MILANO
9 Novembre 2017

EVENTO REL
Rete
Ematologica
Lombarda

Immunoterapia nel
Mieloma Multiplo
e nel Linfoma di
Hodgkin

La terapia del mieloma ricaduto

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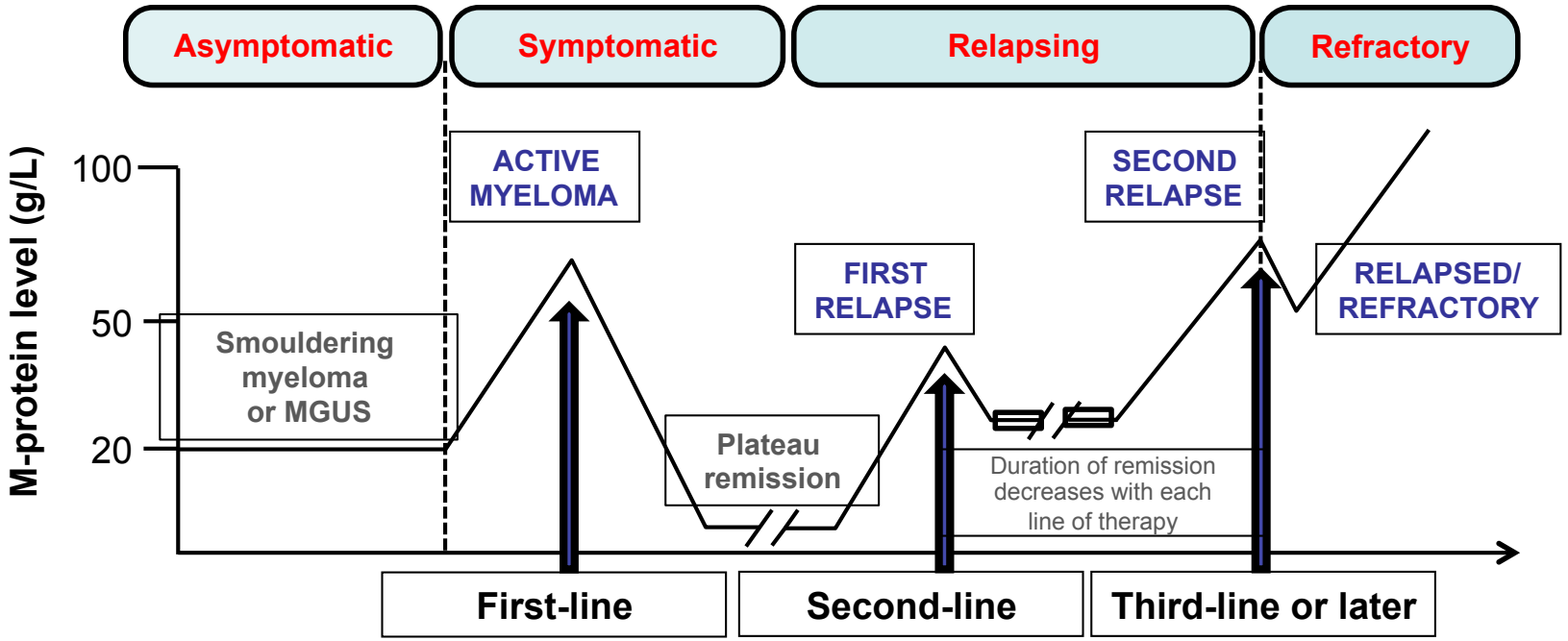
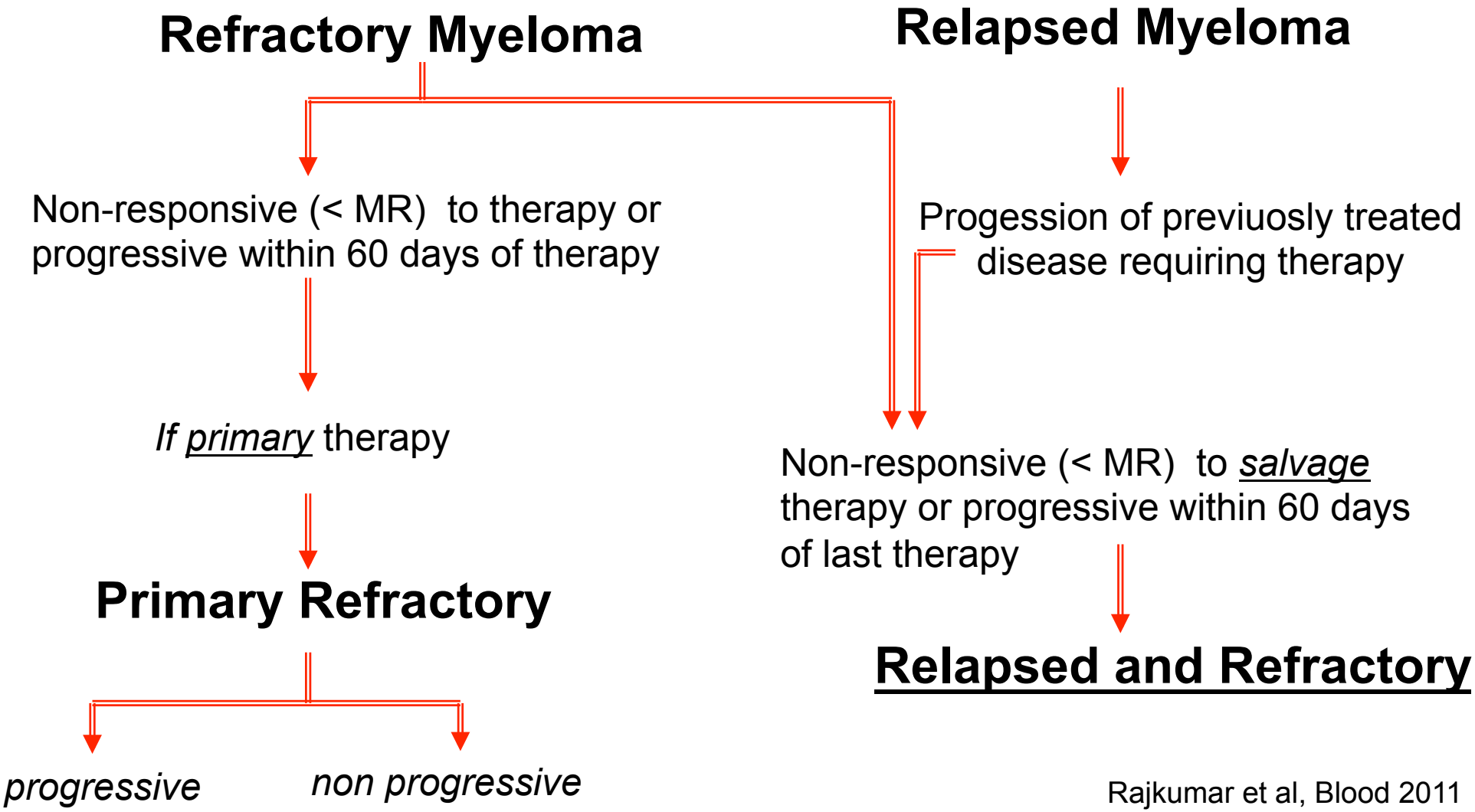
The natural course of MM is characterised by a pattern of remission and relapse



- Hajek R. Strategies for the Treatment of Multiple Myeloma in 2013: Moving Toward the Cure. In: Multiple Myeloma – A Quick Reflection on the Fast Progress, Prof. Roman Hajek (Ed.), InTech 2013; doi:10.5772/55366.

DEFINITIONS

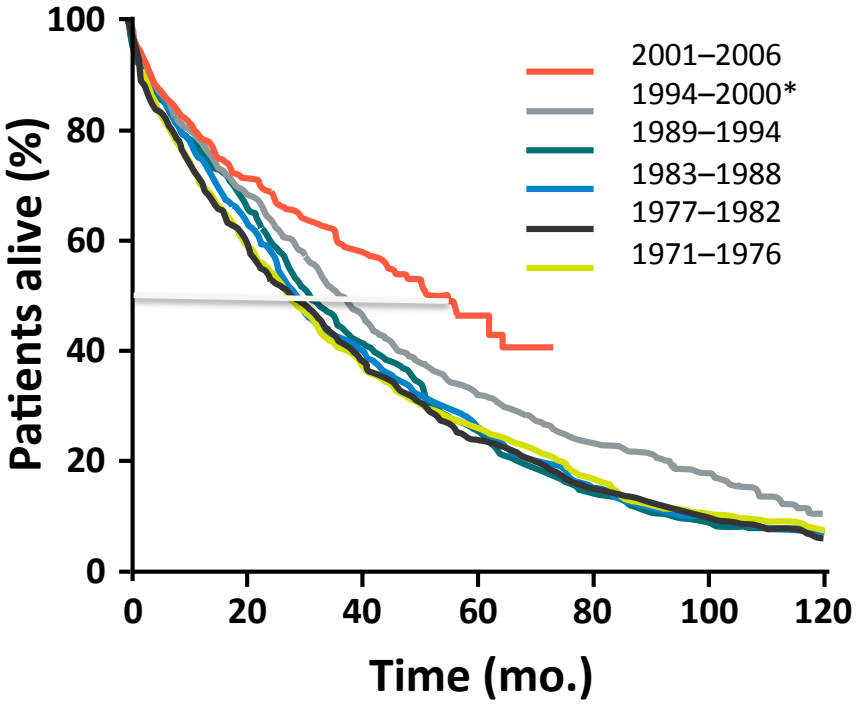
Progression: ↑ ≥ 25% of: serum (or absolute 500 mg/dl) and/or urine (or absolute 200 mg/day) MC and/or ratio involved/uninvolved serum FLC (or absolute increase > 100 mg/dl) and/or appearence of ROTI



