Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

Alessandra Tedeschi

SESSIONE VII
Terapia di altre sindromi immunoproliferative

MALATTIA DI WALDENSTROM

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Advisory Board and Speaker Bureau:

- ✓ **Janssen Spa**
- ✓ **AbbVie**
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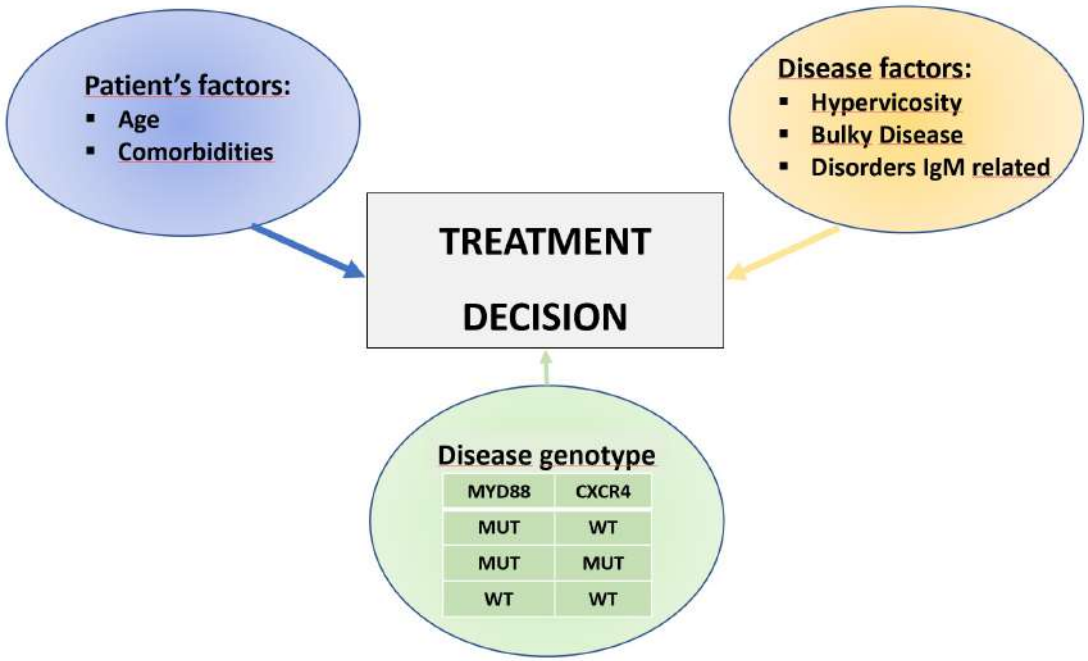
WM TREATMENT

Are there any current standards?

No standard treatment, but a panel of « standard » treatment options!

