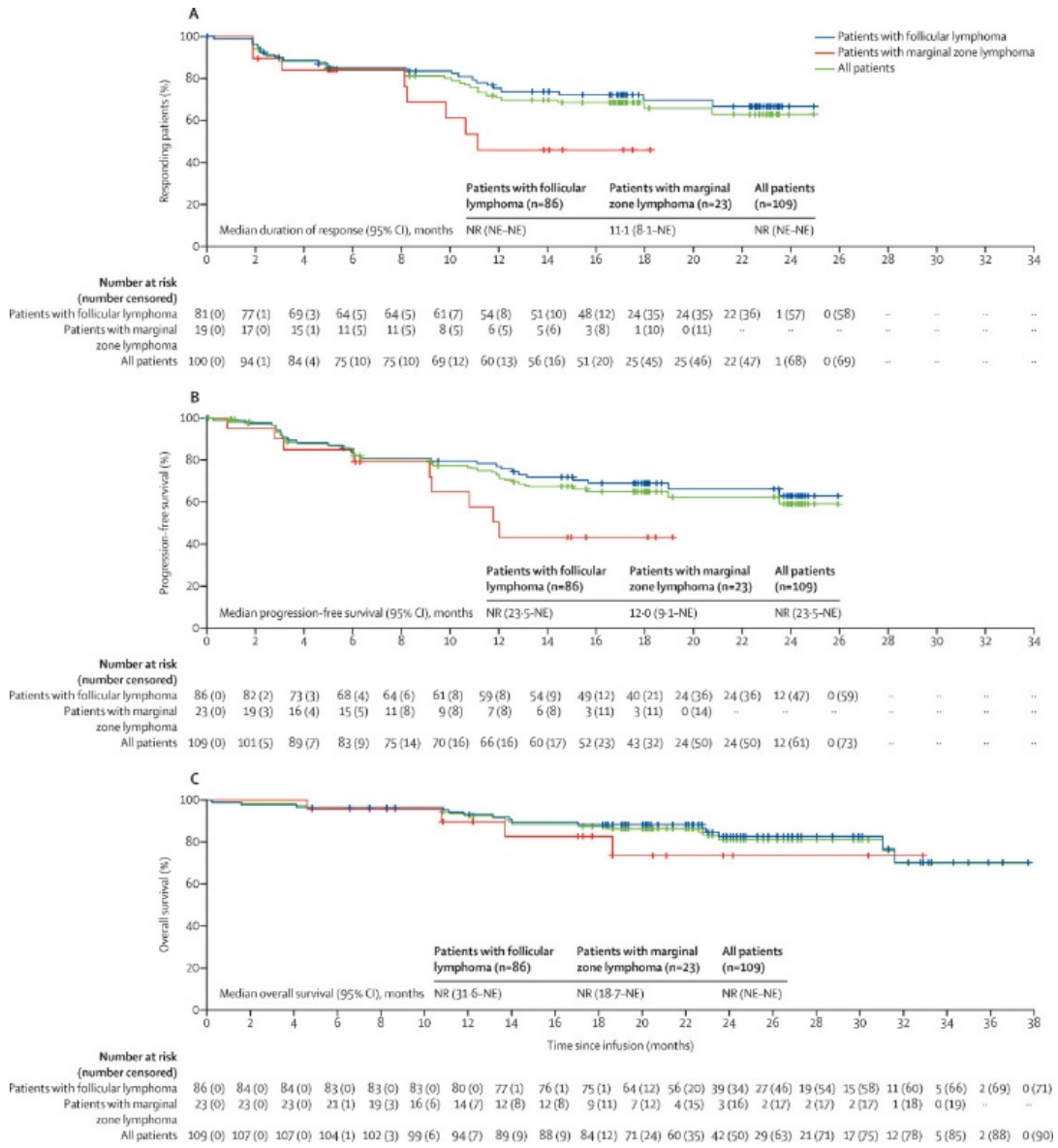
- Results do not yet apply to later-relapsing patients

Follicular Lymphoma

CAR-T cell therapy

Axicabtagene ciloleucel in R/R indolent NHL (ZUMA-5): a single-arm, multicenter, phase 2 trial





Jacobson CA, et al, Lancet Oncol 2022

Comparative effectiveness of ZUMA-5 (axi-cel) vs SCHOLAR-5 external control in relapsed/refractory follicular lymphoma

Ghione et al, *Blood, August 2022*

Key eligibility criteria for SCHOLAR-5 cohort were:

(1) diagnosed r/r FL

(2) starting third or higher line of therapy

(3) on or after 23 July 2014

A prior line of therapy with anti-CD20 monotherapy did not count as line of therapy for eligibility

Key exclusion criteria for the SCHOLAR-5 cohort were:

