Πολλαπλούν Μυέλωμα: πόσο εύκολη είναι η επιλογή θεραπείας στην εποχή των νέων παραγόντων

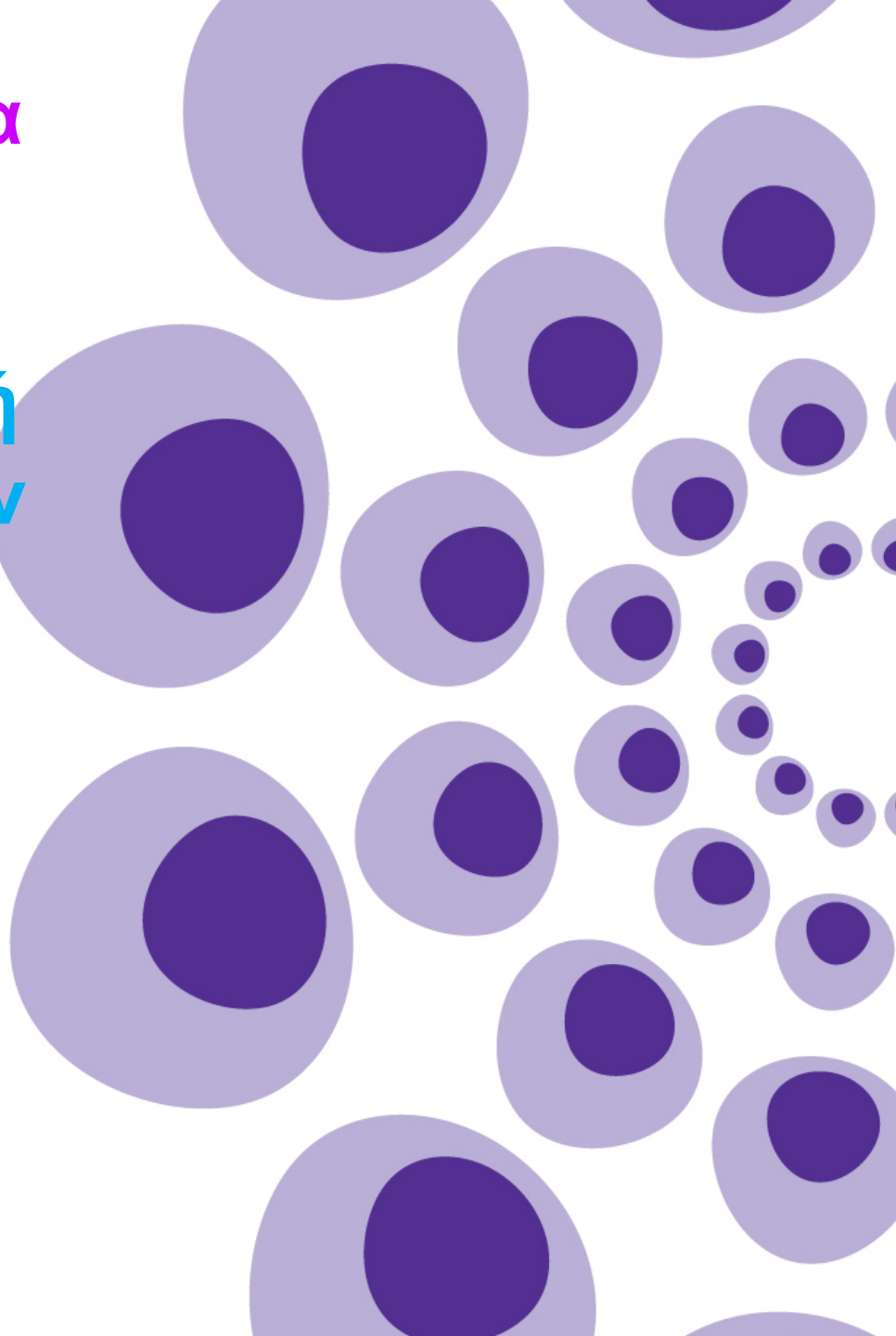
Κ. Λιάπης

Δεν υπάρχει σύγκρουση συμφερόντων με τις παρακάτω χορηγούς εταιρείες:

PFIZER, JANSSEN ONCOLOGY, SOFMEDICA, NOVARTIS, ABBVIE, MSD, WINMEDICA, GENESIS, ROCHE, TAKEDA, ASTELLAS, AMGEN, ANGELINI, ΑΝΤΙΣΕΛ, SERVIER, BRISTOL-MYERS SQUIBB, ABBOTT, GILEAD, SANDOZ, BIANEΞ, RONTIS, MAVROGENIS, AENORASIS, SPECIFAR, KARYO

Πολλαπλούν Μυέλωμα

επιλογή 1ης γραμμής θεραπείας στην εποχή των νέων παραγόντων

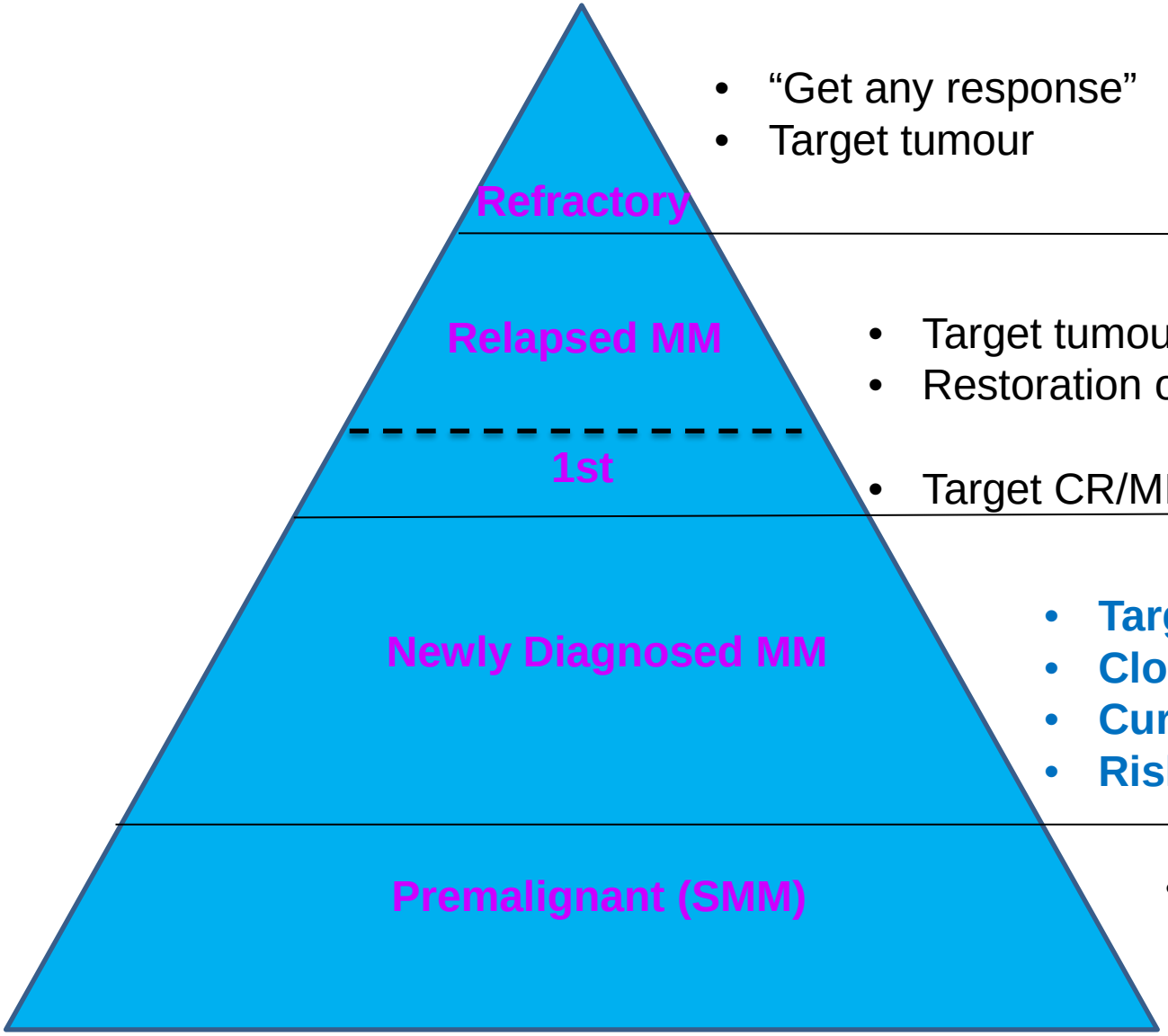


Ερωτήματα

- **Ποια είναι η καλύτερη θεραπεία εφόδου στο ΠΜ ;**

1. Ασθενείς κατάλληλοι για μεταμόσχευση <70

- Ίδια θεραπεία για όλους ή **RISK ADAPTED** therapy;



- "Get any response"
- Target tumour

- Target tumour
- Restoration of function

- Target CR/MRD?

- **Target CR/MRD**
- **Clonal control**
- **Cure?**
- **Risk adapted?**

- Prevent clonal progression (progress to symptomatic)
- Microenvironment
- Immune system
- Cure?

MAYO CLINIC

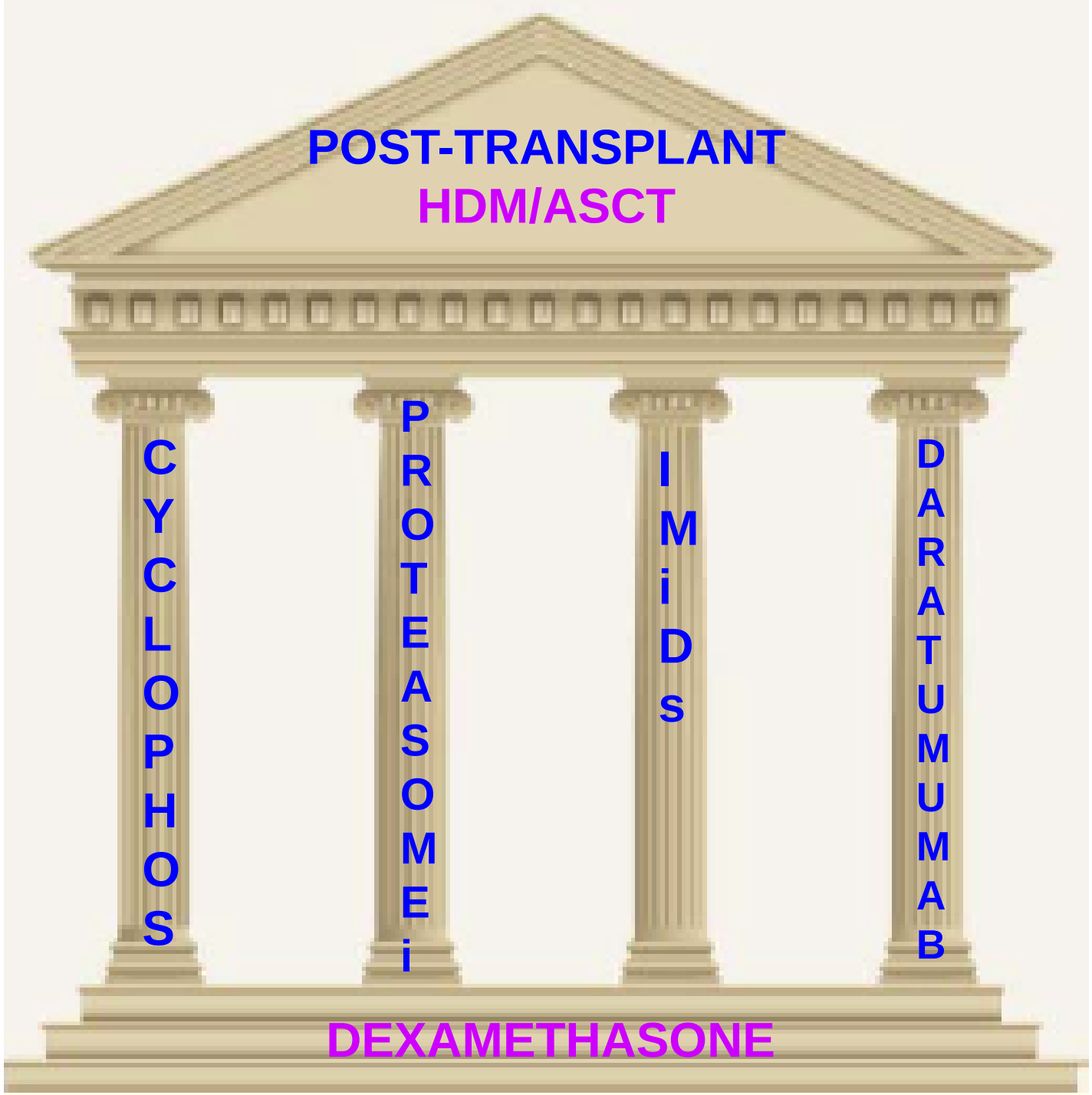
Active Drugs in Multiple Myeloma

Old Drugs	Older Drugs (2003-2007)	Recently Approved Drugs (2013-2015)	Future Drugs
▪ Alkylators ▪ Steroids ▪ Interferon ▪ Anthracyclines	▪ Bortezomib ▪ Thalidomide ▪ Lenalidomide ▪ Liposomal doxorubicin	▪ Carfilzomib ▪ Pomalidomide ▪ Panobinostat ▪ Daratumumab ▪ Ixazomib ▪ Elotuzumab	▪ Ixazomib ▪ Marizomib ▪ Isatuximab ▪ Venetoclax ▪ Dinaciclib ▪ Filanesib ▪ LGH447 ▪ ABT-199