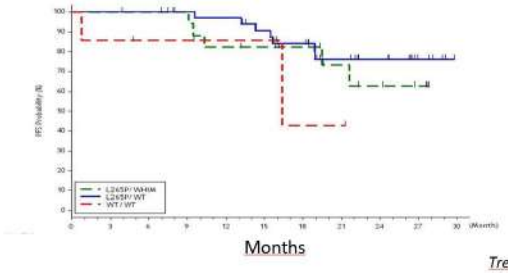
WM TREATMENT



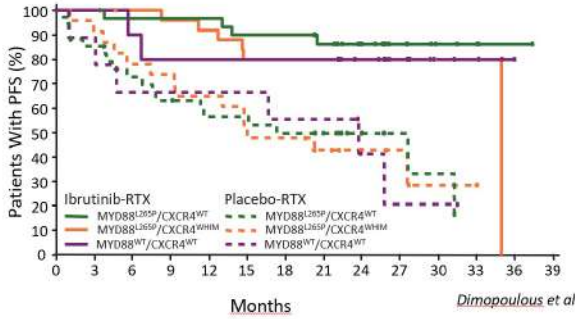
WM TREATMENT

PFS according to MYD88 & CXCR4 mutation status

Ibrutinib Monotherapy R/R

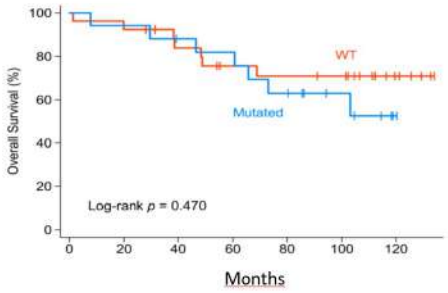


Treon et al, 2015



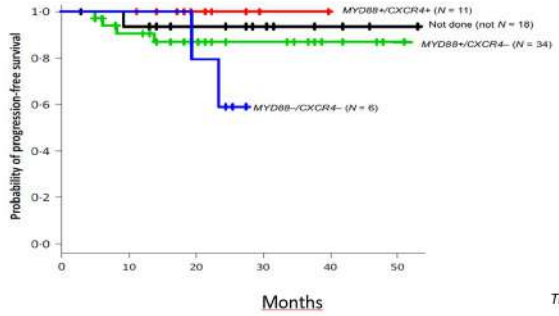
Dimopoulous et al 2018

Bortezomib Rituximab First Line according to CXCR4



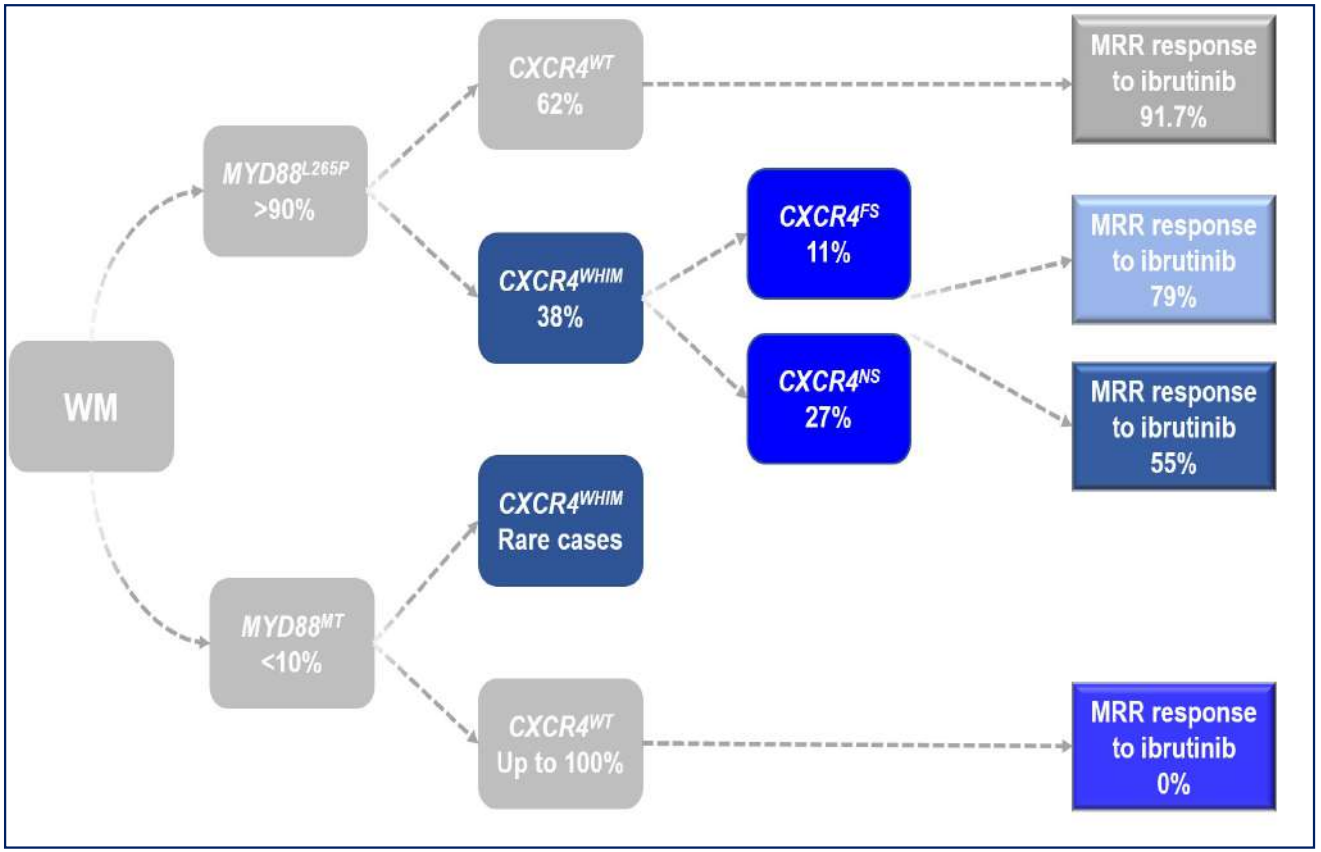
Sklavenitis et al, 2018

Bendamustine Rituximab First Line



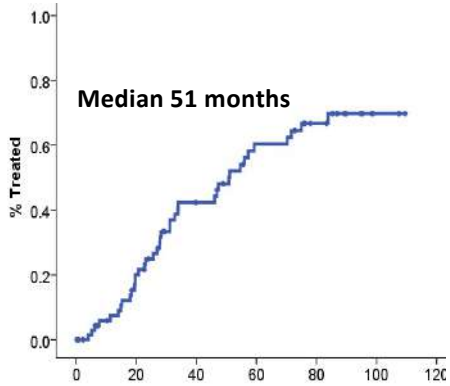
Tricot et al, 2018

Genotype response to therapy



First Line: Rituximab Combination Treatment

DRC



PROS:

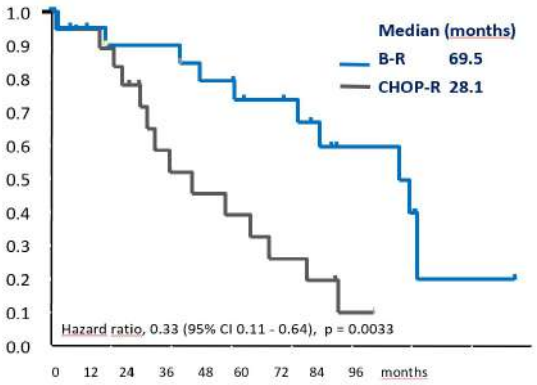
- ✓ Minimal myelo/immuno-suppression
  89% pts completed 6 courses
- ✓ TTN 51 m

CONS:

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

Kastritis et al, 2015

Benda R



PROS:

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

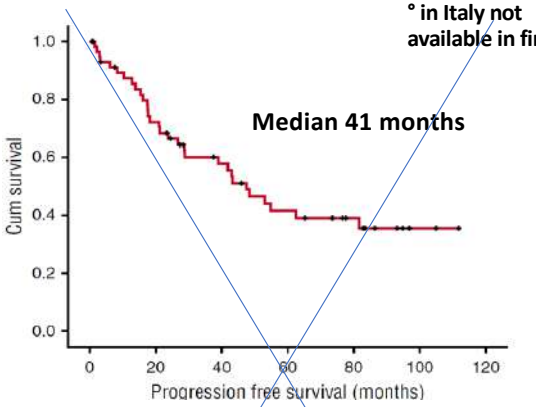
CONS:

- 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:

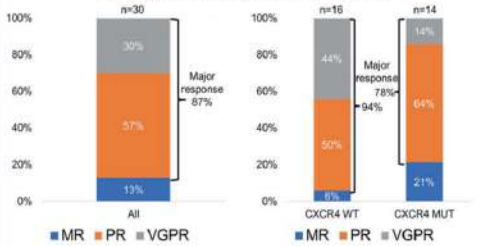
- High rate of Neuropathies

Treon et al, 2009-2015

First Line: BTKi

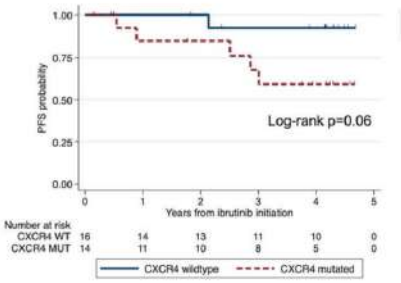
Ibrutinib° in MYD88^{mut}

median follow-up time of 50.1 m



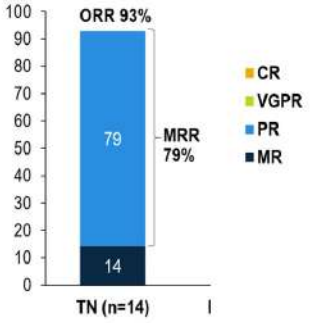
Median time to Major Response: 1.9 m
Median longer for pts with:

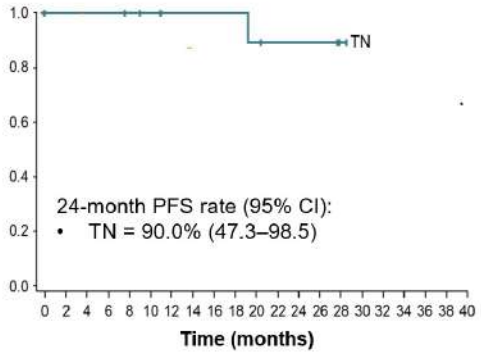
CXCR4^{mut}	7.3 m	*p = 0.02*
CXCR4^{wt}	1.8 m	



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

First Line: BTKi

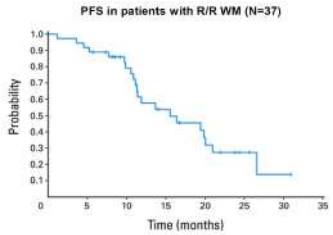
Concerns of BTKi in first line

- ✓ **Data on a low number of pts**
- ✓ **Continuous Treatment:**
  - **AE**
  - **Costs**
- ✓ **Salvage treatment**

Relapsed/Refractory Disease

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 Disease

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.

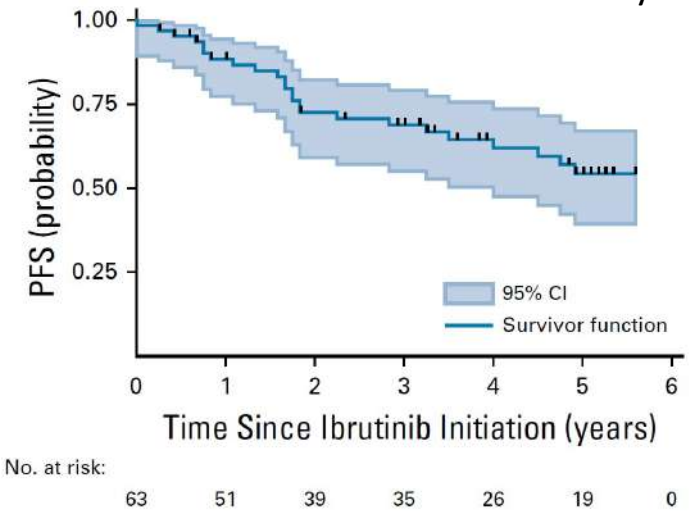
Abbreviations: Mut, mutant; NA, not applicable; WM, Waldenström macroglobulinemia; WT, wild type.

