

Management of Multiple Myeloma: Board Review

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Disclosures

- None

Goals

- Review risk stratification for multiple myeloma
- Review treatment strategies for transplant eligible multiple myeloma
- Review treatment strategies for transplant-ineligible multiple myeloma
- Discuss treatment of relapsed/refractory multiple myeloma

What is the current best practice for treatment?

Transplant Eligible

Induction

3 drug combinations (4 drugs coming soon...)



Autologous transplantation



Maintenance

Standard:

Lenalidomide

High risk:

Bortezomib or other combinations

Not Transplant Eligible

Induction

2 or 3 drug combinations



Maintenance

Supportive Care



Risk stratification in multiple myeloma

- Disease burden: Beta-2-microglobulin (B2M), LDH
- Tumor-specific factors: Circulating plasma cells (extreme example is plasma cell leukemia)
- Genetic factors: Chromosomal abnormalities

Revised-International Staging System for Myeloma

ISS or R-ISS Stage	ISS Criteria	R-ISS Criteria
I	Serum B2M < 3.5 mg/L, Serum albumin ≥ 3.5 g/dL	ISS Stage I AND standard risk CA by iFISH AND normal LDH
II	Not ISS stage I or III	Not R-ISS stage I or III
III	Serum B2M ≥ 5.5 mg/L	ISS Stage III AND either high-risk CA by iFISH OR high LDH

Incidence of chromosomal abnormalities in multiple myeloma

Genomic aberration	Incidence, % (no. of patients analyzed for the aberration)
del(13)	48 (936)
t(11;14)(q13;q32)	21 (746)
t(4;14)(p16;q32)	14 (716)
Hyperdiploidy	39 (657)
MYC translocations	13 (571)
del(17p)	11 (532)

What does “high-risk” myeloma mean?

- Outcomes for many patients with myeloma are improving
- However, a subset of patients (20-25%) with certain biologic, genetic, and excess disease burden have poorer outcomes, even with novel agents and new therapies
- New strategies to identify and offer more effective treatments for these patients are needed

Current conception of high-risk myeloma by the IWMMG and others

- IMWG: Revised ISS definition of high-risk
 - ISS Stage III (Elevated B2M (≥ 5.5 mg/L)) **AND**
 - High risk chromosomal abnormalities: Deletion 17p, t(4;14), t(14;16) **OR**
 - Serum LDH > upper limit of normal
- Circulating tumor cells (plasma cells – extreme case is plasma cell leukemia)
- Gene expression profiling
- Complex karyotypes
- Other chromosomal changes: 1p deletion, 1q amplification, t(14;20) on FISH
- Extramedullary disease
- Plasmablastic morphology

High-risk chromosomal changes

- IgH translocations – 40% of cases (chr 14)
 - t(4;14): 4p16 – *FGFR3* – deregulation of fibroblast growth factor
 - t(14;16): 16q23 – *MAF* – deregulation of *c-MAF* proto-oncogene
 - t(14;20): 20q11 – *MAFB* – deregulation of *MAFB* oncogene
- Del(17p) – *p53* – clonal immortalization, resistance to apoptosis
- 1q amplification – *CKS1B* – activation of cyclin dependent kinase → deregulation of cell cycle control

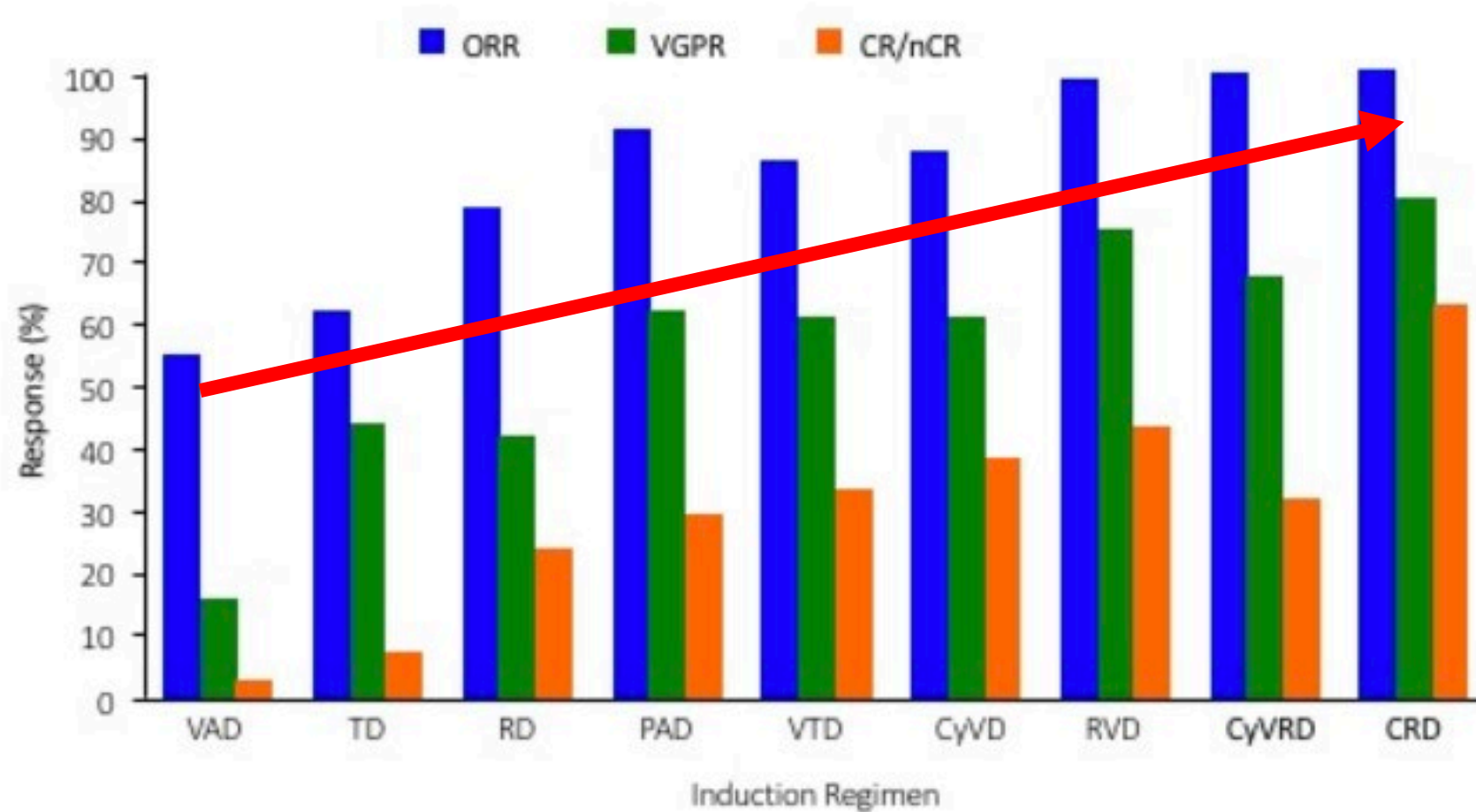
What is the preferred upfront treatment approach?

- Induction with IMiD/PI/dex 3-drug combination, followed by high-dose melphalan and autologous stem cell transplantation (Attal, NEJM 2017)
 - (On the horizon: 4 drug induction including a monoclonal antibody)
- Maintenance therapy with IMiD post transplant, for standard risk (McCarthy JCO 2017)
- Maintenance therapy with PI post transplant for high-risk cytogenetics (Del(17p) and t(4;14) HOVON-65)
- Intravenous bisphosphonates (MRC IX trial)

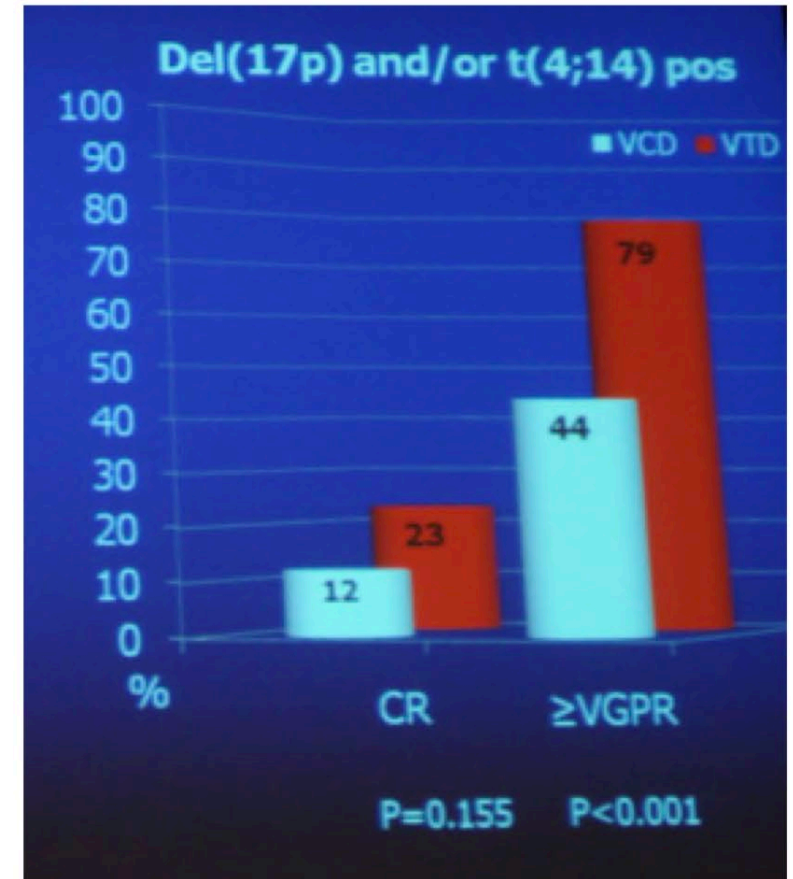
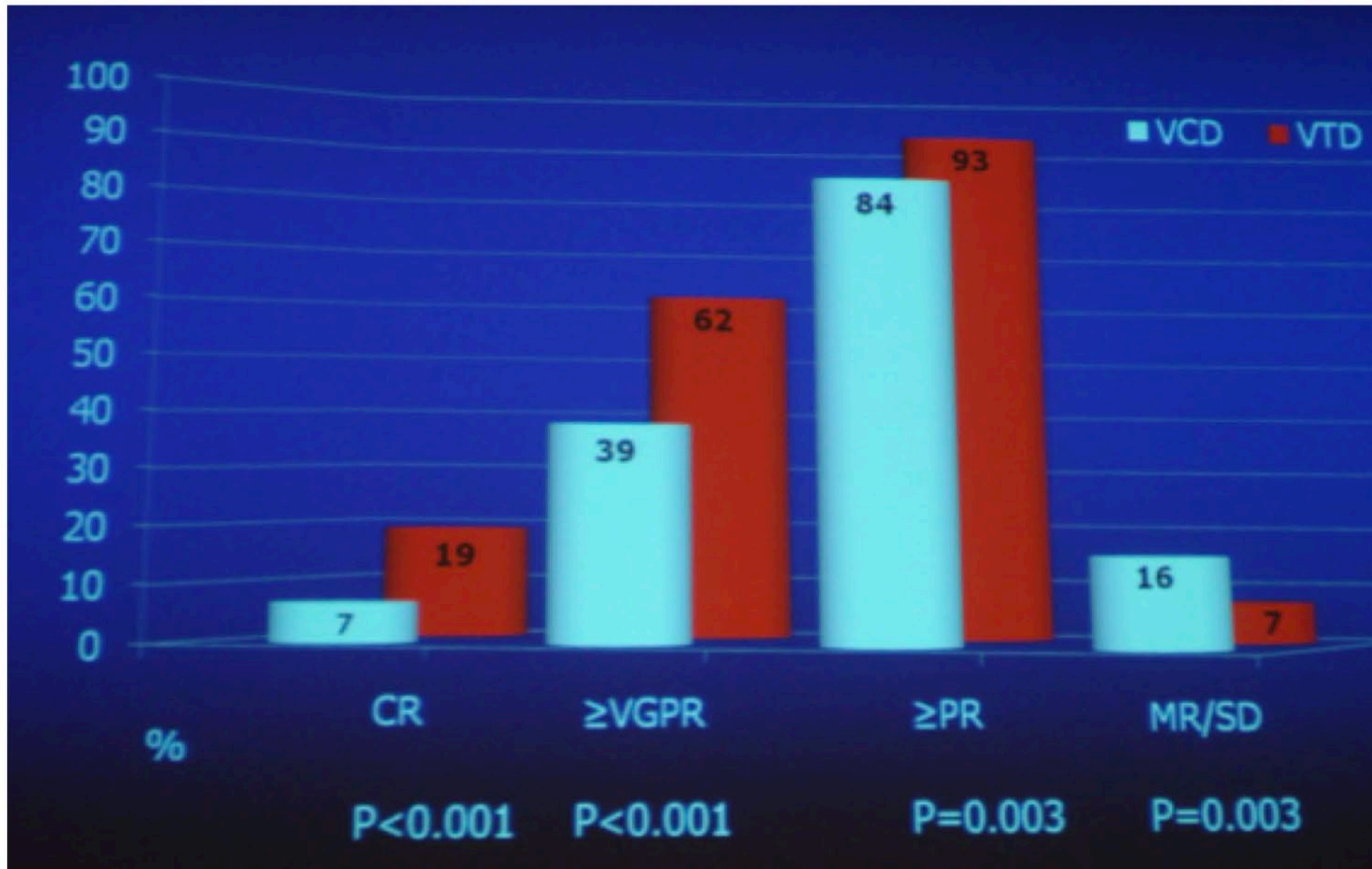
Multiple Myeloma Approved Drugs

- Immunomodulatory Agents
 - Lenalidomide
 - Pomalidomide
 - Thalidomide
- Proteasome Inhibitors
 - Bortezomib
 - Carfilzomib
 - Ixazomib
- Monoclonal Antibodies
 - Daratumumab (CD38)
 - Isatuximab (CD38)
 - Elotuzumab (SLAMF7)
- Alkylating Agents
 - Melphalan
 - Cyclophosphamide
 - Bendamustine
- BCMA antibody-drug conjugate
 - Belantamab mafodotin
- Peptide-drug conjugate
 - Melflufen
- Selective inhibitors of nuclear export (SINE)
 - Selinexor
- Histone Deacetylase (HDAC) inhibitor
 - Panobinostat
- CAR-T cell
 - Idecabtagene vicleucel (BCMA)

The overall, more than VGPR and nCR/CR rates for a selection of phase 2 and phase 3 trials incorporating novel agents.



Does it matter which 3 drugs are used?



IMiD/PI Combination most effective

Table 1. Response to VTD and VCD induction therapy

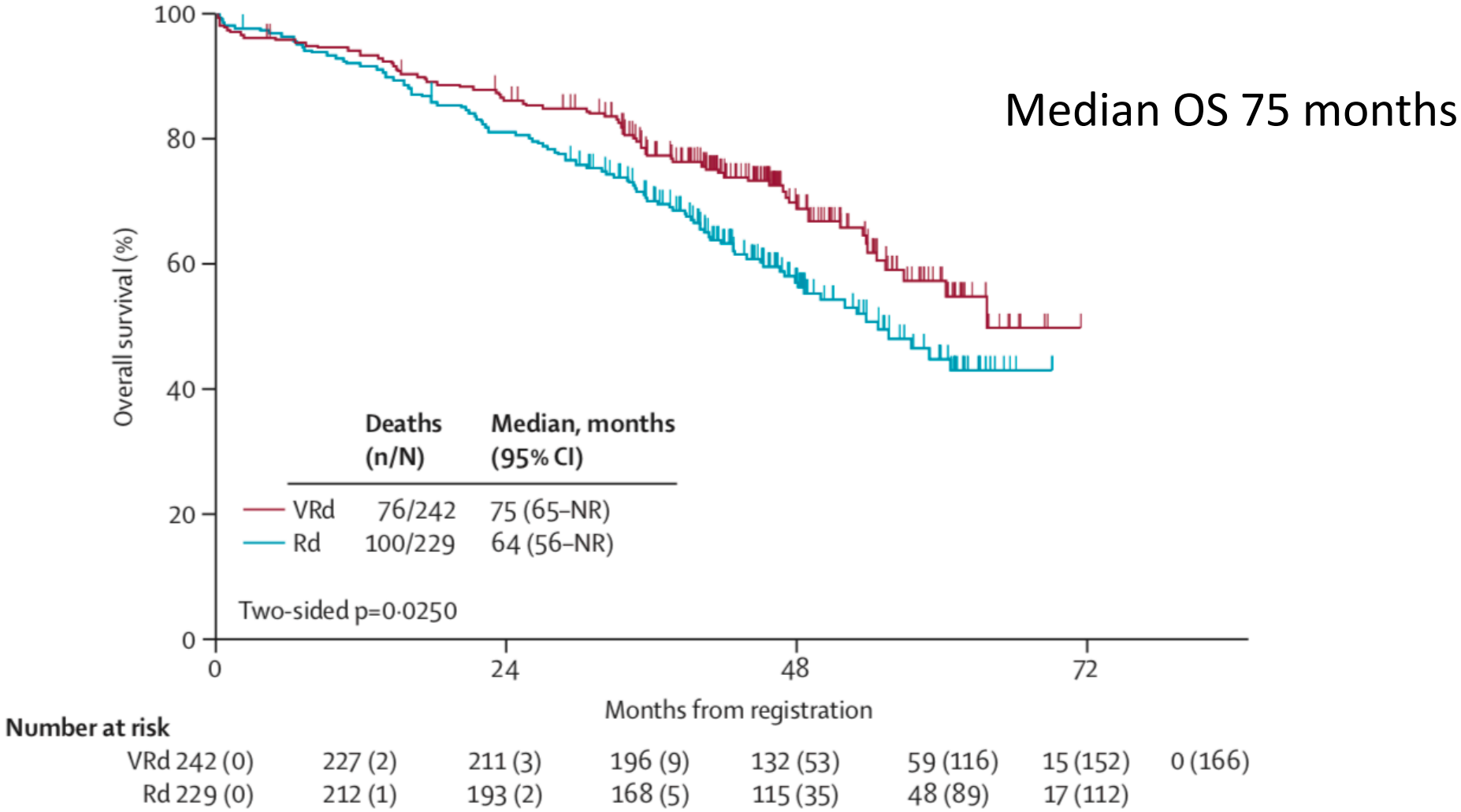
<i>All patients</i>	VTD (n = 236)	VCD (n = 236)	P
Complete response	44 (19%; 14–24)	13 (6%; 3–8)	< 0.001
Very good partial response or better	151 (64%; 58–70)	87 (37%; 31–43)	< 0.001
Partial response or better	220 (93%; 90–96)	192 (81%; 76–86)	< 0.001
Stable disease	16 (7%; 4–10)	38 (16%; 11–21)	0.001
Progressive disease	0 (0%)	6 (3%; 1–5)	0.015
<i>Patients with ISS 2-3</i>	VTD (n = 129)	VCD (n = 129)	
Complete response	26 (20%; 13–27)	5 (4%; 1–7)	< 0.001
Very good partial response or better	86 (67%; 59–75)	45 (35%; 27–43)	< 0.001
<i>Patients with t(4;14) and/or del(17p)</i>	VTD (n = 53)	VCD (n = 53)	
Complete response	12 (23%; 11–34)	4 (8%; 0–15)	0.030
Very good partial response or better	44 (83%; 73–93)	25 (47%; 34–61)	< 0.001

Abbreviations: ISS, international staging system; VCD, bortezomib with cyclophosphamide plus dexamethasone; VTD, bortezomib with thalidomide plus dexamethasone. Data are number of patients (%; 95% CI). Comparisons were performed by χ^2 test or Fisher's test, as appropriate.

