*“Real World Evidence”*

# Nuovi target terapeutici in ematologia

*San Giovanni Rotondo -8,9 novembre 2018*

## Sessione Mieloma: Confronto tra *real world* e studi registrativi

*Silvana F. Capalbo*

*Ematologia e Trapianto Cellule Staminali Emopoietiche; Azienda Ospedaliera – Universitaria Ospedali Riuniti Foggia*

**Most cases of MM are preceded by MGUS**

*( Ladgren O, Weiss BM, Blood 2009)*

IgG < 3.5 g, IgA < 2 g
PC = 10%

IgG > 3 and/or PC >10%
without CRAB
NO progression after
rechecking every 3-6 months

**SYMPTOMS**

IgG > 3.5 g, IgA > 2 g
PC ≥ 30%
C Calcium > 11.5
R crClear < 40 ml/min
A Hb≤10g/dL or drop
of2g/dL
B lytic lesions(RX, TC, MR, PET)

MGUS | Asymptomatic MM | Active MM | Symptomatic MM

**Risk of progression and follow-up**

**TREATMENT**

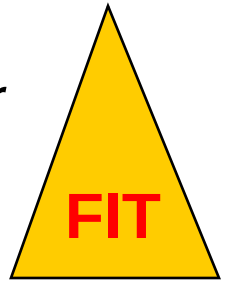
New activity biomarkers:
*(IMWG 2014)*
≥ 60% marrow clonal PC

Serum involved / uninvolved free light chain ratio of 100 or greater

More than one focal lesion on MRI that is at least 5 mm or greater in size

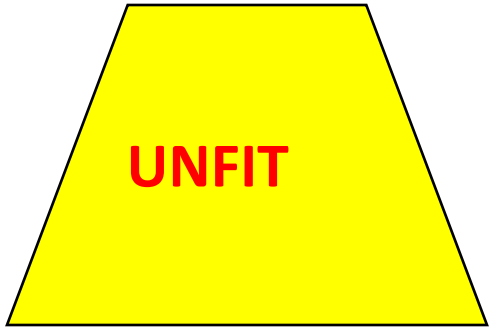
# Trattamento del MM: 3 categorie di pazienti

*No comorbidità No disabilità*
*Pazienti anziani selezionati per gli studi clinici di fase II/III*




*Candidato per ogni forma di terapia standard*

*Tutti gli altri*




*Richiede un approccio individualizzato*

- *Età ≥ 80 anni*
- *≥ 3 comorbidità*
- *≥1 disabilità*
- *≥ 1 Sdr Geriatrica*


*Candidato solo per terapie palliative*

# Trattamento del MM

- Terapia I linea
  - Pazienti candidabili al trapianto
  - Pazienti non candidabili al trapianto
- Terapia della Recidiva (RRMM)
  - I recidiva dopo I linea “IMID-based”
  - I recidiva dopo I linea “Bortezomib based”
  - II o successiva recidiva

## MYELOMA THERAPY[1-4]

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem cell reserve prior to stem cell harvest in patients who may be candidates for transplants.

### PRIMARY THERAPY FOR TRANSPLANT CANDIDATES (assess for response after each cycle)

Preferred Regimens
- Bortezomib/lenalidomide[5]/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone[6]

Other Recommended Regimens
- Bortezomib/doxorubicin/dexamethasone (category 1)
- Carfilzomib[7,8]/lenalidomide[5]/dexamethasone
- Ixazomib/lenalidomide[5]/dexamethasone (category 2B)

Useful In Certain Circumstances
- Bortezomib/dexamethasone (category 1)[9]
- Bortezomib/thalidomide/dexamethasone (category 1)
- Lenalidomide[5]/dexamethasone (category 1)[9]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)

Preferred Regimens

Other recommended Regimens

Useful in Certain Circmstances

## MYELOMA THERAPY[1-4]

### PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES (assess for response after each cycle)

Preferred Regimens
- Bortezomib/lenalidomide/dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)[9,10]
- Bortezomib/cyclophosphamide/dexamethasone[6]

Other Recommended Regimens
- Carfilzomib[8]/lenalidomide/dexamethasone
- Carfilzomib[8]/cyclophosphamide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone

Useful In Certain Circumstances
- Bortezomib/dexamethasone[9]

Preferred Regimens

Other recommended Regimens

Useful in Certain Circmstances

### MAINTENANCE THERAPY

Preferred Regimens
- Lenalidomide[11] (category 1)

Other Recommended Regimens
- Bortezomib

## MYELOMA THERAPY[1-4,12]

### Therapy for Previously Treated Multiple Myeloma (assess for response after each cycle)

Preferred Regimens
- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib (twice weekly)[8]/dexamethasone (category 1)[9]
- Carfilzomib[8]/lenalidomide/dexamethasone (category 1)[13]
- Daratumumab[14]/bortezomib/dexamethasone (category 1)
- Daratumumab[14]/lenalidomide/dexamethasone (category 1)[13]
- Elotuzumab[15]/lenalidomide/dexamethasone (category 1)[13]
- Ixazomib[17]/lenalidomide/dexamethasone (category 1)[13]

Other Recommended Regimens
- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib[8]/cyclophosphamide/dexamethasone
- Carfilzomib (weekly)[8]/dexamethasone[9]
- Cyclophosphamide/lenalidomide/dexamethasone
- Bortezomib/dexamethasone (category 1)[9]
- Daratumumab[14,16]
- Daratumumab[14]/pomalidomide[20]/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Ixazomib[17]/dexamethasone[9]
- Ixazomib/pomalidomide[20]/dexamethasone
- Lenalidomide/dexamethasone[18] (category 1)[9]
- Panobinostat[19]/bortezomib/dexamethasone (category 1)
- Panobinostat[19]/carfilzomib[8,9]
- Panobinostat[19]/lenalidomide/dexamethasone
- Pomalidomide[20]/cyclophosphamide/dexamethasone
- Pomalidomide[20]/dexamethasone[18] (category 1)[9]
- Pomalidomide[20]/bortezomib/dexamethasone
- Pomalidomide[20]/carfilzomib[8]/dexamethasone

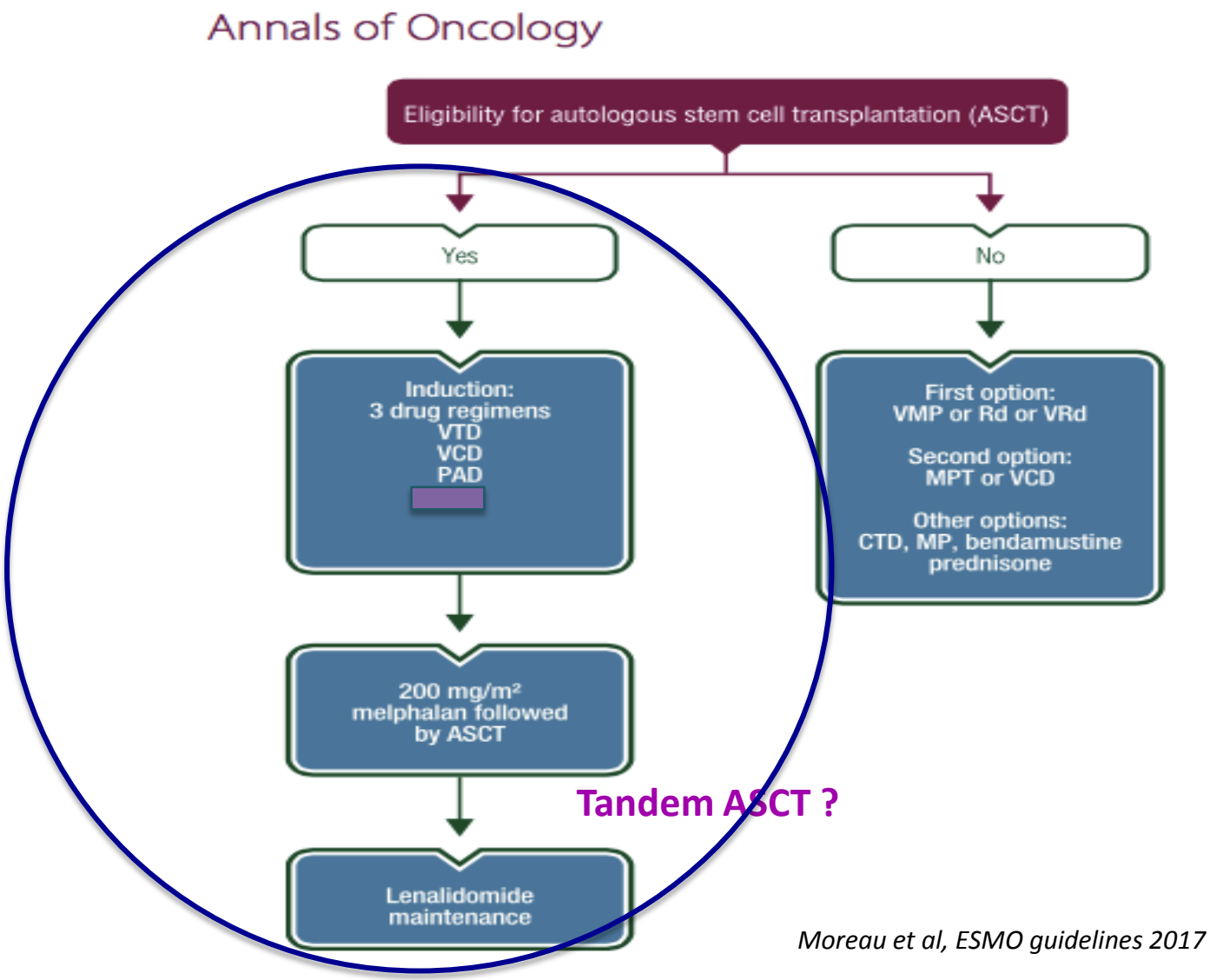
Useful In Certain Circumstances
- Bendamustine
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[21]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[21] ± bortezomib (VTD-PACE)[21]
- High-dose cyclophosphamide

Preferred Regimens

Other recommended Regimens

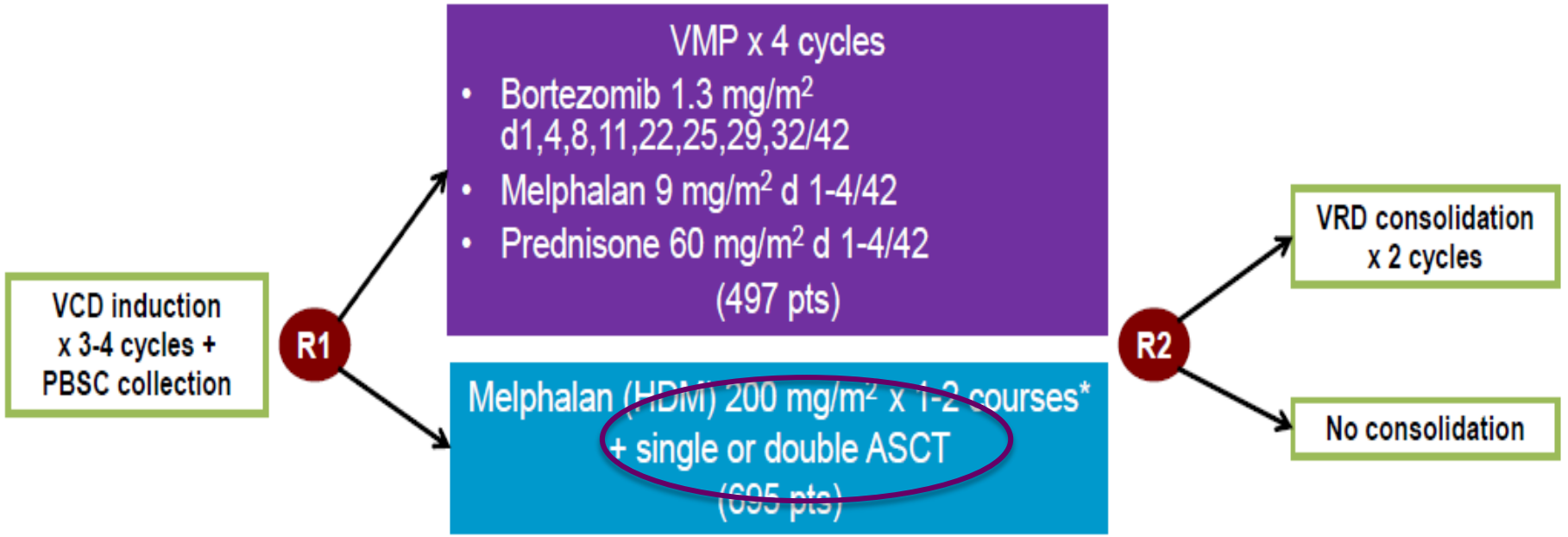
Useful in Certain Circmstances

# Trattamento Prima Linea




*Moreau et al, ESMO guidelines 2017*

# EMN02/HO95 MM Trial: Study Design




**All pts received lenalidomide maintenance until R/P**

**Stratification: ISS I *vs* II *vs* III**

**Randomization to VMP *vs* HDM (1:1) in centers with a fixed single ASCT policy**

**Randomization to VMP *vs* HDM-1 vs HDM-2 (1:1:1) in centers with a double ASCT policy**

**Cavo, ASH 2017**

# EMN02/HO95 Pts Randomized to ASCT: Change in Response After ASCT-2

- 24% of pts had improvement in best response achieved following ASCT-2, as compared with ASCT-1
- 71% had no change in response following ASCT-2
- 5% had worse response following ASCT-2

| Best Response, % | After ASCT-1 | After ASCT-2 |
|---|---|---|
| sCR | 0 | 18 |
| CR | 8 | 36 |
| VGPR | 38 | 36 |
| PR | 41 | 10 |
| SD | 13 | 0 |

Connors JM et al. ASH 2017.

