Myeloma Crowd

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Steps to make an informed treatment decision

Diagnosis and Treatment

- Ask your doctor for your specific diagnosis and write it down
  - Your specific diagnosis is important in determining treatment
- Gather information about all your treatment options
  - Ask your doctor to explain the treatment options

Refer to *Questions to Ask Your Healthcare Provider*

Goals of Treatment

- **Ask your doctor**
  - What is the goal of treatment?
  - Is my cancer curable?
  - What are the options for my treatment?
  - Why are you recommending these options for me?
- **Ask yourself**
  - What are my personal goals for treatment?
    - Your goals are an important part of your treatment decision process.
  - Do I have the information I need to make an informed decision?

Take an active role in making treatment decisions for yourself

Ask Questions, Seek a Second Opinion

- Bring a family member, friend or other advocate to take notes and for support
- Ask who on the cancer care team can answer additional or follow up questions
- Seek a second opinion for diagnosis and/or treatment

Personal Medical Records

- Establish a file and keep it with you for reference
  - Specific diagnosis, including the subtype
  - Laboratory reports
  - Radiology reports
  - Current medications you are taking (including vitamin supplements)
  - Past and current treatments you have had for cancer
  - Medical history
  - List of your healthcare providers and contact information/business cards

Standard Treatment

- Standard treatment is treatment that experts agree is appropriate, accepted, and widely used
- As with any treatment, it will have side effects
- For some blood cancers, the standard treatment may only be somewhat effective
  - In these instances, you may want to consider a clinical trial

Talk to your doctor

**Talk to your doctor about all of your treatment options–
Standard treatment or clinical trials**

Ask as many questions as you have, until the answers are clear to you

Clinical Trials

- Ask about therapies being studied in a clinical trial
  - Ask if a clinical trial might be right for you
  - Ask about benefits and risks of both standard treatment and treatment in the clinical trial and how they differ
- There are risks and benefits in standard treatment and in clinical trials
- Ask about side effects of each treatment option and how these will be managed

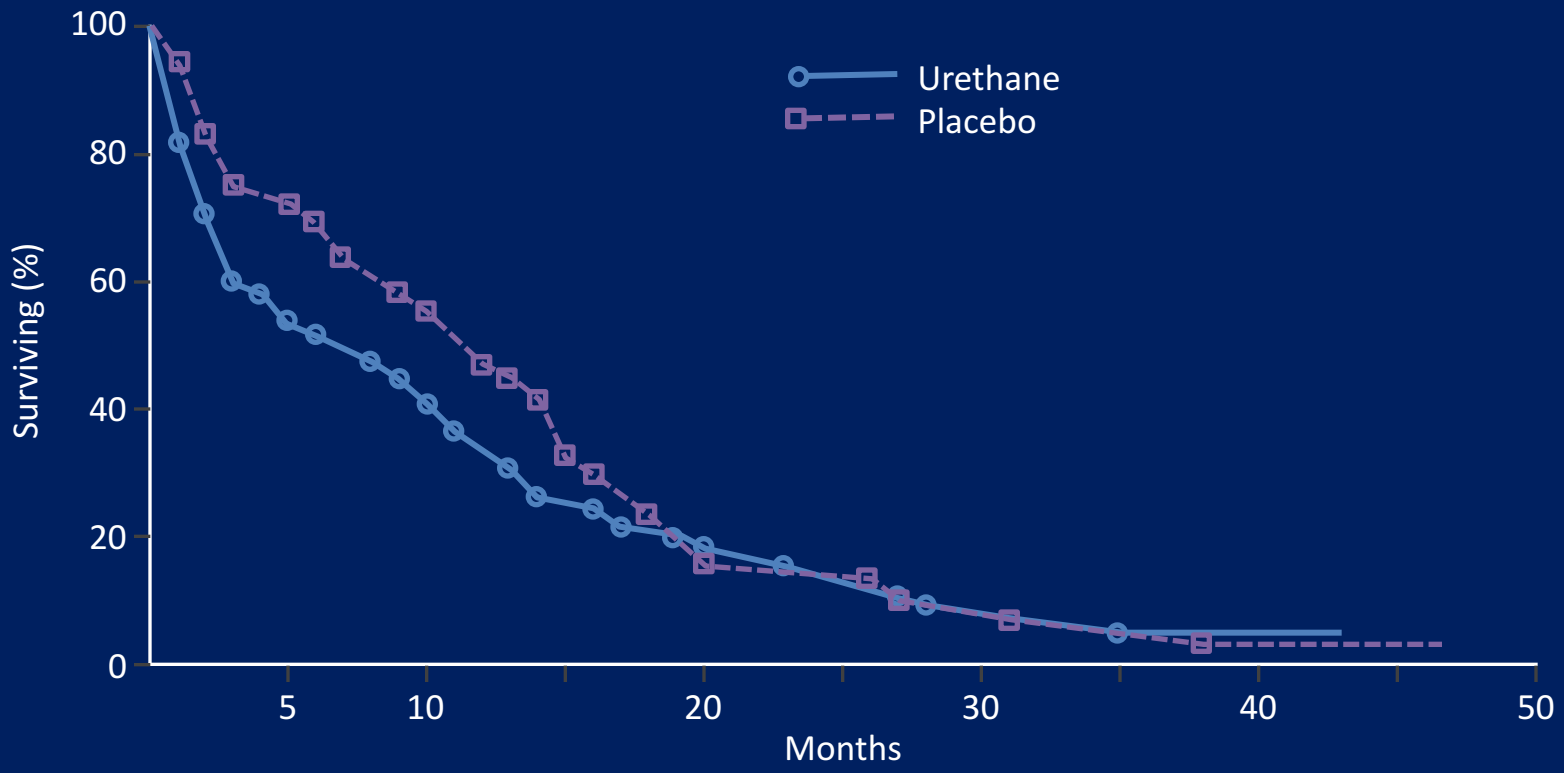
Having more information will help you make decisions and manage challenges

First Randomized Trial in MM

- A controlled trial of urethane treatment in multiple myeloma
- Randomized 83 patients with treated or untreated multiple myeloma to receive urethane or a placebo consisting of a cherry- and cola-flavored syrup
- No difference was seen in objective improvement or in survival in the two treatment groups. In fact, the urethane-treated patients died earlier

Holland JF et al. *Blood*. 1966;27:328.

First Randomized Trial in MM: Results



	Median Survival, Months		
	A	B	C
Urethane	8	8	5
Placebo	15	10.5	12

How do clinical trials work?

Phase I investigates for safety and side effects, dosage and best way to give treatment–includes 20 or more people

Phase II determines effectiveness and safety–typically includes fewer than 100 (may include up to 300) people

Phase III looks at effectiveness, side effects and safety in comparison with other treatments–includes 100s to 1000s of people

Phase IV gathers more information after FDA approval & drug is on market

Placebos are rarely used in cancer clinical trials

Clinical trials

- Are an important option for everyone
- Can be for people newly diagnosed, with limited disease or advanced disease
- Are appropriate for people of different age, gender, and race, depending on the purpose and phase of the study
- Take into account all the above factors as well as stage of disease, other treatments used and presence of any other illness

Remember…communication with your healthcare team is important in making treatment decisions about standard treatment or clinical trial treatment

Why Do So Few Cancer Patients Participate in Clinical Trials?

Patients may:

- Be unaware of clinical trials
- Lack access to trials
- Fear, distrust, or be suspicious of research
- Have practical or personal obstacles
- Face insurance or cost problems
- Be unwilling to go against their physicians' wishes

Why Do So Few Cancer Patients Participate in Clinical Trials?

