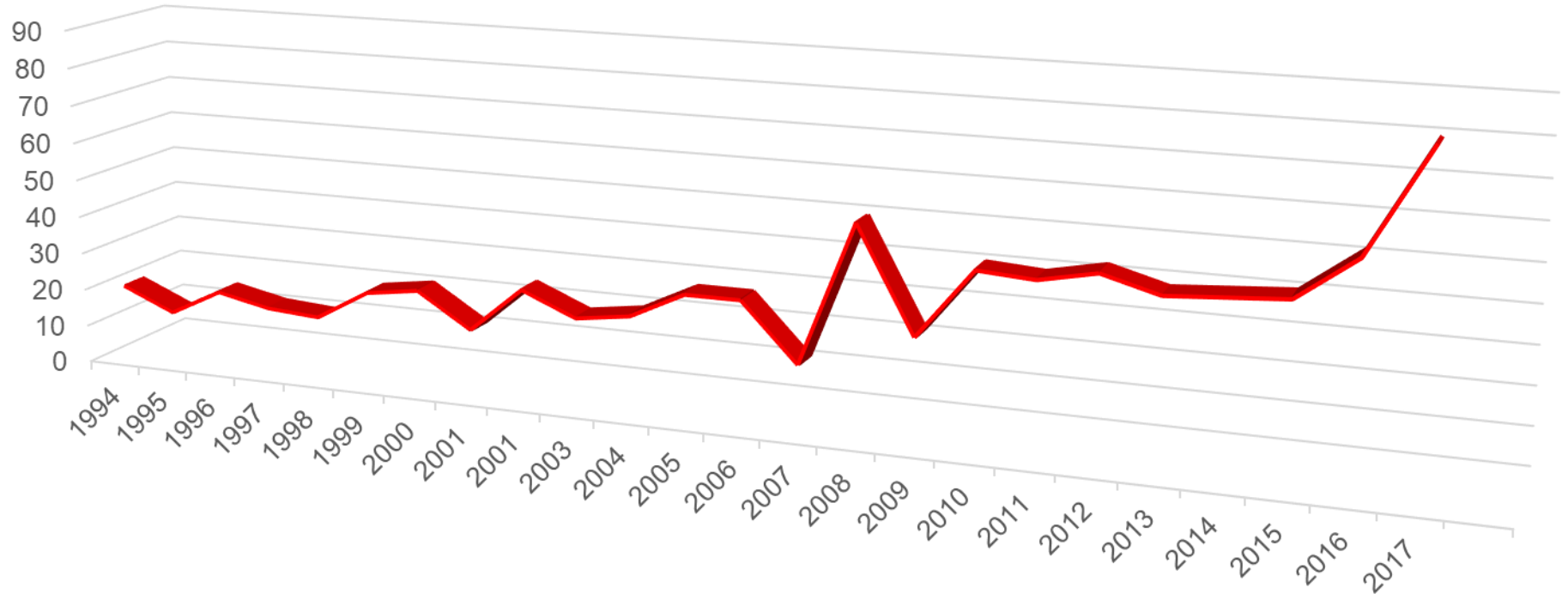
Myeloma multiplex – dijagnoza I tretman

Prof dr Sonja Genadieva Stavrik, Univerzitetska Klinika za Hematologija, Medicinski Fakultet Skopje, Makedonija

Disclousers for
Sonja Genadieva Stavric MD

Research Support	No relevant conflict of interest to declare
Employee	No relevant conflict of interest to declare
Consultant	No relevant conflict of interest to declare
Major Stockholder	No relevant conflict of interest to declare
Speakers Bureau	No relevant conflict of interest to declare
Honorararia	No relevant conflict of interest to declare
Scientific Advisary Borad	No relevant conflict of interest to declare

Incidenca na multipen myelom vo R.Makedonija 1994-2017



The incidence in Europe is 4.5–6.0/100 000/year with a median age at diagnosis of 72 years; the mortality is 4.1/100 000/year

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REVIEW

How is patient care for multiple myeloma advancing?

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European Myeloma Network recommendations on tools for the diagnosis and monitoring of multiple myeloma: what to use and when

Jo Caers,[1,2] Laurent Garderet,[3] K. Martin Kortüm,[4] Michael E. O'Dwyer,[5] Niels W.C.J. van de Donk,[6] Mascha Binder,[7] Sandra Maria Dold,[8] Francesca Gay,[9] Jill Corre,[10] Yves Beguin,[1,2] Heinz Ludwig,[11] Alessandra Larocca,[9] Christoph Driessen,[12] Meletios A. Dimopoulos,[13] Mario Boccadoro,[9] Martin Gramatzki,[14] Sonja Zweegman,[6] Hermann Einsele,[4] Michele Cavo,[15] Hartmut Goldschmidt,[16,17] Pieter Sonneveld,[18] Michel Delforge,[19] Holger W. Auner,[20] Evangelos Terpos[13] and Monika Engelhardt[8]

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Table 2. Recommendations on further examinations at diagnosis, for response assessment, during follow-up and at relapse.

Diagnostic site	Tool	Diagnosis	At response	At follow-up	At relapse
Bone marrow	BM cytology and biopsy to confirm plasmacytosis and monoclonality	Obligatory	Obligatory*	Not required	Obligatory**
	Flow cytometry	Recommended	Optional	Not required	Optional
	Cytogenetics	Obligatory	Not required	Not required	Optional
	Advanced techniques: GEP, NGS	Optional	Not required	Not required	Not required
Blood	Blood count and blood smear	Obligatory	Obligatory	Obligatory	Obligatory
	Serum electrophoresis and IF	Obligatory	Obligatory	Obligatory	Obligatory
	Serum free light chain	Recommended ***	Recommended ***	Recommended ***	Recommended ***
	Serum immunoglobulin levels	Obligatory	Obligatory	Obligatory	Obligatory
	Renal and liver function tests	Obligatory	Obligatory	Obligatory	Obligatory
	Calcium	Obligatory	Obligatory	Obligatory	Obligatory
	Lactate dehydrogenase	Obligatory	Obligatory	Obligatory	Obligatory
	Albumin, β2-microglobulin	Obligatory	Recommended	Recommended	Obligatory
Urine	Urine sample to check for proteinuria and Bence-Jones proteins	Obligatory	Obligatory	Obligatory	Obligatory
	24 h urine collection	Recommended†	Recommended†	Recommended†	Recommended†
Imaging	Low dose whole-body CT	Recommended††	Not required	When symptomatic	Recommended
	PET/CT	Optional	Optional†††	When symptomatic	Optional
	Whole-body MRI	Optional	Not required	When symptomatic	Optional

BM: bone marrow; GEP: gene expression profiling; IF: immunofixation; NGS: next generation sequencing; CT: computed tomography; PET: positron emission tomography; MRI: magnetic resonance imaging; *Obligatory for patients in complete response. **Obligatory for patients with light chain escape, oligosecretory disease, *** SFLC monitoring is obligatory for patients with light-chain disease. †Obligatory in the case of proteinuria. ††Obligatory when radiographs do not show osteolytic lesions †††PET/CT is required for confirmation of minimal residual disease negativity.

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GUIDELINE ARTICLE

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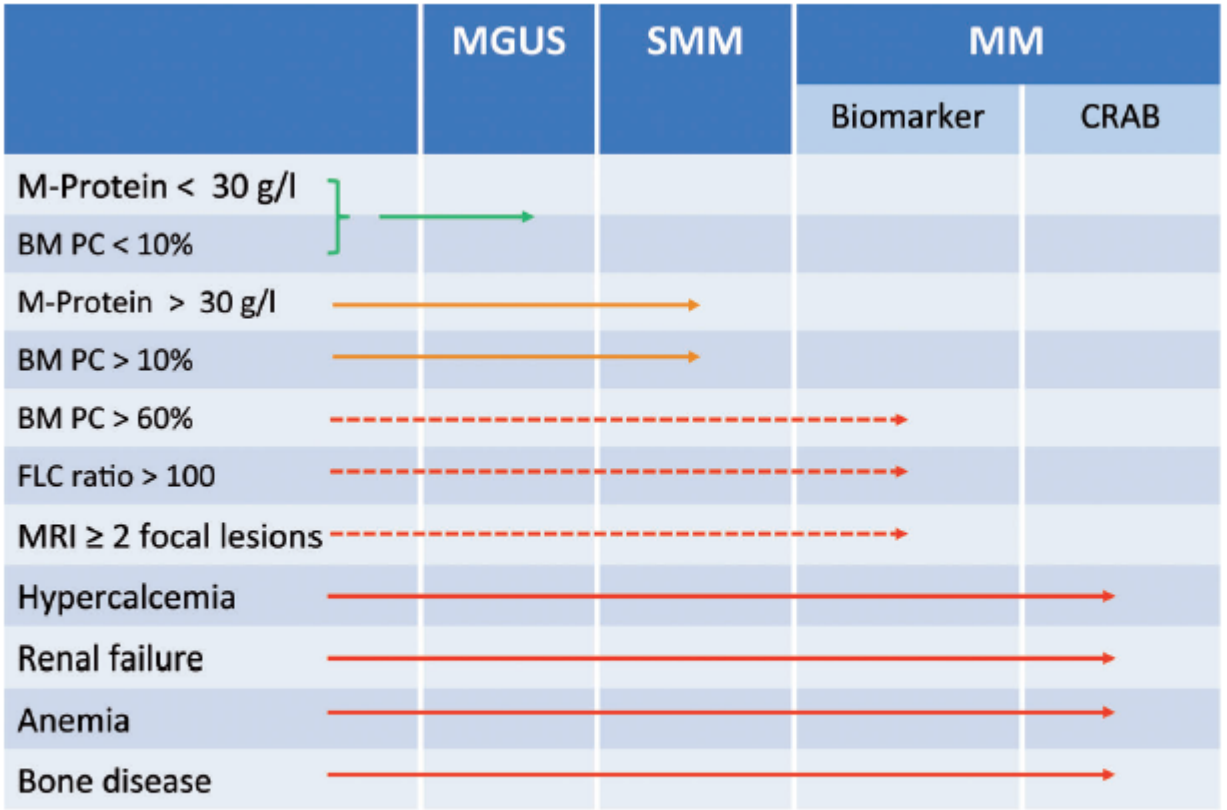

Figure 1. The differential diagnosis between monoclonal gammopathy of undetermined significance, smoldering myeloma and multiple myeloma. The discrimination between these monoclonal gammopathies is based on: (i) the plasma cell infiltration in the bone marrow, (ii) the presence of clinical symptoms related to myeloma disease and (iii) the existence of biomarkers of disease that allow initiation of treatment. MGUS: monoclonal gammopathy of undetermined significance; SMM: smoldering multiple myeloma; MM: multiple myeloma; BM: bone marrow; PC: plasma cells; FLC: free light chain; MRI: magnetic resonance imaging.

