Paziente con WM ad alto rischio

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CATANIA

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NH Catania Centro

P.A., ♂ 72 anni – ECOG PS 2

Gennaio 2018:

- Clinica:
  - astenia, intolleranza allo sforzo con dispnea ingravescente;
  - sudorazioni notturne, calo ponderale (8 kg in 3 mesi);

Aprile 2018:

- Lab tests:
  - Hb 7.4 g/dl, MCV 73 fL, WBC 10.360/mmc (L 7.250/mmc), PLT 93.000/mmc;
  - QSP: P.T. 11 g/dl con CM 5 g/dl in β2, Alb 3.1 g/dl;
  - IFE sieriche positive per IgM kappa (IgM 4.380 mg/dl), uIFE kappa+;
  - β2M 4.6 mg/l, LDH 455 U/L, VES 54/110 mm/h, Ferritina 4 ng/ml, Sat-TRF 8%, Coombs negativi.
- Imaging:
  - Splenomegalia (DL 190 mm)
- CIRS: 12 (IA, BPCO con enfisema in forte fumatore, pregresso k vescica, HBV+).

Diagnostica su PB:

		%	valori normali
linfociti CD3+	=	7.5	(65 - 75 %)
linfociti CD19+	=	88.4	(1.0 -10 %)
linfociti CD19+/CD5+	=	79.8	
linfociti CD22+	=	39(+--)	
linfociti CD79b+	=	86.2(++-)	
linfociti CD23+/CD19+	=	22.9(+--)	
linfociti FMC7+/CD19+	=	75.6(++-)	
linfociti CD19+/CD38+	=	Neg.	
linfociti CD10+/CD19+	=	Neg.	
linfocitiCD19+/CD200+	=	42.9	
catene leggere di tipoκ/CD19+	=	87.2(++-)	
catene leggere di tipoλ/CD19+	=	Neg.	
Cellule CD34+/CD45+	=	Neg.	

OSSERVAZIONI:
Presenza di popolazione B-linfocitaria in quota fortemente aumentata rispetto alla norma, esprimente fenotipo immunologico:CD19+,CD5+, FMC7+,CD79b+,CD22±,CD23±, catene leggere di superficie di tipo Kappa e positività per il marcatore CD200+ sulla metà circa dei B-linfociti, suggestiva per processo B-linfoproliferativo cronico CD 5 positivo, tipo linfoma non Hodgkin periferizzato (Matutes score: 2).
Per un corretto inquadramento diagnostico, si consiglia ulteriore approfondimento diagnostico.

PB: CD19+, CD5+, FMC7+, CD79b+, CD22±, CD23±, slgκ+

Diagnostica su BM (maggio 2018):

CELLULARITA': 40%.
GRANULOPOIESI: PREVALENTE, MATURANTE.
ERITROPOIESI: ADEGUATA.
MEGACARIOCITOPOIESI: NORMO RAPPRESENTATA.
E' PRESENTE, INOLTRE, UN INFILTRATO LINFOIDE INTERSTIZIALE E NODULARE CENTRO LACUNARE COSTITUITO DA ELEMENTI DI PICCOLE DIMENSIONI FRAMMISTI A PLASMACELLULE ED A MASTOCITI.
PRESENTE COMPONENTE ISTIOCITARIA.
TRAMA RETICOLINICA: ADDENSATA IN CORRISPONDENZA DELL' INFILTRATO SOPRA DESCRITTO.

LA CARATTERIZZAZIONE IMMUNOISTOCHIMICA DOCUMENTA COME LA POPOLAZIONE LINFOIDE RISULTI CD20+, CD3- (LINFOCITI T+).
PLASMACELLULE MONOTIPICHE PER LA CATENA LEGGERA KAPPA DELLE IMMUNOGLOBULINE.
CONCOMITANO ISTIOCITI CD68PGM1+ ANCHE NEL CONTESTO DEGLI AGGREGATI LINFOIDI.
QUOTA MIDOLLARE RESIDUA PARI A 705 DELLA CELLULARITA' ESAMINATA.
+ = >75% (+); +/-: 50-75% (+); -/+: 25-50% (+); RARE: 10-25% (+); ECCEZIONALI: <10% (+); -: NESSUNA CELLULA (+).

