# Πρωτοπαθής συστηματική (AL) αμυλοείδωση: Νεώτερες προσεγγίσεις στην αντιμετώπιση του πλασματοκυτταρικού κλώνου

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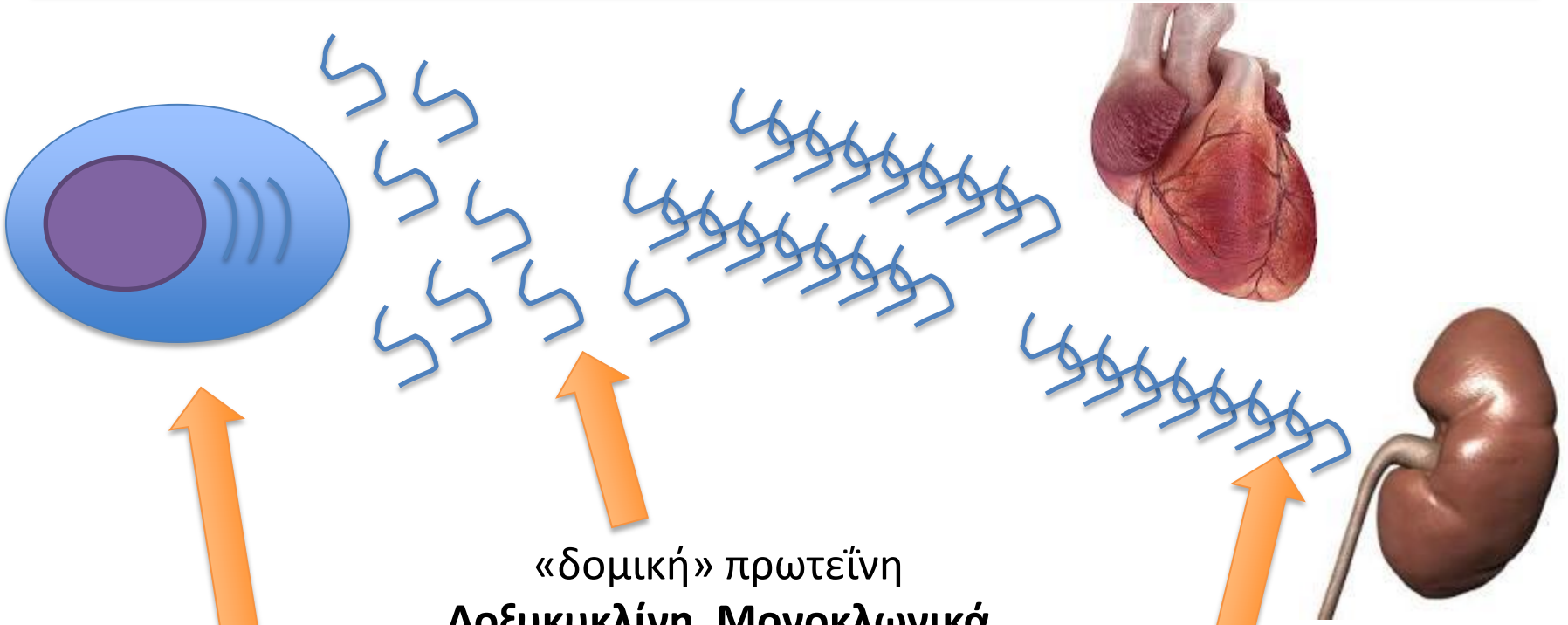
Θεραπευτική Κλινική ΕΚΠΑ

# Θεραπευτική προσέγγιση της αμυλοείδωσης



«δομική» πρωτεΐνη
**Δοξυκυκλίνη, Μονοκλωνικά αντισωματα , CHPHC**

Πλασματοκυταρικός κλώνος
**Χημειοθεραπεία**

**Εναποθέσεις αμυλοειδούς**
Μονοκλωνικά αντισώματα

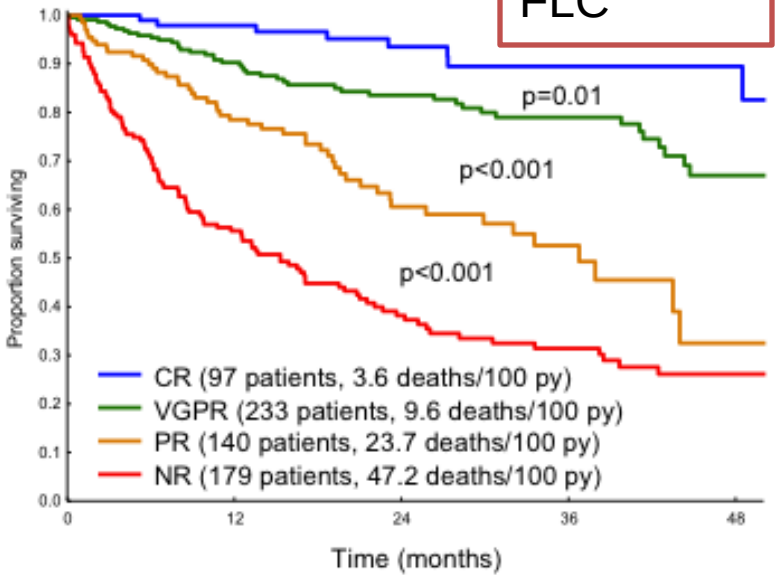
# Ο πλασματοκυτταρικός κλώνος στην AL αμυλοείδωση

- Συνήθως περιορισμένη διήθηση (7%-15% σε διάφορες σειρές) → σημαντικά μικρότερο φορτίο νόσου σε σύγκριση με το ΠΜ
- Ασύνηθες να υπάρχουν κυτταρογενετικά υψηλού κινδύνου → del17p, t(4;14), t(14;16) <8-10%
- Πιο συχνή κυτταρογεννετική βλάβη : t(11;14)
- Συνήθως δεν υπάρχει αναιμία, υπερασβεστιαιμία, οστικές βλάβες, ΟΝΑ λόγω cast nephropathy (CRAB)
- **Small but dangerous clone!! (Merlini & Stone Blood 2006)**

