Early Treatment for High-Risk Smoldering MM: Going for a Cure?

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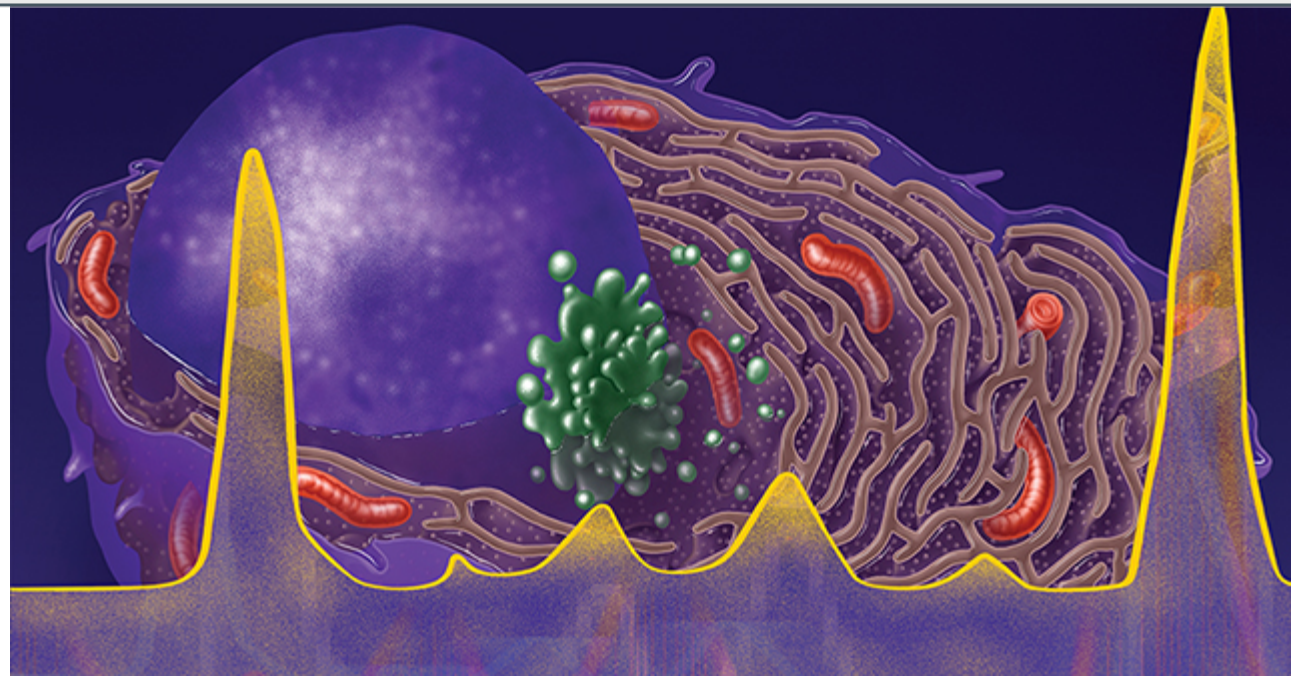

Disclosures

Shaji Kumar, MD, has disclosed that he has received funds for research support from AbbVie, Bristol-Myers Squibb, Celgene, Genentech, Janssen, MedImmune, Oncopeptides, Takeda, and TeneoBio and consulting fees from AbbVie, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Oncopeptides, and Takeda.

Patient Scenario

- A 56-year-old woman was noted to have elevated total protein during routine evaluation and underwent additional testing
  - Hb: 13.2 g/dL
  - Serum calcium: 9.2 mg/dL, creatinine: 0.8 mg/dL, LDH: normal, B2M: 3.7 mg/dL
  - SPEP: 2.3 g/dL M spike (IgG kappa), serum FLC – kappa 40 mg/dL, lambda 1.2 mg/dL, k:l ratio 33
- Bone marrow biopsy showed 40% plasma cells, FISH shows t(4;14)
- Whole body low-dose CT negative for lytic lesions
- MRI spine shows marrow heterogeneity, no lesions

Presurvey 1: In your current practice, what would you recommend next for this patient?

1. Continue observation and repeat testing in 6 months
2. Continue observation and repeat testing in 2 months
3. Start treatment with lenalidomide/dexamethasone
4. Start treatment with bortezomib/lenalidomide/dexamethasone with plans for an ASCT after 4 cycles
5. Enroll in a clinical trial
6. Uncertain

Expert Recommendations

Expert Recommendations	
Brian G.M. Durie, MD	Enroll in a clinical trial
Shaji Kumar, MD	Enroll in a clinical trial
Thomas G. Martin, MD	Enroll in a clinical trial
Philippe Moreau, MD	Enroll in a clinical trial
S. Vincent Rajkumar, MD	Start treatment with lenalidomide/dexamethasone
Jesús San-Miguel, MD	Start treatment with VRD, with plans for ASCT

Smoldering Myeloma

SMOLDERING MULTIPLE MYELOMA

ROBERT A. KYLE, M.D.,
AND PHILIP R. GREIPP, M.D.

MULTIPLE myeloma is characterized by an increase of abnormal plasma cells in the bone marrow and monoclonal protein in the serum, often with osteolytic bone lesions. Its course is progressive: anemia, weakness, fatigue, fractures, bone pain, hypercalcemia, renal insufficiency, recurrent infections, bleeding, and deterioration lead to death. However, we have seen six patients with illnesses that met the criteria for the diagnosis of multiple myeloma[1] but have not had a progressive course. Although no chemotherapy was given, their condition has remained stable for five or more years. We designate these cases as "smoldering multiple myeloma." We wish to call attention to this group because smoldering multiple myeloma should be recognized, and treatment withheld.

Table 1. Characteristics of Six Patients with Smoldering Multiple Myeloma.*

Characteristic	Patient Number					
	1	2	3	4	5	6
Age at diagnosis (yr)	70	73	61	57	63	61
Sex	M	M	M	F	F	F
Hemoglobin (g/dl)						
Initial	13.1	13.5	15.5	11.7	12.2	12.8
Last	12.8	13.8	14.2	12.6	12.7	13.5
Serum M protein						
Mobility	β-γ	β	γ	β	γ	β
g/dl	3.4	3.0	3.6	3.1	3.0	3.6
Class/subclass	$G_2\kappa$	$G_1\lambda$	$G_1\kappa$	$G_2\kappa$	$G_2\kappa$	$A\lambda$
Urinary M protein						
Type	κ	λ	κ	κ	—	λ
g/24 hr	0.30	0.50	0.06	0.39	Negative	0.06
Immunoglobulins (mg/ml)						
IgG	65	25	65	27	23	5
IgA	0.32	0.35	0.9	1.7	0.75	26.6
IgM	0.00	0.23	0.4	0.5	0.67	0.29
Marrow plasma cells (per cent)	16	17	17	11	13	10
Labeling index (per cent)	0.0	0.0	0.0	0.0	0.0	0.0
Asynchrony	0.4	0.0	0.0	0.1	0.1	0.7
Myeloma 0.47±0.33 †						
MGUS ‡ 0.05±0.10 †						
Nucleolar size (μm)	1.4	1.2	0.5	0.7	0.8	1.1
Myeloma 1.6±0.76 †						
MGUS ‡ 0.47±0.44 ‡						
Follow-up (yr)	16	5	5	6	5	5

Kyle. NEJM. 1980;302:1347.

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Why Have We Not Been Treating SMM?

