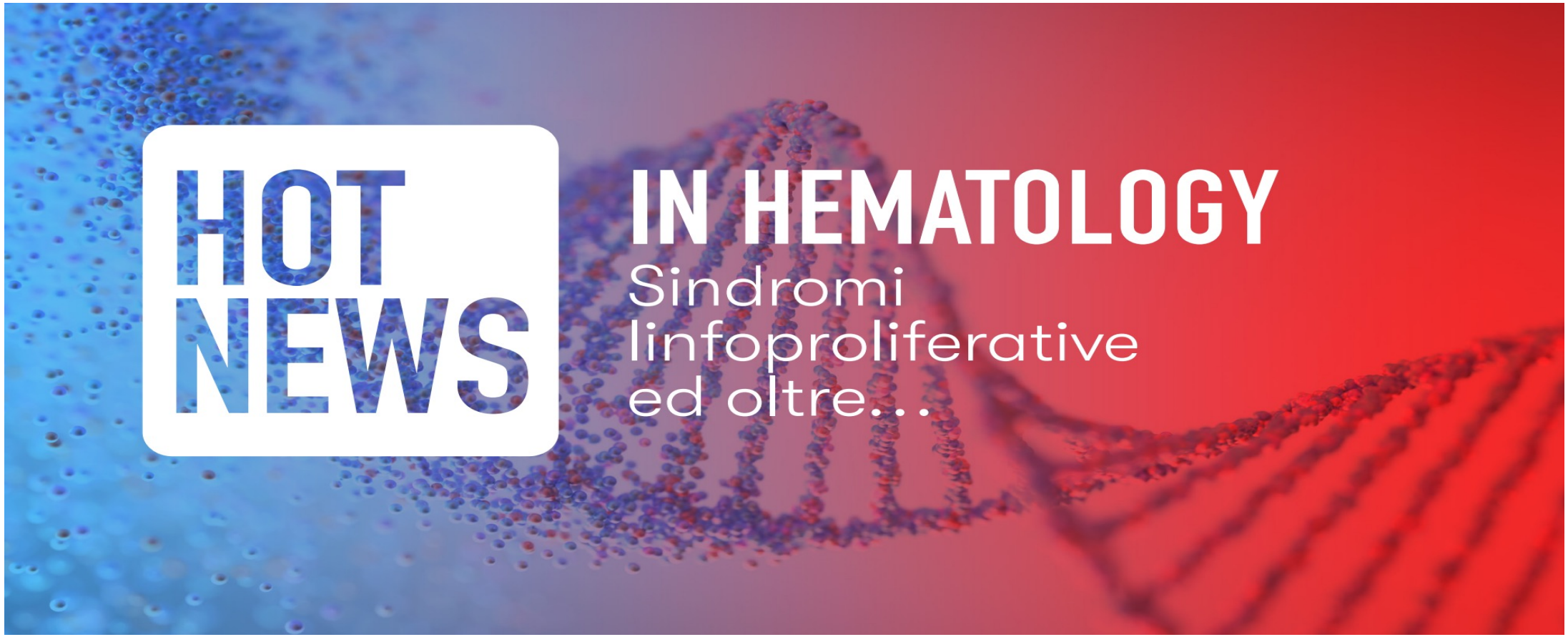
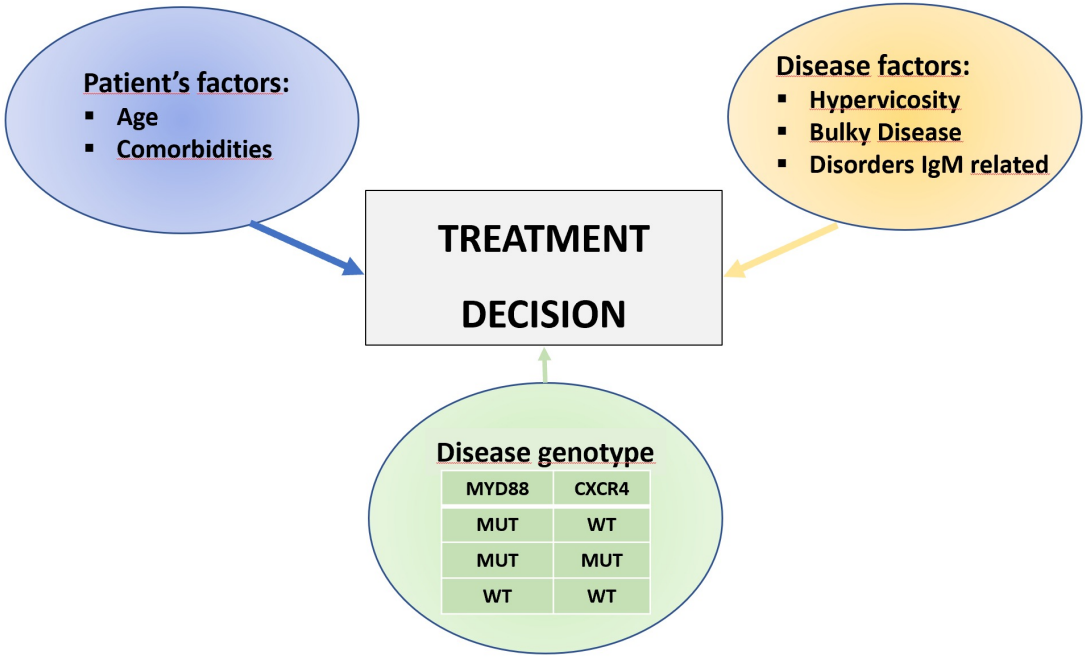


