VCC

VIRTUAL Challenging Case Clinic

B-Cell Lymphomas SERIES

Mantle Cell Lymphoma

May 18, 2022

University of Nebraska Medical Center

Bio Ascend™

Introductions

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Disclosures

John P. Leonard, MD

Consulting Fees: ADC Therapeutics, AstraZeneca, Bayer, Bristol-Myers Squibb Company, Epizyme, Kite, a Gilead Company, MEI Pharma, Miltenyi Biotec, Regeneron, Roche/Genentech, Sutro Biopharma

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Planning Committee

The following planning committee members have nothing to disclose:

UNMC: Brenda Ram, CMP, CHCP

Bio Ascend: Patti Bunyasaranand, MS; Jessica Davis; Tisheeka Graham-Steed, PhD; Kraig Steubing

Learning Objectives

- ✓ Evaluate best available evidence regarding the treatment of indolent and aggressive subtypes of B-cell lymphoma
- ✓ Assess the implications of emerging clinical trial data regarding B-cell lymphoma therapeutic approaches
- ✓ Develop strategies to optimize the outcomes of complicated B-cell lymphoma cases

Reminders!

- ✓ Visit www.OncologyCaseClinic.com to register for upcoming webinars

Patient Case

45-year-old male who presents with diffuse adenopathy, fever, and night sweats. Biopsy consistent with mantle cell lymphoma (MCL) without evidence of blastoid or pleomorphic variant. Ki-67 30%, p53 negative by sequencing.

How would you treat this patient?

1. R-CHOP

2. R-CHOP followed by maintenance rituximab

3. Bendamustine-rituximab

4. Nordic Regimen followed by autologous stem cell transplantation

5. FCR

Patient Case

67-year-old male who presents with abdominal pain found to have massive splenomegaly and leukocytosis. Flow cytometry reveals CD 5+ B cell clone that has detectable (11;14) on FISH. Patient as well noted to have thrombocytopenia and anemia. Has past history significant for cardiomyopathy (EF 24%), DM, peripheral neuropathy and CKD.

How would you treat this patient?

1. R-CHOP

2. R-CHOP followed by maintenance rituximab

3. R-HyperCVAD

4. R^2 (Lenalidomide-Rituximab)

5. R-CHOP/R-HIDAC

Patient Case

70-year-old male who was diagnosed with MCL in 2015 and received high-dose chemotherapy with stem cell consolidation. He remained in remission until 2019 when he was started on ibrutinib for symptomatic relapse. He presents now for follow-up and is found on exam to have progressive disease.

How would you treat this patient?

1. Add venetoclax to ibrutinib

2. R^2

3. Bortezomib

4. Brexucabtagene autoleucel

5. Single-agent venetoclax

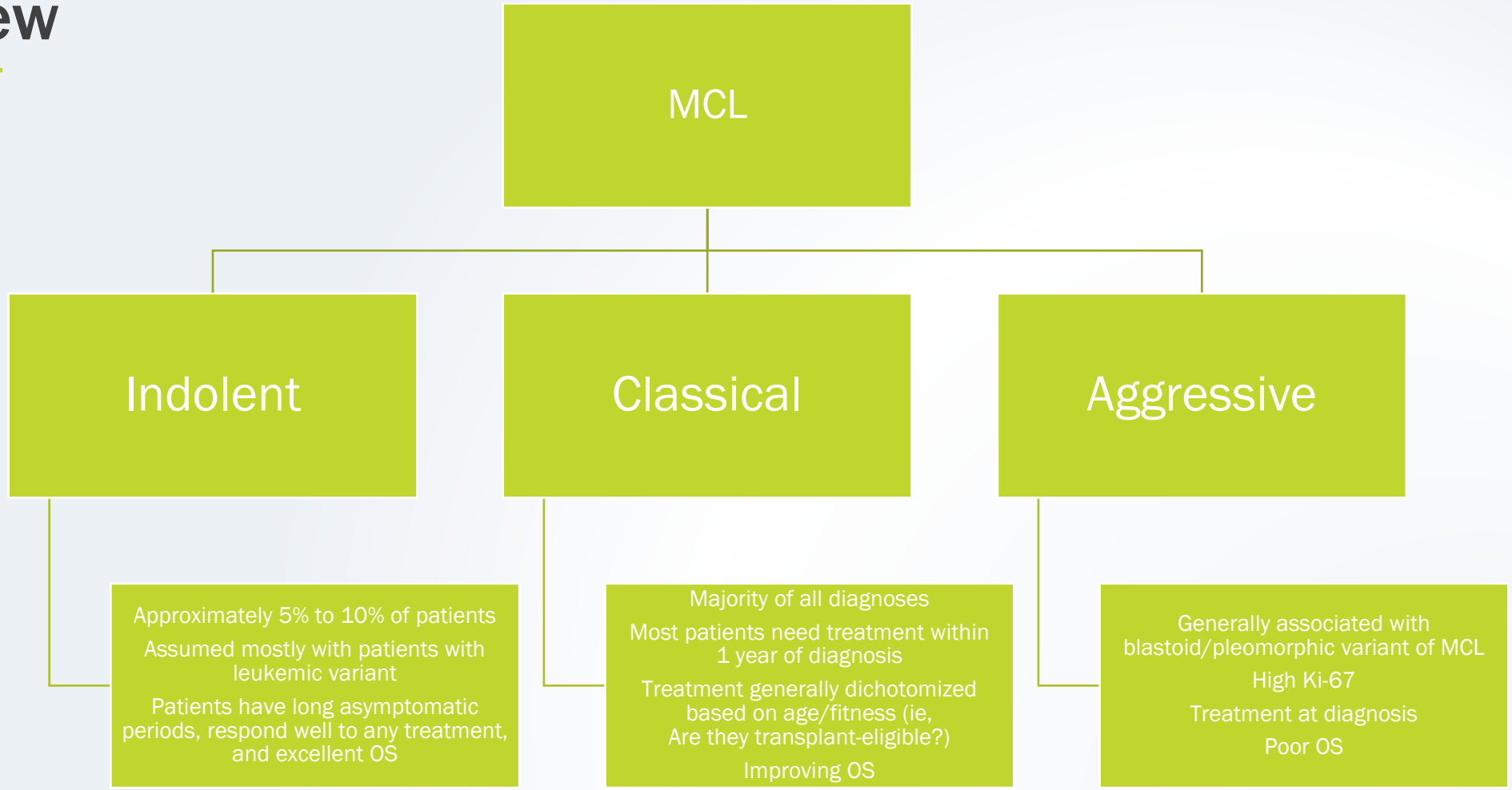
Outline

- Background
- Outcomes in frontline MCL
- Relapsed/refractory (R/R) disease
- Conclusions

Mantle Cell Lymphoma (MCL)

- MCL is a rare form of lymphoma accounting for approximately 5% to 6% of all newly diagnosed cases of NHL; it is treatable but not curable
- Diagnosed by detection of cyclin D1 and/or 11;14 translocation
  - Cyclin D1 by IHC and 11;14 by FISH
  - Importance of additional stains
    - Sox 11 – if no detection of cyclin D1 or 11;14 translocation
    - p53 (IHC stain and/or sequencing) – prognostic
- Outcomes have improved with modern regimens, but treatments are still complicated by toxicity

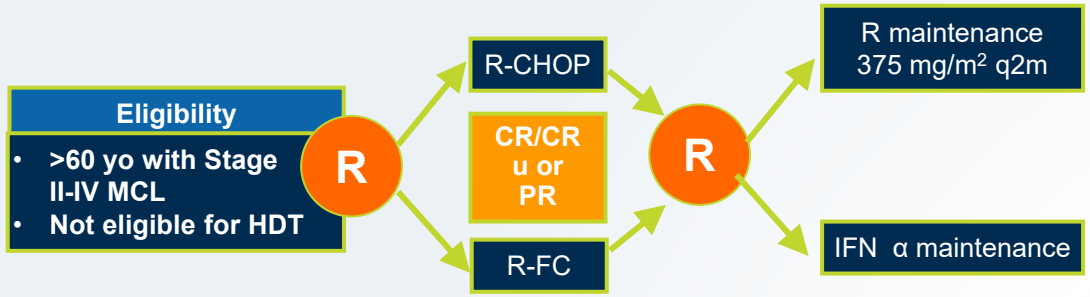
My View


MCL
Indolent
Classical
Aggressive
Approximately 5% to 10% of patients
Assumed mostly with patients with leukemic variant
Patients have long asymptomatic periods, respond well to any treatment, and excellent OS
Majority of all diagnoses
Most patients need treatment within 1 year of diagnosis
Treatment generally dichotomized based on age/fitness (ie, Are they transplant-eligible?)
Improving OS
Generally associated with blastoid/pleomorphic variant of MCL
High Ki-67
Treatment at diagnosis
Poor OS

