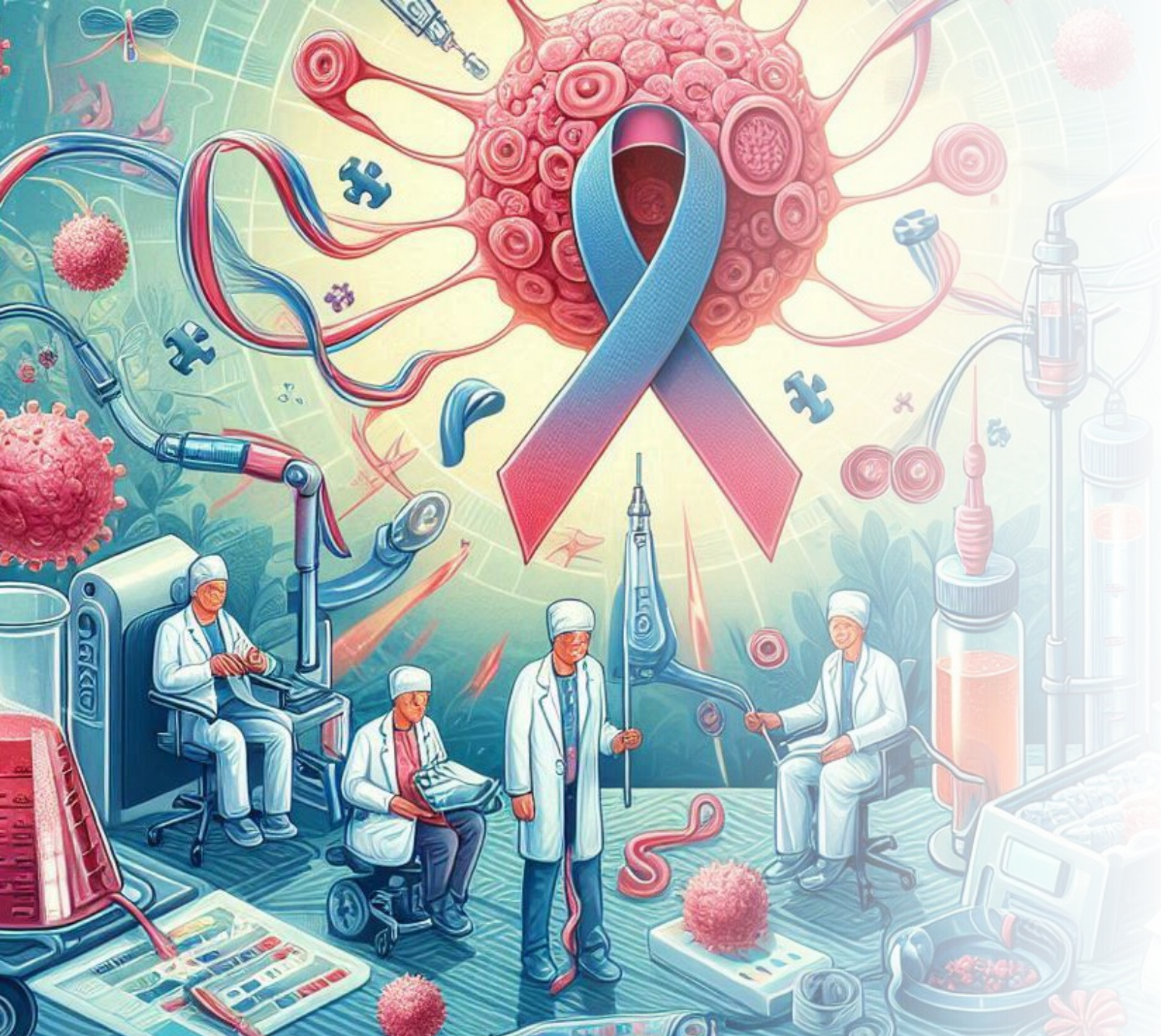




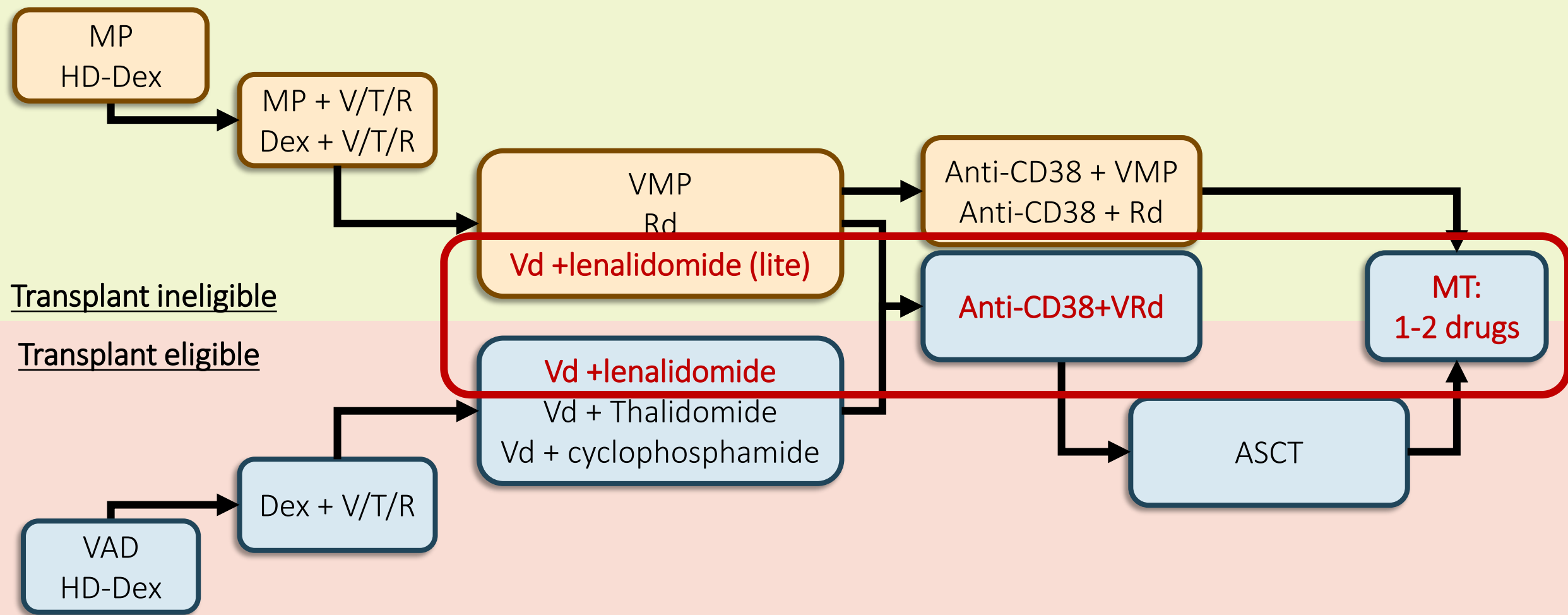
Practical Points in Transplant-Eligible Multiple Myeloma Patients

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Aim of Treatment

Disease

- Rapid and deep control disease: improve organ function
- Long-term control disease: persistent MRD negative, less relapsed, functional cure

Patients

Less toxicity

- Less short and long-term toxicities
- Less stem cell toxicity: melphalan-free regimen

Treatment Selection: Multiple Mechanisms

Disease

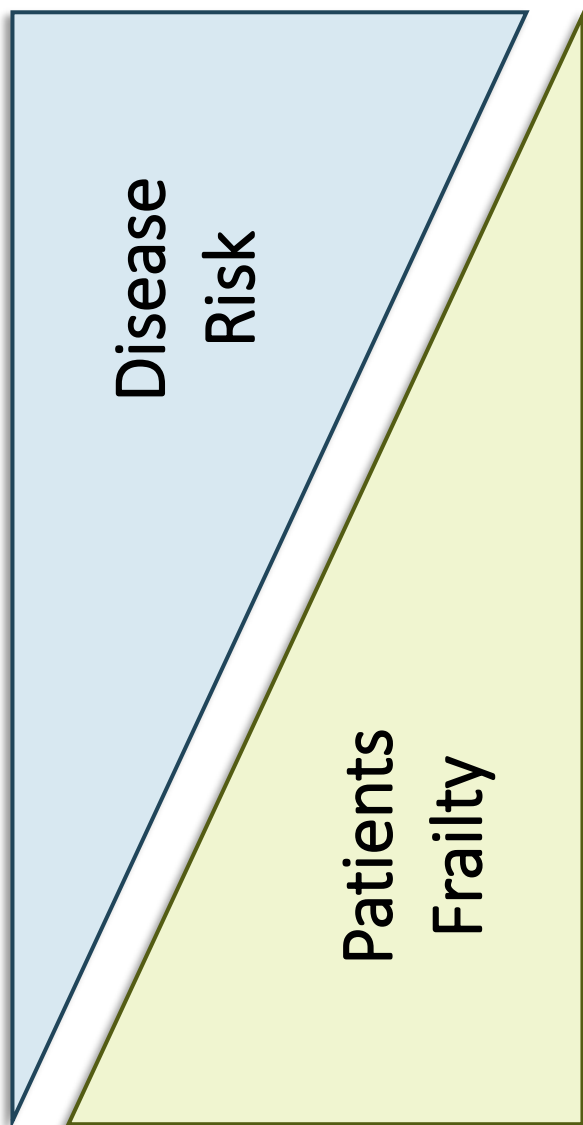
Regimen intensity and Drug selection

- Staging system: ISS, R-ISS, R2-ISS
- Tumor burden, immunoparesis
- Genetics and epigenetic
- Aggressiveness: EMM, PCL

Patients

Tolerability: fitness

- Performance status
- Co-morbidity
- Goal of life



Quadruplet

Triplet → add fourth drug

Doublet → add third drug

ASCT

MT with
1-2 drugs

Induction

In Thailand

ASCT

Role of ASCT:
3 drugs induction
(IFM2009, EMN02)



Relapsed
disease

Factors
EMD

Maintenance

Standard risk
High risk

Case 1: A 54 y/o Male IgA Kappa MM

CRAB

- Back pain
- Hb 9, no hypercalcemia, renal failure

Mass/ PCL

- Plasmacytoma at Rt clavicular 6 x 4 cm.

Clonal disease

- SPEP 8.2, kappa 2384, lambda 7
- BM: plasma cell 60%

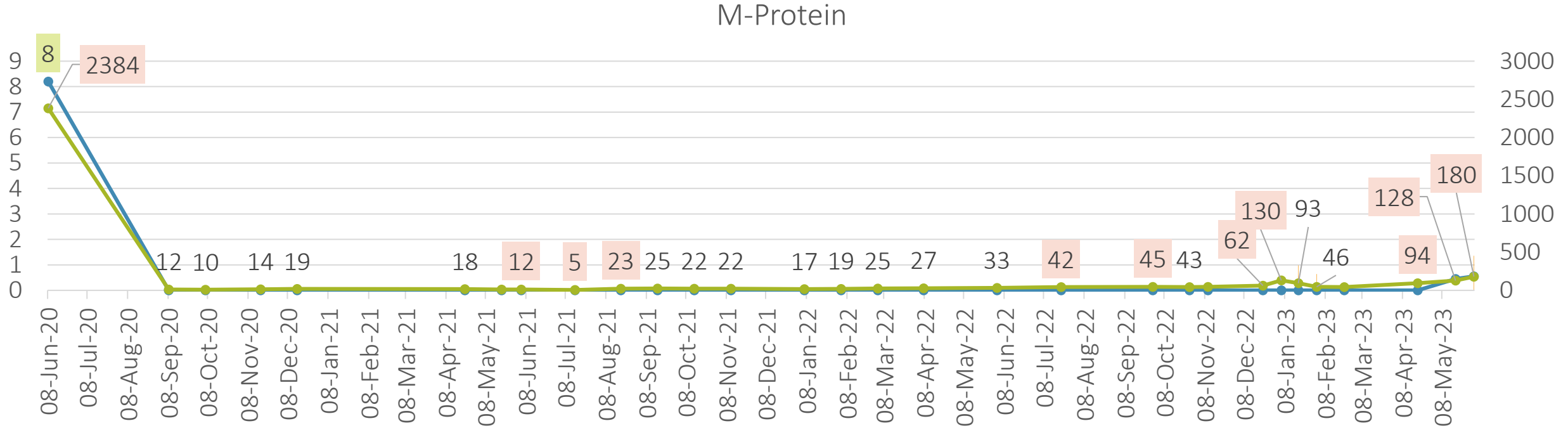
FISH/ Stage

- FISH: negative for t(4;14), t(14;16), del(17p), chrom1
- R-ISS: 3 (B2MG 7.86) (median OS= 38 months)

Dx

- IgA kappa MM, R-ISS 3 with plasmacytoma

Case 1: Progress



Induction:

- VCd x 3: PD (M-protein neg, IF+, clavicular plasmacytoma 75% reduction), new sternal plasmacytoma
- TAd x 1 (waiting for RT)
- Local RT at sternum: CR

ASCT

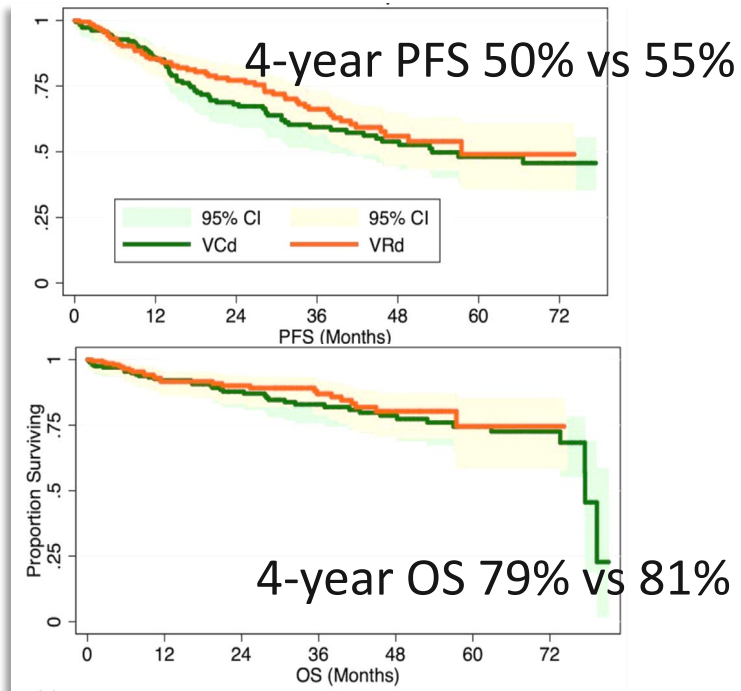
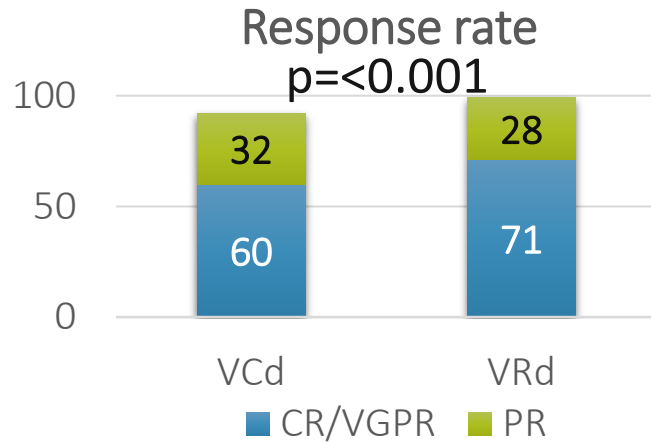
10 Jun 2021

Lenalidomide maintenance

Discussion Point on Case Study (1)

1. The appropriate induction regimen in a country with constrained resources.
2. The appropriate regimen and optimal duration of maintenance?

