Myeloma treatment: : Non-transplant and transplant options

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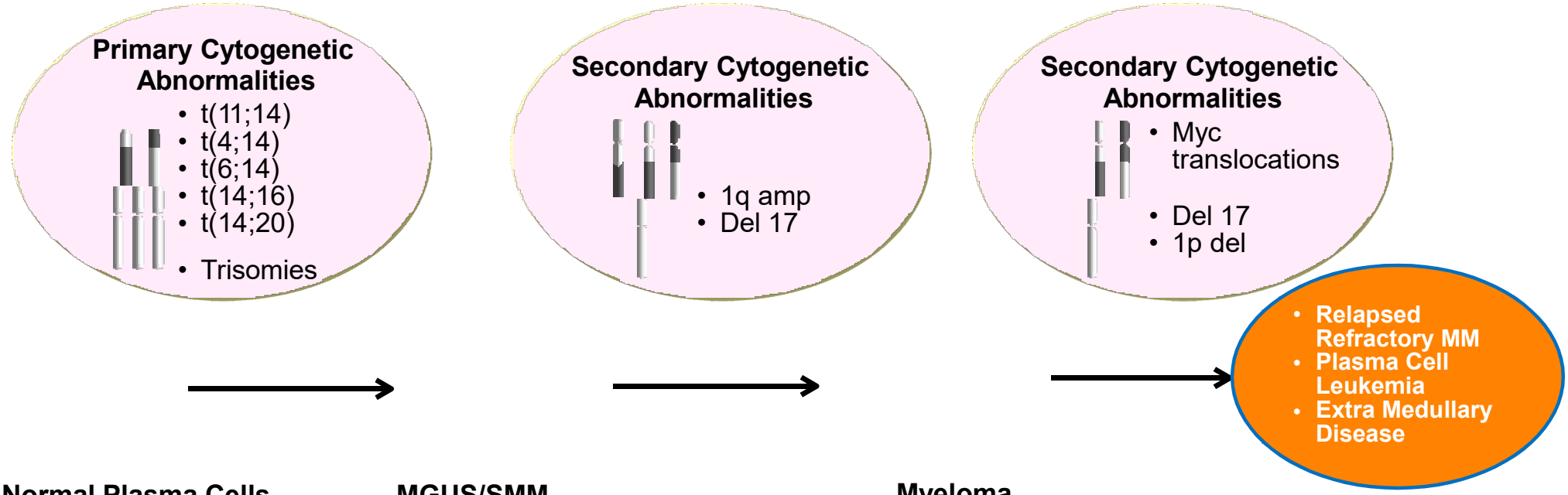
Progression of MGUS to Myeloma



Normal Plasma Cells	MGUS/SMM	Myeloma
Trisomies/IgH Translocations	**Secondary Cytogenetic Abnormalities**	**Secondary Cytogenetic Abnormalities**
Establishment of the clone	**Del(17p), Gain(1q)**	**Occur with progression**

Rajan. Blood Cancer J. 2015; 5: e365.

Revised IMWG Criteria for Myeloma

MGUS	SMM

- **< 10% BMPC AND**
- **< 3 g/dL M protein**
- **No MDE**

- **10-60% BMPC OR**
- **≥ 3 g/dL M protein**
- **No MDE**

- Clonal plasma cell disorder AND
- 1 or more MDE
  - CRAB
  - ≥ 60% BMPC
  - ≥ 100 FLC ratio
  - > 1 MRI focal lesion

No MDE ***MDE***

MDE= Myeloma Defining Events
*CRAB= Hyper**c**alcemia, **r**enal failure, **a**nemia, or lytic **b**one lesions attributable to a clonal plasma cell disorder*

Rajkumar. Lancet Oncol. 2014; 15: PE538.

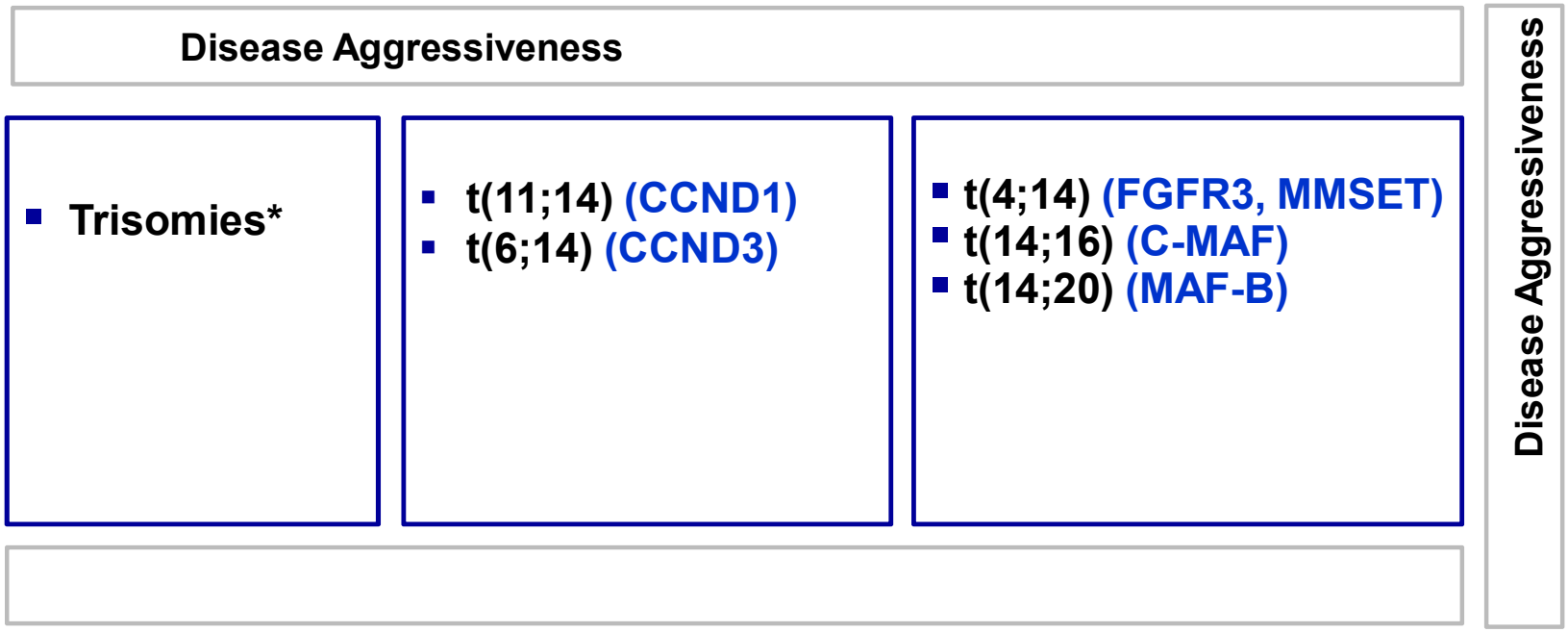
Molecular Classification of Myeloma

Trisomic MM	IgH Translocations	
▪ Trisomies*	▪ t(11;14) (CCND1) ▪ t(6;14) (CCND3)	▪ t(4;14) (FGFR3, MMSET) ▪ t(14;16) (C-MAF) ▪ t(14;20) (MAF-B)

*~10% have both trisomies and IgH translocations

Kumar. Blood. 2012;119:2100.

Cytogenetic Risk Stratification of Myeloma



- Double-Hit Myeloma = Any 2 high risk abnormalities
- Triple-Hit Myeloma = 3 or more high risk abnormalities

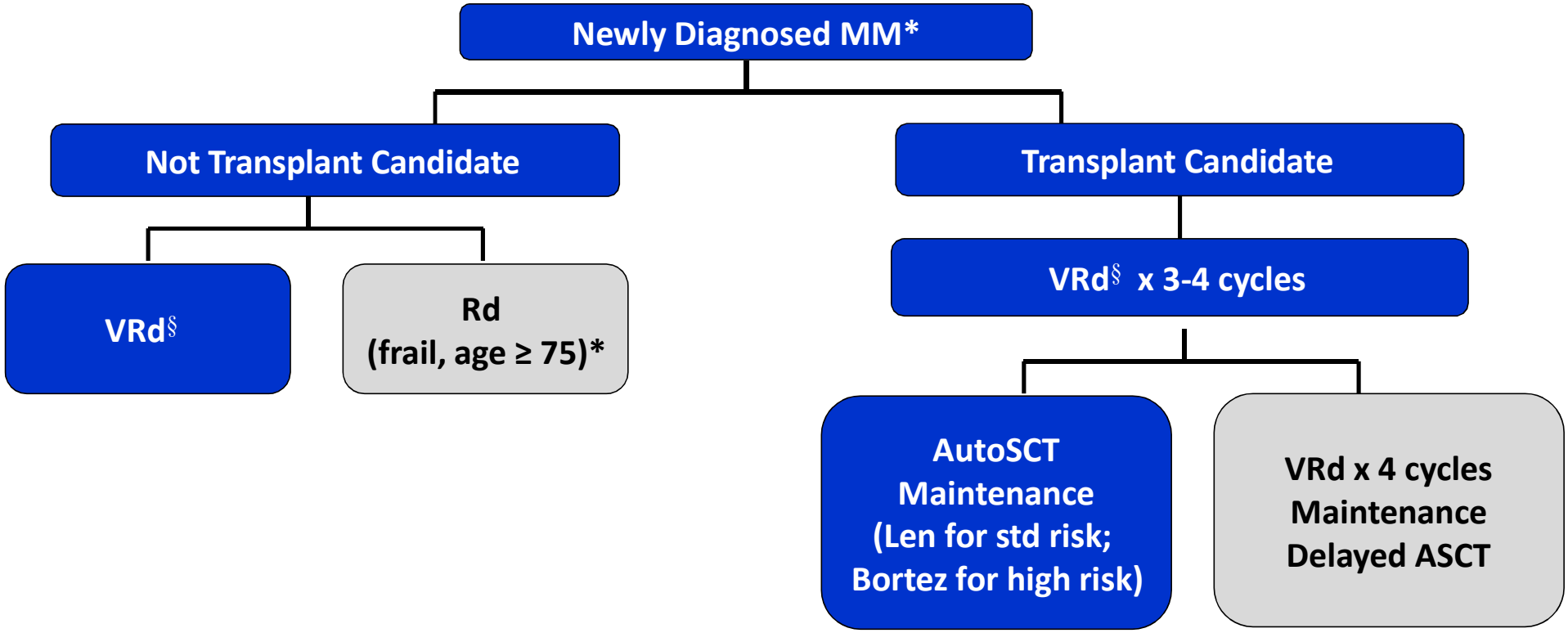
Revised International Staging System

Stage	Frequency (% of patients)	5-year survival rate (%)
Stage I • Serum albumin >3.5 • Serum beta-2-microglobulin <3.5 • No high risk cytogenetics • Normal LDH	28%	82%
Stage II • Neither stage I or III	62%	62%
Stage III • Serum beta-2-microglobulin >5.5 and • High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] *or* elevated LDH	10%	40%

Palumbo. J Clin Oncol. 2015;33:2863.

Myeloma Treatment options

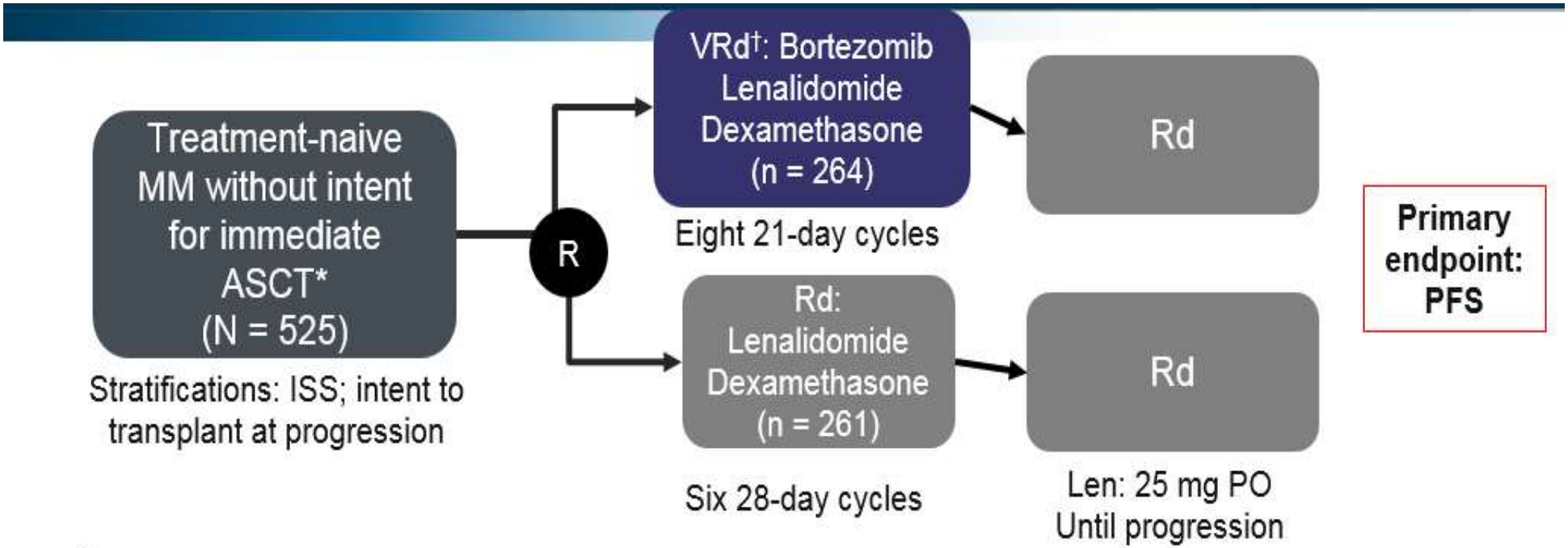
Frontline Treatment of Myeloma



*Based on CALGB 100104, S0777, IFM-DFCI, CTN 0702 HOVON
§ VTd/VCd if VRd not available

Rajkumar SV. 2016.

SWOG 0777 Trial



- *All patients received aspirin (325 mg/d). †Patients received HSV prophylaxis.
- ‡High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.

Durie. Lancet. 2017;389:519. Durie. ASH 2018. Abstr 1992.

SWOG 0777 Trial

Updated Response Results*

	VRd (n = 215)	Rd (n = 207)
Complete response (CR)	24.2% (52)	12.1% (25)
Very good partial response (VGPR)	50.7% (109)	41.1% (85)
VGPR or better	**74.9%**	**53.2%**
Partial response (PR)	15.3% (33)	25.6% (53)
Overall Response Rate (ORR)	**90.2% (194)**	**78.8% (163)**
Stable disease (SD)	7.0% (15)	16.4% (34)
PD or death	2.8% (6)	4.8% (10)

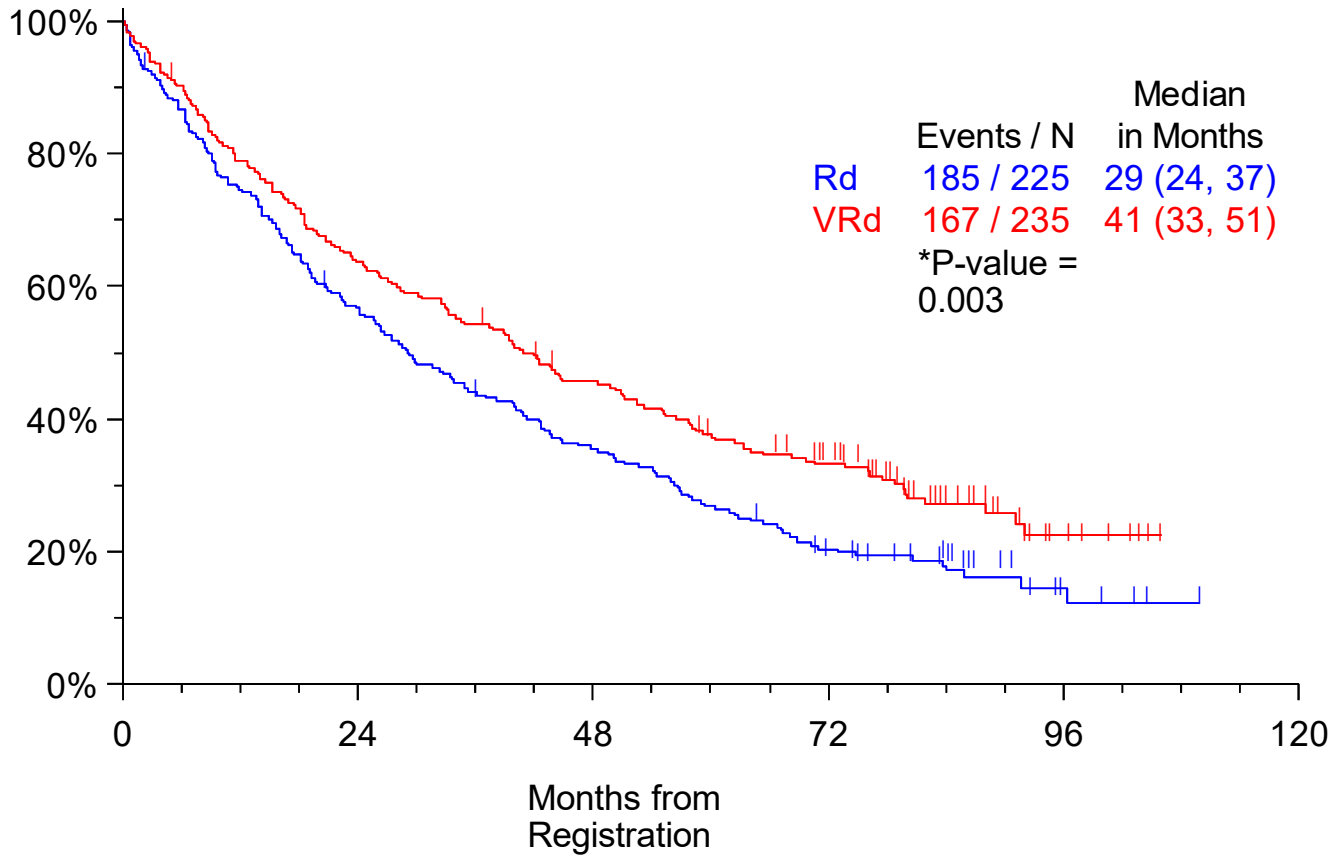
*Both SWOG and IRC stratified Cochran-Mantel-Haenszel analyses indicated improved responses with RVd (odds ratio: 0.528, *P* =.006 [ITT]; odds ratio: 0.38, *P* = .001 [sensitivity analysis])
**Both SWOG and IRC assessments

Durie. Lancet. 2017;389:519. Durie. ASH 2018. Abstr 1992.

