Multiple Myeloma

Transplant and Non-transplant Modalities

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IMWG Diagnostic Criteria for MGUS and Related-Plasma Cell Disorders

	Progression Rate	Primary Progression Events
Non-IgM MGUS	1% per year	MM, solitary plasmacytoma, Ig-related amyloidosis (AL, AH, AHL)
IgM MGUS	1.5% per year	WM, Ig-related amyloidosis (AL, AH, AHL)
Light-chain MGUS	0.3% per year	Light chain MM, Ig light-chain amyloidosis
Solitary Plasmacytoma	~10% within 3 years	MM
Solitary Plasmacytoma with minimal marrow involvement	60% (bone) or 20% (soft tissue) within 3 years	MM
POEMS Syndrome	NA	NA
Systemic AL Amyloidosis	NA	Some patients might develop MM

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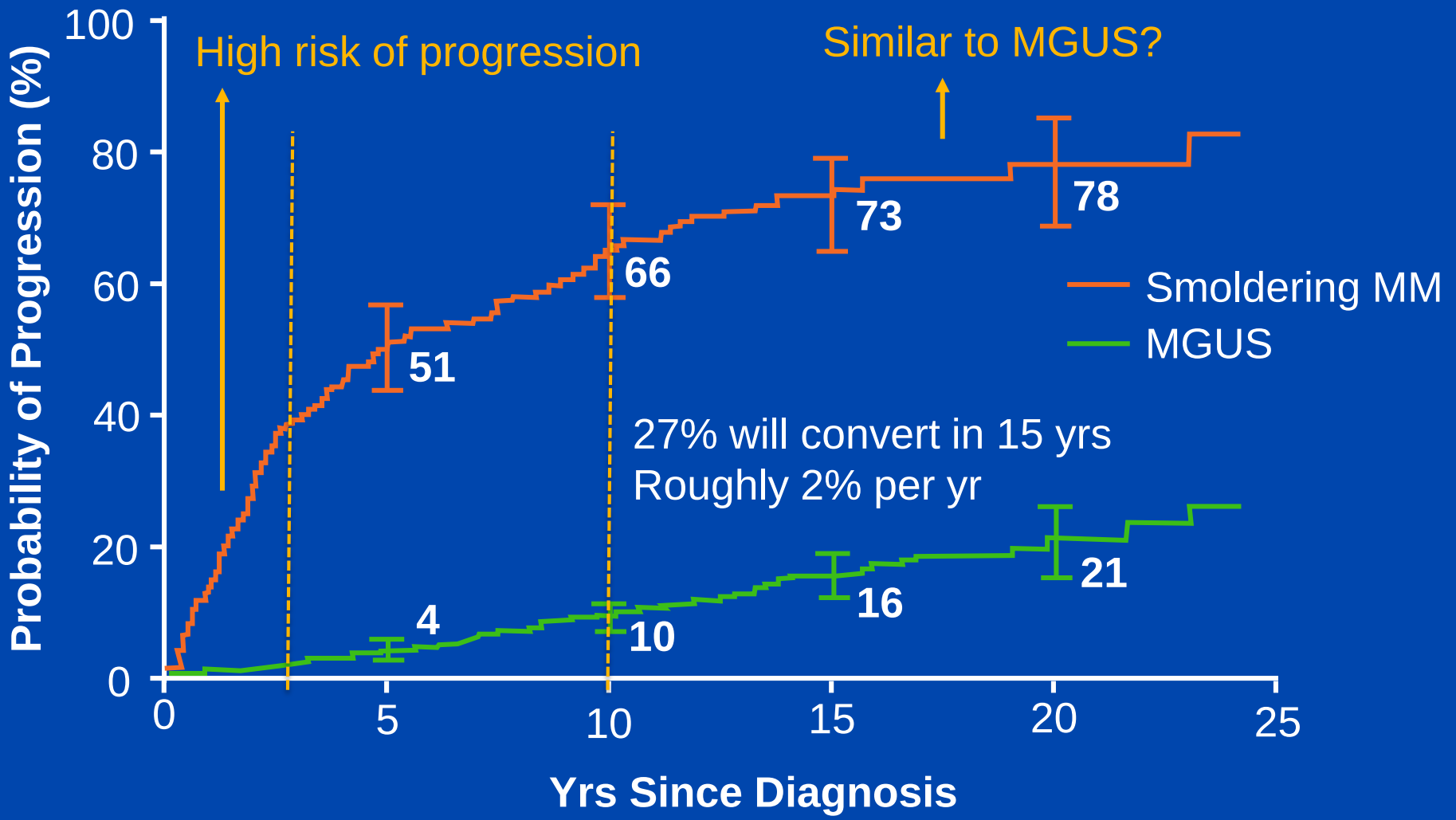
Lancet Oncology IMWG 2014 Diagnostic Criteria



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Kyle R, et al. 2007 N Engl J Med;356:2582-2590.

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Smoldering Myeloma

- M-protein >3 g/dl and/or >10% BM plasma cells
- No “CRAB” criteria
- Evolution into overt MM @ ~3%/year
  - >10% PCs in BM
  - BJ proteinuria detected
  - IgA isotype
- Recently added to “active” MM:
  - BM PCs >60%
  - LC involved/uninvolved >100
  - MRI: ≥1 focal lesion

_S_ixty%, _Li_ght chain, _M_RI=“SLiM” CRAB

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Rajkumar V, et al. 2014 Lancet Oncol;15:e538

Management Updates for MM

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Some General Principles

- Combination regimens are more beneficial
  - “Doublets” vs. “Triplets”
- Longer duration of therapy is beneficial in preventing disease progression
  - Maintenance after “adequate response”
- Depth of response is important, especially in newly diagnosed patients
  - DON’T save the best regimen for later.
- Side effect profile:
  - Need to manage side effects well to stay on beneficial regimens
  - Dosing and schedule may be modified but can affect efficacy.

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Some Newer Principles

- Endpoints
  - Response rates universally good
  - Translating into better PFS and in some cases OS
- Minimal Residual Disease
  - Currently a part of most new clinical trials
  - Prognostic importance established
  - Therapeutic implications being analyzed
  - Being explored as a new FDA-admissible endpoint
  - Some real-world utilization

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FDA Approved MM Therapeutics in the U.S.

The "Big Five"

	Use	Route	Mode of Action	Plus	Minus	Clinical Benefits
Thalidomide	ND, RR	Oral	IMiD	Safe in kidney dysfunction, Minimal myelo-suppression	Neuropathy, Fatigue, Thrombosis	ORR; especially in combinations even in late disease
Lenalidomide	ND, RR	Oral	IMiD	Little neuropathy, Safe over long durations	Thrombosis, GI side effects, Cytopenias, Fatigue, Secondary malignancies	ORR; especially in combinations in early and late disease, Most extensive maintenance data
Pomalidomide	RR	Oral	IMiD	Little neuropathy, more combination data emerging	All similar to Len. May need lower dose (2 mg) in triplet combinations	ORR
Bortezomib	ND, RR	SC/IV	Proteasome	Excellent efficacy, use in renal dysfunction, high risk, manageable cytopenias	Peripheral neuropathy (SC and weekly)	ORR, OS benefit, extensive efficacy and safety data including maintenance
Carfilzomib	ND, RR	IV	Proteasome	All benefits as bortezomib, minimal neuropathy	Twice weekly (so far), cardiopulm toxicity	High CR rate, OS benefit

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ND=Newly Diagnosed, RR=Relapsed/Refractory, SC=Subcutaneous, IV=Intravenous, ORR=Overall Response Rate, CR=Complete Response, OS=Overall Survival

FDA Approved MM Therapeutics in the U.S.

The "New Three"						
	Use	Route	Mode of Action	Plus	Minus	Clinical Benefits
Ixazomib	RR	Oral	Proteasome	All benefits as bortezomib, minimal neuropathy	Specialty medication, GI side effects, thrombocytopenia	ORR; being studied wherever bortezomib used
Daratumumab	RR	IV	Anti-CD38	Less overlapping toxicities with other agents, well-tolerated, significant efficacy even as a single-agent	Long infusion time, infusion reactions, some safety data in renal failure	ORR; Extensive triplet data emerging. Deepest MRD negativity with lenalidomide among all regimens
Elotuzumab	RR	IV	Anti-CS1	Less overlapping toxicities with other agents, well-tolerated	Not much efficacy as single agent, no reported efficacy in patients who are IMiD refractory (even patients progressing on len maintenance)	ORR, better MRD than doublet. Consider when planning lenalidomide+dexamethasone

ND=Newly Diagnosed, RR=Relapsed/Refractory, SC=Subcutaneous, IV=Intravenous, ORR=Overall Response Rate, CR=Complete Response, OS=Overall Survival, MRD=Minimal Residual Disease

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mSMART – Off-Study

Transplant Ineligible

Standard-Risk	Intermediate-Risk	High-Risk
t(11;14), t(6;14), Trisomies	t(4;14)	Del 17p, t(14;16), t(14;20)
↓	↓	↓
VRd for ~12 months; If age ≥75 or frail: Rd [a]	VRd for ~12 months	VRd[c] for ~12 months
↓	↓	↓
Rd x 1 year [a, b]	Bortezomib-based maintenance for minimum of 1 year	Bortezomib-based maintenance for minimum of 1 year

[a] *In patients treated initially with Rd, continuing treatment until progression is an option for patients responding well with low toxicities;*
[b] *Dex is usually discontinued after first year*
[c] *Clinical trials strongly recommended as the first option*

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed July 2016

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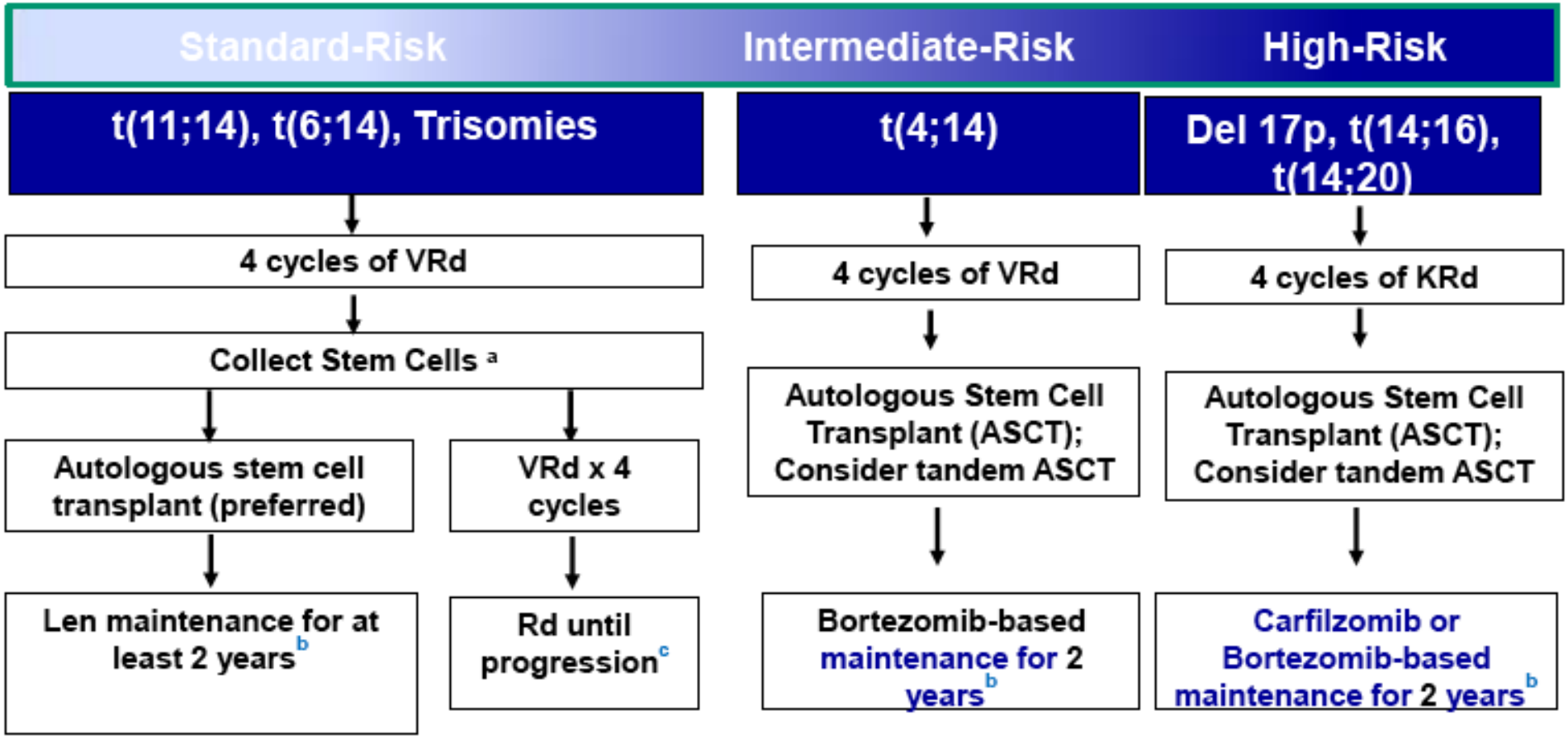
mSMART – Off-Study