DIAGNOSI DEFINITIVA
LOCALIZZAZIONE OSTEOMIDOLLARE DA LINFOMA DI DERIVAZIONE DAI B-LINFOCITI PERIFERICI, INDOLENTE A DIFFERENZIAZIONE PLASMACELLULARE COERENTE CON LINFOMA LINFO-PLASMOCITICO.
UTILE CORRELAZIONE CON L' ESITO DELLA RICERCA DELLA MUTAZIONE L265P A CARICO DI MYD88 RIFERITA IN CORSO A PALERMO.

Genetica Molecolare
SAMPLING: 228118
Materiale: SP
Commento:
MYD88: MUTATO presenza di mutazione L265P nel 38% delle cellule esaminate.
Analisi eseguita mediante PCR e sequenziamento (sensibiltà 20%)

Diagnosi: Linfoma Linfoplasmocitico/Macroglobulinemia di Waldenstom IgM-κ

Gertz MA, et al. Am J Hematol, 2021

WM: Stadiazione

IPSS-WM[1]

TABLE 2 International Prognostic Scoring System for Waldenström macroglobulinemia

Factor Associated With Prognosis		Value
Age, y		>65
Hemoglobin, g/dL		≤11.5
Platelet count, No./mcL		≤100 000
β_2-Microglobulin, mg/L		>3
Monoclonal IgM, g/dL		>7
Risk Stratum and Survival		
Risk Category	**Score[a]**	**Median Survival, mo**
Low	0 or 1 (except age)	142.5
Intermediate	2 or age > 65 y	98.6
High	>2	43.5

rIPSS-WM[2]

Table 2 Assignment of points for the formulation of the revised staging system

	Points
Age < 65	0
Age 66–75	1
Age > 75	2
B2microglobulin > 4 mg/L	1
LDH > 250 IU/L	1

Table 3 Revised ISSWM categories, patient disposition, and outcomes per stage in the derivation cohort

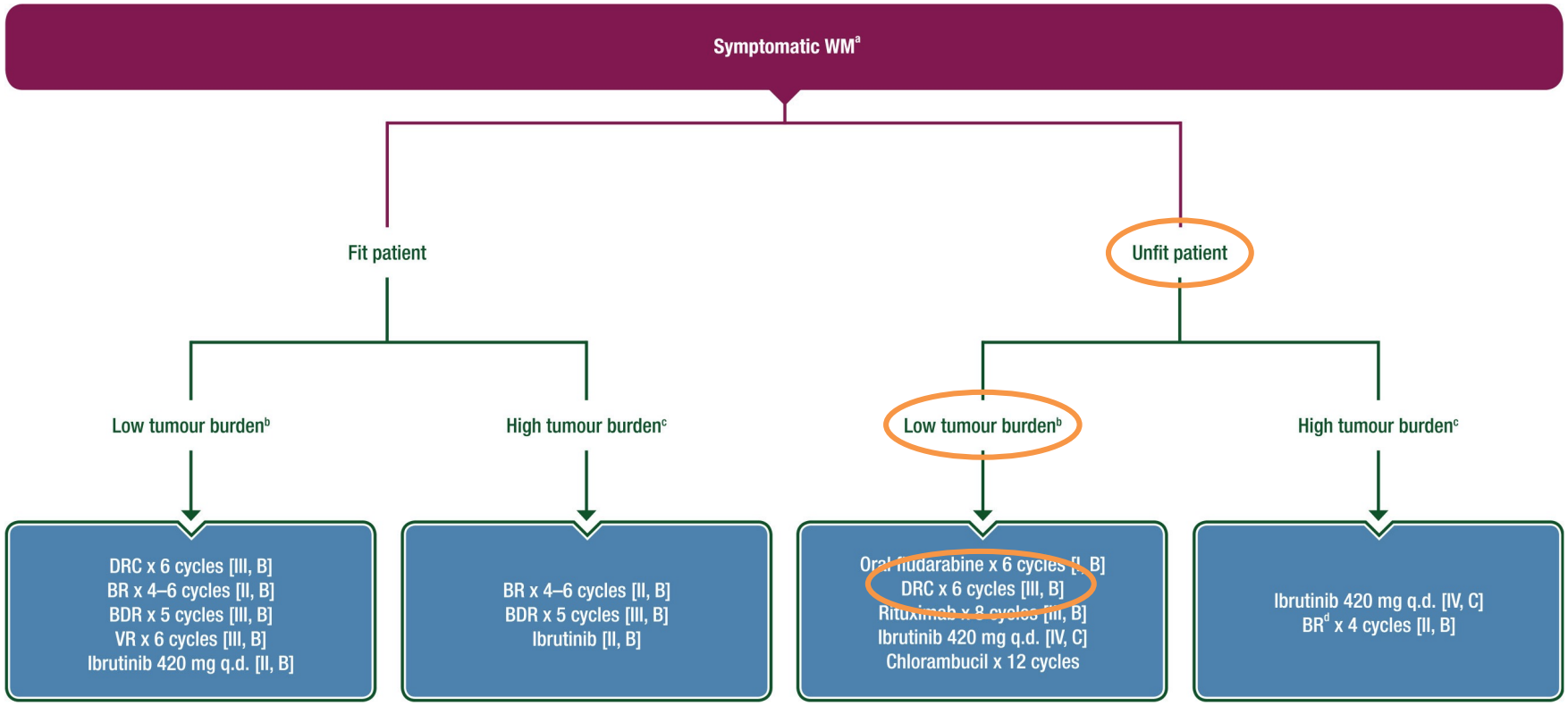
Stage	Score	% of patients	3-year WM related mortality	5-year OS	10-year OS
Very low	0	13%	0%	95%	84%
Low	1	33.5%	10%	86%	59%
Intermediate	2	25.5%	14%	78%	37%
High	3	16%	38%	47%	19%
Very high	4–5	12%	48%	36%	9%