1. Patients are asymptomatic
2. We do not know who will get myeloma
3. Treatments are toxic and have limited efficacy
4. No evidence to suggest that it improves survival

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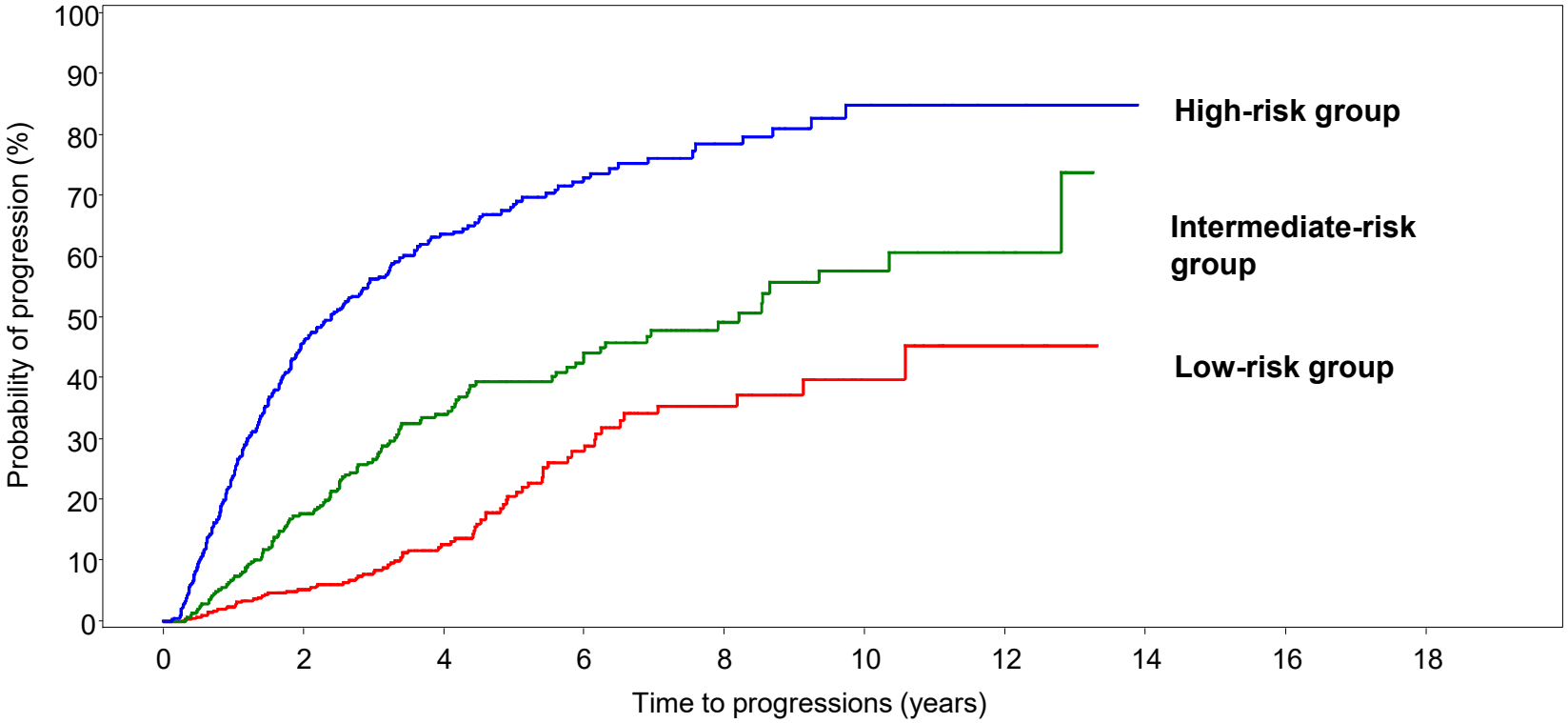
   → We have highly effective therapies
4. No evidence to suggest that it improves survival
   → We have phase III trials now

Progression By Risk Group



Characteristics included in the model:

Serum M Spike: > 2g/dL
FLC Ratio: > 20
BMPC: > 20%

Risk Stratification Groups	Number of risk factors	Hazard Ratio (95% CI) Versus Low-risk group	Risk of Progression at 2 years	Number of patients
Low-risk group	0	Reference	**5%**	**424 (37%)**
Intermediate-risk group	1	2.25 (1.68 to 3.01)	**17%**	**312 (27%)**
High-risk group	2-3	5.63 (4.34 to 7.29)	**46%**	**415 (36%)**

San Miguel. ASCO 2019. Abstr 8000. Mateos Blood Cancer J. 2020;10:102.

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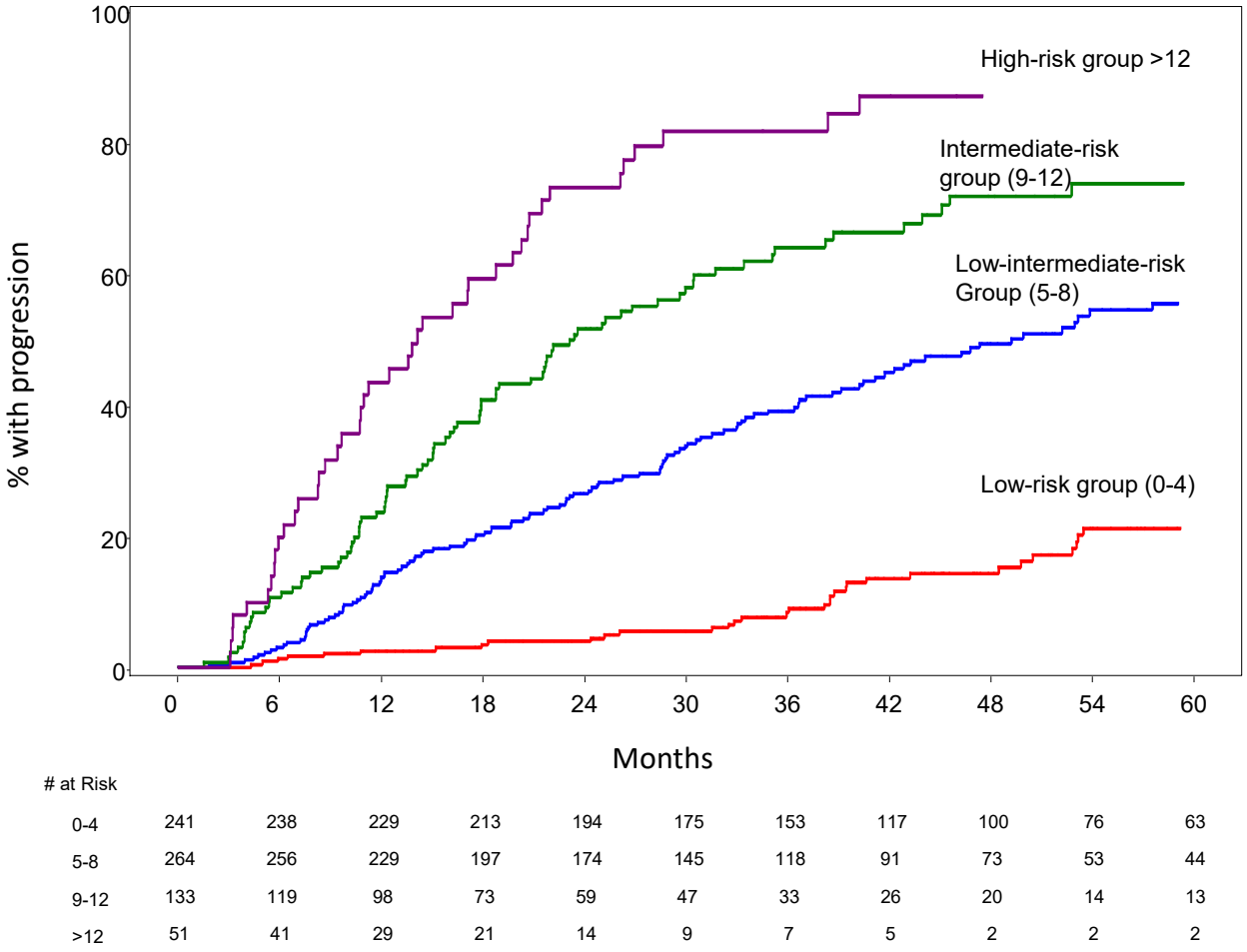
Risk Score to Predict Progression Risk At 2 Years

