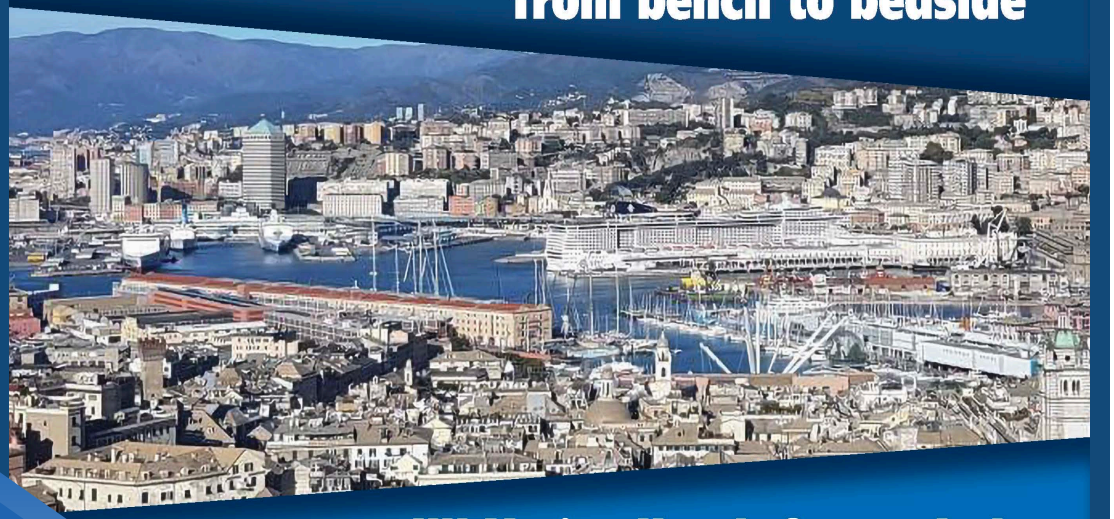
2023 Multiple Myeloma updates: from bench to bedside



NH Marina Hotel, Genoa, Italy
20-21 November 2023

Prof.
Roberto
Ria

TITOLO RELAZIONE

Circulating tumor cells and homing to predict Myeloma progression

Unità per lo Studio e la Terapia delle Gammopatie Monoclonali

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

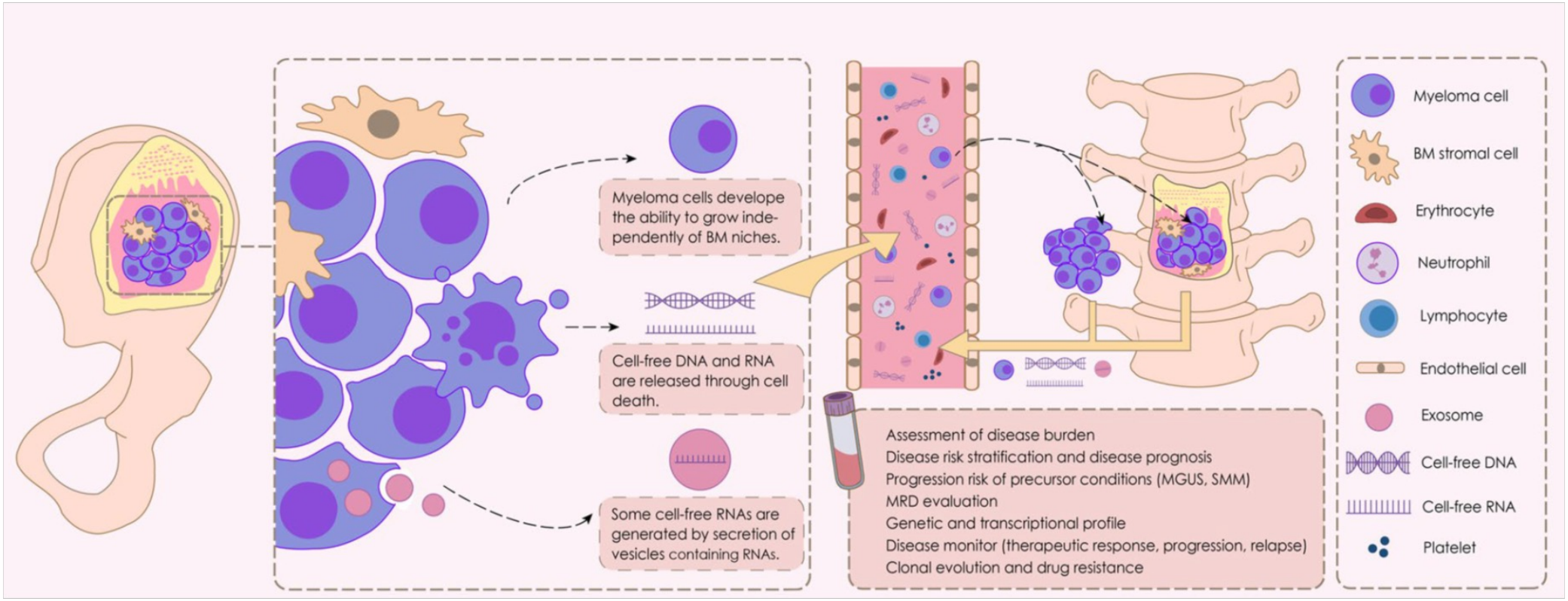
DIPARTIMENTO DI MEDICINA DI PRECISIONE E RIGENERATIVA E AREA JONICA (DIMEPRE-J)

Disclosures for Roberto Ria M.D.

- ✓ Grant/Research Support: no disclosure.
- ✓ Speaker's Bureau: Amgen, BMS-Celgene, CSL Behring, Janssen Cilag, Sanofi, Takeda.
- ✓ Consultant: Amgen, BMS-Celgene, CSL Behring, GSK, Janssen Cilag, Pfizer, Takeda.
- ✓ Major Shareholder: no disclosure.
- ✓ Other: no disclosure.

