



ΤΑ ΜΟΝΟΠΑΤΙΑ ΤΩΝ ΝΟΣΗΜΑΤΩΝ ΩΣ ΠΗΓΗ ΚΑΙΝΟΤΟΜΙΑΣ ΣΤΗ ΘΕΡΑΠΕΥΤΙΚΗ

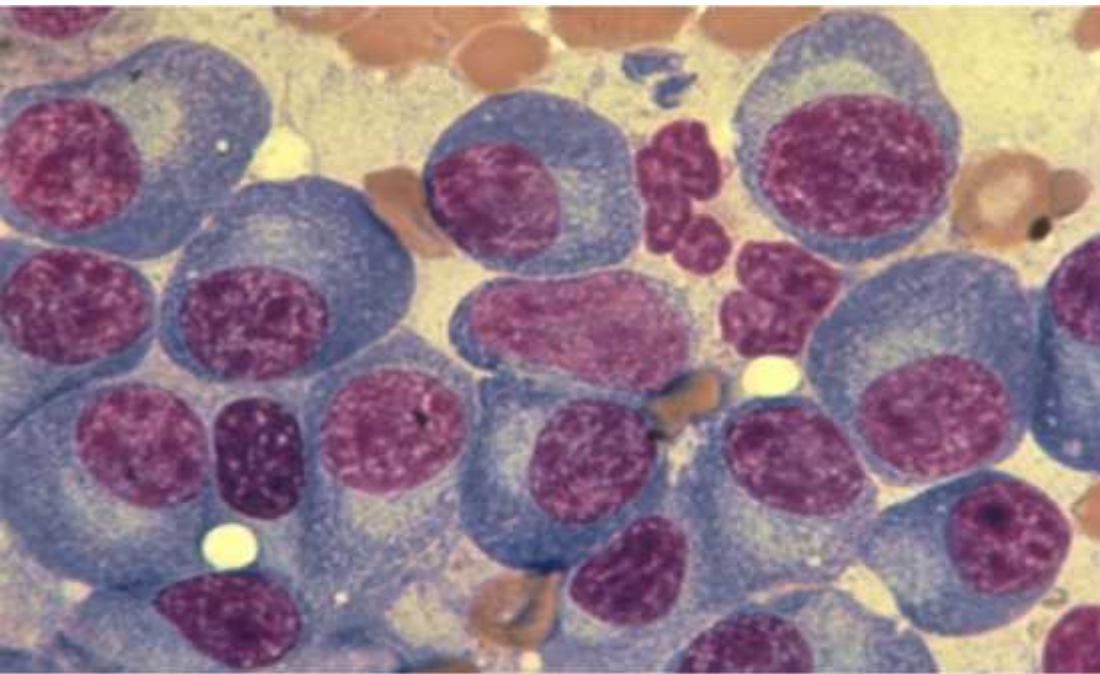
Πολλαπλούν Μυέλωμα



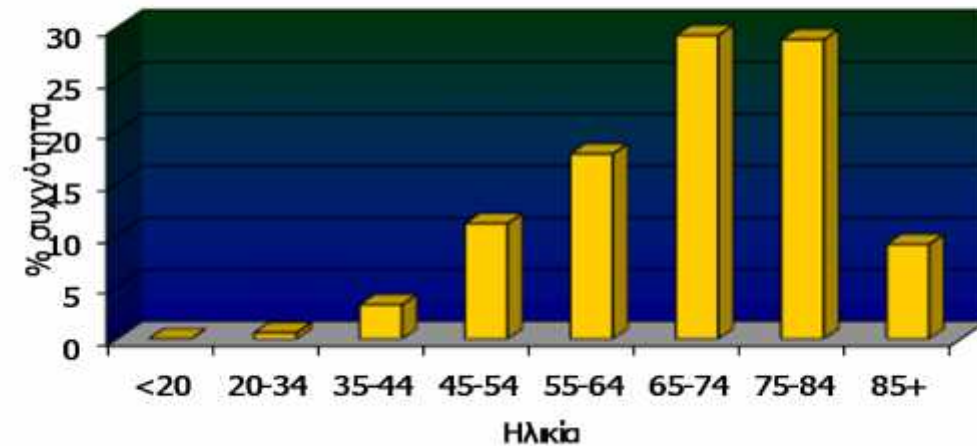
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Εισαγωγή

ο πολλαπλούν μυέλωμα χαρακτηρίζεται από τον μονοκλωνικό πολλαπλασιασμό συσώρευση ανώμαλων πλασματοκυττάρων στο μυελό των οστών.



Ηλικιακή κατανομή του ΠΜ (%) τα έτη 1996-2016 (NCI 2016)



Κλινική Εικόνα του Μυελώματος



Άλλες κλινικές εκδηλώσεις της νόσου

IgG 50%

IgA 25%

BJ 20%

IgD 1% IgE < 1%

ME 1% IgM < 1%



Υπεργλοιοότητα:
10% των ασθενών
IgA > IgG
IgG₃

επιστάξεις, κεφαλαλγία, σύγχυση
οπτικές διαταραχές
διαταραχές από το ΚΑ

Όταν η γλοιοτητα >4 φορές του φυσιολογικού

Διήθηση μυελού:

αναιμία
ουδετεροπενία
θρομβοπενία

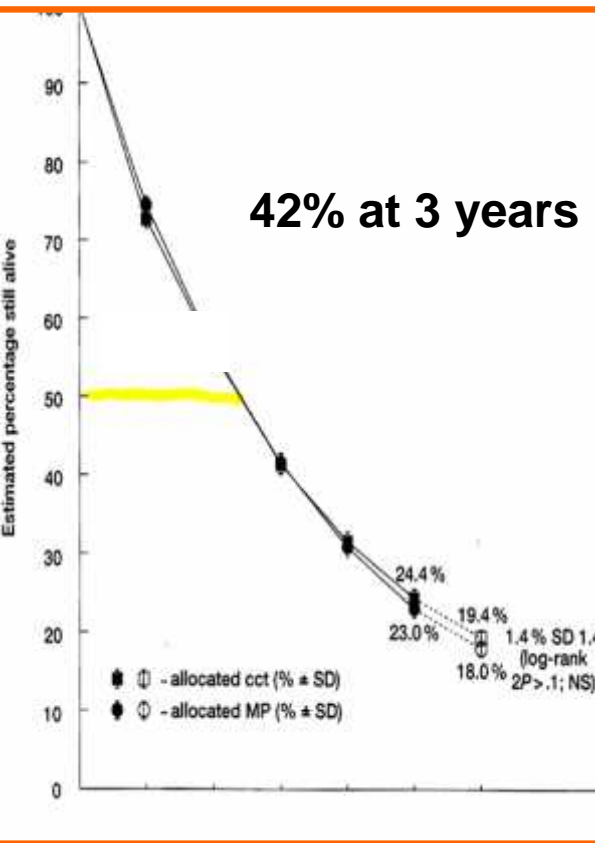
Ανοσοπάρεση

ΛΟΙΜΩΞΕΙΣ
πνευμονιόκοκκος
αιμόφιλος, έρπη

Νεφρική ανεπάρκεια
εναπόθεση ελαφρών αλυσίδων
υπερασβεστιαμία
αμυλοείδωση
λοιμώξεις
υπερουριχαιμία
αντιφλεγμονώδη

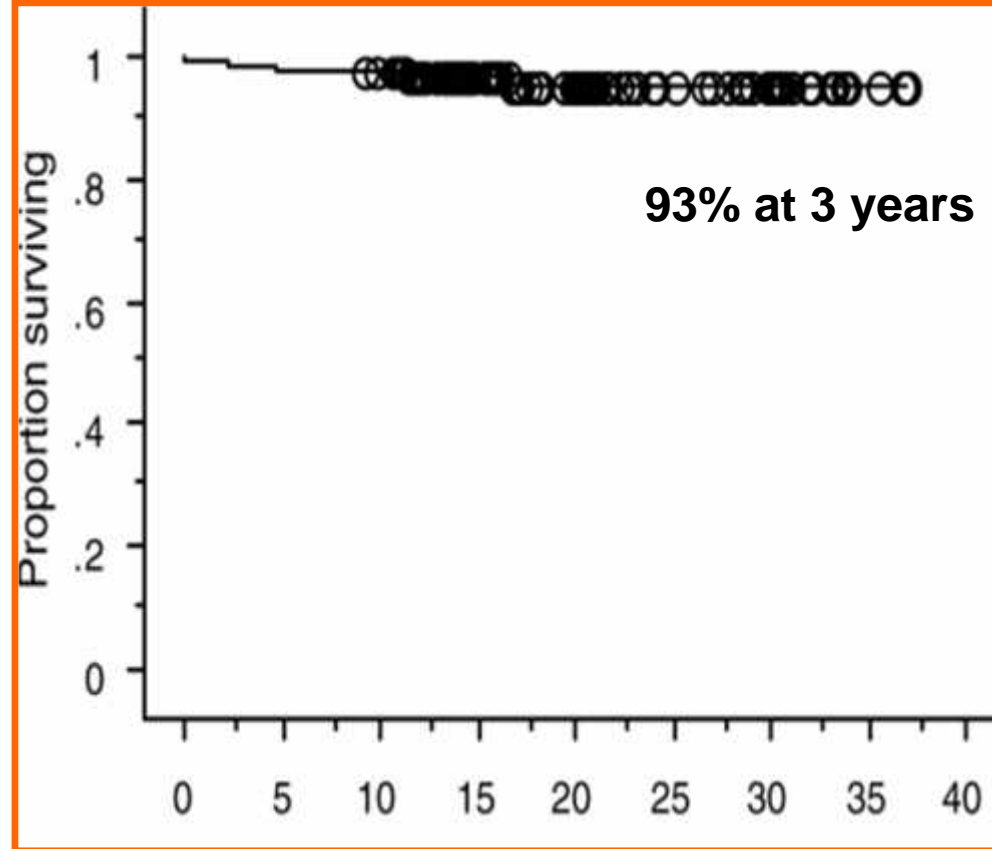
Η Επιβίωση στο Μυέλωμα

1998



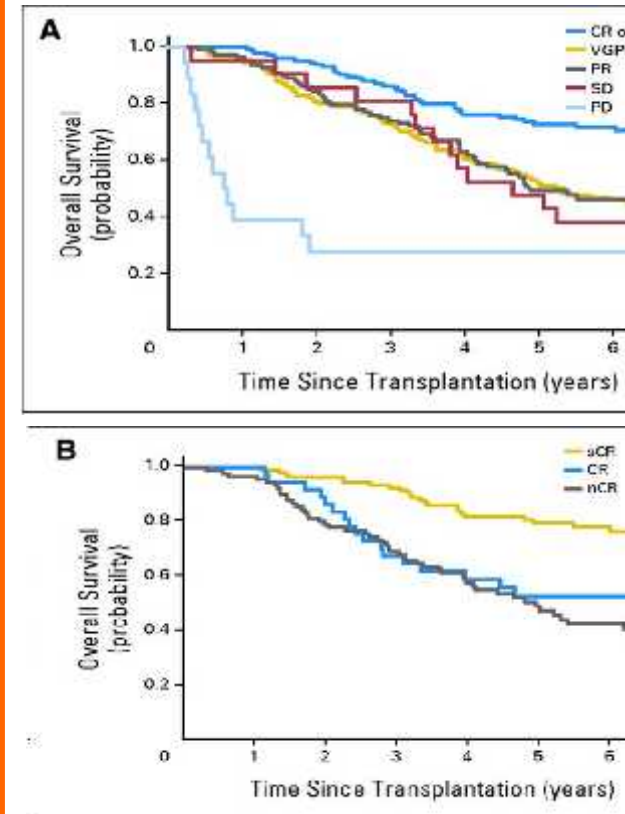
MTCG. J Clin Oncol 1998;16:3832

2008



Menon et al. Cancer 2008;112:1522-8

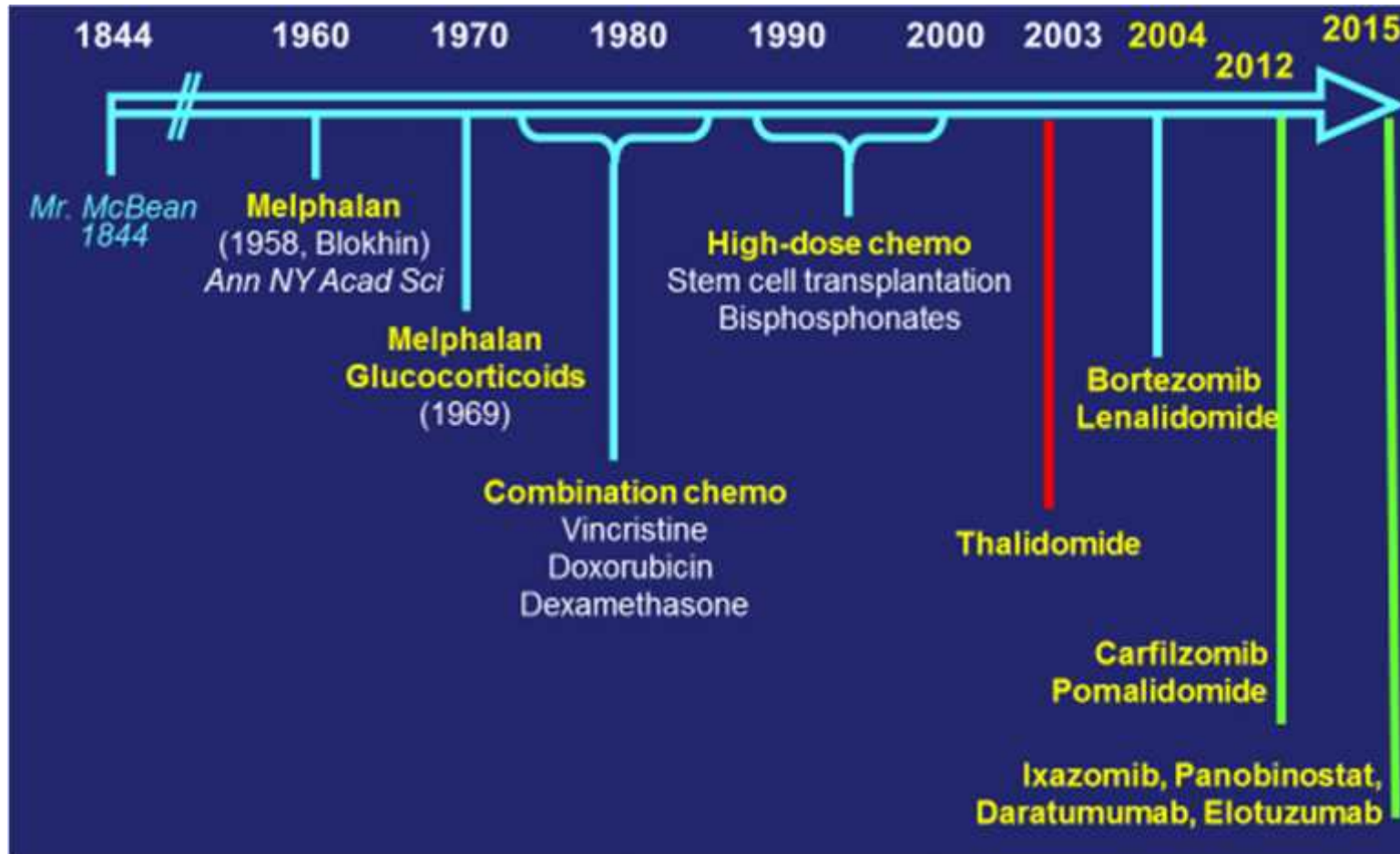
2013



Kapoor et al. J Clin Oncol 2013;31:4529



Θεραπεία του Μυελώματος



Οι γενετικές βλάβες στο Μυέλωμα

Primary events:

IGH translocations

t(4;14)

t(6;14)

t(11;14)

t(14;16)

t(14;20)