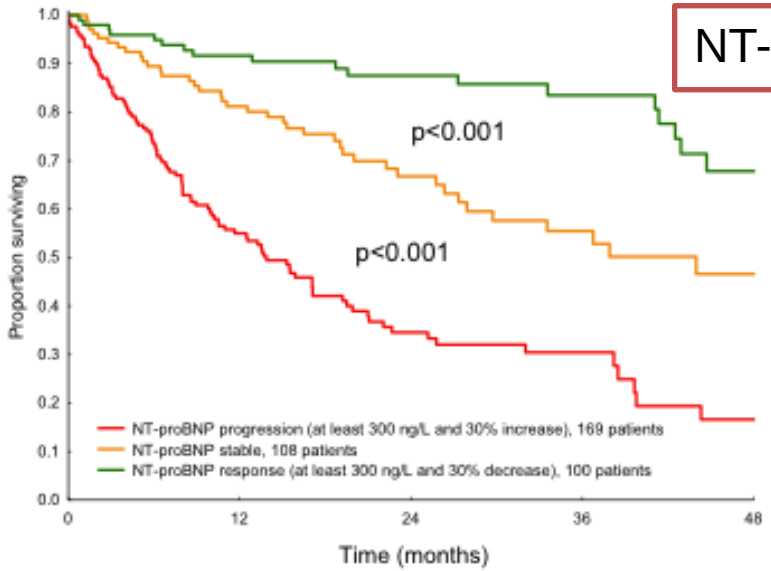
# Θεραπεία της AL αμυλοείδωσης

## ΧΜΘ με στόχο την ταχεία ελάττωση των ελαφρών αλυσίδων και βελτίωση των μυοκαρδιακών δεικτών

FLC




NT-proBNP



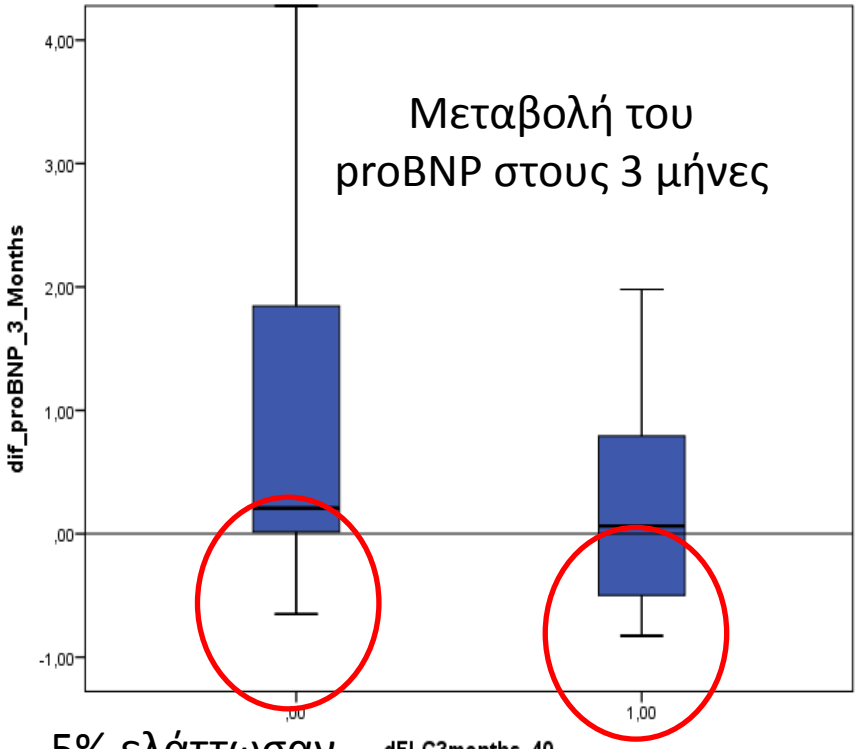

| | |
|---|---|
| **aCR** | **Negative sIF & uIF, normal FLr** |
| **VGPR** | **dFLC <40 mg/L** |
| **PR** | dFLC decrease ≥50% |
| **NR** | other |

dFLC: Involved FLC – uninvolved FLC

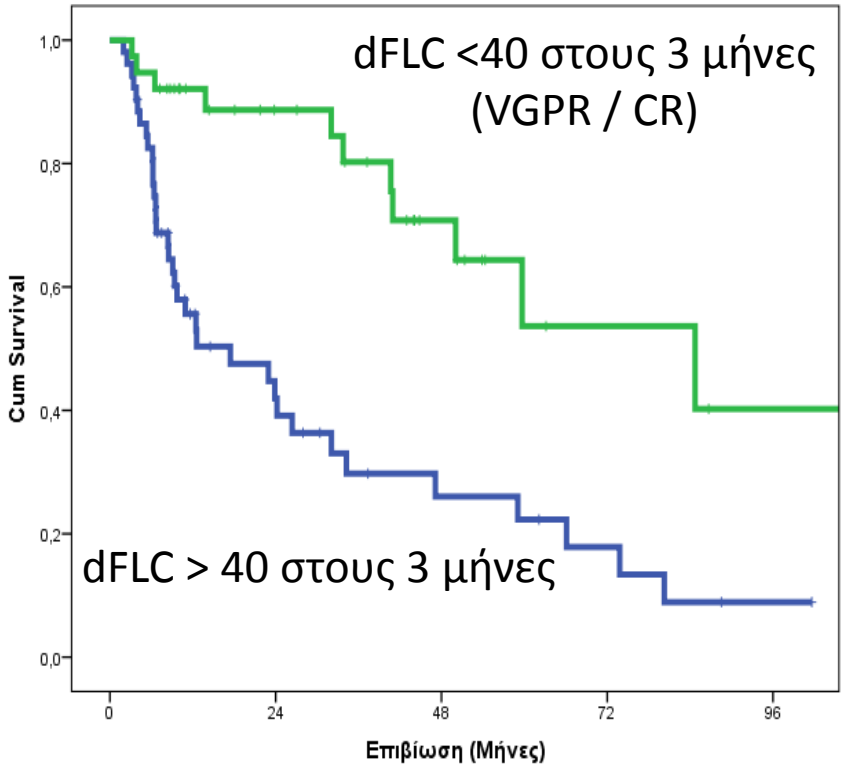
Cardiac response: reduction of NT-proBNP >30% and >300 ng/L

