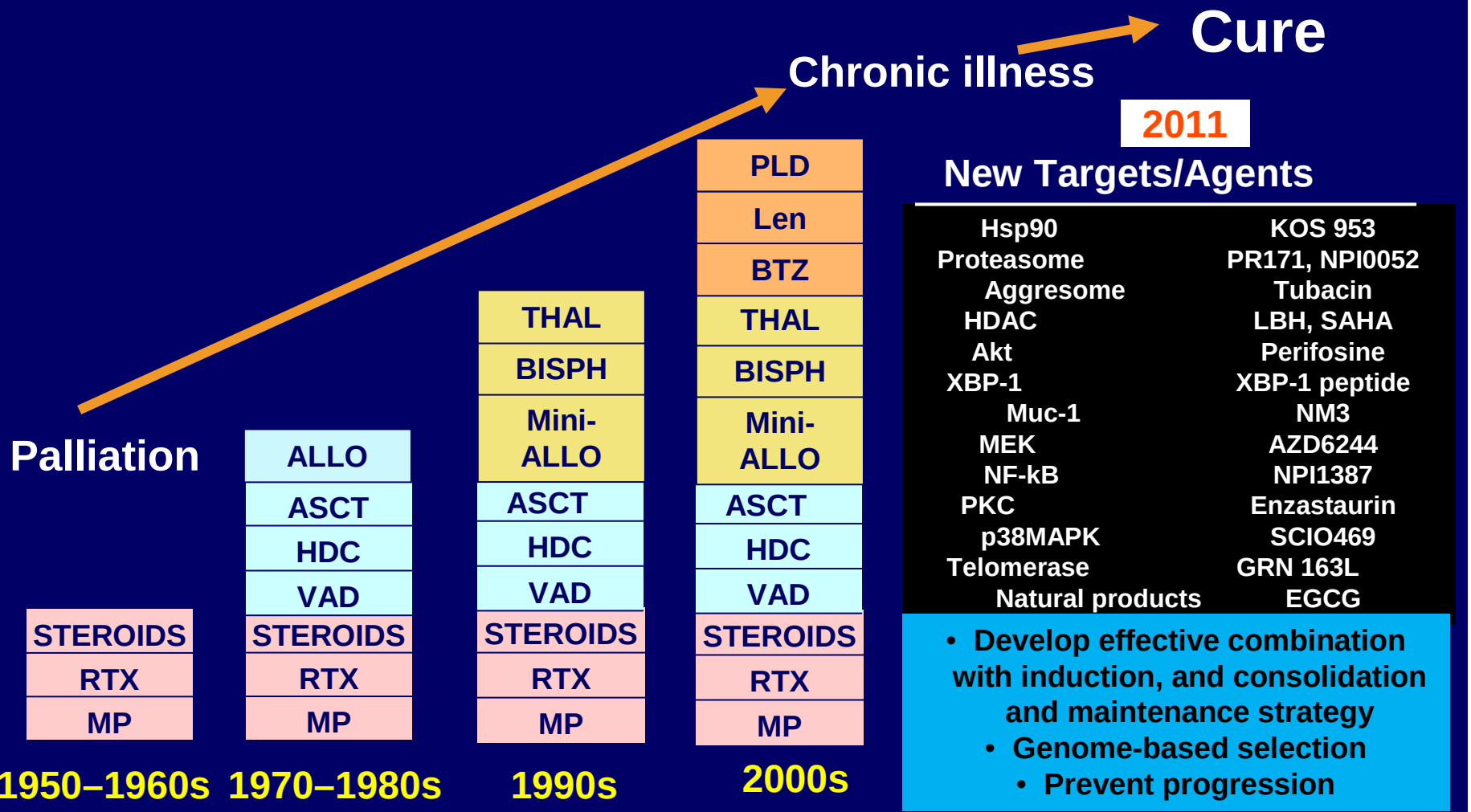
Jak by měl být léčen optimálně nemocný s MM podle guidelines v roce 2012

Roman Hájek

za Českou myelomovu skupinu

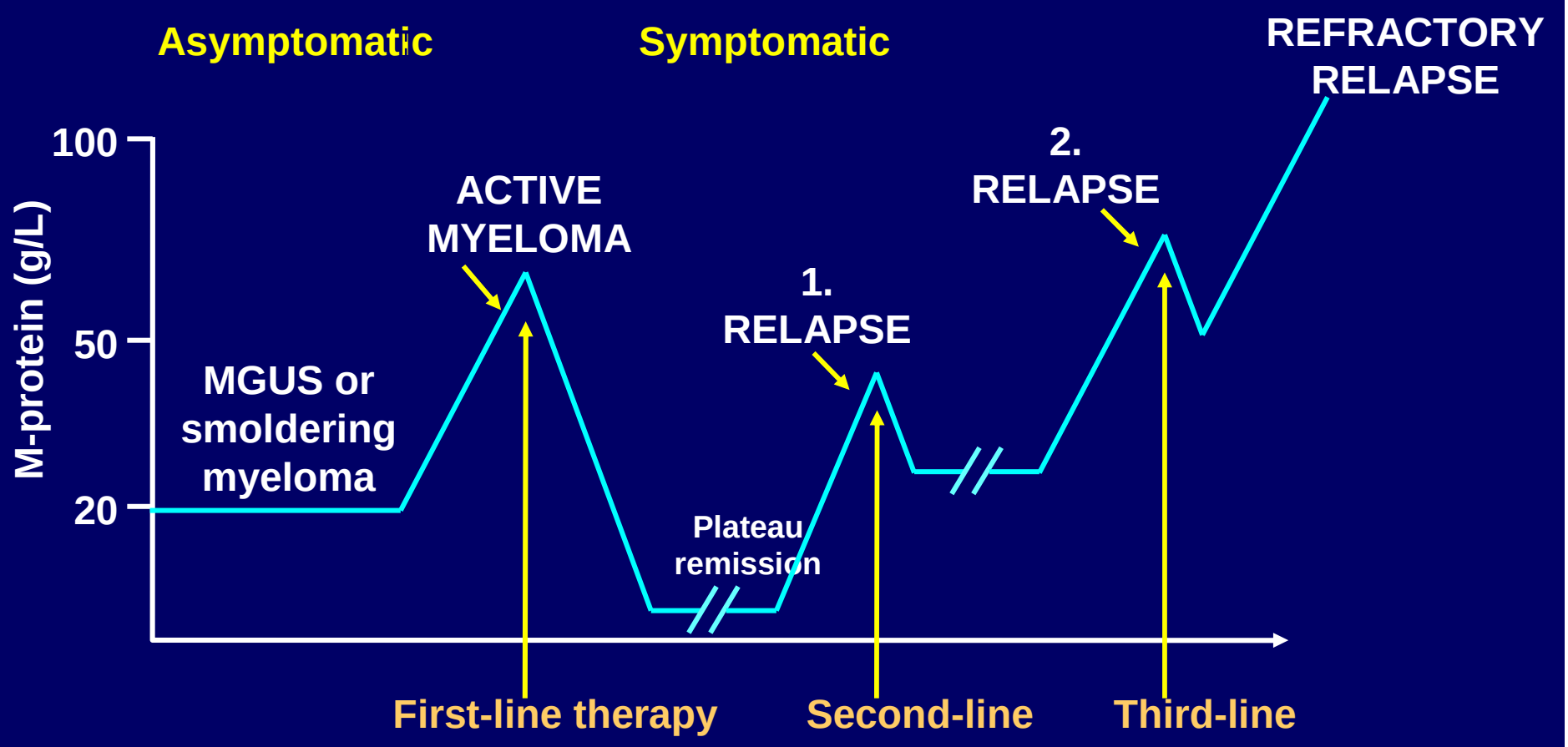
a myelomovou sekci ČHS

Progress in Therapeutic Options



BTZ = Bortezomib
BISPH = Bisphosphonates
THAL = Thalidomide
ASCT = Stem cell transplantation
HDC = High-dose chemotherapy
MP = Melphalan + Prednisone
PLD = Pegylated liposomal doxorubicin

