2021 Virtual Nursing Forum:
Advancing Oncology Nursing in Hematologic Malignancies™

New Treatment Options in Multiple Myeloma

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Outline

- Describe updates in smoldering multiple myeloma (SMM)
  - IMWG diagnostic criteria
  - Progression risk stratification
  - Indication for treatment
- Review new treatment options
  - Newly FDA-approved agents, toxicity profiles, and management in MM.
- Discuss the role of minimum residual disease (MRD) in the monitoring of MM.

SMM Diagnostic Criteria

- Revised International Myeloma Working Group (IMWG) criteria
- Serum monoclonal protein (IgG or IgA ≥3 g/dL or
- *Bence-Jones protein ≥ 500 mg / 24 hours and/or*
- Bone marrow plasma cells (BMPC) ≥10% and <60%

And

- Absence of myeloma-defining events or amyloidosis

Rajkumar SV, et al. Lancet Oncol. 2014;15(12):e538 - e548.
Cavo M, et al. Lancet 2017

Myeloma Defining Events (MDE)

- CRAB features – hypercalcemia, renal insufficiency, anemia, bone lesions
- Clonal BMPC ≥ 60%
- Serum FLC ratio ≥ 100 (involved / uninvolved; involved FLC ≥ 100 mg/L)
- >1 focal lesions (≥ 5 mm) on MRI

Rajkumar SV, et al. Lancet Oncol. 2014;15(12):e538 - e548.
Cavo M, et al. Lancet 2017

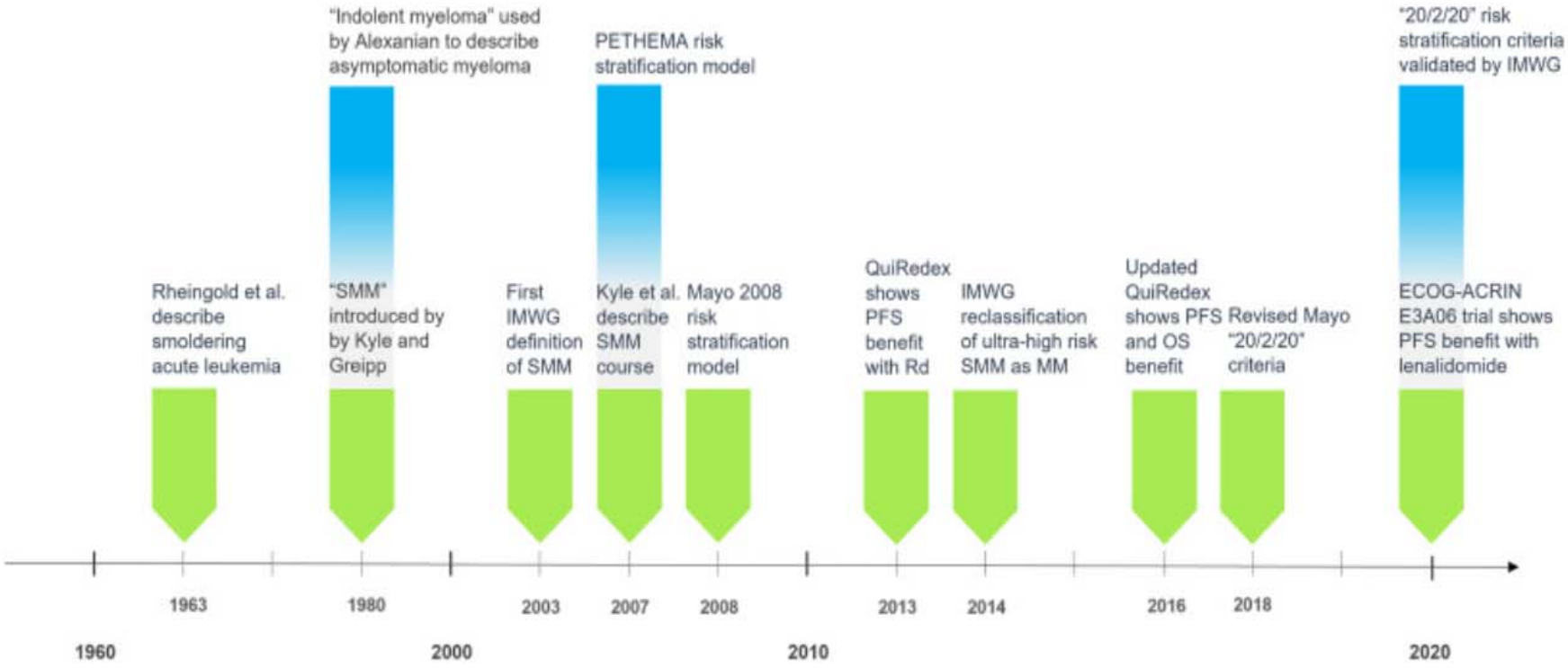
Differentiate SMM from MGUS and Active Myeloma – Revised IMWG Criteria

MGUS	SMM	MM
• <10% BMPC **AND** • <3 gm/dL M protein **AND** • Absence of end-organ damage	• ≥3 gm/dL M protein **OR** • Urinary M protein ≥ 500 mg per 24 hours **And / OR** • ≥10% BMPC **AND** • No MDE or amyloidosis	• ≥10% BMPC **OR** biopsy-proven plasmacytoma **AND** • ≥1 MDE

Risk Factors for Progression

- Bone marrow plasmacytosis
- Size of M protein
- Change in M protein and hemoglobin
- FLC ratio
- Immunoparesis
- Circulating plasma cells
- Immunophenotype
- Cytogenetics
- Imaging features