Wide Variety of 1L Treatments for MCL

- No agreed-upon approach for first-line therapy in MCL
- For fit patients under 70, intensive induction/auto-HCT is an option
- PFS is improved by intensive induction/auto-HCT; however, it remains unclear whether OS is improved
- Although robust risk assessment tools such as MIPI score and proliferation index exist, not overly practical as treatments are not altered based on these risk factors

Outcomes With Nonintensive Induction for MCL



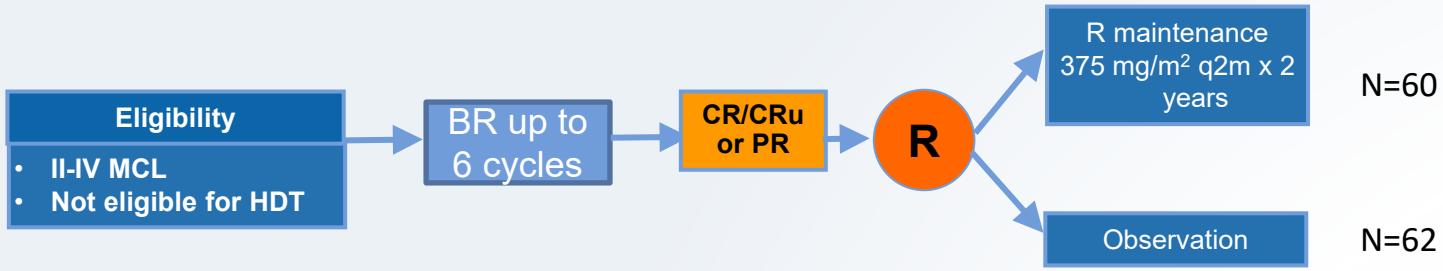
- Maintenance phase for patients responding to R-CHOP

Maintenance regimen	5 yr PFS	5 yr OS
Rituximab	51%	79%
IFN α	22%	59%

- Treatment-emergent adverse events on rituximab maintenance was low

Kluin-Nelemans HC. *N Engl J Med.* 2012;367:520-531. Hoster E, ASH 2017.

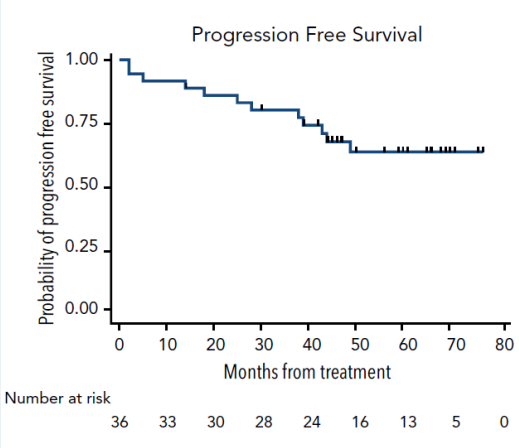
Outcomes With Nonintensive Induction for MCL

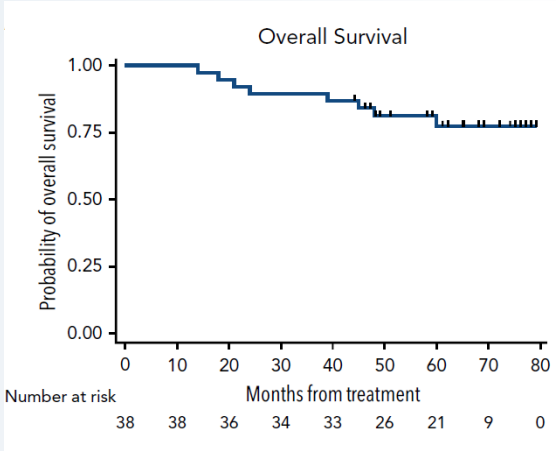


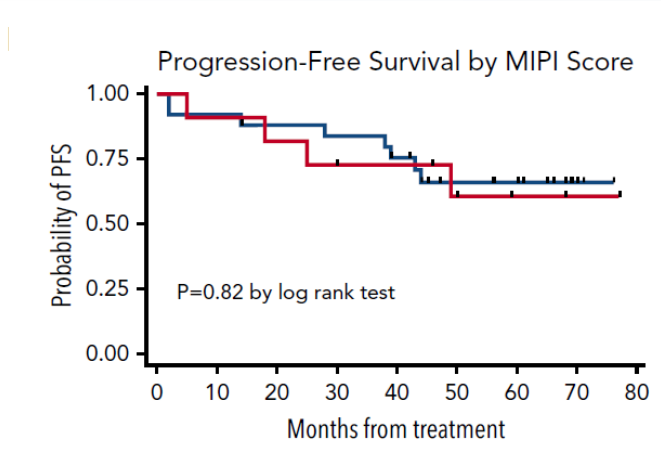
- BR induction: ORR 85%, CR 27%
- R maintenance: median PFS: 72 months
- Observation: median PFS: 55 months
- No PFS benefit with R maintenance: HR 0.71 (95% CI 0.41-1.23), *P*=0.2
- No OS benefit with R maintenance: HR 1.51 (95% CI 0.7-3.25), *P*=0.2

Outcomes With Nonintensive Induction for MCL

- Rituximab + lenalidomide
- N=38 evenly distributed amongst low-, intermediate-, and high-risk MIPI
- ORR: 87%, CR: 64%







Outcomes With Nonintensive Induction for MCL

- Patients with nonintensive approaches have good outcomes
  - Patients can live 10+ years
  - Relapses extended with maintenance (expect after BR) but will generally happen sooner
  - Patients potentially will spend more time on treatment (R^2), but avoid intensive induction
  - Can avoid toxicities associated with intensive treatment

- SO… should we be recommending auto-HCT for patients as part of first-line therapy?

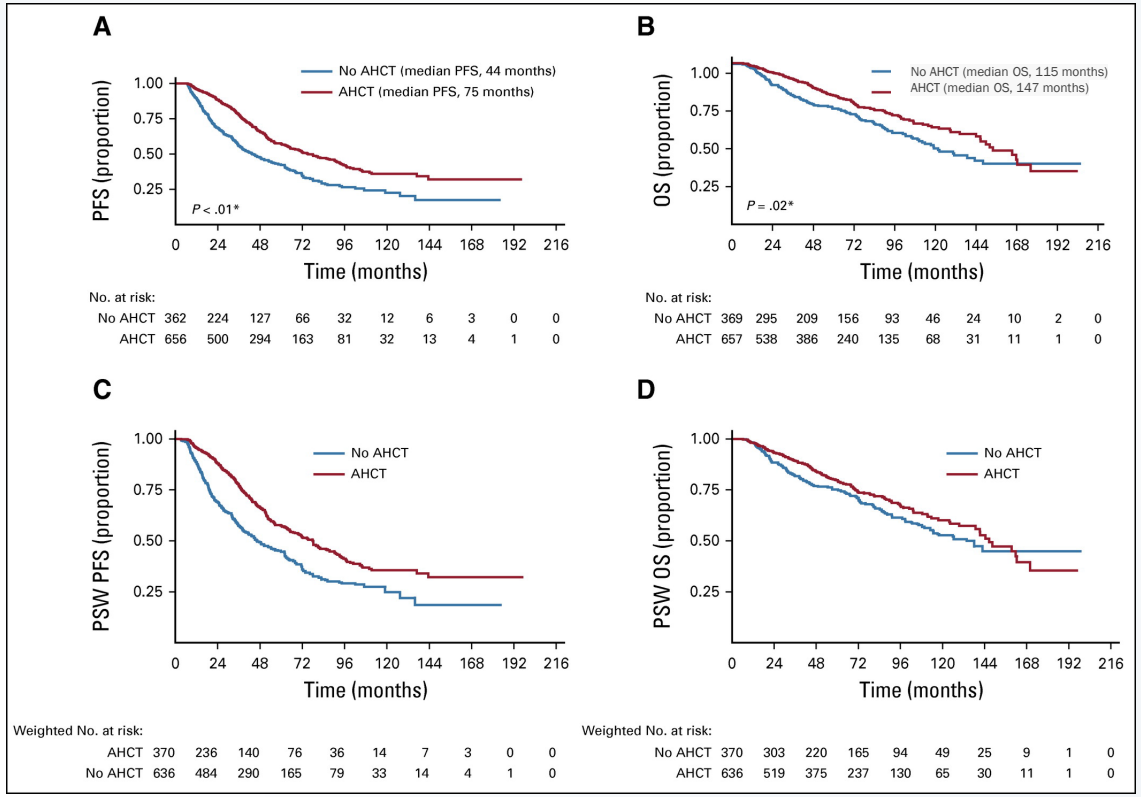
Outcomes With Nonintensive Induction for MCL