Doctors might:

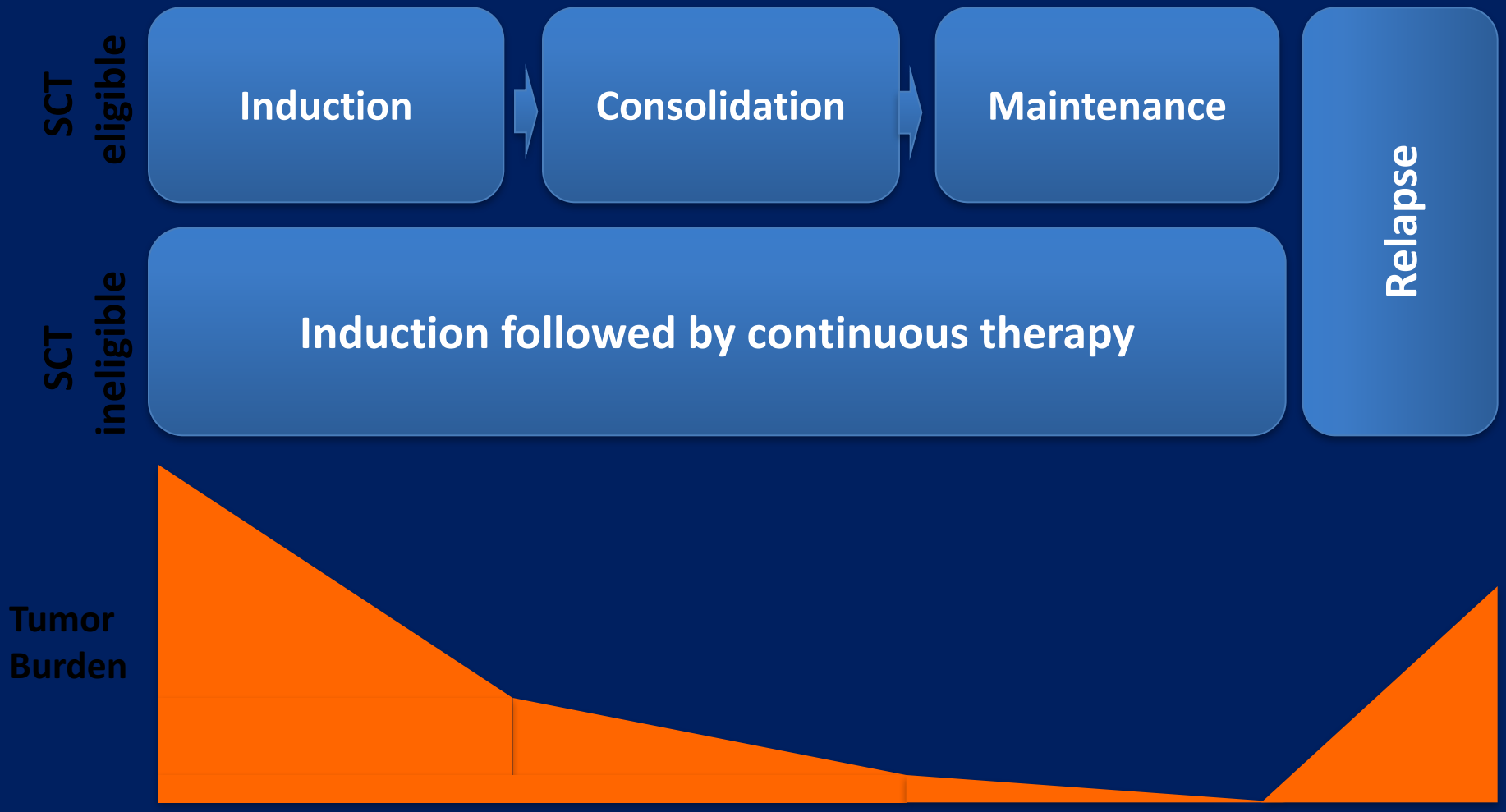
- Lack awareness of appropriate clinical trials
- Be unwilling to “lose control” of a person’s care
- Believe that standard therapy is best
- Be concerned that clinical trials add administrative burdens

Goals of Therapy

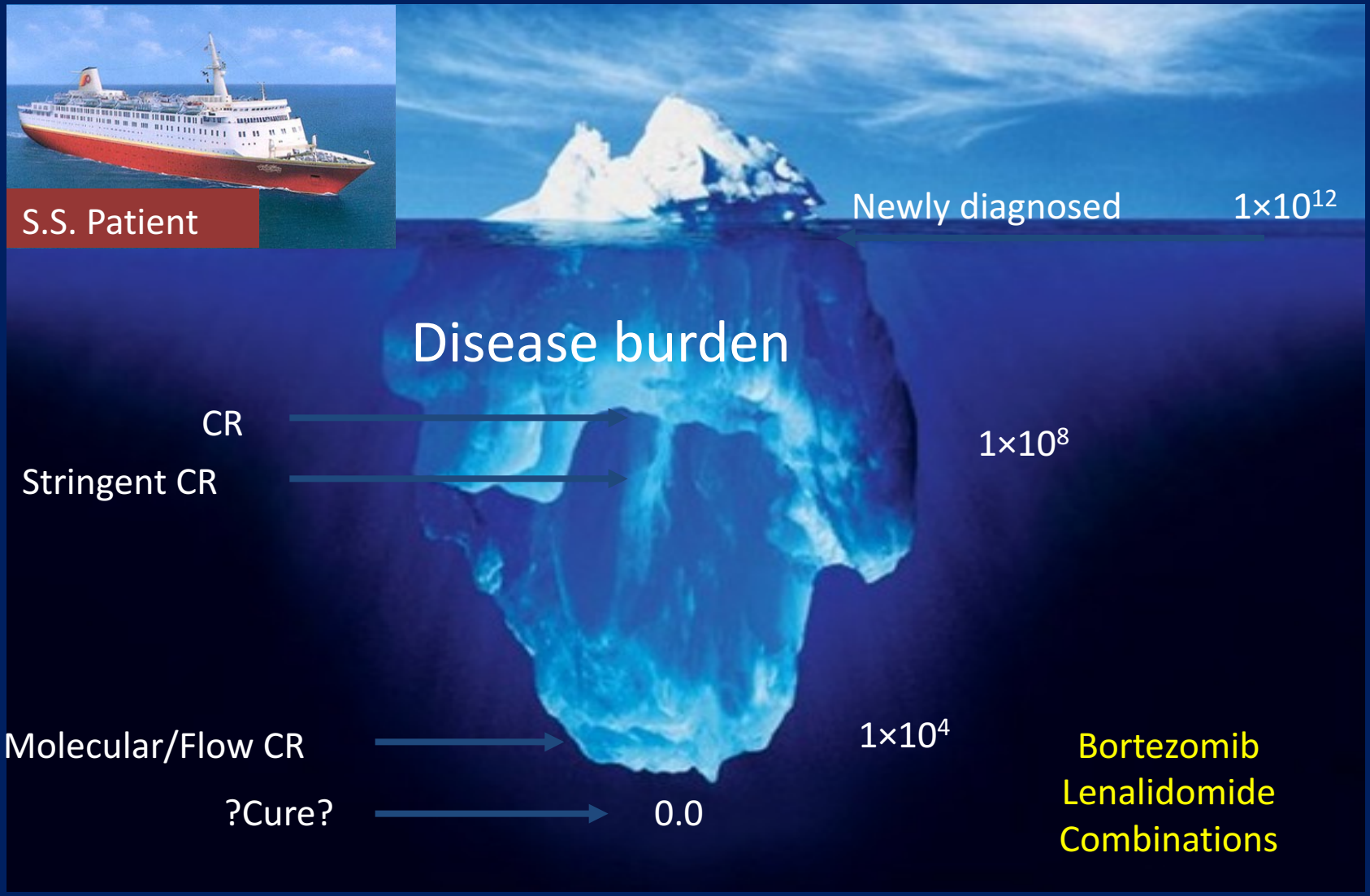
- High response rate
- Depth of response (MRD?)
- Improve performance status and quality of life
- Not limit PBSC mobilization (for younger pts)
- Current issues:
  - Role of transplant
  - Optimal duration of therapy

How deep of a response should we aim for?