**Renal insufficiency and IMiDs may alter NT-proBNP metabolism**

# Γιατί είναι σημαντική η ταχεία αιματολογική ανταπόκριση ;

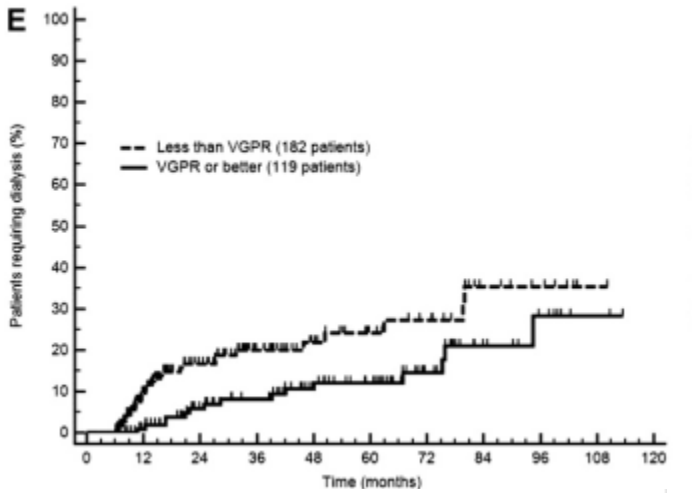



5% ελάττωσαν τα επίπεδα του NTproBNP

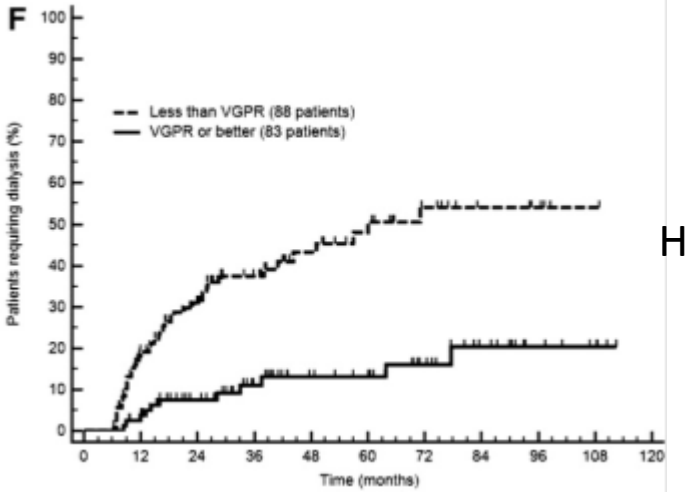



45% ελάττωσαν τα επίπεδα του NTproBNP

# Βαθειά Αιματολογική ύφεση ελαττώνει τον κίνδυνο εξέλιξης προς τελικού σταδίου ΧΝΑ

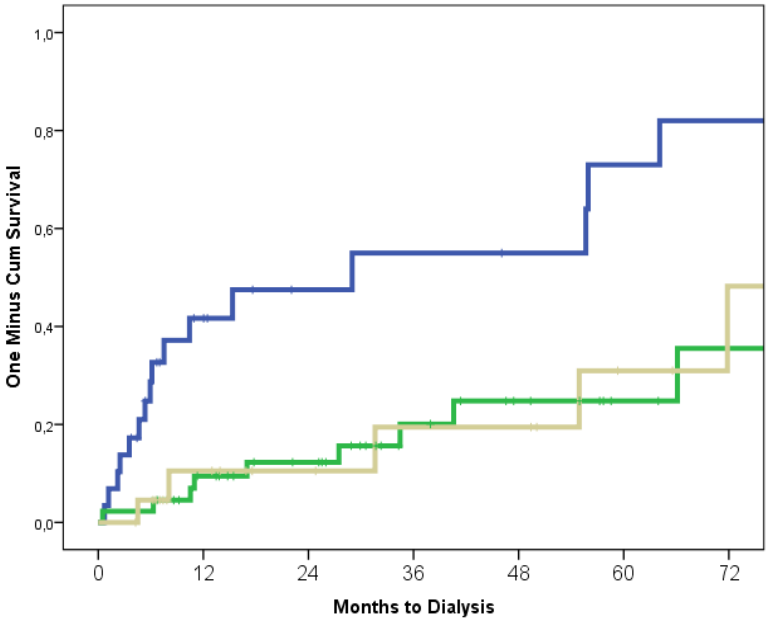



Pavia

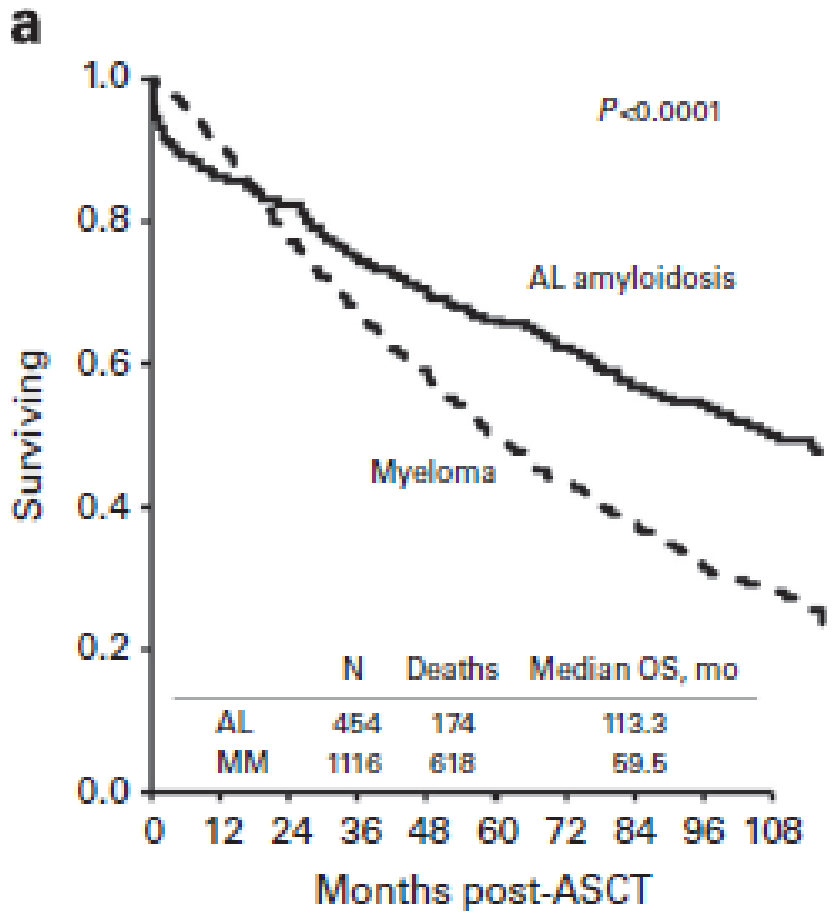



Heidelberg

Athens



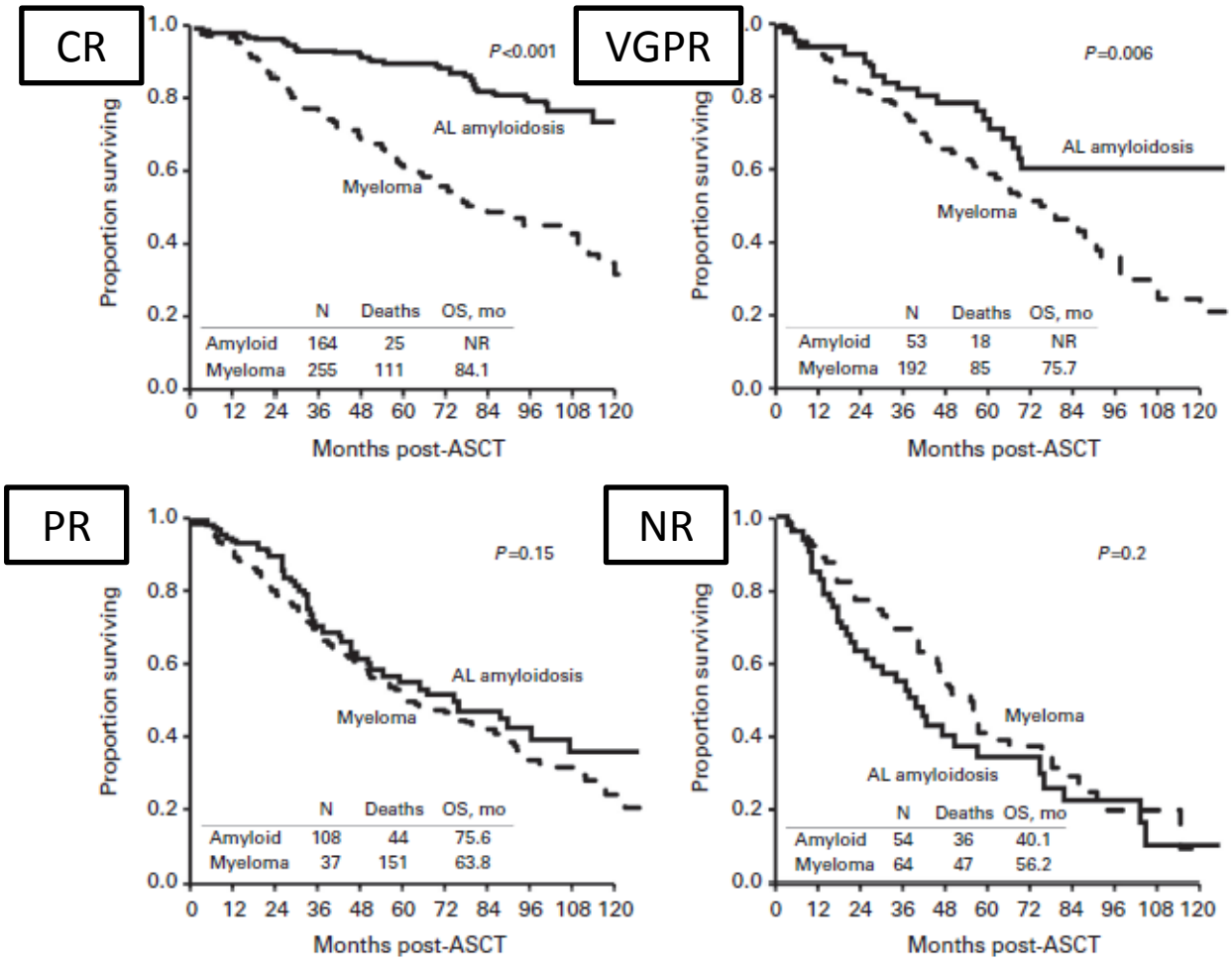
# Patients with AL amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma






Dispenzieri A et al Bone Marrow Transplantation 2013

# Patients with AL amyloidosis undergoing ASCT have superior outcome compared with patients with multiple myeloma: impact of CR



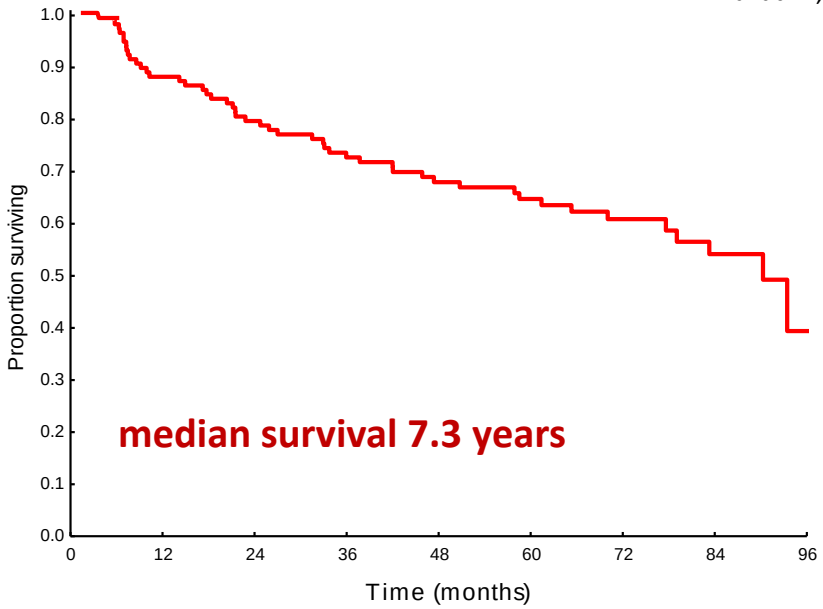

Dispenzieri A et al Bone Marrow Transplantation 2013

# Θεραπεία έναντι του πλασματοκυτταρικού κλώνου: MDex

| Regimen | HR (CR) | OR | Common SAEs | 100-day mortality | PFS / OS (y) |
|---|---|---|---|---|---|
| MDex<br>Palladini 2004 | 67% (33%) | 48% | Overall 11% | 4% | 3.8 / 5.1 |