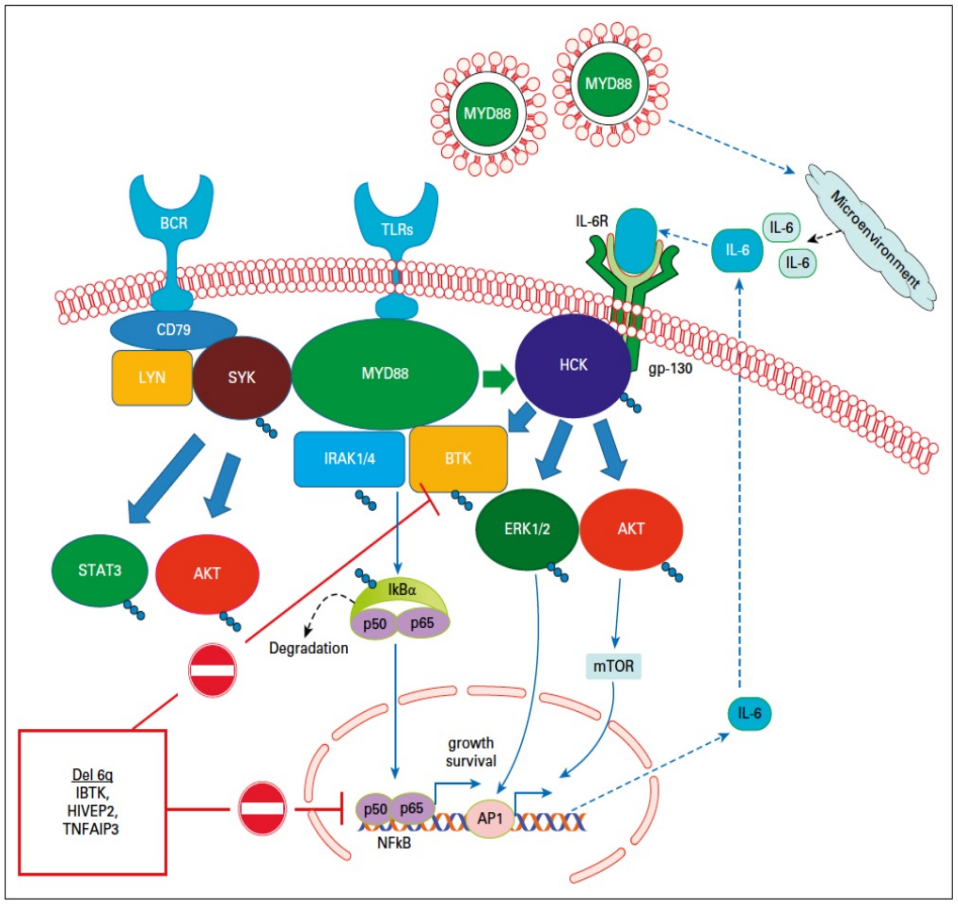
MACROGLOBULINEMIA DI WALDENSTROM

Alessandra Tedeschi
Division of Hematology
Niguarda Hospital, MIlano

WM TREATMENT



MYD88 in WM

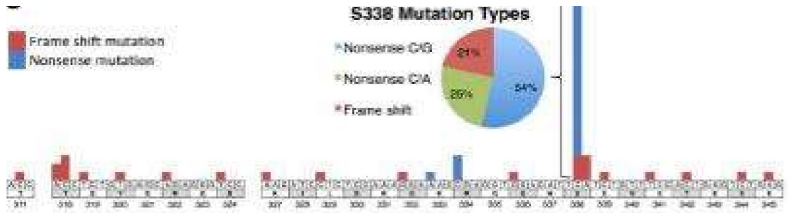


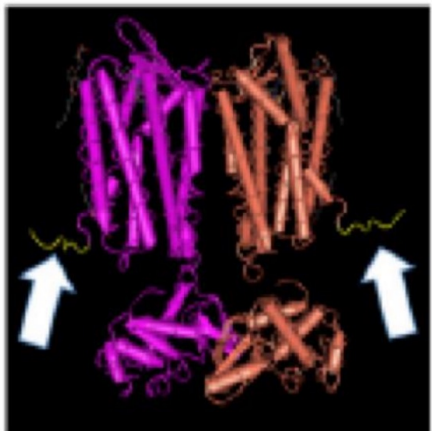
- ~ 95% of WM patients carry the somatic mutation of MYD88 (L265P)
- MYD88, IRAK1/IRAK4 and BTK are components of the Myddosome complex that activates NFKB
- Mutated MYD88 upregulates hematopoietic cell kinase (HCK) transcription and activates HCK via Il-6. Activated HCK promotes survival through BTK, 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

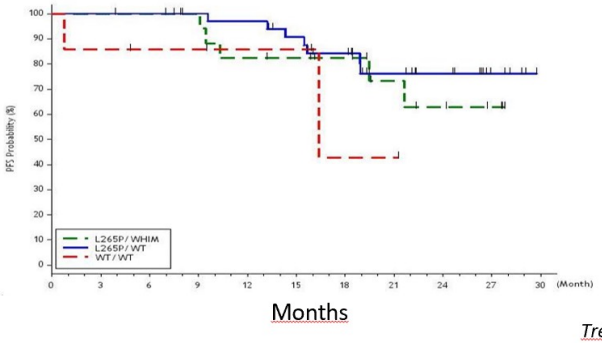
- ✓ **higher IgM levels**
- ✓ **higher incidence of hyperviscosity**
- ✓ **higher BM infiltration**
- ✓ **shorter time to first treatment**

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

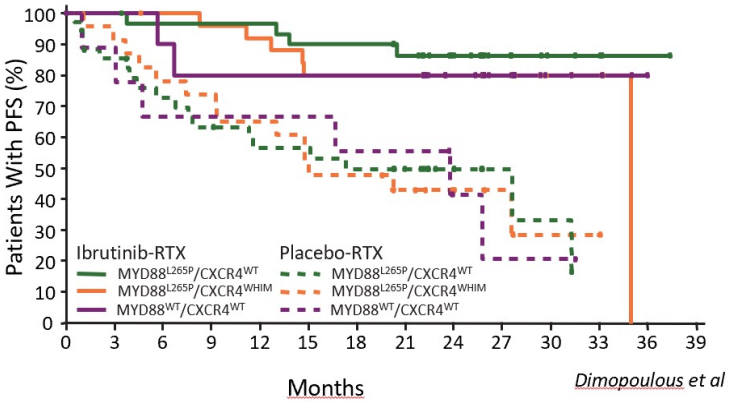
WM TREATMENT

PFS according to MYD88 & CXCR4 mutation status

Ibrutinib Monotherapy R/R

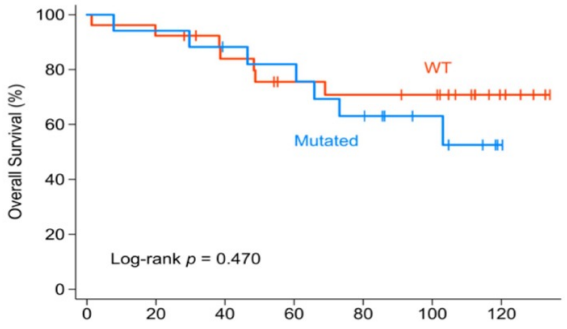


Treon et al, 2015



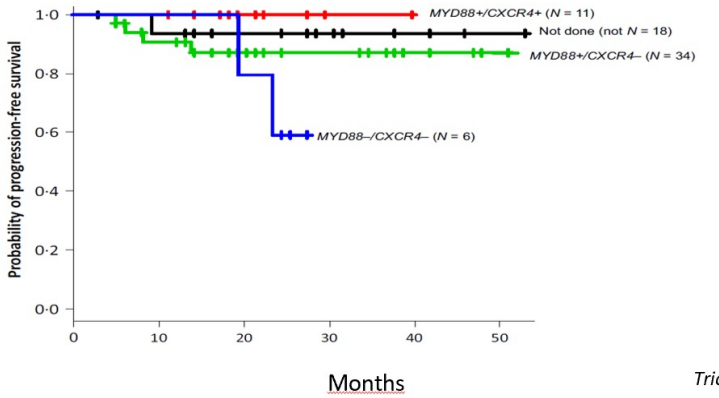
Dimopoulous et al 2018

Bortezomib Rituximab First Line according to CXCR4



Sklavenitis et al, 2018

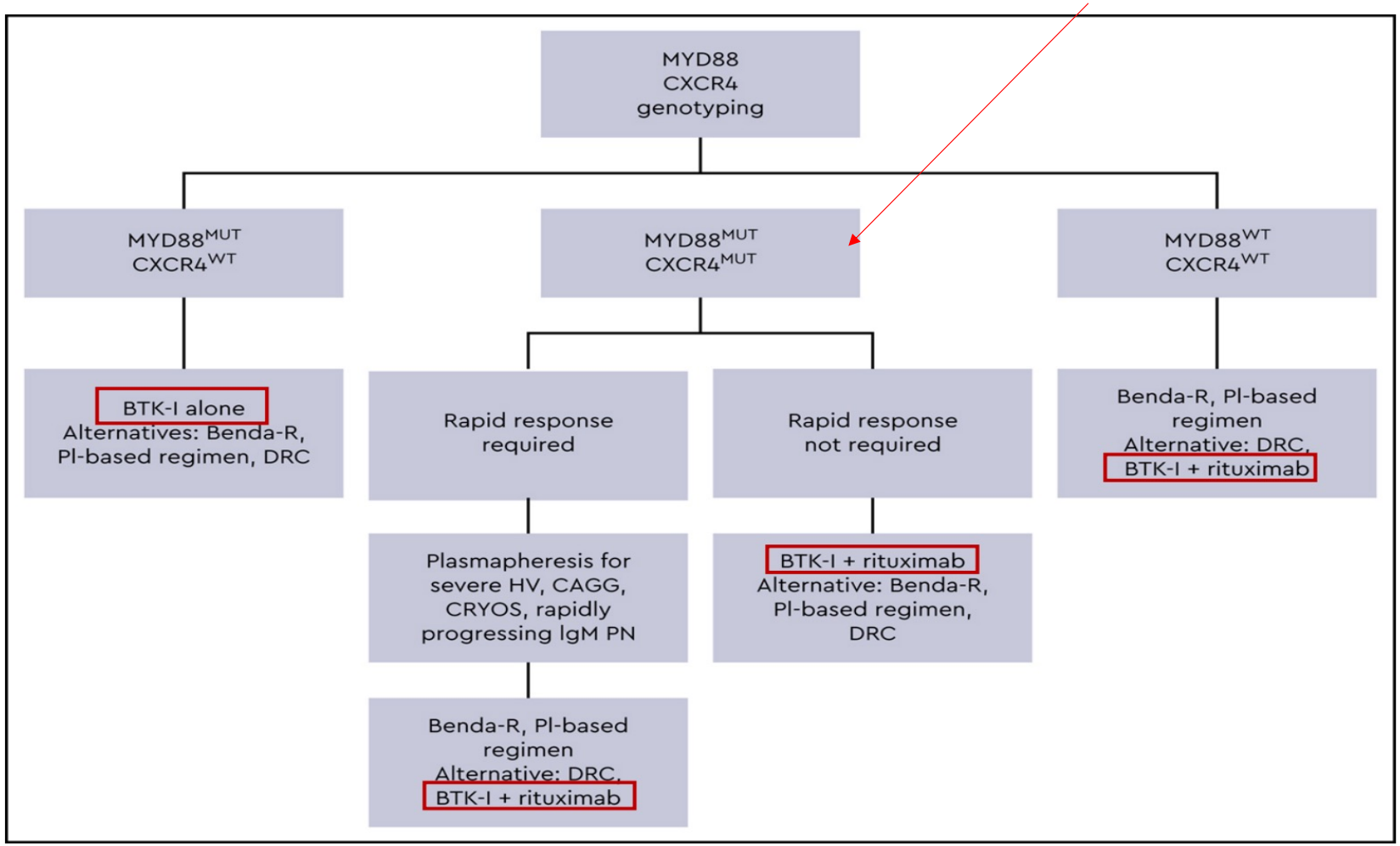
Bendamustine Rituximab First Line



Tricot et al, 2018

WM: Genomic based treatment algorithm

Pre Alpine Trial follow-up…….