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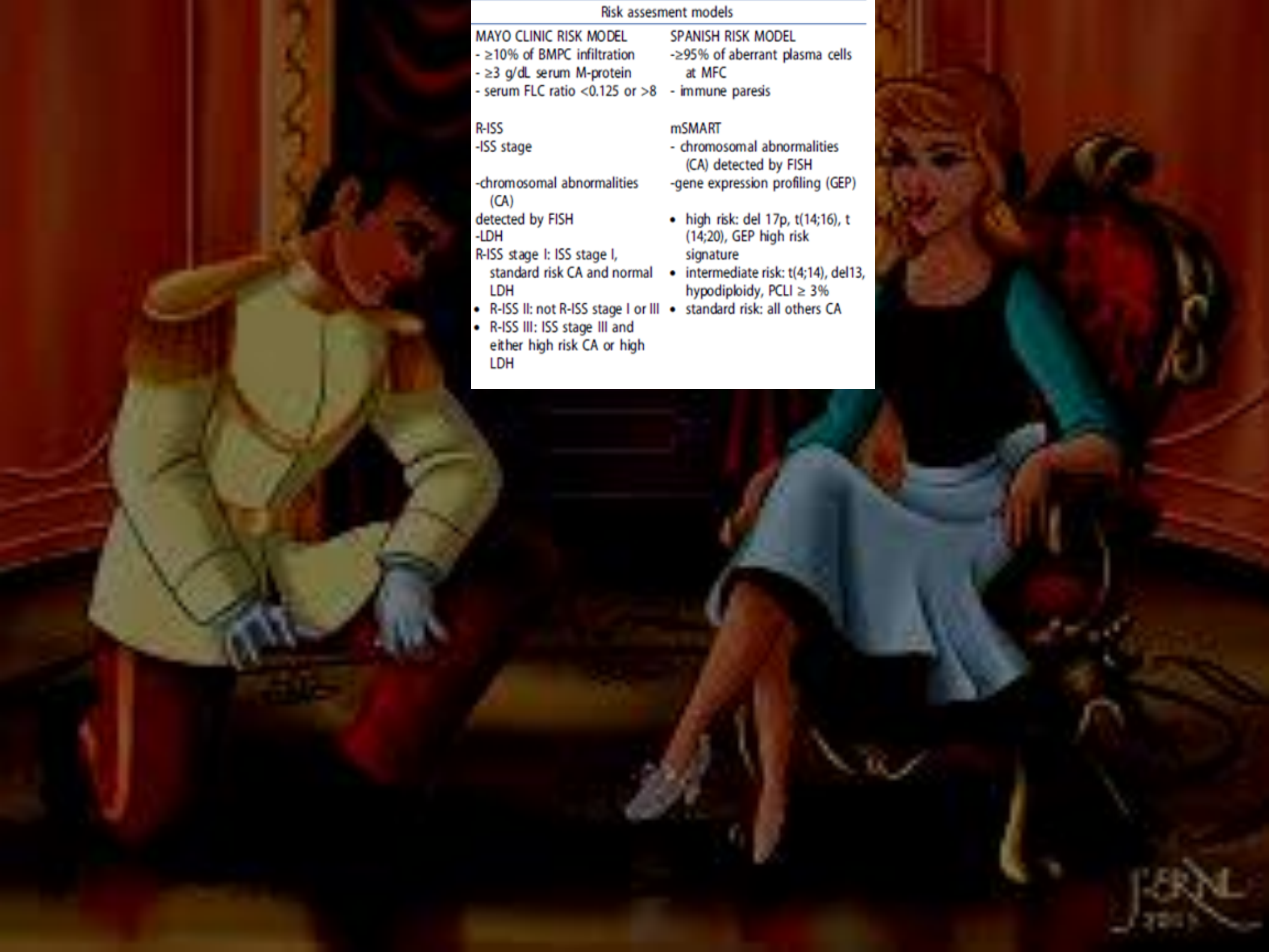
Table 4. The Revised-International Staging System is one of the best stratification methods; it is based on routinely available cytogenetic and biochemistry tests (Palumbo *et al.*).[56]

R-ISS definitions	Determinants	Number	OS (5 years)	Median OS	PFS (5 years)	Median PFS
R-ISS stage I	ISS stage I, no high-risk CA, and normal LDH	871 (28%)	82%	NR	55%	66 months
R-ISS stage II	Other combinations	1894 (62%)	62%	83 months	36%	42 months
R-ISS stage III	ISS stage III plus high-risk CA or high LDH	295 (10%)	40%	43 months	24%	29 months

R-ISS Revised- International Staging System; ISS: International Staging System; OS: overall survival; PFS: progression free survival; CA; cytogenetic abnormalities; LDH: lactate dehydrogenase; NR: not reported.



Risk assesment models

MAYO CLINIC RISK MODEL
- ≥10% of BMPC infiltration
- ≥3 g/dL serum M-protein
- serum FLC ratio <0.125 or >8

R-ISS
-ISS stage

-chromosomal abnormalities (CA)
detected by FISH
-LDH
R-ISS stage I: ISS stage I, standard risk CA and normal LDH
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SPANISH RISK MODEL
-≥95% of aberrant plasma cells at MFC
- immune paresis