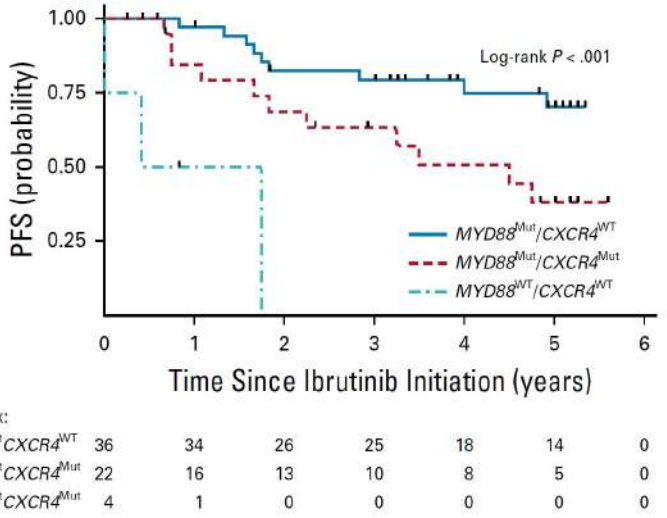
Treon SP *et al. J Clin Oncol* 2021

Relapsed/Refractory Disease

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 Refarctory WM

Ibrutinib Phase II study

Median study follow-up: 59 months

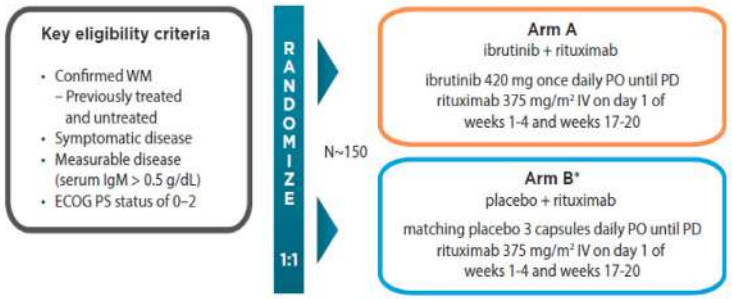
Grade ≥3 adverse:	
neutropenia	15.9%
thrombocytopenia	11.1%
pneumonia	3.2%
Atrial arrhythmia	12.7%

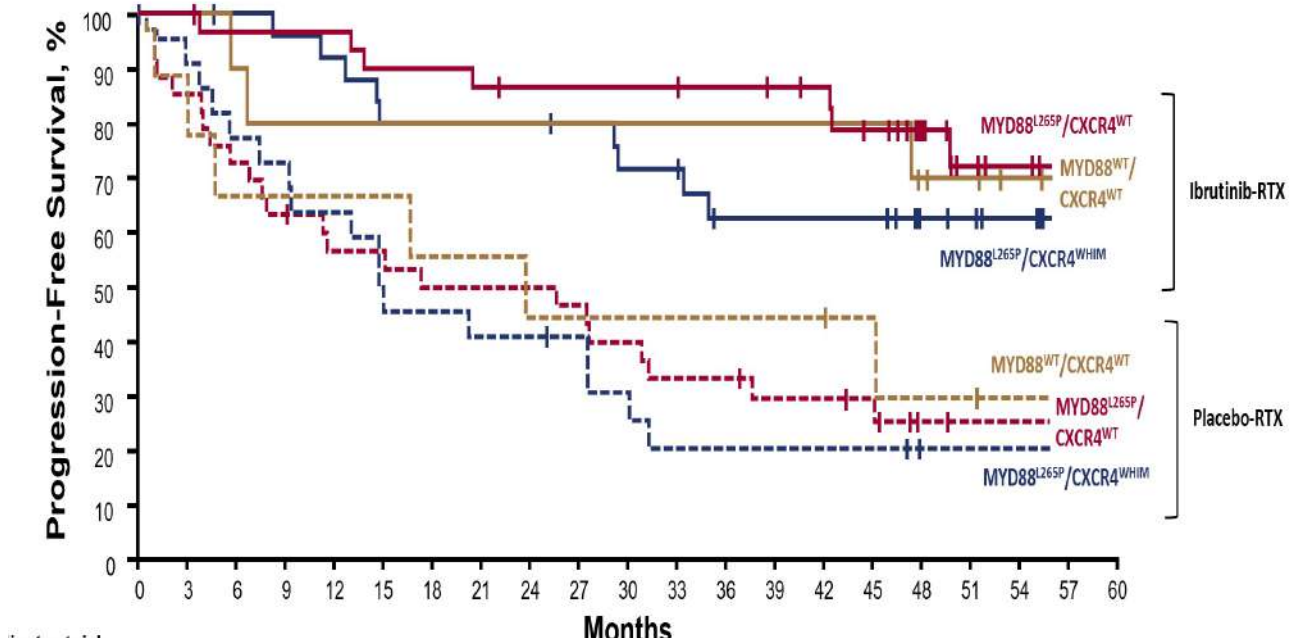
5 patients came off study for AE
12 patients experienced dose reductions