Bortezomib/dex: Cyclophosphamide → Lenalidomide



- Balkan Myeloma Study Group
- VCD (690) vs VRd (526) → sig diff of patients
- VCD (188) vs VRd (188) → Matched pair ASCT and len-MT

Outcomes (match pair)

- VRd improve response
- VRd and VCd: similar PFS and OS (ASCT, LEN-MT)
- **BUT VRd requires less salvage regimen before ASCT**

Subgroup (all cohort)

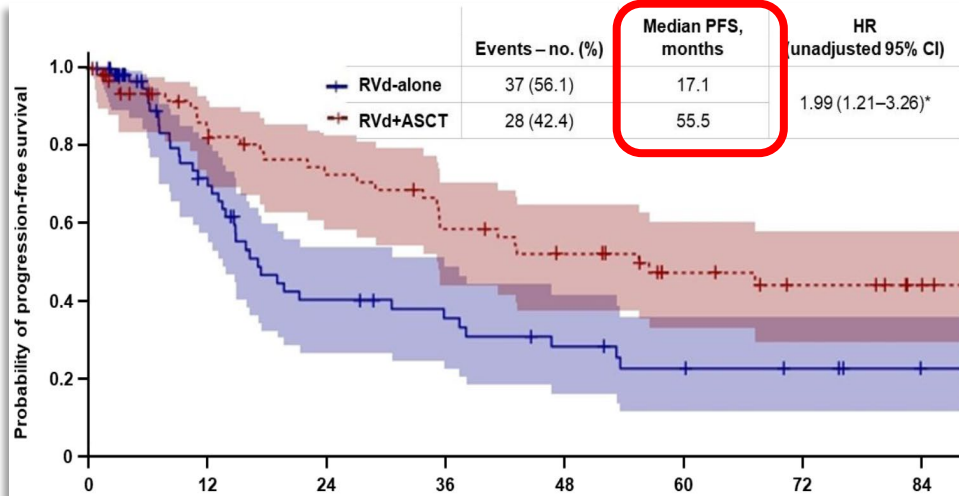
- **VRd sig improves PFS and OS both SR and HR**
 - SR: 4-year PFS 41% vs 52%
 - HR: median PFS of 30 months (poor)

VRD: deeper response, 1 induction regimen

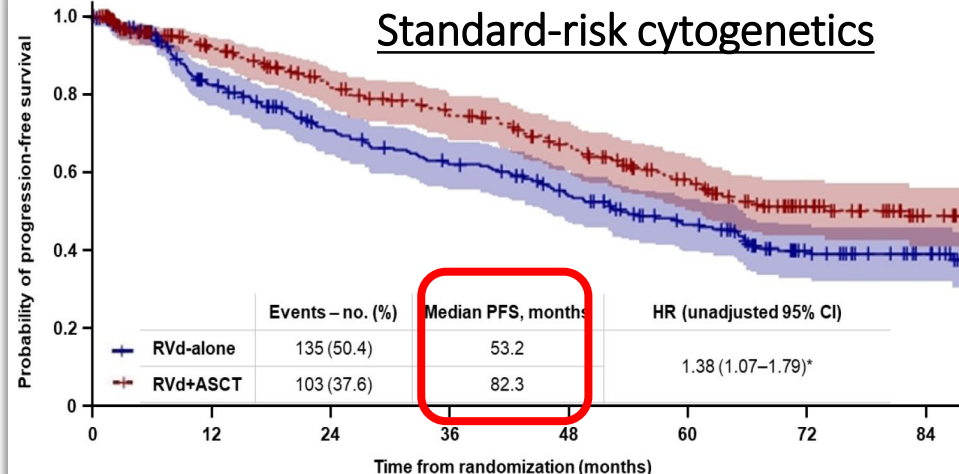
Renal failure: VCd > VRd (toxicities, dose reduction)

Bortezomib/dex + Lenalidomide → ASCT

High-risk cytogenetics



Standard-risk cytogenetics



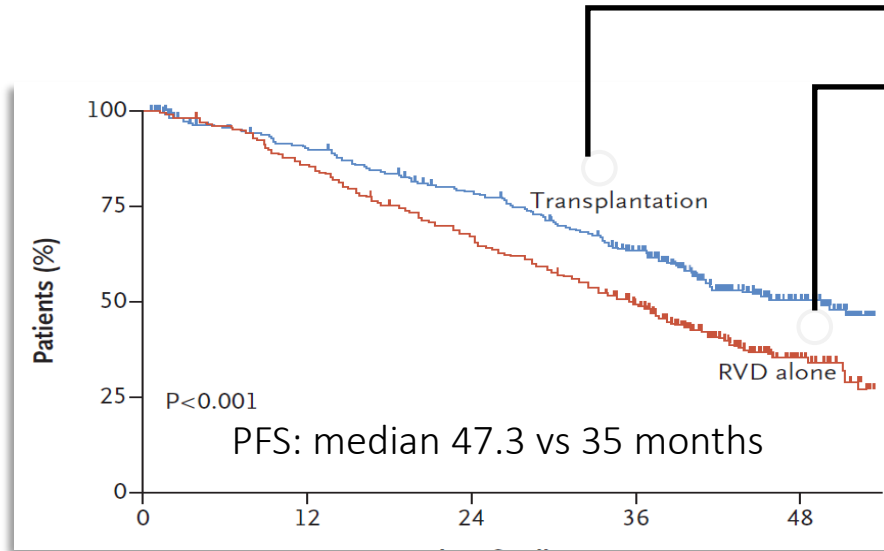
- Median F/U: 76 months
- Duration of MT 36 – 42 months
- ASCT arm:
 - All patients: improve PFS, similar OS
 - HR- and SR-FISH: improve PFS
 - SR: median PFS 82 months (ASCT)
 - HR: median PFS 55 months (ASCT)

Duration of Lenalidomide Maintenance

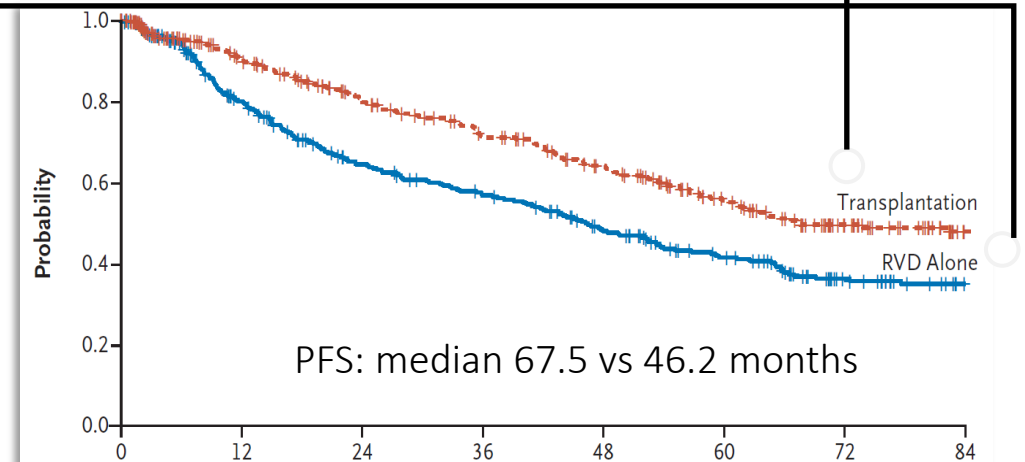
IFM 2009

20.2 months

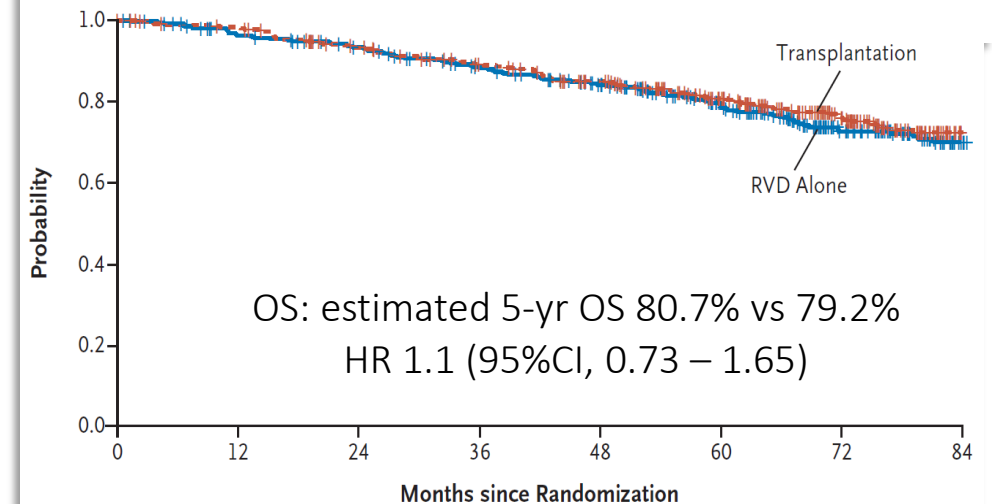
DETERINATION



11.2 months



- Longer lenalidomide maintenance: improve PFS 1 – 2 years in non-ASCT and ASCT
- Myeloma XI: 4 years of MT in SR