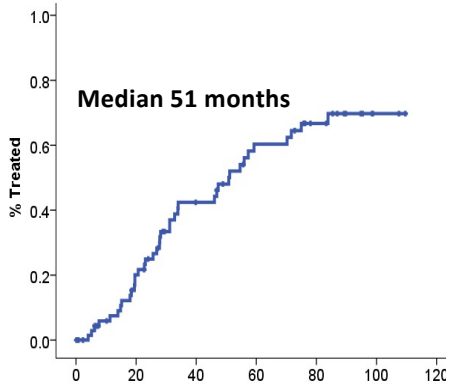


Treon et al. JCO 2020

WM TREATMENT FIRST LINE TREATMENT

Rituximab Combination Treatment

DRC



PROS:

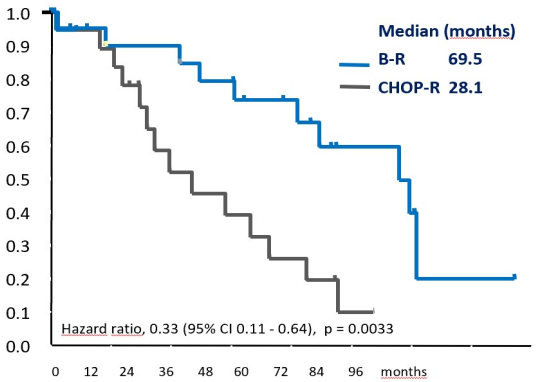
- ✓ **Minimal myelo/immuno-suppression**
  89% pts completed 6 courses
- ✓ **TTN 51 m**

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**

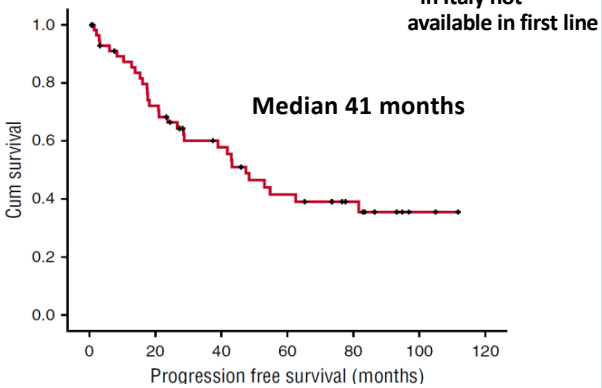
CONS:

- **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**

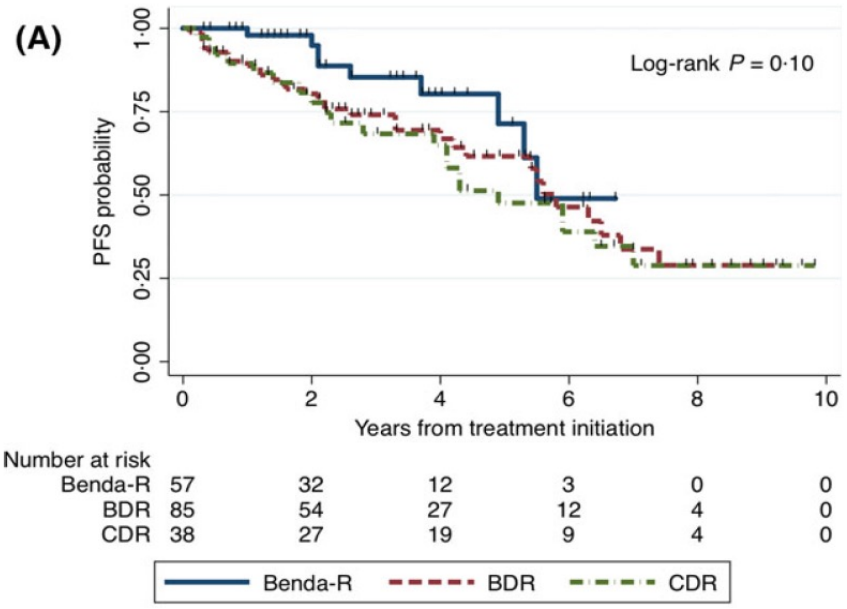
Treon et al, 2009-2015

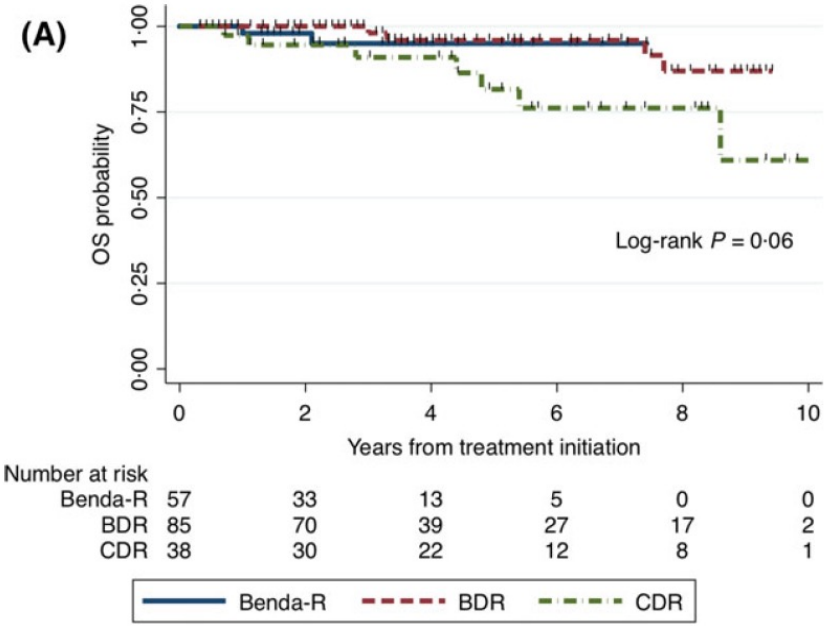
WM TREATMENT FIRST LINE TREATMENT

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





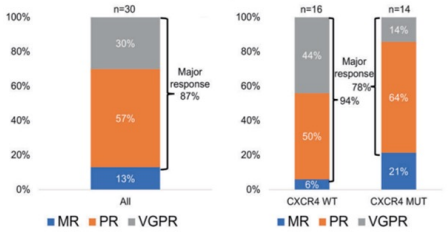
Castillo et al, 2009-2019

WM TREATMENT FIRST LINE TREATMENT

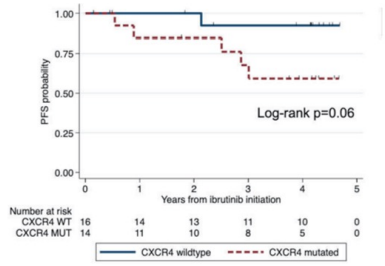
BTKi

Ibrutinib° in MYD88^{mut}

median follow-up time of 50.1 m

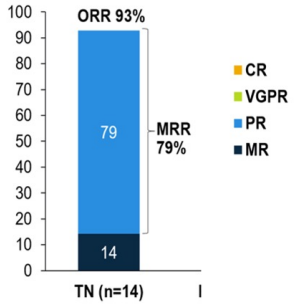


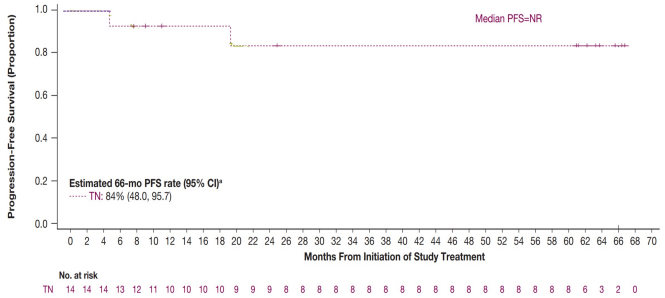
Median time to Major Response: 1.9 m
Median longer for pts with:
CXCR4^{mut} 7.3 m
CXCR4^{wt} 1.8 m
p = 0.02



