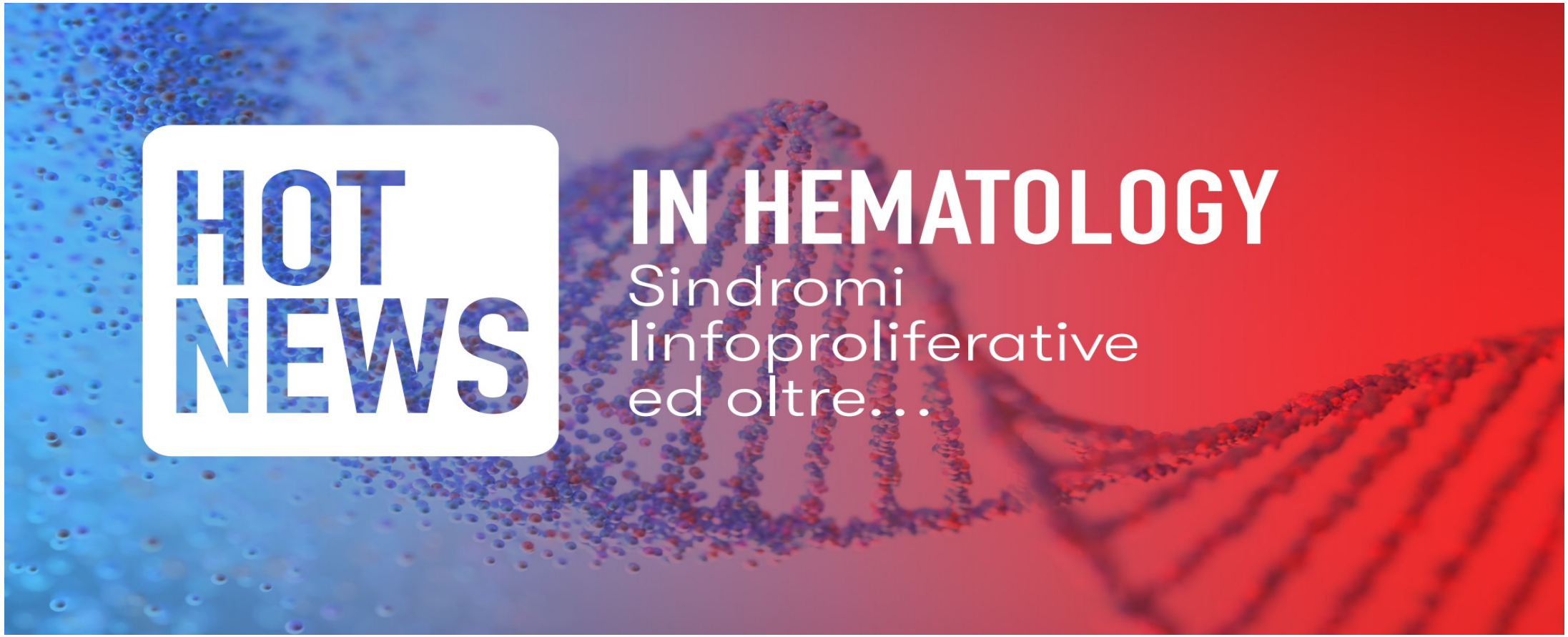
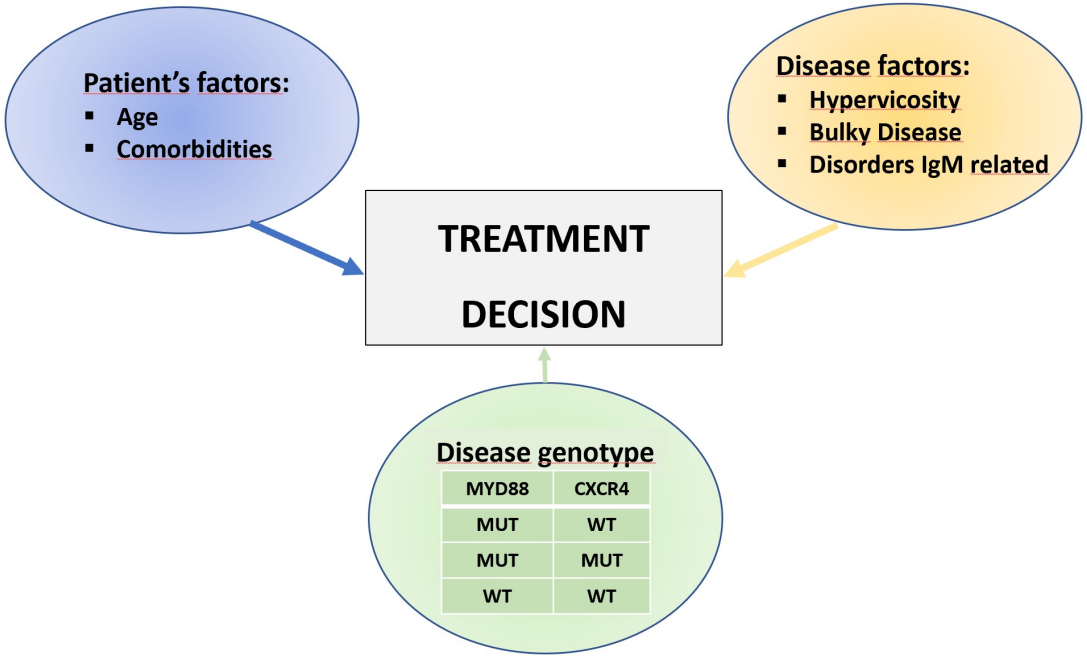


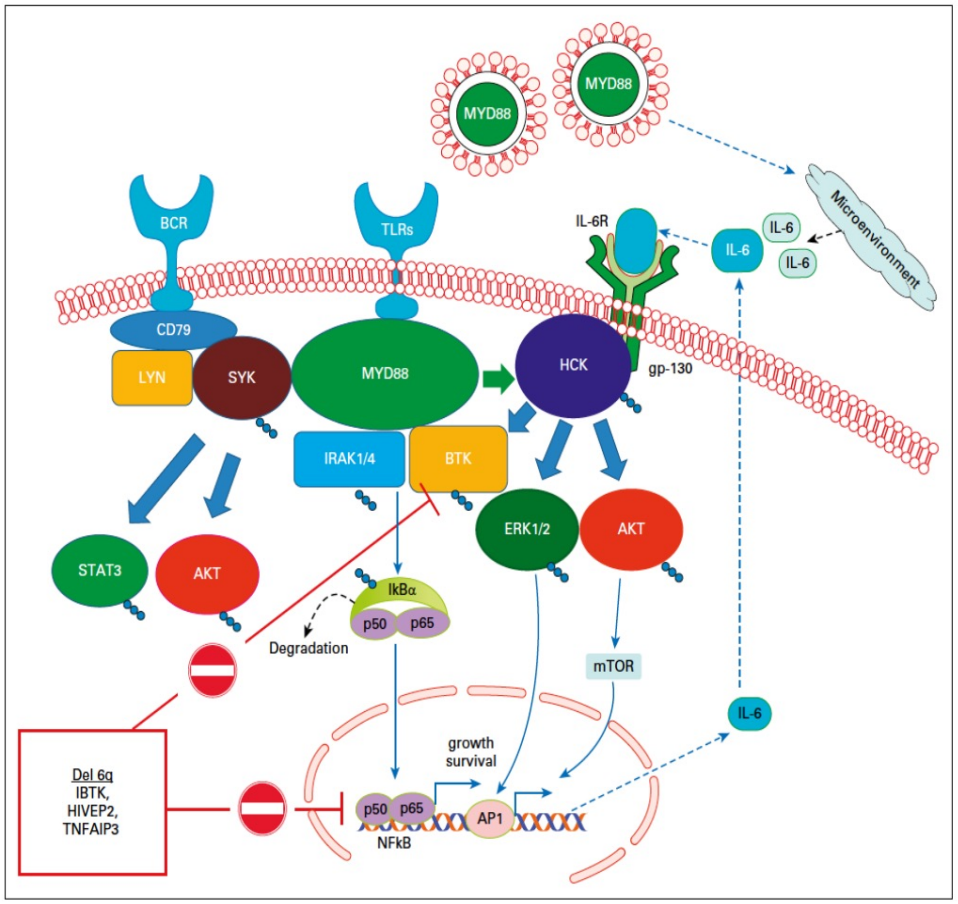
MACROGLOBULINEMIA DI WALDENSTROM

Alessandra Tedeschi
Division of Hematology
Niguarda Hospital, MIlano

WM TREATMENT



MYD88 in WM

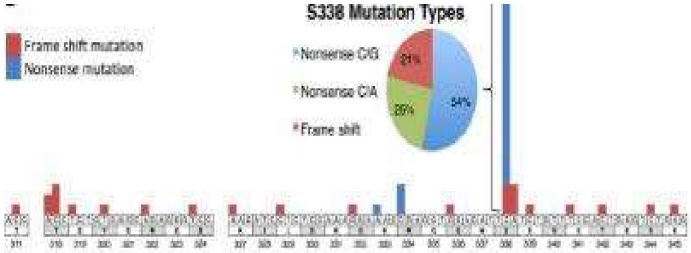


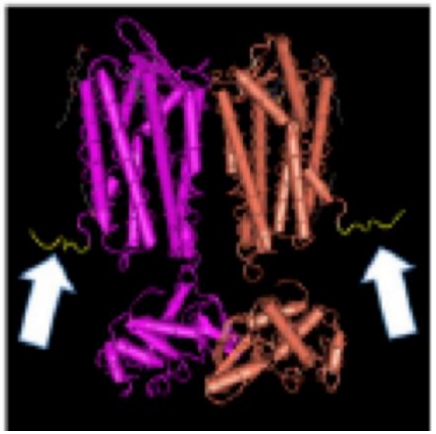
- ~ 95% of WM patients carry the somatic mutation of MYD88 (L265P)
- MYD88, IRAK1/IRAK4 and BTK are components of the Myddosome complex that activates NFKB
- Mutated MYD88 upregulates hematopoietic cell kinase (HCK) transcription and activates HCK via Il-6. Activated HCK promotes survival through BTK, PI3K/AKT and MAPK/ERK1/2
- Evidence of cross talk between mutated MYD88 and BCR pathway with SYK activation that triggers STAT3 and AKT prosurvival signaling