# EMN02/HO95 Pts Randomized to ASCT:

| PFS at 3 Yrs, % (95% CI) | ASCT-1 (n = 208) | ASCT-2 (n = 207) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| All pts | 64.0 (57.3-71.5) | 72.5 (66.2-79.4) | 0.71 (0.50-0.98) | .040 |
| Pts with high cytogenetic risk | 44.2 (31.0-63.2) | 69.2 (54.7-87.5) | 0.42 (0.21-0.84) | .014 |

- PFS similar for pts with standard-risk vs high-risk MM following double ASCT
- 3-year PFS: 76.4% vs 69.2% (HR: 0.79; 95% CI: 0.41-1.52; *P* = .483)
- Randomization to double ASCT independently associated with better PFS

| Variable Assessed in Multivariate Cox Regression Analysis | HR (95% CI) | *P* Value |
|---|---|---|
| Randomization to ASCT-2 | 0.66 (0.45-0.96) | .029 |
| R-ISS I score (vs II/III) | 0.61 (0.37-0.98) | .042 |
| Standard-risk cytogenetics (0 of 3 high-risk abnormalities) | 0.35 (0.22-0.56) | < .001 |
| Best response ≥ VGPR | 0.28 (0.17-0.45) | < .001 |

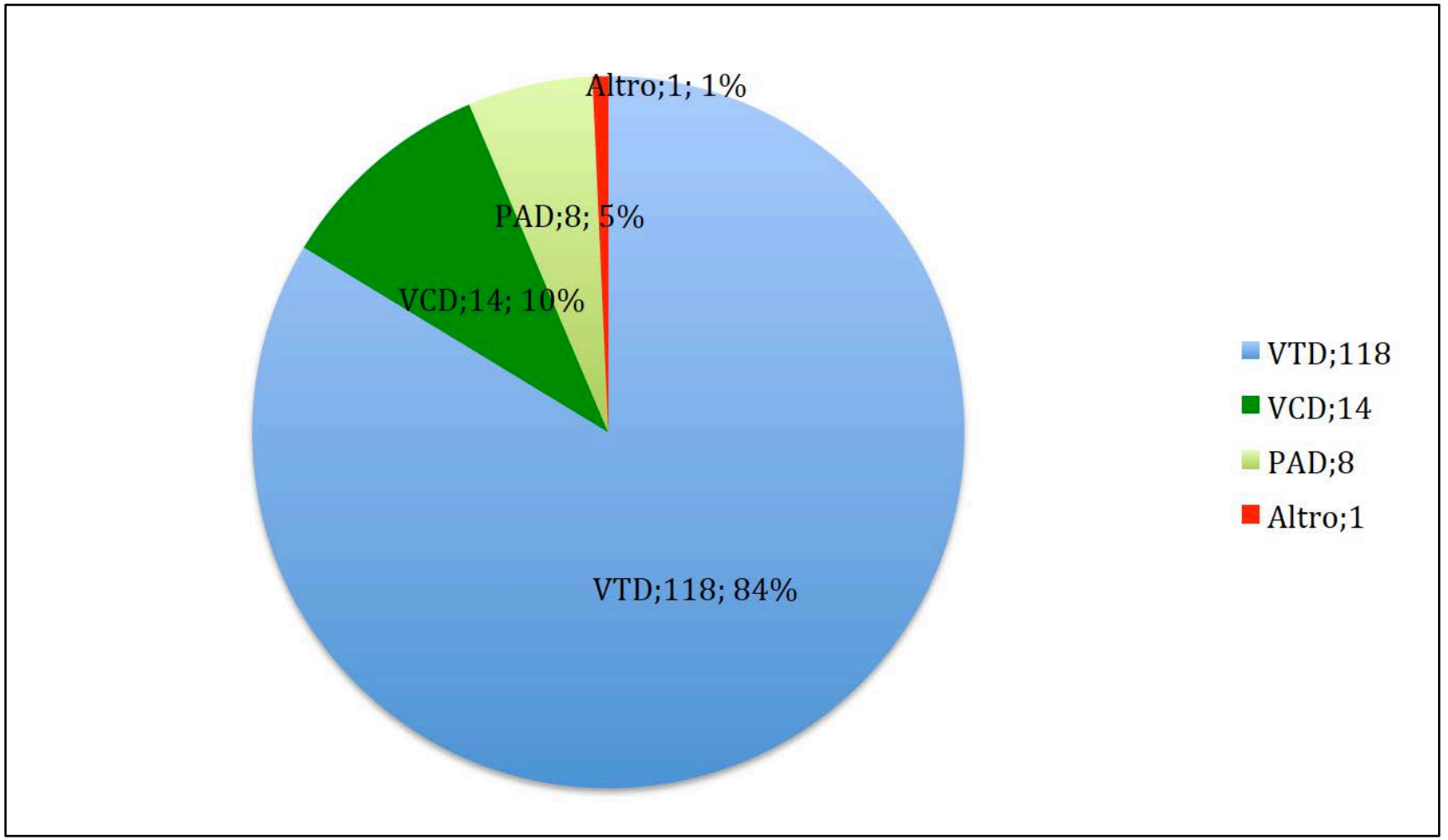
Cavo M, et al. ASH 2017. Abstract 401.

# EMN02/HO95 Pts Randomized to ASCT: OS From First Randomization

| OS at 3 Yrs, % | ASCT-1 (n = 208) | ASCT-2 (n = 207) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| All pts | 81.5 | 88.9 | 0.51 (0.31-0.86) | **.011** |
| Aged ≤ 55 yrs | 86.4 | 87.2 | 0.98 (0.405-2.364) | NR |
| Aged > 55 yrs | 79.1 | 90.1 | 0.37 (0.192-0.7326) | NR |
| ISS I | 87.5 | 91.5 | 0.74 (0.313-1.766) | NR |
| ISS II-III | 76.5 | 86.7 | 0.41 (0.219-0.786) | NR |
| Standard risk | | | | |
| ▪ 0 of 3 high-risk abnormalities* | 88.3 | 92.7 | 0.48 (0.22-1.048) | NR |
| ▪ 0 of 5 high-risk abnormalities† | 95.3 | 94.8 | 0.75 (0.188-3.003) | NR |
| High risk | | | | |
| ▪ ≥ 1 of 3 high-risk abnormalities* | 68.1 | 81.9 | 0.48 (0.193-1.193) | NR |
| ▪ ≥ 1 of 5 high-risk abnormalities† | 72.8 | 84.9 | 0.52 (0.275-0.975) | **.042** |
| R-ISS I | 93.6 | 96.1 | 0.21 (0.024-1.92) | NR |
| R-ISS II-III | 75.2 | 84.9 | 0.48 (0.272-0.856) | **.013** |

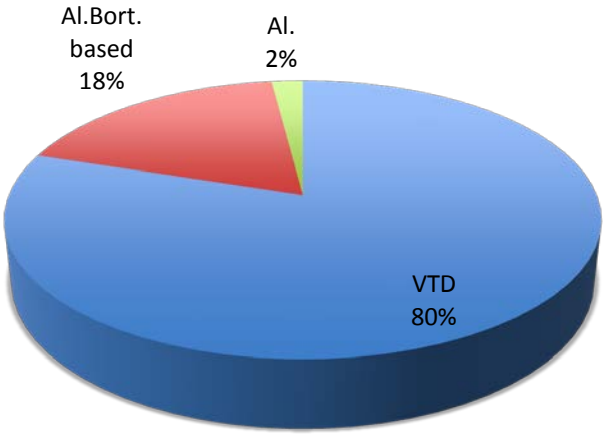
Including del(17p), t(4;14), t(14;16). †Including del(17p), t(4;14), t(14;16), gain 1q, del(1p).

# MM: pazienti eleggibili al trapianto

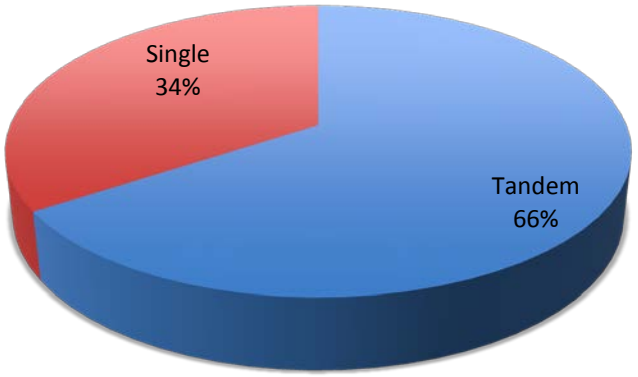


Studio retrospettivo *real-life* sulla strategia *upfront* per i pazienti con MM di nuova diagnosi (NDMM)

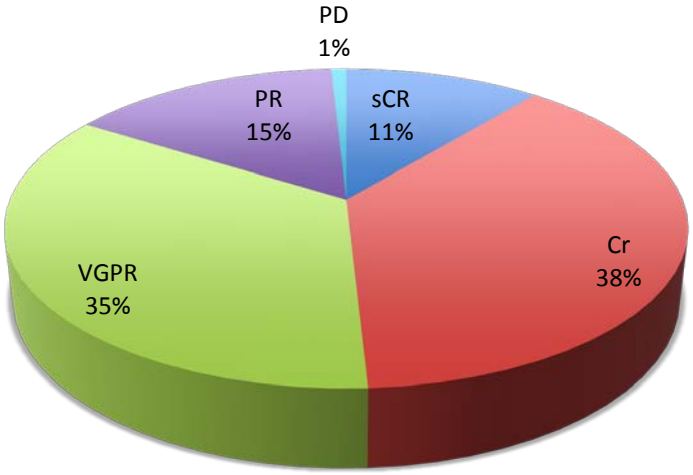
## Induction treatment



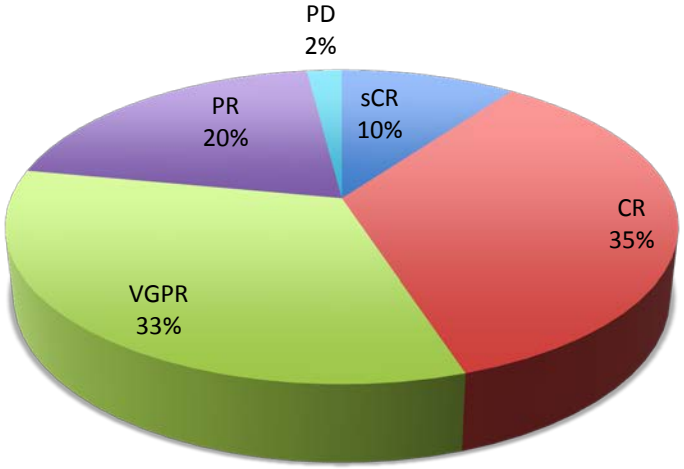

## Single vs Tandem ASCT



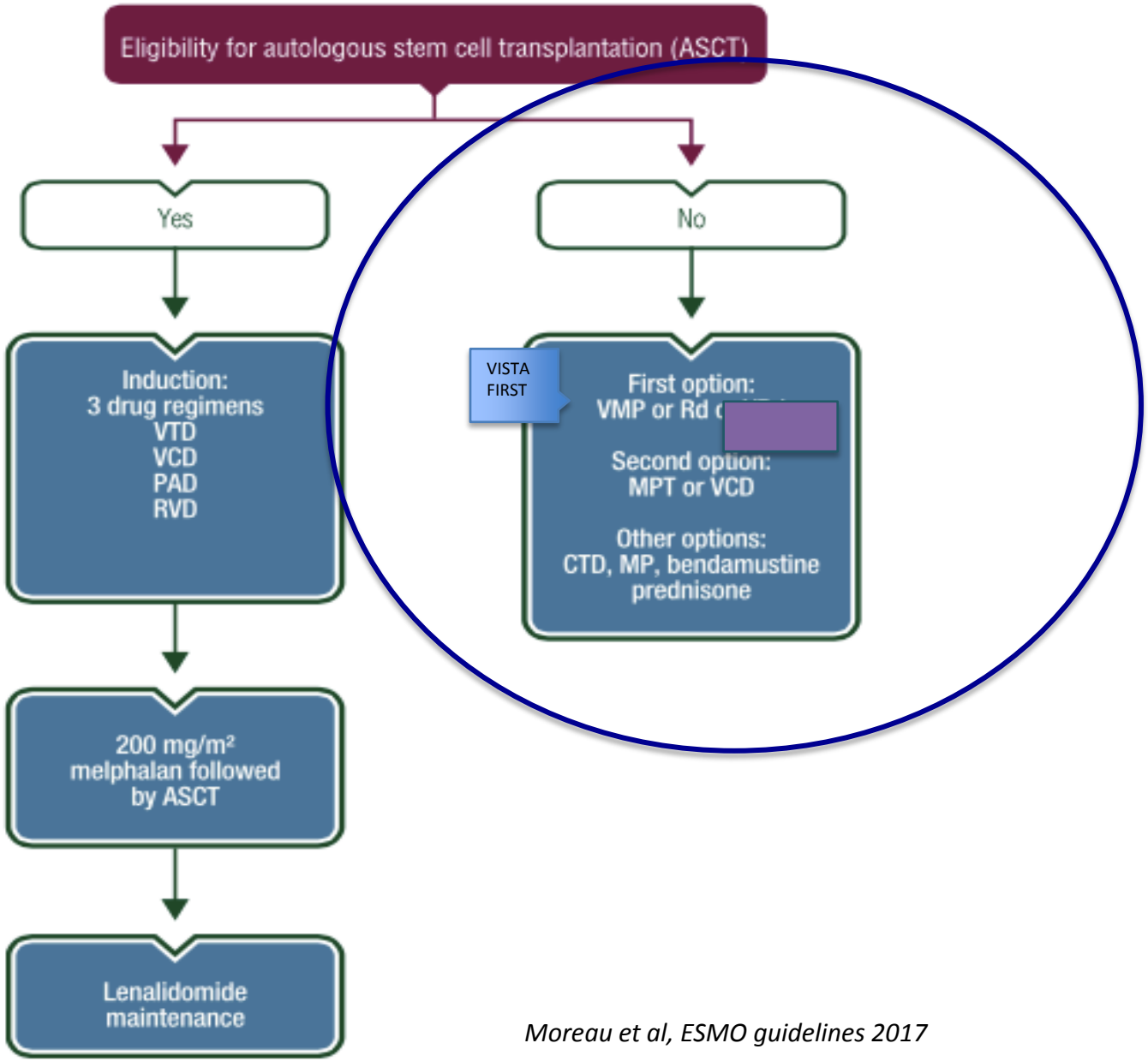

## Response post 1st ASCT




## Response post 2nd ASCT



Annals of Oncology




*Moreau et al, ESMO guidelines 2017*

# FIRST VS VISTA: EFFICACIA

| | Rd (FIRST) | VMP (VISTA) | Altre evidenze |
|---|---|---|---|
| **Efficacia** | | | |
| **PFS (mesi)** | 26[1] | 21,7[2] | **VISTA LONG-TERM FU** (Mateos et al): 20*<br>**CLARION**: KMP vs VMP: 22,1[7]<br>**ALCYONE**: DaraVMP vs VMP: 18,1[8] |
| **OS** | 59,1[3] | 56,4[4] | 61* |
| **TTP** | 32,5[5] | 24[2] | 24,2* |
| **TTNT** | 36,7[3] | 30,7[4] | - |
| **(Responders)** | (VGPR/CR) 69,5[3] | (CR) 37,8[4] | |
| **ORR (%)** | 81%[3] | 74%[6] | 72* |
| **CR** | 22 | 33 | 31* |
| **VGPR** | 26 | 8 | - |
| **PR** | 33 | 33 | 41* |
| **DOR (mesi)** | 32[1] | 19,9[2] | - |