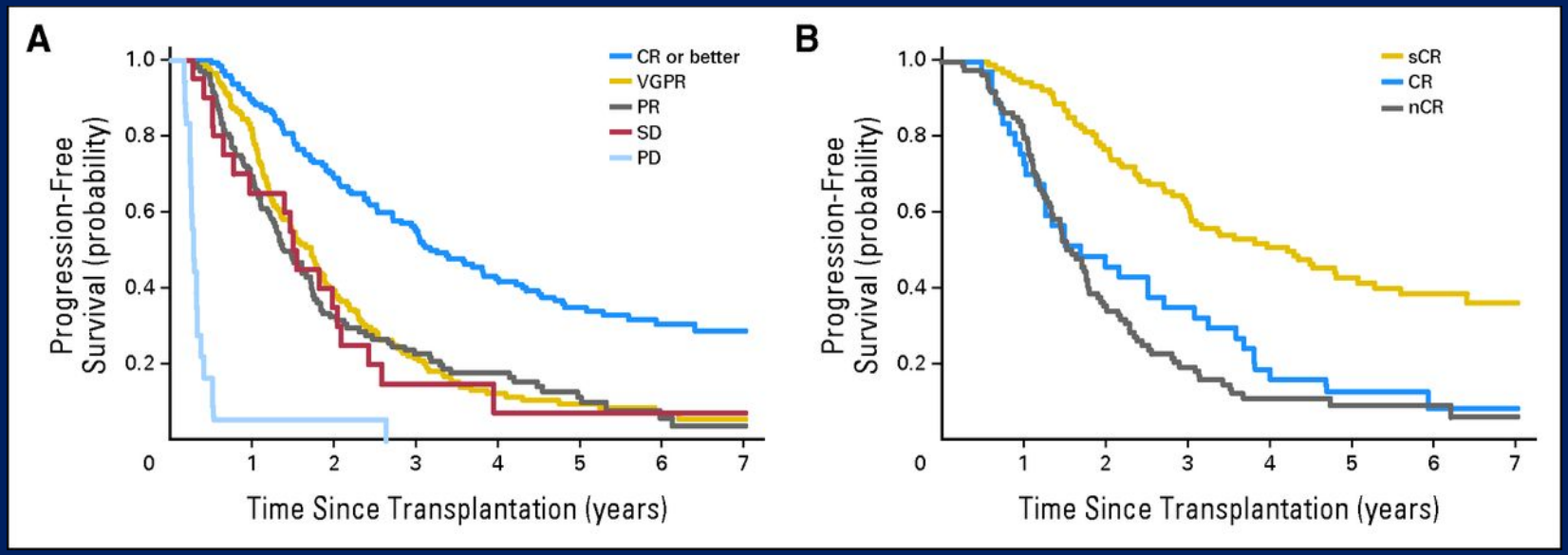
Myeloma treatment paradigm



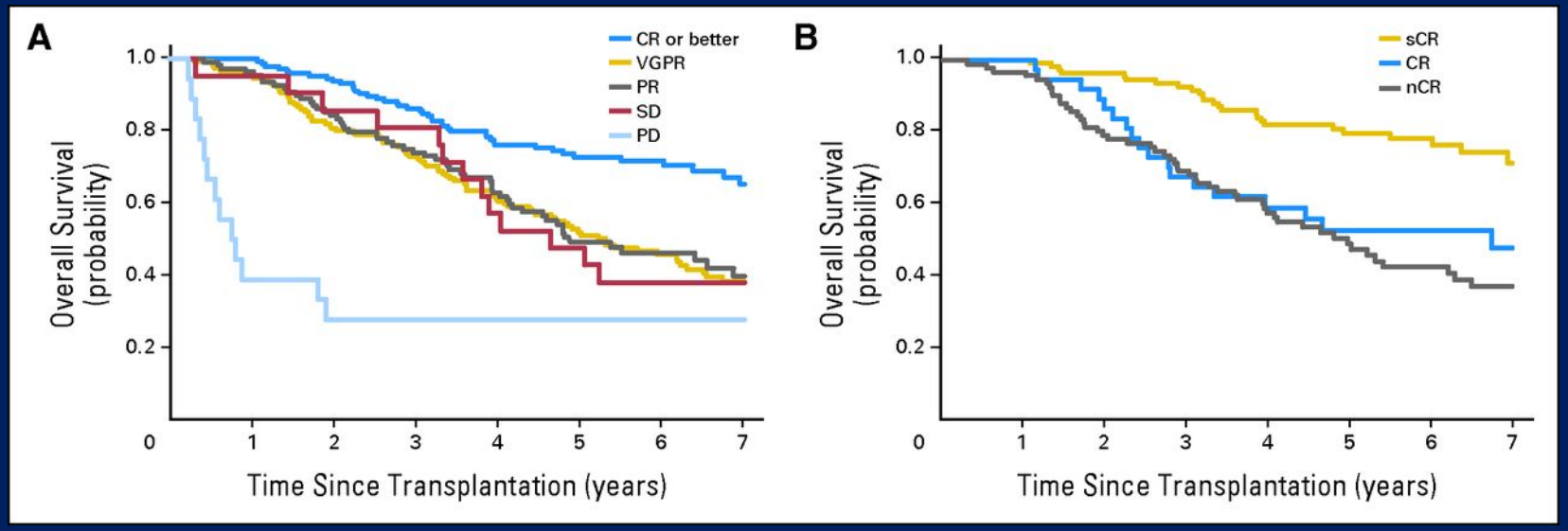
Getting to Minimal Residual Disease (MRD): New Definitions for CR