Triple drug induction is superior to doublet

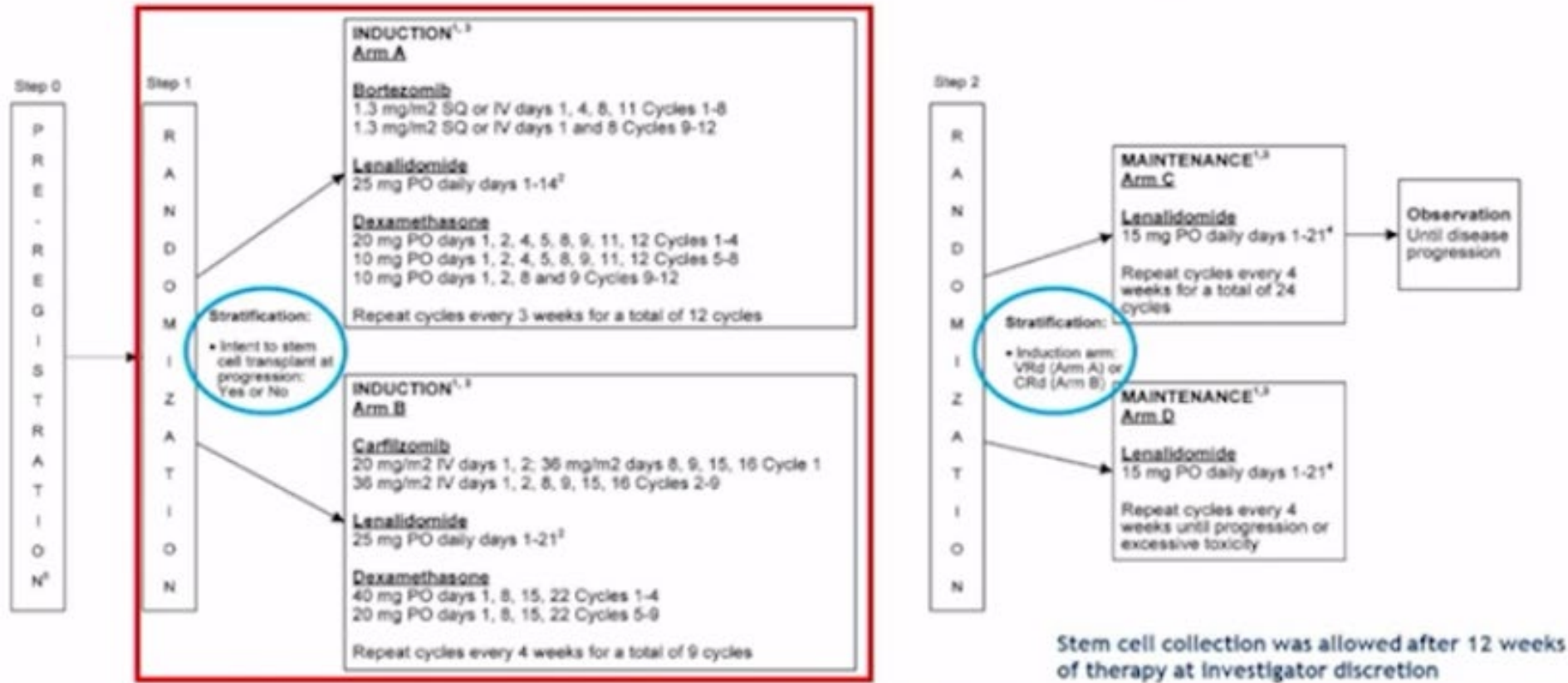
	Patients given bortezomib, lenalidomide, and dexamethasone (VRd group; n=216)	Patients given lenalidomide and dexamethasone (Rd group; n=214)
Complete response	34 (15.7%)	18 (8.4%)
Very good partial response	60 (27.8%)	50 (23.4%)
Partial response	82 (38%)	85 (39.7%)
Overall response rate (partial response or better)	176 (81.5%)	153 (71.5%)
Stable disease	34 (15.7%)	52 (24.3%)
Stable disease or better	210 (97.2%)	205 (95.8%)
Progressive disease or death	6 (2.8%)	9 (4.2%)

Superiority of RVD over Rd: SWOG S0777



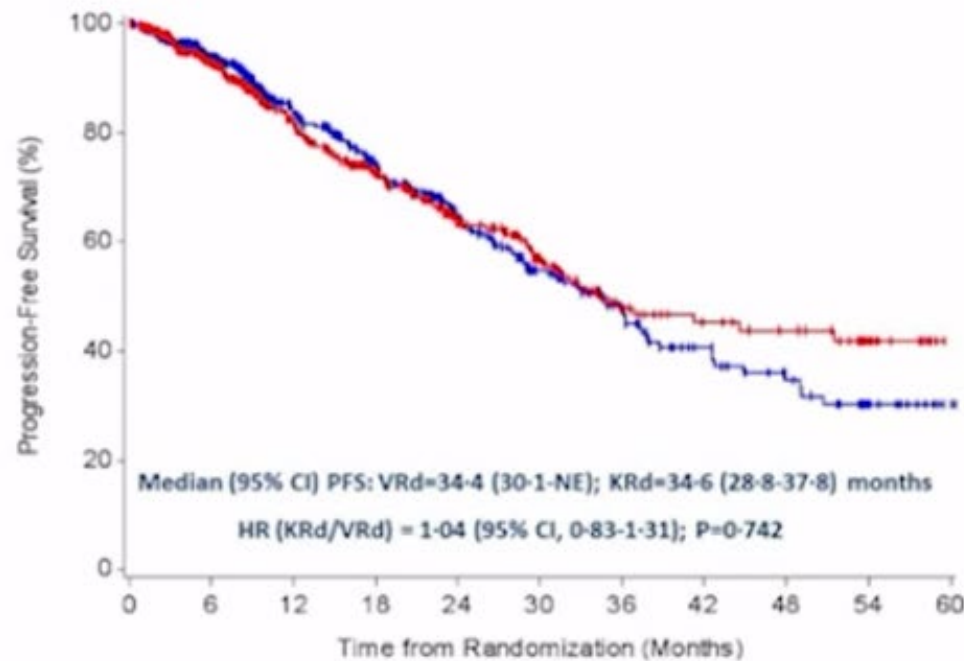
ENDURANCE: RVd vs KRd, ASCO 2020

Patient Randomization and Treatment Schedule



ENDURANCE: RVd vs KRd, ASCO 2020

Progression Free Survival from Induction Randomization



	0	6	12	18	24	30	36	42	48	54	60
KRd	545	401	252	187	127	83	59	38	25	13	3
VRd	542	377	243	183	114	73	43	31	26	14	0

- 2nd interim analysis of PFS (Jan 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow up of 15 (13-18) months
- For patients ≥ 70 years, median PFS(95% CI) for VRd = 37 (29-NE) and KRd = 28 (24-36) months
- With censoring at SCT or alternative therapy: Median PFS (95% CI) for VRd = 31.7 (28.5-44.6) and KRd = 32.8 (27.2-37.5) months

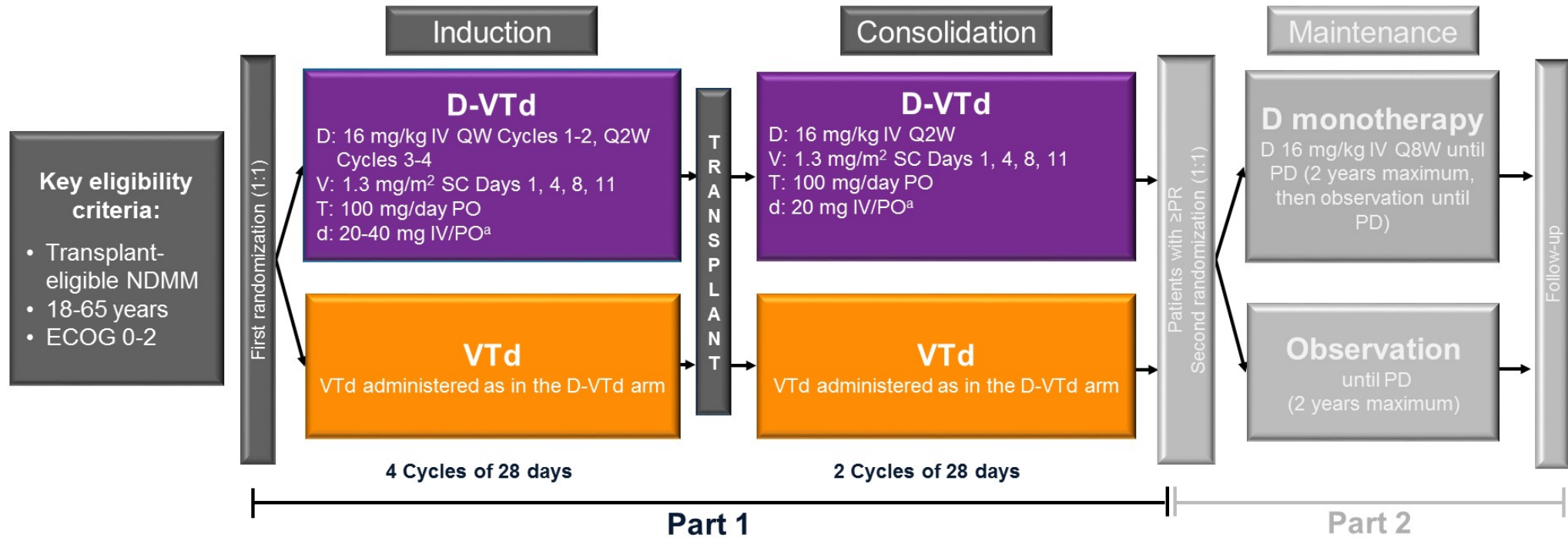
4-drug Combinations

- RVd is the standard of care for newly diagnosed multiple myeloma, but does adding a CD38 antibody improve outcomes?
- 2 key studies in transplant eligible multiple myeloma:
 - CASSIOPEIA: Daratumumab + VTd vs VTd
 - GRIFFIN: Daratumumab + VRd vs VRD

CASSIOPEIA Study Design



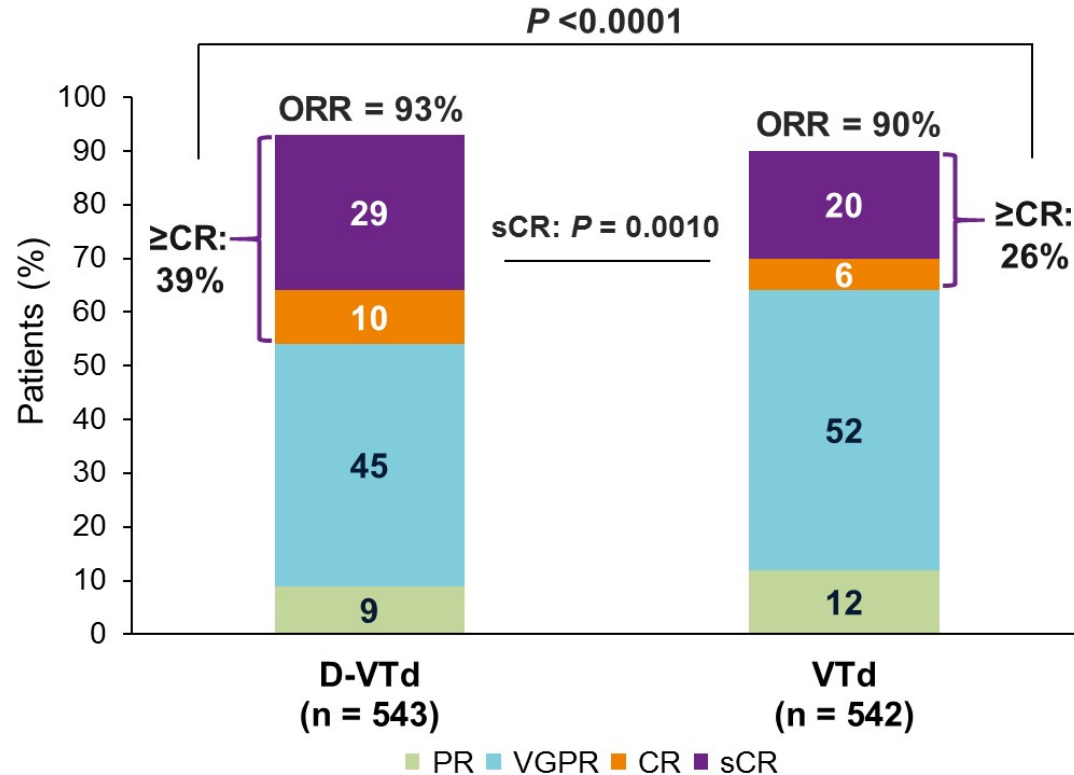
- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017



D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease.

^aDexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.

Efficacy: Post-consolidation Depth of Response



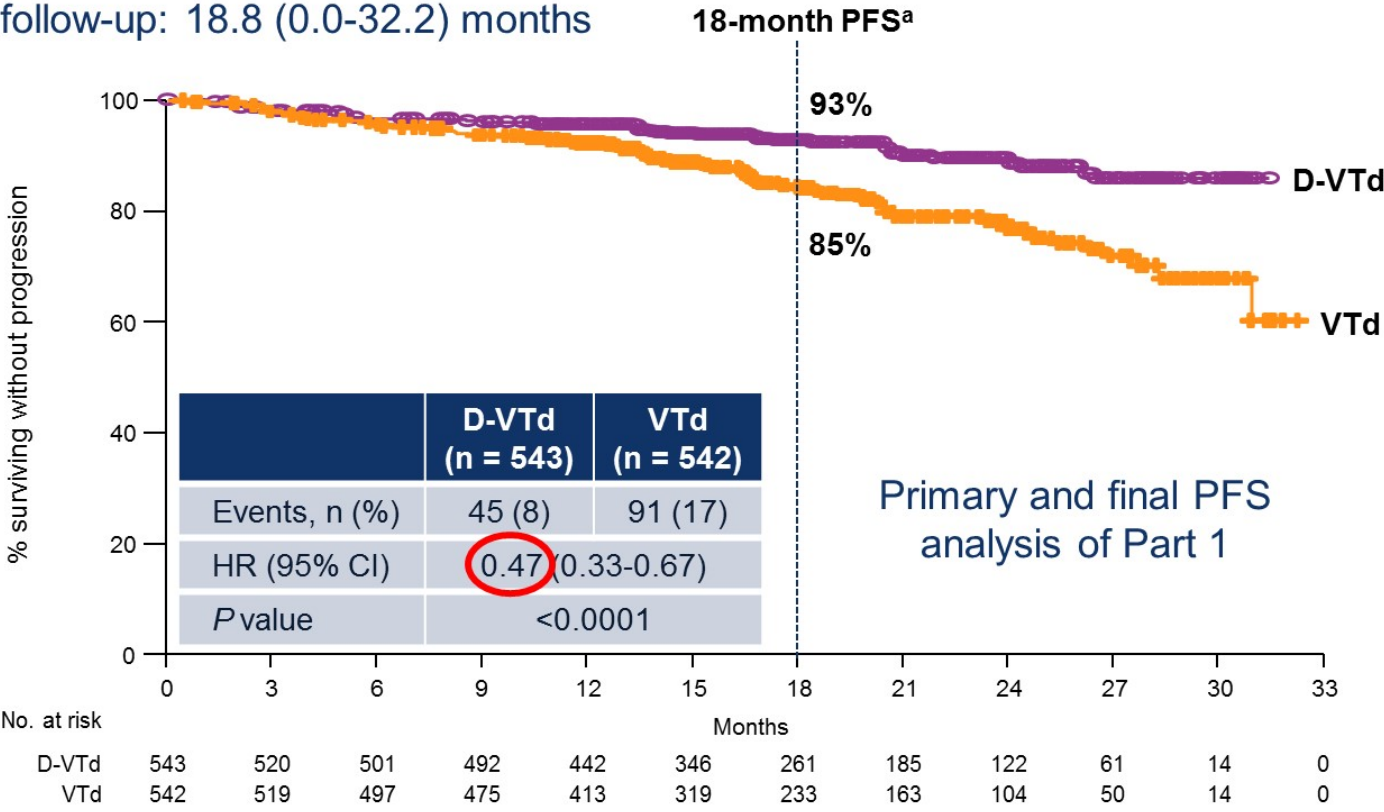
- Primary endpoint
 - Post-consolidation sCR
 - 29% D-VTd vs 20% VTd
 - Odds ratio, 1.60;
 - 95% CI, 1.21-2.12; $P = 0.0010$
- sCR definition
 - All required:
 - SIFE negative
 - UIFE negative
 - <5% plasma cells in the BM
 - Four-color flow negativity
 - Normal FLC ratio
 - Disappearance of all plasmacytomas

The addition of daratumumab to VTd improved depth of response

ORR, overall response rate; VGPR, very good partial response; CI, confidence interval; SIFE, serum immunofixation; UIFE, urine immunofixation; BM, bone marrow; FLC, free light chain.

Efficacy: PFS From First Randomization

- Median (range) follow-up: 18.8 (0.0-32.2) months

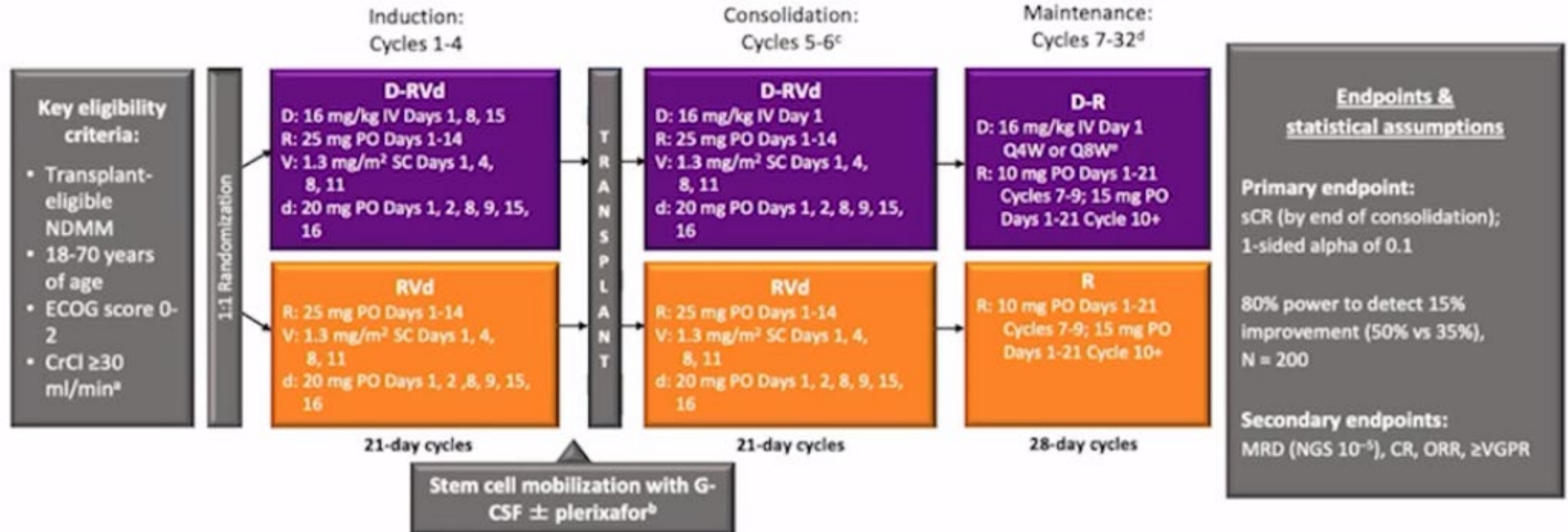


53% reduction in the risk of progression or death in the D-VTd arm

HR, hazard ratio.
^aKaplan-Meier estimate.

