OPTIMIZING THE USE OF STEM CELL TRANSPLANT IN MYELOMA

Controversial cases presented by local physicians with emphasis on local practice

CASE REPORT: Syngeneic SCT in MM

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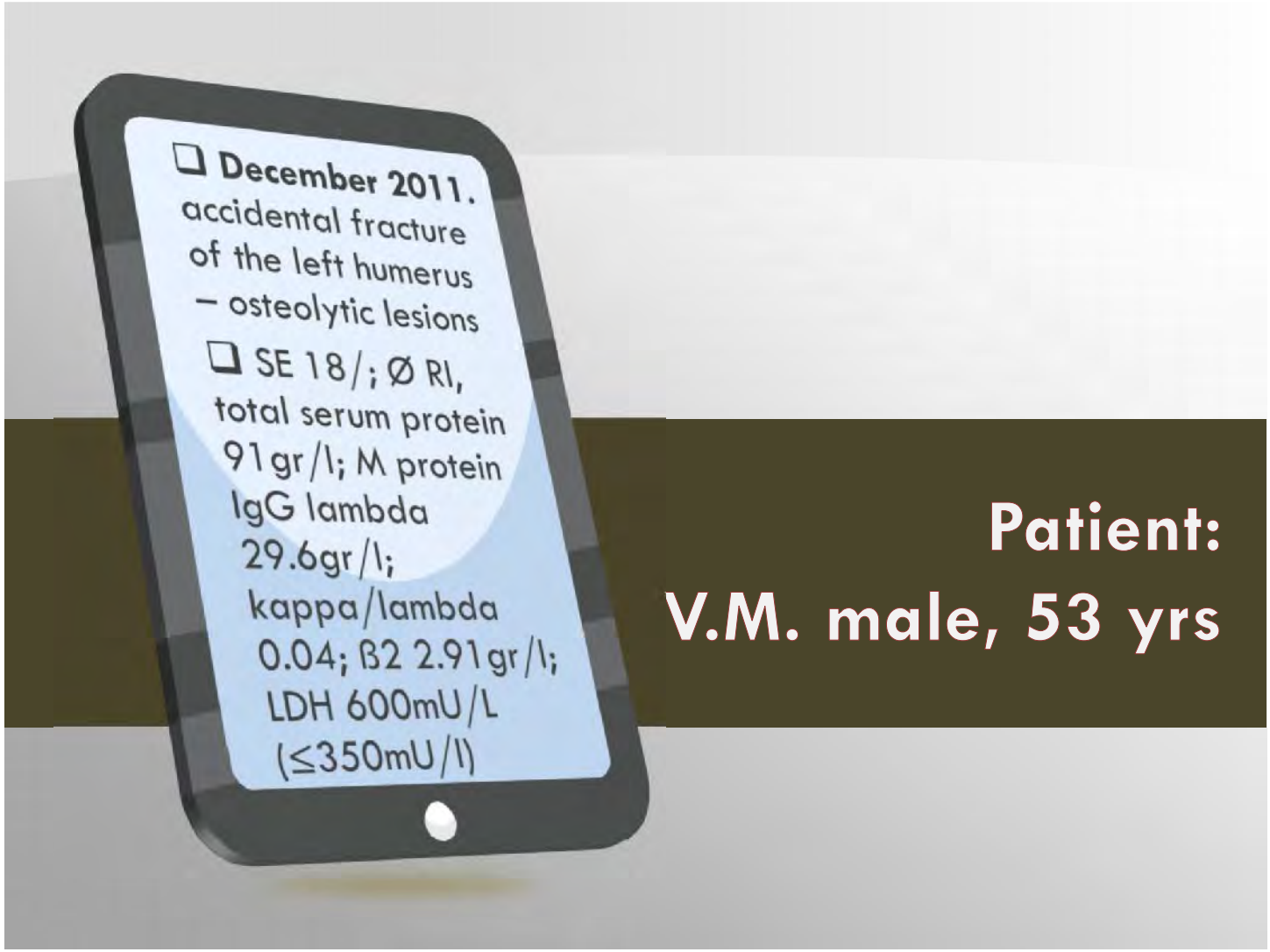
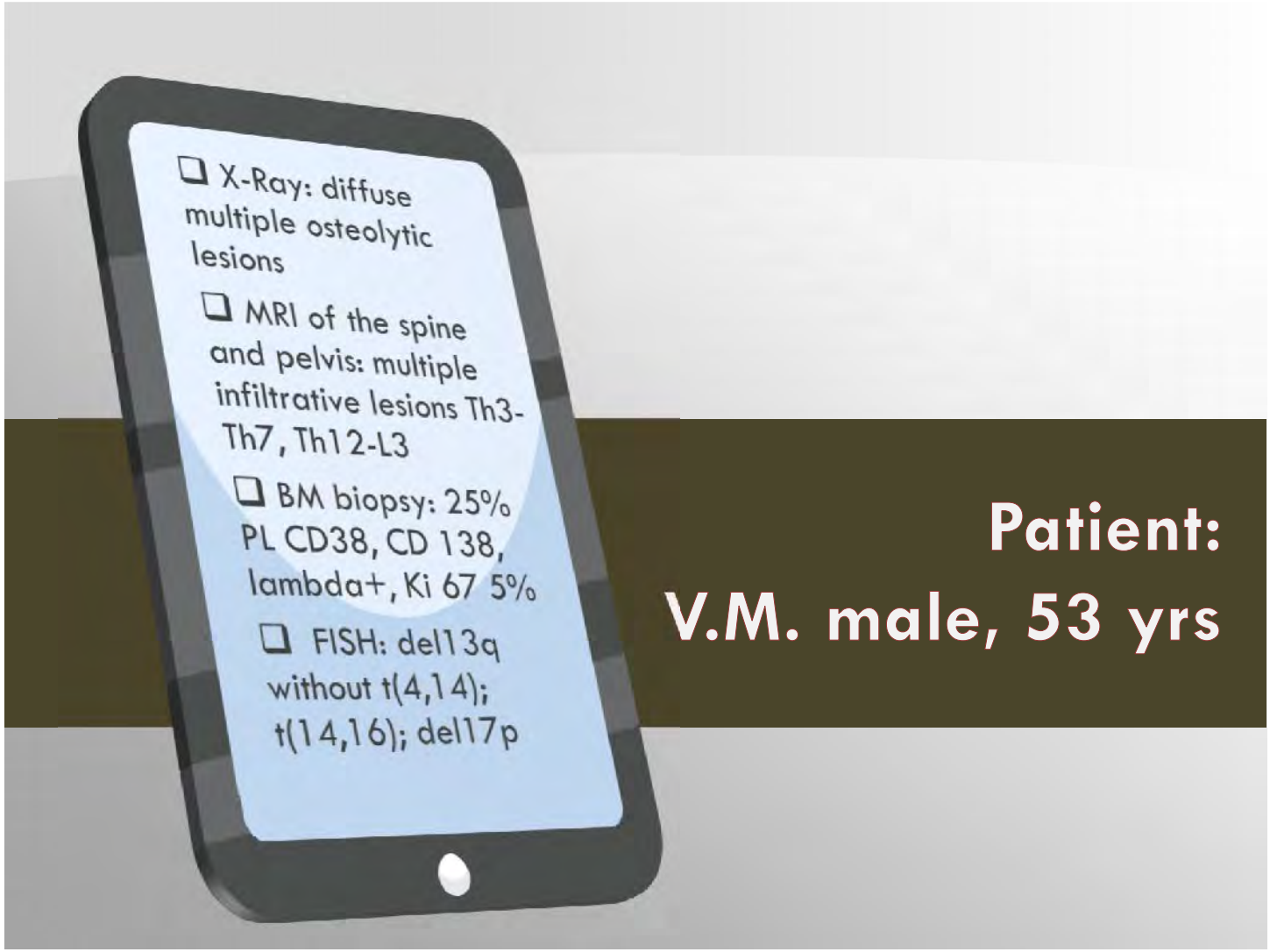
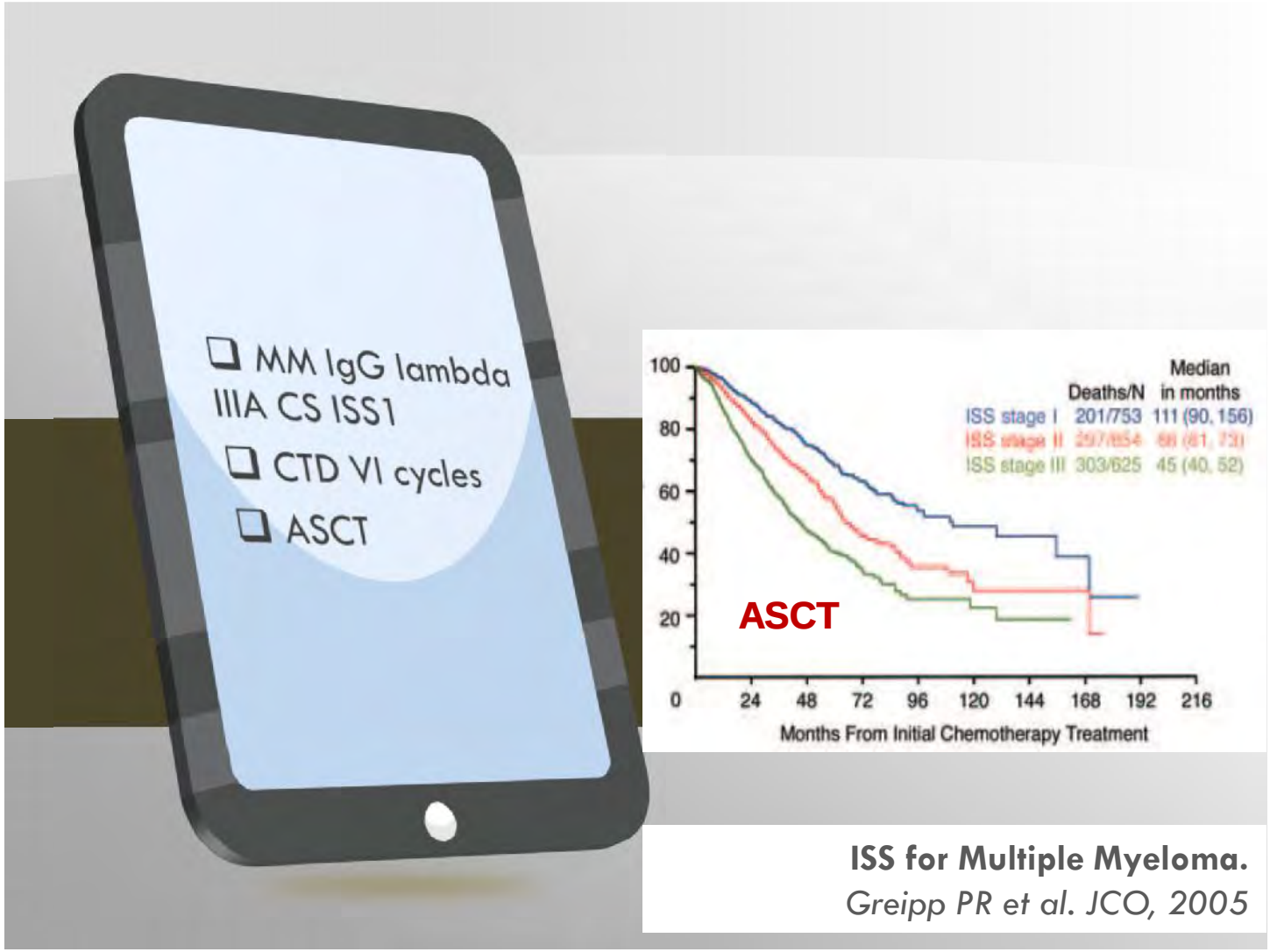
DIAGNOSIS AND STAGING

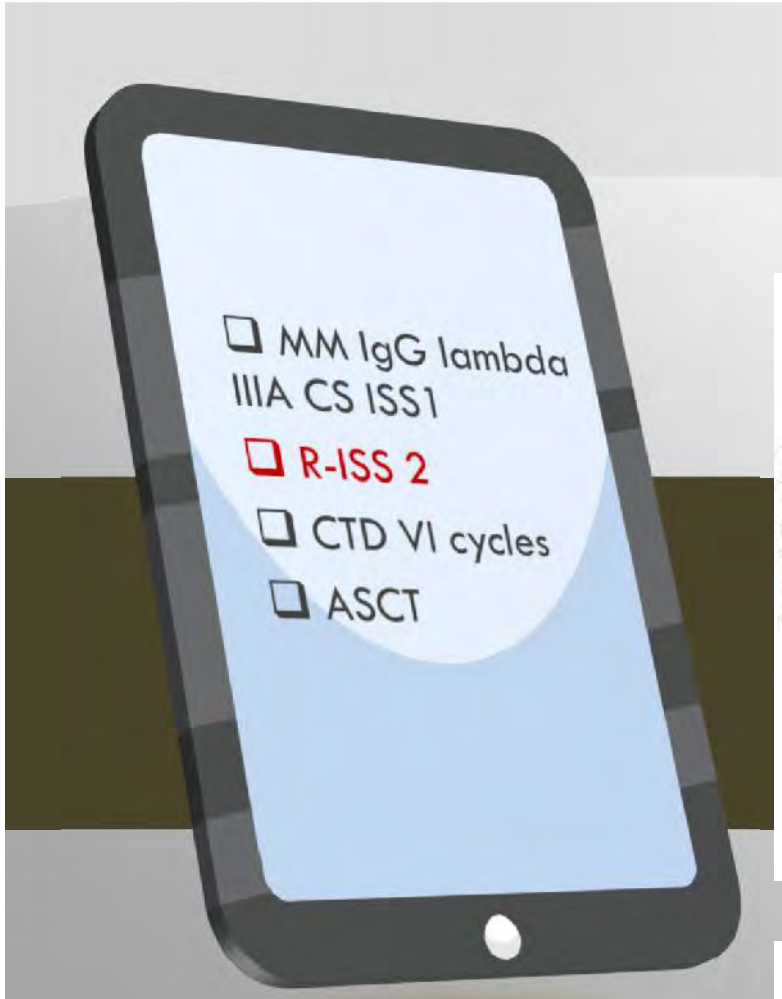

❑ December 2011.
accidental fracture
of the left humerus
– osteolytic lesions
❑ SE 18/; Ø RI,
total serum protein
91 gr/l; M protein
IgG lambda
29.6gr/l;
kappa/lambda
0.04; ß2 2.91 gr/l;
LDH 600mU/L
(≤350mU/l)
Patient:
V.M. male, 53 yrs

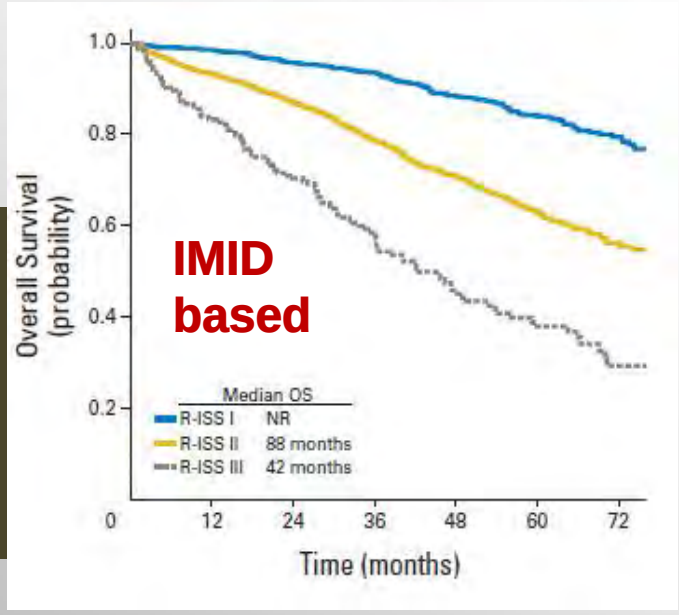

❑ X-Ray: diffuse multiple osteolytic lesions
❑ MRI of the spine and pelvis: multiple infiltrative lesions Th3-Th7, Th12-L3
❑ BM biopsy: 25% PL CD38, CD 138, lambda+, Ki 67 5%
❑ FISH: del13q without t(4,14); t(14,16); del17p
Patient:
V.M. male, 53 yrs

TREATMENT

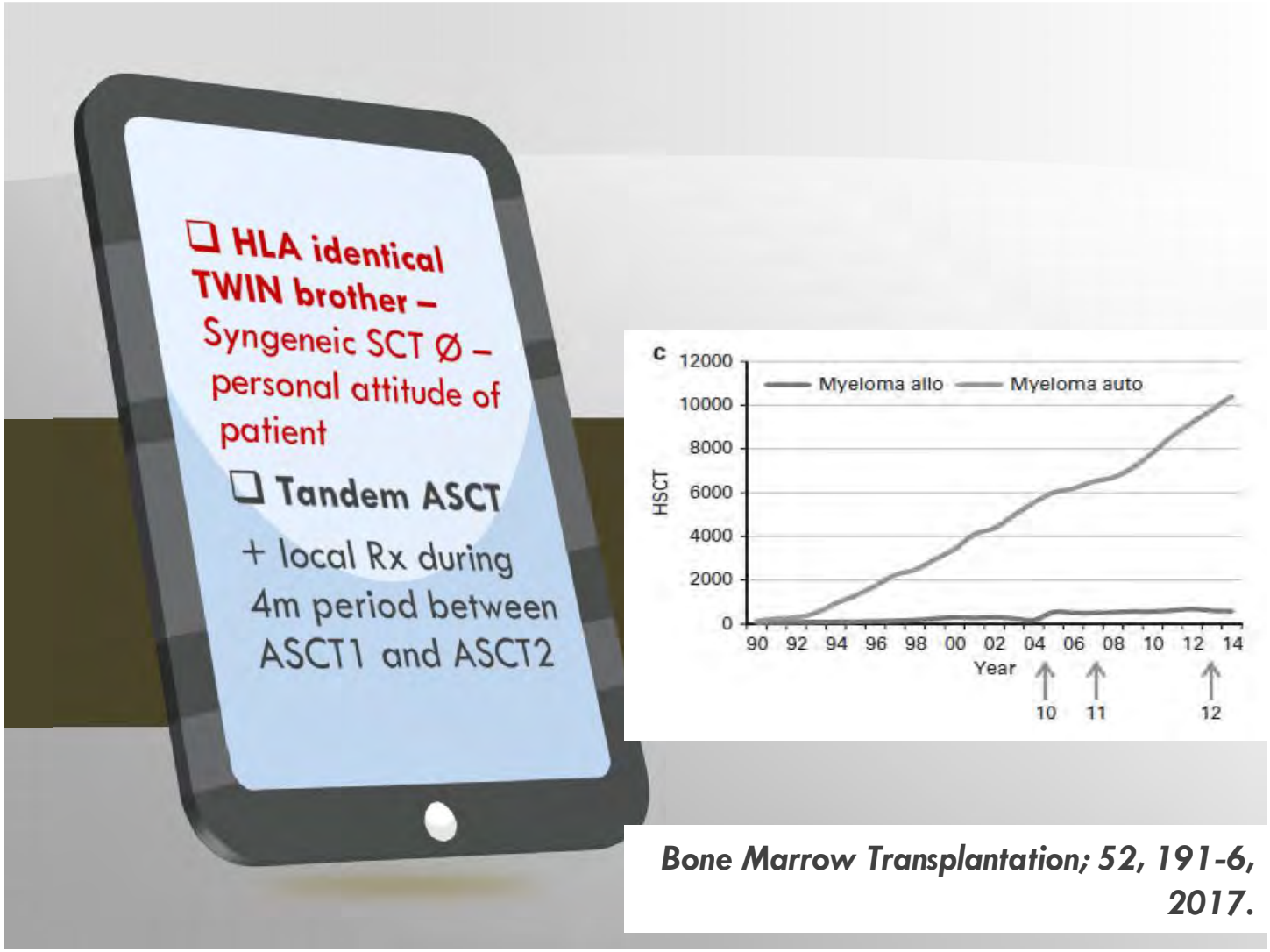


ISS for Multiple Myeloma.
Greipp PR et al. JCO, 2005

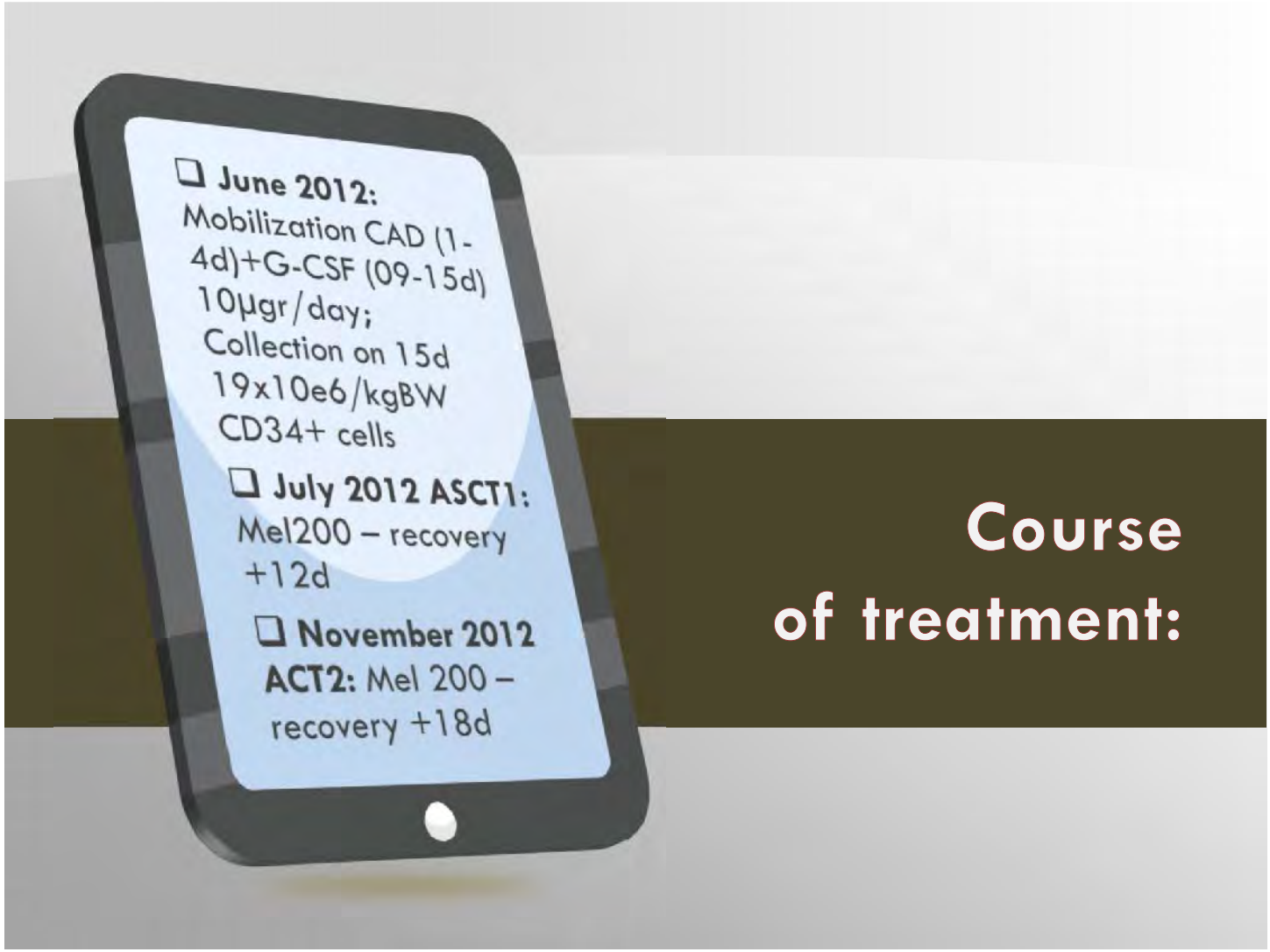




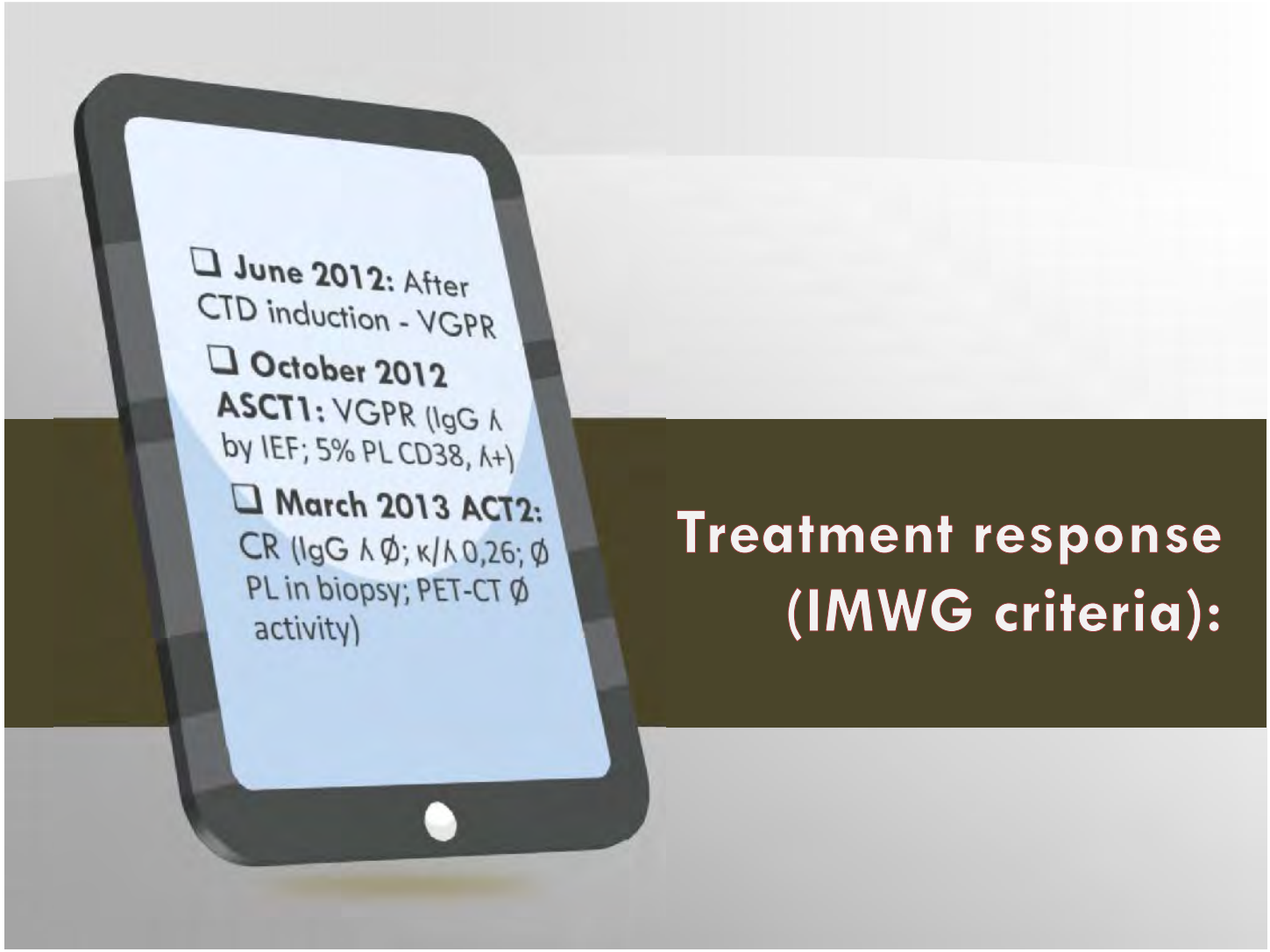
R-ISS for MM: An IMWG Report
Palumbo et al. JCO, 2015



Bone Marrow Transplantation; 52, 191-6, 2017.

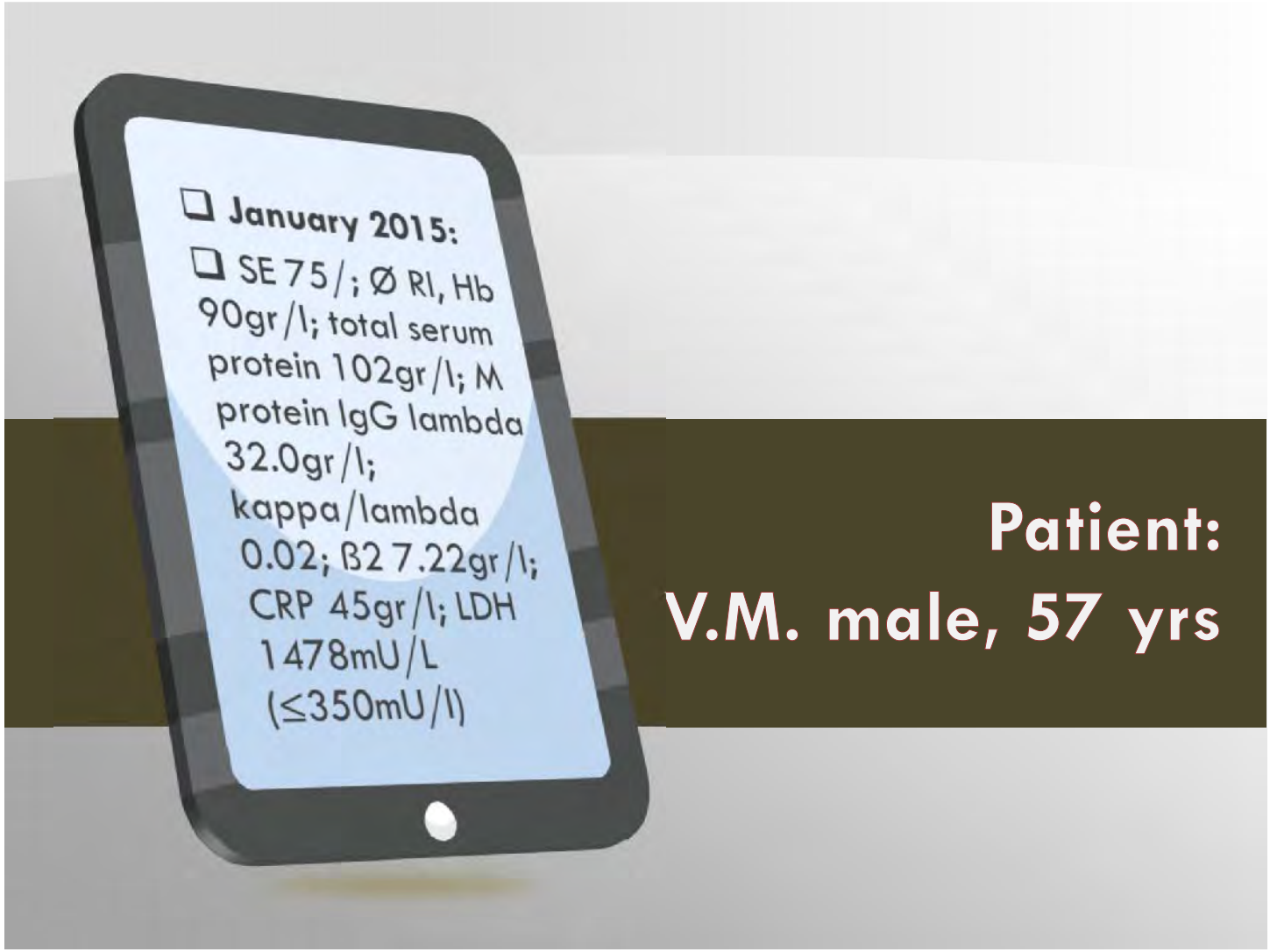

❑ June 2012:
Mobilization CAD (1-4d)+G-CSF (09-15d) 10µgr/day;
Collection on 15d 19x10e6/kgBW CD34+ cells
❑ July 2012 ASCT1:
Mel200 – recovery +12d
❑ November 2012 ACT2: Mel 200 – recovery +18d
Course of treatment:

TREATMENT RESPONSE


❑ June 2012: After CTD induction - VGPR
❑ October 2012 ASCT1: VGPR (IgG λ by IEF; 5% PL CD38, λ+)
❑ March 2013 ACT2: CR (IgG λ Ø; κ/λ 0,26; Ø PL in biopsy; PET-CT Ø activity)
Treatment response (IMWG criteria):

❑ Maintenance:
Thalidomide
100mg/d x12m
❑ Visits in 3m periods
❑ January 2015:
Peristently febrile (38-39°C) without proven infective etiology -
Relapse?
FOLLOW-UP:

1. RELAPSE


January 2015:
SE 75/; Ø RI, Hb 90gr/l; total serum protein 102gr/l; M protein IgG lambda 32.0gr/l; kappa/lambda 0.02; ß2 7.22gr/l; CRP 45gr/l; LDH 1478mU/L (≤350mU/l)
Patient:
V.M. male, 57 yrs

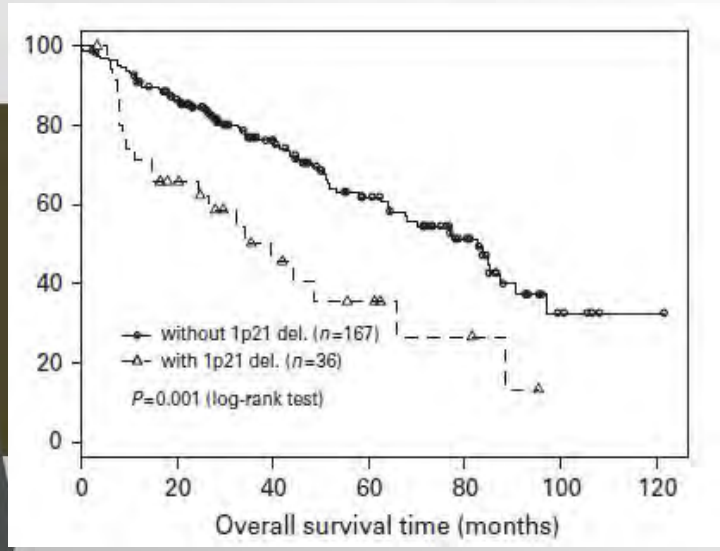
❑ **X-Ray:**

Ø progression of bone disease

❑ **BM biopsy:**

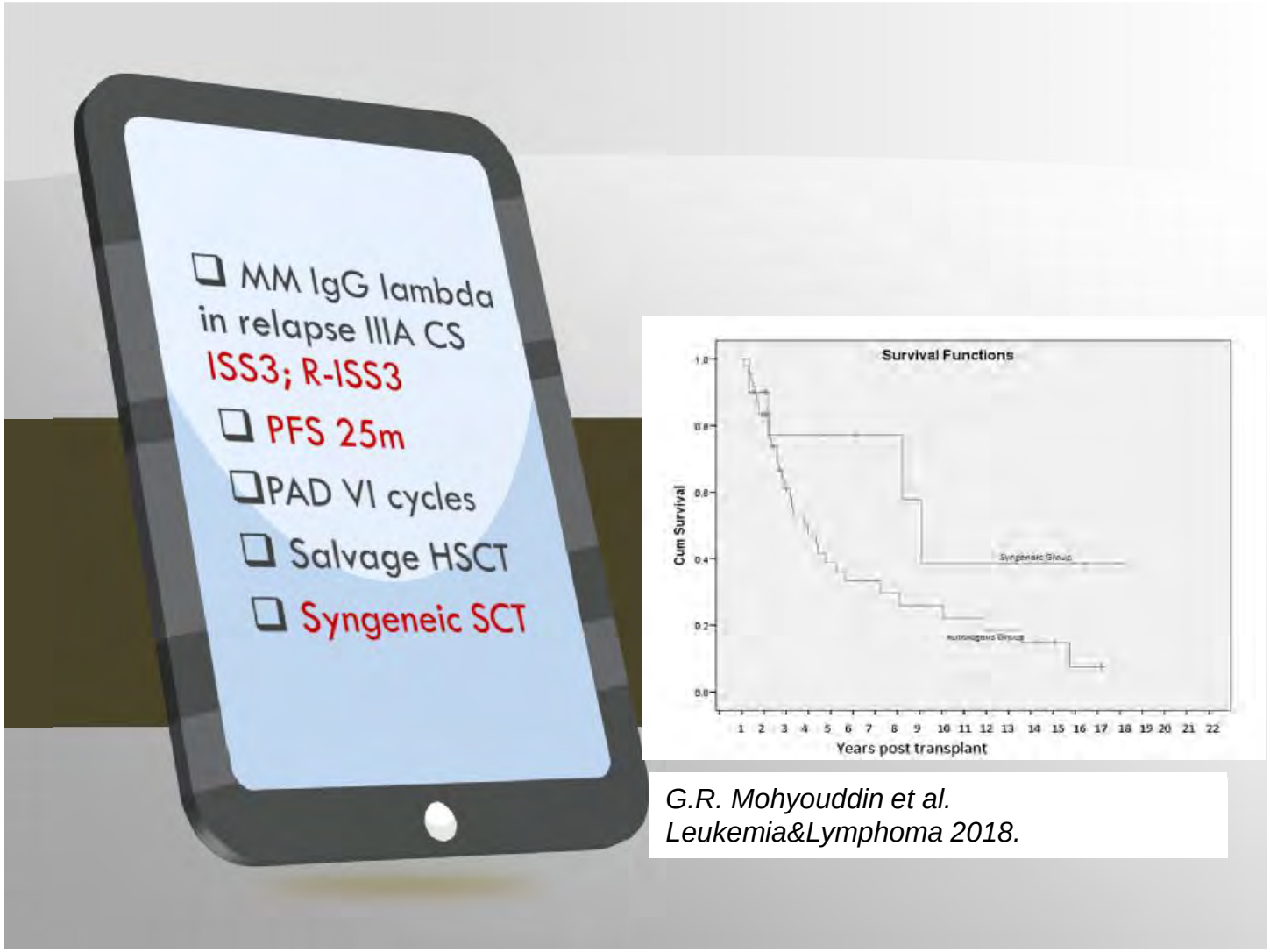
39% PL CD38, CD 138, lambda+ , Ki 67 20%

❑ **Control FISH: del 1p21** (25% nuclei); **del 17p13.1** (10% nuclei)

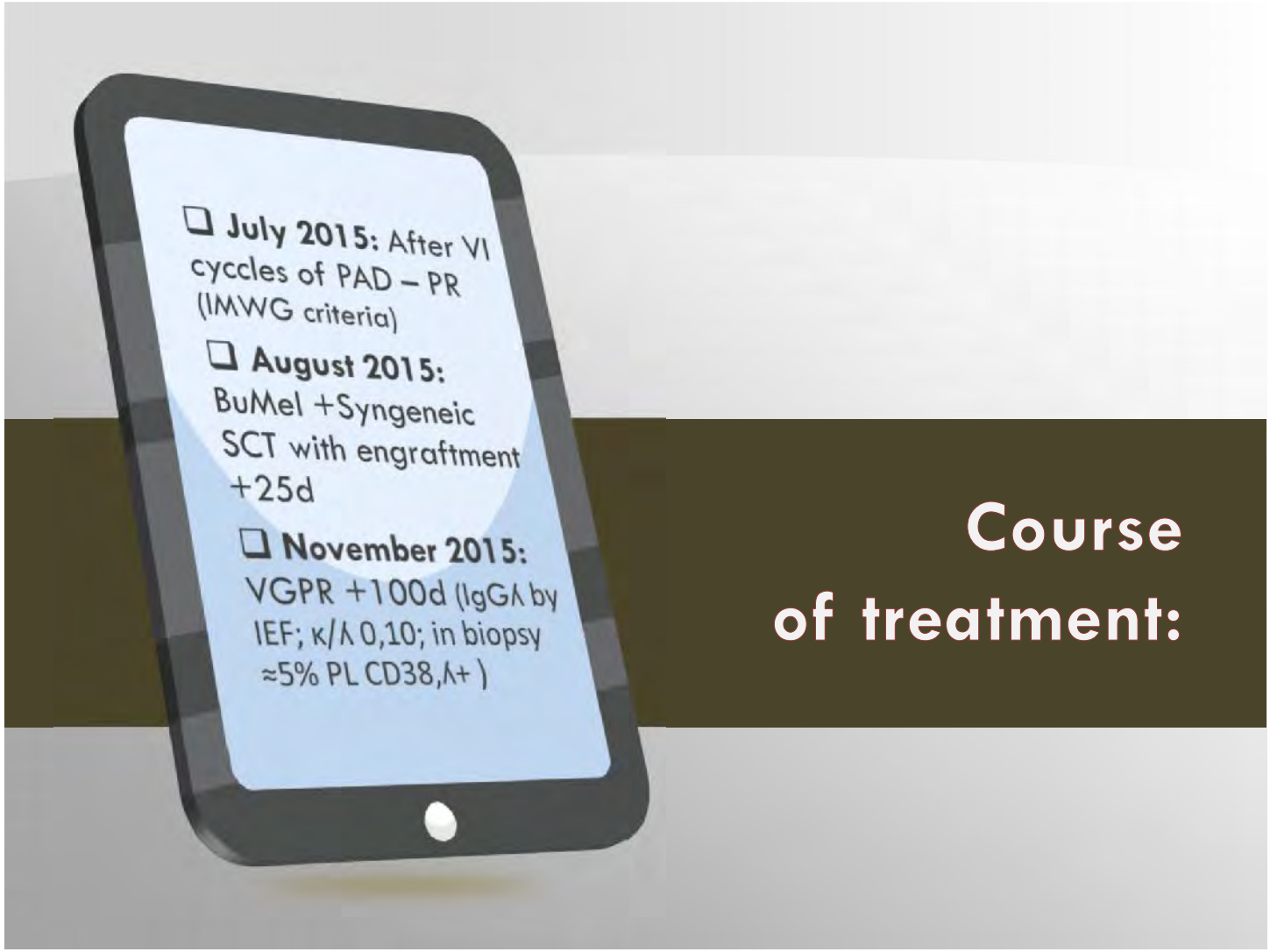


H.Chang et al. 1p21 deletion in myeloma. Bone Marrow Transplantation 2010.

TREATMENT AND COURSE OF DISEASE

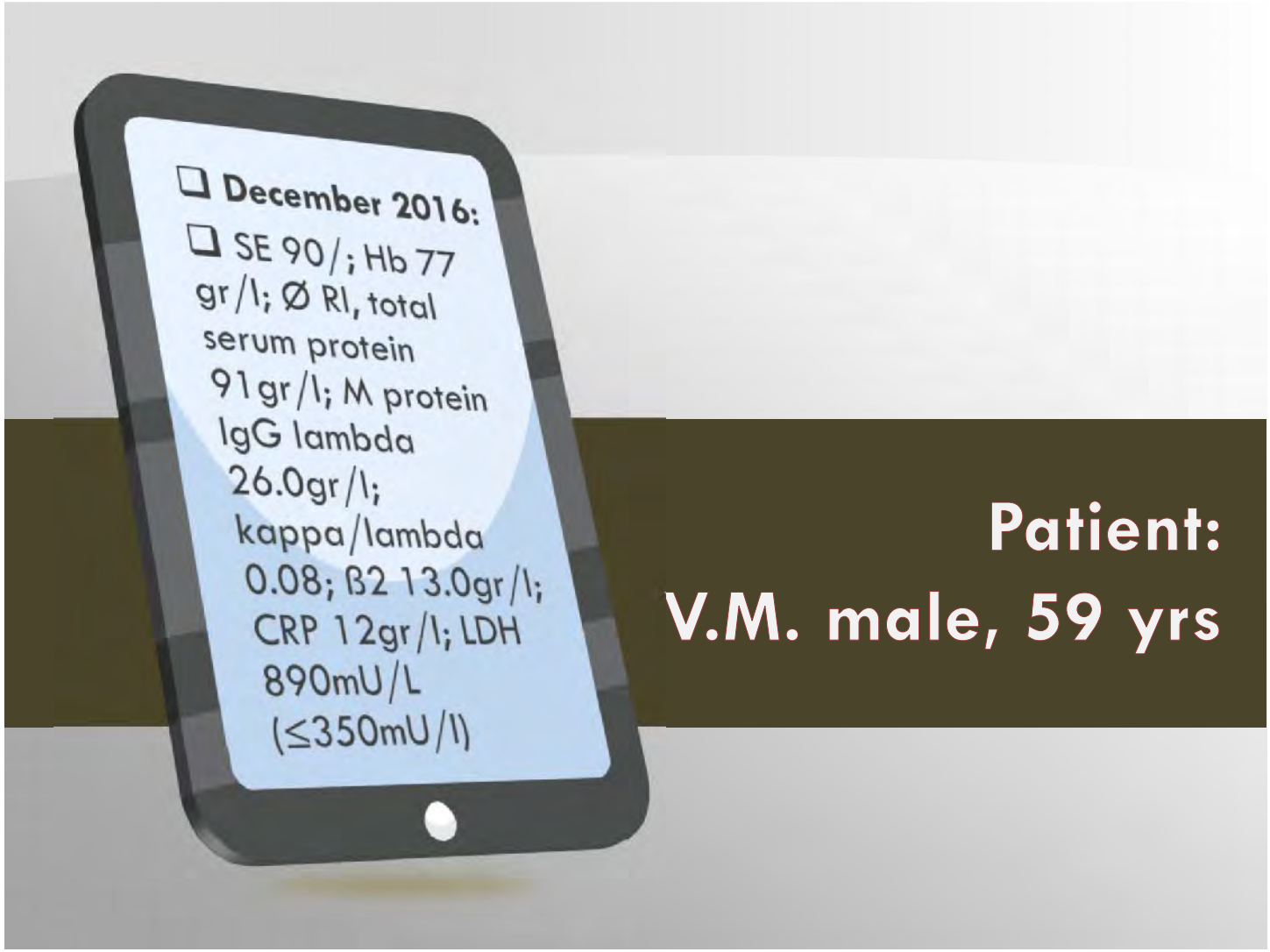


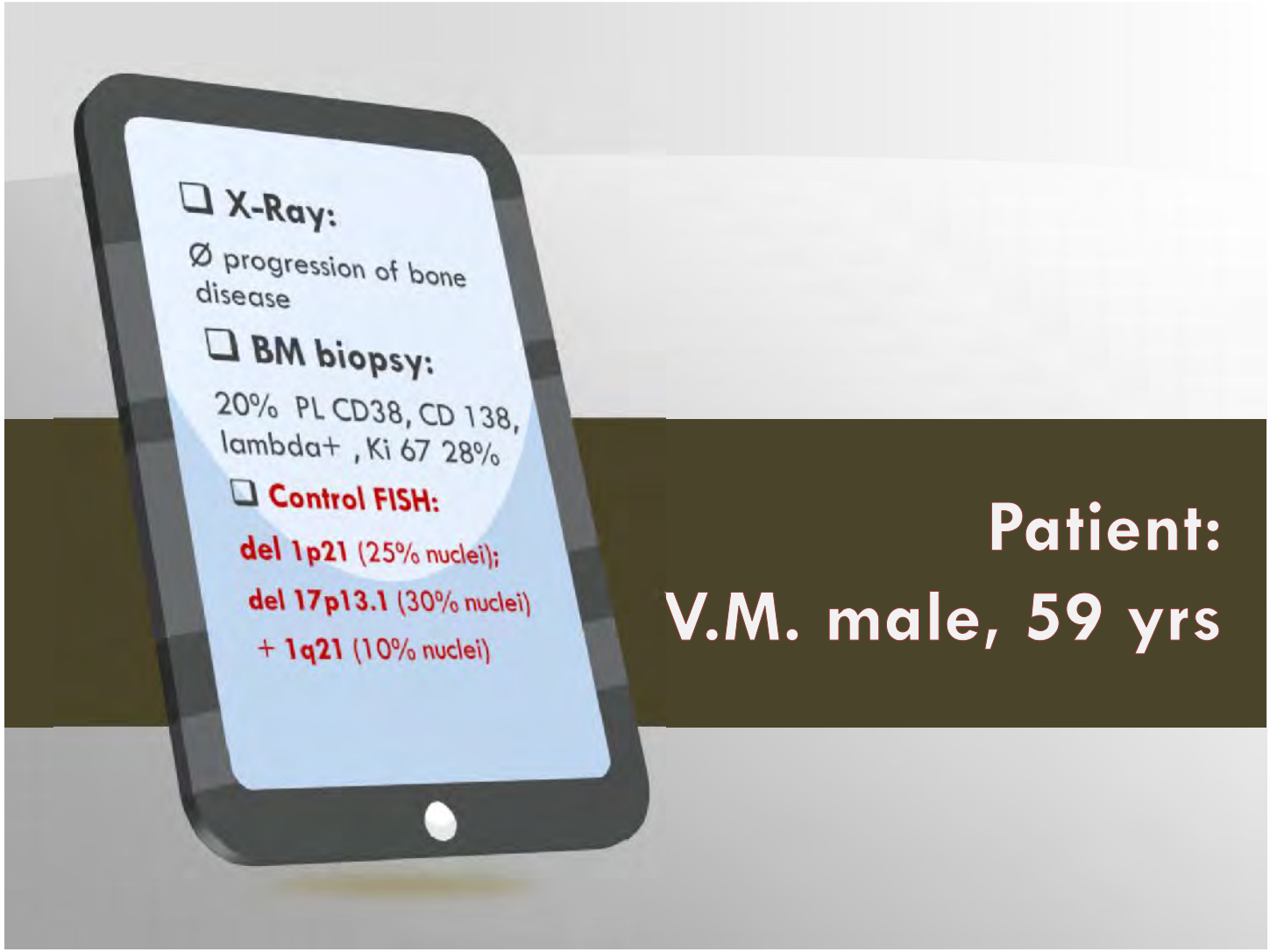
G.R. Mohyouddin et al. Leukemia&Lymphoma 2018.


❑ July 2015: After VI cycles of PAD – PR (IMWG criteria)
❑ August 2015: BuMel +Syngeneic SCT with engraftment +25d
❑ November 2015: VGPR +100d (IgGλ by IEF; κ/λ 0,10; in biopsy ≈5% PL CD38,λ+)
Course of treatment:

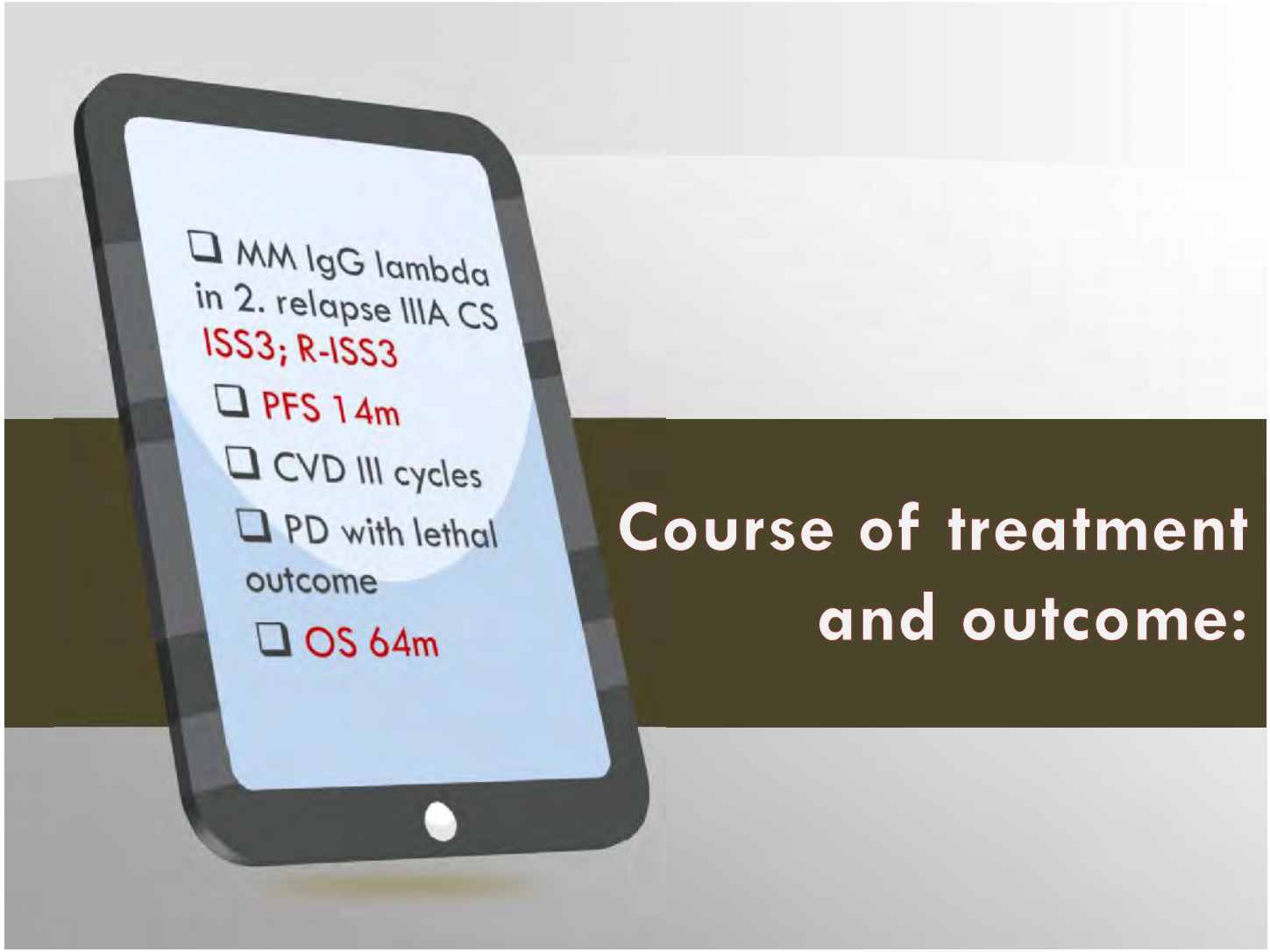
❑ Maintenance:
Thalidomide
100mg/d x12m
❑ Visits in 3m periods
❑ December 2016:
Fatigue, bone pain
❑ Relapse?
FOLLOW-UP:

2. RELAPSE


December 2016:
SE 90/; Hb 77 gr/l; Ø RI, total serum protein 91gr/l; M protein IgG lambda 26.0gr/l; kappa/lambda 0.08; ß2 13.0gr/l; CRP 12gr/l; LDH 890mU/L (≤350mU/l)
Patient:
V.M. male, 59 yrs


❑ X-Ray:
Ø progression of bone disease
❑ BM biopsy:
20% PL CD38, CD 138, lambda+ , Ki 67 28%
❑ Control FISH:
del 1p21 (25% nuclei);
del 17p13.1 (30% nuclei)
+ 1q21 (10% nuclei)
Patient:
V.M. male, 59 yrs

TREATMENT AND OUTCOME


❑ MM IgG lambda
in 2. relapse IIIA CS
ISS3; R-ISS3
❑ PFS 14m
❑ CVD III cycles
❑ PD with lethal
outcome
❑ OS 64m
Course of treatment
and outcome:

OPEN QUESTIONS:

2

Optimal induction
Bz based 3-drug combo
Position of syngeneic SCT
After 1. ASCT

1

Recommended FISH panel
- At diagnosis
- In relapse

3

Position of salvage SCT in the era of new drugs

Optimizing the use of stem cell transplant in myeloma

(Albanian case)

Arben Ivanaj

UMT of Tirana, Albania

Me disclaim

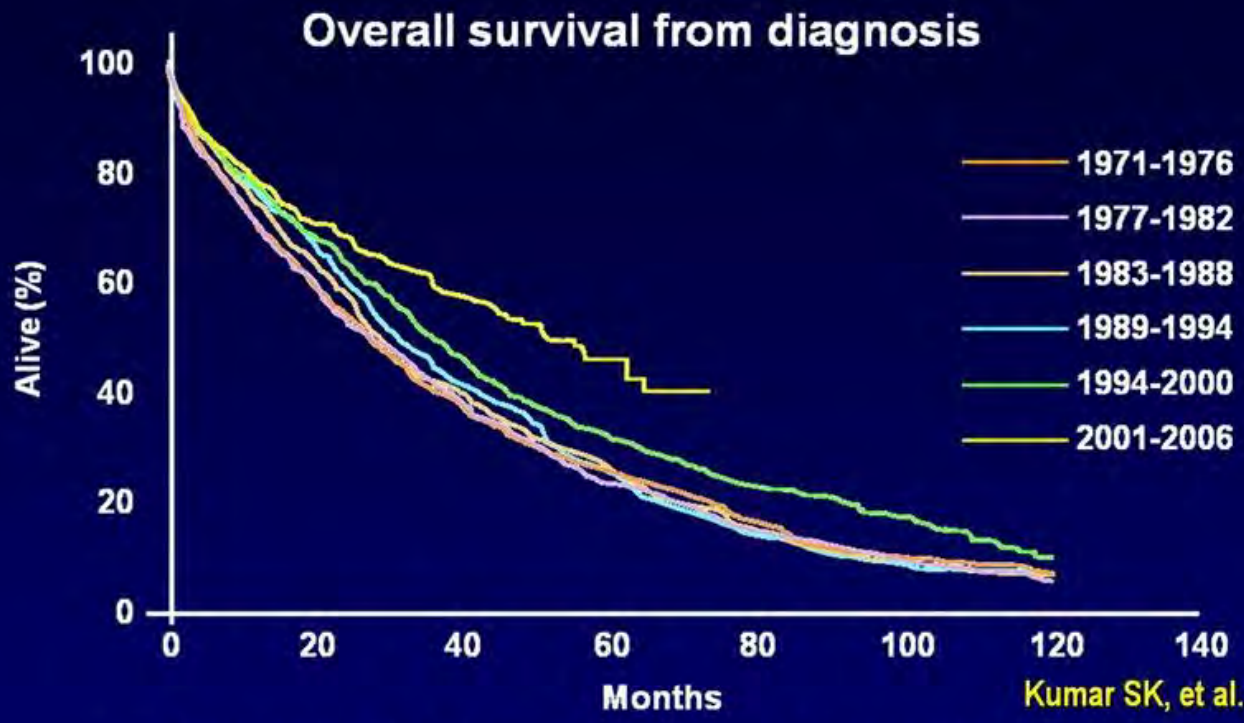
- I received disbursement from Novartis, Roche, Pfizer, etc..

Distribution by age MM in 100 000

No.	*age*	*car*	*population by age*	*Incidence /100 000 people*
2	**25-34 years**	2	426 325	0.47
3	**35-44 years**	14	432 708	3.24
4	**45-54 years**	39	350 491	11.13
5	**55-64 years**	62	240 683	25.76
6	**> 65 years**	49	256 857	19.08
	TOTALI	**166**	**1 707 064**	**9.72**

T. Caja, A Ivanaj, and al. EPIDEMIOLOGICAL DATA OF MULTIPLE MYELOMA IN ALBANIA, Haematologica, June 2013, abstract, B1542

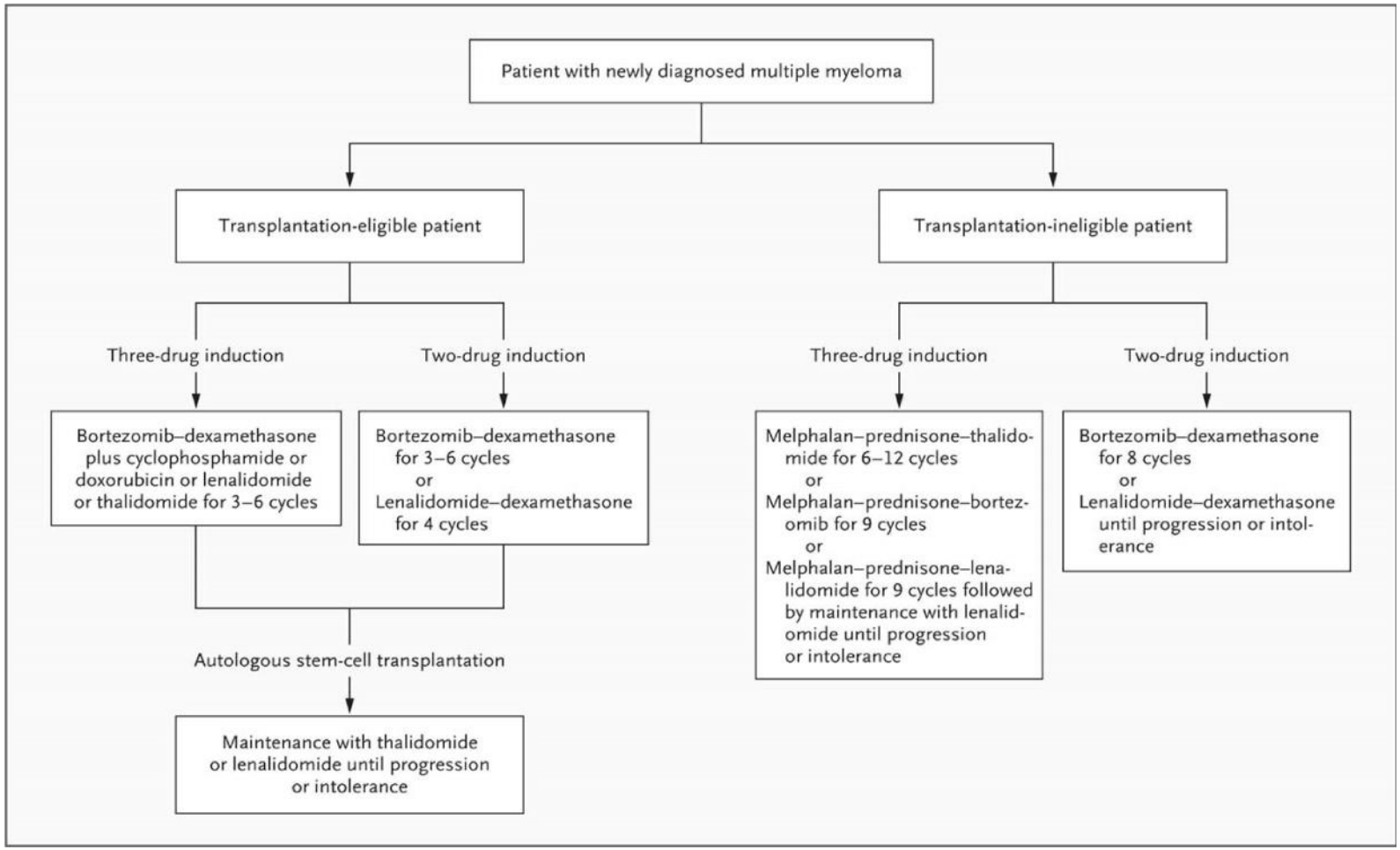
The Good News



Kumar SK, et al. Blood. 2008

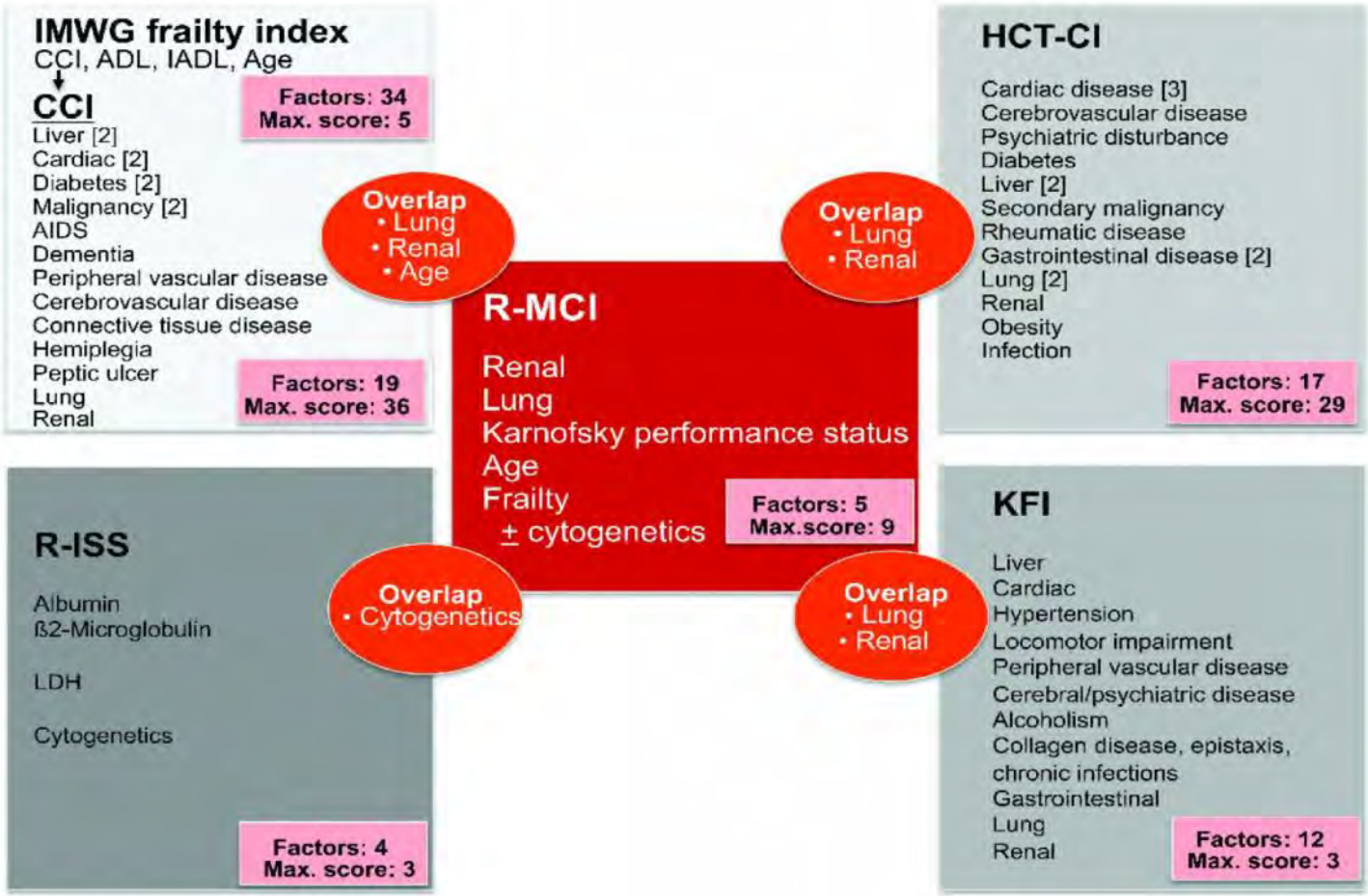
- Outcomes for patients are clearly improved
- The use of HDT or melphaln based novel agent inductions have doubled median survival for nearly all patients

Suggested Approach to the Treatment of Newly Diagnosed Multiple Myeloma



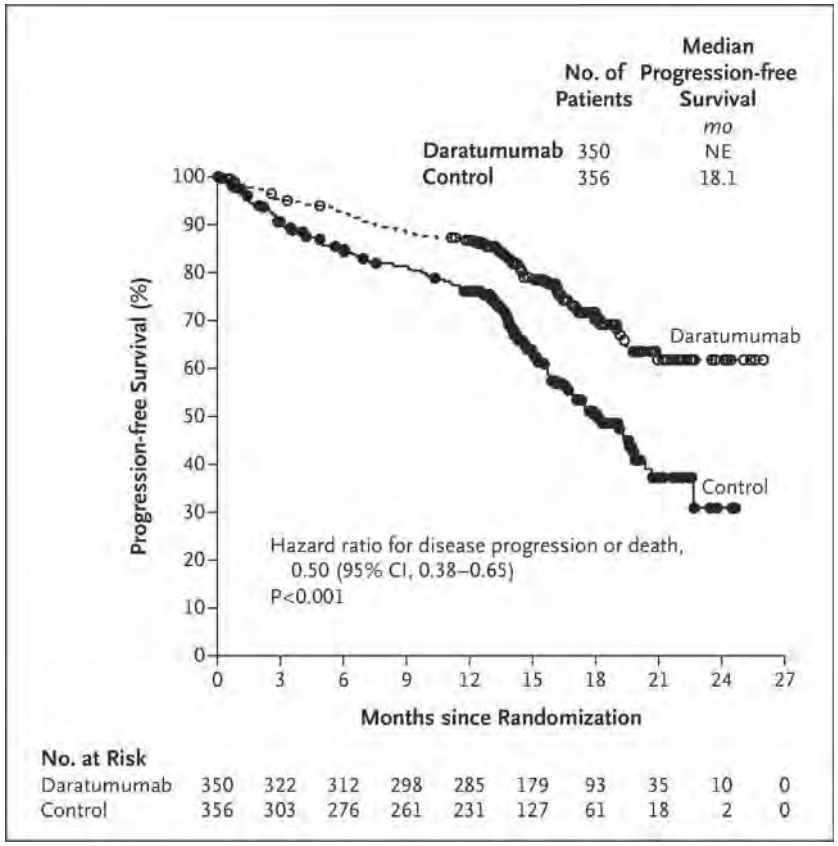
Palumbo A, Anderson K. N Engl J Med 2011;364:1046-1060

Scoring factors and maximum points of the R-MCI as compared to the IMWG frailty index, CCI, HCT-CI, KFI and R-ISS.



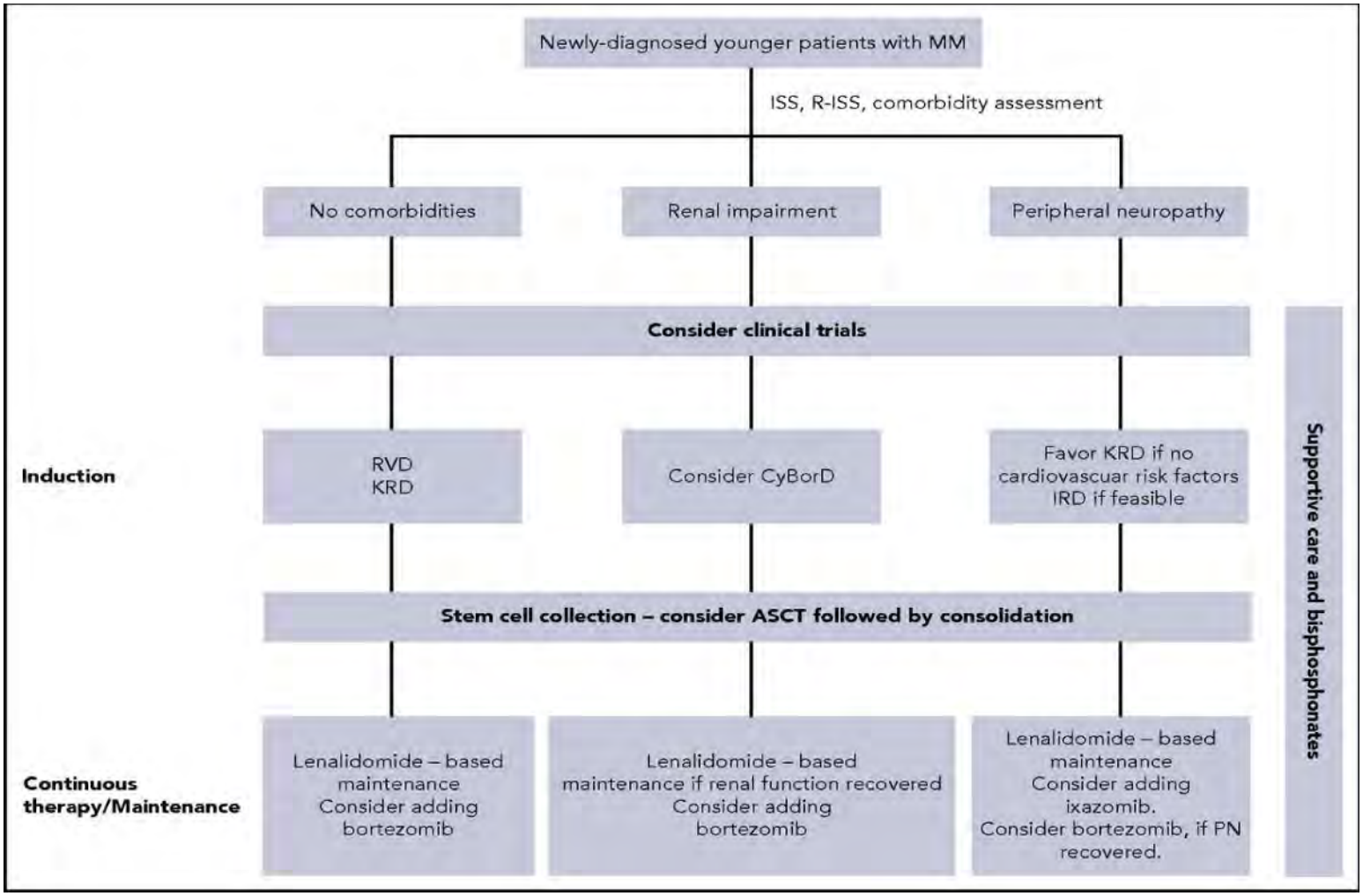
Monika Engelhardt et al. Haematologica 2017;102:910-921

Progression-free Survival.



M Mateos et al. N Engl J Med 2018;378:518-528.

Proposed guidelines for management of younger MM patients.



Sara Gandolfi et al. Blood 2018;132:1114-1124

What is the goal of treatment in elderly multiple myeloma patients?

- Prolong survival
- Delay disease progression → Cure?
- Ensure good quality of life

What is needed to achieve this?

Maximal eradication of tumor clone through achievement of best possible response balanced with acceptable toxicity

Case pts 1

- Hommen 57 y
- MM stage III A

- VAD if CR/PR (no pain, cytologic and serologic PR/ CR) stop the treatment to progression.

- Second line VED, +/- Alkeran

Albania frontline therapy in MM….

- VAD
- VED
- Cyclophosphamide + dexamethasone
- Alkerane + prednisone
- ….

Case pts 2…..Albanian pts treated in London

- Hommen 61 year
- 2005 MM st III A
- VED + SCBT x 2 + lenalidomide
- After 13 y …. progression ….what treatment ??

Case pts 2

- We have 5- 8 pts like this that we follow-up per year,
- We don’t have choices

- The first choice

- Phase I or II study …

- New drugs, CAR T cell, immunotherapy etc …..

phase III ARROW trial

- The study randomly assigned participants to receive either a 30-minute infusion of once-weekly carfilzomib 70 mg/m^2 with dexamethasone or a 10-minute infusion of twice-weekly carfilzomib 27 mg/m^2 with dexamethasone.

- Patients receiving the once-weekly treatment had longer progression-free survival compared with the twice-weekly cohort (11.2 months vs. 7.6 months, respectively; p=0.0014). The overall response rates were 62.9 percent and 40.8 percent in the once-weekly and twice-weekly arms, respectively (p<0.0001).

LANCET, VOL 19, 7, P953-964, JULY 01, 2018

….case pts 1 vs case pts 2

- …big difference …. We know, but ?
- How to reduce the difference….
- The change came from in inside …
- …why not a collaboration..;
- … a project

Conclusion

- In real world there exists a big difference for treatment of the pts with MM
- Only with work we can retrieve the lost time
- Solidarity from the EHA….

Thank you

Myeloma

Case study

Ibricevic Balic Lejla

Case Study

SA, female, born 1952., 58 age

Patients was refered to hemathologist due to elevated SE
Rutne laboratory showed elevated SE in march 2010. , no comorbidities

Check up in In december lab results deteriorated
decembar 2010.godine
SE 57/- >150,
Hgb 134-124 g/L
Creatinin 82 (45-90) umol/L, kreatinin klirens 1.9 (1.36-2.43) ml/s
Ca -2,68 mmol/L
Proteins 74.0-104.0/ serum albumin 39.0-39.0
Serum protein electroforesis: alfa1 glob0,03 alfa2 globulini 0,08 beta globulini 0,28 paraprotein gana globulini 0,10
Bence Jonce : present in urin , kappa 6,7 lambda 153,0 k/lamb. 0.04 /rv 0,75-4,5

IgG 5.4 **IgA 13.1** IgM 0.3.
LDH 306 U/L normalan (rv 230-460)
beta 2mcroglobulin 4.0 - 4.9 umol
Bone marrow citology; infiltration with plasma cells 26%-28%
Bone marrow biopsy: atipic plasma cells 30%:CD38+,CD117+,lambda*,kapa+,MUM-1 +.
Cytogenetics: 46 XX FISH: negative for delp53, t(4;14), t(14;16),
Radiogram:without osteoltic lesions
Diagnosis: Myeloma Multiplex IgA lambda CS IIA ISS II/R-ISS II

Treatment

- **First line: VTD** (Velcade, Thalidomid, Dexamethason)
  2 cycles + biphophonates (zolendronic acid)
- Evaluation after 2 cycles: Hgb 128, urea 7.9, creatinin 86 , Ca 2,56 mmol/L, serum protein 57,0 gL /alb.30,0

  paraprotien in serum electroforesis and Bence Jonce : negative, IgG 3,6 IgA 2,3 IgM 0,2, LDH 306 U/L

  bone marrow smear: 6% plasma cells
- Very good partial response
- Toxicity- polyneuropathy

1. ASCT 13.06.2011.

- mobilisation with cyclophophosphimide conditioning with Melfalan 200 mg/m2 13.06.2011.g.
- no manitenance therapy – biphosphonates

December 2014.

- Back pain in december 2014, following evaluaton: december 2014.

  Se 34 , proteins 80,0/alb.40,0 no paraprotiens

  Hgb 141 g/L, IgG 10,8 IgA 3,56 IgM 0,48

  Ig kappa 12,77 Ig lambda 76,33 (5,7-26,3 mg/l

  light chains in urin lambda 116,97 mg/l

  light chains in serum: kappa 3,63 (1,7-3,7) g/l, lambda 2,16 (0,9-2,1) g/L kapa/lambda 1,68 (1,35-2,65)
- Imunofixation of urin Ig lambda **37,95**

  LDH 295 U/L

  bone marrow smear: 2% plasma cells,

  bone marrow fow cytometry- no monoclonal plasma cells

  MRI - lesions in pubic bone,

  PET/CT metabolic active lesions in pubic and ishiadic bone, sternum, byopsy of te lesions in pubic bone- verified relapse od myeloma extramedulary

- First late relapse / extramedulary: january 2015.g.
- Therapy 2 cycles of VTD
- Evaluation after 2 VTD:
- SE 55, renal function: normal, LDH 448 elevated

  Serum proteins 63,1 albumins 56,4, no paraprotein

  Imunofixason:

  serum IgG 6,2, IgA 0,63, IgM 0,55, IgKappa 5,26 Ig-lambda 7,17 Ig-Lambda lanci 1,36

  Urin: kappa lanci 11,73 (0,012-32,71 mg/L)

  bone marrow biopsy i flow cytometry: normal,

  PET-CT: VGPR

2. ASCT 21.05.2015.

- Second autologus stem cell transplant
  - Melfalan 140mg/m 21.05.2015.

6,0x10 8/kg body weight

Engraftment +11 day

August- october 2015.

- Evaluation within 100 days of PBSCT:

FISH shows10% cells with del p53

- PET-CT in august 2015 shows deposits in left pubic bone
- october 2015. palliative radiation TD 30Gy of left pubic bone
- Maintenance therapy Lenalidomid 10 mg for 2 years

2016

- june 2016.-evaluation
- PET/CT discrete progresion of lesios in ishiadic bone,
- Elevated light chains in serum (IgLambda 242,37 mg/l and Ig kappa 225,25 mg/L)
- Lenalidomid 20 mg/dan 21 + Deax 40 mg 1-4 day
- August 2016.suprarenals insuficiency
- Dexamethason discontinued

August 2016

- August 2016. PET-regresion of lesions -left pubic bone, ishiadic bone -complete regresion

December 2016

- Progression- CT showed tumor mass in sternum 48 mm x 30 mm
- Irradiation in january 2017. TD 20Gy/10f

2017.

- Terapy continued with Revlimid 25 mg from january 2017.
- detetrioration of lab. results in august 2017.
  Anemia, trombocytopenia, IgA 3.86
- Both : Igkappa and Ig lambda elevated,
- Revlimid reduced to 15 mg/day for 21 days
- Stable disease

2018

- In may 2018 evaluation showed stable disease
- In october 2018 progression – tumor mass in sternum has enlarged
- Elevated IgA in serum, Bence Jonce: poz
- Therapy : cyclophophamide/lenalidomide/dexa

Conclusion

- Myeloma Multiplex IgA lambda CS IIA ISS II/R-ISS II
- First line: VTD 2 cycles + HDT+ASCT
- First late relapse after I ASCT extramedullary (osis pubis, ossis ishiadici et sternum)
- Second line : VTD 2 cycles and II HDT+ASCT
- FISH after II ASCT: del p53
- maintenance therapy: Lenalidomid mono
- Progression of lesions after 5 months: extramedullary (osis pubis, ossie et sternum) radiotherapy + Lenalidomid/Dexamethason
- Complications: Mb.Adison,
- Lenalidomid mono : Thrombocythopenia
- Lenalidomid reduced to 15 mg/day
- Partial remission up till october 2018: tumor mass in sternum enlarged with propagation in soft tissues – radiotherapy , Ixazomib ?

Current approach to the treatment for the elderly myeloma patients

Thierry Facon, MD

Professor of Hematology
Service des Maladies du Sang
University of Lille
Lille, France

Disclosures

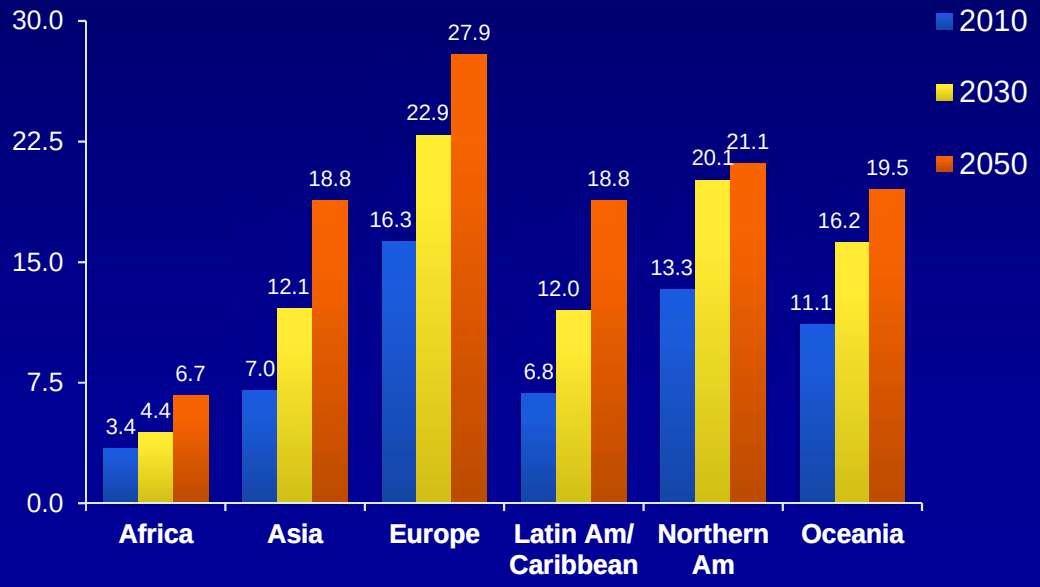
- Member of the speaker's bureau of Celgene and Janssen
- Advisory boards for Celgene, Janssen, BMS, Takeda, Amgen, Novartis, Karyopharm

This presentation will discuss off-label use of myeloma drugs

Multiple Myeloma affects primarily elderly patients

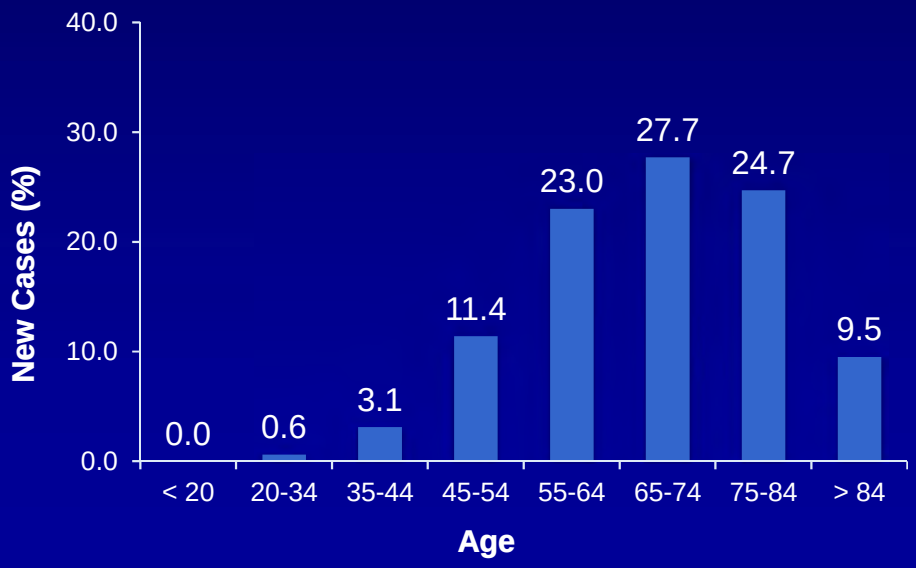
- **Changing demographics:**
  - Increase in life expectancy
  - Aging of the population
  - Increase in the number of elderly

World population: % of people 65+[1]



- **Myeloma is most frequently diagnosed among people aged 65-74**
  - Median age at diagnosis is 69

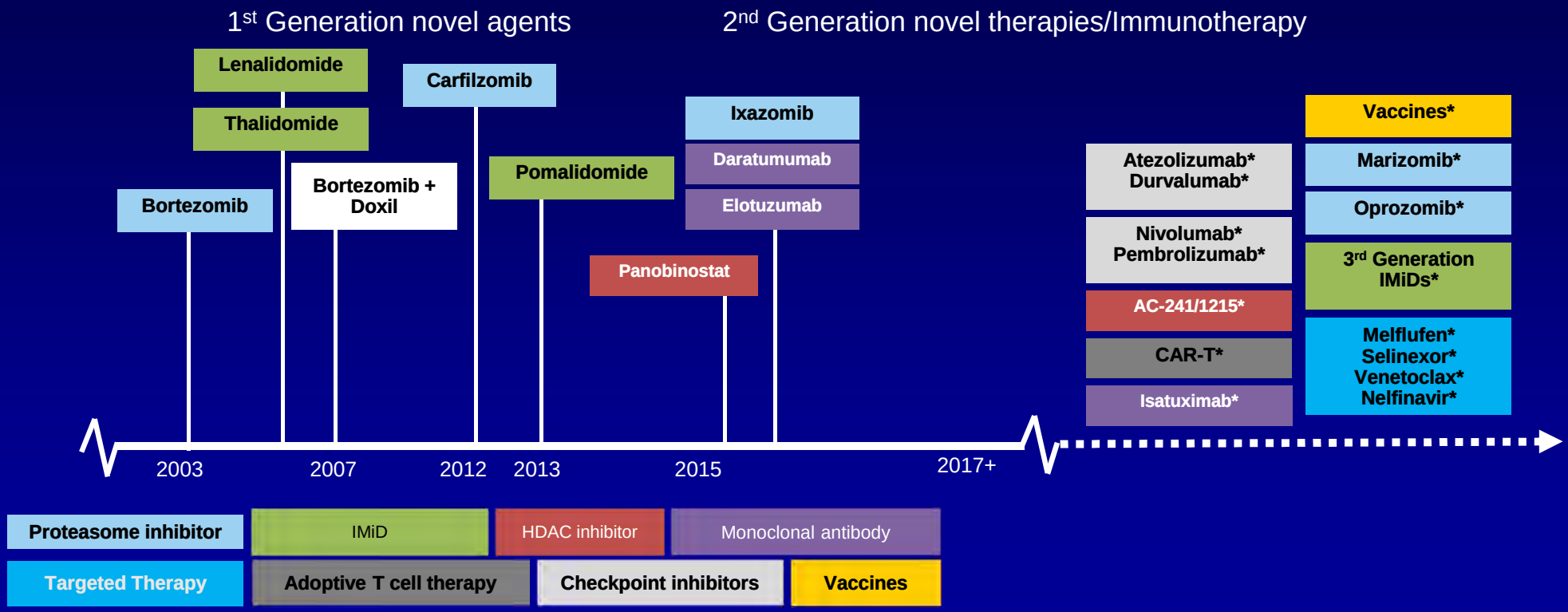
SEER: New MM Cases by Age Group[2]



Am, America; MM, multiple myeloma.

1. 65+ in the United States: 2010 - Census.gov; U.S (June 2014). Census Bureau, 2012b; International Data Base. 2. Available from http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed on 06/2014.

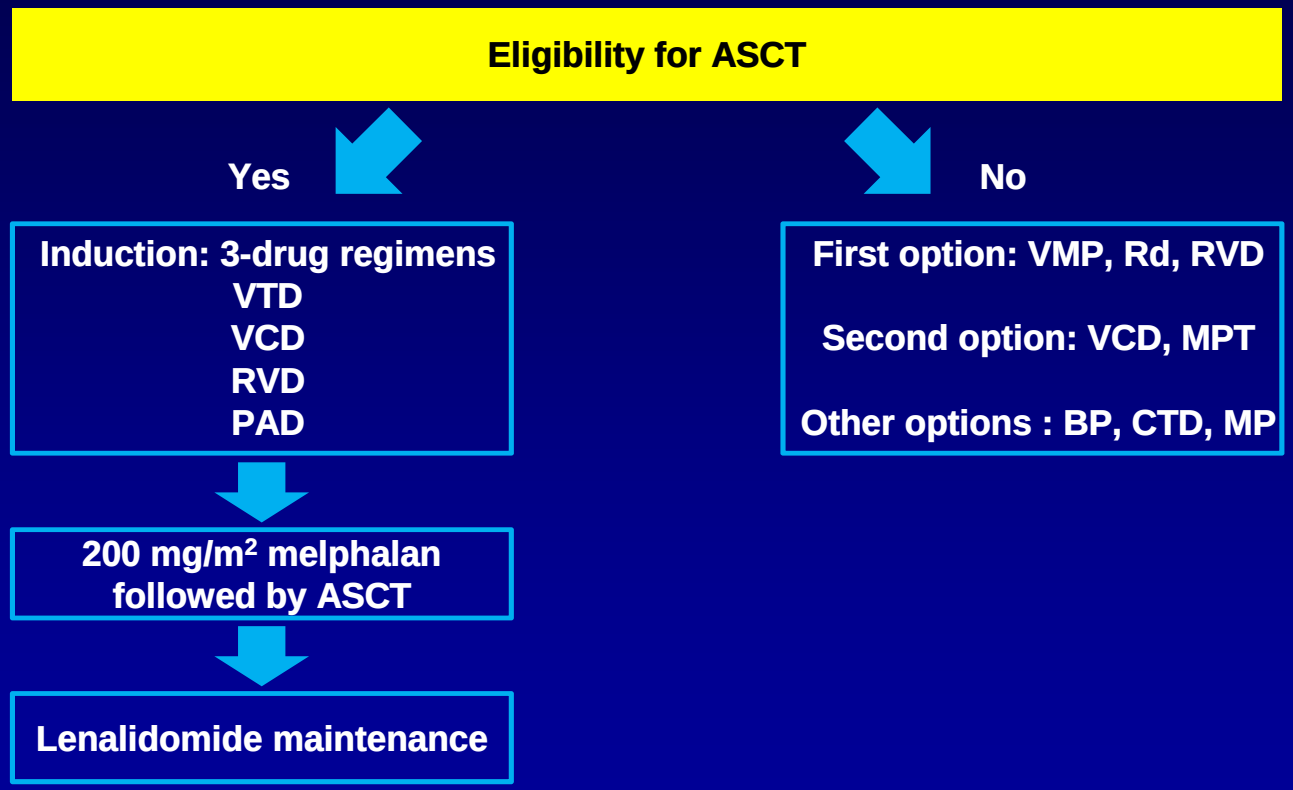
Continuing evolution of multiple myeloma treatment: selected new classes and targets 2017–2018



IMiD, immunomodulatory drug; HDAC, histone deacetylase
*Not yet FDA-approved for MM; available in clinical trials

Adapted from Richardson PG. et al ASH 2015, MMRF 2016

Front-line therapy: ESMO guidelines



Note: high-risk patients not categorized. ASCT, autologous stem cell transplant; BP, bendamustine + prednisone; CTD, cyclophosphamide + thalidomide + dexamethasone; MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; PAD, bortezomib + doxorubicin + dexamethasone; Rd, lenalidomide + low-dose dexamethasone; RVD, lenalidomide + bortezomib + dexamethasone; VCD, bortezomib + cyclophosphamide, dexamethasone; VMP, bortezomib + melphalan + prednisone; VRd, lenalidomide + low-dose dexamethasone + bortezomib; VTD, bortezomib + thalidomide + dexamethasone.

Moreau P, *et al. Annals of Oncology* 2017;**28**:iv52–iv61.

MPT Becomes a Standard of Care

Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial

Thierry Facon, Jean Yves Mary, Cyrille Hulin, Lotfi Benboubker, Michel Attal, Brigitte Pegourie, Marc Renaud, Jean Luc Harousseau, Gaëlle Guillerm, Carine Chaleteix, Mamoun Dib, Laurent Voillat, Hervé Maisonneuve, Jacques Troncy, Véronique Dorvaux, Mathieu Moncanduit, Claude Martin, Philippe Casassus, Jérôme Jaubert, Henry Jardel, Chantal Doyen, Brigitte Kolb, Bruno Anglaret, Bernard Grosbois, Ibrahim Yakoub-Agha, Claire Mathiot, Hervé Avet-Loiseau, on behalf of the Intergroupe Francophone du Myélome

blood

2011 118: 1239-1247
Prepublished online June 13, 2011;
doi:10.1182/blood-2011-03-341669

Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials

Peter M. Fayers, Antonio Palumbo, Cyrille Hulin, Anders Waage, Pierre Wijermans, Meral Beksaç, Sara Bringhen, Jean-Yves Mary, Peter Gimsing, Fabian Termorshuizen, Rauf Haznedar, Tommaso Caravita, Philippe Moreau, Ingemar Turesson, Pellegrino Musto, Lotfi Benboubker, Martijn Schaafsma, Pieter Sonneveld, Thierry Facon and on behalf of the Nordic Myeloma Study Group, Italian Multiple Myeloma Network, Turkish Myeloma Study Group, Hemato-Oncologie voor Volwassenen Nederland, Intergroupe Francophone du Myélome, and European Myeloma Network

Facon T, et al. Lancet. 2007;370:1209-18. Fayers PM, et al. Blood. 2011;118: 1239-47.

VMP Becomes a Standard of Care

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma

Jesús F. San Miguel, M.D., Ph.D., Rudolf Schlag, M.D., Nuriet K. Khuageva, M.D., Ph.D., Meletios A. Dimopoulos, M.D., Ofer Shpilberg, M.D., Ph.D., Martin Kropff, M.D., Ivan Spicka, M.D., Ph.D., Maria T. Petrucci, M.D., Antonio Palumbo, M.D., Olga S. Samoilova, M.D., Ph.D., Anna Dmoszynska, M.D., Ph.D., Kudrat M. Abdulkadyrov, M.D., Ph.D., Rik Schots, M.D., Ph.D., Bin Jiang, M.D., Maria-Victoria Mateos, M.D., Ph.D., Kenneth C. Anderson, M.D., Dixie L. Esseltine, M.D., Kevin Liu, Ph.D., Andrew Cakana, M.D., Helgi van de Velde, M.D., Ph.D., and Paul G. Richardson, M.D., for the VISTA Trial Investigators*

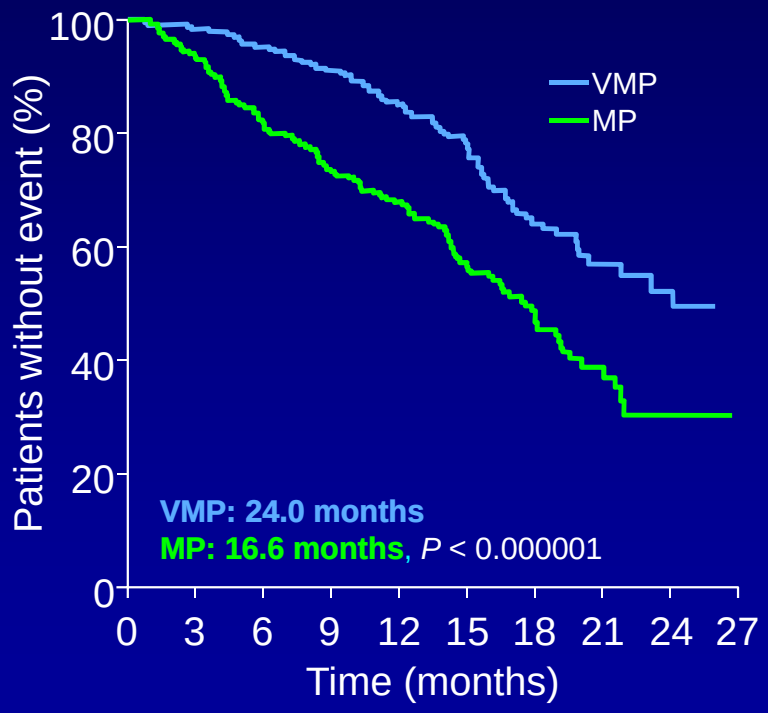
San Miguel JF, et al. N Engl J Med. 2008;359: 906-17.

VISTA Trial: MP + Bortezomib (VMP) vs. MP

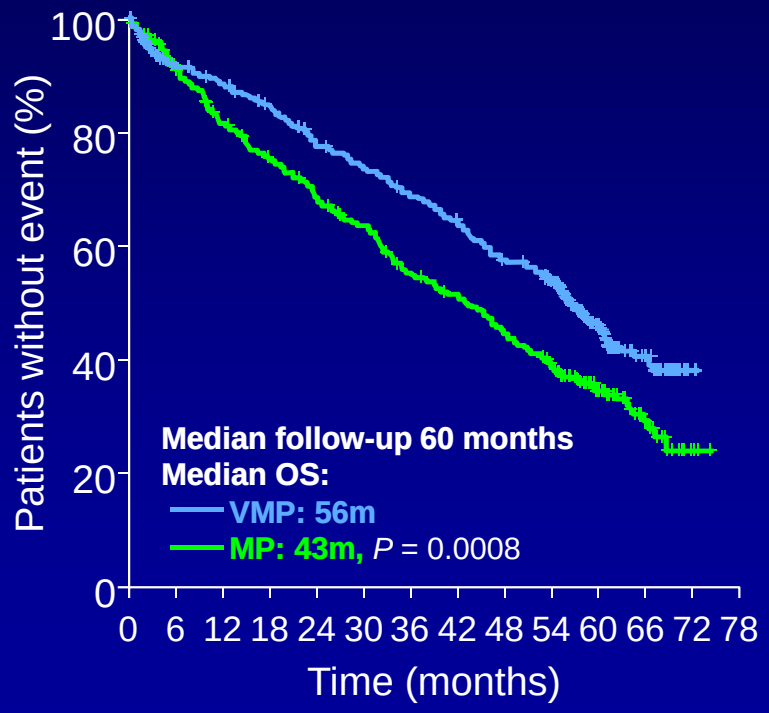
Bortezomib twice a week x 4 cycles + weekly x 5 cycles

RR (CR) (%): 71(30) vs. 35(4)

TTP



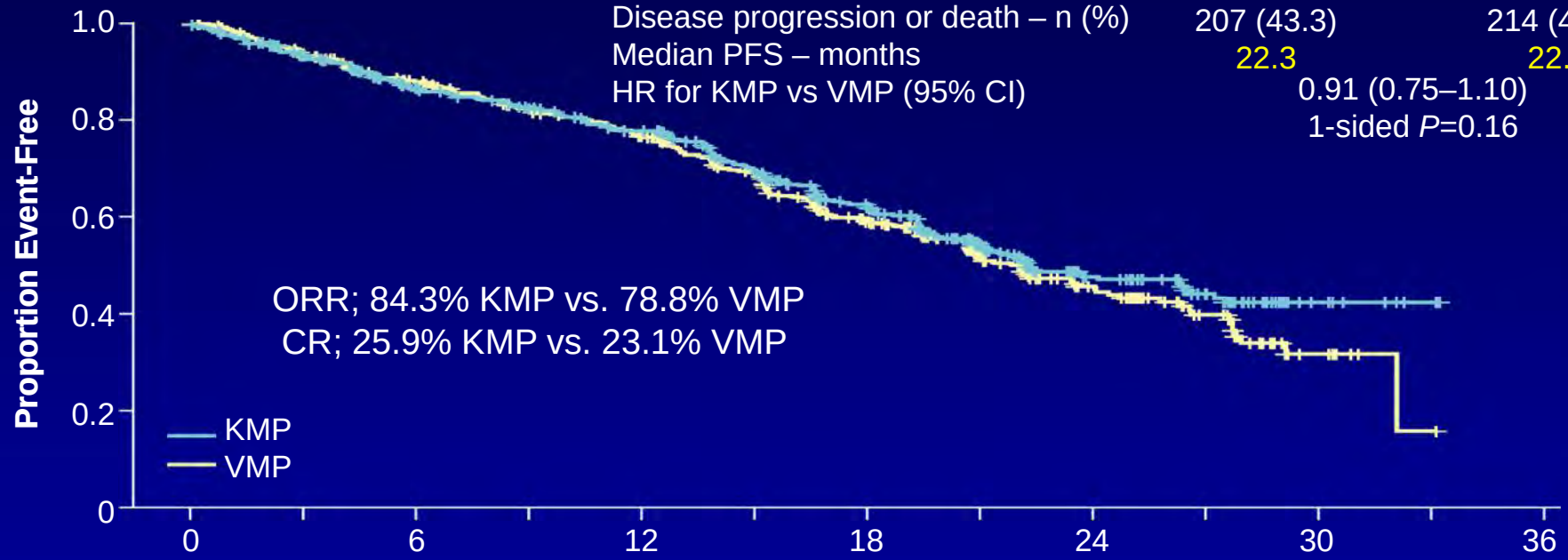
OS



San Miguel et al. JCO 2013; 31(4):448-55.

CLARION study KMP vs VMP
Progression-Free Survival and Response rates

	KMP (n=478)	VMP (n=477)
Disease progression or death – n (%)	207 (43.3)	214 (44.9)
Median PFS – months	22.3	22.1
HR for KMP vs VMP (95% CI)	0.91 (0.75–1.10)	
	1-sided *P*=0.16	

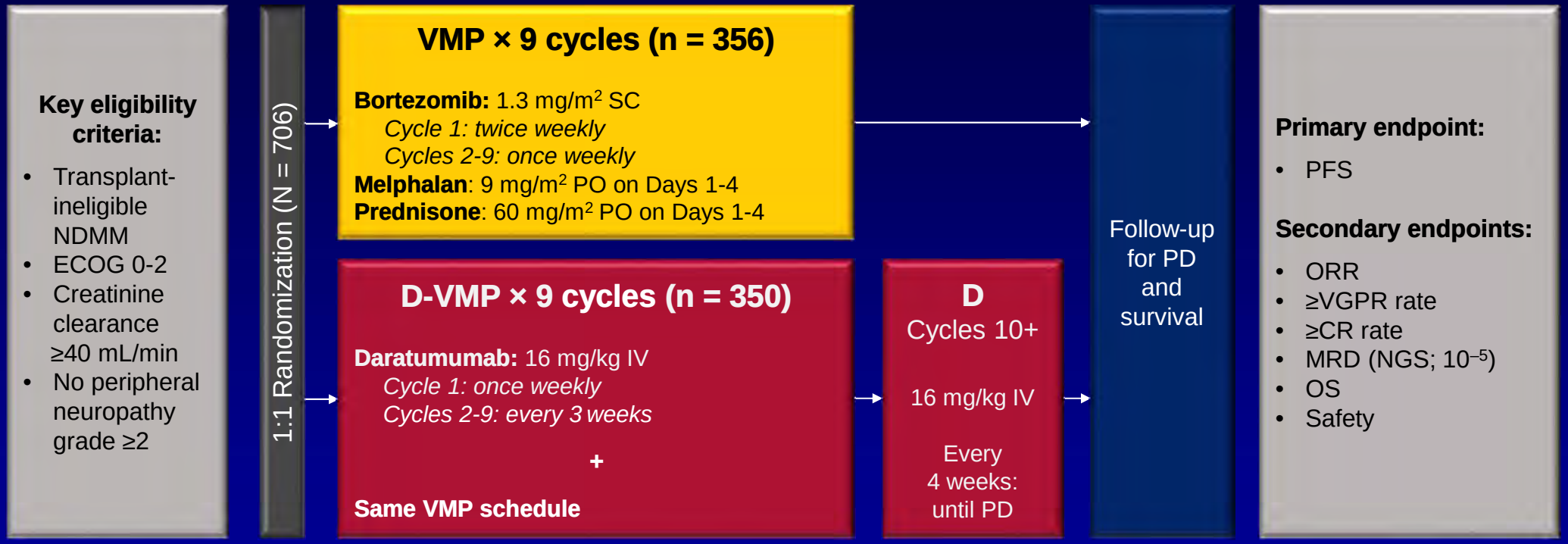


Number at risk:							
KMP	478	384	327	217	85	15	0
VMP	477	367	309	202	77	9	0

- Median follow-up time: 22.2 months for KMP and 21.6 months for VMP
- The absence of PFS difference was consistent across subgroups

Facon et al, IMW meeting 2017, oral presentation

ALCYONE Study Design



Stratification factors
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

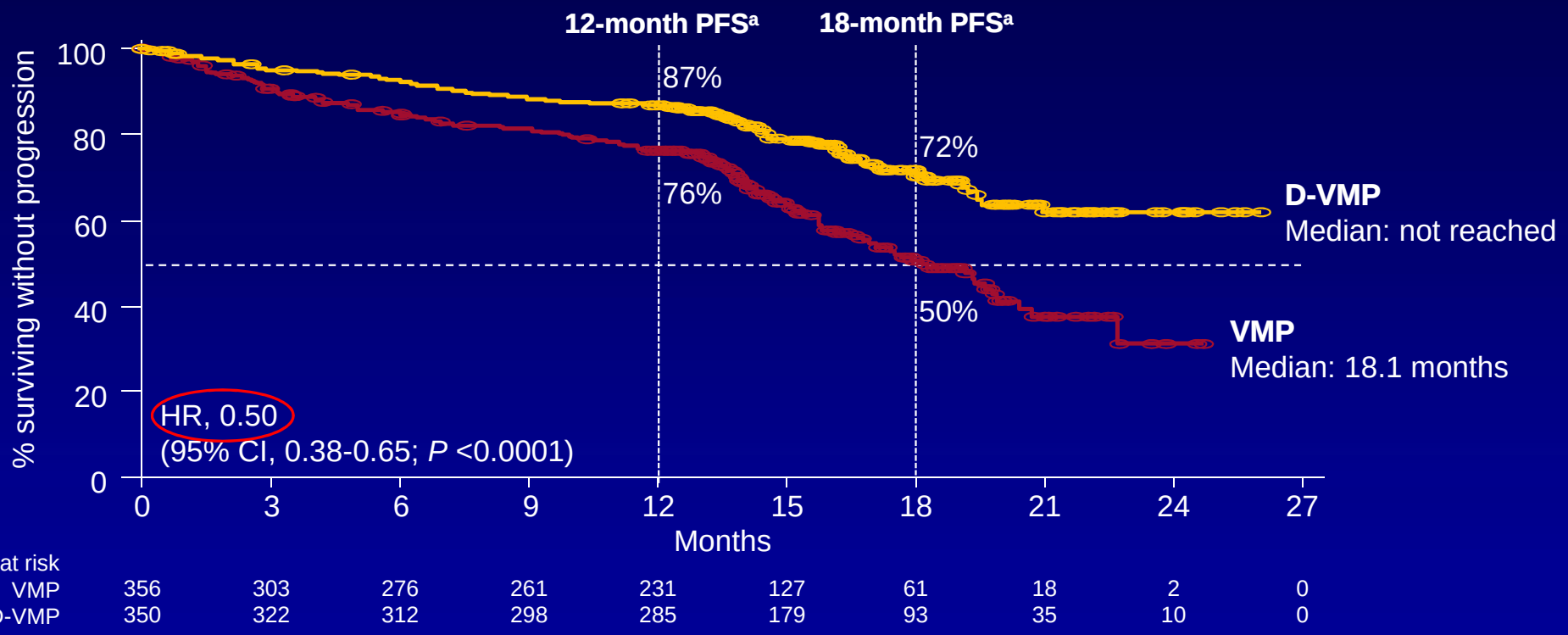
- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

Statistical analyses
- 360 PFS events: 85% power for 8-month PFS improvement[a]
- Interim analysis: ~216 PFS events

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; SC, subcutaneously; PO, orally; D, daratumumab; IV, intravenously; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival.
[a]8-month PFS improvement over 21-month median PFS of VMP.

Efficacy: PFS

- Median (range) follow-up: 16.5 (0.1-28.1) months



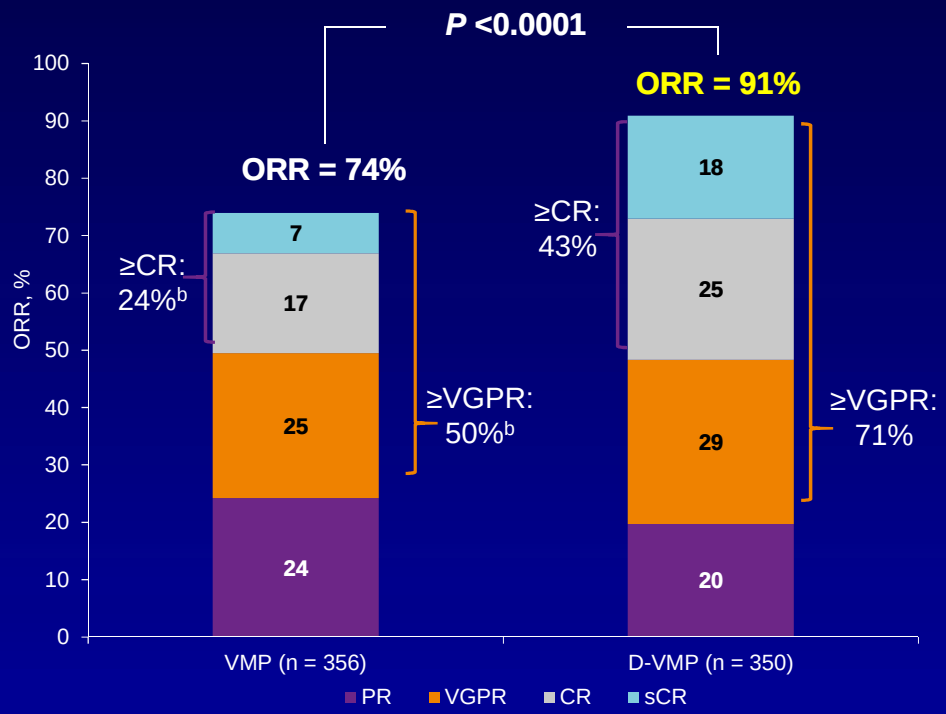
50% reduction in the risk of progression or death in patients receiving D-VMP

HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Mateos et al.NEJM 2017;378:318-21

Efficacy: ORR[a]

- **Median duration of response: 21.3 months in VMP versus not reached in D-VMP**



	VMP (n = 263)[c]	D-VMP (n = 318)[c]
Median (range) time to **first** response, months	0.82 (0.7-12.6)	0.79 (0.4-15.5)
Median (range) time to **best** response, months	4.11 (0.7-20.5)	4.93 (0.5-21.0)

Significantly higher ORR, ≥VGPR rate, and ≥CR rate with D-VMP;
>2-fold increase in rate of sCR with D-VMP

PR, partial response; sCR, stringent complete response.[a]ITT population. [b]*P* <0.0001; *P* value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test. [c]Responders in response-evaluable population.

Mateos et al.NEJM 2017;378:318-21

Safety: Most Common TEAEs[a]

	VMP (n = 354)		D-VMP (n = 346)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hematologic, n (%)				
Neutropenia	186 (53)	137 (39)	172 (50)	138 (40)
Thrombocytopenia	190 (54)	133 (38)	169 (49)	119 (34)
Anemia	133 (38)	70 (20)	97 (28)	55 (16)
Nonhematologic, n (%)				
Peripheral sensory neuropathy	121 (34)	14 (4)	98 (28)	5 (1)
Upper respiratory tract infection	49 (14)	5 (1)	91 (26)	7 (2)
Diarrhea	87 (25)	11 (3)	82 (24)	9 (3)
Pyrexia	74 (21)	2 (1)	80 (23)	2 (1)
Nausea	76 (22)	4 (1)	72 (21)	3 (1)
Pneumonia	17 (5)	14 (4)	53 (15)	39 (11)

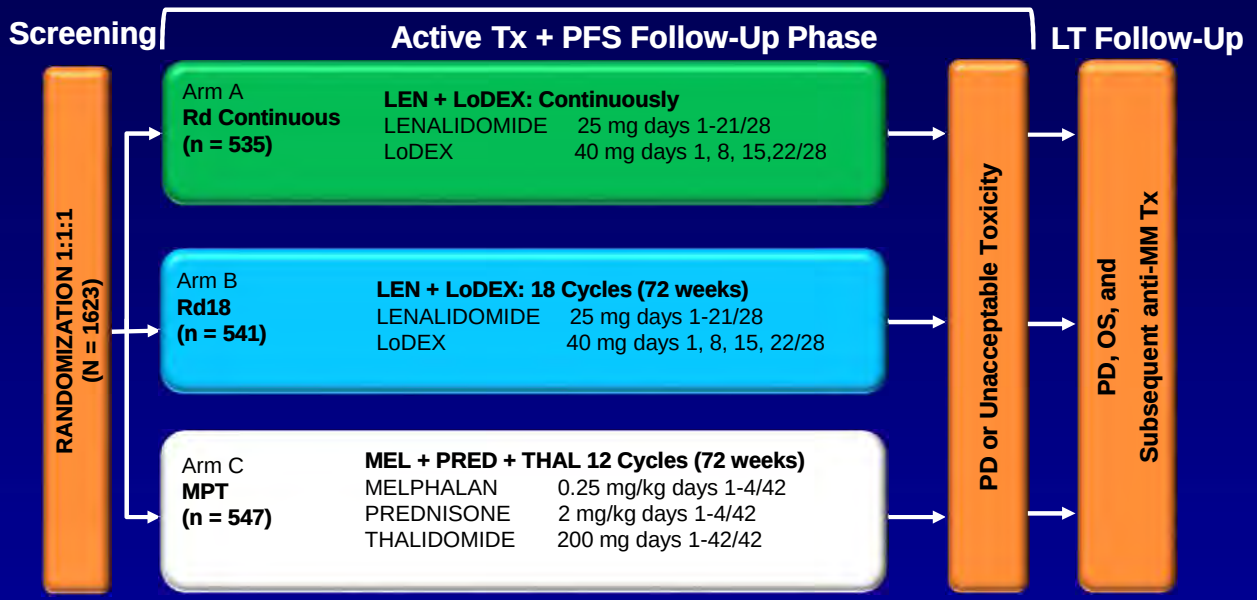
	VMP (n = 354)	D-VMP (n = 346)
Deaths due to TEAEs, n (%)	19 (5)	19 (6)

- **1 patient in each arm discontinued treatment due to pneumonia**
- **1.4% and 0.9% of patients receiving VMP and D-VMP, respectively, discontinued treatment due to infection**

TEAE, treatment-emergent adverse event.
[a]Any grade TEAEs in ≥20% of patients and grade 3 or 4 TEAEs in ≥10% of patients in either treatment group.

FIRST (IFM2007-01-MM-020): Study Design

- **Stratification: Age (≤ 75 vs > 75 yrs), country, and ISS stage (I/II vs III)**
- **Thromboprophylaxis was mandatory**
- **Data cutoff: January 21, 2016**



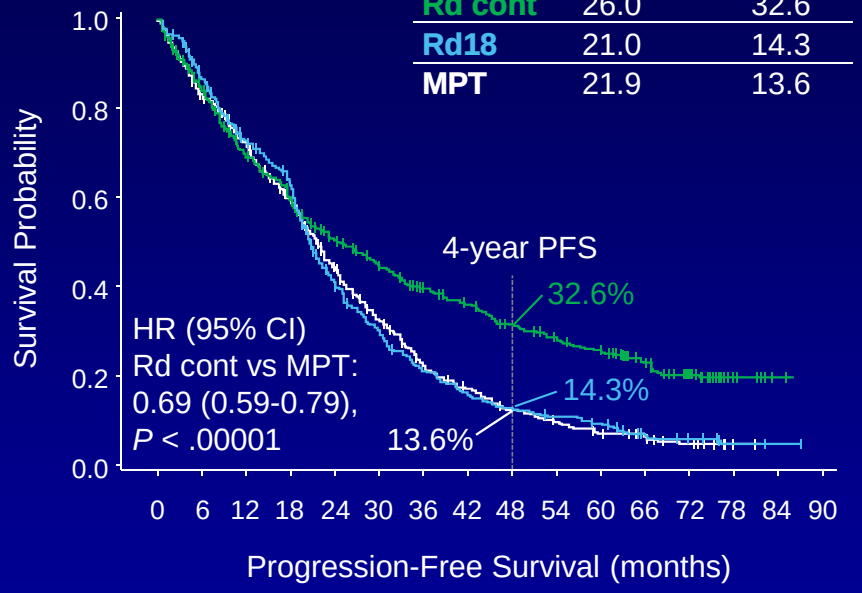
Pts aged > 75 yrs: LoDEX 20 mg days 1, 8, 15, 22/28; THAL 100 mg days 1-42/42; MEL 0.2 mg/kg days 1-4

FIRST, Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide; ISS, International Staging System; LoDex, low-dose dexamethasone; LT, long-term; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pts, patients; Tx, treatment.

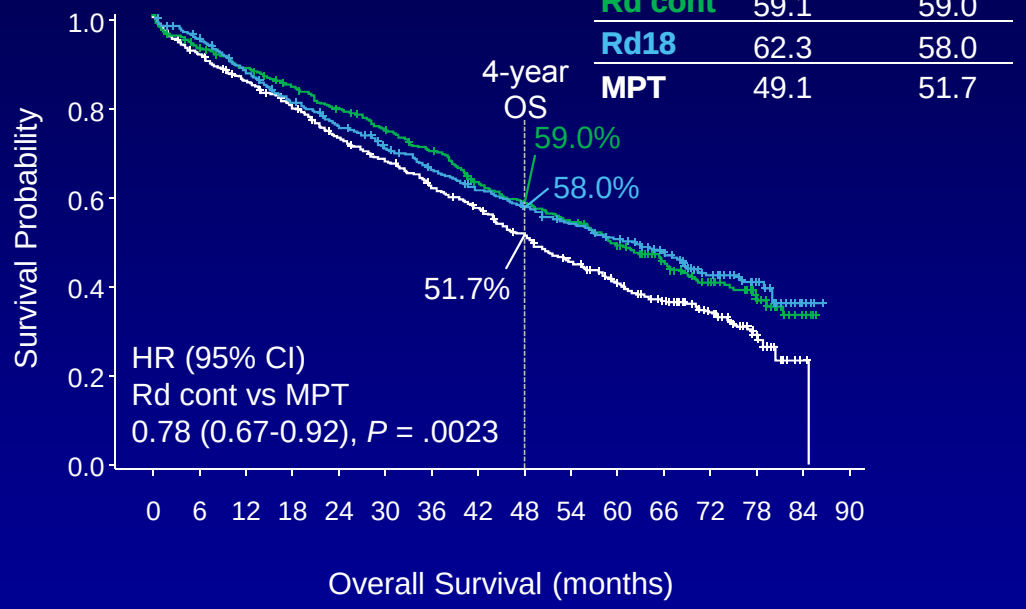
Benboubker L,et al. *N Engl J Med*. 2014;371:906-17. Facon et al. Blood 2018;130:301-10

FIRST Study: PFS[a] and OS

	Median PFS, mo	4-yr PFS, %
Rd cont	26.0	32.6
Rd18	21.0	14.3
MPT	21.9	13.6



	Median OS, mo	4-yr OS, %
Rd cont	59.1	59.0
Rd18	62.3	58.0
MPT	49.1	51.7



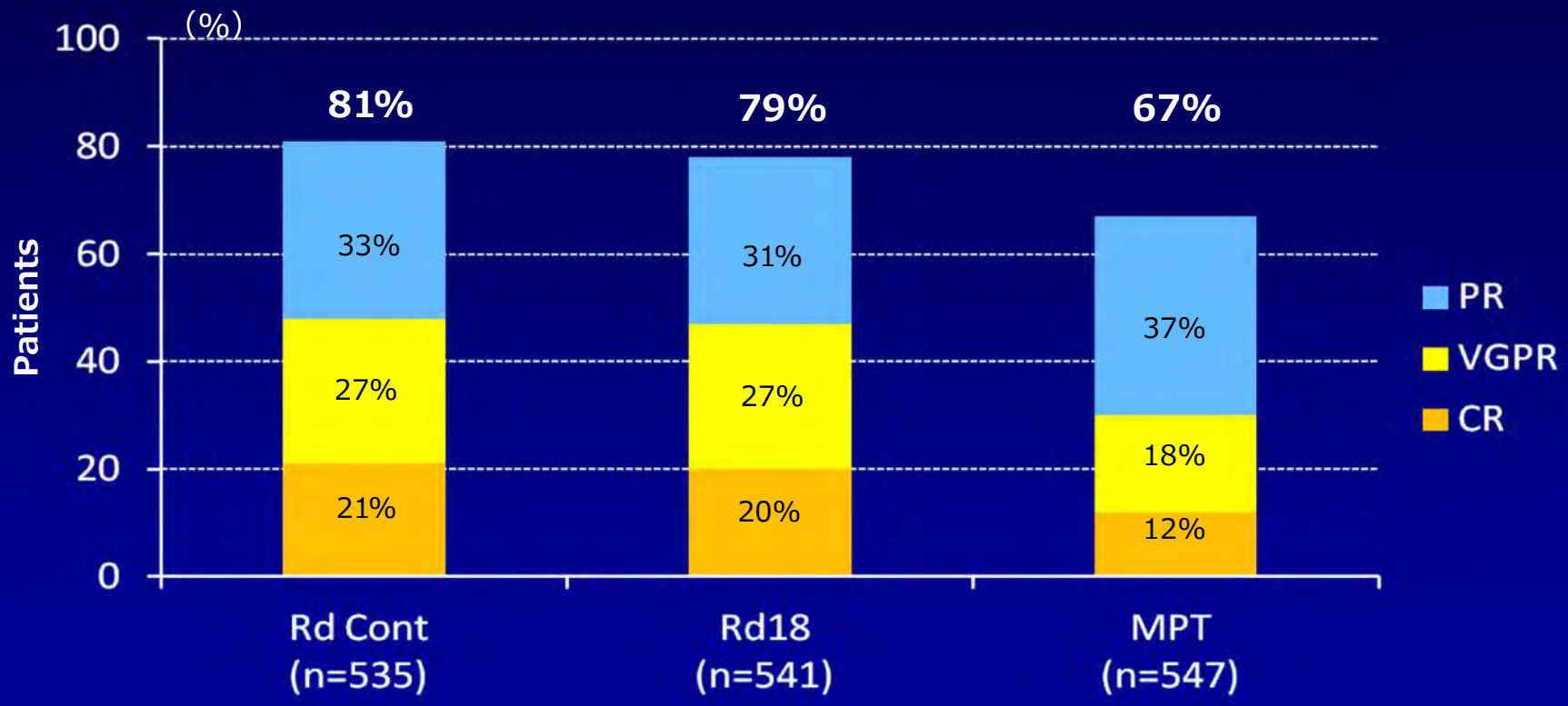
- **The pre-specified final OS analysis for the primary comparison showed that Rd continuous significantly extended OS vs MPT**

[a] PFS is based on investigator assessment of IMWG criteria; data cutoff: January 21, 2016.

cont, continuous; FIRST, Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide; HR, hazard ratio; IMWG, International Myeloma Working Group; MPT, melphalan, prednisone, thalidomide; OS, overall survival; PFS, progression-free survival; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Facon T, et al Blood 2018;130:301-10

IFM 2007-01-MM-020- FIRST;Response – ITT population



Facon et al.Blood 2018;130:301-10

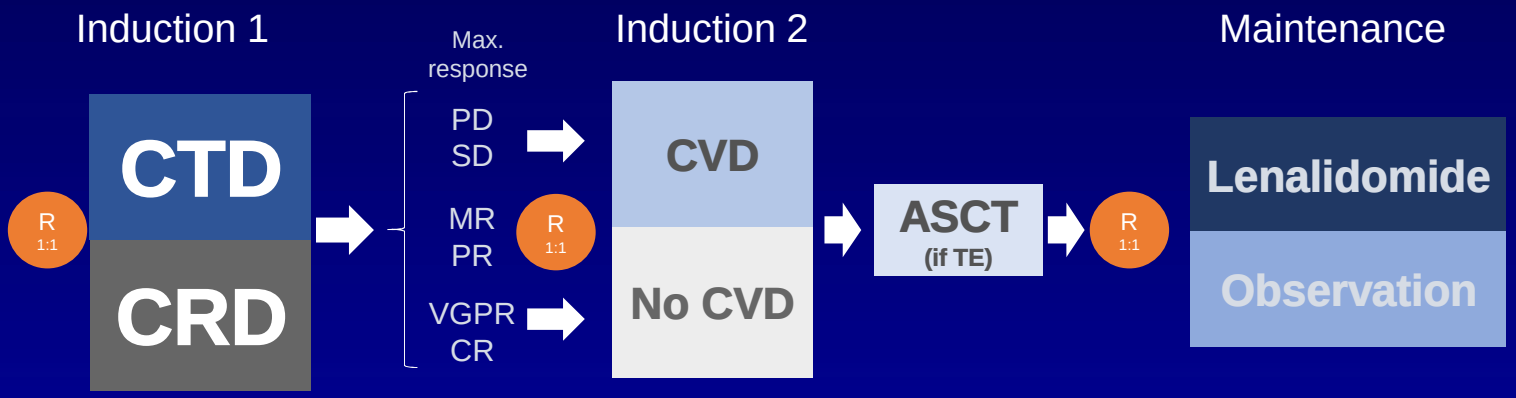
Age Analysis: Grade 3/4 Nonhematologic TEAEs

Grade 3/4 TEAEs, %	Age ≤ 75 Years			Age > 75 Years		
	Rd Continuous (n = 347)	*Rd18 (n = 348)*	*MPT (n = 357)*	*Rd Continuous (n = 185)*	*Rd18 (n = 192)*	*MPT (n = 184)*
Nonhematologic (≥ 10% in either age group)						
Infections	30	21	16	29	23	20
Cardiac disorders	12	6	6	12	9	13
Fatigue	7	8	5	9	10	8
Back pain	6	7	5	10	4	5
Peripheral sensory neuropathy	1	1	10	1	0	8
TEAEs of special interest						
Cataract	8	3	< 1	3	2	1
DVT	7	3	3	3	5	2
PE	4	3	5	4	3	2

DVT, deep vein thrombosis; MPT, melphalan, prednisone, thalidomide; PE, pulmonary embolism; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; TEAE, treatment-emergent adverse event.