"Standard" chemotherapy for patients with AL amyloidosis not eligible for ASCT: un update

Palladini, el al. *Haematologica 2014 ;99:743-50*

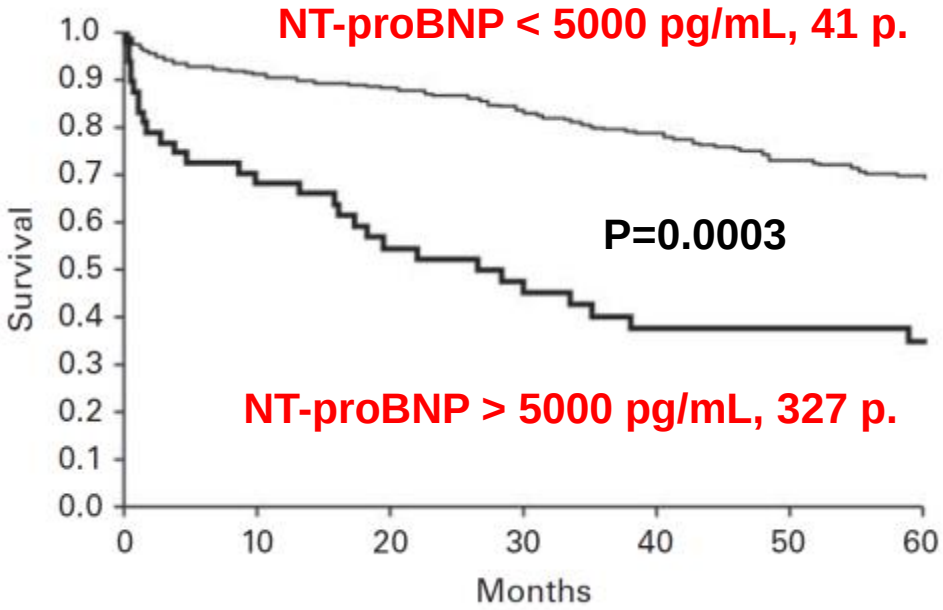


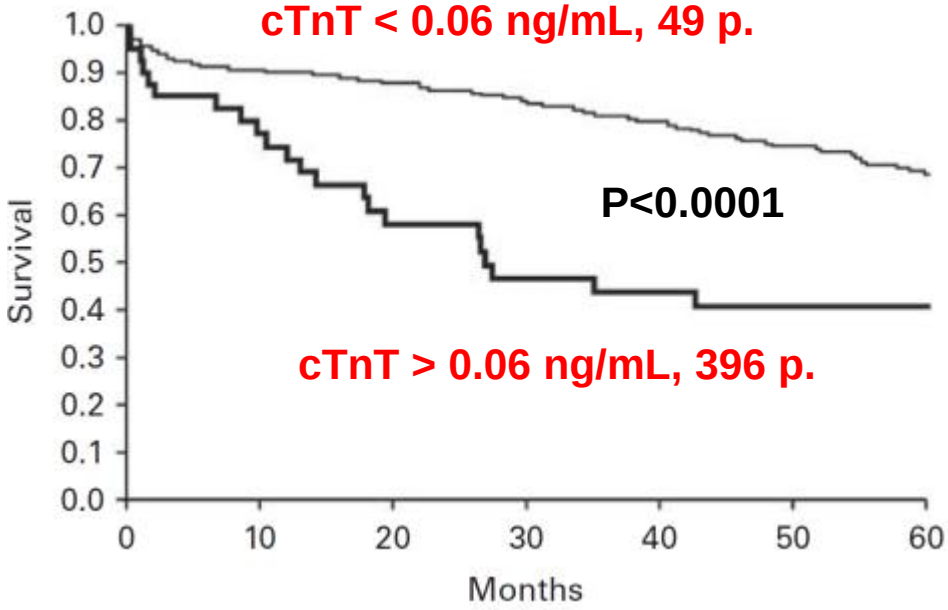

- 119 patients, median age 64y
- Deaths at 3 months 0%, SAE 16%
- **Hematologic Response:**
  - CR: 31%
  - VGPR: 29%
  - PR: 16%
  - } 76%
  - NR: 24%
- **Organ response**
  - heart: 37%
  - kidney: 24%

# Θεραπεία έναντι του πλασματοκυτταρικού κλώνου: ΑΜΑΑΚ

| Author | N | HR (CR) | Org. Resp. | 100-day mortality | PFS / OS (y) |
|---|---|---|---|---|---|
| *Sanchorawala 2013 BU Single Center* | 593 | (34%) | 53% | 10% | -/6.7<br>CR -/>12 |
| *Gertz et al 2010 Mayo Clinic* | 434 | 76% (39%) | 47% | 10% | CR - / **not r.**<br>PR - / 8.9<br>NR - / 2.7 |
| *Parmar et al 2014 MD Anderson* | 80 | 75% (31%) | 39% | 12.5% (1 yr) | @10y<br>-/56% |
| *Hegenbart et al, EHA 2014 Heidelberg* | 174 | 80% (38%) | 40% | 2% | -/11<br>HR -/ not r. |
| Risk-adapted ASCT +adj. BDex *Landau et al 2012* | 40 | 79% (58%) | 70% | ASCT 10%<br>BDex 4% | @2y<br>69% / 82% |
| MDex vs ASCT | 43 | 68% (32%) | 39% | 2% | TTP 2.7/OS 4.7 |
| *Jaccard et al, 2007, 2010* | 37 | 67%(41%) | 45% | 24%* | TTP 2.7/OS 1.8 |

# Κριτήρια επιλογής αρρώστων με AL αμυλοείδωση για ΑΜΑΑΚ




Patients with serum troponin T >0.06 ng/mL or NT-proBNP >5000 pg/mL (not on dialysis) **should not** be considered candidates for SCT because of early mortality.

***Data from a single tertiary center !!***



Gertz et al, *Bone Marrow Transplant. 2013;48:557-61*

# Θεραπεία έναντι του πλασματοκυτταρικού κλώνου: IMiDs

| Regimen | No (front-l) | HR (CR) | Org.R sp | Common SAEs | 100-d mortal. | PFS / OS (y) |
|---|---|---|---|---|---|---|
| CTD<br>Wechalekar 2007 | 75<br>(41%) | 74%<br>(21%) | 27% | Sedation 40%<br>Fluid retent. 21% | 4% | 1.7 / 3.4 |
| LDex+<br>Dispenzieri 2007 | 22<br>(41%) | 41% | 23% | Overall 86%<br>Neutropenia 45% | 18% | 1.6 / - |
| LdC#<br>Kastritis 2012 | 37<br>(65%) | 55%<br>(8%) | 22% | Neutropenia 24%<br>Fatigue 52% | 19% | 10 mos /<br>17 mos |
| MLD<br>Moreau 2010 | 26<br>(100%) | 58%<br>(23%)* | 50% | Overall 81%<br>Neutropenia 11% | - | @2y<br>54% / 81% |
| PomDex§<br>Dispenzieri 2012<br>Palladini 2013 | 33<br>(0) | 48%<br>(3%) | 15% | Neutropenia 30% | 3% | 1.2 / 2.3 |

+also Sanchorawala et al, Blood 2007;109:492-6; #also Kumar et al, Blood. 2012;119:4860-7
*(42% with full-dose L)

# Θεραπεία έναντι του πλασματοκυτταρικού κλώνου:Bortezomib

| Regimen | No (front-l) | HR (CR) | Org. Rsp | Common SAEs | 100-d mortal | PFS / OS (y) |
|---|---|---|---|---|---|---|
| Bortez<br>*Reece 2011*<br>*Reece 2014* | 70<br>(0) | 68%<br>(29%) | 29% K<br>13% H | Fatigue,<br>Thrombcytpn<br>Vomiting<br>Diarrhea | 3% | @1y 74%/<br>@4y 75% |
| BDex<br>*Kastritis 2010* | 94<br>(19%) | 71%<br>(25%) | 30% | PN<br>Edema<br>Orthost. hyp. | 3% | 25.5 mos/<br>@1y 76% |
| CyBorD*§¥<br>*Venner 2012* | 43<br>(47%) | 81%<br>(65% fl) | 46% | 19%<br>discontinued (PN<br>in 14%) | 0 | @2y<br>53% / 98% |
| Ixazomib<br>*Merlini ASH 2012, 2014* | 20<br>(0) | 55%<br>(10%) | 50% H<br>18% K | Fatigue<br>Thrombcytpn | 5% | @1y 60%/<br>@2y 63% |

