New Directions in Treating Multiple Myeloma (MM) in the Era of Novel Agents: A Clinical Perspective from Newly Diagnosed to Relapsed and Refractory MM; ASH 2017

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Disclosures

Research Funding

- Takeda
- Celgene

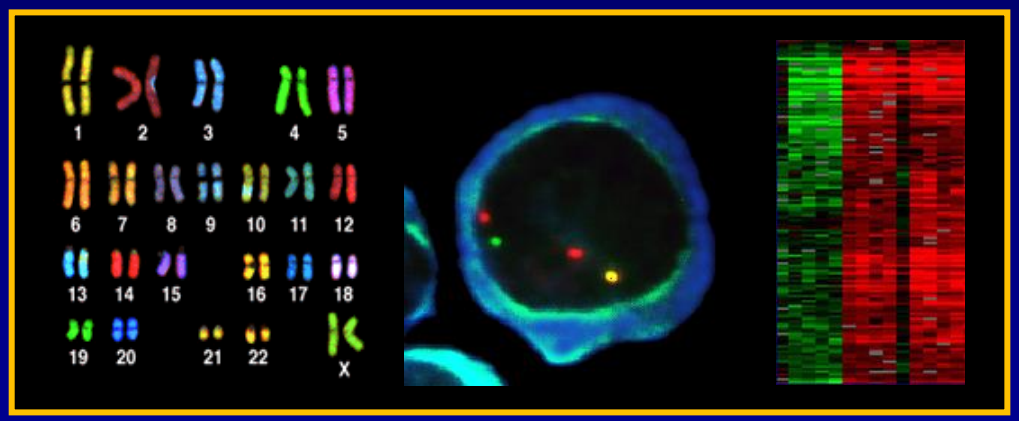
Disclosures

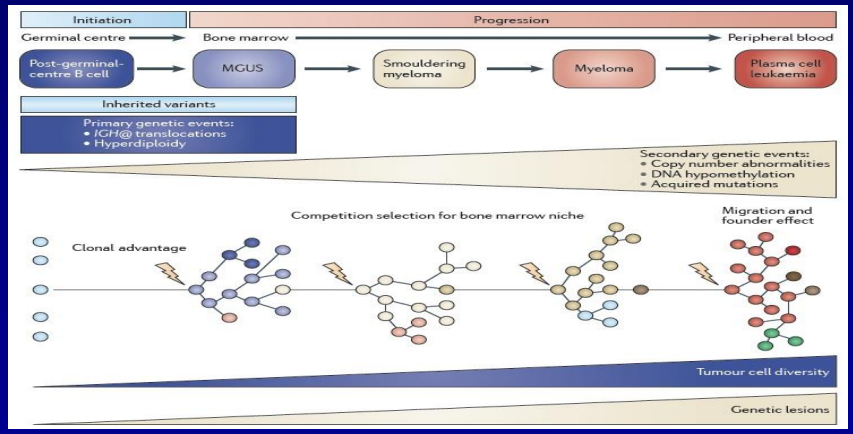
- Janssen
- Celgene
- Takeda

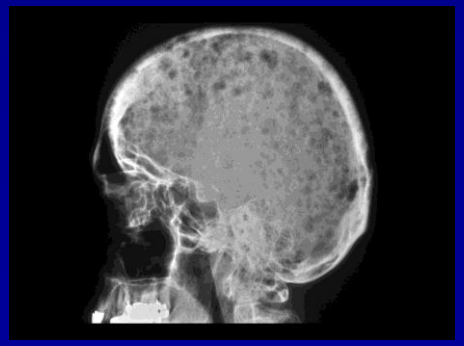
MULTIPLE MYELOMA
…not just one disease!

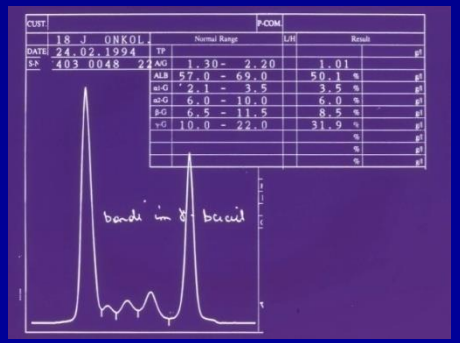
- Risk stratification, recognition of clonal heterogeneity
- Individualization of treatment, advent of novel therapies

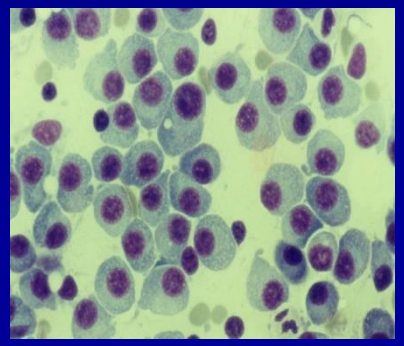
3 decades







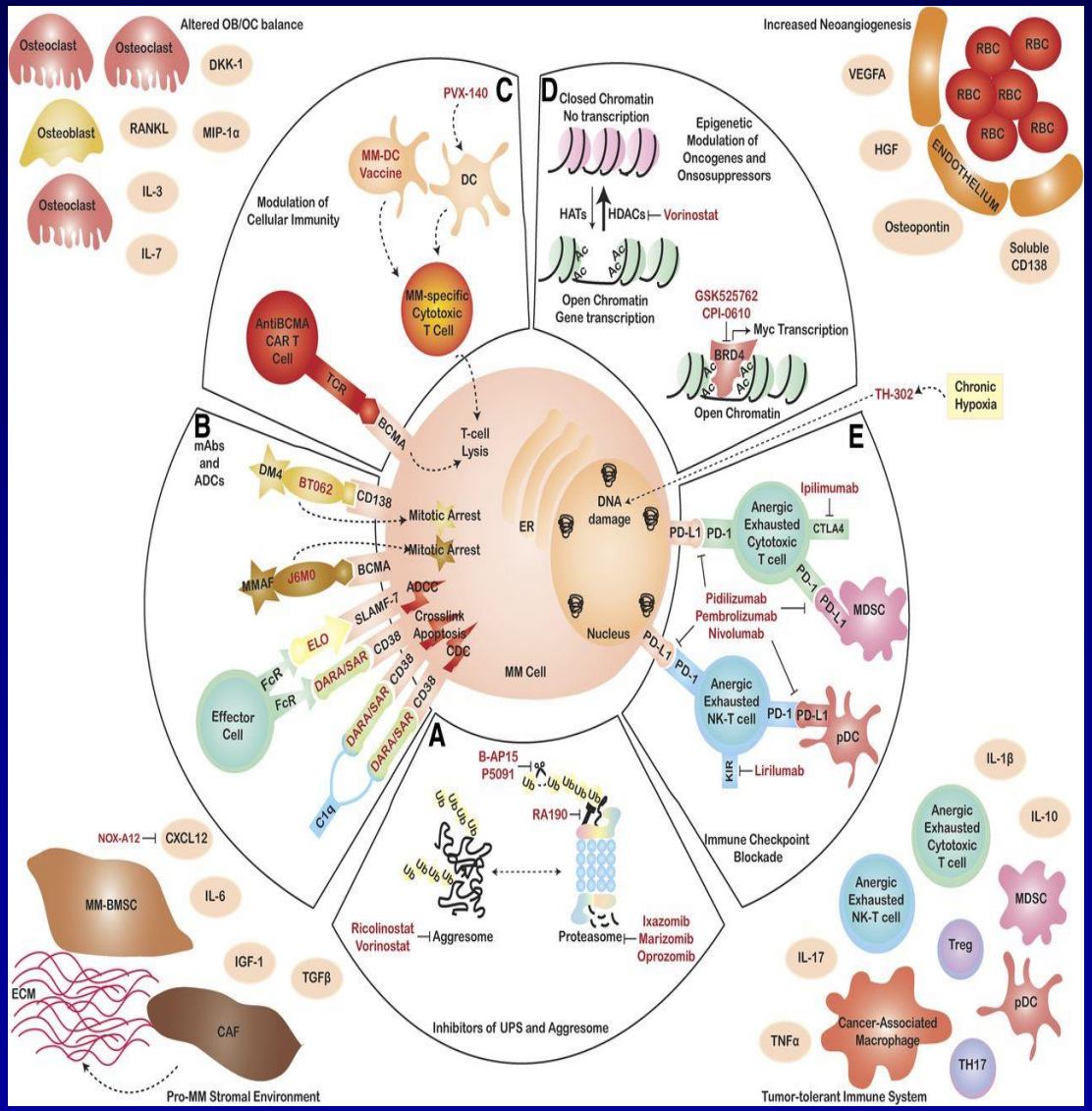




Drach J, ASH 2012

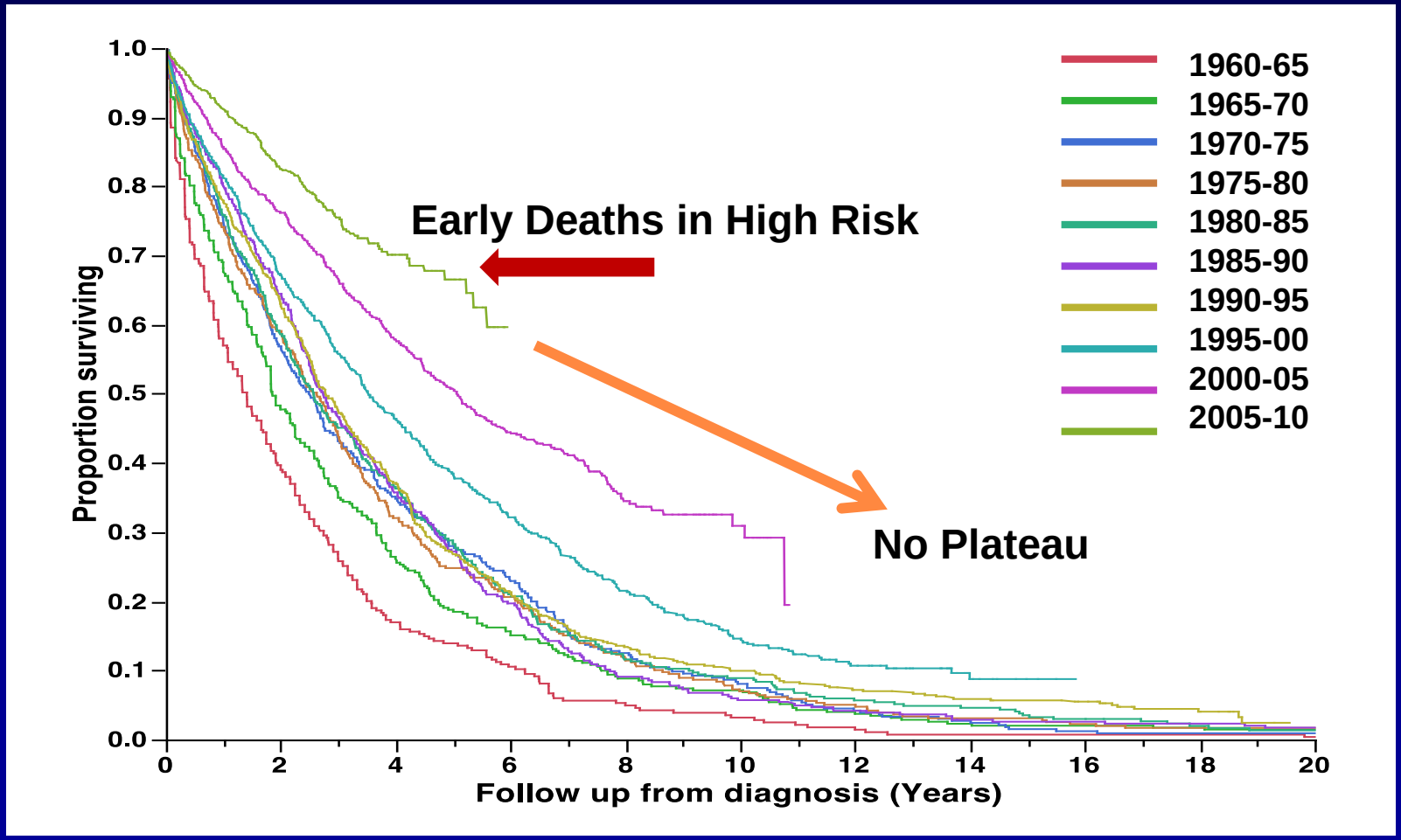
Morgan et al. *Nat Rev Cancer* 2012;12:335-348

Multimodality targeting of MM in the context of the BM microenvironment



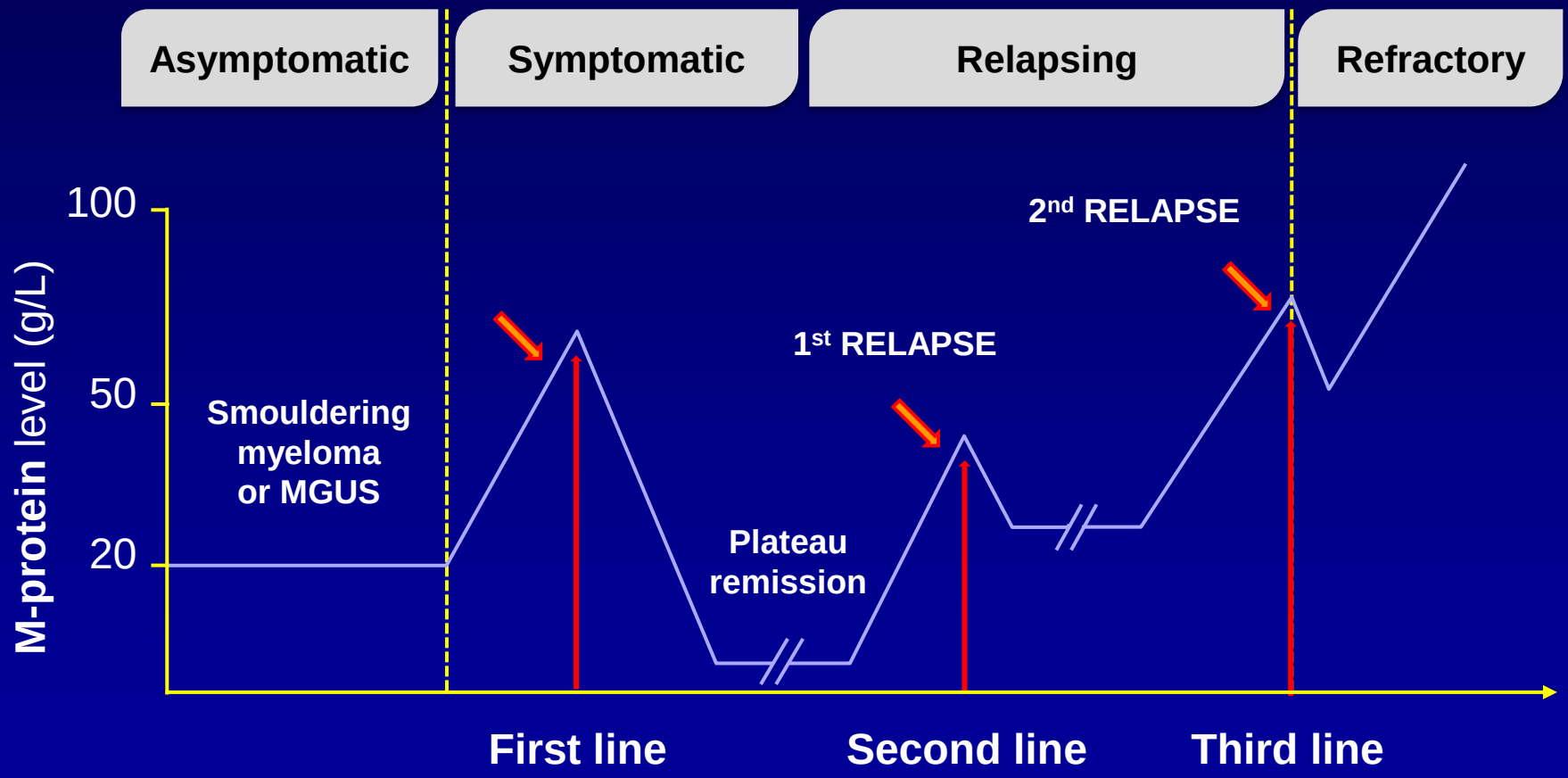
G. Bianchi, PG. Richardson and KC. Anderson, *Blood* 2015; 126:300-310.

Multiple Myeloma survival improving with new drugs: but all patients still relapse after IMiD and PI failure



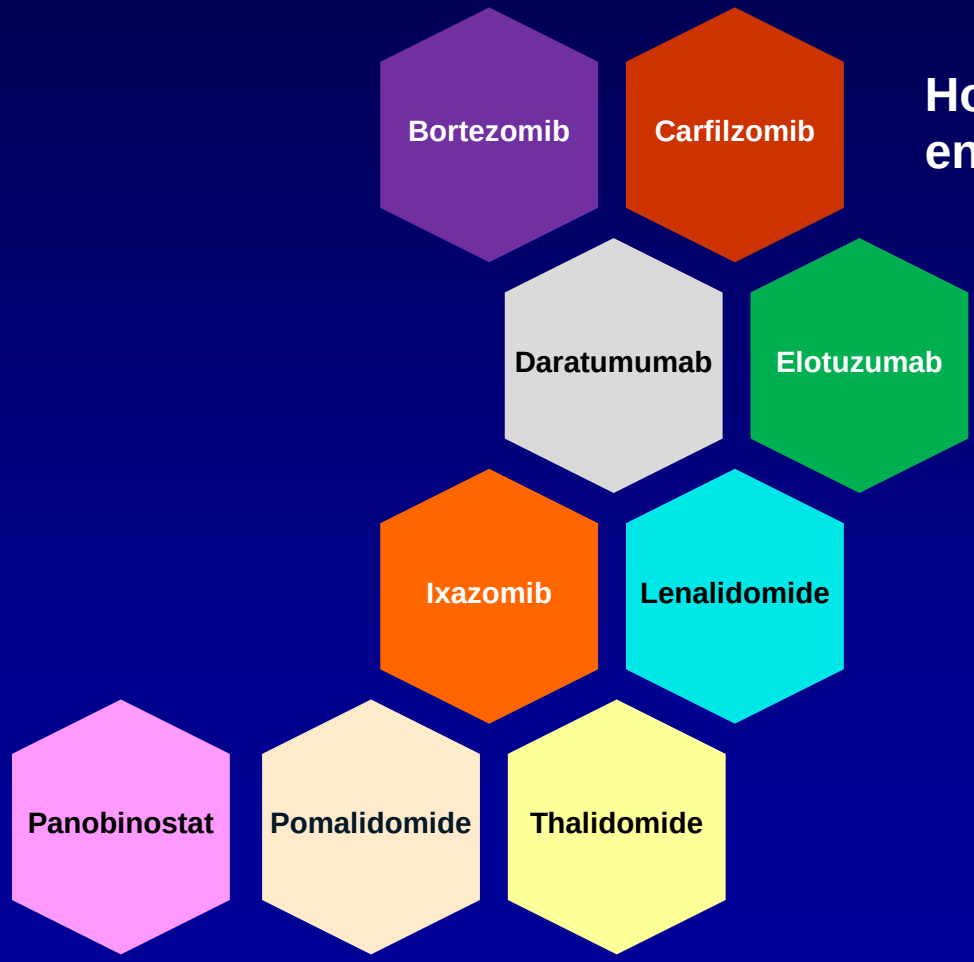
Adapted from Kumar SK, et al. *Leukemia.* 2014;28:1122-8.

MM is a Marathon, not a Sprint

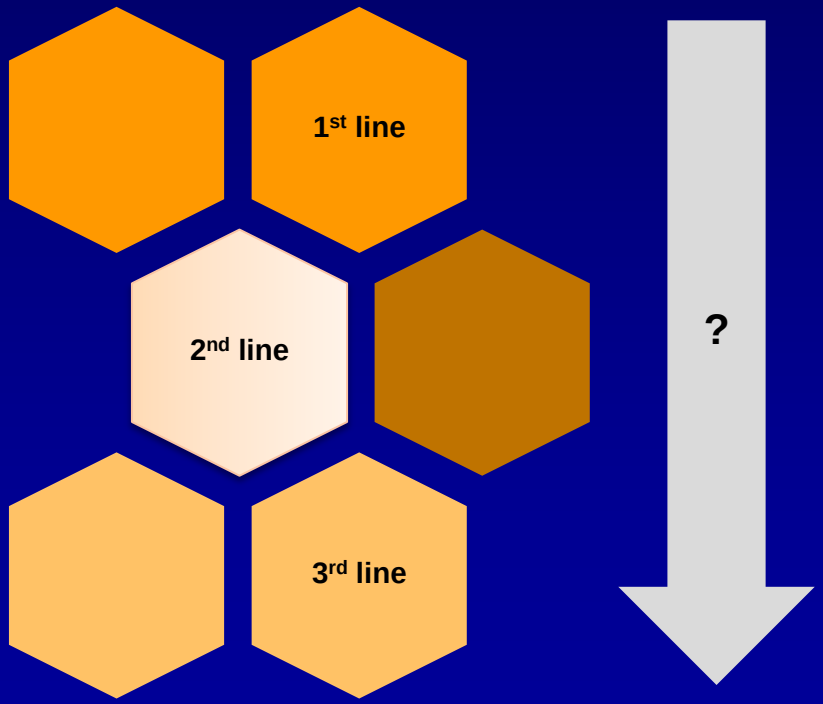


Adapted from Borrello I. *Leuk Res.* 2012;36 Suppl. 1:S3–12.

Multiple Options are now available to treat in NDMM and RR MM…



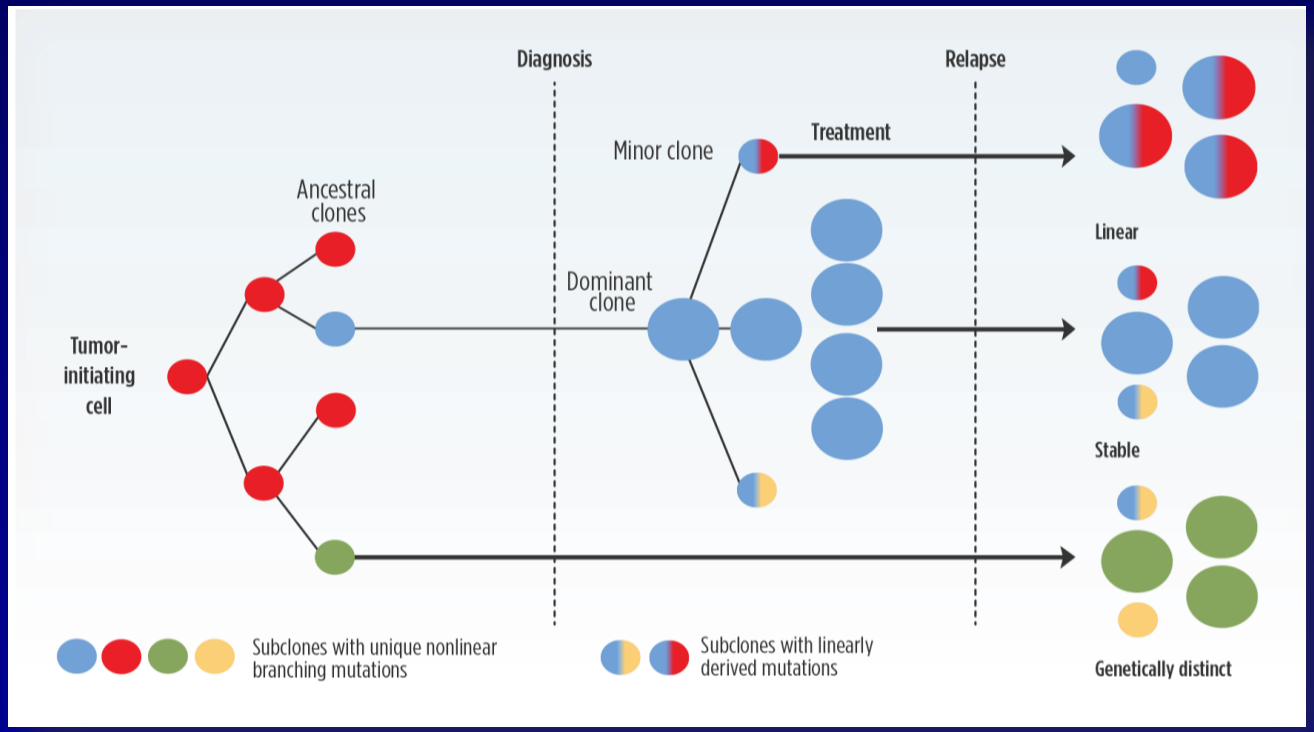
How do we sequence therapies to ensure the best outcomes for patients?



Adapted from Laubach JP et al, *Leukemia* 2016

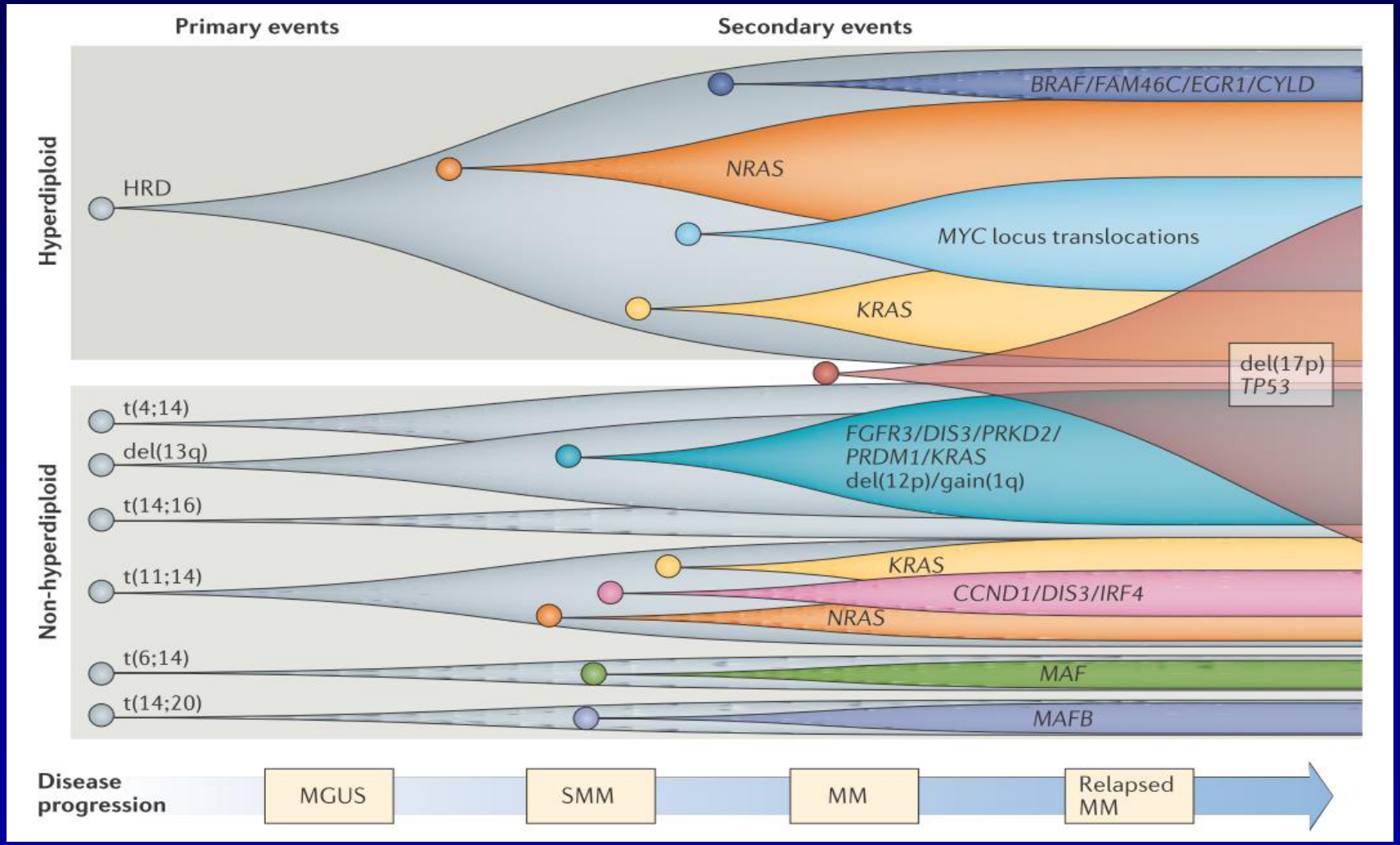
Multiple genetically distinct subclones are present at diagnosis[1-4]

- These evolve over time due to selective pressures from treatment and factors in the microenvironment[1,4]
- This clonal evolution can result in disease progression and treatment resistance[5]



1. Bahlis N et al. *Blood* 2012;120:927–28
2. Keats JJ et al. *Blood* 2012;120:1067–76
3. Bianchi G, Ghobrial IM. *Curr Cancer Ther Rev* 2014;10:70–9
4. Bolli N et al. *Nat Commun* 2014;5:2997
5. Brioli A et al. *Br J Haematol* 2014;165:441–54.

Co-occurrence of genomic events and clonal evolution during progression in MM



Manier S, et al. Nat Rev Clin Oncol. 2017;14:100-13.

Key Targets in MM 2017

Genomic abnormalities:

- Target and overcome mutations
- Critical Role of Combination and Continuous Therapy
- Evolving Position and Timing of ASCT

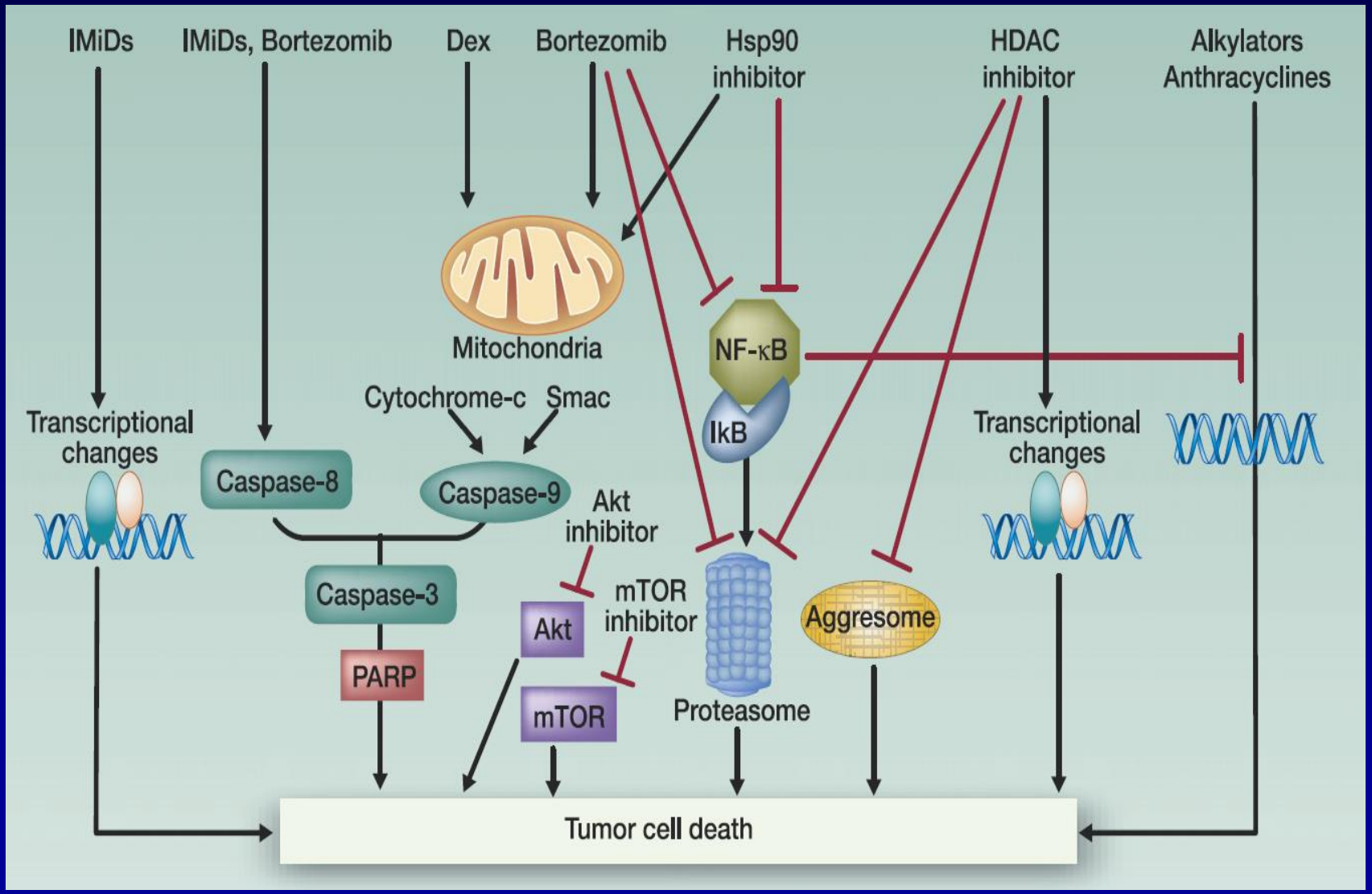
Excess Protein Production:

- Target Protein degradation

Immune Suppression:

- Restore anti-MM immunity

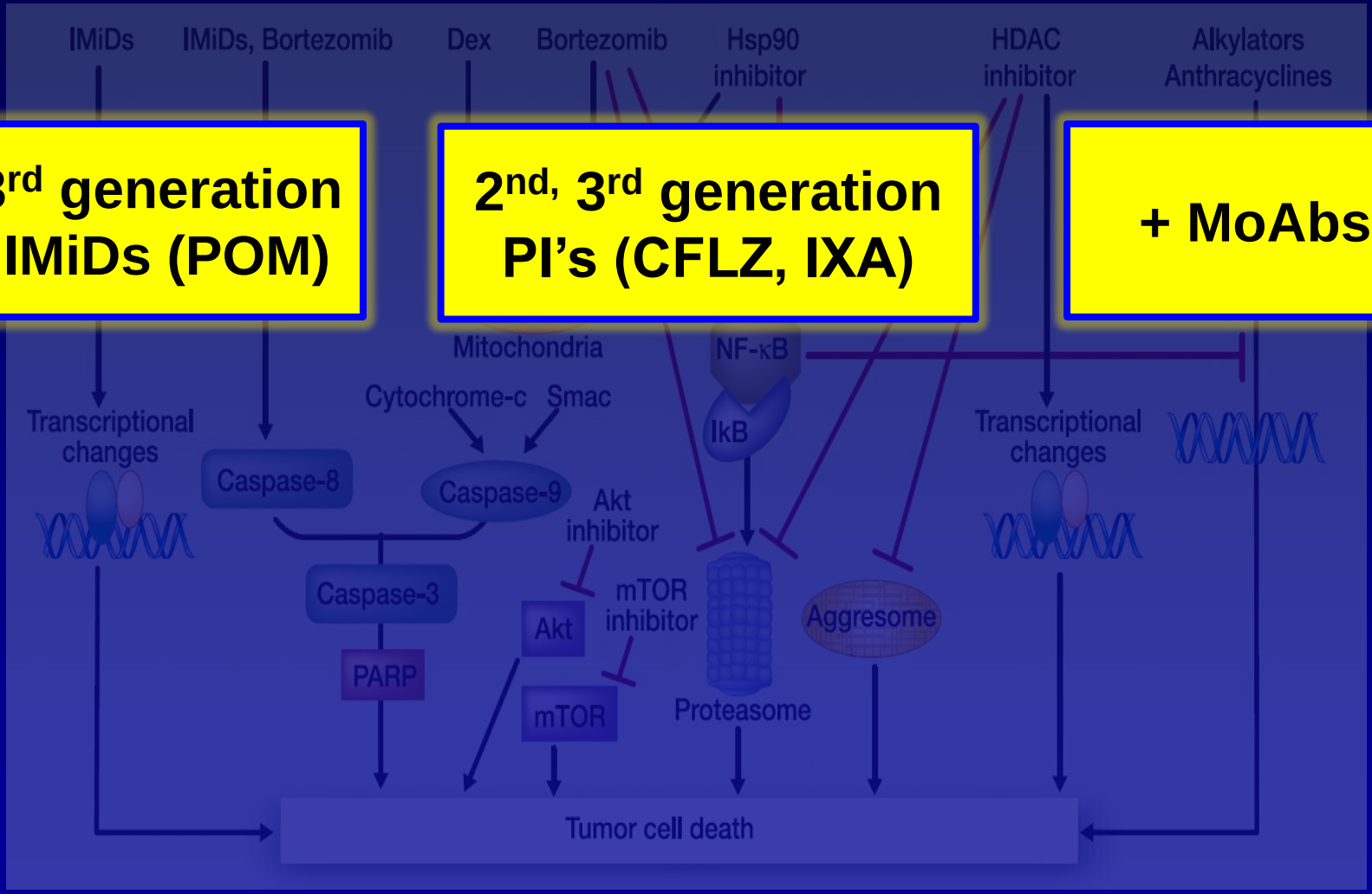
Rational combination strategies in MM



Clinical Cancer Research

Adapted from Lonial S, Mitsiades CS, Richardson PG. *Clin Cancer Res* 2011;17:1264-77.

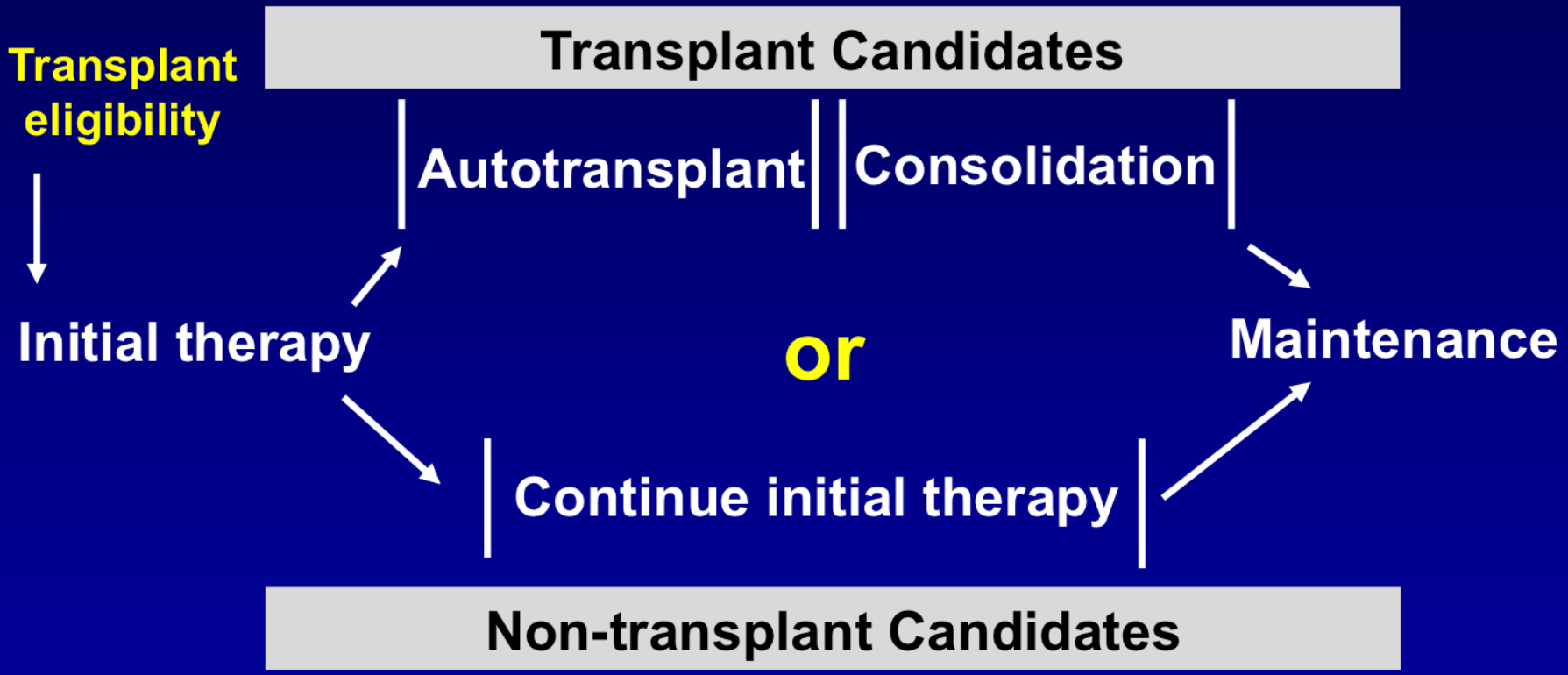
Rational combination strategies in MM



Clinical Cancer Research

Adapted from Lonial S, Mitsiades CS, Richardson PG. *Clin Cancer Res* 2011;17:1264-77.

Current Paradigm of Initial Treatment



Adapted from Ludwig H, et al. *Oncologist.* 2012;17:592-606.
Richardson P et al. *BJH* 2011;154:755-62.

Lenalidomide/Bortezomib-Based Rx in NDMM

Response	RVD[1] n = 66	RVDD[2] n = 72	VDCR[3] n = 48
CR + nCR	40% (57%)*	39%	40%
≥VGPR	67% (74%)*	67%	58%
≥PR	100%	96%	88%

*** Phase 2 Cohort (n=35)**

- **Active in pts with Adverse Cytogenetics**
- **Hematologic toxicity is more severe with addition of Chemo (Cy or doxorubicin)**
- **Risk of DVT does not appear to be increased over Lenalidomide/dex alone**
- **Risk of PN moderately increased over Bortezomib alone**
- **Generally otherwise well tolerated, although TRM seen with VDCR**

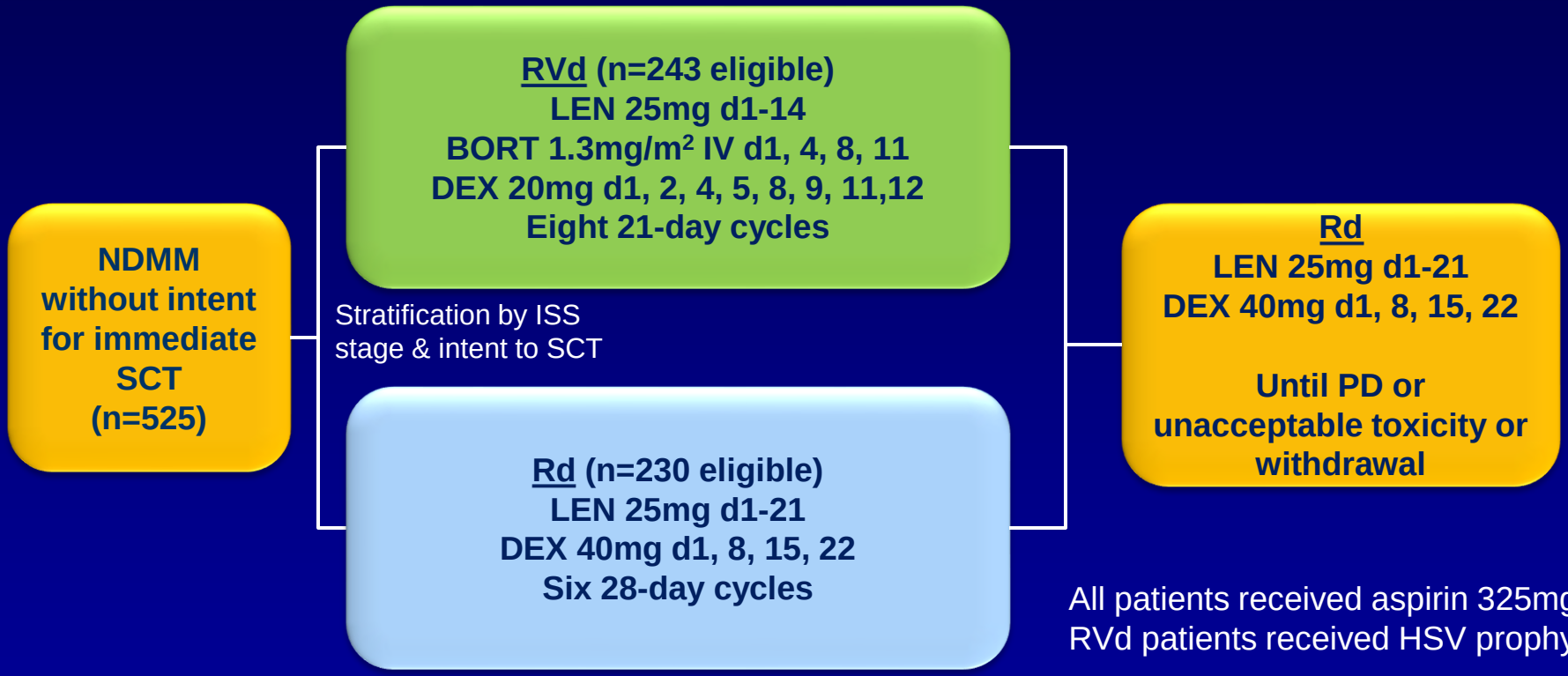
RVD: lenalidomide, bortezomib, dexamethasone; RVDD: RVD with pegylated liposomal doxorubicin; VDCR: VRD plus cyclophosphamide (wkly low dose dex with VRd, vs RVD)

1. Richardson PG, et al. *Blood.* 2010; 116:679-86.
2. Jakubowiak AJ, et al. *Blood*. 2011; 118:535-543.
3. Kumar S et al. *Blood* 2012; 119: 4375-4382.

SWOG S0777: Study Objective and Design

Objective: Ph III trial to compare efficacy & safety of Rd with RVd

Eligibility: ≥18 yrs, active MM, PS 0-3.



