Θεραπευτικές Εξελίξεις 2018

Σάββατο 31/3/2018
Αίθουσα «ΑΛΚΗΣ ΑΡΓΥΡΙΑΔΗΣ»
Κεντρικό Κτίριο Πανεπιστημίου Αθηνών

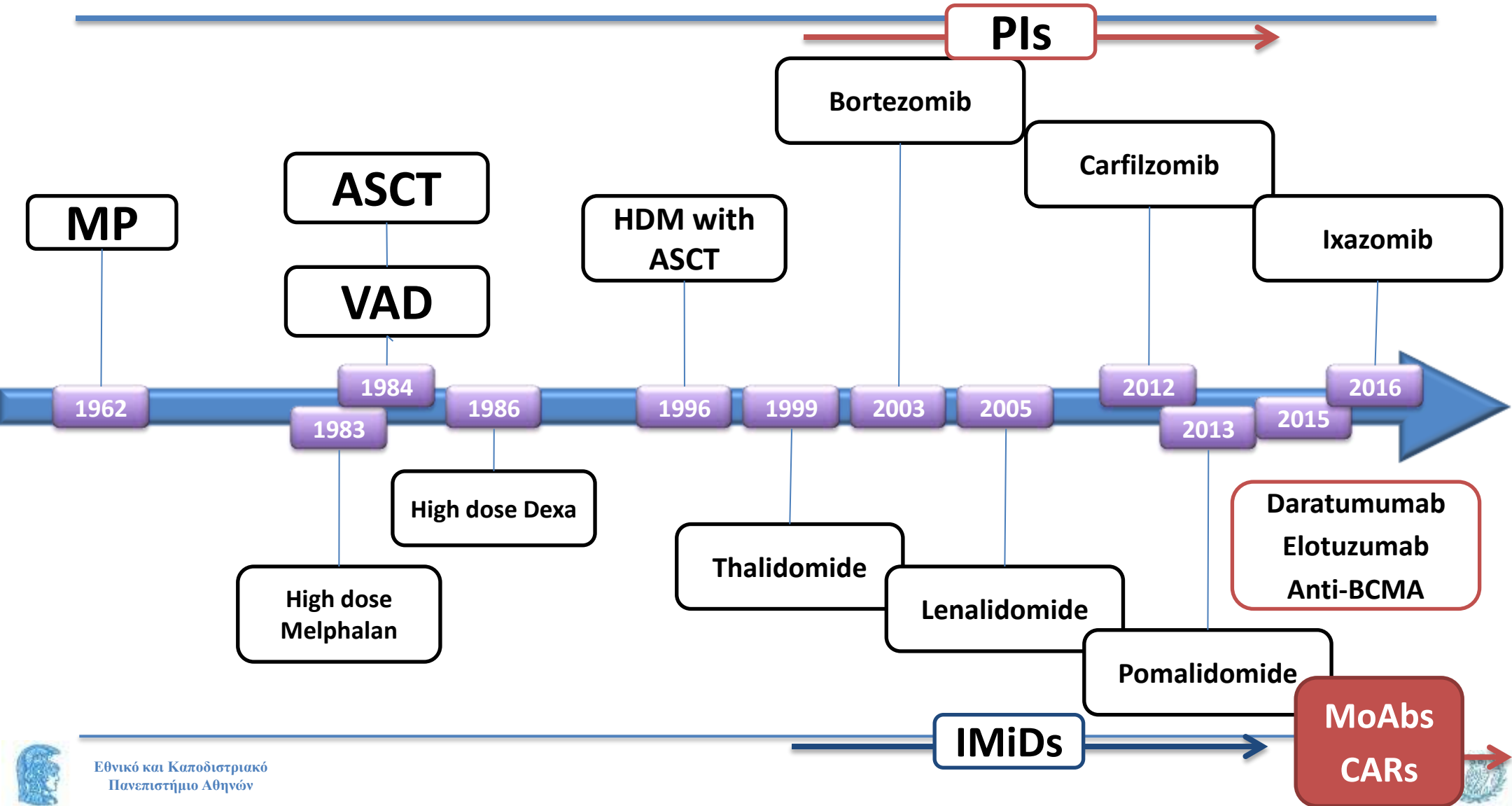
Νεότερα δεδομένα στα πλασματοκυτταρικά νεοπλάσματα

Ε. Καστρίτης

Θεραπευτική Κλινική ΕΚΠΑ

ekastritis@gmail.com

Εξέλιξη των θεραπευτικών επιλογών στο ΠΜ ;

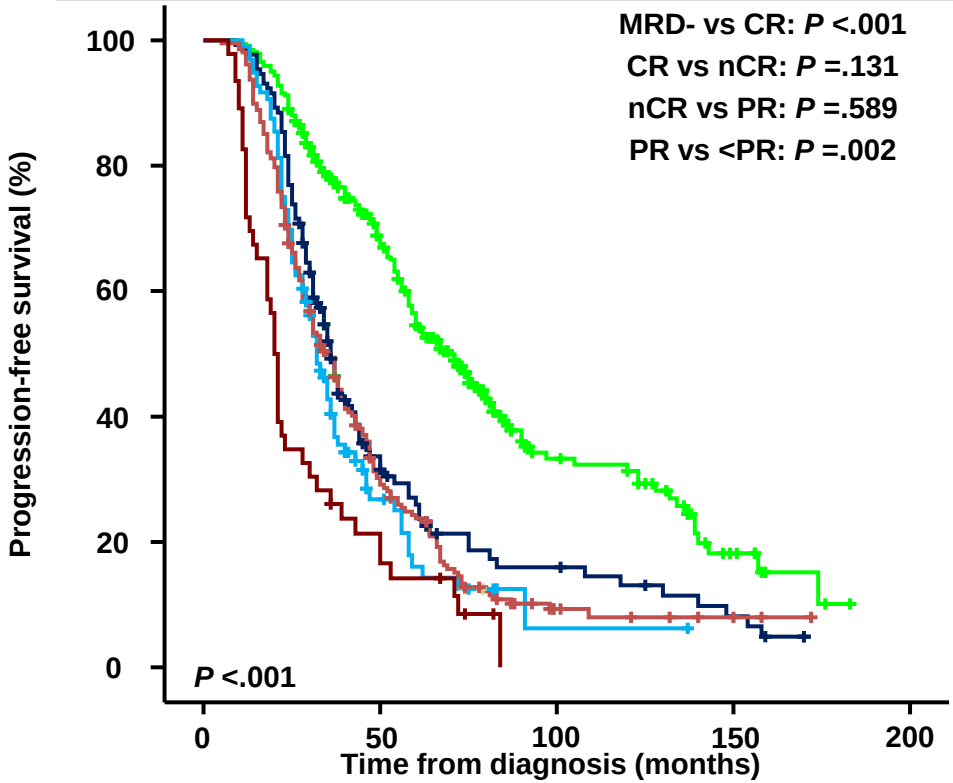


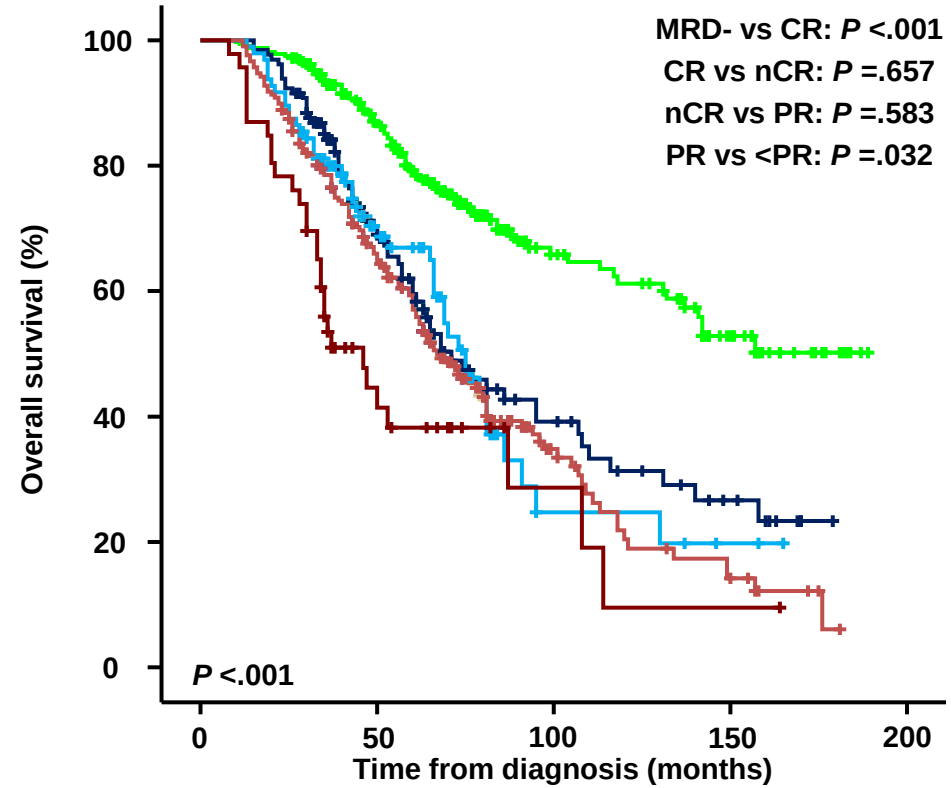
Νέα ερωτήματα στην στρατηγική της θεραπείας

- Ποιος είναι ο στόχος της θεραπείας ;
- Πότε πρέπει να ξεκινάει η θεραπεία ;

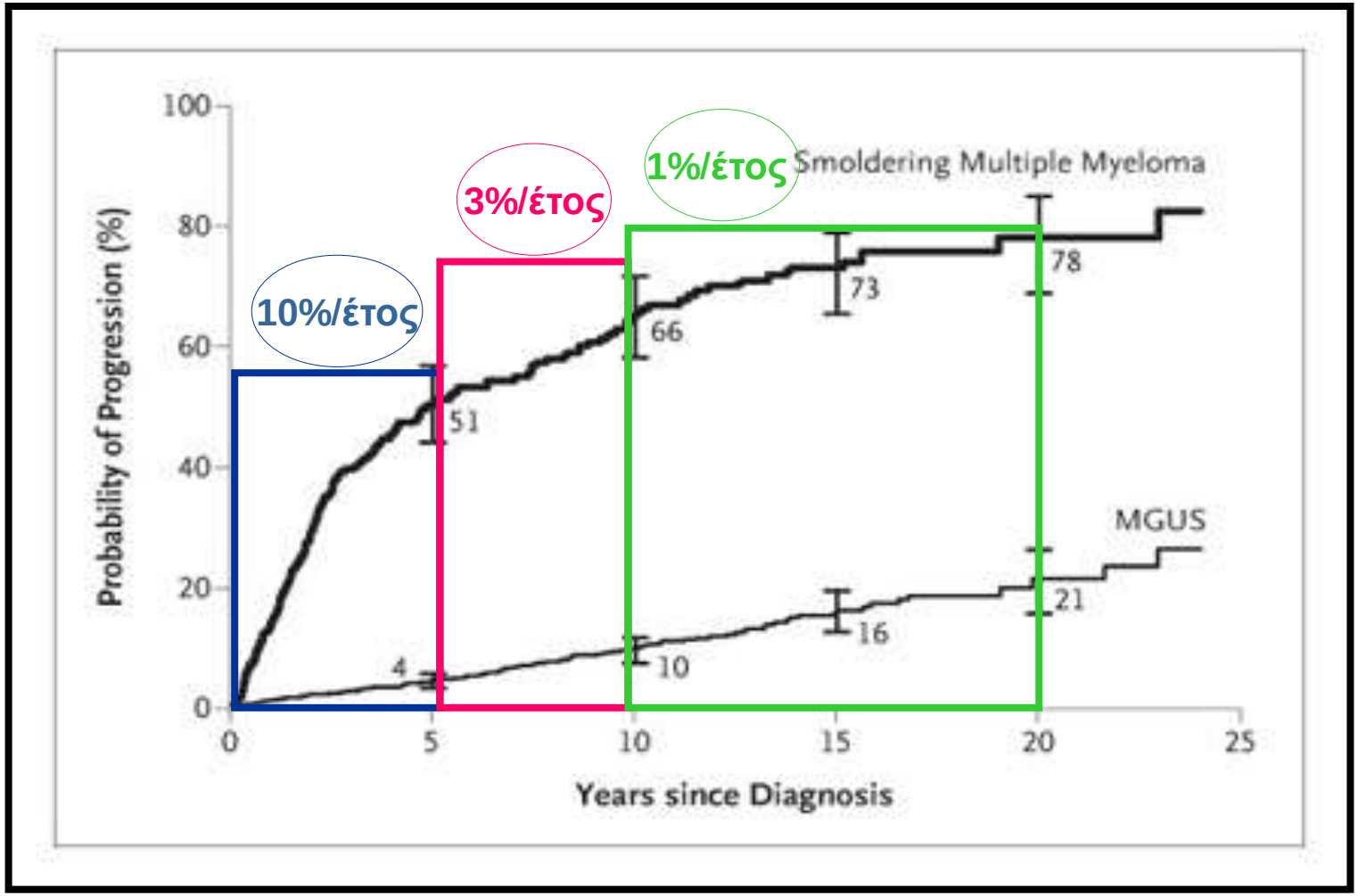
Δεν είναι όλες οι «πλήρεις υφέσεις» ίδιες: CR με MRD- έναντι CR με MRD+

GEM2000, GEM2005MENOS65, GEM2005MAS65, GEM2010MAS65





MGUS & Ασυμπτωματικό Μυέλωμα



Kyle R. N Engl J Med 2007

Kyle R. N Engl J Med 2018

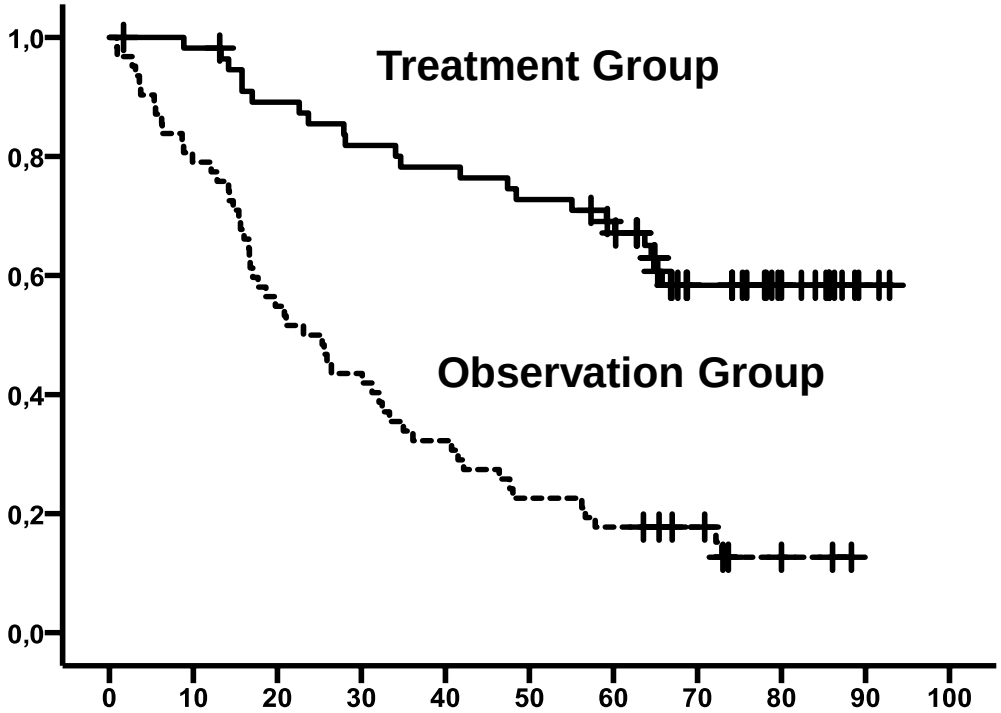
Πότε πρέπει να ξεκινάει η θεραπεία ;

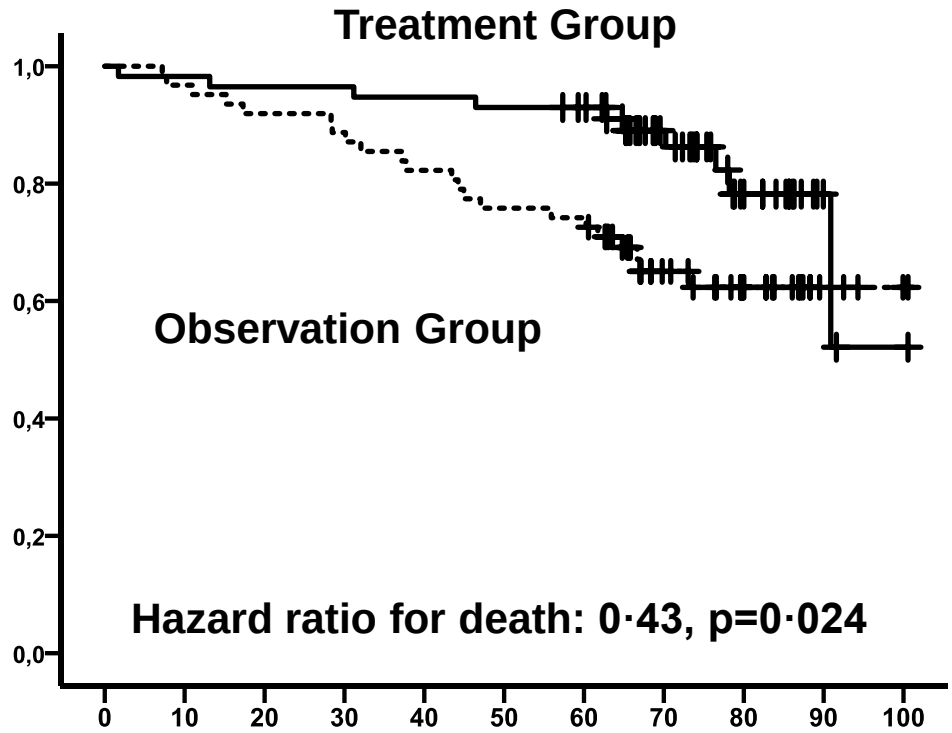
Ασυμπτωματικό ΠΜ

Συμπτωματική νόσος (ΠΜ)

Ασυμπτωματικό ΠΜ <u>υψηλού κινδύνου:</u> Len-dex vs παρακολούθησης : : χρόνος μέχρι την συμπτωματική νόσο & ολική επιβίωση

(Per-protocol Patient population) (n = 119)





Median follow-up: 75 μήνες

Mateos MV, et al. NEJM 2013
Mateos MV, et al. Lancet Oncology 2016

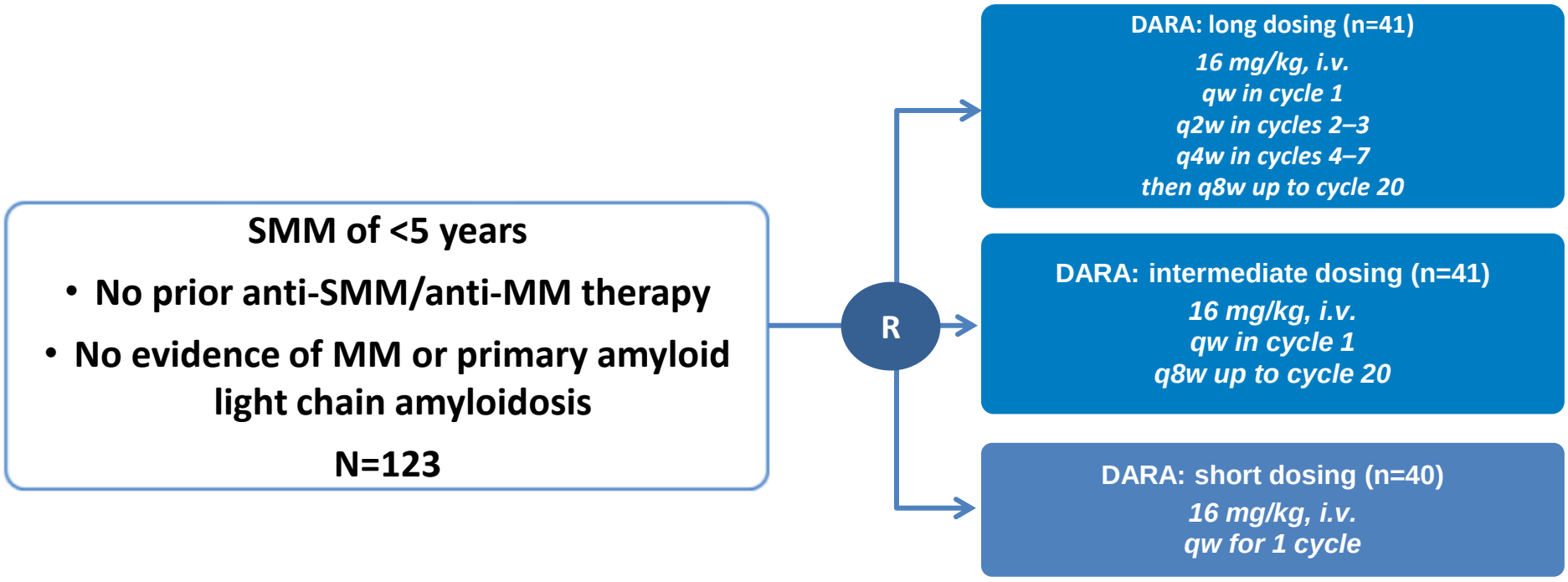
Έναρξη θεραπείας σε «πρώιμο» ΠΜ ;

- μελέτη QuiRedex: η έναρξη θεραπείας σε αρρώστους με υψηλού κινδύνου ασυμπτωματικό ΠΜ πιθανόν βελτιώνει την επιβίωση

Αλλά …

- Χρειάζονται επιπλέον μελέτες με νεώτερα φάρμακα
- Ποιοι είναι πραγματικά οι άρρωστοι με υψηλού κινδύνου ασυμπτωματικό ΠΜ ;
- Ποιοι θα πρέπει να είναι οι στόχοι της θεραπείας σε αρρώστους με ασυμπτωματικό ΠΜ;

CENTAURUS: Phase 2 study of DARA monotherapy in smouldering MM



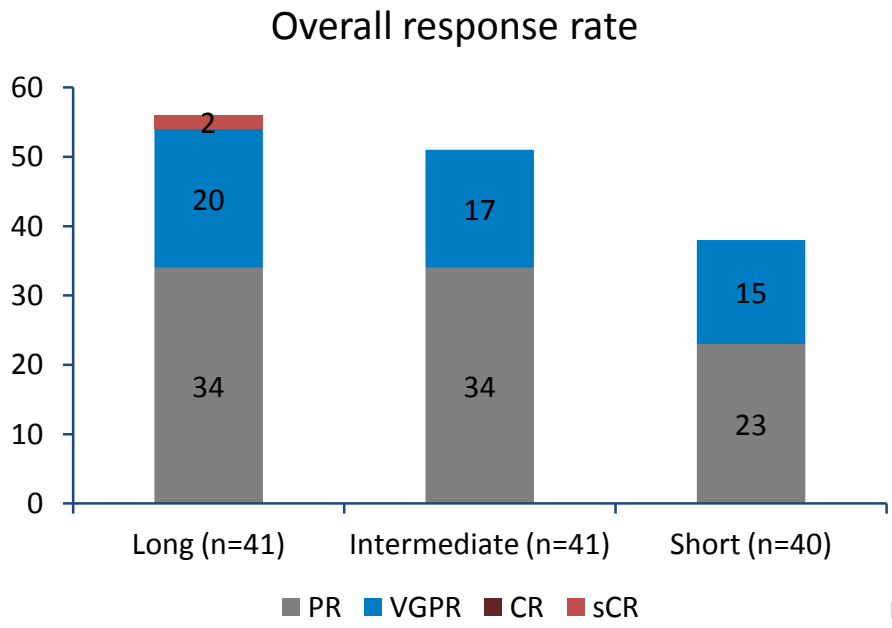
- Co-primary **endpoints**: **CR** rate and **PD/death** rate*
- Other efficacy endpoints: ORR, PFS, time to next treatment, and OS at 4 years

*Proportion of patients who progressed to MM or died per patient-year.
CR, complete response; DARA, daratumumab; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; qw, once every week; q2w, once every 2 weeks; q4w, once every 4 weeks; q8w, once every 8 weeks; SMM, smouldering multiple myeloma.