Treon S l et al, 2020

CXCR4 in WM

- Over 30 nonsense (NS) or frameshift (FS) C-tail mutations
- The most common CXCR4 mutation is S338X (~ 50% of all CXCR4 mutations)
- Similar to germline mutations typical of WHIM syndrome
- Detected in 30-40% of WM patients, and usually associated with MYD88 mutations





PATIENTS WITH CXCR4 mutations

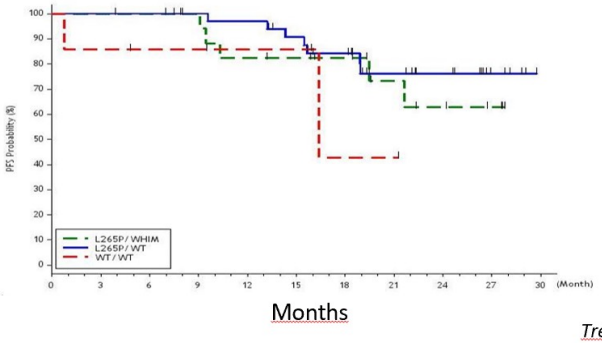
- ✓ **higher IgM levels**
- ✓ **higher incidence of hyperviscosity**
- ✓ **higher BM infiltration**
- ✓ **shorter time to first treatment**

Treon SP et al, 2014;
Poulain S et al, 2016;
Schmidt J et al, 2015;
Treon SP et al, 2015.

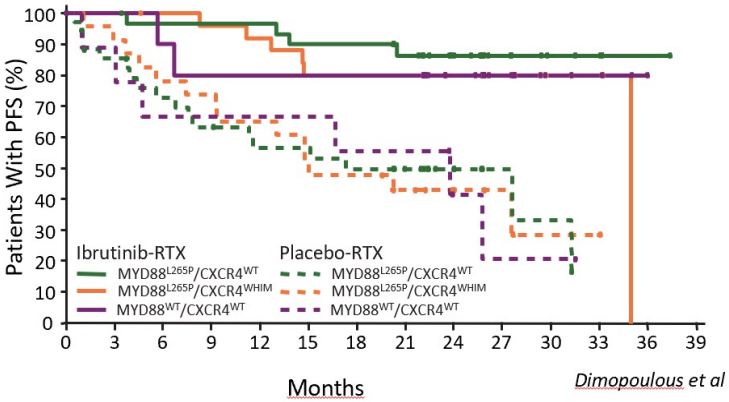
WM TREATMENT

PFS according to MYD88 & CXCR4 mutation status

Ibrutinib Monotherapy R/R

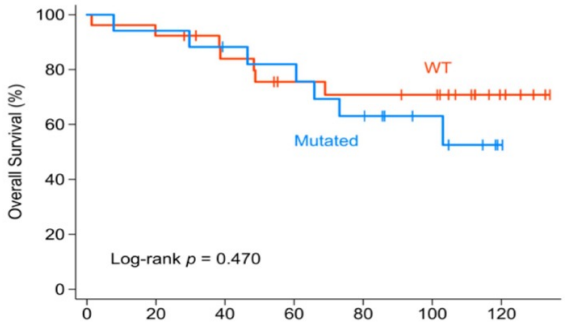


Treon et al, 2015



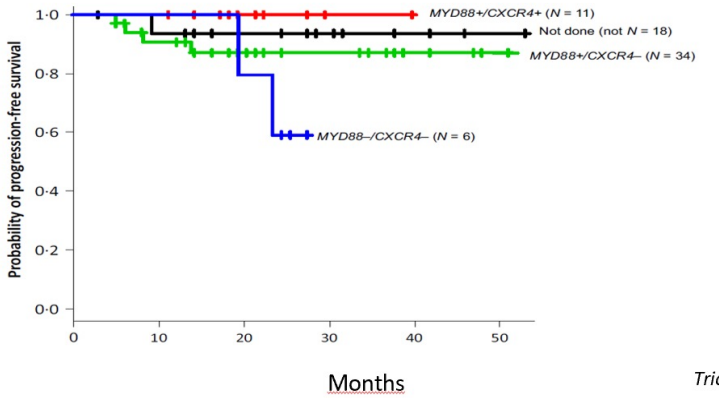
Dimopoulous et al 2018

Bortezomib Rituximab First Line according to CXCR4



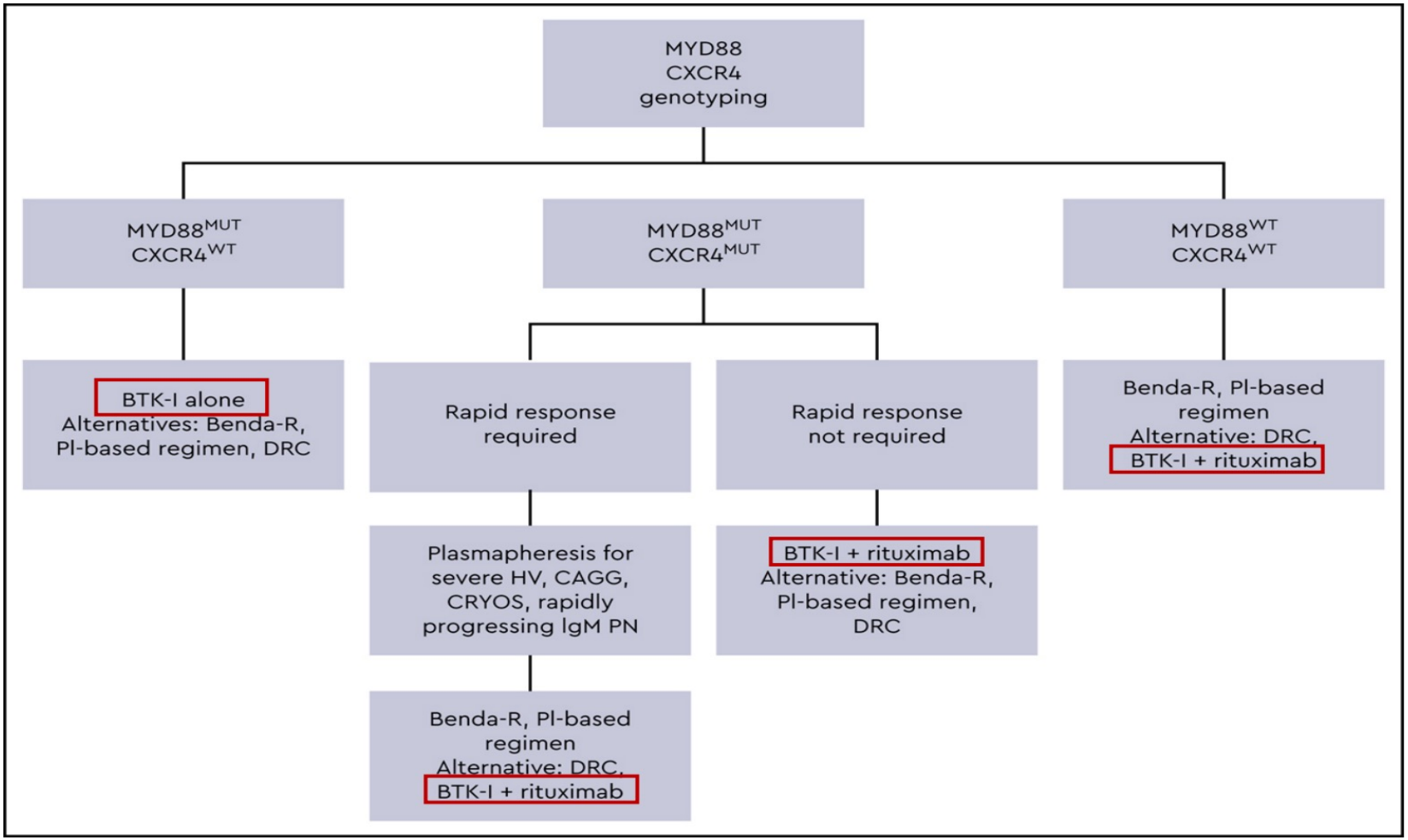
Sklavenitis et al, 2018

Bendamustine Rituximab First Line



Tricot et al, 2018

WM: Genomic based treatment algorithm

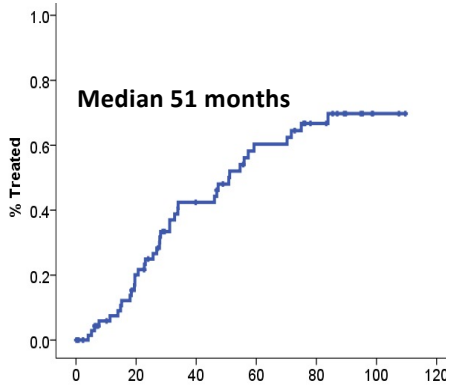


Treon et al. JCO 2020

WM TREATMENT FIRST LINE TREATMENT

Rituximab Combination Treatment

DRC



PROS:

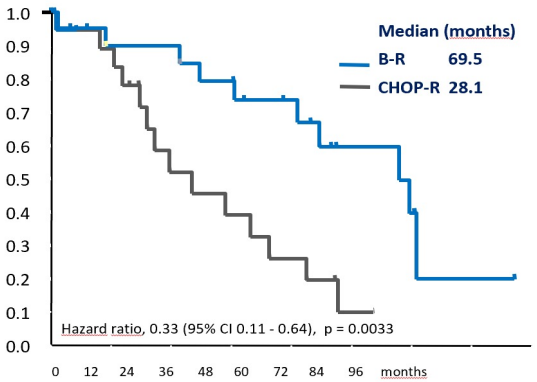
- ✓ **Minimal myelo/immuno-suppression**
  89% pts completed 6 courses
- ✓ **TTN 51 m**

CONS:

- **CR: 7%**
- **Median time to 50% IgM reduction:**
  4.1 m

Kastrititis et al, 2015

Benda R



PROS:

- ✓ **Rapidly effective/ Prolonged PFS**
- ✓ **No impact from CXCR4 mut**

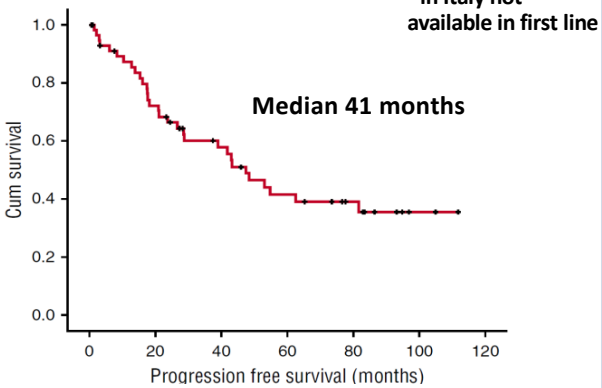
CONS:

- **Myelotoxicity/late infectious toxicities: dose reduction to70 mg/sqm or 4 courses**
- **Secondary MDS/LAM (?): ~0-3%**

Rummel et al, 2013

Bortezomib°R

° in Italy not available in first line



PROS:

- ✓ **Rapid IgM decrease**
- ✓ **Lower myelo/immuno-suppression**

CONS:

- **High rate of Neuropathies**

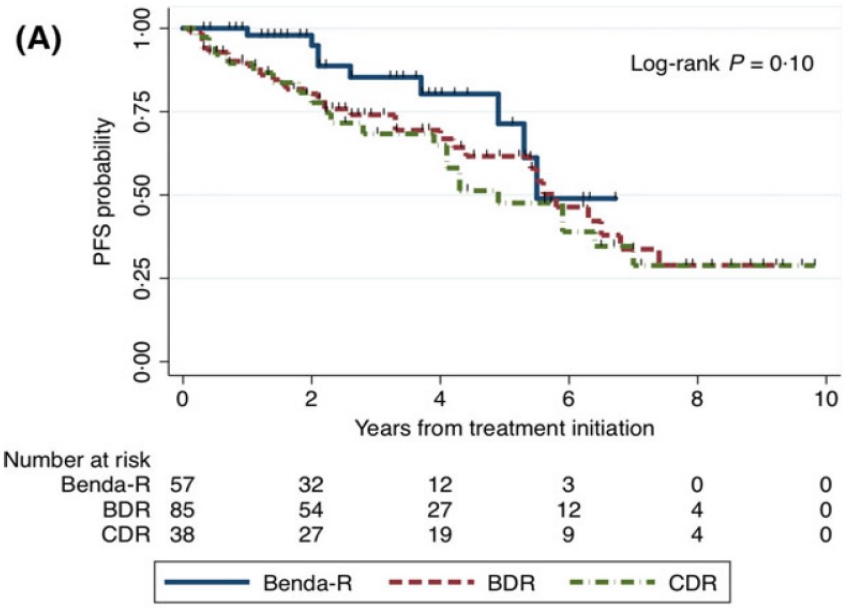
Treon et al, 2009-2015

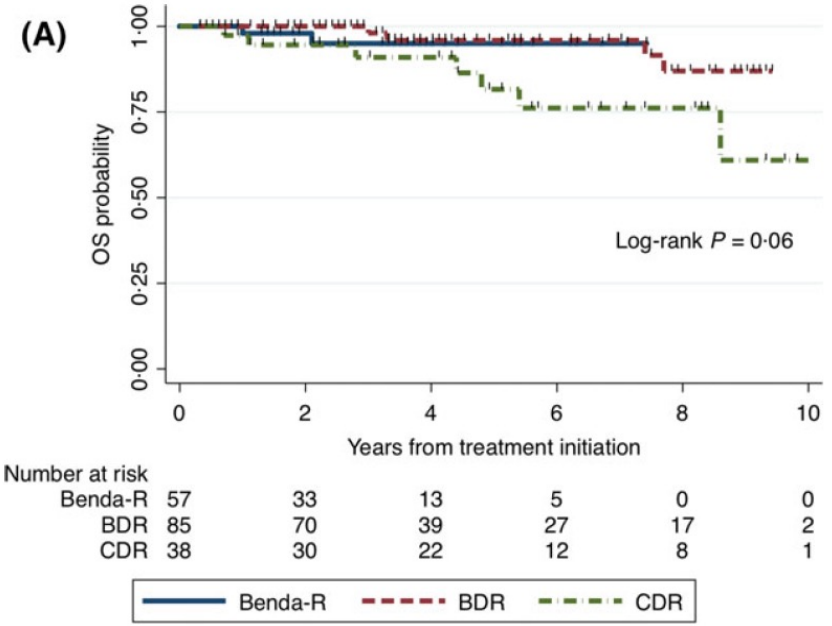
WM TREATMENT FIRST LINE TREATMENT

Response and survival for primary therapy and maintenance rituximab

Benda-R 57 pts (31%)
BDR 87 pts (48%)
CDR 38 pts (21%)

No difference in response rates





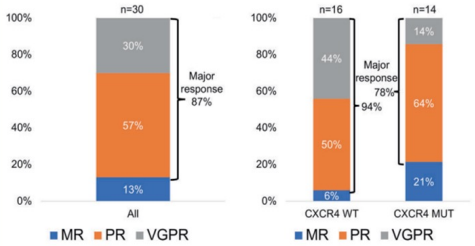
Castillo et al, 2009-2019

WM TREATMENT FIRST LINE TREATMENT

BTKi*

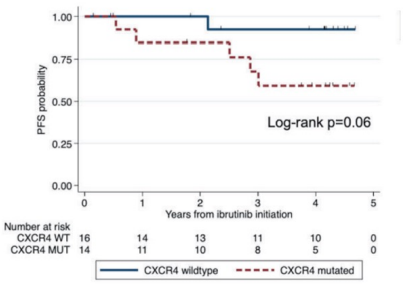
Ibrutinib° in MYD88^{mut}

median follow-up time of 50.1 m



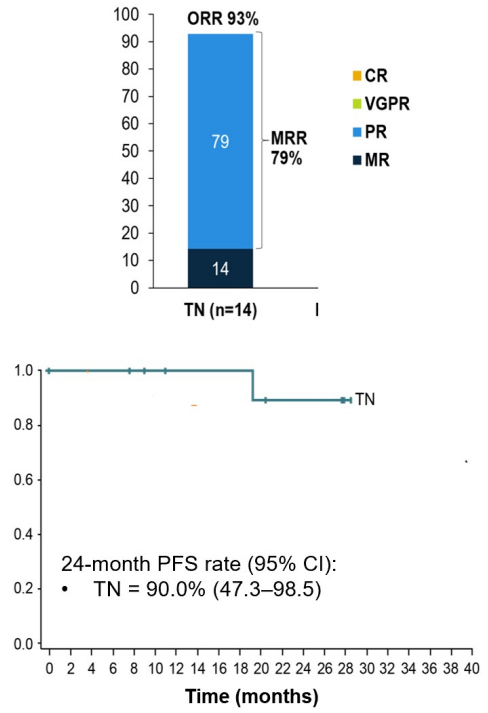
Median time to Major Response: 1.9 m
Median longer for pts with:

CXCR4^{mut}	7.3 m	*p = 0.02*
CXCR4^{wt}	1.8 m	



Castillo et al., 2021

Acalabrutinib



Owen RG et al., 2020

Aspen trial in MYD88^{mut}

median follow-up time of 19.4 m

	TN	
	Ibrutinib (n = 18)	Zanubrutinib (n = 19)
Best overall response, n (%)		
CR	0 (0)	0 (0)
VGPR	3 (17)	5 (26)
PR	9 (50)	9 (47)
MR	4 (22)	4 (21)
SD	1 (6)	0 (0)
PD	0 (0)	1 (5)
Not evaluable*	1 (1)	0 (0)
Response rates, % (95% CI)†		
VGPR or CR	17 (4-41)	26 (9-51)
P	NR	
MRR	67 (41-87)	74 (49-91)
ORR	89 (65-99)	95 (74-100)
Duration of CR/VGPR, mo		
Median (range)	NE (0+, 3+)	NE (0+, 22+)
18-Mo event-free rate, % (95% CI)§	NE (NE, NE)	100 (NE, NE)
Duration of major response, months		
Median (range)	NE (3+, 28+)	NE (0+, 25+)
18-Mo event-free rate, % (95% CI)§	00 (NE, NE)	80 (39-95)
PFS		
Median (range), mo	NE (0+, 31+)	NE (1, 31+)
18-Mo event-free rate, % (95% CI)§	94 (63-99)	78 (52-91)