1 Hulin 2016. 2 San Miguel 2008. 3 Facon Blood 2017. 4 San Miguel 2013. 5 Benboubker 2014
6 Harousseau 2010. 7 Facon abs IMW 2017. 8 press release ALCYONE Aug 2017
* Mateos et al. Ann Hematol 2016

# FIRST VS VISTA: *SAFETY*

| | Rd (FIRST)[1] | VMP (VISTA)[2] |
|---|---|---|
| **Safety** (EA grado 3/4) | | |
| ***Ematologici*** | | |
| Neutropenia | 30 | 40 |
| Trombocitopenia | 9 | 37 |
| Anemia | 19 | 19 |
| ***Non ematologici*** | | |
| Infezioni | 32** | 10 |
| Neuropatia periferica | 1 | 13 |
| ***SPM*** | | |
| Ematologici | 0,8 | 1 |
| Non ematologici | 6 | 5 |

1 Facon Blood 2017. 2 San Miguel 2008.

# *Outcome* in base alla citogenetica

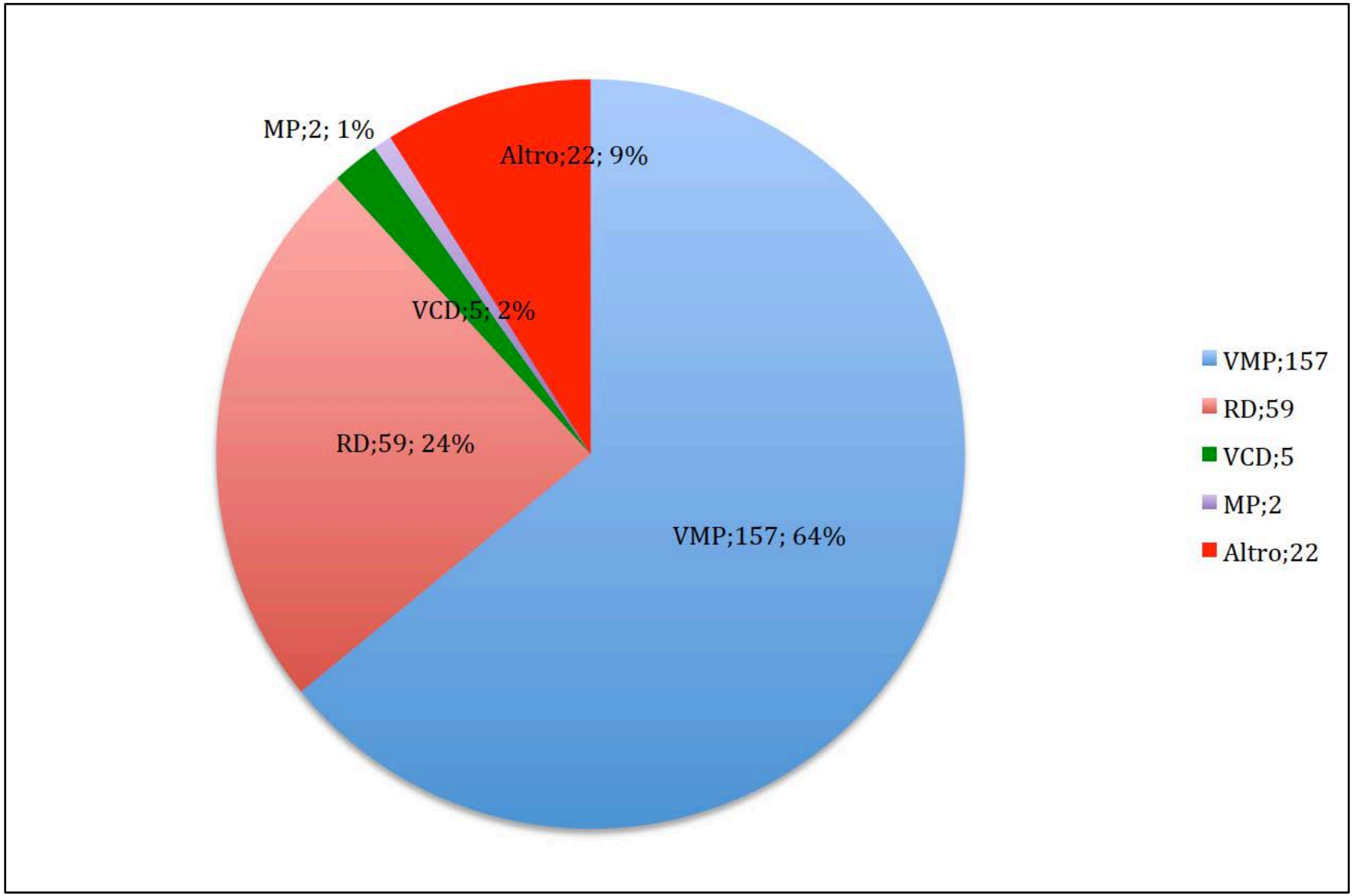
| | n | Standard risk | High risk | n |
|---|---|---|---|---|
| **FIRST[1]: Rd cont (PFS)** | 205 | 31,1 months | 8,4 months | 43 |
| **Rd18** | 209 | 21,2 months | 17,5 months | 52 |
| **VISTA[2]: VMP (TTP)** | 142 | 23,1 months | 19,8 months | 26 |


1. Herve Avet-Loiseau et al, Abstract 730 ASH 2015
2. San Miguel et al, NEJM 2008; 359:906-17

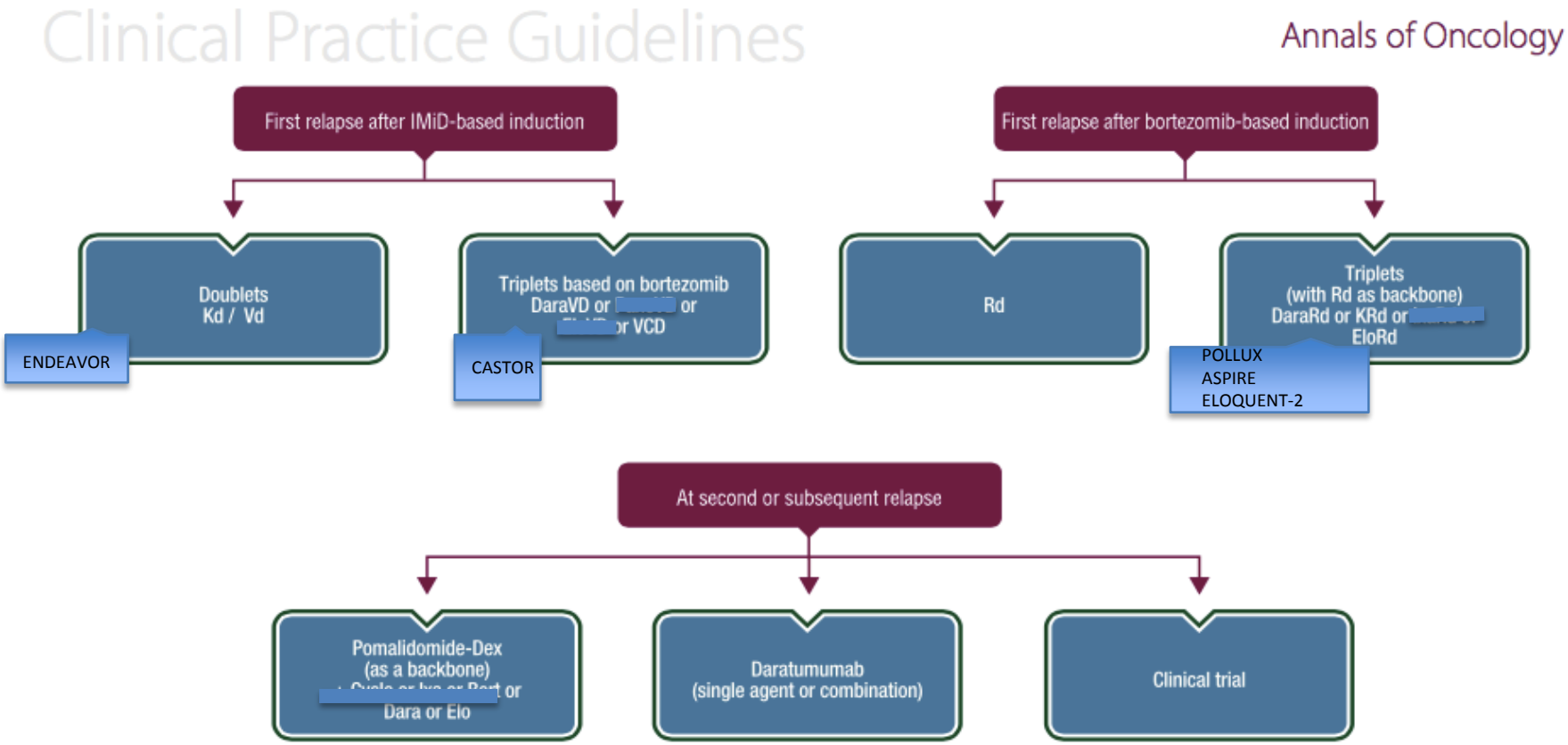
# VMP *vs* Rd nei pazienti con MM ineleggibili al trapianto

| | VMP<br>Bortezomib+melphalan+dexa x 9 cycles | Rd<br>Lenalidomide+dexa until progression |
|---|---|---|
| **Efficacy** | superimposable | superimposable |
| **Tolerability** | more neuropathy | more infections |
| **Overall outcome/future therapy** | rescue with Rd-based regimens | rescue with Vd-based regimens |
| **Renal failure** | preferable in severe renal failure | reduce lena in mild-moderate renal failure |
| **High risk cytogenetics** | better outcome | inferior outcome |
| **Logistics** | | preferable for patients needing caregiver |
| **Age** | | preferable in older patients ? |
| **Unfit/frail patients** | | preferable? |

# MM: pazienti non eleggibili al trapianto



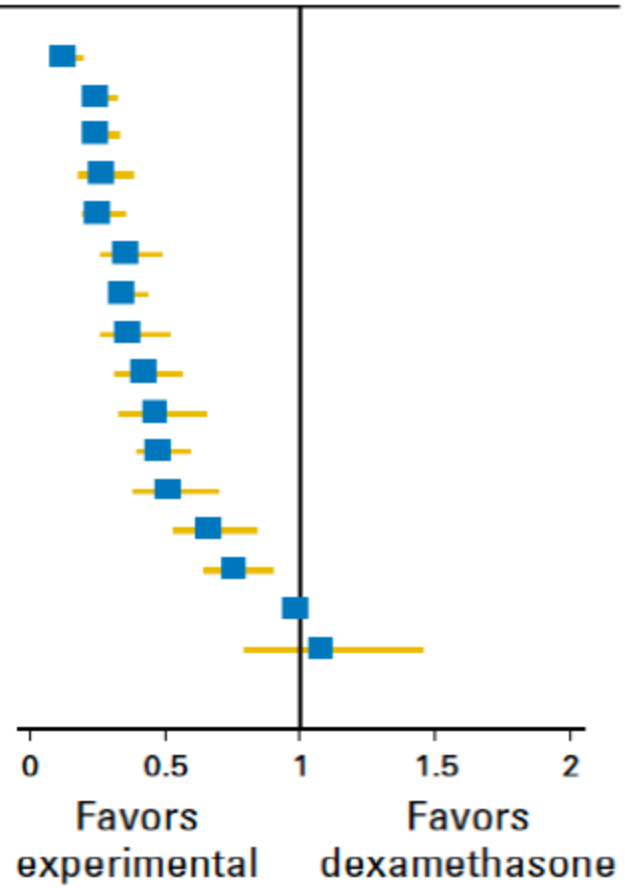
# Trattamento del MM in Recidiva




*Moreau et al, ESMO guidelines 2017*

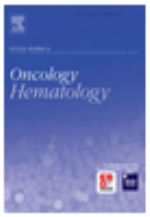
# Systematic Literature Review and Network Meta-Analysis of Treatment Outcomes in Relapsed and/or Refractory Multiple Myeloma.

