Immunoterapia nel Mieloma Multiplo e nel Linfoma di Hodgkin

MILANO
9 Novembre 2017

Caso clinico

Monica Carpenedo
ASST Ospedale San Gerardo di Monza, U.O Ematologia

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

- Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18, 19 dell'Accordo Stato-Regione del 19 aprile 2012, dichiaro che negli ultimi due anni **non** ho avuto rapporti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.

Case report (1)

- Female, born 1939 in Brazil
- Previous clinical history negative (no drugs)
- First occurrence of **anemia** in **Brazil on 2009**. Gastrointestinal diagnostic procedure were negative: she received blood transfusion
- **Proteinuria** was also observed (no quantitative data available)
- She was referred to our Centre in August 2010 for worsening of anemia. Her daughter lives near Monza

Case report (2)

- Routine screening for suspected Multiple Myeloma was performed

Our patient's journey

Parameter	Diagnosis (august 2010)
Hb	**10.5 (8.1)** g/dl
Bone marrow plasmacell	**Massive infiltration (80%)**
Monoclonal component	**0.5 g/dL IgG k**
Albumin	3.8
Proteinuria/ Bence Jones	0/ **+++**
FLC k/lamb	n.a
Ca	9.8
Beta2 microglob	**5.2**
Creatinine	**0.8**

ISS 2

Case report (4)

- CT skeleton on september 2010:

✓osteolitic lesions in the skull (max 16 mm), C1, L1, VIII and IX rib dx, scapula dx and sin

The choice of first line: year 2010

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

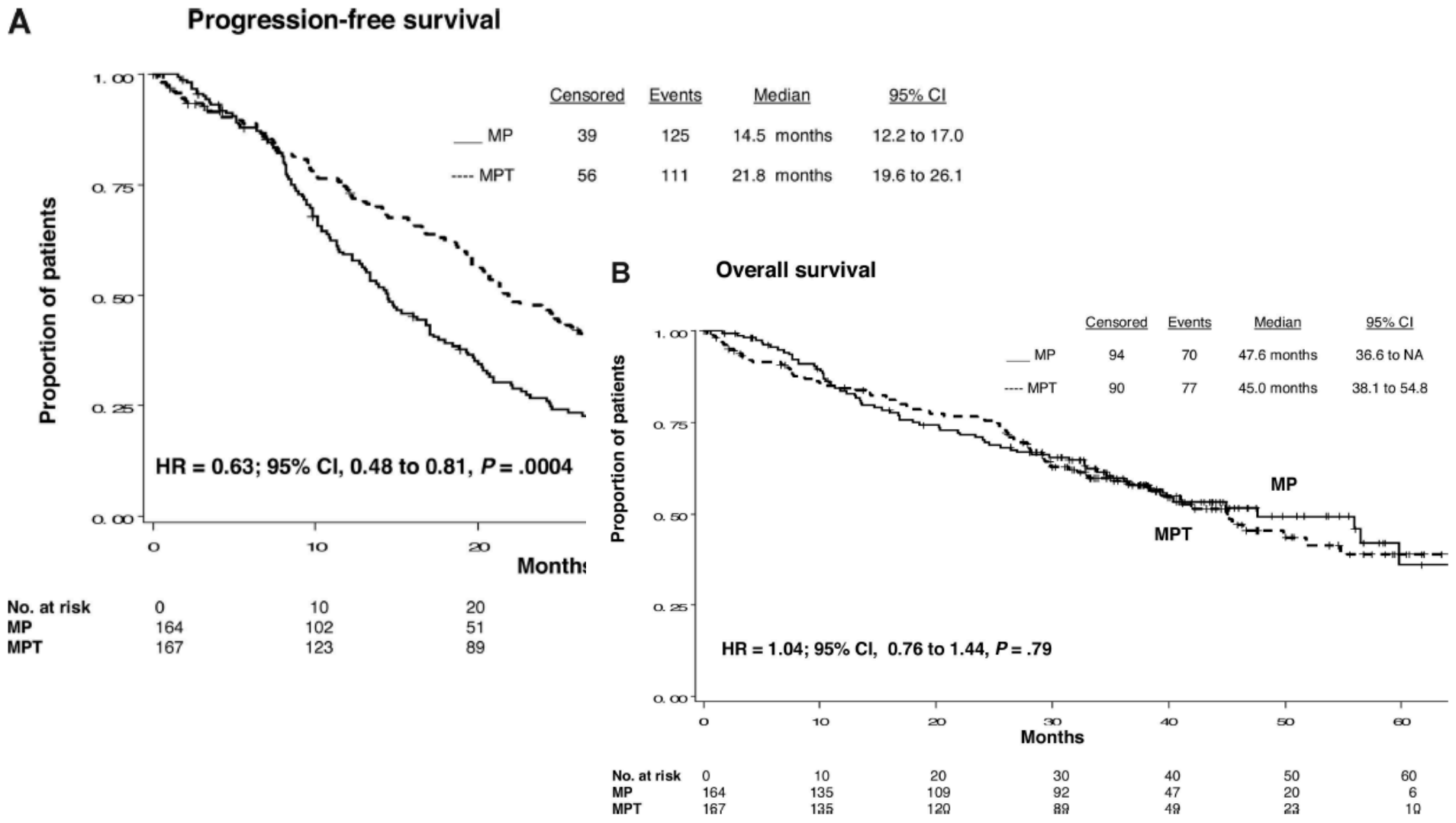
The combination of melphalan–prednisone with thalidomide (100 mg/day) is superior to melphalan–prednisone [I, A].

Melphalan– prednisone plus either thalidomide or bortezomib are the new standards in Europe

NCCN National Comprehensive Cancer Network®

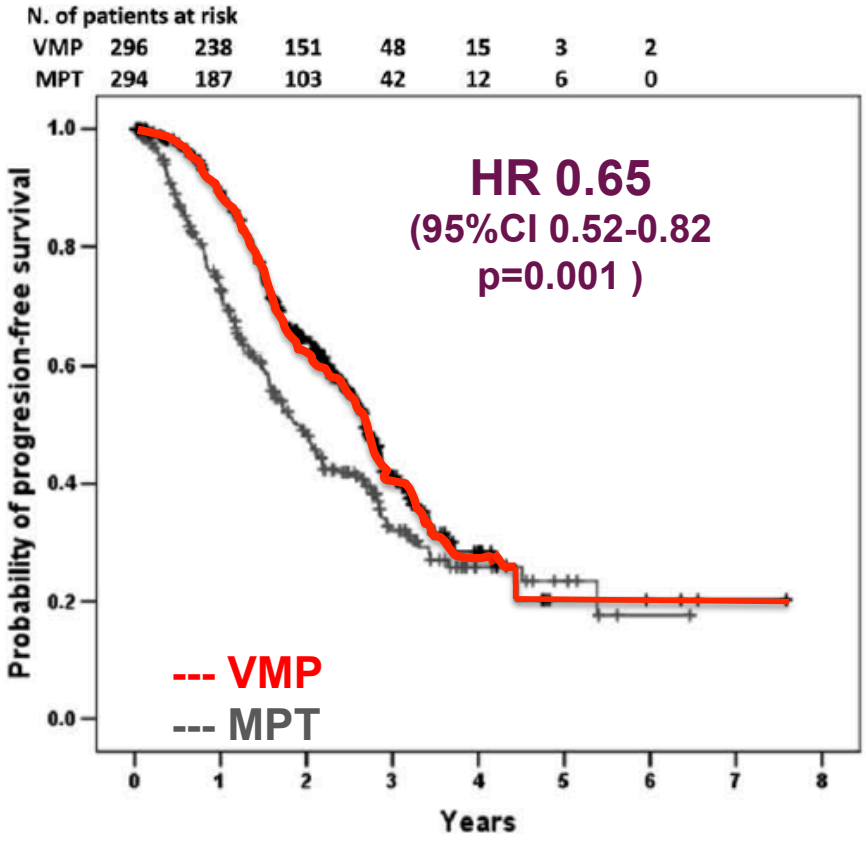
- Primary induction therapy for nontransplant candidates:
  - Dexamethasone (category 2B)
  - Lenalidomide/low-dose dexamethasone (category 1)
  - DVD (category 2B)
  - Melphalan/prednisone (MP)
  - Melphalan/prednisone/bortezomib (MPB; category 1)
  - Melphalan/prednisone/thalidomide (MPT; category 1)
  - Thalidomide/dexamethasone (category 2B)
  - Vincristine/doxorubicin/dexamethasone (VAD; category 2B)