Tam CS et al., 2020

° approved by EMA in unfit PTS not reimbursed in Italy

WM TREATMENT FIRST LINE TREATMENT

Rituximab combination treatments

- Effective, Long Time to Retreatment
- Fixed duration
- Myelosuppression/Immunosuppression

BTKi

- Effective, prolonged PFS
- Continuous treatment
- Resistance Development

WM TREATMENT FIRST LINE TREATMENT

UNFIT PATIENTS ➡ UNMET CLINICAL NEED

Rituximab mono

ORR 44-65%

Short PFS

Effective in specific
IgM related sisease symptoms

Gertz et al , 2009
Dimopoulous et al, 2010

Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia

Lancet Haematol 2020;
7: e827–37

Jorge J Castillo, Ranjana H Advani, Andrew R Branagan, Christian Buske, Meletios A Dimopoulos, Shirley D'Sa, Marie José Kersten, Veronique Leblond, Monique C Minnema, Roger G Owen, M Lia Palomba, Dipti Talaulikar, Alessandra Tedeschi, Judith Trotman, Marzia Varettoni, Josephine M Vos, Steven P Treon, Efstathios Kastritis

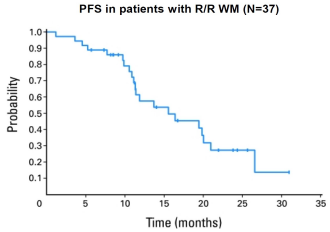
- **CONSENSUS that CDR, or bendamustine plus rituximab, BDR ibrutinib alone, and ibrutinib plus rituximab**
  - **are preferred options as primary therapy**
  - **these regimens can also be used in the management of relapsed or refractory pts**
- **NO consensus on which treatment regimen provides the best safety and efficacy profile. central to this lack of consensus is the absence of prospective randomised studies**
- **NO consensus on the recommendations for fixed or indefinite duration regimens**
- **CONSENSUS that there are currently noconvincing data to recommend the combination of ibrutinib and rituximab over ibrutinib alone.**

THE CHOICE OF PRIMARY AND SUBSEQUENT THERAPY SHOULD BE PERSONALISED CONSIDERING THE: TOXICITY PROFILE
ADMINISTRATION SCHEDULE AND ROUTE
DRUG ACCESSIBILITY
PTS PREFERENCE

RELAPSED/REFRACTORY WM

Long Reponse Duration ⇒

- ✓ **Repeat First Line Treatment**
- ✓ **Change Rituximab Combination Treatment**
  - **- Bortezomib R[1]**



- ✓ **BTKi°**

Short Reponse Duration
Refractory ⇒

- ✓ **BTKi°**

°EMA approved:
Ibruinib (AIFA: reimbursed in monotherapy)
Ibrutinib Rituximab (AIFA: not reimbursed)
Zanubrutinib (AIFA: pending)

RELAPSED/REFRACTORY WM

Ibrutinib Phase II study

Baseline characteristics (ibrutinib n=63):

- Median age: 63 (44-86) yrs
- Median n° of prior therapies: 2 (1-9)
- 40% pts refractory to most recent therapy
- Median bone marrow involvement: 60%

Variable	All	*MYD88*^{Mut} *CXCR4*^{WT}	*MYD88*^{Mut} *CXCR4*^{Mut}	*MYD88*^{WT} *CXCR4*^{WT}	*P*
No. of patients	63	36	22	4	
Overall response rate	57 (90.5)	36 (100.0)	19 (86.4)	2 (50.0)	< .0100
Major response rate	50 (79.4)	35 (97.2)	15 (68.2)	0 (0.0)	< .0001
Categorical responses					
No response	6 (9.5)	0 (0.0)	3 (13.6)	2 (50.0)	< .0001
Minor response	7 (11.1)	1 (2.8)	4 (18.2)	2 (50.0)	
Partial response	31 (49.2)	18 (50.0)	13 (59.1)	0 (0.0)	
Very good partial response	19 (30.2)	17 (47.2)	2 (9.1)	0 (0.0)	
Median time to response, months					
Major response (≥ partial response)	1.8	1.8	4.7	NA	.0200

NOTE. Data presented as No. (%). Response rates, including categorical responses and median time to attainment of least a minor and a major response for all patients and those stratified by *MYD88* and *CXCR4* mutation status, are provided. *P* values denote three-way comparisons among genomic cohorts.

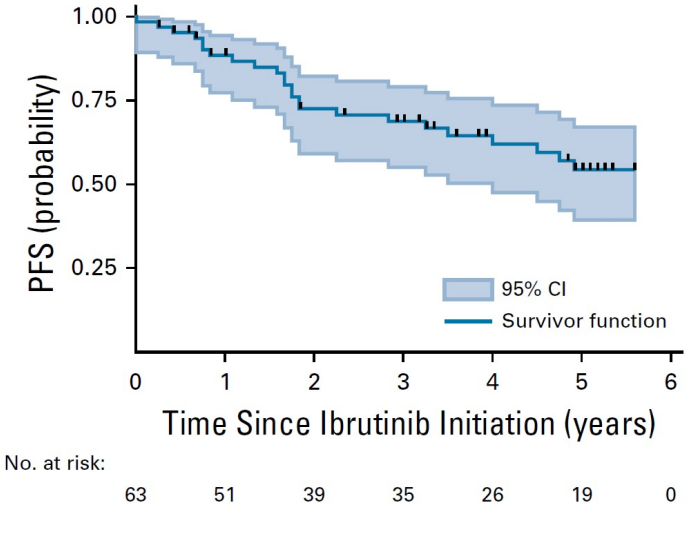
Abbreviations: Mut, mutant; NA, not applicable; WM, Waldenström macroglobulinemia; WT, wild type.

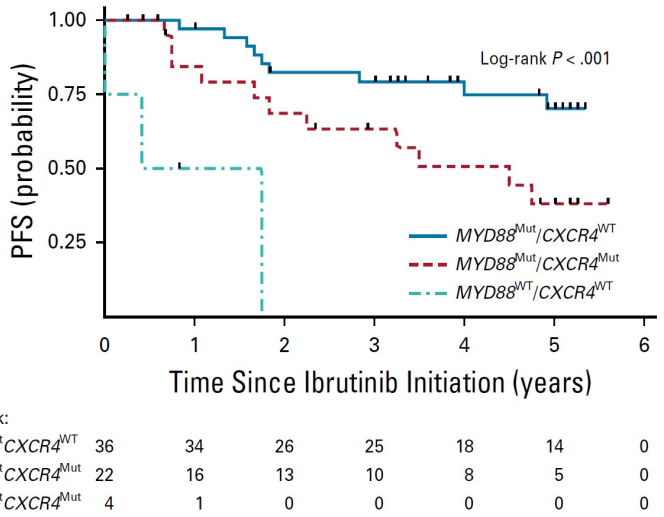
Treon SP et al. J Clin Oncol 2021

RELAPSED/REFRACTORY WM

Ibrutinib Phase II study

Median study follow-up: 59 months





By multivariable analysis:

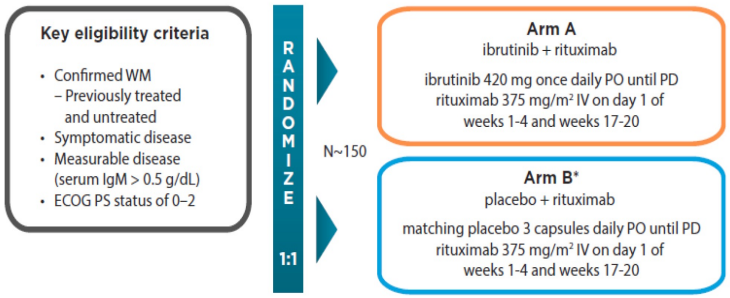
- **BM involvement 50%,**
- **prior treatment with three or more lines of therapy**
- **presence of $MYD88_{WT}$, and $CXCR4_{Mut}$ disease**