I will be discussing "off-label" uses of the following medications: none

Liquid biopsy in multiple myeloma



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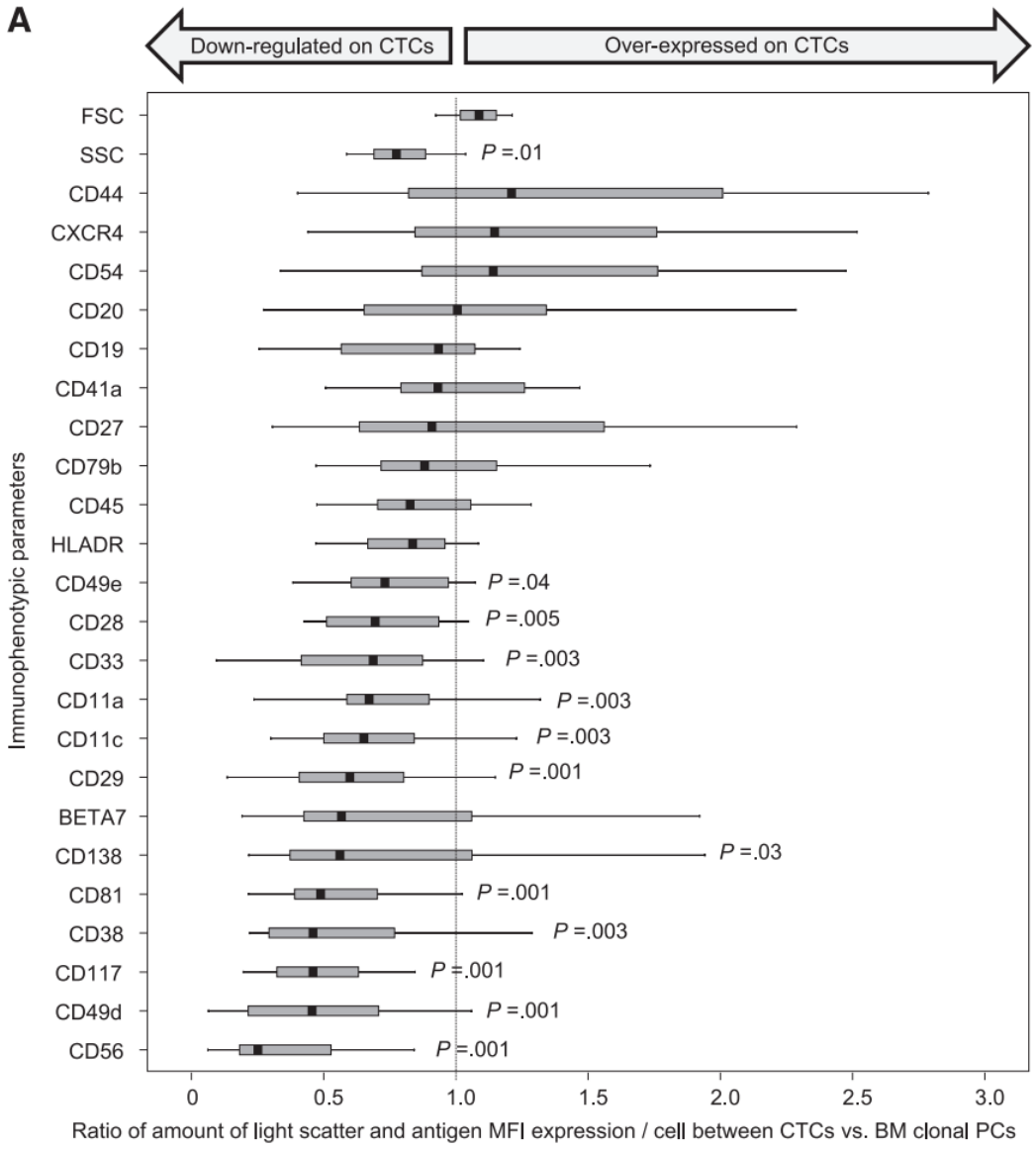
Mechanisms explaining multiple myeloma trafficking through peripheral blood disease dissemination (I)

- ✓ The mechanisms underlying the migration of PCs from the BM to the circulation and EM spread through PB dissemination remained unclear.
- ✓ Circulating MM Cells displayed overlapping immunophenotypic, genomic, and transcriptomic profiles with BM tumor PCs, but there could be minor but consistent differences between myeloma cells in the PB and BM that could indicate hallmarks associated with cell translocation and disease dissemination.
- ✓ A more immature and less proliferative immunophenotype was displayed on Circulating MM Cells.
- ✓ Circulating MM Cells displayed lower expression of integrin and adhesion molecules which potentially enhanced its capacity to exit into the PB.
- ✓ The expression of adhesion-related genes (CD44 and galectin 1) and the pathway involved in epithelial–mesenchymal transition (EMT) were significantly upregulated in Circulating MM Cells.

Characterization of MM circulating tumor cells

Notched boxes represent the 25th and 75th percentile values of the ratio between the amount of FSC, SSC, or antigen MFI expression per paired CTCs/BM clonal PCs; the line in the middle and vertical lines correspond to the median value and both the 10th and 90th percentiles, respectively.



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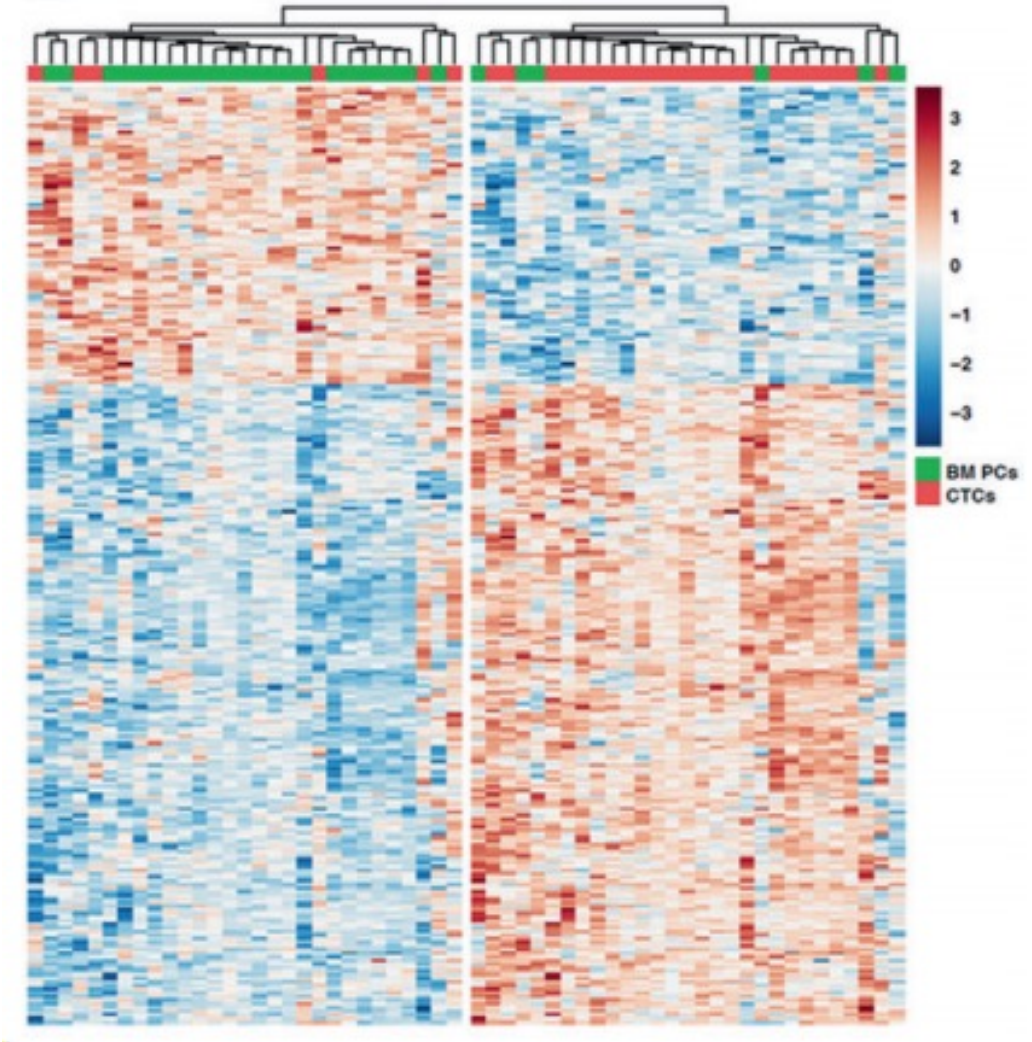
Roberto Ria, MD