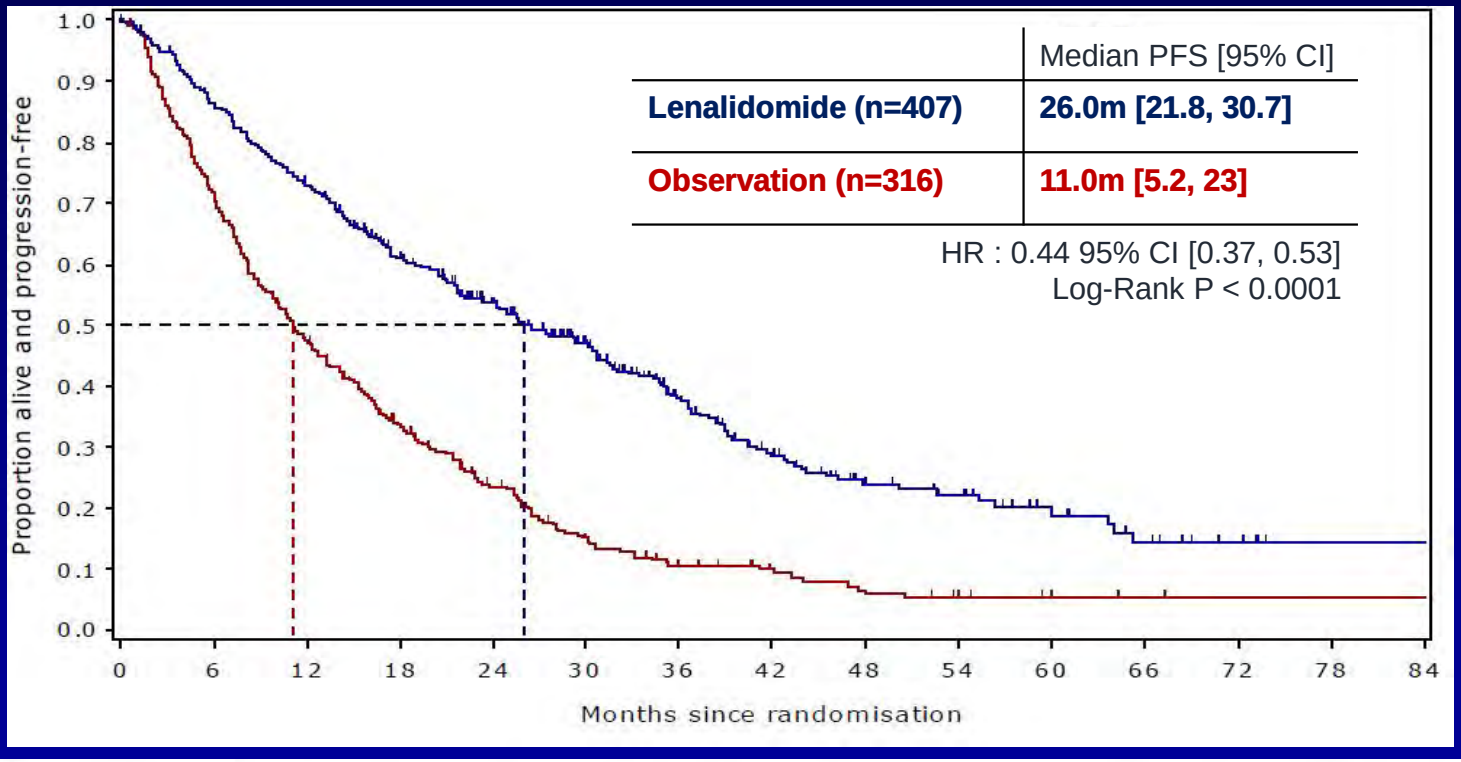
Hulin C et al.JCO 2016;34:3609-18

Myeloma XI – trial outline



Transplant non-eligible pathway

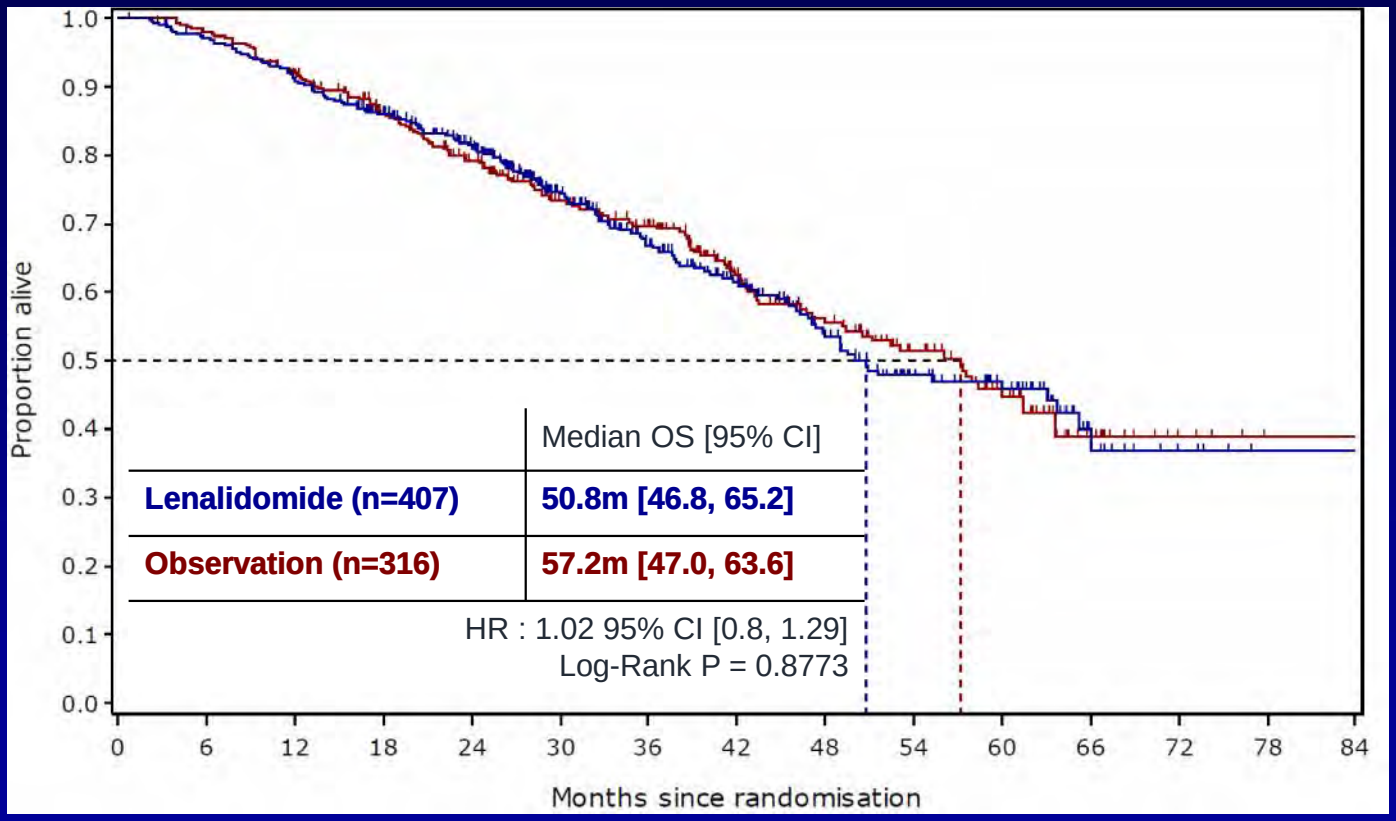
Lenalidomide improved PFS from 11 to 26 months, hazard ratio of 0.44



PFS: progression-free survival

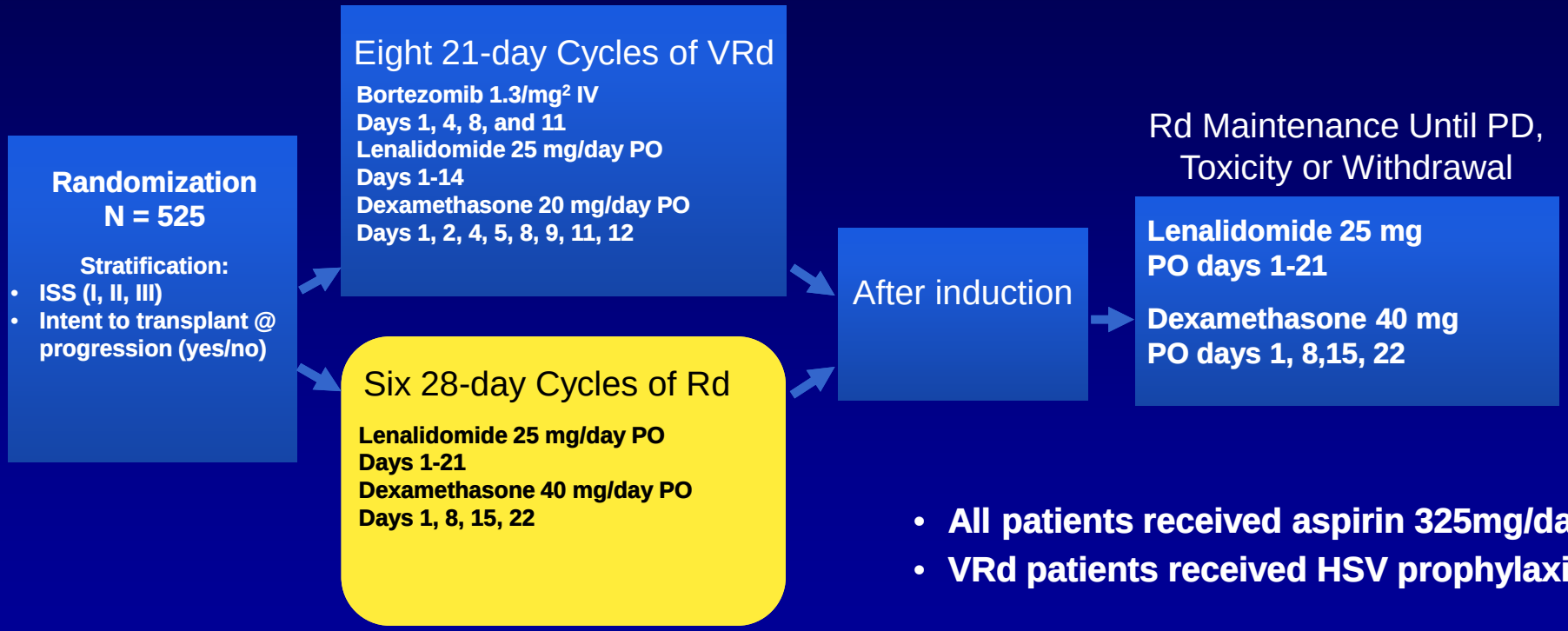
Transplant non-eligible pathway

Overall survival



OS: overall survival

SWOG S0777: Study Design



- **All patients received aspirin 325mg/day**
- **VRd patients received HSV prophylaxis**

HSV, herpes simplex virus; ISS, international staging system; PD, progressive disease; Rd, lenalidomide plus low dose dexamethasone; VRd, bortezomib, lenalidomide and dexamethasone.

Durie et al. Lancet 2017;389:517-527

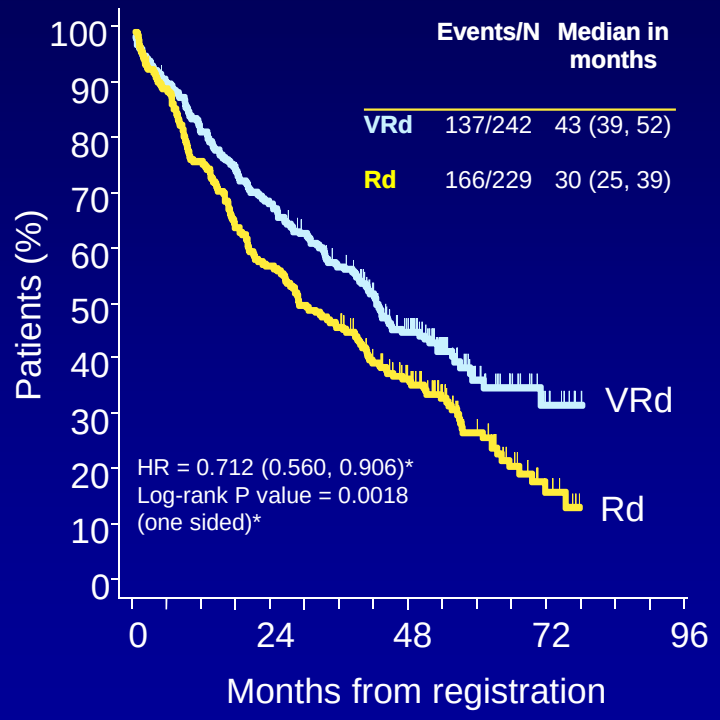
	Total	Patients given bortezomib with lenalidomide and dexamethasone (VRd group)	Patients given lenalidomide and dexamethasone (Rd group)
ECOG performance status > 1	64/471 (14%)	28/242 (12%)	36/229 (16%)
Serum beta 2 microglobulin concentration ≥3·5 mg/L	282/459 (61%)	141/235 (60%)	141/224 (63%)
C-reactive protein concentration ≥8 mg/L	104/444 (23%)	48/225 (21%)	56/219 (26%)
Creatinine concentration ≥2 mg/dL	22/471 (5%)	11/242 (5%)	11/229 (5%)
Lactate dehydrogenase concentration ≥190 U/L	166/462 (36%)	84/236 (36%)	82/226 (36%)
Albumin concentration <3·5 g/dL	197/466 (42%)	98/239 (41%)	99/227 (44%)
Haemoglobin concentration <10 g/dL	151/471 (32%)	79/242 (33%)	72/229 (31%)
Platelet count <150 x 10^9/L	21/469 (4%)	11/241 (5%)	10/228 (4%)
International Staging System stage III	157/471 (33%)	78/242 (32%)	79/229 (34%)
Age ≥65 years	202/471 (43%)	93/242 (38%)	109/229 (48%)
Women	196/471 (42%)	89/242 (37%)	107/229 (47%)
Intent to transplant	324/471 (69%)	168/242 (69%)	156/229 (68%)

Data are n/N (%). ECOG=Eastern Cooperative Oncology Group.

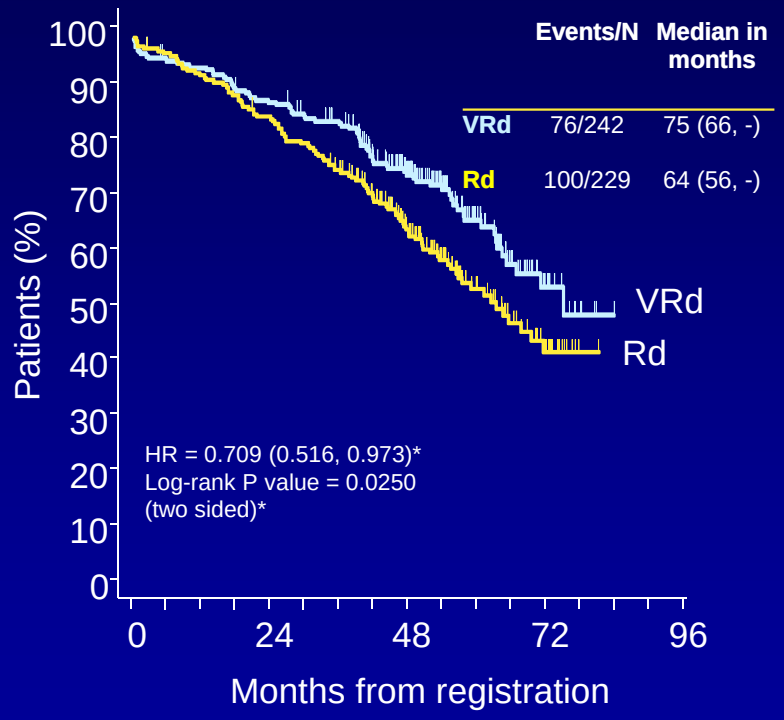
Table 1: **Baseline characteristics**

SWOG S0777: PFS and OS by Assigned Treatment Arm

PFS by assigned treatment arm



OS by assigned treatment arm

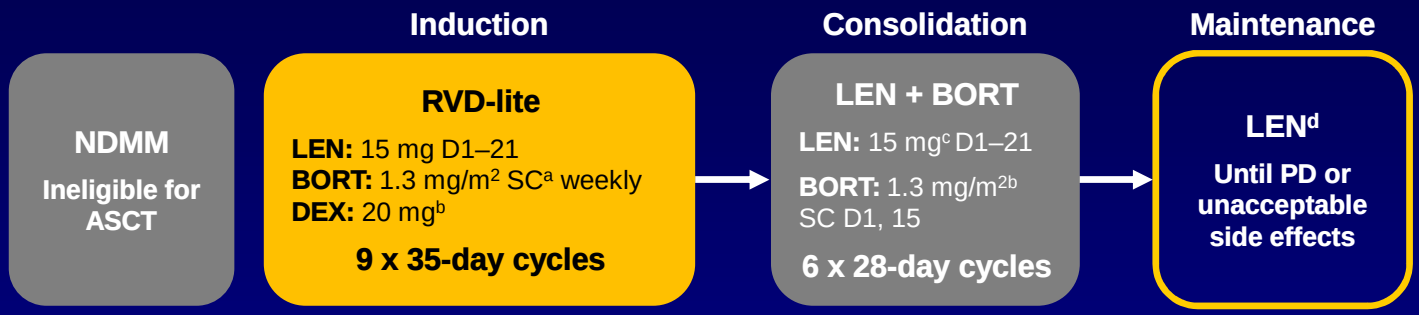


* Stratified

HR, hazard ratio; OS, overall survival; PFS progression free survival; Rd, lenalidomide plus low dose dexamethasone; VRd, bortezomib, lenalidomide and dexamethasone.

Durie et al. Lancet 2017;389:517-527

Modified RVD (RVD-lite) in transplant-ineligible MM



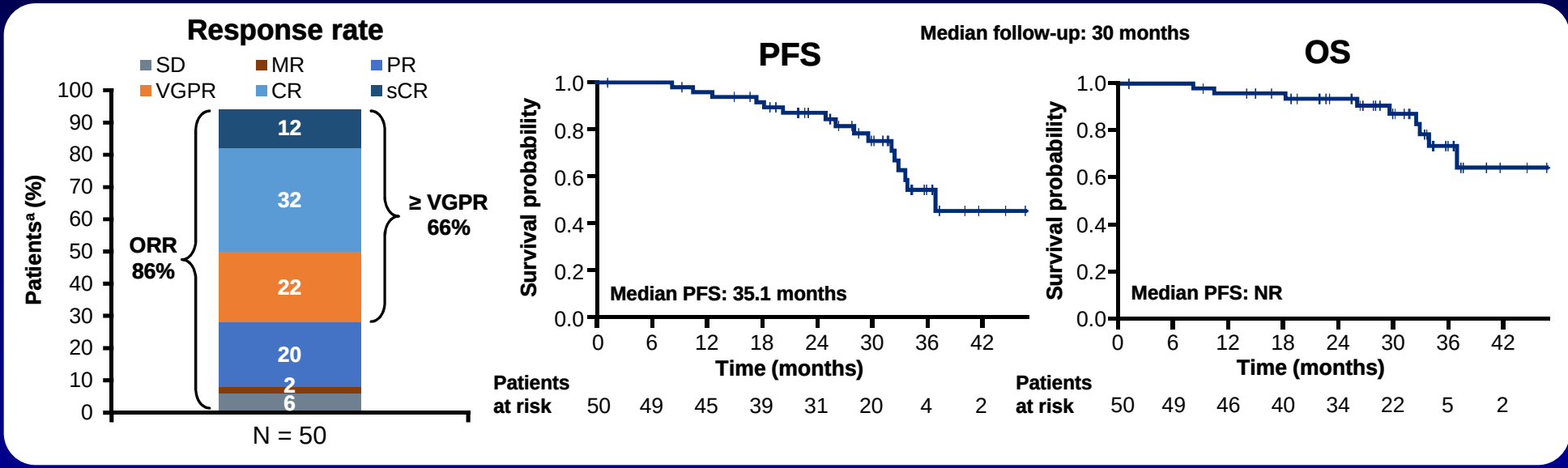
Patient population: NDMM ≥ 65 years and/or ineligible for ASCT

Baseline characteristics, %	N = 50
Median age, years (range)	73 (65–91)
ISS stage at diagnosis	
I	38
II	34
III	28
ECOG PS	
0	50
1	36
2	14

[a]The first 10 patients received bortezomib IV for Cycle 1 only followed by SC administration. Subsequent patients received bortezomib SC; [b]D1, 2, 8, 9, 15, 16, 22, 23 for patients ≤ 75 years); D1, 8, 15, 22 for patients > 75 years; [c]Or last tolerated dose as of Cycle 9; [d]Optional.

O'Donnell EK, *et al. Br J Haematol* 2018; **182**:222–230.

RVD-lite: efficacy

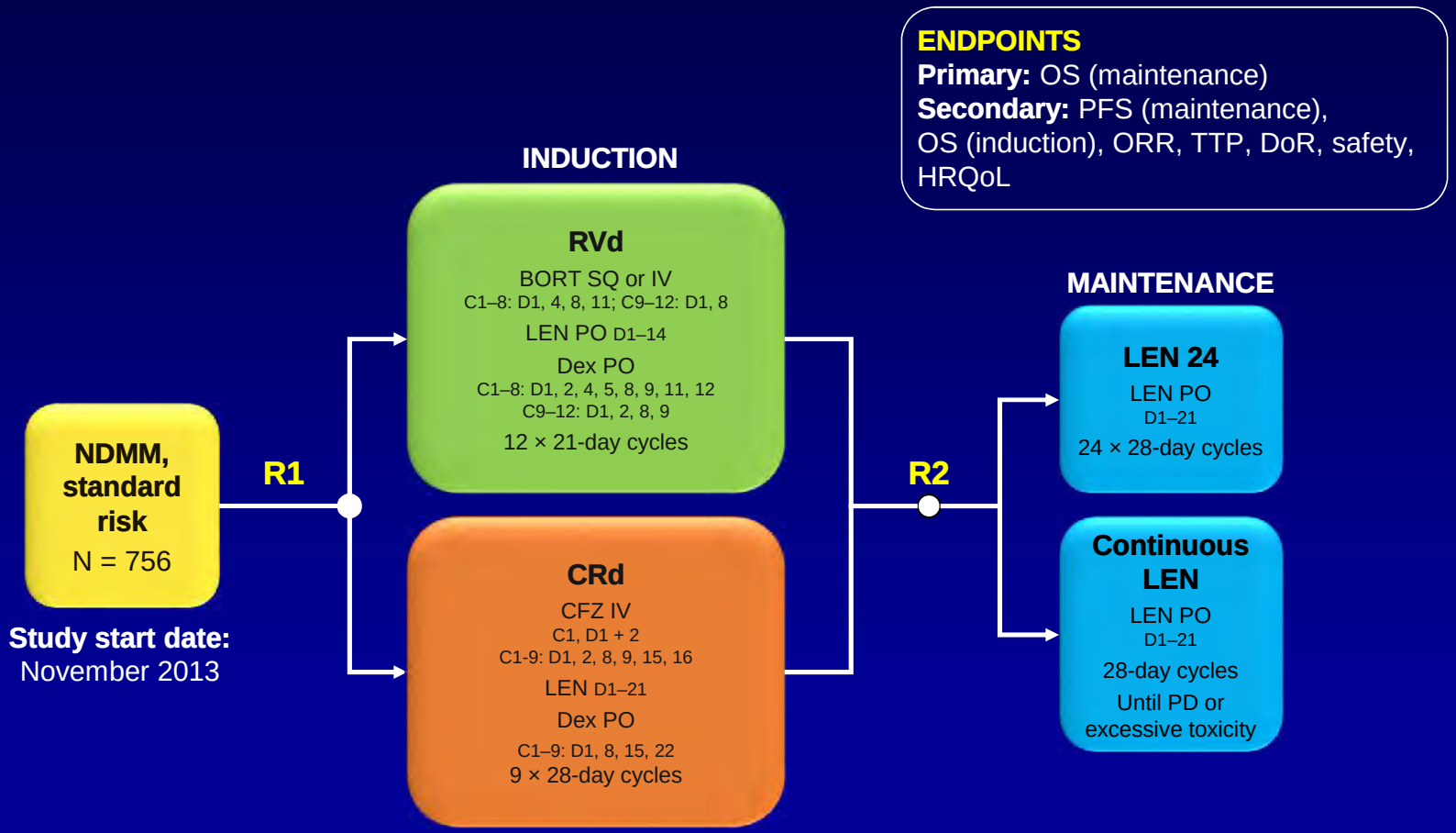


- ≥ CR was 44% (ITT population, N = 50)
- ORR was 86%, ≥ VGPR was 66% for patients evaluable for response[a] after 4 cycles (n = 46)
- Median TTR was 1.1 months

[a]Six percent of patients received < 4 cycles of therapy and were therefore not evaluable.
CR, complete response; ITT, intention to treat; MR, minimal response; ORR, overall response rate; PR, partial response; RVD, lenalidomide, bortezomib and dexamethasone; sCR stringent complete response; SD, stable disease; TTR, time to response; VGPR, very good partial response.

O'Donnell EK, *et al. Br J Haematol* 2018; **182**:222–230.

ENDURANCE (ECOG E1A11): Phase 3 Trial of RVd vs CRd → LEN Maintenance[1]

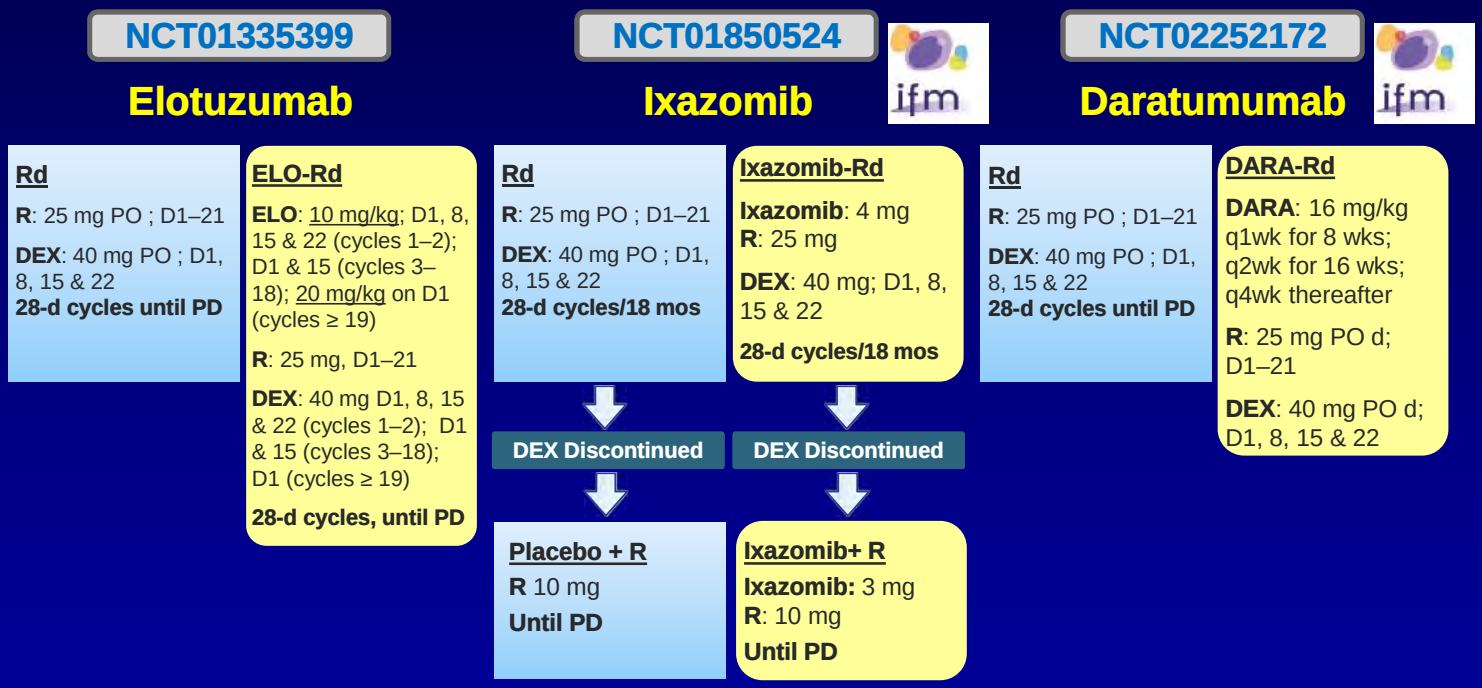


NCT01863550[1]

BORT, bortezomib; CFZ, carfilzomib; DoR, duration of response; HRQoL, health related quality of life; IV, intravenous; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, orally; RVd, lenalidomide, bortezomib, and low-dose dexamethasone SCT, stem cell transplant; SQ, subcutaneous; TTP, time to progression.

1. https://clinicaltrials.gov/ct2/show/NCT01863550; accessed February 9, 2016.

Phase 3 Rd-based Continuous Studies for Elderly Patients

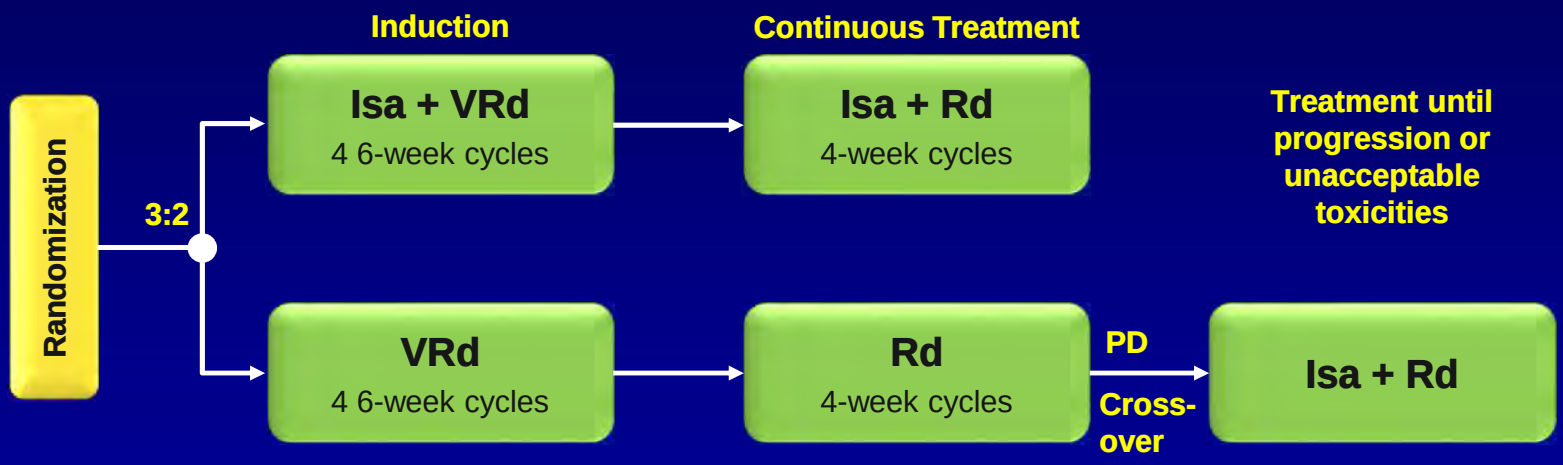


- **Primary endpoint for all studies is PFS**

1. NCT01335399. 2. NCT01850524. 3. NCT02252172.

EFC12522 study design

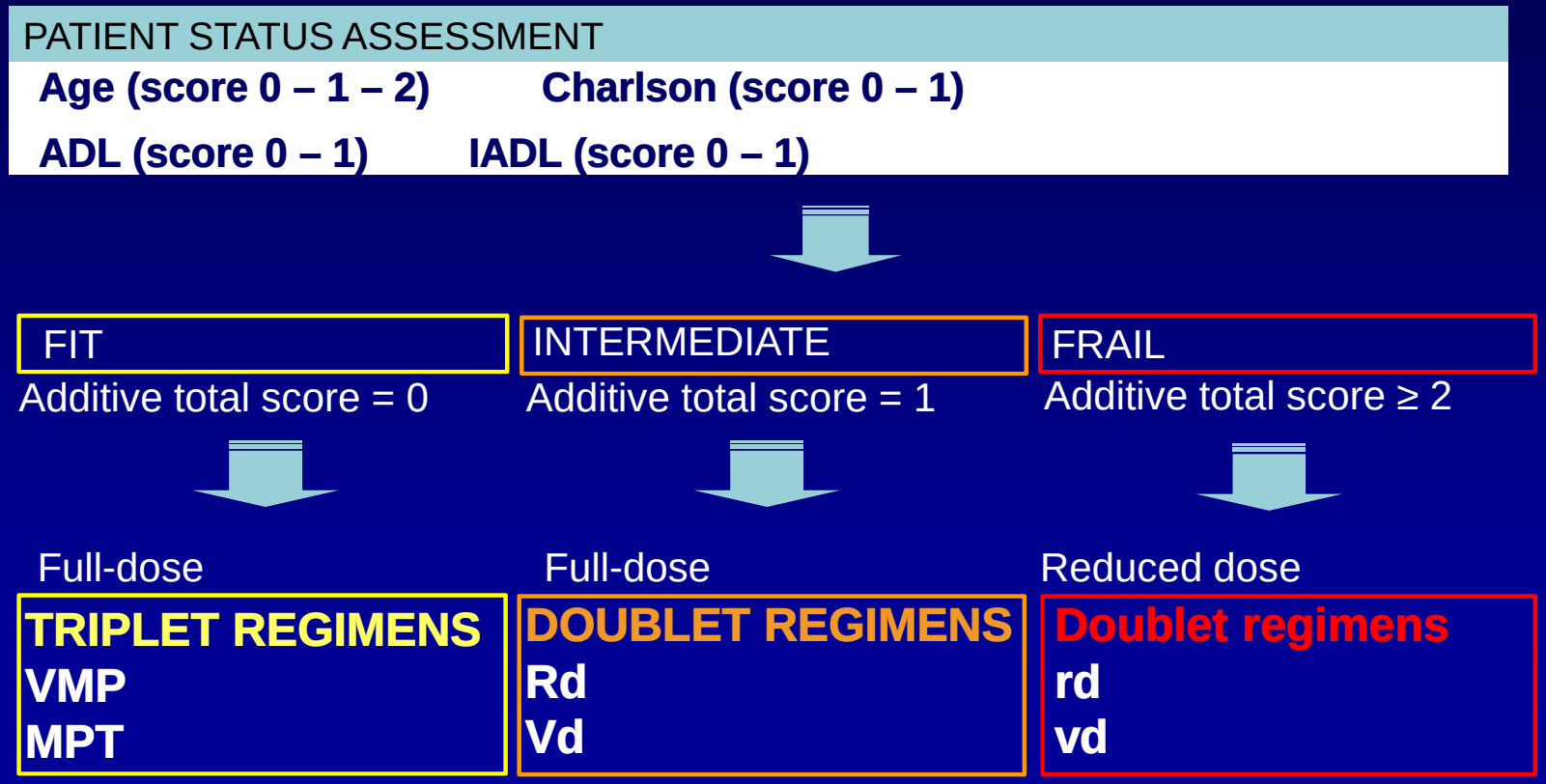
- **Population:**
  - 440 NDMM patients who are not eligible for HDT-ASCT
  - Stratification: age threshold 70 yrs; R-ISS stage 1 and 2 vs stage 3 vs UNK



- **Primary endpoint:** PFS (40 mo vs 62.5 mo)
- **Secondary endpoints:** OS, PFS2, ORR, CR, Safety, QoL, MRD negativity

Asessment of fitness and frailty is relevant for optimal treatment selection

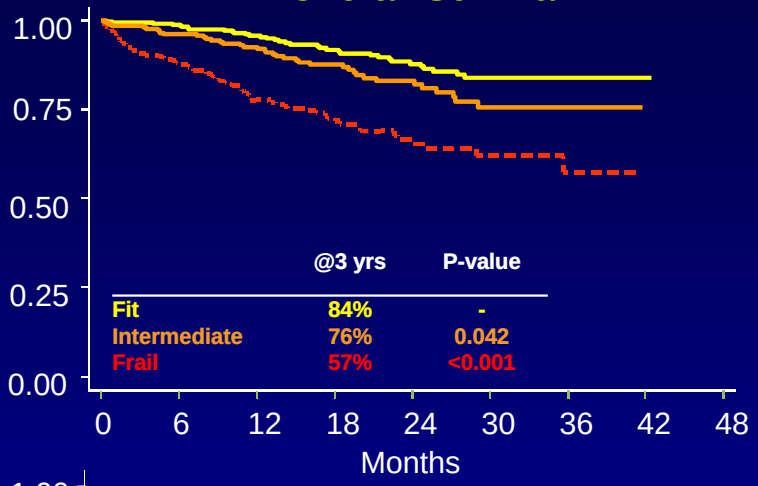
“New” Stratification of Elderly Myeloma Patients IMWG frailty score



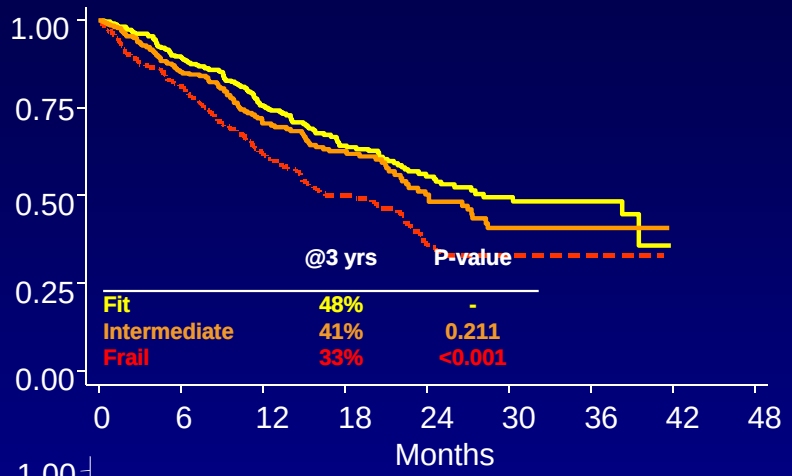
Palumbo A et al, Blood 25(13):2068-74, 2015

MM Frailty Score: long-term outcome

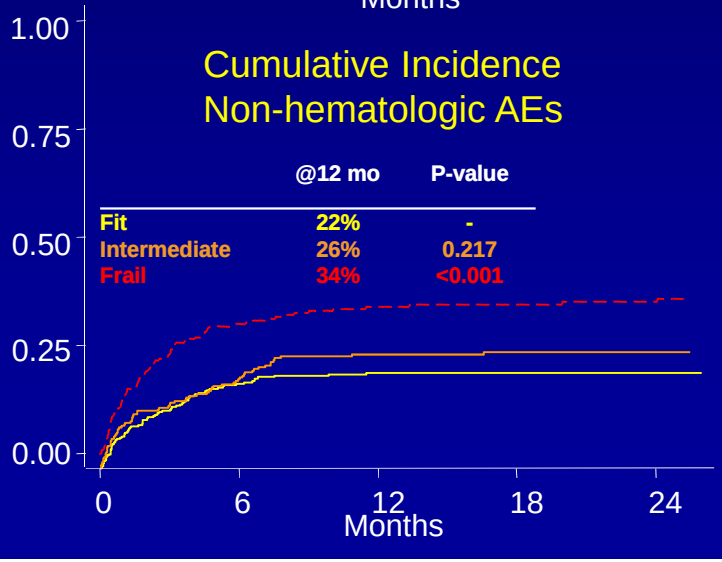
Overall Survival



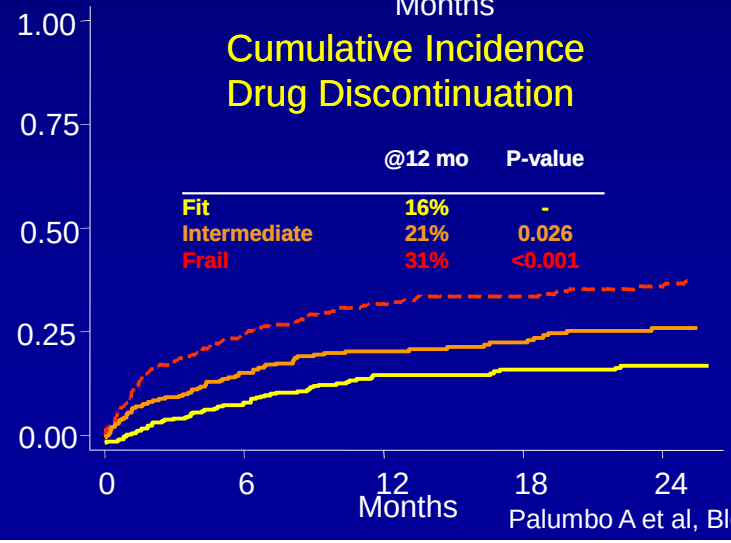
Progression-free Survival



Cumulative Incidence Non-hematologic AEs



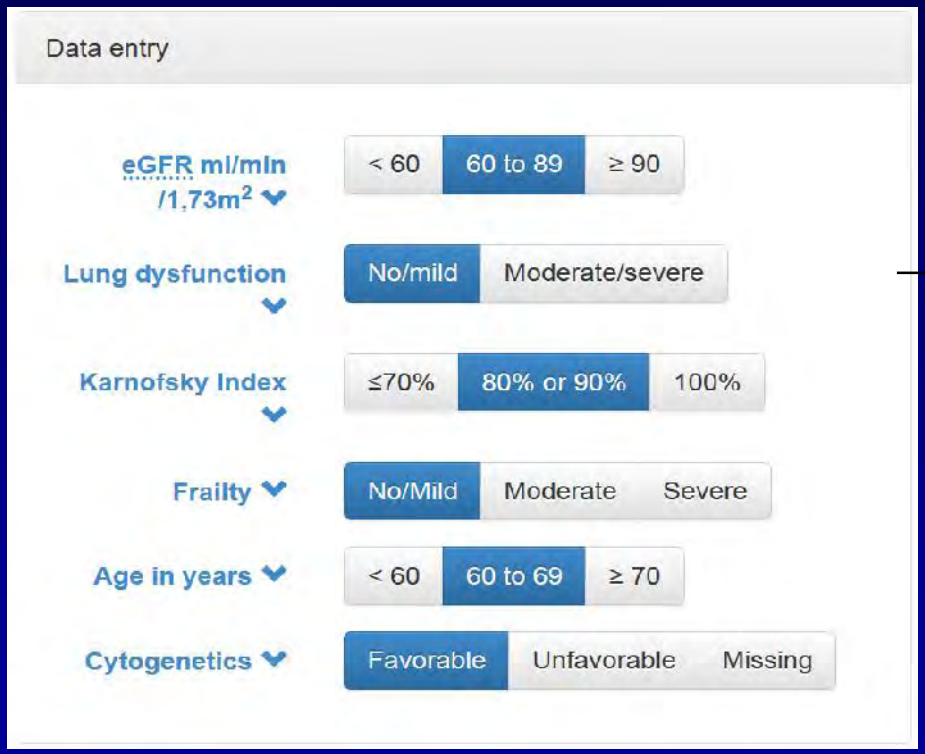
Cumulative Incidence Drug Discontinuation

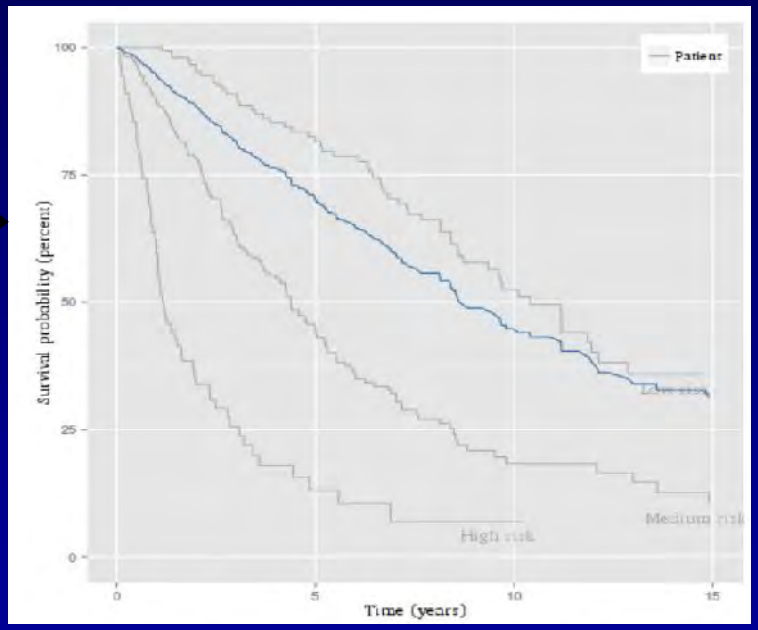


Palumbo A et al, Blood 25(13):2068-74, 2015

R-MCI German Frailty Score- Practical Use

Website: www.myelomacomorbidityindex.org





Pt-specific survival probability (blue graph)

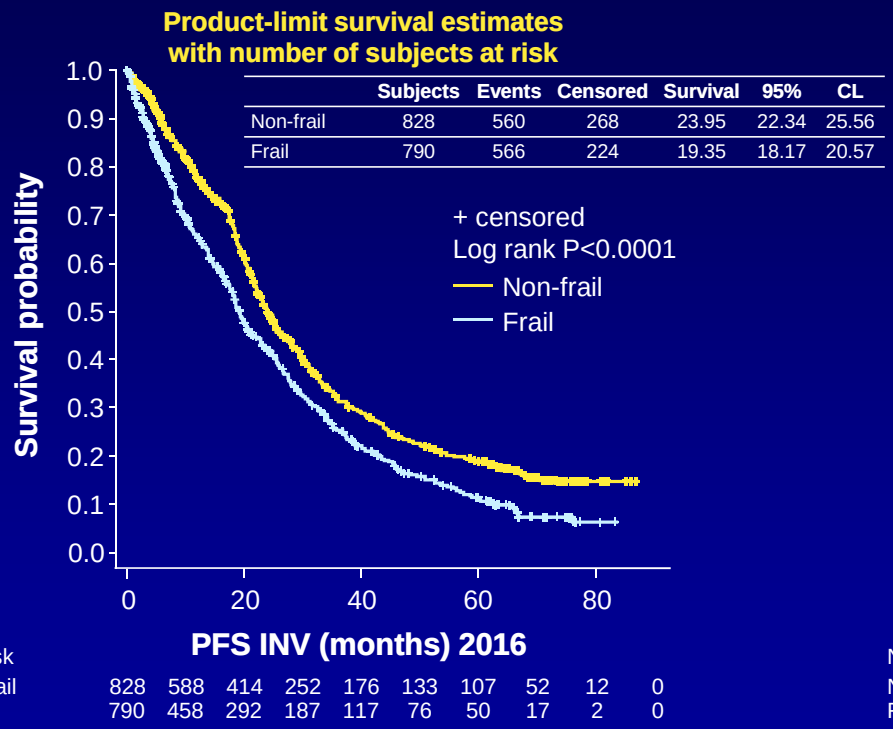
Engelhardt M. Haematologica 101:1110-9, 2016
Engelhardt M. Haematologica 102:910-921, 2017
Engelhardt M. Dtsch Med Wochenschr. 142:e51-e60, 2017
Gay F, Engelhardt M, ...Haematologica 103:197-211, 2018
Ludwig H, ...Engelhardt M, ...Leukemia doi: 10.1038/leu.2017.353, 2018

Revised Frailty Algorithm with ECOG

Category	Score
≤ 75 years 76-80 years > 80 years	0 1 2
Charlson ≤ 1 Charlson > 1	0 1
ECOG =0 ECOG=1 ECOG≥2	0 1 2

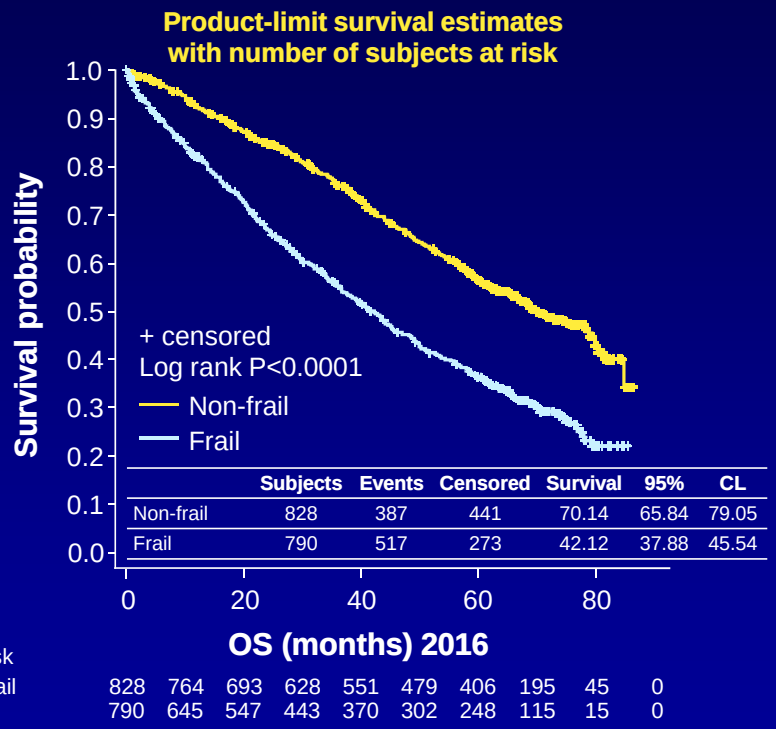
Sum of Scores = 0 or 1	→ NON-FRAIL
Sum of Scores >=2	→ FRAIL

PFS and OS by Frailty Level in the FIRST study



	Subjects	Events	Censored	Survival	95%	CL
Non-frail	828	560	268	23.95	22.34	25.56
Frail	790	566	224	19.35	18.17	20.57

N at risk										
Non-frail	828	588	414	252	176	133	107	52	12	0
Frail	790	458	292	187	117	76	50	17	2	0

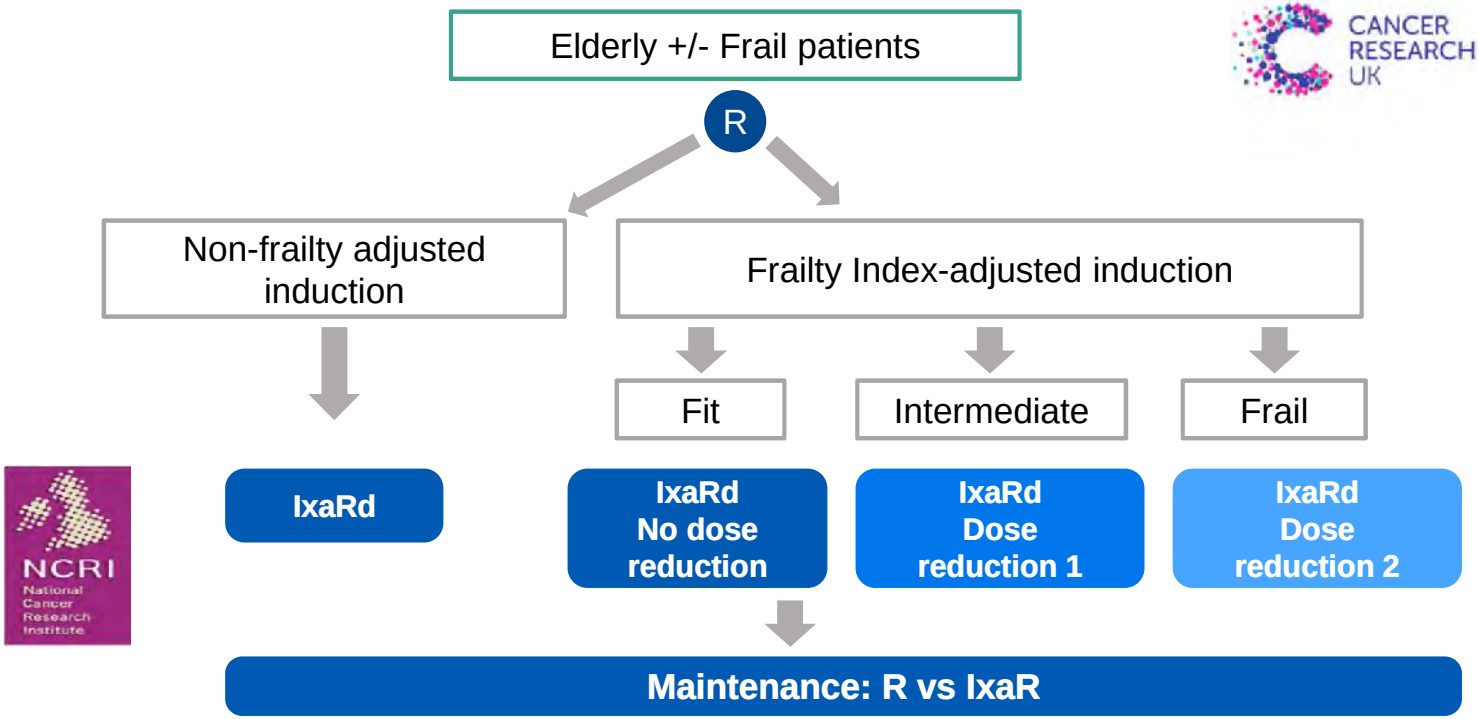


	Subjects	Events	Censored	Survival	95%	CL
Non-frail	828	387	441	70.14	65.84	79.05
Frail	790	517	273	42.12	37.88	45.54

N at risk										
Non-frail	828	764	693	628	551	479	406	195	45	0
Frail	790	645	547	443	370	302	248	115	15	0

Myeloma XIV: FITNESS trial

PI: Prof Gordon Cook and Prof Graham Jackson



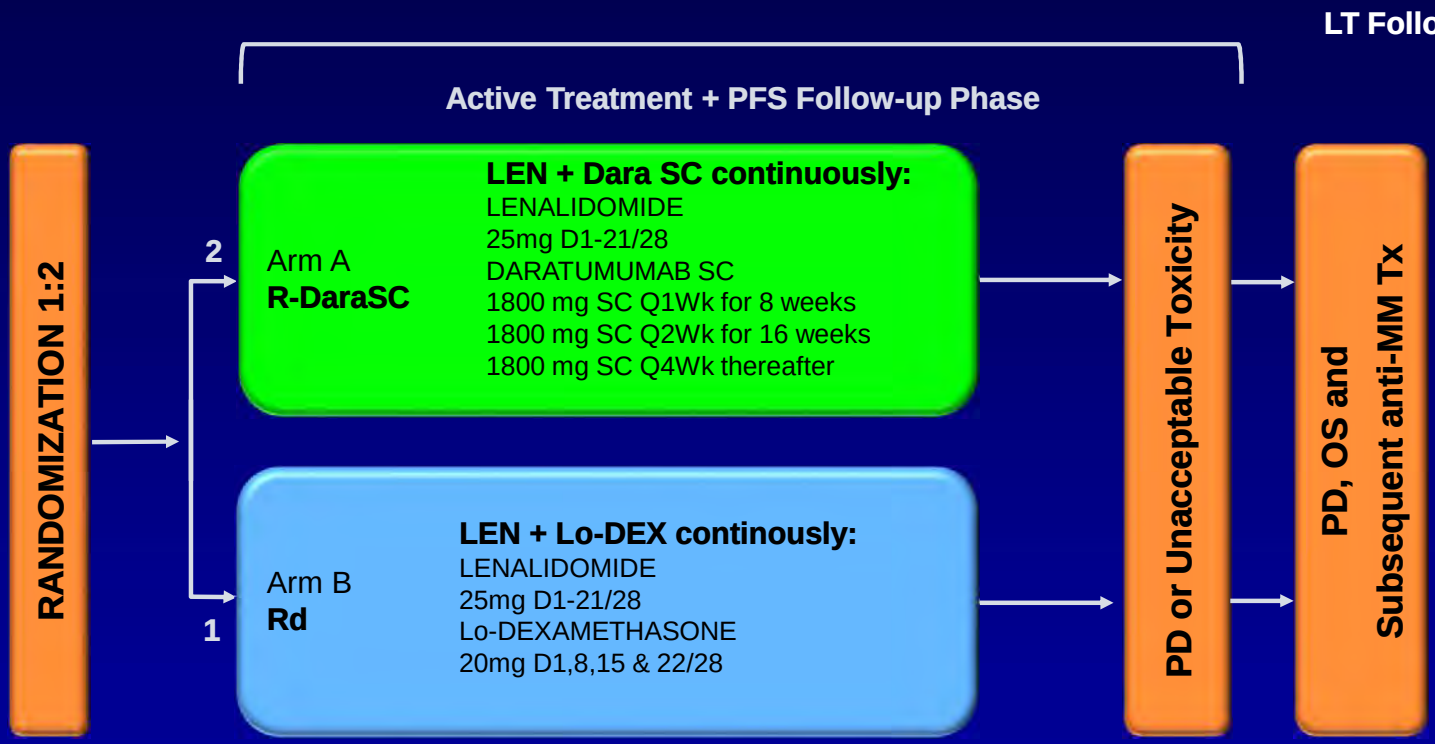
- New research being conducted in this population

FITNESS, Frailty Adjusted therapy In Transplant Non-Eligible patientS with Symptomatic myeloma; IxRd, ixazomib, lenalidomide and dexamethasone; PI, principal investigator; R, lenalidomide.

Slide courtesy of Myeloma UK.

A french study for frail elderly NDMM patients; IFM 2018-01

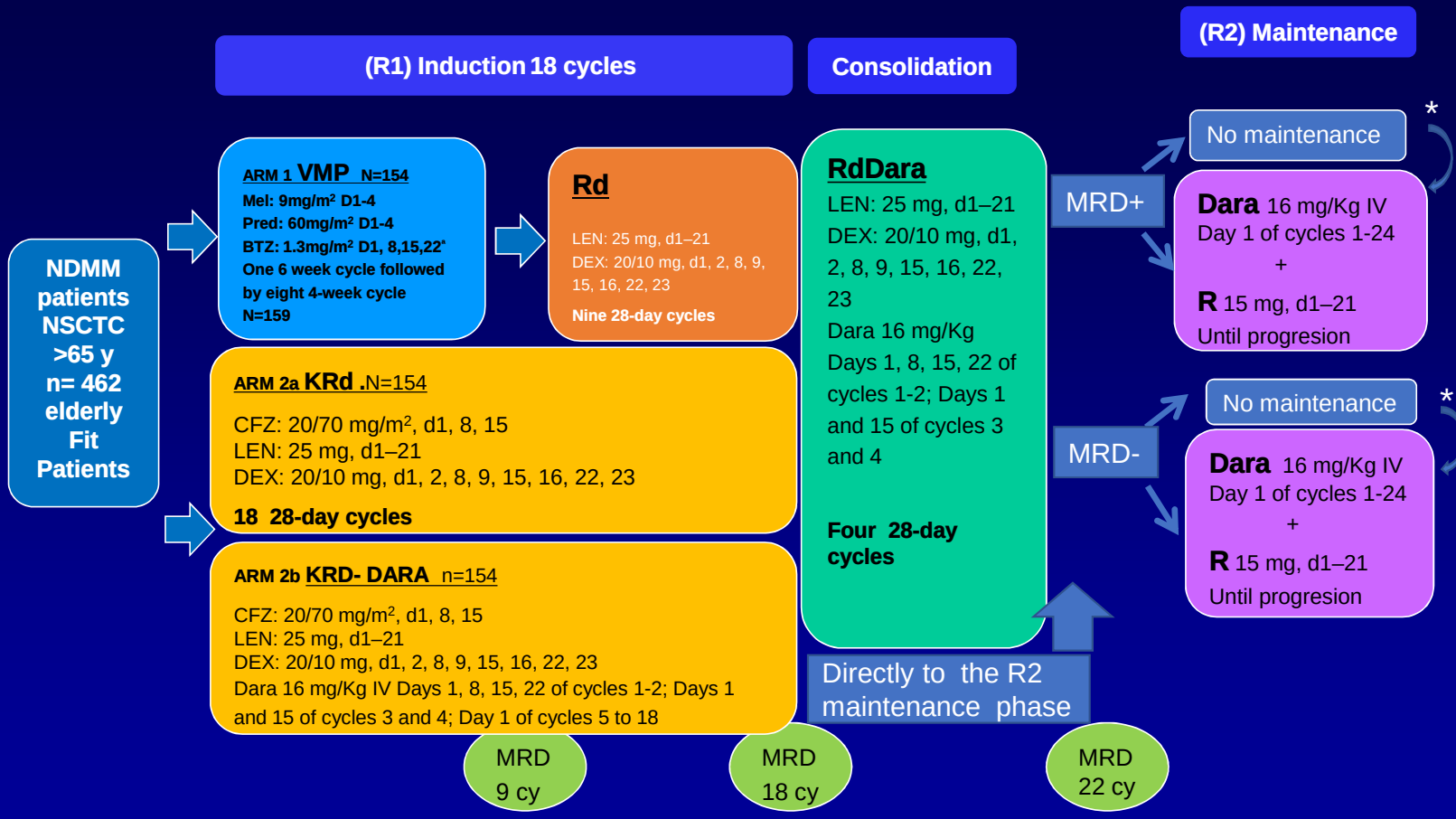
A dexamethasone sparing study



Randomization will be stratified by International Staging System (I vs II vs III) and age (<80 vs ≥80

In Arm A Low Dose Dex (20mg/week) during Cycle 1 and 2 then Methylprednisolone (with SC Dara)

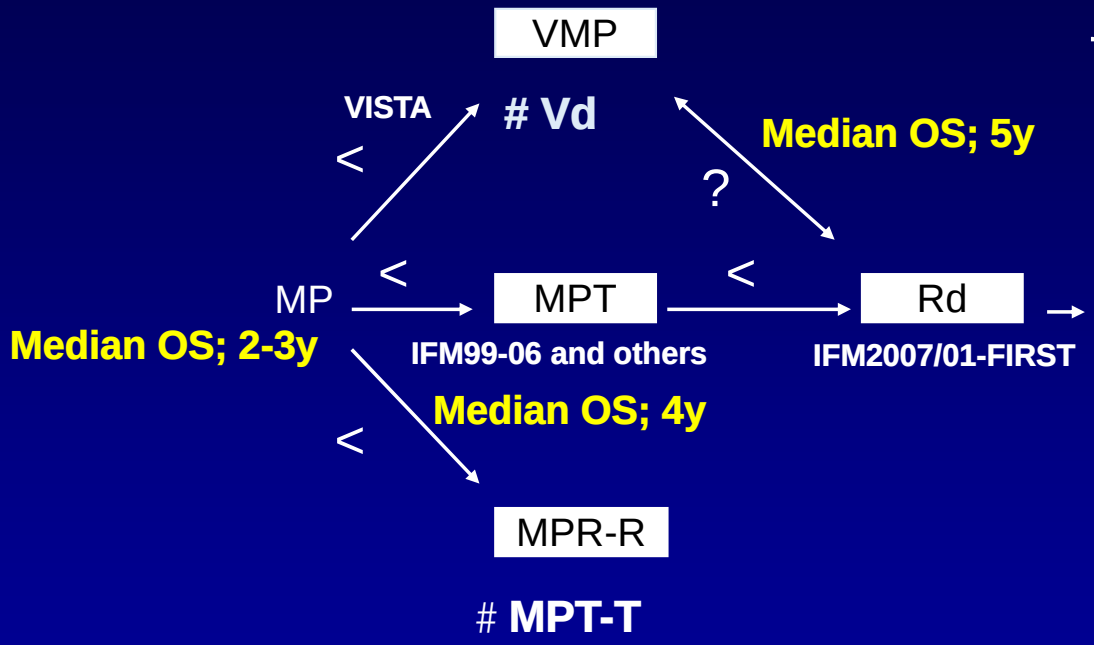
A spanish study for fit elderly NDMM patients; GEMFIT2016



Primary endpoint immonuphenotypic complete response
Secondary exploratory outcome: PFS

Courtesy of Dr MV Mateos

Treatment of MM in Elderly Patients – Landscape and Perspectives



VMP – Daratumumab[1] Alcyone

VRD[2]

Rd – Ixazomib[4] Tourmaline

Rd – Elotuzumab[5] Eloquent

Rd – Daratumumab[6] Maia

+ CD38 Mab
Fit elderly

Median OS; 6-7y ?

MP – Carfilzomib[7] Clarion

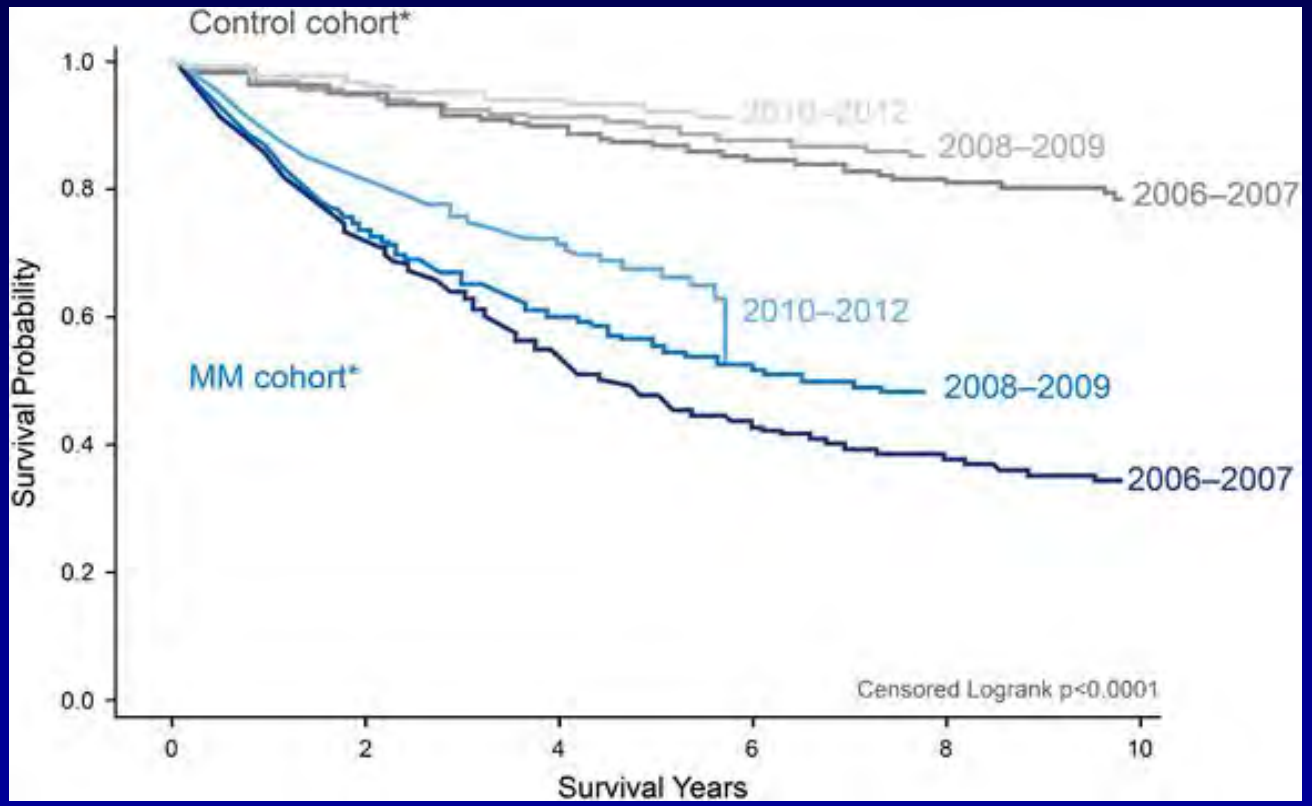
Approved regimens

MP, melphalan and prednisone; MPR, melphalan, prednisone, and lenalidomide; MPT, melphalan, prednisone, and thalidomide; R, lenalidmide; Rd, lenalidomide plus low-dose dexamethasone; T, thalidomide; Vd, bortezomib plus dexamethasone; VMP, bortezomib, melphalan and prednisone; VRD, bortezomib, lenalidomide and dexamethasone

[1]MMY3007, clinical trial.gov ref: NCT02195479. Accessed March 2016; [2] Durie et al. Lancet 2017 [3] ; [4] Tourmaline 2, clinical trial.gov ref: NCT01850524. Accessed June 2014; [5] Eloquent 1, clinical trial.gov ref: NCT01335399. Accessed June 2014; [6] MMY3008, clinical trial.gov ref: NCT02252172. Accessed March 2016; [7] Clarion, clinical trial.gov ref: NCT01818752. Accessed June 2014; .

MM Remains Incurable Despite Improvements

Survival Probability for MM Patients (N=7139) Vs Non-MM Population by year

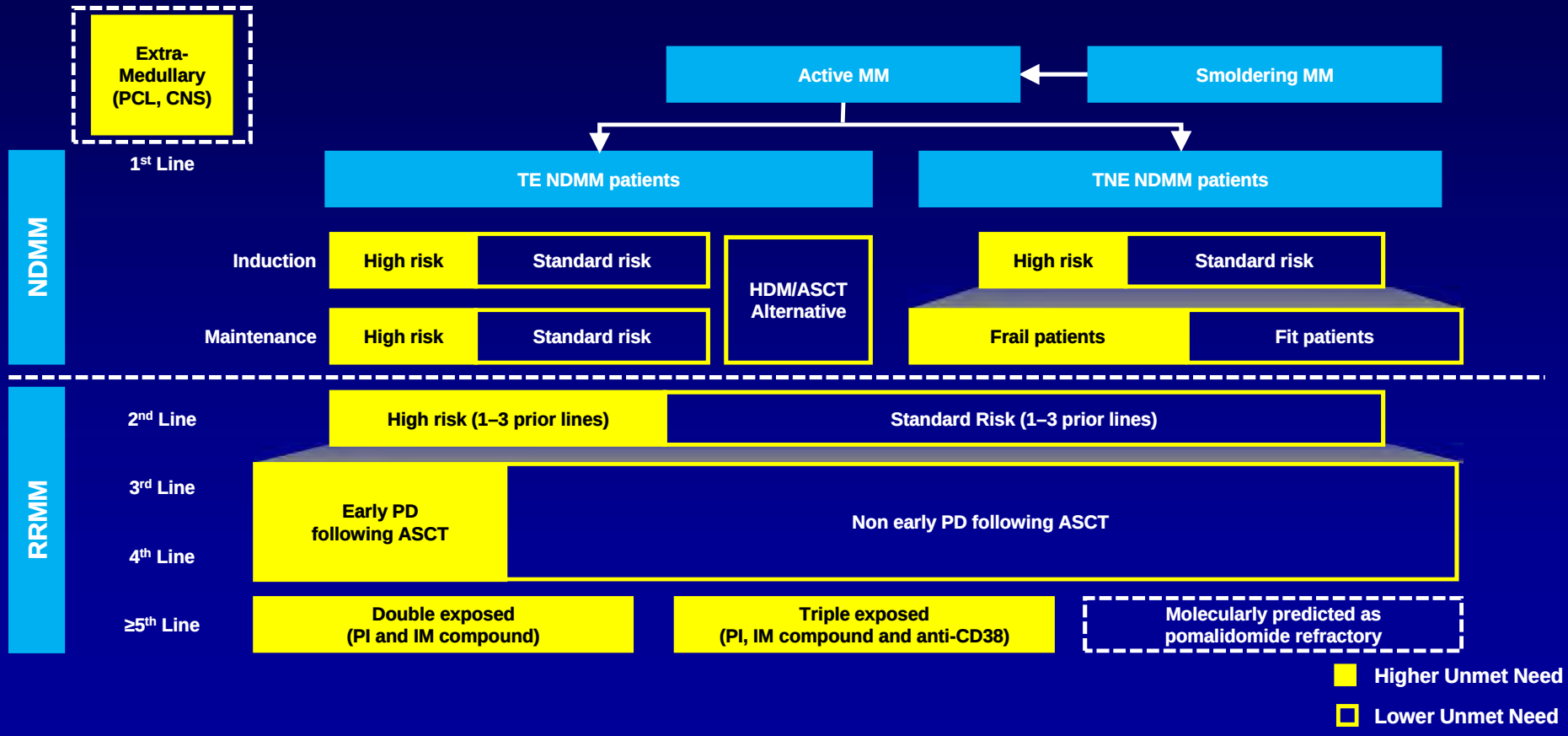


Age matched cohort from Non-MM population

MM Patients

Fonseca et al.Leukemia 2017, Jan20 Epub ahead of print

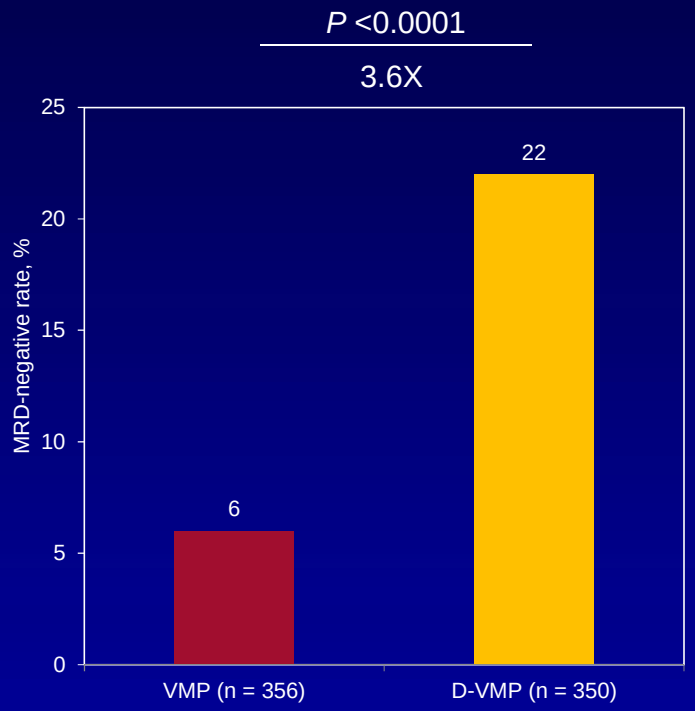
Patient populations with high unmet medical need

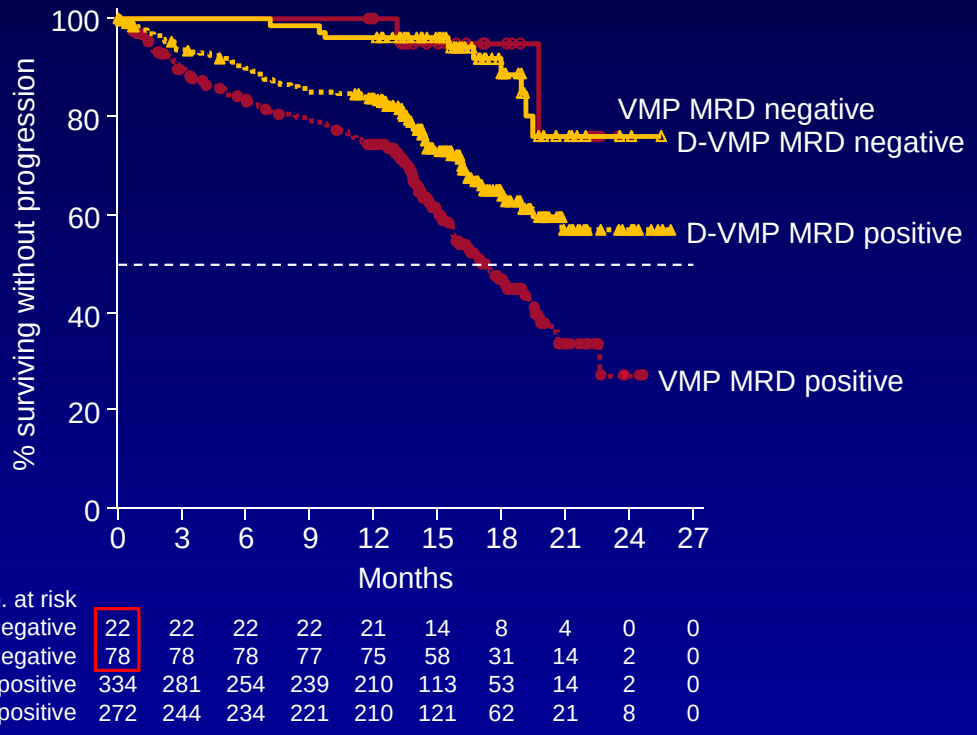


PLAZA
PLAZA

Efficacy: MRD[a] (NGS; 10^{-5} Sensitivity Threshold)

- Median (range) follow-up: 16.5 (0.1-28.1) months





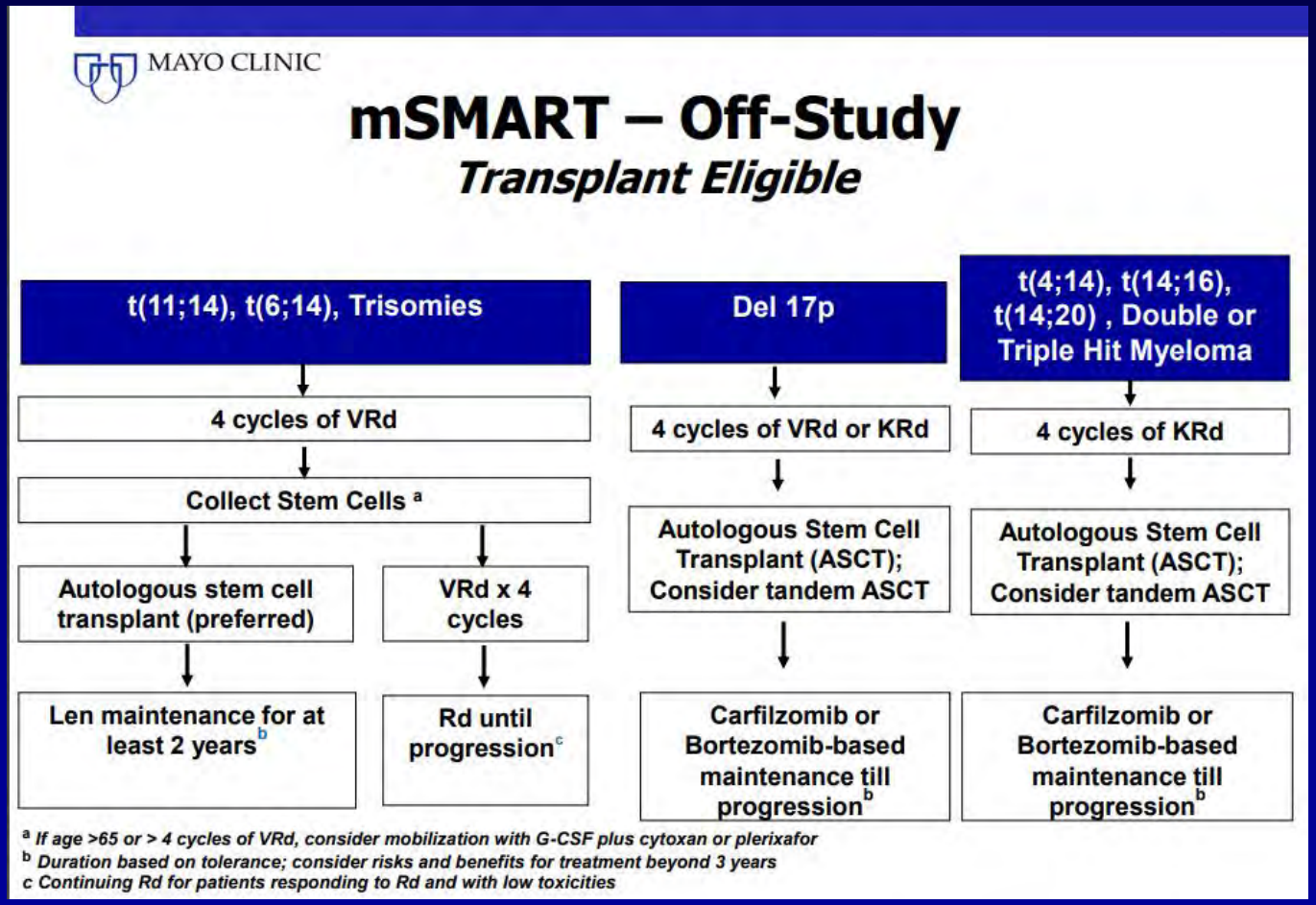
No. at risk										
VMP MRD negative	22	22	22	22	21	14	8	4	0	0
D-VMP MRD negative	78	78	78	77	75	58	31	14	2	0
VMP MRD positive	334	281	254	239	210	113	53	14	2	0
D-VMP MRD positive	272	244	234	221	210	121	62	21	8	0

>3-fold higher MRD-negative rate with D-VMP;
Lower risk of progression or death in all MRD-negative patients

[a]Assessed at time of confirmation of CR/sCR and, if confirmed, at 12, 18, 24, and 30 months after first dose.

Mateos et al.NEJM 2017;378:318-21

mSMART guidelines for NDMM – transplant eligible



Last reviewed May 2018. Dispenzieri A, *et al. Mayo Clin Proc* 2007; **82**:323–341; Kumar SJ, *et al. Mayo Proc Clin* 2009; **84**:1095–1110; Mikhael JR, *et al. Mayo Proc Clin* 2013; **88**:360–376.

MANAGEMENT OF MULTIPLE MYELOMA IN A PATIENT INELIGIBLE FOR ASCT CASE REPORT

Sorina Badelita
Fundeni Clinical Institute Bucharest

Medical history

G.V.

75 years old

Male

Smoker 150 packs/year

Nephrectomy-renal carcinoma (2002)

VHC infection

Disease onset April 2014

ECOG 3

Fatigue

Palour

Confused

Cutanous prurit

Pain and paresthesia on lower limbs

Lower back pain

Fundeni Clinical Institute April 2014

Hb 10 g/dl; Plt 49.000/mmc; WBC 7600/mmc; MCV 98 fl;

Erythrocytes in roulleaux; Macrocytosis; Hypersegmented granulocytes

Vit B12 = 85 pg/ml (211-911 pg/ml);

Parietal Cell and Intrinsec Factor antibodies-negative;

Superior Endoscopy - no abnormalities (performed in an other department, without gastric biopsy)

Creatinine 1.84 mg/dl; creatinine clearance 35 ml/min (C.G)

Proteinuria - absent

Calcium 12.2 mg/dl;

GGT 391 U/l (0-55 U/l); AP 155 U/l (42-128 U/l); AST 53 U/l; ALT 52 U/l;

b2M 7 mg/dl; albumin 3 g/dl;

LDH 57 U/l (105-248 U/l);

*IgA 21.14 g/l (0.7-4.0 g/l);*IgG 0.35 g/l *(7.0-16.0 g/l)*; IgM 0.42 g/l; (0.4-2.3 g/l *)*

Free kappa 147 mg/l (3.3-19.4 mg/l); free lambda 16 mg/l (5.7-26.3 mg/l); kappa/lambda 9.18; difference 131;

M spike 1.5 g/dl;

Immunofixation: IgA kappa

Fundeni
April 2014

Bone marrow biopsy:

20-30% plasma cells;

megaloblastic changes in the erythroid precursors

megaloblastic metamyelocytes

hypersegmented enlarged granulocytes;

scarce megacaryocytes with low platelet production;

Abdominal fat biopsy :

Congo Red stain positive in polarised light

Fundeni
April 2014

EMG:

Peripheral sensory- motor polineuropathy

Bilateral carpal tunnel syndrome

Echocardiography:

diastolyc disfunction, EF 65%; IVS 11 mm

Skeletal Xray:

osteolytic lesions T8,T9,L3

FibroScan:

11.8 kPa- F3

Diagnosis

IgA kappa Multiple Myeloma stage IIIB, ISS III

Systemic AL Amyloidosis with peripheral nervous system and hepatic involvement

Cholestasis

Moderate Anemia – vit B12 deficiency (malabsortion ??) and chronic disease

Sensitive- motor polyneuropathy grade II

Bilateral Carpal tunnel syndrome

Stage III Chronic Kidney Disease

Nephrectomy-renal carcinoma (2002)

Chronic VHC infection

Treatment

April 2014-Oct 2014

Vitamin B12 im with cytopenia resolution

Mel Dex* x 6

Melphalan iv 15 mg/sqm every 28 days

Dexamethasone 20 mg day 1-4

Bisphosphonates

*Bortezomib could not be associated due to peripheral sensory-motor neuropathy

Disease assessment

ECOG 1

Free kappa 83.4 mg/l; M spike: 0.4 g/dl -> PR

March 2016

M spike 0.9 g/dl; Free kappa 518 mg/l;

Amyloid vasculopathy

Cutanous prurit with elevated bilirubin levels

Proteinuria 3.9 g/ 24 hours (albuminuria)

Fish exam-negative for del17p, t(4;14), t(14;16)

Fig 1,2 Vasculitic lesions of forearms

March –August 2016

CyBorD x5 (28 days cycle)

Bortezomib 0.7 mg/sqm sc weekly

Cyclophosphamide 500 mg iv weekly

DXM 16 mg weekly

Disease assessment

M spike 0.2 g/dl; free kappa 102 mg/l; ->PR

proteinuria 0.87 g/24h

Echocardiography:

EF 60%; IV septum 11 mm, Diastolic dysfunction

April 2017

Orthostatisc hypotension

Involuntary weight loss 7 kg/3 months

Progressive neuropathy

Fibroscan F4 metavir 13.8 kPa

Proteinuria 4.45 g/24 hours

M spike 1.2 g/dl ; free kappa 907 mg/l;

LenDex x2 (Lenalidomide from India)

Disease assessment

M spike 0.2 g/dl free kappa 174 mg/dl;->PR

STOP Dexamethasone due to corticosteroid-induced myopathy

Lenalidomide maintainance x4

10 mg/day 1-21

January 2018

Bradylalia

Cephalic edema,

Hyponatremia (131 mmol/l)

Cerebral CT:

vascular degenerative lesions

EEG:

hypoxic-metabolic encephalopathy

Doppler-US:

55% left carotid stenosis

Treatment

Syptomatic + Aspenter

Stop Lenalidomide

Fig 1,2 Cephalic edema, periorbital edema

February 2018

Emergency admission

Fever 39.3^{0}C, Chills

Confusional syndrome, Hypotension

Bradylalia, Periorbital edema

Hb 7.5 g/dl

TSH 108 U/ml fT3 0 ng/ml fT4 0.13 ng/ml

ATPO- negative; Anti Tg ab-negative

Thiroidian US:

without abnormalities

Endocrinology exam :

mixedema probably due to amyloid infiltration of the thyroid

Treatment:

Euthirox - Favorable clinical outcome

Restart Lenalidomide

February 2018	Echocardiography EF 40%; IVS 14 mm; Moderate sistolic dysfunction; Severe diastolic dysfunction NT proBNP 2463 ng/ml;
March 2018	Proteinuria 3.3 g/24 h M spike 0.8 g/l; free kappa 789 mg/l Stop Lenalidomide What's next treatment? Carfilzomib?? Symptomatic and palliative therapy

June 2018

Angor pectoris

NT proBNP 5428 ng/ml;

ECG :

T wave inversion ; ST segment depression

Coronary stent implantation (LAD, LCA, LCx)

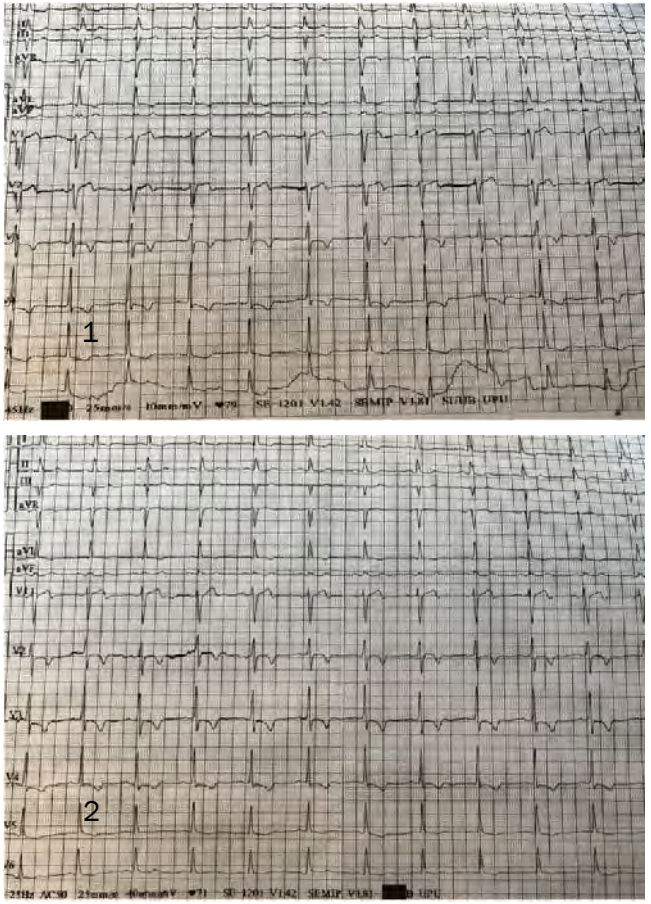


Fig. 1 ECK 11:00 ,2 ECG 16: 00
Acute T wave inversion and ST segment depression

August 2018

Sudden cardiac death at home, 4 years after diagnosis

A case presentation with MM

Prof. RODICA MIHAESCU, Ph.D,
University of Medicine of Timisoara and
Oncohelp Hospital, Timisoara

Athens, 2018

Disclosure

- **Nothing to declare**

History

- T.R.- 65 years old male
- July, 2007

Clinic status: - chest pain,
- weakness and fatigue,
- weight loss,
- pallor

Rx: spinal compression to T10

08 2007 Neurosurgery
Emergency Hospital, Timisoara

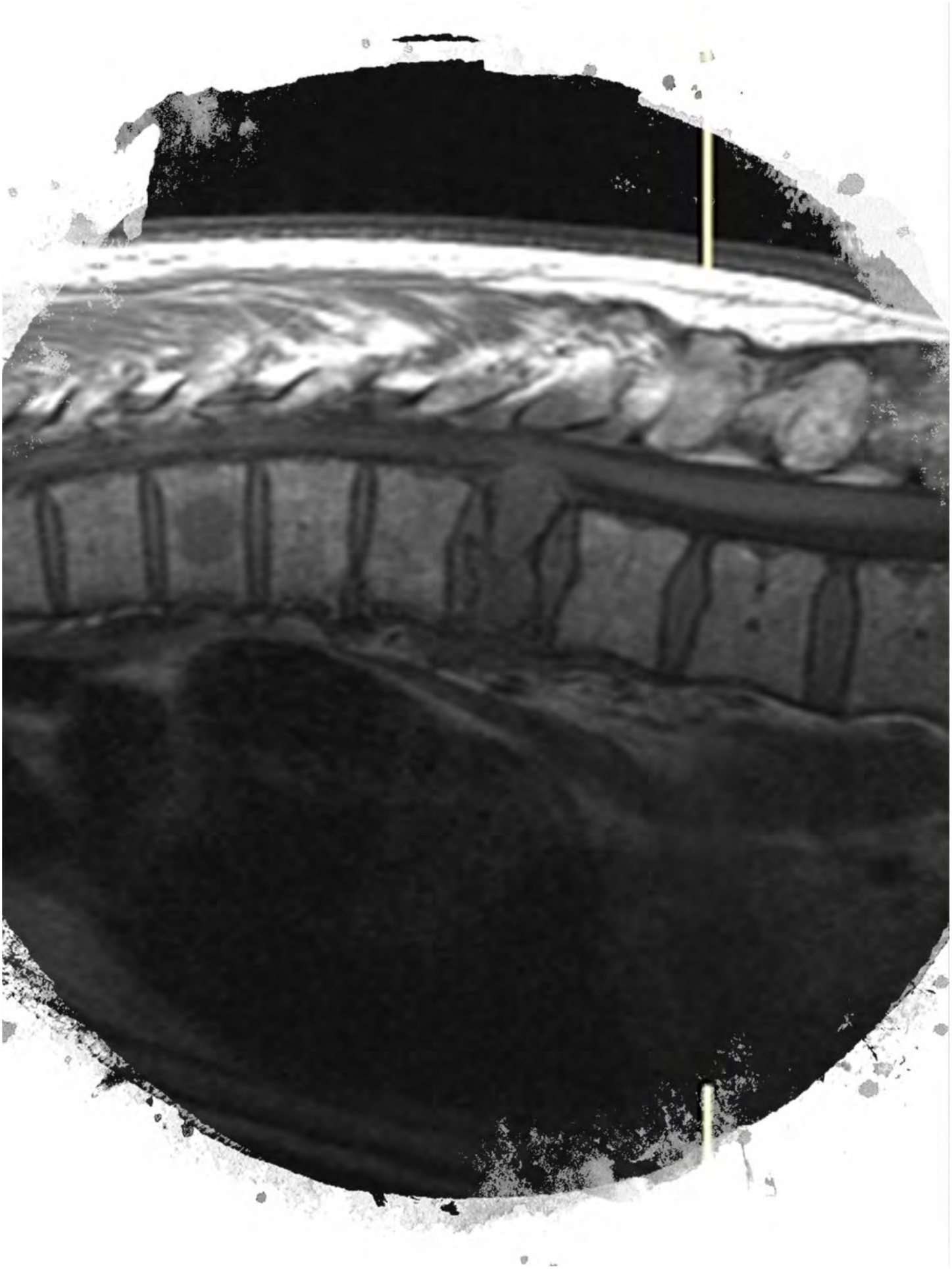
- chest pain
- superficial hyperesthesia skin band – T10-T11 appropriate bilateral
- spastic paraparesis gait

MRI – tumor at T 10 level with spinal cord compression and three secondary vertebral lesions at lumbar spine level

Intervention: decompressive laminectomy and biopsy from the tumor

HP: Plasmacytoma

Im: 6/11
Se: 5007
S
***
***
06/04/1943 M
NEUROMED TIMISOARA
1
SPINE^thoracic+lumbar_spine
T1
A
P
2
WL: 563 WW: 1263 [D]
T: 4.0mm L: 7.7mm
I
TE: 12.0
18/08/2007 2:01:26 AM



September 2007
County Hospital - Hematology
Timisoara

Clinical:

- **asthenia,**
- **pallor,**
- **back and chest pain**
- **postoperative scars**

Laboratory tests

- ESR – 38 mm/h
- WBC: 5800/ mm^3
- Hb: 11,5g/dl, Ht: 39%
- Plt : 220.000/ mm^3
- Electrophoresis:
  - TP-8,7g/dl:
  - Alb 42.6 (alfa 1-7,6%;
  - alfa 2-8,8%; beta –7,9%;
  - gamma-33,1%)
  - monoclonal aspect
- Immunofixation: Ig G kappa light chains
- Beta 2 microglobulin – 2,3 mg/L
- C- reactive protein – 30g/dl
- BM aspiration – 42% plasmocytes

Laboratory tests 2

- Bence Jones urine paraprotein – positive
- Creatinine – 1,2 mg/dl
- Serum calcium – 9,9mg/dl
- MRI: osteolytic lesions and extramedullary plasmacytoma
- HP Dg. of tumor: plasmacytoma

Treatment
September 2007 – January 2008

- Dg. MM, IgG kappa light chains, Stage IIA. Extramedullary Plasmacytoma

  IP ECOG: 1

- 6 x VAD (VCR+ADR+DEXA)
- Bisphosphonate Therapy
- Antalgic therapy

January – November 2008

- **ASCT tandem** in “Louis Turcanu”” Hospital of Timisoara conditioning by Melphalan 200 mg/mp in June and in November 2008, conditioning by Melphalan 140 mg/mp).
- After 2 months he began a consolidation therapy with
- 12 cycles of Velcade - 1,3 mg/m 2, IV, weekly (donation)

Nov 2009 medical examination in “Louis Turcanu” Hospital

Clinical status: generally good condition

LABORATORY INVESTIGATIONS :

- **HLG: Hb —11.9 g/dl; Thrombocytes = 83.000/mm^3**
- **WBC =3900 /mm^3**
- **ESR =2 mm/h**
- **Beta 2 microglobulin - 1,1 mg/l**
- **Immune status: a slight decrease in total LyT accompanied by a moderate increase in LyB (normally after ASCT)**
- **Absolute values : moderate lymphopenia with moderate LyT CD4 + and CD8 + decrease; NK cells slightly below the lower limit of normal. Low CD4 / CD8 ratio.**
- **Immunofixation: normal**
- **No treatment**

2010 – medical examination
"Louis Turcanu" Hospital

Feb : - Immunofixation – normal

- beta 2 microglobulin – 1,32mg/l
- hematologic – normal

April:

- Immunofixation - IgG Kappa light chains positive
- Beta 2 microglobulin – 1,17 mg/l

April 2010 First relapse
Oncohelp Hospital

ESR- 43 mm^3

Serum calcium– 10, 5mg/dl

Creatinine – 1,17mg/dl

HB – 10, 8g/dl

RBC – 3100000/mm3

WBC – 3400/mm3

PLT – 120 000/mm3

LDH – 302UI/l

TP – 8,6g/l

ALB - 3,2 g/d

IgG - 4,5g/dl

Beta 2M – 1,17mg/l

BM aspiration – plasmocytes – 12%

No - Rx, CT, MRI

No cytogenetics, no FISH

Oncohelp Hospital

Dg: MM Ig G kappa light chains, stage IIA

PI: ECOG 1

- April 2010 treatment –
  - Vel/Dex – (Velcade 1mg/m^2 sc weekly = 1,9
  - Dexamethazone 20 mg – 6 Cycles of 4 applications
- Bisphosphonate – monthly
- Later - without maintenance treatment
- No approval for Velcade or IMiDs in Romania

2012 – 2013
medical examination and laboratory tests

- Hb = 12,7 g/dl ;
- Red blood cells=3.870.000 /mm^3
- Thrombocytes =149.000 /mm^3 ,
- Leucocytes = 5400 /mm^3;

  Neu=57,7 %; Mon= 9,7%; Limf=28,7%; Eoz=3,5%; Bazo=0,4%
- Serum calcium level - 9mg/dl
- ESR - 20/mm/h
- Imunofixation – normal
- No urinary light chains

January 2014

- Biopsy for an interscapular tumor with irregular surface

HP: Basal cell carcinoma

- Biopsy for a tumor on the medial face of the left arm

HP: keratoacanthoma

There is no treatment

04 2014 Second relapse !!!
Oncohelp

Clinical status :

- Asthenia
- Anemia
- Back pain

Laboratory tests:

- Hb - 9g/dl
- WBC – 2940/mm^3 (gr-52%,Ba-3,5%, Mo.7,5% Ly-34%, Eo-3%)
- Plt – 184 000/mm^3
- Serum Calcium – 7,31mg/dl
- Creatinine - 2,80mg/dl
- ESR – 43 mm/h
- TP – 8,5 g/l with the range gamma globulin of 29%
- Alb – 5,7mg/l
- Immunofixation - IgG – kappa light chains
- BM aspiration - 11% plasma cells
- Beta 2 M – 5,6mg/l

ESMO guidelines – updated

MM ESMO Clinical Practice Guidelines

Table 2. International staging system for MM

Stage	Criteria
I	Serum β2M < 3.5 mg/mL and serum albumin ≥ 3.5 g/dL
I	Not stage I or III[a]
II	Serum β2M ≥ 5.5 mg/mL

[a]There are two possibilities for stage II:

- Serum β2M < 3.5 mg/L but serum albumin < 3.5 g/dL;

or

- Serum β2M 3.5–5.5 mg/L irrespective of the serum albumin.

β2M, β2 microglobulin; MM, multiple myeloma.

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Table 3. Standard risk factors for MM and the revised ISS

Prognostic factor	Criteria
ISS stage	
I	Serum β2M < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β2M ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

β2M, β2 microglobulin; CA, chromosomal abnormalities; iFISH, interphase fluorescent *in situ* hybridisation; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

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Dg. MM Ig G kappa light chains stage III B
Extramedullary plasmacytoma
PI: ECOG 2

EKG, ECHO cardiography with assessment of diastolic function and measurement of interventricular septal thickness – normal for his age

Treatment

- – Caelyx (40mg/mp)
- –-Thal (100mg)
- –-Dex (40mg x 4 days)

} 4 cycles

- –Maintenance therapy-only Thalidomide 100 mg/day
- –Acenocumarol – prophylactic Deep Vein Thrombosis

September 2015 medical examination

- Clinical – relatively normal

Laboratory tests:

- ESR - 6mm/h
- Immunofixation - normal
- TP - 7,4g/l…Range G -16,2%
- Creatinine – 0,83mg/dl
- Calcium - 9,3 mg/dl
- Hb -14g/dl,
- WBC- 5300/ mm^3
- Plt- 134000/mm^3

Medical examination
March and June 2016

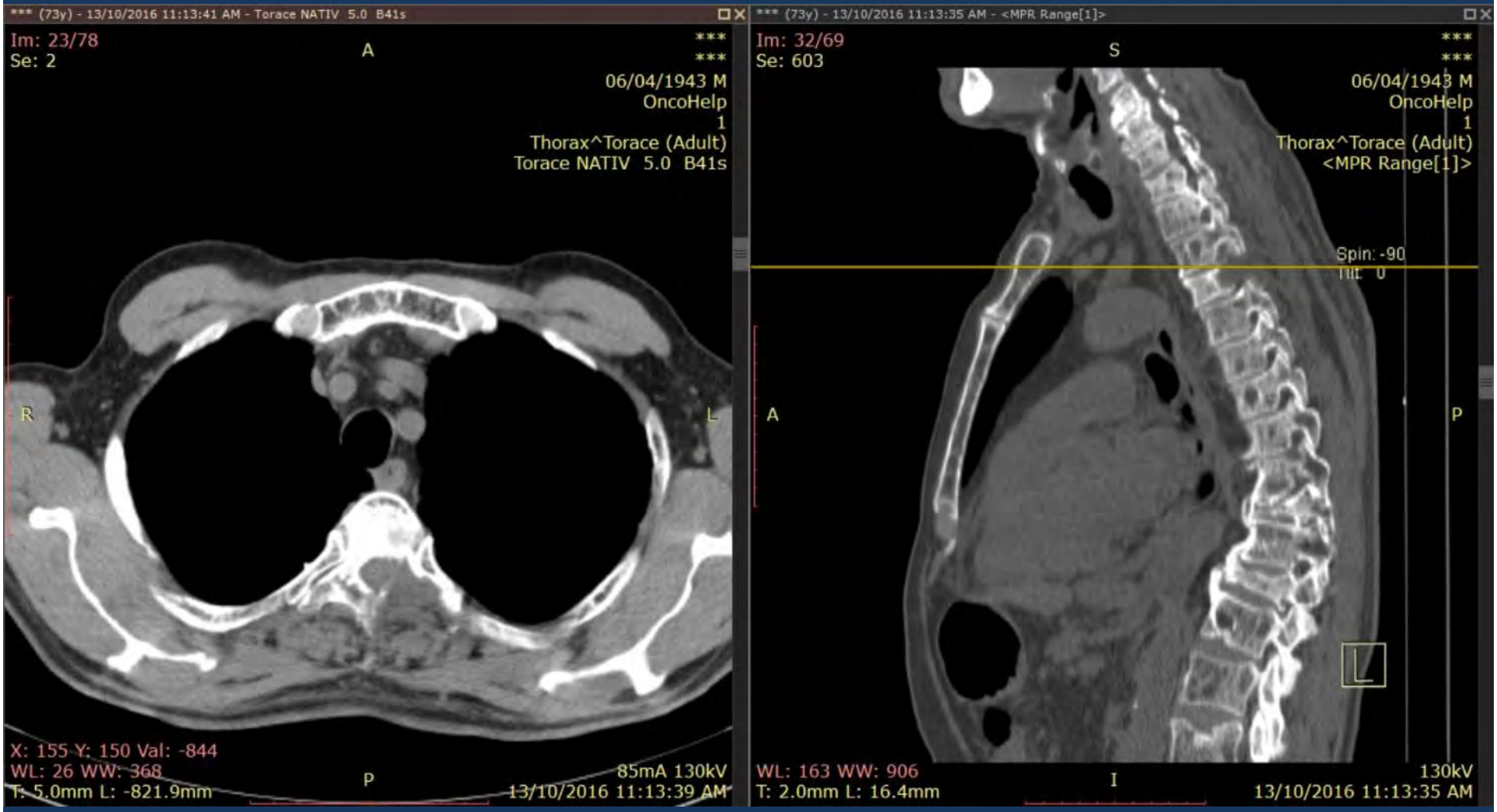
- **ESR - 4 mm/h……12mm/h**
- **Creatinine – 0,93mg/dl……..0,91mg/dl**
- **Serum calcium – 9,1mg/dl……..9,2mg/dl**
- **PT -7,1g/dl……7,3mg/dl**
- **gamma G – 20,5%.....21%**
- **Hb. – 14,6 g/dl……..14,1g/dl**
- **WBC – 5790 /mm³……4980/mm³**
- **Plt – 121000/mm³……117000/mm³**
- **Serum Immunofixation – normal**
- **No Rx, No TC**

August 2016 - 3th relapse!!!
ONCOHELP

- Chest pain
- Gait disturbance
- Marked asthenia

- CT:
  - left paravertebral tumor mass that causes osteolysis of T3 and T4 with invasion into the medullary cavity. Multiple osteolytic lesions

- MRI
  - left paravertebral tumor mass that causes osteolysis to T3 and T4 with invasion into the medullary cavity, with pleura extension. Multiple osteolytic lesions


*** (73y) - 13/10/2016 11:13:41 AM - Torace NATIV 5.0 B41s
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1
Thorax^Torace (Adult)
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WL: 26 WW: 368
T: 5.0mm L: -821.9mm
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WL: 163 WW: 906
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Treatment - Oncohelp

- **6 cycles x MPR - well tolerated**
- **Continue with Lenalidomide - 21 days/month**
- **November and December 2016 - external radiotherapy to linear accelerator**
  - **up to the total dose 30Gy, from 2nd to 5th thoracic level**
  - **good tolerance**
- **MRI December - tumor disappearance but still osteolytic lesions persistance**
- **It remains on Lenalidomide 21 days/month**

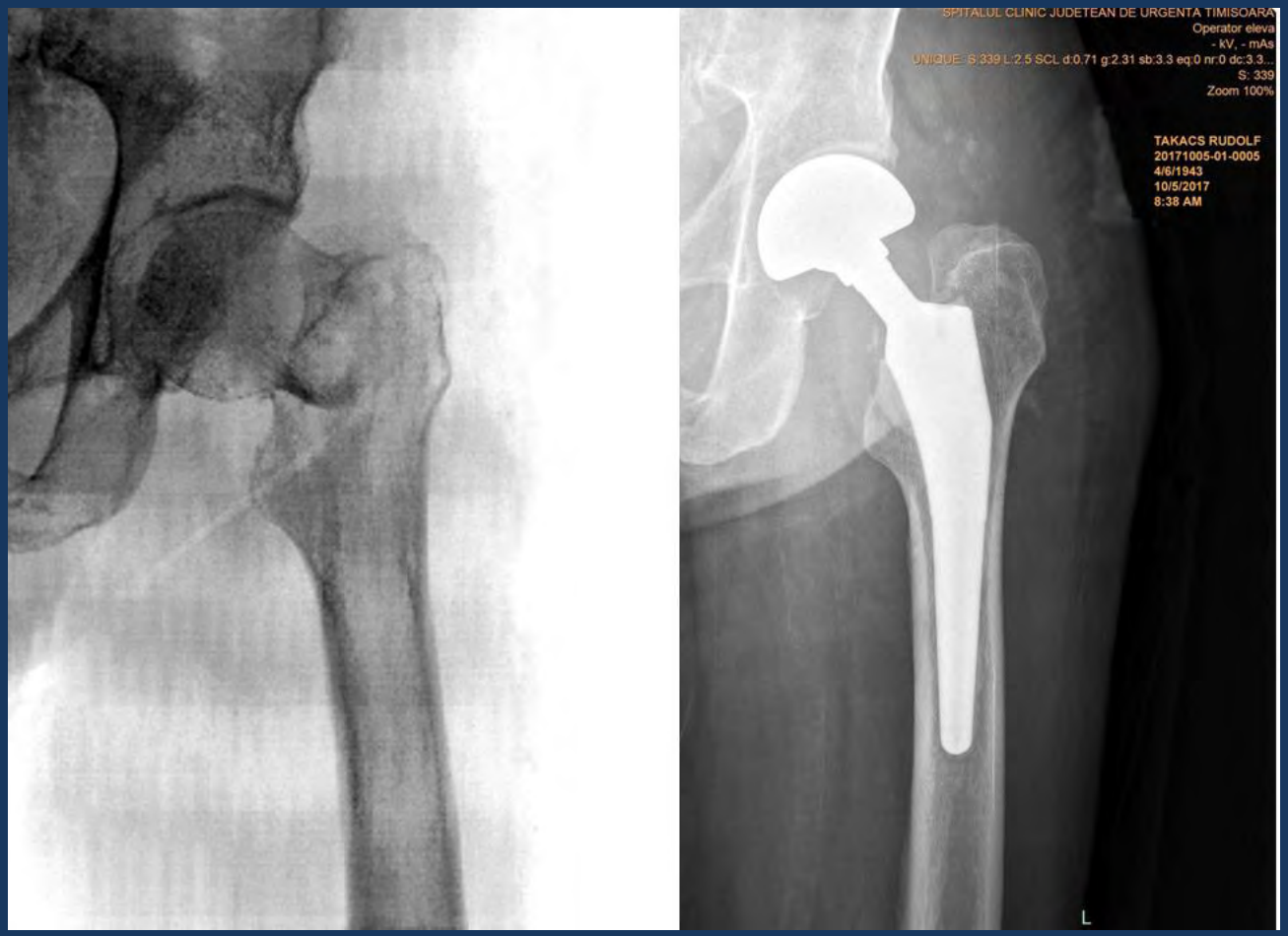
2017 - Oncohelp

- Medical examination at 2 months with good overall condition

- Under treatment with Lenalidomide
  - 21days/month

- Ig G – 12,1 g/l (N: 07-16 g/l)
- Kappa light chains – 0,31g/l (N:1,7 – 3,7)
- Hematologic – moderate thrombocytopenia

August 2017- evolution under Len
Left hip fracture on pathological bone



Orthopedics - County Hospital of Timisoara

- Left Hemiarthroplasty with Cemented Bipolar Prothesis
- Biopsy - HP : plasmacytoma
- Continue with Len
- Antalgic treatment
- No radiotherapy

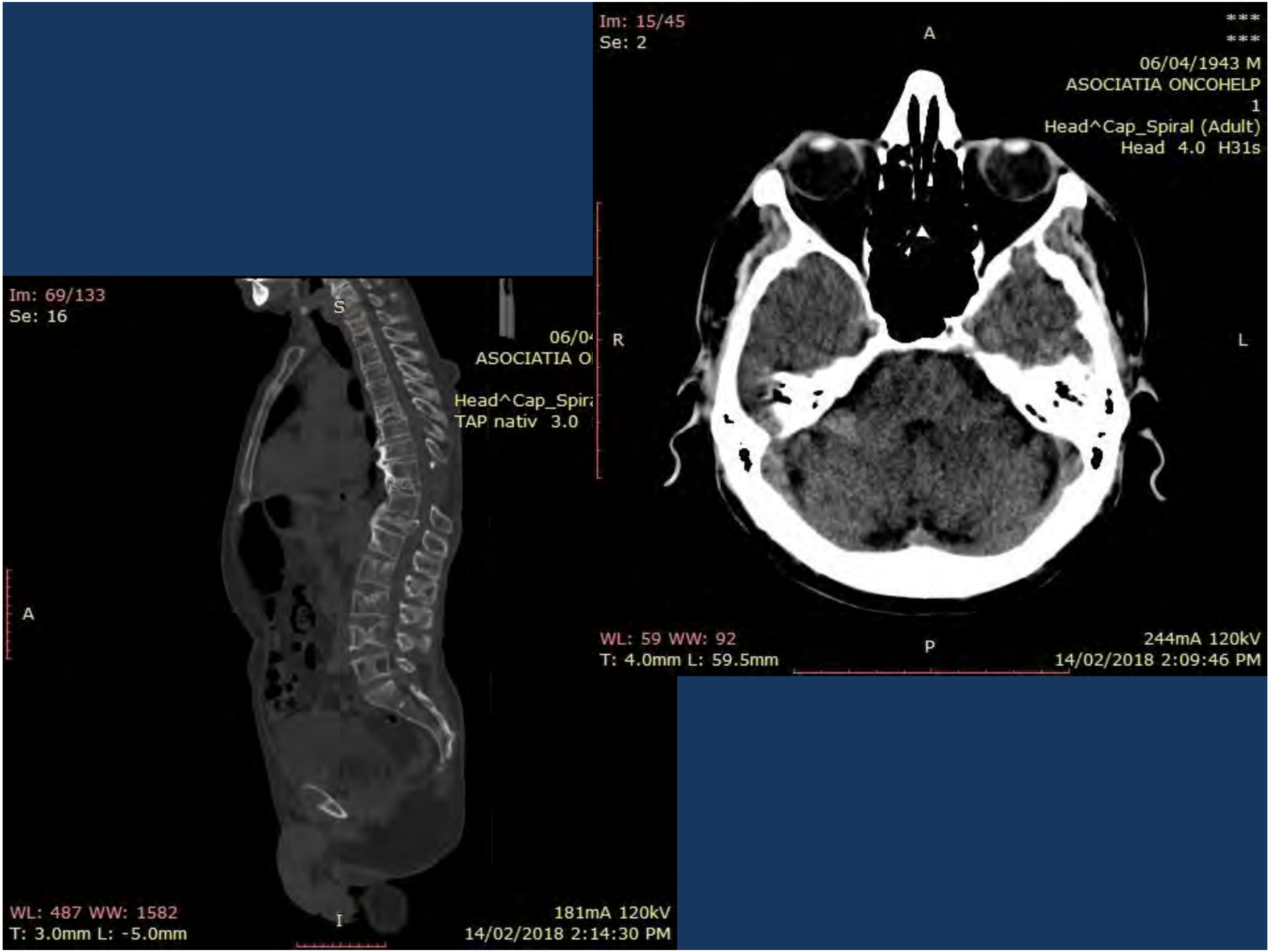
February 2018 - ONCOHELP

- Clinical: chest pain radiating to the anterior chest yielding to opiates, headache, dizziness, balance disorder
- Laboratory:
  - ESR - 45mm/h
  - Serum calcium - 8,1mg/dl
  - Serum creatinine – 0,65mg/dl
  - Hb. - 10,6g/l
  - WBC – 3540/mm^3
  - Plt – 93000/mm^3
  - BM aspiration: plasma cells 3%
  - Imunofixation: monoclonal aspect –

    IgG presence with kappa light chains

Computer Tomography (CT):

- **Progressive disease :**
  - **a spontaneous hyperdensity, round, diameter of about 11 mm located in the pontocerebellar right angle and new osteolytic lesions at the vertebral level**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Kd for the Treatment of RRMM who Have Received 1-3 prior Lines of Therapy

BEST FOR

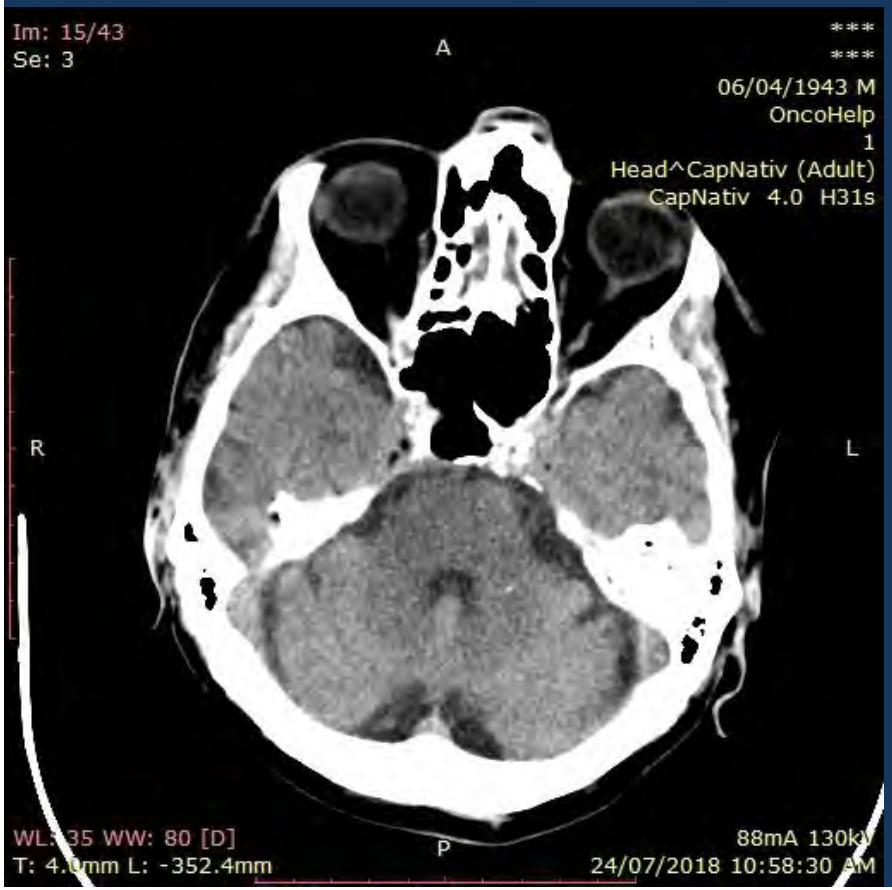
- Patients who progress on lenalidomide
- Patients who are candidates for bortezomib retreatment
- Very good results as 2nd line therapy
- Very good results for elderly patients (>75 years of age)

Therapy – MM high risk - KD

- Kyprolis 56mg/mp , 100mg IV + Dexamethasone 20 mg / cure – from February 2018 until to this date
- Slight thrombocytopenia and anemia
- Non antalgic treatment
- Associated treatment: Acyclovir 200 mg. 2x1 capsule /day, Ca-D3 1 g/day, Allopurinol 100 mg/day, Aspirin 75 mg/day

Medical examination + Computer Tomography (CT) in September 2018

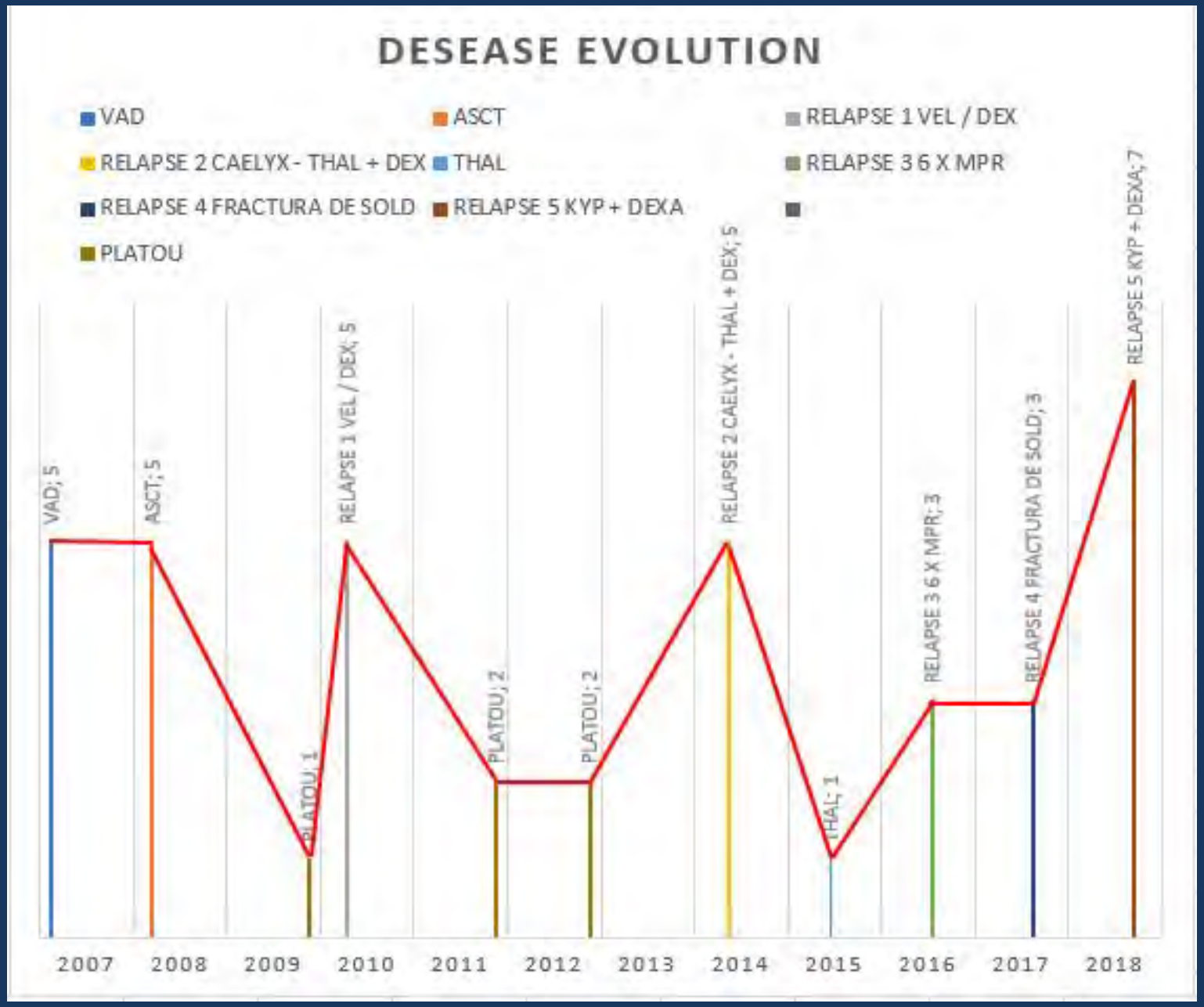
The disappearance of the ponto-cerebellar tumor and the reduction of bone osteolytic lesions



September 2018

Clinical status: fever, chills, myalgia, anemia

- **Hb. – 9,2 g/dl**
- **WBC - 3180/mm^3**
- **Plt – 89.000/mm^3**
- **Creatinine – 1,17mg/dl**
- **Serum calcium – 8,7mg/dl**
- **ESR – 56mm/h**
- **Blood culture - sepsis with Klebsiella pneumoniae**
- **Supportive treatment, antibiotics, antifungal, hydration, urolytic, calcium, aspirin**
- **Timing the cystostatic cure until October**
- **Now under KD**
- **Generally good condition**


DESEASE EVOLUTION
VAD
ASCT
RELAPSE 1 VEL / DEX
RELAPSE 2 CAELYX - THAL + DEX
THAL
RELAPSE 3 6 X MPR
RELAPSE 4 FRACTURA DE SOLD
RELAPSE 5 KYP + DEXA
PLATOU
VAD; 5
ASCT; 5
PLATOU; 1
RELAPSE 1 VEL / DEX; 5
PLATOU; 2
PLATOU; 2
RELAPSE 2 CAELYX - THAL + DEX; 5
THAL; 1
RELAPSE 3 6 X MPR; 3
RELAPSE 4 FRACTURA DE SOLD; 3
RELAPSE 5 KYP + DEXA; 7
2007
2008
2009
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2011
2012
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2015
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2018

Discussions

- Old patient diagnosed in 2007 with multiple myeloma IgG kappa II A, extramedullary plasmacytoma, chemotreated and with ASCT tandem
- Periodic follow-up but no maintenance treatment until relapse, when switched to III B stage
- He was followed in several hematology departments
- With numerous relapses - 5 - all of them, type extramedular plasmacytoma, always with multiple osteolytic lesions

Negative points:

- There is no cytogenetic analysis and no FISH
- Relapse after ASCT tandem + Velcade after 17 months
- There is no continuous follow up with Rx, CT, MRI
- Lack of approval in Romania for maintenance treatment at the time of 1st relapse - the patient agreed to buy thalidomide and late lenalidomide

- **Although with repeated relapses, the patient has an evolution of 11 years without significant comorbidities, now with a very good response to the treatment with Kyprolis - Dexamethasone (10 cycles)**
- **We try to do until 16 cycles**
- **We must have a cytogenetic test**
- **For a new relapse – Daratumumab anti CD38 – it was approved in Romania for patients with refractory MM**

TRAIAN-TM

A Patient With Deep Vein Thrombosis And Pulmonary Thromboembolism As An Initial Presentation Of Multiple Myeloma

Milena Dapcevic
Clinical centre of Montenegro

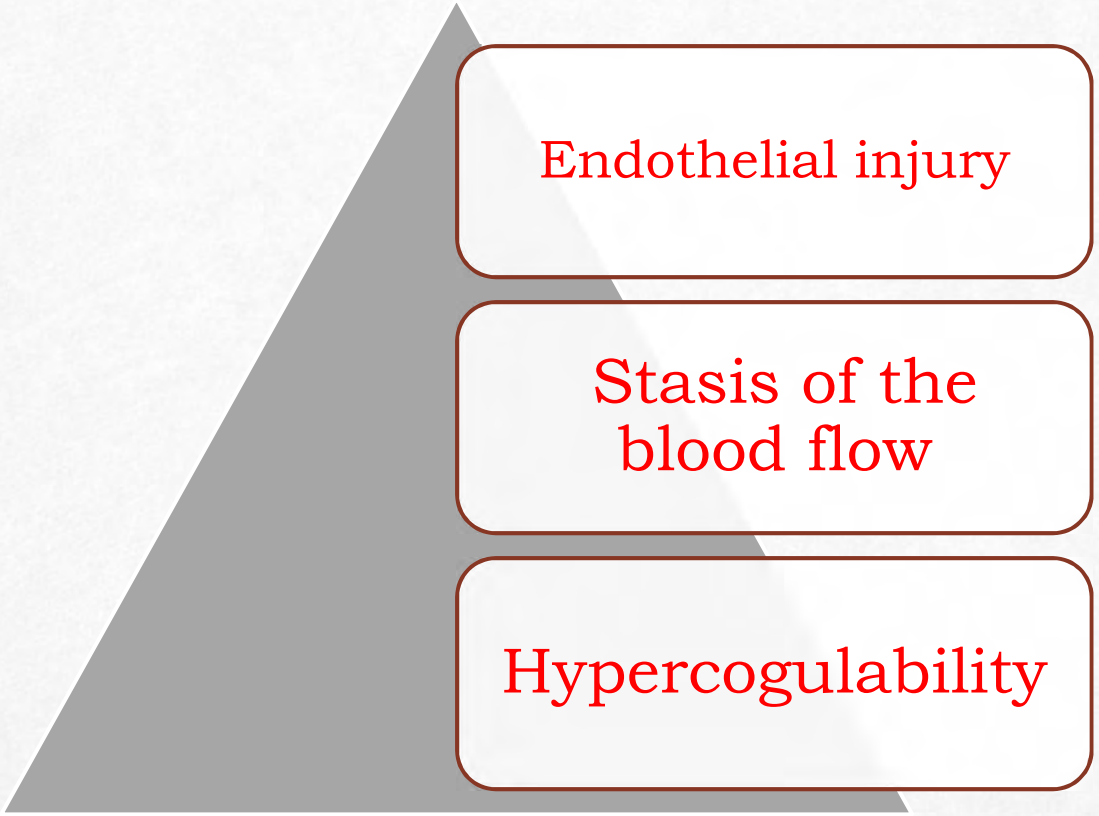
- No disclosures

Multiple Myeloma Facts

- Multiple myeloma (MM) is clonal plasma cell disorder and leading indication for autologous stem cell transplantation worldvide
- Second most prevalent hematological malignancy
- Median age at diagnosis is 70 years
- Survival is increasing but no modality with the possible exception of allogeneic stem cell transplantation is curative in multiple myeloma
- Diverse hemostatic abnormalities have been reported in patients with myeloma which predispose to bleeding and also thrombosis.

Thrombosis

1. The first description of thrombosis pathogenesis was given by Rudolf Virchow in 1856. Virchow-triad
2. Disease is multifactorial:



Vein thromboembolism

Vein thromboembolism comprises deep vein thrombosis and pulmonary embolism

Vein thromboembolism constitutes the third most common cardiovascular disease

Common risc factors with atherotrombosis and coronary disease are obesity, hypertension, diabetes mellitus, cigarette smoking, hypercholesterolemia and metabolic sindrom

Vein thromboembolism

The most important inherited risc factors are major thrombophillias- factor V Leiden and prothrombin 20210 mutations, deficiencies of protein C, protein S and antithrombin III

The most important aquired risc factors are advanced age, immobility, recent trauma, surgery, inflamation, hospitalizaton and cancer (neoplasm)

Vein thromboembolism

Multiple myeloma (MM) is one of the neoplasms that exhibit a high incidence of thromboembolic events (TEs), and approximately 10% patients with MM develop TEs during their clinical courses

- There are no adecvate scoring systems for thrombosis in haematological malignacies
- Wells scoring sistem, Otawa scoring sistem

Wells Scoring System for Diagnosing DVT

Clinical Characteristic	Score*
Active cancer (treatment ongoing, within, 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremity	1
Bedridden for >3 days or major surgery with general/regional anaesthesia within previous 12 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previous documented DVT	1
Alternative diagnosis at least as likely as DVT e.g (Popliteal (Baker) cyst, superficial thrombophlebitis, muscle pulls/tears, chronic venous insufficiency, and others)	-2
Clinical probability simplified score	
DVT *likely*	2 points or more
DVT *unlikely*	1 point or less

- Venous thromboembolism (VTE) is also an increasingly recognized problem in the post-hematopoietic stem cell transplantation (HSCT) setting

- Autologous stem cell transplantation is not curative in multiple myeloma, however, event-free survival and overall survival is improved by approximatly one year after autologous hematopoietic stem cell transplantation compared to conventional chemotherapy

- All patients younger than 65-70 years should be considered for high-dose chemo with autologous stem cell transplantation.