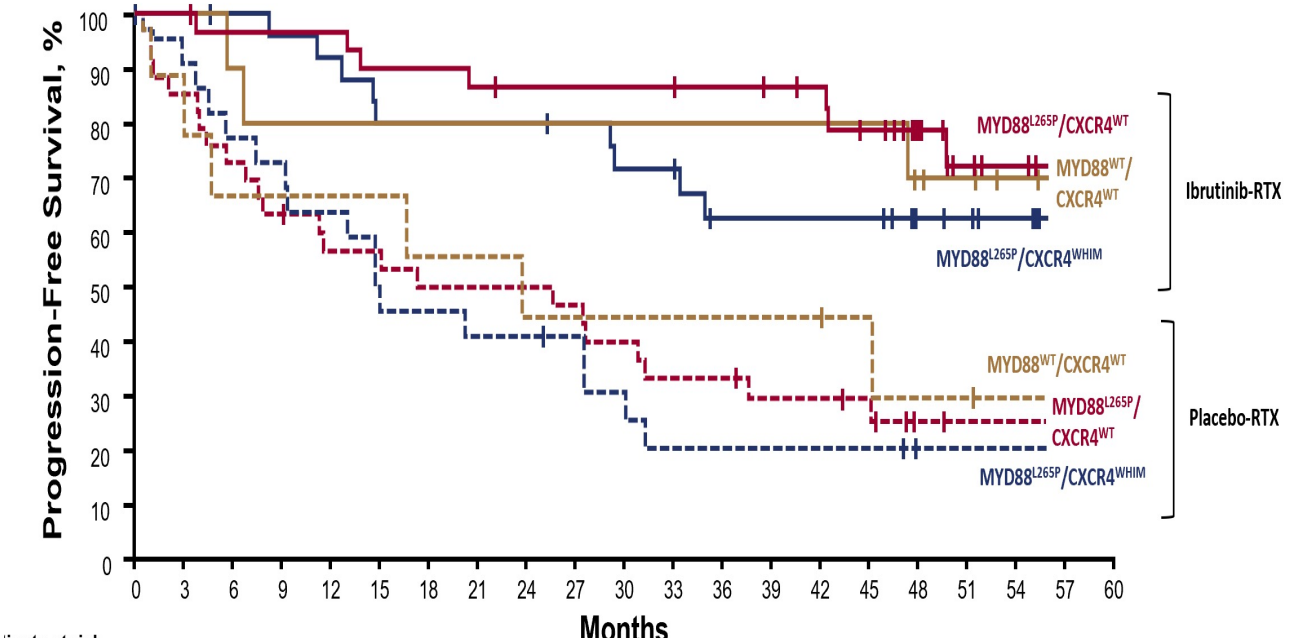
were significant predictors for shorter PFS

Treon SP et al. J Clin Oncol 2021

RELAPSED/REFRACTORY WM

Innovate Study: Ibrutinib plus R *vs* Placebo plus R (Innovate study)





Buske et al., 2020

RELAPSED/REFRACTORY WM

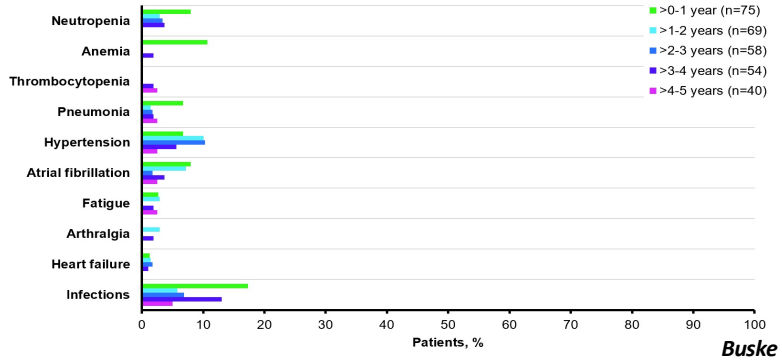
Ibrutinib Toxicity

Safety in 63 RR pts, median FU 59 m

- 12.7% atrial arrhythmia
- 19% patients experienced dose reductions

Treon et al.JCO 2020

Prevalence of Grade ≥3 AEs of Clinical Interest With Ibrutinib-RTX



Buske et et al ,2020

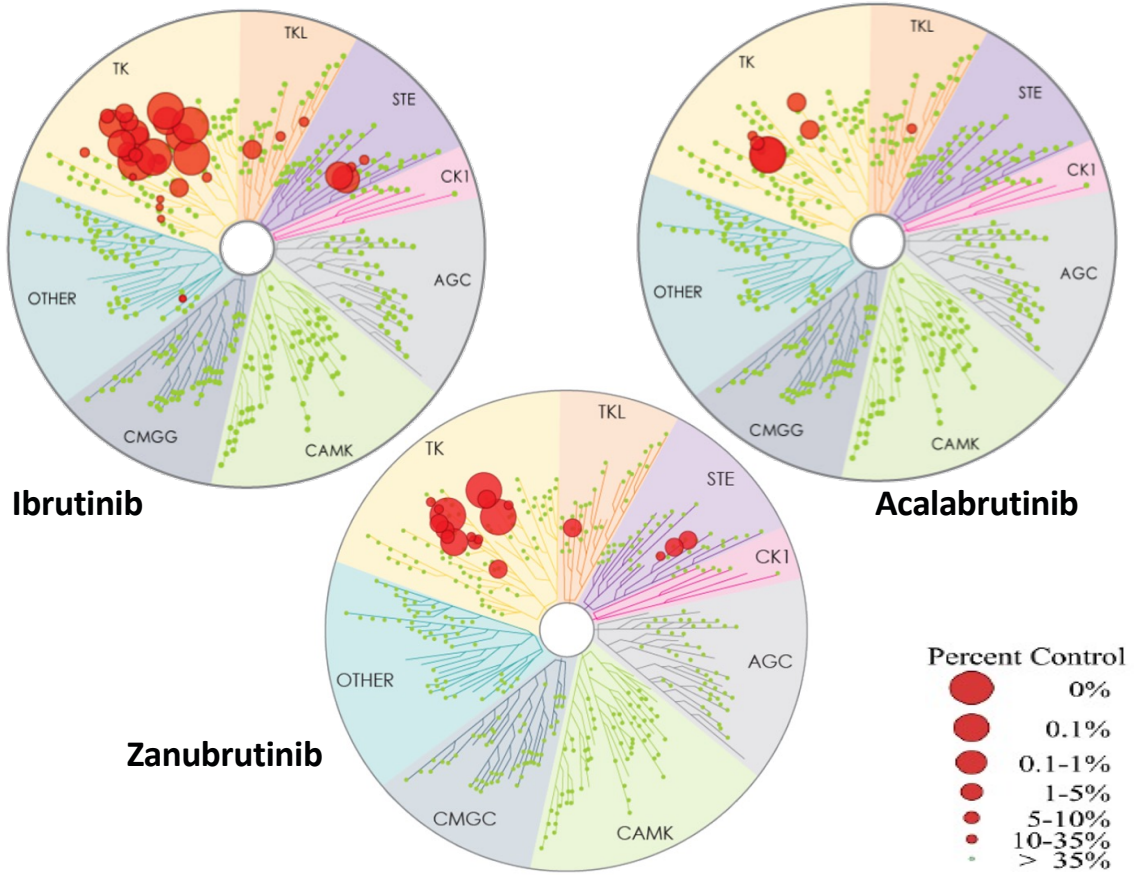
Second generation BTKi

Kinase Selectivity Profiles

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
	IC_{50}/EC_{50} (nM)		
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	>1000	50
BMX	0.8	46	1.4
EGFR	5.3	>1000	21
ERBB4	3.4	16	6.9
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5

Kinase Selectivity Profiling at 1 µmol/L (in vitro)

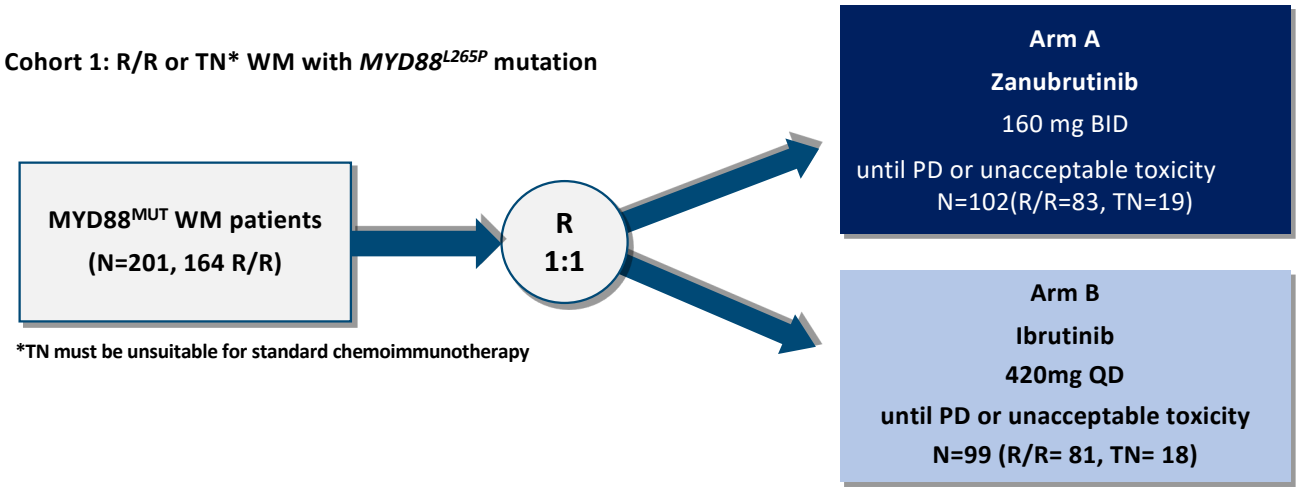
Larger red circles represent stronger inhibition



Kaptein. ASH 2018. Abstr 1871.