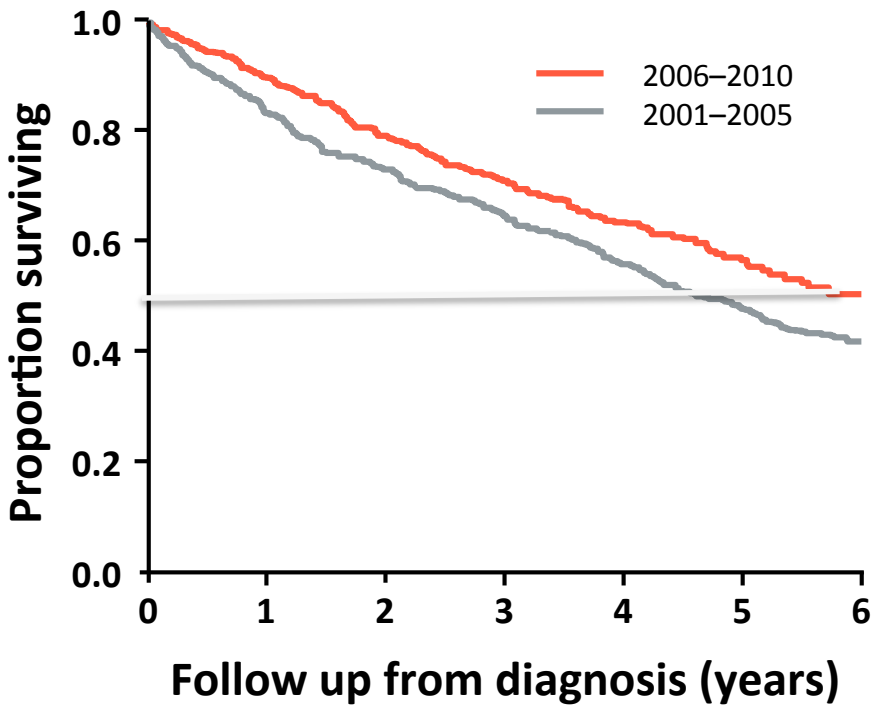
Rajkumar et al, Blood 2011

Overall survival (OS) in MM continues to improve vs. historical estimates

OS from diagnosis between 1971 and 2006 (N = 2,981)[1]



OS from diagnosis between 2001 and 2010 (N = 1,038)[2]

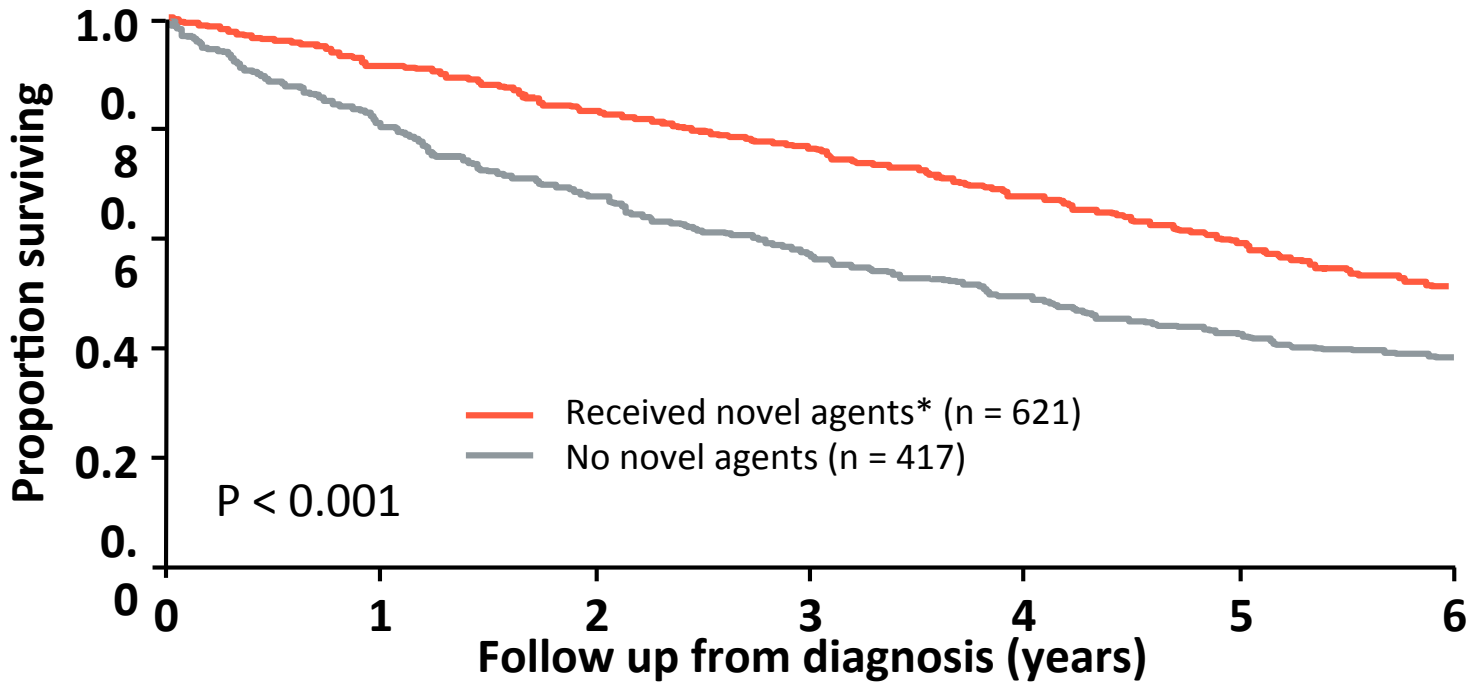


*Trend in improvement in this time period thought to be due to high-dose therapy (HDT) and supportive care

Kumar SJ, et al. Blood 2008;111:2516–2520;
Kumar SK, et al. Leukemia 2014;28:1122–1128.

Improvements in survival have been attributed to the use of novel agents

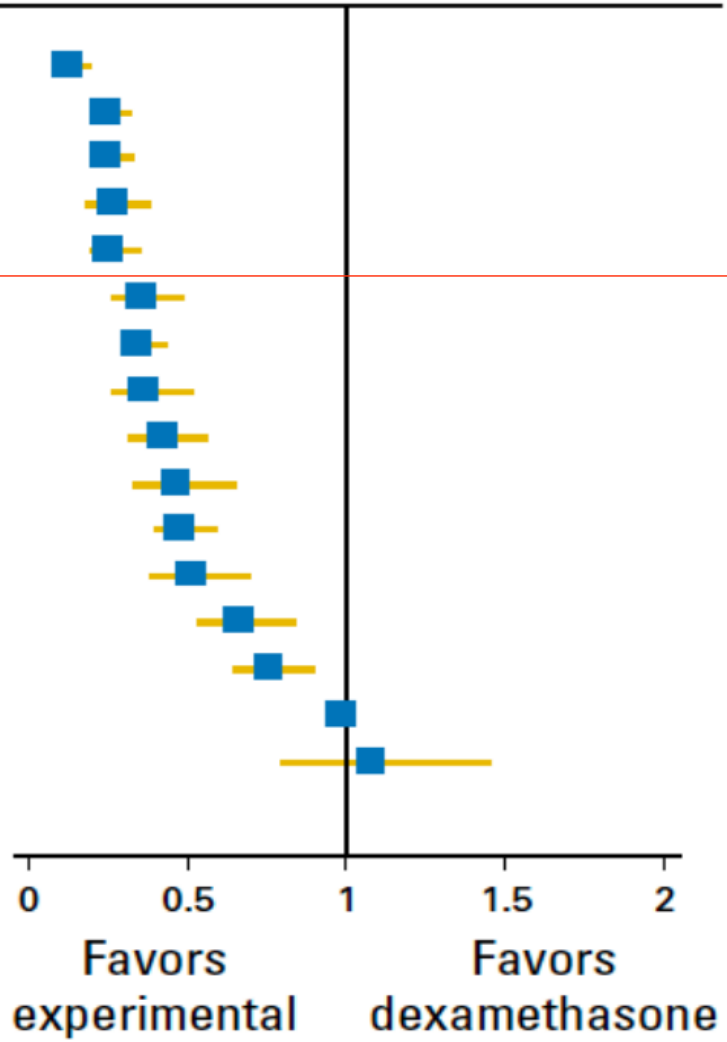
*Bortezomib (BTZ), lenalidomide (LEN) or thalidomide (THAL) as part of initial therapy



Kumar SK, et al. Leukemia 2014;28:1122–1128.