Transplant Eligible



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 2 years*
c *Continuing Rd for patients responding to Rd and with low toxicities*

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed July 2016

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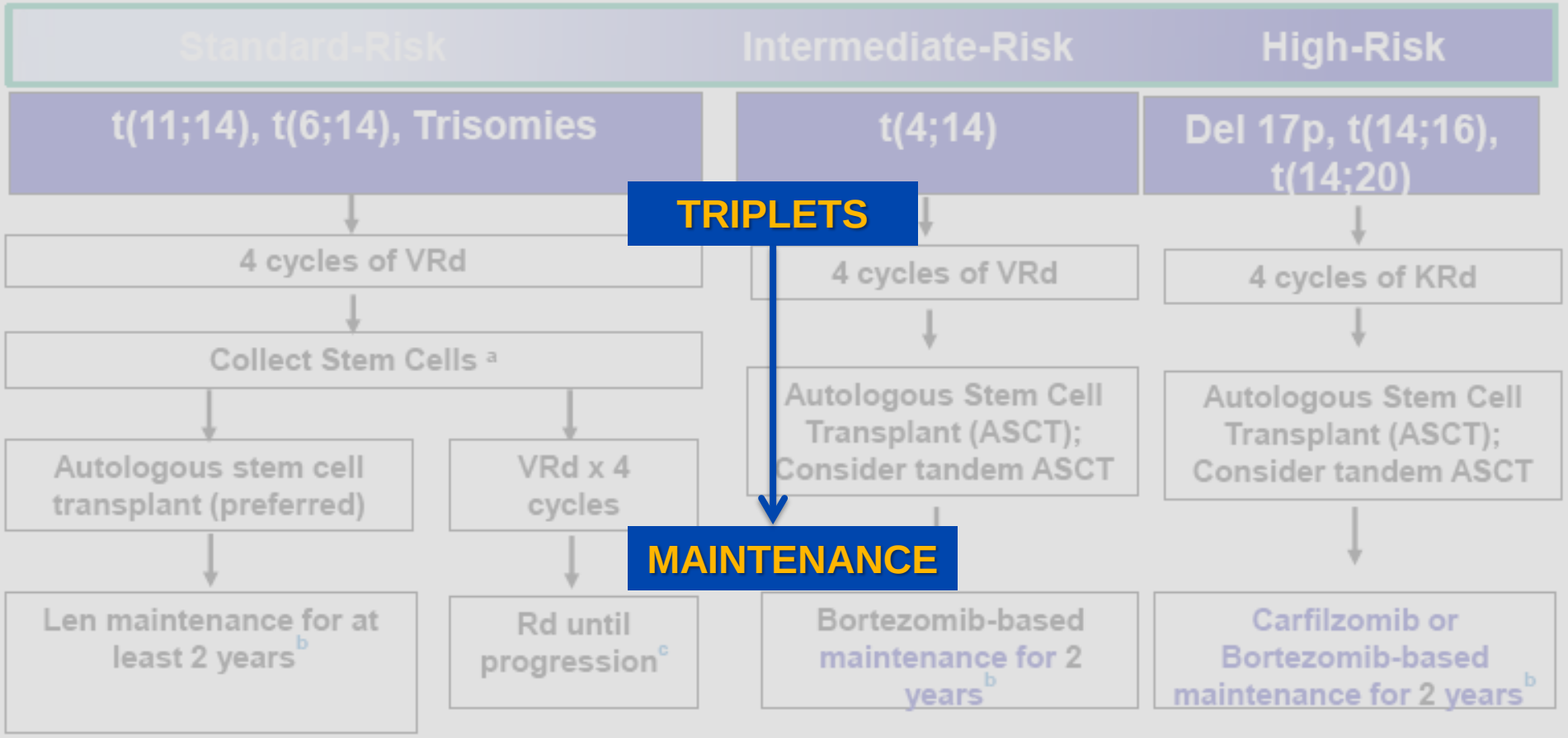
mSMART – Off-Study

Transplant Eligible



[a] *If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor*
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c Continuing Rd for patients responding to Rd and with low toxicities

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed July 2016

Newer Studies Related to Smoldering Myeloma

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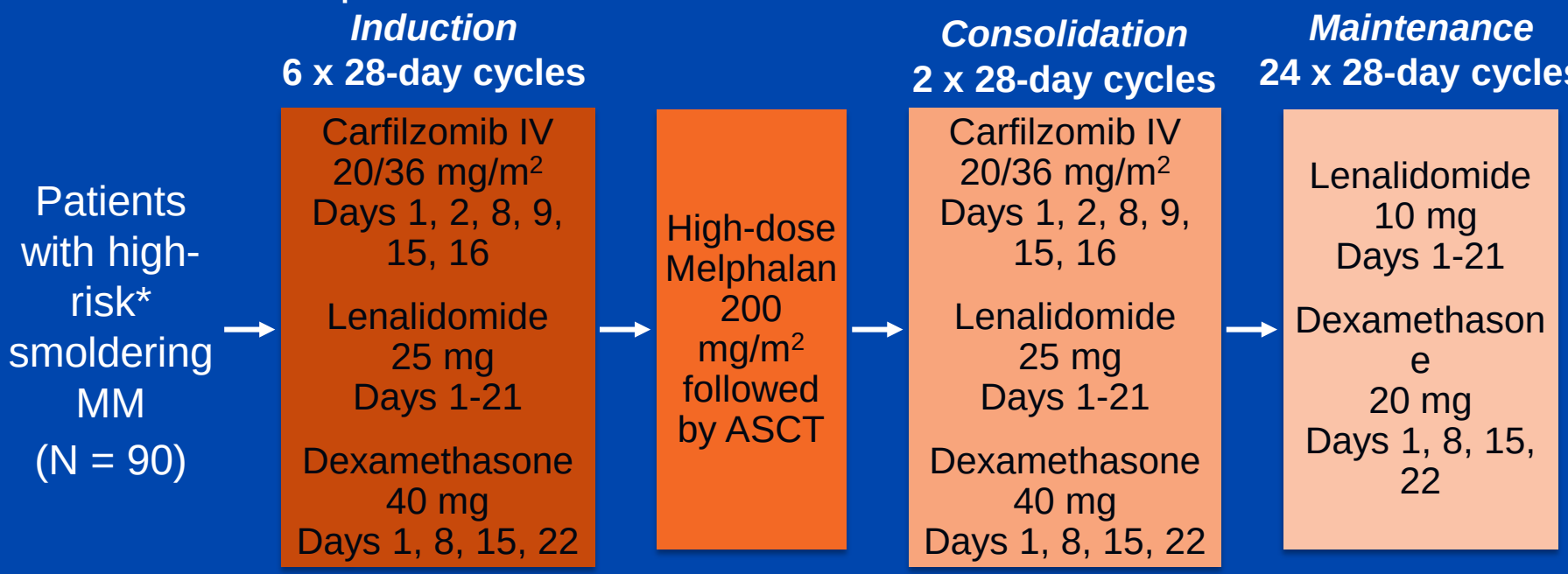
GEM-CESAR: Phase II Study Design

- Multicenter, open-label trial



- Primary endpoint: MRD negative rate (by flow cytometry) after induction, ASCT, consolidation/maintenance, and 3 and 5 yrs after maintenance
- Secondary endpoints: response, TTP, PFS, OS, safety

*High risk defined per Mayo and/or Spanish models

- Pts with ≥ 1 biomarker predicting imminent progression to MM allowed
- Pts w/bone disease on CT or PET/CT at screening excluded

Mateos MV, et al. ASH 2017. Abstract 402.

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GEM-CESAR: Efficacy With KRd Consolidation and Rd Maintenance

Response Category, n (%)	Induction (n = 71)	HDT ASCT (n = 42)	Consolidation (n = 35)	Maintenance (n = 29)
ORR, n (%)	69 (98)	42 (100)	35 (100)	29 (100)
▪ sCR	21 (30)	22 (52)	24 (69)	24 (83)
▪ CR	9 (13)	2 (5)	2 (6)	2 (7)
▪ VGPR	27 (38)	12 (29)	7 (20)	2 (7)
▪ PR	12 (17)	6 (14)	2 (6)	1 (3)
MRD negative, %	31	50	60	NA
Relapse from CR, n (%)	2 (3)	--	--	--

No pt discontinued consolidation or maintenance.

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Mateos MV, et al. ASH 2017. Abstract 402.

GEM-CESAR: Conclusions

- This curative approach for high-risk smoldering MM encouraging according to authors
- Depth of response improved over phases of treatment, with 90% of pts who received maintenance therapy achieving CR with 60% MRD-negative rate
- Authors suggest safety profile acceptable
  - Infections most common treatment-related AE, generally mild/manageable
- Incorporating new imaging assessment allowed identification of 18% of screening failures due to presence of bone disease

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Mateos MV, et al. ASH 2017. Abstract 402.

Studies Related to Newly Diagnosed Multiple Myeloma

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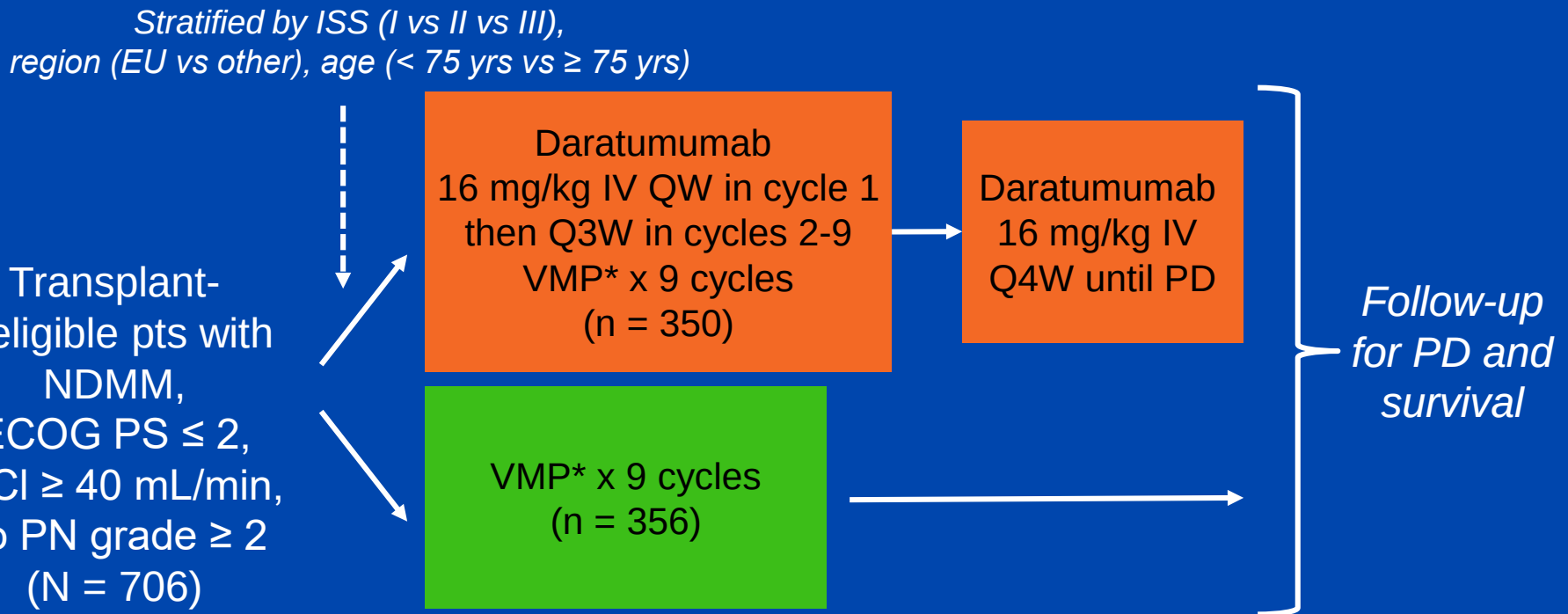
ALCYONE: Open-Label, Phase III Study Design