Standard Risk Multiple Myeloma

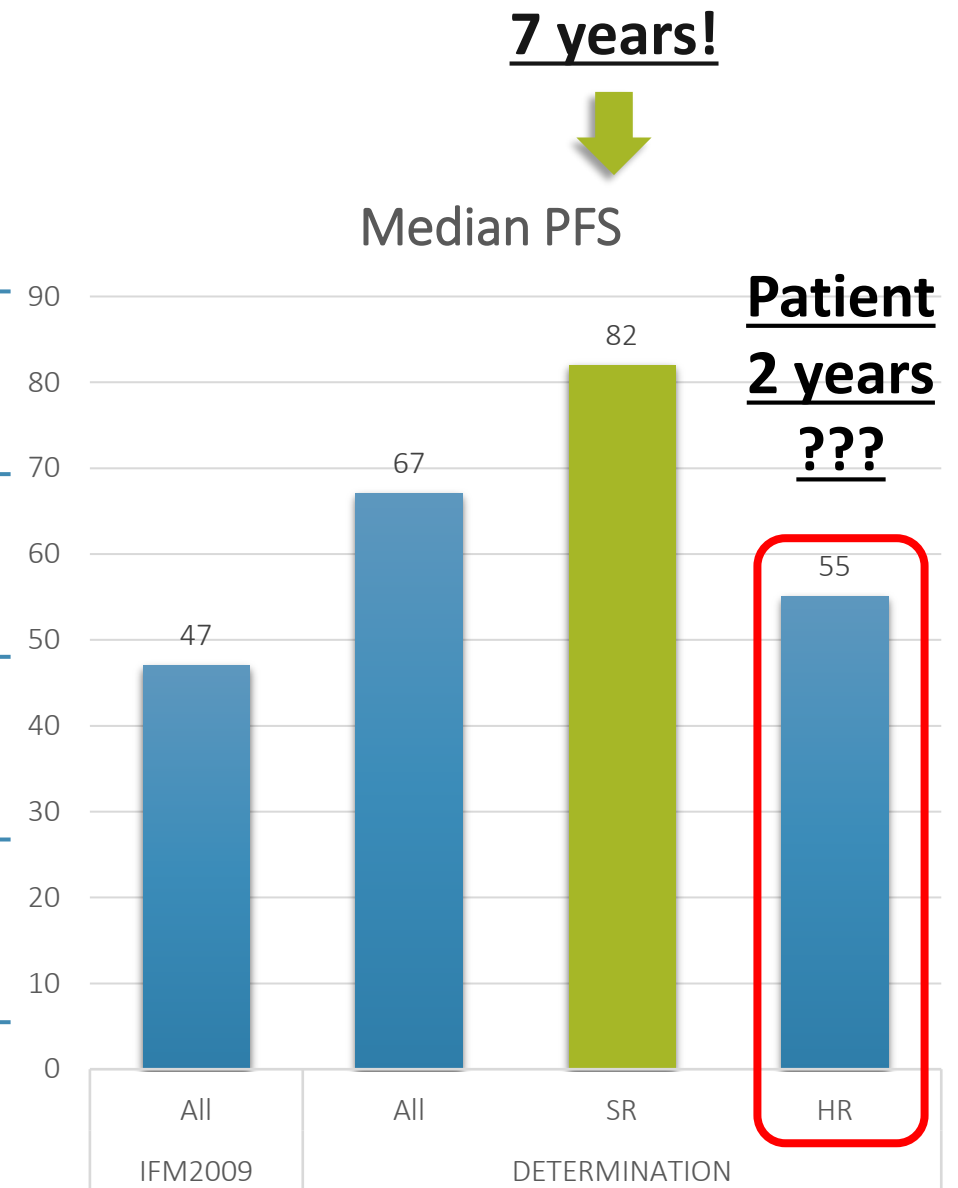
SR: 50% of patients

VRd – ASCT – LEN MT 4 years: median PFS 6-8 years

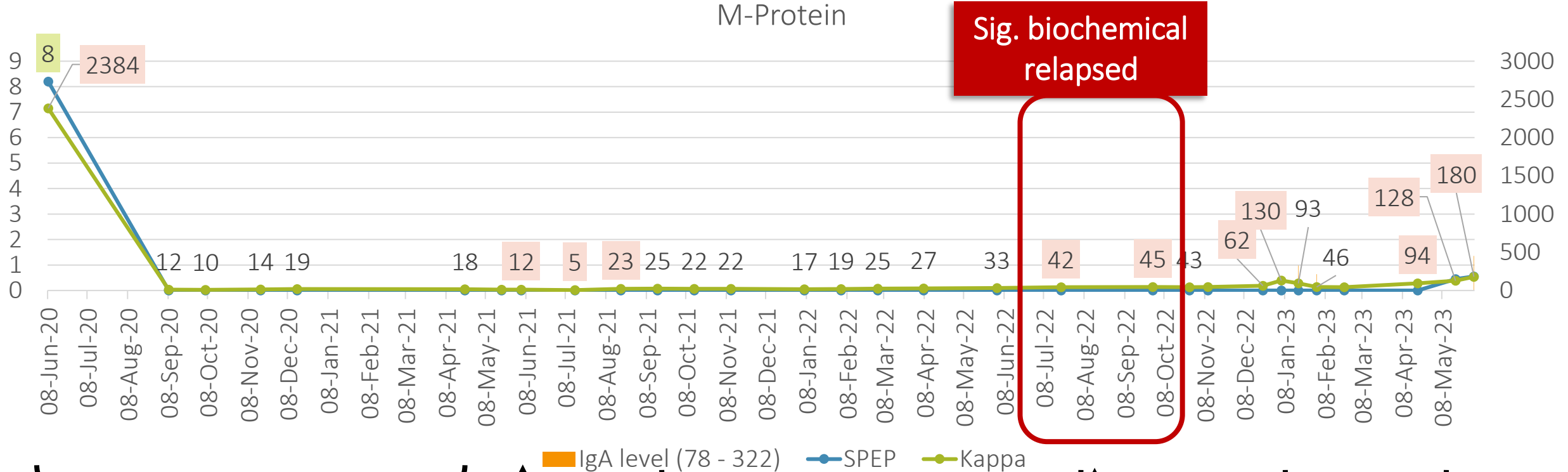
VCd – if VRd not available, improve by ASCT and LEN-MT

VCd in renal failure

HR: VRd not durable enough



Case 1: Progress



Induction:

- VCd x 3: PD (M-protein neg, IF+, clavicular plasmacytoma 75% reduction), new sternal plasmacytoma
- TAd x 1 (waiting for RT)
- Local RT at sternum: CR

ASCT
10 Jun 2021

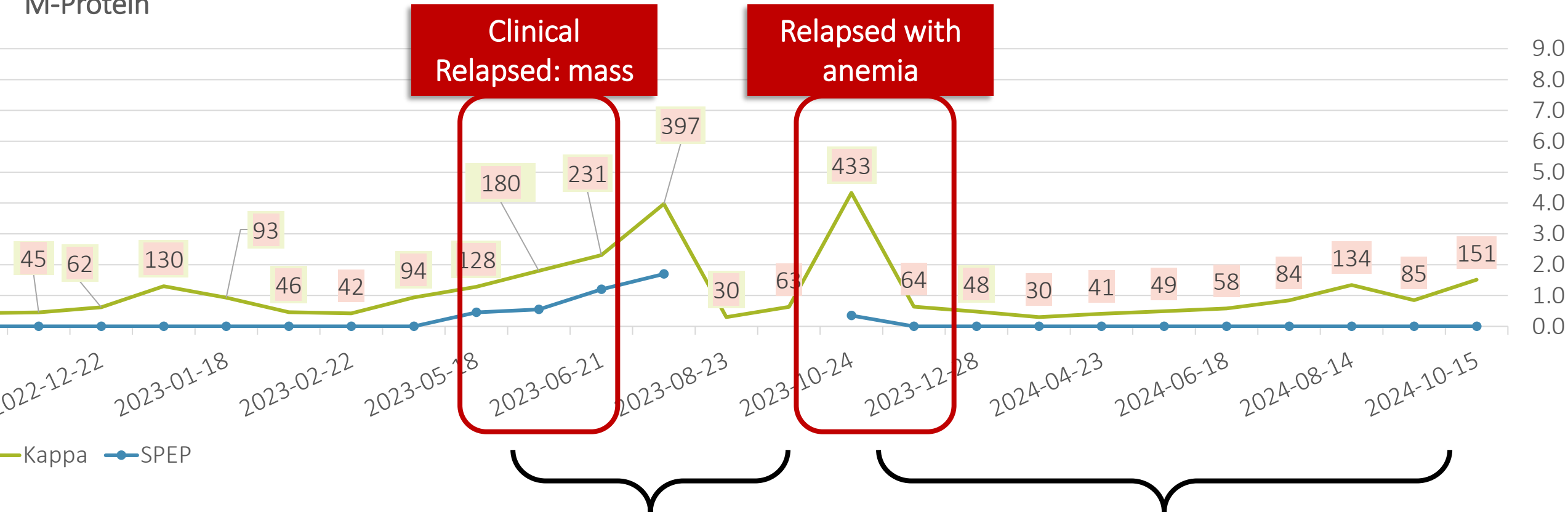
Lenalidomide maintenance

Sig. Biochem
relapsed

Re-induction:

- BM: PC 50%, gain1q21 43%
- D-Vd x 5: PD (new masses)

M-Protein



Re-induction:

- KCd x 1: PD
- KD-PACE x 1: VGPR (intolerance: alternative medicine)

Re-induction:

- Pd x 7: PR then PD; PCd x 4: PD (BM 80%, axillary LN 2 cm, Rt SPC LN 4 x 3 cm.)
 - RRMM, gain1q21 100%, EMD, high tumor burden

Discussion Point on Case Study (2)

3. Factors to consider at relapsed disease
4. The appropriate treatment in patients with plasmacytoma

Treatment Selection

Patients

- Performance status
- Co-morbidity
- Goal of life

Tolerability

Disease

- Staging system: ISS, R-ISS, R2-ISS
- Tumor burden (LDH, β 2-microglobulin), immunoparesis
- Genetics and epigenetic
- Aggressiveness: EMM, PCL

Regimen intensity
and
Drug selection

Prior Treatment

What is the consideration for previously used drugs

Depth of response
Duration of response (DOR)
Treatment free interval (TFI)
Residual adverse effects

Response to Tx

- Primary refractory
- Early relapsed disease (< 12 months)

Survival

Depth of response
Duration of response (DOR)
Treatment free interval (TFI)
Residual adverse effects

```
graph TD; A["Depth of response<br/>Duration of response (DOR)<br/>Treatment free interval (TFI)<br/>Residual adverse effects"] --> B["Biochemical or clinical<br/>relapsed disease"]; A --> C["Retreatment or<br/>new treatment"]; A --> D["Second ASCT"];
```

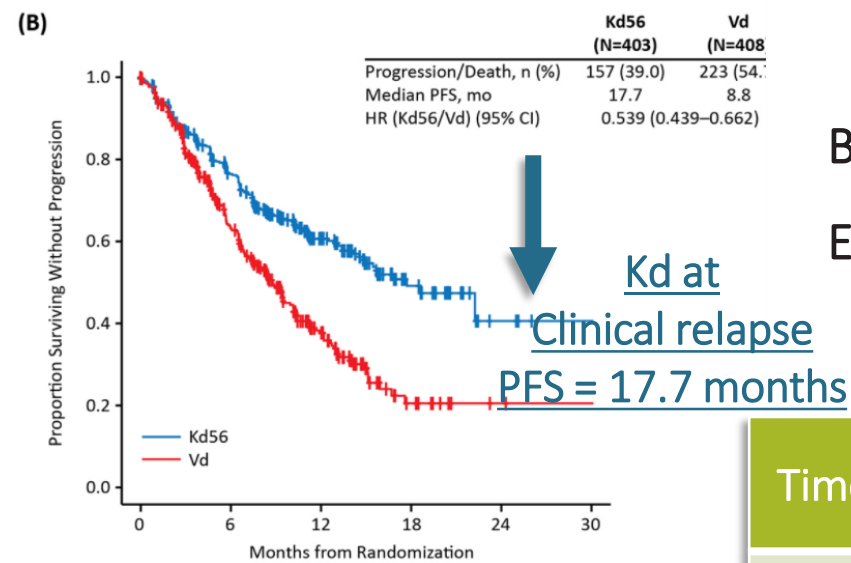
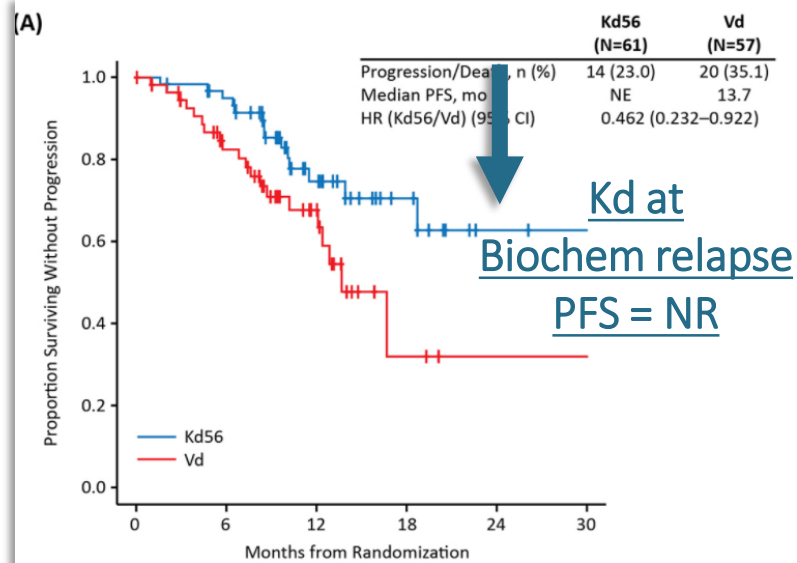
The diagram is a flowchart with a single top node and three bottom nodes. The top node is a light blue rounded rectangle containing four lines of text: 'Depth of response', 'Duration of response (DOR)', 'Treatment free interval (TFI)', and 'Residual adverse effects'. A vertical line descends from the bottom of this node, then a horizontal line branches out to the left, middle, and right. From each end of this horizontal line, a vertical arrow points down to one of the three bottom nodes. The left node is a light green rounded rectangle with the text 'Biochemical or clinical relapsed disease'. The middle node is a light orange rounded rectangle with the text 'Retreatment or new treatment'. The right node is a light red rounded rectangle with the text 'Second ASCT'.

Biochemical or clinical
relapsed disease

Retreatment or
new treatment

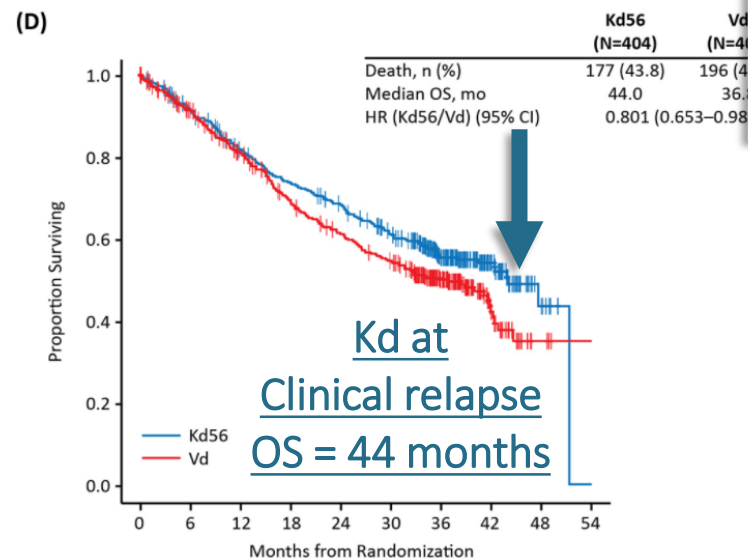
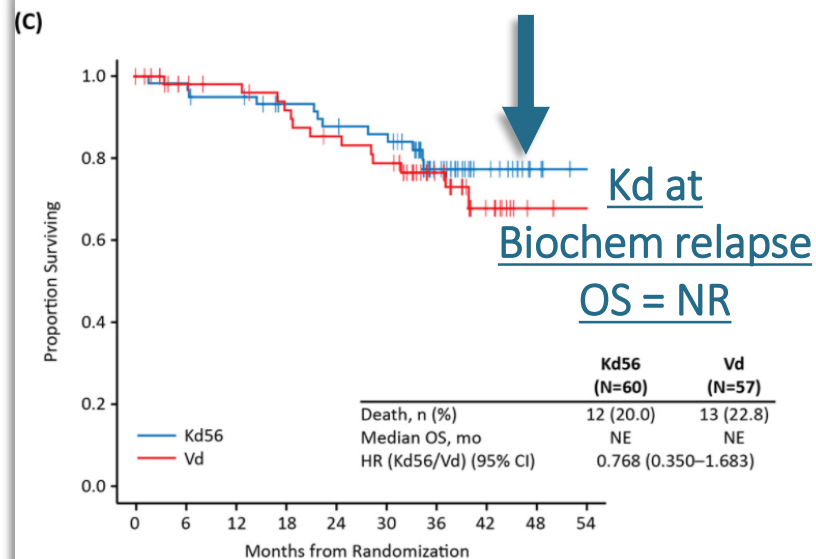
Second ASCT

Should We Start Treatment at Biochemical Relapse?