Case report

A 54 years old man was hospitalized in our department due to high fever, severe anemia, haemoptysis and pleural effusion

He had no significant past medical history

Markedly elevated level of Immunoglobulin G/lambda monoclonal component was detected (IgG 47 g/l)

Greater then 60 per cent of monoclonal plasma cells, CD138 positive, MUM-1 negative, lambda positive, CD20 negative, CD3 negative were found by bone marrow biopsy

Serum creatinin, calcium, albumin and beta2-microglobulin lewels were normal

The skeletal survey X-ray was showed only calvarial osteolytic lesions, but computed tomography (CT) scan was performed showing few more lesions in lumbo-sacral bone structures

No renal impartment

Diagnosis of Multiple myeloma IgG/lambda type clinical stage III A was established

- D dimer elevation (over 35 µg/ml) suggested presence of thrombosis, levels of troponine and natriuretric peptid type B were normal
- Color Doppler ultrasonography of low limbs was performed and it showed signs of deep vein thrombosis
- On Multislice Computed Tomography (MSCT) scan of pulmonary arteries subsegmental pulmonary embolism was detected
- Echocardiography: no right ventricle dilatation, no pulmonary hypertension

Multidisciplinary Team

- The patient was stratified as a "low risc and good prognosis"
- Multidisciplinary approach
- No inherited risc factors

- Chemotherapy strategies in addition to thalidomide were safely performed with anticoagulant therapy

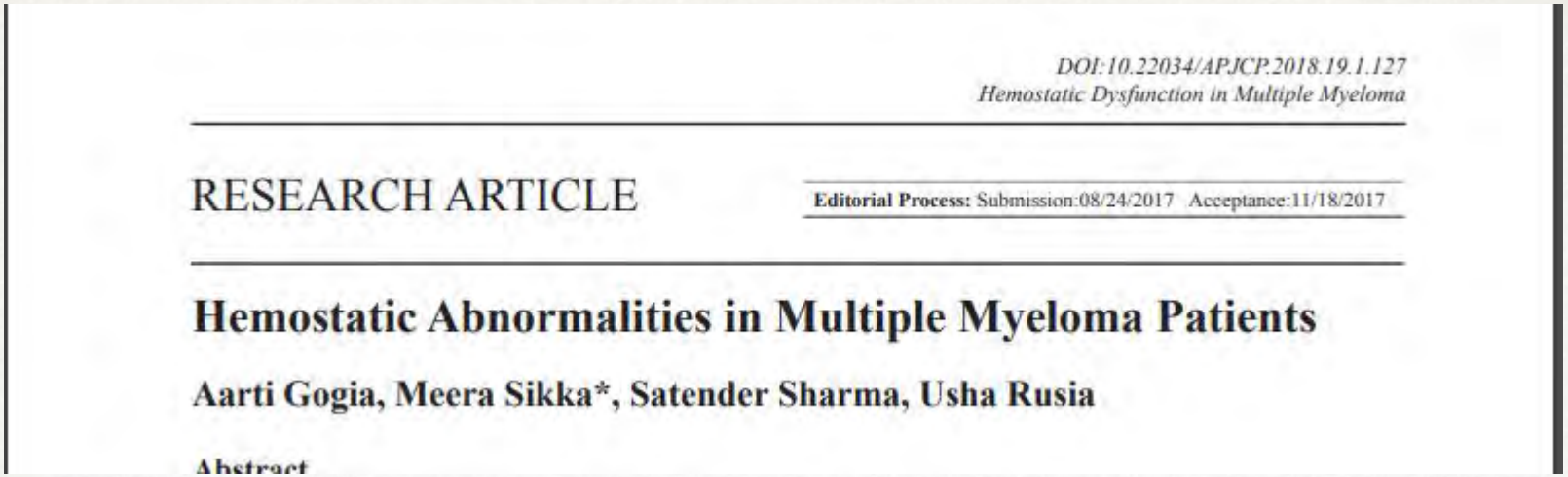
- Patient recived six cycles of CTD protocol (cyclophosphamide, thalidomide, dexamethasone) and achived at least very good partial remission

- Maintenance monotherapy with thalidomide was obtained for another six manths

- Vitamin- K dependent oral antikoagulant profilaxis was continued for next 12 months
- The patient was considered not to be candidate for autologous stem cell transplantation at the time
- Hematologic remission has been maintained over two years

- Now he receives only bisphosphonates (zolendronic acid) with calcium and vitamin D supplements and 100 mg of acetil salyc acid, and has no signs of disease progression

- He is planned for the secondary autologous haematological stem cell transplantation (HSCT) in the relaps



DOI:10.22034/APJCP.2018.19.1.127
Hemostatic Dysfunction in Multiple Myeloma

RESEARCH ARTICLE

Editorial Process: Submission:08/24/2017 Acceptance:11/18/2017

Hemostatic Abnormalities in Multiple Myeloma Patients

Aarti Gogia, Meera Sikka*, Satender Sharma, Usha Rusia

Abstract

There is a higher risc for thromboembolic event in multiple myeloma because of cancer status, intrinsinc risc factors and exsposure to prothrombotic therapies, first of all imunomodulatory agents and steroids.

Many diverse hemostatic abnormalities have been reported: presence of lupus anticoagulant (LA), incrisied levels of factor VIII and fibrinogen, activated protein C resistance, significantly higher endogenous thrombin potential, elevated interleukin 6 (IL6) level, paraprotein interference with fibrin structure and endothelial damage.

There is an increased tendency for thrombosis, which may lead to deep vein thrombosis and pulmonary embolism in about 5% of patients with multiple myeloma, and treatment including steroids and thalidomide, can increase this risk to between 10% to 15%.

Primary thromboprophylaxis in cancer patients is challenging, as the risk of VTE is not equal in all patients and as anticoagulation in those patients is associated with increased bleeding complications compared with patients without cancer.

Discussion- emphasys on clinical practice

❖Thrombotic events (TEs) are increasingly recognized problem in the post- hematopoetic stem cell transplantation setting

❖Concomitant risk for bleeding complications

❖Prior thrombotic event is an additional risk for thrombosis after stem cell transplantation

❖Anticoagulant and antiagregation therapy demand more then 50x10e9/l platelets in the blood count

❖Autologous HSCT is not curative in myeloma

Autologous stem cell transplantation

Cigarette smoking
Immobilisation
Inflamation
Neoplasm

Risc factors before TE

Previous thrombosis

Present Risc faktors

Previous thrombosis
Thrombogenic therapy
Longtherm imobillisation
Hospitalization
Possibile infections
Indwelling catheters
Posttransplant maintenance therapy
Active disease

Dilemas

There are lots of open questions in this area !

- Should secondary autologous transplantation be performed?
- Which protocol for mobilization of progenitor cells should be used?
- Wich protocol for maintenance therapy after autologous stem cell transplantation is the most safe one?
- Risc/benefit of autologous stem cell transplantation in the high risc of thrombosis?
- Duration of thromboprofilaxis after TEs in myeloma?

CONCLUSION

WE NEED MORE "BEST CLINICAL PRACTICE" RECCOMENDATIONS AND ADEQUATE SCORING SYSTEM FOR THROMBOSIS RISC IN MYELOMA

THANK YOU FOR YOUR ATTENTION!

Treatment of Early Relapses in Multiple Myeloma

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Disclosures: Meletios A. Dimopoulos

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Honoraria, Consulting fees, Lecture fees	Celgene, Janssen, Amgen, Takeda, BMS

New criteria for response evaluation during follow-up to check if patient is relapsing/progressing

Relapse category	Response criteria
Progressive disease[*,†]	Any one or more of the following criteria: • Increase of 25% from lowest confirmed response value in one or more of the following criteria: – serum M-protein (absolute increase must be ≥ 0.5 g/dL) – serum M-protein increase ≥ 1g/dL, if the lowest M component was ≥ 5 g/dL – urine M-protein (absolute increase must be ≥ 200 mg/24h) – in patients without measurable disease in serum and urine, the difference between involved and uninvolved FLC levels (absolute increase must be ≥ 10 mg/dL) – in patients without measurable disease in serum, urine and sFLC, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥ 10%) – appearance of new lesion(s), ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1cm in short axis – ≥ 50% increase in circulating plasma cells (minimum of 200 cells per uL) if this is the only measure of disease
Clinical relapse	One or more of the following criteria: • direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder • development of new soft tissue plasmacytomas or bone lesions (not osteoporotic fractures) • definite increase in the size of existing plasmacytomas or bone lesions • hypercalcaemia (> 11 mg/dL) • decrease in haemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions • rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma • hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is DFS)	Any one or more of the following criteria: • reappearance of serum or urine M-protein by immunofixation or electrophoresis • development of ≥ 5% plasma cells in the bone marrow • appearance of any other sign of progression (i.e. new plasmacytoma, lytic bone lesion or hypercalcaemia)
Relapse from MRD negative (to be used only if the end point is DFS)	Any one or more of the following criteria: • loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma) • reappearance of serum or urine M-protein by immunofixation or electrophoresis • development of ≥ 5% clonal plasma cells in the bone marrow • appearance of any other sign of progression (i.e. new plasmacytoma, lytic bone lesion or hypercalcaemia)

Footnote information available in the slide notes.
CRAB, calcium, renal failure, anaemia, bone lesions; DFS, disease-free survival; FLC, free light chain; MRD, minimal residual disease;
NGF, next-generation flow; NGS, next-generation sequencing, sFLC, serum free light chain; SPD, sum of the products of maximal diameters.

Kumar SK, *et al. Lancet Oncol* 2016; **17**:e328–e346.

Recommended work-up at relapse

- **Medical history and physical examination**
- **Haemogram**
- **Biochemistry: creatinine and calcium values***
- **Protein studies**
  - **Total serum protein and serum electrophoresis (serum M-protein)**
  - **24-hour urine protein electrophoresis (urine M-protein)**
  - **Serum and urine immunofixation**
- **Bone marrow aspirate ± biopsy: non-secretory/myelodysplasia/clinical trial†**
- **Imaging techniques**

*B_2-microglobulin or ISS stage not clear at the moment of relapse; †FISH analysis is usually performed at relapse if not available or normal at diagnosis.

FISH, fluorescence *in situ* hybridization; ISS, International Staging System.

Dimopoulos MA, *et al*. *Blood* 2011; **117**:4701–4705.

Work-up at relapse

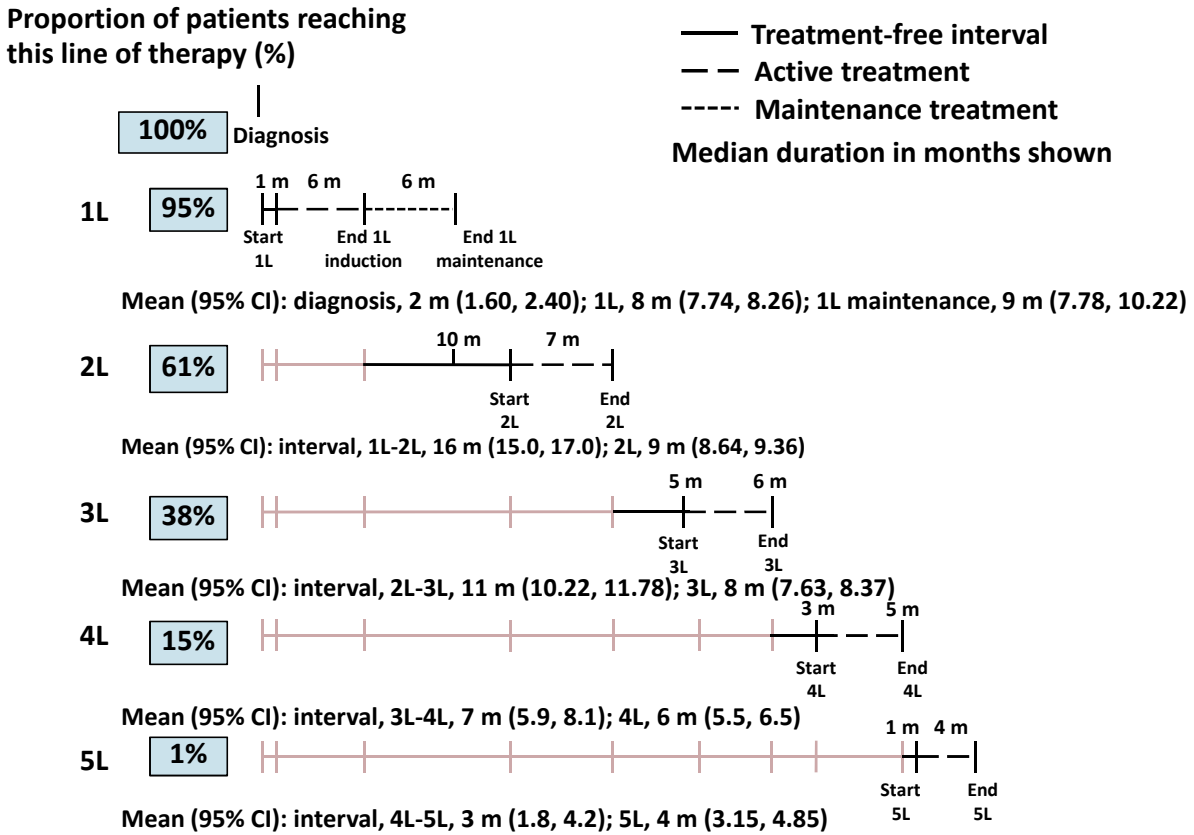
- **Clonal evolution**[1]
  - At relapse, mutational burden was unchanged
  - There are different scenarios: **selection** of very rare subclones present at diagnosis, **appearance/disappearance** of mutations, **stability**
  - Chemo resistance at relapse could be induced by newly acquired mutations in myeloma drivers or pre-existing subclonal mutations
- **Immune profiling**[2]
  - Some studies show associations between MRD status and immune profiling
  - Further studies are needed to determine whether immune profiling can be used to predict outcomes
- **Use of PET-CT/ WBLD-CT/CT at relapse**[3–5]
  - More sensitive assessments
  - Non-invasive monitoring during follow-up

CT, computed tomography; MRD, minimal residual disease; PET-CT, positron emission tomography–computed tomography; WBLD-CT, whole-body low-dose computed tomography.

1. Corre J, *et al. Leukemia* 2018; https://doi.org/10.1038/s41375-018-0153-6; 2. Holstein S, *et al. Biol Blood Marrow Transplant* 2018; **24**:641–648; 3. Zamagni E, *et al. Clin Cancer Res* 2015; **21**:4834–4390; 4. Rasche L, *et al.* Abstract 4510; Presented at ASH 2017; Atlanta, Georgia; 5. Dimopoulos M, *et al. Blood* 2011; **117**:4701–4705.

Multiple Myeloma: Patient Outcomes in Real-World Practice

*Treatment Duration and Treatment-Free Interval by Line of Therapy**



*Data from 4997 patient charts in Belgium, France, Germany, Italy, Spain, Switzerland, and the UK.

The proportion of patients who had received each line are from the cross-sectional review; data on durations of treatment and treatment-free intervals are from the retrospective review.

1L-5L = first line-fifth line treatment; CI = confidence interval; m = month.

Yong K, et al. *Br J Haematol*. 2016;175:252-264.

Factors to Consider When Selecting Treatment at Relapse

Disease-Related Factors[1,2]
- Type and risk status of disease
- Presence of refractory disease
- Aggressiveness of current relapse

Treatment-Related Factors[1,2]
- Type of prior Txs and prior response
- Prior Tx-related toxicity
- Bone marrow reserve
- Expected efficacy and toxicity of proposed Tx
- Expectations of the patient

Patient-Related Factors[1,2,3]
- Age, frailty, and performance status
- Comorbidities
- Renal insufficiency/hepatic impairment
- Preference on mode of administration

Goals of Treatment

- Maximize response and maintain disease control[4,5]
- Delay or prevent disease progression
- Balance efficacy with tolerability and QoL[4,5]
- **Prolong survival[5]**
- Stable disease may be beneficial

QoL = quality of life.

1. Sonnevald, et al. *Haematologica* 2016;101:396-406. 2. Nooka, et al. *Blood*. 2015;125:3085-3099. 3. Laubach, et al. *Leukemia*. 2016;30:1005-1017. 4. Mohty B, et al. *Leukemia* 2012;26:73-85.
5. Pratt G, et al. *Br J Haematol*. 2014;167:131-133.

Should biochemical/asymptomatic relapse be treated?

Clinical trials include patients with asymptomatic relapse; however, in clinical practice the approach is sometimes different, and current recommendations state that treatment can be delayed in the case of asymptomatic relapse[1]

Analysis of the characteristics of relapse in 211 patients after ASCT[2]

For patients with asymptomatic relapse:

- Median time to treatment requirement of 5.6 months
  - (10 months in a recent Spanish trial)[3]
- **26% of patients (n = 12) did not require treatment in 2 years**
  - ISS I or II at diagnosis (n = 12)
  - IgG type (58%)
  - No extramedullary disease (n = 11)
  - Clinical features of aggressiveness at diagnosis were rare
    - Renal failure, n = 1; hypercalcemia, n = 1; anaemia, n = 3
- **Consider early treatment if**
  - **Previous aggressive presentation/clinical behaviour**
  - **Clearly increasing M-protein, particularly light chains in urine**
  - **Decreasing Hb level**

ASCT, autologous stem cell transplantation; Hb, haemoglobin; IgG, immunoglobulin G; ISS, International Staging System.

1. Moreau P, *et al. Ann Oncol* 2017; **28**:iv52–iv61;
2. Fernández de Larrea C, *et al. BMT* 2014; **49**:223–227;
3. García Sanz R, *et al. Haematologica* 2015; **100**:1207–1213.

How Has Treatment Developed in Patients Who Have Received 1-3 Prior Lines of Therapy?

Therapies Using Rd as Backbone

Proteasome Inhibitors

Epoxyketone PI

Carfilzomib[1-6]

- Belongs to the epoxyketone class that is structurally different from boronate PIs
- Selectively and irreversibly binds to the N-threonine active sites of the constitutive proteasome and the immunoproteasome

Boronate PI

Ixazomib[7-9]

- Like bortezomib, belongs to the boronic acid class
- Reversibly Inhibits (β1) caspase-like and (β2) trypsin-like sites of 20S proteasome, but preferentially inhibits (β5) chymotrypsin-like site

Monoclonal Antibodies

Anti-CD38

Daratumumab[10-12]

- Broad-spectrum killing activity of CD38-expressing tumor cells
- Exerts anti-tumor activity via ADCC, ADCP, CDC, and apoptosis

Anti-SLAMF7

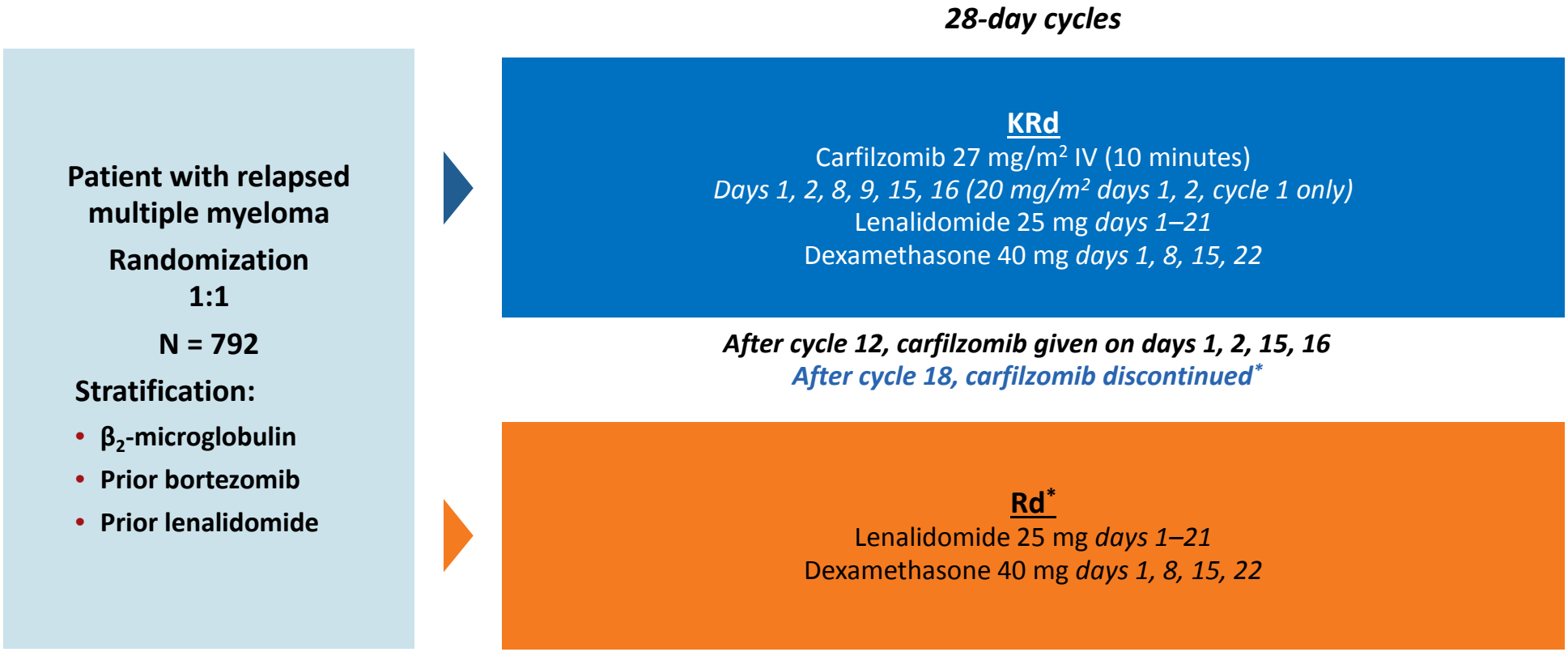
Elotuzumab[13]

- Binds with SLAMF7 on plasma cells, marking them for activation by NK cells
- Binds with SLAMF7 on NK cells and activates them directly

ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; CDC = complement-dependent cytotoxicity; NK = natural killer; Rd = lenalidomide and dexamethasone.

1. Kuhn DJ, et al. *Blood*. 2007;110:3281-3290. 2. Teicher BA, et al. *Biochem Pharmacol*. 2015;1;96:1-9. 3. Lee SJ, et al. *Br J Haematol*. 2016;173:884-895. 4. Demo SD, et al. *Cancer Res*. 2007;67:6383-6391. 5. Arastu-Kapur S, et al. *Clin Cancer Res*. 2011;17:2734-2743. 6. Moreau P, et al. *Blood*. 2012;120:947-959. 7. Wang M. *Oncology (Williston Park)*. 2011;25(suppl 2):19-24. 8. Muz B, et al. *Drug Des Devel Ther*. 2016;10:217-226. 9. Kurtin SE and Bialotti E. *J Adv Pract Oncol*. 2013;4:307-312. 10. Janssen, Darzalex SmPC, 2016; 11. van der Veer MS, et al. *Haematologica*. 2011;96:284-290. 12. Phipps C, et al. *Ther Adv Hematol*. 2015;6:120-127. 13. Bristol-Myers Squibb, Empliciti SmPC, 2016.

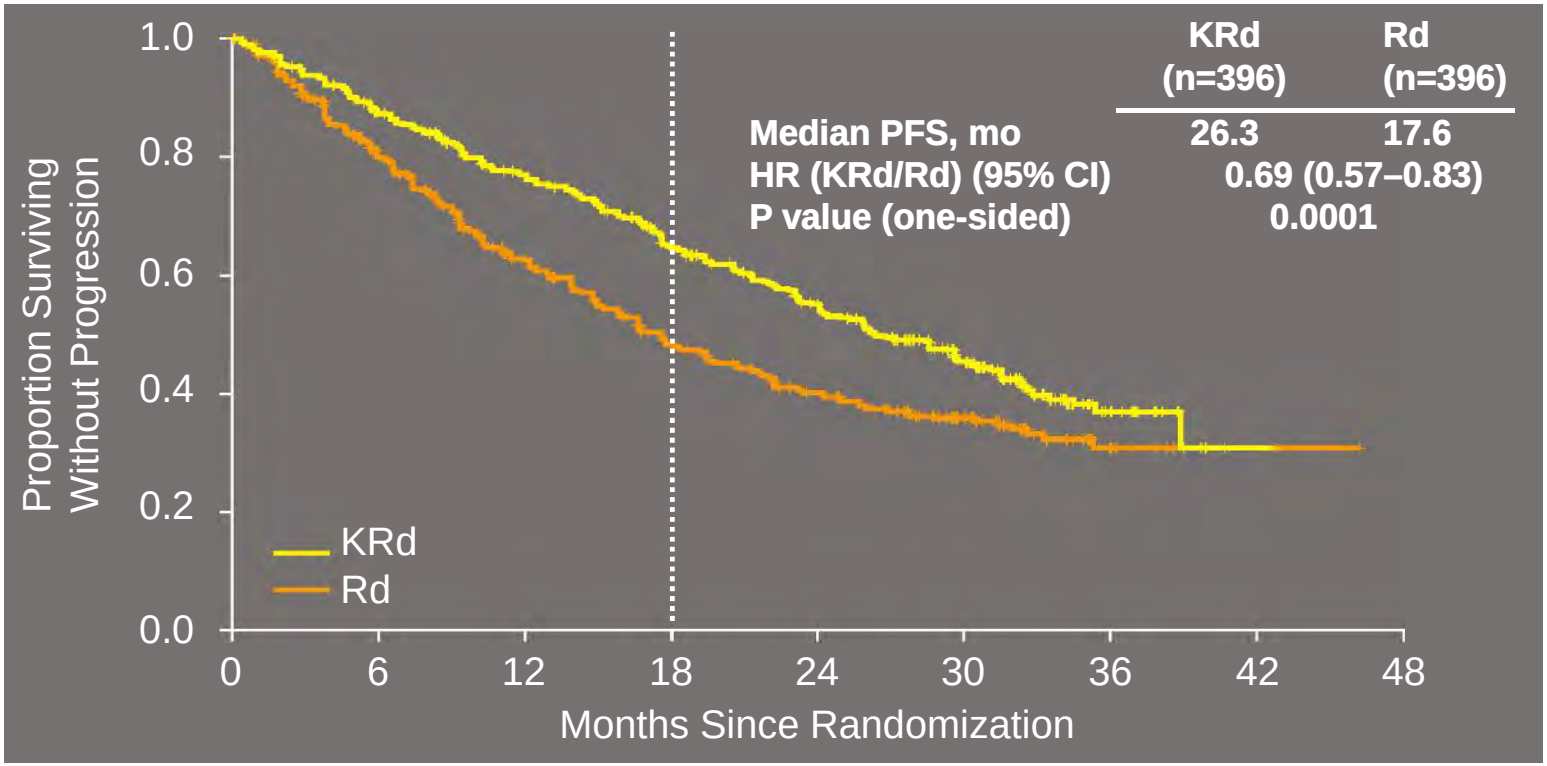
ASPIRE: Study Design



*All patients received Rd until disease progression, withdrawal of consent, or toxicity.

Stewart AK, et al. N Engl J Med 2015;372:142-52; Siegel DS, et al; [published online ahead of print January 17, 2018]. *J Clin Oncol*. doi: 10.1200/JCO.2017.76.5032.

ASPIRE: KRd Extended Median Progression-Free Survival (PFS) by 8.7 Months



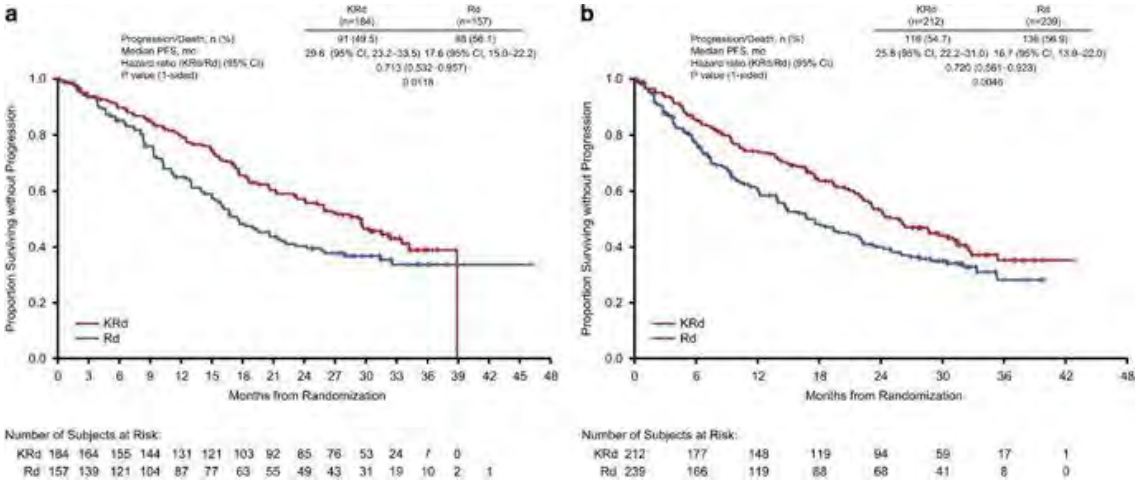
KRd-treated patients had a 31% reduction in the risk of disease progression or death in comparison with Rd

- Median follow-up was 32.3 months for KRd and 31.5 months for Rd

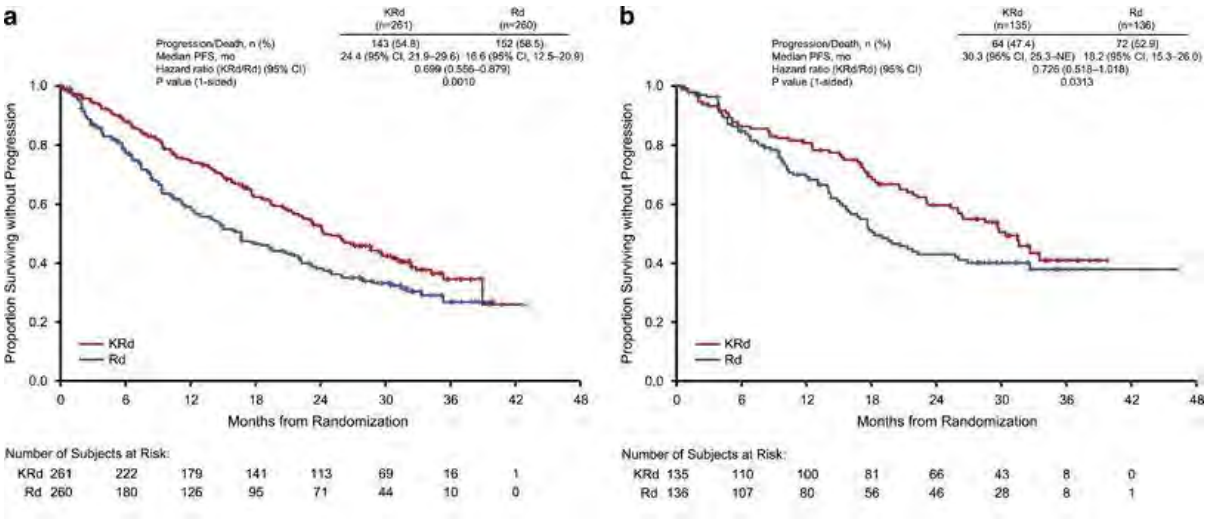
Stewart AK, et al. N Engl J Med 2015;372:142-52.

ASPIRE: Progression-Free Survival Subgroup Analyses

one vs 2-3 prior lines of therapy



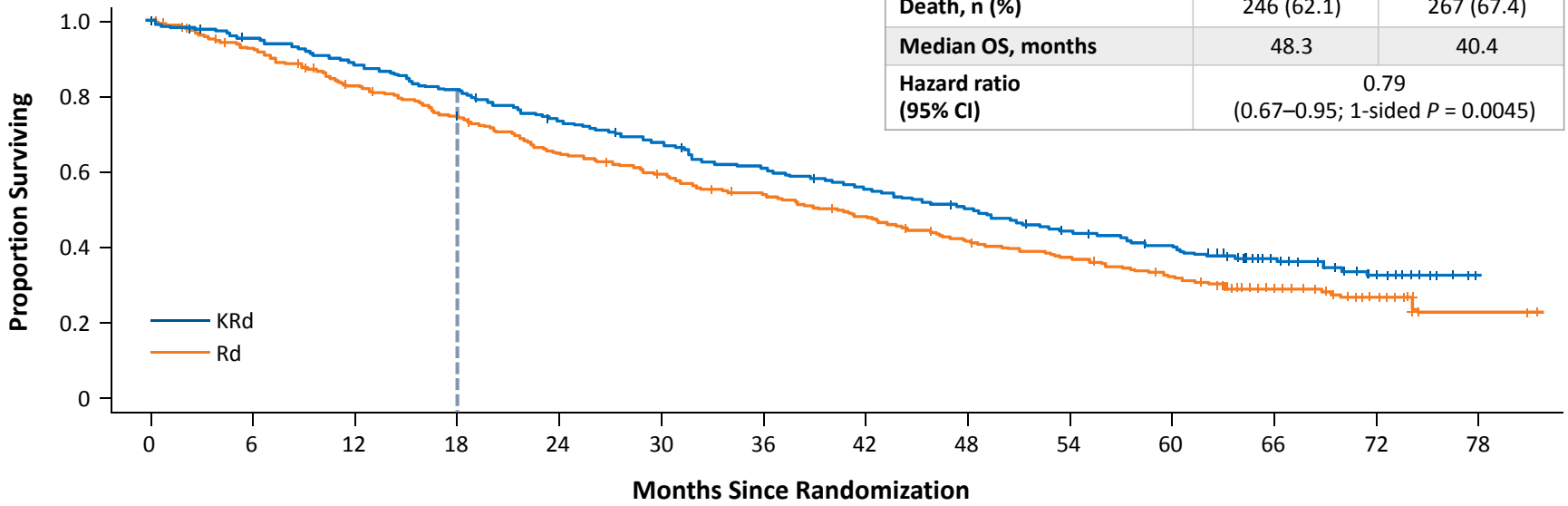
Prior bortezomib or no bortezomib therapy



Dimopoulos MA, et al. *Blood Cancer J*. 2017;7:e554.

ASPIRE: KRd Extended Overall Survival (OS) by 7.9 Months

	KRd (n = 396)	Rd (n = 396)
Median follow-up, months	67.1	
Death, n (%)	246 (62.1)	267 (67.4)
Median OS, months	48.3	40.4
Hazard ratio (95% CI)	0.79 (0.67–0.95; 1-sided *P* = 0.0045)	



Number of patients at risk:

KRd	396	369	343	316	282	259	232	211	190	166	149	88	22	0
Rd	396	356	313	281	243	220	199	176	149	133	113	69	20	3

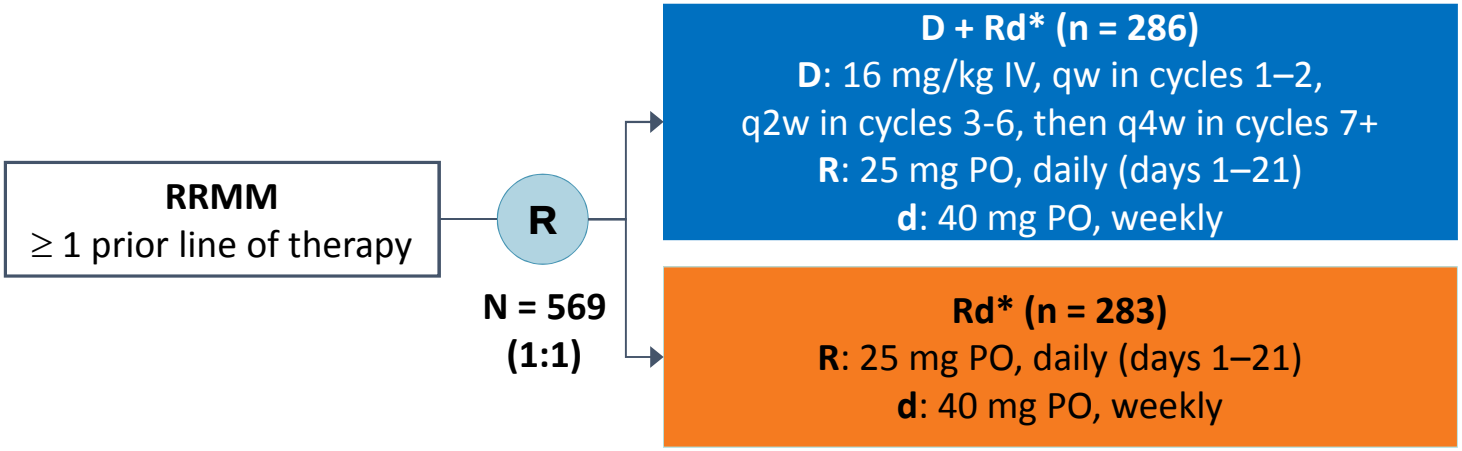
- Carfilzomib discontinued after 18 cycles
- Events at 18 months: KRd, 71 (17.9%); Rd, 97 (24.5%); HR (95% CI) = 0.69 (0.51–0.93)[2]

Using a piecewise Cox model, the 18-month OS HR was estimated as 0.69 (95% CI, 0.51–0.93)

1. Siegel, et al. *J Clin Oncol*. 2018. doi: 10.1200/JCO.2017.76.5032. 2. Stewart AK, et al. Slides presented at: Annual Meeting of the American Society of Hematology; December 9-12, 2017. Atlanta, GA.

POLLUX: Study Design

Comparison of daratumumab (D) + lenalidomide + dexamethasone (Rd) vs Rd



Aims: compare the efficacy and safety of D in combination with Rd vs Rd alone in patients with RRMM in a randomized, open-label, multicenter, phase 3 study

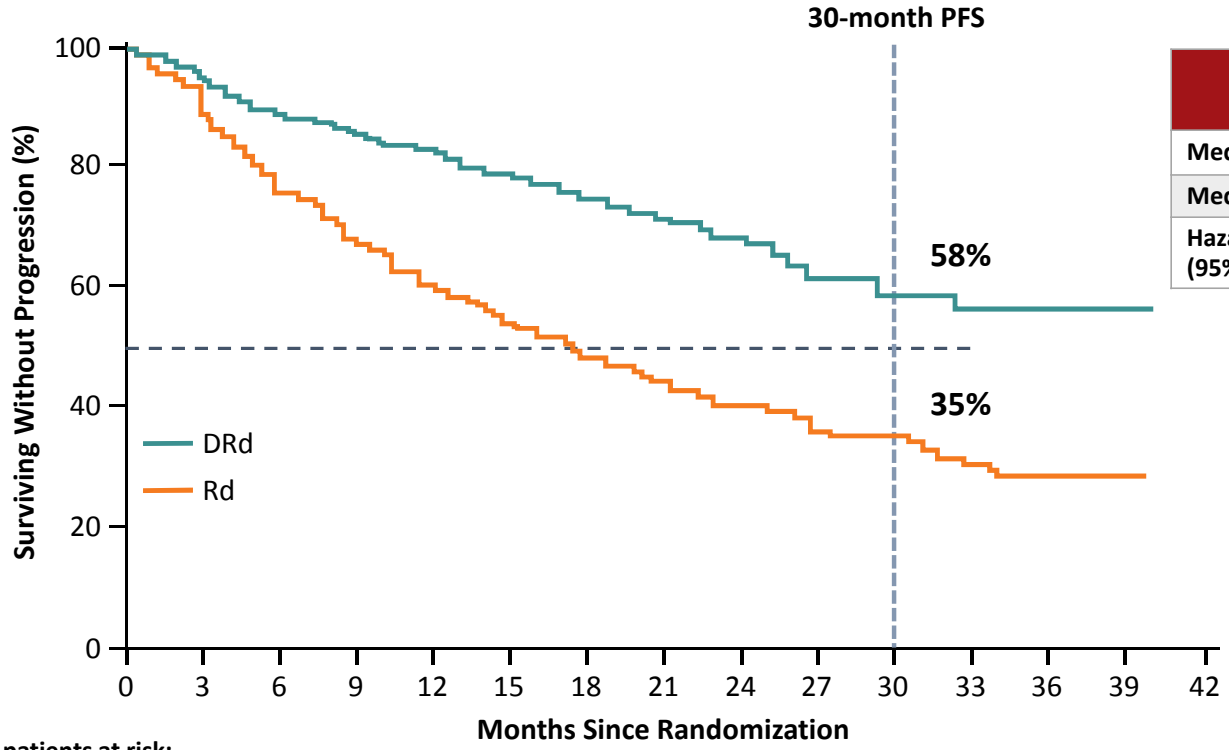
Primary endpoint: PFS

Selected secondary endpoints: TTP, ORR, ≥ VGPR, minimal residual disease-negative rate, OS, duration of response, time to response, safety

*Patients were given the treatment until PD.
D = daratumumab; PO = oral; TTP = time to progression.
Dimopoulous M, et al. *N Engl J Med* 2016;375:1319-1331.

POLLUX: PFS

DRd Reduced Risk of Progression or Death by 56%



	DRd (n = 286)	Rd (n = 283)
Median follow-up, months	32.9	
Median PFS, months	NR	17.5
Hazard ratio (95% CI)	0.44 (0.34–0.55) *P* < 0.0001)	

Number of patients at risk:

Rd	283	249	206	181	160	143	126	111	100	89	80	38	5	1	0
DARA + Rd	286	266	249	238	229	214	203	194	183	167	145	67	16	2	0

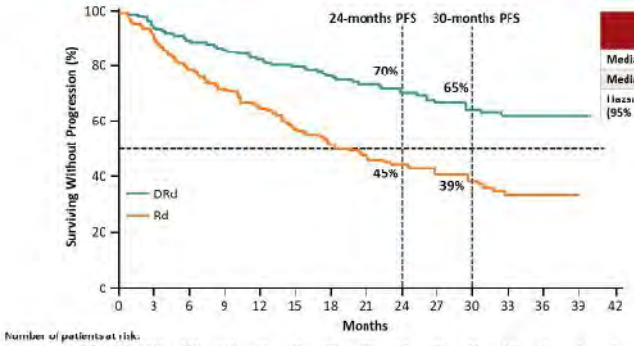
- 56% reduction in risk of progression/death for DRd vs Rd

NR = not reached; DRd = daratumumab, lenalidomide, and dexamethasone.

Dimopoulos MA, et al. Presented at American Society of Hematology Annual Meeting. December 9-12, 2017. Atlanta, GA. Abstract 739.

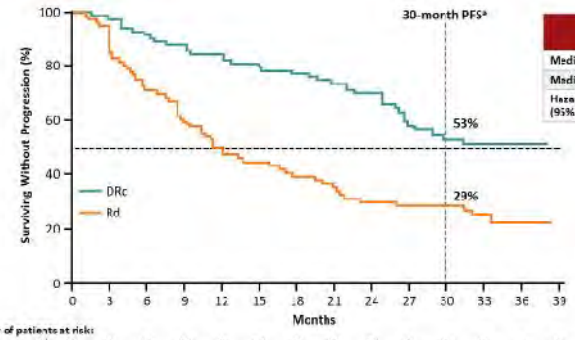
POLLUX: PFS by prior lines of therapy

DRd Reduced Risk of Progression or Death by 59% in Patients With 1 Prior Line of Therapy



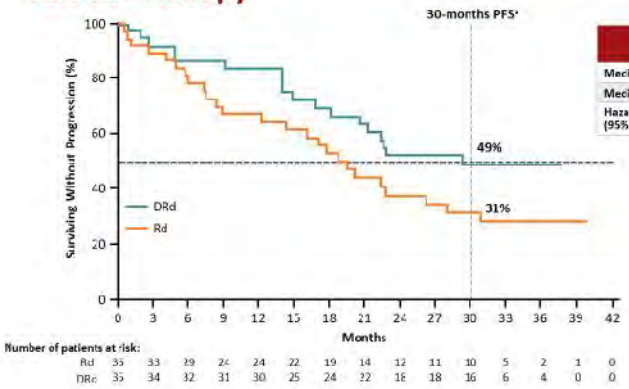
	DRd (n = 149)	Rd (n = 146)
Median follow-up, months	32.9	
Median PFS, months	NR	19.6
Hazard ratio (95% CI)	0.41 (0.29–0.59) P < 0.0001	

DRd Reduced Risk of Progression or Death by 62% in Patients With 2 Prior Lines of Therapy



	DRd (n = 85)	Rd (n = 80)
Median follow-up, months	32.9	
Median PFS, months	NR	11.9
Hazard ratio (95% CI)	0.38 (0.25–0.59) P < 0.0001	

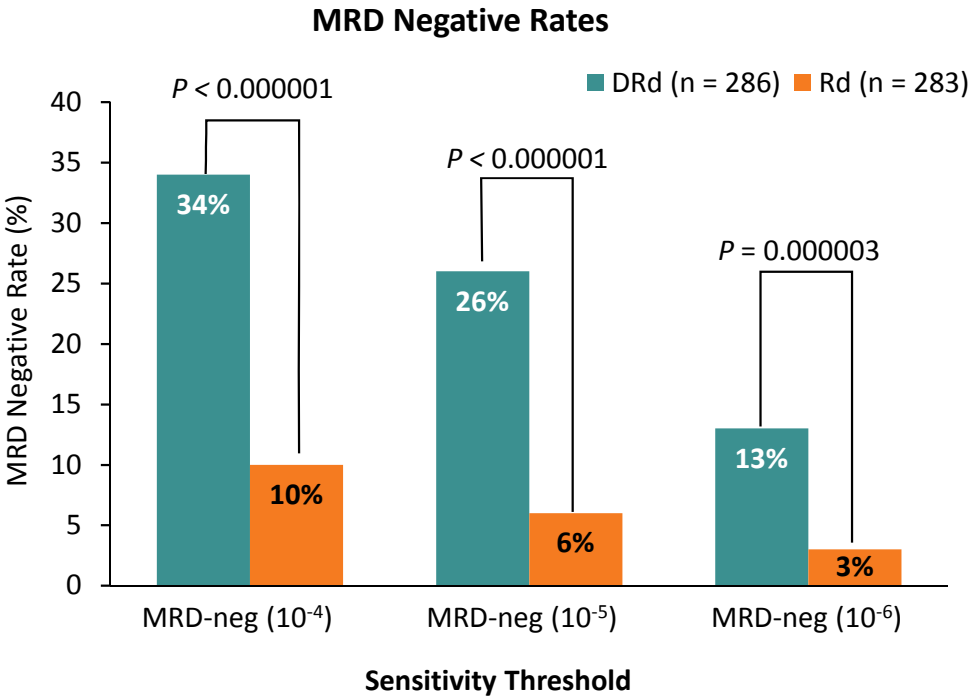
POLLUX: DRd Extended PFS by 9.8 Months in Patients With 3 Prior Lines of Therapy

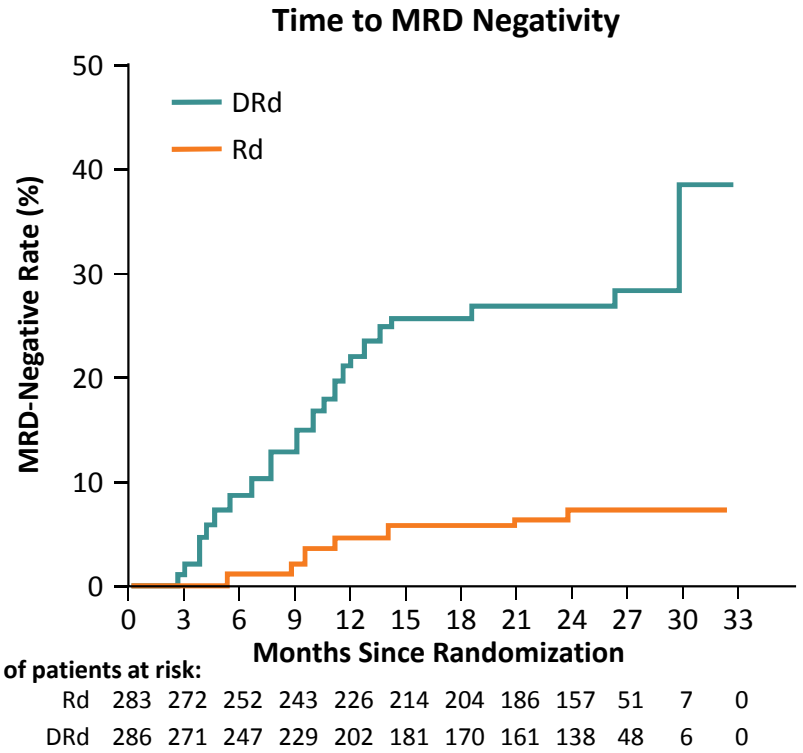


	DRd (n = 45)	Rd (n = 45)
Median follow-up, months	32.9	
Median PFS, months	29.3	19.5
Hazard ratio (95% CI)	0.47 (0.23–0.95) P = 0.0317	

Moreau P, et al. Presented at American Society of Hematology Annual Meeting. December 9-12, 2017. Atlanta, GA. Abstract 1883.

POLLUX: MRD-Negative Rates and Time to MRD Negativity





Number of patients at risk:

Rd	283	272	252	243	226	214	204	186	157	51	7	0
DRd	286	271	247	229	202	181	170	161	138	48	6	0

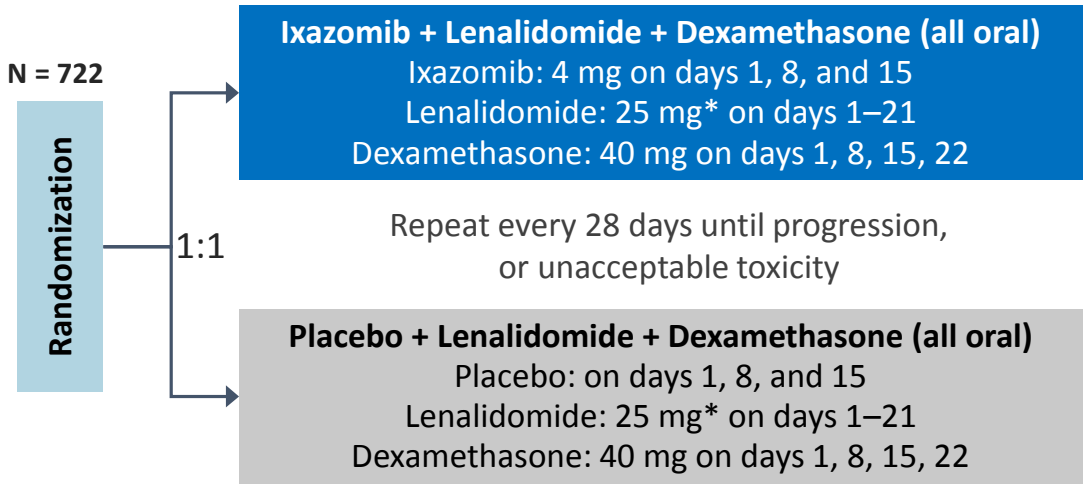
- In the total evaluable population, MRD negative rates were more than 3-fold higher with DRd versus Rd at all sensitivity thresholds
- MRD negative patients (identified at the 10^{-5} sensitivity threshold) accumulated more rapidly with DRd versus Rd

MRD = minimal residual disease.

Dimopoulos MA, et al. Presented at European Hematology Association Annual Meeting. June 22-25, 2017. Madrid, Spain. Abstract P334.

TOURMALINE-MM1: Study Design

Global, double-blind, randomised, placebo-controlled study design



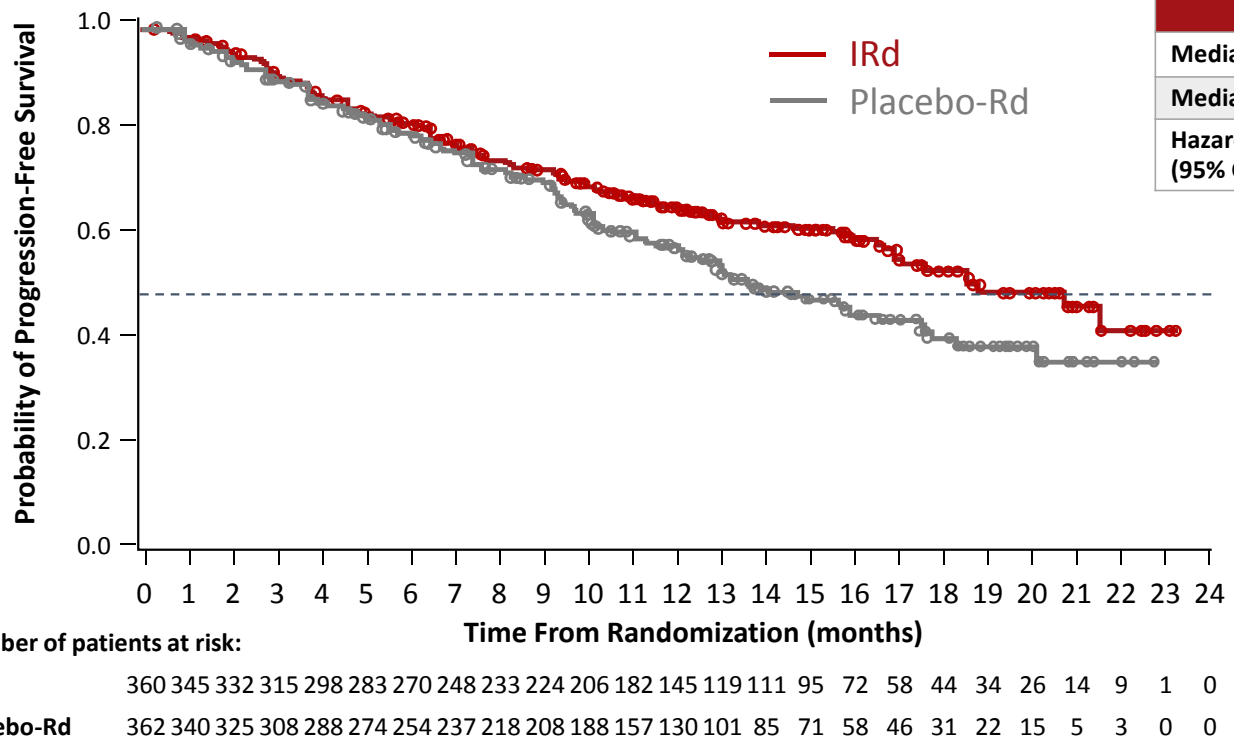
Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

Key secondary endpoints:
- OS
- OS in patients with del(17p)

*10 mg for patients with creatinine clearance ≤ 50 or ≤ 60 mL/min, depending on local label/practice.
ISS = International Staging System.
Moreau P, et al. *N Engl J Med.* 2016;374:1621-1634.

TOURMALINE-MM1: Ixazomib Extended Progression-Free Survival by 5.9 Months

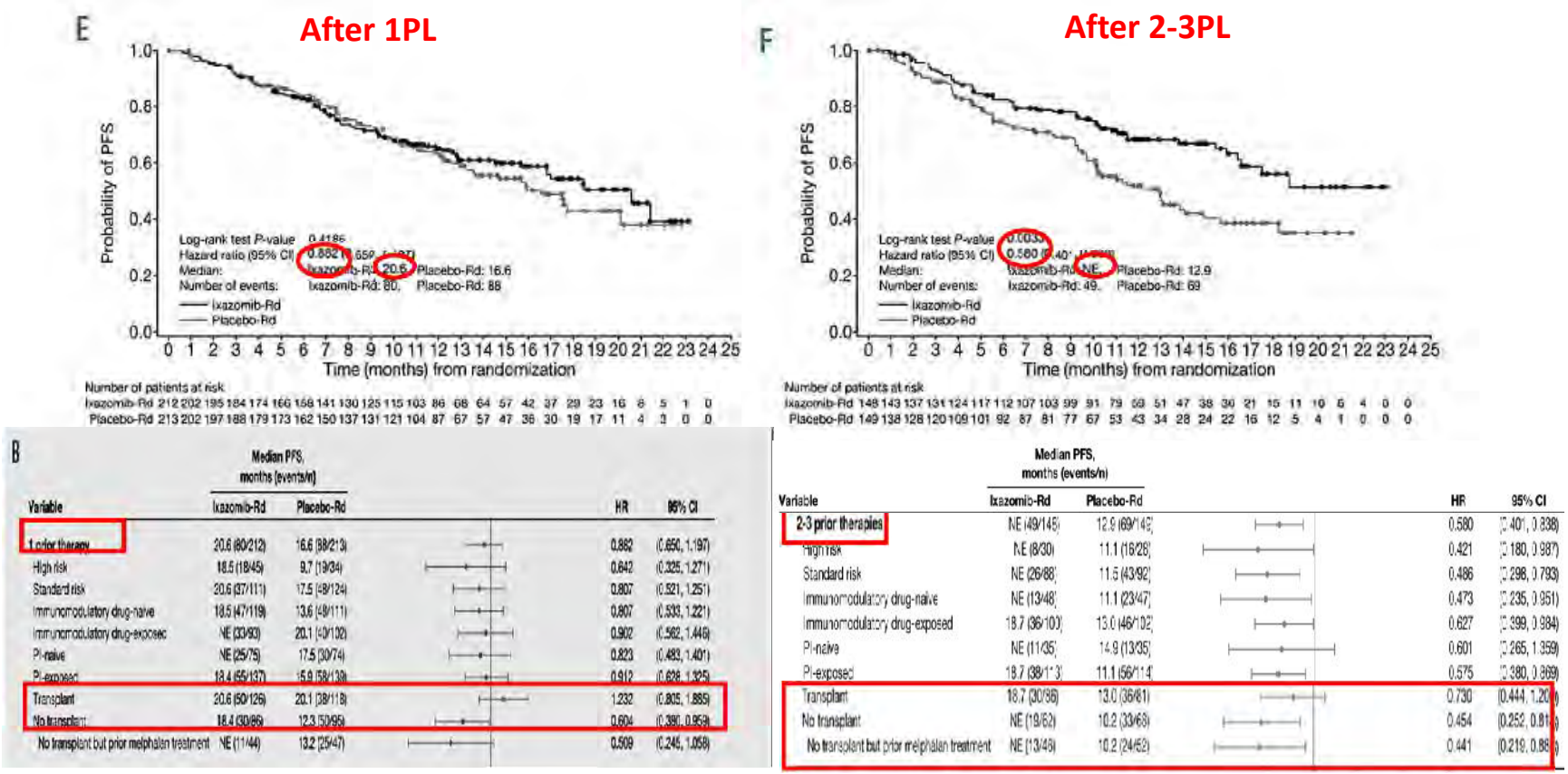


Number of patients at risk:																									
IRd	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo-Rd	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

	IRd (n = 360)	Rd (n = 360)
Median follow-up, months	~ 15	
Median PFS, months	20.6	14.7
Hazard ratio (95% CI)	0.74 (0.59–0.94) Log-rank test *P* = 0.01	

Moreau P, et al. *N Engl J Med.* 2016;374:1621-1634.

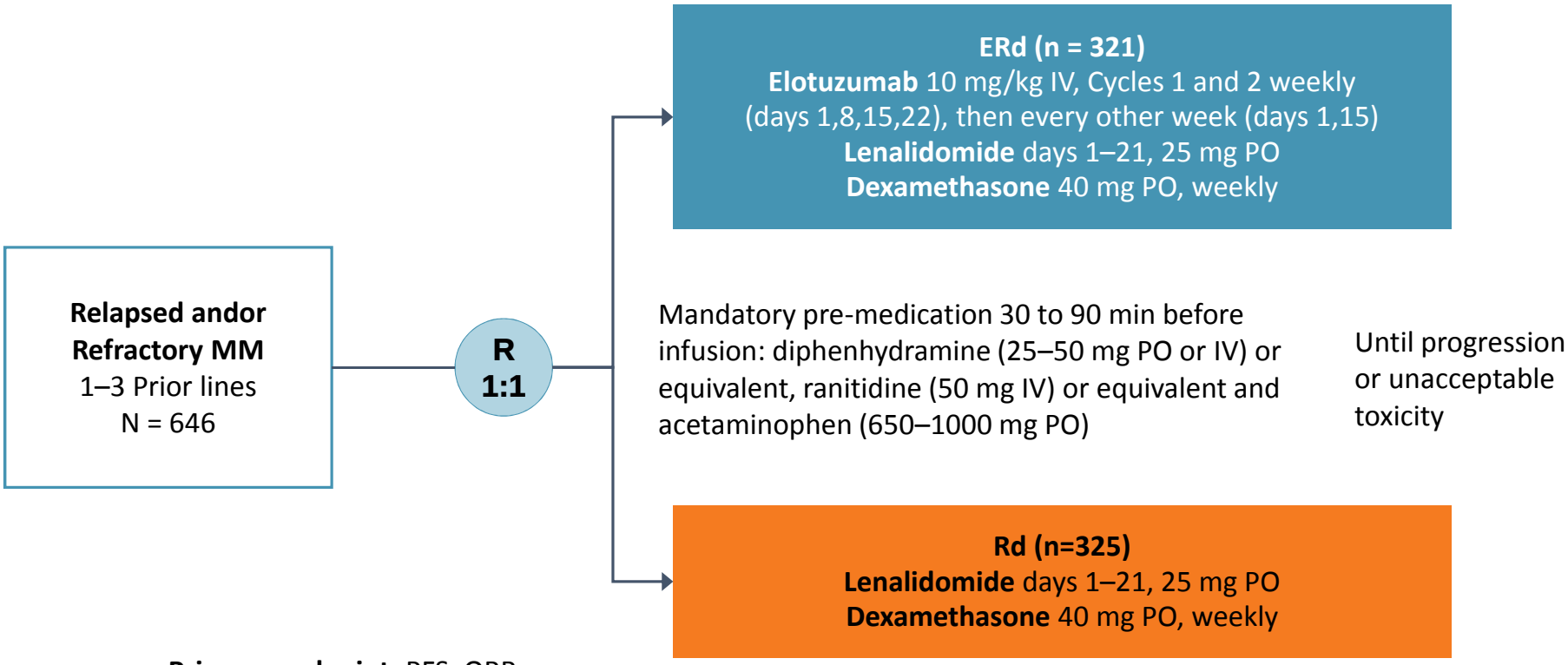
TOURMALINE-MM1: PFS according to the number of prior lines of therapy



Pts with 2 or 3 PL or 1PL without trx seemed to have greater benefit than pts after 1PL and trx

Mateos MV et al. Haematologica. 2017 Oct;102(10):1767-1775.

ELOQUENT-2: Study Design

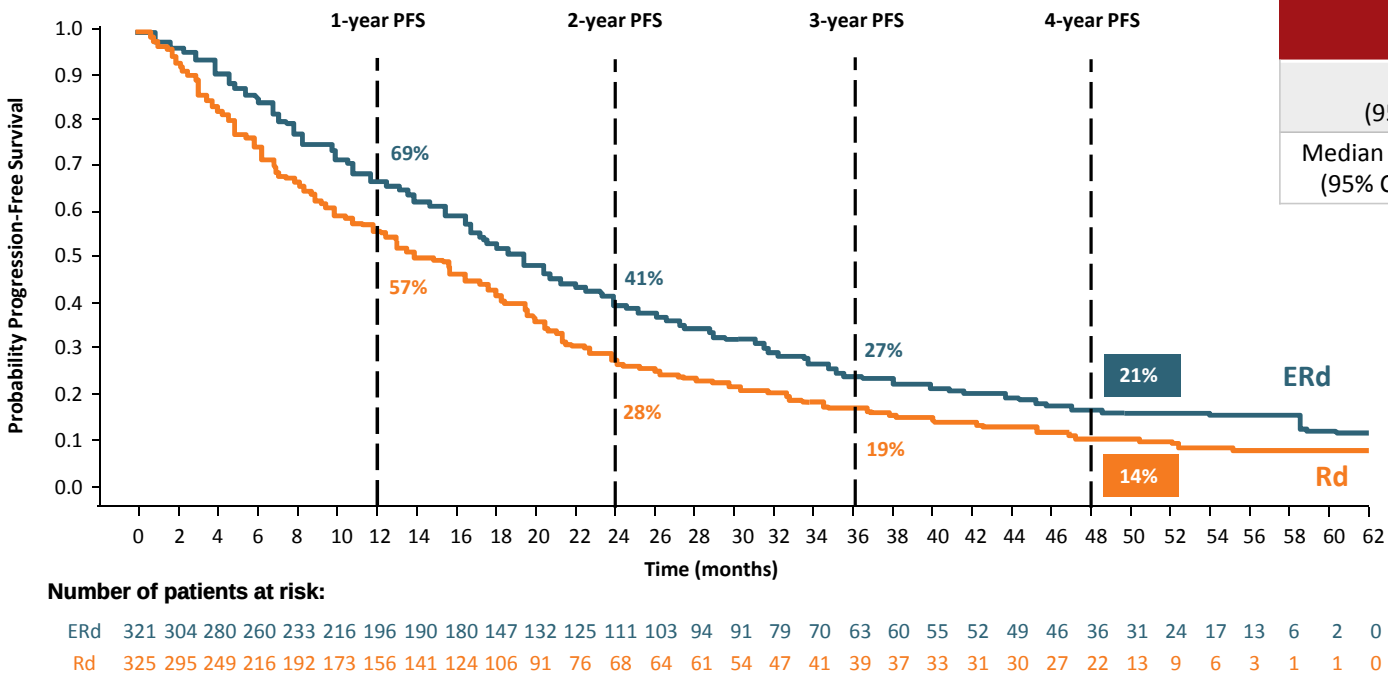


Primary endpoint: PFS, ORR

Selected secondary endpoints: OS, severity of pain or interference with daily life

Lonial S, et al. *N Engl J Med*. 2015;373:621-631.

ELOQUENT-2: Elotuzumab Extended PFS by 4.5 Months at the 4-Year Follow-Up

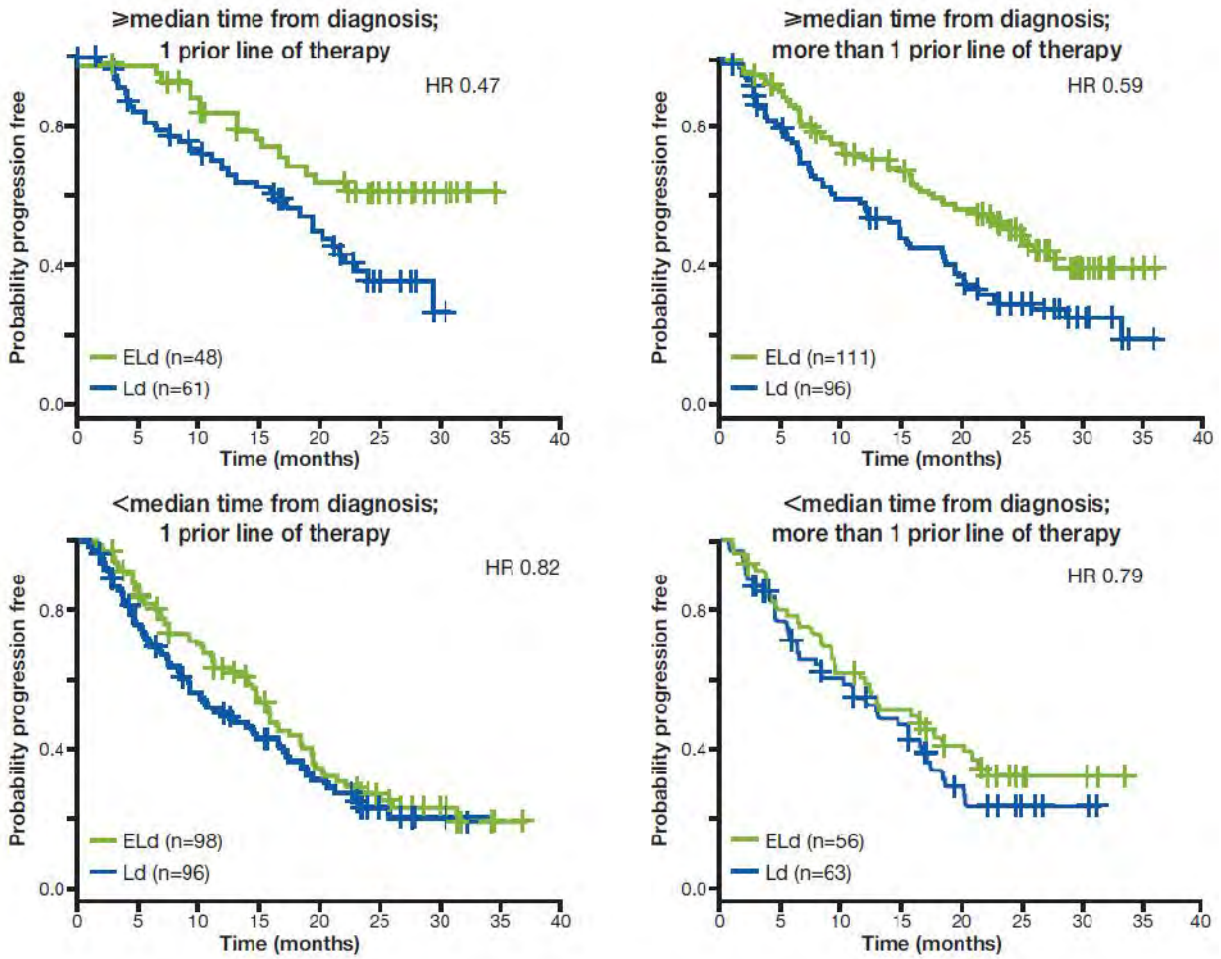


	ERd N = 321	Rd N = 325
HR = 0.71 (95% CI 0.59–0.86), *P* = 0.0004		
Median PFS (95% CI)	19.4 months (15.6–22.3)	14.9 months (12.1–17.3)

- At 4 years, ELOQUENT-2 has the longest follow-up for PFS in RRMM
- 29% reduction in the risk of progression or death (sustained over time)
- 50% relative improvement in the PFS rate at 4 years (21% vs 14%) in favor of ERd

Dimopoulos MA, et al. Presented at European Hematology Association Annual Meeting. June 22-25, 2017. Madrid, Spain. Abstract S456.

ELOQUENT-2: Median Time Since Diagnosis and Prior Lines of Therapy



Dimopoulos MA, et al. EHA 2017; Abstract S456

Lenalidomide-Based Studies in RRMM

	ASPIRE[1] KRd vs Rd	POLLUX[2,3] DRd vs Rd	TOURMALINE-MM1[4] IRd vs Rd	ELOQUENT-2[5,6] ERd vs Rd
Treatment duration	Crfilzomib given for 18 cycles; Rd until progression	Until progression	Until progression	Until progression
PFS HR (95% CI)	0.69 (0.57–0.83)	0.37 (0.27–0.52)	0.74 (0.59–0.94)	0.73 (0.60–0.89)
ORR	87%	93%	78%	79%
≥ VGPR	70%	76%	48%	33%
≥ CR	32%	43%	14%	4%
DoR (months)	28.6	NE	20.5	20.7
OS HR (95% CI)	0.79 (0.63–0.99)	NA	NE	0.78 (0.63–0.96)

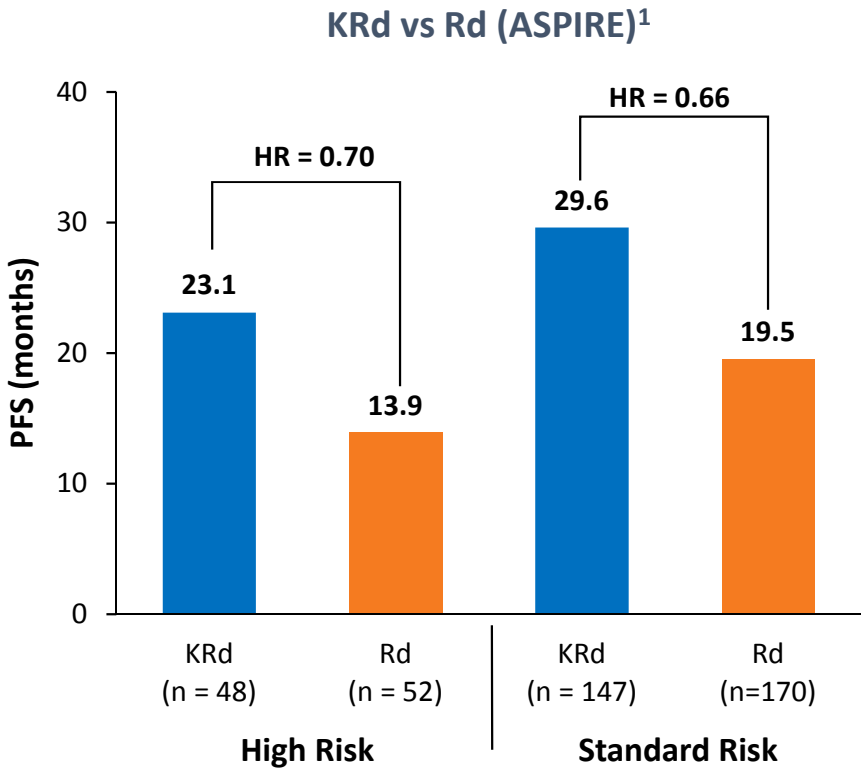
DoR = duration of response; NA = not available; NE = not evaluated.

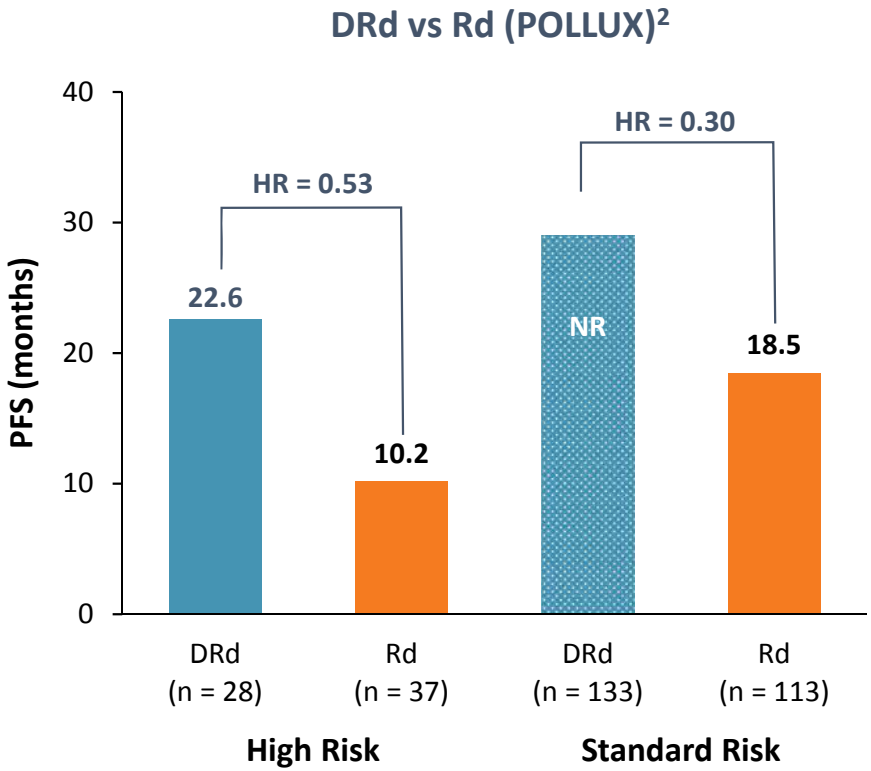
This table is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

1. Stewart AK, et al. *New Engl J Med*. 2015;372:142-152; 2. Dimopoulos MA, et al. *New Engl J Med*. 2016;375:754-766; 3. Usmani SZ, et al. Presented at: American Society of Hematology Annual Meeting. December 3-6, 2016. San Diego, CA. Abstract 1151; 4. Moreau P, et al. *New Engl J Med*. 2016;374:1621-1634; 5. Lonial S, et al. *New Engl J Med*. 2015;373:621-631; 6. Dimopoulos MA, et al. Presented at: 22nd Congress of European Hematology Association. June 22-25, 2017. Madrid, Spain. Abstract S456.

Rd Backbone Treatments in Patients With High-Risk Cytogenetics

New Agents for RRMM Efficacy: PFS by Cytogenetic Risk

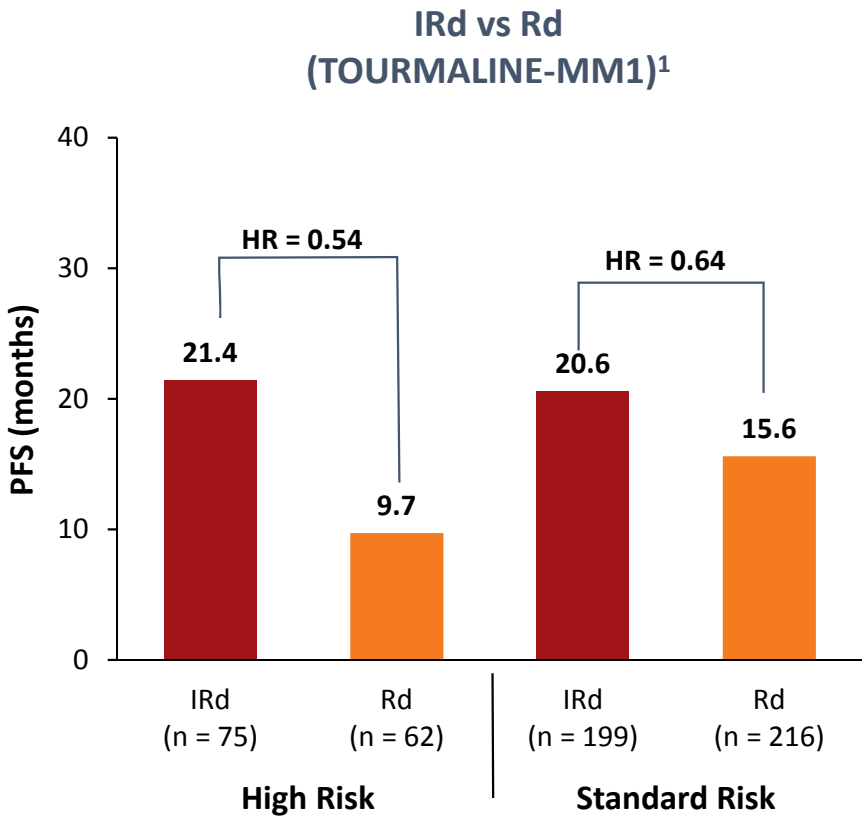


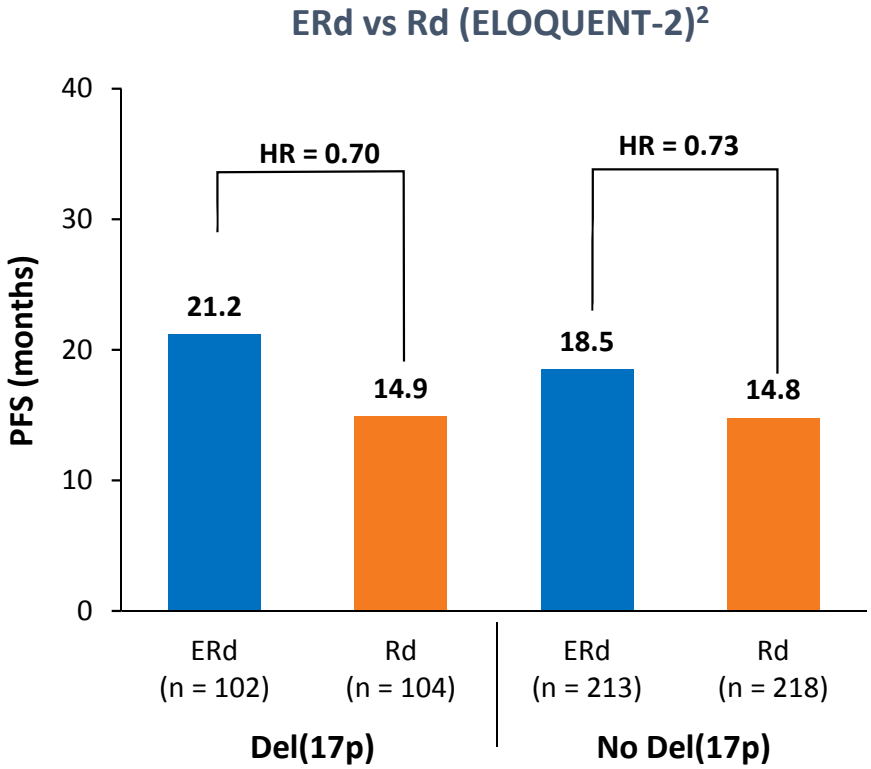


This graph is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

1. Avet-Loiseau H, et al. Presented at: American Society of Hematology Annual Meeting. December 5-8, 2015. Orlando, FL. Abstract 731; 2. San Miguel J, et al. Presented at: 22nd Congress of European Hematology Association. June 22-25, 2017. Madrid, Spain. Abstract S101.

New Agents for RRMM Efficacy: PFS by Cytogenetic Risk





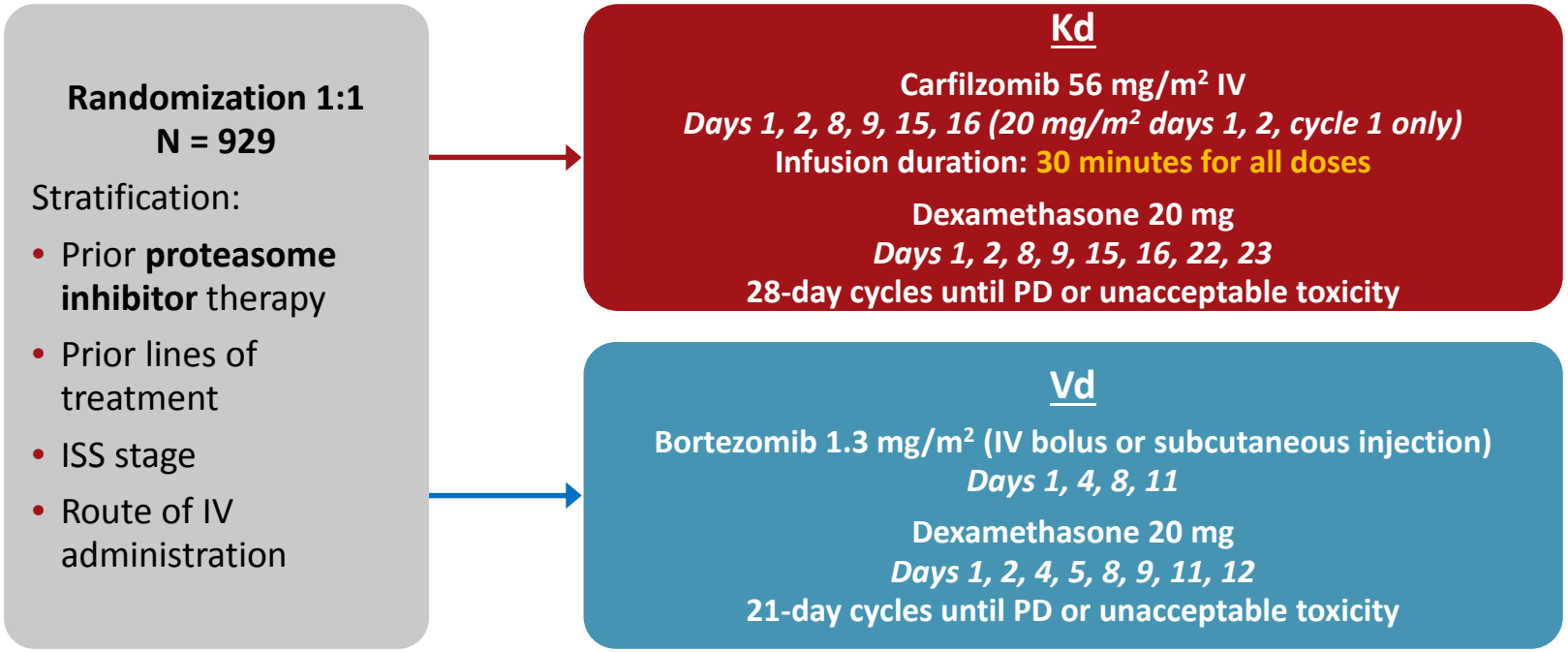
This graph is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

1. Richardson PG, et al. Presented at: American Society of Clinical Oncology Annual Meeting. June 3-7, 2016. Chicago, Illinois. Abstract 8018; 2. Lonial S, et al. Presented at: American Society of Clinical Oncology Annual Meeting. June 3-7, 2016. Chicago, Illinois. Abstract 8037.

Treatment With Non-Rd Backbones

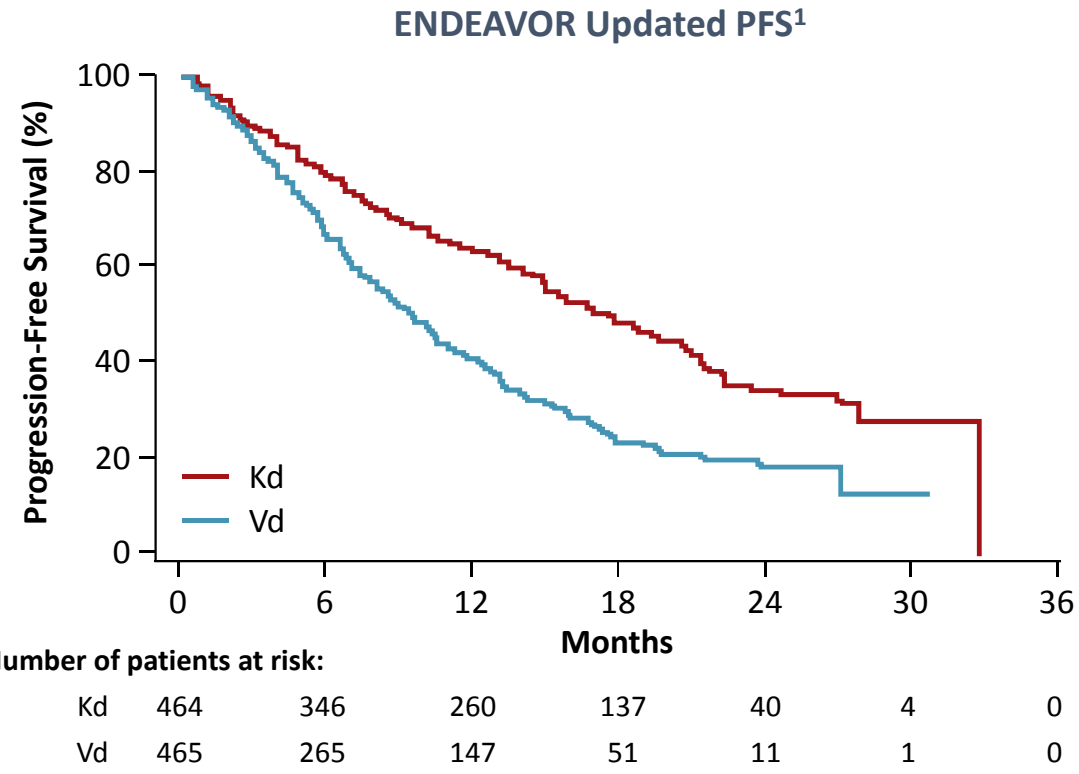
ENDEAVOR: Carfilzomib-Dex vs Bortezomib-Dex

Study Design



Dimopoulos MA, et al. *Lancet Oncol*. 2016;17:27.

ENDEAVOR: Kd Extended Progression-Free Survival by 8.2 Months

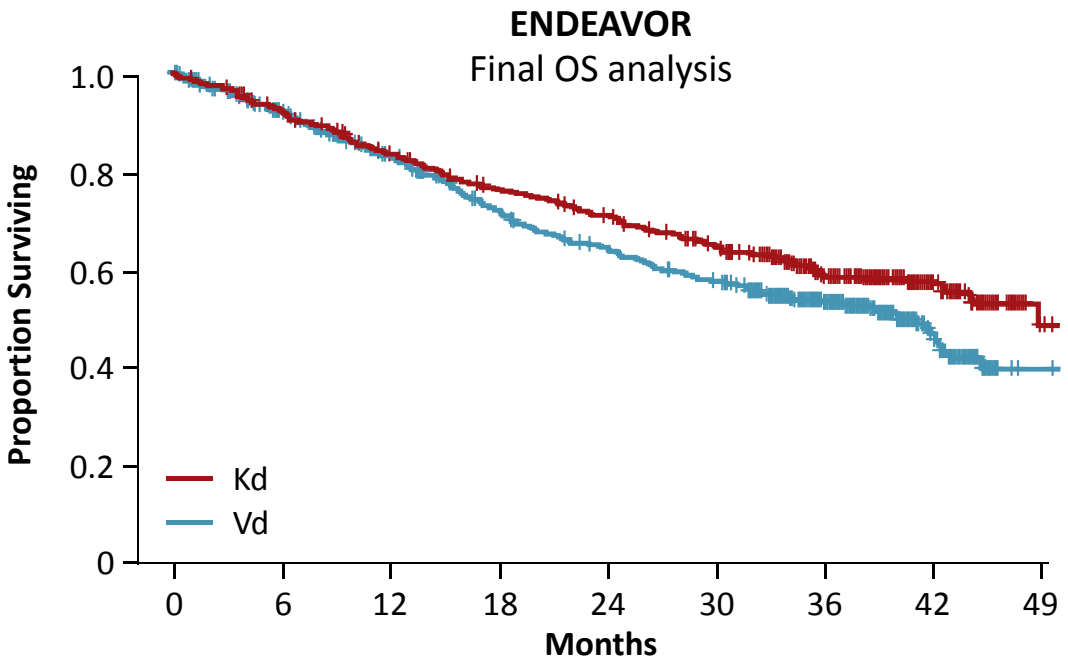


	Initial Analysis[2]		Updated Analysis[1]	
	Kd (n = 464)	Vd (n = 465)	Kd (n = 464)	Vd (n = 465)
Median follow-up, months	11.9	11.1	19.4	17.7
Median treatment duration, months	9.2	6.2	11.0	6.2
Median PFS, months	18.7	9.4	17.6	9.4
Hazard ratio (95% CI)	0.53 (0.44–0.65; $P < 0.0001$)		0.53 (0.44–0.63; $P < 0.0001$)	

[†]Treatment duration in the safety population: Kd (n = 463), Vd (n = 456).

1. Siegel D, et al. Presented at: International Myeloma Workshop. March 1-4, 2017. New Delhi, India. Abstract and poster. 2. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17:27-38.

ENDEAVOR: Kd Extended Overall Survival by 7.6 Months



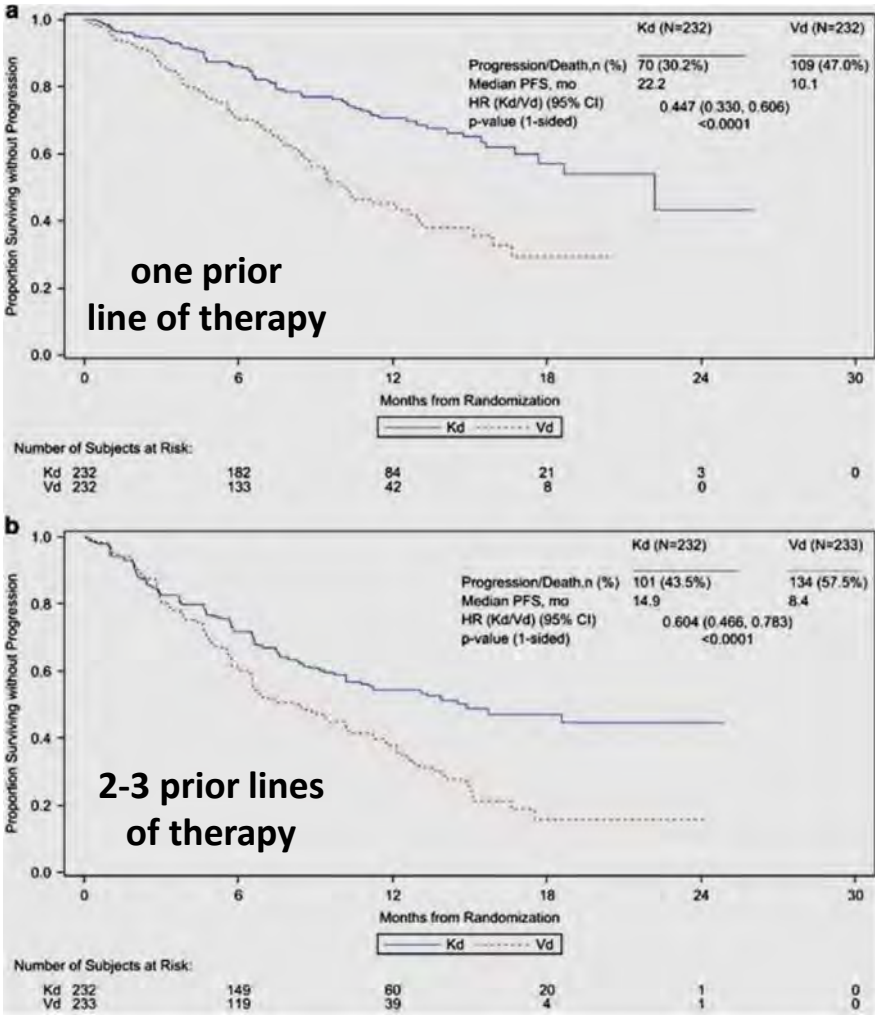
	Initial OS Analysis		Final OS Analysis	
	Kd (n = 464)	Vd (n = 465)	Kd (n = 464)	Vd (n = 465)
Median follow-up, months	12.5	11.9	37.5	36.9
Median OS, months	NE	24.3	47.6	40.0
Hazard ratio (95% CI)	0.79 (0.58–1.08; *P* = 0.13)		0.79 (0.65–0.96; *P* = 0.01)	

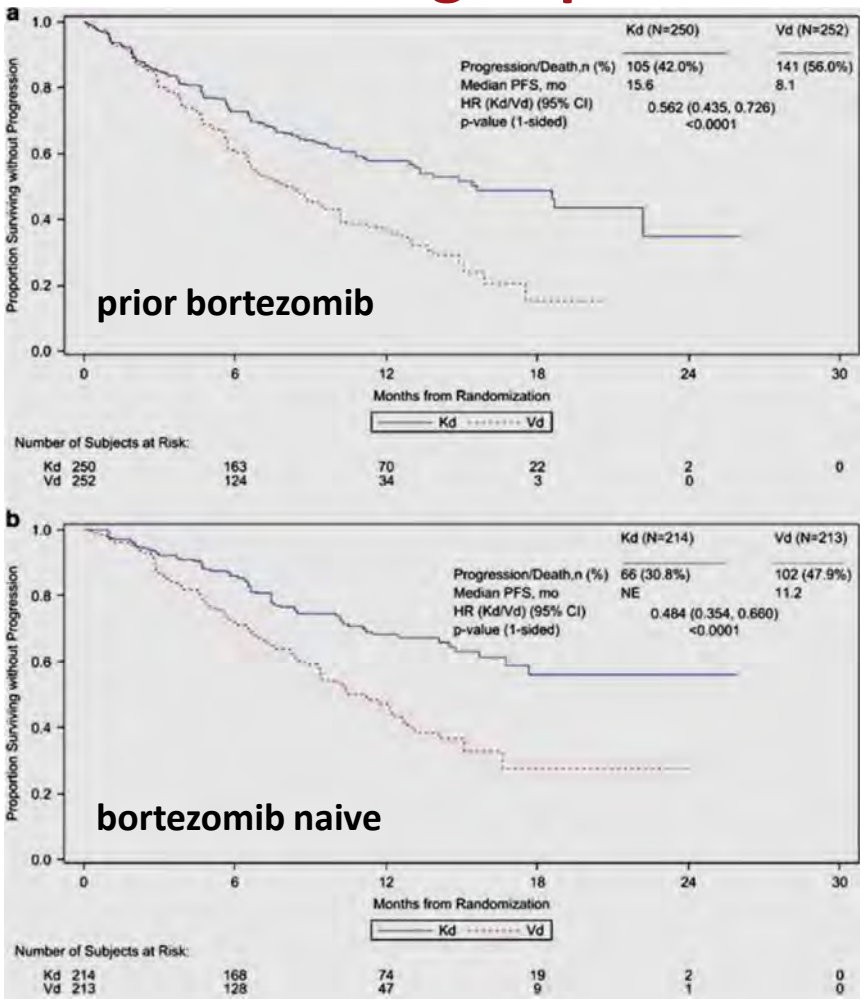
Number of patients at risk (number censored):

Kd	464 (0)	423 (7)	373 (16)	335 (21)	308 (25)	270 (35)	162 (121)	66 (215)	10 (266)
Vd	465 (0)	402 (28)	351 (40)	293 (50)	256 (56)	228 (58)	140 (130)	39 (221)	5 (251)

Dimopoulos MA, et al. *Lancet Oncol*. 2017;18:1327-1337.

ENDEAVOR: Progression-Free Survival according to prior lines

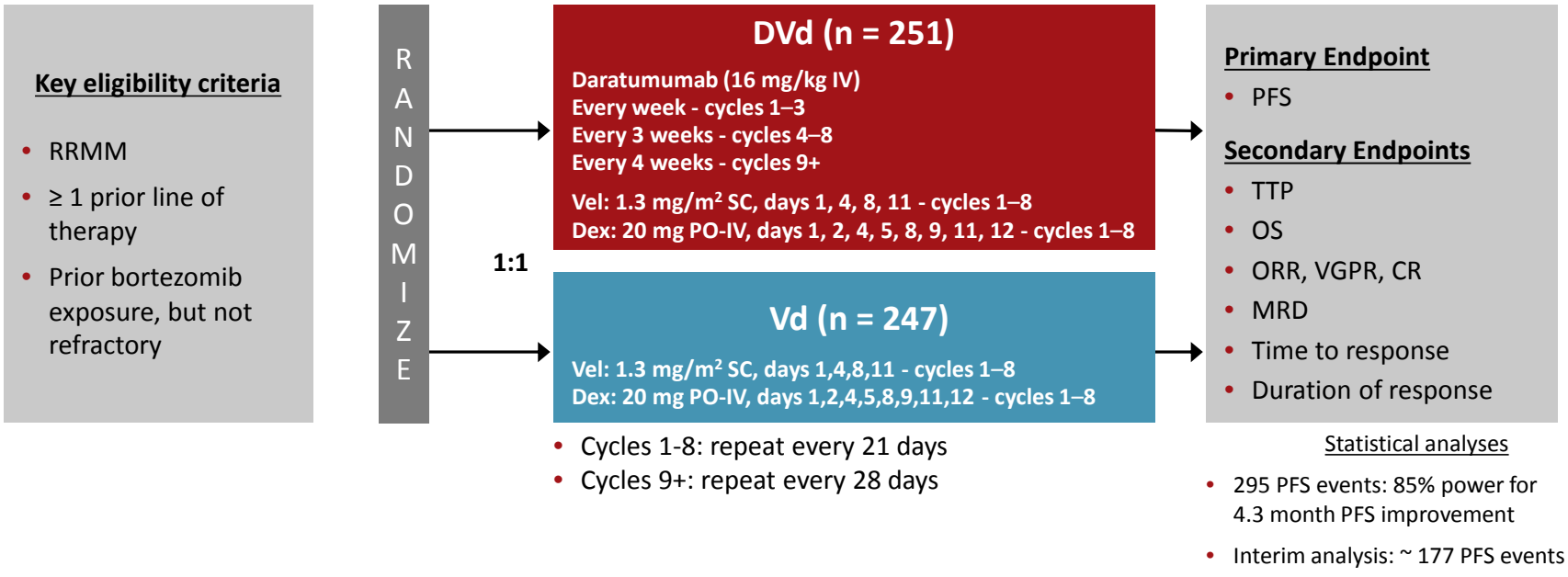




I1. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17:27-38. 2. Moreau P, et al. *Leukemia*. 2017;31:115-122.

CASTOR: Study Design

Multicenter, randomized, open-label, active-controlled phase 3 study[1,2]

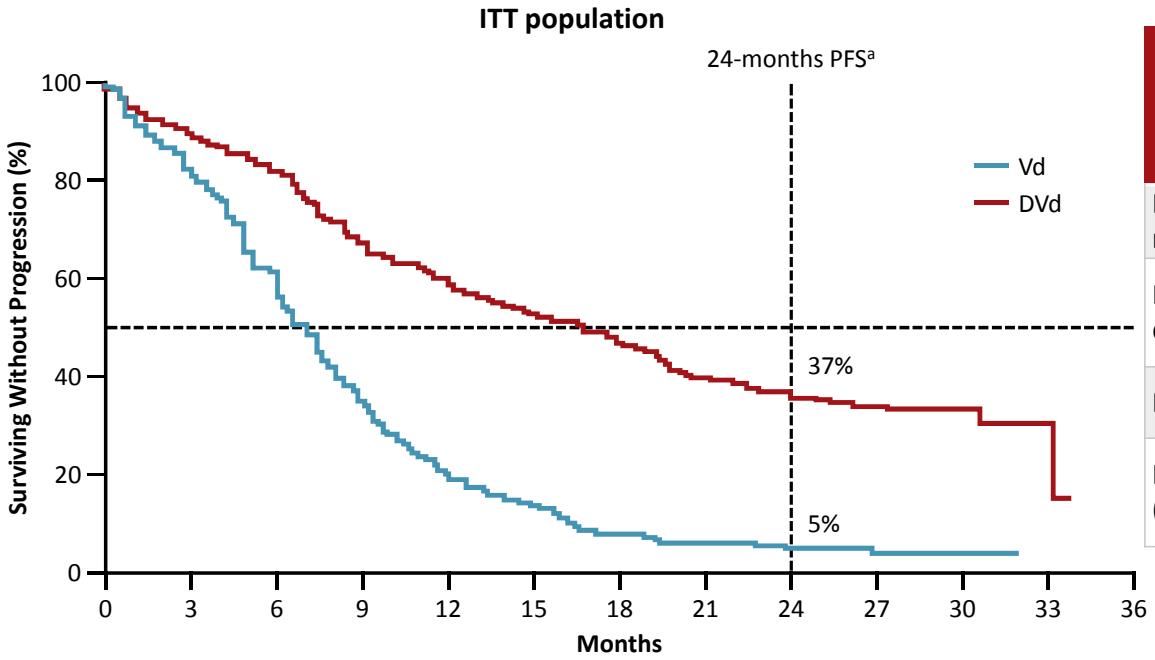


Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/hour permitted[2]

dex = Dexamethasone; DVd = daratumumab/bortezomib/dexamethasone; SC = subcutaneous; Vel = bortezomib; Vd = bortezomib/dexamethasone.

1. Palumbo A, et al. *N Engl J Med*. 2016:375:754-766; 2. Paulmbo A, et al. Presented at Presented at: 21st Congress of European Hematology Association. June 9 - 12, 2016. Copenhagen, Denmark. LB2236.

CASTOR Update: DVd Improved Progression-Free Survival by 9.6 Months



Number of patients at risk:

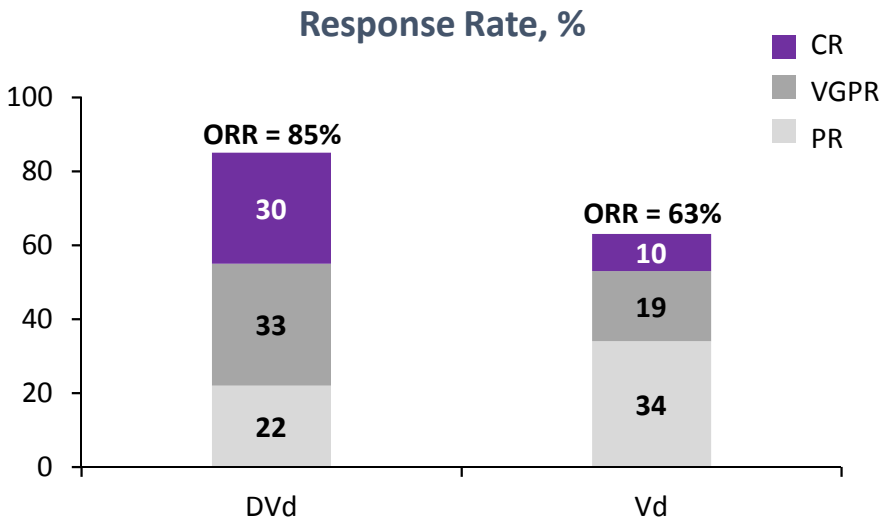
Vd	247	182	129	74	39	27	15	11	9	5	1	0	0
DVd	251	215	198	161	138	123	109	92	83	40	19	3	0

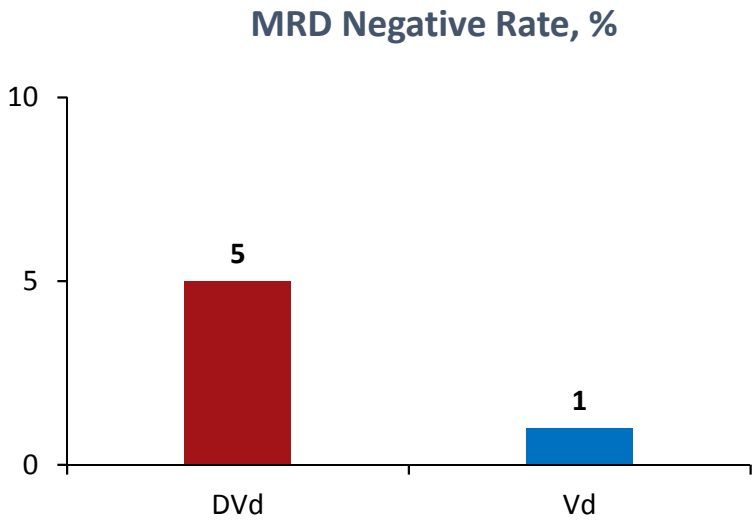
- Median follow up: 26.9 months

	Initial Analysis		Updated Analysis	
	DVd (n = 251)	Vd (n = 247)	DVd (n = 251)	Vd (n = 247)
Median follow-up, months	7.4		19.4	
Median treatment duration, months	5.6 (Vd)	5.6	Dara mono: 11.9	
Median PFS, months	NE	7.2	16.7	7.1
Hazard ratio (95% CI)	0.39 (0.28–0.53; $P < 0.001$)		0.32 (0.25–0.40; $P < 0.0001$)	

Spencer A, et al. Presented at: American Society of Hematology Annual Meeting. December 9-12, 2017. Atlanta, GA. Abstract 3145.

CASTOR: Response Rate and MRD Negativity





	Complete Response Rate	
	DVd (n = 240)	Vd (n = 234)
ñ **CR, %**	30	10
***P* value**	< 0.0001	
CR ratio*	3.0	

	MRD Negative Rate (10^{-6})	
	DVd (n = 251)	Vd (n = 247)
MRD -ve, %	5	1
***P* value**	*P* < 0.005	

1. Spencer A, et al. Presented at: American Society of Hematology Annual Meeting. December 9-12, 2017. Atlanta, GA. Abstract 3145; 2. Weisel K, et al. Presented at: 22nd Congress of European Hematology Association. June 22-25, 2017. Madrid, Spain.

Non-Rd Backbone Treatments in Patients With High-Risk Cytogenetics

Progression-Free Survival in Patients With High-Risk Cytogenetics

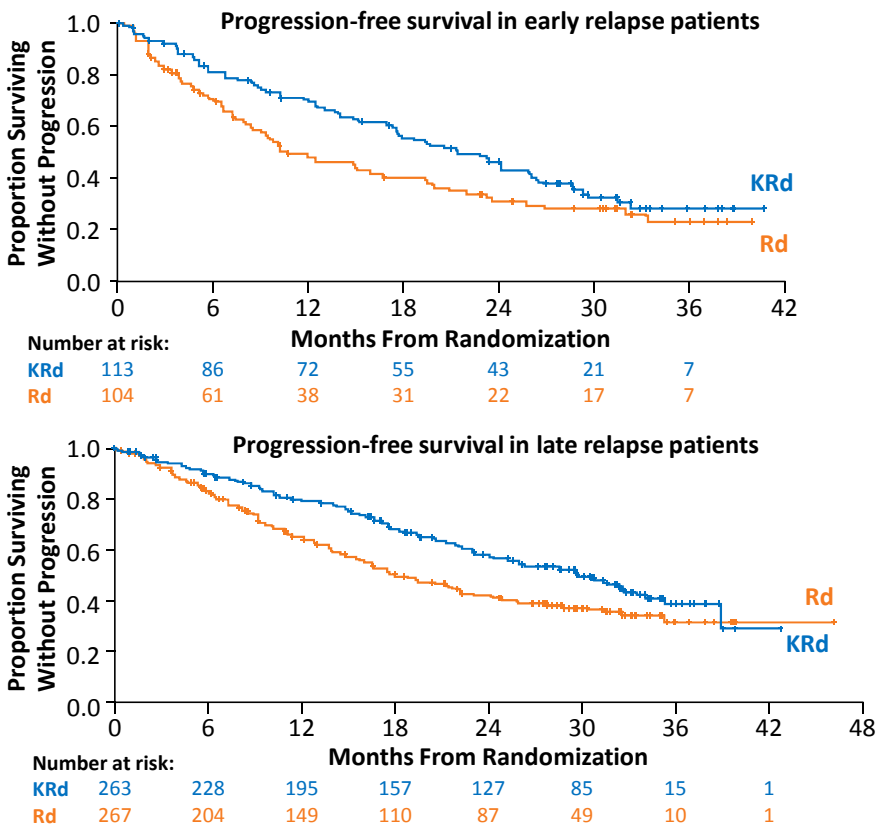
	Carfilzomib[2]		Daratumumab[1]	
	Kd (n = 177)	Vd (n = 177)	DVd (n = 44)	Vd (n = 51)
Median follow-up in ITT, months	11.9	11.1	19.4	
Median PFS, months	8.8	6.0	11.2	7.2
Hazard ratio (95% CI)	0.65 (0.45–0.92; *P* = 0.0075)		0.45 (0.25–0.80; *P* = 0.0053)	

This table is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

1. San Miguel. J, et al Presented at: 22nd Congress of European Hematology Association. June 22-25, 2017. Madrid, Spain; 2. Chng W-J, et al. *Leukemia*. 2017;31:1368-1374.

Patients with Early Relapse (≤12 months from previous therapy)

ASPIRE: Carfilzomib Extended PFS in Early and Late Relapse Patients in ASPIRE



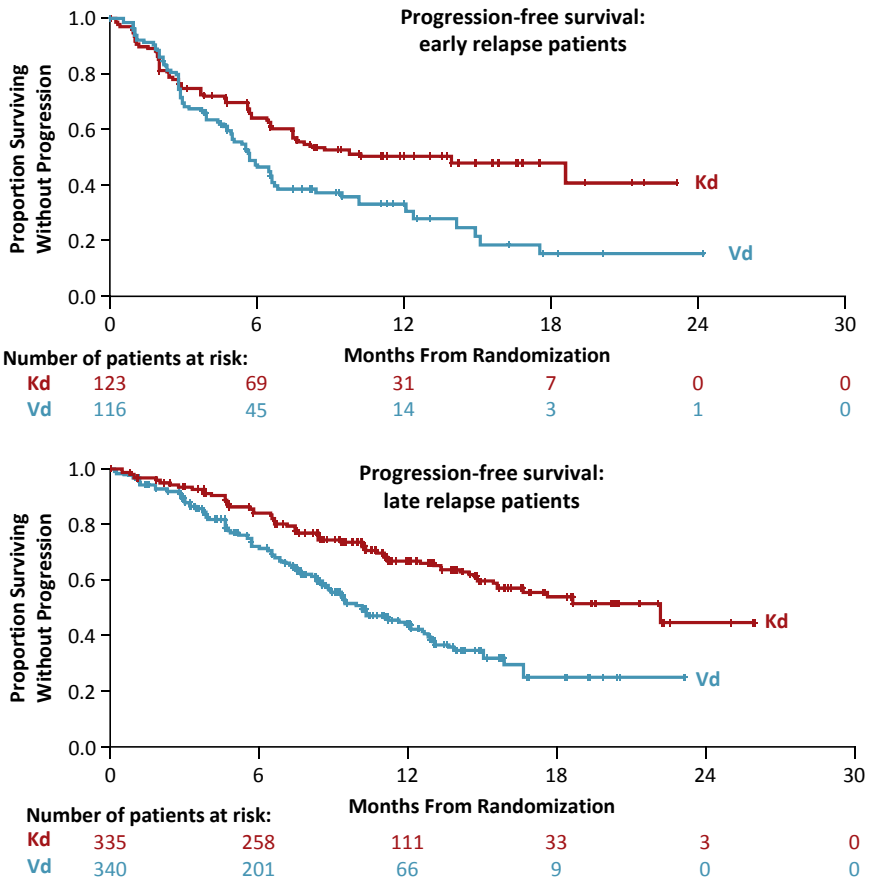
	KRd (n = 113)	Rd (n = 104)
Progression/Death, n (%)	70 (61.9%)	64 (61.5%)
Median PFS, months	**21.4**	**10.7**
HR (KRd/Rd) (95% CI)	**0.714 (0.508, 1.004)**	
P value (1-sided)	0.0257	

	KRd (n = 263)	Rd (n = 267)
Progression/Death, n (%)	70 (61.9%)	64 (61.5%)
Median PFS, months	**29.7**	**18.2**
HR (KRd/Rd) (95% CI)	**0.675 (0.533, 0.854)**	
P value (1-sided)	0.0005	

- In **ASPIRE**, **KRd** vs Rd **extended PFS** in RRMM patients **regardless** of whether they experienced **early or late** relapse
- In both arms, patients with **early relapse had worse PFS outcomes** than those with late relapse

Mateos MV, et al. *Hematol Oncol.* 2018 Feb 15. doi: 10.1002/hon.2499. [Epub ahead of print]

ENDEAVOR: Kd Effects on PFS in Early and Late Relapse Patients



	Kd (n = 123)	Vd (n = 116)
Progression/Death, n (%)	58 (47.2%)	73 (62.9%)
Median PFS, months	**13.9**	**5.7**
HR (Kd/Vd) (95% CI)	**0.598 (0.423, 0.846)**	
P value (1-sided)	0.0017	

	Kd (n = 335)	Vd (n = 340)
Progression/Death, n (%)	111 (33.1%)	167 (49.1%)
Median PFS, months	**22.2**	**10.2**
HR (Kd/Vd) (95% CI)	**0.486 (0.382, 0.620)**	
P value (1-sided)	< 0.0001	

- In **ENDEAVOR**, **Kd vs Vd extended PFS** in RRMM patients **regardless** of whether they experienced **early or late** relapse
- In both arms, patients with **early relapse had worse PFS outcomes** than those with late relapse

Mateos MV, et al. Presented at: American Society of Hematology Annual Meeting. December 9-12, 2017. Atlanta, GA. Abstract 3120.

Regimens for RRMM After 1-3 Prior Lines

Based on previous exposure or refractoriness to bortezomib or lenalidomide (according inclusion/exclusion criteria of respective studies)

		KRD	KD	Elo-RD	IRD	DRd	DVd	Pom-VD
Bortezomib	Exposure	+	+	+	+	+	+	+
	Refractoriness	-	-	+	-	+	-	-
Lenalidomide	Exposure	+	+	+	+	+	+	+
	Refractoriness	-	+	-	-	-	+	+

Lenalidomide refractoriness

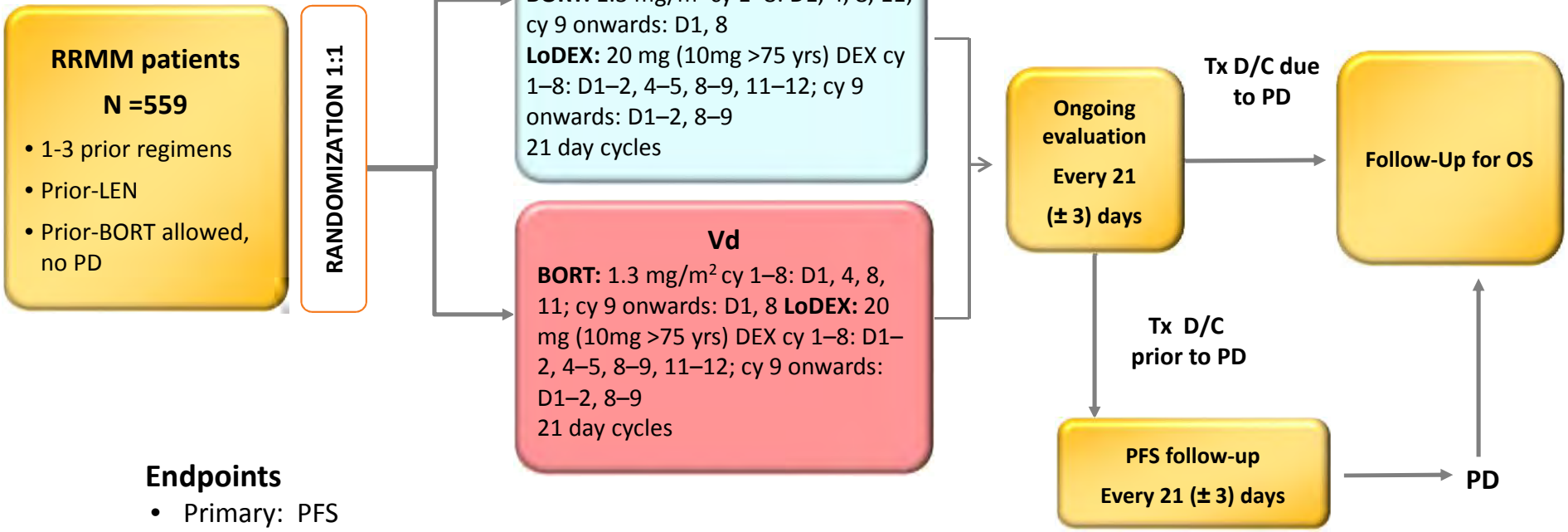
	Lenalidomide-Refractory	
	DVd (n = 45)	Vd (n = 60)
Median follow-up in ITT, months	13.0	
Median PFS, months	10.3	4.4
Hazard ratio (95% CI)	0.37 (0.21–0.65; *P* = 0.0004)	

Chanan-Khan AA, et al. Presented at: American Society of Hematology Annual Meeting. December 1-4, 2016, San Diego, CA. Abstract 3313.

Lenalidomide-Refractory	
Kd (n = 113)	Vd (n = 122)
11.9	11.1
8.6	6.6
0.80 (0.57–1.11)	

1. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17:27-38.
2. Moreau P, et al. *Leukemia*. 2017;31:115-122.

OPTIMISMM Phase 3 study design



Stratification Factors

- Age (≤ 75 vs. > 75 yrs)
- Number of prior anti MM regimens (1 vs. > 1)
- β2M at screening (< 3.5 mg/L vs. ≥ 3.5 mg/L ; ≤ 5.5 mg/L vs. > 5.5 mg/L)

Endpoints

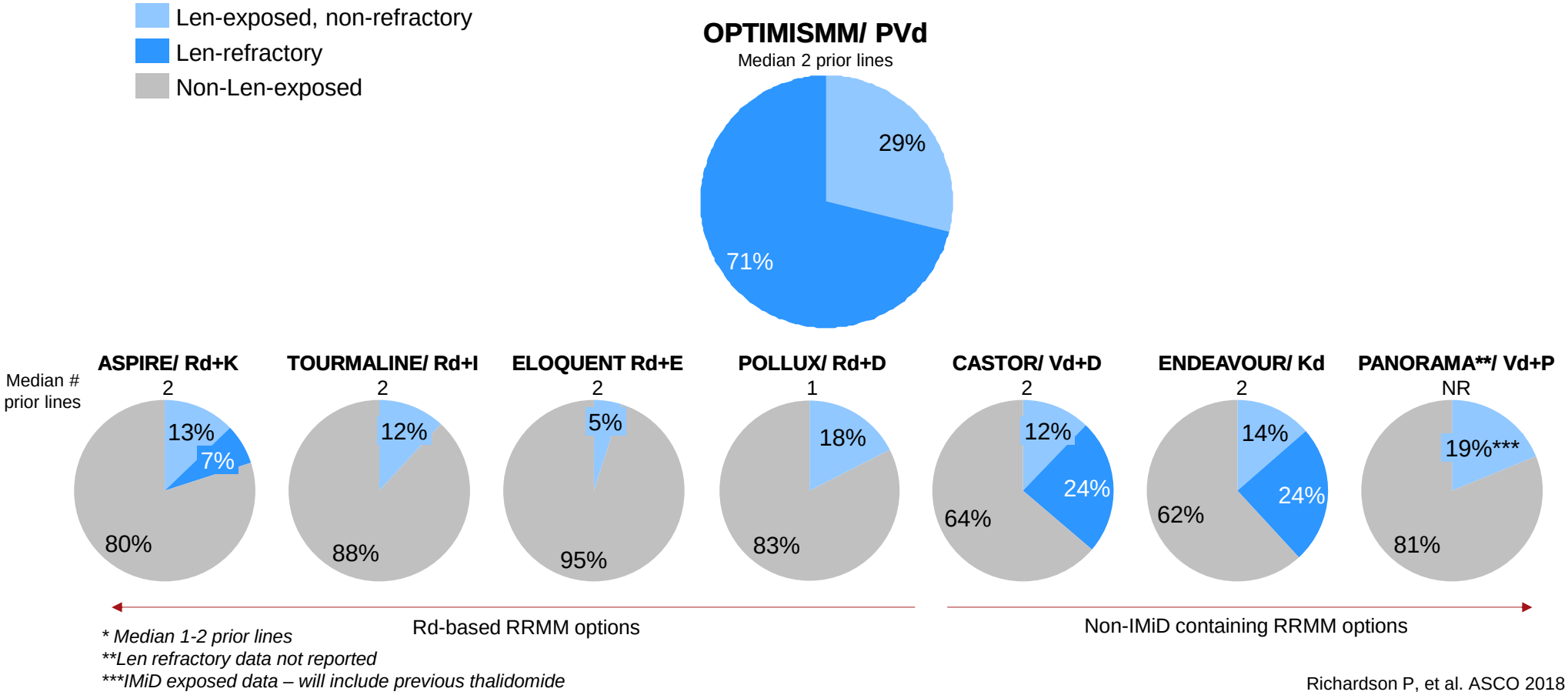
- Primary: PFS
- Secondary: OS, ORR, duration of response
- Exploratory: TTR, PFS2, MRD, HRQoL

Richardson P, et al. ASCO 2018

CONTEXTUALIZING THE PATIENT POPULATION:

OPTIMISMM: 70% of patients were len refractory

% Len-exposed, Len-refractory and non-Len exposed patients in early-RRMM* combination trials

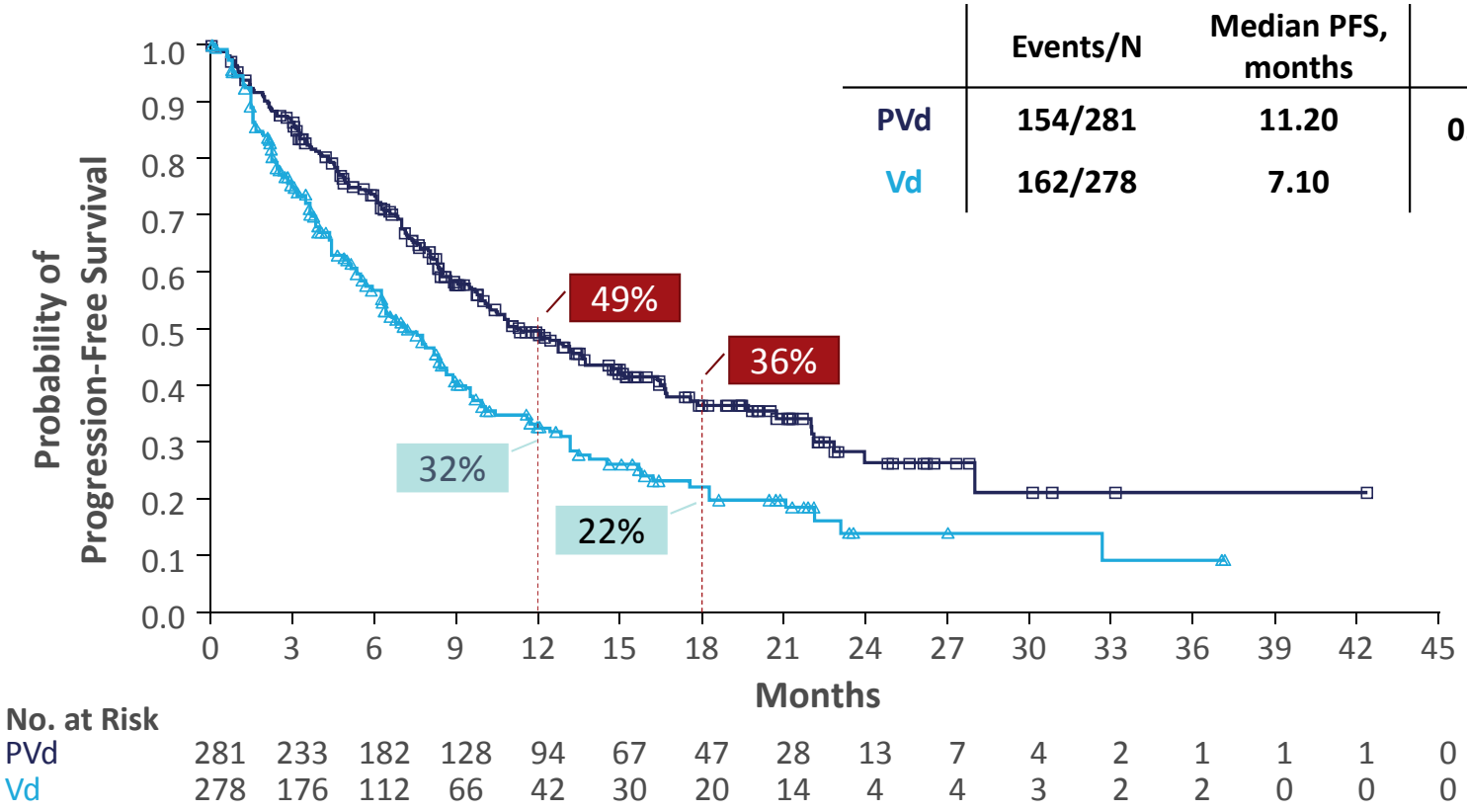


** Median 1-2 prior lines*
***Len refractory data not reported*
****IMiD exposed data – will include previous thalidomide*

Richardson P, et al. ASCO 2018

Progression-Free Survival (ITT)

- **PVd reduced the risk of progression and death by 39% compared with Vd**



	Events/N	Median PFS, months	HR (95% CI) *P* Value
PVd	154/281	11.20	0.61 (0.49-0.77)
Vd	162/278	7.10	< .0001

Abstract 8001: OPTIMISMM—Paul Richardson, MD

Richardson P, et al. ASCO 2018

Progression-Free Survival by len refractoriness

- PFS was improved with PVd regardless of LEN refractoriness

Subgroup	PFS	PVd	Vd
LEN-refractory[a]	n/N	120/200	118/191
	Median, months	9.53	5.59
	HR (95% CI) *P* Value	0.65 (0.50-0.84) < .001	
LEN-nonrefractory	n/N	34/81	44/87
	Median, months	22.01	11.63
	HR (95% CI) *P* Value	0.48 (0.30-0.75) .001	

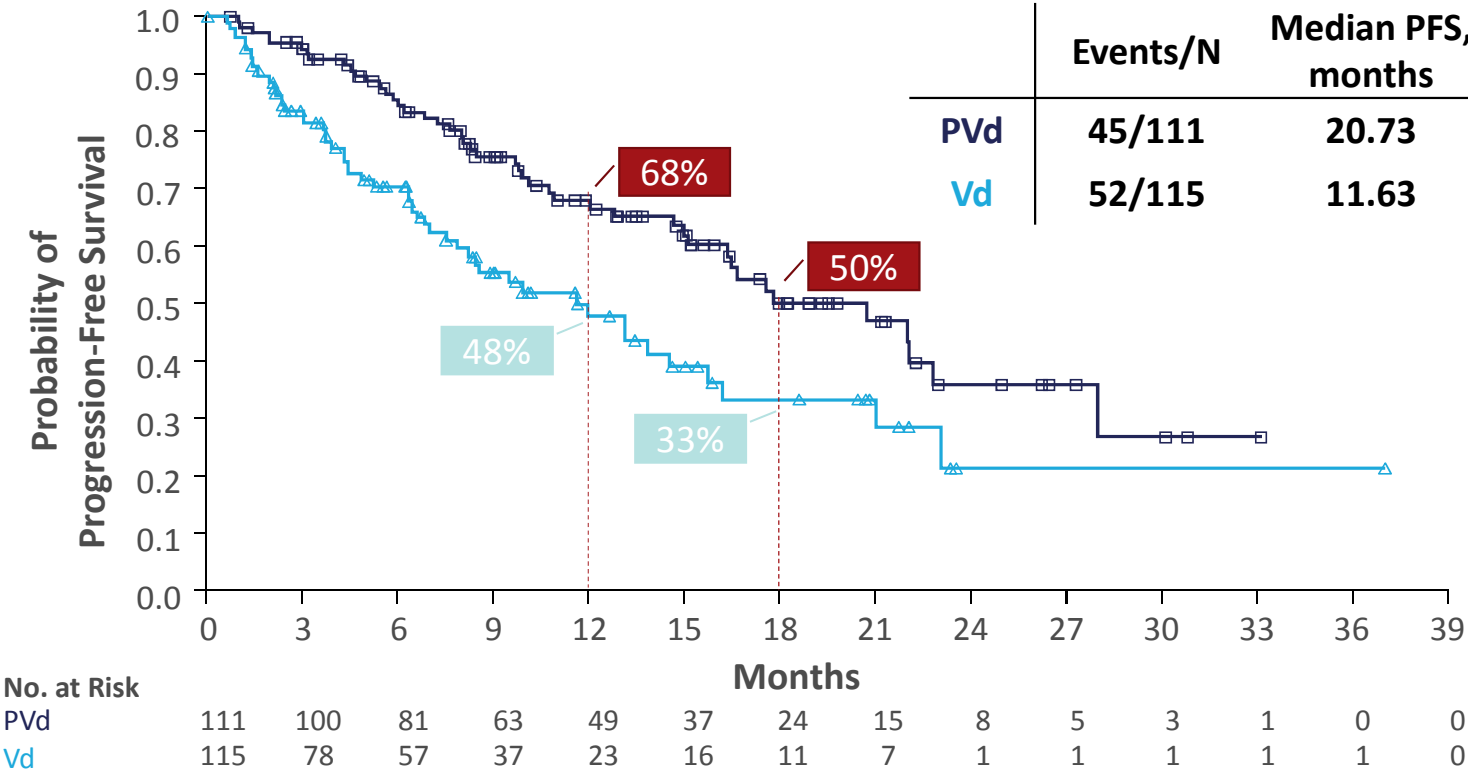
[a] Refractory: failure to achieve minimal response or development of progressive disease during therapy, or progression within 60 days of last dose, inclusive.