Hyperdiploidy

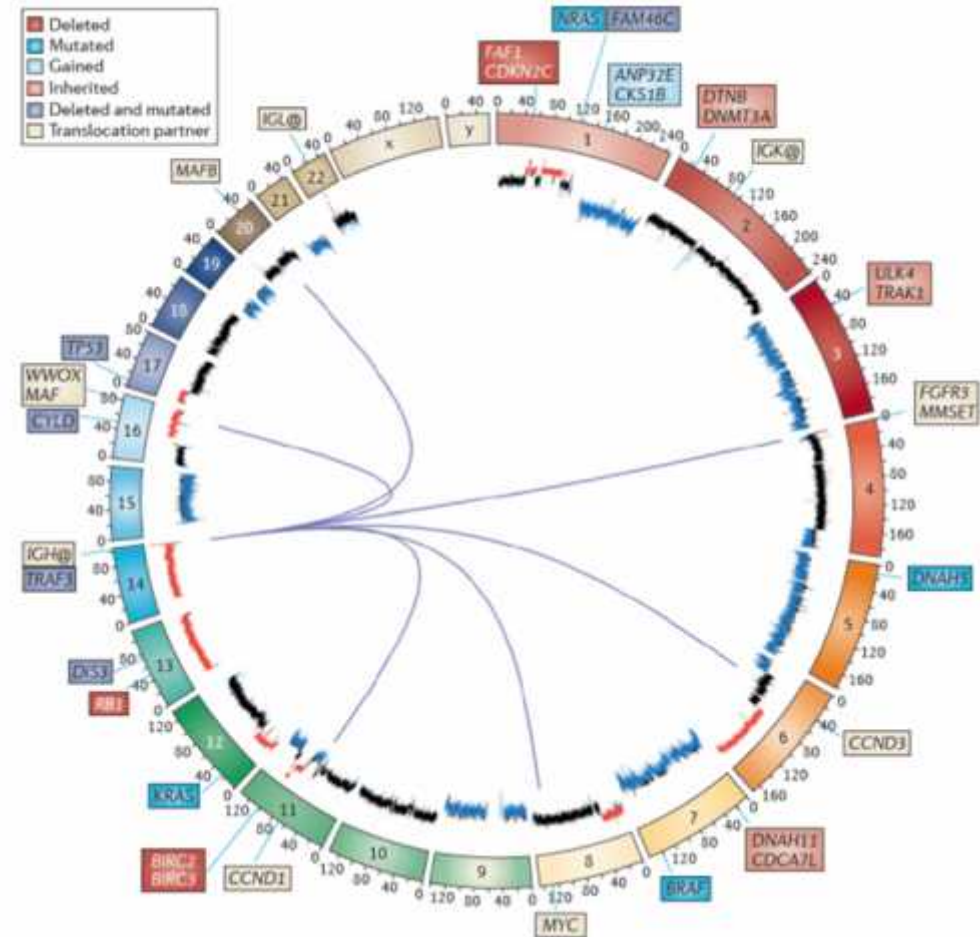
Secondary events:

t(8;14); translocations at 8q24

Copy Number Abnormalities:

Deletions: 1p, 6q, 8p, 12p, 13q,
14q, 16q, 17p

Gains: 1q+,
trisomic chromosomes



Initial genome sequencing and analysis of multiple myeloma

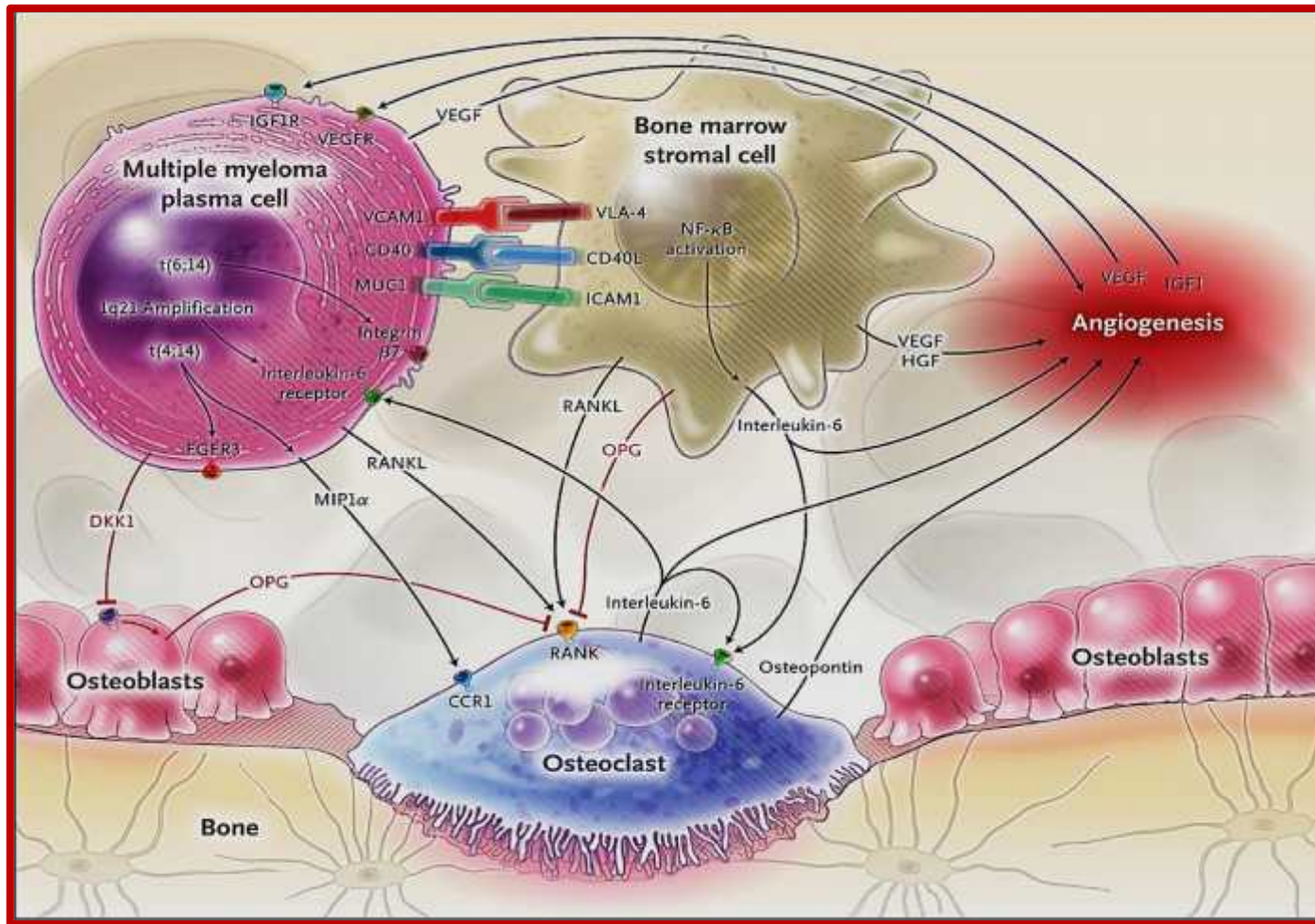
Michael A. Chapman^{1†}, Michael S. Lawrence¹, Jonathan J. Keats^{2,3}, Kristian Cibulskis¹, Carrie Sougnez¹, Anna C. Schinzel⁴, Marina L. Harview¹, Jean-Philippe Brunet¹, Gregory J. Ahmann^{2,3}, Mazhar Adli^{1,5}, Kenneth C. Anderson^{3,4}, Kristin G. Ardlie¹, Benjamin A. Auclair^{3,6}, Angela Baker⁷, P. Leif Bergsagel^{2,3}, Bradley E. Bernstein^{1,5,8,9}, Yotam Drier^{1,10}, Rafael Fonseca^{2,3}, Benjamin B. Gabriel¹, Craig C. Hofmeister^{3,11}, Sundar Jagannath^{3,12}, Andrzej J. Jakubowiak^{3,13}, Amrita Krishnan^{3,14}, Joan Levy^{3,6}, Jeffrey M. Pfeiffer¹, Sagar Lonial^{3,15}, Scott Mahan¹, Bunmi Mfuko^{3,6}, Stefano Monti¹, Louise M. Perkins^{3,6}, Robb Onofrio¹, Trevor J. Pugh¹, Vincent Rajkumar^{3,16}, Alex H. Ramos¹, David S. Siegel^{3,17}, Andrey Sivachenko¹, A. Keith Stewart^{2,3}, Suzanne Trudel^{3,18}, Robert M. Vij^{3,19}, Douglas Voet¹, Wendy Winckler¹, Todd Zimmerman^{3,20}, John Carpten⁷, Jeff Trent⁷, William C. Hahn^{1,4,8}, Michael J. Garraway^{1,4}, Matthew Meyerson^{1,4,8}, Eric S. Lander^{1,8,21}, Gad Getz¹ & Todd R. Golub^{1,4,8,9}

Multiple myeloma is an incurable malignancy of plasma cells, and its pathogenesis is poorly understood. Here we report the results of a massively parallel sequencing of 38 tumour genomes and their comparison to matched normal DNAs. Several new and unexpected oncogenic mechanisms were suggested by the pattern of somatic mutation across the data set. These include the mutation of genes involved in protein translation (seen in nearly half of the patients), genes involved in DNA methylation, and genes involved in blood coagulation. In addition, a broader than anticipated role of NF- κ B signalling was indicated by mutations in 11 members of the NF- κ B pathway. Of potential immediate clinical relevance, activating mutations of the kinase BRAF were observed in 4% of patients, suggesting the evaluation of BRAF inhibitors in multiple myeloma clinical trials. These results indicate that cancer genome sequencing of large collections of samples will yield new insights into cancer not anticipated by existing knowledge.

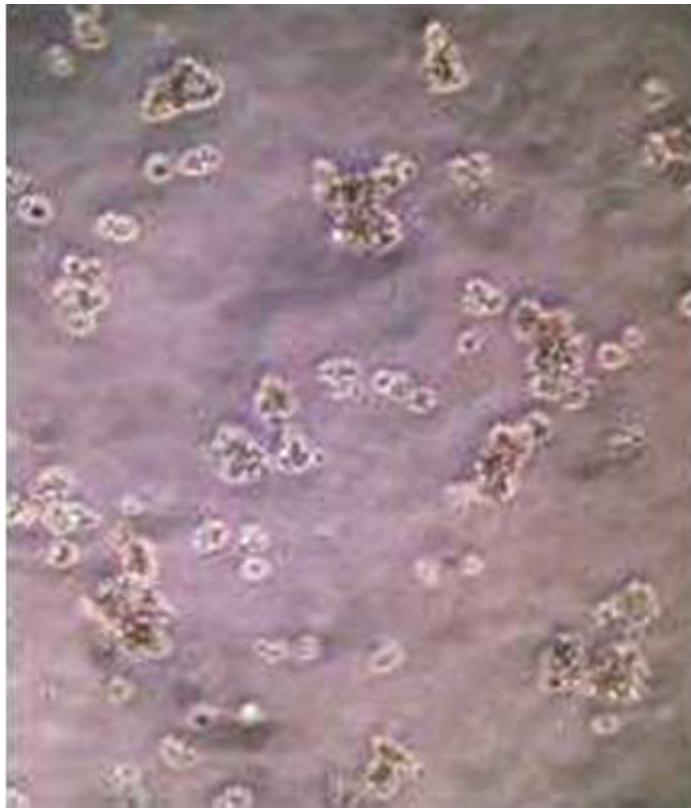
- There is no unifying mutation in myeloma
- Most frequently mutated genes found at 15% in untreated patients
- Requires biological pathway analysis
- Identified NF- κ B pathway, histone modifying enzymes and RNA processing as enriched pathways
- Also identified *BRAF* mutations in 4% of myeloma samples



Αλληλεπιδράσεις του μυελωματικού κυττάρου με το μικροπεριβάλλον του



Αλληλεπιδράσεις του μυελωματικού κυττάρου με το μικροπεριβάλλον του



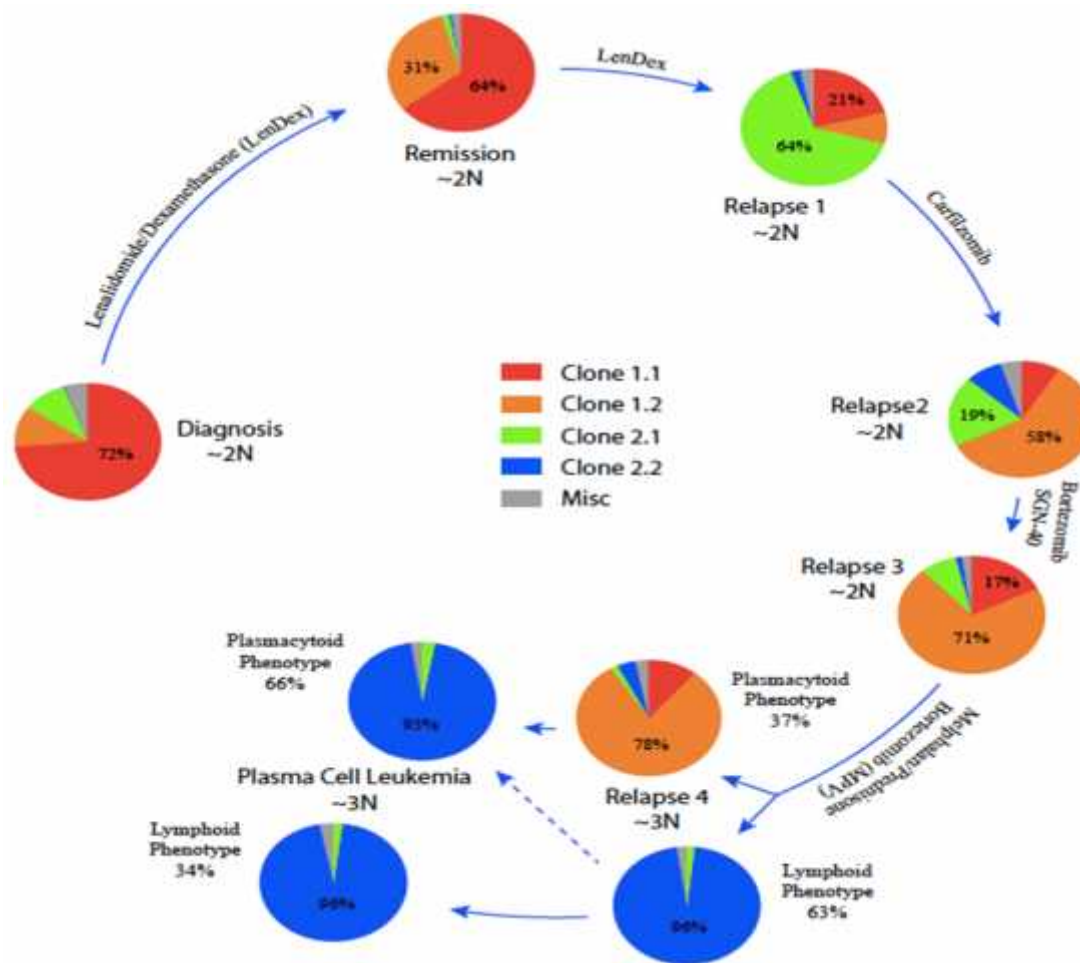
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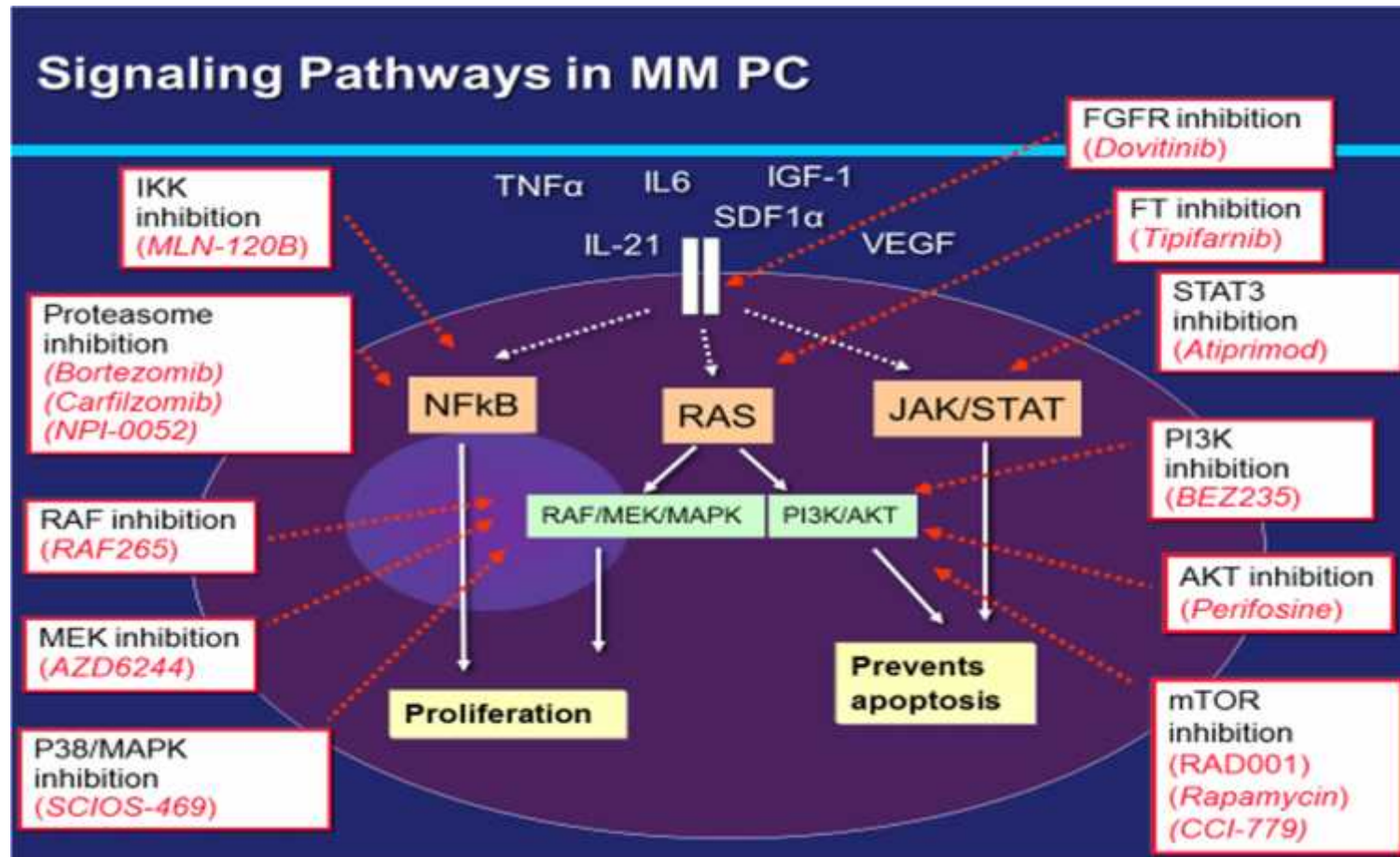
μ 14 μ