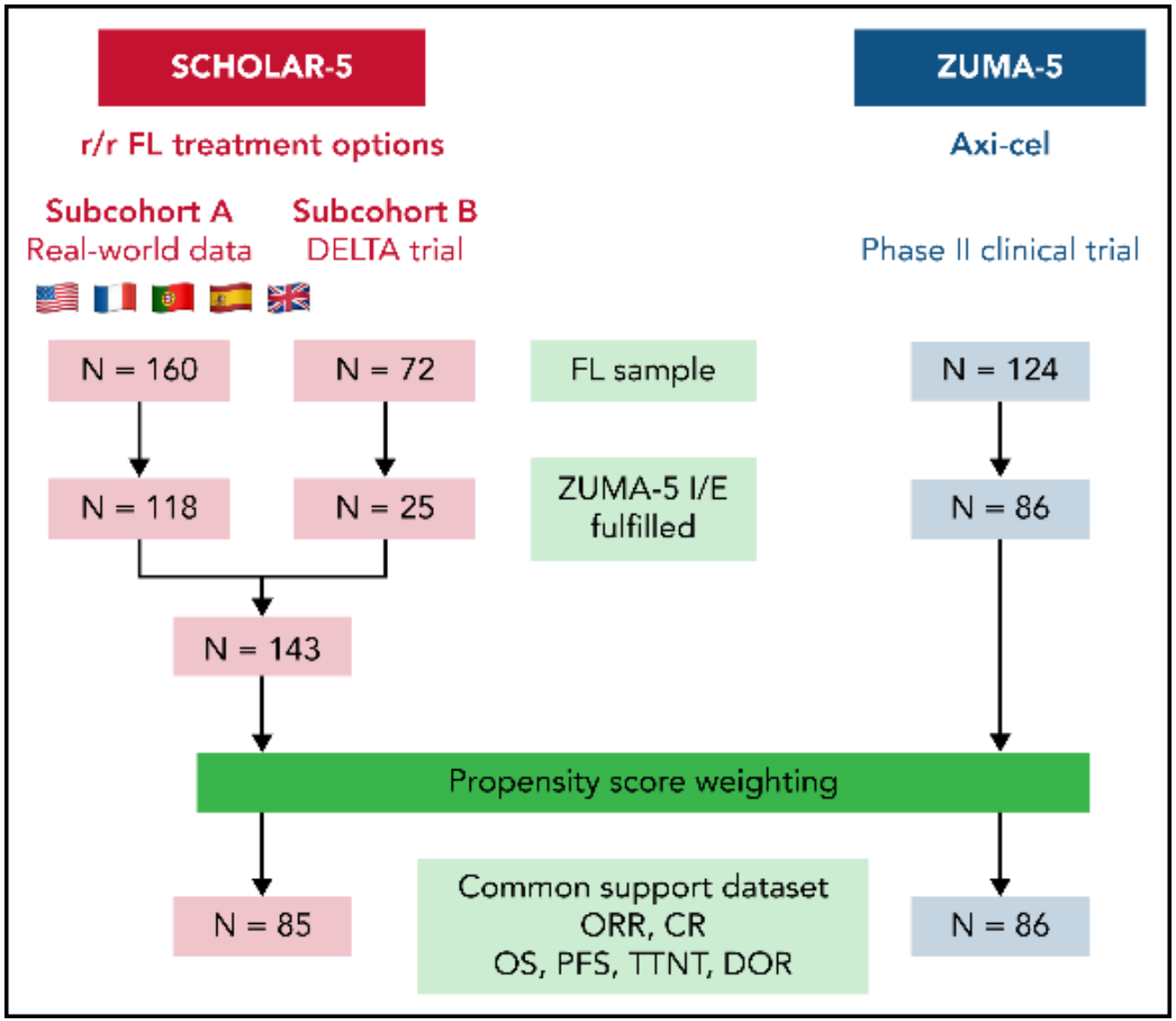
(1) transformed FL

(2) FL histological grade 3b

(3) prior anti-CD19 CAR T-cell therapy or other genetically modified T-cell therapy

Axi-cel was FDA approved March 2021 for R/R FL with >/= 2 prior lines of therapy

Comparative effectiveness of ZUMA-5 (axi-cel) vs SCHOLAR-5 external control in relapsed/refractory follicular lymphoma



Comparative effectiveness of ZUMA-5 (axi-cel) vs SCHOLAR-5 external control in relapsed/refractory follicular lymphoma

Objective: To compare clinical outcomes from the ZUMA-5 trial cohort to the international SCHOLAR-5 external control cohort

Methods: Propensity score methods were used to compare available treatments for r/r FL patients with axi-cel. SCHOLAR-5 patients were successfully re-weighted to align patient characteristics