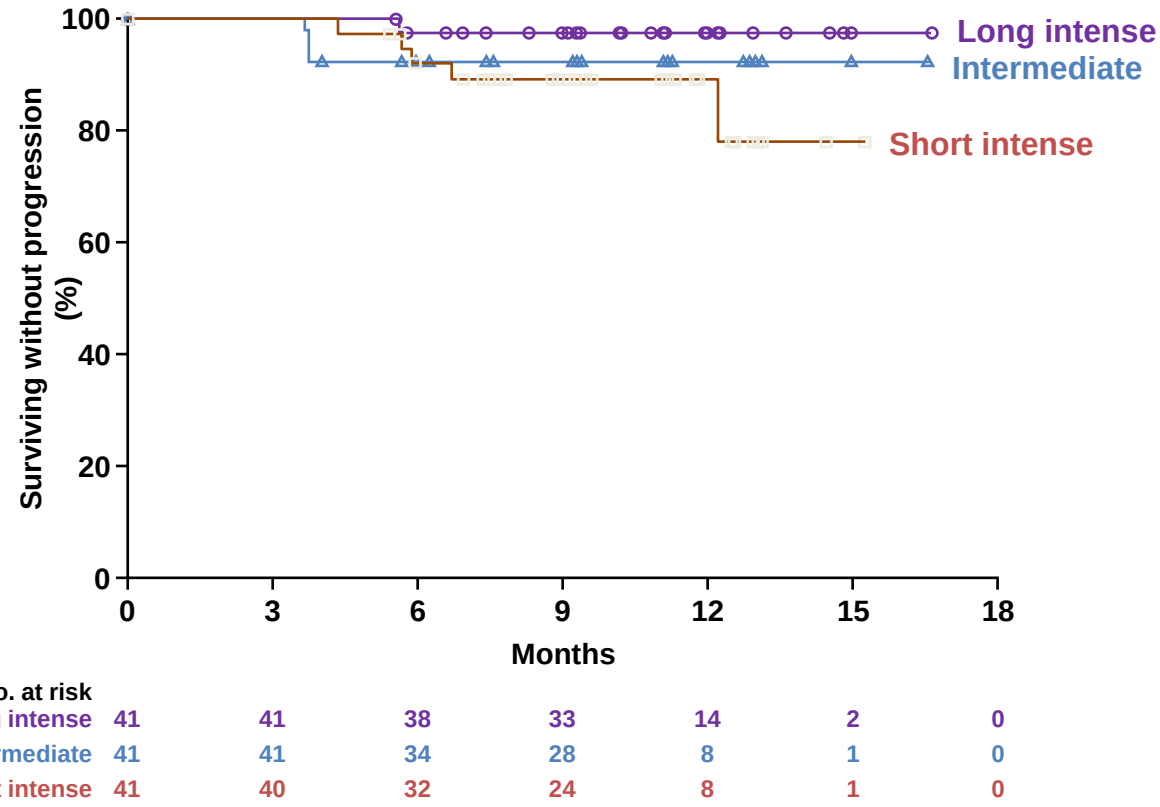
Hofmeister CC et al ASH 2017

CENTAURUS: PFS by length of DARA dosing

Response rates by length of DARA dosing



Progression-free survival



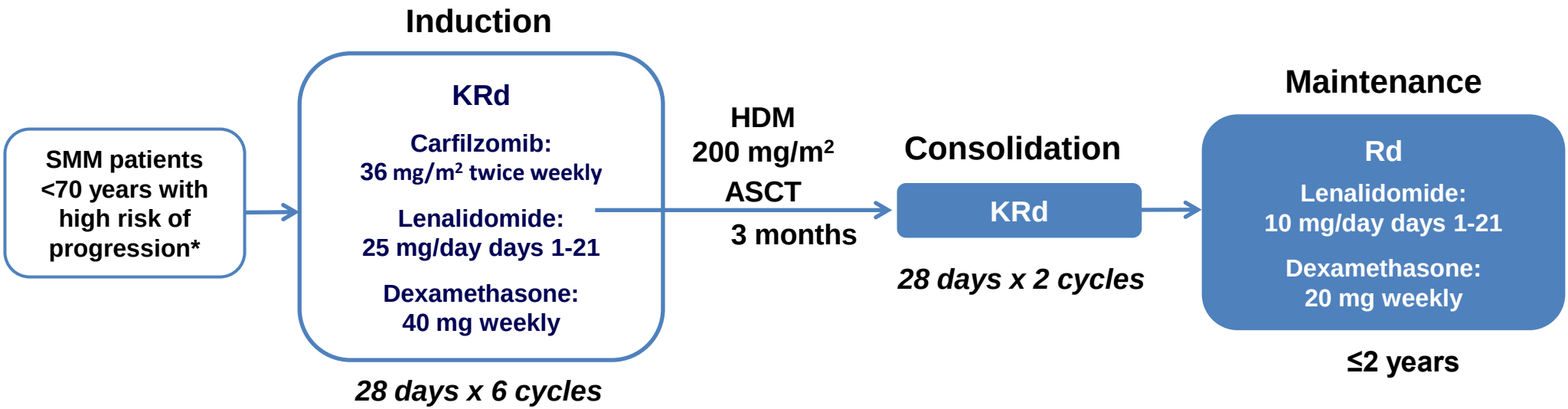
No. at risk							
Long intense	41	41	38	33	14	2	0
Intermediate	41	41	34	28	8	1	0
Short intense	41	40	32	24	8	1	0

- **Estimated 12-month PFS rates were 98%, 93%, and 89% for the long, intermediate, and short dosing groups**

PFS, progression-free survival.

Hofmeister CC et al ASH 2017

KRd induction therapy in patients with smouldering multiple myeloma (SMM) (GEM-CESAR)

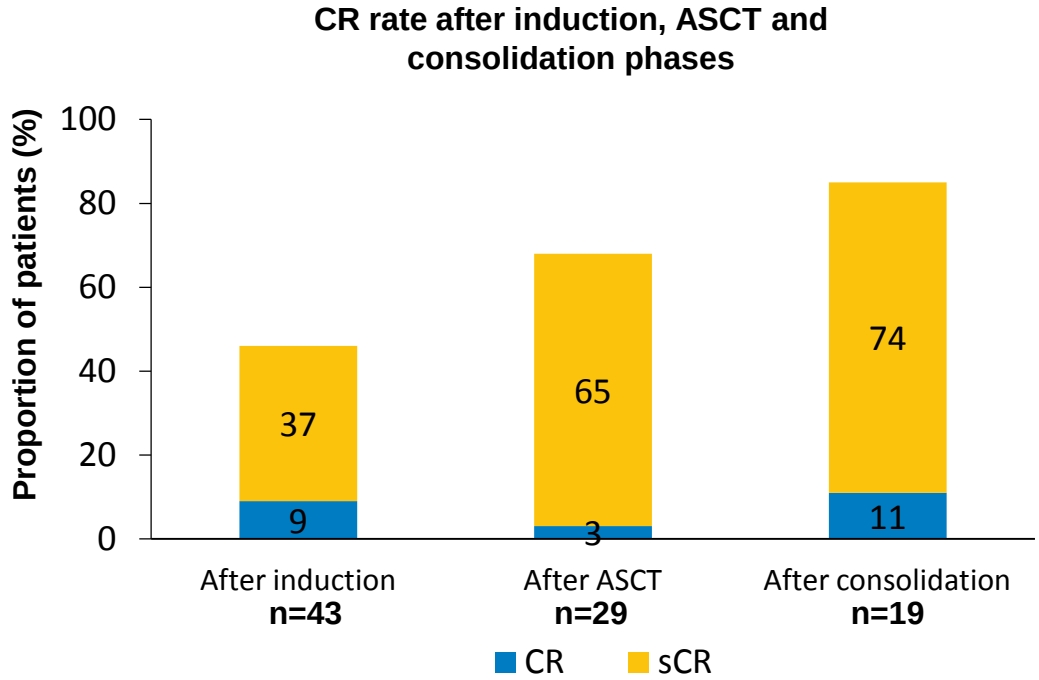


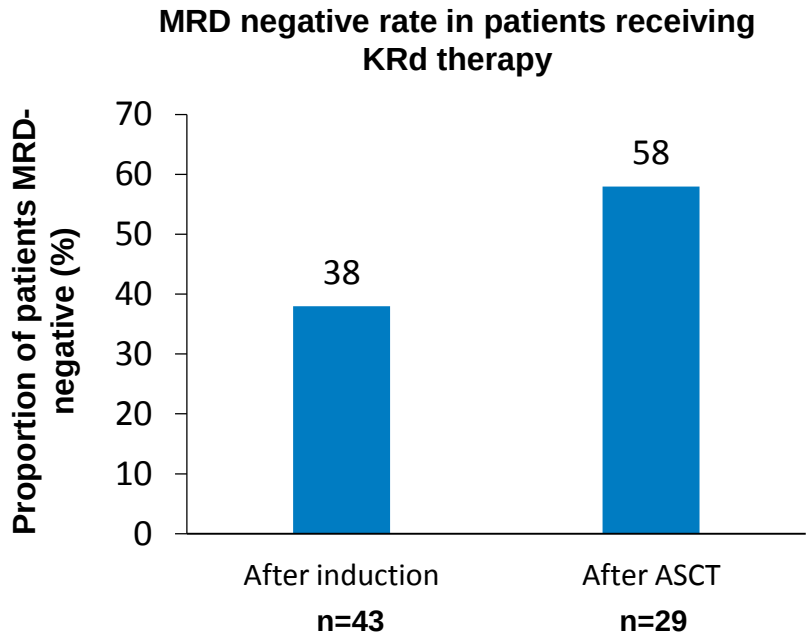
- **MRD** was evaluated by next-generation flow cytometry **after induction**, **ASCT**, **consolidation**, and **annually thereafter**

***High risk defined as having both bone marrow plasma cells ≥10% and serum M-protein ≥3g/dL (Mayo clinic model), or meeting one criterion plus ≥95% aberrant plasma cells within the total plasma cells bone marrow compartment by immunophenotyping of 95% plus immunoparesis (Spanish model).**
ASCT, autologous stem cell transplantation; HDM, high dose melphalan; KRd, carfilzomib, lenalidomide and dexamethasone; MRD, minimal residual disease; Rd, lendalidomide and dexamethasone; SMM, smouldering multiple myeloma.

Mateos et al ASH 2018

KRd induction therapy in patients with smouldering multiple myeloma (SMM) (GEM-CESAR)





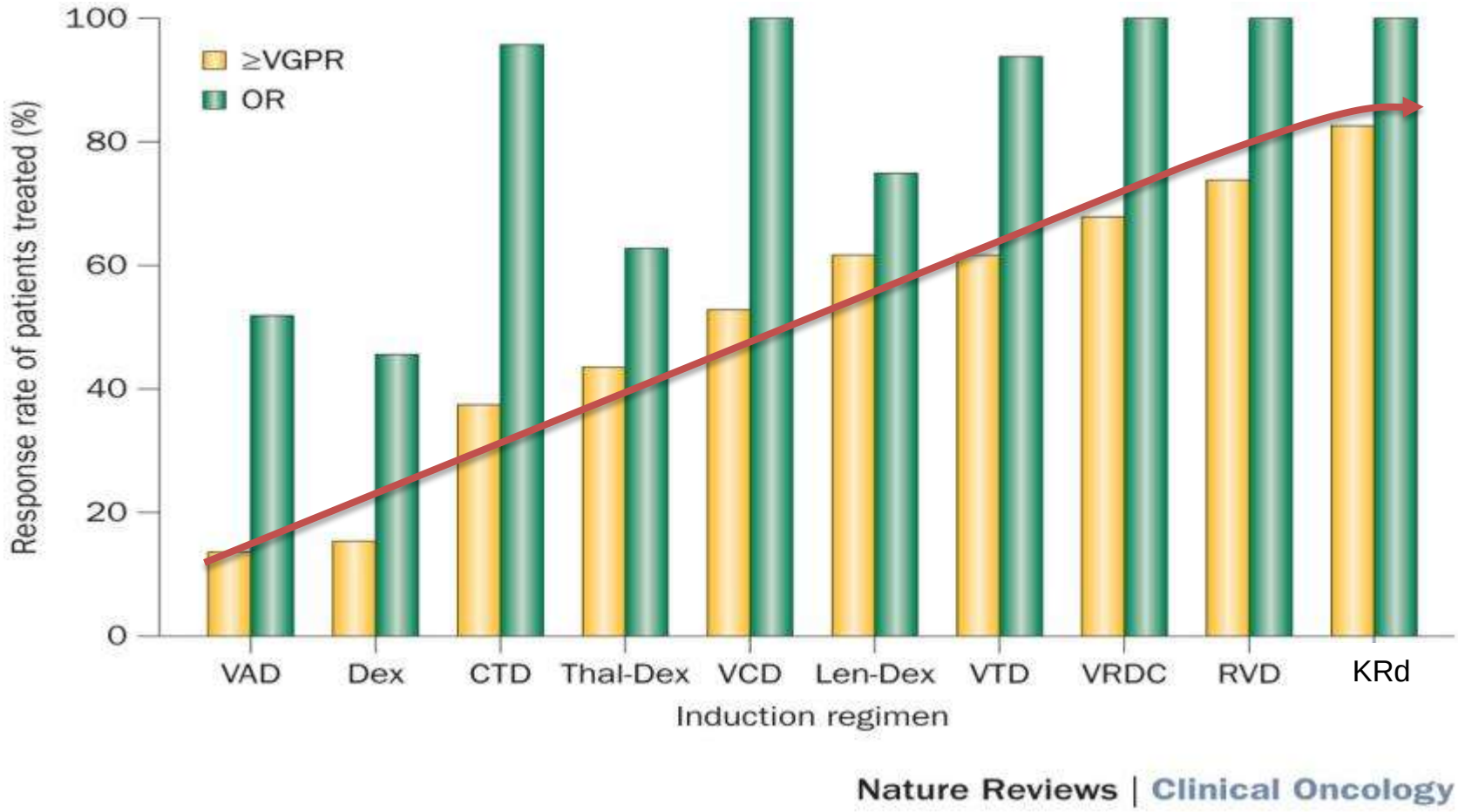
- Depth of response improved at each stage in the treatment schedule
- MRD-negative rate increased after ASCT compared to after the induction phase
- **After a median follow-up of 13 months, PFS rate was 98% and 99% of patients alive**

ASCT, autologous stem cell transplantation; CR, complete response; KRd, carfilzomib, lenalidomide and dexamethasone; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival; sCR, stringent complete response; VGPR, very good partial response.

Mateos et al ASH 2018

Νέα φάρμακα , νέες στρατηγικές ?

Εισαγωγική θεραπεία:
2 έναντι 3 φαρμάκων (ή 4 ή 5;)



Mailankody, S. et al., *National Review of Clinical Oncology*, 2015; doi:10.1038/nrclinonc.2014.239.

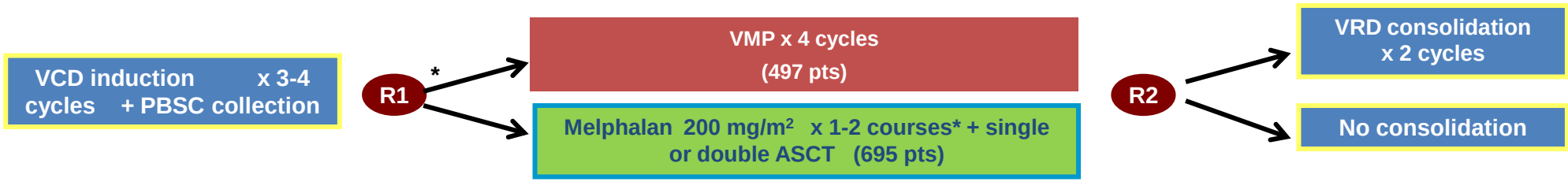
Ο ρόλος της αυτόλογης μεταμόσχευσης

- Στόχος της ΑΜΑΑΚ είναι η εδραίωση του θεραπευτικού αποτελέσματος και η βελτίωση της ποιότητας ανταπόκρισης

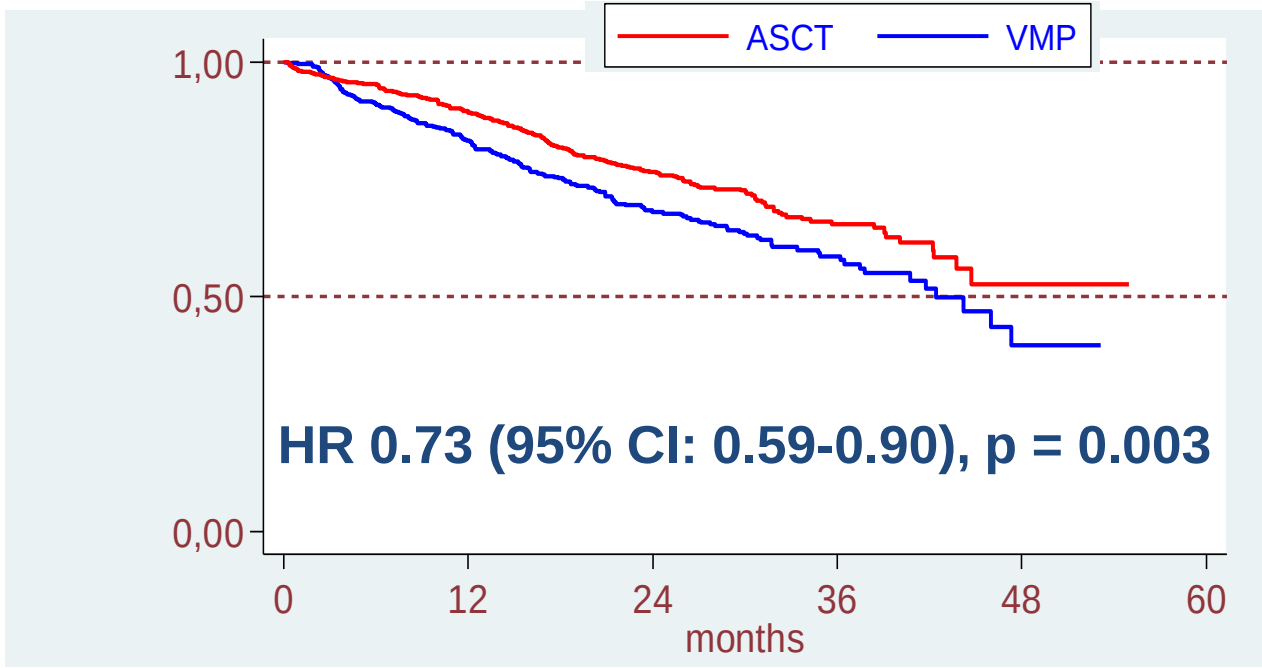
1. Πότε γίνεται η αυτόλογη μεταμόσχευση;

2. Μπορεί να αναβληθεί σε αρρώστους που πετυχαίνουν ύφεση με την εισαγωγική θεραπεία;