2018: IPSS-WM 4 → HR (mOS 43.5 mo)[1]

2022: rIPSS-WM 3 → HR (5y OS 47%)[2]

[1]Morel P, et al. Blood, 2009
[2]Kastritis E, et al. Leukemia, 2019

Symptomatic WM treatment



*Paziente considerato con LTB per concomitanti anemia sideropenica ed epatopatia HBV-correlata

Kastritis E, et al. Ann Oncol, 2018

First line (May 2018) → DRC (every 21 days for 6 courses)[1]

- **Dexamethasone** 20 mg i.v. (day 1)
- **Rituximab** 375 mg/m^2 i.v. (day 1)
- oral **Cyclophosphamide** 100 mg/m^2 bid on days 1 to 5 (total dose 1 g/m^2)

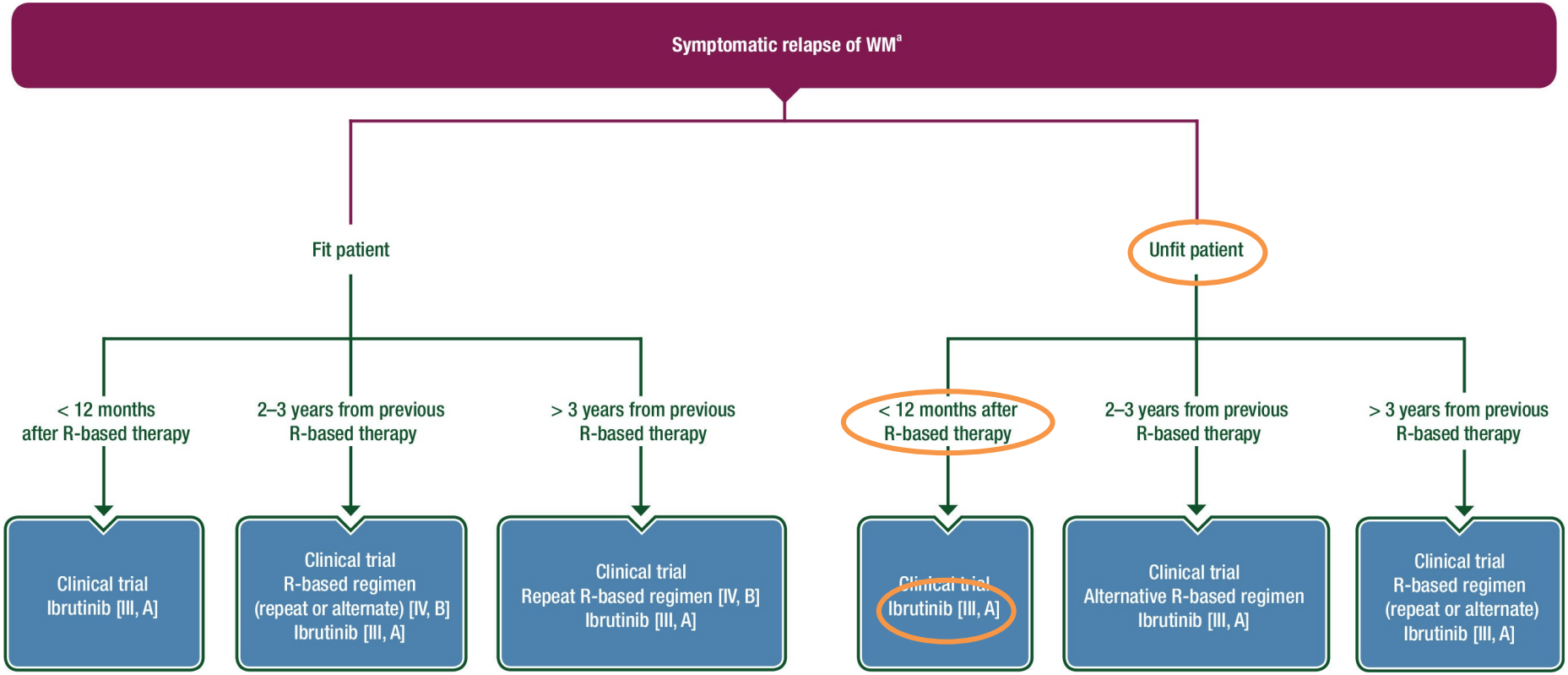
AE: anaphylaxis to rituximab (withdrawn after 2nd course), hyperviscosity syndrome (IgM flare), febrile neutropenia with lobular pneumonia that required hospitalization.

Response (Dec 2018) → SD (with partial recovery CBC)

IgM 4.160 mg/dl, spleen LD 185 mm, Hb 9 g/dl, WBC 6.200/mmc (L 4.220/mmc), β2M 5.8 mg/l, LDH 198 U/L

[1]Dimopoulos MA E, et al. JCO, 2007

Symptomatic refractory WM treatment



Kastritis E, et al. Ann Oncol, 2018

2nd line (Dec 2018) → Ibrutinib 420 mg/day[1,2] until PD or intol

Response after 20 months (Jul 2020) → PD