SCHOLAR-5

Standard of care

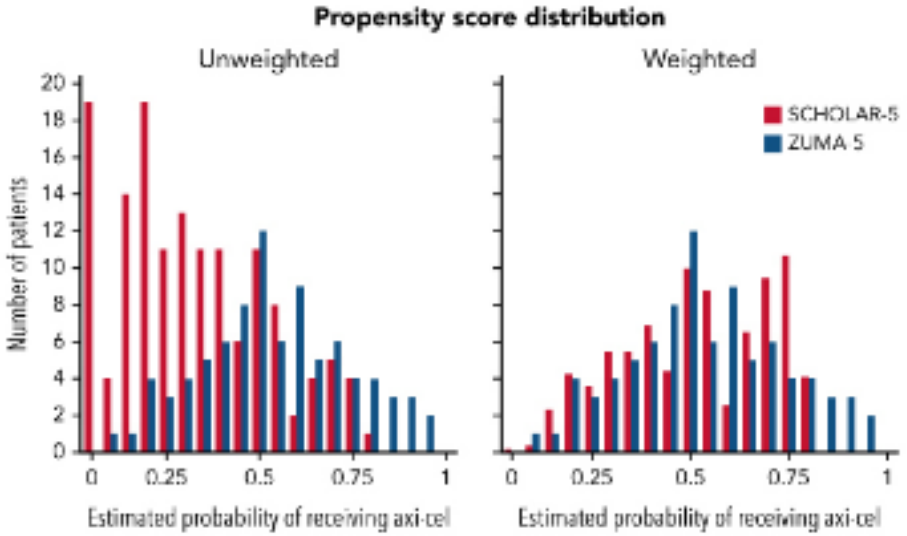
ZUMA-5

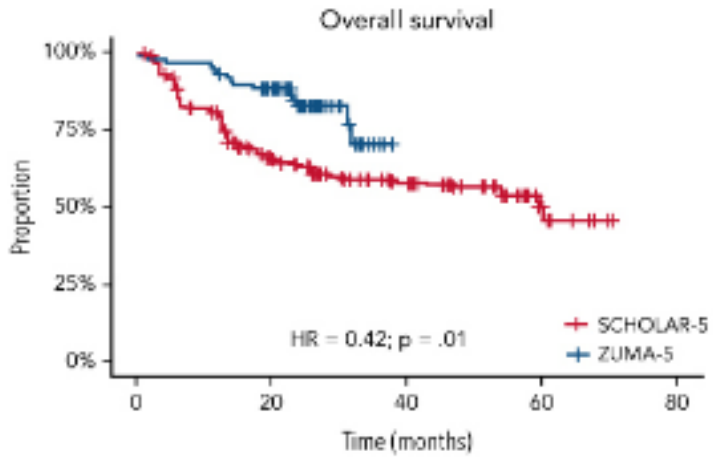
Axi-cel
NCT03105336

Propensity score weighting

Common support dataset ORR, CR, OS, PFS, TTNT, DOR

- Axi-cel demonstrated a substantial improvement in all clinical endpoints including OS, PFS, TTNT, ORR and CR
- Findings support that axi-cel represents a significant improvement in treatment options for patients with r/r FL





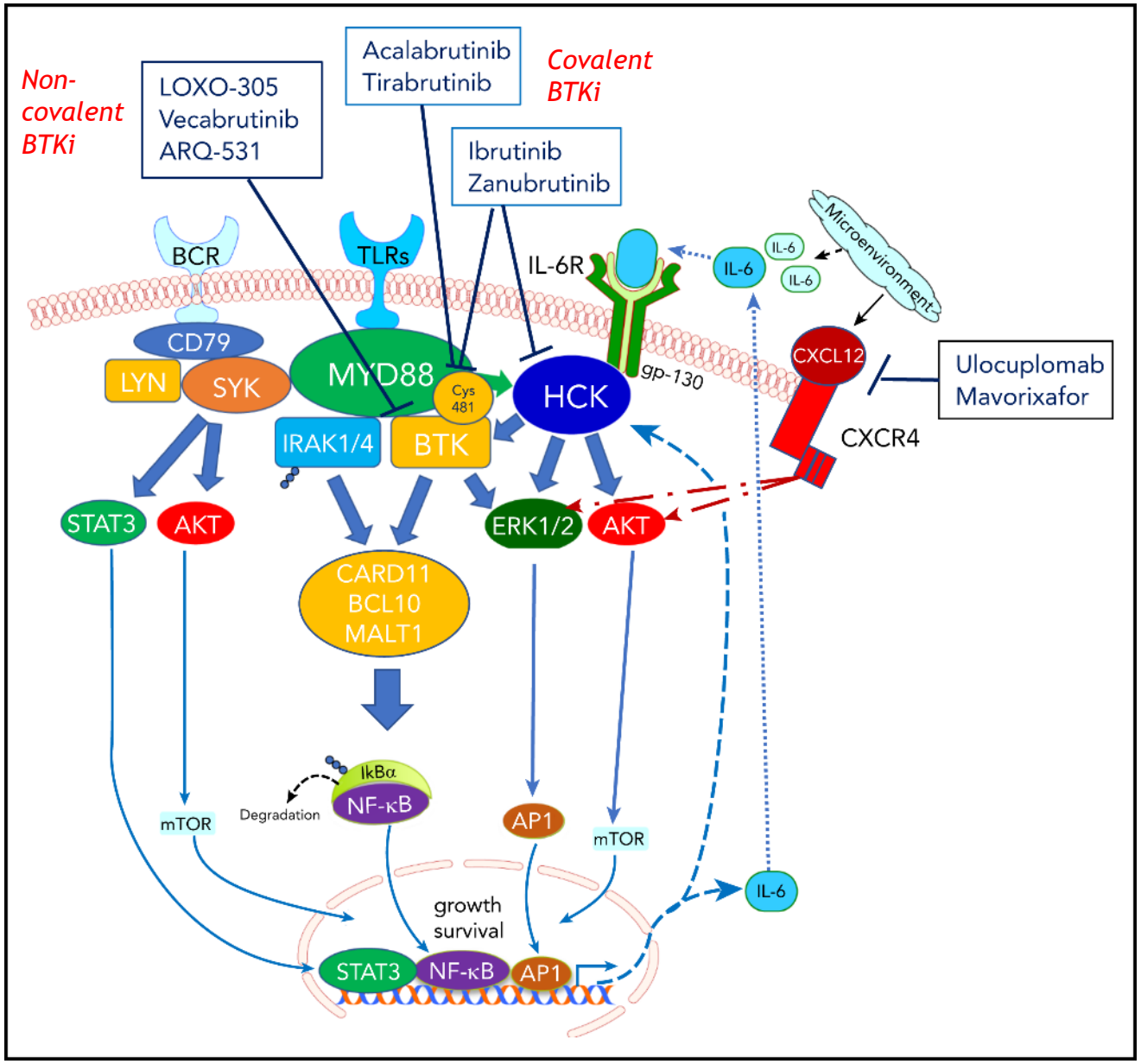
Waldenstrom macroglobulinemia/ Lymphoplasmacytic Lymphoma