Natural history of multiple myeloma

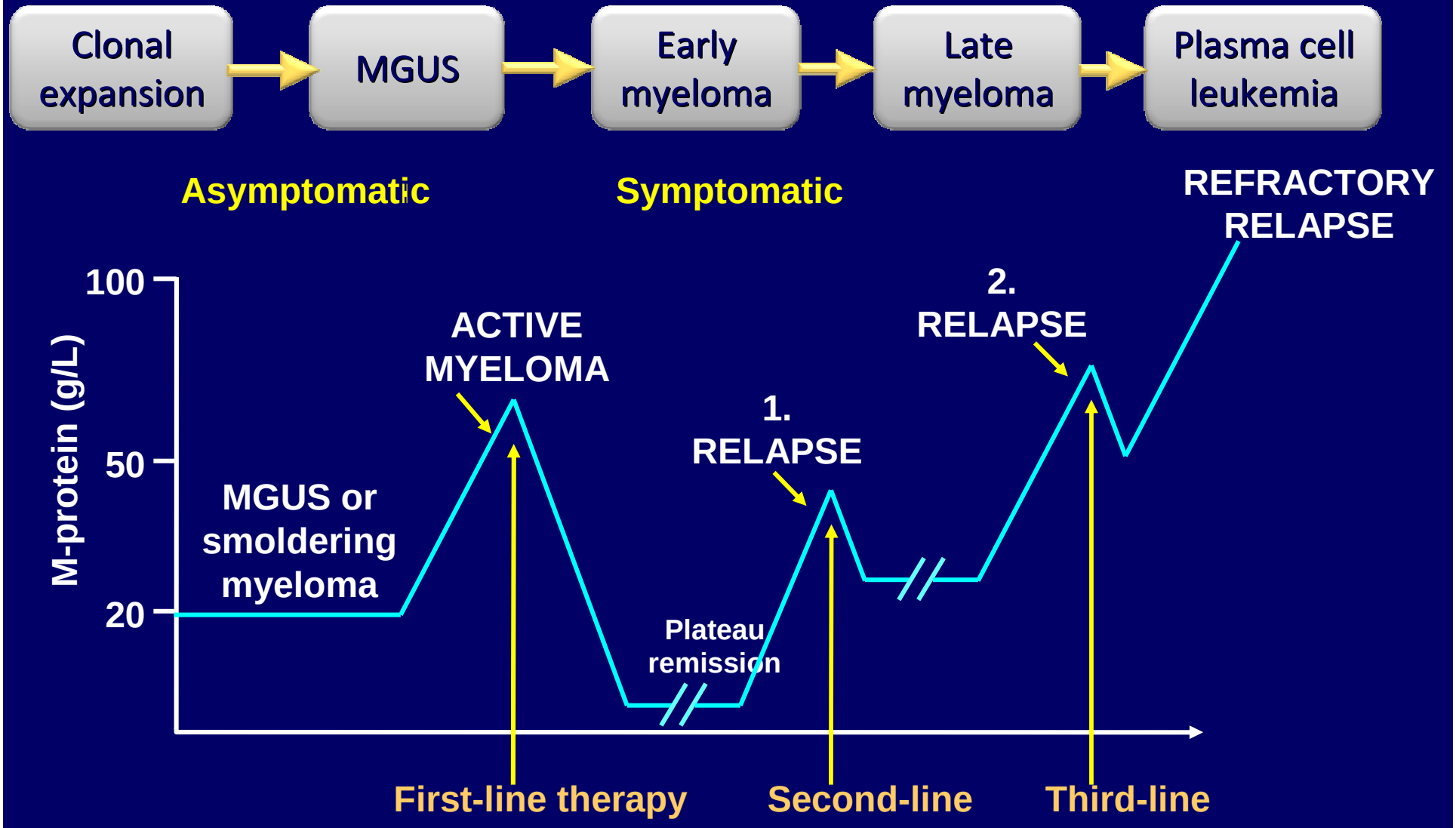


MGUS, monoclonal gammopathy of undetermined significance

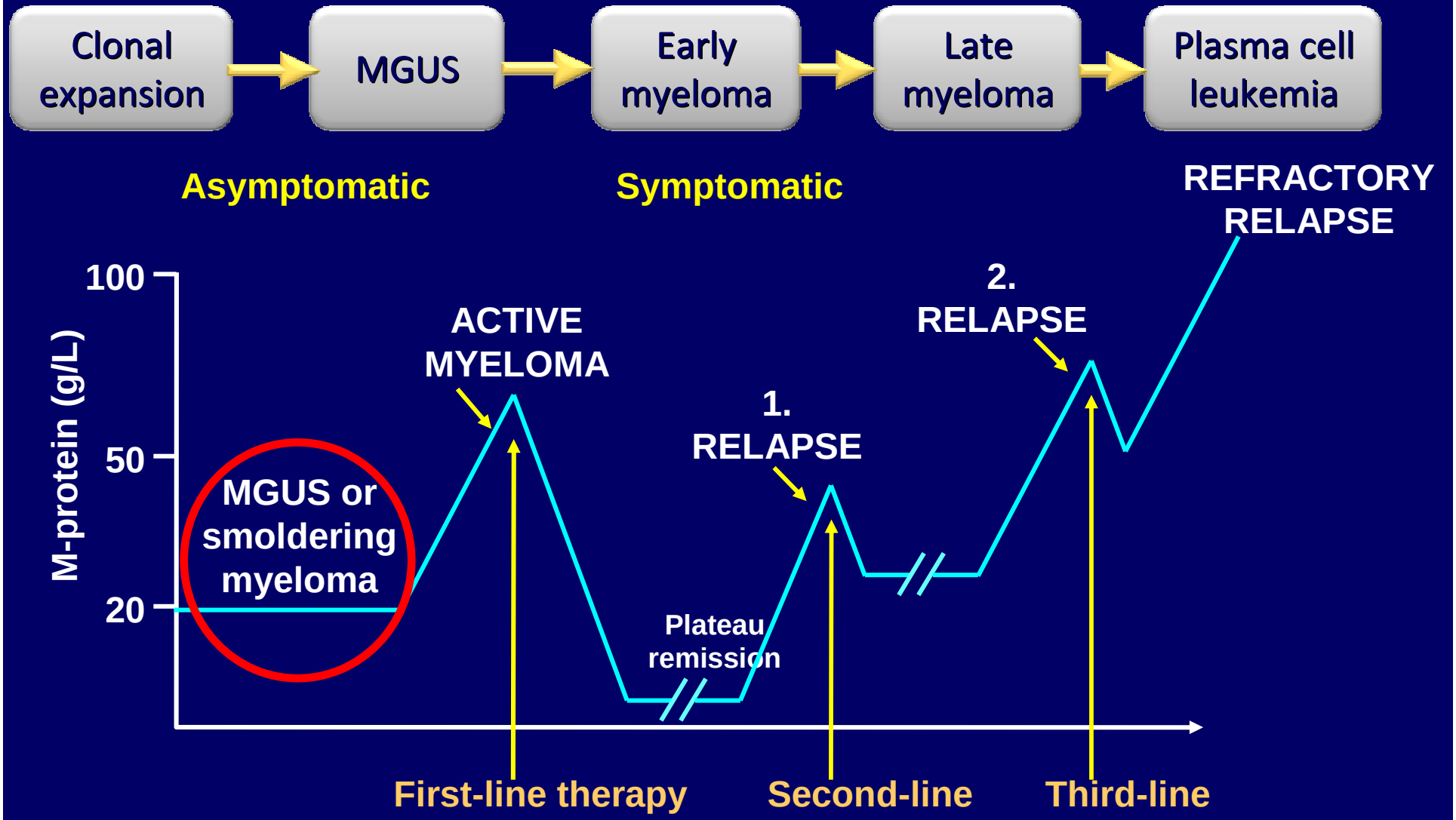
Natural history of multiple myeloma

- MM is preceded by MGUS as precancerosis.
- There are subsets of Multiple Myeloma
- There are several CLONES of Multiple Myeloma

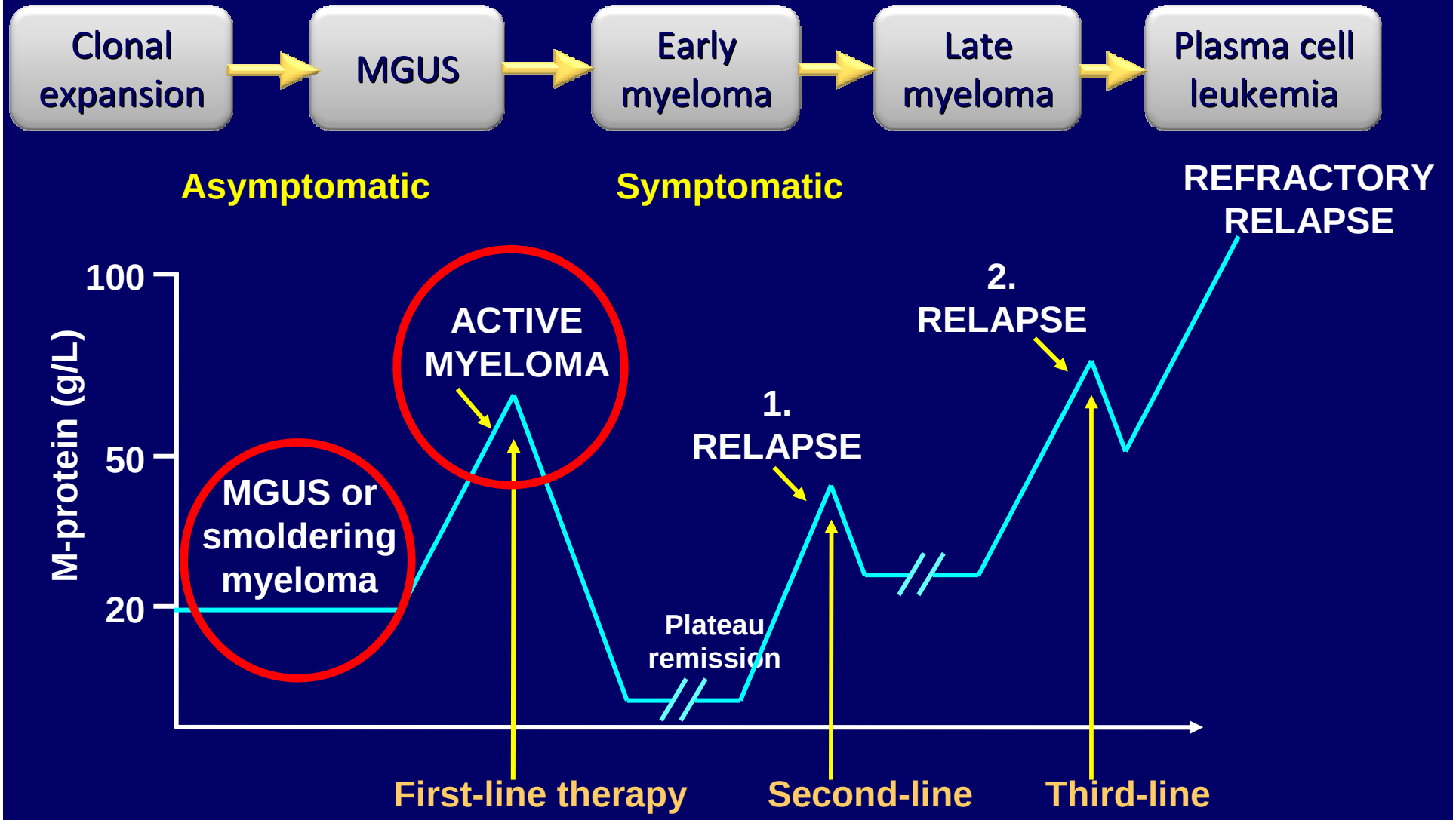
Natural history of multiple myeloma



Natural history of multiple myeloma



Natural history of multiple myeloma



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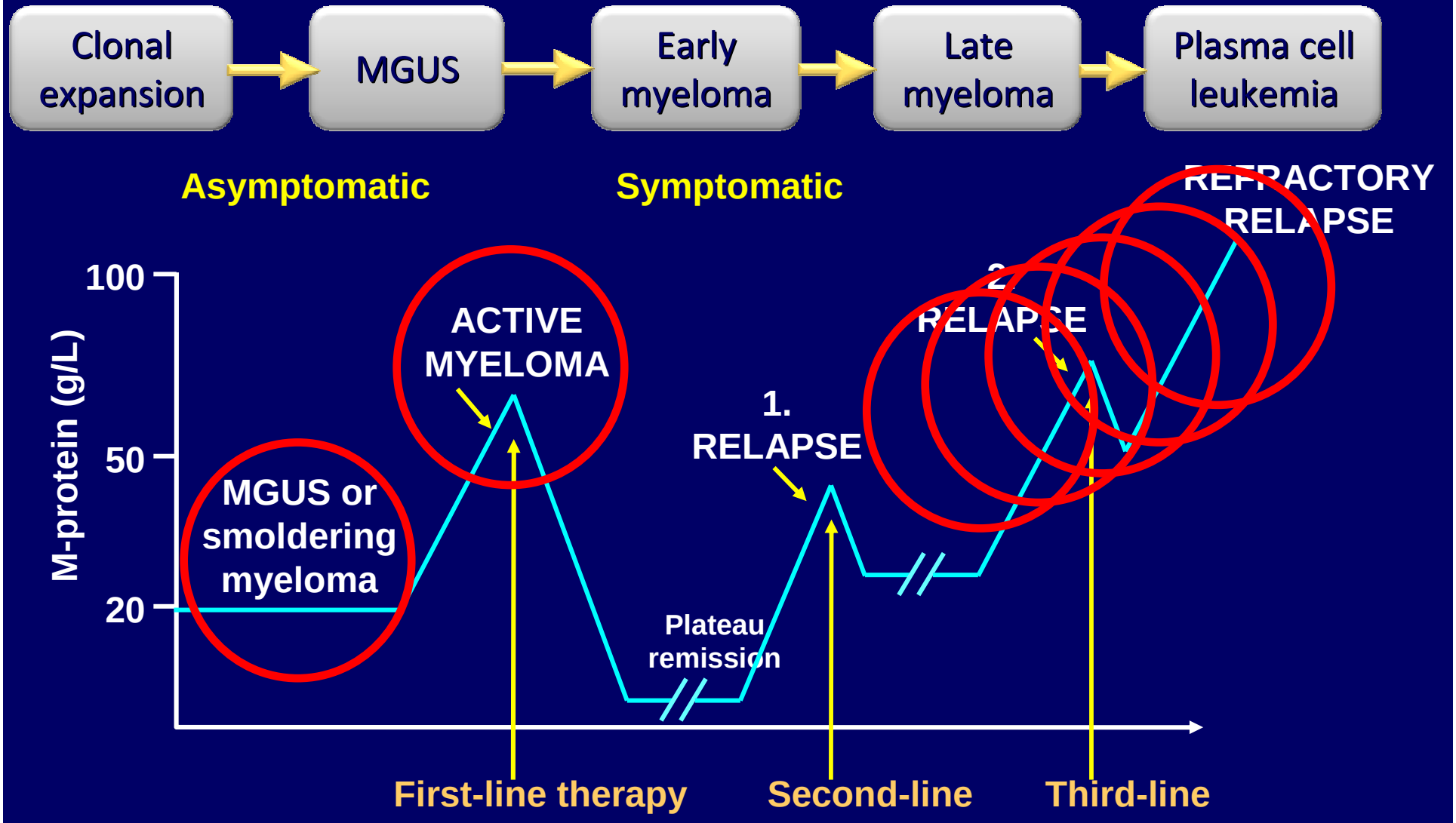