Mechanisms explaining multiple myeloma trafficking through peripheral blood disease dissemination (II)

- ✓ It is unclear whether myeloma cells with distinct genetic features are more prone to spread the disease.
- ✓ Some data indicated that the Circulating MM Cells population represented a more genetically abnormal subclone than the BM clonal PC .
- ✓ An appreciable number of mutations that were identified in EM clones although absent in BM clones were identified in Circulating MM Cells.
- ✓ Circulating MM Cells are the most likely precursor of EM plasmacytomas and may act as a cellular bridge between BM and EM lesions.
- ✓ Circulating MM Cells had considerably increased levels of altered genes and pathways associated with hypoxia, inflammation, tumor migration, invasiveness, and metastasis, suggesting that the hypoxic and inflammatory microenvironment in BM niches would inhibit myeloma cell proliferation, forcing their migration into the PB and invasion of other niches.
- ✓ Another possible mechanism is increased auto-secretion and self-feeding of myeloma cells.

Molecular hallmarks of MM trafficking into the bloodstream.



Bi-clustering heatmap with differentially expressed genes (n = 259). Red and green colors differentiate CTCs and BM clonal PCs, respectively; blue–red gradient shows the expression level for each gene from low to high (scaled).

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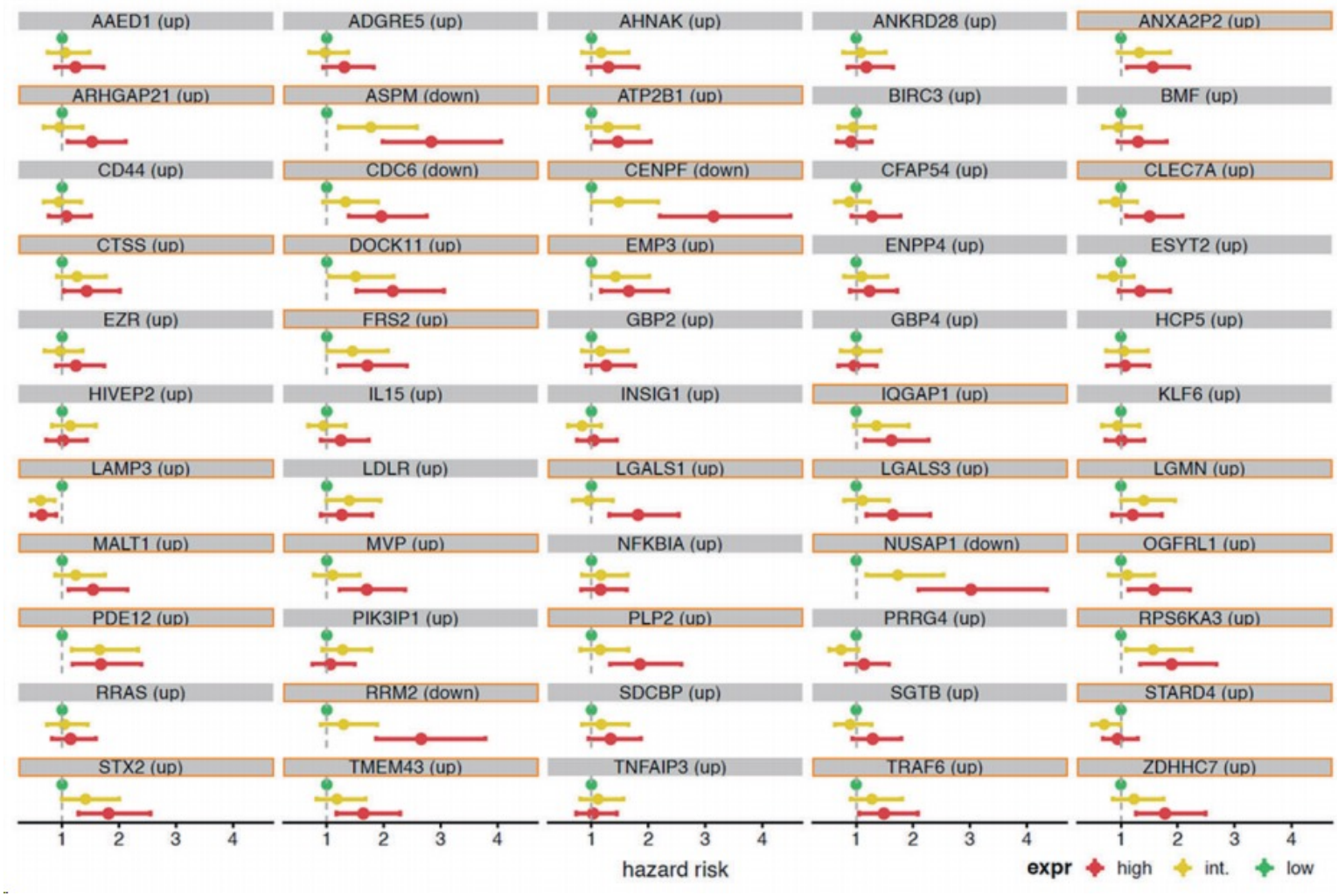
Genes differentially expressed in CTCs are associated with poor prognosis



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The detection efficiency and sensitivity of different methods in liquid biopsy

