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# MULTIPLE MYELOMA

What have we learnt in recent years?  
Some personal highlights

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Editorial Board Member of Journal of Leukemia, OMICs Group

Update: August 2014

**META-  
ANALYSIS**

**SYSTEMATIC  
REVIEW**

**RANDOMIZED  
CONTROLLED TRIAL**

**COHORT STUDIES**

**CASE CONTROL STUDIES**

**CASE SERIES / CASE REPORTS**

**ANIMAL RESEARCH**

**THE RULES OF**

**EVIDENCE-BASED  
MEDICINE**

**THE GAME**

# DEFINITION

## SYMPTOMATIC OR CLINICAL MM

MM is a plasma cell (PC) neoplasm characterized by the infiltration of clonal PC in the bone marrow that secrete a monoclonal immunoglobulin in serum and/or urine in the majority of patients causing myeloma-related organ or tissue impairment (ROTI) the most common being hypercalcemia, renal failure, anemia and bone lesion (CRAB)

MONOCLONAL  
PROTEIN

BONE  
MARROW PC

TISSUE  
IMPAIRMENT

# THE MULTISTEP MODEL OF EVOLUTION

MM virtually always arises from an asymptomatic precursor condition:

- MGUS: Monoclonal Gammopathy of Undetermined Significance
- SMM: Smoldering MM

Sometimes, at the end of this evolutionary process, a secondary Plasma Cell Leukemia (PCL) may appear



Kyle, 1980;2007  
Borrello, 2012  
Boyle, 2014

Landgren, 2009  
Weiss, 2009  
Dispenzieri, 2010;2013

# MM BACKGROUND

1-2 % ALL CANCER

10-15 % HEMATOLOGIC MALIGNANCIES



HETEROGENEITY

CLINICAL

MOLECULAR

# MM RISK FACTORS

LEVEL OF EVIDENCE



- MGUS
- AGE  $\geq$  65
- FAMILY HISTORY
- MALE GENDER
- BLACK RACE
- OBESITY
- TYPE 2 DIABETES
- DIET: LOW FISH & VEGETABLES
- AIDS
- OCCUPATION: FARMING
- CHEMICAL EXPOSURE
- AUTOIMMUNE DISEASES
- RHEUMATOID ARTHRITIS ...

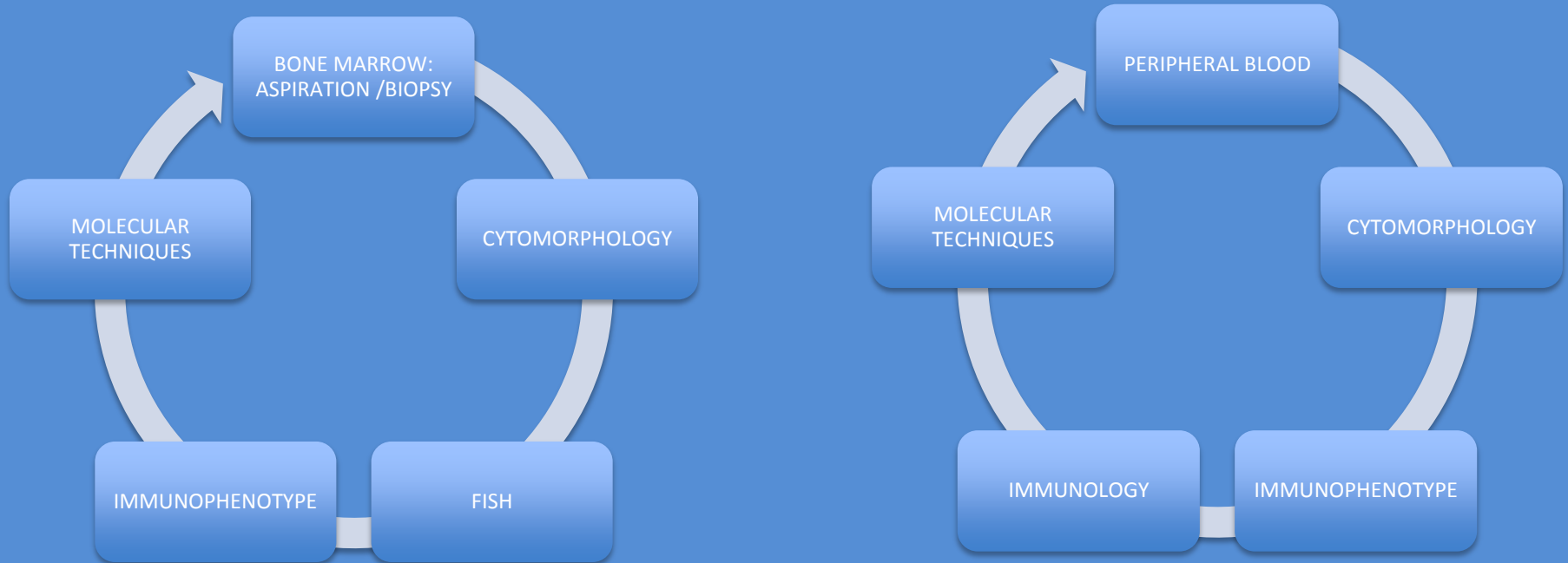
Alexander, 2007  
Brighen, 2013  
Chretien, 2014