Presentation and Etiology of LPL/WM

- 1-2% of NHL, median age 70 yr
  - Anemia, other cytopenias
  - Hyperviscosity
  - Peripheral neuropathy
- *Etiologies:*
  - Hepatitis C
    - LPL may respond to antiviral therapy
    - May be associated with mixed cryoglobulinemia
- Autoimmune disorders
  - Rheumatologic, chronic immune-stimulating conditions
- Familial
  - ~20% of WM patients, usually present at younger age

LPL/WM Prognosis

- Incurable with standard therapies, but median survival is usually >5-10 yr
- May have MGUS or ‘Smoldering macroglobulinemia’ prodrome, often for many years
- Asymptomatic patients are monitored w/o Rx
  - No IgM threshold level at which Rx is required
- Survival improving with newer therapeutics
- *MYD88* and *CXCR4* mutation status are informative
- May transform to DLBCL
- May present as amyloidosis or Bing-Neel Syndrome (CNS)



BCR Pathway: Targeting BTK, MYD88 and CXCR4

Kapoor, Treon, Editorial, Blood 2020

Long-term follow of ibrutinib monotherapy in symptomatic, previously treated WM

S.Treon et al, JCO 2021; 39:565-75
S. Treon et al, NEJM 2015; 372:1430-40

- Median 2 prior therapies (range 1-9)
- Ibrutinib 420 mg/d until progression or toxicity
- MYD88 mutation not required

Summary: A practice-changing study

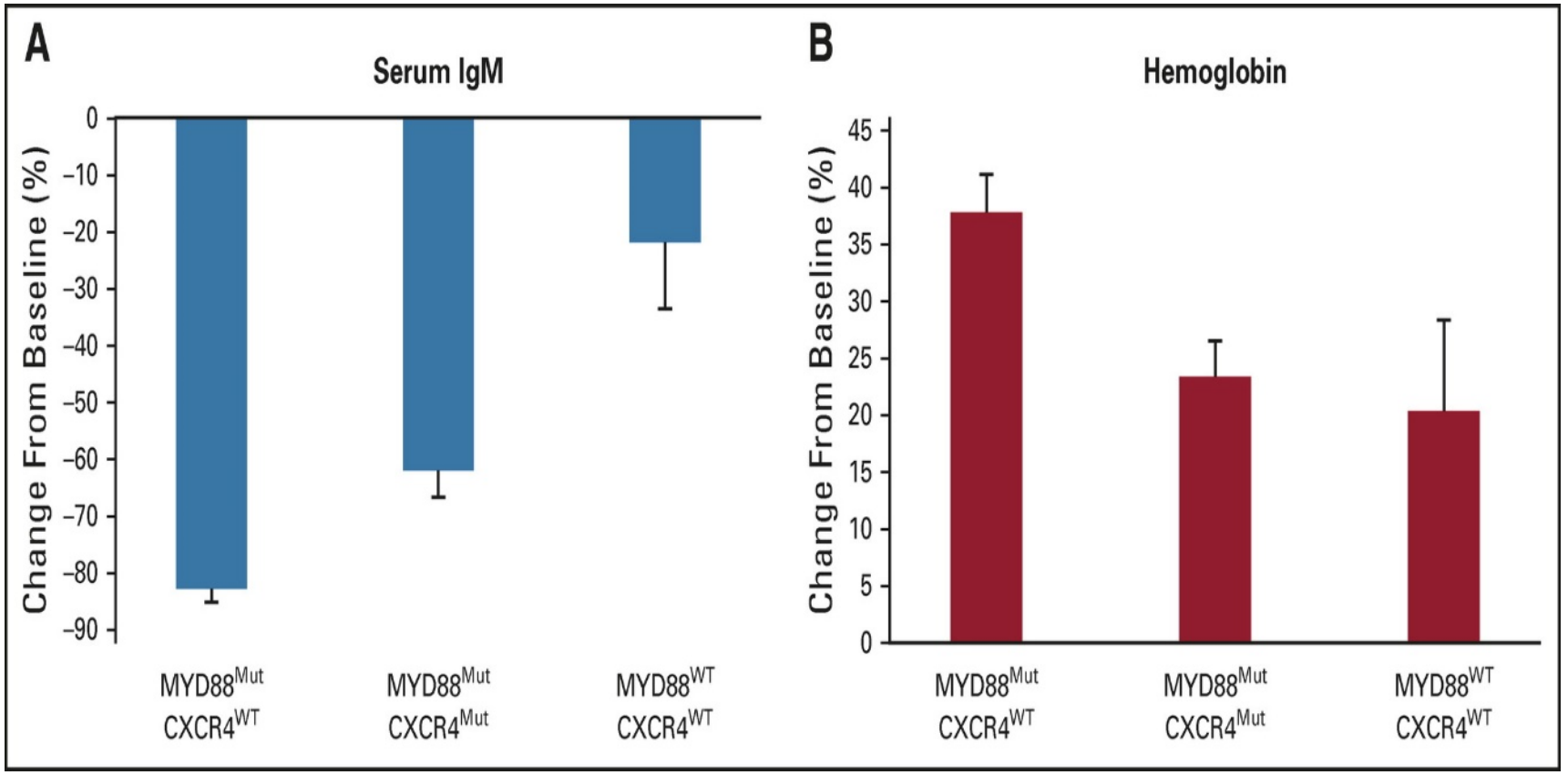
- 63 patients enrolled, median f/u 59 mo.
- Ibrutinib was highly active
- 5 d/c Rx due to AE
- Response differed by MYD88 and CXCR4 status