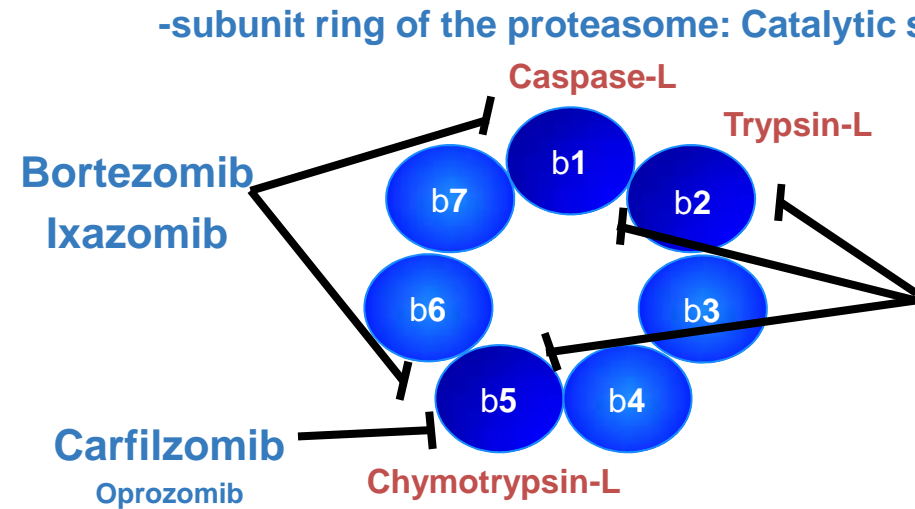
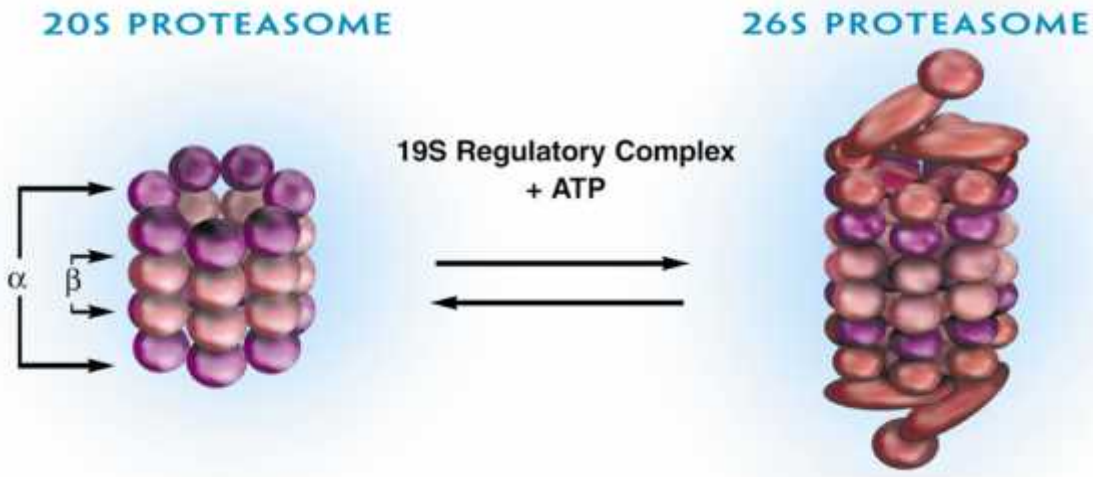
Κλωνική Ετερογένεια στο Πολλαπλό Μυέλωμα



Φάρμακα που στοχεύουν βιολογικούς δρόμους στο ΠΜ



Οι αναστολείς πρωτεασώματος στο Μυέλωμα

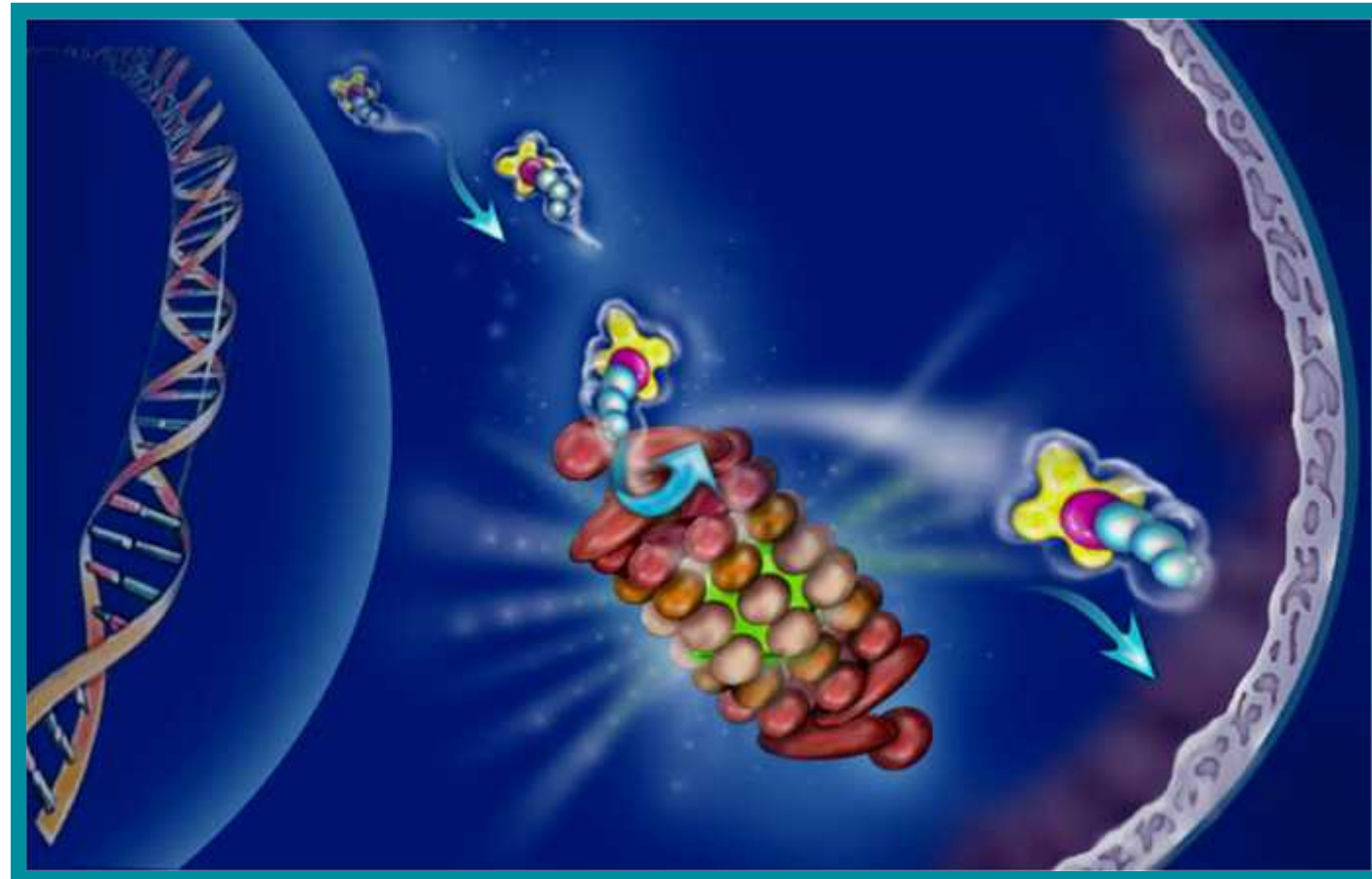
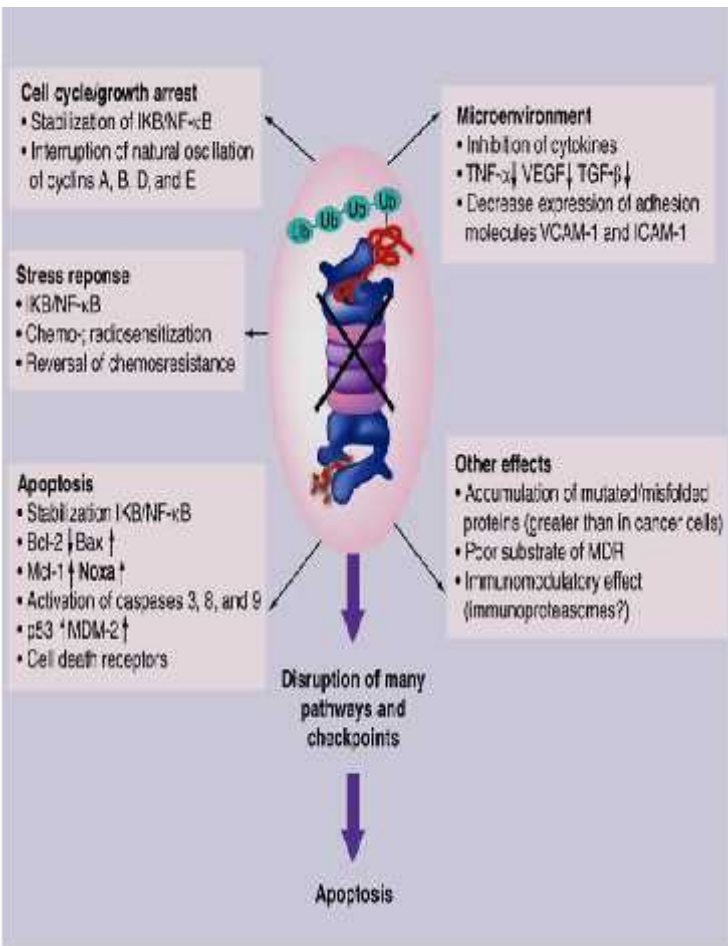


The proteasome is an intracellular enzyme complex responsible for the degradation of regulatory and misfolded and potentially toxic proteins.

Biological effects of proteasome inhibition:
 Inhibition of proliferation
 Cell cycle arrest
 Induction of stress and unfolded protein response
 Inhibition of NF-κB pathway

	Type	Catalytic inhibition			Reversibility	PO/IV	Dose
		Chymotrypsin	Caspase	Trypsin			
Bortezomib	Boronate	X	X		Reversible	IV	1, 4, 8, 12
Ixazomib	Boronate	X	X		Reversible	PO	1, 8, 12
Carfilzomib	Epoxi-ketone	X			Irreversible	IV	1-2, 8-9, 12
Oprozomib (PR-047)	Epoxi-ketone	x			Irreversible	PO	BID
Marizomib (NPI-0052)	Salinospore	X	X	X	Irreversible	IV	1, 4, 8, 12
CEP-18770	Boronate	X	X		Reversible	IV	1, 4, 8, 12

Αναστολείς πρωτεασώματος: μηχανισμοί δράσης



Bortezomib: απαραίτητο στα σχήματα προετοιμασίας για αυτόλογη μεταμόσχευση

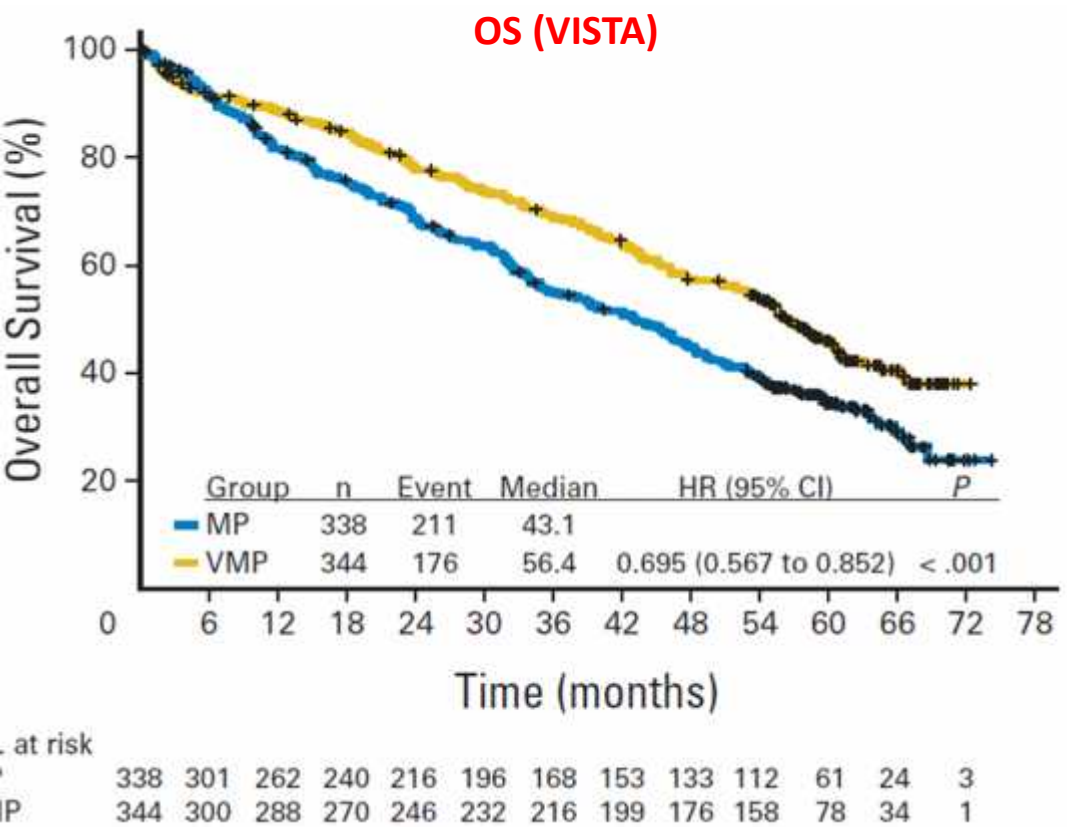
Integrated analysis (n=1572) of 3 randomized trials:
Bortezomib-based versus non-bortezomib-based induction regimens

Response rate	Bortezomib-based induction (n=775)	Non-bortezomib-based induction (n=772)	OR	95% CI	P
Post-transplant (%)					
CR+nCR	38	24	2.05	1.64–2.56	< 0.001