Landgren, 2006;2009  
Vachon, 2009  
Perrotta, 2012

Anderson, 2009  
Wang, 2012  
Coker, 2013

Castillo, 2012  
Greenberg, 2012  
Carson, 2014

# DIAGNOSIS AND PROGNOSIS OF MM: TWO INTERLACED AND UNREPEATABLE PROCESSES



IT ALL STARTS WITH A GOOD CLINICAL HISTORY

Paiva, 2008;2009;2013  
Yuan, 2011  
Johansson, 2014  
Gonsalves, 2014

Woessner, 2006  
Chng, 2013  
Ludwig, 2014  
Palumbo, 2014



# MM IS A DISEASE OF CONTRAST

CONTROL



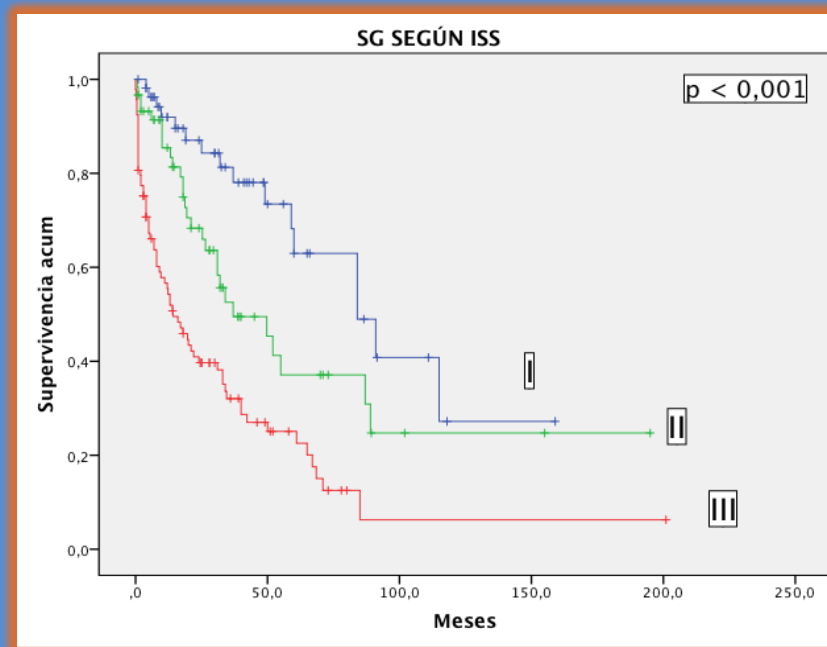
CURE

RESPONSE

# THE PROGNOSTIC IMPACT OF ISS STAGING

## International Staging System (ISS)

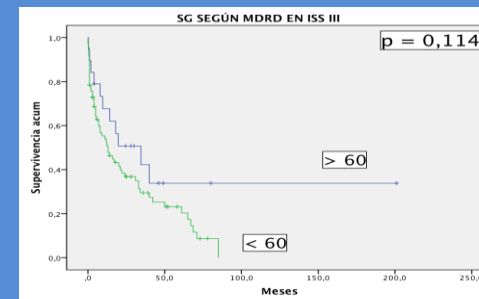
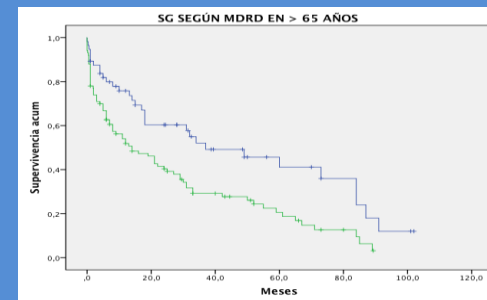
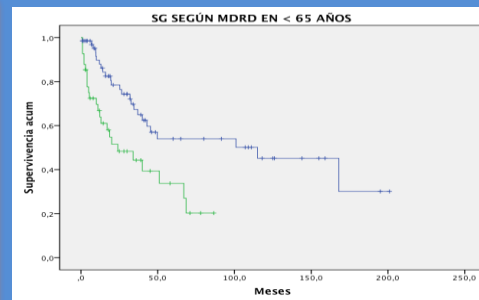
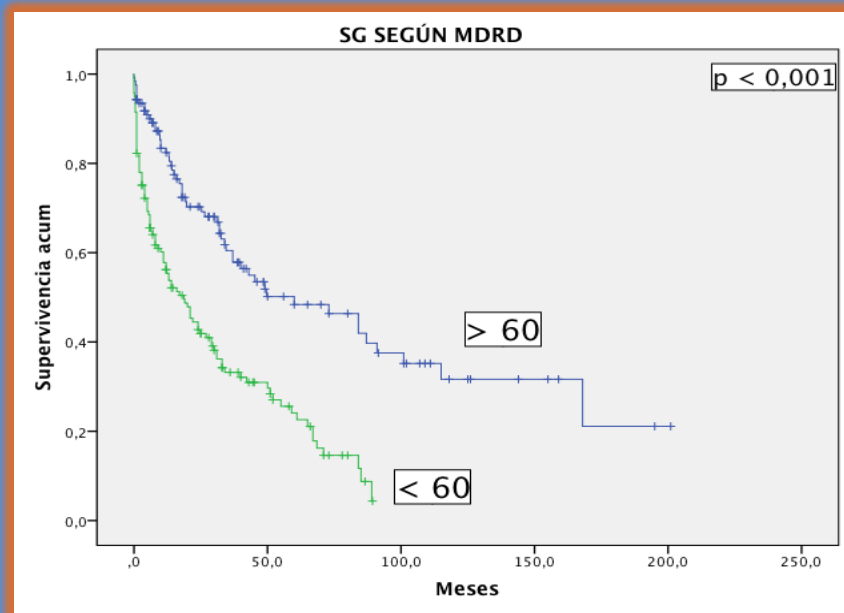
Stage	Criteria	Median Survival (months)
I	Serum $\beta_2m < 3.5$ mg/L Serum albumin $\geq 3.5$ g/dL	62
II	Neither stage I nor III	44
III	Serum $\beta_2m \geq 5.5$ mg/L	29