| Treatment | % Being Best Treatment | Hazard Ratio *v* Dexamethasone (95% CrI), PFS |
|---|---|---|
| DaraLenDex | 99 | 0.13 (0.09 to 0.19) |
| CarLenDex | 0 | 0.24 (0.18 to 0.32) |
| EloLenDex | 0 | 0.25 (0.19 to 0.33) |
| DaraBorDex | 1 | 0.27 (0.18 to 0.38) |
| IxaLenDex | 0 | 0.26 (0.19 to 0.35) |
| CarDex | 0 | 0.36 (0.26 to 0.48) |
| LenDex | 0 | 0.35 (0.29 to 0.43) |
| PegDoxBor | 0 | 0.37 (0.26 to 0.52) |
| PanoBorDex | 0 | 0.43 (0.31 to 0.56) |
| BorThalDex | 0 | 0.47 (0.33 to 0.65) |
| PomDex | 0 | 0.48 (0.39 to 0.6) |
| VorinoBor | 0 | 0.52 (0.38 to 0.69) |
| BorDex | 0 | 0.67 (0.53 to 0.84) |
| ThalDex | 0 | 0.76 (0.64 to 0.9) |
| Dex | 0 | 1 |
| ObiDex | 0 | 1.08 (0.79 to 1.45) |




van Beurden-Tan, J Clin Oncol. 2017 Feb 27

Critical Reviews in Oncology/Hematology
Volume 113, May 2017, Pages 249-255



# Triplet versus doublet combination regimens for the treatment of relapsed or refractory multiple myeloma: A meta-analysis of phase III randomized controlled trials

Zhiqiang Sun [a], Fang Zheng [b], Suwan Wu [c], Yanjuan Liu [d], Hehe Guo [d], Yichen Liu [d]

Triplet vs doublet combination regimens (considerando anche altri studi non confrontati nel *paper*):
vantaggio statisticamente significativo a favore delle triplette in termini di:
•ORR
•VGPR
•CR (no ELOQUENT-2)
•PFS
Vantaggio non statisticamente significativo in termini di:
•OS

| Author/year | Phase | No. of patients | median age | Treatment regimens |
|---|---|---|---|---|
| | | | | 20 mg |
| Garderet et al. (2012) (MMVAR) | III | 269 | 60 | Bortezomib 1.3 mg/m$^2$ + thalidomide 200 mg + dexamethasone 40 mg |
| | | | 62.6 | Thalidomide 200 mg + dexamethasone 40 mg |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

A. Keith Stewart, M.B., Ch.B., S. Vincent Rajkumar, M.D., Meletios A. Dimopoulos, M.D., Tamás Masszi, M.D., Ph.D., Ivan Špička, M.D., Ph.D., Albert Oriol, M.D., Roman Hájek, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., David S. Siegel, M.D., Ph.D., Georgi G. Mihaylov, M.D., Ph.D., Vesselina Goranova-Marinova, M.D., Ph.D., Péter Rajnics, M.D., Ph.D., Aleksandr Suvorov, M.D., Ruben Niesvizky, M.D., Andrzej J. Jakubowiak, M.D., Ph.D., Jesus F. San-Miguel, M.D., Ph.D., Hei[illegible] Ludwig, M.D., Michael Wang, M.D., Vladimír Maisnar, M.D., Ph.D., Jir[illegible] M.D., Ph.D., William I. Bensinger, M.D., Maria-Victoria Mateos, M.D., Ph.D., D[illegible]n-Yehuda, M.D., Vishal Kukreti, M.D., Naseem Zojwalla, M.D., Ma[illegible] E. Tonda, Pharm.D., Xinqun Yang, Ph.D., Biao Xing, Ph.D., Philippe M[illegible] M.D., and Antonio Palumbo, M.D., for the ASPIRE Investigators*

# ASPIRE study design: randomised, open-label, multicentre, phase 3 trial

**Relapsed MM**
1–3 prior treatments

**R**
1:1

**KRd (n = 396)**
**Carfilzomib 27 mg/m² i.v. (10 min)**
***Days 1*-2*, 8-9, 15-16 for Cycles 1–12, then Days 1-2, 15-16 for Cycles 13–18, then discontinued***
**Lenalidomide 25 mg *Days 1–21***
**Dexamethasone 40 mg *Days 1, 8, 15, 22***

**Rd† (n = 396)**
Lenalidomide 25 mg *Days 1–21*
Dexamethasone 40 mg *Days 1, 8, 15, 22*

28-day cycles

*20 mg/m² on Days 1, 2, Cycle 1 only;
†Continued until disease progression

**PRIMARY ENDPOINT**
- ***PFS by 8.7 months vs Rd***

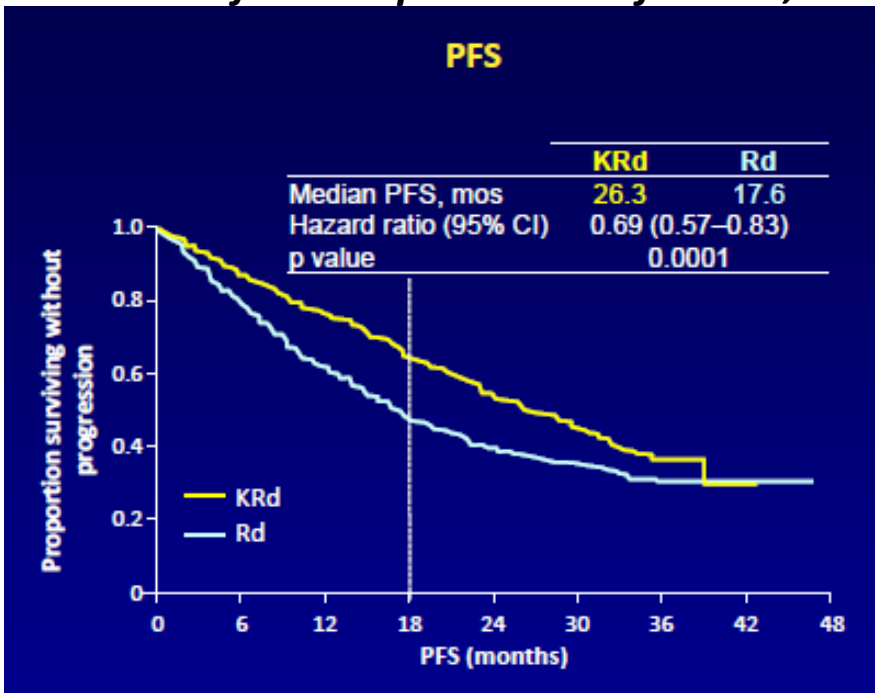
**SECONDARY ENDPOINTS**
- ***Median OS, ORR, Safety***

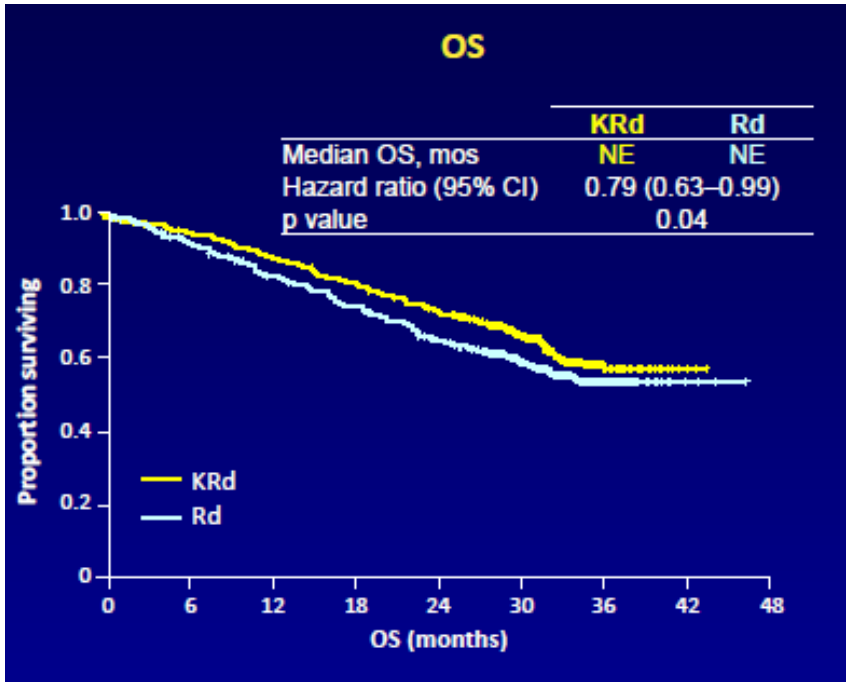
*(AEs and rates of death due to AEs)*

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

**ASPIRE: KRd vs Rd in RRMM**

***Median follow-up: 32.3 mos for KRd; 31.5 mos for Rd***



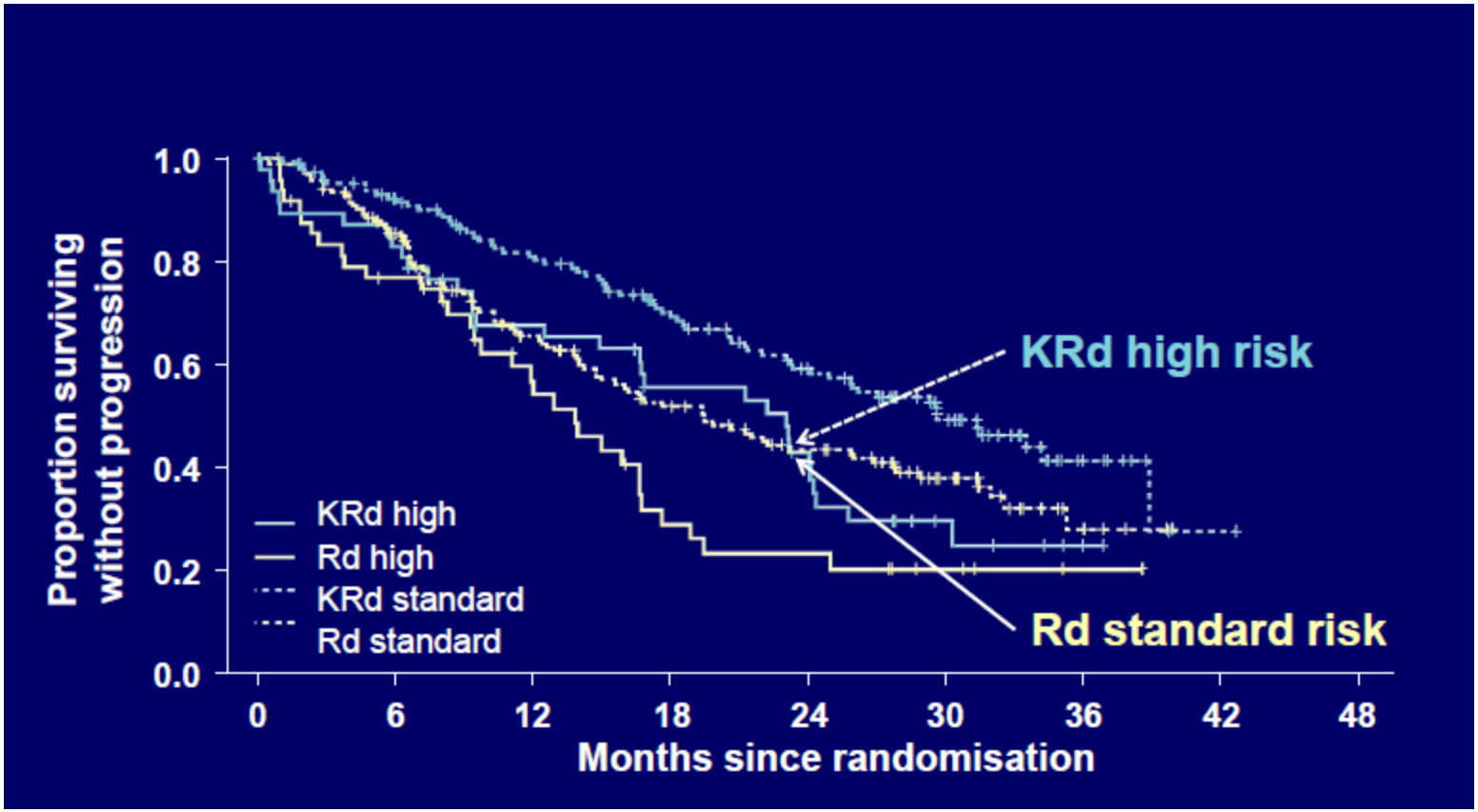




Response: KRd vs Rd

ORR: 87.1% vs 66.7% (*P < 0.001); ≥ CR: 31.8% vs 9.3% (P < 0.001)*

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

# KRd vs RD: PFS by cytogenetic risk status




*Avet-Loiseau H, et al. Blood 2015;126*

# Carfilzomib: ASPIRE (KRd)

## Adverse events of interest*
### *Safety population (N=781)*

| Adverse event, % | KRd (n=392) | | Rd (n=389) | |
|---|---|---|---|---|
| | All Grade | Grade ≥3 | All Grade | Grade ≥3 |
| Dyspnoea | 19.4 | 2.8 | 14.9 | 1.8 |
| Peripheral neuropathy† | 17.1 | 2.6 | 17.0 | 3.1 |
| Hypertension | 14.3 | 4.3 | 6.9 | 1.8 |
| Acute renal failure† | 8.4 | 3.3 | 7.2 | 3.1 |
| Cardiac failure† | 6.4 | 3.8 | 4.1 | 1.8 |
| Deep vein thrombosis/PE | 10.2 | 4.9 | 6.2 | 3.3 |
| Ischaemic heart disease† | 5.9 | 3.3 | 4.6 | 2.1 |
| Second primary malignancy† | 2.8 | 2.3 | 3.3 | 2.8 |
| **Haematologic AEs** | | | | |
| Anaemia | 42.6 | 17.9 | 39.8 | 17.2 |
| Neutropenia | 37.8 | 29.6 | 33.7 | 26.5 |
| Thrombocytopenia | 29.1 | 16.6 | 22.6 | 12.3 |