mSMART
- chromosomal abnormalities (CA) detected by FISH
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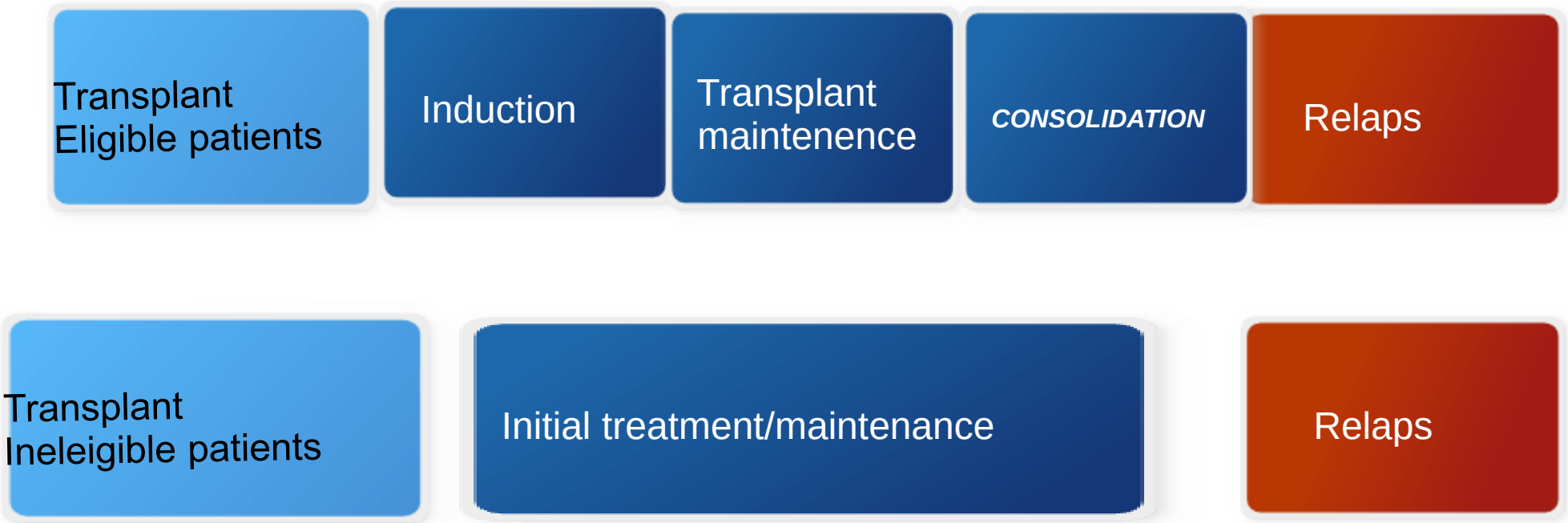
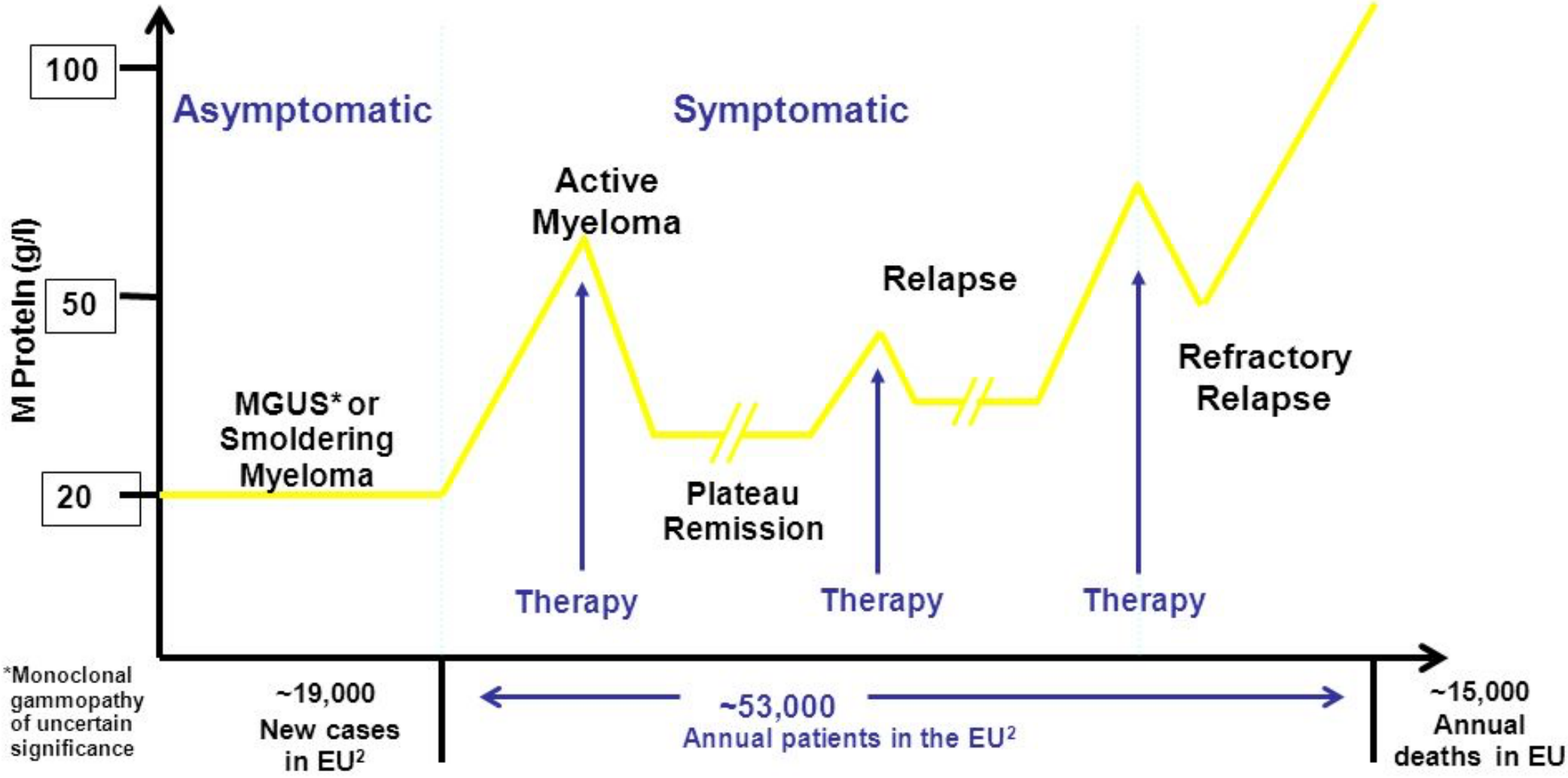
Table 1. Determinants of therapy in the era of individualized medicine.

Choice of therapy			
Disease charachteristics	Patient charachteristics	Goal of care	Setting
• cytogenetic risk • stage • tumor burden • organ function • types and response to eventual previous therapies	• age • performance status • comorbidities • independence and functional status • social context	• complete remission/MRD • disease control • quality of life	• availability of clinical trials

Treatman na multipen myelom



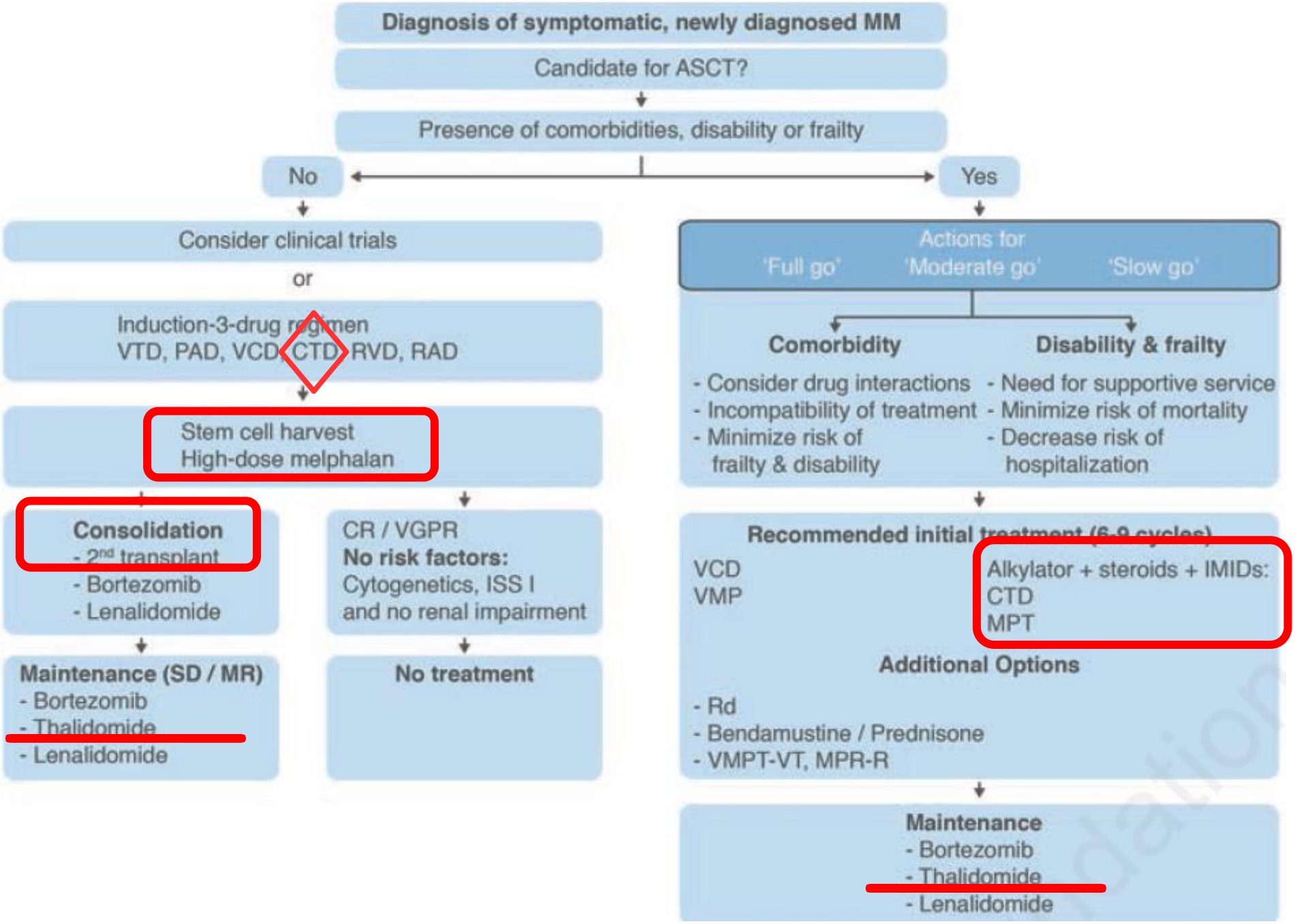
Multiple Myeloma Disease Progression[1]



1. Adapted from International Myeloma Foundation; 2001. Reprinted with permission.
2. International Agency for Research on Cancer, World Health Organisation; Ferlay J, Bray F, Pisani, P and Parkin DM. Globocan 2000

Effective treatment should be concentrated at the early phase of disease, when clones are more drug sensitive, long – lasting remission are more frequent, and serious adverse events are less prominent. This approach significantly improves quality of life and may be ultimately prolong overall survival.

Palumbo A, Cavallo F:Have drug combinations supplanted stem cell transplantation in myeloma. Hematology 2012


Diagnosis of symptomatic, newly diagnosed MM
Candidate for ASCT?
Presence of comorbidities, disability or frailty
No
Yes
Consider clinical trials
or
Induction-3-drug regimen
VTD, PAD, VCD, CTD, RVD, RAD
Stem cell harvest
High-dose melphalan
Consolidation
- 2nd transplant
- Bortezomib
- Lenalidomide
Maintenance (SD / MR)
- Bortezomib
- Thalidomide
- Lenalidomide
CR / VGPR
No risk factors:
Cytogenetics, ISS I
and no renal impairment
No treatment
Actions for
'Full go' 'Moderate go' 'Slow go'
Comorbidity
- Consider drug interactions
- Incompatibility of treatment
- Minimize risk of frailty & disability
Disability & frailty
- Need for supportive service
- Minimize risk of mortality
- Decrease risk of hospitalization
Recommended initial treatment (6-9 cycles)
VCD
VMP
Alkylator + steroids + IMIDs:
CTD
MPT
Additional Options
- Rd
- Bendamustine / Prednisone
- VMPT-VT, MPR-R
Maintenance
- Bortezomib
- Thalidomide
- Lenalidomide

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv52–iv61, 2017
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Published online 27 April 2017