Αναστολείς πρωτεασώματος: Bortezomib (Velcade), Carfilzomib (Kyprolis), Ixazomib (Ninlaro)
Ανοσοτροποποιητικά (IMiDs): Thalidomide, Lenalidomide (Revlmid), Pomalidomide (Imnovid)
Μονοκλωνικά αντισώματα: Daratumumab (Darzalex), Elotuzumab (Empliciti)

The Four Pillars of Cancer Therapy

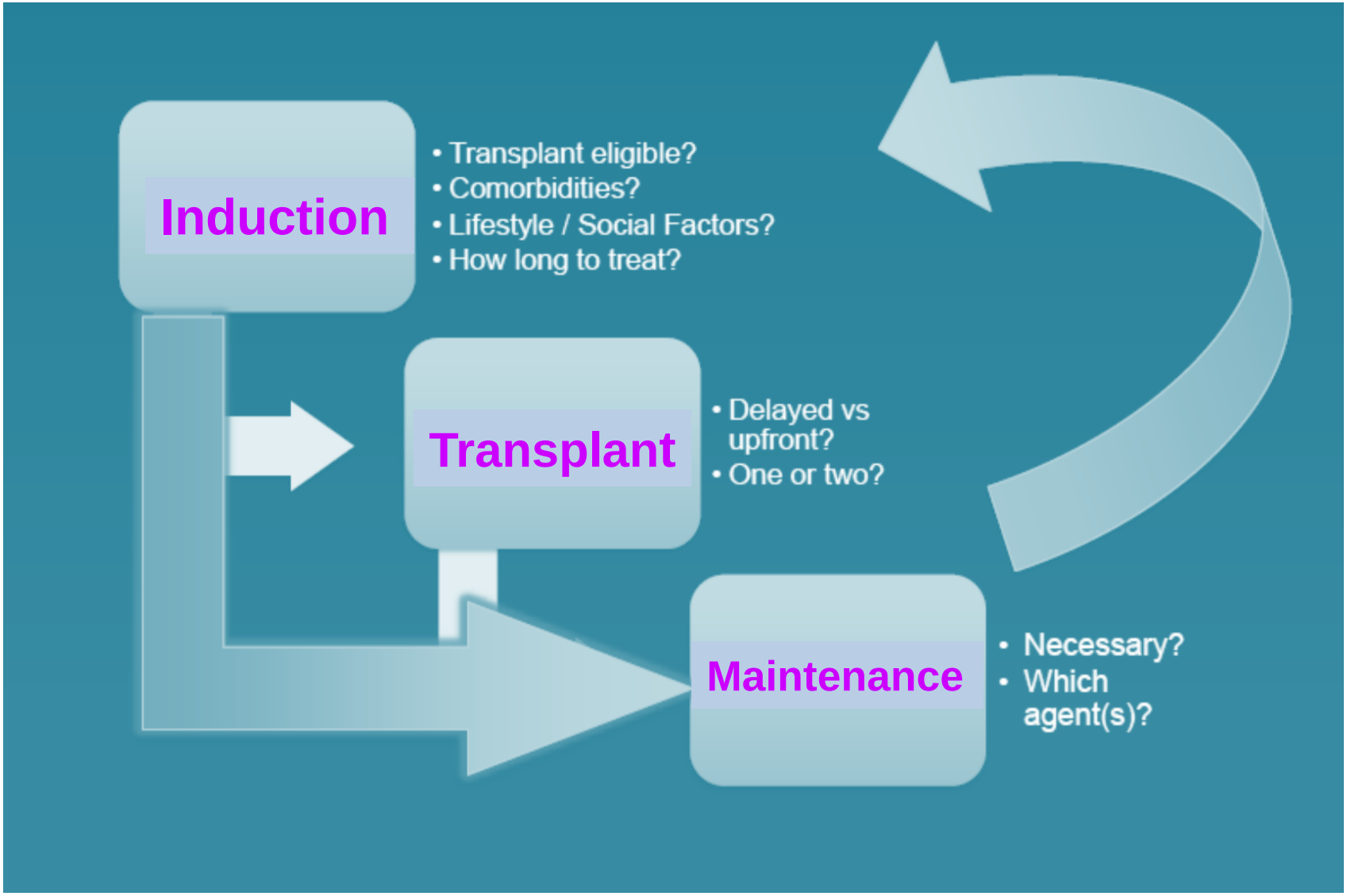
- Surgery
- Radiation therapy
- Chemotherapy
- Immunotherapy
  - Monoclonal antibodies
  - Vaccines
  - Adoptive cell transfer
  - Checkpoint inhibitors