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

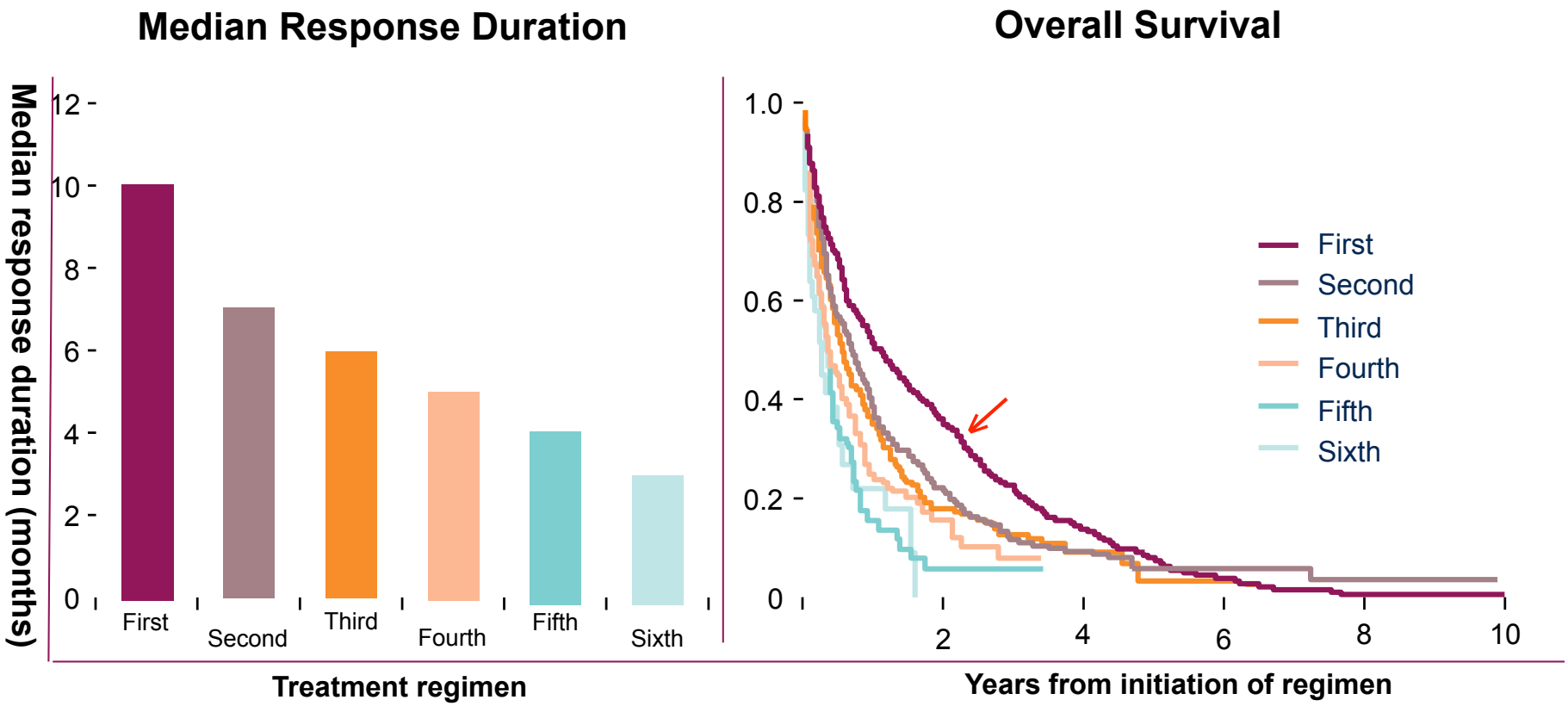
Treatment	% Being Best Treatment	Hazard Ratio *v* Dexamethasone (95% CrI), PFS
DaraLenDex	99	0.13 (0.09 to 0.19)
CarLenDex	0	0.24 (0.18 to 0.32)
EloLenDex	0	0.25 (0.19 to 0.33)
DaraBorDex	1	0.27 (0.18 to 0.38)
IxaLenDex	0	0.26 (0.19 to 0.35)
CarDex	0	0.36 (0.26 to 0.48)
LenDex	0	0.35 (0.29 to 0.43)
PegDoxBor	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

Relapses Associate with Adverse Prognosis

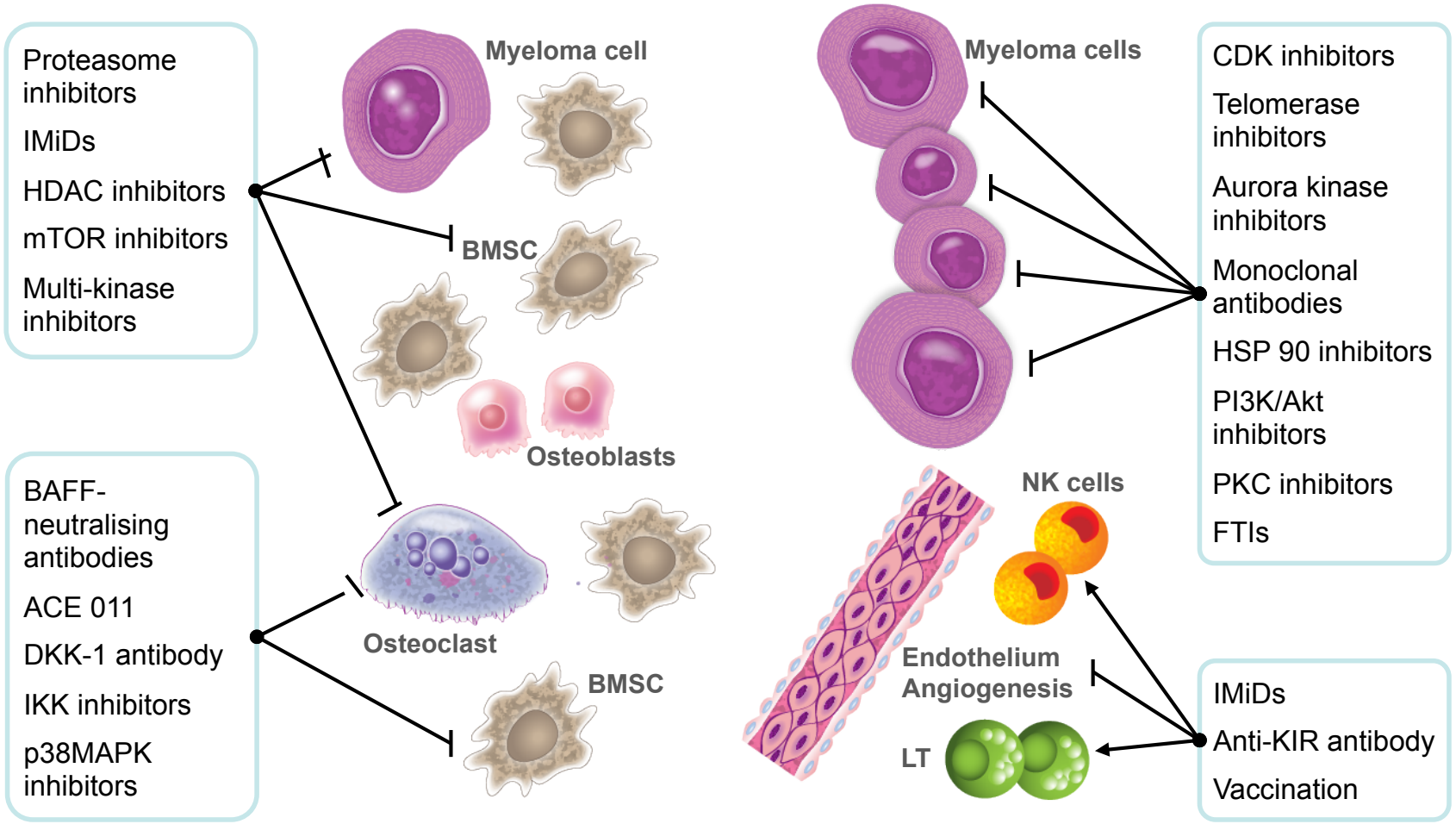
Response Duration and Overall Survival



Kumar et al., Mayo Clin Proc. 2004.