REGIMEN	EFFICACY	TOXICITY
Nordic (R-maxiCHOP/R-araC) followed by auto-HCT[1]	Median PFS: 8.5 years Median OS: 12.5 years	NRM: 7.5% MDS/AML: 3.1%
RCHOP/RDHAP followed by auto-HCT[2]	Median PFS: 9.1 years Median OS: 9.8 years	NRM: 3.4% MDS/AML: 2.4%
Any induction followed by auto-HCT (CIBMTR real world data)[3]	5 yr PFS: 52% 5 yr OS: 61%	NRM: 3%
R-HyperCVAD (without auto-HCT)[4]	Median PFS: 4.6 years 10 yr OS: 64%	NRM: 8% MDS/AML: 5%

1. Eskelund CW. *JH*. 2016. 2. Hermaine O. *Lancet*. 2016. 3. Fenske T. *JCO*. 2014. 4. Romaguera JE. *BJH*. 2010.

Does Auto-HCT Improve Outcomes?

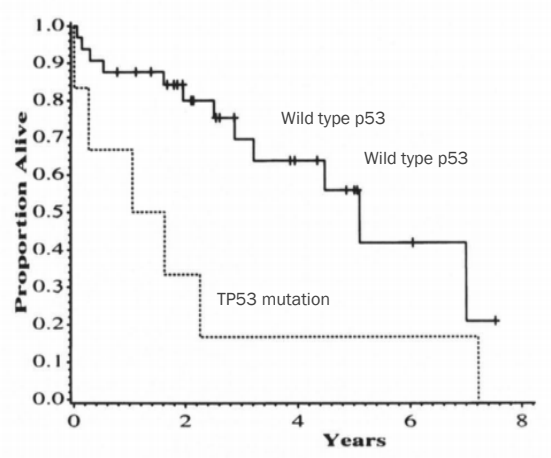
- Retrospective study in 1029 patients
- Auto-HCT demonstrated a clear PFS benefit but OS benefit not significant; restricted to patients who would have been transplant-eligible
- 2/3 got auto up front; 1/3 did not
- On initial analysis, PFS and OS benefit in favor of auto-HCT
- After propensity weighted analysis



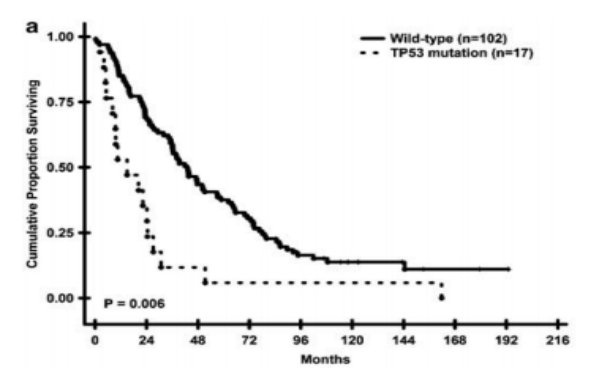
1. Eskelund CV. *BJH*. 2016. 2. Hermaine O. *Lancet*. 2016. 3. Fenske T. *JCO*. 2014. 4. Romaguera JE. *BJH*. 2010.

Patients Do Poorly With p53 Mutations

- Outcomes are poor even after auto transplant

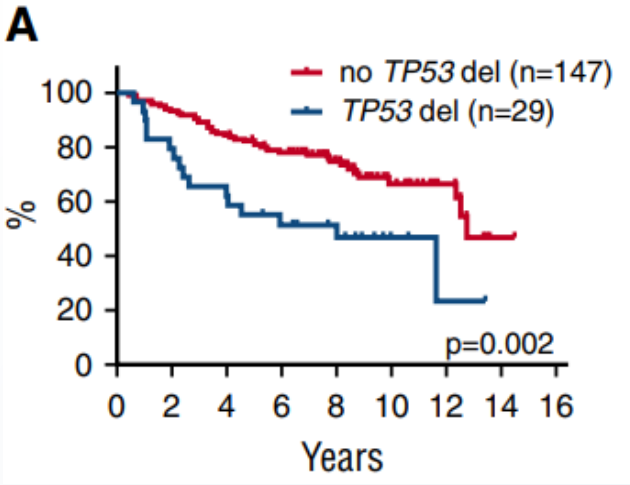


Greiner TC. *Blood.* 1996.



Halldórsdóttir AM. *Leukemia.* 2011.

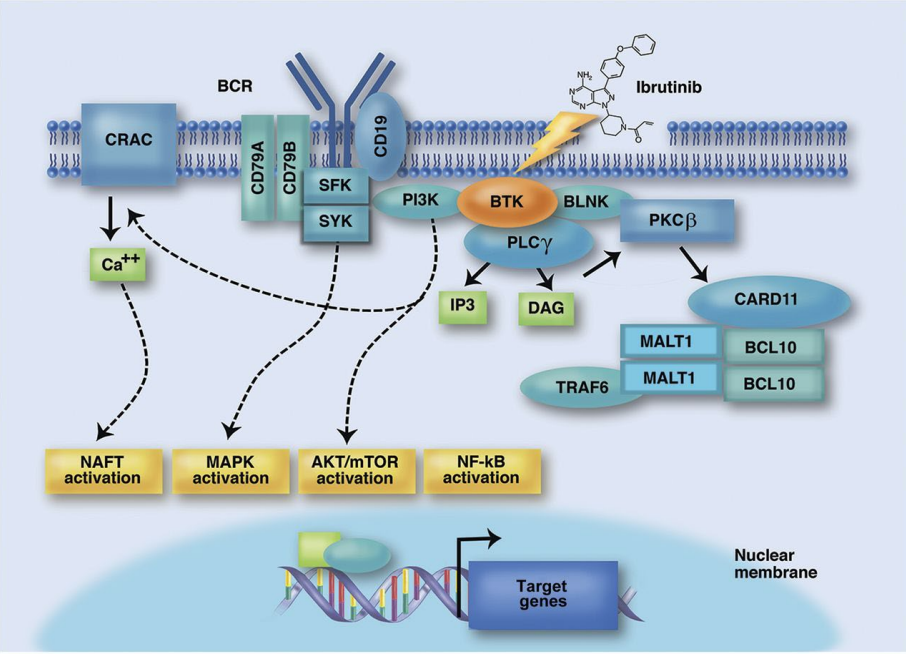
R-CHOP/R-HiDAC
ASCT **OS**



Eskelund CW. *Blood.* 2017.

1. Eskelund CW. *BJH*. 2016. 2. Hermaine O. *Lancet* 2016. 3. Fenske T. *JCO* 2014. 4. Romaguera JE. *BJH* .2010..

B-Cell Signaling



Rossi D, Gaidano G. *Blood.* 2014;123(12):1772-1774.