CLINICAL PRACTICE GUIDELINES

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Annals of Oncology

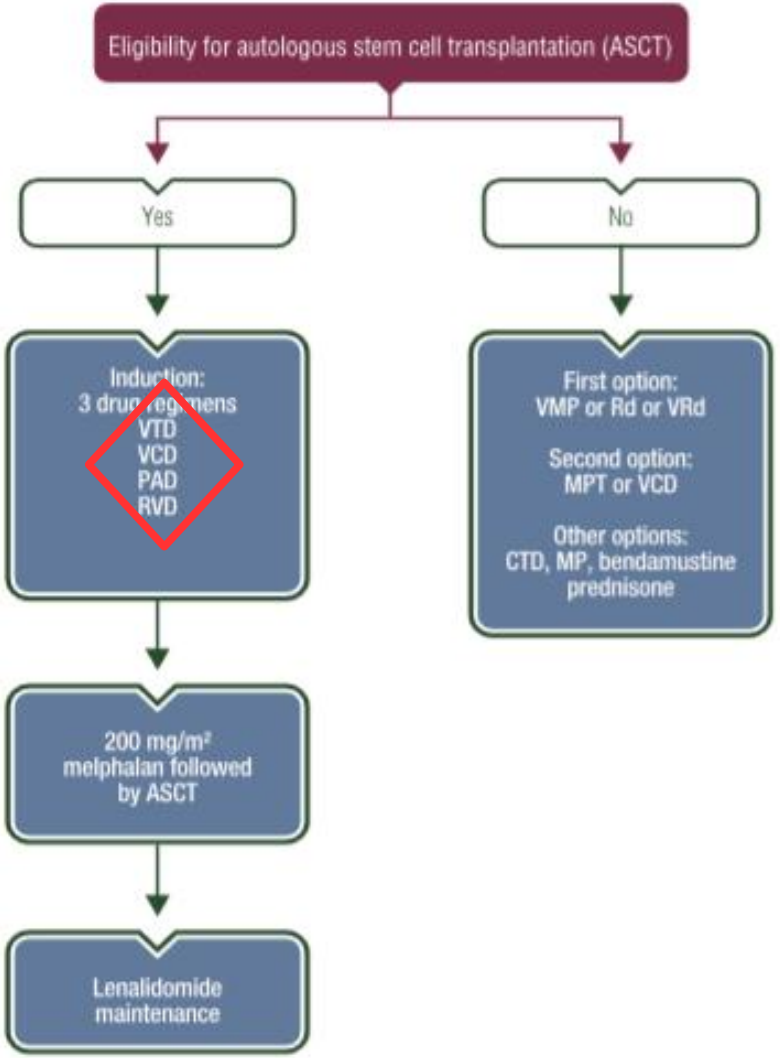


Figure 1. Front-line treatment of symptomatic multiple myeloma outside clinical trials.

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Multiple Myeloma

MYELOMA THERAPY[1-4]

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem cell reserve prior to stem cell harvest in patients who may be candidates for transplants.

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES (assess for response after each cycle

Preferred Regimens

- Bortezomib/lenalidomide[5]/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone[6]

Other Recommended Regimens

- Bortezomib/doxorubicin/dexamethasone (category 1)
- Carfilzomib[7,8]/lenalidomide[5]/dexamethasone
- Ixazomib/lenalidomide[5]/dexamethasone (category 2B)

Useful In Certain Circumstances

- Bortezomib/dexamethasone (category 1)[9]
- Bortezomib/thalidomide/dexamethasone (category 1)
- Lenalidomide[5]/dexamethasone (category 1)[9]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)

MAINTENANCE THERAPY

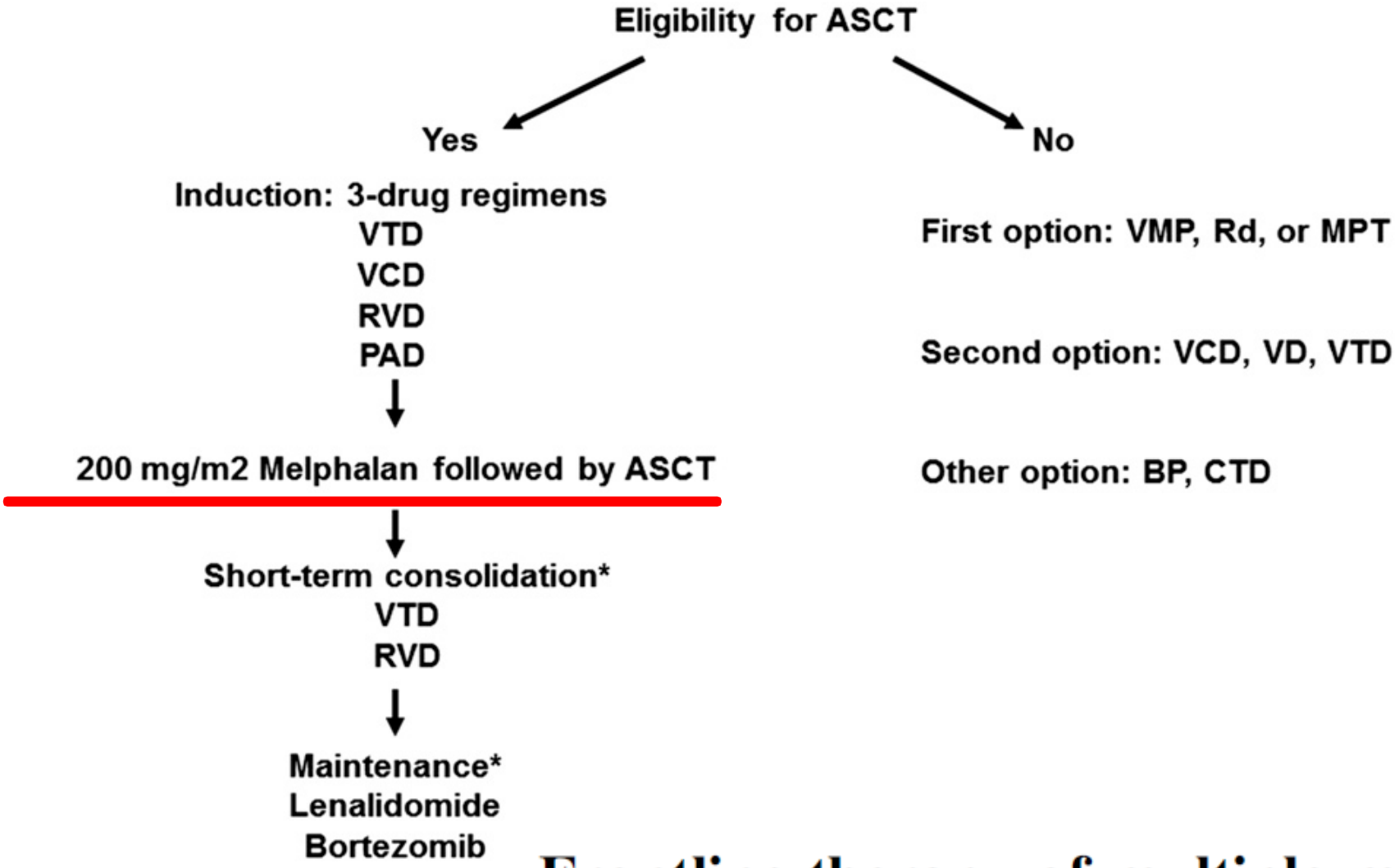
Preferred Regimens

- Lenalidomide[11] (category 1)

Other Recommended Regimens

- Bortezomib

Frontline therapy



BLOOD, 2015

Frontline therapy of multiple myeloma

Philippe Moreau,[1] Michel Attal,[2] and Thierry Facon[3]

How we manage autologous stem cell transplantation for patients with multiple myeloma

Morie A. Gertz[1] and David Dingli[1,2]

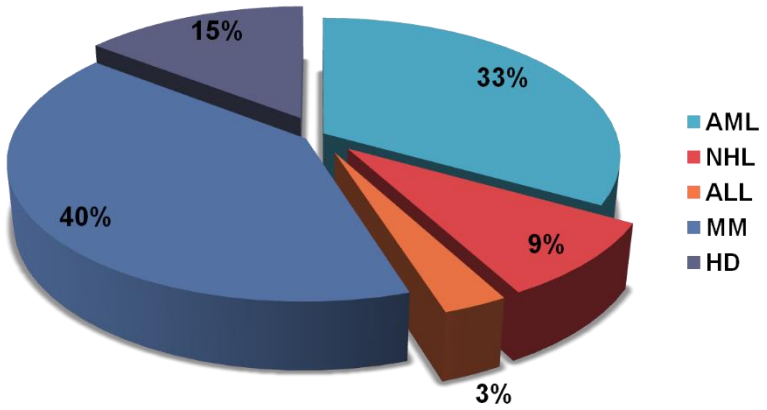
[1]Division of Hematology and [2]Department of Molecular Medicine, Mayo Clinic, Rochester, MN

