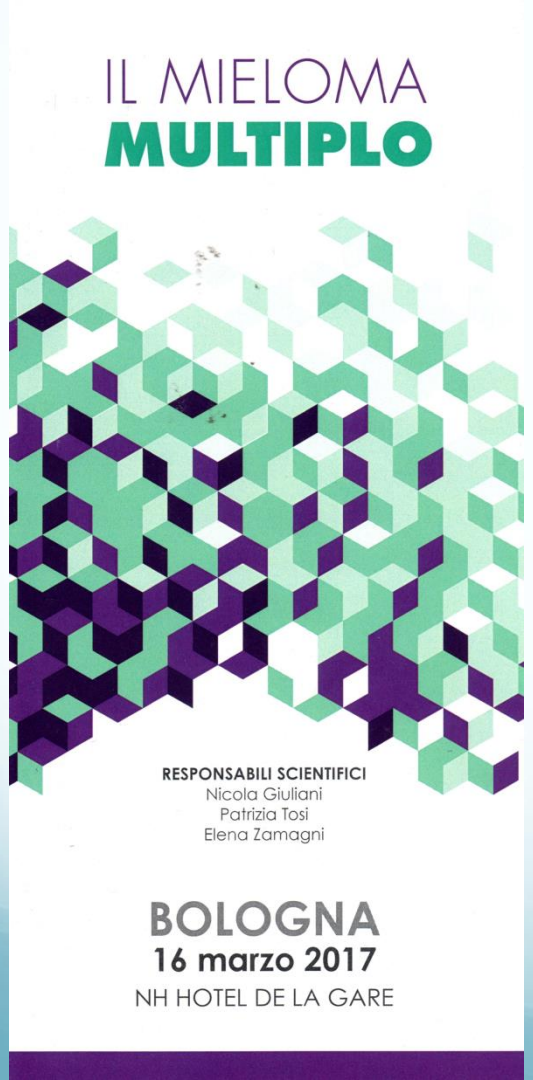


CASO CLINICO
La gestione del paziente con Mieloma Multiplo

Nicola Giuliani

Bologna 16 marzo 2017

Caso clinico - I

- ♂, 55 anni
- Comorbidità/principali dati anamnestici:
  - Fumatore
  - DM tipo II, ipertensione arteriosa, ipercolesterolemia, vasculopatia
  - GERD
- Gennaio 2008: primo riscontro di gammopatia monoclonale IgG kappa

Caso clinico - II

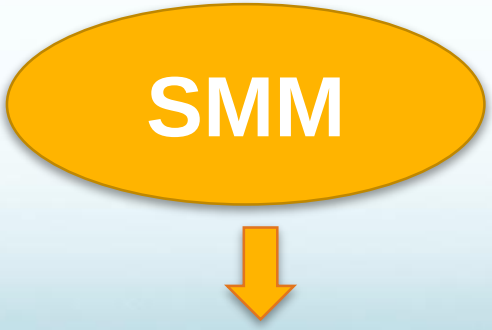
- Esami diagnostici:
  - Bioumorali →
    - ✓ Hb14.8 g/dL, creatinina 0.8 mg/dL, calcemia 9.4 mg/dL, beta2-microglobulina 2.6 mg/L
    - ✓ ELF: gamma globuline 24%, CM IgG kappa 1.6 g/dL, immunoparesi IgA/IgM,
  - BOM: infiltrato plasmacellulare monotipico kappa pari al 25% della cellularità midollare totale
  - Strumentali →
    - ✓ Rx scheletrico in toto: negativo per lesioni litiche

Come proseguire l'iter diagnostico-tp?

1. Diagnosi di SMM: paziente avviato a follow-up
2. Diagnosi di MM: inizio terapia di I linea
3. Proseguo con le indagini di II livello

Caso clinico - III

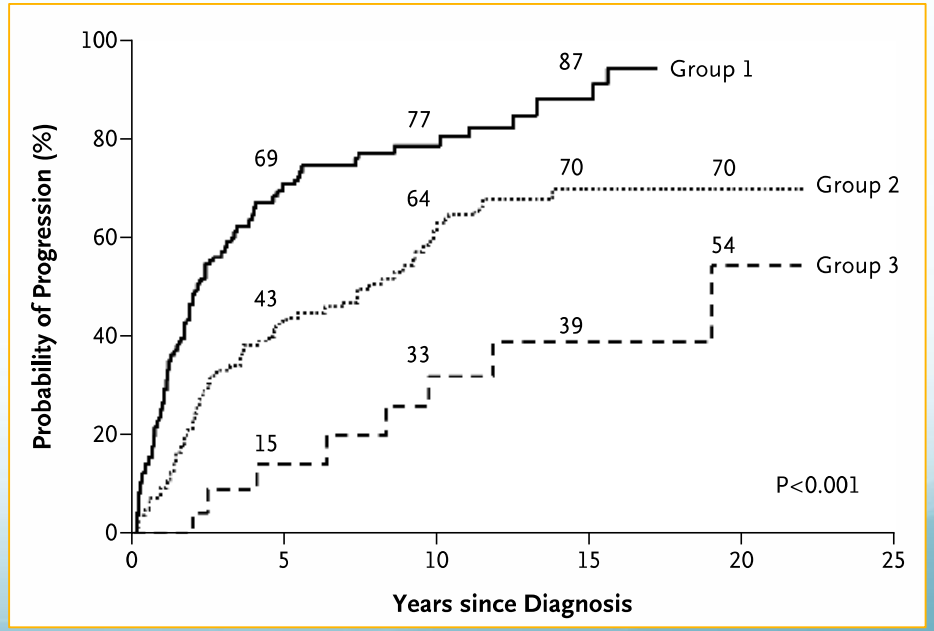
- Esami diagnostici di II livello:
  a) RMN rachide: **2** lesioni focali (D6 e L4)
  b) PET/TC total-body: non aree ad aumentata attività metabolica, non segnalata osteolisi alle immagini TC
  c) Dosaggio Free Light Chain → non disponibile a Parma nel 2008…