IgM 5.290 mg/dl, Hb 9.4 g/dl, WBC 10.450/mmc (L 8.100/mmc), PLT 50.000/mmc, β2M 7.6 mg/l, LDH 198 U/L; hyperviscosity syndrome, spleen LD 210 mm, PET/TC NR

AE: neutropenia G2, IgM flare, diarrhea, arthralgia, petechiae

Restaging with Histological revaluation

[1]Treon SP, et al. NEJM, 2015
[2]Dimopoulos MA E, et al. NEJM, 2018

Rivalutazione istologica BM (agosto 2020):

CELLULARITA': 20%.
GRANULOPOIESI: PREVALENTE, MATURANTE.
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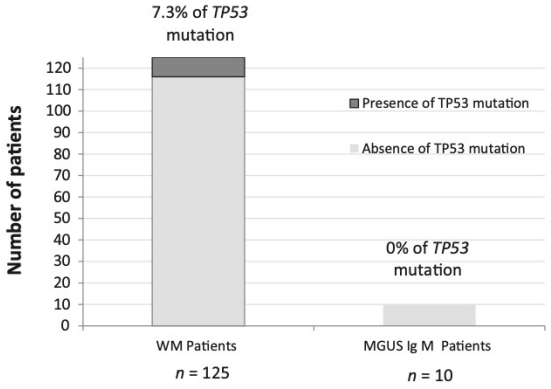
Genetica Molecolare
REARRANGE IGH: MONOCLONALE "MUTATED"
TP53: MUTATO
SAMPLING: 435519
Materiale: S.P.
Commento: PRESENZA DEL RIARRANGIAMENTIO MONOCLONALE PRODUTTIVO VH1-18*01 DH1-26*01 JH4*02
Stato mutazionale "MUTATED" (OMOLOGIA 91.7%). Protocollo BIOMED
TP53 MUTATO c.783-1G>T (splice site esone 8 , VAF 77%) Sequenziamento NGS (piattaforma ION TORRENT, COVERAGE medio 13064 (500X al 100%) Analisi secondo le raccomandaziioni ERIC e IARC TP53 database.Le mutazioni di TP53 sono associate a valore prognostico sfavorevole e a resistenza a chemio e immuno terapia.
Il laboratorio ha conseguito la certificazione ERIC nel 2018

