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UNMET MEDICAL NEED IN MULTIPLE MYELOMA

- SMOULDERING MYELOMA

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

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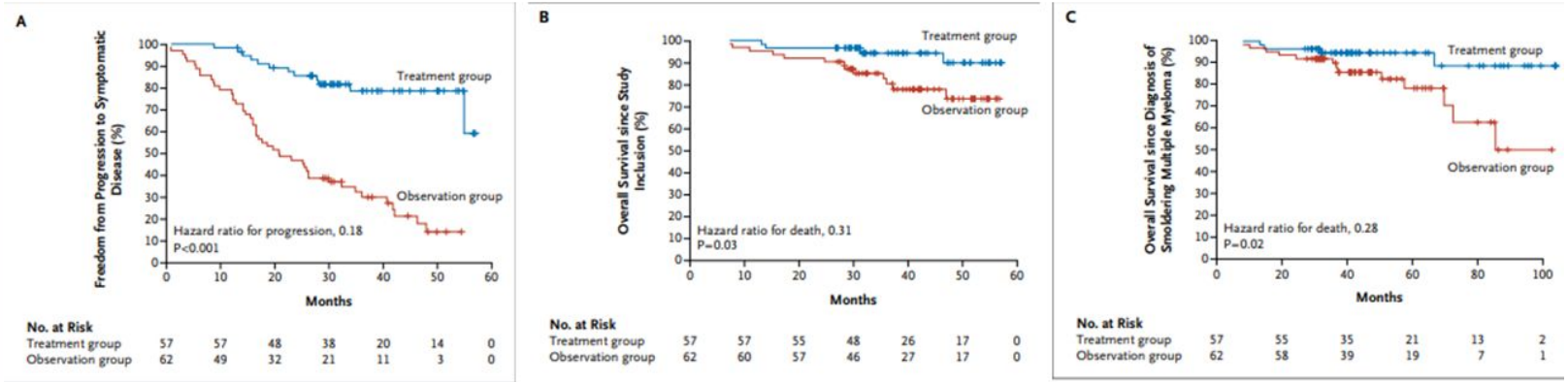

Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

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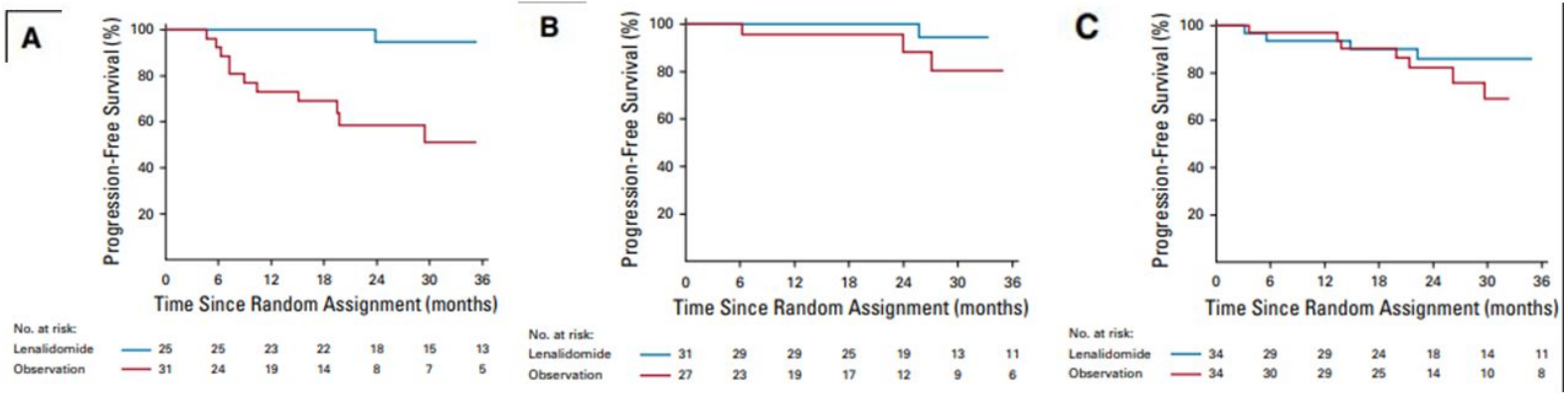


FIG 5. Kaplan-Meier estimates of progression-free survival by treatment arm within Mayo 2018 risk subgroup: (A) high risk, (B) intermediate risk, and (C) low risk.