Treon et al., 2021

Relapsed Refarctory WM

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





Buske et al., 2020

Relapsed Refractory WM

Zanubrutinib vs Ibrutinib (Aspen study)

Cohort 1: R/R or TN* WM with *MYD88^{L265P}* mutation

MYD88^{MUT} WM patients
(N=201, 164 R/R)

R
1:1

Arm A
Zanubrutinib
160 mg BID
until PD or unacceptable toxicity
N=102(R/R=83, TN=19)

Arm B
Ibrutinib
420mg QD
until PD or unacceptable toxicity
N=99 (R/R= 81, TN= 18)

***TN must be unsuitable for standard chemoimmunotherapy**

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.

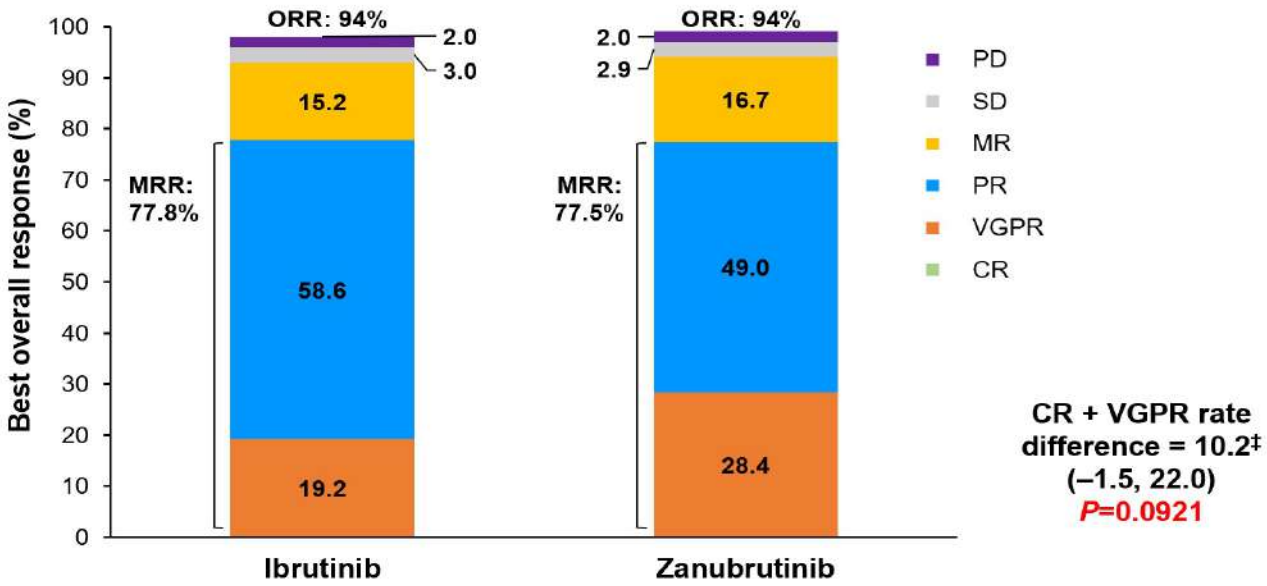
Tam CS et al., 2020

Relapsed Refractory WM

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

Best overall response in the ITT population*



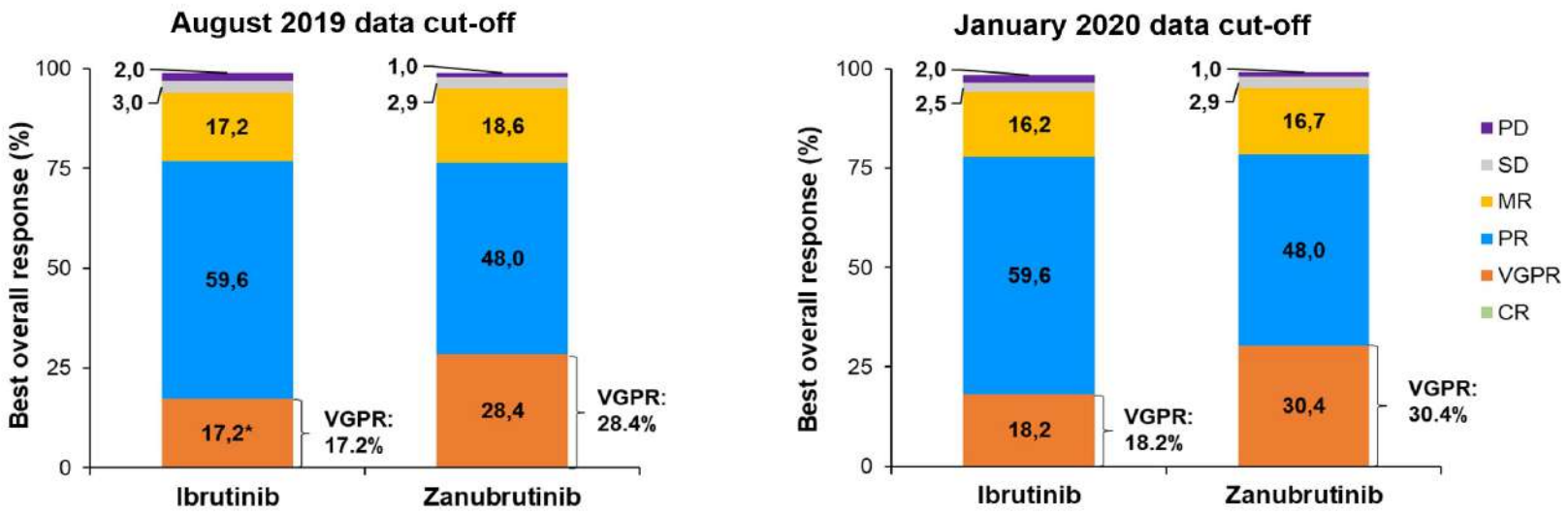
CR + VGPR rate difference = 10.2‡ (–1.5, 22.0)