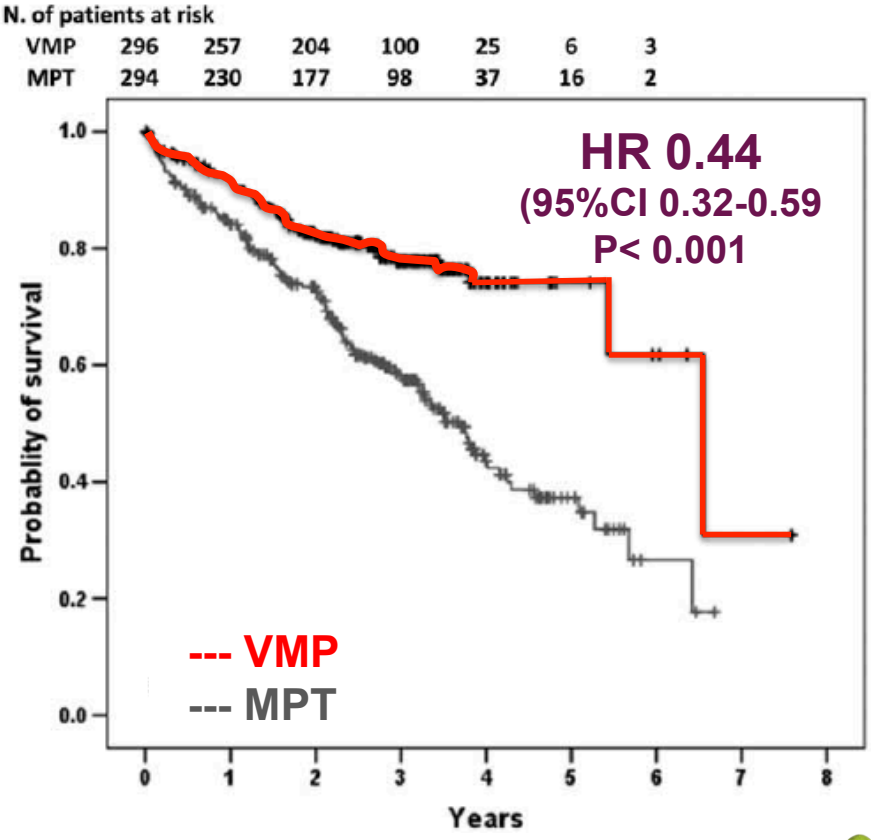
MPT vs MP in 2010



Palumbo A et al , Blood 2008

MPT vs VMP





Morabito F, Am. J. Hematol 2014

The choice of first line: year 2017

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Front-line:

Bortezomib/melphalan/prednisone (VMP) [11]

Lenalidomide/low-dose dexamethasone (Rd) [12]

Melphalan/prednisone/thalidomide (MPT) [13]

Moreau P et al. Annals of Oncology 2017

NCCN National Comprehensive Cancer Network®

Primary Therapy for Non-Transplant Candidates
(assess for response after 2 cycles)

Preferred Regimens	Other Regimens
• Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1)[6,7]	• Bortezomib/dexamethasone[6] • Carfilzomib[10]/lenalidomide/dexamethasone (category 2B) • Ixazomib/lenalidomide/dexamethasone

Kumar S.K et al *J Natl Compr Canc Netw 2017*

Case report: action taken

- **MPT** was started: programmed 8 cycles
- Zolendronic acid

- Adverse events:
  - Neuropathy
  - Bradicardia (cardiologic evaluation required)
  - Hypertension with poor pharmacological control

- After 6 MPT cycles restaging

Our patient's journey

Parameter	Diagnosis (august 2010)	After 6 MPT (Feb 2011)
Hb	10.5 (8.1) g/dl	**13 g/dL**
Bone marrow Plasma cell	Massive infiltration (80%)	**5%**
Monoclonal component	0.5 g/dL IgG k	**Under the limit of det**
Albumin	3.6	3.8
Proteinuria/ BJ	0/+++	0/ **neg**
FLC k/lamb	n.a	n.a
Ca	9.8	9.2
Beta2 microglob	5.2	2.1
IgG	1070	568
Creatinine	0.8	0.7

Restaging: bone marrow, skeleton, blood

- On April 2011 bone marrow plasmacell = **5%**
- CT skeleton: unmodified since diagnosis, **no new osteolytic lesions**
- Situation: **VGPR**
- **Thalidomide as maintenance** 50 mg/die until November 2011 (**14 months**) then stopped

Time goes by so fast...

- February 2012 (**+18 months since start of first line**): CT skeleton unmodified
- Peripheral neuropathy (feet)

- Increased dosage of Pregabalin, vitamin D and B supplementation
- Zolendronic acid continues

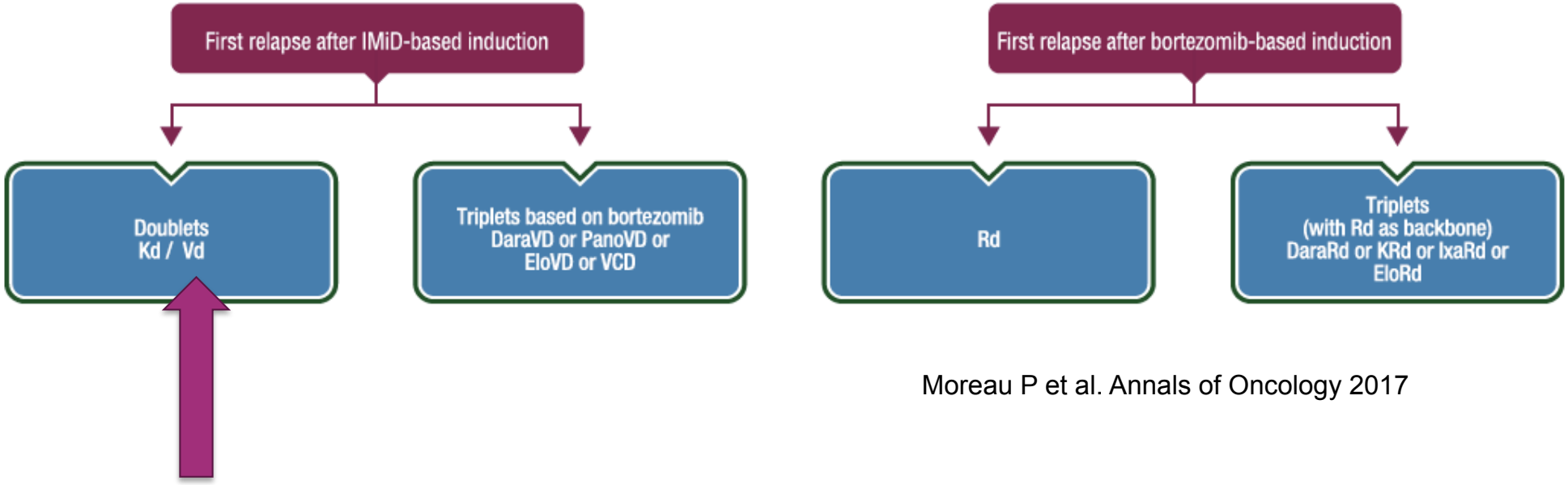
- On May 2013 (**+ 34 months since start of 1° line**):
- Asthenia, **Hb 10.7**
- CT skeleton: **new osteolitic lesion D12**, enlargment of skull lesions