Risk Factor	Score
FLC Ratio	
0-10 (ref)	**0**
> 10-25	**2**
> 25-40	**3**
> 40	**5**
M protein (g/dL)	
0-1.5 (ref)	**0**
> 1.5-3	**3**
> 3	**4**
BMPC%	
0-15 (ref)	**0**
> 15-20	**2**
> 20-30	**3**
> 30-40	**5**
> 40	**6**
FISH abnormality	**2**



Risk Stratification Groups	Hazard Ratio (95% CI) Versus Low-risk group (censored 2 year)
0-4	**Reference**
5-8	**7.56 (3.77 to 15.2)**
9-12	**17.3 (8.63 to 34.8)**
> 12	**31.9 (15.4 to 66.3)**

Total Risk Score	2-year Progression n (%)
0-4	9 / 241 **(3.7%)**
5-8	67 / 264 **(25.4%)**
9-12	65 / 133 **(48.9%)**
> 12	37 / 51 **(72.6%)**

San Miguel. ASCO 2019. Abstr 8000. Mateos Blood Cancer J. 2020;10:102.

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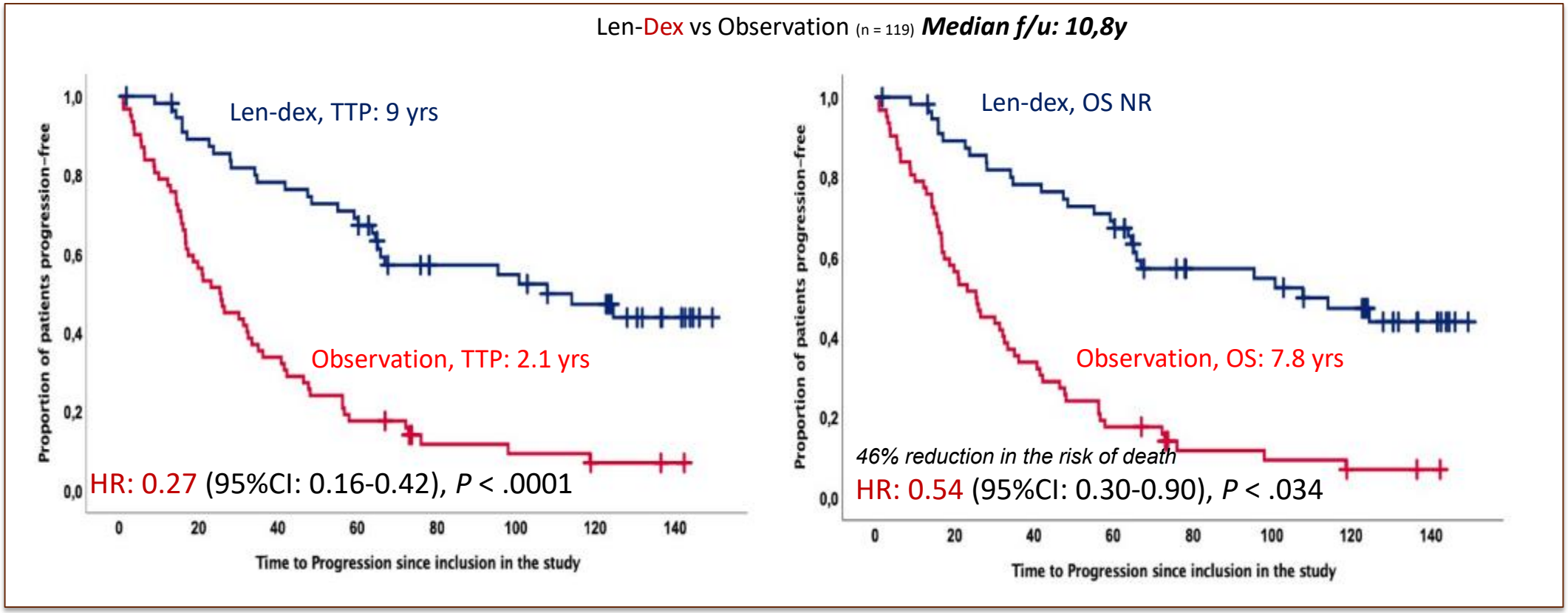
Phase III QuiRedex: Lenalidomide/Dex vs Observation



Caveat: No advanced imaging → many patients may have had active myeloma

Mateos. NEJM. 2013.
Mateos. Lancet Oncology 2016.
Mateos. EHA 2020. Abstr EP950.

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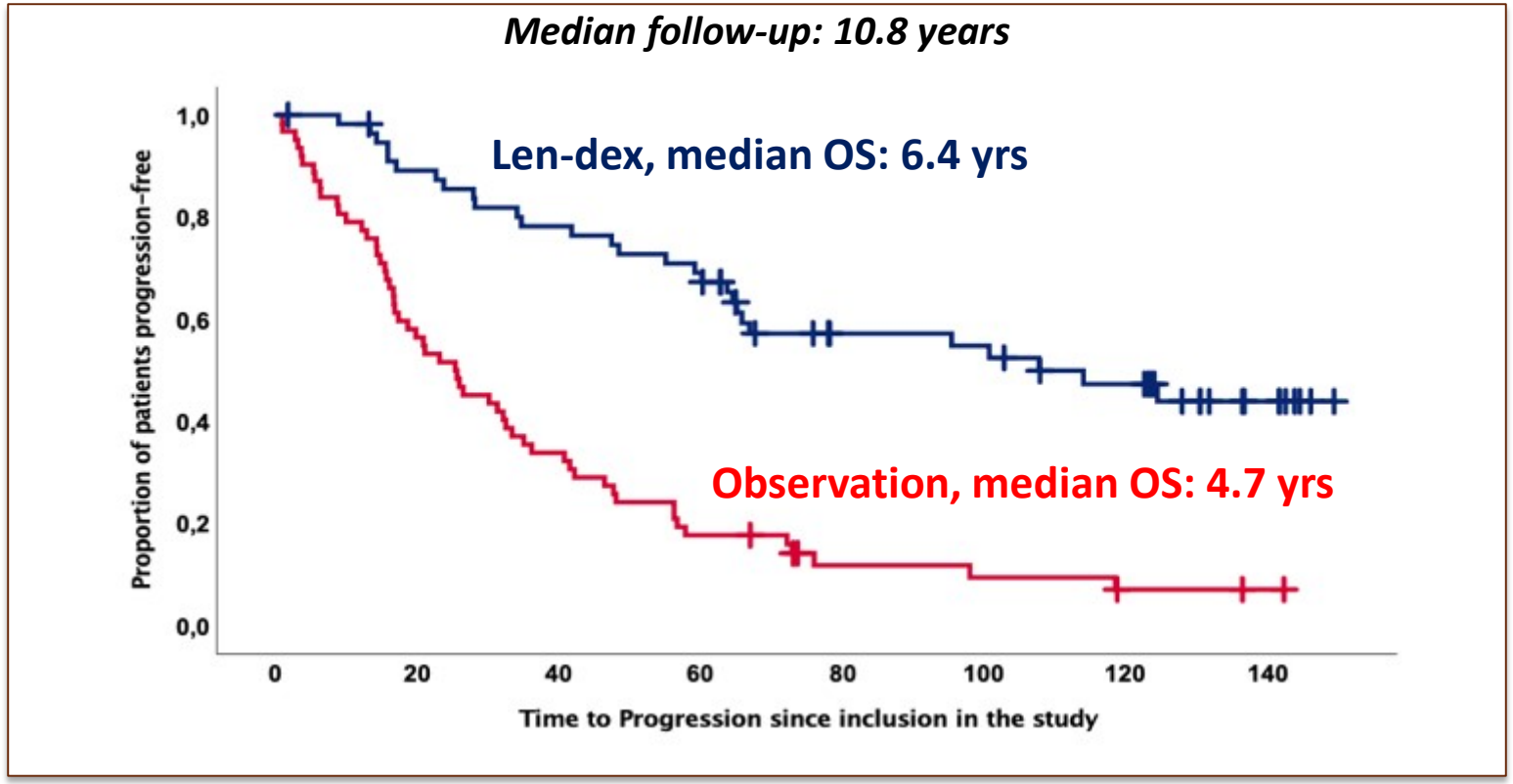
Phase III QuiRedex with Len/Dex vs Observation: OS From Progression To Active Disease