All patients received aspirin 325mg / day
RVd patients received HSV prophylaxis

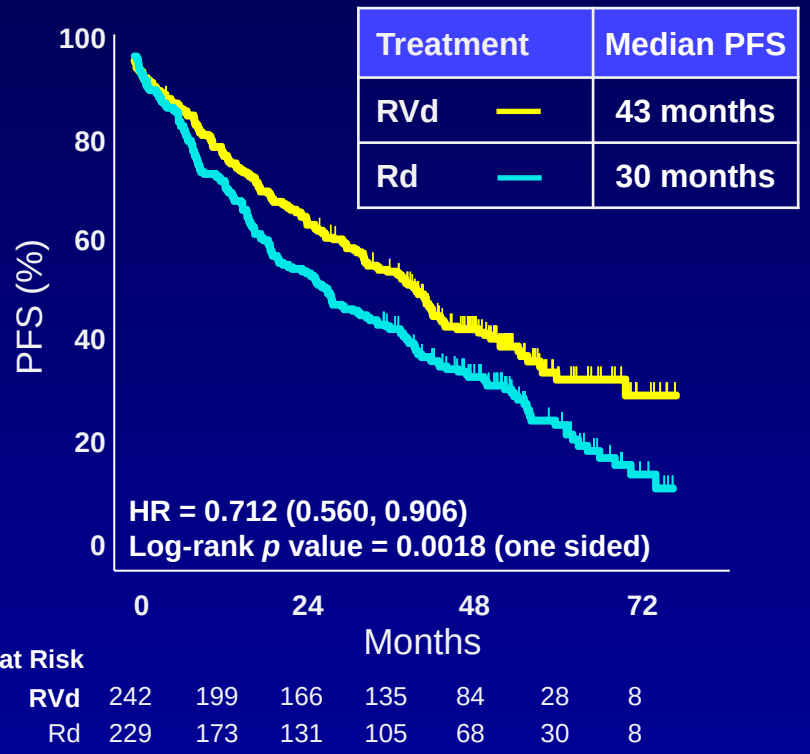
- **Primary Endpoint: PFS**
- **Secondary Endpoints: ORR, OS and Safety**

BORT, bortezomib; d, day; DEX, dexamethasone; HSV, herpes simplex virus; ISS, International Staging System; LEN, lenalidomide; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Ph, phase; PS, performance status; pt, patient; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide and low-dose dexamethasone; SCT, stem cell transplant; SWOG, Southwest Oncology Group.

Durie BGM et al. *Lancet.* 2017; 389: 519-527

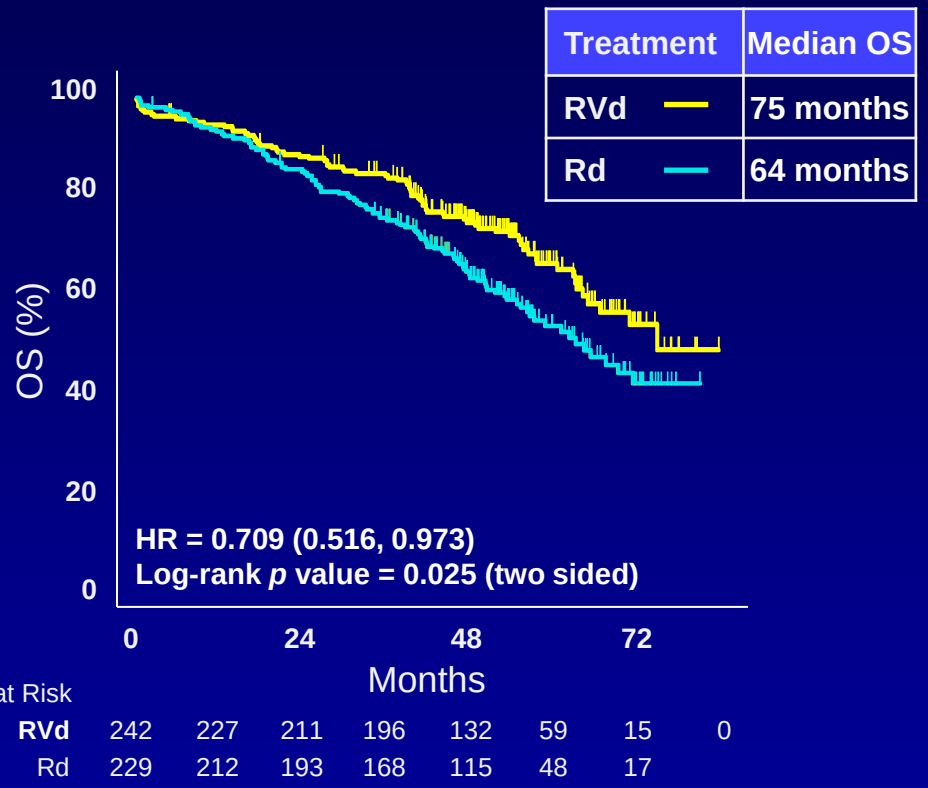
SWOG S0777: PFS and OS

Progression Free Survival



No. at Risk							
RVd	242	199	166	135	84	28	8
Rd	229	173	131	105	68	30	8

Overall Survival



No. at Risk								
RVd	242	227	211	196	132	59	15	0
Rd	229	212	193	168	115	48	17	

AE, adverse event; HR, hazard ratio; OS, overall survival; PFS progression free survival; Rd, lenalidomide plus low dose dexamethasone; RVd, lenalidomide, bortezomib and dexamethasone.

Durie BGM et al. *Lancet.* 2017; 389: 519-527

Novel Agent-based Induction Therapies
ASH 2017

	Thal-based	Len-based	Bort-Based	Bort+IMiD-based	New agents
2-drug combinations	TD	RD Rd	VD		
3-drug combinations	TAD CTD	RAD RCD BiRD	PAD VCD	VTD RVD	*KTD KRd **IRd
4-drug combinations				VTDC RVDC RVDD	***R2V2 PanRVD MoAbs

Thal = Thalidomide, Len = Lenalidomide, Bortz = Bortezomib
Cfz: carfilzomib, MoAbs – monoclonal antibodies, Pan: panobinostat
***R2V2: RVD + vorinostat
**IRd: lenalidomide, ixazomib (mln 9708), dex

Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients (pts) With Newly Diagnosed Multiple Myeloma (MMY1001): an Open-label, Phase 1b Study (updated ASH 2017)

Andrzej Jakubowiak,[1] Ajai Chari,[2] Sagar Lonial,[3] Brendan Weiss,[4] Raymond L. Comenzo,[5] Kaida Wu,[6] Nushmia Z. Khokhar,[6] Jianping Wang,[7] Parul Doshi,[6] Saad Z. Usmani[8]

[1]University of Chicago Medical Center, Chicago, IL; [2]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [3]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; [4]Abramson Cancer Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]Division of Hematology/Oncology, John C. Davis Myeloma and Amyloid Program, Tufts Medical Center, Boston, MA; [6]Janssen Research & Development, LLC, Spring House, PA, USA; [7]Janssen Research & Development, LLC, Raritan, NJ, USA; [8]Levine Cancer Institute/Carolinas HealthCare System, Charlotte, NC, USA.

ClinicalTrials.gov Identifier: NCT01998971

Study Design

Open-label, Multicenter, Phase 1b Study (N = 22)

Eligibility/Treatment

- NDMM
- Transplant eligible and non-eligible
- Treatment duration: ≤13 cycles or until elective discontinuation for ASCT
- No clinically significant cardiac disease; echo required at screening

Dosing Schedule (28-d cycles)

Daratumumab:

- **Split dose: 8 mg/kg Days 1-2 of Cycle 1**
- 16 mg/kg QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter

Carfilzomib:

- 20 mg/m^2 C1D1
- Escalated to 70 mg/m^2 C1D8+; **weekly (Days 1, 8, 15)**

Lenalidomide:

- 25 mg; Days 1-21 of each cycle

Dexamethasone: 40 mg/week[a]

Endpoints

Primary

- Safety, tolerability

Secondary

- ORR, duration of response, time to response, IRR

Exploratory

- PFS

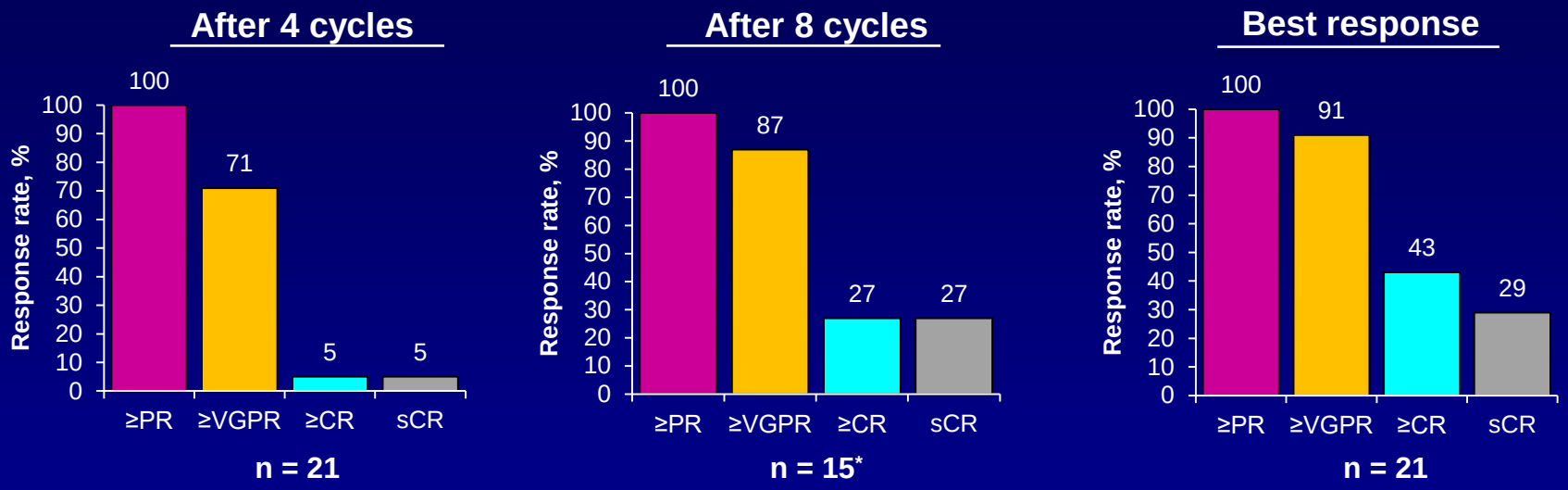
Pre- and post-infusion medications:

Dexamethasone 20 mg[b]; Diphenhydramine 25-50 mg; paracetamol 650-1,000 mg; montelukast 10 mg[c]

Echo, echocardiogram; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; C1D1, Cycle 1 Day 1; C1D8, Cycle 1 Day 8; IRR, infusion-related reaction; C1D3, Cycle 1 Day 3.
[a]20 mg if >75 y. [b]On daratumumab dosing days, dexamethasone 20 mg IV was administered as pre-medication on infusion day and 20 mg PO the day after infusion; for DARA, split first dose dexamethasone 20 mg IV was administered as a pre-medication on C1D1 and C1D2; on C1D3, administration of low-rose methylprednisolone (≤20 mg PO) was optional. [c]Required before first daratumumab dose, optional for subsequent doses.

Response Rate[a,b]

- Median number of treatment cycles: 11.5 (range, 1.0-13.0)

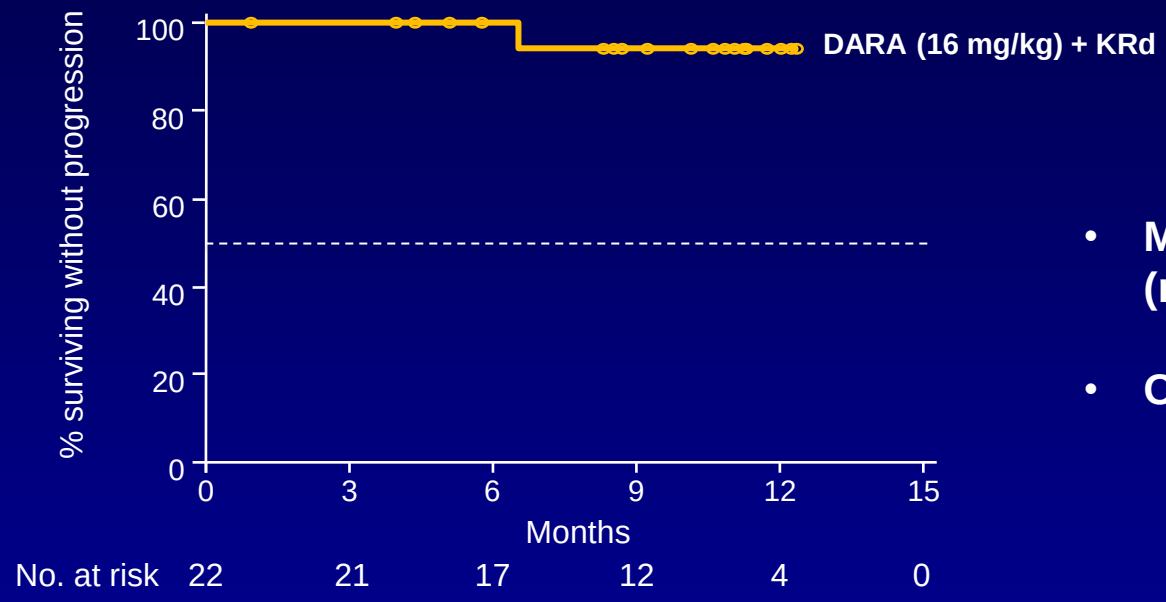


Depth of response improved with duration of treatment

*5 patients who proceeded to ASCT before C8 and 1 patient who discontinued due to PD at C7 were excluded.

PR, partial response; CR, complete response.
[a]Response-evaluable population. [b]Response rate (≥PR) evaluated by IMWG criteria; M-protein measurements by central lab assessment.

PFS



- **Median follow-up: 10.8 (range, 4.0-12.5) months**
- **Overall survival = 100%**

12-month PFS rate[a] = 94%

[a]Kaplan-Meier estimate.

Conclusions

- DARA + KRd was well tolerated
  - Safety is consistent with previous reports of DARA and KRd
  - Low IRR rates associated with split first dose; no grade 3/4
- Highly effective with 100% ORR
  - 91% ≥VGPR and 43% ≥CR
  - Depth of response improved with duration of treatment
- No adverse impact on stem cell collection (10.4×10^6 cells/kg)
  - DARA is feasible as part of induction therapy

Data from this study support further investigation of DARA-KRd in NDMM

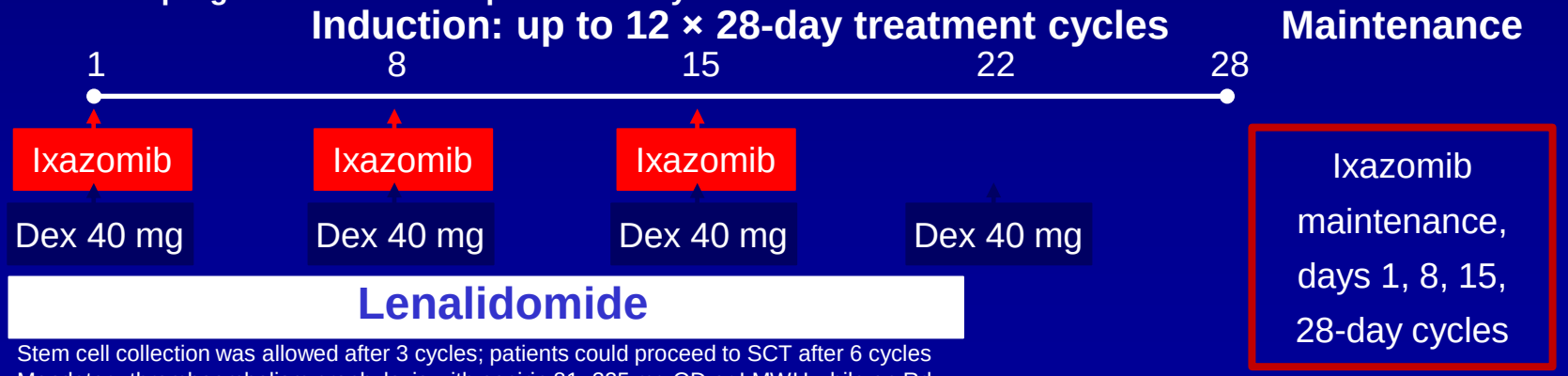
Ixazomib Lenalidomide dexamethasone: IRd
Single-arm phase 1/2 study of weekly in NDMM

Primary Endpoint (Phase 2): ≥VGPR (CR + VGPR)

Patient Characteristics: 65 pts enrolled (15 Phase 1, 50 Phase 2; 23 (35%) discontinued during induction to undergo SCT and 42 (65% did not receive SCT). 25 (38%) went on to ixazomib maintenance.

Characteristic	All patients (N=65)	Did not receive SCT (N=42)
Median age, years (range)	66 (34–86)	68 (34-86)
ECOG PS 0/ 1/ 2, n (%)	28 (43) /34 (52)/ 3 (5)	20 (48) /19 (45) /3 (7)
ISS stage at diagnosis I/II/III, n (%)	28 (43)/ 28 (43)/9 (14)	17 (40)/18 (43)/ 7 (17)
High-risk cytogenetics,* n (%)	5 (8)	3 (7)

Dose and Schedule: Phase 1: oral ixazomib standard 3+3 dose escalation(1.68–3.95 mg/m^2 weekly); Phase 2: oral ixazomib at RP2D from phase 1 (4.0 mg weekly); Single-agent ixazomib maintenance (at last tolerated dose) continued until disease progression or unacceptable toxicity**



Stem cell collection was allowed after 3 cycles; patients could proceed to SCT after 6 cycles
Mandatory thromboembolism prophylaxis with aspirin 81–325 mg QD or LMWH while on Rd

*High-risk cytogenetics includes del(17), t(4;14) and t(14;16) abnormalities.

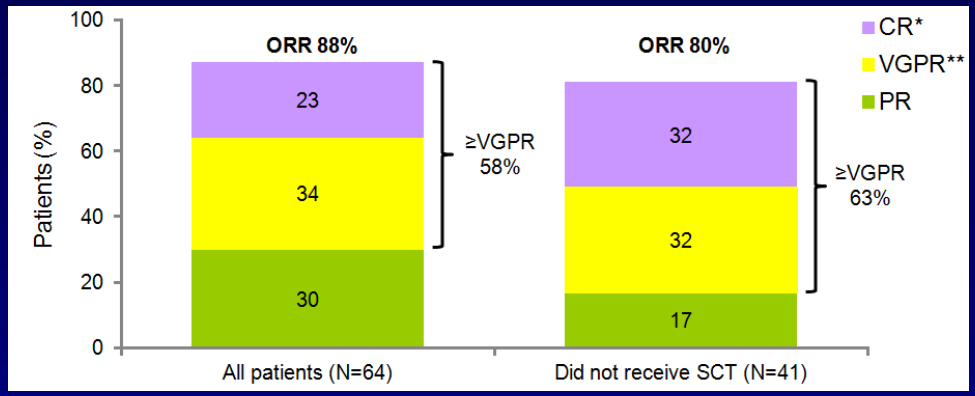
**Based on dose-limiting toxicities in cycle 1 LMWH, low molecular-weight heparin; QD, every day

Kumar et al. EHA 2017

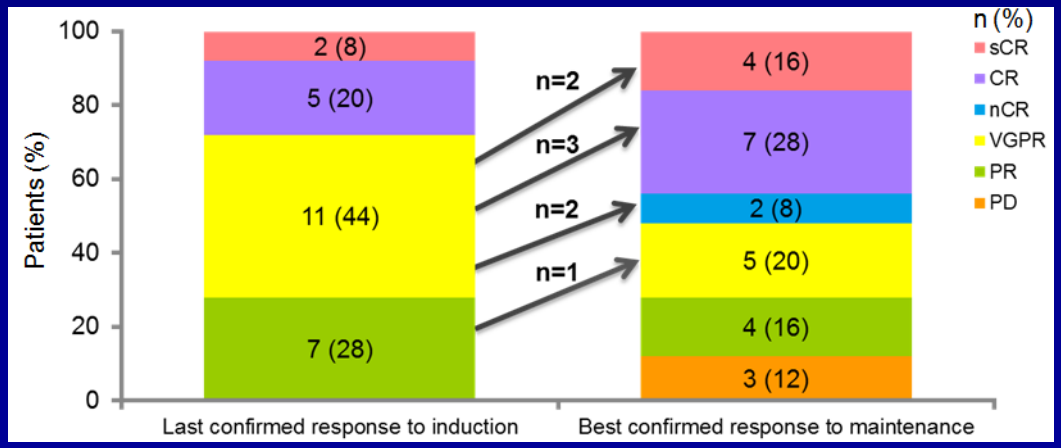
Ixazomib Lenalidomide dexamethasone: IRd
Single-arm phase 1/2 study of weekly in NDMM

Response Rates:

Best confirmed response (evaluable)



Deeping of response in pts receiving ixazomib Maintenance (N=25)



MRD evaluation (response-evaluable pts)

Patients	All patients (N=64)	Did not receive SCT (N=41)
MRD evaluation, n (%)	16 (25)	10 (24)
Best response of sCR/CR, n	9	7
Achieved MRD-negative status, n (% of patients with sCR/CR)	8 (89)	6 (86)

*Includes sCR; **Includes nCR (defined per Richardson PG et al, N Engl J Med. 2003;348:2609–17)

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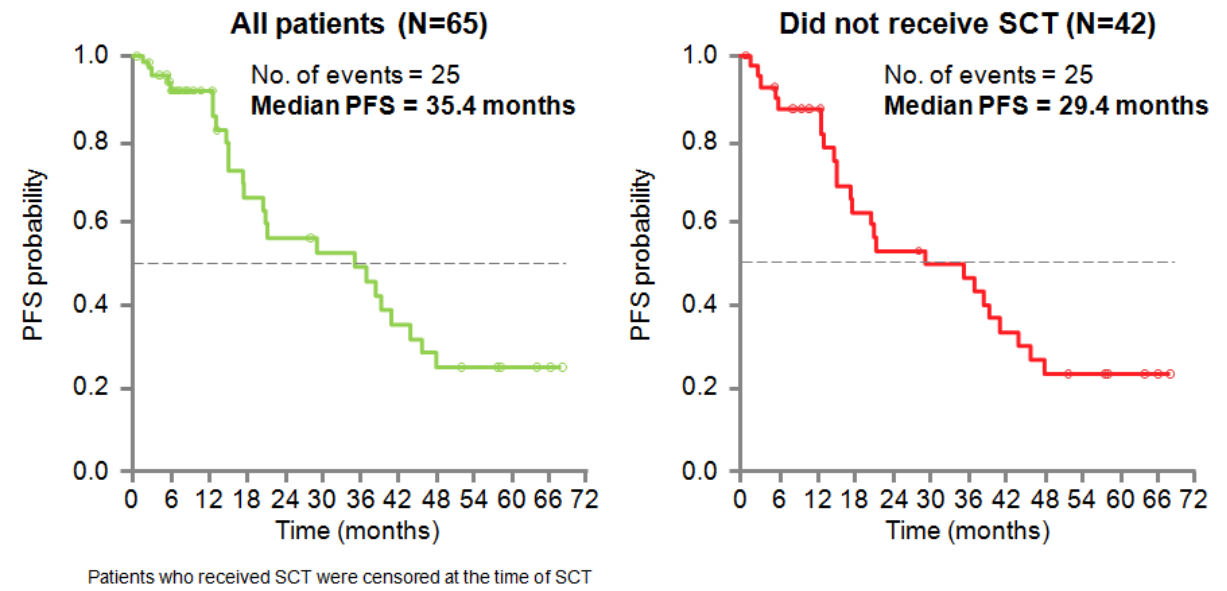
Ixazomib Lenalidomide dexamethasone: IRd
Single-arm phase 1/2 study of weekly in NDMM

PFS:

Median follow up of ~56 mos



Efficacy Outcomes:

Clinical outcome	All patients (N=64)	Did not receive SCT (N=41)
Median follow-up for OS, months	56.3	55.2
Median PFS, months	35.4	29.4
Median OS, months	NE	NE
Landmark OS rate, % 1 year 2 year 4 year	 94 89 84	 90 87 82
Median time to best response ≥VGPR, months	4.9	6.6
Median time to best response sCR/CR, months	5.6	5.6

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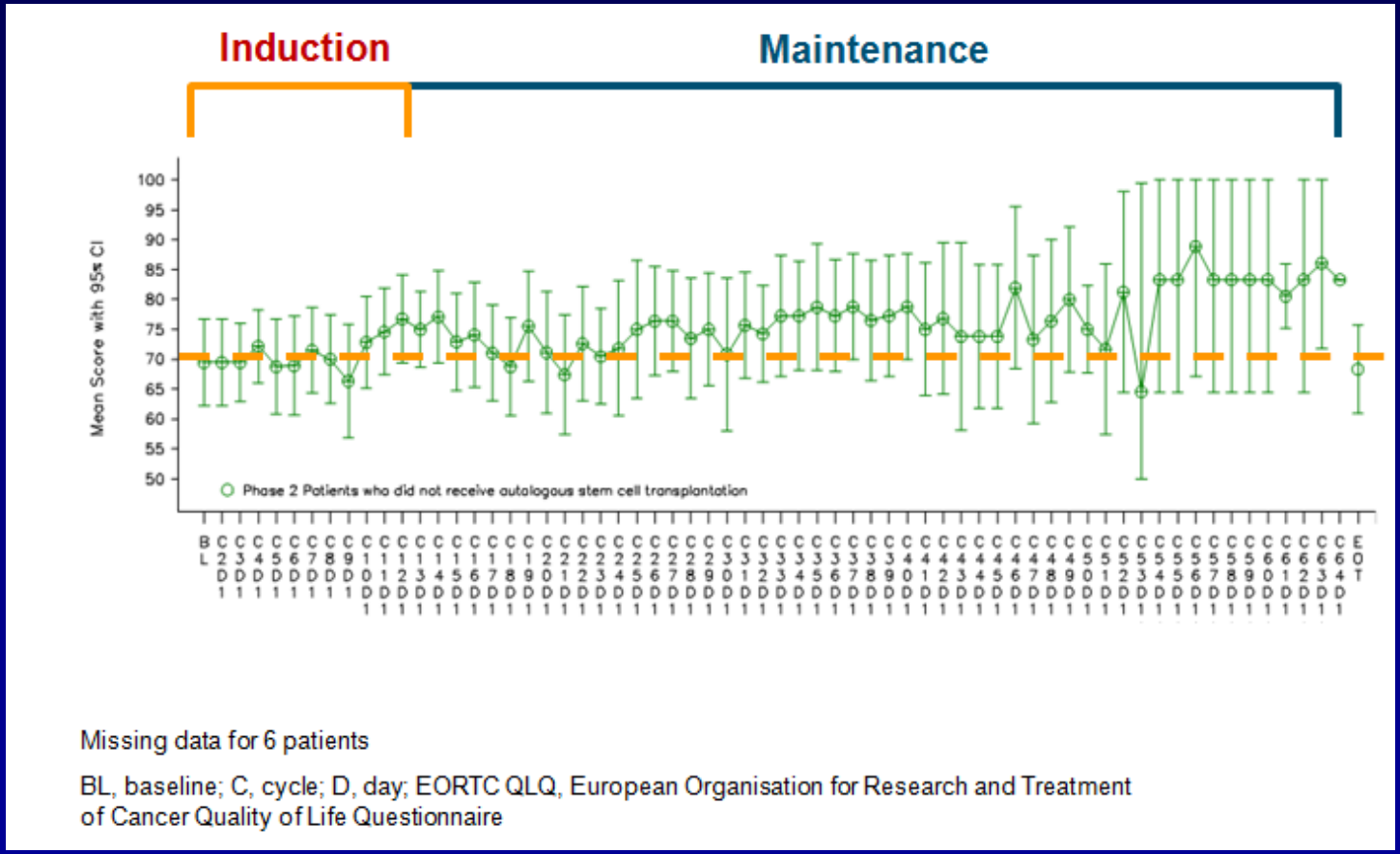
Ixazomib Lenalidomide dexamethasone: IRd
Single-arm phase 1/2 study of weekly in NDMM

Quality of life: Mean EORTC QLQ-C30 scores in phase 2 pts who did not receive SCT (N=36)



Missing data for 6 patients

BL, baseline; C, cycle; D, day; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire

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Ixazomib Lenalidomide dexamethasone: IRd

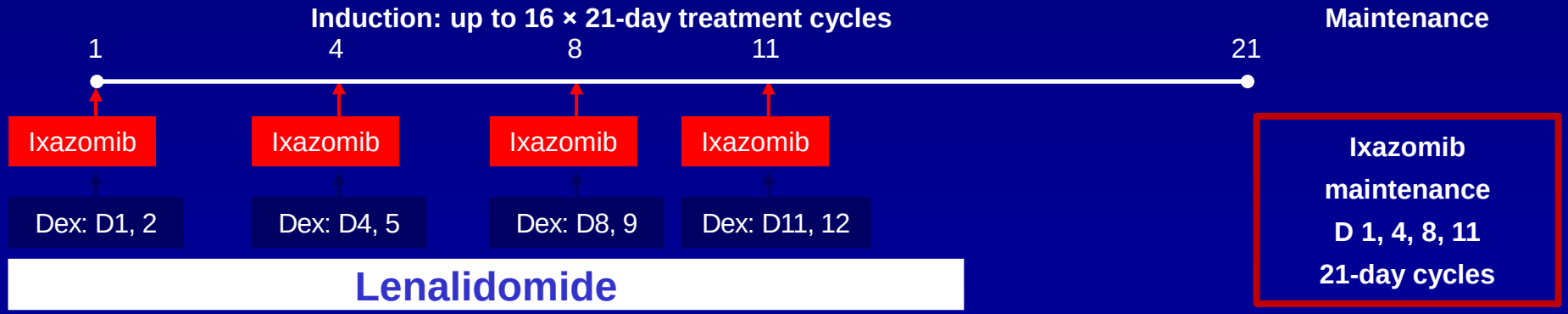
Phase 1/2 study of twice-weekly ixazomib + Rd in NDMM

Primary Endpoint (Phase 2): ≥VGPR (CR + VGPR)

Patient Characteristics: 64 pts enrolled (14 Phase 1, 50 Phase 2; 20 (31%) withdrew during induction to undergo SCT and 41 (64% did not receive SCT); 3(5%) withdrew during induction for reasons other than SCT but then went on to receive SCT. 18 (28%) went on to ixazomib maintenance.

Characteristic	All patients (N=65)	Did not receive SCT (N=42)
Median age, years (range)	66 (34–82)	66 (44-82)
ECOG PS 0/ 1/ 2, %	53/44/4	51/46/2
ISS stage at diagnosis I/II/III, %	48/34/17	46/37/17
High-risk cytogenetics,* %	9	15

Dose and Schedule: Phase 1: oral ixazomib standard 3+3 dose escalation(3.0 or 3.7 mg twice weekly); Phase 2: oral ixazomib at RP2D from phase 1 (3.0 mg twice weekly); Single-agent ixazomib maintenance (at last tolerated dose) continued until disease progression or unacceptable toxicity**



Dex was dosed at 20 / 10 mg in cycles 1–8 / 9–16
Stem cell collection was allowed after 4 cycles; patients could proceed to autologous SCT after 8 cycles
Mandatory thromboembolism prophylaxis with aspirin 81–325 mg QD or LMWH while on Rd

*High-risk cytogenetics includes del 17, t(4;14) and t(14;16) abnormalities.

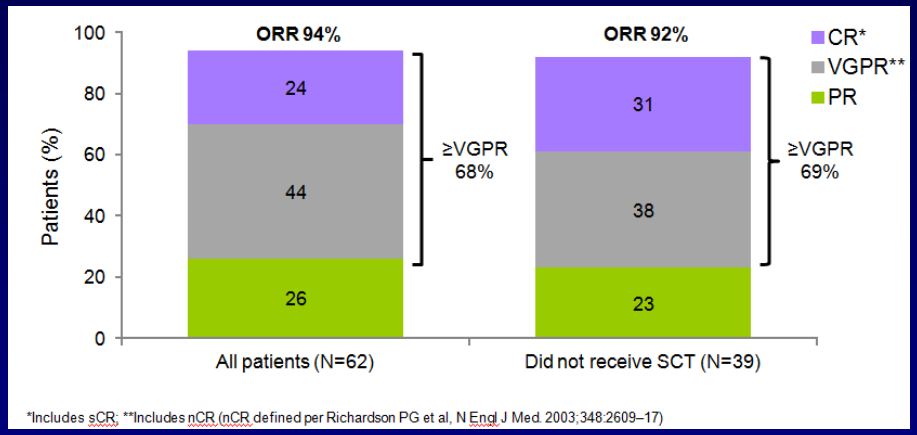
**Based on dose-limiting toxicities in cycle 1

Richardson et al. EHA 2017

Open-label, non-randomized phase 1/2 study of twice-weekly ixazomib + Rd in NDMM

Response Rates:

Best confirmed response (evaluable)



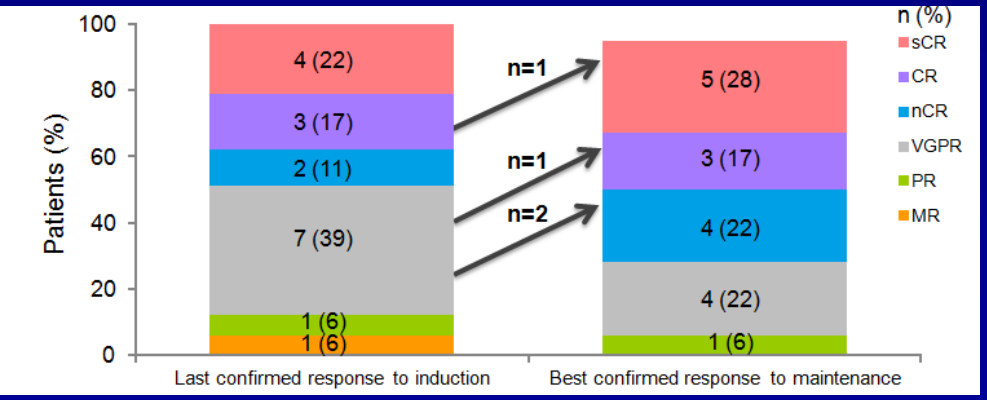
*Includes sCR; **Includes nCR (nCR defined per Richardson PG et al, N Engl J Med. 2003;348:2609–17)

Best confirmed response: high risk patients

Patients	All patients (N=62)	Did not receive SCT (N=39)
Patients with high-risk cytogenetics,* n (%)	6 (10)	6 (15)
Best response ≥PR, n	5	5
CR	4	4
PR	1	1
Duration of response in high-risk patients achieving CR (n=3),† months	38.5–51.3	

*High-risk cytogenetic abnormalities include del(17), t(4;14), and t(14;16)
†1 patient withdrew consent after achieving CR and could not be followed up

Evolution of response in pts receiving ixazomib Maintenance (N=18)



MRD evaluation (response-evaluable pts)

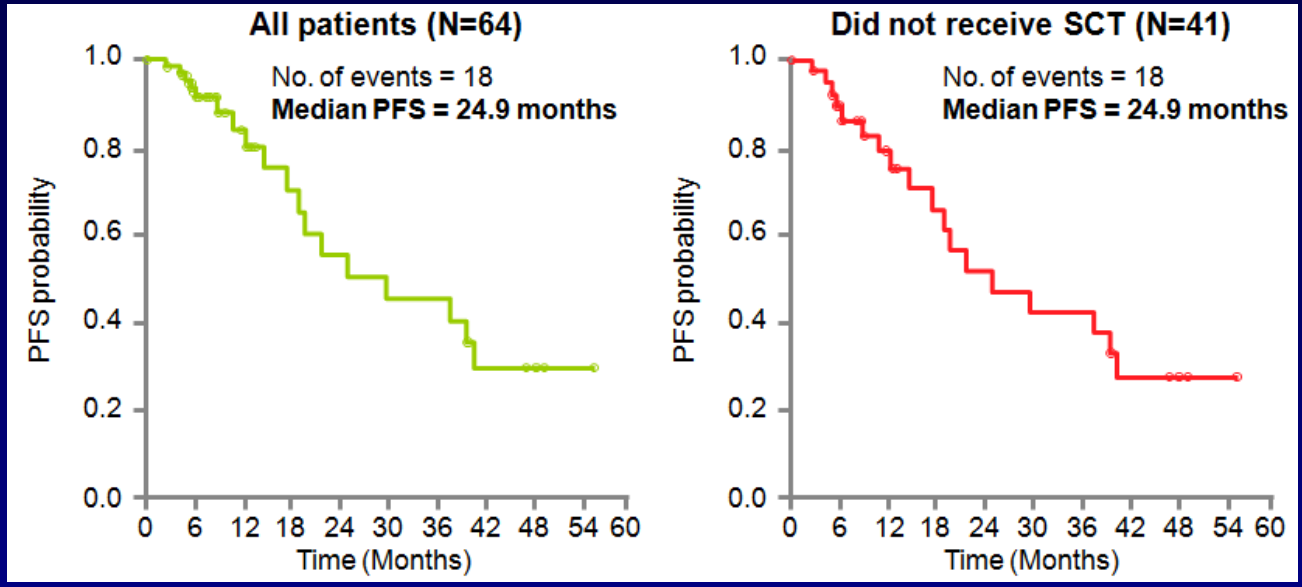
Patients	All patients (N=62)	Did not receive SCT (N=39)
MRD evaluation, n (%)	27 (44)	20 (51)
Best response of sCR/CR, n	10	9
Achieved MRD-negative status, n (% of patients with sCR/CR)	8 (80)	8 (89)

Richardson et al. EHA 2017

Open-label, non-randomized phase 1/2 study of twice-weekly ixazomib + Rd in NDMM

PFS:

Median follow up of ~47 mos



Efficacy Outcomes:

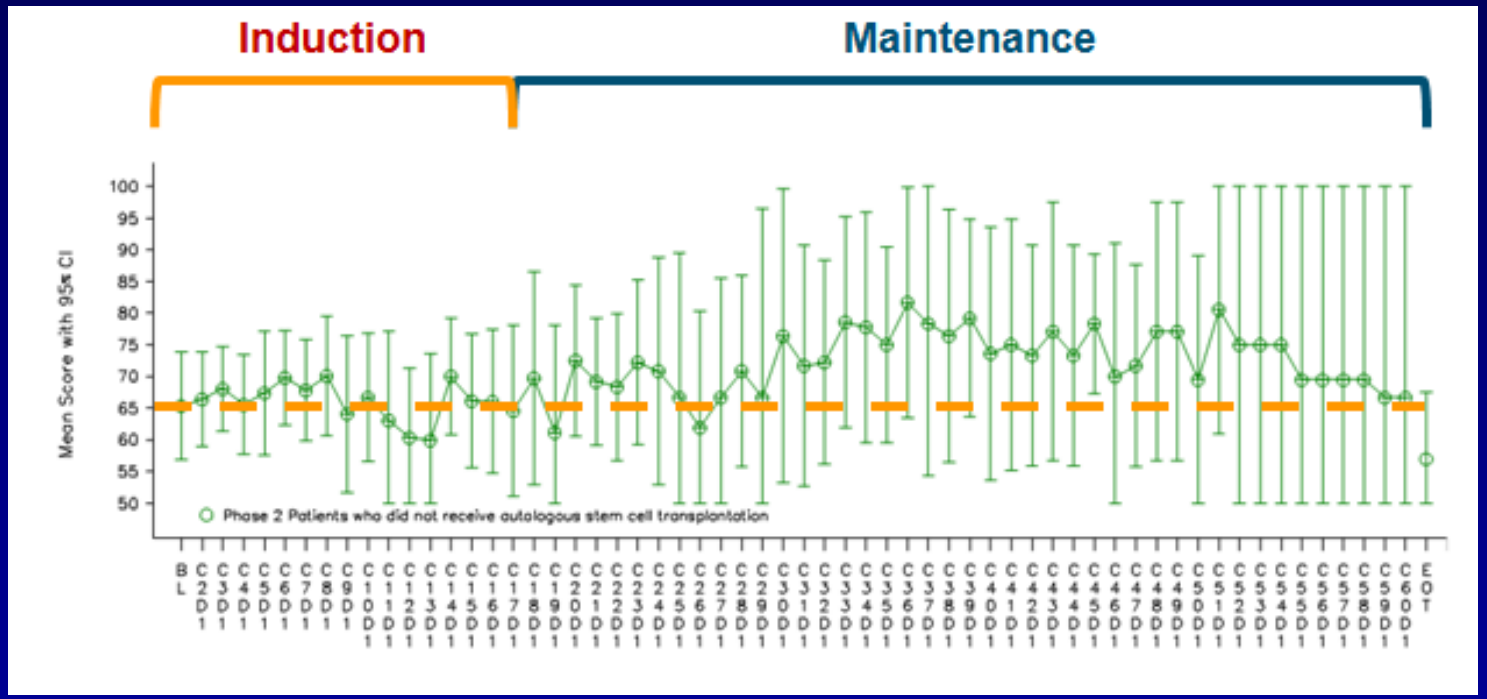
Clinical outcome	All patients (N=62)	Did not receive SCT (N=39)
Median follow-up for OS, months	*46.9*	*47.0*
Median PFS, months	24.9	24.9
Median OS, months	NE	NE
Landmark OS rate, % 1 year 2 year 3 year	 95 95 91	 92 92 86
Median time to best response ≥VGPR, months*	3.4	3.5
Median time to best response sCR/CR, months*	4.2	4.2

*In patients achieving these levels of response
NE, not estimable

Richardson, et al EHA 2017

Open-label, non-randomized phase 1/2 study of twice-weekly ixazomib + Rd in NDMM

Quality of life: Mean EORTC QLQ-C30 scores in phase 2 pts who did not receive SCT (N=31)

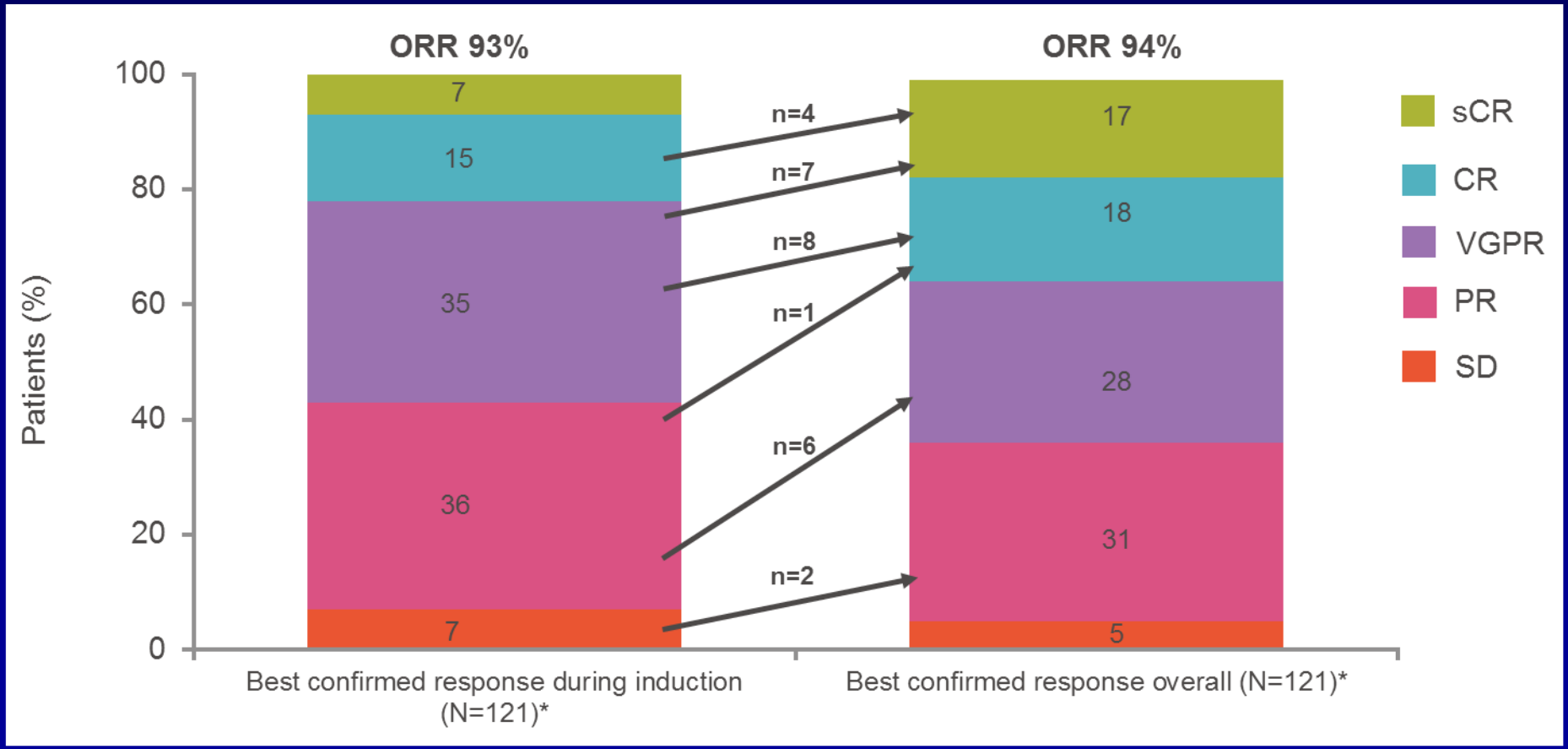


Richardson et al. EHA 2017

Data from a pooled analysis of phase 2 study pts who did not undergo ASCT and received ixazomib maintenance show promising PFS, an increase in depth of response during maintenance

Efficacy and Safety of Long-term Ixazomib Maintenance Therapy in Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) Not Undergoing Transplant: an Integrated Analysis of Four Phase 1/2 Studies *(Dimopoulos, Abstract 902.)*

- **28 (23%) pts improved their response during ixazomib maintenance**



Ixazomib is only indicated for RRMM in Japan

Dimopoulos M et al. ,ASH2017 Abstract 902.