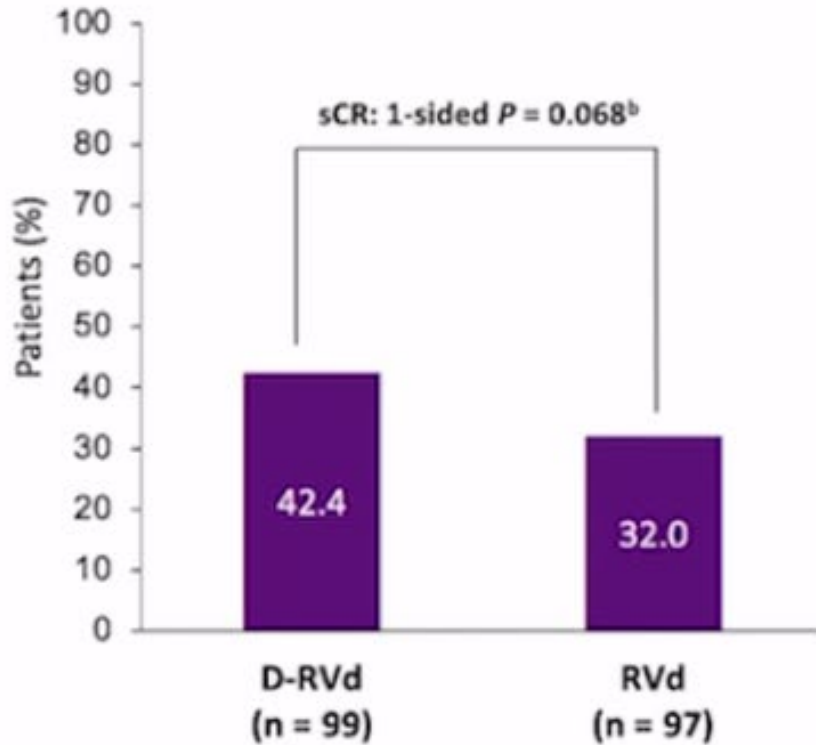
GRIFFIN (NCT02874742): Randomized Phase

- Phase 2 study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 and 4/2018

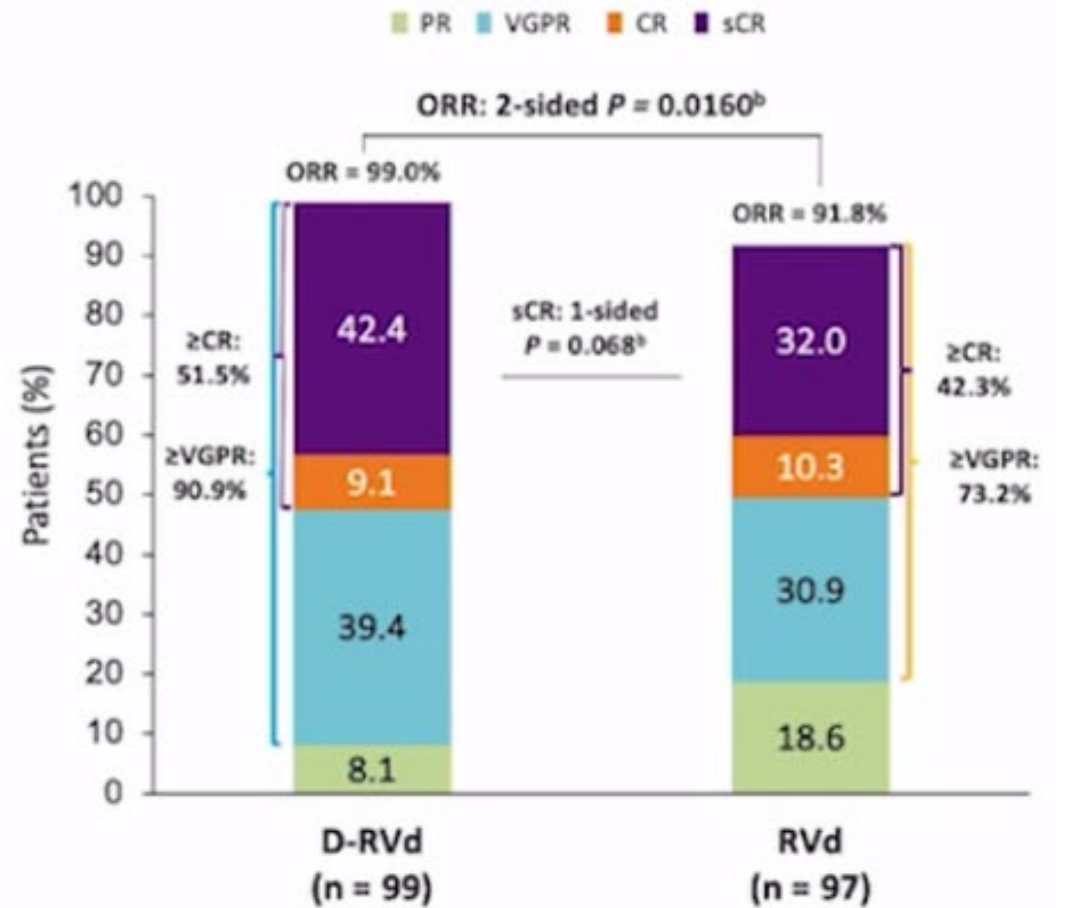


Primary Endpoint: sCR by the End of Consolidation^a

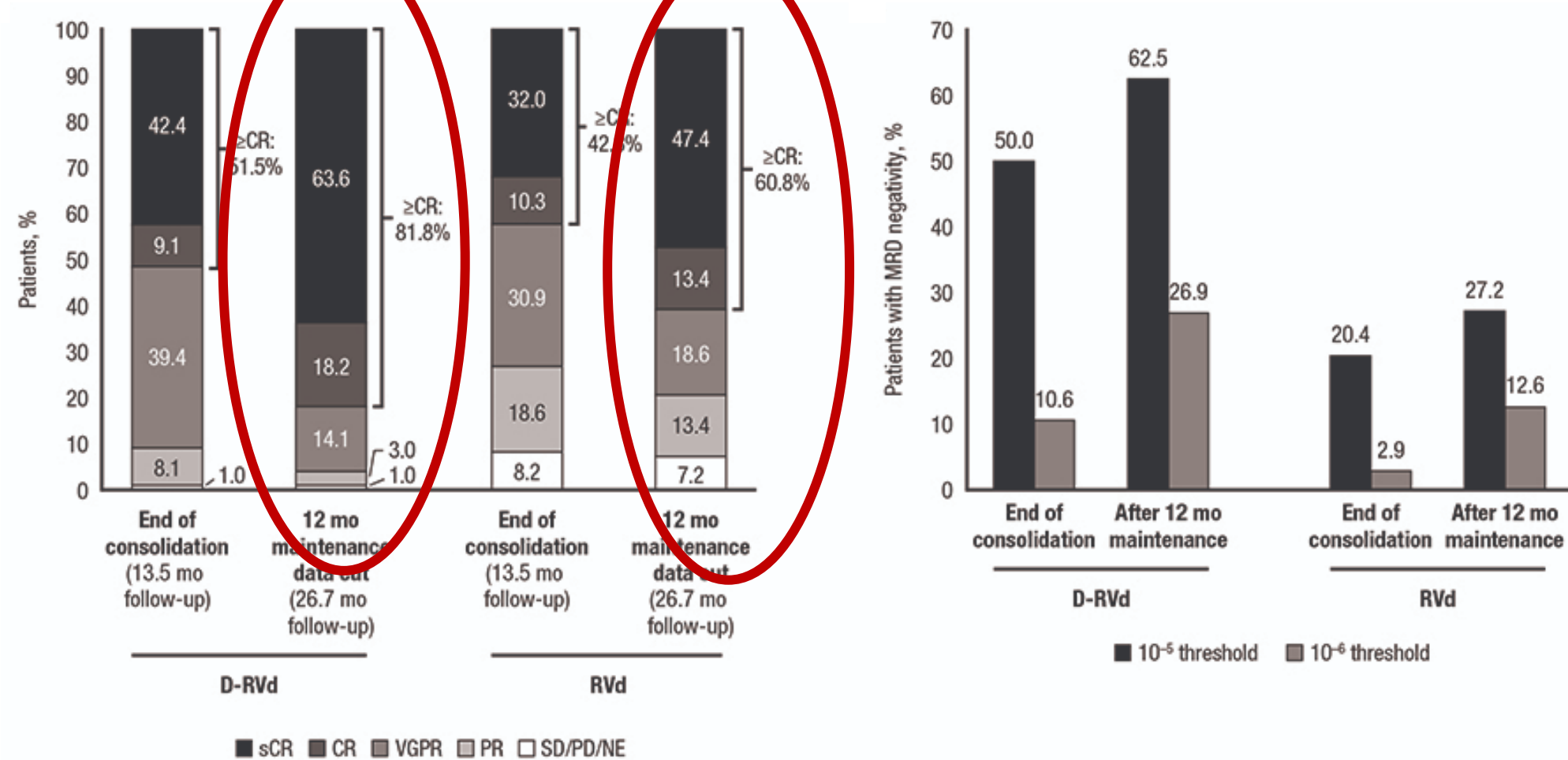
- Primary endpoint met at pre-set 1-sided alpha of 0.1
 - sCR by end of consolidation
 - 42.4% D-RVd vs 32.0% RVd
 - Odds ratio, 1.57; 95% CI, 0.87-2.82; 1-sided $P = 0.068^b$



Post-consolidation depth of response^a



Updated response rates over time



Treatment considerations for high-risk chromosomal abnormalities

- IFM 2005 01 – bortezomib showed better EFS and OS for patients with t(4;14)
- HOVON65/GMMG-HD4 – bortezomib based induction and maintenance showed improved outcomes for Del(17p)
- GIMEMA trial of VTD vs TD – in t(4;14) pts, OS was improved with VTD
- Conclusion: bortezomib *partly* overcomes the adverse effect of t(4;14) on PFS and OS, and del(17p) on PFS

Summary – induction treatment

- Modern PI/IMiD combinations can overcome high-risk changes and improve outcomes for standard-risk patients
- 4-drug combinations including a CD38 antibody are likely the future of induction therapy
- Can consider alkylator/PI combo for acute renal insufficiency, change to PI/IMiD after renal function improves
- Goal of induction: deep hematological response!
 - Usually like to see at least PR, ideally VGPR or better before autologous transplant

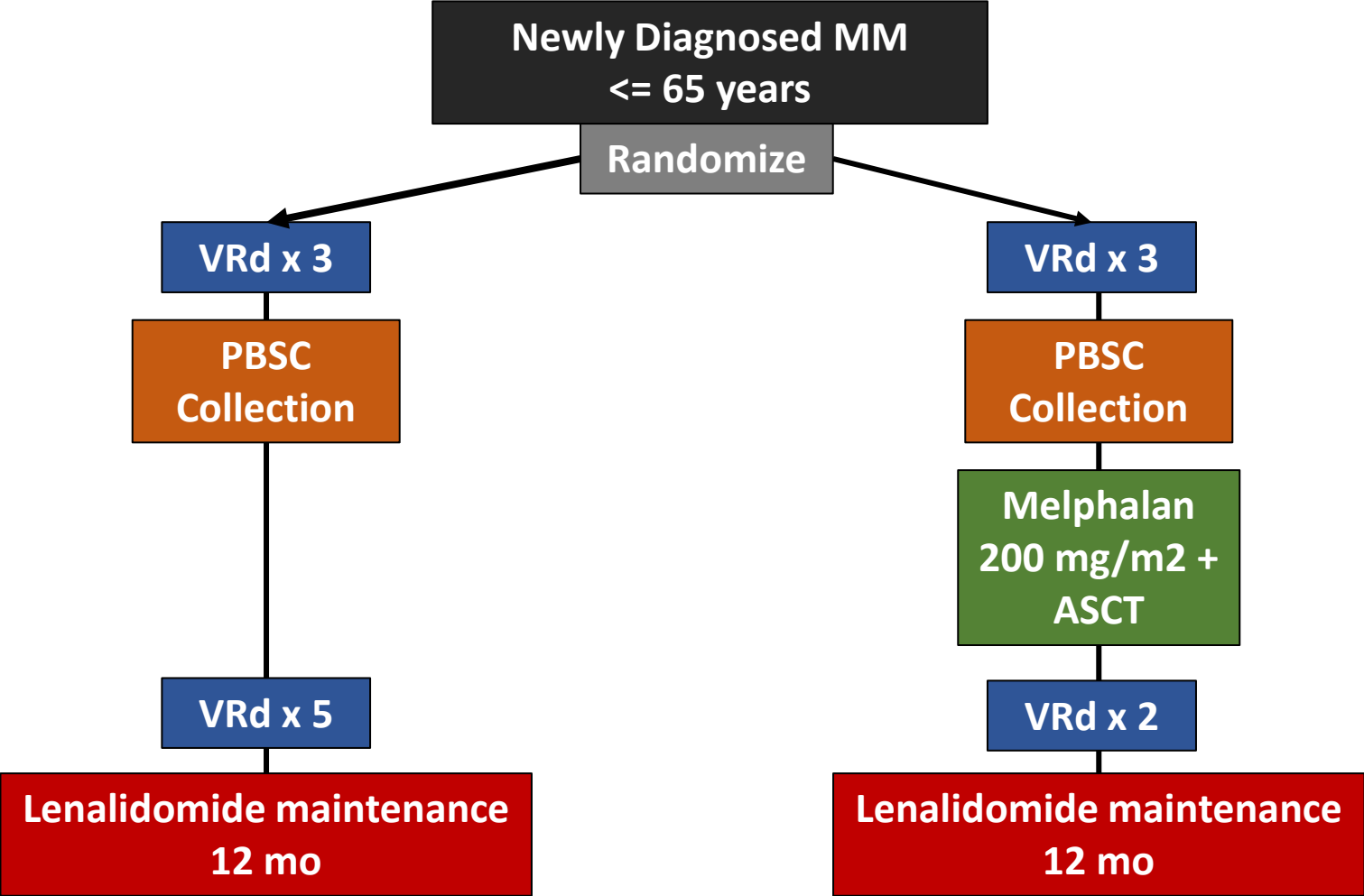
Autologous stem cell transplantation for multiple myeloma

- Remains a cornerstone of management for eligible newly diagnosed patients – randomized trials show benefit for EFS and OS
- Most recommend early or delayed transplant, rather than no transplant after induction therapy
- Very low treatment related mortality in modern era (1-2%)
- Acute regimen toxicities (mucositis, infections, diarrhea) are manageable

Transplant eligible vs ineligible

- What factors are important?
 - Age – not an absolute contraindication
 - Comorbidities, general level of health (“eyeball test”)
 - Patient preference

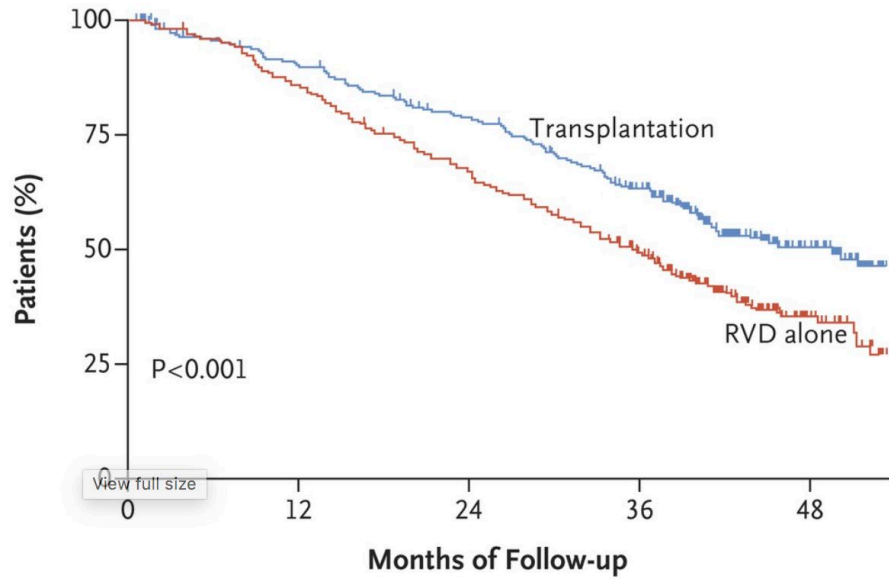
IFM 2009: Study Design



*ASCT at relapse

IFM 2009 Results

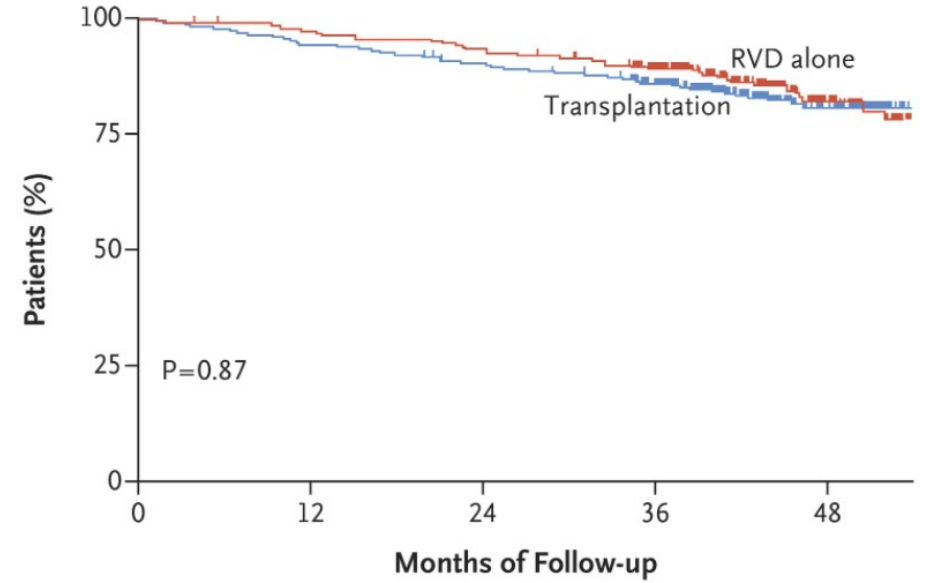
A Progression-free Survival



No. at Risk

	0	12	24	36	48
RVD alone	350	294	228	157	32
Transplantation	350	308	264	196	50

B Overall Survival



No. at Risk

	0	12	24	36	48
RVD alone	350	339	325	293	95
Transplantation	350	330	313	281	89

IFM 2009 Results

- Median PFS significantly longer in the ASCT arm, 50 mos vs 36 mos ($p < 0.001$) – primary endpoint
- Benefit observed across all subgroups (high risk vs standard)
- Higher percentage of CR in the transplant arm
- No overall survival benefit observed

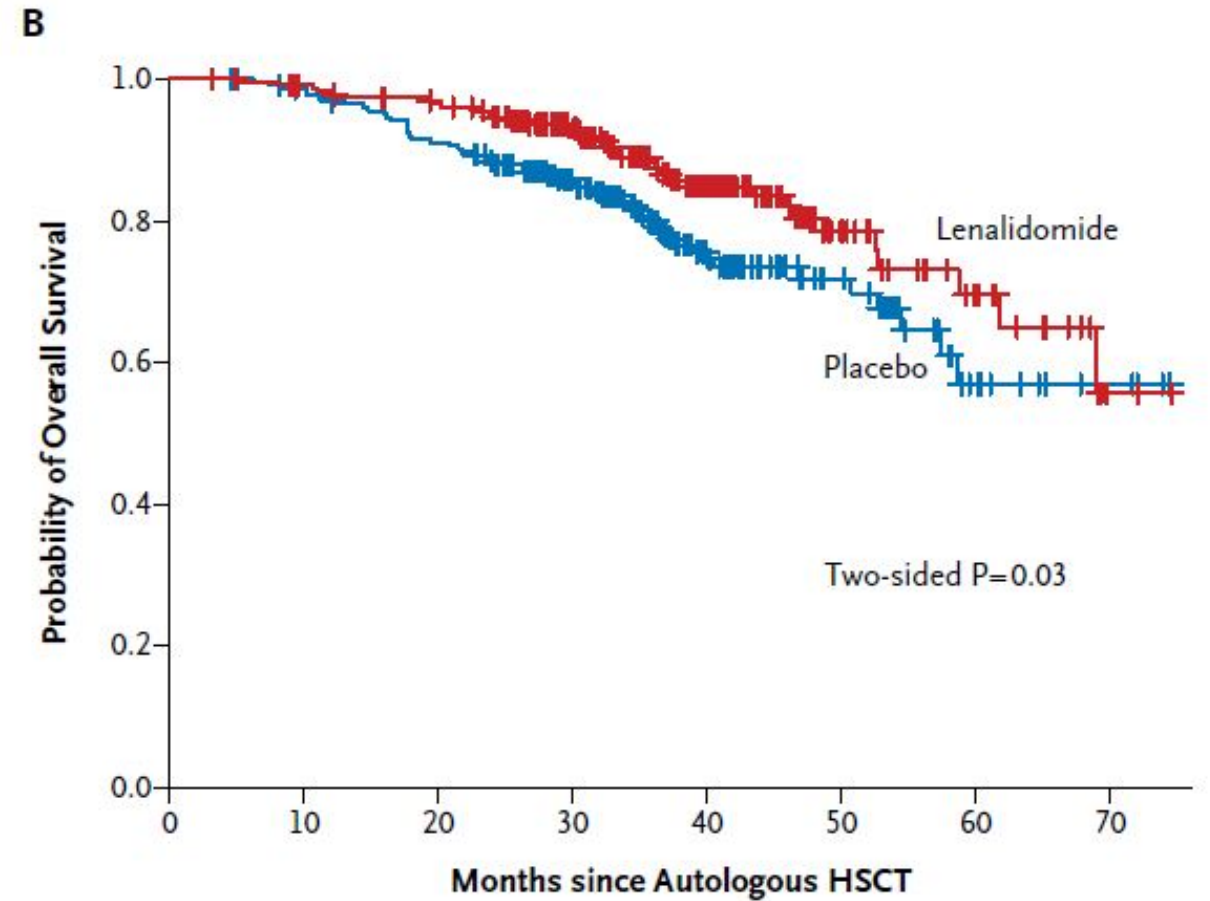
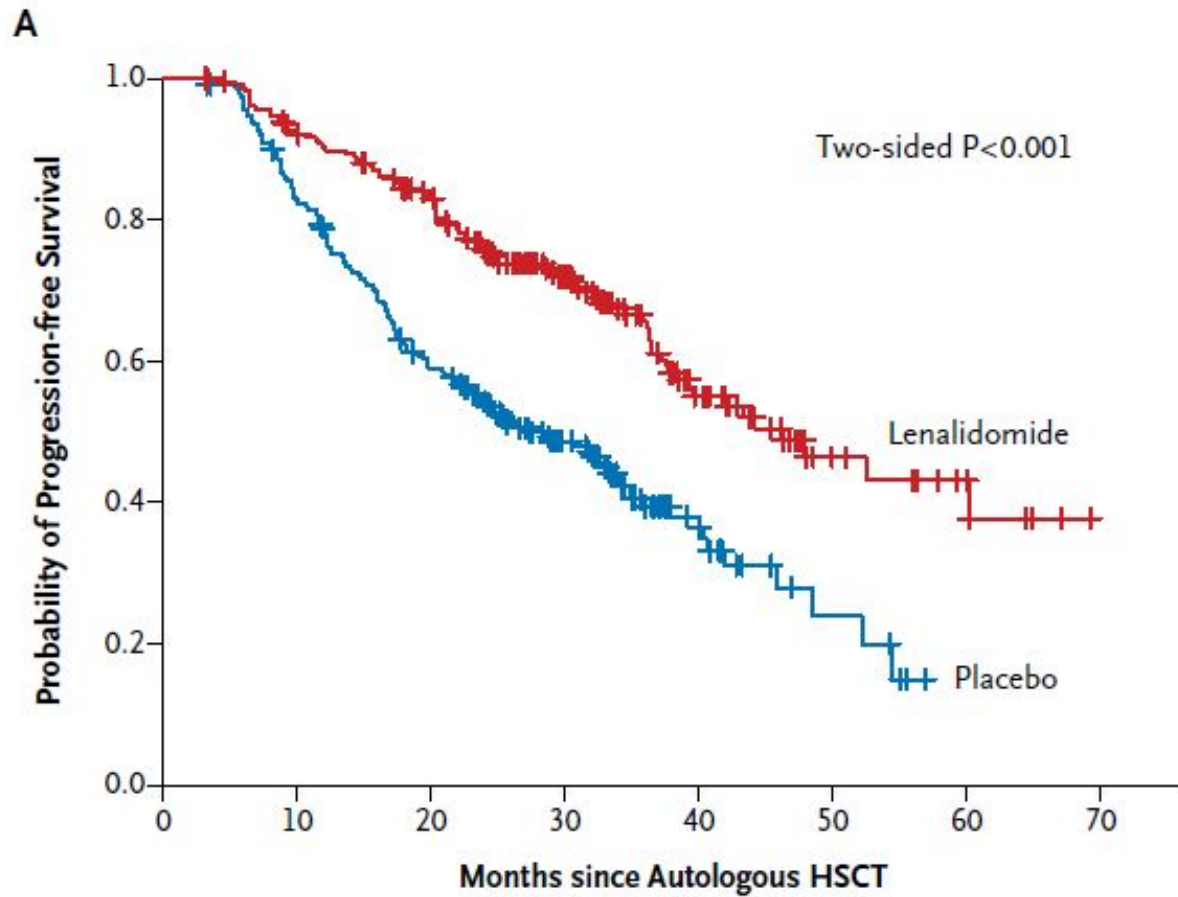
Lenalidomide maintenance post-ASCT improves PFS

- Lenalidomide maintenance improves PFS post ASCT
 - Attal et al, NEJM 2012:
 - 614 patients; Len maintenance 10 mg daily, increased to 15 mg if tolerated, vs Placebo
 - Primary end point: PFS
 - PFS 41 mos vs 23 mos, $p < 0.001$.
 - Attal ASH 2013, update:
 - 5-year PFS: 42 vs 18 mo. No difference in 5-year OS!
 - Lenalidomide stopped at median of 2 years due to secondary primary malignancy (SPM) concern

Lenalidomide maintenance post-ASCT improved PFS *and* OS in 1 study

- McCarthy et al, NEJM 2012
 - 460 patients, randomized to lenalidomide at starting dose of 10 mg, or placebo, post ASCT, daily, until progression
 - Median time to progression, 46 mos vs 27 mos ($p < 0.001$)
 - 3-year OS rate 88% vs 80%