RISK STRATIFICATION MODEL FOR SMOULDERING MYELOMA

- SERUM M PROTEIN ≥ 2g/dL
- INVOLVED TO UNIVOLVED SERUM FREE LIGHT CHAIN RATIO ≥ 20
- MARROW PLASMA CELL PERCENTAGE › 20%

	2-YR PROGR (%)
LOW RISK = 0 FACTORS	5
INTERMEDIATE RISK = 1 FACTOR	17
HIGH RISK = 2 OR MORE FACTORS	46

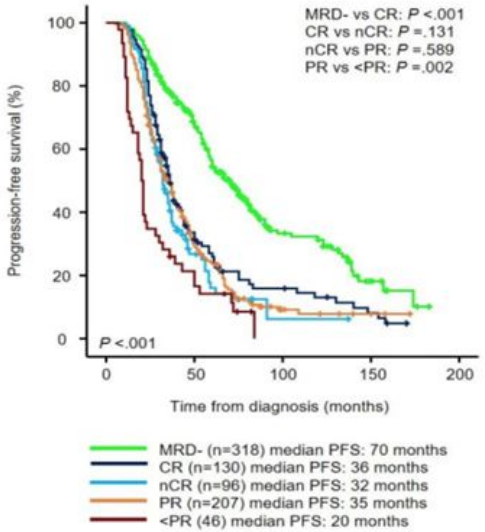
RISK STRATIFICATION MODEL FOR SMOULDERING MYELOMA

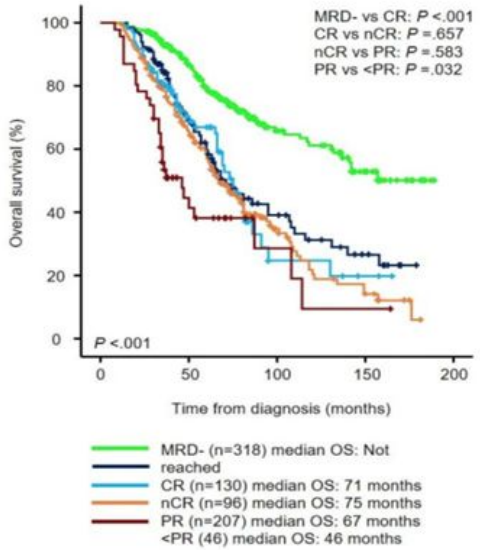
- MYELOMA SMOULDERING
- RUOLO MRD-NEGATIVITA'

Criteria	Definition
Standard IMWG response criteria	
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirate
Stringent complete response	CR as defined above plus normal free light-chain ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)
IMWG MRD criteria (requires a CR as defined above)	
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT/ClonoSEQ platform (or a validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET-CT or decrease to less than mediastinal blood pool standardized uptake value or decrease to less than that of surrounding normal tissue
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined above, confirmed minimum of 1 y apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g, MRD-negative at 5 y)

Davies F.E. et al, ASH 2017

Likely the true value of CR relies on the MRD status: CR without MRD in no better than PR