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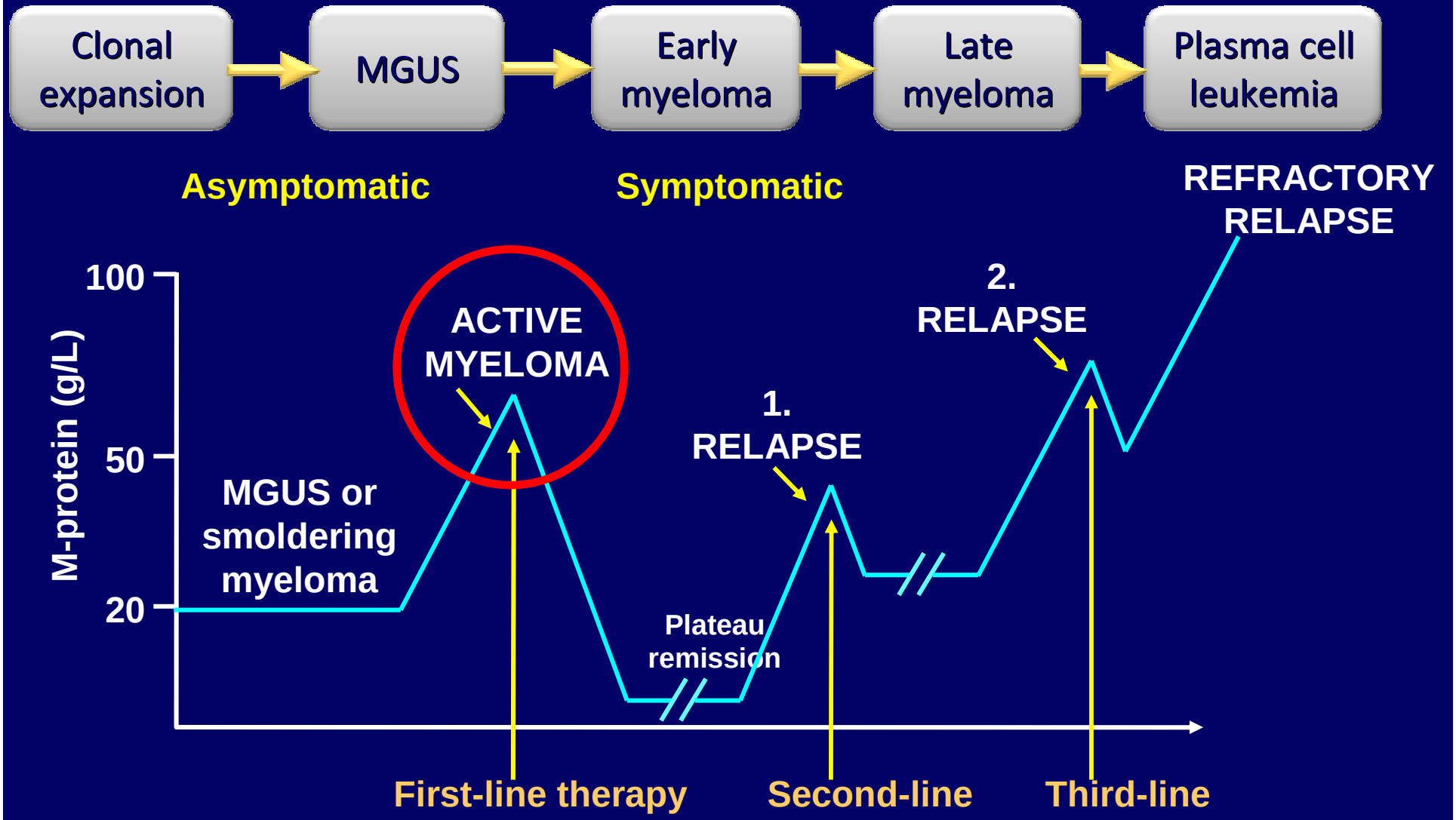
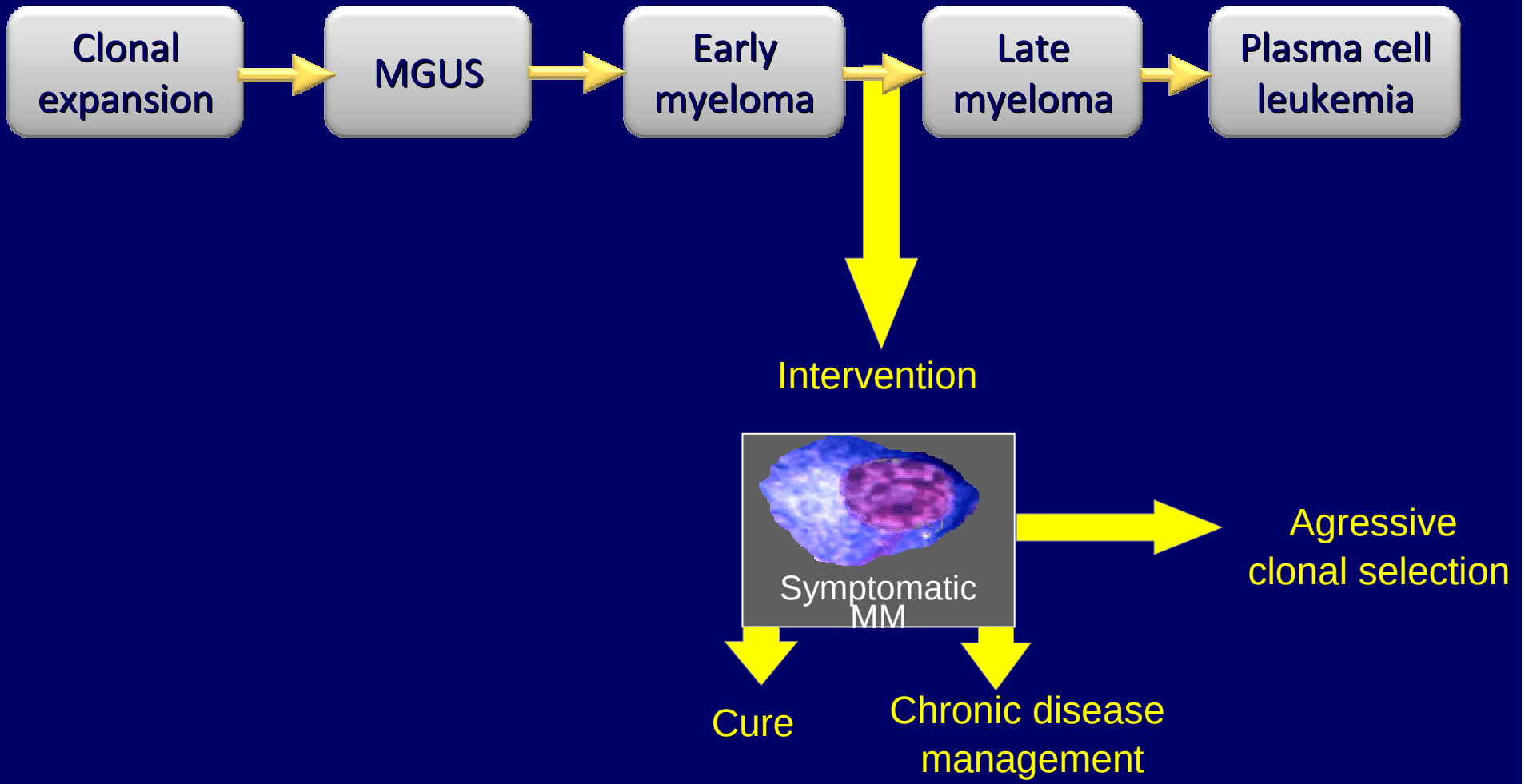


MM: Oncology perspective



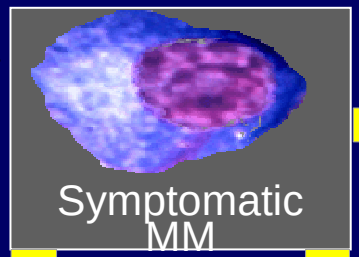
MM: Oncology perspective

Clonal expansion → MGUS → Early myeloma → Late myeloma → Plasma cell leukemia

Intervention

MILESTONES:

1. ***Molecular or Immunophenotypic REMISSION***
2. ***Sustained REMISSION***

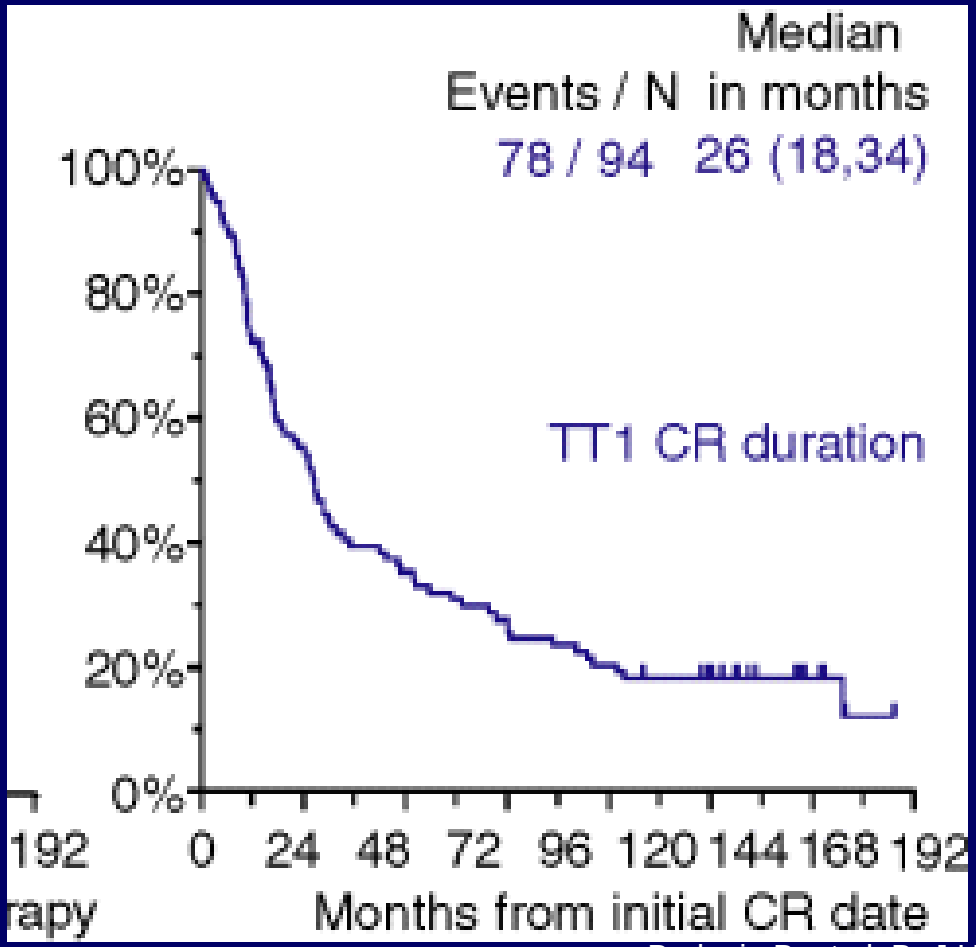


Agressive clonal selection

Cure

Chronic disease management

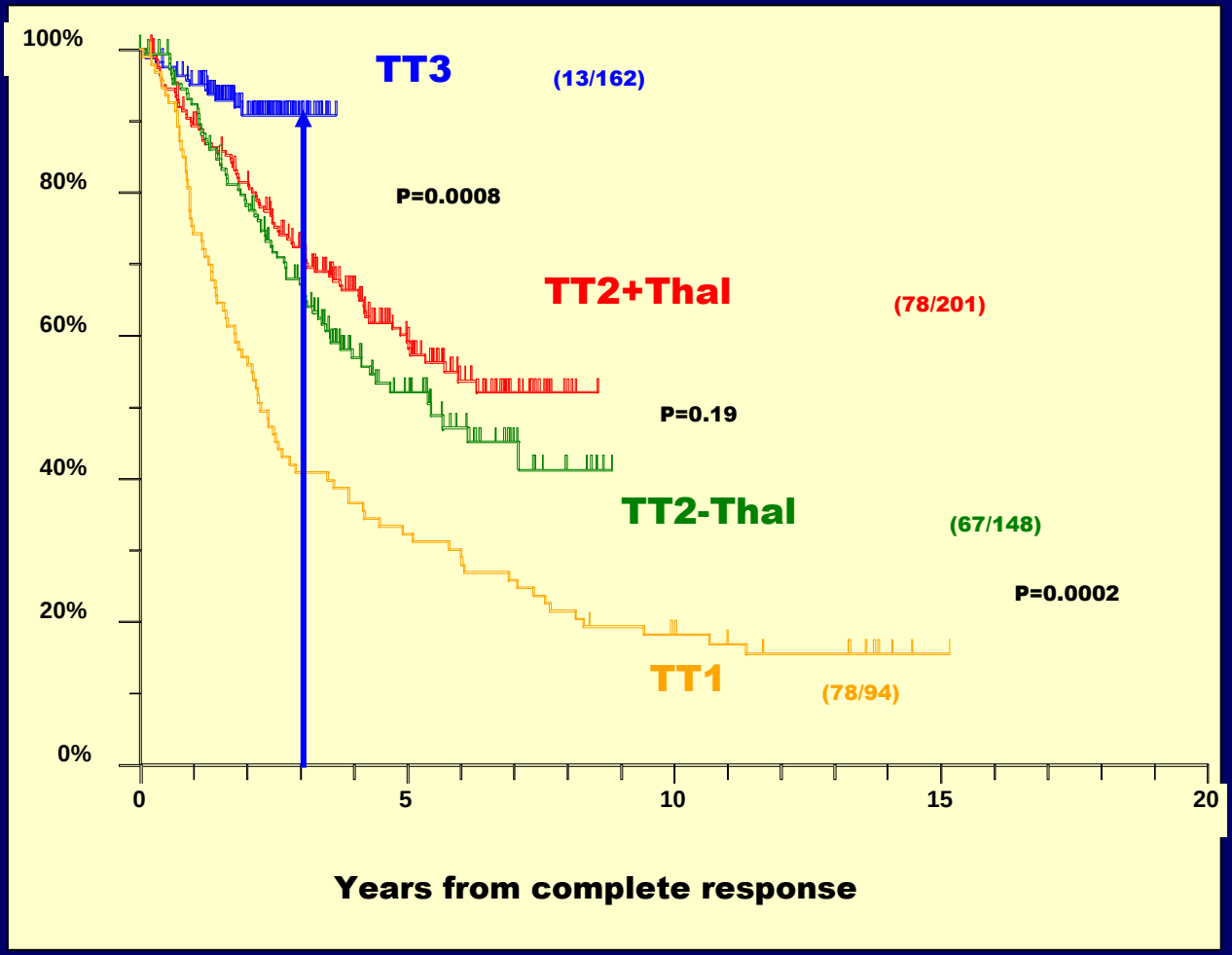
What is the Status of Cure in Myeloma Today?



Barlogie B, et al. Br J Haematol. 2006:135;158-164.

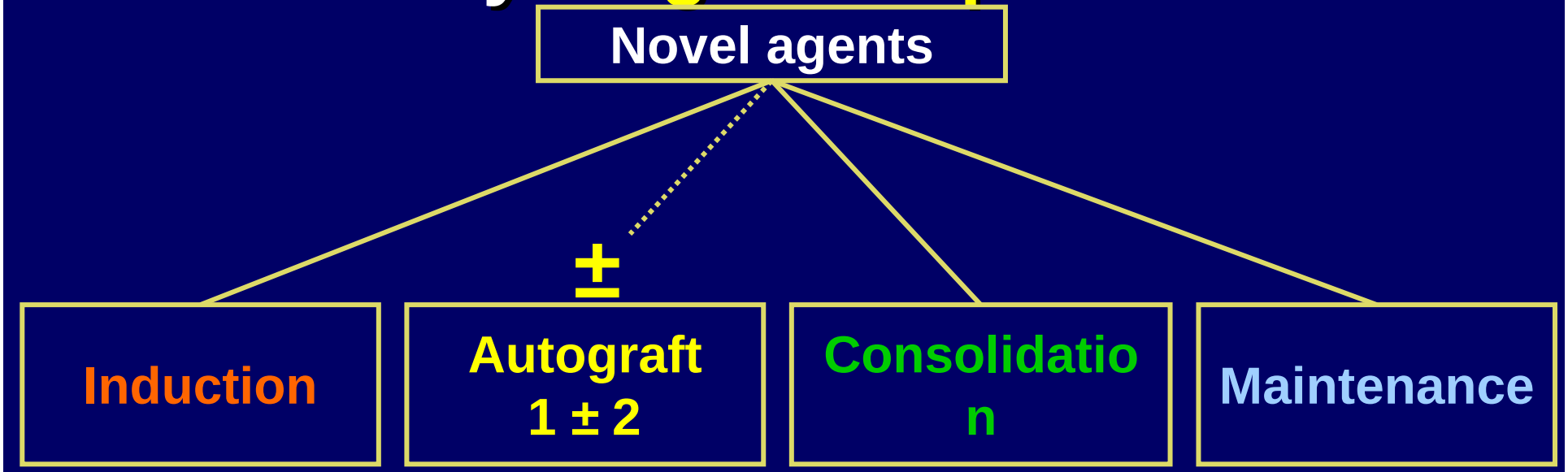
Change in Outlook And Potential Cure with Upfront Novel Agent-based Therapies

Multi Agent Sequential Therapy Improves Sustained CR – Is it a Cure?



Barlogie B, et al. Leukemia. 2008; 22, 1633-1636.

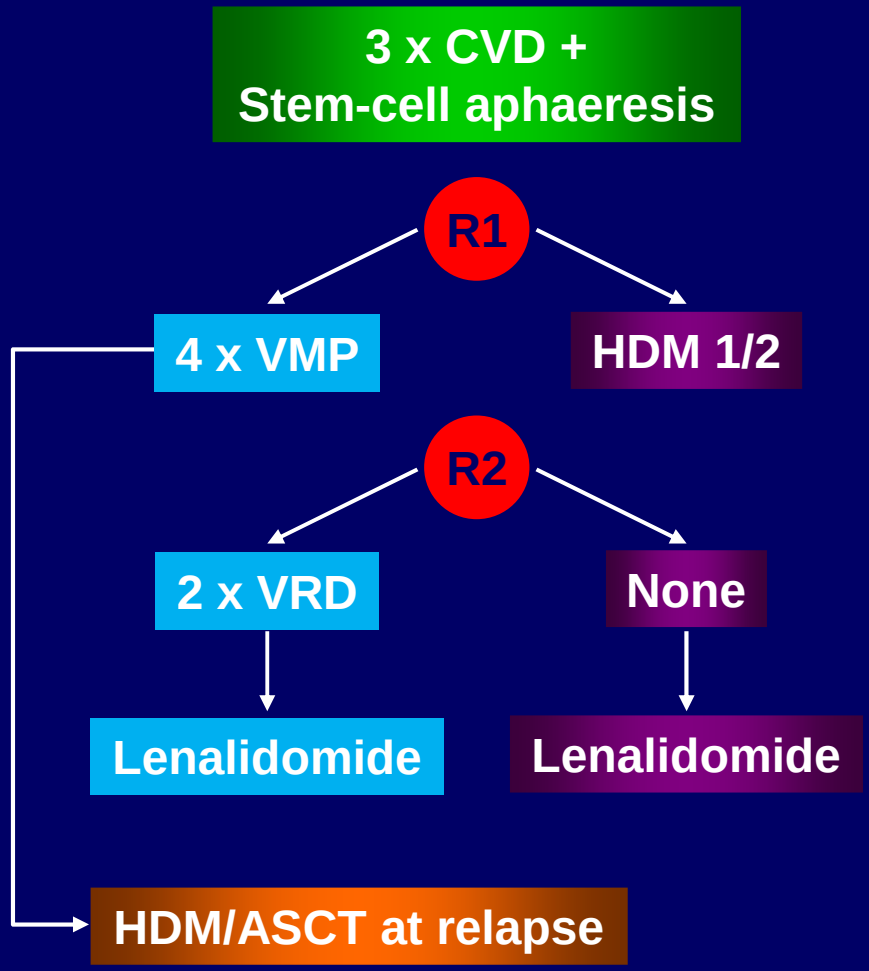
NEW treatment paradigm for newly diagnosed patients



Multi Agent Sequential Therapy Targeting Different Clones

Novel agents alone versus intensive therapy + novel agents:

European Intergroup trial (EMN02)



Induction
Stem-cell mobilization in all patients

Consolidation

Maintenance until replacement

EMN

NCT01208766. Available from: http://clinicaltrials.gov. Accessed October 2011.