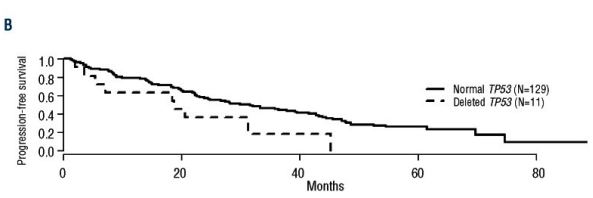
Diagnosi: Linfoma Linfoplasmocitico/Macroglobulinemia di Waldenstom IgM-κ[1]
IPSS-WM 4, rIPSS-WM 3 – HR[2], TP53 mutato

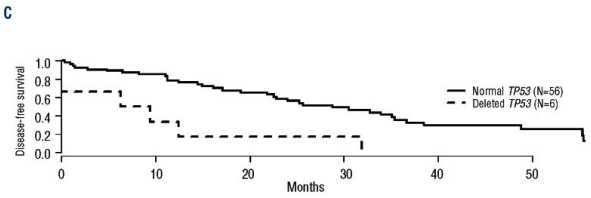
[1]Gertz MA, et al. Am J Hematol, 2021
[2]Kastritis E, et al. Leukemia, 2019

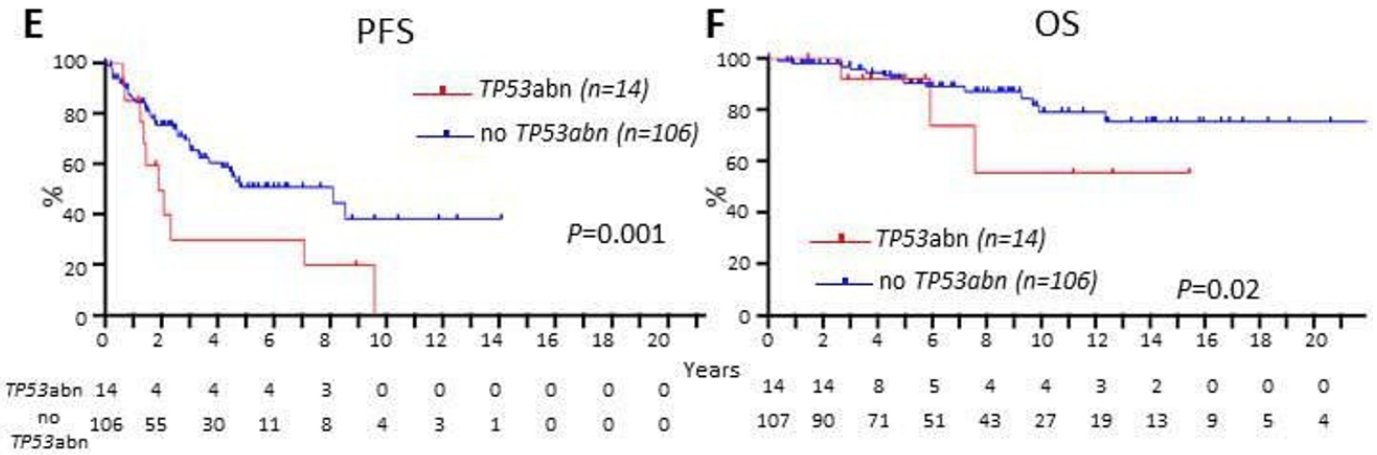
Prognostic impact of TP53 mutations in WM (1)