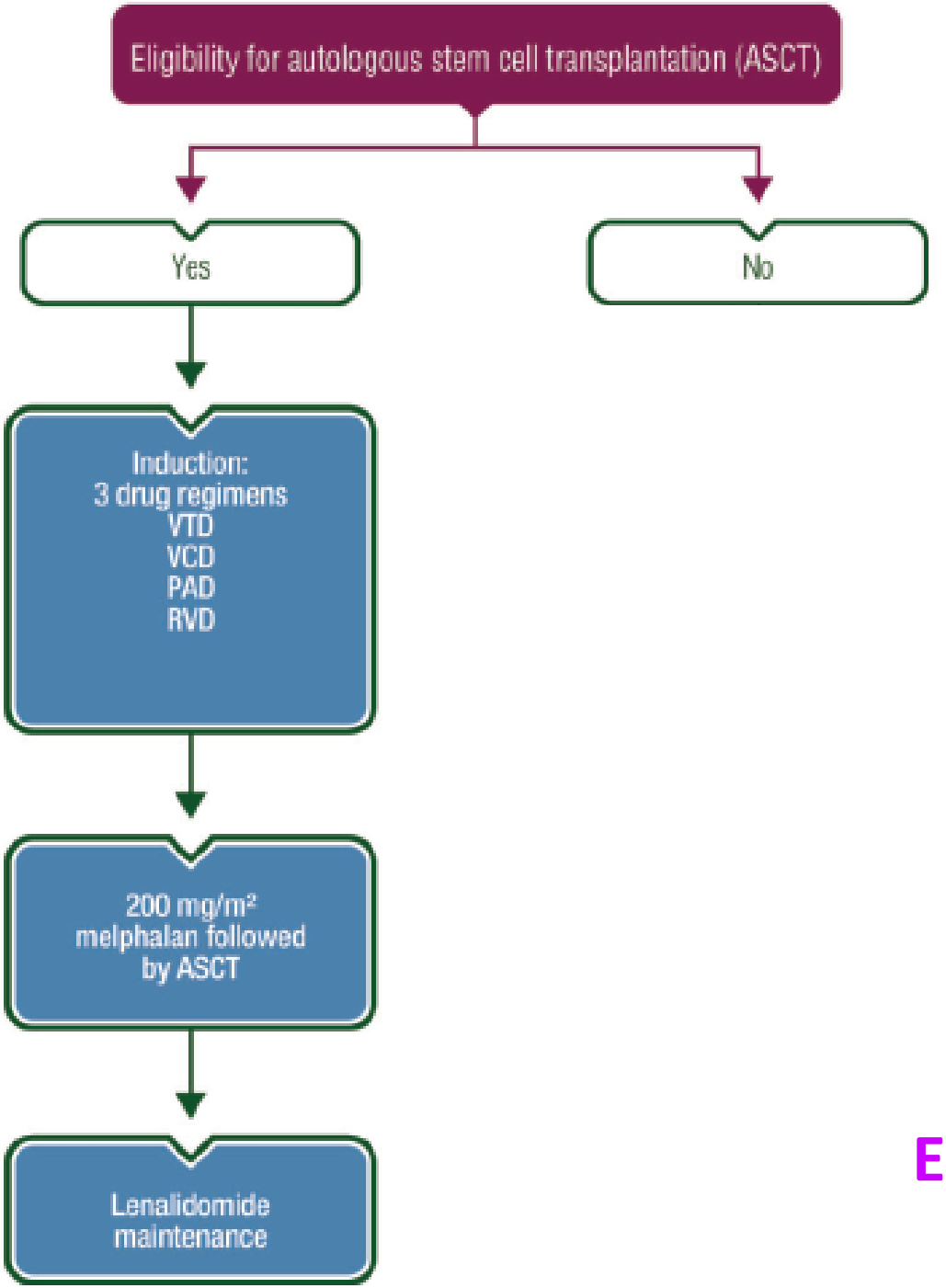

POST-TRANSPLANT
HDM/ASCT
CYCLOPHOS
PROTEASOMEi
IMiDs
DARATUMUMAB
DEXAMETHASONE

3>2

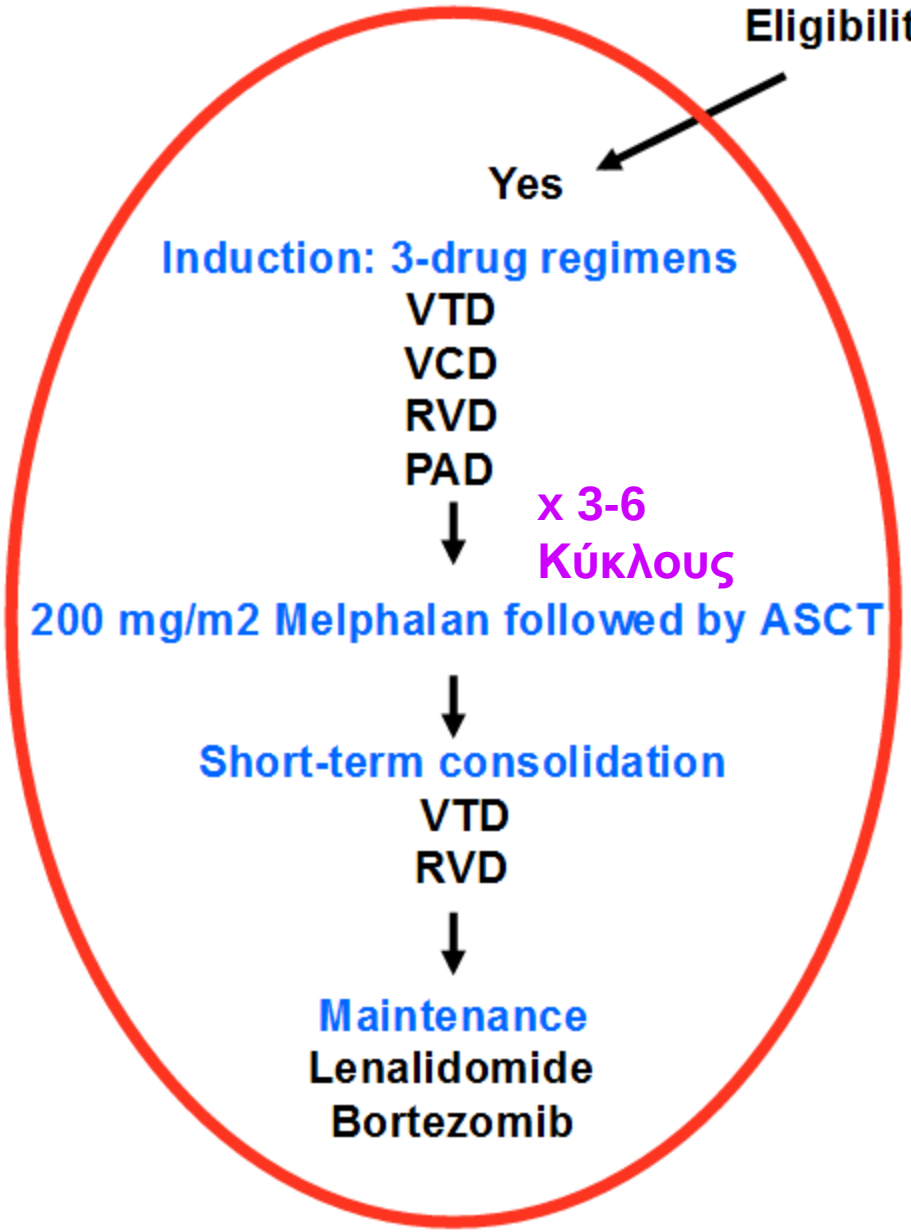
4>3?

Newly Diagnosed Myeloma Plan




Eligibility for autologous stem cell transplantation (ASCT)
Yes
No
Induction:
3 drug regimens
VTD
VCD
PAD
RVD
200 mg/m²
melphalan followed
by ASCT
Lenalidomide
maintenance

ESMO 2017



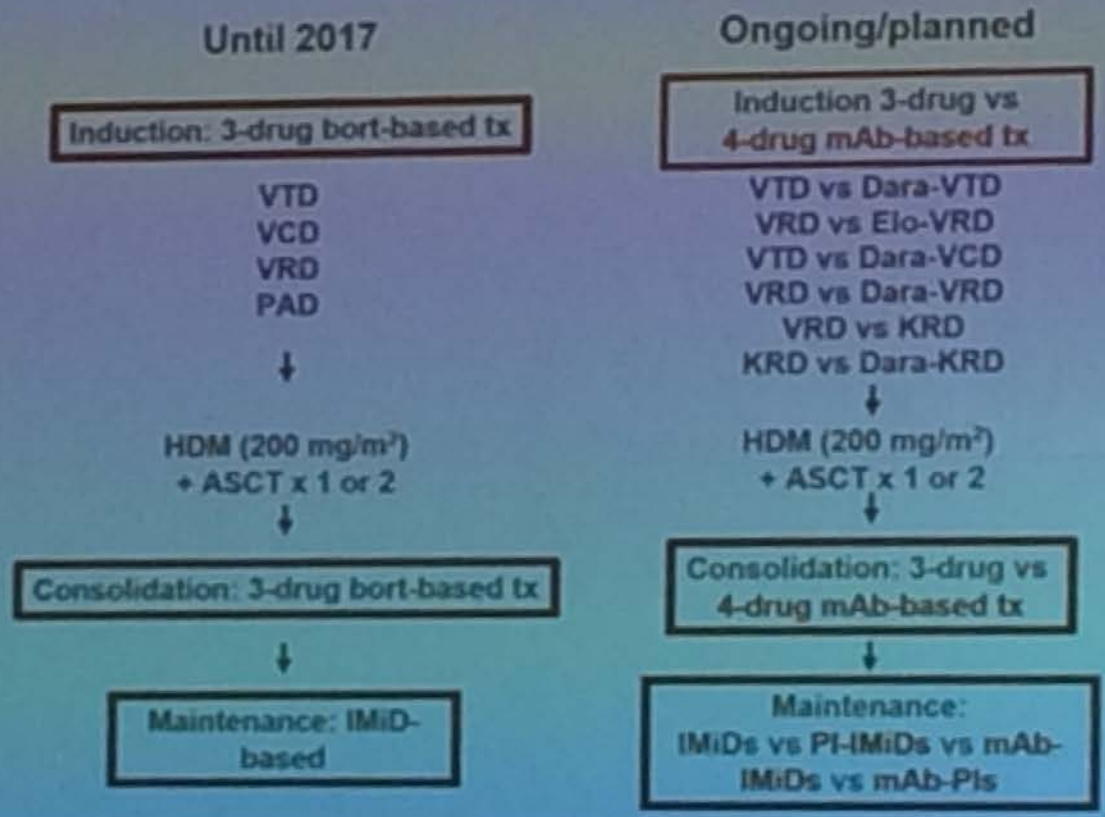
VCD = PAD (VCD λιγότερο τοξικό)
VTD > VCD (VCD καλύτερα ανεκτό)
VTD ~ VRD (VRD καλύτερα ανεκτό)

Πιθανώς 6 > 4 κύκλους

FRONTLINE THERAPY

Frontline therapy of multiple myeloma.
Moreau P, Attal M, Facon T.

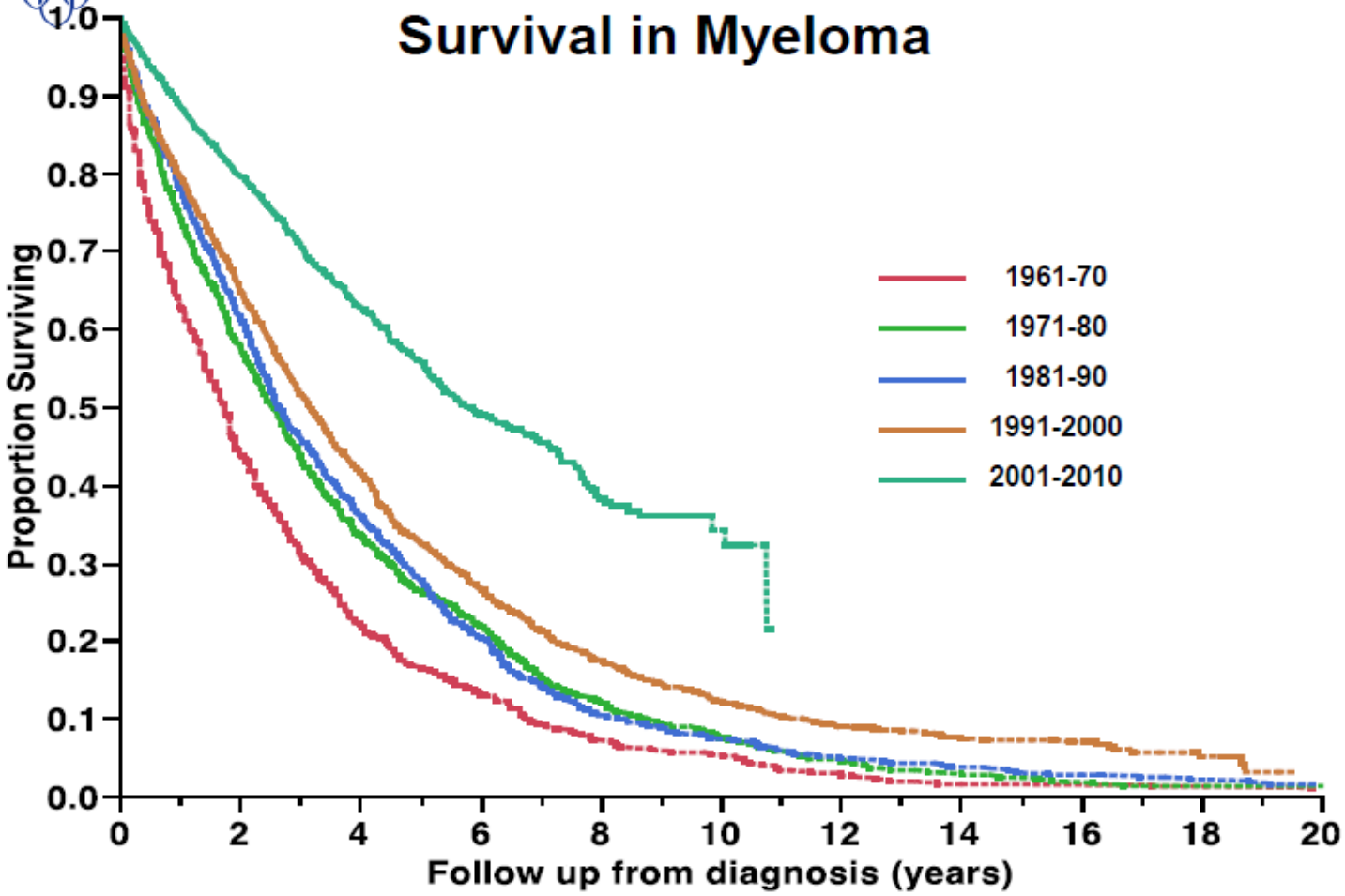
Summary current and future treatment algorithm for transplant-eligible MM patients



Moreau P, et al. Ann Oncol 2017;00:1–11. Cavo, personal communication; clinicaltrials.gov identifiers: NCT02874742; NCT02541383; NCT02406222; NCT01863550

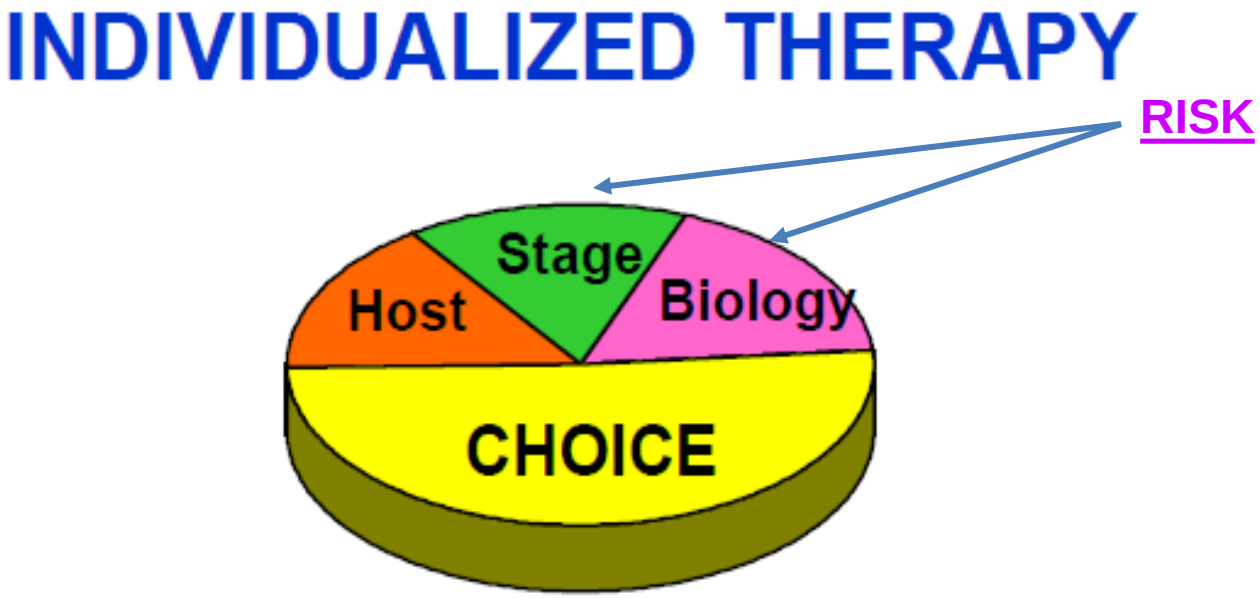
MAYO CLINIC

Survival in Myeloma



Kumar S. Blood 2008;111: 2516 – 2520; Kumar S. Leukemia (2014) 28, 1122–1128.