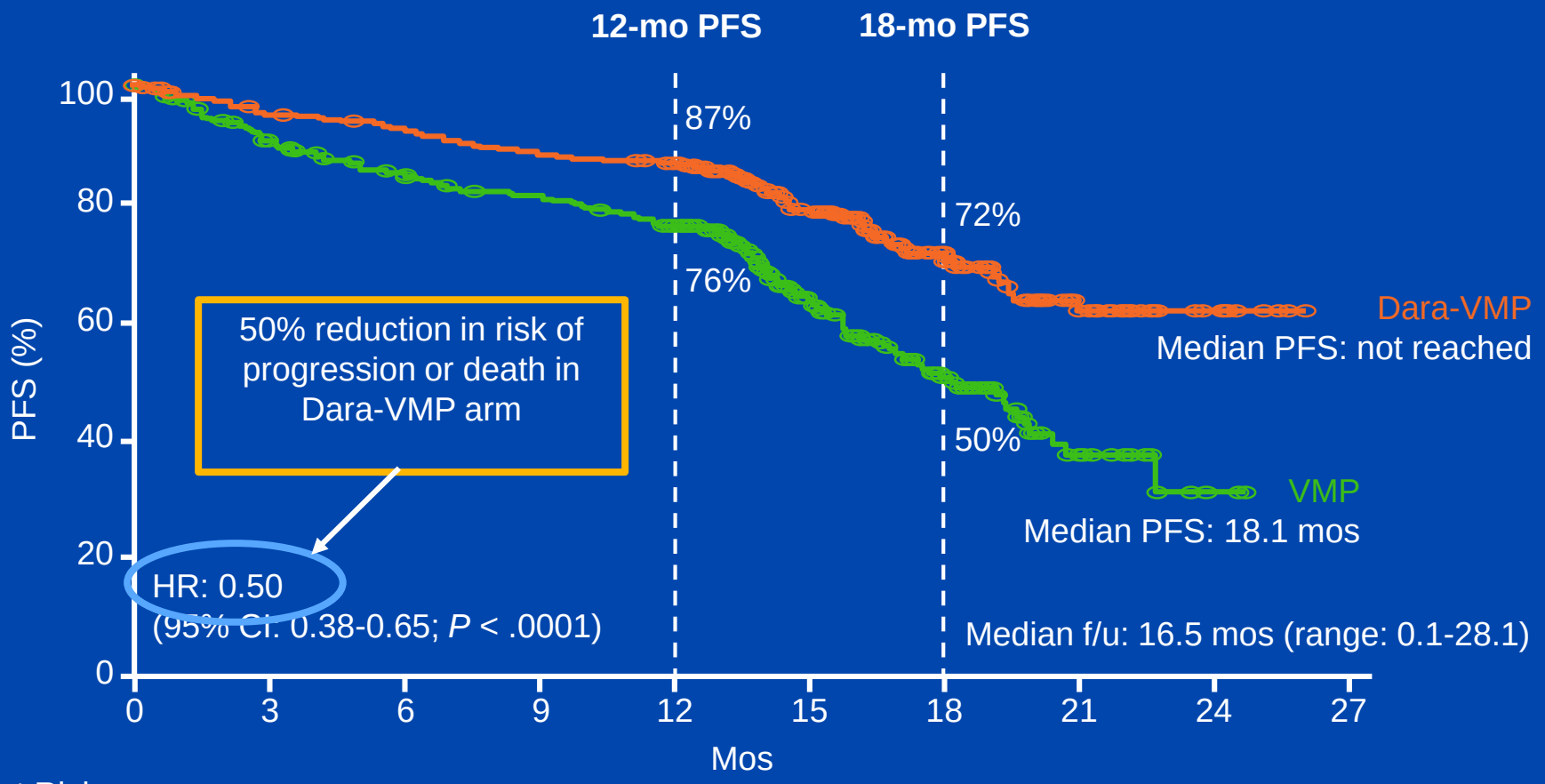


*VMP: bortezomib 1.3 mg/m^2 SC twice weekly in cycle 1, QW in cycles 2-9; melphalan 9 mg/m^2 PO Days 1-4; prednisone 60 mg/m^2 PO Days 1-4.
Cycles 1-9: 6-wk cycles

- Primary endpoint: PFS
- Secondary endpoints: ORR, ≥ VGPR, ≥ CR, MRD, OS, safety
- Statistical analysis: 360 PFS events with 85% power for 8-mo improvement
- Interim analysis at ~ 216 PFS events

Mateos MV, et al. ASH 2017. Abstract LBA-4.

ALCYONE: PFS



Pts at Risk, n

VMP	356	303	276	261	231	127	61	18	2	0
Dara-VMP	350	322	312	298	285	179	93	35	10	0

- Consistent PFS benefit across subgroups

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Mateos MV, et al. ASH 2017. Abstract LBA-4.

ALCYONE: Conclusions

- Dara-VMP reduced risk of progression or death by 50% vs VMP alone
  - First phase III randomized study of an mAb in newly diagnosed myeloma
- Dara-VMP induced significantly deeper response, including a > 3-fold higher rate of MRD negativity
- No new safety signals except higher rates of infections which resolved
- Ongoing frontline daratumumab studies
  - Phase III: MAIA (Dara-Rd) and CASSIOPEA (Dara-VTD)
  - Phase II: GRIFFIN (Dara-VRd) and LYRA (Dara-CyBord)

Study investigators conclude that these results strongly support Dara-VMP as a new standard of care in transplant-ineligible newly diagnosed myeloma

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Mateos MV, et al. ASH 2017. Abstract LBA-4.

Upfront autologous stem cell transplantation versus novel agent-based therapy for Multiple Myeloma: A randomized phase 3 study of the European Myeloma Network (EMN02/HO95 MM trial)

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

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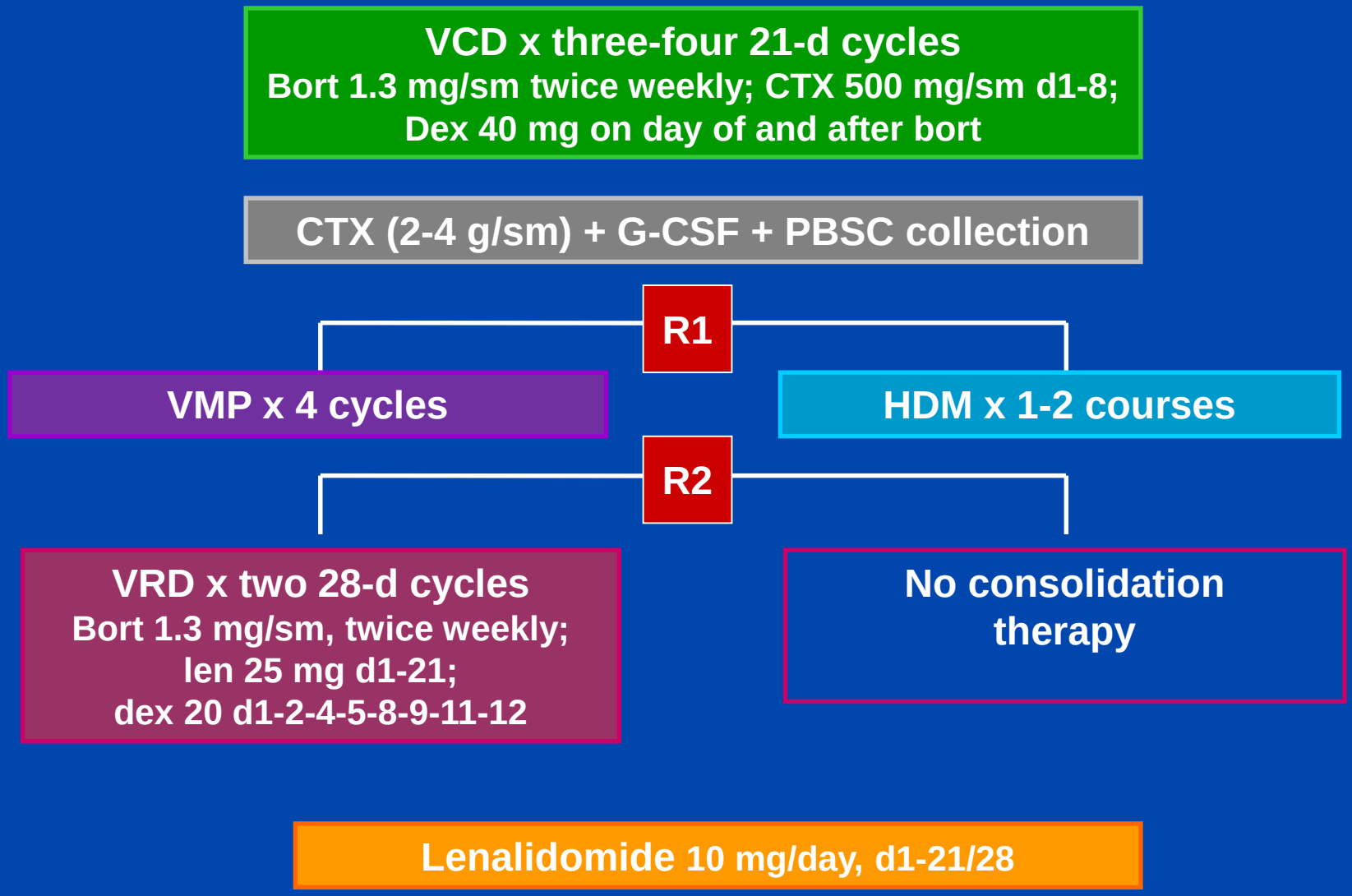
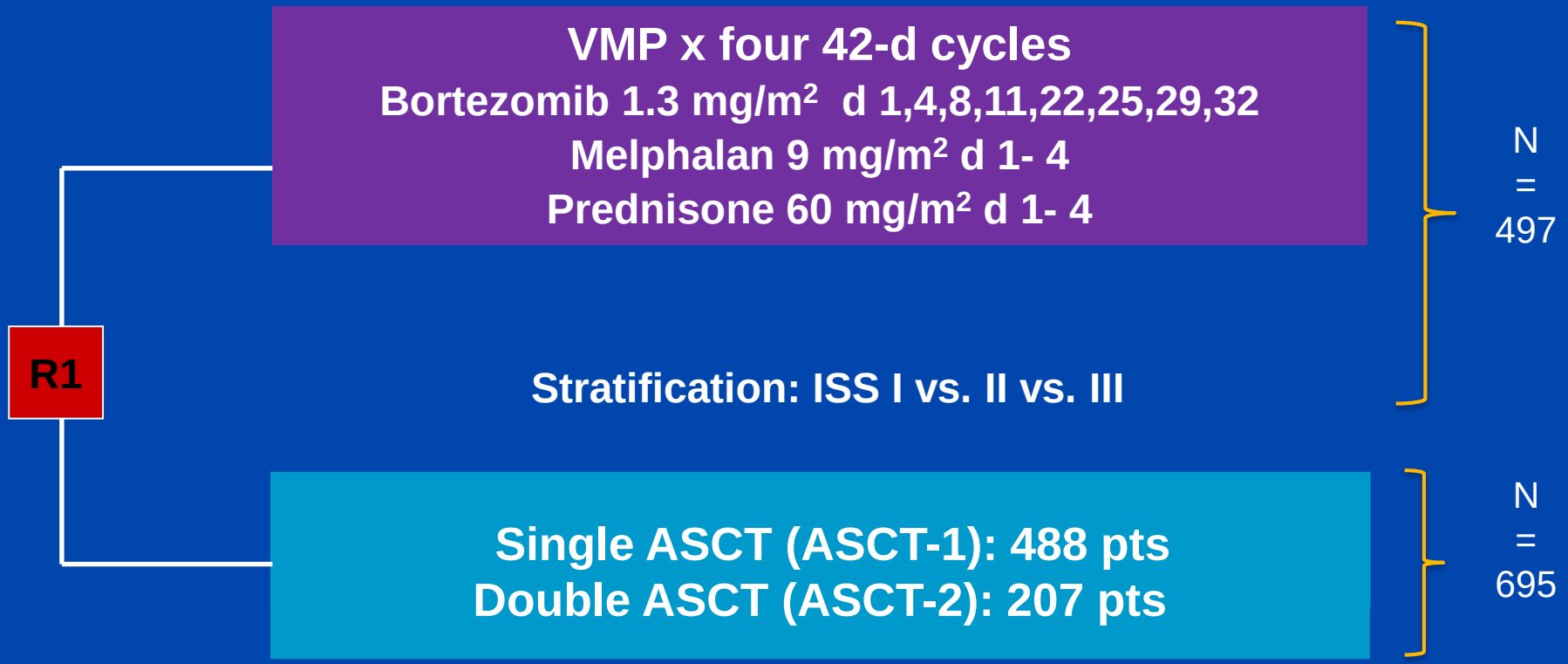
EMN02/HO95 MM trial: study design