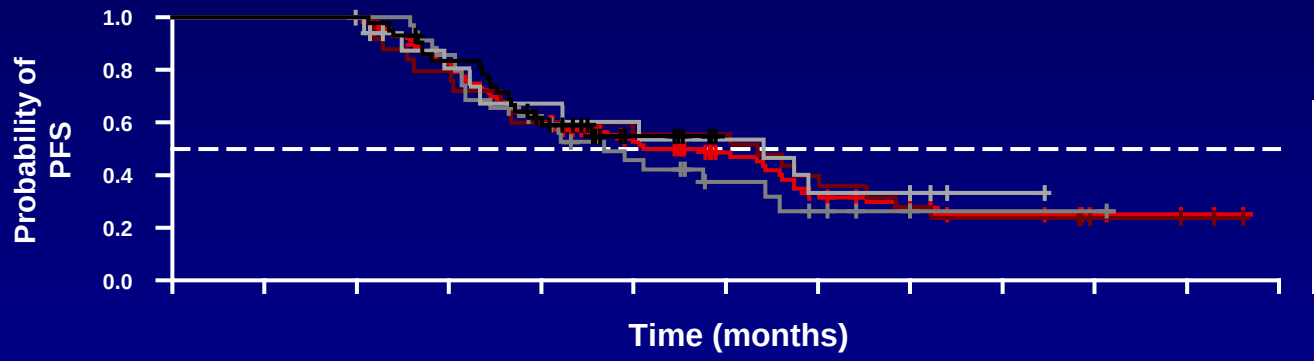
Data from a pooled analysis of phase 2 study pts who did not undergo ASCT and received ixazomib maintenance show promising PFS, an increase in depth of response during maintenance

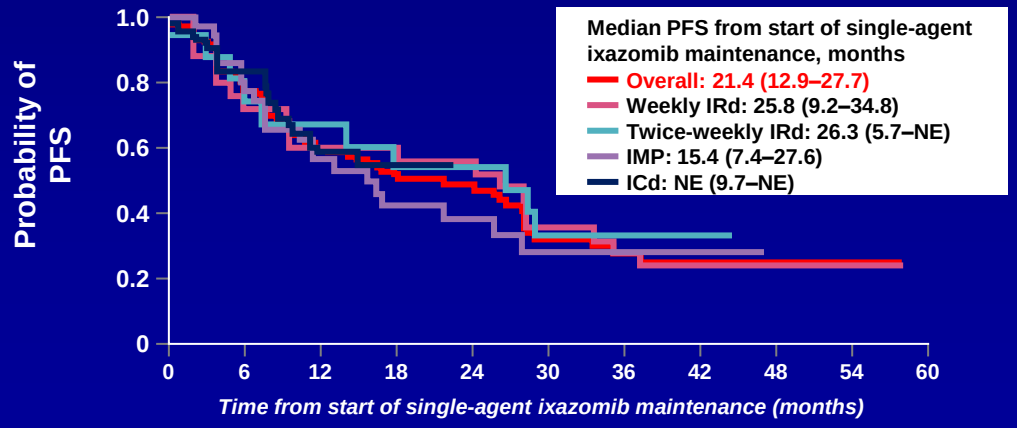
Study design:

- Pts from 4 studies of weekly/twice-weekly ixazomib (C16005, twice-weekly IRd; C16008, weekly IRd; C16006, weekly/twice-weekly IMP; C16020, weekly ICd) who completed induction without PD and, in the IRd studies, were not withdrawn for ASCT, could receive single-agent ixazomib maintenance

Results:

- N=121, median age 72 years (range 34–90)
- Median duration of ixazomib maintenance was 10.6 months (9.9 – 26.7 mo in individual studies)





2-yr PFS estimate for patients with high-risk cytogenetics (n=12) was 51% (18-77) from study entry and 56% (24-79) from the start of maintenance

Efficacy and Safety of Long-term Ixazomib Maintenance Therapy in Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) Not Undergoing Transplant: an Integrated Analysis of Four Phase 1/2 Studies

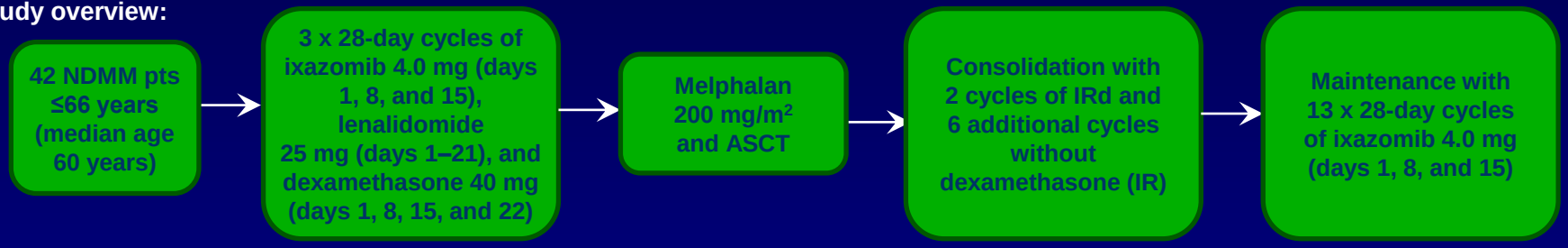
Ixazomib is only indicated for RRMM in Japan

Dimopoulos M et al. ,ASH2017 Abstract 902.

All-oral IRd as induction prior to and consolidation after ASCT, followed by single-agent ixazomib maintenance, is well tolerated, convenient, and effective

Ixazomib-Lenalidomide-Dexamethasone (IRd) Combination before and after Autologous Stem Cell Transplantation (ASCT) Followed By Ixazomib Maintenance Is a Safe and Effective Strategy in Patients with Newly Diagnosed Multiple Myeloma (NDMM): A Phase 2 Study from the Intergroupe Francophone Du Myélome (IFM)

Study overview:

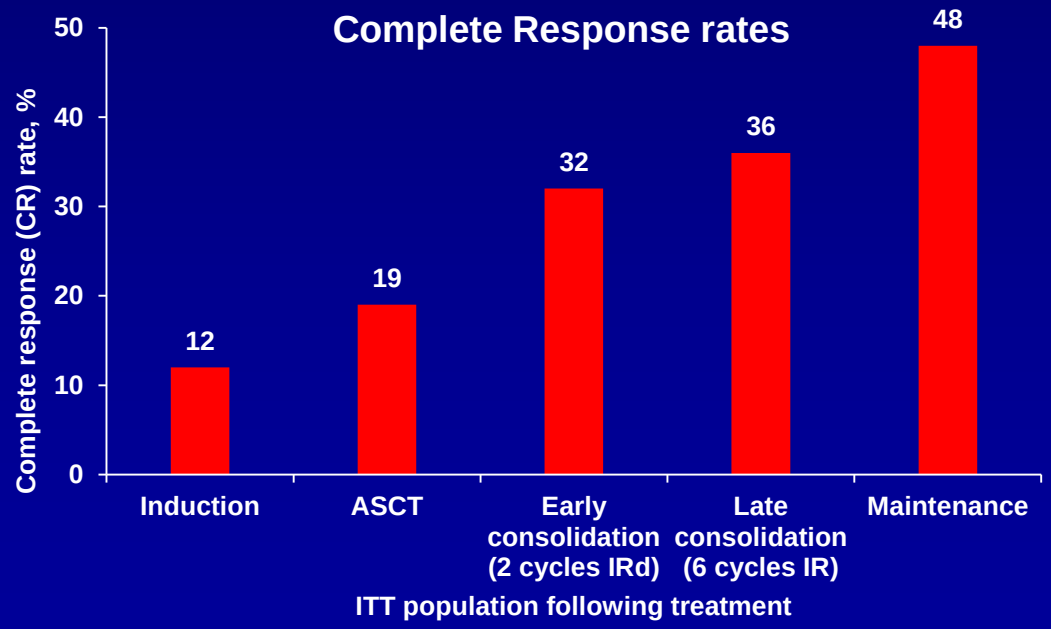


Endpoints:

- Primary: CR rate post-consolidation
- Other: PFS, OS, safety

Results:

- Median follow-up 24 months:
  - 2-year PFS was 83%
  - 2-year OS was 95%
- 32/37 (86%) pts and 26/31 (84%) pts completed the planned cycles of consolidation and maintenance, respectively
- 5 pts discontinued due to adverse events; rash n=3 (during induction, late consolidation, and maintenance, n=1 each), thrombocytopenia n=1 (before maintenance), infection n=1 (during maintenance)
- No renal or liver toxicity and no cardiac failure or ischemic heart disease was reported



Moreau P et al., ASH2017 abstract 2021

Updated data from a phase 2 study of ixazomib plus lenalidomide as maintenance therapy post-ASCT supports the long-term feasibility of this treatment approach in pts with NDMM

Update on a Phase II Study of Ixazomib with Lenalidomide As Maintenance Therapy Following Autologous Stem Cell Transplant in Patients with Multiple Myeloma

64 NDMM pts following ASCT with high-dose melphalan,

median age 60 years (range: 39–74 years)

→

Maintenance: 60–180 days post-ASCT
28-day cycles of weekly ixazomib 4.0 mg (3.0 mg from Aug 2013, n=48), and daily lenalidomide 10.0 mg

Study design:

- Endpoints: PFS, ORR, safety, incidence of second primary malignancies (SPMs)

Results:

- 29 pts had an improvement in their best overall response from their baseline response
- 22 pts had grade 1/2 PN and 6 pts had grade 3 PN
- 3 pts were diagnosed with SPMs while on maintenance (post-ASCT); breast ductal carcinoma in situ, n=1, and squamous cell carcinoma of the skin, n=2

Patel et al., ASH2017 Abstract 437

Updated data from a phase 2 study of ixazomib plus lenalidomide as maintenance therapy post-ASCT supports the long-term feasibility of this treatment approach in pts with NDMM

Update on a Phase II Study of Ixazomib with Lenalidomide As Maintenance Therapy Following Autologous Stem Cell Transplant in Patients with Multiple Myeloma

Adverse event	Number of pts (%)	
	Grade 3	Grade 4
Anemia	2 (3)	
Neutropenia	26 (41)	3 (5)
Thrombocytopenia	4 (6)	5 (8)
Elevated aspartate aminotransferase	4 (6)	
Elevated alanine aminotransferase	1 (1.6)	
Elevated alkaline phosphatase	1 (1.6)	
Elevated total bilirubin	1 (1.6)	
Back pain	2 (3)	
Constipation	4 (6)	
Elevated creatinine	1 (1.6)	
Nausea	5 (8)	
Vomiting	2 (3)	
Diarrhea	6 (9)	
Fatigue	7 (11)	
Rash	8 (13)	
Peripheral neuropathy	6 (9)	
Myalgia	3 (5)	
Respiratory failure		1 (1.6)
Urinary tract infection	3 (5)	
Upper respiratory infection	5 (8)	
Lung infection	16 (25)	
Influenza	2 (3)	

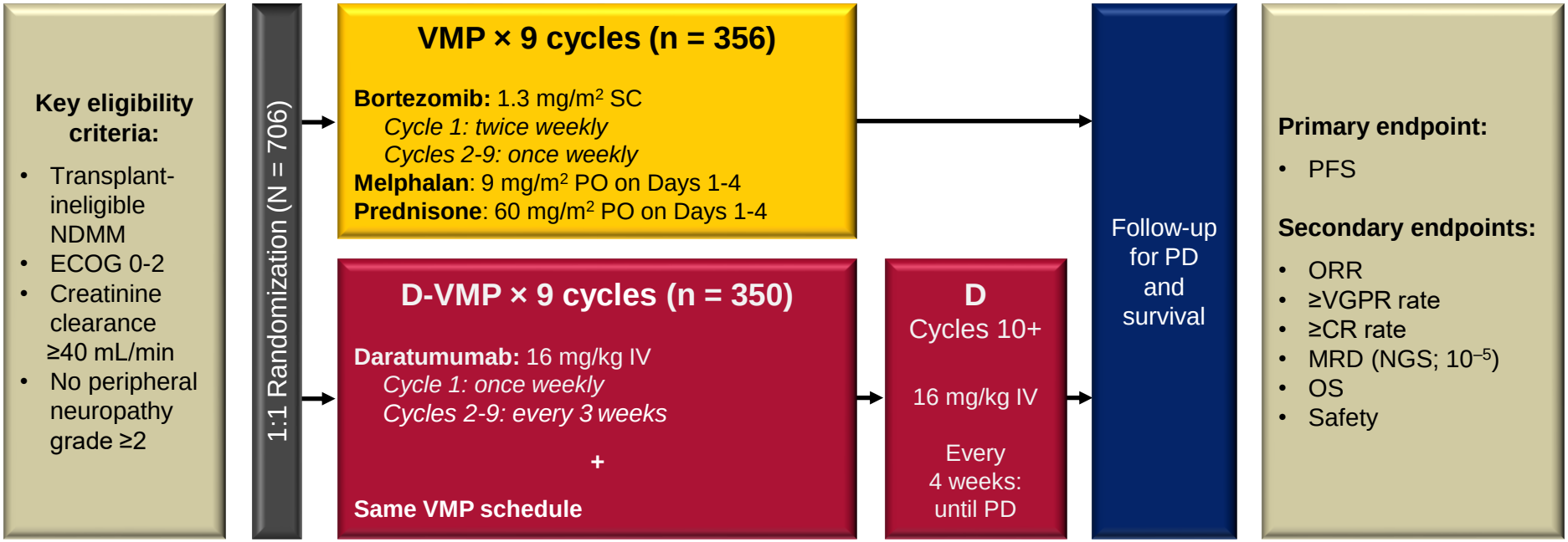
Results	
Median follow-up, months	37.8
Pts remaining on therapy, n (%)	34 (53)
Medium no. of cycles received, n (range)	28 (1–51)
Best response, %	
sCR	7.8
CR	26.5
VGPR	53
PR	10.9
Median PFS, months	NR
Median PFS in pts with high-risk cytogenetics	NR
Estimated 2-year PFS, %	81
Discontinuation rate, n (%)	30 (47)
Reasons:	
PD	16 (53)
Principal investigator discretion	3 (10)
Consent withdrawal	11 (37)

Key messages

- **Findings demonstrate the long-term feasibility of post-ASCT maintenance therapy with IR, with similar incidence of AEs vs historical data for lenalidomide alone, manageable hematologic AEs, PN was mostly grade ≤2 (grade 3, n=6) and no other unexpected toxicities**
- **Based on clinical experience, the protocol was amended in Aug 2013 to reduce the starting dose of ixazomib to 3.0 mg, aligned with the dosing schedule of the phase 3 TOURMALINE-MM3 study**

Patel et al., ASH 2017 Abstract 437

Mateos et al, ASH 2017ALCYONE Study Design



Stratification factors

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

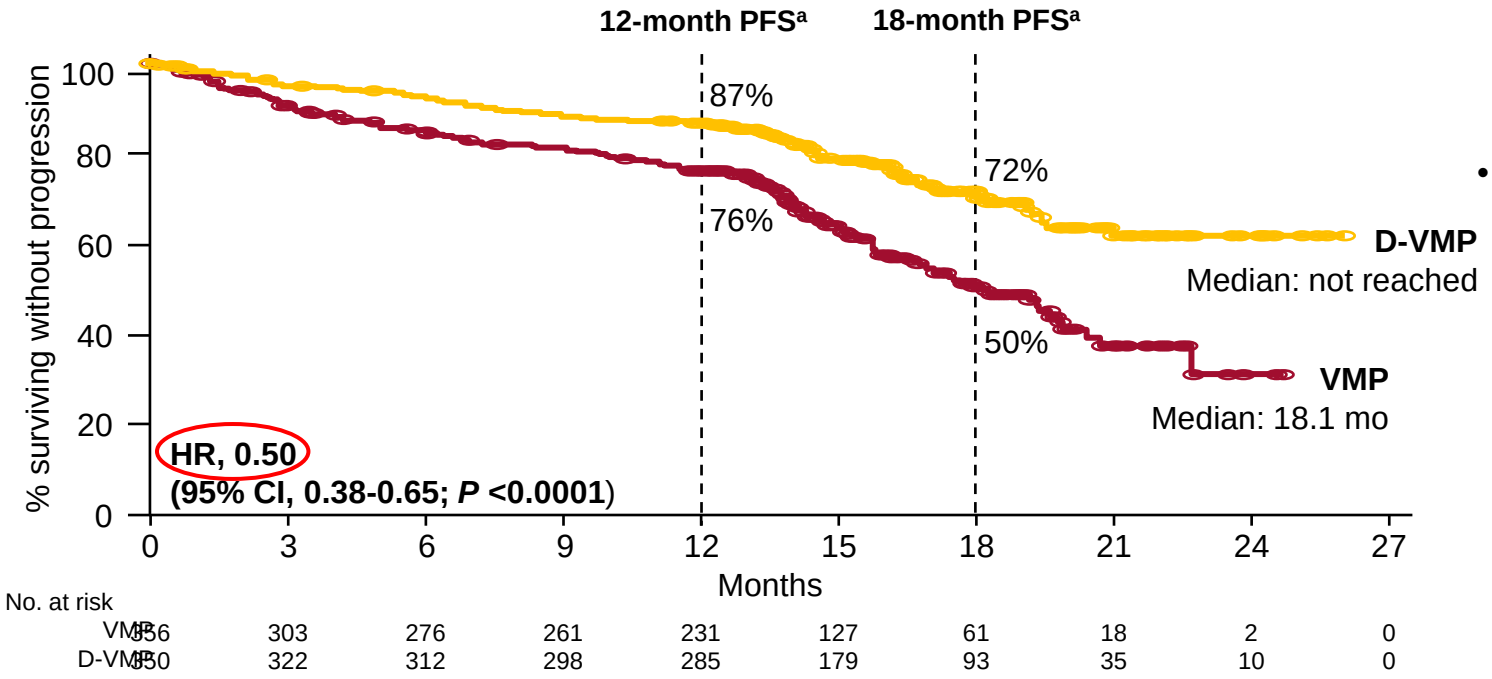
- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

Statistical analyses

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

NDMM, newly diagnosed multiple myeloma; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; VMP, bortezomib/melphalan/prednisone; SC, subcutaneously; PO, orally; D, daratumumab; IV, intravenously;
PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; OS, overall survival.

Efficacy: PFS

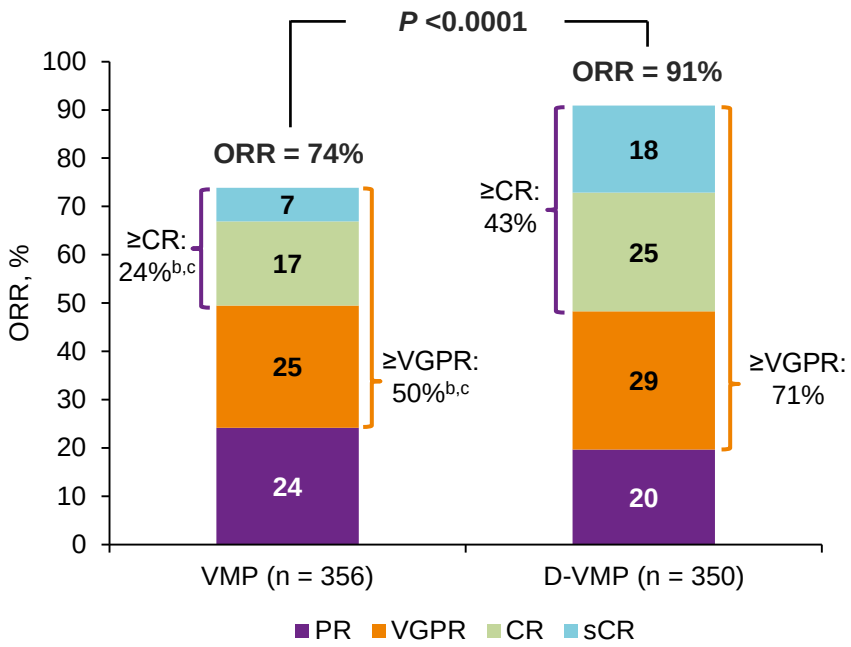


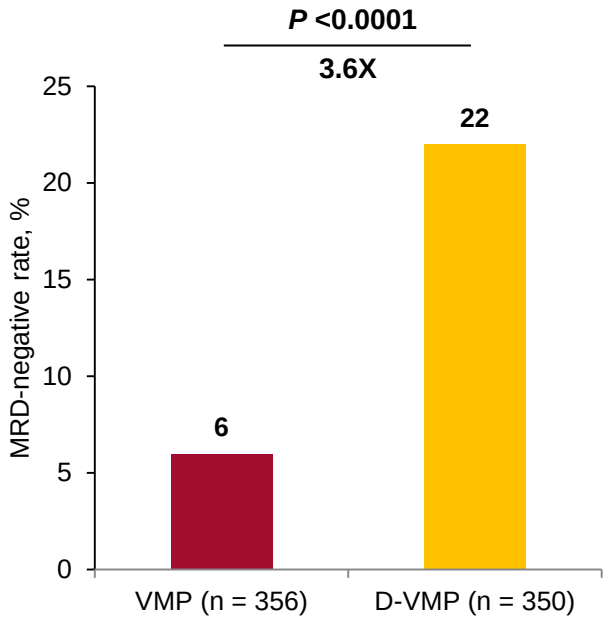
- **Median (range) follow-up: 16.5 (0.1-28.1) months**
- **Consistent PFS treatment benefit across subgroups**

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

PFS, progression-free survival; VMP, bortezomib/melphalan/prednisone; D, daratumumab; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

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



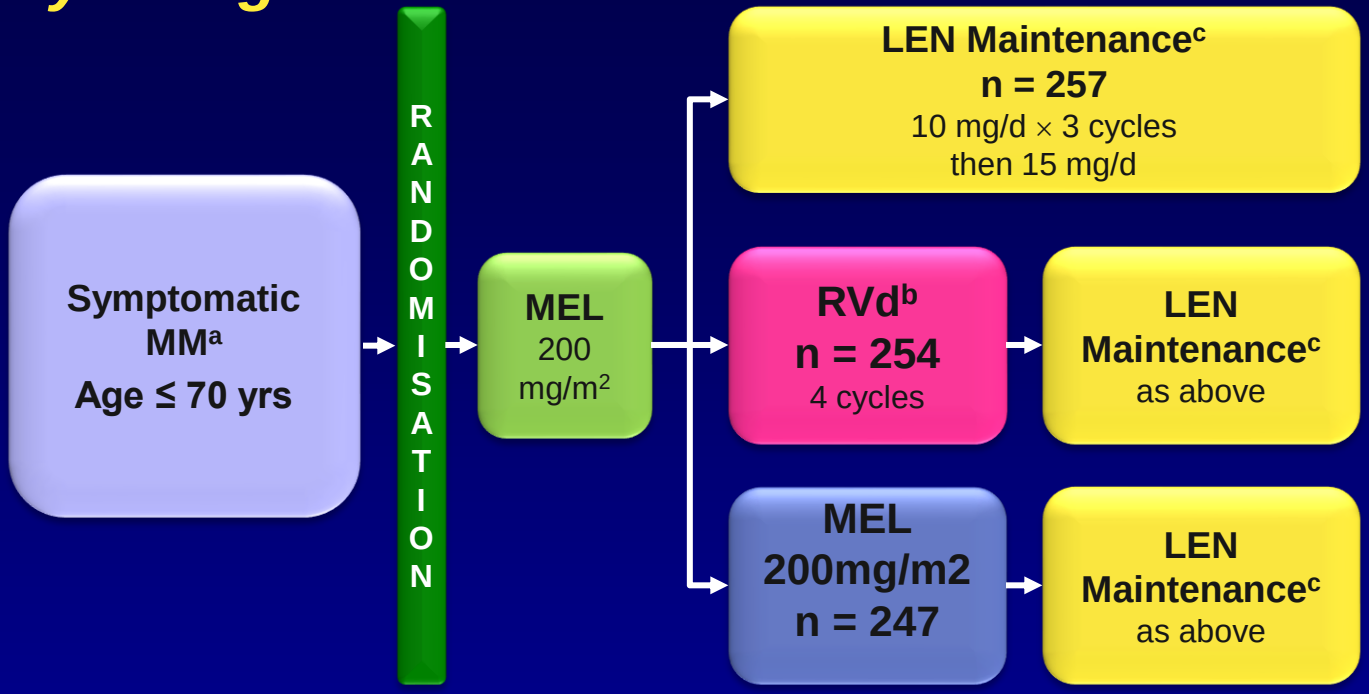


Significantly higher ORR, ≥VGPR, and ≥CR with D-VMP
>3-fold higher MRD-negativity rate with D-VMP

ORR, overall response rate; VMP, bortezomib/melphalan/prednisone; D, daratumumab; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response. MRD, minimal residual disease; NGS, next-generation sequencing using clonoSEQ version 2.0 (Adaptive) [a]Intent-to-treat population. [b]*P* value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test. [c]*P* <0.0001.

STaMINA: ASCT + RVd vs Tandem ASCT

Study Design



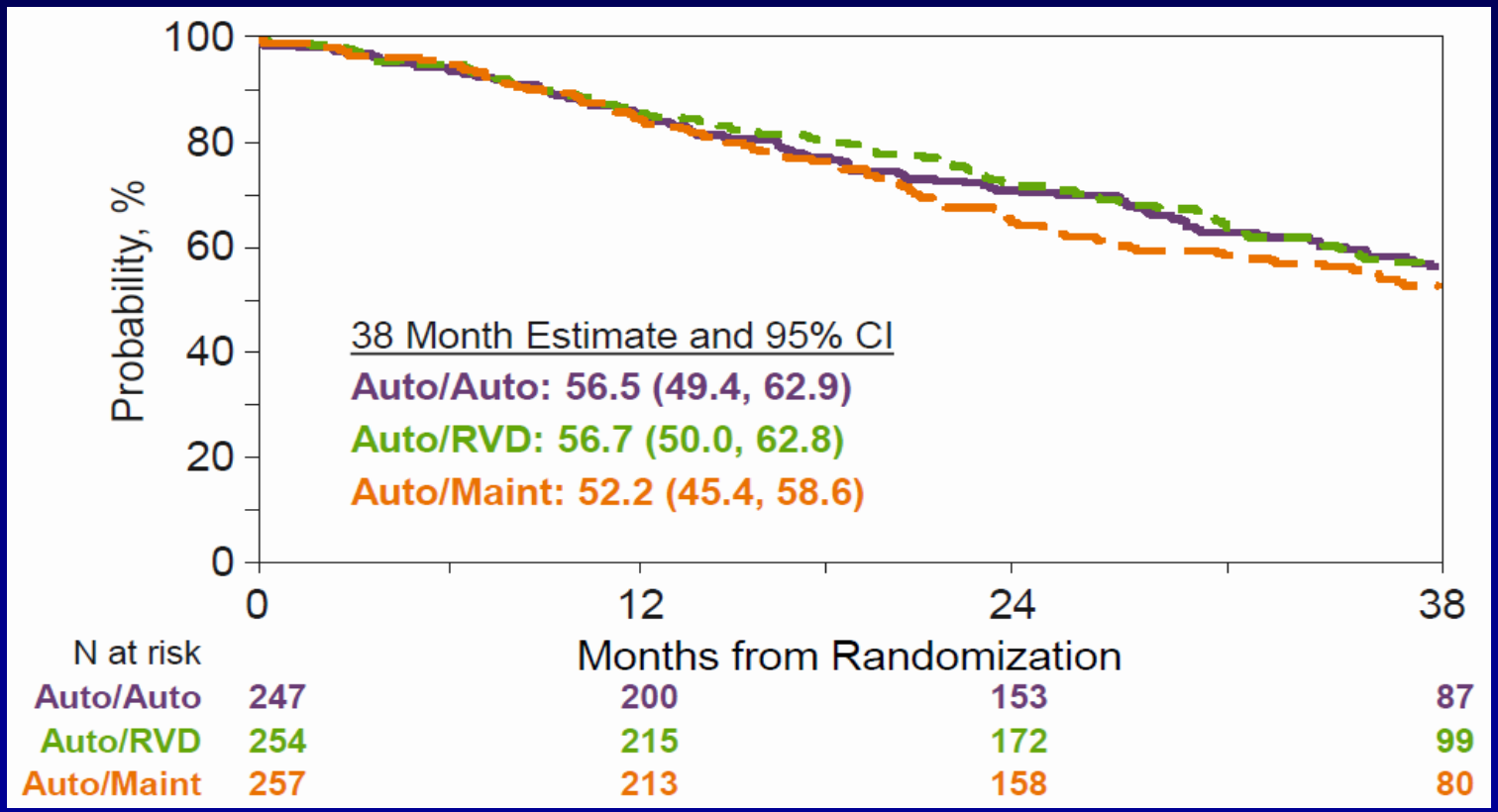
- **Primary endpoint: PFS**
- **Secondary endpoints: OS, response rates (particularly ≥ VGPR), the rate of CR conversion for pts not in CR, toxicity and infections after each intervention and long term, the rate of nonadherence, Tx-related mortality, QoL**

[a] Pts must have received ≥ 2 cycles of systemic therapy within 2-12 months of initial Tx. [b] Bortezomib 1.3 mg/m^2 d1, 4, 8, 11; Lenalidomide 15 mg d1-15; Dexamethasone 40 mg d1, 8, 15; 21 days per cycle. [c] LEN maintenance x 3 years amended to LEN maintenance until PD in 2014 amendment after report of CALGB 100104.
ASCT, autologous stem cell transplant; CR, complete response; d, day; LEN, lenalidomide; MEL, melphalan; MM, multiple myeloma; OS, overall survival; pt, patient; PD, progressive disease; PFS, progression-free survival; pt, patient; QoL, quality of life; RVd, lenalidomide, bortezomib, dexamethasone; Tx, treatment; VGPR, very good partial response.

Stadtmauer E et al. *ASH* 2016; Oral Presentation and Abstract LBA-1

STaMINA: ASCT + RVd vs Tandem ASCT
Primary Endpoint: Progression-Free Survival

- **At 38 mos follow-up, PFS was similar across all 3 Tx arms**



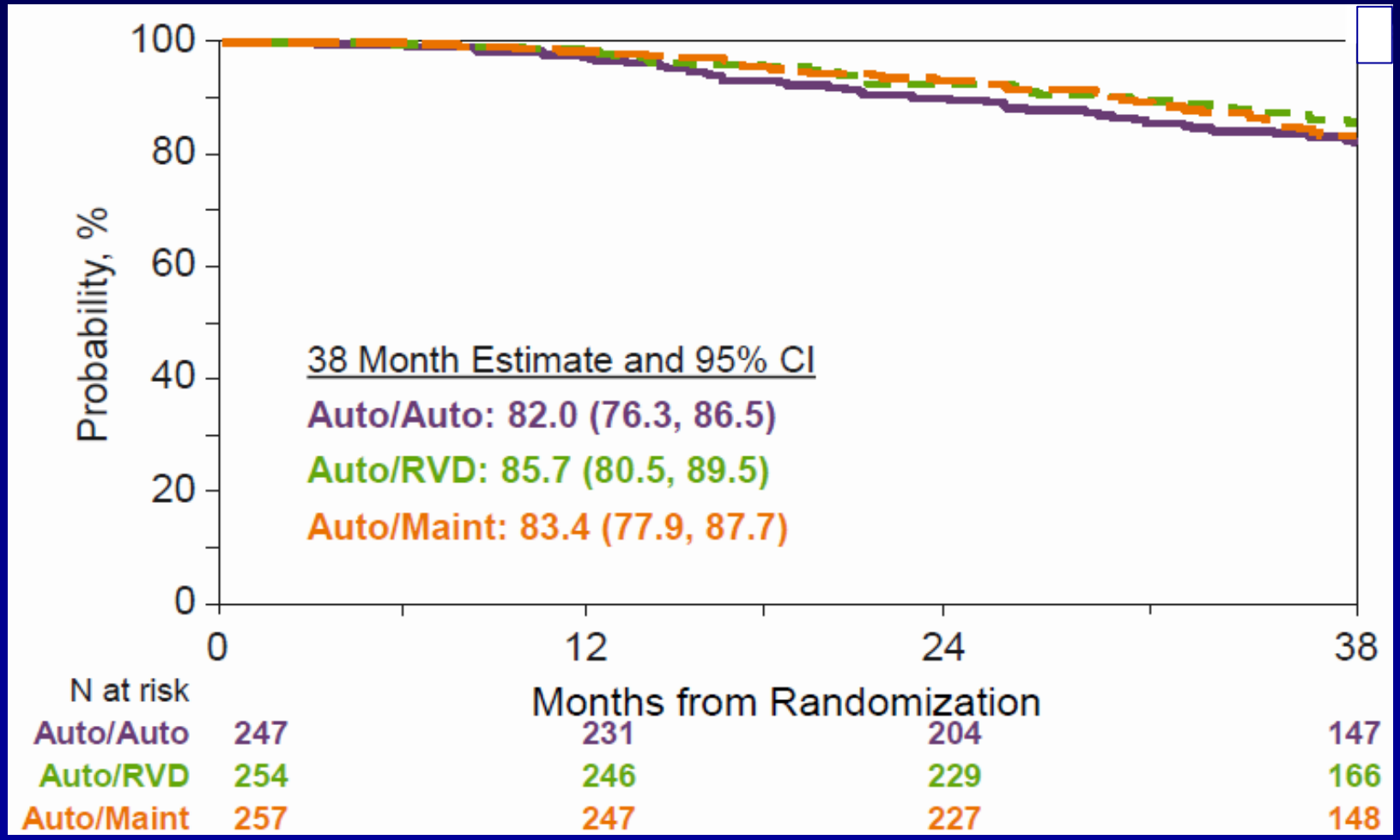
- **PFS in high risk pts was similar to standard risk group across all arms**

ASCT, autologous stem cell transplant; Auto, autologous stem cell transplant; Maint, maintenance; PFS, progression-free survival; RVd, lenalidomide, bortezomib, dexamethasone; Tx, treatment.

Stadtmauer E et al. *ASH* 2016; Oral Presentation and Abstract LBA-1

STaMINA: ASCT + RVd vs Tandem ASCT
Overall Survival

- **At 38 mos follow-up, OS was similar across all 3 Tx arms**



ASCT, autologous stem cell transplant; Auto, autologous stem cell transplant; Maint, maintenance; OS, overall survival; RVd, lenalidomide, bortezomib, dexamethasone; Tx, treatment.

Stadtmauer E et al. *ASH* 2016; Oral Presentation and Abstract LBA-1

Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival

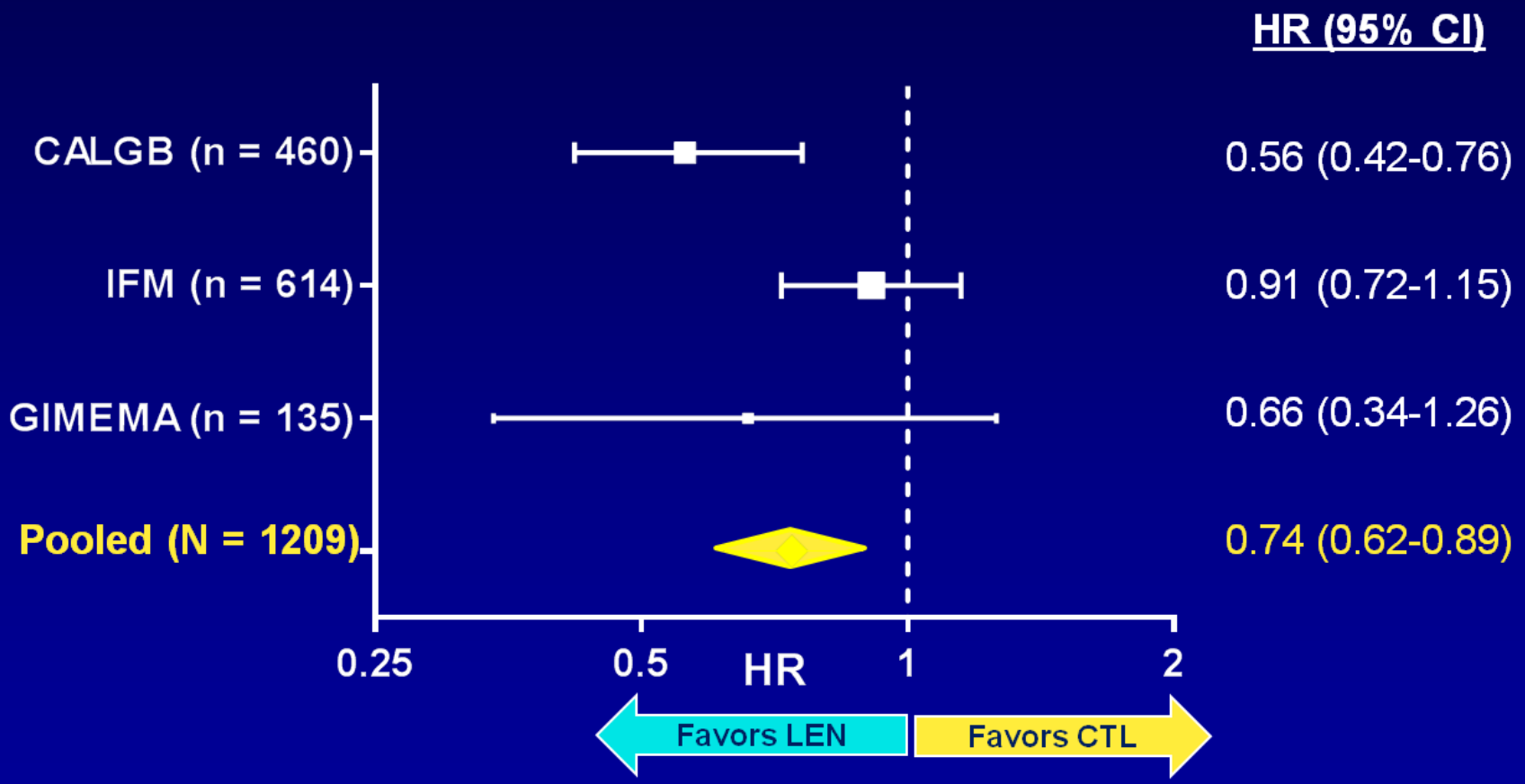
Michel Attal,[1] Antonio Palumbo,[2] Sarah A. Holstein,[3] Valérie Lauwers-Cances,[1] Maria Teresa Petrucci,[4] Paul Richardson,[5] Cyrille Hulin,[6] Patrizia Tosi,[7] Kenneth C. Anderson,[5] Denis Caillot,[8] Valeria Magarotto,[9] Philippe Moreau,[10] Gerald Marit,[11] Zhinuan Yu,[12] Philip L. McCarthy[13]

[1]Institut Universitaire du Cancer, Toulouse-Oncopole, France; [2]The Myeloma Unit, Department of Hematology, University of Turin, Turin, Italy; [3]Roswell Park Cancer Institute, Buffalo, NY; [4]University La Sapienza, Rome, Italy; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Bordeaux Hospital University Center (CHU), Bordeaux, France; [7]Seràgnoli Institute of Hematology and Medical Oncology, Bologna University, Bologna, Italy; [8]Dijon University Hospital Center, Dijon, France; [9]University of Torino, Torino, Italy; [10]University Hospital Hôtel-Dieu, Nantes, France; [11]Centre Hospitalier Universitaire, Bordeaux, France; [12]Celgene Corporation, Summit, NJ; [13]Blood and Marrow Transplant Program, Roswell Park Cancer Institute, Buffalo, NY

Attal M, et al. *ASCO 2016. Oral Presentation and Abstract #8001.*

LEN Maintenance After ASCT in MM: OS Analysis

Hazard Ratios by study



ASCT, autologous stem cell transplant; CTL, control; HR, hazard ratio; LEN, lenalidomide; MM, multiple myeloma; OS, overall survival.

Attal M, et al. *ASCO 2016. Oral Presentation and Abstract #8001.*

ASH 2017: Lenalidomide Maintenance Significantly Improves Outcomes Compared to Observation Irrespective of Cytogenetic Risk: Results of the Myeloma XI Trial

Graham Jackson[1], Faith E Davies[2], Charlotte Pawlyn[3,5], David Cairns[4], Alina Striha[4], Anna Hockaday[4], Inga Sakauskiene[4], John R Jones[3,5], Bhuvan Kishore[6], Mamta Garg[7], Cathy Williams[8], Kamaraj Karunanithi[9], Jindriska Lindsay[10], Matthew W Jenner[11], Gordon Cook[12], Martin F Kaiser[3,5], Mark T Drayson[13], Roger G Owen[14], Nigel H. Russell[8], Walter M Gregory[4] and Gareth J. Morgan[2]

1)Department of Haematology, University of Newcastle, Newcastle Upon Tyne; 2)Myeloma Institute, University of Arkansas for Medical Sciences, Little Rock, AR; 3)The Institute of Cancer Research, London 4)Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, Leeds; 5)Department of Haematology, The Royal Marsden Hospital NHS Foundation Trust, London; 6)Heart of England Foundation Trust, Birmingham; 7)Leicester Royal Infirmary, Leicester; 8)Centre for Clinical Haematology, Nottingham University Hospital, Nottingham; 9)University Hospital of North Midlands, Stoke on Trent; 10)Kent and Canterbury NHS Trust, Canterbury; 11)Department of Haematology, University Hospital Southampton NHS Foundation Trust, Southampton; 12)Leeds Institute of Cancer and Pathology, University of Leeds, Leeds; 13)Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham; 14)St James's University Hospital, Leeds

On behalf of the Myeloma XI Trial Management Group and NCRI Haem-Onc CSG

Myeloma XI

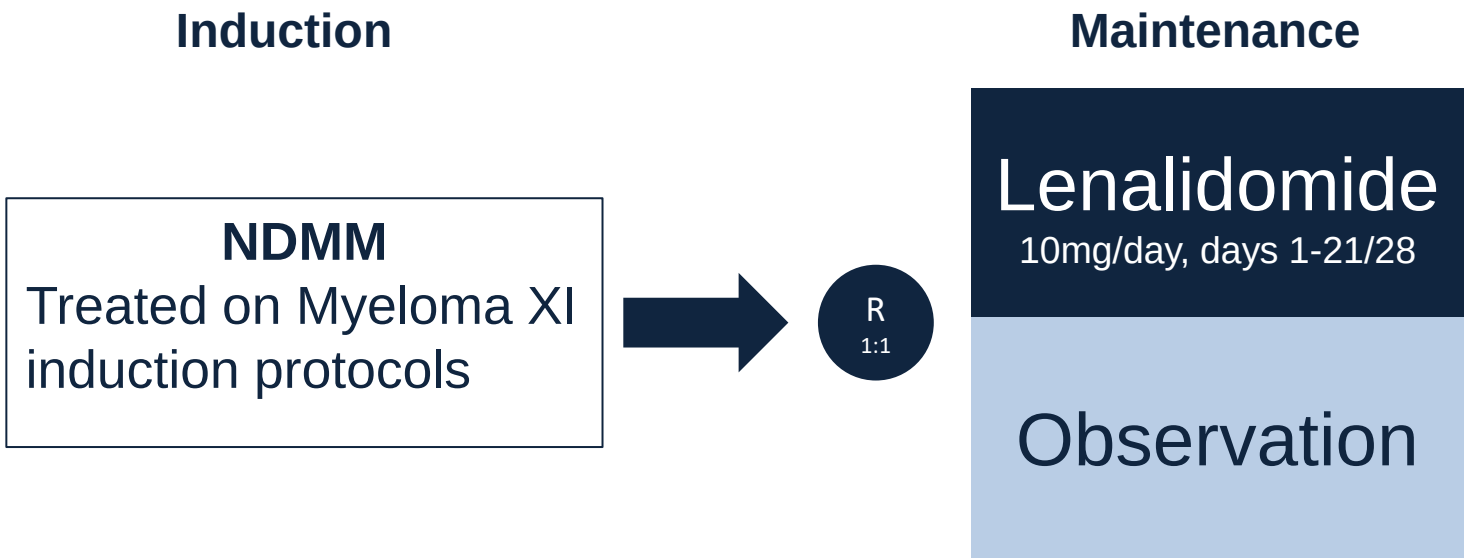
Study objective:

- To determine the efficacy and safety of lenalidomide continued to disease progression.

Study design:

- Phase III, multicentre, open label, parallel group, randomised controlled trial.
- Newly diagnosed symptomatic myeloma patients of all ages.
- Randomisation at 3 months post ASCT (TE) or at maximum response (TNE).
- Primary endpoints: PFS and OS.