Early treatment does not induce more resistant relapses

Mateos. EHA 2020. Abstr EP950.

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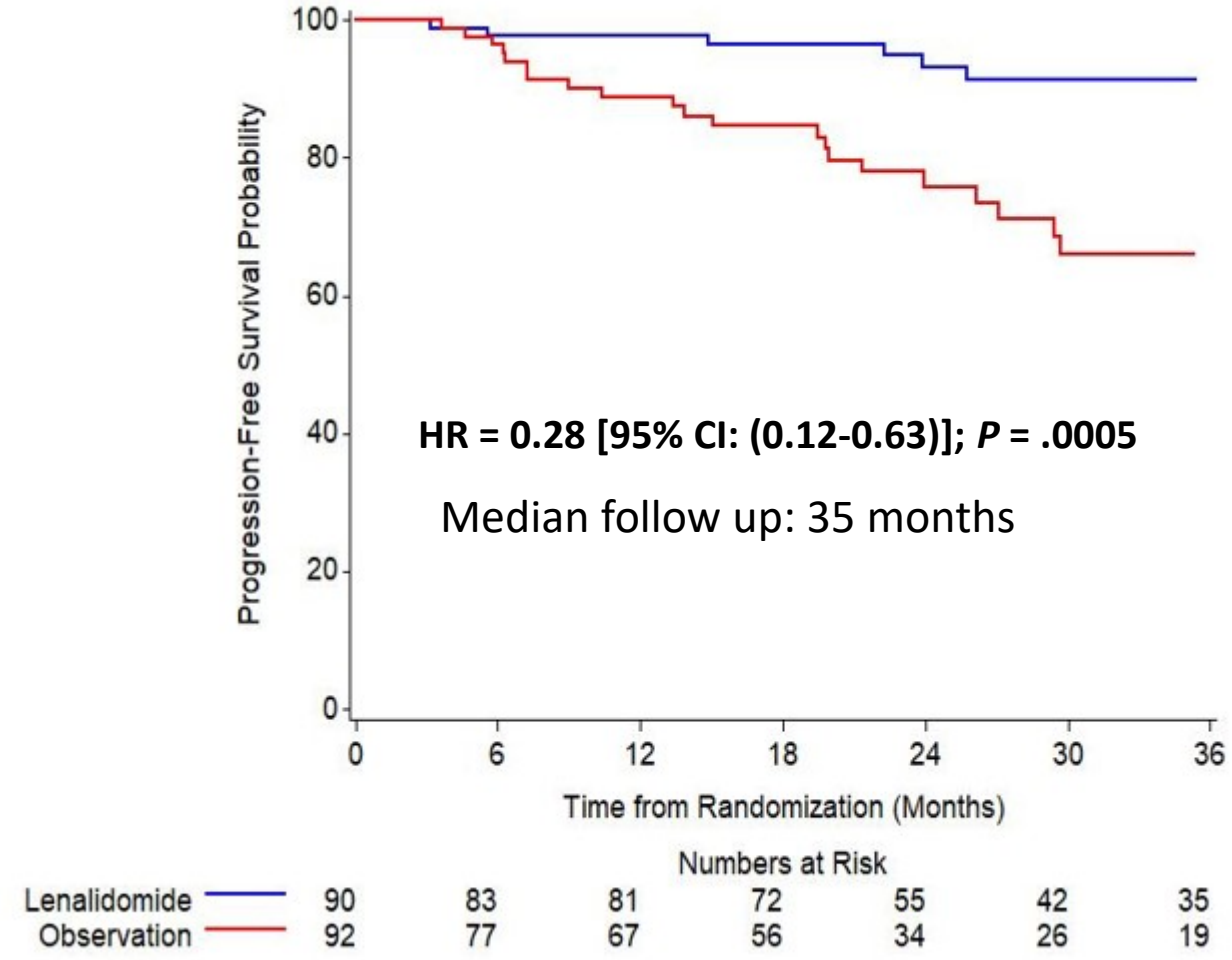
Phase II/III E3A06: Lenalidomide vs Observation



	Lenalidomide [n=44]	Lenalidomide [n=90]	Observation [n=92]
	Phase II	Phase III	
Category	N (%)	N (%)	N (%)
VGPR or Better	4 (9.1)	4 (4.4)	0 (0.0)
PR or Better	21 (47.7)	44 (48.9)	0 (0.0)
SD or Better	42 (95.5)	84 (93.3)	80 (87.0)

Phase III PFS	Len	Obs
1 year	0.98	0.89
2 year	0.93	0.76
3 year	0.91	0.66

Lonial. ASCO 2019. Abstr 8001. Lonial. JCO. 2020;38:1126.