SWOG 0777: Progression-Free Survival

CURRENT ELIGIBILITY (N = 460) – CURRENT DATA

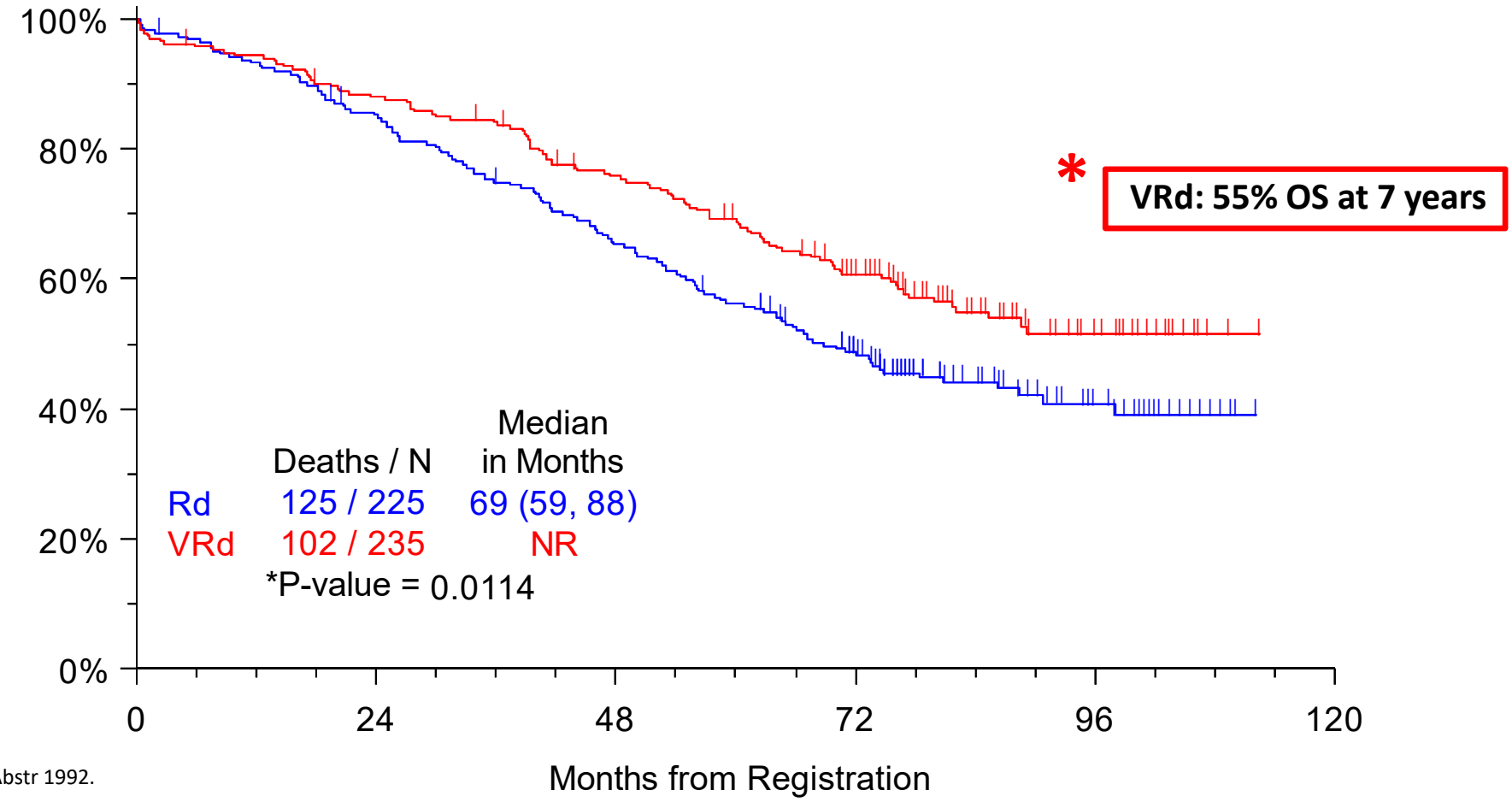
PFS



Durie. ASH 2018. Abstr 1992.

SWOG 0777: Overall Survival

CURRENT ELIGIBILITY (N = 460) – CURRENT DATA



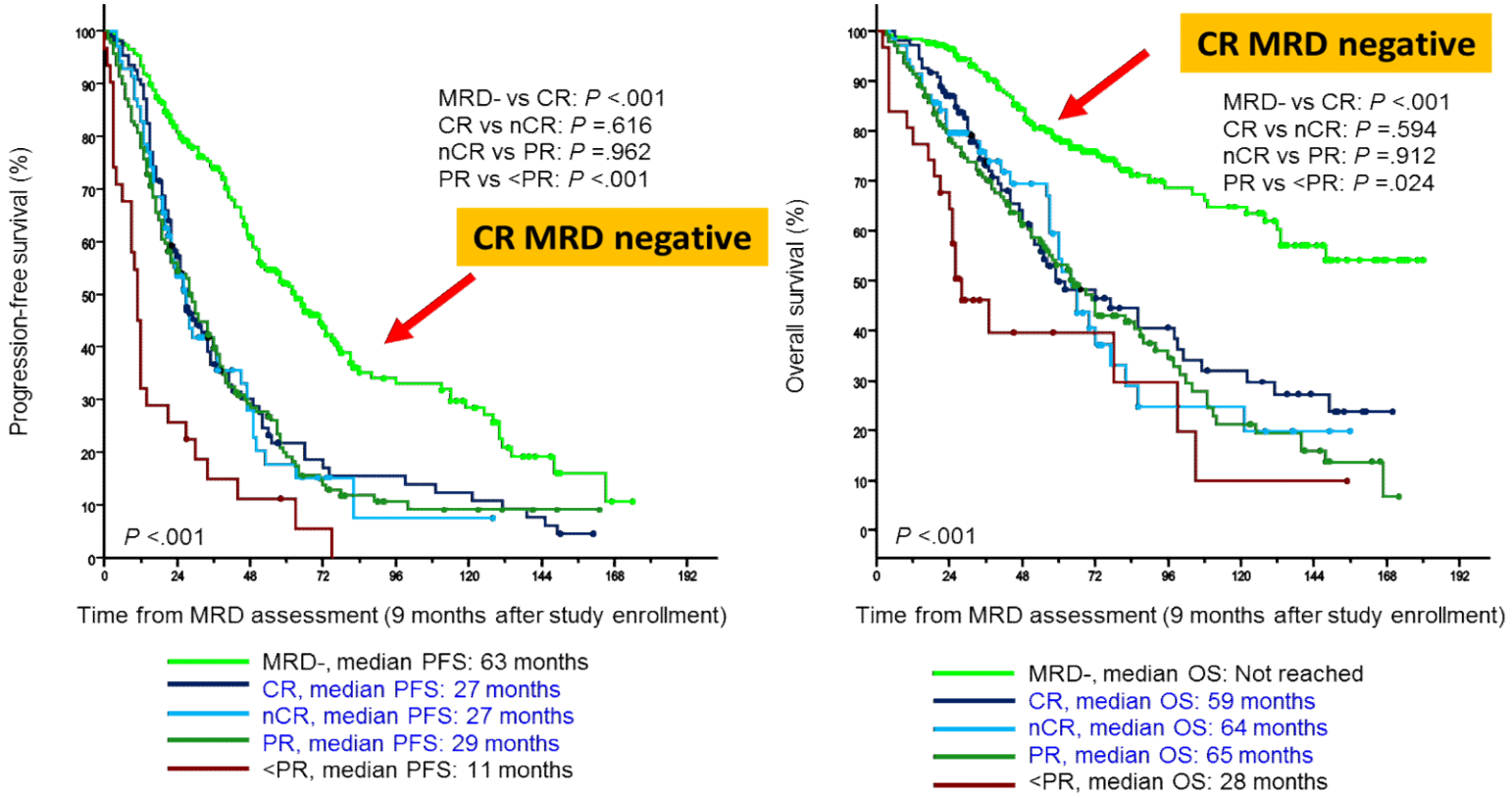
Durie. ASH 2018. Abstr 1992.

In 2018/2019:

Achievement of MRD undetected status at 10^{-6} is the goal of therapy.

Concept to Influence Decisions

True value of CR comes from the MRD status



Lahuerta. J Clin Oncol. 2017;35:2900.

MAJOR GOAL OF I²TEAMM SUBMISSIONS

MRD approved by FDA and EMA as surrogate endpoint for myeloma

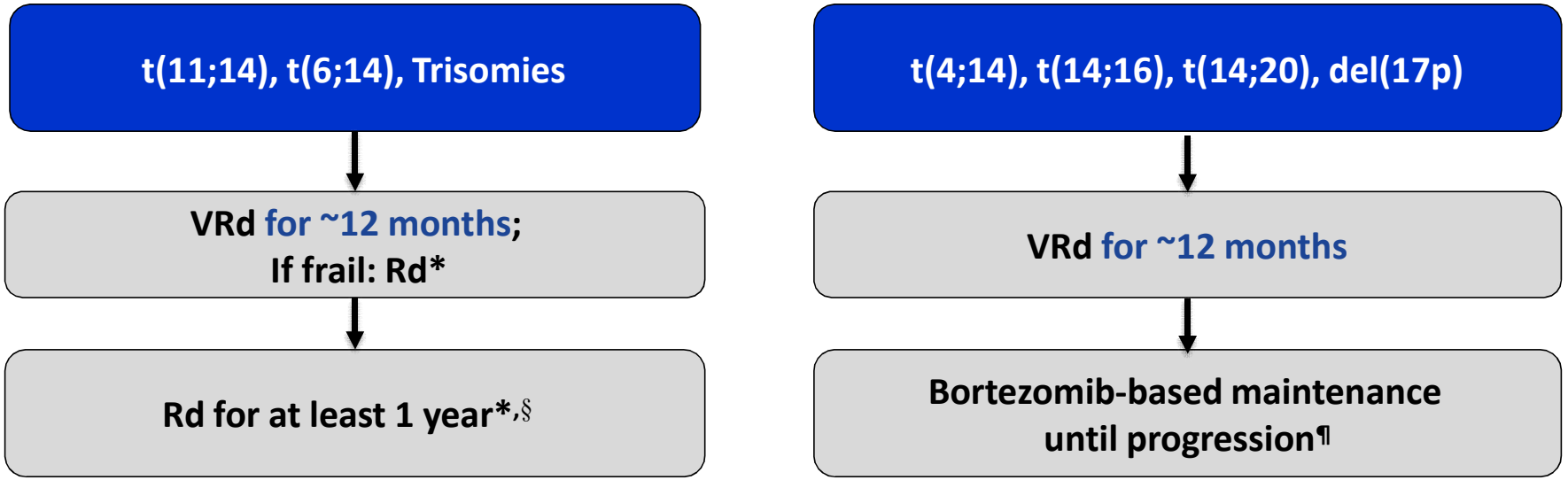
Trials included:

- IFM 2009
- EMN/Hovon
- MM05 [Heidelberg]
- STAMINA
- MRC
- Clarion
- CASTOR/POLLUX
- C16010
- IXA maintenance: C16019

→ **FDA meeting December 11th, 2018**

Frontline Treatment of Myeloma

Non-Transplant Candidate: Off-Study



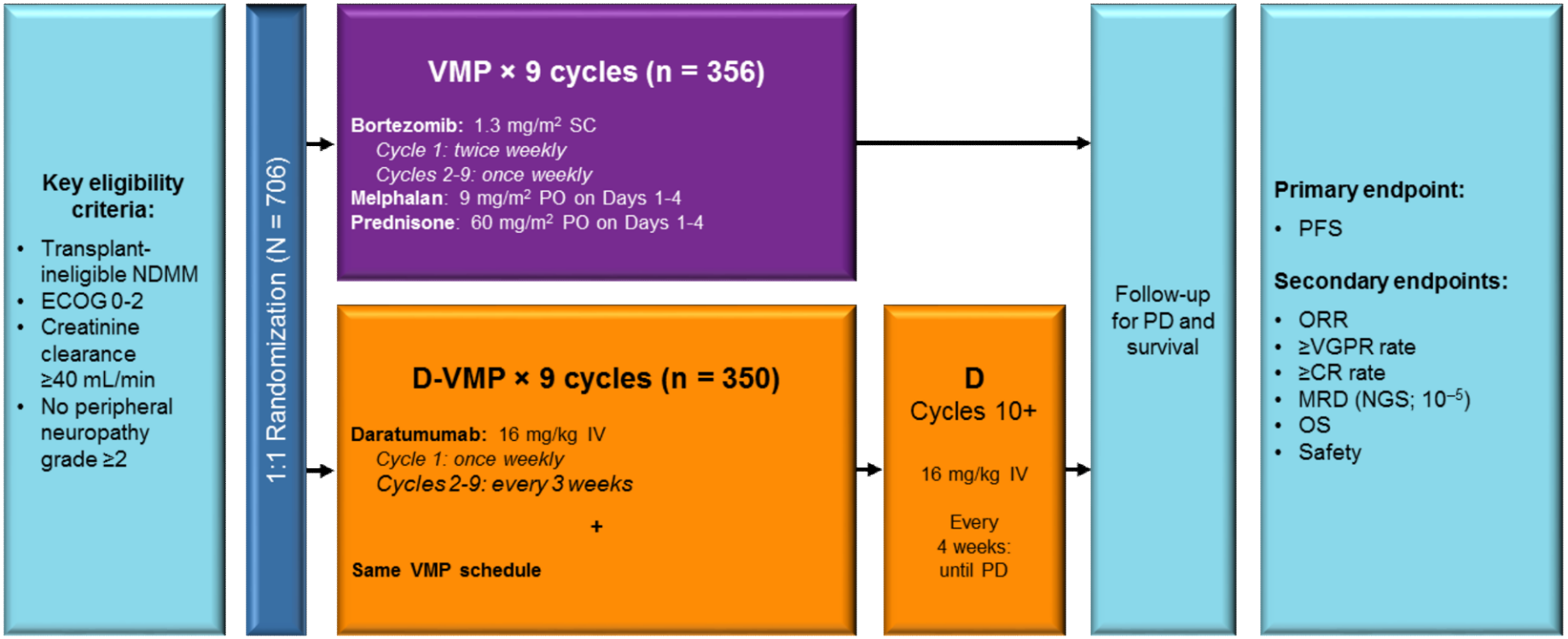
***In patients treated initially with Rd, continuing treatment until progression is an options for patients responding well with low toxicities**

§ Dex is usually discontinued after first year

¶Duration based on tolerance; consider risks and benefits for treatment beyond 3 years

Dispenzieri. Mayo Clin Proc. 2007;82:323; Kumar. Mayo Clin Proc. 2009;84:1095. Mikhael. Mayo Clin Proc. 2013;88:360. v14 ///last reviewed May 2018