ZANUBRUTINIB IN WM

ASPEN STUDY: Zanubrutinib vs Ibrutinib



Primary endpoint:

superiority of zanubrutinib in terms of CR or VGPR, per modified IWWM6, by independent review

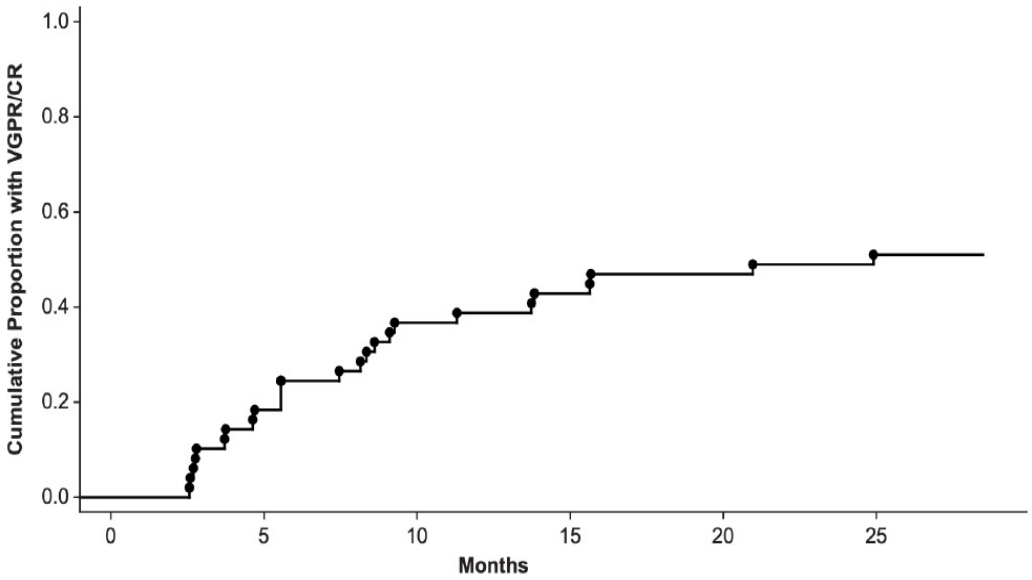
WM=Waldenström's macroglobulinemia, BID=twice daily, CR=complete response, ITT=intent-to-treat, MRR=major response rate, MUT=mutation, PD=progressive disease, PFS=progression-free survival, PR=partial response, QD=once daily, R=randomization, R/R=relapsed/refractory, TN=treatment naïve, VGPR=very good partial response, WM=Waldenström's macroglobulinemia, WT=wild type.

Tam CS et al., 2020

Phase 1/2 BGB-3111-AU-003 Study Efficacy Results

	TN (n = 24)	R/R (n = 49)	Total (N = 73)
Duration of follow-up, median, mo	23.5	35.8	30.3
Best overall response, n (%)			
CR	0	1 (2.0)	1 (1.4)
VGPR	8 (33.3)	24 (49.0)	32 (43.8)
PR	13 (54.2)	14 (28.6)	27 (37.0)
MR	3 (12.5)	7 (14.3)	10 (13.7)
SD	0	3 (6.1)	3 (4.1)
PD	0	0	0
VGPR/CR rate, % (95% CI)	33.3 (15.6-55.3)	51.0 (36.3-65.6)	45.2 (33.5-57.3)
VGPR/CR rate by genotype, % (95% CI)			
MYD88^{L265P}/*CXCR4*^{WT} (n = 39)			59.0 (42.1-74.4)
MYD88^{L265P}/*CXCR4*^{WHIM} (n = 11)			27.3 (6.0-61.0)
MYD88^{L265P}/*CXCR4*^{FS} (n = 6)			33.3 (4.3-77.7)
MYD88^{L265P}/*CXCR4*^{NS} (n = 5)			20.0 (0.5-71.6)
MYD88^{WT} (n = 8)			25.0 (3.2-65.1)
ORR (MR or better), % (95% CI)	100.0 (85.8-100.0)	93.9 (83.1-98.7)	95.9 (88.5-99.1)
MRR (PR or better), % (95% CI)	87.5 (67.6-97.3)	79.6 (65.7-89.8)	82.2 (71.5-90.2)

VGPR/CR Rate Increases Over Time (R/R Pts WM Cohort)

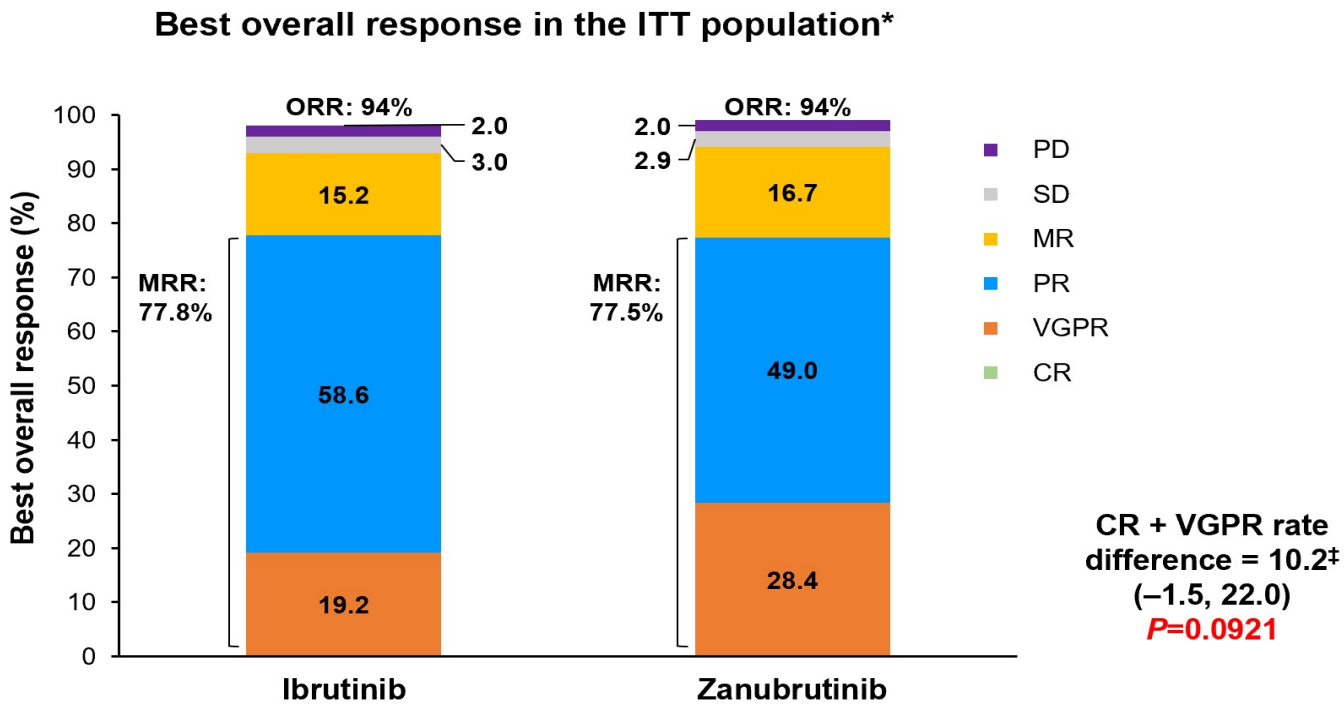


Trotman et al 2020

ZANUBRUTINIB IN WM

ASPEN STUDY: Zanubrutinib vs Ibrutinib
Efficacy According to IRC

- Superiority **in CR + VGPR rate** for zanubrutinib compared with ibrutinib in the R/R population (primary study hypothesis) was not significant

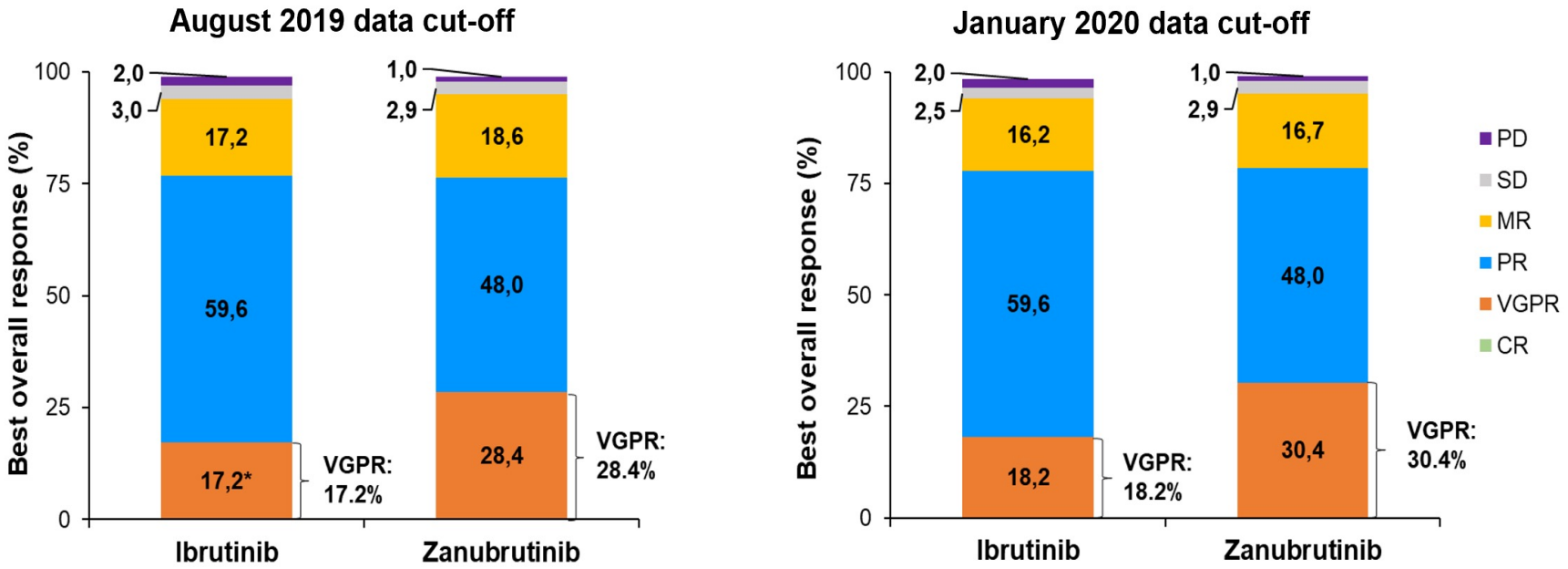


Overall concordance between IRC and investigators = 94%. *Data cut-off: August 31, 2019. ‡Adjusted for stratification factors and age group.
CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MR, minor response; MRR, major response rate; ORR, overall response rate; PD, progressive disease, PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good partial response.
Tam CS *et al*. Abstract 8007 presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting (virtual); May 29–31, 2020.