BLOOD, 7 AUGUST 2014 • VOLUME 124, NUMBER 6

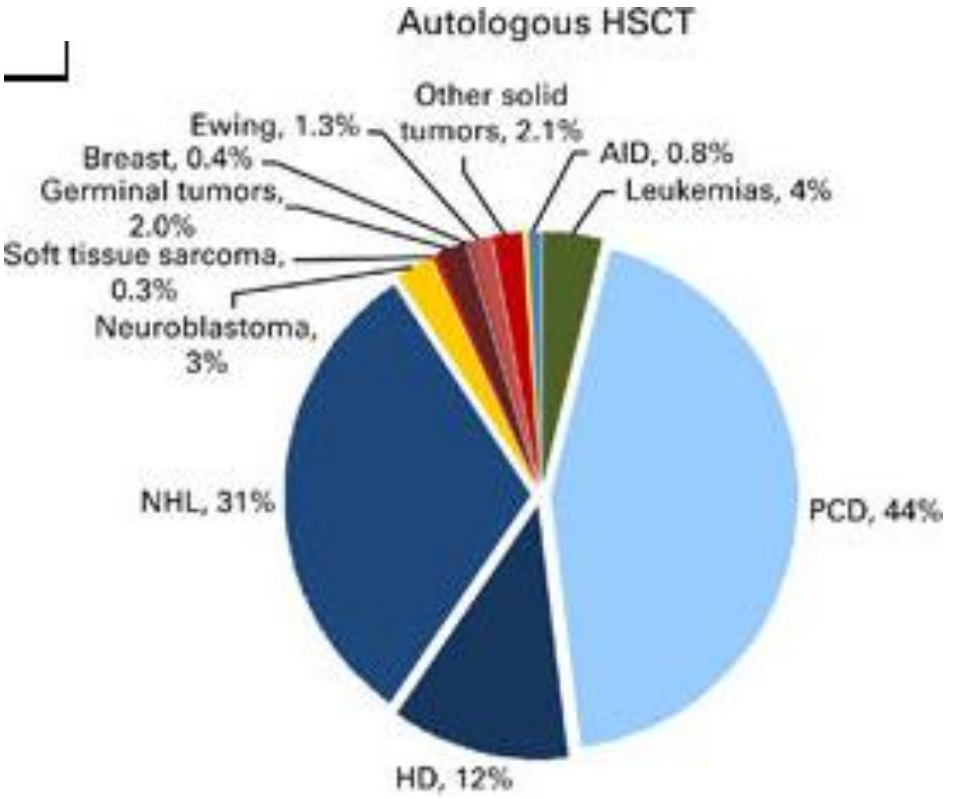
Table 3. Summary of how we transplant

Technique and the mobilization procedure
Selection
Up to age 76 years.
No restriction for renal function.
No requirement for response to induction.
Mobilization (see Table 1)
Patients aged <70 routinely undergo collection for 2 transplants.
Plerixafor not standard.
Chemotherapy mobilization if circulating cells by flow or if no response to induction.
Conditioning
Standard nonprotocol remains melphalan (200 mg/m^2) for fit patients.
Melphalan (140 mg/m^2) if patient is frail or serum creatinine ≥2.0 mg/dL.
Procedural
Conditioning, infusion, and postinfusion monitoring usually are performed on an outpatient basis.
• Oral antibiotic prophylaxis: penicillin, levofloxacin, acyclovir, and fluconazole
• Manage breakthrough fever of >38.5°C with vancomycin (3 days if culture negative) and cefepime (outpatient).
• Anticipate that half of patients will complete treatment as outpatients.

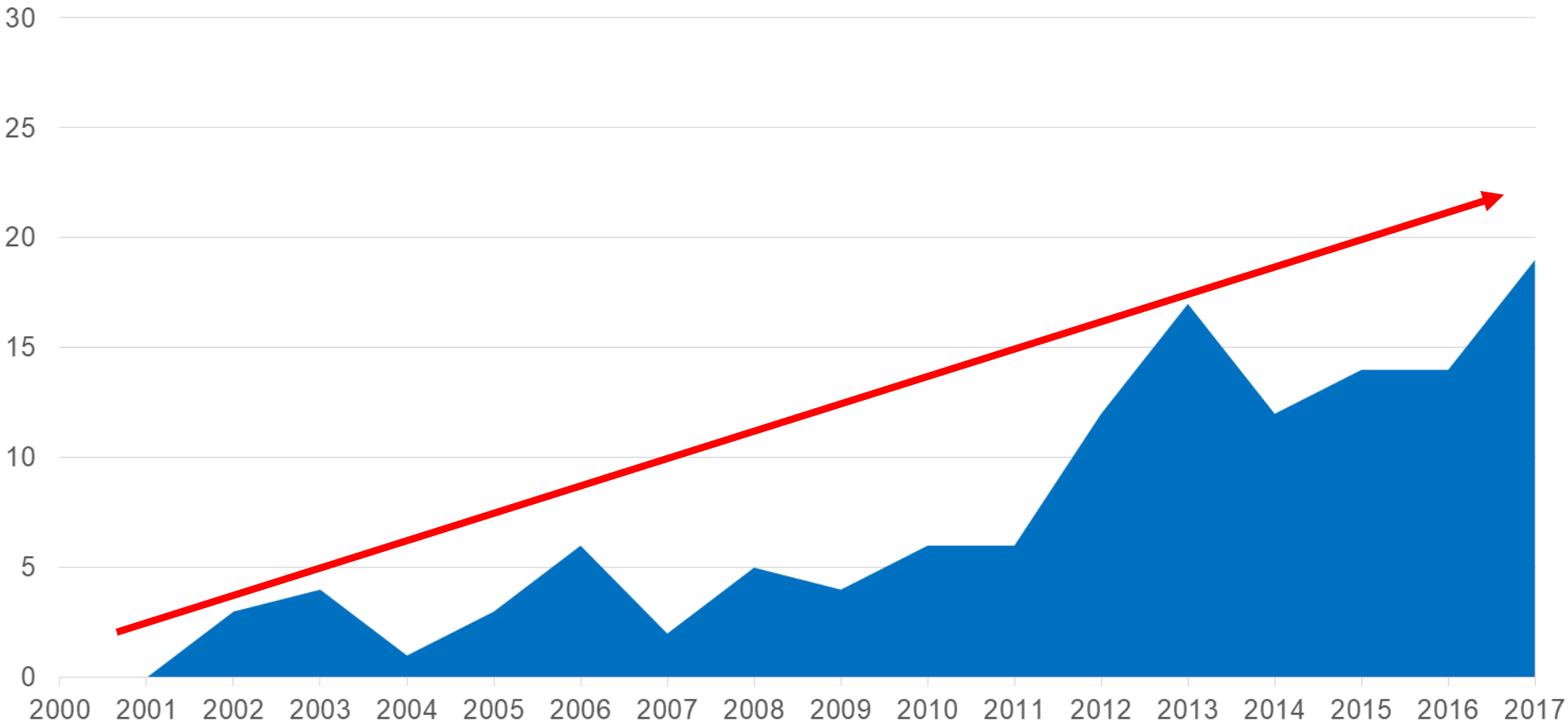
Indikacija za autologna transplantacija vo R.Makedonija (2000-2015)



Indikacija za autologna transplantacija u Evropa 2013



Autologna transplantacija i multpni mijelom



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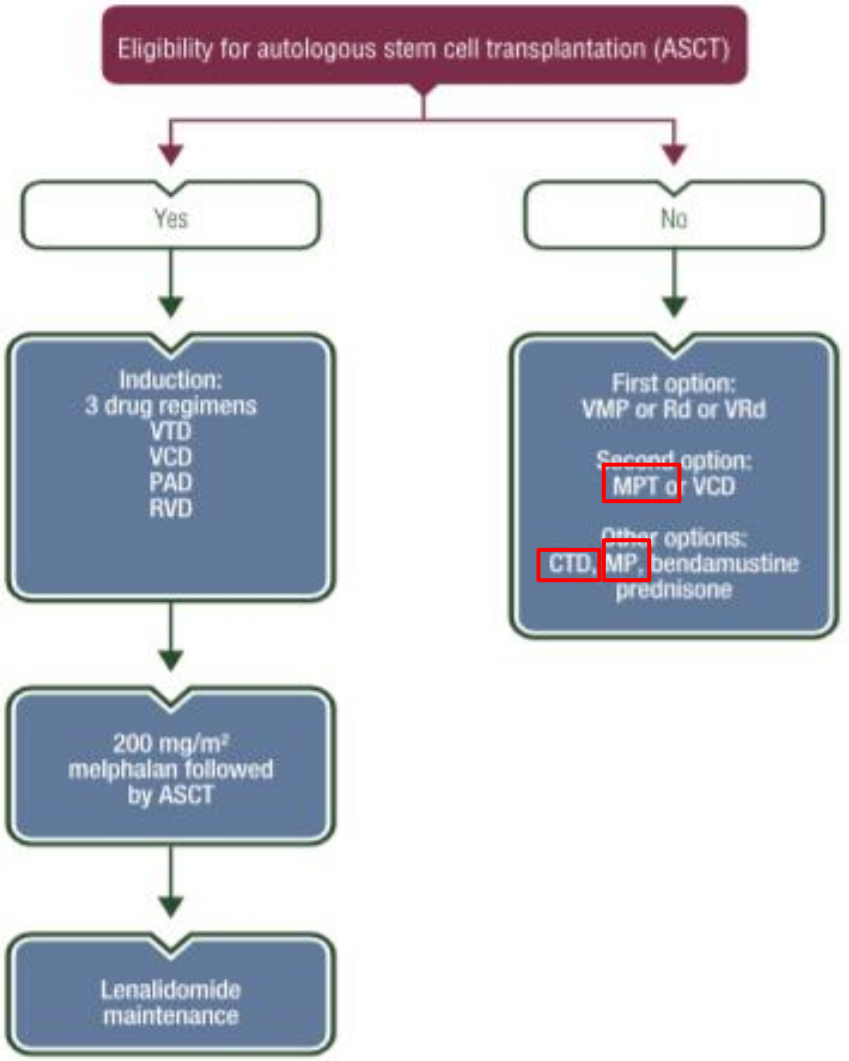

Figure 1. Front-line treatment of symptomatic multiple myeloma outside clinical trials.