Our patient's journey

Parameter	Diagnosis (august 2010)	After 6 MPT (Feb 2011)	May 2013
Hb	10.5 (8.1) g/dl	13 g/dL	**10.7**
Bone marrow Plasma cell	Massive infiltration (80%)	5%	**Massive infiltration (70%) FISH n.a**
Monoclonal component	0.5 g/dL IgG k	Under the limit of det	**0.3 g/dL**
Albumin	3.6	3.8	4.08
Proteinuria/ BJ	0/+++	0/neg	**0.5 g/24 h; +++**
FLC k/lamb	n.a	n.a	n.a
Ca	9.8	9.2	9.3
Beta2 microglob	5.2		
IgG	1078	568	
Creatinine	0.8	0.7	0.8

First relapse: action taken

- **VD** treatment was scheduled (no proteasome inhibitor given so far)



Moreau P et al. Annals of Oncology 2017

First relapse: action taken

- **VD** treatment was scheduled (no proteasome inhibitor given so far)
- She received **8 cycles of VD**
- Side effects: peripheral neuropathy unchanged

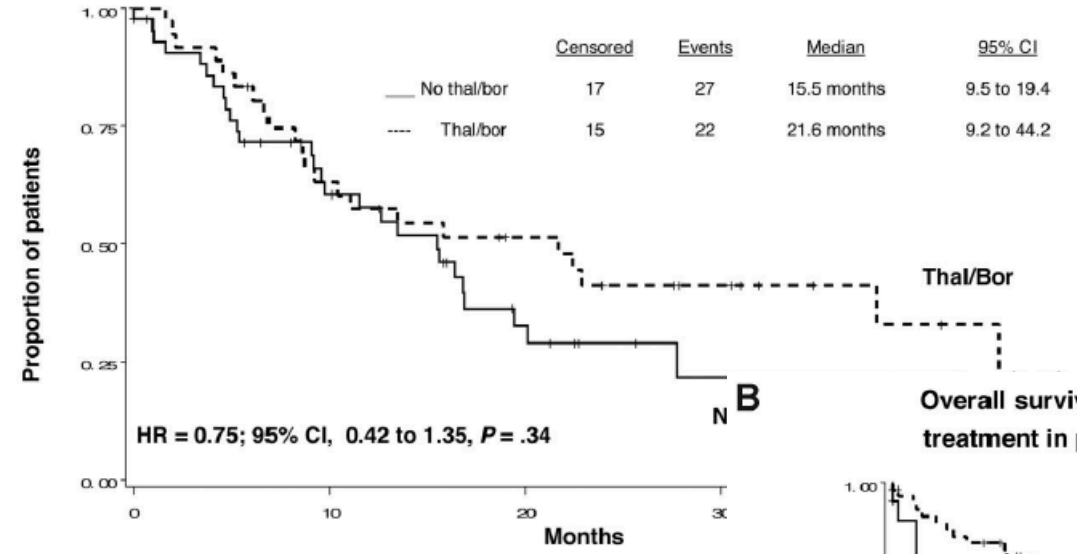
- **Pneumonia**: 2 episodes, required antibiotics, no hospital admission

- **Restaging on February 2014**: stable disease/minimal response

Salvage therapy after MPT or MP

C

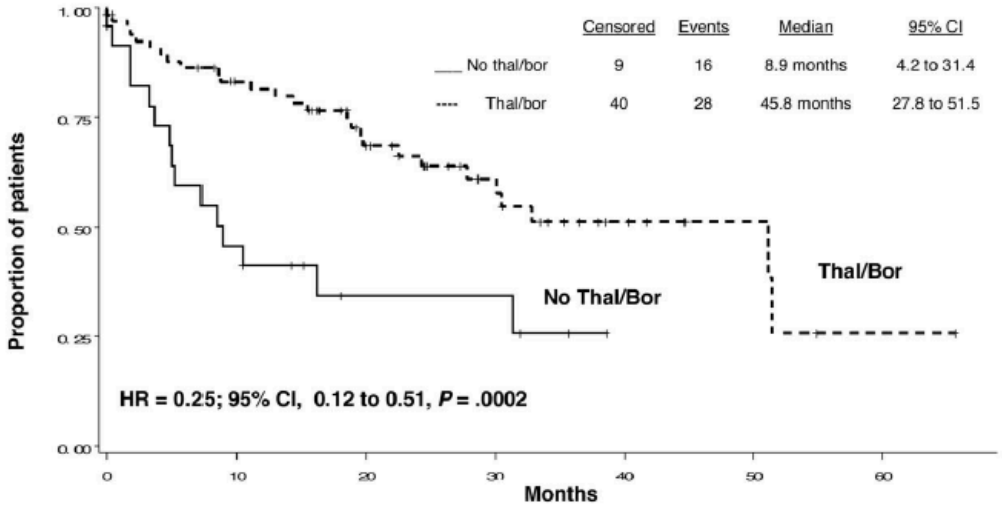
Overall survival from relapse according to thalidomide/bortezomib salvage treatment in MPT patients



No. at risk	0	10	20
No thal/bor	44	22	9
Thal/bor	37	22	15

B

Overall survival from relapse according to thalidomide/bortezomib salvage treatment in patients given MP



No. at risk	0	10	20	30	40	50	60
No thal/bor	25	10	4	4	0	0	0
Thal/bor	68	55	37	22	11	4	1

Palumbo A et al , Blood 2008

Our patient's journey

Parameter	Diagnosis (august 2010)	After 6 MPT (Feb 2011)	May 2013	Feb 2014
Hb	10.5 (8.1) g/dl	13 g/dL	9.8 g/dL	**11.1**
Bone marrow Plasma cell	Massive infiltration (80%)	5%	Massive infiltration (70%)	**40%**
Monoclonal component	0.5 g/dL IgG k	Under the limit of det	0.3 g/dL	**0.3 g/dL**
Albumin	3.6	3.8	4.08	
Proteinuria/ BJ	0/+++	0/neg	0.5 g/24 h; +++	**0.5 g/24 h +++**
FLC k/lamb	n.a	n.a	n.a	n-.a
Ca	9.8	9.2	9.3	9.0
Beta2 microglob	5.2			
IgG				
Creatinine	0.8	0.7	0.8	0.7

1° relapse: start VD

Follow up and third line

- On may 2014: decrease of Hb, increase of proteinuria
- Screening for thrombophilia was negative