ALCYONE Study Design



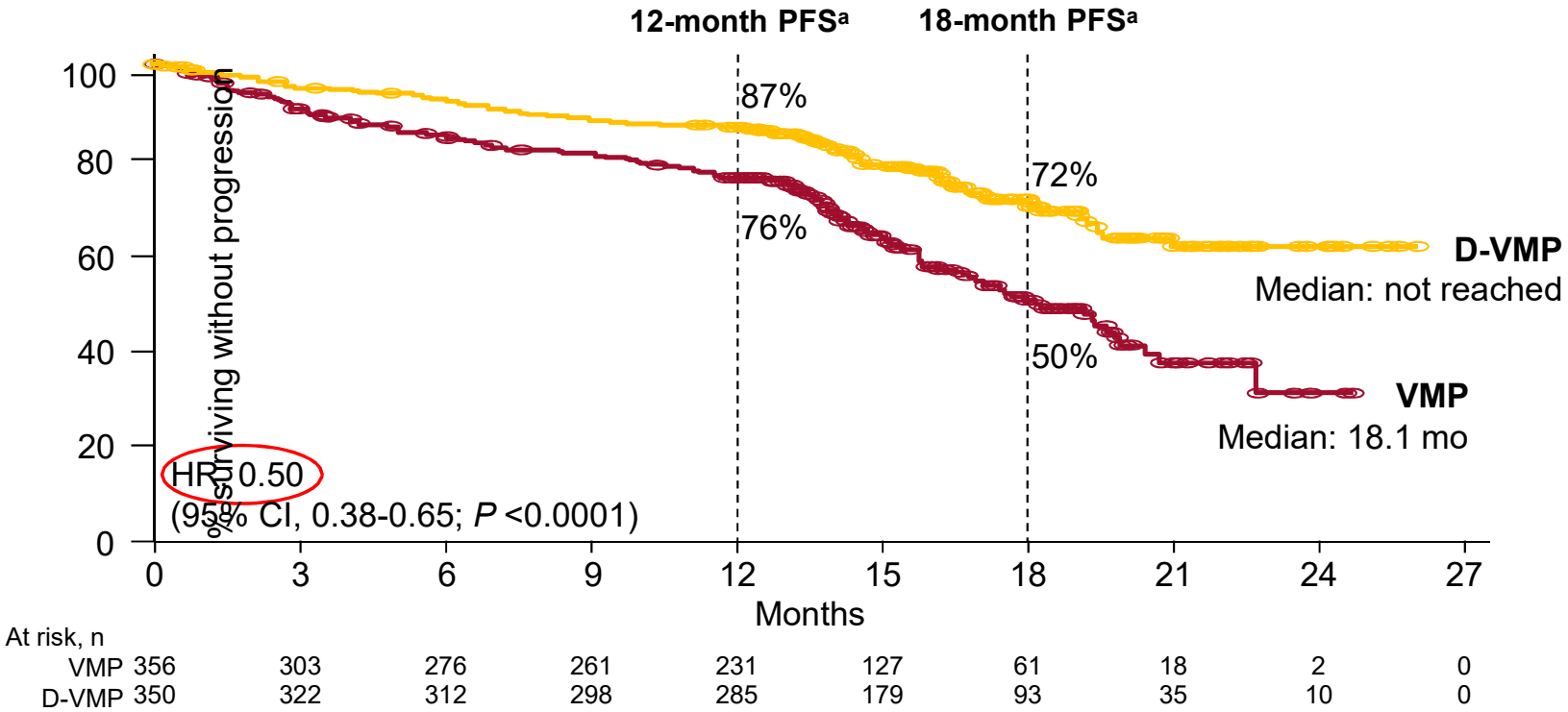
Stratification factors
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

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

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

Mateos. NEJM. 2018; 378:518.

Efficacy: PFS

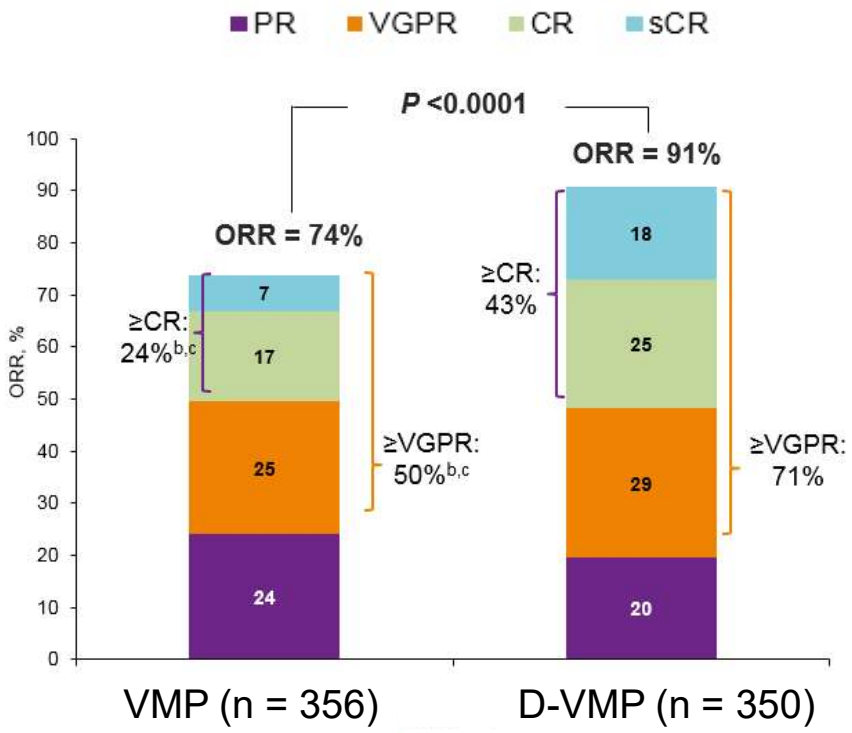


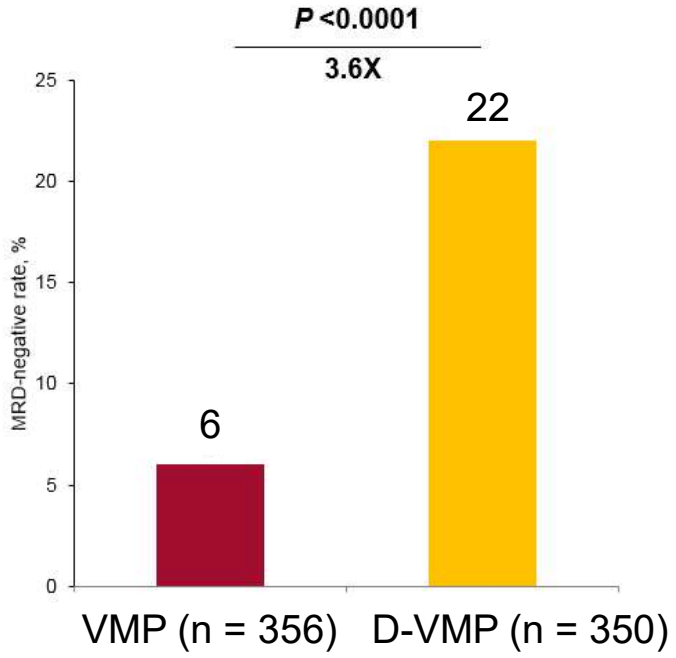
- **Median follow-up: 16.5 months (range: 0.1-28.1)**
- **Consistent PFS treatment benefit across subgroups**

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

Mateos. NEJM. 2018; 378:518.

Efficacy: ORR and MRD (NGS; 10^{-5} Threshold)



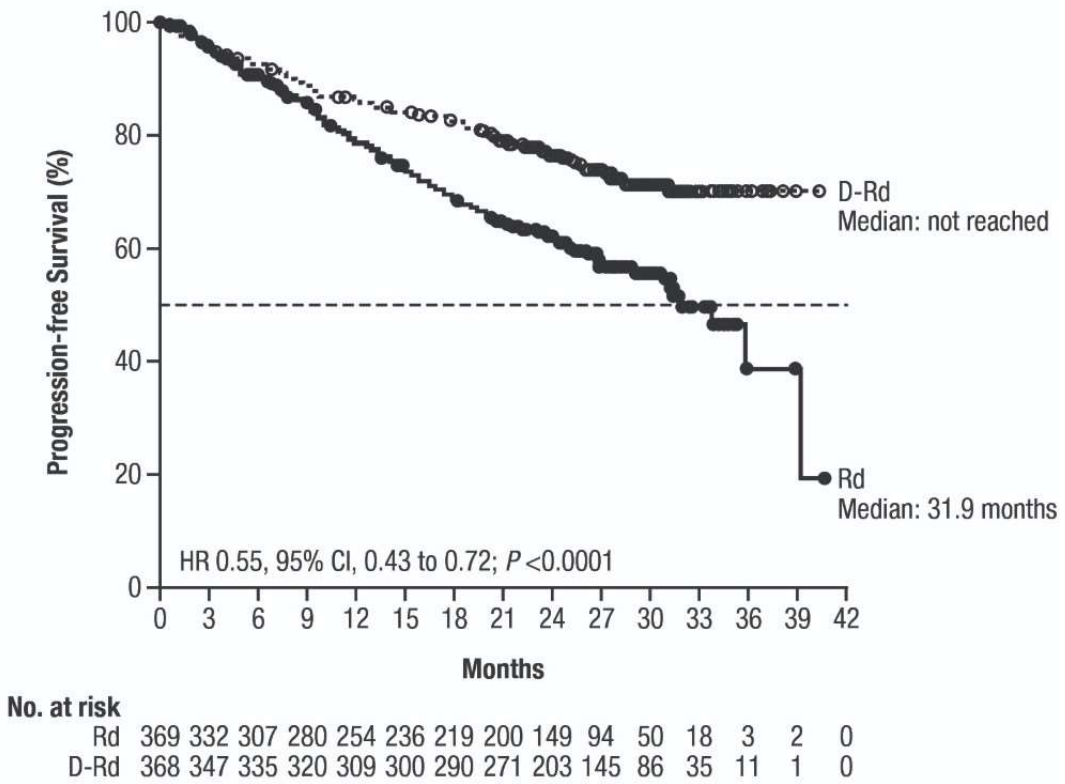


Significantly higher ORR, ≥VGPR, and ≥CR with D-VMP
>3-fold higher MRD-negativity rate with D-VMP

Mateos. NEJM. 2018; 378:518.

Updates at ASH 2018

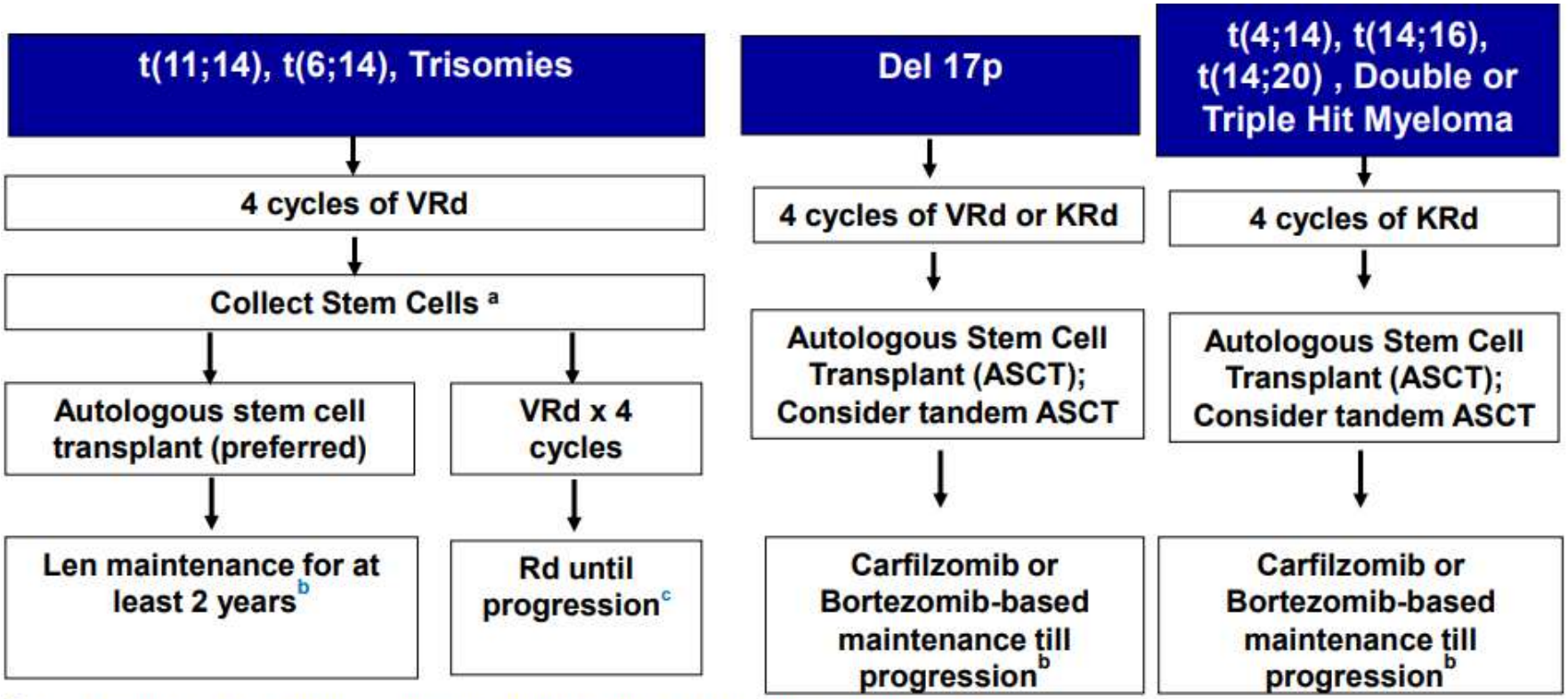
- **LBA-2 Phase 3 dara/len/dex (dara Rd) versus len/dex (Rd)**
  - **NDMM not eligible for transplant**



Facon. ASH 2018. Abstract LBA-2.

Initial Treatment of Myeloma

Transplant Candidate: Off-Study



[a] *If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor*
[b] *Duration based on tolerance; consider risks and benefits for treatment beyond 3 years*
c Continuing Rd for patients responding to Rd and with low toxicities

Dispenzieri. Mayo Clin Proc. 2007;82:323; Kumar. Mayo Clin Proc. 2009;84:1095; Mikhael. Mayo Clin Proc. 2013;88:360. v14 ///last reviewed May 2018

Controversies in 2018/2019

Triplets:

- KRd/KCd/KTd
- Dara-Rd or Vd or Cyd or Td
- IxaRd/IxaCyD/IxaTd (also combos with elotuzumab or pomalidomide if feasible)

Four-drug combos:

- Dara Rd + K or Ixa triplets
- Globally, Dara + VRd/VTd/VCd or VMP

New Agents in Frontline Setting

- **Daratumumab (or isatuximab): Add to create 4-drug combo?**
- **Venetoclax (or Mcl-1 inhibitions): Add if t(11;14) present?**
- **CAR T or BiTEs: Consider adding early in high risk and/or with suboptimal response?**

Can CAR T Therapy Be Introduced Early?

- **Can consider harvesting T-cells early!**

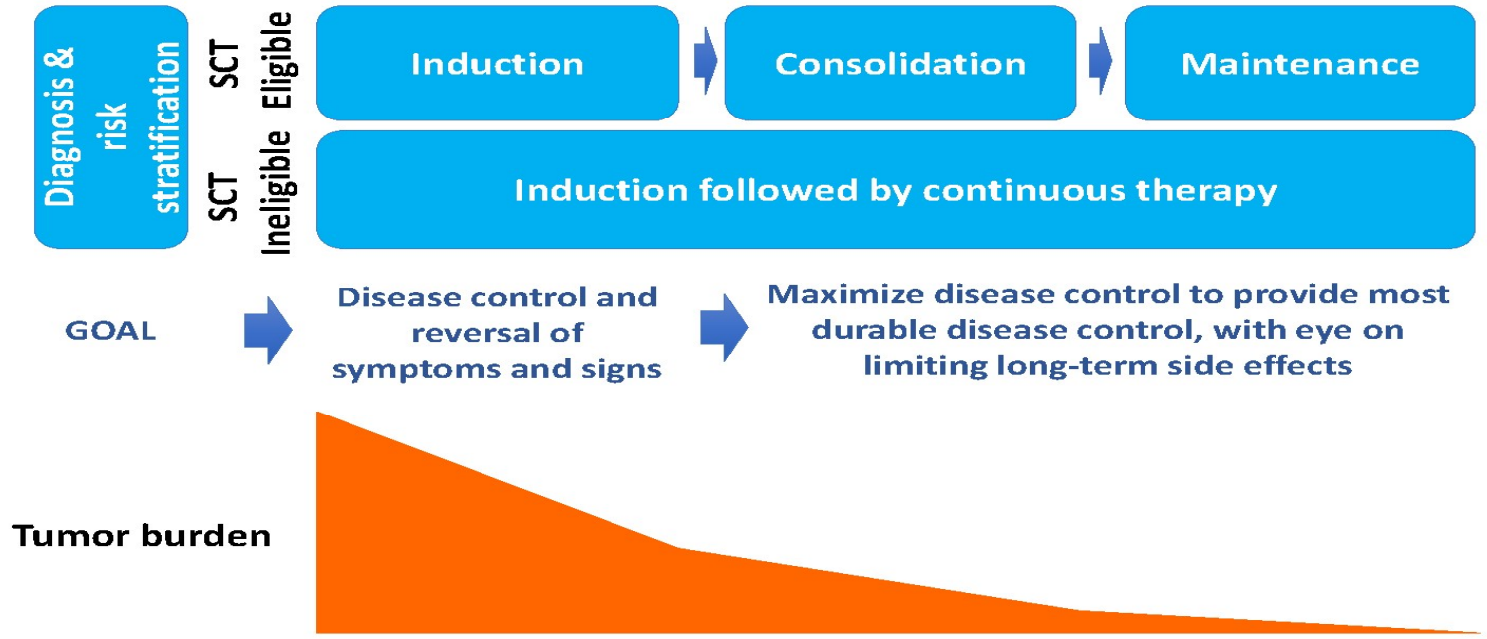
  Potential of great efficiency BUT concerns about both short term and long-term toxicities.