*also *Mikhael et al, Blood 2012; 119:4391-4* § *Bortezomib s.c. Shah et al, Clin Ther 2013*

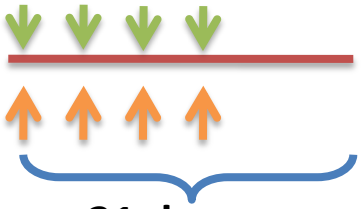
¥*Jaccard et al, Haematologica 2014* Median times to first and best HR: 0.7 and 1.2 months

# Risk adapted therapy based on bortezomib

- ECOG PS 0-1
- Mayo stage -1 ή -2
- proBNP <1285 ng/L
- Age < 70 years

**All of the above**

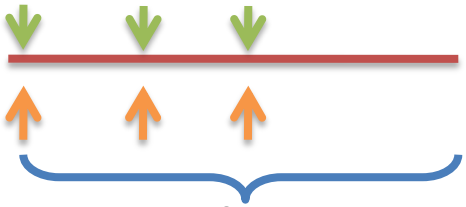
**Bortezomib 1.3 mg/m$^2$ <u>days 1,4, 8 & 11</u>**
**Dexamethasone 40 mg days 1,4, 8 & 11**
**every 21 days (up to 6 cycles)**




- ECOG PS ≥2
- Cardiac dysfunction (Mayo stage-2 with proBNP>1285 ng/L or stage -3)
- Age≥70 έτη
- Peripheral Neuropathy
- Symptomatic orthostasis
- SBP < 100 mmHg

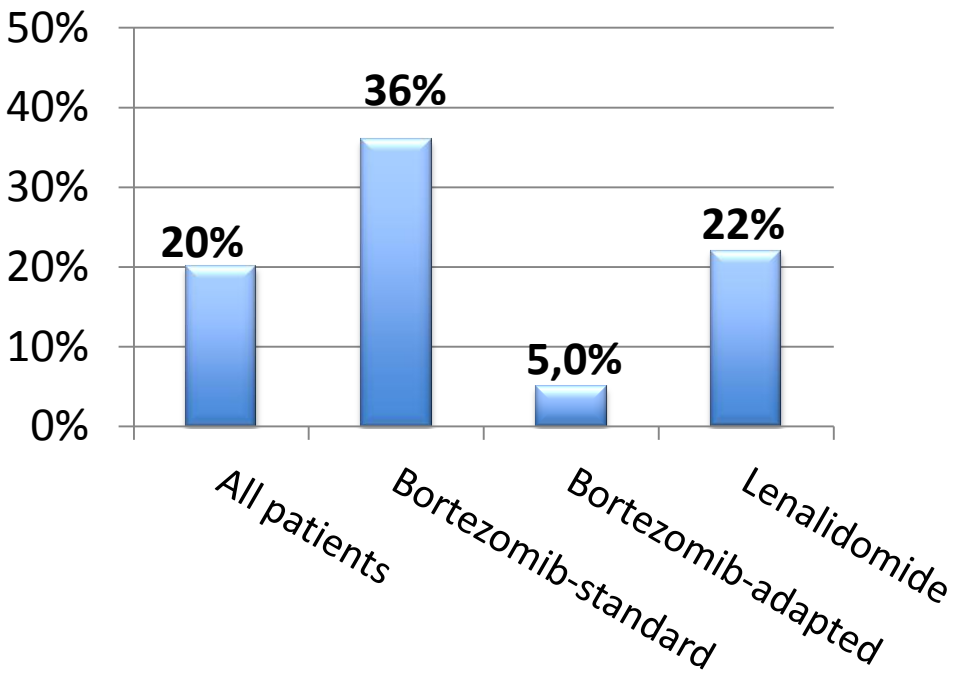
**Any of the above**

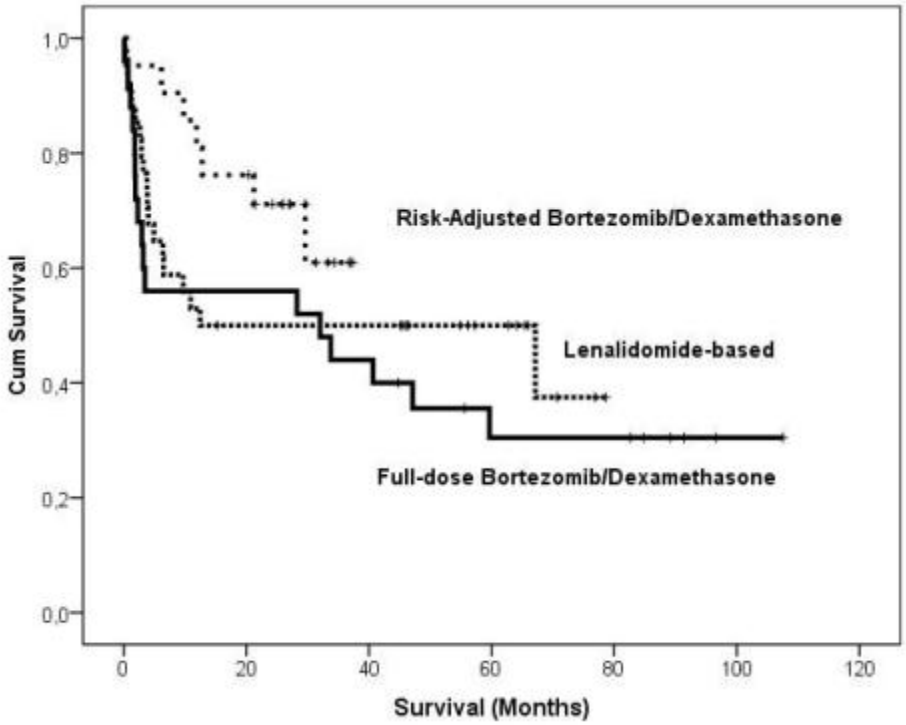
**Bortezomib 1.3 mg/m$^2$ <u>days 1, 8 & 15</u>**
**Dexamethasone 24mg days 1, 8 & 15 every 28 days (up to 6 cycles)**




Kastritis E, et al . Am J Hematol. 2015

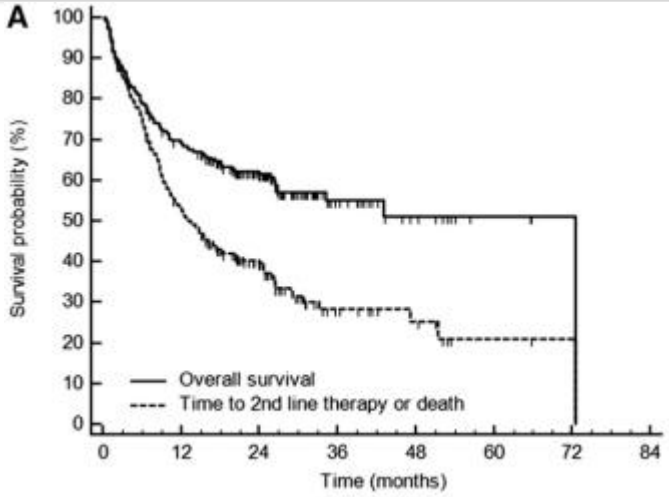
# Early Mortality (<3 months)