Time To Progression

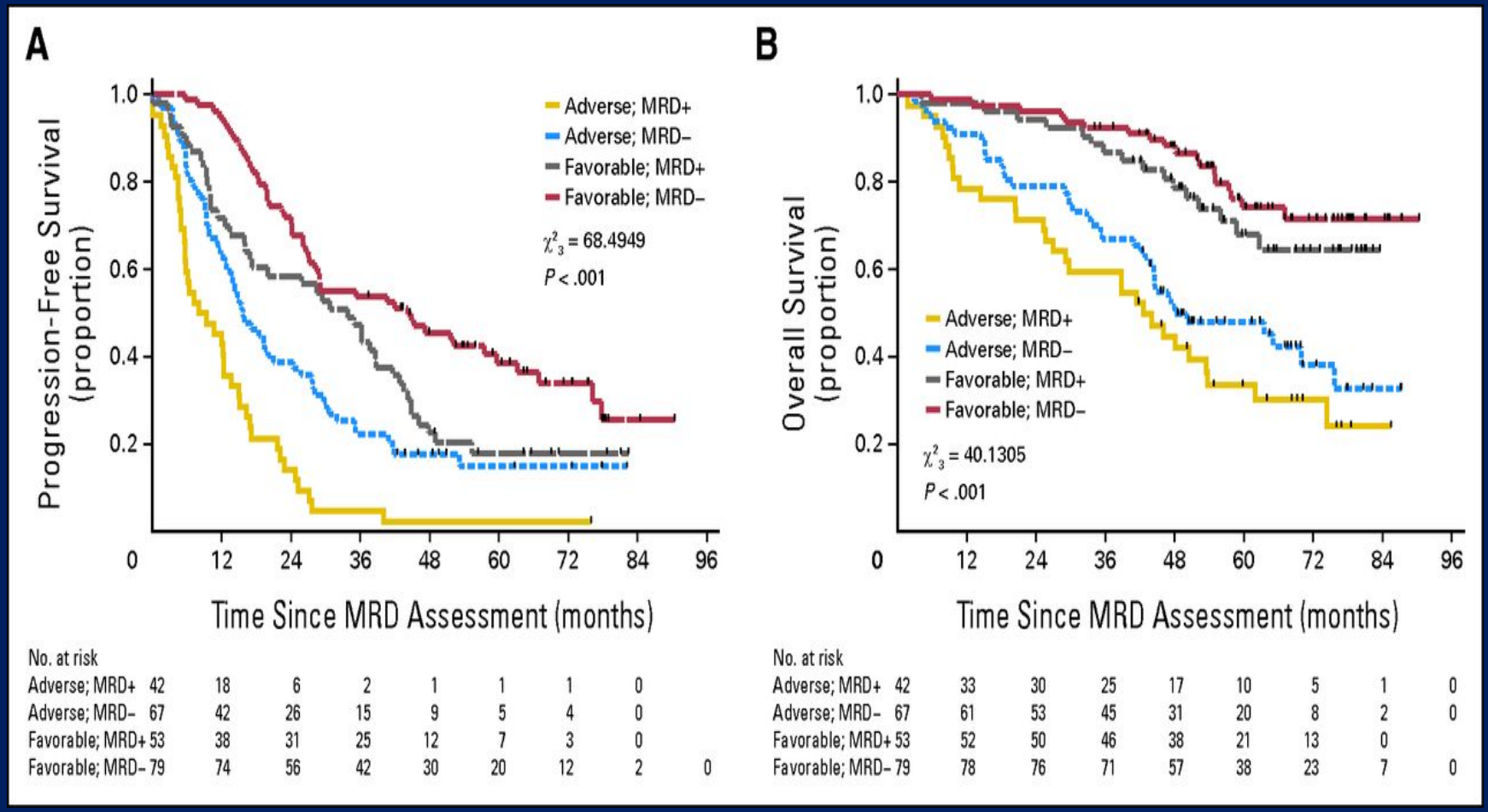


Overall Survival



Kapoor P et al. JCO 2013;31:4529-4535

Minimal Residual Disease (MRD)



- Techniques using PCR and Multi Parameter Flow (MPF) are the best ways to get closer
- PCR is able to identify at lower levels than MPF

Rawstron A C et al. JCO 2013;31:2540-2547

Induction Regimens

- Three classes of drugs are being used in the management of multiple myeloma patients:
  - Proteasome inhibitors: borezomib, carfilzomib, ixazomib
  - Immune modulatory drugs: thalidomide, lenalidomide, pomalidomide
  - Corticosteroids: dexamethasone, prednisone
- The choice of initial induction therapy can be influenced by the underlying medical conditions of the patients and their prognostic features.

MYELOMA THERAPY[1-4]

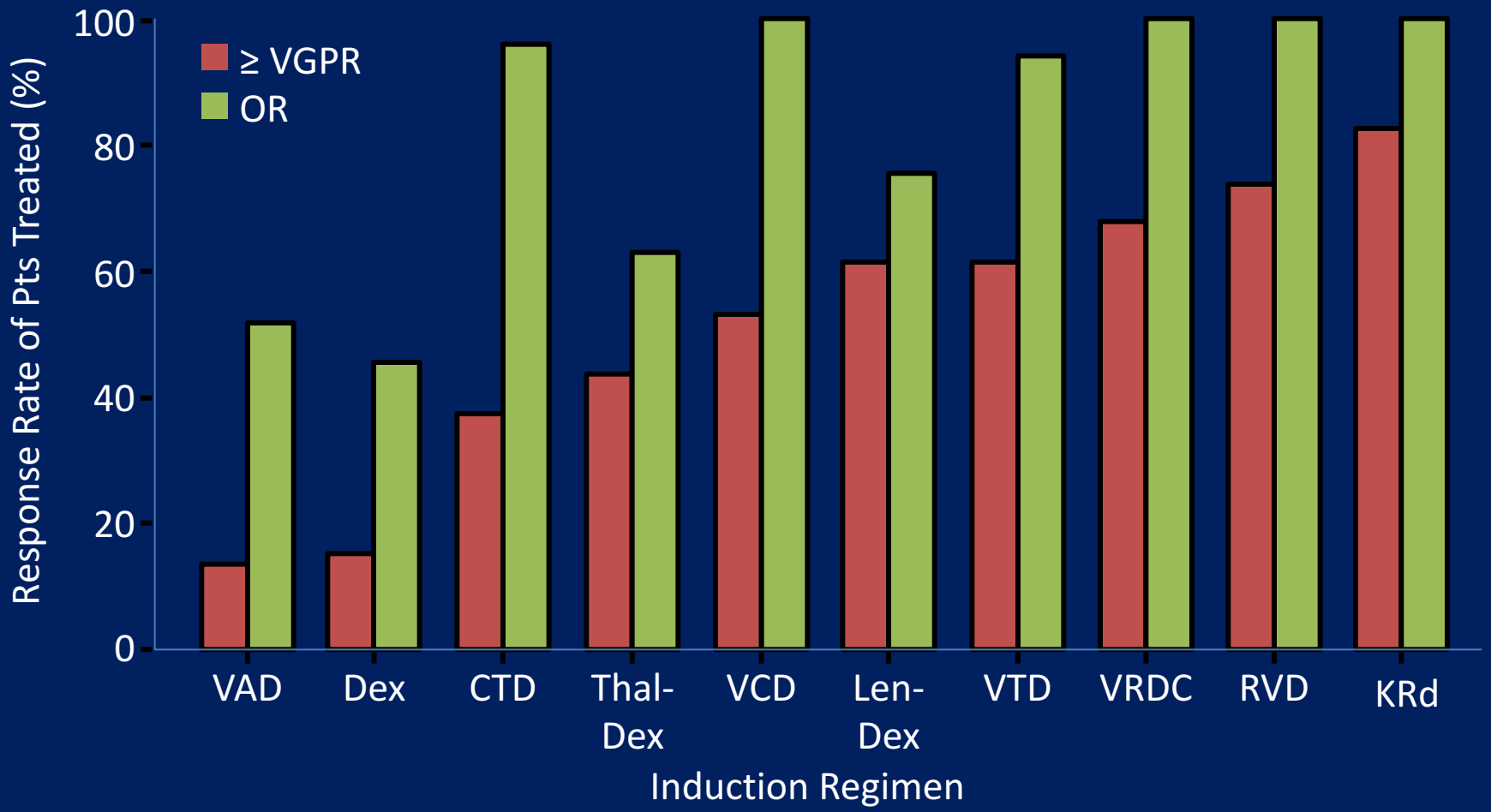
Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem cell reserve prior to stem cell harvest in patients who may be candidates for transplants.

Primary Therapy for Transplant Candidates (assess for response after 2 cycles)	
Preferred Regimens:	**Other Regimens:**
• Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone (category 1) • Bortezomib/lenalidomide[5]/dexamethasone (category 1)	• Bortezomib/dexamethasone (category 1)[6] • Carfilzomib[7]/lenalidomide[5]/dexamethasone • Ixazomib/lenalidomide[5]/dexamethasone • Lenalidomide[5]/dexamethasone (category 1)[6]
Primary Therapy for Non-Transplant Candidates (assess for response after 2 cycles)	
Preferred Regimens	**Other Regimens**
• Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1)[6,9]	• Bortezomib/dexamethasone[6] • Carfilzomib/lenalidomide/dexamethasone (category 2B)[10] • Ixazomib/lenalidomide/dexamethasone
Maintenance Therapy	
• Bortezomib • Lenalidomide[8] (category 1)	

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors.
[3]Subcutaneous bortezomib is the preferred method of administration for patients with pre-existing or high-risk peripheral neuropathy.
[4]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[5]Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
[6]Triplet regimens should be used as the standard for patients with previously treated multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.
[7]Optimal dosing in this regimen has not been defined.
[8]There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.
[9]Continuously until progression. Facon T, Dimopoulos MA, Dispenzieri A, et al. Continuous lenalidomide and low-dose dexamethasone demonstrates a significant PFS and OS advantage in transplant ineligible NDMM patients. The FIRST: MM-020/IFM0701 [oral]. Oral presented at: 55th Annual Meeting of the American Society of Hematology (ASH) 2013; December 7-10.
[10]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Newer Myeloma Drugs Are Associated With Better Clinical Response