EMN02/HO95 MM trial: VMP vs MEL200 ± VRD Consolidation + Len maintenance in NDMM



All patients received lenalidomide maintenance until relapse/progression



Cavo M, et al. ASCO 2016
Cavo M, et al. ASH 2017

Phase III IFM 2009: RVD ± AMAAK

Stratified by ISS stage and cytogenetics

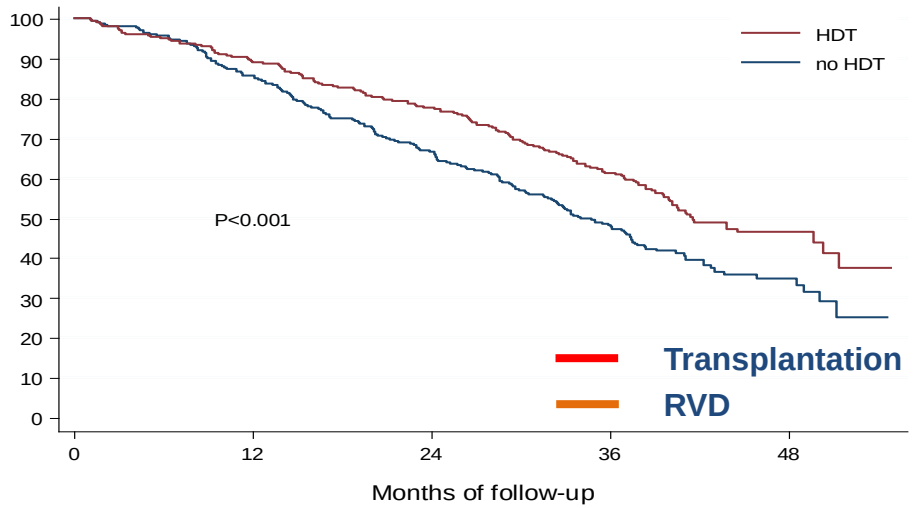
Pts 65 yrs old of age or younger with symptomatic NDMM; ECOG PS < 2 with organ damage and measurable disease*; treated with 1 cycle RVD† (N = 700)

RVD† Cycles 2, 3
PBSC collection → RVD† Cycles 4-8
(n = 350)

RVD† Cycles 2, 3
PBSC collection, ASCT (MEL200) → RVD† Cycles 4, 5
(n = 350)

Lenalidomide Maintenance 10-15 mg/day for 12 mos

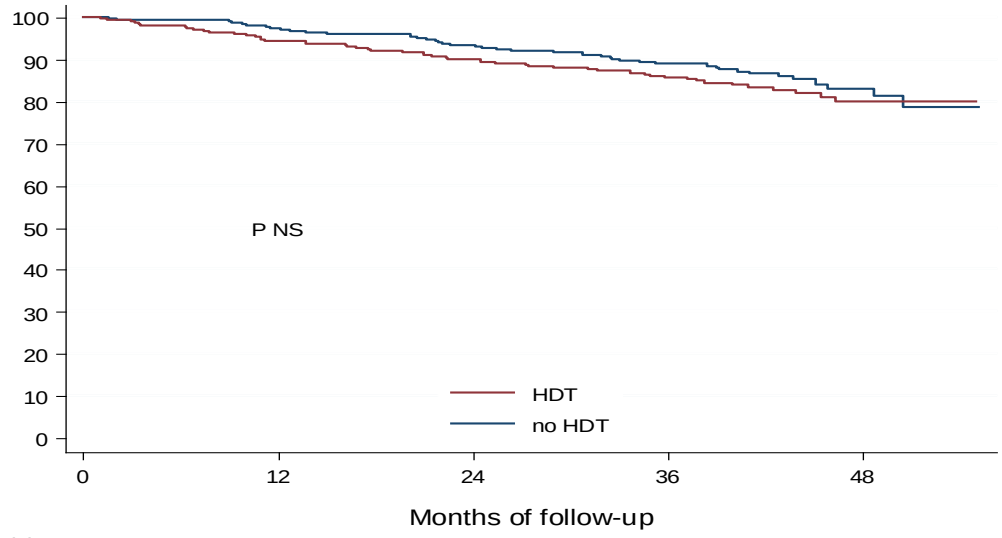
Progression-Free Survival



N at risk

HDT	350	309	261	153	27
no HDT	350	296	228	128	24

Overall Survival



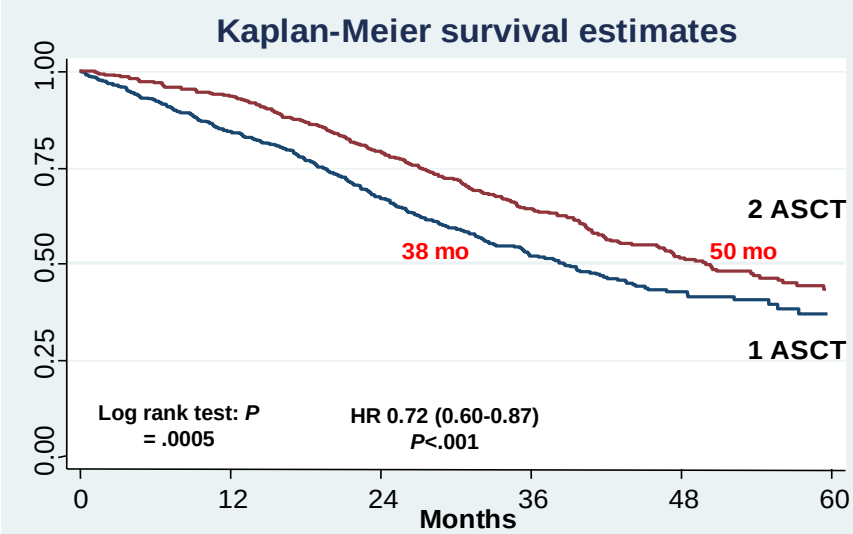
N at risk

HDT	350	328	309	226	55
no HDT	350	338	320	244	56

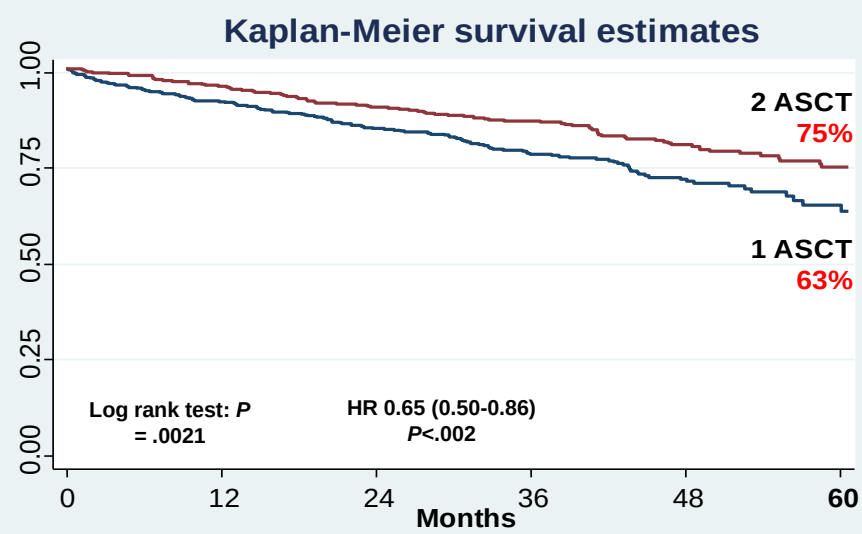
Attal M, et al. *Blood.* 2015;126(23): Abstract 391.

1 ή 2 AMAAK ?

Progression-Free Survival



Overall Survival



- **Compilation of European phase III studies**
- **Όφελος σε αρρώστους με ΠΜ υψηλού κινδύνου [κυρίως με *del(17p)* και t(4;14)]**

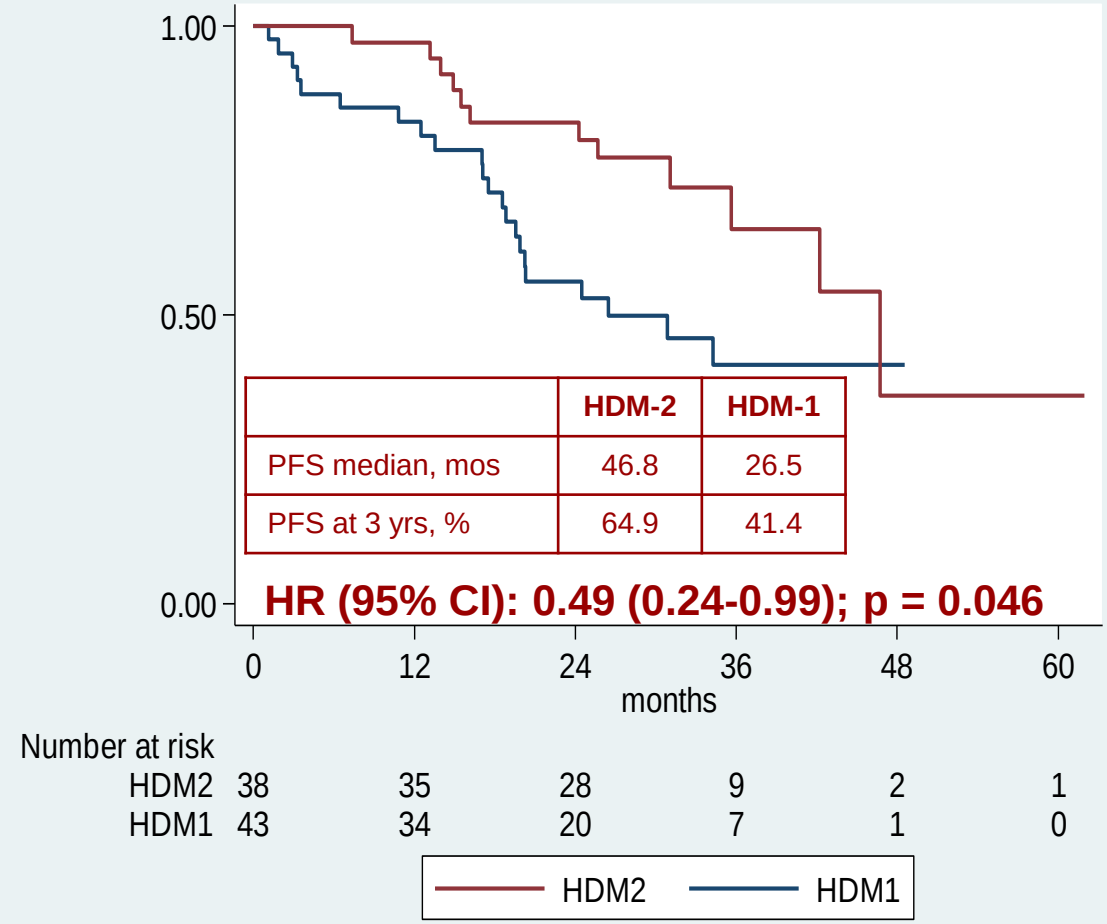
Cavo M, et al. *Blood*. 2013;122(21): Abstract 767.

1 ή 2 AMAAK ?

EMN02 / HO95 MM Study: Single vs double ASCT

PFS by high-risk cytogenetics

- Median PFS for overall population with VMP was 42.5 months
- Similar to median PFS with double ASCT in patients with high-risk cytogenetics

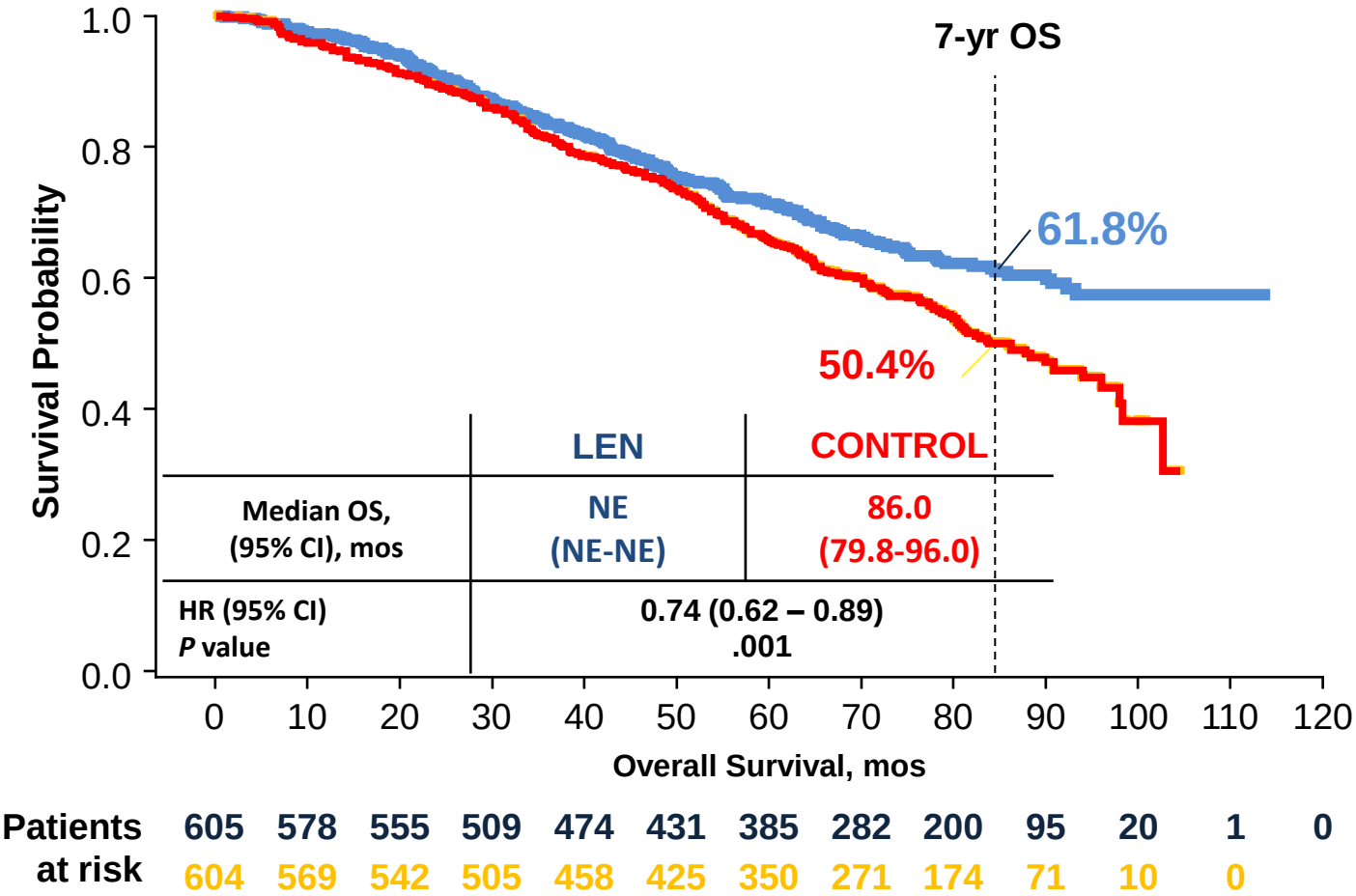


ASCT, autologous stem cell transplant; HDM-1, high-dose melphalan-1 (single transplant); HDM-2, high-dose melphalan-2 (double transplant); HR, hazard ratio; PFS, progression-free survival; VMP, bortezomib, melphalan, prednisone.

Cavo M, et al. Presented at ASH 2016

Cavo M, et al. Presented at ASH 2017

Μέτα-ανάλυση 3 μελετών συντήρησης με lenalidomide μετά AMAAK Ολική επιβίωση : διάμεση παρακολούθηση 80 μήνες



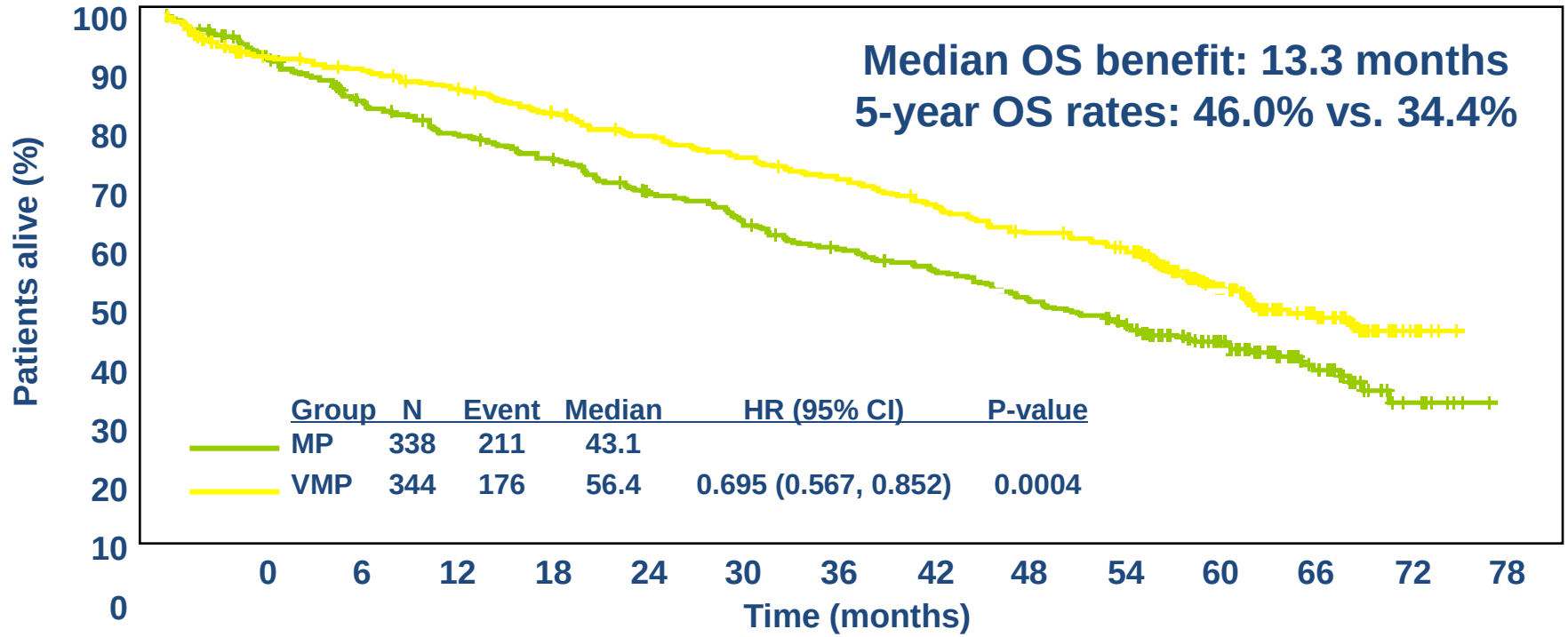
HR, hazard ratio; LEN, lenalidomide; NE, not estimable; OS, overall survival
[a] Median for LEN treatment arm was extrapolated based on median of Control arm and HR.