- Incidence: 2 – 8%[1,2]
- > both CXCR4 and MYD88 mutated[3]
- < MYD88-mutated alone
- Ibrutinib response
- Worsened prognosis[2]









[1]Nguyen-Khac F, et al. Hematol, 2013
[2]Poulain S, et al. Clin Cancer Res, 2017
[3]Krzisch D, et al. Am J Hematol, 2021

Prognostic impact of TP53 mutations in WM (2)

Natural history of Waldenström macroglobulinemia following acquired resistance to ibrutinib monotherapy

Joshua N. Gustine,[1,2] Shayna Sarosiek,[1,3] Catherine A. Flynn,[1] Kirsten Meid,[1] Carly Leventoff,[1] Timothy White,[1] Maria Luisa Guerrera,[1] Lian Xu,[1] Amanda Kofides,[1] Nicholas Tsakmaklis,[1] Manit Munshi,[1] Maria Demos,[1] Christopher J. Patterson,[1] Xia Liu,[1] Guang Yang,[1,3] Zachary R. Hunter,[1,3] Andrew R. Branagan,[3,4] Steven P. Treon[1,3] and Jorge J. Castillo[1,3]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute; [2]Boston University School of Medicine; [3]Department of Medicine, Harvard Medical School and [4]Division of Medical Oncology, Massachusetts General Hospital, Boston, MA, USA

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TP53 mutations

Three of 20 patients (15%) had a *TP53* mutation detected. Two *TP53* mutations were detected in one patient, and all *TP53* mutations localized to the DNA-binding domain. All three patients had mutated *MYD88*, and two patients had a *CXCR4* mutation; no concurrent *BTK* mutations were identified in the two patients tested. All three patients with a *TP53* mutation had an IgM rebound following T_0. No patient with a *TP53* mutation responded to salvage therapy, and all were quadruple-class exposed. Patients with a *TP53* mutation had a significantly shorter median OS following T_0 *versus* those without (0.5 *vs.* 21.3 months; *P*=0.02; *Online Supplementary Figure S6*).

Gustine JN, et al. Haematol, 2022

Agosto 2020: WM IPSS-WM 4, rIPSS-WM 3 – HR, TP53 mut

- IgM 5.290 mg/dl, β2M 7.6 mg/l, LDH 198 U/L;
- Hb 9.4 g/dl, WBC 10.450/mmc (L 8.100/mmc), PLT 50.000/mmc;
- hyperviscosity syndrome, spleen LD 210 mm, D6 and L4 deformation, PET/TC NR

- 3rd line (Sep 2020 – Feb 2021) → Bendamustina-R (90 mg/m^2) ogni 28 giorni per 6 cicli[1];
- 4th line (Feb 2021 – Oct 2021) → Bortezomib – Rituximab – Dexamethasone (weekly Bort, 28d)[2];