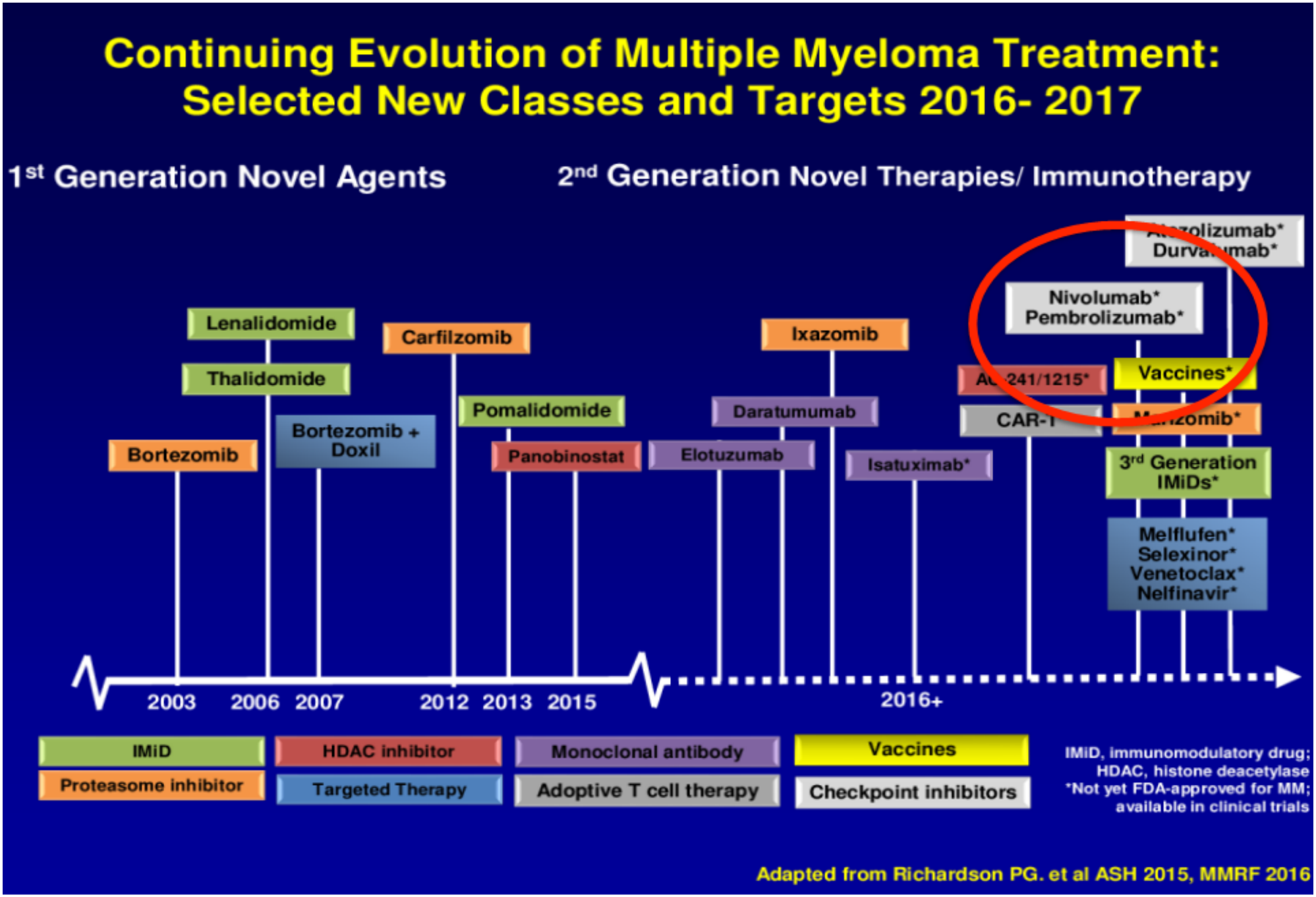
Available therapies

Novel agents target myeloma cells and the BM microenvironment

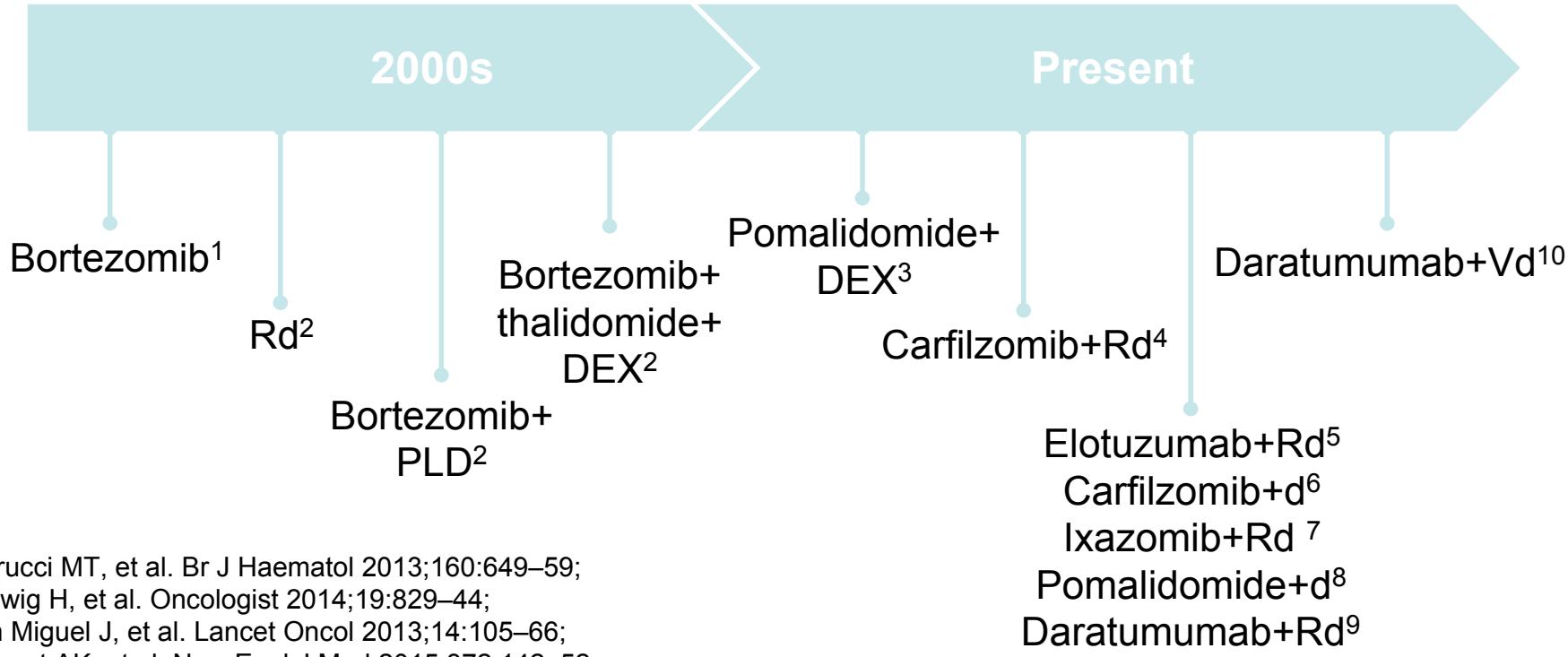


BMSC, bone marrow stromal cells; HDAC, histone deacetylase; IMiD, immunomodulatory drug; LT, lymphotoxin; NK, natural killer.

- Mahindra A, et al. Nat Rev Clin Oncol 2012;9:135–43.


Continuing Evolution of Multiple Myeloma Treatment: Selected New Classes and Targets 2016- 2017
1st Generation Novel Agents
2nd Generation Novel Therapies/ Immunotherapy
Lenalidomide
Thalidomide
Bortezomib
Bortezomib + Doxil
Carfilzomib
Pomalidomide
Panobinostat
Ixazomib
Daratumumab
Elotuzumab
Isatuximab*
Nivolumab*
Pembrolizumab*
241/1215*
CAR-T
Vaccines*
3rd Generation IMiDs*
Melflufen*
Selexinor*
Venetoclax*
Nelfinavir*
2003
2006
2007
2012
2013
2015
2016+
IMiD
Proteasome inhibitor
HDAC inhibitor
Targeted Therapy
Monoclonal antibody
Adoptive T cell therapy
Vaccines
Checkpoint inhibitors
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

Next generation of agents in randomised trials in RRMM



1. Petrucci MT, et al. Br J Haematol 2013;160:649–59;
2. Ludwig H, et al. Oncologist 2014;19:829–44;
3. San Miguel J, et al. Lancet Oncol 2013;14:105–66;
4. Stewart AK, et al. New Engl J Med 2015;372:142–52;
5. Lonial NEJM 2015
6. Dimopolous The Lancet Oncol 2015
7. Moreau NEJM 2016
8. Dimopolous Blood 2016
9. Dimopoulos NEJM 2016
10. Palumbo NEJM 2016

DEX, dexamethasone; PLD, pegylated liposomal doxorubicin; Rd, lenalidomide+dexamethasone; RRMM, relapsed/refractory multiple myeloma; Vd, bortezomib+dexamethasone.

Overview of Phase III Trials With Len and Bortezomib in Relapsed/Refractory MM

DOUBLETS "era"

Regimen	Trial	ORR, %	CR or nCR, %	≥ VGPR, %	DOR, Mos	TTP or PFS, Mos	Median OS, Mos
Len + dex	MM-009[1]	61	24	NE	16	11	35[5]
Len + dex	MM-010[2]	60	25	NE	17	11	
Bortezomib	APEX[3]	43	16	NE	8	6	30
Vdox	MMY-3001[4]	44	13	27	10	9	NE

1. Weber DM, et al. N Engl J Med. 2007;357:2133-2142. 2. Dimopoulos M, et al. N Engl J Med. 2007;357:2123-2132.
3. Richardson PG, et al. Blood. 2007;110:3557-3560. 4. Orlowski RZ, et al. J Clin Oncol. 2007;25:3892-3901.
5. Weber D, et al. Blood. 2007;110:Abstract 412.

Phase III Lenalidomide-Based Treatment Options for R/R Myeloma

TRIPLETS "era"

	ORR, %	CR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos	Median F/u, Mos
ASPIRE: KRd vs Rd[1] **(prior R: 19.9 vs 19.7%)**	87 vs 67	32 vs 9	70 vs 40	26.3 vs 17.6 HR: 0.69	NR HR: 0.79	32.3
TOURMALINE-MM1: IRd vs Rd[2] **(prior R: 12 vs 12%)**	78 vs 72	14 vs 7	48 vs 39	20.6 vs 14.7 HR: 0.74	NR	23
POLLUX: DRd vs Rd[3-5] **(prior R: 18 vs 18%)**	93 vs 76	46 vs 20	78 vs 45	NR vs 17.5 HR: 0.37	NR vs 20.3 HR: 0.64	17.3
ELOQUENT-2: ERd vs Rd[6,7] **(prior R: 5 vs 5%)**	79 vs 66	5 vs 9	35 vs 29	19.4 vs 14.9 HR: 0.73	48.3 vs 39.6 HR: 0.78	48

1. Stewart AK, et al. N Engl J Med. 2015;372:142-152. 2. Moreau P, et al. N Engl J Med. 2016;374:1621-1634. 3. Dimopoulos M, et al. N Engl J Med. 2016;375:1319-1331. 4. Dimopoulos M, et al. EHA 2016. Abstract LB238. 5. Dimopoulos M, et al. EHA 2017. Abstract P334. 6. Lonial S, et al. N Engl J Med. 2015;373:621-631. 7. Dimopoulos MA, et al. EHA 2017. Abstract S456.