Lenalidomide maintenance improves PFS and OS



Meta-analysis of lenalidomide maintenance after ASCT

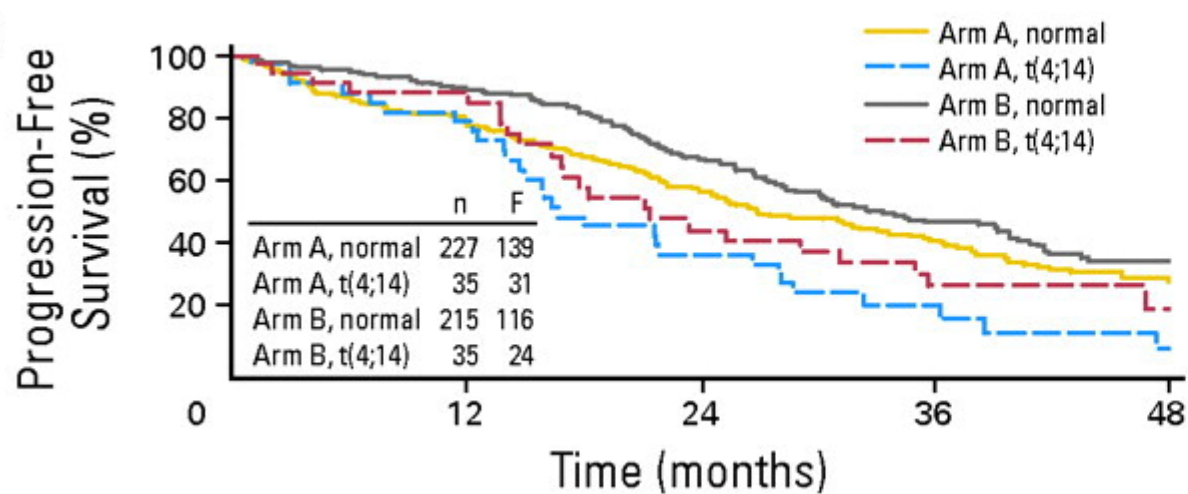
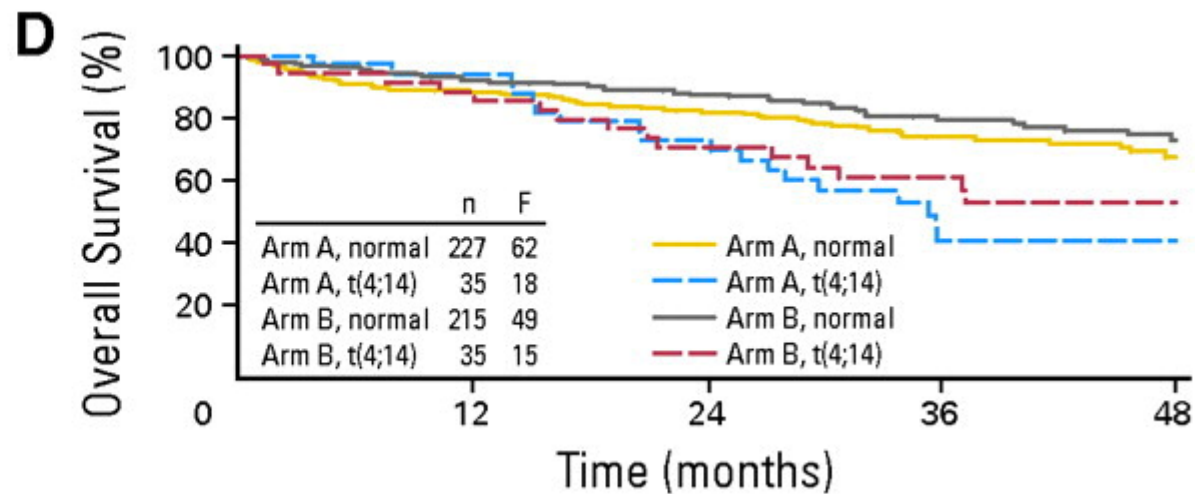
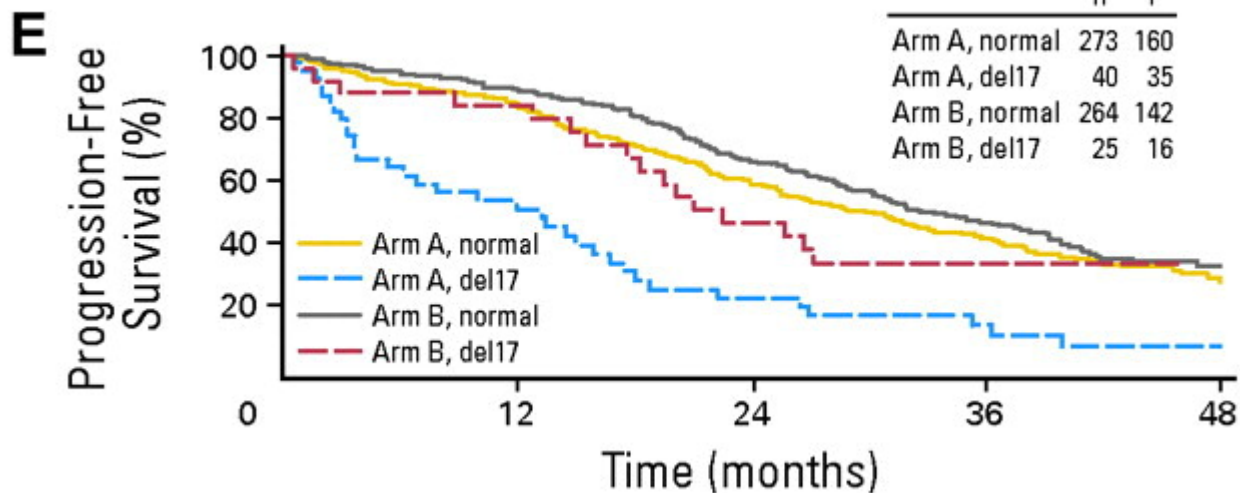
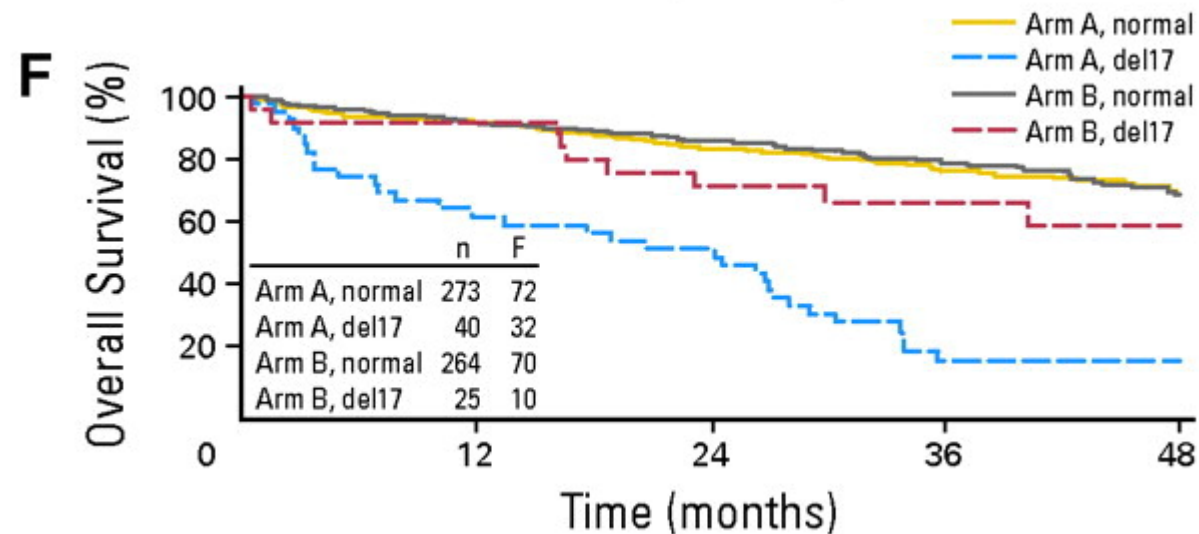
- McCarthy et al, JCO 2017
- Used documentation from 3 RCTS (CALGB 100104, GIMEMA, IFM 2005)
- 1208 patients in meta-analysis
- Median OS:
 - Not reached for lenalidomide maintenance group
 - 86 months for the placebo/observation group
 - $p = 0.001$

Summary – lenalidomide maintenance post-ASCT

- Lenalidomide maintenance post-ASCT improved PFS in several large studies
- Lenalidomide maintenance post-ASCT improved OS in one study (McCarthy et al.)
- Meta analysis of 3 RCTs showed OS benefit with lenalidomide maintenance

Bortezomib maintenance: HOVON-65/GMMG-HD4

- Study design:
 - Randomized study – PAD (bortezomib) vs VAD induction, followed by transplant, followed by maintenance with either
 - Thalidomide 50 mg daily x 2 years
 - Bortezomib 1.3 mg/m² Q2week x 2 years
- CR rate superior:
 - After PAD induction, 15 vs 31%
 - After bortezomib maintenance, 34 vs 49%

t(4;14) – PFS**t(4;14) – OS****Del(17p) – PFS****Del(17p) – OS**

Bortezomib maintenance post-ASCT improves outcome for del(17p)

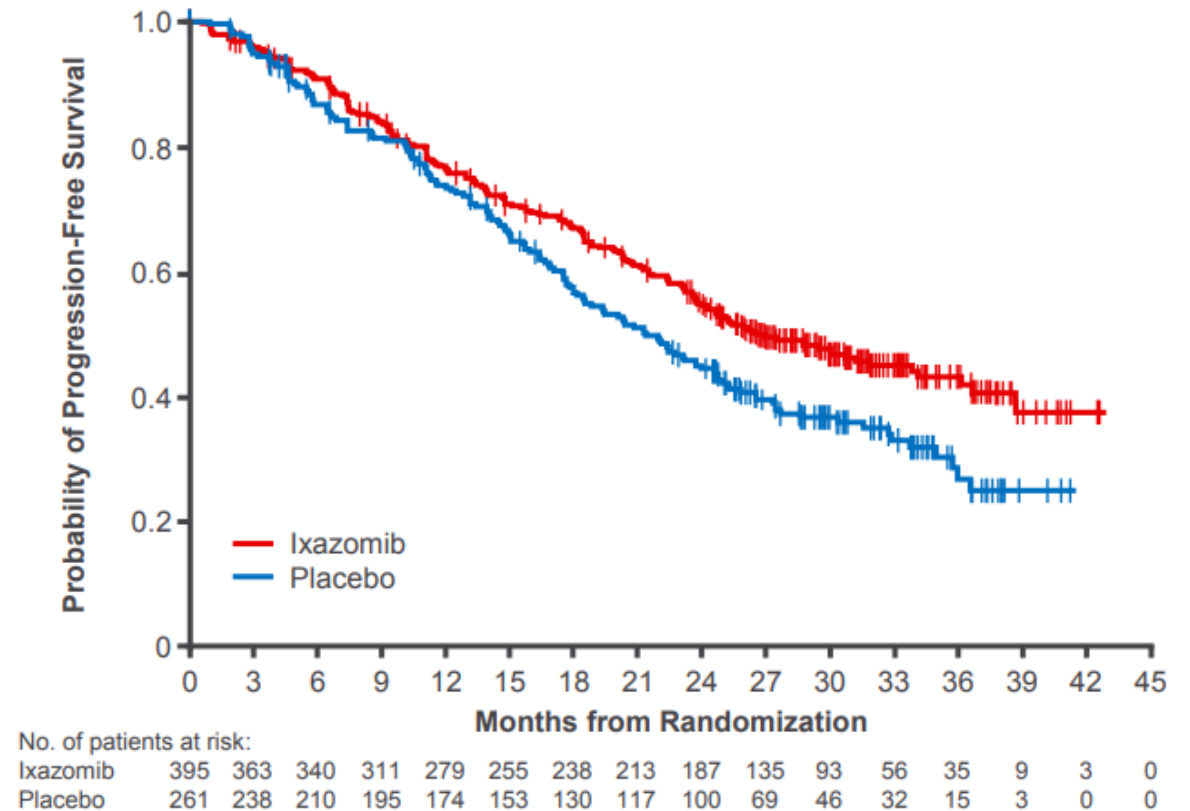
- Analysis of the HOVON-65 trial data
- Looked at the prognostic value of 12 chromosomal abnormalities
- Patients with t(4;14) receiving bortezomib based treatment had a prolonged median PFS (25.3 vs 21.7 mos), and improved 3-year OS rate (66 vs 44%)
- Patients with del(17p13) receiving bortezomib had a prolonged median PFS (26 vs 12 mos), and improved 3-year OS (17 vs 69%)

Summary – bortezomib maintenance for high-risk myeloma

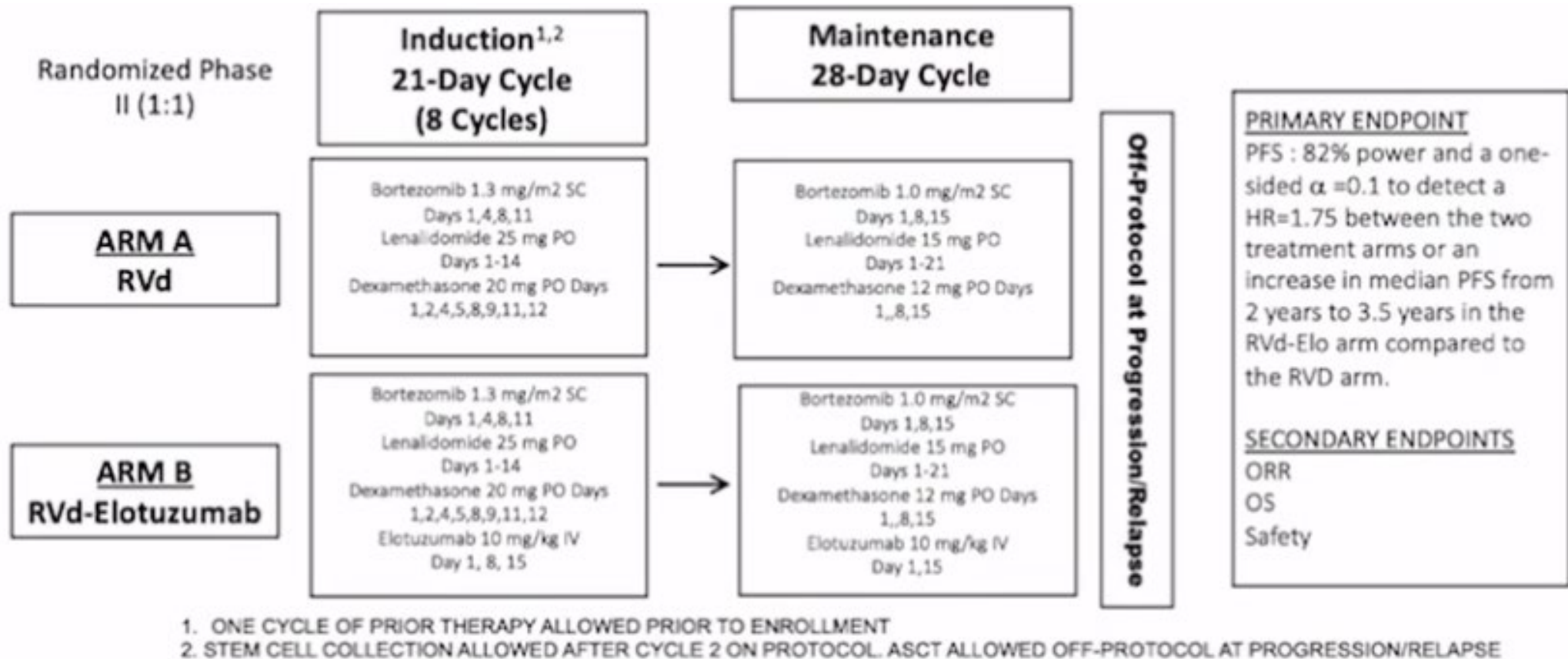
- Aggregate data from analysis of the HOVON-65/GMMG HD4 trial indicates a benefit for bortezomib maintenance post-ASCT, given every 2 weeks for 2 years. Particularly for those patients with the following chromosomal abnormalities:
 - **Del(17p)**
 - **t(4;14)**

Ixazomib maintenance improves PFS post-ASCT

- 39% improvement in overall PFS from time of randomization for patients receiving ixazomib vs placebo maintenance:
 - HR: 0.72; 95% CI: 0.582-0.890
 - $p=0.002$
 - Median 26.5 mos vs 21.3 mos
- At a median follow-up of 31 months, median OS not reached in either treatment arm



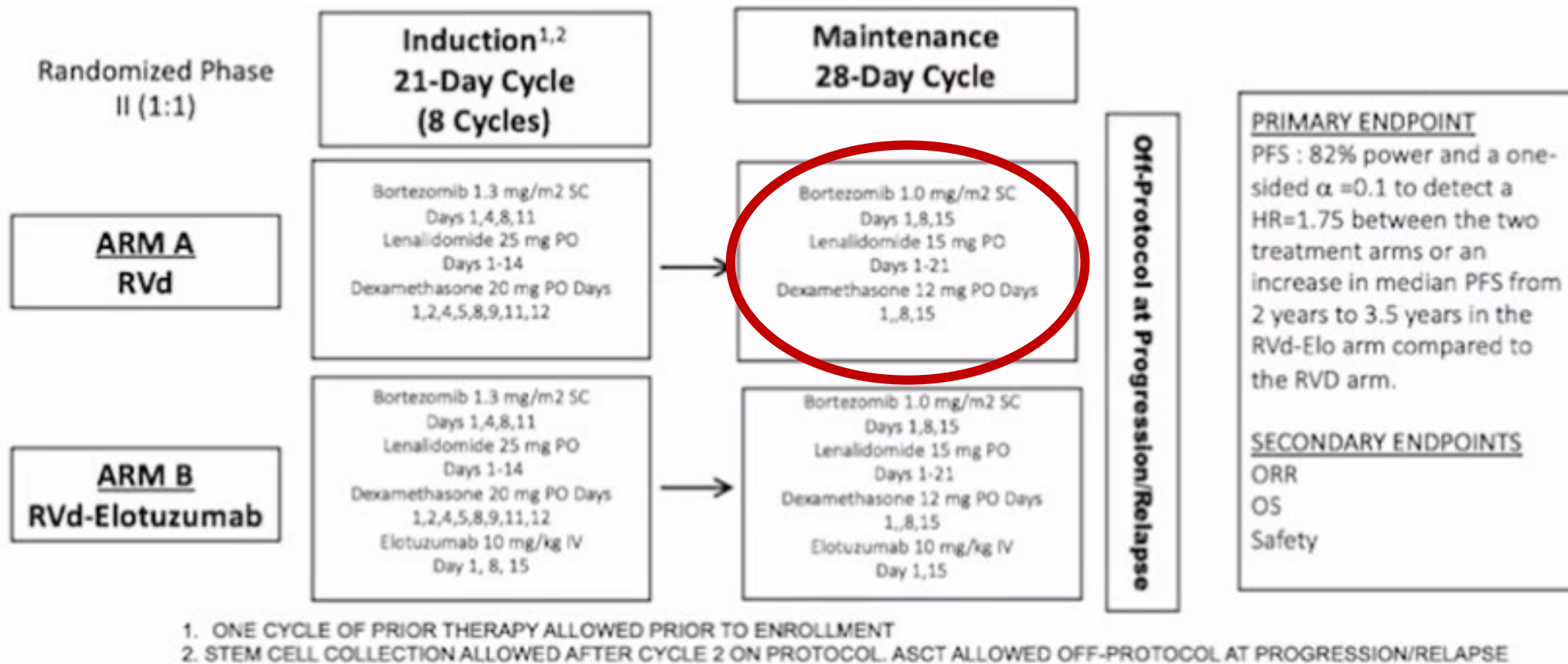
RVd maintenance for high-risk MM: SWOG 1211 schema



Opened to all National Clinical Trials Network members



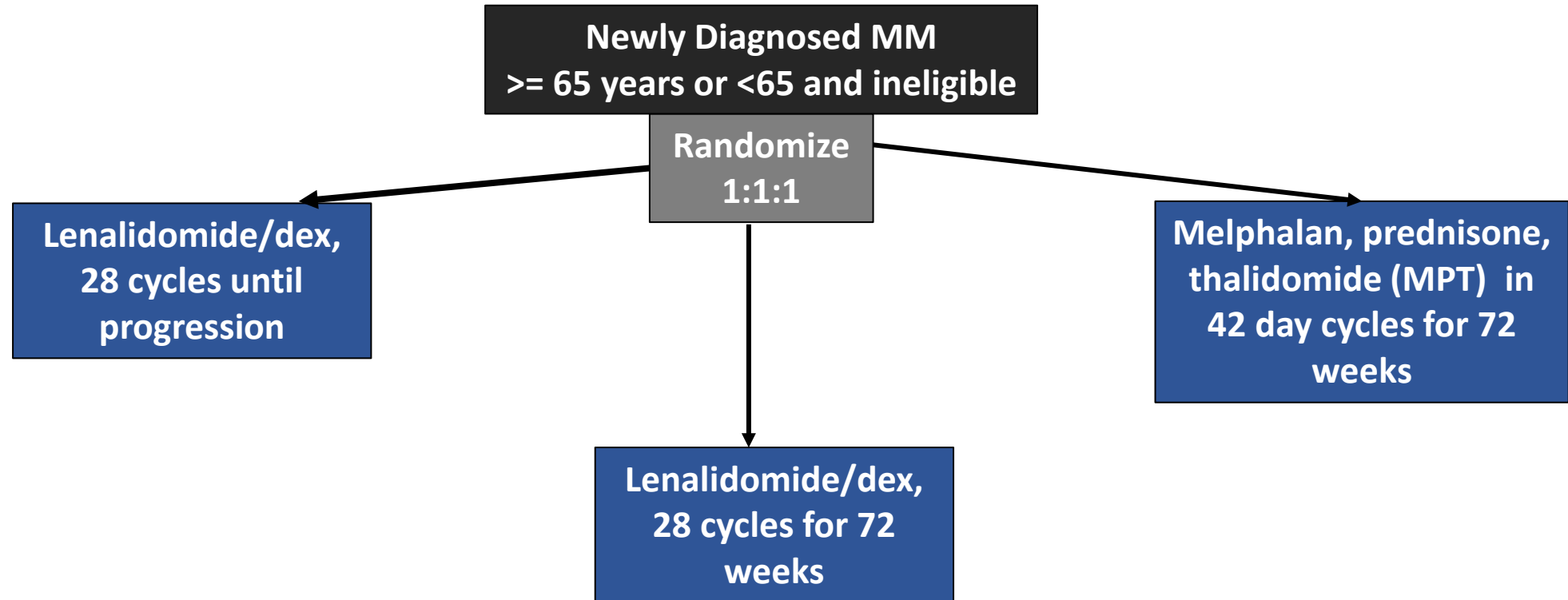
RVd maintenance for high-risk MM: SWOG 1211 schema



Treatment of newly diagnosed, transplant *ineligible* myeloma

- Consider triplet combination
 - IMiD/PI/dex triplet combination – RVD lite
 - Daratumumab, lenalidomide, dexamethasone – (MAiA trial, NEJM 2019)
- Consider doublet for frail/elderly
 - Lenalidomide/low-dose dexamethasone
 - Bortezomib/low-dose dexamethasone
- Other options
 - Alkylator/PI combination (CyBorD)
 - Daratumumab+VMP (ALCYONE Trial, NEJM 2018)

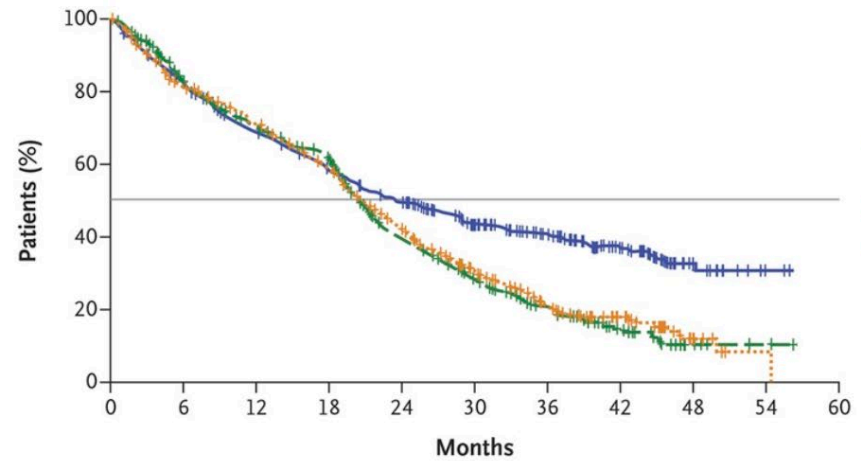
FIRST Trial – randomized study of Rd vs MPT



All patients received antithrombotic prophylaxis:

- Low dose aspirin, 70-100 mg/day
- DVT/PET within 5 years: LMWH, Heparin, Warfarin

A Progression-free Survival



Median Progression-free Survival (mo)

- Continuous Ld (N=535) 25.5
- Ld18 (N=541) 20.7
- MPT (N=547) 21.2

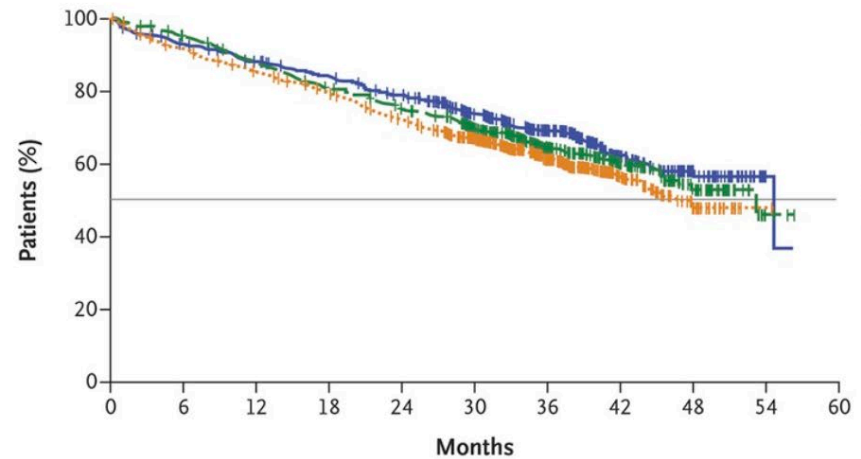
Hazard ratio:
Continuous Ld vs. MPT, 0.72; P<0.001

Continuous Ld vs. Ld18, 0.70; P<0.001

No. at Risk

Continuous Ld	535	400	319	265	218	168	105	55	19	2	0
Ld18	541	391	319	265	167	108	56	30	7	2	0
MPT	547	380	304	244	170	116	58	28	6	1	0

B Overall Survival



4-Yr Overall Survival (%)

- Continuous Ld (N=535) 59
- Ld18 (N=541) 56
- MPT (N=547) 51

Hazard ratio:
Continuous Ld vs. MPT, 0.78; P=0.02

Continuous Ld vs. Ld18, 0.90; P=0.31

No. at Risk

Continuous Ld	535	488	457	433	403	338	224	121	43	5	0
Ld18	541	505	465	425	393	324	209	124	44	6	0
MPT	547	484	448	418	375	312	205	106	30	3	0

Table 2. Response Rates and Time to Response.