Paziente avviato a follow-up

Risk of progression in SMM – Mayo model

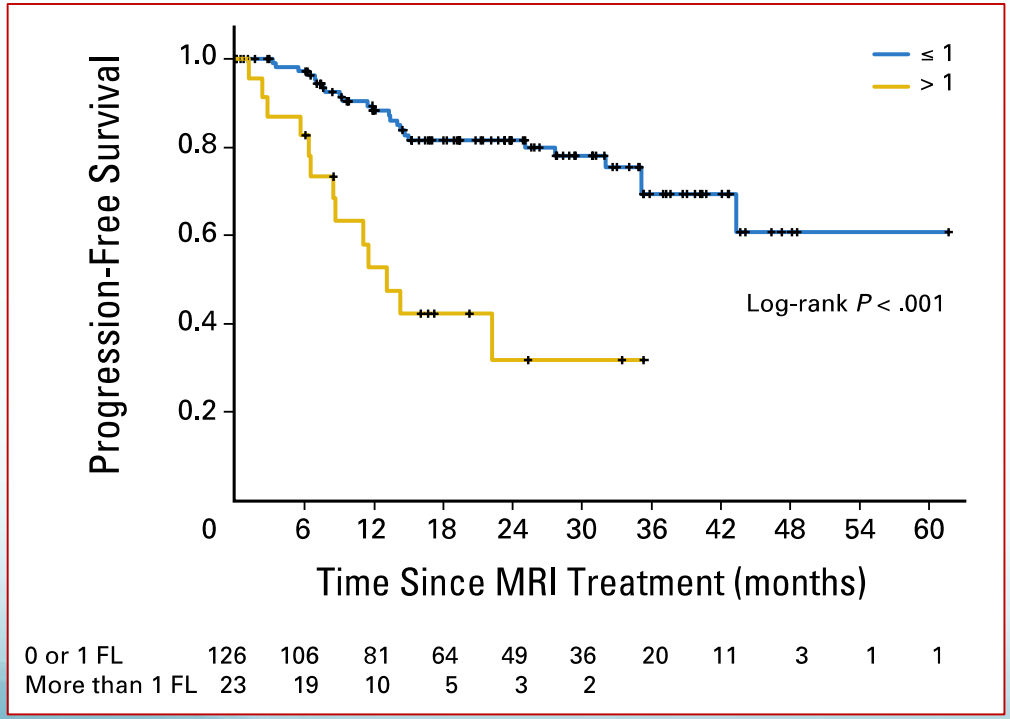
Risk factors		Median TTP, years
≥ 10% clonal BMPC infiltration	1 factor	10
≥ 3 g/dl of serum M-protein	2 factors	5
Serum FLC ratio ≤ 0.125 or ≥ 8	3 factors	1.9



Kyle RA et al, NEJM, 2007

MM biomarkers of malignity

3. Focal lesion >1 on MRI studies



Median time to progression was not reached (last event at 43 months) for the patient group with no or one FL and 13 months for the patient group with greater than one FL, respectively.

Hillengass J, JCO, 2010

IMWG 2014 updated criteria – SMM

Both criteria must be met:

1. Serum monoclonal protein (IgG or IgA) ≥ 30 g/L or urinary monoclonal protein ≥ 500 mg per 24h and/or clonal bone marrow plasma cells 10-60%
2. Absence of myeloma defining events or amyloidosis

CRAB criteria

Biomarkers of malignity:

- ✓ Clonal BM plasma cells ≥ 60%
- ✓ Involved/uninvolved serum FLC ratio ≥ 100
- ✓ Focal lesions > 1 on MRI studies

Rajkumar SV, Lancet Oncol, 2014

Caso clinico - IV

- Marzo 2012 8 (58 anni): dolore acuto al rachide e riscontro di frattura vertebrale di **D6**→ cifoplastica con biopsia: localizzazione di plasmocitoma

- RISTADIAZIONE:
  - Esami bioumorali →
    - ✓ anemia normocitica (Hb 10 g/dL), creatininemia 1.2 mg/dL, calcemia 9.8 mg/dL, LDH 410 U/L, beta2-microglobulina 7.7 mg/L
    - ✓ Gamma globuline 31.6%, CM IgG κ 2.8 g/dL, IgG 3220 mg/dL con retroinibizione di IgG e IgM, free κ 520 mg/L, free λ 26.3 mg/L, rFLC 19.77
  - BOM → infiltrato plasmacellulare monotipico kappa pari al 40% della cellularità midollare totale

Caso clinico - V

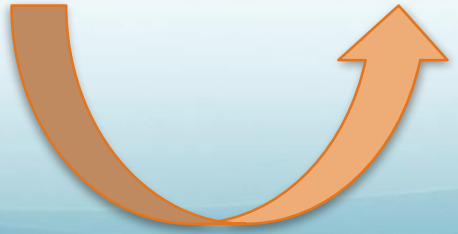
- FISH → non iperdiploide, neg del(13q), del(17p), pos t(4;14), neg Ampl 1q21 e del 1p32
- Valutazione scheletrica →
  - ✓ Rx scheletro in toto: areole a stampo di rarefazione ossea a livello delle diafisi omerali
  - ✓ RMN vertebrale: Collasso D6 e riduzione 40% del soma di L3, micro-disomogeneità di aspetto diffuso a livello del sacro e bacino
  - ✓ PET/TC: iperaccumulo in sede omerale dx (SUV 2.2), L2 e L3 (SUV max 3.7)

Symptomatic MM
ISS III
(R-ISS III)

Prognostic factors in MM

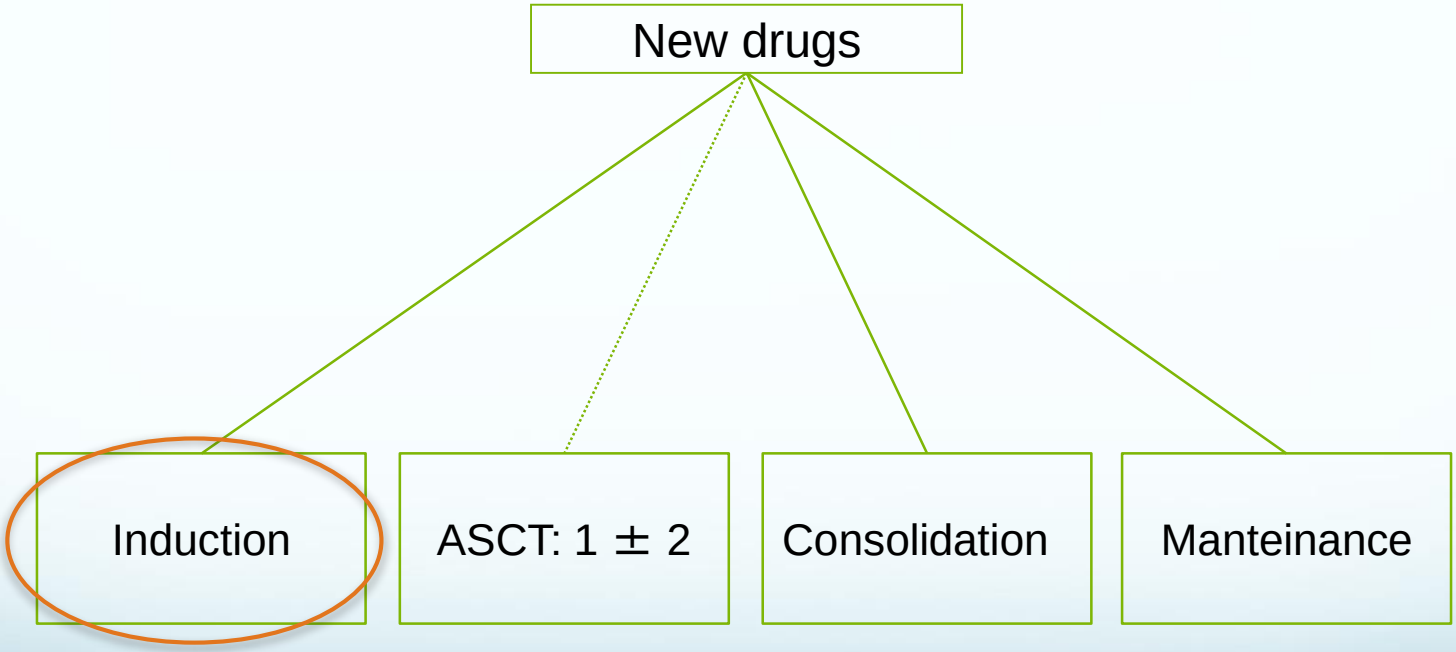
Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal

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



Palumbo A et al, JCO 2015

Frontline treatment – young patients



Caso clinico – VI
Induction therapy: VTD

- VTD (schema protocollo Cavo[1,2]):
  - Bortezomib 1.3 mg/m^2 day 1; 4; 8; 11
  - Thalidomide 100 mg/die day 1-14, 200 mg/die
  - Desametasone 40 mg day 1-2; 4-5; 8-9; 11-12

  → Ogni 21 giorni per 3 cicli

[1] Cavo M et al, Lancet 2010; [2] Cavo M et al, Blood 2011

Caso clinico - VII

- Aprile – luglio 2012: 3 cicli secondo schema VTD
- Principali AE: neuropatia grado II
- Risposta dopo induzione (IMWG 2006): **VGPR**

Table 2. International Myeloma Working Group Response Criteria[a]

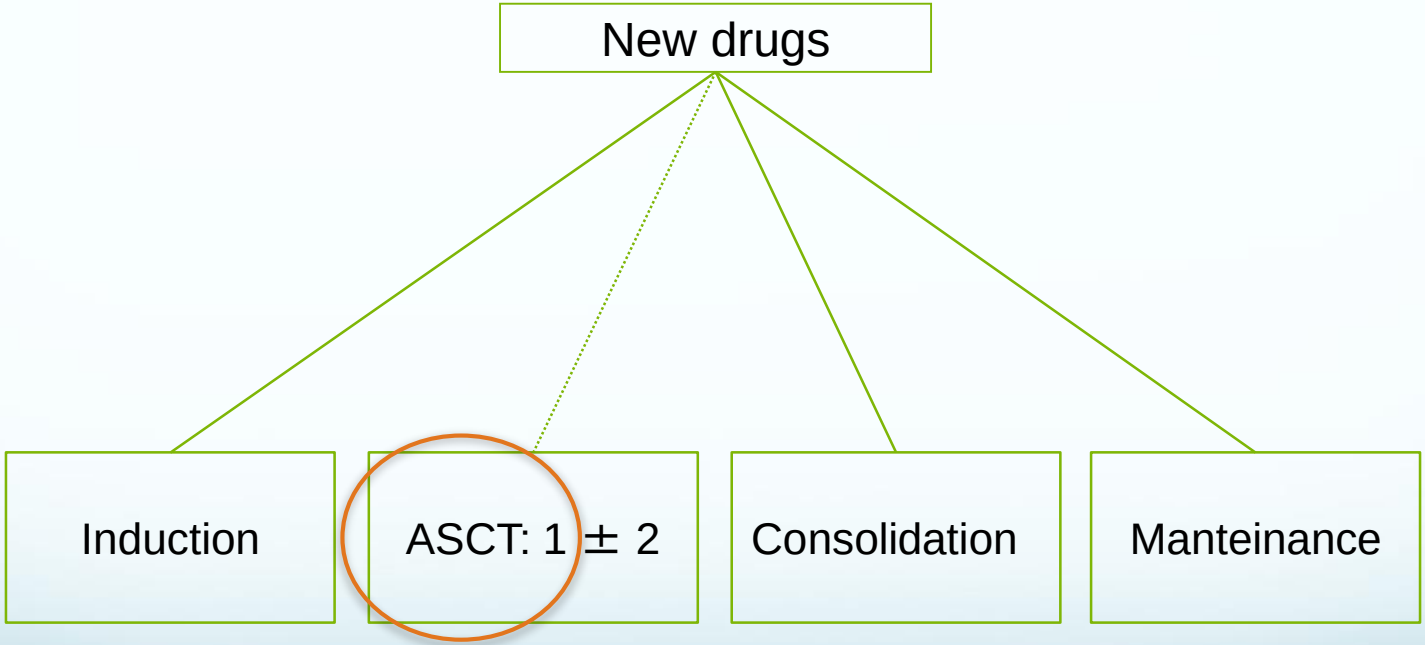
sCR	CR as defined below plus: Normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
CR	Negative immunofixation on the serum and urine plus disappearance of any soft-tissue plasmacytomas and < 5% plasma cells in bone marrow
VGPR	Serum and urine M protein detectable by immunofixation but not by electrophoresis or ≥ 90% reduction in serum M protein plus urine M protein level < 100 mg/24 hr
PR	≥ 50% reduction of serum M protein and reduction in 24-hr urinary M protein by ≥ 90% or to < 200 mg/24 hr. If serum and urine M protein are not measurable: ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required AND if serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size of soft-tissue plasmacytomas is also required
MR[b]	All of the following: 25%–49% reduction in serum M protein; 50%–89% reduction in urinary light chain excretion; 25%–49% reduction in the size of soft tissue plasmacytomas; no increase in the size or number of lytic bone lesions; and 25%–49% reduction in plasma cells (for patients with nonsecretory myeloma only)
SD	Not meeting criteria for CR, VGPR, PR, or PD
PD	≥ 25% increase from lowest response value in any 1 or more of M component (serum or urine), difference between involved and uninvolved FLC, bone marrow plasma cell percentage, new bone lesions/ plasmacytomas or increase in size of existing lesions/plasmacytomas, hypercalcemia that can be attributed solely to myeloma

Note. sCR = stringent complete response; CR = complete response; FLC = free light chain; VGPR = very good partial response; M protein = myeloma protein; PR = partial response; MR = minimal response; SD = stable disease; PD = progressive disease.
[a]Adapted from Durie et al. (2006). [b]MR from Blade et al. (1998).

Come proseguire l'iter terapeutico?

1. Proseguo con ciclo di mobilizzazione e raccolta CSE periferiche ?
2. Procedo con ulteriori cicli VTD ?
3. Passo a terapia di II linea?