Indukční léčba

Novel agent-based induction therapies

	Thalidomide-based	Lenalidomide-based	Bortezomib-based	Bortezomib + IMiD-based
2-drug combinations	TD	RD Rd	VD	
3-drug combinations	TAD CTD	RAD RCD BiRD	PAD VCD	VTD VRD
4-drug combinations				VTDC RVDC

Bortezomib + IMiD-based induction regimens

Induction regimen	Study details	Response post-induction (%)		Response post-ASCT (%)		PFS (months)	(months)
		CR	≥ VGPR	CR	≥ VGPR		
VTD vs TD[1]	Phase 3: VTD vs TD as induction and consolidation	19* 5	62* 28	42* 30	82* 64	68%* 56% (3-yr)	86% 84% (3-yr)
VTD vs TD[2]	Phase 3: VBMCP/VBAD+V vs TD vs VTD induction plus a-IFN, thal or thal/bortezomib maintenance	35* 14	60* 29	46* 24	65* 40	Not reached* 27	Not reached
vtD vs VD[3]	Phase 3: comparison of doublet vs. triplet induction regimens	13 12	49* 36	29 31	74* 58	not reported	

* p-value statistically significant

[1]*Cavo et al. Lancet 2010;376:2075-85; Cavo et al. ASH 2011 (Abstract 1871), poster presentation*
[2]*Rosinol et al. Haematologica 2011; 96 (s1): S69 (Abstract P-138); poster presentation at IMW 2011*
[3]*Moreau et al. Blood 2011;118(22):5752-8*

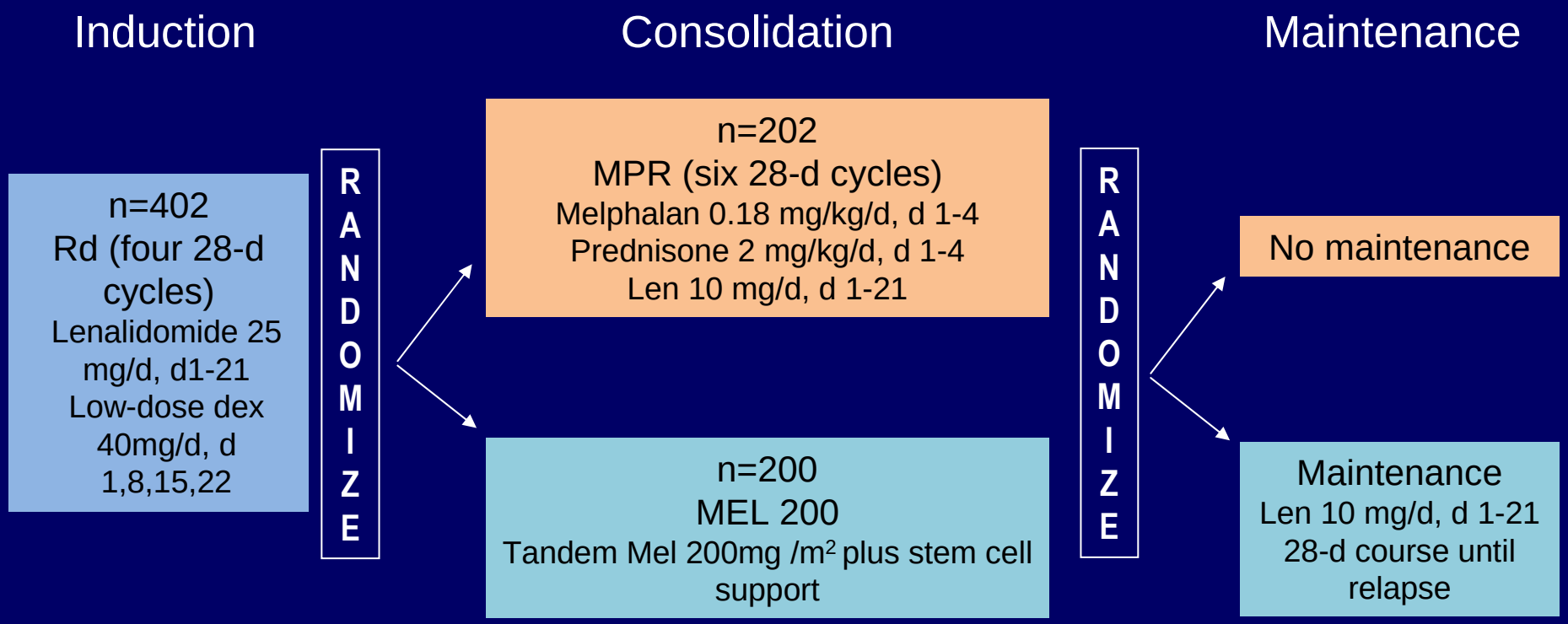
Summary / Conclusion

- Novel-agent-based induction regimens affect higher rates of response than conventional chemotherapy[1]
- Unprecedented rates of ≥ VGPR and CR-nCR after 3-6 cycles that rival those previously seen with ASCT preceded by conventional chemotherapy
- Bortezomib-based induction regimens highly effective
- Bortezomib/dex: a backbone for induction therapy before autologous transplantation[2]
- 3-drug regimens (VTD, VRD, PAD, VCD) superior to 2-drug regimens[1]
- In general, highest response rates seen with triplet regimens combining bortezomib with an IMiD

[1] Cavo et al. Blood. 2011;117(23):6063-73
[2] Moreau et al. Leukemia 2010 ;24:1233-5

Role autologní transplantace

Phase 3: MPR versus tandem ASCT



Primary end point: PFS

Palumbo et al. ASH 2011 (Abstract 3069), poster presentation

Phase 3 study: MPR versus tandem ASCT

Median follow up 26 months

	MPR (n=202)	MEL 200 (n=200)	p
CR	20%	25%	0.49
≥VGPR	60%	58%	0.24
2-year PFS	54%	73%	<0.001
2-year OS	87%	90%	0.19
Standard-risk patients 2-year PFS	46%	78%	0.007
High-risk patients 2-year PFS	27%	71%	0.004
Patients who achieved CR 2-year PFS	66%	87%	<0.001
Patients who achieved PR 2-year PFS	56%	77%	<0.001
Gr 3/4 neutropenia	55%	89%	<0.001
Gr 3/4 infections	0%	17%	<0.001
Gr 3/4 gastrointestinal toxicity	0%	21%	<0.001
DVT	2.44%	1.13%	0.43
Second tumors	0.5%	1.5%	0.12

Palumbo et al. ASH 2011 (Abstract 3069), poster presentation

Konsolidační léčba

Phase 3: VTD vs TD (GIMEMA study)
Impact of VTD consolidation

Per-protocol analysis: n=321, received entire treatment program

	VTD	TD	p
CR post-consolidation	61%	47%	0.012
Upgrade to CR post-consolidation	30.4%	16.6%	0.030
Landmark analysis from start of consolidation (30 months median follow up)			
3-yr probability of relapse or progression	38%	52%	0.039
3-yr PFS	62%	46%	0.025

- Frequency of grade 3/4 AEs comparable in both groups
  - 9.3% VTD, 8.6% TD
- PN with VTD: 0.6%
- Skin rash, DVT: 0.6% in each group
- VTD arm: patients received 93% of planned doses of bortezomib and thal

Cavo et al. ASH 2011 (Abstract 1871), oral presentation

Phase 3 trial: Bortezomib monotherapy as consolidation
(Nordic Myeloma Study Group [NMSG 15/05] trial)

- Randomization (3 months post-ASCT)
  - Bortezomib (n=188) versus observation (n=182)

Median follow-up: 27 months

	Bortezomib	Control	p value
Median PFS	27 months	20 months	0.037
OS @ 27 months	87%	87%	ns
Incidence of neuropathy CTC ≥ III			
Neuropathic pain	6%	0.5%	
Peripheral sensory neuropathy	5%	2%	

Mellqvist et al. Haematologica 2011; 96 (s1): S31 (Abstract O-11); oral presentation at IMW 2011

Udržovací léčba

Lenalidomide maintenance therapy

Study details	n	Treatment	Outcome	
			PFS	**5-year OS**
IFM 2005-02[1]	307	Lenalidomide	41 months	79%
	307	Placebo	24 months $p<10^{-9}$	73% p=0.8
			TTP	**Deaths**
CALGB 100104[2]	231	Lenalidomide	48 months	n=23
	229	Placebo	30.9 months p<0.0001	n=39 p=0.018

- **Significant improvement in PFS/TTP in both studies**
- **Significant survival advantage in CALGB 100104 study**

[1]Attal et al. Haematologica 2011; 96 (s1): S23; oral presentation at IMW 2011
[2]McCarthy et al. Haematologica 2011; 96 (s1): S23; oral presentation at IMW 2011

Incidence of secondary malignancies

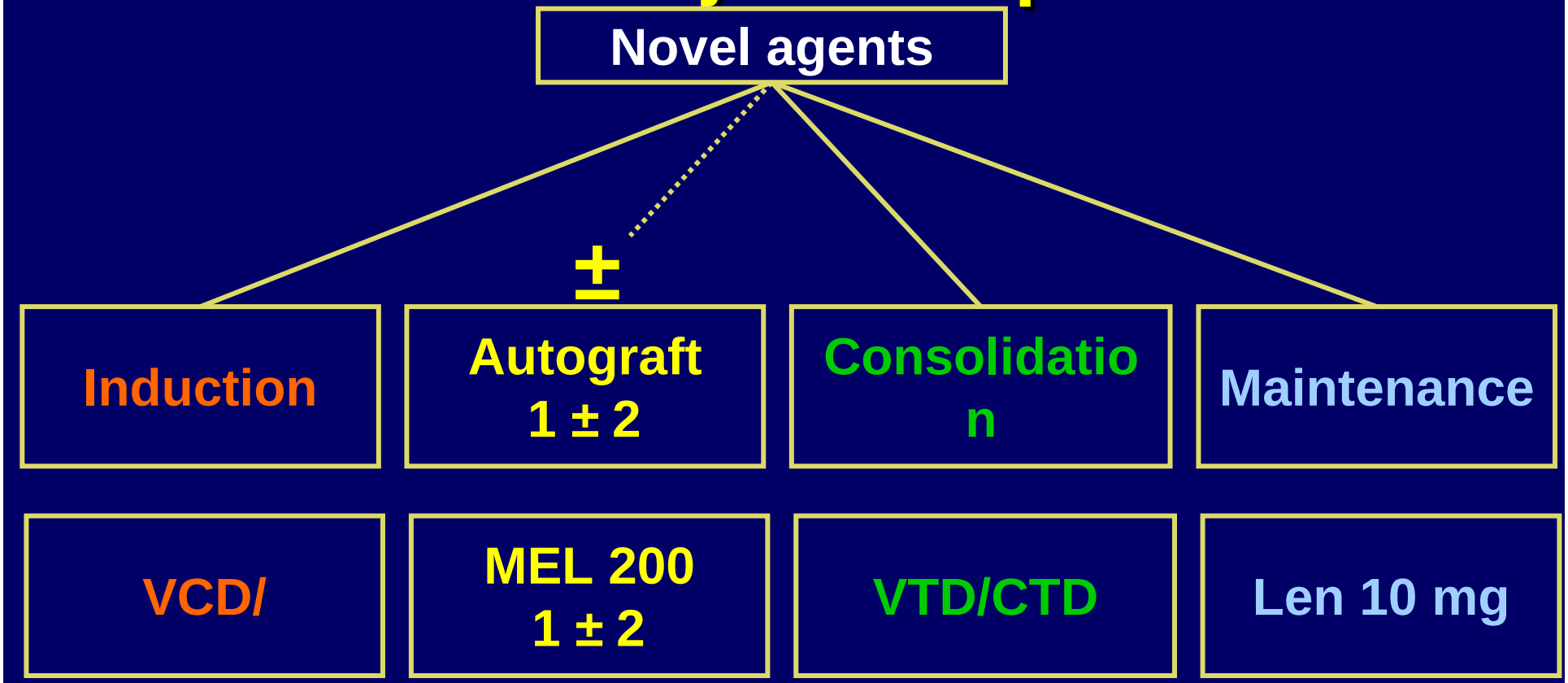
	Hematological malignancies (n)		Solid tumors (n)	
	Len	Placebo	Len	Placebo
IFM 2005-01[1] Len (n=307) Placebo (n=307)	11 5 AML/MDS 2 ALL 4 HL	3 3 AML/MDS 0 ALL 0 HL	12 2 Oesophageal/hypopharynx 2 Colon 2 Prostate 4 Basal cell carcinoma 2 Breast	3 1 Prostate 2 Basal cell carcinoma
CALGB 100104[2]* Len (n=231) Placebo (n=229)	8 6 AML/MDS 1 ALL 1 HL	0	10 2 GI 2 Breast 2 Gyn 1 CNS 1 Prostate 1 Thyroid 1 Melanoma	4 1 Carcinoid 1 Sarcoma 2 Melanoma