?ίαση → Το μυέλωμα είναι ετερογενής νόσος.



INDIVIDUALISED: RISK – βαθιά CR – Continuous Tx

Revised ISS

Durie-Salmon (1975)
ISS - JCO 2005 (Greipp)
R-ISS - JCO 2015 (Palumbo)

The revised International Staging System (R-ISS) incorporates FISH analysis, LDH, and the International Staging System (albumin and β2m levels) to asses risk for patients with newly diagnosed MM (Table 1). Patients should be staged before therapy begins based on their serum LDH, β2m, albumin, and cytogenetics based on CD138 sorted bone marrow cells.

Table 1. Revised International Staging System (R-ISS) for Multiple Myeloma

R-ISS Stage	ISS Stage		Chromosomal Abnormality *		Serum LDH	5-year PFS, %	5-year OS, %
I	I	and	Standard risk	and	<ULN	55	82
II	II		Not R-ISS stage I or III			36	62
III	III	and	High risk	or	>ULN	24	40

28%
62%
10%

ISS I = serum β_2 microglobulin <3.5 mg/L and serum albumin ≥3.5 g/dL.

ISS II = not ISS stage I or III.

ISS III = serum β_2 microglobulin ≥5.5 mg/L.

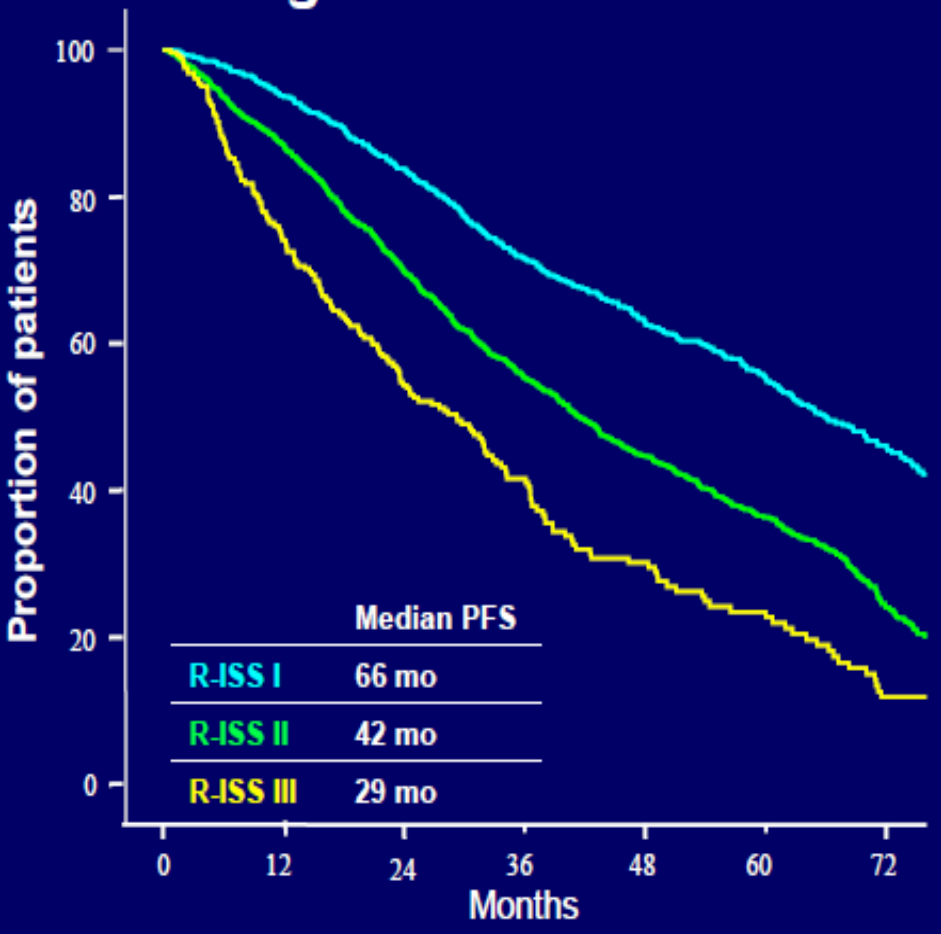
*Testing by FISH; standard risk = no chromosome abnormality; high risk = del(17p) and/or t(4:14) and/or t(14:16).

LDH = lactic acid dehydrogenase; OS = overall survival; PFS = progression-free survival; ULN= upper limit of normal

A recent consensus statement by the IMWG on cytogenetic risk affirms the use of the ISS, LDH, and FISH for risk stratification but incorporates other considerations. For example, GEP signatures may also be used if available. In addition to t(4;14), del(17p), and +1q21, the cytogenetic abnormalities t(14;20), t(14;16), del(17/17p), and any nonhyperdiploid karyotype should be considered high risk. Combinations of more than 3 cytogenetic abnormalities confer ultra-high risk. According to the IMWG, patients should be tested routinely for t(4:14) and del(17p).

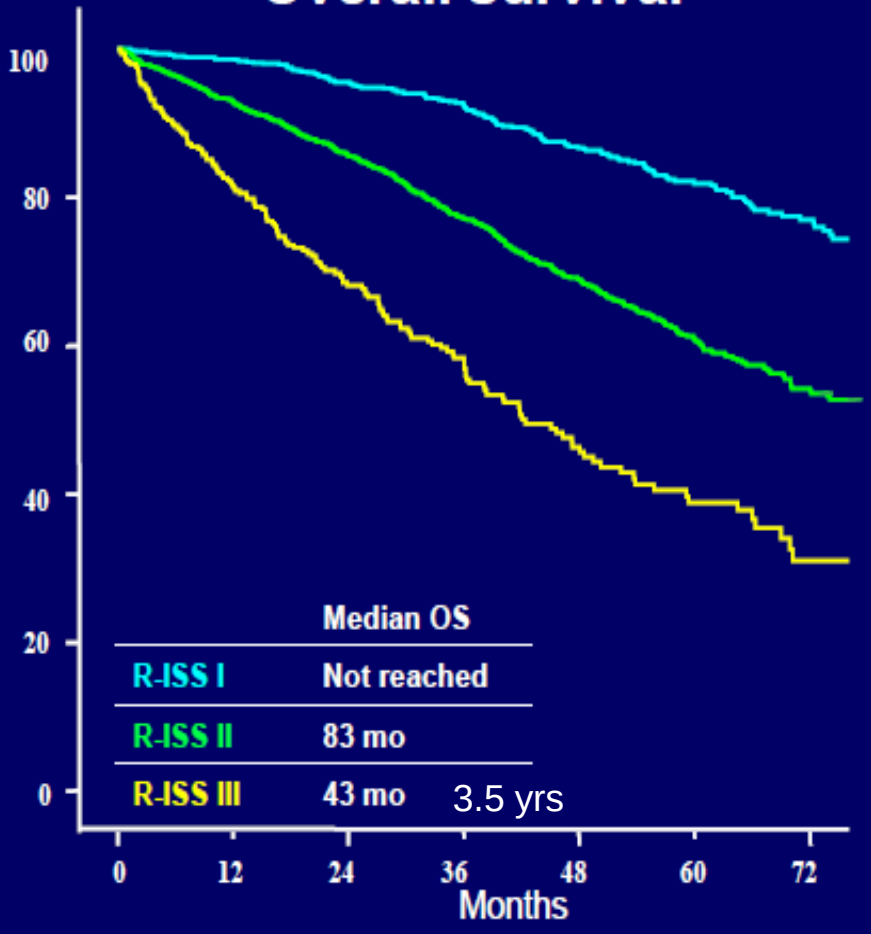
Revised-ISS
New risk stratification

Progression-free survival



	HR (95% CI)	p value
R-ISS II vs I	2.09 (1.75-2.49)	<0.001
R-ISS III vs I	3.58(2.70-4.74)	<0.001

Overall survival



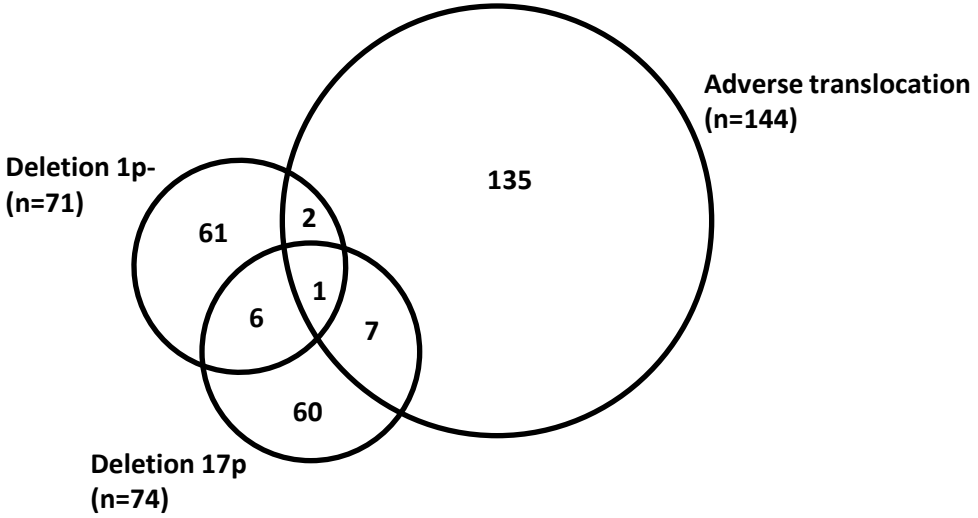
	HR (95% CI)	p value
R-ISS II vs I	3.68 (2.75-4.92)	<0.001
R-ISS III vs I	9.95 (6.45-15.36)	<0.001

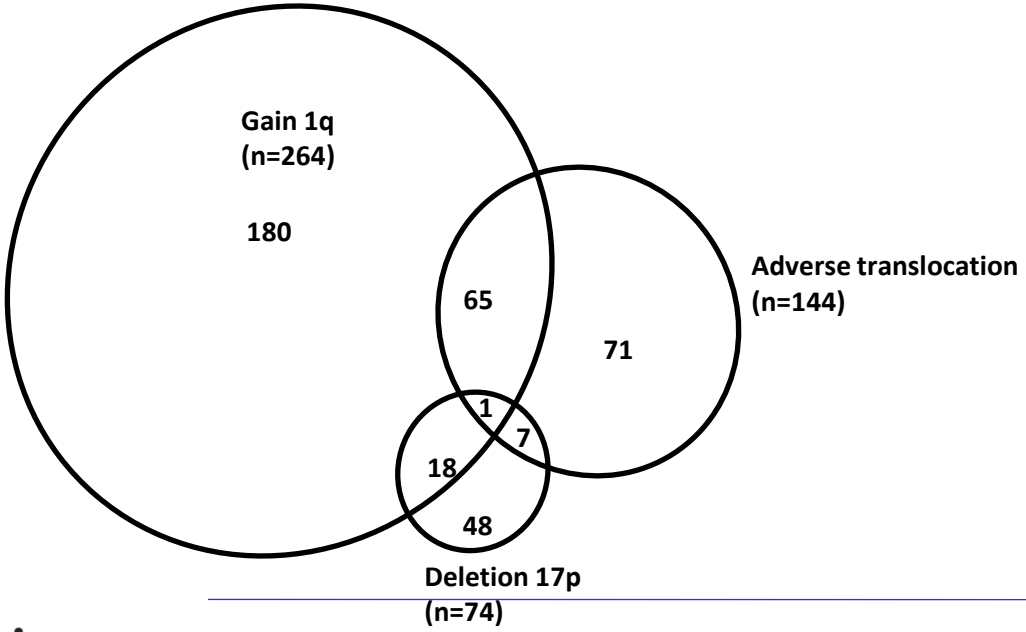
Palumbo A. et al *J Clin Oncol* 2015 33(26):2863-9