LEN-refractory: refractoriness to the last LEN-containing regimen, LEN-nonrefractory: nonrefractory to LEN in last LEN-containing regimen

Richardson P, et al. ASCO 2018[47]

Progression-Free Survival (1 Prior Line of Therapy)

- **In patients with 1 prior line, PVd reduced the risk of progression and death by 46% compared with Vd**
- **57.7% of patients treated with PVd and 56.5% treated with Vd were refractory to LEN**

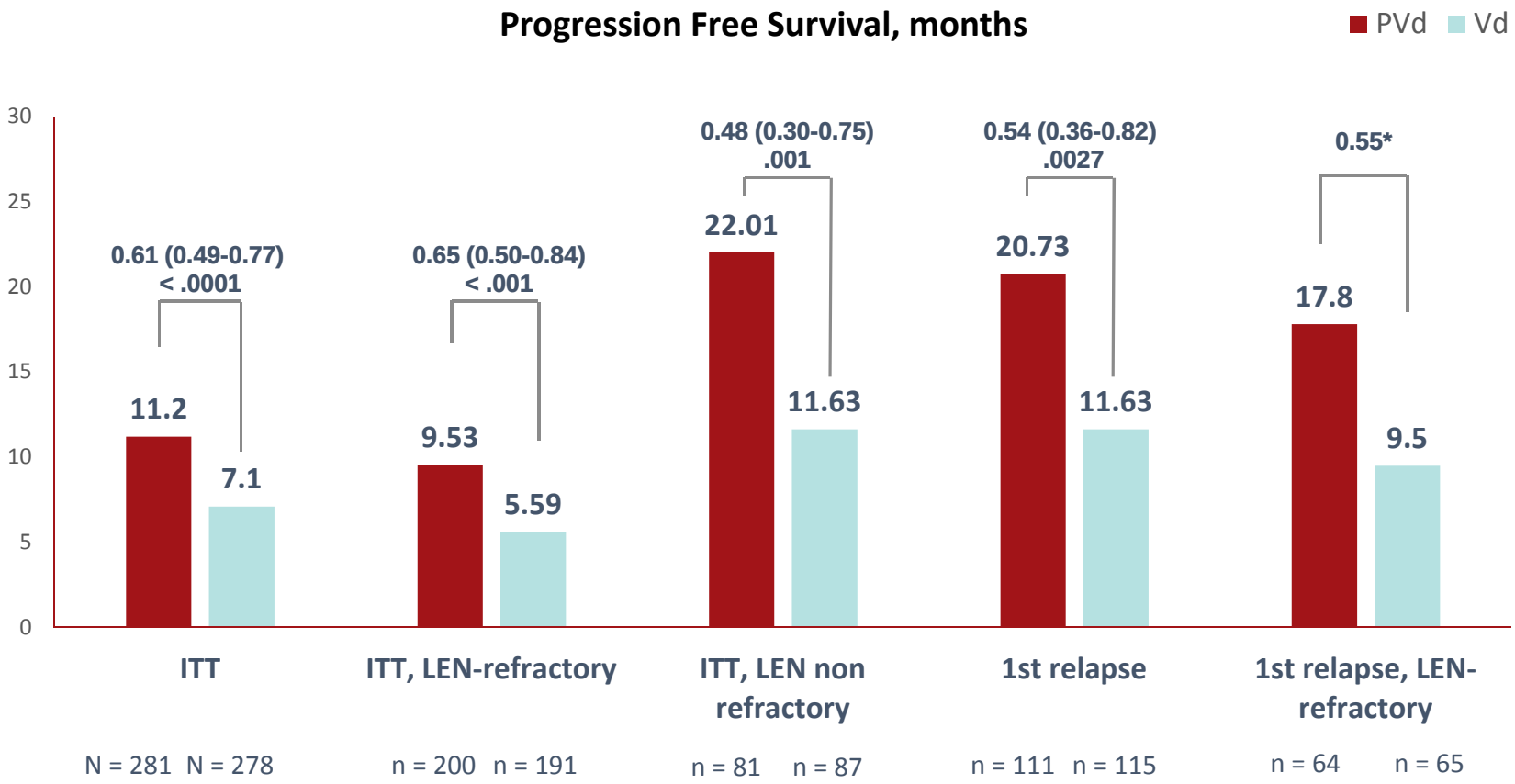


	Events/N	Median PFS, months	HR (95% CI) *P* Value
PVd	45/111	20.73	0.54 (0.36-0.82) .0027
Vd	52/115	11.63	

Abstract 8001: OPTIMISMM—Paul Richardson, MD

Richardson P, et al. ASCO 2018

Progression free survival in ITT and subgroups



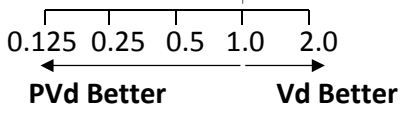
Abstract 8001: OPTIMISMM—Paul Richardson

* Verbal Communication during EHA; unpublished data

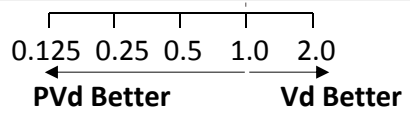
Progression-Free Survival in Patient subgroups

- PFS was improved with PVd vs Vd across all patient subgroups

Subgroup	PVd n/N	Vd n/N	Hazard Ratio (95% CI)
Age			
≤ 75 y	126/235	134/231	0.59 (0.46–0.76)
> 75 y	28/46	28/47	0.78 (0.46–1.32)
≤ 65 y	60/123	67/120	0.58 (0.41–0. 83)
> 65 y	94/158	95/158	0.64 (0.48–0.86)
ECOG PS			
0	69/149	71/137	0.62 (0.45–0.87)
> 0	85/132	91/141	0.60 (0.45–0.82)
High risk cytogenetics			
Yes	37/61	34/49	0.56 (0.35–0.90)
No	73/137	80/132	0.56 (0.41–0.77)
No. of lines of prior therapy			
1	45/111	52/115	0.54 (0.36–0.82)
> 1	109/170	110/163	0.63 (0.48–0.83)
2	74/117	67/104	0.67 (0.48–0.94)
> 2	35/53	43/59	0.60 (0.38–0.95)



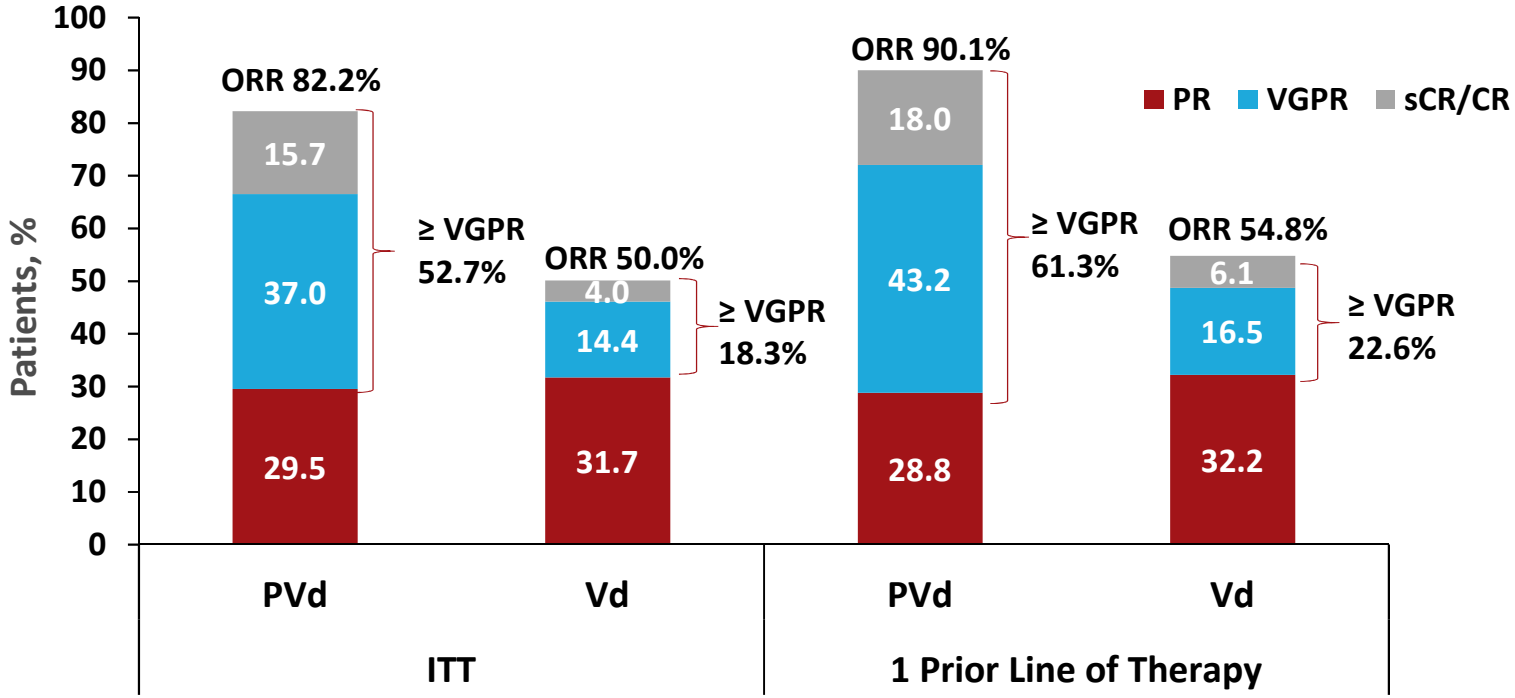
Subgroup	PVd n/N	Vd n/N	Hazard Ratio (95% CI)
ISS stage at study entry			
I	67/149	69/138	0.56 (0.40–0.78)
II	51/85	55/90	0.68 (0.46–0.99)
III	36/47	38/50	0.72 (0.46–1.15)
Prior SCT			
Yes	82/161	93/163	0.57 (0.43–0.78)
No	72/120	69/115	0.67 (0.48–0.94)
Refractory to LEN in last LEN-containing regimen	120/200	118/191	0.65 (0.50–0.84)
Nonrefractory to LEN in last LEN-containing regimen	34/81	44/87	0.48 (0.30–0.75)
Refractory to last prior therapy	110/196	112/184	0.60 (0.46–0.78)
Prior exposure to PIs	118/212	132/213	0.57 (0.44–0.73)



Abstract 8001: OPTIMISMM—Paul Richardson, MD

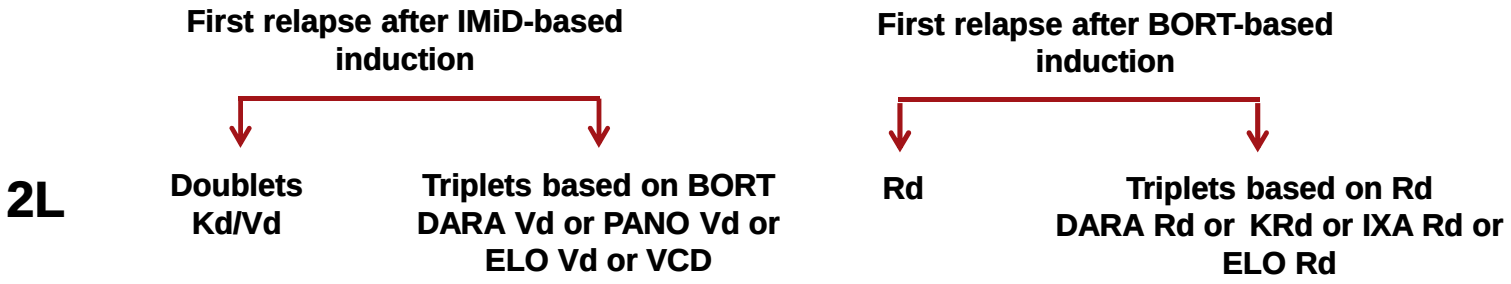
Response

- ORR was significantly higher with PVd vs Vd in the ITT population ($P < .001$) and in patients with 1 prior line of therapy ($P < .001$)
  - PVd led to deeper responses with higher sCR/CR and ≥ VGPR rates vs Vd
- Median TTR was 0.9 vs 1.4 months, and median DOR was 13.7 vs 10.9 months (ITT)



Abstract 8001: OPTIMISMM—Paul Richardson, MD

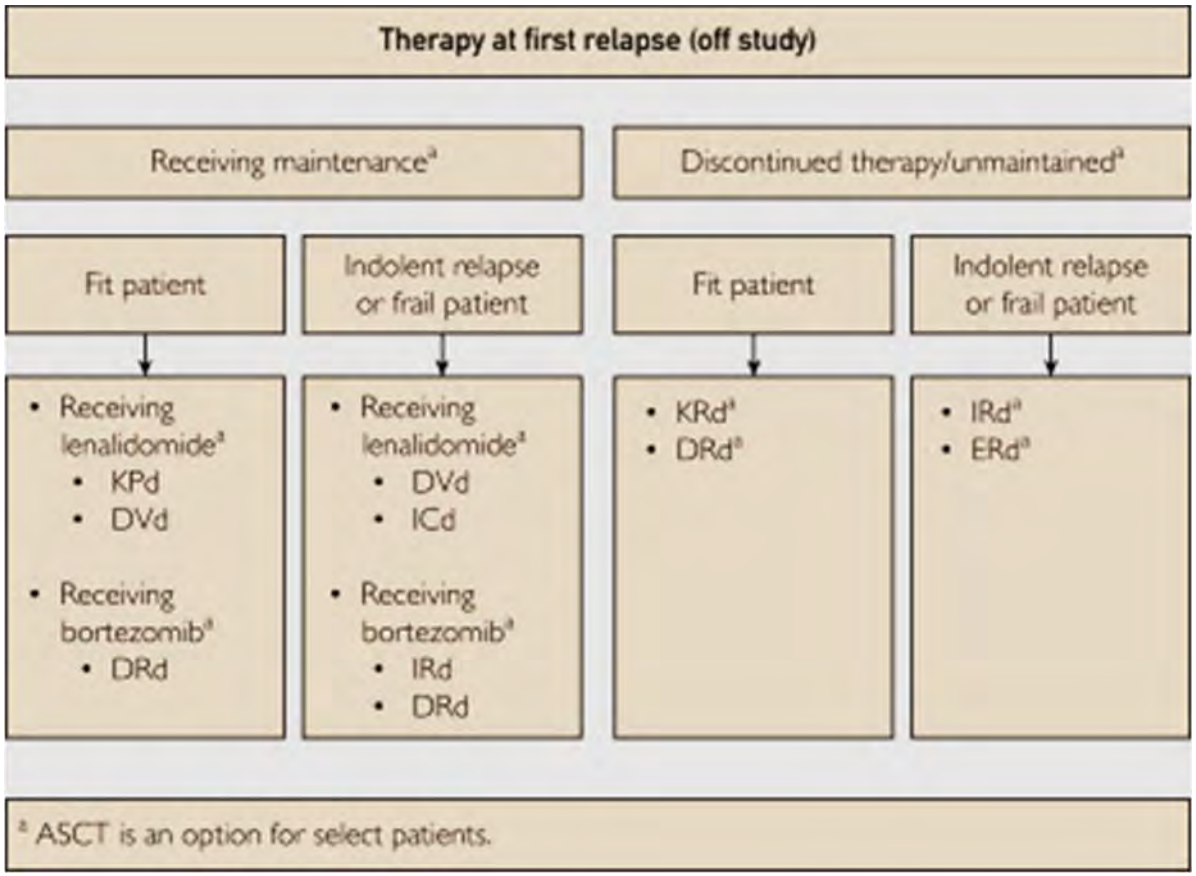
Relapsed/refractory multiple myeloma
ESMO guidelines 2017



2L, second line; 3L, third line; BORT, bortezomib; CYCLO, cyclophosphamide; DEX, dexamethasone; DARA, daratumumab; ELO, elotuzumab; IMiD, immunomodulatory drug; IXA, ixazomib; Kd, carfilzomib and DEX; KRd, carfilzomib, lenalidomide and DEX; POM, pomalidomide; Rd, lenalidomide and DEX; Vd, bortezomib and DEX.

Moreau P, *et al. Ann Oncol* 2017; **28**:iv52–iv61.

Mayo Guidelines for the Relapsed Patients
Mayo Risk Adapted Groups



Dingli D et al. *Mayo Clin Proc* 2017;92:578-598

Consensus guidelines for salvage ASCT in RRMM
(ASBMT, EBMT, BMT CTN, and IMWG)

1. In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with autologous HCT as part of salvage therapy should be considered standard

2. High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of >18 months

3. High-dose therapy and autologous HCT can be used as a bridging strategy to allogeneic HCT

Girault, S. et al. Biol Blood Marrow Transplant 2015;21:2039-2051.

Conclusions for patients with early realapses

- Patients who received bortezomib-based regimens may be given RD-based triplets
  - For standard-risk patients: DaraRd shows the best results to-date
  - For high-risk patients: KRd, IRd, DaraRd
  - For bortezomib refractory patients: DaraRd, EloRd
  - For lenalidomide refractory patients: PomVd, DaraVd, Kd
  - For early relapsing patients: KRd but still not satisfactory for young patients; UNMET NEED
- Lenalidomide refractoriness is a considerable problem: PomVd gives the best results in this setting
- Salvage transplant maybe considered for patients with EFS >2 years after previous transplant; however this maybe >3 years for patients who receive lenalidomide maintenance

- Optimal sequencing is an important consideration for individual patient care

Thank you

Treatment of Patients Refractory to PIs and Lenalidomide

Jean Luc Harousseau
Institut de Cancérologie de l'Ouest
Intergroupe Francophone du Myélome

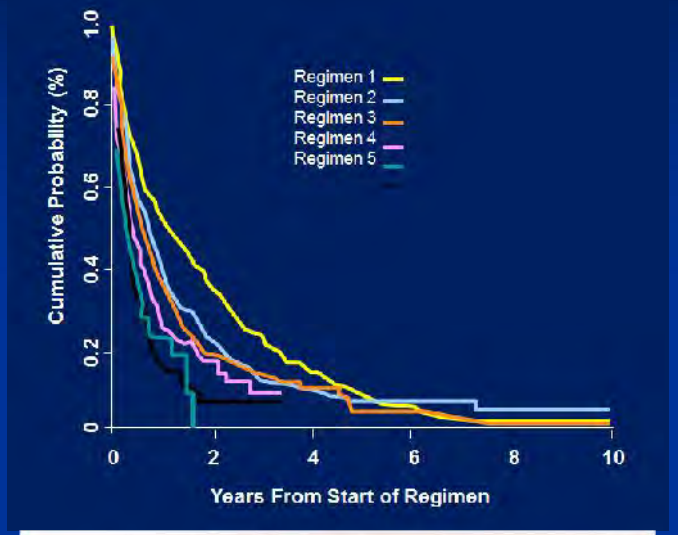
General considerations

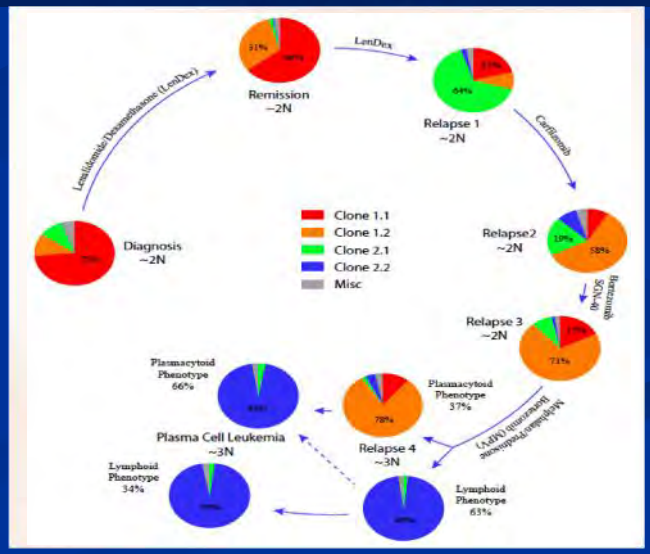
- At each relapse remission duration decreases
- At each therapy a more resistant clone occurs

- BTZ/PI and Len are now used in frontline therapy:

  RVd,KRd,Rd,maintenance..
- BTZ/PI and Len refractory relapses occur earlier

- Cytotoxic combinations (DCEP, DT PACE, bendamustine-based) remain possible treatments in this situation





Keats JJ Blood 2012;120:1067

DEFINITION

- No response or Progressive disease during therapy or within 60 days after completion of last therapy [1]

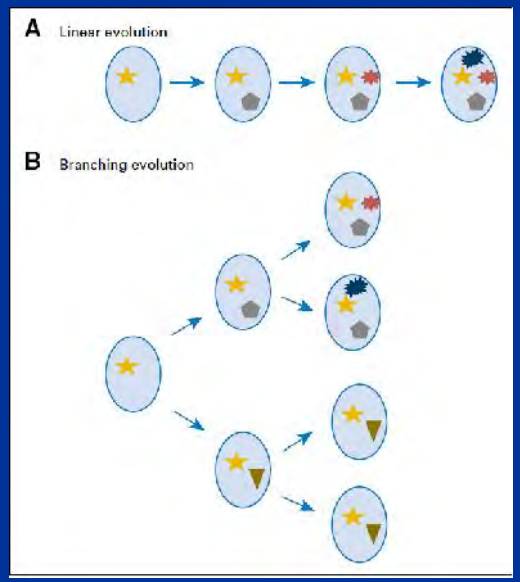
BUT some questions

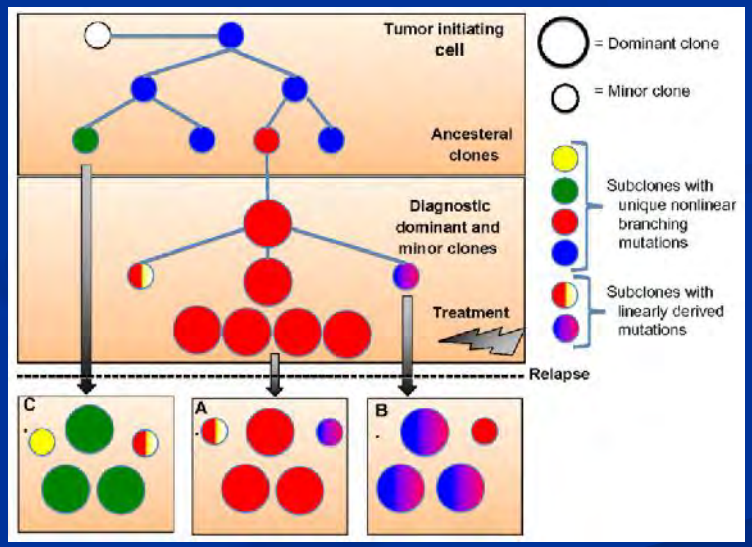
- **For lenalidomide :** the dose of lenalidomide if progression (10mg as in maintenance or 25 mg as in induction)
- **For Bortezomib:** if no response when treatment is stopped for toxicity
- This information is not always available in reported results of treatment of RRMM

1 Rajkumar SV Blood 2011;117:4691

Clonal Evolution in MM

- During the evolution expansion of resistant clones that either existed before treatment or result of new alterations gained during therapy
- Branching model may explain the re-emergence of subclones that possibly retained sensitivity to previously used therapies



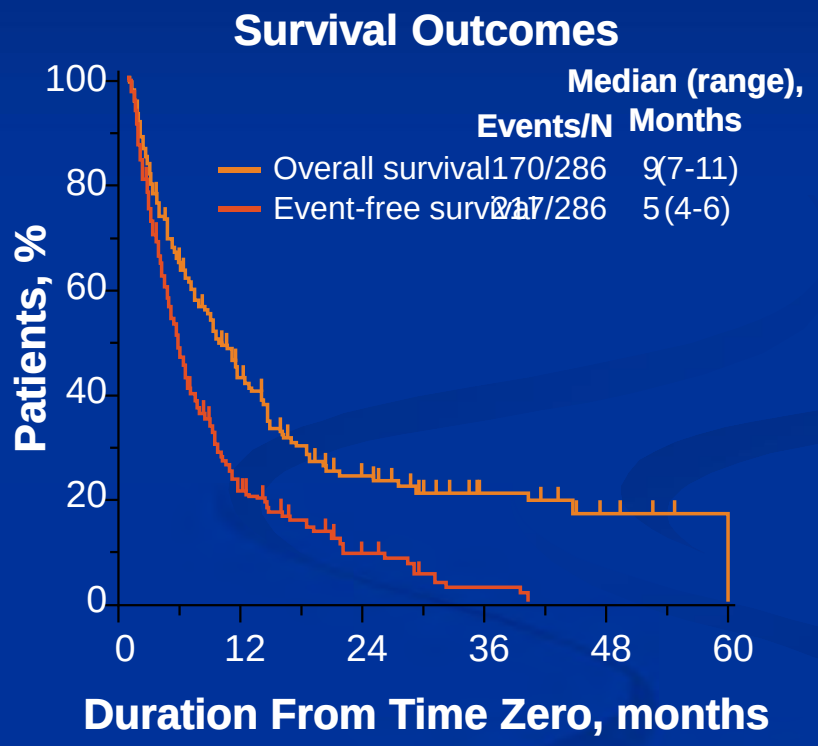


- **Refractory to a drug as last treatment**

Bahlis NJ Blood 2012;120:927 Keats JJ Blood 2012;120:1067 Robiou du Pont S JCO 2016;35:963

Double Refractory Multiple Myeloma

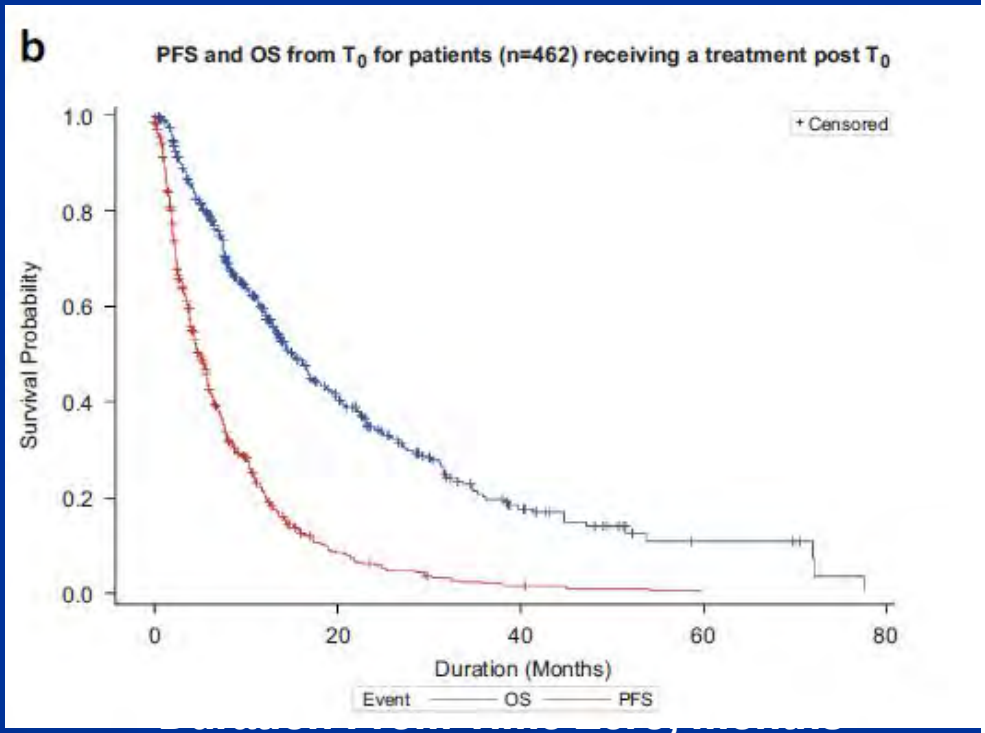
- Retrospective analysis of 286 patients refractory to BTZ and were relapsed from, refractory to, or ineligible for IMiDs[1]
- Initial response after relapsed/ refractory criteria was met: **24%**
  - Response, including all subsequent therapies, was **32%**
- Median OS = **9 months**
- Median EFS = **5 months**
- These endpoints have been used as benchmarks for clinical trials for novel agents in this setting



Kumar et al, Leukemia 2012

Double refractory MM

- At least 3 lines of treatment
- Ref to Len or Pom and to Bort or Car (last 2 lines)
- 462 pts (who received at least 1 treatment after)
- RR to first treatment 12%
  if Bort or Len
- 35 % if Pom or Car
- Med PFS 5m
- Med OS 15m



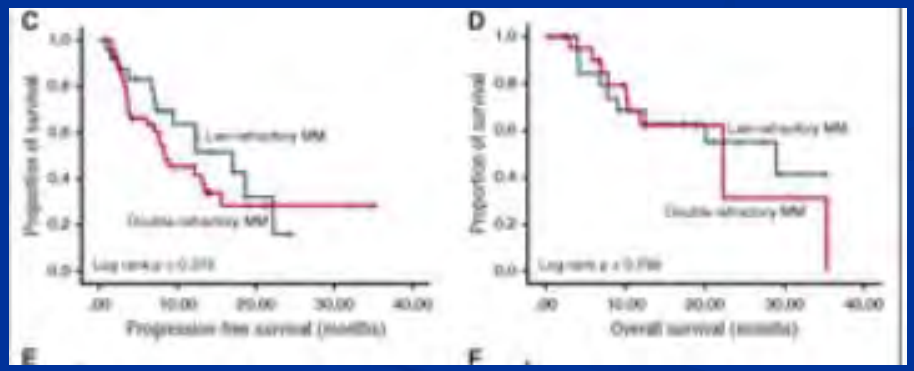
Kumar S Leukemia 2017

Can efficacy of Lenalidomide be restored in synergistic combinations? The REP regimen

Len 25mg/D D1-21
Cyclo 50mg/D
PDN 20mg/d

Median PFS 12m OS 29m

	L-ref	L and B-ref
N	66	42
≥ PR	67%	60%
≥ VGPR	23%	24%



Nijhoff S Blood 2016 :128 :2297

Can Bortezomib efficacy be restored in synergistic combinations The role of Nelfinavir

Six 21 days cycles

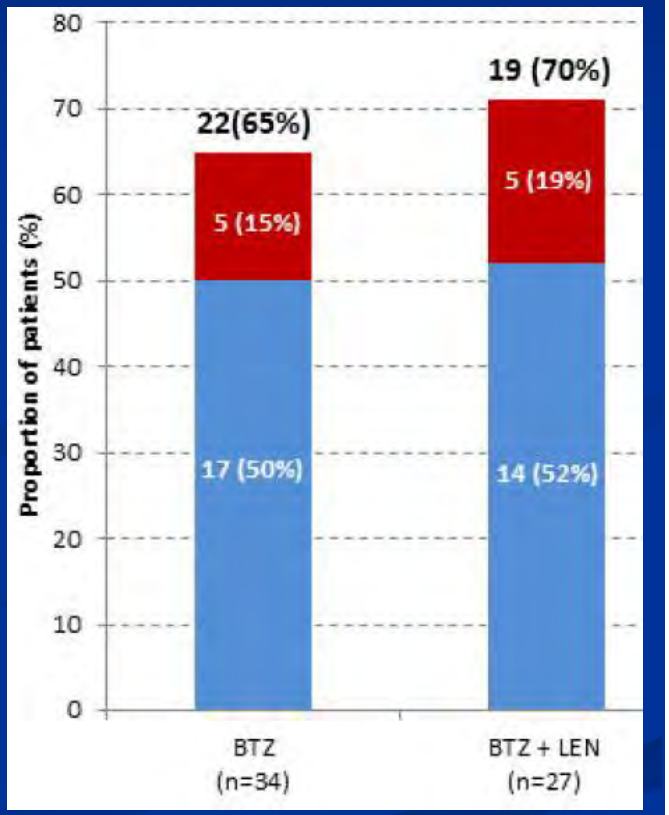
Nelfinavir 2500mg D1-14

BTZ 1.3mg/m2 D1,4,8,11

Dex 20mg/D D 1-2, 4-5,8-9,11-12

- 34 BTZ-refractory patients
- Median number or prior lines 5
- 38% high-risk cytogenetic abnormlities
- Median PFS **12 weeks** (≥ PR)

		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematological	Anemia	11 (32%)	12 (35%)	10 (29%)		
	Neutropenia	1 (3%)	3 (9%)	2 (6%)	2 (6%)	
	Thrombocytopenia	8 (24%)	5 (15%)	8 (24%)	7 (21%)	
Infections	Lung infection			7 (21%)	1 (3%)	
	Sepsis				1 (3%)	3 (9%)
Non-hematological	Diarrhea	8 (24%)	6 (18%)	2 (6%)		
	Edema limbs	4 (12%)	4 (12%)	1 (3%)		
	Fatigue	3 (9%)	5 (15%)	5 (15%)		
	Peripheral sensory neuropathy		7 (21%)	3 (9%)		
	Hypertension	4 (12%)	8 (24%)	6 (18%)		
	Dyspnea	6 (18%)	5 (15%)	1 (3%)		
	Heart failure		1 (3%)			1 (3%)



Driessen C Blood 2018 online

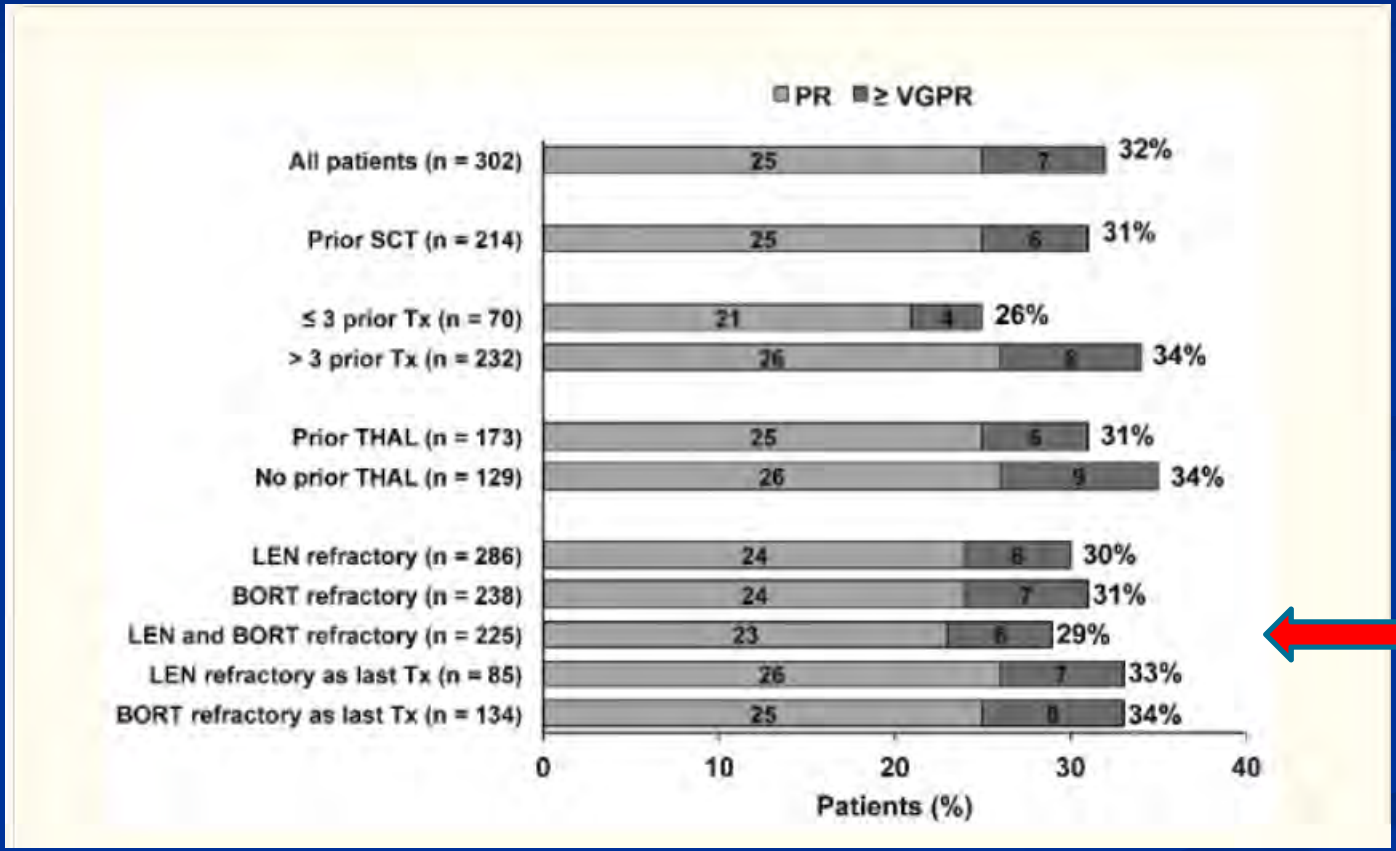
APPROVED DRUGS

IMIDs	PIs	HDAC	Antibodies
Thalidomide	Bortezomib	Panobinostat	Daratumumab
Lenalidomide	Carfilzomib		Elotuzumab
Pomalidomide	Ixazomib		

In pivotal randomized studies comparing Rd or Vd to triplets with one of these new agents patients refractory to Len or Bort were not included

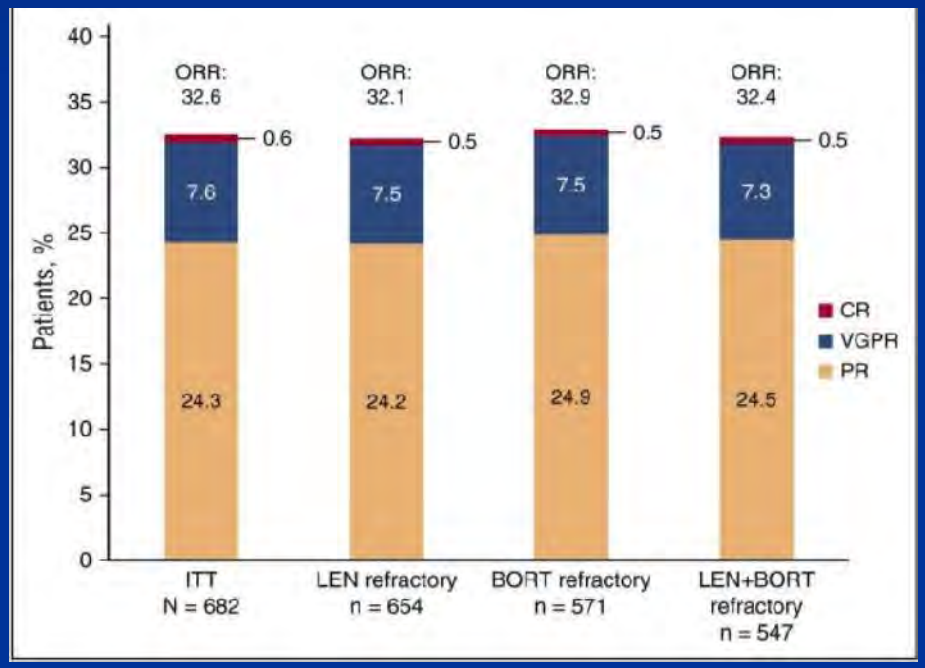
Is pomalidomide active in Len-refractory patients ?

Randomized study comparing Pom-dex versus high-dose dex (MM003)



San Miguel JF et al Haematologica 2015;100:1334

Efficacy of Pomalidomide-Low dose Dexamethasone in refractory patients Stratus-MM010



- Median PFS in pts refractory to Len and Bort 4.2 months

Dimopoulos MA et al Blood 2016;128:497

Pomalidomide-dex in RRMM
The IFM experience (IFM 2009-02)

	N	RR(%)	Median PFS
Ref to LEN	84	27	4.2
Ref to LEN last line	75	6	4.4
Ref to Bort	68	20	3.8
Double Ref	64	20	3.8

Leleu X Blood .2013;121:1968

Is Carfilzomib active in BTZ-refractory patients ?

Carf 20/27 mg/m2 D1,2, 8,9,15,16

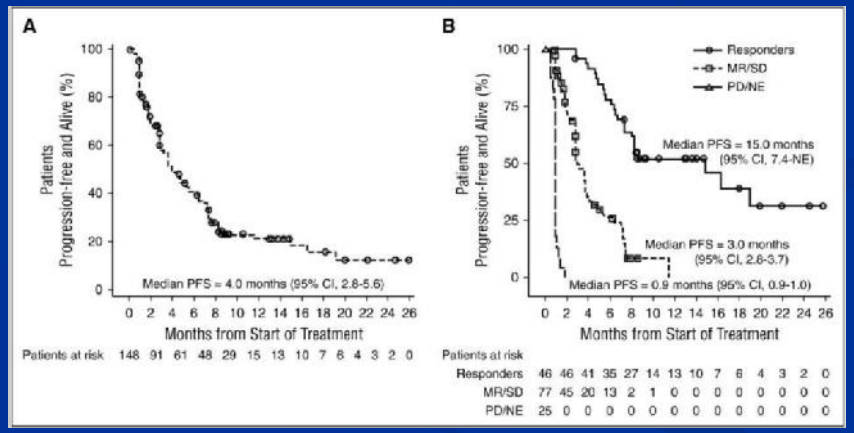
	n	RR %	DOR
All (75% Bort-ref)	257	23.7	7.8m
Ref/or intol to B and L	214	20.1	7.4m
Ref to B and L	169	15.4	7.8m

Siegel Blood 2012;120:2817

Daratumumab monotherapy in RRMM

- 148 pts treated in the GEN 501 and in the Sirius trials at the dose of 16mg/kg

	N	RR rate
All patients	148	31.1%
Ref to B and L	114	29.8%
Ref to B-L and P	70	27.1%
Ref to B-L and K	49	22.4%



Usmani SZ 2016;128:37

Pom-dex combinations

- + chemotherapy
  - cyclophosphamide
  - bendamustine
- + PI
  - Bortezomib
  - Carfilzomib
  - Ixazomib
- + antibodies
  - Daratumumab
  - Isatuximab
  - Elotuzumab

Pomalidomide Cyclophosphamide dex

Rand: Pom Cy dex vs Pom dex
Pom 4mg/d D1-21 dex 40mg/W
Cyclo 40mg po D1,8 ,15-21

	Pom-dex N=36	Pom-Cy-dex N=34
Len-ref	100%	100%
Bort-ref	78%	71%
Carf- ref	44%	48%
RR	39%	65%
Med PFS	4.4m	9.5 m

Baz RC Blood 2016;27:2561

Phase ½ study
Pom 1-2.5 mg/d D1-21Cyclo and PDN 50 mg every other day

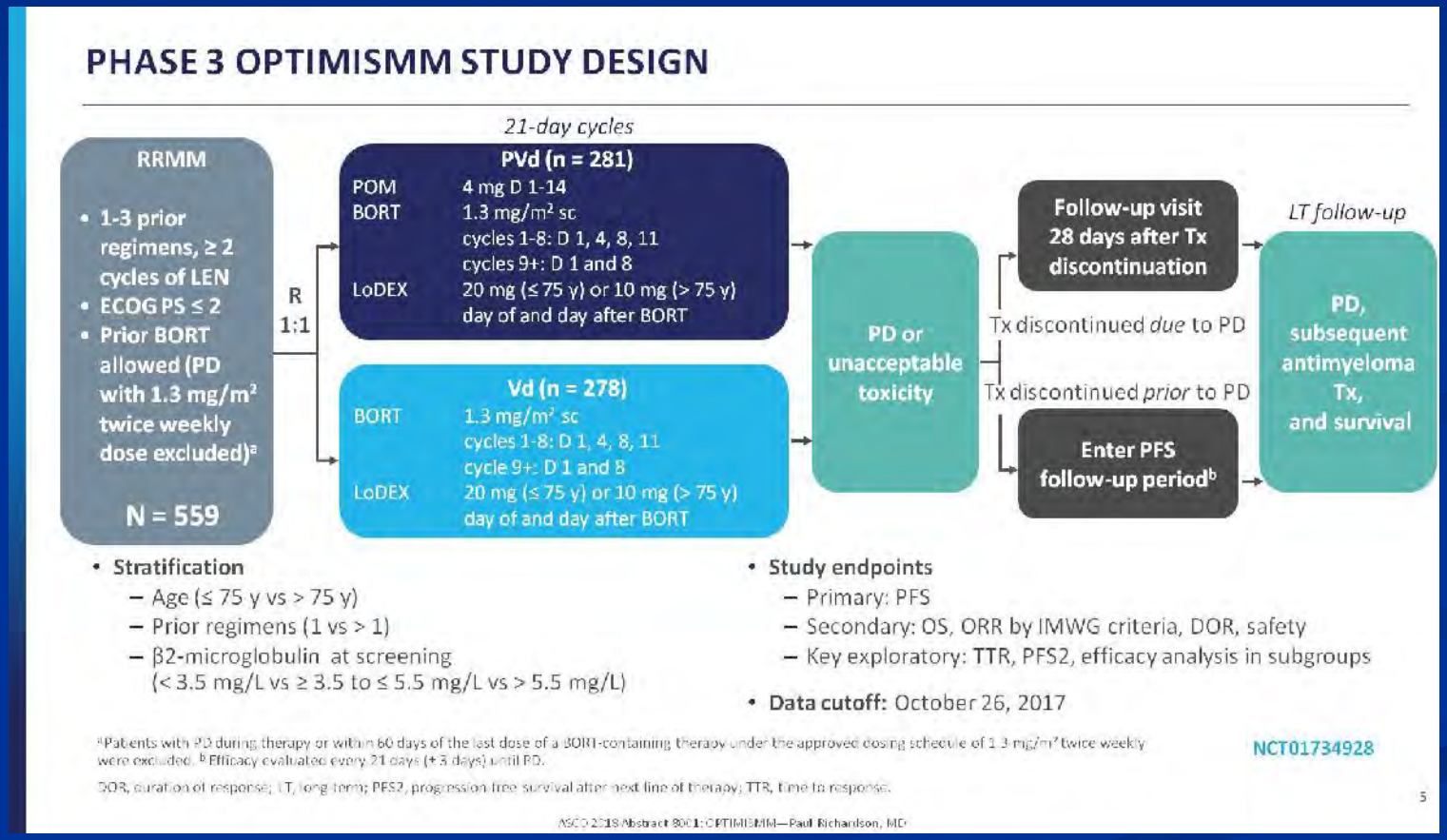
- 69 pts (22 pts ref to L and B)
- MTD Pom 2.5 mg
- At the MTD

	All pts (55)	B and L ref (16)
ORR	51%	50%

Med PFS 10.4m (all pts)

Larocca A Blood 2013;122:2799

Pomalidomide Bortezomib dex



Richardson P ASCO 2018

PRIOR THERAPY (ITT)

- As per protocol, 100% of patients received prior treatment with LEN

Characteristic	PVd (n = 281)	Vd (n = 278)
Median no. of prior lines of therapy (range)	2 (1-3)	2 (1-4)[a]
1 prior line, %	40	41
2 prior lines, %	42	37
≥ 3 prior lines, %	19	21
Prior SCT, %	57	59
Prior LEN, %	100	100
LEN-refractory, %	71	69
Refractory to LEN in last prior regimen, %	63	60
Prior PI, %	75	77
PI-refractory, %	13	13
Prior BORT, %	72	73
BORT-refractory, %	9	12
Refractory to last prior regimen, %	70	66

[a] One patient in the Vd arm received > 3 prior lines of therapy.

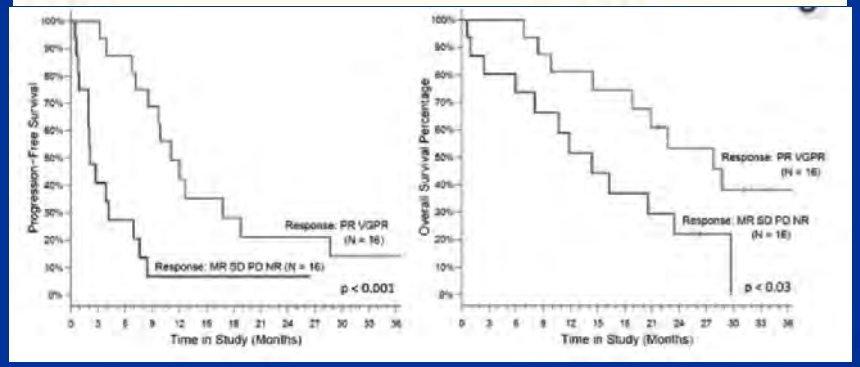
Pomalidomide Carfilzomib dex

Carf 27mg/M2 D1,2;8,9;15,16

Pom 4mg D 1-21Dex 40mg/w

- 32 pts all refractory to L including 30 pts also ref to B

Response category, n (%)	All evaluable patients, N = 32
ORR	16 (50)
VGPR	5 (16)
PR	11 (34)
MR	5 (16)

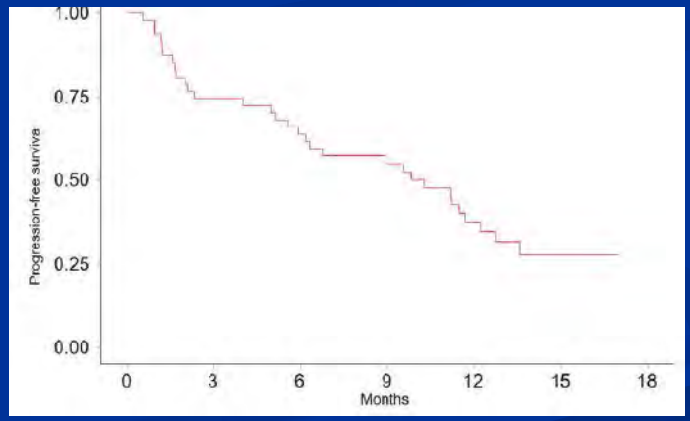


- Med PFS 7.2 m

Phase ½ study Carf weekly

Pom 4mg:d D1-21 Dex 40mg/w

- 57 pts
  MTD Carf 27mg/m2
- In pts refractory to L and B
  71%/ ≥PR
  19% ≥ VGPR



- PFS 10.3 m

Shah JJ Blood 2015;126:2294

S Bringhen Leukemia 2018;32:1803

Pomalidomide Ixazomib Dex

Phase ½ Ixa 3mg or 4mg D1,8,15 28-d cycles

Pomalidomide 4mg D1-21

Dexamethasone (40mg D1,8 15, 22)

- 32 pts

100% Len-ref (but 17 ≤ 15mg/d)

59 % Bort-ref (Double-refractory 59%)

- 4mg recommended Phase 2 dose
- At this dose (25 pts) 48% ≥ PR and 20% VGPR

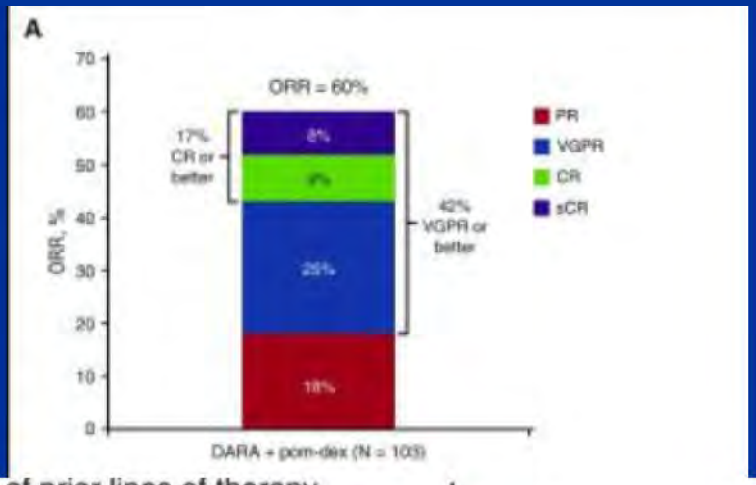
but only 29% for 14 double-refractory pts

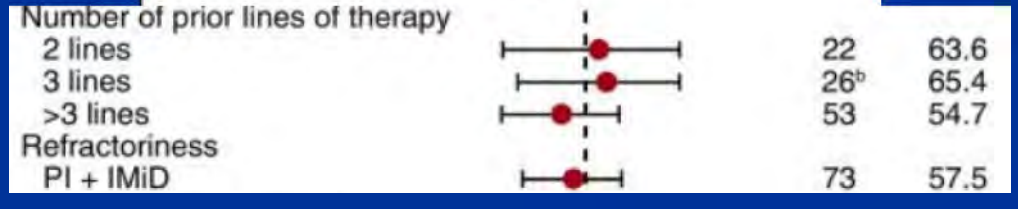
Krishnan A Leukemia 2017 Dec18 online

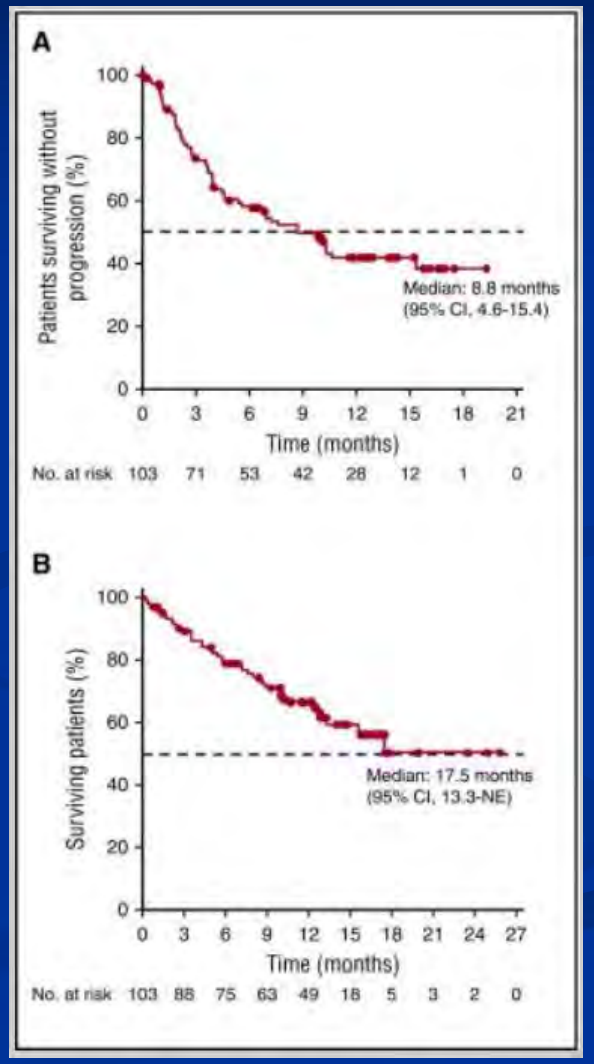
Dara Pom dex

Dara 16-mg/kg
Pom 4mg D1-21
Dex 40mg/W

- 103 Pts Prior lines of therapy Median 3
- 71% refractory to both B and L







Chari A Blood 2017;130:974

Daratumumab-Carfilzomib-dexamethasone

- 85 pts (1-3 lines of Tt including B and L)
- 51 L-ref (60%)
- 25 PI and IMID ref (29%)

Dosing schedule (28-day cycles)

DARA:

- **Split first dose[a]: 8 mg/kg Days 1-2 of Cycle 1**
- Single first dose: 16 mg/kg on C1D1
- 16 mg/kg IV QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter until PD

Carfilzomib[b]:

- 20 mg/m^2 IV Cycle 1 Day 1
- Escalated to 70 mg/m^2 Cycle 1 Day 8+; **weekly (Days 1, 8, 15)** until PD

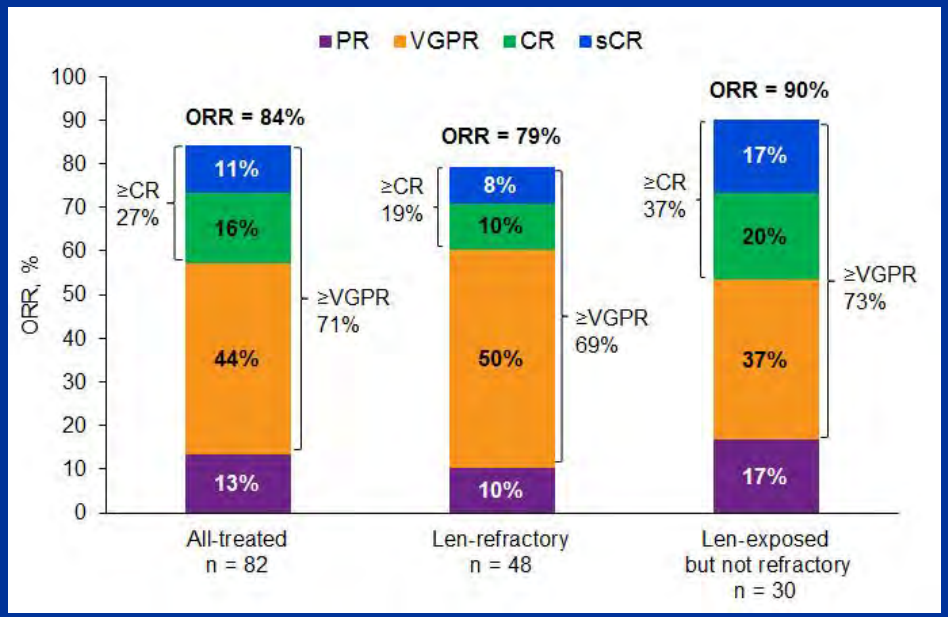
Dexamethasone:

- 40 mg/week (Days 1, 8, 15, 22) IV or PO until PD

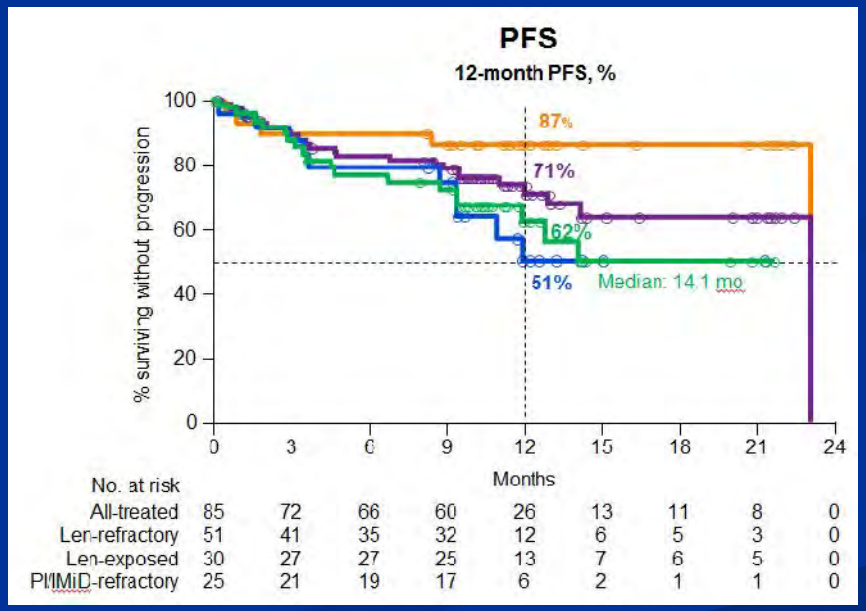
Moreau P ESH 2018

Dara-Kd
Preliminary results (12months f-up)

RR

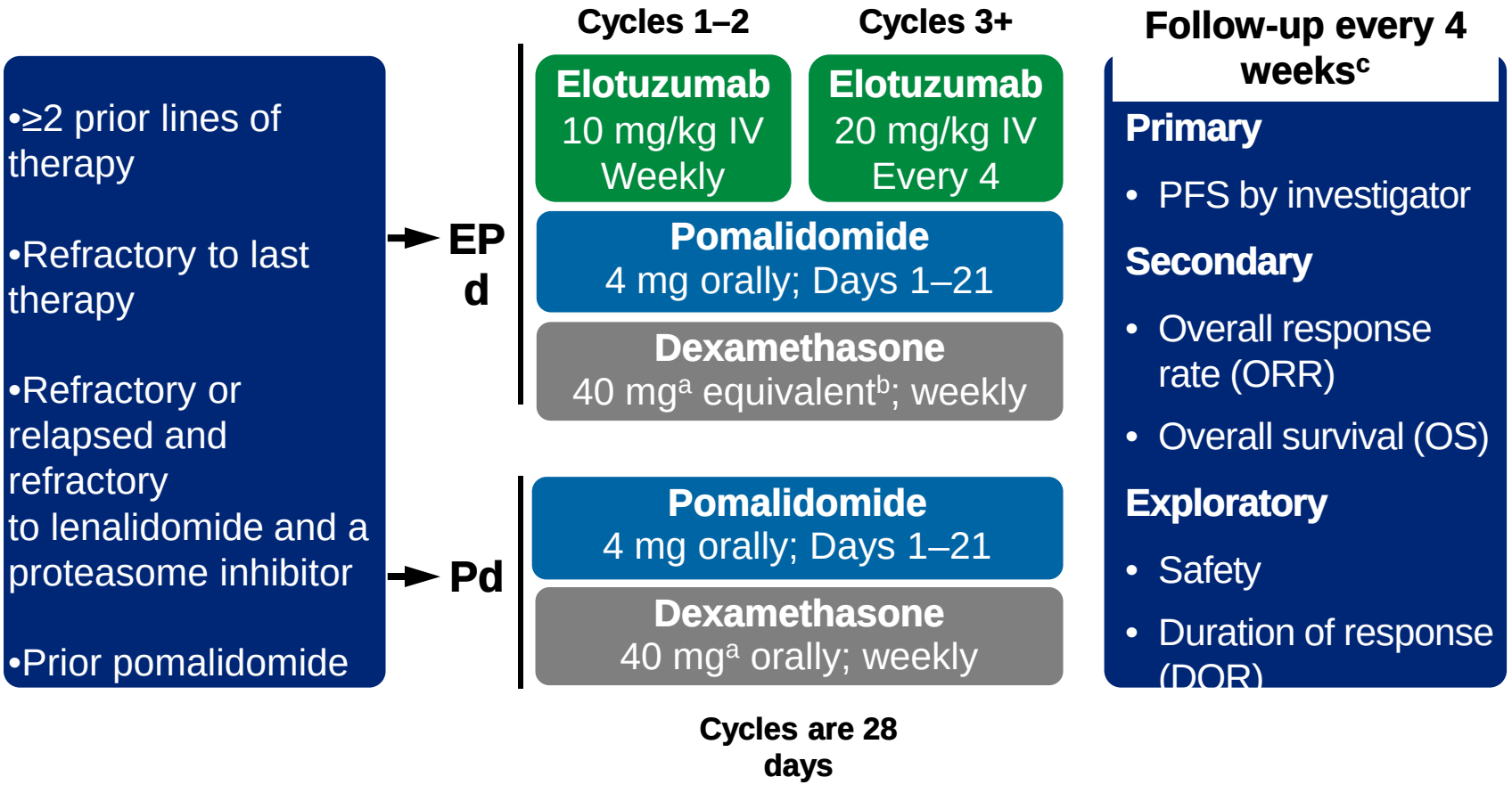


PFS



ELOQUENT-3 Study Design

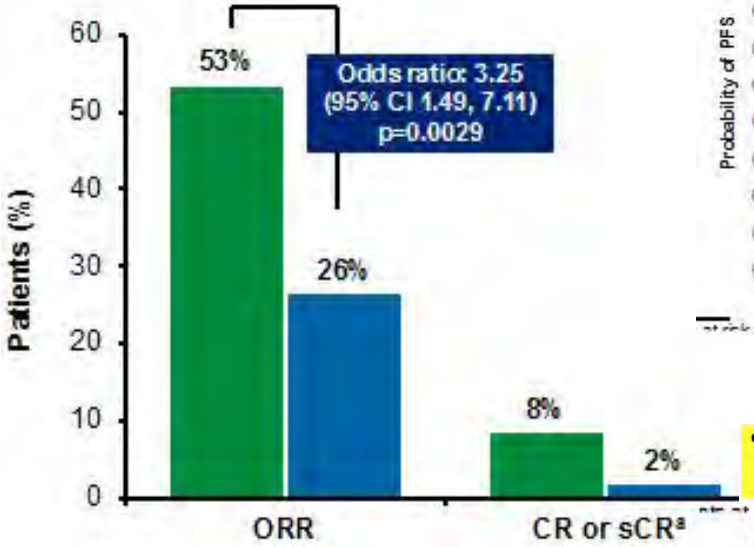
An international, open-label, randomized, phase 2 trial (NCT02654132), with a 2-sided ~=0.2 and 85% power to detect a true HR of 0.57

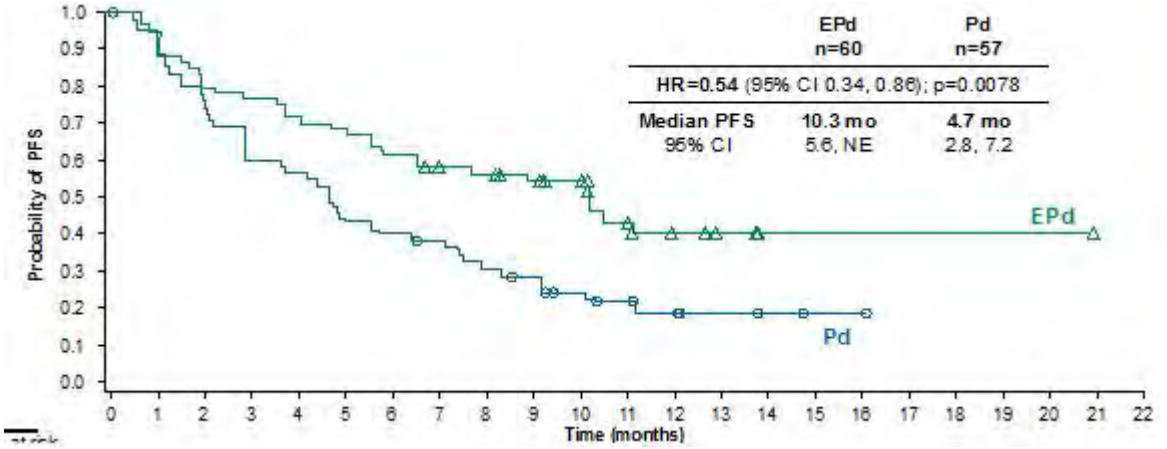


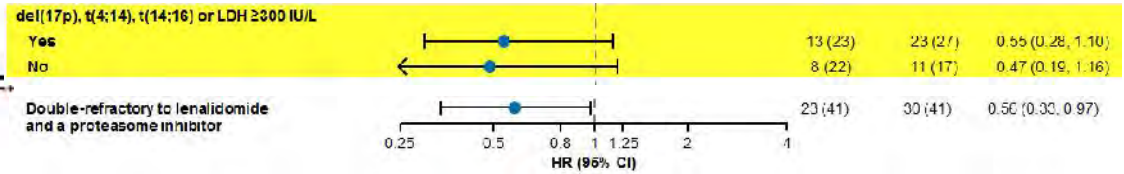
[a]20 mg in patients aged >75 years [b]Dexamethasone was split between oral (28 or 8 mg in patients aged ≤75 or >75 years) and IV (8 mg) doses on days with elotuzumab
[c]Follow-up continued until disease progression; follow-up for survival occurred at least every 12 weeks
HR, hazard ratio

ELOQUENT-3 Results

Characteristic	EPd (n=60)	Pd (n=57)
Age, median (range), years	69 (43–81)	66 (36–81)
Prior lines of therapy, median (range)	3 (2–8)	3 (2–8)
Refractory to lenalidomide, n (%)	54 (90)	48 (84)
Refractory to a proteasome inhibitor, n (%)	47 (78)	47 (82)
Refractory to lenalidomide and a proteasome inhibitor, n (%)	41 (68)	41 (72)







Dimopoulos MA EHA 2018

Triple combinations with Approved drugs in Dual-refractory MM

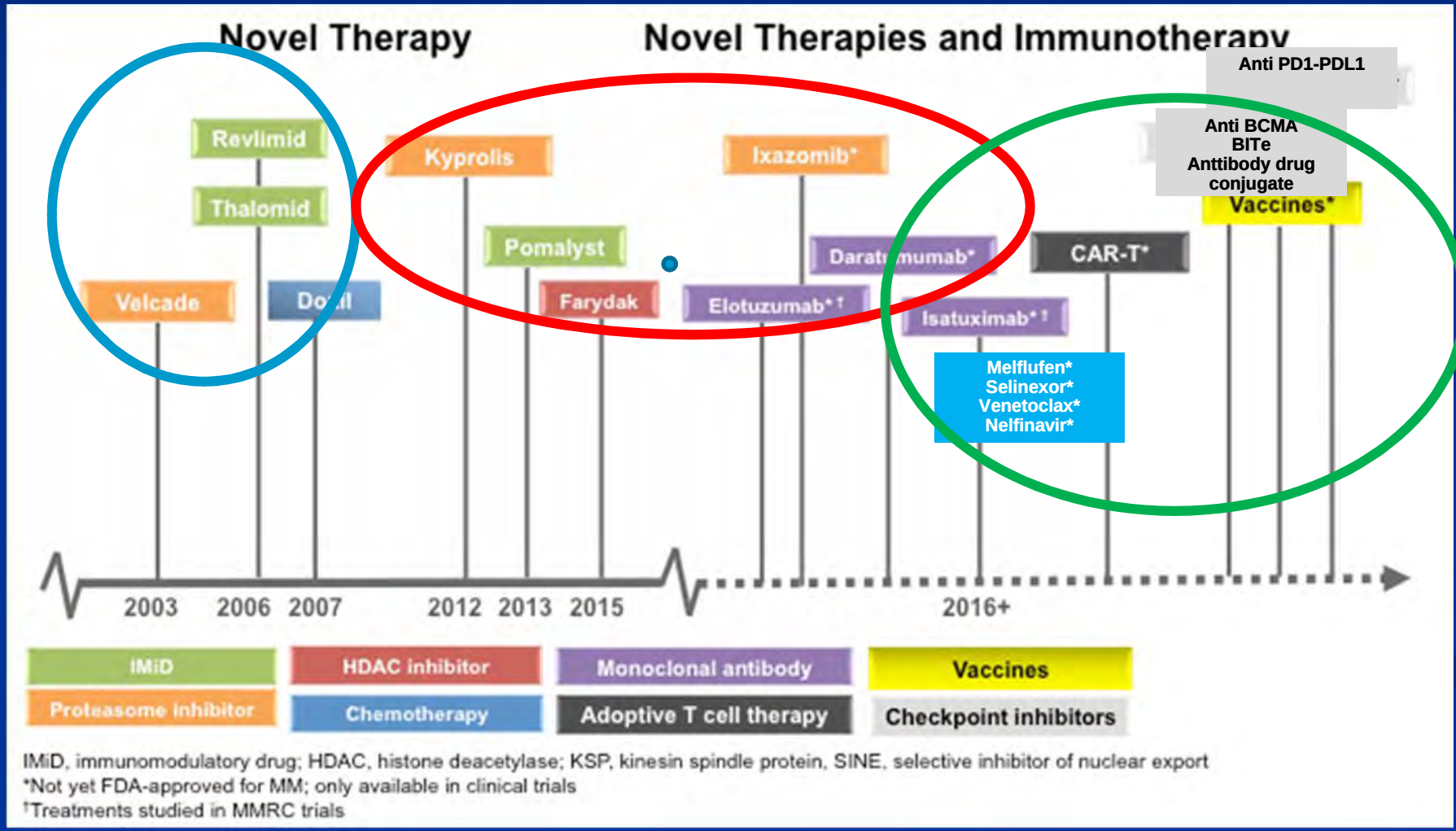
	Pom-dex	Pom-Cd	Pom-Kd	Dara-Pd
≥ PR	20-35%	50%	50%	60%
≥ VGPR	7-8%		16%	17%
Med PFS	4m	9m ?	7m	8m

- With **Dara K-dex and Elo Pom-dex**

  median PFS of 10 to 12 m ?

- The choice depends on other relapse/patient characteristics **but mostly on drug availability**

Treatment of relapsed MM
What are the newer agents?



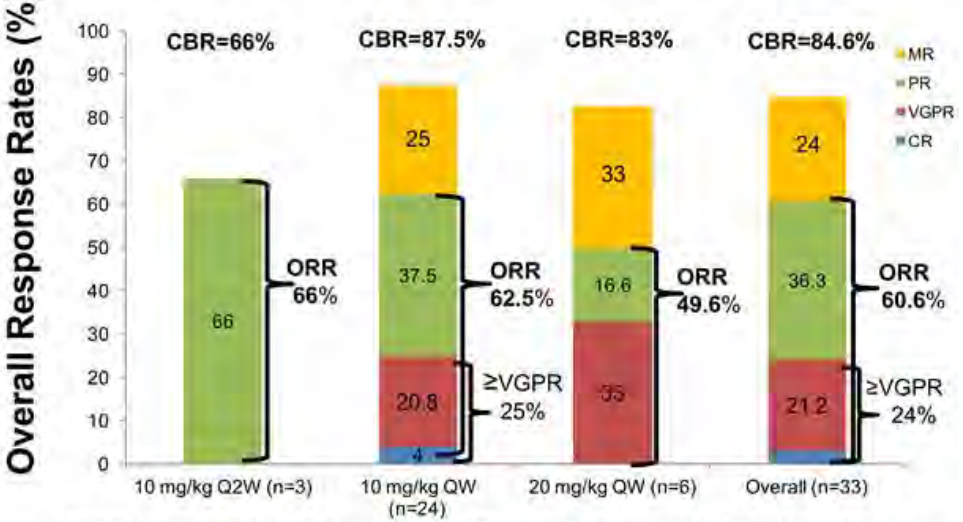
IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
*Not yet FDA-approved for MM; only available in clinical trials
†Treatments studied in MMRC trials

Isatuximab Carfilzomib dex

- Phase 1b
- Increasing doses of Isa
- Car 27mg/m2
- 33 pts

Refractory disease at enrollment, %	
Refractory to IMiD	91%
Len (%)	82%
Pom (%)	52%
Refractory to Proteasome Inh (%)	85%
Bor/Ixaz (%)	64%
CFL (%)	30%
Double refractory (%)	79%

- Median PFS 10.3m

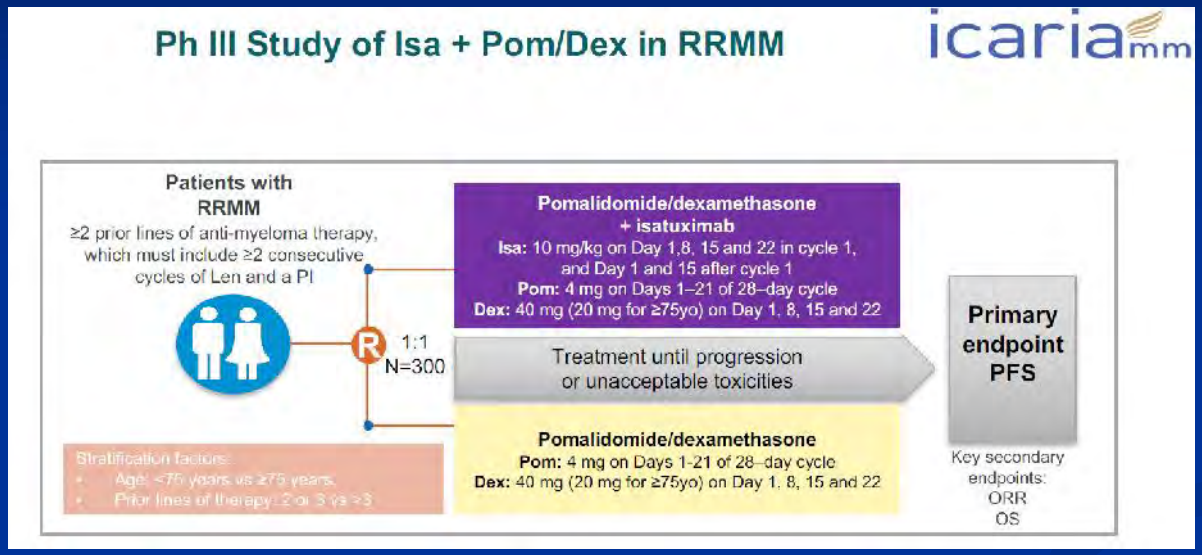


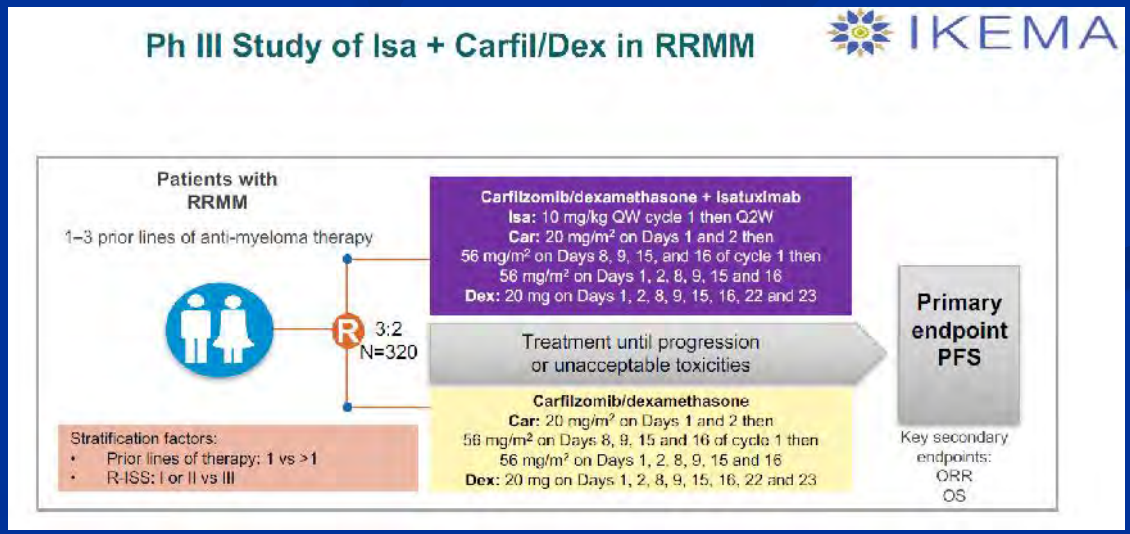
VGPR= very good partial response, PR=partial response, MR= minimal response
ORR= overall response rate, CBR=clinical benefit response

- ORR = 60.6%, CBR 84.6%; N= 33 - all patients
- ORR = 58% in double refractory; N= 26
- ORR = 71% in high risk cytogenetics/fish; N= 7
- ORR = 50% in CFL refractory; N= 10

Chari A ASCO 2018 Abs

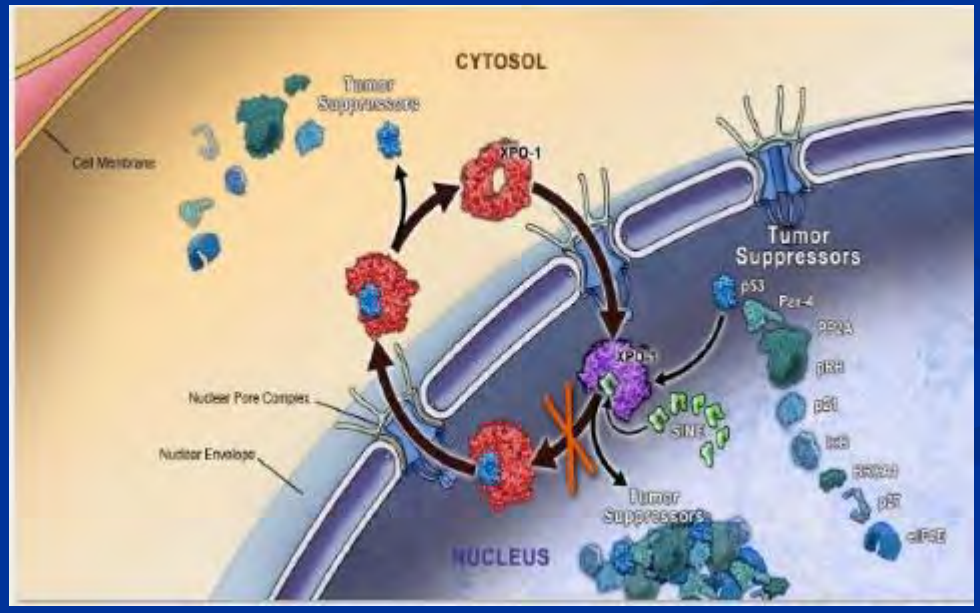
Randomized Phase III studies with Isatuximab in RRMM





SELINEXOR

- Selinexor is the first-in-class of the Selective Inhibitor of Nuclear Export (SINE) which are XPO1- inhibitors
- XPO1 transport tumor-suppressor genes from the nucleus to the cytoplasm



SELINEXOR
INITIAL RESULTS

Sd

Sel 80 mg po D 1,3,8,9,15,17

Dex 20mg same days

28-D cycles

- 79 pts
- med number of prior lines 7
- HR cytogenetics 50%

	Quad Ref (B,K,L,P)	Penta Ref (+Dara)
ORR	21%	20%

- Median duration of response 5m

Vogl JCO 2018;36:859

Phase 1/2 SVd

Sel 100 mg po W

Bort 1.3 mg/m2 W

Dex 40 mg/W

- 40 pts including 19 pts refractory to PI and IMIds

In PI and IMID ref pts
43% ORR 21%≥ VGPR

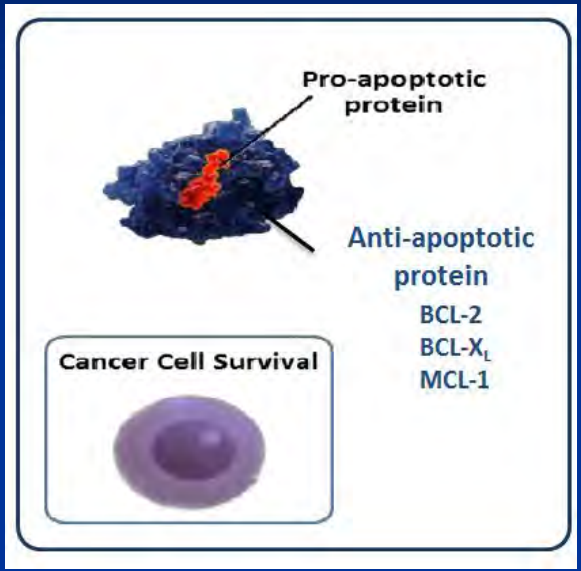
Bahlis NJ Blood 2018, in press

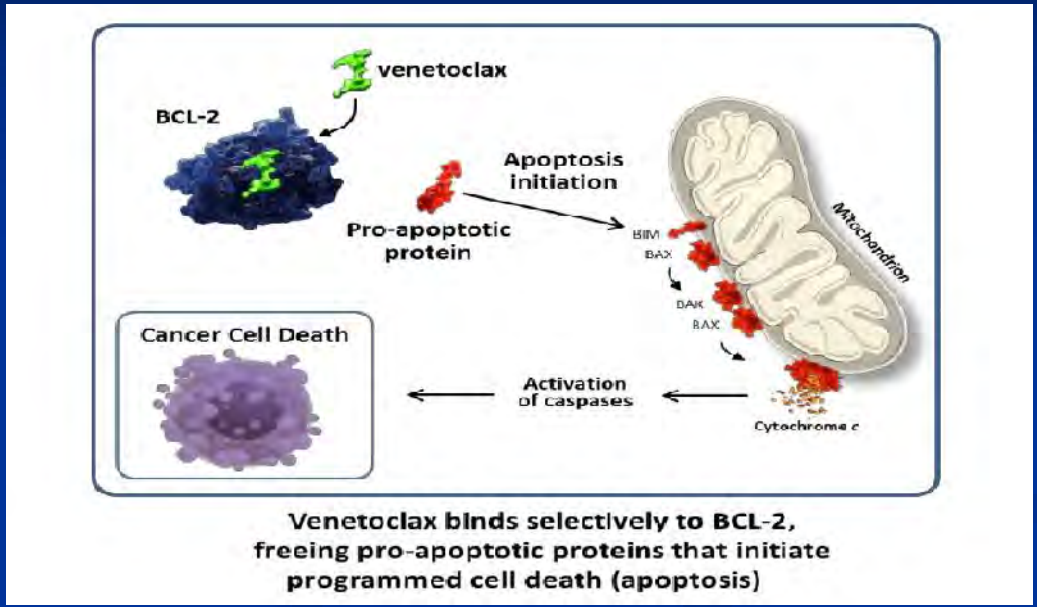
Selinexor Toxicity

	Sd		SVd	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Nausea	66%	8%	57%	5%
Vomiting	40%	4%	28%	2%
Diarrhea	38%	5%	36%	7%
Fatigue	48%	15%	45 %	14%
Appetite	47%	3%	57%	2%
Thrombo Cytopenia	14%	59%	4%	46%
StopTreatment Due to AE		18%		19%

Venetoclax

- Targets MM with high levels of BCL-2





Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis)

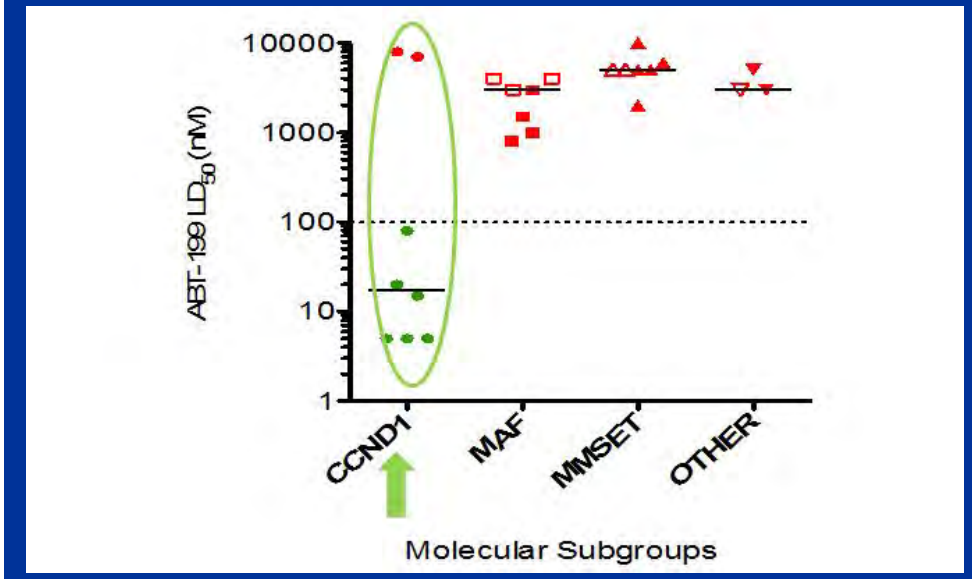
- Sensitivity is restricted to t(11.14)
- However rationale for combining Venetoclax and PI (which target MCL-1)
- Encouraging results in combination with Bort and Carf

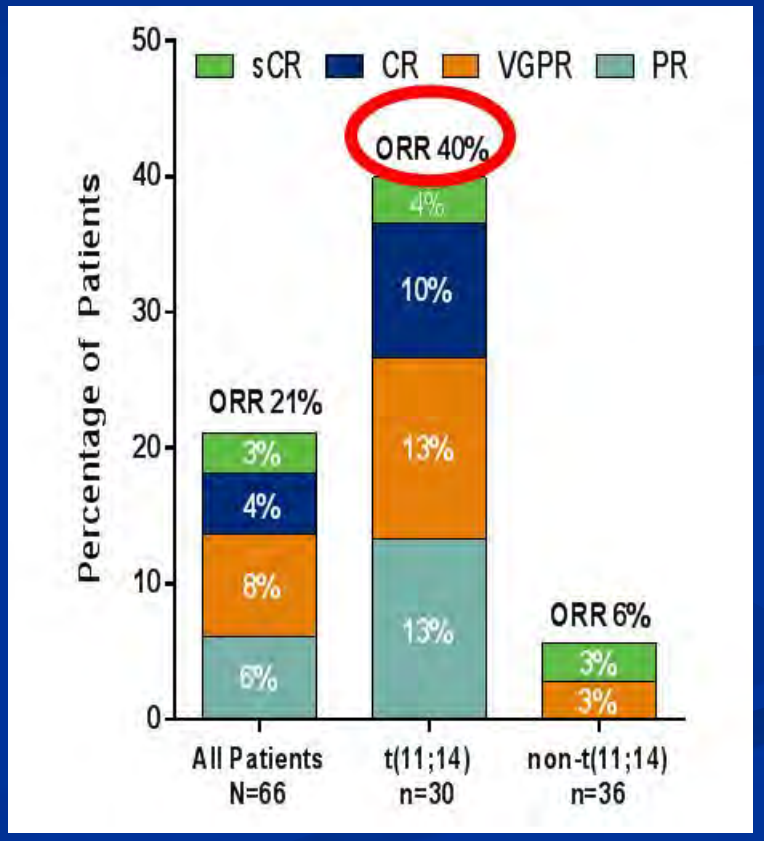
  in Bort-ref and double-ref

Moreau P Blood 2017;130:239 Costa L ASCO 2018

Venetoclax in t(11;14) MM

The response rate is the same in B-L refractory patients harboring t(11.14)

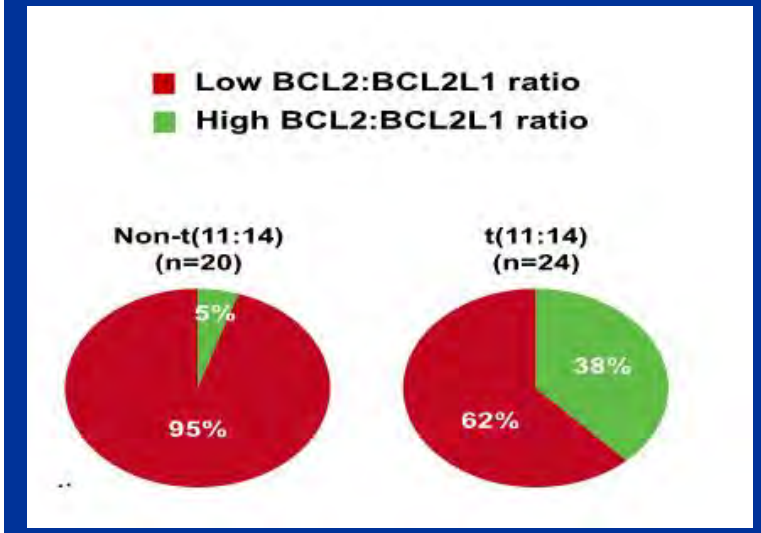


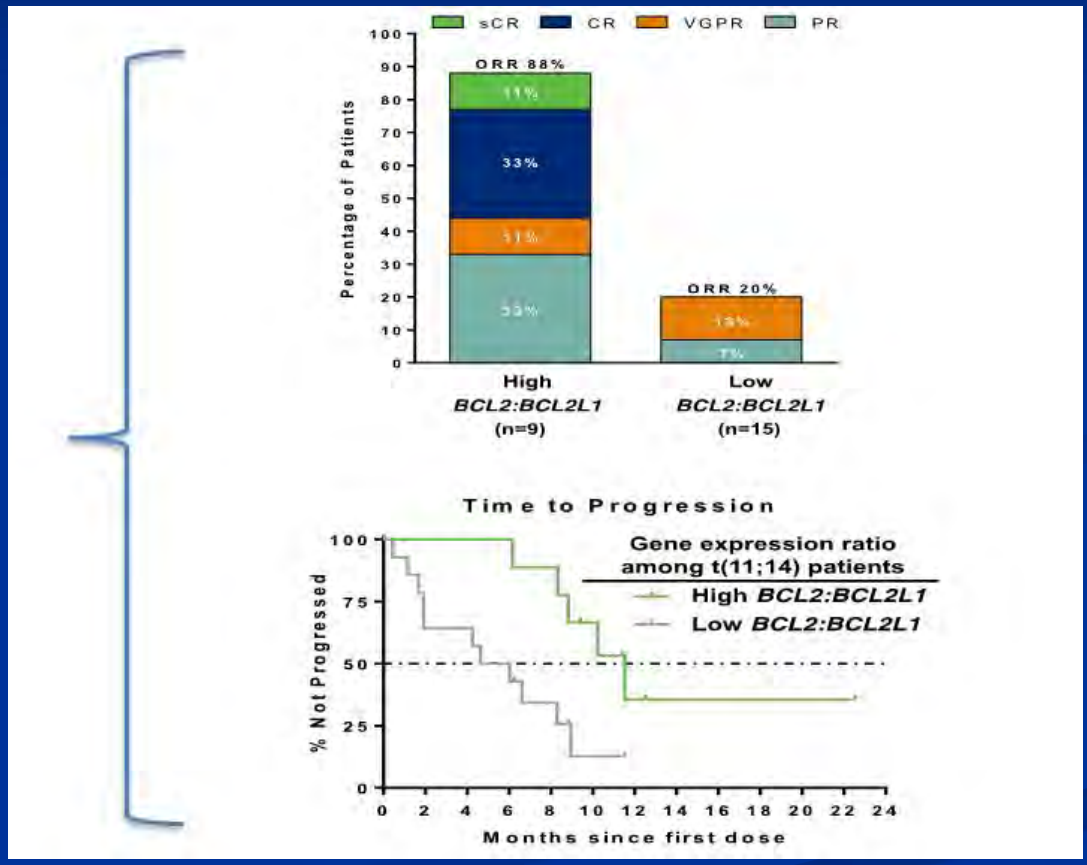


Touzeau Leukemia 2014;28:210

Kumar S Blood 2017;130:2401

Efficacy of Venetoclax is related to the BCL-2/BCL2L1 ratio

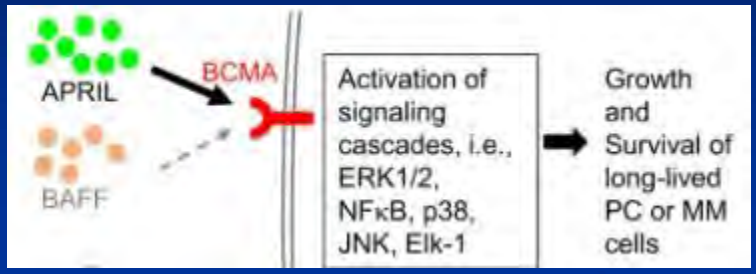




Kumar S Blood 2018

Targeting BCMA in MM

- B-cell Maturation antigen
- Is expressed on normal and MM PC



- New anti-BCMA Immunotherapies
  - Bispecific T-cell engagers (BiTE)
  - Antibody Drug Conjugate

First in Human Study with GSK2857916, an Antibody Drug Conjugated to Microtubule–Disrupting Agent Directed Against B–Cell Maturation Antigen (BCMA) in Patients with Relapsed/Refractory Multiple Myeloma (MM): Results from Study BMA117159 Part 1 Dose Escalation

Adam D. Cohen, Rakesh Popat, Suzanne Trudel, Paul G Richardson, Ed N. Libby III, Nikoletta Lendvai, Larry D. Anderson Jr., Heather J. Sutherland, Stephen DeWall, Catherine E Ellis, Zangdong He, Jolly Mazumdar, Catherine Wang, Joanna B. Opalinska, and Peter M. Voorhees

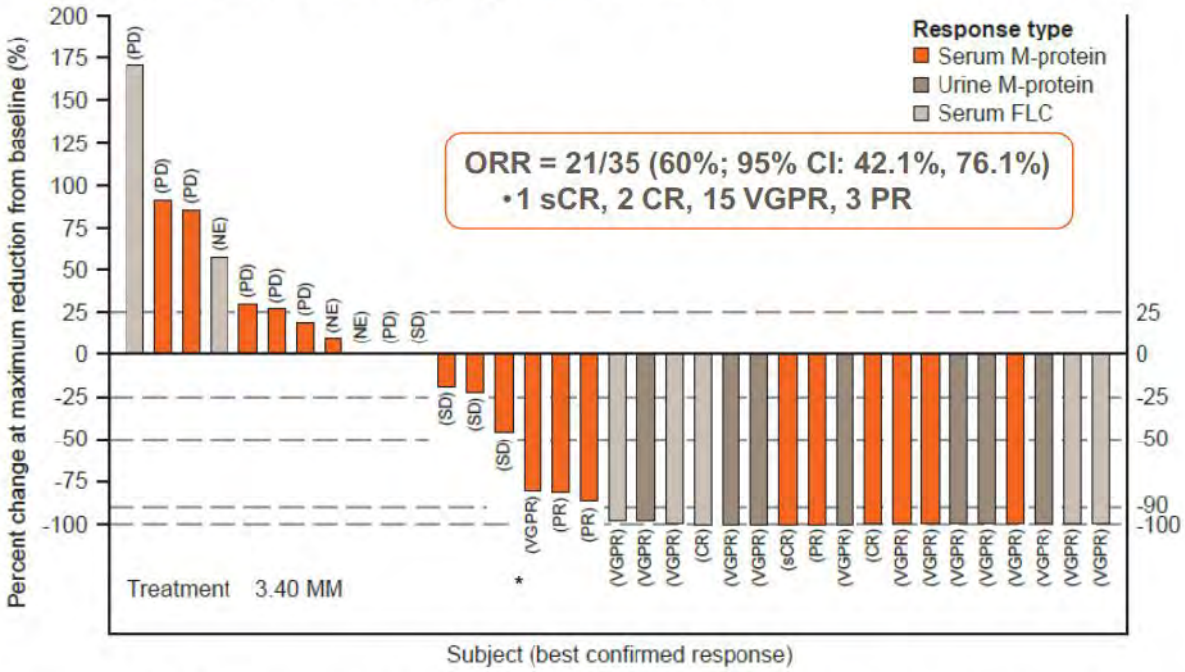
Blood 2016 128:1148;

  - Anti BCMA CAR T-cells

Anti BCMA Antibody Drug Conjugate

GSK-ADC: DREAMM1 Phase 2 Part 2:

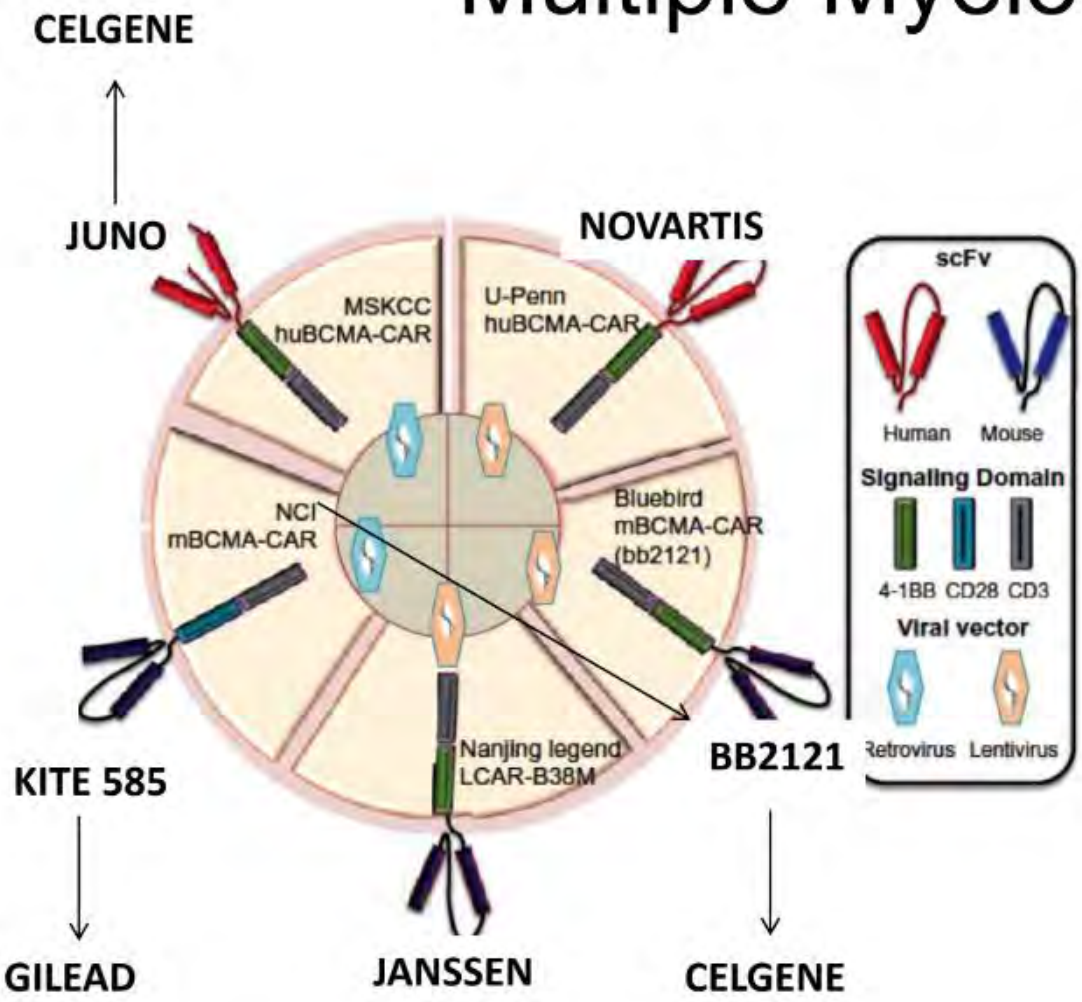
- Results at 3.4 mg/kg IV Q3 Wk



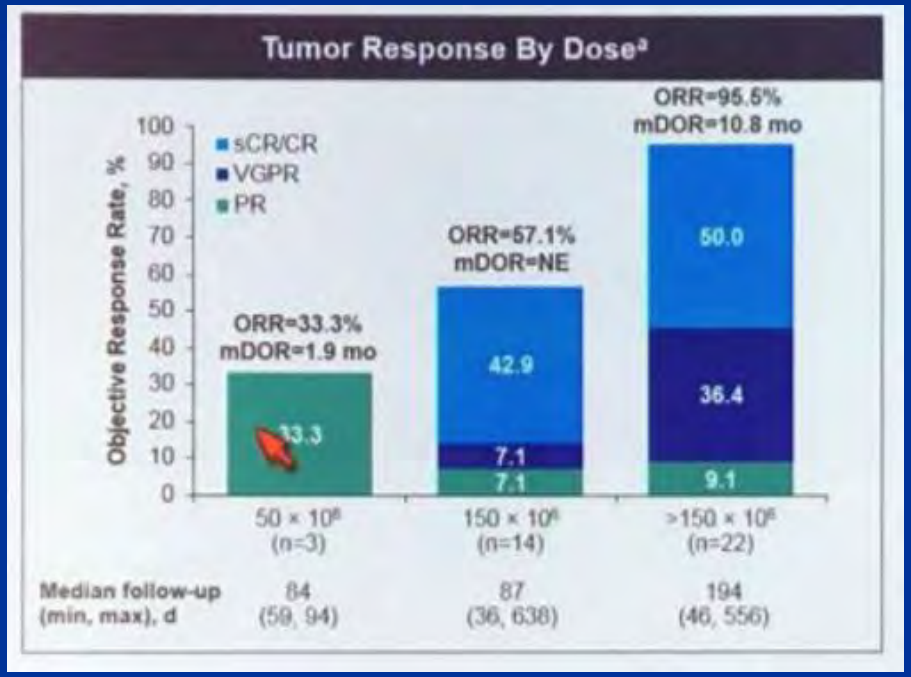
89% Double refractory; 34% double + Dara refractory ; Cyto High-risk 29%

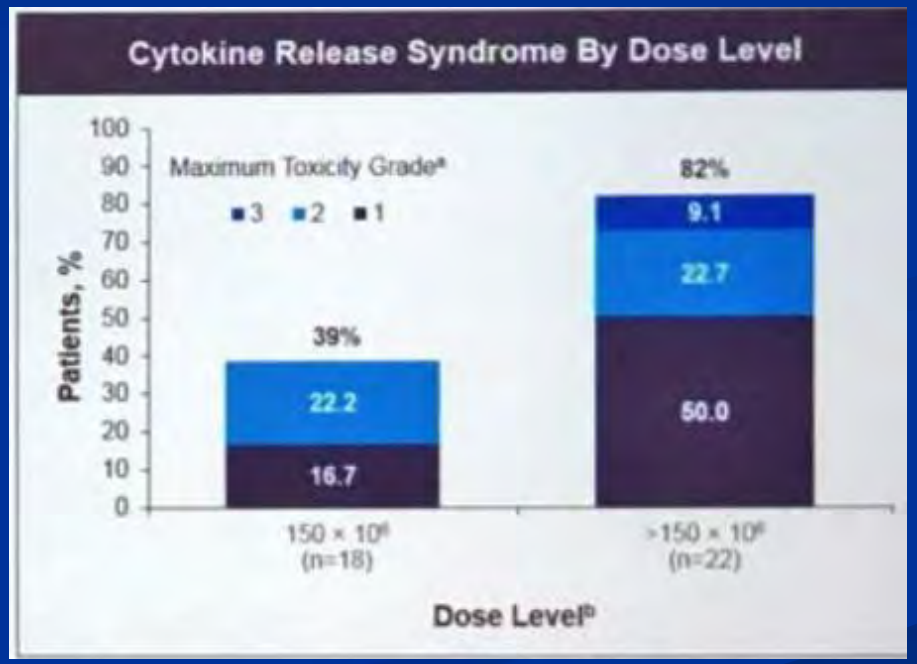
Trudel et al. Ash 2017

CAR T Cell BCMA Multiple Myeloma



bb2121 Anti-BCMA CAR T Cell Therapy in Patients With Relapsed/Refractory Multiple Myeloma: Updated Results From a Multicenter Phase I Study

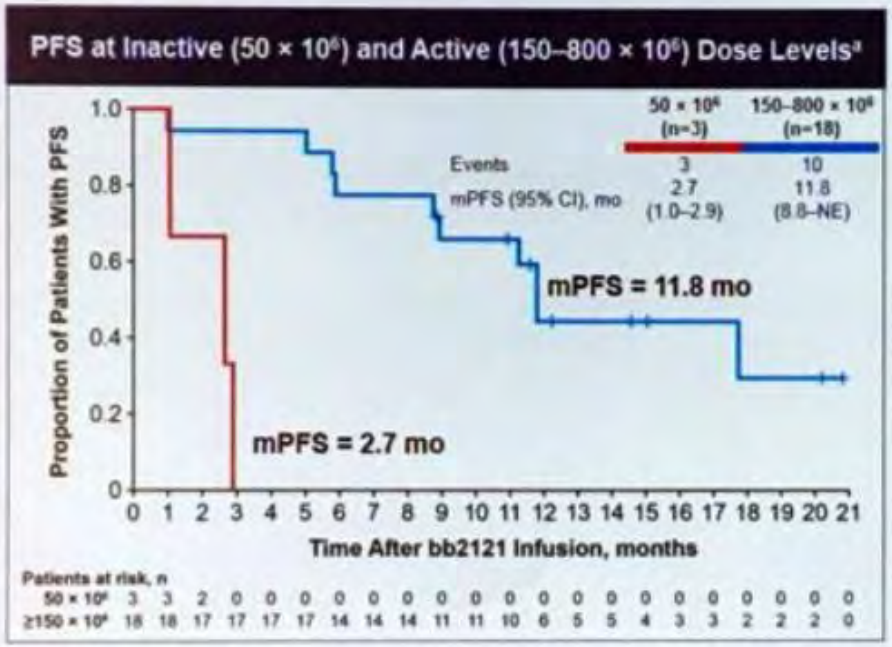


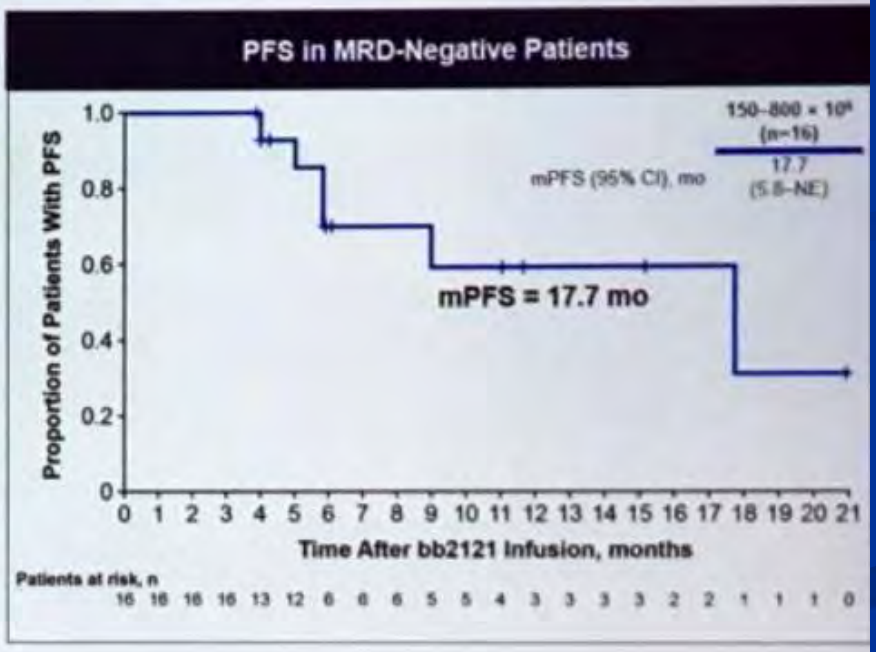


N Raje ASCO 2018

PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative





Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. [a]PFS in dose escalation cohort.

N Raje ASCO 2018

Conclusions

- MM refractory to both Len and Bort occur earlier in the course of the disease
- Pomalidomide and Daratumumab-based combinations offer new possibilities
- The incidence of MM refractory to all IMIDs and PIs (quadri-refractory :Len,Bort, Pom, Carf) and even of penta-refractory (+ Dara) is increasing
- New approaches such as Selinexor, Venetoclax and anti-BCMA immunotherapy including CAR-T cells are being rapidly developed

TEL-AVIV SOURASKY
MEDICAL CENTER
MEDICAL EXCELLENCE AND COMPASSIONATE

Management of Side Effects

IMS Athens October 2018

Irit Avivi , Tel Aviv Medical center, TA

Agenda

Importance of recognizing and managing adverse events

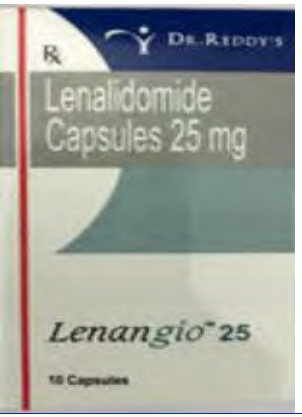
Therapy related side effects

Management of therapy related adverse events

Introduction

During the last years, options for multiple myeloma have increased substantially , including IMiDs, PIs & MoABs.

The new drugs differ not only in their mode of action, but also in their toxicity profile, from previous standard treatments.



NINLARO
ixazomib capsule

Adverse events profile

How does it affect our clinical decisions?

The treatment of Myeloma has currently become a “ continues, non-ending therapy”, a policy which requires the achievement of high tolerance to therapy

Many drugs are oral and high tolerability is associated with better compliance ,which results in improved outcome

Recognition of AEs helps in choosing the right treatment to the right patient

Recognition and early detection of AEs, would translate into an improved outcome

Adverse Events

Case 1 (IMiDs)

A 55 yr old lady.

Prior Medical history

Obesity,

Breast Ca , 4 yrs earlier, treated with lumpectomy + radiotherapy and is currently receiving tamoxifen.

Treatment plan

VRD followed by ASCT and Lenalidomide maintenance.

IMiDs

Lenalidomide

“Real life Practice”
What do you tell your patient?

Lenalidomide

Less likely then thalidomide to cause Neuropathy, constipation and somnolence

First Trial

Grade ≥3 neutropenia - 26% with Rd18 ; 28% with continuous Rd

Grade ≥3 thrombocytopenia -8% of patients in either arm.

Non-hematological grade ≥3 AEs with Rd18:

Infections (22%),

Fatigue (9%),

Cardiac disorders (7%),

VTE (6%)

Facon T , Blood 2018

How are you going to thrombo-prophylax this patient?

A 65 year old lady.

Prior Medical history of breast Ca (currently in remission) , Obesity.

Planned for VRD .

What would be your thromboprophlaxis ?

Thromboprophylactic options

LMWH - 10%

LMWH during the first few cycles (disease control), followed by Aspirin -30%

Aspirin- 60%

Thrombosis prophylaxis (Palumbo A, 2008 ; Trepos 2017)

Thromboembolic events occur more frequently during the initial phase of treatment, less commonly in well-controlled disease or at relapse.

Risk Factor

Patient Related

- Obesity
- S/P VTE
- Central Catheter or pacemaker
- Comorbidities: diabetes, infections, cardiac diseases, CRD, immobilization
- Inherited thrombophilia

Myeloma related

- Uncontrolled disease

Drug Related

- EPO, IMiDs, Doxo, MultiChemo,

Patient and MM Risk Factors

1 RF- Aspirin (81-325 mg/d)

≥2 RF – LMWH (40/d; CCT>30ml/min)

Drug Related

LMWH (CCT>30ml/min)/ warfarin

New oral anticoagulants (NOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban, have been shown to be useful for initial and extended VTE treatment [48].

Case 1 (Cont)

The patient was treated with RVD followed by ASCT, achieving VGPR.

She is considered now for lenalidomide maintenance therapy.

She is in complete remission of her breast CA for the last 4 years

Would you give her lenalidomide maintenance?

Yes -30%
No –70%

Lenalidomide- Related SPMs

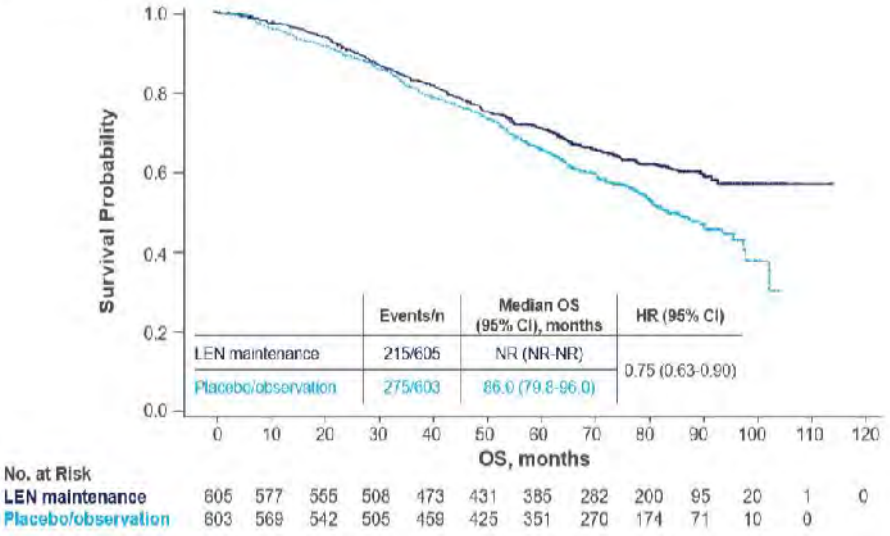
- An increase of hematologic plus solid tumor SPMs, notably AML and MDS, have been observed
- A higher incidence of invasive SPM was not observed with LEN treatment until PD vs fixed-duration LEN

SPMs, %	NDMM			Following HDM/ASCT		RRMM	
	LEN + MEL	MEL	LEN + DEX	LEN Maint	Placebo	LEN + DEX	DEX
Hematologic[a]	5.3	1.3	—	7.5	3.3	—	—
AML and MDS	—	—	0.4	—	—	—	—
Hematologic + solid tumors[b]	—	—	—	14.9	8.8	2.3	0.6
Nonmelanoma skin cancer[c]	—	—	—	3.9	2.6	3.1	0.6

SPMs following HD Melphalan & transplantation

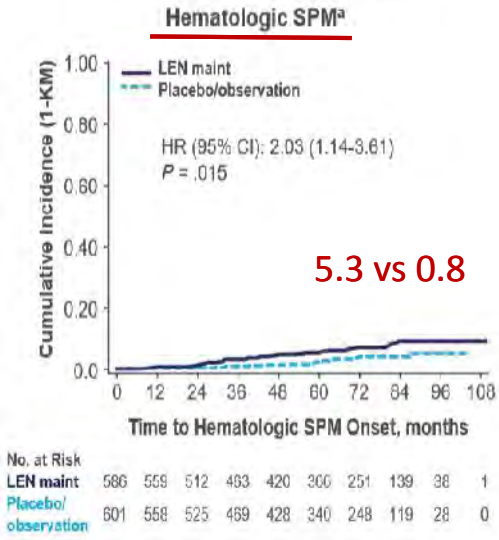
LEN MAINTENANCE AFTER ASCT IN NDMM
META-ANALYSIS: OS (MEDIAN FOLLOW-UP, 79.5 MONTHS)

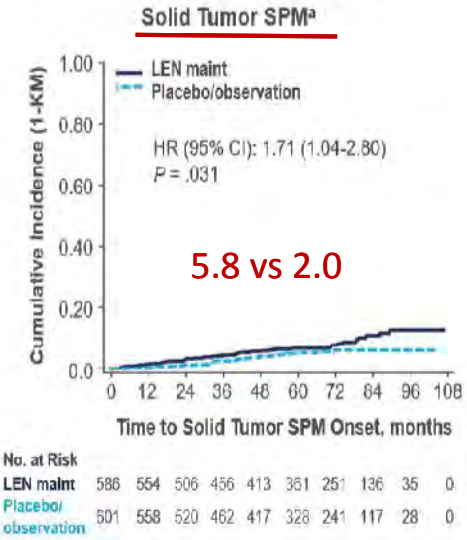
- LEN maintenance reduced the risk of death by 25% vs placebo/observation
- The 7-year survival rate was 62% with LEN maintenance and 50% with placebo/observation



LEN MAINTENANCE AFTER ASCT IN NDMM
META-ANALYSIS: CUMULATIVE INCIDENCE OF SPM

- Consistent with previous CALGB and IFM reports, a higher frequency of SPMs was seen with LEN maintenance vs placebo/observation
  - Before PD, frequencies of hematologic and solid tumor SPMs, respectively, were 5.3% and 5.8% with LEN maintenance and 0.8% and 2.0% with placebo/observation

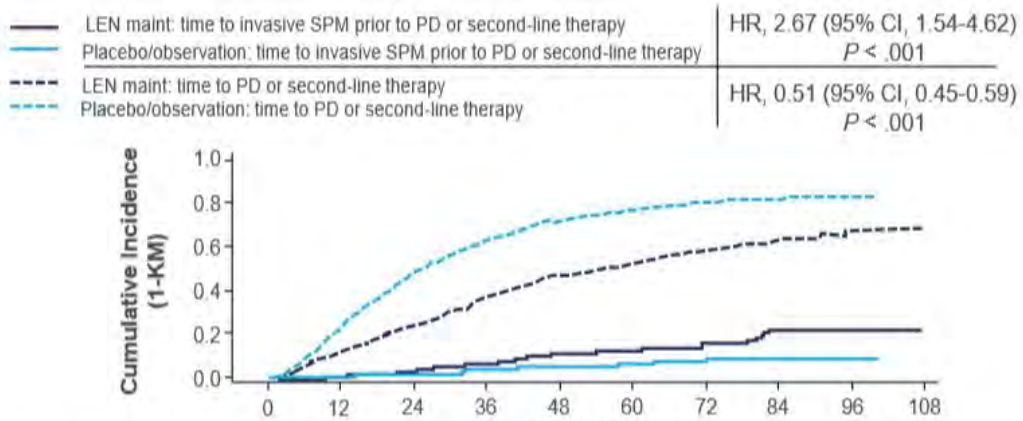




Attal, M JCO 2017; Attal *NEJM* 2012; McCarthy *NEJM* 2012; Palumbo *NEJM* 2014

LEN MAINTENANCE AFTER ASCT IN NDMM
META-ANALYSIS: SECOND PRIMARY MALIGNANCIES

- Time to PD or second-line therapy was longer with LEN maintenance vs placebo/observation
- The risk of developing PD was higher than the risk of developing an invasive SPM in both groups



No. at Risk										
LEN maint: time to invasive SPM prior to PD or second-line therapy	586	490	403	314	245	196	125	65	12	0
Placebo/observation: time to invasive SPM prior to PD or second-line therapy	601	434	282	195	142	98	59	31	5	0
LEN maint: time to PD or second-line therapy	586	498	414	335	268	219	144	79	15	0
Placebo/observation: time to PD or second-line therapy	601	437	284	200	148	104	60	31	5	0

Attal, M JCO 2017; Attal *NEJM* 2012; McCarthy *NEJM* 2012; Palumbo *NEJM* 2014

Lenalidomid amd SPM - Unsorted Questions

No data regarding the risk of recurrence of prior malignancy in receiving lenalidomide

No data on risk of developing a cancer in a patients with a

No guidelines how to manage a patient that was diagnosed with cancer while being treated with lenalidomide

Case 1, (Continue)

The patient was treated with lenalidomide maintenance therapy, 10 mg/day .

She felt very well, with almost no side effects for almost 24 months.

However, she started to suffer from “diarrhea attacks” which significant impaired her quality of life.

Diarrhea

- Diarrhea is most frequently observed with bortezomib , ixazomib and lenalidomide.

- Diarrhea in general was rare in patients exposed to C-Rd (4%) or Rd18 (3%). (Facon T , Blood 2018).

- However, long-term therapy with lenalidomide may induce a specific form of diarrhea:

  Bile salt malabsorption syndrome,
  resulting from damage of the intestinal mucosa due to increased accumulation of bile acids in the small bowel [Pawlyn C, Blood 2014].

Diarrhea – Diagnosis and Management

Stool cultures + C Diff, ruling out infection

Diagnosis of bile salt malabsorption syndrome can be established by non-invasive selenium homocholic acid taurine (SeHCAT) scanning or supported by an improvement to reatment with bile acid binders such as colesevelam (Westergaad H, Gastroentrol 2007).

Treatment of bile salt malabsorption syndrome :
Reduced fat intake diet (<20% of calories) and/or bile acid sequestrant, (colesevelam, up to 6×625mg in split doses with food (Westergaad H, Gastroentrol 2007).

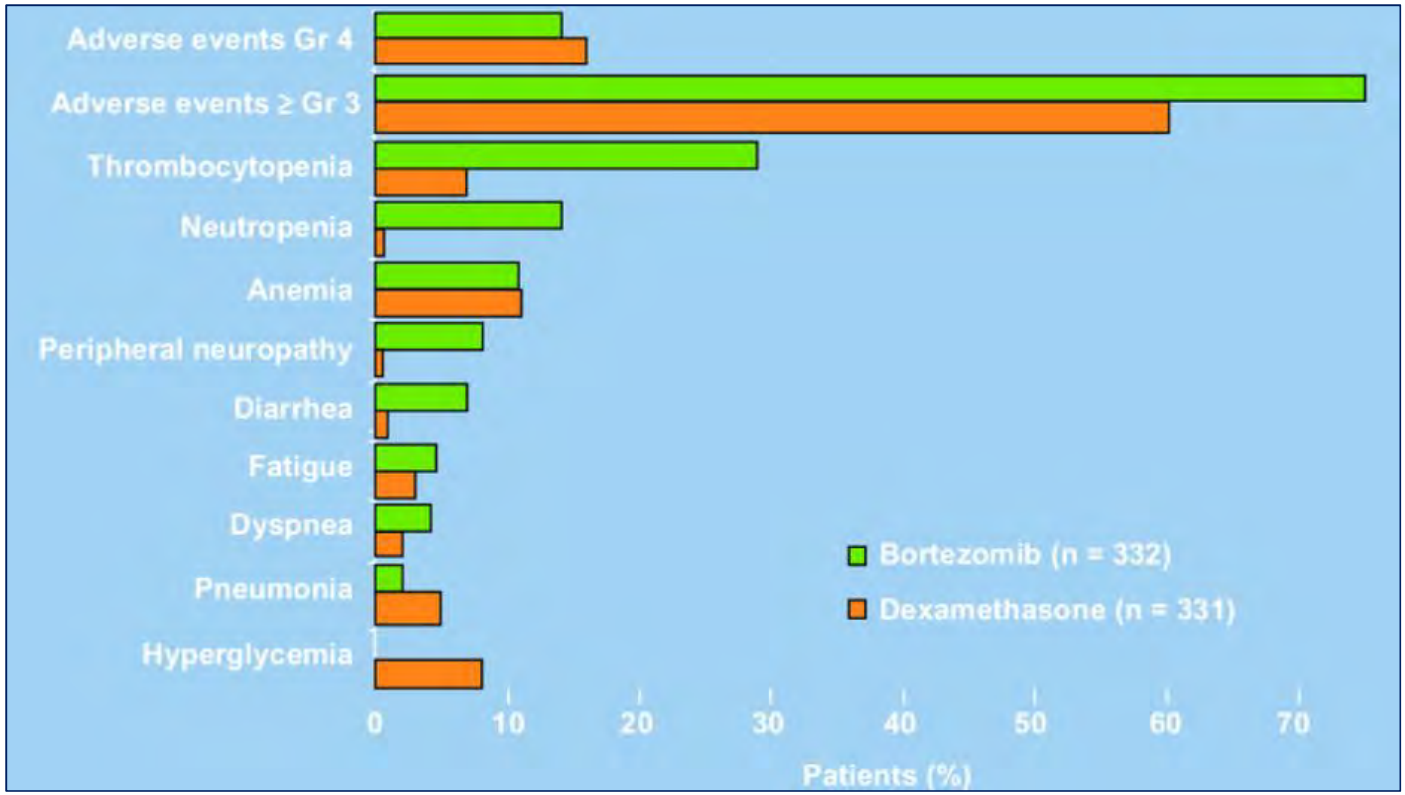
Supportive:
Active opioids, such as loperamide, deodorized tincture of opium, and a combination of diphenoxylate plus atropine (Andreyev HJ Gut 2012; Benson AB, JCO 2004).

Case 2

A 73 yr old man. Prior medical history of NIDDM, HT, IHD.
Recently diagnosed with MM, planned for VCD

"Real life Practice": What do you tell patients?

Bortezomib; Grade 3-4 AEs



APEX trial, Richardson P, 2005

Case 2 cont.

The patient has already completed 3 cycles of VCD , achieving a VGPR.

However, he is currently complaining on bilateral eye swelling and discomfort

In addition, he developed a progressing burning pain in his legs.

“On the other hand” , he is happy to report a significant improvement in his blood pressure that used to be high despite taking pills.

“ Sometimes, the blood pressure is even too low ,resulting in lightheadness”.

Bortezomib- Induced PNP

- Among PIs, bortezomib was shown to induce severe PNP .
- Neurodegeneration occurs via a proteasome-independent mechanism , therefore not considered a class effect (Arastu –Kapur S, Clin Cancer Reresechm, 2011)

- BiPN is predominantly sensory, with prominent small fiber involvement

- May involve the autonomic nervous system, including orthostatic hypotension, suppressed heart rate variability, and delayed gastric emptying.

- IV administration of bortezomib leads to 10-fold higher peak plasma levels and to higher rates of BiPNP than subcutaneous administration.
- Subcutaneous administration, though preferable, still results in PNP

Ludwig H Leukemia 2018

Management of Bortezomib Induced PNP

BiPNP grade 1 with pain, or grade 2 - Bortezomib should be reduced to 1.0mg/m2 twice weekly or 1.3mg/m2 once per week.

BiPNP grade 2 with pain, or grade 3 - Withhold Tx until symptoms resolved. Treatment can be re-initiated at a dose of 0.7mg/m2 once per week.

Grade 4 - Treatment must be discontinued [30,31.

Ludwig H Leukemia 2018

Treatment of Polyneuropathy

Still unsatisfactory

Painful polyneuropathy

Anti-convulsive agents (gabapentin and pergabalin) ,Atidepressants and Opioids (Palumbo A JCO 2014;Ludwig H, Leukemia 2014)

Topical pain medications include lidocaine and capsaicin (Stacey BR 2005).

Orthostatic dysregulation

Vasoconstrictor drugs, volume expansion, compression garments, and postural adjustment, together with reduction or discontinuation of any concomitant blood pressure lowering medication.

Drugs such as midodrine, pyridostigmine, and fludrocortisone can be administered, and physical inactivity should be avoided (Figueroa JJ 2010)

Bortezomib induced Blepharitis

- Reported in up to 15% of Bortezomib treated patients
- Improves after stopping therapy
- Responds to local eye drops ; AB in combination with steroids and/ or oral doxycycline

Case 3 (Cont)

Bortezomib dose was reduced and the patient was treated with weekly bortezomib, 1mg/m2, with no further deterioration in his neuropathy.

He felt generally well and stopped taking all pills you prescribed him when he started therapy.