Method	Detection efficiency and sensitivity
Wright–Giemsa-stained blood smears	CMMCs were detected in approximately 14.1%–20.8% of patients with NDMM at diagnosis
Slide-based immunofluorescence	Sensitivity: 0.01% CMMCs were detected in 19.4%, 25%, and 80% of patients with MGUS, SMM, and NDMM, respectively
MFC (2-color: CD45 and CD38)	Sensitivity: 0.01% CMMCs were detected in 20%, 40%, 73%–83.6%, and 38.6% of patients with MGUS, SMM, NDMM at diagnosis, and MM before ASCT, respectively
MFC (5-color: CD38, CD138, CD45, CD19, and CD56)	Sensitivity: 0.01% CMMCs were detected in approximately 69.2%–74.1%, 60.5%, 0%, and 14% of patients with NDMM at diagnosis, in PR, in CR, and at relapse, respectively
MFC (6-color: CD38, CD138, CD45, CD19, cytoplasmic κ, and λ light chains)	Sensitivity: 20 cells/150,000 events (0.013%) CMMCs were detected in 24%, approximately 51.4%–67%, approximately 19.3%–19.4%, and 62/145 of patients with SMM, NDMM before therapy, MM before ASCT, and MM at relapse, respectively
MFC (7-color: CD38, CD138, CD45, CD19, CD56, cytoplasmic κ, and λ light chains)	Sensitivity: 0.01% CMMCs were detected in 60.1% and 18.8% of patients with NDMM at diagnosis and MM before ASCT, respectively
2 tubes/MFC (7-color: CD38, CD138, CD45, CD19, CD56, cytoplasmic κ, and λ light chains)	Sensitivity: approximately 0.004%–0.0001% CMMCs were detected in 119/191 (approximately 67%) of patients with NDMM at diagnosis
Magnetic cell sorting (MACS) (CD38 or CD138) combined with MFC (5-color: CD38, CD138, CD45, CD19, and CD56)	Sensitivity: 0.001% CMMCs were detected in 87.2%, approximately 83.7%–86%, approximately 5%–10%, and 85% of patients with NDMM at diagnosis, in PR, in CR, and at relapse, respectively
MACS (CD138) combined with MFC (7-color: CD45, CD19, CD81, CD27, CD117, CD56, and CD200)	CMMCs were detected in 83.3% and 9.9% of patients with NDMM/MM at relapse and MM who achieved CR, respectively
NGF (2-tube/8-color)	Sensitivity: 0.0001% CMMCs were detected in approximately 92%–100%, 100%, 59%, 25%, 18%, 17%, and 100% of patients with NDMM at diagnosis, SMM, MGUS, macro focal MM, solitary plasmacytoma, MM who achieved CR/sCR, and relapsed/refractory multiple myeloma (RRMM), respectively
CellSearch platform	CMMCs were detected in 98%, 93.7%, and approximately 56%–86% of patients with NDMM at baseline, intermediate/high-risk SMM, and MGUS, respectively
Epic platform	Sensitivity: one MM cell in $3*10^6$ WBCs
CD138-coated microfluidic device (Herringbone-shaped)	Sensitivity: < 10 CMMCs/mL using 1-mL sample
CD138-coated microfluidic device (Sinusoidal-shaped)	CMMCs were detected in 78% of patients with MGUS and 100% of those with SMM and MM
ASO-PCR of IGH rearrangements	Sensitivity: 0.001% CMMCs were detected in 13/16, 6/8, and 13/15 of patients with MGUS, SMM, and active MM, respectively
Real-time quantitative PCR of IGH rearrangements	Sensitivity: approximately 0.01%–0.001% CMMCs were detected in 67%, 43%, 25%, and 73% of patients with NDMM at diagnosis, NDMM before HDT for ASCT, NDMM 3 months after HDT, and RRMM at the time of relapse, respectively
LymphoSIGHT assay of IGH and IGK rearrangements	Sensitivity: well below 0.0001% 1. CMMCs were detected in 78% of patients with MM using DNA assay and 96% of patients with MM using DNA and RNA assays 2. ctDNA was detected in 83% of patients with MM using DNA assay 3. Tumor clones were detected in 98% of patients with MM using the combination of CMMCs and ctDNA
Ion Torrent of IGH rearrangements	Sensitivity: 0.001% MM clones in cfDNA were detected in 100% of patients with MM at relapse
NGS of IGK and IGL rearrangements	MM clones in cfDNA were detected in 71.4% of patients with NDMM/MM at relapse and 22.2% of samples from MM who achieved CR. All ctDNA-detectable CR samples were from a patient with nonsecretory MM
NGS of IGH, IGK, and IGL rearrangements	CMMCs were detected in 71% of patients with MM at baseline. MM clones in cfDNA were detected in 100% of patients with MM at baseline. MM clones in CMMCs and/or cfDNA were detected in 91% and 41% of patients with MM with stable or progressive disease and MM with PR or better, respectively
ULP-WGS	Lower limit: TF ≥ 3% In NDMM/RRMM, ≥ 3% TF was detected in 76% cfDNA samples and 100% CMMC samples; ≥ 10% TF was detected in approximately 24%–32% cfDNA samples and in 31% CMMC samples In MGUS/SMM/NDMM/RRMM, ≥ 3% TF was detected in 58% cfDNA samples and 96% CMMC samples; ≥ 10% TF was detected in 17% cfDNA samples and 21% CMMC samples
LP-WGS	Lower limit: TF ≥ 5% ≥ 5% TF was detected in 62% of cfDNA samples from patients with RRMM, in 75% of cfDNA samples from patients with NDMM, and in none of cfDNA samples from patients with MM post-treatment

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CTCs in MM and MGUS

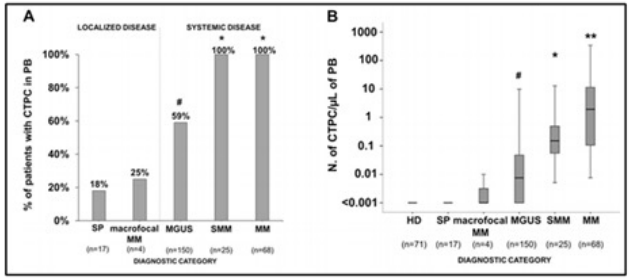
Sanoja-Flores et al. *Blood Cancer Journal* (2018)8:117
DOI 10.1038/s41408-018-0153-9

Blood Cancer Journal

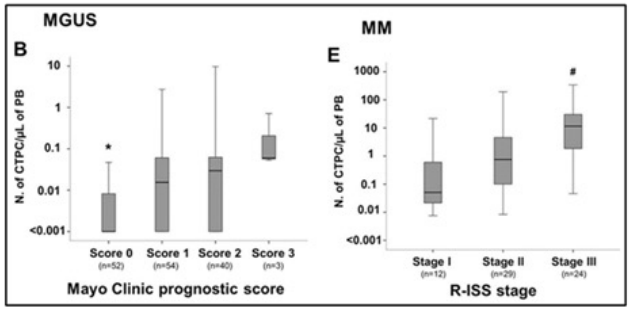
ARTICLE Open Access

Next generation flow for minimally-invasive blood characterization of MGUS and multiple myeloma at diagnosis based on circulating tumor plasma cells (CTPC)