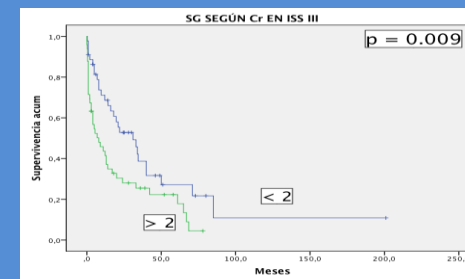
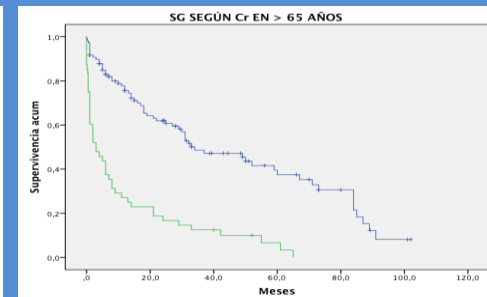
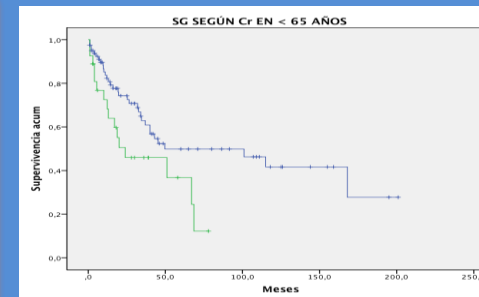
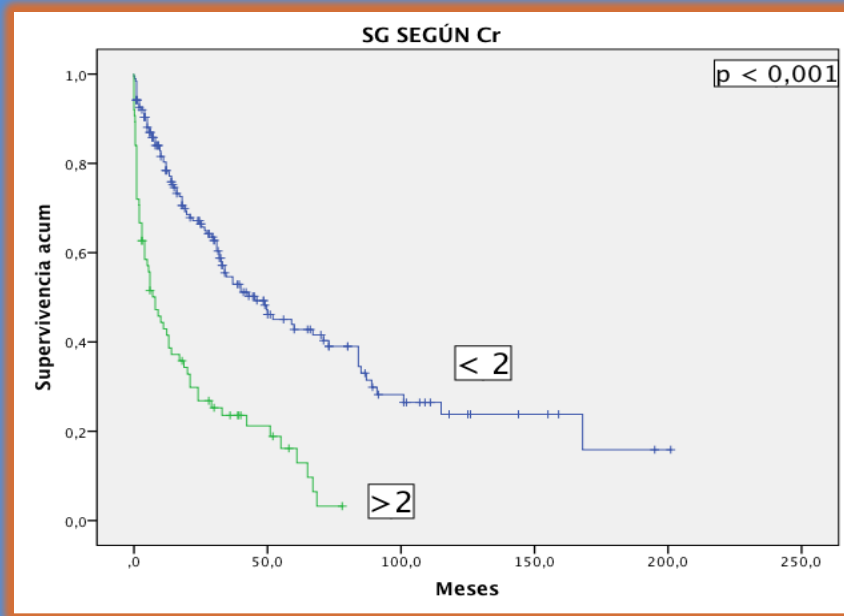
ISS: ISS IS GOOD BUT WE NEED MORE