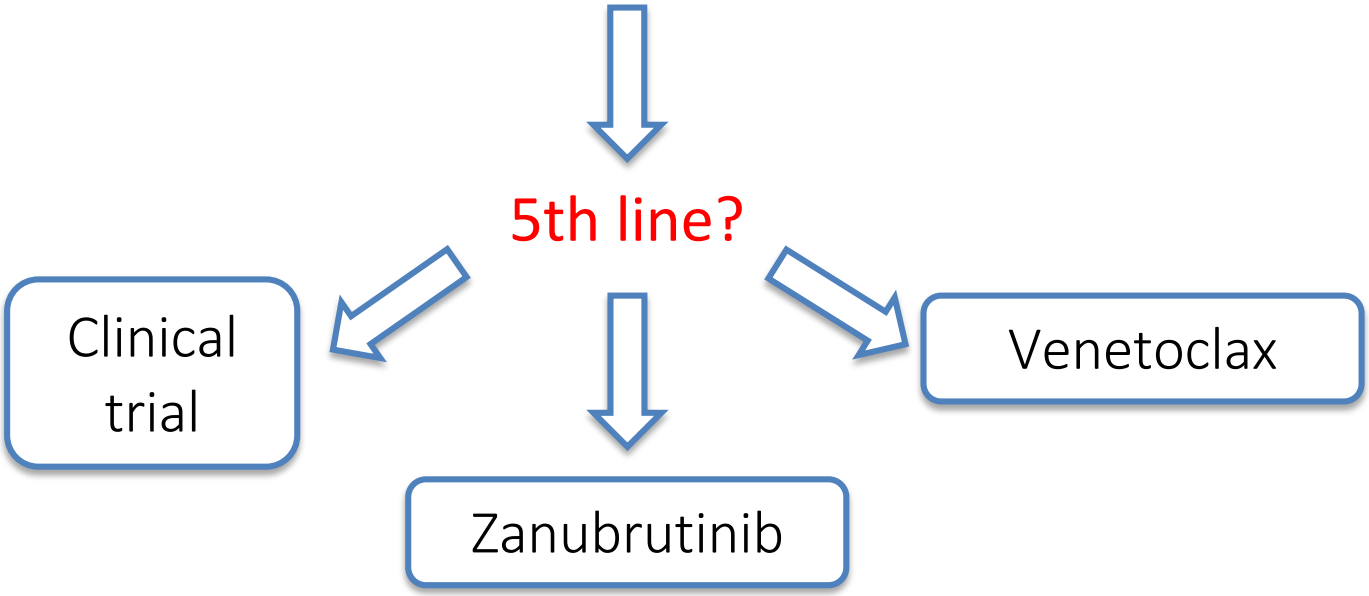
Response (Dec 2021) → PD

IgM 7.456 mg/dl, spleen LD 230 mm, Hb 10.4 g/dl, WBC 3.600/mmc (L 500/mmc), PLT 125.000/mmc, β2M 6.6 mg/l, LDH 450 U/L (v.n. <243)

[1]Tedeschi A, et al. Leuk Lymph, 2015
[2]Dimopoulos MA, 2010. Chen C, 2009

Dicembre 2021 (75 yrs): WM IPSS-WM 4, rIPSS-WM 4 – very HR

- IgM 7.456 mg/dl, β2M 6.6 mg/l, LDH 450 U/L;
- Hb 10.4 g/dl, WBC 3.600/mmc (L 500/mmc), PLT 125.000/mmc;
- hyperviscosity syndrome, spleen LD 230 mm

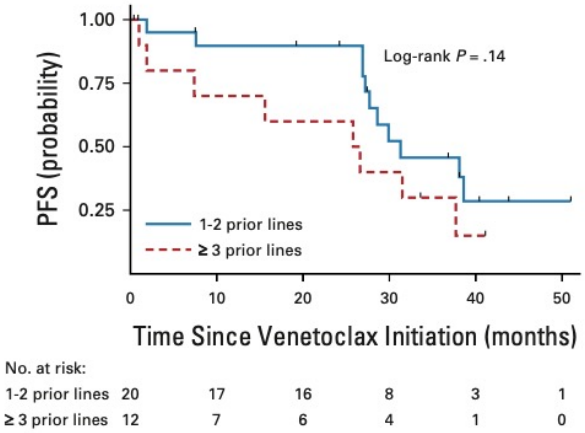


Dicembre 2021 (75 yrs): WM IPSS-WM 4, rIPSS-WM 4 – very HR

5th line?

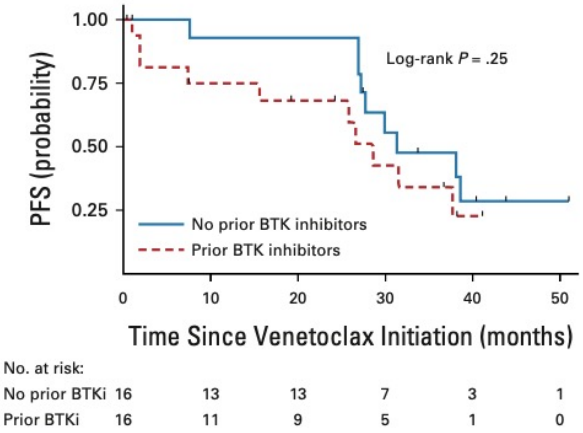
Venetoclax in Previously Treated Waldenström Macroglobulinemia