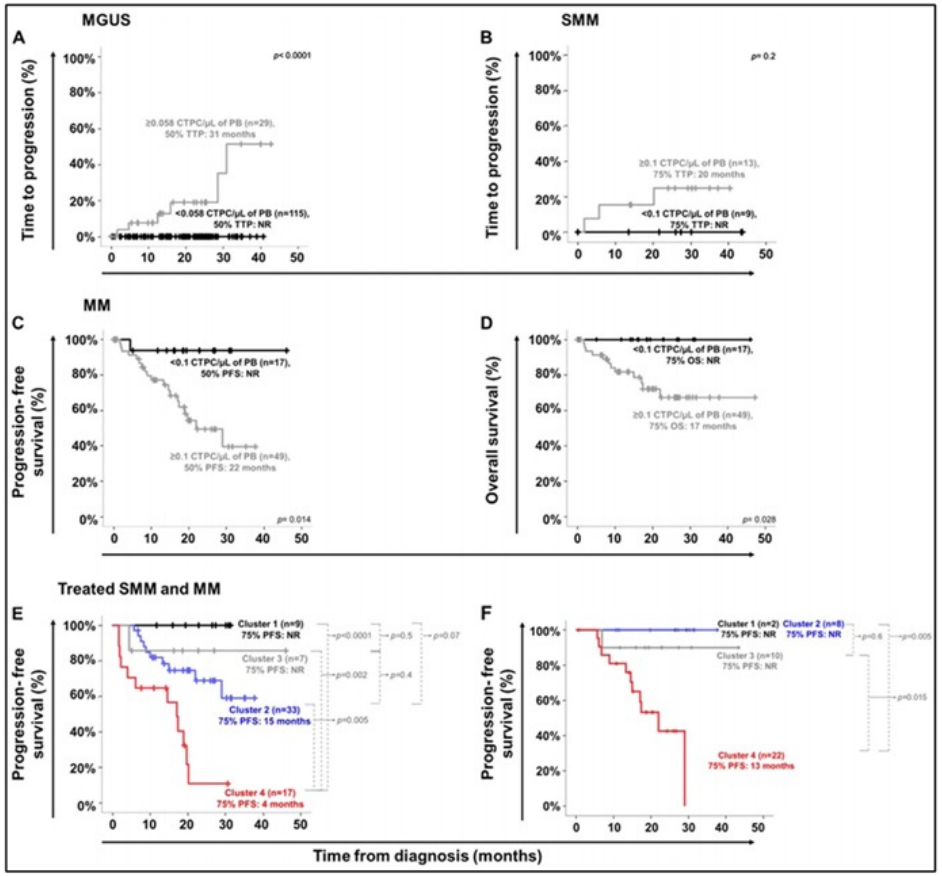
L. Sanoja-Flores[1,2], J. Flores-Montero[1,2], J. J. Garcés[3], B. Paiva[3], N. Puig[4], A. García-Mateo[5], O. García-Sánchez[4], A. Corral-Mateos[1,2], L. Burgos[3], E. Blanco[1,2], J. Hernández-Martín[3], R. Pontes[6], M. Díez-Campelo[4], P. Millacoy[7], P. Rodríguez-Otero[3], F. Prosper[3], J. Merino[3], M. B. Vidriales[4], R. García-Sanz[4], A. Romero[8], L. Palomera[9], R. Ríos-Tamayo[10], M. Pérez-Andrés[1,2], J. F. Blanco[11], M. González[4], J. J. M. van Dongen[12], B. Durie[13], M. V. Mateos[4], J. San-Miguel[3] and A. Orfao[1,2], on behalf of the EuroFlow consortium



Frequency of CTPC by NGF in PB of newly diagnosed PCN patients



Frequency and distribution of circulating tumor PC in PB of MGUS and MM patients classified into distinct risk-groups and clinical stages, respectively



Impact of PB CTPC counts at diagnosis on the outcome of MGUS, SMM, and MM patients

The presence of CTPC in PB as assessed by NGF is a hallmark of both SMM and MM and a highly frequent finding among MGUS, while absent in most SP and macrofocal MM cases. Higher numbers of CTPC in PB were strongly associated with features of malignant disease, providing a powerful minimally-invasive blood test to discriminate between MGUS and MM at diagnosis and to identify both (i) MGUS cases at high-risk of progression to MM, and (ii) a small subset of MM patients with low number of CTPC (within the range of MGUS cases) that display a significantly longer survival despite not achieving BM MRD negativity or CR.

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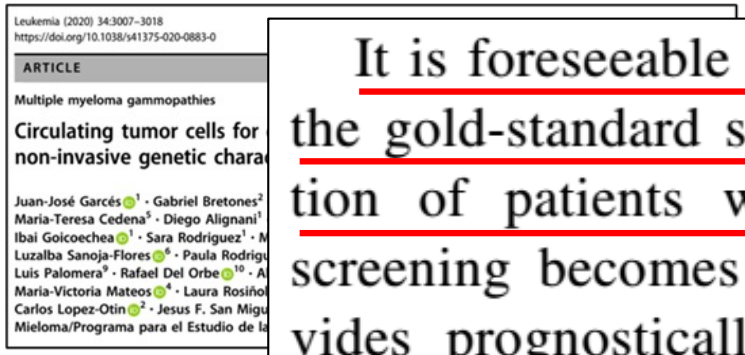
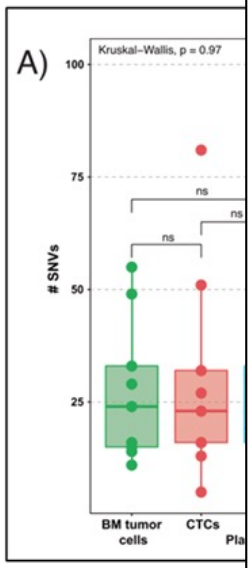
Roberto Ria, MD

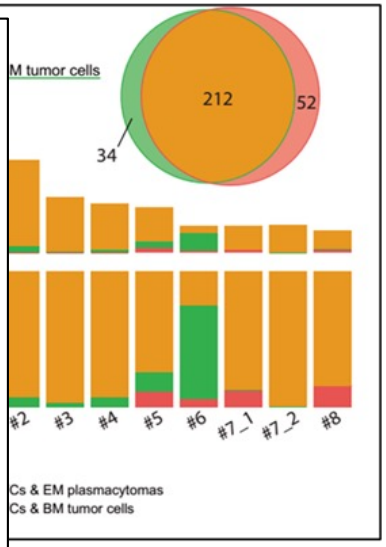
CTCs for characterization of MM



It is foreseeable that BM aspirates will continue to be the gold-standard specimen for the genetic characterization of patients with MM. However, if noninvasive screening becomes feasible, highly applicable and provides prognostically relevant information, it could be considered as a complementary approach to avoid some BM aspirates in certain time points during the clinical course of selected patients. Because CTC numbers in PB are per se prognostic [17, 26–30], this study suggests that quantification, isolation, and genetic characterization of CTCs using methods with potential for standardization may emerge as a complimentary approach for noninvasive risk-stratification of MM patients based on CTC numbers and genetic profile.