Castillo et al., 2021

Acalabrutinib





Owen R et al., 2022

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

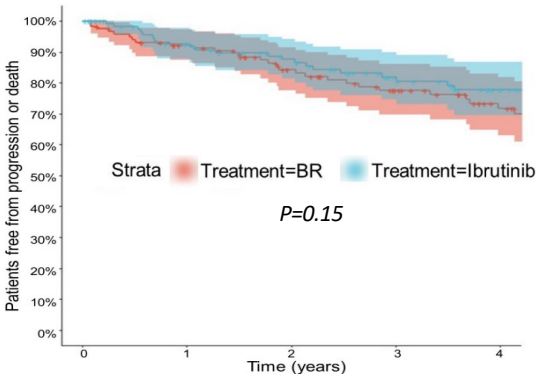
Bendamustine rituximab (BR) versus ibrutinib (Ibr) as primary therapy for Waldenström macroglobulinemia (WM): An international collaborative study

Multi-institutional, international study in Europe and the USA
Median follow-up: 4.2 years

347 TN pts:
- **208 BR**
- **139 ibrutinib**

1:1 age-matched analysis of 246 pts *MYD88*^{mut}
Ibrutinib (n=123) BR (n=123)
Significant higher responses with BR
Discontinuation due to AE: 13% BR and 33% ibrutinib

Progression-free survival



4-year OS: BR 95% (95% CI 91–99)
versus
Ibrutinib 86% (95% CI 80-93)
p=0.3

In a bivariate analysis adjusting for age and the treatment type only age emerged as a predictor for OS (HR 7.2, p=0.0001)

For patients with *MYD88* L265P mutation, selection between the two approaches should be dictated by:
- **Potential toxicities**
- **Patient comorbidities**
- **Patient/clinician preference (parenteral fixed duration vs. continuous oral)**
- **Access to therapies**

AE, adverse event; BR, bendamustine–rituximab; CI, confidence interval; HR, hazard ratio; MUT, mutant; OS, overall survival; PFS, progression-free survival; pts, patients; TN, treatment-naive; WM, Waldenström's macroglobulinemia.

Abeykoon JP *et al*. Abstract 7566 presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; Chicago, IL, USA, June 3–7, 2022.

WM TREATMENT FIRST LINE TREATMENT

UNFIT PATIENTS ➡ UNMET CLINICAL NEED

Rituximab mono

ORR 44-65%

Short PFS

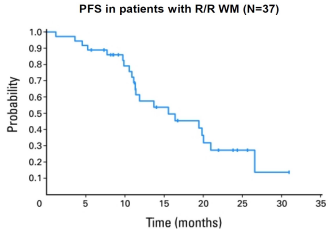
Effective in specific
IgM related sisease symptoms

Gertz et al , 2009
Dimopoulous et al, 2010

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

Median study follow-up: 59 months

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.

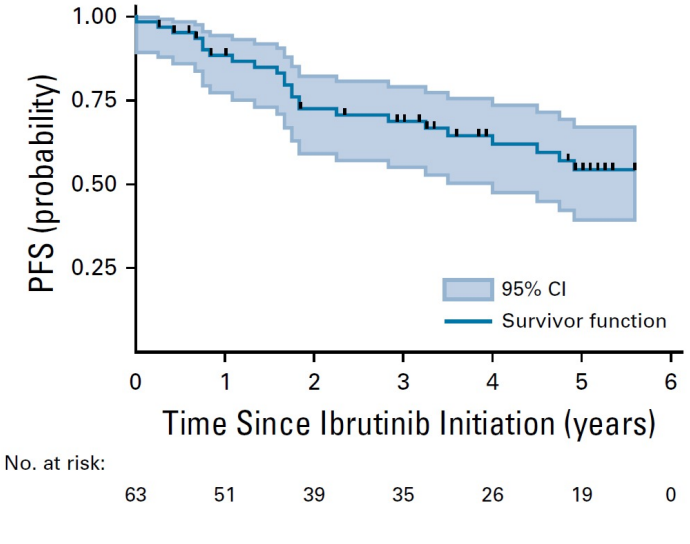
Abbreviations: Mut, mutant; NA, not applicable; WM, Waldenström macroglobulinemia; WT, wild type.

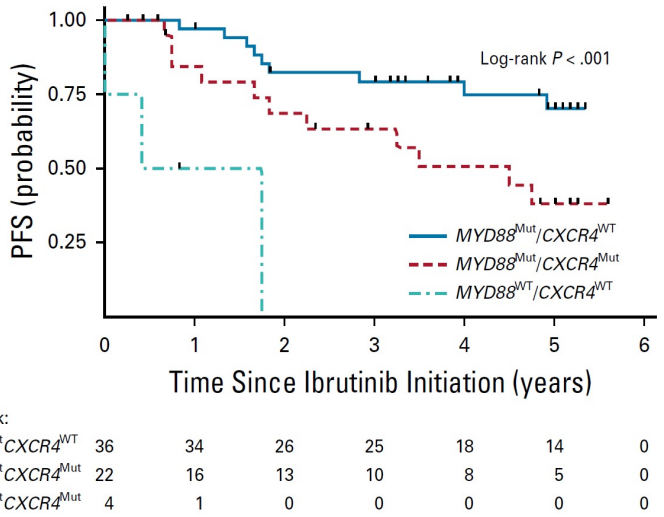
Treon SP et al. J Clin Oncol 2021

RELAPSED/REFRACTORY WM

Ibrutinib Phase II study

Median study follow-up: 59 months





By multivariable analysis:

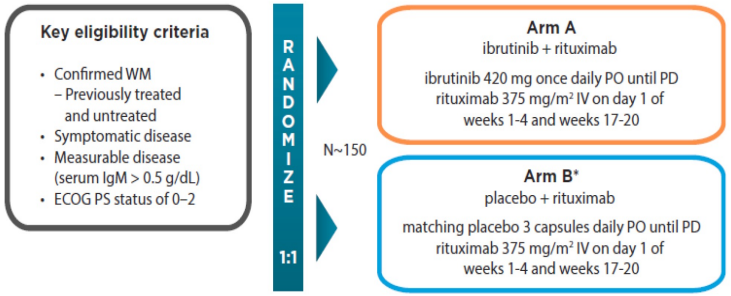
- **BM involvement 50%,**
- **prior treatment with three or more lines of therapy**
- **presence of $MYD88_{WT}$, and $CXCR4_{Mut}$ disease**