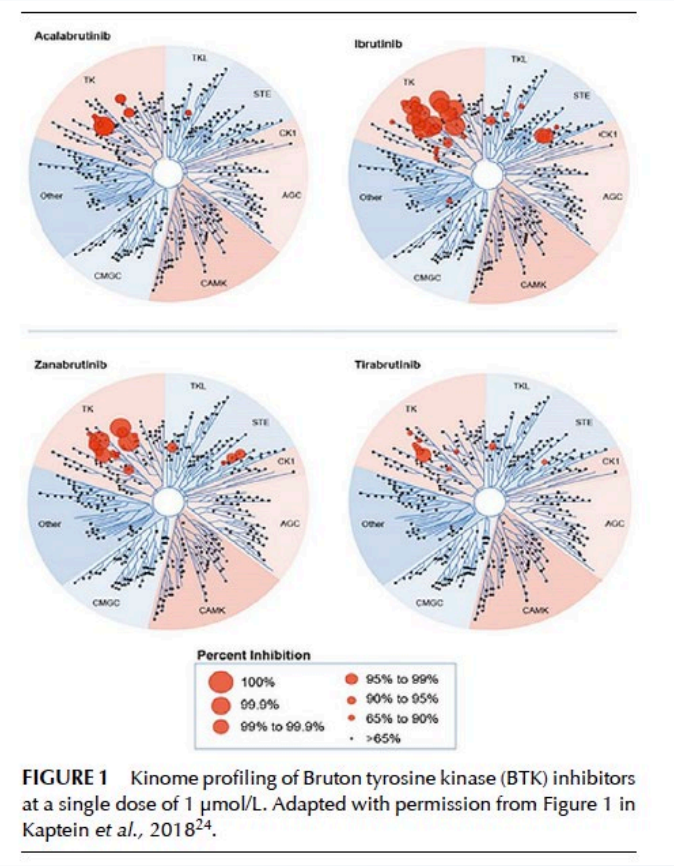
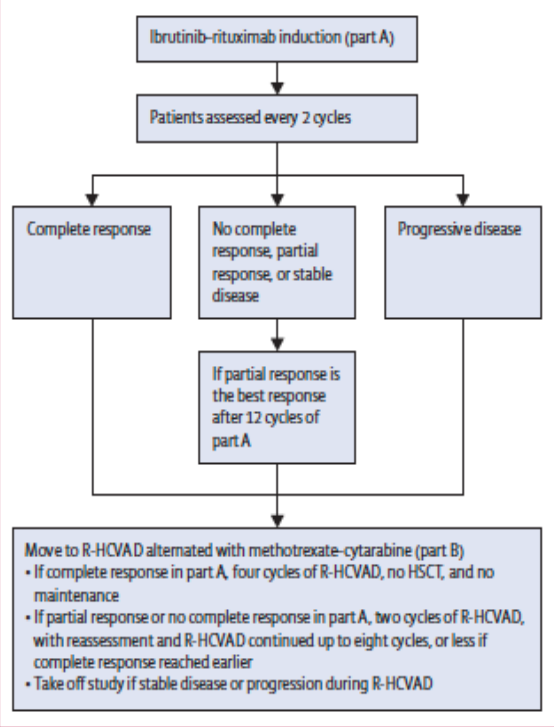


FIGURE 1 Kinome profiling of Bruton tyrosine kinase (BTK) inhibitors at a single dose of 1 µmol/L. Adapted with permission from Figure 1 in Kaptein *et al.*, 2018[24].

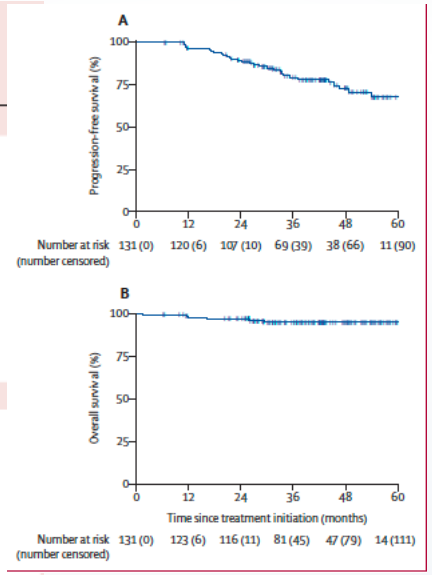
Diet Chemo...BTKi in Frontline



Simplified MIPI	
Low risk	105 (80%)
Intermediate risk	16 (12%)
High risk	10 (8%)
Biological MIPI‡	
Low risk	41 (31%)
Intermediate risk	43 (33%)
High risk	47 (36%)
Cytomorphology of mantle cell lymphoma	
Classic	112/127 (88%)
Blastoid or pleomorphic	15/127 (12%)
SOX-11 status	
Positive	56/63 (89%)
Negative	7/63 (11%)
Serum lactate dehydrogenase more that the upper limit of normal	29 (22%)
Ki-67 percentage§	
<30%	59 (45%)
≥30%	58 (44%)
Unavailable	14 (11%)
TP53 status¶	
Positive	11/34 (32%)
Negative	23/34 (68%)

CR for p53 mut 55% vs 91% for those without.

	Patients with positive PET-CT at baseline (n=97)*	All patients (n=131)
Part A best response†		
Evaluable patients	93‡	129
Overall response	93/131 (71%)	129 (98%)
Complete response	91/131 (69%)	114 (87%)
Partial response	2/131 (2%)	15 (11%)
Time to complete response in part A, months	..	5 (4-7)
Overall response after part A	..	129 (98%)
Complete response	..	114 (87%)
Partial response	..	15 (11%)
Part B best response§		
Evaluable patients	108	118
Overall response	108 (82%)	118 (90%)
Complete response	108 (82%)	117 (89%)
Partial response	0	1 (1%)
Overall response after part A and part B	..	117 (89%)
Complete response	..	90 (77%)
Partial response	..	1 (<1%)
Minimal residual disease-negative at best response¶	..	86 (65%)
Duration of response, months	..	28 (18-41)



Ibrutinib in R/R MCL

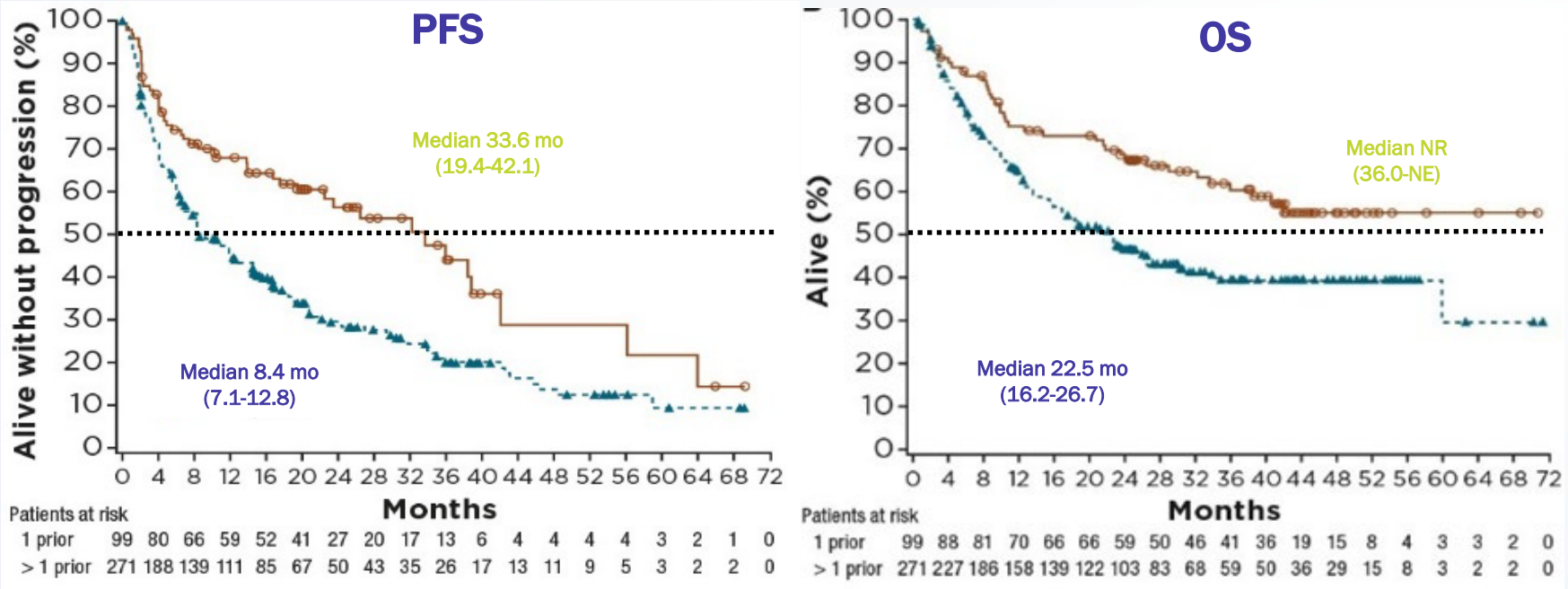
Table 3. Best Response to Therapy.*

Variable	No Prior Treatment with Bortezomib (N=63)	Prior Treatment with Bortezomib (N=48)	All Patients (N=111)
Response — no. (%)			
Overall	43 (68)	32 (67)	75 (68)
Complete	12 (19)	11 (23)	23 (21)
Partial	31 (49)	21 (44)	52 (47)
None†	20 (32)	15 (31)	35 (32)
Response duration — mo			
Median	15.8	NR	17.5
95% CI	5.6–NR	NR–NR	15.8–NR
Progression-free survival — mo			
Median	7.4	16.6	13.9
95% CI	5.3–19.2	8.3–NR	7.0–NR
Overall survival — mo			
Median	NR	NR	NR
95% CI	10.0–NR	11.9–NR	13.2–NR