Greipp, 2005  
Ríos, 2013

# THE IMPACT OF RENAL IMPAIRMENT ON OVERALL SURVIVAL

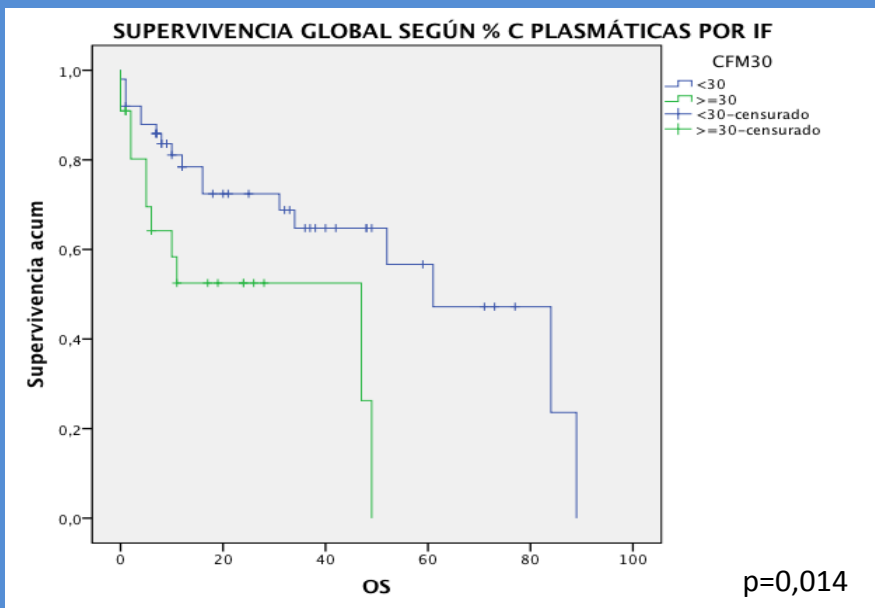
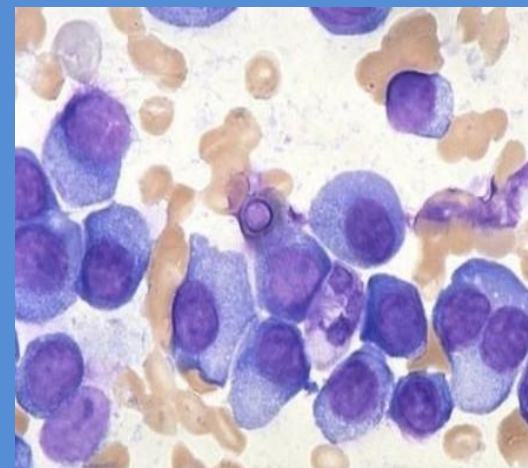
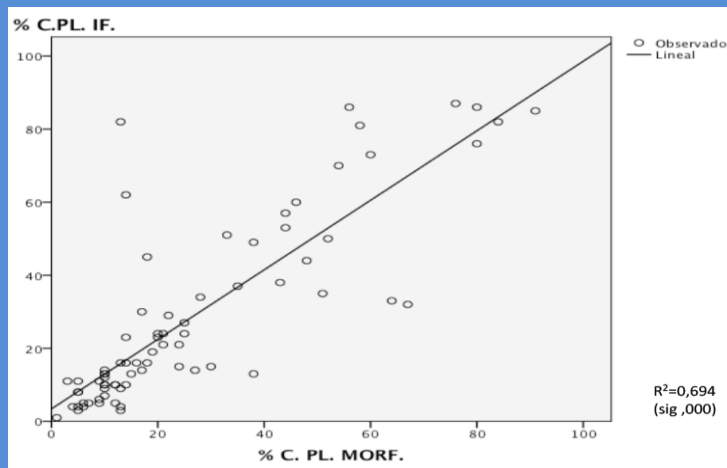
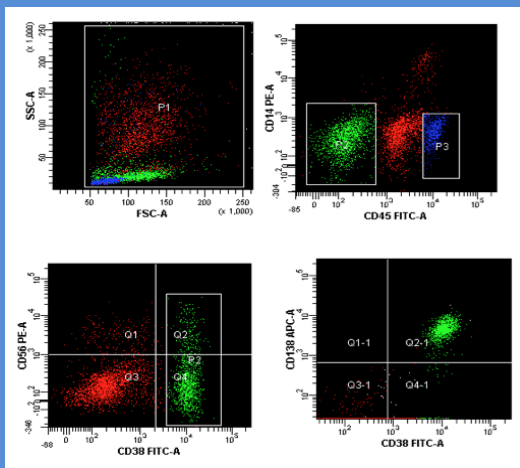


MDRD: Modification of Diet in Renal Disease formula for estimated glomerular filtration rate (ml/min/1.73 m2)

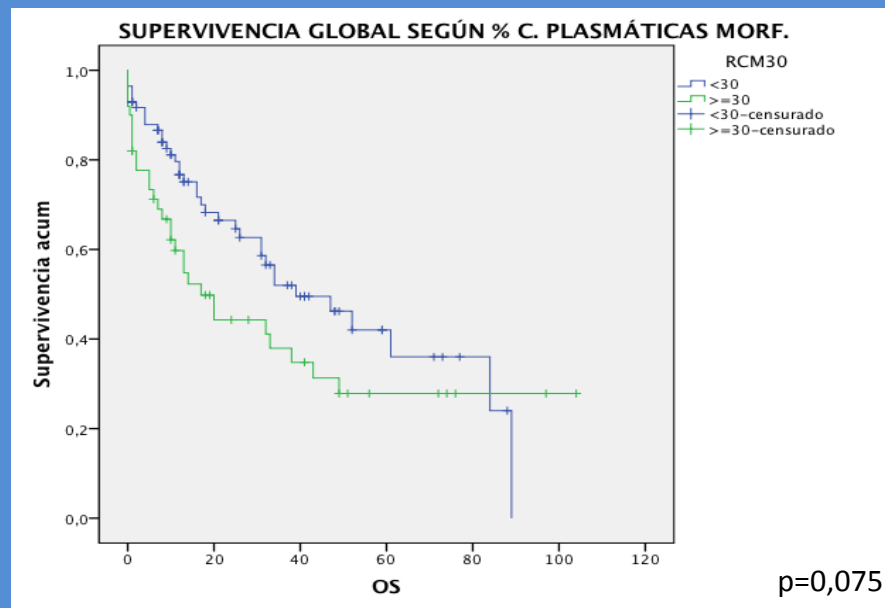


Cr: Serum creatinine (mg/dl)

# THE IMPACT OF PERCENTAGE OF BONE MARROW INFILTRATION (Cutoff 30 % PC) ON OVERALL SURVIVAL AND COMPARISON OF IMMUNOPHENOTYPE & MORPHOLOGY