He attend your clinic , complaining on a “ new back pain”

Physical examination revealed a rash :

Herpes Zoster Prevention

Post-herpetic neuralgia is the most common morbidity associated with herpes zoster reactivation.

Herpes zoster infection reported in 3–13% of patients receiving bortezomib monotherapy [EPAR 2016].

Herpetic infections have also been patients receiving daratumumab, therefore, prevention of HZ in patients receiving PIs or daratumumab is mandatory [NCCN, Dec 2017].

Prevention & Treatment of Herpes Zoster Infection

- Present herpes zoster vaccines are live vaccines and controversy exists whether they can be offered to patients with well-controlled disease.
- As an alternative to live attenuated vaccines, which are contraindicated for immunocompromised individuals are heat-inactivated varicella zoster vaccines and recombinant subunit vaccines, both are being currenty studied [Aaoro MS Eur J cancer 2011; Trepos Ehaematologica 2015;Anderson KC J Nat Comr Cancer Net 201664–66].

- In patients with HZ, Valaciclovir and penciclovir have greater bioavailability than acyclovir, making them preferable for outpatient treatment [Sampathkumar P, Mayo Clin Proc 2009].

- Valaciclovir was shown to significantly reduce the incidence of post-herpetic neuralgia in patients that experience HZ, [MacFarlane LL, JANFP 1998], though, randomized controlled trials comparing various agents are not available.

Case 3

A 55 year old lady ,

Started pomalidomide dexamethasone quite recently due to relapsed myeloma. Attended clinic due to the development of mild rash on her arms.

Severe Skin Reactions [Van de Donk, Cancer Mang res 2012].

- Severe skin reactions are most common with all IMiDs or ixazomib

- Limited, localized rash - antihistamines or topical steroids are recommended.

- Mild but extensive rash - a short course of low-dose prednisone
- Grade 2/3 skin rash - treatment should be discontinued and reinstated in case of complete resolution.

- Rarely, severe skin reactions such as Steven–Johnson syndrome or even TDN
- In such severe cases, treatment should be permanently discontinued.
- [EPAR 2015;EPAR 2017;FDA 2016].

- For lenalidomide, desensitization with progressively increased doses and dosing frequencies to reach a target dose of 10mg/day has been proposed [Lee MJBJH 2014].

- Patients experiencing skin reactions during thalidomide should not receive lenalidomide or in case of limited alternatives, should be started at a low dose [EPAR Oct 2017;FDA 2017].

Case 4

A 76 year old

MM since 2011

Treated with VCD followed by ASCT , achieving durable response, lasting for almost 5 years.

He was then treated with Rd, but has recently developed disease relapse, for which was started on carflizomib- cytoxan and dexamethasone.

Prior Medical history is unremarkable except of hypertension

Carflizomib

“Real life Practice”

What do you tell your patient?

Carfilzomib

Carfilzomib is generally well tolerated.

The most commonly reported ADRs are
Anemia,
Fatigue,
Diarrhea,
Thrombocytopenia,
Nausea,
Pyrexia,
Dyspnea,
Respiratory tract infection,
Cough,
Peripheral edema

Carflizomib related Cardio Vascular Toxicity

Eligibility and Cardiovascular Risk Factors in Phase 3, R/R MM Studies

	ASPIRE (N = 792)[1]	ENDEAVOR (N = 929)[2]	FOCUS (N = 315)[3]
	KRd vs Rd	Kd56 vs Vd	K vs BSC
Blood Pressure	Uncontrolled hypertension excluded	Uncontrolled hypertension not excluded	Randomized K vs BSC
Heart function	LVEF not specified	LVEF ≥ 40%	LVEF ≥ 40%
	EXCLUSIONS		
	▪ MI within 4 months prior to randomization ▪ NYHA Class III or IV heart failure ▪ Uncontrolled angina or history of severe CAD ▪ SSS , uncontrolled V arrhythmias, conduction abnormalities	▪ MI in the previous 4 months ▪ NYHA Class III or IV heart failure ▪ Symptomatic ischemia or uncontrolled conduction abnormalities	▪ MI in the previous 3 months ▪ NYHA Class III or IV heart failure ▪ Congestive heart failure
Renal function	CrCl ≥ 50 mL/min	CrCl ≥ 15 mL/min	CrCl ≥ 15 mL/min
Dose	20/27 mg/m2 infused over 10 min	20/56 mg/m2 infused over 30 min	20/27 mg/m2 infused , 10 min
Duration	K fixed: up to 18 cycles Rd to progression or toxicity	Kd to progression or toxicity	K to progression or toxicity

Carfilzomib -Related Cardiac Toxicities

	ASPIRE[1]		ENDEAVOR[2]		FOCUS[3]	
Carfilzomib Dose (mg/m²)*	**20/27**		**20/56**		**20/27**	
Safety Population	**KRd n = 396**	**Rd n = 389**	**Kd56 n = 463**	**Vd n = 456**	**K n = 157**	**Control n = 153**
Duration, median weeks	**72**	**57**	**48**	**27**	**16**	**11**
Relative dose intensity for proteasome inhibitor	94%	NA	91%	85%	99.9%	NA
AEs of interest†, any grade, %						
Cardiac Failure	7.1	4.1	10.8	3.3	5	1
Hypertension	17.1	8.7	32.2	14.5	15	6
Ischemic heart disease	6.9	4.6	3.9	2.0	NR	NR
AEs of interest†, grade ñ 3, %						
Cardiac Failure	4.3	2.1	5.8	2.0	2	1
Hypertension	6.4	2.3	14.5	3.3	3	0
Ischemic heart disease	3.8	2.3	2.6	1.5	NR	NR

Patient 4 (Cont.)

The patient, a 76 year old gentleman, was started on Carflizomib 20/27+ dexamethasone 20 mg/w , after being refractory to both bortezomib & lenalidomide-based combinations.

He completed 1 cycle of therapy, achieving a very good response, Before being admitted to E.R , complaining on shortens of breath. Physical examination revealed an increased BP (160/85) , dyspnea (26 breaths/min) and wet crepitation on both lungs

Echocardiogram showed globaly decreased LVEF ≈40%

Blood count was normal (HB-12) and chemistry was also within the normal range.

What would do next ?

-Stop and restart therapy if EF has improved

-Stop and switch to other drugs

Cardiac Toxicity

- Hypertension – Most common cardiac AE. Mostly after infusion.

- Mechanism is not fully defined.
- Carflizomib affects endothelial cells and is associated with an acute rise in NT-proBNP [Pawlyn C Blood 2014].

- Reductions in left ventricular ejection fraction were mostly reversible.

- The utility of echocardiography and blood cardiac markers as a predictive tool for cardiac events are limited

[Chari A Blood 2016, abst 2142].

How to reduce the Risk of CardioVascular Events ?

Prior to Treatment

Identify patients at greater risk for CHF: Age>75

A known pre-existing cardiac disease

Risk minimization measures:

Control hypertension prior to starting carfilzomib treatment (<140)

Plan fluid management:

Oral: 30 mL fluid per kg at least 48 hours before Cycle 1, Day 1
IV: 250–500mL fluid prior to each dose in Cycle 1
Adjust total fluid intake as clinically appropriate in patients with baseline or risk of cardiac failure

During Treatment

Monitor blood pressure:

Regular blood pressure measured in all patients

Monitor for evidence of volume overload:

Monitor patients for evidence of volume overload and adjust as clinically appropriate, especially patients at risk for cardiac failure

How to reduce the Risk of CardioVascular Events and how to manage them ?(II)

- Before administration, BP should be tightly controlled:<140mmHg.
- Adherence to 30-min infusion time is recommended.
- Shortening infusion time after 1/2 cycle to 10min can be considered [Nijhof IS Blood 2016].
- In case of grade 3- 4 cardiac events, carfilzomib should be interrupted until recovery.
- Carfilzomib may be restarted >2 weeks after patient recovery(with a complete resolution of cardiac complication), employing a reduced dose afte a thorough benefit/risk assessment [Tacchetti P Am J Hem 2011;Dimopoulos MA Eur J Hematol 2011].
- The patient should be assessed for fluid overload [Nijhof IS Blood 2016].

- Currently, no clear dose effect on cardiac toxicity was demonstrated
- Starting with a lower dose in patients aged >75 years and in those with a history of mild cardiac disease is recommended.

Case 6

A 76 year old gentleman, planned for single agent Daratumumab ,

being already refractory now to Lenalidomide, bortezomib and Carflizomib

Planned for single agent daratumumab

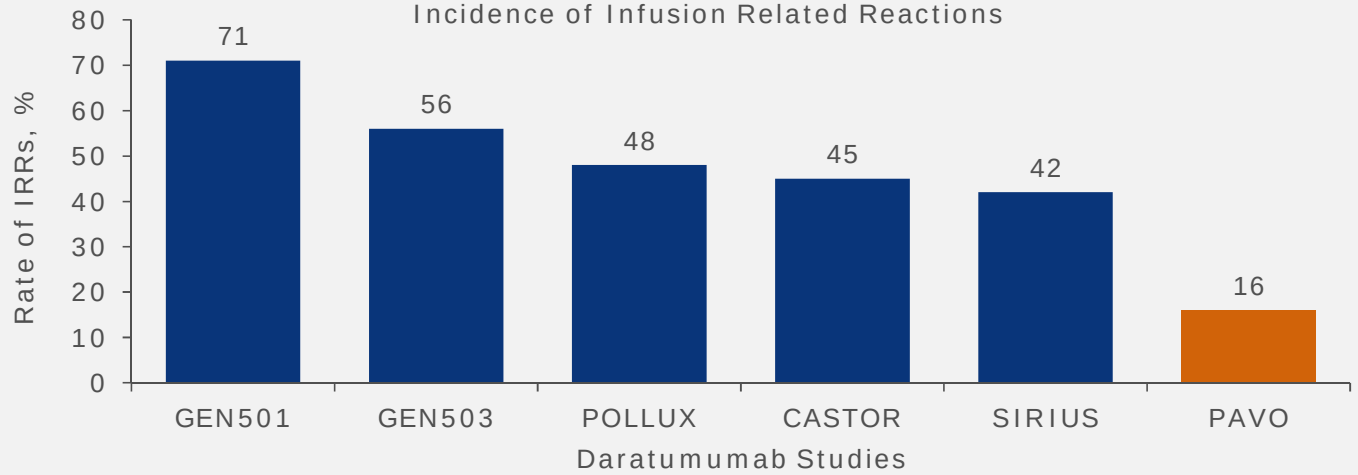
Daratumumab
ALCYONE (MMY3007) Safety: Most Common TEAEs[a]

	VMP (n = 354)		D-VMP (n = 346)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hematologic, n (%)				
Neutropenia	186 (53)	137 (39)	172 (50)	138 (40)
Thrombocytopenia	190 (54)	133 (38)	169 (49)	119 (34)
Anemia	133 (38)	70 (20)	97 (28)	55 (16)
Nonhematologic, n (%)				
Peripheral sensory neuropathy	121 (34)	14 (4)	98 (28)	5 (1)
Infections URTI Pneumonia	170 (48) 49 (14) 17 (5)	52 (15) 5 (1) 14 (4)	231 (67) 91 (26) 53 (15)	80 (23) 7 (2) 39 (11)
Diarrhea	87 (25)	11 (3)	82 (24)	9 (3)
Pyrexia	74 (21)	2 (1)	80 (23)	2 (1)
Nausea	76 (22)	4 (1)	72 (21)	3 (1)
Pneumonia	17 (5)	14 (4)	53 (15)	39 (11)
Second primary cancer[b]	9 (2.5)	NA	8 (2.3)	NA
Any infusion-related reaction	NA	NA	96 (27.7)	15 (4.3)

- IRR- in 50%
- Mostly in 1th infusion
- Grade 3-4 IRR to D – 5%
- 1.4% and 0.9% of patients receiving VMP and D-VMP, respectively, discontinued treatment due to infection
- 5 (1.4%) patients discontinued daratumumab due to IRRs

Incidence of IRRs in Patients Treated with Daratumumab IV and SC

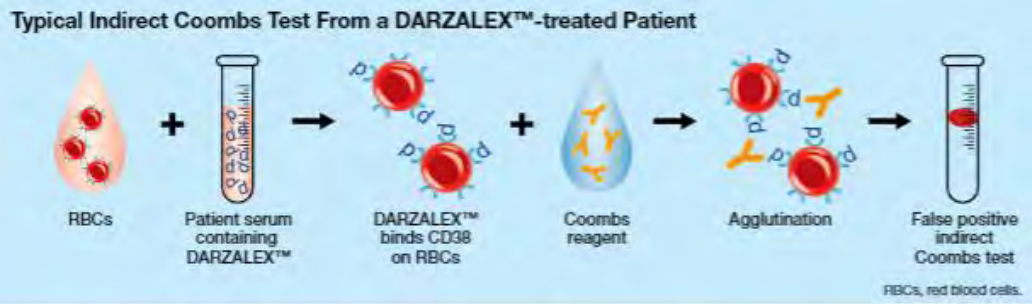
	IV					SC
	GEN501[1]	GEN503[2]	POLLUX[3]	CASTOR[4]	SIRIUS[5]	PAVO[6]
Patients	N=42	N=32	N=283	N=243	N=106	N=25
Patient Population	R/R to ≥2 prior therapies	R/R to ≥1 prior therapy	R/R to ≥1 prior therapy	R/R to ≥1 prior therapy	R/R to ≥2 prior therapies	R/R to ≥2 prior therapies
Dose	Daratumumab 16 mg/kg IV					Daratumumab 1,800 mg SC



Daratumumab (Cont)

Daratumumab interferes with blood group serological testing,

: it binds to CD38 on RBC and results in a positive indirect antiglobulin test



Being an IgGk Ab, it may interfere with M protein assessment in patients with an IgGk

It may also with interfere with EUROFLOW MRD assessment , as it binds to CD38-positive residual MM cells

Management of IRR

Elotuzumab and daratumumab, are both IgG1κ isotype Abs.

IRR – reported in 10% of patients receiving 20mg/kg of elotuzumab, all grade 1 -2 [89].

Single-agent daratumumab resulted in IRR in 45%, with only few grade 3 [90].

For both drugs, prophylactic measures are recommended:

- IV 100mg methylprednisolone, ~1h before daratumumab infusion,
- Oral antipyretic (paracetamol 650–1000mg),
- Oral or IV antihistamine (diphenhydramine 25–50mg).
- Post-infusion treatment with 20mg methylprednisolone for 2 days following infusion.

- Special precautions need to be taken in patients with pre-existing COPD.
- Premedication with 10mg montelukast, an oral leukotriene receptor antagonist, 30min before daratumumab should be considered as well as post-infusion

Management of IRR (Cont)

- The infusion should be interrupted at any grade/severity.

- If grade 1–2 IRR occurs, the infusion may be resumed at half the rate at which it occurred, provided the patient is stabilized;
- In case of no recurrence of IRR, escalation can be resumed.
- If grade 3 IRR occurs, once IRR decreases to grade ≤2, the infusion may be restarted at no more than half the rate at which the IRR occurred.
- If no recurrence of IRR, escalation can be resumed.
- Patients have to discontinue daratumumab therapy in case of grade 4 (life threatening) IRRs at first or subsequent infusion.

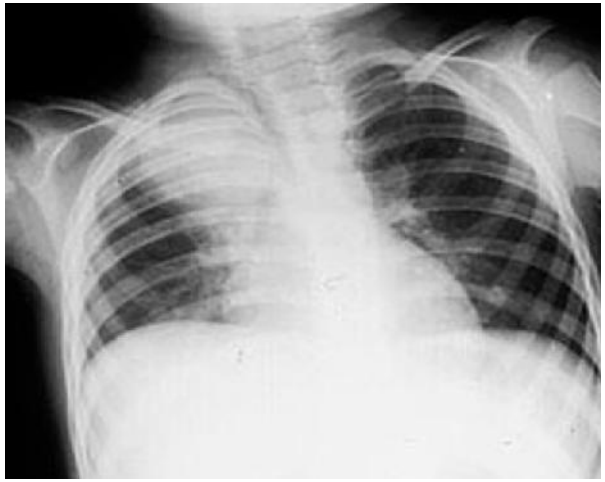
Case 7

A 66 year old lady, followed in the hematology division since 2015, due to SMM

Recently diagnosed with MM ,and is currently receiving VRD.

She attended day care due to fever, cough and shortness of breath, reporting runny nose and cough which started 4 days earlier

CXR showed lobar pneumonia.



Vaccines

What do you recommend a newly diagnosed pt with HR SMM ?

- No recommendations unless planned to start Anti MM Tx shortly - 30%
- Anti -Herpes Zoster vaccine only - 0%
- Anti Flu vaccine only – 50%
- Anti Flu vaccine to the pt and her caregivers - 10%
- Anti Pneumococcal (1?/ 2 ?) vaccine only -0%
- Anti Flu+ Anti Pneumococcal -10%

Recommendations for Vaccination

- Patients should be vaccinated against influenza virus, pneumococci, and haemophilus influenzae.

- A trivalent/ quadrivalent influenza vaccine should be used in patients and caregivers.
- Vaccination against pneumococci should be started with a 13-valent vaccine (PCV13) and followed at least 8 weeks later by a dose of PCV23 (23 valent polysaccharide conjugate) [Musto P, NJH 1995].

- Response to vaccines frequently is suboptimal

- Repeated vaccinations with the same influenza vaccine may enhances anti-vaccine Ab [CDC 2016].

- Ideally, patients should already be vaccinated in the premalignant state; MGUS or SMM or, when feasible, during periods of optimal disease control.

Case 7

A 32 year old lady, 27th week first pregnancy

Diagnosed with Myeloma, presenting with lytic lesions in her ribs and sternum , in the presence of 60% PCs in BM.

Teratogenicity

Almost all novel agents and backbone agents showed a certain embryo-fetal risk, especially the thalidomide analogs of the IMiD group , but also Pis.

Pregnancy must be excluded before start of treatment.

Women of reproductive potential and their partners should be informed about the embryo-fetal risk of the respective drugs and about adequate contraceptive measures.

In case of diagnosis of MM during pregnancy , steroids or Cytoxan-steroids , or VAD are all optional.

Conclusions

- A number of novel drugs have recently been introduced in the treatment of multiple myeloma.
- These drugs differ in their mode of action and their side effect and safety profile.
- Knowledge of their potential risks and of established measures to prevent occurrence of complications is essential

  for preventing severe symptoms,

  dose reductions,

  and/or treatment discontinuations

REGIONAL IMS
MYELOMA MEETING IN ISRAEL 2019
INTERNATIONAL MYELOMA SOCIETY
IMS
SAVE THE DATE 21–22.2.2019
International Convention Center | Jerusalem

Thanks and best wishes for good health !

IMS – Educational Workshop Athens

How to make the right choices in the relapsed patients?

Case report

Josip Batinić; MD
University Hospital Centre Zagreb, Croatia

Patient born in 1953, male

- medical history: at 20 years of age - vertebral fracture Th12-L4

- August 2008 diagnosed with multiple myeloma kappa light chains
- Osteolytic lesions of lumbar vertebra
- DS IIIA, ISS II
- Induction therapy: 4 cycles of VAD (vincristine, adriamycin, dexamethasone)
- March 2009 autologus HSCT
- Response: CR

- Hb 112 g/L
- L 5.3x10e9/L
- Creatinin 93 µmol/L
- Ca 2.3 mmol/L
- sFLC: kappa 5300 mg/L; lambda 350 mg/L
- Kappa/lambda 15.14
- IgG 6.3; IgA 2.7; IgM 0.6 g/L
- Albumin 33 g/L
- Beta2 microglobulin 4.8 mg/L
- Bone marrow: 48% plasma cells
- X-ray: multiple osteolyses

Patient born in 1953, male – MM kappa light chains

- December 2012 - biochemical relapse: sFLC kappa 800 mg/L
- No end organ damage
- maintanance therapy with dexamethasone 40 mg weekly
- February 2013 – IFE: hypogammaglobulinemia, sFLC kappa 92.0 mg/L

- December 2015 - neck pain and pain in left hip, no neurological deficite
  - sFLC (mg/L): kappa 664.0, lambda 8.87; kappa/lambda 74.86
- Bone marrow: no plasma cell infiltration
- Soft tissue tumor in the right clavicular region - cytology: plasma and proplasma cells – extramedullary relaps

Patient born in 1953, male – MM kappa light chains

MSCT: pathological fracture of atlas, with soft tissue tumor paravertebraly, lytic lesions of right condile of occipital bone

Patient born in 1953, male – MM kappa light chains

- 2nd line therapy: CyBorDex (cyclophosphamide 500 mg weekly, dexamethasone 40 mg iv weekly, bortezomib 1,6 mg/m^2 weekly) + local irradiation (30 Gy /10 fractions)
- Reevaluation after 4 cycles – partial regression of soft tissue lesions on CT scan
- Continued with chemotherapy with 4 cycles of CyBorDex protocol

- sFLC(mg/L): kappa 160.00; lambda 8.24; kappa/lambda 19.4; sIF: monoclonal light chain kappa
- Adverse effects: peripheral neuropathy (gr. I-II)

- 2nd autologous HSCT recommended – patient refused at that time

Patient born in 1953, male – MM kappa light chains

- January 2017 – sFLC (mg/L): kappa 1470.00, lambda 14.20 kappa/lambda 103.52
- IF (serum and urin) monoclonal light chains kappa

- MSCT (Feb 2017): anterior mediastinum, paravertebraly 2 nodal soft tissue lesions: 2.3x1.4cm and 3x1.2cm; posterior mediastinum soft tissue tumor 5.6 x 1.3 cm; accidental finding: subacute pulmonary embolism

- 3rd line therapy: IRd (ixazomib, lenalidomide, dexamethasone) + local radiotherapy: TD 30Gy/10 fractions
- September 2017 – sFLC (mg/L): kappa 60.5, lambda 16.6; kappa/lambda 3.64
- IF (serum and urine): normal (hypogammaglobulinemia)
- Received 16 cycles IRd; adverse effect: worsening of peripheral neuropathy (gr. II-III)

Patient born in 1953, male – MM kappa light chains

- August 2018 MSCT: no change in the size of preegzisting soft tissue tumors BUT new soft tissue tumors (VII rib right 5x3cm; VIII rib left 6x4cm)
- sFLC (mg/L): kappa 63.0, lambda 15.4; kappa/lambda 4.09; IF (serum and urine): normal (hypogammaglobulinemia)
- Progression!?

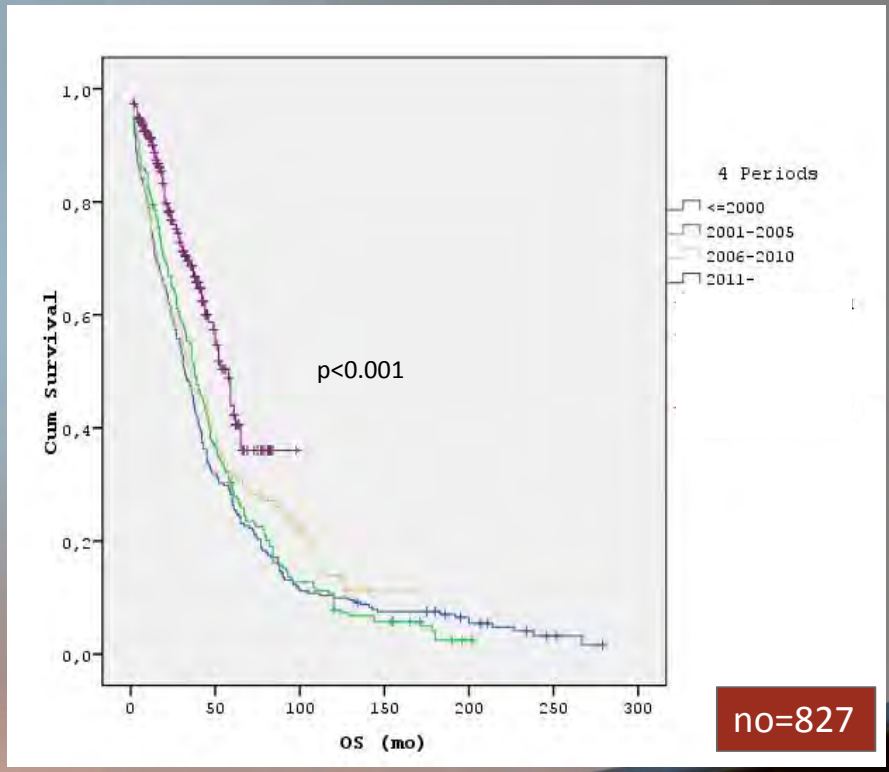
- What to do next?
  - Rd + cyclophosphamide?
  - Pomalidomide? – available
  - MP +/- PI or IMID?
  - 2nd autologous HSCT – after/if acheive response…

Thank You for Your attention

Controversial cases with emphasis on local practice
Case presentation

Dr Eirini Katodritou
Hematologist, Director,
Theagenion Cancer Hospital,
Thessaloniki Greece

Real-world data on OS in the era of novel agents



Katodritou E, et al. Theagenion database

Case 1: a success story

- **Diagnosis October 2010**
  - 61 year old female, IgAλ symptomatic MM (advanced bone disease, moderate anemia), standard risk MM (FISH), ISS1, RISS1, Bence Jones (-) , 45% BM monoclonal plasma cells, absence of clonal PCs in the peripheral blood

- **1st line therapy:** VD+ ASCT: response CR.
- **Maintenance:** dexamethasone 20mg x 2years
- Zoledronic acid 4mg/mo x 2 years

- **Relapse April 2017**

- **2nd line treatment:** DRd: CR documented in 8 months. Currently at cycle 14, in CR
  - PFS: 79 mo
  - OS: 93 months

Theagenion Database: standard risk pts who underwent ASCT (34%) : median PFS: 52mo
Median OS: 124 mo

Case 2: The dark side of the moon…

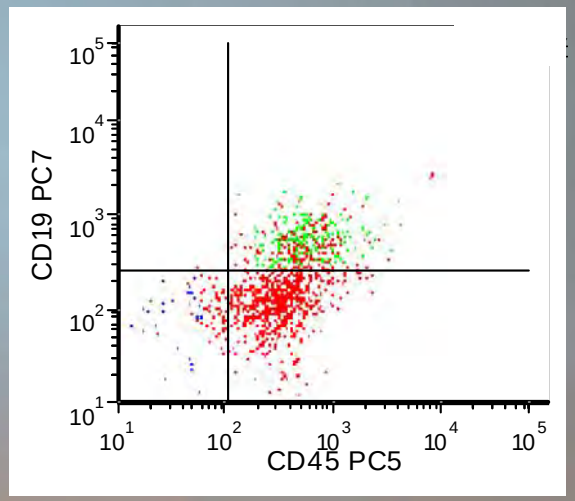
- **Diagnosis November 2014**
  - 64 year old male
  - IgAκ MM, standard risk (FISH including 1q+), normal karyotype, ISS1, RISS1, LDH normal
  - anemia (Hb: 9.5g/dL)
  - WBXR: lytic lesion right femur, 11th thoracic vertebra collapse
  - 48% BM monoclonal plasma cells, no PCs in the peripheral blood

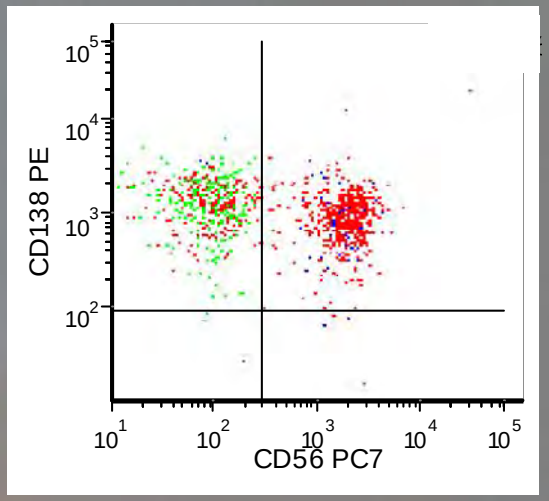
- **1st line treatment:**
  - VCD + ASCT

Response:

vgPR

MRD (MFC): 0.36%, CD45 dim/-, CD38/138 (+), CD19 (-), CD56(+)





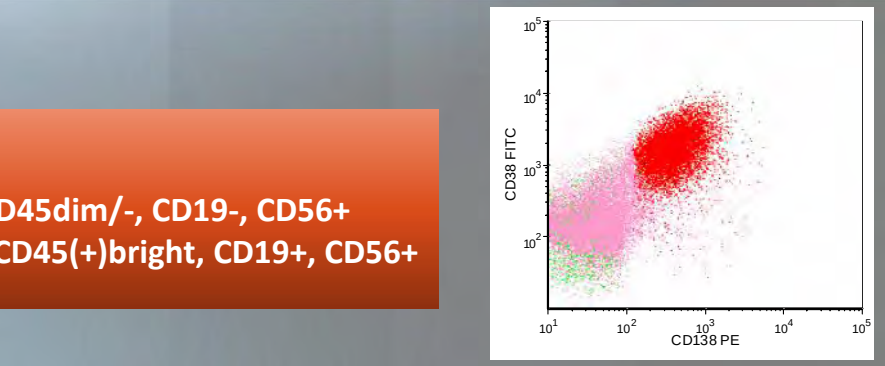
- **Maintenance:** Dexamethasone 20mg/wk
  (Len maintenance was not approved at that time)

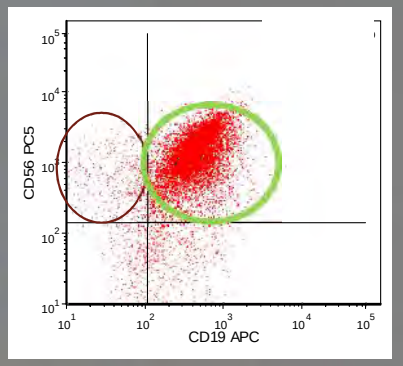
- Zoledronic acid 4mg/mo

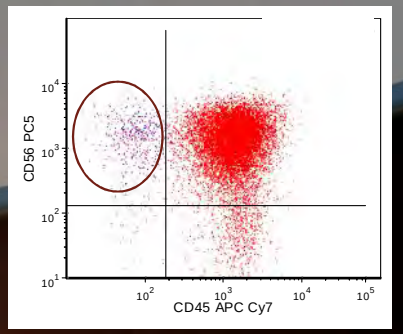
Case 2

- **Relapse May 2017 (PFS: 31mo)**
  - Gradual increase of M-Component (4.5g/dL), moderate anemia (Hb: 11g/dL)
  - Bence Jones (-)
  - Repeat FISH for Del 17p and 1q+: both neg
  - spine and pelvis MRI were normal

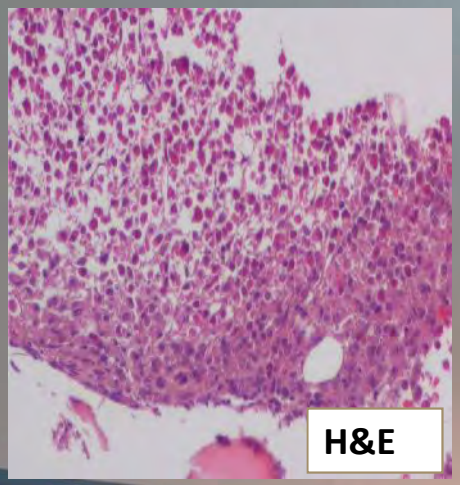
MFC:
1) old clone CD45dim/-, CD19-, CD56+
2) new clone CD45(+)bright, CD19+, CD56+

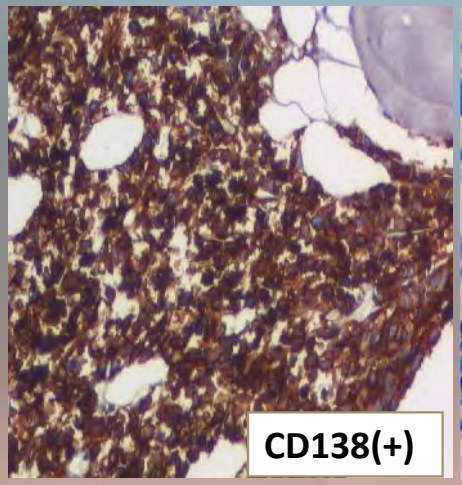


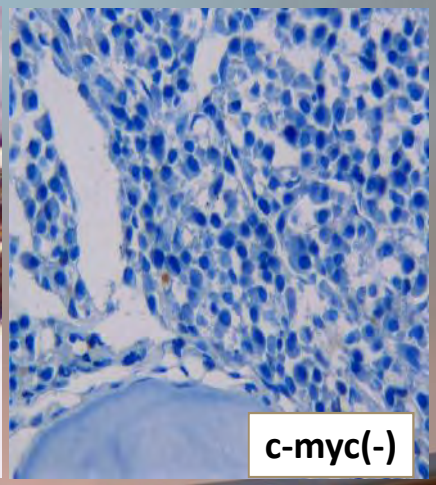




Bone marrow biopsy: 90% clonal PCs CD38/CD138+, CD19(-), CD56+, c-myc (-)





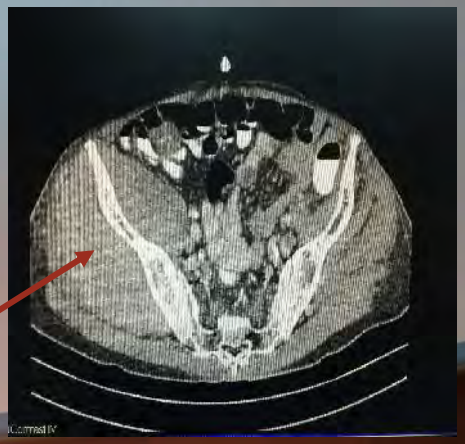


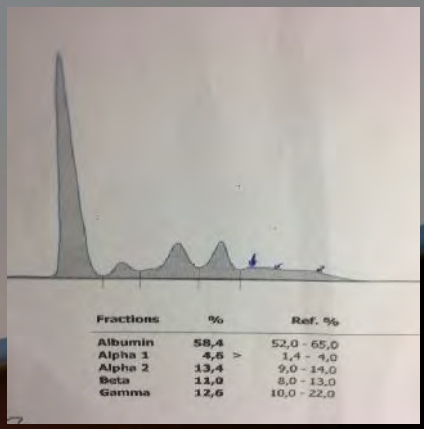
A. Papanikolaou with permission

Case 2

- 2nd line therapy (May 2017)
- KRd
  - M-component after 1 cycle 80% reduction
  - CR documented after 6 months. MRD (-)
  - Continue treatment
  - side effects (bradycardia, no signs of cardiac failure)
- After 13 cycles (June 2018)
  - He presented complaining about strong pain in the hip joint and the pelvis.
  - A CT scan and an MRI of the hip and pelvis revealed a large soft tissue mass surrounding the iliac bone without evidence of cortical disruption

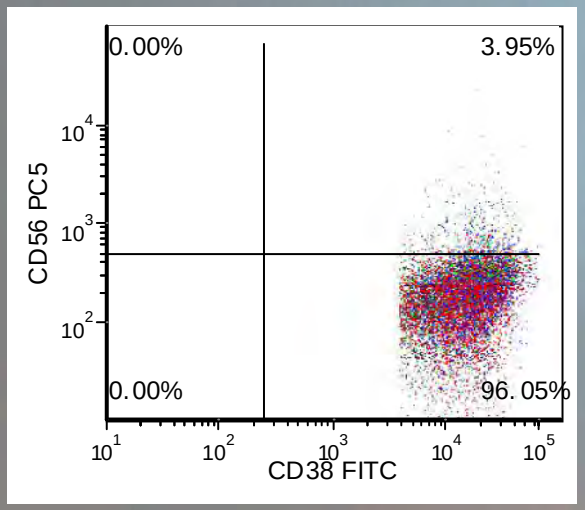
- A restaging was performed
  - Bone marrow aspiration and trephine : negative
  - SPE/IFE: inconspicuous M-component/ IgA , FLCR: normal, Bence Jones (+) (κ light chain: 0.3g/24h)

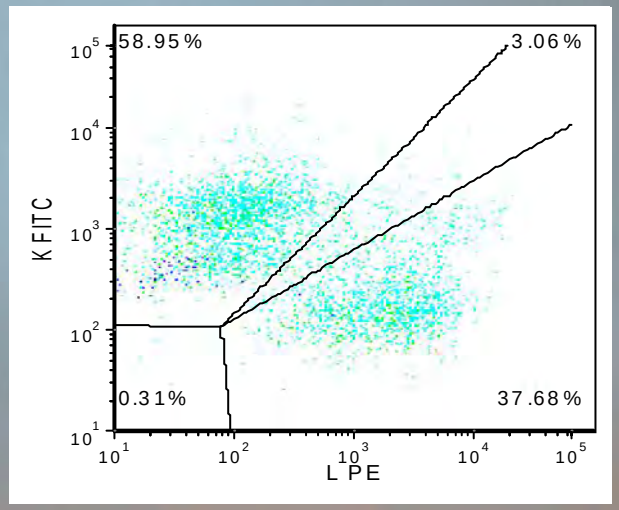


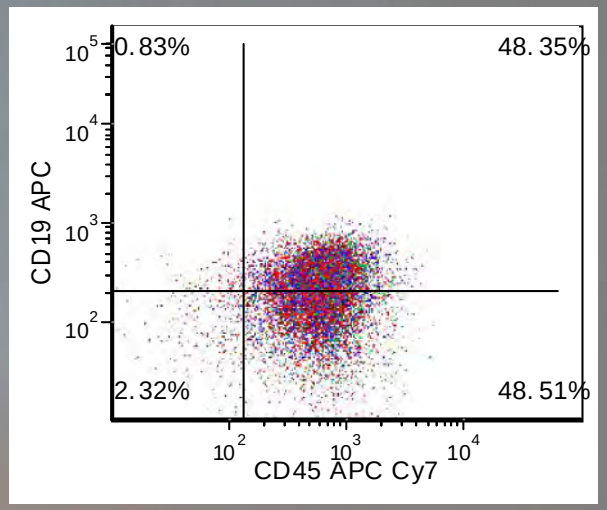


Case 2

MFC 2018: 1% Polyclonal PCs in the bone marrow

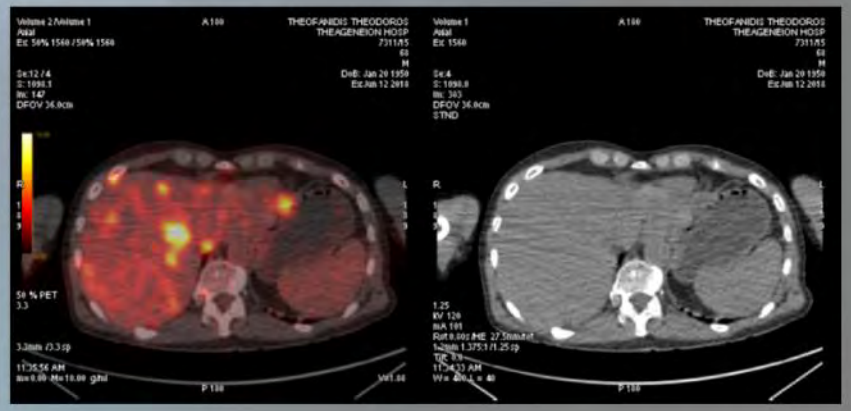




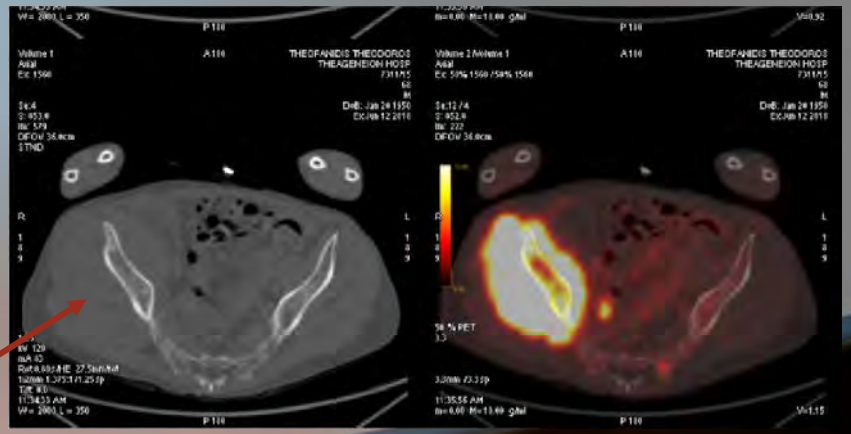


PET-CT at relapse

Multiple hypermetabolic foci throughout the skeleton, most of them without corresponding bone lysis (medullary lesions).
Extramedullary foci involving the liver, lungs, pleura, lymph nodes (thoracic and abdominal), peritoneum and carvenous sinus

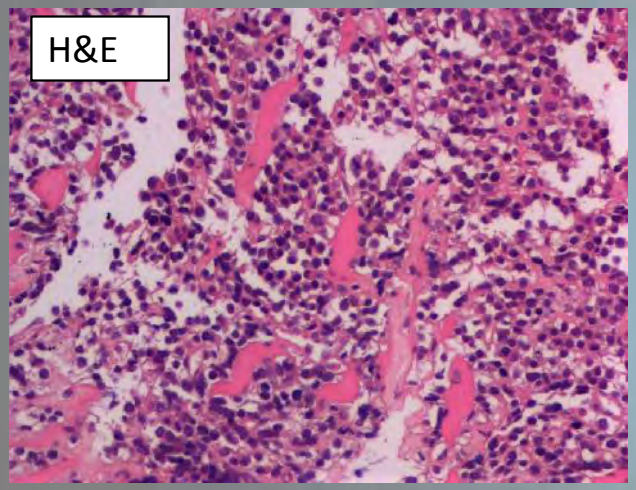


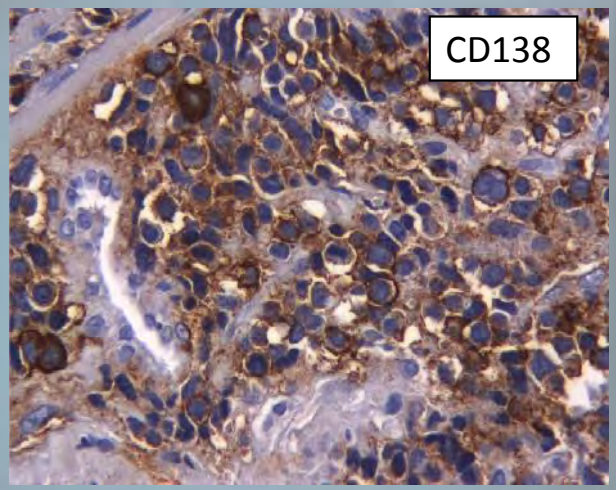
Multiple hypermetabolic lesions in the liver

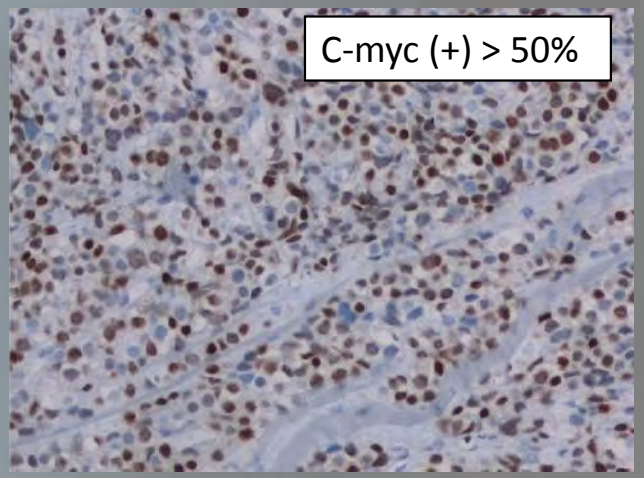


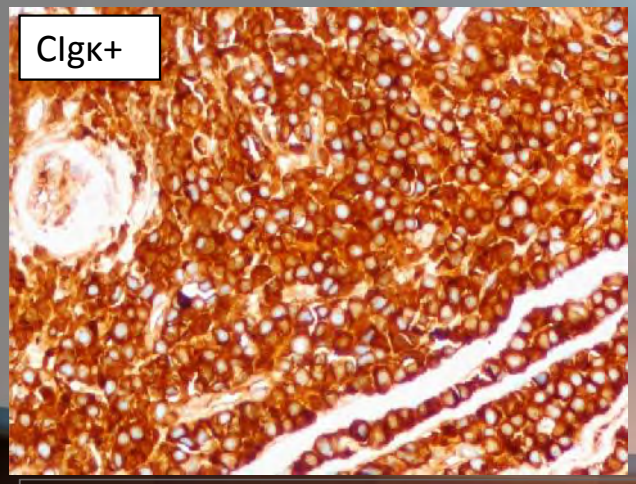
Large gluteal mass (surrounding the iliac bone without cortical erosion (Suv$_{max}$ 21.2)

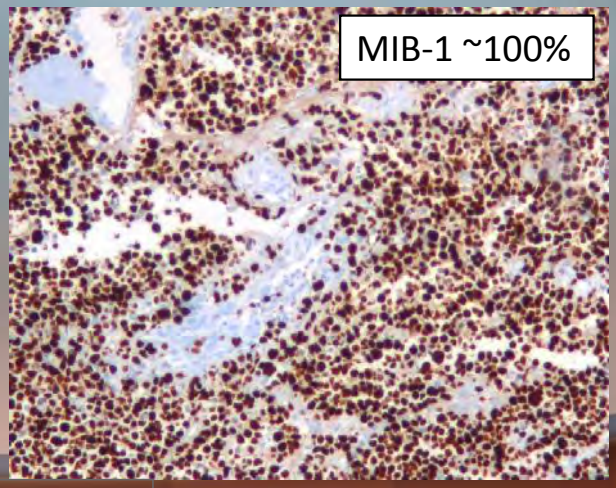
Gluteal mass biopsy*

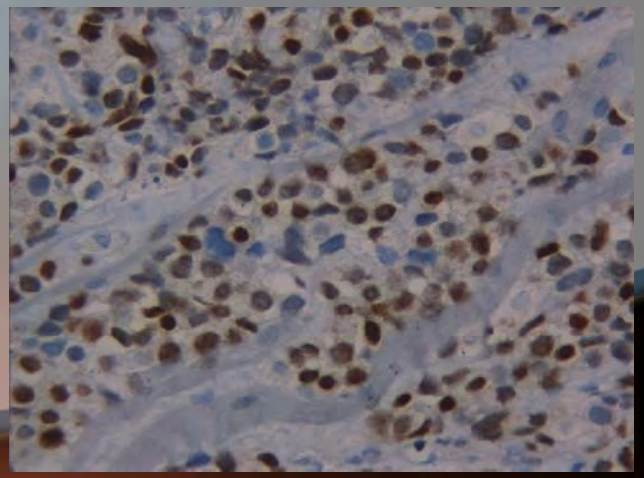












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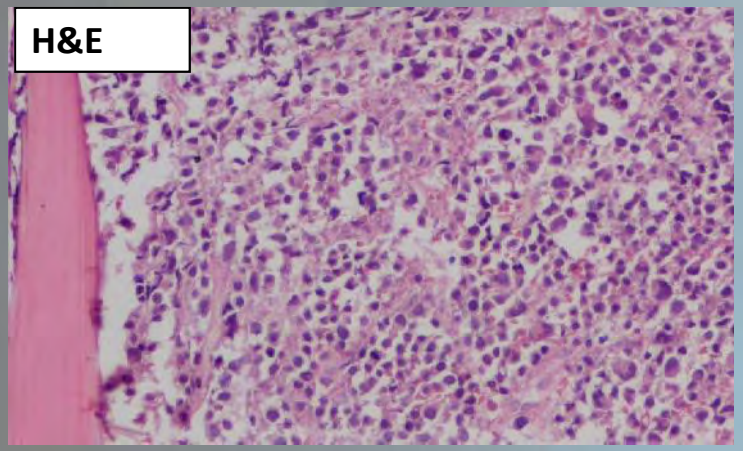
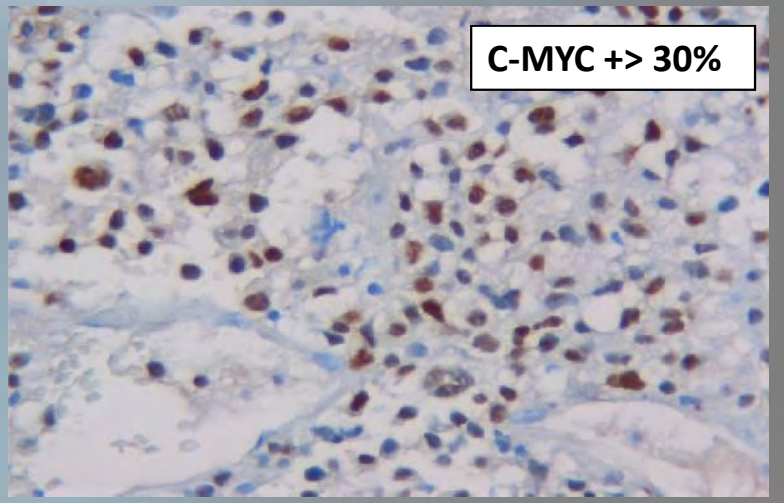
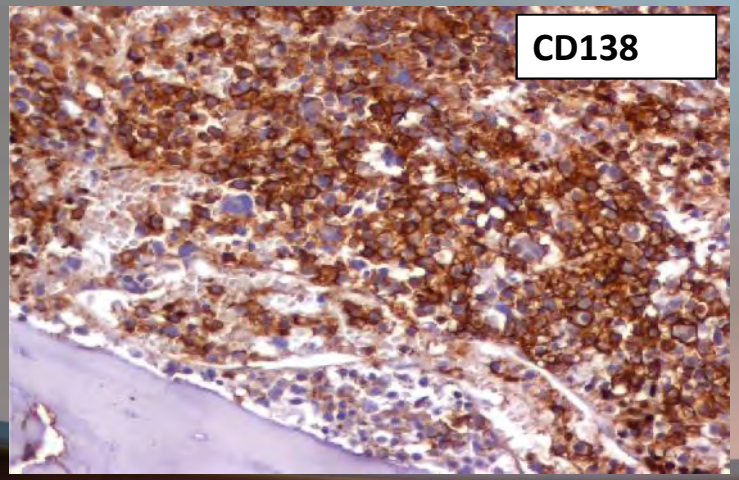
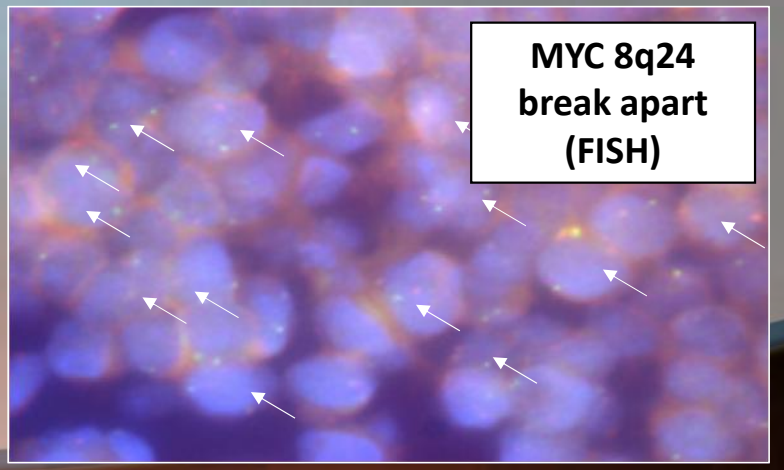
*CD56 (-) CD19/20 (-)

Iliac bone biopsy









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Case summary

- **Extramedullary relapse**
- **Absence of BM infiltration (bone marrow aspiration, MFC, and biopsy)**
- **Recognition of at least 3 different subclones during the course of the disease (clonal evolution):**
  - **In the bone marrow**
    - **A typical CD45dim/CD138/38+, CD19-/CD56+ clone**
    - **An additional CD45bright/CD19+/CD56+ clone at relapse (c-myc expression: negative)**
  - **In the soft tissue and iliac biopsy**
    - **CD138/38+, CD19-/CD56- (MIB-1 100%, c-myc expression >50%)**

What would be the best treatment option for a patient relapsing with aggressive extramedullary disease who is Len and PI refractory?
PomDex? Daratumumab-monotherapy_clinical trial (DaraPomDex)? Conventional chemo?

Case 2 outcome

- The patient was treated with
  - PomDex 1 cycle and 1 cycle DCEP: no response, disease progressed rapidly
- He deceased 3 months after relapse from disease progression and multiorgan failure
- OS: 45mo

Discussion

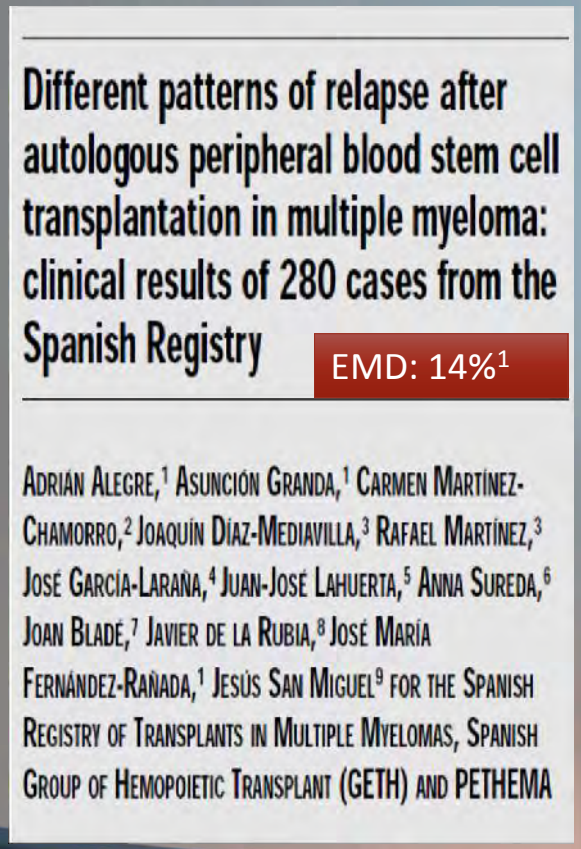
- The incidence of extramedullary relapse ranges from 6-20% (inconsistencies in the definition that confuse the true incidence)
- The most common sides of EMD at relapse:
  liver and pleura (Infiltration was evident in 40% of post mortal liver autopsy)
- Soft tissues may have different origins:
  1) Direct growth from bone lesions by disrupting the cortical bone
  2) hematogenous dissemination (escape phenomenon)
  3) triggered by previous surgical procedures.
- EMD is associated with shorter survival

Biological characteristics of extramedullary myeloma

Biologic mechanism	*Characteristics of extramedullary multiple myeloma lesions*
High plasma cell proliferation	Overexpression of MIB-1
Compromise of production of heavy chains	Light chain escape
Adhesion molecules changes	Down regulation of CD56 Overexpression of CD44
Genetic mutations	*P53* deletion CCND1 overexpression *RAS* mutations Deletion of chromosome 13
Angiogenesis gene expression profile	Overexpression of angiopoietin 1, notch 3, fibronectin 1 Increased CD31 and endoglin protein expression

Blade J, et al. J Clin Oncol, 2011; 29: 3905-3812; , Varettoni et al, Ann Oncol 2010; 21: 325-330; Usmani SZ, et al. haematologica, 2012; 97: 1761-1767

Has the incidence of extramedullary disease increased in the modern therapeutic era?



Different patterns of relapse after autologous peripheral blood stem cell transplantation in multiple myeloma: clinical results of 280 cases from the Spanish Registry

EMD: 14%[1]

Adrián Alegre,[1] Asunción Granda,[1] Carmen Martínez-Chamorro,[2] Joaquín Díaz-Mediavilla,[3] Rafael Martínez,[3] José García-Laraña,[4] Juan-José Lahuerta,[5] Anna Sureda,[6] Joan Bladé,[7] Javier de la Rubia,[8] José María Fernández-Rañada,[1] Jesús San Miguel[9] for the Spanish Registry of Transplants in Multiple Myelomas, Spanish Group of Hemopoietic Transplant (GETH) and PETHEMA

EMD: 7.5%[2]

Leukemia (2011), 1–3
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www.nature.com/leu

REVIEW

Incidence of extramedullary disease in patients with multiple myeloma in the era of novel therapy, and the activity of pomalidomide on extramedullary myeloma

K Detweiler Short[1], SV Rajkumar[1], D Larson[2], F Buadi[1], S Hayman[1], A Dispenzieri[1], M Gertz[1], S Kumar[1], J Mikhael[3], V Roy[4], RA Kyle[1], MQ Lacy[1]

Leukemia Research 33 (2009) 1137–1140

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Brief communication

Extramedullary (EMP) relapse in unusual locations in multiple myeloma: Is there an association with precedent thalidomide administration and a correlation of special biological features with treatment and outcome?

E. Katodritou[a,*], V. Gastari[a], E. Verrou[a,b], C. Hadjiaggelidou[a], M. Varthaliti[a], S. Georgiadou[a], K. Laschos[a], P. Xirou[c], E. Yiannaki[d], N. Constantinou[a], D. Markala[d], K. Zervas[a]

EMD in 9 patients treated with Thal-based regimens: PCs detected in the soft tissue displayed anaplastic morphology and were CD56 (-)[3]

1. Allegre A, et al. Haematologica, 2002; 87: 609-614; 2. Short D, et al. Leukemia, 2011; 1-3; 3. Katodritou E, et al. Leukemia Res, 2009; 33: 1137-1140

Has the incidence of extramedullary disease increased in the modern therapeutic era?

bjh research paper

6%

Incidence and clinical features of extramedullary multiple myeloma in patients who underwent stem cell transplantation

bjh research paper

18% osseous, 7% extraosseous, 9% both

Development of extramedullary myeloma in the era of novel agents: no evidence of increased risk with lenalidomide–bortezomib combinations

7%

original article

Annals of Oncology 21: 325–330, 2010
doi:10.1093/annonc/mdp329
Published online 24 July 2009

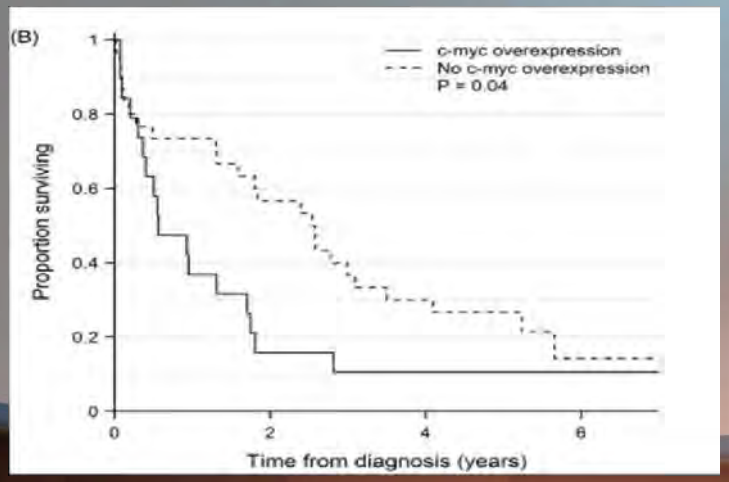
Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients

M. Varettoni*, A. Corso, G. Pica, S. Mangiacavalli, C. Pascutto & M. Lazzarino

Weinstock M, et al. Br J Haematol, 2015; 169: 851-858; Varga C, et al. Br J Haematol, 2015; Varettoni M, et al. Ann Oncol, 2010; 21: 325-330

C-myc in MM

- C-myc is expressed in about 2/3 of MM patients but not in MGUS
- Its activation is involved in secondary genetic events leading to the transition from MGUS to MM
- C-myc overexpression correlates with high PC proliferative rate (high Ki67 expression) and shorter OS



Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: http://www.tandfonline.com/loi/ilal20

Overexpression of c-myc is associated with adverse clinical features and worse overall survival in multiple myeloma

Agoston Gyula Szabo, Anne Ortved Gang, Mette Ølgod Pedersen, Tim Svenstrup Poulsen, Tobias Wirenfeldt Klausen & Peter Nørgaard

LEUKEMIA & LYMPHOMA, 2016

MYC Protein Expression Is Detected in Plasma Cell Myeloma but Not in Monoclonal Gammopathy of Undetermined Significance (MGUS)

Ruobing Xiao, MD, Jan Cerny, MD, PhD,† Katherine Devitt, MD,* Karen Dresser, BS,* Rajneesh Nath, MD,† Muthalagu Ramanathan, MD,† Scott J. Rodig, MD, PhD,‡,§ Benjamin J. Chen, MD, PhD,* Bruce A. Woda, MD,* and Hongbo Yu, MD, PhD**

(*Am J Surg Pathol* 2014;38:776–783)

Clinical and biological implications of MYC activation: a common difference between MGUS and newly diagnosed multiple myeloma

W-J Chng[1,2,3], GF Huang[2], TH Chung[3], SB Ng[4], N Gonzalez-Paz[5], T Troska-Price[5], G Mulligan[6], M Chesi[1], PL Bergsagel[1] and R Fonseca[1]

[1]*Department of Haematology/Oncology, Mayo Clinic Comprehensive Cancer Center, Scottsdale, AZ, USA;* [2]*Department of Haematology-Oncology, National University Cancer Institute Singapore, National University Health System, National University of Singapore, Singapore;* [3]*Cancer Science Institute Singapore, National University of Singapore, Singapore;* [4]*Department of Pathology, National University of Singapore, Singapore;* [5]*Department of Haematology, Mayo Clinic, Rochester, MN, USA and* [6]*Translational Medicine, Millenium Pharmaceuticals, Boston, MA, USA*

Leukemia (2011), 1–10

Rationale of extramedullary relapse in MM

1) The combination of novel agents lead to suppression of more benign clones and the emergence of highly aggressive drug resistant clones that have the capacity to migrate outside BM microenvironment

2) Novel drugs induce better disease control and prolong OS leading indirectly to high risk progressive disease (i.e. extramedullary disease)

3) Increased use of advanced imaging allows higher sensitivity in detecting extramedullary masses

4) EMD at diagnosis is a strong predictor for EMD at relapse suggesting that Inherent disease characteristics (preexisting aggressive subclones) may lead to the development of extramedullary disease rather the exposition to novel agents

Questions

- Do next generation novel agents correlate with the development of extramedullary disease?
- Are there any reliable biomarkers that could predict extramedullary disease?
- Could monitoring with advanced imaging be helpful for early recognition of extramedullary relapse?
- What are the exact mechanisms of hematogenous spread ?
- What is the best treatment approach for these patients?

Thank you

Multiple extramedullary plasmacytoma (?)

Educational Workshops

Artur Jurczyszyn MD, PhD, Assoc. Prof.
Department of Hematology
Jagiellonian University Medical College

ATHENES, October 26-27 2018

CASE REPORT

- 54 y old woman
- ***no medical history***
- ***medications***: iron supplements 2x 0,5y in the past
- ***PMH***:
  - mild anemia
  - tuberculosis (1992)- TB treatment completed
  - ovarian cyst removal (2002)
- ***allergies***: tramadol, penicillin
- ***addictives***: cigarettes- av. 5/d yet; 10/d overall
- ***FH***
  - mother: G-B disease
  - sister: G-B disease
  - son: asthma, atopic dermatitis, food allergy
- ***gynecologic history***: regular cycles; periods 4-5d, moderate blood loss; G3, P3
- ***occupation***: nurse

CC/HPI

[01/2016] **sacral region**: small pea-sized cohesive **lump** with red aerola

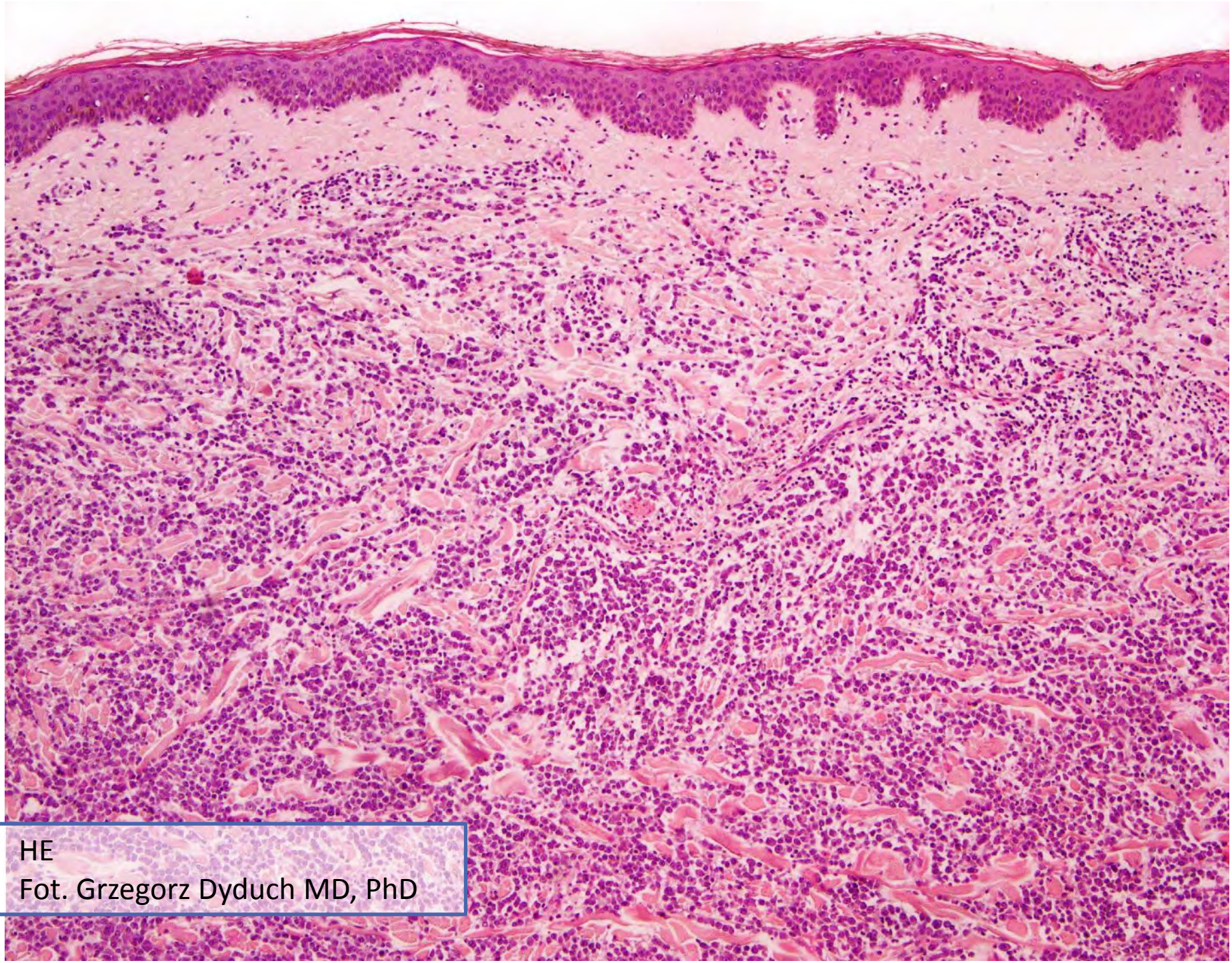
[05/2016] hospital in Dębica – **surgical removal** of skin lump

hist-pat: diffused infiltration with plasma-cell line cells,

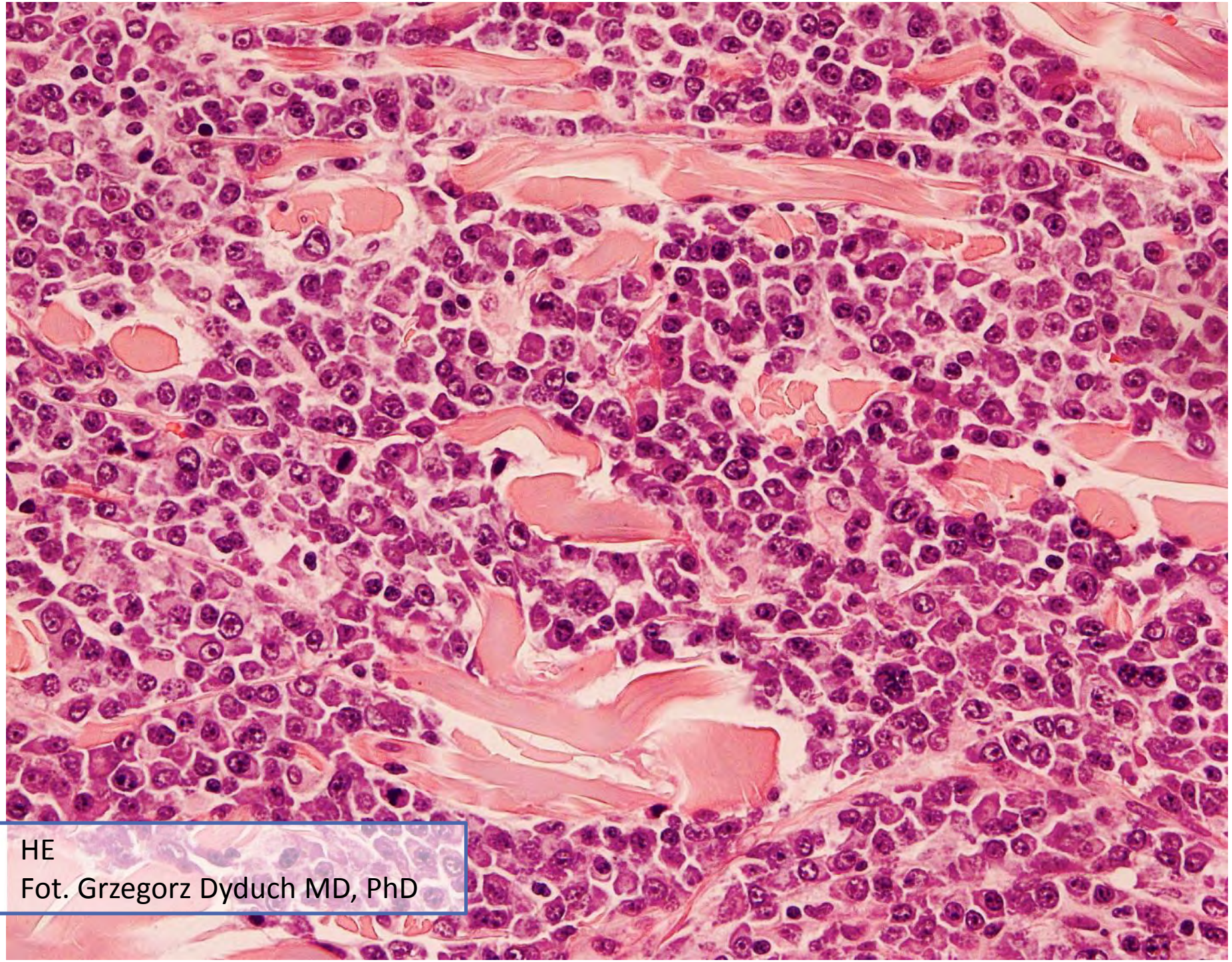
CD3(-), CD20(-), kappa(-), lambda(+), CD138(+), CD56(+), CD30(-), CD123(-), ALK(-), Ki67-50%

EXTRAOSSEUS PLASMACYTOMA

[05/07/2016] Department of Hematology, University Hospital in Krakow



HE
Fot. Grzegorz Dyduch MD, PhD



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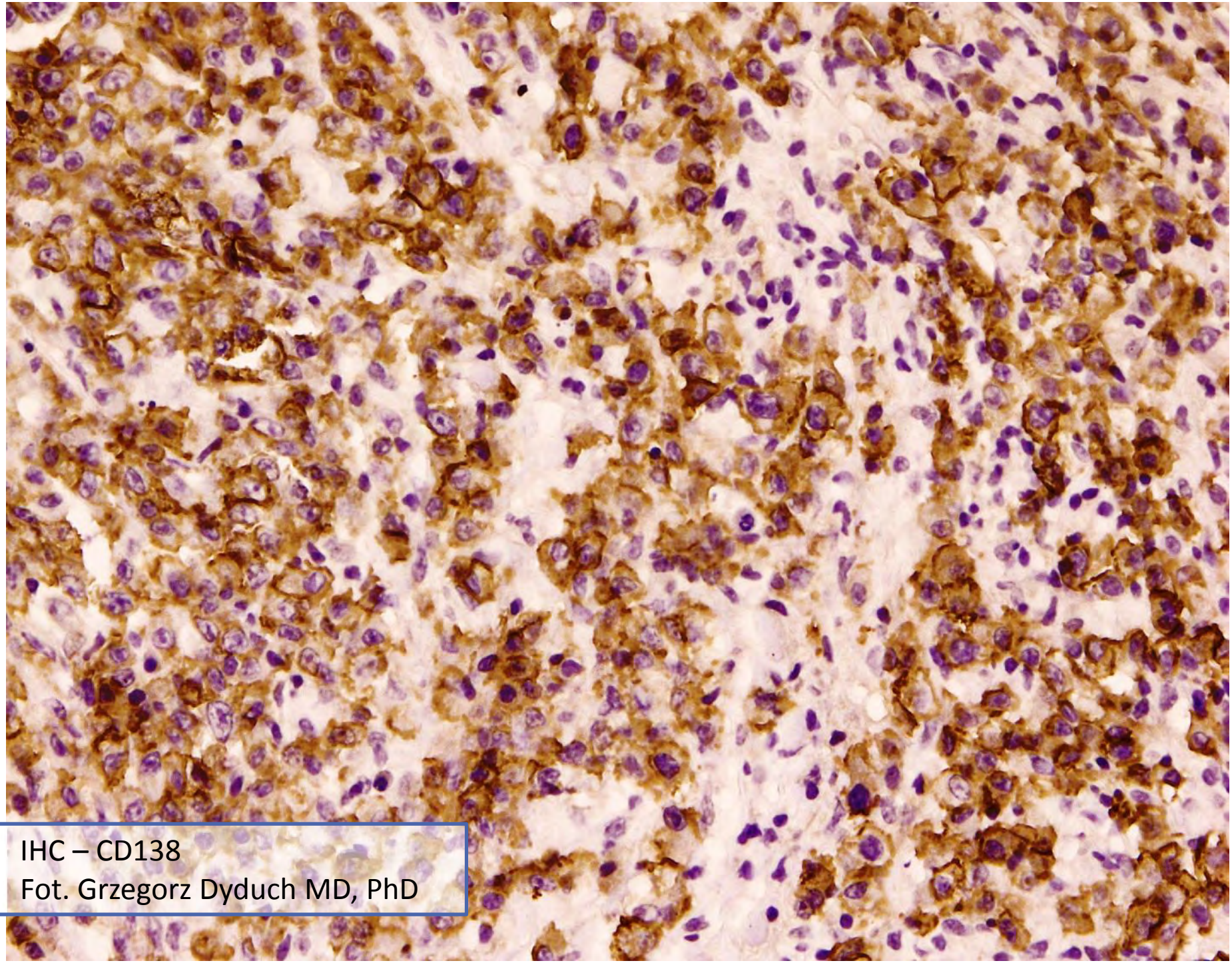
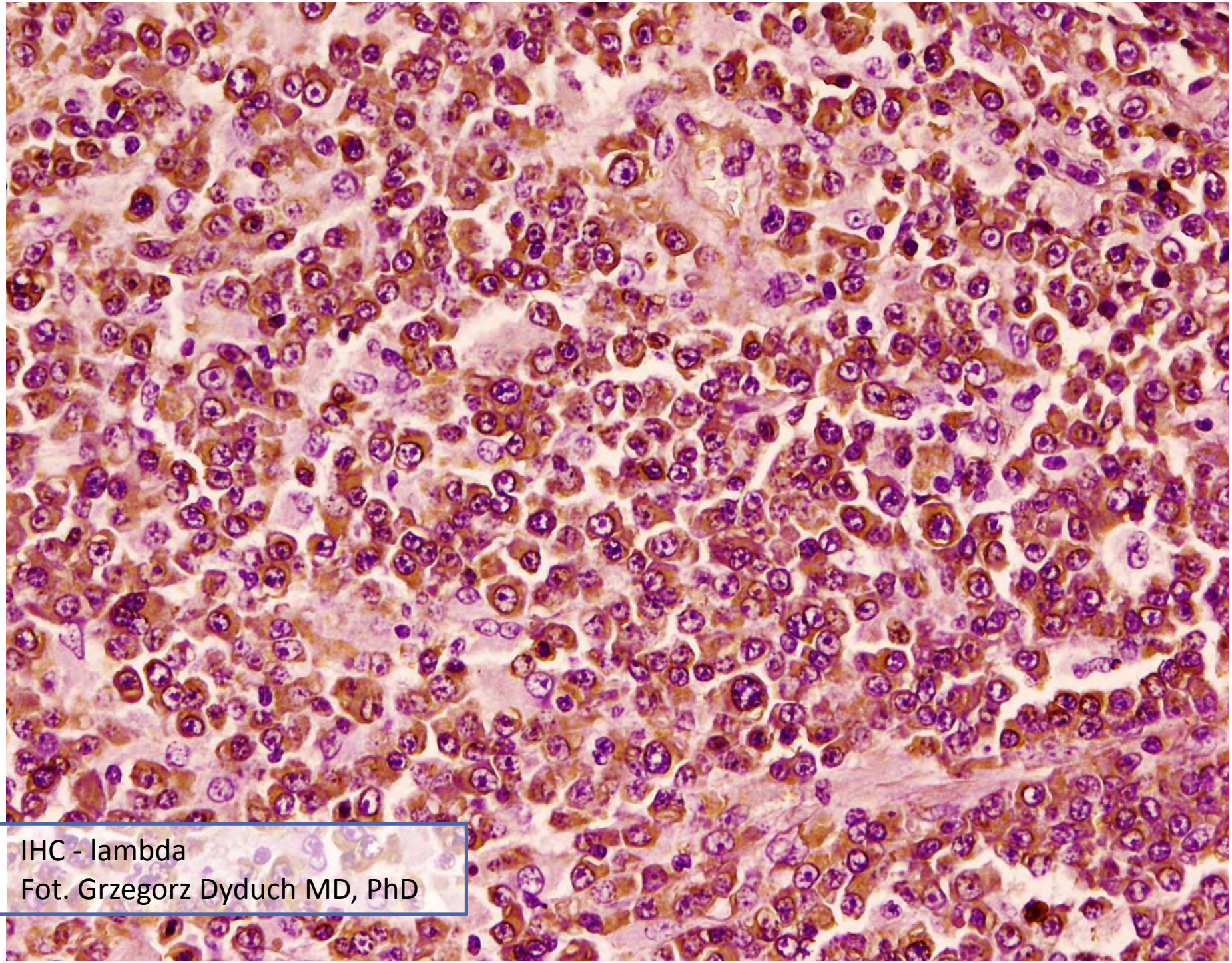
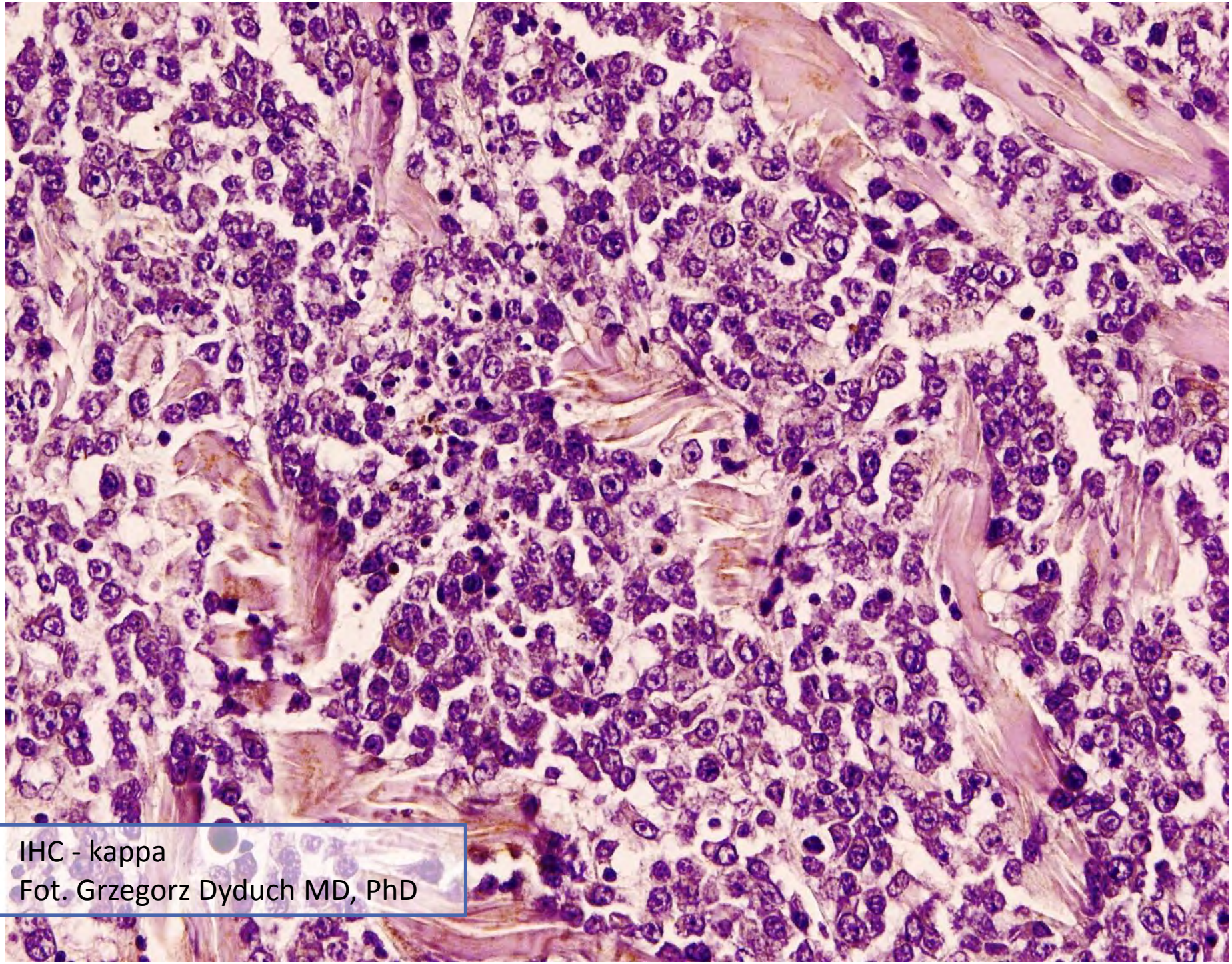
Fot. Grzegorz Dyduch MD, PhD



IHC – CD138
Fot. Grzegorz Dyduch MD, PhD



IHC - lambda
Fot. Grzegorz Dyduch MD, PhD



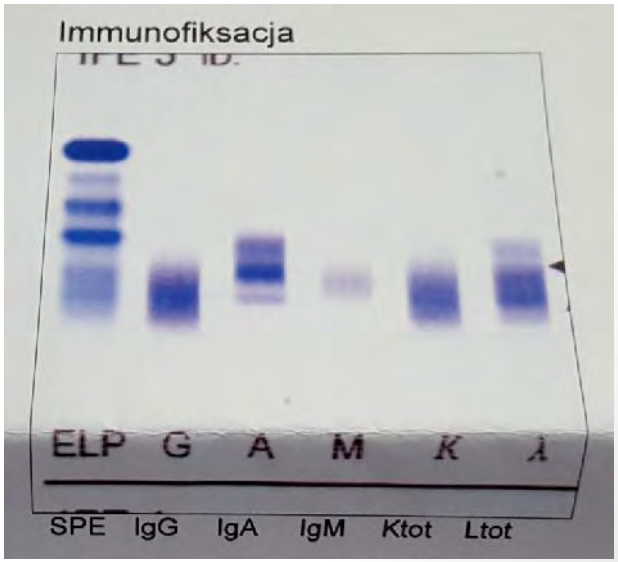
IHC - kappa
Fot. Grzegorz Dyduch MD, PhD

Lab tests

calcium	2,32 mmol/l	[2,15 - 2,55]
iron	**4,00 umol/l**	**[5,83 - 34,50]**
ferritin	**5 ug/l**	**[13 - 400]**
TIBC	**85,80 umol/l**	**[40,80 - 76,60]**
creatinin	64,0 umol/l	[44 - 80]
eGFR MDRD	> 60 ml/min/1,73m2	[> 60]
protein	70,0 g/l	[66,0 - 87,0]
albumin	43,00 g/l	[35,00 - 52,00]
LDH	392 U/l	[240 - 480]
APTT	34,2 sec	[26,0 - 36,0]
INR	1,01	[0,90 - 1,20]
fibrinogen	3,7 g/l	[1,8 - 3,5]
CRP	2,33 mg/l	[< 5,00]

IgA	3,87 g/l	[0,70 - 4,00]
IgG	8,09 g/l	[6,38 - 17,00]
IgM	1,16 g/l	[0,40 - 2,30]
κ	12,90 mg/l	[6,70 - 22,40]
λ	19,20 mg/l	[8,30 - 27,00]
κ/λ	0,6719	[0,31 - 1,56]
β2m	2,03 mg/L	[1,09 - 2,53]

IFE: poorly isolated monoclonal IgAλ with triple zone- 1 in β fraction, other in γ fraction



Lab tests

SPE

Albumins %	50,30 %	[60,00 - 71,00]
α-1 globulins %	3,60 %	[1,40 - 2,90]
α-2 globulins %	14,80 %	[7,00 - 11,00]
β-globulins %	15,50 %	[8,00 - 13,00]
γ-globulins %	15,80 %	[9,00 - 16,00]
Albumins	35,21 g/l	[35,00 - 55,00]
α-1 globulins	**2,52 g/l**	**[0,90 - 2,10]**
α-2 globulins	**10,36 g/l**	**[5,00 - 7,90]**
β-globulins	**10,85 g/l**	**[5,70 - 7,90]**
γ-globulins	11,06 g/l	[6,50 - 11,50]
A/G	1,01	

Trephine biopsy

cellularity : 40-60%

IHC: CD138(+), kappa(+), lambda(+) – 4-5%

no histological evidence of neoplastic plasma cells

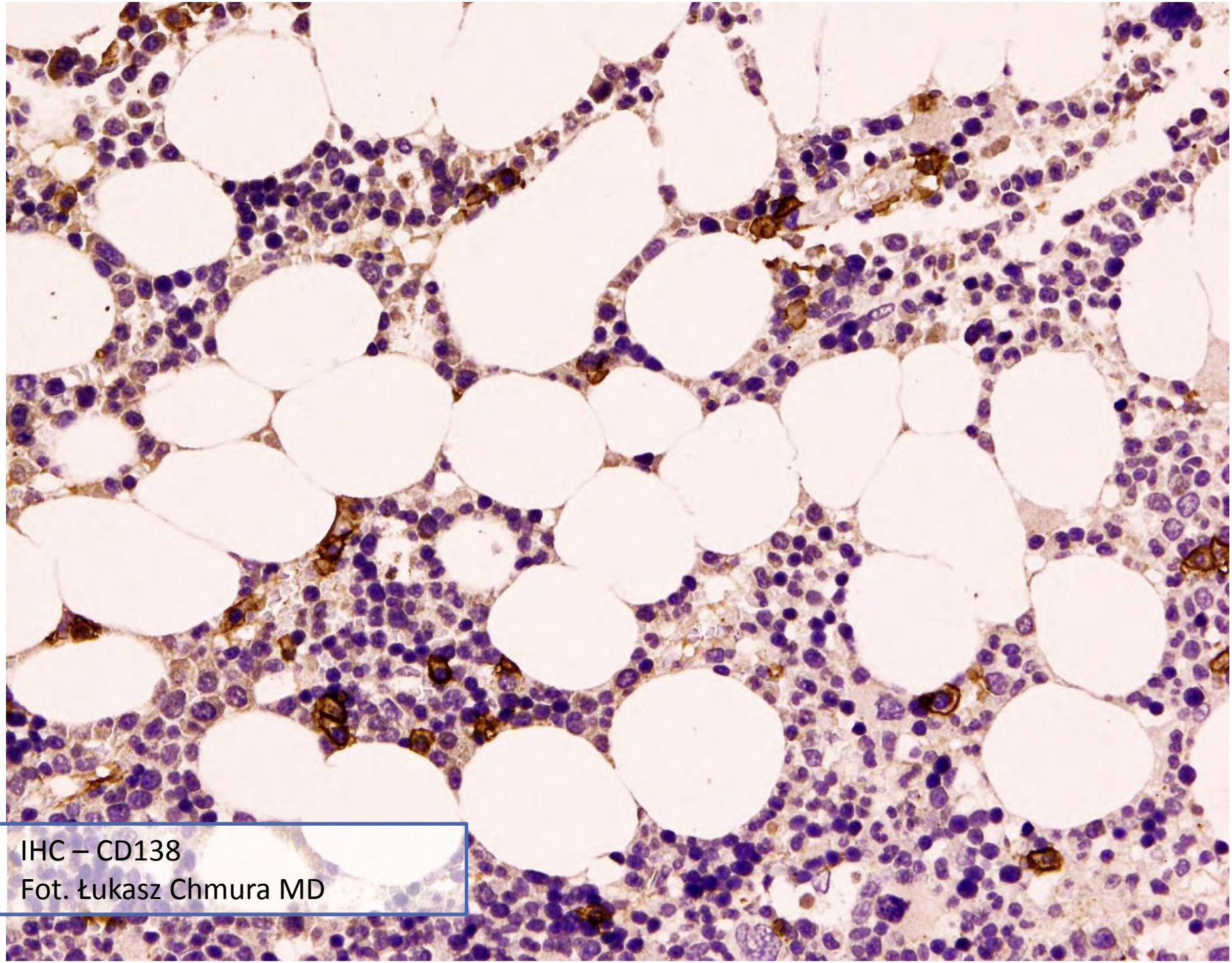
Cytogenetics

plasma cells: 3,3%

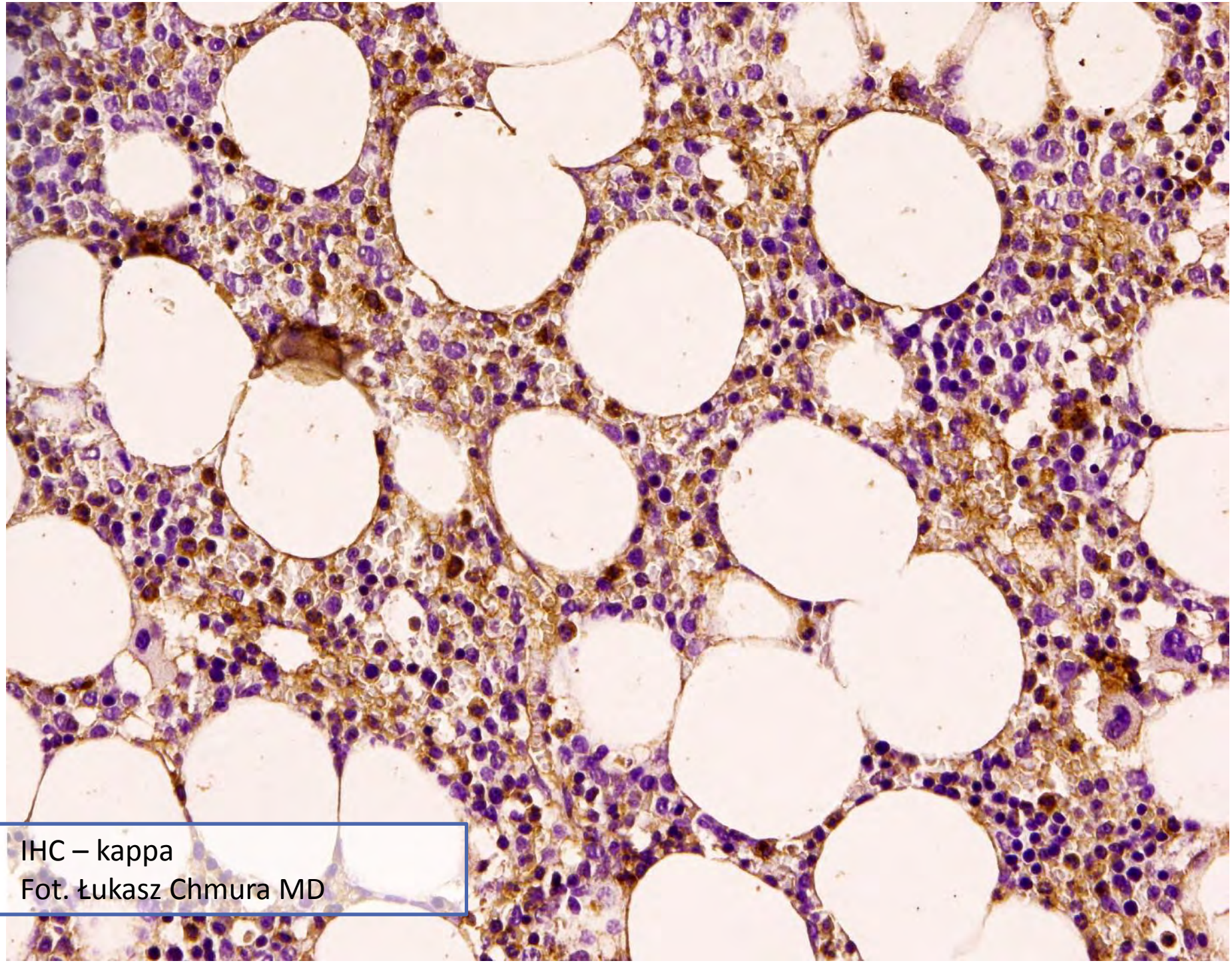
no CD138 positive segregation

Myelogram

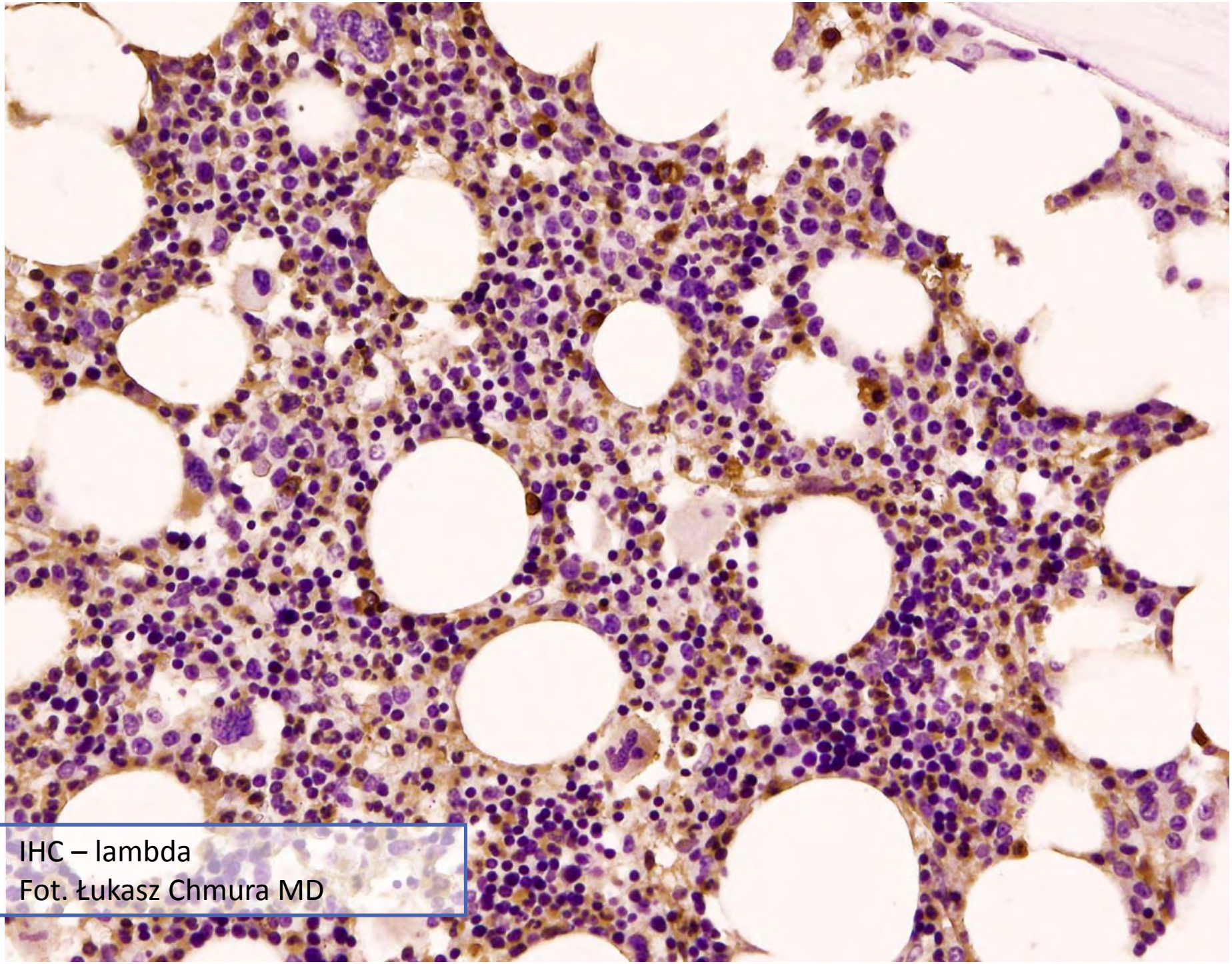
metamyelocytes neutrophilic	5,3%	8,0-25,0
eosinophilic bands	0,0%	0,4-1,0
segmented neutrophils	24,5%	11,0-20,0
lymphocytes	18,3%	3,0-12,0
plasmablasts	0,0%	0,0
plasma cells	3,3%	0,2-2,0
megakariocytes	0,0%	0,01-0,40
ratio granulo/erythro	3,4:1	3:1-4:1



IHC – CD138
Fot. Łukasz Chmura MD



IHC – kappa
Fot. Łukasz Chmura MD



IHC – lambda
Fot. Łukasz Chmura MD

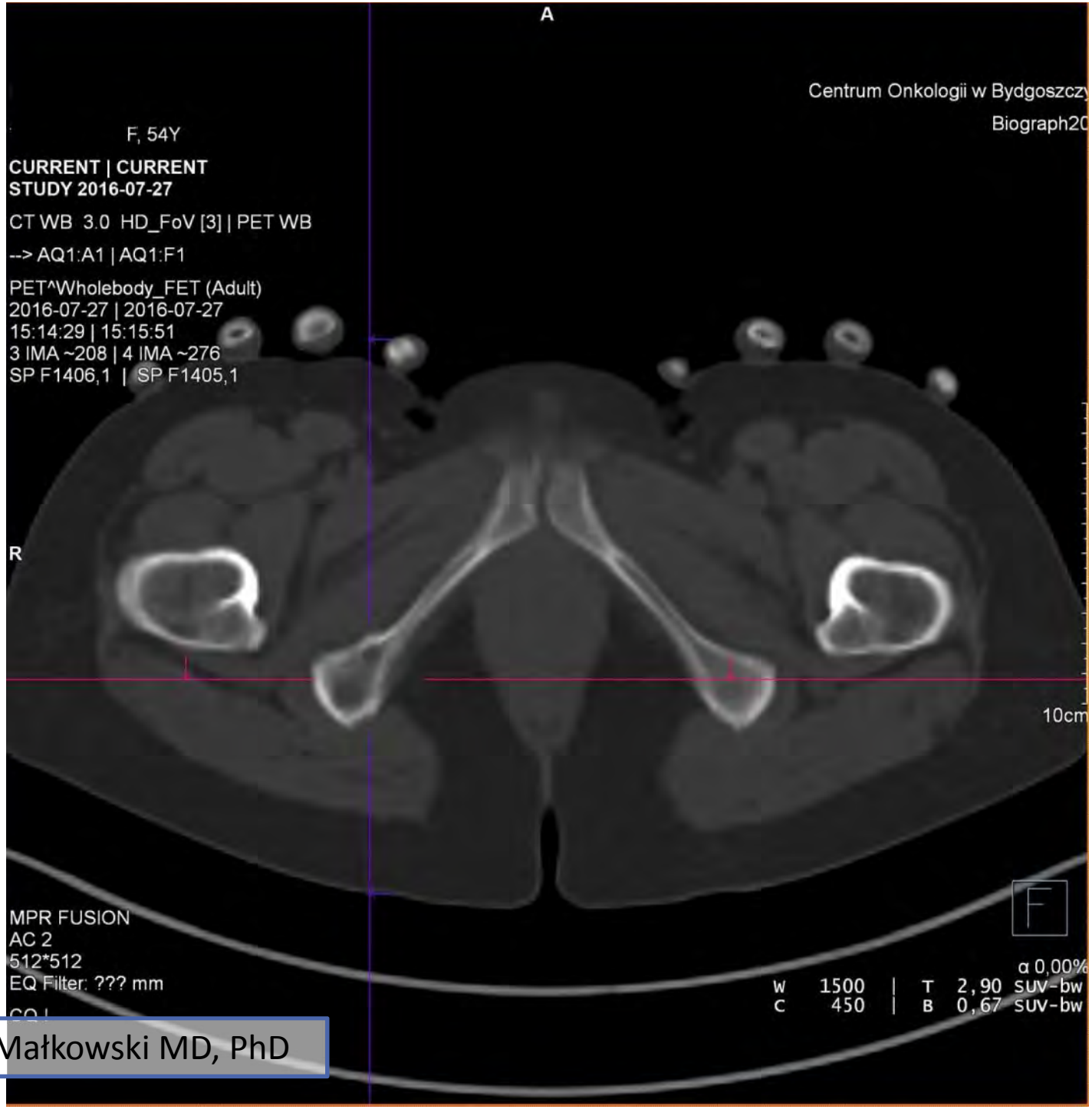
[27/07/2016] Department of Nuclear Medicine, Oncology Centre in Bydgoszcz

PET/CT

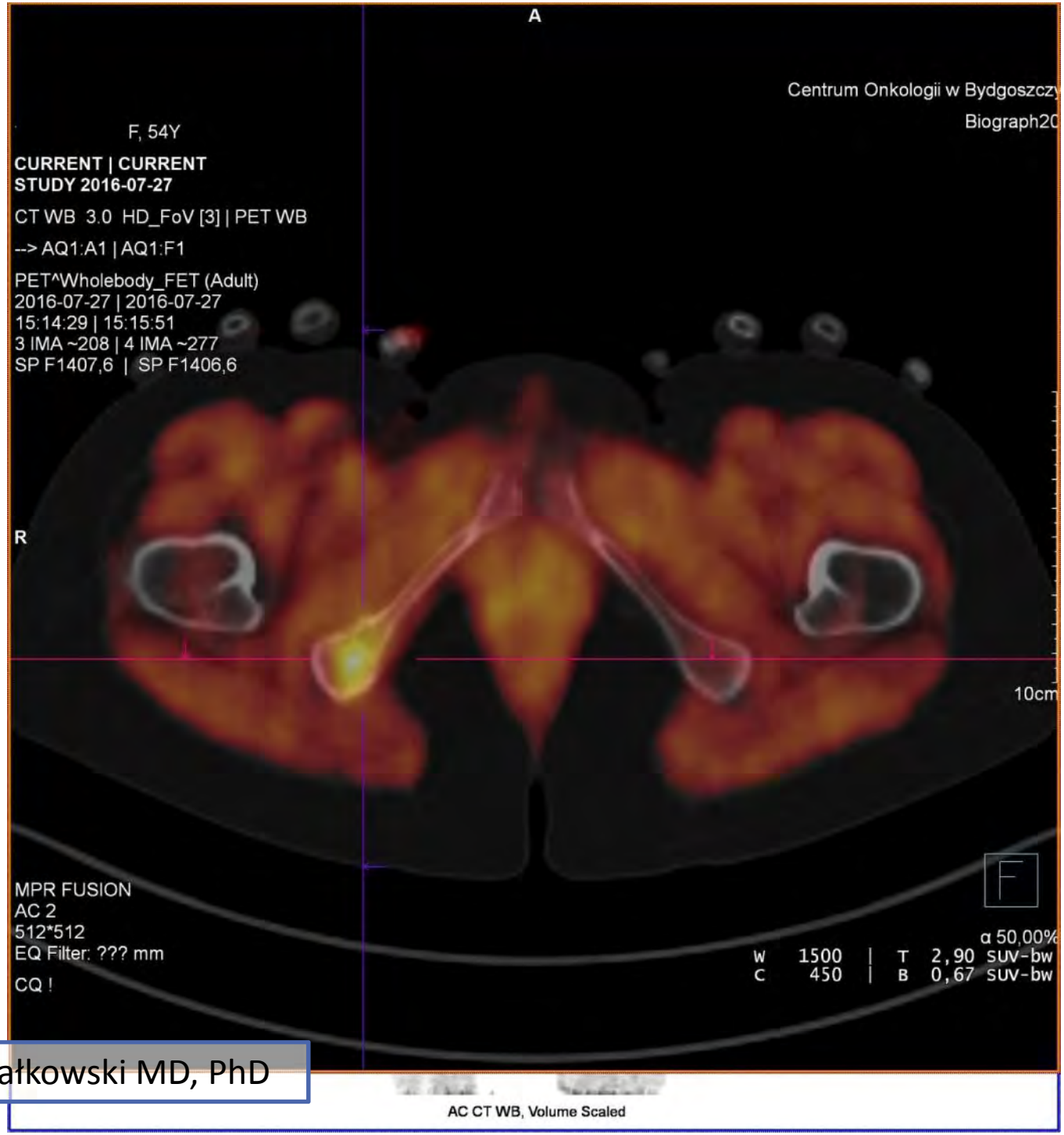
- **right sciatic tuber**: osteolytic lesion 9mm; *SUV 2,9*
- **ascending colon:** mass-like lesion infiltrating the colon wall 39x13x42 mm; *SUV 4,12*

EXTRAOSSEUS FOCUS

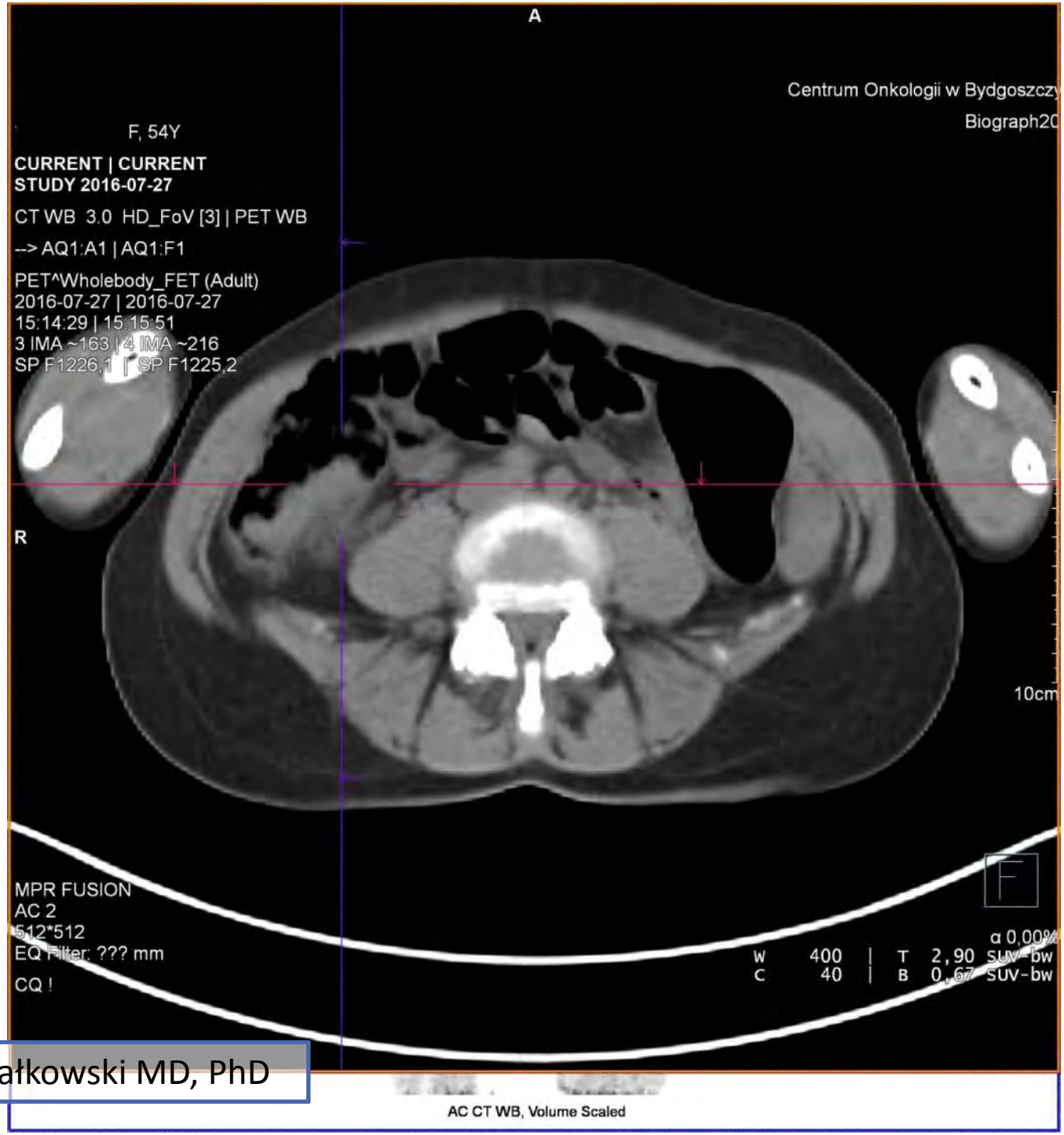
or SIMULTANEOUS PRIMARY COLON MALIGNANCY ???



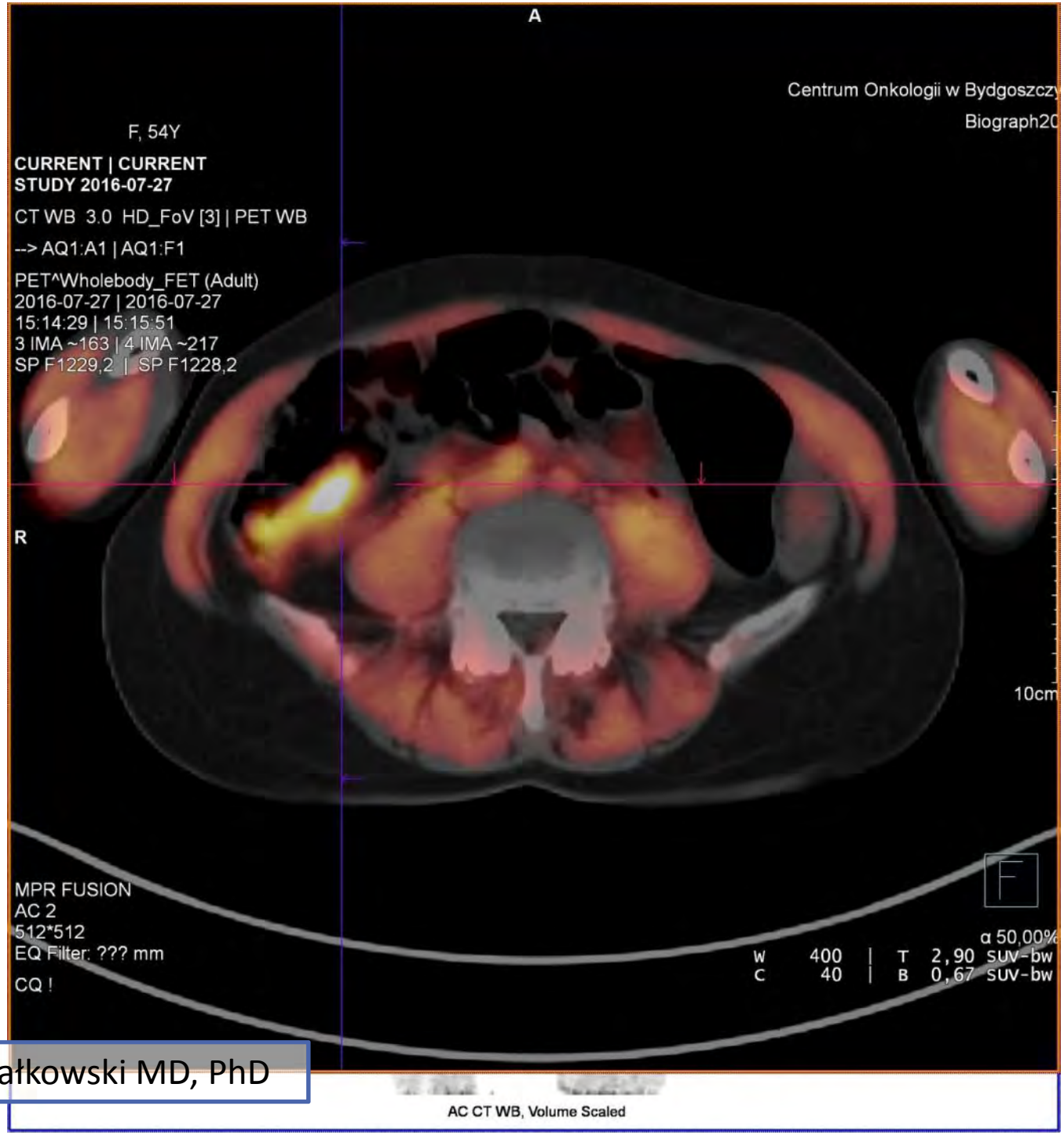
Fot. Bodan Małkowski MD, PhD



Fot. Bodan Małkowski MD, PhD



Fot. Bodan Małkowski MD, PhD



Fot. Bodan Małkowski MD, PhD

THERAPY & results

[08/09/2016] Hospital in Dębica; General Surgery Ward – **right hemicolectomy**

hist-pat: EXTRAOSSTEUS PLASMACYTOMA infiltrating the muscular layer of the colon wall, focally- serous membrane; no angioinvasion; surgical magins clear

[11-12/2016] **rth VMAT** - total dose of 50 Gy/25 fractions

[02/2017] **hematological CR**

calcium	2,34 mmol/l	[2,15 - 2,55]
iron	25,30 umol/l	[5,83 - 34,50]
ferritin	30 ug/l	[13 - 400]
creatinin	70,0 umol/l	[44 - 80]
protein	63,0 g/l	[66,0 - 87,0]
albumin	44,00 g/l	[35,00 - 52,00]
LDH	302 U/l	[240 - 480]
CRP	<1 mg/l	[< 5,00]

IgA	2,79 g/l	[0,70 - 4,00]
IgG	8,34 g/l	[6,38 - 17,00]
IgM	1,34 g/l	[0,40 - 2,30]
κ	19,20 mg/l	[6,70 - 22,40]
λ	17,10 mg/l	[8,30 - 27,00]
κ/λ	1,1228	[0,31 - 1,56]
κ urine	7,570 mg/l	[< 7,300]
λ urine	< 3,690 mg/l	[< 4,000]

THERAPY & results

SPE

Albumins %	54,60 %	[60,00 - 71,00]
α-1 globulins %	2,90 %	[1,40 - 2,90]
α-2 globulins %	13,20 %	[7,00 - 11,00]
β-globulins %	13,40 %	[8,00 - 13,00]
γ-globulins %	15,90 %	[9,00 - 16,00]
Albumins	37,13 g/l	[35,00 - 55,00]
α-1 globulins	1,97 g/l	[0,90 - 2,10]
α-2 globulins	**8,98 g/l**	**[5,00 - 7,90]**
β-globulins	**9,11 g/l**	**[5,70 - 7,90]**
γ-globulins	10,81 g/l	[6,50 - 11,50]
A/G	1,2	

[02/2017] **disqualification from auto-PBSCT**

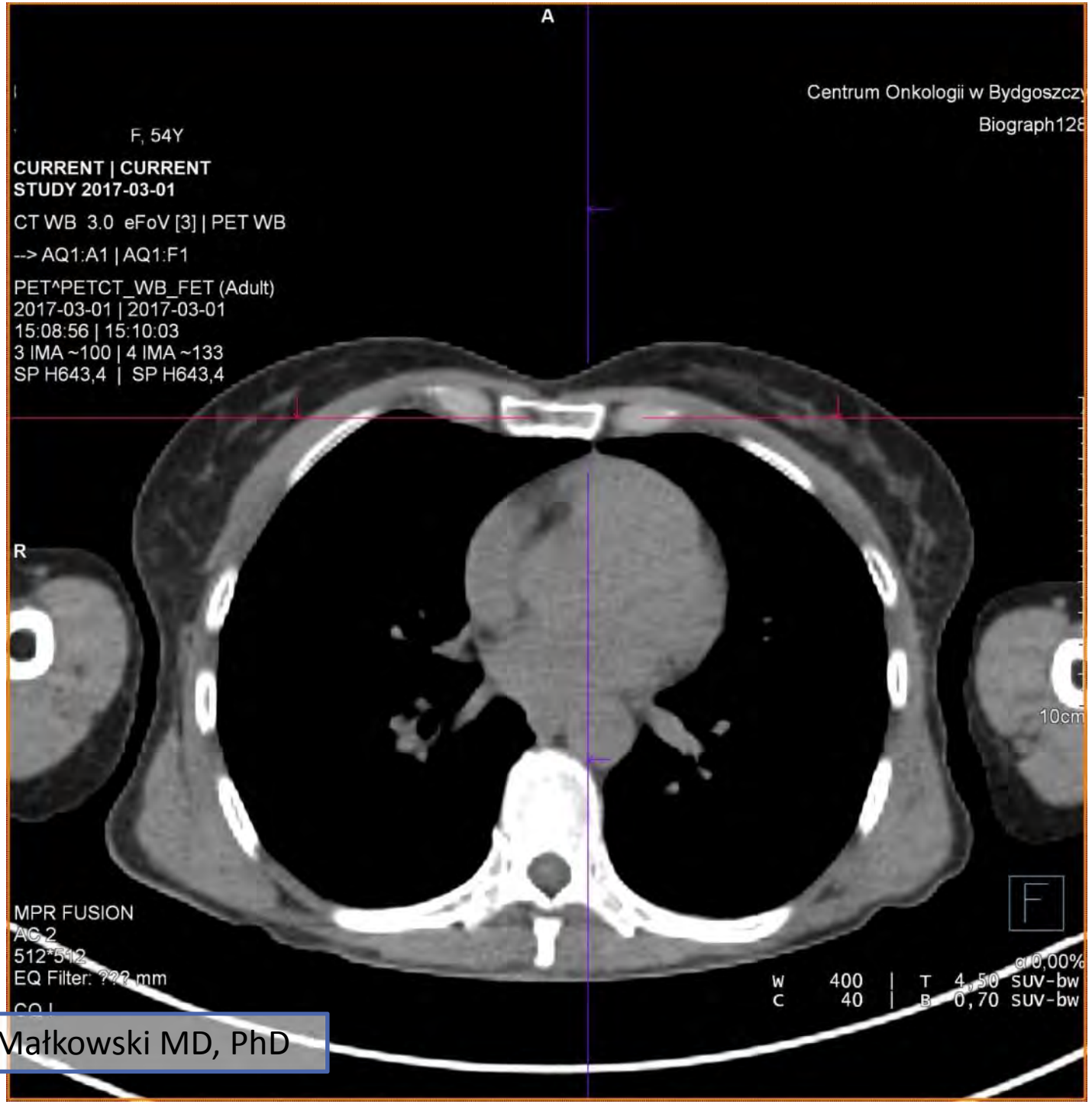
return to work

[01/03/2017] Department of Nuclear Medicine, Oncology Centre in Bydgoszcz

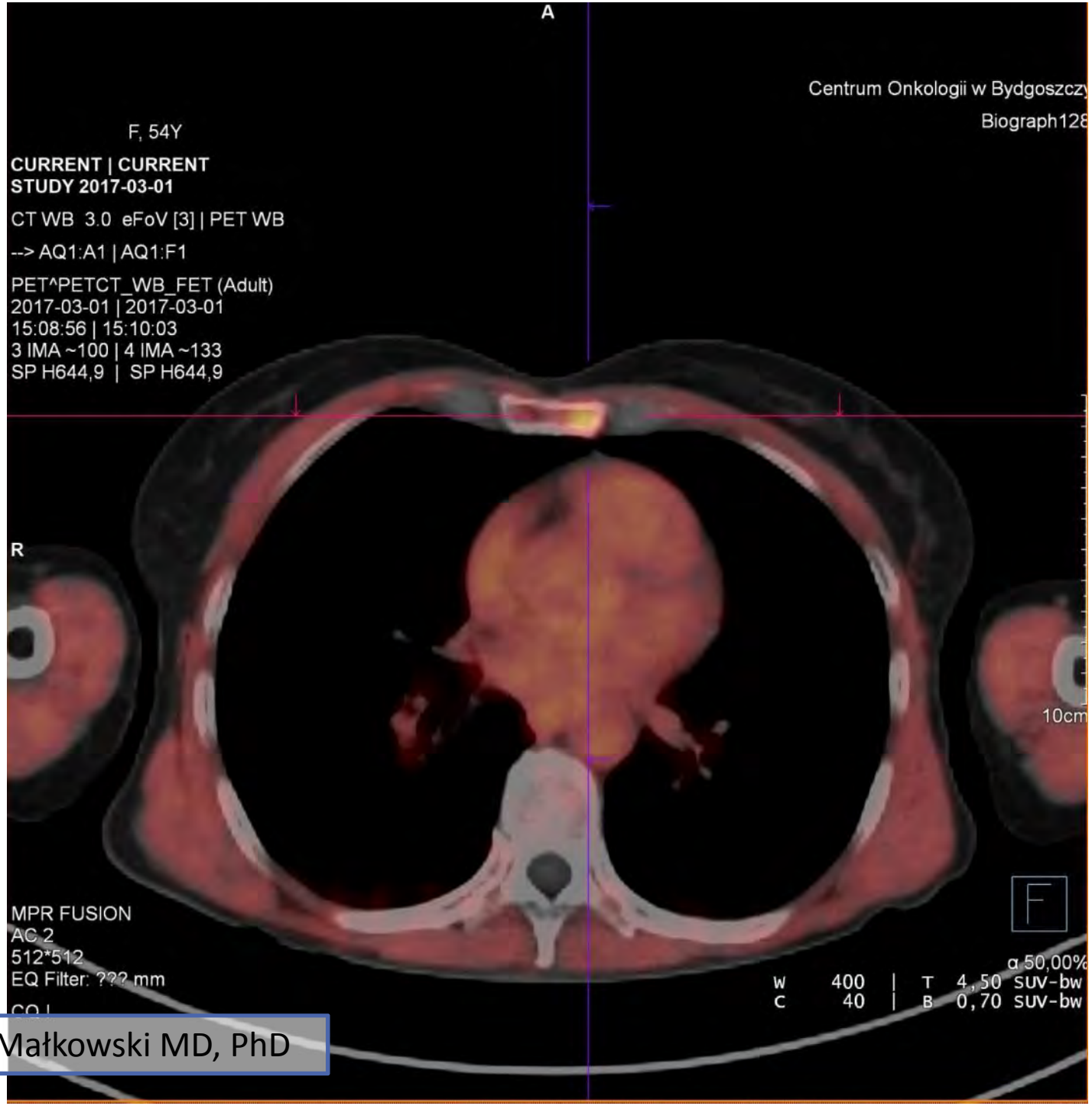
PET/CT

- **sternum-** inferior part, left side, at the level of 4th rib attachement increased 18F-FET uptake sized 11x9mm; *SUV 3,64*
- **left 4th rib-** *SUV 2,94*
- **right sciatic tuber**: osteolytic lesion 16x17mm; *SUV 2,27* (↓activity)