* Response data included only those patients who received ibrutinib and had at least one postbaseline efficacy assessment. CI denotes confidence interval, and NR not reached.
† No response was defined as stable or progressive disease.

Wang ML, et al. *N Engl J Med*. 2013;369:507-516. Wang ML, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015. Dickerson T, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. *Blood*. 2019.

PFS and OS by Prior Line of Therapy



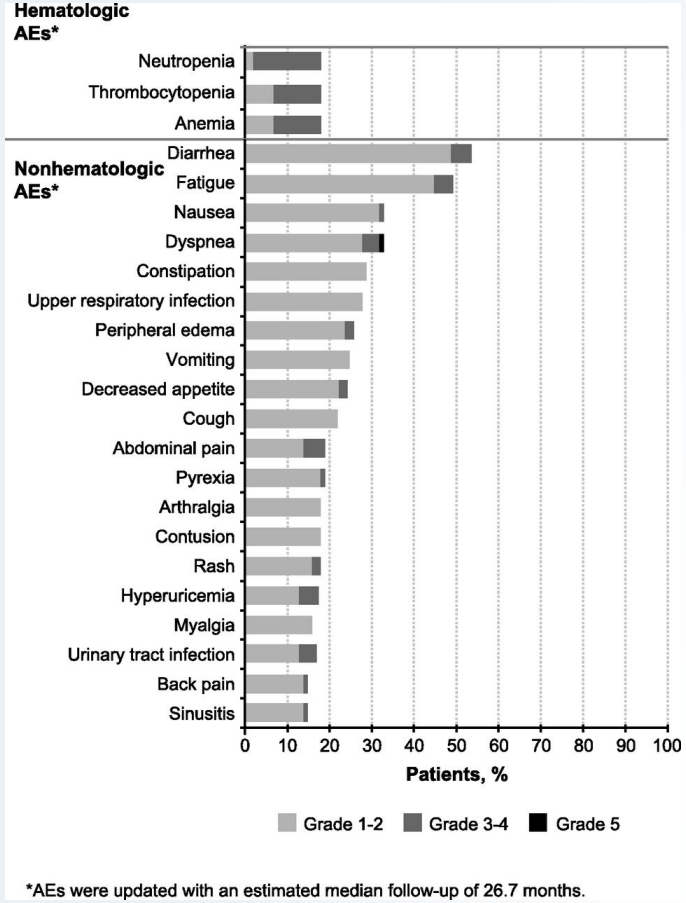
- Median PFS was nearly 3 years in patients with 1 prior line of therapy. Median DOR was 4.5 years in patients achieving a CR
- Patients with 1 prior line had 2× longer DOR than patients with >1 prior line

DOR by Best Response and Line of Therapy

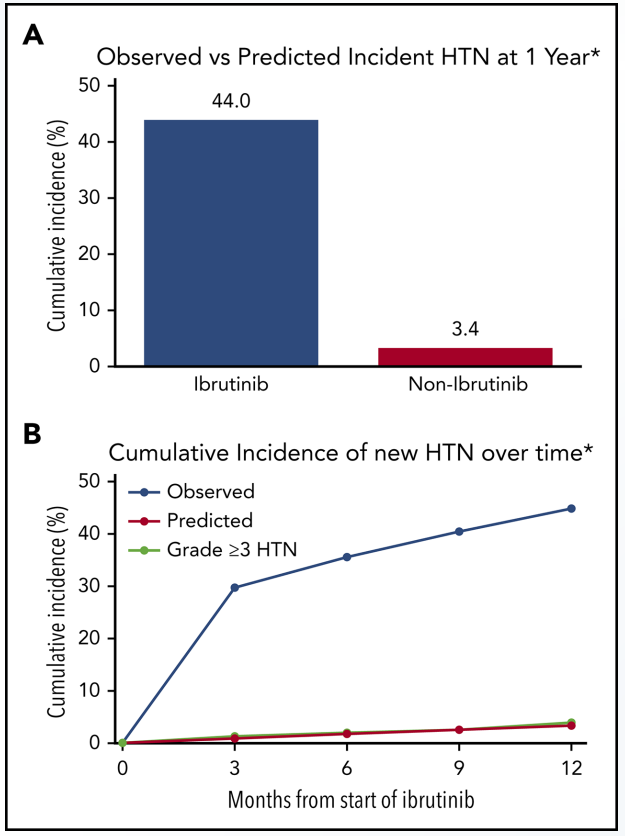
Median DOR, Months (95% CI)	Overall (n = 258)	Prior Lines of Therapy	
		1 (n = 77)	> 1 (n = 181)
Overall (n = 258)	22.2 (16.5-28.8)	34.4 (23.1-NE)	16.0 (12.9-23.5)
CR (n = 98)	55.7 (55.7-NE)	55.7 (33.1-NE)	NE (40.7-NE)
PR (n = 160)	10.4 (7.7-14.9)	22.1 (10.6-34.4)	8.5 (6.2-12.1)

- **Median DOR was 4.5 years in patients achieving a CR**
- **Patients with 1 prior line had 2× longer DOR than patients with >1 prior line**

When the Toll Is Due



*AEs were updated with an estimated median follow-up of 26.7 months.



Hypertension and incident cardiovascular events following ibrutinib initiation

Response to Acalabrutinib

- The primary endpoint was investigator-assessed ORR according to the 2014 Lugano Classification[1]
- Only 1.6% of patients required dose reductions and only 6.5% of patients discontinued acalabrutinib due to adverse events
- Atrial fibrillation was not observed. The most common side effects were headaches (36%) and diarrhea (38%), both of which were typically grades 1-2 and self-limited
- Bleeding events were usually grades 1-2 and consisted of bruising and petechiae; there was 1 case of grade 3 gastrointestinal hemorrhage

ORR using the 2014 Lugano Classification

	N=124	
	Investigator assessed n (%)	IRC assessed n (%)
ORR (CR + PR)	100 (81)	99 (80)
Best response		
CR	49 (40)	49 (40)
PR	51 (41)	50 (40)
SD	11 (9)	9 (7)
PD	10 (8)	11 (9)
Not evaluable	3 (2)	5 (4)