Biochem to clinical relapse: 5.1 months

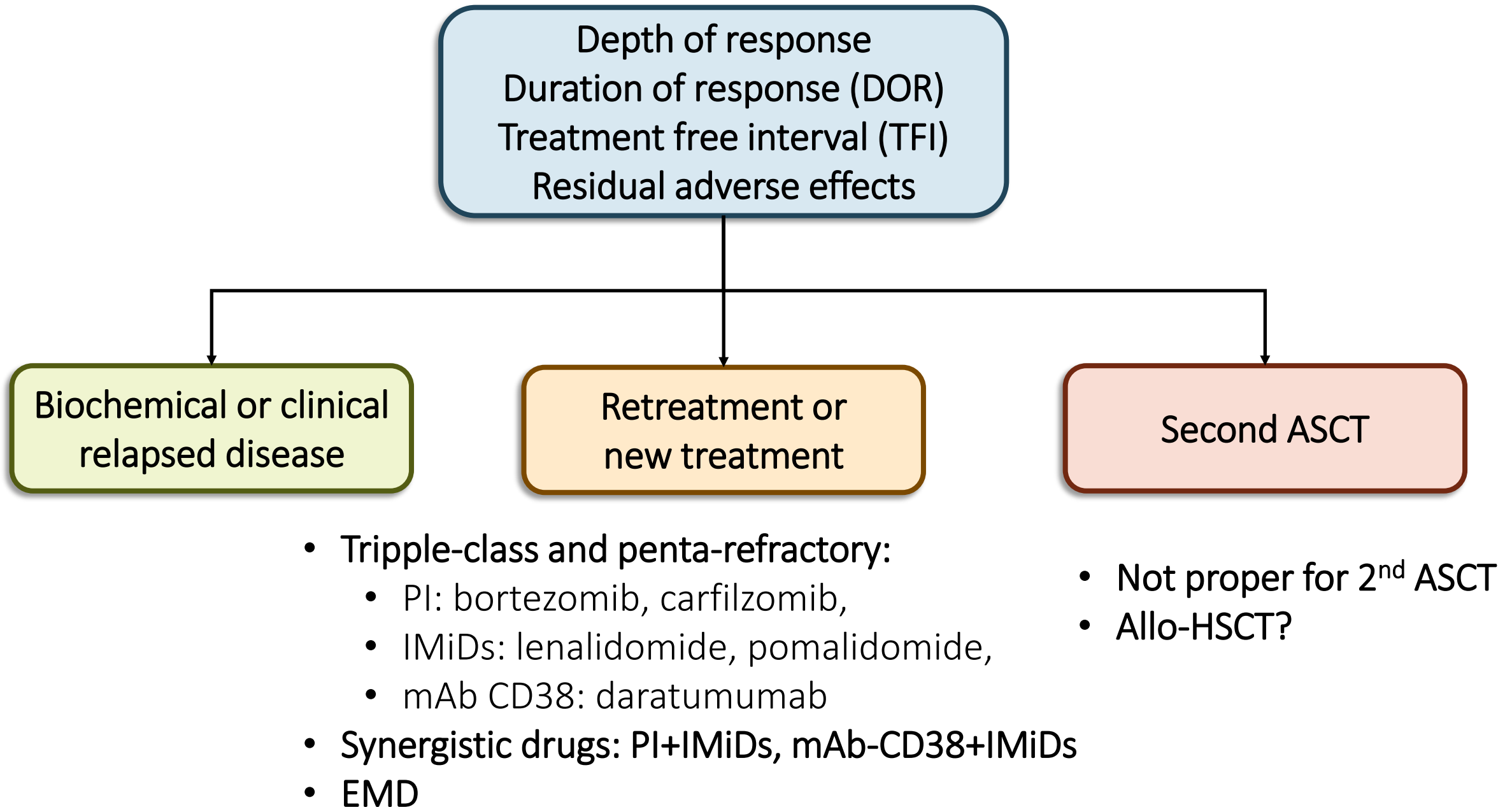
ENDEAVOR subgroup: Kd56 arm



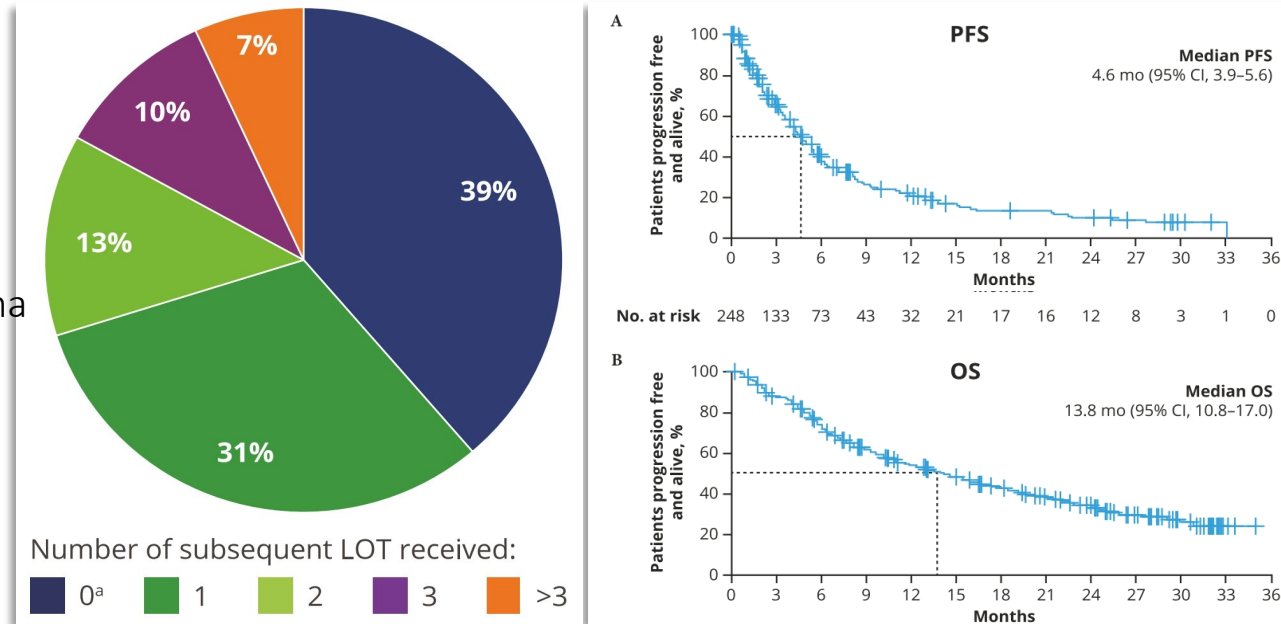
Time of retreatment	PFS (months)	OS
Biochemical relapse	Not reach	Not reach
Clinical relapse	17.7	Not reach

Controversy

- Improve outcomes
- 10% of Biochem relapse: long-term stable disease
- High-risk, end organ damage



- Triple-class
 - Proteasome inhibitor
 - Immunomodulatory drugs
 - Monoclonal Ab to CD38
- EMD, extramedullary plasmacytoma
- LOT, line of therapy

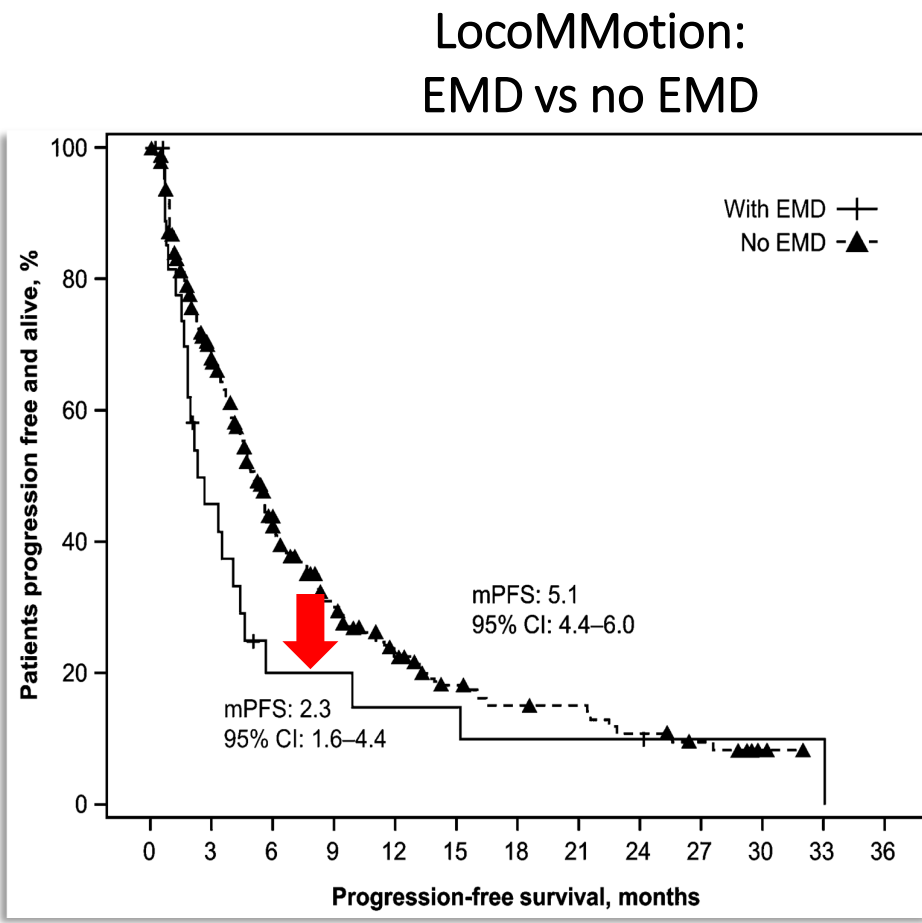
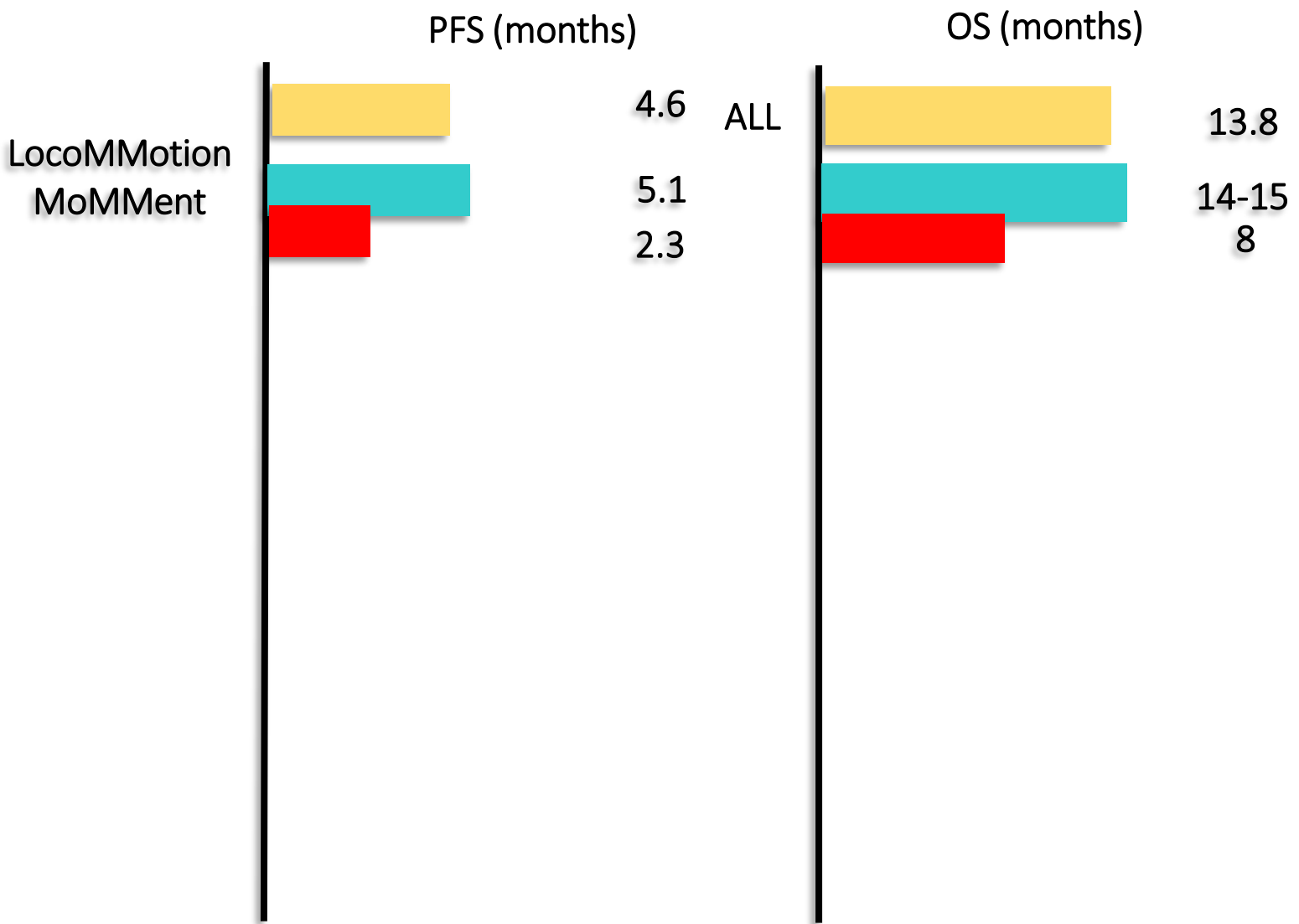


Triple-class exposure and refractory to PI, IMiDs (LocoMMotion): Median 4 (2-13) LOT