Phase III Bortezomib-Based Treatment Options for R/R Myeloma

TRIPLETS "era"

Trial	ORR, %	CR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos	Median F/u, Mos
ENDEAVOR: Kd vs Vd[1] **(prior Bor: 12 vs 14%)**	77 vs 63	13 vs 6	54 vs 29	18.7 vs 9.4 HR: 0.53	NR vs 24.3 HR: 0.79	12
CASTOR: DVd vs Vd[2] **(prior Bor: 66 vs 65%)**	83 vs 63	19 vs 9	59 vs 29	NR vs 7.1 HR: 0.33	NR HR 0.77	13
PANORAMA-1: PanoVd vs Vd[3,4] **(prior Bor: 36 vs 43%)**	61 vs 55	11 vs 6	28 vs 16	12.0 vs 8.1 HR: 0.63	40 vs 36 HR: 0.94	NR
Elotuzumab (*Phase II*): EVd vs Vd[5] **(prior Bor: 50 vs 50%)**	66 vs 63	4 vs 3	36 vs 27	9.7 vs 6.9 HR: 0.72	NR HR: 0.61	16

1. Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38. 2. Palumbo A, et al. N Engl J Med. 2016;375:754-766. 3. San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206. 4. San-Miguel JF, et al. ASH 2015. Abstract 3026. 5. Jakubowiak A, et al. Blood. 2016;127:2833-2840

Efficacy of second-line new agents (single)

ADVANCED RELAPSE

Agent	INCLUSION CRITERA	N° pts	N° prior lines	ORR, %	≥ VGPR, %	DOR, Mos	TTP or PFS, median Mos	Median OS, Mos
Poma 2mg/day (1)	Len refract	60	2	63	33	NR at 7 mo	11.6	NR
Poma 4 mg/day (2)	> 1 line	43	5	35	4	6.4	11	
Poma 4 mg/day (3)	62% Len-Bort refractory	108	5	18	CR 2%	8.3	2.7	13.6
Ixazomib 4 mg-5.5 mg d 1,8,15 (5)	>1 line, not Bort refract	70	4	4	22-30	16,7	8.4	100% at 6 mo
Daratumumab 16 mg/kg, weekly x 8, twice/mo x 8 Montly (6)	> 3 line > 86% PI-IMID refract	148	5	31	13.5	7.6	4	20.1

1. Lacy et al, JCO, 2009; 2. Leleu et al, Blood, 2013; 3. Richardson et al, Blood, 2014; 4. Siegel et al, Blood, 2012; 5. Kumar et al, Blood, 2016; 6. Usmani et al, Blood, 2016

Earlier Phase Trials of Pomalidomide-Based Treatment Options for R/R Myeloma

Trial	Pt Population	Primary Endpoint	ORR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos
Bortezomib + Pom/Dex[1] (N = 34)	1-4 lines of tx Len refractory Prior PI allowed	MTD	65	41	NR	NR
Carfilzomib + Pom/Dex[2] (N = 32)	Relapsed or refractory to most recent tx Len refractory	MTD	50 (80 in del[17p])	16	7.2	20.6
Daratumumab + Pom/Dex[3] (N = 98)	≥ 2 lines of tx, including len and btz	---	71	43	NR (6-Mo: 66%)	---
Ixazomib + Pom/Dex[4] (N = 32)	1-5 lines of tx, including len and PI Len refractory	MTD Activity	48 (58 in high risk)	20	---	---

1. Richardson PG, et al. Leukemia. 2017;[Epub ahead of print]. 2. Shah JJ, et al. Blood. 2015;126: 2284-2290. 3. Chari A, et al. ASH 2015. Abstract 508. 4. Krishnan A, et al. ASH 2016. Abstract 3316.

MM Treatment: Key AEs, Considerations

Drug Class	Name	Key Potential AEs	Nursing Considerations
Proteasome inhibitors	Bortezomib	PN, T, M, F	IV, SC; monitor platelets; safe in renal failure
	Carfilzomib	PN, C, M, F, DVT	Hydration, cardio/pulmonary
	Ixazomib	PN, T, GI, R	Reduce dose for hepatic/renal disease
Immunomodulatory agents	Lenalidomide	DVT, M, BD, R, D	ASA or LMWH if high risk for clots; weekly CBC x 8 wks
	Thalidomide	DVT, M, BD	As above
	Pomalidomide	DVT, M, BD, F	As above
Monoclonal antibodies	Daratumumab	IR, M, RD	Infusion reaction risk; pre/post med as directed; interrupt infusion if reaction
	Elotuzumab	IR, M, RD	As above
HDAC inhibitors	Panobinostat	C, D	Baseline EKG and mag/K+ monitoring; loperamide for diarrhea

C: cardiac; D: diarrhea; DVT: deep vein thrombosis; F: fatigue; IR: infusion reaction; M: myelosuppression; T: thrombocytopenia; PN: peripheral neuropathy; GI: gastrointestinal toxicities (nausea, diarrhea, vomiting, constipation); R: renal dose adjustment necessary, BD: birth defects; RD: response disruption (mAbs can disrupt M protein assays, indicating potential lack of response).
CBC: complete blood count

Promising Agents in Clinical Trials for MM

Agent	MOA	Phase in Development
Pembrolizumab	PD-1 antibody	III
Ibrutinib	Tyrosine kinase inhibitor	III
Oprozomib	Proteasome inhibitor	III
Filanesib	Kinesin spindle protein inhibitor	II
Selinexor	XPO1 inhibitor	II
MOR202	CD38 antibody	I/II
Indatuximab ravtansine	CD138 antibody–drug conjugate	I/II
Ricolinostat	HDAC inhibitor	I/II
Durvalumab	PD-L1 antibody	I/II
Isatuximab	CD38 antibody	Ib
Venetoclax	Selective BCL-2 inhibitor	I

ClinicalTrials.gov

Most Recent FDA Approved Agents and Regimens for Relapsed/Refractory Myeloma

Treatment	Previous Lines of Therapy
✓ Carfilzomib (IV proteasome inhibitor) monotherapy	≥ 1
✓ Carfilzomib (IV proteasome inhibitor) + dexamethasone ± lenalidomide	1-3
✓ Daratumumab (IV CD38-targeted antibody) monotherapy	≥ 3
✓ Daratumumab (IV CD38-targeted antibody) + dexamethasone + either lenalidomide or bortezomib	≥ 1
✓ Daratumumab (IV CD38-targeted antibody) + dexamethasone + pomalidomide	≥ 2
✓ Elotuzumab (IV SLAMF7-targeted antibody) + lenalidomide + dexamethasone	1-3
✓ Ixazomib (PO proteasome inhibitor) + lenalidomide + dexamethasone	≥ 1
✓ Panobinostat (PO HDAC inhibitor) + bortezomib + dexamethasone	≥ 2

AIFA APPROVED AGENTS FOR RR-MM (30.9.2017)

- **IMIDs**: Lenalidomide (**Revlimd**)+ Dex
  Pomalidomide (**Imnovid**)+ Dex (third line)

- **Proteasome inhibitor**: Bortezomib (**Velcade**) + Dex
  Carfilzomib (**Kyprolis**) + Dex (coming soon also in Italy)

- **Combo:** Bortezomib + Peg-Liposomal Doxorubicine (**Caelyx**)
  Bendamustina + Bortezomib+ Dex
  Carfilzomib + Lenalidomide+ Dex (second line)
  Elotuzumab (**Empliciti**) + Lenalidomide + Dex (second line)

- **MoAbs**: Daratumumab (**Darzalex**) (third line)

- **Cytotoxic agents**: Cyclophosphamide, Etoposide,
  Cisplatin, Doxorubicin, Bendamustine

COSTO INDICATIVO TERAPIE INNOVATIVE PER IL MM RIMBORSABILI DALL'AIFA

Farmaco/ Combinazione	Costo mensile medio	Costo annuale	Note
RD	3.8-4.800	46-58.000	
VD	2.000	16-18.000	
PomaD	7.750	93.000	Succes fee (primi 3 mesi)
Daratumumab	----	94-66.00	1° vs 2° anno
KD	???	???	
KRD	8.000	96.000	Gratis after 16° cycle
ERD	7.500	90.000	
ASCT	------	50.000 (cad)	

Nov 2017

Questions at relapse in MM

- Wich diagnosticwork-up?
- When to treat?

  When treatment can be safely delayed?
  When early treatment should be activated?

- Which is the best treatment?
- How to use available drugs?
- How many time?
- When to consider a second ASCT?
- When to consider ABMT?

DIAGNOSTIC WORK-UP AT RELAPSE IN R/R MM

- medical history and physical examination
- complete blood count, serum creatinine, calcium and lactate dehydrogenase (LDH) determination, serum and urine (24-h collection) protein electrophoresis and immunofixation, serum FLC assay
- bone marrow aspirate with FISH to identify new chromosomal abnormalities
- Imaging with low-dose CT, magnetic resonance imaging; FDG-positron emission tomography, in selected cases, particularly in suspicion of extramedullary disease
- the role of ISS stage at relapse is unclear

About when

- Early re-treatment can be unnecessary as asymtomatic /biochemical relapse emerges; this may happen months or, in some cases, years later. In any case observation of biochemical relapse should be strict (6-8 ws), but:

  - ✓ *When patients show rapid increase in tumor load treatment should be started (clinical relapseop myeloma-related organ or tissue impairment (ROTI), or have a)*
  - ✓ *Elevated LDH value, rapidly rising of MC in the serum (< 1g/dl) or in the urine (<0.5 g/24 h) and light-chain escape (> 200 MG/L) should suggest to start (progressive biochemical relapse)*
  - ✓ *Previous complications MM-related (renal failure, EM disease) may indicate an earlier initiation of therapy*

FACTORS INFLUENCING CHOICE OF THERAPY

Disease-related factors

- ✓ Risk stratification (high-risk vs low-risk status)
- ✓ Acquired chromosomal aberrations
- ✓ Presence of end-organ damage
- ✓ Extramedullary disease
- ✓ Serum level of LDH

Treatment-related factors

- ✓ Prior drug therapy
- ✓ Toxicity/tolerability of previous regimen (PN, Myelosuppression)
- ✓ Depth and duration of response to prior drug

Patient-related factors

- ✓ Frailty score
- ✓ Comorbidity
- ✓ Susecptibility to infections
- ✓ Preference regarding the mode of treatment administration

The gol of Treatment in RR MM

- In end-stage and in frail R/ReMM, the therapeutic objective should be the quality of life.