- **Third line** was started: **RD** + LMWH

Our patient's journey

Parameter	Diagnosis (august 2010)	After 6 MPT (Feb 2011)	May 2013	Feb 2014	May 2014
Hb	10.5 (8.1) g/dl	13 g/dL	9.8 g/dL	**11.1**	**9.0 g/dL**
Bone marrow Plasma cell	Massive infiltration (80%)	5%	Massive infiltration (70%)	**40%**	
Monoclonal component	0.5 g/dL IgG k	Under the limit of det	0.3 g/dL	**0.3 g/dL**	**0.6 g/dL**
Albumin	3.6	3.8	4.08		
Proteinuria/BJ	0/+++	0/neg	0.5 g/24 h; ++ +	**0.5 g/24 h +++**	**0.8 g/24 h +++++**
FLC k/lamb	n.a	n.a	n.a	n-.a	1203/5.5
Ca	9.8	9.2	9.3	9.0	9.3
Beta2 microglob	5.2				
IgG					
Creatinine	0.8	0.7	0.8	0.7	0.8

1° relapse: start VD

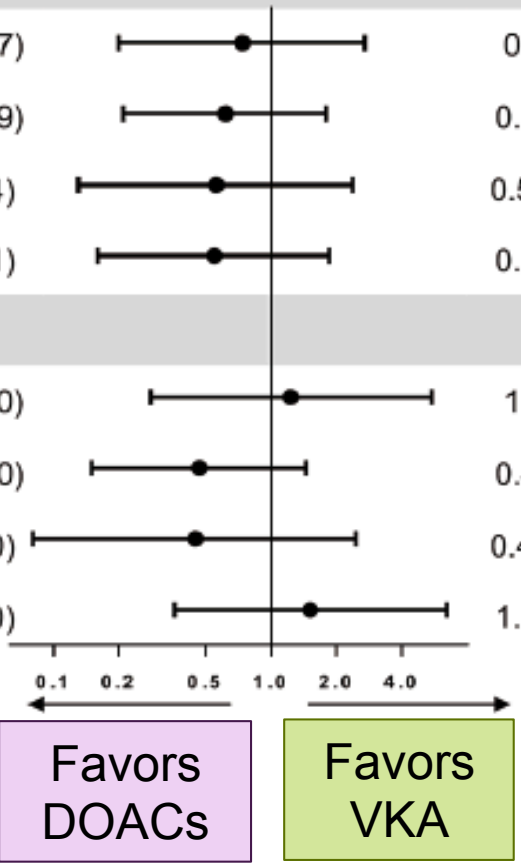
2° relapse: start RD

Follow up during 3rd line

- **Progressive decrease** of proteinuria
- Switch LMWH -> **ASA after 6 cycles**
- On december 2014 (during cycle n 9) she went **in Brazil for 2 months**
- She started again observation on Feb 2015
- On **April 2015** (during **RD cycle n 11**) **deep vein thrombosis** (femoral common and superficial vein, popliteal vein -> LMWH full dose
- **RD was stopped and restarted on June 2015**

Anticoagulant therapy in cancer patients

Study		Event Rate, n/N (%) DOAC	VKA	HR (95% CI)
Recurrent VTE				
RE-COVER I+II[57]	Dabigatran (150 mg BID)	4/114 (3.5)	5/107 (4.7)	0.74 (0.20–2.7)
EINSTEIN DVT+PE[54]	Rivaroxaban (20 mg OD)[a]	6/258 (2.3)	8/204 (3.9)	0.62 (0.21–1.79)
AMPLIFY[55]	Apixaban (5 mg BID)[b]	3/81 (3.7)	5/78 (6.4)	0.56 (0.13–2.37)[c]
HOKUSAI-VTE[56]	Edoxaban (60 mg OD)[d]	4/109 (3.7)	7/99 (7.1)	0.55 (0.16–1.85)
Major Bleeding				
RE-COVER I+II[57]	Dabigatran (150 mg BID)	4/105 (3.8)	3/100 (3.0)	1.23 (0.28–5.5)
EINSTEIN DVT+PE[54]	Rivaroxaban (20 mg OD)[a]	5/257 (1.9)	8/202 (4.0)	0.47 (0.15–1.45)
AMPLIFY[55]	Apixaban (5 mg BID)[b]	2/87 (2.3)	4/80 (5.0)	0.45 (0.08–2.46)[c]
HOKUSAI-VTE[56]	Edoxaban (60 mg OD)[d]	5/109 (4.6)	3/99 (3.0)	1.52 (0.36–6.43)



Ay C, et al. ESMO Open 2017

DOACs and Multiple Myeloma

- Only 1 retrospective study on **IMIDs** and concomitant **warfarin or DOACs**
- Data on DVT treatement in solid cancer with VKA or DOACs are definitely **not valid also for Multiple Myeloma**
- **Ongoing clinical trials** comparing VKA and DOACS **may not include** an appropriate number of **patients with MM**
- Specific clinical trial on MM **are warranted**

The long course of 3rd line

- **RD star**
- After DVT episod recorded
- Good performa of life perceived as good (**General H**
- On **October 201** **dose reduced** (15 mg)
- CT skeleton on J s
- **On April 2017 (3**

Results RAND 36-Item Health Survey v1.0

Physical functioning:
65%

Role limitations due to physical health:
100%

Role limitations due to emotional problems:
100%

Energy/fatigue:
55%

Emotional well-being:
68%

Social functioning:
63%

Pain:
68%

General health:
50%

Health change:
50%

Our patient's journey

Parameter	Diagnosis (august 2010)	After 6 MPT	May 2013	April 2014	May 2014	April 2017
Hb	10.5 (8.1) g/dl	13 g/dL	9.8		9 g/dL	**8.2 g/dL**
Bone marrow Plasma cell	Massive infiltration (80%)	5%	Mas infilt (70%			**Massive infiltration (90%)**
Monoclonal component	0.5 g/dL IgG k	Under the limit of det	0.3 g/dL	0.6 g/dL	0.6 g/dL	0.4 g/dL
Albumin	3.6	3.8	4.08			
Proteinuria/ BJ	0/+++	0/neg	0.5 g/24 h; +++	0.5 g/24 h + +++	0.8 g/24 h + +++	**1 g/24 h ++ ++**
FLC k/lamb	n.a	n.a	n.a	n-.a	1203/5.5	**1609; 29.2**
Ca	9.8	9.2	9.3	9.0		9.0
Beta2 microglob	5.2					
IgG						969
Creatinine	0.8	0.7	0.8	0.7		0.7

7 years

78 years old

1° relapse: start VD

2° relapse: start RD

3° relapse:

MM Frailty score, PFS, OS and toxicities

MYELOMA FRAILTY SCORE CALCULATOR

Developed by International Myeloma Working Group for the prognosis of elderly myeloma patients.

The score system (range 0-5), based on age, comorbidities, cognitive and physical conditions, developed by Palumbo A. et al[1], identifies 3 groups of patients:

- fit (score=0)
- intermediate-fitness (score=1)
- frail (score≥2)

The 3-year overall survival was 84% in fit patients, 76% in intermediate-fitness patients (HR 1.61, 95%CI 1.02-2.56, p=0.042) and 57% in frail patients (HR 3.57 CI 95% 2.37-5.39, p<0.001). The cumulative incidence of grade ≥3 non-hematologic adverse events at 12 months was 22.2% in fit, 26.4% in intermediate-fitness (HR 1.23, 95%CI 0.89-1.71; p 0.217) and 34.0% (HR 1.74, 95%CI 1.28-2.38; p<0.001) in frail patients. The cumulative incidence of treatment discontinuation at 12 months was 16.5% in fit, 20.8% in intermediate-fitness (HR 1.41, 95%CI 1.00-2.01, p=0.052) and 31.2% (HR 2.21, 95%CI 1.57-3.09; p<0.001) in frail patients.