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

## POLLUX study

**Dara-RD**
**Dara 16 mg/Kg**
**weekly x 8 wks,**
**then Q2w x 16 wks**
**then Q4w thereafter**

**Lena 25 mg 1-21**
**Dexa 40 md weekly**

R

RD

Lena 25 mg 1-21
Dexa 20 md weekly

**Dimopoulos et al, NEJM 2016**
**follow-up 13,5 months**

## CASTOR study

**Dara-VD**
**Dara 16 mg/Kg sc**
**weekly x 10 wks,**
**then Q3 until VD end,**
**then Q4w thereafter**

**Bortezomib 1,4,8,11**
**Dexa 20 mg 1,2,4,5,8,9,11,12**
**(for 1 °8 cycles)**

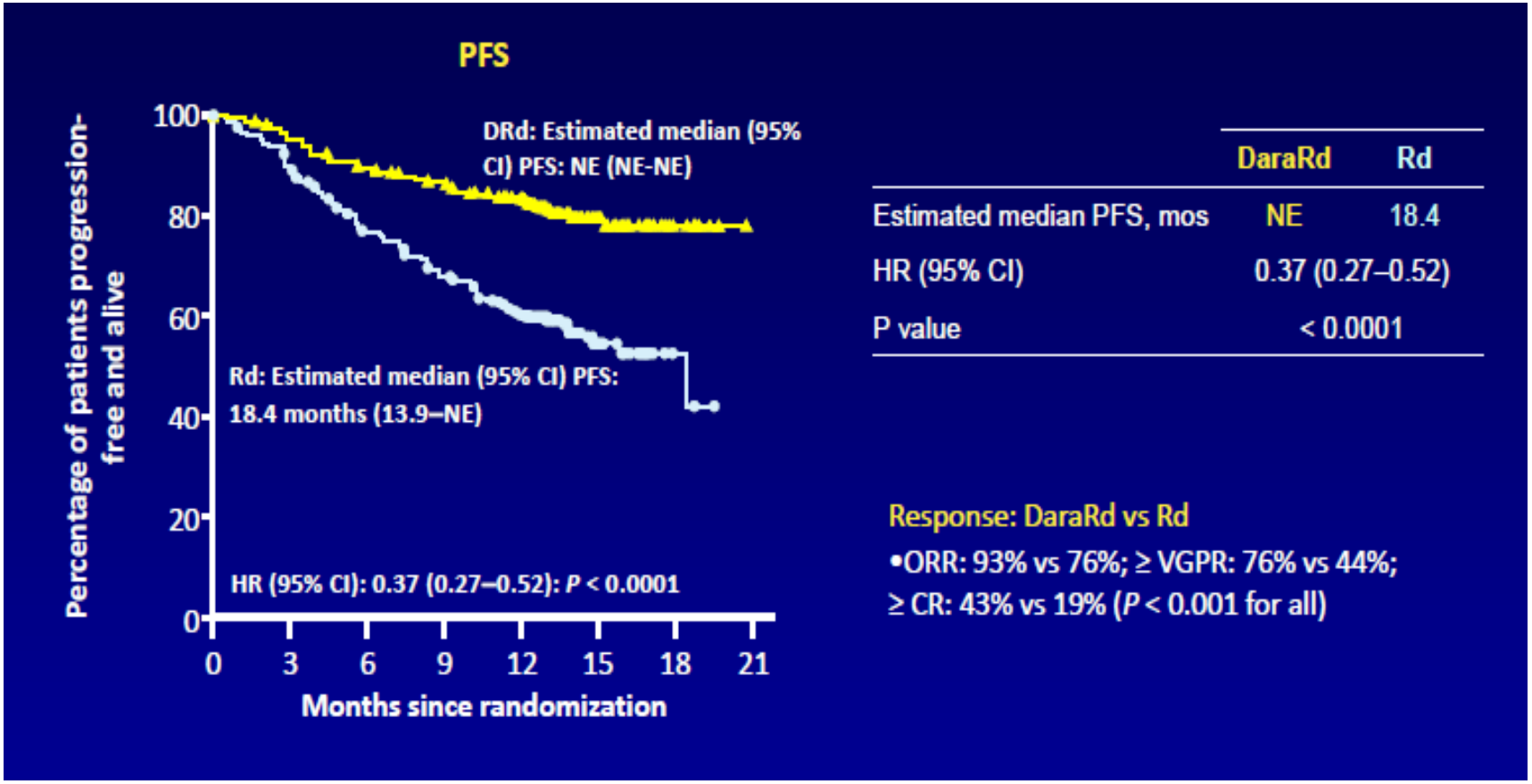
R

**VD**

**Bortezomib 1,4,8,11**
**Dexa 20 mg 1,2,4,5,8,9,11,12**
**(for 1° 8 cycles)**

**Palumbo et al, NEJM 2016**
**follow-up 7,4 months**

# POLLUX: Daratumumab-Lenalidomide-Dexamethasone (DaraRd) vs Lenalidomide-Dexamethasone (Rd)




| | DaraRd | Rd |
|---|---|---|
| Estimated median PFS, mos | NE | 18.4 |
| HR (95% CI) | 0.37 (0.27–0.52) | |
| P value | < 0.0001 | |

Response: DaraRd vs Rd

- ORR: 93% vs 76%; ≥ VGPR: 76% vs 44%; ≥ CR: 43% vs 19% ($P < 0.001$ for all)

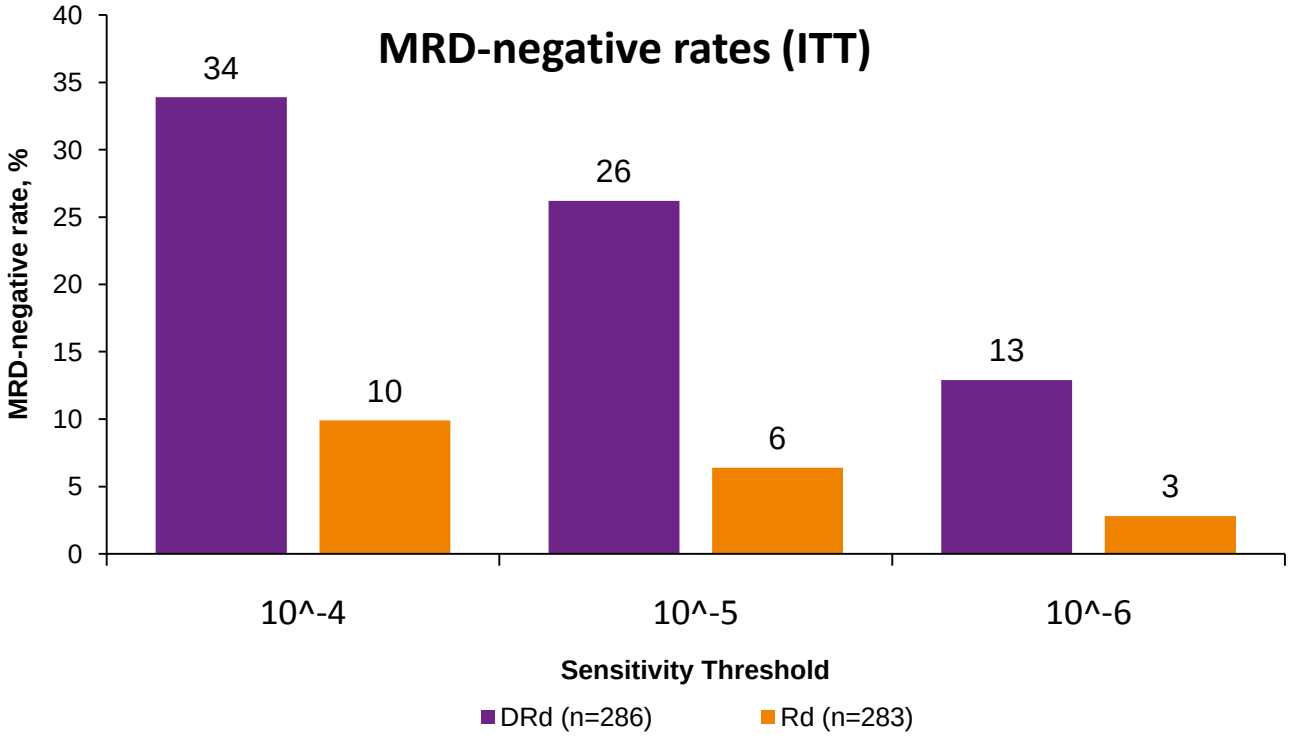
Safety profile: DaraRd vs Rd

Most common grade 3/4 TEAEs were neutropenia (52% vs 37%), thrombocytopenia (13% vs 14%) and anaemia (12% vs 20%)

Infusion reactions (48%) mostly were grade 1/2 (grade 3/4, 5% vs 0%)

# Efficacy and Safety of Daratumumab, Lenalidomide, and Dexamethasone (DRd) Versus Rd Alone in Relapsed or Refractory Multiple Myeloma (RRMM)

## MRD evaluation by NGS in the Updated Analysis of POLLUX



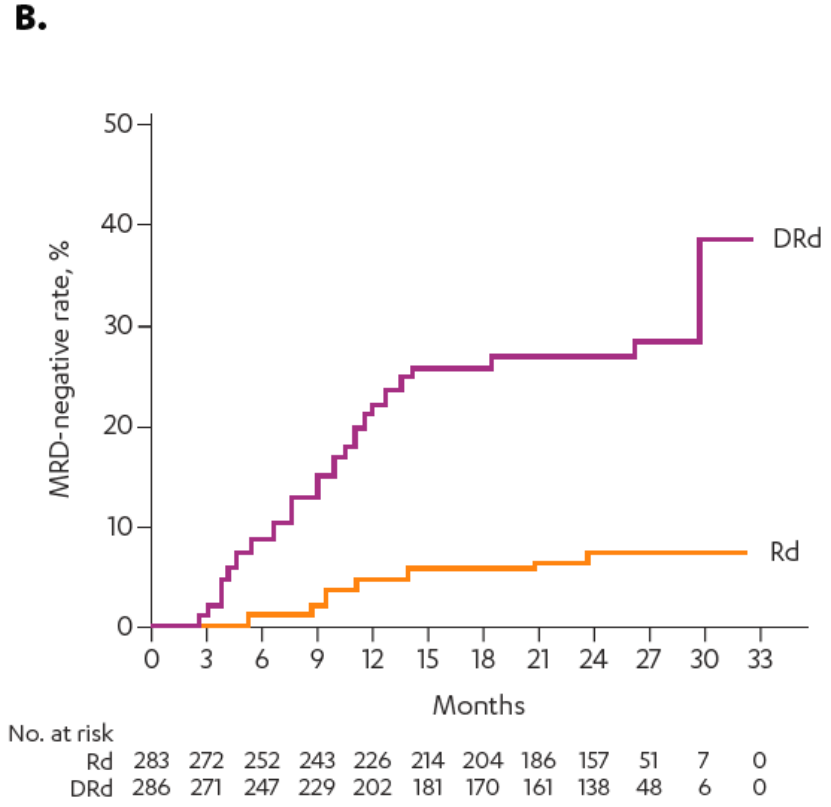

*P*<0.000001

Abstract P334: Dimopoulos, et al EHA 2017

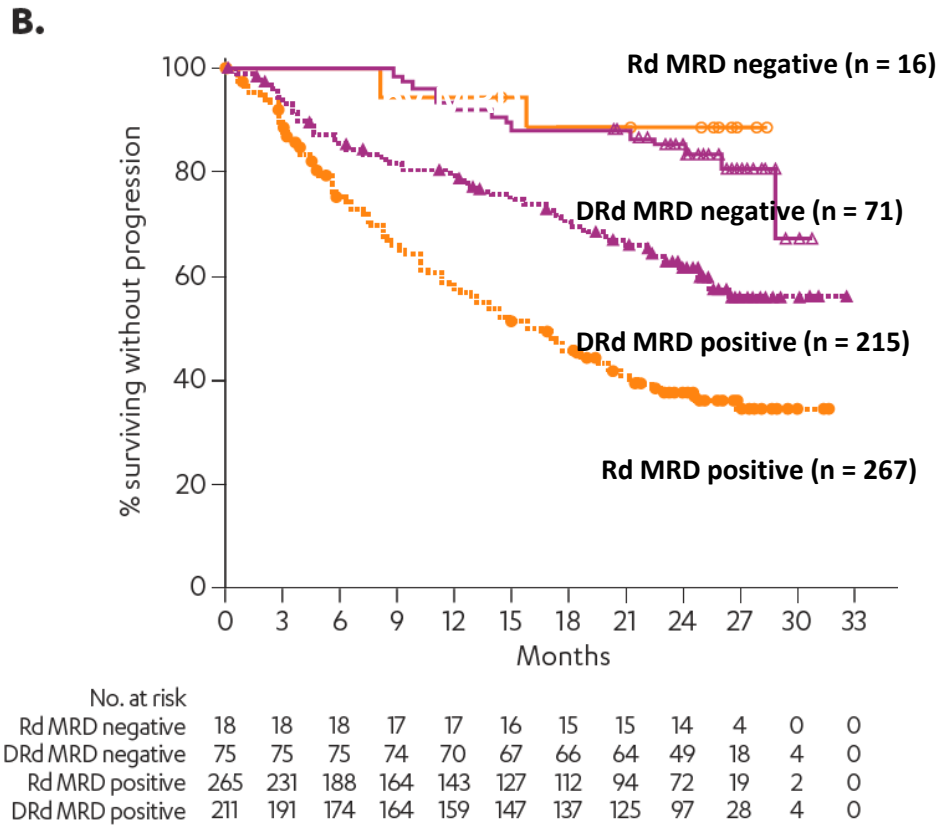
# Efficacy and Safety of Daratumumab, Lenalidomide, and Dexamethasone (DRd) Versus Rd Alone in Relapsed or Refractory Multiple Myeloma (RRMM)