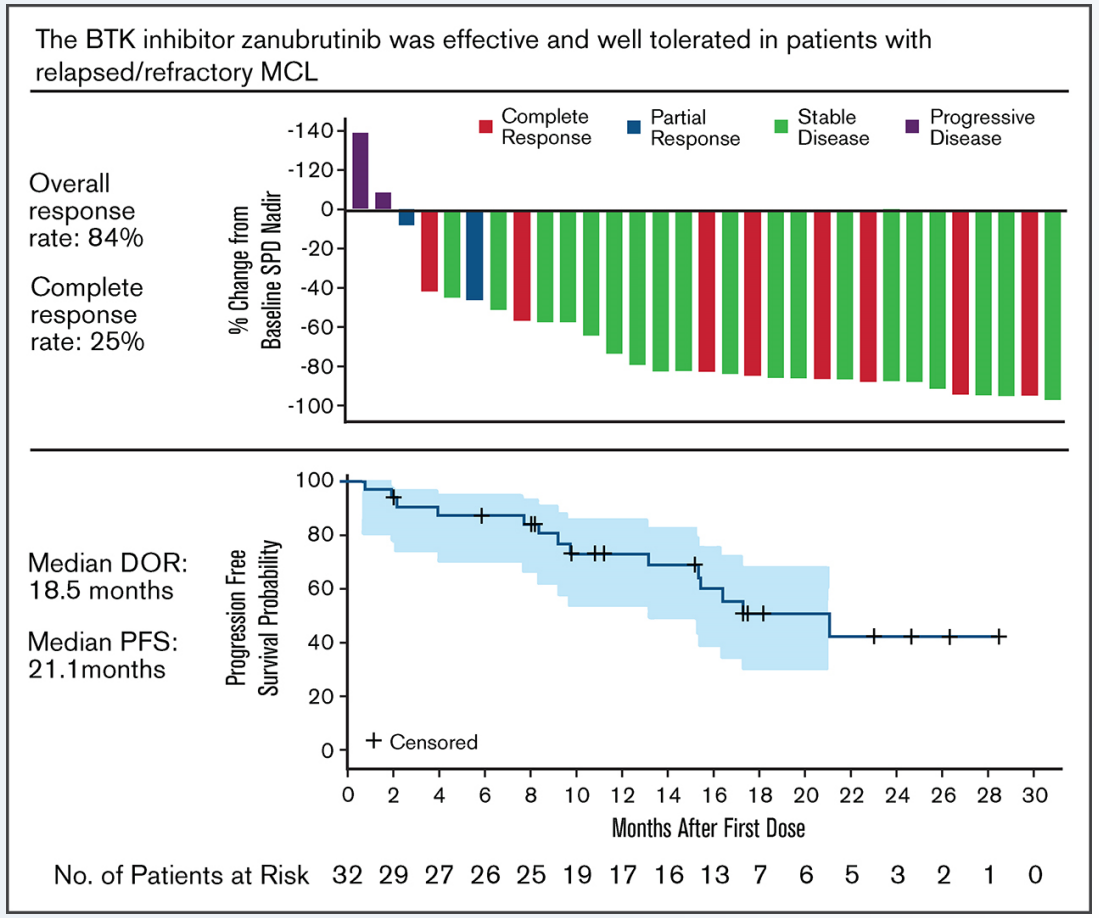
1. Wang M, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet.* 2018;391(10121):659-667.

Zanubrutinib in R/R Mantle Cell Lymphoma

Response assessment	Investigator-assessed response (N = 32)	IRC-assessed response (N = 32)
ORR 95% CI*	29 (90.6) (75.0-98.0)	27 (84.4) (67.2-94.7)
Best response		
CR	10 (31.3)	8 (25.0)
PR	19 (59.4)	19 (59.4)
Stable disease	1 (3.1)	2 (6.3)
PD	2 (6.3)	2 (6.3)
Unknown†	0	1 (3.1)

Constantine S. Tam, et al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. *Blood Adv*. 2021.

PFS and AEs



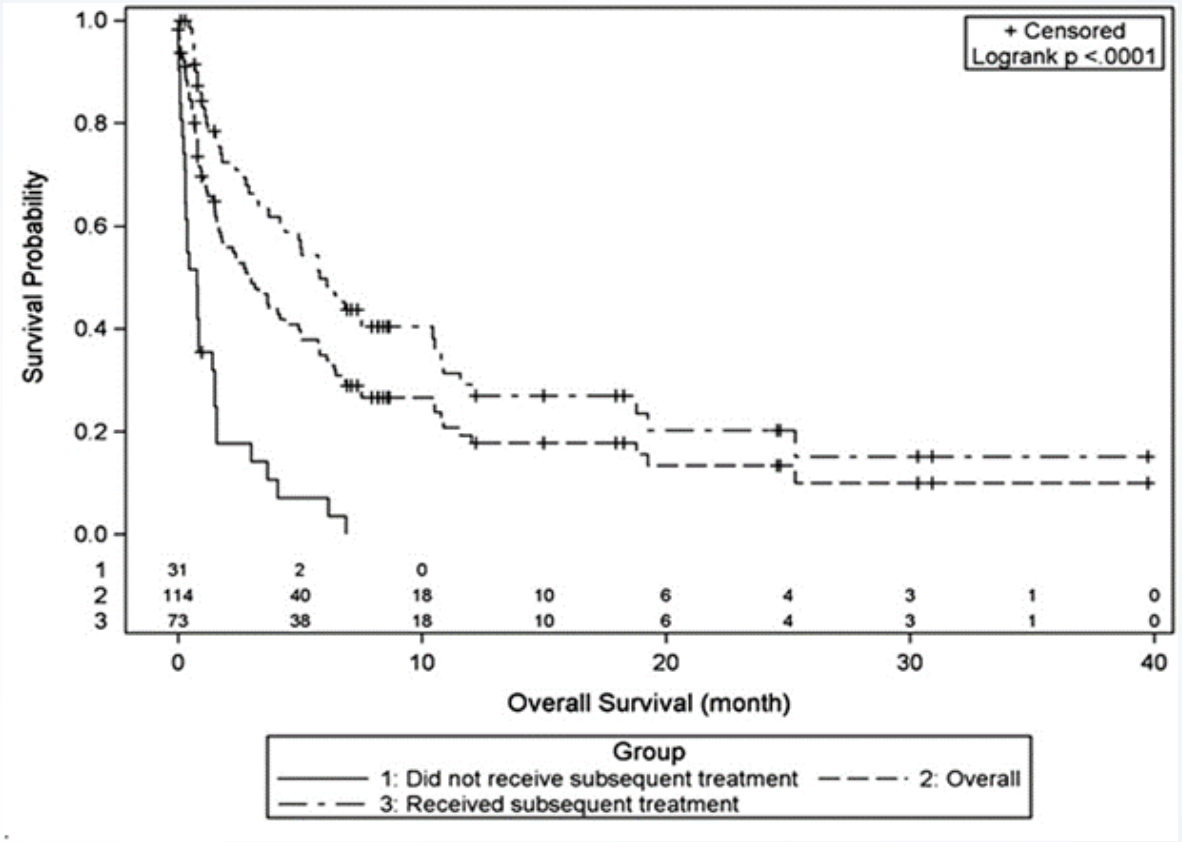
- Most common AEs
  - Diarrhea, contusion, constipation, URI, fatigue, dyspnea, and edema
- Grade 3 or above AEs of special interest
  - Major hemorrhage (9.4%), afib/flutter (3.1%), HTN (3.1%), infections (18.8%)

Key Points

- **Ibrutinib crosses the BBB while other BTKis do not based on the current data**
- **Second-generation BTKis are currently believed to have a better toxicity profile (Kinome Map)**
  - Less afib, bleeding, rash, and arthralgia/myalgia; edema likely equal among 3 covalent agents
  - Follow-up short compared to ibrutinib, so long-term sequelae TBD
  - Acalabrutinib – avoid PPI and short-term HA
  - Zanubrutinib – likely more neutropenia compared to others
- **Dose reduction is the main method to overcome most AEs except for afib**
  - Patients with afib will likely need assistance of cardiologist for initiation of beta-blocker or cardioversion
  - Avoid amiodarone or others in class given drug-drug interaction causing prolonged QTC interval
    - Long half-life of amiodarone so higher levels = very long time to eliminate drug