Need New Response Criteria to Encompass Very Rapid Responses

- MRD assessment at 1, 3, 6 and 12 months
- Consider adding mass spec for M-component monitoring
- Define “sustained response” as endpoint

Treatment after induction for transplant-eligible patients

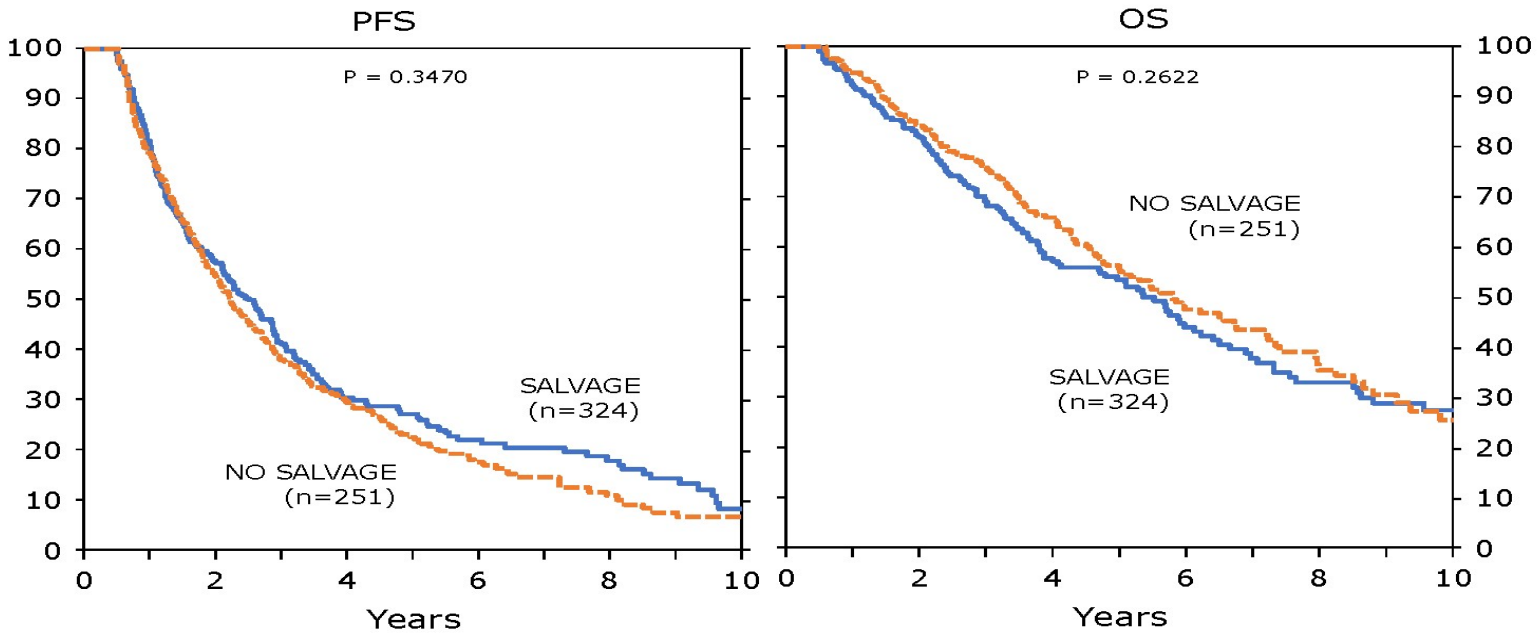
Myeloma Treatment Paradigm



Consolidation and Maintenance

- Stem cell transplantation (SCT): one or two?
- Post-transplantation consolidation?
- Post-transplantation maintenance?

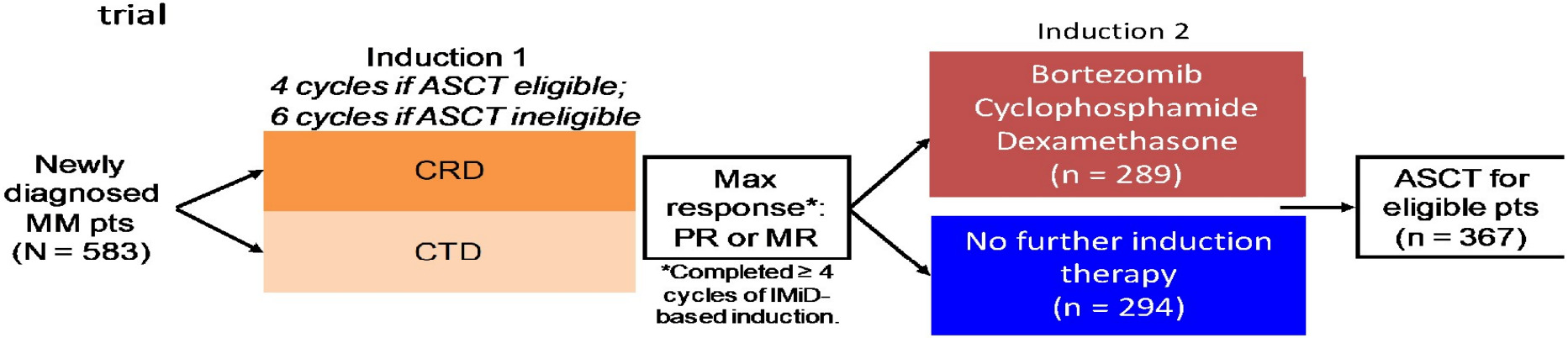
When Do You Stop Induction Therapy?



Vij R, Biol Blood Marrow Transplant. 2014.

Ideal Duration of Induction Prior to SCT?

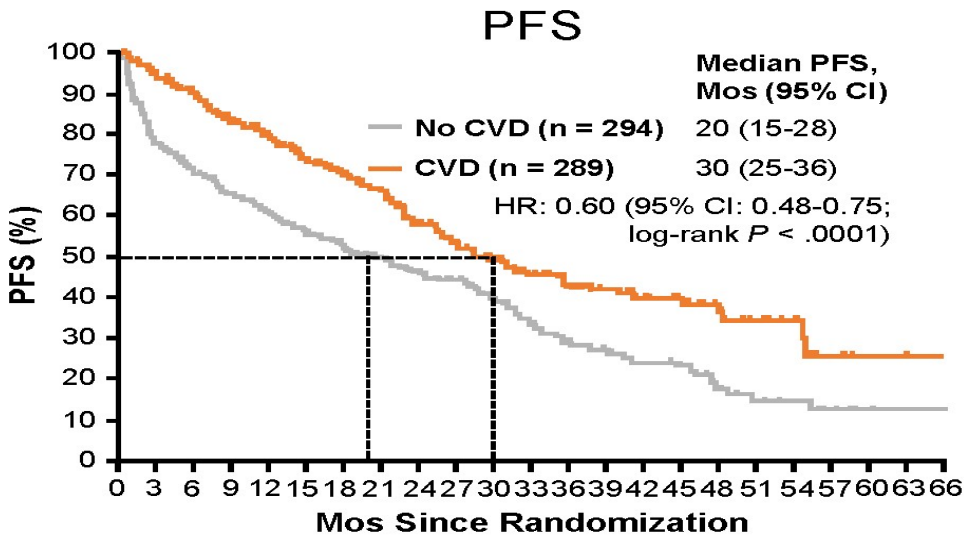
- UK-based multicenter, open-label, parallel group, randomized controlled phase III trial

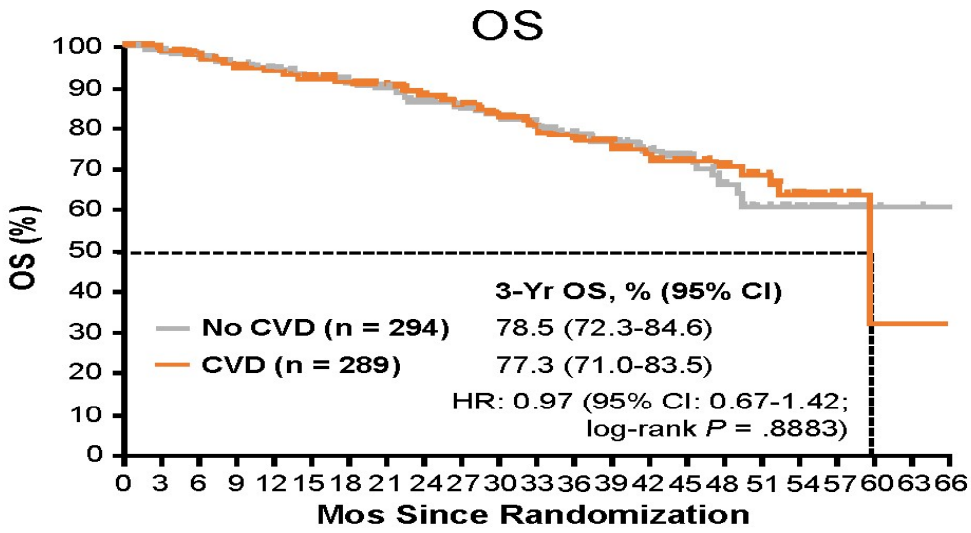


- Primary endpoints: PFS, OS
- Secondary endpoints: Improved response vs baseline, PI effect in high-risk pt group

Jackson. ASH 2016. Abstr 244.

Myeloma XI: Results

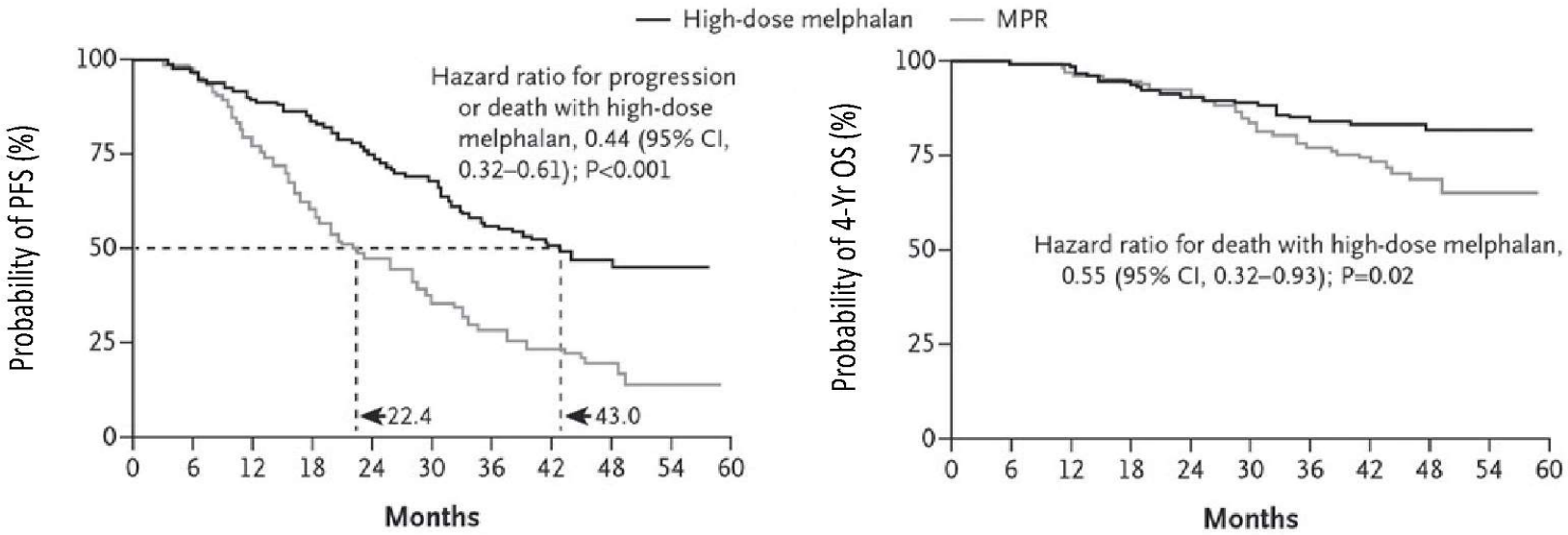




Recommendation: 4-6 cycles of induction and then transplant

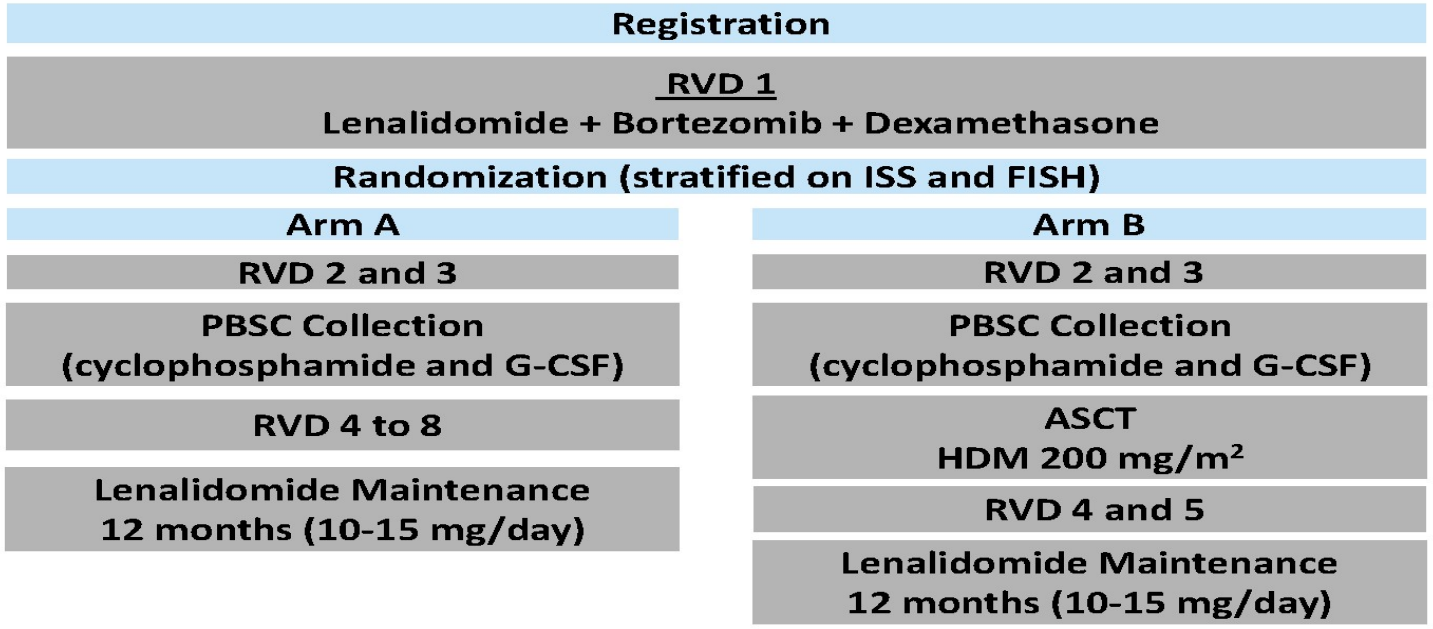
Jackson. ASH 2016. Abstr 244.

Do We Still Need ASCT with Novel Drugs?



Palumbo. N Engl J Med 2014;371:895.