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

EMN02/HO95 MM trial: study design



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

Randomization VMP vs HDM1 vs HDM2 (1:1:1) in centers with a double ASCT policy

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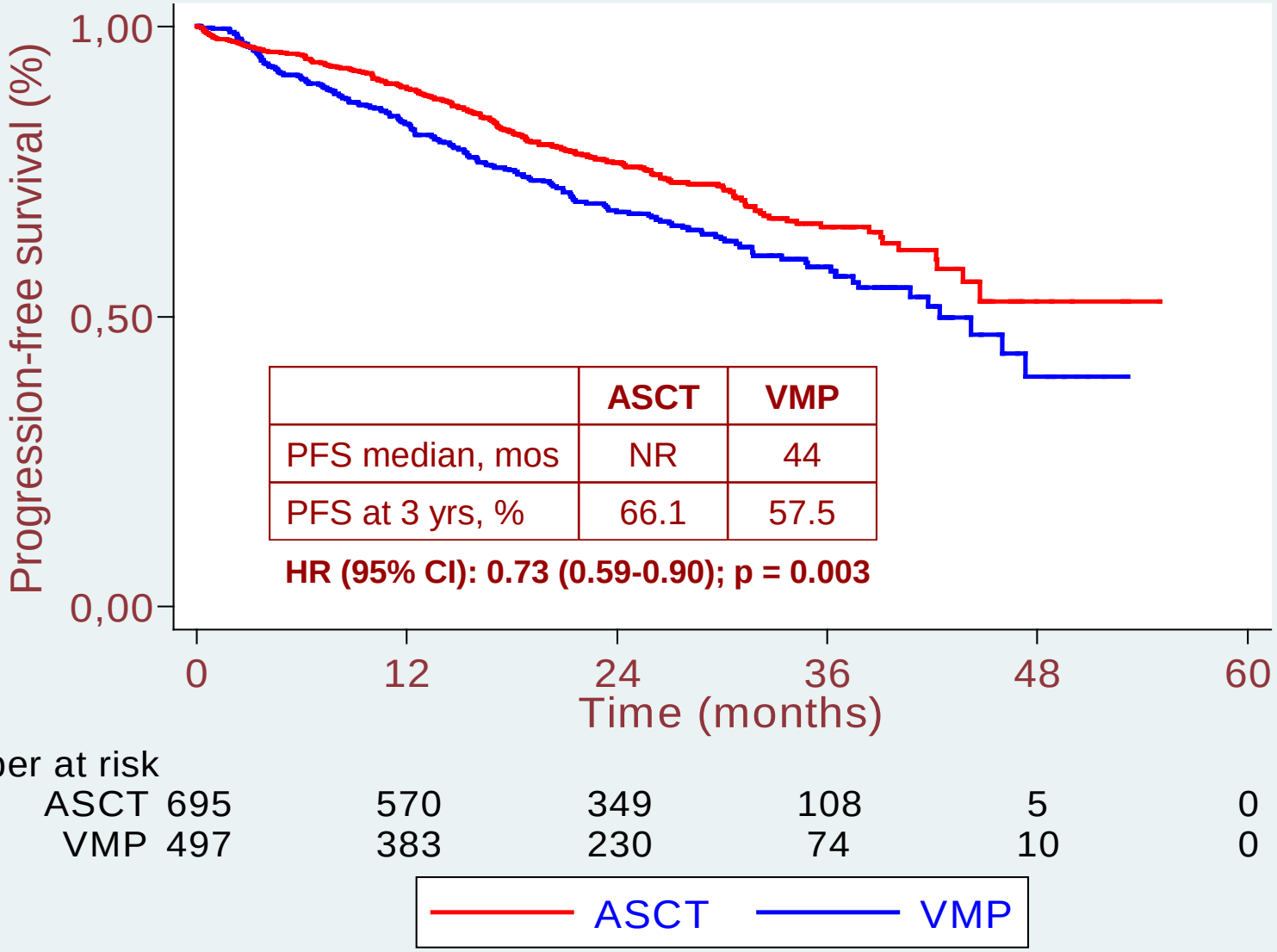
Cavo M, et al. ASH 2017; Abstract 401.

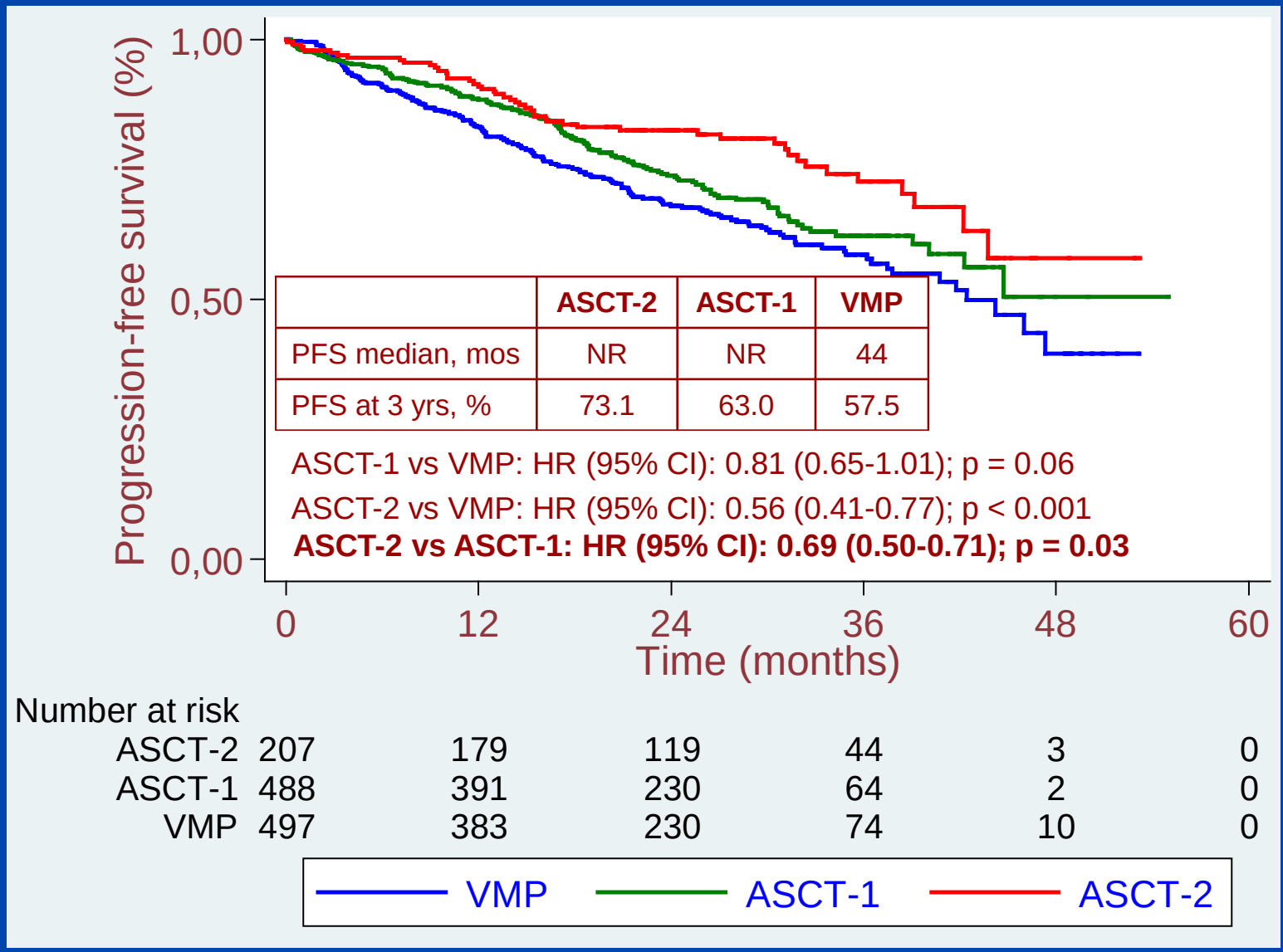
PFS by Randomization



Median Follow Up = 26 months (Range 19-37 months)

Cavo M, et al. ASCO 2016; Abstract 8000.

PFS by Randomization to ASCT-1 or ASCT-2



	ASCT-2	ASCT-1	VMP
PFS median, mos	NR	NR	44
PFS at 3 yrs, %	73.1	63.0	57.5

Cavo M, et al. ASCO 2016; Abstract 8000.

EMN02/HO95 Pts Randomized to ASCT: PFS From First Randomization

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 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)

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

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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).

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

EMN02/HO95 Pts Randomized to ASCT: Conclusions

- Double ASCT significantly improved PFS and OS in pts with NDMM following VCD induction vs single ASCT *(VCD)*
  - Pts with high-risk cytogenetics most likely to benefit from double ASCT
    - 3-yr PFS for ASCT-2 vs ASCT-1: 69.2% vs 44.2% (HR: 0.42; *P* = .014)
  - Depth of response improved in 24% of pts after second planned ASCT
  - Investigators concluded that results may support use of upfront double ASCT in newly diagnosed MM, particularly in pts with high-risk disease.