## MRD evaluation in the Updated Analysis of POLLUX

### Time to MRD negativity ($10^{-5}$)

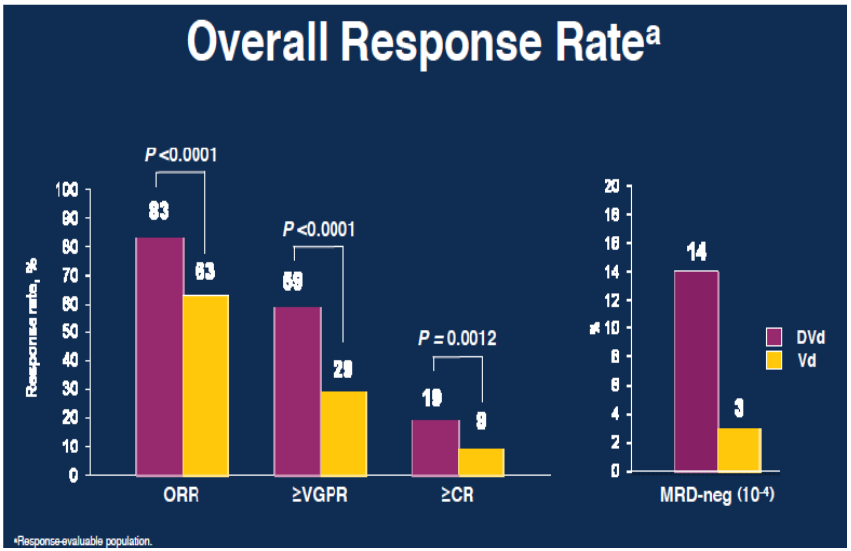


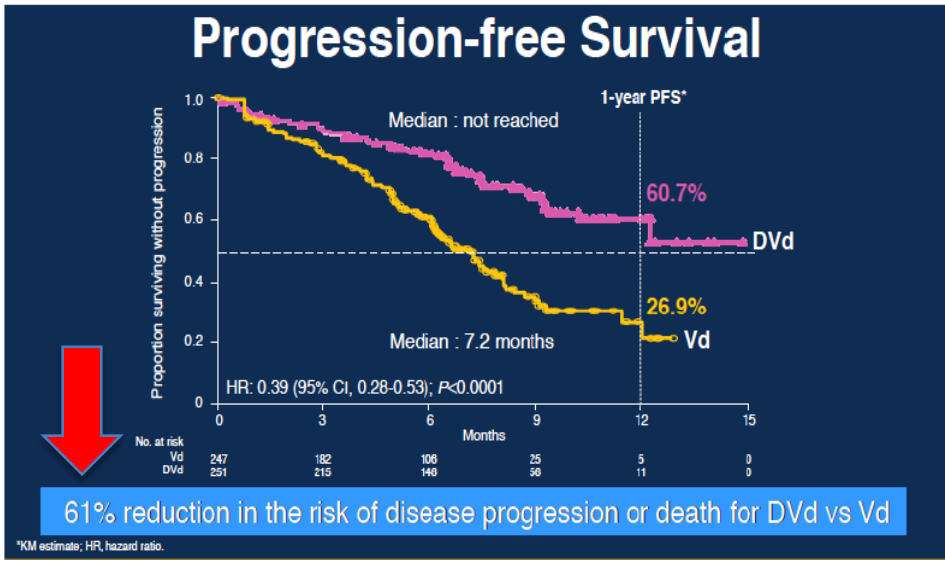

### PFS by MRD status ($10^{-5}$)




Abstract P334: Dimopoulos, et al EHA 2017

# CASTOR :Daratumumab, Lenalidomide, and Dexamethasone (DRd) Versus Bortezomib-Dexamethasone (Vd) Alone in Relapsed or Refractory Multiple Myeloma (RRMM)



## POLLUX
### *Incidence of Most Common TEAEs*

| Adverse Event | Dara/Len/Dex, % n = 286 | Len/Dex, % n = 283 |
|---|---|---|
| **Neutropenia** | **59** | **43** |
| **Diarrhea** | **43** | **25** |
| **Fatigue** | **35** | **28** |
| **Upper respiratory tract infection** | **32** | **21** |
| Anemia | 31 | 35 |
| Constipation | 29 | 25 |
| **Cough** | **29** | **13** |
| Thrombocytopenia | 27 | 27 |
| **Muscle spasms** | **26** | **19** |

Adverse events in **bold** were more common in daratumumab-containing arm.

Dimopoulos MA. EHA.

## POLLUX
### *Daratumumab Infusion-Related Reactions*

- 48% incidence of infusion-related reactions
  - Grade 3: 5%
  - Grade 4: 0%

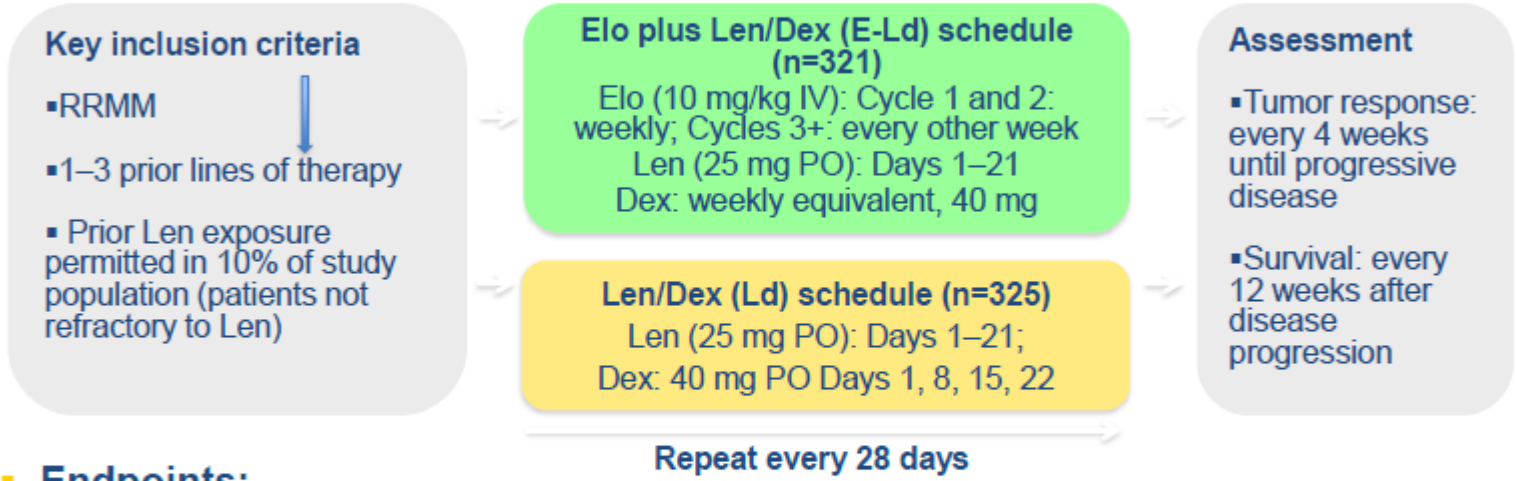
## CASTOR
### *Grade 3/4 TEAEs*

| | Dara+Bor/Dex (n=243) | Bor/Dex (n=237) |
|---|---|---|
| ***Hematologic TEAEs, %*** | | |
| Thrombocytopenia | 45.3 | 32.9 |
| Anemia | 14.4 | 16.0 |
| Neutropenia | 12.8 | 4.2 |
| Lymphopenia | 9.5 | 2.5 |
| ***Nonhematologic TEAEs, %*** | | |
| Pneumonia | 8.2 | 9.7 |
| Hypertension | 6.6 | 0.8 |
| Peripheral neuropathy | 4.5 | 6.8 |
| ***Discontinued, %*** | | |
| Due to peripheral neuropathy | 0.4 | 2.5 |
| Due to TEAEs | 7.4 | 9.3 |

Palumbo A, et al. *J Clin Oncol*.2016;34(suppl).

# ELOQUENT-2: Elotuzumab-Rd vs Rd

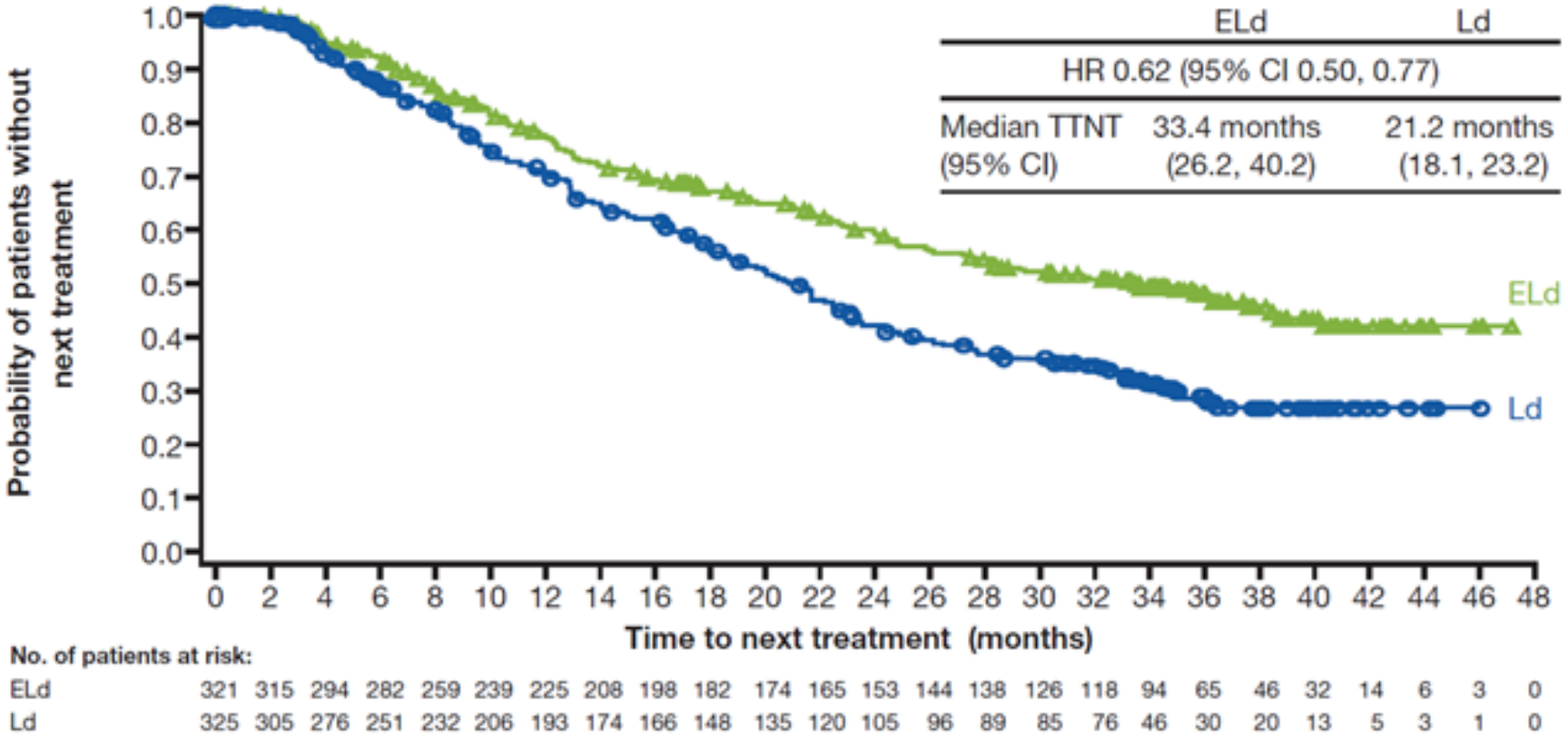
- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)



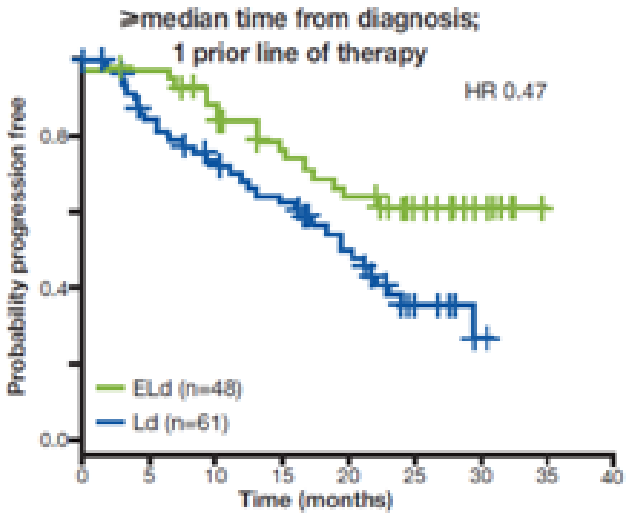

- **Endpoints:**
  - **Co-primary: PFS and ORR**
  - **Other: overall survival (data not yet mature), duration of response, quality of life, safety**
- **All patients received premedication to mitigate infusion reactions prior to elotuzumab administration**
- **Elotuzumab IV infusion administered ~ 2–3 hours**