*3 hematological and 4 solid tumors occurred before randomization

[1]Attal et al. Haematologica 2011; 96 (s1): S23; oral presentation at IMW 2011
[2]McCarthy et al. Haematologica 2011; 96 (s1): S23; oral presentation at IMW 2011

Závěr

Nemocný by měl být léčen intenzivněji než doposud



Multi Agent Sequential Therapy Targeting Different Clones

Senioři

Therapeutic Algorithm
Level of Evidence 1b (> 1 Randomized Trial)

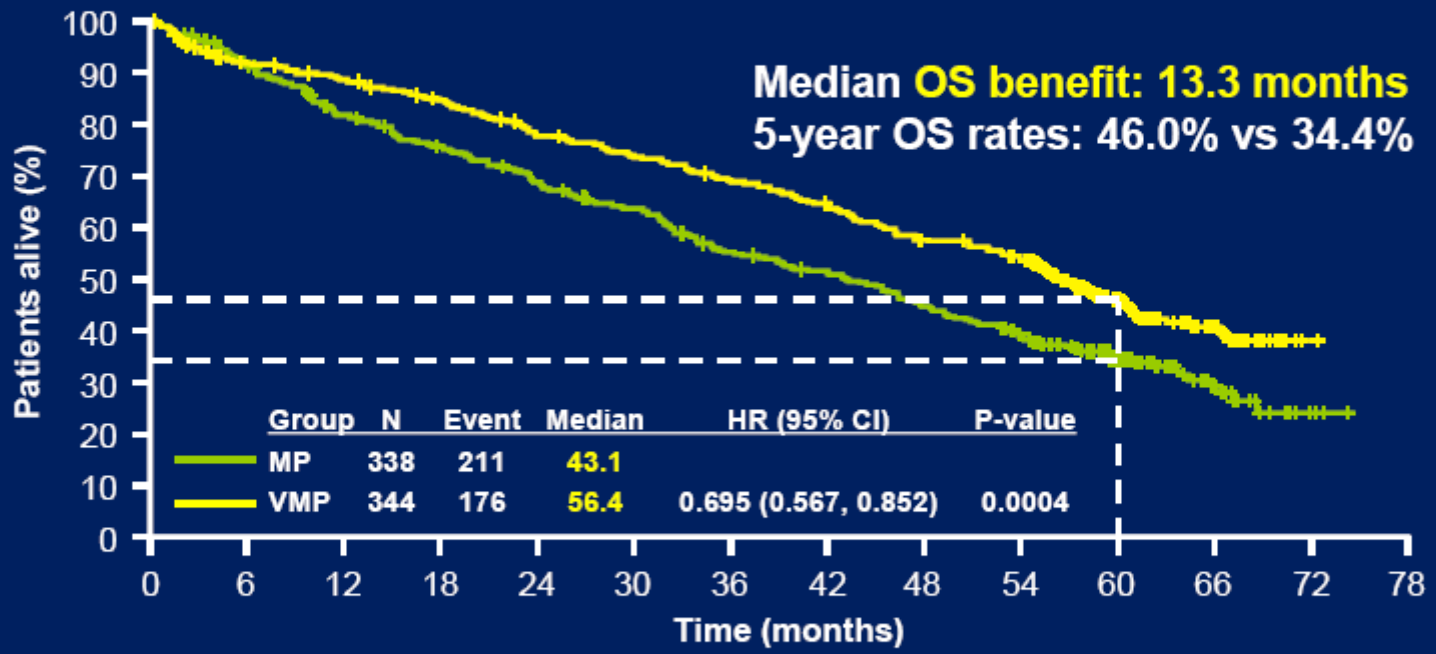
MPT	>	MP	5 randomized trials
MPV	>	MP	1 randomized trial
MPR-R	>	MP	1 randomized trial
VMPT-VT	>	VMP	1 randomized trial

VD RD commonly used alternatives

VISTA: Final updated OS analysis

31% reduced risk of death with VMP

Median follow-up 60.1 months



- Meta-analysis of six phase 3 trials of thalidomide–MP (MPT) vs MP:[1]
  - Median OS: 39.3 vs 32.7 months (6.6-month benefit), HR 0.83, 17% reduced risk of death

Favers PM, et al. Blood 2011;118:1239–47

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

MM-015: Updated results for patients 65-75 years old

Median follow-up 30 months

	MPR-R	MPR	MP	p
Overall no. of pts	152	153	154	
No. of pts 65-75 years	116	116	116	
ORR	79%*	n/a	47%*	*<0.001
≥ VGPR	35%	n/a	10%	*<0.001
Median PFS	31 months*†	15 months†‡	12 months*‡	*†<0.001 ‡0.009

Palumbo et al. ASH 2011 (Abstract 475), oral presentation

Optimalizace !

Flexible dosing: Comparable efficacy with improved tolerability

Study details	Efficacy				Sensory PN		Discont. due to PN	Discont. due to AEs overall
	ORR	CR	Median PFS	3-yr OS	All grades	Grade 3/4		
VMP with twice-weekly bortezomib administration								
VISTA[1-3,7]	71%	30%	21.7m	68.5%	47%	13%	14%*	34%
VMP with once-weekly bortezomib administration								
GIMEMA[4,5,7]	79%	23%	27m	87%	22%	2%	4%	17%
PETHEMA/GEM[6,7]	80%	20%	34m	74%	n/a	7%	n/a	12%†

*3% discontinued VMP; 11% selectively discontinued bortezomib due to PN

†Discontinuations due to SAEs

1. San Miguel et al. NEJM 2008; 359: 906-917
2. San Miguel et al. NEJM 2008; 359: 906; Suppl. App.
3. Mateos et al. J Clin Oncol 2010; 28: 2259-2266
4. Palumbo et al. J Clin Oncol 2010; 28: 5101-5109
5. Bringhen et al. Blood 2010; 116: 4745-4753
6. Mateos et al. Lancet Oncol 2010; 11: 934-941
7. Mateos et al. Haematologica 2011; 96 (s1): S81 (Abstract P-175); poster presentation at IMW 2011

Frail patients: treatment algorithm

RISK FACTORS
- Age over 65 years
- Mild, moderate or severe frailty: help needed for households and personal care
- Comorbidities and organ dysfunction Cardiac Pulmonary Hepatic Renal

Go-go	*moderate-go*	*slow-go*
DOSE LEVEL 0	DOSE LEVEL – 1	DOSE LEVEL – 2
No risk factors	At least one risk factor	At least one risk factor + any Gr 3-4 non hematologic AE

Palumbo et al. Blood. 2011;

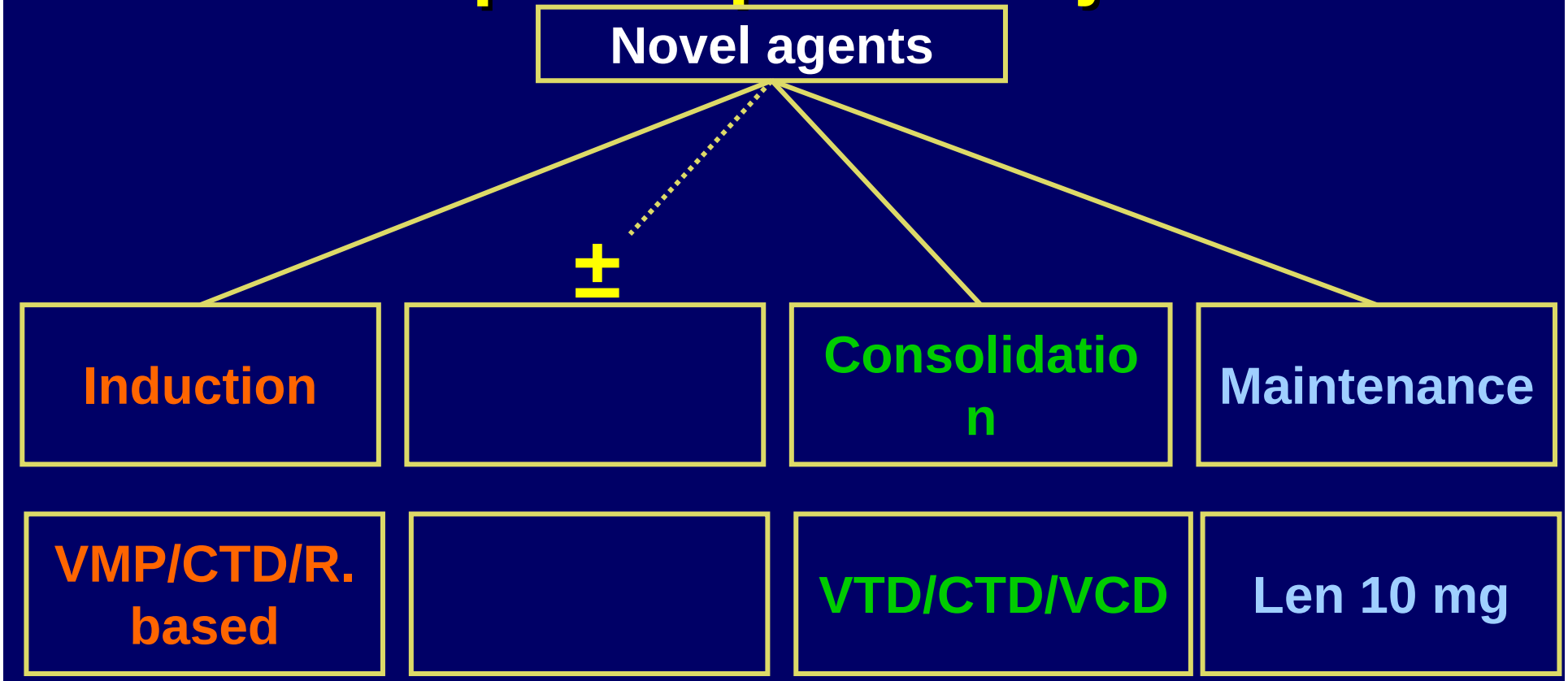
Treatment algorithm

DOSE LEVEL 0	DOSE LEVEL −1	DOSE LEVEL −2
Lenalidomide 25 mg/d d 1-21 / 4 wks	15 mg/d d 1-21 / 4 wks	10 mg/d d 1-21 / 4 wks
Thalidomide 100 mg/d	50 mg/d	50 mg/every other day
Bortezomib 1.3 mg/m^2 d 1,8,15,22 / 5 wks	1.0 mg/m^2 d 1,8,15,22 / 5 wks	1.3 mg/m^2 d 1,15 / 4 wks
Melphalan 0.2 mg/kg/d d 1-4 / 5 wks	0.15 mg/kg d 1-4 / 5 wks	0.10 mg/kg d 1-4 / 5 wks
Prednisone 2 mg/kg/d d 1-4 / 5 wks	1.5 mg/kg/d d 1-4 / 5 wks	1 mg/kg/d d 1-4 / 5 wks