Frontline treatment – young patients



Caso clinico - VIII

- Agosto 2012: ciclo di mobilizzazione (Ciclofosfamide 3 gr/m^2 + G-CSF) e raccolta C.S.E. ($CD34^+$ 6.4 x 10^6/Kg) da sangue periferico

- Settembre 2012**:** chemioterapia ad alte dosi (Melphalan 200 mg/m2 ev) seguita da reinfusione di staminali emopoietiche

Upront therapy –6 cycles VTD ?

blood
2012 120: 1589-1596
doi:10.1182/blood-2012-02-408922 originally published online July 12, 2012

Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study

Laura Rosiñol, Albert Oriol, Ana Isabel Teruel, Dolores Hernández, Javier López-Jiménez, Javier de la Rubia, Miquel Granell, Joan Besalduch, Luis Palomera, Yolanda González, Mª Asunción Etxebeste, Joaquín Díaz-Mediavilla, Miguel T. Hernández, Felipe de Arriba, Norma C. Gutiérrez, Mª Luisa Martín-Ramos, Mª Teresa Cibeira, Mª Victoria Mateos, Joaquín Martínez, Adrián Alegre, Juan José Lahuerta, Jesús San Miguel and Joan Bladé

- **VBMCP/VBAD**: 4 cycles followed by Bortezomib for 2 cycles
- **TD**: (Tal: 50 mg 1-14 and 100 mg 15-28; Dex: 40 mg 1-4, 9-12) for 6 cycles every 28 days
- **VTD**: TD plus Bortezomib 1, 4, 8, 11 every 28 days for 6 cycles

Upront therapy –6 cycles VTD ?

Pethema protocol[1]

Response after induction therapy

	QT + V, n = 129	TD, n = 127	VTD, n = 130
CR, %	21*	14*	35*
VGPR, %	15	15	25
PR, %	39	33	25
SD, %	12	12	6
PD, %	12†	23	7‡
Early deaths, %	1	1	2

QT + V indicates chemotherapy + bortezomib; TD, thalidomide/dexametha sone; VTD, bortezomib/thalidomide/dexamethasone; CR, complete response; VGPR very good partial response; PR, partial response; SD, stable disease; and PD progressive disease.

*VTD vs QT + V, $P = .01$; VTD vs TD, $P = .0001$.

†QT + V vs TD, $P = .02$.

‡VTD vs TD, $P = .0004$.

Cavo protocol[2]

	VTD (n=236)	TD (n=238)	p value
After induction therapy			
Complete response	44 (19%, 13·7–23·6)	11 (5%, 2·0–7·3)	<0·0001
Complete or near complete response*†	73 (31%, 25·0–36·8)	27 (11%, 7·3–15·4)	<0·0001
Very good partial response or better	146 (62%, 55·7–68·1)	66 (28%, 22·0–33·4)	<0·0001
Partial response or better	220 (93%, 90·0–96·4)	187 (79%, 73·4–83·8)	<0·0001
Minimal response or stable disease	16 (7%, 3·6–10·0)	39 (16%, 11·7–21·1)	0·0011
Progressive disease	0	12 (5%, 2·3–7·8)	0·0005
After consolidation therapy			
Complete response	116 (49%, 42·8–55·5)	82 (34%, 28·4–40·5)	0·0012
Complete or near complete response*	147 (62%, 56·1–68·5)	108 (45%, 39·1–51·7)	0·0002
Very good partial response or better	201 (85%, 80·6–89·7)	162 (68%, 62·1–74·0)	<0·0001
Partial response or better	218 (92%, 89·0–95·8)	201 (84%, 79·9–89·1)	0·0071
Minimal response or stable disease	12 (5%, 2·3–7·9)	16 (7%, 3·5–9·9)	0·45
Progressive disease	6 (3%, 0·5–4·6)	21 (9%, 5·2–12·4)	0·0032

[1] Rosinol L et al, Blood 2012; [2] Cavo M et al, Lancet 2010

Caso clinico - IX

Dicembre 2012: rivalutazione di malattia →

- Esami ematochimici: IF siero/urine negativa, free κ 62.40 mg/L, free λ 10.30 mg/L, rFLC 6.05 (v.n. <1.65)
- Biopsia ossea: plasmacellule politipiche < 5%

CR

Table 2. International Myeloma Working Group Response Criteria[a]

sCR	CR as defined below plus: Normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
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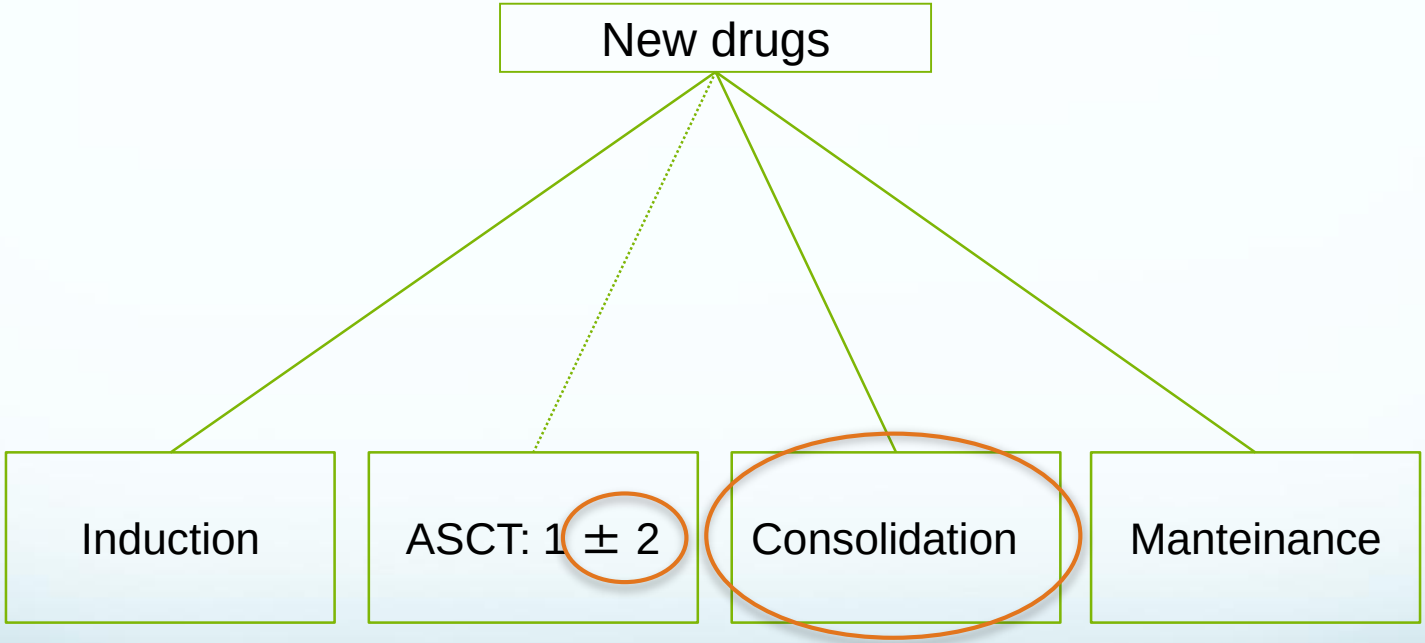
[a]Adapted from Durie et al. (2006). [b]MR from Blade et al. (1998).