Tam CS et al., 2020

ZANUBRUTINIB IN WM

ASPEN STUDY: Zanubrutinib vs Ibrutinib
Efficacy According to Investigators



IgM reduction: AUC for IgM reduction over time was significantly greater for zanubrutinib vs. ibrutinib (*P*=0.037)

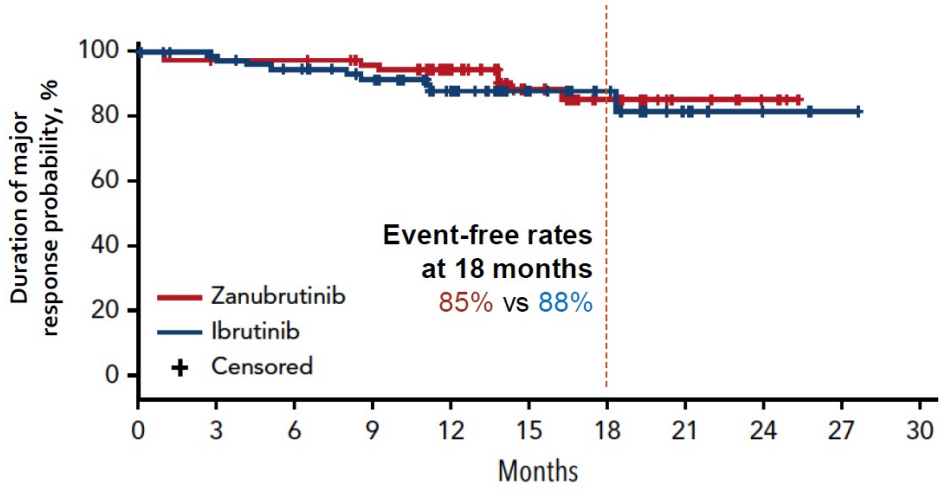
*Excluded 2 patients with VGPR by IRC: MR (extramedullary disease present) and PR (immunoglobulin M assessment by local serum protein electrophoresis M-protein test).
AUC, area under the curve; CR, complete response; IgM, immunoglobulin M; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Tam CS et al., 2020

ZANUBRUTINIB IN WM

Zanubrutinib vs Ibrutinib: Duration of major response and CR/VGPR

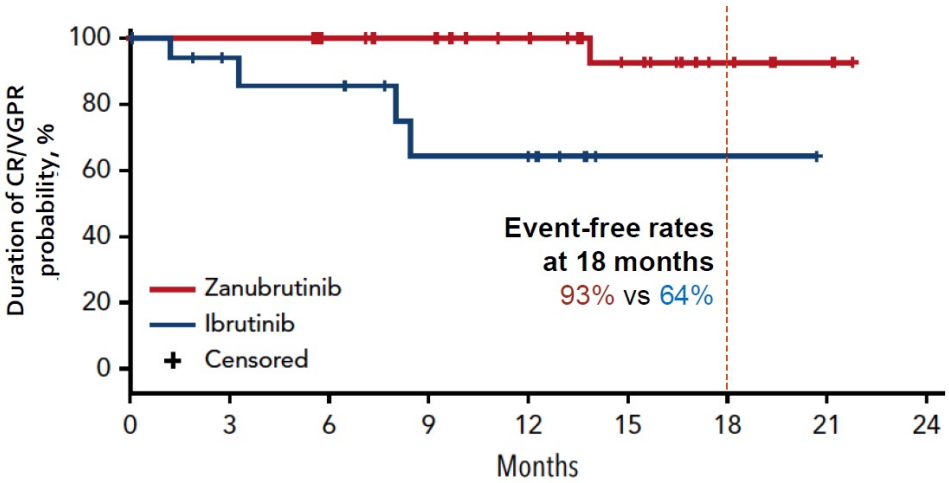
Duration of major response



No. of Patients at Risk

Zanubrutinib	79	72	71	66	52	32	21	10	6	0
Ibrutinib	77	72	67	59	44	29	15	7	3	1	0

Duration of CR/VGPR



29	27	24	22	18	12	5	2	0
19	11	10	6	5	1	1	0	

- CR, complete response; VGPR, very good partial response.

Tam CS et al., Blood 2020

ZANUBRUTINIB IN WM

Zanubrutinib vs Ibrutinib: Tollerability

Category, n (%)	Zanubrutinib (n=101)	Ibrutinib (n=98)
Patients with ≥1 AE	98 (97.0)	97 (99.0)
Grade ≥3	59 (58.4)	62 (63.3)
Serious	40 (39.6)	40 (40.8)
Fatal AEs	1 (1.0)*	4 (4.1)‡
AEs leading to treatment discontinuation	4 (4.0)†	9 (9.2)§
AEs leading to dose reduction	14 (13.9)	23 (23.5)
AEs leading to dose held	47 (46.5)	55 (56.1)
Patients with ≥1 treatment-related AE	80 (79.2)	84 (85.7)
Patients with ≥1 AE of interest	86 (85.1)	81 (82.7)

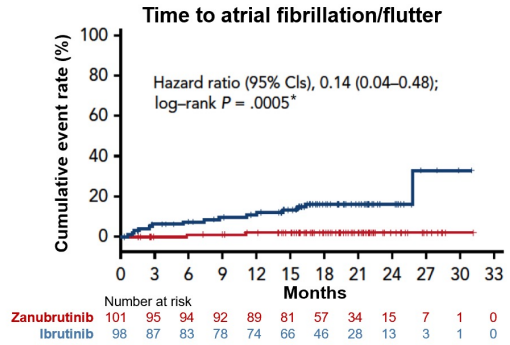
- *Cardiac arrest after plasmapheresis. †G5 cardiac arrest after plasmapheresis; G4 neutropenia; G4 subdural hemorrhage; G2 plasma cell myeloma. ‡Cardiac failure acute; sepsis (n=2); unexplained death. §G5 sepsis (n=2); G5 unexplained death; G3 acute myocardial infarction; G3 hepatitis; G3 pneumonia; G2 drug-induced liver injury; G2 pneumonitis; G1 pneumonitis.
- AE, adverse event.

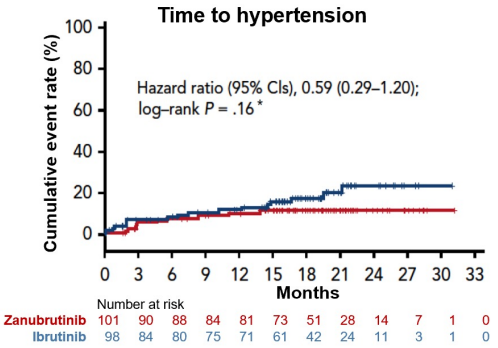
Tam CS et al., Blood 2020

ZANUBRUTINIB IN WM

Zanubrutinib vs Ibrutinib: AE of interest

Event preferred term, n (%)	All grades (≥20%)		Grade ≥3 (≥5%)	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/Flutter	**18 (18.4)**	3 (3.0)	7 (7.1)	0 (0.0)
Diarrhea (PT)	**32 (32.7)**	22 (21.8)	2 (1.0)	3 (3.0)
Hemorrhage	**59 (60.2)**	51 (50.5)	9 (9.2)	6 (5.9)
Major hemorrhage	10 (10.2)	6 (5.9)	9 (9.2)	6 (5.9)
Hypertension	20 (20.4)	13 (12.9)	**15 (15.3)**	8 (7.9)



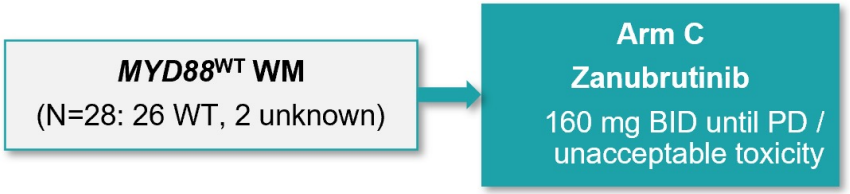


AE, adverse event; CI, confidence interval; PT, preferred term.