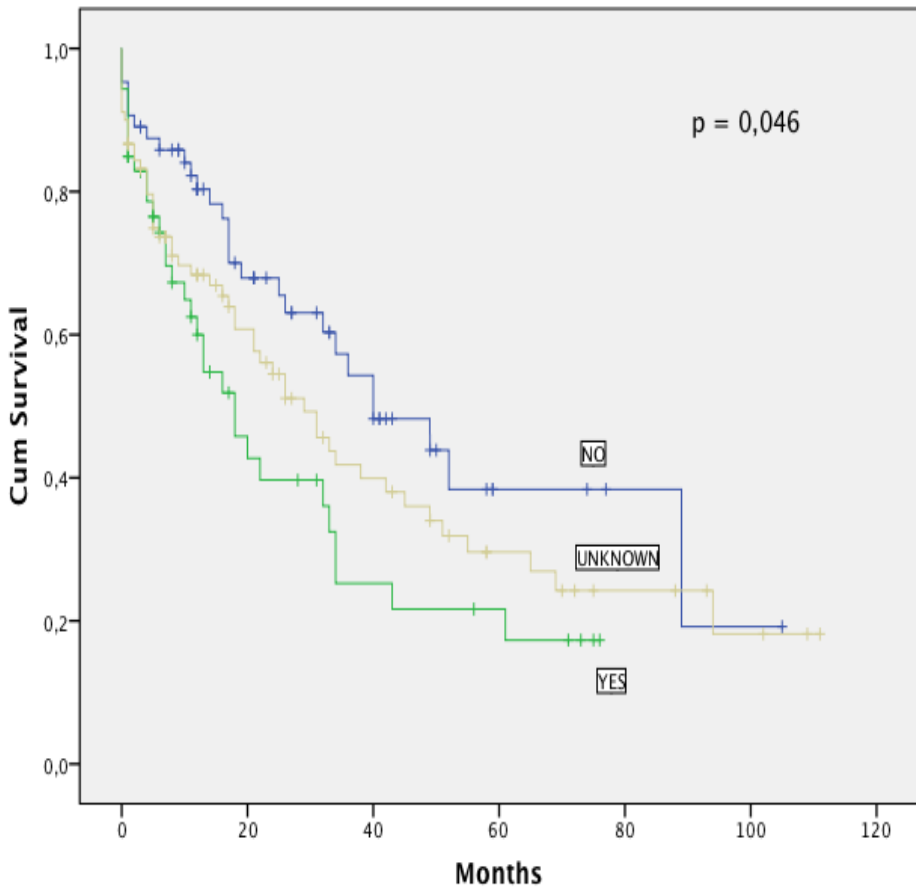
BONE MARROW PC BY IMMUNOPHENOTYPE



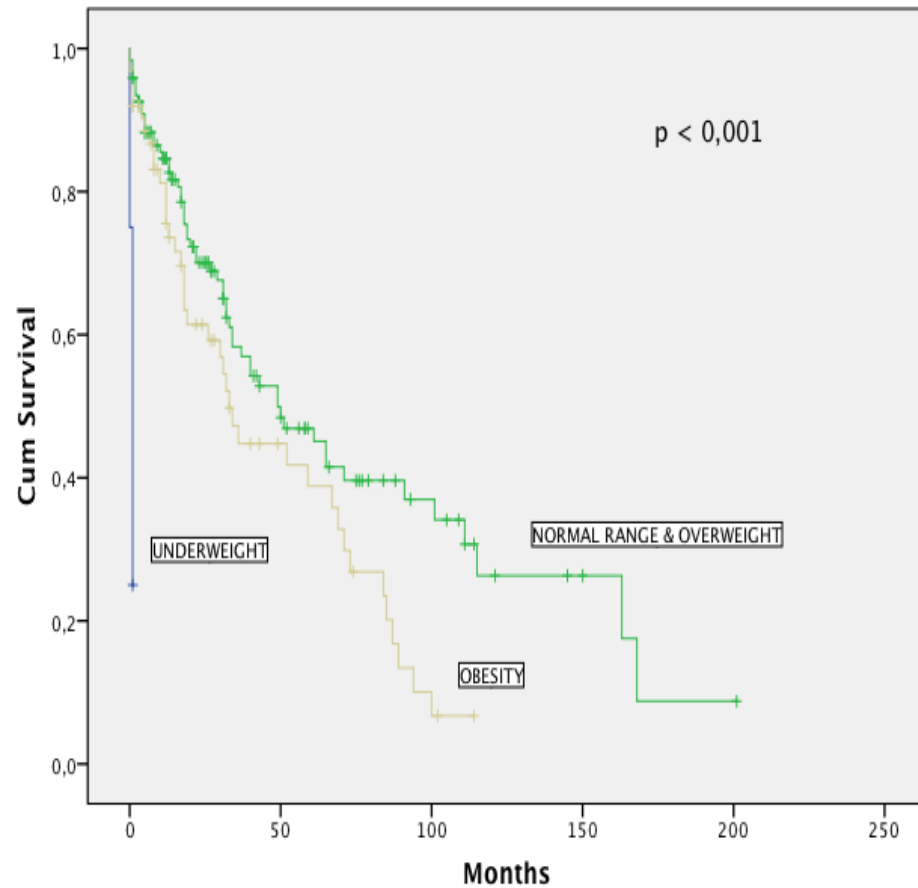
BONE MARROW PC BY CYTOMORPHOLOGY

# OVERALL SURVIVAL ACCORDING WITH THE PRESENCE OF WEIGHT LOSS AND THE BODY MASS INDEX AT DIAGNOSIS

## OS ACCORDING TO WEIGHT LOSS



## OS ACCORDING TO BMI



# LEVEL OF RESPONSE: HOW DEEP ?

## CLINICAL SYMPTOMS

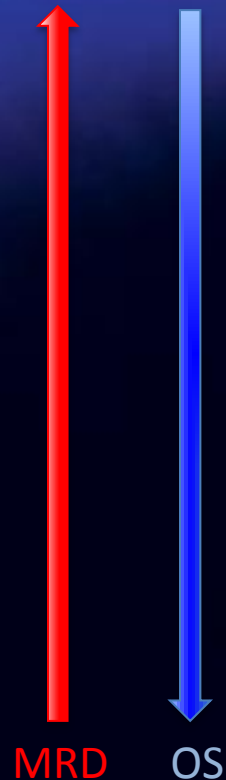
CR  
sCR

< 5 % bm pl.  
n sFLCr

IR  
MR

$10^{-4} - 10^{-5}$   
 $10^{-3} - 10^{-6}$

CURE



# MM THERAPY



PERSONALIZED

RISK ADAPTED



Palumbo, 2011  
Katsanis, 2013

Rajkumar, 2011;2013  
Munshi, 2011

RESPONSE

RESPONSE

# THERAPY IN MM: RISK / BENEFIT RATIO



OS: Overall Survival; QOL: Quality of life; PFS: Progression Free Survival



# MM INDUCTION THERAPY

## WHICH DRUGS ?: THE LABYRINTH OF THE WORD SEARCH

THERAPY	T-BASED	L-BASED	B-BASED	OTHER
2 DRUGS	TD	LD	VD	PD, CD
3 DRUGS	MPT, CTD	MPR, CRD, BiRd	VMP, VCD, PAD	VRD, VTD, BLD, CRd
4 DRUGS	CCTD	DVDR	ABCD	DCEPI, DTPACE

T:Thalidomide  
 L:Lenalidomide  