MYD88 and CXCR4 Mutations: Relation to Ibrutinib Response in previously treated WM (n=63)

- Mutated *MYD88* triggers pro-survival signaling via BTK
- *CXCR4* mutations confer variable degrees of resistance to BTKi

Mutation status	No. of Patients	Major response	5-year PFS
MYD88 ^{Mut} CXCR4 ^{WT}	36	97%	70%
MYD88 ^{Mut} CXCR4 ^{Mut}	22	68%	38%
MYD88 ^{WT} CXCR4 ^{WT}	4	0	0

Treon S, et al. J Clin Oncol 2021
Table adapted from Kahl B. *The Hematologist* 2021



Changes in IgM and hemoglobin levels by MYD88 and CXCR4 mutation status

Published in: Steven P. Treon; Kirsten Meid; Joshua Gustine; Guang Yang; Lian Xu; Xia Liu; Christopher J. Patterson; Zachary R. Hunter; Andrew R. Branagan; Jacob P. Laubach; Irene M. Ghobrial; M. Lia Palomba; Ranjana Advani; Jorge J. Castillo; *Journal of Clinical Oncology* 2021 39565-575.
DOI: 10.1200/JCO.20.00555

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

Owen RG, et al. Lancet Haematol 2020

- Treatment naïve (n=14) or R/R (n=92), needing Rx
  - No prior BTKi
- Acala 100 mg bid until progression or toxicity