Myeloma XI



N=1971 **TE** = 1248, **TNE** = 723

Median follow up: 30.6 months (IQR 17.9-50.7)

Exclusion criteria

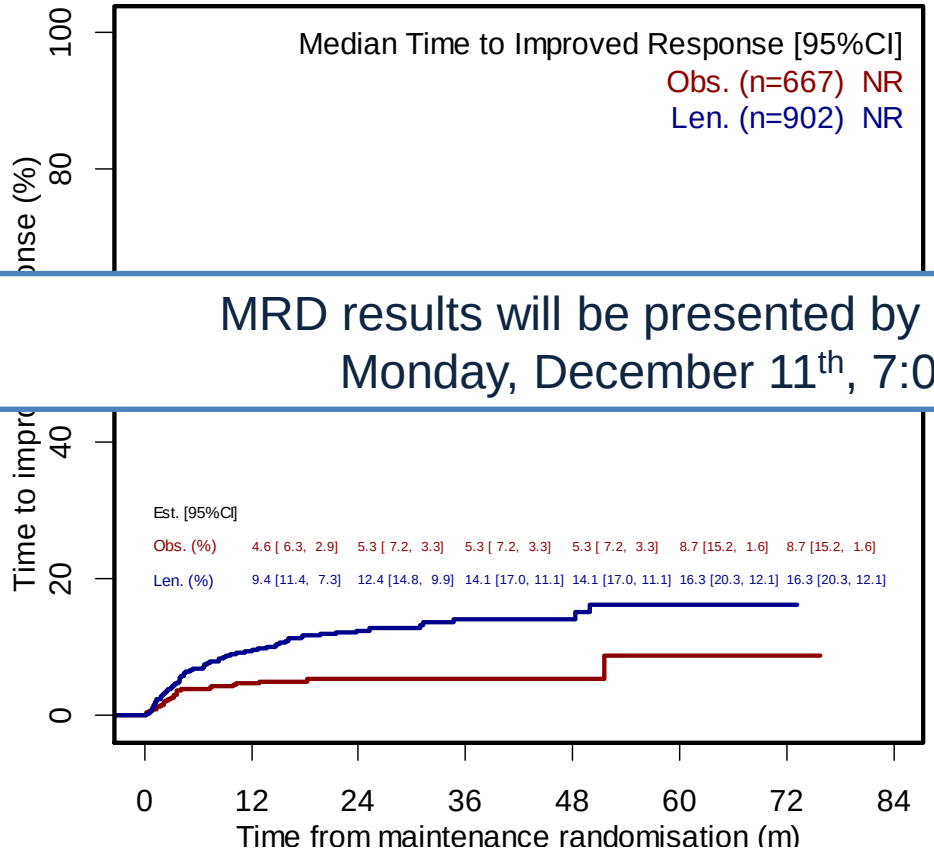
- Failure to respond to lenalidomide as induction IMiD or progressive disease
- Previous or concurrent active malignancies

TE: transplant eligible

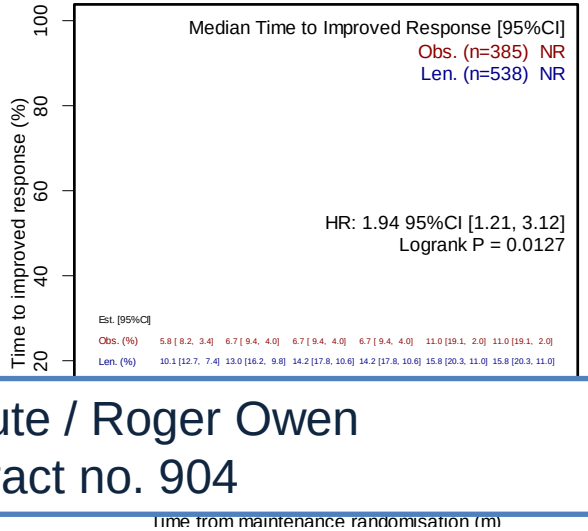
TNE: transplant non-eligible

Lenalidomide improved response during maintenance

All:

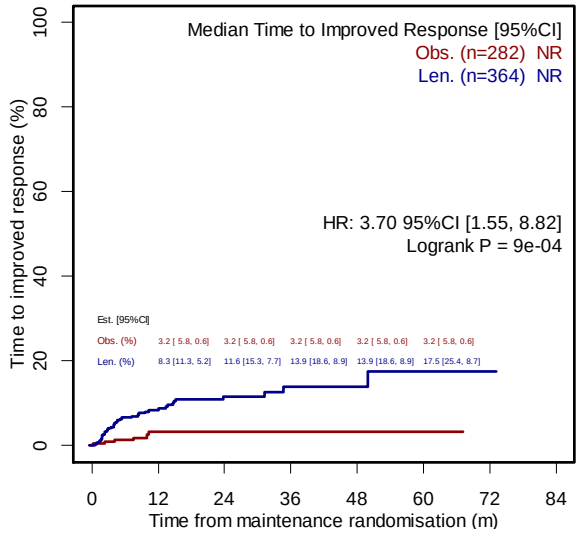


TE:



MRD results will be presented by Ruth de Tute / Roger Owen
Monday, December 11th, 7:00PM Abstract no. 904

TNE:



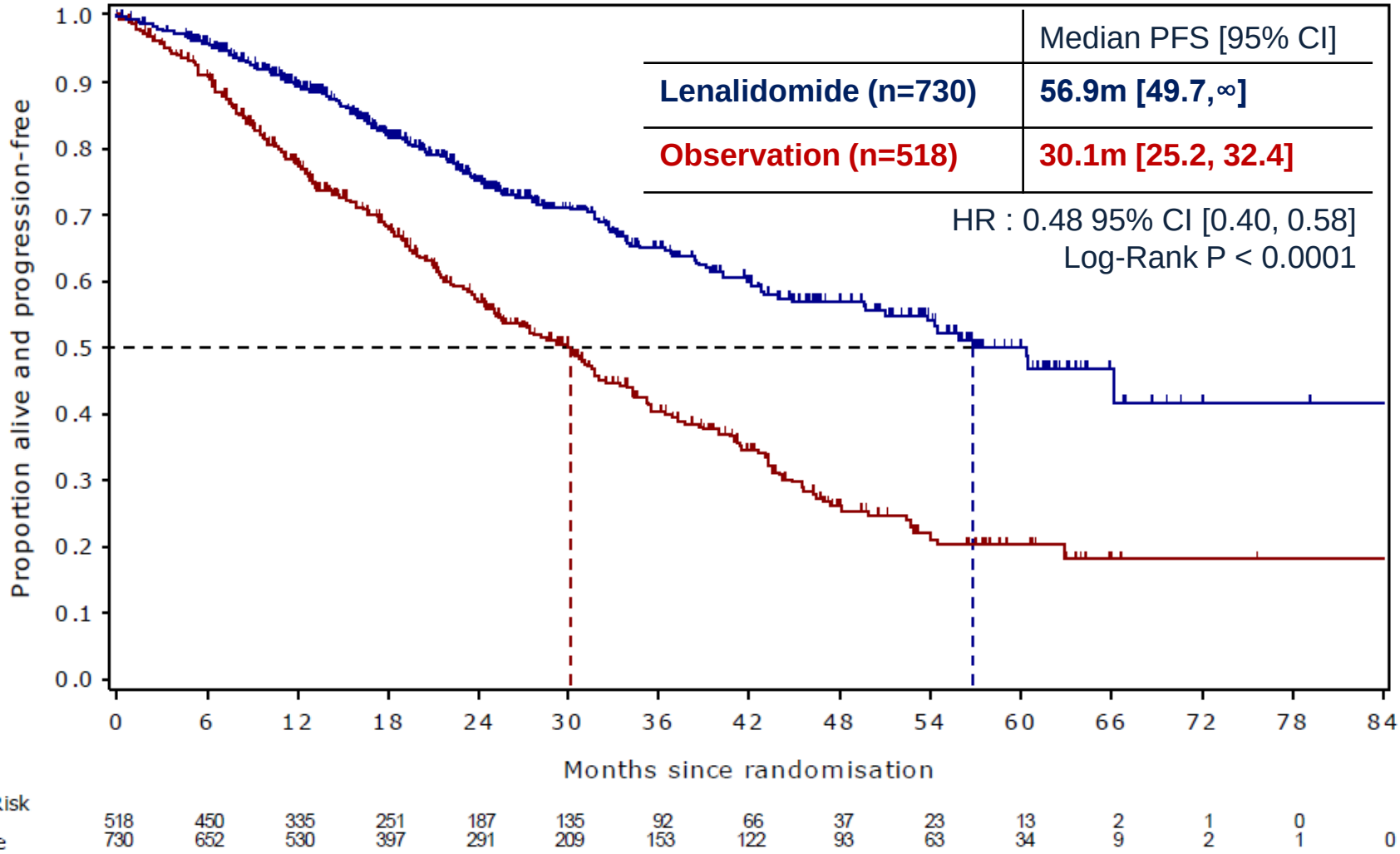
Improved response = achievement of VGPR/CR

TE: transplant eligible

TNE: transplant non-eligible

Transplant eligible pathway

Lenalidomide improved PFS from 30 to 57 months, hazard ratio of 0.47

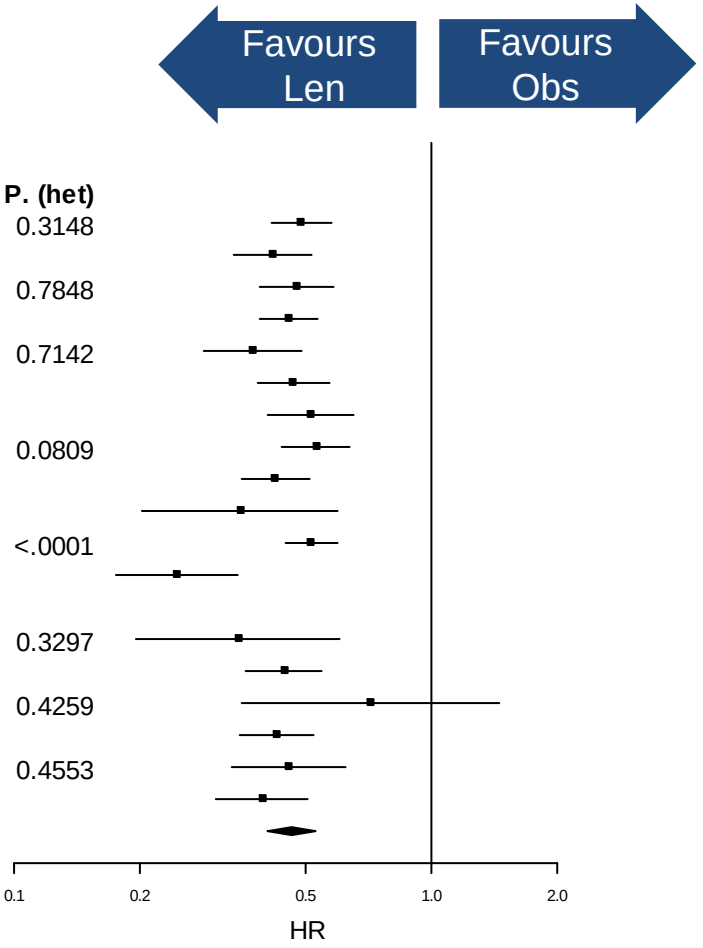


PFS: progression-free survival

Subgroup analysis

Across both pathways lenalidomide improved PFS from 20 to 39 months, Hazard ratio of 0.46

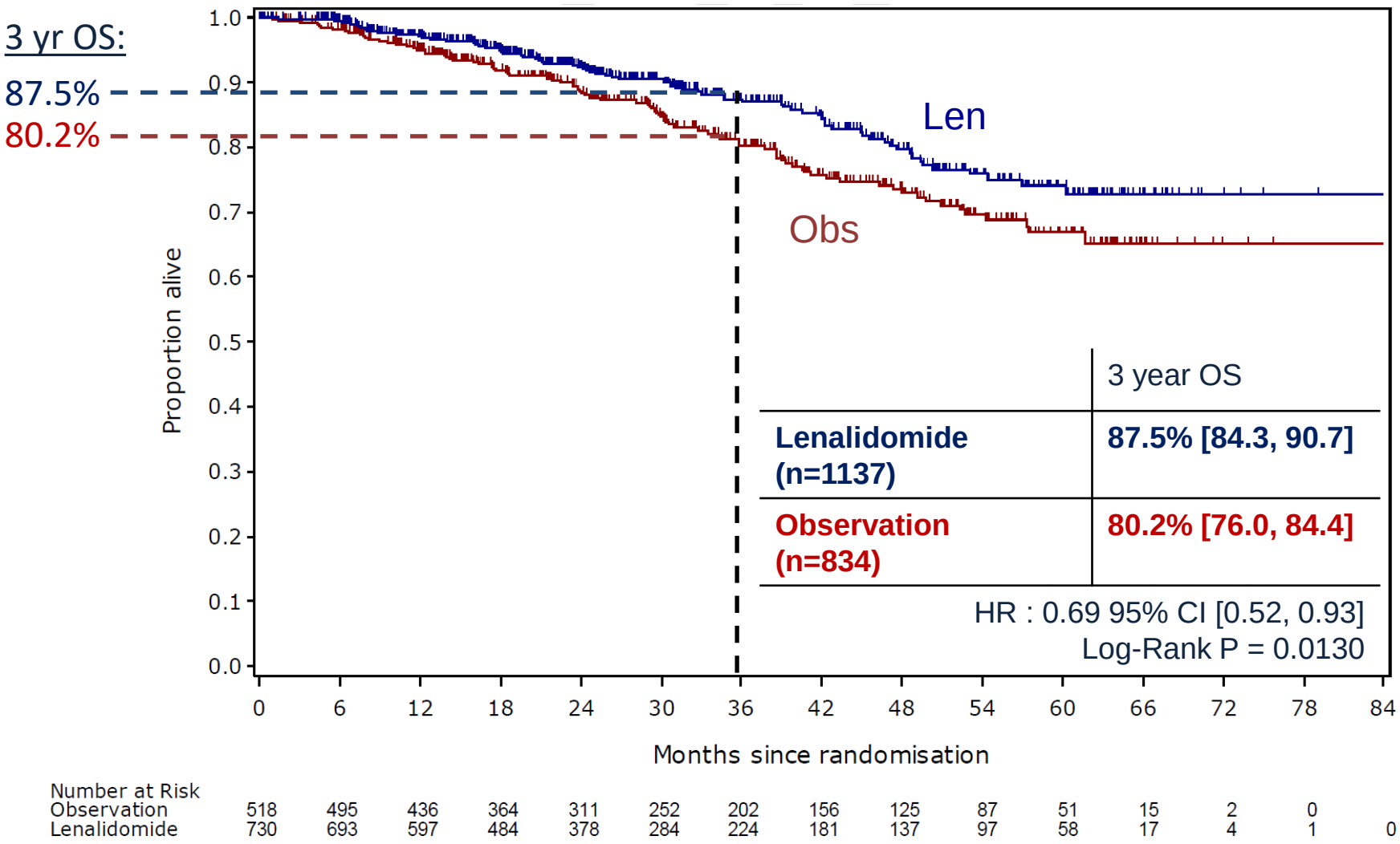
Subgroup	Level	Observation n/N	Lenalidomide n/N	HR [95%CI]	P. (het)
Gender	Male	336/527	294/696	0.49 (0.42, 0.57)	0.3148
	Female	197/307	162/441	0.42 (0.34, 0.52)	
Age	<=65 years	219/421	164/596	0.47 (0.39, 0.58)	0.7848
	>65 years	314/413	292/541	0.45 (0.39, 0.53)	
ISS	Stage I	131/239	97/327	0.37 (0.28, 0.49)	0.7142
	Stage II	229/349	182/439	0.47 (0.38, 0.57)	
	Stage III	138/192	149/291	0.51 (0.41, 0.65)	
Induction therapy	CTD/CTDa	242/344	224/430	0.53 (0.44, 0.64)	0.0809
	RCD/RCDa	262/373	207/473	0.42 (0.35, 0.51)	
	CCRD	29/117	25/234	0.35 (0.20, 0.60)	
Response before maintenance	CR or VGPR	433/706	371/947	0.52 (0.45, 0.59)	<.0001
	PR or MR	95/117	74/171	0.25 (0.18, 0.34)	
	NC or PD	3/6	5/8		
t(4,14)	Present	32/32	25/51	0.35 (0.20, 0.60)	0.3297
	Absent	199/295	173/396	0.44 (0.36, 0.55)	
del(17p)	Present	21/24	20/37	0.71 (0.35, 1.45)	0.4259
	Absent	210/303	178/410	0.43 (0.35, 0.52)	
1q gain	Present	84/107	84/162	0.46 (0.33, 0.62)	0.4553
	Absent	147/220	114/285	0.39 (0.31, 0.51)	
Overall		**533/834**	**456/1137**	**0.46 (0.41, 0.53)**	



PFS: progression-free survival

Transplant eligible pathway

Lenalidomide improved 3 yr OS from 80.2% to 87.5%, hazard ratio of 0.69

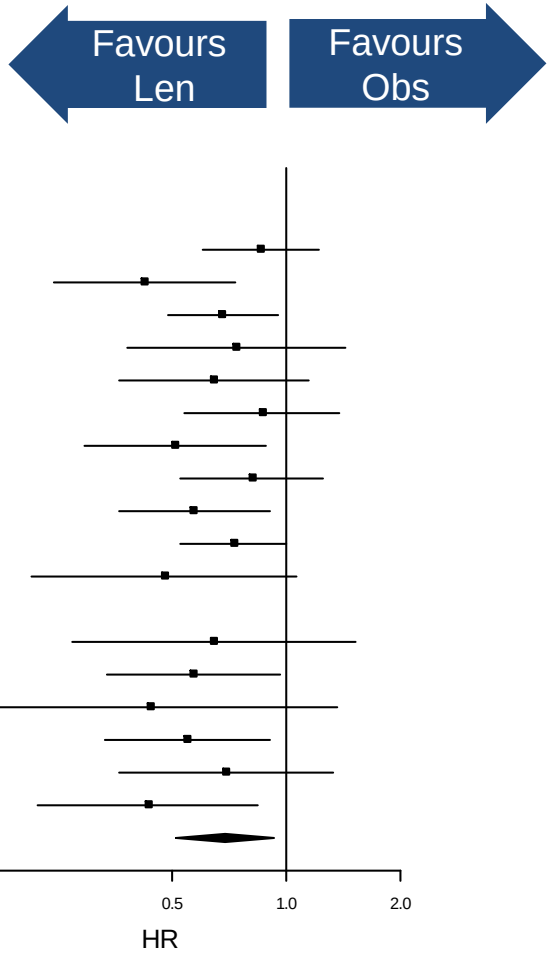


OS: overall survival

Transplant eligible pathway

Lenalidomide improved 3 yr OS from 80.2% to 87.5%, hazard ratio of 0.69

Subgroup	Level	Observation n/N	Lenalidomide n/N	HR [95%CI]	P. (het)
Gender	Male	58/327	65/459	0.86 (0.60, 1.22)	0.0243
	Female	40/191	19/271	0.42 (0.24, 0.74)	
Age	<=65 years	80/406	65/577	0.68 (0.49, 0.95)	0.8075
	>65 years	18/112	19/153	0.74 (0.38, 1.43)	
ISS	Stage I	28/180	21/251	0.64 (0.36, 1.14)	0.4784
	Stage II	35/206	37/266	0.86 (0.54, 1.38)	
	Stage III	31/101	22/157	0.51 (0.30, 0.89)	
Induction therapy	CTD	43/194	40/236	0.81 (0.53, 1.25)	0.5242
	RCD	47/207	31/260	0.57 (0.36, 0.90)	
Response before maintenance	CR or VGPR	81/449	70/626	0.73 (0.53, 1.00)	0.7076
	PR or MR	15/60	11/93	0.48 (0.22, 1.06)	
	NC or PD	1/4	1/4		
t(4,14)	Present	10/24	12/42	0.65 (0.28, 1.52)	0.8304
	Absent	35/177	25/229	0.57 (0.34, 0.96)	
del(17p)	Present	7/13	10/25	0.44 (0.14, 1.36)	0.6927
	Absent	38/188	27/246	0.55 (0.34, 0.91)	
1q gain	Present	17/58	24/104	0.70 (0.36, 1.33)	0.287
	Absent	28/143	13/167	0.43 (0.22, 0.84)	
Overall		**98/518**	**84/730**	**0.69 (0.52, 0.93)**	



OS: overall survival

Conclusions

- **Treatment with lenalidomide until disease progression resulted in a highly significant improvement in PFS for newly diagnosed myeloma patients of all ages.**
- **Overall survival was prolonged in transplant eligible patients.**
- **The benefit was attenuated in transplant non-eligible patients by subsequent treatment regimens.**
- **There was no evidence of an increase in mutational instability or significant toxicity with lenalidomide maintenance.**
- **Lenalidomide maintenance is effective irrespective of cytogenetic risk status.**

DETERMINATION

DFCI 10-106 / IFM DFCI 2009 / BMT CTN 1304

Delayed vs. Early Transplant with Revlimid Maintenance and Antimyeloma Triple therapy

Objectives

1) Compare progression-free survival between Arm A and Arm B for patients with newly diagnosed symptomatic MM
2) Evaluate the impact of lenalidomide maintenance given until progression

Eligibility

Multiple myeloma diagnosis based on IMF 2003 Diagnostic Criteria
Diagnostic assessments w/in 21 days of protocol therapy
Age 18 to 65 years

REGISTRATION

INITIAL THERAPY
Lenalidomide+ bortezomib + dexamethasone (RVD)
1 Cycle (21 days)

RANDOMIZATION
Stratify according to:
- ISS stage (stage I, II or III)
- Cytogenetics: standard vs. high-risk vs FISH failures. High-risk is defined as presence of del(17p), or t(4:14), or t(14;16) using FISH.

ARM A

- **RVD q 21 days (2 cycles)**
- **Collection of peripheral blood stem cells (PBSCs)** using cyclophosphamide and filgrastim or G-CSF type Granocyte® or equivalent
- **RVD q 21 days (5 cycles)**
- **Maintenance Lenalidomide** q28 days (until disease progression)

ARM B

- **RVD q 21 days (2 cycles)**
- **Collection of peripheral blood stem cells (PBSCs)** using cyclophosphamide and filgrastim or G-CSF type Granocyte® or equivalent
- **Autologous stem cell transplant**
  - Melphalan: infused over two days or as a single infusion
  - Re-infusion of PBSCs
- **RVD q 21 days (2 cycles)**
- **Maintenance Lenalidomide** q28 days (until disease progression)

- ***Study treatment provided free of charge to all study participants***
- ***BMT CTN accrual credit provided to all BMT CTN centers***

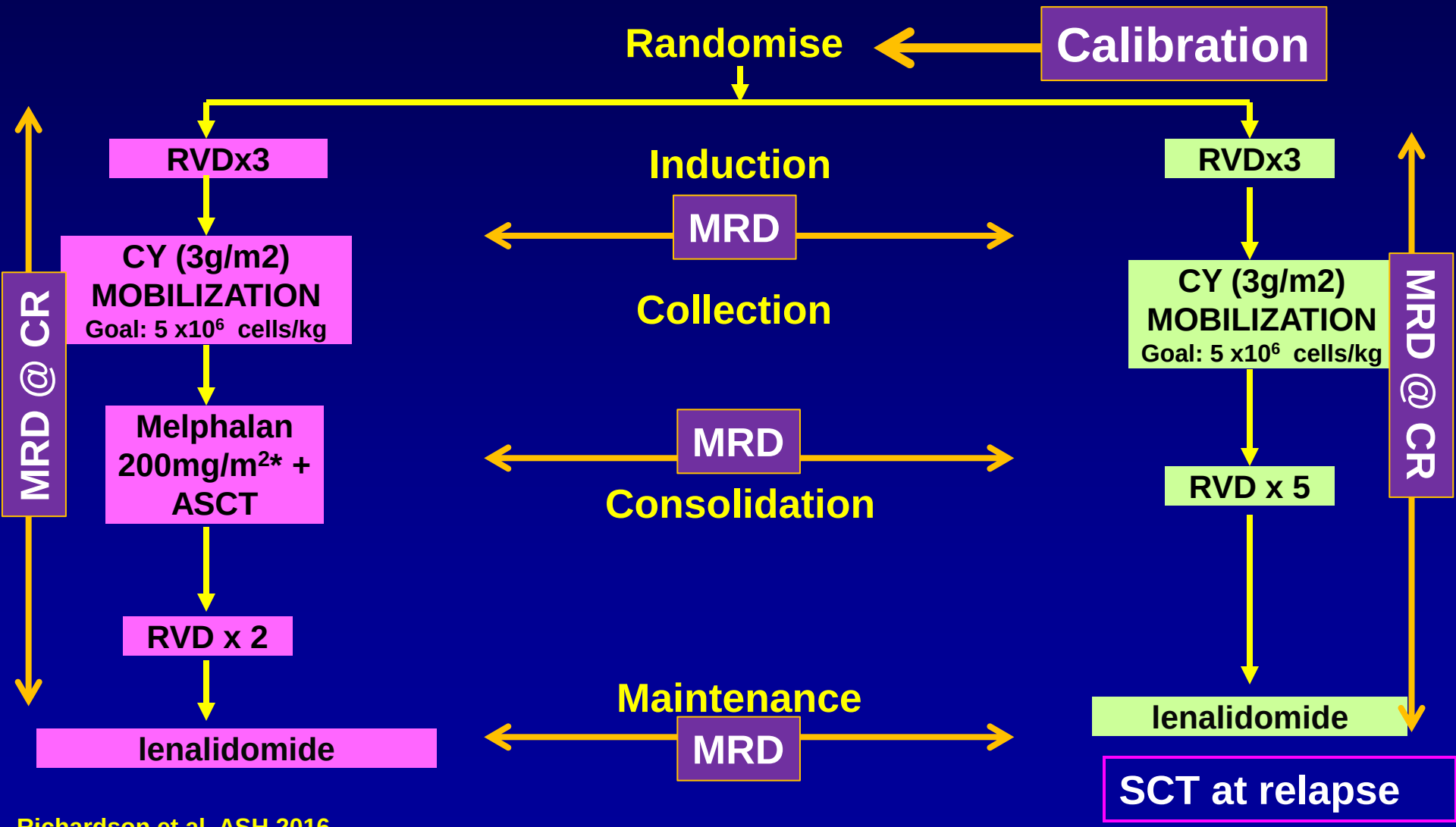
Protocol Chair: PG Richardson: paul_richardson@dfci.harvard.edu
Protocol Coordinator: A Zeytoonjian: andreaA_zeytoonjian@dfci.harvard.edu
BMT CTN Project Manager: Ann Foley, MA, CCRP: afoley@nmdp.org

To view the entire protocol, go to www.bmtctn.net Posted to http://clinicaltrials.gov/ as NCT01208662

DANA-FARBER CANCER INSTITUTE

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Ph.III: IFM/DFCI 2009 Study (US and France)
Newly Diagnosed MM (N=1,420)



Richardson et al, ASH 2016

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 6, 2017 VOL. 376 NO. 14

Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma

Michel Attal, M.D., Valerie Lauwers-Cances, M.D., Cyrille Hulin, M.D., Xavier Leleu, M.D., Denis Caillot, M.D., Martine Escoffre, M.D., Bertrand Arnulf, M.D., Margaret Macro, M.D., Karim Belhadj, M.D., Laurent Garderet, M.D., Murielle Roussel, M.D., Catherine Payen, M.D., Claire Mathiot, M.D., Jean P. Fermand, M.D., Nathalie Meuleman, M.D., Sandrine Rollet, M.S., Michelle E. Maglio, B.S., Andrea A. Zeytoonjian, B.S., Edie A. Weller, Ph.D., Nikhil Munshi, M.D., Kenneth C. Anderson, M.D., Paul G. Richardson, M.D., Thierry Facon, M.D., Hervé Avet-Loiseau, M.D., Jean-Luc Harousseau, M.D., and Philippe Moreau, M.D., for the IFM 2009 Study*

Attal M et al. *N Engl J Med* 2017;376:1311-1320

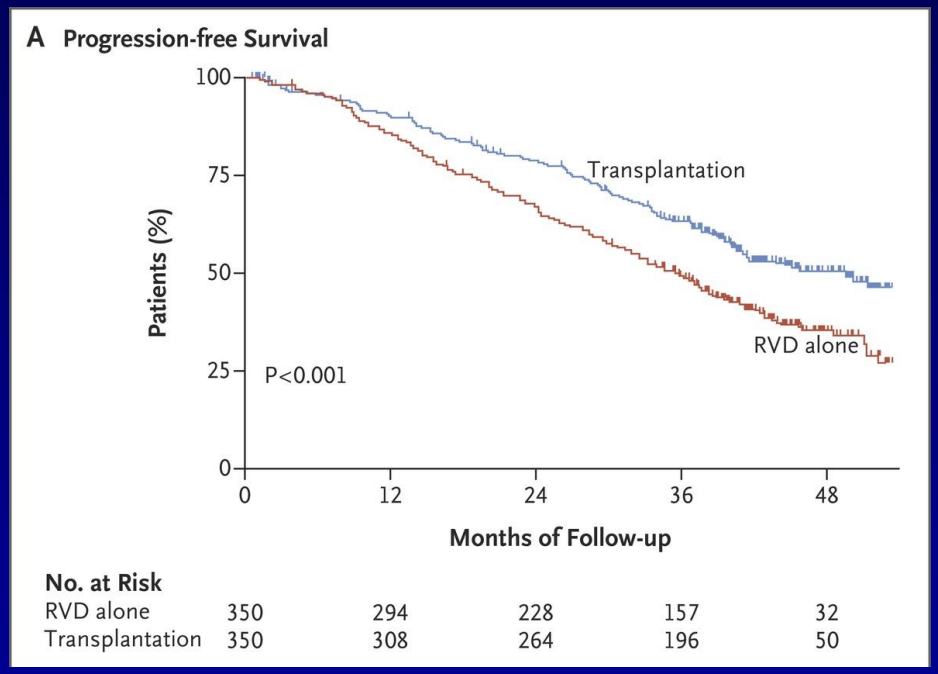
Phase III: IFM 2009: Patient Characteristics

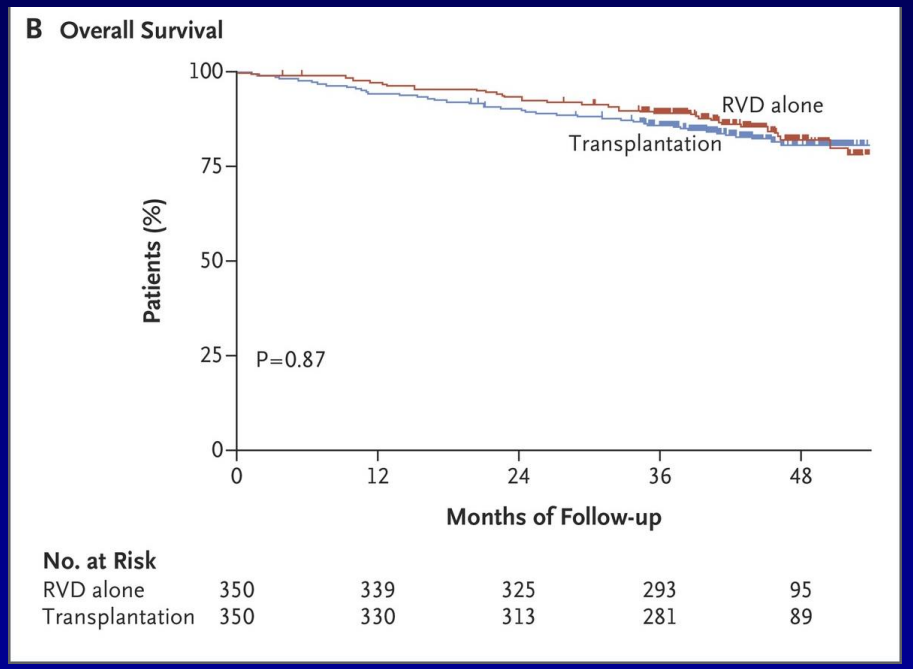
Characteristic	RVD-Alone Group (N = 350)	Transplantation Group (N = 350)
Median Age (Range), yr.	59 (29-66)	60 (30-60)
Male, n (%)	208 (59)	214 (61)
Type of myeloma, n (%)		
IgG	209 (60)	223 (64)
IgA	71 (20)	73 (21)
Light Chain	57 (16)	46 (13)
Other	13 (4)	8 (2)
ISS, n (%)		
I	115 (33)	118 (34)
II	170 (49)	171 (49)
III	65 (19)	61 (17)
B2M, n (%)		
<3.5mg/l	169 (48)	178 (51)
>3.5mg/l	181 (52)	172 (49)
Cytogenetics		
t(4:14)	26/256	28/259
del 17p	15/256	16/258
t (14:16)	6/256	6/258
t (4:14) or t(14:16) or del 17p	44/256	46/259

ISS, international staging system; RVD, lenalidomide, bortezomib, dexamethasone.

Attal M et al. *N Engl J Med* 2017;376:1311-1320

Phase III: IFM 2009: PFS & OS Curves





- **Data cut off 1st Sep 2015**

PFS, progression free survival; OS, overall survival; RVD, lenalidomide, bortezomib, dexamethasone.

Attal M et al. *N Engl J Med* 2017;376:1311-1320

Phase III: IFM 2009: Response to Treatment

Table 2. Response to Treatment.*

Outcome	RVD-Alone Group (N=350)	Transplantation Group (N=350)	Adjusted P Value†
Best response during the study — no. (%)			0.02
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 — no. (%)	169 (48)	205 (59)	0.03
Complete response or very good partial response — no. (%)	270 (77)	307 (88)	0.001
Minimal residual disease not detected during the study — no./ total no. with complete or very good partial response (%)‡	171/265 (65)	220/278 (79)	<0.001

* Responses were assessed according to the International Uniform Response Criteria for Multiple Myeloma. Percentages may not total 100 because of rounding.

† P values were adjusted for multiplicity with the use of the Holm procedure to control the family-wise error rate at 0.05.

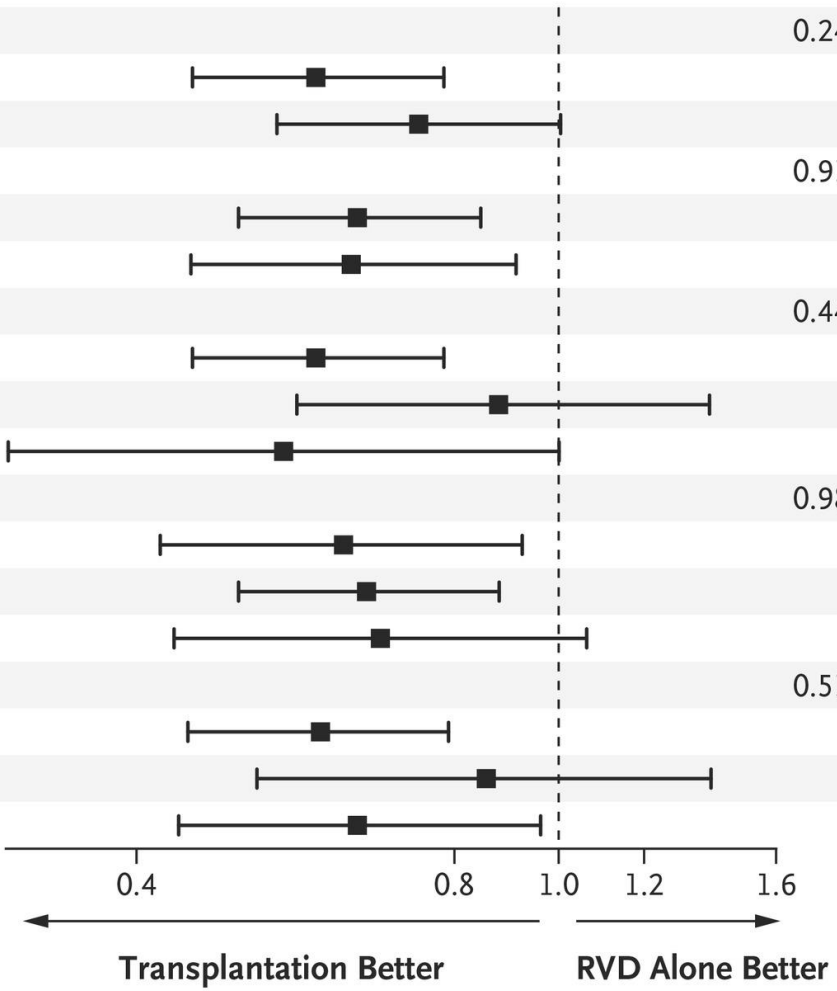
‡ Minimal residual disease was detected by means of flow cytometry. As a result of decisions made by the patient or the investigator, 5 patients in the RVD-alone group and 29 patients in the transplantation group were not tested.

RVD, lenalidomide, bortezomib, dexamethasone.

Attal M et al. *N Engl J Med* 2017;376:1311-1320

Phase III: IFM 2009: Subgroup Analyses of PFS

Subgroup	Transplantation	RVD Alone	Hazard Ratio (95% CI) for Progression or Death	P Value for Interaction
	no. of events/no. of patients			
Age				0.24
18–59 yr	126/196	85/185		
60–65 yr	85/154	72/165		
Sex				0.91
Male	129/208	102/214		
Female	82/142	55/136		
Type of multiple myeloma				0.44
IgG	133/209	96/223		
IgA	38/71	39/73		
Light chain	31/57	17/46		
International Staging System disease stage				0.98
I	60/115	44/118		
II	107/170	81/171		
III	44/65	32/61		
Cytogenetic risk at screening				0.51
Standard risk	122/212	83/213		
High risk	32/44	31/46		
Test failure	57/94	43/91		



PFS, progression free survival; RVD, lenalidomide, bortezomib, dexamethasone.

Attal M et al. N Engl J Med 2017;376:1311-1320

Phase III: IFM 2009: Adverse Events

Grade 3 / 4 AEs in ≥2%	RVD-Alone Group (N = 350)	Transplantation Group (N = 350)
Neutropenia	166 (47.4)	322 (92.0)
Febrile neutropenia	12 (3.4)	52 (14.9)
Anaemia	31 (8.9)	69 (19.7)
Thrombocytopenia	50 (14.3)	291 (83.1)
Nausea and vomiting	5 (1.4)	25 (7.1)
Stomatitis	0	59 (16.9)
Diarrhoea	10 (2.9)	15 (4.3)
Cytolytic hepatitis	11 (3.1)	7 (2.0)
Fatigue	7 (2.0)	6 (1.7)
Pyrexia	1 (0.3)	13 (3.7)
Infections	31 (8.9)	71 (20.3)
Peripheral neuropathy	42 (12.0)	45 (12.9)
Rash	7 (2.0)	4 (1.1)
Any thromboembolic event*	13 (3.7)	19 (5.4)

AE, adverse event; RVD, lenalidomide, bortezomib, dexamethasone.

Attal M et al. *N Engl J Med* 2017;376:1311-1320

IFM 2009: Causes of Mortality (9/2015)

	RVD arm N=48	Transplant N=54
Myeloma, n (%)	40/48 (83%)	35/54 (65%)
Toxicity, n (%)	4/48 (8%)	9*/54 (16%)
SPM (AML/MDS)	1/48 (2%)	6/54 (11%)
Others	3/48 (6%)	4/54 (7%)

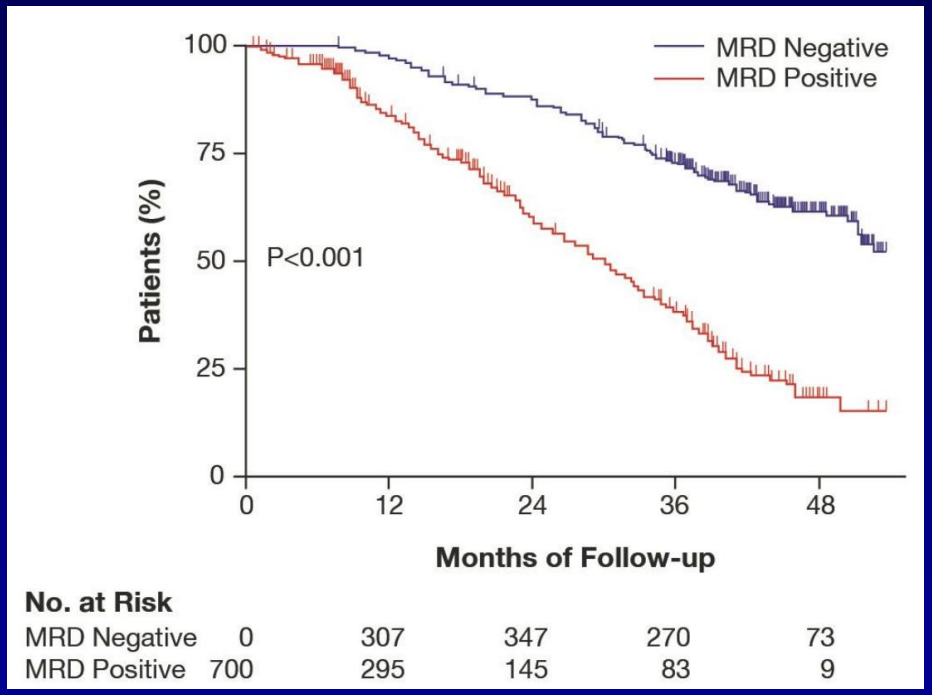
*Included 5 transplant related deaths

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; RVD, lenalidomide, bortezomib, dexamethasone; SPM second primary malignancies.

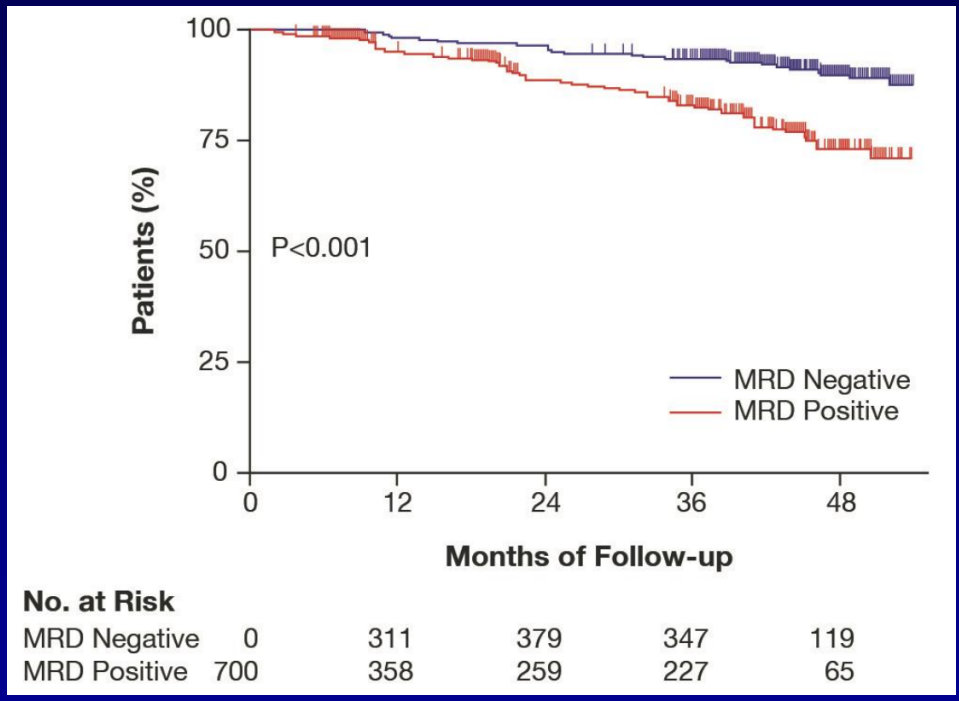
Attal M, et al. *ASH 2015. Oral Presentation and Abstract 391.*

Phase III: IFM 2009: PFS & OS According to MRD Status

Progression Free Survival



Overall Survival



- **Progression-free survival was prolonged in patients who were MRD negative versus those who were MRD positive (adjusted hazard ratio, 0.30; 95% confidence interval, 0.23 to 0.37; P<0.001).**
- **Overall survival was prolonged in patients who were MRD negative versus those who were MRD positive (adjusted hazard ratio, 0.34; 95% confidence interval, 0.22 to 0.51; P<0.001).**

MRD, minimal residual disease; OS, overall survival; PFS, progression free survival.