Timeline of Milestones in SMM



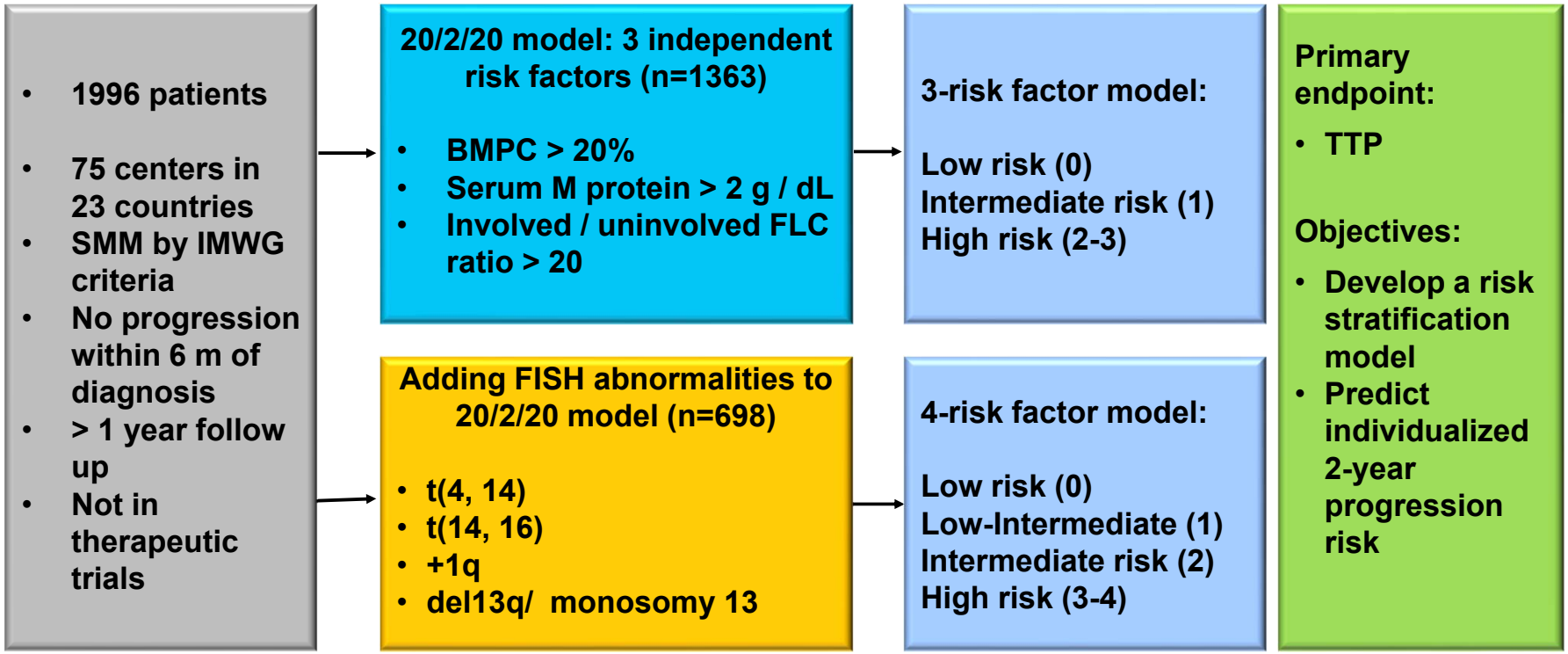
Mann H et al. Blood Reviews, 2021

20/2/20 Risk Stratification Model

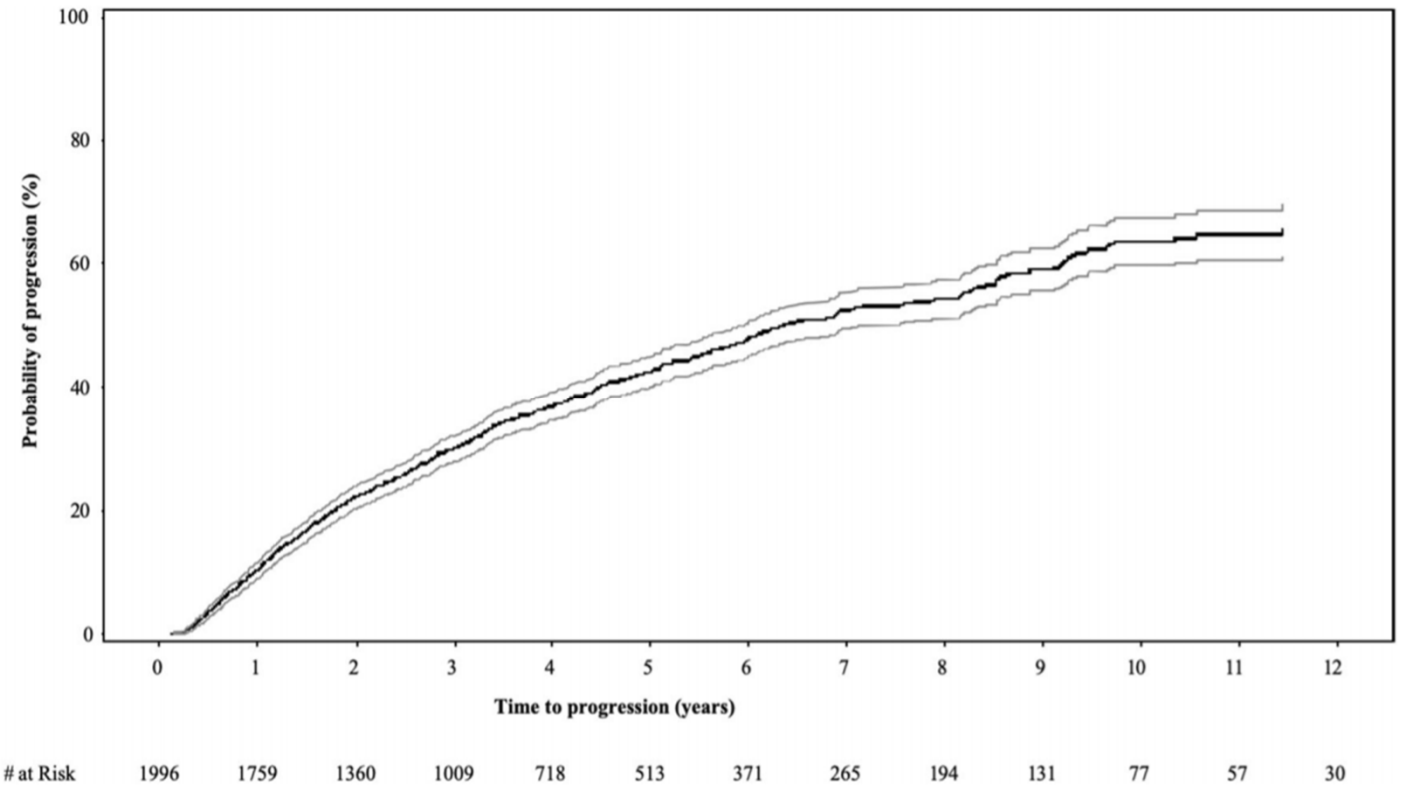
Risk Group (N)	Risk Factors (N) BMPC > 20% M-protein > 2 g/dL FLC ratio > 20	Median TTP (months)	Risk of Progression at Time from Diagnosis (%)		
			2 years	5 years	10 years
Low Risk (N=143)	0	110	9.7	22.5	52.7
Intermediate Risk (N=121)	1	68	26.3	46.7	65.3
High Risk (N=153)	2-3	29	47.4	81.5	96.5

Lakshman A, et al. Blood Cancer J, 2018

IMWG Risk Stratification Model



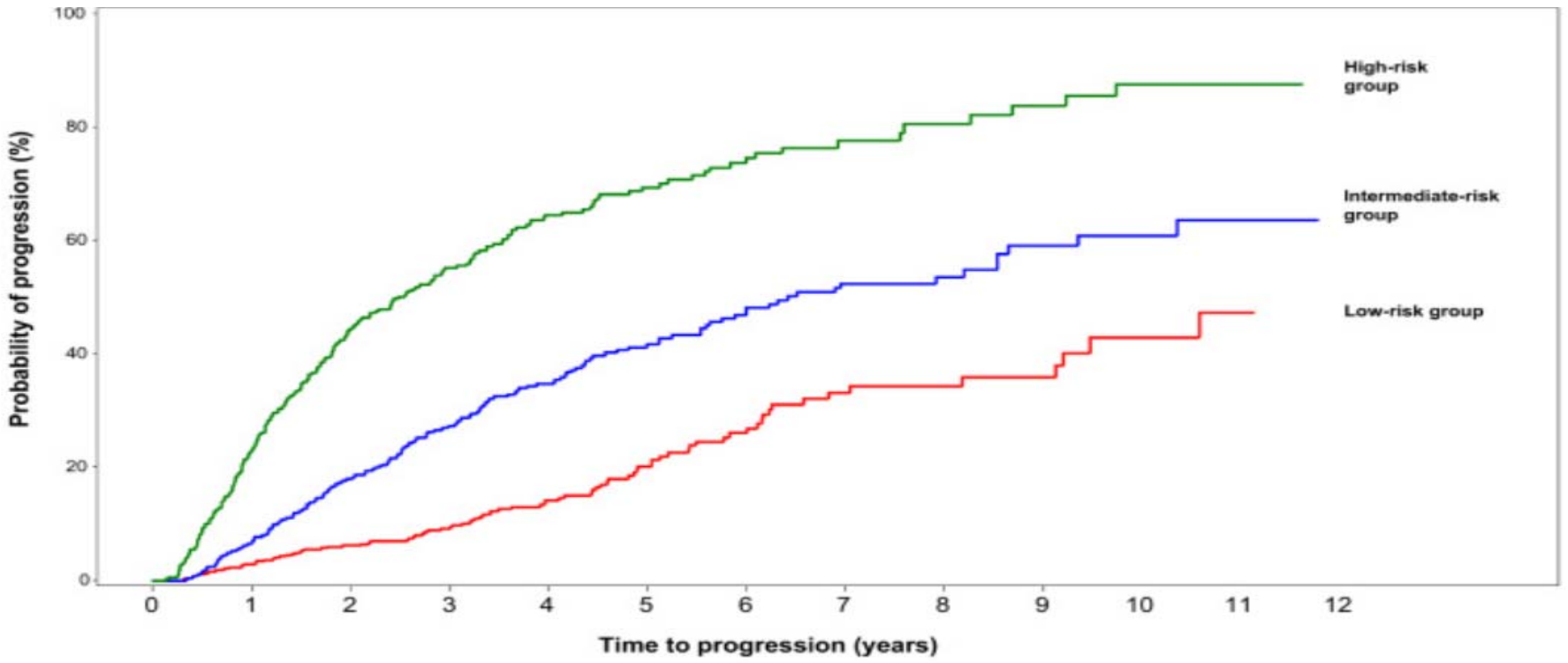
Mateos MV, Kumar S et al. Blood Cancer J 2020