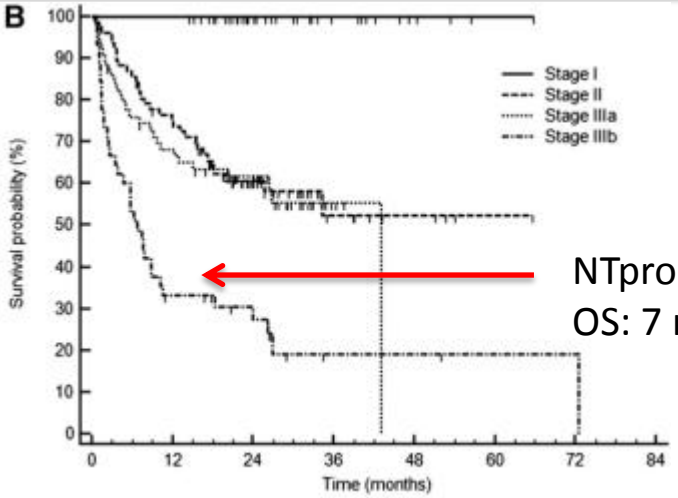


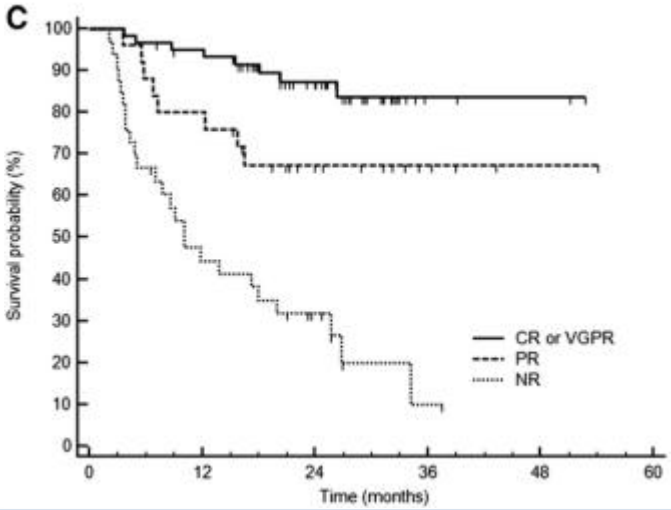

**Kastritis E, et al . Am J Hematol. 2015**

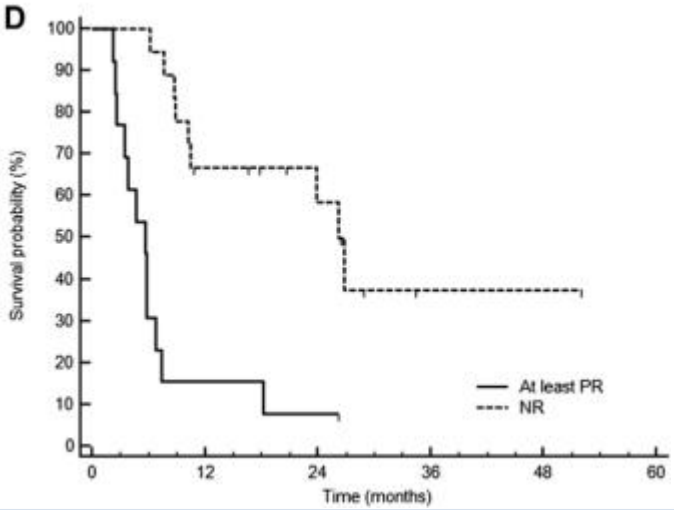
# A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis




NTproBNP>8500 pg/ml
OS: 7 months

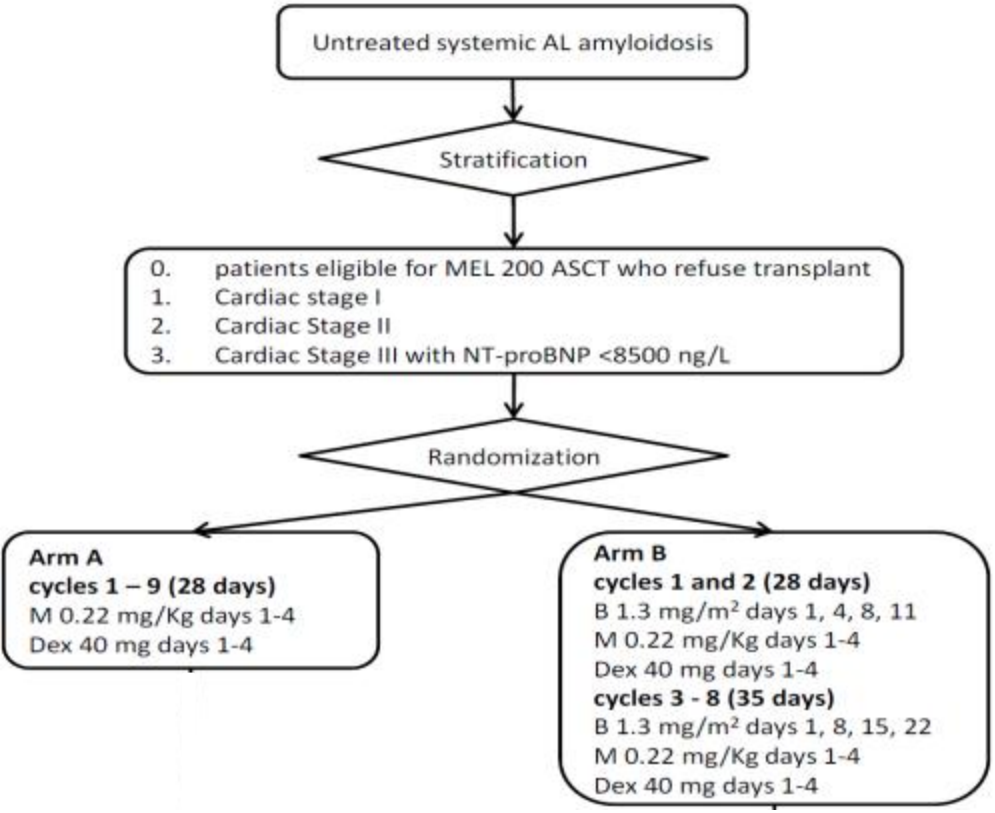



Palladini et al, ***Blood 2015***

# A Randomized Phase III Trial of Melphalan and Dexamethasone (MDex) versus Bortezomib, Melphalan and Dexamethasone (BMDex) for Untreated Patients with AL Amyloidosis

E Kastritis, X Leleu, B Arnulf, E Zamagni, MT Cibeira, F Kwok, P Mollee,R Hájek, P Moreau, A Jaccard, S Schönland,R Filshie, E Nicolas-Virelizier, B Augustson, MV Mateos, A Wechalekar, E Hachulla, P Milani, MA Dimopoulos, JP Fermand, A Foli, M Gavriatopoulou, A Palumbo, P Sonneveld, HE Johnsen, G Merlini, G Palladini




**Treatment is continued until:**

- MDex cycle 9 or BMDex cycle 8
- CR after cycle 6
- PR plus organ response after cycle 6
- <PR after cycle 3
- progression of clonal plasma cell disease

# Hematologic response

## Response after cycle 3 (study primary endpoint)

| Response | MDex (56 pts) | BMDex (53 pts) | P |
|---|---|---|---|
| **Overall Hem.** | **29 (52%)** | **42 (79%)** | **0.002** |
| CR | 2 (4%) | 4 (8%) | 0.313 |
| **VGPR** | **14 (25%)** | **24 (45%)** | **0.021** |
| PR | 13 (23%) | 14 (29%) | 0.434 |
| Heart | 8/35 (23%) | 8/26 (31%) | 0.342 |
| Kidney | 14/34 (41%) | 14/36 (39%) | 0.512 |

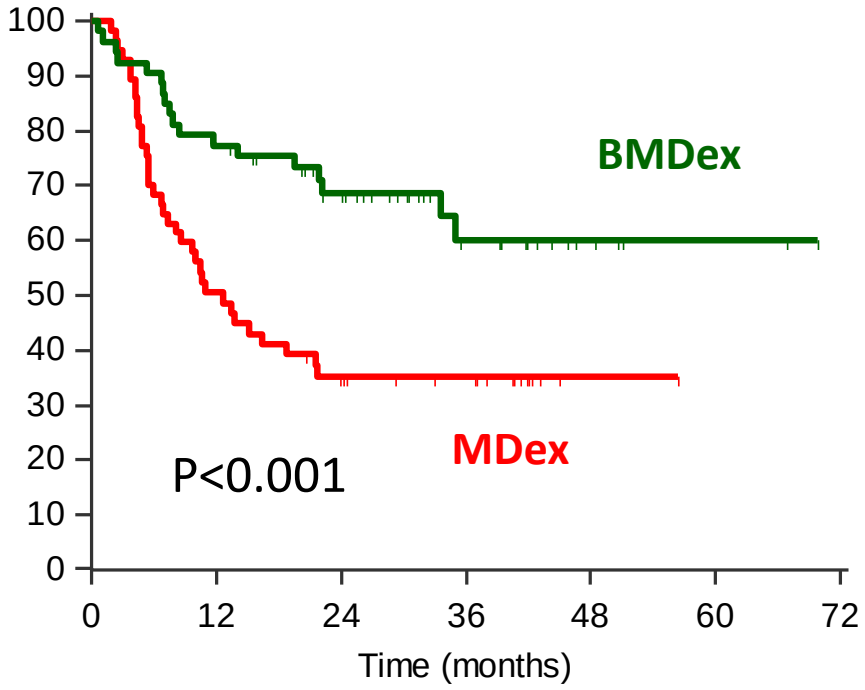
## Best response (median 5 cycles)

| Response | MDex (56 pts) | BMDex (53 pts) | P |
|---|---|---|---|
| **Overall Hem.** | **32 (57%)** | **43 (81%)** | **0.005** |
| CR | 11 (20%) | 12 (23%) | 0.440 |
| **VGPR** | **11 (20%)** | **21 (39%)** | **0.018** |
| PR | 10 (17%) | 10 (19%) | 0.543 |
| Heart | 10/35 (29%) | 10/26 (38%) | 0.294 |
| Kidney | 15/34 (44%) | 16/36 (44%) | 0.584 |