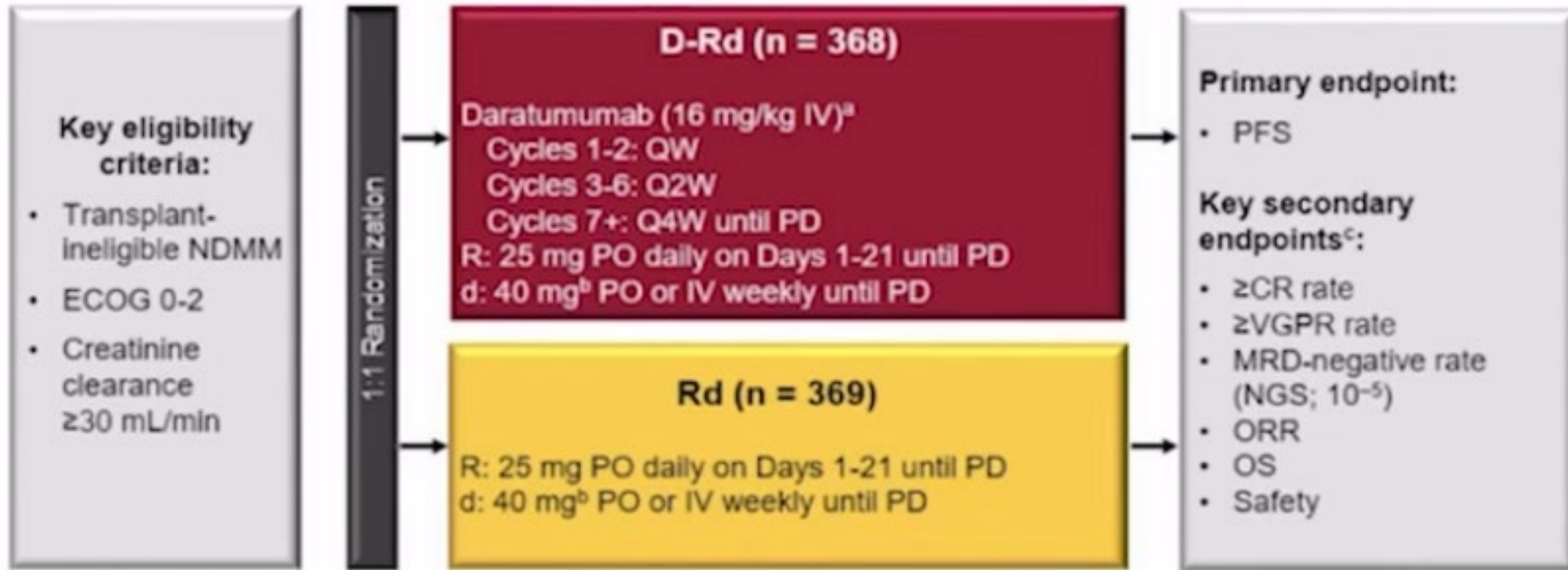
Variable	Continuous Lenalidomide– Dexamethasone (N = 535)	Lenalidomide– Dexamethasone for 18 Cycles (N = 541)	MPT (N = 547)
Overall response — no. (%)	402 (75)*	397 (73)*	341 (62)
Complete response	81 (15)	77 (14)	51 (9)
Very good partial response	152 (28)	154 (28)	103 (19)
Partial response	169 (32)	166 (31)	187 (34)
Stable disease — no. (%)	101 (19)	111 (21)	145 (27)
Progressive disease — no. (%)	7 (1)	12 (2)	19 (3)
Response could not be evaluated — no. (%)	25 (5)	21 (4)	42 (8)
Median time to response — mo†	1.8‡	1.8‡	2.8

Modified RVD (“RVD-Lite”) for elderly/frail

- Dosing
 - Lenalidomide 15 mg days 1-21 of a 35-day cycle
 - Bortezomib 1.3 mg/m² weekly days 1, 8, 15, 22
 - Dexamethasone 20 mg twice weekly for pts ≤75 yo, and days 1, 8, 15, 22 for pts > 75 yo
- 53 patients treated
- Median age of patients: 72 years
- iORR - 90% (10 CR, 14 VGPR, 12 PR, 4 SD)
- Toxicities manageable:
 - Grade 3 or greater toxicities included hypophosphatemia in 15 (31%) and rash in 5 (10%) pts
 - Fatigue most common, in 31/49 (63%) patients, mostly grade 1-2
 - Peripheral neuropathy of any grade was reported in 21/49 (43%) pts including grade 1 (11/22%), 2 (9/18%), and 3 (1/2%)

Dara-Rd vs Rd: MAIA trial study design

- Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)



Stratification factors

- ISS (I vs II vs III)
- Region (NA vs other)
- Age (<75 vs ≥ 75 years)

Cycle: 28 days

^aOn days when daratumumab was administered, dexamethasone was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication.

^bFor patients older than 75 years of age or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.

^cEfficacy endpoints were sequentially tested in the order shown.

MAIA Trial: Dara-Rd vs Rd upfront treatment for ASCT-ineligible Patients

Figure. Updated progression-free survival with D-Rd and Rd in MAIA.

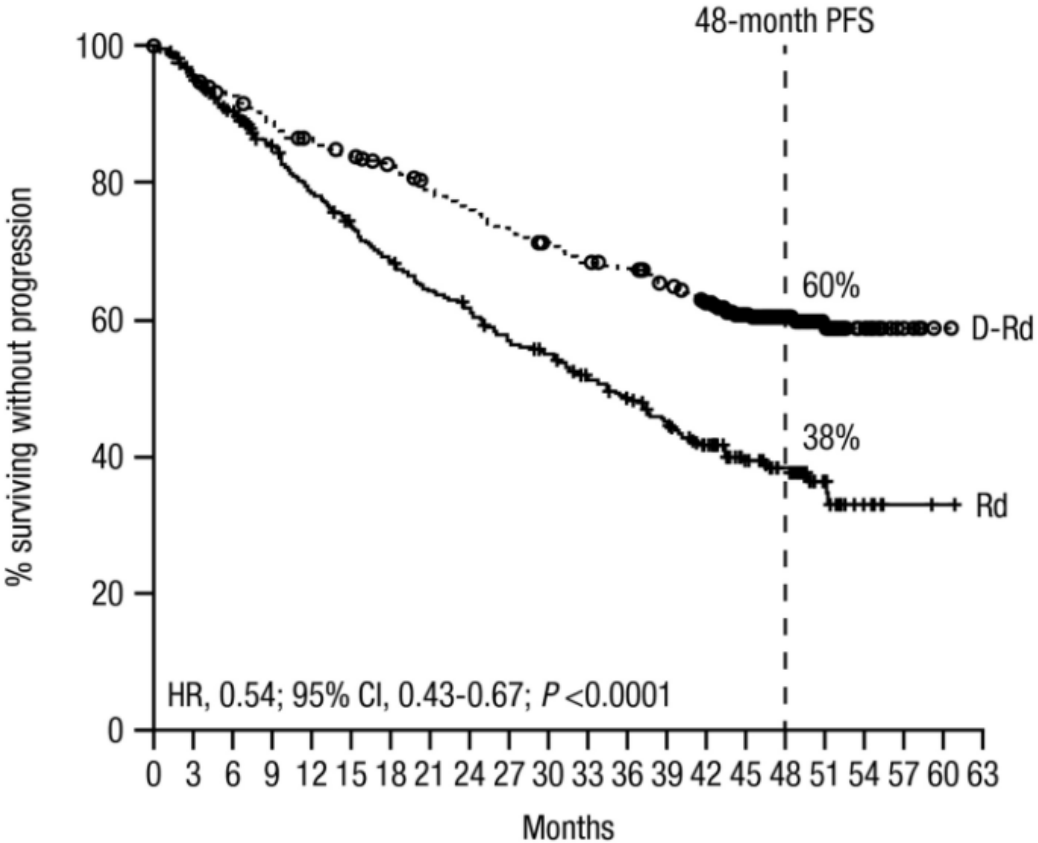


Table. Updated Overall Responses With D-Rd and Rd in MAIA

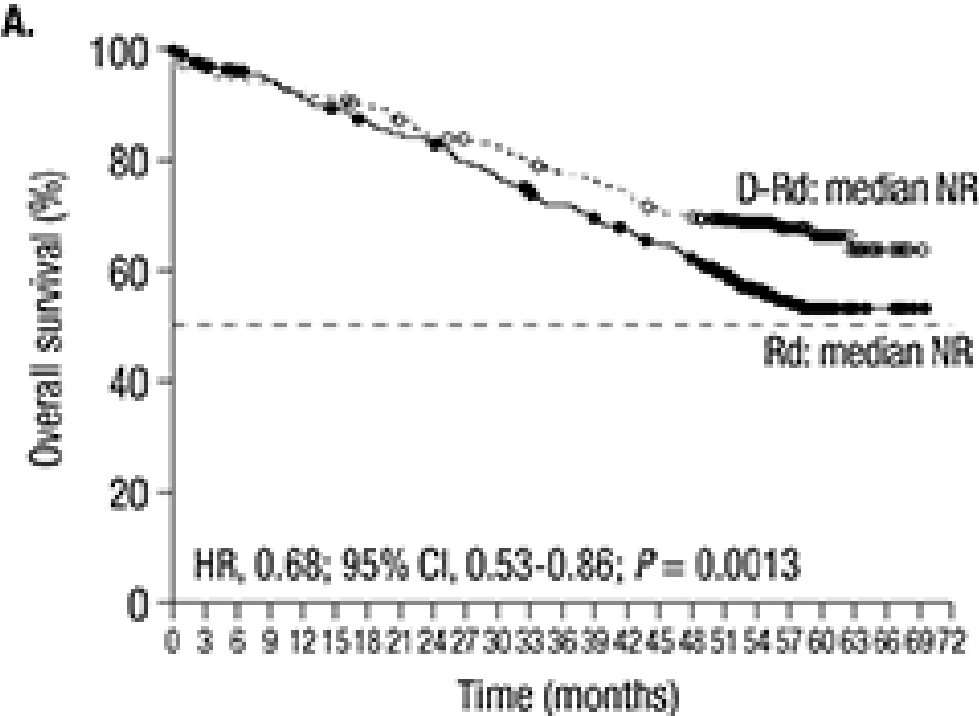
n (%)	D-Rd (n = 368)	Rd (n = 369)	P value
ORR	342 (92.9)	301 (81.6)	<0.0001
sCR	126 (34.2)	52 (14.1)	<0.0001
CR	62 (16.8)	57 (15.4)	-
VGPR	109 (29.6)	101 (27.4)	-
PR	45 (12.2)	91 (24.7)	-
≥VGPR	297 (80.7)	210 (56.9)	<0.0001
≥CR	188 (51.1)	109 (29.5)	<0.0001

No. at risk

Rd	369	333	307	280	255	237	220	205	196	179	172	155	145	132	114	79	53	22	9	2	1	0
D-Rd	368	347	335	320	309	300	290	276	266	256	246	237	232	221	201	153	111	63	26	7	1	0

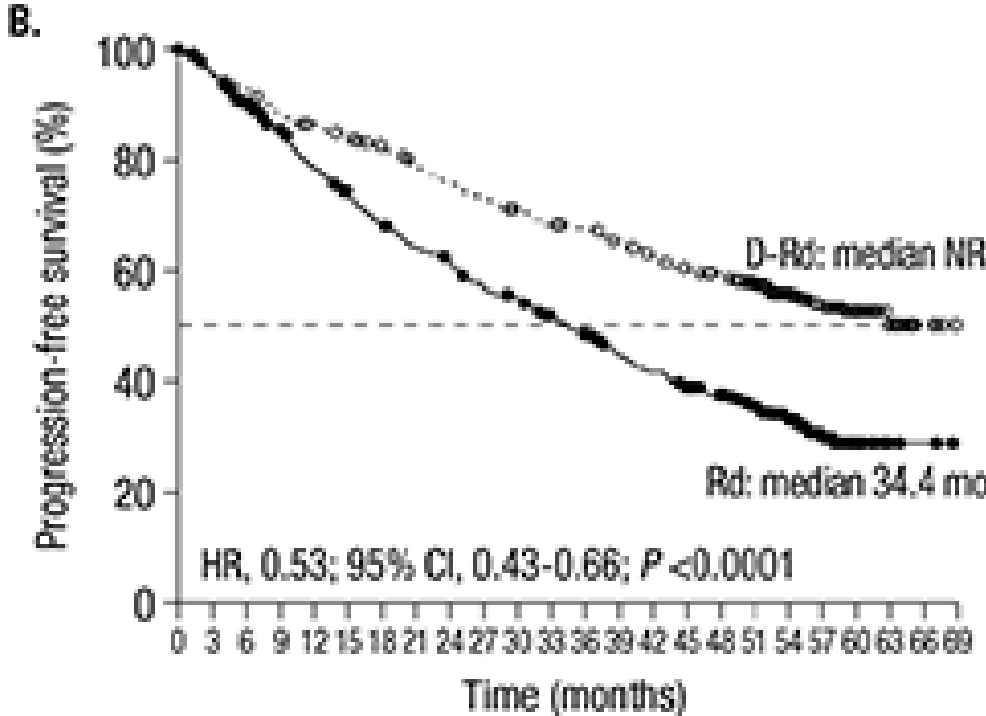
MAIA Trial: Dara-Rd vs Rd upfront treatment for ASCT-ineligible Patients

Figure: Overall survival (A) and progression-free survival (B) with D-Rd and Rd.



Number at risk

Rd	369	351	343	336	324	317	308	300	294	281	270	258	251	241	232	222	213	193	174	155	142	14	5	1	0
D-Rd	368	350	346	344	328	324	328	316	305	302	297	290	280	273	266	258	248	228	170	118	63	22	6	1	0



Number at risk

Rd	369	333	307	284	258	237	220	205	196	179	172	155	146	133	123	113	105	94	63	36	12	4	2	0
D-Rd	368	347	326	325	309	300	290	274	266	256	246	237	232	227	210	198	185	170	129	87	51	17	5	0

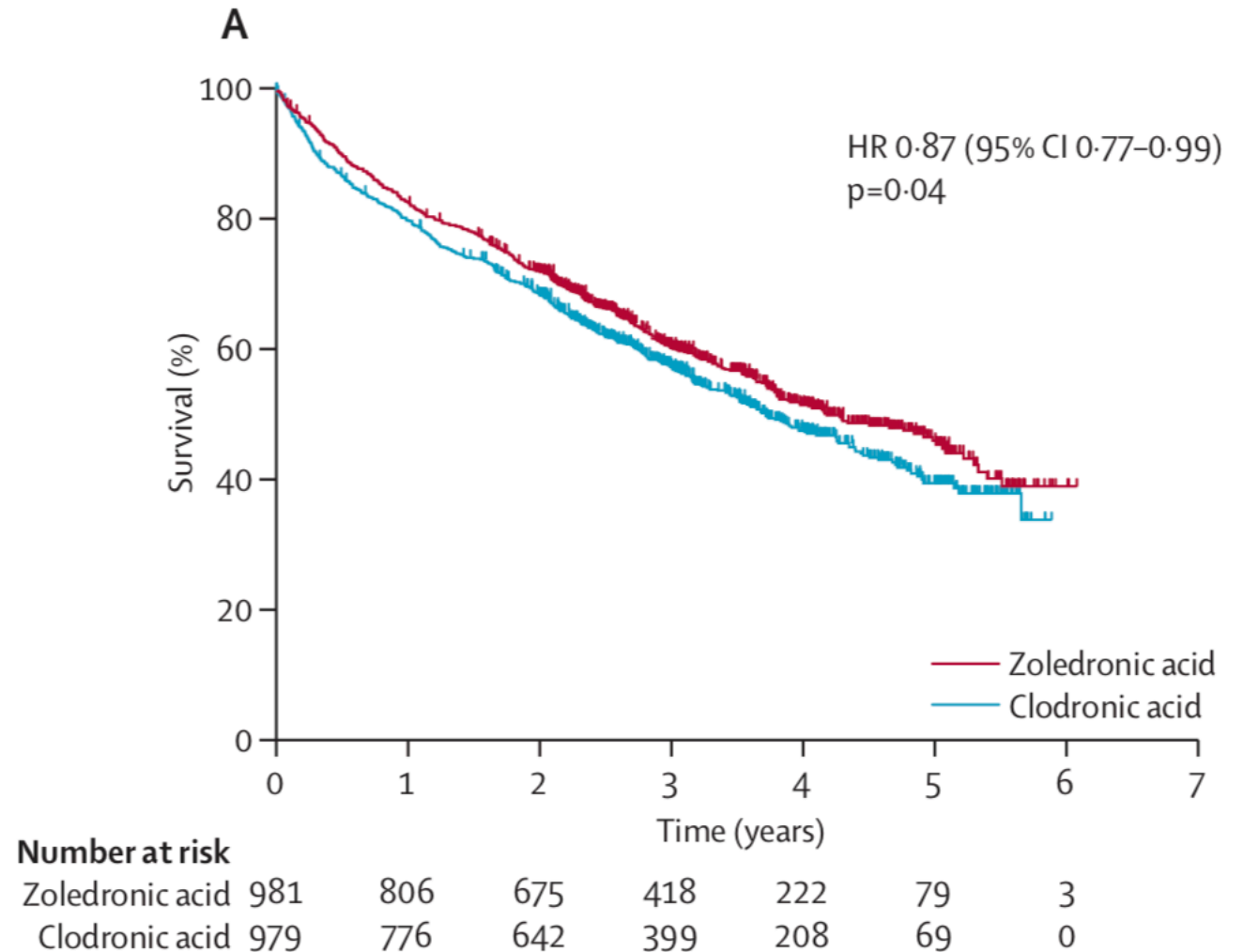
D-Rd, daratumumab plus lenalidomide and dexamethasone; Rd, lenalidomide and dexamethasone; HR, hazard ratio; CI, confidence interval; NR, not reached.