This frailty score predicts mortality and the risk of toxicity in elderly myeloma patients. The International Myeloma Working group proposes this score for the measurement of frailty in the treatment decision-making process and in designing future clinical trials.

[1]Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015 Mar 26;125(13):2068-7

Supported by FO.NE.SA onlus

Click here to calculator

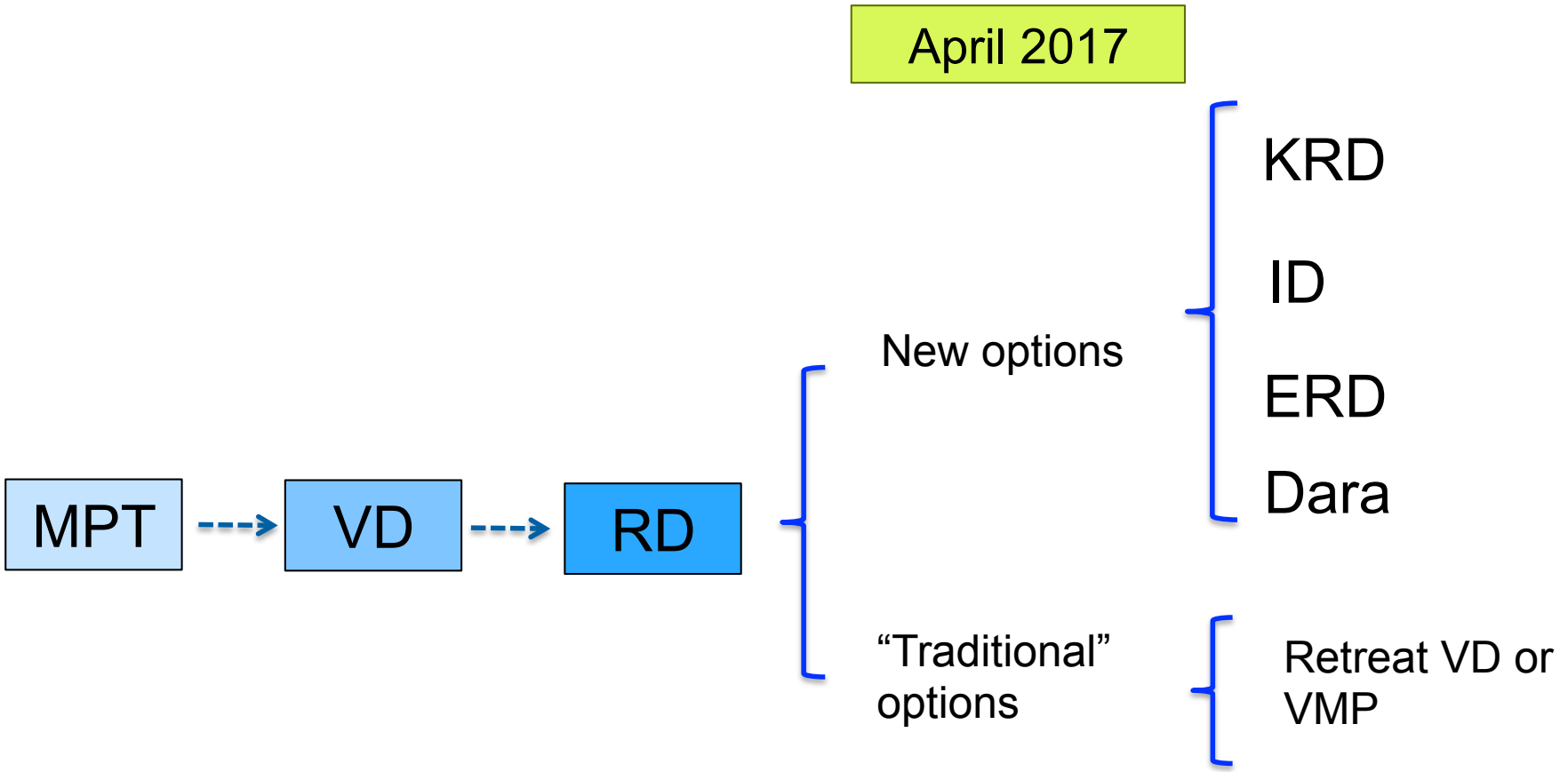
MM Frailty score, PFS, OS and toxicities

Table 3. Additive total score and related rate of OS and PFS at 3 years

Additive total score	Patient status	No. of patients (%)	% (95% CI)		Cumulative incidence at 12 mo, %	
			OS	PFS	Treatment discontinuation	Grade 3-4 nonhematologic AEs
0	Fit	340 (39)	84 (78-89)	48 (41-56)	16	22
1	Intermediate-fitness	269 (31)	76 (67-82)	41 (32-49)	21	26
≥2	Frail	260 (30)	57 (45-68)	33 (25-41)	31	34