Palumbo et al N Engl J Med. 2011;364:1046-60

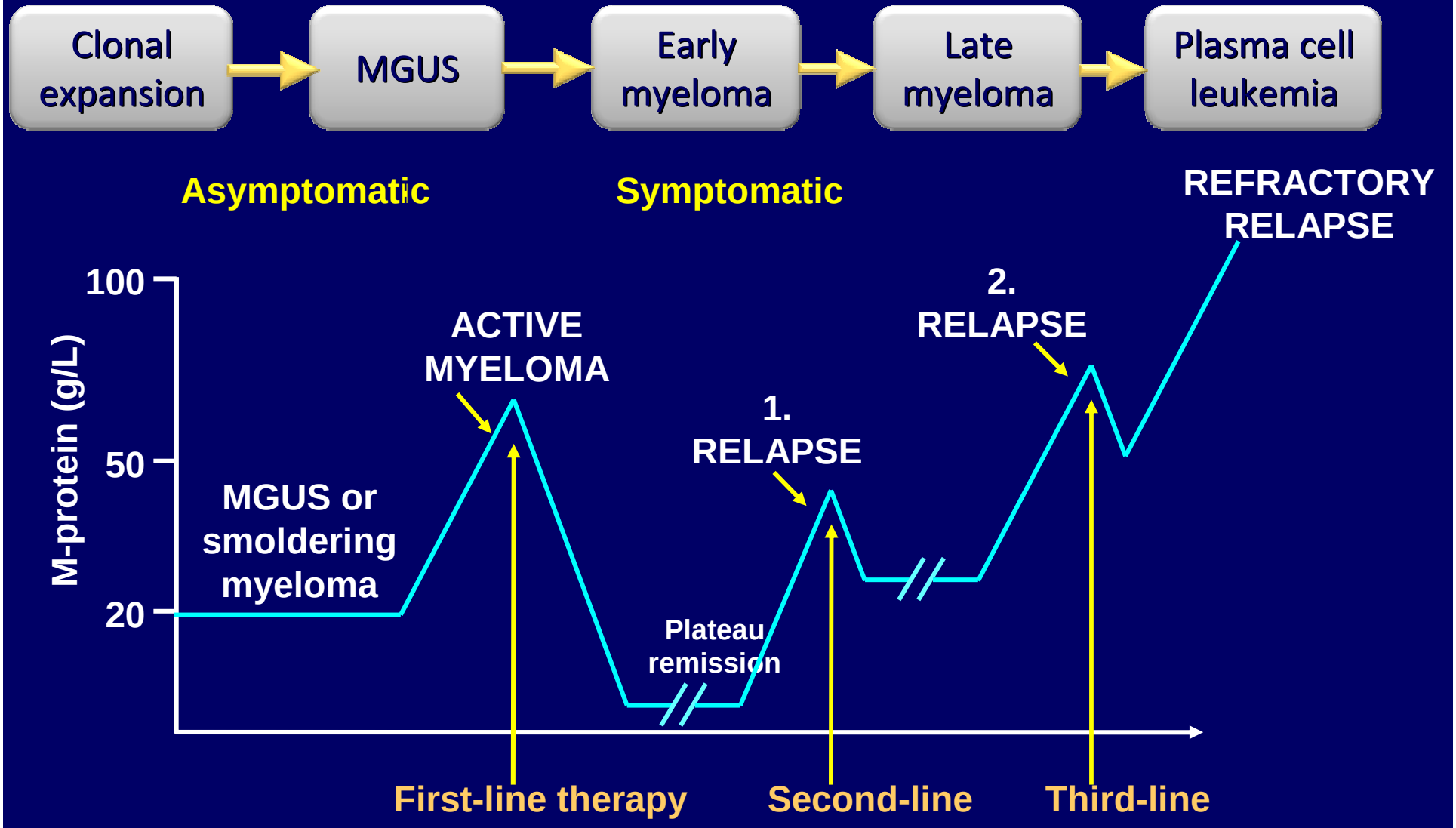
Závěr

I senior měl být léčen intenzivněji než doposud pokud to jde



Multi Agent Sequential Therapy Targeting Different Clones

Natural history of multiple myeloma



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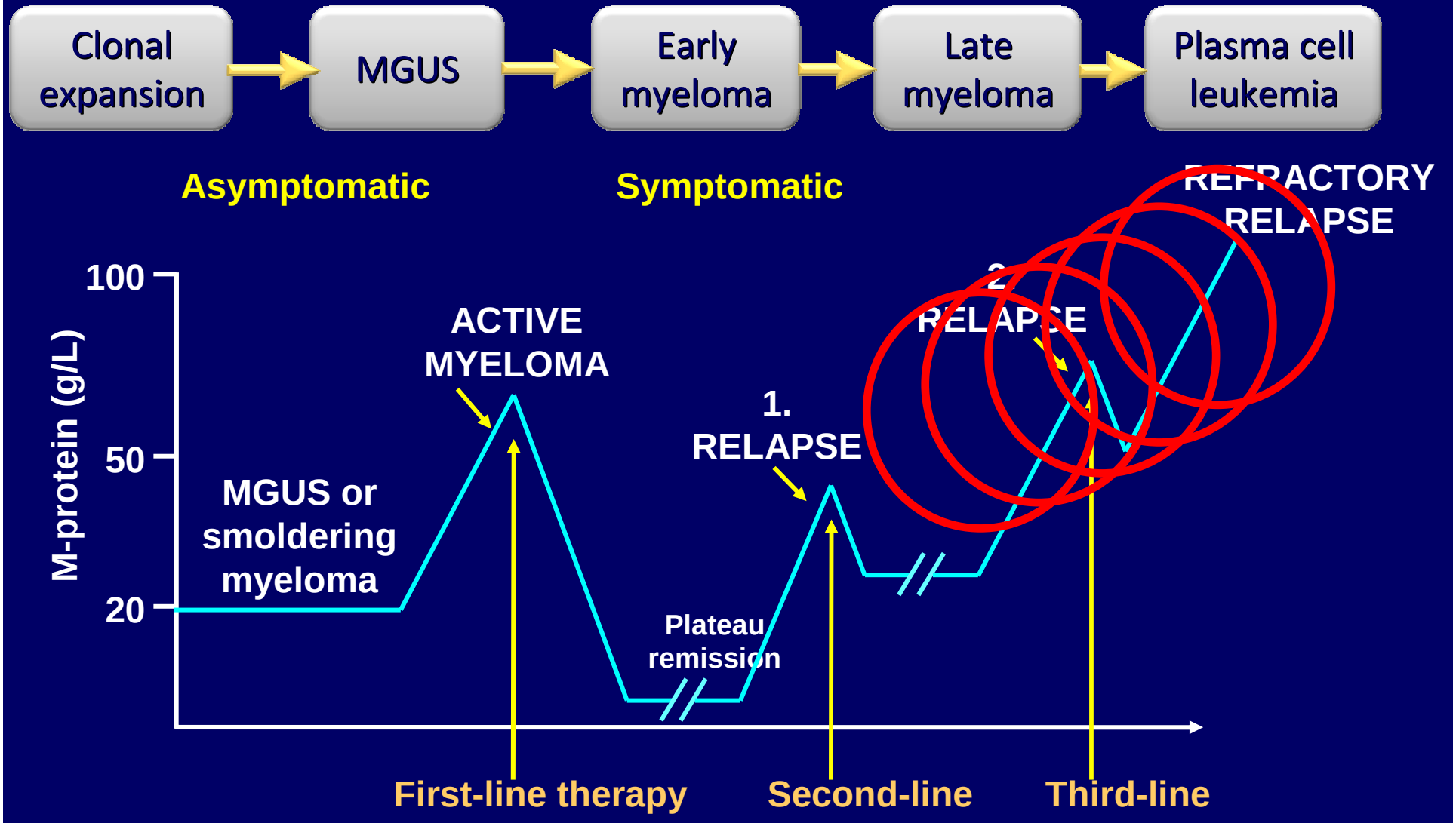
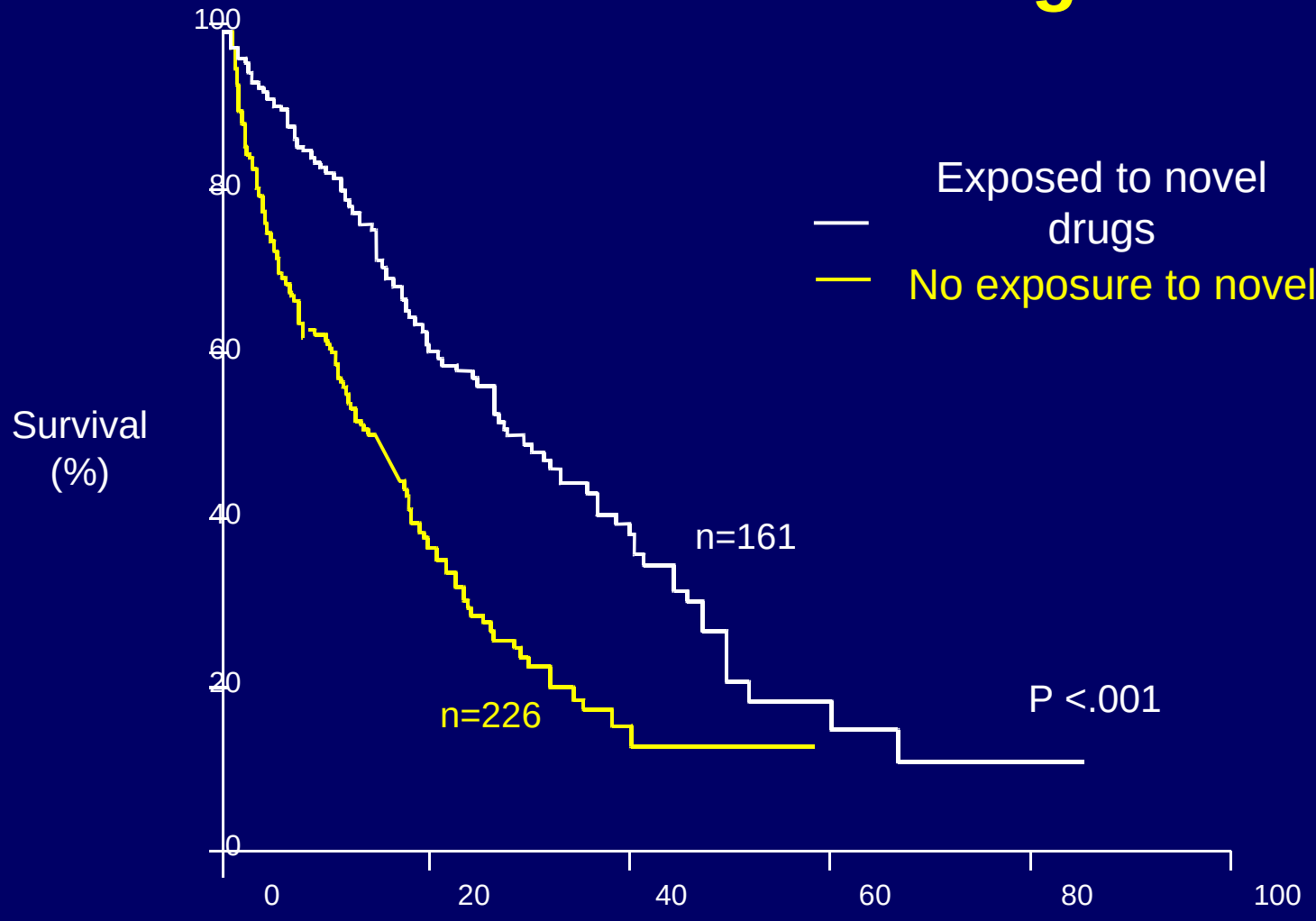