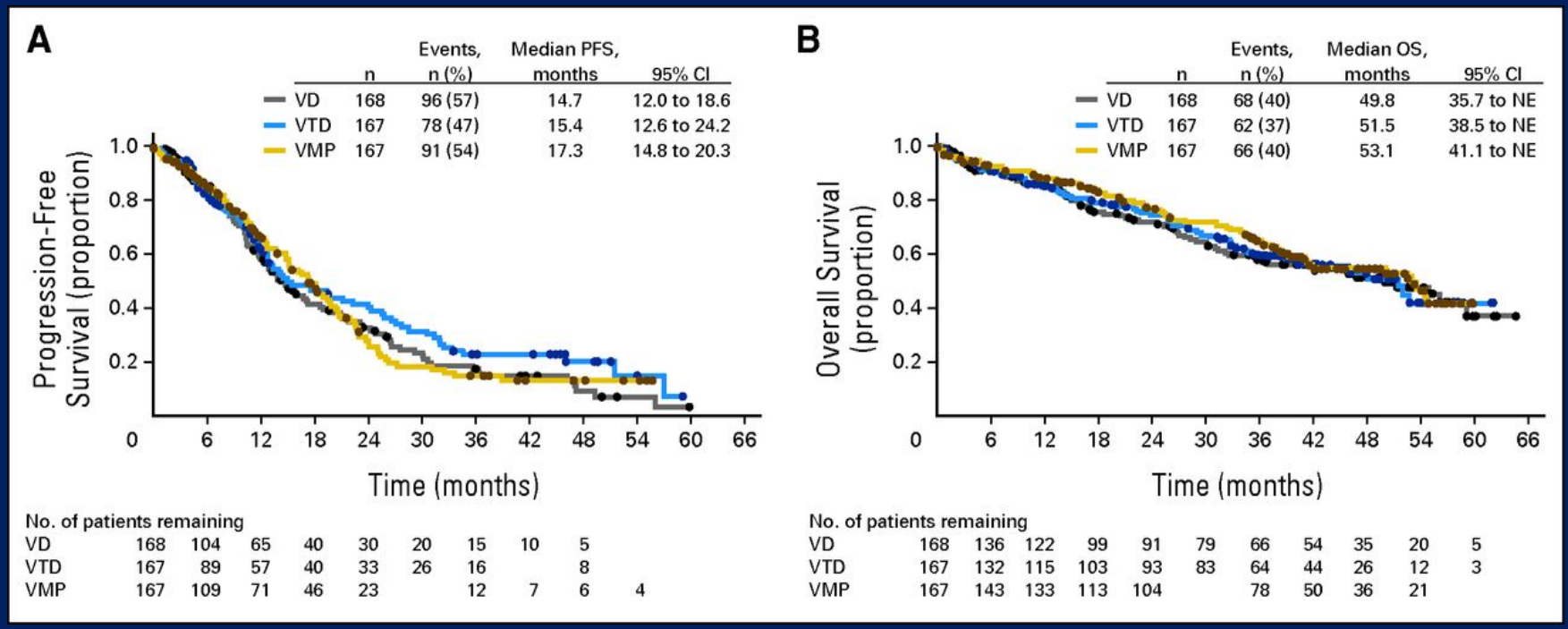
Mailankody S, et al. Nat Rev Clin Oncol. 2015;[Epub ahead of print].

Phase IIIB UPFRONT Trial: VD, VTD, and VMP in Transplant-Ineligible MM Pts

8 cycles induction: VD, VTD, or VMP; 5 cycles of V maintenance

No statistically significant difference in survival outcomes

- 1-year PFS estimates: 57.4% (VD), 63.8% (VTD), 67.3% (VMP)
- 2-year OS estimates: 73.7% (VD), 73.6% (VTD), 77.6% (VMP)



Kaplan-Meier analysis of (A) progression-free survival (PFS) and (B) overall survival (OS) in the intent-to-treat population.

Niesvizky et al. /JCO

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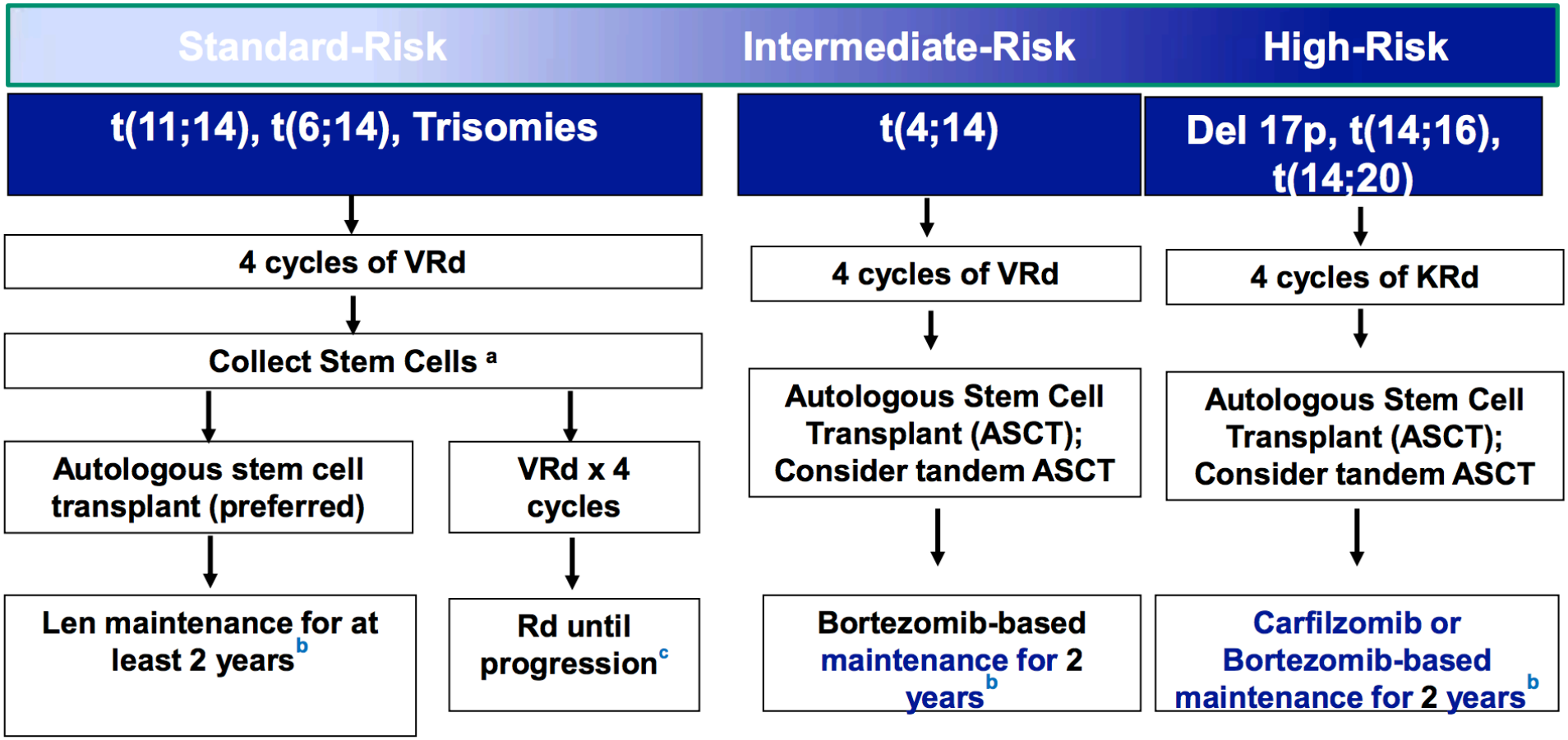
Grade ≥ 3 AEs, %	VD Induction	VTD Induction	VMP Induction
≥ 1 grade 3+ AE	74	84	82
Peripheral neuropathy	19	24	19
Fatigue	10	12	8
Diarrhea	9	3	7
Pneumonia	10	6	5
Neutropenia	2	3	18
Thrombocytopenia	2	4	14

Niesvizky R, et al. J Clin Oncol. 2015 Jun 8.