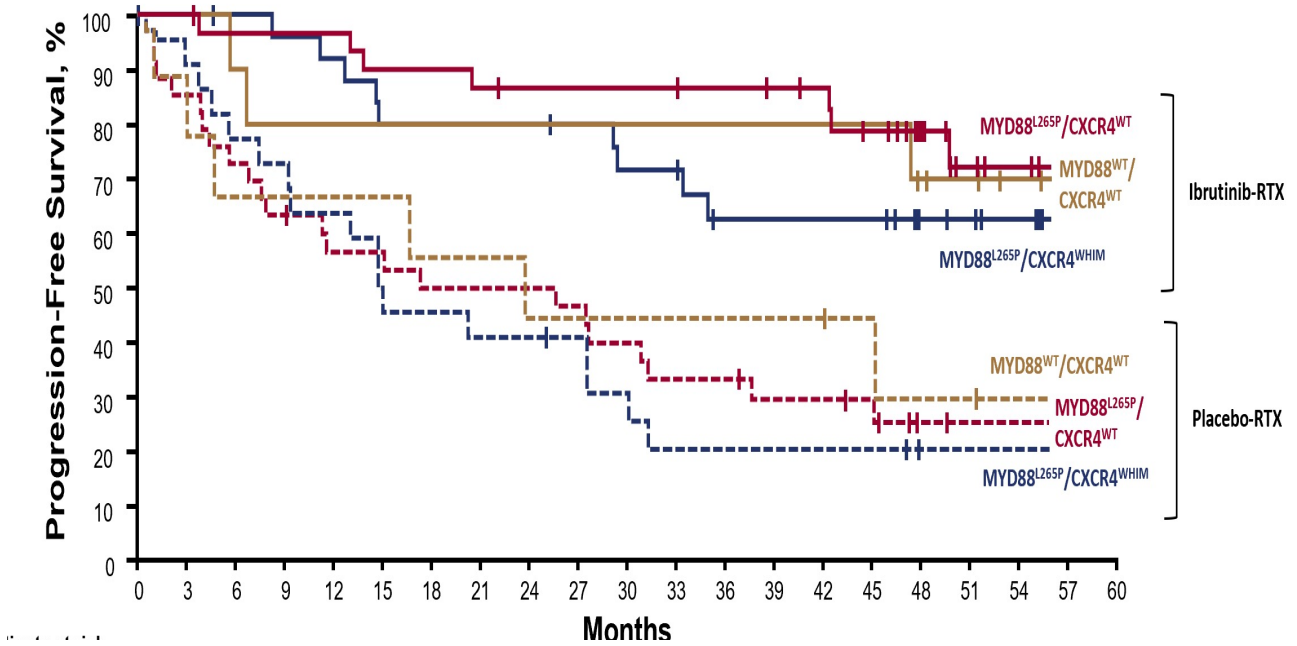
were significant predictors for shorter PFS

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

Ibrutinib in R/R WM Clinical Trials

Adverse Events/Tollerability

Ibrutinib monotherapy: phase II study

Median FU 59 m

Hematological AE Grade ≥ 3
- **Neutropenia: 15.9%**
- **Thrombocytopenia: 11.1%**

AE of interest with BTKi
- **Atrial arrhythmia any grade 12.7%**
- **Hypertension grade 2: 6%**
- **Pneumonia grade 2-4: 8%**

- ✓ ***8% off-study due to AE***
- ✓ ***19% dose reductions*** *(cytopenia, dermatitis/rash, stomatitis)*

Treon SP et al. J Clin Oncol 2021

Ibrutinib plus R: Innovate study

Median FU: 50 months

Hematological AE Grade ≥ 3
- **Neutropenia: 13%**
- **Thrombocytopenia: 1%**

- **AE of clinical interest any grade**
  - **Atrial fibrillation 19%**
  - **Hypertension: 25%**
  - **Infections≥3: 29%**

- ✓ ***11% off-study due to AE***
- ✓ ***23% dose reductions***

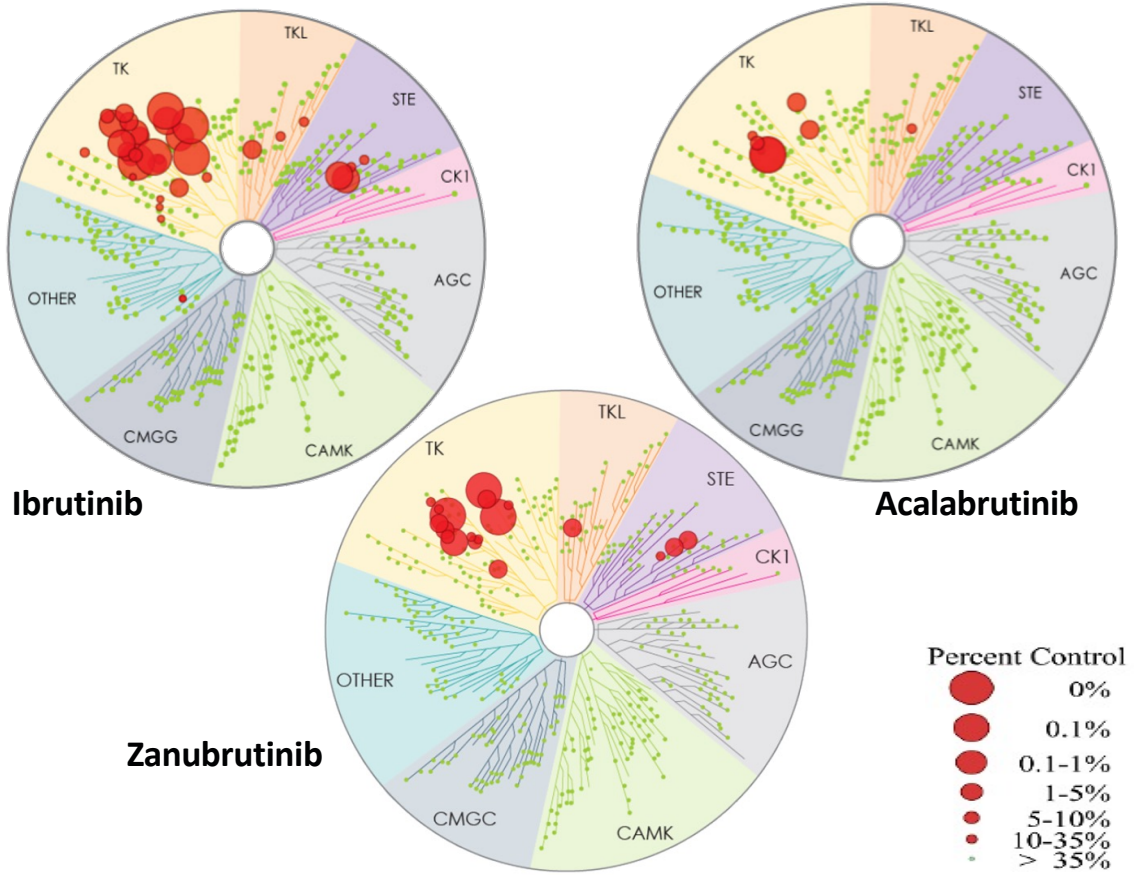
Buske C et al, JCO 2022

Second generation BTKi

Kinase Selectivity Profiles

Kinase	IC_{50}/EC_{50} (nM)		
	Ibrutinib	Acalabrutinib	Zanubrutinib
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

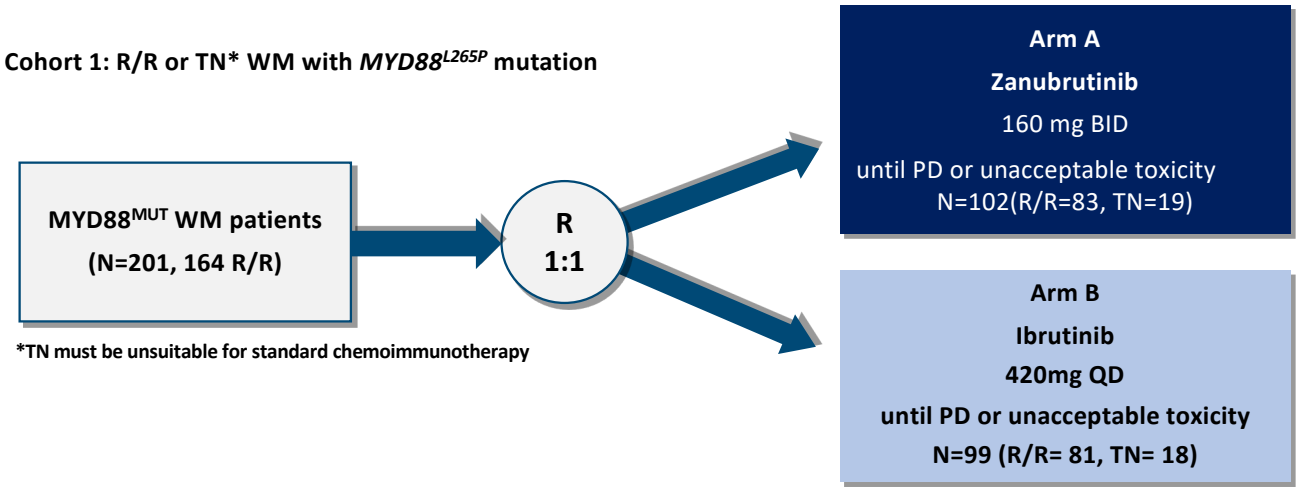
Kinase Selectivity Profiling at 1 µmol/L (in vitro)
Larger red circles represent stronger inhibition