 R:Revlimid  
 B:Bortezomib  
 V:Velcade  
 D:Dexamethasone  
 D:Low dose D  
 P:Prednisone  
 P:Pomalidomide  
 C:Cyclophosphamide  
 M:Melphalan  
 A:Doxorubicin  
 E:Etoposide  
 Pl:Cisplatin



# RELAPSE

KIND

Clinical vs Serological  
Aggressive vs slowly progressive

SETTING

Fragility

TIMING

Early vs Late

# RELAAPSE

## TREATMENT

WHEN TO START

WHAT ARE THE  
GOALS

WHAT IS THE  
REGIMEN OF CHOICE

# RELAAPSE

## TREATMENT

RETREATMENT

NEW DRUGS

STEM CELL  
TRANSPLANT

# SALVAGE THERAPY OF RRMM: SLOW PROGRESS

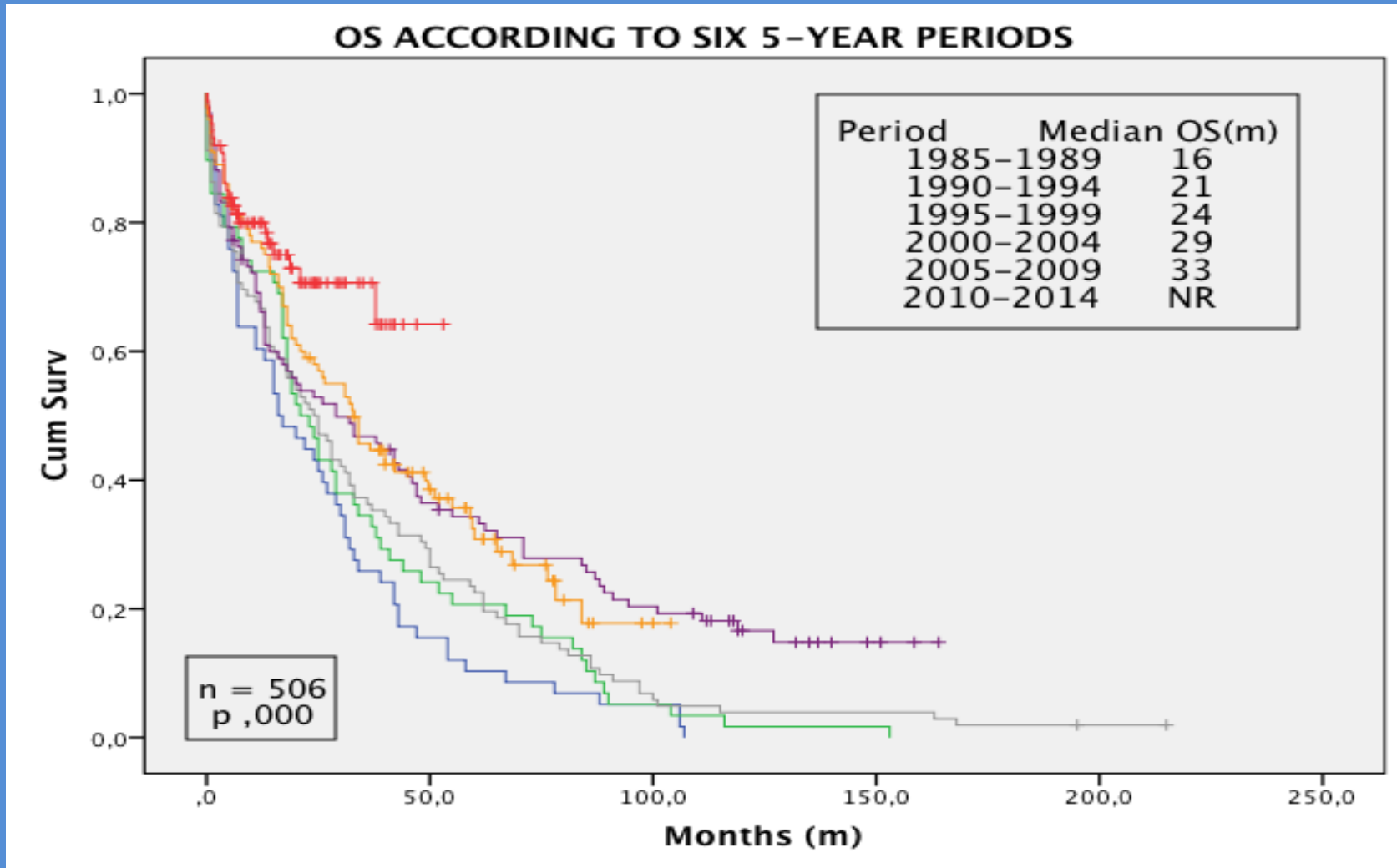
	CP	BBD	PM	VD	LD	DCEP	PD	VRD	ABCD
n	56	79	40	85	212	59	221	64	24
OR	59,2	60,8	7,5 /33	55	77,4	45,1	33	64	50
CR	3,7	15,2	0	19	20,2	1,7	3	11	8
OS m	8	25,6	-	22	-	8	16,5	30	22,5
Age	-	64	65,4	58	68	58	63	65	69
ISS3	-	26,6	-	-	19,8	28,6	67	23	67
Disc	-	-	100%	5,9	38,9	-	2,5	-	4,1
Death	-	5,06	-	-	0,9	14,8	8,6	2	4,1
Year	2014	2014	2014	2014	2014	2014	2014	2014	2014
Author	Zhou	Ludwig	Berenson	Pantani	Katodritou	Park	Richardson	Richardson	Romano