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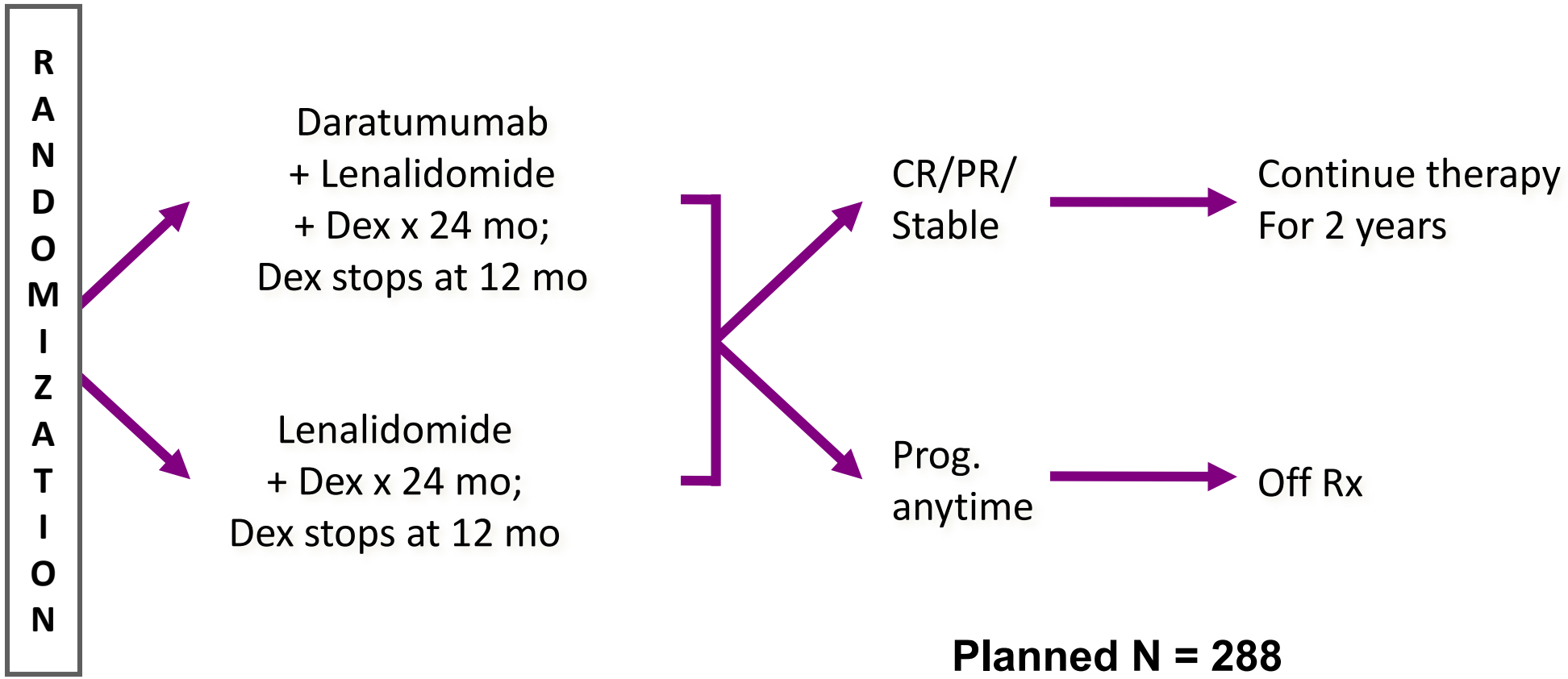
More questions than answers

- If we treat, should we be treating like myeloma?
- Or should it be a low intensity to delay progression?
- Or should it be more aggressive to potentially cure the disease?
- What is a good surrogate for cure?
- When do we stop treatment?

Phase III EAA173: Daratumumab to Enhance Therapeutic Effectiveness of Lenalidomide in Smoldering Myeloma (DETER-SMM)



Planned N = 288

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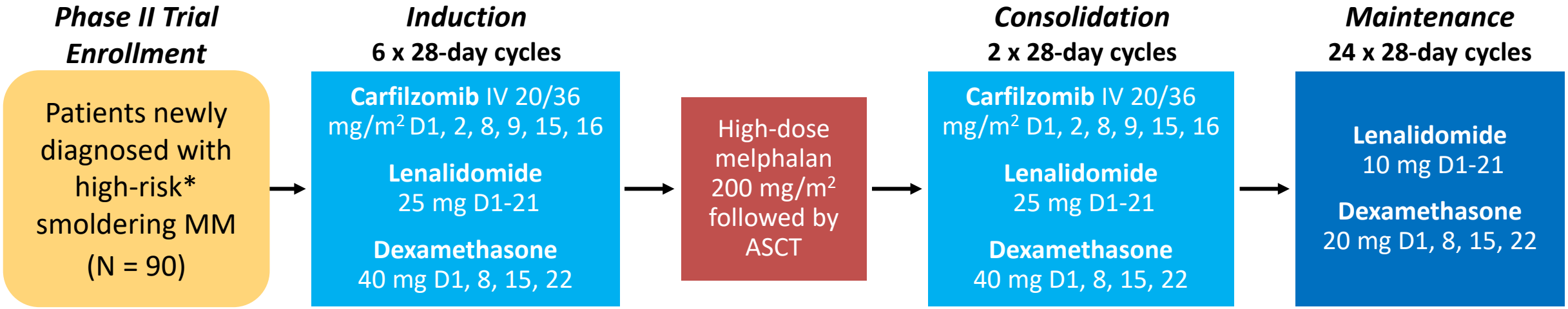
CurativE StrAtegy for High-Risk Smoldering Myeloma (GEM-CESAR)



Response Category, n (%)	Induction (n = 90)	HDM-ASCT (n = 83)	High Risk (n = 55)	Ultrahigh Risk (n = 28)
ORR, n (%)	85 (94)	82 (99)	54 (95)	28 (100)
▪ ≥ CR	**37 (41)**	**53 (64)**	**35 (64)**	**18 (64)**
▪ VGPR	35 (39)	18 (22)	12 (22)	6 (21)
▪ PR	13 (14)	11 (13)	7 (13)	4 (14)
Stable disease	1 (1)	1(1)	1 (2)	--
Progressive disease	2 (3)	--	--	--
MRD negative	**27 (30)**	**47 (56)**	**32 (58)**	**15 (54)**

- **5 patients did not undergo ASCT**: PD after induction (n = 2); ASCT mobilization failure (n = 2); patient decision (n = 1)
- PBSC mobilization after C 4 of induction: **93% successful with G-CSF**, 7% required plerixafor; mean CD34 cells collected: 4 x 10^6/kg and 11 patients required second mobilization

Mateos. ASH 2019. Abstr 781.

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CurativE StrAtegy for High-Risk Smoldering Myeloma (GEM-CESAR)

Outcomes including Consolidation & 1 year maintenance

77 patients completed induction, HDT-ASCT, consolidation, and 1 yr of maintenance

Response, %	Induction (KRd x 6) (n = 77)	HDT-ASCT (n = 77)	Consolidation (KRd x 2) (n = 77)	Maintenance (Rd x 1 Yr) (n = 77)
≥ CR	**43**	**63**	**75**	**81**
VGPR	43	24	18	13
PR	13	13	7	5
Progressive disease	--	--	--	1*
MRD negative	**33**	**49**	**65**	**62**

*Biological progressive disease at end of maintenance, MRD positive.

Mateos. ASH 2019. Abstr 781.