Do We Still Need ASCT? IFM 2009



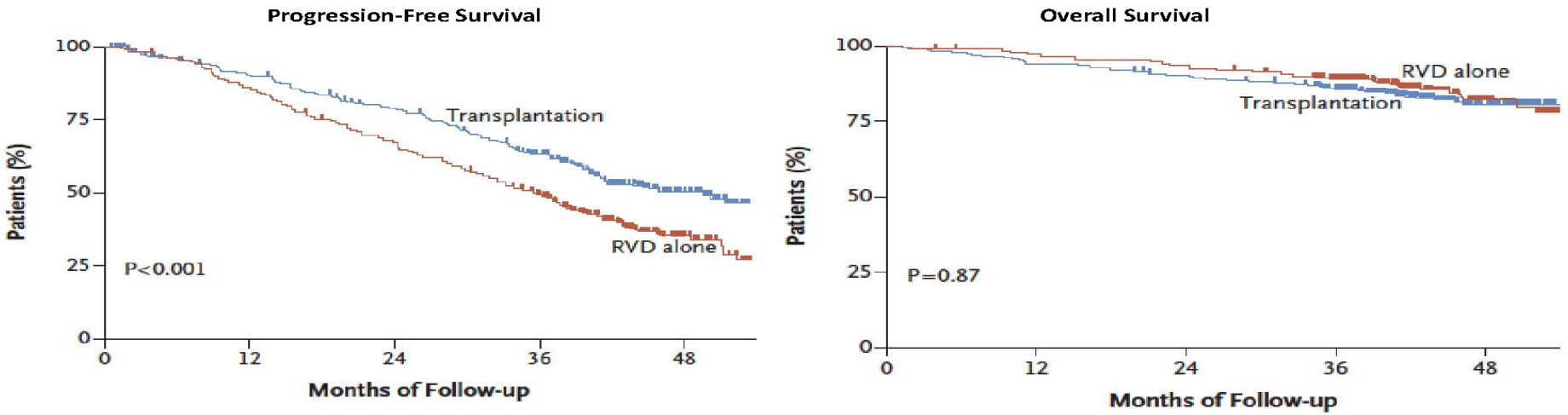
Attal. NEJM. 2017;376:1311.

Deeper Responses With SCT

Outcome	RVD-Alone Group (N = 350)	Transplantation Group (N = 350)
Best response during the study , n (%)		
Complete response	169 (48)	205 (59)
Very good partial response	101 (29)	102 (29)
Partial response	70 (20)	37 (11)
Stable disease	10 (3)	6 (2)
Complete response, n (%)	169 (48)	205 (59)
Complete response or very good partial response, n (%)	270 (77)	307 (88)
Minimal residual disease not detected during study, n/ total n with complete or very good partial response (%)	171/265 (65)	220/278 (79)

Attal. NEJM. 2017;376:1311.

Better PFS; Comparable OS



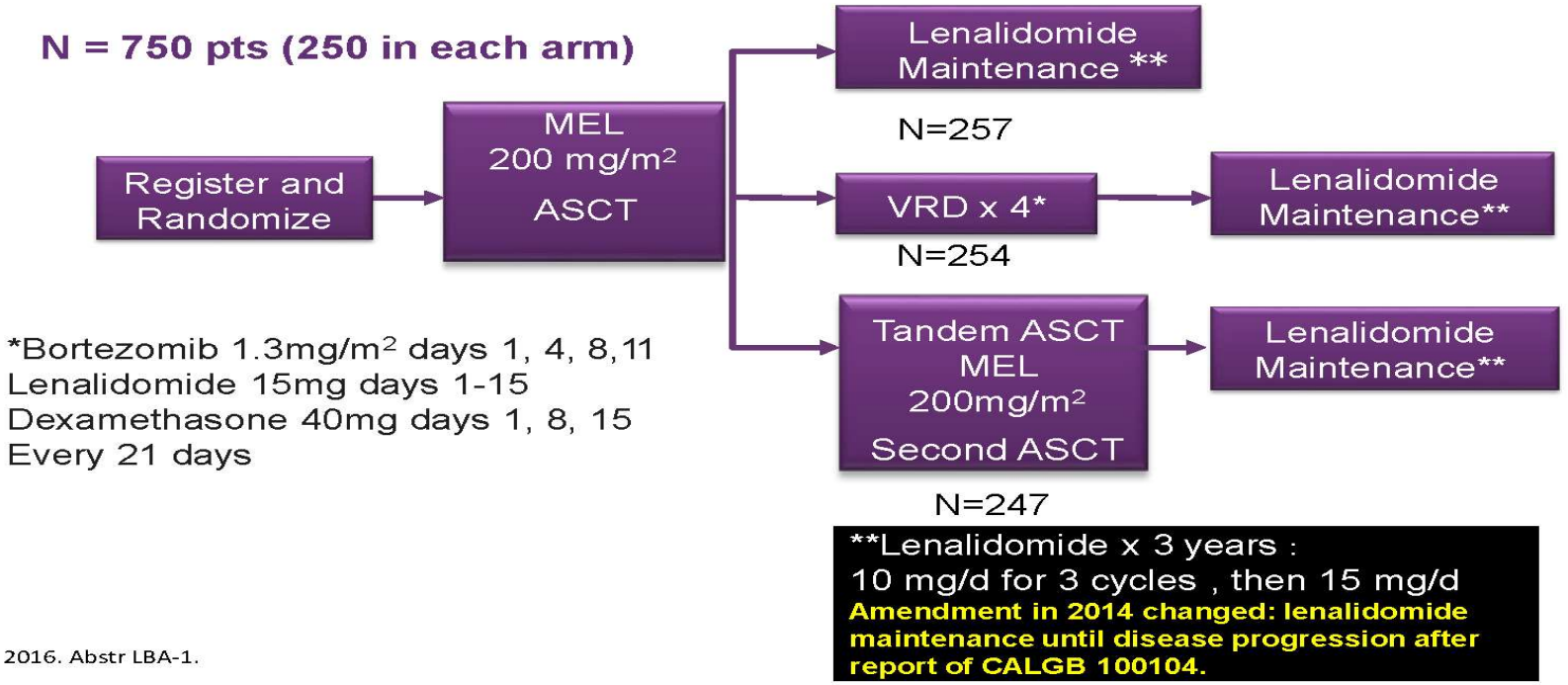
Recommendation: upfront SCT recommended, but a delayed approach is acceptable

Attal. NEJM. 2017;376:1311.

What Should Be Done Post ASCT?

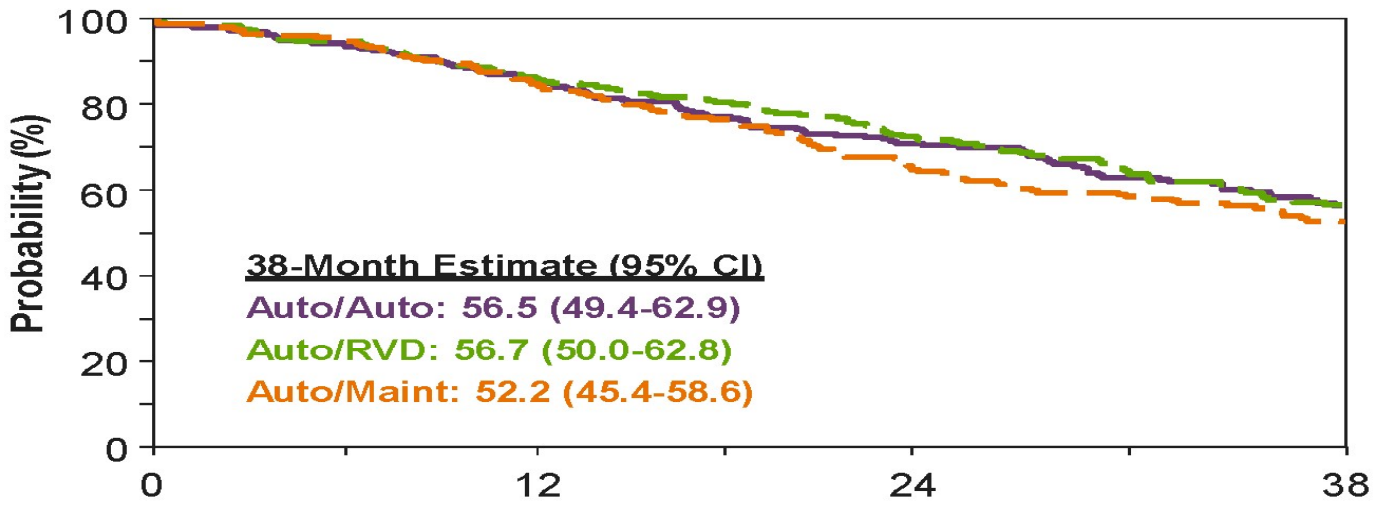
- Consolidation with tandem ASCT?
- Non-transplant consolidation?
- Maintenance?

STaMINA Trial: BMT CTN 0702



Stadtmauer. ASH 2016. Abstr LBA-1.

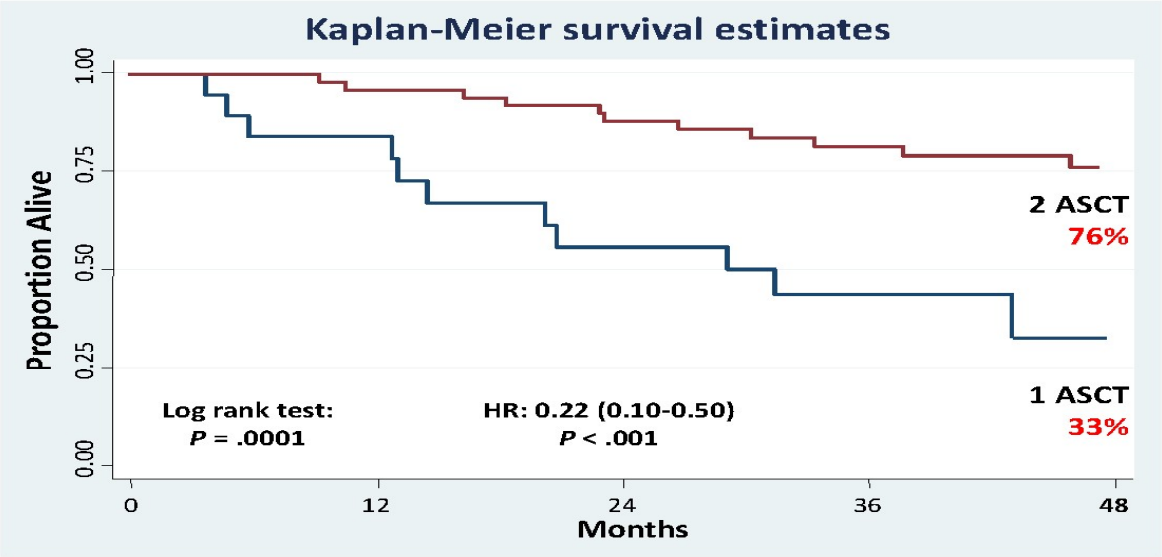
STaMINA Trial: Primary Endpoint—PFS



Recommendation: with VRd induction, no role for additional VRd consolidation

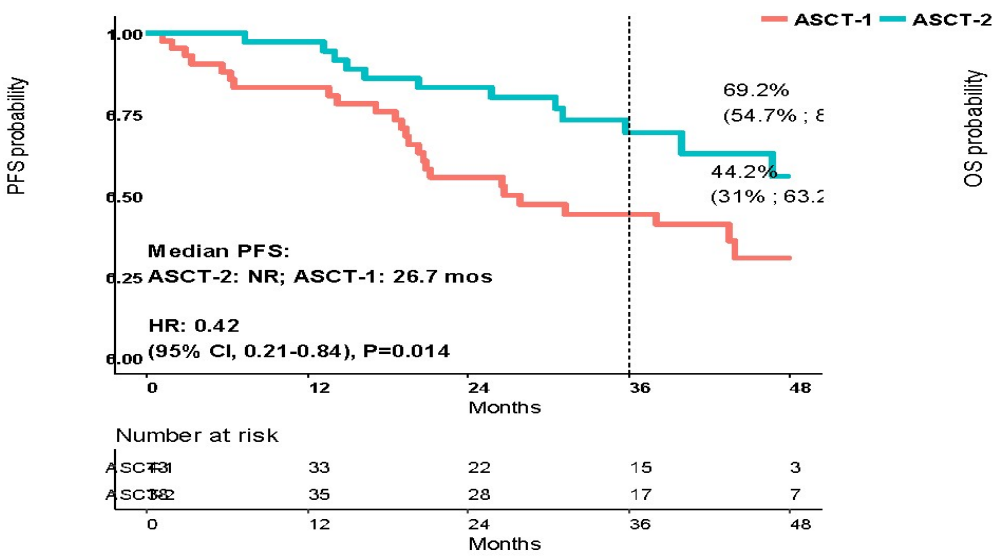
Stadtmauer. ASH 2016. Abstr LBA-1.

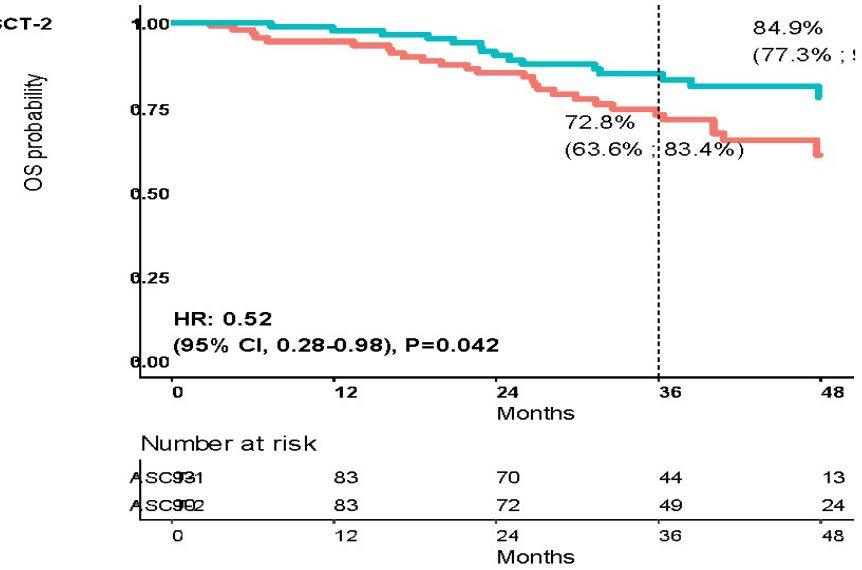
Tandem ASCT: del(17p) ± t(4;14)



Cavo. ASH 2013. Abstr 767.

EMN02: Single vs Tandem: High Risk Genetics

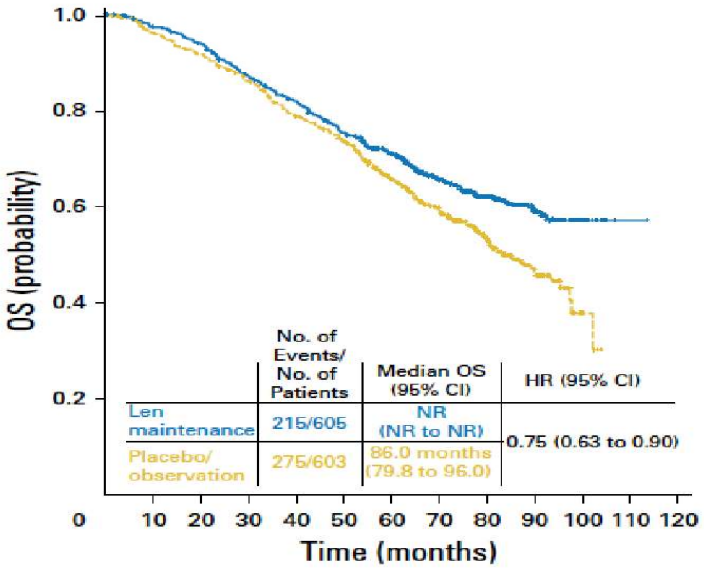


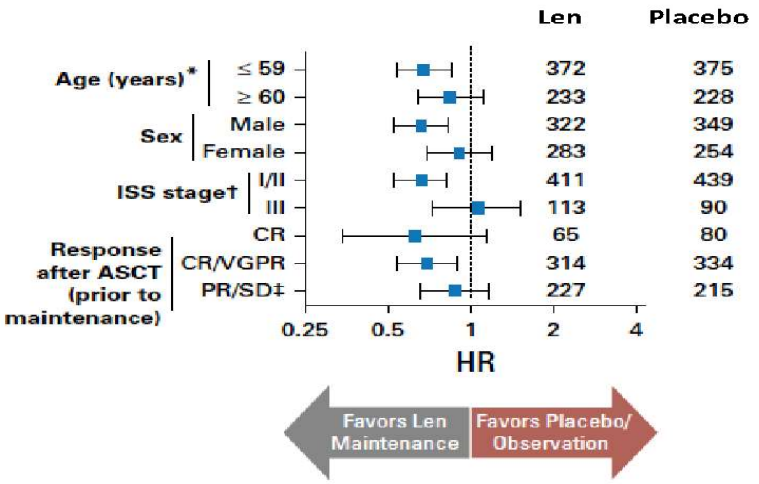


Recommendation: in high-risk patients, a discussion regarding tandem SCT is warranted

Cavo. ASH 2017. Abstr 401.