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

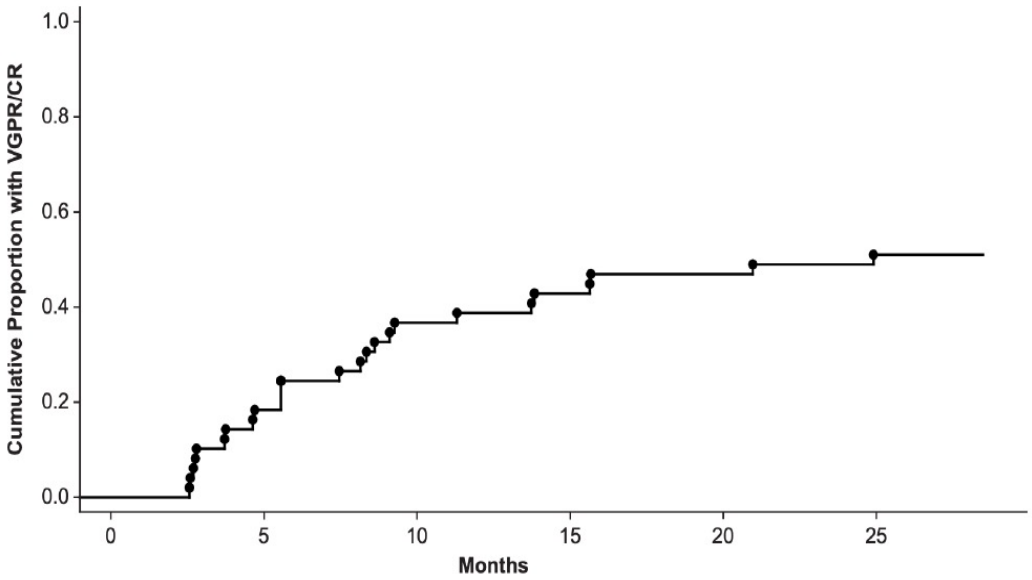
WM=Waldenström's macroglobulinemia, BID=twice daily, CR=complete response, ITT=intent-to-treat, MRR=major response rate, MUT=mutation, PD=progressive disease, PFS=progression-free survival, PR=partial response, QD=once daily, R=randomization, R/R=relapsed/refractory, TN=treatment naïve, VGPR=very good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

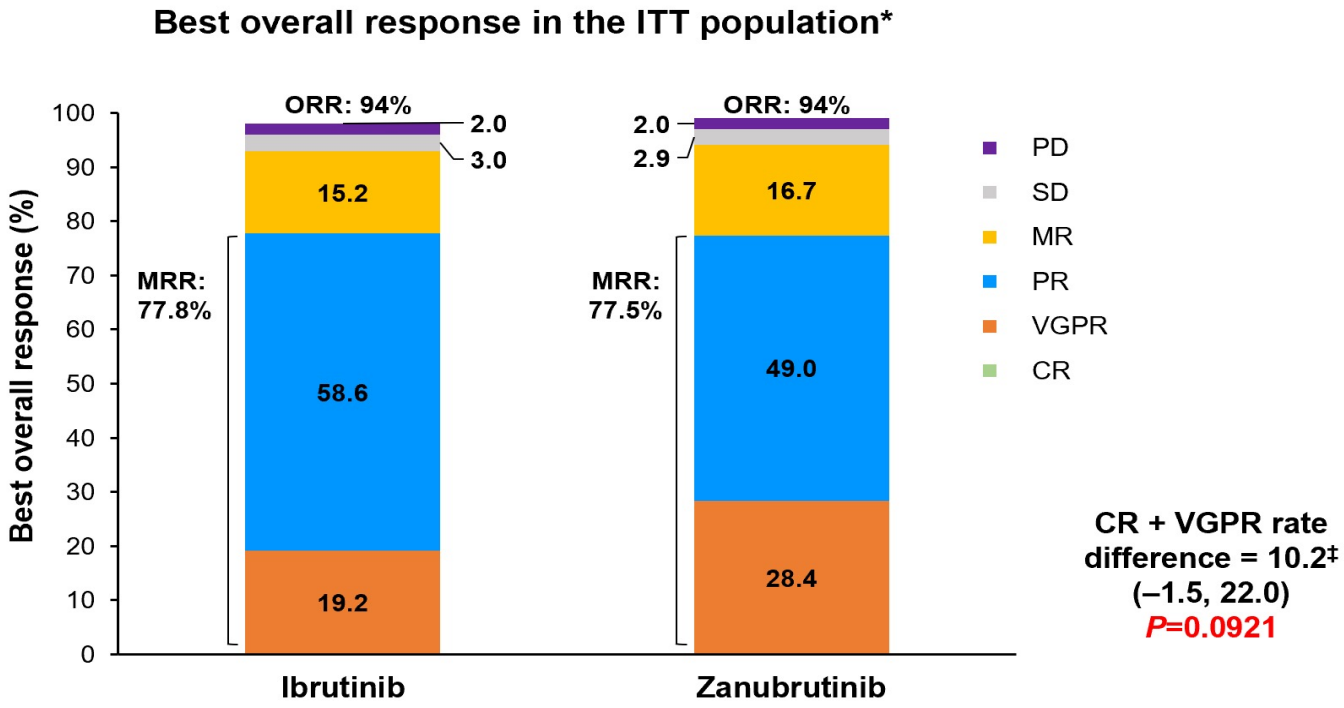
ZANUBRUTINIB IN WM

ASPEN STUDY: Zanubrutinib vs Ibrutinib

Efficacy According to IRC

Median Follow-up 19.4 m

- 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

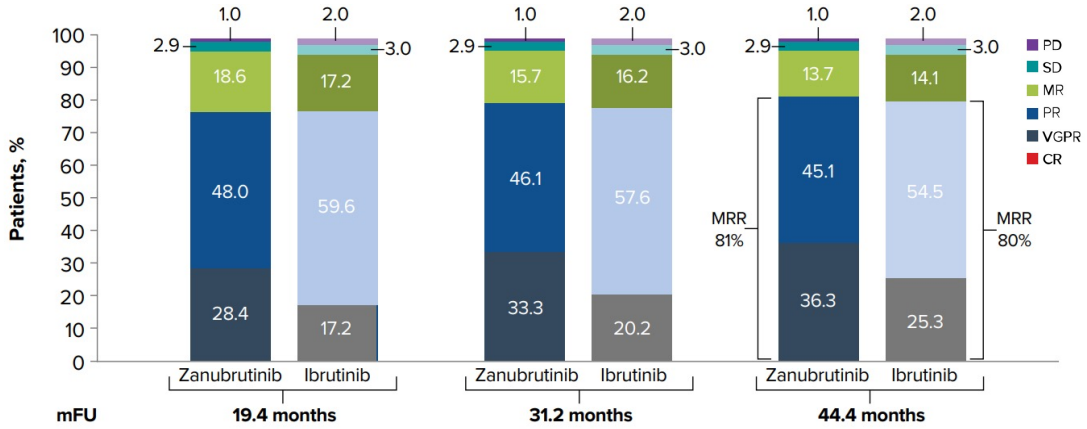
ZANUBRUTINIB IN WM

ASPEN STUDY: Zanubrutinib vs Ibrutinib

Efficacy

Follow-up 44 m

Responses by investigators



Median time to CR+VGPR:
shorter for zanubrutinib 6.7 m vs ibrutinib: 16.6 m

Responses by CXCR4 status

	$CXCR4^{MUT}$		$CXCR4^{WT}$	
	Ibrutinib (n=20)	Zanubrutinib (n=33)	Ibrutinib (n=72)	Zanubrutinib (n=65)
VGPR or better	2 (10.0)	**7 (21.2)**	22 (30.6)	**29 (44.6)**
Major response	13 (65.0)	**26 (78.8)**	61 (84.7)	54 (83.1)
Overall response	19 (95.0)	30 (90.9)	68 (94.4)	63 (96.9)
Time to major response, median (months)	6.6	3.4	2.8	2.8
Time to VGPR, median (months)	31.3	11.1	11.3	6.5

Primary objective ignificant superior CR+VGPR
According to IRC with zanubruitnib: not achieved