Jorge J. Castillo, MD[1,2]; John N. Allan, MD[3]; Tanya Siddiqi, MD[4]; Ranjana H. Advani, MD[5]; Kirsten Meid, MPH[1]; Carly Leventoff, BA[1]; Timothy P. White, BA[1]; Catherine A. Flynn, NP[1]; Shayna Sarosiek, MD[1,2]; Andrew R. Branagan, MD[2,6]; Maria G. Demos, BA[1]; Maria L. Guerrera, MD[1]; Amanda Kofides, BA[1]; Xia Liu, BA[1]; Manit Munshi, BA[1]; Nicholas Tsakmaklis, BA[1]; Lian Xu, BA[1]; Guang Yang, BA[1]; Christopher J. Patterson, BA[1]; Zachary R. Hunter, PhD[1,2]; Matthew S. Davids, MD[2,7]; Richard R. Furman, MD[3]; and Steven P. Treon, MD, PhD[1,2]



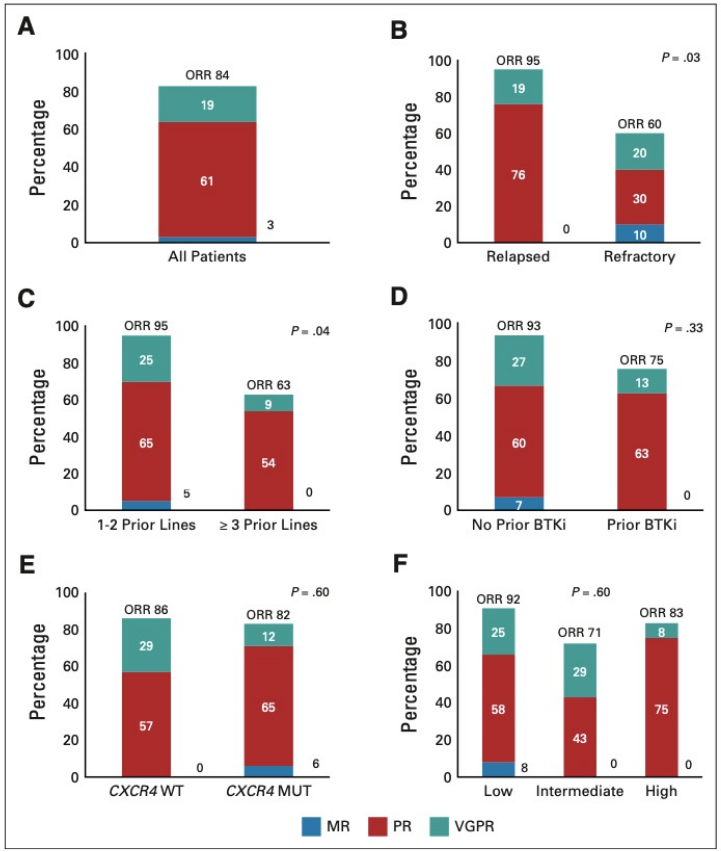
No. at risk:

1-2 prior lines	20	17	16	8	3	1
≥ 3 prior lines	12	7	6	4	1	0



No. at risk:

No prior BTKi	16	13	13	7	3	1
Prior BTKi	16	11	9	5	1	0



Castillo JJ, et al. J Clin Oncol, 2022

Mar 2022 (75 yrs): WM IPSS-WM 4, rIPSS-WM 4 – very HR

Start Venetoclax compassionevole

1. First week: 200 mg/day
2. Second week: 400 mg/day
3. From Third week: 800 md/day for 2 years

After 28 days:

- Hb 10.6 g/dl, WBC 6.120/mmc (N 4.320/mmc), PLT 320.000/mmc;
- IgM 2.650/mmc, β2M 5.4 mg/l, LDH 375 U/L;
- Urea 39 mg/dl, Creat 0.93 mg/dl, Uricemia 2.6 mg/dl;
- SARS-CoV2 positive → death after 20 days hospitalization in ICU.

Final considerations:

- CXCR4 assessment in all patients at onset
- WM as CLL? → del(17p), trisomy 12, del(11q), TP53 abn, ...
- DRC or Benda-R as first line?
- BTKi upfront in all HR patients?
- Proteasome inhibitors in combination with Rituximab?
- 2nd generation BTKi after prior exposure to 1st generation BTKi?
- Mutational study in BTKi refractory patients?

Grazie per l'attenzione

CATANIA

14 settembre 2022

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