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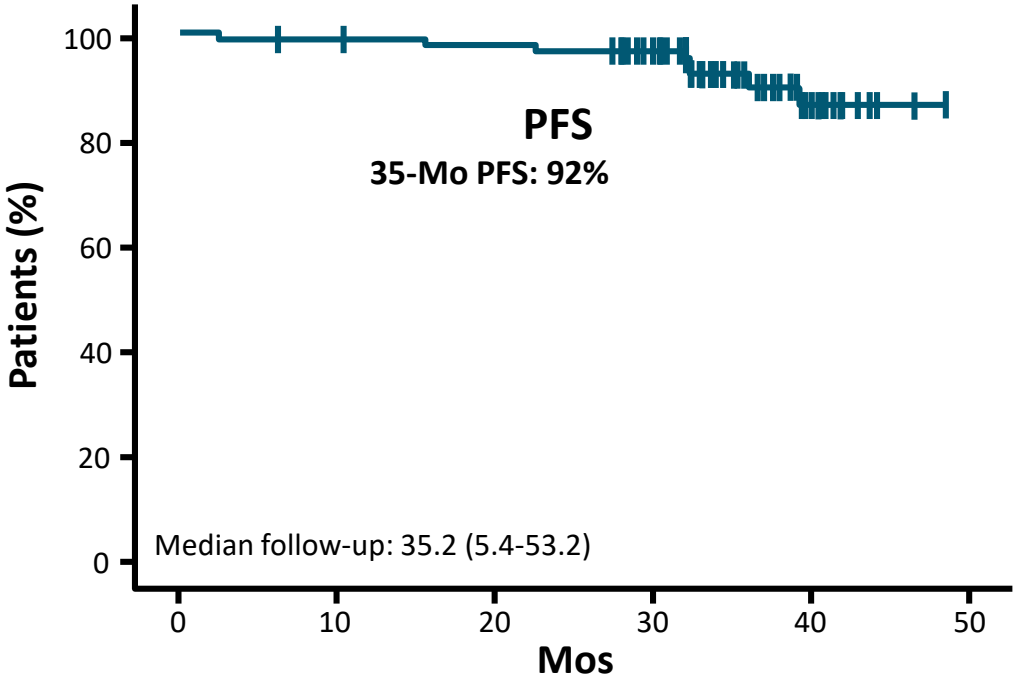
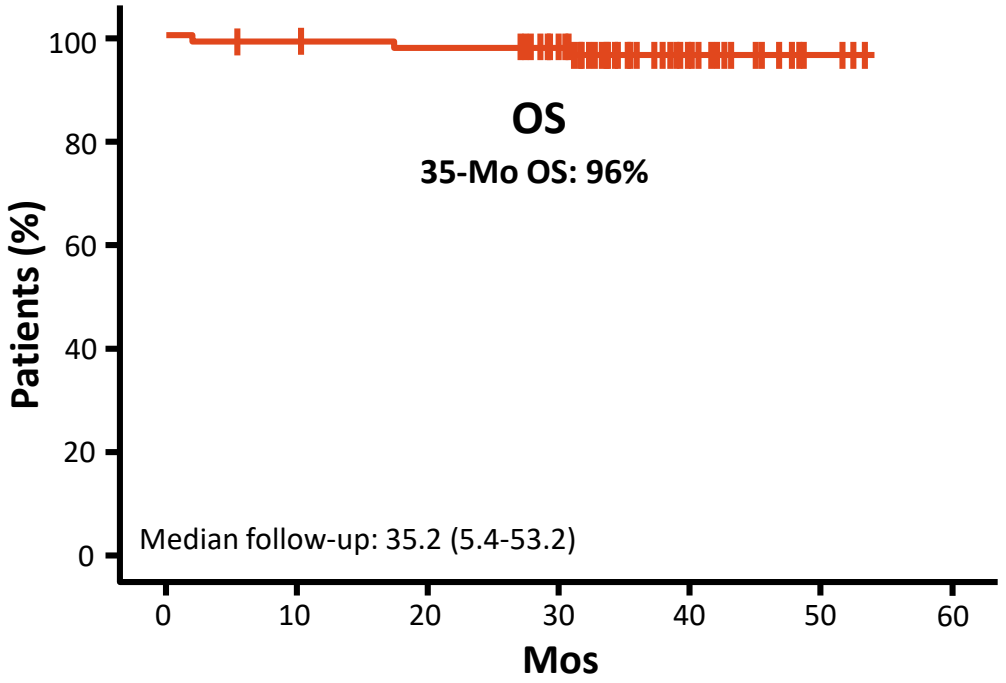
CurativE StrAtegy for High-Risk Smoldering Myeloma (GEM-CESAR): PFS and OS





- 6 patients progressed (biological PD, n = 5)
  - 4 patients with PD were at ultrahigh risk
- 3 patients died; only 1 was considered a treatment-related death

Mateos. ASH 2019. Abstr 781.

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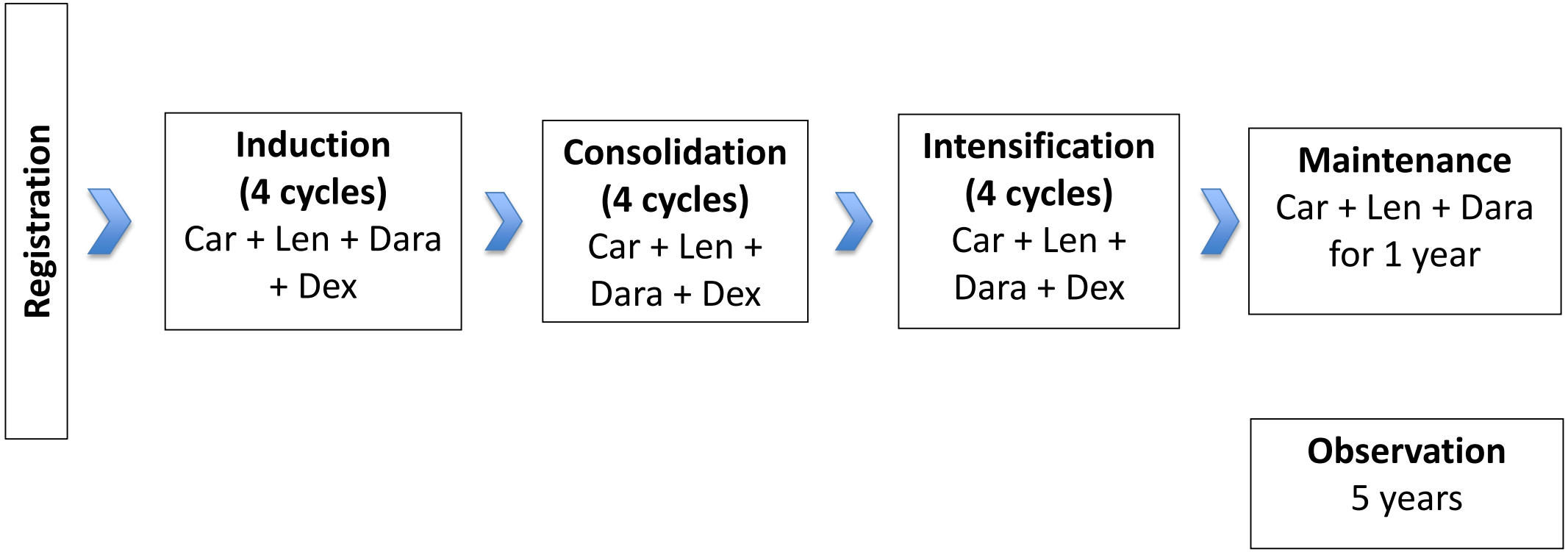
Aggressive Smoldering Curative Approach Evaluating Novel Therapies (ASCENT)