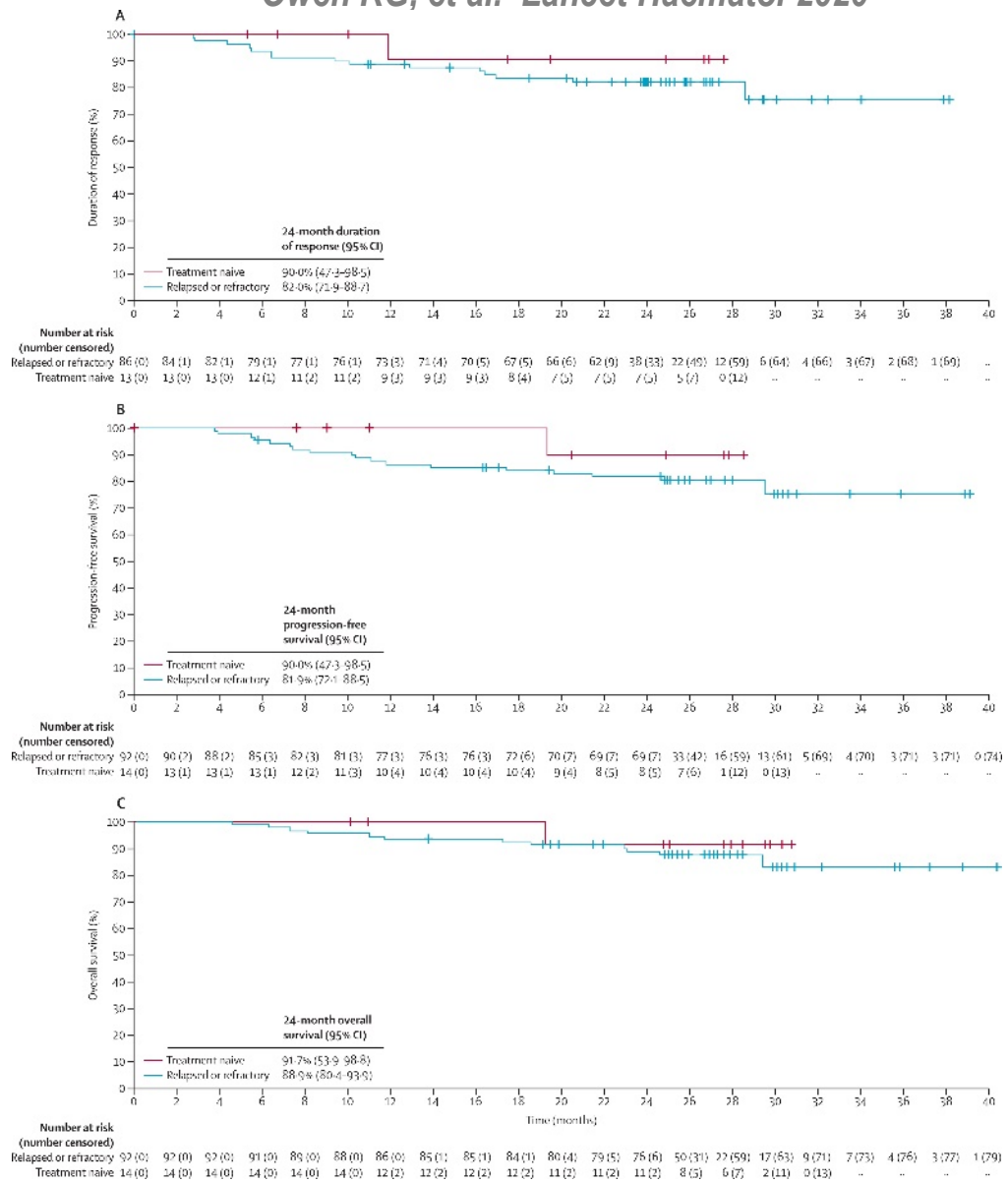
Summary:

- Median f/u 27 mo, ORR 93% in both groups
- Ongoing response at 24 mo in 90% (TN) and 82% (R/R)
- 28% d/c Rx, grade 3-4 AE: infections, bleeding (3%, including 1 fatal IC bleed); only 1 Afib event

- Acala has high activity in WM as single agent *(Not FDA approved for this indication as of August 2022)*