Post-BTKi Exposure

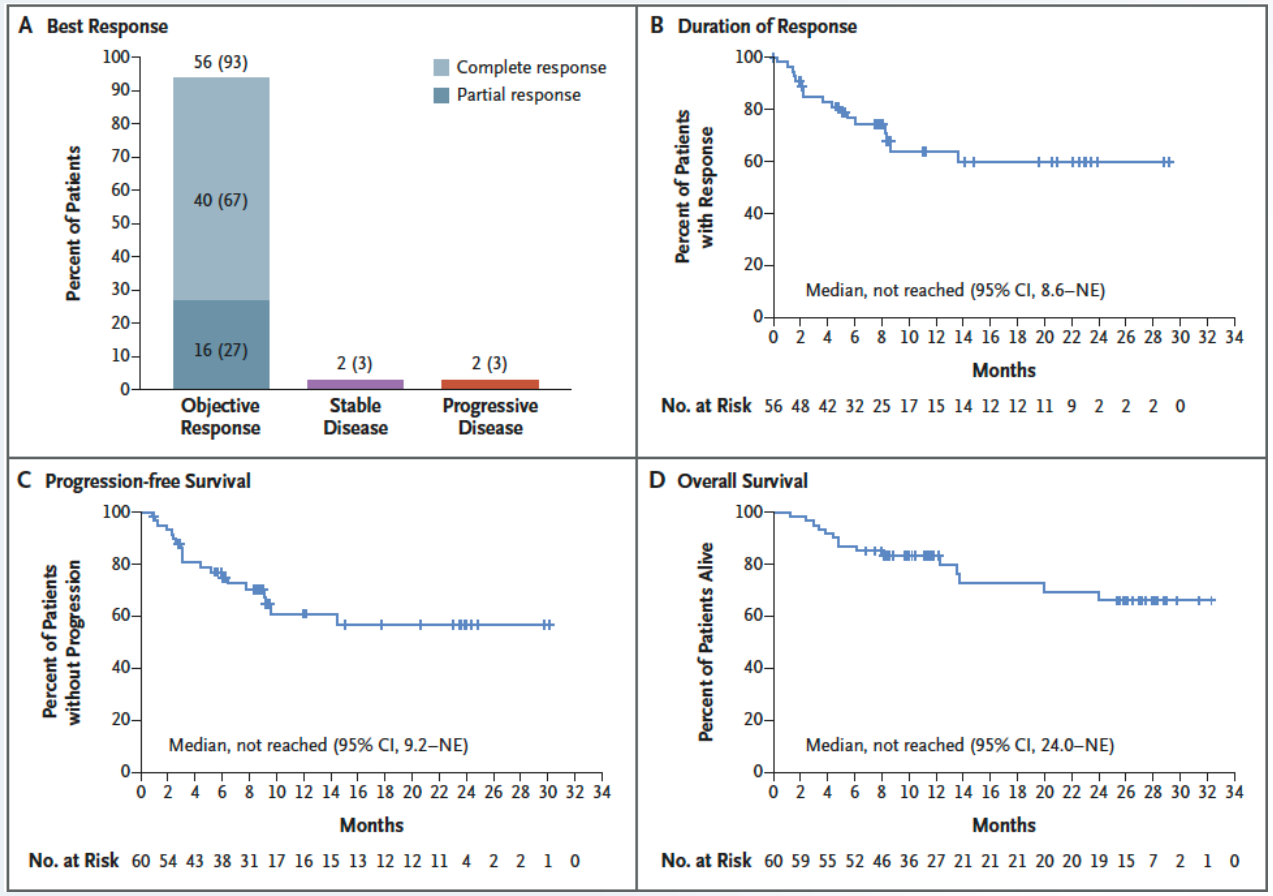
- Documented outcomes post-BTKi have been poor
- Martin et al published the first report of outcomes in this group as indicated below
- Unimpressive outcomes with lenalidomide; Wang et al, Eyre et al, and Zhao et al with venetoclax
- Retrospective R-BAC by McCullough et al with mPFS 10.1 months and mOS 12.5 months



DR2IVE

- DR2IVE, dexamethasone, rituximab, lenalidomide, and bortezomib
- Treatment schedule (given for 6 cycles)
  - Dexamethasone 20–40 mg PO or IV 1, 8, 15, 22
  - Rituximab 375 mg/m^2 IV 1, 8, 15, 22
  - Lenalidomide 15–20 mg PO 1–21
  - Bortezomib 3 mg/m^2 SC 1, 8, 15, 22
- Five patients from MD Anderson
  - ORR 100% (3 CRs, 2 PRs)
  - 3 patients alive (11.5 months, 9 months, and 3 months) at follow up
    - 1 of 3 completed therapy without PD, 1 of 3 obtained a CR but stopped therapy and then progressed

Brexucabtagene Autoleucel



- Median PFS and median OS were not reached after a median follow-up of 12.3 months
- The median DOR has not been reached after a median follow-up of 12.3 months
- 57% of all patients and 78% of patients with a CR remain in remission

Wang M et al, KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *N Engl J Med*. 2020 Apr 2;382(14):1331-1342. doi: 10.1056/NEJMoa1914347. PMID: 32242358; PMCID: PMC7731441.

Cytokine Release

Parameter	N = 68
Neurologic events, n (%)[a]	
Any grade	43 (63)
Grade ≥ 3	21 (31)
Most common any grade symptoms, n (%)	
Tremor	24 (35)
Encephalopathy	21 (31)
Confusional state	14 (21)
AE management, n (%)	
Tocilizumab	18 (26)
Corticosteroids	26 (38)
Median time to onset (range), days	7 (1 – 32)
Median duration of events, days	12
Patients with resolved events, n (%)	37/43 (86)[b]

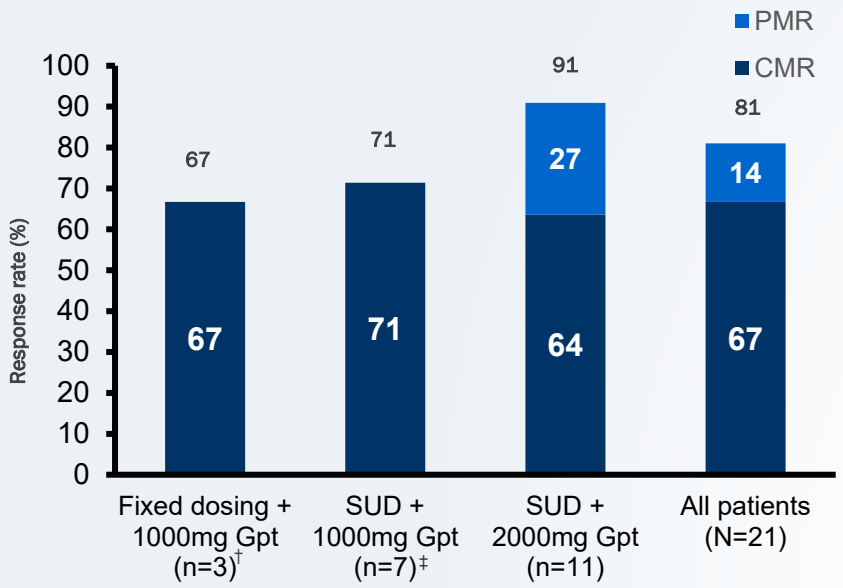
Parameter	N = 68
CRS, n (%)[a]	
Any grade	62 (91)
Grade ≥ 3	10 (15)
Most common any grade symptoms of CRS, n (%)	
Pyrexia	62 (91)
Hypotension	35 (51)
Hypoxia	23 (34)
AE management, n (%)	
Tocilizumab	40 (59)
Corticosteroids	15 (22)
Median time to onset (range), days	2 (1 – 13)
Median duration of events, days	11
Patients with resolved events, n (%)	62/62 (100)

[a] CRS was graded per Lee DW, et al. *Blood*. 2014;124:188-195. Individual symptoms of CRS were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03.

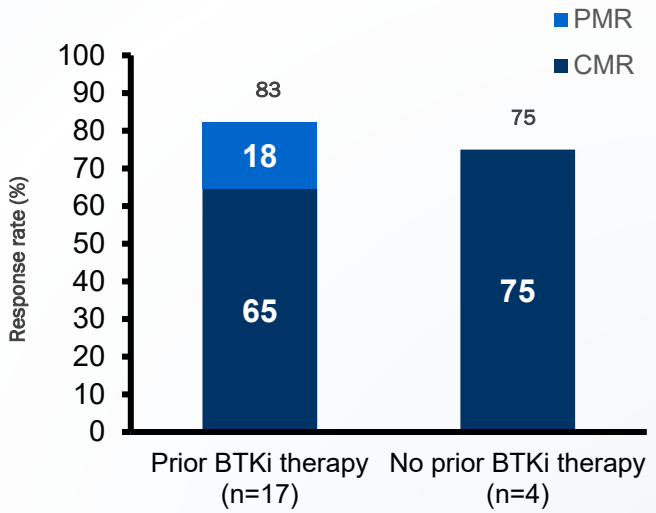
AE, adverse event; CRS, cytokine release syndrome.