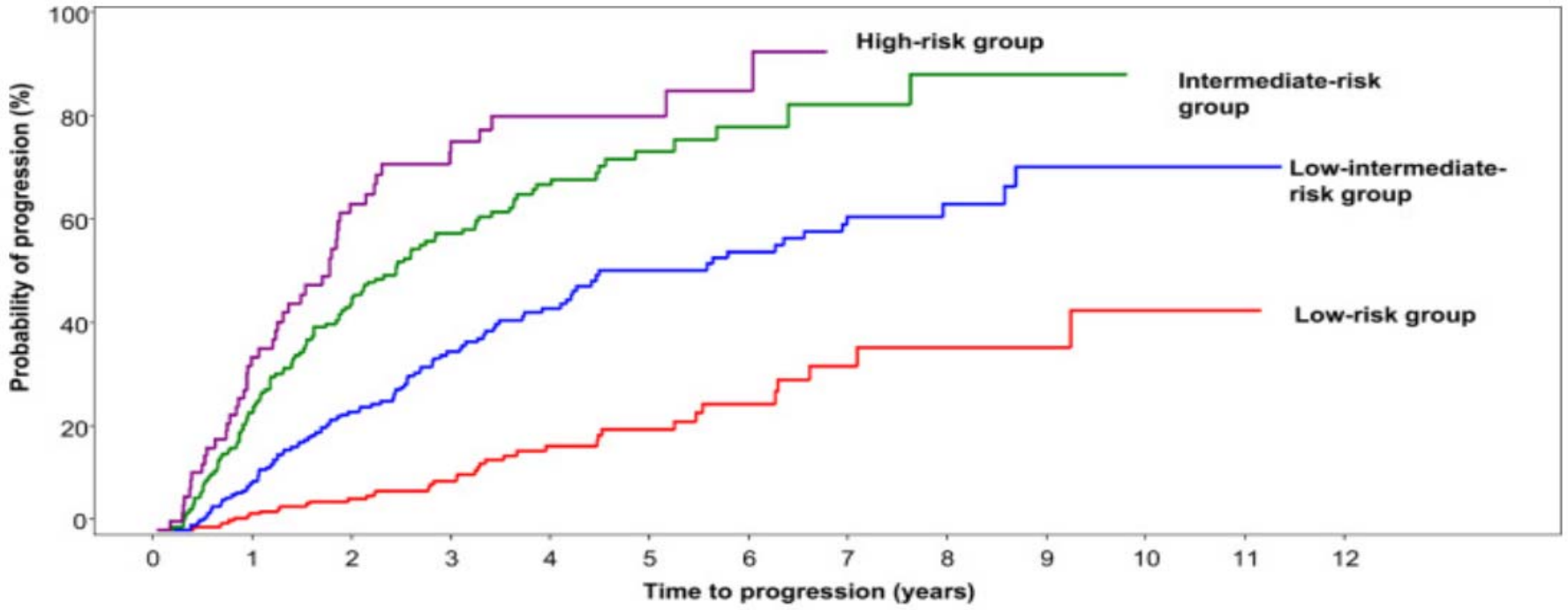
TTP in entire cohort (n=1996)

- **Median: 6.4 y**
- **2-year: 22%**
- **5-year: 42%**
- **10-year: 64%**

Mateos MV, Kumar S et al. Blood Cancer J 2020



Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low-Risk	0	Reference	6.2%	522 (38.3%)
Intermediate	1	2.99 (1.97 – 4.54)	17.9%	445 (32.7%)
High	2-3	9.02 (6.15 – 13.2)	44.2%	396 (29.1%)



Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low	0	Reference	6.0%	225 (32.7%)
Low-intermediate	1	4.16 (2.26 – 7.67)	22.8%	224 (32.5%)
Intermediate	2	9.82 (5.46 – 17.7)	45.5%	177 (25.7%)
High	3-4	15.5 (8.23 – 29.0)	63.1%	63 (9.1%)

To Treat or Not to Treat?

When to Treat?

Whom to Treat?

How to Treat?

What We Do Know

- Standard care
  - Observation with close surveillance
- Ultra-high risk SMM
  - IMGW revised diagnostic criteria to active MM
  - Treat as MM
- Recommend more sensitive imaging tests
  - CT, PET/CT or MRI
  - At diagnosis and follow up

Dilemma

High risk SMM

- Unclear of early intervention
  - Lack of benefits from early studies
    - Melphalan / prednisone
    - Thalidomide
    - Bisphosphonate
  - Treatment-related toxicities
- Two approaches of recent trials
  - Delay progression
  - Intent to cure

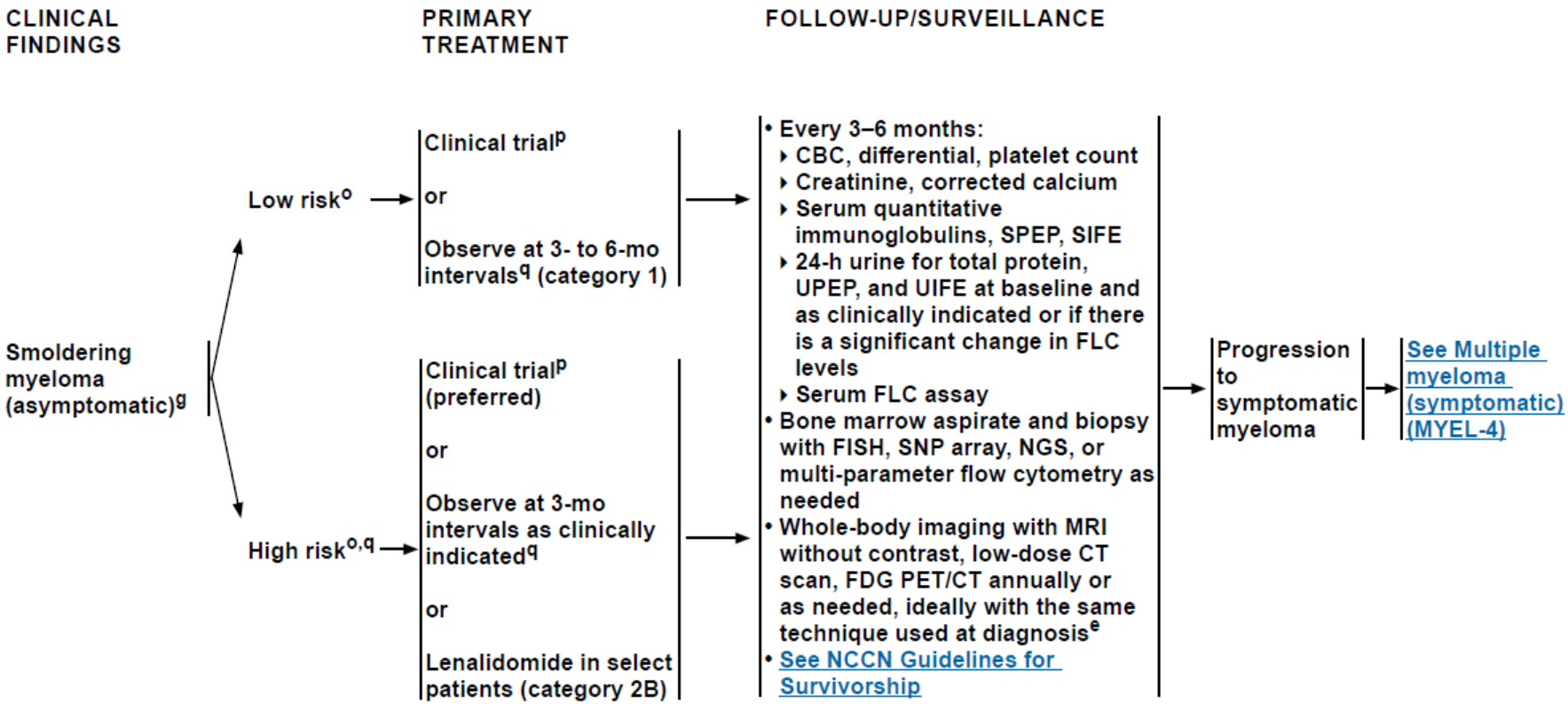
Early Intervention – Delay Progression

- QuiRedex trial
  - Lenalidomide / dexamethasone vs observation
    - Progression: 23% vs 76%
    - 3-year OS: 94% vs 80%
- ECOG trial (E3A06)
  - Lenalidomide vs observation
    - 3-year PFS 91% vs 66%
- CENTAURUS trial
  - Daratumumab at 3 dosing schedule
- AQUILA trial
  - SQ daratumumab

Early Intervention – Curative Intent

- National Institutes of Health Clinical Center – small pilot study (n=12)
  - Intent for MRD negative state and potentially cure
  - Carfilzomib / Lenalidomide / dexamethasone (8 cycles)
  - Followed by lenalidomide (24 cycles)
- GEM-CESAR
  - Carfilzomib / Lenalidomide /dexamethasone as induction
  - Followed by HDT-ASCT, consolidation with KRd and maintenance with Rd
- ASCENT trial
  - daratumumab, carfilzomib, lenalidomide, and dexamethasone

NCCN Guidelines Version 1.2022



Selinexor

- Selective inhibitor of nuclear export
- Binding exportin 1 to block cell proliferation
- Relapsed / refractory MM
- Adverse effects
  - Myelosuppression
    - anemia, leukopenia, neutropenia, thrombocytopenia
  - Risk for infection and sepsis
  - GI toxicities
  - Fatigue