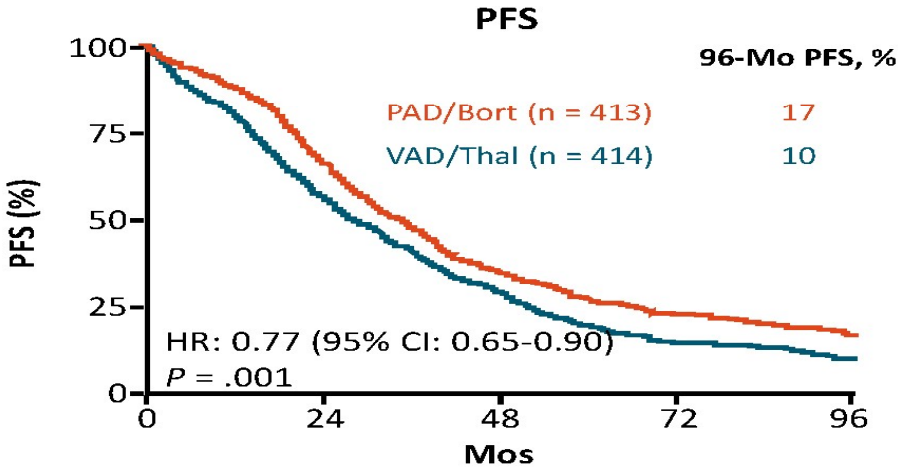
Lenalidomide Maintenance

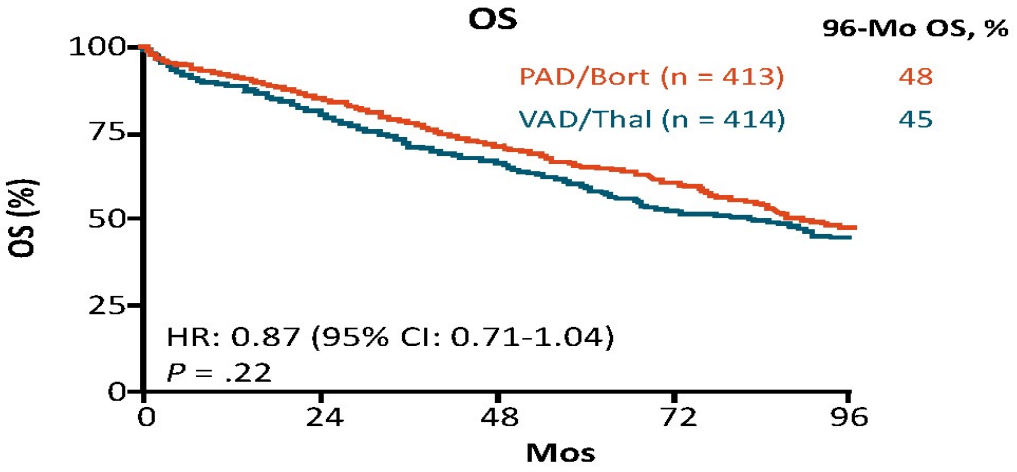




McCarthy. JCO. 2017;35:3279.

Phase III HOVON-65/GMMG-HD4 Trial: Bortezomib Maintenance



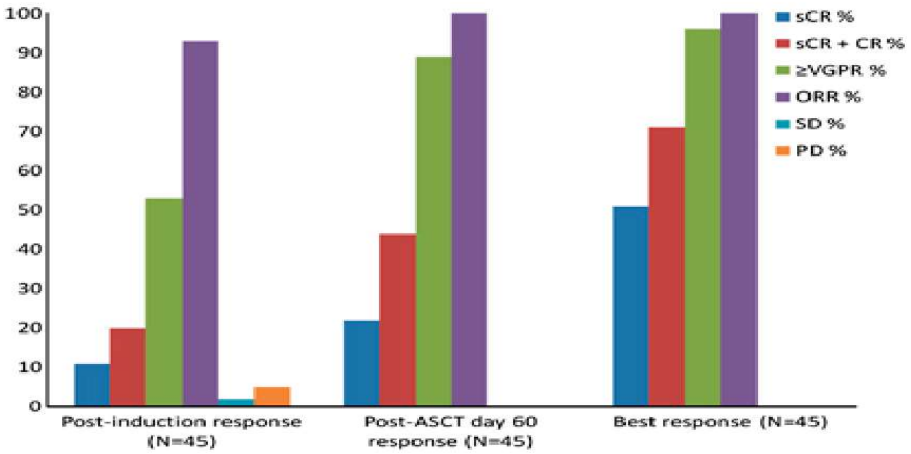


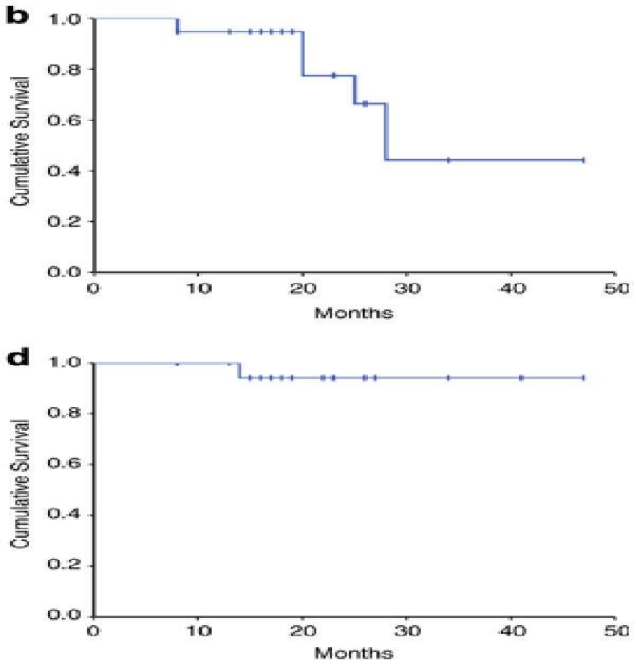
Outcome, %	PAD/Bort	VAD/Thal
CR/nCR	50	35
≥ VGPR	75	56
ORR	91	83

Recommendation: Lenalidomide maintenance should be considered for standard risk and bortezomib maintenance for high risk

Goldschmidt. Leukemia. 2018;32:383.

Different strategy for HR? VRD Maintenance





Nooka. Leukemia. 2014;28:690.

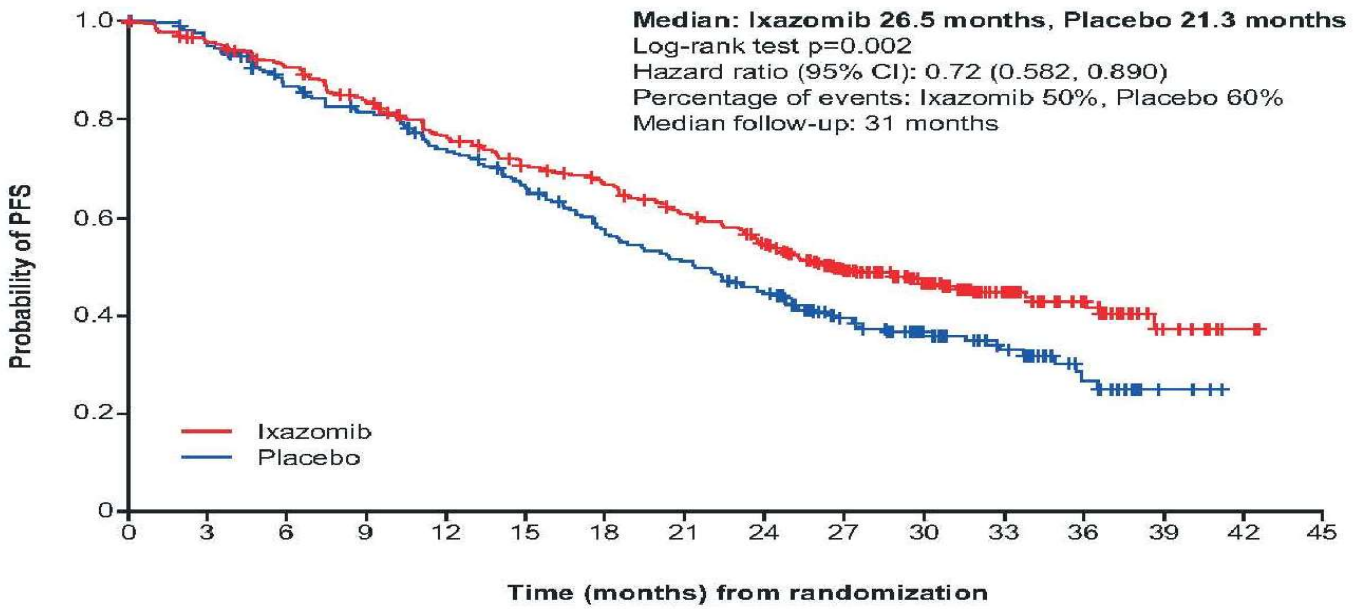
Take Home Points

- In transplant-eligible patients: upfront transplant after 4-6 cycles of induction regardless of the depth of response is standard
  - Delayed SCT at first relapse is acceptable
- If VRd induction is used, additional consolidation with VRd is not recommended
- Tandem transplant is not standard approach
  - In high-risk MM, possibility of benefit should be discussed
- Lenalidomide maintenance recommended for all standard-risk MM and bortezomib based maintenance for high risk
  - del17p: VRd maintenance could be considered

TOURMALINE MM-3

- Ixazomib vs placebo, phase 3
- In patients responding to ASCT
- Randomization 3:2
- 656 patients
- D1,8,15 in 28-day cycles
- Primary endpoint: PFS

Dimopoulos. ASH 2018. Abstr 301; NCT02181413



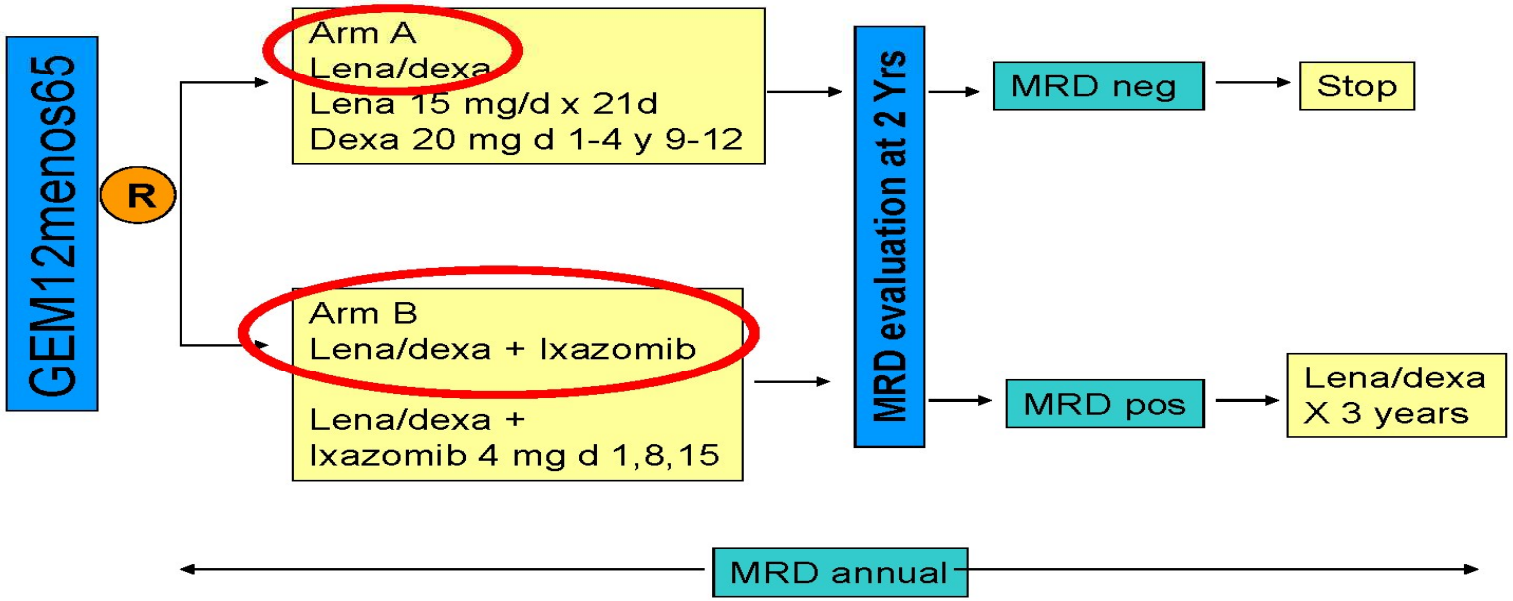
Number of patients at risk

Ixazomib	395	363	340	311	279	255	238	213	187	135	93	56	35	9	3	0
Placebo	261	238	210	195	174	153	130	117	100	69	46	32	15	3	0	0

Dimopoulos et al. ASH 2018; oral abstract 301. Sunday, December 2, 2018: 7:30 AM

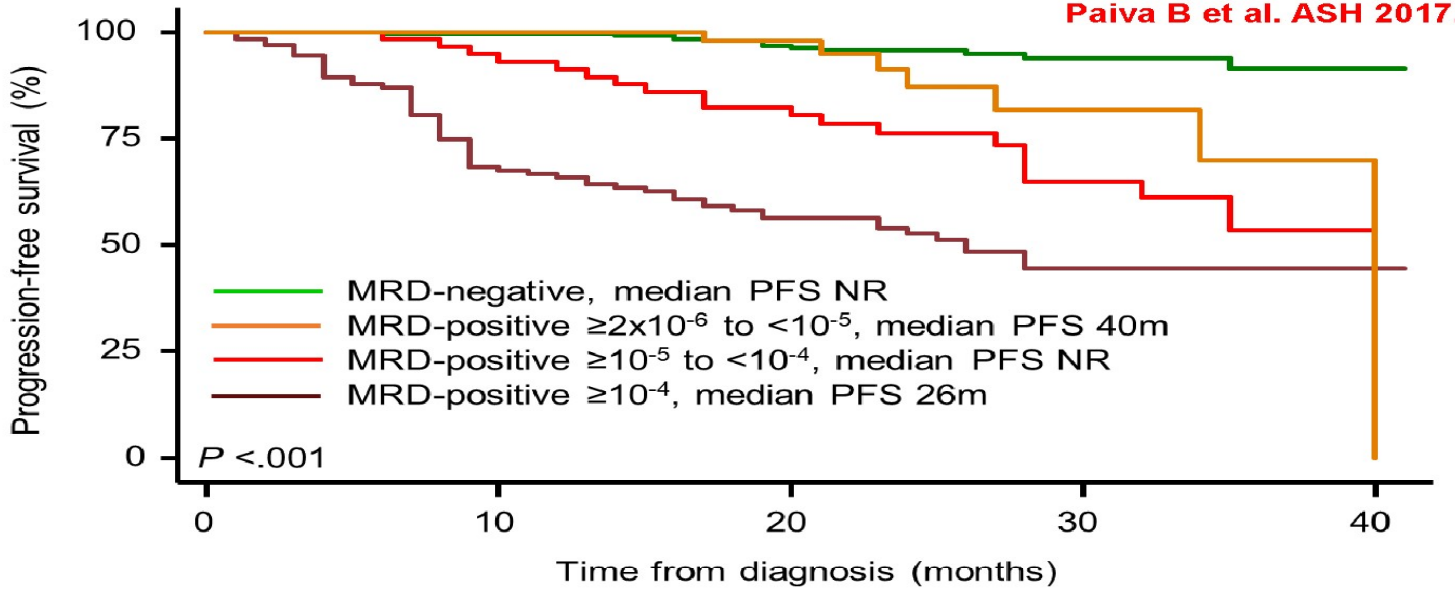
GEM14

Second trial as continuation of the previous one



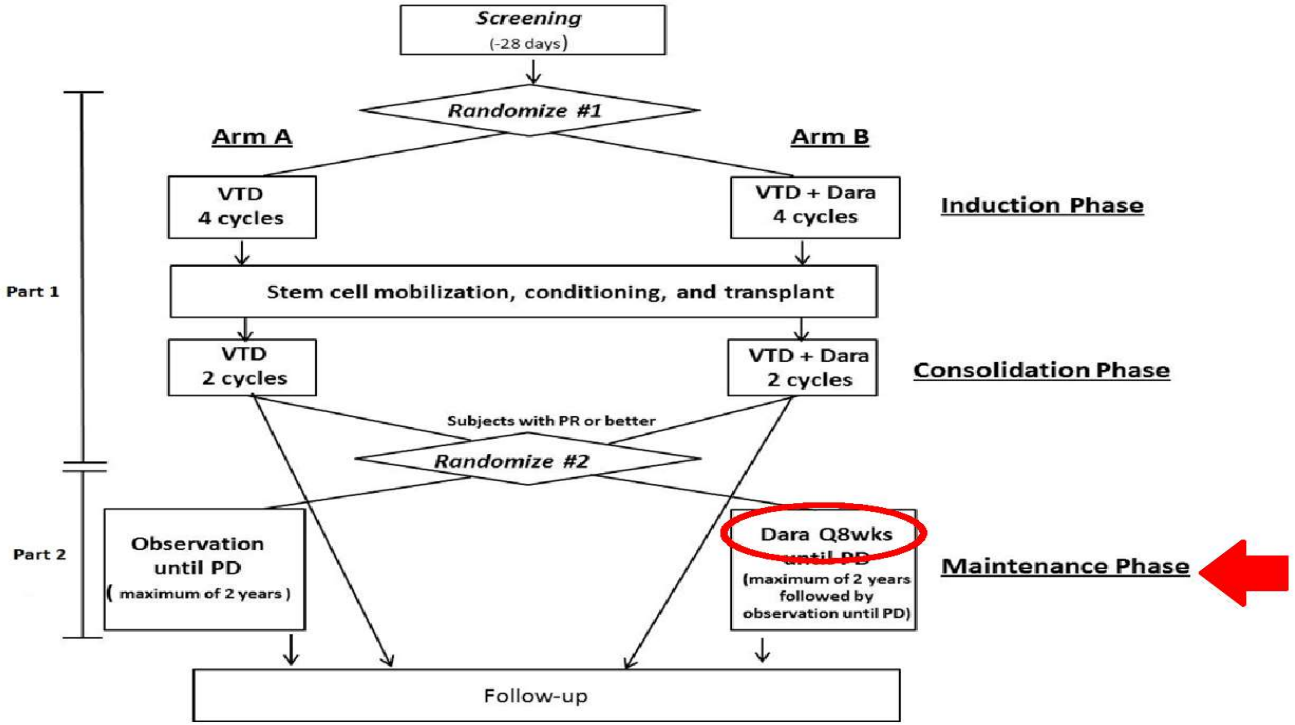
NCT02253316.