(SCT may overcome high-risk markers in absence of PI-IMiD induction)

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

Phase III STaMINA Trial: Similar PFS With Single ASCT, Single ASCT Followed by RVD Consolidation, and Tandem ASCT in Frontline MM Treatment

Stadtmauer EA, et al. ASH 2016. Abstract LBA-1

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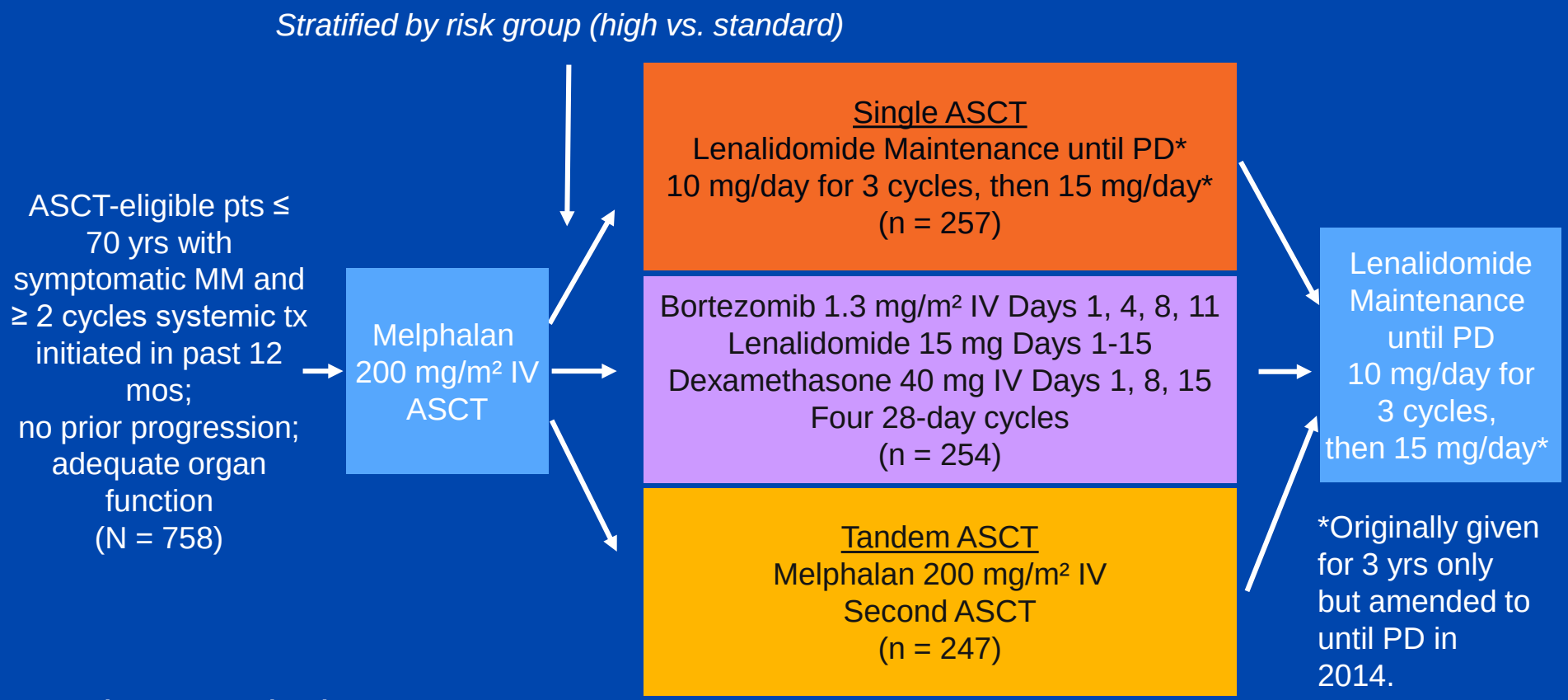
STaMINA: Phase III Study Design



- Primary endpoint: PFS at 38 mos
- Secondary endpoints: OS, ORR, CR conversion rate, safety, infections, tx-related mortality, QoL

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Stadtmauer EA, et al. ASH 2016. Abstract LBA-1

STaMINA: Baseline Characteristics

Characteristic, %	Single ASCT (n = 257)	RVD Consolidation (n = 254)	Tandem ASCT (n = 247)
Male	62.6	57.5	59.5
Karnofsky score ≥ 90	66.9	66.5	73.7
High risk (β_2-M > 5.5 mg/L or cytogenetics)	23.0	25.6	23.1
Induction regimens before first ASCT			
▪RVD	55.6	52.8	57.1
▪CyBorD	15.6	13.8	13.4
▪RD	8.6	11.0	9.7
▪VD	12.5	12.6	11.3
▪Other	7.8	9.8	8.5

Protocol Compliance, %	Single ASCT (n = 257)	RVD Consolidation (n = 254)	Tandem ASCT (n = 247)
Received second intervention	NA	88.2	68.0
Started lenalidomide maintenance	94.6	83.1	83.4

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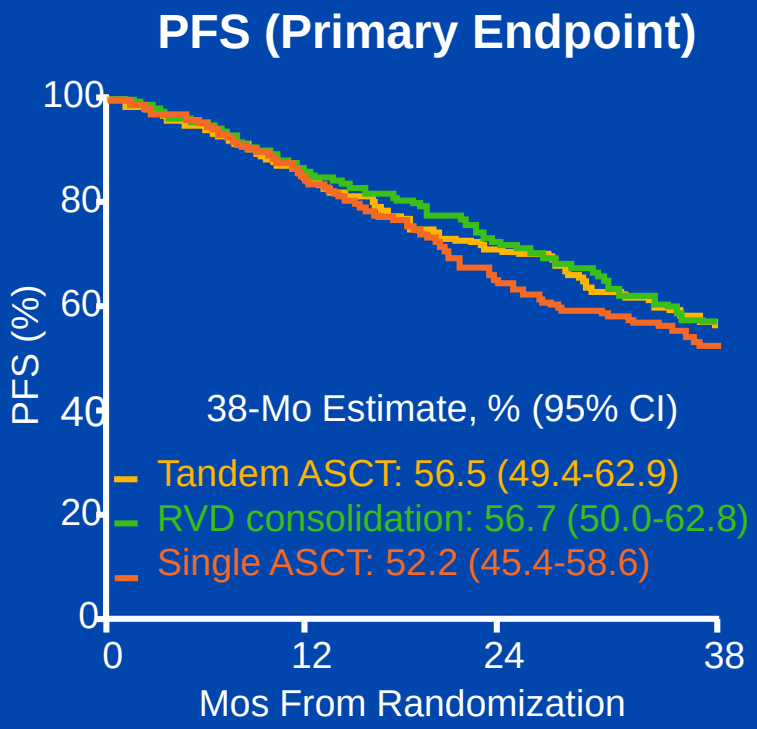
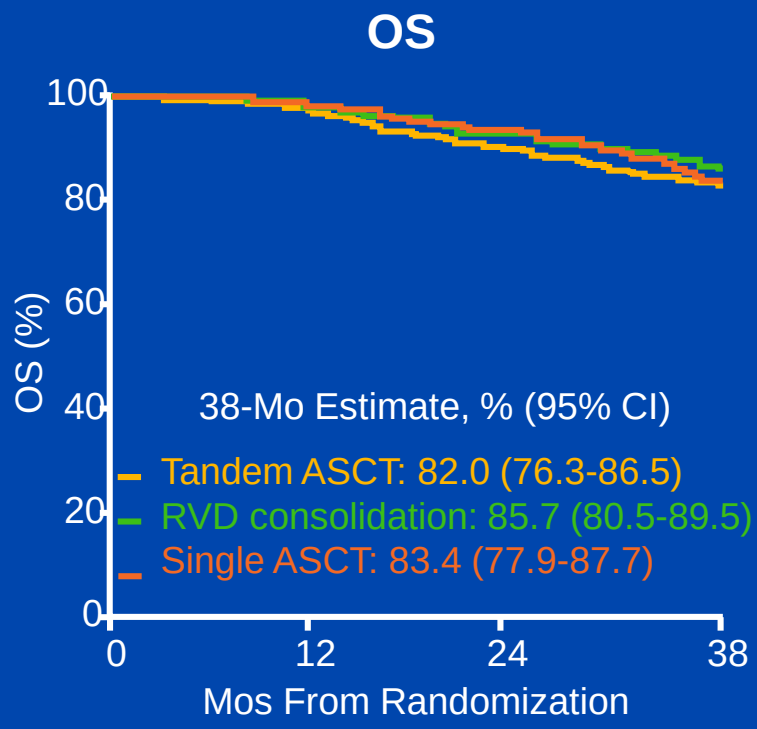
Stadtmauer EA, et al. ASH 2016. Abstract LBA-1

STaMINA: PFS and OS for Overall Population





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Stadtmauer EA, et al. ASH 2016. Abstract LBA-1

STaMINA: Investigator Conclusions

- Largest randomized comparison to date of therapeutic approaches after first ASCT in MM in US
  - No difference in PFS, OS after 38 mos
  - No difference between arms for pts with high-risk disease
  - Cumulative incidence of first secondary malignancies similar in first 38 mos

- After induction therapy with IMiDs and/or PIs for ND MM, tandem ASCT or additional consolidation with RVD followed by lenalidomide maintenance provides no additional PFS or OS benefit vs single ASCT followed by lenalidomide maintenance

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Stadtmauer EA, et al. ASH 2016. Abstract LBA-1

Relapsed/Refractory Multiple Myeloma (RRMM)

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First Relapse Off-Study

On maintenance		Off-therapy/ Unmaintained*	
Fit Patients*	Indolent Relapse* or Frail patients	Fit Patients*	Indolent Relapse* or Frail patients
↓	↓	↓	↓
KPd or DVd if Rev maintenance DRd if Vel maintenance	DVd or ICd if Rev maintenance IRd or DRd if Vel maintenance	KRd or DRd	IRd or ERd

Triplets being used in most situations

*Consider salvage auto SCT in patients eligible for ASCT who have not had transplant before; Consider 2nd auto SCT if eligible and >18 months unmaintained or >36 months maintained response to first auto

v5 //last reviewed July 2016

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Second or later Relapse – Off-Study

Quadruple-refractory (Lenalidomide, Pomalidomide, Bortezomib, and Carfilzomib)

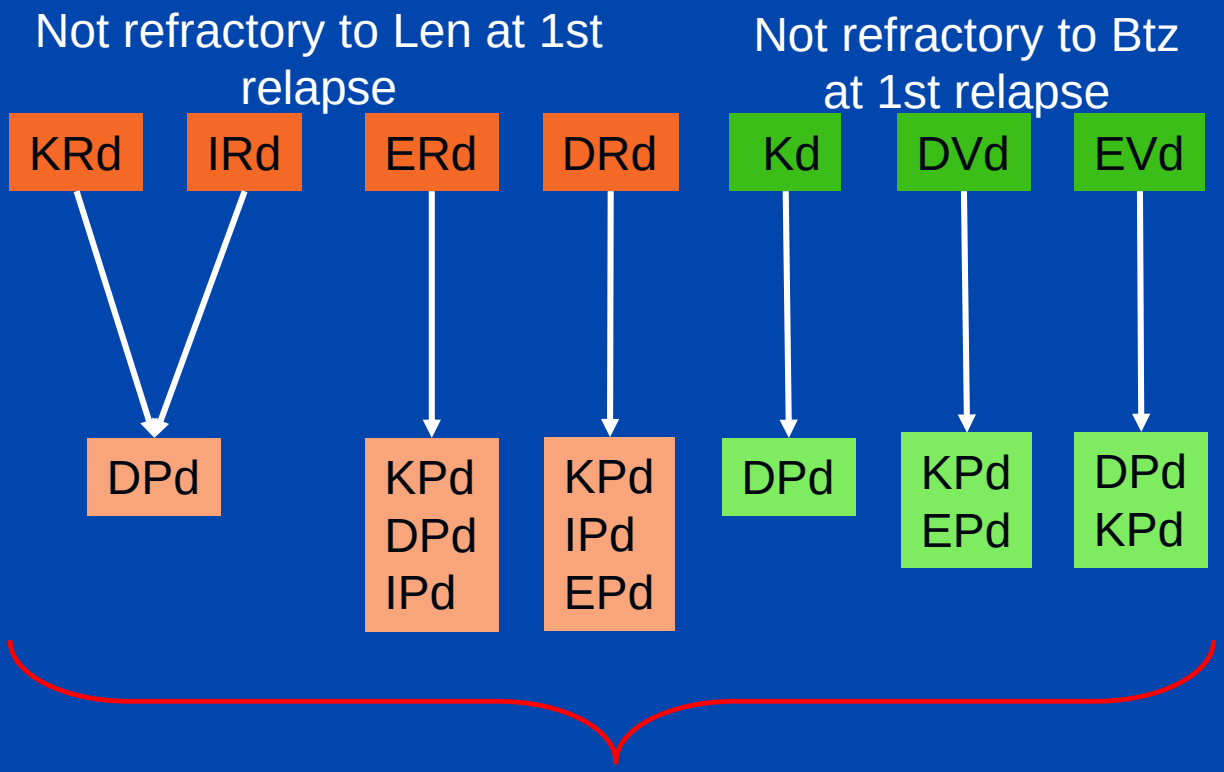
↓

VDT-PACE* x 2 cycles if possible.*
Auto transplant if transplant candidate; if not, treat with regimens that the patient is not known to be refractory to (eg., daratumumab-containing regimen; panobinostat-containing regimen; bendamustine; alkylator-containing combination if not alkylator refractory; or anthracycline containing regimen such as RAD, VDD, PAD, or CHOP)