- 248 Patients: 73% triple class refractory, 92% refractory to last LOT

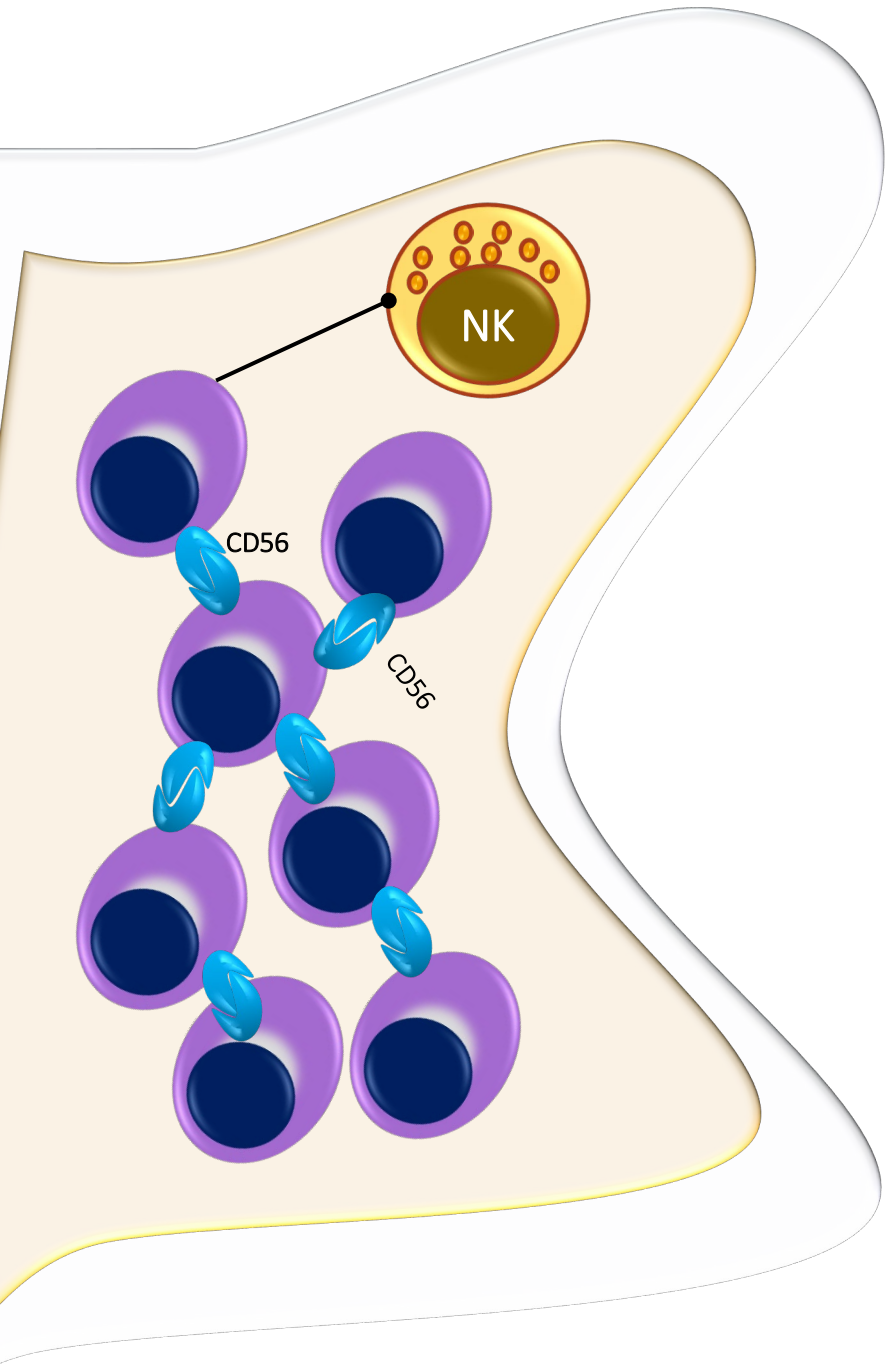
Poor outcome

- **91 unique regimens:** steroid (92%), PI (54%), IMiDs (49%), anti-CD38 (10%), belantamab (3%)
- **ORR: 31%; CR/VGPR/PR: 0.4/13/18**
- **Median PFS/OS: 4.6/13.8 months** (poorer: EMD, penta-refractory, low platelet, high LDH)
- Median duration of Tx: 4 months
- 60% receive subsequent regimen

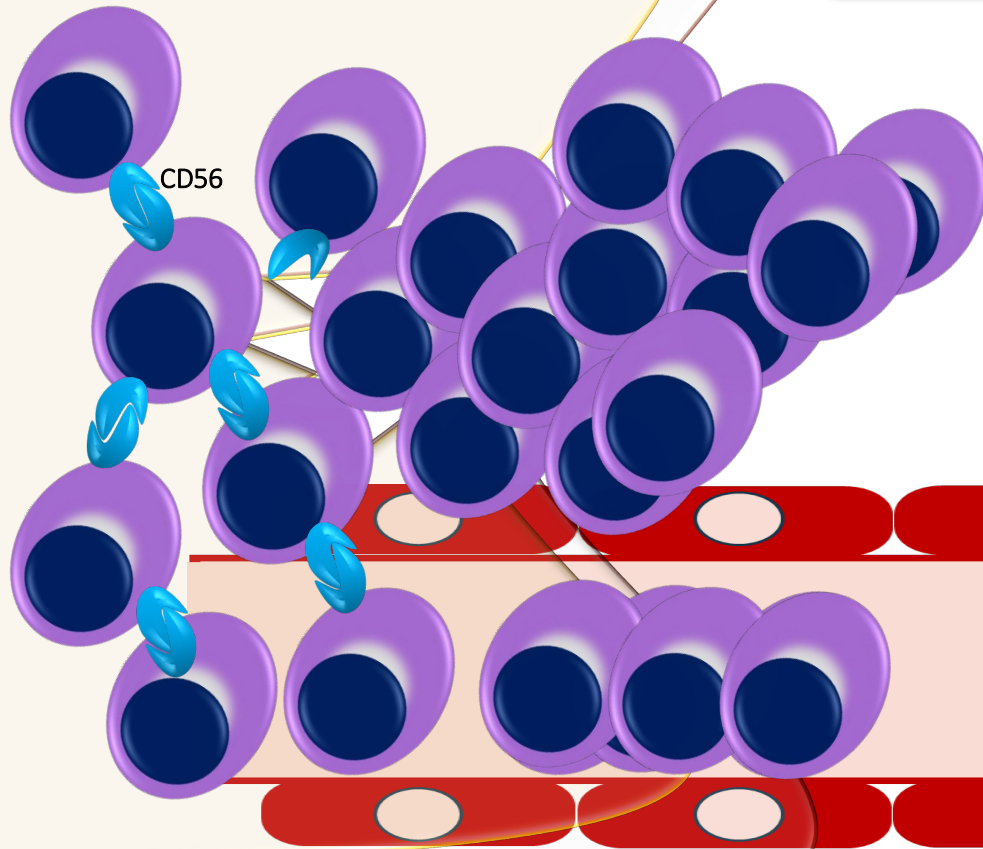


No EMD
EMD

	Definition
Solitary plasmacytoma	Single mass of clonal plasma cells (bone or extramedullary); no other symptoms
Paraskeletal plasmacytoma (PS)	Soft tissue plasmacytoma directly growth from skeletal tumors following cortical bone disruption
Extramedullary plasmacytoma (EMD)	Aggressive form of MM with soft tissue plasmacytomas result from hematogenous spread
Plasma cell leukemia (PCL)	Aggressive form of MM with circulating plasma cells $\geq 5\%$

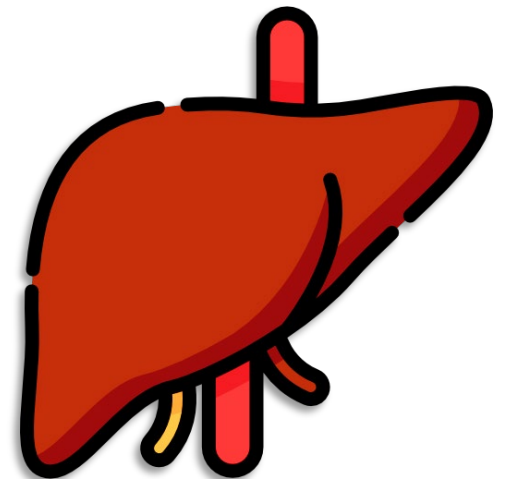
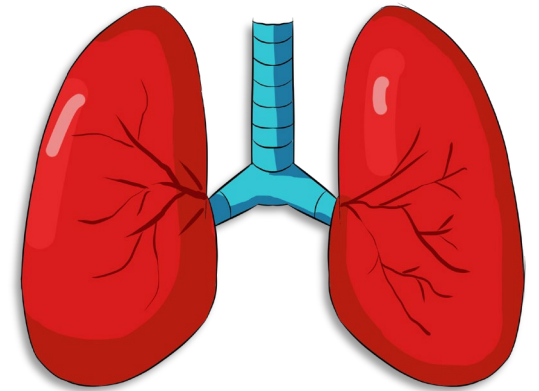
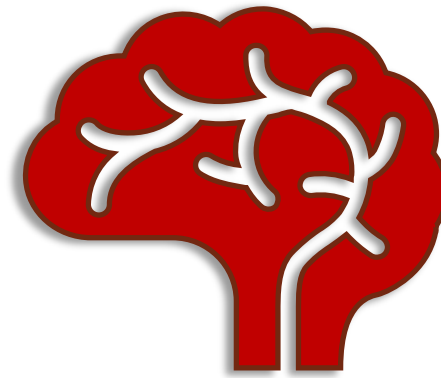


Paraskeletal
plasmacytoma (PS)



Downregulate CD56
Upregulate CD44:
motility, proliferation

Extramedullary
Plasmacytoma (EMD)



Paraskeletal
plasmacytoma (PS)

Extramedullary
Plasmacytoma (EMD)

Incidence

5 – 24%

Physician awareness
Diagnostic approach tools

NDMM: 0.5 – 5% → 6 – 10%
RRMM: 4 – 14%

Prognosis

Better than EMM

Poor
Esp. CNS and liver

Treatment

?

Treatment: Paraskeletal Plasmacytoma (1)

Alkylating agents

- Cyclophosphamide, melphalan
- ASCT: HD-melphalan

Proteasome inhibitor

- Bortezomib: good impact
- Carfilzomib: no data
- Ixazomib: no data

IMiDs

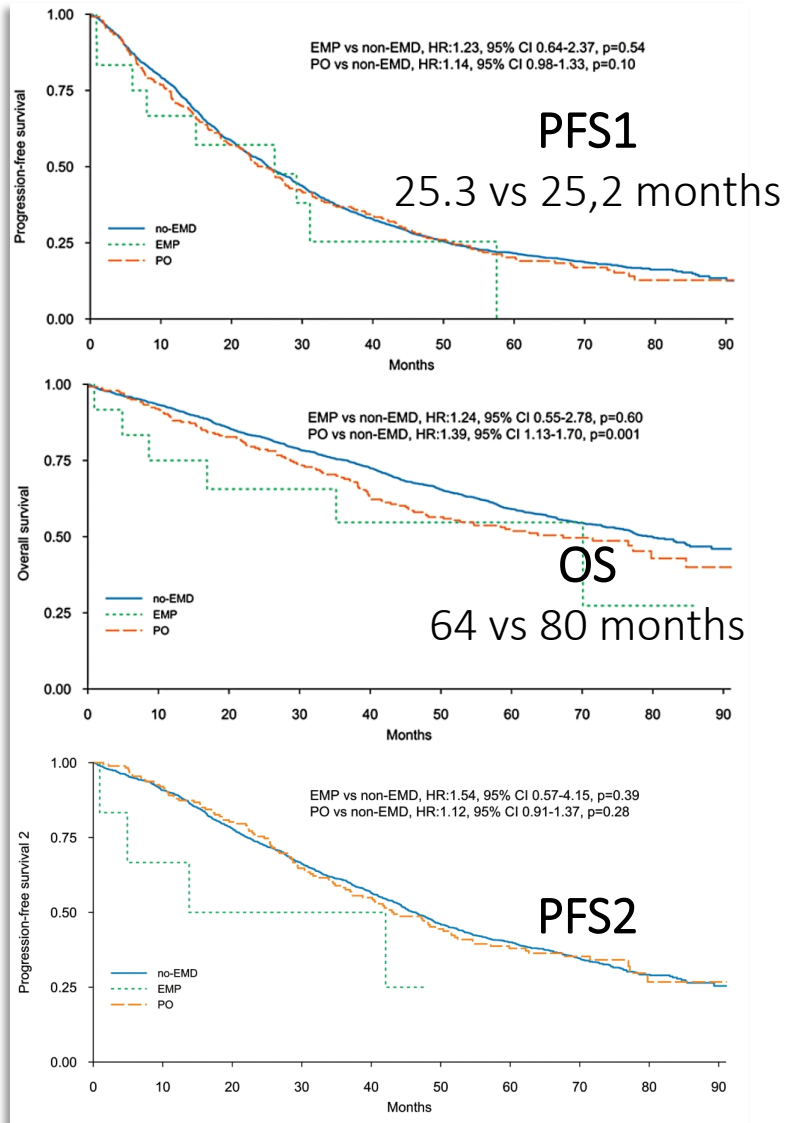
- Thalidomide: no efficacy
- Lenalidomide: no data
- Pomalidomide: ORR 30%, controversy

mAb-CD38

- Daratumumab: no data

Treatment: Paraskeletal Plasmacytoma (2)

- 2,332 NDMM: 267 PS, 12 EMD
- Tx: PI 25%, IMiDs 60%, PI+IMiDs 15%
- Similar PFS btw PS vs non mass, but lower OS
- Novel treatment: improve outcomes in PS



TE

- VTd/PAD/VCd/VRD +/- daratumumab

TIE

- VMP +/- daratumumab
- VRd +/- daratumumab
- VCd +/- daratumumab

ASCT
(No benefit of tandem in PS)

Local RT: spinal cord compression, pain, bulky mass, persistent local disease

Paraskeletal
plasmacytoma (PS)

Extramedullary
Plasmacytoma (EMD)

Incidence

5 – 24%

NDMM: 0.5 – 5% → 6 – 10%
RRMM: 4 – 14%

Prognosis

Better than EMM

Poor
Esp. CNS and liver

Treatment

- Conventional CMT
- Multiple novel agents:
PI plus IMiDs
- ASCT

?