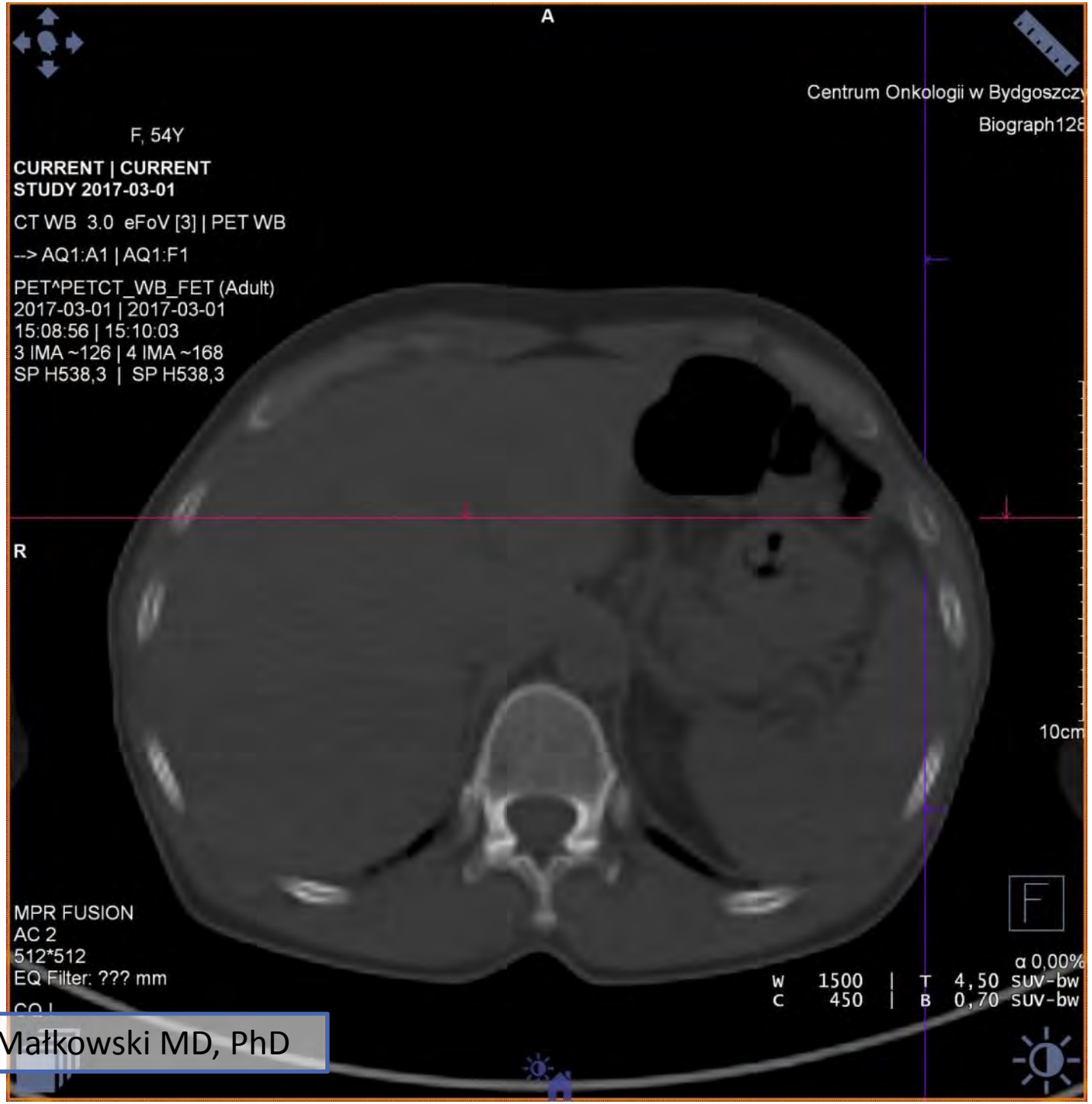
RECURRENCE



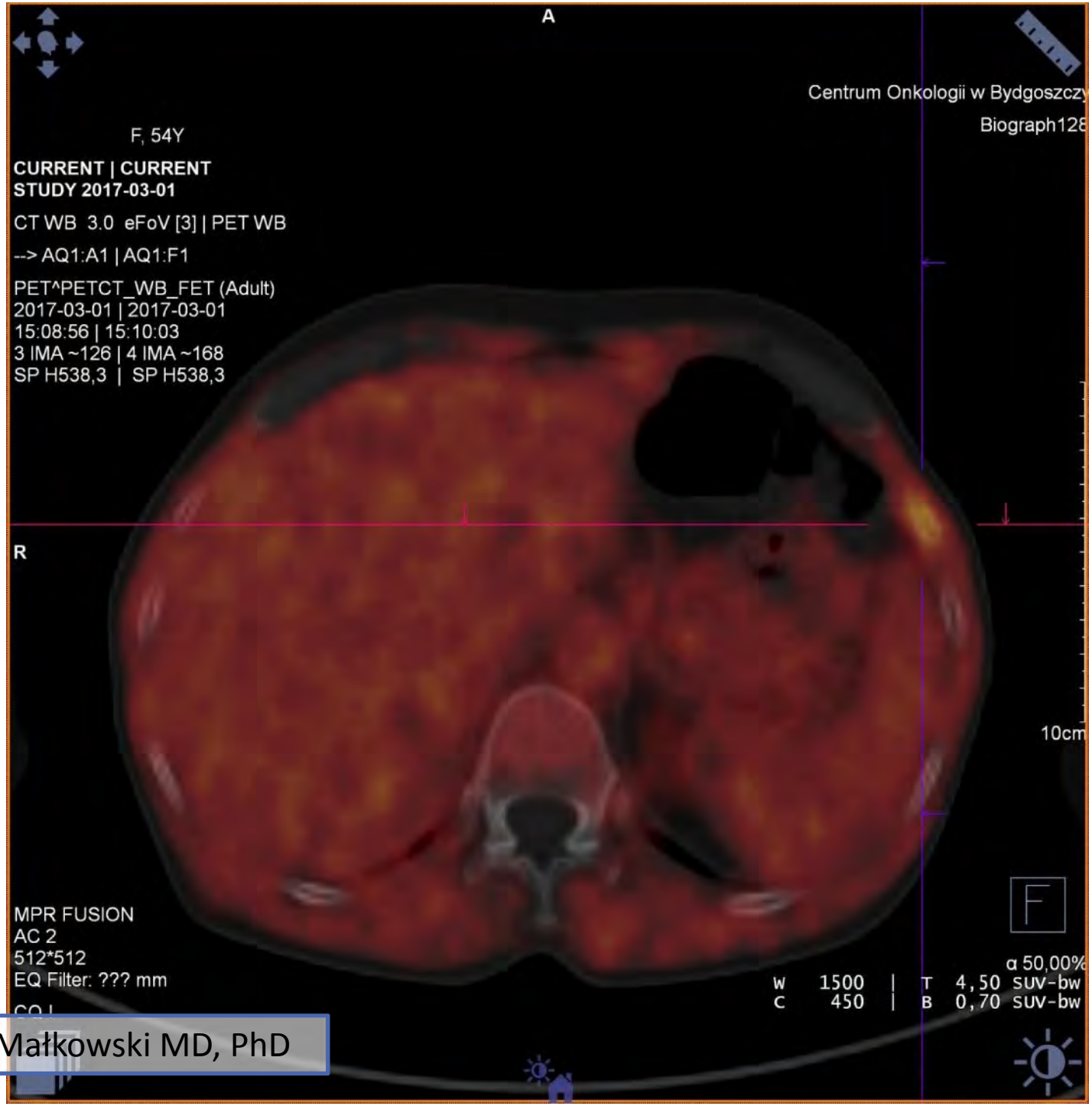
Fot. Bodan Małkowski MD, PhD



Fot. Bodan Małkowski MD, PhD



Fot. Bodan Małkowski MD, PhD



Fot. Bodan Małkowski MD, PhD

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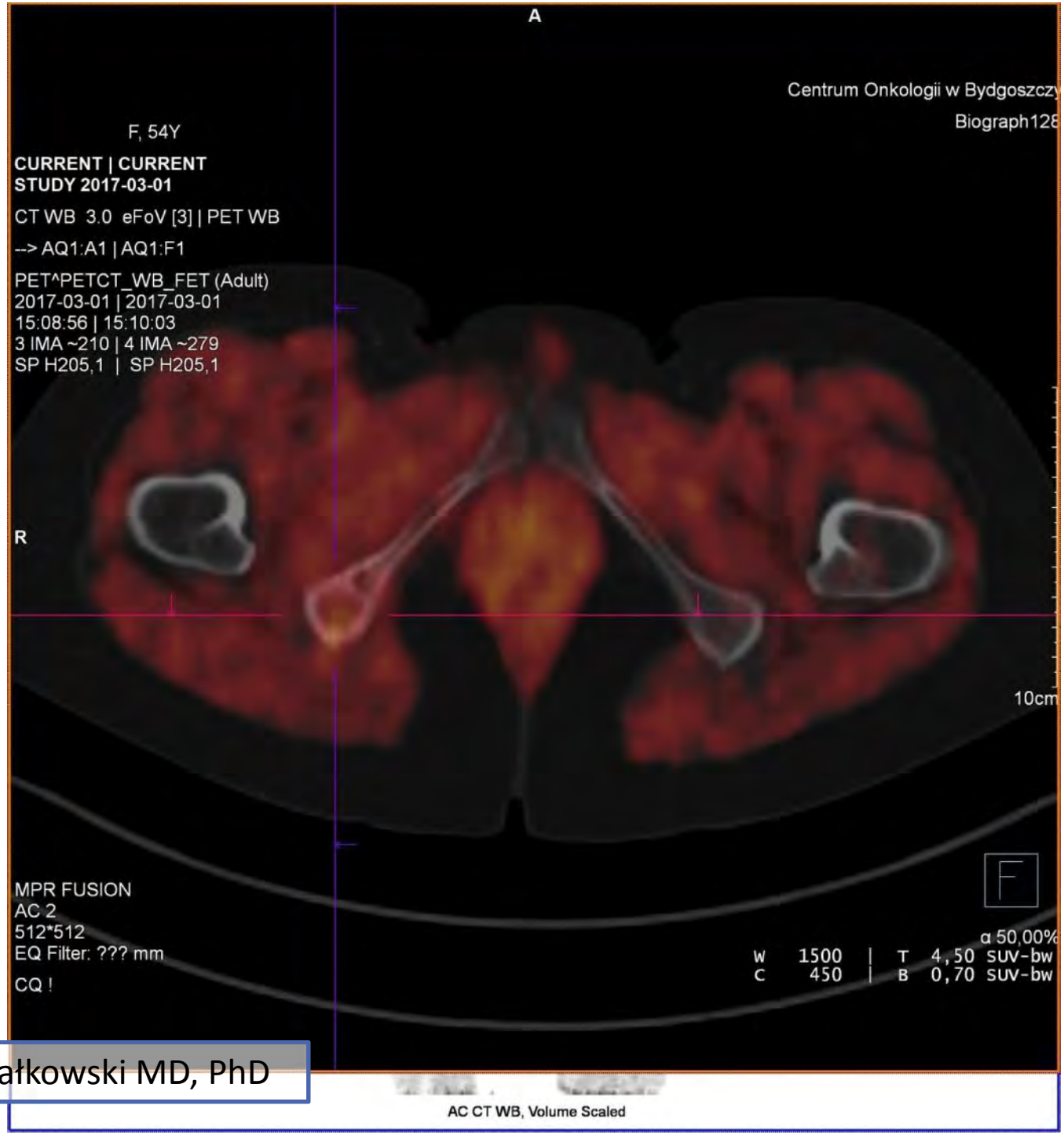


Fot. Bodan Małkowski MD, PhD

THERAPY & results

[20/03/2017] start of **chemotherapy VTD (She received 6 cycles)**

+ LMWH + biphosphonate + antiviral prophylaxix

IgA	2,88 g/l	[0,70 - 4,00]
IgG	9,05 g/l	[6,38 - 17,00]
IgM	1,21 g/l	[0,40 - 2,30]
κ FLC	21,70 mg/l	[3,30 - 19,40]
λ FLC	27,00 mg/l	[5,71 - 26,30]
κ/λ	0,8037	[0,26 - 1,65]
β2m	1,84 mg/L	[1,09 - 2,53]

IFE: trace of IgA

κ urine	< 6,690 mg/l	[< 7,300]
λ urine	< 3,690 mg/l	[< 4,000]

SPE

Albumins %	59,40 %	[60,00 - 71,00]
α-1 globulins %	2,60 %	[1,40 - 2,90]
α-2 globulins %	12,20 %	[7,00 - 11,00]
β-globulins %	11,60 %	[8,00 - 13,00]
γ-globulins %	14,20 %	[9,00 - 16,00]
Albumins	43,48 g/l	[35,00 - 55,00]
α-1 globulins	1,90 g/l	[0,90 - 2,10]
α-2 globulins	**8,93 g/l**	**[5,00 - 7,90]**
β-globulins	**8,49 g/l**	**[5,70 - 7,90]**
γ-globulins	10,39 g/l	[6,50 - 11,50]
A/G	1,46	

THERAPY & results

[10/04/2017] signs of peripheral polyneuropathy → pregabalin

IgA	1,07 g/l	[0,70 - 4,00]
IgG	6,21 g/l	[6,38 - 17,00]
IgM	0,88 g/l	[0,40 - 2,30]
κ FLC	20,10 mg/l	[3,30 - 19,40]
λ FLC	14,20 mg/l	[5,71 - 26,30]
κ/λ	1,4155	[0,26 - 1,65]

IFE: negative

[05/07/2017] Department of Nuclear Medicine, Oncology Centre in Bydgoszcz

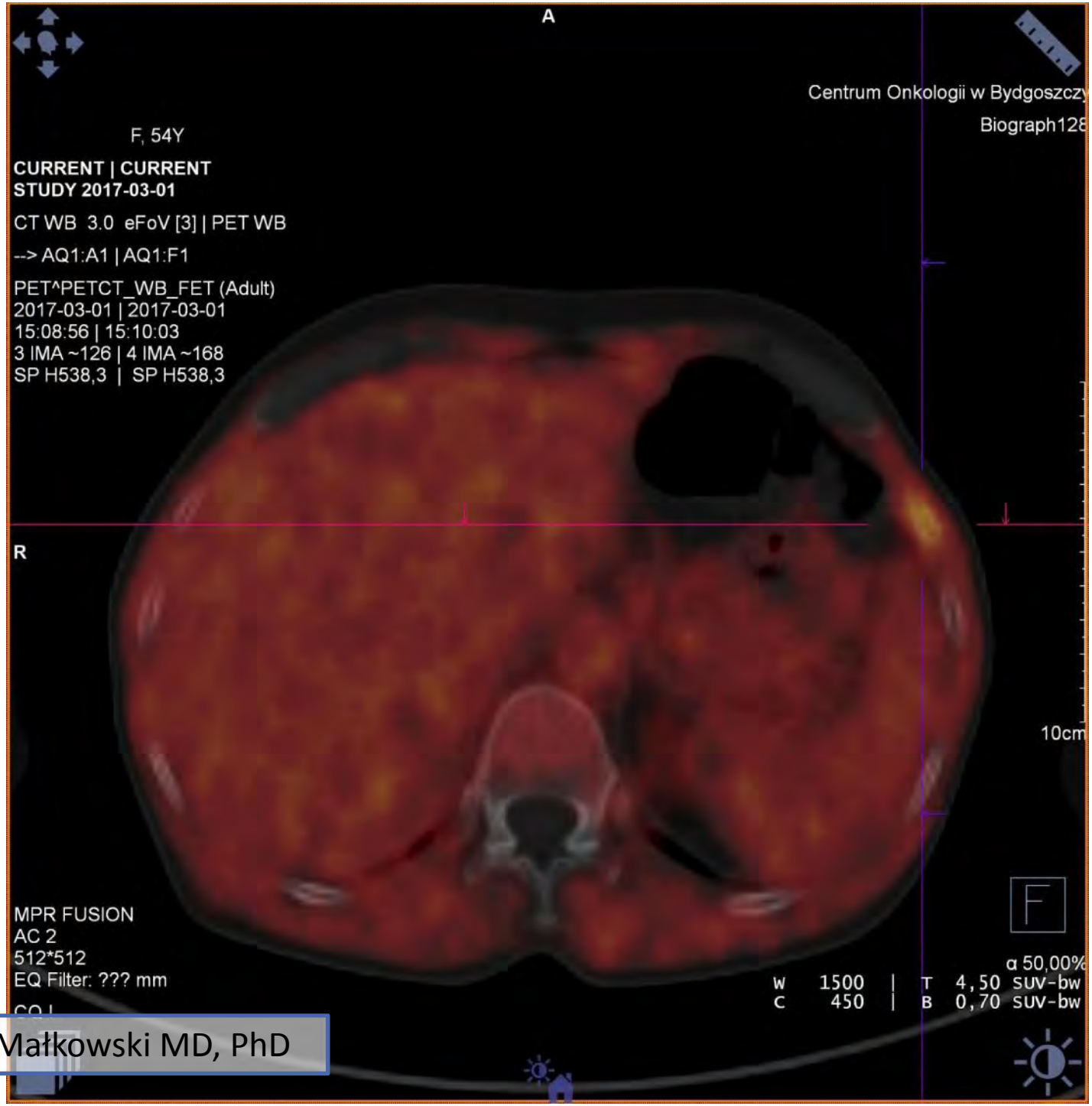
PET/CT

- **4th rib**- moderately increased 18F-FET uptake sized 11mm; *SUV 2,43* (↓)
- **right sciatic tuber**: osteolytic lesion 16x17mm; *SUV 1,8* (↓)

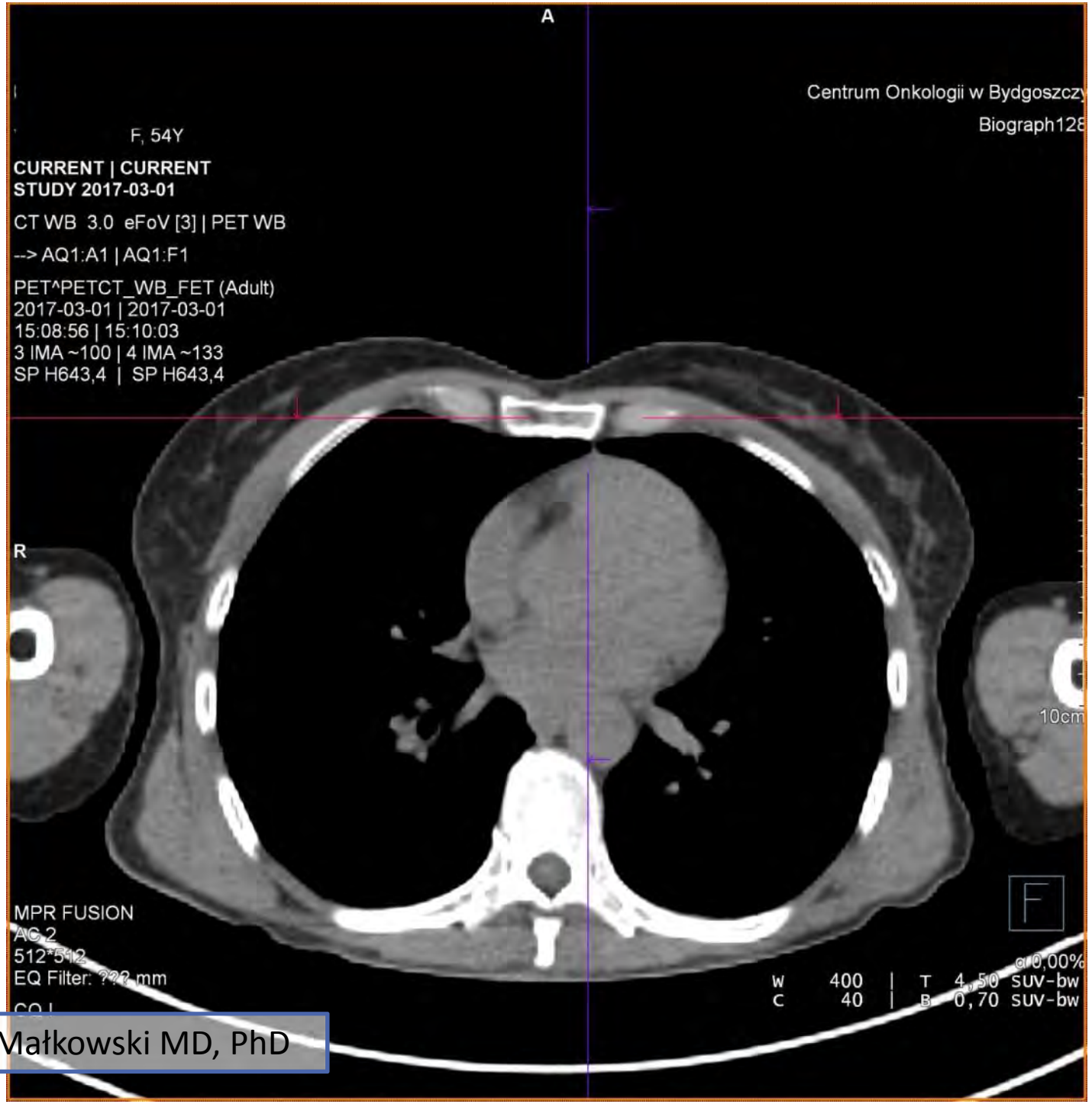
WITHOUT ACTIVE PROLIFERATIVE PROCESS

[> 09/2017] preparation for **auto-PBSCT;** after 6 cycles VTD

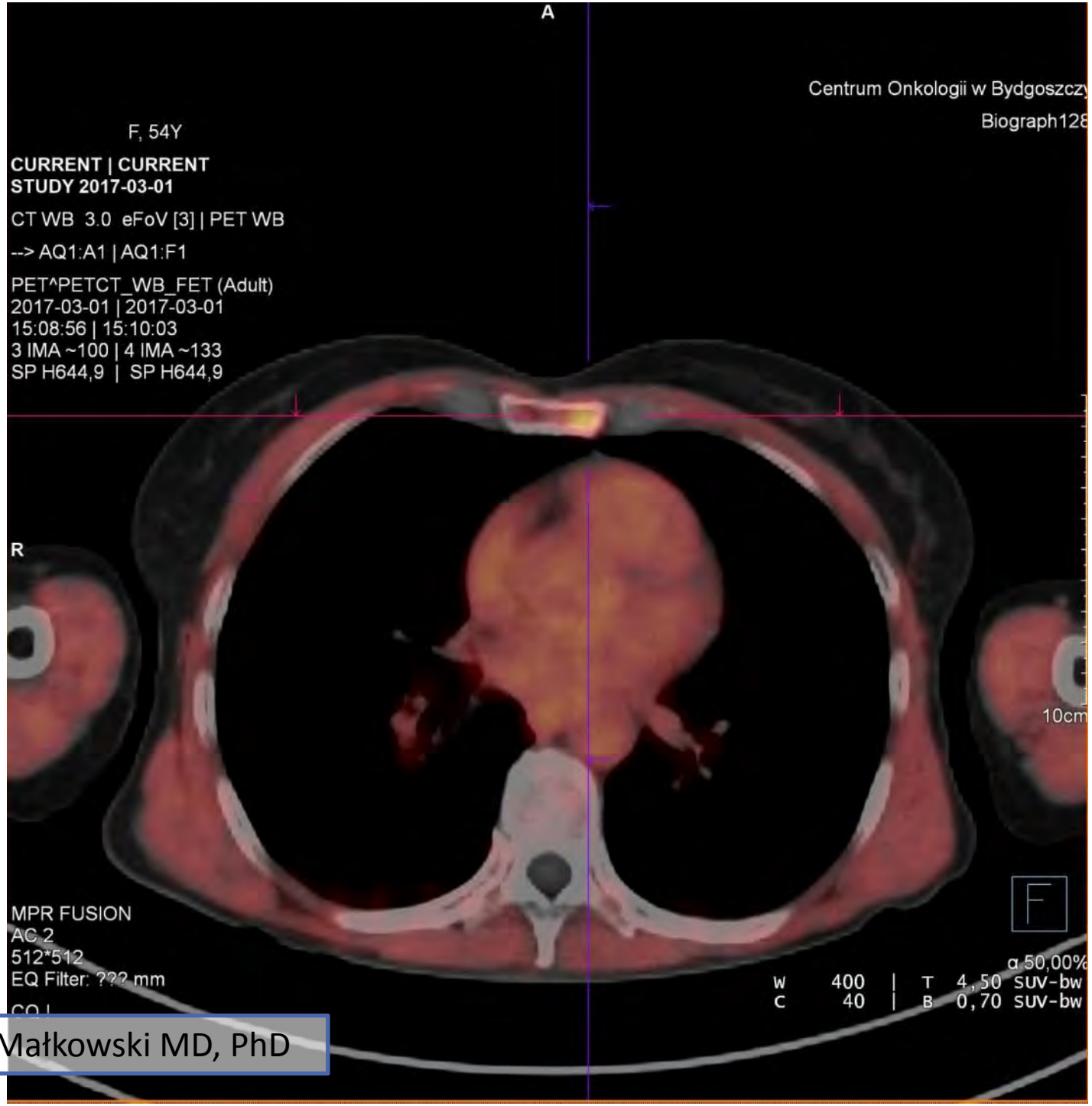
Tandem auto-PBSCT – November 2017 and April 2018
July 2018 – consolidation 1 cycle VDT-PACE; October 2018 - CR



Fot. Bodan Małkowski MD, PhD



Fot. Bodan Małkowski MD, PhD



Fot. Bodan Małkowski MD, PhD

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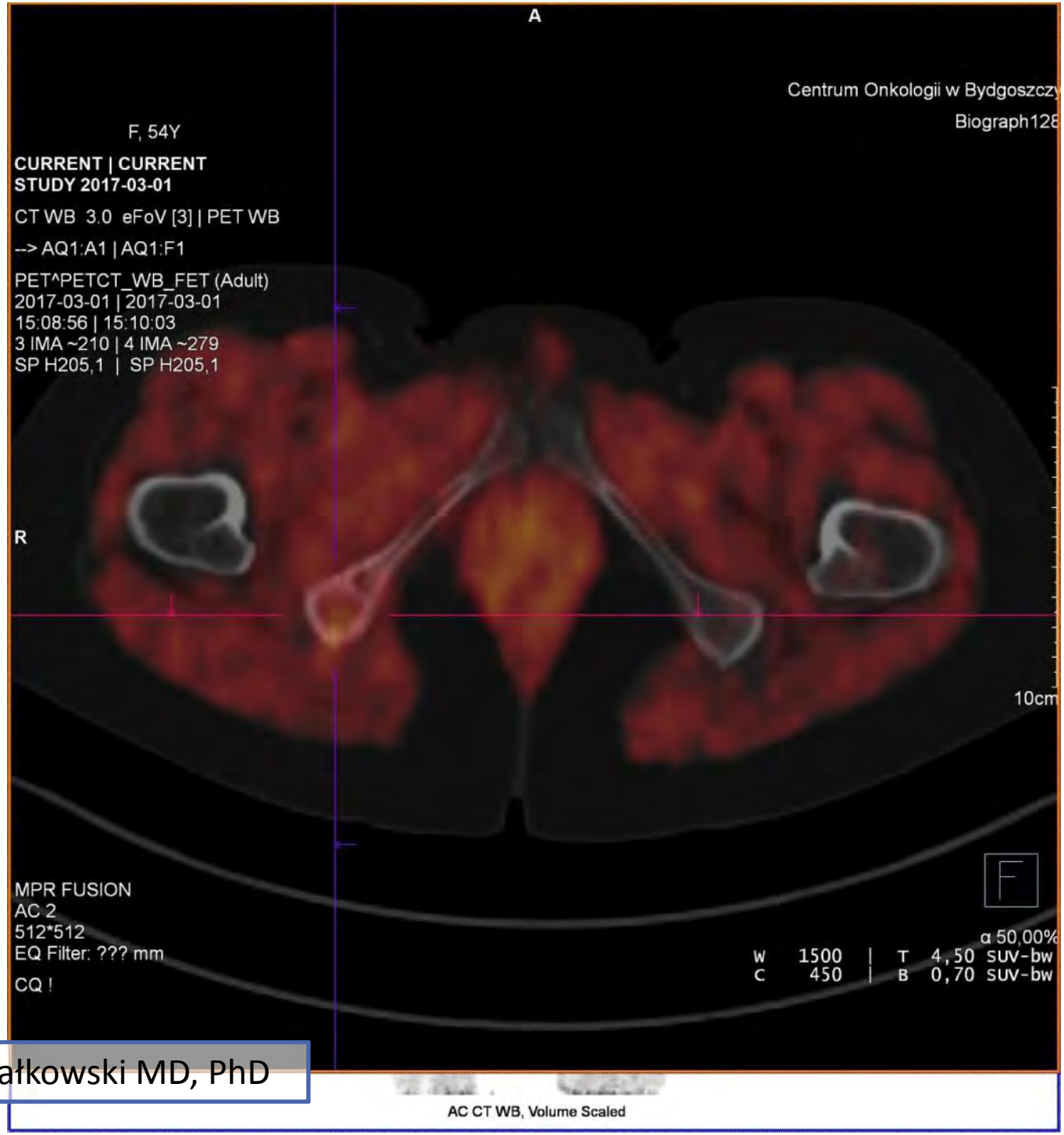

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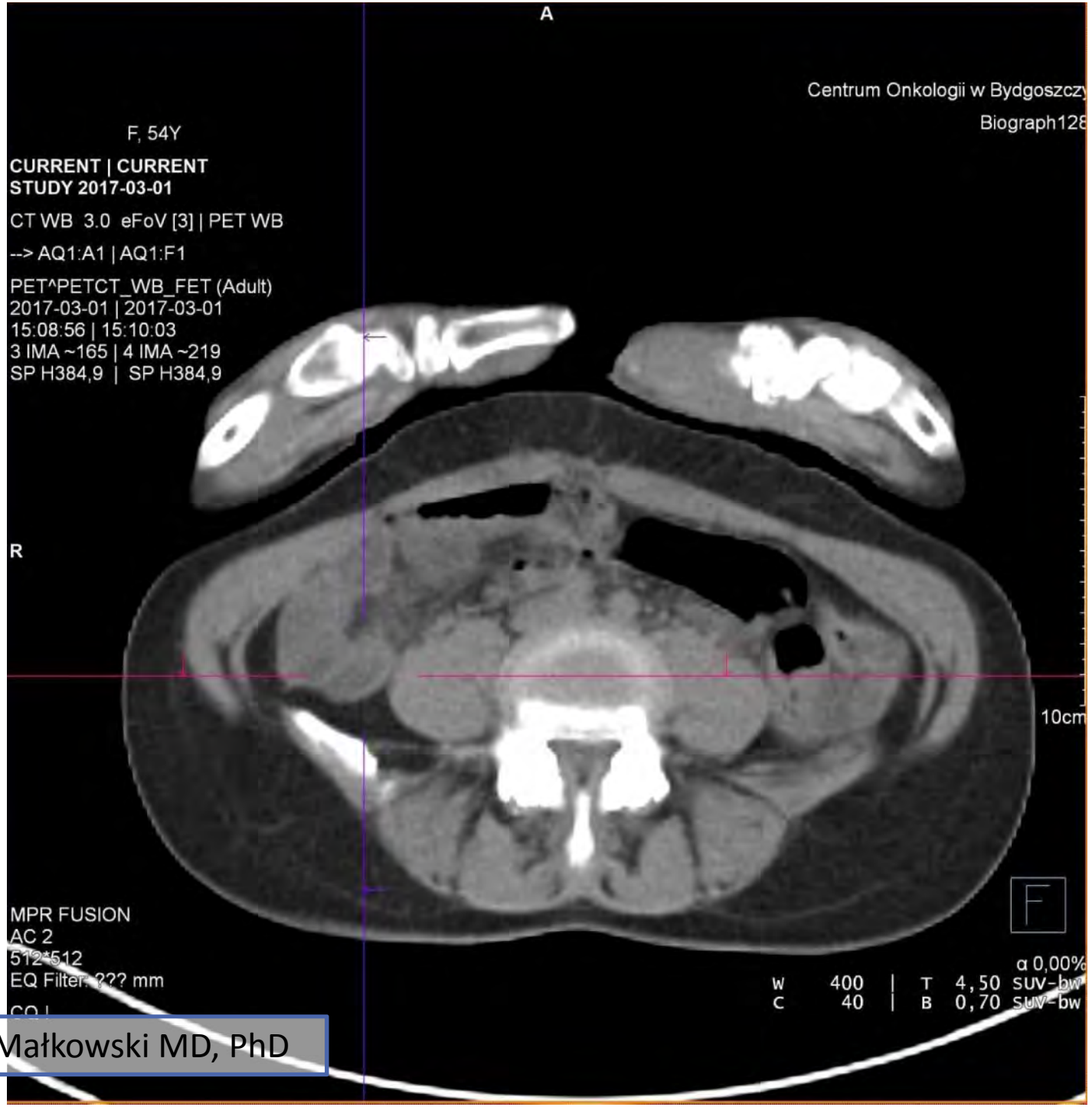

Fot. Bodan Małkowski MD, PhD

Fot. Bodan Małkowski MD, PhD

DISCUSSION

What is the exact diagnosis?

Multiple extramedullary plasmacytomas or…?

What is the best treatment?

Case Report

Multiple Extramedullary Plasmacytoma with Lytic Bony Lesions: A Rare Case Report

Akhlak Hussain,[1] Mohinder Singh,[1] Kuldip Singh,[1] and Harjot Bagga[2]

[1] *Department of Surgery, Rajindra Hospital, Patiala 147001, India*
[2] *Department of Radiotherapy, Rajindra Hospital, Patiala 147001, India*

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Academic Editor: Abhay R. Satoskar

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Objective. Multiple extramedullary plasmacytoma lesions involving subcutaneous tissue, breast, mediastinal tissue, spleen, and soft tissue of pelvic region along with multiple bones plasmacytomas without marrow plasmacytosis are a very rare presentation. *Design*. Case report. *Result*. A 54-year-old female was found to have multiple small bony lytic lesions, multiple extramedullary soft tissue plasmacytomas, serum M protein >3 g/dL, and elevated ESR. Bone marrow aspirate did not reveal any evidence of multiple myeloma/plasmacytosis. There was no anemia, hypercalcemia, or renal insufficiency. *Conclusion*. Extramedullary plasmacytoma can involve multiple organs at a time including bones and soft tissue without involving bone marrow.

Combination chemotherapy was started with melphalan, dexamethasone, and thalidomide. The patient has shown a very good response to chemotherapy even after 2 cycles. A total of 12 cycles were given. Currently the patient is maintaining well.

Hussain et al., Case Rep Med. 2013;2013:291359

Leukemia and Lymphoma, 2003 Vol. 44 (1), pp. 153–155

Taylor & Francis
healthsciences

High Dose Therapy with Autologous Stem Cell Transplantation for Solitary Bone Plasmacytoma Complicated by Local Relapse or Isolated Distant Recurrence

MELETIOS A. DIMOPOULOS[a,*], CHRISTOS PAPADIMITRIOU[a], ATHANASSIOS ANAGNOSTOPOULOS[a], DIMITRIOS MITSIBOUNAS[a] and JEAN-PAUL FERMAND[b]

[a]*Department of Clinical Therapeutics, University of Athens, School of Medicine, Athens, Greece;* [b]*Department of Immuno-Hematology, Hospital Saint-Louis, Paris, France*

(Received 10 July 2002)

We report three patients with solitary bone plasmacytoma (SBP) who developed either local recurrence within the radiotherapy field or an isolated distal recurrence and who were treated with high dose therapy supported by autologous stem cell transplantation. All patients remain without evidence of disease for 4–10 years after the procedure. High dose therapy may be of value and require further study in patients with SBP who develop local or distant failure.

Dimopoulos et al., Leuk Lymphoma. 2003; 44(1)

bjh guideline

Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma

Most patients with plasma cell neoplasia have generalized disease at diagnosis, i.e. multiple myeloma (MM). However, a minority (<5%) of patients with plasma cell malignancies present with either a single bone lesion, or less commonly, a soft tissue mass, of monoclonal plasma cells: solitary bone plasmacytoma (SBP) or extramedullary plasmacytoma (SEP). SBP has a high risk of progression to MM and on magnetic resonance imaging (MRI) examination at least 25% of patients

Solitary bone plasmacytoma

Context

Epidemiology and clinical features. Solitary bone plasmacytoma has a male:female ratio of 2:1, with a median age of 55 years and primarily affects the axial skeleton especially the vertebrae (see Table II) (Dimopoulos *et al*, 2000). Malignant bone

- *It is recommended that SBP is treated with **radical radiotherapy** with a margin of at least 2 cm and treating to a dose of 40 Gy in 20 fractions* .
  (grade B recommendation, level III evidence)
- *Patients not responding to radiotherapy should be treated with **chemotherapy**.*
  *A suggested approach is to follow guidelines for the treatment **of MM**.*
  *In younger patients, this would include **high dose therapy and ASCT*** (grade C, level IV)
- *Surgery is contra-indicated in the absence of structural compromise or neurological compromise* (grade C, level IV evidence).

Soutar et al., Br J Haematol. 2004; 124(6)

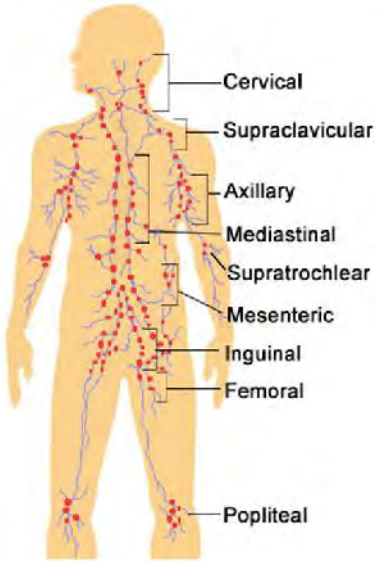
Waldenström's Macroglobulinemia

Steve Treon MD, PhD
Bing Center for Waldenstrom's Macroglobulinemia
Dana Farber Cancer Institute
Harvard Medical School

17th International Workshop on MM
Boston, USA - September 12-14,2018
www.imw2019boston.org

Manifestations of WM Disease

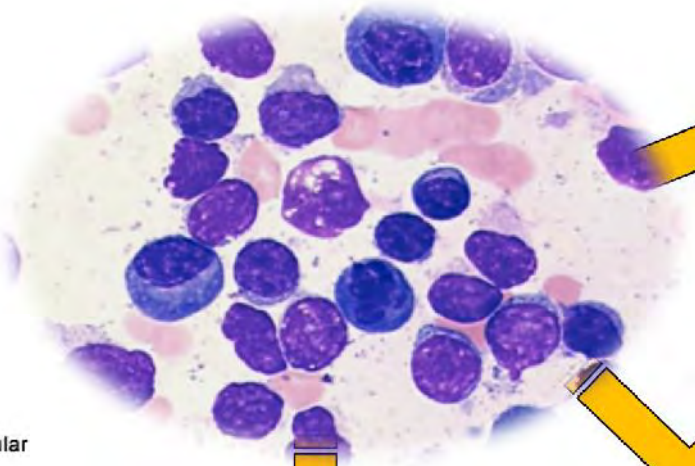
Bing Neel Syndrome



≤20% at diagnosis;
50-60% at relapse.

Bone Marrow

↓Hb>>> ↓PLT> ↓WBC



Hepcidin
↓Fe Anemia

Hyperviscosity Syndrome:
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP

Cold Agglutinemia (5%)
Cryoglobulinemia (10%)
IgM Neuropathy (22%)
Amyloidosis (10-15%)

Treon S., Hematol Oncol. 2013; 31:76-80.

NCCN Guidelines for Initiation of Therapy in WM

- Hb ≤10 g/dL on basis of disease
- PLT <100,000 mm^3 on basis of disease
- Symptomatic hyperviscosity
- Moderate/severe peripheral neuropathy
- Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloid.

Kyle RA, et al. Semin Oncol. 2003;30(2):116-120; Anderson et al, JNCCN 2012; 10(10):1211-9.

ta3

Primary Therapy of WM with Rituximab

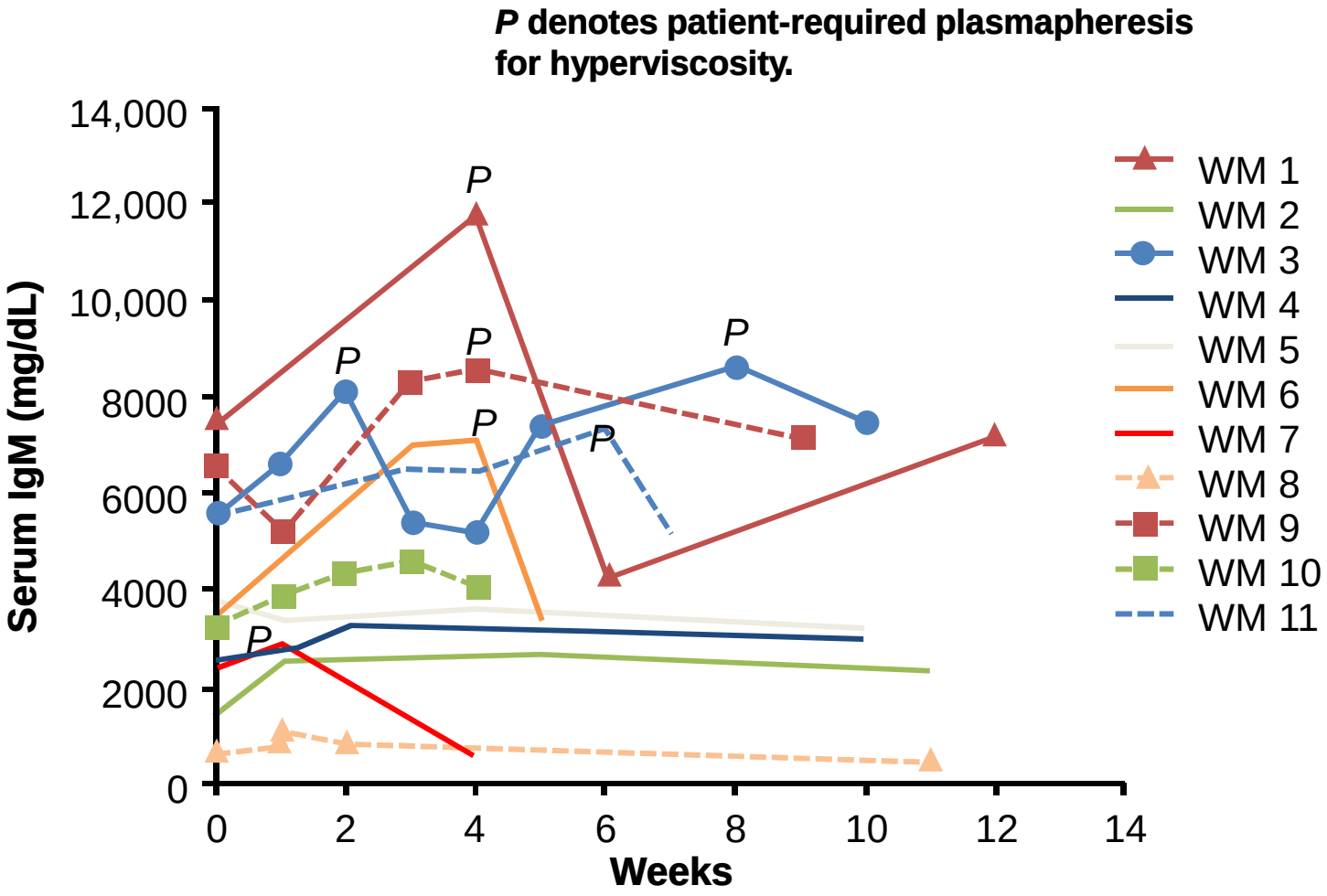
Regimen	ORR	VGPR/CR	TTP (mo)
Rituximab x 4	25-30%	0-5%	13
Rituximab x 8	40-45%	5-10%	16-22
Rituximab/thalidomide	70%	10%	30
Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, CDR	70-80%	20-25%	30-36
Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R	70-90%	20-30%	36-62
Rituximab/Proteasome Inhibitor i.e. BDR, VR, CaRD	70-90%	20-40%	42-66
Rituximab/bendamustine	90%	30-40%	69

Reviewed in Dimopoulos et al, Blood 2014; 124(9):1404-11; Treon et al, Blood 2015; How I Treat WM

Slide 5

ta3 I don't know what the references for this are.
tristin.abair, 6/6/2011

Rituximab induced IgM Flare in WM Patients



Dimopoulos et al, JCO 2002; Ghobrial et al, Leukemia 2004; Treon et al. Ann Oncol. 2004.

Nucleoside Analogues in WM

- Risk of Transformation or MDS/AML is 10-15%;
- Risk of secondary malignant events in 1/3 patients with FCR;
- Stem cell collection impacted by nucleoside analogues: avoid in ASCT candidates;
- Consider Impact on future therapy (Bendamustine);
- **Role in CNS Disease (Bing Neel Syndrome)**

Treon et al, Blood 2008; 113(16):3673-8; Leleu et al, JCO 2009; 27(2): 250-5; Thomas et al, Proc. 5th International Workshop on WM 2008; Treon et al, Clin Lymphoma 2011; 11(1):133-5. Tdeschi et al, ASH 2015; Abstract 3958.; Vos et al, BJH 2015.

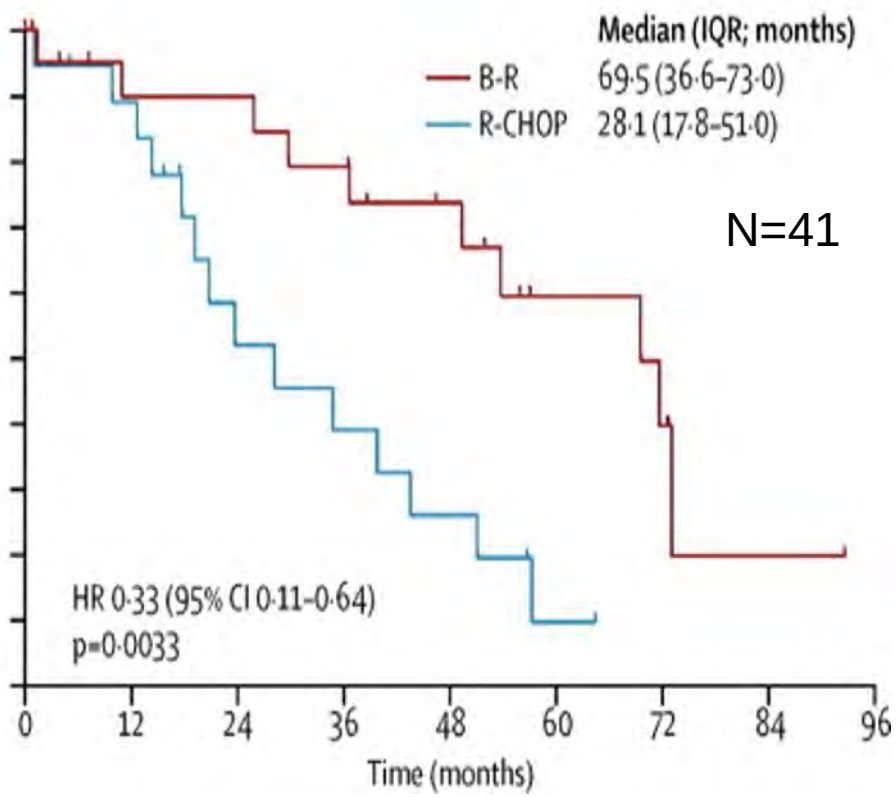
Cyclophosphamide-Based Therapy

- CDR (Cyclophosphamide, Dex, Rituximab) widely used.
- Adriamycin and vincristine may be dispensed as they not appear to impact response rates or PFS and are associated with more toxicity.
- ORR to CDR is 83%; Major RR 74%.
- Median PFS is 3 years. (Without maintenance)

Dimopoulos MA, et al. J Clin Oncol. 2007;25(22):3344-3349. Buske C, et al. Leukemia. 2009;23(1):152-161. Ioakimidis L, et al. Clin Lymphoma Myeloma. 2009;9(1):62-66.

Bendamustine-R in WM

- German STiL Study



- Prolonged cytopenias >4 cycles
- Secondary MDS/AML 5-8%.

- Mayo Study: 2 yr PFS 88% vs. 61% for Benda-R vs. CDR

Treon et al, CLM 2011; Rummel et al, Lancet. 2013; Tedeschi et al, Leuk. Lymphoma 2015; Paludo et al, Ann Hematol 2018.

Proteasome Inhibitor Therapy in Frontline WM

	REGIMEN	ORR	Major RR	PFS	Maintenance
GHOBRIAL ET AL	VR	88%	66%	75% PFS at 1 yr.	No
TREON ET AL	BDR	96%	83%	66 mos	Yes
DIMOPOULOS ET AL	BORT →BDR	85%	68%	42 mos	No
TREON ET AL	CaRD	81%	71%	46 mos.	Yes
CASTILLO ET AL	IDR	96%	77%	>22 mos.	Yes

Chen et al, JCO 2007; 25(12): 1570-5; Ghobrial et al, AJH 2010; 85(9): 670-4; Treon et al, JCO 2009; 27(23):3830-5 Dimopoulos et al, Blood 2013; 122(19):3276-82; Treon et al, Blood 2014; 124(4):503-10. Treon et al, ASH 2015; Abstract 1833.

PI-Related Peripheral Neuropathy

	GRADE 1,2	GRADE ≥3	PI-DISCONTINUED
2X WEEK BORT	40-70%	20-30%*	20-30%
1X WEEK BORT	20-40%	5-20%	10-20%
CaRD	**20%**	**0%**	**<5%**
IDR	**15%**	**3%**	**<5%**

Chen et al, JCO 2007; 25(12): 1570-5; Treon et al, CCR 2007; 13(11): 3320-5; JCO 2009; 27(23): 3830-5; Ghobrial, JCO 2010; 28(8):1422-8; AJH 2010; 85(9): 670-4; Agathocleous et al, BJH 2010; 151(4): 346-53; Dimopoulos et al, Blood 2013. 122(19):3276-82.

Discovery of the MYD88 Mutation in WM -2012-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

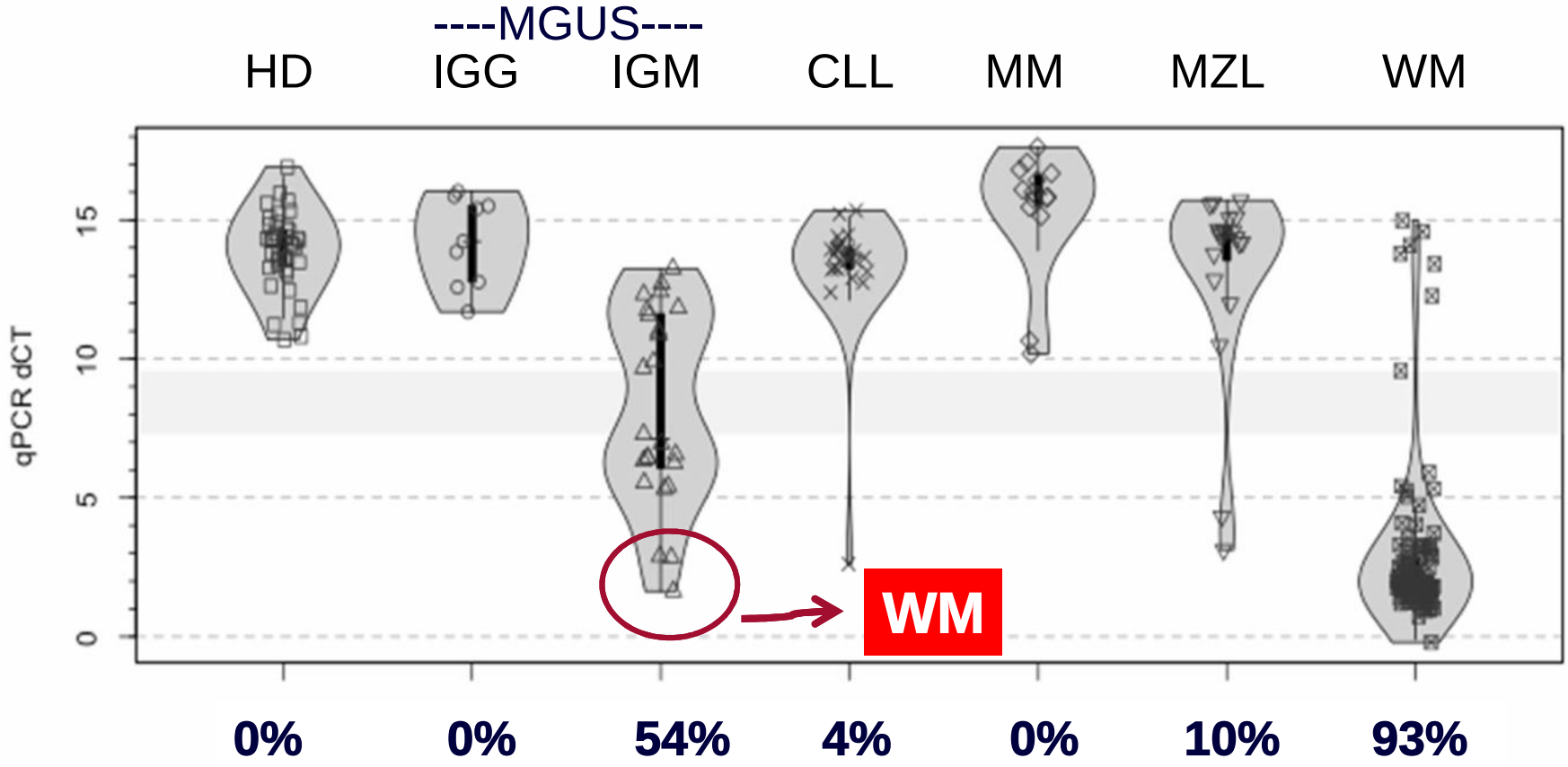
MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

MYD88 L265P in WM/IGM MGUS
>50 confirmatory studies

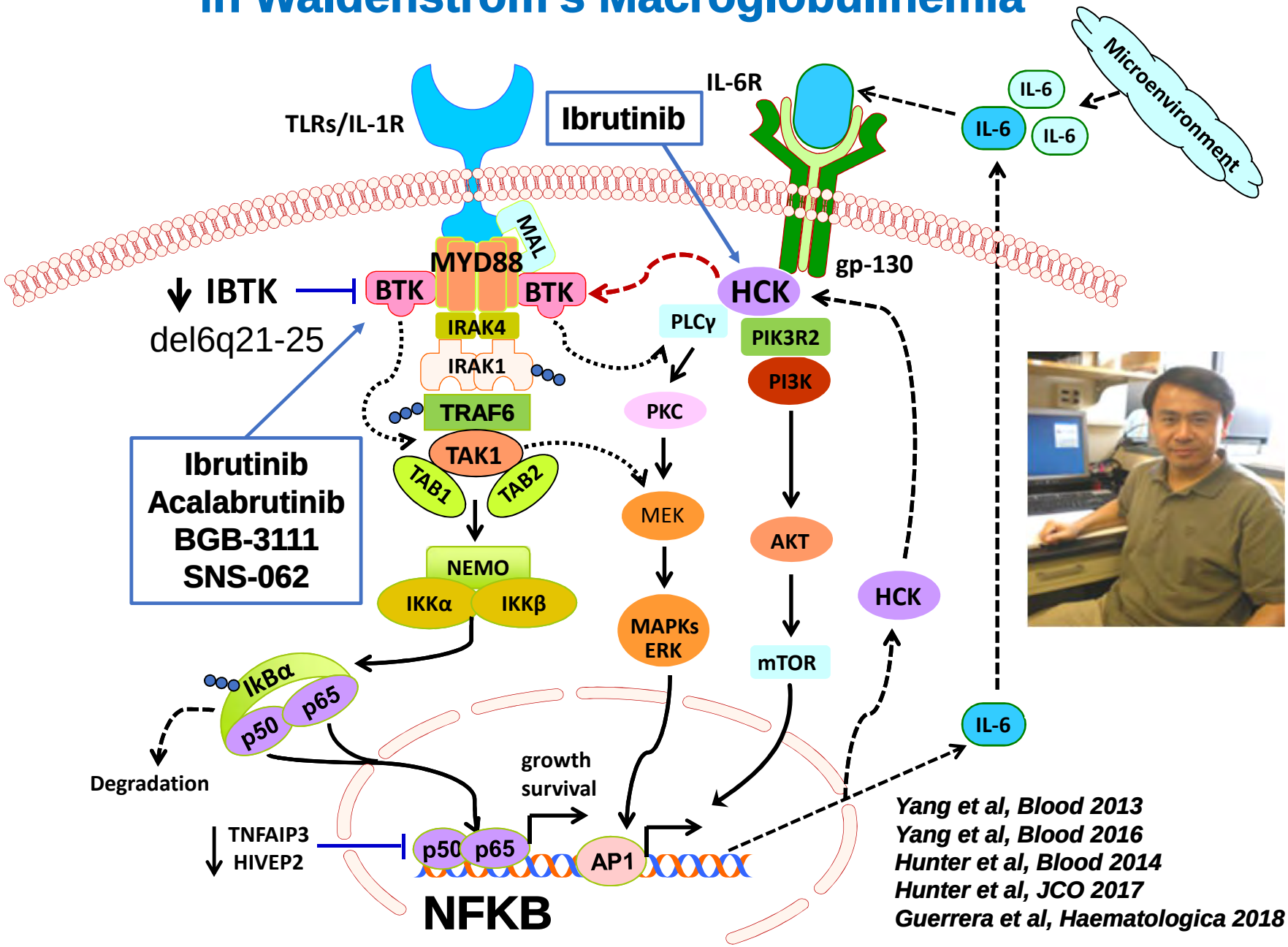
	METHOD	TISSUE	WM	IGM MGUS
Treon	WGS/Sanger	BM CD19$^+$	91%	10%
Xu	AS-PCR	BM CD19$^+$	93%	54%
Gachard	PCR	BM	70%	
Varettoni	AS-PCR	BM	100%	47%
Landgren	Sanger	BM		54%
Jiminez	AS-PCR	BM	86%	87%
Poulain	PCR	BM CD19$^+$	80%	
Argentou	PCR-RFLP	BM	92%	1/1 MGUS
Willenbacher	Sanger	BM	86%	
Mori	AS-PCR/BSiE1	BM	80%	
Ondrejka	AS-PCR	BM	100%	
Ansell	WES/AS-PCR	BM	97%	
Patkar	AS-PCR	BM	85%	

MYD88 L265P by AS-PCR can help distinguish WM from overlapping entities



Xu et al, Blood 2013

Pro-Survival Signaling Driven by Mutated MYD88 in Waldenström's Macroglobulinemia



Yang et al, Blood 2013
Yang et al, Blood 2016
Hunter et al, Blood 2014
Hunter et al, JCO 2017
Guerrera et al, Haematologica 2018

Discovery of CXCR4 mutations in WM -2013-

From www.bloodjournal.org by guest on May 6, 2018. For personal use only.

Plenary Paper

LYMPHOID NEOPLASIA

The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis

Zachary R. Hunter,[1,2] Lian Xu,[1] Guang Yang,[1] Yangsheng Zhou,[1] Xia Liu,[1] Yang Cao,[1] Robert J. Manning,[1] Christina Tripsas,[1] Christopher J. Patterson,[1] Patricia Sheehy,[1] and Steven P. Treon[1,3]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [2]Department of Pathology and Laboratory Medicine, Boston University School of Graduate Medical Sciences, Boston, MA; and [3]Harvard Medical School, Boston, MA

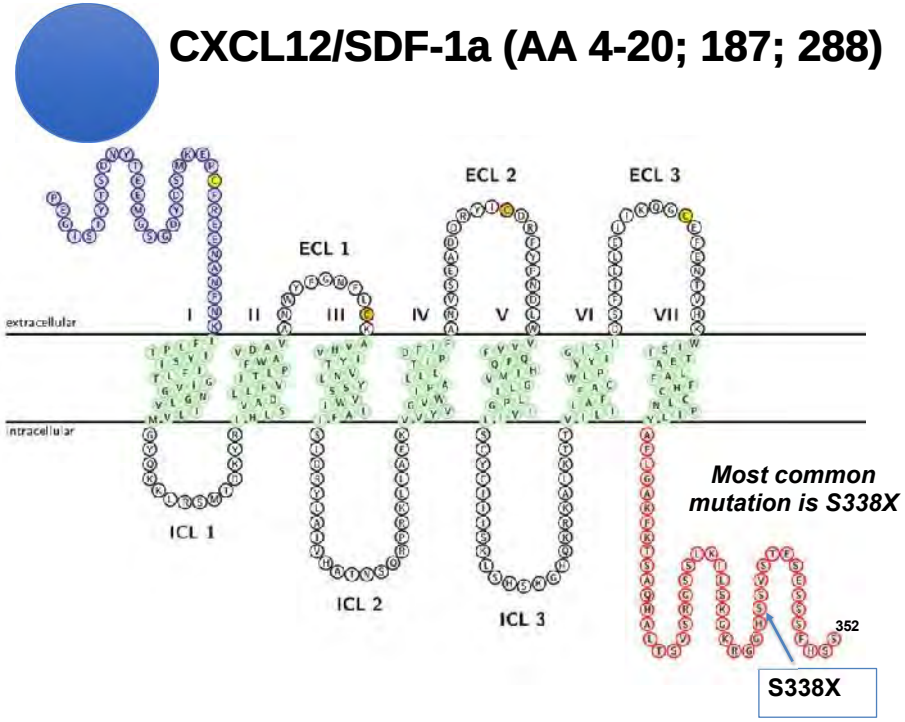
Key Points

- Highly recurring mutations are present in WM, including MYD88 L265P, warts, hypogammaglobulinemia, infection, and myelokathexis-syndrome–like mutations in CXCR4, and ARID1A.
- Small, previously undetected CNAs affecting B-cell regulatory genes are highly prevalent in WM.

The genetic basis for Waldenström macroglobulinemia (WM) remains to be clarified. Although 6q losses are commonly present, recurring gene losses in this region remain to be defined. We therefore performed whole genome sequencing (WGS) in 30 WM patients, which included germline/tumor sequencing for 10 patients. Validated somatic mutations occurring in >10% of patients included *MYD88*, *CXCR4*, and *ARID1A* that were present in 90%, 27%, and 17% of patients, respectively, and included the activating mutation L265P in MYD88 and warts, hypogammaglobulinemia, infection, and myelokathexis-syndrome–like mutations in CXCR4 that previously have only been described in the germline. WGS also delineated copy number alterations (CNAs) and structural variants in the 10 paired patients. The CXCR4 and CNA findings were validated in independent expansion cohorts of 147 and 30 WM patients, respectively. Validated gene losses due to CNAs involved *PRDM2* (93%), *BTG1* (87%), *HIVEP2* (77%), *MKLN1* (77%), *PLEKHG1* (70%), *LYN* (60%), *ARID1B* (50%), and *FOXP1* (37%). Losses in *PLEKHG1*, *HIVEP2*, *ARID1B*, and *BCLAF1* constituted the most common deletions within chromosome 6. Although no recurrent translocations were observed, in 2 patients deletions in 6q corresponded with translocation events. These studies evidence highly recurring somatic events, and provide a genomic basis for understanding the pathogenesis of WM. (*Blood*. 2014;123(11):1637-1646)

WHIM-like CXCR4 mutations in Waldenstrom's Macroglobulinemia

- 25-40% of WM patients
- Receptor for CXCL12
- Higher incidence in MYD88 mutated patients
- > 40 types of Nonsense and Frameshift Mutations
- Nonsense mutations associated with high serum IgM levels.
- Promotes in vitro drug resistance through AKT and ERK activation.



Hunter et al, Blood 2013;
Rocarro et al, Blood 2014:
Poulain et al, Blood 2016;
Poulain et al, CCR 2016
Xu et al, BJH 2016
Varettoni et al, Haematologica 2017

Multicenter study of Ibrutinib in Relapsed/Refractory WM (≥1 prior therapy)

Screening

Registration

420 mg po qD Ibrutinib

Progressive Disease (PD) or Unacceptable Toxicity

Stop Ibrutinib

Event Monitoring

Stable Disease or Response Continue

Event Monitoring

✔ **MYD88, CXCR4 Mutation Status**

NCT01614821

Baseline Characteristics for Study Participants (n=63)

	Median	Range
Age (yrs)	63	44-86
Prior therapies	**2**	**1-9**
Refractory to prior therapy	**25 (40%)**	**N/A**
Hemoglobin (mg/dL)	10.5	8.2-13.8
Serum IgM (mg/dL)	3,520	724-8,390
B_2M (mg/dL)	3.9	1.3-14.2
BM Involvement (%)	60	3-95
Adenopathy >1.5 cm	37 (59%)	N/A
Splenomegaly >15 cm	7 (11%)	N/A

Treon et al, NEJM 372: 1430, 2015

Updated Clinical Responses to Ibrutinib

ORR: 91% (No change) Major RR (≥ PR): 73 → 78%

	(N=)	(%)
VGPR	**10→18**	**16%→29%**
PR	**36→31**	**57%→49%**
MR	**11→8**	**17%→13%**

Median time to ≥ MR: 4 weeks
Median time to ≥ PR or better: 8 weeks

Data cutoff: December, 2017
Median time on treatment: 47 months

Treon et al, N Engl J Med. 2015; EHA 2018

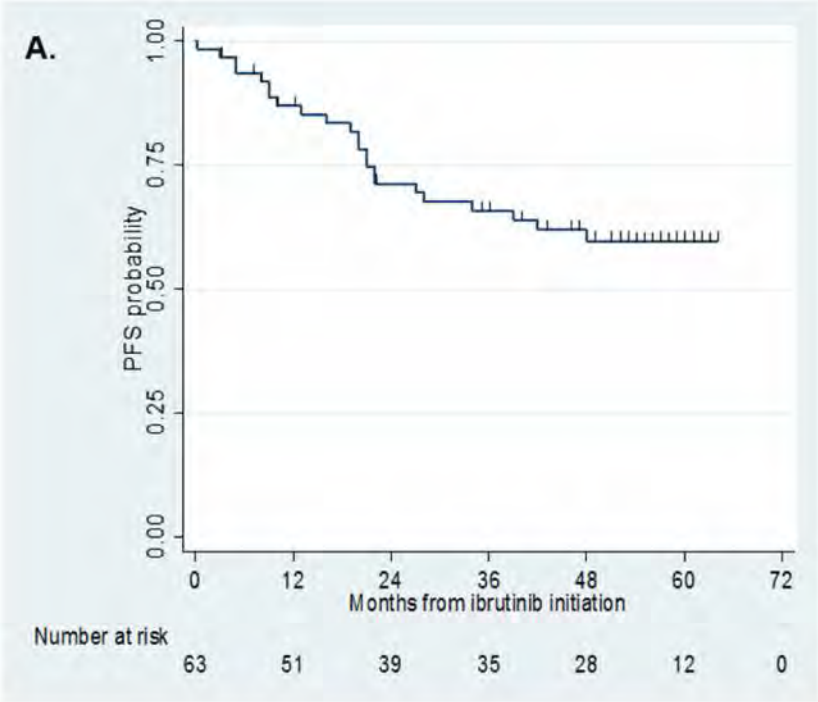
Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations.

	ALL	$MYD88^{Mut}$ $CXCR4^{WT}$	$MYD88^{Mut}$ $CXCR4^{Mut}$	$MYD88^{WT}$ $CXCR4^{WT}$	P-value
N=	63	36	21	5*	
ORR	91%	100%	85.7%	60%	0.005
Major (>PR)	78%	97%	67%	0%	<0.001
VGPR	29%	44%	10%	0%	0.007
Time to Minor Response (mos.)	1.0	1.0	1.0	1.0	0.10
Time to Major response (mos.)	2.0	2.0	6.0	N/A	0.05

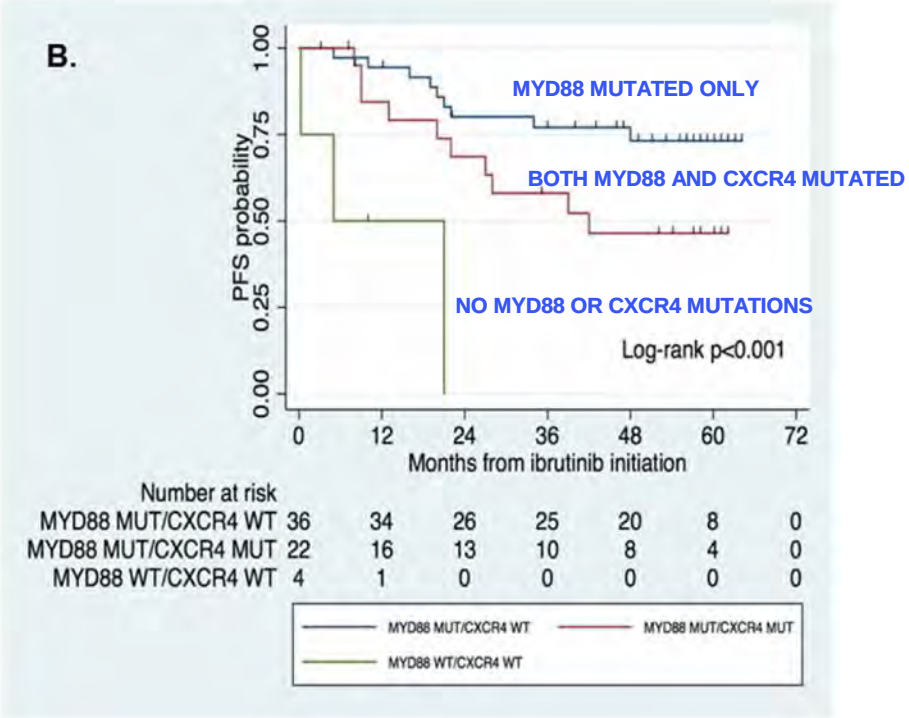
*2 patients at initial reporting with major responses were discovered subsequently to have MYD88 mutated disease (S243N, L265P). One patient at initial reporting was subsequently found to CXCR4 mutated disease upon genotyping of CD19-selected WM cells.

Ibrutinib in Previously Treated WM: Updated PFS

All patients



MYD88 and CXCR4 Status

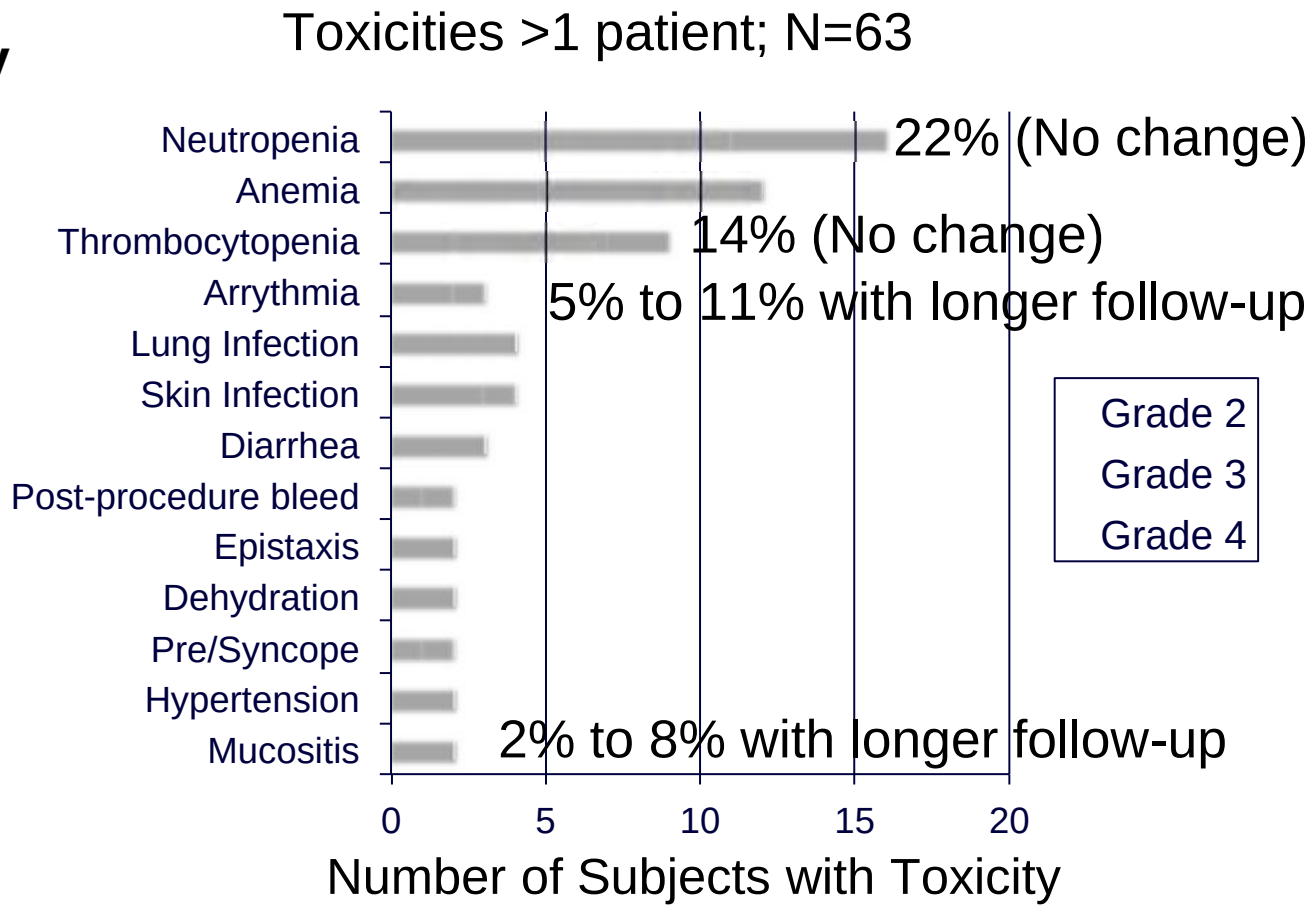


5 year PFS: 60% (95% CI 46-71%).

Data cutoff: December, 2017

Ibrutinib Related Adverse Events in previously treated WM patients

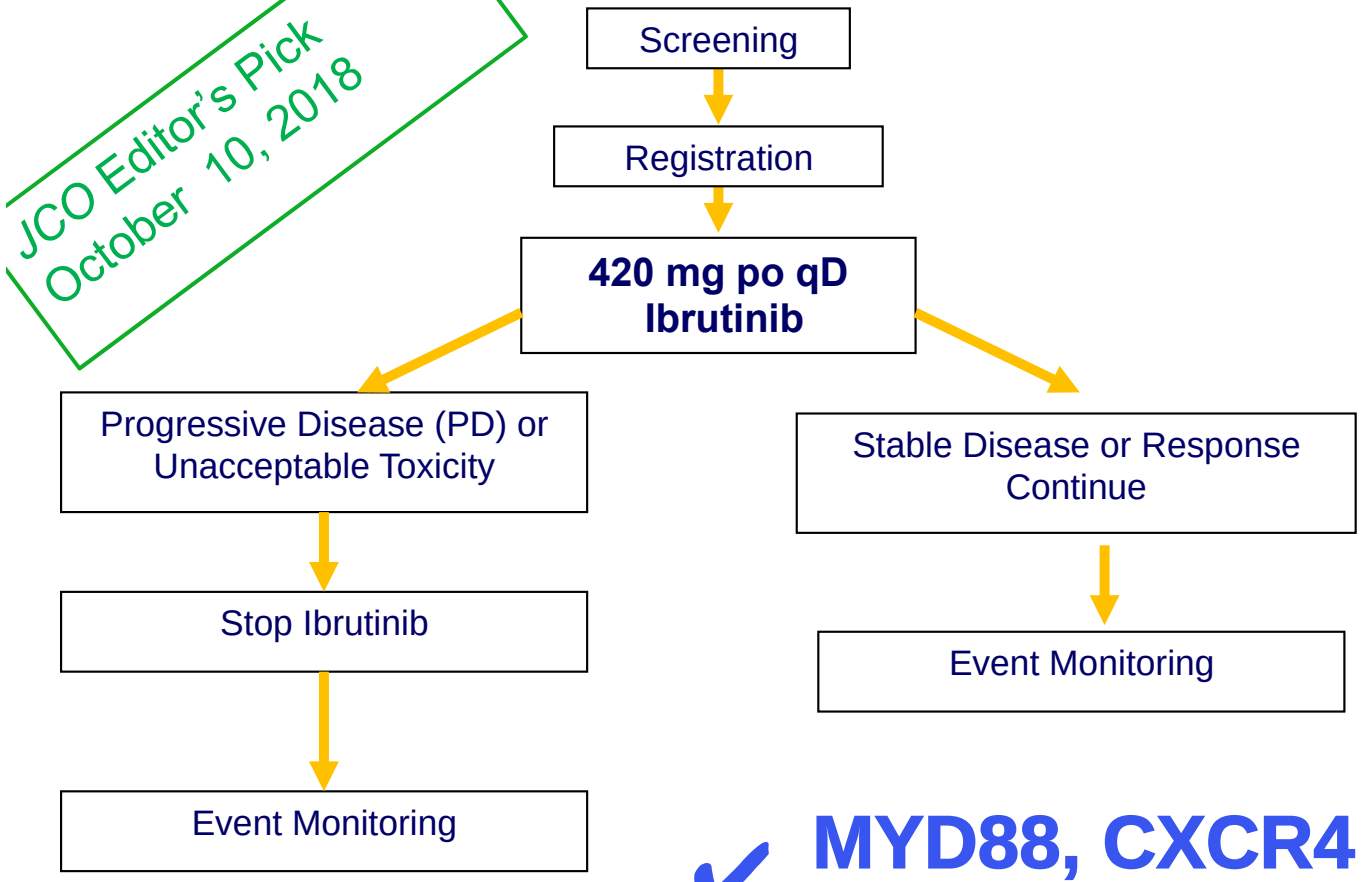
Original Study



Update on Adverse Events (Grade ≥2) in ≥5% of patients: Neutropenia (22%); Thrombocytopenia (14%), Pneumonia (9%); GERD (8%); Hypertension (8%); anemia (6%); and skin infection (5%). Seven patients (11%) had atrial arrhythmia [Grade 1 (n=1); Grade 2 (n=5); Grade 3 (n=1)], and 6 continued ibrutinib following medical management.

Ibrutinib Monotherapy in Symptomatic Treatment Naive WM

JCO Editor's Pick
October 10, 2018



✔ **MYD88, CXCR4 Mutation Status**

NCT02604511

Treon et al, JCO 2018

Time to and depth of response to ibrutinib are impacted by CXCR4 mutations.

	All Patients	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	P-value
N=	30	16	14	N/A
Overall Response Rate-no. (%)	30 (100%)	16 (100%)	14 (100%)	1.00
Major Response Rate-no. (%)	25 (83%)	15 (94%)	10 (71%)	0.16
Categorical responses				
Minor responses-no. (%)	5 (17%)	1 (6%)	4 (29%)	0.16
Partial responses-no. (%)	19 (63%)	10 (63%)	9 (64%)	1.00
Very good partial responses-no. (%)	6 (20%)	5 (31%)	1 (7%)	0.18
Median time to response (months)				
Minor response (≥Minor response)	1.0	0.9	1.7	0.07
Major response (≥Partial response)	1.9	1.8	7.3	0.01

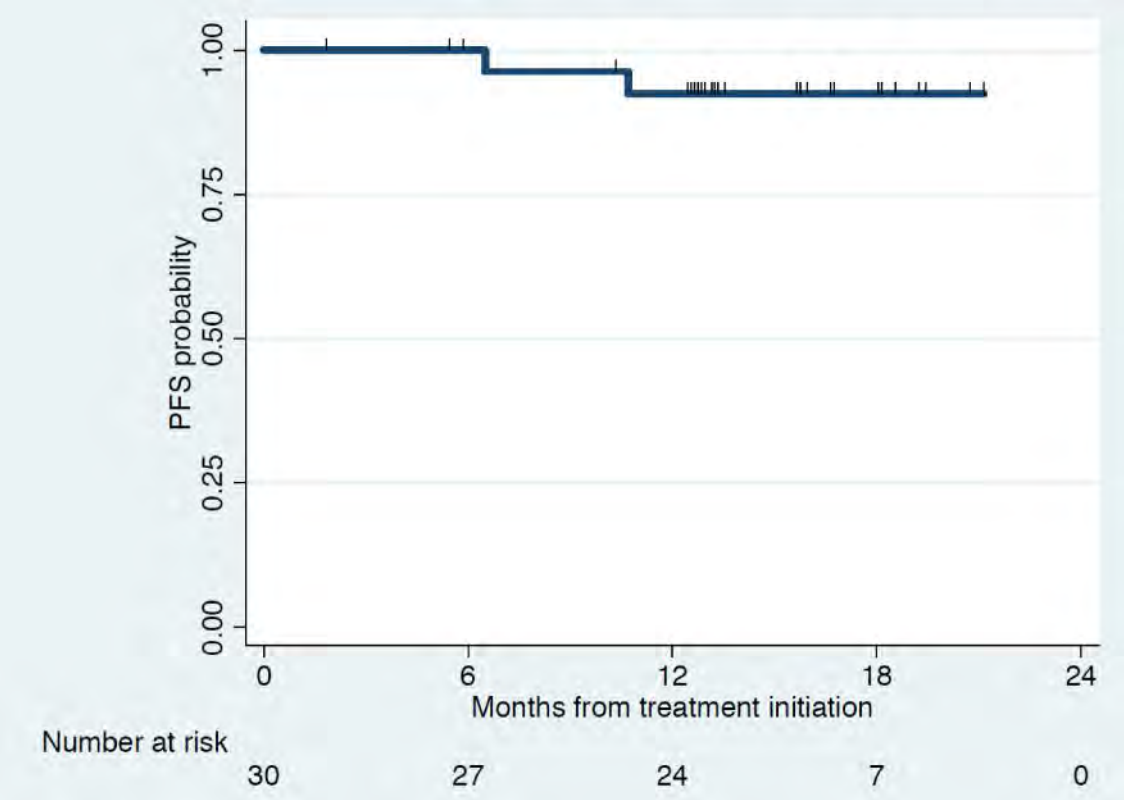
Data cutoff: Jan. 22, 2018 Median f/u: 14.6 (range 1.8-21.6 months)

Adverse Events (≥5%)

Event or Abnormality	Grade 2	Grade 3	Grade 4	Total Grades 2-4
Arthralgia	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Atrial fibrillation	3 (10%)	0 (0%)	0 (0%)	3 (10%)
Bruising	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Hypertension	2 (7%)	2 (7%)	0 (0%)	4 (13%)
Neutropenia	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Upper respiratory infection	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Urinary tract infection	2 (7%)	0 (0%)	0 (0%)	2 (7%)

- Minimal hematological toxicity
- Median serum IgA levels decreased from 62 to 39 mg/dL; p=0.04
- Median serum IgG levels declined from 563 to 462; p=0.003
- Afib medically managed in 2 patients who continue on treatment; cardiac ablation for one patient with left atrial enlargement off treatment.

Ibrutinib Monotherapy in Frontline WM: PFS

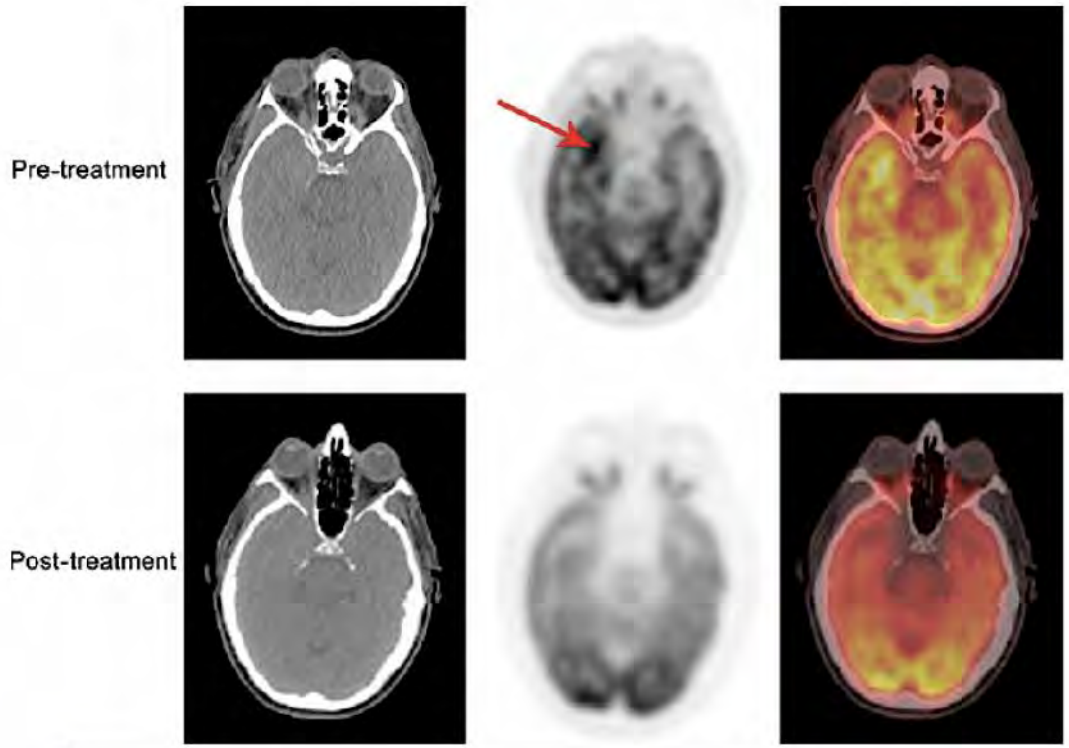


18 mo: PFS 92%;
All patients alive.

PD patients were both CXCR4 mutated.

Data cutoff: Jan. 22, 2018 Median f/u: 14.6 (range 1.8-21.6 months)

Ibrutinib (560 mg/day) induced response in a WM patient with Bing Neel Syndrome



		Ibrutinib (nM)		
Study Day	Time post-dose (h)	CSF	Plasma	%CSF/Plasma
Day 1	0	BLQ	BLQ	NA
	2	34	1133	3·0
1 Month	3	16	463	3·5
4 Months	2·5	7	318	2·2

Mason et al, BJH 2016

Other BTK Inhibitors

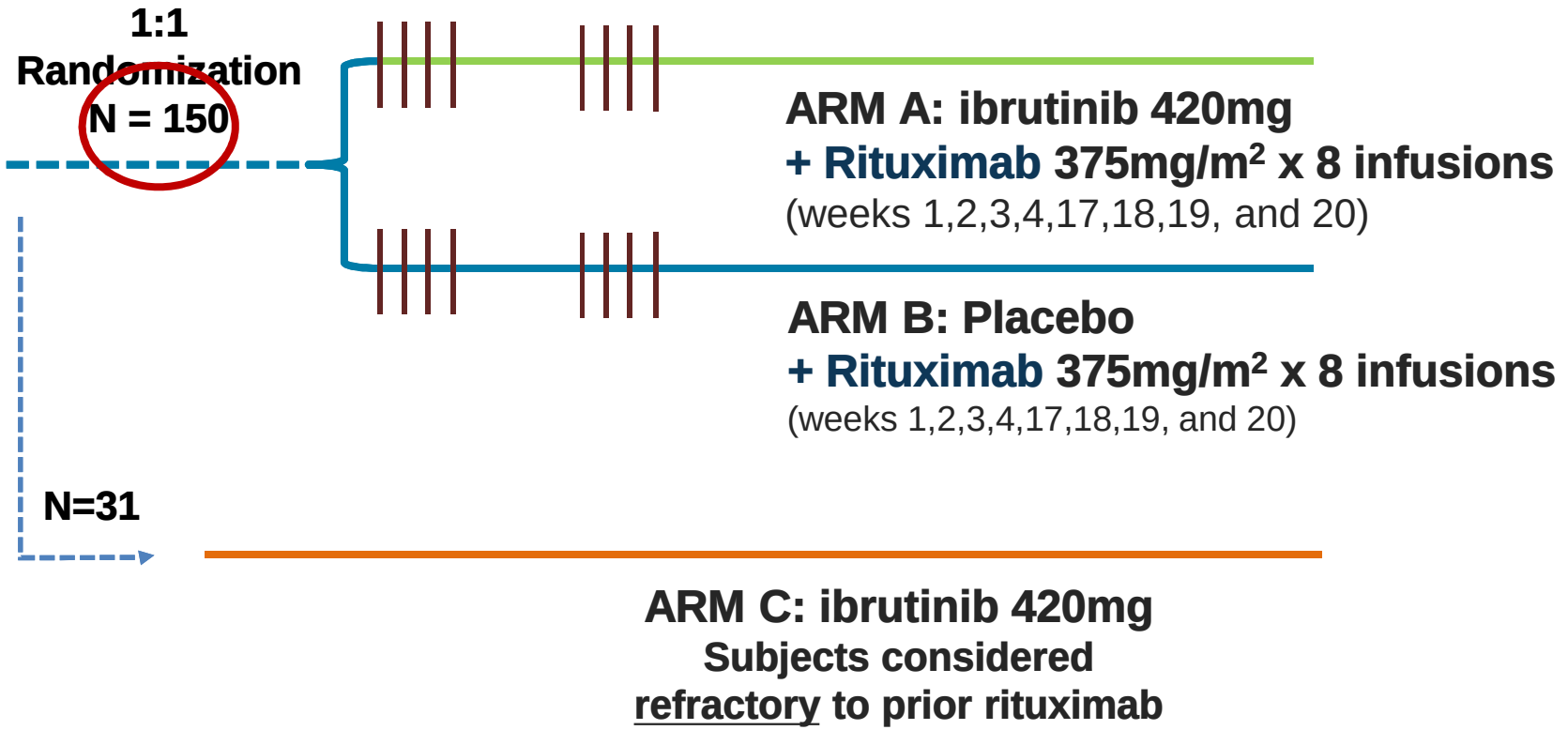
- **Acalabrutinib:** BID dosed; Phase II Study Reported.
- **Zanubrutinib:** BID dosed; Phase I/II Study Reported, Phase III randomized study is ongoing.
- **Vecabrutinib:** Non-covalent inhibitor that binds to a different site from other BTK inhibitors; use in resistant disease due to BTK mutations; study ongoing.

Strategies to Enhance BTK Inhibitors in WM

iNNOVATE Study in WM

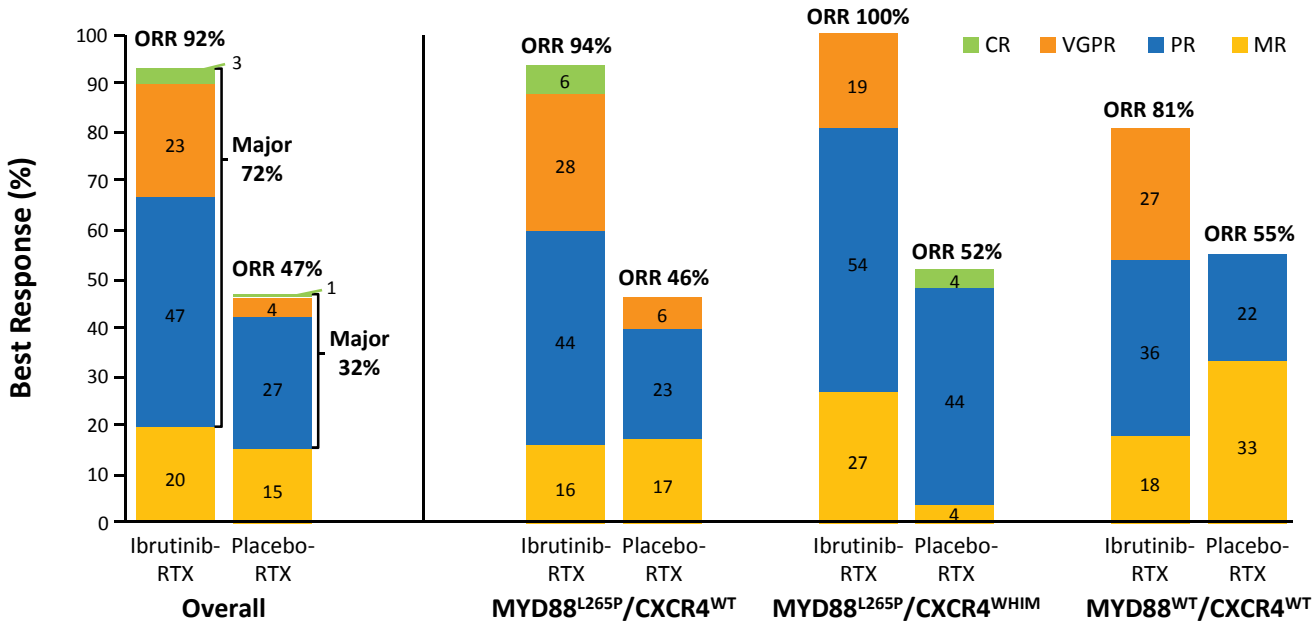
Treatment Naïve + Previously Treated

45 centers in 9 countries



ABC patients genotyped for MYD88 and CXCR4

Response rates in Innovate A/B

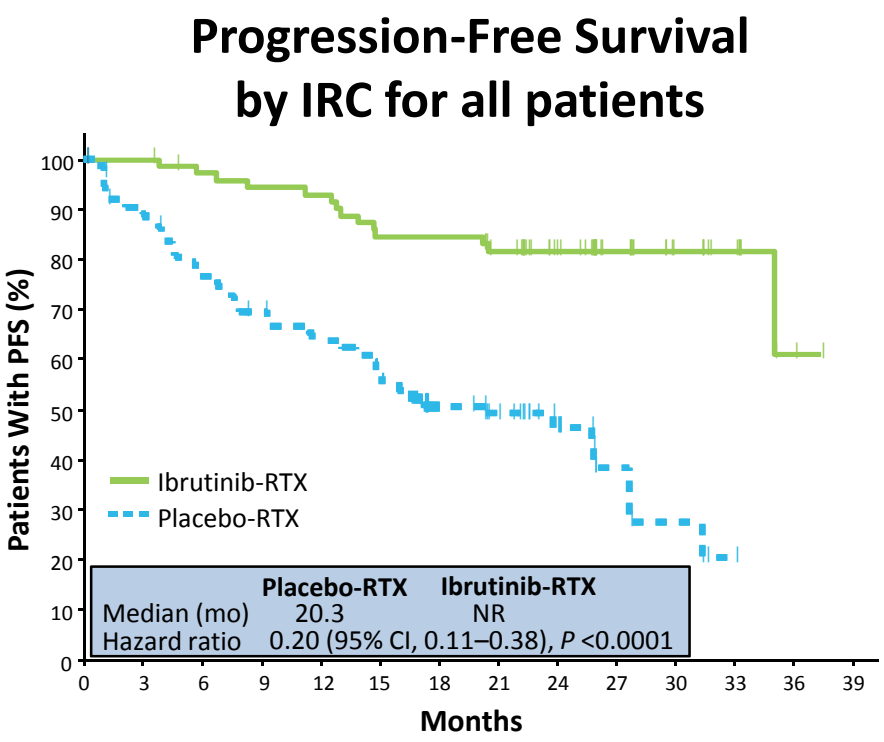


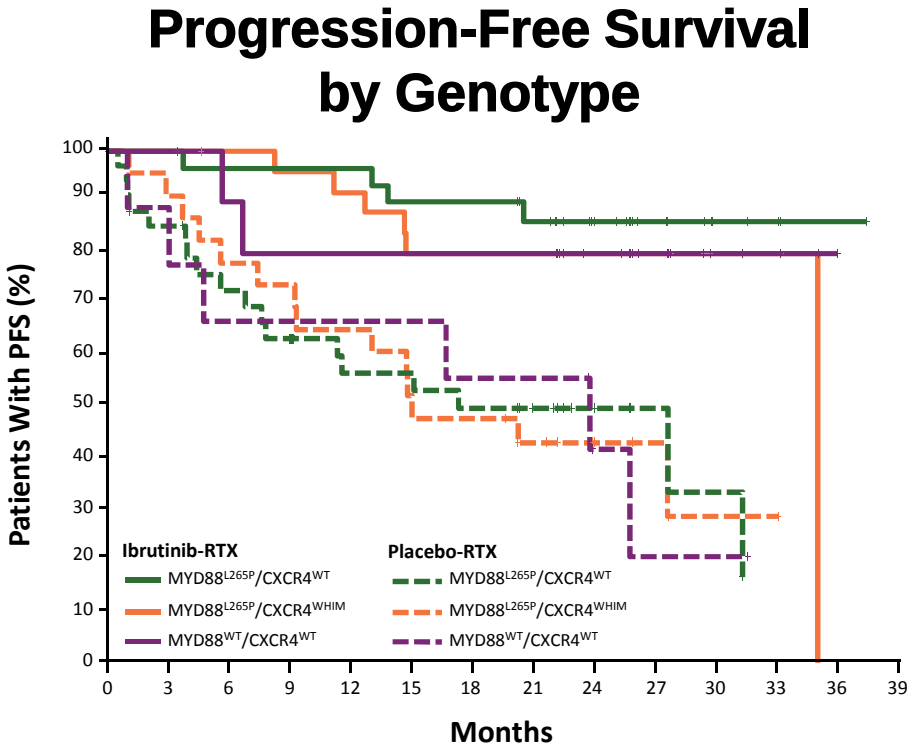
- **Proportion of patients with genetic subtype†, ibrutinib-RTX vs placebo-RTX:**
  - **MYD88^{L265P}/CXCR4^{WT}: 46% vs 52%**
  - **MYD88^{L265P}/CXCR4^{WHIM}: 38% vs 34%**
  - **MYD88^{WT}/CXCR4^{WT}: 16% vs 13%**

*Following modified 6th IWWM Response Criteria (NCCN 2014); required two consecutive assessments.
†Proportion of patients calculated after excluding patients for whom data were missing or unknown (ibrutinib-RTX: n = 6; placebo-RTX: n = 8).

Dimopoulos et al, EHA 2018; NEJM 2018

Progression-Free Survival for Innovate A/B





Median follow-up 26.5 months

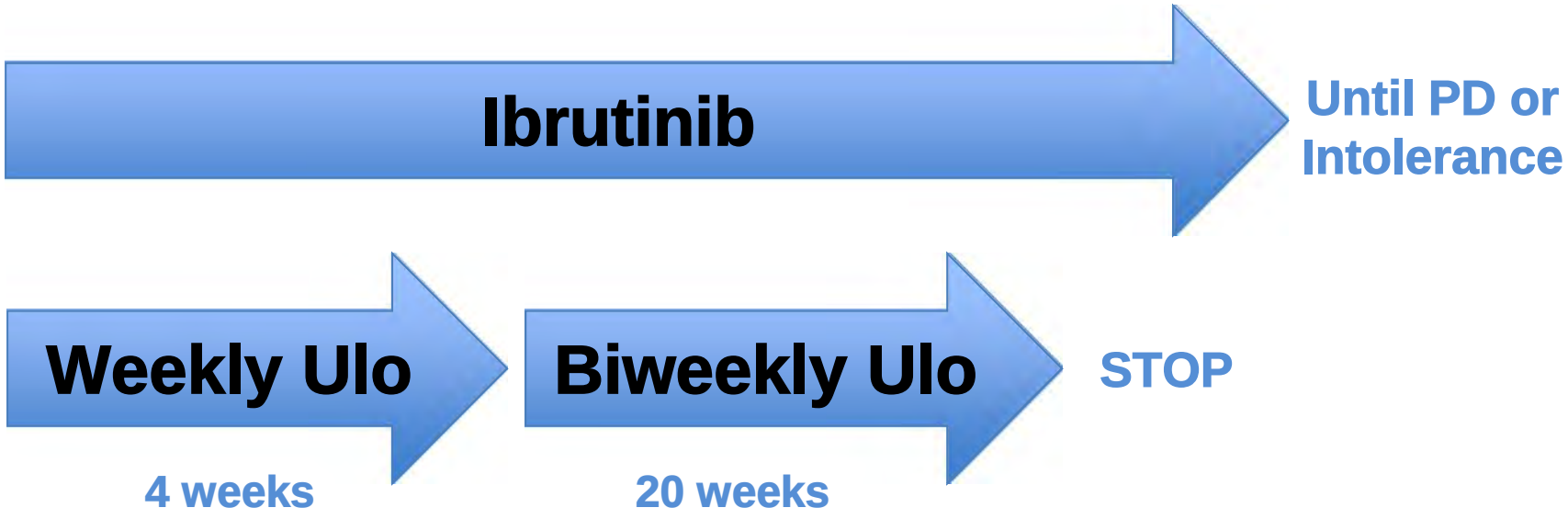
Dimopoulos et al, EHA 2018; NEJM 2018

What is still unknown after iNNOVATE?

- Is IR better than Ibrutinib alone??
- Is IR a better choice vs. other chemo-R regimens such as Benda-R?
- Are there other ways to improve outcome ibrutinib outcome in WM beside combining with rituximab?

Phase I/II Trial of Ulocuplumab and Ibrutinib in CXCR4 mutated patients with symptomatic WM

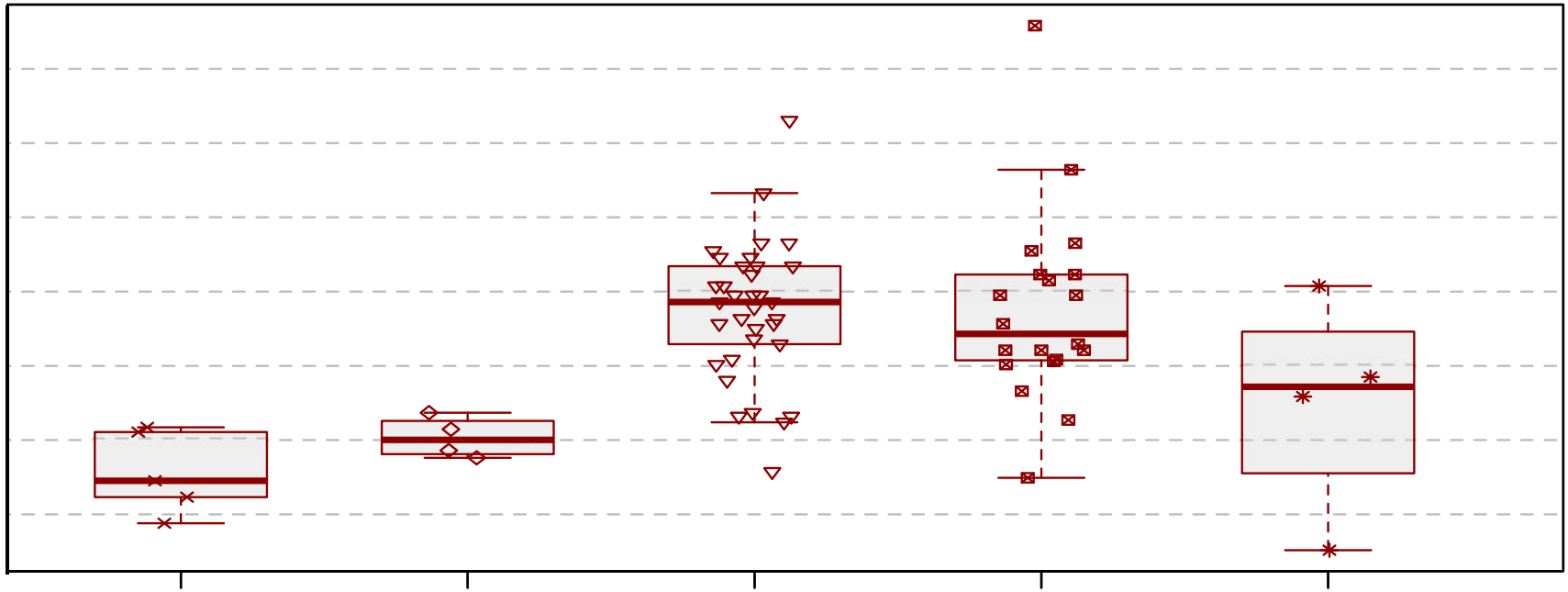
Schema



Dose Level	Ibrutinib	Ulocuplumab Cycle 1	Ulocuplumab Cycles 2-6
Level 1 –Starting dose	420mg PO DQ	400 mg weekly	800 mg every other week
Level 2	420mg PO DQ	800 mg weekly	1200 mg every other week
Level 3	420mg PO DQ	800 mg weekly	1600 mg every other week

ClinicalTrials.gov Identifier: NCT03225716

BCL-2 is overexpressed in primary WM patient cells by transciptome analysis in MYD88 mutated patients regardless of CXCR4 mutation status.



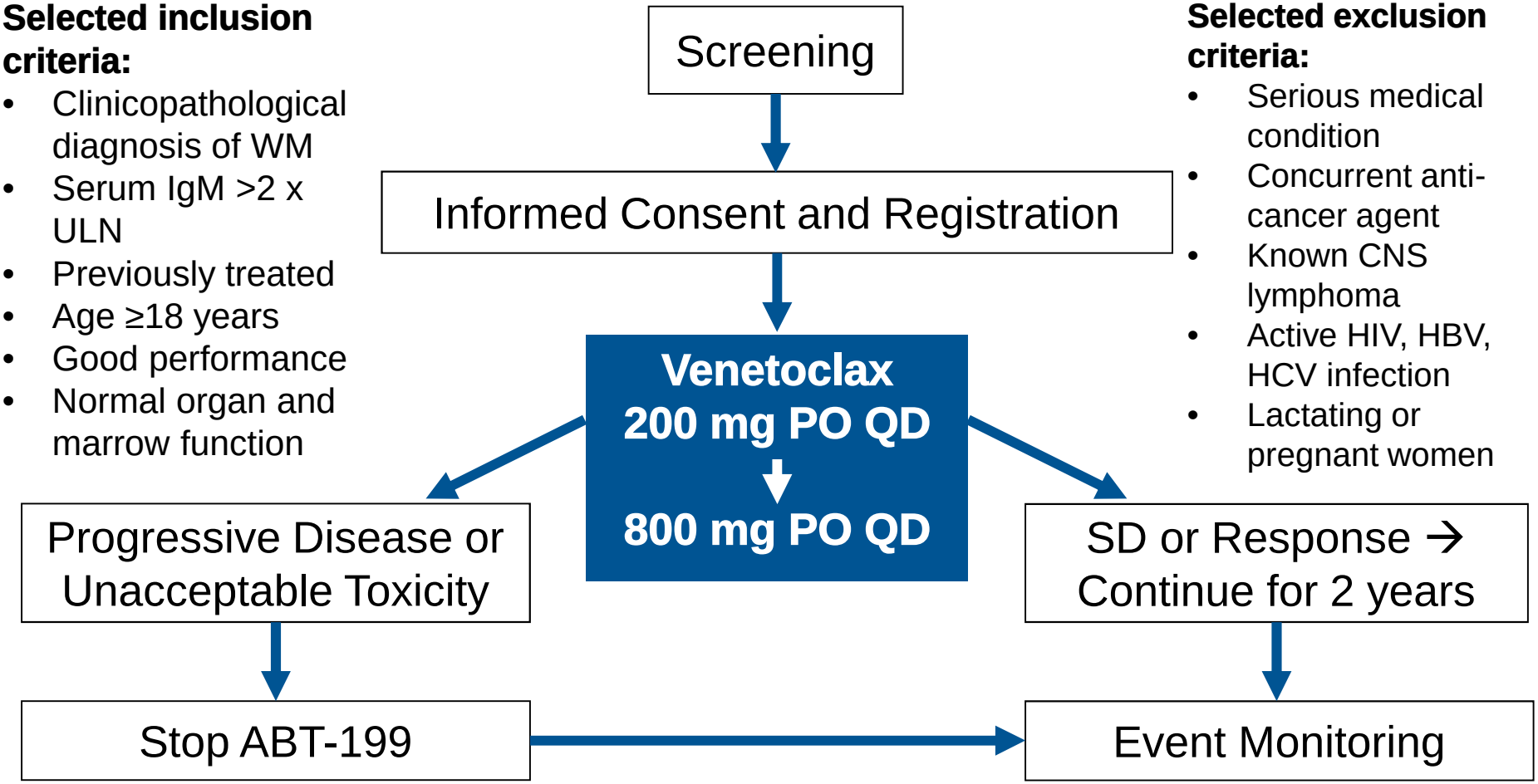
p<0.001 for healthy donor samples versus any MYD88^{L265P}CXCR4$^{WT\ or\ WHIM}$

Hunter et al, BLOOD 2016

Phase II Study of Venetoclax in Previously Treated WM

Selected inclusion criteria:

- Clinicopathological diagnosis of WM
- Serum IgM >2 x ULN
- Previously treated
- Age ≥18 years
- Good performance
- Normal organ and marrow function



Selected exclusion criteria:

- Serious medical condition
- Concurrent anti-cancer agent
- Known CNS lymphoma
- Active HIV, HBV, HCV infection
- Lactating or pregnant women

www.clinicaltrials.gov: NCT02677324

Castillo et al. EHA 2018

Phase II Study of Venetoclax in Previously Treated WM

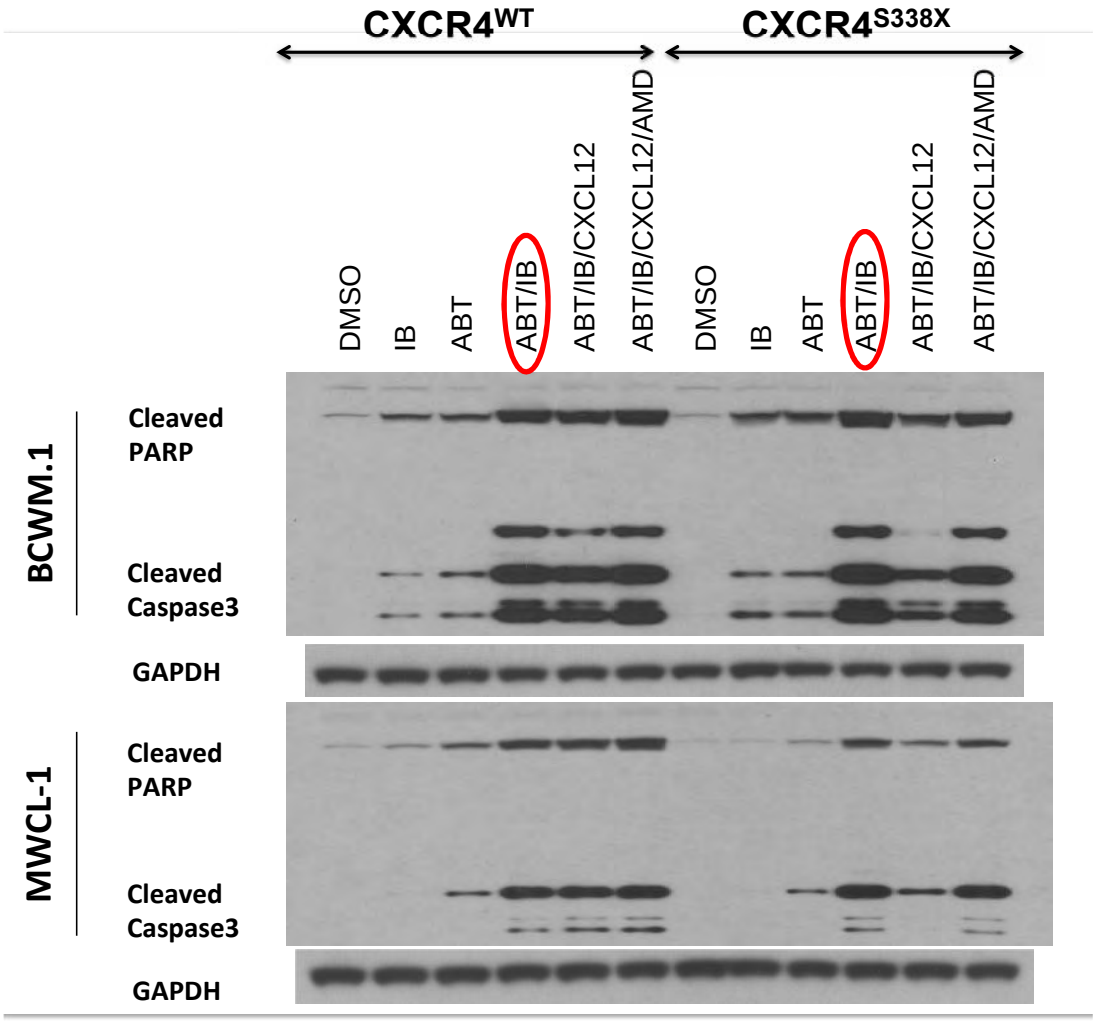
Response	No prior ibrutinib (n=15)	Prior ibrutinib (n=15)	CXCR4 WT (n=14)	CXCR4 MUT (n=16)
Overall	14 (93%)	12 (80%)	12 (86%)	14 (87%)
Major	13 (87%)	9 (60%)	9 (86%)	13 (63%)
Very good	4 (27%)	1 (7%)	4 (29%)	1 (7%)
Partial	9 (60%)	8 (53%)	8 (57%)	9 (56%)
Minor	1 (7%)	3 (20%)	0 (0%)	4 (25%)
Stable	1 (7%)	3 (20%)	2 (14%)	2 (13%)

Median follow-up: 11 months

1 patient had progressive disease at 9 months (MYD88, CXCR4, TP53)

Castillo et al. EHA 2018

Addition of Venetoclax (ABT-199) augments ibrutinib triggered apoptosis in CXCR4 WT and mutated WM Cells.



Cao et al, BJH 2015

Ibrutinib and Venetoclax in Treatment Naïve WM

24 months

Ibrutinib 420 mg/day x 4 weeks	Ibrutinib 420 mg/day Add Venetoclax 100 mg/day week 5 200 mg/day week 6 400 mg/day weeks 7,8	Ibrutinib 420 mg/day And Venetoclax 400 mg/day	Observation
4 weeks	4 weeks	22 months	Follow to PD or off study

Jorge Castillo, PI (DFCI)

Approach to Frontline Therapy of Symptomatic WM

Hyperviscosity, Severe Cryos, CAGG, PN➔ Plasmapheresis

MYD88 Mutated/No CXCR4 mutation

No bulky disease, no contraindications➔ Ibrutinib (if available)

Bulky disease ➔ Benda-R +Ibrutinib and Rituximab

Amyloidosis ➔ Bortezomib/Dex/Rituximab (BDR)

IgM Peripheral Neuropathy ➔ Rituximab ± Alkylator

MYD88 Mutated/CXCR4 mutation +Ibrutinib and Rituximab

Same caveats as above

If immediate response needed, either BDR or Benda-R

MYD88 Wild-Type

✓non-L265P MYD88 mutations

BDR > Benda-R

- **Hold Rituximab until IgM <4000 mg/dL or empiric pheresis is performed.**
- **Consider Maintenance Rituximab**
- **Consider Ofatumumab if R intolerant.**

Hunter et al, JCO 2017; LeBlond IWWM10

Salvage Therapy of Symptomatic WM

Consider repeat primary therapy if response >2 years

MYD88 Mutated/No CXCR4 mutation
Same caveats as primary therapy

+Venetoclax for pts previously exposed to IB

MYD88 Mutated/CXCR4 mutation
Same caveats as primary therapy
If immediate response needed, either BDR or Benda-R

MYD88 Wild-Type
Same caveats as primary therapy
✓non-L265P MYD88 mutations

- **Everolimus >2 prior therapies**
- **Nucleoside analogues (non-ASCT candidates)**
- **ASCT in multiple relapses, chemosensitive disease**

Hunter et al, JCO 2017

Bing Center for WM

Educational Workshop

October 26-27, 2018 | Royal Olympic Hotel | Athens, Greece

Amyloidosis: “Under-diagnosed disorder”

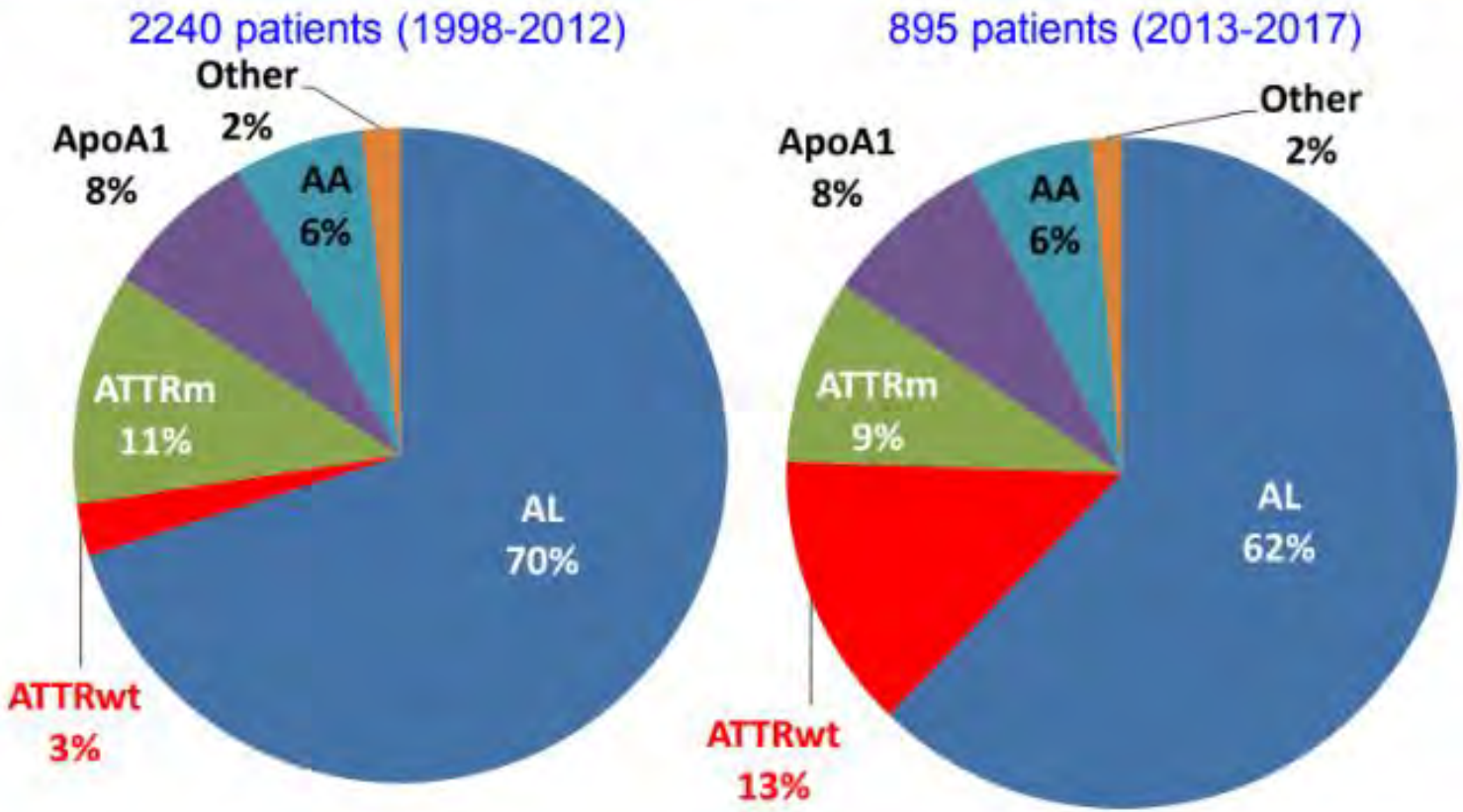
Giampaolo Merlini

Amyloidosis Research and Treatment Center
IRCCS Policlinico San Matteo and
Department of Molecular Medicine
University of Pavia, Italy

OUTLINE

- Diagnosis red flags
- Early diagnosis ➔ Biomarkers
- Risk assessment ➔ Treatment selection
- Treatment outline

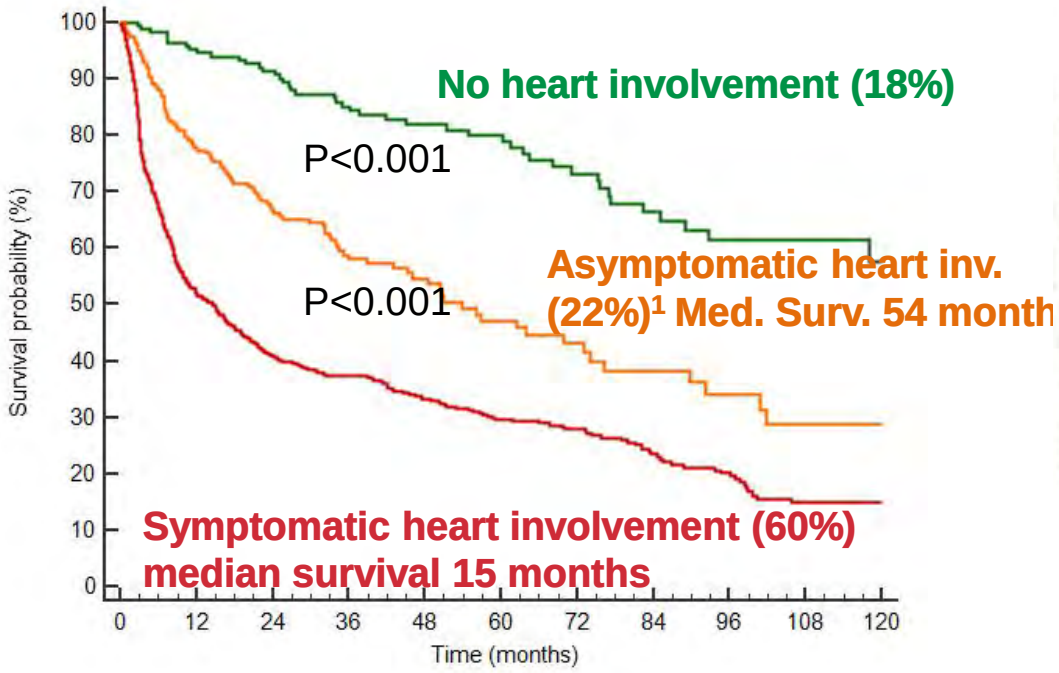
Patients referred to the Pavia Center for Amyloidosis



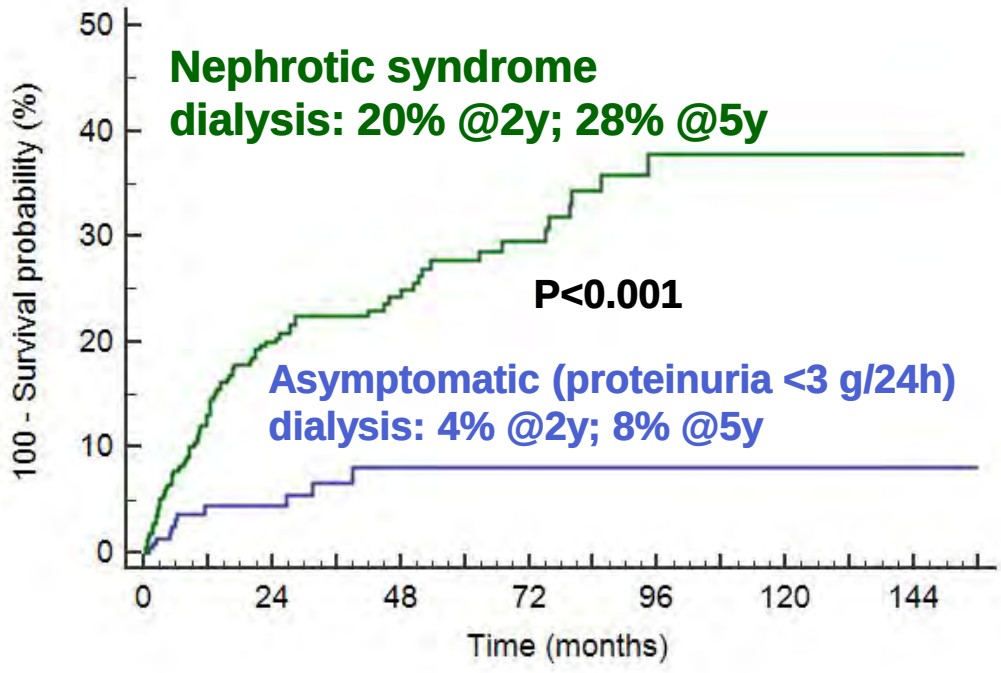
Wild-type TTR could be the most frequent form of cardiac amyloidosis, affecting mostly males (>80%) in the late 70s. ~25% of patients have a monoclonal protein (Geller et al, *Mayo Clin Proc. 2017)*

Outcomes in 1065 patients with AL amyloidosis

Patient survival



Renal survival



EARLY DIAGNOSIS IS VITAL

1. Basset et al, *EHA23 PS 1335*

Light Chain (AL) Amyloidosis: The Journey to Diagnosis.

Lousada et al, Adv Ther. 2015
McCausland et al, Patient 2017

Figure 1. Time from initial symptoms to diagnosis of amyloidosis.

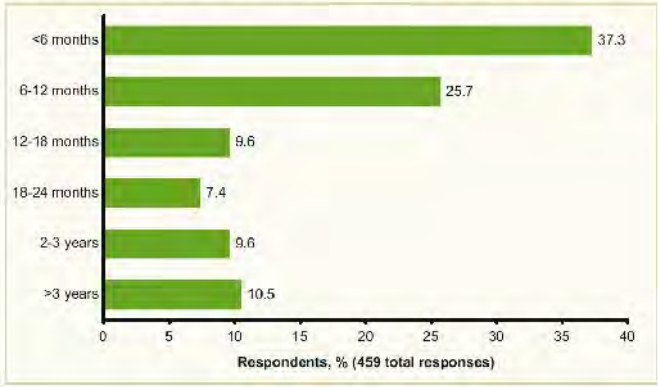


Figure 2. Number of physician visits before establishment of a diagnosis.

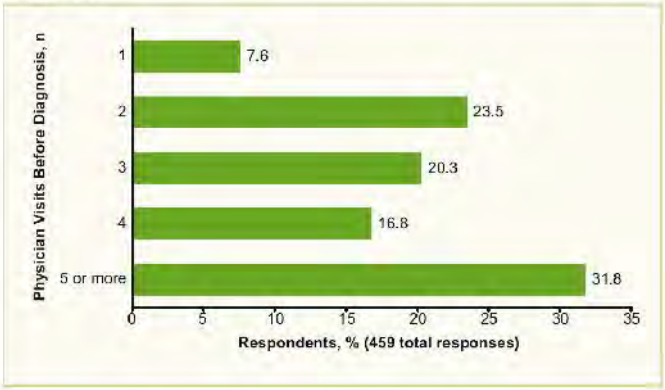
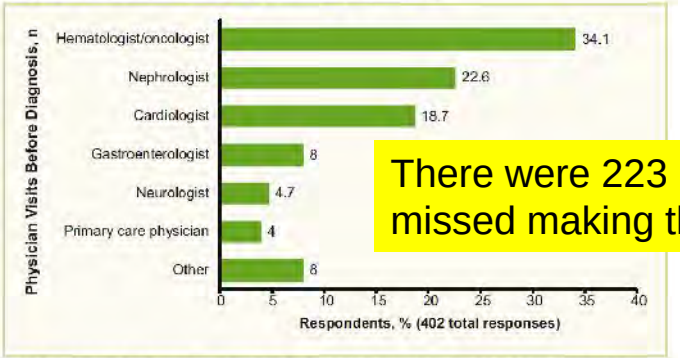
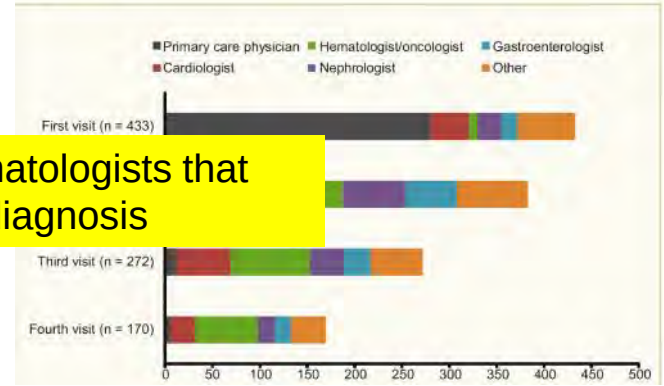


Figure 3. Specialty of diagnosing physician.



"Other" includes internists, hepatologists, ophthalmologists, and dermatologists.

Figure 4. Types of physicians visited before a diagnosis of amyloidosis.



There were 223 hematologists that missed making the diagnosis

When should an hematologist think about amyloidosis?