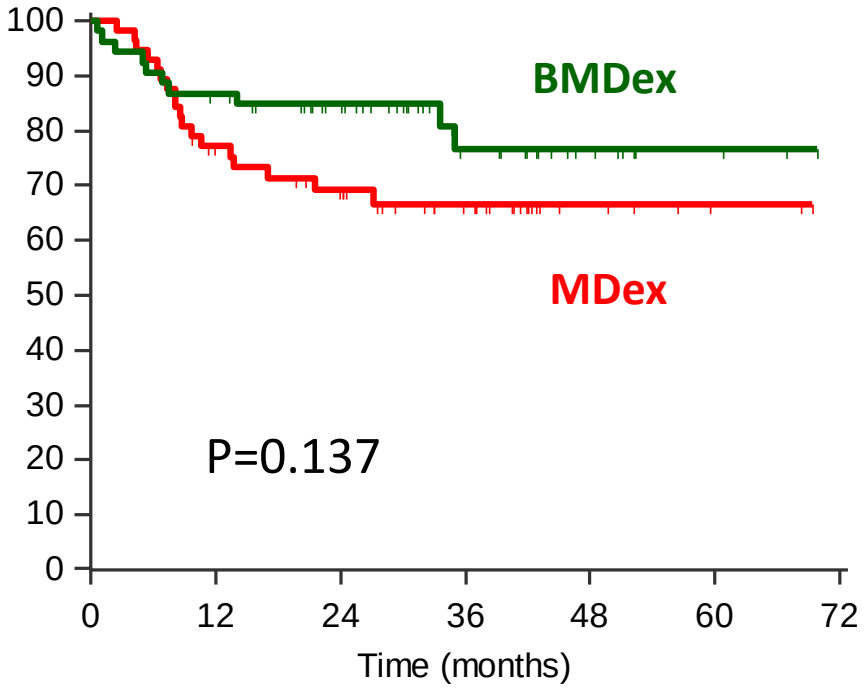
# Survival

- 28 patients died, 18 (32%) in the MDex arm and 10 (19%) in the BMDex arm
- The median follow-up of living patients is 33 months

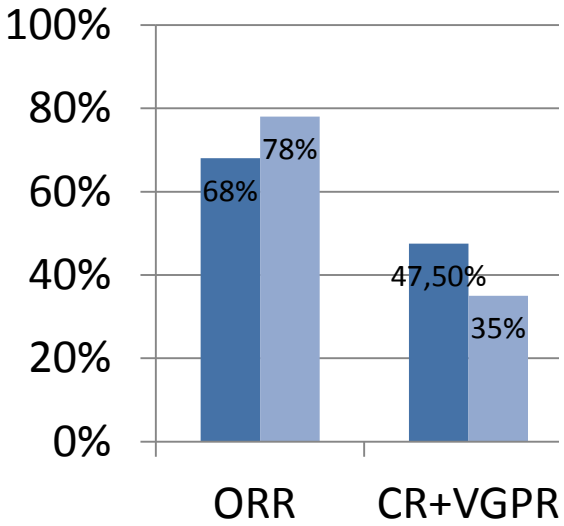
**Time to second-line therapy or death**

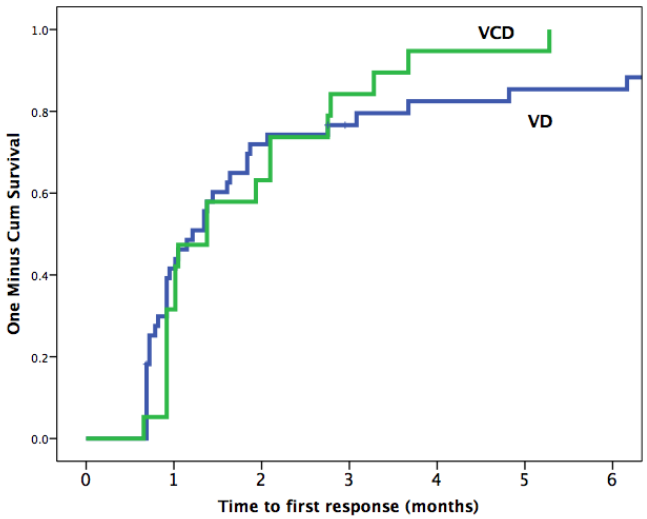


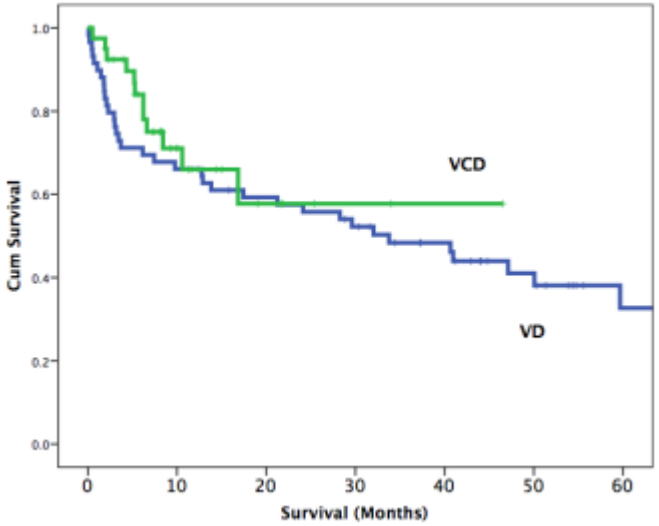

**Overall survival**



# Bortezomib/Dex with or without cyclophosphamide




Bortezomib/Dex is very active

Adding just cyclo does not make significant difference

We need a new approach to anti-plasma cell therapy → immunotherapy ??

# Bortezomib with IMiDs in AL Amyloidosis
# Phase I Trial of Frontline Pom+Bort+Dex

**Phase I Trial of Pomalidomide, Bortezomib, and Dexamethasone As Frontline Treatment of AL Amyloidosis**

- *N=18* pts (17 AL, 1 LCDD), Mayo stage 1/2/3/unknown: 4/8/3/3.

- **MTD: POM 3 mg (d1-21) & BTZ 1.0 mg/m$^2$ (d 1,8,15) & DEX 20 mg (d1,8,15,22)**