- In early clinical relapse and progressive primary refractory carry a poor prognosis, therefore in these cases the maximum tolerable therapy should be administered.
  The therapeutic objective should be the PFS

- Patients whose disease relapses or progresses after a long plateau phase are likely to respond well to further treatment.
  The choice at first relapse is critical, since subsequent relapse are usually shorter.
  In these cases the main objective could be the OS

Aggressive Relapse

CRITERIA:

- Elevated lactate dehydrogenase (LDH) level
- Doubling M protein in short time (within 2 months)
- Extra-osseous disease
- Cytogenetic risk factors: t(4;14), del(17p), ampl(1q21)
- Appearence of circulating plasma cells

"Recommendations: Patients with symptomatic or aggressive relapse can be treated with KRD or KPD"

Rajkumar SV. American Journal of Hematology. 2016:91(7):719-734

Candidates for Len-based Therapy

- Disease progression on Bortezomib Regimen
- Disease progression after a prior course of Bortezomib-based Regimen (< 12 mos)
- Intolerance to Bortezomib
- Lenalidomide naive (or sensitive)

Len-based Therapy selection

- Frail-unfit patient: Rd (rd)
- Compliance, logistic problems: Rd
- High-risk, clinical progression, fit patient: KRD (dara-rD)
- Bridge to salvage first or second ASCT in fit patient: KRD (dara-RD); limited data on feasibility SC collection for dara-RD
- Biochemical progression, standard risk: ERD

Candidates for non-Len-based Therapy

- Disease progression on Len-based regimen
- Disease progression on Len maintenance therapy
- Intolerance to Len

Non-Len-based Therapy selection

- VD no longer an appropriate standard of care (selected patients)
- Clinical or biochemical progression: KD (dara-KD)
- Consider trials or off-label regimenBridge to salvage first or second ASCT in fit patient: KRD (dara-RD); limited data on feasibility SC collection for dara-RD
- Co-morbidities: PNP, cardiopulmonary disease, severe COPD/asthma

Non-Len-based Therapy selection

- VD no longer an appropriate standard of care (selected patients)
- Clinical or biochemical progression: KD (dara-KD)
- K is reasonable in pts with Len, Bor or Ixazomib resistant disease
- Consider trials or off-label regimens (KCyD or KPomD or Pom-Dara-Dex)
- Co-morbidities: PNP, cardiopulmonary disease, severe COPD/asthm
- VD-panobinostat ??

IN SECOND RELAPSE AND BEYOND

- Pomalidomide combined with dexamethasone is reimbursed in patients who have received at least two prior treatment regimens, including both bortezomib and lenalidomide, and have demonstrated disease progression on the last therapy. Efficacy can be increased in triplet combination using cyclophosphamide

- Daratumumab has been approved in monotherapy for the treatment of RRMM patients who have received at least two prior treatment regimens including both bortezomib and lenalidomide, and have demonstrated disease progression on the last therapy

ADVANCED RELAPSE

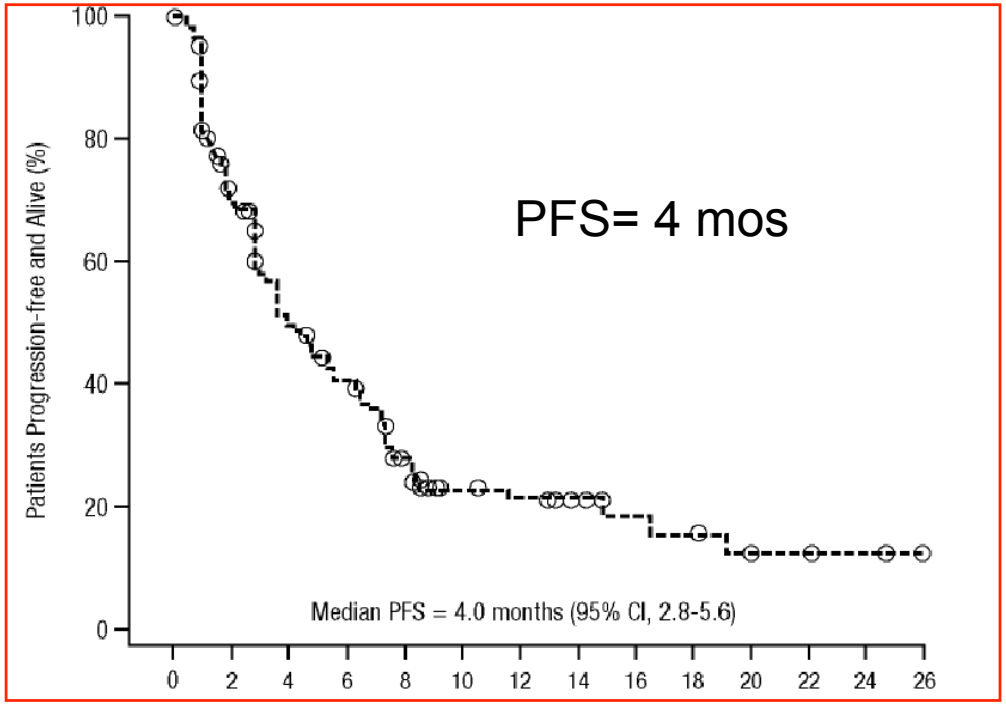
Treatments available at advanced relapse

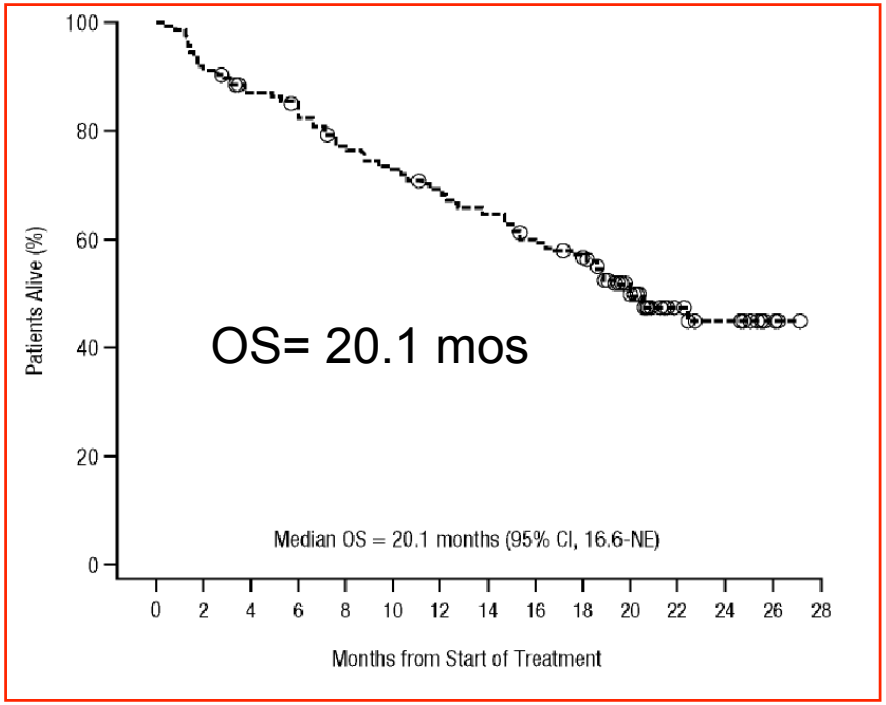
Regimen	ORR	PFS	OS
PomDexa	32%	4 m	13 m
Dara	31%	4 m	20 m

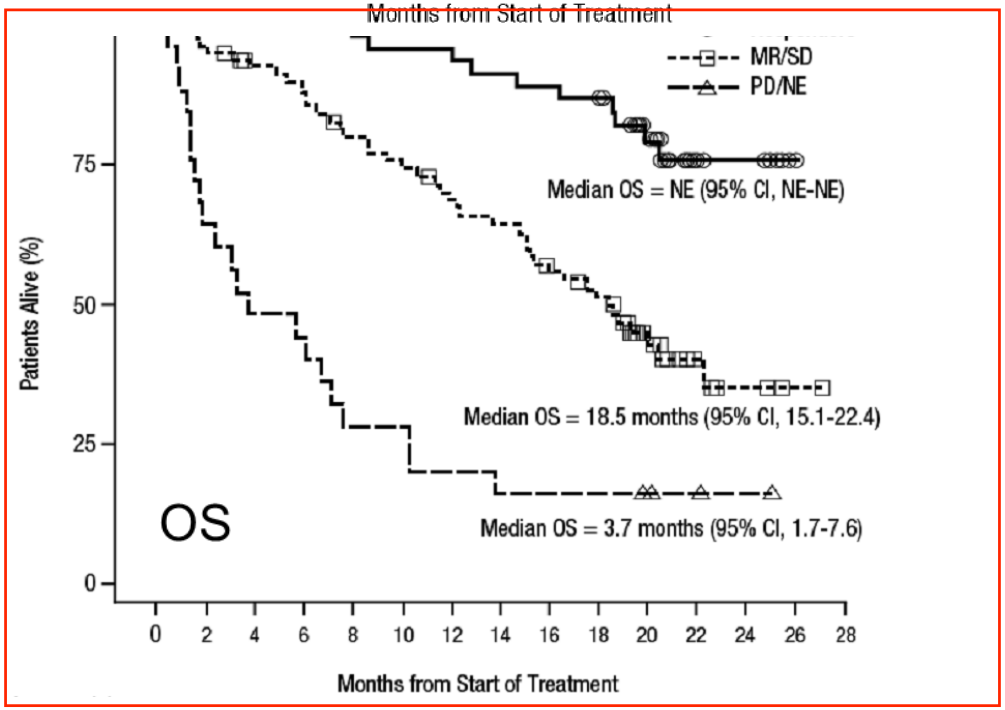
San Miguel, Lancet Oncol, 2013; Usmani, Blood, 2016