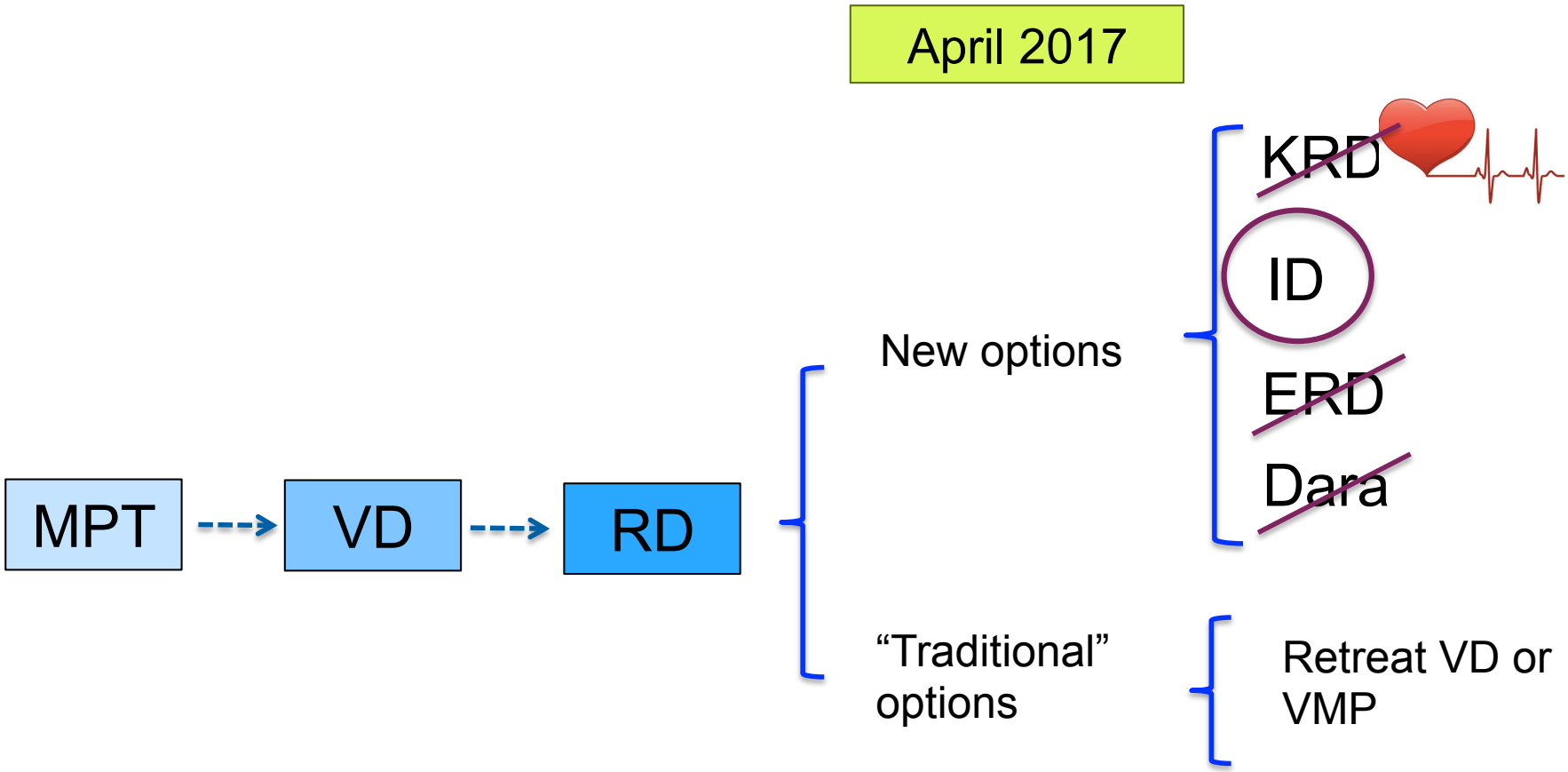
Palumbo A, Blood 2015

Progression: time to 4th line



Ti Piace Vincere Facile?

Progression: time to 4th line



Our patient's journey

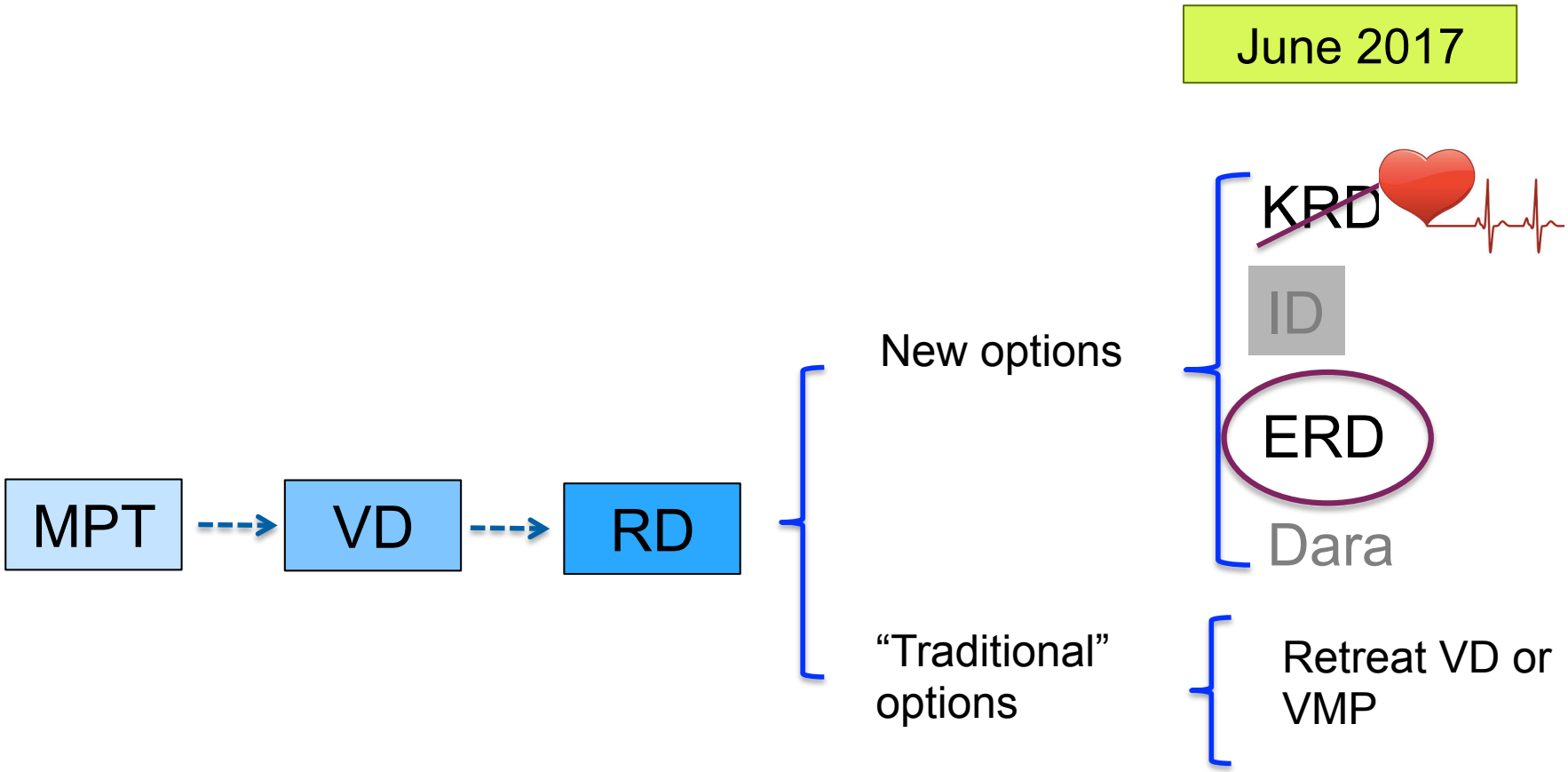
Parameter	Diagnosis (august 2010)	After 6 MPT (Feb 2011)	May 2013	April 2014	May 2014	April 2017	June 2017 (after 2 ID cycles)
Hb	10.5 (8.1) g/dl	13 g/dL	9.8 g/dL	11.1	9 g/dL	8.2 g/dL	**9.0 g/dL**
Bone marrow Plasma cell	Massive infiltration (80%)	5%	Massive infiltration (70%)	40%		Massive infiltration (90%)	
Monoclonal component	0.5 g/dL IgG k	Under the limit of det	0.3 g/dL	0.6 g/dL	0.8 g/dL	0.4 g/dL	**0.3 g/dL**
Albumin	3.6	3.8	4.08				
Proteinuria/ BJ	0/+++	0/neg	0.5 g/24 h; +++	0.5 g/24 h + +++	0.8 g/24 h + +++	1 g/24 h ++ ++	**1.1 g/24 h**
FLC k/lamb	n.a	n.a	n.a	n-.a	n.a	1609; 29,2	**2058;**
Ca	9.8	9.2	9.3	9.0		9.0	
Beta2 microglob	5.2						
IgG						969	
Creatinine	0.8	0.7	0.8	0.7		0.7	