In a patient with a monoclonal protein

Late
red flags

- Severe fatigue, unexplained weight loss
- Exertional dyspnea (very late symptom!)
- Leg swelling (proteinuria)
- Carpal tunnel syndrome (bilateral)
- Peripheral neuropathy
- Autonomic neuropathy (postural hypotension, erectile /bladder / bowel dysfunction)
- Hepatomegaly with normal imaging
- Macroglossia and/or periorbital purpura

EARLY DIAGNOSIS

Biomarkers

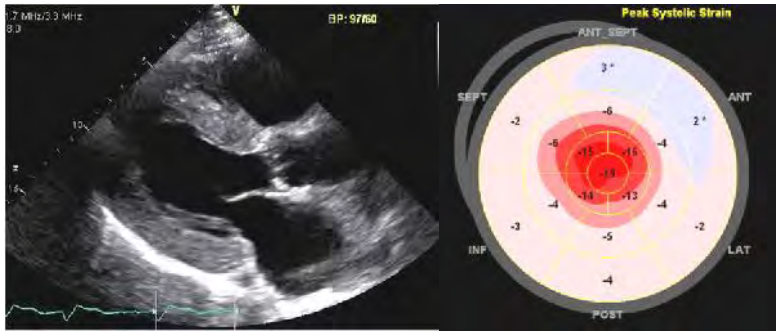
- sFLC
- NT-proBNP
- u. Albumin

Imaging

- Echocardiography (SVI)
- CMR
- DPD/PYP scintigraphy
- ^{18}F-florbetapir PET/CT

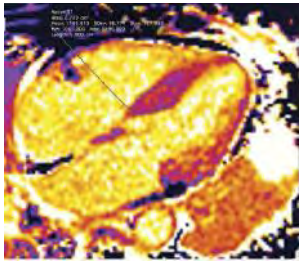
Diagnosis: imaging cardiac amyloidosis

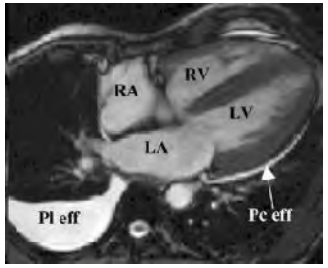
Mainstay: Echocardiography

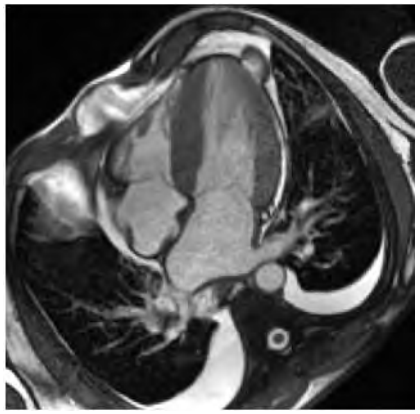


Strain Doppler imaging *"bulls eye" (apical sparing)* *Courtesy Martha Grogan*
Stroke volume index (Milani et al, *Circ Cardiovasc Img. 2018*)

Cardiac MRI - T1 map - LGE

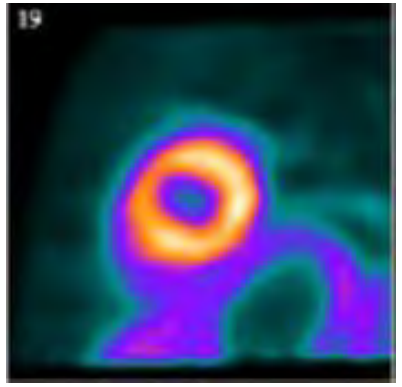






Maceira et al, *Circulation 2005*
Banypersad et al, *Circ Cardiovasc Img. 2013*
Fontana et al, *JACC Cardiovasc Img. 2017*
Martinez-Naharro et al, *ISA 2018 PA060*
Knight et al, *JACC Cardiovasc Img. 2018*

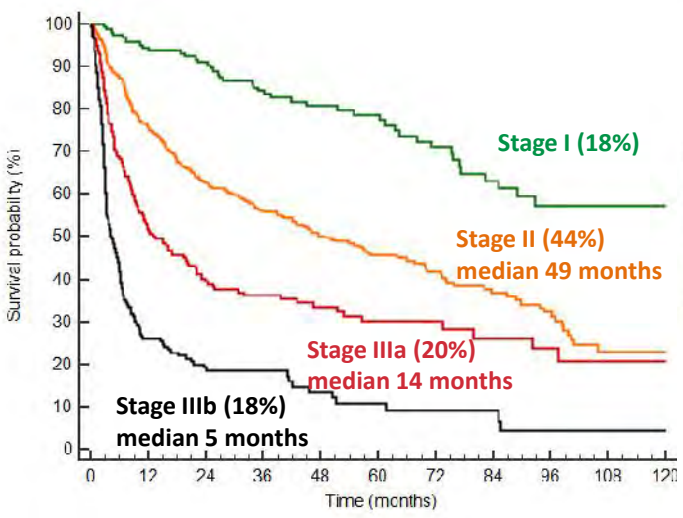
^{18}F-florbetapir
^{18}F-florbetaben
^{11}C-Pittsburgh compound B



Dorbala et al, *EJNMMI 2014*
Park et al, *Circ Cardiov Img. 2015*
Law et al, *J Nucl Med 2016*
Pilebro et al, *J Nucl Cardiol. 2017*
Manwani et al, *ISA 2018 PB054*
Wagner et al, *Eur J Nucl Med Mol Imaging. 2018*

Predicting outcomes in AL amyloidosis

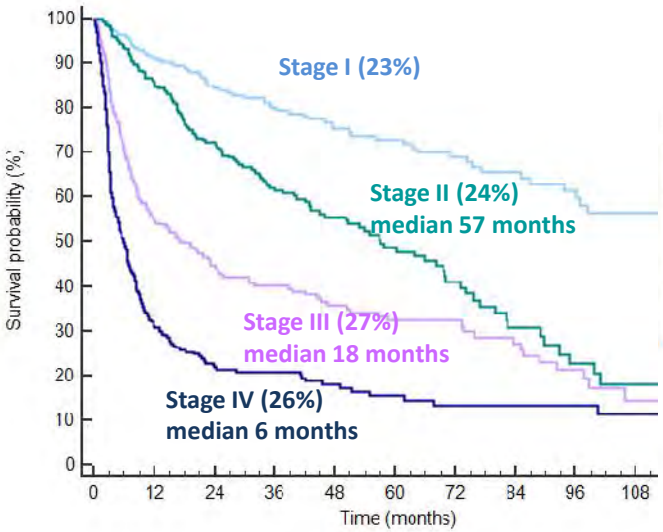
Mayo Clinic / European staging system



Staging is based on **NT-proBNP (cutoff 332 ng/L)** and **troponin I (cutoff 0.1 ng/mL)**
Very high (>8500 ng/L) NT-proBNP identifies patients with advanced cardiac dysfunction (Stage IIIb)

Dispenzieri, et al. *JCO 2004* - Wechalekar, et al. *Blood 2013* - Palladini, et al. *Haematologica 2014* - Sharpley et al. *EHA PF553*

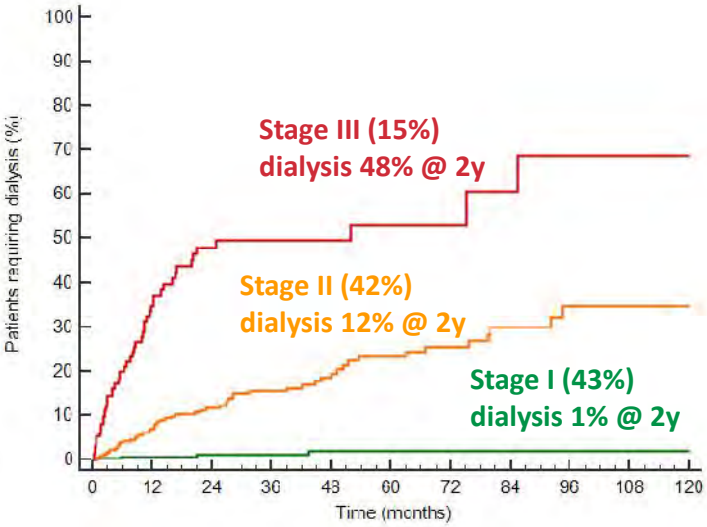
Revised Mayo Clinic staging system



Staging is based on **NT-proBNP** (cutoff 1800 ng/L), **troponin I (cutoff 0.07 ng/mL)**, and **dFLC (cutoff 180 mg/L)**

Kumar et al, *JCO 2012*

Renal staging system



Staging is based on **proteinuria** (cutoff 5g/24h) and **eGFR** (cutoff 50 mL/min per 1.73 m^2)

Palladini, et al. *Blood 2014*

- GDF-15 is a strong predictor for renal outcomes
- GDF-15 reduction after therapy is associated with better outcome

Kastritis et al, *Blood 2018*

Diagnostic algorithm for systemic amyloidosis

Suspect systemic amyloidosis

- Heart failure & preserved ejection fraction, low ECG voltage
- Proteinuria (Leg swelling) – Fatigue & weight loss
- Axonal sensorimotor polyneuropathy (carpal tunnel synd. 50%)
- Hepatomegaly, non-infectious diarrhea-
- **MGUS with abnormal FLC ratio and elevated NT-proBNP and/or proteinuria**

Periorbital purpura 11%

Macroglossia 14%

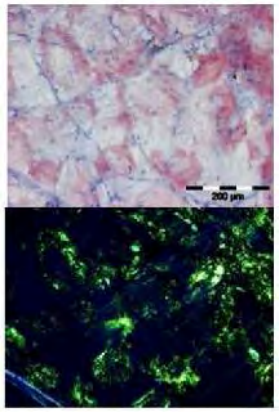
↓

Serum and urine immunofixation electrophoreses + sFLC

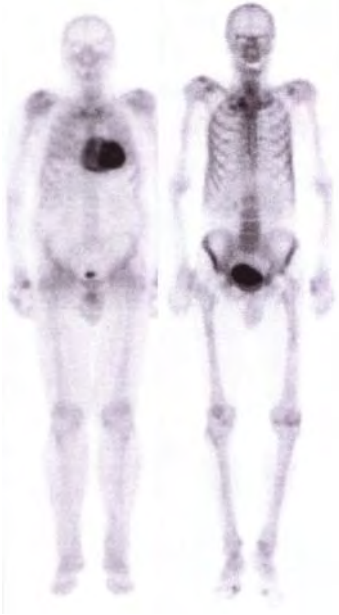
Add cardiac PYP or DPD scan[1] if heart symptoms/suggestive echo

↓

Abdominal fat aspirate: (underutilised):[2] sensitivity 81-84%[3,4]
Possible lip/minor salivary gland biopsy for Congo red



ATTR AL



↓ **Negative**

↓ Cardiac MRI

↓ Organ biopsy

↓ **Positive**

↓

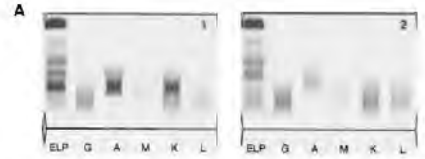
Type amyloid deposits

- **Proteomics-MS[5,6]**
- Immuno-EM[7]
- Immunohistochemistry[8]

1. Gillmore et al, *Circulation 2005;* 2. Muchtar et al, *Ann Med. 2017* – 3. Fernandez de Larrea et al, *Blood 2015 – 4*. Quarta et al, *Eur Heart J 2017* – 5. Vrana et al, *Blood 2009;* 6. Lavatelli et al, *Mol Cell Proteom. 2008;* 7. Arbustini et al, *Amyloid 2002;* 8. Schonland et al, *Blood 2012*

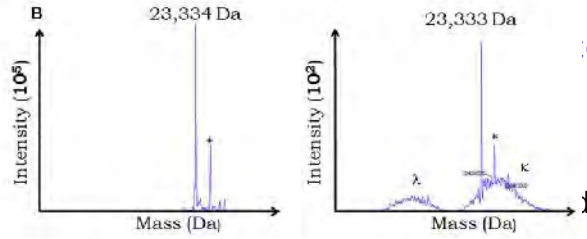
Characterization of the amyloidogenic clone

Serum and urine immunofixation and FLC measurement (mass spectrometry)
(Palladini et al, *Clin Chem. 2009*)



Mills et al, *Methods 2015*
Milani et al, *Am J Hematol. 2017*
Muchtar et al, *ASH 2017 Abstr 4353*

- Poor prognosis if BMPC>10% (AL+MM) Bortez/Len *(*Rodriguez-Lobato et al, *EHA23 PS1314)*
- High PC proliferative index (Sidiqi et al, *Haematol*

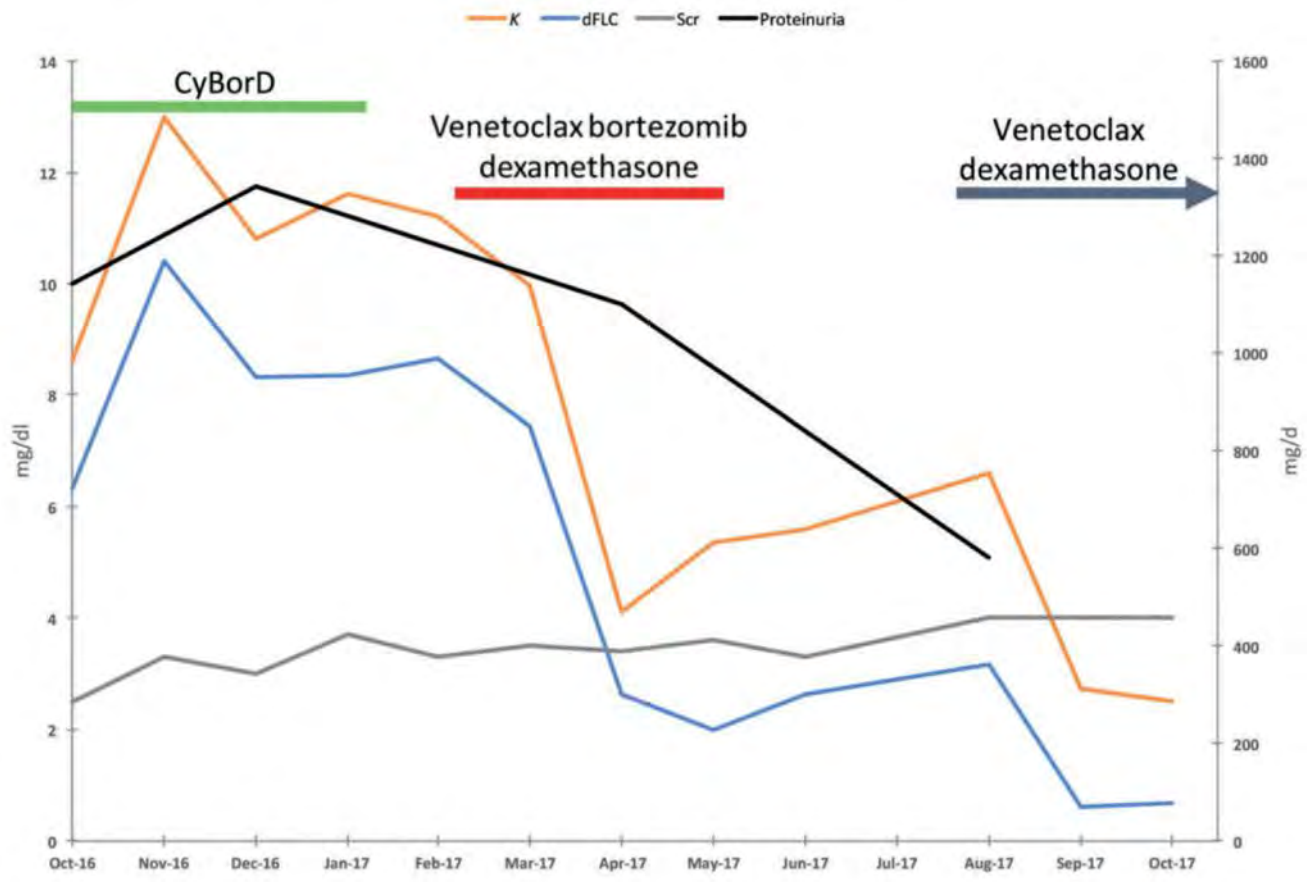


ome by

lana et al, *Leukemia 2018*)

- t(11;14) translocation (~40-60% vs 17% in MM): lower benefit from bortezomib and IMiDs than from M-Dex and HDM (Bochtler et al, *J Clin Oncol. 2015* - Muchtar et al, *Leukemia 2016)*
- Gain of 1q21 (∼25%): poor outcome with M-Dex (Bochtler et al, *Amyloid 2014)* overcome by HDM and bortezomib (Bochtler et al *J Clin Oncol 2015*, *Blood 2016*)
- WES showed common genetic susceptibility with MM, but also distinct mutations, and lower complexity mutational pattern than MM (Zhou et al, *Clin Lymph M & L 2012* - Da Silva et al, *Leukemia 2017* - Granzow et al, *Haematologica 2017* – Cuenca et al, *EHA23 PS1261* - Rossi et al, *Blood Cancer J 2017*)

Venetoclax induced a complete response in a patient with immunoglobulin light chain amyloidosis plateaued on cyclophosphamide, bortezomib and dexamethasone.



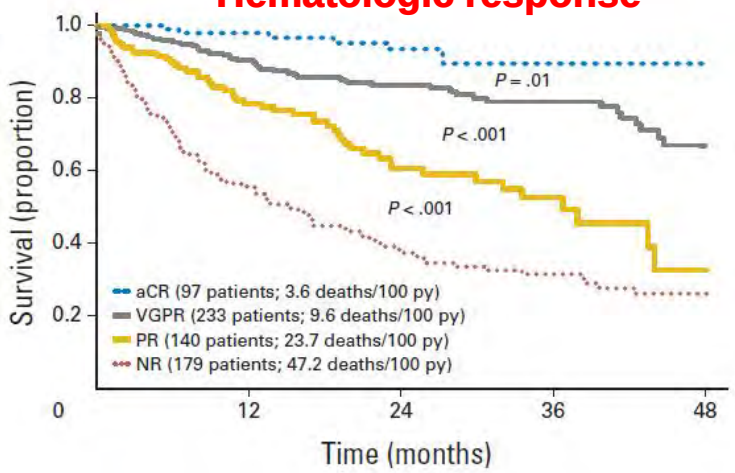
Leung et al, *Haematologica 2018*

Validated criteria for early (3 & 6 months) assessment of response

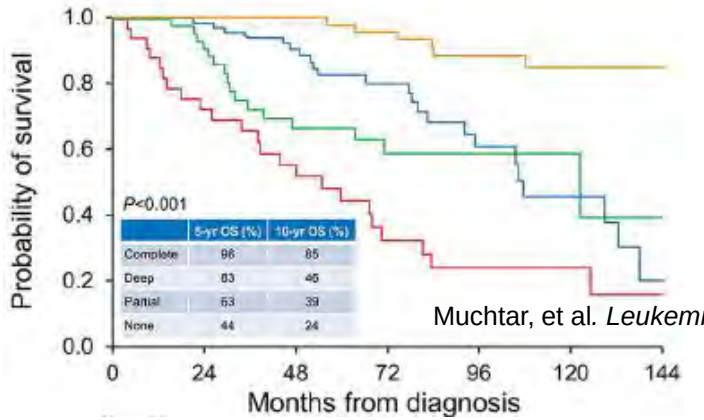
Response	Definition
Hematologic	**CR:** negative s&u IFE + normal FLCR **VGPR:** dFLC <40 mg/L **PR:** dFLC decrease >50%
dFLC 20-50 mg/L	**Low-dFLC response:** dFLC <10 mg/L
Cardiac	NT-proBNP decrease >30% & >300 ng/L
Renal	Proteinuria decrease >30%

Health-related QoL McCausland et al. *EHA23 S147*

Hematologic response



Grading of cardiac response (215 patients)

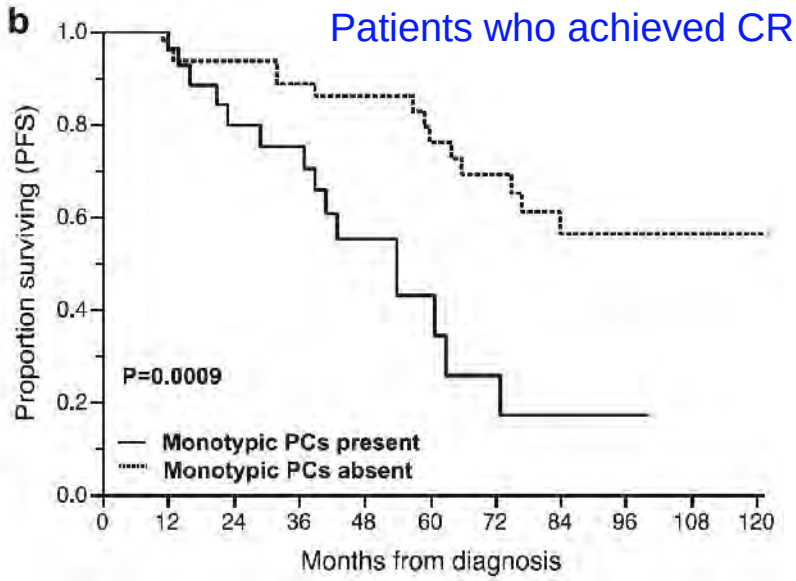


Muchtar, et al. *Leukemia 2018*

Hematologic CR → 54% Cardiac response
→ 68% Renal response

Palladini, et al. *J Clin Oncol 2012* - Palladini, et al. *Blood 2014* - Milani, et al. *Blood 2017* - Dittrich, et al. *Blood 2017* - Sidana et al, *Leukemia 2018* – Gavriatopoulou et al, *EHA23 PF585* – Palladini et al, *EHA23 PS1320* – Milani et al, *EHA23 PS1325*

Minimal residual disease in AL amyloidosis



- Improvement in **cardiac response**
  - 33% in mPC- vs 15% in mPC+ (p = 0.003)
- **Renal response**
  - 19% in mPC- vs 3% in mPC+ (p = 0.02).

Sidana et al, *Leukemia 2018*

34 patients in CR
21 (62%) MRD negative
Compared to the time of aCR achievement, further renal response was obtained in 9 of 13 evaluable MRD negative patients (69%) and in 2 of 11 MRD positive patients (18%, P=0.034)

Palladini et al, *ASH 2016, Abstract #3261 updated*
Kastritis et al, *EHA23 PS1304*

Patients who do not achieve organ response despite sustained complete hematologic response should be tested for MRD by NGF.

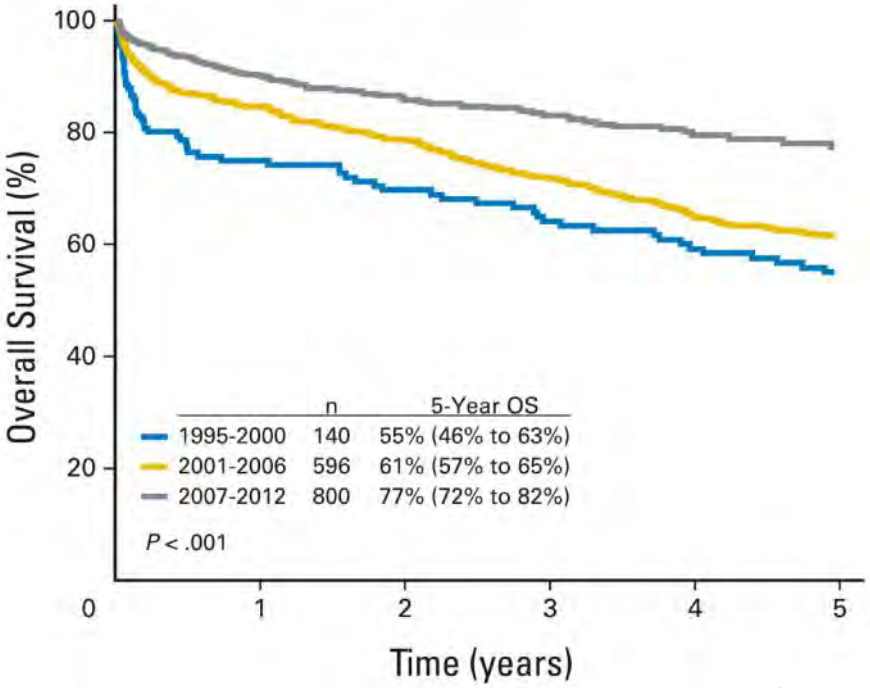
Further treatment may be considered in MRD positive patients **if risk assessment allows**

ASCT in AL amyloidosis

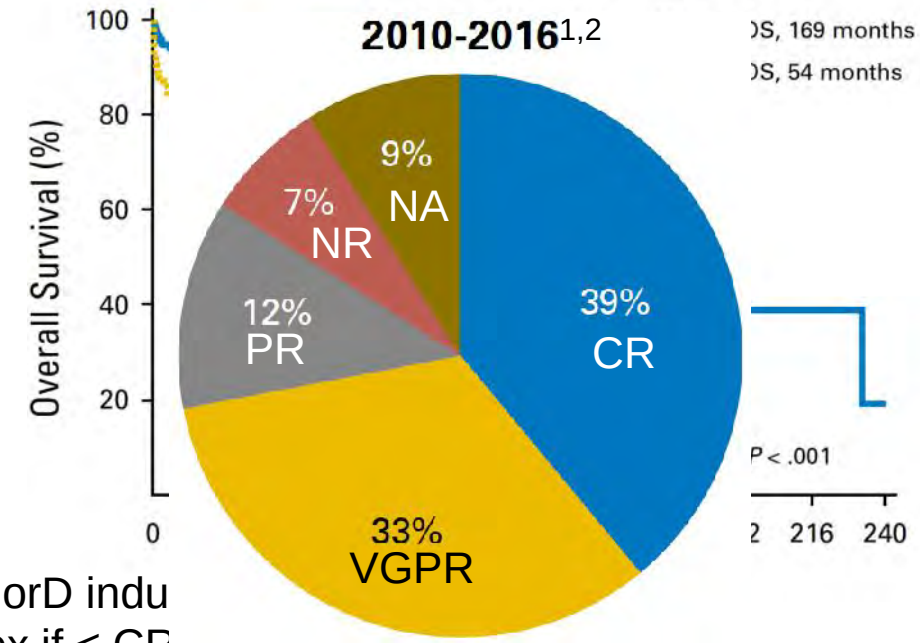
- 1,536 patients at 134 centers from1995 to 2012
- HR/CR 61/33%, TRM 4% (2007-2012)
- Renal response 30%

Fit patients: ~20%

age < 70 years, ECOG PS≤2, BP >90 mmHg, cTnT < 0.06 ng/mL, Creatinine clear. >30 mL/min, NYHA I or II, ≤ 2 organs involved



D'Souza et al, *J Clin Oncol 2015*



- CyBorD indu
- BDex if < CR

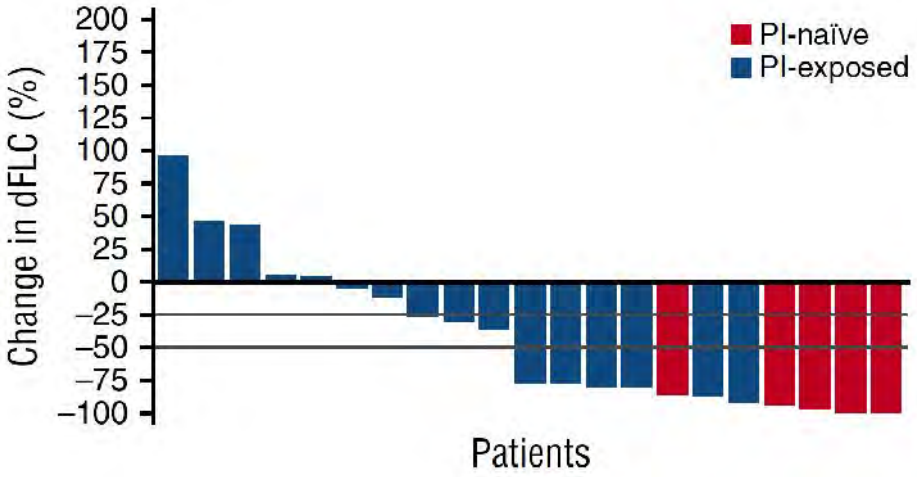
1. Tandon et al, *BMT 2017* - 2. Sidiqi et al, *JCO 2018*
3. Hwa et al, *Am J Hematol, 2016* - 4. Scharman et al, *ASH 2017 Abstr .4552* - 5. Landau et al, *Leukemia 2017*

Treatment of intermediate-risk patients (¼60%)
(ineligible for ASCT, stages I-IIIa)

Standard of care: Bortezomib-based regimens → VGPR/CR~50%
(BDex, CyBorD, BMDex) → VGPR/CR ~40-20% in Stage IIIa/IIIb

Kastritis et al. *J Clin Oncol 2010* - Mikhael et al. *Blood 2012* - Venner et al. *Blood 2012* - Reece et al. *Blood 2014* - Palladini et al. *Leukemia 2014* - Venner et al. *Leukemia 2014* - Jaccard et al. *Haematologica 2014* - Palladini et al. *Blood 2015* - Lim et al, *ASH 2017 Abstr. 3114* - Manwami et al, *ASH 2017 Abstr.1816*

Phase I/II study of ixazomib in relapsed refractory AL amyloidosis



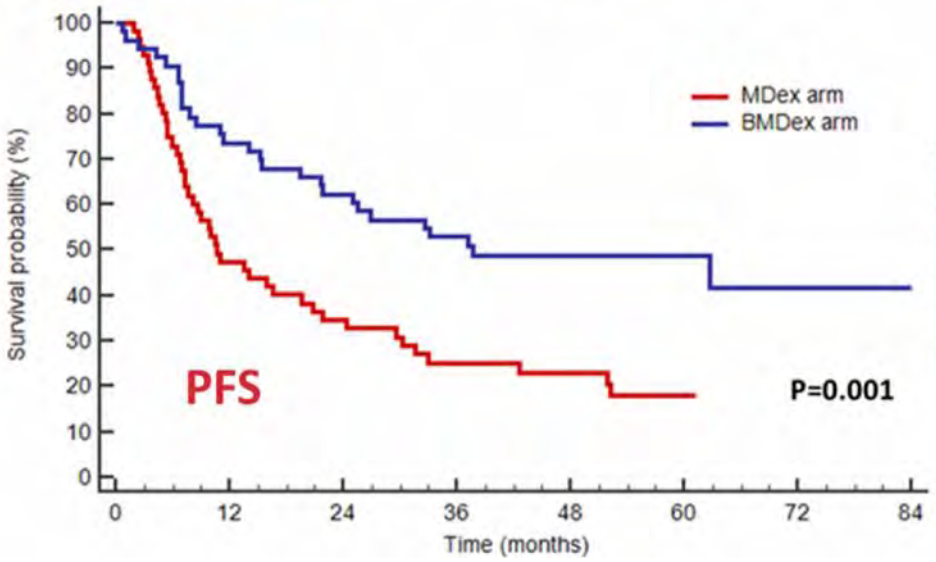
27 patients - Overall hematologic response rate: 52%, ≥VGPR 43%
Cardiac response 45%, renal response 45%

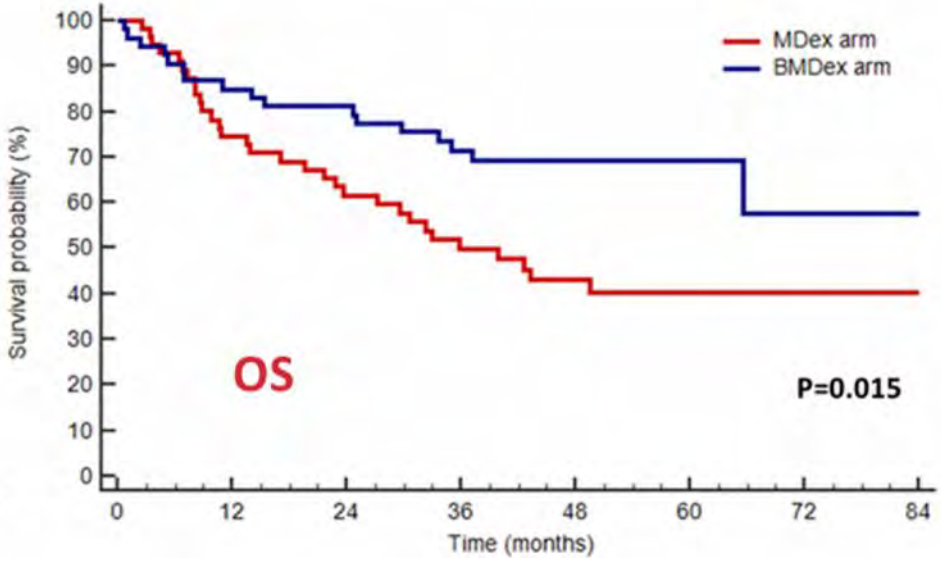
Phase III study of ixazomib vs. physician's best choice in rel/ref AL amyloidosis ongoing (NCT01659658)

A phase III trial of BMDex vs. MDex in newly-diagnosed AL

Active Sites
Italy
• Pavia
• Bologna
France
• Lille
• Paris
• Nantes
• Limoges
• Lyon
Greece (Athens)
UK (London)
Australia
• Brisbane
• Perth
• Melbourne
• Sidney
Spain
• Barcelona

Response	MDex (56 pts)	BMDex (53 pts)	P
Overall Hem.	**32 (57%)**	**43 (81%)**	**0.005**
CR	11 (20%)	12 (23%)	0.440
VGPR	11 (20%)	22 (%)	0.007
PR	10 (17%)	9 (%)	0.454
Heart	10/36 (28%)	10/26 (38%)	0.195
Kidney	15/35 (43%)	16/36 (44%)	0.448

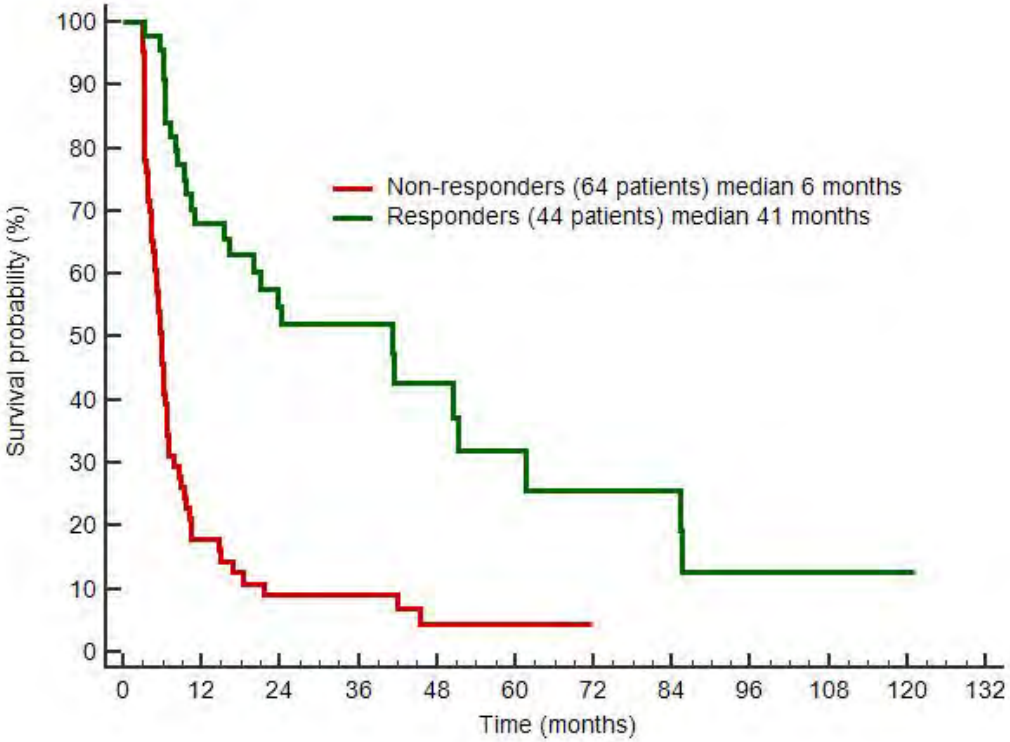




Kastritis, et al. Manuscript in preparation

Hematologic response at 3 months prolongs survival in frail patients with advanced heart involvement

Stage IIIb: NT-proBNP> 8500 ng/L (~20%)

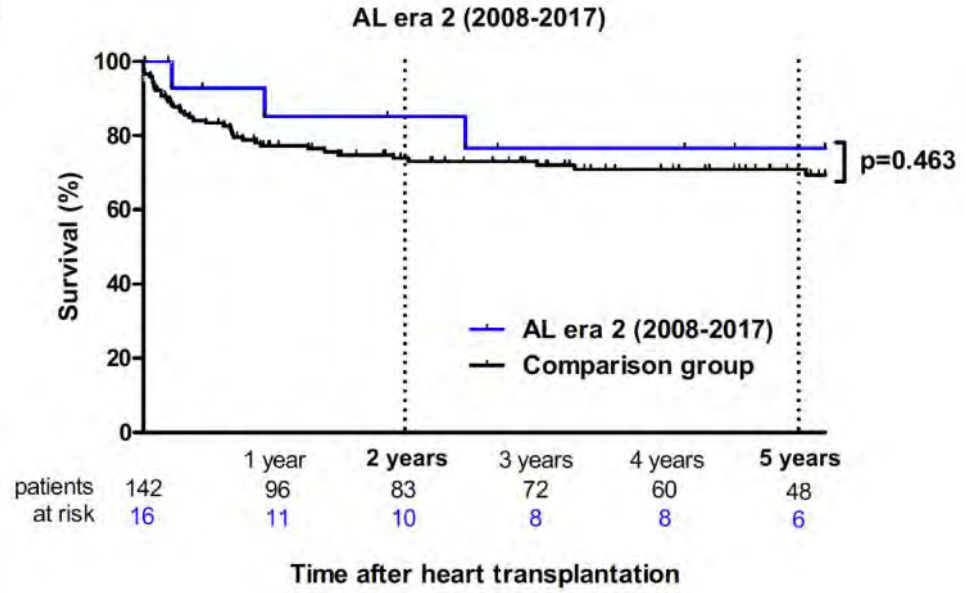


Bortezomib-based regimens

Palladini et al, *Blood 2015* – Le Bras et al, *Eur J Cancer 2017* – Manwani et al, *Haematologica 2018*

Heart transplantation

- age < 65 yrs,
- no significant extra-cardiac amyloidosis
- ASCT after HTx very effective[1-4]
- outcomes comparable to non-amyloid[5]

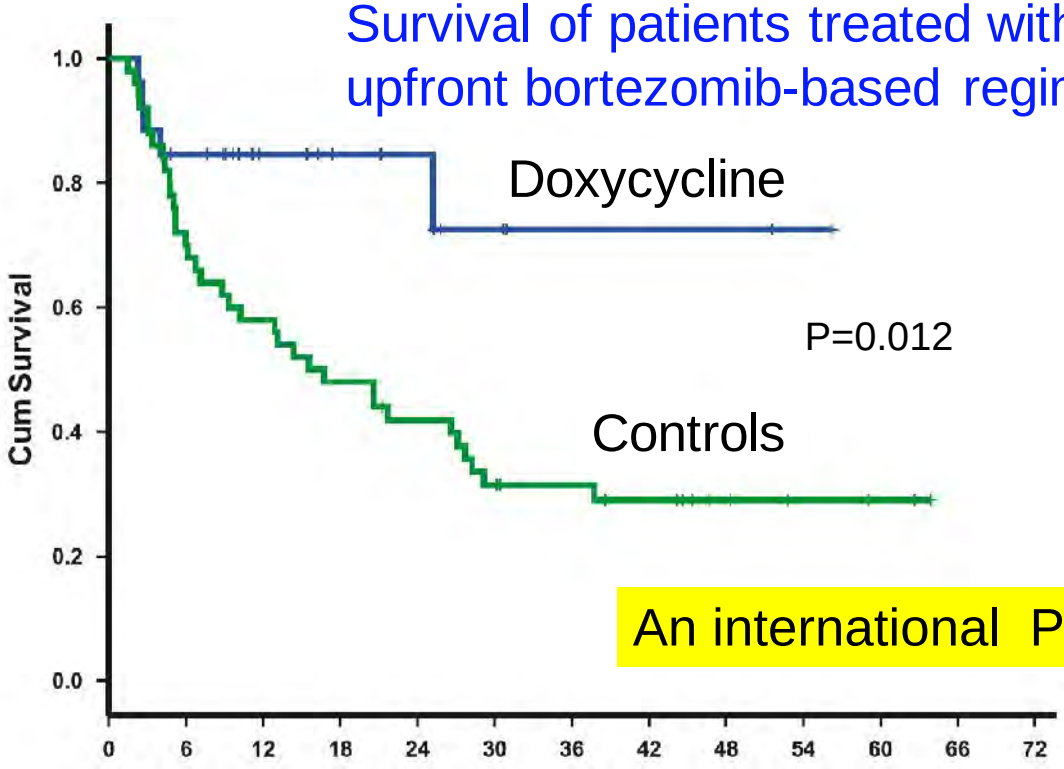


1. Lacy et al, *J Heart Lung Transplant. 2008 – 2*. Dey et al, *Transplantation 2010 –* 3. Sattianayagam et al, *Am J Transplant. 2010* - 4. Gray Gilstrap, et al, *J Heart Lung Transpl 2014* – 5. Kristen et al, *J Heart Lung Transplant. 2018*

Interfering with cardiac toxicity in AL amyloidosis

30 patients treated with doxycycline (100 mg bid) + CT
73 matched controls CT

Survival of patients treated with an upfront bortezomib-based regime



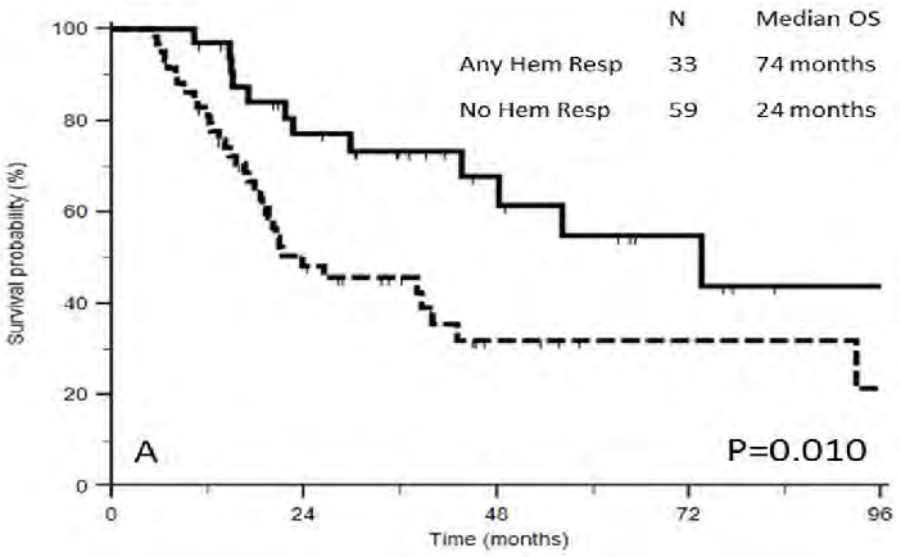
An international Phase III trial is ongoing

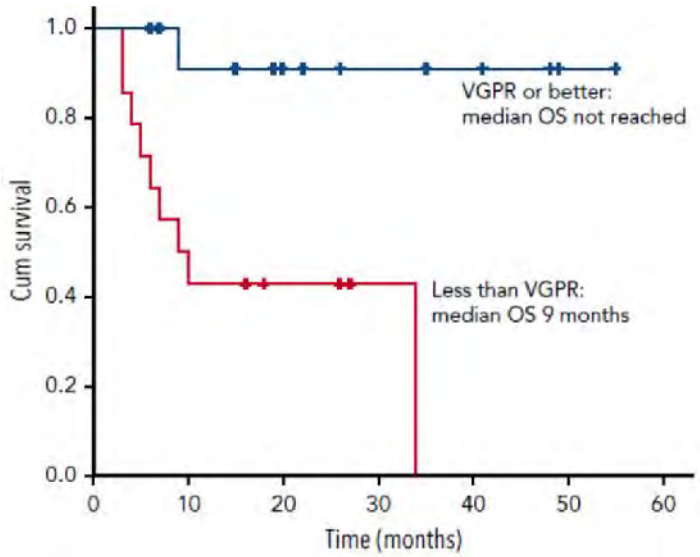
Wechalekar et al, *Blood Cancer J 2017*

Newer (and older) chemotherapy approaches - bendamustine

Hematologic response

- 35% (CR 2%, VGPR 8%)
- 55-59% in patients with IgM-AL (CR 8-11%, VGPR 25-37%)





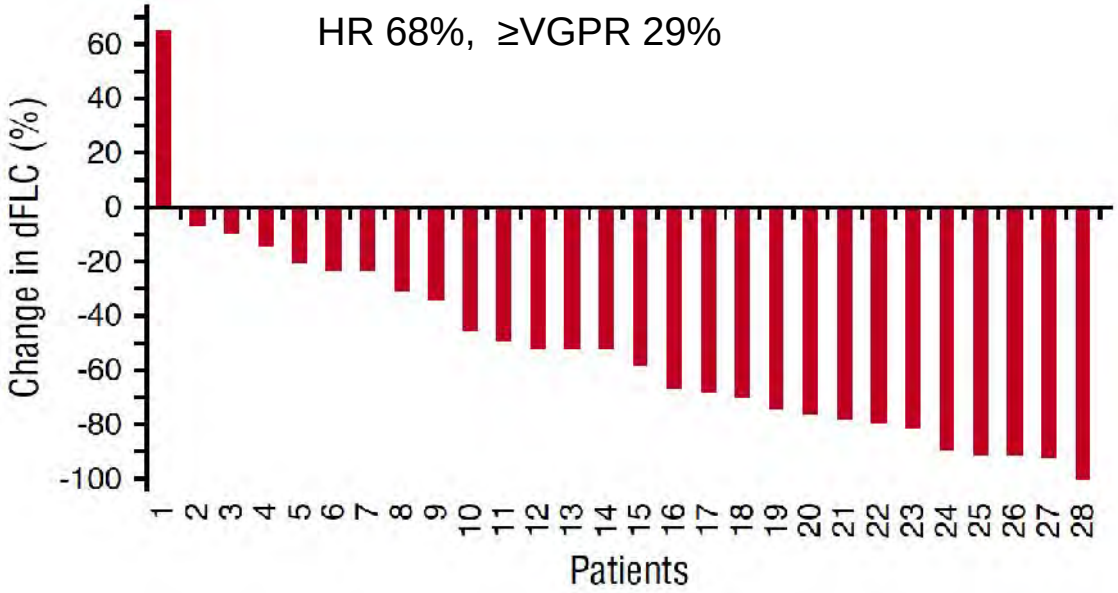
1. Milani, et al. *Blood 2018*
2. Manwani, et al. *Blood 2018*

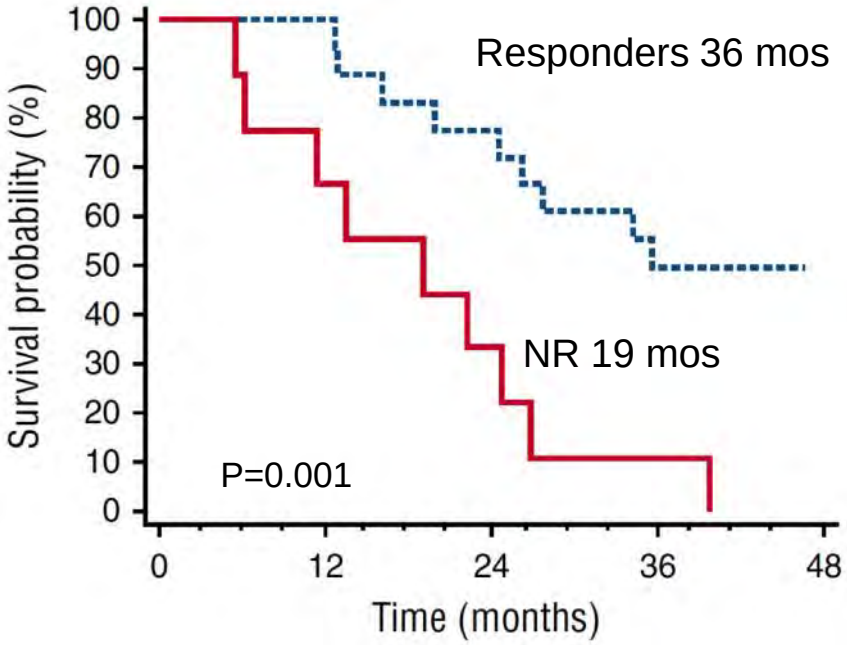
Treatment of relapsing/refractory patients

IMiDs are effective rescue agents (increase in NT-proBNP, Len potential nephrotoxicity)

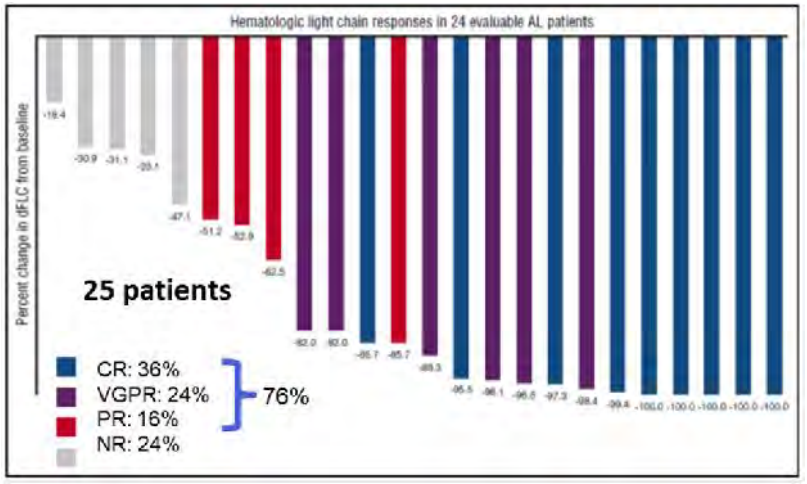
Pomalidomide produces rapid and profound responses

(Dispenzieri et al, *Blood 2012*, Sanchorawala et al., *Blood 2016* – Palladini et al, *Blood 2017*)

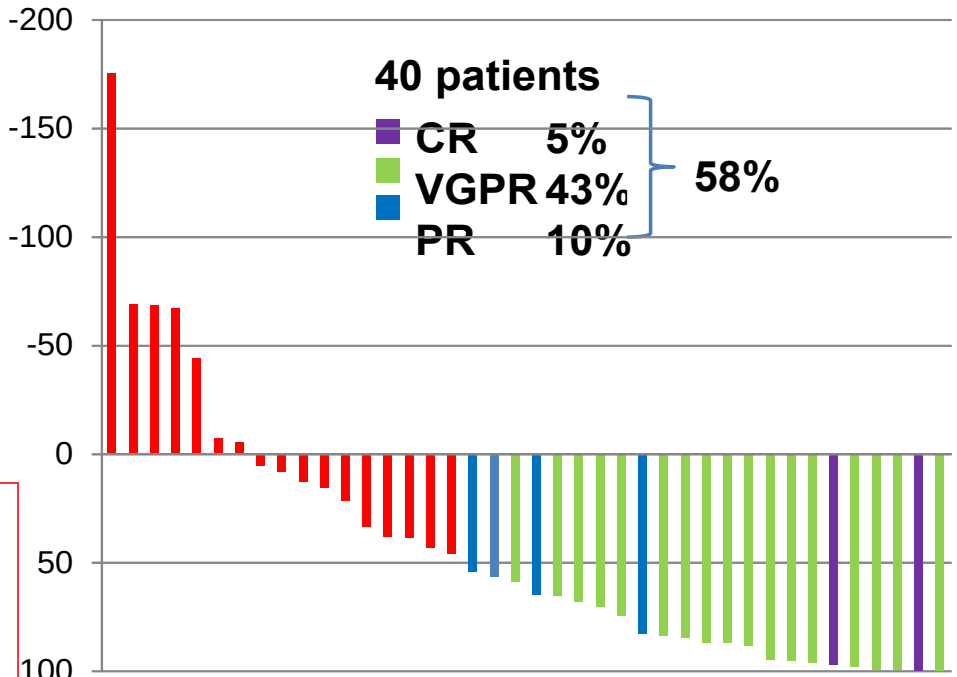




Daratumumab in AL amyloidosis



Kaufman et al, *Blood 2017* & Kaufman et al, *EHA23 PS1305*



Jaccard et al, *EHA23 S851*

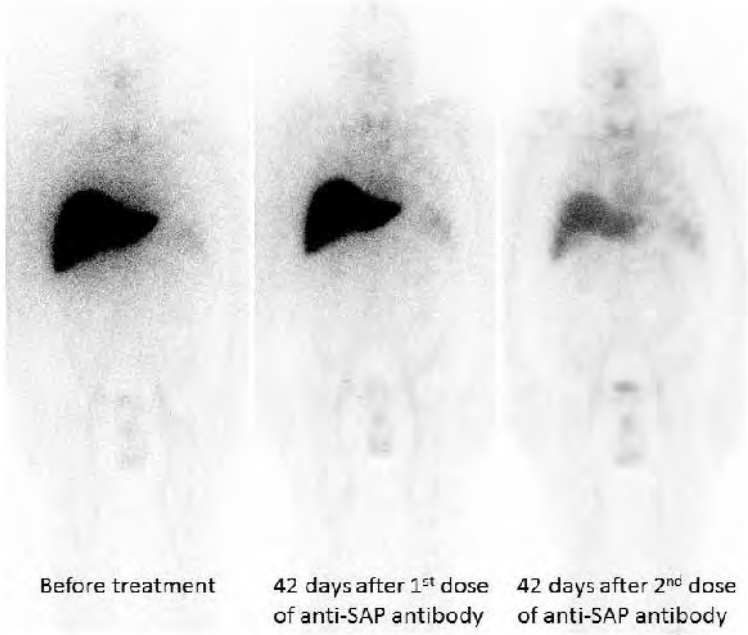
No	44
Prior lines of therapy, n (range)	3 (1–8)
ORR n (%)	25 (83)
CR n (%)	5 (17)
VGPR n (%)	19 (63)
PR n (%)	1 (3)
Time to 1st/ best response, months (95% CI)	2.2 (1.7–4.8) / 5.7(3.4-7.7)

Abeykoon et al, *Leukemia 2018*

Phase III international study of CyBorD vs CyBorD+Dara upfront (ANDROMEDA) - Safety run-in results: Merlini et al, *EHA23 PS1318*

Anti-SAP antibodies

1. CPHPC to deplete circulating SAP
2. monoclonal IgG1 anti-SAP antibody



Anterior SAP scintigraphy scans of systemic AL amyloidosis patient who received two treatments with CPHPC + anti-SAP antibody

Richards et al, *NEJM 2015;373:1106-14*

Richards et al, Sci Transl Med. 2018;10(422).

ents receiving >
f anti-SAP
had manageable
eaction

Phase 2: patients with cardiac amyloidosis NCT03044353

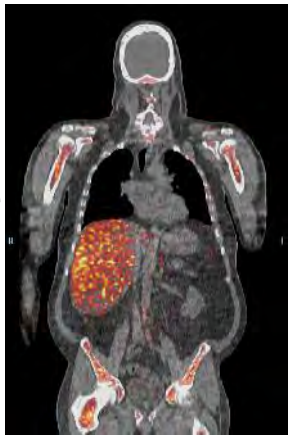
Fibril-reactive antibody 11-1F4

Phase 1a 8 patients

Single IV infusion 0.5 to 500 mg/m^2 Week 1

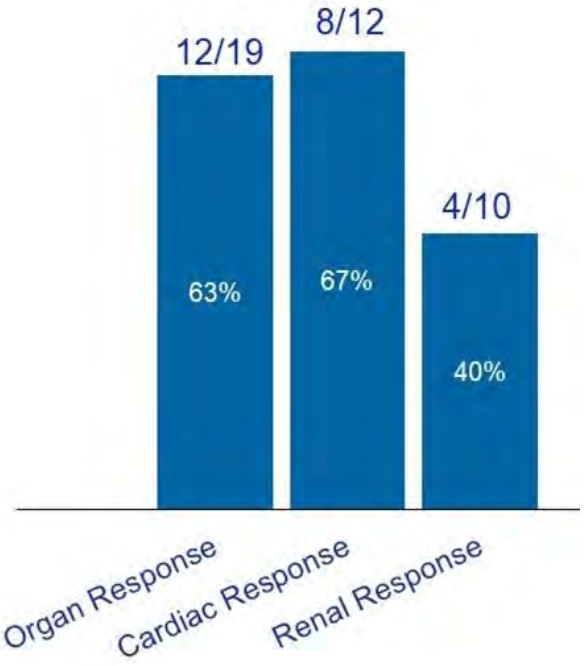
Phase 1b 19 patients

Weekly IV infusion for 4 weeks



Wall et al, *Blood 2010*

SAE ≥3 in 5 patients
(diarrhea, pain, pruritus, pleural/pericardial effusion)



Edwards et al, *Amyloid 2017* and *ASH 2017 Abstr.509*

Conclusions

- Early diagnosis, novel agents, biomarker-guided treatment strategy are improving the outcome of patients with amyloidosis
- Advanced cardiac AL amyloidosis remains an unmet need: improve the understanding of the mechanisms of cardiac damage
- In the near future the treatment of systemic amyloidosis will include the combination of agents targeting critical steps of the amyloid cascade increasing efficacy, but raising concerns about sustainability and access to drugs
- Novel collaborative models are necessary to tackle these challenges. Pharma companies, patients' advocacy groups and scientific societies, regulatory and funding agencies and academia are all essential for progress and hope

CAR-T cells and the Immune System in Multiple Myeloma

Nikhil C. Munshi, MD

Professor of Medicine
Harvard Medical School

Director Basic and Correlative Sciences

Dana-Farber Cancer Institute
Boston VA Healthcare System

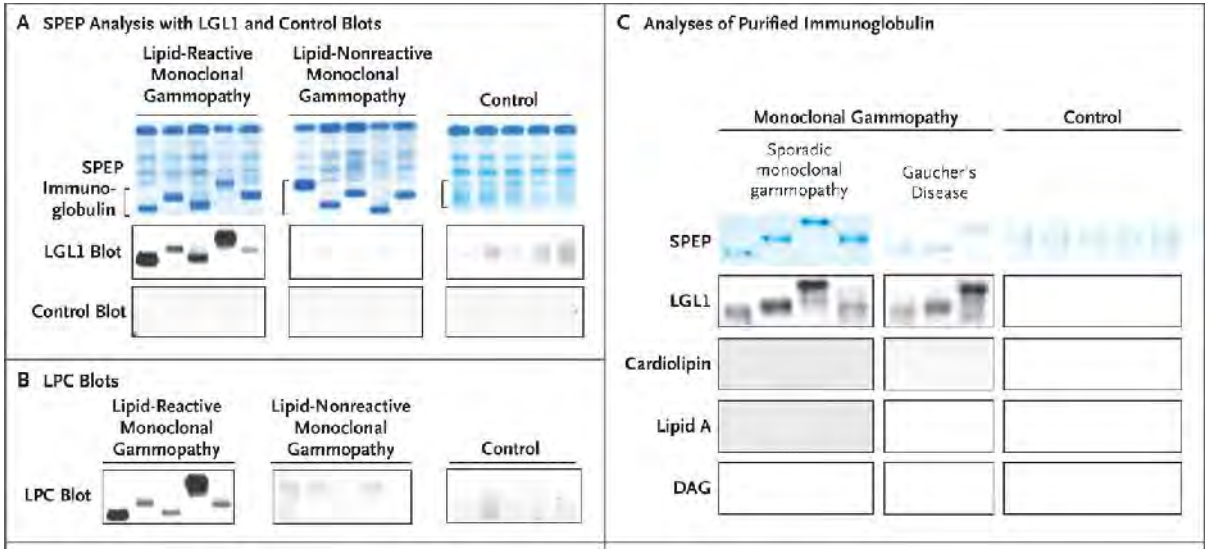
DANA-FARBER
CANCER INSTITUTE

Origin of the Disease

- Chronic antigenic stimulation of the plasma cell
- Repeated infections
- Chronic inflammation
- Autoimmune disorders
- A Patient with a prior therapy with horse anti-serum against tetanus
  - Developed MGUS
  - Stable for 30 years then progressed to MM.
  - The serum IgG component was found to react specifically against horse ~-2 macroglobulin.

Clonal Immunoglobulin Against Lysolipids in The Origin of Myeloma

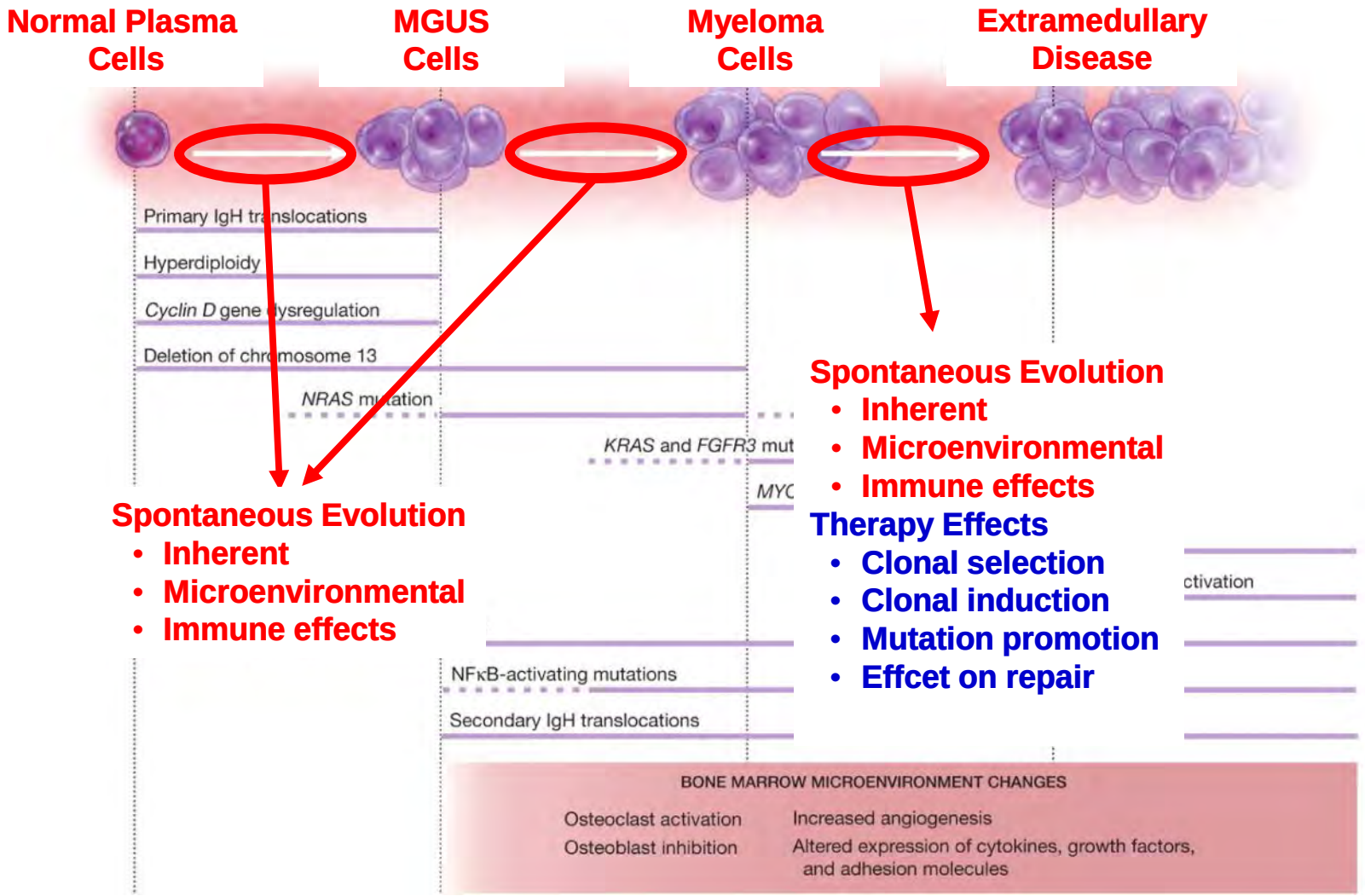
- MGUS developing during the course of Gaucher's disease are reactive against lyso-glucosylceramide (LGL1), which is elevated as a consequence of the metabolic defect.
- Binding to this antigen was noted in one third of sporadic human monoclonal gammopathies.



Nair et al. NEJM 2016

The NEW ENGLAND JOURNAL of MEDICINE

Evolution of Multiple Myeloma – Genomic Changes

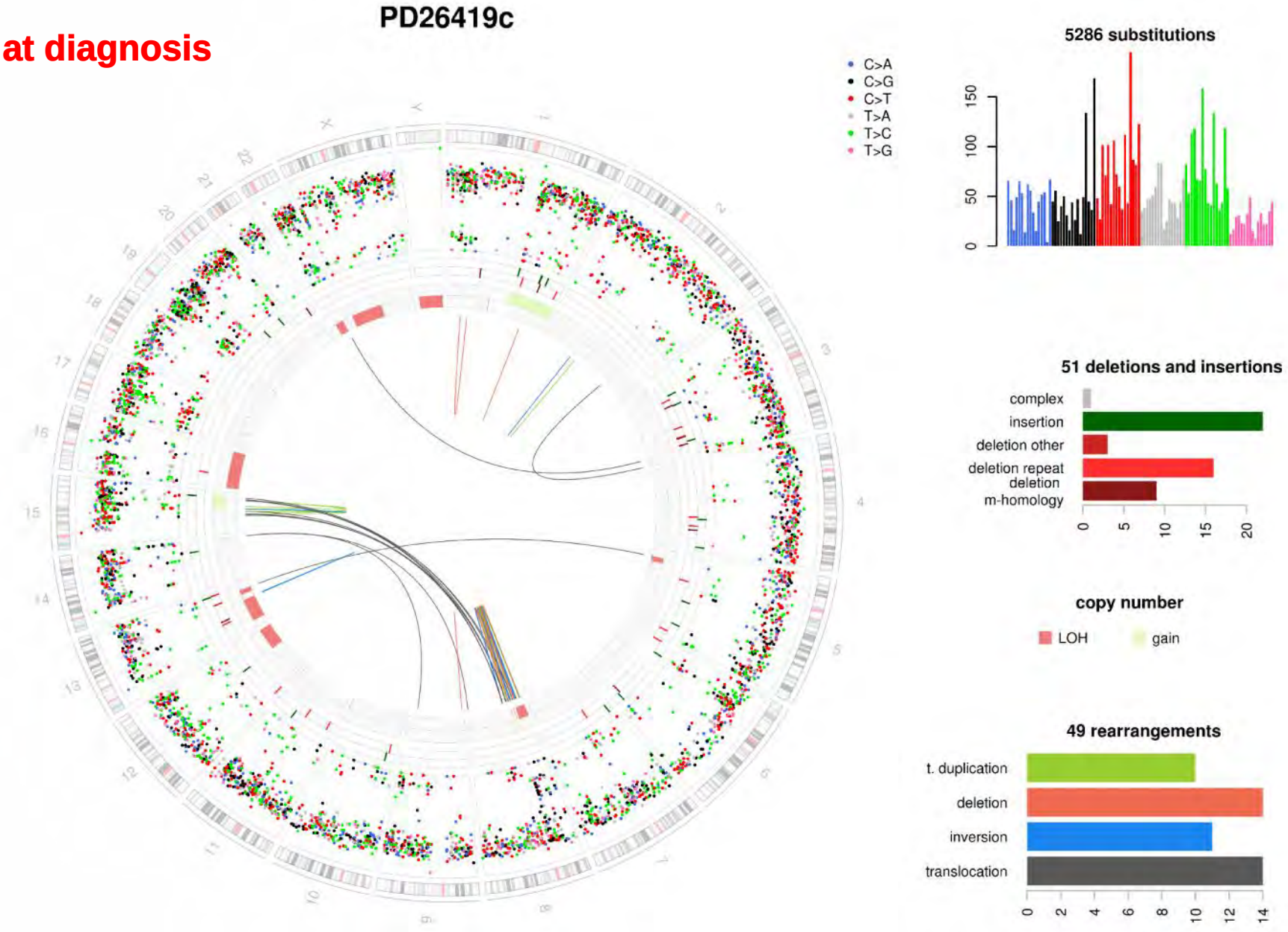


Neha Korde et al. Blood 2011;117:5573-5581

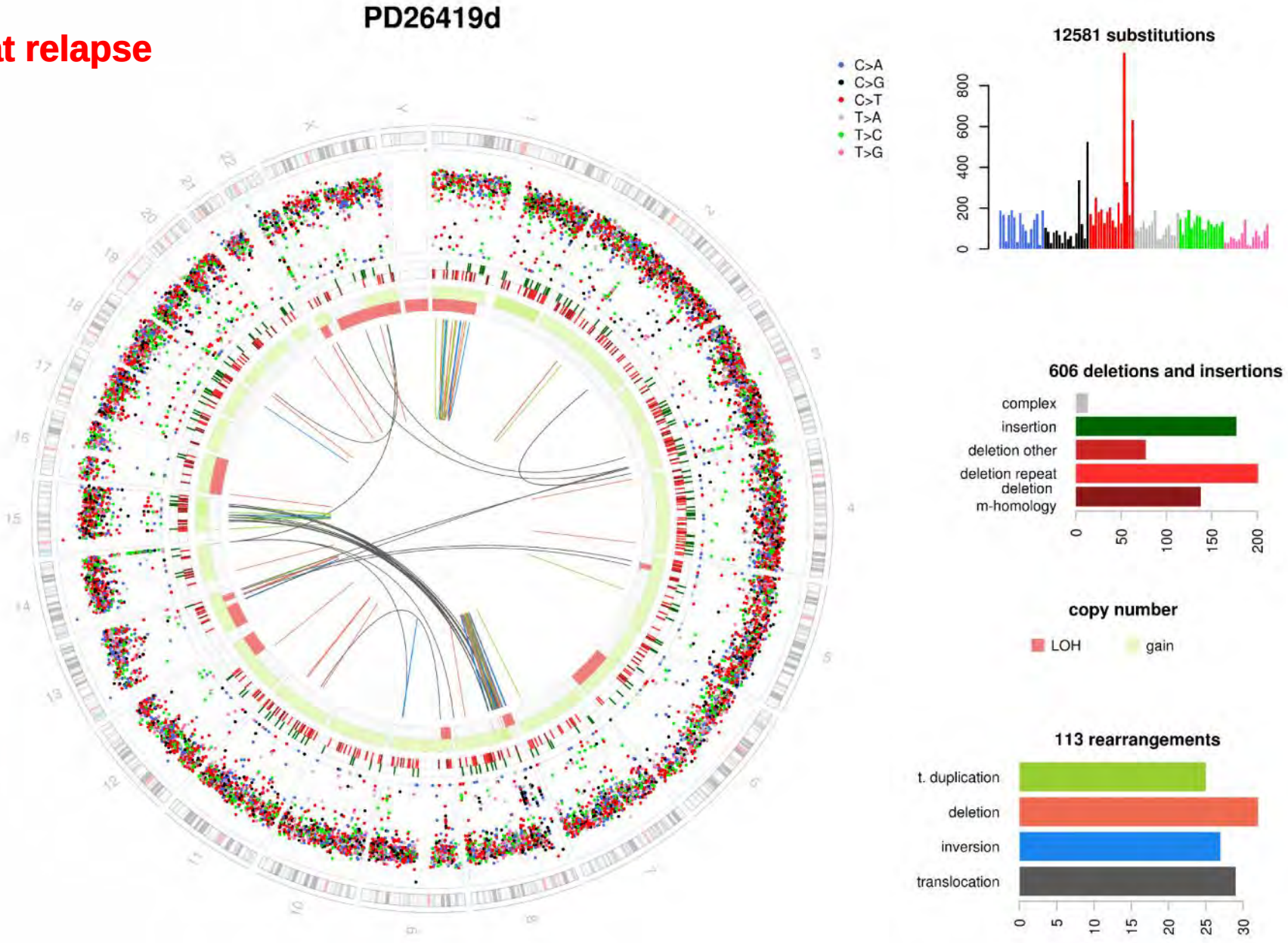
blood

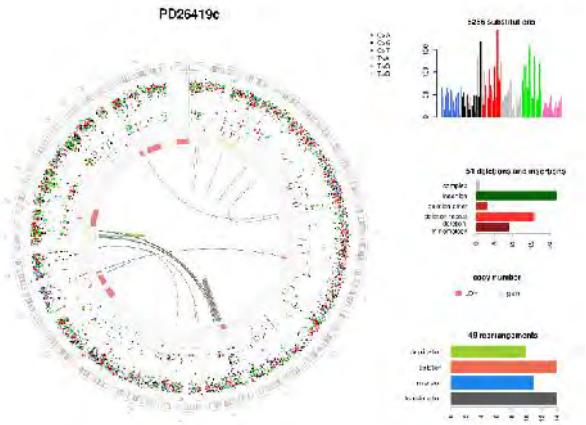
©2011 by American Society of Hematology

WGS at diagnosis

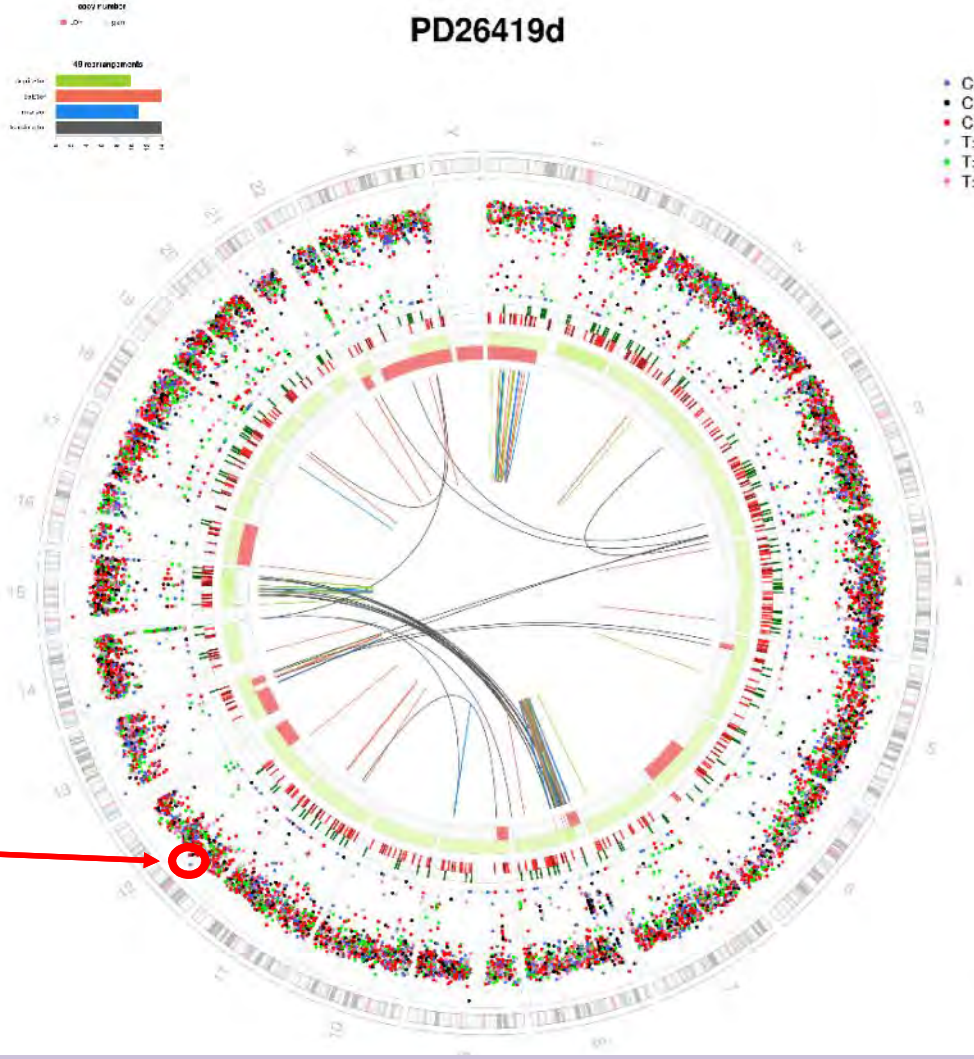


WGS at relapse



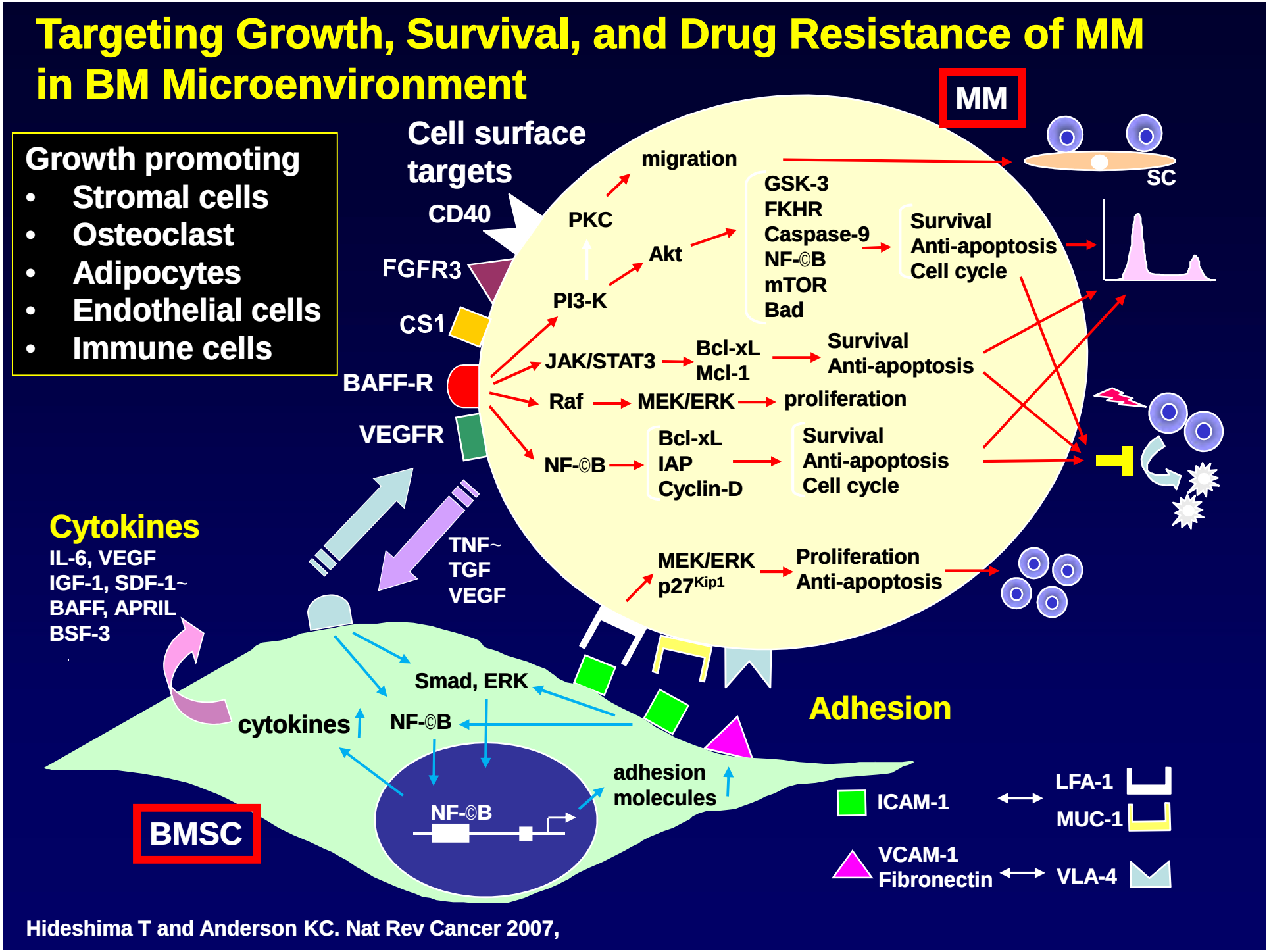


WGS at diagnosis and relapse – Significant increase in complexity



Rise of Immunotherapy !!

Targeting Growth, Survival, and Drug Resistance of MM in BM Microenvironment

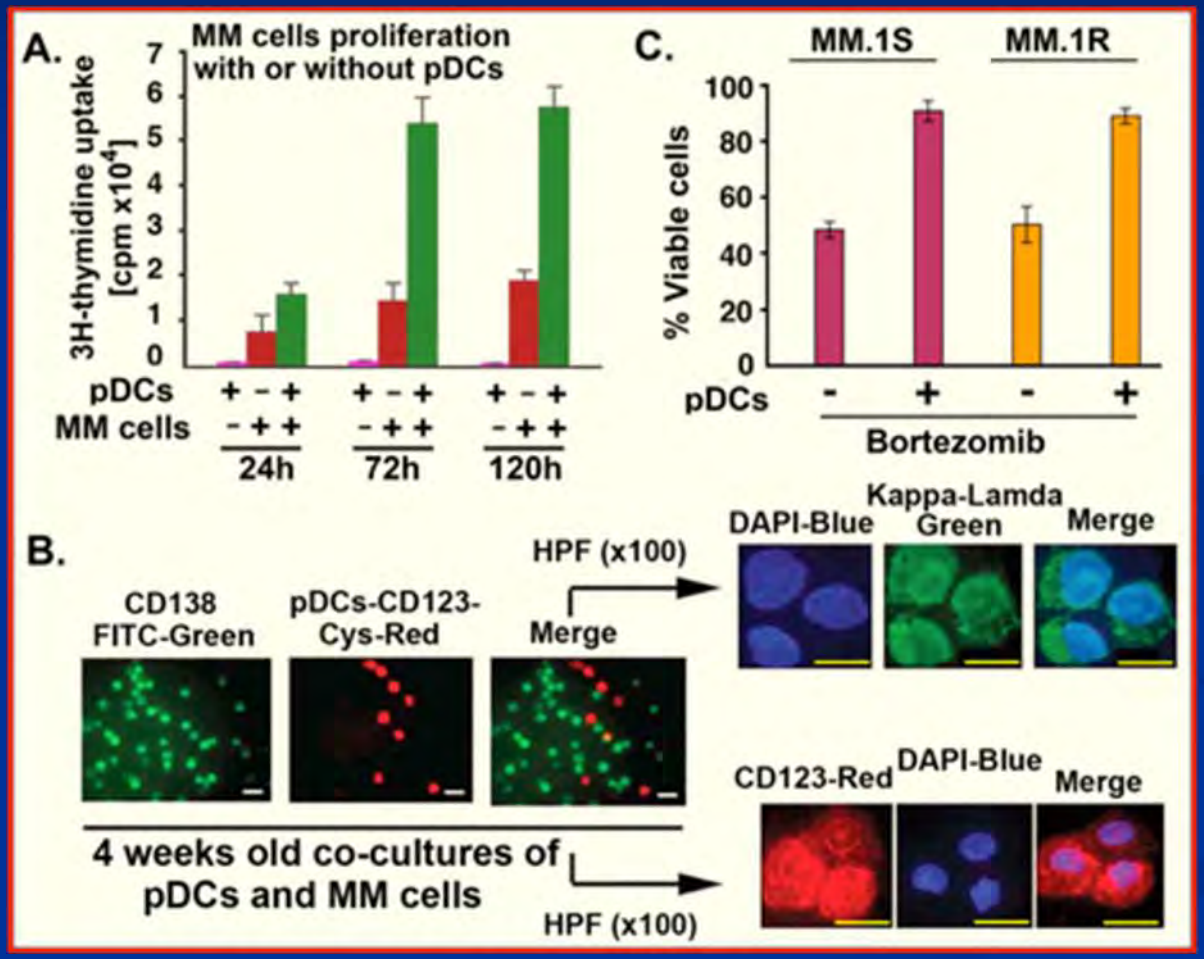


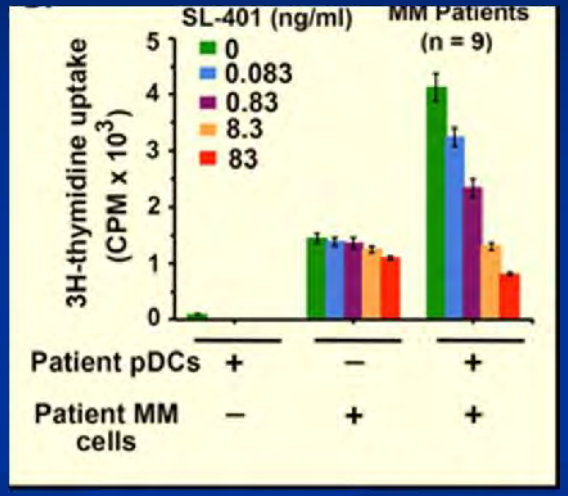
Hideshima T and Anderson KC. Nat Rev Cancer 2007,

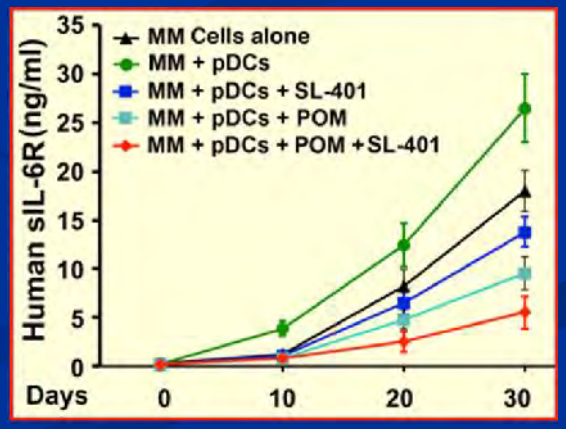
Fundamental immune Consequence in Myeloma

- Augmentation of myeloma promoting immune responses
  - Plasmacytoid Dendritic cells (pDC)
  - Myeloid Derived suppressor cells (MDSC)
  - T Helper 17 and 22 cells (Th17, Th22)
- Suppression of myeloma protecting immune responses
  - B cell, NK and NKT cell, T cell - Treg, Th17, Th9, Tfh Cell dysfunction

Plasmacytoid DCs Promote Growth, Survival, and Drug-Resistance in Myeloma



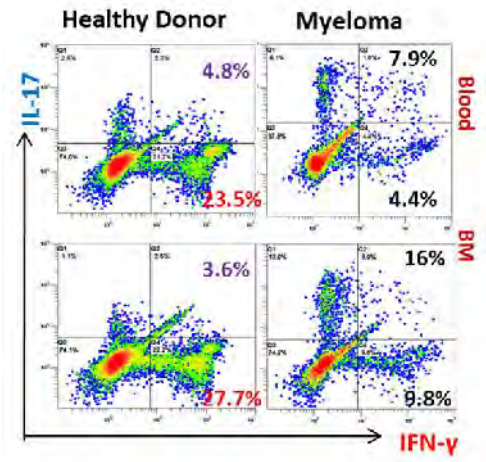


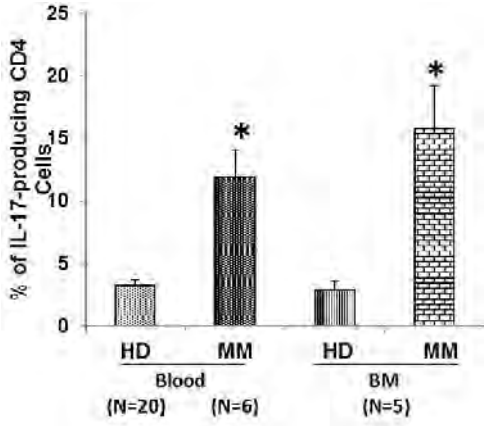


Chauhan et al: Cancer Cell 2009

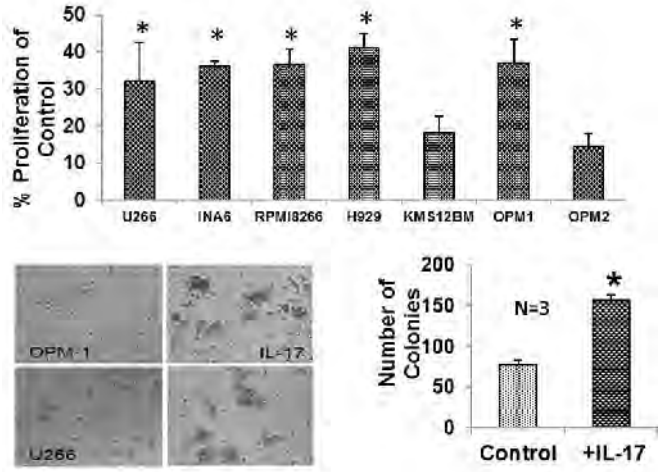
Elevated Th17 supports MM cell growth

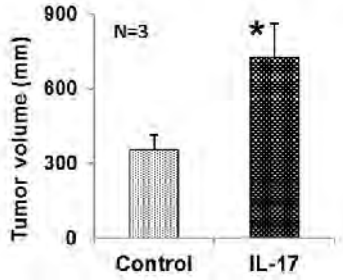
Elevated Th17 cells in Myeloma





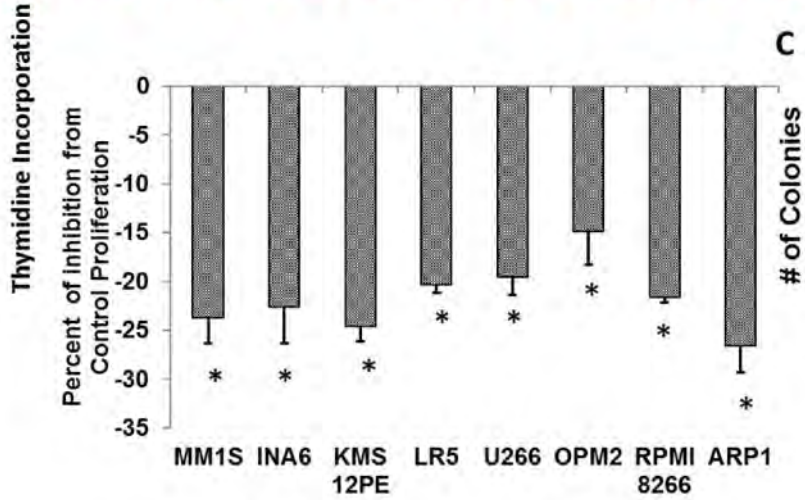
IL-17A increases Myeloma Growth

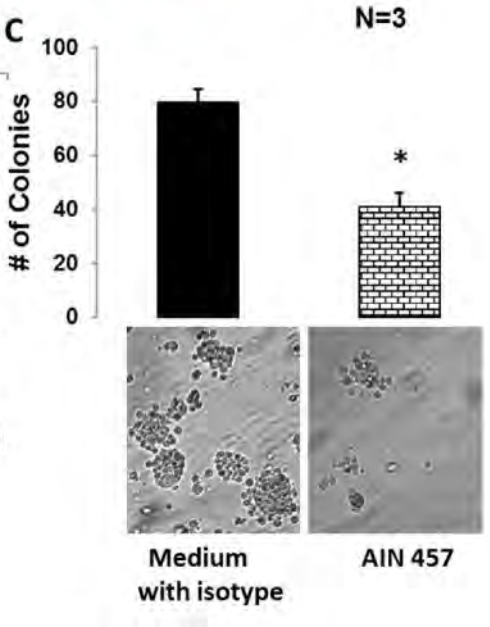


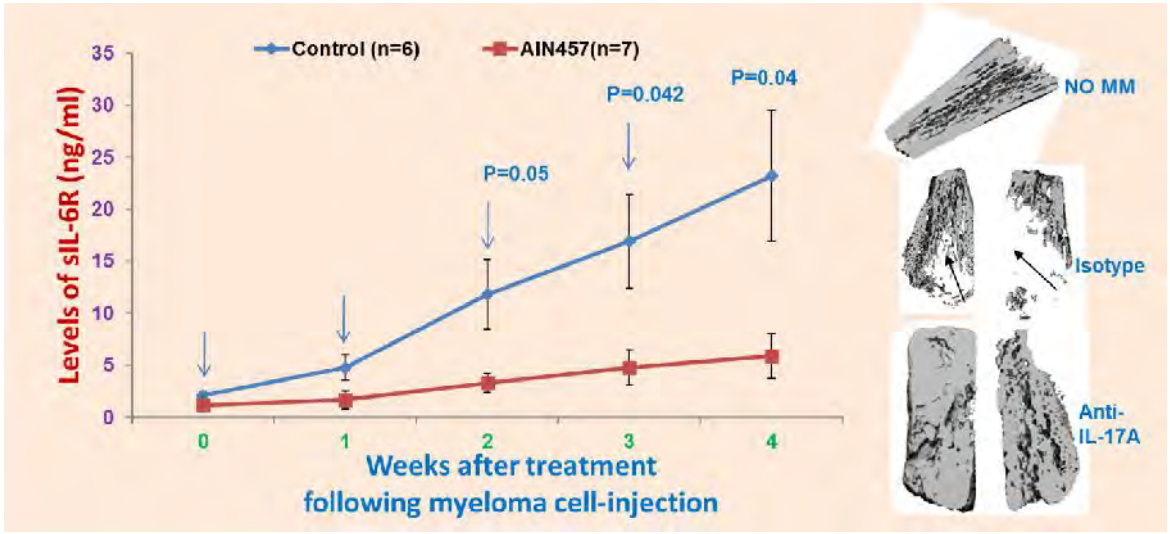


Prabhala RH et al Blood 2011

Reduced Myeloma Growth by Anti-IL-17A mAb Secukinumab in Vitro and in vivo







Prabhala RH et al Leukemia 2016

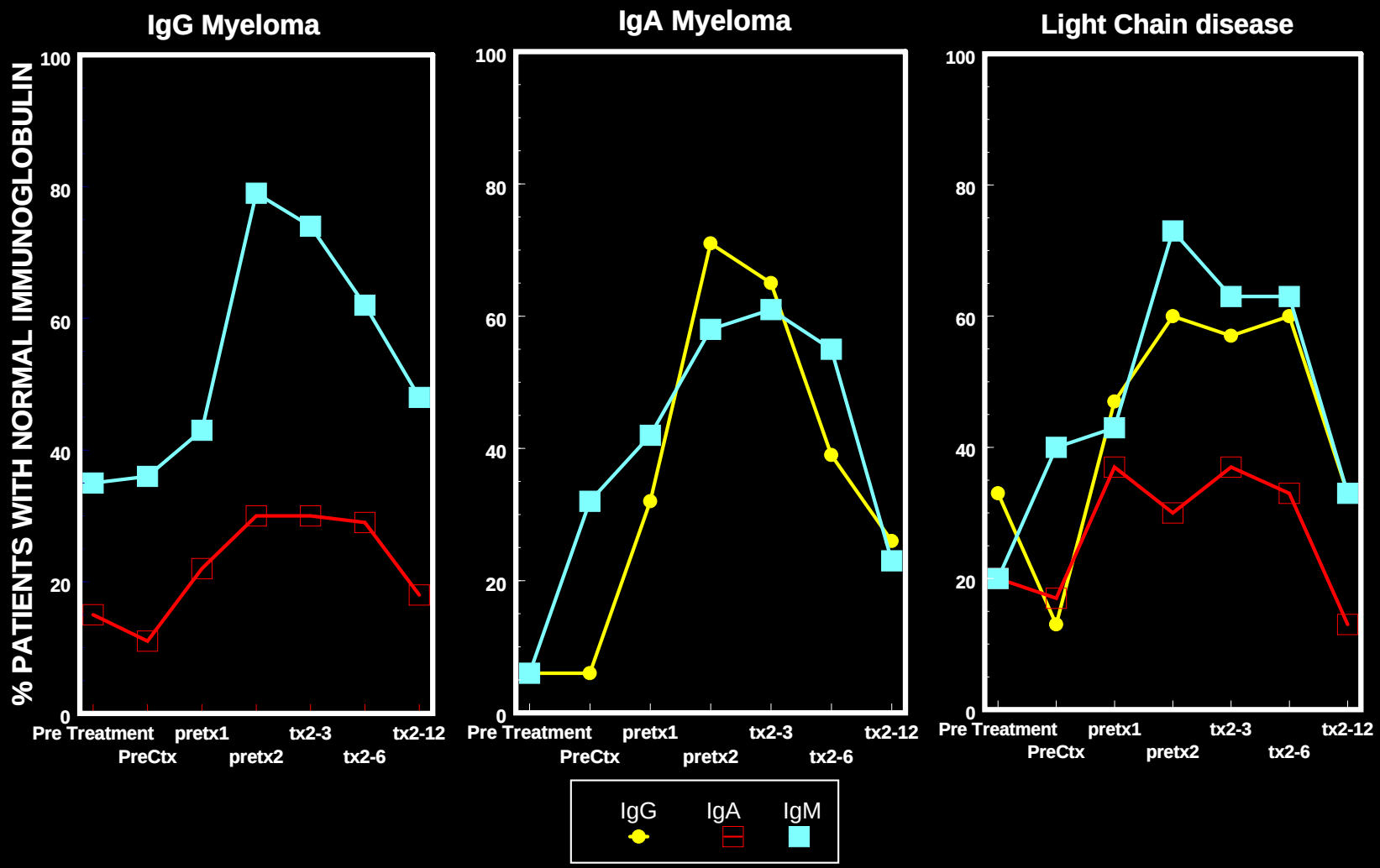
Antibodies and Small molecules Targeting Pro-inflammatory Pathways

Target	Drug	Company
IL-17	AIN457	Novartis
IL-17	LY2439821	Eli Lilly
IL-17R	AMG 827	Amgen
IL-20	Anti-IL-20	NovoNordisk
IL-22	ILV094	Pfizer
JAK3	CP-690,550	Pfizer
IL-23	LY2525623	Eli Lilly
IL-23	CNTO1959	Jansen
IL23p19	SCH 900222	Scheringh/Merck
IL-23+IL6	AZ17	Allozyne

Suppressed Myeloma Protecting Immune Responses

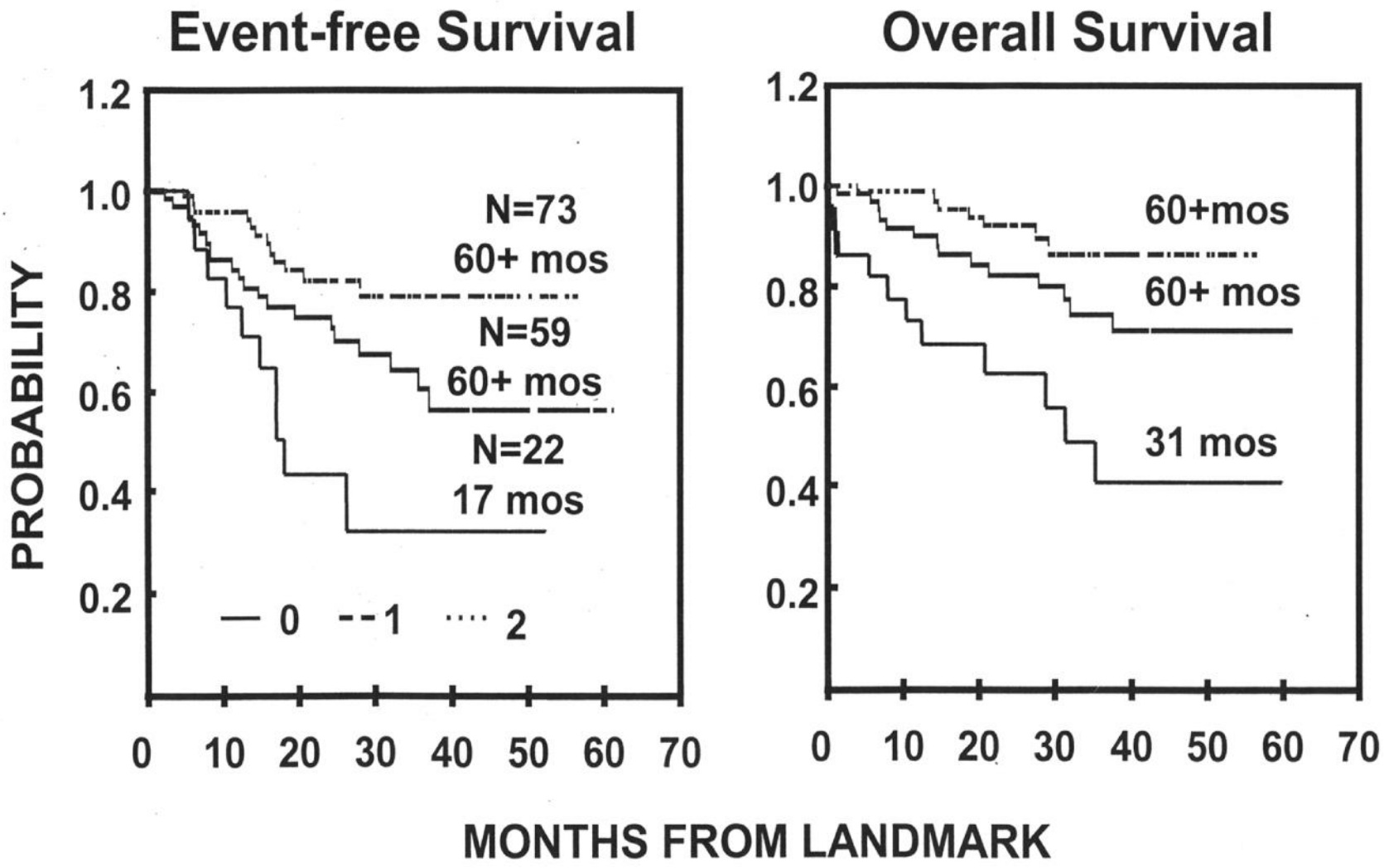
- B cell defect
  - Suppression of uninvolved immunoglobulins
- T cell dysfunction
- NK cell activity – relatively preserved
- NKT cell dysfunction that can recover following in vitro culture

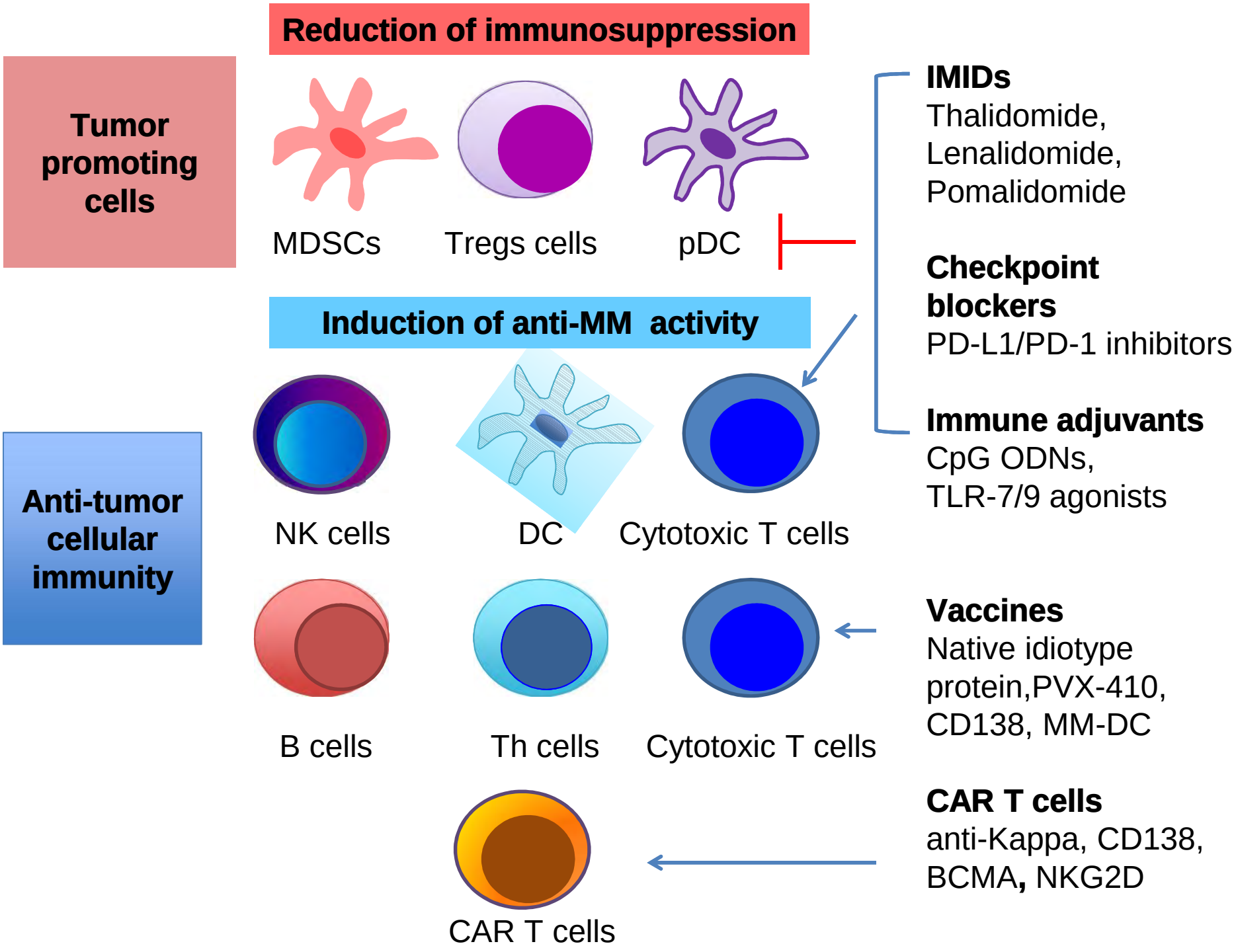
Time course of Ulg recovery



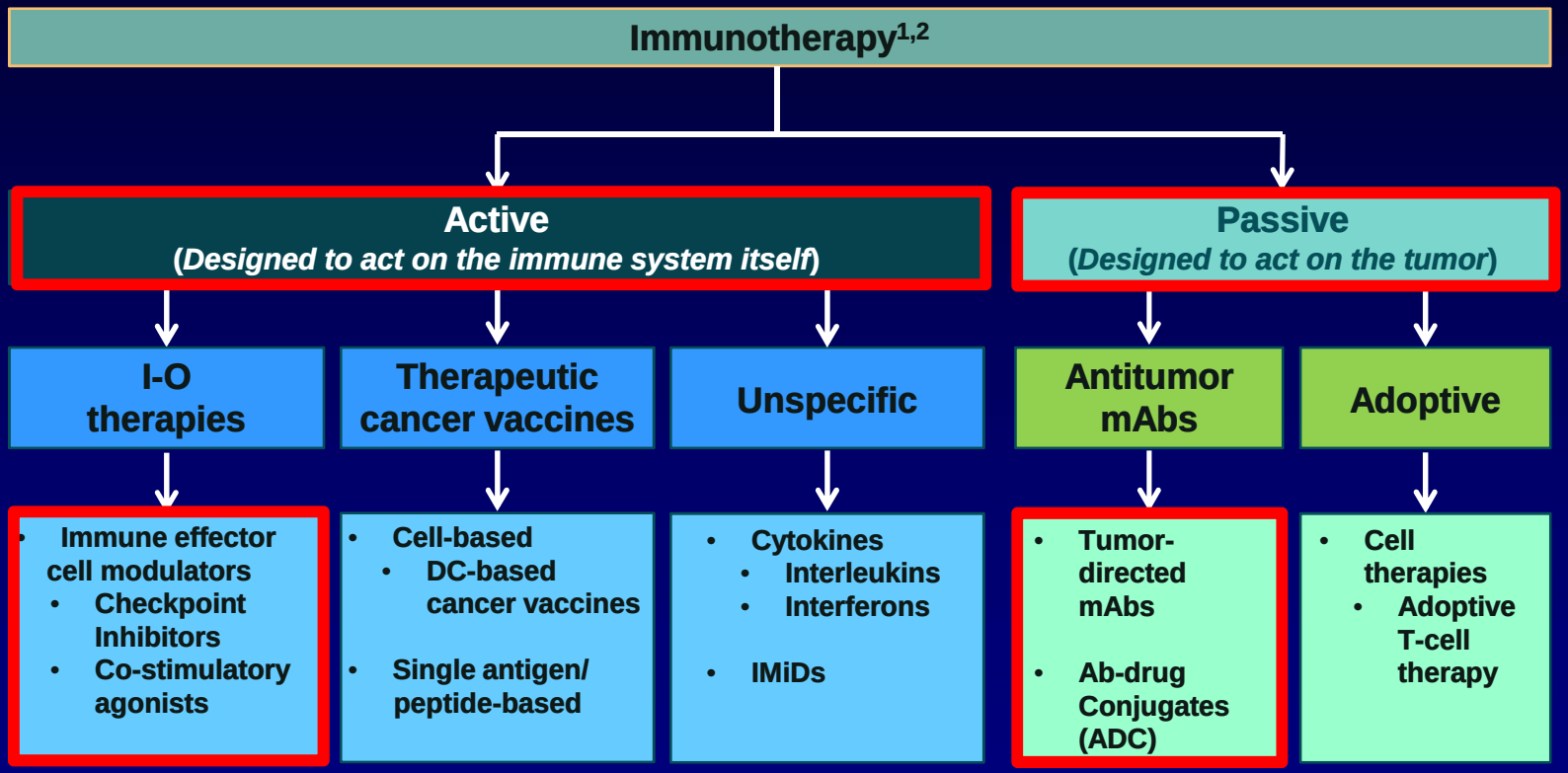
Munshi et al Blood 2000

Normalization of IgM Post-Transplant Predicts for Better Survival




Reduction of immunosuppression
Tumor promoting cells
MDSCs
Tregs cells
pDC
IMIDs
Thalidomide,
Lenalidomide,
Pomalidomide
Checkpoint blockers
PD-L1/PD-1 inhibitors
Induction of anti-MM activity
Anti-tumor cellular immunity
NK cells
DC
Cytotoxic T cells
Immune adjuvants
CpG ODNs,
TLR-7/9 agonists
B cells
Th cells
Cytotoxic T cells
Vaccines
Native idiotype protein,PVX-410,
CD138, MM-DC
CAR T cells
CAR T cells
anti-Kappa, CD138,
BCMA, NKG2D

Immune-therapies under investigation in Myeloma

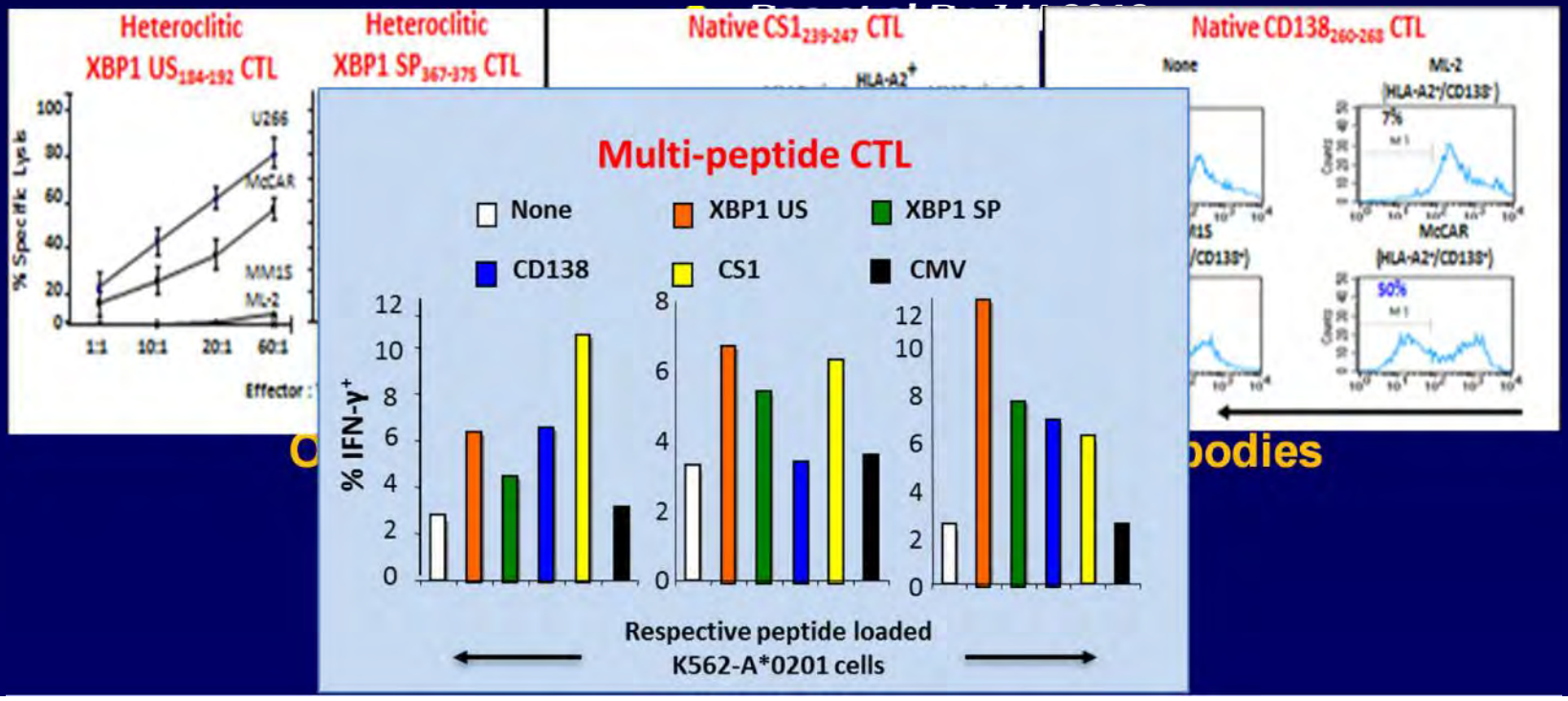


DC, dendritic cell; IMiD, immunomodulatory agent; I-O, immuno-oncology; mAb, monoclonal antibody.

1. Finn OJ. Ann Oncol. 2012;23(suppl 8):viii6-viii9. 2. Mellman I et al. Nature. 2011;480:480-489.

Peptide-based Vaccination

- **Single Antigen Targeting Peptides**
  - *Bae et al Blood 2006*
  - *Bae et al Blood 2007*
  - *Bae et al CCR 2010*
- **Vaccination Using Cocktail of Peptides**



Vaccines Targeting MM Specific Peptides in Smoldering Multiple Myeloma

Goal is to prevent evolution of smoldering to active myeloma

- **Cocktails of immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses**

Clinical trials (LLS TAP Program):

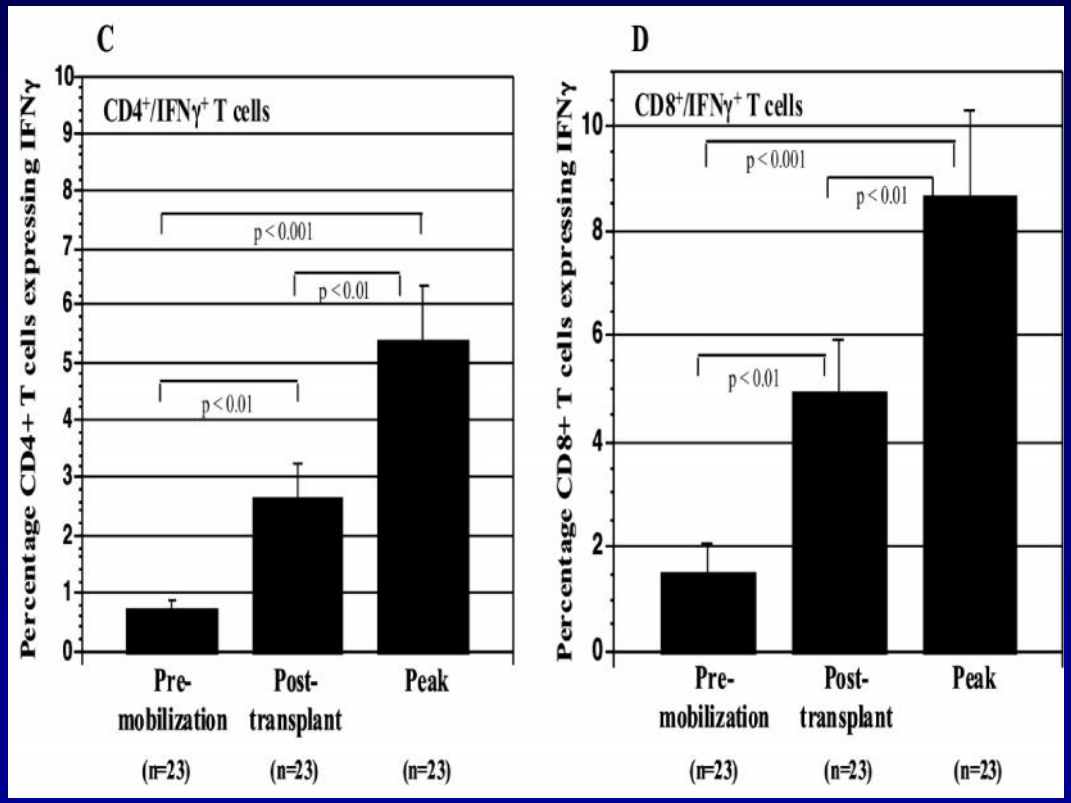
Immune responses to vaccine in all patients including tetramer positive cells and type I cytokines

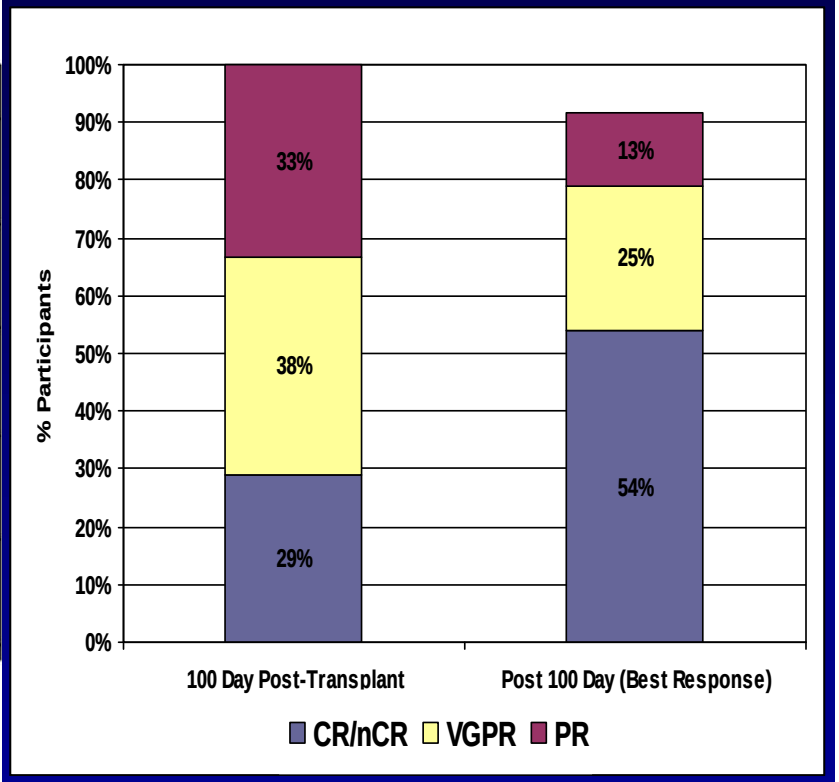
Lenalidomide with vaccine augments these immune response

Lenalidomide and PDL-1, HDAC 6i 241 with vaccine to induce memory Immune response against myeloma

Bae et al, Leukemia 2011; 25:1610-9.
Bae et al, Brit J Hematol 2012; 157: 687-701.
Bae et al, Leukemia 2015
Bae et al, Brit J Hematol 2011; 155: 349-61.
Bae et al, Clin Can Res 2012; 17:4850-60.

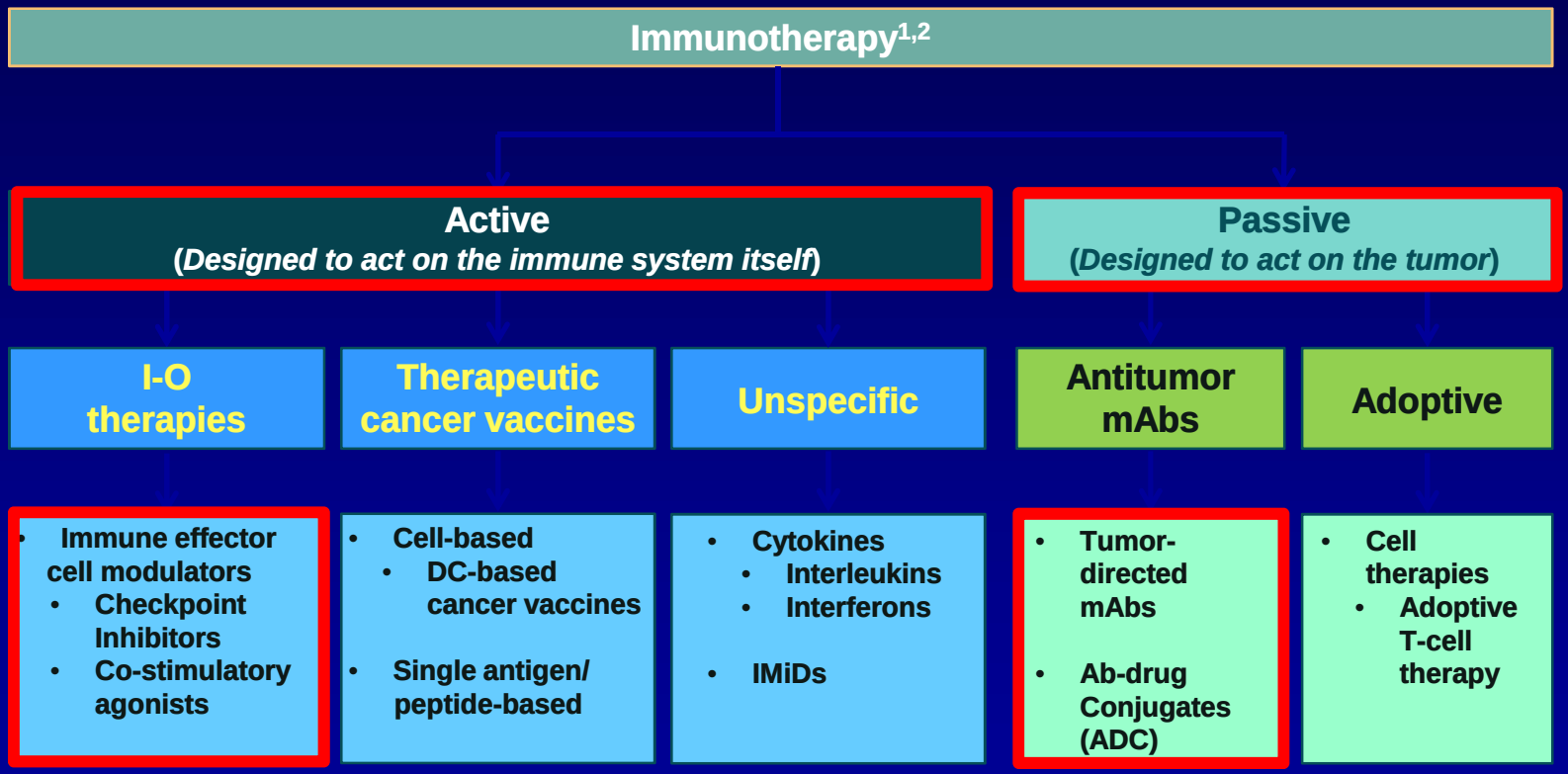
MM/DC Vaccination following Autologous PBSCT for Myeloma





Rosenblatt et al, CCR 2013; 19: 3640-8.

Immune-therapies under investigation in Myeloma



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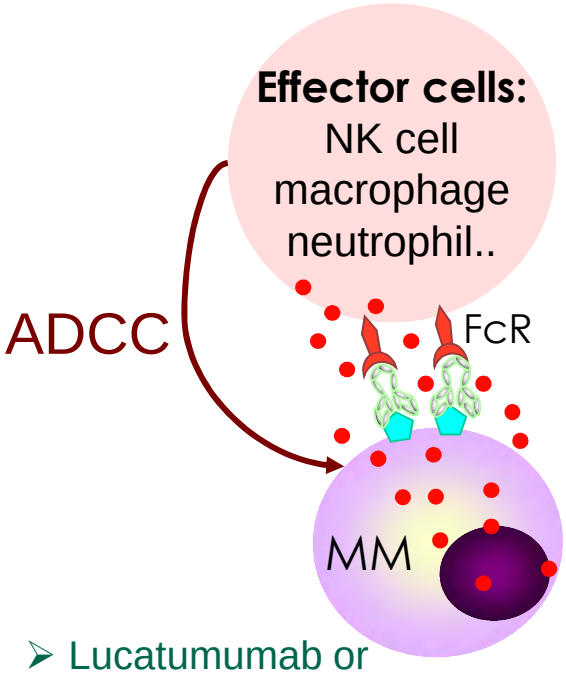
1. Finn OJ. Ann Oncol. 2012;23(suppl 8):viii6-viii9. 2. Mellman I et al. Nature. 2011;480:480-489.

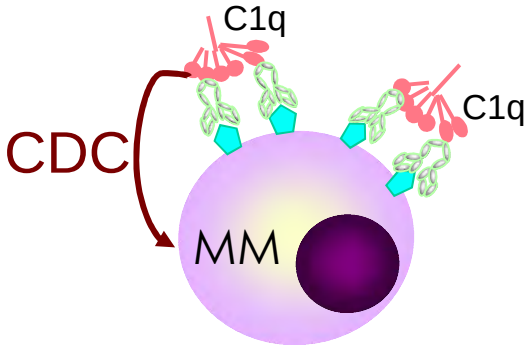
MAb Based Therapeutic Targeting of MM

Antibody-dependent Cellular Cytotoxicity (ADCC)



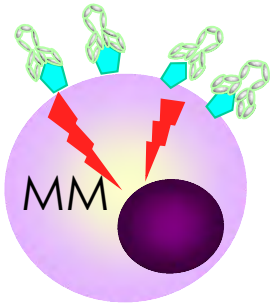
- Lucatumumab or Dacetuzumab (CD40)
- **Elotuzumab (CS1)**
- **Daratumumab (CD38)**
- XmAb®5592 (HM1.24)
- **Isatuximab (CD38)**

Complement-dependent Cytotoxicity (CDC)



- **Daratumumab (CD38)**
- **Isatuximab (CD38)**

Apoptosis/growth arrest via intracellular signaling pathways



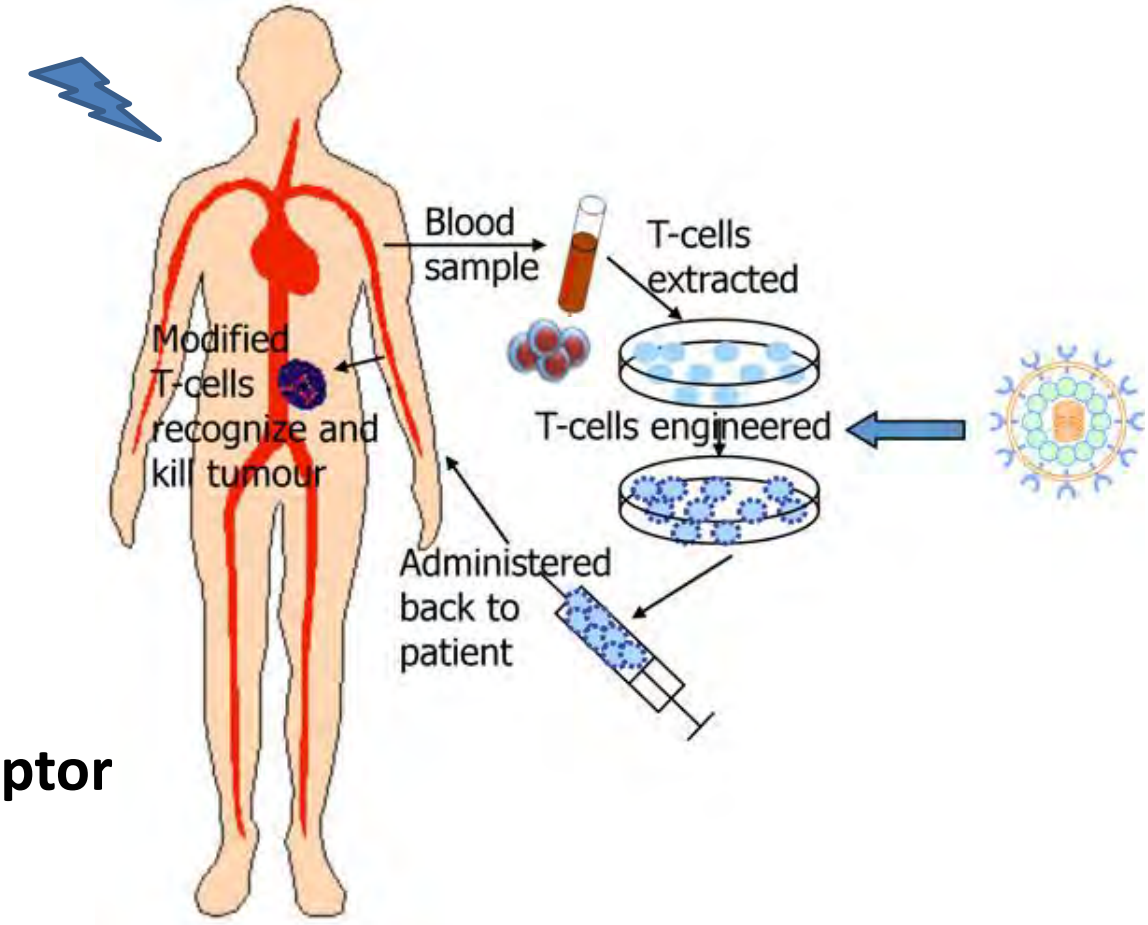
- **huN901-DM1* (CD56)**
- **nBT062-maytansinoid /DM4* (CD138)**
- 1339 (IL-6)
- BHQ880 (DKK)
- RAP-011 (activin A)
- **Daratumumab (CD38)**
- **Isatuximab (CD38)**
- **J6M0-MMAF* (BCMA)**

*** Ab drug conjugate**

Updated from
Tai & Anderson Bone Marrow Research 2011

Explosion in Adoptive Cellular Therapies!