Selinexor / dexamethasone

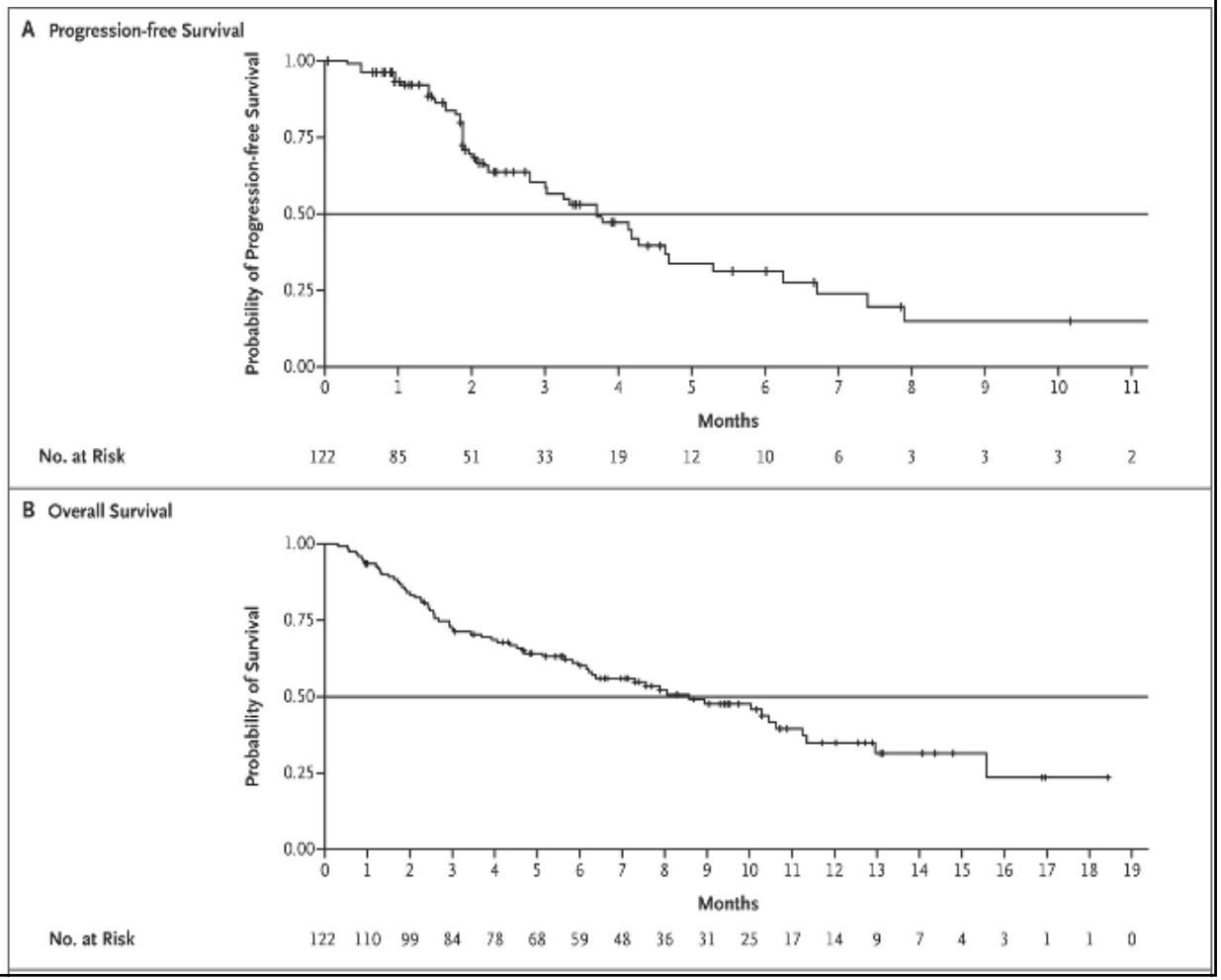
- FDA-approval in 2019
- NCCN – Useful in certain circumstances
- ≥ 4 prior lines
- Phase IIb trial (STORM)
  - 122 patients
  - Refractory to Lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab
  - ≥ PR (26%)
    - PR (20%); VGPR (5%); stringent CR (2%)

Chari A. et al. *N Engl J Med.* 2019

STORM Trial

- Median PFS
  - 3.7 months
- Median OS
  - 8.6 months (ALL)
  - 15.6 months (≥ PR)

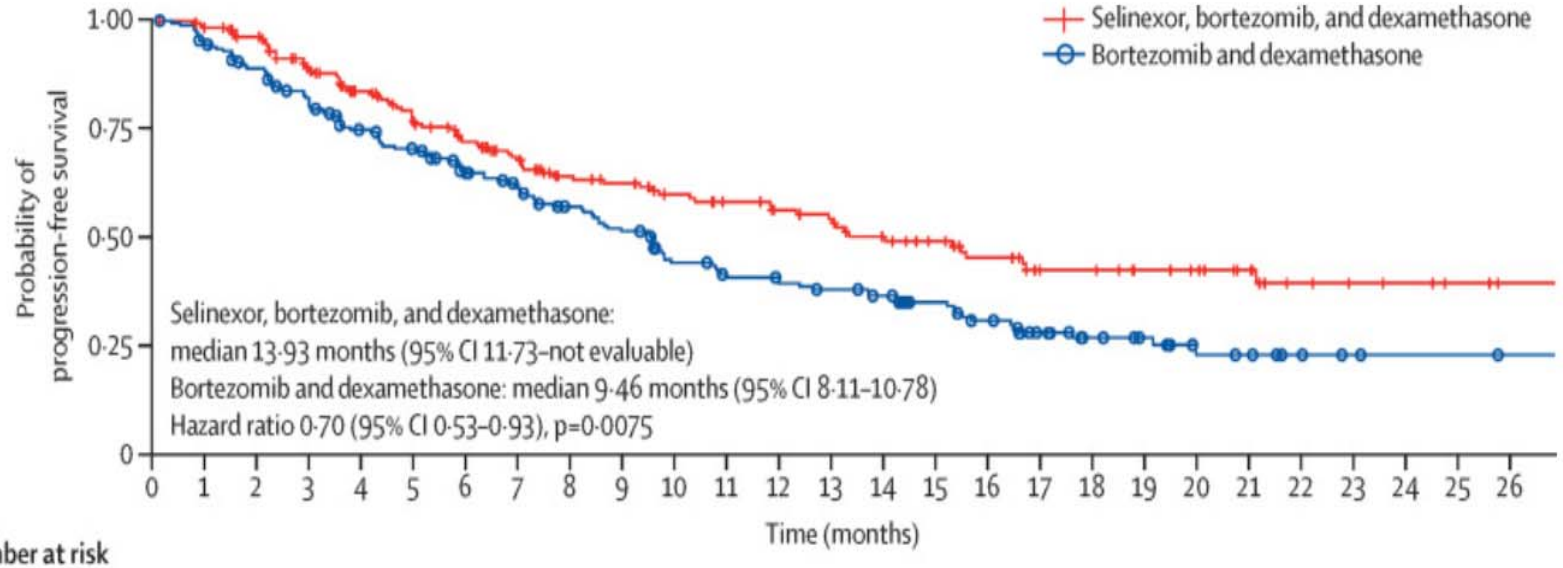
Chari A. et al. *N Engl J Med.* 2019



Selinexor / bortezomib / dexamethasone

- FDA approved in December 2020
- ≥ 1 prior therapies
- NCCN – Other recommended regimens
- Phase III BOSTON trial
  - Selinexor / bortezomib (weekly) / dex
  - **VS**
  - Bortezomib (twice weekly) / dex

BOSTON Trial - PFS



Number at risk (number censored)

Selinexor, bortezomib, and dexamethasone	195 (0)	187 (5)	175 (12)	152 (21)	135 (31)	117 (37)	106 (42)	89 (50)	79 (57)	76 (59)	69 (63)	64 (66)	57 (71)	51 (73)	45 (76)	41 (80)	35 (83)	27 (89)	26 (90)	22 (94)	19 (97)	14 (102)	9 (106)	7 (108)	6 (109)	4 (111)	2 (113)
Bortezomib and dexamethasone	207 (0)	187 (8)	175 (10)	152 (15)	138 (20)	127 (22)	111 (29)	100 (32)	90 (37)	81 (37)	66 (41)	59 (43)	56 (44)	53 (45)	49 (47)	42 (52)	35 (55)	26 (60)	20 (65)	16 (69)	10 (73)	8 (75)	5 (78)	4 (79)	3 (80)	3 (80)	2 (81)

Grosicki S. et al. *Lancet.* 2020

BOSTON Trial – Treatment Response

	Selinexor, bortezomib, and dexamethasone group (n=195)	Bortezomib and dexamethasone group (n=207)
Overall response rate	149 (76·4%)	129 (62·3%)
Stringent complete response	19 (10%)	13 (6%)
Complete response	14 (7%)	9 (4%)
Very good partial response	54 (28%)	45 (22%)
Partial response	62 (32%)	62 (30%)
Minimal residual disease negativity	9 (5%)	8 (4%)