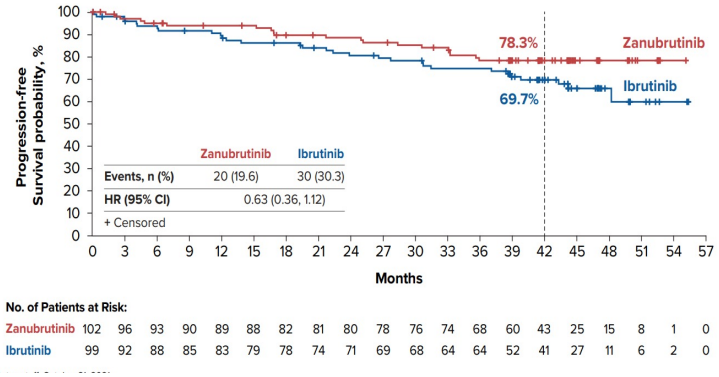
Dimopoulous M et al., EHA 2022

Zanubrutinib in R/R WM

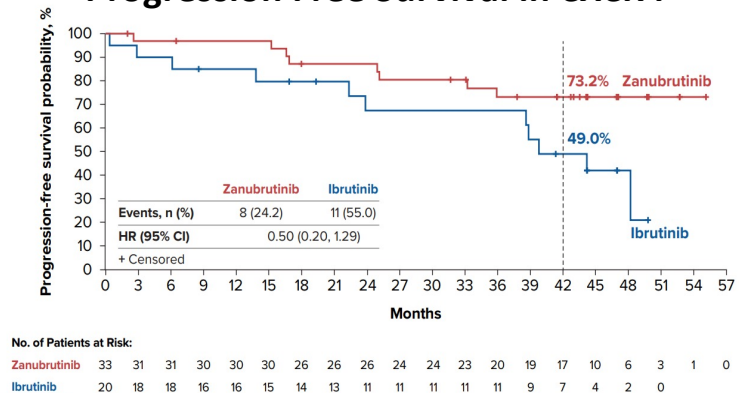
Phase III randomized study: Ibrutinib versus Zanubrutinib (Aspen study)

MYD88^{MUT}

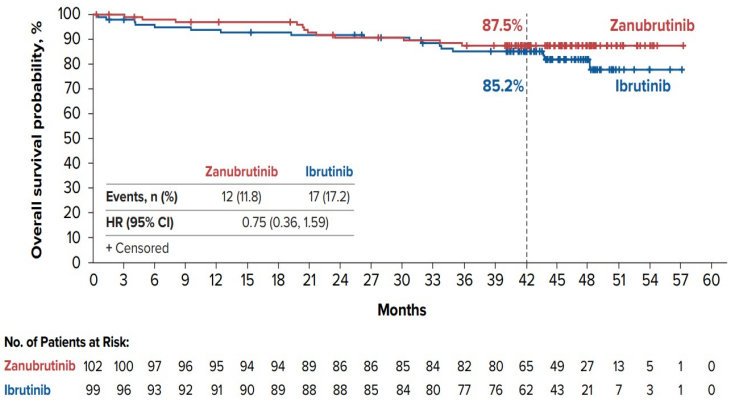
Progression Free Survival



Progression Free Survival in *CXCR4^{mut}*



Overall Survival



Dimopoulous M et al., EHA 2022

Zanubrutinib in R/R WM

Phase III randomized study: Ibrutinib versus Zanubrutinib (Aspen study)

Long-Term Safety and Tolerability

Overall Safety Summary

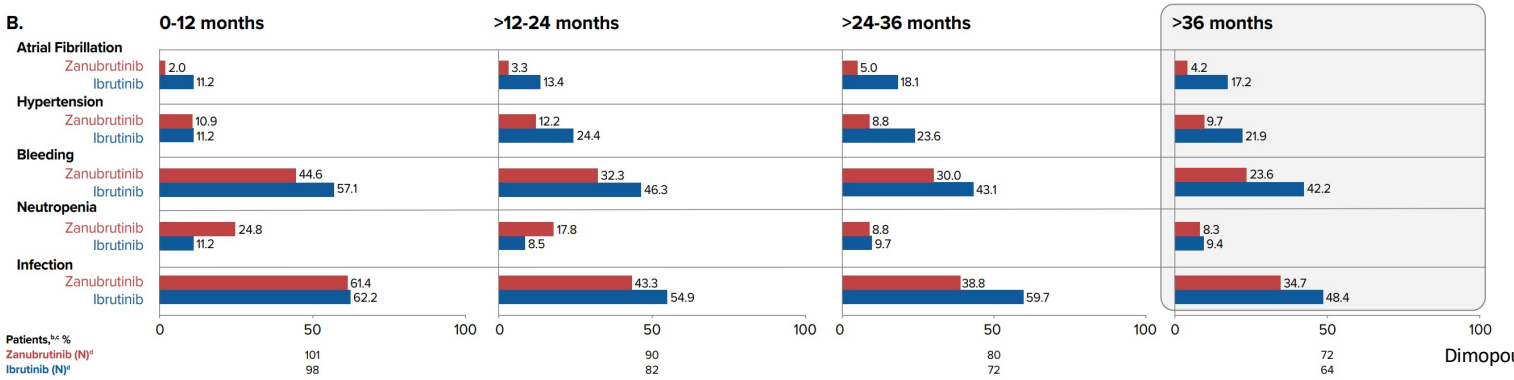
Category, n (%)	Cohort 1 Ibrutinib (n=98)	Cohort 1 Zanubrutinib (n=101)
Patients with ≥1 AE	98 (100.0)	100 (99.0)
Grade ≥3	71 (72.4)	75 (74.3)
Serious	49 (50.0)	57 (56.4)
AE leading to death	5 (5.1)[a]	3 (3.0)[b]
AE leading to treatment discontinuation	20 (20.4)[d]	9 (8.9)[e]
AE leading to dose reduction	26 (26.5)	16 (15.8)
AE leading to dose held	62 (63.3)	63 (62.4)
COVID-19–related AE	4 (4.1)	4 (4.0)

Advers Events of interest

AEs,[a] n (%)	All grades Ibrutinib (n=98)	All grades Zanubrutinib (n=101)	Grade ≥3 Ibrutinib (n=98)	Grade ≥3 Zanubrutinib (n=101)
Infection	78 (79.6)	80 (79.2)	**27 (27.6)**	22 (21.8)
Bleeding	61 (62.2)	56 (55.4)	10 (10.2)	9 (8.9)
Diarrhea	**34 (34.7)**	23 (22.8)	2 (2.0)	3 (3.0)
Hypertension*	**25 (25.5)**	15 (14.9)	**20 (20.4)***	10 (9.9)
Atrial fibrillation/flutter*	**23 (23.5)***	8 (7.9)	**8 (8.2)***	2 (2.0)
Anemia	22 (22.4)	18 (17.8)	6 (6.1)	**12 (11.9)**
Neutropenia*[b]	20 (20.4)	**35 (34.7)***	10 (10.2)	**24 (23.8)***
Thrombocytopenia	17 (17.3)	17 (16.8)	6 (6.1)	11 (10.9)
Second primary malignancy/ nonskin cancers	17 (17.3)/ 6 (6.1)	17 (16.8)/ 6 (5.9)	3 (3.1)/ 3 (3.1)	6 (5.9)/ 4 (4.0)

Bold text indicates rate of AEs with ≥10% (all grades) or ≥5% (grade ≥3) difference between arms.
Data cutoff: October 31, 2021. *Descriptive purposes only, 1-sided P < 0.025 in rate difference in all grades and/or grade ≥3.
[a]AE categories (grouped terms) of preferred terms by Medical Dictionary for Regulatory Activities v24.0. [b]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.