***P*=0.0921**

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

Relapsed Refractory WM

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)

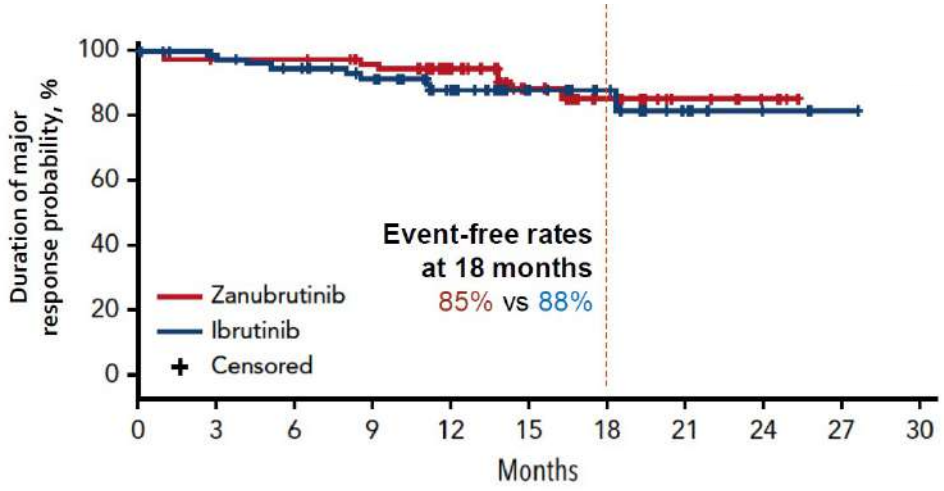
*Excluded 2 patients with VGPR by IRC: MR (extramedullary disease present) and PR (immunoglobulin M assessment by local serum protein electrophoresis M-protein test).
AUC, area under the curve; CR, complete response; IgM, immunoglobulin M; MR, minimal response; PD, progressive disease; PR, partial response;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

Tam CS et al., 2020

Relapsed Refractory WM

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

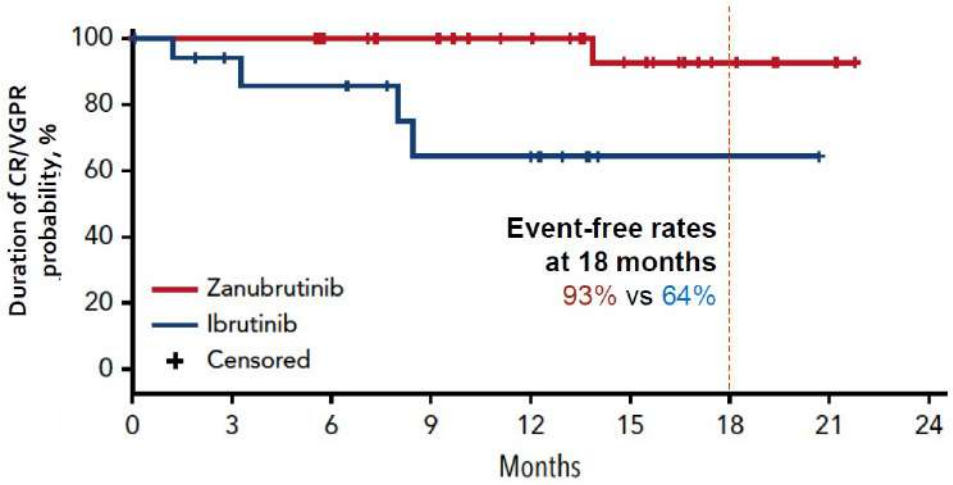
Duration of major response



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

Relapsed Refractory 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)