Come proseguire l'iter terapeutico?

- II° ASCT + consolidamento +/- mantenimento
- II° ASCT +/- mantenimento
- No II° ASCT, proseguo con terapia di consolidamento+/- mantenimento
- No II° ASCT, terapia di mantenimento

Frontline treatment – young patients



Caso clinico - IX

Dicembre 2012: II ASCT (Melphalan 200 mg/m2 ev)

Marzo 2013: 2 cicli di consolidamento secondo schema VTD →

- Bortezomib 1.3 mg/m2 day 1; 8; 15; 22 q35
- Desametasone 20 mg day 1; 8; 15; 22 q35
- Talidomide 100 mg/die day 1-70

Caso clinico - X

Rivalutazione dopo consolidamento:

- Esami ematochimici → scomparsa della CM all'elettroforesi, IF siero/urine negativa, FLC ratio nei limiti
- PET/TC → negativa
- BOM → plasmacellule < 5% politipiche
- **IF: MRD +**

sCR

Paziente avviato a follow-up

Table 2. International Myeloma Working Group Response Criteria[a]

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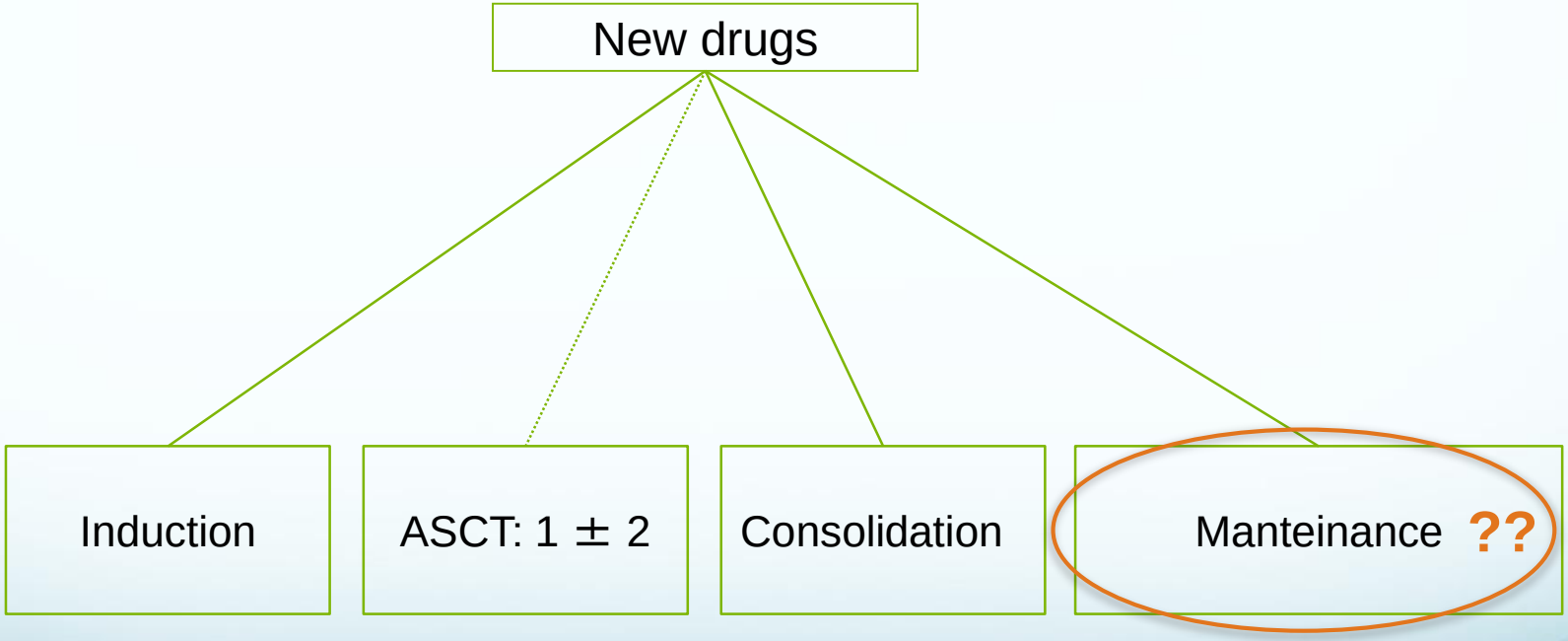
Frontline treatment – young patients



Maintenance therapy- talidomide

Pro

- **<u>Unico regime a tutt'oggi approvato in Italia</u>**
- Terapia di lunga durata (2 anni) finalizzata al controllo della malattia nel tempo
- Un significativo impatto sulla PFS è stato osservato in 5 RCTs

Contro

- Scarsa tollerabilità: neuropatia periferica, stipsi, necessità di profilassi antitrombotica.
- Non sufficienti evidenze di miglioramento della OS da studi di metanalisi.
- Vantaggio ristretto a chi ottiene una risposta ≤ VGPR dopo autotrapianto e **non è portatore di alterazioni cromosomiche sfavorevoli**.