Attal M et al. *N Engl J Med* 2017;376:1311-1320

Key Targets in MM 2017

Genomic abnormalities:

- Target and Overcome Mutations
- Critical Role of Combination Therapy
- Evolving Position and Timing of ASCT

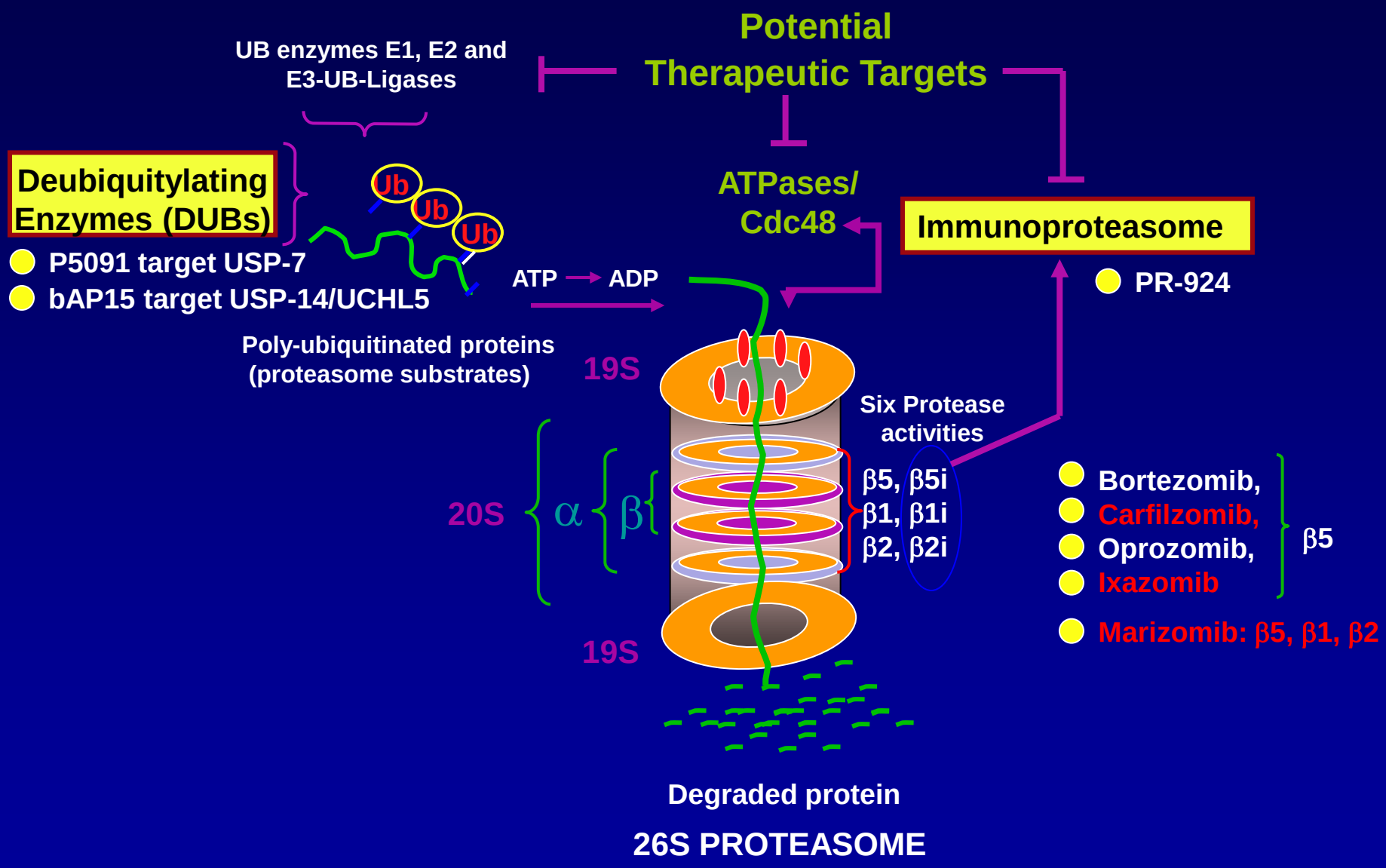
Excess Protein Production:

- Target Protein Degradation

Immune Suppression:

- Restore anti-MM immunity

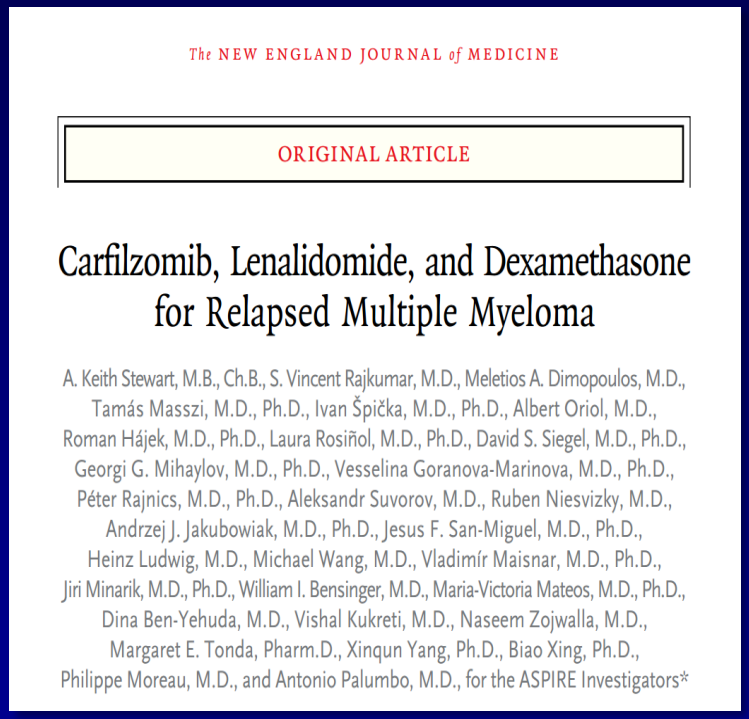
Targeting the Ubiquitin Proteasome System In MM; The Central Role of Proteasome Inhibition (PI)



Adapted from Lawasut, P, Chauhan D, Hideshima T, Richardson PG et al. IMW 2013

Phase III ASPIRE Study: KRd vs. Rd (n=792)

Primary endpoint = PFS; OS update ASH 2017



The NEW ENGLAND JOURNAL of MEDICINE

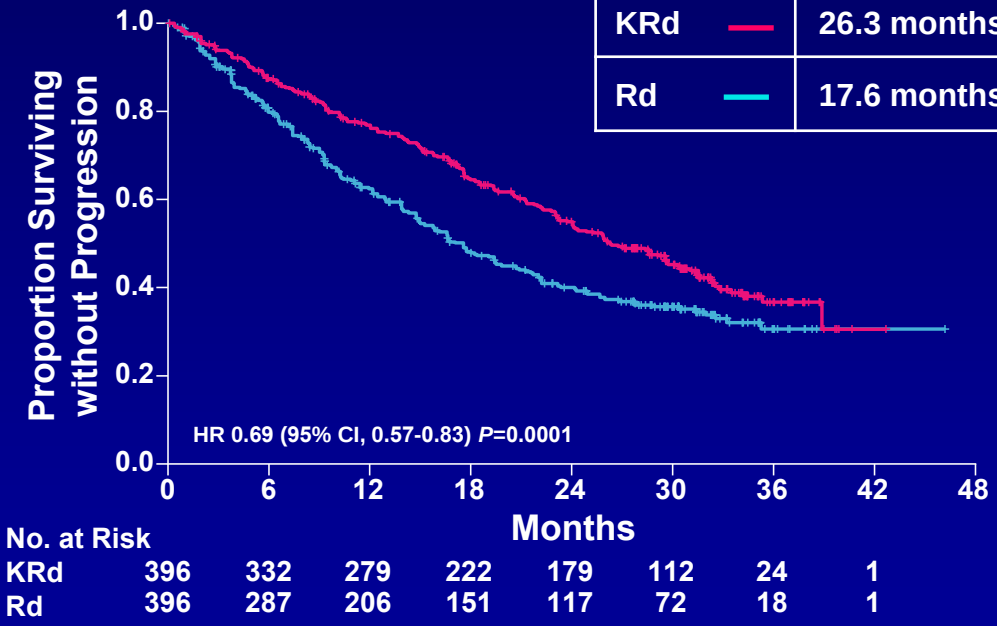
ORIGINAL ARTICLE

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

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

	KRd (n = 396)	Rd (n = 396)	*p*-Value
ORR (≥PR)	87.1%	66.7%	<0.001
≥CR	31.8%	9.3%	<0.001

Treatment	Median PFS
KRd	26.3 months
Rd	17.6 months



- Median follow-up for KRd: 32.3 months

AE, adverse event; ASPIRE: CArfilzomib, Lenalidomide, and DexamethaSone versus Lenalidomide and Dexamethasone for the treatment of Patients with Relapsed Multiple MyEloma; CI, confidence interval; CR, complete response; KRd, carfilzomib, lenalidomide, low-dose dexamethasone; ORR, overall response rate; Rd, lenalidomide and low-dose dexamethasone; PR, partial response; URTI, upper respiratory tract infection

Stewart AK et al. *N Engl J Med*. 2015; 372 (2): 142-52.

Ixazomib (MLN 9708) – a first in class oral proteasome inhibitor (PI)

- Ixazomib is the first oral proteasome inhibitor to be studied in the clinic
  - Ixazomib is a peptide boronic acid proteasome inhibitor that has a distinct physicochemical structure and pharmacology compared to bortezomib[1,2]
  - Preclinical studies indicated synergy with lenalidomide[3]
- An early-phase study[4] of ixazomib plus lenalidomide-dexamethasone (IRd) in newly diagnosed MM:
  - Substantial activity (overall response rate 92%)
  - Tolerable and manageable safety profile, enabling long-term treatment
- Rationale for the phase 3 TOURMALINE-MM1 study assessing IRd (vs. placebo) plus lenalidomide-dexamethasone in patients with relapsed and/or refractory MM
  - IRd: first all-oral triplet regimen containing a proteasome inhibitor and an immunomodulatory drug

1. Kupperman E, et al. *Cancer Res* 2010;70:1970–80.
2. Lee EC, et al. *Clin Cancer Res* 2011; 2011;17:7313–23.
3. Chauhan D, et al. *Clin Cancer Res* 2011;17:5311–21.
4. Kumar SK, et al., *Lancet Oncol.* 2014;15:1503–12.

TOURMALINE-MM1

The NEW ENGLAND JOURNAL of MEDICINE

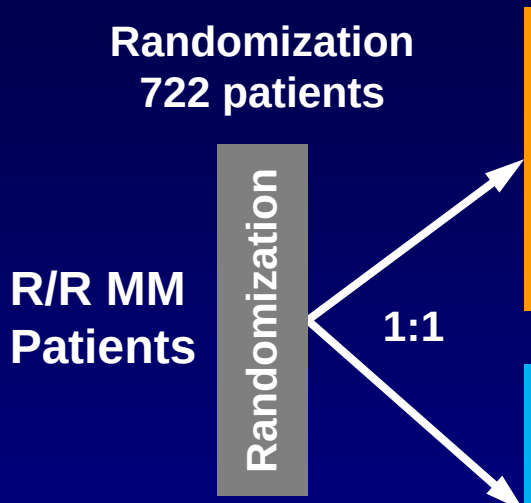
ORIGINAL ARTICLE

Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

P. Moreau, T. Masszi, N. Grzasko, N.J. Bahlis, M. Hansson, L. Pour, I. Sandhu, P. Ganly, B.W. Baker, S.R. Jackson, A.-M. Stoppa, D.R. Simpson, P. Gimsing, A. Palumbo, L. Garderet, M. Cavo, S. Kumar, C. Touzeau, F.K. Buadi, J.P. Laubach, D.T. Berg, J. Lin, A. Di Bacco, A.-M. Hui, H. van de Velde, and P.G. Richardson, for the TOURMALINE-MM1 Study Group*

Moreau P. et al. *N Engl J Med.* 2016; 374:1621-34.

TOURMALINE-MM1 Study Design



Ixazomib – Lenalidomide - Dexamethasone

- Ixazomib 4 mg PO Days 1, 8, 15
- Lenalidomide* 25 mg PO Days 1–21
- Dexamethasone 40 mg PO Days 1, 8, 15 and 22
- Repeat every 28 days until disease progression

Placebo - Lenalidomide - Dexamethasone

- Placebo PO Days 1, 8, 15
- Lenalidomide *25 mg PO Days 1–21
- Dexamethasone 40 mg PO Days 1, 8, 15 and 22
- Repeat every 28 days until disease progression

Stratification:

- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

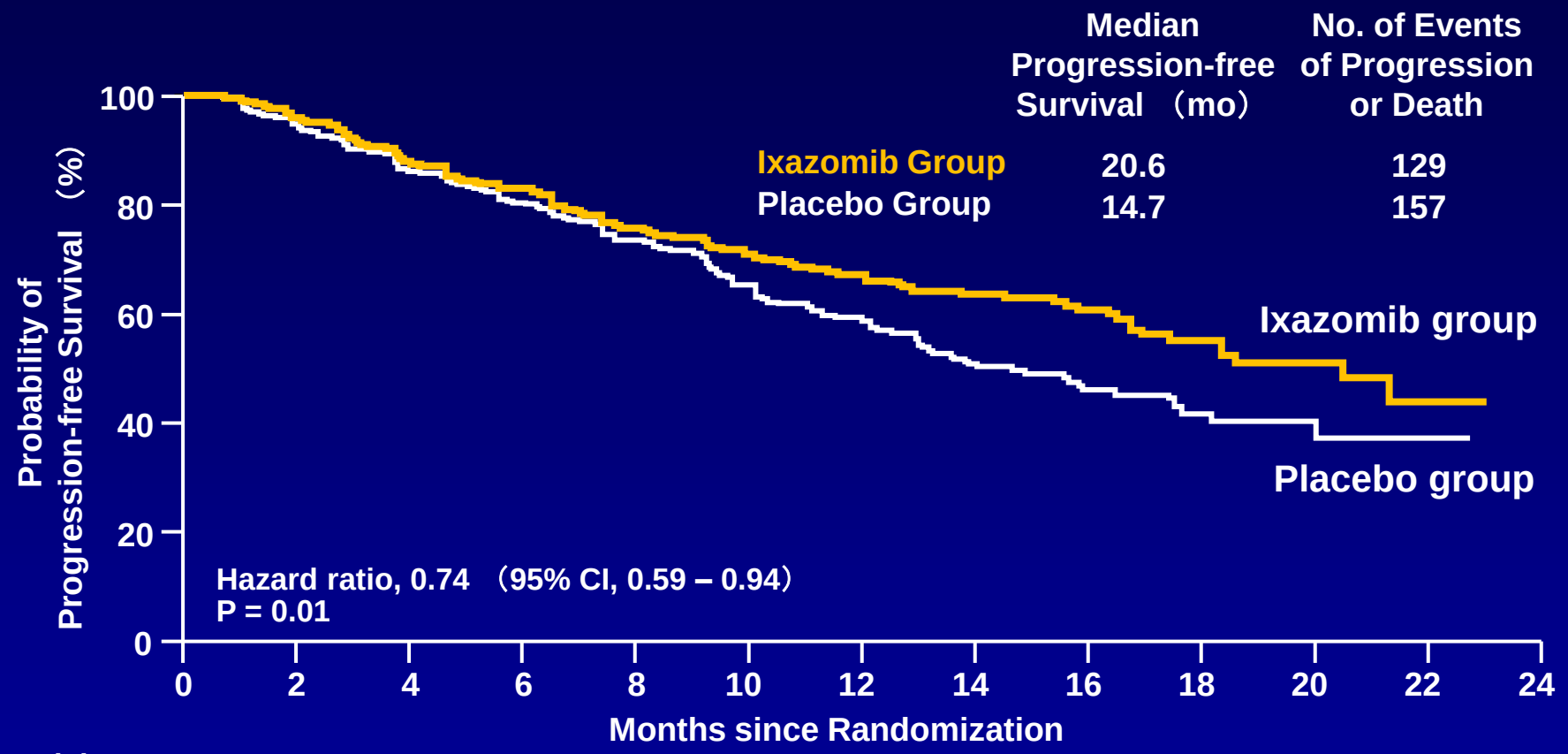
Select inclusion/exclusion criteria:

- Relapsed and/or refractory MM
- Measurable disease
- Received one to three prior therapies
- ECOG PS 0–2
- Cannot be refractory to proteasome inhibition or lenalidomide

Primary endpoint	PFS
Key secondary endpoints	OS, OS in patients with del（17p）
Secondary endpoints	ORR, CR + VGPR, DOR, TTP, PFS in pts with high-risk cytogenetic abnormalities, AEs

Moreau P, et al. *New Engl J Med* 2016; 374（17）: 1621-1634.

Final PFS analysis: Significant, 35% improvement in PFS with IRd vs placebo-Rd



No. at Risk

Ixazomib group	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo group	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Moreau P et al. *N Engl J Med* 2016;374(17):1621–34.

Outcomes by Cytogenetic Risk Group

	ORR, %		≥VGPR, %		≥CR, %		Median PFS, months			Median TTP, months	
	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	HR	IRd	Placebo-Rd
All patients	78.3*	71.5	48.1*	39	11.7*	6.6	20.6	14.7	0.742*	21.4	15.7
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*	20.6	15.9
All high-risk patients	79*	60	45*	21	12*	2	21.4	9.7	0.543*	21.4	12.0
Patients with del(17p)†	72	48	39	15	11*	0	21.4	9.7	0.596	21.4	12.9
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12.0	0.645	18.5	12.0

- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics
  - Median duration of response with IRd vs placebo-Rd was 20.5 vs 11.3 months in high-risk and NE vs 15.0 months in standard-risk patients
  - At a pre-planned analysis for OS (median follow-up ~23 months in the overall study population), OS data were not mature
  - In the IRd vs placebo-Rd arms, 37/199 (19%) vs 47/216 (22%) patients in the standard-risk group, and 15/75 (20%) vs 24/62 (39%) patients
  - in the high-risk group had died

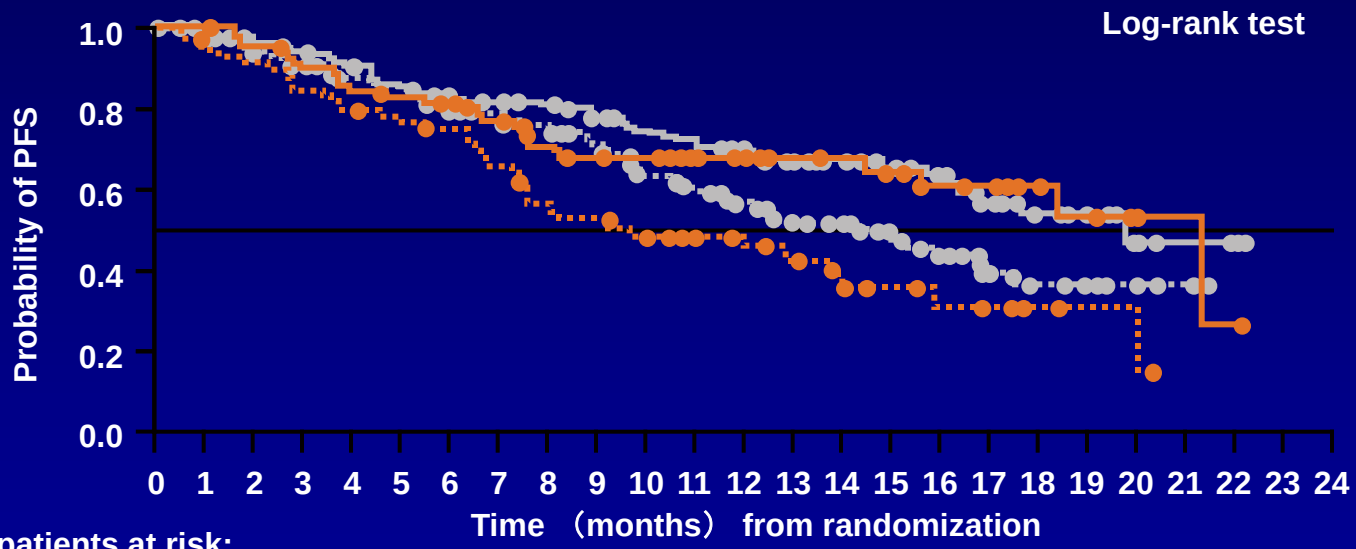
*p<0.05 for comparison between regimens. †Alone or in combination with t(4;14) or t(14;16). Data not included on patients with t(14;16) alone due to small numbers (n=7).

Avet-Loiseau H, et al. EHA 2016 abstract P269.
Moreau P, et al. *N Engl J Med* 2016;374:1621-1634.

PFS in High-risk and Standard-risk Patients.

High-risk	Number of events	Median, months	HR（95% CI）	*p* value
Ixazomib-Rd	26	21.4	0.543 （0.321-0.918）	0.021
Placebo-Rd	35	9.7		

Standard-risk	Number of events	Median, months	HR（95% CI）	*p* value
Ixazomib-Rd	63	20.6	0.640 （0.462-0.888）	0.007
Placebo-Rd	91	15.6		



Number of patients at risk:

High-risk																								
Ixazomib-Rd	75	74	70	66	62	59	57	52	45	42	40	34	26	22	21	18	14	13	9	7	3	2	1	0	0
Placebo-Rd	62	58	56	52	49	47	43	36	28	26	23	20	18	14	11	8	6	5	3	2	2	0	0	0	0
Standard-risk																								
Ixazomib-Rd	199	190	183	175	168	157	151	142	138	133	121	106	81	64	60	50	34	29	19	14	10	4	3	1	0
Placebo-Rd	216	200	190	179	169	164	153	144	136	130	119	96	76	57	49	42	32	25	14	11	8	3	2	0	0

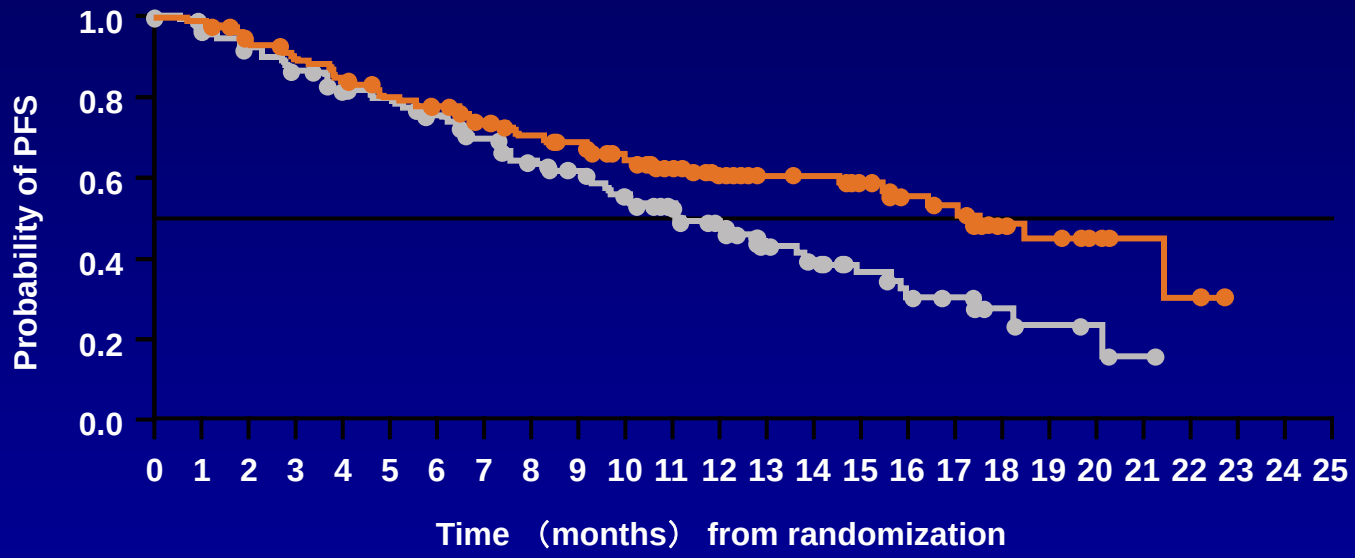
※High-risk：del（17p），t（4;14），and/or t（14;16）

Avet-Loiseau H et al., *Blood*. 2017

PFS in Expanded High-risk Patients

	Number of events	Median, months	HR（95% CI）	*p* value
Ixazomib-Rd	62	17.5	0.664 （0.474-0.928）	0.016
Placebo-Rd	83	11.1		

Log-rank test



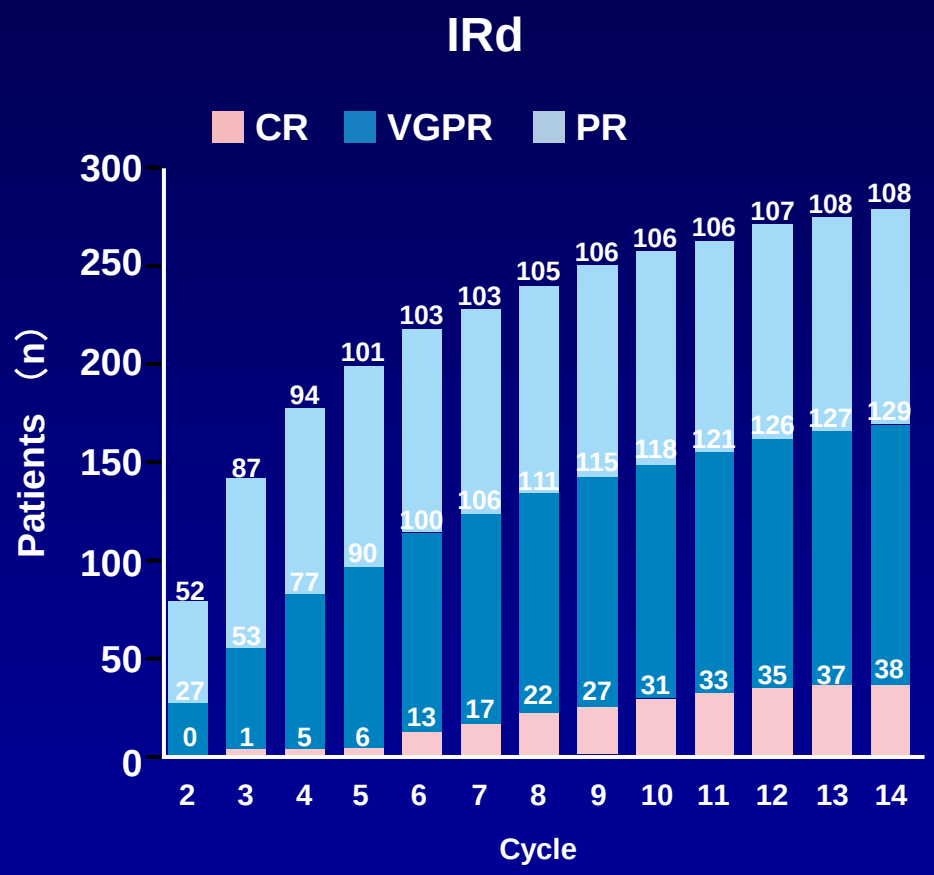
Number of patients at risk:

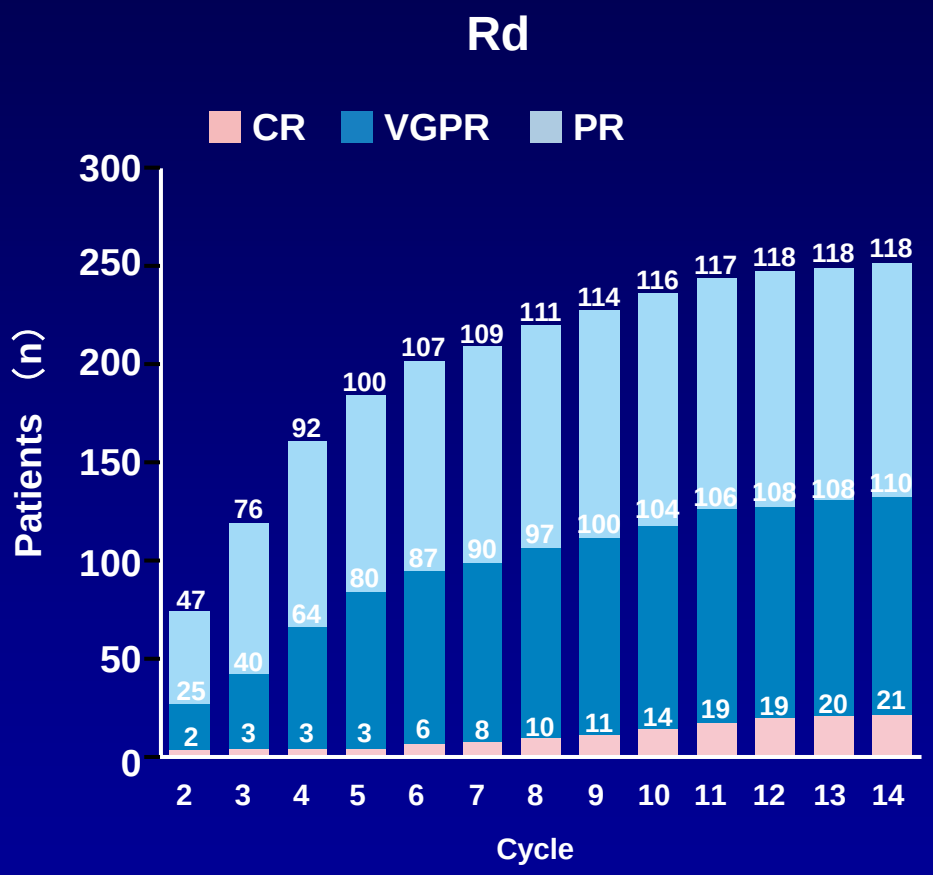
Ixazomib-Rd	155	146	139	130	122	114	109	101	93	89	77	66	50	40	39	34	27	25	14	12	6	3	2	0	0	0
Placebo-Rd	154	143	135	126	116	112	102	90	79	74	66	53	43	30	24	18	14	11	7	4	3	1	0	0	0	0

※Expanded high-risk : Any of del（17p）,t（4;14）, t（14;16）, or 1q21 amplification

Avet-Loiseau H et al., *Blood*. 2017

Cumulative best responses over time in the ITT population





Moreau P, et al. *New Engl J Med* 2016; 374（17）: 1621-1634. Supplementary Appendix

There is a gap between efficacy in clinical trials and effectiveness in the real-world for pts with RRMM *PI-IMiD combinations*

Real-world and clinical trial data in relapsed/refractory multiple myeloma (RRMM): evaluating treatment duration and comparing effectiveness and efficacy

Literature review of real-world RRMM data published in the past 10 years (n=47)

		Median PFS/TTNT		
		Real-world reports		
Regimens	Phase 3 clinical studies	All	Studies/registry analyses	EMR/chart review analyses†
All regimens combined	Not applicable	6–15.1	6.4–14.1	6–15.1
PI doublet / PI-based‡	Btz: 6.2–9.4 Cfz: 14.9–22.2	Btz: 5.7–11.9 Cfz: 3.2–9.4	Btz: 5.7–11.3 Cfz: 5.6	Btz: 6.9–11.9 Cfz: 3.2–9.4
PI-alkylator triplet	12–18.4#	16.2	NR	16.2
Injectable PI-immunomodulatory drug triplet	18.3–29.6	9.4–12.7	NR	9.4–12.7
Oral PI-immunomodulatory drug triplet	17.5–20.6	19.2	NR	19.2
Len doublet / len-based‡	11.1–18.4	6.6–21	6.6–8.7	7–21

Richardson PG et al.,ASH2017 Abstract 3149

There is a gap between efficacy in clinical trials and effectiveness in the real-world for pts with RRMM

Other regimens

Real-world and clinical trial data in relapsed/refractory multiple myeloma (RRMM): evaluating treatment duration and comparing effectiveness and efficacy

Literature review of real-world RRMM data published in the past 10 years (n=47)

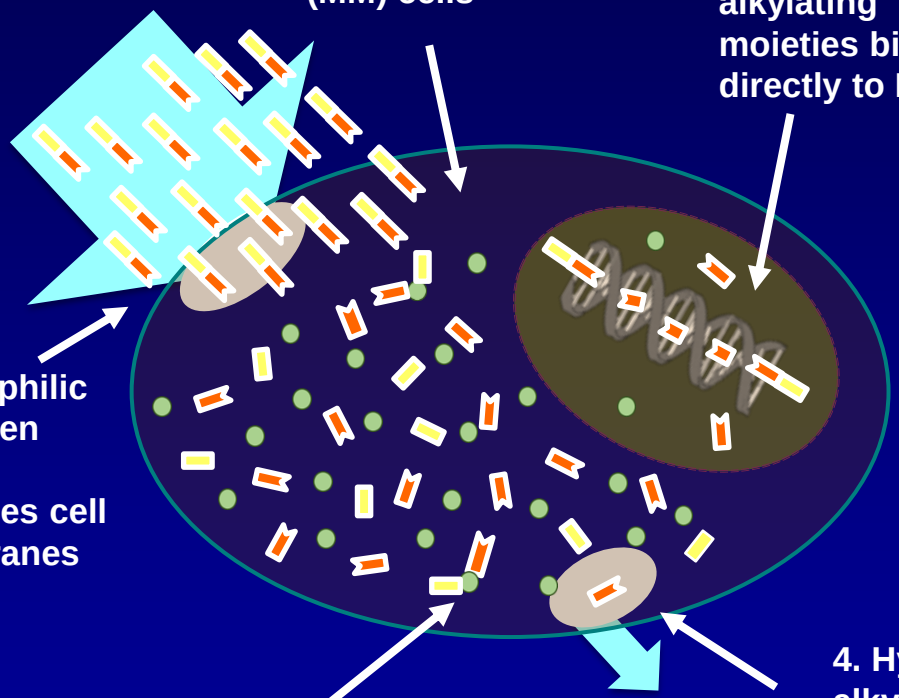
Regimens	Phase 2 / 3 clinical studies			Real-world reports		
	Prior therapies	DOT	PFS/TTNT	Prior therapies	DOT	PFS/TTNT
Pom-dex	5	4.9	4.0–4.6	≥2–4	1.4–5.9	3.4–9.6
K-Pom-dex	6	7	7.2	4	2	3.3
Pano-Vd	1–3	5	12	5–6	2	2.4–3.3
Daratumumab-based	4–5	4	3.7–5.6	4	4.4	5.5

Richardson PG et al.,ASH2017 Abstract 3149

Targeting Peptidase - Melflufen is a peptidase enhanced therapy with an alkylating payload

1. Amino-peptidases highly over expressed in multiple myeloma (MM) cells

5. Melflufen and hydrophilic alkylating moieties binds directly to DNA



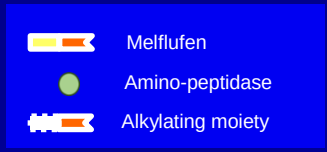
2. Lipophilic melflufen rapidly traverses cell membranes

3. Amino-peptidase potentiated release of hydrophilic alkylating moieties

4. Hydrophilic alkylating moieties trapped inside the cell

Peptidase enhanced activity in MM cells results in:

- Approx. 50-fold higher intra-cellular exposure in MM cells[1,5]
- Approx. 50-fold higher anti-MM potency[1,2,5]
- Alkylation of DNA with limited or no induction of DNA repair[3,5]
- Strong anti-angiogenic properties [1,4,5]
- Therapeutic index of 20 - 40 (MM cells compared with peripheral blood mononuclear cells)[1,5]



1. Chauhan et al. (2013) Clin Cancer Res 19(11): 3019-303.
2. Wickstrom et al. (2008) Invest New Drugs 26(3): 195-204.
3. Ray et al. (2016) Br J Hematol 174: 397-409
4. Strese et al. (2013) Biochem Pharmacol 86: 888–895.
5. Wickström et al. (2017) Oncotarget E-pub June 08.

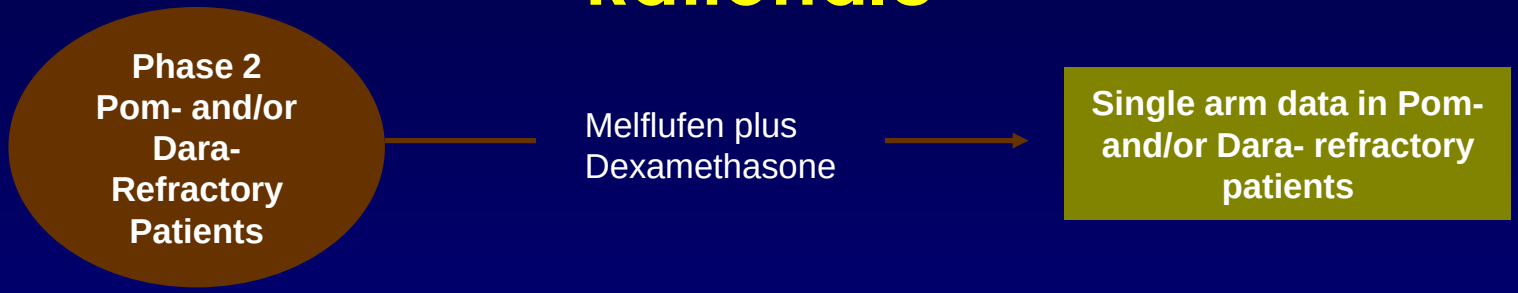
O-12-M1 study - Melflufen Phase 2 in RR MM (Richardson PG et al, ASH 2017)

- RRMM pts with ≥ 2 prior lines of therapy, including lenalidomide and bortezomib
- Disease progression while on therapy or within 60 days of last dose
- Primary end point: ORR according to IMWG criteria

- Phase 1 determined the MTD of melflufen to be 40 mg given i.v. monthly in combination with oral dexamethasone 40 mg weekly (28-day cycles)
- Phase 2 enrolled 45 patients who received 227 doses of melflufen
- Melflufen demonstrated rapid and durable response activity in heavily pre-treated RR MM patients (IMiD and PI exposed and disease progression while on therapy or within 60 days of last dose in their last line of therapy) in RR MM.
- The ORR was 41% and CBR is 65% with median PFS of 5.7 months, and median OS of 20.7 months

- Favorable tolerability - hematologic toxicity was common but clinically manageable, non-hematologic AEs were infrequent

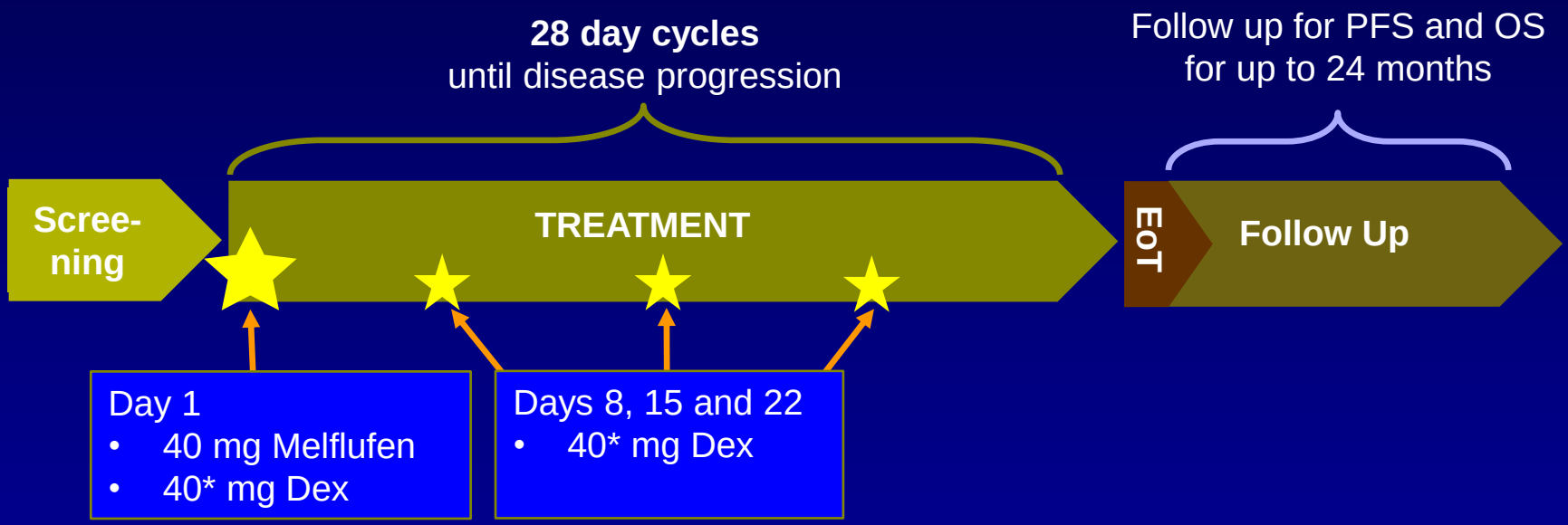
Mateos MV et al ASH 2017: Horizon Study Rationale



- **Clear lack of treatment options in the patient group**
- **Data suggest considerable clinical benefit of melflufen treatment in patients that are single (IMiD or PI), double (IMiD and PI) and even triple (IMiD, PI and alkylator) refractory**
- **Side effect profile in this group seems similar as expected for alkylators**

=> Melflufen may offer a meaningful benefit with acceptable toxicity profile for patients with heavily pre-treated disease and refractory to pomalidomide and/or daratumumab.