Myeloma therapy - dosing in frail patients

Frontline treatment	Second-line treatment	Following lines of treatment
<p>Lenalidomide-steroid R: 10-15 mg/d, d 1-21 d: 10 mg/d once weekly (P: 25 mg/d every other d)</p>	<p>Bortezomib-steroid V: 1.3 mg/m² once weekly d: 10 mg/d once weekly (P: 25 mg/d every other d)</p>	<p>Melphalan-prednisone M: 2 mg every other d P: 25 mg/d every other d</p>
<p>Bortezomib-steroid V: 1.3 mg/m² once weekly d: 10 mg/d once weekly (P: 25 mg/d every other d)</p>	<p>Lenalidomide-steroid R: 10-15 mg/d, d 1-21 d: 10 mg/d once weekly (P: 25 mg/d every other d)</p>	<p>Cyclophosphamide-prednisone C: 50 mg every other d P: 25 mg/d every other d</p>
	<p>Re-treatment</p>	<p>Thalidomide-prednisone T: 50 mg every other d P: 25 mg/d every other d</p>

Bisphosphonates for bone health in multiple myeloma: MRC IX trial

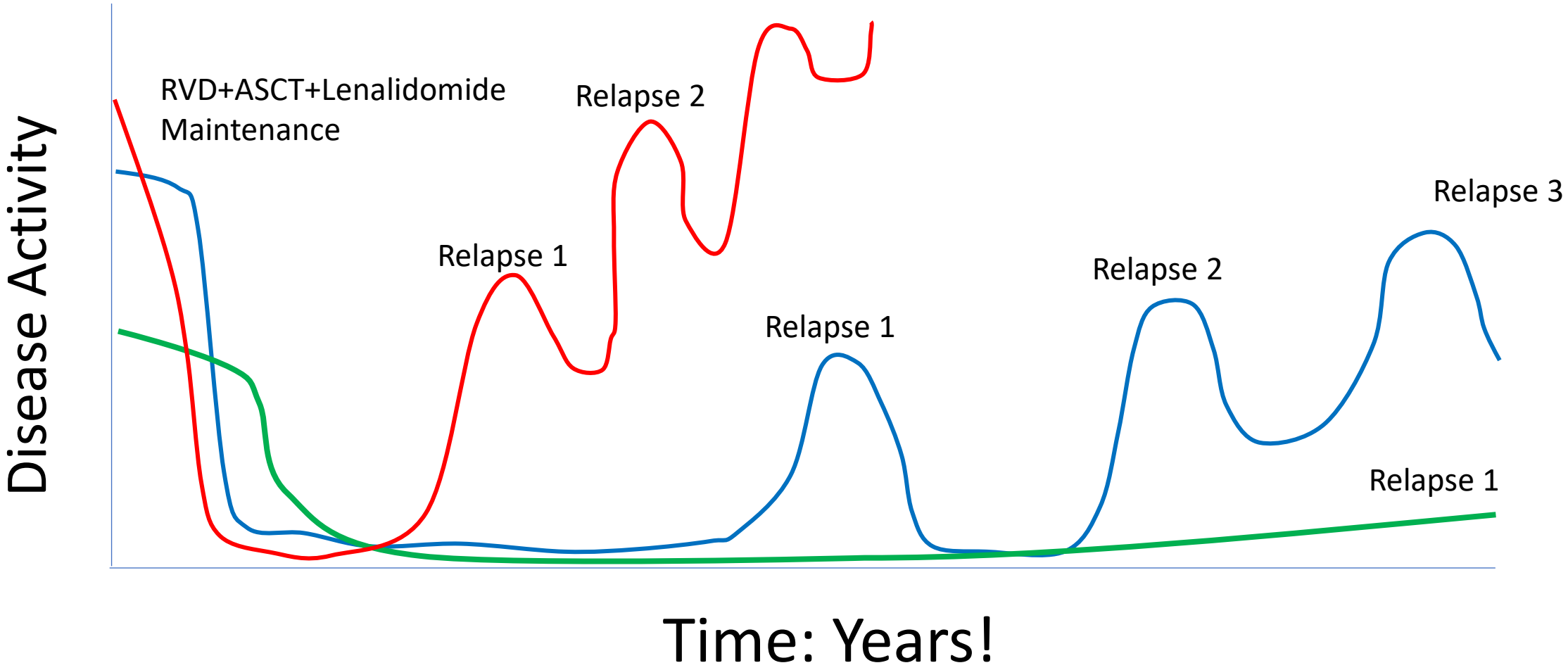
- MRC IX: Randomized study comparing first-line treatment with zoledronic acid as compared with clodronate in newly diagnosed multiple myeloma
- Only reported bisphosphonate to show survival benefit (5.5 mos)
- 3-4% risk of ONJ seen in this study



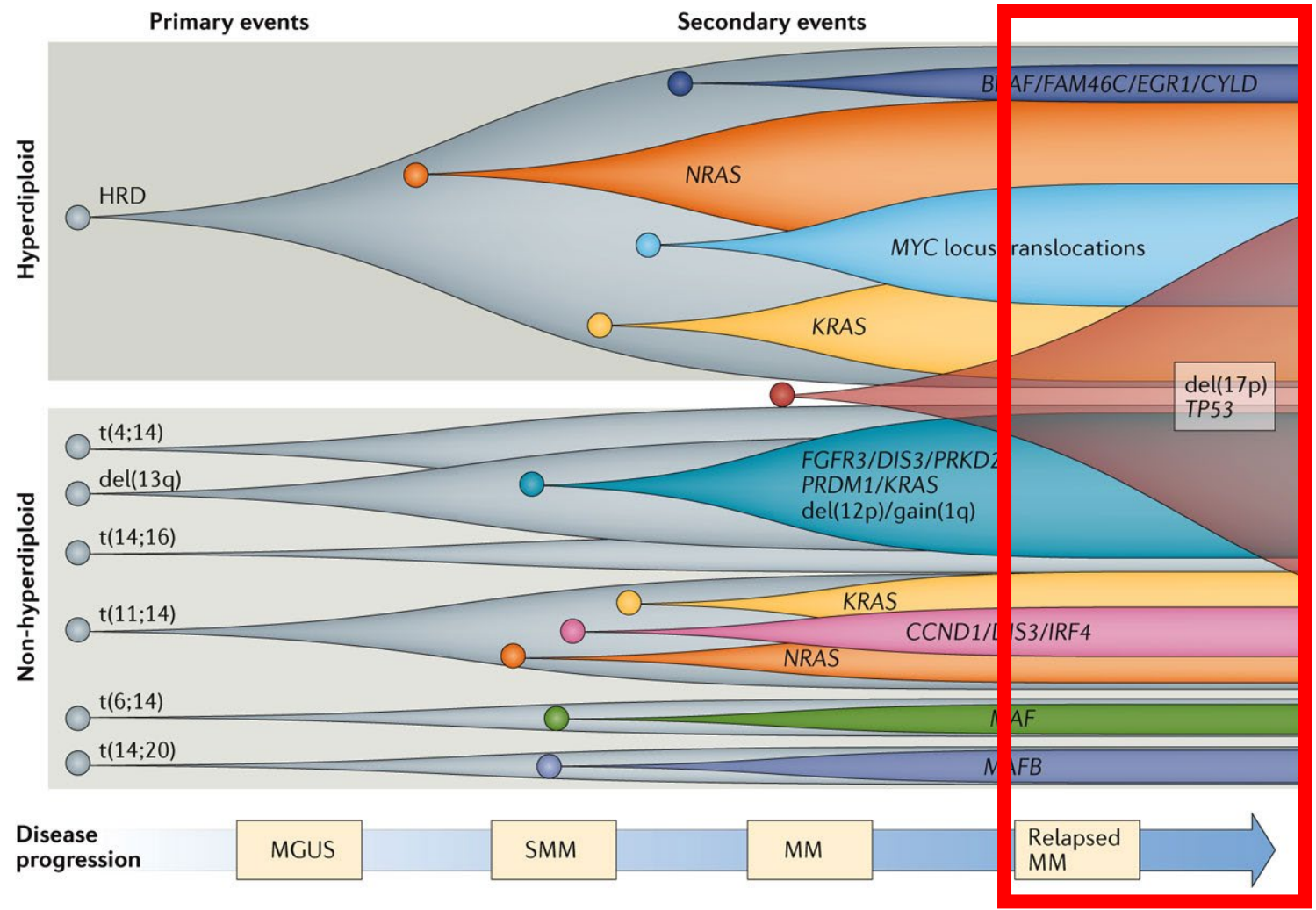
Supportive care – hypercalcemia, HSV/VZV and VTE

- Hypercalcemia:
 - Hydration, bisphosphonates (Zoledronic acid), steroids, +/- calcitonin
- Herpes zoster prophylaxis
 - Acyclovir or valacyclovir
 - For ALL patients receiving proteasome inhibitors or daratumumab
- VTE
 - Aspirin 81-325 mg PO daily for all patients receiving IMiDS
 - Therapeutic anticoagulation for patients at high risk for VTE

Relapsed multiple myeloma is not one disease!



Relapsed myeloma is a biologically and genetically heterogeneous disease



Nature Reviews | Clinical Oncology

Key questions to ask for relapsed/refractory multiple myeloma (RRMM)

- Sensitivity to PI/IMiD/CD38?
- Toxicity from prior therapy, and baseline comorbidities?
- Urgent need to treat/how aggressive?
- Prior autologous stem cell transplant?

Key phase 3 trials for RRMM

Trial	Regimen and Comparator	Prior Therapies	N	Median PFS, Mo	Population
POLLUX ^[a]	DRd vs Rd	≥1	569	NR vs 18.4	IMiD sensitive
ELOQUENT-2 ^[b]	ERd vs Rd	1 – 3	646	19.4 vs 14.9	IMiD sensitive
ASPIRE ^[c]	KRd vs Rd	1 – 3	792	26.3 vs 17.6	PI/IMiD sensitive
TOURMALINE-MM1 ^[d]	IRd vs Rd	1 – 3	722	20.6 vs 14.7	PI/IMiD sensitive
CASTOR ^[e]	DVd vs Vd	≥1	498	NR vs 7.2	PI sensitive
ENDEAVOR ^[f]	Kd vs Vd	1 – 3	929	18.7 vs 9.4	PI sensitive
PANORAMA ^[g]	PanoVd vs Vd	1 – 3	768	12 vs 8.7	PI sensitive
ARROW ^[h]	Kd weekly vs Kd twice wk	≥2	478	11.2 vs 7.6	Carfilzomib naive

[a] Dimopoulos et al, NEJM 2016 Oct 6;275(14):1319-1331; [b] Lonial S et al, NEJM 2015 Aug 13;373(7):621-31; [c] Stewart AK et al, NEJM 2015 Jan 8;372(2):142-52; [d] Moreau P et al, NEJM 2016 Apr 28;374(17):1621-34; [e] Palumbo et al, NEJM 2016 Aug 25;375(8):754-66; [f] Dimopoulos et al Lancet Oncol 2016 Jan;17(1):27-38 [g] San-Miguel JF et al, Lancet Haematol 2016 Nov;3(11):e506-e515; Moreau P et al, Lancet Oncol 2018 Jul;19(7):953-964

In general, 3 drugs >> 2 drugs

- Many studies have shown that 3 drug treatment is superior to 2 drug therapy for relapsed multiple myeloma
- In general, 3 drug regimens should be the standard for treatment of relapsed MM
- However, cannot always use a one size fits all approach – personalization is key

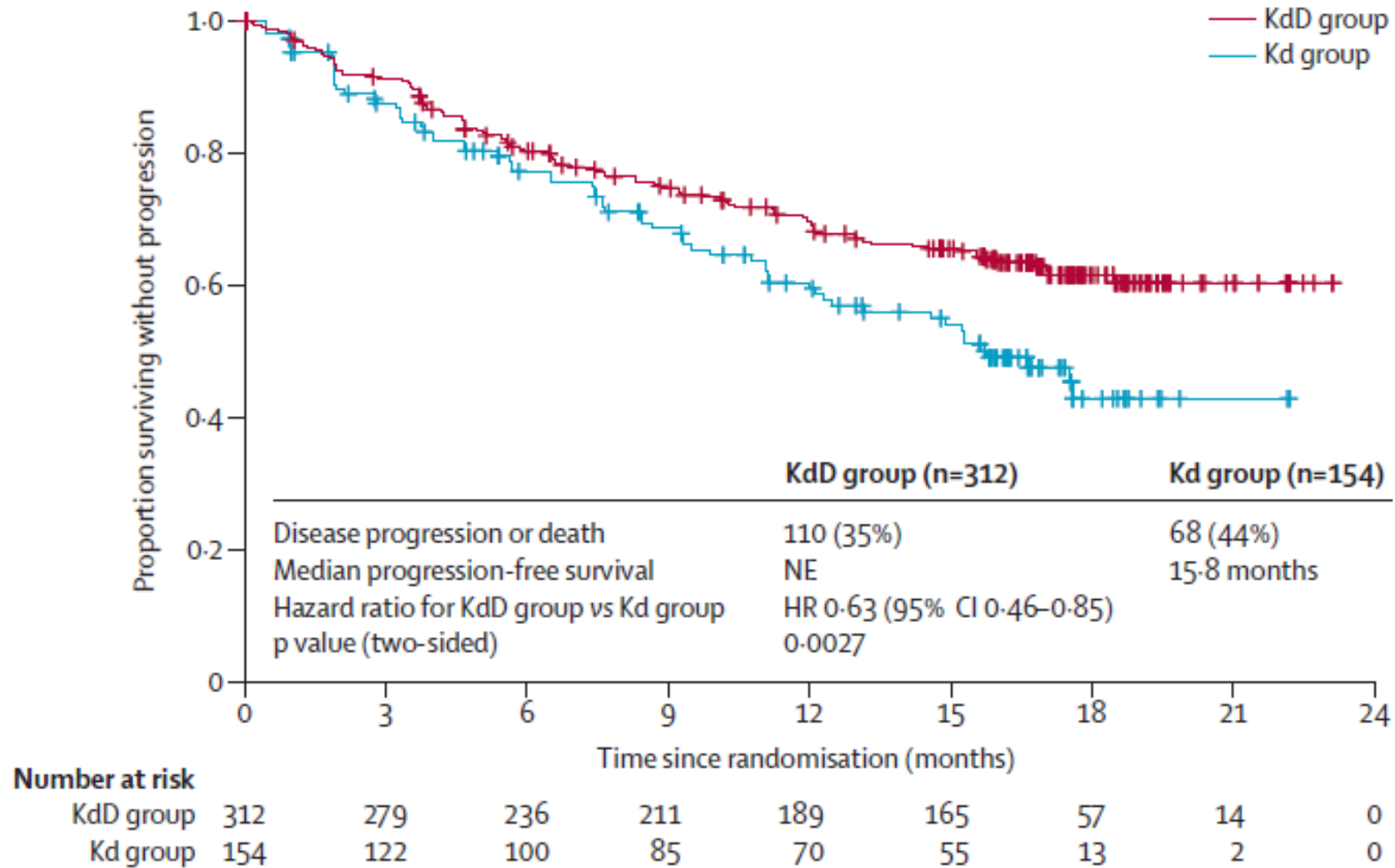
Toxicities from prior therapy & other comorbidities to consider

- Bortezomib – peripheral neuropathy (with or without pain)
- COPD/asthma – can use daratumumab, but cautiously
- Congestive heart failure – careful with carfilzomib
- General frailty – 2 drug vs 3 drug

Carfilzomib for RRMM

- Options for use:
 - Carfilzomib + dexathasone (ENDEAVOR)^a
 - Carfilzomib + IMiD (ASPIRE)^b
 - Carfilzomib + alkylator^c
 - Carfilzomib + monoclonal antibody (MMY1001)^d
- Is retreatment with bortezomib an option?
- Choice of PI should be driven by safety issues, patient preference (e.g., peripheral neuropathy history, or cardiac/renal issues)
- Consider for ‘aggressive relapse’ – proteasome inhibitors tend to work quickly

CANDOR trial: Dara-Kd vs Kd in RRMM



Weekly carfilzomib – ARROW trial

Arm A: Once-weekly carfilzomib + dex

(30 min infusion of K)

Carfilzomib 20 mg/m² IV D1 (Cycle 1)
 Carfilzomib 70 mg/m² IV D8, 15 (Cycle 1), D1, 8, 15 (Cycle 2+)
 Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
 Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

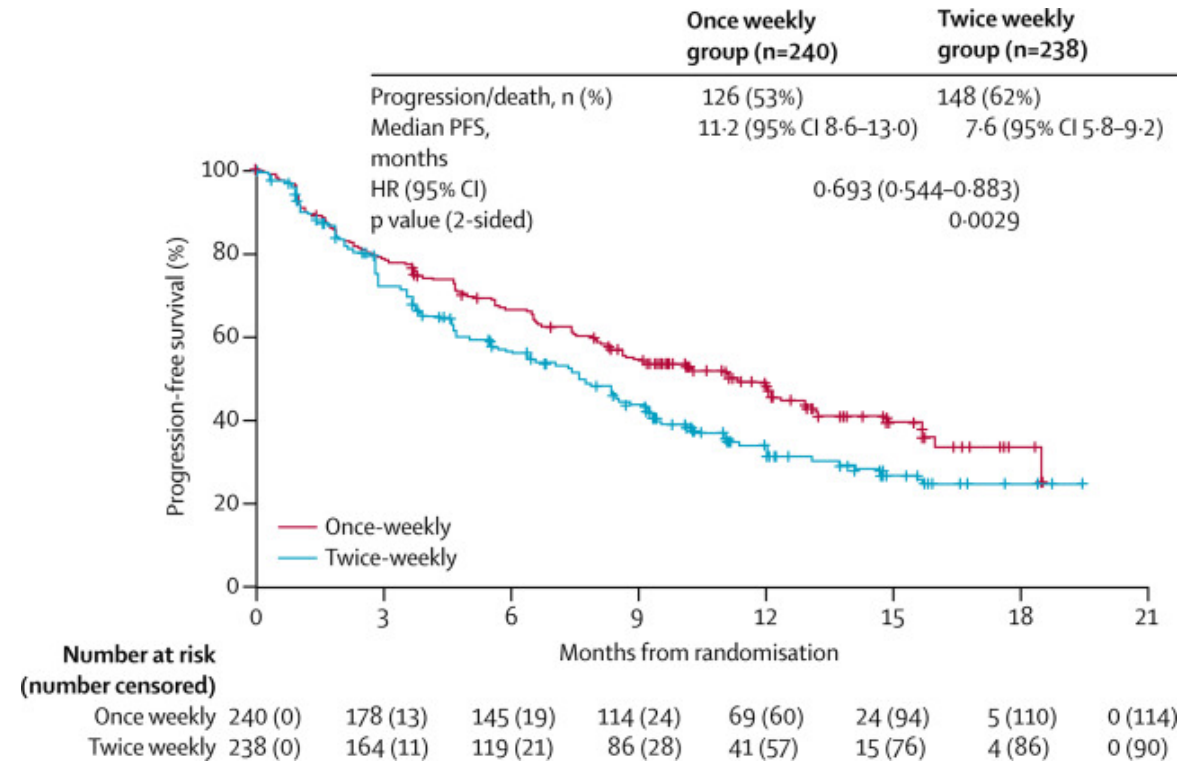
28-day cycles

Arm B: Twice-weekly carfilzomib + dex

(10 min infusion of K)

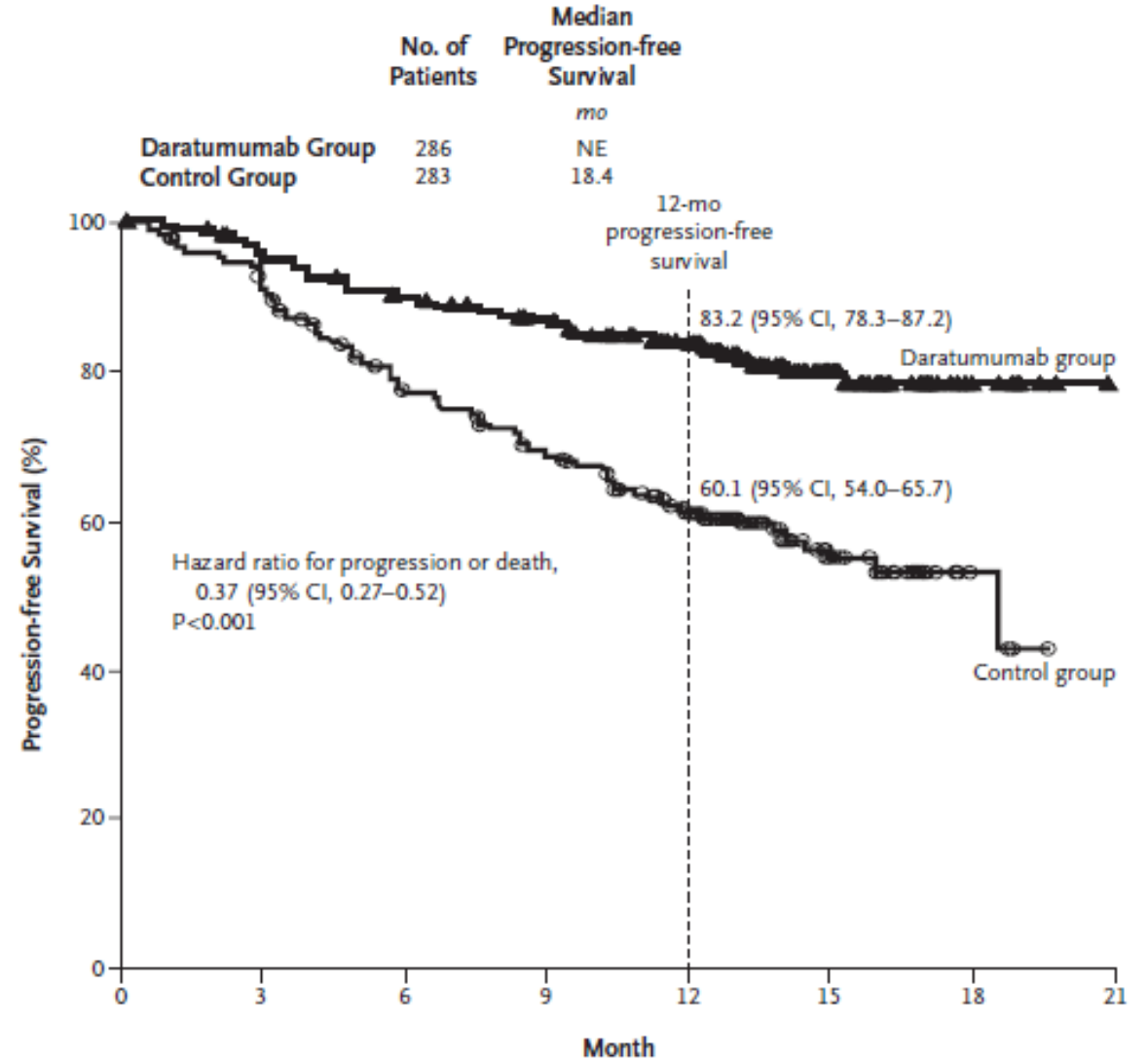
Carfilzomib 20 mg/m² IV D1, 2 (Cycle 1)
 Carfilzomib 27 mg/m² IV D8, 9, 15, 16 (Cycle 1), D1, 2, 8, 9, 15, 16 (Cycle 2+)
 Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
 Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