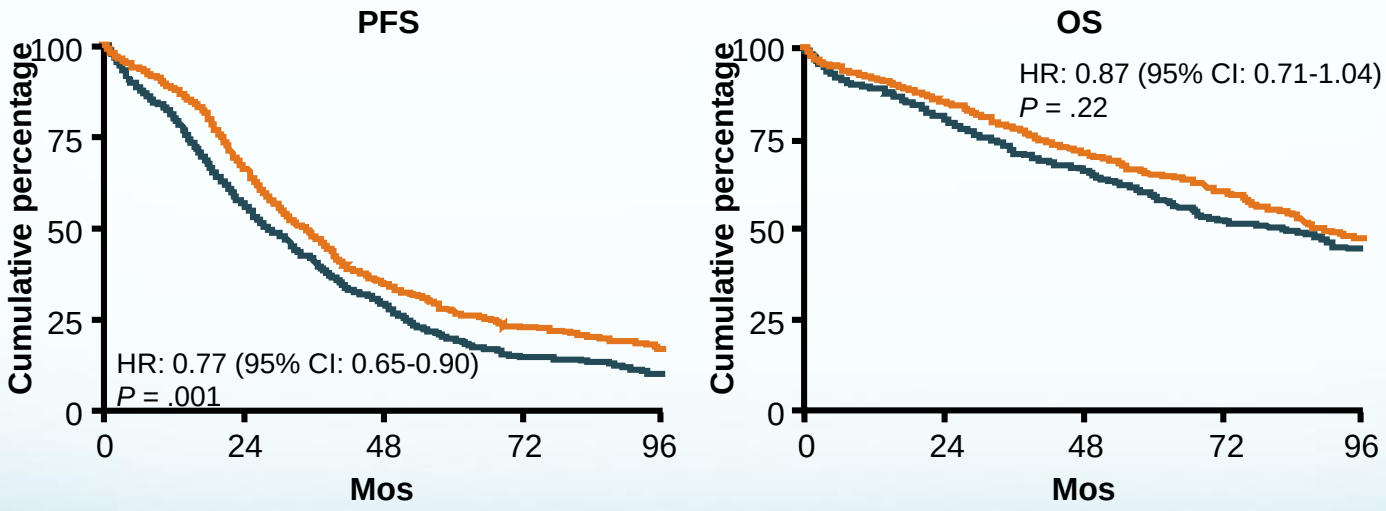
Wang Y et al, J Natl Cancer Inst 2016

Manteinance therapy - Lenalidomide

- Meta-analysis: lenalidomide maintenance significantly increased OS post-ASCT in MM
  - Effect seen in all 3 studies considered (CALGB 100104, IFM 2005-0, GIMEMA RV-MM-PI-209); magnitude varied
  - Estimated median OS improvement: 2.5 yrs
- Feasible for long-term disease control
- Survival benefit of lenalidomide maintenance outweighs risk of second primary malignancies
- Investigators suggest lenalidomide maintenance after ASCT should be considered standard of care in MM
  - Surrogate endpoints for OS and long-term outcomes critical for future trials, MRD may have role to guide treatment decisions
  - Immune reconstitution following ASCT important to further improve OS

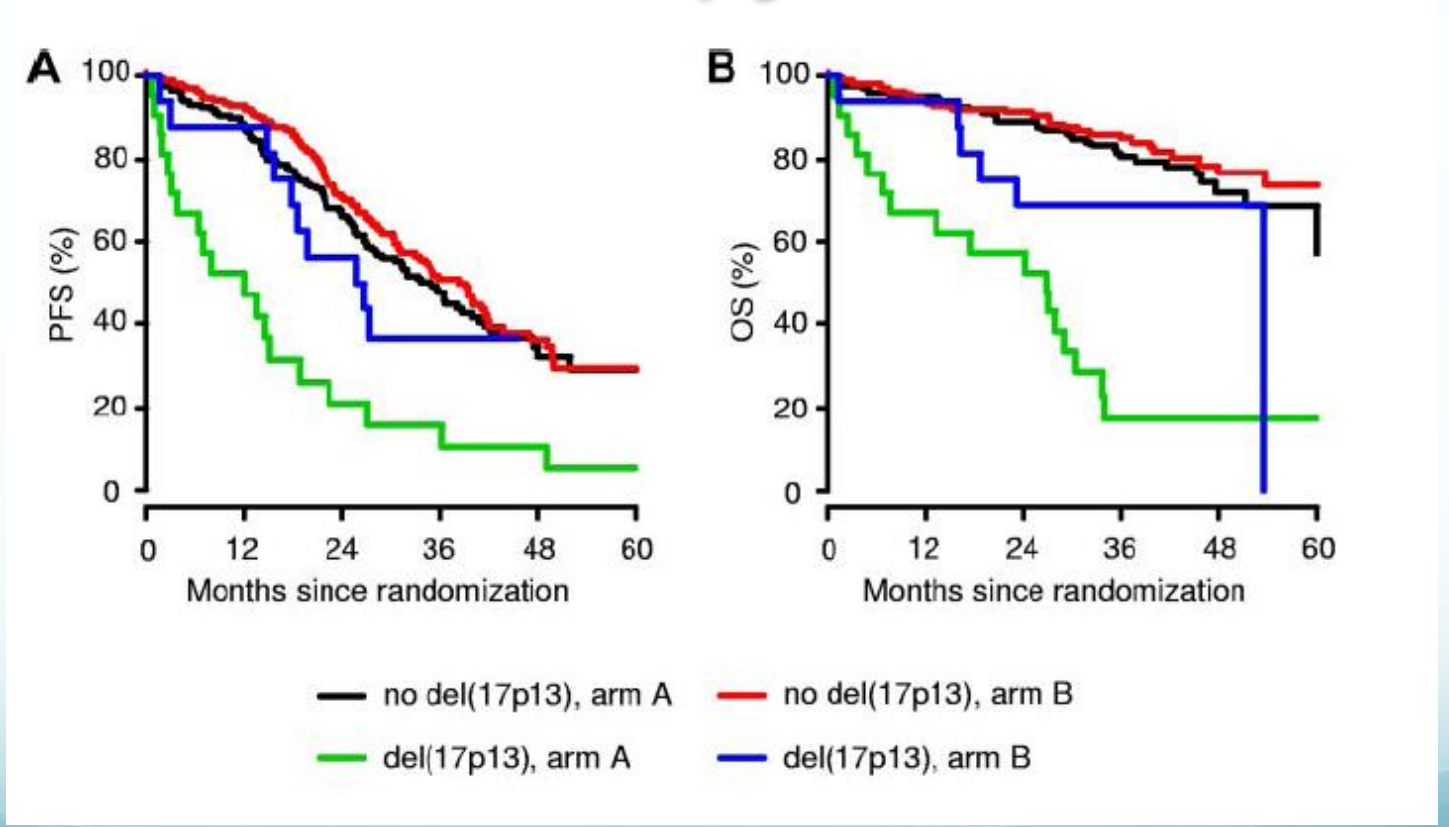
Attal M, et al. ASCO 2016. Abstract 8001.