Horizon Treatment schedule

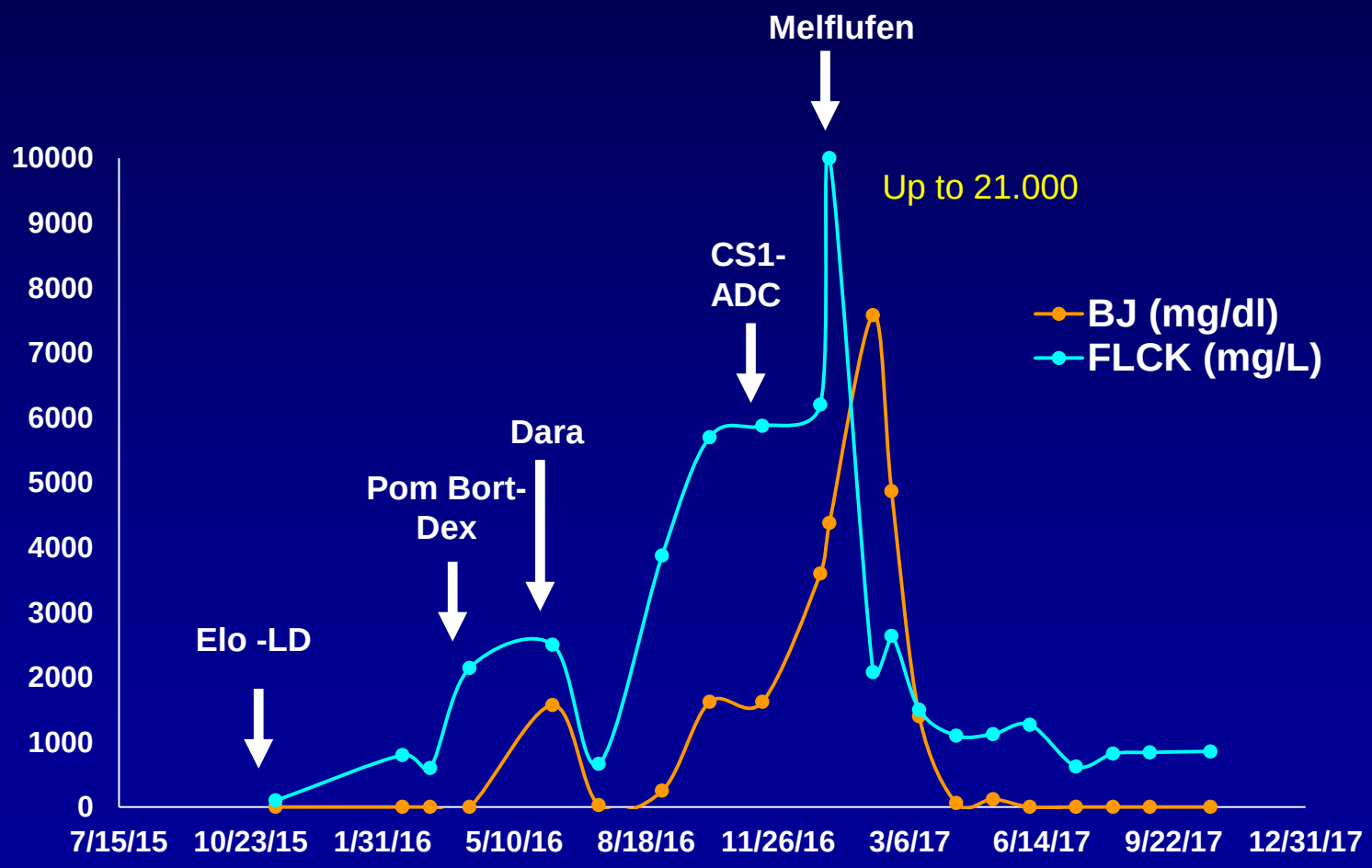


**Patients over the age of 75 receive 20 mg Dex*

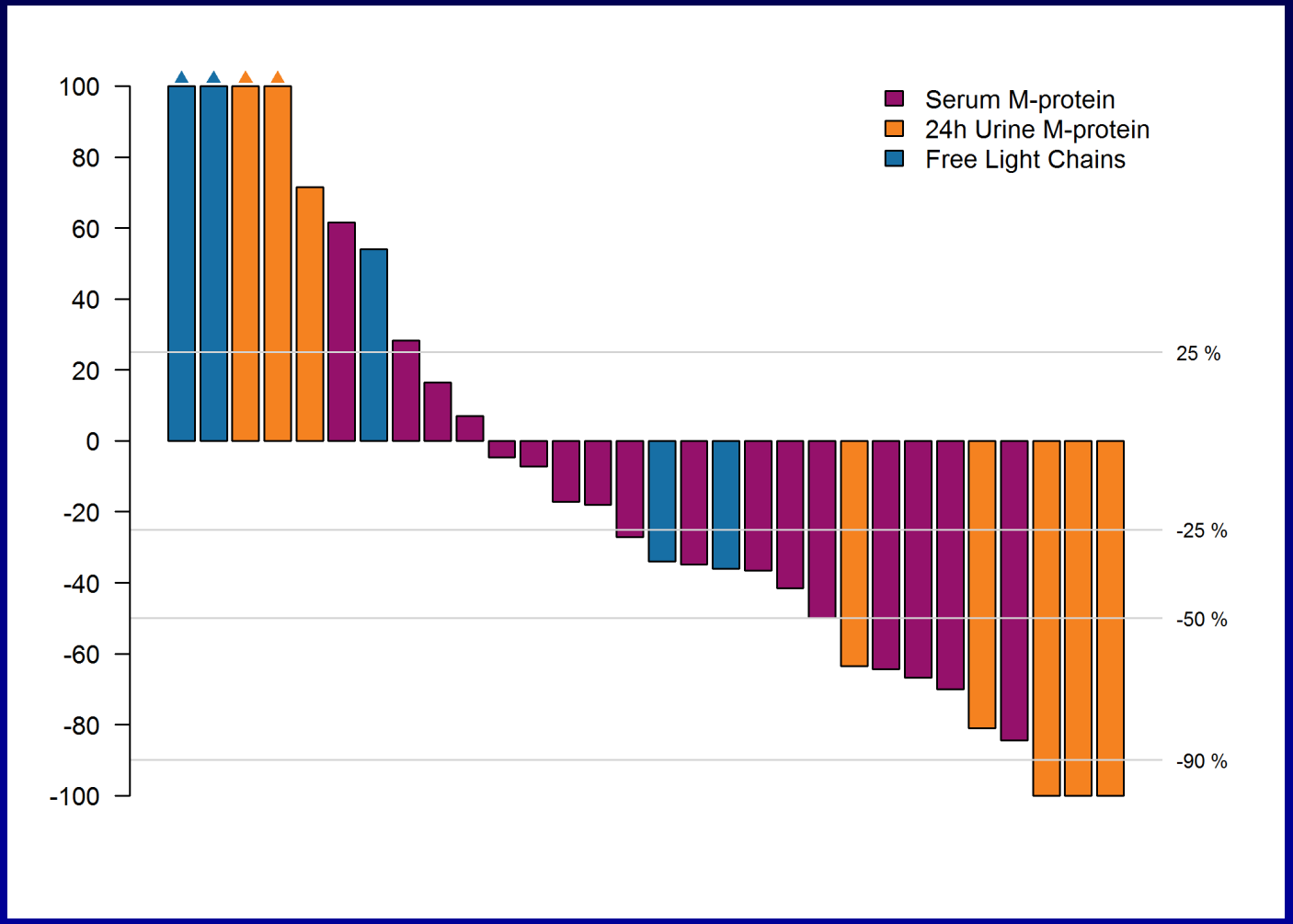
Patient case study

2007 MM BJ Kappa
42 years old

- Thal-Dex → CR
  + ASCT
- Bort-Dex x6→ CR
  + 2nd ASCT
- Len – Dex x 20
- VTD x2
- DCEP x 2
- Pom-Dex
- VBCMP/VBAD→ SD
  + Allo – SCT
  (June'15)

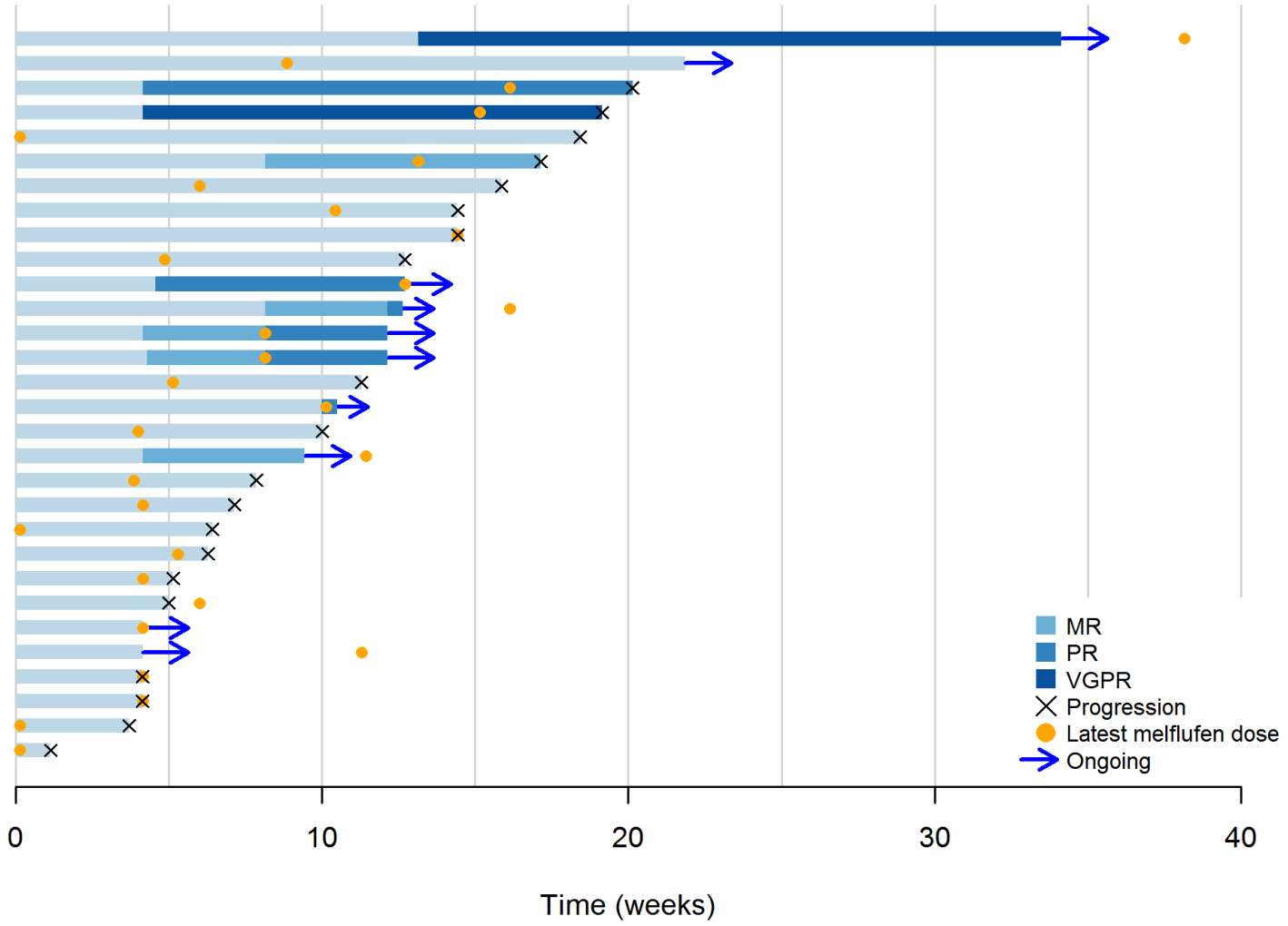


Waterfall plot of best M-protein change (N=30)



Data cut-off 13 Nov 2017

Swim-lane plot (N=30)



Data cut-off 13 Nov 2017

Safety and tolerability (N=38)

- **Grade 3/4 treatment-related AEs**

	GRADE 3 OR 4, n (%)	GRADE 4, n (%)
Any treatment-related AE	22 (58)	15 (39)
Blood and lymphatic system disorders	20 (53)	14 (37)
Thrombocytopenia	17 (45)	12 (32)
Neutropenia	15 (39)	9 (24)
Leukopenia	3 (8)	3 (8)
Anemia	8 (21)	0
Lymphopenia	3 (8)	0
Hemolytic anemia	2 (5)	0

Data cut-off 13 Nov 2017

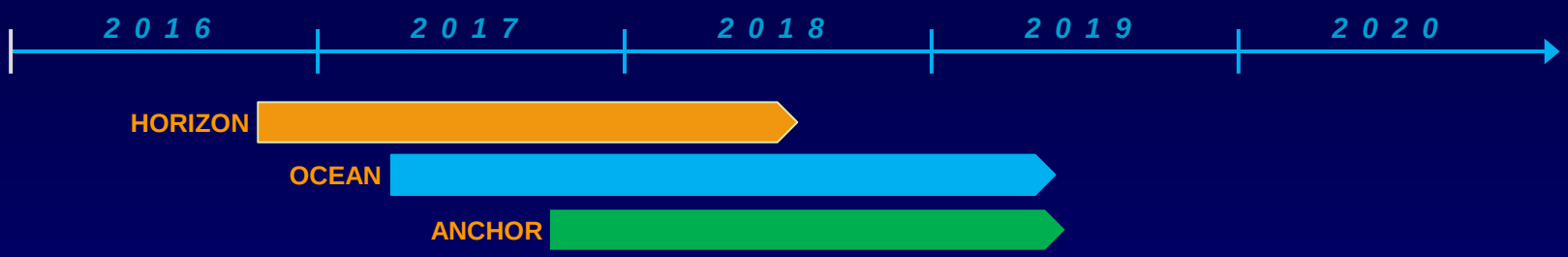
Safety and tolerability (N=38)

- **Melflufen-related SAEs**

ADVERSE EVENT TERM	n (%)
Any melflufen-related SAE	4 (11)
Febrile neutropenia	1 (3)
Pyrexia	1 (3)
Hypercalcemia	1 (3)
Soft tissue infection	1 (3)

Data cut-off 13 Nov 2017

Melflufen ongoing or planned studies in RR MM



	OCEAN	HORIZON	ANCHOR
	Phase 3 Randomized comparative study	Phase 2 Single Arm Multi-refractory study	Phase 1/2 – Triple combination study
QUESTION ASKED	How does melflufen compare to standard of care in late-stage RRMM?	How does melflufen work in RRMM patients with limited treatment options?	How is melflufen dosed in triple combinations in RRMM?
COMMENT	Recruitment ongoing H2H melflufen vs pomalidomide	Recruitment ongoing Pomalidomide- and/or daratumumab-refractory patients	Planned FPI Q4-17 Combination with bortexomib or daratumumab

Summary: ASH 2017

- Melflufen shows promising activity in this heavily pretreated patient population where patients have a median of 6 prior lines of therapy.
- In the reported data set, 97% of patients have rapid disease progression while on previous therapy or within 60 days of last dose, 100% of patients have stopped responding or are refractory to lenalidomide and PIs, 100% of patients are refractory to pomalidomide or daratumumab and 62% of patients are refractory to pomalidomide and daratumumab.
- Thrombocytopenia and neutropenia are as expected the most common AEs, and non-hematologic AEs are infrequent.
- The ORR and CBR of 27% and 33% respectively are encouraging and patient recruitment continues.

Key Targets in MM 2017

Genomic abnormalities:

- Target and overcome mutations
- Critical Role of Combination Therapy
- Evolving Position and Timing of ASCT

Excess Protein Production:

- Target Protein degradation

Immune Suppression:

- Restore anti-MM immunity

Restoring Immune function

Immunomodulatory drugs, other small molecules (e.g. HDACi's)

Monoclonal antibodies

Checkpoint inhibitors

Vaccines

Cellular therapies

Options for 2nd+ Relapse
Comparison of Pom-Dex Trials (& Combinations)

	MM-003[1]	STRATUS (MM-010)[2]	Pom-Dex vs Pom-Cyclo-Dex[3]		Pom-Btz-Dex[4]
Treatment	PD	PD	PD	PCD	PVD
n	302	682	36	34	47
Population	Failed Bort & Len & refr to last line		At least 2 prior lines & Len-refractory		1-4 prior lines & Len-refractory
ORR, %	31	32.6	39	65	85
≥VGPR, %			14	12	45
PFS, months	4.0	4.6	4.4	9.5	10.7
OS, months	13.1[5]	11.9	16.8	NR	94*

1. San Miguel J, et al. *Lancet Oncol.* 2013;14(11):1055-1066. 2. Dimopoulos MA, et al. *Blood.* 2016;128(4):497-503. 3. Baz RC, et al. *Blood.* 2016;127(21):2561-2568. 4. Lacy MQ, et al. *Blood.* 2014;124: Abstract 304. 5. Dimopoulos MA, et al. *Haematologica.* 2015;100(10):1327-1333.

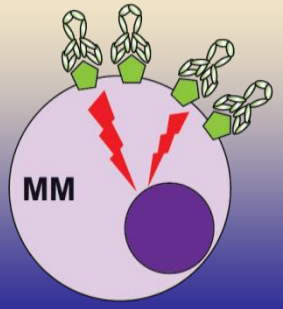
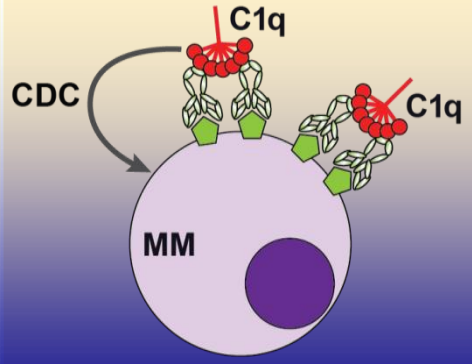
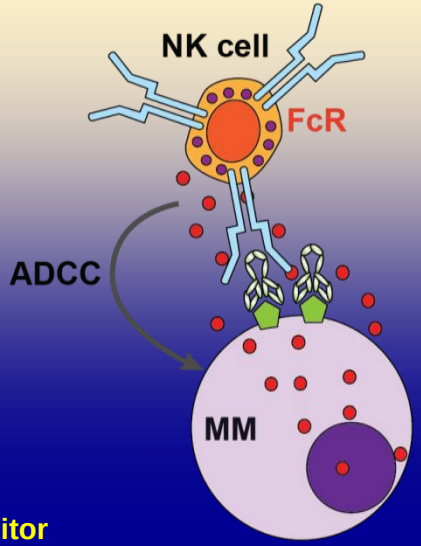
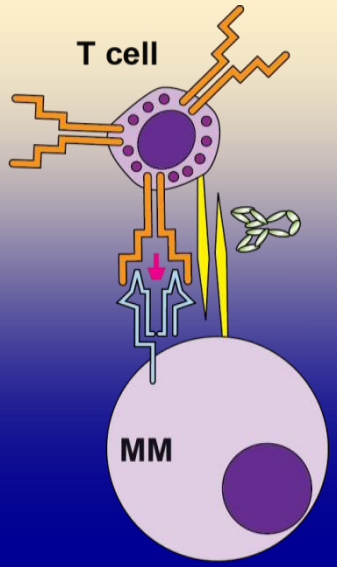
Other Pom/dex Combinations

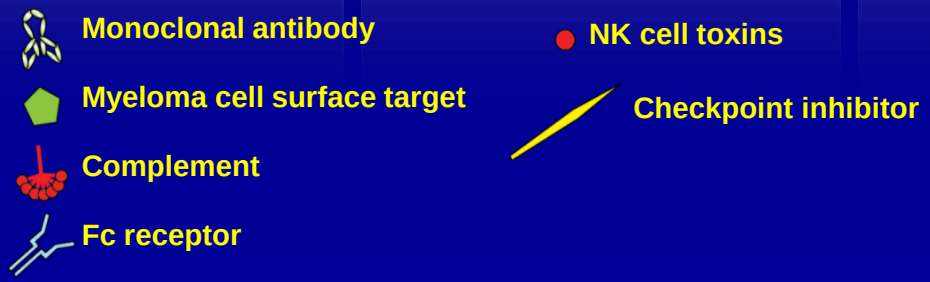
	POM + Vd[1]	K + POMdex[2]	Ixa + POMdex[3]	Dara + POMdex[4]	Isa+ POMdex[5]	MOR202+ POMdex[6]
Regimen	POM 1–4 mg PO D1–14 + BORT 1 mg/m² IV or 1.3 mg/m² IV or SC C1-8: D1,4,8,11; C9+: D1,8 + LoDex 20 mg (>75 y: 10 mg) C1-8: D1,2,4,5,8,9,11,12; C9+: D1,2,8,9 (n = 34) †	Carfilzomib 20/27/36 mg/m² D1,2,15,16 + POM 3 or 4 mg/day D1–21 + Dex QW 40 mg C1–4 (20 mg C5–8) (n = 46)‡ The same combination but K weekly (n = 57)	Ixazomib 3 or 4 mg D1,8,15 + POM 4 mg/day D1–21 + Dex 40 mg D1,8,15,22 (>75 y: 20 mg) (All, n = 32; Ixa 4 mg, n = 25)	Daratumumab 16 mg/kg C1–2 QW; C3–6 Q2W; C7–13 or until PD Q4W + POM 4 mg/day D1–21 + Dex 40 mg (>75 y: 20 mg) (n = 98)	Isatuximab 10 mg/Kg IV C1 QW; Q2W thereafter + POM 4 mg/day D1–21 + Dex 40 mg (>75 y: 20 mg) (n = 14)	MOR202 at dose of 4, 8, 16 mg/kg QW + POM 4 mg/day D1–21 + Dex 40 mg (>75 y: 20 mg) (n = 11)
Study phase	I	I/II	I/II	I	I/II	I/II
Prior lines of therapy, n	1–4		1–5 including PI and Len	≥2 (2–13)	4.5 (2-11)	3
Refractory to Len, n (%)	All patients were Len-refractory	40 (87)/41(72)	32 (100); 25 (100)	87 (89)	15(75)	11(100)
Refractory to PI, n (%)	All pts were PI-exposed (but not refractory)	NR	20 (63); 15 (60)*	74 (76)	-	-
ORR, %	65	64/64	44	71	64	56
Median (range) DOR	7.4 (4.4–9.6) months	NR	56 (28-160) months	NR	4 months	-
Median PFS, months	NR	12.9/9.2	NR	6-m rate = 66%	-	-

1.Richardson P, et al. *Haematologica.* 2016;101(s1): Abstract P653. 2.Rosenbaum CA, et al. *Blood.* 2015;126: Abstract 8007. 3.Krishnan AY, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 8008. 4.Chari A, et al. *Blood.* 2015;126: Abstract 508. 5.Richardson PG, et al. Blood. 2016;128: Abstract 2123. 6.Raab M, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 8024.

Monoclonal Antibodies Kill MM Through Multiple Mechanisms

DIRECT EFFECTS — **INDIRECT EFFECTS**

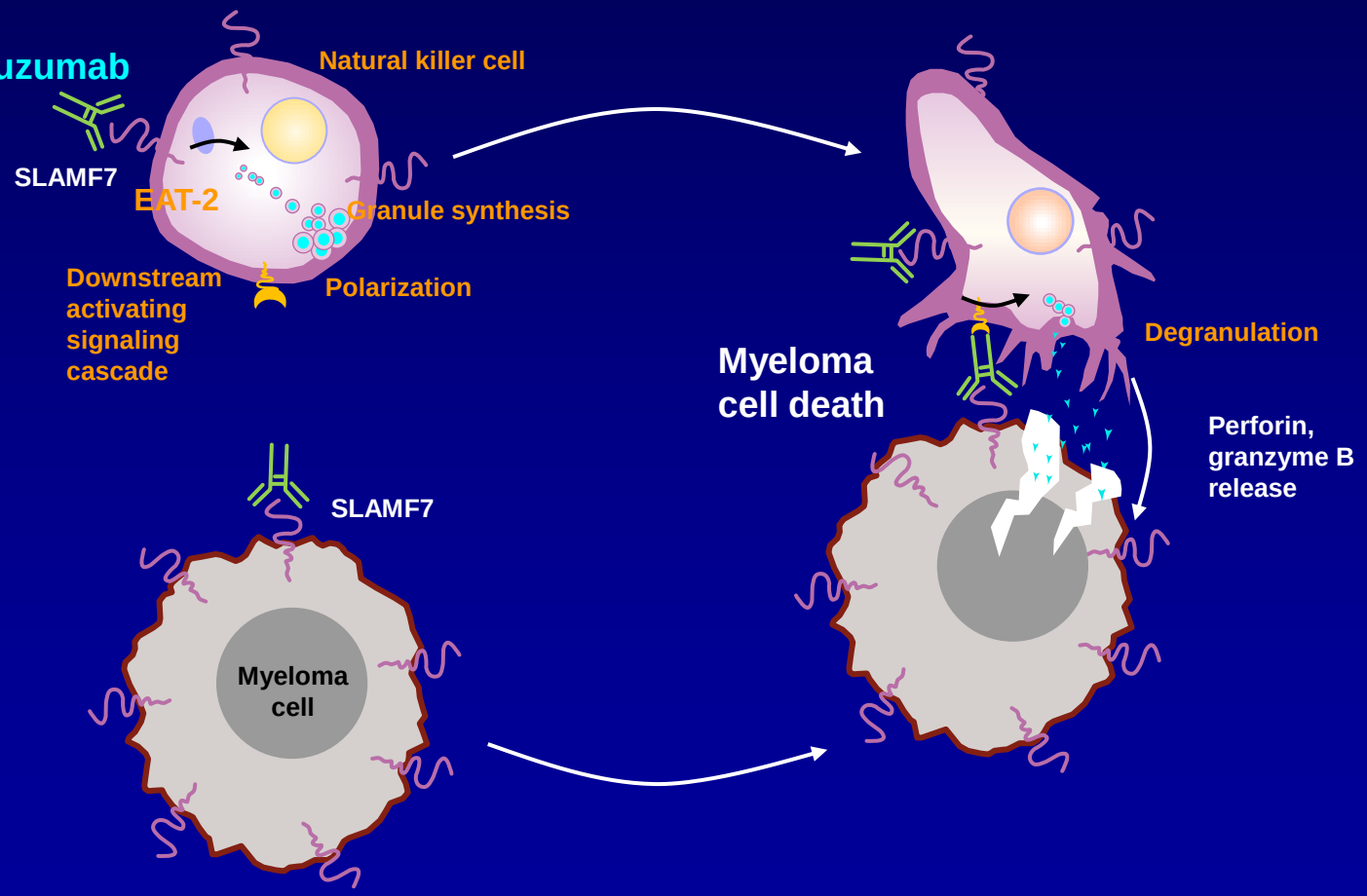
Interferes with survival or delivers myeloma-killing substances	Labels myeloma cells for killing by complement	Labels myeloma cells for killing by NK cells	Activates T cells by taking the brakes off
			



Adapted from Richardson PG, ASH 2016

Elotuzumab: Immunostimulatory Mechanism of Action

- Elotuzumab is an immunostimulatory monoclonal antibody that recognises SLAMF7, a protein highly expressed by myeloma and natural killer cells[1]
- Elotuzumab causes myeloma cell death via a dual mechanism of action[2]



ADCC=antibody-dependent cell-mediated cytotoxicity; SLAMF7=signaling lymphocytic activation molecule F7

1. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84
2. Collins SM et al. *Cancer Immunol Immunother* 2013;62:1841–9.

Phase III ELOQUENT-2 Study: ERd vs. Rd (n=646)

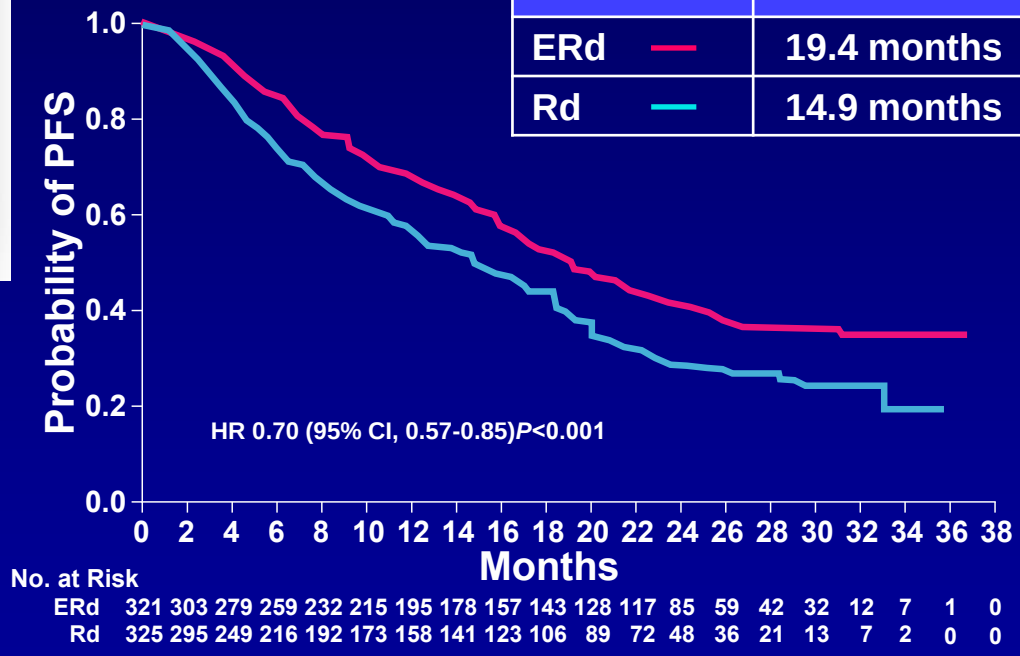
ORIGINAL ARTICLE

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Sagar Lonial, M.D., Meletios Dimopoulos, M.D., Antonio Palumbo, M.D., Darrell White, M.D., Sebastian Grosicki, M.D., Ph.D., Ivan Spicka, M.D., Adam Walter-Croneck, M.D., Philippe Moreau, M.D., Maria-Victoria Mateos, M.D., Ph.D., Hila Magen, M.D., Andrew Belch, M.D., Donna Reece, M.D., Meral Beksac, M.D., Andrew Spencer, M.D., Heather Oakervee, M.D., Robert Z. Orlowski, M.D., Masafumi Taniwaki, M.D., Christoph Röllig, M.D., Hermann Einsele, M.D., Ka Lung Wu, M.D., Anil Singhal, Ph.D., Jesus San-Miguel, M.D., Morio Matsumoto, M.D., Jessica Katz, M.D., Ph.D., Eric Bleickardt, M.D., Valerie Poulart, M.Sc., Kenneth C. Anderson, M.D., and Paul Richardson, M.D., for the ELOQUENT-2 Investigators

	ERd (n=321)	Rd (n=325)	*p*-Value
ORR (≥PR)	79%	66%	<0.001
≥CR*	4%	7%	NR

Treatment	Median PFS
ERd	19.4 months
Rd	14.9 months



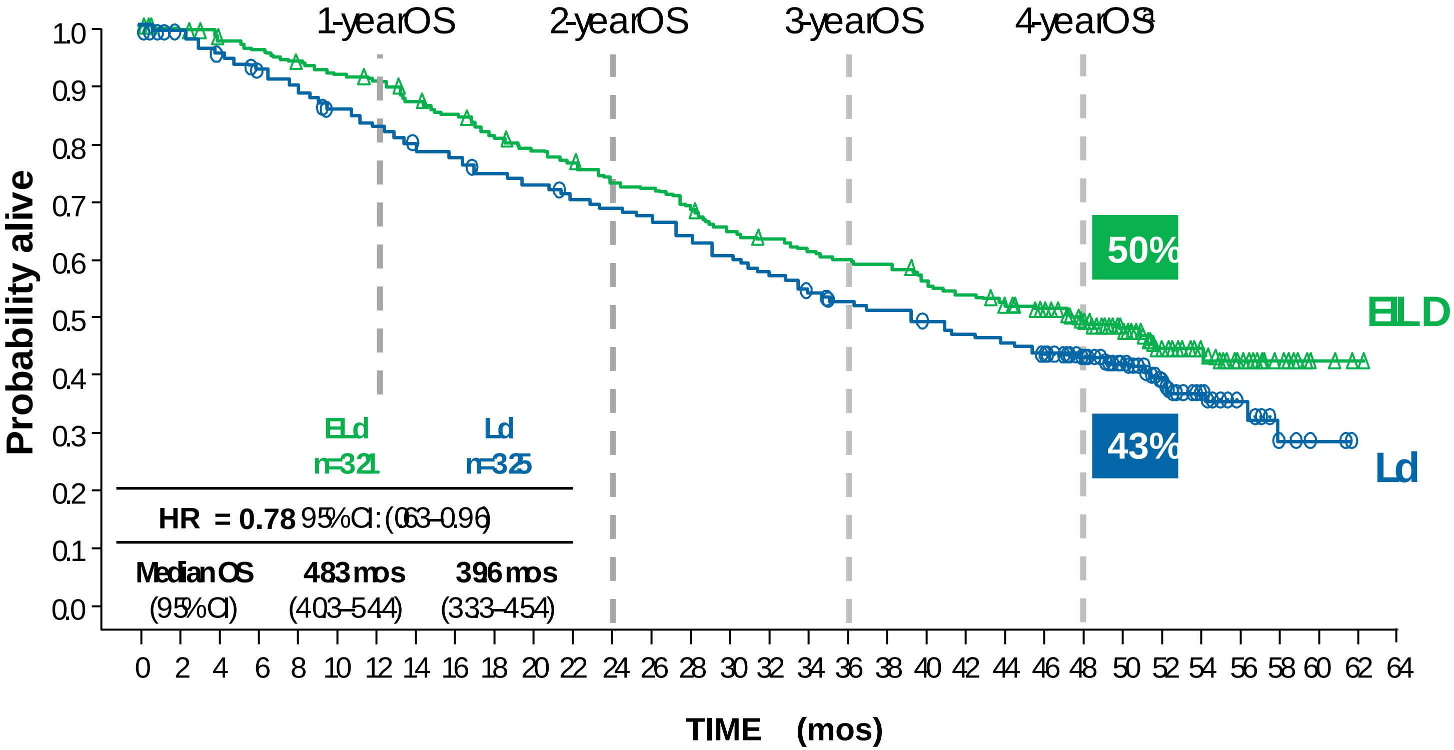
- Median follow-up: 24.5 months

*Complete response rates in the ERd group may be underestimated owing to interference from the presence of therapeutic antibody in results on immunofixation and serum protein electrophoresis assays

AE, adverse event; CI, confidence interval; CR, complete response; ERd, elotuzumab, lenalidomide, low-dose dexamethasone ; NR, not reported; ORR, overall response rate; PR, partial response; Pts, patients; Rd, lenalidomide, low-dose dexamethasone; Yr, year

Lonial S et al. *NEJM.* 2015; 373(7) :621-631

Overall Survival: Elotuzumab Rd vs Rd



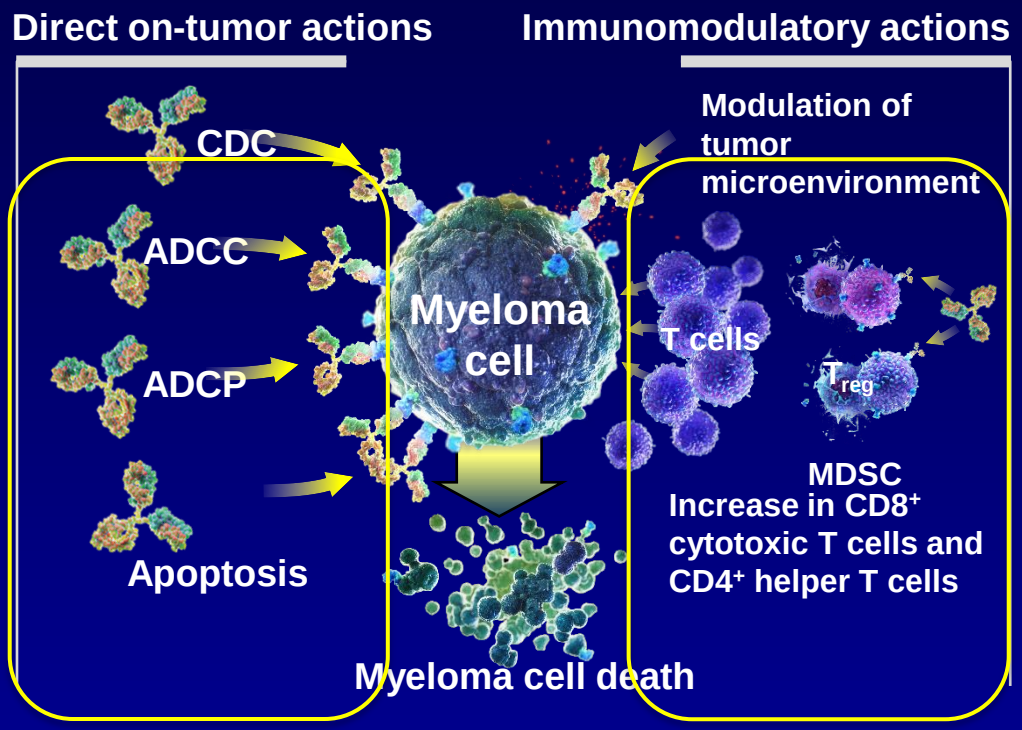
Patients at risk

ELd	321	316	308	303	296	288	283	270	262	250	242	236	224	221	210	197	192	187	181	178	170	163	155	150	132	93	64	4	24	10	4	2	0
Ld	325	312	298	287	278	264	255	243	4	228	222	213	208	202	193	184	174	164	158	154	147	141	137	128	109	80	53	2	13	7	3	0	0

Dimopoulos et al, EHA 2017

Daratumumab (DARA)

- Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory MoA[1]
- Approved as monotherapy in many countries for heavily pretreated RRMM
- Approved in combination with standard of care regimens in RRMM after ≥1 prior therapy in the USA, EU, and other countries
- DARA induces rapid, deep and durable responses in combination with a PI (bortezomib) or an IMiD (lenalidomide) in RRMM[2,3]



MoA, mechanism of action; RRMM, relapsed/refractory multiple myeloma; CDC, cellular dependent cytotoxicity; ADCC, antibody dependent cellular cytotoxicity; ADCP, antibody dependent cellular phagocytosis; MDSC, myeloid-derived suppressor cell.

1. Touzeau C, Moreau P. *Expert Opin Biol Ther*. 2017.
2. Mateos MV, et al. Oral presentation at the 58th ASH Annual Meeting and Exposition, December 3-6, 2016. San Diego, CA; Abstract 1150.
3. Usmani SZ, et al. Oral presentation at the 58th ASH Annual Meeting and Exposition, December 3-6, 2016. San Diego, CA; Abstract 1151.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma

H.M. Lokhorst, T. Plesner, J.P. Laubach, H. Nahi, P. Gimsing, M. Hansson, M.C. Minnema, U. Lassen, J. Krejcik, A. Palumbo, N.W.C.J. van de Donk, T. Ahmadi, I. Khan, C.M. Uhlar, J. Wang, A.K. Sasser, N. Losic, S. Lisby, L. Basse, N. Brun, and P.G. Richardson

THE LANCET Oncology

Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

Sagar Lonial, Brendan M Weiss, Saad Z Usmani, Seema Singhal, Ajai Chari, Nizar J Bahlis, Andrew Belch, Amrita Krishnan, Robert A Vescio, Maria Victoria Mateos, Amitabha Mazumder, Robert Z Orlowski, Heather J Sutherland, Joan Bladé, Emma C Scott, Albert Oriol, Jesus Berdeja, Mecide Gharibo, Don A Stevens, Richard LeBlanc, Michael Sebag, Natalie Callander, Andrzej Jakubowiak, Darrell White, Javier de la Rubia, Paul G Richardson, Steen Lisby, Huaibao Feng, Clarissa M Uhlar, Imran Khan, Tahamtan Ahmadi, Peter M Voorhees

***N Engl J Med* 2015 Sep 24;373(13):1207-19; *Lancet* 2016 Apr 9;387(10027):1551-60.**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*

POLLUX: Study Design

Multicentre, randomised (1:1), open-label, active-controlled phase 3 study

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Patients with creatinine clearance ≥30 mL/min

Stratification factors

- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

RANDOMISE 1:1

DRd (n = 286)

Daratumumab 16 mg/kg IV
- Qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Rd (n = 283)

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Cycles: 28 days

Primary endpoint

- PFS

Secondary endpoints

- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

Statistical analyses

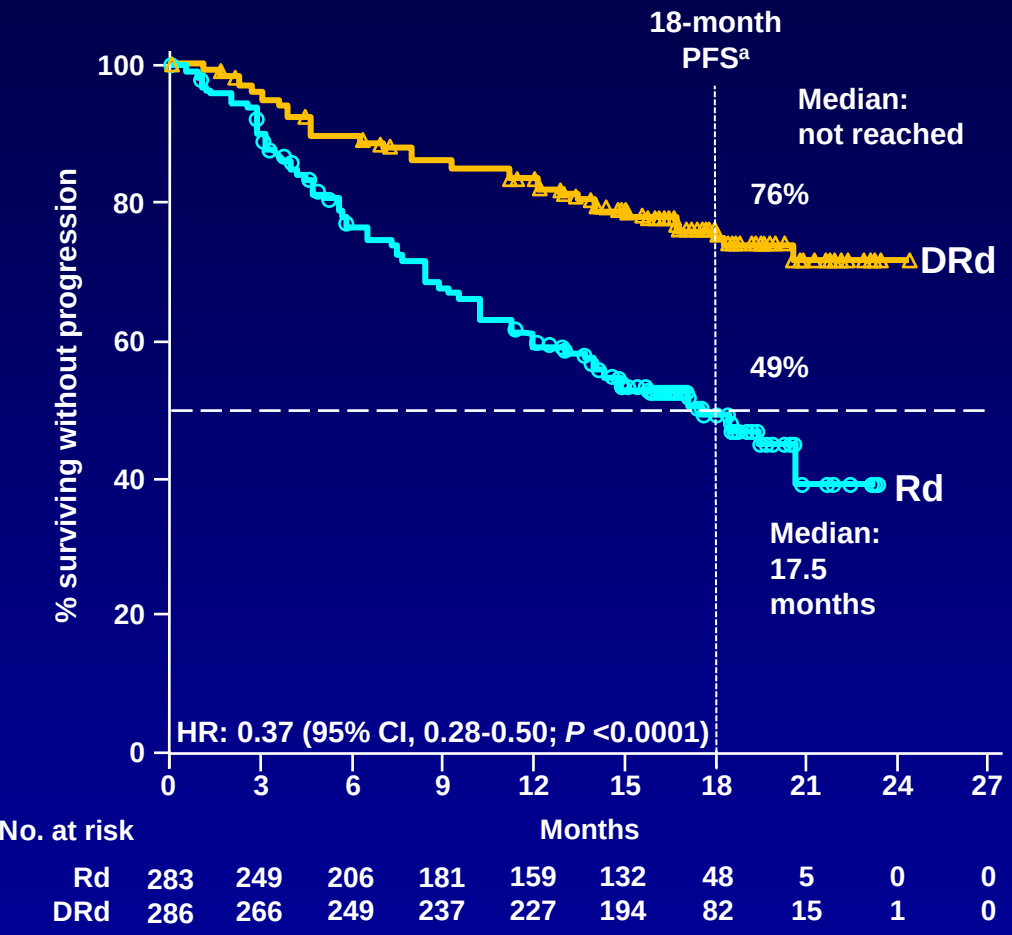
- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

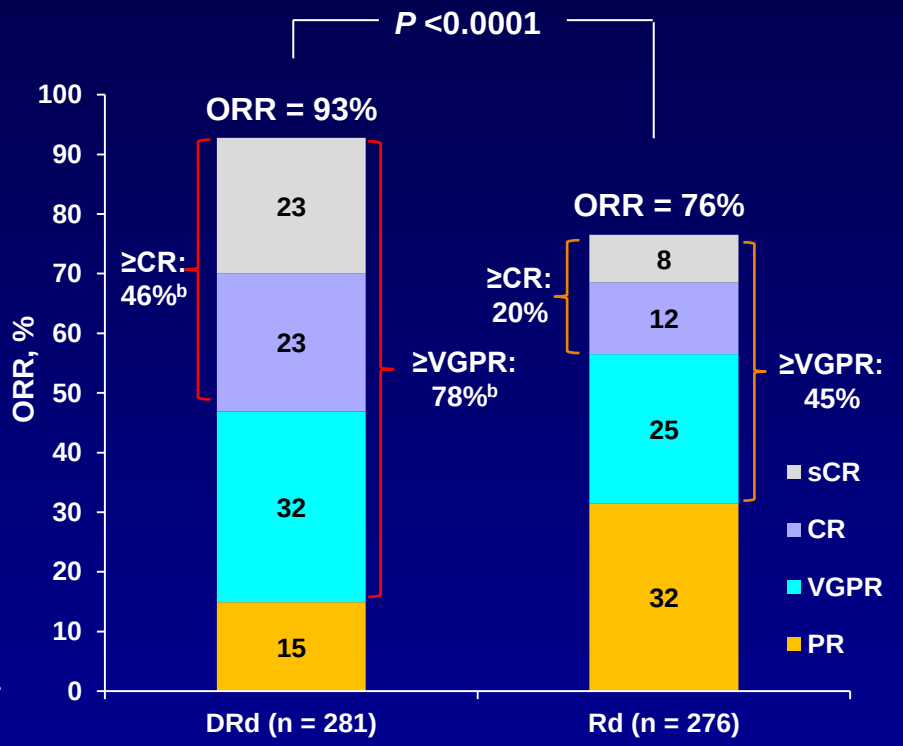
Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

[a]On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.

Dimopoulos M et al. *N Engl J Med*. 2016;375:1319.

Updated Efficacy; ASH 2016





- **Median (range) follow-up: 17.3 (0-24.5) months**

Responses continue to deepen in the DRd group with longer follow-up

HR, hazard ratio; CI, confidence interval; sCR, stringent complete response; PR, partial response.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate;
[b]*P* <0.0001 for DRd vs Rd.

Usmani SZ et al, *ASH 2016.* Oral Presentation and Abstract 1151

Conclusions

- DRd significantly improved outcomes for patients with myeloma
  - 63% reduction in risk of progression or death for DRd vs. Rd
  - Similar findings observed across all analyses in the 1 to 3 prior lines population
- More patients achieve deeper responses including MRD negativity with DRd
- DRd is superior to Rd regardless of time since last therapy refractoriness to last line of therapy or cyctogenetic risk

These data support the use of DRd for patients who received ≥1 prior therapy regardless of risk status or refractoriness to prior Tx

DRd, daratumumab, lenalidomide, and dexamethasone; Rd, lenalidomide, dexamethasone; Tx, treatment

Usmani SZ et al, *ASH 2016.* Oral Presentation and Abstract 1151

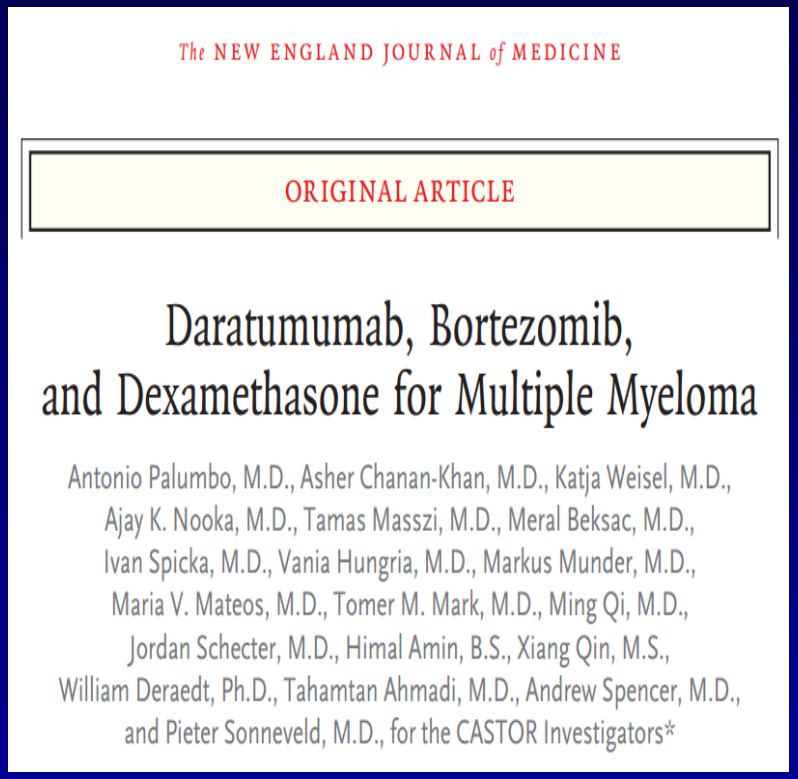
Lenalidomide-based Studies in RR MM

	POLLUX DRd vs Rd	ASPIRE KRd vs Rd[1]	ELOQUENT-2 ERd vs Rd[2,3]	TOURMALINE-MM1 NRd vs Rd[4]
PFS HR (95% CI)	0.37 (0.27-0.52)	0.69 (0.57-0.83)	0.73 (0.60-0.89)	0.74 (0.59-0.94)
ORR	93%	87%	79%	78%
≥VGPR	76%	70%	33%	48%
≥CR	43%	32%	4%	14%
Duration of response, mo	NE	28.6	20.7	20.5
OS HR (95% CI)	0.64 (0.40-1.01)	0.79 (0.63-0.99)	0.77 (0.61-0.97)	NE

1. Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152.
2. Lonial S, et al. *N Engl J Med*. 2015;373(7):621-631.
3. Dimopoulos MA, et al. *Blood*. 2015;126(23):Abstract 28.
4. Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634.

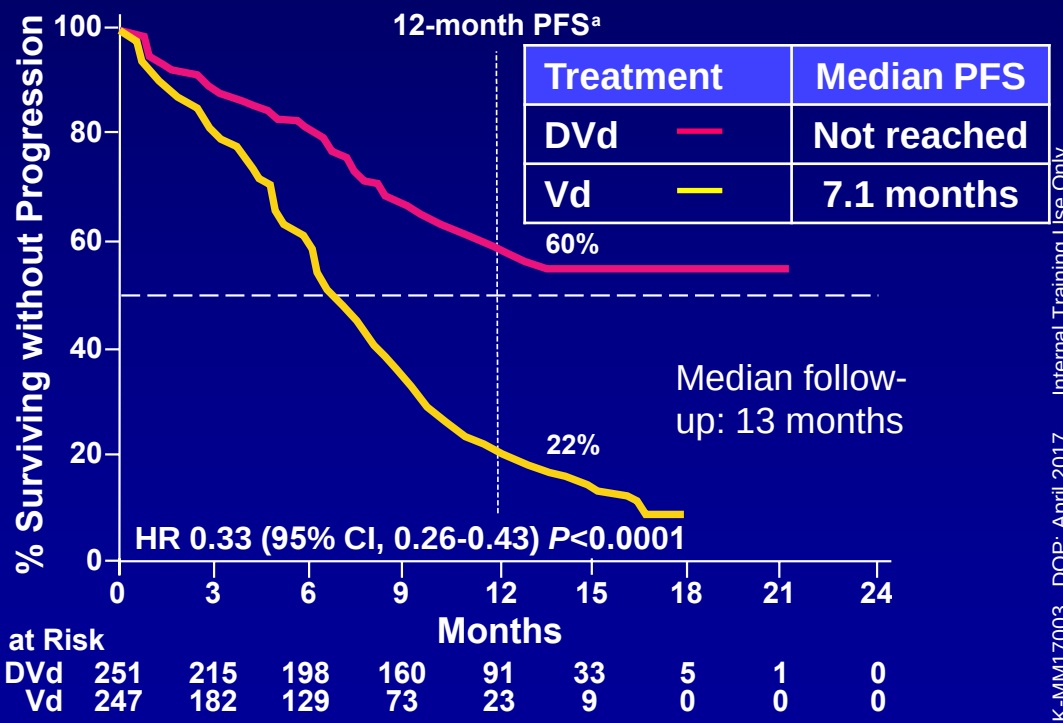
K, carfilzomib; E, elotuzumab; N, ixazomib.