Attal M et al J Clin Oncol 2017

Θεραπεία ασθενών που δεν είναι υποψήφιοι για αυτόλογη μεταμόσχευση

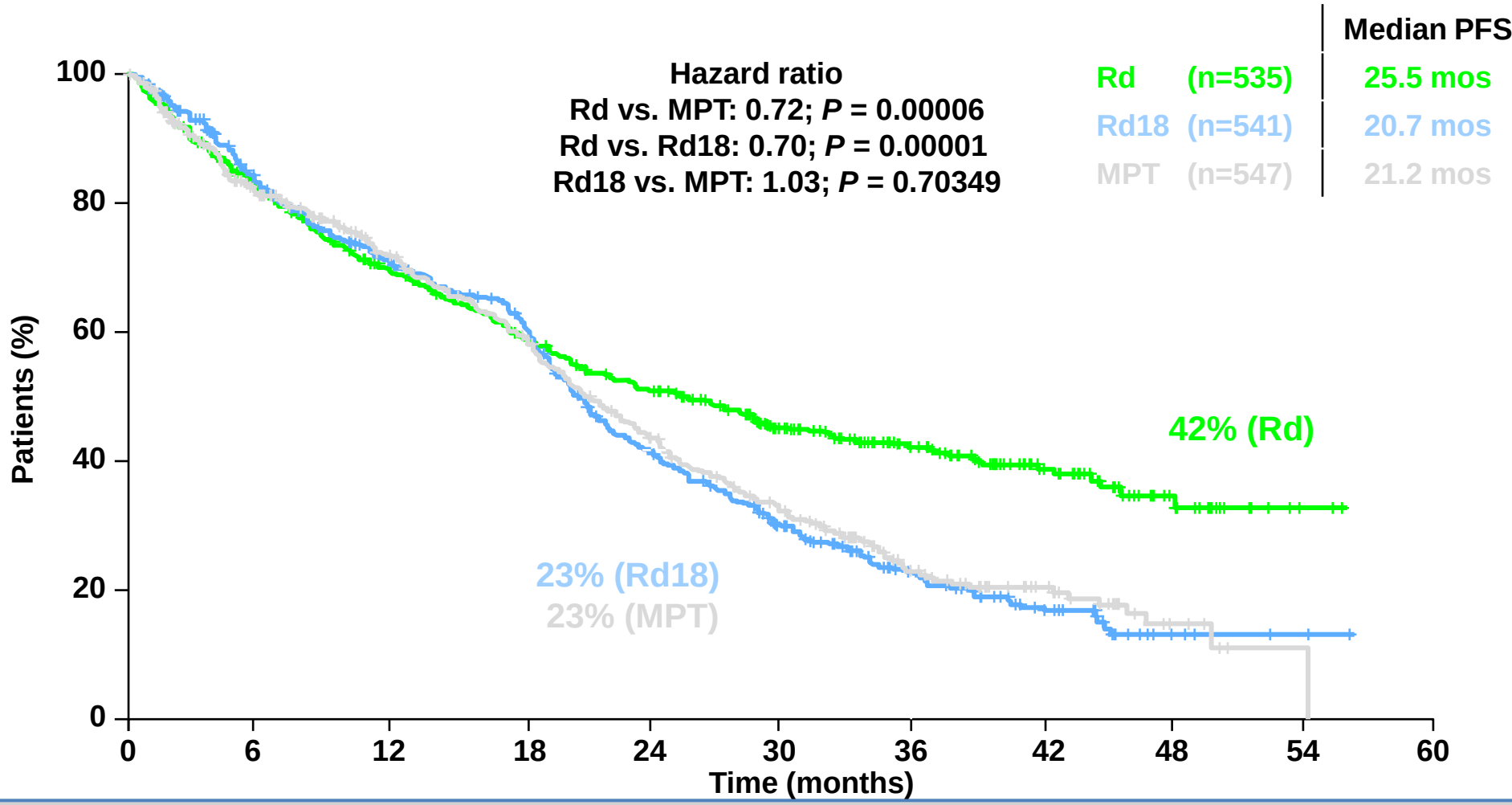
Θεραπεία με VMP έναντι MP σε αρρώστους που δεν είναι υποψήφιοι για αυτόλογη μεταμόσχευση

Median follow-up 60.1 months



San Miguel et al. J Clin Oncol 2013;31:448-55

Θεραπεία με Rd συνεχώς έναντι Rdx18 κύκλους έναντι MPTx18 μήνες σε αρρώστους που δεν είναι υποψήφιοι για AMAAK

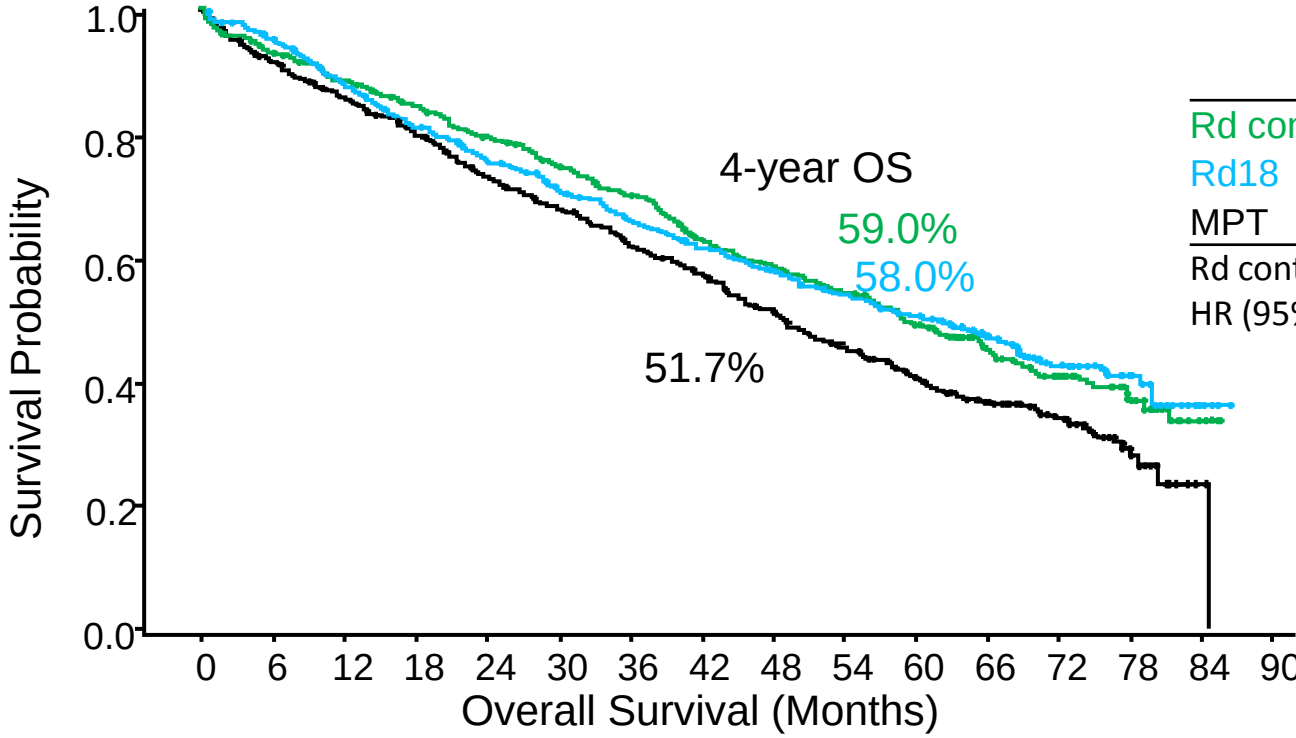


Facon T, et al. Haematologica. 2014;99:abstract S643.

Facon T, et al. Presented at ASH 2016 (Abstract 241), oral presentation.

Θεραπεία με Rd συνεχώς έναντι Rdx18 κύκλους έναντι MPTx18 μήνες σε αρρώστους που δεν είναι υποψήφιοι για AMAAK

FIRST study final results: overall survival

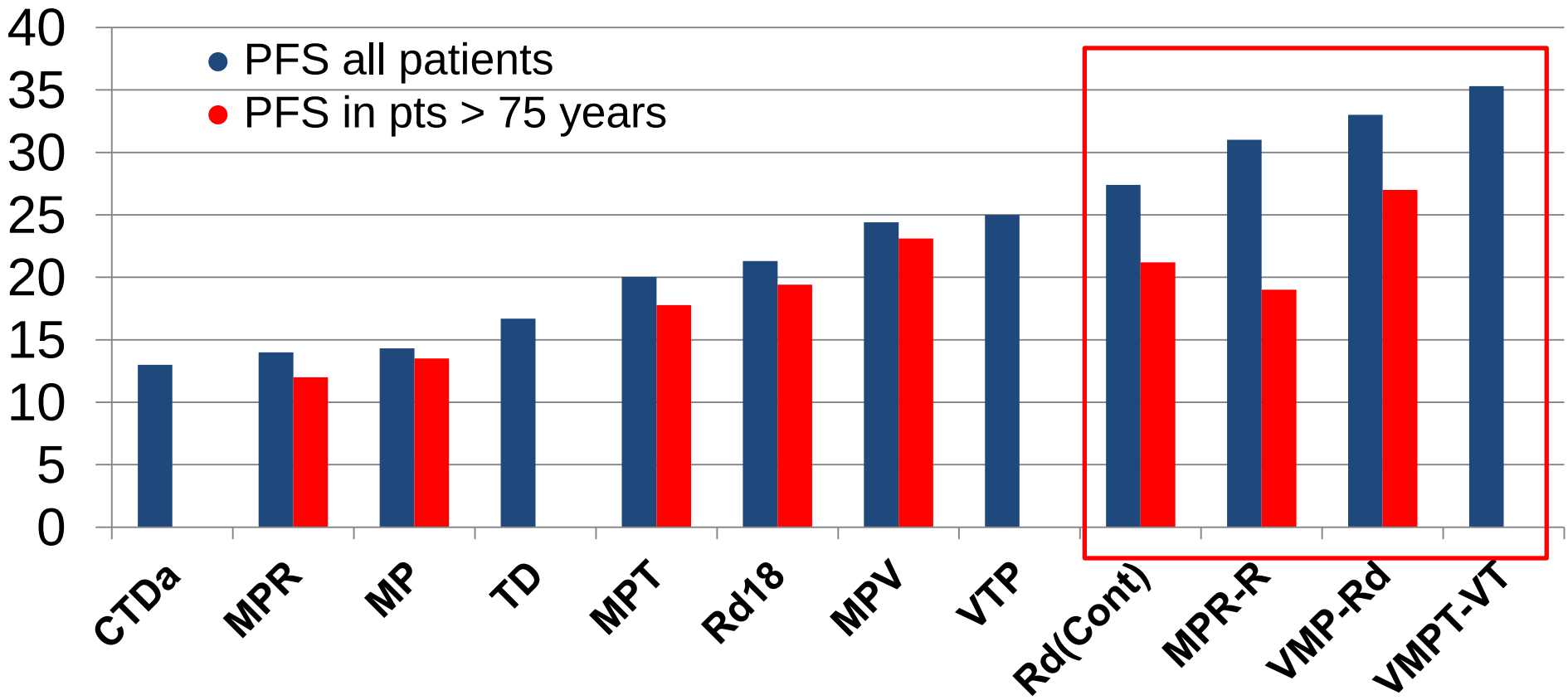


	Median OS, mos	4-yr OS, %
Rd continuous	59.1	59.0
Rd18	62.3	58.0
MPT	49.1	51.7
Rd continuous vs MPT HR (95% CI)	0.78 (0.67-0.92) *P* = .0023	

- Median follow-up: 67 months
- Rd continuous significantly improved OS compared with MPT

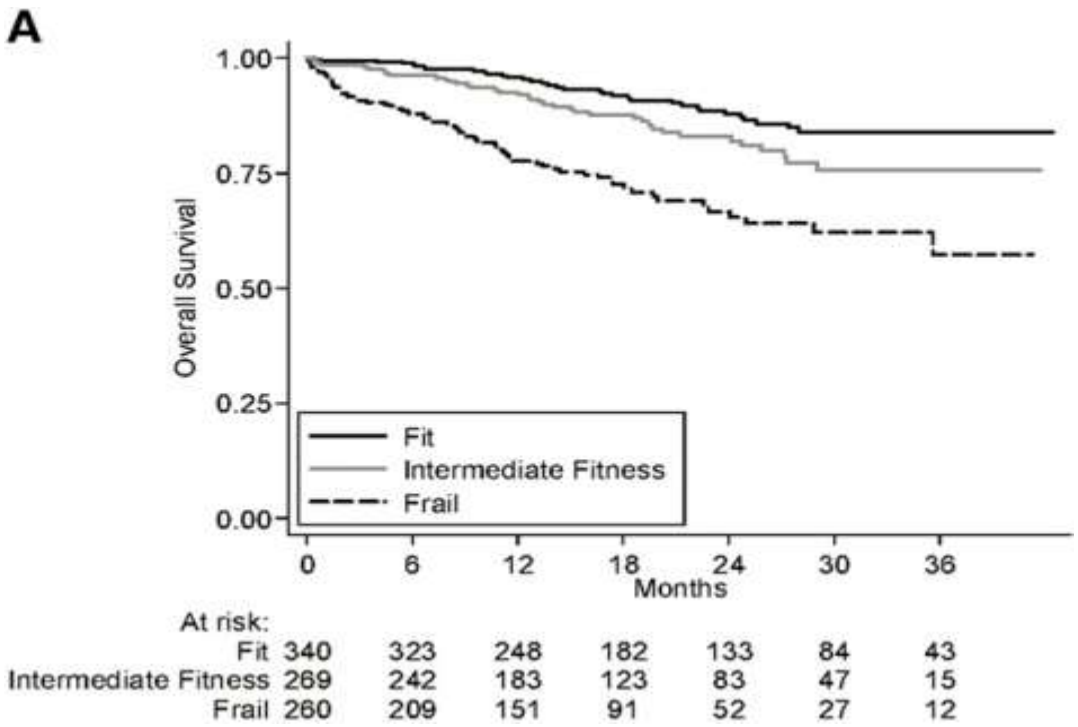
Facon T, et al. Presented at ASH 2016 (Abstract 241), oral presentation.

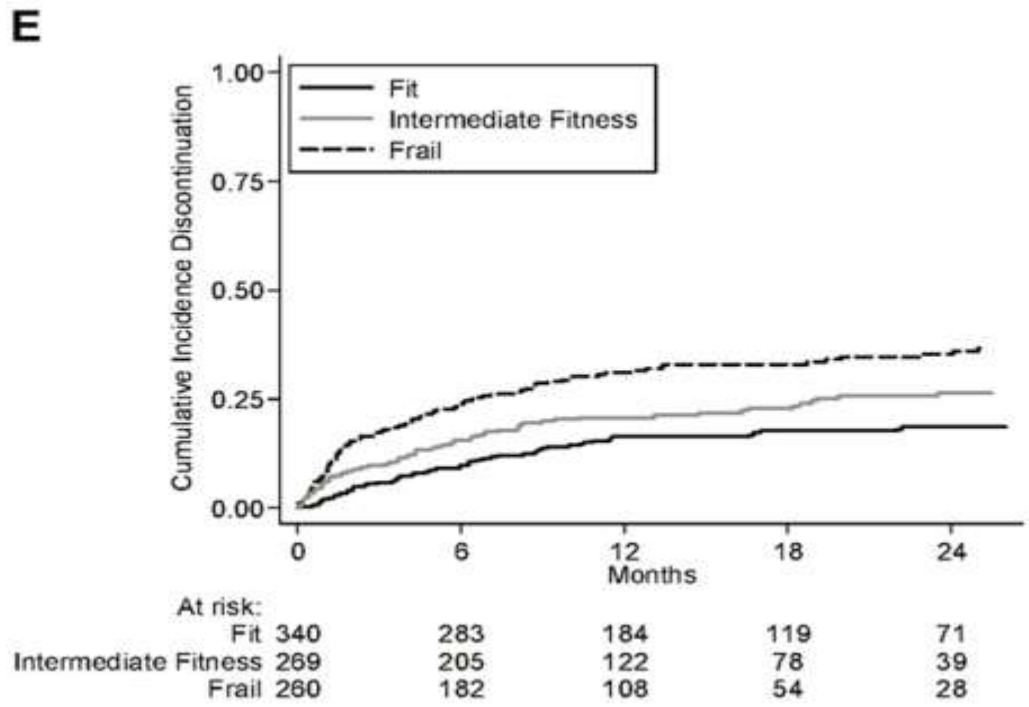
PFS σε ηλικιωμένους ασθενείς που έλαβαν θεραπεία σε κλινικές μελέτες



[1]Palumbo Lancet 2006, [2]Wijermans J Clin Oncol 2010, [3]Hulin J Clin Oncol 2009, [4]San Miguel N Engl J Med 2008 , [5]Palumbo N Engl J Med 2012, [6]Benboubker et al N Engl J Med 2014 [7]Palumbo J Clin Oncol 2010, [8]Morgan et al Blood 2011, [9]Ludwig et al Bood 2009, [10] Mateos et al Lancet Oncol 2010

Frailty score: Long term outcomes

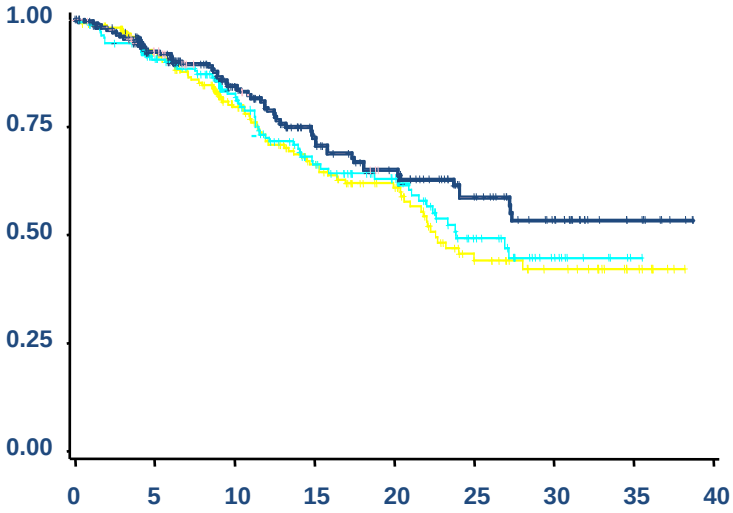




Palumbo A et al. Blood. 2015;125(13):2068-2074)

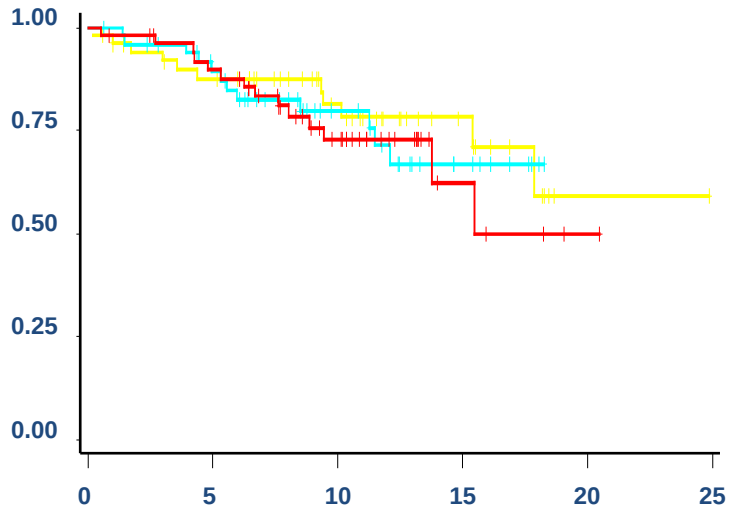
Ηλικιωμένοι ασθενείς: συνδυασμοί με 2 ή 3 φάρμακα ; Progression-free survival

Rd **CPR** **MPR**



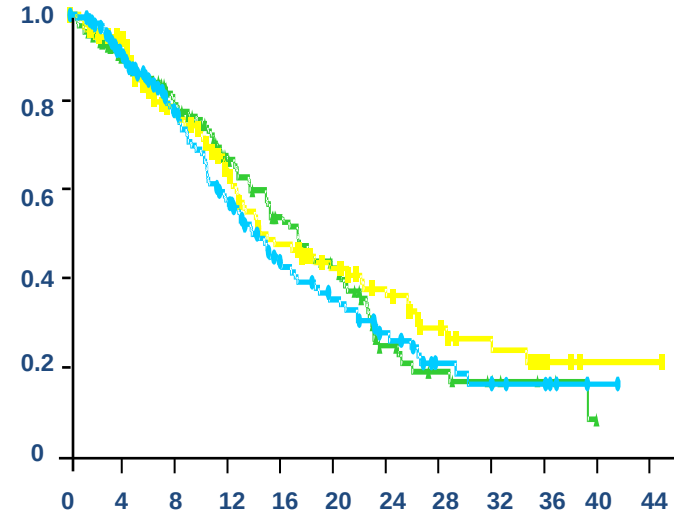
Larocca A, et al. 2013[1]

CVP **VMP** **VP**



Larocca A, et al. 2012[2]

VD **VTD** **VMP**



Niesvizky R, et al. 2010[3]

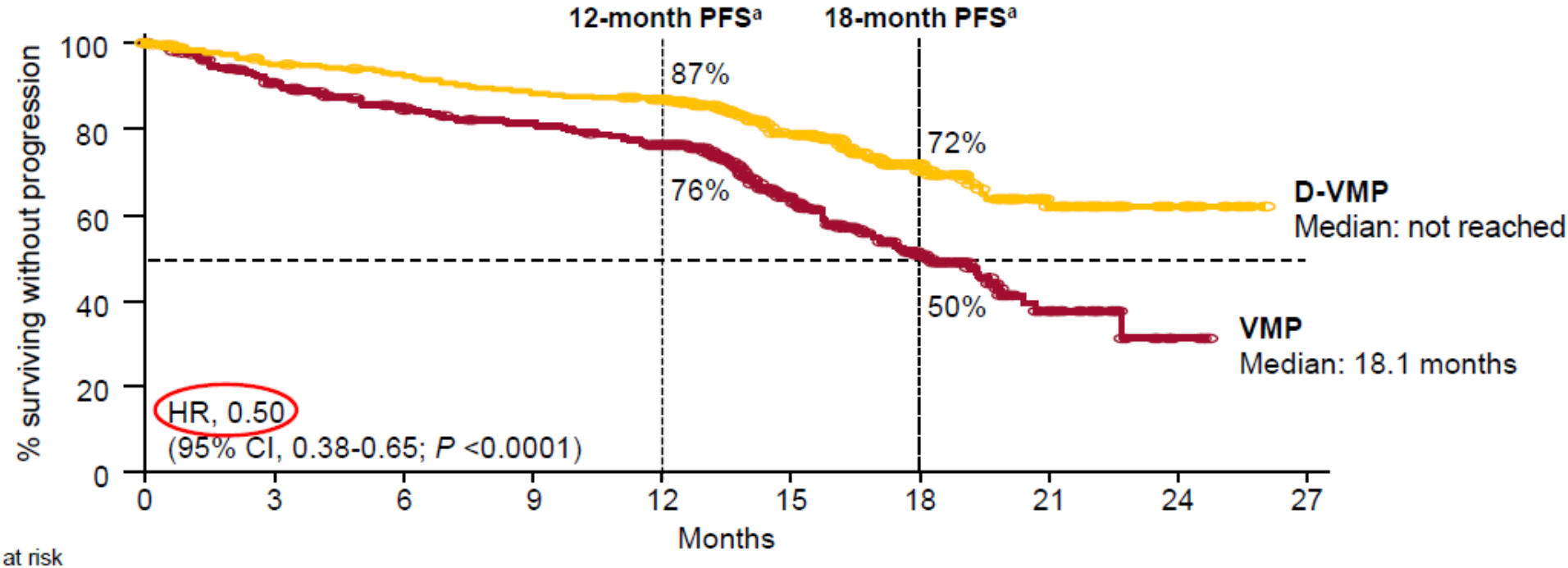
Rd, lenalidomide-dexamethasone; CPR, cyclophosphamide-prednisone-lenalidomide; MPR, melphalan-prednisone-lenalidomide; CVP, cyclophosphamide-bortezomib-prednisone; VMP, bortezomib-melphalan-prednisone; VP, bortezomib-prednisone; VD, bortezomib-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.

[1] Larocca A, et al. Clin Lymphoma Myeloma Leuk. 2013;13(suppl1): abstract P-147. Updated data presented at IMW 2013.
[2] Larocca A, et al. Gr. Emat Milano. 2012.
[3] Niesvizky R, et al. Haematologica. 2010;95(suppl2):abstract O358. Updated data presented at EHA 2010.