Maintenance therapy - Bortezomib



Sonneveld P, et al. ASH 2015. Abs 27

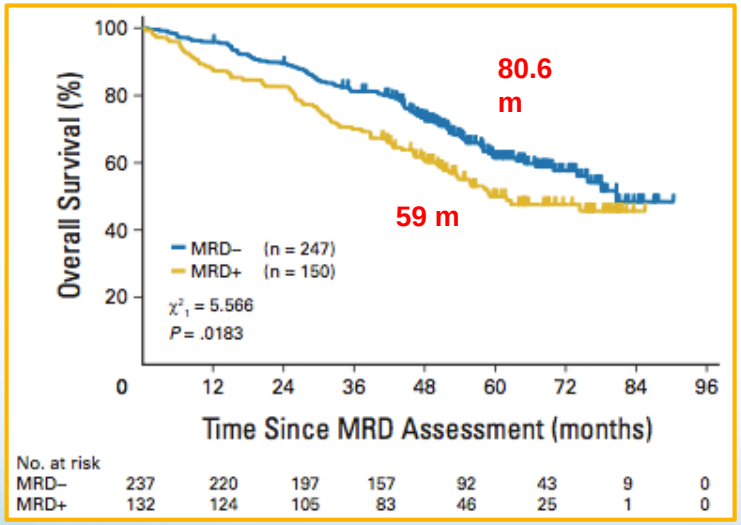
Maintenance therapy - Bortezomib

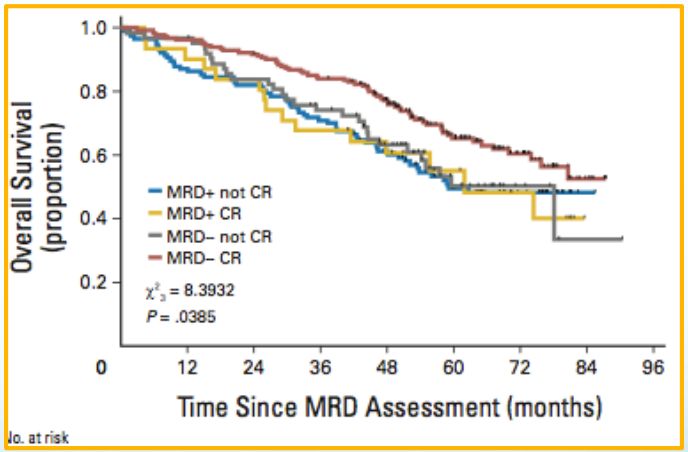


Neben k et al. Blood 2012

MRD in transplant-eligible patients

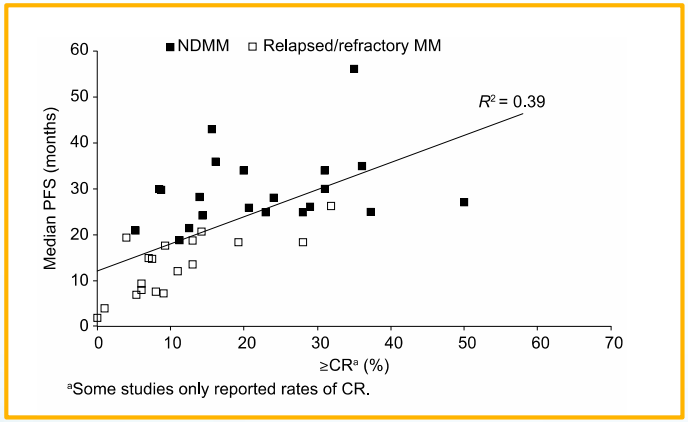
Prognostic impact on OS of MRD status by MFC (4 color flow) at day 100 after ASCT Myeloma IX trial, CTD vs CVAD plus ASCT +/- thalidomide maintenance).

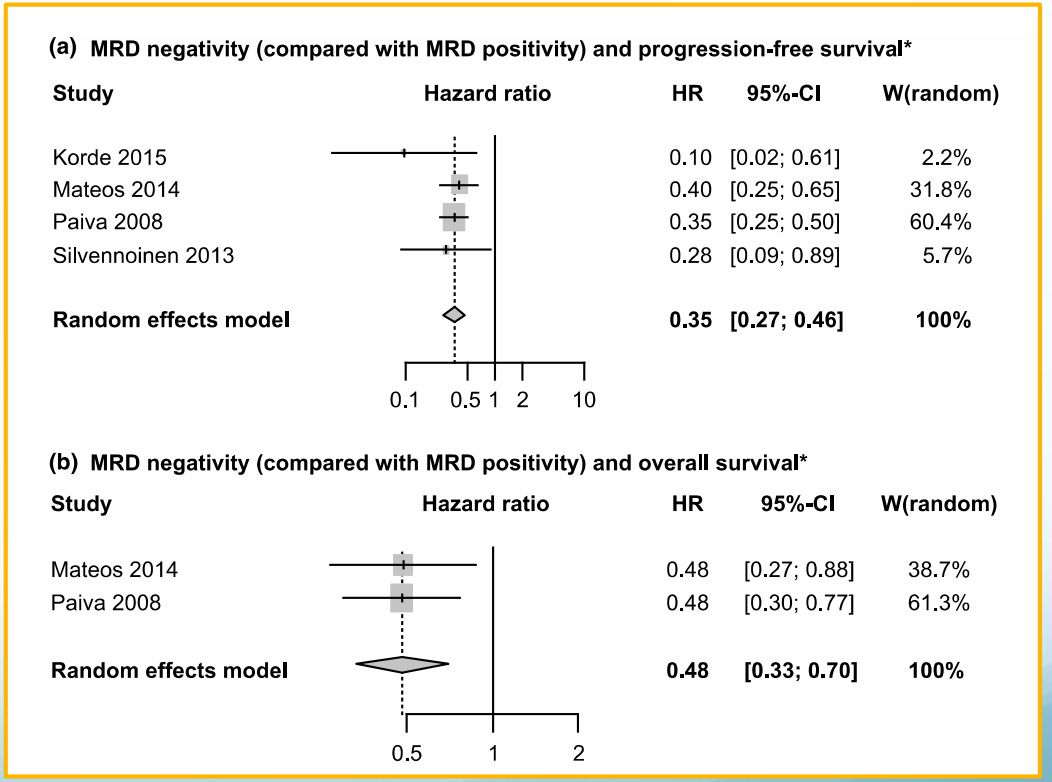




Rawstron A et al, JCO 2013

MRD metanalysis





Landgren O, J Intern Med, 2017

Caso clinico - XI

- ✓ Giugno 2016 (62 anni) – I recidiva →
  - ❖ Esami ematochimici: Hb 10.2 g/dL, creatinina 0.9 mg/dL, calcemia 8.1 mg/dL; CM sierica IgG lambda 2.1 g/dL, IgG 2050 mg/dL, FLC: free κ 1190 mg/L, free λ 73.2 mg/L, ratio 16.26
  - ❖ BOM: cellularità abbondante, plasmacellule monotipiche per la catena lambda 40%
  - ❖ FISH: 95% t(4;14)
  - ❖ Imaging: Low-dose TC → multiple aree osteolitiche a livello vertebrale e omerale