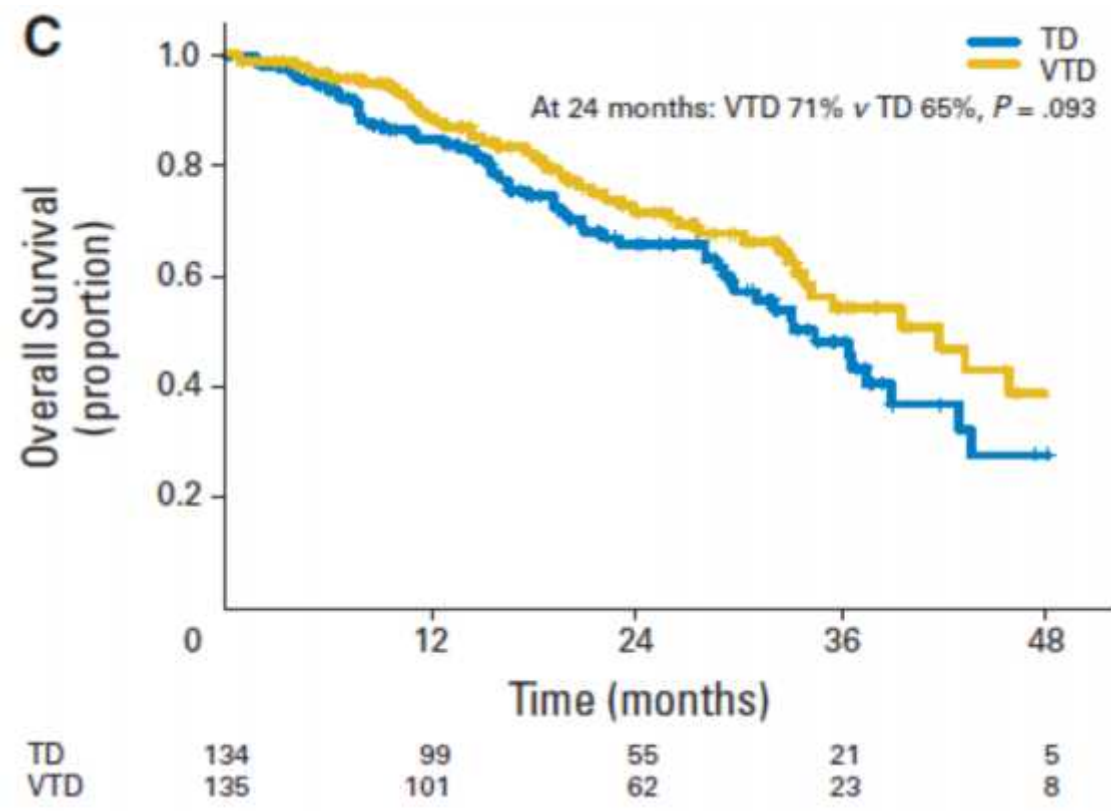
Median follow-up ~37 months

	Bortezomib-based induction	Non-bortezomib-based induction	HR	95% CI	P
Median PFS, mos	35.9	28.6	0.75	0.65–0.85	< 0.001
3-yr PFS, %	50.0	41.1			

Bortezomib και στην πρώτη γραμμή των ηλικιωμένων και στο υποτροπιάζον Μυέλωμα

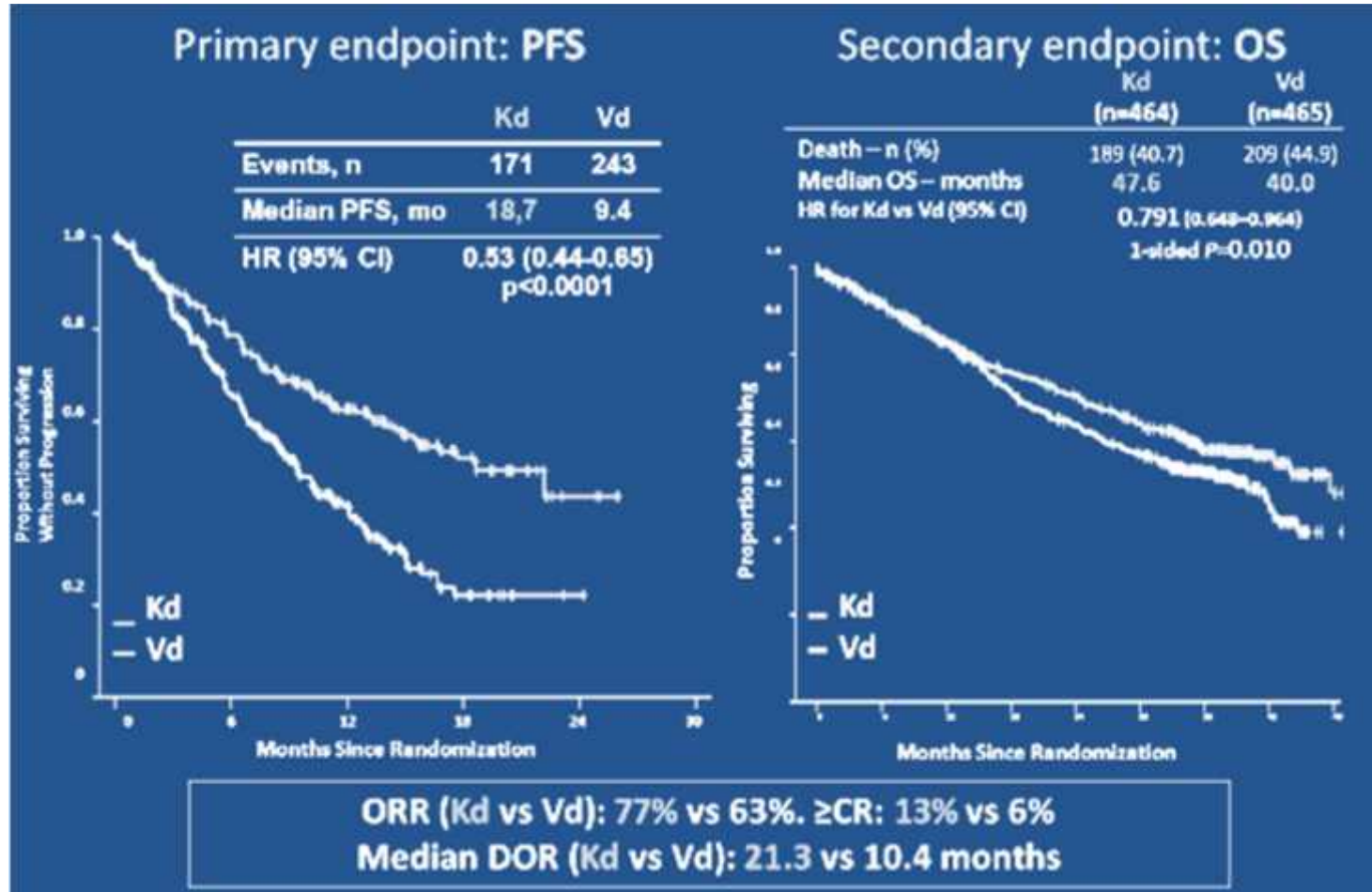


San Miguel JF, et al. J Clin Oncol 2013; 31:448-455;

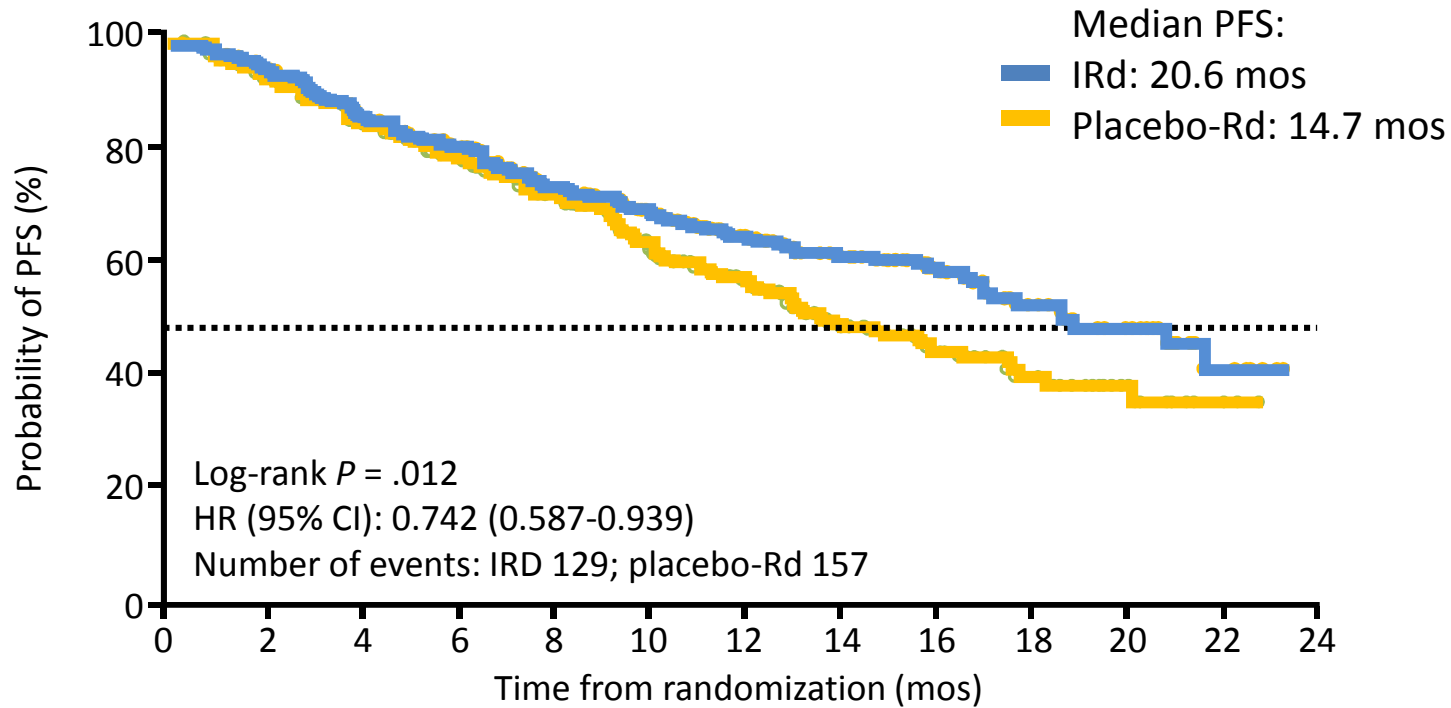


Garderet L, et al. J Clin Oncol 2012;30:2475-82.

Carfilzomib: νέος ανασταλτής πρωτεασώματος



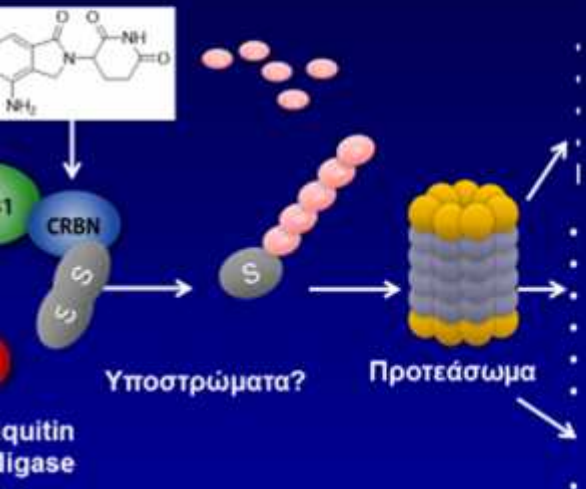
Ιxazomib: ο πρώτος από του στόματος ανασταλτής πρωτεασώματος



FS benefit with ixazomib seen in all prespecified subgroups, including cytogenetic high risk, PI and IMiD exposed

Ανοσοτροποποιητικά Φάρμακα (IMiDs): Μηχανισμοί δράσης

IMiDs® δεσμεύονται από μίαν E3 Ligase μέσω του CRBN με πλειότροπες κλινικές επιδράσεις



Τα IMiDs® δεσμεύονται από μία E3 Ligase μέσω του CRBN με πλειότροπες κλινικές επιδράσεις



potency + = potency factor of 10

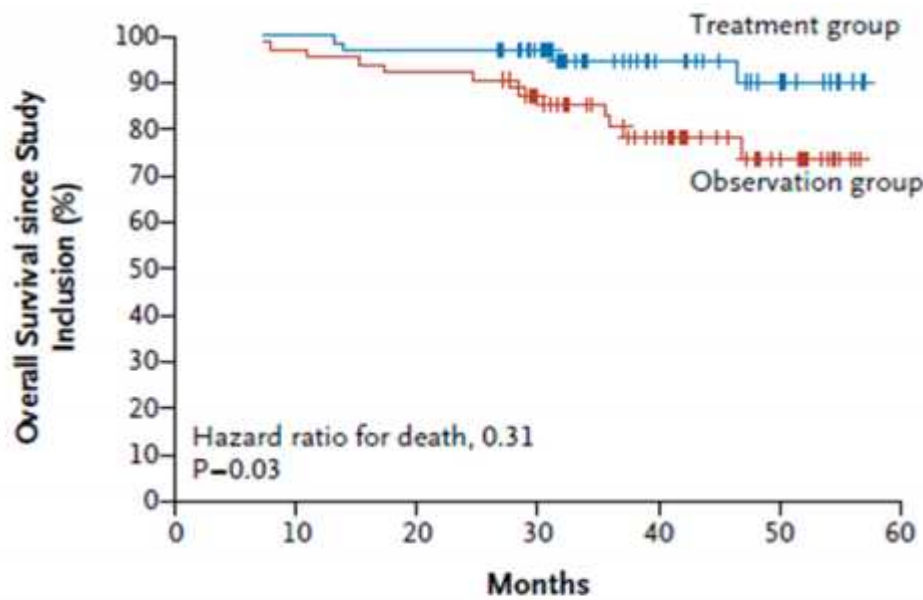
	Lenalidomide	Pomalidomide
	++++	+++++
	+	+
	++++	+++++
	++++	+++++
	++++	++++
	+++	+++
	++++	+++++
	+++	+++
	Primarily urinary excretion; ~80% as parent	Urinary excretion; ~2% as parent
	Myelosuppression, DVT	Myelosuppression

Lopez-Girona A, et al. Leukemia. 2012;26:2328-35.
Carter S, et al. Nat Cell Biol. 2007;9:428-35.
Xu Y, et al. Blood. 2009;114:338-45.
Noonan K. Clin Cancer Res. 2012;18:1426-34.
Chauhan D. Blood. 2010;115:834-45.

Quach H, et al. Leukemia. 2010

Λεναλιδομίδη στο Μυέλωμα

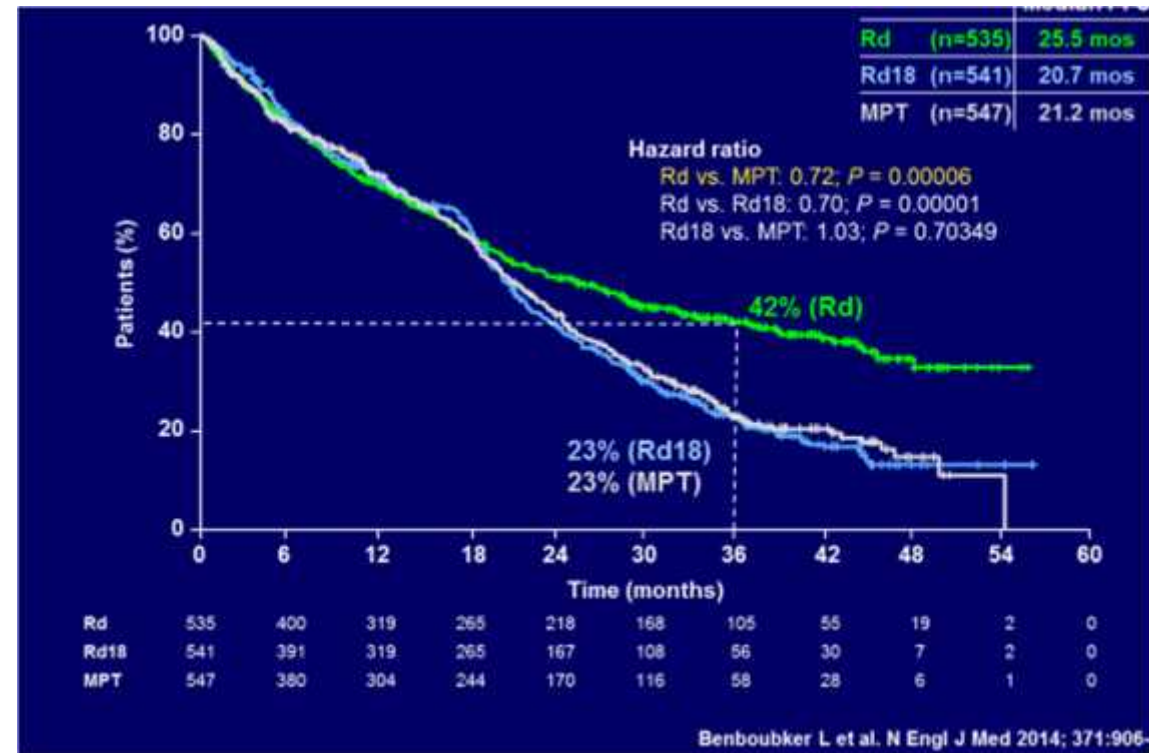
Ασυμπτωματικό ΠΜ



At risk	0	6	12	18	24	30	36	42	48	54	60
Treatment group	57	57	55	48	26	17	0				
Observation group	62	60	57	46	27	17	0				

Mateos et al. N Engl J Med 2013;369:438-47.