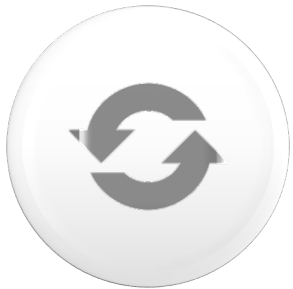
Considerations



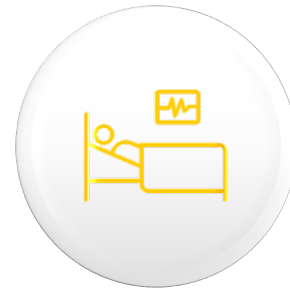
Cannot compare with early relapsed studies: POLLUX, CASTOR, OPTIMISMM, etc



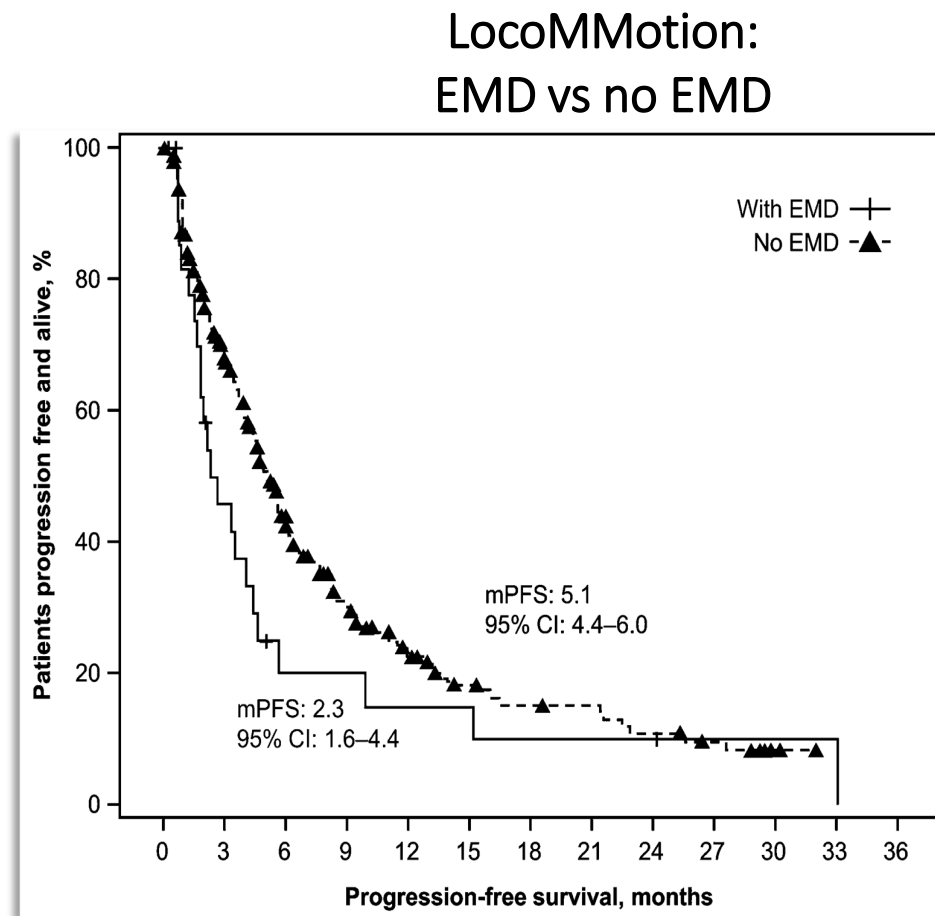
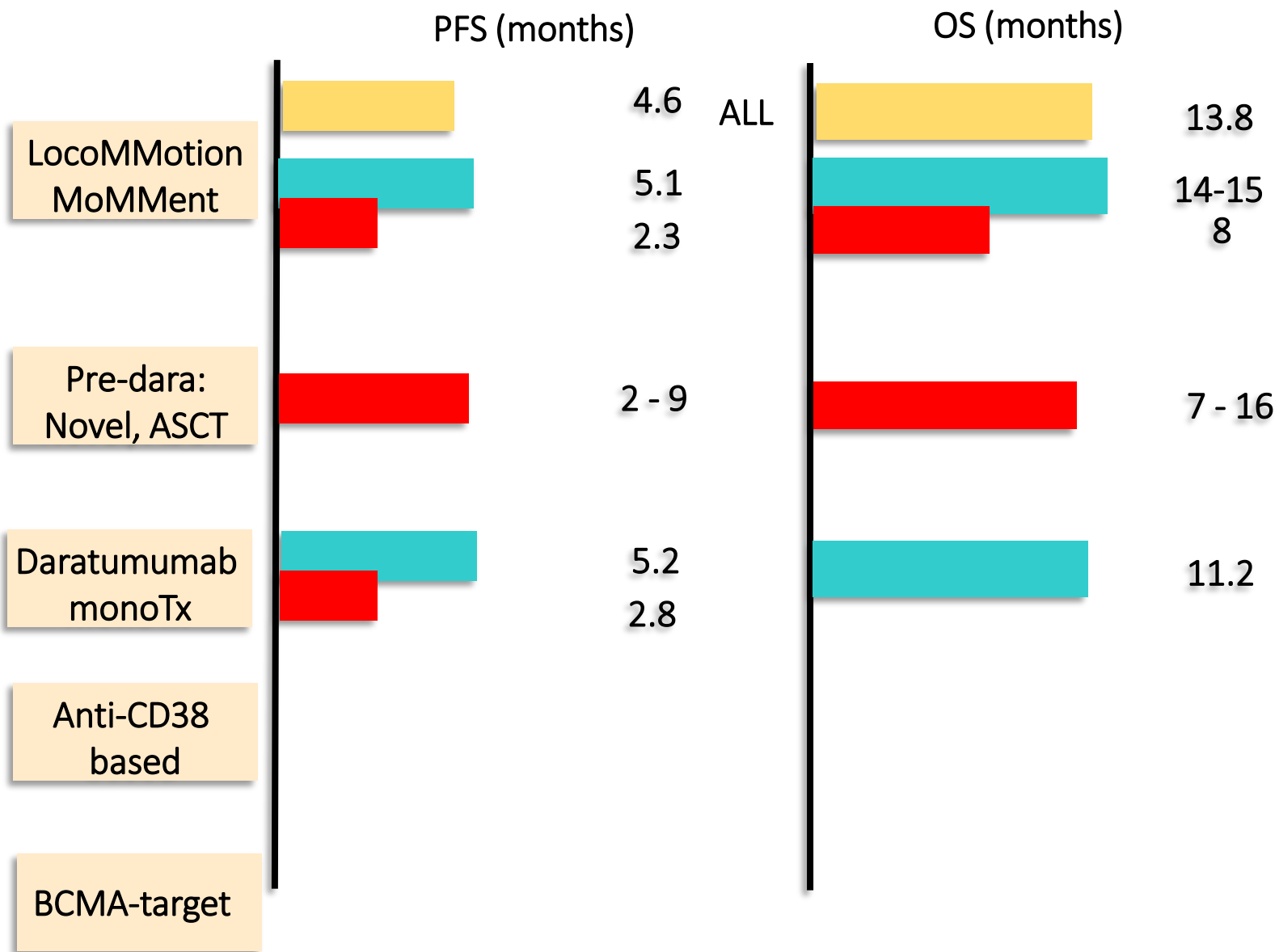
Late relapsed disease: phase 3 new agents, monotherapy



Combination regimen:
Retrospective, RWCP



Included patients,
treatment protocol,
evaluation response varies



Phase 1

MMY1003

- Dara i.v. 2/50

PAVO

- Dara s.c 4/120

COLUMBA

- Dara i.v. 18/259
- Dara s.c. 17/258

Phase 3

POLLUX

- D-Rd: 9/286
- Rd: 6/283

APOLLO

- D-Pd: 15/1516
- Pd: 8/153

CASTOR

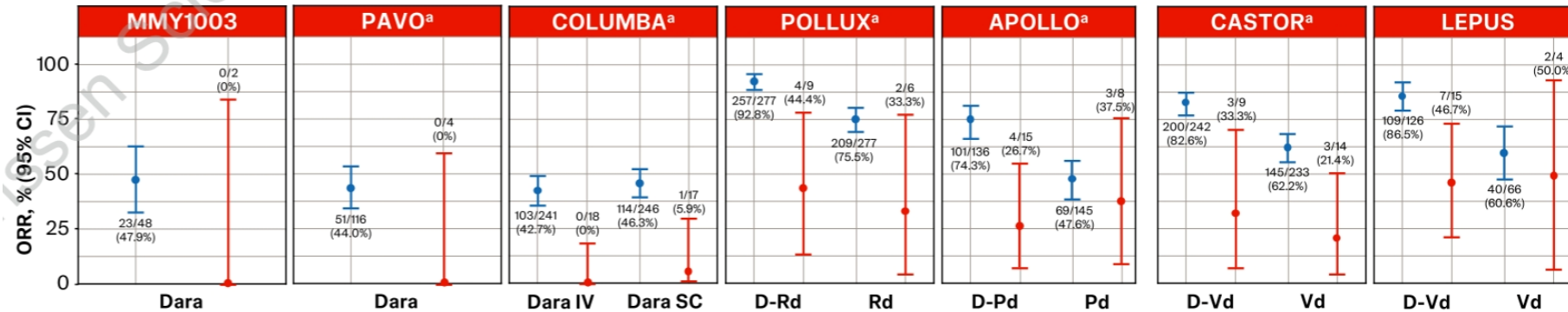
- D-Vd: 9/251
- Vd: 14/247

LEPUS

- D-Vd: 15/141
- Vd: 4/70

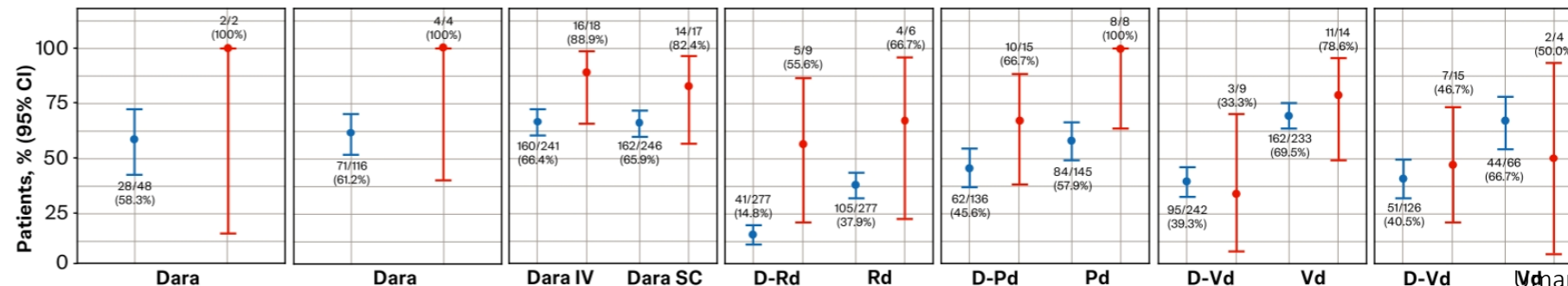
No. of pt
EMD/All

Figure 2A: Estimated ORR



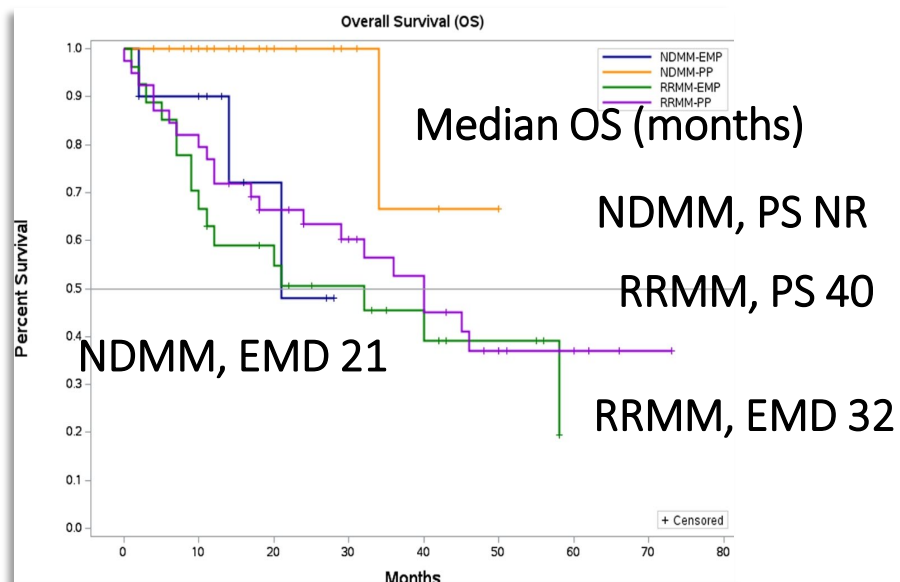
Lower
response rate

Figure 2B: Estimated proportion of patients who progressed or died in the first year of treatment



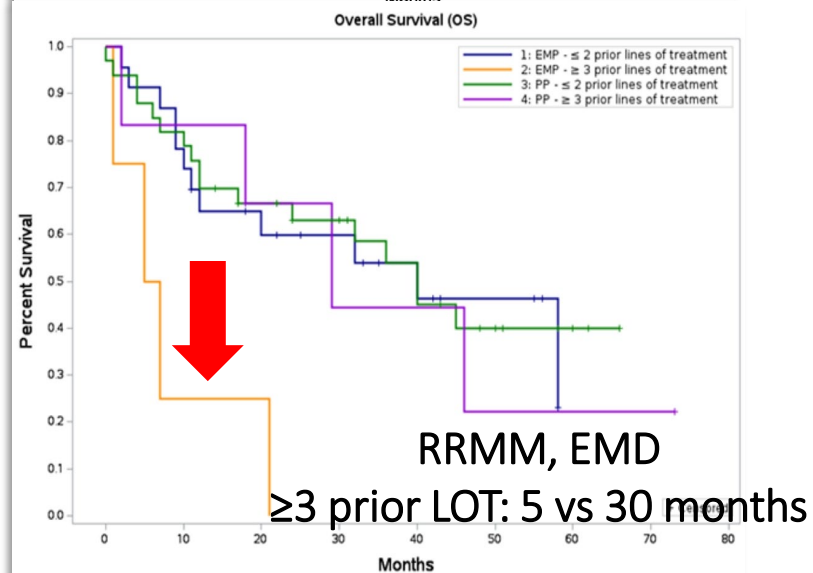
Higher
death rate

Anti-CD38 Based Regimen



Daratumumab-based regimen

- D-VTd, D-Rd, D-VMP: EMD poorer OS comparing with PS
- No data on median prior LOT



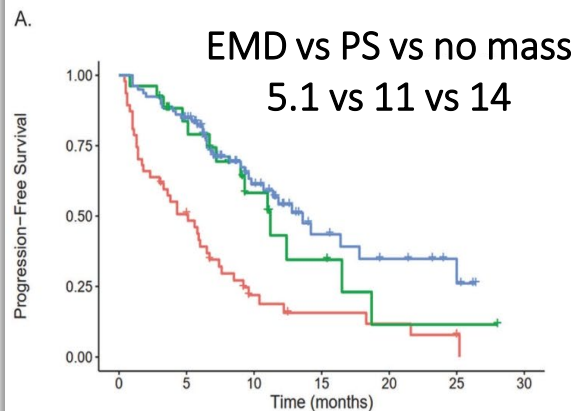
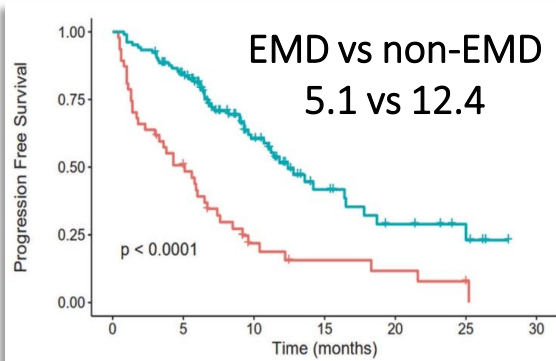
Daratumumab-based regimen