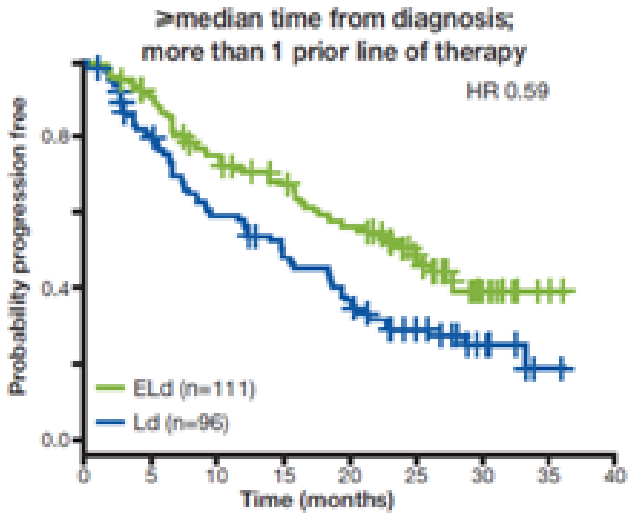
***Lonial S et al N Engl J Med, 2015: 1-11***

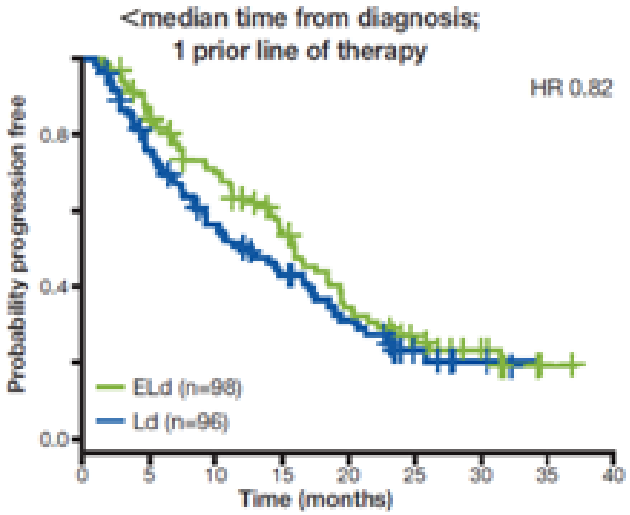
# Time to Next Treatment

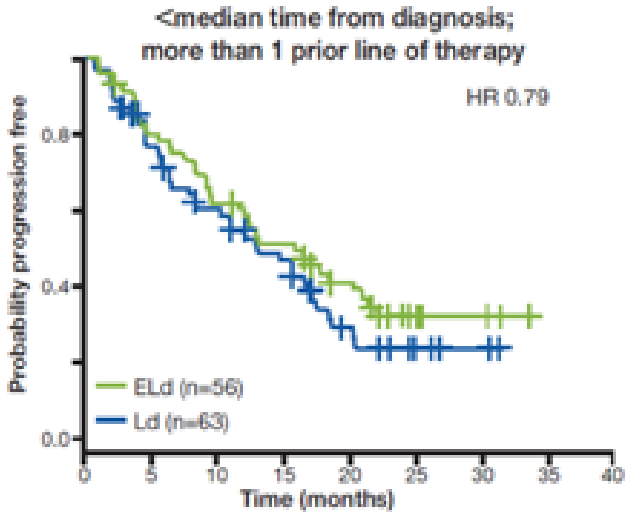


# ELOQUENT-2: PFS stratified by median time from diagnosis and number of prior lines of therapy



# ELOQUENT 2: *Safety*

| Adverse events reported in ≥30% of patients, n (%) | E-Ld (n=318) | | Ld (n=317) | |
|---|---|---|---|---|
| | Any grade | Grade 3–4 | Any grade | Grade 3–4 |
| **All AEs regardless of relationship** | **316 (99)** | **248 (78)** | **314 (99)** | **212 (67)** |
| Non-Hematologic Adverse Events | | | | |
| Fatigue | 154 (48) | **29 (9)** | 128 (40) | **26 (8)** |
| Diarrhea | 152 (48) | **17 (5)** | 118 (37) | **15 (5)** |
| Pyrexia | 122 (38) | **9 (3)** | 79 (25) | **9 (3)** |
| Constipation | 114 (36) | **4 (1)** | 88 (28) | **1 (<1)** |
| Cough | 105 (33) | **1 (<1)** | 60 (19) | **0** |
| Muscle spasms | 96 (30) | **2 (<1)** | 84 (27) | **3 (<1)** |
| Hematologic Adverse Events | | | | |
| Anemia | 130 (41) | **49 (15)** | 118 (37) | **52 (16)** |
| Neutropenia | 108 (34) | **81 (26)** | 137 (43) | **105 (33)** |

# MM:Trattamenti disponibili nella "*early relapse*"

| Regimen | ORR (VGPR) | Median PFS | HR | 2-year OS |
|---|---|---|---|---|
| KRD Carfilzomib-lenalidomide-dexa | 87% (69%) | 26.3 m | 0.70 | 73% |
| Elo-RD Elotuzuman-lenalidomide-dexa | 79% (33%) | 19.4 m | 0.68 | 74% |
| Daratumumab-VD | 86% (33%) | 16.7 m (26.2 mo in first R) | 0.33 | NA |
| Daratumumab-RD | 93% (55%) | 17.5 m (32.9 in first R) | 0.37 | NA |

Sstewart et al, NEJM 2017; Lonial et al , NEJM 2015
Spencer et al, ASH 2017, Moreau et al, ASH 2017

# MM:Trattamenti disponibili nella "*advanced relapse*"

| Regimen | ORR | PFS | OS |
|---|---|---|---|
| **Pomalidomide-Dexametasone** | **32%** | **4 m** | **13 m** |
| **Daratumumab** | **31%** | **4 m** | **20 m** |

**San Miguel, Lancet Oncol, 2013; Usman, Blood, 2016**

# Considerazioni sulla sicurezza dei trattamenti del MM R/R

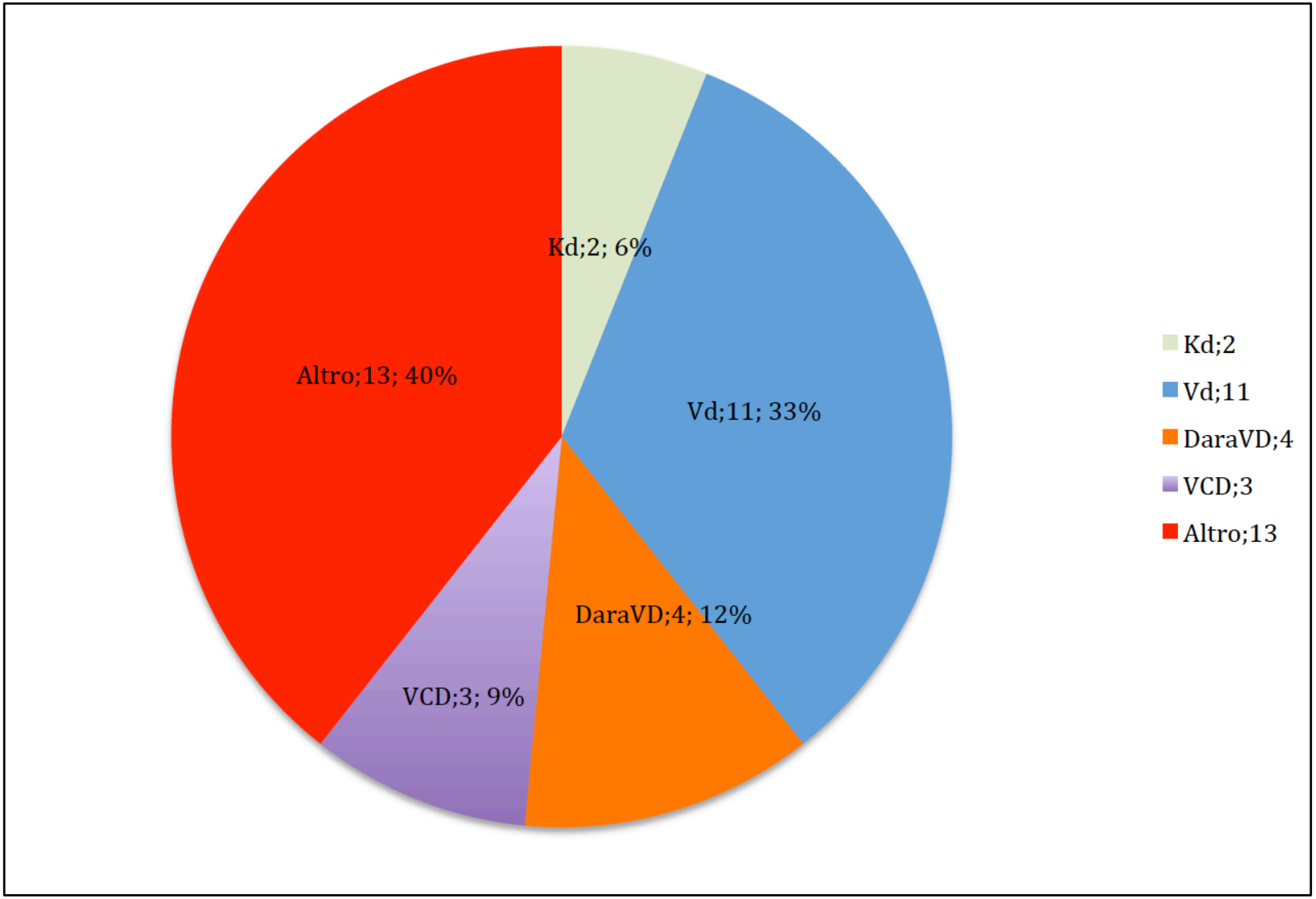
| | Poma-dexa | KRD | Elo-RD | Daratumumab |
|---|---|---|---|---|
| Neuropathy | | | | |
| Cardiac disorders | | ✔ | | |
| Infusion reactions | | | ✔ | ✔ |
| Neutropenia | ✔ | ✔ | ✔ | |
| Thrombocytopenia | ✔ | ✔ | ✔ | |
| Thrombosis | ✔ | ✔ | ✔ | |

# Considerazioni pratiche in merito ai trattamenti del MM RR

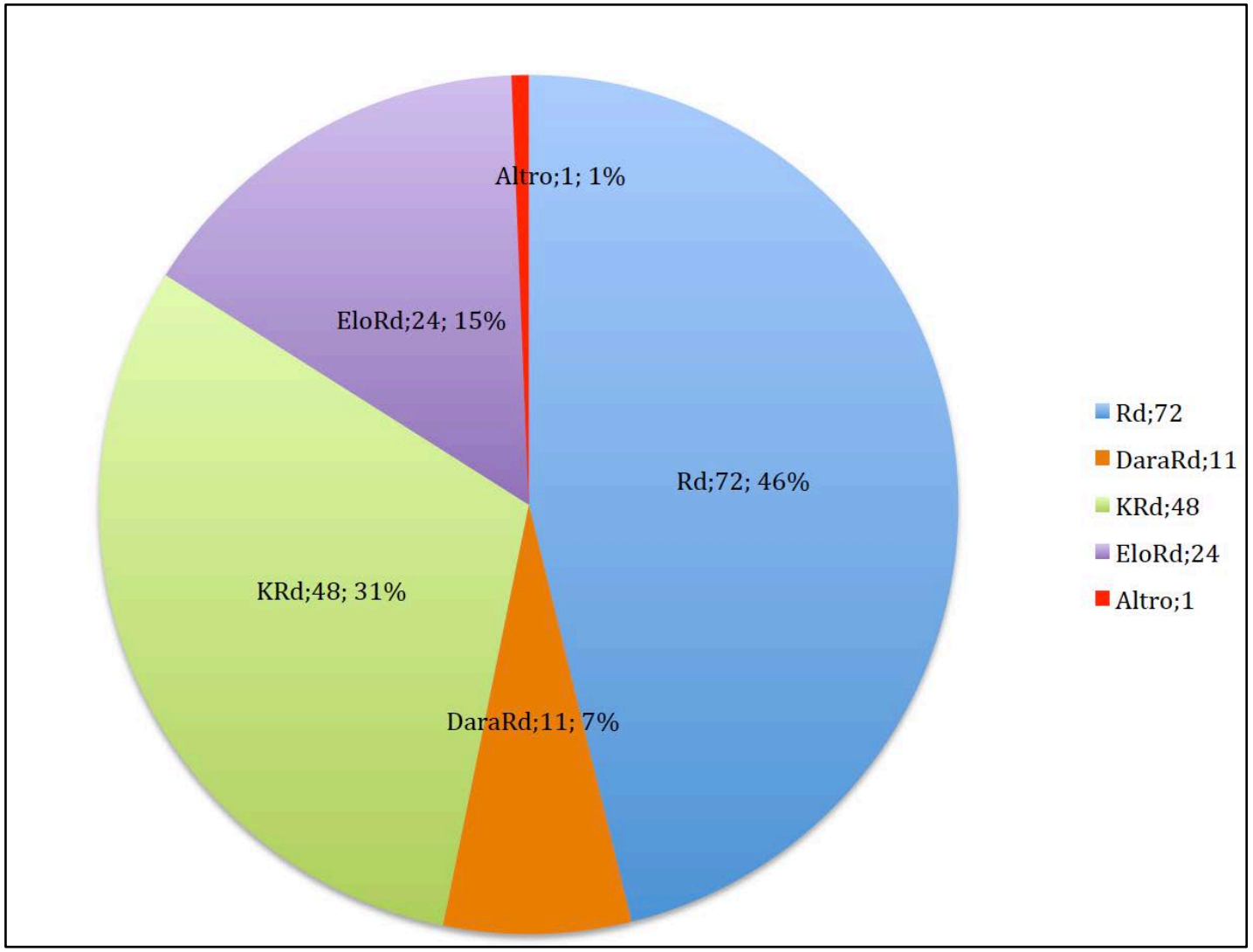
| | Poma-dexa | KRD | Elo-RD | daratumumab |
|---|---|---|---|---|
| Continuous therapy | ✔ | ✔ | ✔ | ✔ |
| Hospital access | Fully outpatient | 72/year | 28/year | 22/year |
| Drug cost | ✔ | ✔ | ✔ | ✔ |