Approach to the Treatment of Patient with Relapse after Conventional Treatment

1) Re-induction with the same protocol as used the first time
2) Immediate second autologous transplantation
3) Allogeneic stem cell transplantation
4) Re-induction plus autologous transplantation
5) Thalidomide based regimen
6) Lenalidomide based regimen
7) Bortezomib based regimen
8) Other novel agens in the clinical trials,
9) Best Paliative Care

Overall Survival from Relapse - Benefit of the Novel Agens



Kumar S K et al, Blood, 2008

Agents in Phase III Studies

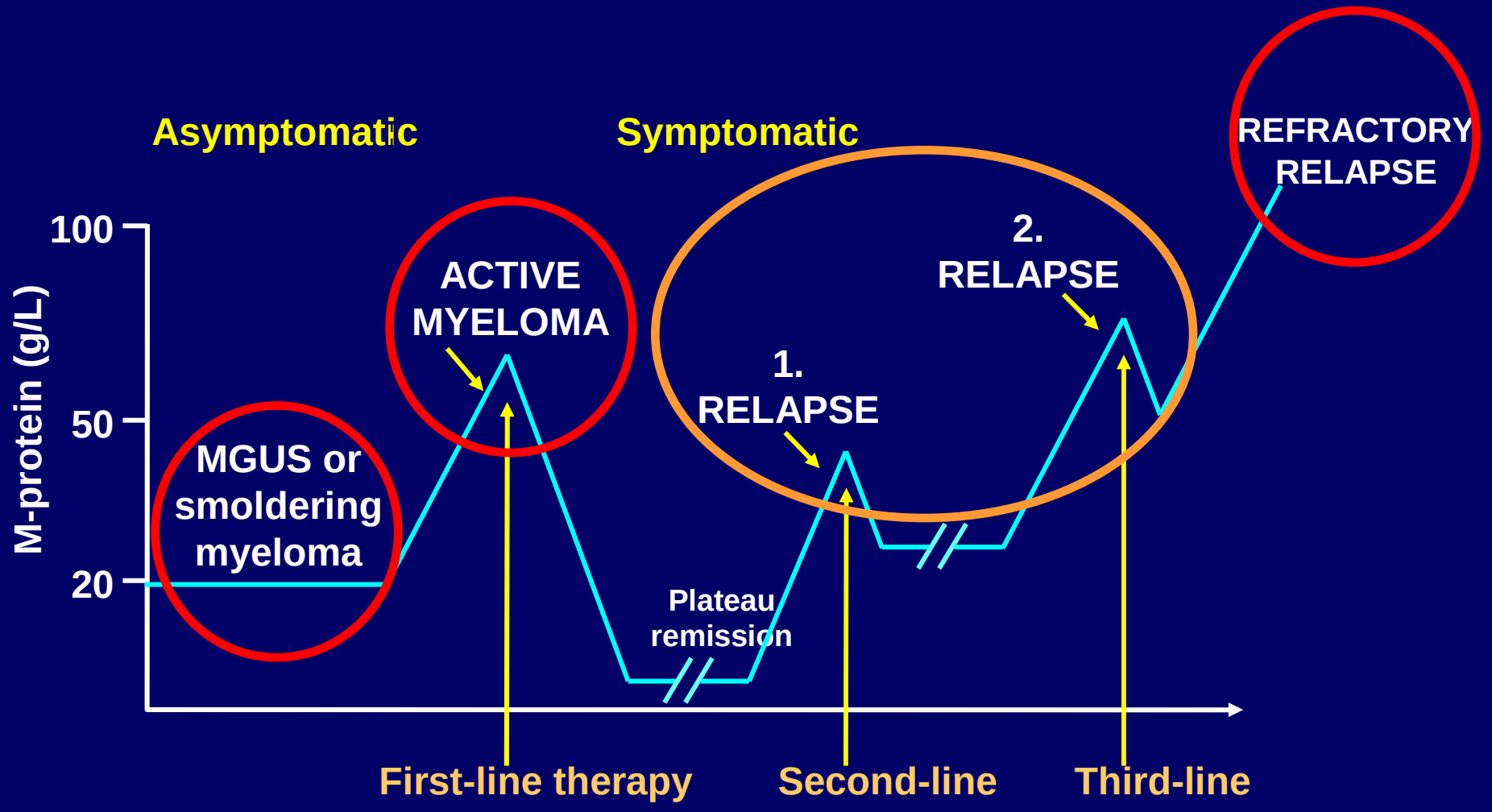
	Target	Combination /Partner(s)
1.	Pomalidomide	Dexamethasone
2.	Carfilzomib	Lenalidomide and Dex
3.	Vorinostat	Bortezomib
4.	Panobinostat	Bortezomib
5.	Elotuzumab	Lenalidomide and Dex
6.	Perifosine	Bortezomib
7.	Siltuximab	Bortezomib

Nejperspektivnější

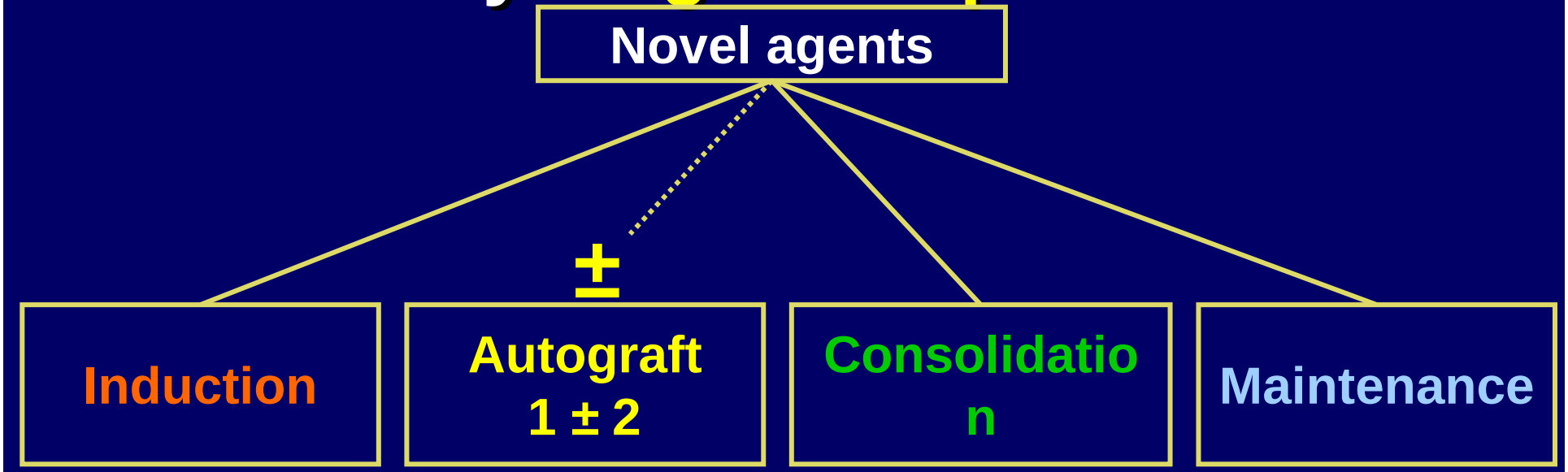
Relapse after thalidomide, lenalidomide, and bortezomib

Výzvy pro budoucnost

WE NEED NEW treatment paradigm for Relapsed patients



NEW treatment paradigm for newly diagnosed patients



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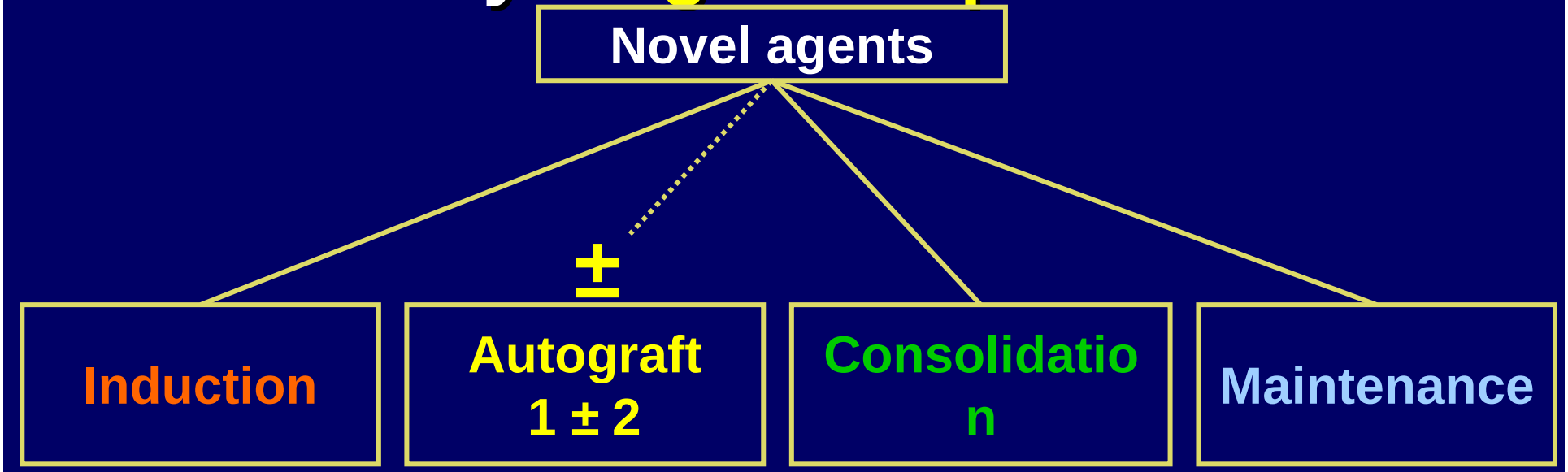

OLD treatment paradigm for relapsed patients (1-2 relapse)

Induction	X (90% NO)	x	x

Conlusion

We have now strong tools
and natural course of MM
can be changed

- **A**: Early intervention strategy-future
- **B**: More effective treatment in NDMM
- **C**: More options for advance disease

Thank you for your attention