CP: Cyclophosphamide-Prednisone. BBD: Bendamustine-Bortezomib-Dexamethasone PM: Panobinostat-Melphalan. VD: Bortezomib-Dexamethasone LD: Lenalidomide-Dexamethasone. DCEP: Dexamethasone-Cyclophosphamide-Etoposide-Cisplatin. PD: Pomalidomide-Dexamethasone. VRD: Bortezomib-Lenalidomide-Dexamethasone. ABCD: Doxorubicin-Bortezomib-Cyclophosphamide-Dexamethasone. OR: Overall response. CR: Complete Response. OS: Overall Survival, m: months. Disc.: Discontinuation.

THERE IS NO  
GENERALLY ACCEPTED  
STANDARD THERAPY  
FOR RRMM



# OVERALL SURVIVAL IS INCREASING STEADILY



# HEALTH-RELATED QUALITY OF LIFE ALSO MATTERS IN MM

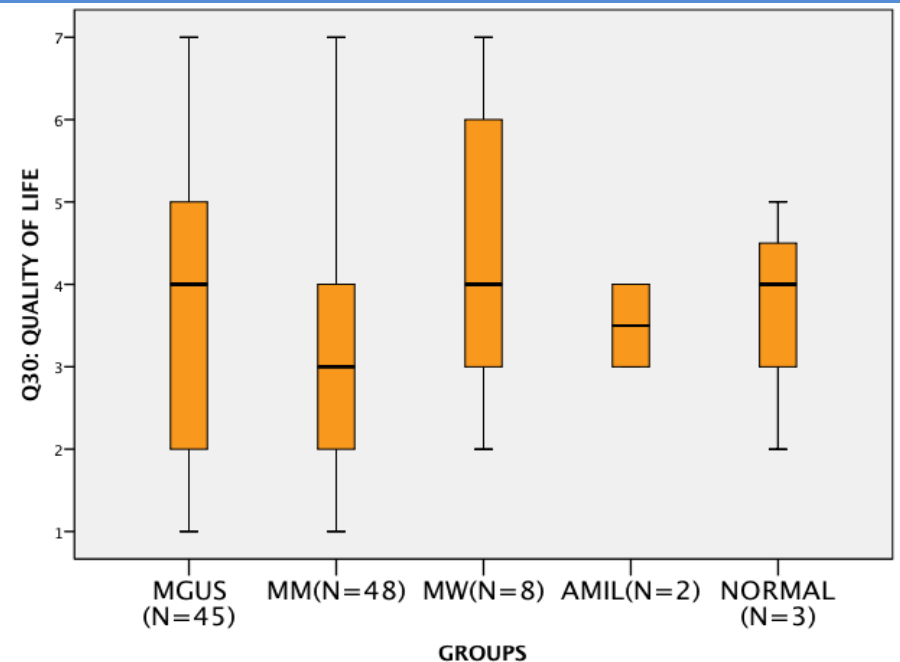
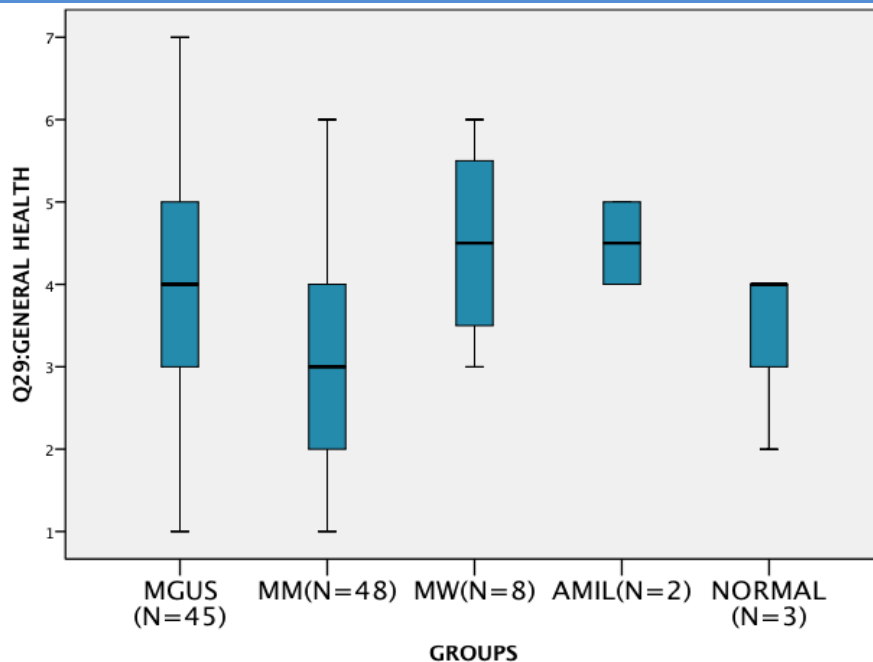