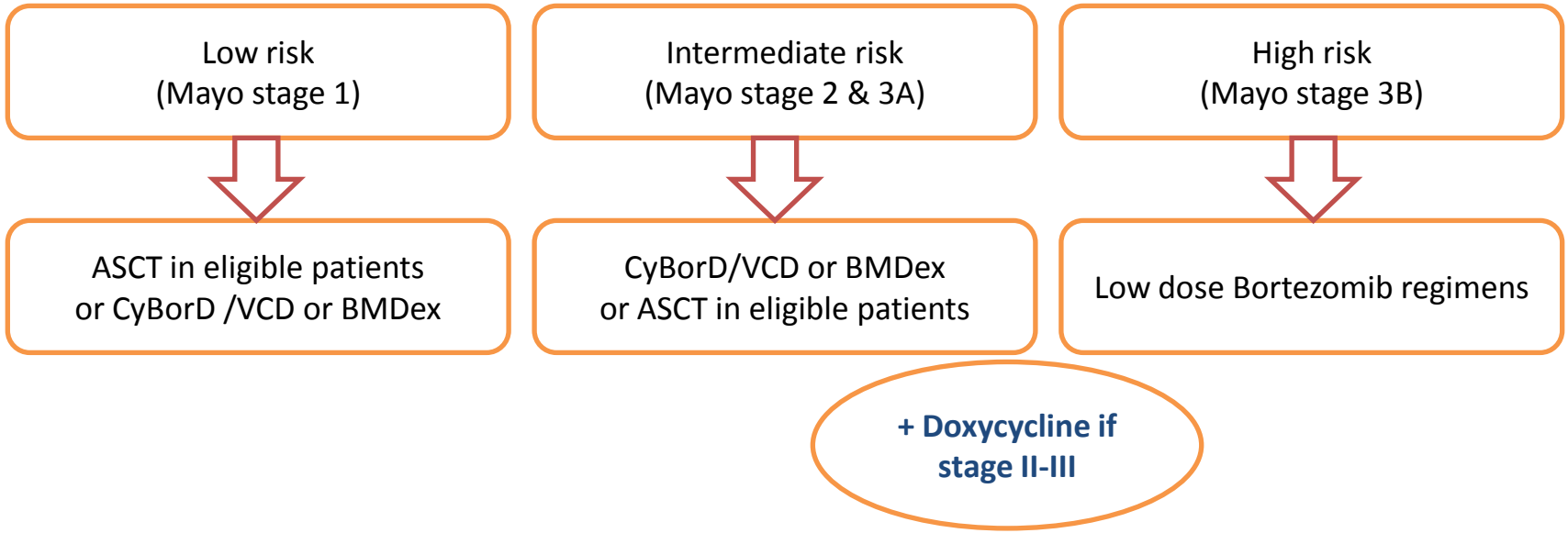
- AEs: fatigue (n=15), diarrhea (n=8), constipation (n=8), anemia (n=12), neutropenia (n=7).
- A median of 3 cycles was given (range 1-27).
- N=8 pts have died, 4 of sudden death

- **Hematologic response rate: 50% (4 PR, 3 VGPR, 2 CR)**

**Authors' Conclusion:** **PVd difficult to administer.** The on-trial deaths, all attributed to cardiac AL, underscore the complexity of clinical research in pts with previously untreated AL. Observed HR rate was similar to that for CyBorD

# Current Treatment approach of AL amyloidosis

- Standard of care: Bortezomib combos →VGPR/CR~ 50%
- Risk adapted therapy



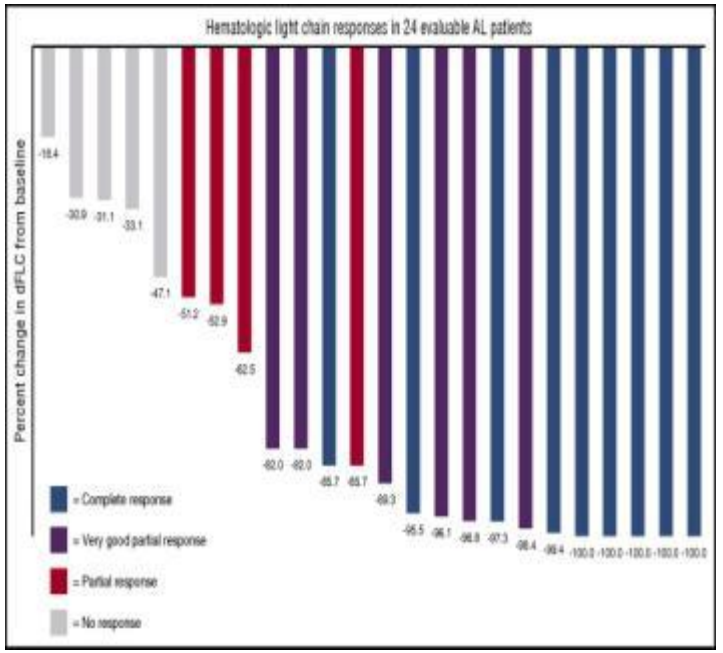

**Frequent assessment of response**

- **At least VGPR at 3 months**
- **if not, then consider change of therapy (or +IMiD?)**

# Daratumumab in AL amyloidosis retrospective data

- Daratumumab in AL amyloidosis: rapid activity, no cardiac toxicity, no myelotoxicity

– N=25 consecutive **previously treated AL patients**
– 72% cardiac involvement
– median: 3 prior lines
– Daratumumab standard dose and schedule
– HemORR : 76% (CR: 36%, VGPR: 24%).
– Median time to response: 1 month.
– no Gr3- 4 IRRs ; Gr1-2: 15/24 patients.




Kaufman GP et al Blood 2017;130(7):900-902

# Daratumumab in AL amyloidosis retrospective data

| | Khouri J et al Abstract # 1819 | Kimmich C et al Abstract #1837 |
|---|---|---|
| **Number of patients** | 15 | 32 |
| **Schedule / duration** | IV Standard / until PD | IV Standard in 17 & every other week in15 / NR |
| **Prior therapies** | 4 | 3 |
| **HDM/ASCT / IMiDs / PIs** | 60% / NR / NR | 34% / 91% / 91% |
| **ORR** | 9/11 (82%) | 23/32 (72%) |
| **CR / VGPR** | 1 (9%)/ 8 (73%) | 3 (9%)/ 14 (44%) |
| **Organ Response** | 4/8 cardiac | 3/9 renal , 2/14 NTproBNP response |

# 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

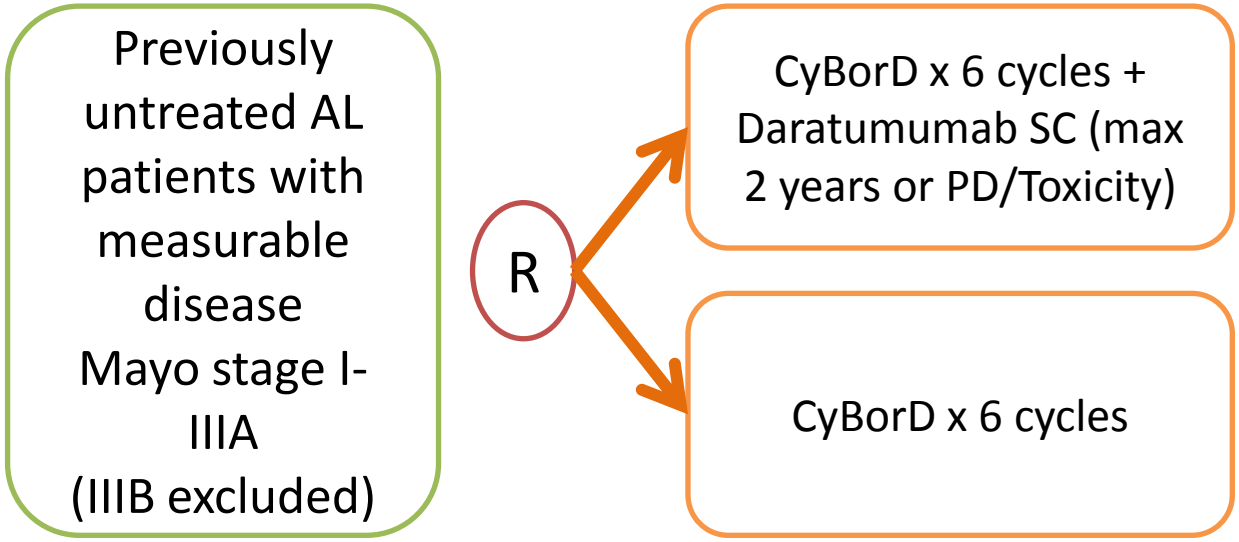
# Daratumumab in AL amyloidosis: prospective, Phase 2 data

| | 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

# Θεραπεία του πλασματοκυτταρικού κλώνου : Σύγχρονη προσέγγιση

- **<u>Στόχος:</u>** Ταχεία αιματολογική ανταπόκριση για την επίτευξη CR / VGPR εντός 1-2 μηνών
- Αναγκαιότητα για βαθιά και διατηρήσιμη ανταπόκριση ($MRD^{neg}$;)
- Τα διαθέσιμα αντινεοπλασματικά φάρμακα έχουν πιθανόν φτάσει στα όρια της αποτελεσματικότητάς τους στην AL (?)
- Καρδιοτοξικότητα και νεφροτοξικότητα: πρόκληση σε αρρώστους με AL
- Επείγουσα ανάγκη: θεραπεία ασθενών πολύ υψηλού κινδύνου (στάδιο 3B) - απαιτούνται αποτελεσματικότερες θεραπείες έναντι του πλασματοκυτταρικού κλώνου και έναντι του αμυλοειδούς


Ευχαριστώ