Grosicki S. et al. *Lancet.* 2020

BOSTON Trial – Adverse Events

	Selinexor, bortezomib, dexamethasone (n=195)		Bortezomib and dexamethasone (n=204)	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3–4**
Hematological AEs				
Thrombocytopenia	117 (60%)	77 (39%)	55 (27%)	35 (17%)
Anemia	71 (36%)	31 (16%)	47 (23%)	20 (10%)
Neutropenia	29 (15%)	17 (9%)	12 (6%)	7 (3%)
Non-hematological AEs				
Fatigue	82 (42%)	26 (13%)	37 (18%)	2 (1%)
Nausea	98 (50%)	15 (8%)	20 (10%)	0
Diarrhea	63 (32%)	12 (6%)	51 (25%)	1 (<1%)
Peripheral neuropathy	63 (32%)	9 (5%)	96 (47%)	18 (9%)
Decreased appetite	69 (35%)	7 (4%)	11 (5%)	0
Asthenia	48 (25%)	16 (8%)	27 (13%)	9 (4%)
Pneumonia	35 (18%)	24 (12%)	34 (17%)	21 (10%)
Cataract	42 (22%)	17 (9%)	13 (6%)	3 (1%)
Vomiting	40 (21%)	8 (4%)	9 (4%)	0

Grosicki S. et al. *Lancet.* 2020

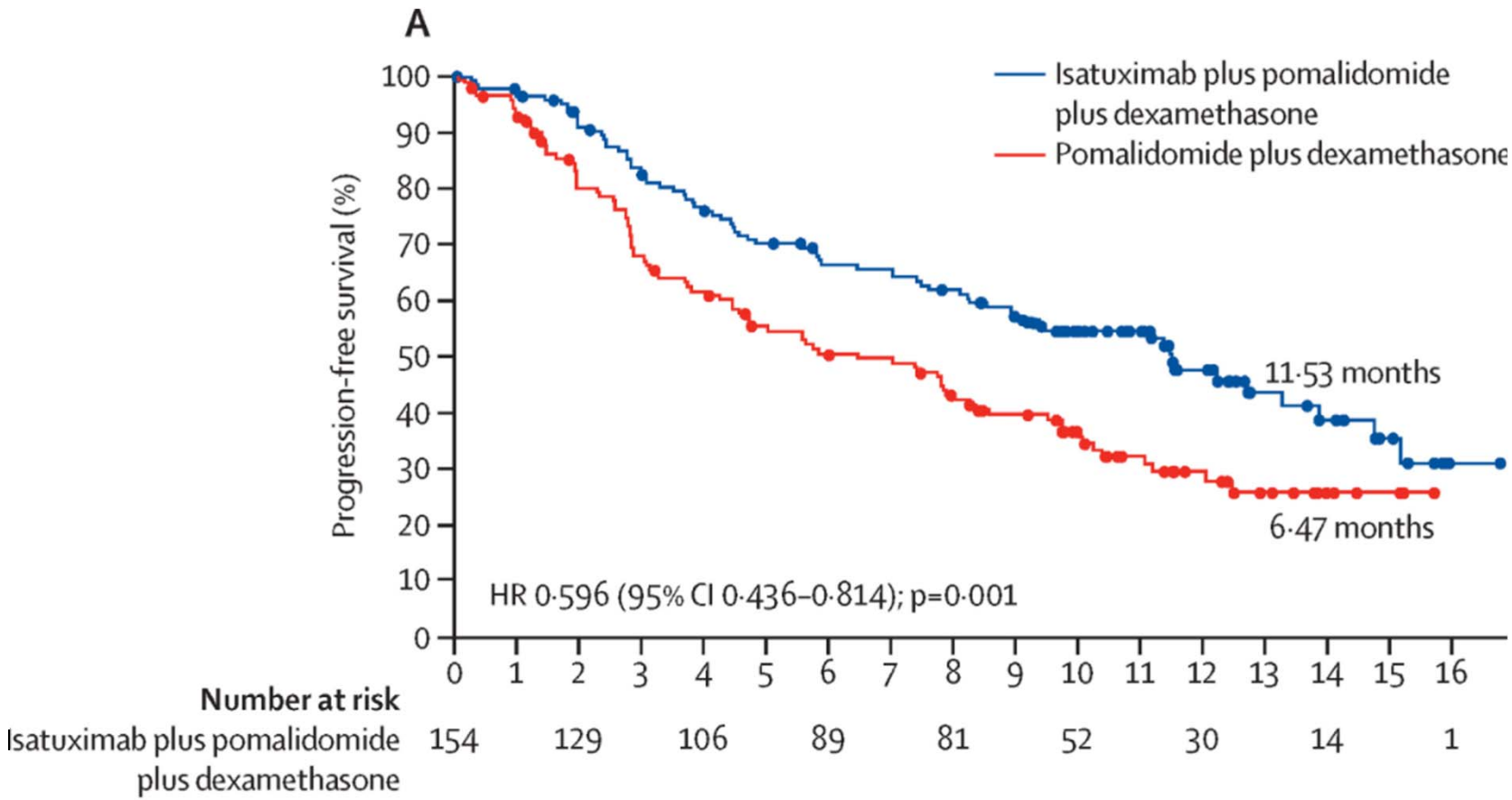
Isatuximab

- Monoclonal antibody
- CD-38 targeting
- Relapsed / refractory MM
- Adverse effects
  - Infusion – related reactions
    - dyspnea, cough, nasal congestion, nausea
    - Anaphylactic reaction
  - Respiratory infection, pneumonia
  - Neutropenia
  - Diarrhea

Isatuximab / pomalidomide / dexamethasone

- NCCN – preferred regimen
- Approved by FDA in March 2020
- ICARIA- MM trial
  - ≥ 2 prior therapies
    - lenalidomide and proteasome inhibitor
  - Randomized to isatuximab / pom/ dex vs pom /dex
  - ORR: 60% vs 35%
  - Median PFS: 11.5 vs 6.5 months
  - Improved ORR and PFS in renal patients

Attal M. et al. *Lancet.* 2019

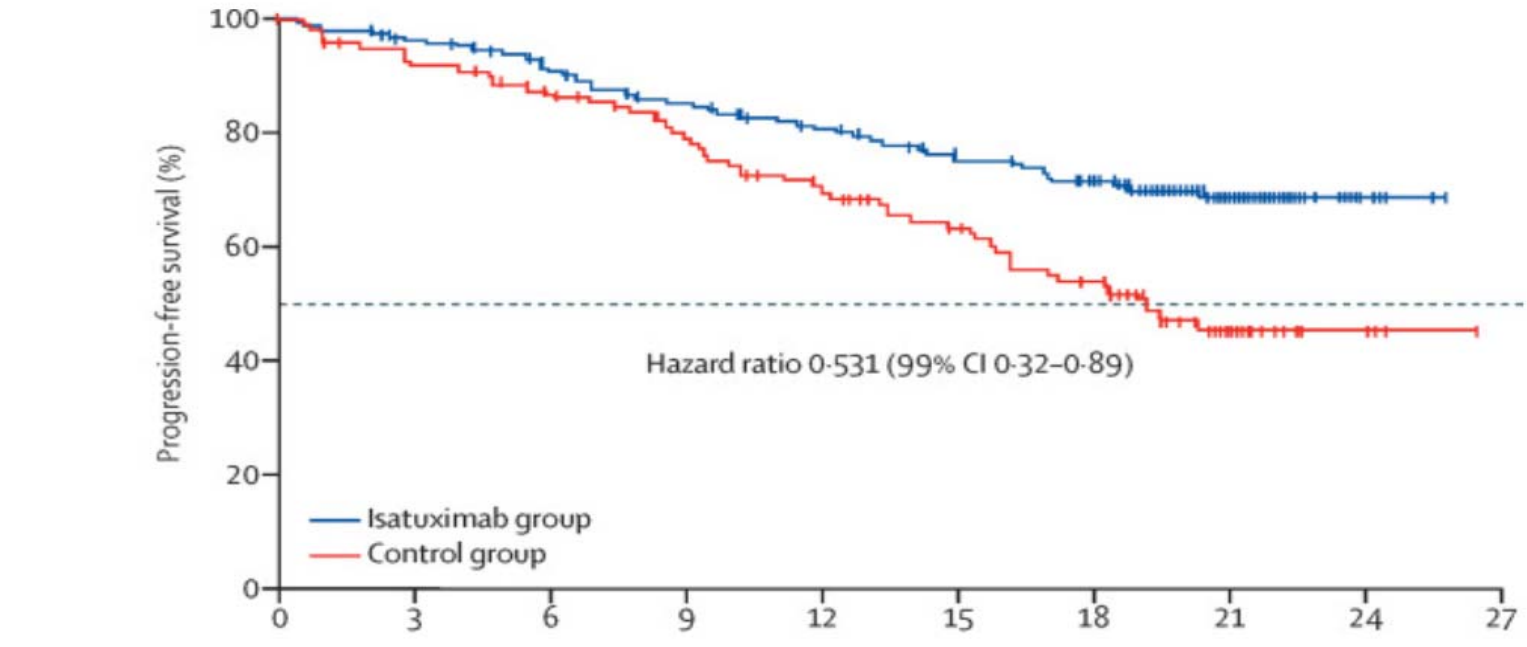


Attal M. et al. *Lancet.* 2019

Isatuximab / Carfilzomib / dexamethasone

- NCCN – Other recommended regimens
- Approved by FDA in March 2021
- IKEMA phase III trial
  - 302 patients
  - 1-3 prior therapies
  - Randomized to
    - isatuximab / carfilzomib/ dex vs carfilzomib /dex
    - Primary endpoint: PFS