Spatial mutational heterogeneity



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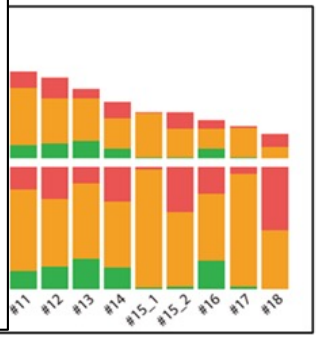

Concordance between mutations, CNA, and translocations found in CTCs vs BM tumor cells

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Roberto Ria, MD

The role of liquid biopsy in predicting therapeutic responses and disease prognosis in MM and precursor conditions

Sample	Detection time	Method	Cut-off	Prognostic value
NDMM	Before ASCT	MFC (6-color)	Presence of CMMC	1. A prognostic factor for PFS and OS independent of post-transplant sCR 2. A prognostic factor for post-trans- plant response status
NDMM	At diagnosis, before ASCT and day 100 post-transplant	MFC (6-color)	1. Presence of CMMC 2. Dynamics of CMMCs at diagnosis and before ASCT (−/−), (+/−), (+/+), (−/+)	1. CMMC (+/+) or (−/+) were fac- tors for lower incidence of pre-transplant ≥VGPR and post-transplant sCR 2. CMMC (+/+) or (−/+) was an independent factor for inferior PFS and OS 3. Patients with CMMCs at day 100 post-transplant had inferior PFS and OS
MM with EM	/	Combination of MACS and MFC (6-color)	Presence of CMMC	The presence of CMMCs in patients with EM disease had worse OS
NDMM	At diagnosis	MFC (7-color)	≥0.10% CMMCs/150,000 events	A prognostic factor for inferior PFS and OS independent of R-ISS stage and age
NDMM	At diagnosis	MFC (2-tube/7-color)	≥0.038% CMMCs	1. An independent prognostic factor for inferior PFS and OS 2. A factor for higher incidence of ≥VGPR and ≥PR
Transplant-eligible NDMM At diagnosis	At diagnosis	MFC (2-tube/7-color)	≥0.07% CMMCs (≥5 cells/μL)	1. A factor for lower incidences of MRD negativity and ≥CR at premaintenance 2. A factor for inferior PFS and OS independent of ISS, cytogenetics, and LDH level 3. A similar prognostic value between the cut-of value and continuous variable
NDMM	Before ASCT	MFC (7-color)	Presence of CMMCs	1. A factor for lower incidence of VGPR or better 2. A prognostic factor for inferior PFS, independent of ISS stage, cytogenetics, and maintenance therapy 3. The presence of CMMC enhanced the stratification of VGPR or better
MGUS, SMM, MM	At diagnosis	MFC (8-color)	>0.0035% CMMCs	An independent prognostic factor of inferior PFS and OS
MGUS, SMM, MM	At diagnosis	NGF	≥0.058 CMMCs/μL (for MGUS) ≥0.1 CMMCs/μL (for SMM and MM)	1 A factor for MGUS of higher incidence of progression in 30 months 2. A factor for SMM of higher incidence of progression to MM in 2 years 3. A factor for MM of inferior PFS and OS independent of CR status or MRD status

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Roberto Ria, MD

The role of liquid biopsy in predicting therapeutic responses and disease prognosis in MM and precursor conditions

Sample	Detection time	Method	Cut-off	Prognostic value
Treated MM	After therapy	NGF	1. Presence of CMMC 2. Kinetics of CMMCs	1. An independent prognostic factor for inferior PFS 2. The presence of CMMC enhanced the stratifcation of CR/sCR 3. Patients with CMMC−/−or+/−in sequential monitoring showed better PFS than those with CMMC+/+or−/+inde- pendent of sIF status
NDMM	At diagnosis	NGF	≥0.01% CMMCs (0.6 CMMCs/mL)	1. A factor for inferior PFS independ- ent of ISS stage, LDH, and cytogenet- ics 2. A prognostic factor for inferior PFS independent of CR status and MRD status
NDMM	At remission	CellSearch platform	≥100 CMMCs/4 mL of blood	A prognostic factor for inferior PFS and OS
NDMM	At diagnosis and 3 months after HDT for ASCT	ASO-qPCR of IgH rearrangement	Presence of CMMC	1. At diagnosis: a prognostic factor for inferior EFS 2. Three months after HDT for ASCT: a prognostic factor for inferior EFS and OS

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Roberto Ria, MD

CTCs for defining high risk MM

Leukemia (2014) 28, 2060–2065

www.nature.com/leu

ORIGINAL ARTICLE

Quantification of clonal circulating plasma cells in newly diagnosed multiple myeloma: implications for redefining high-risk myeloma

WI Gonsalves[1,2], SV Rajkumar[1,2], V Gupta[1,2], WG Morice[1,2], MM Timm[1,2], PP Singh[1,2], A Dispenzieri[1,2], FK Buadi[1,2], MQ Lacy[1,2], P Kapoor[1,2], MA Gertz[1,2] and SK Kumar[1,2]

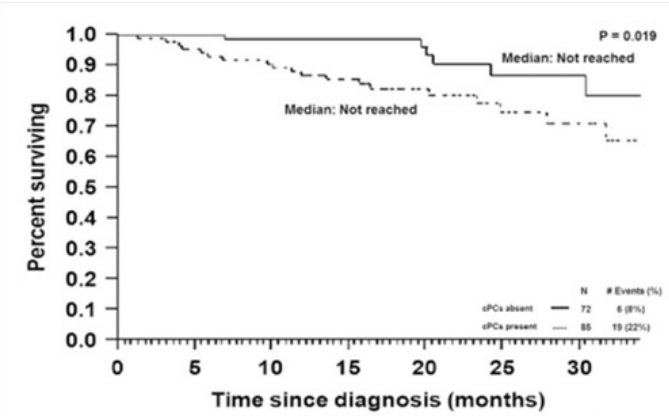

Figure 2. The Kaplan–Meier curve for OS in patients based on the presence of cPCs is shown.