1° relapse: start VD

2° relapse: start RD

3° relapse: ID

No response to ID: time to 5th line

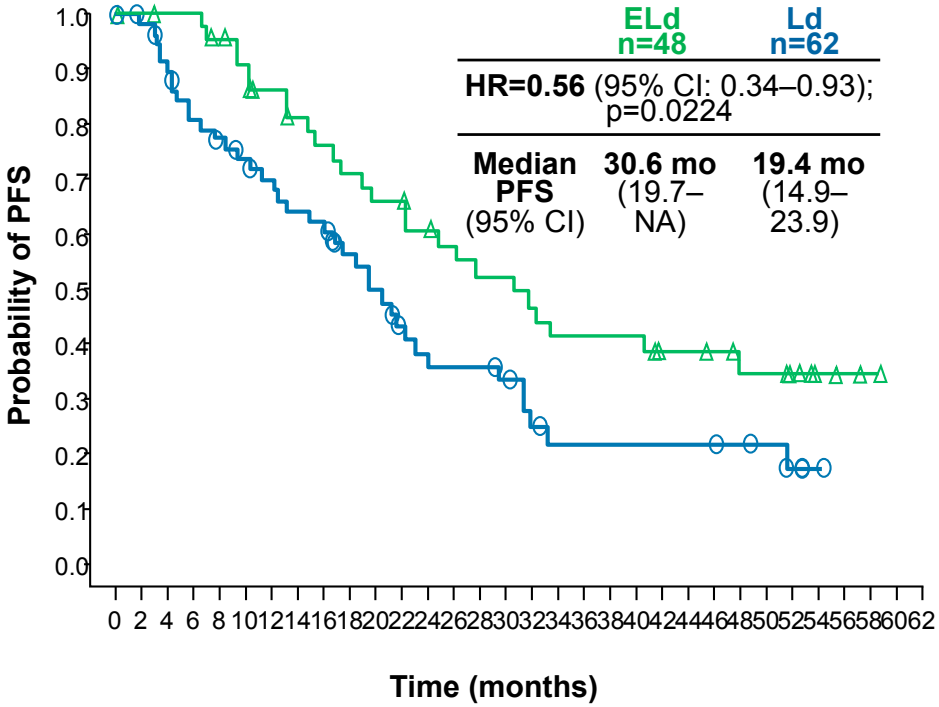


Progression-Free Survival – Median Time Since Diagnosis (3.5 years) and Prior Lines of Therapy

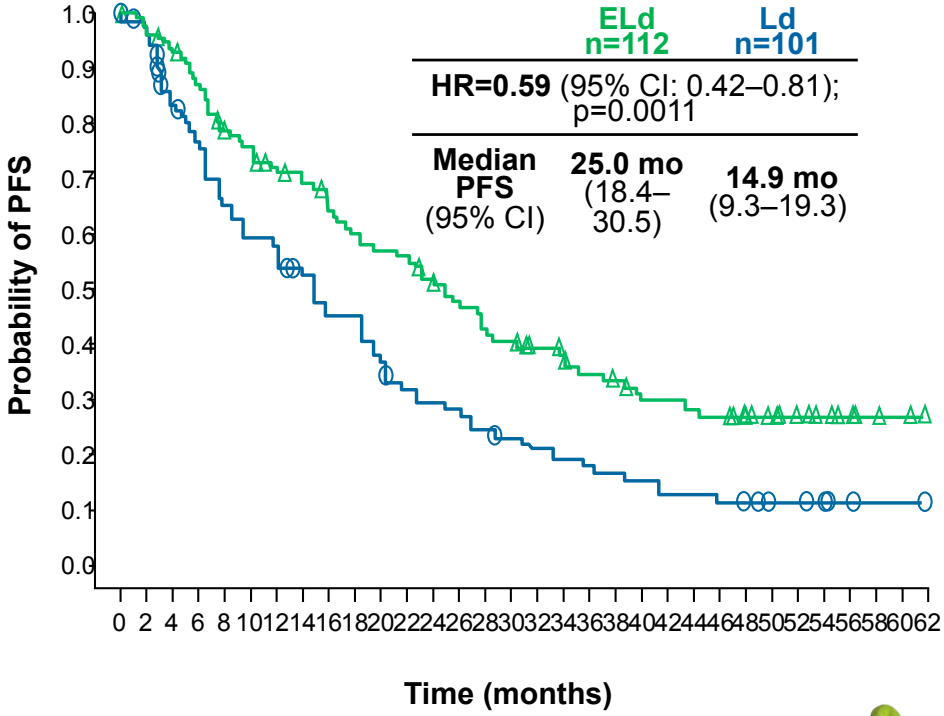
ELOQUENT-2: 4-Year Follow-up

≥Median time from diagnosis

1 prior line of therapy



>1 prior line of therapy



- **Greatest benefit in patients with ≥3.5 years (median time) since diagnosis and 1 prior line of therapy**
- **44% reduction in the risk of progression or death**

NA, not available

ELOQUENT 2: Baseline Demographics and Disease Characteristics

Characteristic	E-Ld (n=321)	Ld (n=325)
Prior regimens, median (range)	2 (1–4)	2 (1–4)
Prior therapies, %		
Bortezomib	68	71
Melphalan*	69	61
Thalidomide	48	48
Lenalidomide†	5	7
Response to most recent line of therapy, %‡		
Refractory	35	35
Bortezomib refractory	22	21
Thalidomide refractory	9	11
Relapsed	65	65
Prior stem cell transplantation, %	52	57

*Oral or intravenous. †Prior lenalidomide was permitted if best response was ≥partial response and patients were not refractory to prior lenalidomide treatment; patients could not receive more than 9 cycles of lenalidomide and had at least 9 months between the last dose of lenalidomide and progression. ‡One patient in the elotuzumab group had an unknown response to the most recent line of therapy

Our patient's journey

Parameter	Diagnosis (august 2010)	After 6 MPT (Feb 2011)	May 2013	April 2014	May 2014	April 2017	June 2017 (after 2 ID cycles)
Hb	10.5 (8.1) g/dl	13 g/dL	9.8 g/dL	11.1	9 g/dL	8.2 g/dL	**9.0 g/dL**
Bone marrow Plasma cell	Massive infiltration (80%)	5%	Massive infiltration (70%)	40%		Massive infiltration (90%)	
Monoclonal component	0.5 g/dL IgG k	Under the limit of det	0.3 g/dL	0.6 g/dL	0.8 g/dL	0.4 g/dL	**0.3 g/dL**
Albumin	3.6	3.8	4.08				
Proteinuria/ BJ	0/+++	0/neg	0.5 g/24 h; +++	0.5 g/24 h + +++	0.8 g/24 h + +++	1 g/24 h ++ ++	**1.1 g/24 h**
FLC k/lamb	n.a	n.a	n.a	n-.a	n.a	1609; 29,2	**2058;**
Ca	9.8	9.2	9.3	9.0		9.0	
Beta2 microglob	5.2						
IgG						969	
Creatinine	0.8	0.7	0.8	0.7		0.7	

1° relapse: start VD

2° relapse: start RD

3° relapse: ID

4° relapse: ERD

Our patient's journey

Parameter	May 2014	April 2017	June 2017 (after 2 ID cycles)
Hb	9 g/dL	8.2 g/dL	**9.0 g/dL**
Bone marrow Plasma cell		Massive infiltration (90%)	
Monoclonal component	0.8 g/dL	0.4 g/dL	**0.3**
Albumin			
Proteinuria/BJ	0.8 g/24 h ++++	1 g/24 h +++ +	**1.1 g/24 h**
FLC k	n.a	1609	**2058;**
Ca		9.0	
Beta2 microglob			
IgG		969	
Creatinine		0.7	0.7