Glofitamab

Response rates[1] by glofitamab regimen*



Response rates[1] by prior BTKi therapy*



Glofitamab resulted in high response rates in patients with R/R MCL

*21/29 patients were efficacy-evaluable: the secondary efficacy-evaluable population includes all patients who had a response assessment performed (investigator-assessed), or who were still on treatment at the time of their first scheduled response assessment (2014 Lugano classification)[1]. †Due to a data issue, the response (CR) from one patient is reported as missing, and two patients treated with a combination of glofitamab and obinutuzumab (G-combo); ‡One patient treated with G-combo. CMR, complete metabolic response; PMR, partial metabolic response;

Cytokine Release Syndrome/ICANS

AE, n (%)	All patients (N=29)
Any grade ICANS* AE	1 (3.4)
Grade 1	1 (3.4)
Grade 2	0
Serious	0
Any grade tumor flare	3 (10.3)
Grade 1	2 (6.9)
Grade 2	1 (3.4)
Serious	2 (6.9)
Any grade neutropenia	9 (31.0)
Grade ≥3	5 (17.2)
Serious	0
Febrile neutropenia	2 (6.9)
Serious	1 (3.4)
Any grade infections	12 (41.4)
Grade ≥3	4 (13.8)†
Serious	3 (10.3)

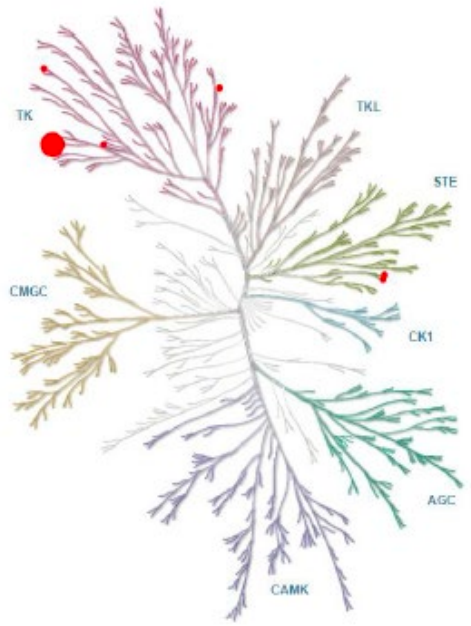
n (%) of patients with ≥1 AE unless stated	All patients (N=29)
Any CRS	17 (58.6)
Grade 1	10 (34.5)
Grade 2	6 (20.7)
Grade 3	0
Grade 4†	1 (3.4)
Serious AE of CRS (any grade)	11 (37.9)
Median time to first CRS event, hrs (range)	9.9 (3.0–32.7)
Tocilizumab use in patients with CRS	7 (24.1)
CRS events resolved	13 (76.5)§
Median time to CRS resolution, hrs (range)	38.8 (3.8–171.4)

Most CRS events occurred during C1, were Grade 1 or 2, and resolved

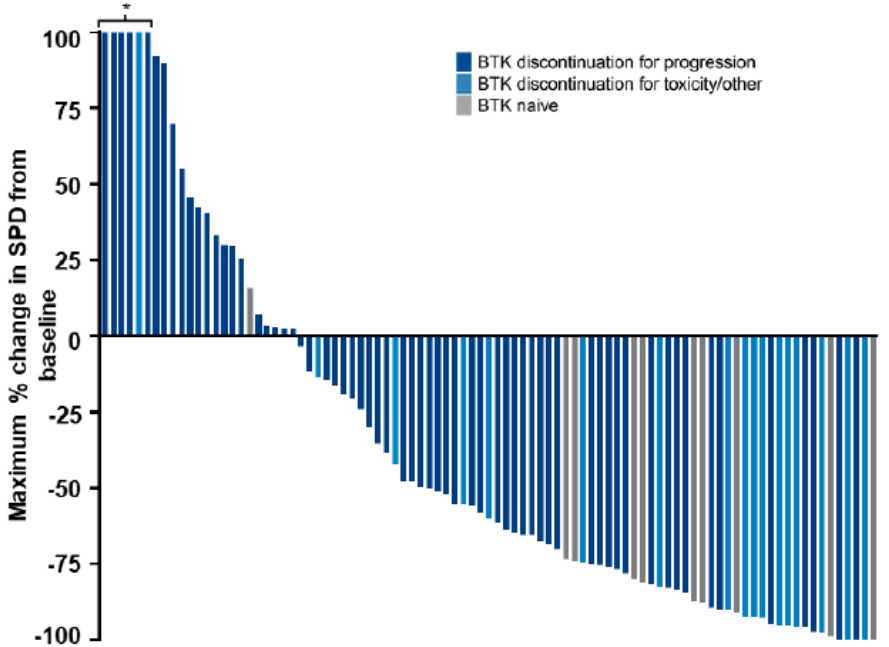
Most CRS events occurred during C1, were Grade 1 or 2, and resolved

*By American Society for Transplantation and Cellular Therapy (ASTCT) criteria; †Grade 4 CRS in the SUD + 1000 mg Gpt cohort (patient died due to cardiopulmonary insufficiency as a result of rapid PD; at time of death CRS was persisting). §3/4 remaining CRS events resolved post data cut-off.

Pirtobrutinib



Pirtobrutinib Efficacy in Mantle Cell Lymphoma



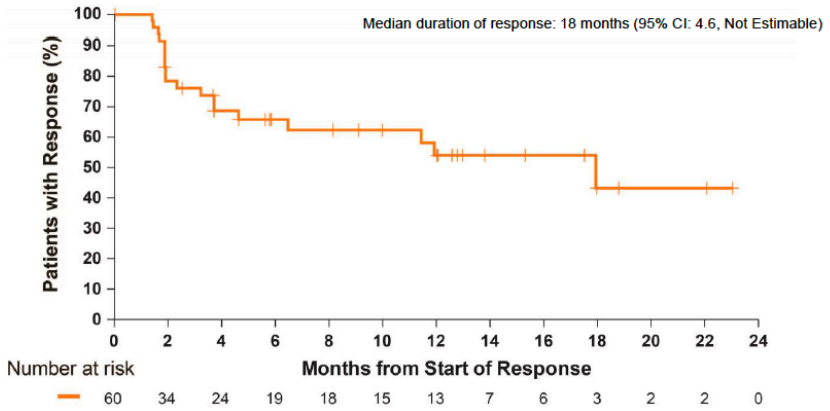
BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

Efficacy also seen in patients with prior:
- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Data cutoff date of 16 July 2021. Data for 20 MCL patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR and PR. Response status per Lugano 2014 criteria based on investigator assessment. Total % may be different than the sum of the individual components due to rounding.

Pirtobrutinib: Safety and Efficacy in MCL

Pirtobrutinib Duration of Response in Mantle Cell Lymphoma



- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

Data cutoff date of 16 July 2021. Response status per Lugano 2014 criteria based on investigator assessment.

BTK Class AEs

AEs of special interest[b]					
Bruising[c]	20%	2%	-	-	22%
Rash[d]	9%	2%	<1%	-	11%
Arthralgia	8%	3%	<1%	-	11%
Hemorrhage[e]	5%	2%	1%[g]	-	8%
Hypertension	1%	4%	2%	-	7%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]

Conclusions

Multiple options in frontline MCL

- Several clinical trials exploring combinations of BTKi and chemo-immunotherapy as well as studies using combinations of small molecules/targeted therapies only

Relapsed/refractory with several novel options

- BTKi in combination or single agent likely to remain backbone of 2L therapy
- Historically poor outcomes post-BTKi but several new options with promising outcomes
  - Pirtobrutinib (noncovalent BTKi)
  - CAR T-cell therapy (brexucabtagene autoleucel) is FDA approved for R/R after failure of 1L therapy
  - Bispecifics – several being explored in clinical studies (epcoritamab, glofitamab, mosunetuzumab, odronextamab, plamotamab)
  - ROR1 inhibitor (zilovertamab vedotin**)** –ADC conjugated to MMAE

Thank You!

Visit OncologyCaseClinic.com to register for upcoming webinars.

Next presentation: Wednesday, June 8, 2022
CAR T-cell Therapy
Mehdi Hamadani, MD