MAYO CLINIC

mSMART – Off-Study

Transplant Eligible



[a] *If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor*
[b] *Duration based on tolerance; consider risks and benefits for treatment beyond 2 years*
c Continuing Rd for patients responding to Rd and with low toxicities

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 July 2016

Treatment sequence

NEW

VD
Rev/Dex
CyBorD
VRD
KRD
Dara-VMP
Dara-KRD

SCT
RD/VRD

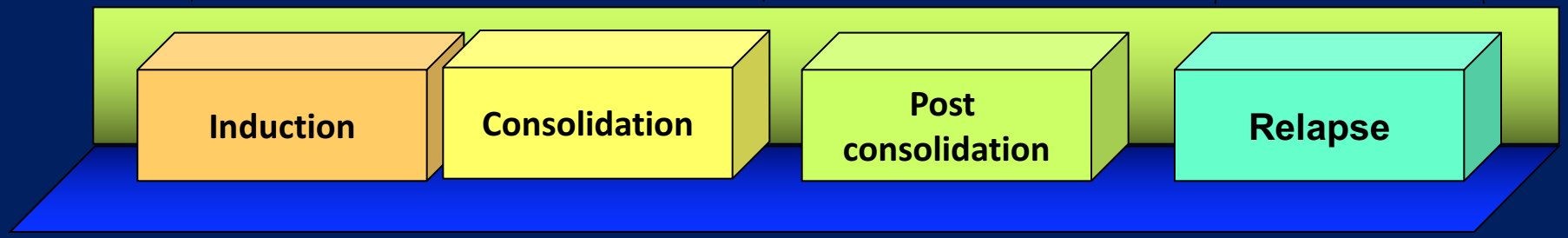
Nothing
Thalidomide?
Bortezomib?
Lenalidomide?

Bortezomib
Lenalidomide
Thalidomide
Carfilzomib
Pomalidomide
Daratumuab
Elotuzumab
Panobinostat
Bendamustine
Venetoclax
Nelfinavir
CAR T cells

Front line treatment

Maintenance

Relapsed



OLD

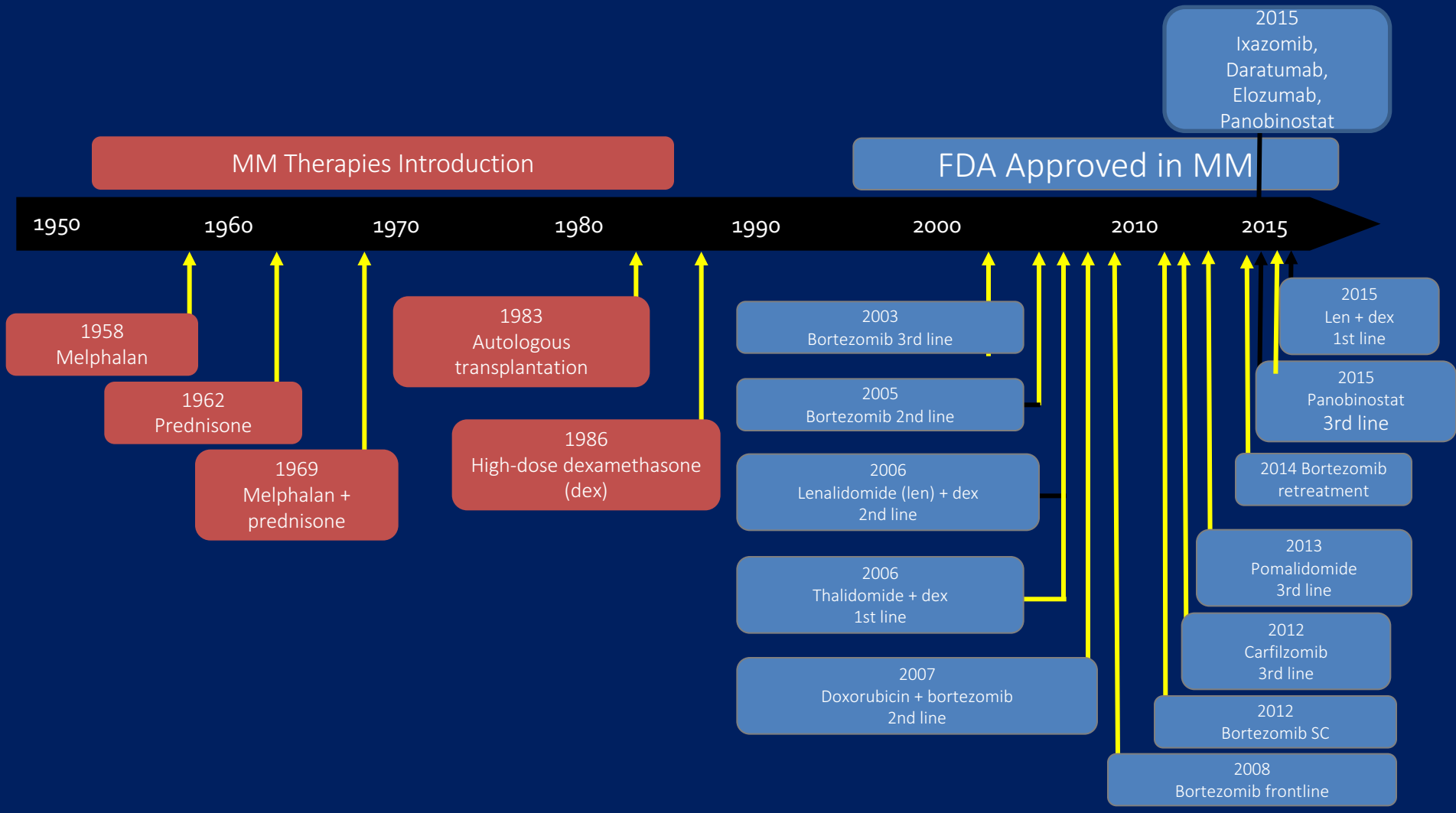
VAD
DEX

SCT

Nothing
Prednisone
Thalidomide

Few options

The Expanding MM Therapeutic Armamentarium



When to Consider Retreatment

- Differences between biochemical relapse and symptomatic relapse need to be considered
- Patients with asymptomatic rise in M-protein can be observed to determine the rate of rise and nature of the relapse
  - Caveat: patients with known aggressive or high-risk disease should be considered for salvage even in the setting of biochemical relapse
- CRAB criteria are still listed as the indication to treat in the relapsed setting-however, in patients with progression, treatment can avoid CRAB
  - C: Calcium elevation (> 11.5 mg/L or ULN)
    R: Renal dysfunction (serum creatinine > 2 mg/dL)
    A: Anemia (Hb < 10 g/dL or 2 g < normal)
    B: Bone disease (lytic lesions or osteoporosis)

Considerations in Patients With Relapsed/Refractory Myeloma

- Previous therapy
- Response to previous therapy
- Patient characteristics and other prognostic factors
  - Older than 65 yrs of age
  - Increased β_2-M, decreased serum albumin, low platelet count
  - Cytogenetic abnormalities: del(13q), t(4;14)
  - Renal dysfunction
    - Up to 50% of patients with MM have renal dysfunction
    - Between 20% and 30% of patients have concomitant renal failure
  - Extensive bone disease; extramedullary MM

Kyle RA, et al. Mayo Clin Proc. 2003;78:21-33. Kumar SK, et al. Mayo Clin Proc. 2004;79:867-874. Facon T, et al. Blood. 2001;97:1566-1571. Barlogie B, et al. Blood. 2004;103:20-32. Fonseca R, et al. Cancer Res. 2004;64:1546-1558. Kyle RA. Stem Cells. 1995;13(suppl 2):56-63. Bladé J, et al. Arch Intern Med. 1998;158:1889-1893.

Therapy for relapsed disease

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Multiple Myeloma

NCCN Guidelines Index
Multiple Myeloma Table of Contents
Discussion

MYELOMA THERAPY[1,2,3,8]

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.