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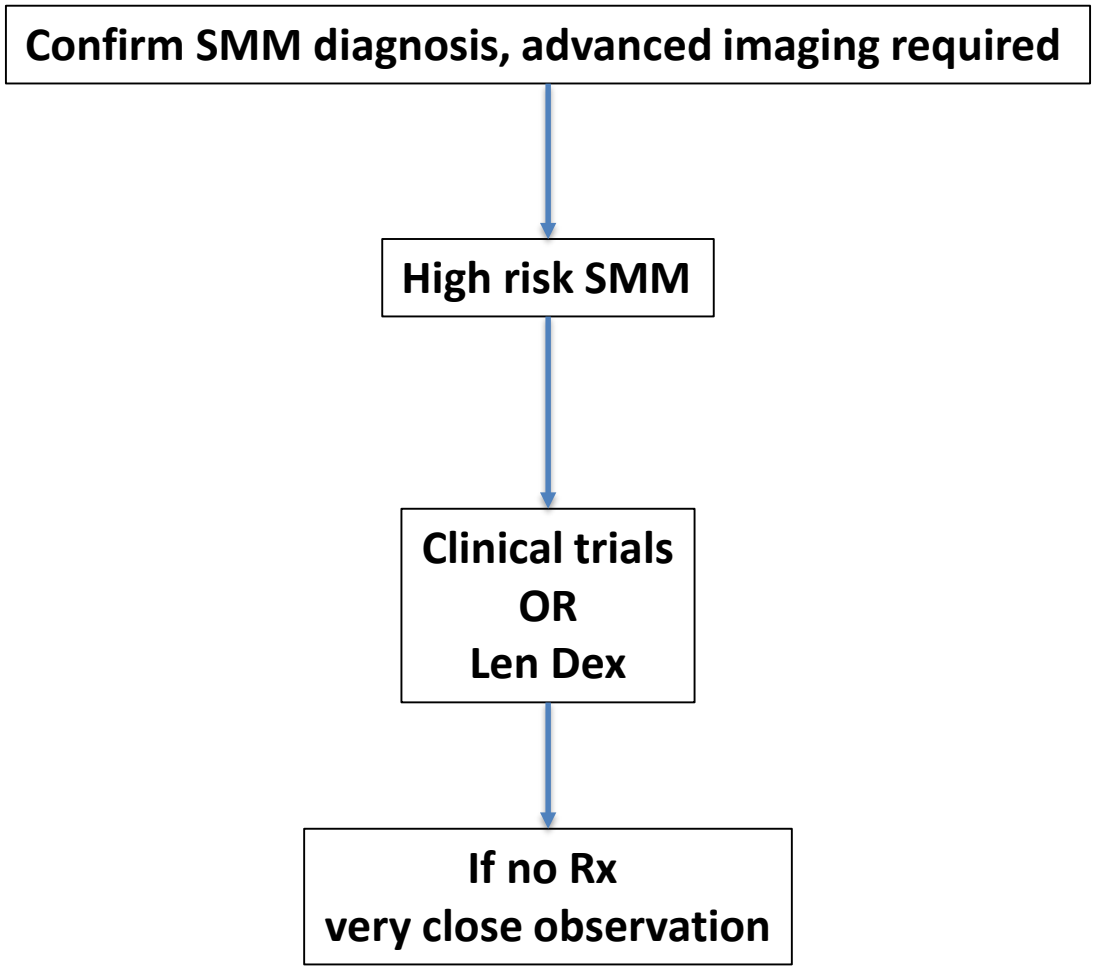
So What Should We Do Today?



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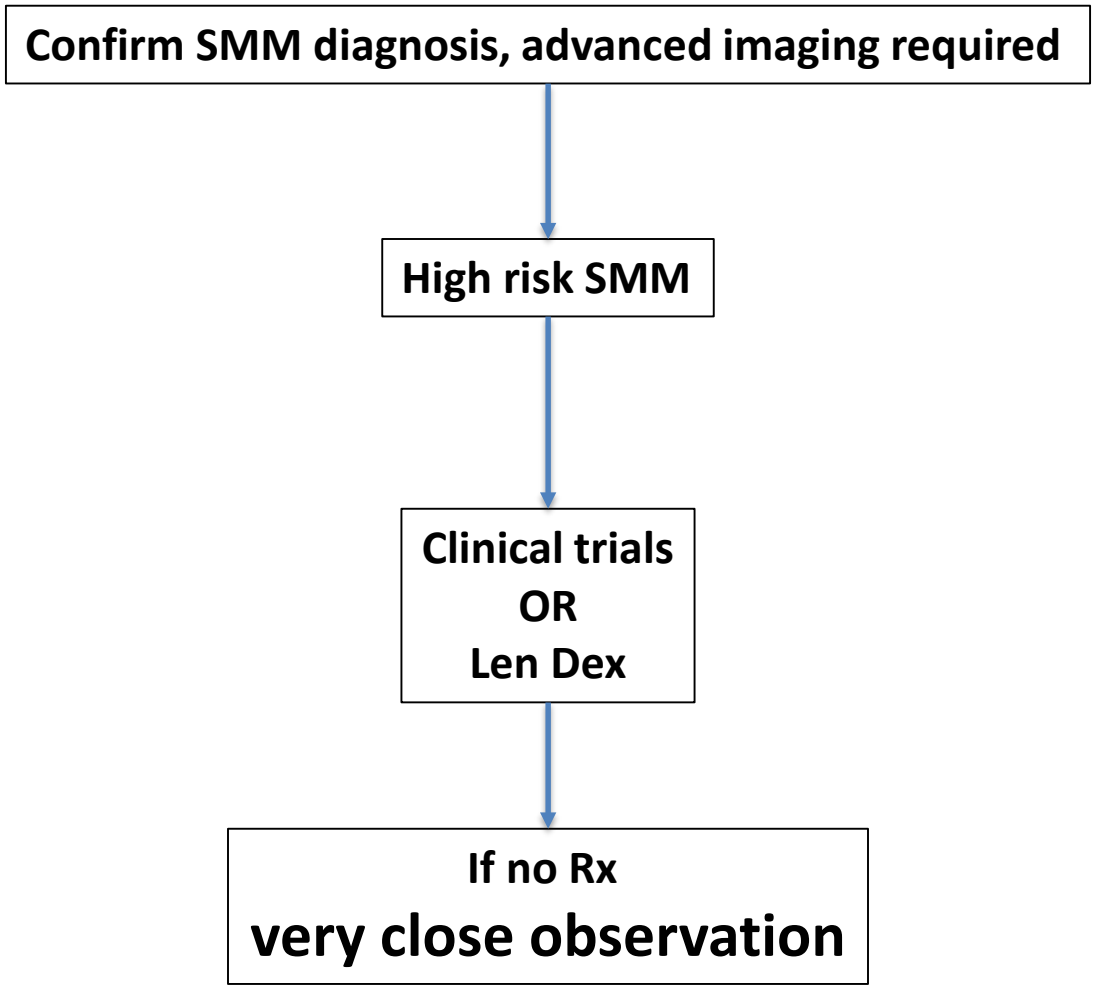