Paiva B et al. ASH 2017. Abstr 905.



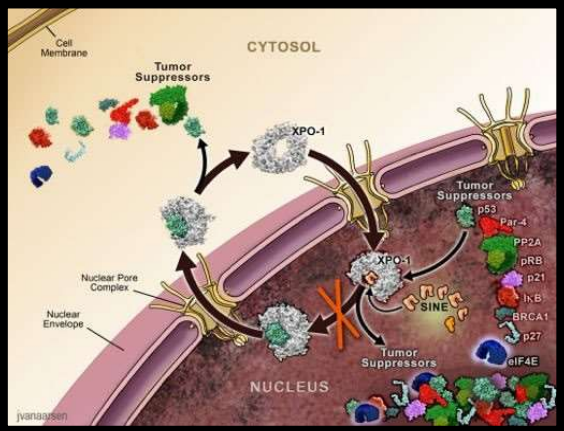
Number at risk					
MRD-neg	225	224	177	86	4
MRD ≥2x10^{-6} to <10^{-5}	49	49	36	10	1
MRD ≥10^{-5} to <10^{-4}	57	54	43	20	1
MRD ≥10^{-4}	127	84	57	20	2

CASSIOPEIA – 1080 Patients – ASCO 2019



XPO1-Inhibitor Selinexor in RRMM. Summary of Phase I data

First-in-class, oral Selective Inhibitor of Nuclear Export (SINE) that inhibits XPO1 and activates tumor suppressor proteins & reduces oncoproteins



- Cancer cells (and MM) overexpress XPO1, causing increased export of tumor suppressors and growth regulatory proteins from the nucleus
- Selinexor inhibit XPO1 mediated nuclear-cytoplasmic transport by transiently binding to XPO1 cargo binding site.
- Accumulation of Tumor suppressors in the nucleus amplifies the natural apoptotic function in cancer cells with damaged DNA.

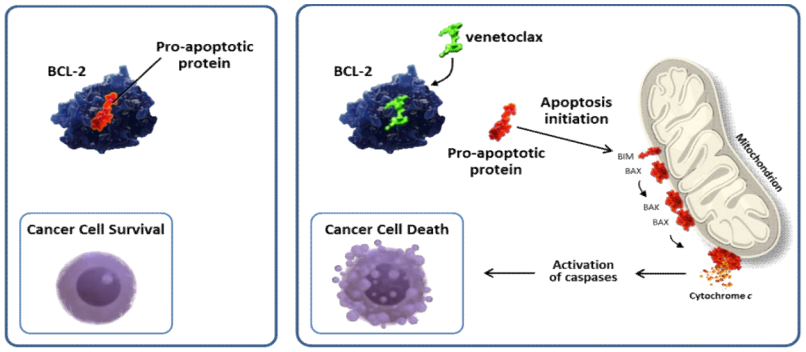
Tai et al. Leukemia 2014

PHASE I OF SELINEXOR PLUS/MINUS DEX IN RRMM →

- **Single agent** (oral:3-45 mg twice/ w)…. **17% MR,** *Chen et al. ASH 2014*
  Main AEs: Anorexia, nausea/vomiting, fatigue, thrombocytopenia.
- **+Dex** (n=122) (STORM)……..…….…….…….....**26% ORR** (Pent a-Refrct) PFS: 3,7m *Vogl et al. JCO 2018; Chari ASH 2018 (Abs 598)*
  AEs: nausea 73%, vomiting 49%, anorexia 49%, thrombocytopenia 73%/59% gr 3-4)
- **+ Bortz/dex** (n=42)…..... 63% (**43%** in Btz Rfct) (PFS: 9 (6,1)m)*Bahlis NJ, Blood 2018, (PH III BOSTON trial ongoing)*
  AEs: anorexia 33%, nausea 67%, Thrombocytopenia 17%
- **+ Pom/dex** (n=24)…..... 65% %in Pom Naive/Len R(**29%** in Pom/Len Rft). *Chen et al, ASH 2017)*
- **+ Dara/dex** (n=25)…..... **74%** %in double Rft. *Gasparetto et al, ASH 2018, Abs 599)*

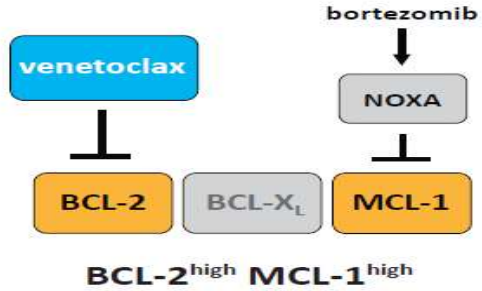
Venetoclax (bcl-2 inhibitor) in RRMM. Summary of Ph1 data

- Venetoclax is a selective, orally available small molecule BCL-2 inhibitor[1], induces cell death in multiple myeloma (MM) cell lines and primary samples, particularly those positive for the translocation t(11;14), which correlates with higher ratios of *BCL2* to *MCL1* and *BCL2* to *BCL2L1* ($BCL\text{-}X_L$) mRNA[1],



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]



1. Roberts AW et al. *NEJM* 2015
2. Punnoose E et al. *Mol Cancer Ther* 2016

1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279ra40. 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279–296. 4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.

- **Monotherapy** (n=66) (61% double Ref) ..... **ORR 21% (40% in t(11;14) DOR: 9.7m**

  G3-4 AEs: thrombocytopenia (26%) & neutropenia (21%)

- **+Btz/Dex** (n=66) ..... **ORR 67% (90% in BTz sensitive & 94% in BCL2 high)**

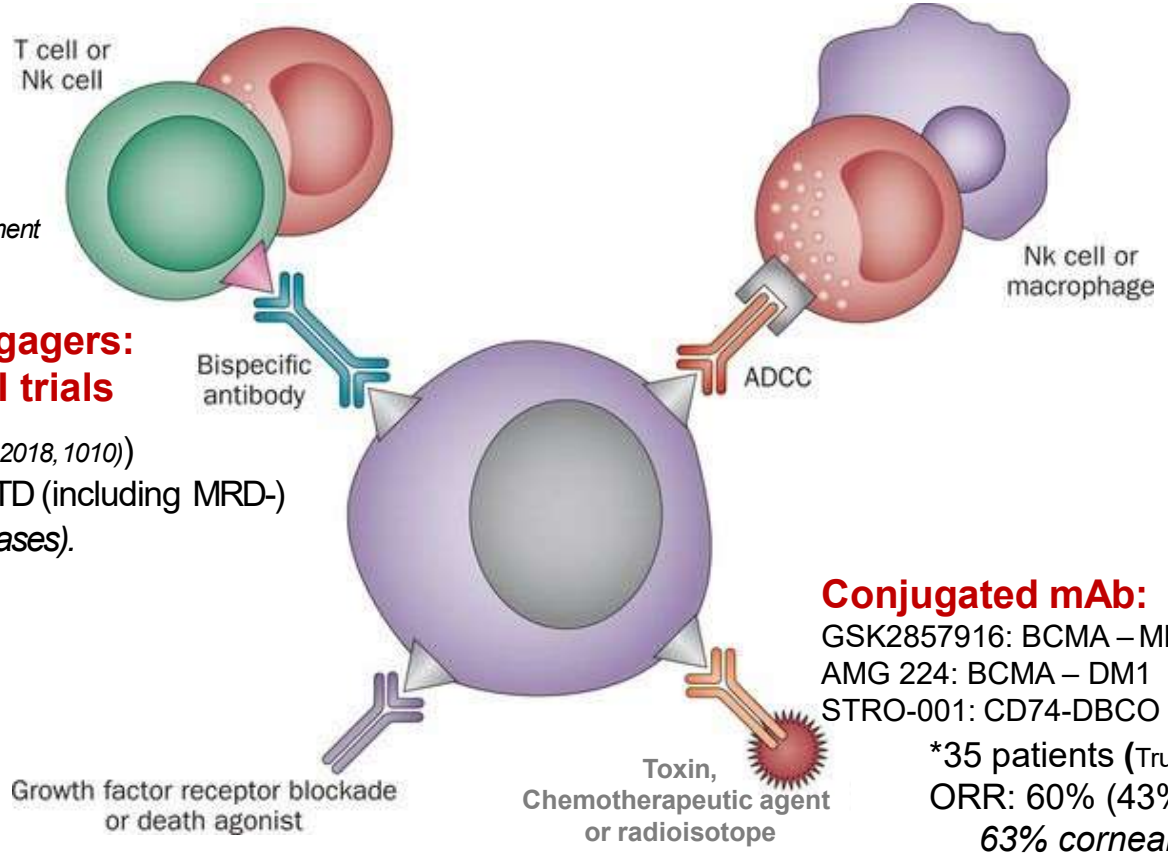
  G3-4 AEs: Thrombocytopenia (29%), anemia (15%), neutropenia (14%),

- **+Cfz/Dex** (n=42) (33% double Ref)..... **ORR 78% (PFS: 5,7m. The VGPR in t(11,14): 88%)**

Kumar, et al. Blood 2017; 130: 2401-09, Moreau P, et al. Blood 2017 130:2392-4; Costa et al ASH 2018, Abst 303

Monoclonal Antibodies: Futures Perspectives

To overcome the limitations of an immunosuppressive tumor microenvironment by linking CTLs with the tumor cell.



Bispecific T-cell engagers: BCMA–CD3 Phase I trials

- AMG 420: 35 pts: *(Topp et al ASH2018, 1010)*)
  28% ORR (6CR). 83% ORR at MTD (including MRD-)
  SAE: 49% (infections); CRS (3 cases).

Conjugated mAb:

GSK2857916: BCMA – MMAF*
AMG 224: BCMA – DM1
STRO-001: CD74-DBCO

*35 patients (Trudel S, *et al. Blood* 2017;130:741)
ORR: 60% (43% previous dara) PFS: 7.9m
63% corneal events most G1-2

*

Mackall CL, *et al. Nat Rev Clin Oncol* 2014;11:693-703.

MMAF, monomethyl auristatin F; DM1, maytansinoid N(2')- deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine.

BCMA CAR T-Cells in MM

Trial site	ScFv	Co-s domain	Gene transfer	Conditioning therapy	T-cell dose CAR+ T-cells/kg
NCI	11D5-3	CD28	Y- retroviral	Cy 300 mg/m^2 x3 + Flu 30 mg/m^2 x3	0.3–9.0 x 10^6
Bluebird Celgene	NR, murine	4-1BB	Lentiviral	Cy 300 mg/m^2 x3 + Flu 30 mg/m^2 x3	50, 150, 450 and 800 x 10^6
University of Pennsylvania	NR, human	4-1BB	Lentiviral	None or Cy 1.5 g/m^2	10–50 x 10^6 or 100–500 x 10^6
Nanjing Legend Biotech	NR	NR	Lentiviral	Cy 300 mg/m^2 x3	1.5–7.0 × 10^6
Memorial Sloan Kettering Cancer Center	NR, human	4-1BB	Y- retroviral	Cy 3000 mg/m^2 or Cy 300 mg/m^2 x 3 + Flu 30 mg/m^2 x3	1x10^6 150, 450 and 800 x 10^6

This slide is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.
ScFv, single-chain fragment variable.

BCMA CAR T-cell Therapies for MM

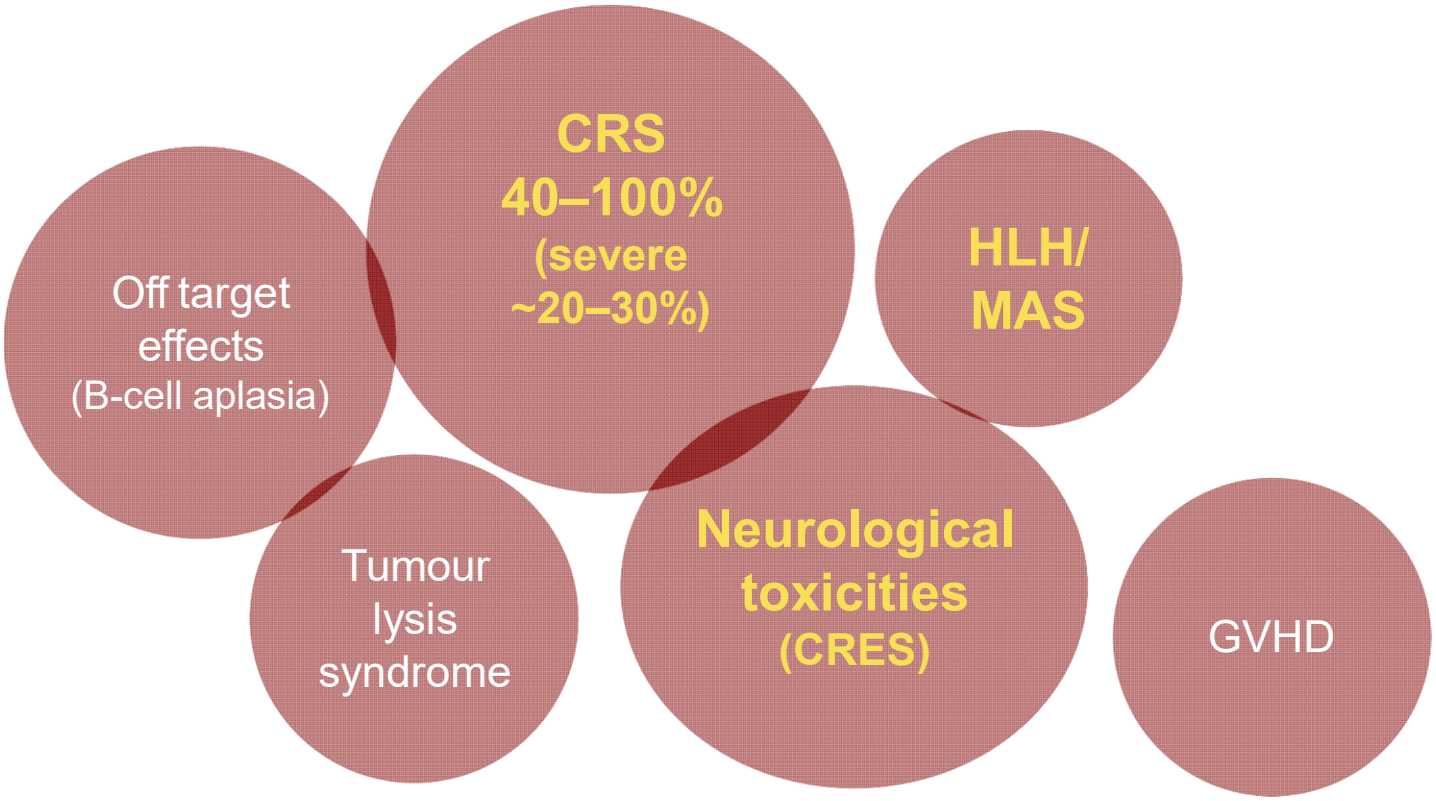
	Anti-BCMA CAR[1] NCT02215967	Bb2121[2] NCT02658929	CART-BCMA[3] NCT02546167	LCAR-B38M[4] NCT03090659
Group/company	***NIH***	***Bluebird/Celgene***	***University of Pennsylvania/ Novartis***	***Nanjing Legend Biotech***
Patients	**16** patients at 9x10^6/kg dose level	22 (>150 x 10^6 cells)	**21** (**3 cohorts**): 9 (10-500 x 10^6, No Cyt) 5 (10–50 x 10^6, Cyt) 7 (5 (100–500 x 10^6, Cyt)	**57**
BCMA expression required?	Yes	Yes; ≥ 50% BCMA expression	No	Yes
Median prior lines of therapy	7	7	7 (3–11)	3
Reported efficacy	ORR 14/16 (**81%**) 11/14 (**79%**) MRD- EFS: **7.2 months**	**86.4%** ≥VGPR (**50%** sCR/CR) **PFS: 11.8 months**	#1**: 67%** (1 sCR, 1VGPR) #2: (**40%**) 1 PR, 1 MR both PD #3: (**83%**) 1 CR, 3 PR, 1 MR	ORR: **88%** **CR: 74%** **MRD-: 93% of CR** **PFS:15m**
Safety data	CRS all grades:100%, 37%G3-4	CRS all grades: 63% 2 events of CRS grade ≥3 resolved within 24 hours	CRS: 17 pts (grade 3: 32%) Neurotoxicity: 3 (2 grade 4) 1 death – PD candidaemia	Transient CRS (5,7% G3) No neurotoxicity

This slide is provided for ease of vie
BCMA, B-cell maturation antigen; C
partialresponse.
[1] Ali A, et al. Presented at ASH 20
S103.