	Preferred Regimens	Other Regimens
Therapy for Previously Treated Multiple Myeloma	• Repeat primary induction therapy (if relapse at >6 mo) • Bortezomib (category 1) • Bortezomib/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin (category 1) • Bortezomib/thalidomide/dexamethasone • Carfilzomib • Carfilzomib/dexamethasone • Carfilzomib/lenalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) • High-dose cyclophosphamide • Lenalidomide/dexamethasone[9] (category 1) • Panobinostat/bortezomib/dexamethasone[10] (category 1) • Pomalidomide[11]/dexamethasone[9] (category 1) • Thalidomide/dexamethasone[9]	• Bendamustine • Bortezomib/vorinostat • Lenalidomide/bendamustine/dexamethasone

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with bortezomib and carfilzomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
[3]Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
[8]Consideration for appropriate regimen is based on the context of clinical relapse.
[9]Consider single-agent lenalidomide, pomalidomide, or thalidomide for steroid-intolerant individuals.
[10]Indicated in patients who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.
[11]Indicated for patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

MYEL-D
(2 OF 2)

MAYO CLINIC

First Relapse Off-Study

Relapsing after Auto Transplant

On Maintenance	Off-therapy/ Unmaintained
CyBorD if Rev maintenance*; Rd, or KRd if Vel maintenance*	Rd or CyBorD if standard-risk*; CyBorD or VRd if high risk*

Relapsing after Non-Transplant Therapy

On Therapy/ Maintenance		Off-therapy/ Unmaintained
Not Eligible for ASCT	Transplant Eligible	Not Eligible for ASCT
CyBorD if Rev maintenance; Rd, or KRd if Vel maintenance	Auto SCT	Repeat first-line Rx if remission off therapy is >12months; If not, CyBorD if relapsing after ImiD based Rx; otherwise Pom/dex or KRd

*Consider 2nd auto if eligible and >18 months unmaintained or >36 months maintained response to first auto

v3 //last reviewed Mar 2015

MAYO CLINIC

Second or later Relapse* Off-Study

Not Plasma Cell Leukemia (PCL) or Similar extramedullary disease (EMD)

Dual-Refractory (Bortezomib and Lenalidomide)**	Triple-Refractory (Bortezomib, Lenalidomide and Carfilzomib)**	Triple-Refractory (Bortezomib, Len, and Pomalidomide)**
KRd or Pom/dex to maximum response or 18 months, then Rd	PCD, PVD or Car-Pom-Dex to maximum response or 18 months, then Pom/dex	KRd or Car-Pom-Dex to maximum response or 18 months, then Rd or Pom/dex

* If single refractory, refer to First Relapse algorithm; **Auto transplant is an option, if transplant candidate and feasible; Doublets such as Cylco-Pred, Pd or Kd could be considered in patients with indolent disease

v3 //last reviewed Mar 2015

COMPARISON OF PHASE 3 TRIALS

Study	Regimen	Overall Response(%)	Complete Response (%)	PFS (months)
TOURMALINE-1	IRd* vs Rd	78.5 vs 71.5	11.7 vs 6.6	20.6 vs 14.7
ASPIRE	KRd vs Rd	87.1 vs 66.7	31.8 vs 9.3	26.3 vs 17.6
ELOQUENT-2	ERd vs Rd	79 vs 66	5 vs 9	19.4 vs 14.9
ENDEAVOR	Kd vs Vd	83 vs 66	11.6 vs 7.8	18.7 vs 9.4
CASTOR	DVd vs Vd	83 vs 63	19 vs 9	61% vs 27% (12 months)
POLLUX	DRd vs Rd	93 vs 76	43 vs 19	78% vs 52% (18 months)

I = Ixazomib (Ninlaro);R = Lenalidomide (Revlimid); K = Carfilzomib (Kyprolis)

E = Elotuzumab (Empliciti); D = Daratumumab (Darzalex)

Treating Relapsed/Refractory Myeloma

Carfilzomib-Based Salvage

- Intolerance or resistance to bortezomib
- Dexamethasone-sparing treatment as part of a combination
- Intolerance to IMiDs

Pomalidomide-Based Salvage

- Lenalidomide refractory
- Refractory to standard-dose PI
- Pts with del(17p)?

Other Salvage

- Refractory to pomalidomide and carfilzomib
- Monoclonal antibody candidate
- Clinical trials

Treating Indolent, Slow-Growing Myeloma in First Relapse

IMiD-Based Salvage

- Initial treatment with bortezomib
- May consider single agent without dexamethasone
- Underlying PN

PI-Based Salvage

- Initial treatment with IMiD
- Previous bortezomib therapy but good or long response
- Renal dysfunction

Transplant-Based Salvage

- Transplant not part of initial therapy
- Long remission posttransplant

Treating Aggressive Myeloma With Rapid, Multiple Relapses

Likely Combination Therapy
Do Not Wait for Symptomatic Relapse

Chemotherapy-Based Salvage	Chemotherapy + Novel Agent	Transplant-Based Salvage
• DCEP vs DT-PACE • Oral vs IV chemo • Performance status of pt plays important role	▪ Combinations of lenalidomide/ bortezomib and other chemotherapy agents	▪ Likely to be short lived ▪ Rapid disease control ▪ Reconstitute marrow

MAYO CLINIC

mSMART 2.0: Classification of Relapsed MM

High-Risk

- Relapse <12 months from transplant or progression within first year of diagnosis
- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- High risk GEP

Intermediate-Risk

- FISH
  - t(4;14)
  - 1q gain
- High PC S-phase

Standard-Risk

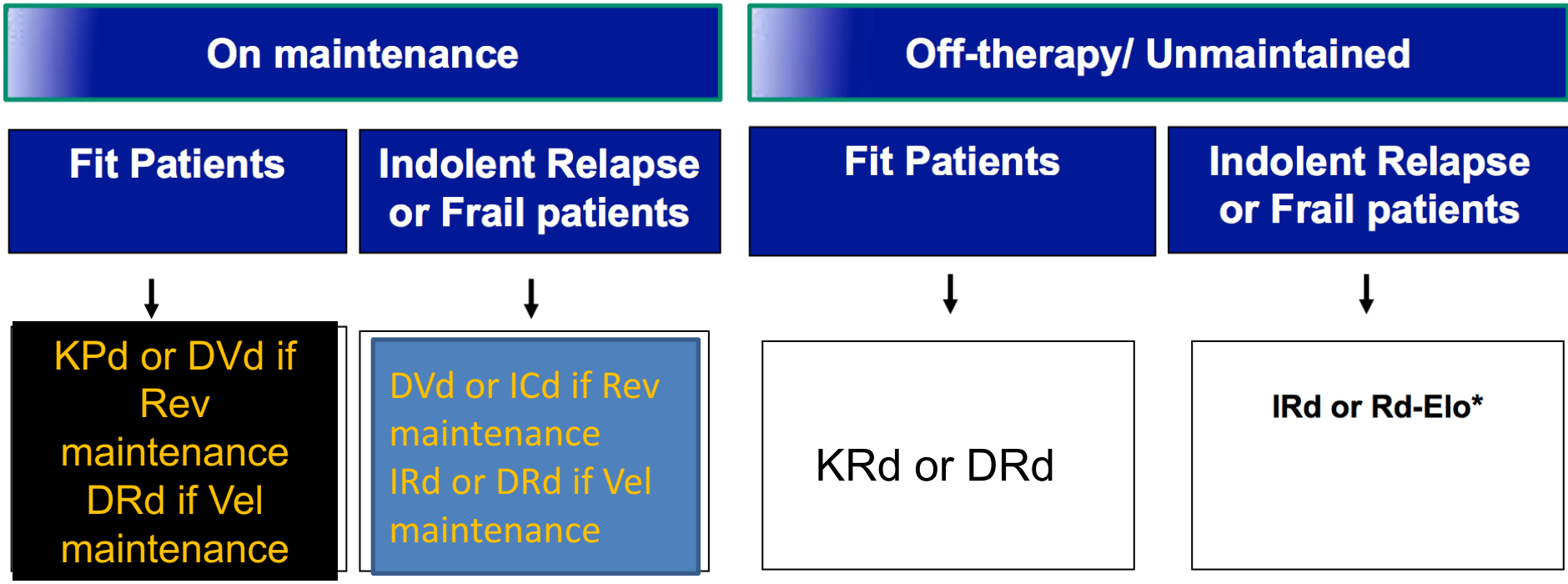
All others including:

- Trisomies
- t(11;14)
- t(6;14)

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.