MYELOMA THERAPY[1-4]

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES (assess for response after each cycle)

Preferred Regimens

- Bortezomib/lenalidomide/dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)[9,10]
- Bortezomib/cyclophosphamide/dexamethasone[6]

Other Recommended Regimens

- Carfilzomib[8]/lenalidomide/dexamethasone
- Carfilzomib[8]/cyclophosphamide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone

Useful In Certain Circumstances

- Bortezomib/dexamethasone[9]

MAINTENANCE THERAPY

Preferred Regimens

- Lenalidomide[11] (category 1)

Other Recommended Regimens

- Bortezomib

How to Better Select Therapy for Patients in Relapse?

Duration of Prior Response

Efficacy and Toxicity of Prior Treatments

Type of Relapse

Available Therapies

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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CLINICAL PRACTICE GUIDELINES

Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

P. Moreau[1], J. San Miguel[2], P. Sonneveld[3], M. V. Mateos[4], E. Zamagni[5], H. Avet-Loiseau[6], R. Hajek[7], M. A. Dimopoulos[8], H. Ludwig[9], H. Einsele[10], S. Zweegman[11], T. Facon[12], M. Cavo[5], E. Terpos[8], H. Goldschmidt[13], M. Attal[6] & C. Buske[14], on behalf of the ESMO Guidelines Committee*

Annals of Oncology

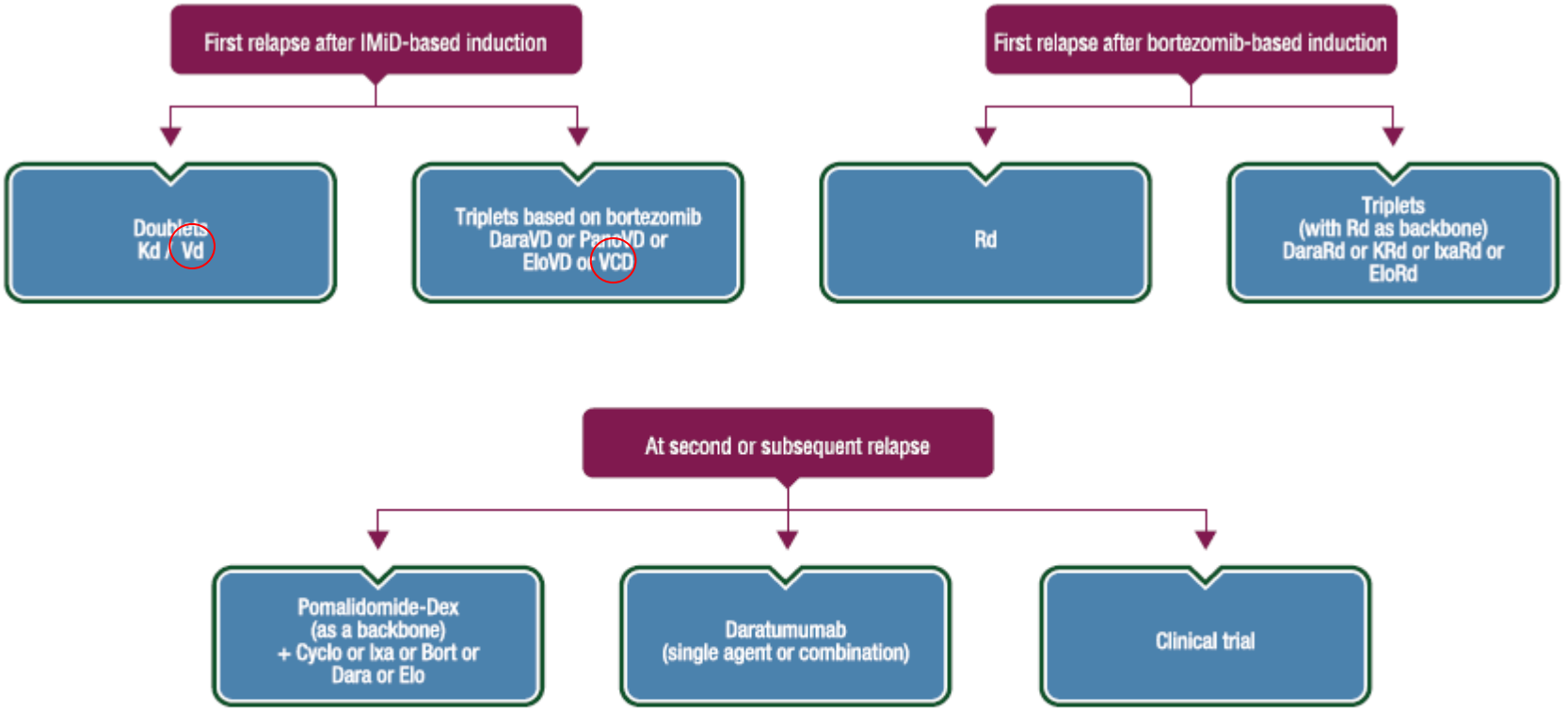


Figure 2. Treatment of relapse.
Bort, bortezomib; Cyclo, cyclophosphamide; Dara, daratumumab; DaraRd, daratumumab, lenalidomide, low dose dexamethasone; DaraVD, daratumumab, bortezomib, dexamethasone; Dex, dexamethasone; Elo, elotuzumab; EloRd, elotuzumab, lenalidomide, low dose dexamethasone; EloVD, elotuzumab, bortezomib, dexamethasone; IMiD, immunomodulatory drug; Ixa, izaxomib; IxaRd, izaxomib, lenalidomide, low dose dexamethasone; Kd, carfilzomib, low dose dexamethasone; KRd, carfilzomib, lenalidomide, low dose dexamethasone; PanoVD, panobinostat, bortezomib, dexamethasone; Rd, lenalidomide, low-dose dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; Vd, bortezomib, low dose dexamethasone.

MYELOMA THERAPY[1-4,12]

Therapy for Previously Treated Multiple Myeloma (assess for response after each cycle)

Preferred Regimens

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib (twice weekly)[8]/dexamethasone (category 1)[9]
- Carfilzomib[8]/lenalidomide/dexamethasone (category 1)[13]
- Daratumumab[14]/bortezomib/dexamethasone (category 1)
- Daratumumab[14]/lenalidomide/dexamethasone (category 1)
- Elotuzumab[15]/lenalidomide/dexamethasone (category 1)[13]
- Ixazomib[17]/lenalidomide/dexamethasone (category 1)[13]