EORTC QLQ-C30



QOL SHOULD BE MEASURED  
IN CLINICAL TRIALS  
AS WELL AS  
IN REAL-LIFE PATIENTS

EORTC QLQ-C30  
HAS DEMONSTRATED  
RELIABILITY AND VALIDITY IN  
MM PATIENTS





# BOTH WORLDS ARE NEEDED TO FIGHT MM

CLINICAL TRIALS



REAL-LIFE PATIENTS

The concept of CURE in MM is feasible

Operational CURE in MM is achievable in selected patients

Research in MM: helping us knowing better our enemy



Don't give  
up the  
fight !

MM remains incurable in the majority of patients

Translational medicine is slow

Unmet clinical needs





Oct. 2011, Volume 8, No. 10 (Serial No. 83), pp. 588-595  
Journal of US-China Medical Science, ISSN 1548-6648, USA

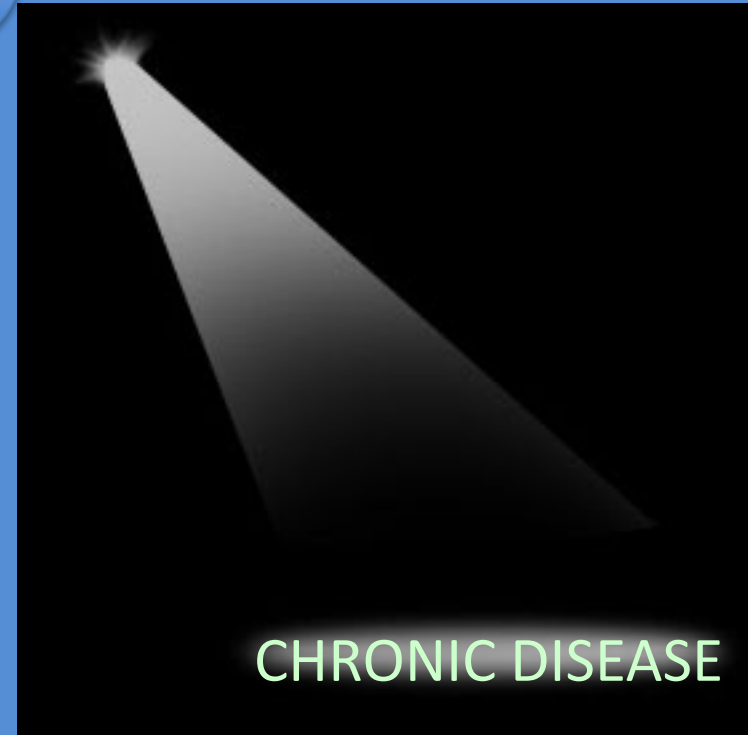
# Health Impact Assessment and the Role of Accredited Clinical Laboratory on ISO 15189:2007 International Standard

Rafael Ríos Tamayo<sup>1</sup>, Francisco Javier Pérez Zenni<sup>1</sup>, Almudena García Ruiz<sup>1</sup>, Aurora Bueno Cavanillas<sup>2</sup>, José Juan Jiménez-Moleón<sup>2</sup>, Juan Sainz Pérez<sup>3</sup>, María José Sánchez Pérez<sup>4</sup> and Manuel Jurado Chacón<sup>1</sup>

IF WE ARE LOOKING FOR EXCELLENCE,  
WE MUST BE ABLE TO TRANSLATE TO DAILY CLINICAL PRACTICE  
THE STANDARDISED APPROACH WE CURRENTLY USE IN CLINICAL LABORATORY

# A NEW HOPE...A NEW LANDSCAPE

MM



Check every day as we improve the survival and quality of life of our patients is an experience that should give us strength to keep fighting this frightening disease

*Thank you  
Dr R Rios*

# Leukemia Related Conferences

- Thrombosis and Hemostasis Conference
- 3rd Hematology and Blood Disorders Conference
- 4th Blood Malignancies Conference

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