VMP +/- Daratumumab σε ασθενείς που δεν είναι υποψήφιοι για ΑΜΑΑΚ

Efficacy: PFS

- Median (range) follow-up: 16.5 (0.1-28.1) months

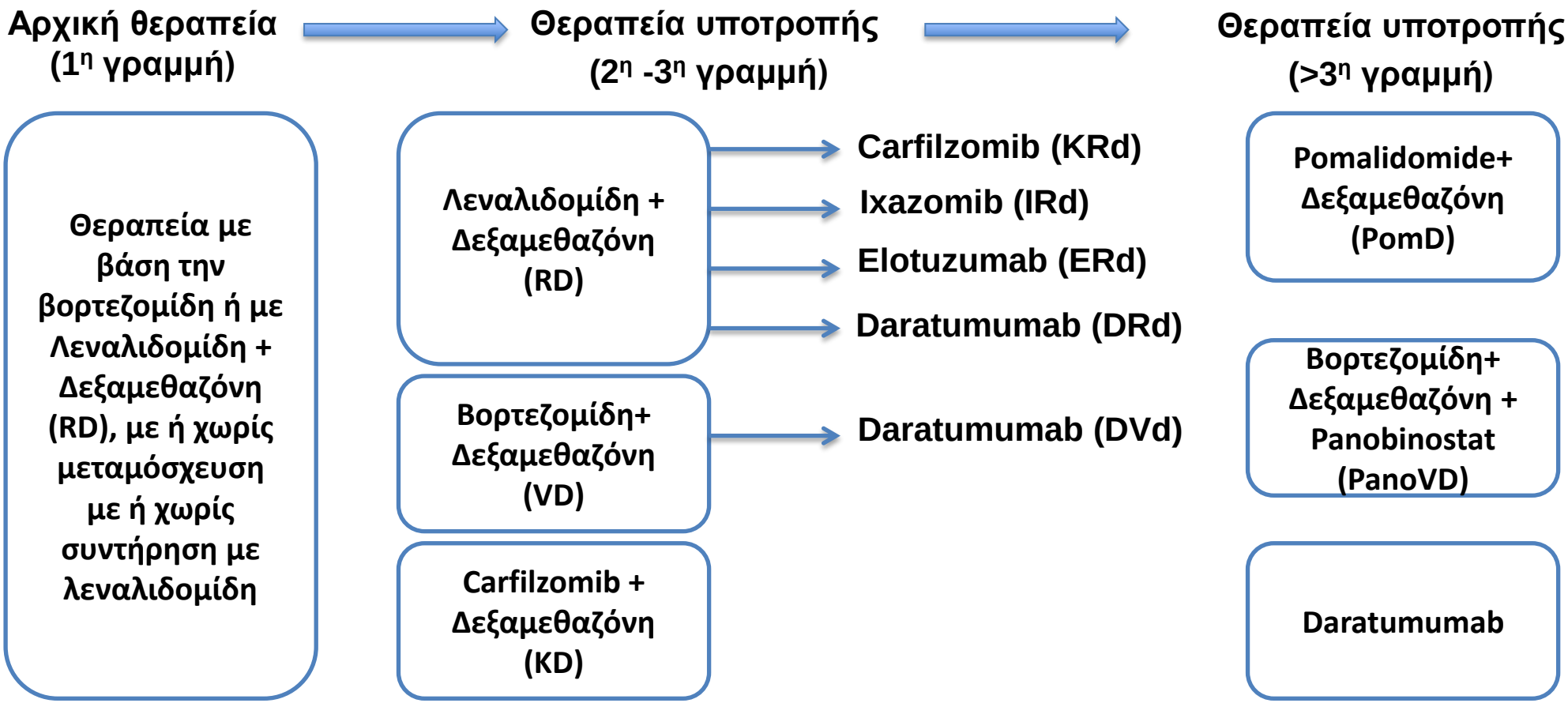


No. at risk										
VMP	356	303	276	261	231	127	61	18	2	0
D-VMP	350	322	312	298	285	179	93	35	10	0

Mateos MV et al ASH 2017

Αντιμετώπιση της υποτροπής της νόσου

Αντιμετώπιση της υποτροπής της νόσου

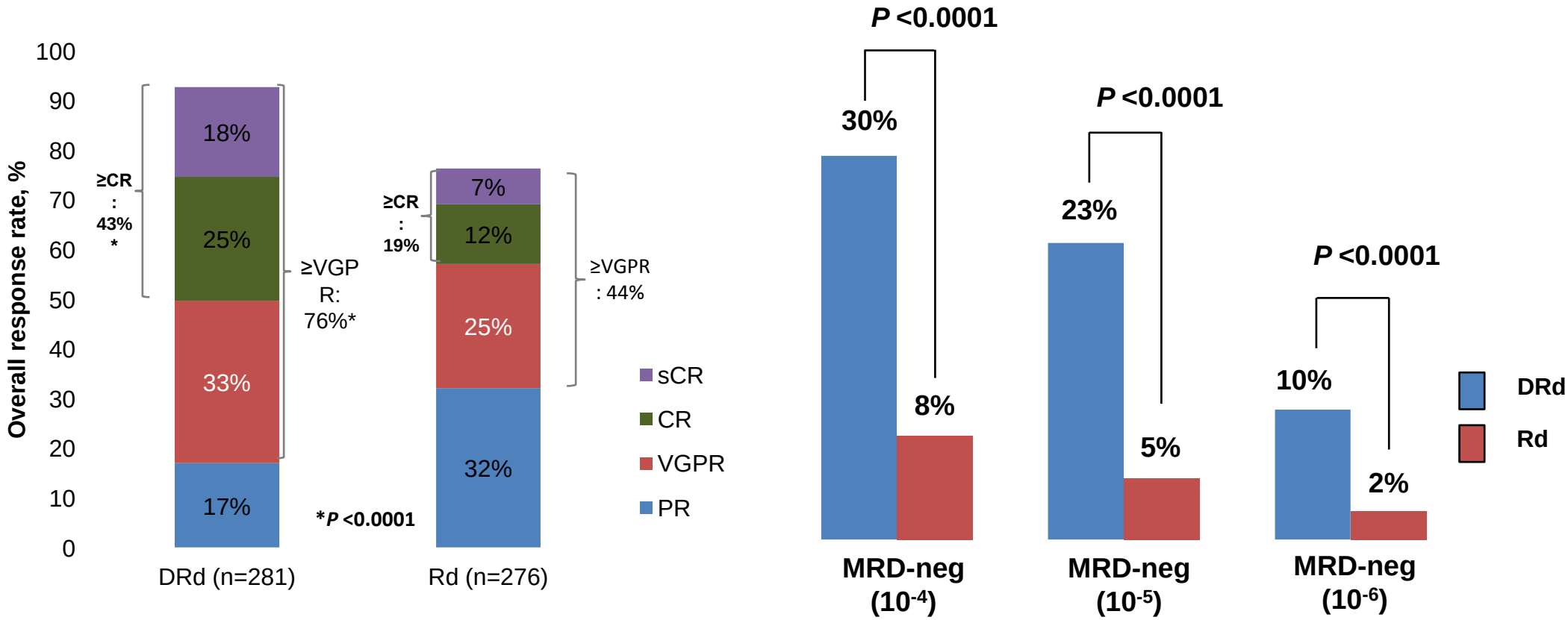


Θεραπευτικά σχήματα για αρρώστους με 1-3 γραμμές θεραπείας

	DRd vs Rd	KRd vs Rd	ERd vs Rd	IRd vs Rd	DVd vs Vd	Kd vs Vd	PnVD vs VD
PFS (HR)	0.37	0.69	0.73	0.74	0.39	0.53	0.63
OS (HR)	NA	0.79	0.78	NA	NA	0.791	0.94
OS (months)	NA	48.3 vs 40.4	48 vs 40.3	NA	NA	47.6 vs 40	40.3 vs 35.8
ΔOS (months)	-	7.9	7.7	-	-	7.6	4.5

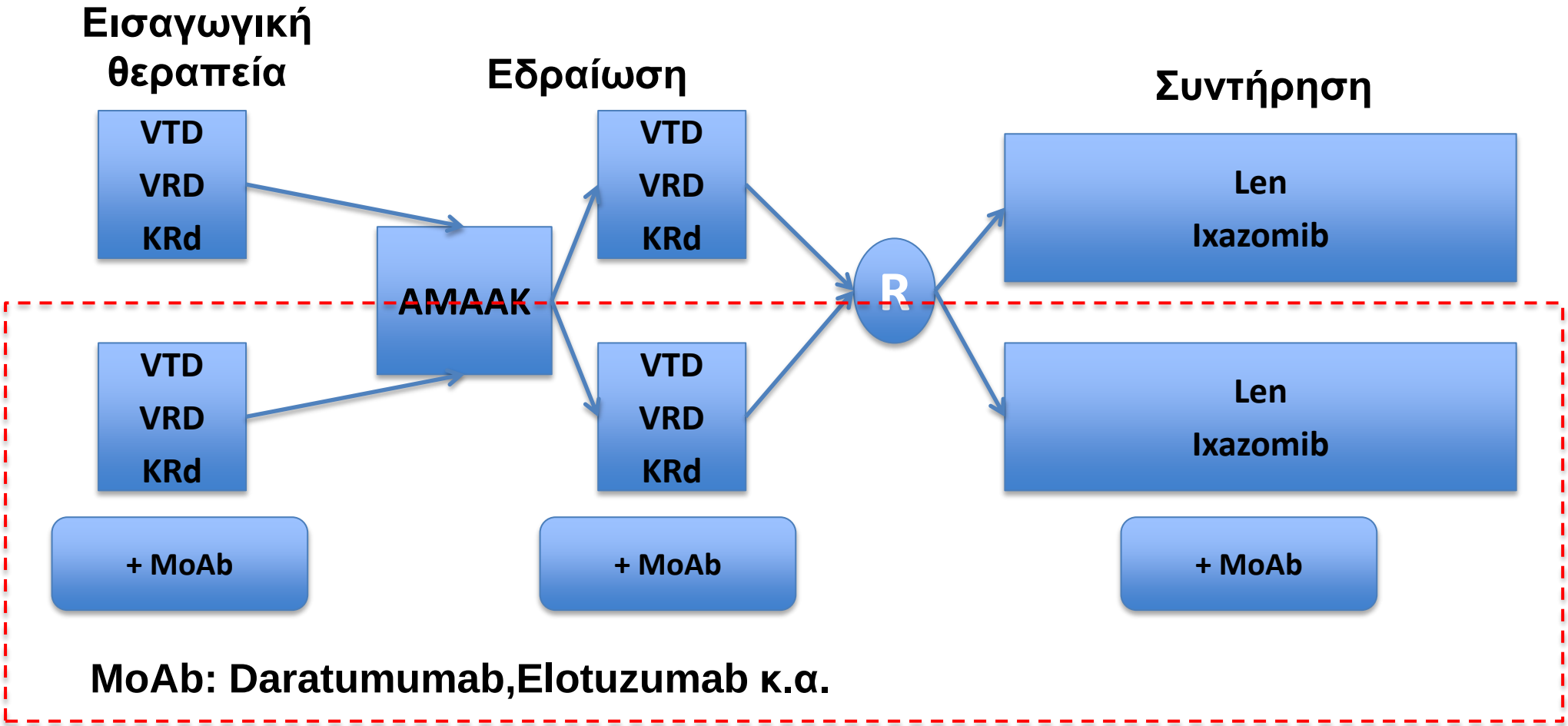
Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38.
San-Miguel JF, et al. *Lancet Oncol*. 2014;15(11):1195-1206.
San-Miguel JF, et al. *Blood*. 2015;126(23):Abstract 3026.
Jakubowiak A, et al. *Blood*. 2016. Epub ahead of print.
Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152.
Lonial S, et al. *N Engl J Med*. 2015;373(7):621-631.
Dimopoulos MA, et al. *Blood*. 2015;126(23):Abstract 28.
Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634.
Dimopoulos MA, et al. *EHA 2017*

Daratumumab+RD : επίτευξη MRD (-)

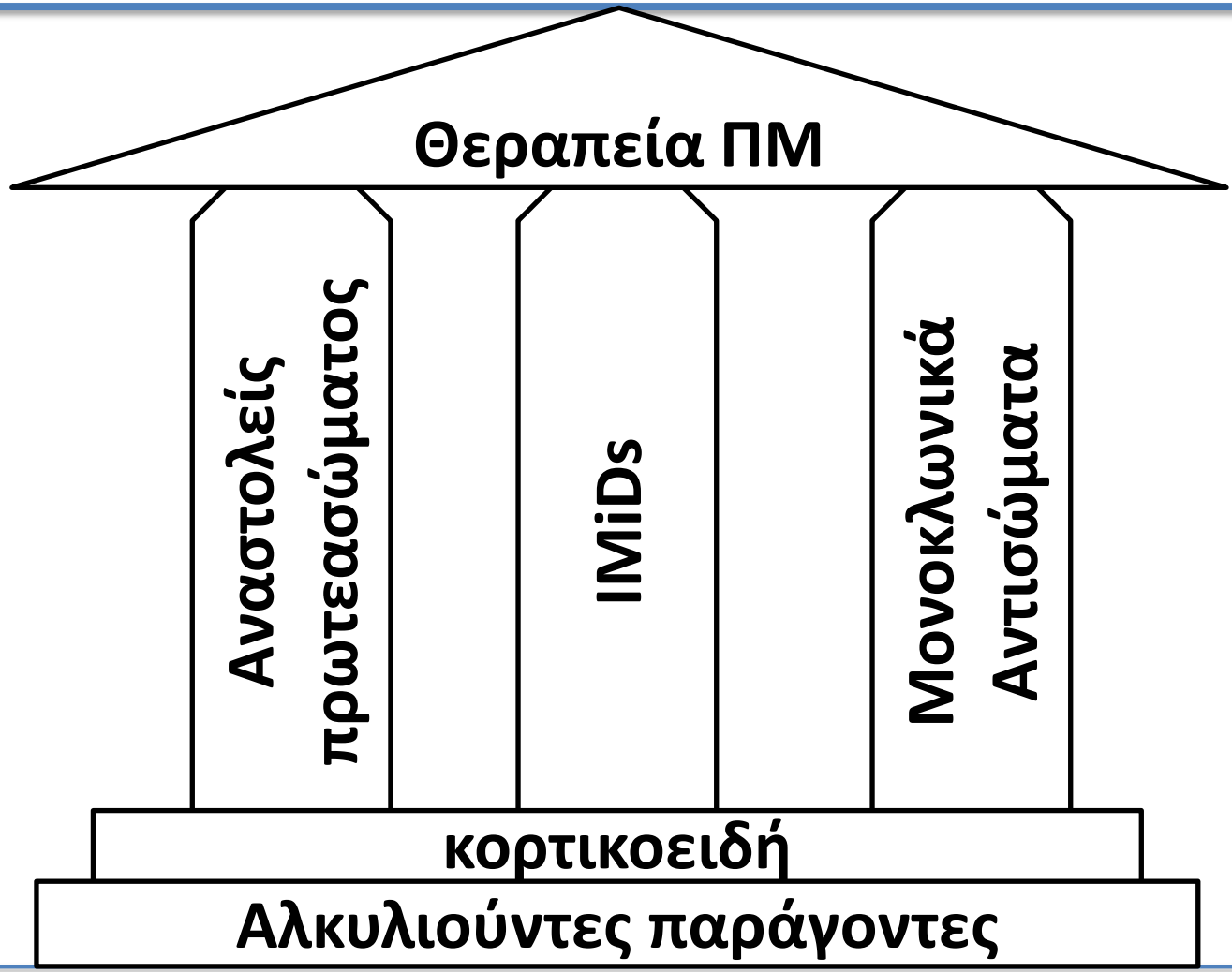


Dimopoulos MA et al N Engl J Med 2016

«R-CHOP» στο ΠΜ?

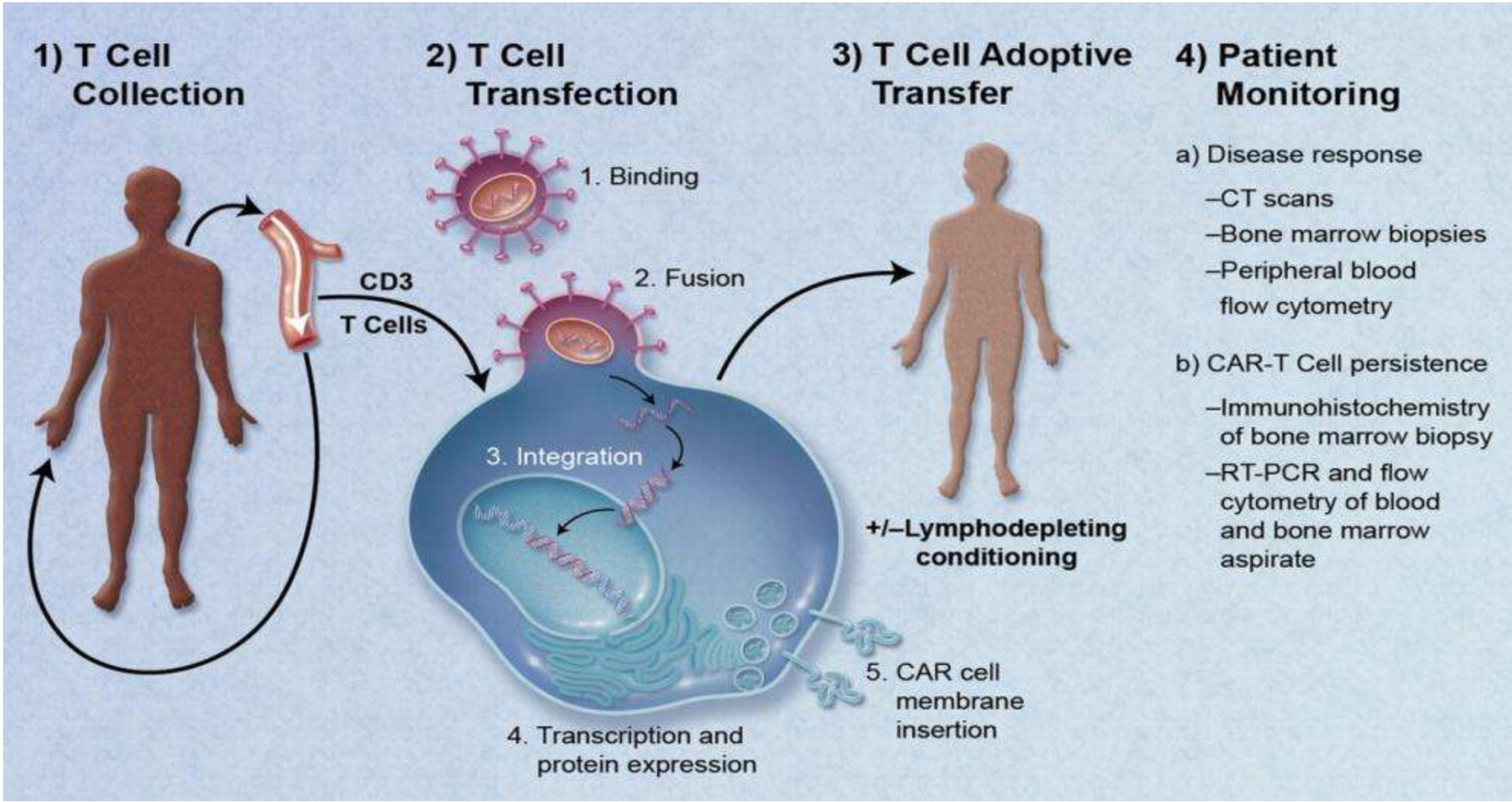

Εισαγωγική θεραπεία
Εδραίωση
Συντήρηση
VTD
VRD
KRd
AMAAK
VTD
VRD
KRd
R
Len
Ixazomib
VTD
VRD
KRd
VTD
VRD
KRd
Len
Ixazomib
+ MoAb
+ MoAb
+ MoAb
MoAb: Daratumumab,Elotuzumab κ.α.