Utility of Cytotoxic Chemotherapy

*CVAD or similar regimen can be used in place of VDT-PACE in older patients or patients with poor functional status

Potential Approaches at Relapse



Clinical trials OR repeat combinations of agents most remotely used

<u>Overall</u>: while triplets are preferred, lower-dose triplets or doublets can be used in frail and older pts

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Relapsed/Refractory Multiple Myeloma (RRMM): Daratumumab

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Daratumumab Combinations in RRMM: Increased MRD Negativity

POLLUX and CASTOR: randomized, multicenter, open-label, controlled phase III studies with ≥ 1 previous therapy for R/R MM

POLLUX: daratumumab + lenalidomide/dexamethasone; BM MRD assessed at suspected CR and 3/6 mos after suspected CR for pts who maintained response

CASTOR: daratumumab + bortezomib/dexamethasone; BM MRD assessed at time of suspected CR and 6/12 mos after first dose

Characteristic	POLLUX (N = 286)	CASTOR (N = 251)
Median prior lines of therapy, n (range)	1 (1-11)	2 (1-10)
Prior bortezomib, %	84	66
Prior lenalidomide, %	18	42

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Avet-Loiseau H, et al. ASH 2016. Abstract 246.

Daratumumab in R/R MM: MRD Negativity

- Dara+Rd or Vd significantly improved MRD negativity rate vs Rd or Vd alone

MRD Negative, %	POLLUX (N = 286)			CASTOR (N = 251)		
	Dara + Rd	Rd	*P* Value	Dara + Vd	Vd	*P* Value
All pts						
▪10^{-4}	31.8	8.8	< .0001	18.3	3.6	< .0001
▪10^{-5}	24.8	5.7	< .0001	10.4	2.4	< .005
▪10^{-6}	11.9	2.5	< .0001	4.4	0.8	< .05
Pts with ≥ CR						
▪10^{-4}	65	42	< .005	60	35	< .05
▪10^{-5}	52	27	< .005	37	22	--
▪10^{-6}	26	13	< .05	16	9	--
By cytogenetic risk						
▪ High*	18	0	< .005	14	0	< .005
▪ Standard	30	10	< .0001	12	2	< .005

*Includes pts with t(4;14), t(14;16), or del(17p).

- MRD-negative events accumulated rapidly and increased over time (within 3-18 mos)

MAYO CLINIC

Avet-Loiseau H, et al. ASH 2016. Abstract 246.

Daratumumab in R/R MM: PFS/Conclusions

- Lower risk of progression in pts who achieve MRD negativity, regardless of therapy
  - DRd MRD-negative pts (n = 71); estimated 12-mo PFS > 90%
  - DVd MRD-negative pts (26); estimated 12-mo PFS > 90%
  - Rd MRD-negative pts (n = 16 in POLLUX and n = 6 in CASTOR); estimated 12-mo PFS > 90%
- Daratumumab + Rd or Vd shows PFS benefit in MRD-positive pts vs doublets alone
  - POLLUX: estimated median PFS NR vs 17 mos for DRd MRD-positive (n = 215) vs Rd MRD-positive (n = 267) pts
  - CASTOR: estimated median PFS NR vs 7 mos for DVd MRD-positive (n = 225) vs Vd MRD-positive (n = 241) pts

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Avet-Loiseau H, et al. ASH 2016. Abstract 246.

Analysis of Dara/Pom/Dex in R/R MM: Baseline Characteristics

- Retrospective analysis of all pts from Emory University who received daratumumab/pomalidomide/dexamethasone for relapsed or R/R MM from January 2015 - July 2016 (N = 41)

	Cohort 1: Dara and Pom Naïve (n=19)	Cohort 2: Dara and/or Pom Refractory (n=22)	Cohort 3: Dara and Pom Refractory (n=12)
Median Prior Lines of Therapy	3	5	6.5
Quad Refractory (%) (Len, Bort, Car, Pom)	0	69	67
Median follow up (months)	16	17	8
ORR (%)	89	41	33
Median PFS (months)	7	NR	3

- AEs similar to phase 1 trial.
- 56% pts required dose reductions *(May be starting at lower Pom dose)*

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Nooka AK, et al ASH 2016. Abstract 492.

Phase 1 PAVO Study: SC Dara in RRMM

- Primary endpoints: C_{trough} of daratumumab at cycle 3 Day 1 and safety; secondary endpoints: ORR, CR, DoR, time to response

Pts with measurable R/R MM, ≥ 2 lines of therapy, no prior anti-CD38 therapy (N = 53)

→ Daratumumab 1200 mg SC + rHuPH20 30,000 U SC (n = 8)*

→ Daratumumab 1800 mg SC + rHuPH20 45,000 U SC (n = 45)*

4-wk treatment cycles
- Every wk for 8 wks
- Every 2 wks for 16 wks
- Every 4 wks thereafter

Infusion time
- 1200 mg: 20 min (60 mL)
- 1800 mg: 30 min (90 mL)

*Pre/postinfusion medication includes acetaminophen, diphenhydramine, montelukast, and methylprednisolone.

Characteristic	1200 mg (n = 8)	1800 mg (n = 45)
Prior lines of therapy, median (range)	5 (2-10)	4 (2-11)
Refractory to PI only/IMiD only, %	0/13	4/20
Refractory to both PI and IMiD, %	63	58
Refractory to last line of therapy, %	88	71

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Usmani SZ, et al. ASH 2016. Abstract 1149.

PAVO: Outcomes and Conclusions

	Cohort 1: 1200 mg (n=8)	Cohort 2: 1800 mg (n=45)
Median Follow up (months)	6.4	4.3
Median Duration of Treatment (months)	2.6	3.4
Treatment Discontinuation (%) *(mostly PD and Death)*	88	33
ORR (%)	25	38
IRR (%) (Overall)	13	24

- 1800 mg SC dose PK similar to 16 mg/kg IV dose
- IRRs:
  - No grade 4 IRRs in either group
  - All IRRs occurred during first infusion and within first 4 hrs
  - Overall IRRs similar to IV Dara
- Preliminary efficacy similar to IV Dara: 38% ORR (1 sCR)

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Usmani SZ, et al. ASH 2016. Abstract 1149.

Relapsed/Refractory Multiple Myeloma (RRMM): Carfilzomib

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A.R.R.O.W.: Once vs. Twice Weekly Carfilzomib for RRMM

- Randomized Phase 3 trial (n=478)
- Weekly dose: 70 mg/m^2
- Twice weekly dose: 27 mg/m^2
- PFS 11.2 months vs. 7.6 months (HR=0.69, 95% CI, 0.54-0.78); superior with weekly carfilzomib
- Safety profile comparable

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Relapsed/Refractory Multiple Myeloma (RRMM): New Agents

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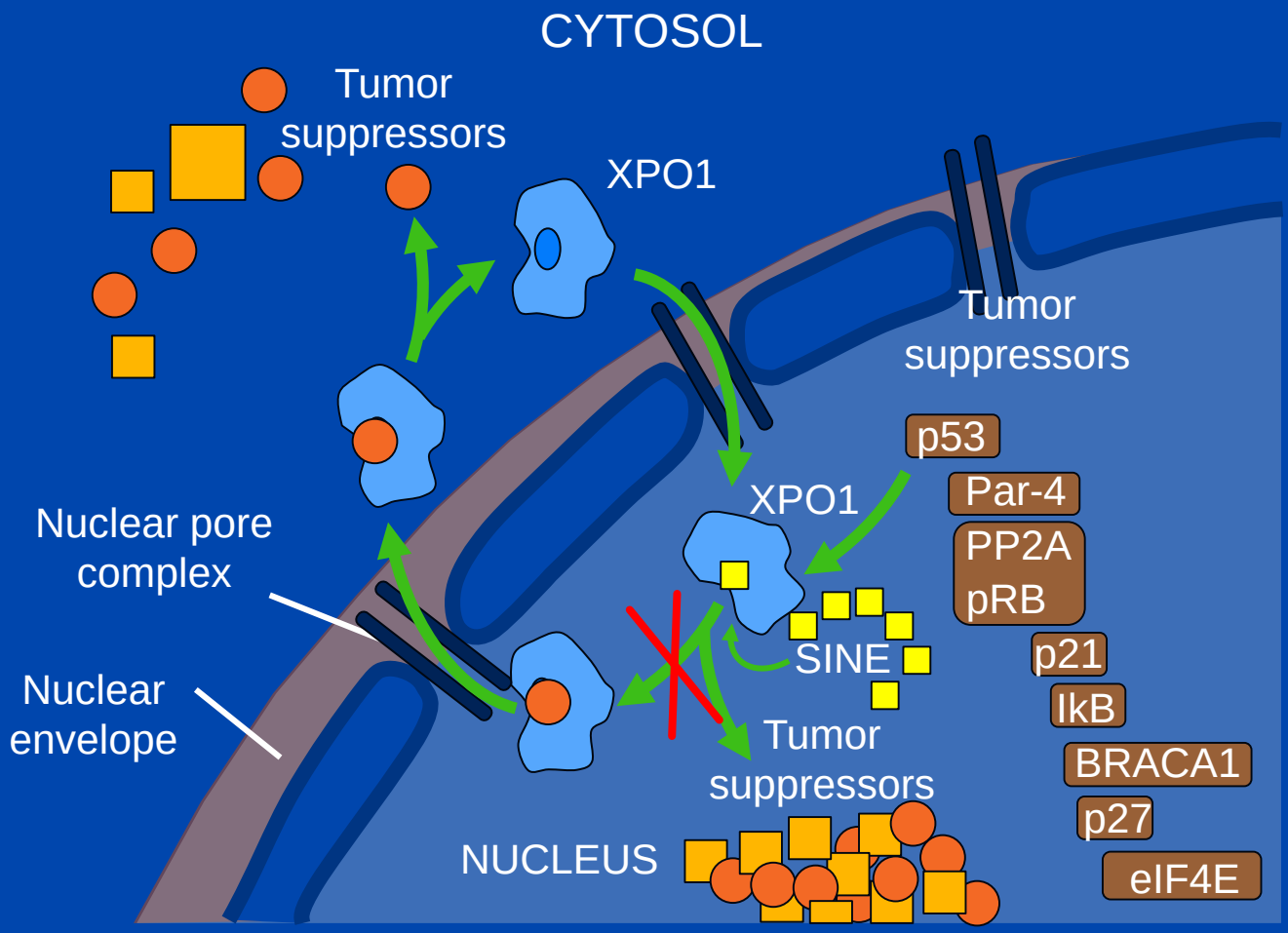
Selinexor: Mechanism of Action



- Selinexor
  - STORM trial: Phase II Selinexor+Dex *(All PO)*
  - ORR 21% even in quad- and penta-refractory
  - Median DoR: 5 months *(similar in standard and high-risk)*
  - AEs: GI and Heme, ~20% discontinuation, ~40% reductions