Current molecular variables that have important clinical value:

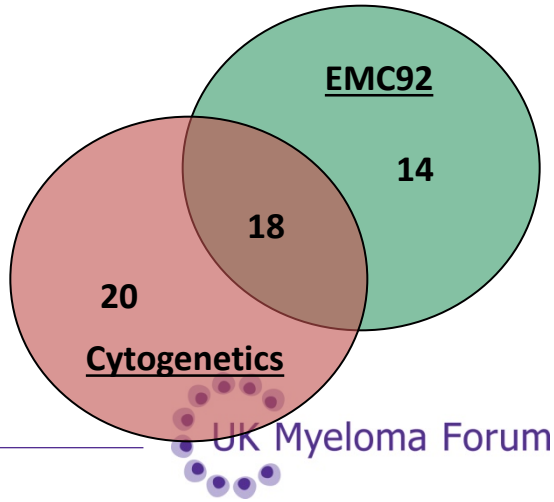
Lesion	Prognosis	Prevalence
17p-	Poor prognosis	8%
1q+	Poor prognosis	33%
1p-	Poor prognosis	8%
t(4;14)	Poor prognosis	15%
t(11;14)	Neutral prognosis	19%
t(14;16)	Probably poor prognosis	1%
t(14;20)	Poor prognosis	3.2%
Hyperdiploidy	Neutral prognosis	48%
BRAF	Response to BRAF inhibition	4%
TP53	Poor prognosis	4%
t(8;14)	Poor prognosis	6%

Cytogenetic inter-relationship



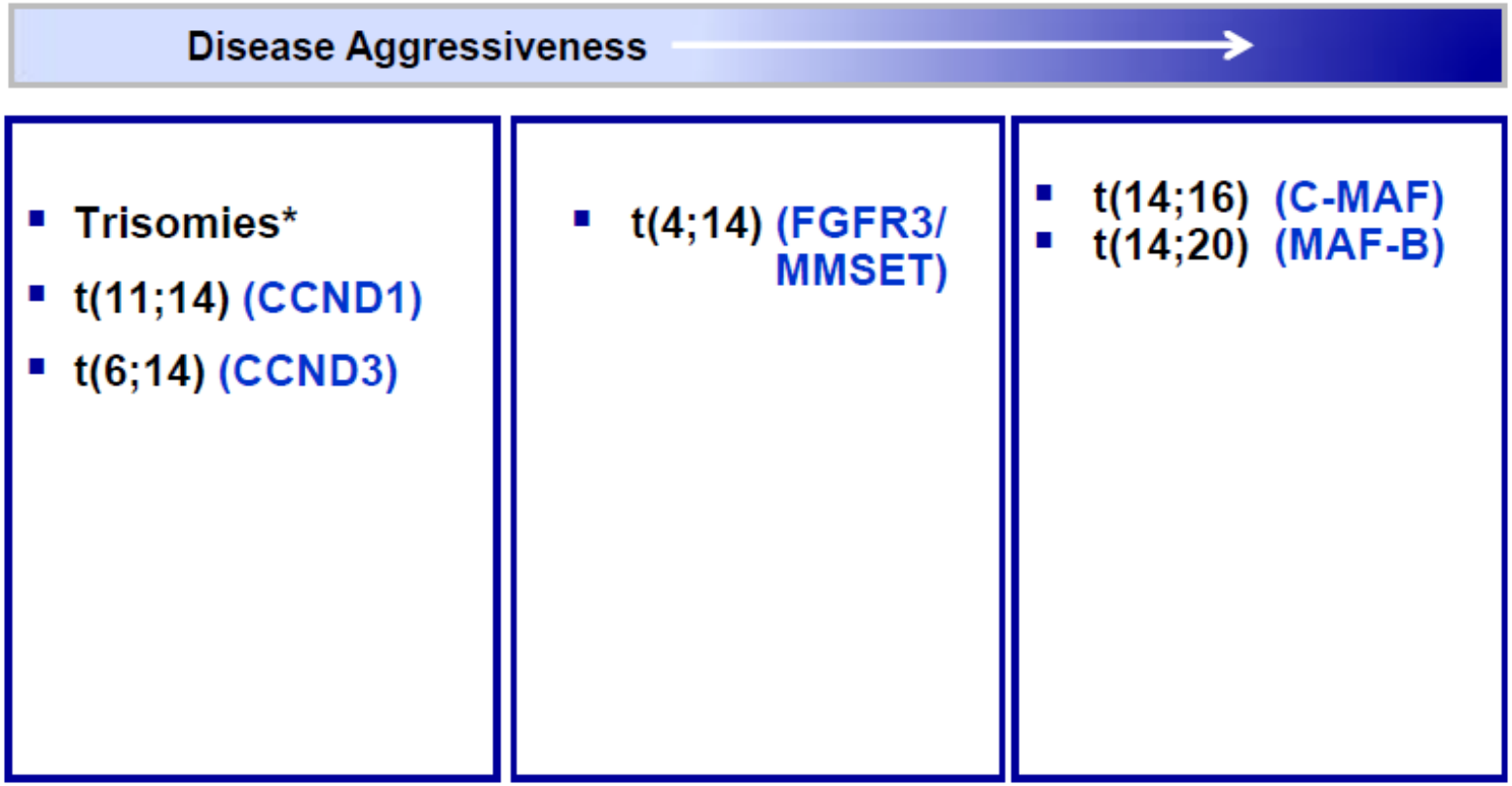


Number gained	Frequency
1p-	10%
1q+	34%
17p-	9%
Adverse Translocation	21%
GEP	20%
Overall	25-35%



MAYO CLINIC

Molecular Classification of Myeloma



*~10% have both trisomies and IgH translocations

Kumar S, et al. *Blood.* 2012;119:2100-2105

MAYO CLINIC

mSMART

- Multiple myeloma is increasingly recognized as more than one disease, characterized by marked cytogenetic, molecular, and proliferative heterogeneity.
- The result is widely varied outcome ranging from low to very high risk.
- Treatment is evolving rapidly as more effective agents and combinations become available.
- mSMART (Mayo Stratification for Myeloma And Risk-adapted Therapy) is a consensus opinion that takes into account genetically determined risk status and the various treatment strategies currently available.
- Risk stratification and individualizing treatment options is complex and based not just on the cytogenetic classification presented here, but also on various host factors, disease stage, and a variety of other prognostic factors
- **Therefore we recommend all patients with newly diagnosed myeloma be seen at least once at a referral center with expertise in the disease**

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed May2018

MAYO CLINIC

mSMART 3.0: Classification of Active MM

High-Risk

- High Risk genetic Abnormalities [a,b]
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - p53 mutation
  - Gain 1q
- RISS Stage 3
- High Plasma Cell S-phase[c]
- GEP: High risk signature

- Double Hit Myeloma: Any 2 high risk genetic abnormalities
- Triple Hit Myeloma: 3 or more high risk genetic abnormalities

Standard-Risk[a]

All others including:

- Trisomies
- t(11;14)[d]
- t(6;14)

[a] Trisomies may ameliorate
[b] By FISH or equivalent method
[c] Cut-offs vary
[d] t(11;14) may be associated with plasma cell leukemia

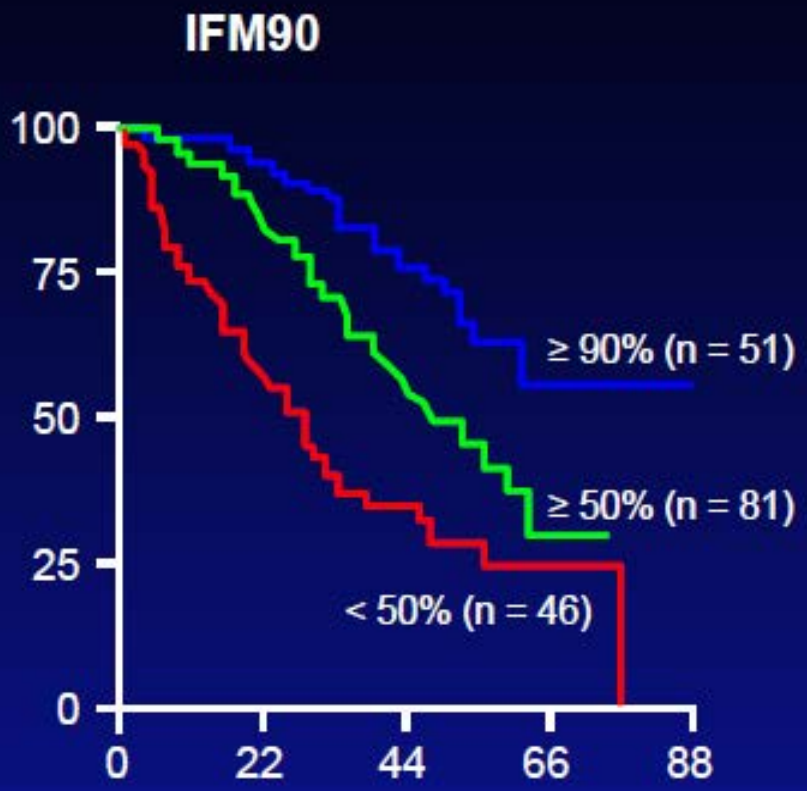
Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed August 2018

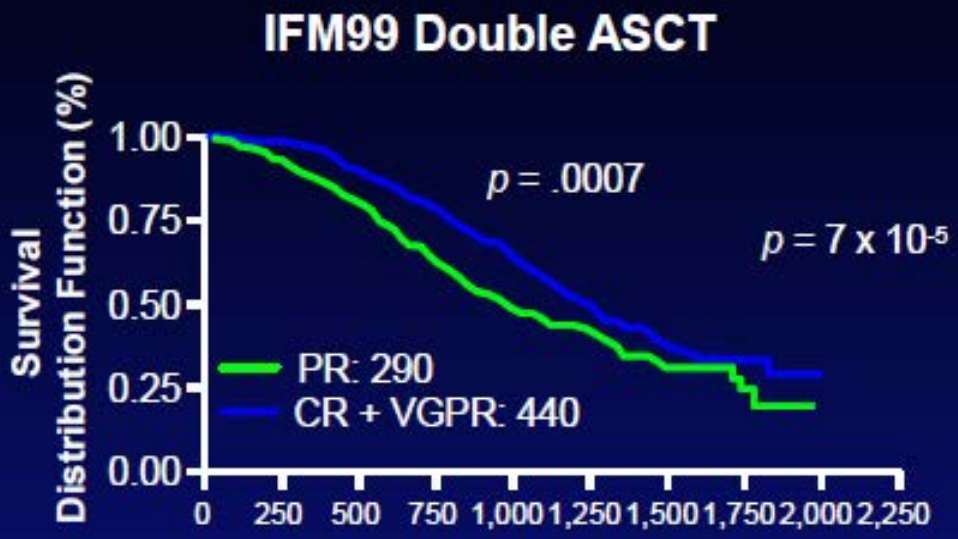
I define risk status based on the following criteria:

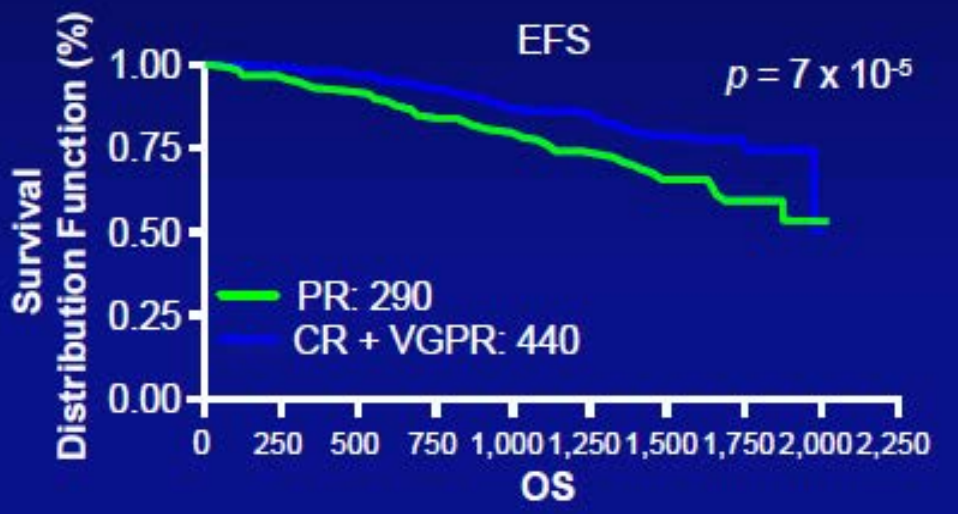
Risk group	Group
Standard risk 60% **~ R-ISS 1**	The rest **8-10 y**
Intermediate risk 20%	Single t(4;14), t(14;16), t(14;20), 17p-, 1q+, 1p-, myc@ and β2M <5.5 OR Blastic morphology **4-5 y**
High risk 20% **~ R-ISS 3**	Single t(4;14), t(14;16), t(14;20), 17p-, 1q+, 1p-, myc@ AND β2M ≥5.5 **3 y**
Ultra-high risk	>1 adverse lesion or GEP of high risk disease or plasma cell leukaemia

Στόχος: βέλτιστη ανταπόκριση+ διαρκής ανταπόκριση

Deeper Responses are Better: Impact of CR + VGPR on Outcome



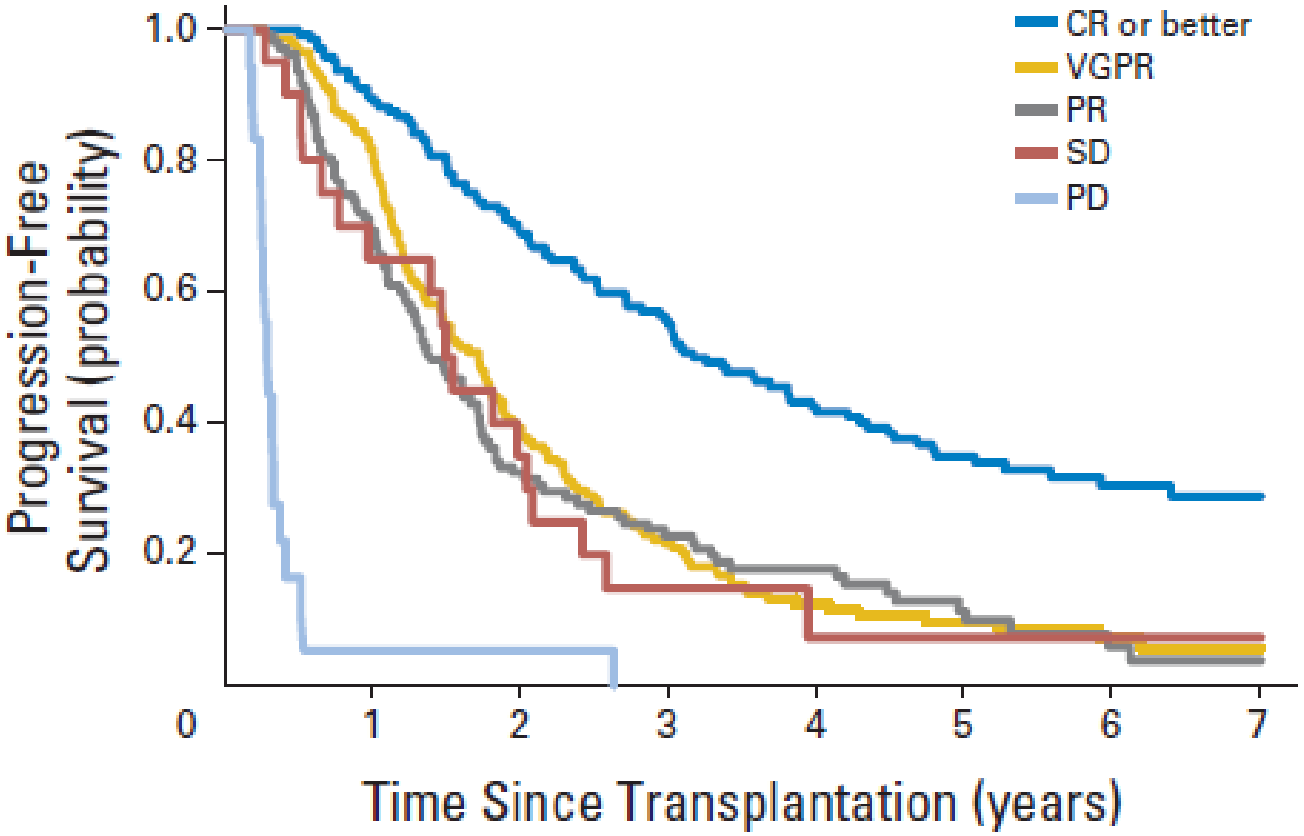




EFS = event-free survival.

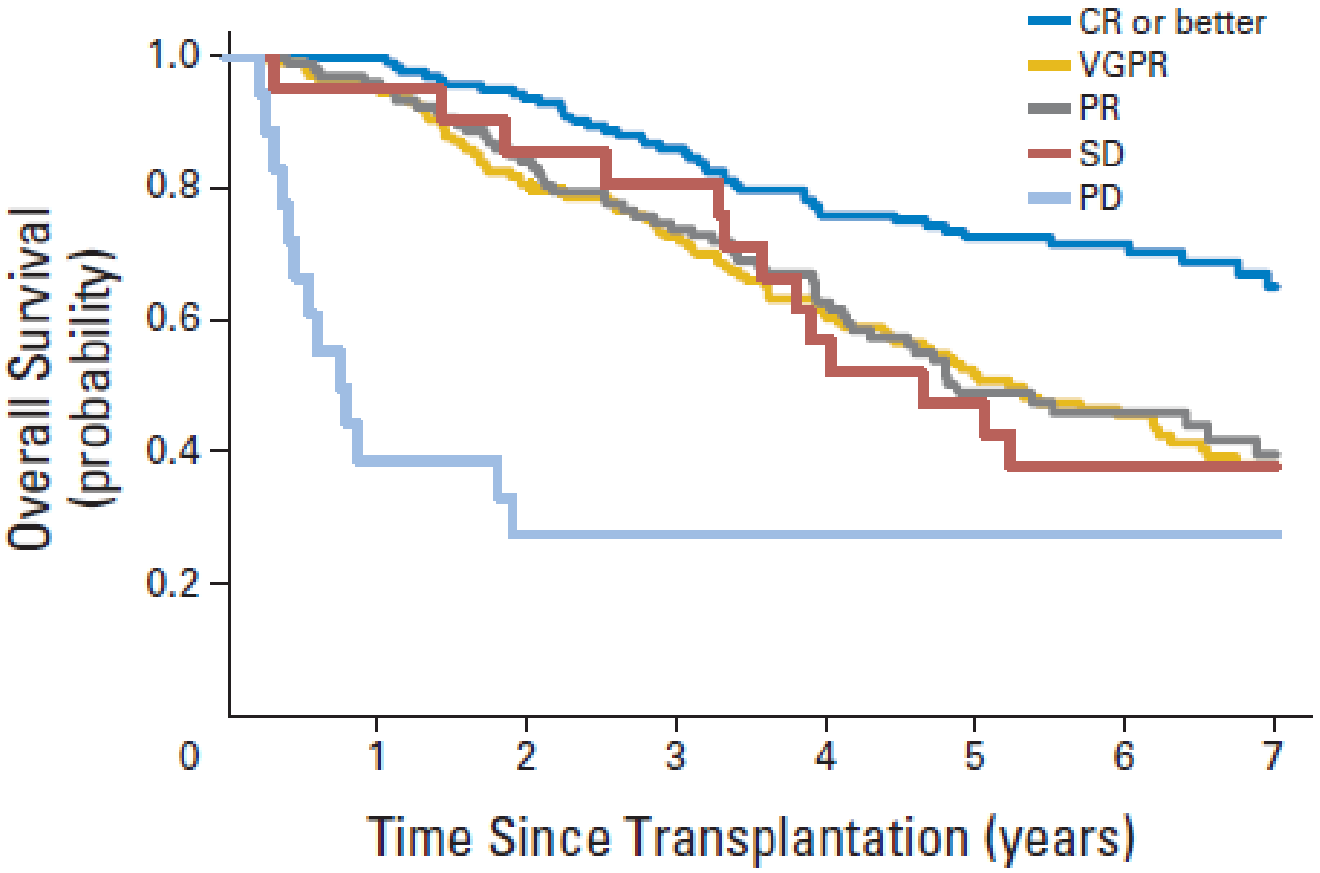
Moreau et al, 2008; Attal et al, 1996, 2006.