- **Antigen-Directed T cells**
  - **Engineered T-cell Receptors**
  - **Anti-viral or tumor-peptide Cytotoxic T Lymphocytes**
  - **Chimeric Antigen Receptor T cells**



Chimeric Antigen Receptor T cells (CAR T Cells)

- These T cells exploit native antibody or T cell recognition and signaling pathways
- Introduction of unique genes through viral vectors to allow recognition of tumor cells
- Dramatic expansion after infusion, and effective tumor cell killing
- After initial trials proving the efficacy in B cell malignancies, other targets, cancers and molecular constructs are being explored

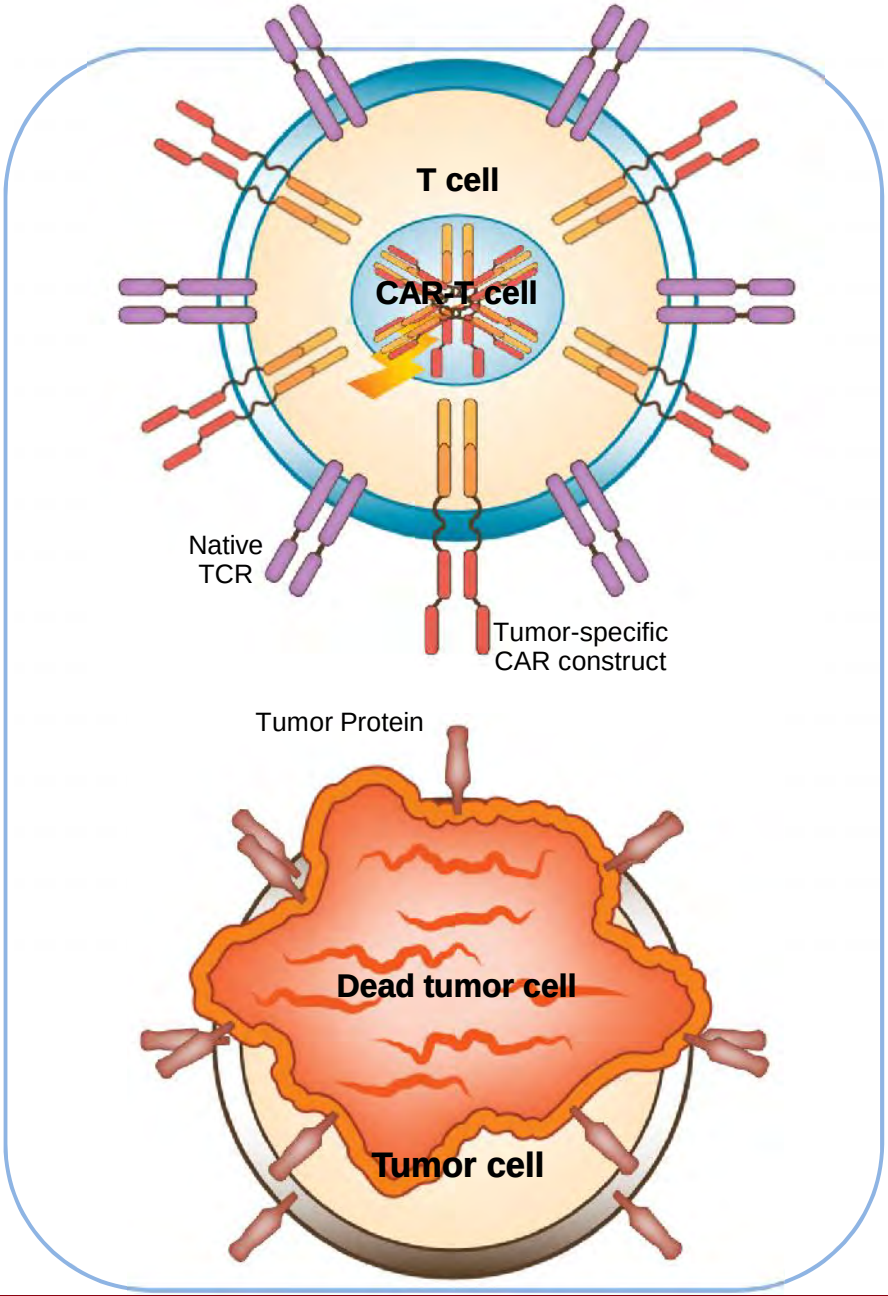
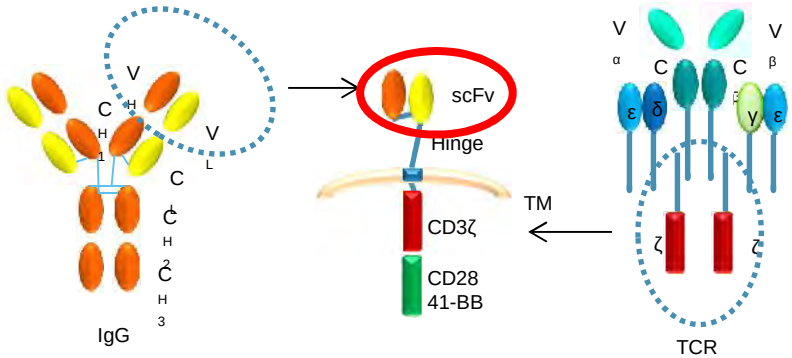


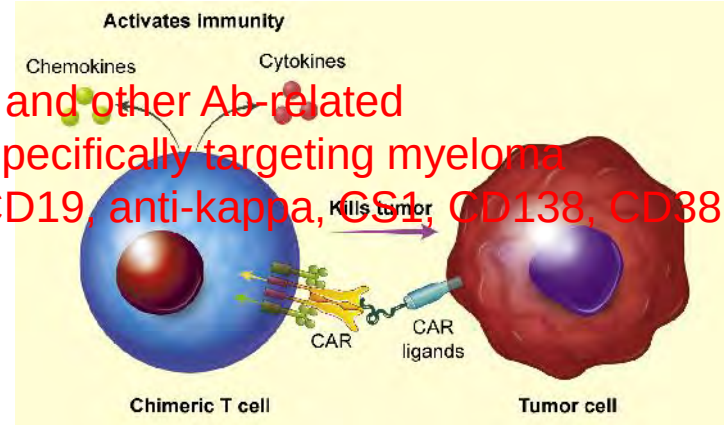
Image courtesy of Stephan Grupp, UPenn

“Classic” CAR T-cell construct



Classic CAR

- scFv and other Ab-related
  - Specifically targeting myeloma
  - CD19, anti-kappa, CS1, CD138, CD38,BCMA



Target Antigens for Multiple Myeloma CAR-T Cell Therapy

Antigen	Expression in nonmalignant cells	Expression in MM	Clinical trial of CAR-Ts in myeloma
CD44v6	Activated T cells, activated monocytes, keratinocytes	Reported to be expressed by 43% of advanced MM cases	**No**
CD70	Activated lymphoid cells	Only a portion of the myeloma cells express CD70 in most cases	**No**
CD56	NK cells, T cells, neuronal cells	Strongly expressed in 70% of patients with myeloma	**No**
CD38	Precursor B cells, **plasma cells,** T cells, NK cells, myeloid precursors, prostate cells, nervous system, osteoclasts, muscle cells	Strong, uniform expression on myeloma cells	**No**
CD138	**Plasma cells,** salivary glands, liver, skin	Expressed on MM cells	**Yes**
CD19	B cells	Minimal expression on MM cell surface. $CD19^+$ cells may represent cancer stem cell in MM	**Yes**
Immunoglobulin κ light chain	Mature B cells	Potential target on B cells that represent MM stem cells and that express surface immunoglobulins	**Yes**
SLAMF7	**Plasma cells,** NK cells, $CD8^+$ cells, activated monocytes and B cells, dendritic cells	Strongly expressed by MM cells	**No**
BCMA	**Plasma cells,** small subset of B cells	Expressed on MM cells	**Yes**

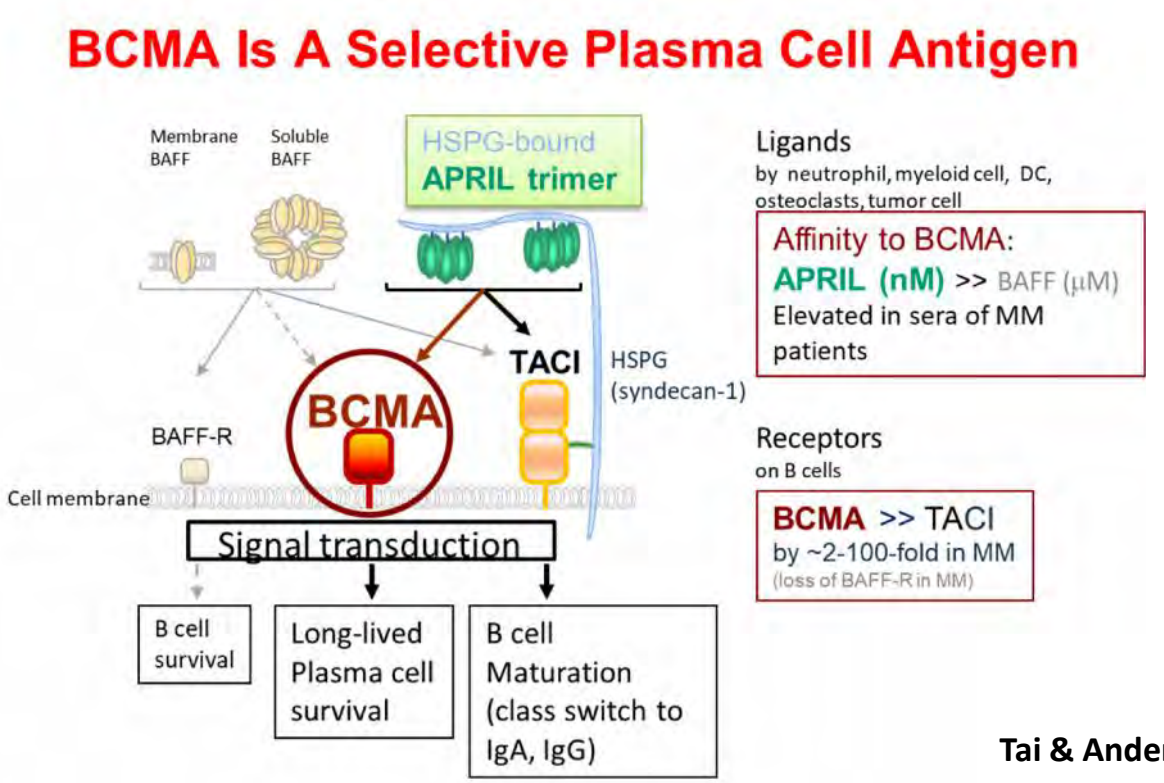
Mikkilineni et al Blood 2017

Clinical trials of CAR-Ts for MM with published results

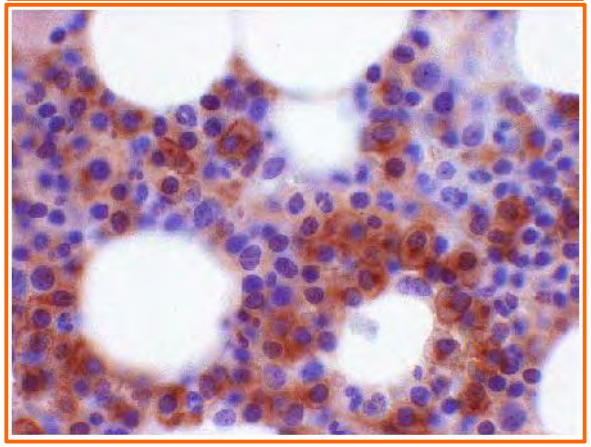
Target	Institution	CAR construct	Conditioning chemotherapy	Response
CD138	Chinese People's Liberation Army Hospital	Lentivirus; CD28 murine scFv	**Varied chemotherapy shortly before cell infusion**	**5 patients treated; best responses: 4 SD, 1 PD**
CD19	University of Pennsylvania	Lentivirus 4-1BB murine scFv	**Melphalan 140-200 mg/m^2 prior to ASCT**	**10 patients treated; median PFS 185 d (range, 42-479 d)**
Immunoglobulin κ light chain	Baylor College of Medicine	γ- retrovirus; CD28 murine scFv	**Salvage chemotherapy or cyclophosphamide 4 days**	**7 patients treated: 4 SD, 3 no response**
BCMA	National Cancer Institute	γ-retrovirus; CD28 murine scFv	**Fludarabine/Cyclophosphamide**	**12 patients treated ORR – 4 (1 sCR); 8 SD**
BCMA	Multicenter; Bluebird Bio	Lentivirus; 4-1BB murine scFv	**Fludarabine/Cyclophosphamide**	**18 patients treated ORR – 17 (94%); 10 CR (56%) and 9/10 MRD-. negative**
BCMA	University of Pennsylvania	Lentivirus; 4-1BB human scFv	**None**	**6 patients treated; 1 sCR; 1 VGPR; 4 with minimal or no response**
BCMA	The 2nd Affiliated Hospital of Xi'an Jiaotong University	Not published	**Not published**	**19 patients treated ORR 100%; 18 patients obtaining sCR or VGPR**

BCMA – A Promising Target in Multiple Myeloma

- **BCMA is member of the TNF receptor superfamily**
  - Expressed nearly universally on MM cells
  - Expression largely restricted to plasma cells and some mature B cells



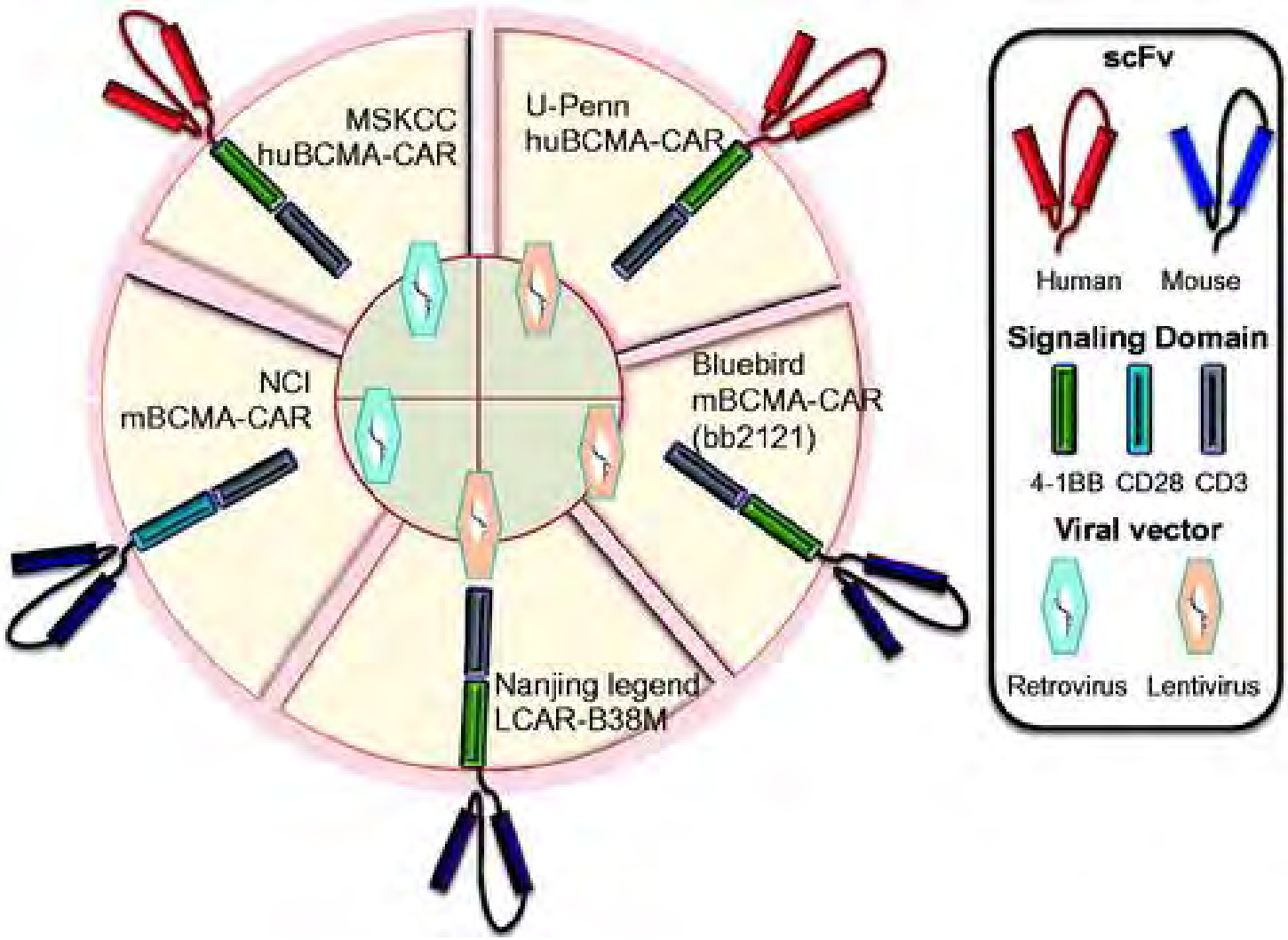
Multiple myeloma cells expressing BCMA



(brown color = BCMA protein)

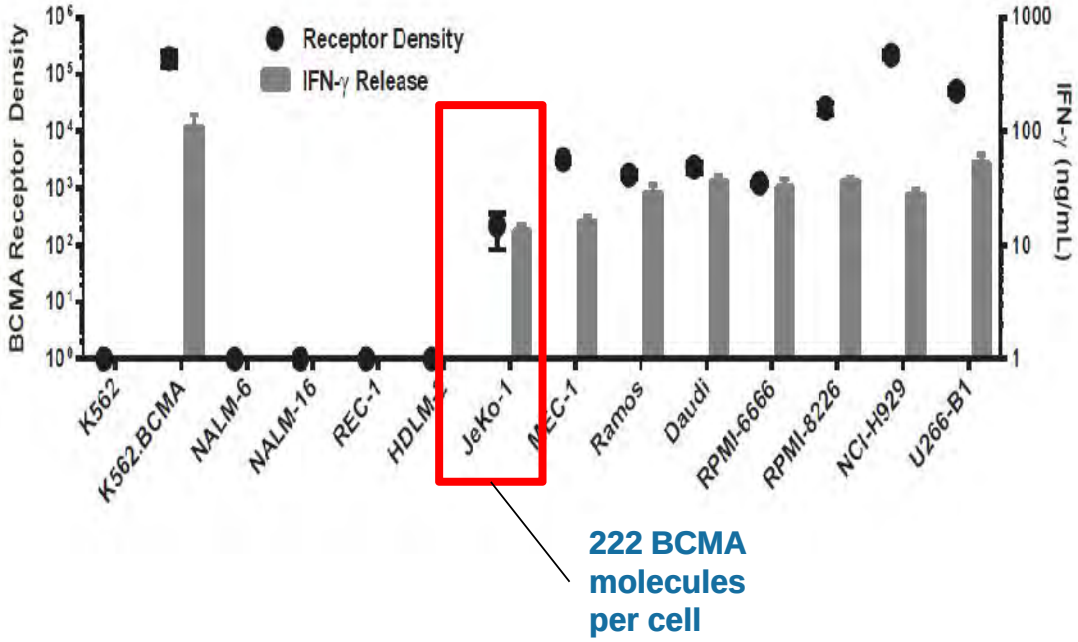
Tai & Anderson Immunotherapy 2015; 7: 1187-99.

BCMA CAR T Studies



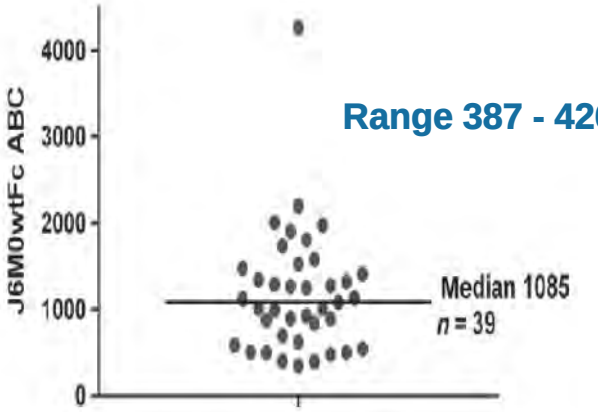
Low level BCMA expression sufficient to activate bb2121

BCMA Receptor Density and bb2121 Activity



222 BCMA molecules per cell

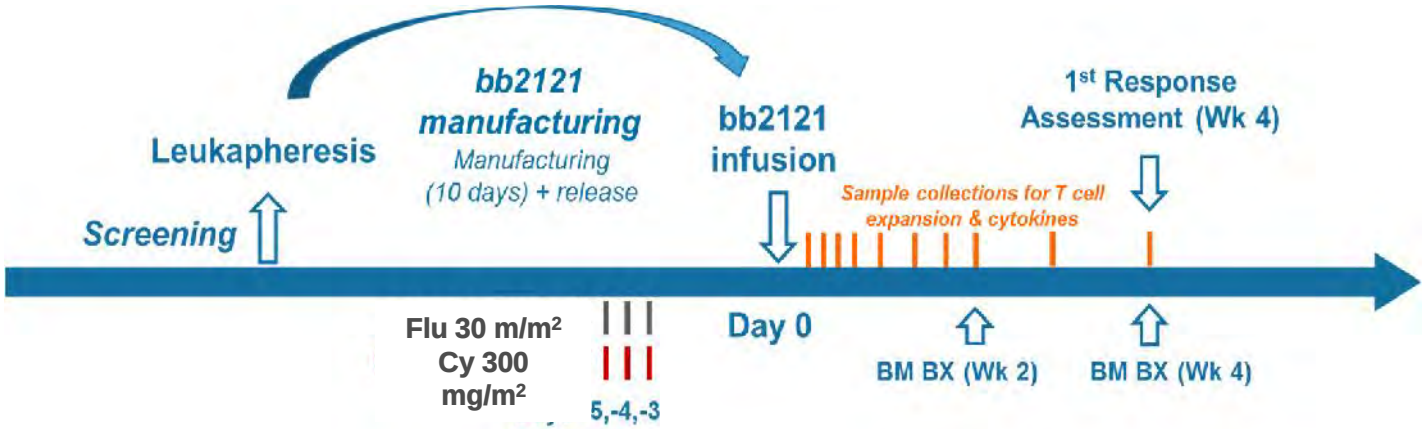
BCMA Receptor Density on Human Myeloma Cells



Range 387 - 4268

All human MM expected to express levels of BCMA sufficient to trigger bb2121 killing activity

CRB-401 PHASE 1 STUDY DESIGN



Dose Escalation (N=21)

≥50% BCMA expression

50 × 10^6 → 150 × 10^6 → 450 × 10^6 → 800 × 10^6

Dose Expansion (N=22)

<50% BCMA expression (n=10)

≥50% BCMA expression (n=12)

Dose range: 150–450 × 10^6 CAR+ cells

TREATMENT HISTORY

Parameter	Escalation (N=21)	Expansion (N=22)
Median (min, max) prior regimens	7 (3, 14)	8 (3, 23)
Prior autologous SCT, n (%)	21 (100)	19 (86)
0	0	3 (14)
1	15 (71)	14 (64)
>1	6 (29)	5 (23)

	Escalation (N=21)		Expansion (N=22)	
Parameter	**Exposed**	**Refractory**	**Exposed**	**Refractory**
Prior therapies, n (%)				
Bortezomib	21 (100)	14 (67)	22 (100)	16 (73)
Carfilzomib	19 (91)	12 (57)	21 (96)	14 (64)
Lenalidomide	21 (100)	19 (91)	22 (100)	18 (82)
Pomalidomide	19 (91)	15 (71)	22 (100)	21 (96)
Daratumumab	15 (71)	10 (48)	22 (100)	19 (86)
Cumulative exposure, n (%)				
Bort/Len	21 (100)	14 (67)	22 (100)	14 (64)
Bort/Len/Car/Pom/Dara	15 (71)	6 (29)	21 (96)	7 (32)

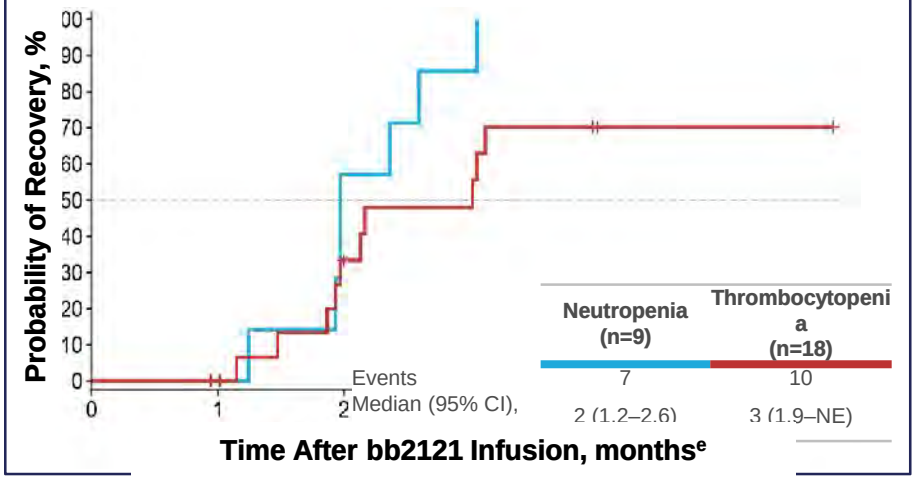
Data cutoff: March 29, 2018. SCT, stem cell transplant.

ADVERSE EVENTS OF SPECIAL INTEREST

CAR T Treatment-Emergent Adverse Events All Infused Patients (N=43)

TEAE, n (%)	Overall	Grade ≥3
Cytokine release syndrome[a]	27 (63)	2 (5)
Neurotoxicity[b]	14 (33)	1 (2)
Neutropenia	35 (81)	34 (79)
Thrombocytopenia	26 (61)	22 (51)
Anemia	24 (56)	19 (44)
Infection[c]		
Overall	26 (61)	9 (21)
First Month	10 (23)	2 (5)

Time to Recovery of Grade 3/4 Cytopenias in Patients Without Recovery by Month 1[d]



- No grade 4 CRS events
- No fatal CRS or neurotoxicity events

- 31/40 (78%) recovered ANC to ≥1000/µL by Day 32
- 22/40 (55%) recovered PLT to ≥50,000/µL by Day 32

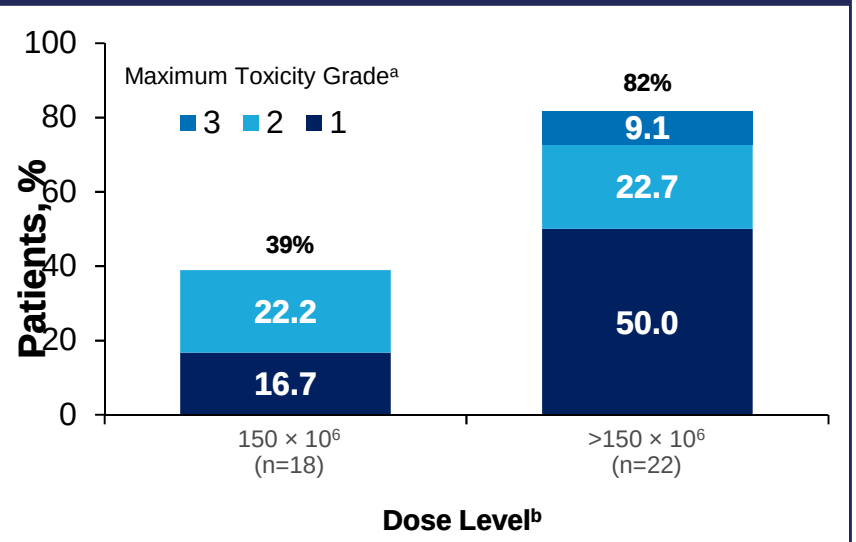
Data cutoff: March 29, 2018. NE, not estimable. [a]CRS uniformly graded per Lee DW, et al. *Blood.* 2014;124(2):188-195. [b]Events occurring in first 28 d and including dizziness, bradyphrenia, somnolence, confusional state, nystagnmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination. [c]Includes the SOC Infections and Infestations. Events observed in >10% include upper respiratory tract infection and pneumonia. [d]Includes patients treated with active doses (150–800 × 10^6 CAR+ T cells; N=40). Median and 95% CI from Kaplan-Meier estimate. [e]Time from first bb2121 infusion to the first grade ≤2 event after day 32.

CYTOKINE RELEASE SYNDROME

Cytokine Release Syndrome Parameters

Parameter	Dosed Patients (N=43)
Patients with a CRS event, n (%)	27 (63)
Maximum CRS grade[a]	
None	16 (37)
1	16 (37)
2	9 (21)
3	2 (5)
4	0
Median (min, max) time to onset, d	2 (1, 25)
Median (min, max) duration, d	6 (1, 32)
Tocilizumab use, n (%)	9 (21)
Corticosteroid use, n (%)	4 (9)

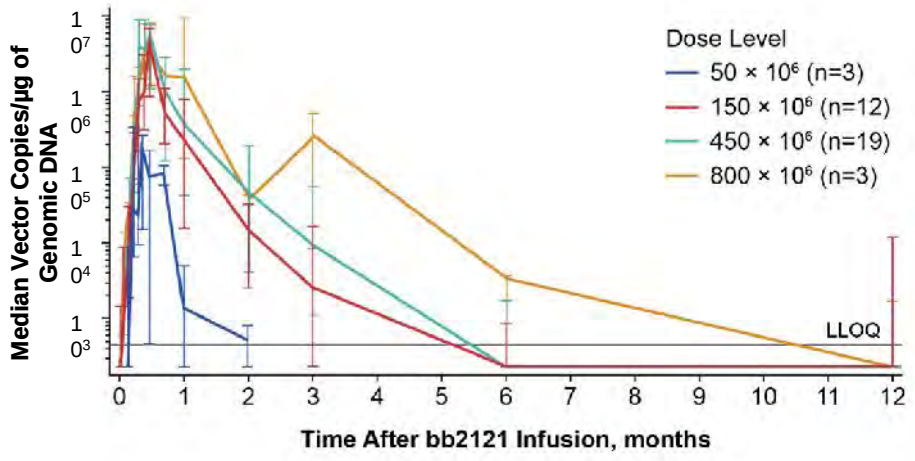
Cytokine Release Syndrome By Dose Level



Data cutoff: March 29, 2018. [a]CRS uniformly graded according to Lee DW, et al. *Blood.* 2014;124(2):188-195. [b]3 patients were treated at the 50 x 10^6 dose level for a total of 43 patients.

ROBUST bb2121 CAR+ T CELL EXPANSION WITH LONG-TERM PERSISTENCE

Median (Q1, Q3) Vector Copies in CD3-Enriched Peripheral Blood by Dose Cohorts

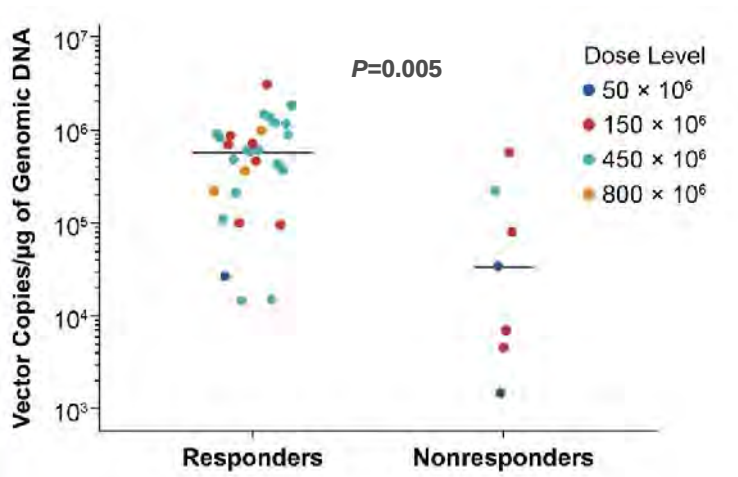


Patients with a post-baseline vector copy value were included. One patient was dosed at 205 × 10^6 CAR+ T cells instead of the planned 450 × 10^6 and was included in the 450 × 10^6 dose group.

	Month 1	Month 3	Month 6	Month 12
At risk, n	32	26	16	10
With detectable vector, n (%)	31 (97)	22 (85)	7 (44)	2 (20)

Data cutoff: March 29, 2018. C_{max}, maximum serum concentration; LLOQ, lower limit of quantitation.

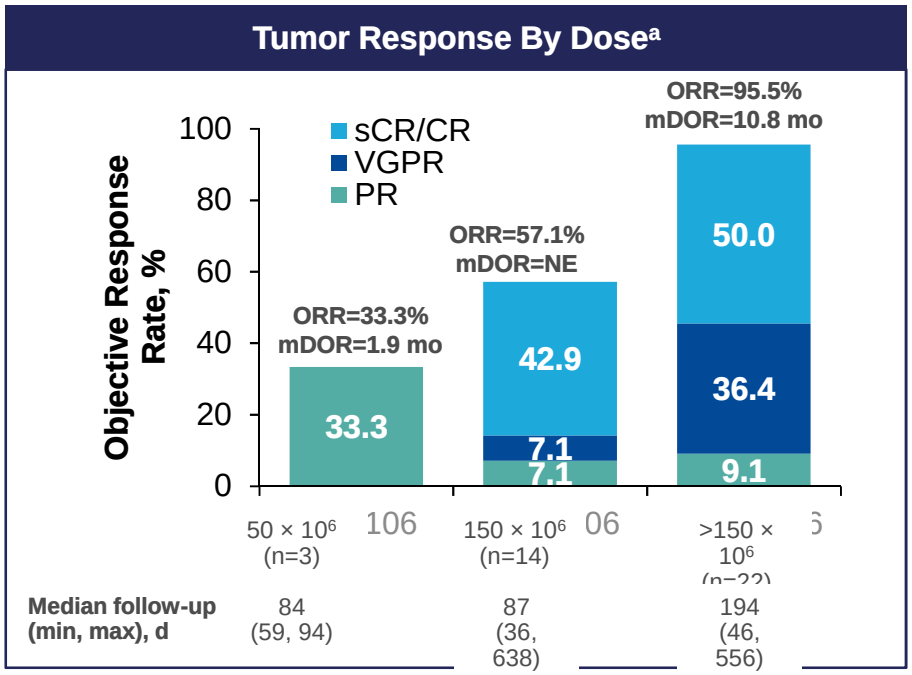
Peak bb2121 Vector Copies in Responders vs Nonresponders

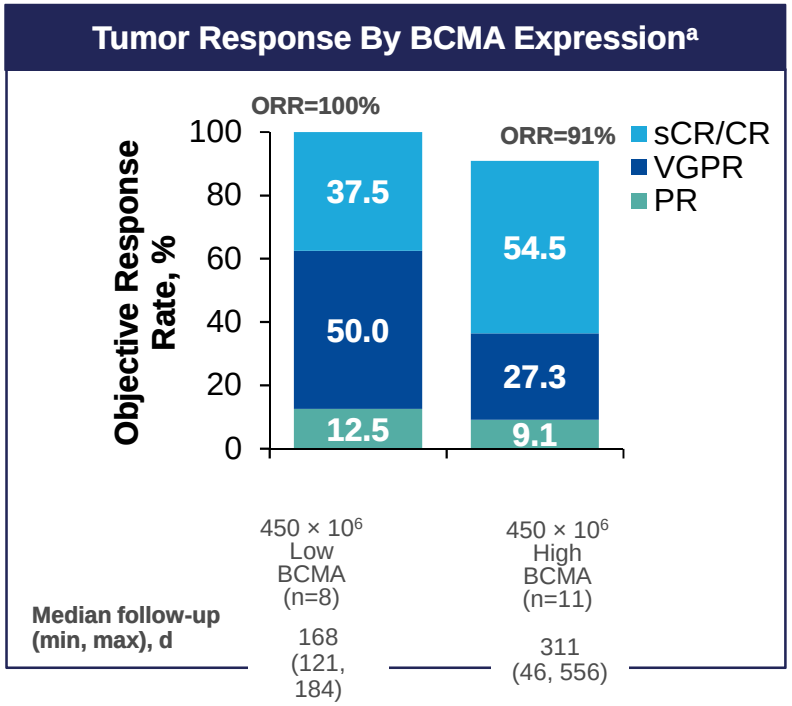


Patients with ≥2 months of response data and 1 month of vector copy data (N=36). *P* value based on a 2-sided Wilcoxon rank sum test.

- Comparable C_{max} in active dose cohorts (≥150 × 10^6 CAR+ T cells)
- Durable bb2121 persistence (≥6 months) in 44%
- Higher peak expansion in patients with response

TUMOR RESPONSE: DOSE-RELATED; INDEPENDENT OF TUMOR BCMA EXPRESSION





Data cutoff: March 29, 2018. CR, complete response; mDOR, median duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response. [a]Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.

TUMOR RESPONSE: DEEP MRD-NEGATIVE RESPONSES OBSERVED

Response	50×10^6	150×10^6	450×10^6	800×10^6	Total
MRD-evaluable responders	0	4	11	1	16
MRD-neg[a]	0	4 (100)	11 (100)	1 (100)	16 (100)

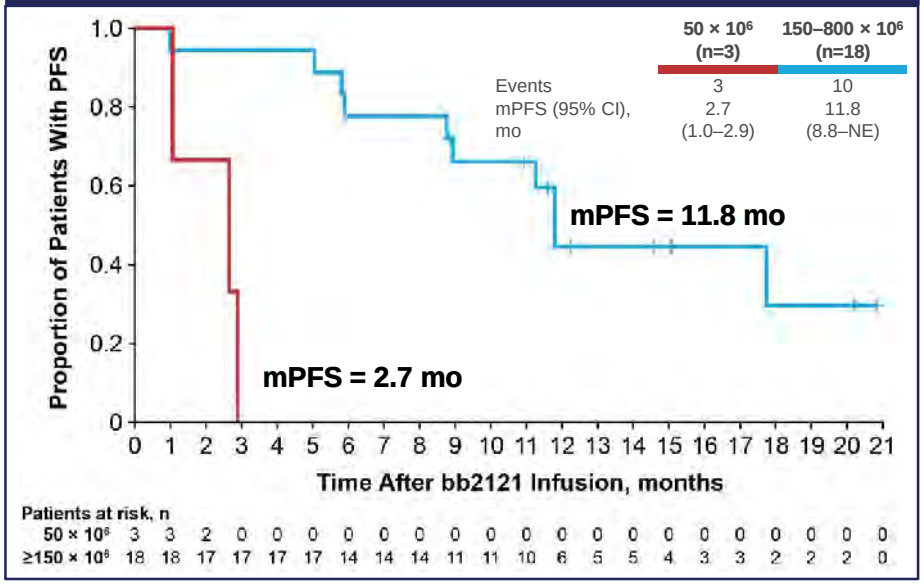
Data cutoff: March 29, 2018. [a]Of 16 MRD-negative responses: 4 at 10^{-6}, 11 at 10^{-5}, 1 at 10^{-4} sensitivity by Adaptive next-generation sequencing assay.

- All responding patients evaluated for MRD were MRD negative at 1 or more time points
- 2 nonresponders evaluated for MRD were MRD positive at month 1

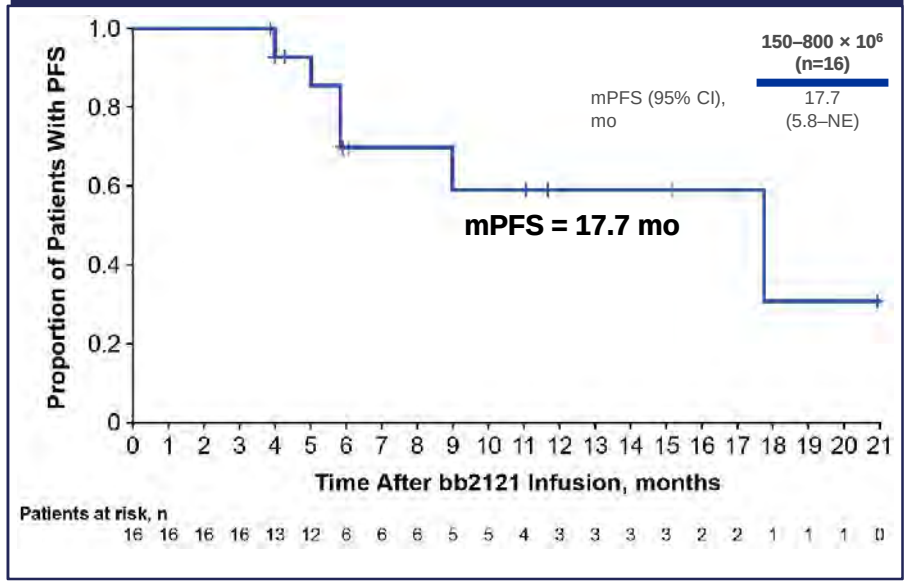
PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels[a]



PFS in MRD-Negative Patients[a]



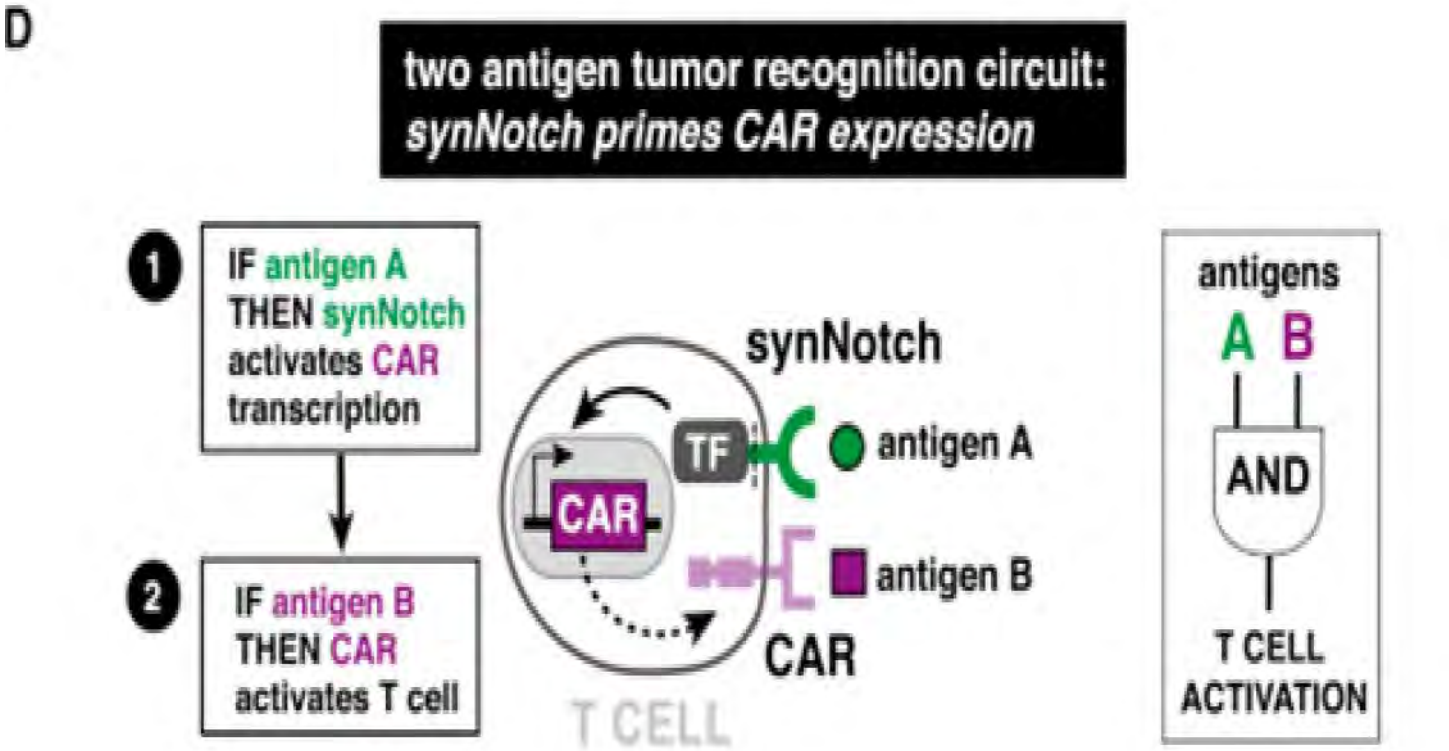
Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. [a]PFS in dose escalation cohort.

LCAR-B38M - NANJING LEGEND STUDY

- **A LCAR-B38M is based on a bispecific antibody platform with potent target selectivity**
- **Engineered to optimize the CAR target–binding mechanism and subsequent CAR signal transduction**
- **Pilot I/II study in 35 patients who received at least 3 prior lines of therapy, 19 with > 4 months f/p.**
- **High response ratre ≥ 100%**
  - sCR - 74%
- **Well tolerated – CRS in 83% of 35 patients.**
  - Grade 1 in 17 patients,
  - Grade 2 in 10 patients
  - Grade 3 in 2 patients with no grade 4 events.
  - Tocilizumab - 40% of patients

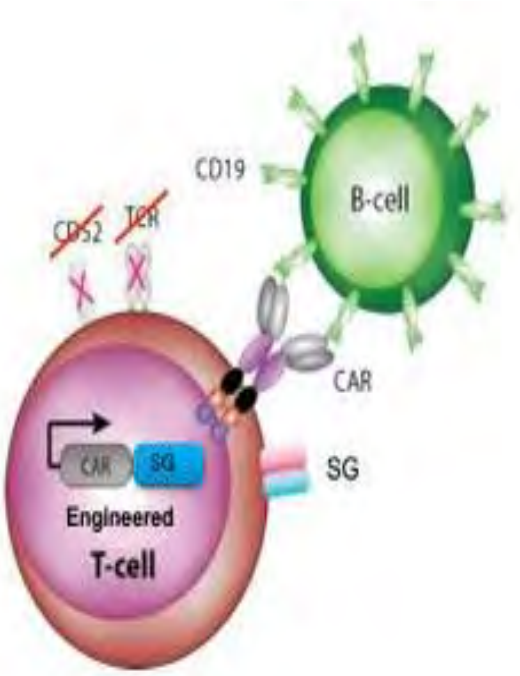
Future directions in BCMA Cellular Therapies

- **Novel constructs, vectors (SynNotch-binding to one Ag drives expression of CAR for second Ag)**

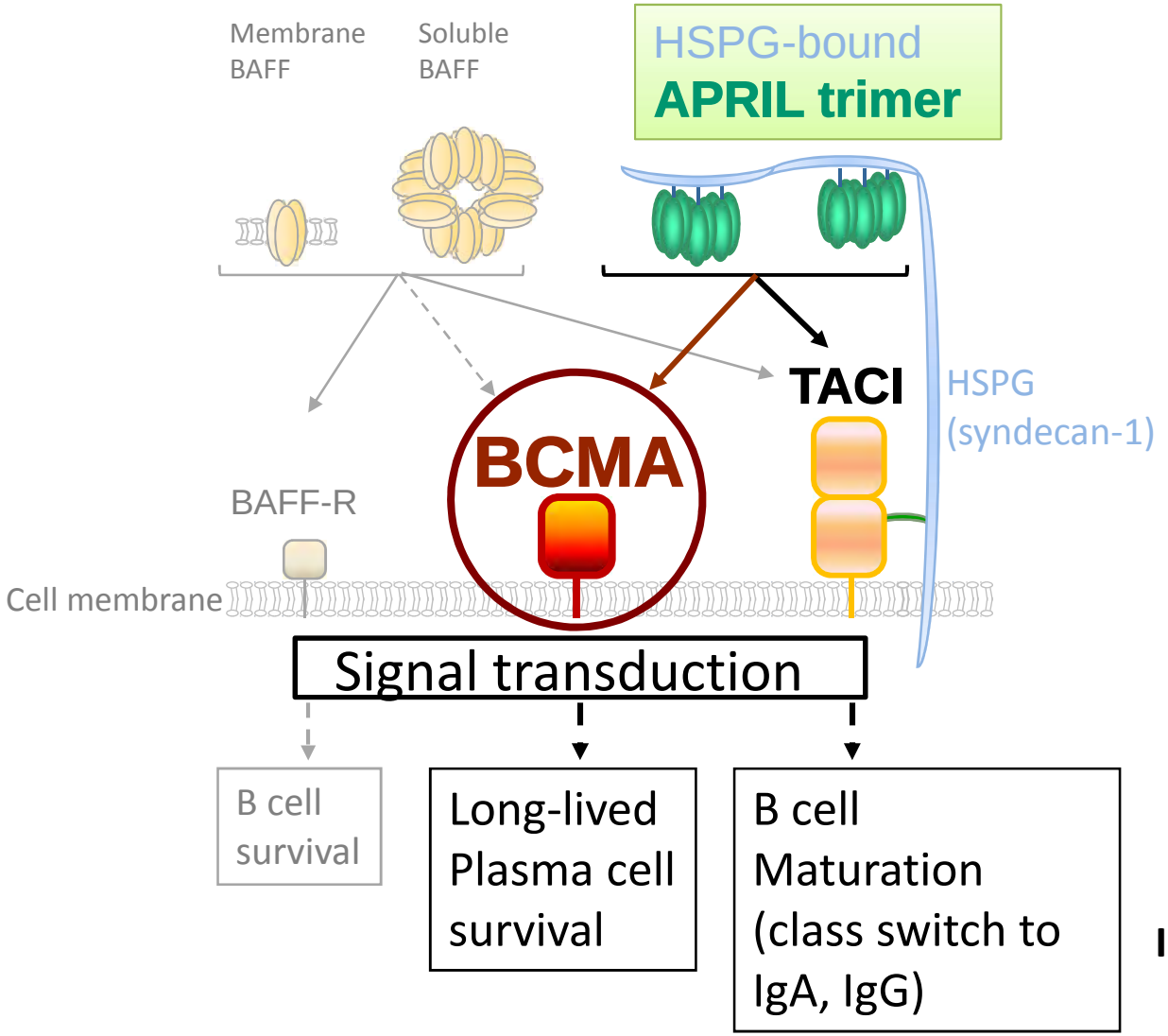


Universal SLAMF7-Specific CAR T (abs 502)

- "Off-the-shelf"
- Normal healthy PB donors
- Inactivation of the *TCRα constant* (*TRAC*) gene using gene-editing technology to prevent GVHD and expression of T cell SLAMF7.
- Campath MoAb targeting CD 52 can be used if needed to prevent host rejection of normal donor CAR T cells



BCMA Growth, Survival, Drug Resistance Signaling in MM



Ligands

by neutrophil, myeloid cell, DC, osteoclasts, tumor cell

Affinity to BCMA:
APRIL (nM) >> BAFF (μM)
Elevated in sera of MM patients

Receptors

on B cells

BCMA >> TACI
by ~2-100-fold in MM
(loss of BAFF-R in MM)

Tai & Anderson
Immunotherapy 2015; 7: 1187-99.

GSK2857916 Aurostatin Immunotoxin Targeting BCMA in Relapsed/Refractory Multiple Myeloma

- BCMA Selectively expressed on MM/plasma cells
- BCMA MoAb linked to aurostatin immunotoxin
- Median follow-up 6.6 months
- ORR of 60% in heavily pre-treated MM
- Median PFS 7.9 months
- Well tolerated and side effects manageable
  - Thrombocytopenia and corneal events most frequent AEs
  - IRRs occurred in only 23% of patients without pre-medication; no IRRs occurred on subsequent infusions
- Additional monotherapy and combination studies are planned

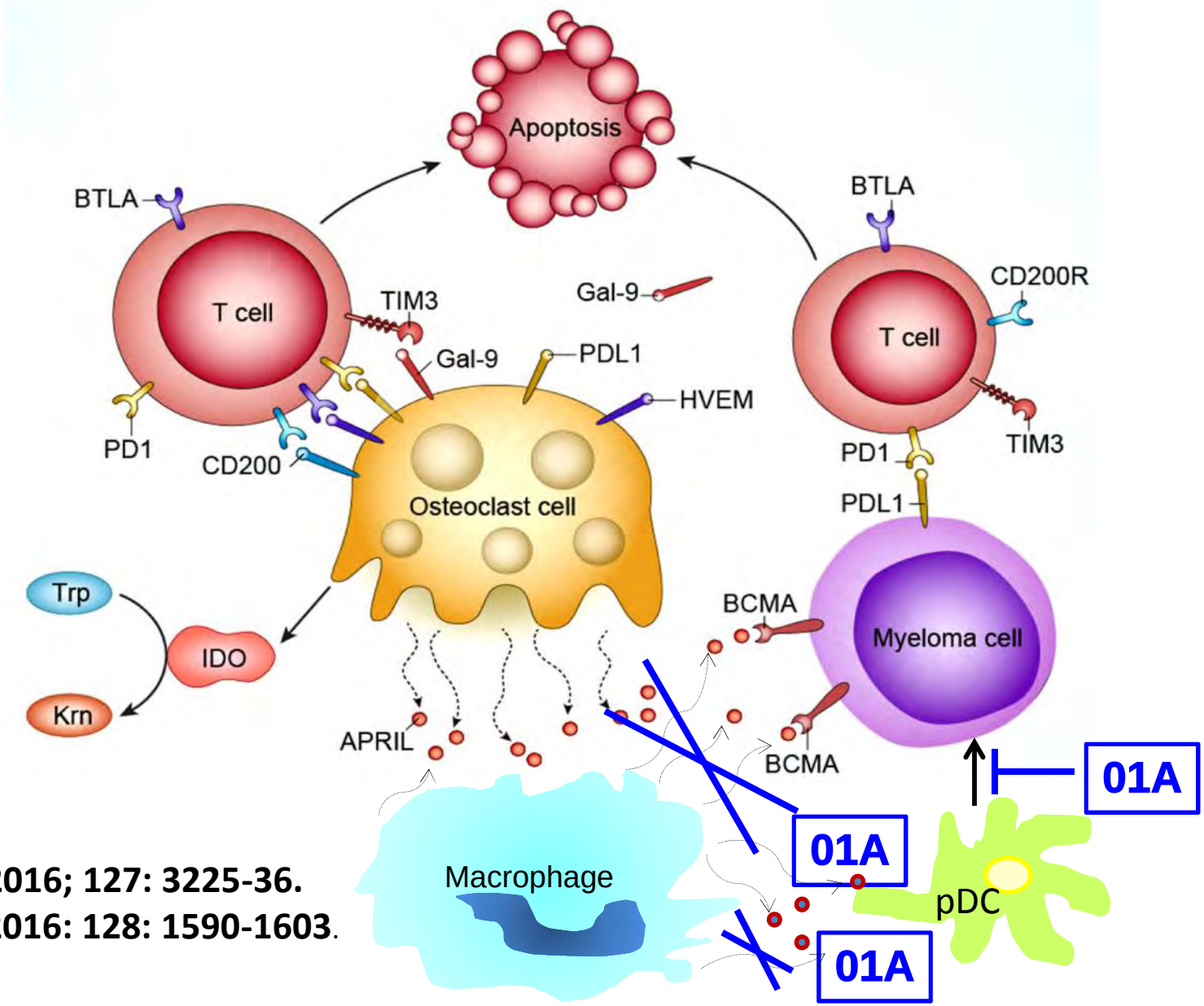
Trudel et al ASH 2017

DOR, duration of response; IRR, infusion-related reaction; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response

Targeting APRIL in MM

01A

Anti-APRIL



Tai et al Blood 2016; 127: 3225-36.
An et al Blood 2016: 128: 1590-1603.

Conclusion

- Immune-based therapies are achieving impressive responses
- Adoptive Transfer of CAR-T cells has great promise
- Task for us is to sustain/maintain the great responses achieved with CAR-T cell infusion
  - Newer generation of CAR-T cells
  - Combination with conventional agents
  - Reinfusion of CAR-T cells – maintenance dosage
  - Develop more convenient CAR-T generation methods and process

Masood Shammas, PhD
Pra
Mar
Wei
Jag
Pur
Jian
Mar
Ada
Wei
Tere

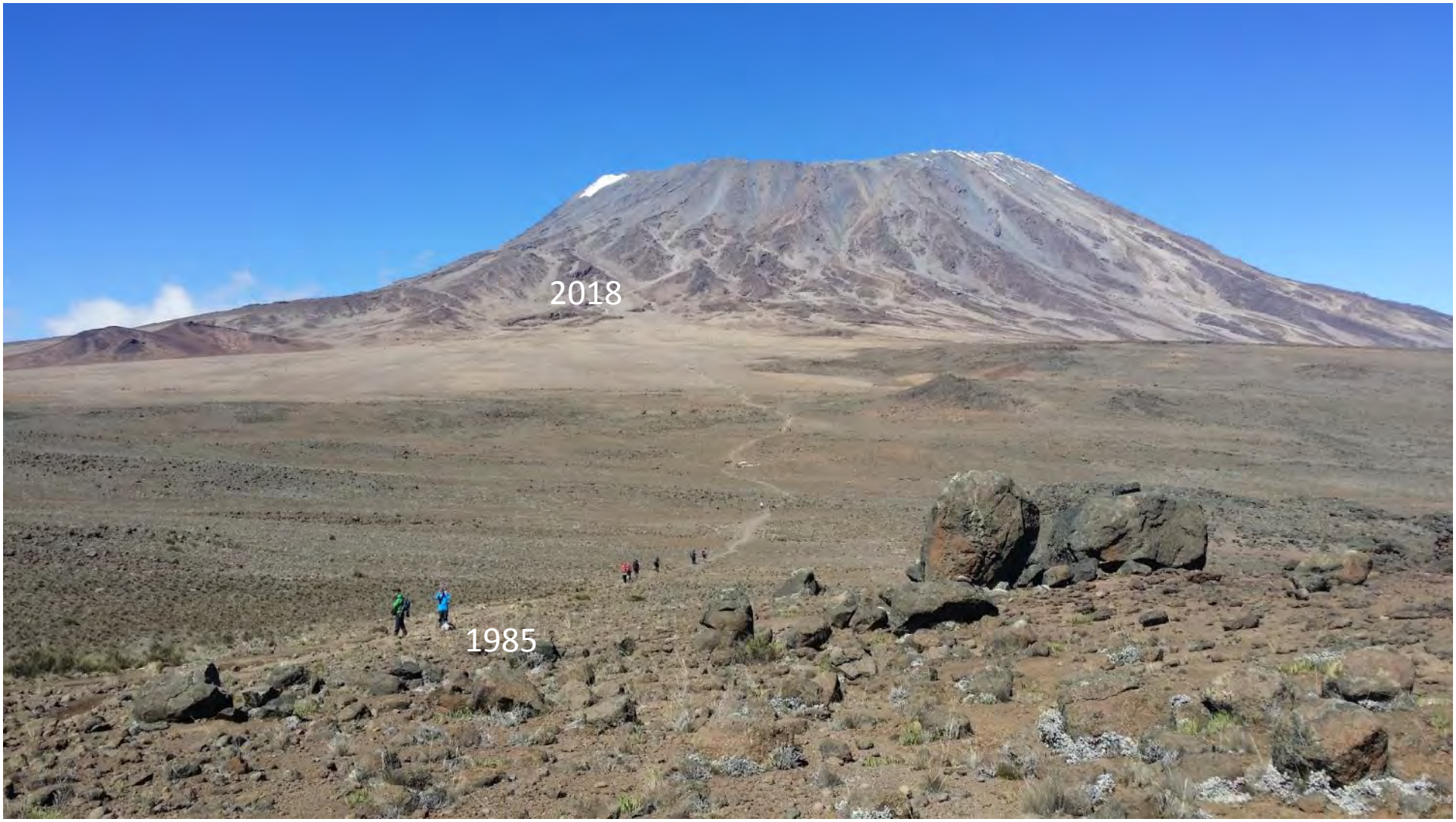
Kenneth Anderson, MD

Giovanni Parmigiani, PhD
Cheng Li, PhD
Yi Li, PhD
Naim Rashid, PhD and
Mehmet Samur, PhD
Bioinformatics Group

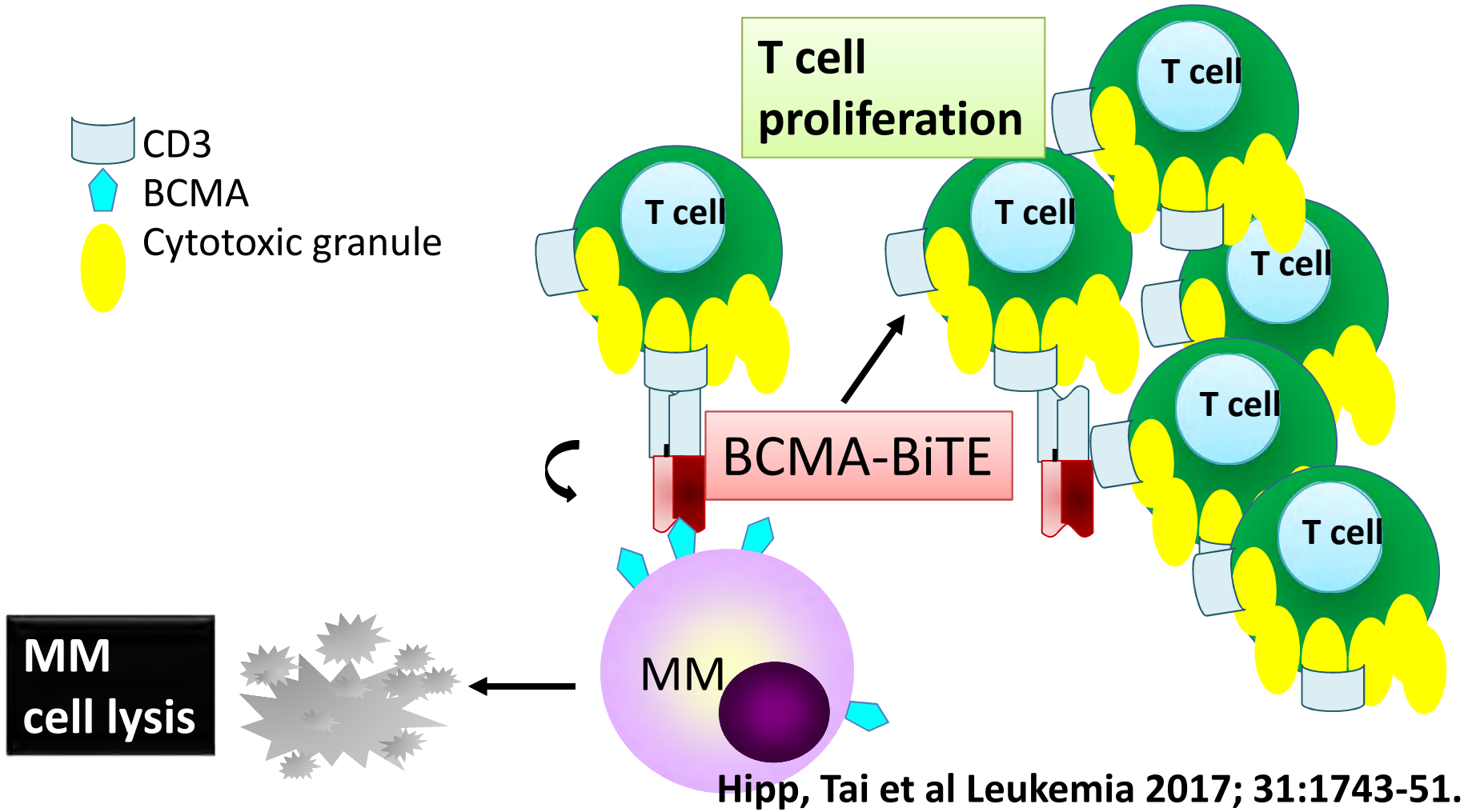
Dr. Herve Avet-Lousieu
Dr Stephane Miniville,
Dr. Philippe Moreau
Dr. Florence MAGRANGEAS
Dr. Michel Attal and IFM

Peter Campbell
Andy Futreal
Graham Bignell
Niccolo Boli
David Wage

Climb To Cure Multiple Myeloma



BCMA-BiTE-Based Immunotherpaies



Hipp, Tai et al Leukemia 2017; 31:1743-51.

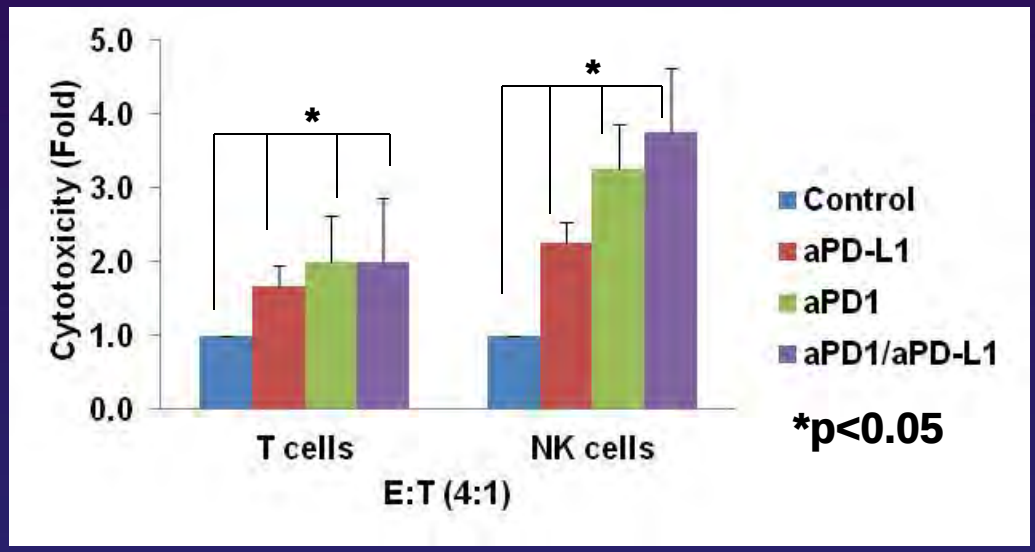
CRB 401 BCMA CAR T cells

bb2121 at active doses (≥150 × 10^6 CAR+ T cells) induces deep and durable responses in a heavily pretreated population with R/R MM

- **Median PFS of 11.8 months for patients in the dose escalation cohort**
- **MRD-negative results in 100% of 16 evaluable responding patients; median PFS of 17.7 months**
- **Mostly grade 1/2 CRS observed with infrequent tocilizumab and corticosteroid use**
- **Ongoing trial for FDA approval.**

Raje N, et al. EHA 2018, abstract S138.

Checkpoint Blockade Induces Effector Cell Mediated MM Cytotoxicity

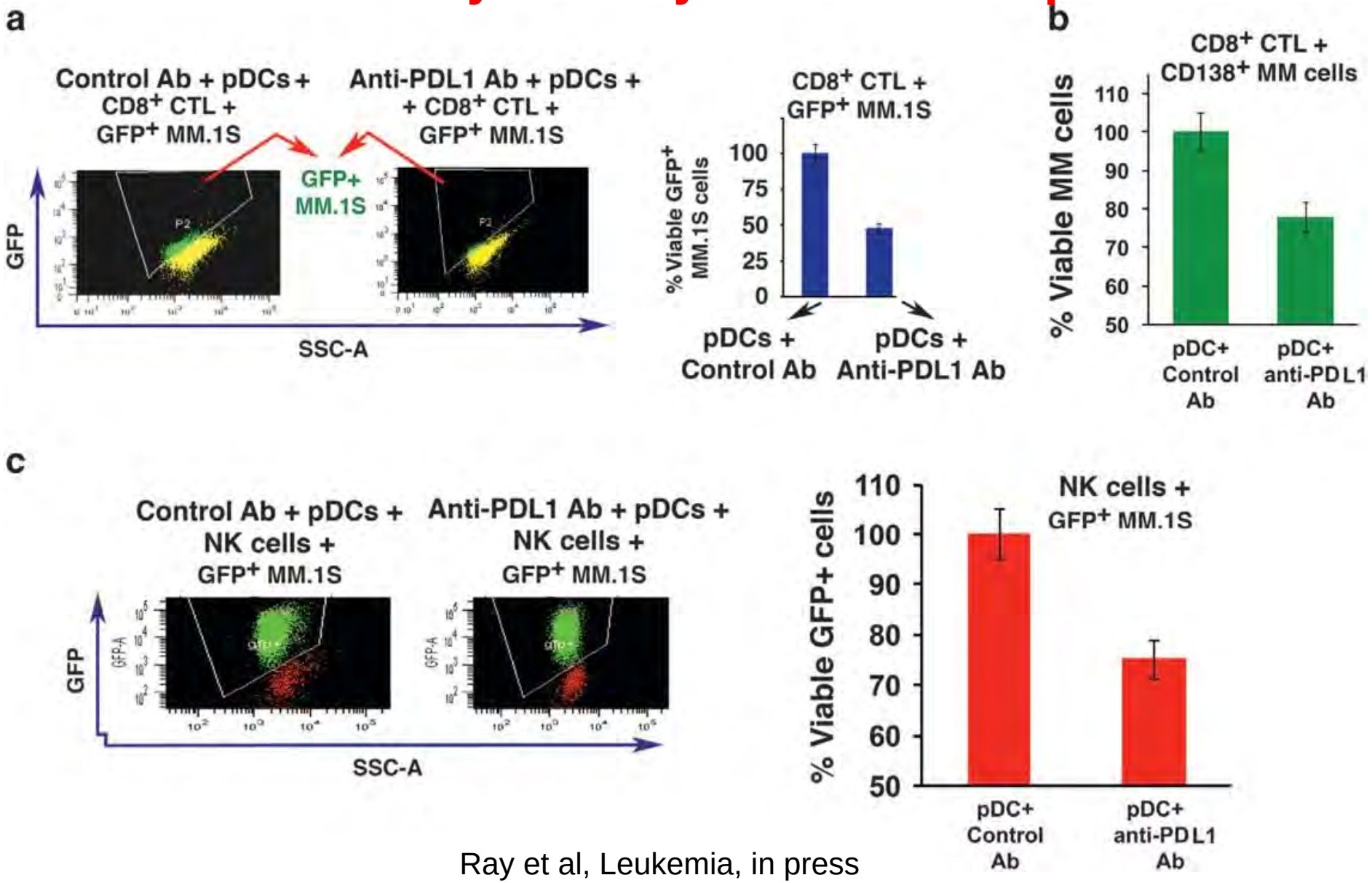


Effector: Autologous effector cells (CD3T cells, NK cells)

Target: CD138^{+} MM cells from Rel/Ref MM-BM

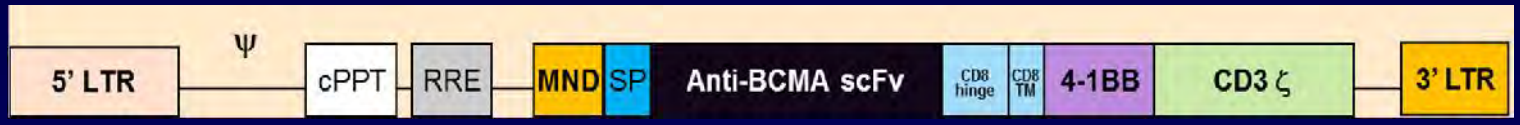
Görgün G. et al. Clin Cancer Res, in press

Anti-PDL1 Ab Induces MM-Specific CD8+ CTLs and NK cell-Mediated Cytotoxicity in Presence of pDCs



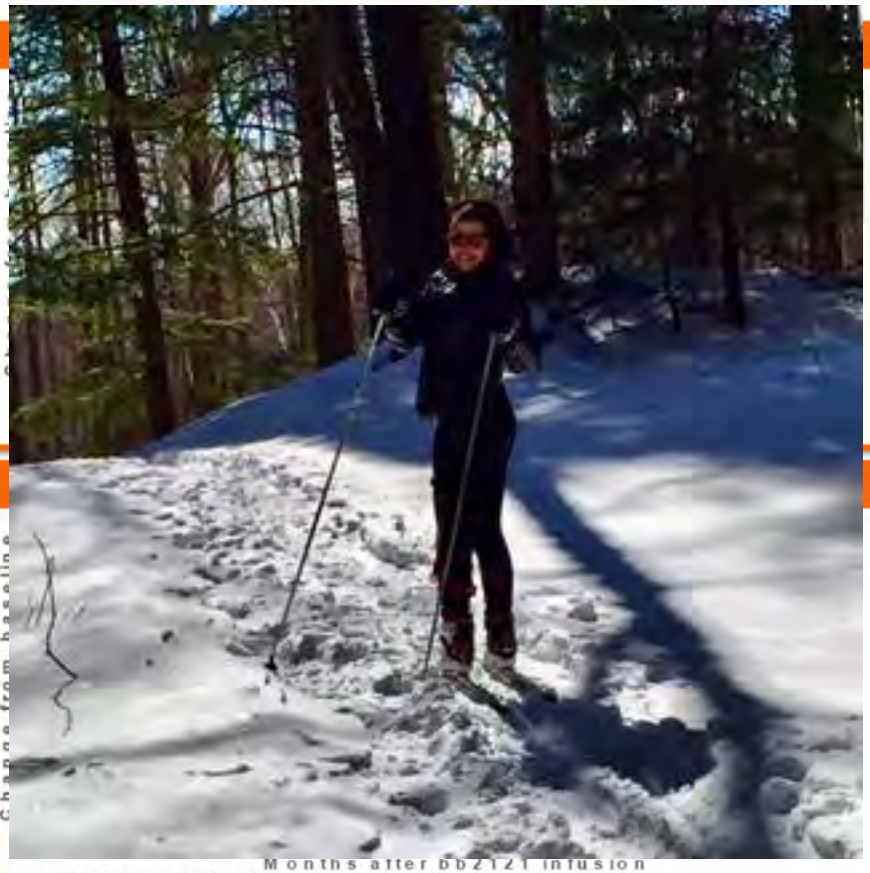
Ray et al, Leukemia, in press

bb2121: Anti-BCMA Chimeric Antigen Receptor T-Cell in Multiple Myeloma



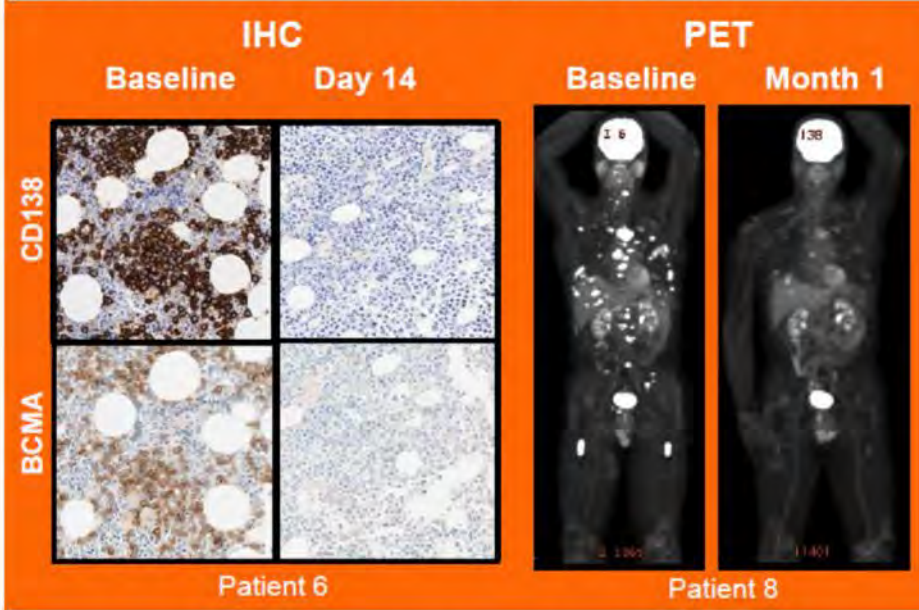
anti-BCMA CAR design

Responses to bb2121 Infusion



*ratio=involved LC-uninvolved LC, calculated only in patients with a baseline LC > 10 mg/dL

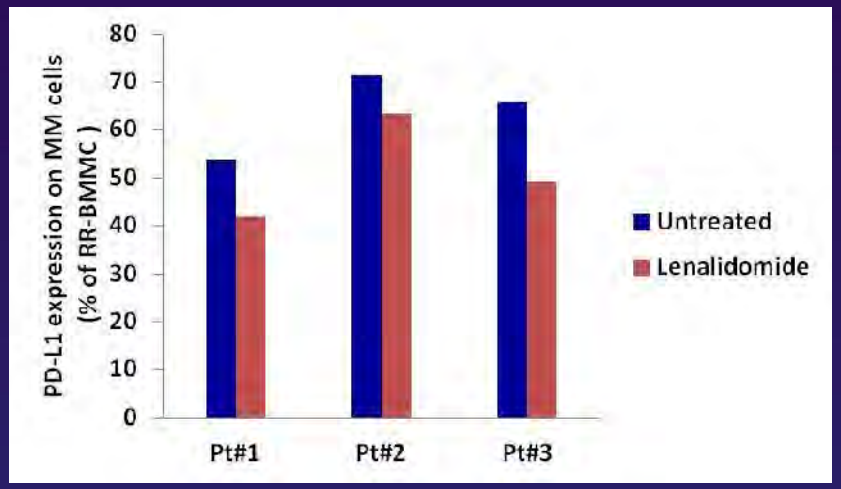
Bone marrow response and tumor burden reduction



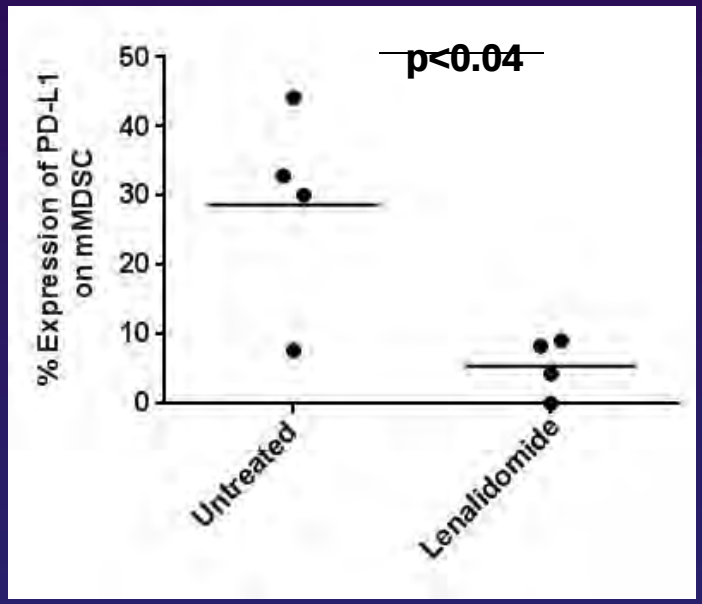
All patients treated at doses > $5x10^7$ with bone marrow involvement at baseline have had no detectable bone marrow disease on Day 14 or beyond

Lenalidomide Reduces PD1 and PD-L1 Expression on RR-MM Bone Marrow Cells

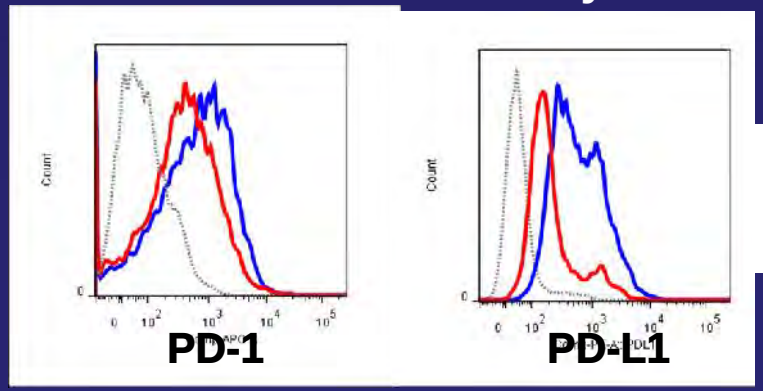
CD138⁺ MM cells



mMDSC



T cells **CD14⁺Myeloid cells**



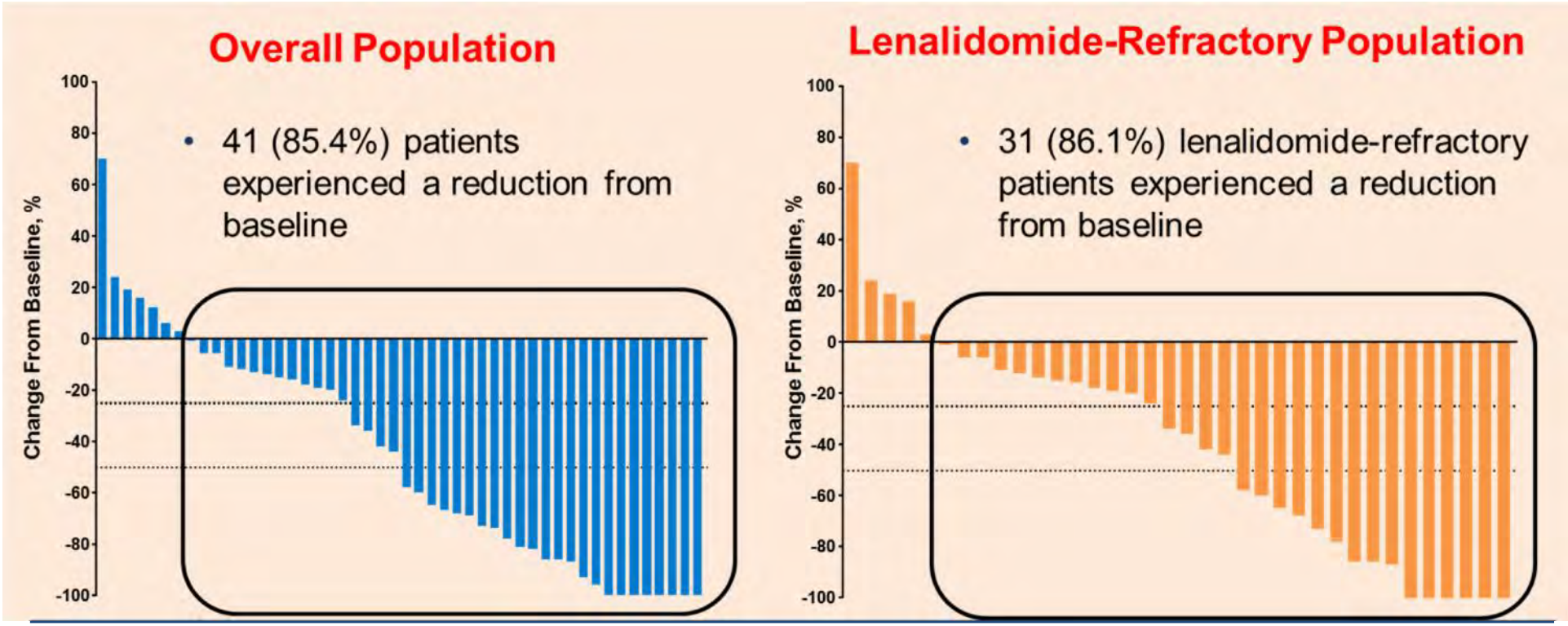
Untreated

Lenalidomide

Görgün G. et al. Clin Cancer Res, in press

Pembrolizumab Plus Lenalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Overall Response

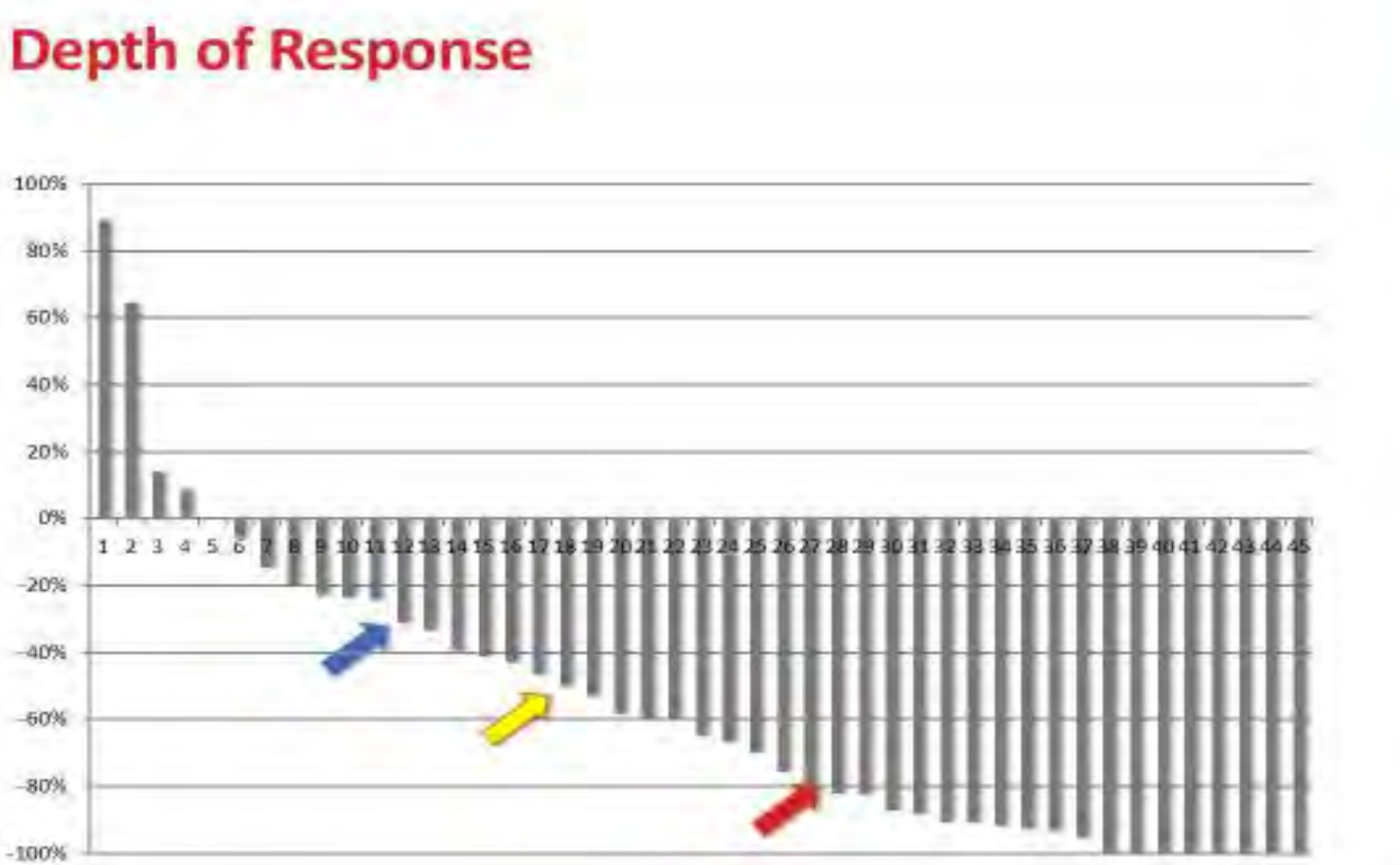
Change From Baseline in M Protein or Free Light Chain



[a]12 patients were not included because they did not have ≥2 postbaseline efficacy assessments or they had major protocol violations.
[b]DCR = sCR + CR + VGPR + PR + SD.
[c]Assessments were not available for 2 (4%) patients who recently enrolled in the study.
Data cutoff: March 10, 2017.

Rodríguez-Otero et al EHA 2017

Pembrolizumab, Pomalidomide and Dex in RR Myeloma: Summary of Responses



Badros et al ASH 2016

Role of NK and NKT cells in Myeloma

Cancer Therapy: Preclinical

Generation of Antitumor Invariant Natural Killer T Cell Lines in Multiple Myeloma and Promotion of Their Functions via Lenalidomide: A Strategy for Immunotherapy

Weihua Song,[1] Hans J.J. van der Vliet,[2] Yu-Tzu Tai,[1] Rao Prabhala,[1,3] Ruojie Wang,[2] Klaus Podar,[1] Laurence Catley,[1] Masood A. Shammas,[3] Kenneth C. Anderson,[1] Steven P. Balk,[2] Mark A. Exley,[2] and Nikhil C. Munshi[1,3]

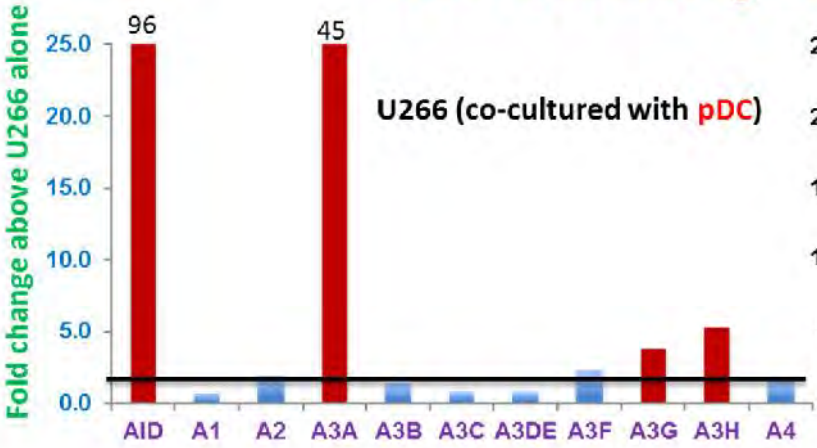
PNAS

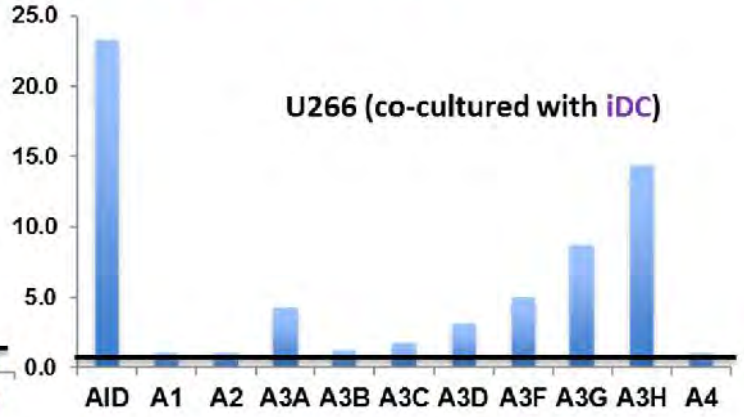
MHC class I chain-related protein A antibodies and shedding are associated with the progression of multiple myeloma

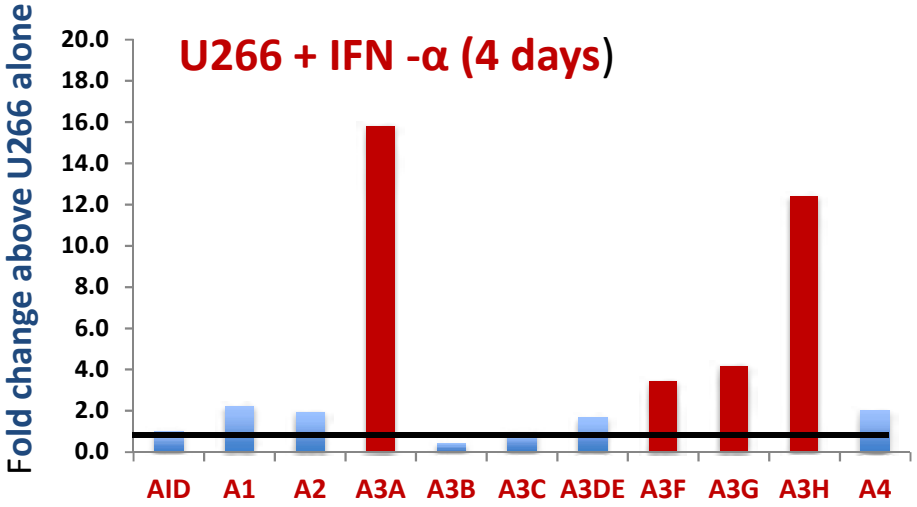
Masahisa Jinushi*, Matthew Vanneman*, Nikhil C. Munshi*, Yu-Tzu Tai*, Rao H. Prabhala*, Jerome Ritz*, Donna Neuberg†, Kenneth C. Anderson*, Daniel Ruben Carrasco*‡, and Glenn Dranoff*§

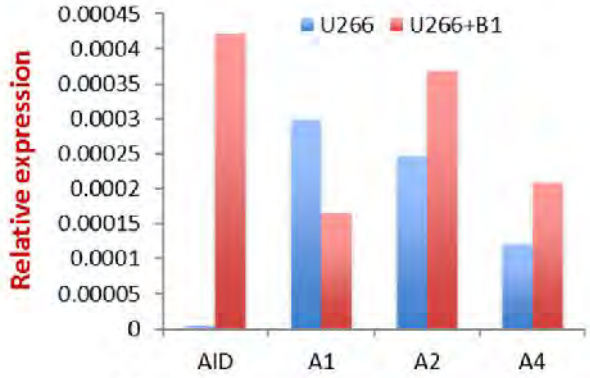
*Department of Medical Oncology and Cancer Vaccine Center, Dana–Farber Cancer Institute and Department of Medicine, and ‡Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115; and †Department of Biostatistics and Computational Biology, Dana–Farber Cancer Institute, Harvard Medical School, Boston, MA 02115

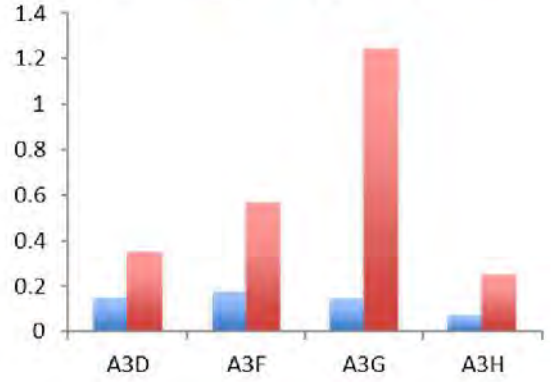
Immune Cells Contribute to Genomic Instability in Myeloma





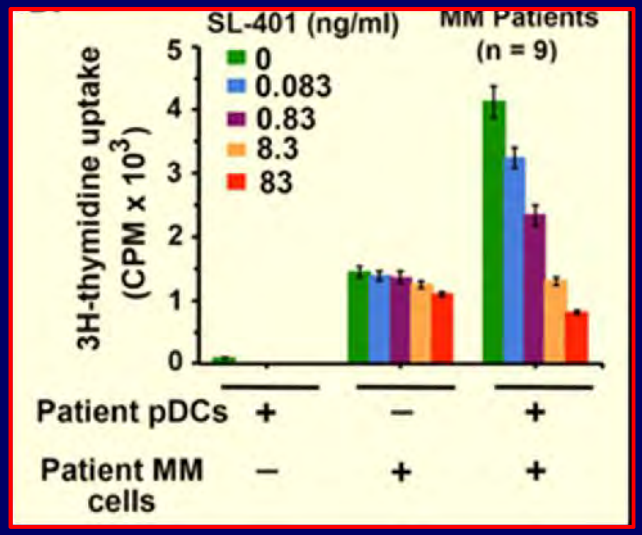


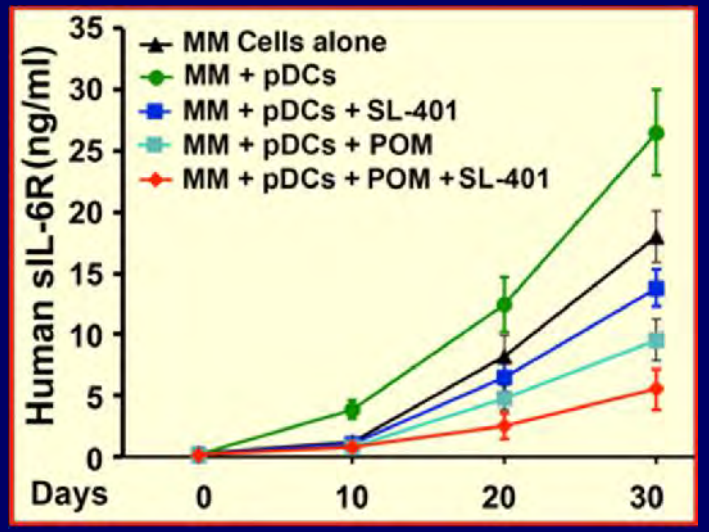




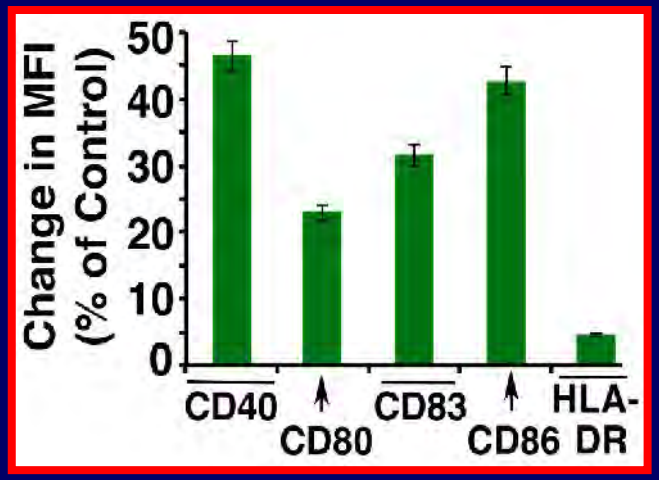
Targeting pDC-MM Interaction By pDC cytotoxicity OR pDC Maturation

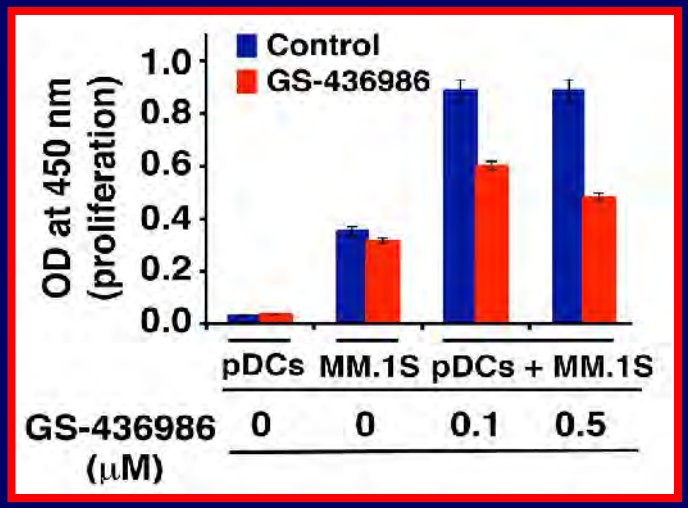
IL-3R
SL-401





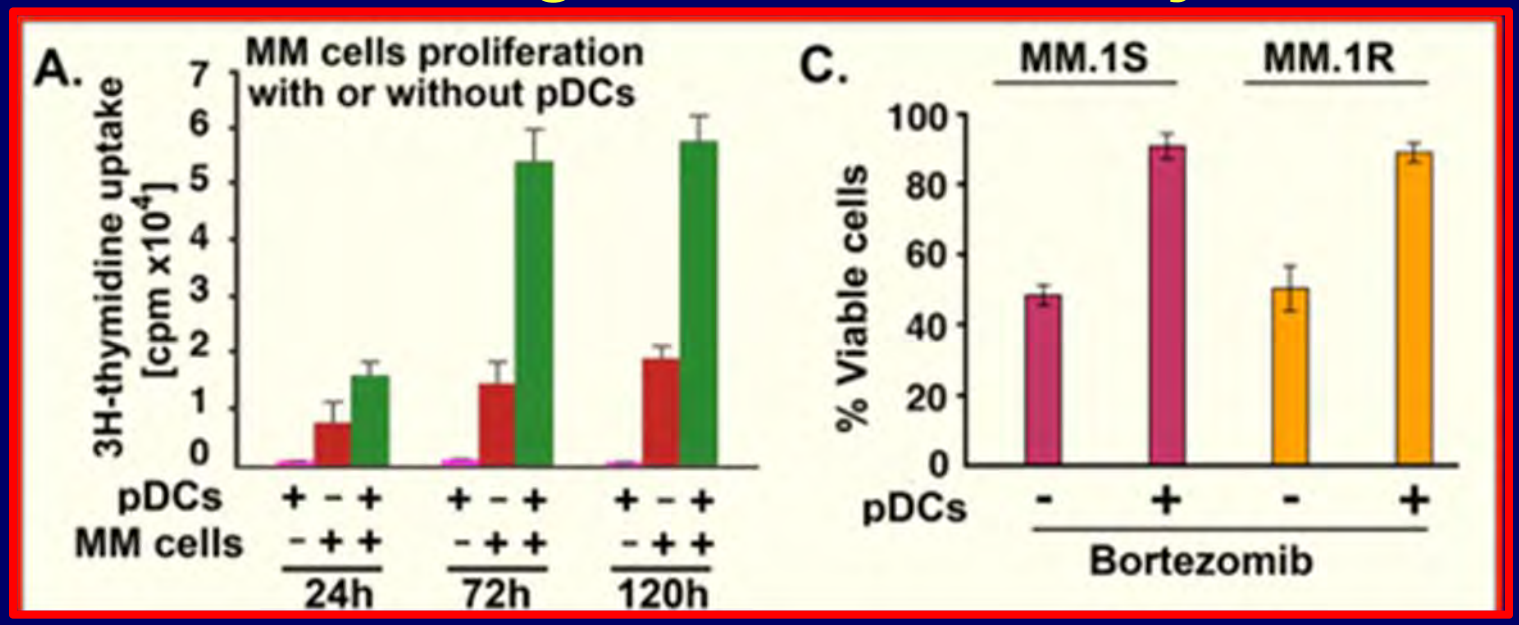
TLR-7
GS4369869

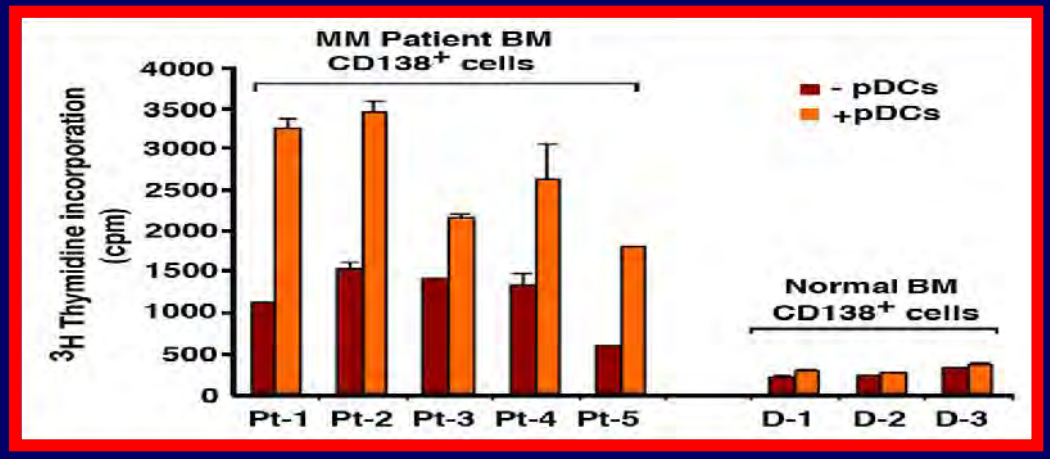




Chauhan et al: Cancer Cell 2009

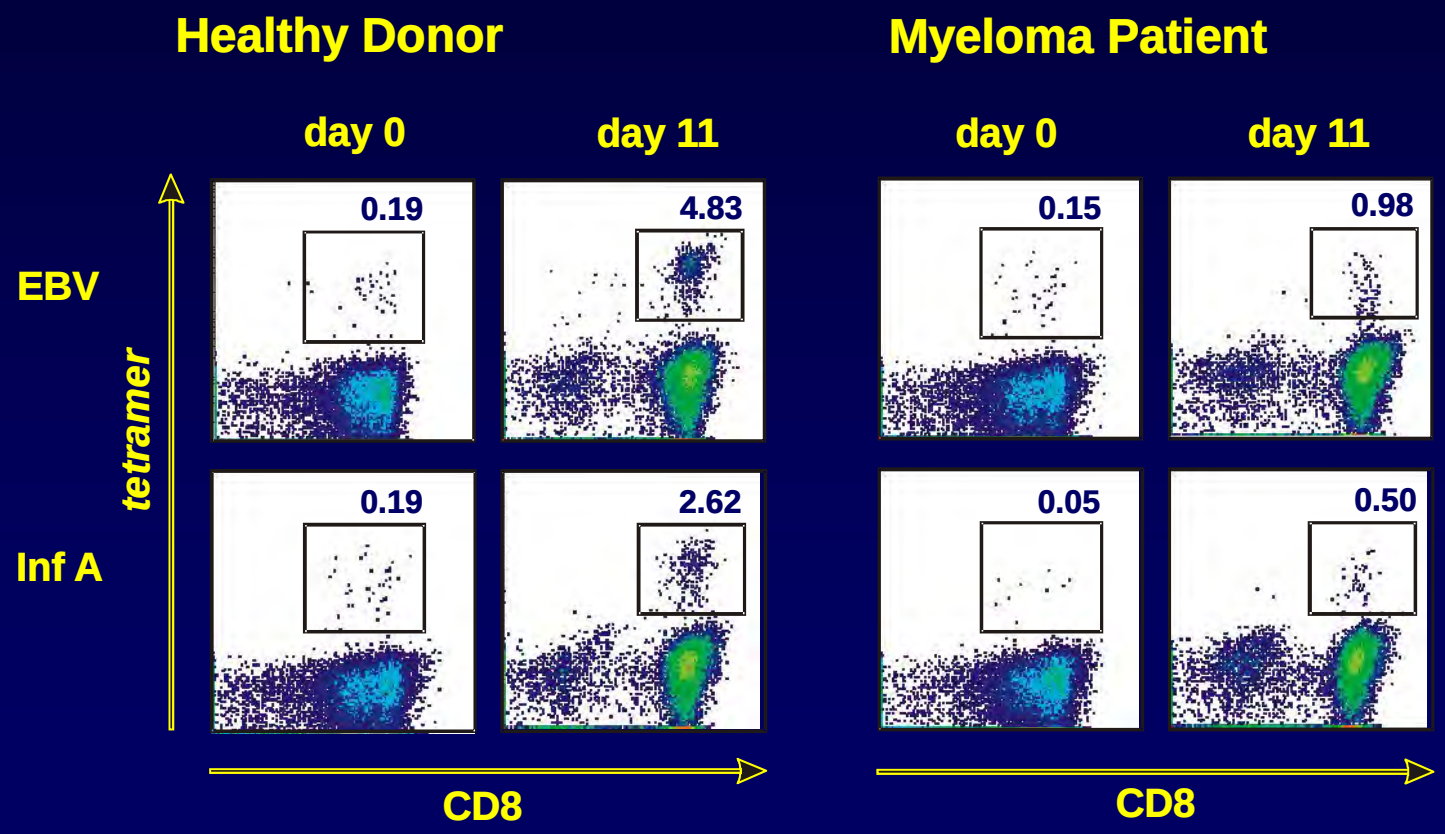
Plasmacytoid DCs Promote Growth, Survival, and Drug-Resistance in Myeloma



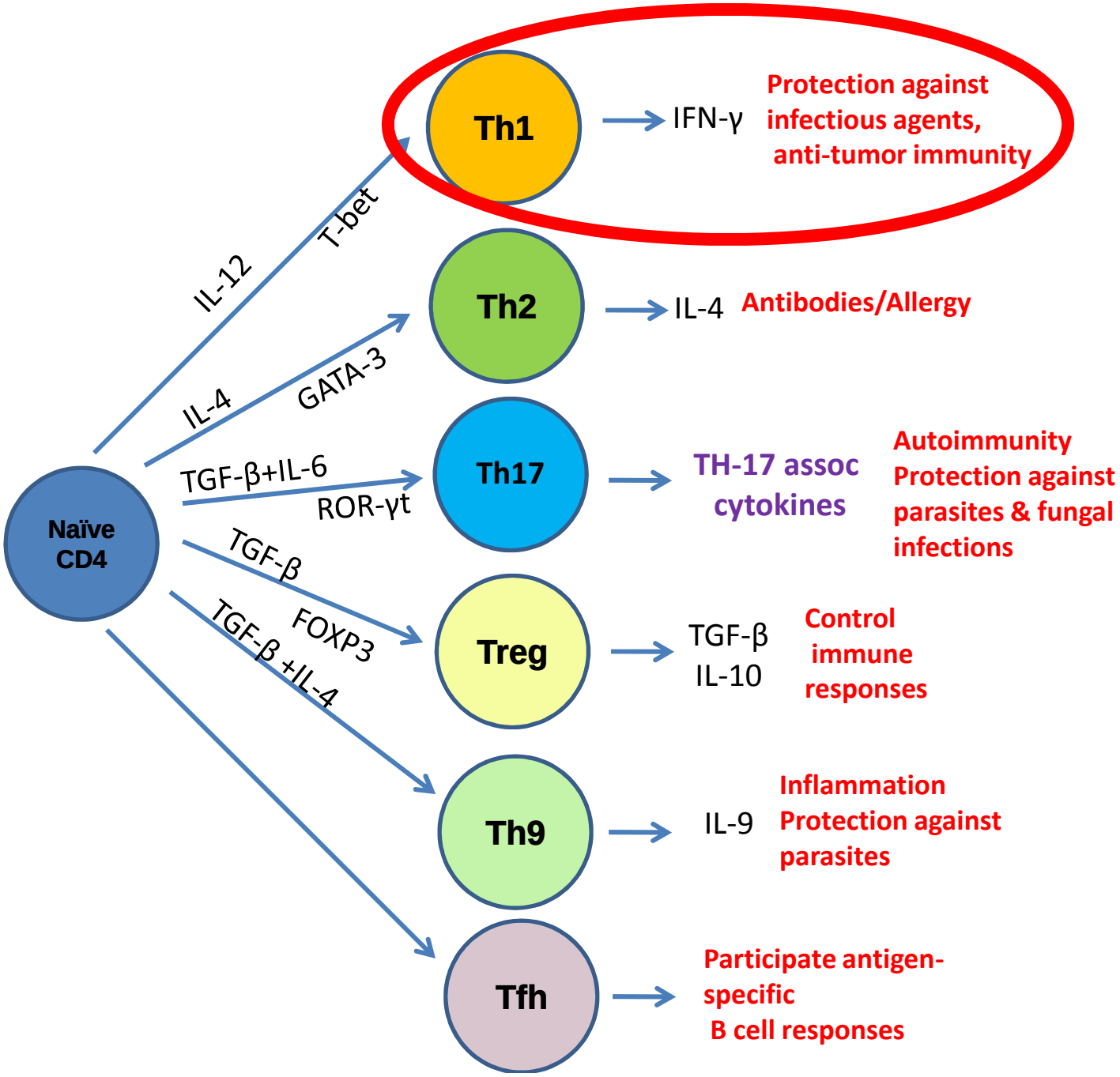


Chauhan et al: Cancer Cell 2009

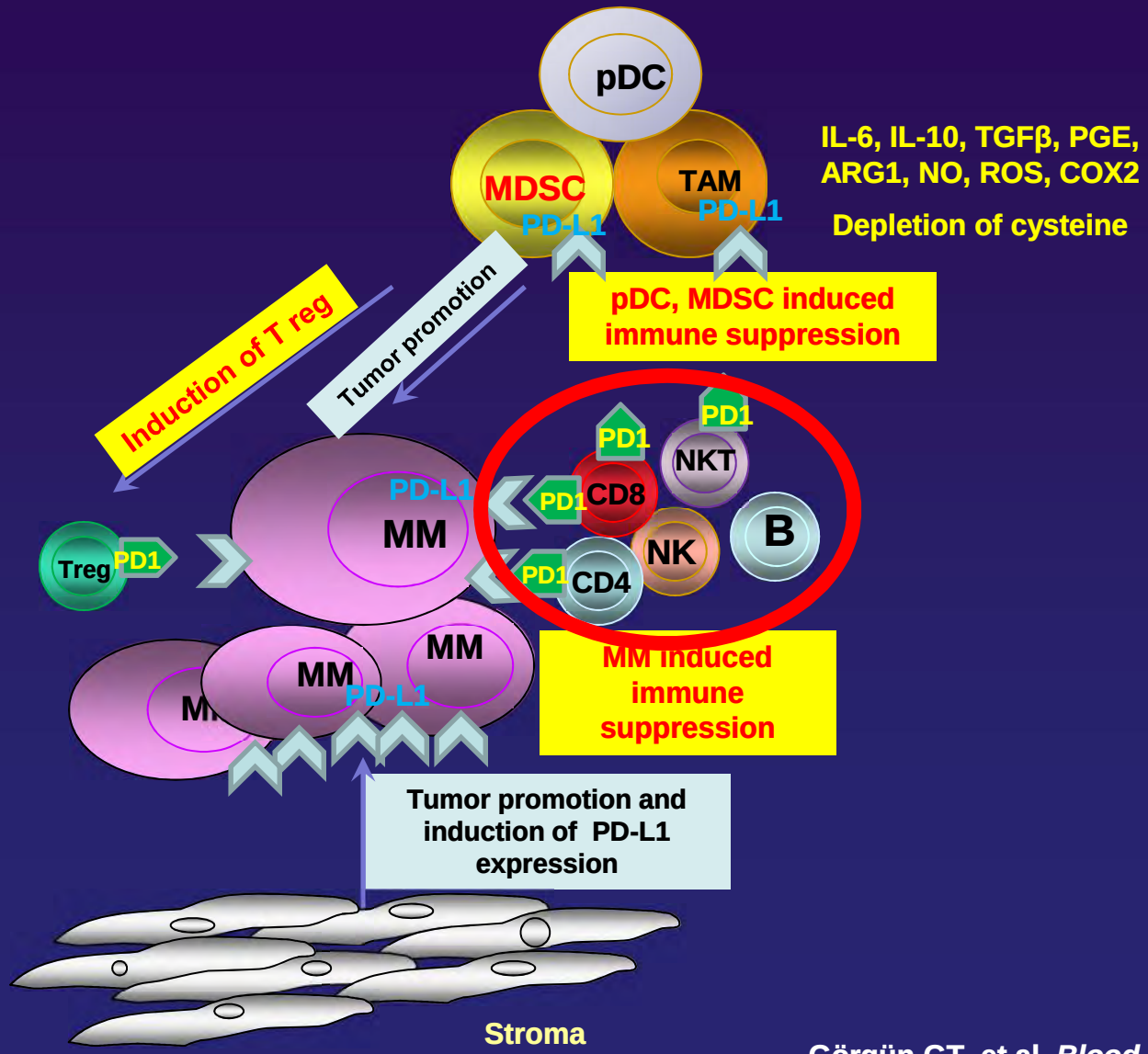
Suppressed Virus-Specific T cells in Myeloma
Responsive to *in vitro* Stimulation



Development of T lymphocyte helper Subsets

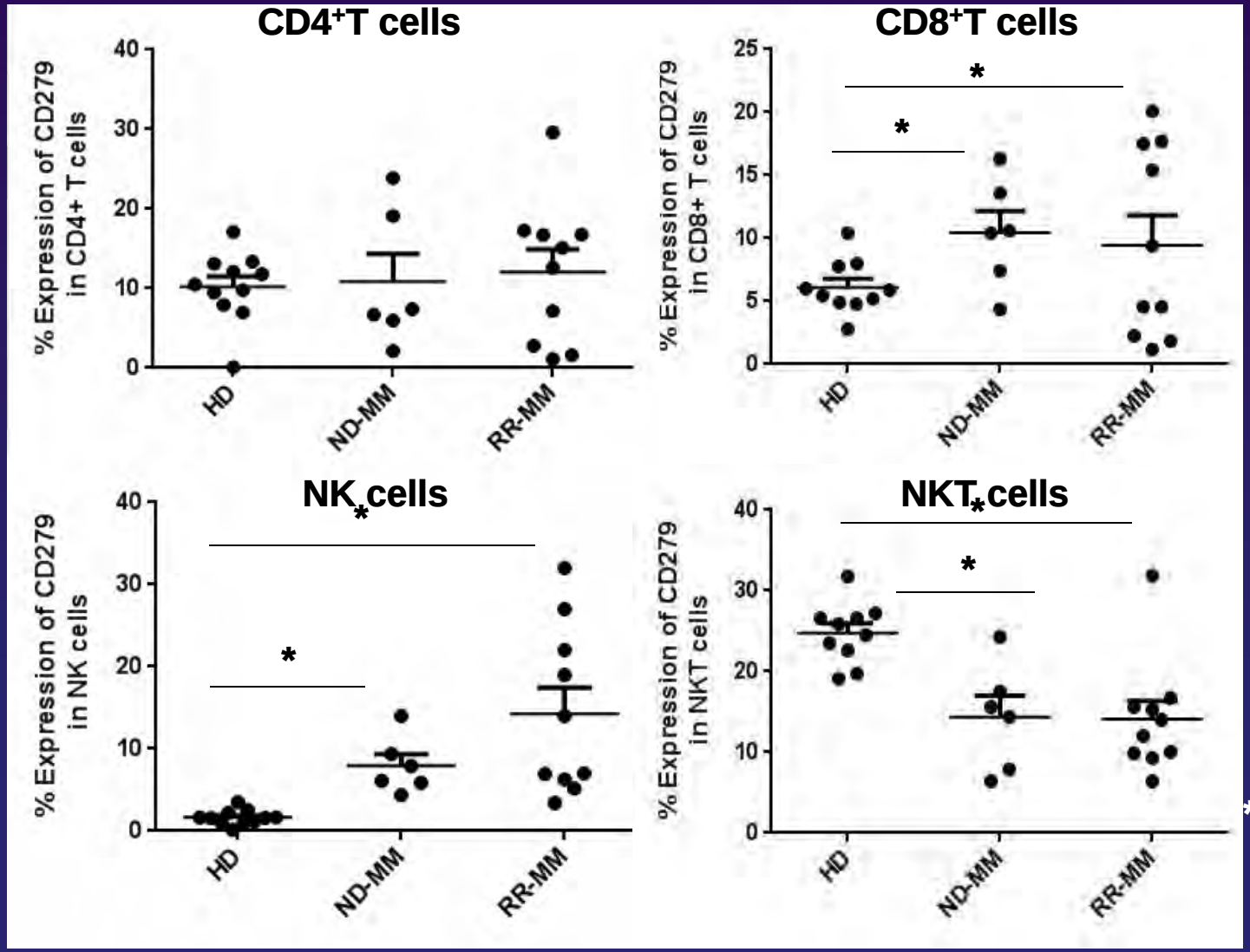


Immune Suppressive Microenvironment in MM



Görgün GT, et al. *Blood* 2013;121:2975-87

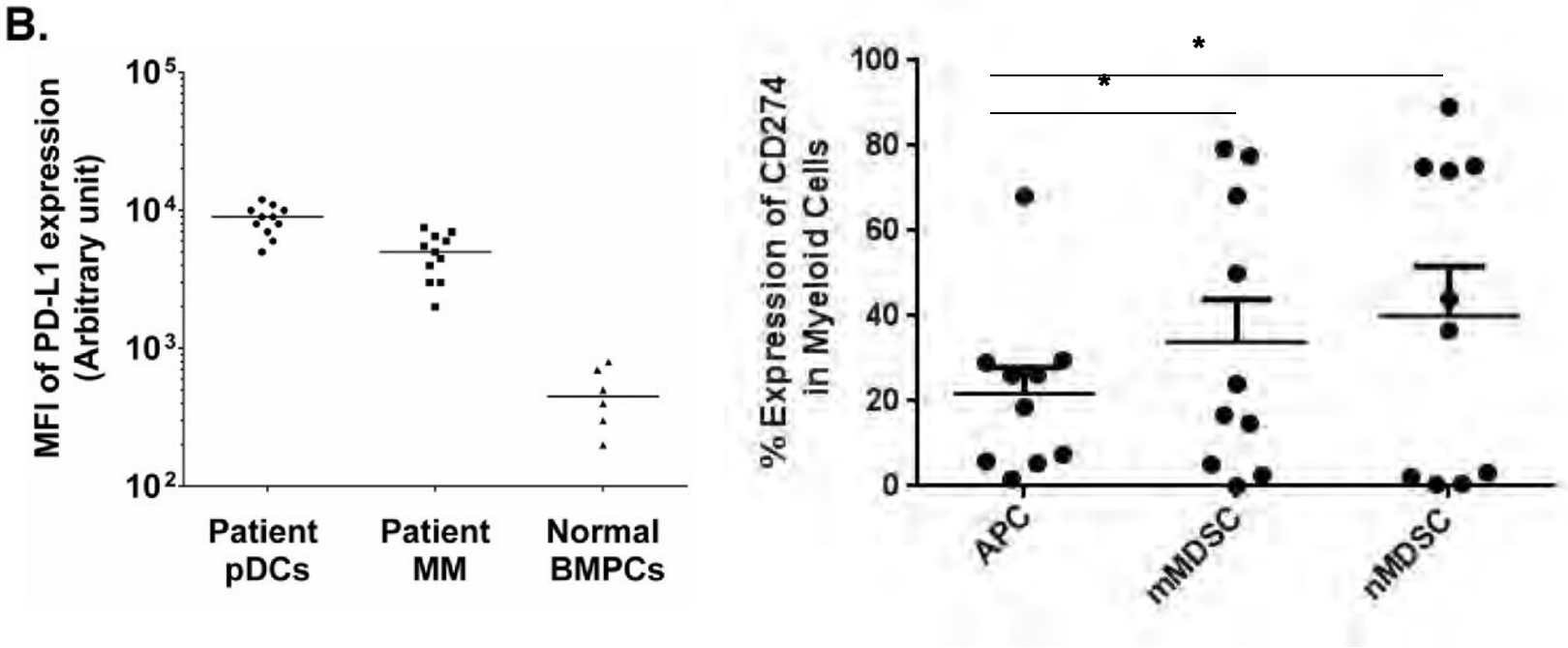
Increased PD1 Expression on Effector cells in MM



*p<0.05

Görgün G. et al. Clin Cancer Res, 2016

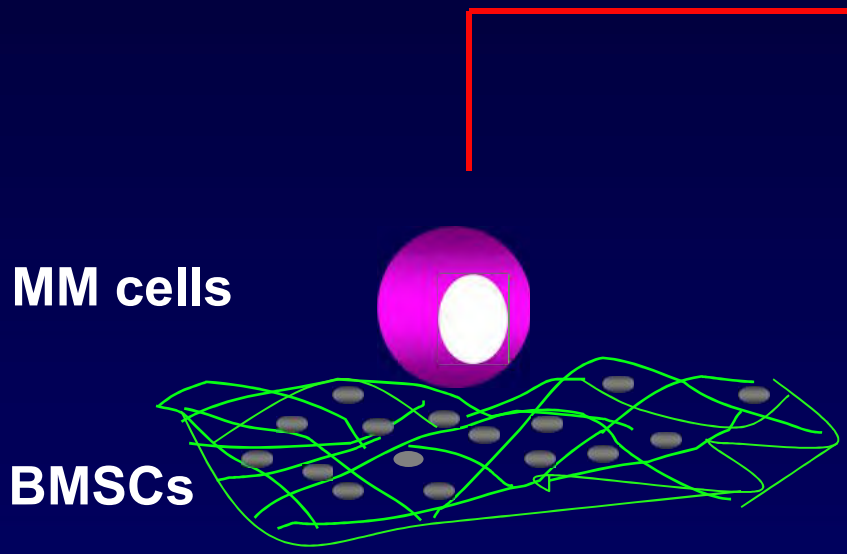
High PDL1 Expression on MM Cells, pDCs and MDSCs in Myeloma

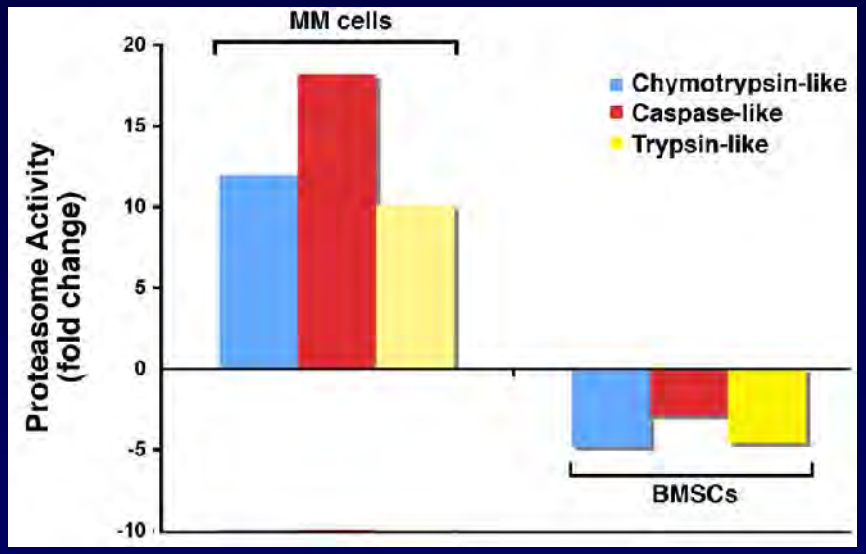


Görgün G. et al. Clin Cancer Res, 2016

Ray et al, Leukemia, in press

BM Microenvironment Triggers Proteasome Activity in MM Cells

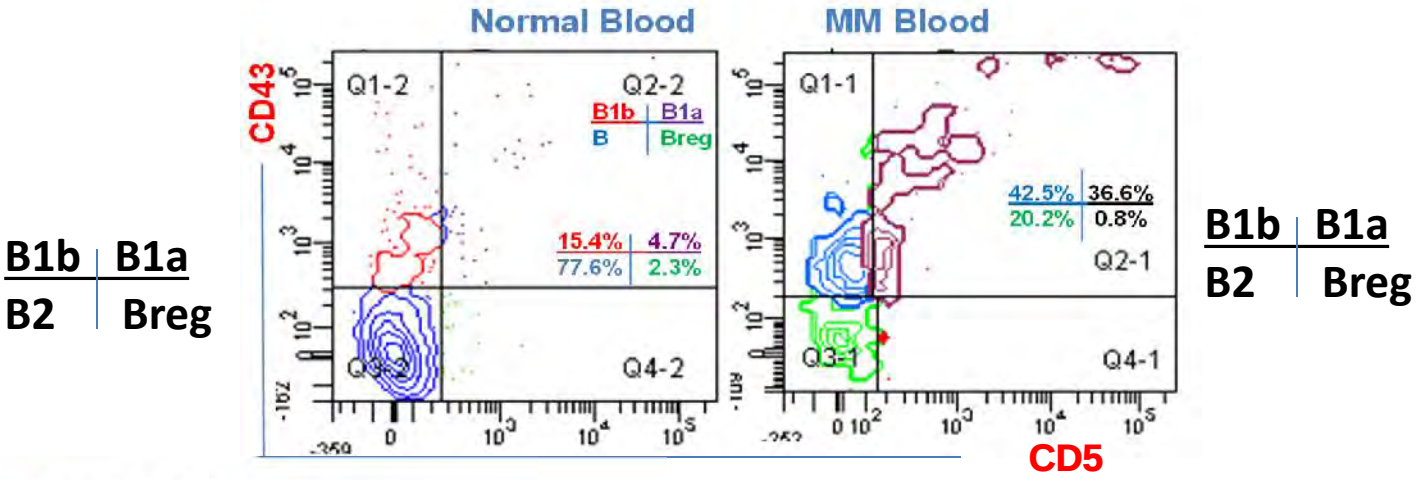




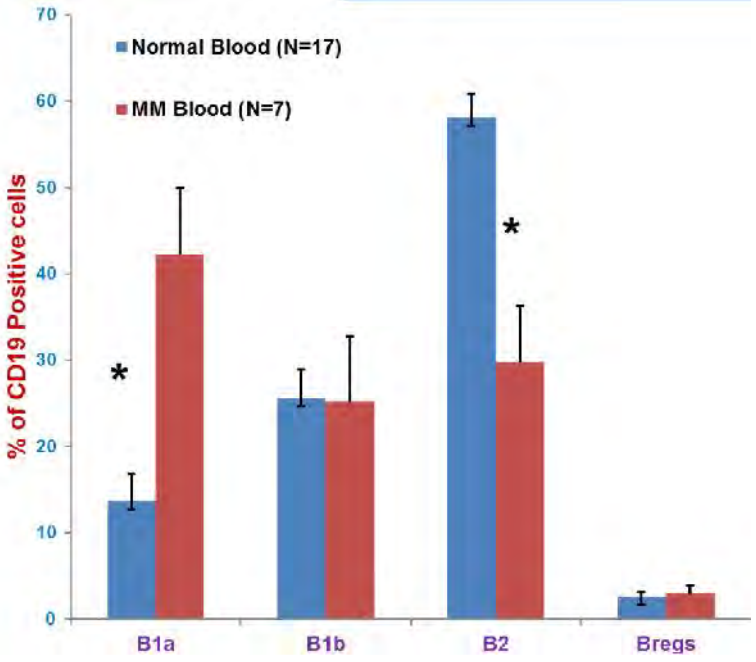
Key role of protein homeostasis and protein degradation pathway in myeloma

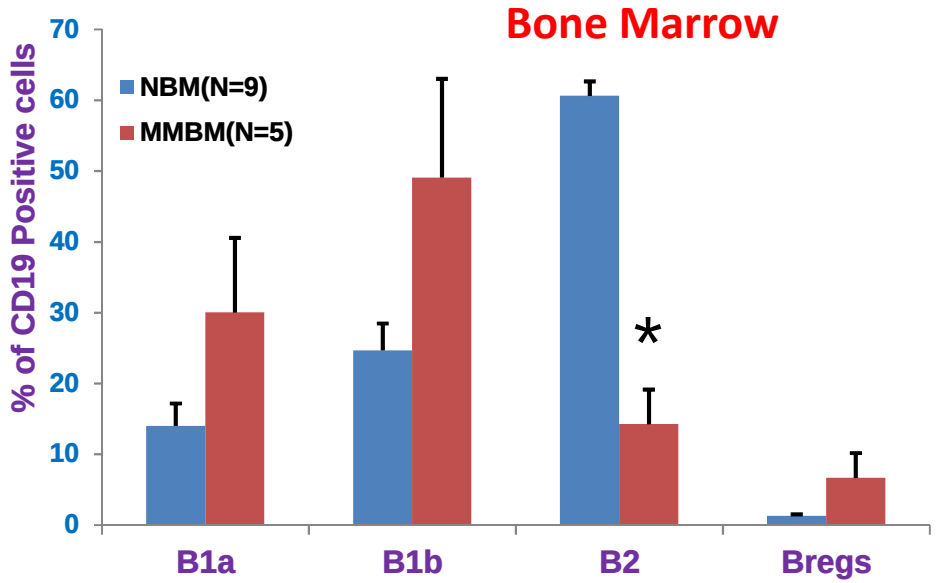
Chauhan et. al., 2006

Abnormal B cell-subsets in Myeloma

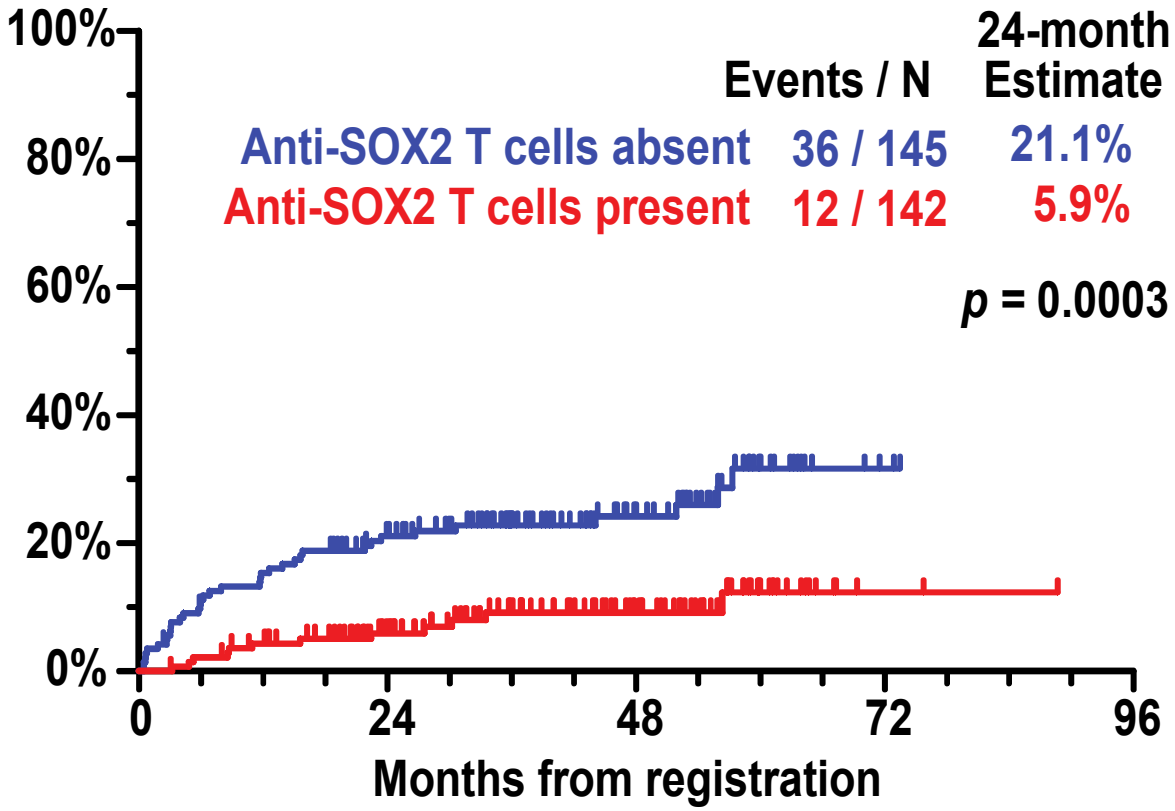


B1b | B1a
B2 | Breg





T Cell Immunity Against SOX2 At Baseline Correlates With Reduced Risk Of Progression To Symptomatic MM



Dhodapkar et al, Blood 2015