2° relapse: start RD

3° relapse: ID

4° relapse: ERD

Our patient's journey

Parameter	May 2014	April 2017	June 2017 (after 2 ID cycles)	August 2017 (after 2 cycles ERD)
Hb	9 g/dL	**8.2 g/dL**	**9.0 g/dL**	**9.1 g/dL**
Bone marrow Plasma cell		**Massive infiltration (90%)**		
Monoclonal component	0.8 g/dL	**0.4 g/dL**	**0.3 g/dL**	**0.4 g/dL**
Albumin				
Proteinuria/BJ	0.8 g/24 h ++++	**0.9 g/24 h ++++**	**1.1 g/24 h**	**1.2 g/24 h**
FLC k	n.a	**1609**	**2058**	**2158**
Ca	9.1	9.0	9.0	9.1
Beta2 microglob				
IgG		969		
Creatinine		0.7	0.7	0.8

Our patient's journey

Parameter	May 2014	April 2017	June 2017 (after 2 ID cycles)	August 2017 (after 2 cycles ERD)	September 2017 (after 4 ERD cycles)
Hb	9 g/dL	**8.2 g/dL**	**9.0 g/dL**	**9.1 g/dL**	**9.4 g/dL**
Bone marrow Plasma cell		**Massive infiltration (90%)**			
Monoclonal component	0.8 g/dL	**0.4 g/dL**	**0.3 g/dL**	**0.4 g/dL**	**0.3 g/dL**
Albumin					
Proteinuria/BJ	0.8 g/24 h ++++	**0.9 g/24 h ++++**	**1.1 g/24 h**	**1.2 g/24 h**	**0.8 g/24 h**
FLC k	n.a	**1609**	**2058**	**2158**	**2449**
Ca	9.1	9.0	9.0	9.1	9.0
Beta2 microglob					
IgG		969			
Creatinine		0.7	0.7	0.8	0.7

2° relapse: start RD

3° relapse: ID

4° relapse: ERD

Our patient's journey

Parameter	May 2014	April 2017	June 2017 (after 2 ID cycles)	August 2017 (after 2 cycles ERD)	September 2017 (after 4 ERD cycles)	October 2017 (after 5 ERD cycles)
Hb	9 g/dL	**8.2 g/dL**	**9.0 g/dL**	**9.1 g/dL**	**9.4 g/dL**	**9.0 g/dL**
Bone marrow Plasma cell		**Massive infiltration (90%)**				
Monoclonal component	0.8 g/dL	**0.4 g/dL**	**0.3 g/dL**	**0.4 g/dL**	**0.3 g/dL**	**0.2 g/dL**
Albumin						
Proteinuria/BJ	0.8 g/24 h ++++	**0.9 g/24 h ++++**	**1.1 g/24 h**	**1.2 g/24 h**	**0.8 g/24 h**	**0.2 g/24 h**
FLC k	n.a	**1609**	**2058**	**2158**	**2449**	**1467**
Ca	9.1	9.0	9.0	9.1	9.0	
Beta2 microglob						
IgG		969				
Creatinine		0.7	0.7	0.8	0.7	0.6

2° relapse: start RD

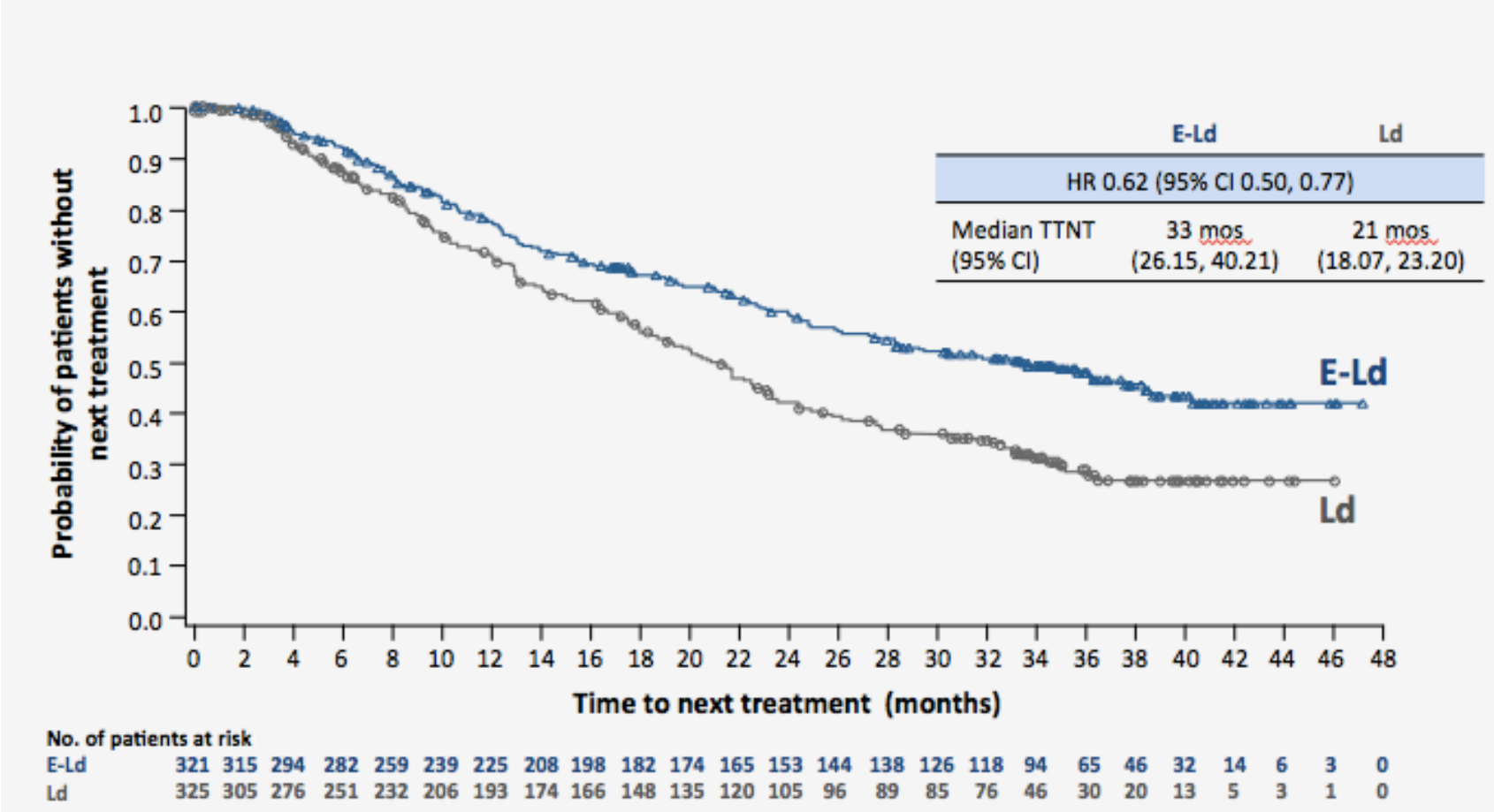
3° relapse: ID

4° relapse: ERD

Our patient's journey...?

- Subject quality of life slightly better...
- Stable neuropathy
- No infectious adverse events

Time to next treatment



ELOQUENT 2

Open questions

- What about next line of therapy, if needed (and if possible..)?
- How to choose RRMM treatment sequence in the era of multiple available therapies?

Quando la scelta è ampia...

Grazie per l'attenzione