IKEMA Trial - PFS



Number at risk										
Isatuximab group	179	164	151	136	124	110	100	36	5	0
Control group	123	108	99	85	72	61	50	19	6	0

Moreau P. et al. *Lancet.* 2021

Melphalan Flufenamide

- Peptide – drug conjugate
  - Targets aminopeptidases
  - Releases alkylating agents
- FDA – March 2021
- Relapsed / refractory
- ≥ 4 prior therapies
- NCCN – Other recommended regimens
- Phase II HORIZON trial
  - Melphalan flufenamide / dexamethasone

HORIZON Trial

- Melphalan flufenamide 40 mg IV, day 1
- Dexamethasone 40 mg weekly (20 mg for age > 75 yr)
- 157 patients (119 triple-class-refractory)
  - ORR 29% (26%)
  - Median duration of response 5.5 mon (4.4 mon)
- Adverse events
  - Neutropenia (79%); thrombocytopenia (76%); anemia (43%)
  - GI (62%)
  - No alopecia or neuropathy

Richardson et al. *J Clin Oncol.* 2021

HORIZON Survival Data

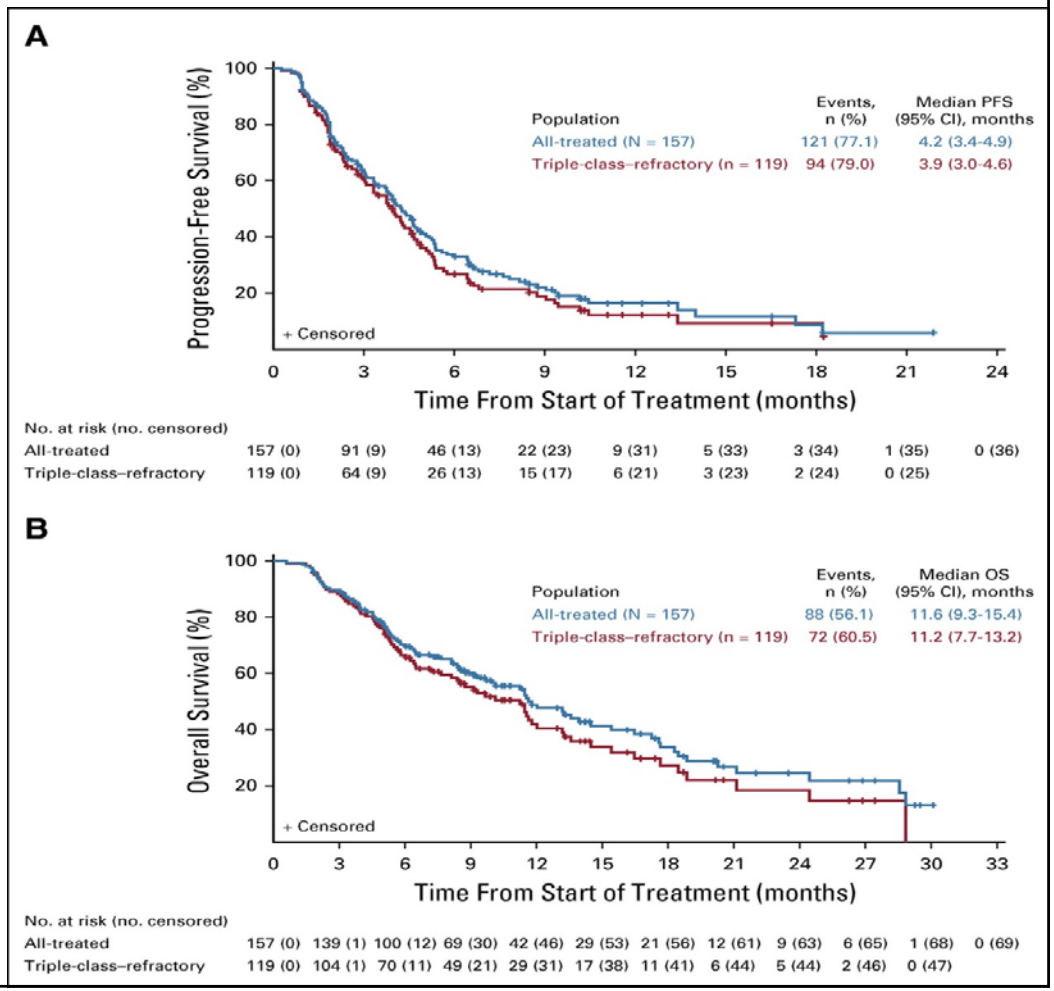
PFS

- All – 4.2 mon
- Triple-class-refractory – 3.9 mon

OS

- All – 11.6 mon
- Triple-class-refractory- 11.2 mon

Richardson et al. *J Clin Oncol.* 2021



Belantamab Mafodotin

- Anti- BCMA
- FDA – August 2020
- Single agent
- Relapsed / refractory
- ≥ 4 prior therapies
- NCCN – Other recommended regimens
- Phase II DREAMM-2 trial
  - 196 patients (median 7 prior lines)
  - Two dosage arm: 2.5 mg/kg and 3.4 mg/kg
  - IV every 3 weeks

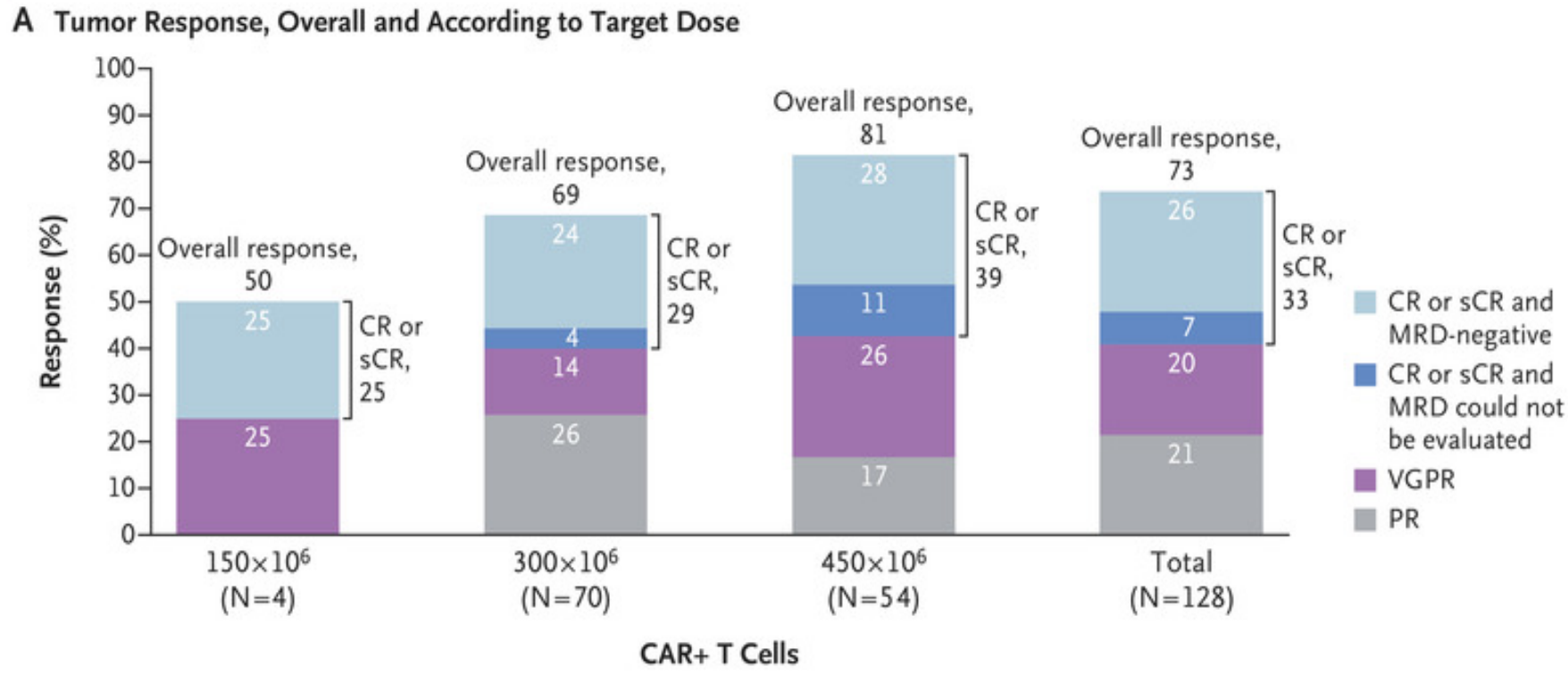
DREAMM-2 Trial

Treatment response	2.5 mg/kg	3.4 mg/kg
Overall response rate (ORR)	31%	34%
≥ Very good partial response (VGPR)	19%	20%
Keratopathy	27%	21%
Thrombocytopenia	20%	33%
Anemia	20%	25%
Serious AEs	40%	47%

Lonial S. et al. *Lancet Oncol.* 2020

Idecabtagene Vicleucel

- First CAR-T cell therapy for MM
- Targets BCMA
- FDA – March 2021
- Relapsed / refractory
- ≥ 4 prior therapies
- NCCN – Other recommended regimens
- Phase 2 KarMMa trial
  - 128 patients (median 6 prior lines)
  - target doses
    - 150×10^6 - 450×10^6 CAR+ T cells



Munshi NC. et al. *N Engl J Med.* 2021.