Isatuximab-Pd vs Pd (ICARIA subgroup – early RRMM)

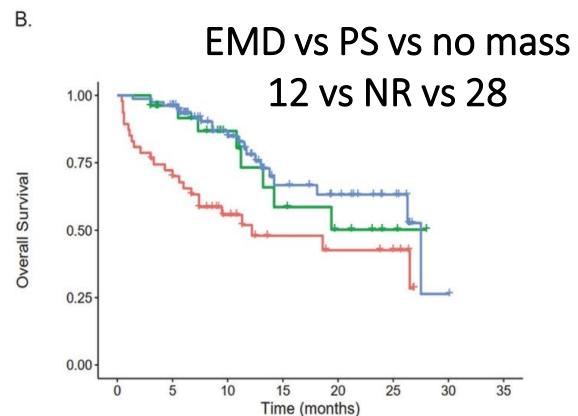
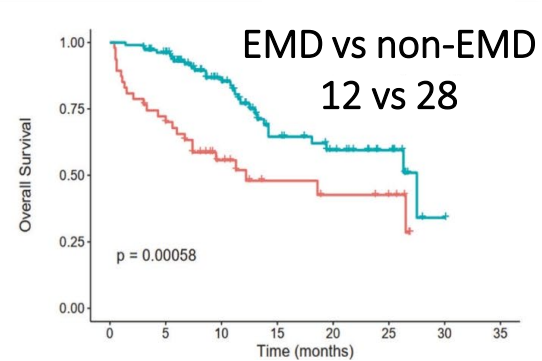
- Prior LOT: 3.5 vs 5.5
- ORR: 50% vs 10%
- Median PFS: 4.5 vs 1.56 months

T cell Redirecting Therapy: BCMA CAR-T

PFS



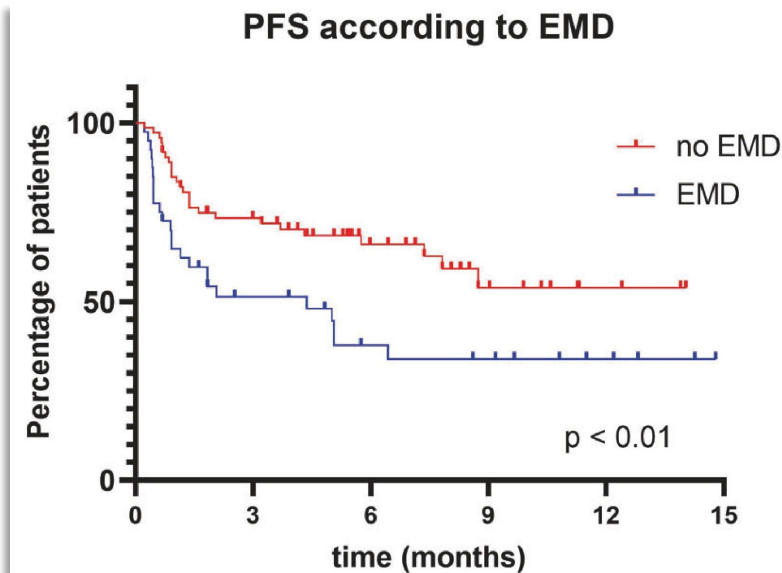
OS



Ide-Cel and Cilta-Cel

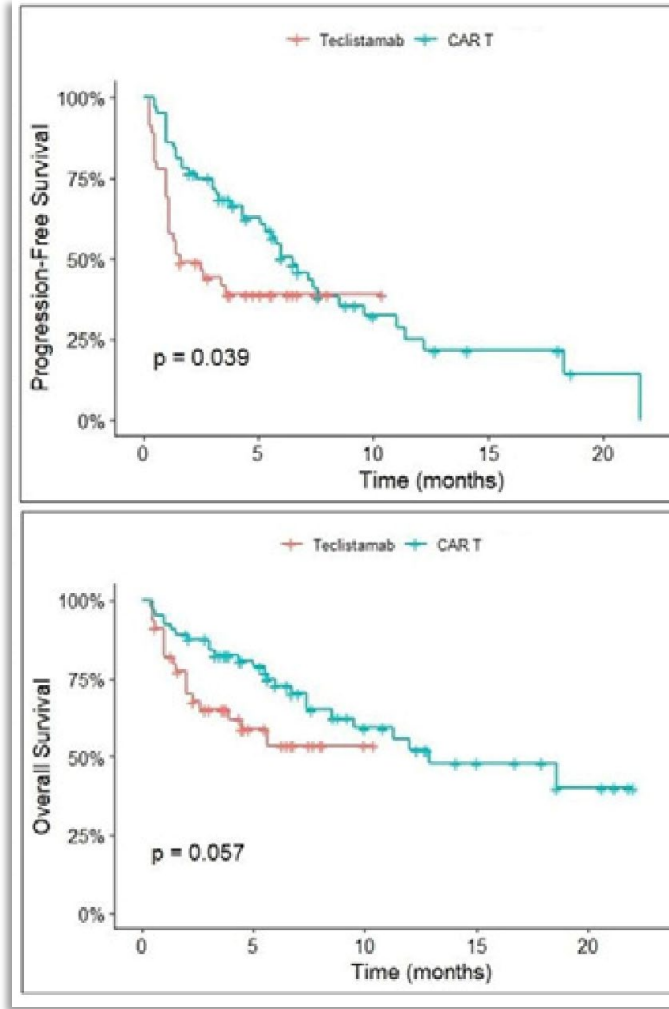
- Final result (non-EMD and EMD)
 - Ide-Cel: median F/U 25 months
 - Median PFS 8.8 months
 - Median OS 22 months
 - Cilta-cel: median F/U 33 months
 - Median PFS 35 months
 - Median OS NR
- KarMM-1/CARTITUDE-1: EMD = PS+true EMD
- Real world data: 47 EMD, 105 no EMD (75% Ide-Cel)
 - EMD: sig. poor ORR, PFS, OS
 - PS as good outcome as non-plasmacytoma

T cell Redirecting Therapy: BCMA bsAb



- **123 RRMM Teclistamab:** median of 5 LOT, 37% prior BCMA target, 17% BCMA CAR-T
- **Comparing EMD vs non-EMD**
 - ORR: 37% vs 59%
 - PFS: 2 vs 9 months

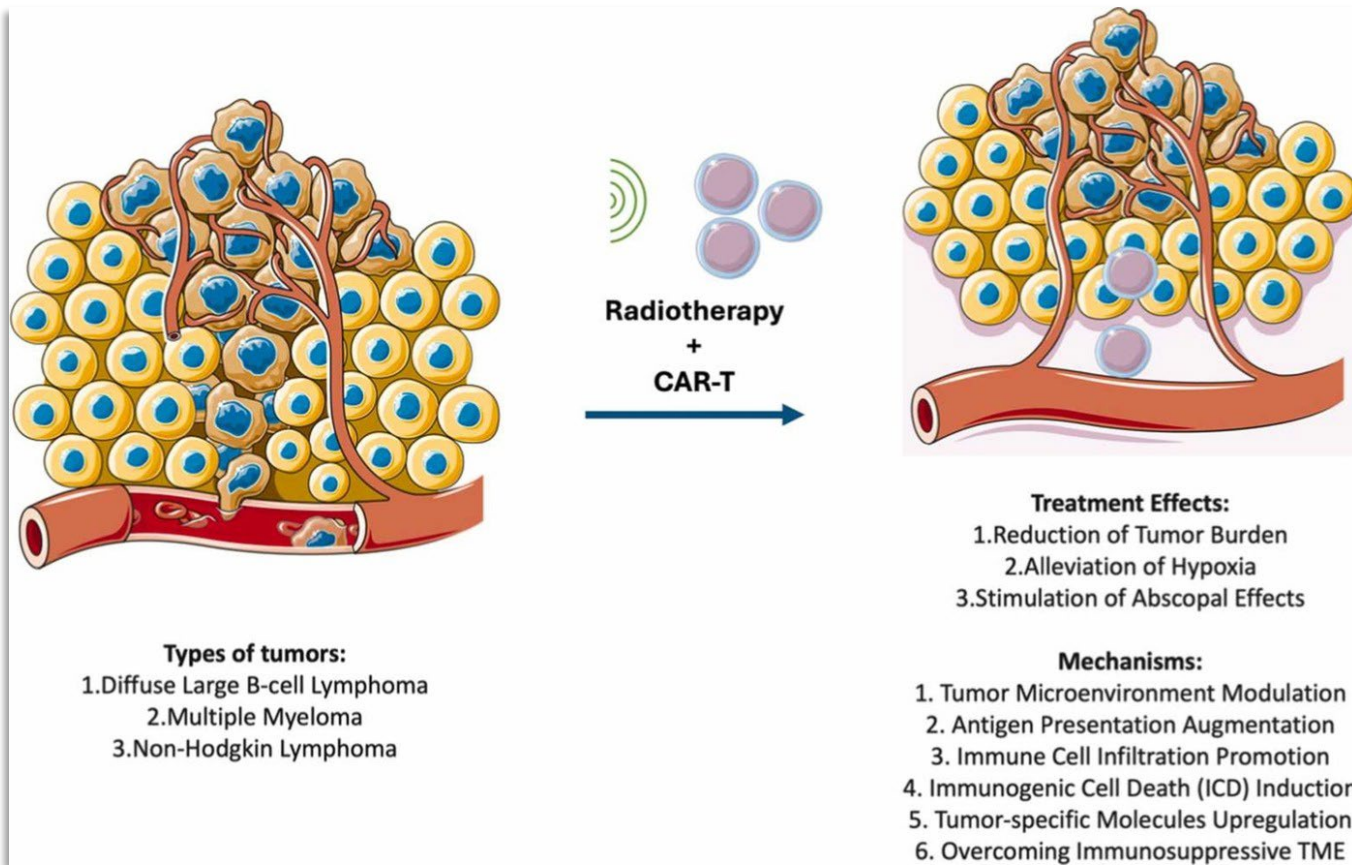
T cell Redirecting Therapy: BCMA bsAb vs CAR-T



110 BCMA: 45Teclistamab, 65 BCMA CAR-T with median of 6 LOT

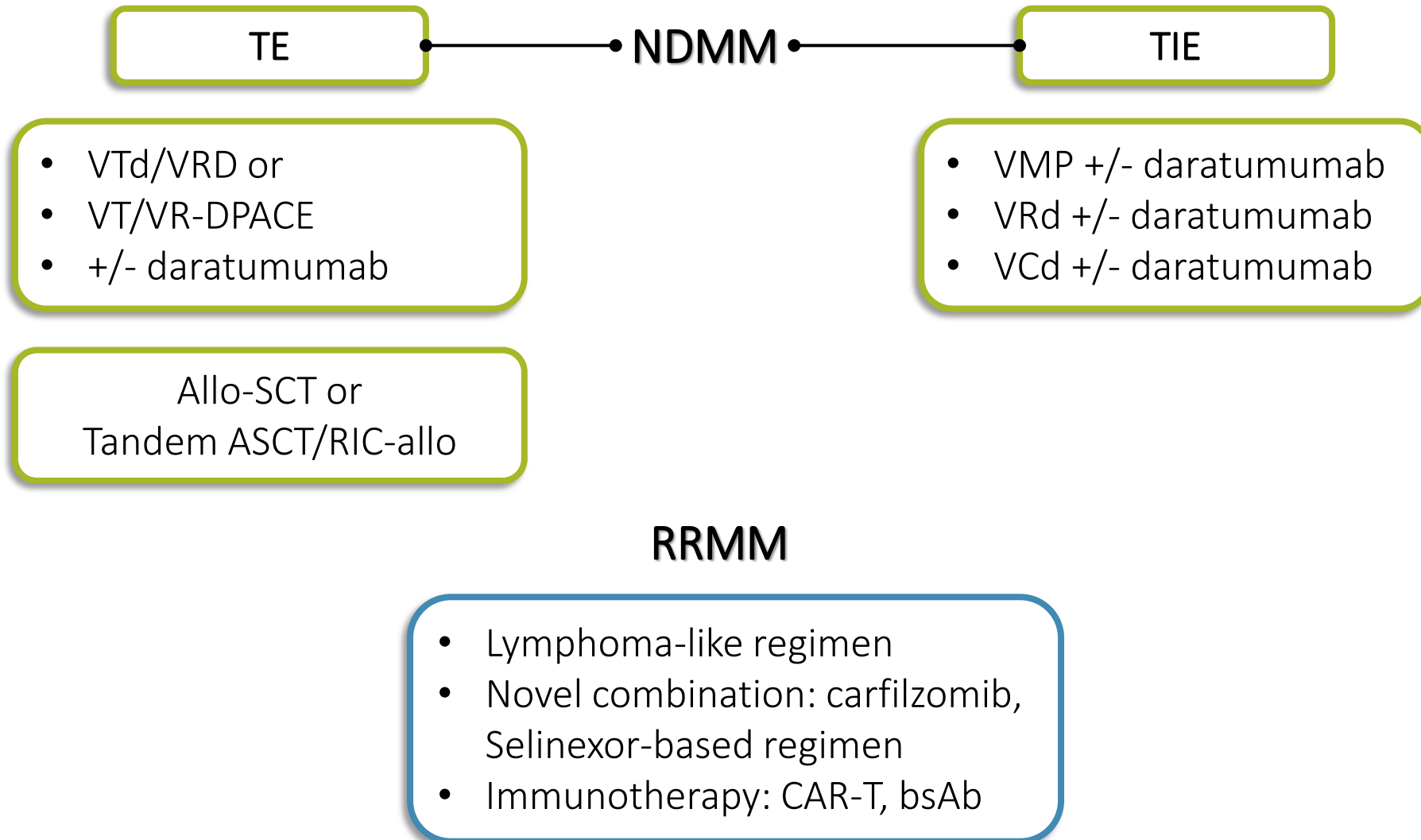
- **Teclistamab:** poorer PS, higher disease burden, higher HR cytogenetic (56% vs 29%)
- **ORR/CR (%):** 47/20 vs 77/42, $p=0.002$
- **Median PFS:** 2 vs 6.5 months, $p=0.039$
- **Median OS:** NR vs 13 months, ns