Η κλινική ανταπόκριση στη θεραπεία επηρεάζει το PFS



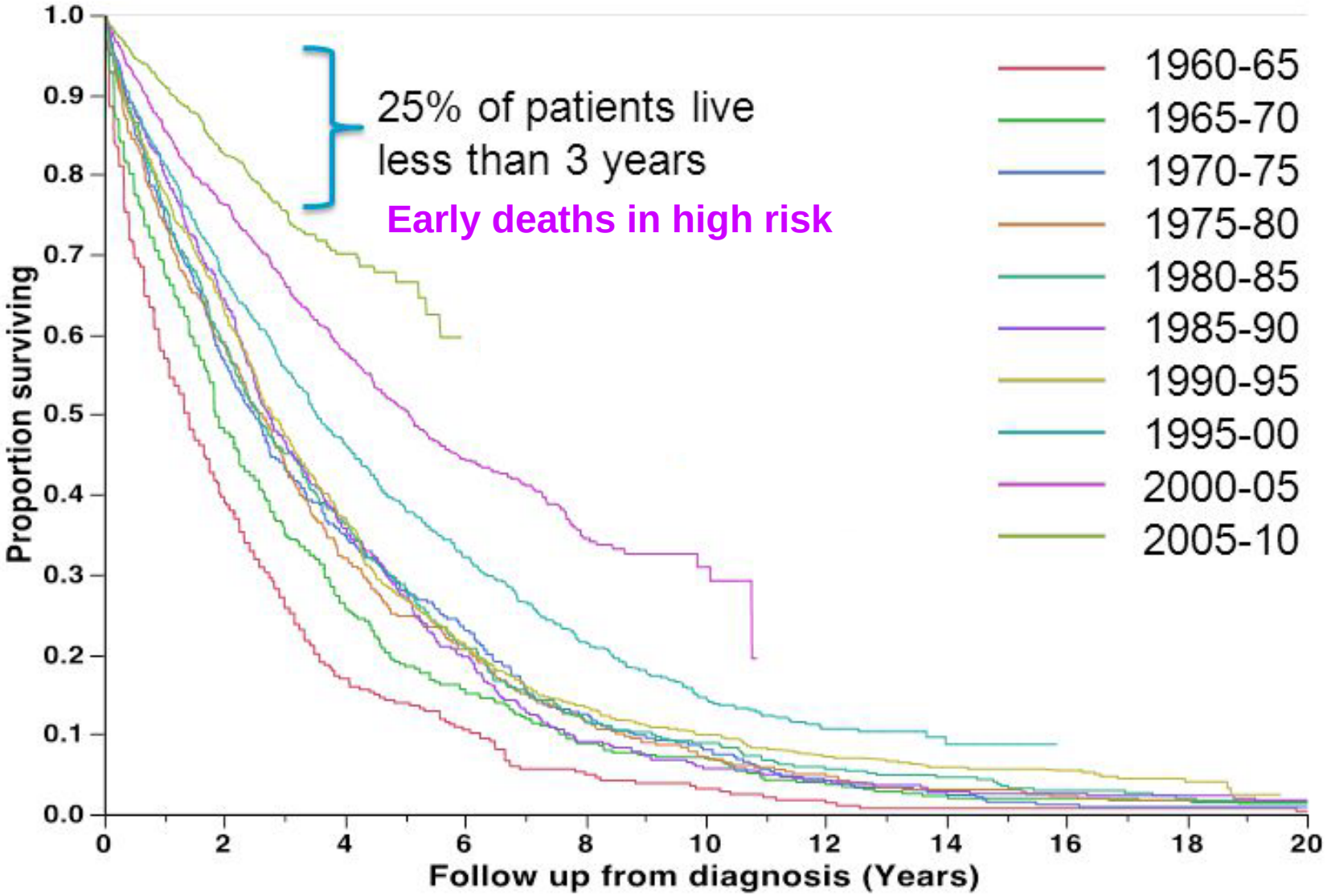
Kapoor et al. *J Clin Oncol 2013*

Η κλινική ανταπόκριση στη θεραπεία επηρεάζει την OS



Kapoor et al. *J Clin Oncol 2013*

Improving Survival in MM



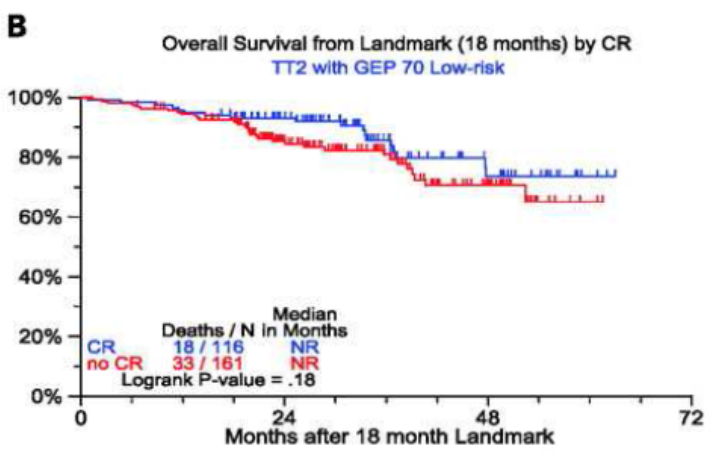
Kumar et al *Leukemia* 2014

• ΜΥΕΛΩΜΑ ΥΨΗΛΟΥ ΚΙΝΔΥΝΟΥ

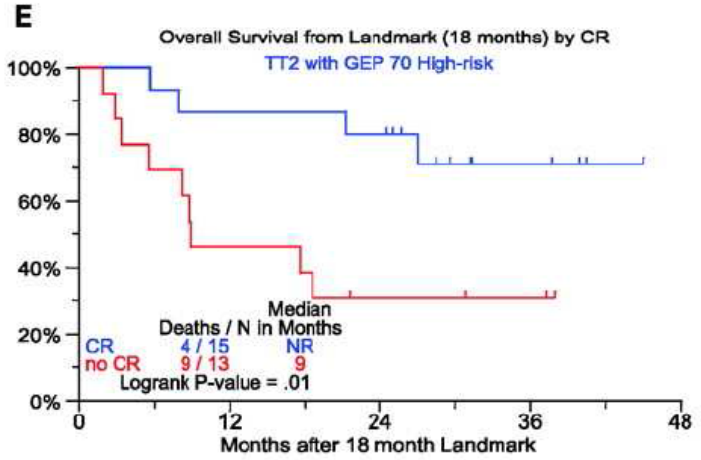
- **20-25%**
- **This subset of patients do not benefit from current treatment approaches**
- **There is a need for this population to develop both good diagnostic tools to identify these patients and new treatment strategies**

Η CR είναι πολύ σημαντική στο ΠΜ υψηλού κινδύνου

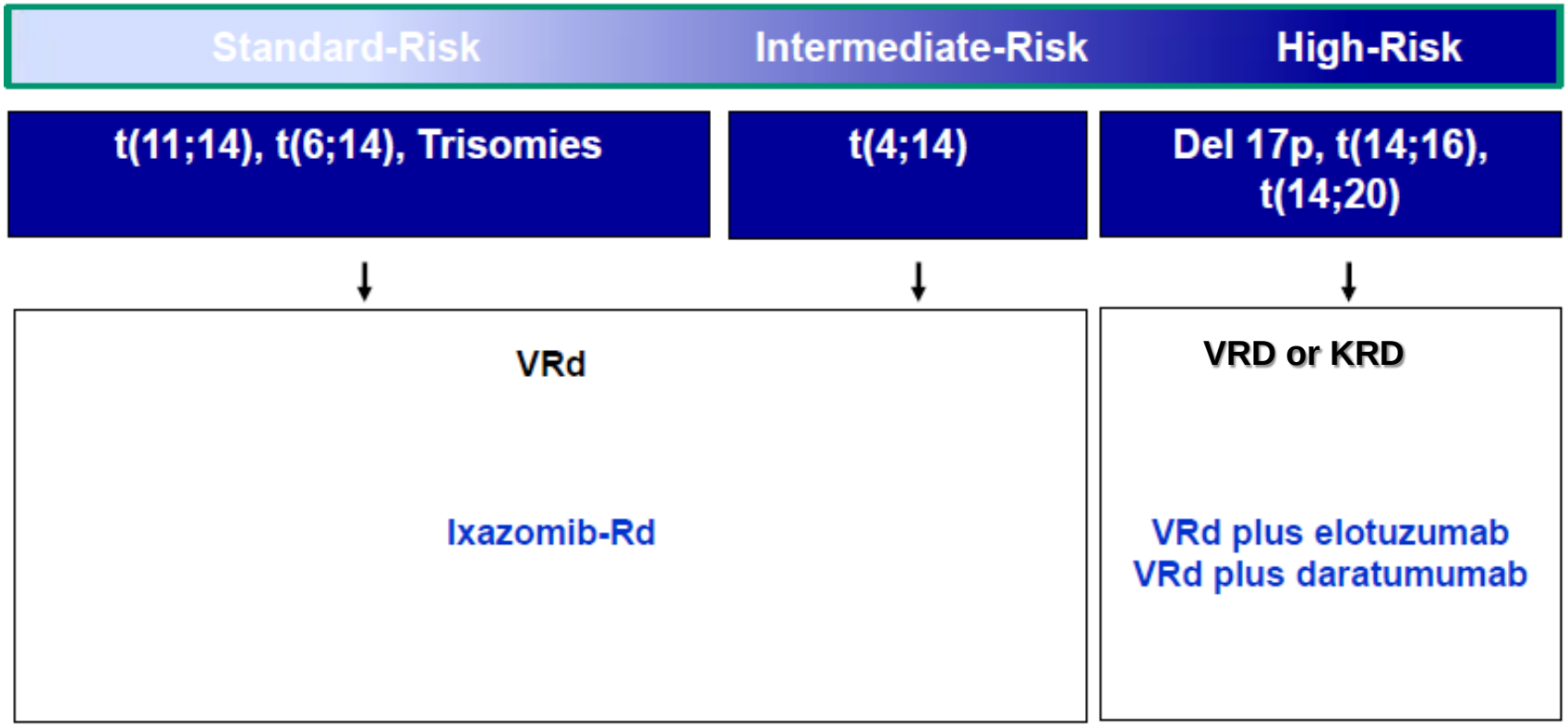
Low-Risk MM (87%)



High-Risk MM (13%)