KarMMa Trial

- Response 73% (PR or better)
- CR 33%
- MRD- negative CR 26%
- Median PFS 8.8 months
- Adverse effects
  - Neutropenia (91%); anemia (70%); thrombocytopenia (63%)
  - Cytokine release syndrome (84%)
    - ≥ grade 3 (5%)
  - Neurotoxicity (18%)
    - ≥ grade 3 (3%)

Munshi NC. et al. *N Engl J Med.* 2021.

Venetoclax / dexamethasone

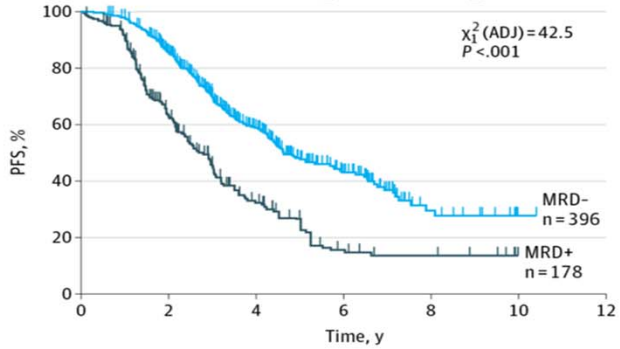
- Only for t(11; 14)
- NCCN – Useful in certain circumstances
- Relapse / refractory
- Phase I study (n= 66)
  - Median 5 prior lines
  - ORR - 21%
    - t(11; 14) – 40%
    - without t(11; 14) – 6%

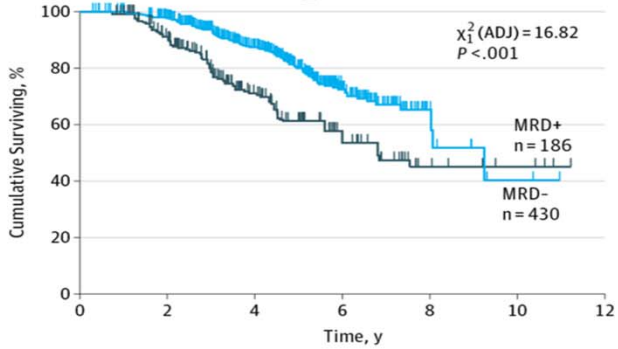
Kumar, S. et al. Blood, 2017

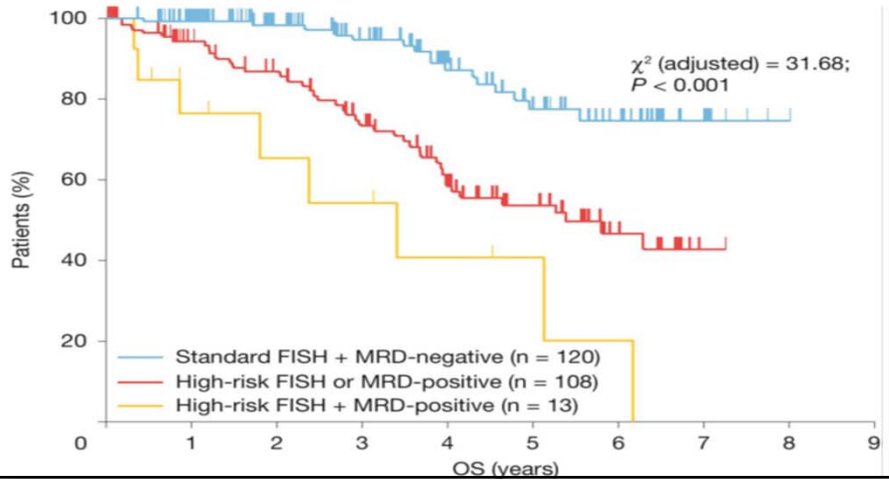
Minimal Residual Disease (MRD)

- Bone marrow-based technologies
  - Next generation flow
  - Next generation sequencing
- Sensitive detection and monitoring
  - detect 10^{-6} cells or lower
- Prognostic value for MRD negativity
- IMWG updated MM response criteria

Association of MRD With Superior Survival Outcomes in Multiple Myeloma: A Meta-analysis