T cell Redirecting Therapy: How to Improve Efficacy



- Higher toxicities: CRS/ICANS/ cytopenia
- Bridging therapy
- Consolidation/maintenance treatment
 - Target Tx: IMiDs, HDAC inh., daratumumab
 - Allo-HSCT
 - Radiation
- Sig. improve PFS and OS:
 - PFS 12 vs 3 months
 - OS 28 vs 12 months

Recommendation: EMD



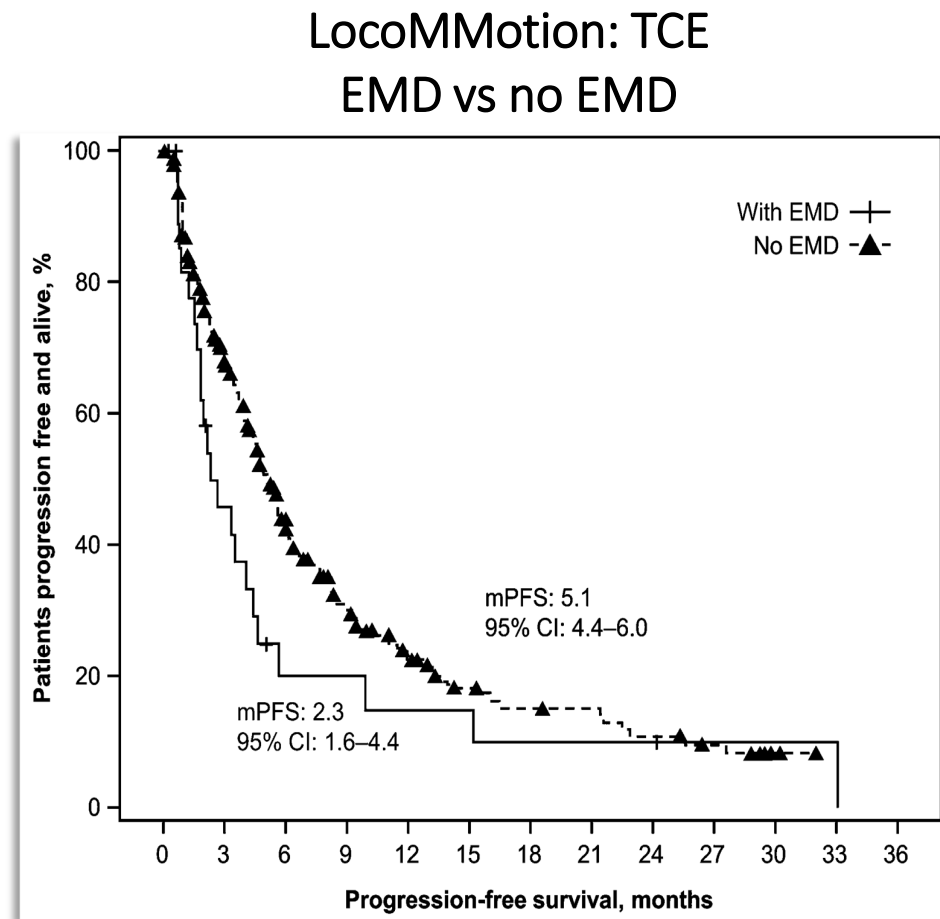
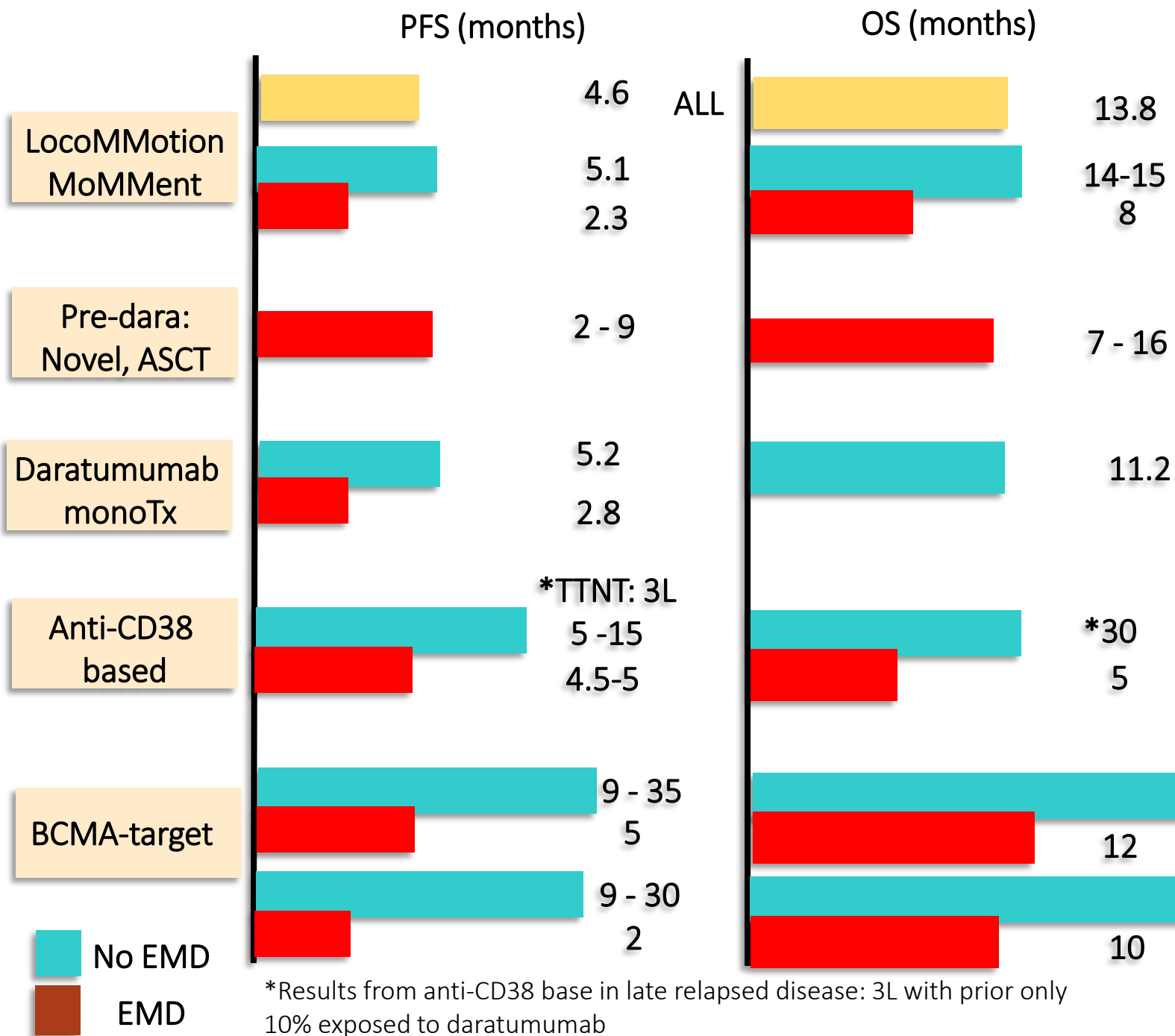
Disparity Between EMD and Monoclonal Protein Level

Relapsed disease:

- 40% relapsed with pure EMD
- 60% relapsed with BM disease and EMD

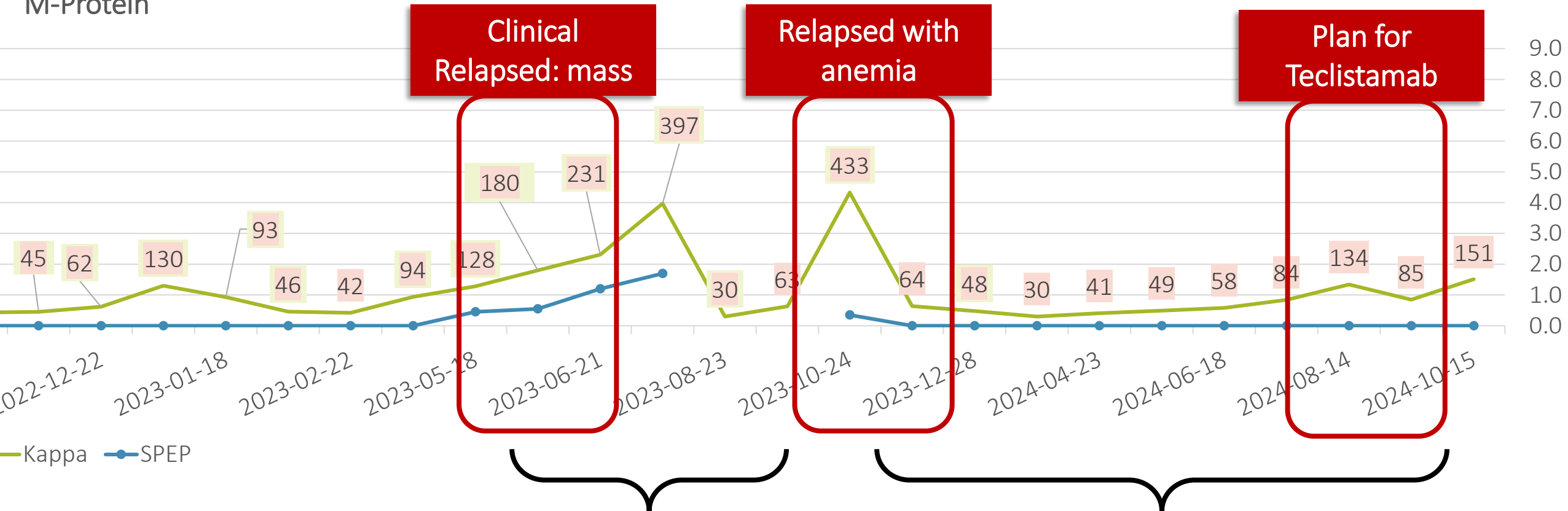
BM and monoclonal protein: not enough

Imaging: necessary



Derman *et al*, Blood neoplasia 2024
 Mateos *et al*; Leukemia, 2024
 Garfall *et al*; ASCO 2024
 Monreau *et al*, ASH abstract 2023

M-Protein

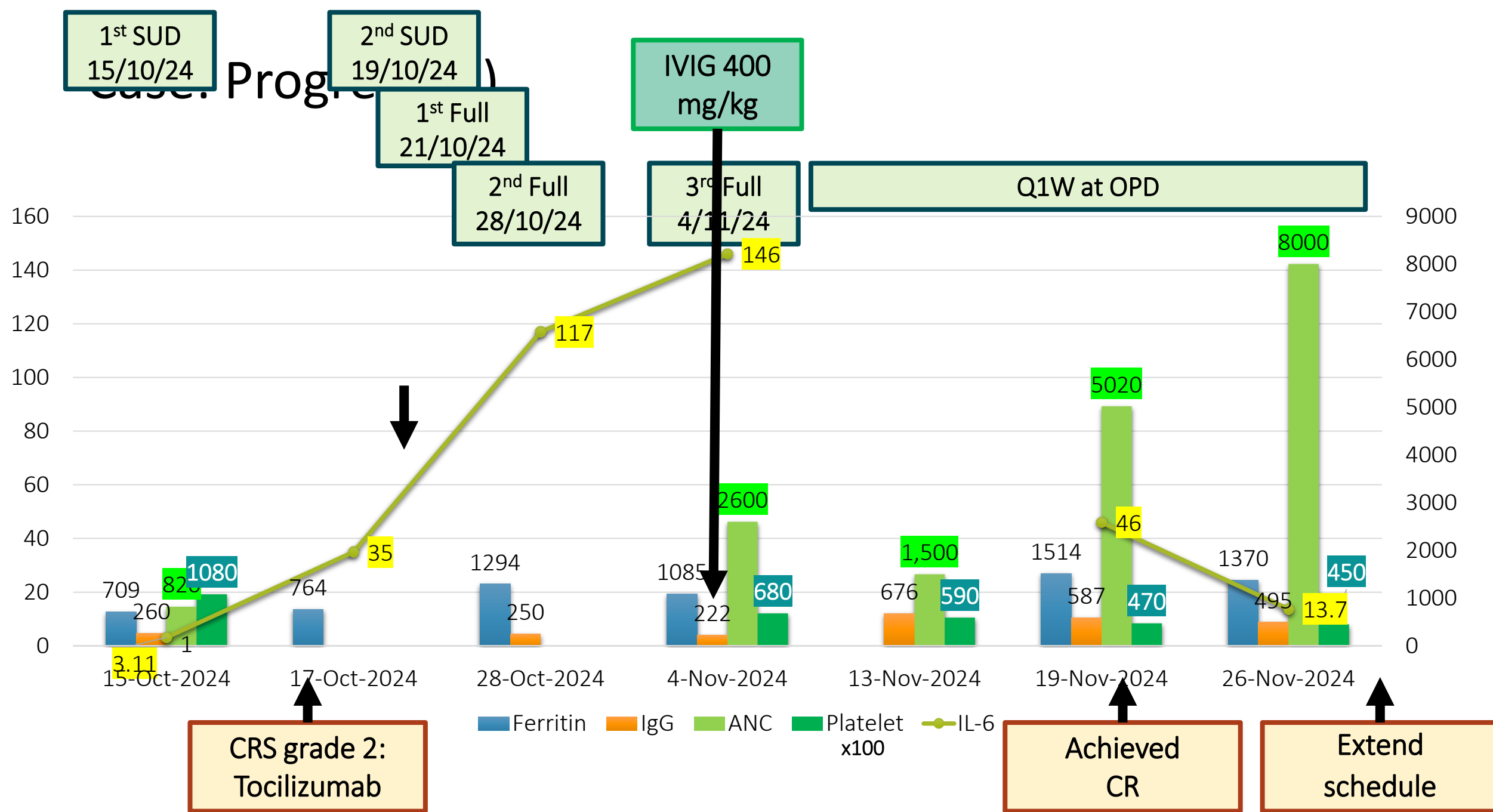


Re-induction:

- KCd x 1: PD
- KD-PACE x 1: VGPR (intolerance: alternative medicine)

Re-induction:

- Pd x 7: PR then PD; PCd x 4: PD (BM 80%, axillary LN 2 cm, Rt SPC LN 4 x 3 cm.)
 - RRMM, gain1q21 100%, EMD, high tumor burden



Conclusion

- Multiple myeloma is not curable but treatable.
- Treatment selection must consider several factors.
- EMD differs from skeletal plasmacytoma with different pathogenesis, prognosis, and treatment consideration.