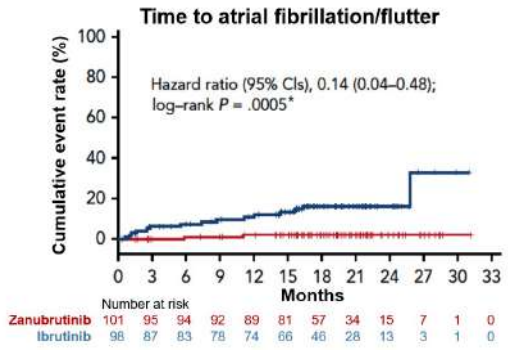
- *Cardiac arrest after plasmapheresis. †G5 cardiac arrest after plasmapheresis; G4 neutropenia; G4 subdural hemorrhage; G2 plasma cell myeloma. ‡Cardiac failure acute; sepsis (n=2); unexplained death. §G5 sepsis (n=2); G5 unexplained death; G3 acute myocardial infarction; G3 hepatitis; G3 pneumonia;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

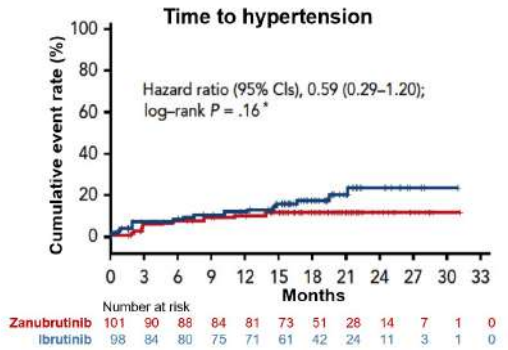
Tam CS et al., 2020

Relapsed Refractory 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., 2020

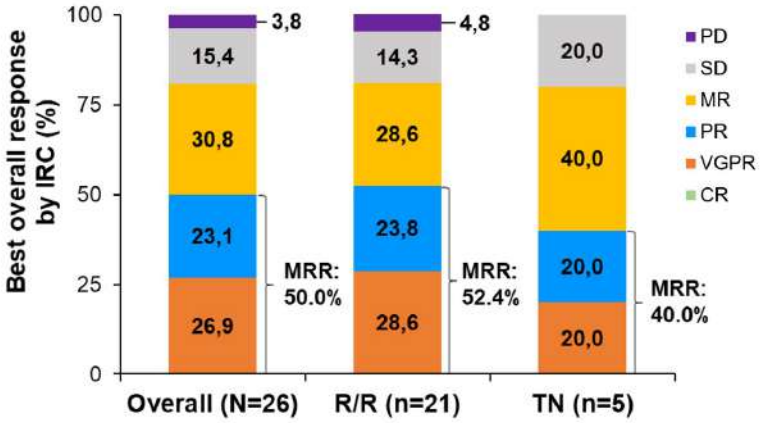
Relapsed Refractory WM

Zanubrutinib in MY88^{wt}

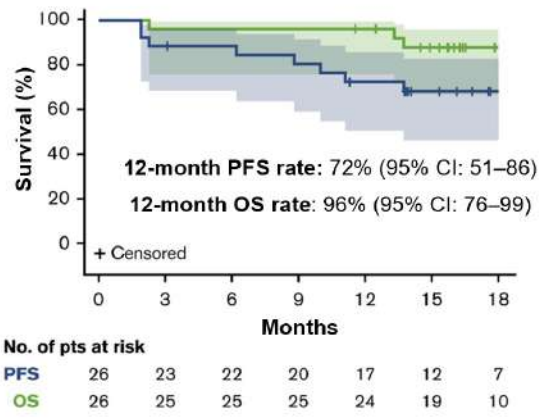
***MYD88*^{WT} WM**
(N=28: 26 WT, 2 unknown)

Arm C
Zanubrutinib
160 mg BID until PD / unacceptable toxicity

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?