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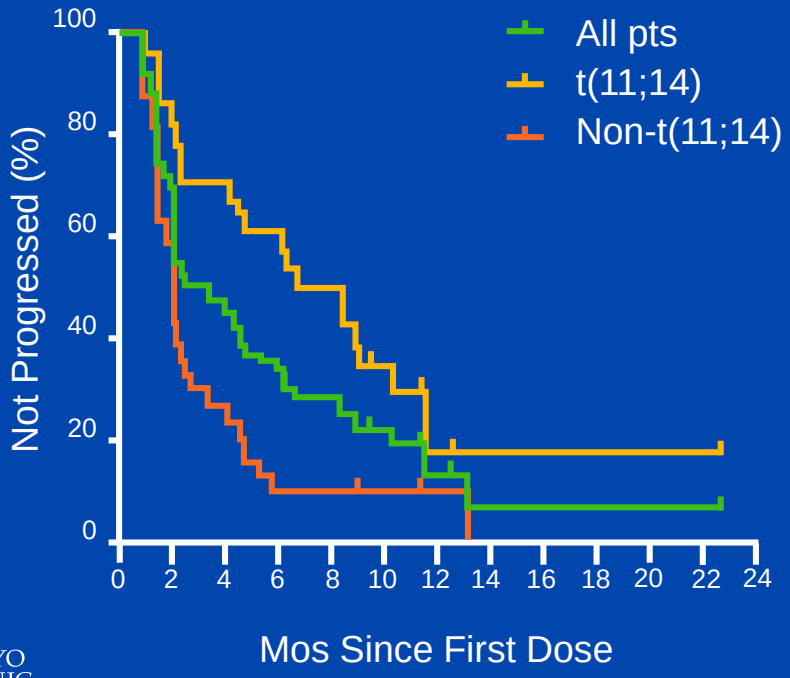
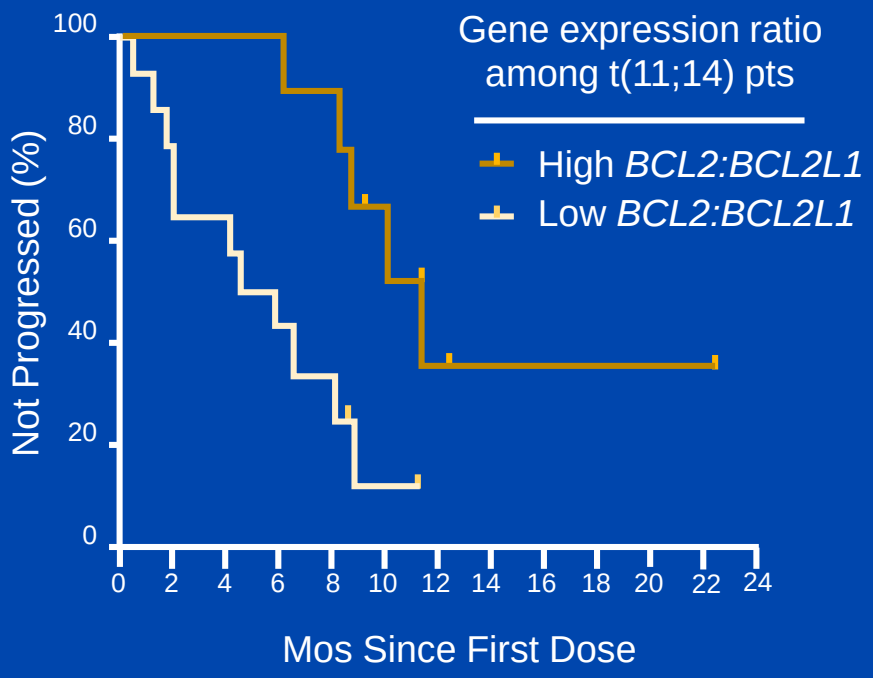
Vogl DT, et al. ASH 2016. Abstract 491.

- Venetoclax
  - Monotherapy Phase I (n=66)
  - ORR: 21% (40% in t(11;14) and 88% in *BCL2* by GEP)
  - Safe *(~10% discontinuation due to AEs)*
  - Grade 3/4 AEs in 68%, DLTs: abdominal pain and nausea.





Kumar S, et al. ASH 2016. Abstract 488.

CAR-T Cell Therapy for Relapsed Refractory multiple Myeloma

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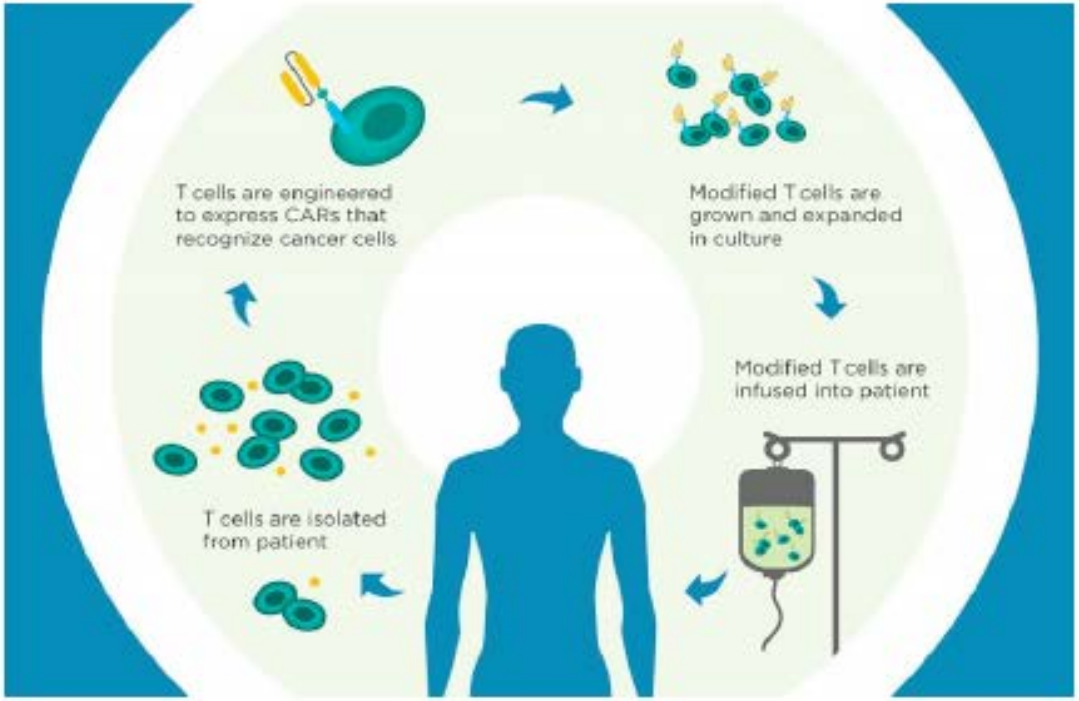
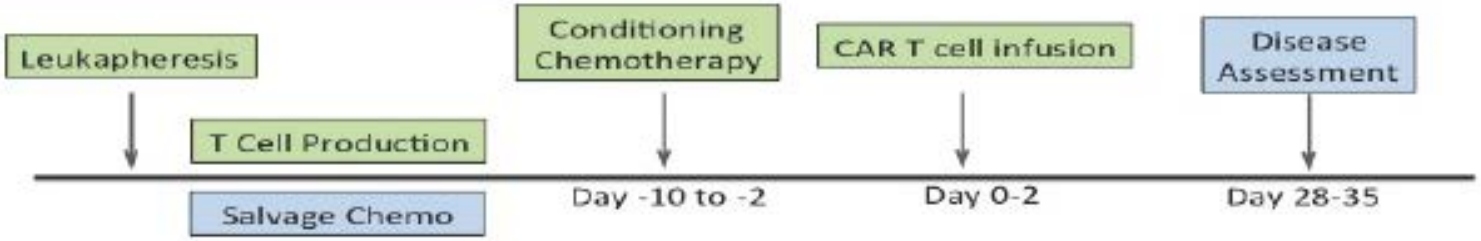
CAR T Cells as Cancer Therapy



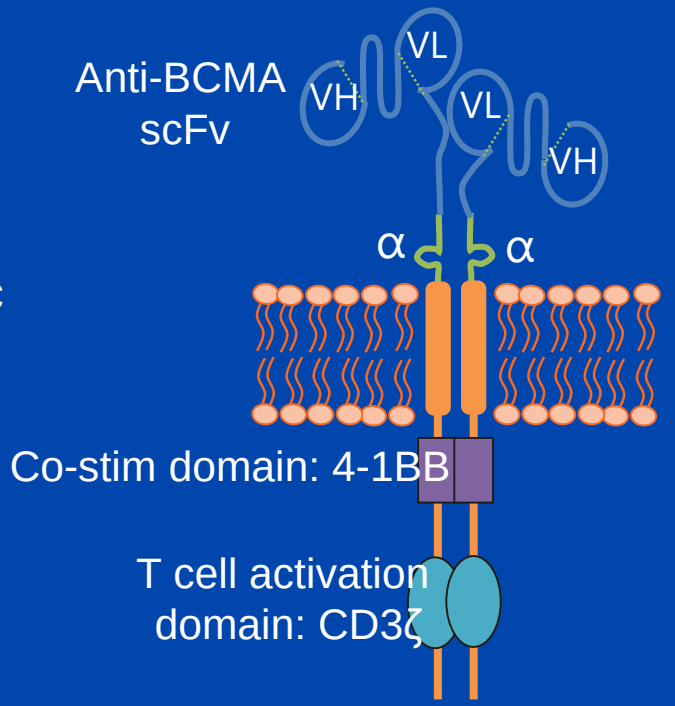
Study Scheme of CD19 CAR T cells



bb2121 Anti-BCMA CAR T-Cell Therapy: Background

- Novel treatment options needed for pts with R/R MM to confer deep, durable remission
  - BCMA-specific CAR T-cells have demonstrated activity in MM[1,2]
    - BCMA: TNF receptor superfamily expressed on MM tumor cells, nonmalignant plasma cells, and some mature B-cells
    - bb2121 construct demonstrated potent preclinical in vivo activity with low nonspecific signaling
  - Current study reports updated results from phase I trial of bb2121 anti-BCMA CAR T-cell therapy in heavily pretreated patients with R/R MM[3]

<u>bb2121: 2nd-Generation</u>
Autologous T-cells transduced with lentiviral vector



1. Ali SA, et al. Blood. 2016;128:1688-1700. 2. Brudno, et al. ASH 2017. Abstract 524.
3. Berdeja JG, et al. ASH 2017. Abstract 740.

bb2121 Anti-BCMA CAR T-Cell Therapy: CRB-401 Phase I Study Design

- Multicenter, open-label, dose-escalation and dose-expansion trial in pts with R/R MM who received ≥ 3 prior lines of therapy or pts with double-refractory MM
  - Dose-escalation phase: ≥ 50% BCMA expression required
  - Dose-expansion phase: no BCMA expression required; prior daratumumab required
- Treatment approach
  - Screening: T-cell apheresis to collect cells for creation of individualized bb2121 construct
  - Days -5, -4, -3: lymphodepletion with fludarabine 30 mg/m^2 + cyclophosphamide 300 mg/m^2
  - Day 0: infusion of 50, 150, 450, or 800 x 10^6 bb2121 CAR T-cells according to 3 + 3 dose escalation design

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Berdeja JG et al. ASH 2017. Abstract 740.

CRB-401: Baseline Characteristics

- 21 pts dosed to date in dose-escalation phase (median follow-up: 35 wks)

Baseline Characteristics	Pts (N = 21)
Median age, yrs (range)	58 (37-74)
Male, n (%)	13 (62)
Median time since diagnosis, yrs (range)	4 (1.3-15.8)
ECOG PS, n (%)	
▪ 0	10 (48)
▪ 1	11 (52)
ISS stage, n (%)	
▪ I	6 (29)
▪ II	11 (52)
▪ III	4 (19)
High-risk cytogenetics,* n (%)	9 (43)
Median prior lines of therapy, n (range)	7 (3-14)
Prior ASCT, n (%)	21 (100)

Baseline Characteristics, n (%) (N = 21)	Exposed	Refractory
Previous therapy		
▪ Bortezomib	21 (100)	14 (67)
▪ Carfilzomib	19 (91)	12 (57)
▪ Lenalidomide	21 (100)	18 (86)
▪ Pomalidomide	19 (91)	15 (71)
▪ Daratumumab	15 (71)	10 (48)
Cumulative exposure		
▪ Bort/len	21 (100)	14 (57)
▪ Bort/len/carf	19 (91)	10 (48)
▪ Bort/len/pom	19 (91)	12 (57)
▪ Bort/len/carf/pom	18 (86)	9 (43)
▪ Bort/len/carf/pom/dara	15 (71)	6 (29)

*del17p, t(4;14), t(14;16)

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Berdeja JG et al. ASH 2017. Abstract 740.