Phase III CASTOR Study: DVd vs. Vd (n=498)[1,2]



Updated Efficacy at ASH 2016[2]

	DVd (n=240)	Vd (n=234)	*p*-Value
ORR (≥PR)	84%	63%	<0.0001
≥CR	26%	10%	<0.0001



[a] Kaplan-Meier estimate

AE, adverse event; CI, confidence interval; CR, complete response; DVd, daratumumab, bortezomib, low-dose dexamethasone; HR, hazard ratio; ORR, overall response rate; PFS, progression free survival; PR, partial response; URTI; upper respiratory tract infection; Vd, bortezomib, dexamethasone

1. Palumbo et al. *NEJM* 2016. 375:754-66
2. Mateos M et al. *ASH 2016*. Oral Presentation and Abstract 1150

Conclusions

- PFS benefit continues to be maintained with DVd over time
- DVd is superior to Vd regardless of prior lines of therapy
- Largest magnitude of benefit with DVd is observed in patients with 1 prior line of therapy
  - 78% reduction in risk of progression or death for DVd versus Vd
- More patients in DVd achieved deeper responses with longer follow-up
  - Higher CR and MRD-negative rates
  - MRD negativity translated into longer PFS
- DVd is superior to Vd regardless of cytogenetic risk or time since last therapy
- No new safety signals were reported

These data further support the use of this newly approved regimen of DVd in RRMM, with most benefit in patients with 1 prior line of therapy

CR, complete response; DVd, daratumumab, bortezomib, low-dose dexamethasone; MRD, minimal residual disease; Vd, bortezomib, dexamethasone.

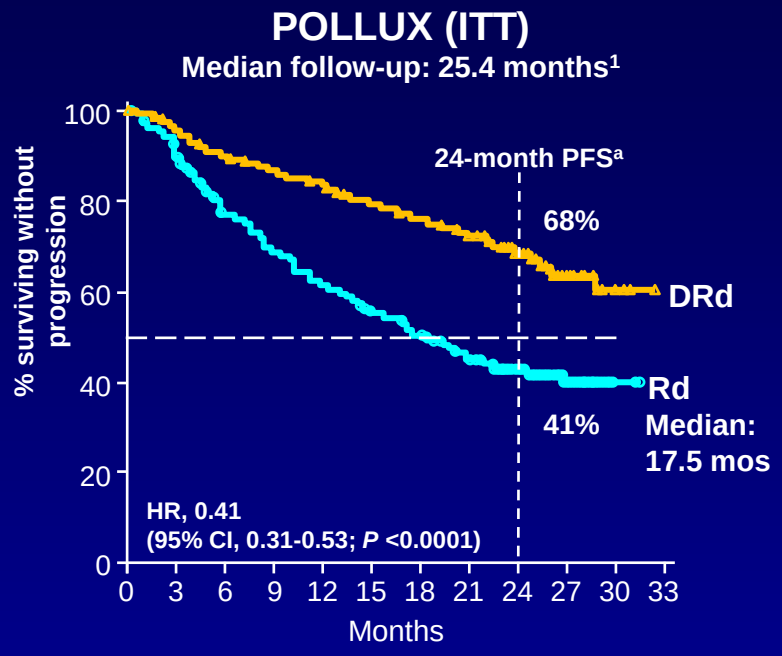
Mateos M et al. *ASH 2016*. Oral Presentation and Abstract 1150

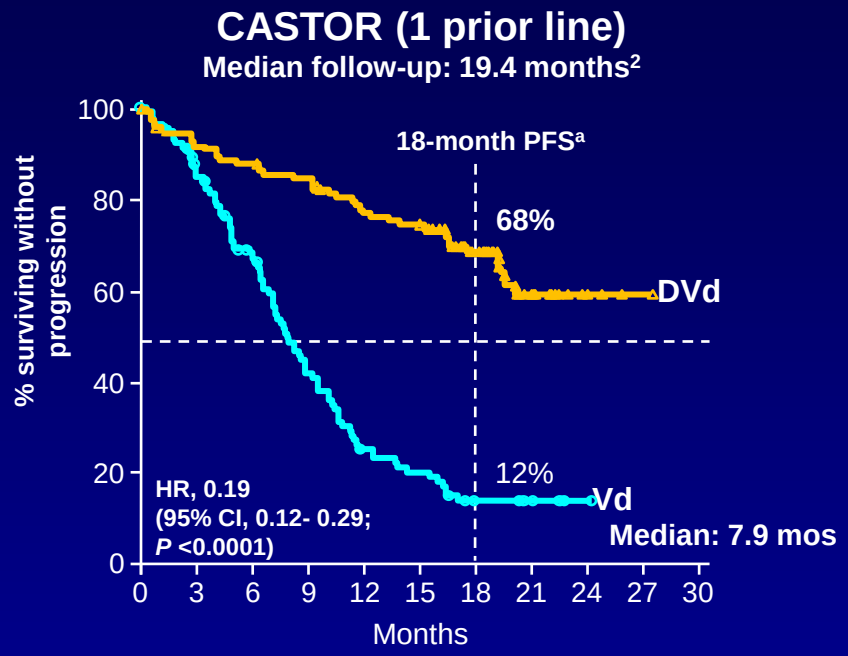
Proteasome Inhibitor-based Studies in RR MM

	Daratumumab DVd vs Vd	Carfilzomib Kd vs Vd[1]	Panobinostat PVd vs Vd[2,3]	Elotuzumab EVd vs Vd[4]
PFS HR (95% CI)	0.39 (0.28-0.53)	0.53 (0.44-0.65)	0.63 (0.52-0.76)	0.72 (0.59-0.88)
PFS, median mo	NE	18.7	12.0	9.7
≥VGPR	59%	54%	28%	36%
≥CR	19%	13%	11%	4%
Duration of response, mos	NE	21.3	13.1	11.4
OS HR (95% CI)	0.77 (0.47, 1.26)	0.79 (0.58-1.08)	0.94 (0.78-1.14)	0.61 (0.32-1.15)

1. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38.
2. San-Miguel JF, et al. *Lancet Oncol*. 2014;15(11):1195-1206.
3. San-Miguel JF, et al. *Blood*. 2015;126(23):Abstract 3026.
4. Jakubowiak A, et al. *Blood*. 2016. Epub ahead of print.

DARA Plus Rd or Vd in RRMM: Updated PFS (ASCO 2017)





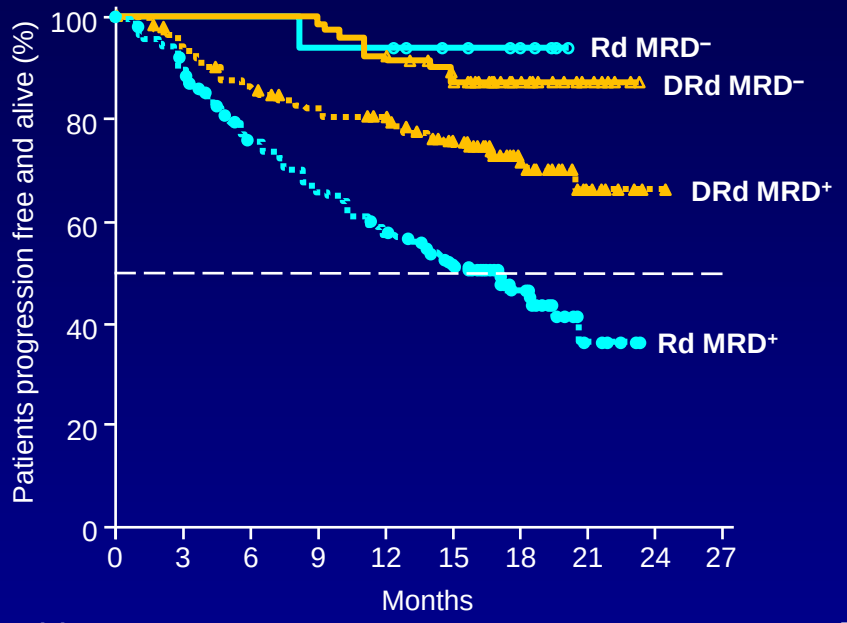
SOC, standard of care; ITT, intent-to-treat; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.
[a]Kaplan-Meier estimates.

Exploratory analyses based on clinical cut-off: January 11, 2017 for CASTOR; March 7, 2017 for POLLUX.

1. Bahlis NZ, et al. Poster ASCO 2017 Annual Meeting, June 2-6 , 2017. Chicago, IL; Abstract 8025.
2. Lentzsch S, et al. Poster ASCO 2017 Annual Meeting, June 2-6 , 2017. Chicago, IL; Abstract 8036.

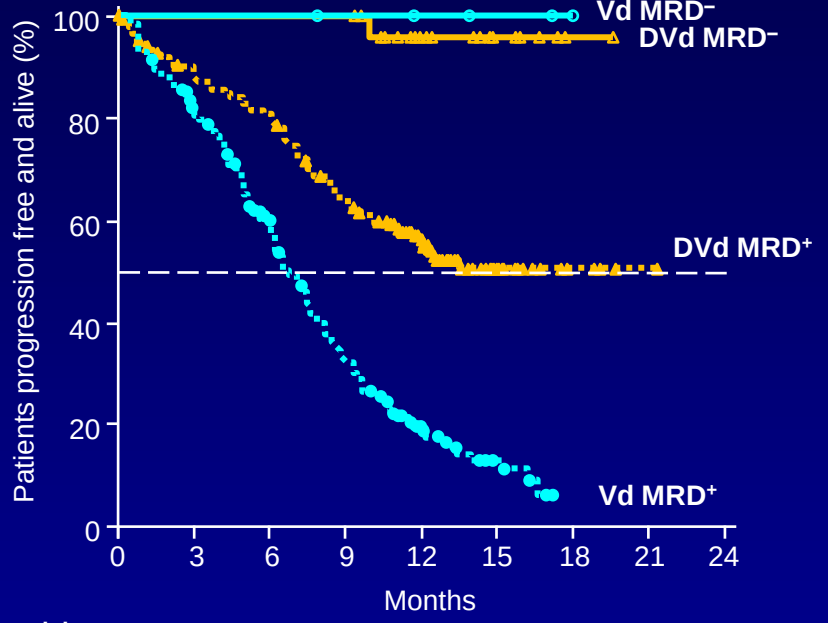
PFS According to MRD Status at 10^{-5}

POLLUX



Patients at risk										
Rd MRD negative	16	16	16	15	15	12	10	0	0	0
DRd MRD negative	71	71	71	70	66	57	28	6	0	0
Rd MRD positive	267	233	190	166	144	120	38	5	0	0
DRd MRD positive	215	195	178	167	161	137	54	9	1	0

CASTOR



Patients at risk										
Vd MRD negative	6	6	6	5	3	2	0	0	0	
DVd MRD negative	26	26	26	26	15	7	1	0	0	
Vd MRD positive	241	176	123	68	20	7	0	0	0	
DVd MRD positive	225	189	172	134	76	26	4	1	0	

- **Lower risk of progression in MRD-negative patients**
- **PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care**

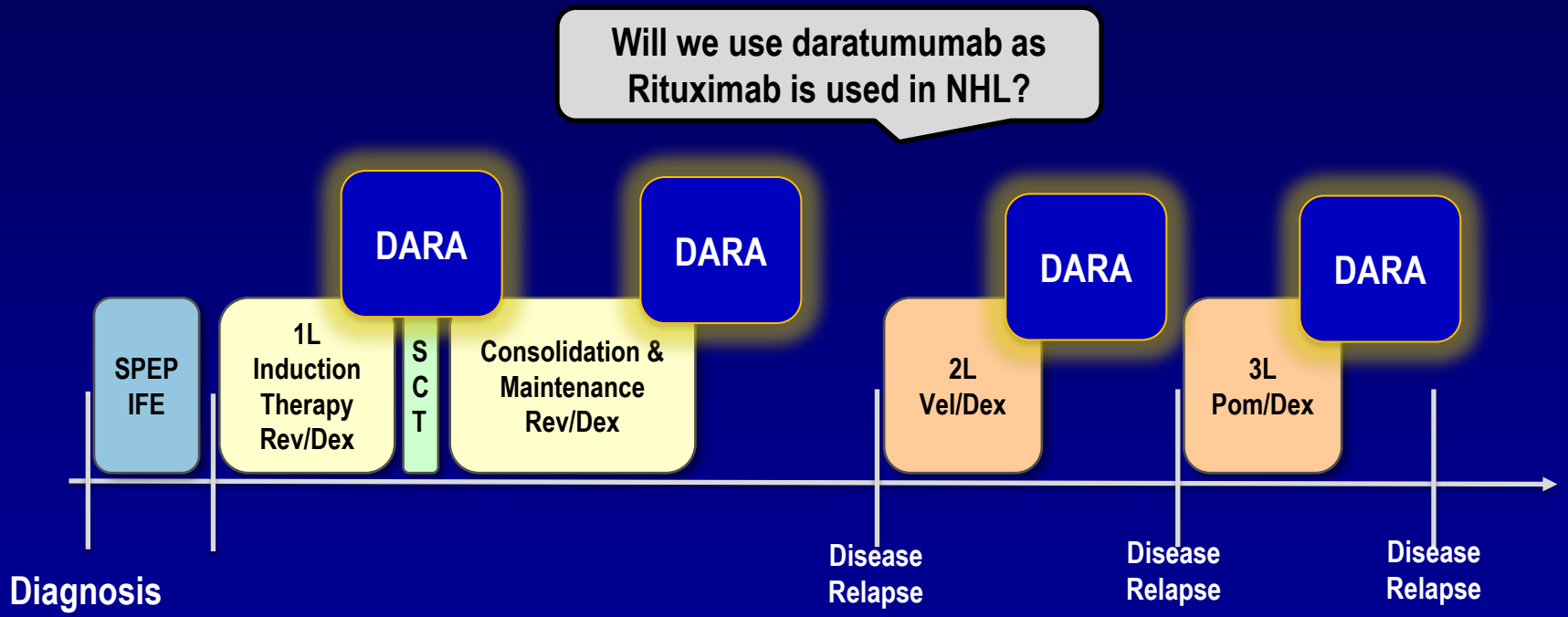
Avet-Loiseau al, ASH 2016

Efficacy by Cytogenetic Risk Status for Daratumumab With Lenalidomide and Dex or Bortezomib and Dex in Relapsed or Refractory Multiple Myeloma

- First prospective assessment of cytogenetic status by NGS in phase 3 studies
- DARA plus standard of care showed significant benefit in both high-risk and standard-risk patients in terms of PFS, ORR, and MRD-negative rates
- In high-risk patients, MRD negativity was achieved only with DARA
- Preliminary data indicate possible OS benefit of DARA; longer follow-up is needed

San Miguel et al, EHA 2017

Where Do We Envision Using Daratumumab?

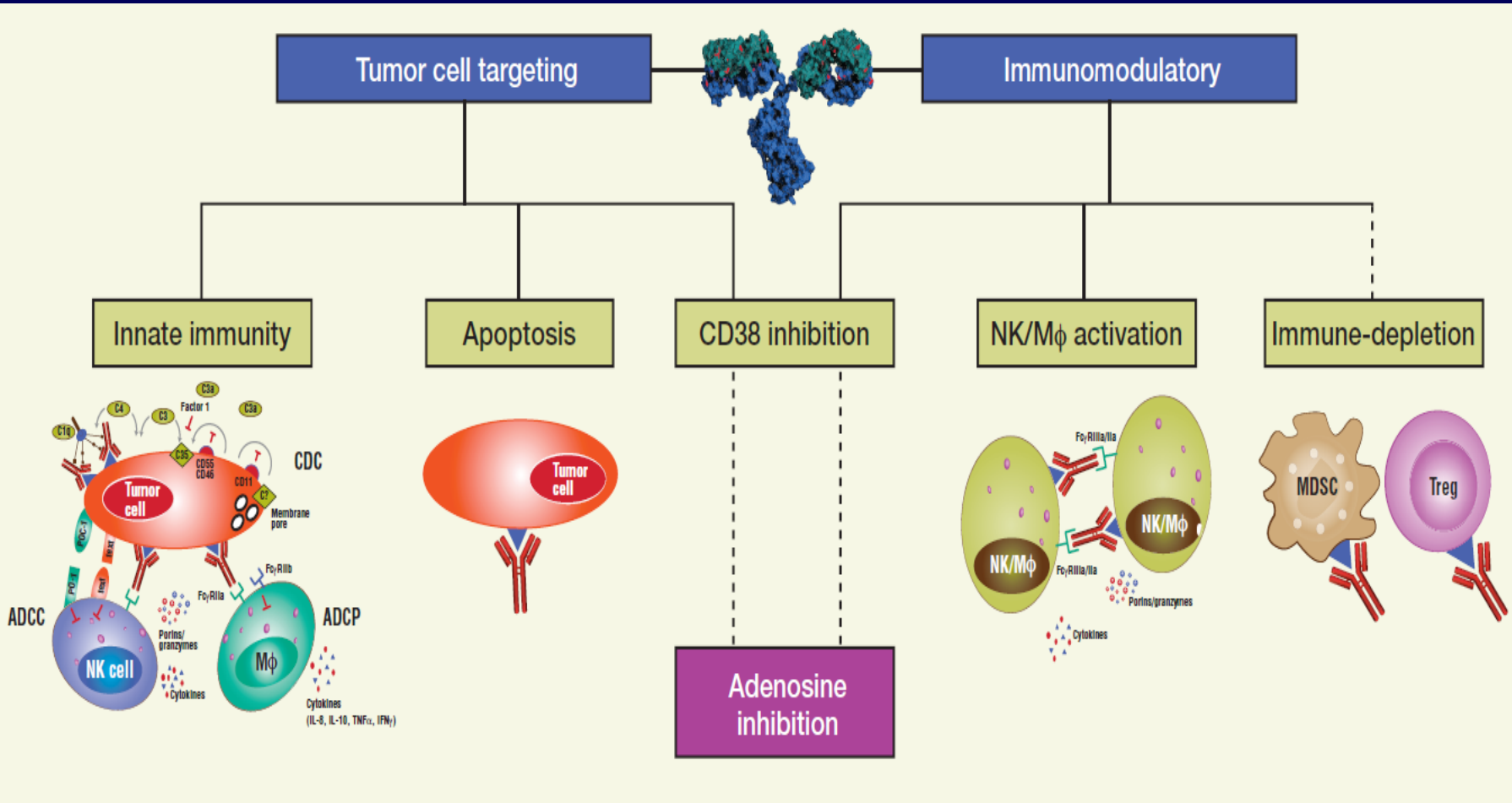


DARA – Future Considerations and Next Steps

- Better understanding of the immunomodulatory effects of Dara combination regimens: ASH 2017
- While significantly number of pts achieve MRD neg, durability and significance of MRD is still not known: ASH 2017
- Combo of Dara plus RVD, KRD with ASCT under evaluation (GRIFFIN and others)
- Stem cell harvest is not impacted by DARA plus RVd, KRd or VTD, but the ph3 studies will determine this for sure…
- How will Dara plus PD-1/PDL-1 data look? Early data suggests synergy with favorable safety: ASH 2017
- Can Dara be combined with CAR-T and/or anti-BCMA?
- Alcyone (D-VMP) and Maia (DRD): data anticipated 2017/2018
- Dara SC + hylauridanase in smaller volumes: ASH 2017

Phase Ib Study of Isatuximab+Pom+dex in RRMM

Modes of action of isatuximab



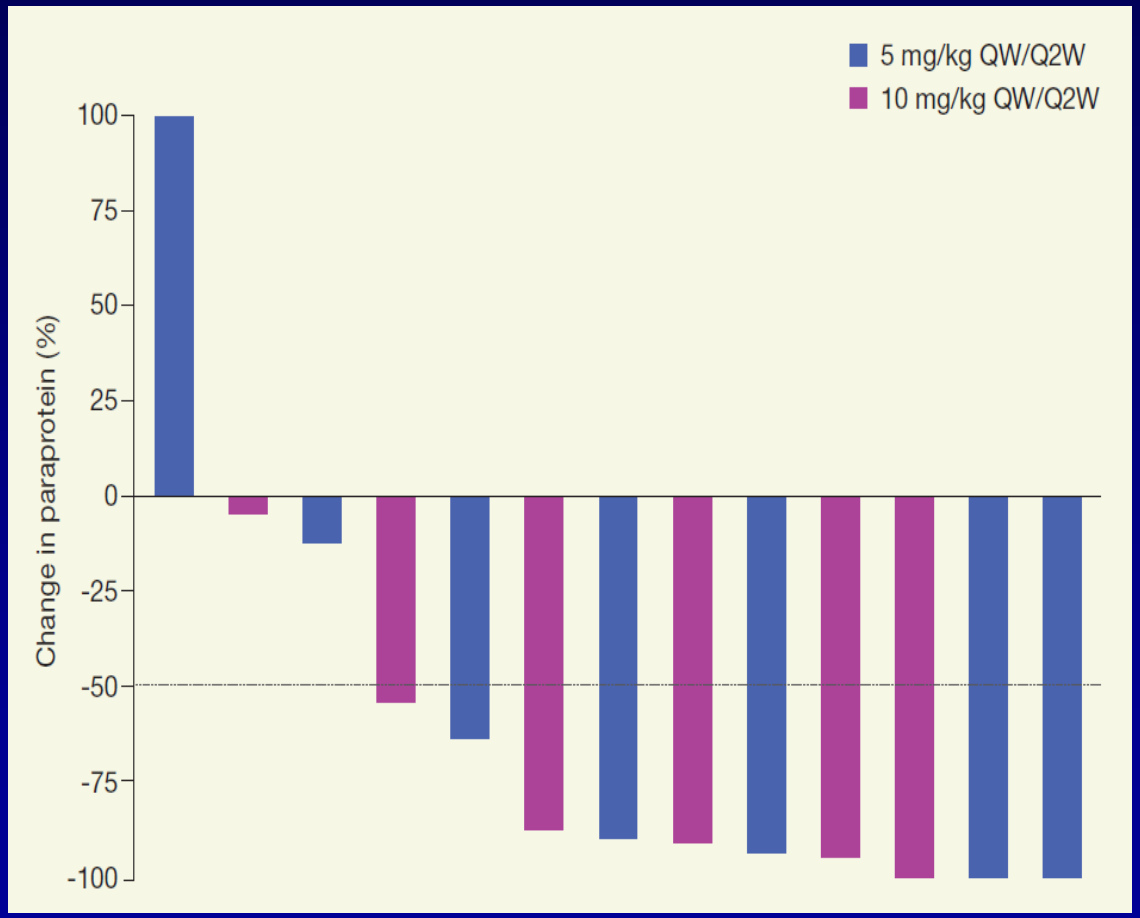
ADCC/CP, antibody-dependent cellular cytotoxicity/phagocytosis; CDC, complement-dependent cytotoxicity; Mφ, macrophage; MDSC, myeloid-derived suppressor cell; NK, natural killer cell; Pom, pomalidomide; RRMM, relapsed refractory multiple myeloma.

Richardson P et al. *ASH 2016*. Poster Presentation and Abstract 2123

Phase Ib Study of Isatuximab+Pom+dex in RRMM (n=20)

Reductions in paraprotein levels were recorded in the majority of patients.

Waterfall plot of best percentage change in paraprotein levels



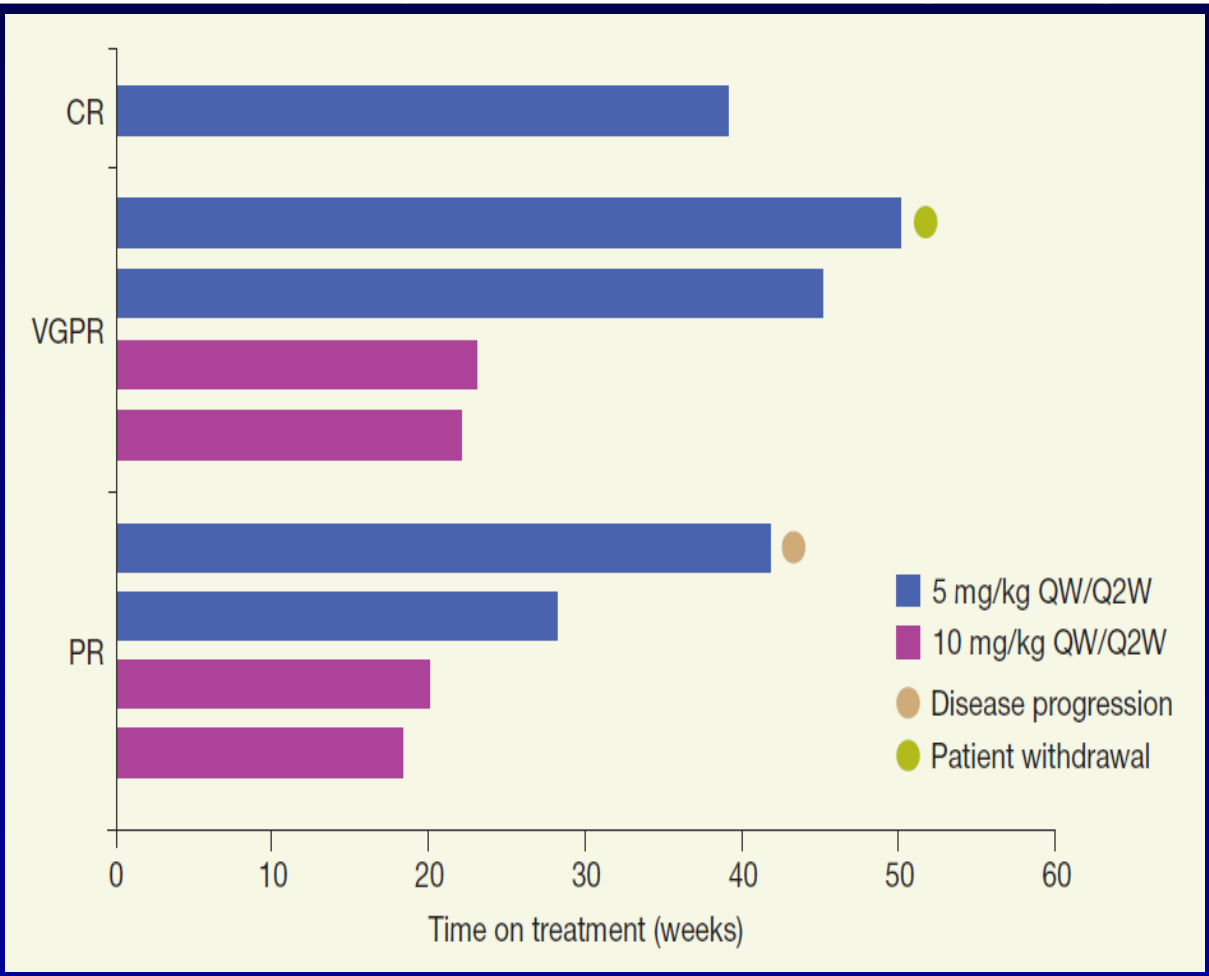
Post-baseline paraprotein data were not available for one patient in the 5 mg/kg cohort.
QW, weekly; Q2W, once every 2 weeks.

Richardson P et al. *ASH 2016*. Abstract 2123

Up-dated at ASH 2017

Phase Ib Study of Isatuximab+Pom+dex in RRMM (n=20)

Time on treatment by best confirmed response (at least PR)



- **Seven patients who achieved at least PR remained on treatment at data cutoff.**

CR, complete response; PR, partial response; QW, weekly; Q2W, once every 2 weeks; VGPR, very good partial response.

Richardson P et al. *ASH 2016*. Poster Presentation and Abstract 2123

Author's Conclusions

- The combination of isatuximab with Pom/Dex is generally well tolerated in patients with RRMM
  - The AEs observed are generally consistent with the known safety profiles of the individual agents
- IARs were all Gr 1/2 in intensity and tended to occur with the first infusion.
- The PK parameters of isatuximab do not appear to be affected by Pom/Dex co-administration.
- The combination of isatuximab with Pom/Dex was clinically active in this heavily pretreated patient population
  - Confirmed ORR was 64%; confirmed ORR with isatuximab 10 mg/kg was 67%
  - Confirmed ORR in IMiD-refractory patients was 64%
- The MTD for this combination was not reached at the highest isatuximab dose level tested; 10 mg/kg was the selected dose for the expansion cohort based on these preliminary clinical, efficacy, safety, and PK data
- A global Phase III study of isatuximab plus Pom/Dex is planned to start in 2016

AEs, adverse events; Dex, dexamethasone; IARs, infusion adverse reactions; MTD, maximum tolerated dose; ORR, overall response rate; PK, pharmacokinetic; Pom, pomalidomide; RRMM, relapsed refractory multiple myeloma.

Richardson P et al. *ASH 2016*. Poster Presentation and Abstract 2123

ASH 2017: Deep and Durable Responses in Patients with Relapsed/Refractory Multiple Myeloma Treated with Monotherapy GSK2857916, an Antibody Drug Conjugate Against B-cell Maturation Antigen: Preliminary Results from Part 2 of Study BMA117159 (DREAMM-1)

Suzanne Trudel[1], Nikoletta Lendvai[2], Rakesh Popat[3], Peter M. Voorhees[4], Brandi Reeves[5], Edward N. Libby[6], Paul G. Richardson[7], Larry D. Anderson Jr[8], Heather J. Sutherland[9], Kwee Yong[3], Axel Hoos[10], Michele M. Gorczyca[10], Soumi Lahiri[10], Zangdong He[10], Daren Austin[10], Joanna Opalinska[10], Adam D. Cohen[11]

[1]Princess Margaret Cancer Centre Toronto, Ontario, Canada; [2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [3]University College London Hospitals NHS Foundation Trust, London, UK; [4]Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA; [5]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA; [6] University of Washington, Seattle WA, USA; [7]Dana-Farber Cancer Institute, Boston, MA, USA; Canada; [8]University of Texas Southwestern, Dallas, TX, USA; [9]Vancouver General Hospital, Vancouver, BC, Canada; [10]GlaxoSmithKline, USA/UK; [11]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

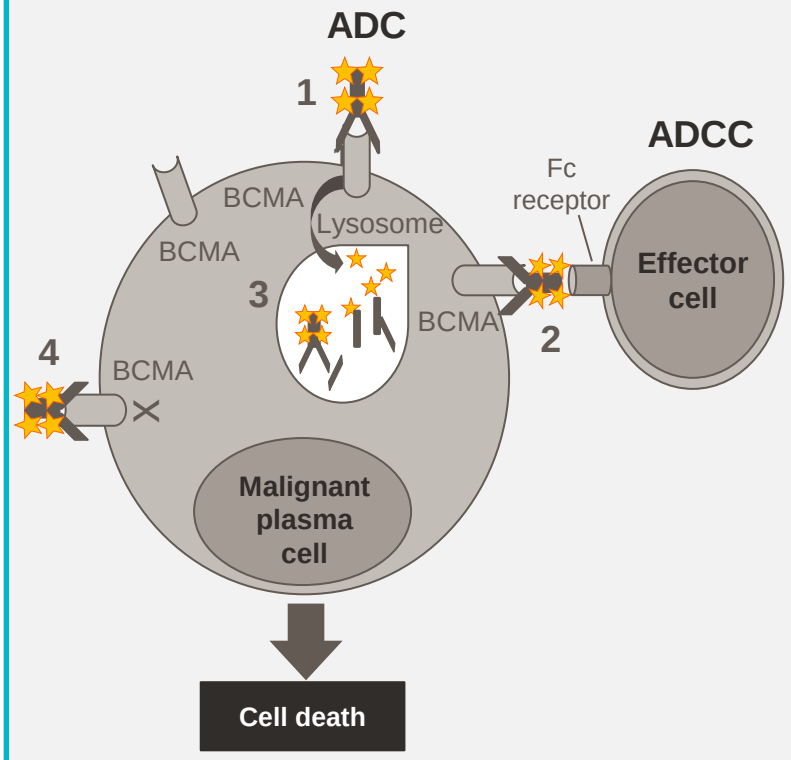
Background

- BCMA: expressed on differentiated B cells; requisite for long-lived plasma cells' survival
- **BCMA is broadly expressed on malignant plasma cells**
- **GSK2857916:** humanized, afucosylated IgG1 **anti-BCMA antibody;** neutralization of soluble BCMA
  - Preclinical studies demonstrate its selective and potent activity[1]

GSK2857916	
Toxin	– MMAF (non-cell permeable, highly potent auristatin
Afucosylation	– Enhanced ADCC
Linker	– Stable in circulation

Four mechanisms of action:

1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death
4. BCMA receptor signaling inhibition

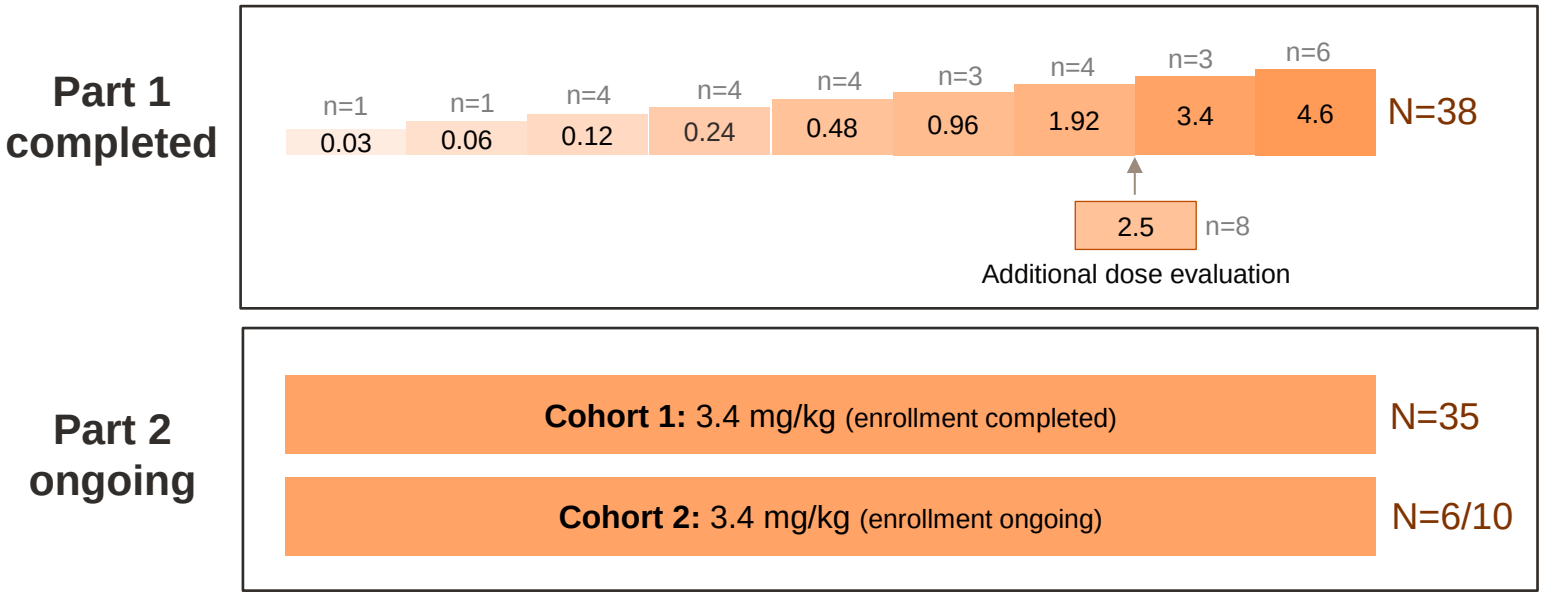


[1]Tai YT, et al. Blood 2014;123(20):3128-38.

ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; IgG, immunoglobulin G; MMAF, monomethyl auristatin-F

DREAMM-1: FTIH Study Design

- Overall, 38 patients were evaluated in **Part 1 – no DLTs were observed**
- **Part 2: Expansion**
  - **Cohort 1:** relapsed/refractory MM (N=35; enrollment complete)
  - **Cohort 2:** BCMA-positive relapsed DLBCL or follicular lymphoma (N≈10; ongoing)
- **Expansion dose:** 3.4 mg/kg
- **Schedule:** 1h IV, once every 3 weeks
- **Treatment duration:** up to 16 cycles (up to 1 year)



BCMA, B-cell maturation antigen; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; FTIH, first-time-in-human; IV, intravenous; MM, multiple myeloma

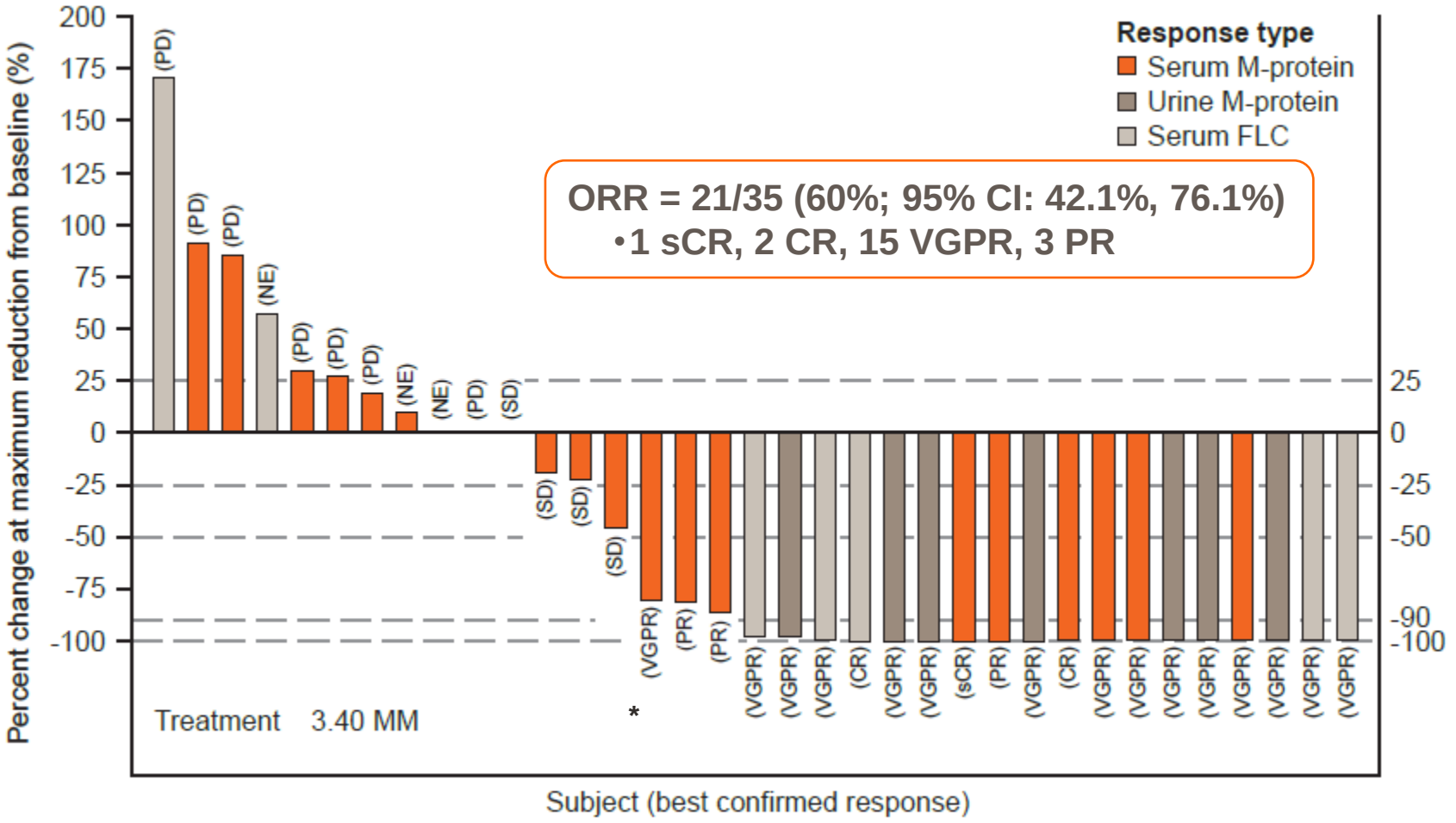
DREAMM-1 Part 2: Demographics and Baseline Characteristics

Characteristic	Part 2 (N=35)
Age (years), median (min, max)	60 (46–75)
Females/males, %	51/49
≥5 prior lines, n (%)	20 (57)
ASCT	31 (89)
IMiDs Lenalidomide Pomalidomide Thalidomide **Refractory to IMiD**	**35 (100)** 33 (94) 21 (60) 12 (34) **32 (91)**
PI Bortezomib Carfilzomib **Refractory to PI**	**35 (100)** 34 (97) 28 (80) **34 (97)**
Daratumumab **Refractory to daratumumab**	**14 (40)** **13 (37)**
Refractory to IMiD/PI	**31 (89)**
Refractory to IMiD/PI and prior daratumumab	**12 (34)**
Cytogenetics risk, n (%)* High risk Other Missing	 20 (58) 15 (43) 11 (31)

*Patients with any of the following genetic abnormalities were considered high risk: t(4:14), del3; del17, t(14:16), t(14:20) or gain 1q. Multiple categories per subject possible: total may exceed 100%

ASCT, autologous stem cell transplant; IMiD, immunomodulator; PI, proteasome inhibitor

DREAMM-1 Part 2: Maximum % Reduction in M-Protein or Free Light Chain from Baseline



*One patient with a VGPR had a <90% reduction in serum M-protein due to missing laboratory data, which was confirmed by investigators as too small to quantify after the data cut-off

CI, confidence interval; CR, complete response; FLC, free light chain; M-protein, myeloma protein; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

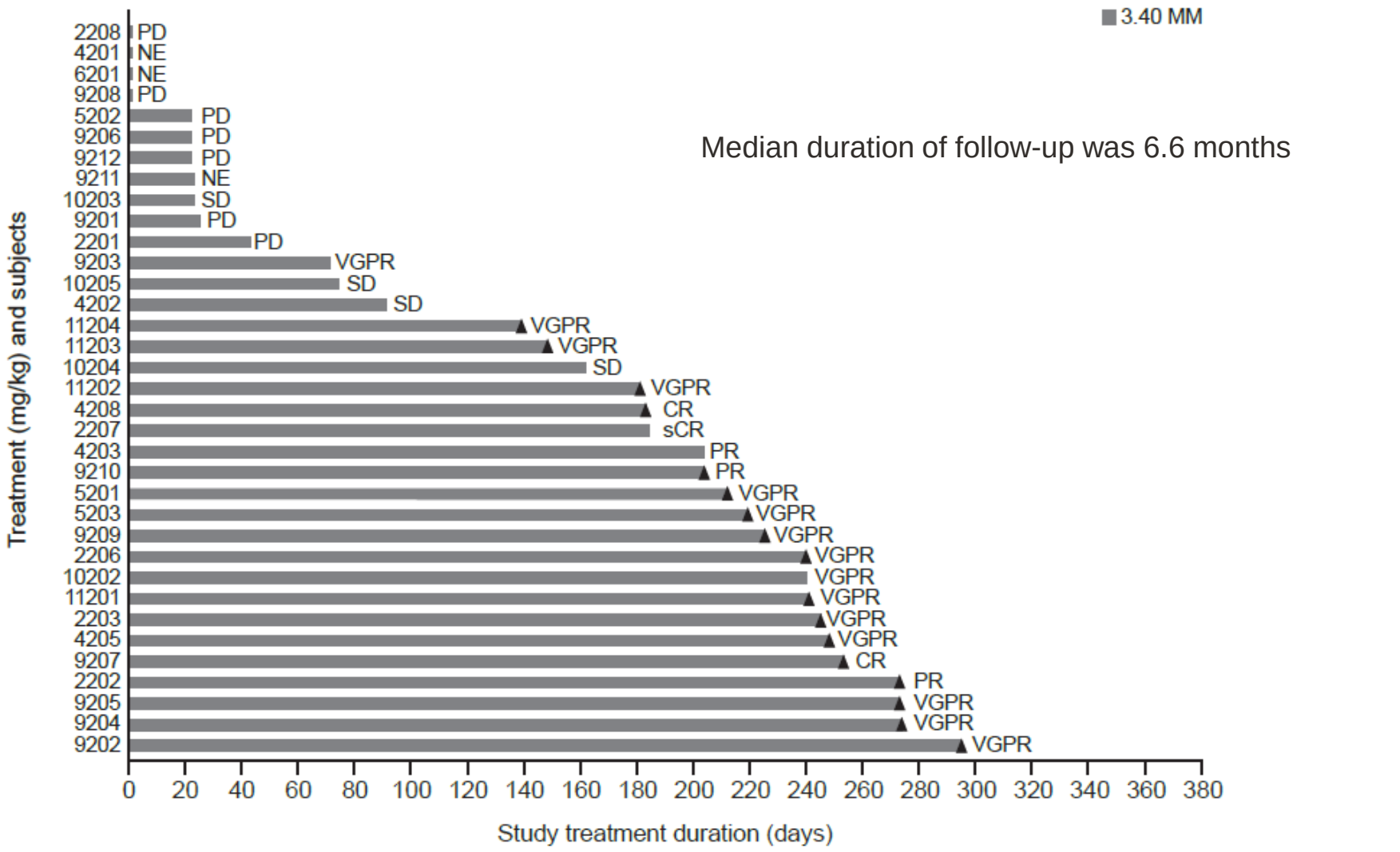
DREAMM-1 Part 2: Efficacy – Overall Response Rate

%	sCR	CR	VGPR	PR	NE	ORR*
Part 2 (N=35)	**3 (n=1)**	**6 (n=2)**	**43 (n=15)**	**9 (n=3)**	**9 (n=3)**	**60 (n=21)**
Prior daratumumab (N=14)	7 (n=1)	0	21 (n=3)	14 (n=2)	14 (n=2)	**43 (n=6)**
Refractory to both IMiD and PI (N=31)	3 (n=1)	6 (n=2)	42 (n=13)	6 (n=2)	10 (n=3)	**58 (n=18)**
Refractory to IMiD, PI and prior daratumumab (N=12)	8 (n=1)	0	25 (n=3)	8 (n=1)	17 (n=2)	**42 (n=5)**

Note: subjects with NE discontinued treatment after one or two doses
*Any discrepancies in % due to rounding error