Adverse Events of Interest



Dimopoulous M, *et al*. EHA 2022 Poster: 1161

Zanubrutinib in R/R WM

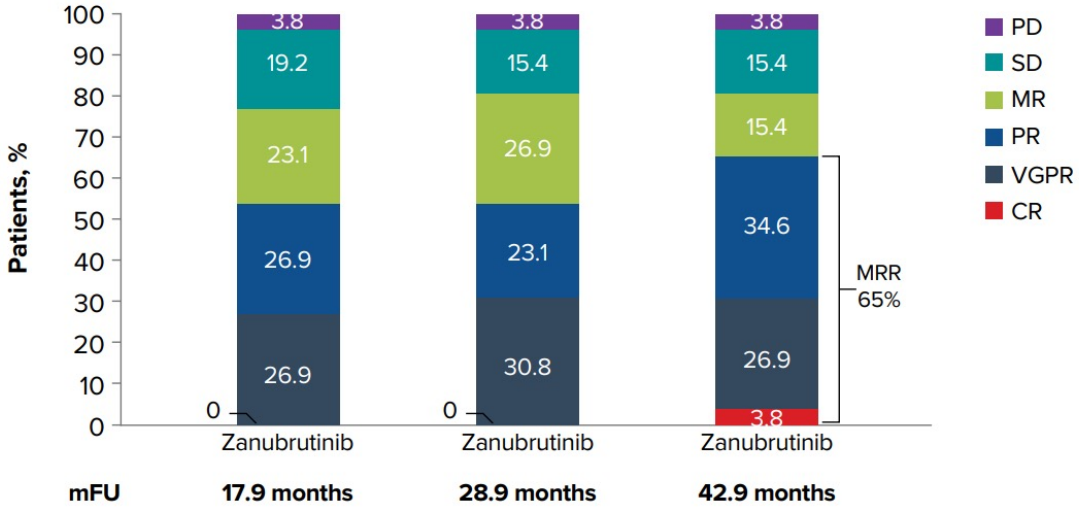
Aspen Trial Outcomes Cohort 2 *MYD88^{WT}*

Patients with *MYD88^{WT}* WM
N=28 (23 R/R)

→

Arm C: Zanubrutinib
N=28
160 mg BID until PD

Responses Overtime



At 42 months:

PFS: **53.8% (95% CI: 33.3, 70.6)**

OS: **83.9% (95% CI: 62.6, 93.7)**

Dimopoulous M, *et al*. EHA 2022 Poster: 1161

A Phase II, expanded access study of zanubrutinib in pts with WM

BGB-3111-216 is a single-arm, expanded access study of zanubrutinib in TN patients who were unsuitable for standard chemoimmunotherapy or pts with R/R WM

Treatment response

BOR, n (%)	Overall (N=41)
Very good partial response	16 (39.0)
Partial response	14 (34.1)
Minor response	5 (12.2)
Stable disease	2 (4.9)
Progressive disease	4 (9.8)
Major response rate	30 (73.2)
Overall response rate	35 (85.4)

Between December 2019 and June 2021:
50 patients: 17 TN
33 R/R (median prior therapies = 2)
IPSSWM: 54% intermediate, 40% high-risk disease

Median treatment exposure was 9.2 months (range: 1.4–20.0)

Grade ≥3 TEAEs of special interest were:

- Hypertension 8%
- Infection 8%
- Atrial fibrillation/flutter 2%
- Neutropenia 2%
- Second primary malignancy 2%

Real-world expanded access study results were consistent with the established zanubrutinib profile in WM or other B-cell malignancies when administered as oral monotherapy at 160 mg BID or 320 mg QD in pts with intermediate or high-risk R/R or TN WM

BID, twice daily; BOR, best overall response; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia; pts, patients; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; TN, treatment-naive; WM, Waldenström's macroglobulinemia.

Castillo J *et al.* Abstract e19522 presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; Chicago, IL, USA, June 3–7, 2022.

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

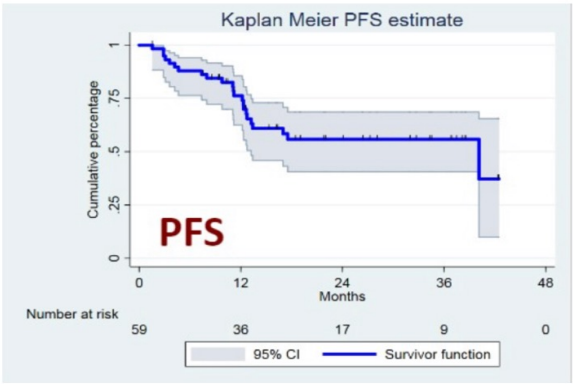
> SD

Maintenance:
2 years q3months

- Rituximab 1400 mg sc d1

59 pts
Mdian prior tx: 2

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

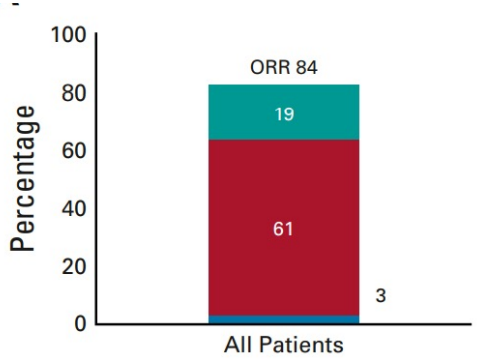


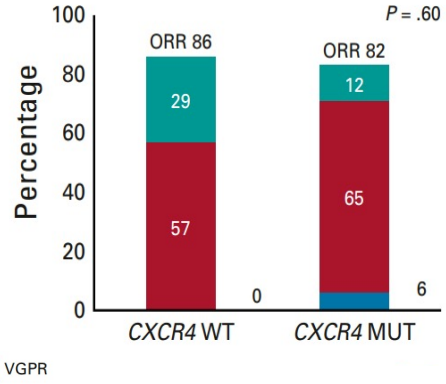
Kersten et al, 2019

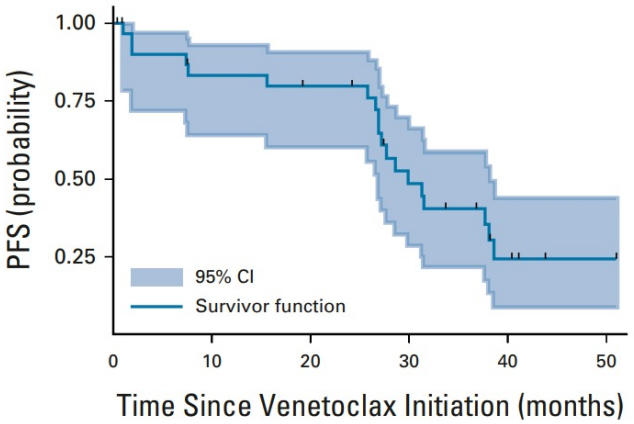
WHAT COMES NEXT IN WM?

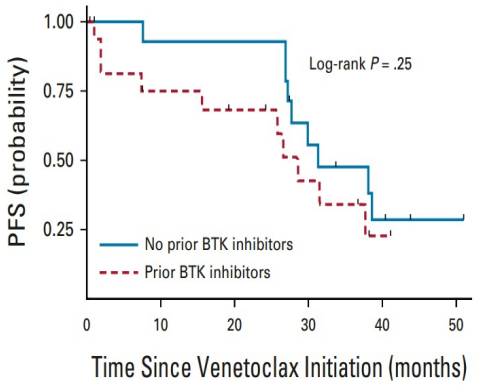
Venetoclax Monotherapy

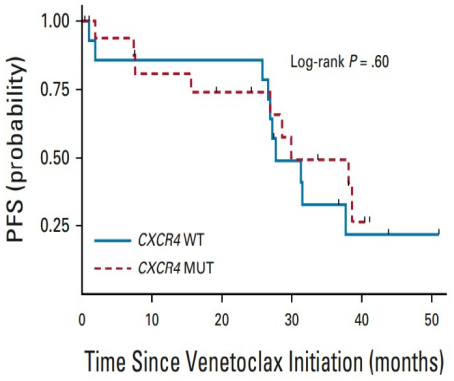
32 pts	
Median prior Tx:	**2(1-10)**
Prior BTKi:	**66%**
MYD88^{mut}:	**100%**
CXCR4^{mut}:	**53%**







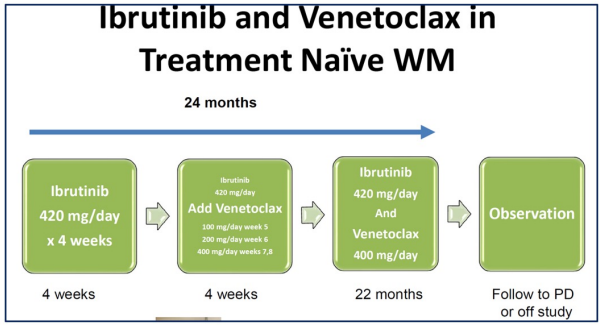




Castillo et al 2021

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

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**
  - **Effective, prolonged PFS**
    - **Zanubrutinib: Deeper responses**
      Better outcomes in MYD88^{wt} and CXCR4^{mut}
      Better tolerability=adhererence dose intesnity

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