Στην πρώτη γραμμής θεραπεία ΠΜ

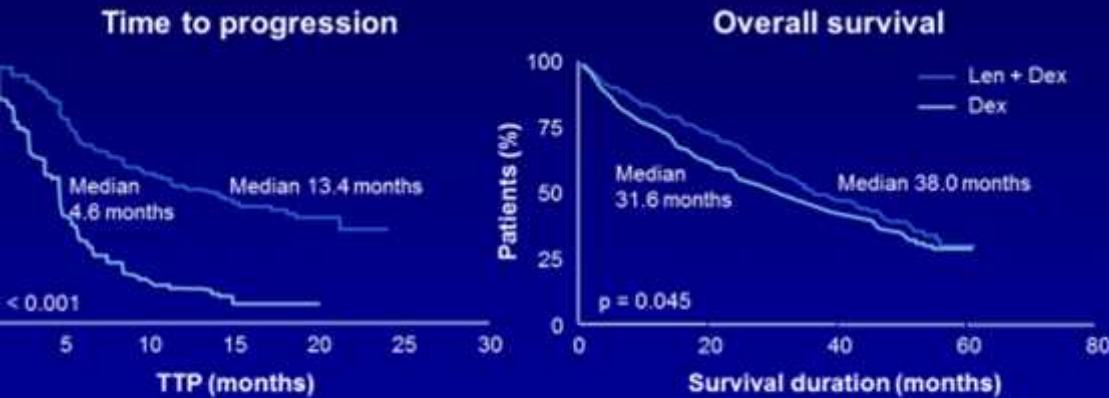


IMiDs στο υποτροπιάζον Μυέλωμα

Longer TTP and OS with Len + Dex vs Dex alone in relapsed/refractory patients

13

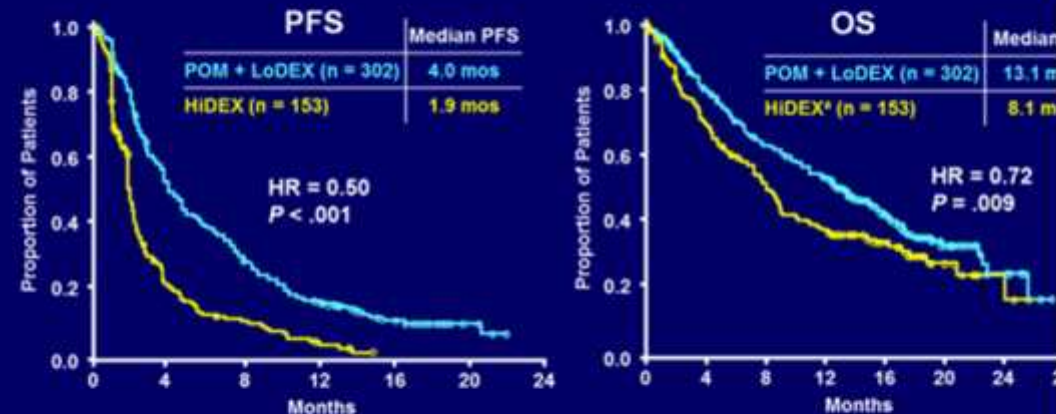
MM-009 and MM-010: pooled analysis



despite 47.6% cross-over of patients who were randomized to dexamethasone-placebo

Dimopoulos MA, et al. Leukemia. 2009;23:2147-52.

Pomalidomide + LoDex vs HiDex (MM-003): PFS



Significant reduction in PD

Significant improvement in OS

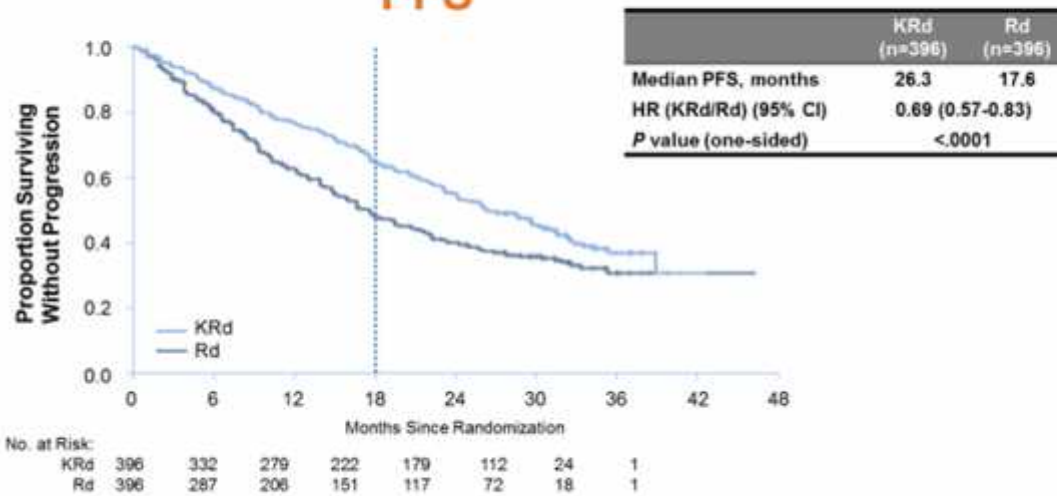
POM + LoDEX consistently resulted in favorable HRQoL vs. HiDEX in MM-

San Miguel et al. Lancet Oncol 2013;14



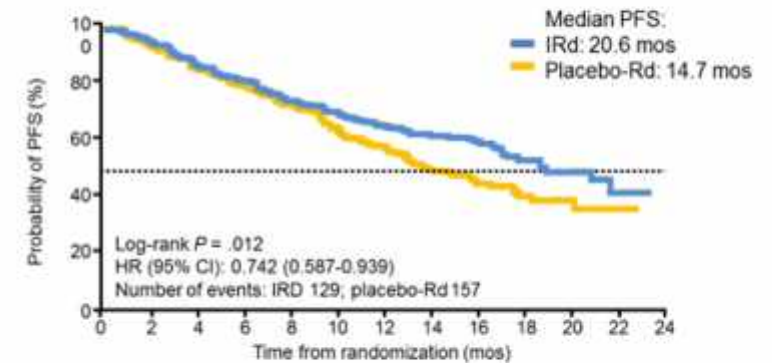
Συνδυασμοί PIs + IMiDs στο υποτροπιάζον Μυέλωμα

E: Lenalidomide/Dexamethasone +/- Carfilzomib – PFS



et al. *N Engl J Med.* 2015;372(2):142-152.

TOURMALINE-MM1: RD +/- Ixazomib – PFS



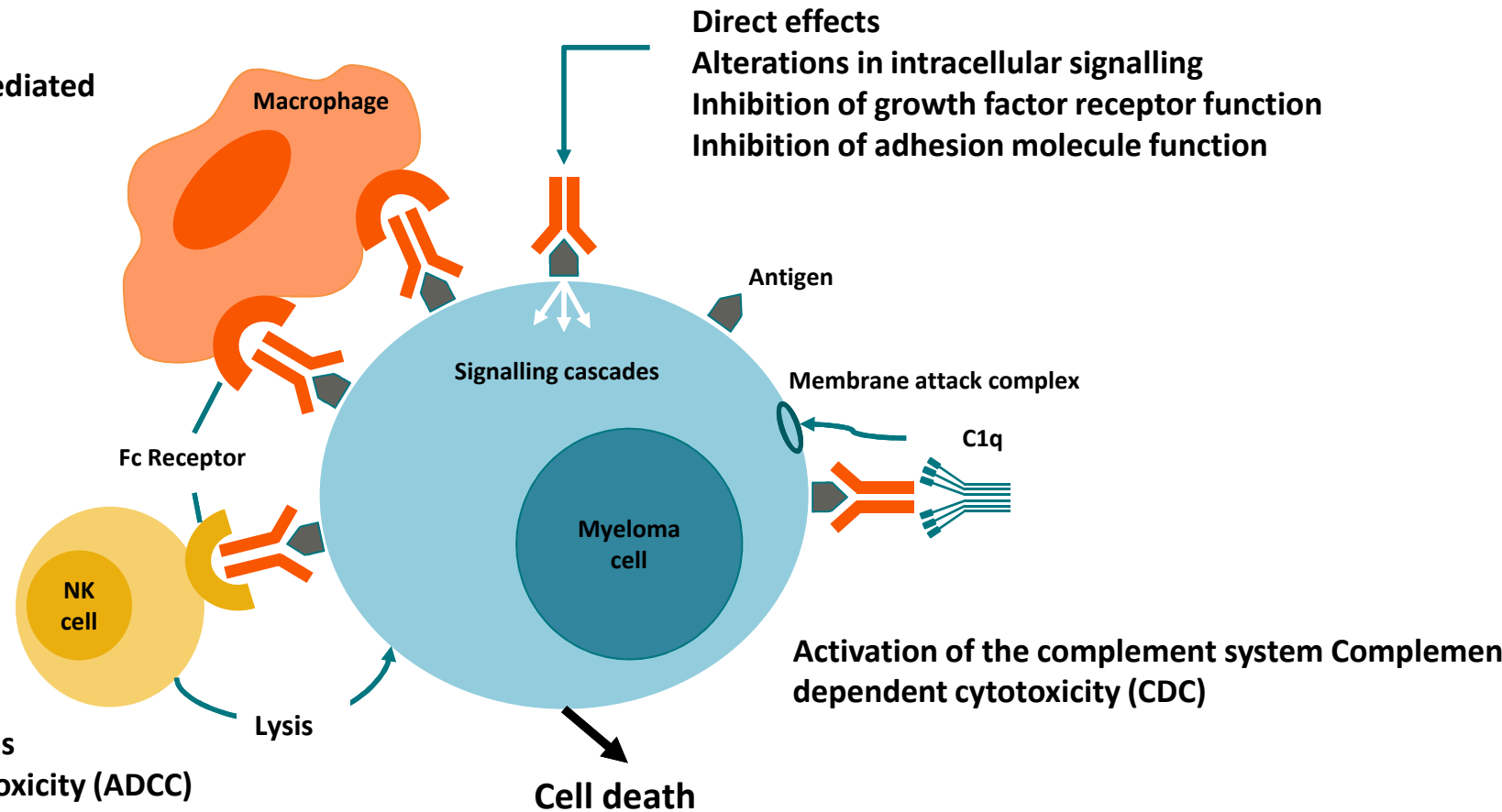
- PFS benefit with ixazomib seen in all prespecified subgroups, including cytogenetic high IMiD exposed

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



MAbs στο Μυέλωμα

Activation of macrophages
Antibody-dependent cell-mediated phagocytosis (ADCP)



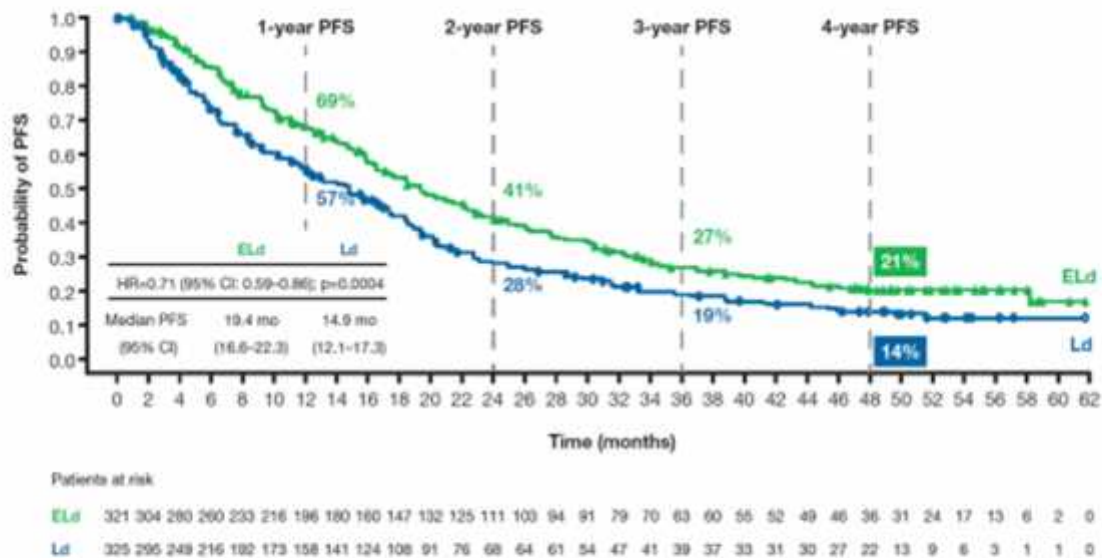
Activation of natural killer (NK) cells
Antibody-dependent cellular cytotoxicity (ADCC)



Elotuzumab στο υποτροπιάζον Μυέλωμα

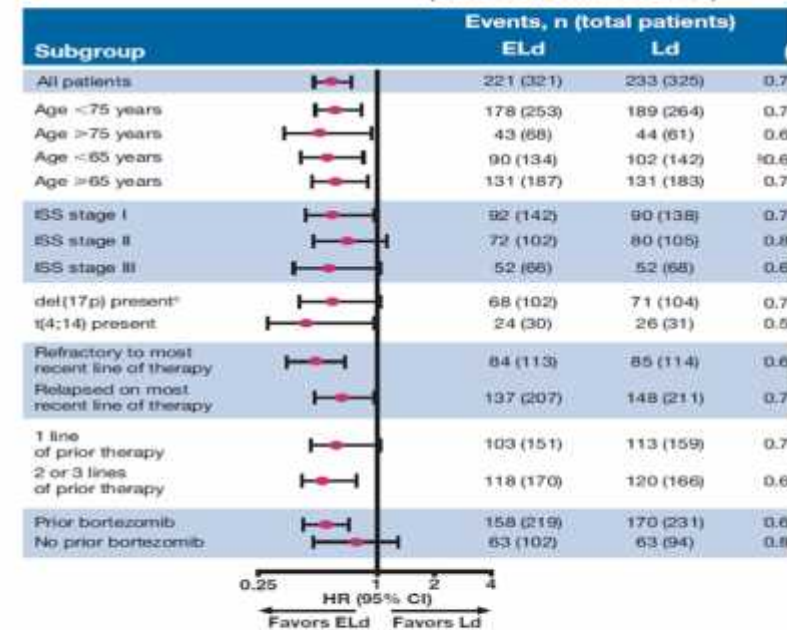
INT-2: 4-Year Follow-up

COQUENT-2: Elotuzumab + Len/dex vs Len/dex – PFS



A 29% reduction in the risk of progression or death and a relative improvement of 50% in the PFS rate (21% vs 14%) were observed with ELd vs Ld

4-year FU
(data cut-off: Oct 2016)*

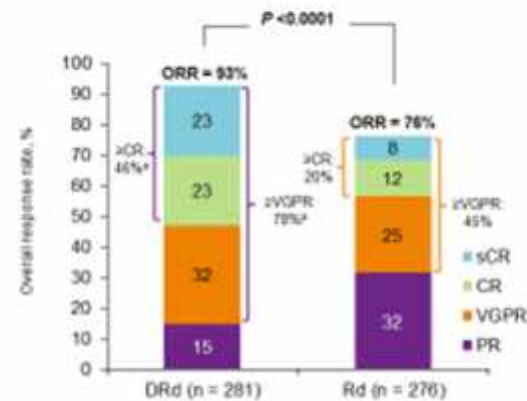
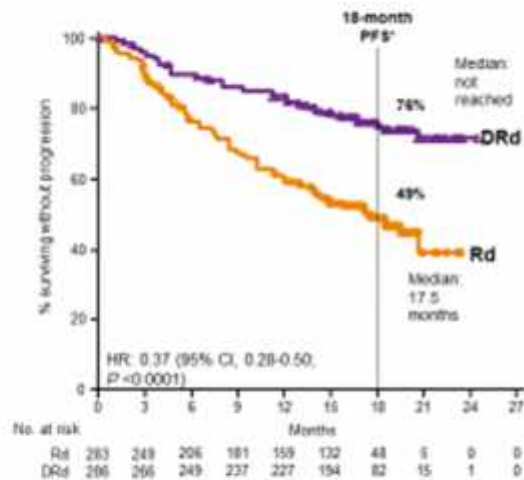


Lin S, et al. ASCO 2017;126: Abstract 8028



Daratumumab στο υποτροπιάζον Μυέλωμα

POLLUX: DaraRd vs Rd – Updated Efficacy



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

DRd-treated patients had a 63% reduction in the risk of disease progression or death in comparison with Rd
Responses continue to deepen in the DRd group with longer follow-up

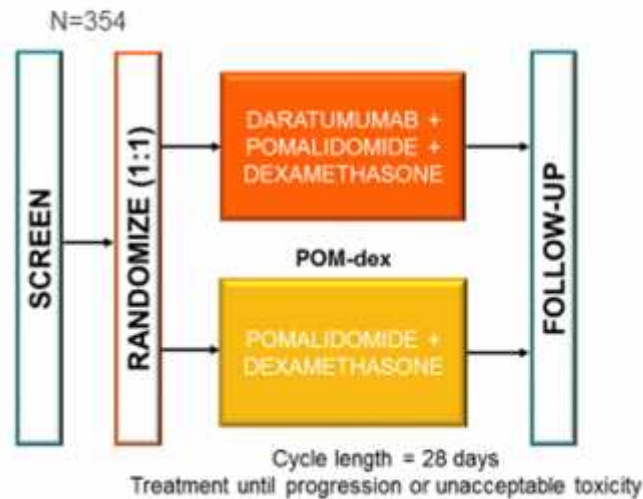
Usmani SZ, et al. *Blood*. 2016;128: Abstract 1151.