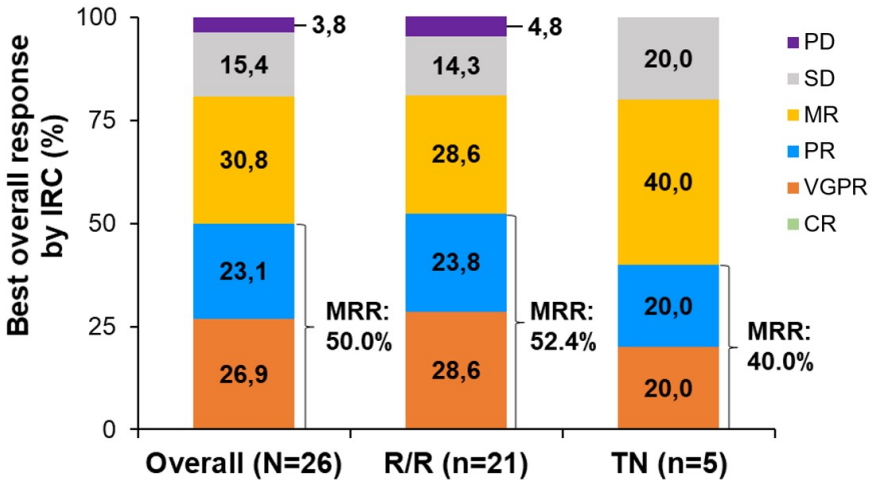
Tam CS et al., Blood 2020

ZANUBRUTINIB IN WM

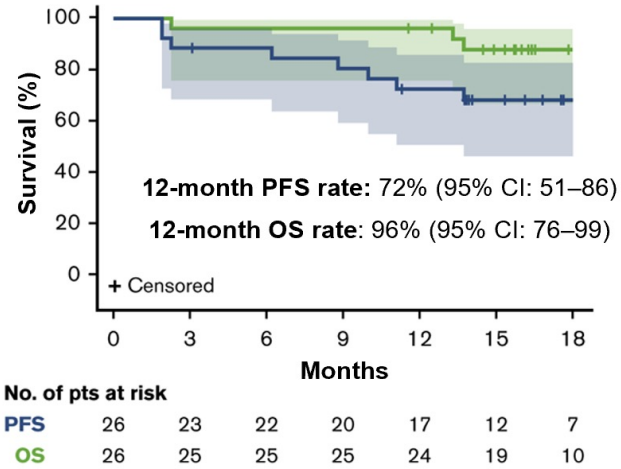
Zanubrutinib in MYD88^{wt}



Best overall response in R/R or TN WM



Survival in R/R or TN† WM



BID, twice a day; CI, confidence interval; CR, complete response; IRC, independent review committee; MR, minimal response; MRR, major response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; pts, patients; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive; VGPR, very good partial response; WM, Waldenström's macroglobulinemia; WT, wild-type..

Dimopoulos M et al. 2020

WHAT COMES NEXT IN WM?

Proteasome inhibitors

First Line

CARFILZOMIB

Induction (q 21 days x 6 cycles)
iv CFZ, DEXA, Rituximab

Maintenance: (every 8 w for 8 cycles)
iv CFZ, DEXA, Rituximab

Median PFS: 51 m

ORR: 87.1%

MR: 67.7%

CR/VGPR: 36%

IXAZOMIB

Induction: (q 21 days x 6 cycles)
Oral Ixazomib, DEXA, Rituximab

Maintenance: (every 8 w for 8 cycles)
iv CFZ, DEXA, Rituximab

18 m PFS: 90%

ORR: 96%

MR: 77%

VGPR: 15%

Low Neuropathy Rate: ~20%
Grade 2: 0
Grade 3: 3,2%

NO impact from CXCR4 mut

Treon et al, 2014; Meid et al, 2018 Castillo et al, 2018

Relapsed Refractory

Induction:
8 cycles q28 days

- Ixazomib citrate 4 mg d1,8,15
- Rituximab 1400 mg sc d1
  cycle 3-8 (1st dose iv)
- Dexamethasone 20 mg d1,8,15,22

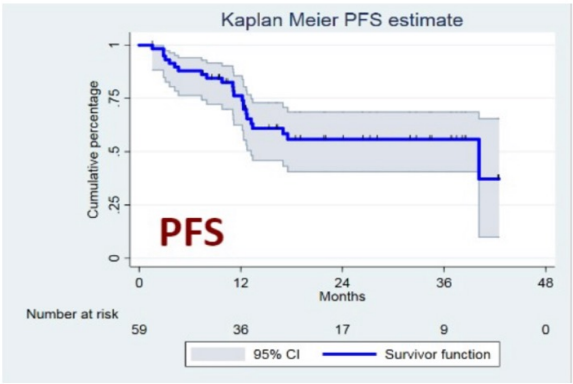
> SD

Maintenance:
2 years q3months

- Rituximab 1400 mg sc d1

59 pts
Mdian prior tx: 2

ORR:	**85%**
VGPR:	**15%**
PR	**46%**

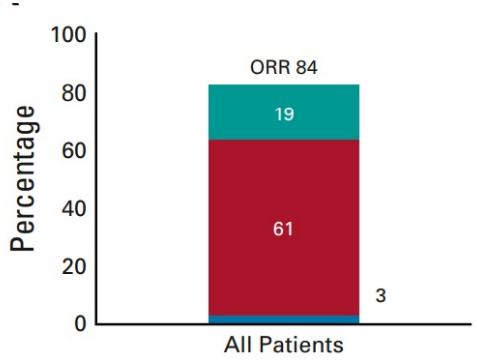


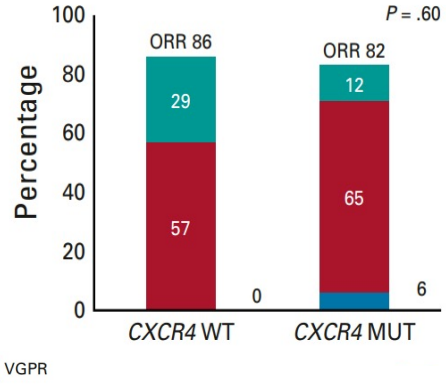
Kersten et al, 2019

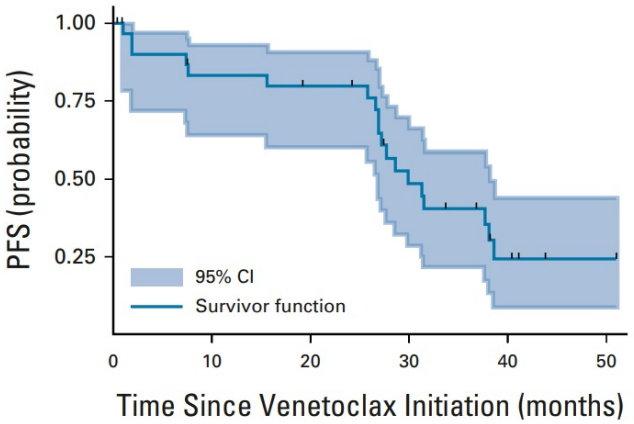
WHAT COMES NEXT IN WM?

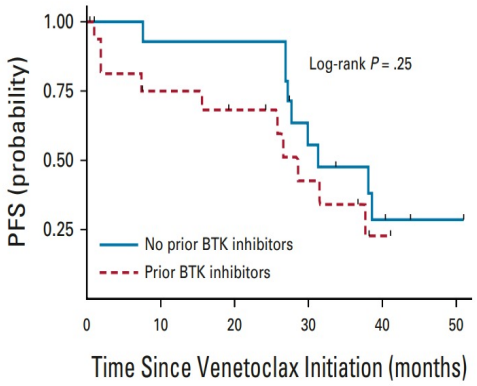
Venetoclax Monotherapy

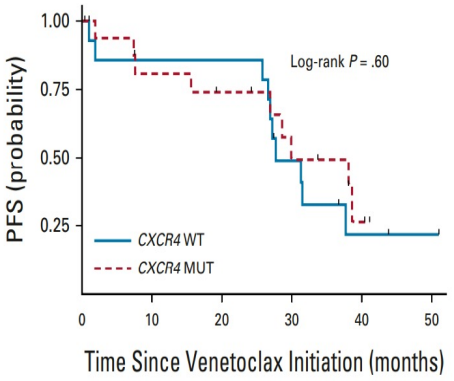
32 pts	
Median prior Tx:	**2(1-10)**
Prior BTKi:	**66%**
MYD88^{mut}:	**100%**
CXCR4^{mut}:	**53%**







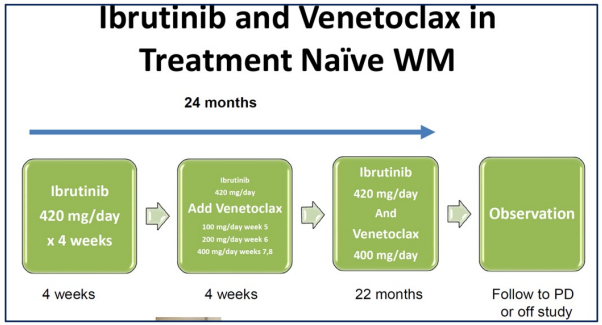




Castillo et al 2021

WHAT COMES NEXT IN WM?

Combination treatments to allow therapy discontinuation



New target agents

- ✓ **Pirtobrutinib (19 WM: ORR 68% no difference if prior BTKi)**
- ✓ **Anti MALT1** Mato et al 2021
- ✓ **Anti ERK in combination with Ibrutinib**

Daratumumab

- ✓ **Monotherapy: 23%ORR, median PFS 2 m** Castillo et al 2020
- ✓ **In combination with Ibrutinib:ongoing**

European Study Ongoing: Phase II randomized study (CZAR-1)

- **Carfilzomib Ibrutinib**
- **Ibrutinib**

HOT NEWS IN WM CONCLUSIONS

Conclusions

FIRST LINE

- **The choice of primary therapy should be personalized (consider toxicity, patients and disease characteristics)**

- **Allthough there is a lack of of prospective randomised studies consensus that DRC or Bendamustine Rituximab are preferred options**

- **Monotherapy may be a choice in unfit patients (BTKi)**

RELAPSED/REFRACTORY

- **BTKi best salvage regimens**
  - **Zanubrutinib: better tolerability=adhererence dose intesnity**

- **Everyday clinical practice: Lack of salvage regimens after BTKi failure!!!!**