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

> SD

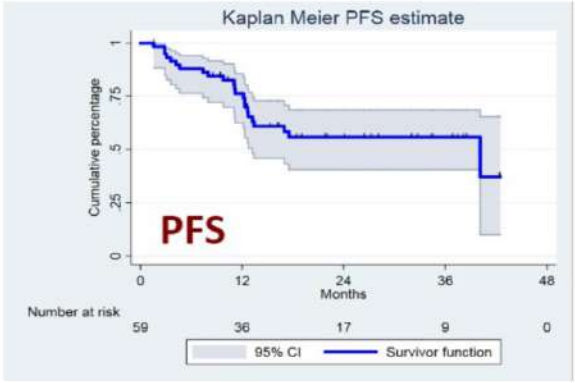
Maintenance:
2 years q3months

- 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

- Rituximab 1400 mg sc d1

59 pts
Mdian prior tx: 2

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

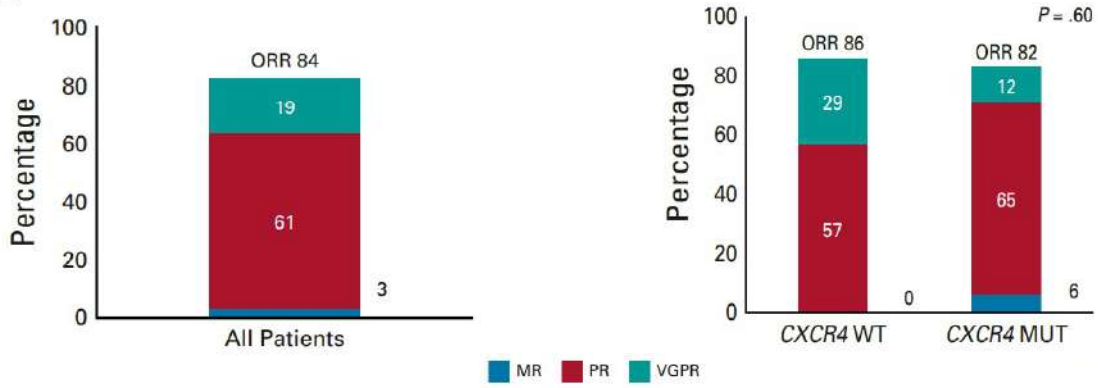


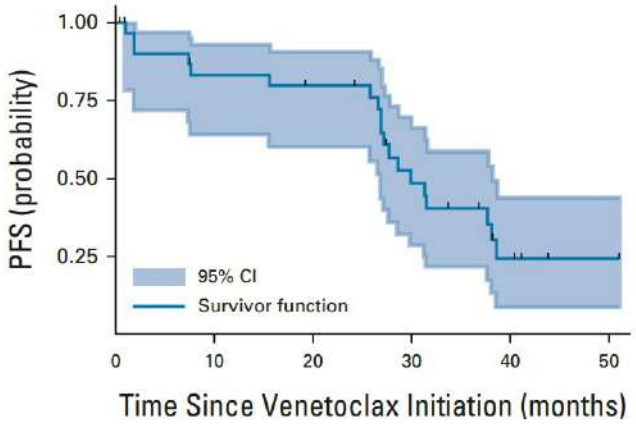
Kersten et al, 2019

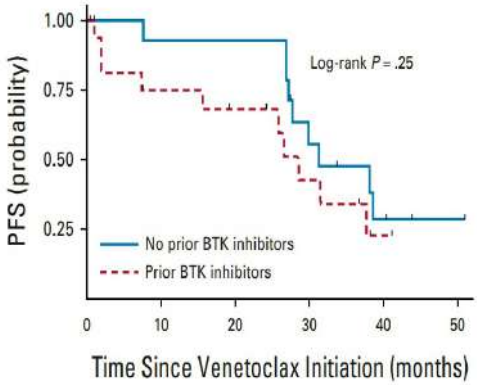
What comes next?

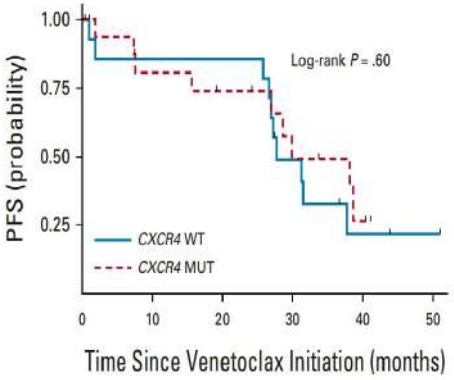
Venetoclax Monotherapy

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





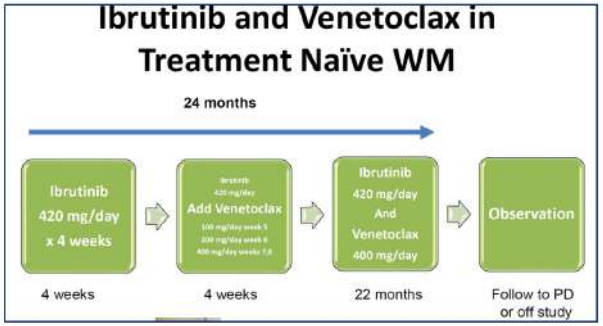




Castillo et al 2021

What comes next?

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** Catillo et al 2020
- ✓ **In combination with Ibrutinib:ongoing**

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

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

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 (Rituximab, Ibrutinib)**

RELAPSED/REFRACTORY

- **Retreatment with rituximab based therapy may be a choice if prolonged first response duration**

- **BTKi best salvage regimens**

- **Lack of salvage regimns after BTKi failure**