Abstracts ASH 2018: 488, 955-7, 959, 960, 1009, 1011-14

Safety Concerns Regarding CAR T-Cell Therapy

CRS is the most common toxicity triggered by the activation of T-cells and bystander immune cells → release of cytokines and chemokines: IFN-γ, soluble IL-2R, IL-6, etc



CRS, cytokine release syndrome, (Tocilizumab & Corticosteroids) CRES, CAR T-cell-related encephalopathy syndrome, GVHD, graft-versus-host disease, HLH, haemophagocytic lymphohistiocytosis, MAS, macrophage activation syndrome.

Improvements of CAR T-Cell Therapies

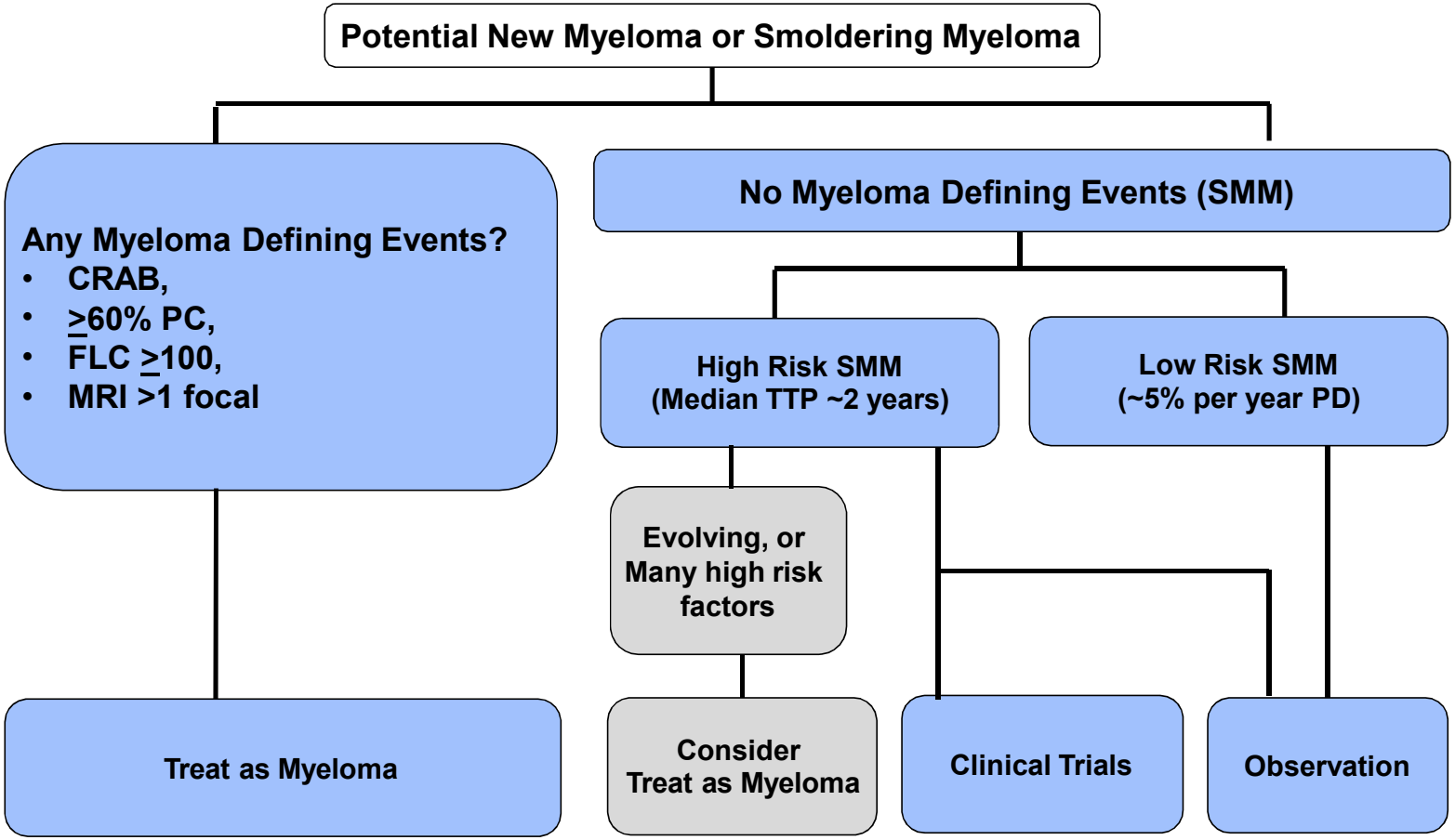
Limitation	Potential Improvements
Immunological rejection & safety	• **Humanised** CARs to reduce immunogenicity • **Allogeneic CAR T:** Gene editing (CRISPR/Cas9) of normal donor T-cells to remove naive TCR (to avoid GVHD) and transfection with a CAR with post-conditioning vaccination to improve memory • **Safety marker gene** to extinguish the CAR-T activity.
Immune system limitations	• Rational **combination strategies** : Checkpoint inhibitors, IMiDs, BTK inhibitors
Efficacy & antigen escape	• **Bi-specific CAR** (e.g. CD19, CD123, BCMA, SLAMF7) • Use of **specific T-cell subpopulations** (from naive to **central memory** and to terminal effector T-cells) • **APRIL** as the natural BCMA/TACI ligand instead of the Ab (anti-BCMA) • **Antibody-Coupled T-Cell Receptor (ACTR):** engages antibody to direct T-cell attack against many different Ags • **Armored CAR** (*2nd gene that generate a cytokine: i.e. IL12)*

AICD, activation-induced cell death, ScFv, single-chain fragment variable, TRAC, T-cell receptor α constant.
Brudno JN & Kochenderfer JN. *Nat Rev Clin Oncol* 2018;15:31–46.

2019 Algorithms

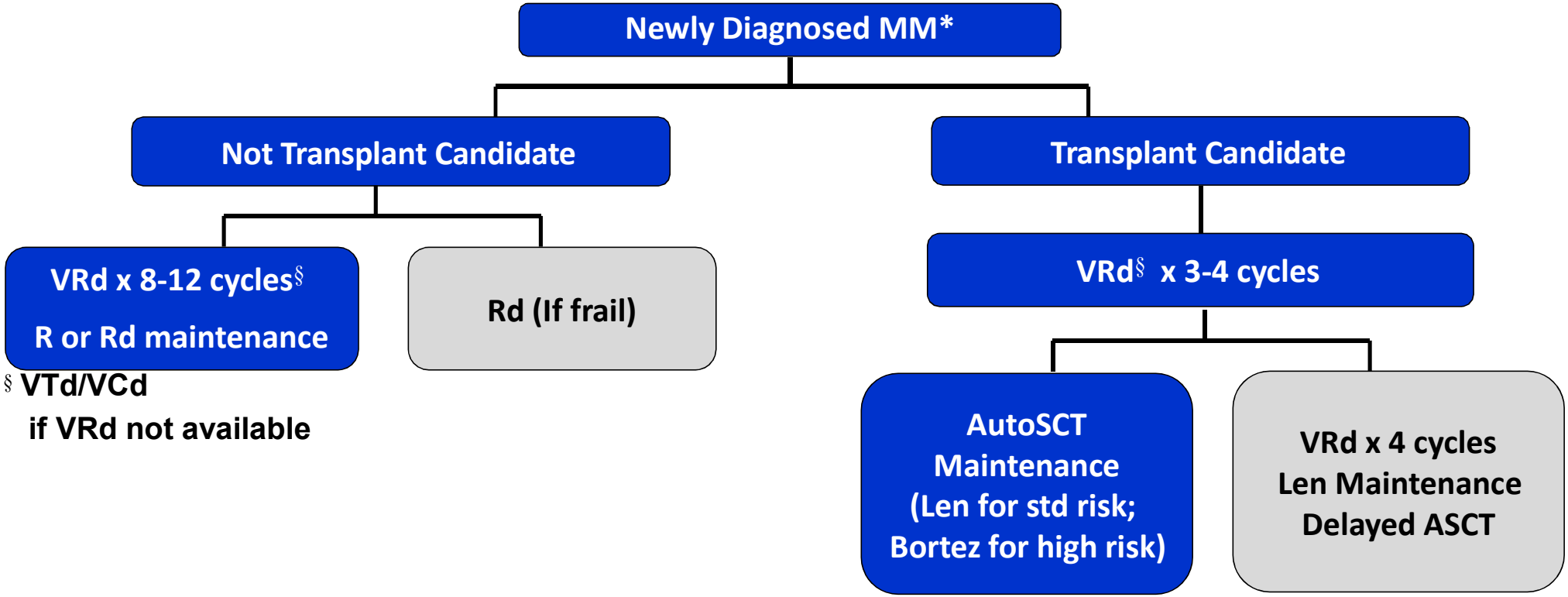
- Clinical Trials preferred
- Only commercially available options
- Assumes all drugs available

When Should Treatment Be Initiated?



Rajkumar SV, Landgren O, Mateos MV. Blood 2015

Myeloma: Frontline Treatment

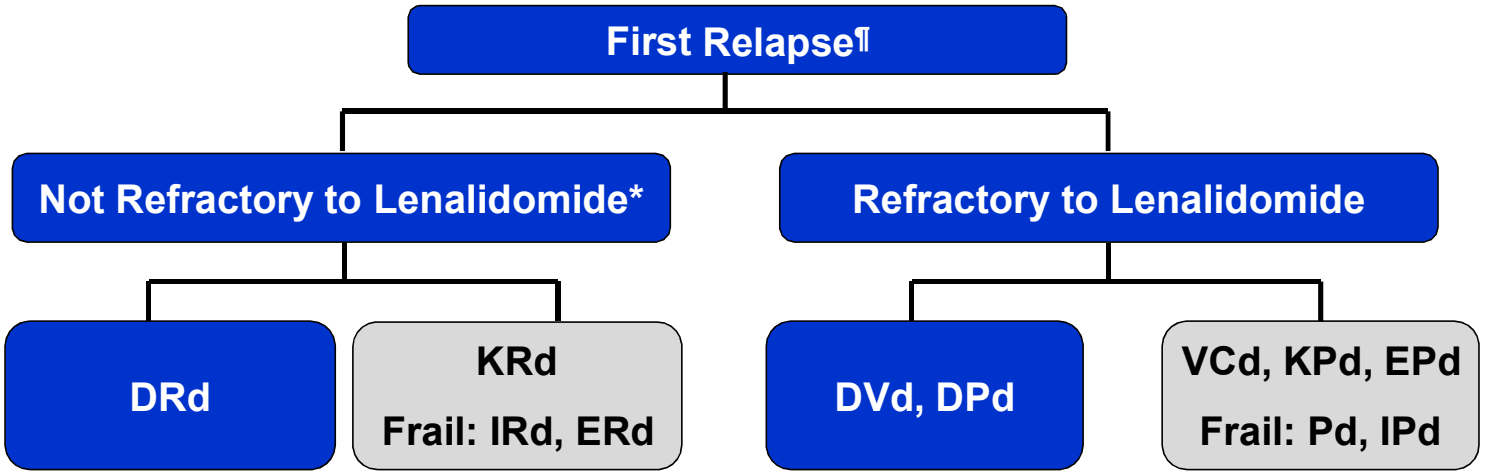


§ VTd/VCd
if VRd not available

*Based on CALGB 100104, S0777, IFM-DFCI, CTN 0702 HOVON

Rajkumar SV. 2019.

Myeloma: First Relapse

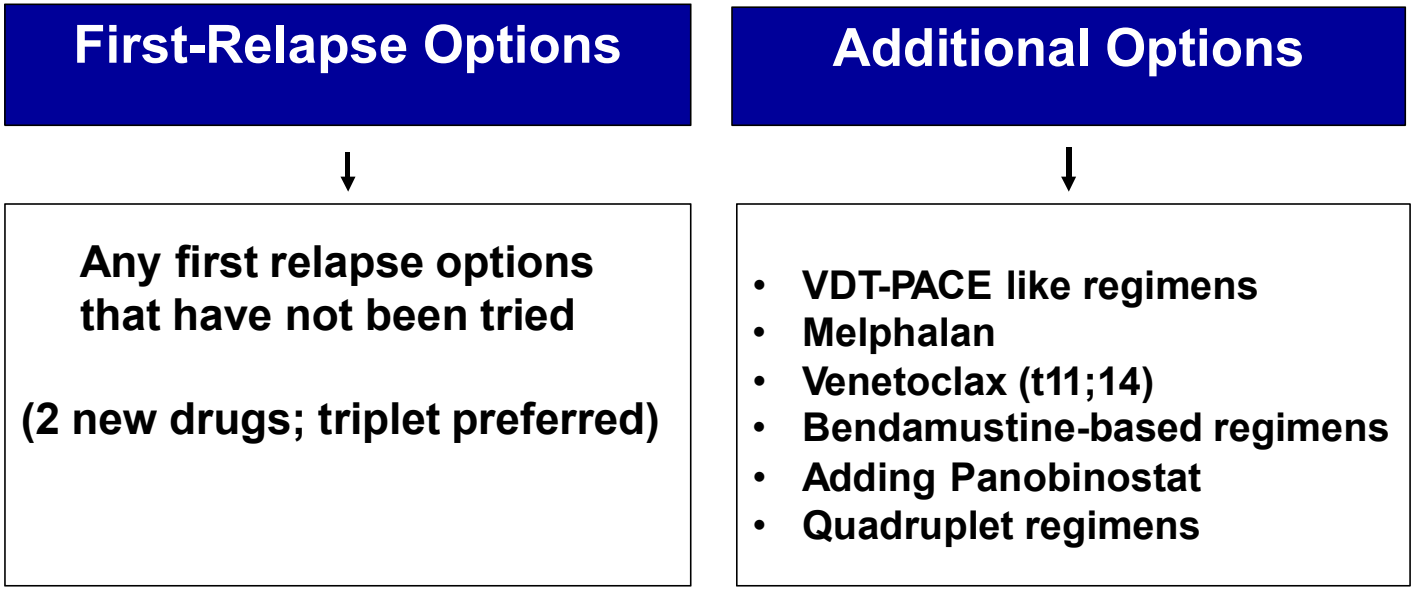


*Relapse occurring while off all therapy, or while on small doses of single-agent lenalidomide, or on bortezomib maintenance

¶ Consider salvage auto transplant in eligible patients

Rajkumar SV, Kyle RA. Progress in Myeloma: A Monoclonal Breakthrough. N Engl J Med 2016;375:1390-1392

Myeloma: Second or Higher Relapse



Rajkumar SV. 2019.