Θεραπεία του ΠΜ το 2018

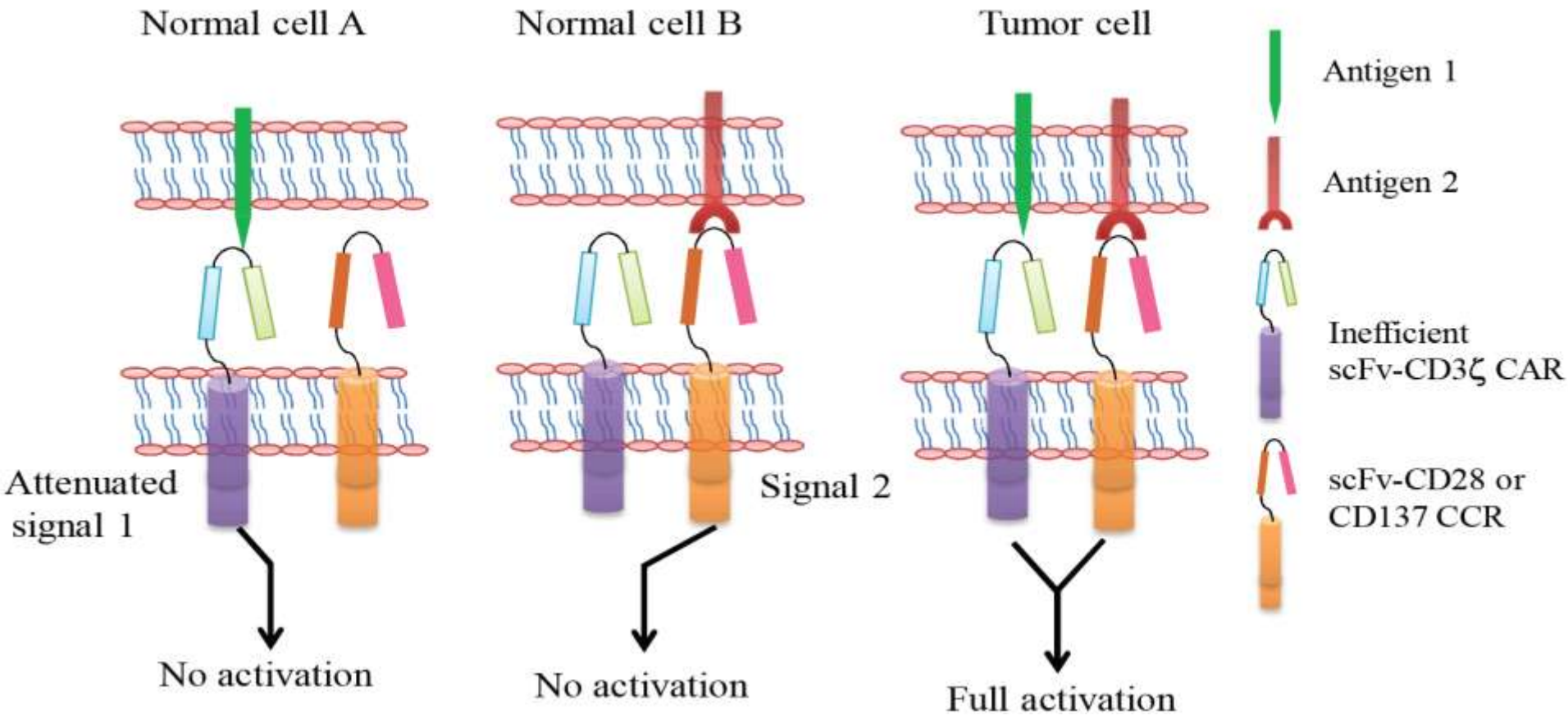


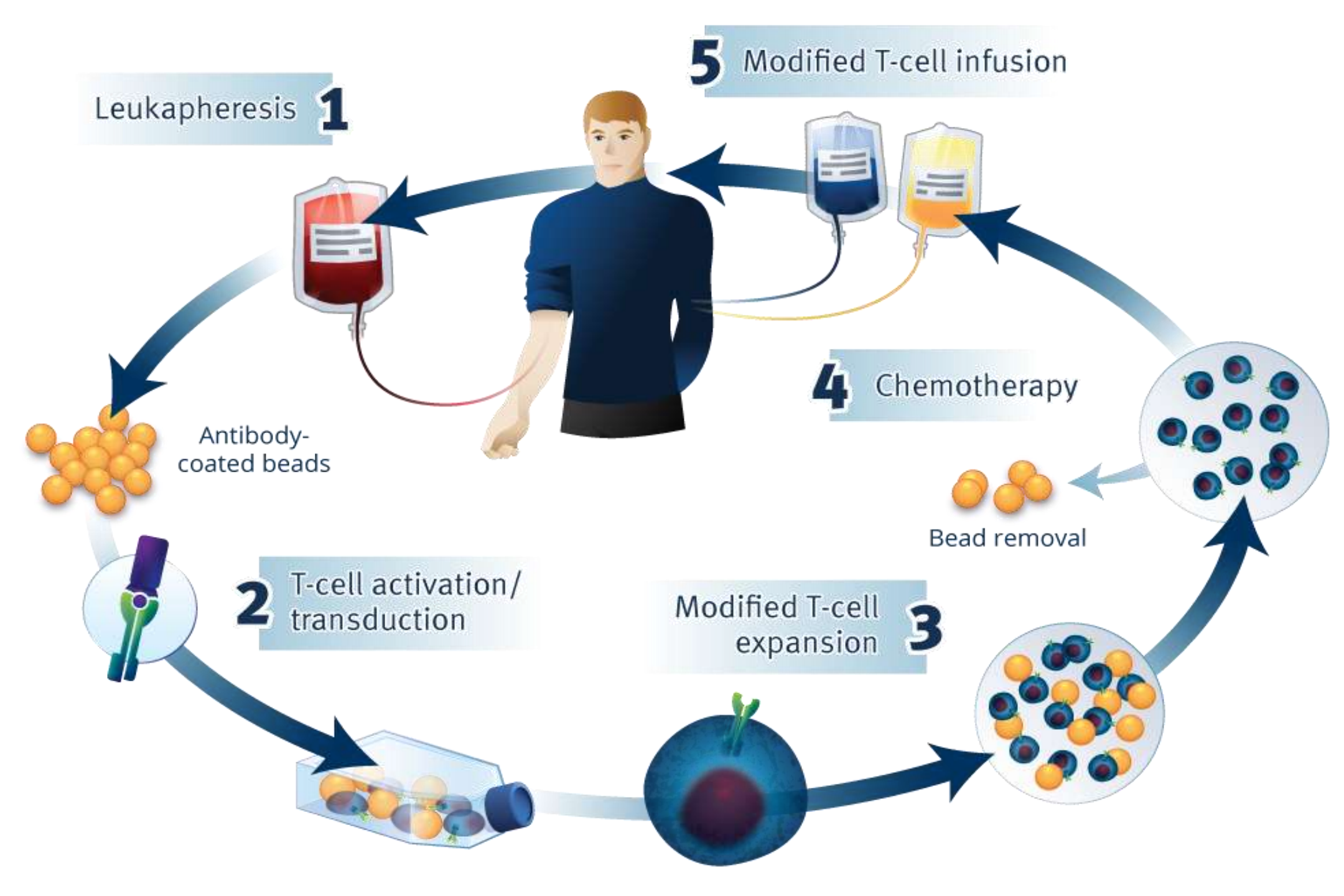
Νέοι θεραπευτικοί στόχοι και νέες στρατηγικές

CAR T cells

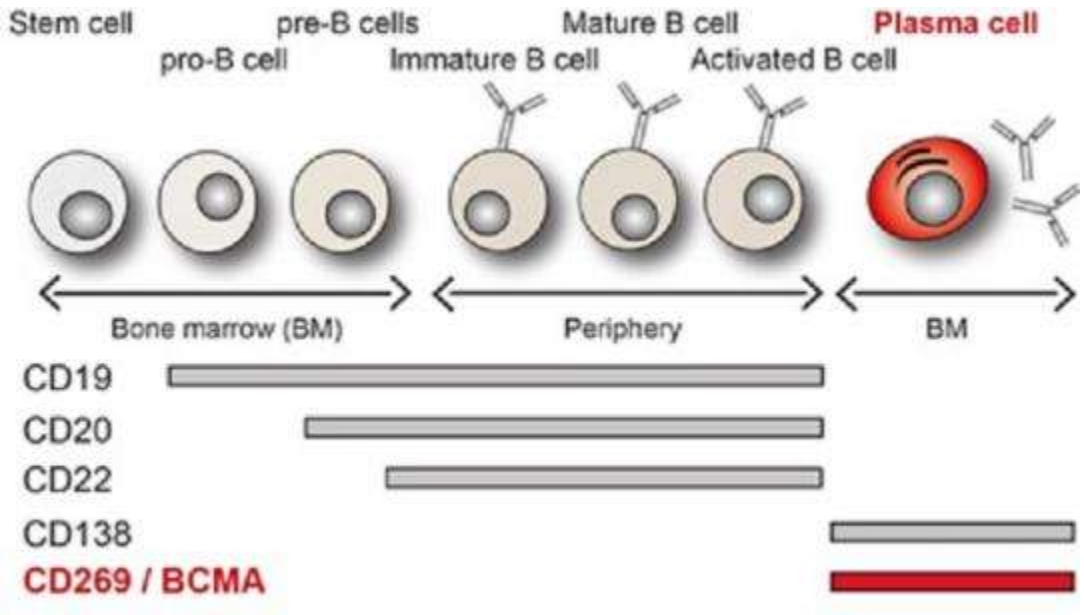

1) T Cell Collection
2) T Cell Transfection
3) T Cell Adoptive Transfer
4) Patient Monitoring
CD3
T Cells
1. Binding
2. Fusion
3. Integration
4. Transcription and protein expression
5. CAR cell membrane insertion
+/–Lymphodepleting conditioning
a) Disease response
–CT scans
–Bone marrow biopsies
–Peripheral blood flow cytometry
b) CAR-T Cell persistence
–Immunohistochemistry of bone marrow biopsy
–RT-PCR and flow cytometry of blood and bone marrow aspirate

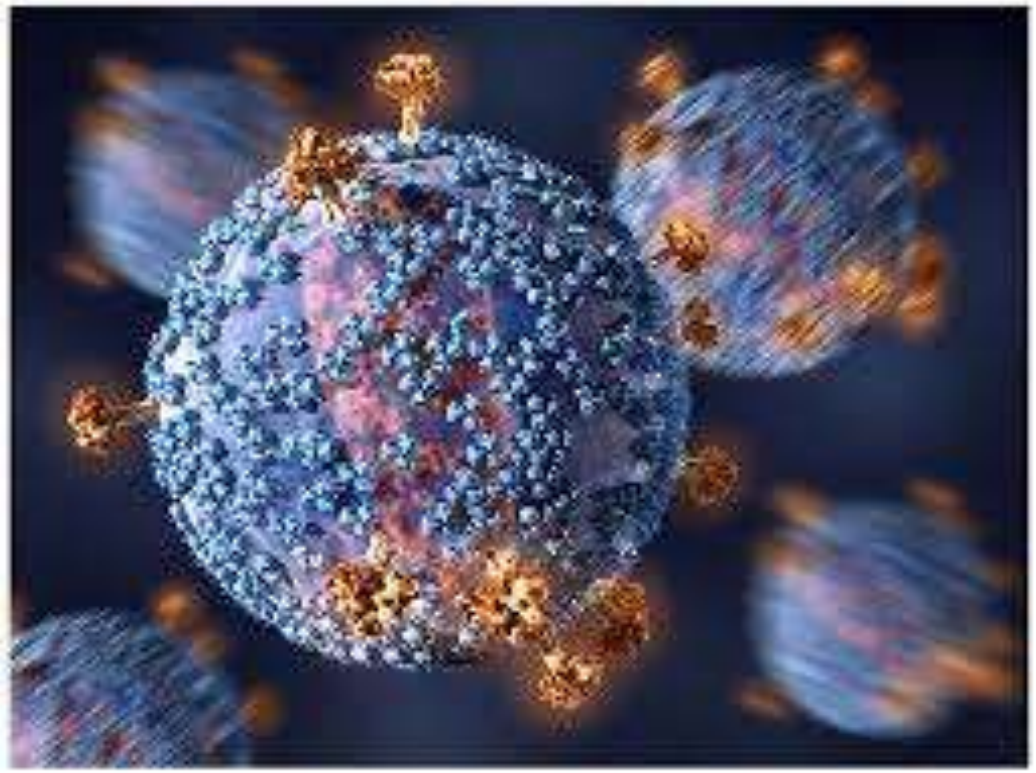
CAR T cells


Normal cell A
Normal cell B
Tumor cell
Antigen 1
Antigen 2
Inefficient
scFv-CD3ζ CAR
scFv-CD28 or
CD137 CCR
Attenuated
signal 1
Signal 2
No activation
No activation
Full activation

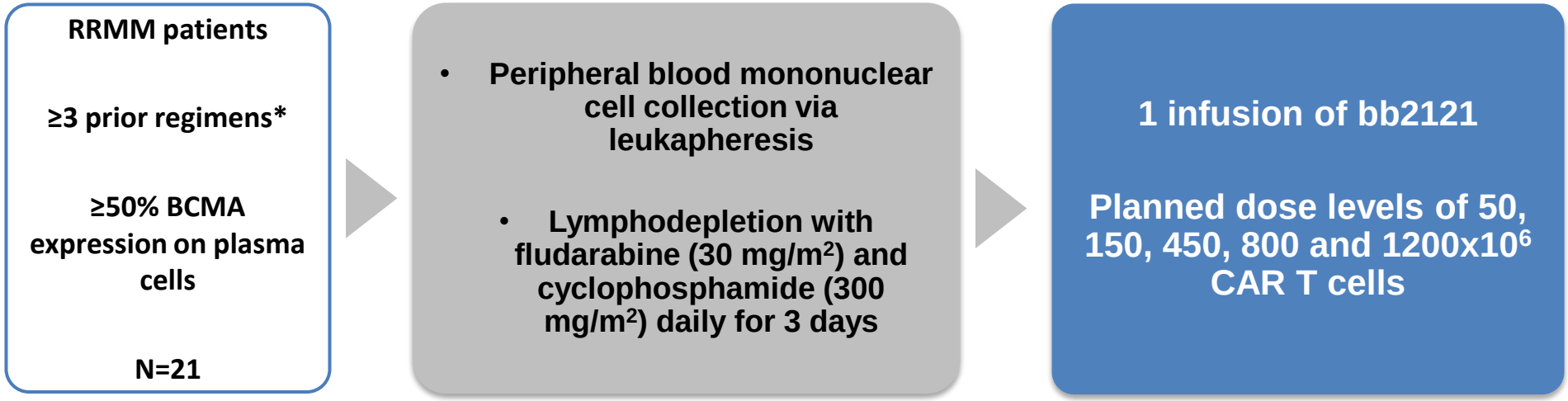

Leukapheresis 1
5 Modified T-cell infusion
Antibody-coated beads
2 T-cell activation/ transduction
Modified T-cell expansion 3
4 Chemotherapy
Bead removal

BCMA στο πολλαπλούν μυέλωμα





CRB-401: Phase 1 dose escalation study of bb2121 CAR T cell therapy in RRMM



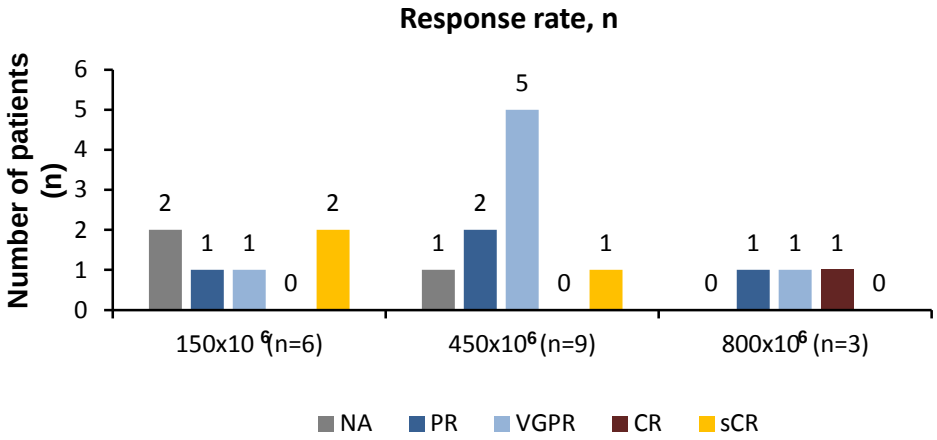
- Background: BCMA is a member of the tumour necrosis factor superfamily and is expressed primarily by malignant myeloma cells, plasma cells, and some mature B-cells
- Primary outcome: incidence of AEs, including DLTs
- Other outcomes: quality and duration of clinical response, MRD, PFS, OS, quantification of bb2121 in blood, and quantification of circulating soluble BCMA over time

*Including proteasome inhibitor and an immunomodulatory agent, or double refractory.

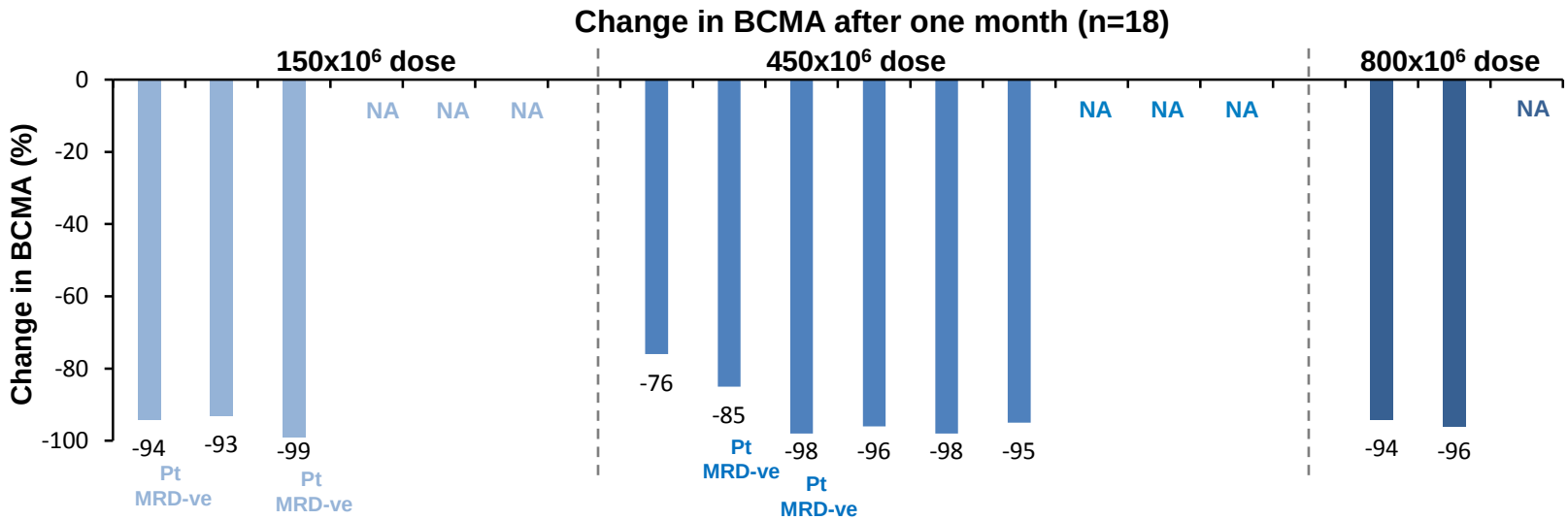
AE, adverse event; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; DLT, dose-limiting toxicities; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.

Berdeja JG et al ASH 2017

Efficacy by bb2121 CAR T cell dose level



- Patients had a median of 7 prior lines of therapy (range 3 to 14)
- Median follow-up after bb2121 infusion was 15.4 weeks (range: 1.4 to 54.4 weeks)
- bb2121 at **≥150x10⁶** dose level shows **promising efficacy**:
  - **No** patients had **progressive disease**
  - **ORR was 100%**
  - **MRD negative** results were obtained in **all 4 evaluable patients**



BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; MRD, minimal residual disease; NA, not available; ORR, overall response rate; Pt, patient; PR, Partial response; sCR, stringent complete response; VGPR, very good partial response.

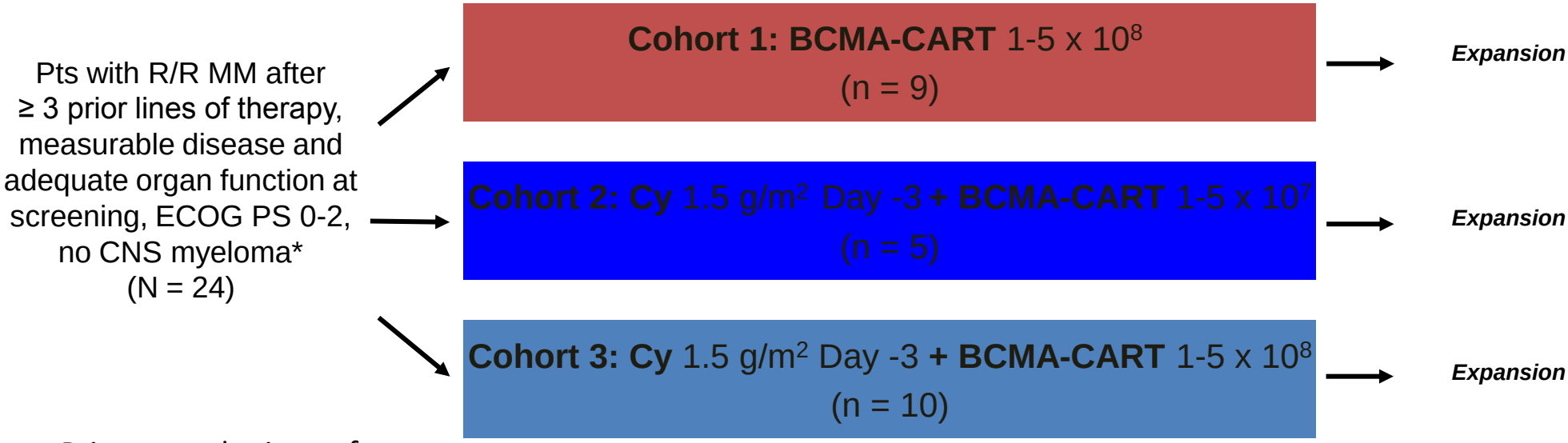
Berdeja JG et al ASH 2017

Toxicity profile of bb2121 CAR T cell therapy

- **No DLTs** and **no treatment-emergent ≥grade 3 neuro-toxicities**, similar to those reported in other CAR T clinical studies, have been observed
- **CRS**, **primarily grade 1 or 2**, was reported in **71%** (15/21) of patients
- 2 patients had grade 3 CRS
- **CRS was more common in the higher dose groups** but did not appear related to tumour burden

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLT, dose limiting toxicity.

BCMA-CART in R/R MM: Phase I Study Design



- Primary endpoint: safety
- Secondary endpoints: feasibility, efficacy (response, PFS, OS, MRD)

*Pts with R/R MM after ≥ 2 lines prior therapy also eligible if refractory to both PI and IMiD. Adequate organ function: serum creatinine ≤ 2.5 mg/dL or estimated CrCl ≥ 30 mL/min; ANC ≥ 1000/μL, platelets ≥ 50/μL (≥ 30 if BM PC ≥ 50%); AST ≤ 3 x ULN and total bilirubin ≤ 2.0); and left ventricle EF ≥ 45%. Eligibility did not depend on BCMA expression.

Cohen AD, et al. ASH 2017. Abstract 505.