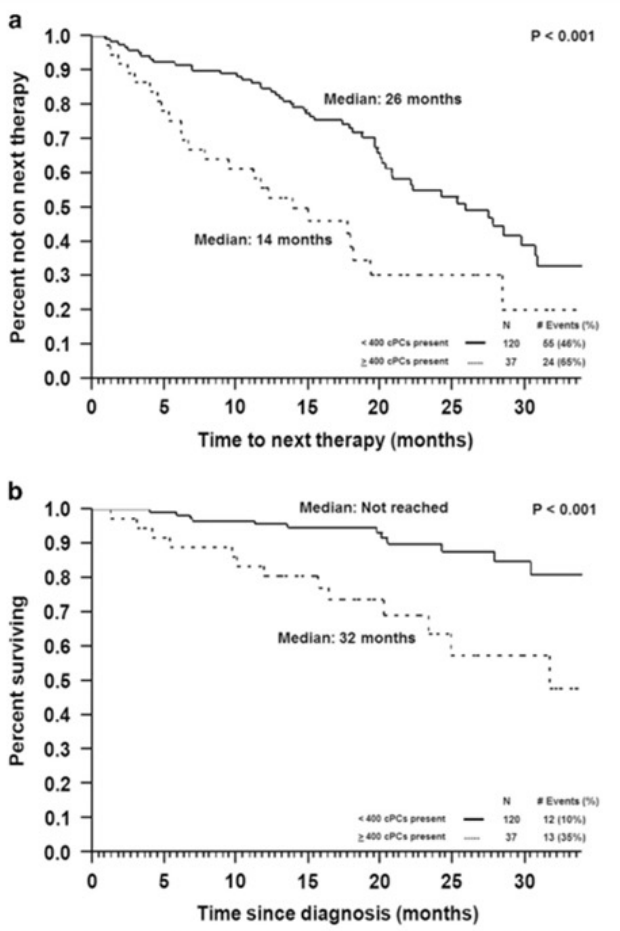

Figure 3. The Kaplan–Meier curve for TTNT (**a**) and OS (**b**) in patients based on the presence of ⩾400 cPCs is shown.

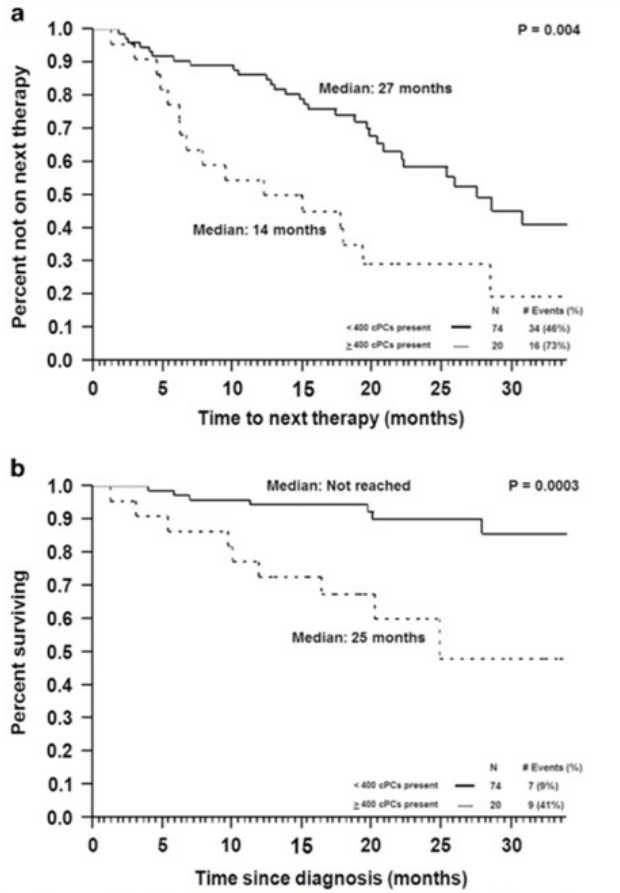

Figure 4. The Kaplan–Meier curve for TTNT (**a**) and OS (**b**) in patients with standard risk disease by FISH cytogenetics based on the presence of ⩾400 cPCs.

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Roberto Ria, MD

CTCs predict survival of MM patients

CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Circulating plasma cells detected by flow cytometry as a predictor of survival in 302 patients with newly diagnosed multiple myeloma

Grzegorz S. Nowakowski, Thomas E. Witzig, David Dingli, Michal J. Tracz, Morie A. Gertz, Martha Q. Lacy, John A. Lust, Angela Dispenzieri, Philip R. Greipp, Robert A. Kyle, and S. Vincent Rajkumar

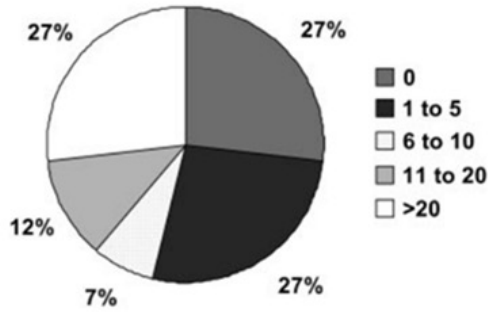

Figure 2. Distribution of circulating PCs in 302 study patients. Patients were divided into 5 groups based on the number of PCs.

Table 4. Risk stratification groups based on the circulating PCs and risk factors used in ISS

	No. patients at risk (%)	Median survival, mo
Risk factor		
B2M, more than 3.5 mg/L	190	41
Albumin level, less than 3.5 g/dL	127	28
Circulating PCs, more than 10	115	37
Risk stratification group		
Low-risk (none of the risk factors present)	56 (19)	79+
Low-intermediate risk (1 of the risk factors present)	98 (32)	48
High-intermediate risk (2 of the risk factors present)	91 (30)	32
High risk (3 risk factors present)	57 (19)	13

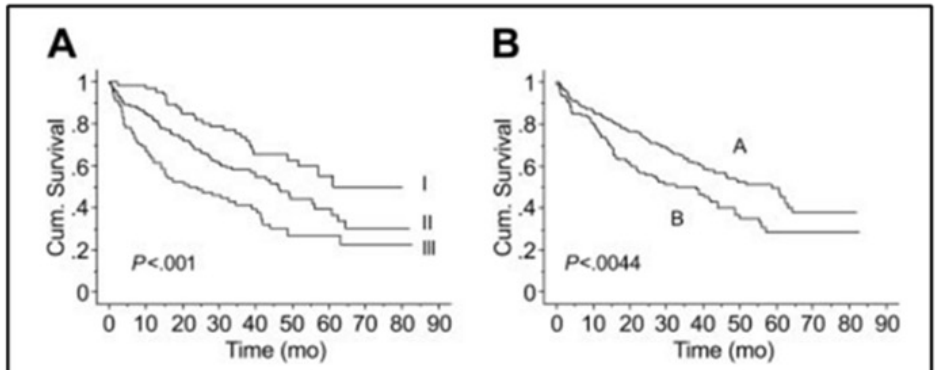

Figure 3. Kaplan-Meier estimates of OS. (A) Survival by ISS (ISS 1-I, ISS 2-II, ISS 3-III). (B) Survival by number of circulating PCs (A, 10 or less; B, more than 10).