MAYO CLINIC

First Relapse Off-Study

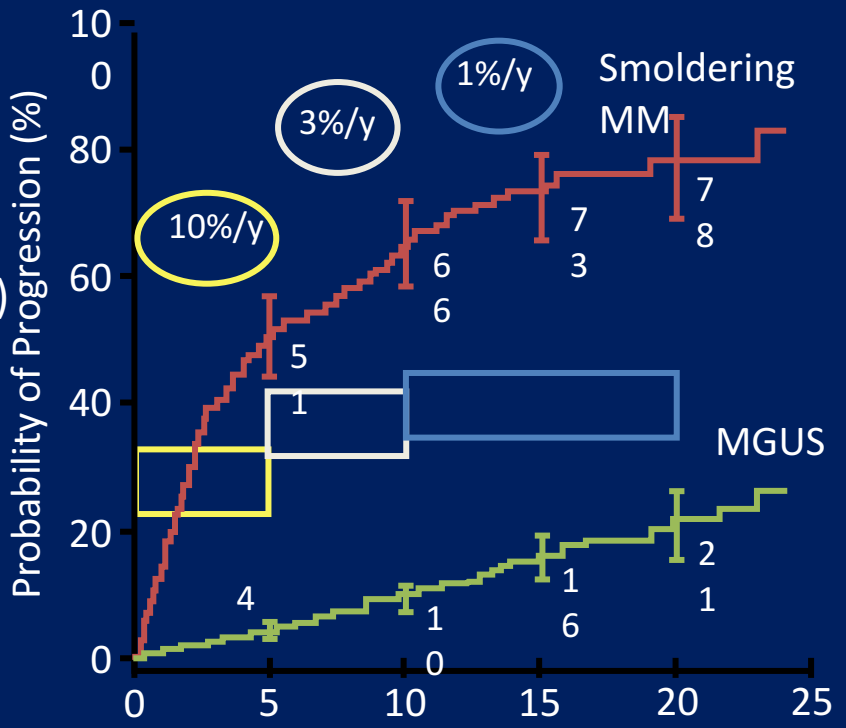


*Consider salvage auto SCT in patients eligible for ASCT who have not had transplant before; Consider 2nd auto SCT if eligible and >18 months unmaintained or >36 months maintained response to first auto;

Smoldering Myeloma: Background

- Smoldering MM currently defined as:[1]
  - M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)
  - Clonal plasma cells in BM 10% to 60%
  - No myeloma-defining events (≥ 1 CRAB feature or ≥ 1 biomarker of malignancy)
- Biomarkers of active myeloma[1]
  - Clonal plasma cells in BM ≥ 60%
  - Serum FLC ratio ≥ 100
  - > 1 MRI focal lesion ≥ 5 mm on MRI
  - CRAB criteria

Risk of Progression in Pre-CRAB MM[2]

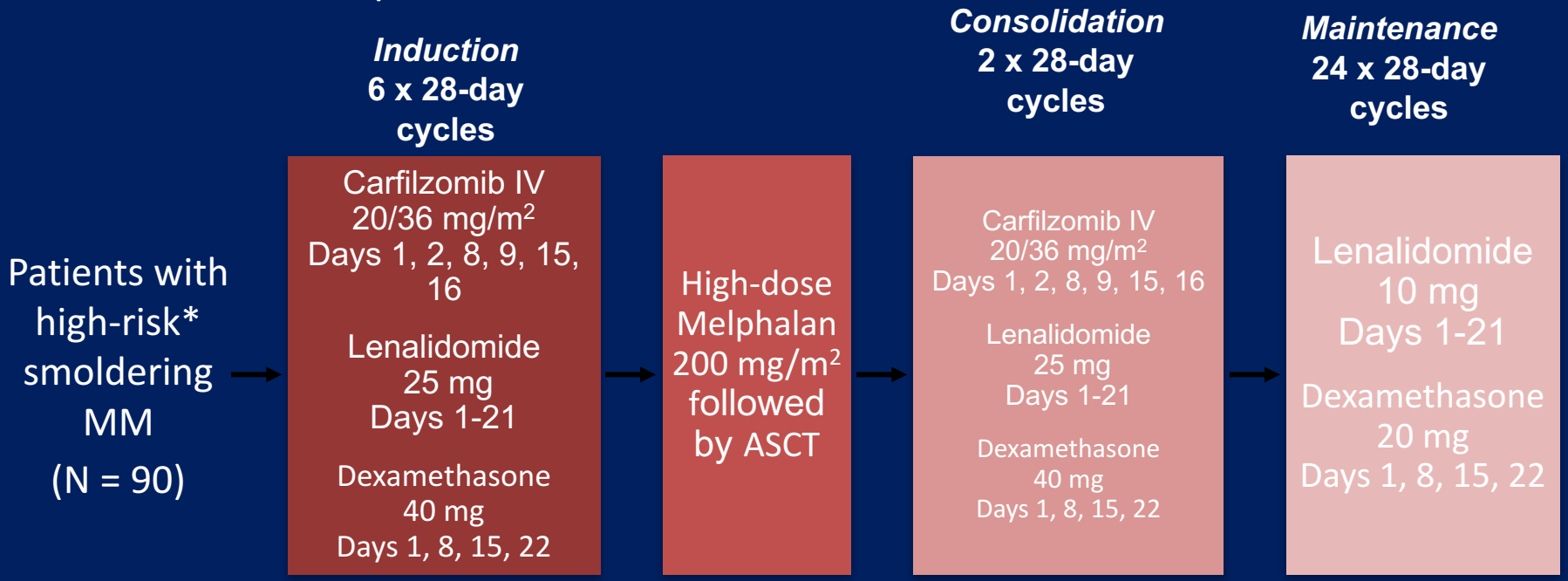


C: Calcium elevation (> 11 mg/dL or > 1 mg/dL above ULN)
R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)

1. Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.
2. Kyle R, et al. N Engl J Med. 2007;356:2582-2590.

GEM-CESAR: Phase II Study Design

- Multicenter, open-label trial



- Primary endpoint: MRD negative rate (by flow cytometry) after induction, ASCT, consolidation/maintenance, and 3 and 5 yrs after maintenance
- Secondary endpoints: response, TTP, PFS, OS, safety

*High risk defined per Mayo and/or Spanish models (pre-2014 diagnostic criteria)

- Pts with both BM PCs ≥ 10% and serum M-protein ≥ 3g/dL, or 1 plus > 95% aberrant BM PCs by immunophenotyping plus immunoparesis

Mateos MV, et al. ASH 2017. Abstract 402.

GEM-CESAR: Efficacy After KRd Consolidation and Rd Maintenance

Response Category, n (%)	Induction (n = 71)	HDT ASCT (n = 42)	Consolidation (n = 35)	Maintenance (n = 29)
ORR, n (%)	69 (98)	42 (100)	35 (100)	29 (100)
▪ sCR	21 (30)	22 (52)	24 (69)	24 (83)
▪ CR	9 (13)	2 (5)	2 (6)	2 (7)
▪ VGPR	27 (38)	12 (29)	7 (20)	2 (7)
▪ PR	12 (17)	6 (14)	2 (6)	1 (3)
MRD negative, %	31	50	60	NA
Relapse from CR, n (%)	2 (3)	--	--	--
Clinical progression, n (%)	--	--	--	--

Mateos MV, et al. ASH 2017. Abstract 402.