GEM2000, GEM2005MENOS65, GEM2005MAS65, GEM2010MAS65

MRD IN MULTIPLE MYELOMA

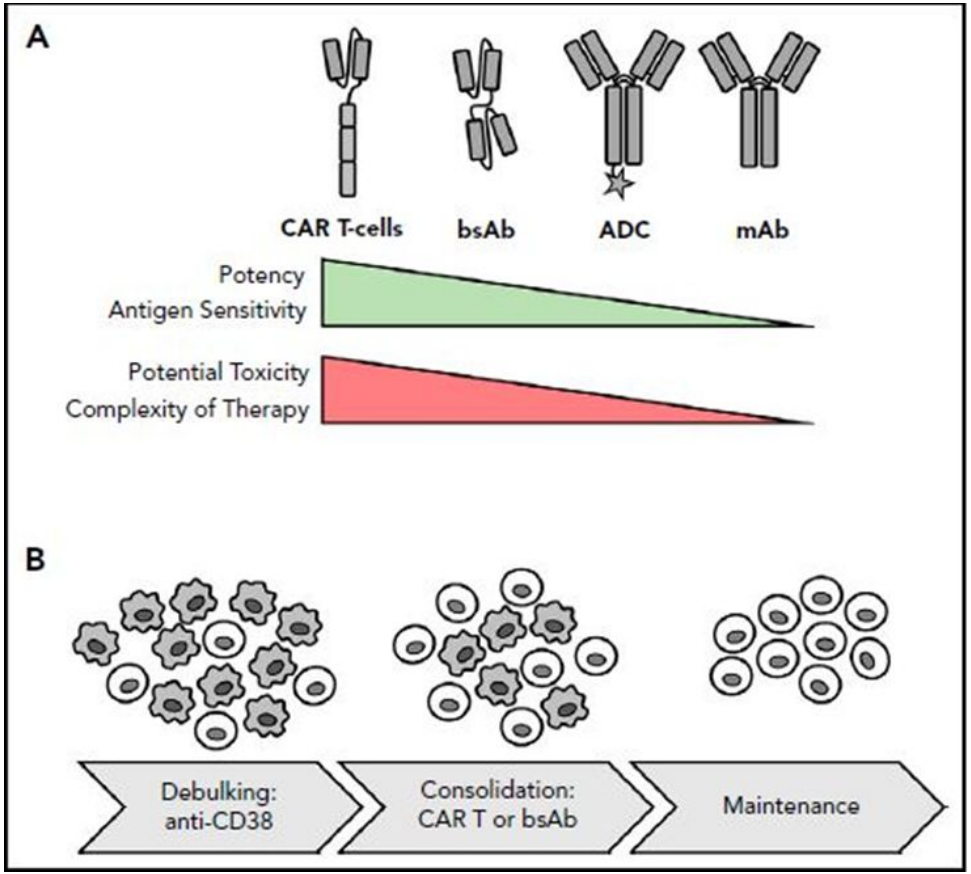
VALIDATED POINTS	OPEN ISSUES
MRD NEGATIVITY IS A SURROGATE FOR PFS.	OPTIMAL THRESHOLD FOR PFS/OS PREDICTION BY NGS OR NGF.
MRD NEGATIVITY IS A SURROGATE FOR OS.	NEED FOR BOTH NGS AND NGF.
MRD BY NGS IS STANDARDIZED.	TIME INTERVAL TO DEFINE SUSTAINED MRD-NEGATIVITY.
MRD BY NGF (EUROFLOW) IS STANDARDIZED.	DEFINITION OF LOSS OF MRD-NEGATIVE STATUS.
MRD BY NGS OR NGF AND PET-CT ARE COMPLEMENTARY.	OPTIMAL TIMING FOR MRD ASSESSMENT DURING AND AFTER TREATMENT.
MRD USEFUL TO COMPARE TREATMENT OPTIONS.	STANDARDIZATION OF MRD BY PET-CT.
	BEST TRACER FOR PET-CT.
	MRD TO MODIFY THERAPY: DURATION OF MAINTENANCE, CHANGE TREATMENT, ADD OTHER AGENTS.
	MRD AS END-POINT FOR DRUG APPROVAL.
	BLOOD-BASED MRD ASSESSMENT.
	MEANING OF MRD-NEGATIVITY IN SPECIFIC SUBGROUPS (HIGH RISK CYTOGENETICS).

RISK STRATIFICATION MODEL FOR SMOULDERING MYELOMA

- MYELOMA SMOULDERING
- RUOLO MRD-NEGATIVITA'
- FUTURO DELL'IMMUNOTERAPIA

IMMUNOTERAPIA NEL MIELOMA MULTIPLO

- ANTICORPI MONOCLONALI
  - DARATUMUMAB — anti-CD38
  - ISATUXIMAB — anti-CD38
  - ELOTUZUMAB — anti-SLAMF7
- ANTIBODY-DRUG CONJUGATES (ADC)
  - BELANTAMAB-MAFADOTIN (ANTICORPO ANTI-BCMA + AURISTATINA F)
- ANTICORPI BI-SPECIFICI
- AMG-420 (CD3 X BCMA BISPECIFIC T-CELL ENGAGER CONSTRUCT)
- CAR-T CELLS (MONOSPECIFICI O MULTISPECIFICI)


A
CAR T-cells
bsAb
ADC
mAb
Potency
Antigen Sensitivity
Potential Toxicity
Complexity of Therapy
B
Debulking:
anti-CD38
Consolidation:
CAR T or bsAb
Maintenance