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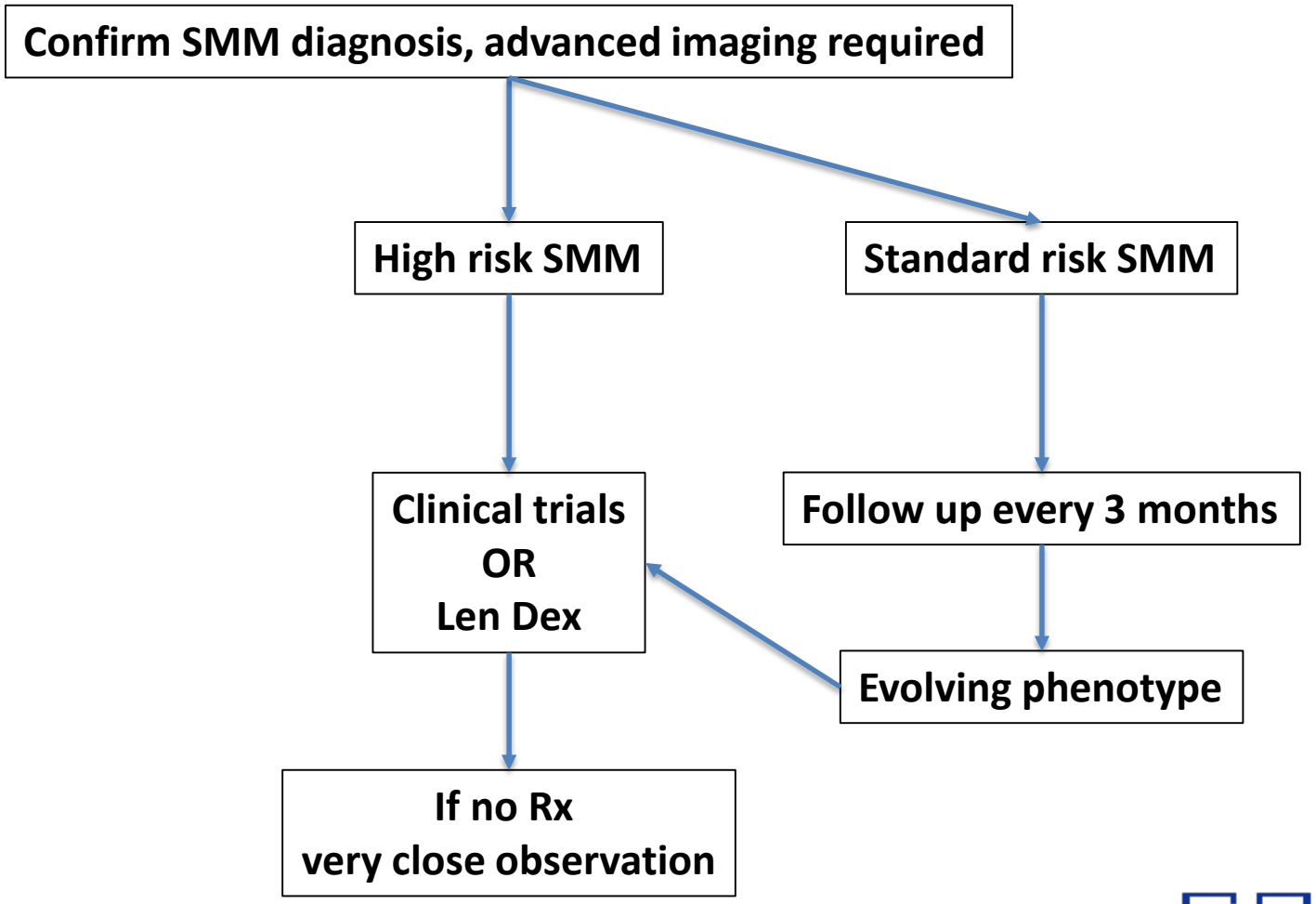

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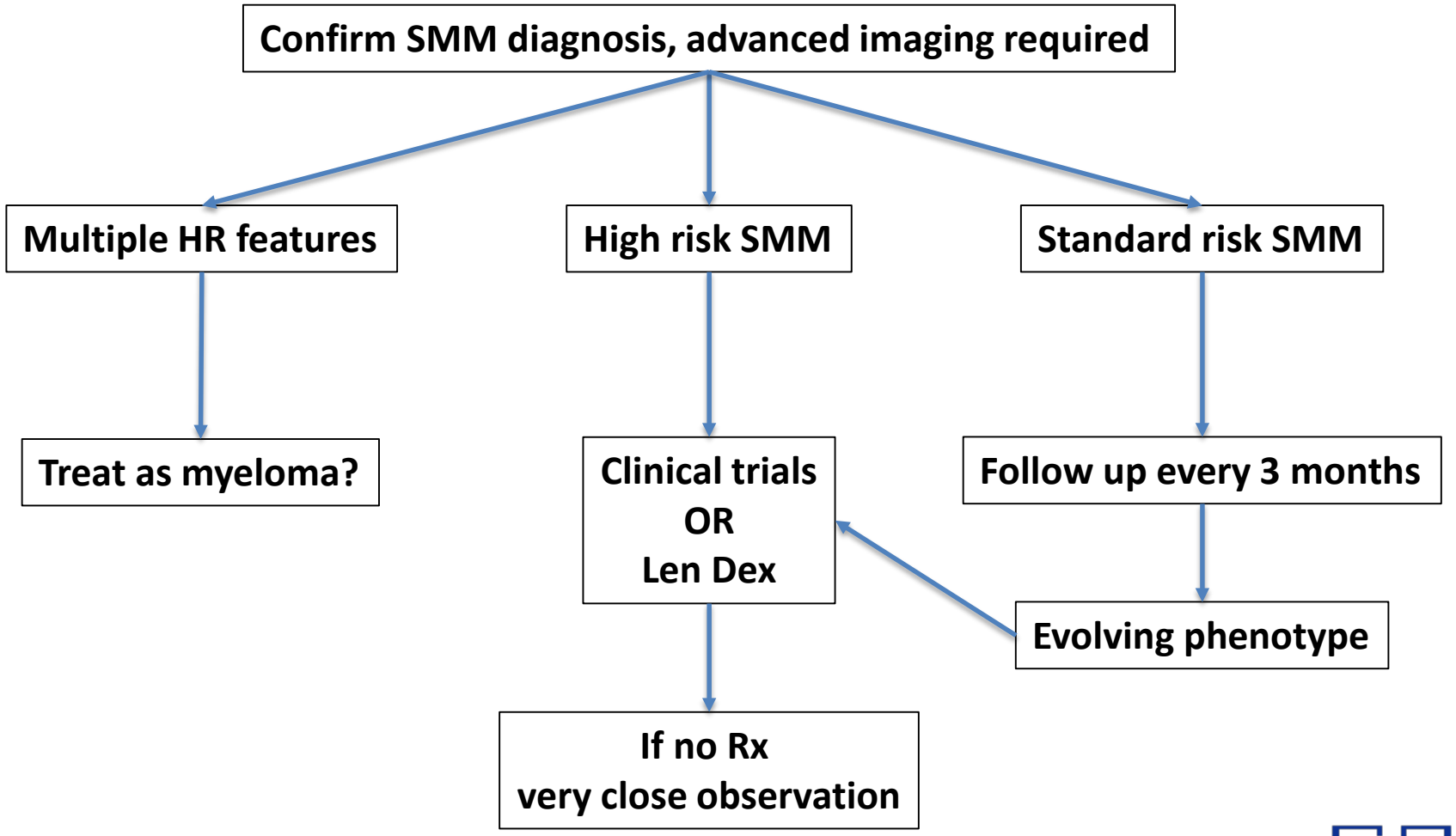

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THANK YOU

Now, let’s return to our patient case

INTERNATIONAL
MYELOMA
FOUNDATION

Patient Scenario

- A 56-year-old woman was noted to have elevated total protein during routine evaluation and underwent additional testing
  - Hb: 13.2 g/dL
  - Serum calcium: 9.2 mg/dL, creatinine: 0.8 mg/dL, LDH: normal, B2M: 3.7 mg/dL
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- Bone marrow biopsy showed 40% plasma cells, FISH shows t(4;14)
- Whole body low-dose CT negative for lytic lesions
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Assessment 1: Now, what would you recommend next for this patient?

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Panel Discussion:
Diagnosis and How to Manage Smoldering Myeloma

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