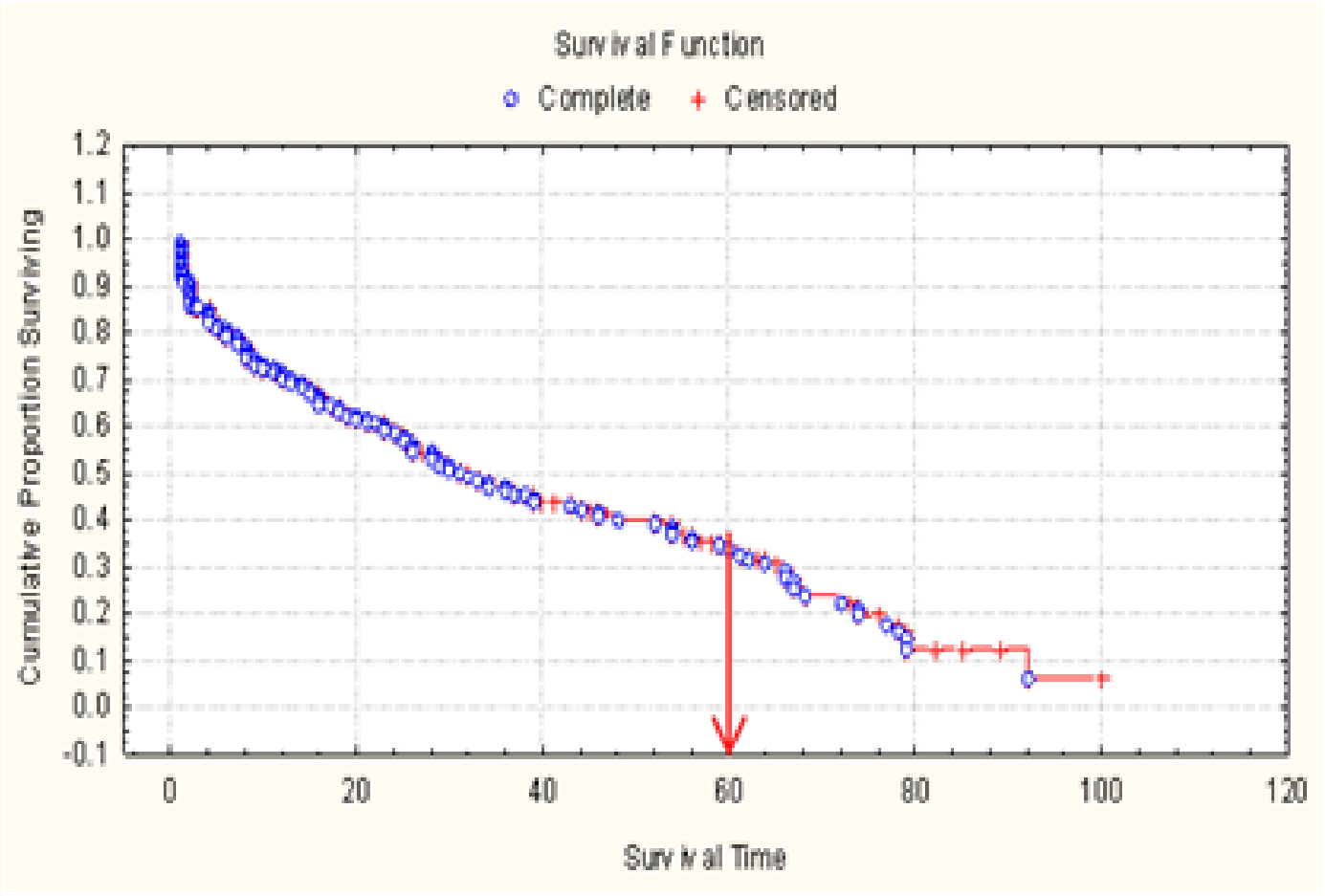
Other Recommended Regimens

- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib[8]/cyclophosphamide/dexamethasone
- Carfilzomib (weekly)[8]/dexamethasone[9]
- Cyclophosphamide/lenalidomide/dexamethasone
- Bortezomib/dexamethasone (category 1)[9]
- Daratumumab[14,16]
- Daratumumab[14]/pomalidomide[20]/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Ixazomib[17]/dexamethasone[9]
- Ixazomib/pomalidomide[20]/dexamethasone
- Lenalidomide/dexamethasone[18] (category 1)[9]
- Panobinostat[19]/bortezomib/dexamethasone (category 1)
- Panobinostat[19]/carfilzomib[8,9]
- Panobinostat[19]/lenalidomide/dexamethasone
- Pomalidomide[20]/cyclophosphamide/dexamethasone
- Pomalidomide[20]/dexamethasone[18] (category 1)[9]
- Pomalidomide[20]/bortezomib/dexamethasone
- Pomalidomide[20]/carfilzomib[8]/dexamethasone

Useful In Certain Circumstances

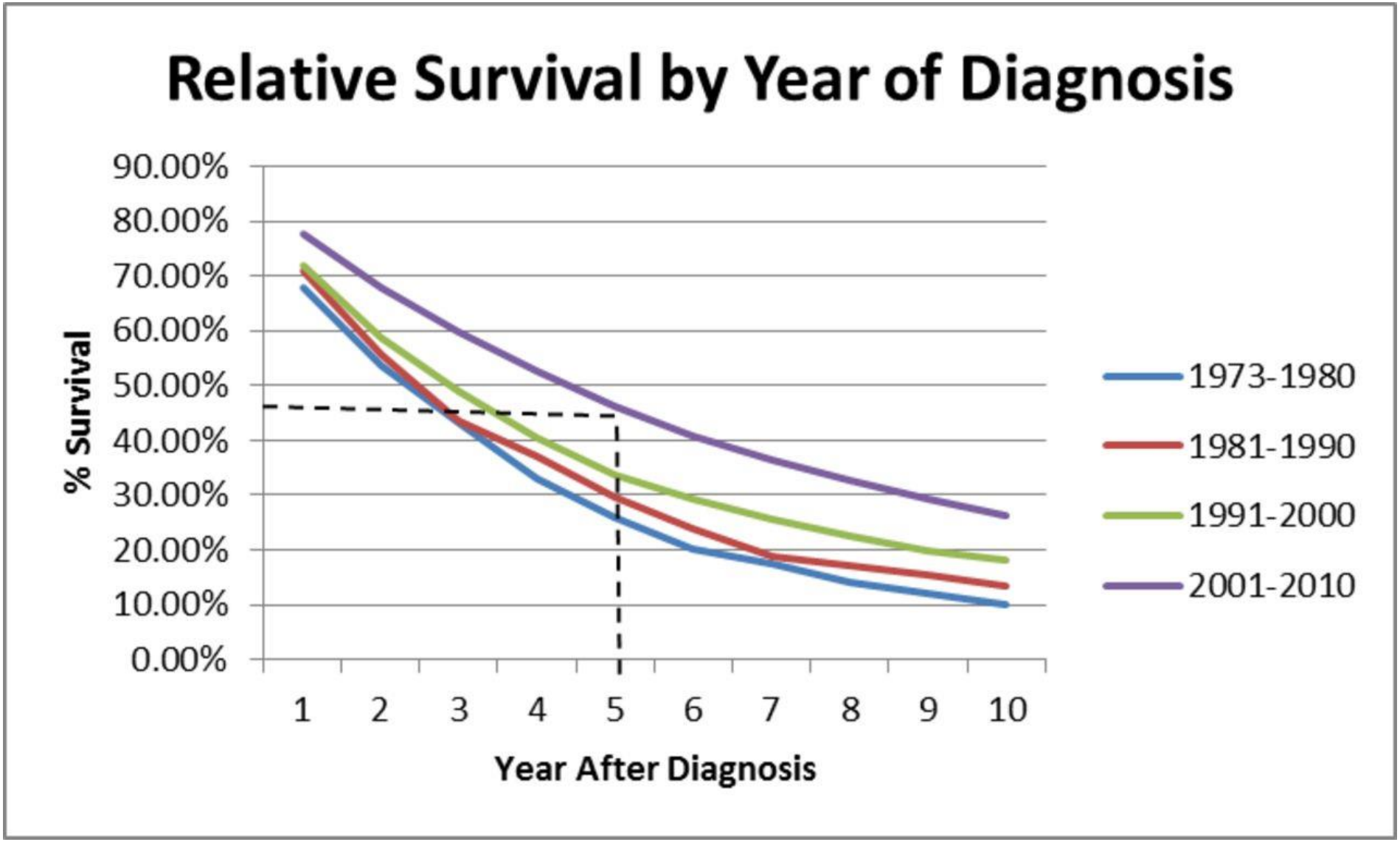
- Bendamustine
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[21]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[21] ± bortezomib (VTD-PACE)[21]
- High-dose cyclophosphamide

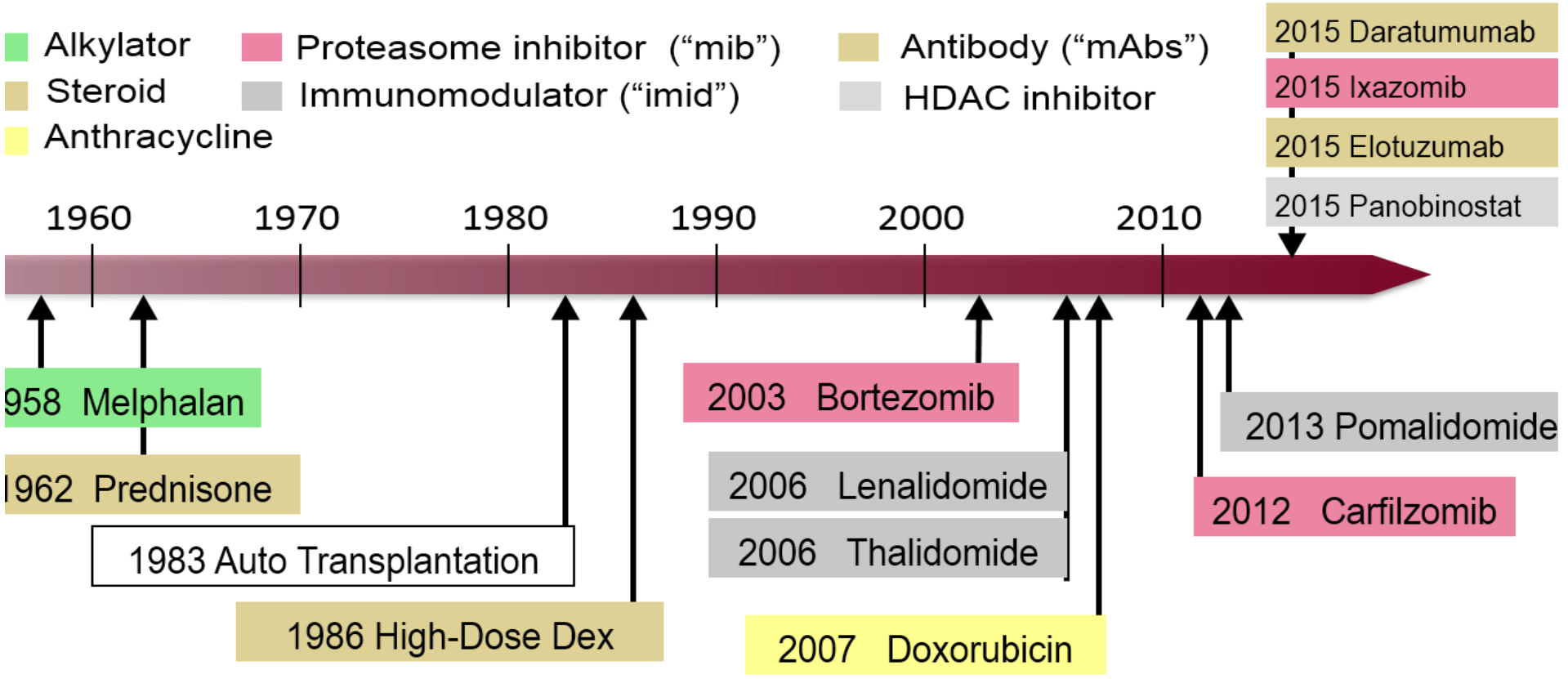
Overall survival (2005-2015)



Whit permission DocDr S.Krstevska Blakanov

Impact of Novel Treatments on Multiple Myeloma Survival
David Robinson, Satyin Kaura, Daniel Kiely, Mohamad A. Hussein, Knar Nersesyan and Brian G. M. Durie
Blood 2014 124:5676;