Clinical Efficacy of Daratumumab Monotherapy in Patients With Heavily Pretreated RR-MM
Usmani et al, Blood 2016

An updated pooled analysis of 148 patients treated with daratumumab 16 mg/kg. (GEN501 and SIRIUS trials) refractory to ≥2 or ≥3 prior therapies



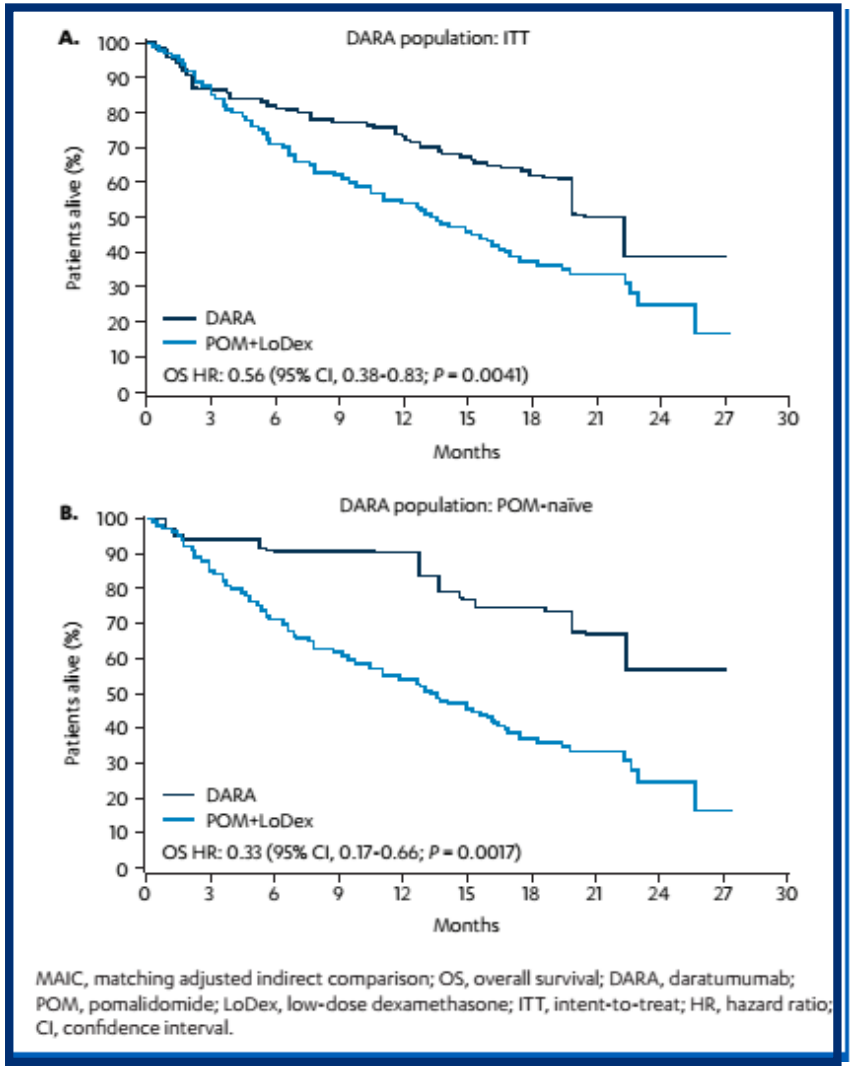




Comparative Efficacy of Daratumumab Monotherapy vs POM+LoDex in the Treatment of Multiple Myeloma: A Matching Adjusted Indirect Comparison (MAIC)

MAIC of data from Gens501, Sirius and MM03 trial showed that DARA improved clinical outcomes compared to POM+LoDex in patients with heavily pretreated and refractory MM

- The primary analysis suggests a 44% reduction in the risk of death (HR = 0.56) compared with POM+LoDex (A)
- Comparison of POM-naïve patients from both studies suggests a 67% reduction in the risk of death (HR = 0.33) compared with POM+LoDex (B)



MAIC, matching adjusted indirect comparison; OS, overall survival; DARA, daratumumab; POM, pomalidomide; LoDex, low-dose dexamethasone; ITT, intent-to-treat; HR, hazard ratio; CI, confidence interval.

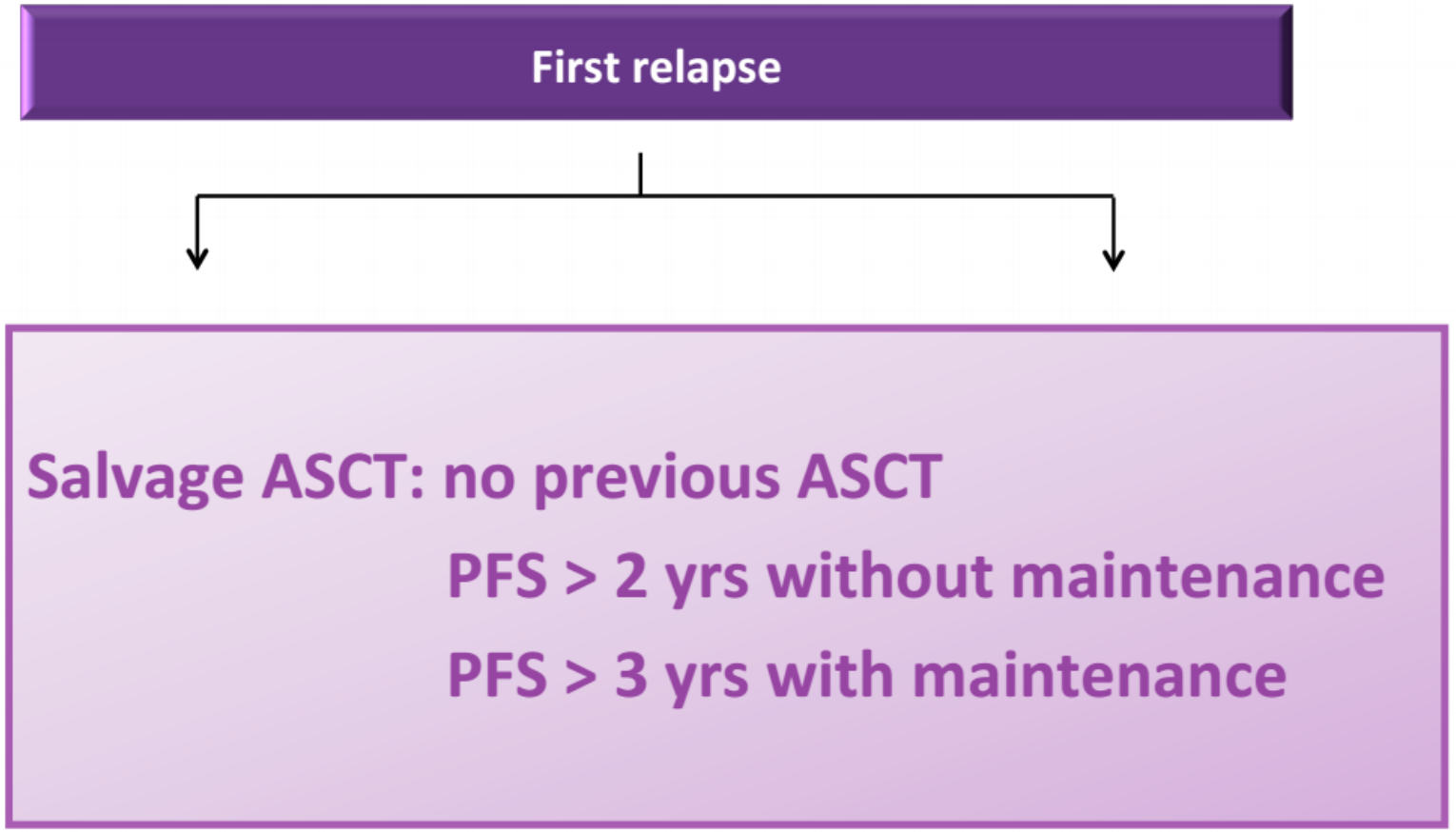
Van Sanden et al, 2016(ISPOR-EU)

Salvage ASCT in the Relapsed Setting: Reasonable Option?

- Data from Mayo Clinic Transplant Center suggests that ASCT2 appears safe and effective treatment for relapsed MM (N = 98)
  - ORR: 86%; median PFS: 10.3 mos; median OS: 33 mos
  - Rate of TRM: 4%, suggesting a favorable benefit-to-risk ratio
- Shorter TTP after ASCT1 predicts shorter OS post–ASCT2

TTP After ASCT1	Median From ASCT2, Mos (Range)	
	PFS	OS
< 12 mos	5.6 (3-8)	12.6 (4-23)
< 18 mos	7.1 (6-8)	19.4 (10-42)
< 24 mos	7.3 (6-10)	22.7 (13-62)
< 36 mos	7.6 (7-12)	30.5 (19-62)

Gonsalves WI, et al. Bone Marrow Transplant. 2013;48:568-573.