Primary end point: PFS



Daratumumab for RRMM

- Daratumumab, lenalidomide, and dexamethasone
 - POLLUX Trial, NEJM 2016^a
- Daratumumab, bortezomib, dexamethasone
 - CASTOR Trial, NEJM 2016^b
- Daratumumab, pomalidomide, dexamethasone
 - EQUULEUS, Blood 2017^c
- Daratumumab and dexamethasone
 - SIRIUS Trial, Blood 2016^d



a. Dimopoulos et al, NEJM 2016 Oct 6;275(14):1319-1331

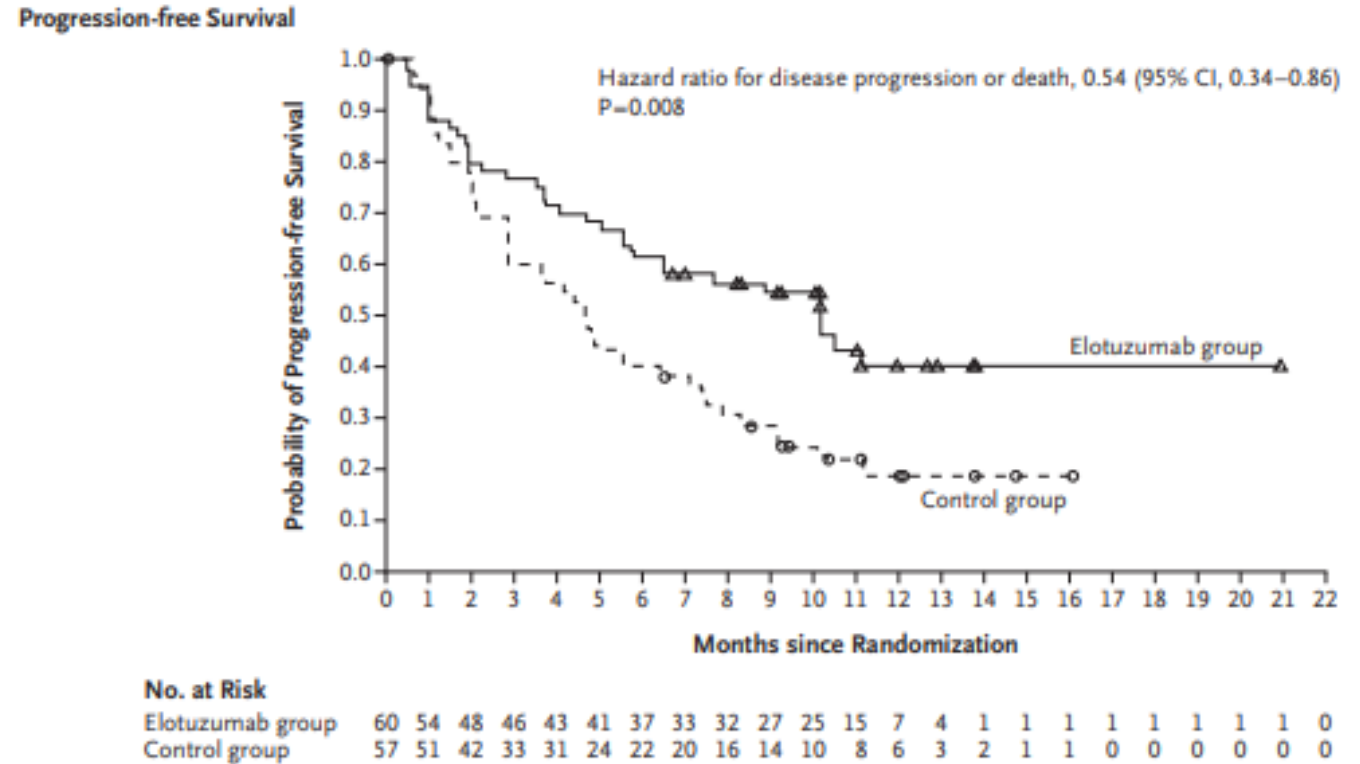
b. Palumbo et al, NEJM 2016 Aug 25;375(8):754-66

c. Chari A et al, Blood 2017 Aug 24;130(8):974-981

d. Lonial S et al, Lancet 2016 Apr 9;387(10027):1551-60

Elotuzumab/IMiD for RRMM

- Important – Elotuzumab has no single agent activity
- SLAMF7 Monoclonal Antibody
- ELOQUENT-2 Trial: Elotuzumab, lenalidomide, dexamethasone^a
- ELOQUENT-3 Trial: Elotuzumab, pomalidomide, dexamethasone^b

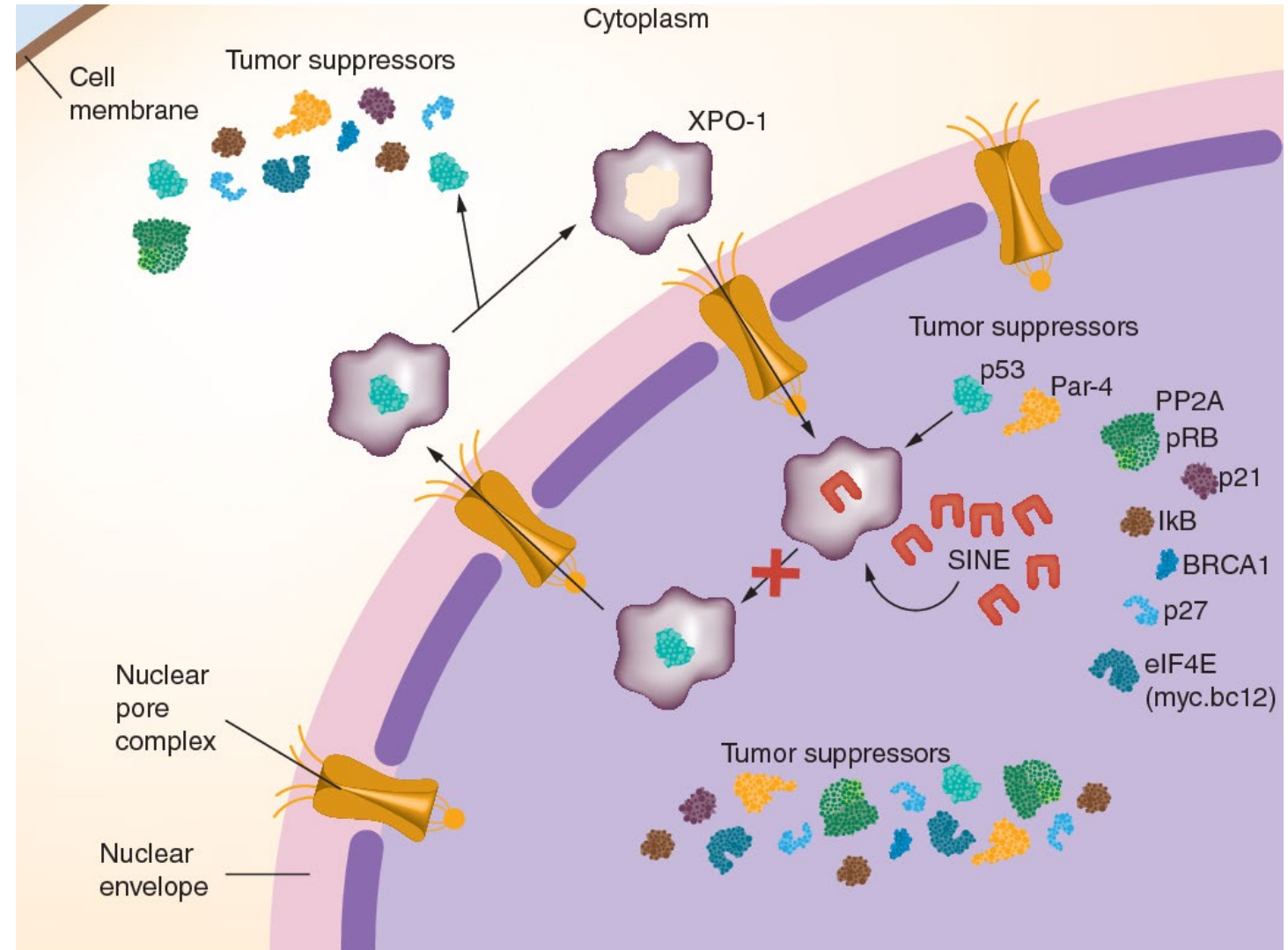


a. Lonial S et al, NEJM 2015 Aug 13;373(7):621-31

b. Dimopoulos et al, NEJM 2018 Nov 8;379(19):1811-1822

Selinexor: First in class, oral Selective Inhibitor of Nuclear Export (SINE)¹⁻³

- Exportin 1 (XPO1): major nuclear export protein for:
 - Tumor suppressor proteins, Glucocorticoid receptor, oncoprotein mRNAs
- XPO1 – highly overexpressed in MM; correlate with poor prognosis, drug resistance

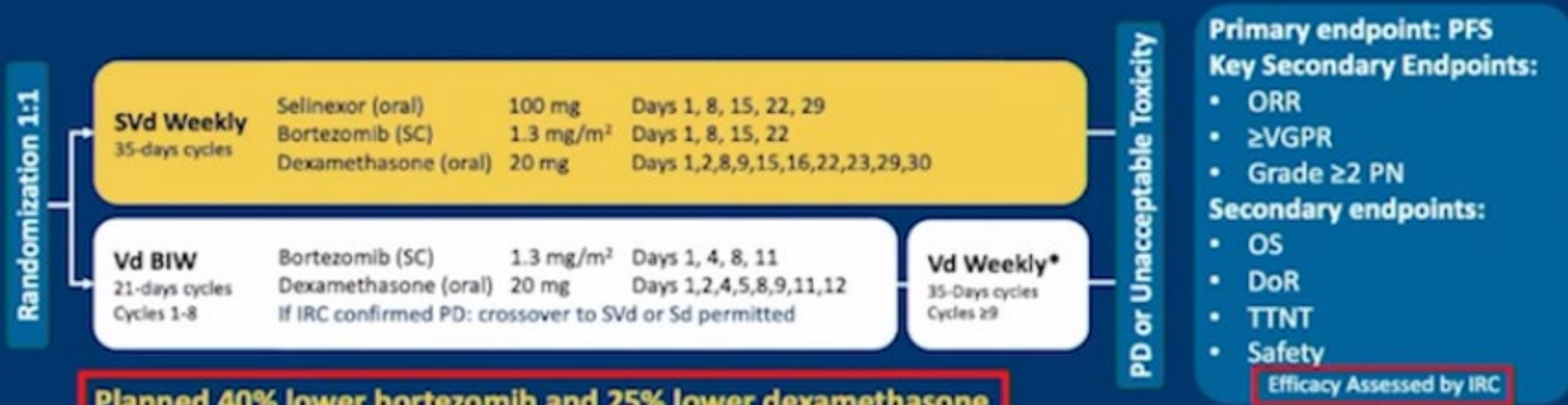


- a. Schmidt et al, Leukemia, 2013
- b. Tai et al, Leukemia 2013
- c. Argueta et al, Oncotarget 2018
- d. Talati et al, Int J Hematologic Onc 2018

Selinexor: Phase 2B STORM trial

- STORM Trial: Selinexor 80 mg and Dexamethasone 20 mg twice weekly
- Population: PI/IMiD and daratumumab resistant
- Overall response rate: 26.2%
 - sCR (2), VGPR (6), PR (24)
- Median PFS 3.7 mos (5.3 mos if \geq PR), median OS of 8.6 months
- FDA Approval 7/2019 for RRMM

BOSTON Trial: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients with Multiple Myeloma who Had Received 1-3 Prior Therapies



Planned 40% lower bortezomib and 25% lower dexamethasone dose at 24 weeks (8 cycles) in SVd arm vs. Vd arm

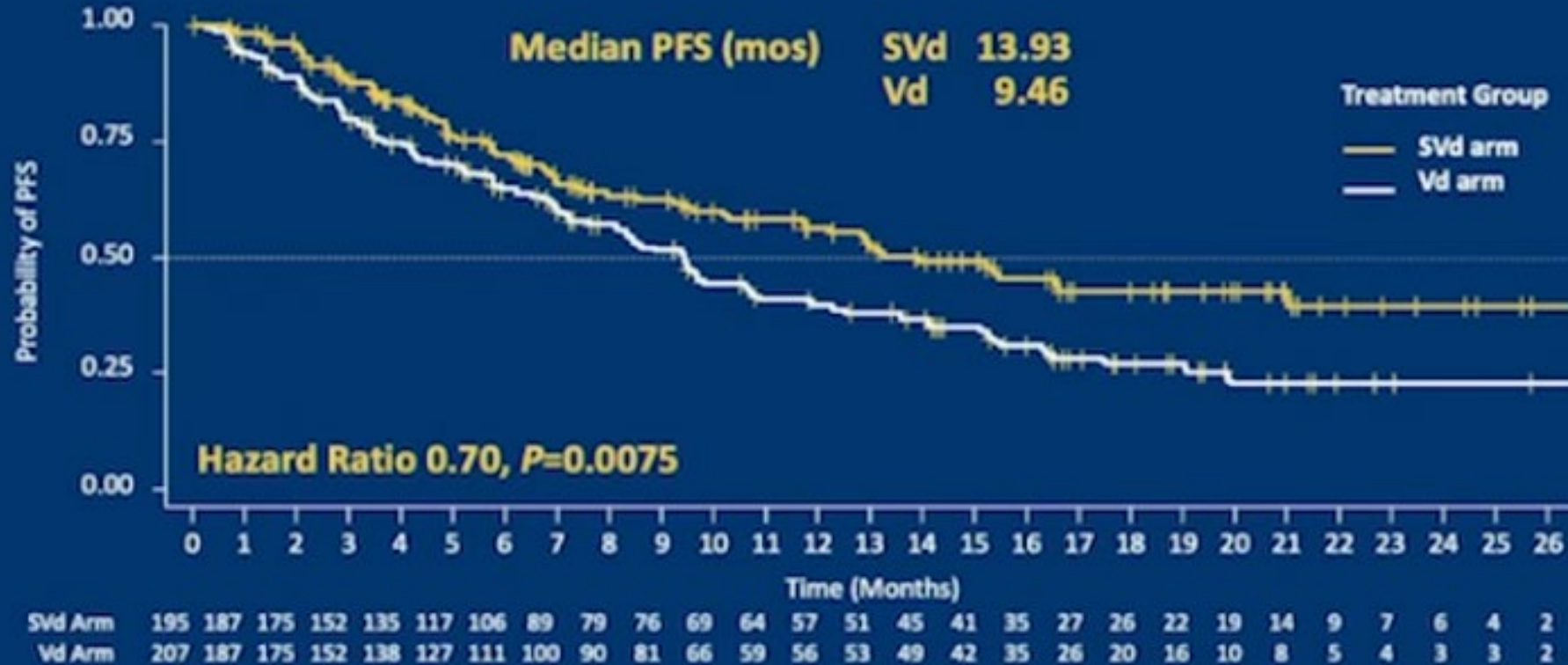
Stratification : Prior Proteasome Inhibitor (PI) therapies (Yes vs No)
Number of prior anti-MM regimens (1 vs >1)
R-ISS stage at study entry (Stage III vs Stage I/II)

SHT-3 prophylactic recommended in SVd arm

MM = Multiple Myeloma, PD = Progressive Disease, ORR = Overall Response Rate, CR = Complete Response, sCR = Stringent Complete Response, VGPR = Very Good Partial Response, PR = Partial Response, PN = Peripheral Neuropathy, PFS = Progression-Free Survival, OS = Overall Survival, DoR = Duration of Response, TTNT: Time to Next Therapy, IRC = Independent Review Committee, IMWG = International Myeloma Working Group. PFS defined as: Time from date of randomization until the first date of progressive disease, per IMWG response criteria, or death due to any cause, whichever occurred first, as assessed by IRC. ORR: Any response ≥PR (i.e., PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria (Durie et al. Lancet Oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments. * Vd weekly dosing and schedule for cycles 9 as per SVd arm description.

BOSTON Trial: PFS significantly longer with SVd compared to Vd

Early and Sustained PFS benefit (assessed by IRC)

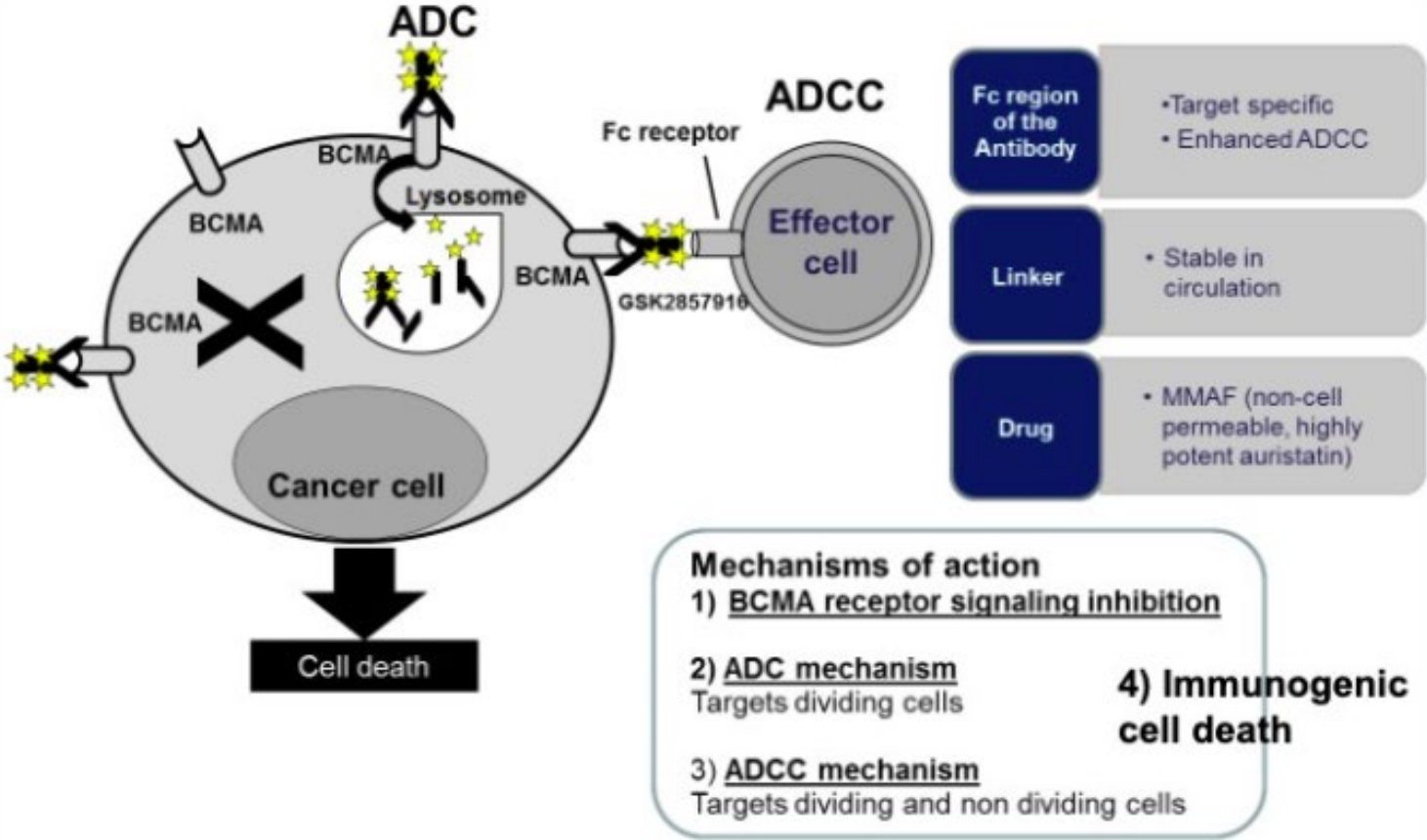


Intention-to-treat (ITT) population N=402, Data cut-off February 18, 2020
 *95% Hazard Ratio 95% CI=0.53-0.93 one-sided P value

Median follow-up 13.2 and 16.5 months in SVd and Vd arms respectively

Belantamab mafodotin: First in class, BCMA antibody-drug conjugate

- B-cell maturation antigen (BCMA) is a cell-surface protein expressed on myeloma cells
- Binds to BCMA, is internalized and releases a cytotoxic payload (potent microtubule disruptor)



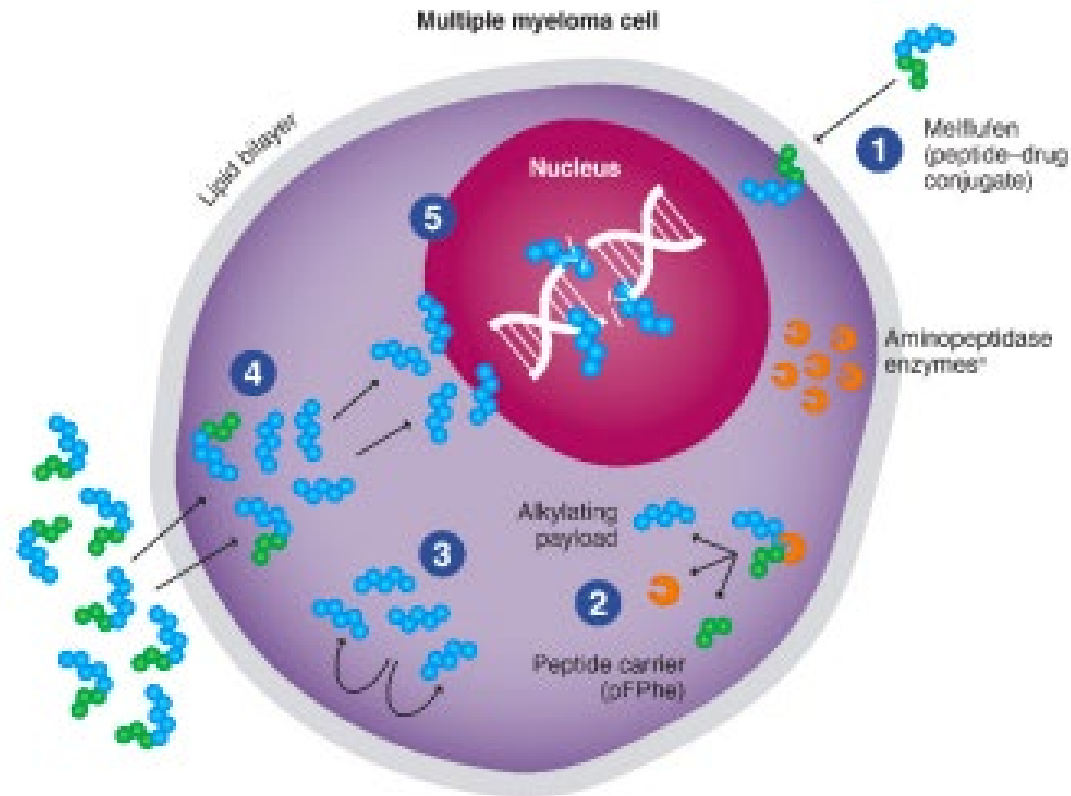
ADC, antibody-dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B cell maturation antigen; MMAF, monomethyl auristatin-F.