Acalabrutinib monotherapy in patients with WM: DofR, PFS and OS

Owen RG, et al. Lancet Haematol 2020



TN: red

R/R: Blue

A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic WM: the ASPEN study

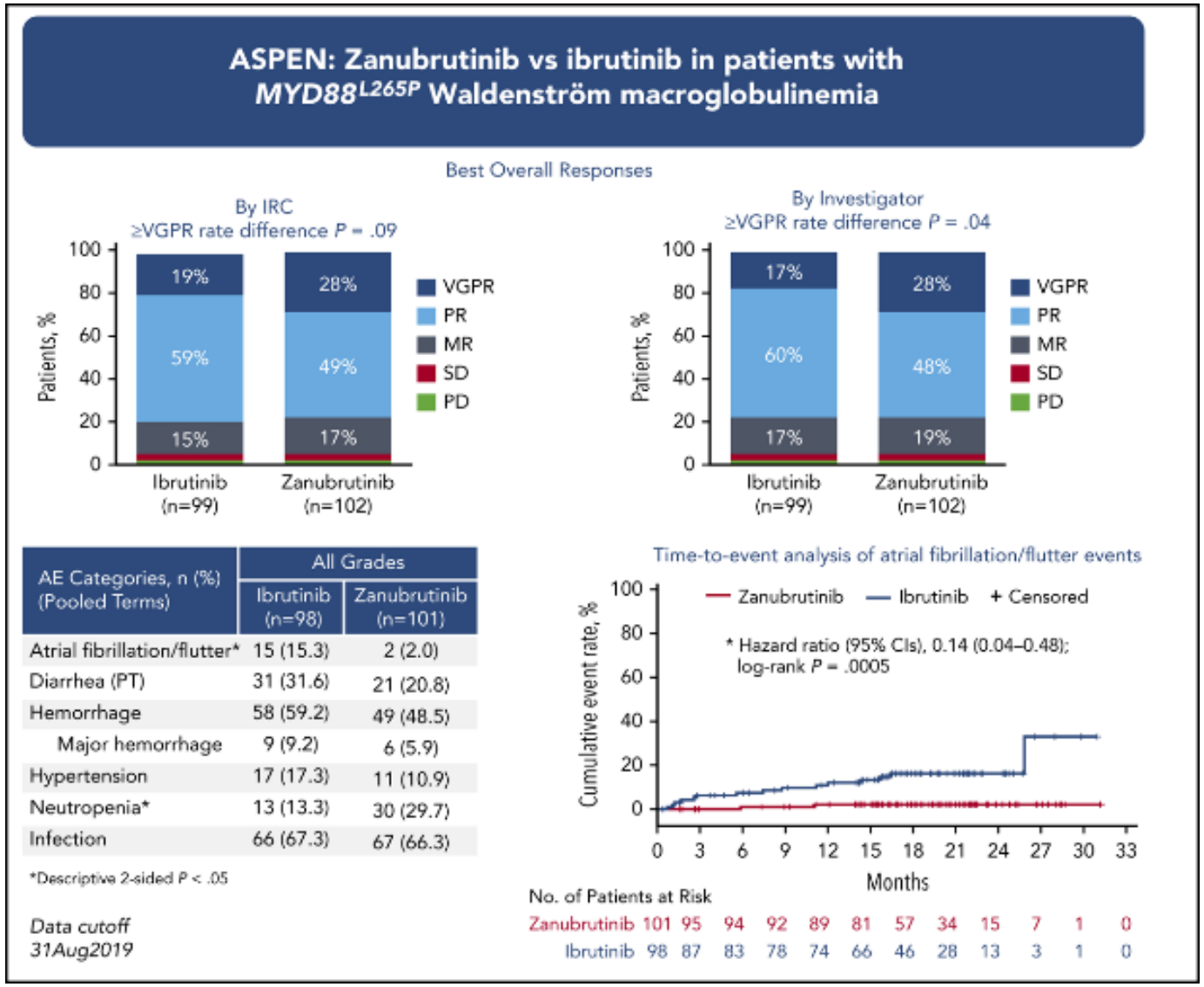
Tam CS et al, Blood 2020;136: 2038

- R/R WM in need of Rx, >/= 1 prior Rx, no prior BTKi
- Pts with $MYD88^{L265P}$ randomized 1:1 Zanu 160 mg bid vs Ibr 420 mg/d
  - $MYD88^{WT}$ or unknown status → zanu on a 3rd non-randomized arm
- Primary endpoint = VGPR or CR

Summary:

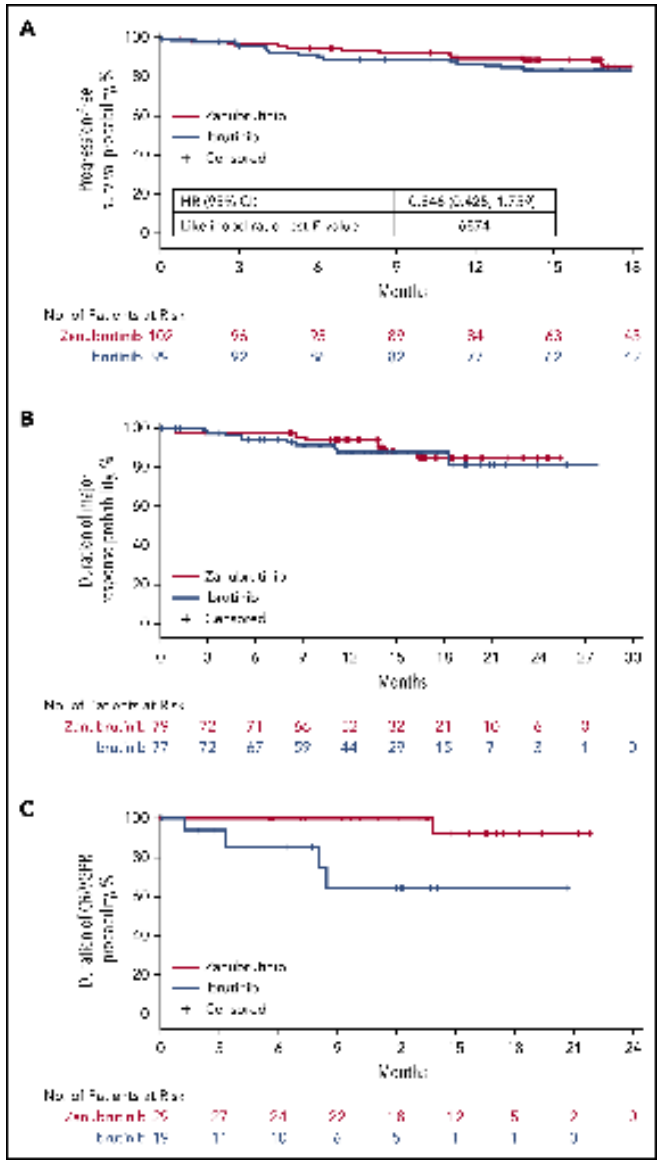
- 199 patients enrolled; No patient achieved CR
- VGPR in 28% Zanu and 19% Ibr
  - More pts in Zanu arm with mutated CXCR4 (34% vs 22% Ibr)
- PFS at 18 mo did not differ (84% vs 85%)
- Lower AE w Zanu, except higher neutropenia events