CRB-401: Safety

Select TEAEs During Dose Escalation, n (%)	All Grades	Grade ≥ 3
Cytokine release syndrome	15 (71)	2 (10)
Neurotoxicity*	5 (24)	0
Neutropenia	18 (86)	18 (86)
Thrombocytopenia	11 (52)	9 (43)
Anemia	14 (67)	12 (57)

*Includes preferred terms: depressed level of consciousness, confusional state, bradyphrenia, somnolence.

- No DLTs during dose-escalation phase
- Cytopenias primarily related to fludarabine/cyclophosphamide lymphodepletion; majority of pts recovered to grade < 3 by Month 2
- 14 pts experienced ≥ 1 serious AE, including grade 1/2 CRS requiring hospitalization per protocol (n = 4) and pyrexia (n = 2)
- 5 deaths: 3 due to PD at 50 x 10^6 dose, 2 in patients in CR at time of death

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Berdeja JG et al. ASH 2017. Abstract 740.

CRB-401: CRS and Management

CRS Event	Pts (N = 21)
Incidence, n (%)	15 (71)
Time to onset of first CRS, days (range)	2 (1-19)
Duration of any CRS, days (range)	7 (1-11)
Time to onset of grade ≥ 3 CRS, days (range)	5 (4-6)
Duration of grade ≥ 3 CRS, days (range)	2 (2-2)

- CRS events manageable
  - Most CRS events were grade 1-2
  - Grade 3 CRS N = 2; resolved in 24 hrs
  - 4 pts received tocilizumab, 1 with steroids
- Cytokine elevation highest in pts with grade 3 CRS

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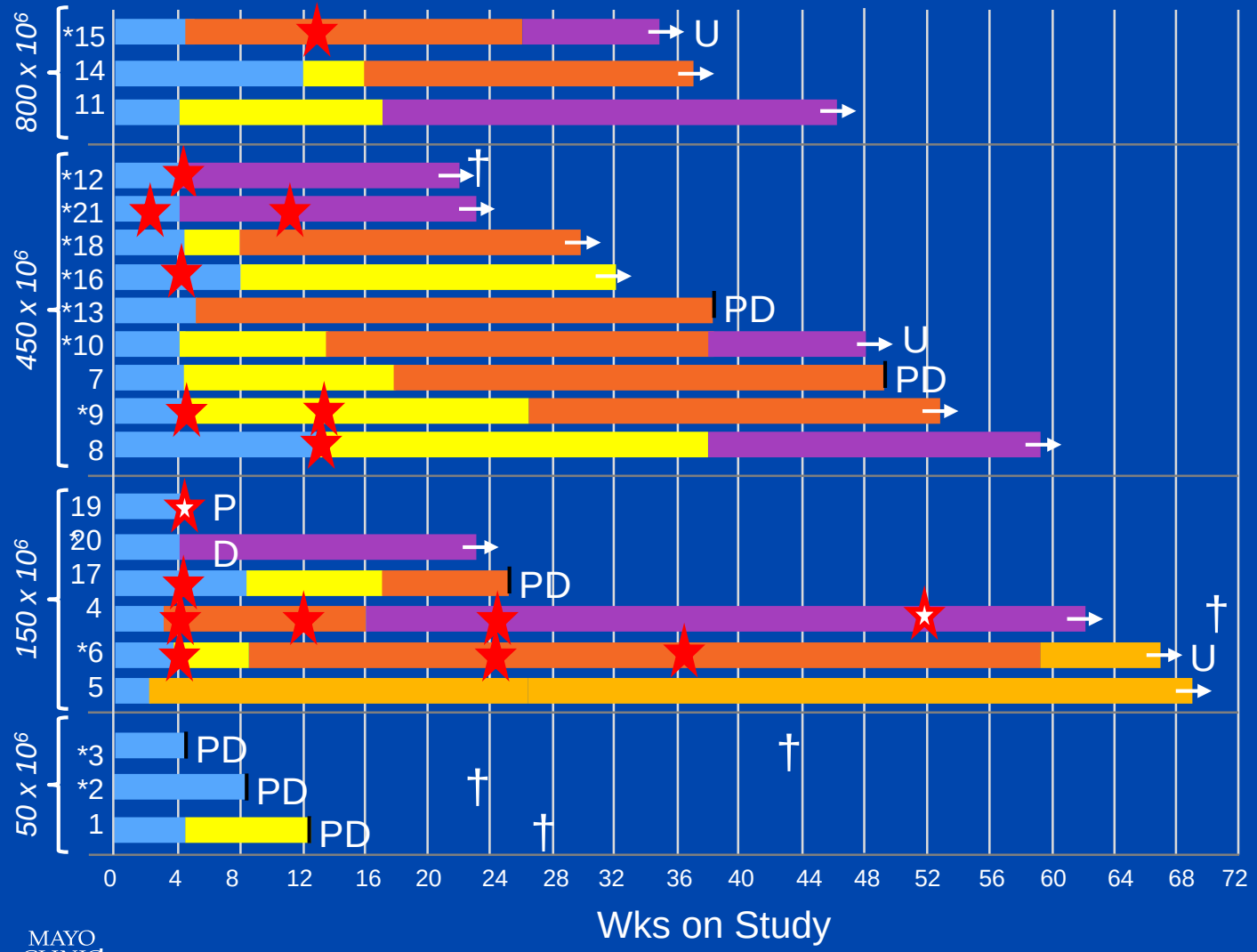
Berdeja JG et al. ASH 2017. Abstract 740.

CRB-401: Tumor Response to bb2121



- ORR: 94% (CR: 56%)
- MRD neg: 9 of 10 evaluable pts
- 5 patients with ongoing responses > 1 yr
- Responses continue to improve as late as Month 15 (VGPR to CR)

CR/sCR
VGPR
PR
Stable Disease
MRD-
MRD+
† Deceased
PD Progressive disease
U Unconfirmed response

High tumor burden (>50% Bone Marrow Involvement)

Berdeja JG et al. ASH 2017. Abstract 740.

CRB-401: Conclusions

- Investigators conclude that bb2121 confers deep, durable responses at active doses (150-800 x 10^6 CAR T cells) in heavily pretreated pts with R/R MM
  - ORR: 94%, ≥ VGPR: 89%, CR: 56%
  - 90% of evaluable pts MRD negative at 40 wks of follow-up
  - PD in 4 pts; 3 of 3 evaluable patients remain BCMA positive at progression
- Safety profile of bb2121 manageable up to 800 x 10^6 CAR T-cell dose
  - 2 cases of grade 3 CRS during dose escalation; resolved within 24 hours
  - 1 case of delayed, reversible grade 4 neurotoxicity during dose expansion associated with TLS and CRS in patient with highest tumor burden

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Berdeja JG et al. ASH 2017. Abstract 740.

Administration Considerations for PIs

	Bortezomib	Carfilzomib	Ixazomib
Route	IV, SQ	IV	PO
Dosing and schedule	**1.3 mg/m²** once weekly ***OR*** on Days 1, 4, 8, 11 of 28-day cycle	**20/27 mg/m²** on Days 1, 2, 8, 9, 15, 16 of 28-day cycle or once weekly	**4 mg** on Days 1, 8, 15 of 28-day cycle
Select AEs to watch	▪ Peripheral neuropathy ▪ Hypotension ▪ Cardiac toxicity ▪ Pulmonary toxicity ▪ GI toxicity ▪ Thrombocytopenia ▪ Neutropenia	▪ Cardiac failure ▪ Renal insufficiency ▪ Pulmonary toxicity, dyspnea ▪ Hypertension ▪ Venous thrombosis ▪ Hemorrhage ▪ Thrombocytopenia ▪ Hepatic toxicity	▪ Thrombocytopenia ▪ GI toxicity ▪ Peripheral neuropathy ▪ Rash ▪ Hepatotoxicity
Rate of PN with PI + Rd	▪ Any grade: 35% ▪ Grade ≥ 3: 12%	▪ Any grade: 11% ▪ Grade ≥ 3: 2%	▪ Any grade: 28% ▪ Grade ≥ 3: 2%
Management considerations	Monitor platelets; safe in renal failure	Hydration, cardio/pulmonary	Reduce dose for hepatic/renal disease

- Pts should receive VZV prophylaxis when receiving PIs

Administration Considerations for IMiDs

	Lenalidomide	Pomalidomide	Thalidomide
Route	PO	PO	PO
Dosing schedule	**25 mg/day** 3 wks on, 1 wk off	**4 mg/day** 3 wks on, 1 wk off	**200 mg** once daily
Select AEs to watch	▪ Venous thromboembolism ▪ Neutropenia ▪ Thrombocytopenia ▪ Fatigue ▪ Hepatotoxicity ▪ Skin rash ▪ GI disturbances ▪ Impaired stem cell mobilization ▪ Second primary malignancies	▪ Venous thromboembolism ▪ Neutropenia ▪ Fatigue ▪ Hepatotoxicity ▪ Skin rash	▪ Venous thromboembolism ▪ Constipation ▪ Peripheral neuropathy ▪ Dizziness/orthostatic hypotension ▪ Bradycardia ▪ Skin rash ▪ Somnolence
Management considerations	ASA (81-325 mg/d) or LMWH (enoxaparin 40 mg/day equiv.) or full-dose warfarin (target INR: 2-3) if high risk for clots; weekly CBC x 8 wks		

- Pts should receive VTE prophylaxis for individual risk factors (eg, age or obesity) or myeloma-related risk factors (eg, immobilization or hyperviscosity)

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Administration Considerations for mAbs

	Daratumumab	Elotuzumab
Route of administration	IV	IV
Dosing schedule	**16 mg/kg** once weekly in cycles 1-2; Q2W in cycle 3-6; Q4W in cycle 7+	**10 mg/kg** once weekly in cycles 1-2; Q2W in cycle 3+
Prophylaxis	Pre/post medication with corticosteroids, antipyretics, and antihistamines ± inhaled steroids for pts with COPD	Pre/post medication with corticosteroids, diphenhydramine, ranitidine, and acetaminophen
Select AEs to watch	▪ Infusion reactions ▪ Interference with cross-matching, red blood cell antibody screening, and determination of CR ▪ Infections	▪ Infusion reactions ▪ Infection ▪ Second primary malignancy ▪ Hepatotoxicity ▪ Interference with determination of CR
Management considerations	For infusion reaction risk, pre/post medicate as directed; interrupt infusion if reaction	

- Pts should receive VZV prophylaxis when receiving daratumumab

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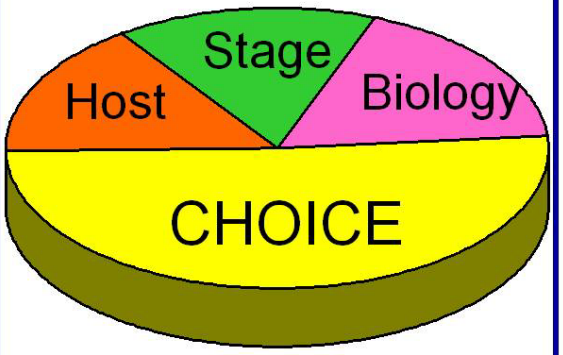
Myeloma Treatment

Early therapy

- Prevention
- Curative Approach

PATIENT



Risk-adapted Therapy

- **Response and MRD directed**
- **Overcome high risk features**