First relapse
Salvage ASCT: no previous ASCT
PFS > 2 yrs without maintenance
PFS > 3 yrs with maintenance

Allogeneic SCT in RR-MM

- Graft-vs-myeloma effect
- Can potentially provide sustained disease control (ie, cure)
- High treatment-related mortality
- Morbidity from GVHD
- No definite OS advantage vs autologous SCT
- Should be offered to high-risk pts in trials

"allogeneic stem cell transplantation remains a curative but experimental option to be performed in the context of clinical trials, particularly in high-risk disease and in the presence of an unfavourable karyotype during first-line treatment or at first therapy-sensitive relapse"

Dhakal B, et al. Bone Marrow Transplant. 2016;51:492-500.

AUTO-ALLO in MM

- In plasma cell leukemias the auto-allo strategy showed a significant OS advantage

- A long-term follow-up of patients with MM treated with auto-allo demonstrated a longer median EFS , OS and OS after first relapse in comparison with patients receiving auto, suggesting a synergism between new drugs and graft-versus-myeloma effect

- Patients relapsing after allo and treated with daratumumab ± Imids showed 22% rate of GVHD, indicating feasibility of Mo Ab after allo.

Knop et al, 2015

TRIAL n°	Allogeneic transplant trials registered at Clinical trials.gov for allotransplant in MM	STATUS
NCT02440464 (BMT CTN 1302)	Phase II, multicenter double-blind trial that randomizes patients with high-risk MM to ixazomib maintenance or placebo 60–120 days after allogeneic HSCT	Not yet recruiting
NCT02308280	A phase II, open-label study of bortezomib following non-myeloablative allogeneic stem cell transplant in patients with high-risk MM	Recruiting
NCT01460420	Phase I/II trial on RIC allogeneic transplantation: an optimized program for high-risk relapsed patients	Recruiting
NCT01131169	Phase II trial to assess the PFS and overall survival, as well as the safety and efficacy of allogeneic HSCT using a preparative regimen with busulfan, melphalan, fludarabine and ATG, and a T-cell-depleted stem cell transplant from a histocompatible-related or -unrelated donor in patients with relapsed or high-risk MM	Recruiting
NCT02447055	Allogeneic stem cell transplantation for patients with relapsed/refractory MM: a pilot study using a novel protocol	Not yet recruiting

Dhakal et al, BMT 2016

RELAPSE / REFRACTORY MULTIPLE MYELOMA
ESMO guidelines 2017

First relapse after IMiD-based induction

- Doublets: Kd / Vd
- Triplets based on Bortezomib: DaraVd or PanoVd or EloVd or VCD

First relapse after Bortezomib-based induction

- Rd
- Triplets (with Rd as backbone): DaraRd or KRd or IxaRd or EloRD

At second or subsequent relapse

- Pomalidomide-Dex (as a backbone) + Cyclo or Ixa or Bort or Dara or Elo
- Daratumumab (single agent or combination)
- Clinical Trial

Moreau et al. Ann Oncol 2017

TREATMENT ALGOTITHM FOR FIRST RELAPSE OF MM PATIENTS

Early relapse

No refractory to LENALIDOMIDE

KRd | **DRd** | **ERd** | IRd | **Rd**

FIT
All the options
No IRd if ASCT

HIGH RISK - AGGRESSIVE
KRd or DRd

Intermediate
Erd or DRd or IRd

STANDARD
All the options

Frail
IRd or Rd

No refractory to BORTEZOMIB

Kd | **DVd** | **PVd** | **Vd**

FIT
All the options

Intermediate
DVd or Vd

Frail
Vd

HIGH RISK - AGGRESSIVE
Kd or DVd

STANDARD
All the options

Late relapse

POMALIDOMIDE and DEXAMETHASONE
DARATUMUMAB
CLINICAL TRIALS

ASCT IF INDICATED

CT (D-PACE) IF AGGRESSIVE

Frailty score: based on age, comorbidities, cognitive and physical conditions identifies 3 groups of patients: fit (score=0); intermediate-fitness (score=1); frail (score≥2).
High-Risk defined as cytogenetic: Presence of Del(17p) and/or t(4;14) and/or t(14;16)
Aggressive disease: extramedullary disease, elevated LDH, doubling MC in 2 months, circulating PC

Modified from Bringhen, SIE 2017

Conclusions: R/R Myeloma Therapy

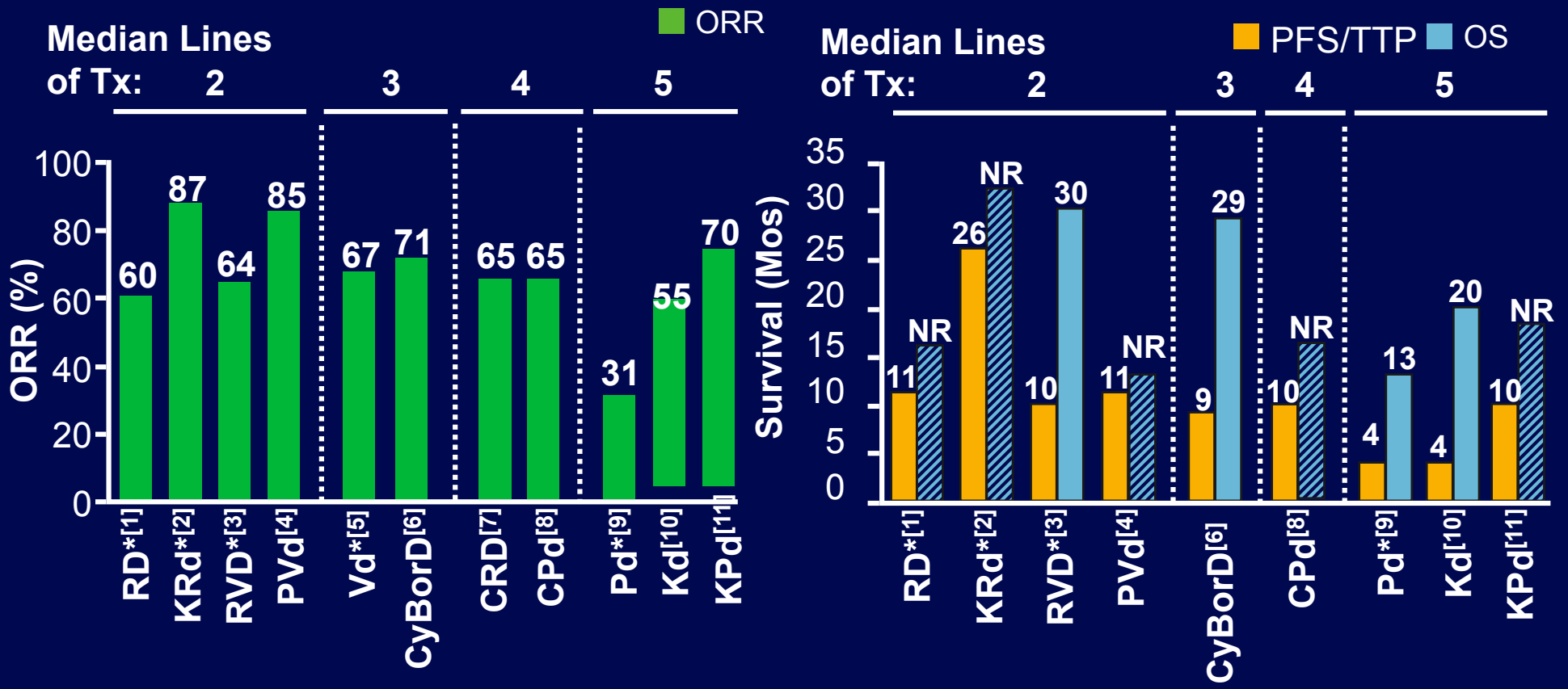
- At relapse, multidrug combinations incorporating new agents can provide maximum benefit
  - - Triplet regimens preferred (2 drug classes + steroids) with at least 1 agent from a different class than previous treatment
  - - Even minor responses have clinical value in relapsed disease and there is some evidence that some drug restore chemosensitivity to prior theraphy
- Because no therapy is curative, all options need to be tried sequentially

However, there are no data on optimum sequence of regimens for R/R disease

- Pts should be treated to achieve **best response** while taking into account potential AEs and maximizing supportive care
- There are promising new agents in development and pts should be encouraged to participate in **clinical trials**

Summary of Combination Therapy in RR MM

*Data from phase III trials, all others from phase I or II trials



1. Dimopoulos M, et al. N Engl J Med. 2007;357:2123-2132. 2. Stewart AK, et al. N Engl J Med. 2015;372:142-152. 3. Richardson PG, et al. Blood. 2014;123:1461-1469. 4. Lacy MQ, et al. ASH 2014. Abstract 304. 5. Mikhael JR, et al. Br J Haematol. 2009;144:169-175. 6. Monge J, et al. ASCO 2014. Abstract 8586. 7. Morgan JG, et al. Br J Haematol. 2007;137:268-269. 8. Baz R, et al. ASH 2014. Abstract 303. 9. San Miguel J, et al. Lancet Oncol. 2013;14:1055-1066. 10. Lendvai N, et al. Blood. 2014;124:899-906. 11. Shah JJ, et al. ASH 2013. Abstract 690; Chng WJ, et al. Leukemia 2014;28:269–77