A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic WM: the ASPEN study



Tam CS et al. Blood 2020

A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic WM: the ASPEN study



PFS

Red = Zanubrutinib
Blue = Ibrutinib

Duration of major response

Duration of CR/VGPR

Tam CS, et al. Blood 2020

Pirtobrutinib* (LOXO-305) in R/R B-cell Malignancies

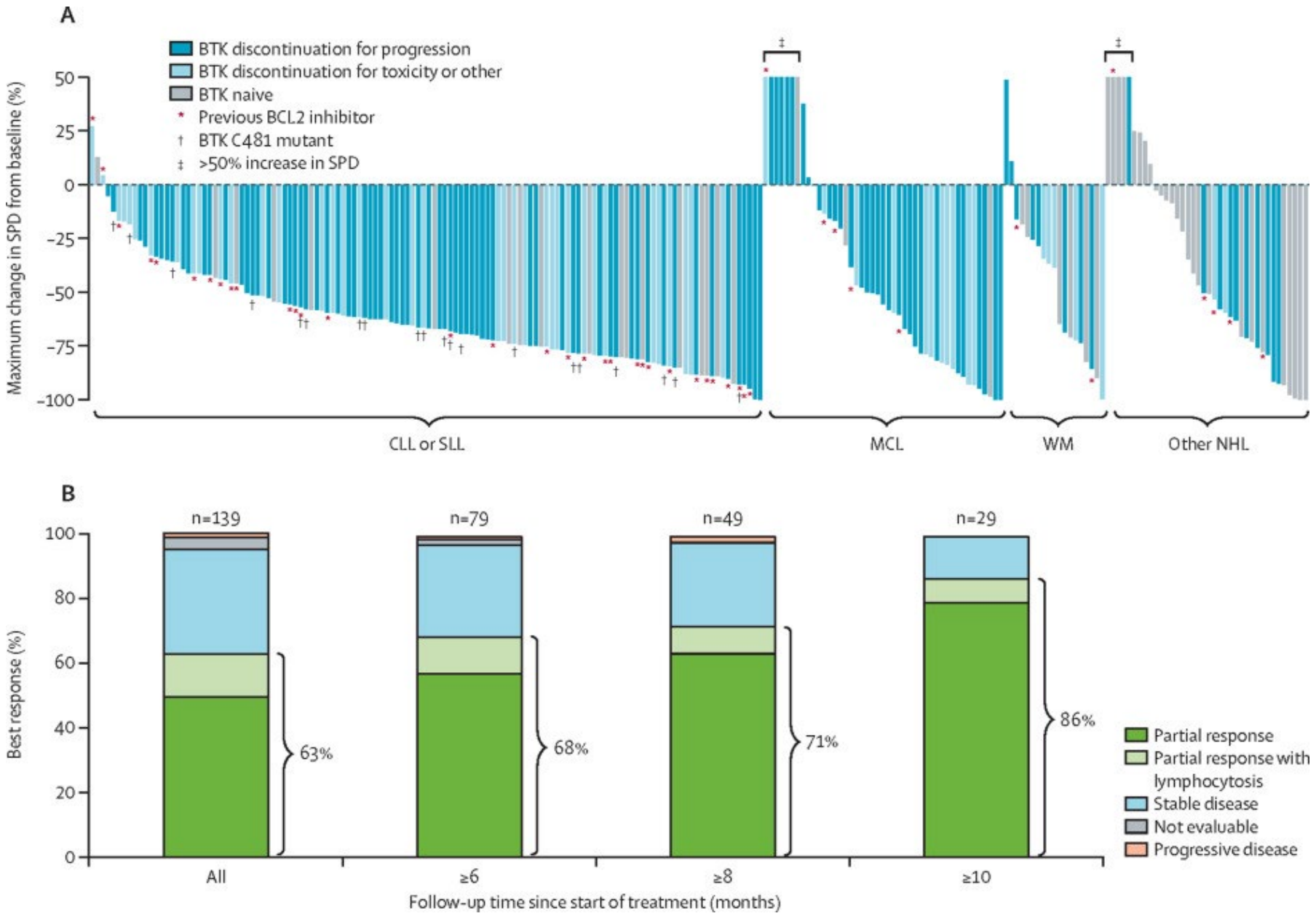
Mato et al, Lancet 2021; 397:892

- Oral, non-covalent, reversible BTK inhibitor
  - **Active in C481-mutated BTK**
- Phase 1-2 BRUIN trial: CLL/SLL, MCL, Waldenstrom
- Active at all doses tested
  - **Phase 2 dose 200 mg/d, continued indefinitely**
- Well-tolerated, low-grade fatigue, diarrhea, bruising
  - **No atrial fibrillation; hemorrhage 2%**
- Responses in those previously treated with BTKi:
  - **CLL 62%**
  - **MCL 52%**
  - **WM 69%**

*Not FDA approved as of August 2022

Pirtobrutinib (LOXO-305): **Response Rates**

Mato et al, Lancet 2021; 397:892



Conclusions

- Treatment of symptomatic WM has evolved to include biomarker-driven BTKi therapies
- Combination regimens including anti-CD20 plus chemotherapy and proteasome inhibitors continue to have a role
- Limited prospective trials to date that compare agents and regimens
- Clinical judgement is needed to weigh Rx necessity, comorbidities, Rx type, potential toxicities and financial impact

Thanks for your attention!

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Q&A