BCMA-CART in R/R MM: Baseline Pt Characteristics

Characteristic	All Pts (N = 24)
Median age, yrs (range)	58 (44-75)
Male, %	67
Median time since diagnosis, yrs (range)	4.6 (1.8-14.5)
Median prior therapies, n (range)	7 (3-13)
Prior therapy, %	
▪ Lenalidomide	100
▪ Bortezomib	100
▪ Pomalidomide	92
▪ Carfilzomib or oprozomib	96
▪ Daratumumab*	75

Characteristic	All Pts (N = 24)
Dual/quad/penta refractory,† %	96/54/42
Autologous/allogeneic SCT, %	92/4
Cyclophosphamide, %	100
Anti-PD1, %	29
High-risk genetics, %	96
▪ del(17p) or *TP53* mutation	71
Extramedullary disease, %	29
Median BM plasma cells, % (range)	70 (0-95)

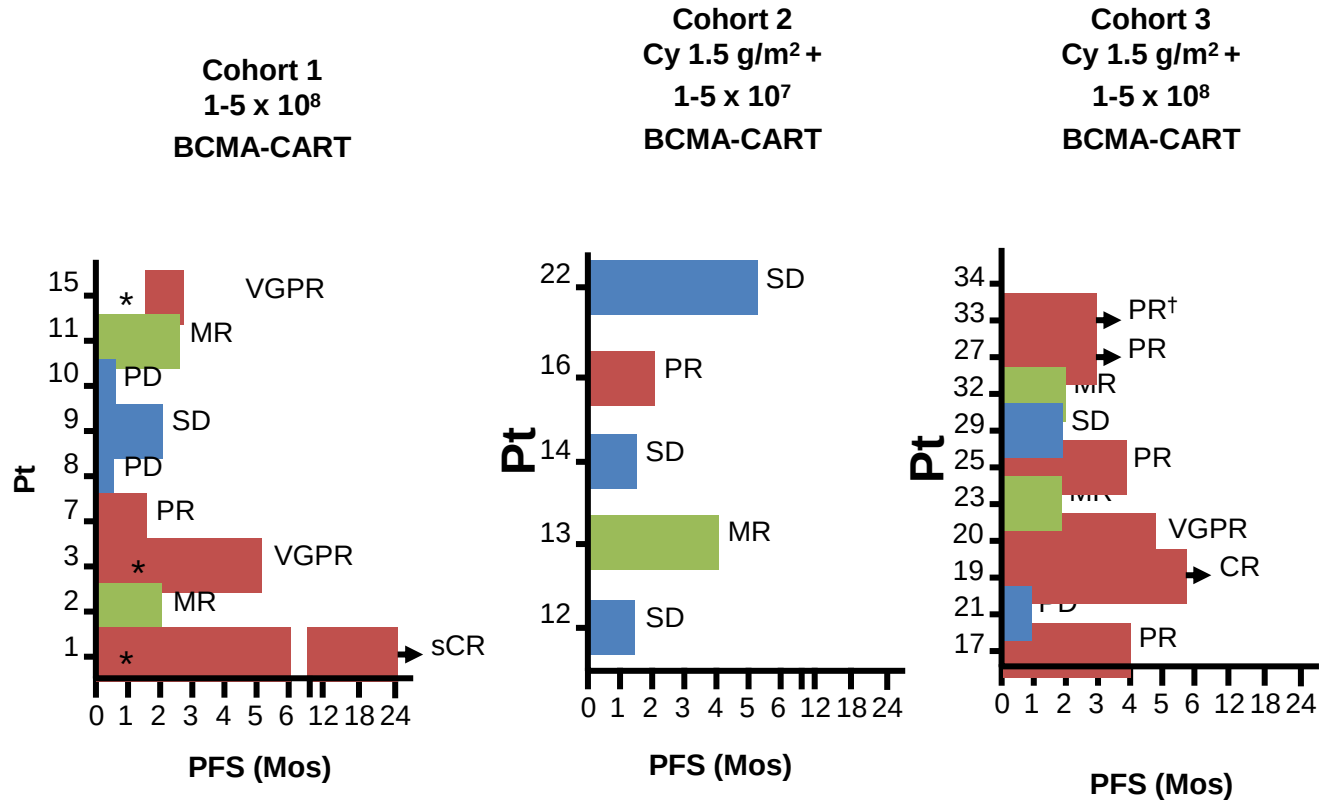
*Daratumumab exposure: cohort 1, 44%; cohort 2, 80%; cohort 3, 100%.

†Treatment refractory status: cohort 1, 89%/56%/33%; cohort 2, 100%/60%/40%; cohort 3, 100%/50%/50%.

Cohen AD, et al. ASH 2017. Abstract 505.

BCMA-CART in R/R MM: Efficacy Outcomes

- ORR
  - ≥ PR: 11/24 (46%)
  - ≥ MR: 16/24 (67%)
- ORR with 10^8 BCMA-CART
  - ≥ PR: 10/19 (53%)
- Median DoR: 4 mos



*MRD negative. †Measurable by PET/CT; FDG negative at Day 28, 90.

Cohen AD, et al. ASH 2017. Abstract 505.

Μονοκλωνικά αντισώματα έναντι του BCMA

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

Patients with RRMM and other haematologic malignancies

MM patients treated with alkylators, PI, IMiDs and SCT (if eligible)

Part 1: dose escalation (N=38)

GSK2857916 (anti-BCMA antibody)

Recommended phase 2 dose determined to be 3.4 mg/kg

Part 2: expansion (N=35)

GSK2857916 (anti-BCMA antibody)

3.4 mg/kg

q3w, i.v. as 1-hour infusion

- **No prophylaxis for IRR was included**
- **Steroid eye drops given for 4 days with each infusion to mitigate corneal events**

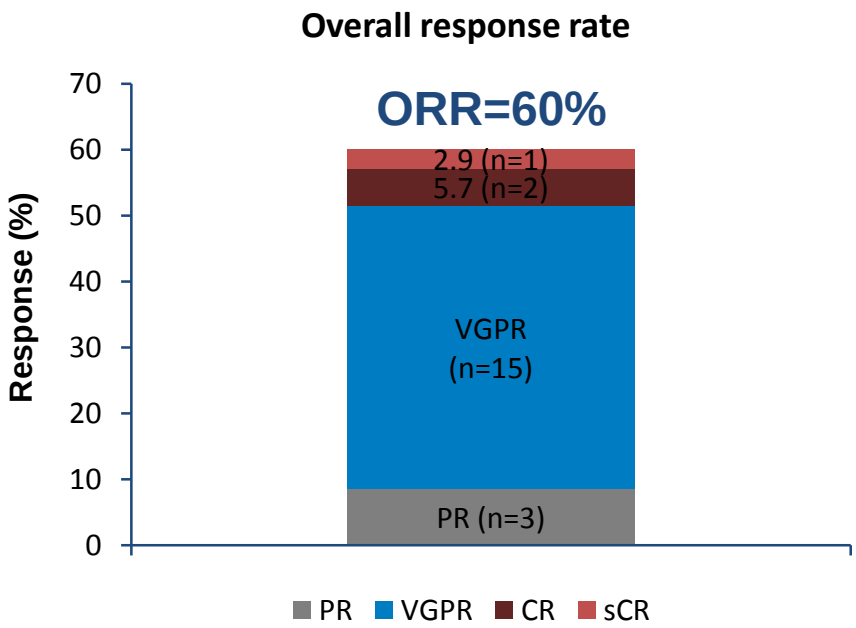
Treatment up to 16 cycles, or until progression/unacceptable toxicity

- **Primary objectives: safety, and determination of maximum tolerated dose and recommended phase 2 dose**
- **Secondary objectives: PK, antidrug antibody incidence, and ORR**
- **Dose escalation (Part 1) and expansion (Part 2) in MM patients are complete, and enrolment into a lymphoma cohort is ongoing**

BCMA, B-cell maturation antigen; IMiD, immunomodulators; IRR, infusion-related reaction; i.v. intravenous; MM, multiple myeloma; ORR, overall response rate; PI, proteasome inhibitor; PK, pharmacokinetics; q3w, once every 3 weeks; RRMM, relapsed/refractory multiple myeloma; SCT, stem cell transplantation.

Trudel S et al ASH 2017

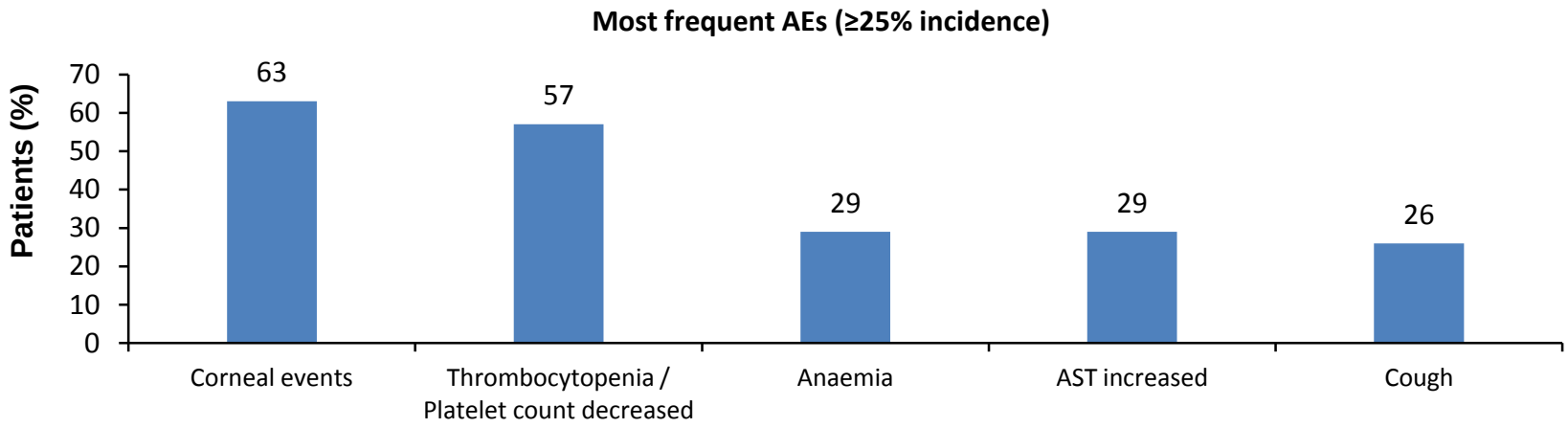
Efficacy of GSK2857916 as a single agent



- **The patient population was heavily pre-treated, with 57% of patients having received ≥5 prior lines of therapy**
- **The median number of infusions was 5 (range: 1–13)**
- **The ORR for patients previously treated with DARA was 43% (6/14)**
- **Median PFS was 7.9 months**
- **Median duration of response was not reached**

CR, complete response; DARA, daratumumab; ORR, overall response rate; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

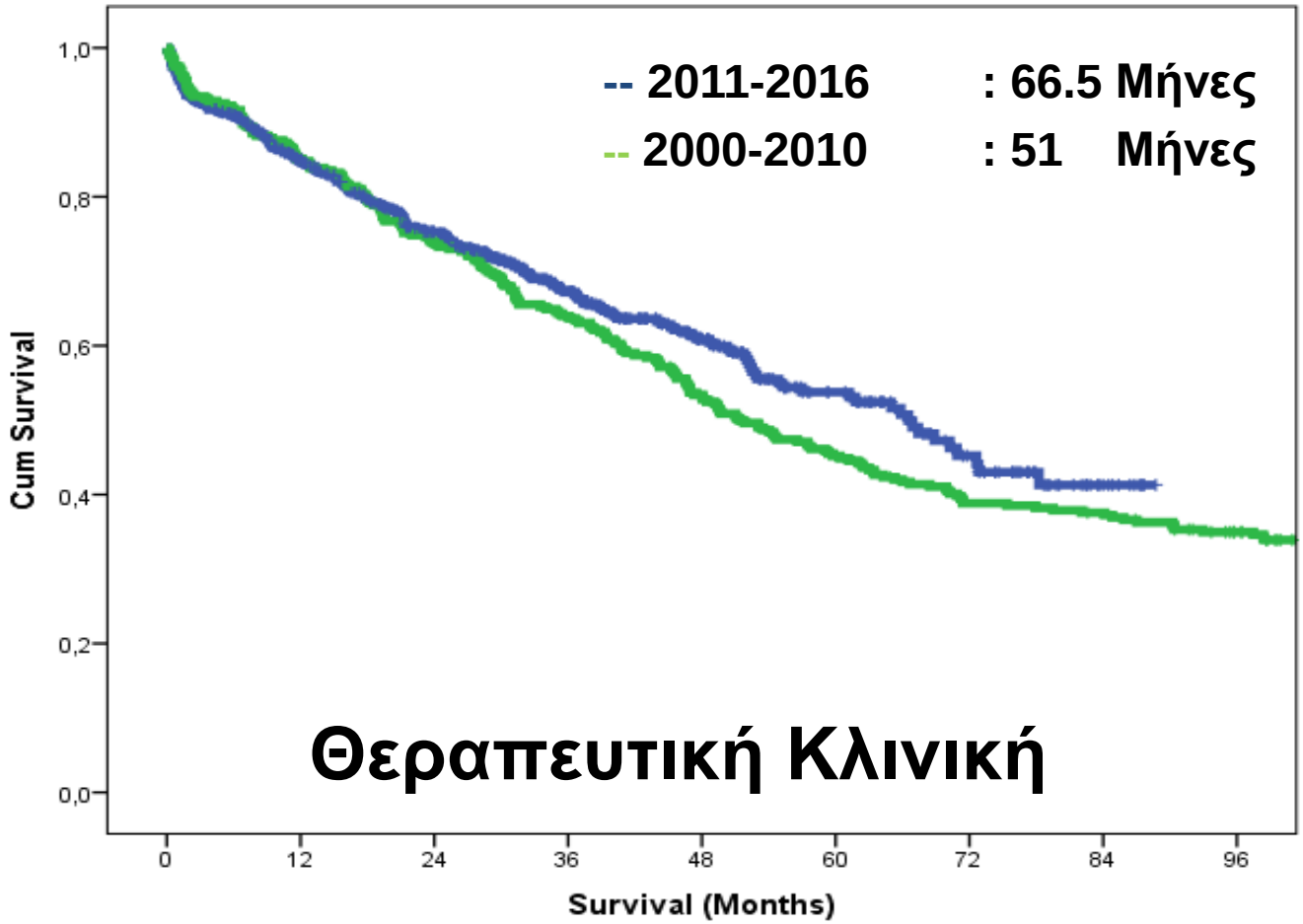
Safety profile of GSK2857916



- **All patients had ≥1 AE**
- **Serious AEs occurred in 40% (14/35) of patients**
- **Grade 3 or 4 AEs reported in ≥10% of patients were thrombocytopenia/platelet count decrease (34%) and anaemia (14%)**
- **Corneal events were mostly grade 1 or 2 and were reversible**
- **With no IRR prophylaxis given, 8 patients had IRRs**

AST, aspartate aminotransferase; AE, adverse event; IRR, infusion-related reaction.

Αυξάνουν οι διαθέσιμες θεραπείες την συνολική επιβίωση;



Αμυλοείδωση AL

Daratumumab in AL amyloidosis: prospective, Phase 2 data

	V Sanchorawala et al Abstract #507	M Roussel et al Abstract #508
Number of patients	12	36
eGFR	>20 ml/min/1.73 m^2	NR
NTproBNP	All <8500 pg/ml , median: 1357 (469-3962)	All < 8500 pg/ml, Median: 1118 (60-6825)
Schedule / duration	IV Standard / 24 months	IV Standard / 6 months
Prior therapies	3 (1-6)	3 (1-5)
Refractory to last therapy	7 (58.3%)	NR
HDM/ASCT / IMiDs / PIs	9 (75%) / 6 (50%) / 10 (83%)	NR / 19 (53%) / 34 (94%)

Sanchorawala V, et al. ASH 2017 (Abstract 507) oral presentation; Russel et al. ASH 2017 (Abstract 508) oral presentation

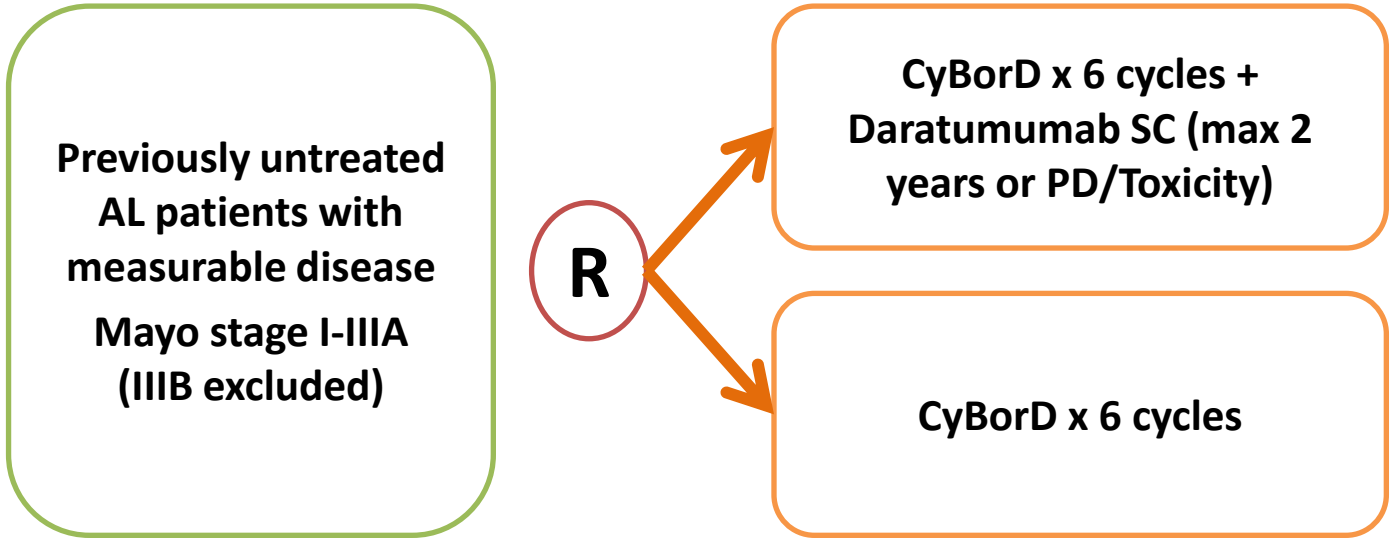
Daratumumab in AL amyloidosis: prospective, Phase 2 data

	V Sanchorawala et al Abstract #507	M Roussel et al Abstract #508
Number of patients	12	36 (32 evaluable for ORR)
Response after 1st infusion	11/12 (92%)	16/29 (55%)
ORR	11 (92%)	19 (59%)
CR / VGPR	2 / 6 (22%/ 67%)	14 (44%)
Discontinued Due to PD	1	3
Toxicity	IRR Gr1-2: 25%	IRR Gr1-2: 31%
Discontinued Due to toxicity	0	0

- **Highly active as monotherapy , Safe and tolerable**
- **Selected patients (R/R AL) able to receive multiple lines of therapy prior to Dara**
- **No stage 3B**
- **Cannot extrapolate these results for newly diagnosed AL patients**

Sanchorawala V, et al. ASH 2017 (Abstract 507) oral presentation; Russel et al. ASH 2017 (Abstract 508) oral presentation

Daratumumab in AL amyloidosis: Phase 3 study in newly diagnosed AL (stage 1-3A)



Primary Outcome: Overall Complete Hematologic Response

Secondary Outcomes : Major Organ Deterioration Progression-Free Survival (MOD-PFS), Progression-Free Survival (PFS), Organ Response Rate (OrRR), Overall Survival (OS), QOL measureements, Time to Next Treatment (TNT), Hematologic VGPR, Time to CR, VGPR, Duration of CR, Time to Organ Response, Duration of Organ Response

CyBorD: dexamethasone (40 mg PO or IV, followed by cyclophosphamide (300 mg /m^2 PO or IV), then bortezomib (1.3 mg/m^2 SC) weekly on Days 1, 8, 15, 22 in every 28-day cycle for a maximum of 6 cycles.