Νέες μελέτες με MAbs που στοχεύουν το CD38

APOLLO (MMY3013) phase 3 study: Daratumumab + POM-D

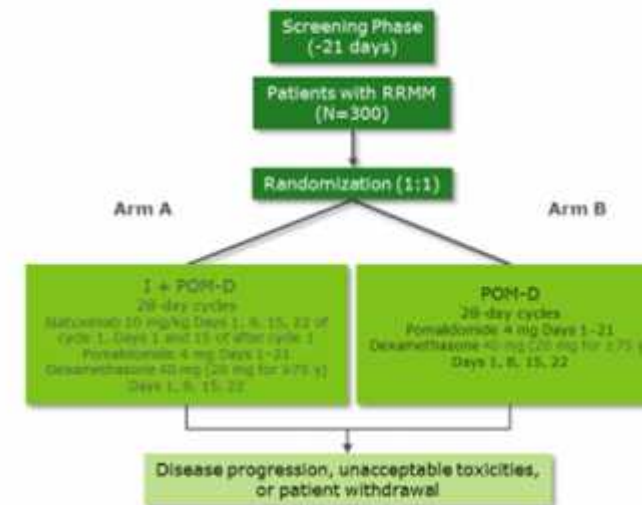
- Patients: RRMM, ≥1 prior line of therapy (IMiD and PI; len-refractory if only 1 prior regimen), ≥PR on prior therapy, PD on/after last regimen;
- Exclusion criteria included prior anti-CD38 mAb or pomalidomide
- Primary endpoint: PFS



clinicaltrials.gov: <https://www.clinicaltrials.gov/ct2/show/NCT03180736?term=daratumumab&rank=32>

ICARIA-MM phase 3 study: isatuximab + POM-D in RRMM

- Patients:
 - ≥2 prior lines of therapy
 - Failed treatment with lenalidomide and a PI alone or combination
 - Refractory to last line of treatment
 - Pomalidomide naïve
- Primary endpoint: PFS
- Secondary endpoints include:
 - Overall response rate
 - Overall survival
 - Time to progression
 - PFS in high risk cytogenetic population
 - Duration of response
 - Safety
 - QoL

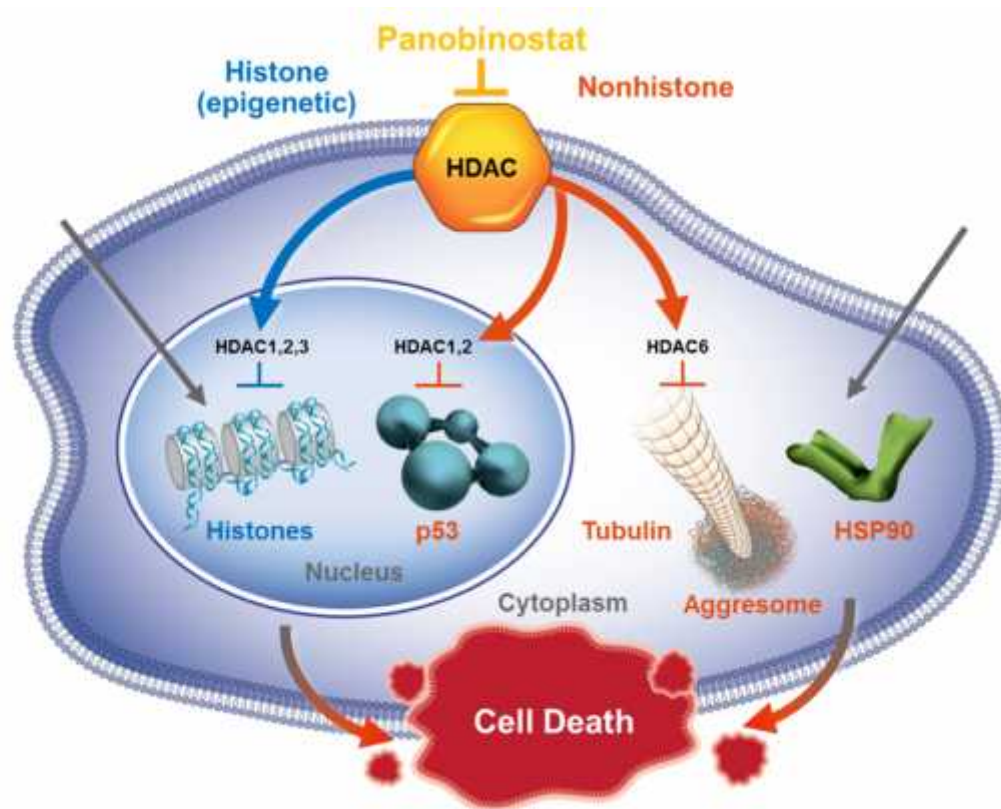


Richardson P, et al. Presented at DMW 2017 (Abstract PS-249)



αν-αναστολείς αποακετυλασών των ιστονών: Μηχανισμός Δράσης

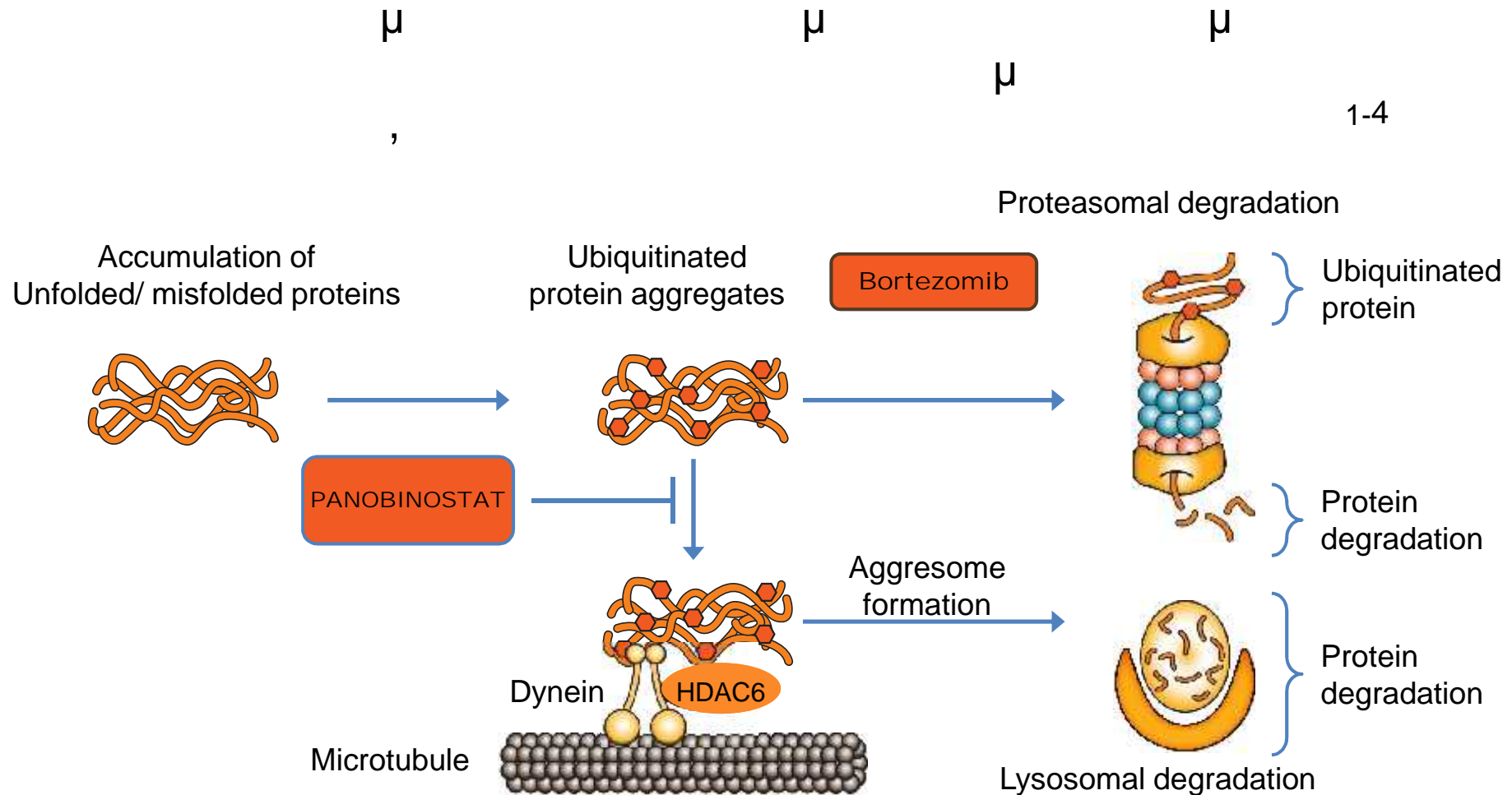
Οι Pan-DACi, όπως το panobinostat, αναστέλλουν ένα ευρύ φάσμα των ενζύμων αποακετυλάσες οι οποίες στοχεύουν τις ιστόνες αλλά και μη ιστονικές πρωτεΐνες που εμπλέκονται στην ογκογένεση¹



Οι Pan-DACi αναστέλλουν την ανάπτυξη και προάγουν τον θάνατο των μυελωματικών κυττάρων μέσω της αναστολής των ενζύμων HDAC:

- Ιστόνες, που εμπλέκονται στην επιγενετική απορρύθμιση, οδηγώντας στην ενεργοποίηση των ογκοκατασταλτικών γονιδίων²⁻⁴
- Μη ιστόνες, που προάγουν την τοξική συσσώρευση των αποδιαταγμένων πρωτεϊνών, προκαλώντας κυτταρικό στρες^{2,5,6}

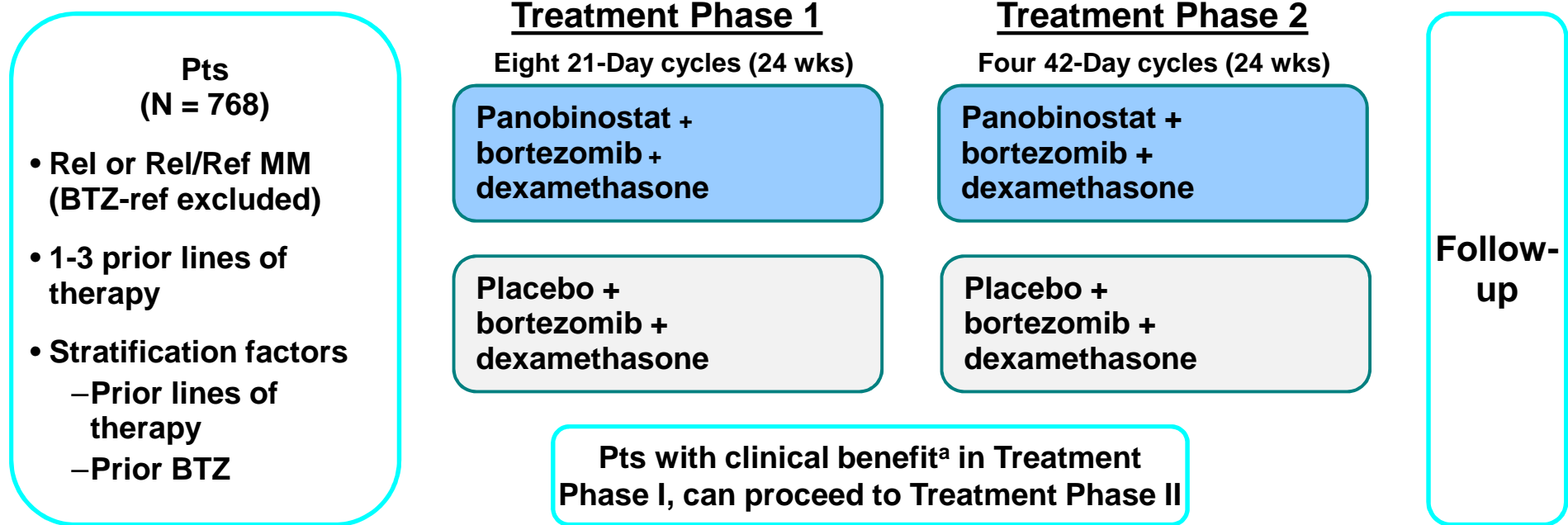
Σκεπτικό συνδυασμού HDACs + Bortezomib



1. Hideshima T, et al. *Proc Natl Acad Sci USA*. 2005;102:8
2. Ocio EM, et al. *Haematologica*. 2010;9:
3. Catley L, et al. *Blood*. 2006;108:3
4. Hideshima T, et al. *Mol Cancer Ther*. 2011;10:2

Σχεδιασμός Μελέτης PANORAMA 1

Τυχαιοποιημένη, διπλά τυφλή μελέτη φάσης 3 σε υποτροπιάζον ή υποτροπιάζον και ανθεκτικό ΠΜ



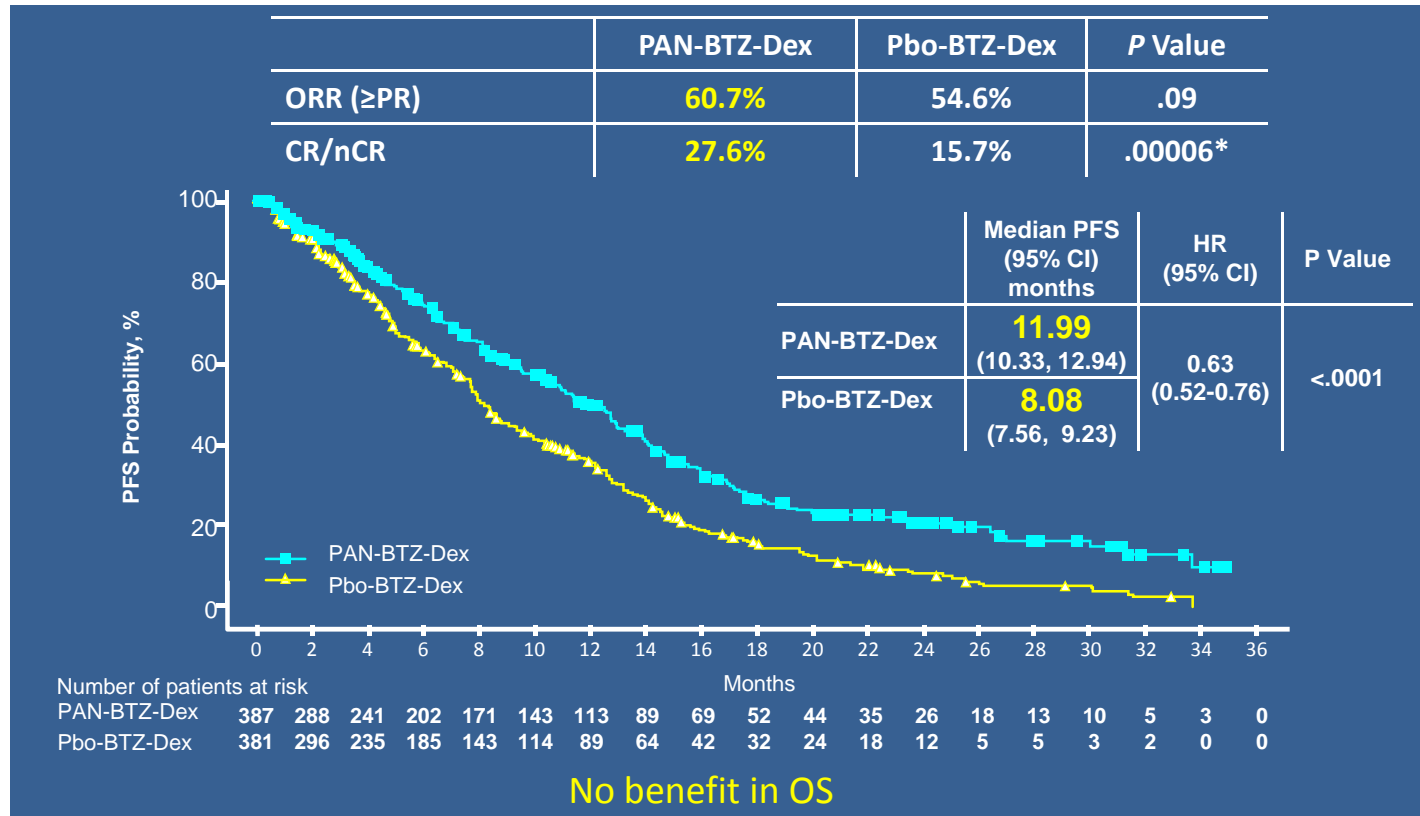
Πρωτεύον καταληκτικό σημείο: επιβίωση χωρίς εξέλιξη νόσου PFS (σύμφωνα με τα αναθεωρημένα κριτήρια EBMT (εκτίμησης των ερευνητών)