Caso clinico - XII

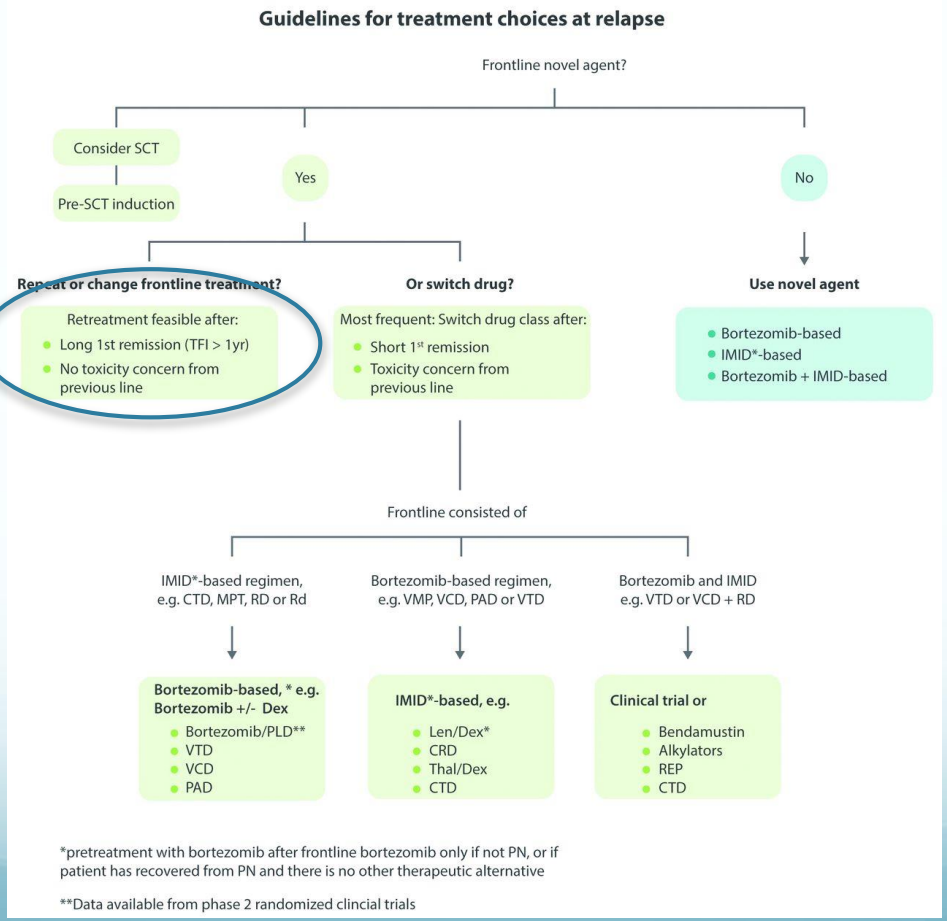
- ✓ I recidiva – VALUTAZIONE COMORBIDITA’
  - ❖ Condizioni generali del paziente:
    - 63 anni
    - ECOG PS = 1
    - Comorbidità: DM tipo II, ipertensione arteriosa, ipercolesterolemia, vasculopatia
  - ❖ PFS: 50 mesi
  - ❖ tossicità pregresse: neuropatia grado II

Quali opzioni terapeutiche per la I recidiva?

- “Retreatment” con Bortezomib
- ASCT di salvataggio
- Lenalidomide – desametasone

- KRd (Carfilzomib – Lenalidomide - Desametasone)
- Elo-Rd (Elotuzumab – Lenalidomide – Desametasone)
- Ixa-Rd (Ixazomib – Lenalidomide – Desametasone)

Relapsed/refractory MM



Sonneveld P, Haematologica 2016

Caso clinico – XIII

✓ Terapia di II linea - *Retreatment*

- Luglio 2016: inizia terapia con
  - Bortezomib 1.3 mg/m2 day 1; 8; 15; 22
  - Desametasone 20 mg day 1; 8; 15; 22 (ridotto a 10 mg dopo il II ciclo per evitare eccessivo scompenso glicemico)

→ Rivalutazione (esami ematochimici) dopo 4 cicli: **SD**

Switch precoce ad altra linea di terapia

Relapsed/refractory MM – Therapeutic options

Regimen	Reference/Trial	Outcome
Salvage ASCT	BSBMT/UKMF Myeloma X[1]	Median TTP: 19 months
Rd “continuous”	MM009-010[2]	Median TTP: 11.1 months
KRd	ASPIRE[3]	Median PFS: 26.3 months
Elo-Rd	Eloquence-2[4]	Median PFS: 19.4 months
Ixa-Rd	Tourmaline-MM1[5]	Median PFS: 20.6 months

1. Cook G et al, Lancet Hematol, 2016 2. Dimopoulos MS, NEJM, 2007 3. Stewart AK, NEJM, 2015. 4. Lonial S, NEJM, 2015 5. Moreau P et al, NEJM, 2016

ASPIRE: Responses in ITT Population

Response	KRd (N = 396)	Rd (N = 396)	P Value
≥ CR, % ▪sCR ▪CR	31.8 14.1 17.7	9.3 4.3 5.1	< .001
≥ VGPR% %	69.9	40.4	< .001
SD or PD, %	3.5	14.9	
Median TTR, mos	1.0	1.0	
Median DoR, mos (95% CI)	28.6 (24.9-31.3)	21.2 (16.7-25.8)	

- Significant improvement in ORR in KRd arm vs Rd (87.1% vs 66.7%, respectively; *P* < .001)

Stewart AK et al., N Engl J Med., 2015

Caso clinico – XIV…e oltre

Dicembre 2016: start KRd

- Rivalutazione dopo III cicli → **VGPR**

↓

Prosegue KRd

Table 2. International Myeloma Working Group Response Criteria[a]

sCR	CR as defined below plus: Normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
CR	Negative immunofixation on the serum and urine plus disappearance of any soft-tissue plasmacytomas and < 5% plasma cells in bone marrow
VGPR	Serum and urine M protein detectable by immunofixation but not by electrophoresis or ≥ 90% reduction in serum M protein plus urine M protein level < 100 mg/24 hr
PR	≥ 50% reduction of serum M protein and reduction in 24-hr urinary M protein by ≥ 90% or to < 200 mg/24 hr. If serum and urine M protein are not measurable: ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required AND if serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size of soft-tissue plasmacytomas is also required
MR[b]	All of the following: 25%–49% reduction in serum M protein; 50%–89% reduction in urinary light chain excretion; 25%–49% reduction in the size of soft tissue plasmacytomas; no increase in the size or number of lytic bone lesions; and 25%–49% reduction in plasma cells (for patients with nonsecretory myeloma only)
SD	Not meeting criteria for CR, VGPR, PR, or PD
PD	≥ 25% increase from lowest response value in any 1 or more of M component (serum or urine), difference between involved and uninvolved FLC, bone marrow plasma cell percentage, new bone lesions/plasmacytomas or increase in size of existing lesions/plasmacytomas, hypercalcemia that can be attributed solely to myeloma

Note. sCR = stringent complete response; CR = complete response; FLC = free light chain; VGPR = very good partial response; M protein = myeloma protein; PR = partial response; MR = minimal response; SD = stable disease; PD = progressive disease.
[a]Adapted from Durie et al. (2006). [b]MR from Blade et al. (1998).

Quali opzioni terapeutiche future?

- Paziente recidivato dopo terapia con Bortezomib e KRd →
  1. Pomalidomide
  2. …Daratumumab?