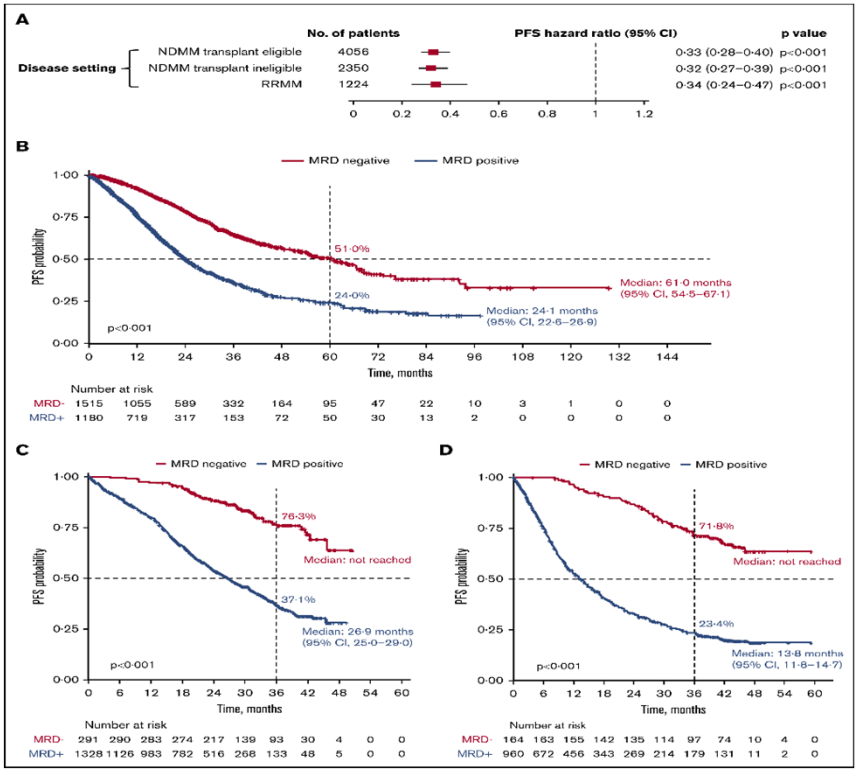


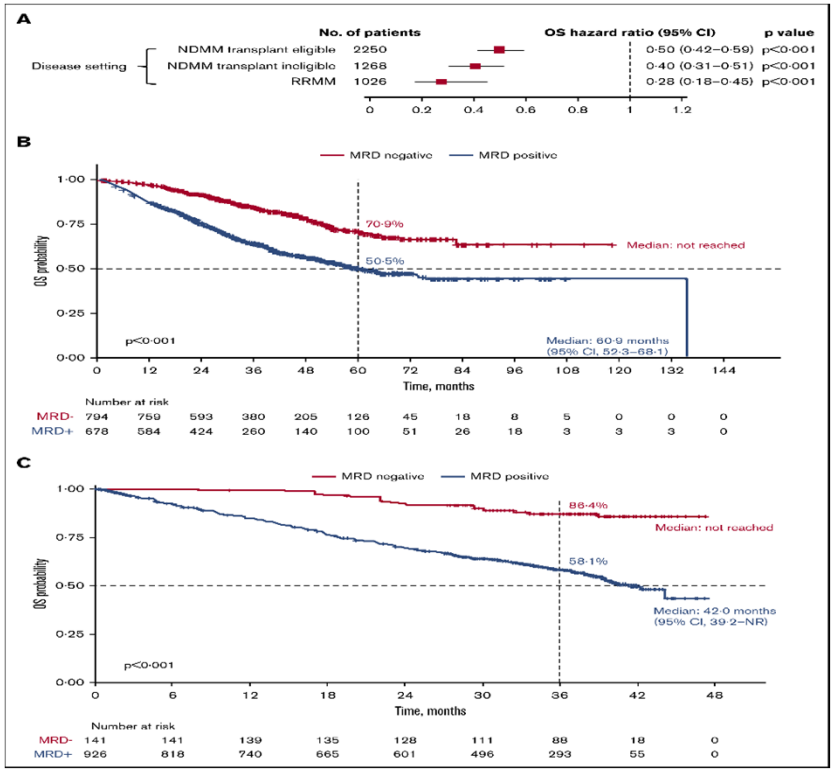




Munshi, N. et al. JAMA Oncol. 2017

A Large Meta-analysis of the Prognostic Value of MRD





Munshi, N. et al. Blood Adv, 2020

Updated IMWG Response Criteria

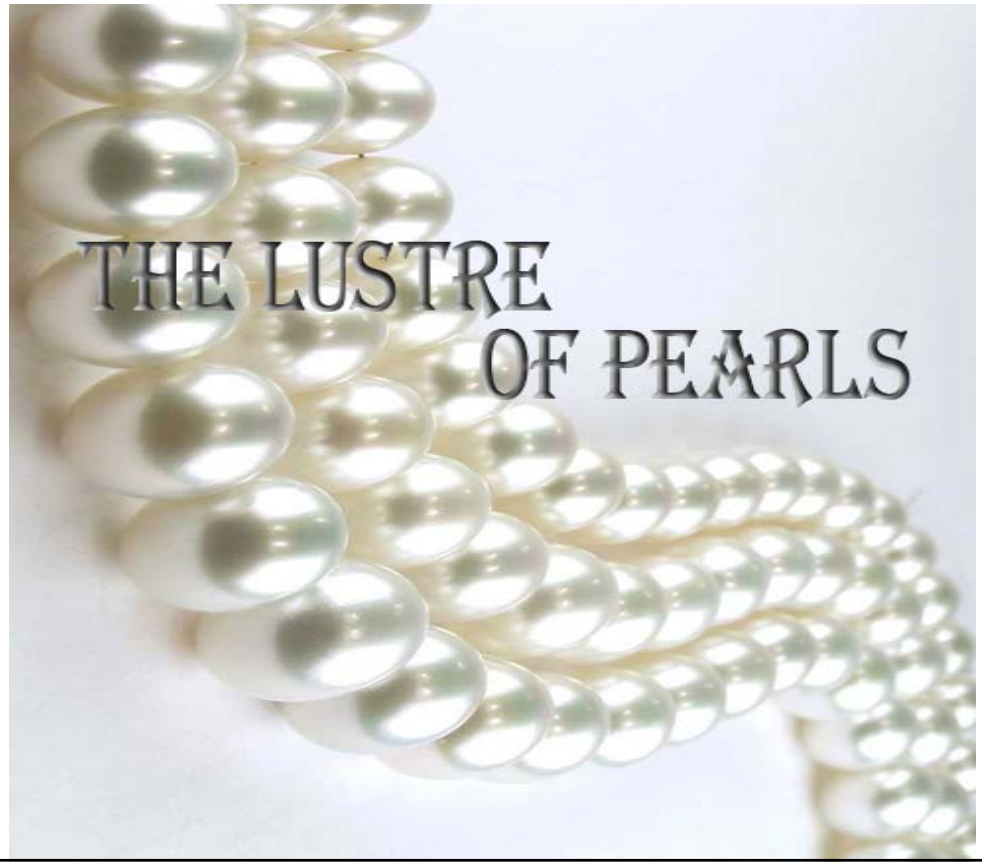
	Standard IMWG Response Criteria				IMWG MRD Criteria	
Lab value reduction	PR	VGPR	CR	sCR	MRD-negative	Imaging plus MRD-negative
Serum M protein	>50%	> 90%	0	0	0	0
24-h urine M protein	≥ 90% or to < 200 mg	< 100 mg	0	0	0	0
IF		positive	negative	negative	negative	negative
BMPC (unmeasurable M protein and dFLC)	≥ 50% (baseline ≥ 30%)		< 5%	No clonal cells	MRD negative in BM	MRD negative in BM
Serum dFLC (unmeasurable M)	≥ 50%			Normal FLC ratio		
PET scan						Negative

Kumar S. et al. Lancet Oncology, August 2016

MRD in Clinical Application

- FDA guidance
  - Regulatory considerations for use of MRD in drug development
- Clinical trials
  - MRD status as endpoint assessment
- Clinical use of MRD
  - No guideline for treatment decision based on MRD status
  - Data from prospective trials are not yet available

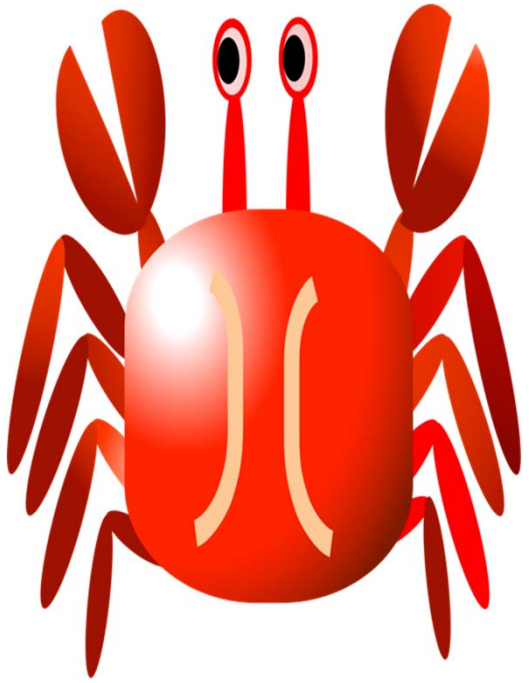
Take Home Messages



Pearl: Is It SMM?

SMM: NO SLiM CRAB

S (Sixty % BMPC)
Li (Light chains I/U >100)
M (MRI >1 focal lesion)
C (Calcium elevation)
R (Renal insufficiency)
A (Anemia)
B (Bone disease)



Pearl # 2

High-risk SMM (20/2/20)

- 2-year progression risk is ~ 50%
- Strongly recommend clinical trials (NCCN preferred)

Pearl # 3

Idecabtagene Vicleucel

- First FDA-approved CAR T for MM
- ≥ 4 prior lines (IMiDs, PI, CD-38)
- Common AEs
  - CRS
  - Neurotoxicity
  - Cytopenia

Pearl # 4

MRD-negative

- Improved survival
- No current guideline for treatment decision

Acknowledgment

Thank Dr. Shaji Kumar for his support

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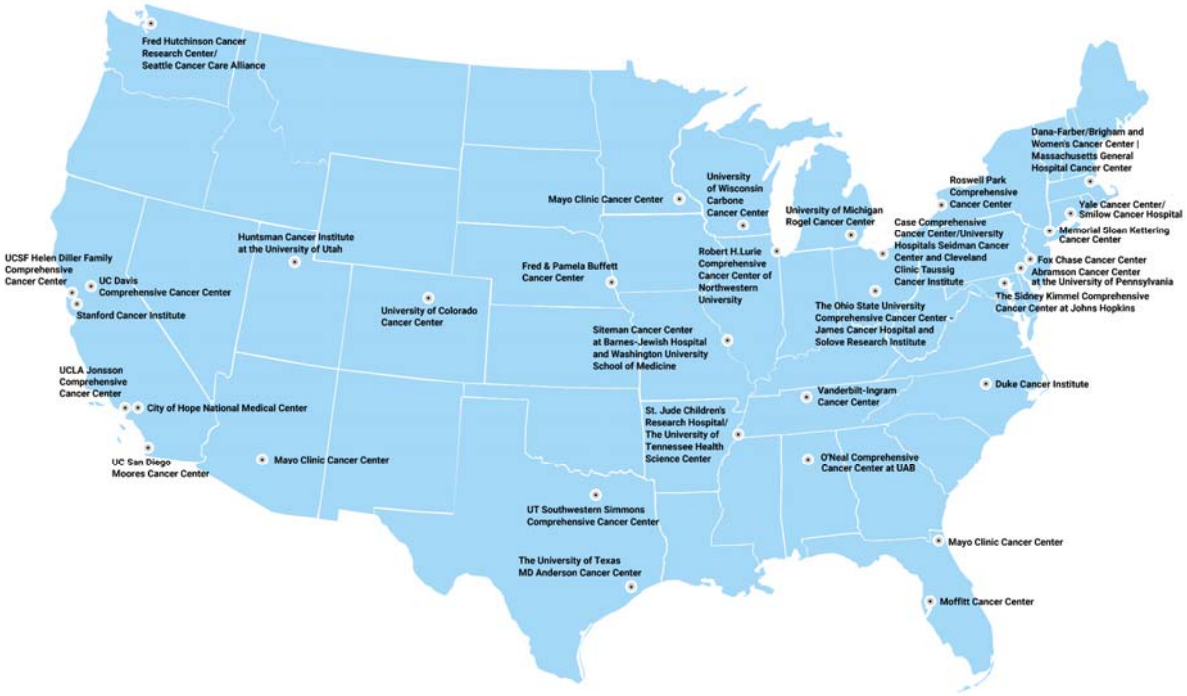

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