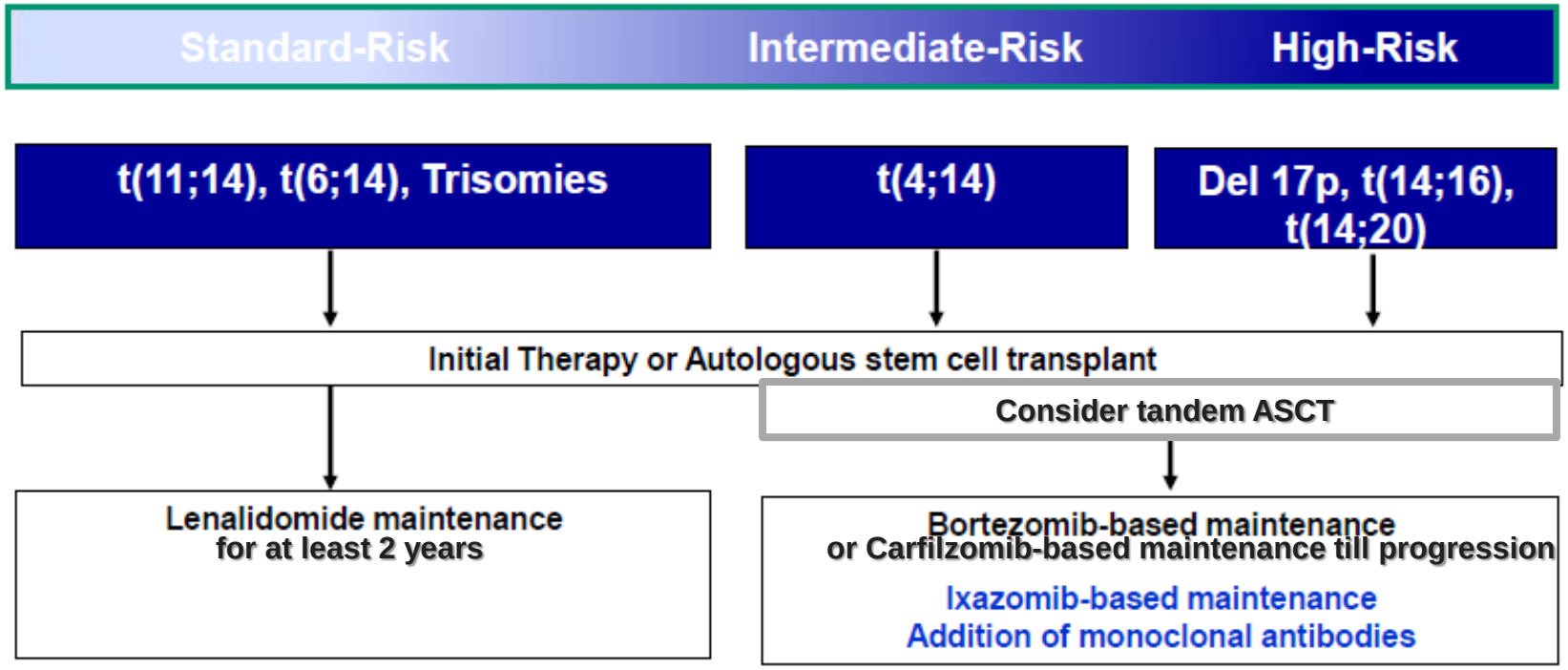


Haessler, J. et al. Clin Cancer Res 2007;13:7073-7079



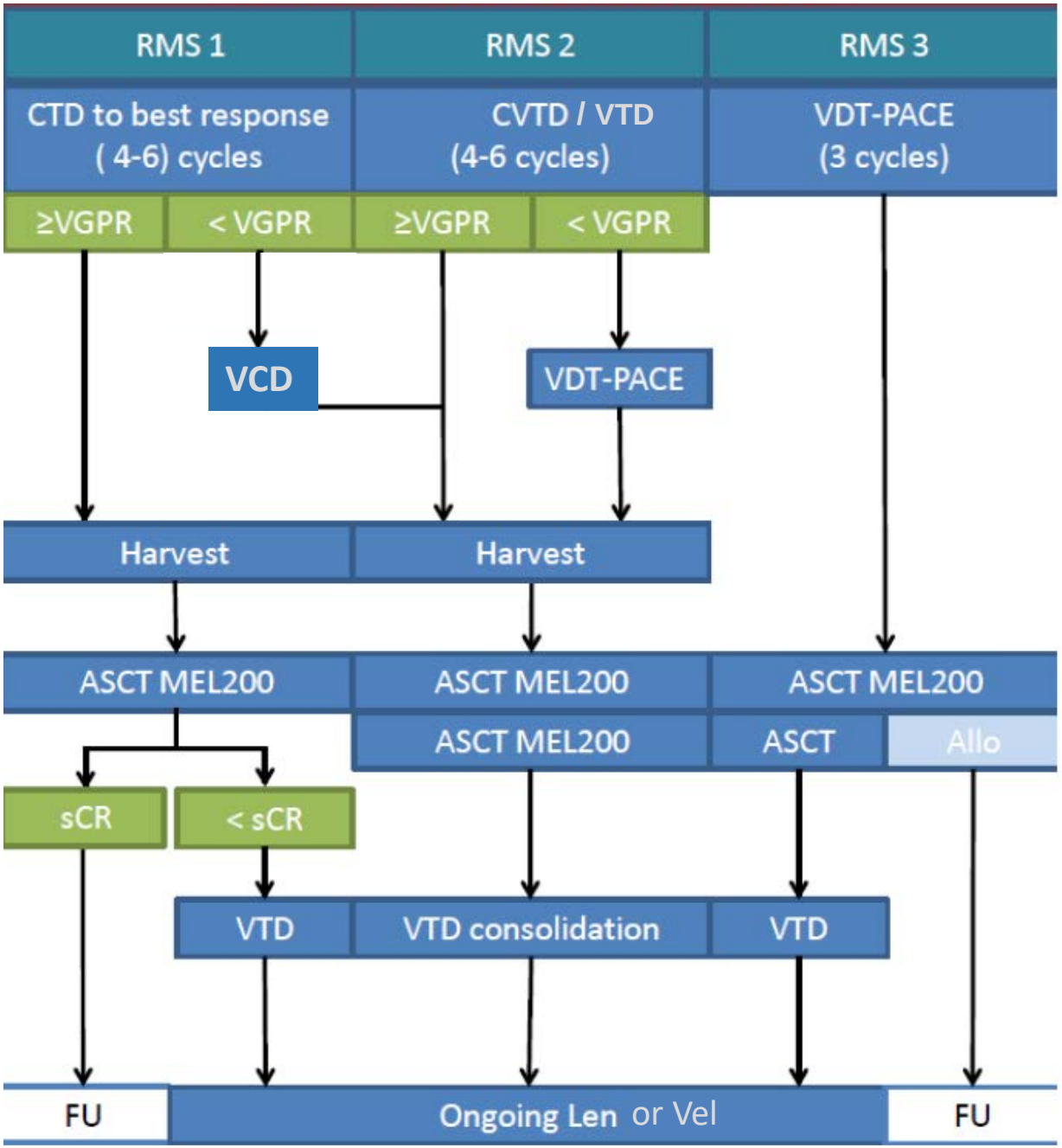
Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v13 //last reviewed Dec 2015

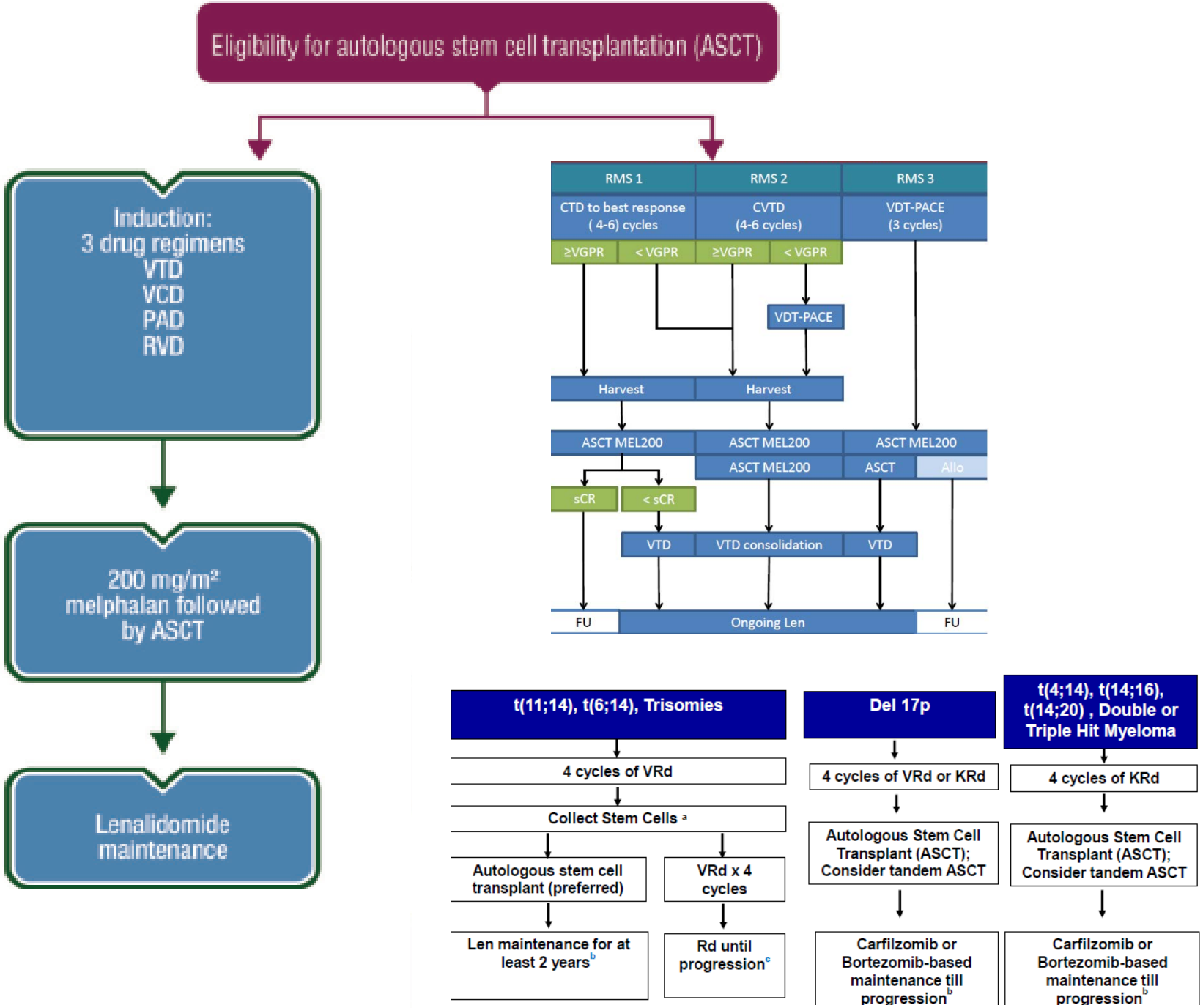
Maintenance Therapy

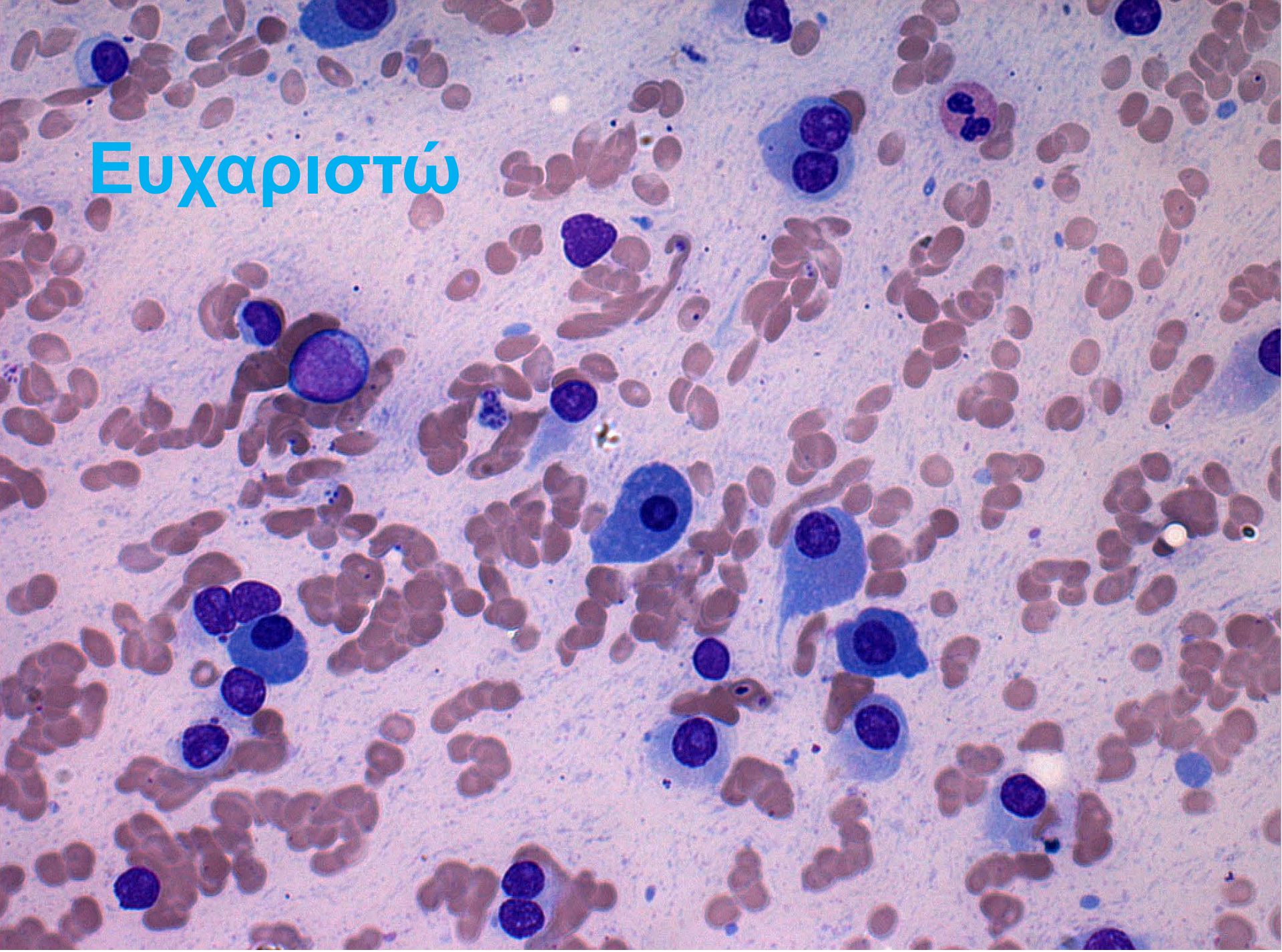


Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v12

RMH 2013


RMS 1
RMS 2
RMS 3
CTD to best response (4-6) cycles
CVTD / VTD (4-6 cycles)
VDT-PACE (3 cycles)
≥VGPR
< VGPR
≥VGPR
< VGPR
VCD
VDT-PACE
Harvest
Harvest
ASCT MEL200
ASCT MEL200
ASCT MEL200
ASCT MEL200
ASCT
Allo
sCR
< sCR
VTD
VTD consolidation
VTD
FU
Ongoing Len or Vel
FU


Eligibility for autologous stem cell transplantation (ASCT)
Induction:
3 drug regimens
VTD
VCD
PAD
RVD
200 mg/m² melphalan followed by ASCT
Lenalidomide maintenance
RMS 1
RMS 2
RMS 3
CTD to best response (4-6) cycles
CVTD (4-6 cycles)
VDT-PACE (3 cycles)
≥VGPR
< VGPR
≥VGPR
< VGPR
VDT-PACE
Harvest
Harvest
ASCT MEL200
ASCT MEL200
ASCT MEL200
ASCT MEL200
ASCT
Allo
sCR
< sCR
VTD
VTD consolidation
VTD
FU
Ongoing Len
FU
t(11;14), t(6;14), Trisomies
4 cycles of VRd
Collect Stem Cells a
Autologous stem cell transplant (preferred)
VRd x 4 cycles
Len maintenance for at least 2 years b
Rd until progression c
Del 17p
4 cycles of VRd or KRd
Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
Carfilzomib or Bortezomib-based maintenance till progression b
t(4;14), t(14;16), t(14;20) , Double or Triple Hit Myeloma
4 cycles of KRd
Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
Carfilzomib or Bortezomib-based maintenance till progression b


Ευχαριστώ