Δευτερεύον καταληκτικό σημείο: συνολική επιβίωση (OS)

Εκτός Δευτερεύοντα καταληκτικά σημεία: ORR, nCR/CR rate, DOR, TTR, TTP, QoL, και ασφάλεια

Η μελέτη διενεργήθηκε σε 215 κέντρα 34 χωρών

PANORAMA 1: Panobinostat + Bort + Dex vs Bort + Dex

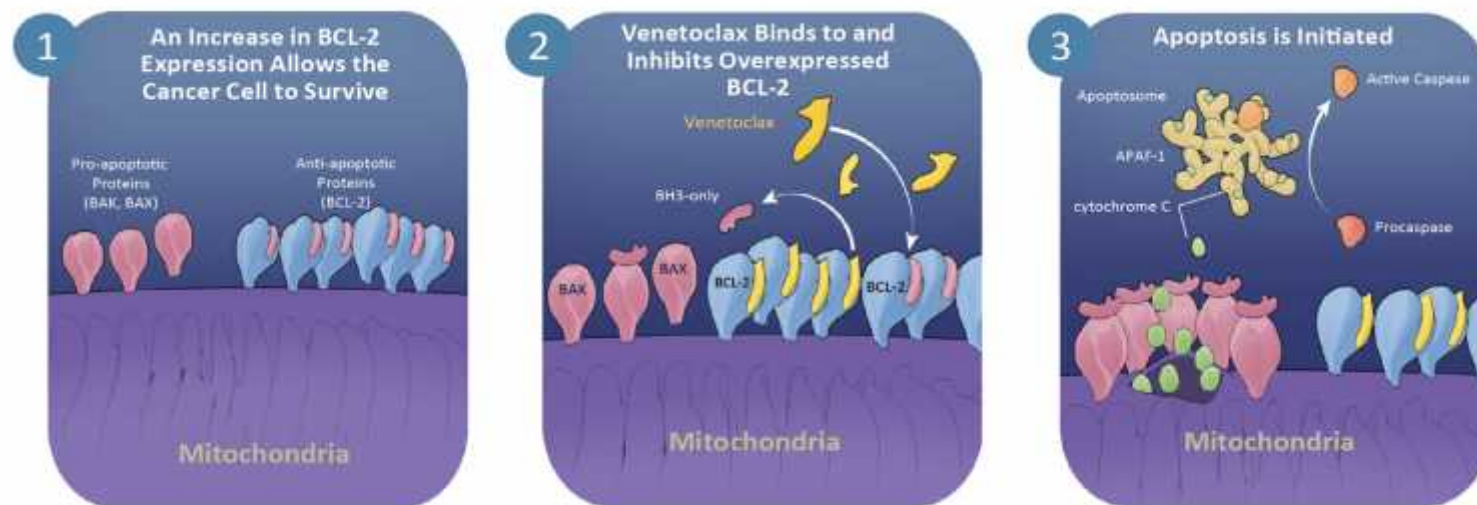


PAN-BTZ-Dex-treated patients had a 37% reduction in the risk of disease progression or death in comparison with BTZ-Dex

*based on post-hoc testing

Venetoclax (Bcl-2 inhibitor)

- Venetoclax (ABT-199 / GDC-0199) is a potent, selective, orally bioavailable, small-molecule, BCL-2 inhibitor¹
- MM cells harboring the t(11;14) have a high level of BCL-2 and low level of MCL-1²



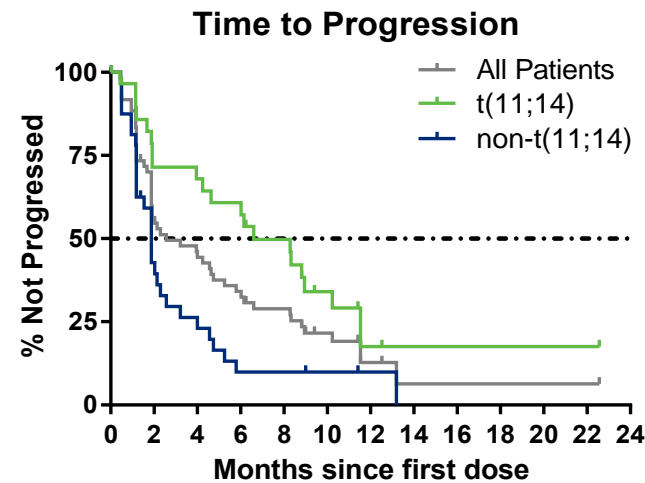
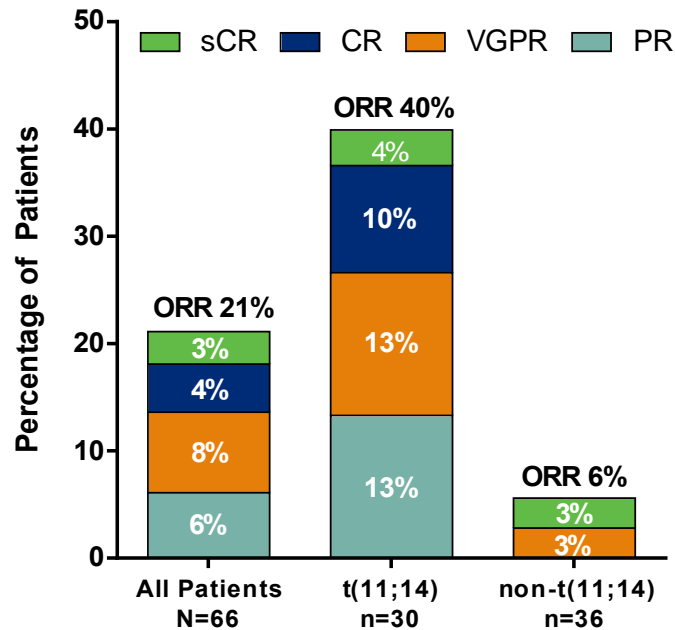
BH3-only family member proteins include BIM, BAD, PUMA, and NOXA.



Venetoclax monotherapy: Ph1 in RRMM patients

30-1200 mg oral admin (MTD: 1200 mg)

66 pts after a median of 5 prior lines of therapy: 79% refractory to last line of therapy;
61% double refractory to bortezomib and lenalidomide



No. at risk	66	33	27	20	16	9	3	1	1	1	1	1
No. at risk	30	20	19	17	13	7	2	1	1	1	1	1
No. at risk	36	13	8	3	3	2	1					

Higher ORR (88% vs 20%) were seen in t(11;14) with a high BCL2:BCL2L1 ratio

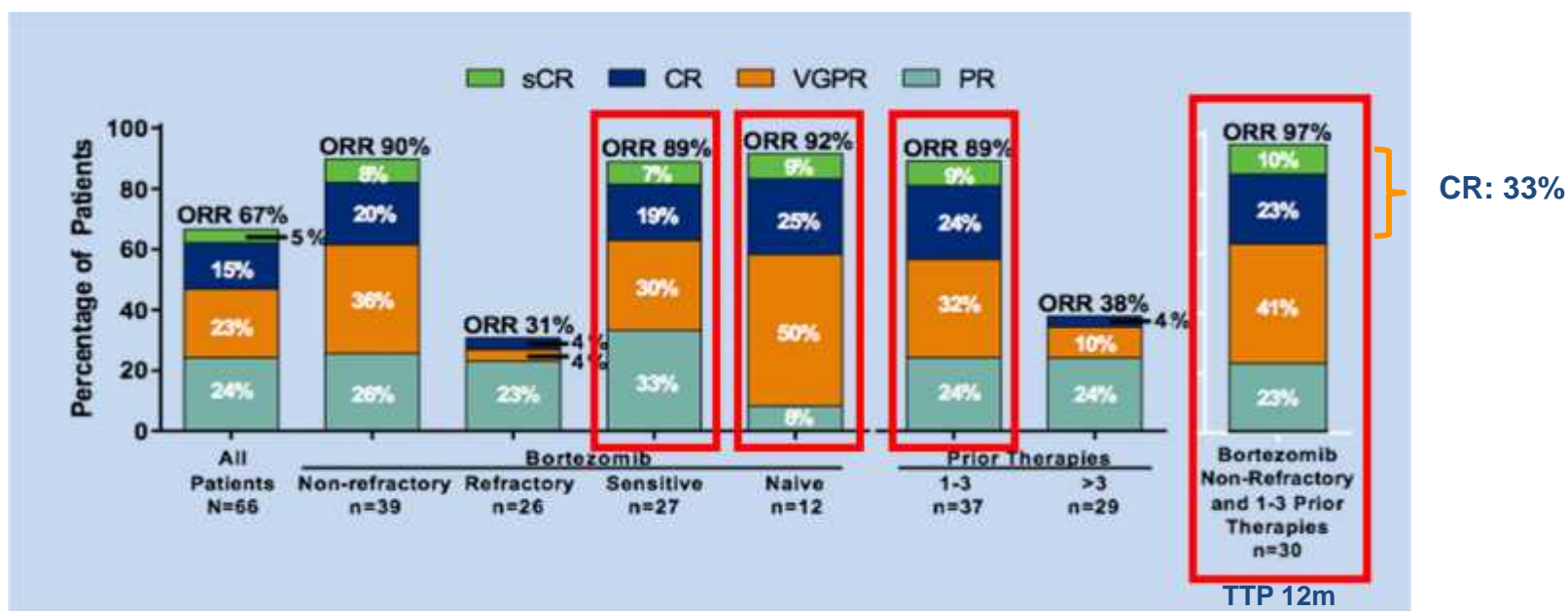
Main toxicities are thrombocytopenia (26% G3-4) and neutropenia (21% G3-4)

Serious AEs: pneumoniae (8%) and sepsis (5%)



Venetoclax plus bortezomib and dexamethasone

50-1200 mg oral daily + 1.3 mg/m² SC TW x cycles 1-8, QW 9-11 + 20-20 mg (days 1,2,4,5,8,9,11,12) x cycles 1-8



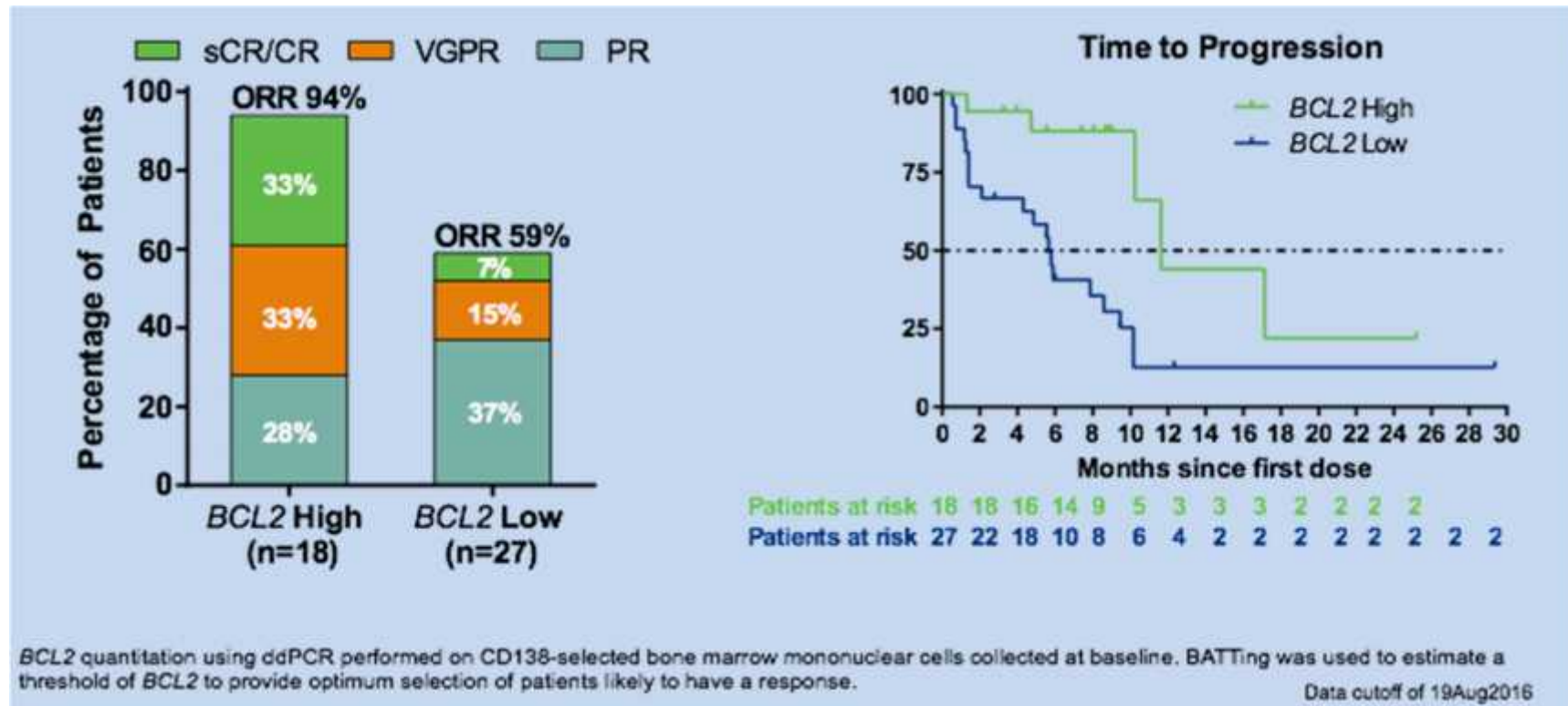
AEs were manageable. G3-4 AEs: Thrombocytopenia (29%), anemia (15%), neutropenia (14%), diarrhea (6%), PN(3%), dyspnea (6%)

Rationale for a phase 3 trial: Vd +/- Venetoclax

Venetoclax plus bortezomib and dexamethasone

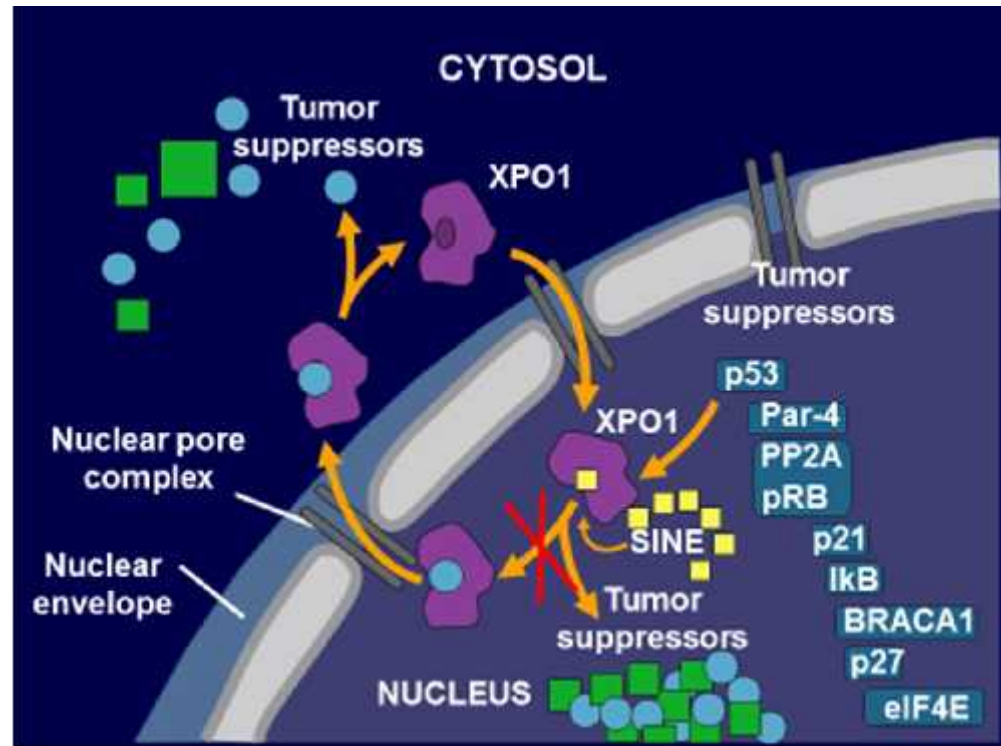
50-1200 mg oral daily + 1.3 mg/m² SC TW x cycles 1-8, QW 9-11 + 20-20 mg x cycles 1-8