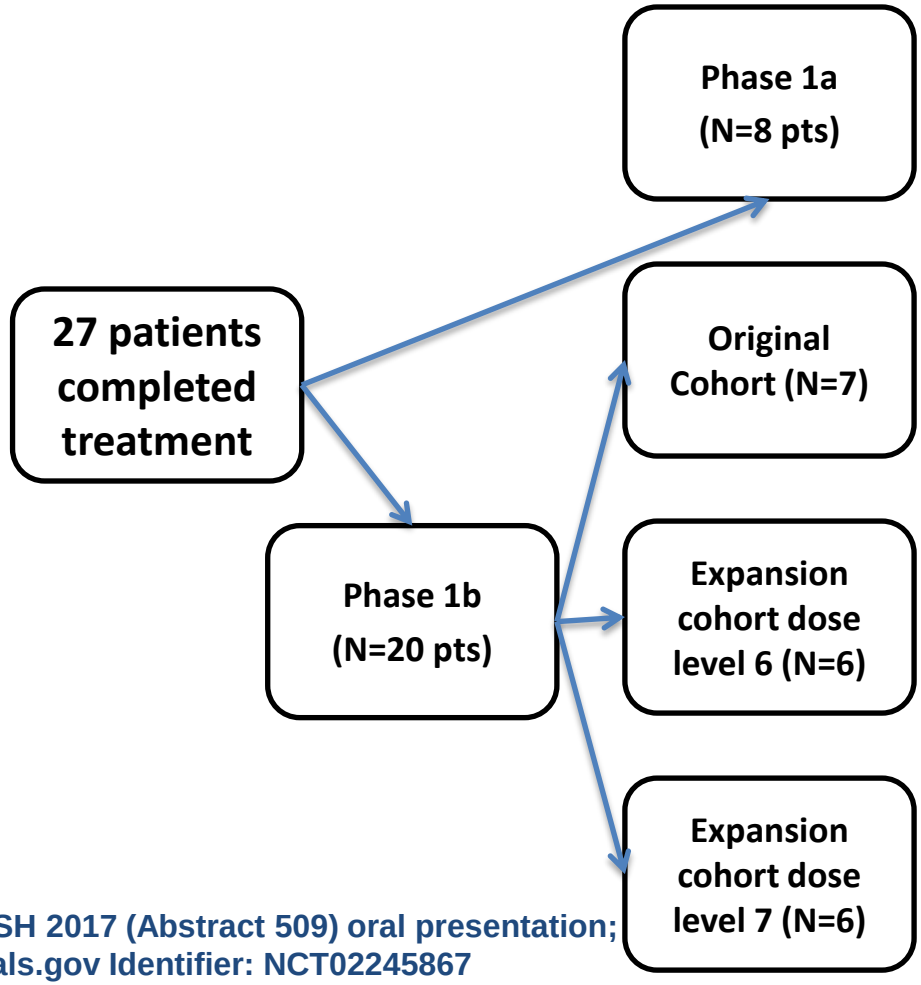
ClinicalTrials.gov Identifier: NCT03201965

Monoclonal antibodies targeting amyloid fibrils

	NEOD001[1–4]	11-1F4[5] (CAEL-101)	GSK2315698[6]
Target	• Light chain • serum amyloid protein A (sAA)	• Light chain • sAA	Serum Amyloid P component (SAP)
Class	IgG1	IgG1	IgG1
Type	humanized murine	Chimeric	Fully Humanized
Dose	24mg/kg (maximum dose 2500 mg)	500 mg/m2	Up to 1200 mg
Route of administration	IV	IV	IV following CPHPC to deplete SAP
Clinical Development	Phase 2/3	Phase 1/2/3	Phase 2

ClinicalTrials.gov Identifiers: 1. NCT03168906; 2, NCT02632786; 3. NCT02312206; 4. NCT01707264; 5. NCT02245867; 6. NCT02603172

Phase Ia/Ib Study of Chimeric Fibril-Reactive Monoclonal Antibody 11-1F4 (CAEL-101) in Patients with AL Amyloidosis

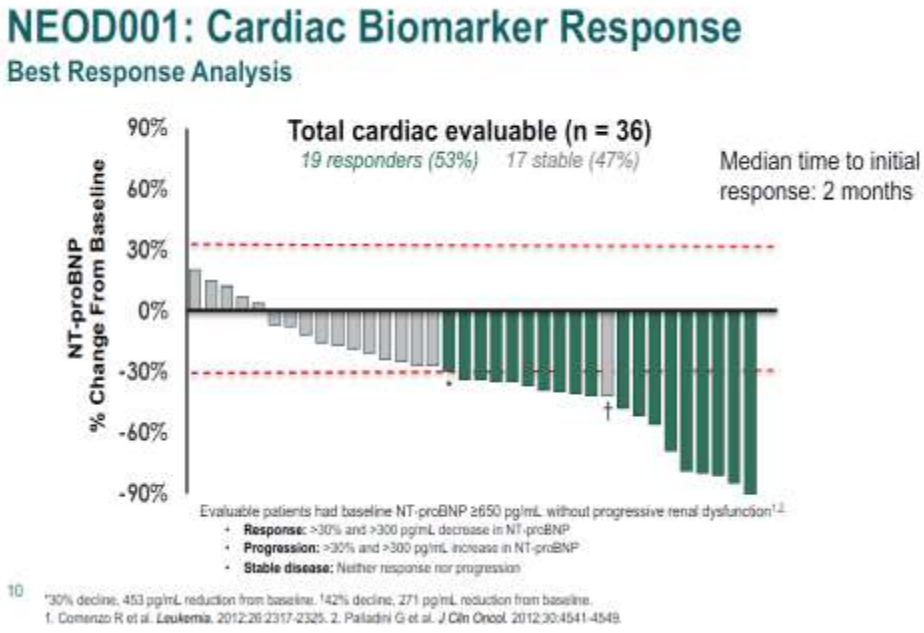


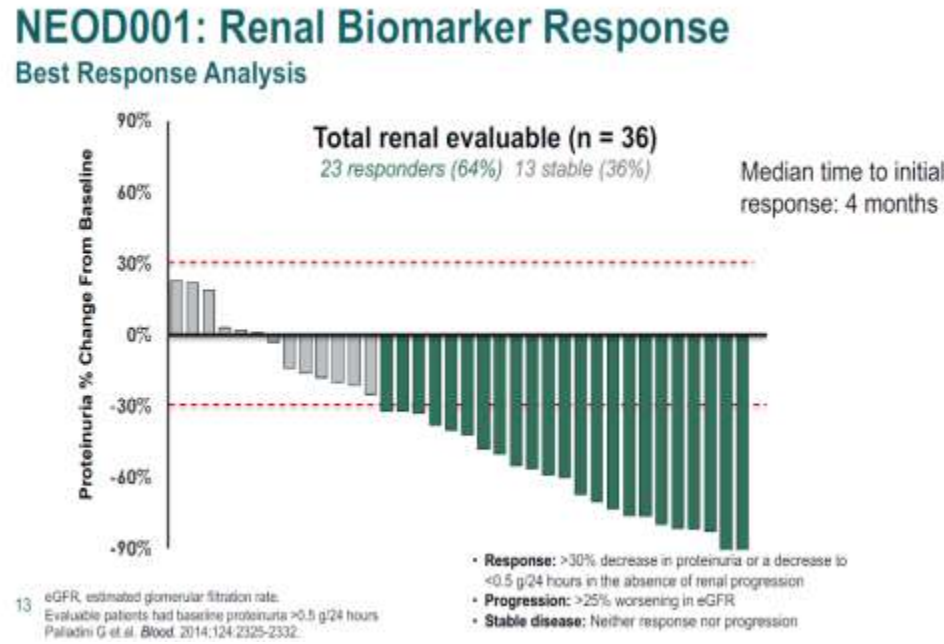
N=24 evaluable for organ response

- 12/18 (67%) ORs
- 8/12 cardiac
- 5/10 renal
- No organ progression
- Median time to response: 3 weeks

Edwards CV, et al ASH 2017 (Abstract 509) oral presentation;
ClinicalTrials.gov Identifier: NCT02245867

NEOD-001: phase 1/2 clinical efficacy





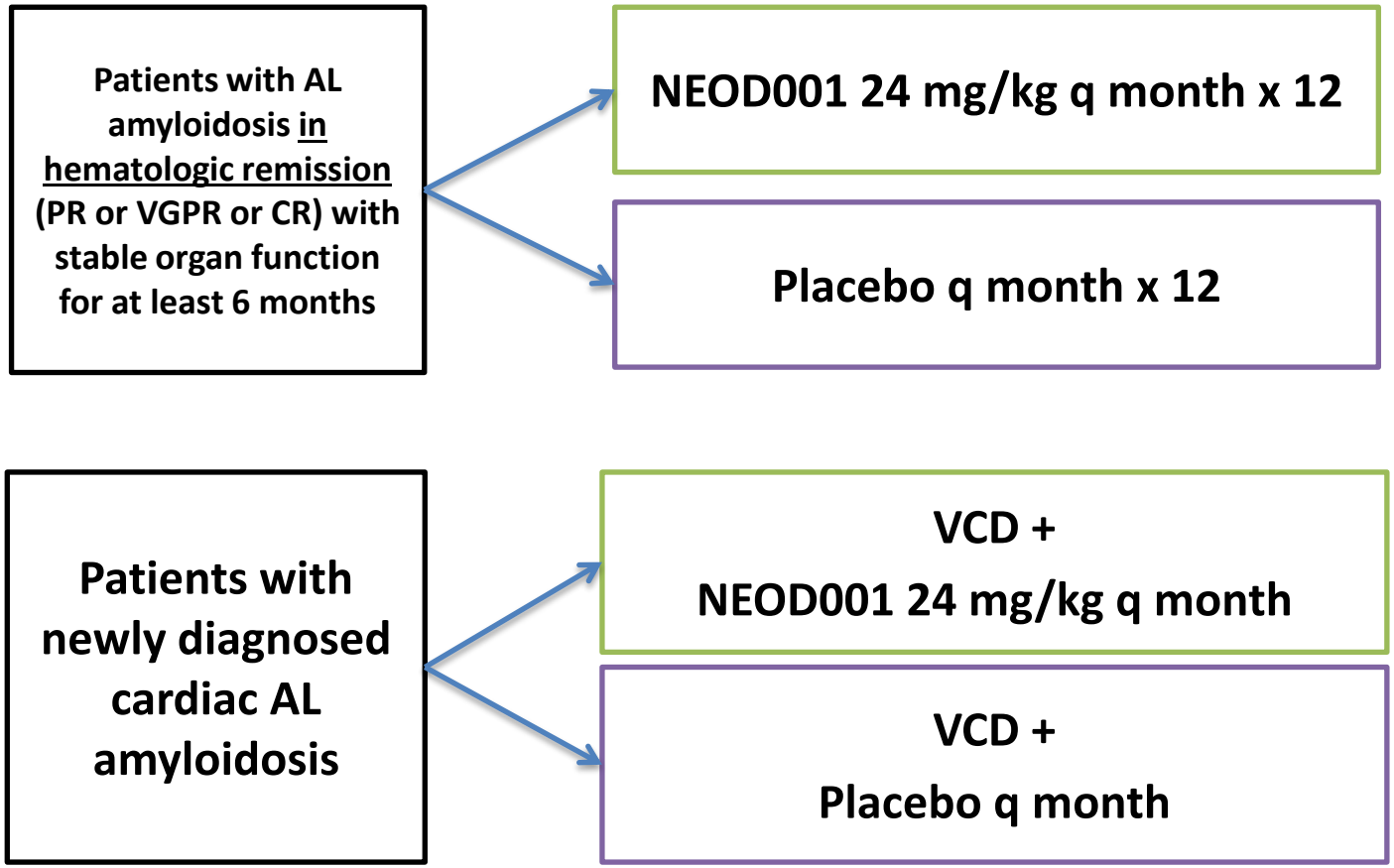
No significant toxicity

IRR rates low

All patients were in sustained hematologic remission

Gertz et al ASH 2016 (Abstract 644) oral presentation

PRONTO & VITAL studies (both have completed accrual)



ClinicalTrials.gov Identifiers: NCT02632786 (PRONTO); NCT02312206 (VITAL)

Μακροσφαιριναιμία Waldenström

PCYC-1127 (iNNOVATE™) Study Design

Key eligibility criteria

- Confirmed WM (N=~150)
- Measurable disease (serum IgM > 0.5 g/dL)
- ECOG PS status of 0–2

RANDOMIZE 1:1

Arm A

ibrutinib + rituximab

Oral ibrutinib 420 mg once daily PO until PD

rituximab 375 mg/m² IV

on day 1 of weeks 1-4 and weeks 17-20

Arm B*

placebo + rituximab

3 matching placebo capsules until PD

rituximab 375 mg/m2 IV

on day 1 of weeks 1-4 and weeks 17-20

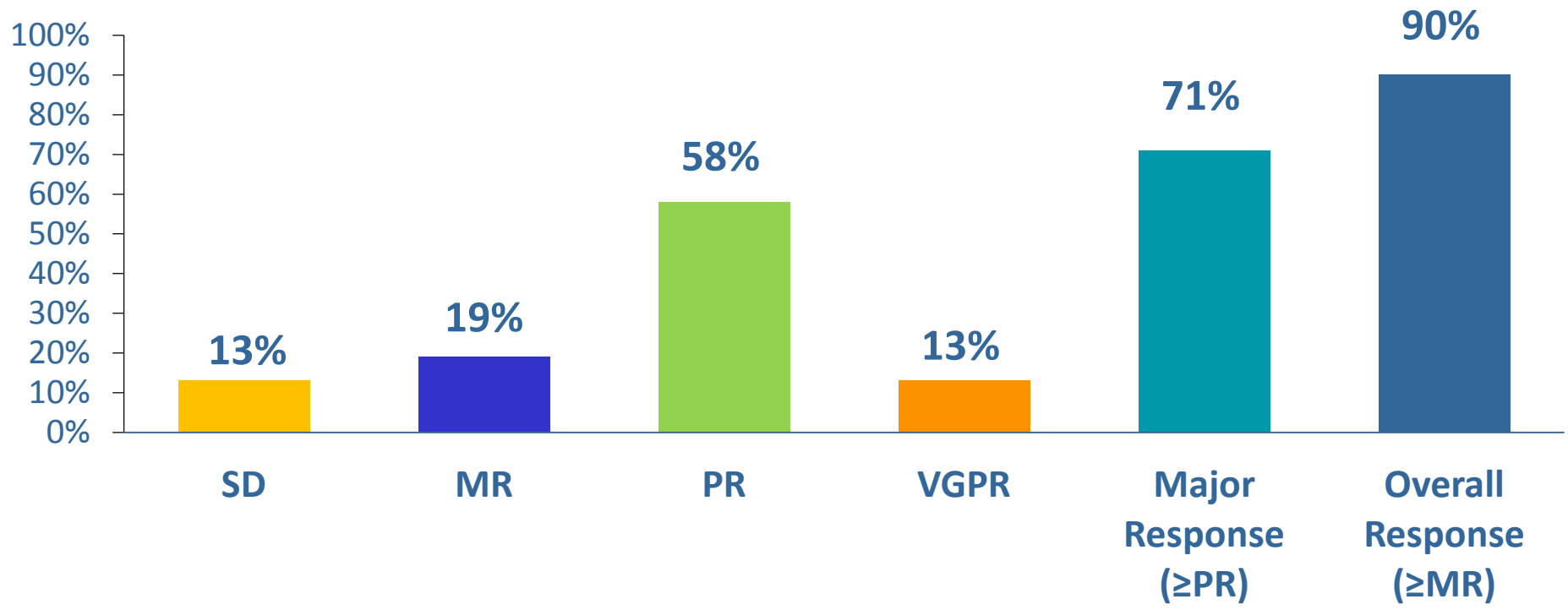
*crossover to ibrutinib for patients treated with placebo confirmed disease progression (by IRC) and disease requiring treatment.

- If refractory to last rituximab-containing regimen defined as
  - Relapse after <12 months of treatment
  - **OR**
  - Failure to achieve at least a MR

Arm C (Open-label substudy; N=31)†
Not eligible for randomization

ibrutinib 420 mg once daily PO until PD

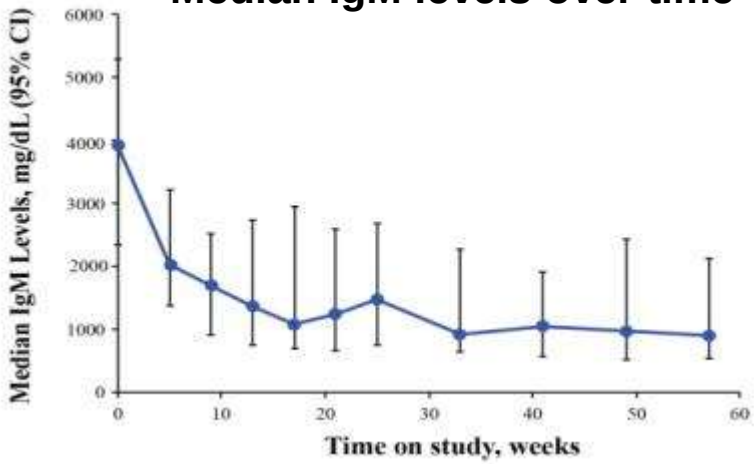
Response to single agent ibrutinib in patients refractory to rituximab (N=31)



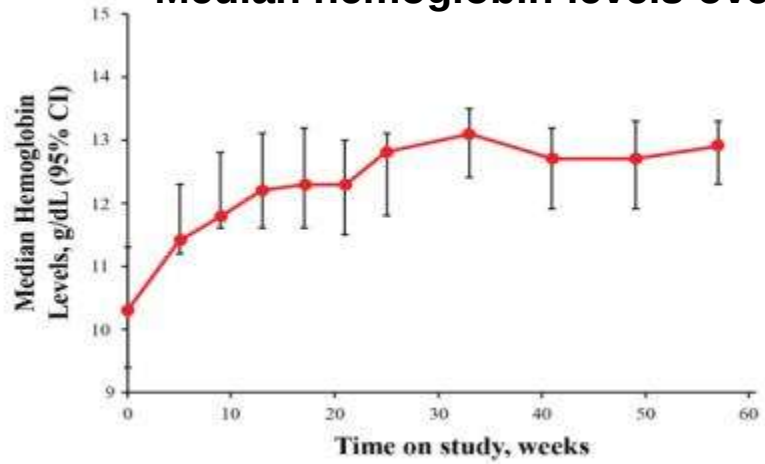
Dimopoulos MA et al Lancet Oncol 2016

Response to single agent ibrutinib: IgM & hemoglobin response, PFS & OS

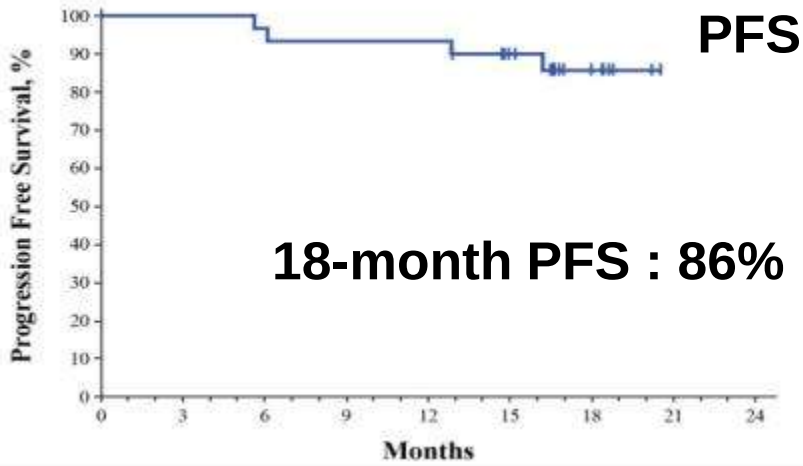
Median IgM levels over time



Median hemoglobin levels over time

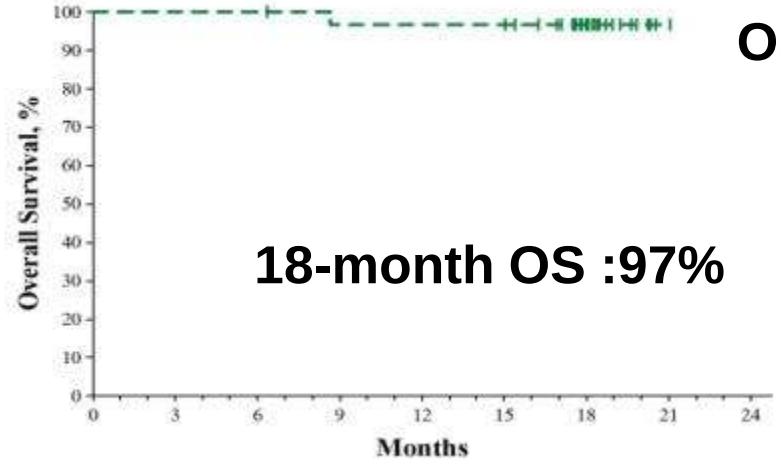


PFS



18-month PFS : 86%

OS



18-month OS :97%

Dimopoulos MA et al Lancet Oncol 2016

Ibrutinib Is Highly Active As First Line Therapy in Symptomatic Waldenström's Macroglobulinemia

- N=30 patients with newly diagnosed WM (median age 67)
- All patients expressed $MYD88^{L265P}$ - 14 (47%) had a $CXCR4^{mut}$.
- ORR: 96.7% , ≥PR: 80%, VGPR: 17% - No CRs
- Median follow-up: 8.1 months, two patients PD, both $CXCR4^{mut}$
- Three patients (10%) had treatment-related atrial arrhythmia
- $CXCR4^{mut}$ associated with delays in ibrutinib response

(ClinicalTrials.gov number, NCT02604511).

Treon SP et al ASH 2017 Abstract #2767

New BTK-Inhibitors in WM

1. BGB3111[1]
   - Phase 1/2 – pretreated WM (relapsed or refractory)
   - **≥PR: 83% (20/24), with VGPR in 33% (8/24)**
   - **Median time to initial response and major response were 29 days and 34 days**
   - **Ongoing clinical trial: BGB3111 vs ibrutinib in patients with WM (NCT03053440)**

2. Acalabrutinib
   - Phase 2 study completed
   - Results to be announced in ASCO 2018

[1]Tam CS ASH 2016 Abstr#1216

Targeting Bcl-2: Venetoclax in WM

- Phase 1 study in patients with Relapsed or Refractory NHL
- N=4 patients with RR-WM (median 4 prior lines)
- High Bcl-2 expression : 3/3*

*** (by IHC defined as ≥ 50% lymphoma cells scored 2+ or 3+)**

Table 3. Objective Responses by Histology (all doses, intention to treat)

Best Objective Response	All Patients (N = 106)*	MCL (n = 28)	FL (n = 29)	DLBCL (n = 34)*†	DLBCL-RT* (n = 7)	MZL (n = 3)
	No. (%)					
Overall response	47 (44)	21 (75)	11 (38)	6 (18)	3 (43)	2 (67)
CR	14 (13)	6 (21)	4 (14)	4 (12)	0	0
PR	33 (31)	15 (54)	7 (24)	2 (6)	3 (43)	2 (67)
SD	32 (30)	5 (18)	17 (59)	8 (24)	2 (29)	0
PD	24 (23)	2 (7)	1 (3)	19 (56)	1 (14)	1 (33)

WM (n = 4)
4 (100)
0
4 (100)
0
0

Median time to first response 74.5 days

DOR for the four patients with WM was 11.1, 12.4, 38.2, and 41.5 months

Phase 2 study in Relapsed Or Refractory WM ongoing (NCT02677324)

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