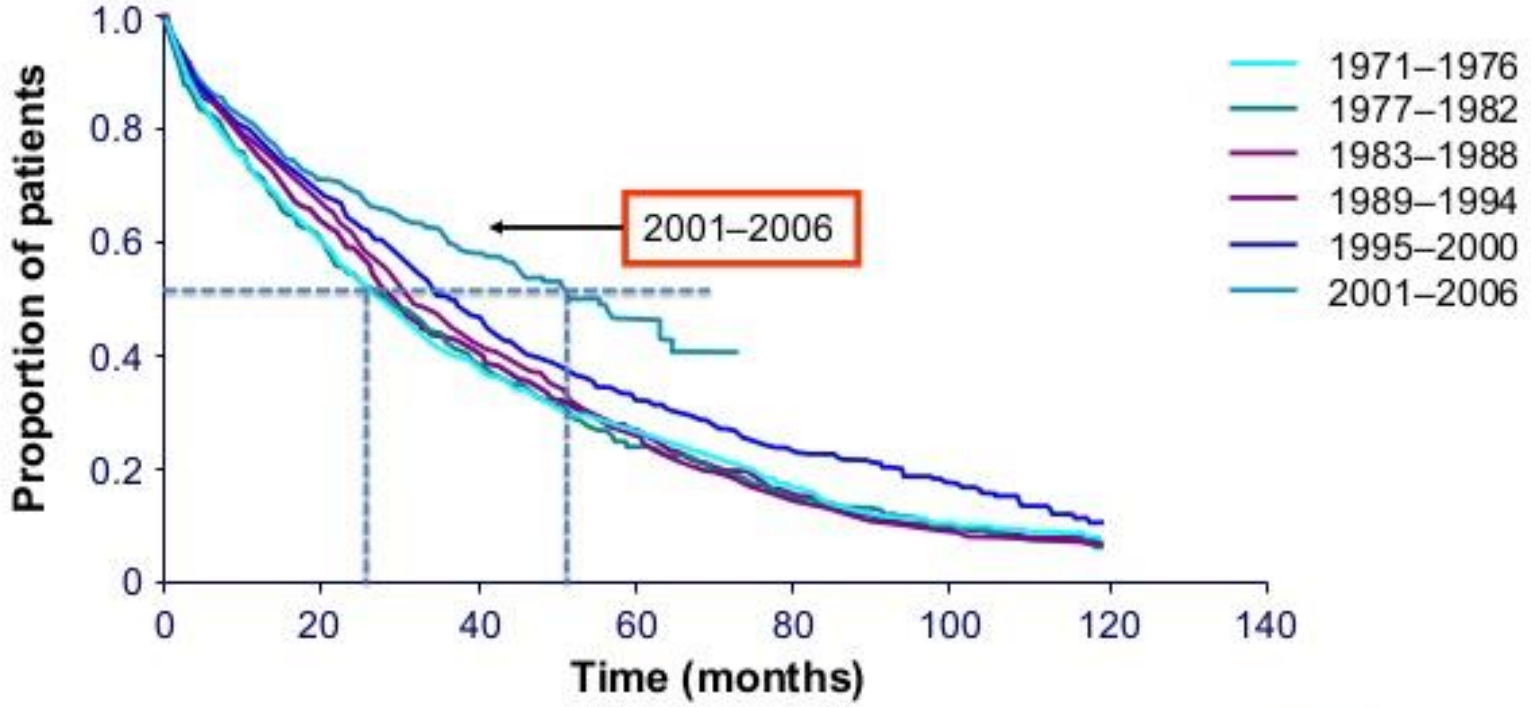




Auto = Autologous; Dex= Dexamethasone

Have we made progress?

Overall survival in 6-year intervals from time of diagnosis



Kumar SK, et al. Blood. 2008;111:2516-20.

MAYO CLINIC

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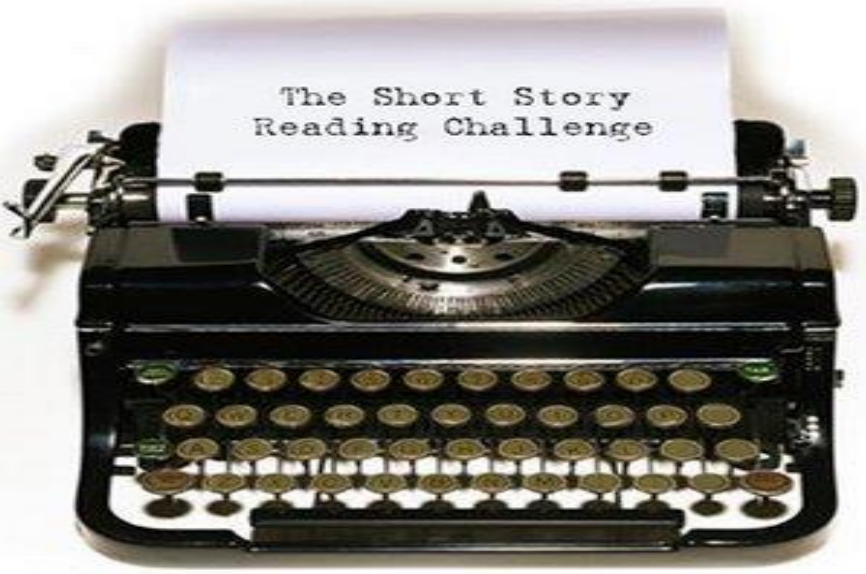

Table 7. Summary of recommendations

- The diagnosis of MM must include the criteria updated in 2014 by the International Myeloma Working Group.
- Immediate treatment is not recommended for patients with indolent myeloma.
- For patients < 70 years in good clinical condition, induction followed by high-dose therapy with ASCT is the standard treatment.
- For relapsed/refractory MM, the most commonly used regimens are proteasome inhibitor- or lenalidomide-containing regimens. New triplet combinations are increasing PFS.
- In advanced cases, pomalidomide plus low-dose dexamethasone and daratumumab are approved.

ASCT, autologous stem cell transplantation; PFS, progression-free survival; MM, multiple myeloma.


Vision

Review | Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12590

Modern multiple myeloma therapy: deep, sustained treatment response and good clinical outcomes

O. Landgren[1] & K. Iskander[2]

Table 1 *Characteristics of traditional and modern myeloma therapy*

Characteristics of traditional myeloma therapy	Characteristics of modern myeloma therapy
• Few agents available	• Many drug classes and treatment options available
• Toxic	• Relatively less toxic
• Limited efficacy	• Highly effective
• Response captured using clinical response criteria	• Response captured using highly sensitive MRD assays

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REVIEW

How is patient care for multiple myeloma advancing?

Sonja Genadieva Stavric[a], Francesca Bonello[b], Sara Bringhen[b], Mario Boccadoro[b] and Alessandra Larocca[b]

[a]Medical Faculty, University Hematology Clinic, Skopje, Macedonia; [b]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

ABSTRACT

Introduction: Treatment of multiple myeloma has undergone profound changes in the past years thanks to the increased understanding of the biology of the disease and the new treatment options. New drugs and effective approaches are currently available for the treatment of multiple myeloma, including immunomodulatory agents, proteasome inhibitors and autologous stem cell transplantation.

Areas covered: We have described the recent updated criteria to start treatment in multiple myeloma and summarized clinical data from major studies including most recent agents. Particularly, results with pomalidomide, carfilzomib, ixazomib, monoclonal antibodies such as elotuzumab, daratumumab, and checkpoint inhibitors have been reported. Both transplant and non-transplant settings have been covered.

Expert commentary: Despite the successful improvement in overall survival and time to relapse, multiple myeloma still remains incurable. Therefore, there is still an unmet need for new treatment strategies with novel mechanisms of action, like monoclonal antibodies, novel immunomodulators, and novel proteasome inhibitors. Implementation of these novel drugs in rationally designed therapies with a good balance of efficacy and safety should be carefully considered in order to improve outcome.

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KEYWORDS
Multiple myeloma; immunomodulatory agents; pomalidomide; proteasome inhibitors; carfilzomib; monoclonal antibody; elotuzumab; daratumumab; panobinostat; ixazomib; check point inhibitors

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[a]Medical Faculty, University Hematology Clinic, Skopje, Macedonia; [b]Myeloma Unit, Division of Her
Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

Key issues

- Despite the advances in treatment of patients with MM due to the introduction of new agents, including immunomodulatory drugs, proteasome inhibitors and the use of autologous stem cell transplant, patients eventually relapse and may become refractory to previous therapies.
- There is an urgent unmet need for novel anti-myeloma agents, especially for patients who have become refractory to currently available therapeutic options.
- Pomalidomide is more potent and better tolerated than its predecessors, thalidomide and lenalidomide, thus in 2013 FDA approved it either alone or in combination with dexamethasone in relapsed/refractory MM patients who received at least two prior therapies.
- Ixazomib is an oral proteasome inhibitor with advantage of lower incidence of neurotoxicity and once-weekly oral administration for patients with newly diagnosed and relapsed/refractory MM.
- Monoclonal antibodies represent the next step in the treatment of MM. Elotuzumab, a SLAM7-target humanized monoclonal antibody, seems to have synergistic activity when combined with anti-myeloma therapies that stimulate host immunity. Anti – CD 38 antibody – Daratumumab as monotherapy and in combination regimens showed impressive results with favorable safety profile without significant increase in toxicity in relapsed/refractory MM patients.
- Clinical trials with multiple checkpoint inhibitors are underway or are planned in MM, like pembrolizumab (MK-3475) – monoclonal antibody considered as immune checkpoint inhibitor that targets the programmed cell death receptor.
- Despite the availability of numerous anti-myeloma drugs, many questions still remain unanswered. The best combination, the optimal sequence and proper target and setting of newer myeloma are relevant issues that need to be clarified in the next future.