Belantamab mafodotin: Phase 2 DREAMM-2 trial

- DREAMM-2 Trial: Randomized to belantamab 2.5 mg/kg every 21 days vs 3.4 mg/kg every 21 days
- Population: PI/IMiD and CD38 antibody resistant
- Overall response rate: 31%; 12% had VGPR or better
- Median PFS 2.8 mos, median OS of 13.7 months
- FDA Approval 8/2020 for RRMM
 - REMS to manage the risk of ocular toxicity

Melflufen: First in class, peptide-drug conjugate

- Melflufen is highly lipophilic
- Inside the cell releases its hydrophilic alkylator payloads via intracellular peptidases

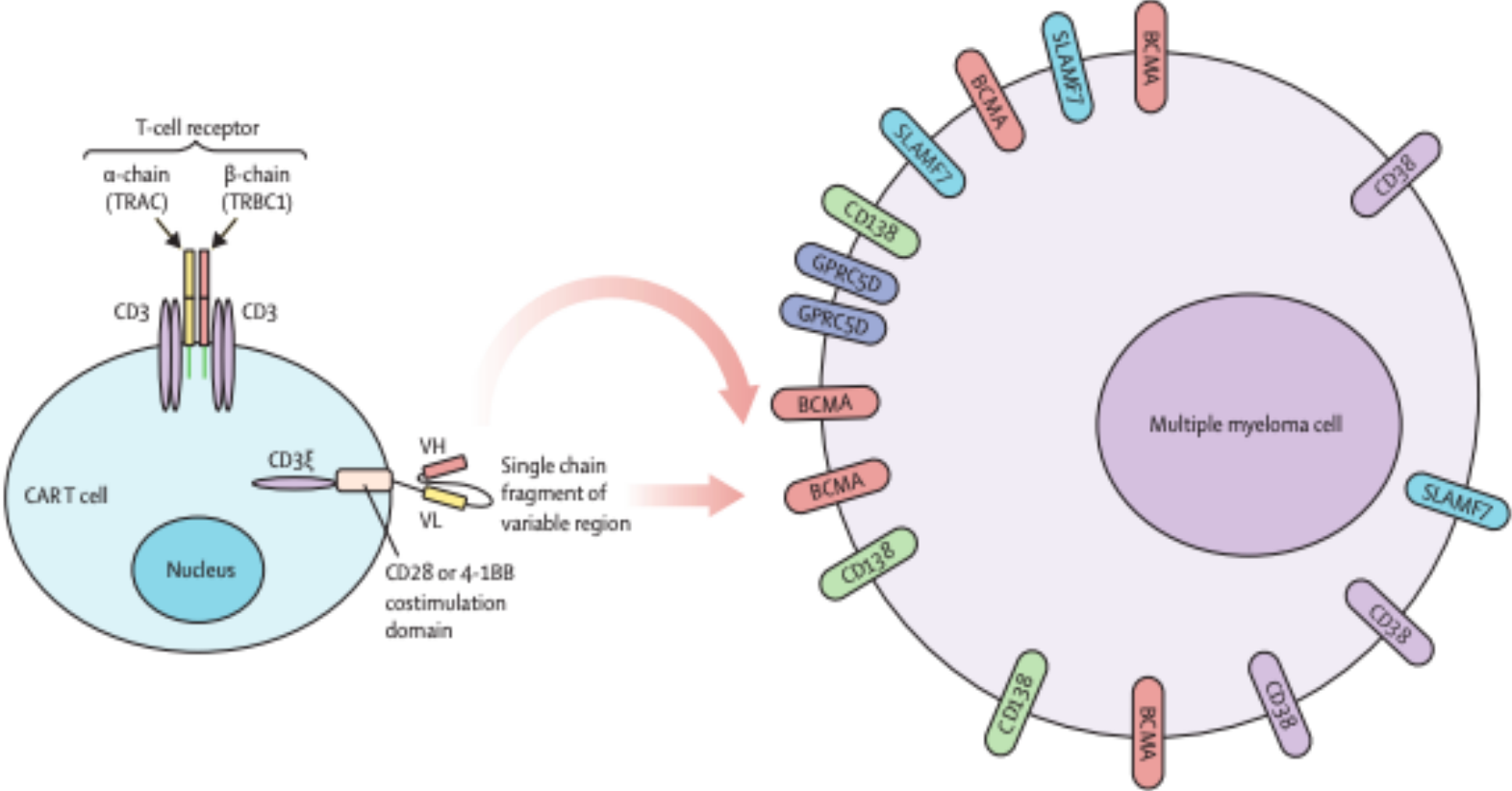


- 1** Melflufen (melphalan flufenamide) is highly lipophilic and readily diffuses through the cell membrane
- 2** Once inside the myeloma cell, melflufen is cleaved by aminopeptidases to release the alkylating payload
- 3** The hydrophilic alkylating payload remains entrapped within the cell
- 4** Increased diffusion of melflufen into the cell is driven by a high concentration gradient between the outside environment and the inside of the cell
- 5** Within the nucleus, the alkylating payload induces DNA damage resulting in cell death

Melflufen: Phase 2 HORIZON trial

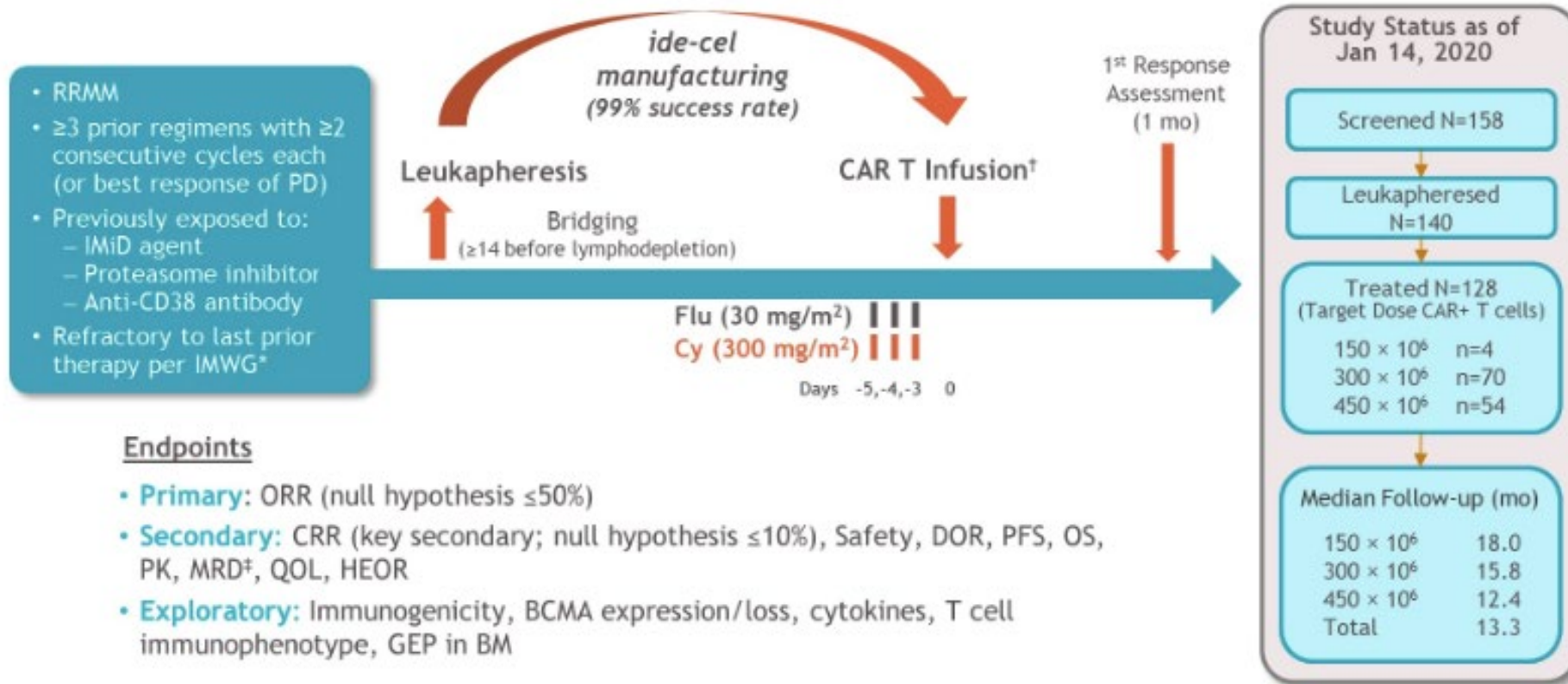
- HORIZON Trial: Melflufen 40 mg IV on day 1 of 28-day cycle plus once weekly 20-40 mg dexamethasone
- Population: Pomalidomide and/or CD38 antibody refractory
- Overall response rate: 29%; 26% in triple-class-refractory patients
- Median PFS 4.2 mos, median OS of 11.6 months
- FDA Approval 2/2021 for RRMM

Idecabtagene vicleucel: BCMA-directed chimeric antigen receptor (CAR) T-cell therapy



Idecabtagene vicleucel: Phase 2 KarMMA trial

Phase II Pivotal KarMMA Study



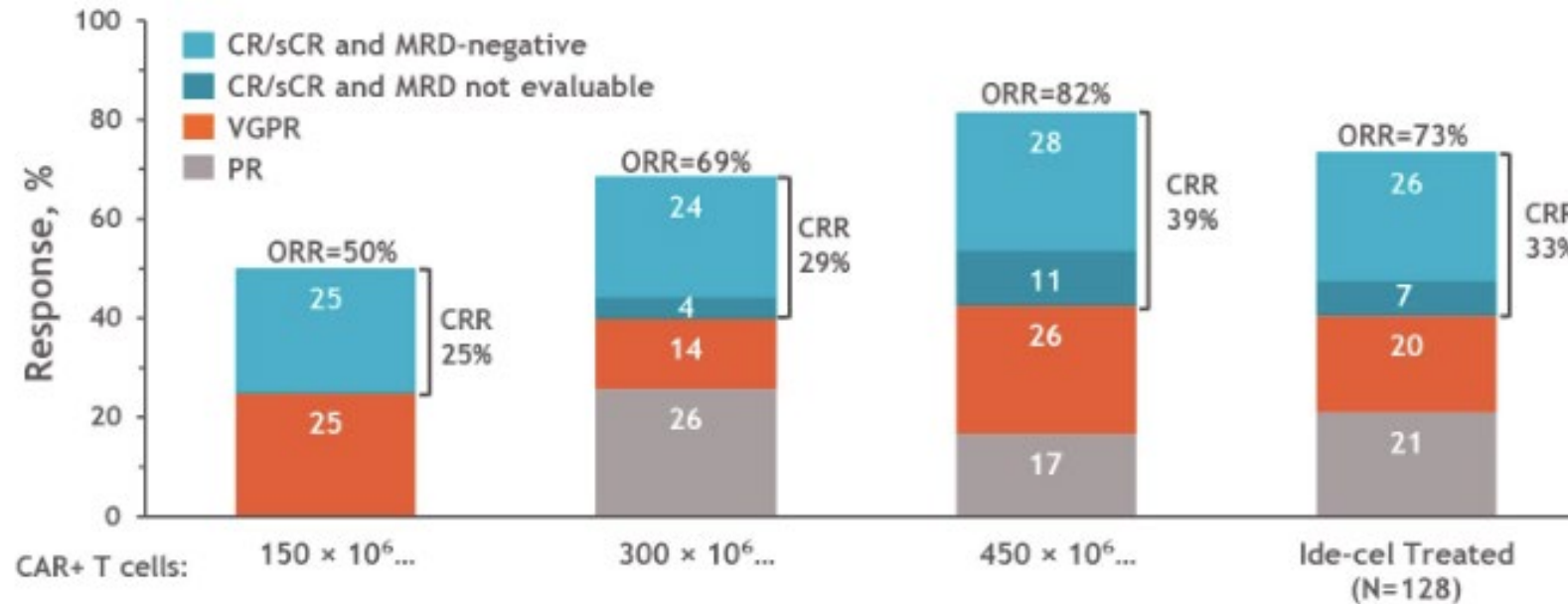
CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.
 *Defined as documented disease progression during or within 60 d from last dose of prior anti-myeloma regimen. †Patients were required to be hospitalized for 14 d post-infusion. Ide-cel retreatment was allowed at disease progression for best response of at least stable disease. ‡By next-generation sequencing.

EudraCT: 2017-002245-29
 ClinicalTrials.gov: NCT03361748

Idecabtagene vicleucel: Phase 2 KarMMA trial



Best Overall Response



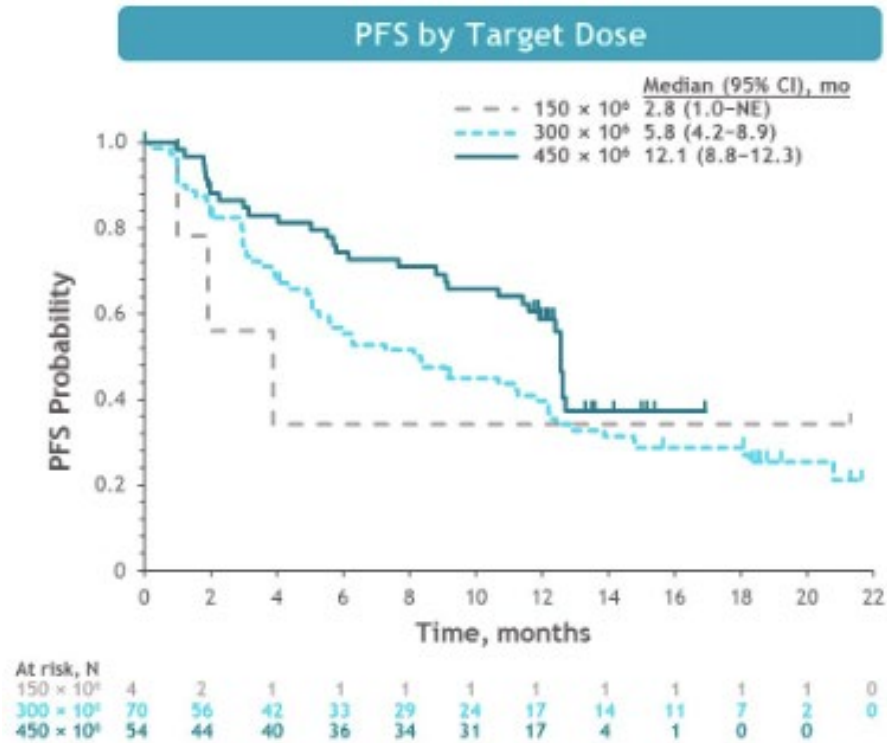
- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel treated population
 - ORR of **73%** (95% CI, 65.8–81.1; $P < 0.0001^*$)
 - CRR (CR/sCR) of **33%** (95% CI, 24.7–40.9; $P < 0.0001^*$)
- Median time to first response of 1.0 mo (range, 0.5–8.8); median time to CR of 2.8 mo (range, 1.0–11.8)
- Median follow-up of 13.3 mo across target dose levels

Data cutoff: 14 Jan 2020. MRD-negative defined as $< 10^{-5}$ nucleated cells by next generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered. Values may not add up due to rounding. CR/sCR, complete response/stringent CR; CRR, CR rate; MRD, minimal residual disease; ORR, overall response rate (±PR); PR, partial response; VGPR, very good PR. *P value at the primary data cutoff with same ORR and 95% CI.

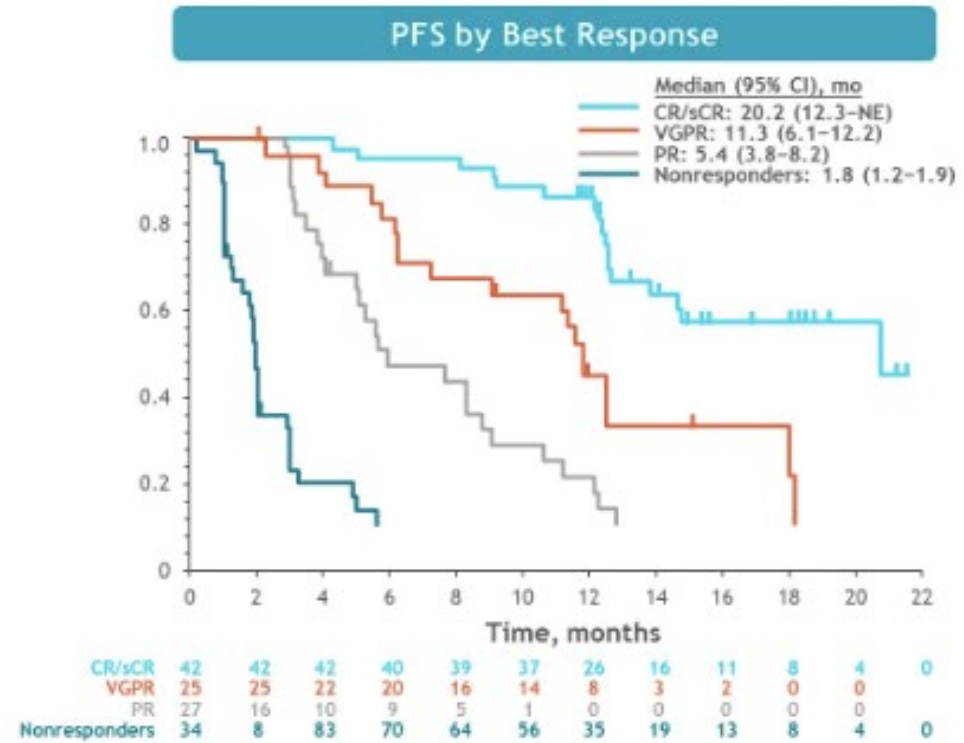
Idecabtagene vicleucel: Phase 2 KarMMA trial



Progression-Free Survival



- PFS increased with higher target dose; median PFS was 12 mo at 450 × 10⁶ CAR+ T cells

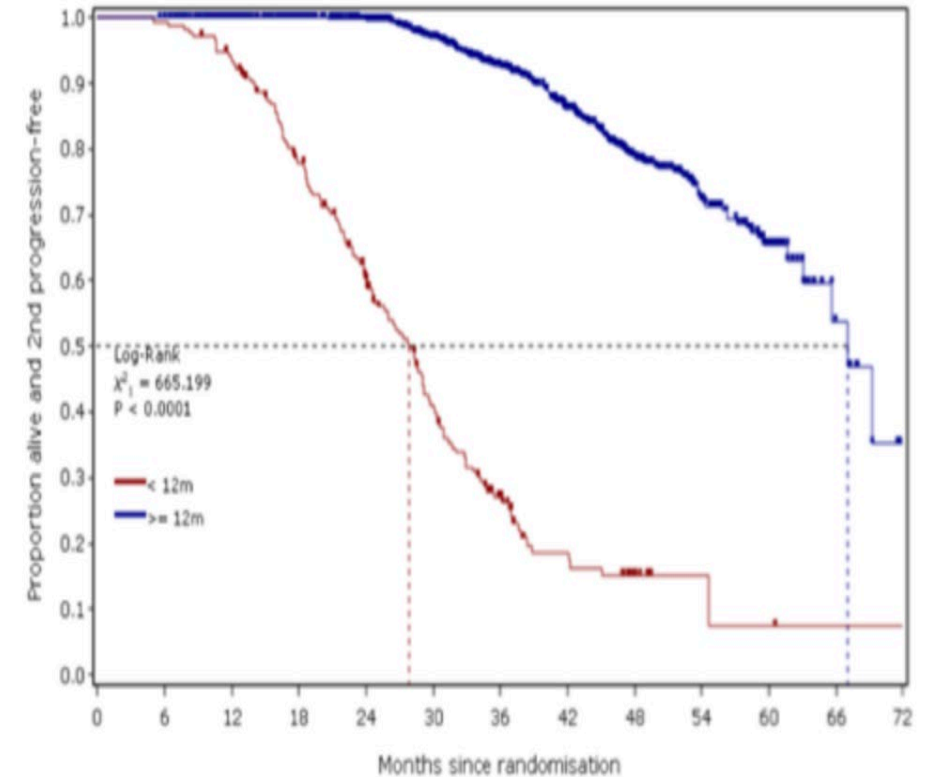


- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

*FDA Approval 3/2021 for RRMM

Type and timing of MM relapse is important

- Biochemical (i.e., rise in M protein or serum free light chains), vs clinical (i.e., new onset CRAB symptoms or extramedullary disease)
- Timing of relapse - example: relapse post autologous
 - In MRC IX Trial: Relapse at < 12 months post autologous stem cell transplant associated with worse PFS^a



Number at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72
< 12m	178	177	165	130	93	57	30	16	8	2	1	0	0
>= 12m	1096	1095	1035	966	876	729	559	400	252	140	51	8	0

Using genetic changes to guide treatment choice

- High-risk myeloma: e.g., Del(17p), t(4;14), t(14;16), t(14;20), 1q+/1p-, continuous therapy, 3 drug regimens.
- t(11;14) – sensitivity to Venetoclax, a BCL2 inhibitor
- Plasma cell leukemia – unique disease biology. Anthracycline based regimens (e.g., VTD PACE, Hyper CVAD)

What about late relapse after transplant?

- Current state of underlying organ function/frailty index?
- Stem cells still stored? (viability has been good at our center up to 10 years and beyond)
- Relapse on maintenance or not on maintenance?
- Age, willingness to undergo second transplant?

When to consider 2nd transplant as a treatment for RRMM

- A patient who previously underwent autologous transplantation may be eligible for a second transplant if the duration of remission from the first transplant was > 18-24 months (probably 3-4 years if on maintenance therapy)
- If no maintenance was received post transplant #1, then it should be considered strongly after transplant #2
- If initial therapy only included RVD and maintenance (no transplant), then autologous transplant should be **STRONGLY** considered as the next best therapy once in remission

Outcomes for Salvage Transplant in Relapsed MM

	Months from auto-SCT2, median (range)	
Time to progression after auto-SCT1 (N)	PFS	OS
<12 months (9)	5.6 (3–8)	12.6 (4–23)
<18 months (25)	7.1 (6–8)	19.4 (10–42)
<24 months (47)	7.3 (6–10)	22.7 (13–62)
<36 months (68)	7.6 (7–12)	30.5 (19–62)

Summary

- Upfront myeloma treatment
 - First decide if transplant eligible vs ineligible
 - 3-drugs are superior than 2; 4-drug combos are coming soon
- There are many options for treating RRMM = Personalization is key!
- Choose therapies based on prior sensitivity, disease status, toxicities, and general state of the patient (frail vs robust)
- Autologous transplantation should be considered in appropriate patients

Thank you – PATIENTS AND FAMILIES

- UW/FHCRC/SCCA Heme Malignancies and Plasma Cell Disorders
 - Ajay Gopal
 - Ed Libby
 - Leona Holmberg
 - Damien Green
 - Andrew Cowan
 - Mary Kwok
 - Teresa Hyun
 - David Coffey
 - Sherilyn Tuazon