# MM: prima recidiva dopo I linea

## *"IMID-based"*

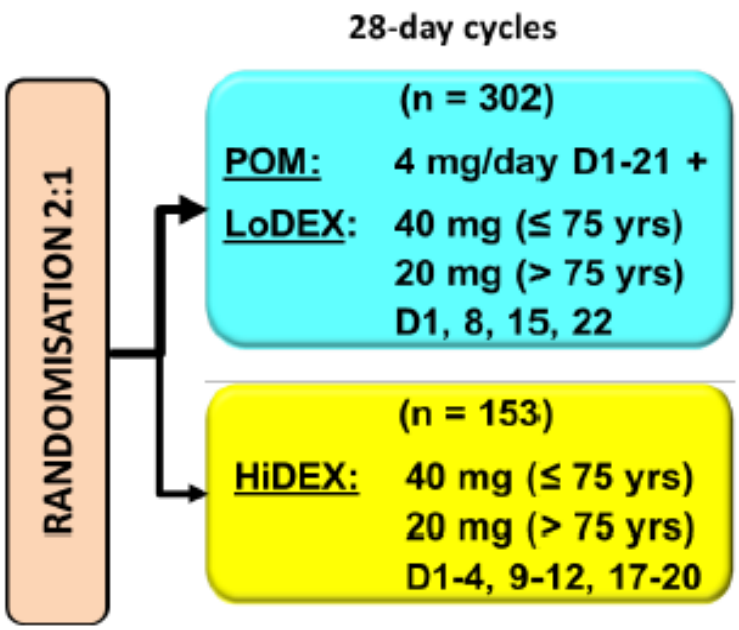


# MM:prima recidiva dopo I linea *"Bortezomib-based"*



# MM-003 Study: POM + LoDEX vs HiDEX

Open-label, multicenter, phase III trial designed to compare the efficacy and safety of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in a population of patients refractory to both lenalidomide and bortezomib




Primary endpoint: PFS

Key secondary endpoints: OS, ORR (≥ PR), DoR, Safety

| Baseline Characteristic | POM + LoDEX (n = 302) | HiDEX (n = 153) |
|---|---|---|
| Prior SCT | 71% | 69% |
| LEN-refractory | 95% | 92% |
| BORT-refractory | 79% | 79% |
| LEN+BORT-refrac | 75% | 74% |

**Best Response Rate**

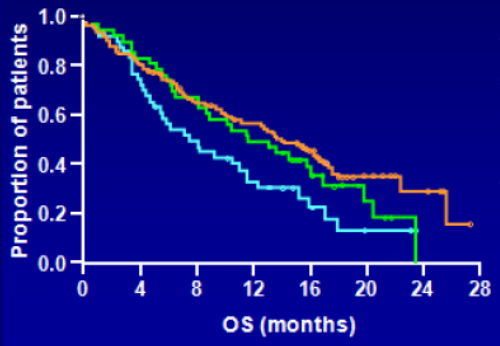
| Response | POM + LoDEX (N = 302) | HiDEX[a] (N = 153) | *P* Value |
|---|---|---|---|
| ORR (≥ PR), n (%) | 97 (32) | 17 (11) | < .001 |
| ≥ VGPR | 21 (7) | 1 (1) | — |
| sCR/CR | 4 (1) | 0 (0) | — |
| ≥ MR, n (%) | 122 (40) | 23 (15) | — |
| Median DOR, mos (95% CI) | 7.5 (6.0-9.5) | 5.1 (1.7-8.5) | .031 |

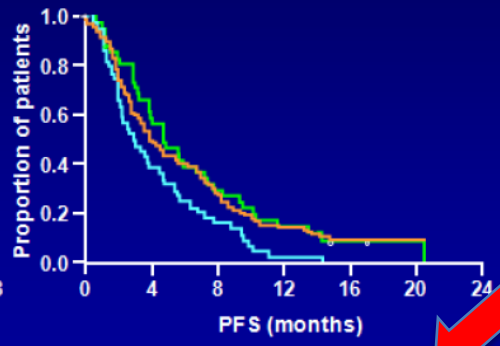
San Miguel et al: ASCO 2013; Oral & Abstract 8510.

## 2. PFS and OS by cytogenetic risk group *(MM-003 Trial)*

| POM + LoDEX | Median OS | HR | Logrank *P*ª |
|---|---|---|---|
| Standard risk (n = 148) | 14.0 months | – | – |
| del(17p) (n = 44) | 12.6 months | 1.22 | 0.358 |
| t(4;14) (n = 44) | 7.5 months | 1.72 | 0.008 |

| POM + LoDEX | Median PFS | HR | Logrank *P*ª |
|---|---|---|---|
| Standard risk (n = 148) | 4.2 months | – | – |
| del(17p) (n = 44) | 4.6 months | 0.99 | 0.942 |
| t(4;14) (n = 44) | 2.8 months | 1.50 | 0.023 |




**Pom + Dex is efficacious in patients with RRMM and del(17p)**

## MM-003: Progression-free and overall survival by cytogenetic risk group

| | del(17p) | | t(4;14) | | Standard risk | |
|---|---|---|---|---|---|---|
| | POM + LoDEX (n = 44) | HiDEX (n = 23) | POM + LoDEX (n = 44) | HiDEX (n = 15) | POM + LoDEX (n = 148) | HiDEX (n = 72) |
| Median PFS, months | 4.6 | 1.1 | 2.8 | 1.9 | 4.2 | 2.3 |
| HR (*P*-value) | 0.34 (< 0.001) | | 0.49 (0.028) | | 0.55 (< 0.001) | |
| Median OS, months | 12.6 | 7.7 | 7.5 | 4.9 | 14.0 | 9.0 |
| HR (*P*-value) | 0.45 (0.008) | | 1.12 (0.761) | | 0.85 (0.380) | |

- POM + LoDEX significantly improved PFS vs HiDEX regardless of the presence of del17p or t(4;14)

blood®
Prepublished online May 25, 2016;
doi:10.1182/blood-2016-02-700872

# Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS ™ (MM-010): a phase 3b study in refractory multiple myeloma

Meletios A. Dimopoulos, Antonio Palumbo, Paolo Corradini, Michele Cavo, Michel Delforge, Francesco Di Raimondo, Katja C. Weisel, Albert
Hartmut Goldschmidt, Chantal Do
Reinier Raymakers, Jesus San Mi
Gareth Morgan, Neil Miller, Mathe
Zaki and Philippe Moreau

## STRATUS: Efficacy by prior treatment

| Patient population | Median PFS, months (95% CI) | Median OS, months (95% CI) |
|---|---|---|
| ITT population | 4.4 (3.9–4.9) | 12.0 (10.6–13.6) |
| LEN refractory | 4.4 (3.8–4.9) | 12.0 (10.5–13.4) |
| BORT refractory | 4.2 (3.7–4.9) | 11.9 (10.5–13.4) |
| LEN + BORT refractory | 4.2 (3.7–4.8) | 12.0 (10.4–13.4) |

Patients with RRMM (up to 720)[a]

Follow-up for subsequent Tx, OS, and SPM until 5 yrs post-enrollment of last patient

Throm

or equivalent was required for all pts

# Pomalidomide plus low-dose dexamethasone in multiple myeloma with deletion 17p and/or translocation (4;14): IFM 2010-02 trial results

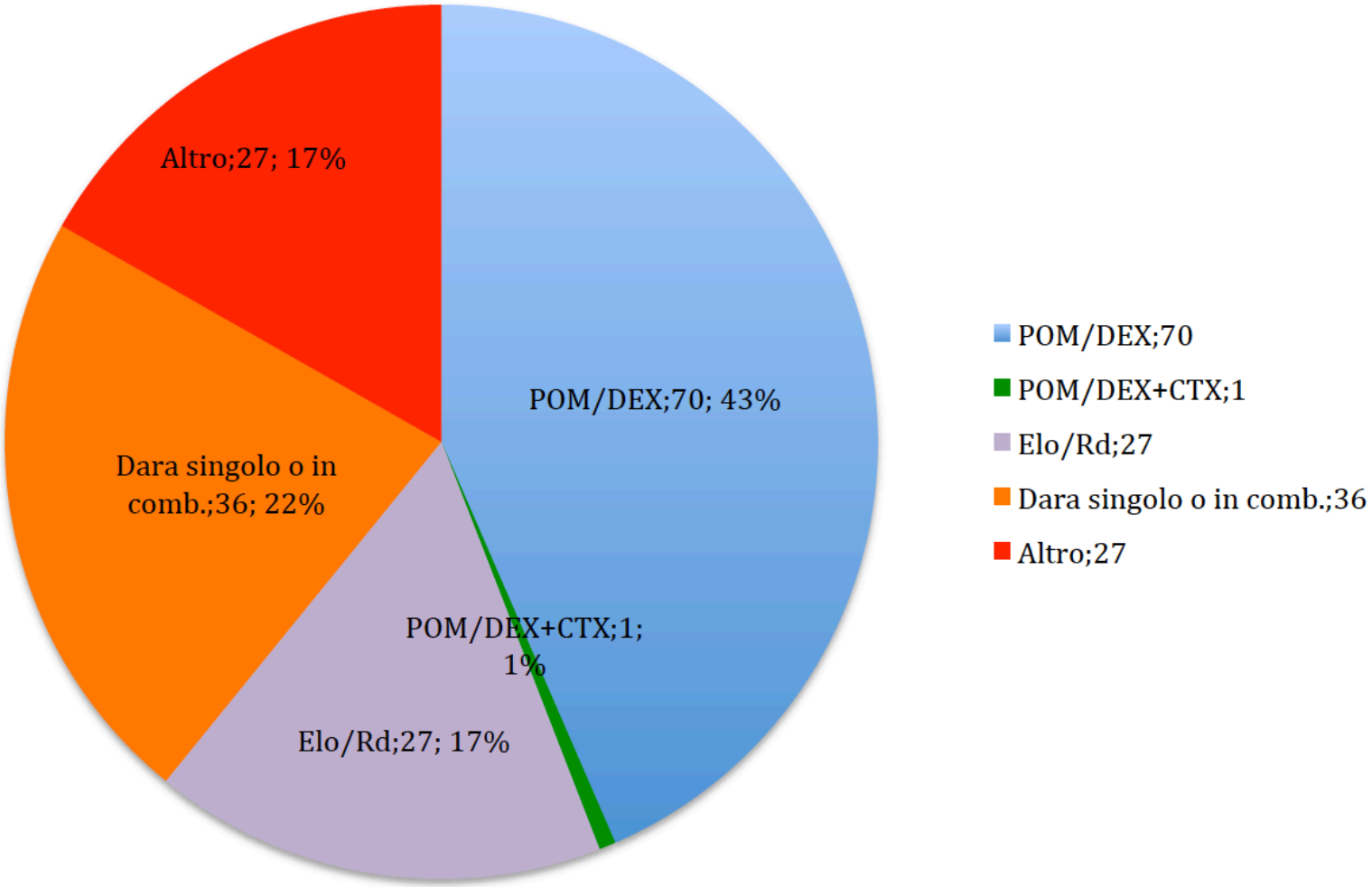
Xavier Leleu,[1] Lionel Karlin,[2] Margaret Macro,[3] Cyrille Hulin,[4] Laurent Garderet,[5] Murielle Roussel,[6] Bertrand Arnulf,[7] Brigitte Pegourie,[8] Brigitte Kolb,[9] Anne Marie Stoppa,[10] Sabine Brechiniac,[11] Gerald Marit,[12] Beatrice Thielemans,[1] Brigitte Onraed,[1] Claire Mathiot,[13] Anne Banos,[14] Laurence Lacotte,[15] Mourad Tiab,[16] Mamoun Dib,[17] Jean-Gabriel Fuzibet,[18] Marie Odile Petillon,[1] Philippe Rodon,[19] Marc Wetterwald,[20] Bruno Royer,[21] Laurence Legros,[18] Lotfi Benboubker,[22] Olivier Decaux,[23] Martine Escoffre-Barbe,[24] Denis Caillot,[25] Jean Paul Fermand,[7] Philippe Moreau,[26] Michel Attal,[6] Herve Avet-Loiseau,[6] and Thierry Facon,[1] for the Intergroupe Francophone du Myélome (IFM)

| | del17p (n = 22)[a] | t(4;14) (n = 32)[a] | Total (N = 50) |
|---|---|---|---|
| **Median TTP, months (95% CI)** | 7.3 (2.7–14.7) | 2.8 (1.9–4.0) | 2.96 (2.7–5.0) |
| 8-month TTP, % | 41 | 12.4 | 22 |
| **Median OS, months (95% CI)** | 12 (2–NR) | 9.2 (5–NR) | 12 (5–15) |
| 8-month OS, % | 58 | 50.5 | 55 |

Median TTP was longer in patients with del17p compared with patients with t(4;14): 7.3 and 2.8 months, respectively

***Leleu et al, Blood 2015***

# MM: seconda o successiva recidiva



# Scelta della strategia terapeutica nel MM

| | | |
|---|---|---|
| Patient characteristics | •**Age, PS, Geriatric assessment,Toxicity** | **STUDI CLINICI & REAL LIFE** |
| **Disease characteristics** | •**ISS stage, FISH Cytogenetics (?), LDH, Extramedullary disease, Renal failure, Plasma cell leukemia** | **STUDI CLINICI & REAL LIFE** |
| | •**FISH Cytogenetics, GEP, High LI** | **STUDI CLINICI** |
| **Tumor burden** | •**D-S stage, MRI, FLC + HLC** | **STUDI CLINICI & REAL LIFE** |
| | •**PET scan** | **STUDI CLINICI ?** |
| **Response** | •**CR *vs* other** | **STUDI CLINICI & REAL LIFE** |
| | •**MRD** | **STUDI CLINICI** |