BCL2 Gene Expression and Clinical Response



Selinexor: Μηχανισμός δράσης

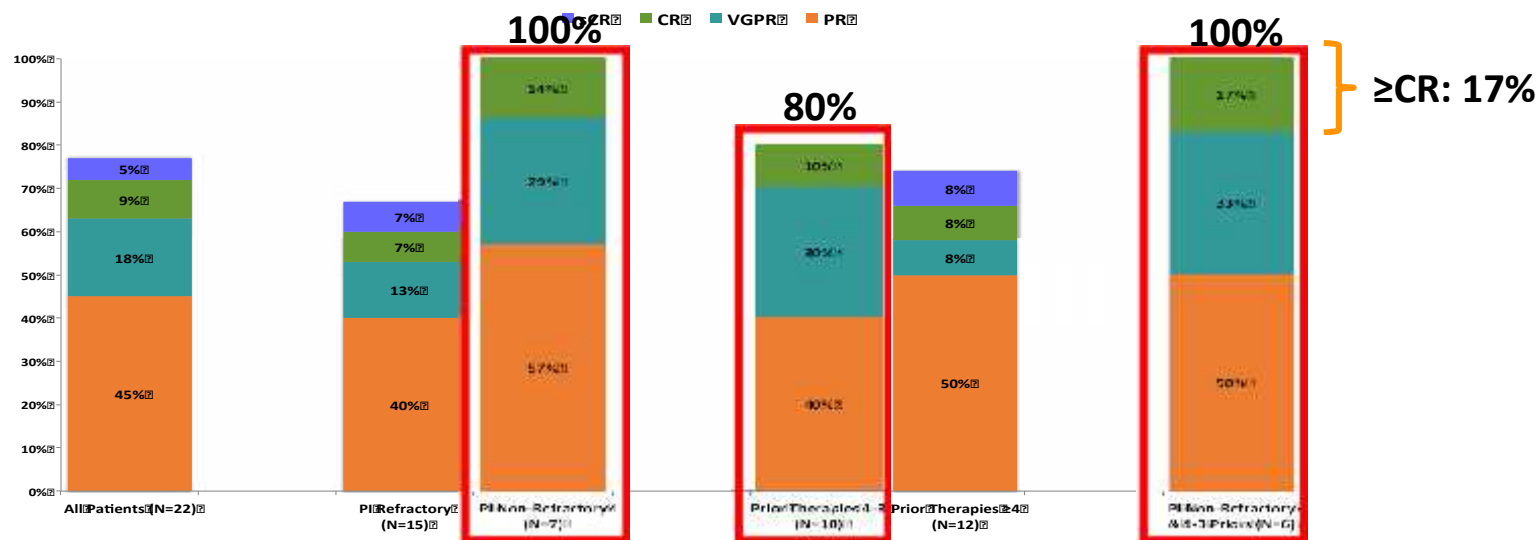
- XPO1 is the nuclear exporter for the majority of TSPs, the GR, and eIF4E-bound oncoprotein mRNAs
- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression



Ph1 study of Selinexor + bortezomib + Dex

100 mg oral QW + 1.3 mg/m² SC QW x 4 / 5 + 40 mg QW

22 patients after ≥1 prior lines of therapy (median=4), prior therapy could include bortezomib as long as not refractory to bortezomib in last line



Vd → ORR: 75%; CR rate: 10%

events were manageable (mostly grade 1/2) and included nausea, fatigue, anorexia, thrombocytopenia

events: Thrombocytopenia (18%), diarrhea (6%), fatigue (6%), abdominal pain (6%)

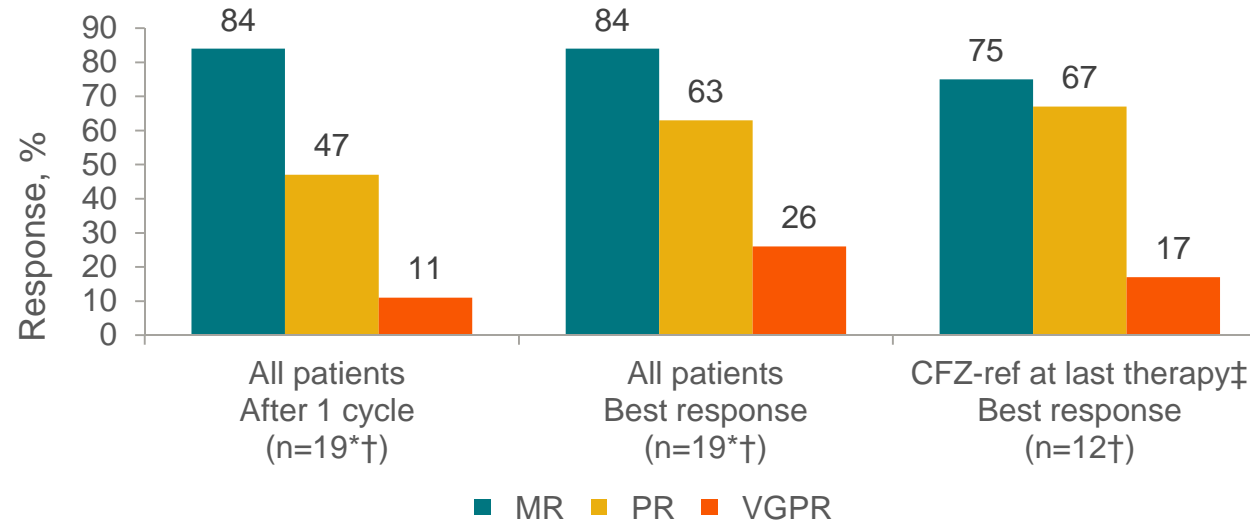
Rationale for the BOSTON, phase 3 trial: Vd +/- Selinexor

MMRC study of Selinexor + Carfilzomib + Dex

60 mg oral QW + 20/27mg/m² + 40 mg QW

19 patients after ≥ 2 prior lines of therapy (median=4), all refractory to the last line.

12 pts refractory to carfilzomib at last line of therapy

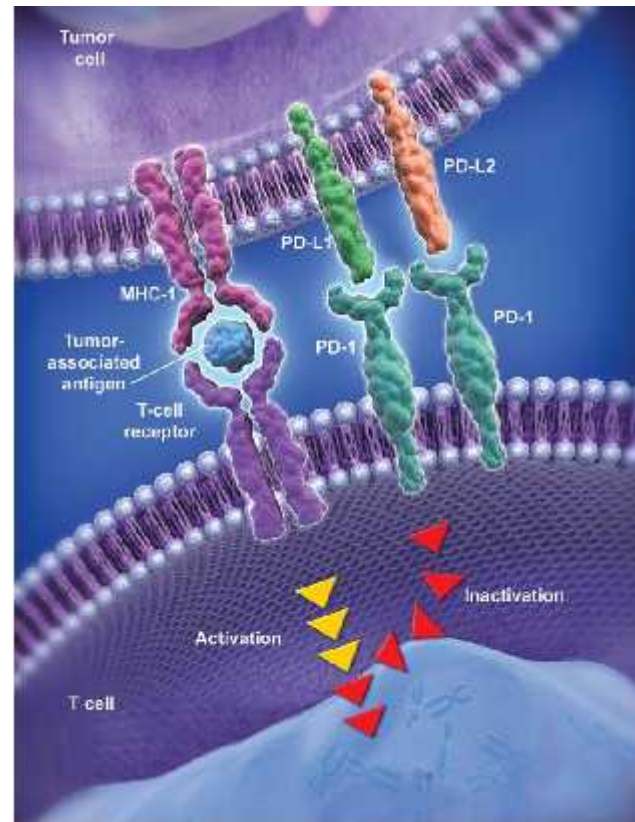


Main toxicities are thrombocytopenia (67% G3-4) and neutropenia (31% G3-4), fatigue (17% G3-4) and infections (11%, G3-4), which are manageable with dose modifications



PD-1/ PD-L1: Programmed Death Receptor MAbs

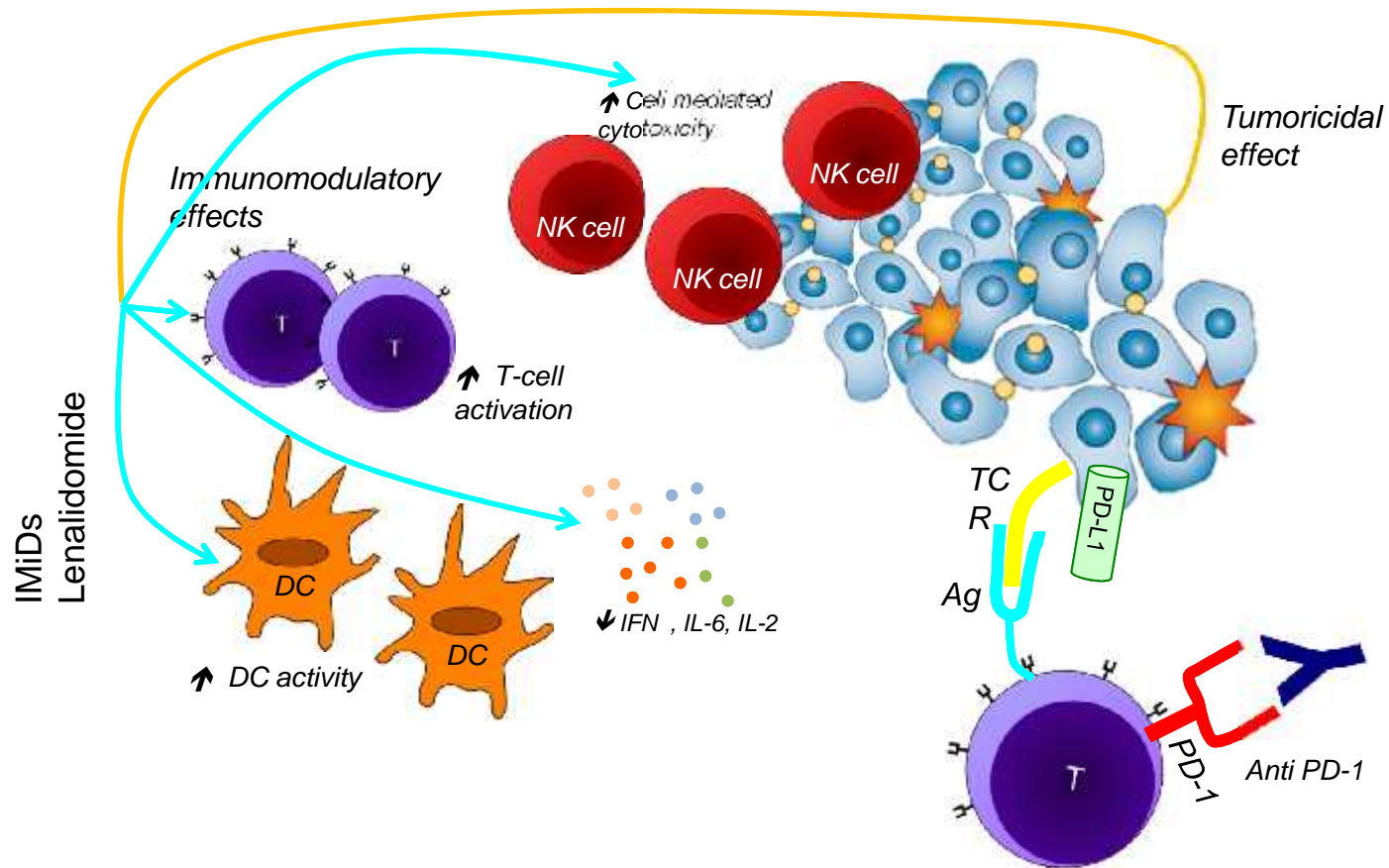
- PD1 Upregulated on the surface of *activated T-cells*
- *Ligands: PD-L1 & PD-L2*, are expressed on the surface of *APC & Tumor cells*
- *Binding of the PD-1 receptor to its ligands, PD-L1 and PD-L2, inhibits T-cell activation*
- The PD-1 pathway is often exploited by tumors to evade immune surveillance^{1,2,3}
- *TILs have been shown to express significantly higher levels of PD-1⁴*
- *Up-regulation of PD-L1 expression levels have been described in: melanoma (40-100%), NSCLC (35-95%), and linked to poor clinical outcomes^{5, 6}*



Selective MoAb against PD-1 (pembrolizumab) or PD-L1: Directly blocks interaction between PD-1 and PD-L1/PD-L2



IMiDs και αναστολείς PD-1: συνεργική δράση στο ΠΜ;



Pembrolizumab + Len-dex στο υποτροπιάζον ΠΜ

Best Overall Response n (%)	Efficacy Population [†] (n = 40)	Len-Refractory (n = 29)
Overall response rate	20 (50)	11 (38)
Stringent complete response (sCR)	1 (3)	1 (3)
Very good partial response (VGPR)	5 (13)	3 (10)
Partial response (PR)	14 (35)	7 (24)
Stable disease (SD)	19 (48)	17 (59)
Disease control rate (CR+PR+SD)	39 (98)	28 (97)
Progressive disease (PD)	1 (3)	1 (3)

- Median follow-up:
9 months (range, 1-25)
- Median DOR: 11.3 months
- Median time to achieve first
objective response:
1.5 months (range, 1.0-6.6)
- 4 patients who responded
(20%) upgraded the quality of
response
- 75% of patients were still alive



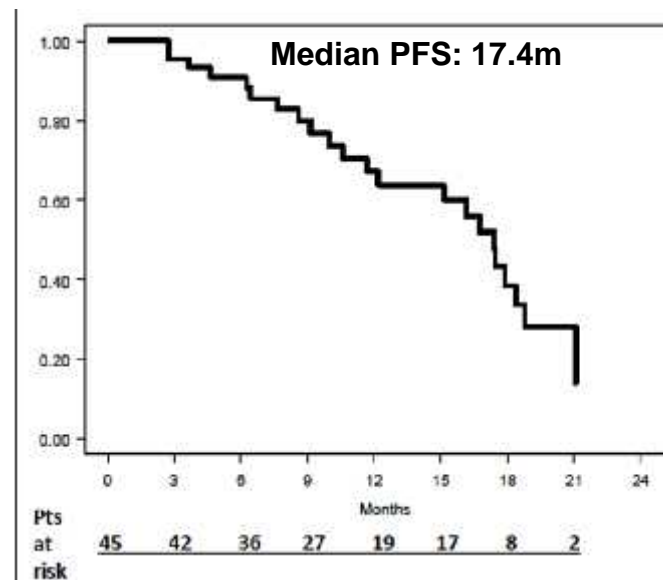
Pembrolizumab + Pom-dex στο υποτροπιάζον ΠΜ

200 mg Q2W

4 mg (1-21) 40 mg QW

45pts refractory a median of 3 prior lines; double refractory to PI&IMiD's 73%

Response category	Evaluable Patients (N=45)	Double refractory (N=32)
Overall response, n (%)	29 (65)	22 (68)
Best response, n (%)		
sCR	3 (7)	1 (3)
CR	1 (2) 29%	1 (3) 24%
VGPR	9 (20)	6 (18)
PR	16 (36)	14 (44)
MR	3 (7)	1 (3)
SD	11 (23)	7 (22)
PD	2 (5)	2 (4)



- 6 pts (12%) had G3-4 pneumonitis and 4 required discontinuation
- Correlation between PD-L1 expression in PCs and ORR but no between PD-1&CD3 and ORR

Συμπεράσματα

- Η κατανόηση της βιολογίας του ΠΜ έχει οδηγήσει στην έγκριση πολλών φαρμάκων που στοχεύουν τους βιολογικούς δρόμους ανάπτυξης και πολλαπλασιασμού των μυελωματικών κυττάρων
- Έγκριση 10 νέων φαρμάκων σε 10 χρόνια
- Αύξηση της επιβίωσης των ασθενών από 2-3 έτη το 1990 σε 7-10 το 2017
- Η ανάπτυξη των νέων φαρμάκων έχει οδηγήσει σε μεγάλη ανάγκη για διενέργεια κλινικών μελετών ώστε να κατανοήσουμε ποιος είναι ο καλύτερος συνδυασμός για τον κάθε ασθενή με Μυέλωμα



Σας ευχαριστώ