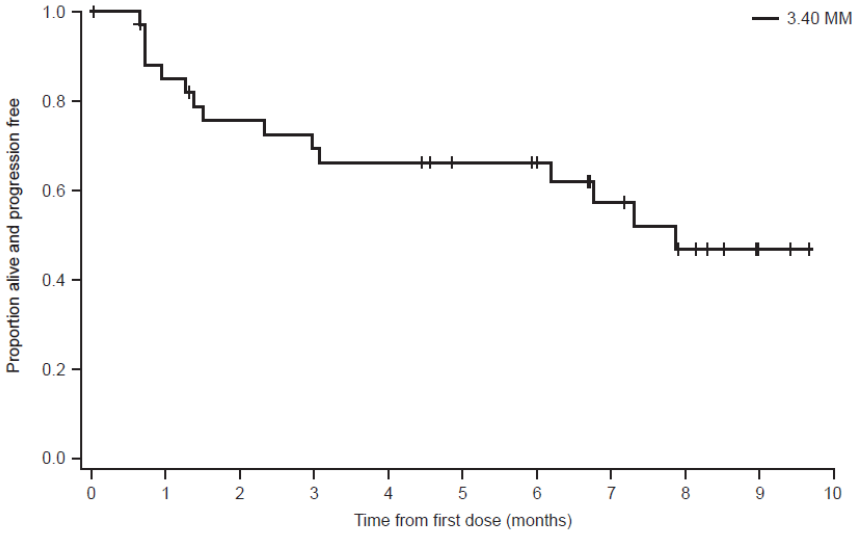
CR, complete response; IMiD, immunomodulator; NE, not evaluable; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

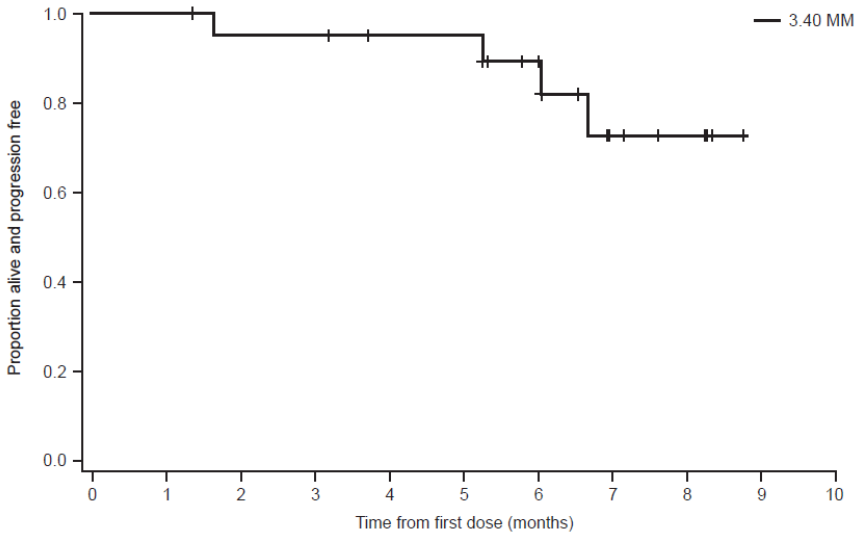
DREAMM-1 Part 2: Duration of Study Treatment by Response



CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

DREAMM-1 Part 2: Efficacy – Progression-free Survival and duration of response





Number of subjects	**35**
Progressed or died	15 (43%)
Censored, f/u ended	3 (9%)
Censored, f/u ongoing	17 (49%)

Number of subjects	**21**
Progressed or died	4 (19%)
Censored, f/u ended	0
Censored, f/u ongoing	17 (81%)

Progression-free survival (months)	
Q1 (95% CI)	2.3 (0.7, 6.8)
Median (95% CI)	**7.9 (3.1, -)**
Q3 (95% CI)	N/A

Duration of response (months)	
Q1 (95% CI)	6.7 (1.6, -)
Median (95% CI)	**N/A**
Q3 (95% CI)	N/A

CI, confidence interval; f/u, follow-up; N/A, not available; Q, quartile

Conclusions

- Median time of follow-up was 6.6 months; the study is ongoing with the Part 2 cohort still receiving therapy
- GSK2857916 resulted in an ORR of 60% in heavily pre-treated patients with MM
  - 51% of patients in Part 2 had VGPR or better
- Median PFS was 7.9 months and DOR was not estimable as only 4 responders had progressed at the time of the data cut-off. The 25th percentile for DOR is 6.7 months.
- GSK2857916 was well tolerated and side effects were manageable
  - Thrombocytopenia and corneal events emerged as the most frequent AEs and reasons for dose modification
  - IRRs occurred in only 23% of patients and without pre-medication; no IRRs occurred on subsequent infusions
- The target and therapeutic mechanisms of action differentiate GSK2857916 from currently approved drugs in MM
- Additional monotherapy and combination studies are planned

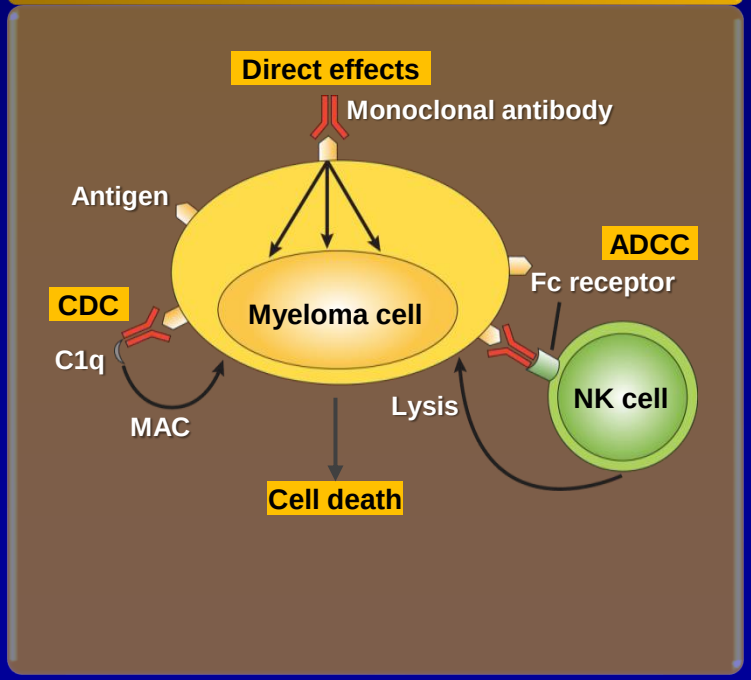
DOR, duration of response; IRR, infusion-related reaction; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response

Harnessing the Immune System to Fight Myeloma:

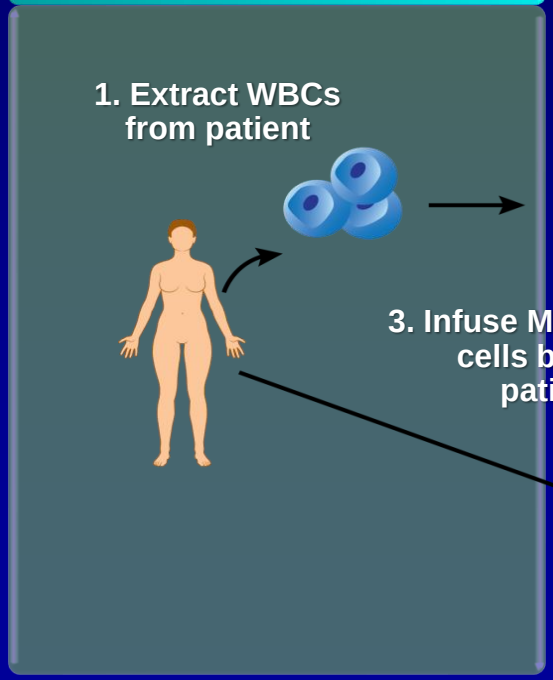
Types of Immunotherapy, Immuno-Oncology

Passive ——— Active ———

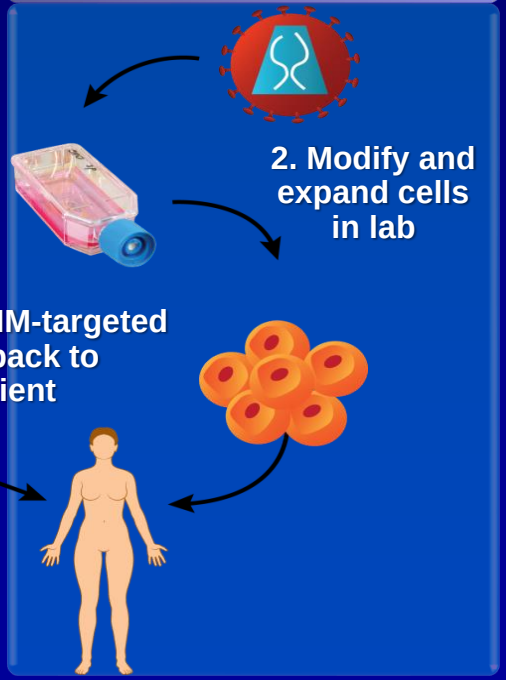
Monoclonal antibodies



Chimeric antigen receptor (CAR) T cells



Vaccines (therapeutic *not* preventive)

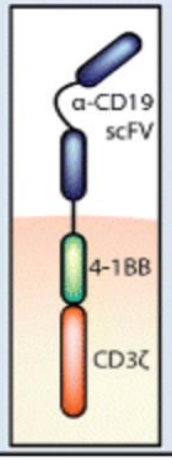
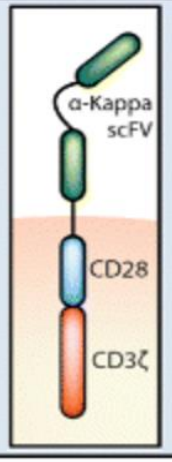
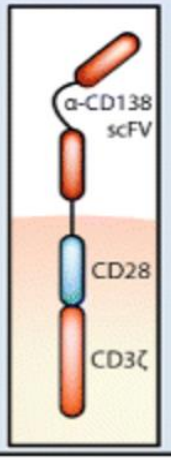
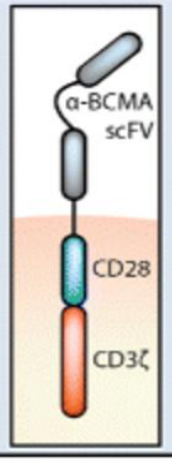
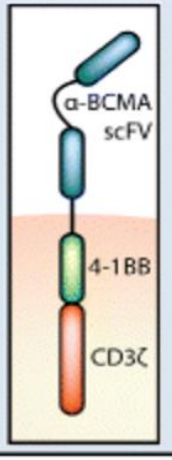
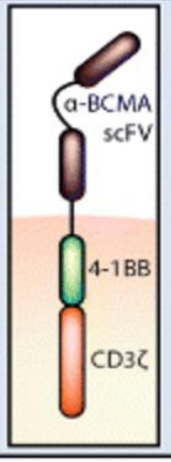


Richardson PG et al, ASH 2017

Myeloma CAR therapy: ASH 2017

- Multiple promising targets:
  - CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1 (SLAMF7), BCMA
- Functional CAR T cells can be generated from MM patients
- CAR T and NK cells have in vitro and in vivo activity against MM
- Clinical trials underway
  - Anecdotal prolonged responses but no robust efficacy data available yet
- Many questions remain about CAR design:
  - optimal co-stimulatory domains
  - optimal vector
  - optimal dose and schedule
  - need for chemotherapy
  - Perhaps ‘cocktails’ of multiple CARs or CARs + chemotherapy will be required for best outcomes

CAR T Cells in Development for Myeloma 2017

	α-CD19-BBz	α-Kappa-28z	α-CD138-28z	α-BCMA-28z	α-BCMA-BBz	α-BCMA-BBz
						
Institution	Penn	Baylor	Chinese PLA General Hospital	NCI	Penn	bluebird bio
scFV Clone	FMC63	CRL-1758	NK-92	11D5-3	ND	bb2121
scFV Origin	Murine	Murine	Murine	Murine	Human	Humanized
Gene Transfer System	Lentivirus	Retrovirus	Lentivirus	Retrovirus	Lentivirus	Lentivirus
Intracellular Domain	4-1BB ICD-CD3zeta	CD28 ICD-CD3zeta	CD28 ICD-CD3zeta	CD28 ICD-CD3zeta	4-1BB ICD-CD3zeta	4-1BB ICD-CD3zeta
Patients Treated	11	8	5	12	6	9
Dose(s)	1-5e7 CARTs/pt	0.2-2e8 CARTs/m2	0.44-1.51e7 CARTs/kg	0.3-9e6 CARTs/kg	1e7-5e8 CARTs/pt	5-80e7 CARTs/pt
Best Response (number of patients)	CR (1), VGRP (6), PR (2), PD (2)	SD (5), NR (3)	SD (4), PD (1)	Stringent CR (1), VGPR (2), PR (1), SD (8)	Stringent CR (1), VGPR (1), SD (1), MR (2), PD (1)	Stringent CR (2), VGPR (1), PR (4), SD (1), PD (1)
Reference(s)	25··	27··	26	28	29	ASH 2016 Abstract

Maria Ormhøj Current Hematologic Malignancy Reports April 2017, vol. 2 12 (2) pp 119–125

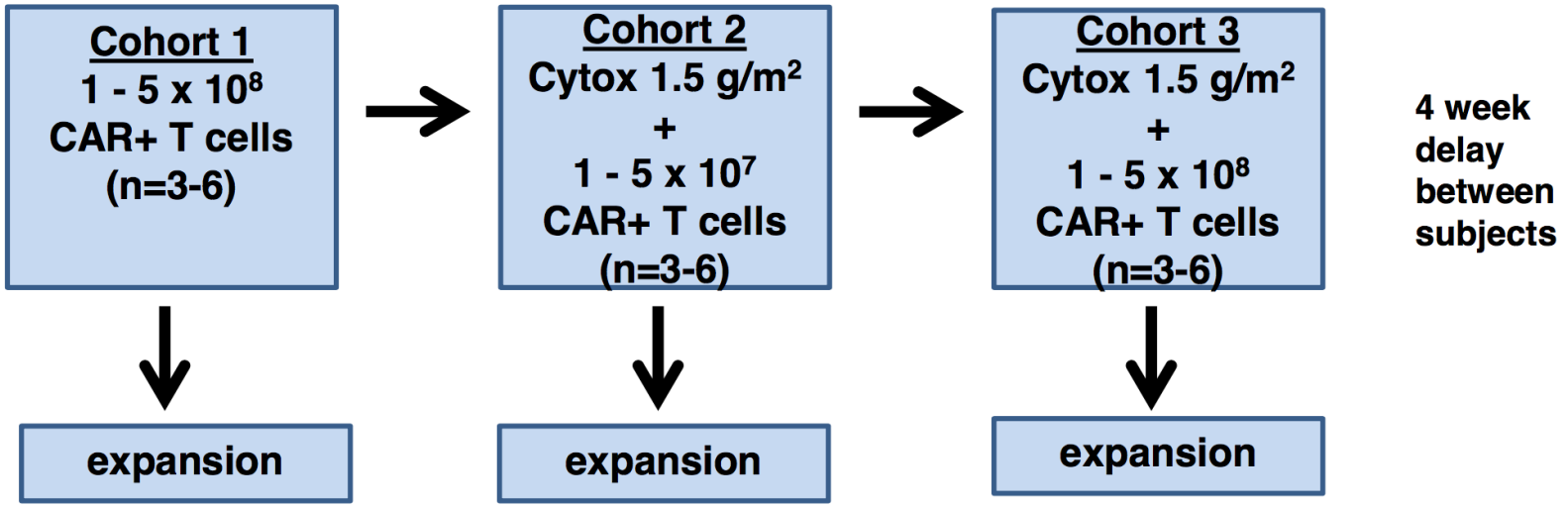
Penn Medicine

Safety and Efficacy of B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T cell (CART-BCMA) with Cyclophosphamide Conditioni for Refractory Multiple Myeloma (MM)

Adam D. Cohen, Alfred L. Garfall, Edward A. Stadtmauer, Simon F. Lacey, Eric Lancaster, Dan T. Vogl, Brendan M Weiss, David E. Ambrose, Anne Marie Nelson, Fang Chen, Gabriela Plesa, Irina Kulikovskaya, Vanessa Gonzalez, Minnal Gupta, Regina Young, Karen Dengel, Laura O'Keefe, Samantha Le, Celeste Richardson, Randi E. Isaacs, J. Joseph Melenhorst, Bruce L. Levine, Carl H. June, Michael C. Milone

ASH 2017

Study design



- **24 treated**
  - 9 in cohort 1: 1-5 x 10^8 CART-BCMA (no lymphodepleting chemo)
  - 5 in cohort 2: Cytox + 1-5 x 10^7 CART-BCMA
  - 10 in cohort 3: Cytox + 1-5 x 10^8 CART-BCMA

- **All successfully manufactured at least minimum target dose**
  - 1 required 2 collections
  - Median transduction efficiency=17.4% (7.5 – 33.3%)

- **20/24 got 100% of planned dose**
  - 4 got 40% due to fevers/CRS on day 2

Toxicity	Cohort 1 (n=9)	Cohort 2 (n=5)	Cohort 3 (n=10)
Cytokine release syndrome			
All grade	8 (89%)	3 (60%)	9 (90%)
Penn Grade 3/4	3 (33%)	0 (0%)	5 (50%)
Toci/Siltux used	4 (44%)	0 (0%)	2 (20%)
Neurotoxicity			
All grade	3 (33%)	0 (0%)	3 (33%)
Grade 3/4	2 (22%)	0 (0%)	1 (10%)

- **Responses: ≥PR in 11/24 (47%)**
  - 4 ongoing at 3+, 3+, 6+ and 24+ months
  - 1-5 x10^8 dose more active
  - Not clearly associated with baseline BCMA expression or sBCMA concentration
- **Decreased BCMA expression may be escape mechanism**

CRB-401 Phase 1 Study in Relapsed / Refractory Multiple Myeloma

CRB-401 Open-label Phase 1 Clinical Study of bb2121

- **Objectives: Determine preliminary safety and efficacy and recommended phase 2 dose**

ASH 2017

9 U.S. Clinical Sites, 1 Centralized Manufacturing Site

MAYO CLINIC

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

DANA-FARBER CANCER INSTITUTE

Beth Israel Deaconess Medical Center

SARAH CANNON Fighting Cancer Together

Mount Sinai

HackensackUMC Where medicine meets innovation

NIH NATIONAL CANCER INSTITUTE

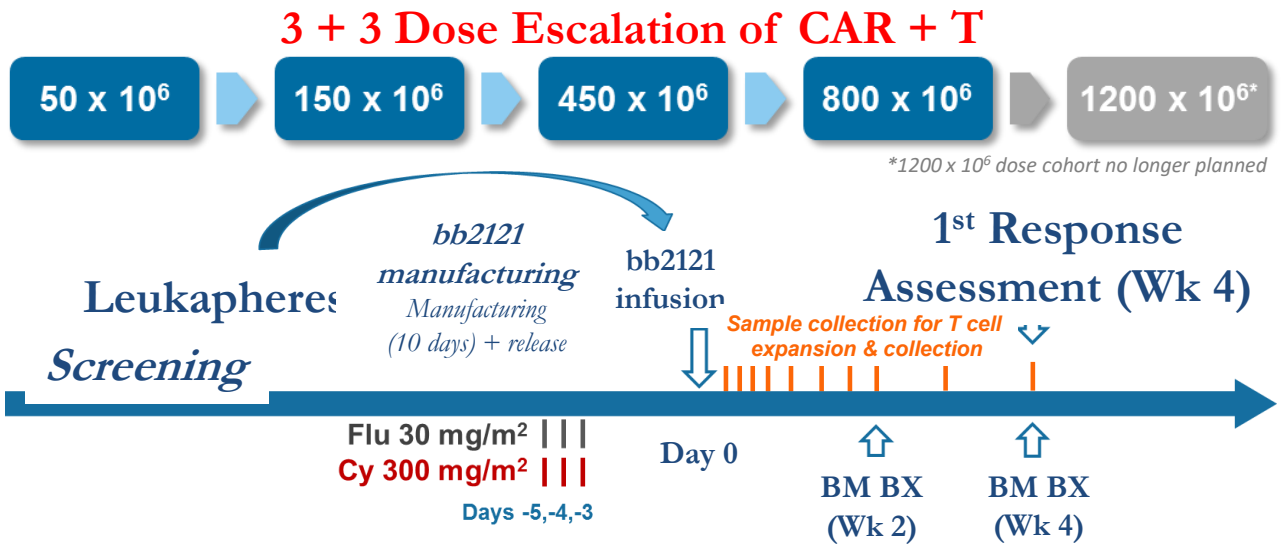
Stanford MEDICINE

bb2121: An Anti-BCMA Chimeric Antigen Receptor T Cell Product Candidate

- bb2121 is a second-generation CAR construct targeting BCMA, consisting of autologous T cells transduced with a lentiviral vector encoding a novel CAR incorporating an anti-BCMA scFv,

  a 4-1BB costimulatory motif to promote proliferation and persistence, and a CD3ζ T cell activation domain

CRB-401 Study Design and Status



Study Status (Escalation)

Cells Collected N=24

Dosed N=21

Evaluable for Response N=21

Manufacturing success rate of 100%

Expansion Cohort Initiated in August 2017

- **12 additional patients have been collected and dosed in the Expansion Cohort as of 02 Nov 2017**

Dose Escalation Patients (N = 21)

Preferred Term	Overall n (%)	Grade 3 or higher n (%)
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)

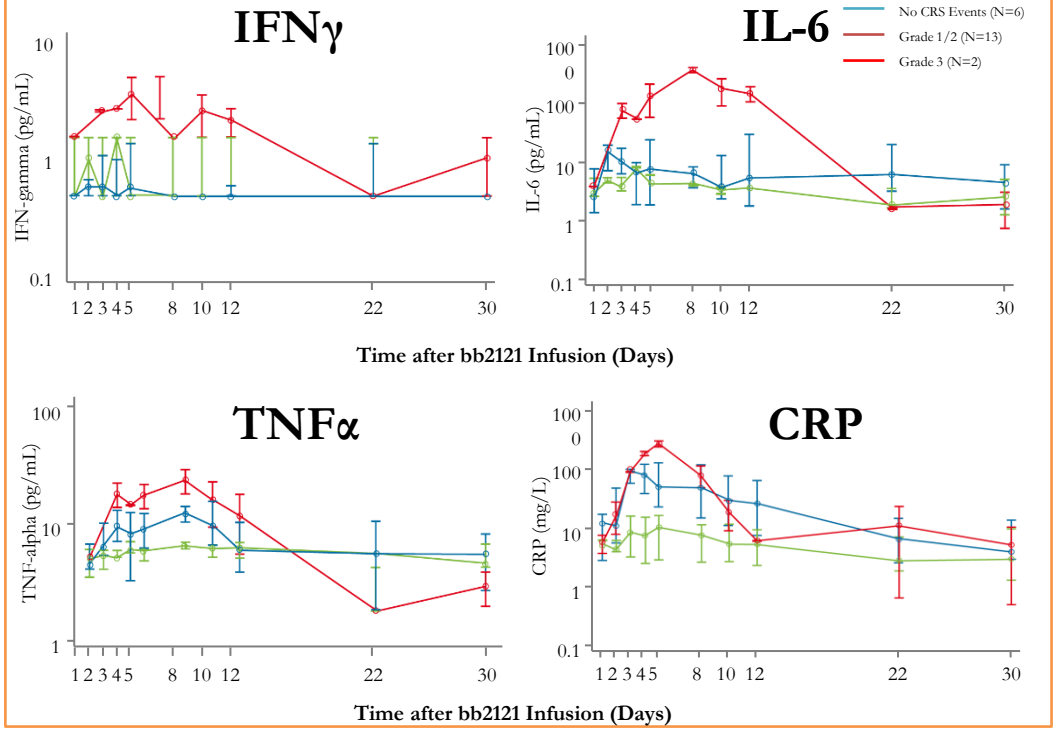
Dose Escalation: Cytokine Release Syndrome

Onset and Duration of CRS

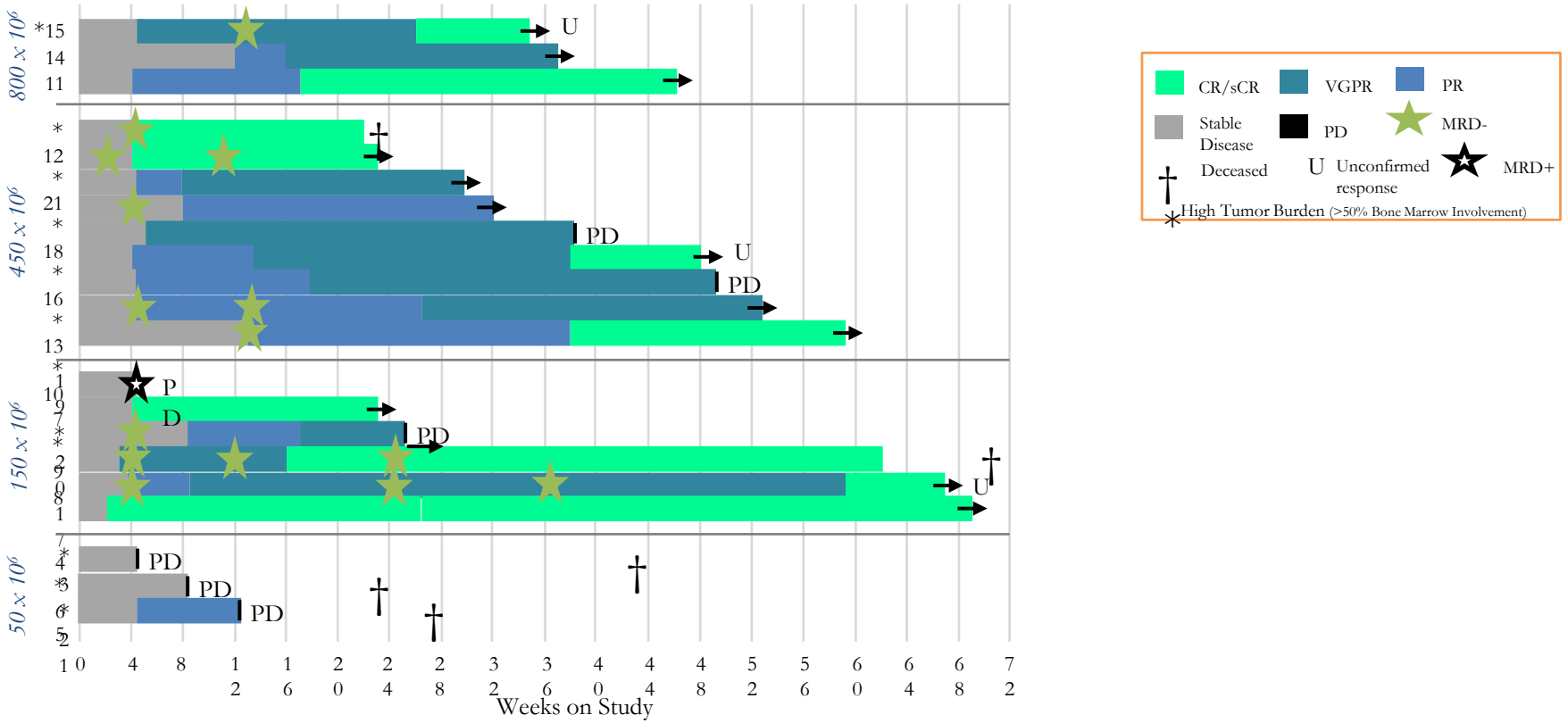
Parameter	Statistic	Dosed Patients (N = 21)
Patients with a CRS event	n (%)	15 (71)
Time (days) to onset of first CRS	Median (min, max)	2 (1,19)
Duration (days) of CRS	Median (min, max)	7 (1, 11)
Time (days) to onset of grade ≥3 CRS	Median (min, max)	5 (4, 6)
Duration (days) of grade ≥3 CRS	Median (min, max)	2 (2, 2)

- CRS generally manageable
  - Mostly Grade 1-2
  - 2 patients with Grade 3 CRS that resolved in 24 hours
  - 4 patients received tocilizumab, 1 with steroids
- Cytokine elevation highest in pts with Grade 3 CRS

Median (Q1, Q3) Over Time by CRS Grade Subjects Treated in Escalation



Reversible Life Threatening Grade 4 Neurotoxicity (PRESS) Associated with Rapid Myeloma Response in One Patient with Low BCMA Expression (Expansion Cohort)



- **17/18 (94%) ORR at active doses**
- **9/10 evaluable patients MRD negative**
- **Durable ongoing responses over 1 year**
- **Median PFS not reached in active dose cohorts**
  - **4 patients progressed**
  - **Median follow up 40 weeks**

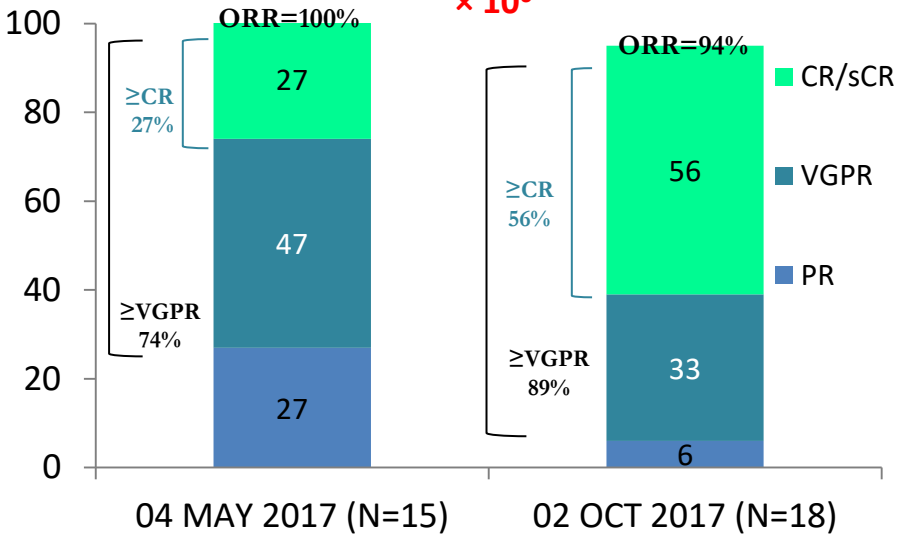
Clinical Response: Deepening of Response over Time (ASH 2017)

Dose Escalation: Cohorts ≥150 × 10^6 CAR T Cells (N=18)

Median duration of follow up 40 weeks (min, max: 6.6, 69.1)

Efficacy Parameter	Statistic	Result
Time (months) to First Response	Median (min, max)	1.02 (0.5, 3.0)
Time (months) to Best Response	Median (min, max)	3.74 (0.5, 13.7)
Time (months) to Complete Response	Median (min, max)	3.84 (0.5, 13.7)
Duration of Response	Median (min, max)	NR
Progression free survival	Median (min, max)	NR
Progression free survival rate @ 6 mos	%	81%
Progression free survival rate @ 9 mos	%	71%

Objective Response Rate
Subjects Treated in Escalation – Cohorts ≥150 × 10^6



Note: Objective Response defined as attaining Stringent Complete Response, Complete Response, Very Good Partial Response, or Partial Response. Including unconfirmed responses.

NR, not reached

Preliminary Characteristics of Patients Who Progressed

Subject	Tumor Burden*	Dose (10^6 CAR T cells)	Best Response	Time to progression (mos)	% CD138+ cells expressing BCMA by IHC (Prescreen / PD)	CRS (Max Grade)	Detectable Vector at Last Evaluation
7	Low	450	VGPR	11	80% / 60%	2	No
17	Low	150	VGPR	6	80% / 10%	No events	No
13	High	450	VGPR	9	80% / NE	2	Yes
19	Low	150	SD	1	50% / 40%	No events	Yes

- No evidence of BCMA expression loss at disease progression (N = 3 evaluable)
- Progression to date is independent of:
  - Tumor burden
  - bb2121 dose
  - CRS
  - bb2121 persistence

MM 2017: Integration and Impact of Novel Agents

- Innovations (PIs, IMiDs) to date have produced significant improvements in PFS, OS: recent approvals (e.g. Carfilzomib, Ixazomib, HDACi, MoAbs) will augment this, with the next wave of therapies agnostic to mutational thrust
- Baseline immune function appears a key barrier to success and is targetable (e.g. use of PD1/PDL1 blockade)
- MoAbs (Elo, DARA, ISA, MOR 202) active in high risk disease, represent true new novel mechanisms, as well as other immuno-therapeutics (e.g. checkpoint inhibitors, vaccines)
- New insights to mechanisms of drug action (e.g. IMiDs, Ixazomib, Marizomib, Panobinostat, AC 241) will further expand therapeutic opportunities
- Numerous other small molecule inhibitors, targeted chemotherapeutics show promise (e.g. HDACi's, CXCR4, BCL, AKT, CDK, HSP 90, Nuclear Transport, KSP, BET bromodomain proteins/Myc, DUBs, MEK, melflufen) – with nelfinavir, venetoclax, melflufen and selexinor showing promise moving forward into advanced phase studies
- Further refinement of prognostics and MRD will guide therapy

The Impact Of Novel Therapies in MM ~ Case Report

2009 –
Patient DG, age 62 years
High Risk IgG kappa MM
DSS 3, ISS 2,
Elevated LDH
17 del positive ,
13 del positive (by FISH) **PMH – HTN, nil else.**

RD + Zometa => RVD (VGPR) **Well tolerated, minimal PN (G1)**

2010 ASCT (CY – HDM) (CR)
R/Z maintenance

2011 PD – RVD (PR)

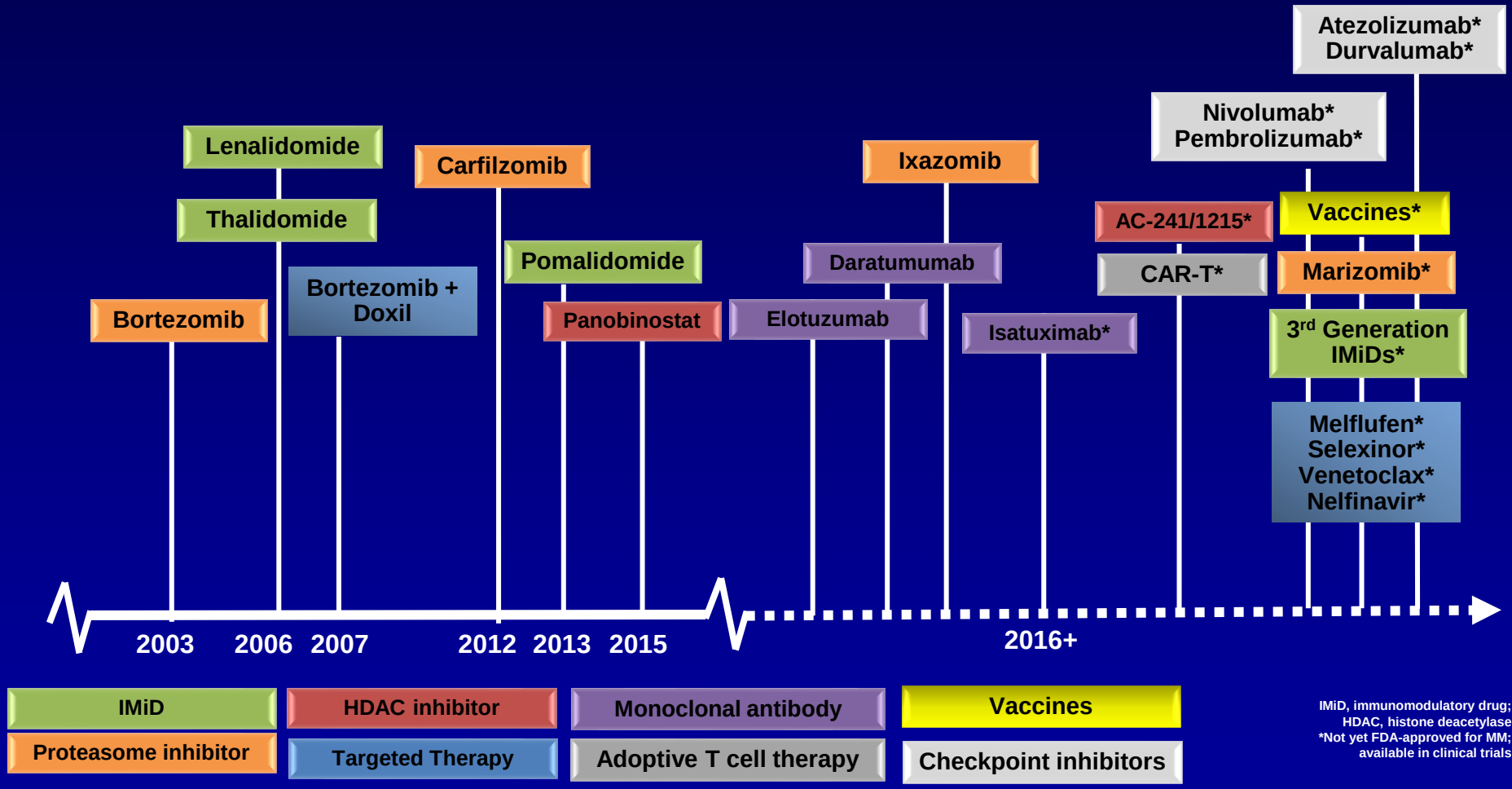
2012 PD – PomVD (VGPR)

2013 PD (aggressive relapse with extra-medullary disease) DARA [501] 16 mg/kg (CR) to present (> 4 years) "Best I have ever felt since prior to diagnosis"

Continuing Evolution of Multiple Myeloma Treatment: Selected New Classes and Targets 2016- 2017

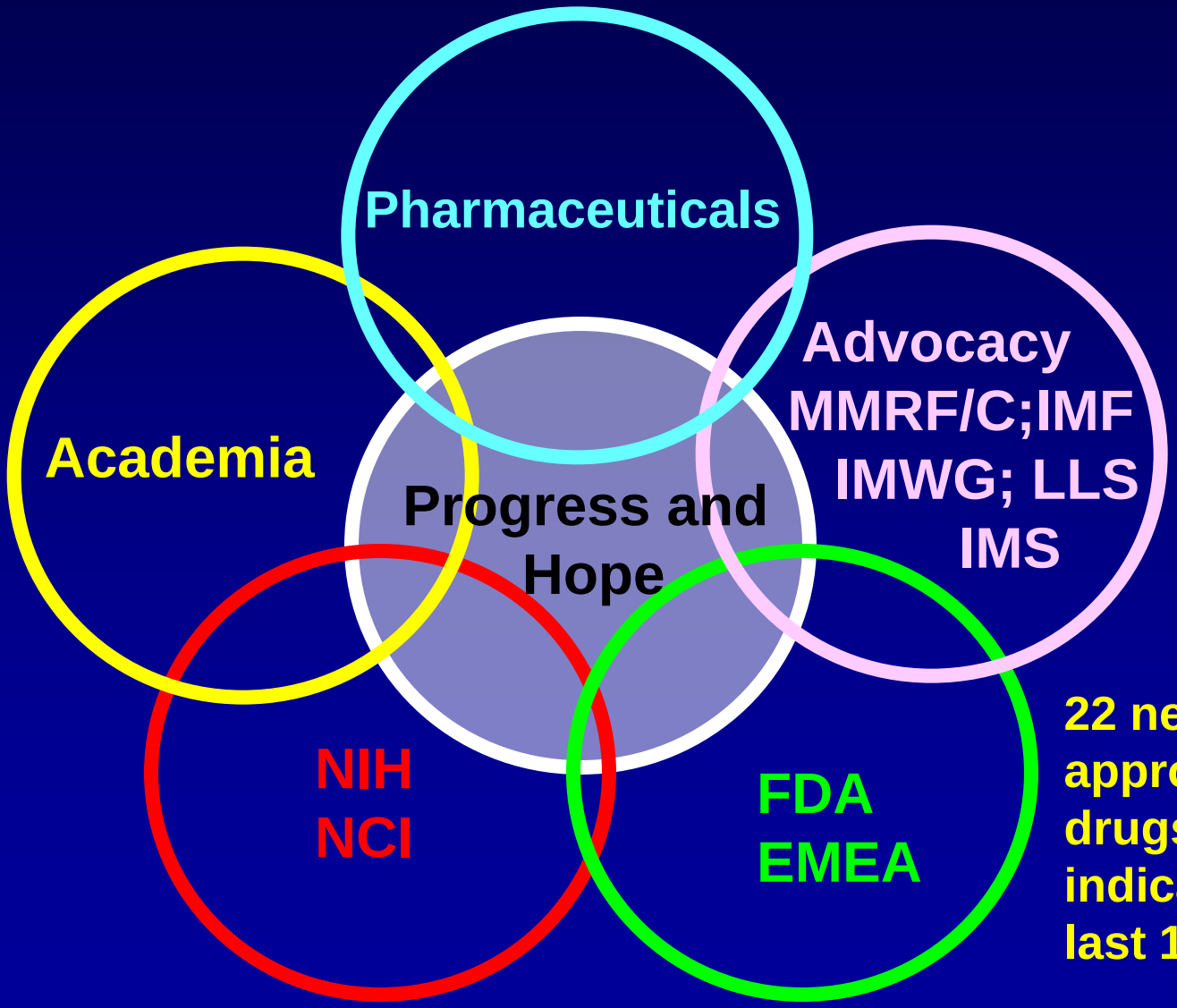
1st Generation Novel Agents

2nd Generation Novel Therapies/ Immunotherapy



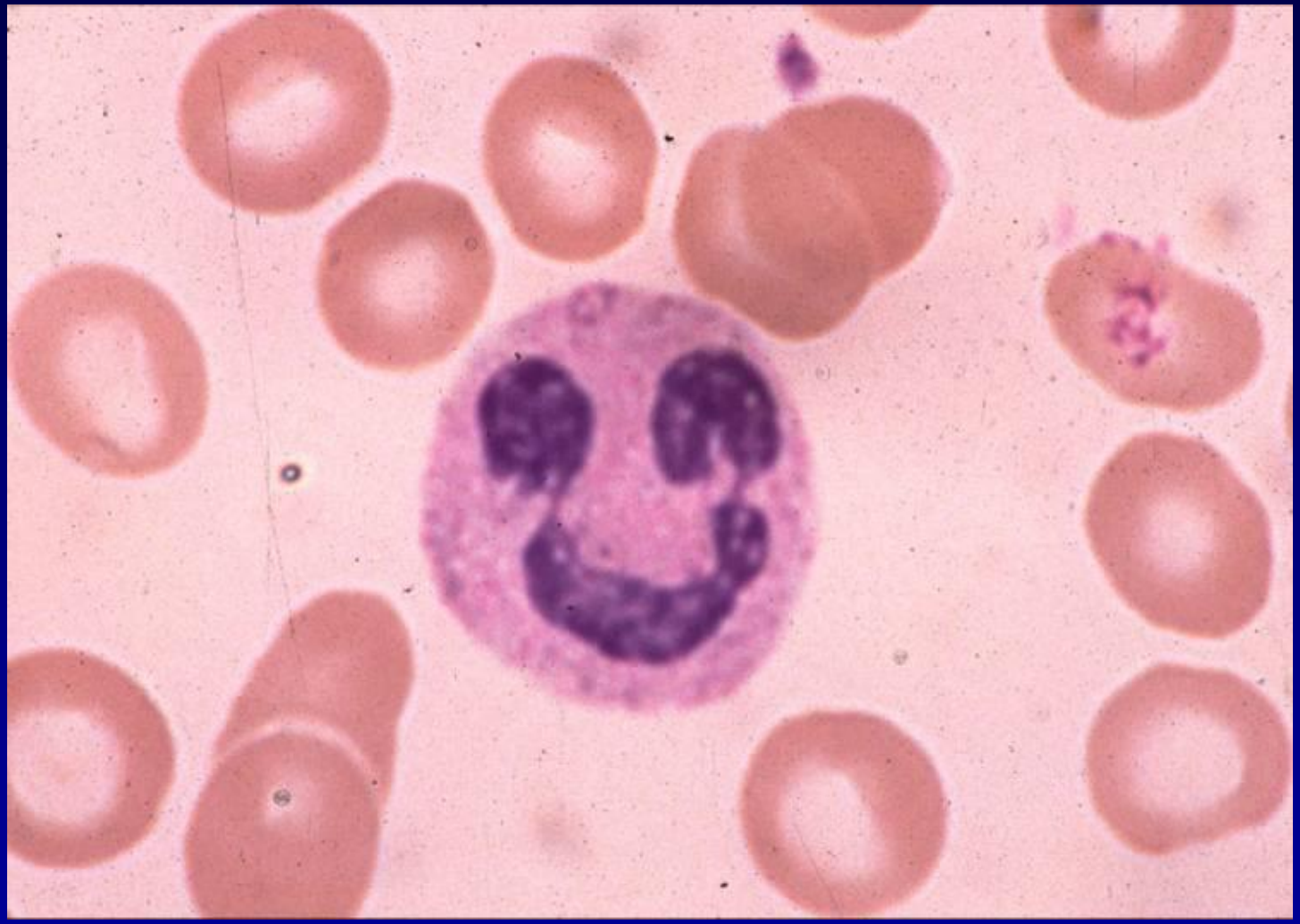
IMiD, immunomodulatory drug; HDAC, histone deacetylase
*Not yet FDA-approved for MM; available in clinical trials

Ongoing MM Collaborative Model for Rapid Translation From Bench to Bedside



22 new FDA-approved drugs/combos/ indications in last 14 yrs

Thank YOU



Slide Courtesy of Phil McCarthy MD

DANA-FARBER CANCER INSTITUTE

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Alliance for Clinical Trials in Oncology

VE RI TAS