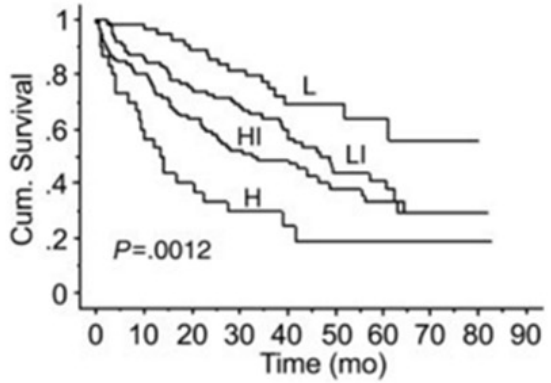

Figure 4. Kaplan-Meier estimates of OS in the risk stratification model using B2M, albumin levels, and circulating PCs. L indicates low-risk group; LI, low-intermediate risk group; HI, high-intermediate risk group; H, high-risk group.

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Roberto Ria, MD

CTCs for MM risk stratification

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ORIGINAL ARTICLE

Risk stratification in myeloma by detection of circulating plasma cells prior to autologous stem cell transplantation in the novel agent era

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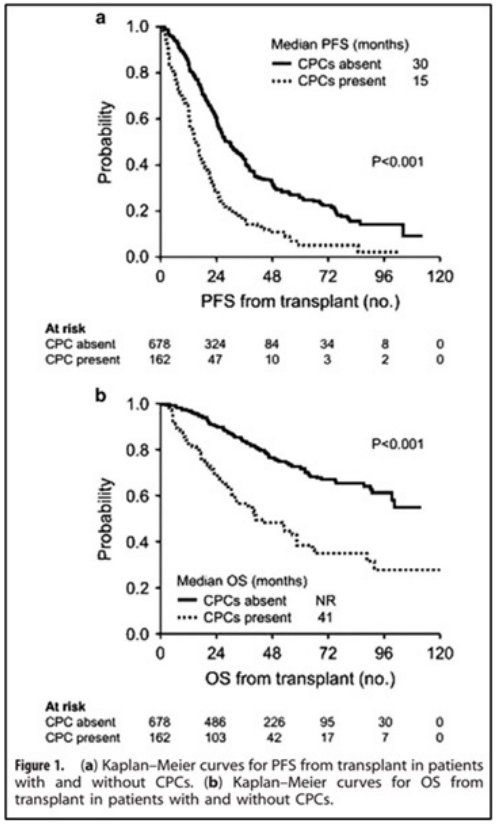

Figure 1. (**a**) Kaplan–Meier curves for PFS from transplant in patients with and without CPCs. (**b**) Kaplan–Meier curves for OS from transplant in patients with and without CPCs.

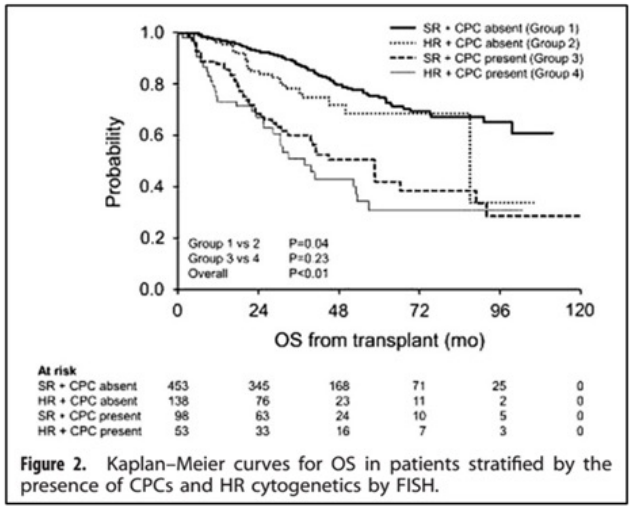

Figure 2. Kaplan–Meier curves for OS in patients stratified by the presence of CPCs and HR cytogenetics by FISH.

The proposed risk stratification with CPCs is easily reproducible and cost-effective. Detailed epigenomic, genomic and transcriptomic analysis of CPCs in large cohorts of patients is urgently needed to uncover the biological basis of their resistance to both high-dose cytotoxic therapy and novel agents and identify potential avenues of targeted therapy against CPCs. Quantification of CPCs along the entire trajectory of the disease should be actively incorporated in clinical trials to study the clonal evolution and kinetics of CPCs, and its impact on disease outcomes.

Table 3. Univariate and multivariate analysis for PFS and OS by Cox proportional hazards model

Variable	*Progression-free survival (PFS)*				*Overall survival (OS)*			
	Univariate Hazard ratio (95% CI)	*P-value*	*Multivariate Hazard ratio (95% CI)*	*P-value*	*Univariate Hazard ratio (95% CI)*	*P-value*	*Multivariate Hazard ratio (95% CI)*	*P-value*
Age ⩾65	0.87 (0.72–1.05)	0.144	NA	NA	1.09 (0.82–1.44)	0.538	NA	NA
HR FISH cytogenetics	1.30 (1.05–1.60)	0.015	1.20 (0.97–1.48)	0.088	1.71 (1.24–2.32)	0.001	1.26 (0.86–1.81)	0.231
CPCs present	2.28 (1.87–2.76)	< 0.0001	**2.03 (1.64–2.50)**	**< 0.001**	2.97 (2.25–3.88)	< 0.001	**2.52 (1.78–3.55)**	**< 0.001**
⩾VGPR at transplant	0.80 (0.67–0.95)	0.012	1.15 (0.92–1.42)	0.209	0.95 (0.72–1.24)	0.727	NA	NA
sCR post transplant	0.45 (0.37–0.55)	< 0.001	**0.44 (0.34–0.55)**	**< 0.001**	0.42 (0.30–0.59)	< 0.001	**0.39 (0.25–0.61)**	**< 0.001**
ISS stage 3	1.15 (0.94–1.41)	0.168	NA	NA	1.48 (1.08–2.01)	0.015	1.21 (0.86–1.70)	0.270
Reduced-dose melphalan	1.03 (0.78–1.32)	0.829	NA	NA	1.40 (0.96–1.99)	0.076	1.27 (0.78–1.98)	0.322

Abbreviations: CI, confidence interval; CPC, circulating plasma cells; FISH, fluorescence *in situ* hybridization; HR, high risk; ISS, International staging system; NA, not applicable; sCR, stringent complete response; VGPR, very good partial response. Bold values indicate statistically significance parameters.

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CTCs define plasma cell leukemia-like MM

original reports

More Than 2% of Circulating Tumor Plasma Cells Defines Plasma Cell Leukemia–Like Multiple Myeloma

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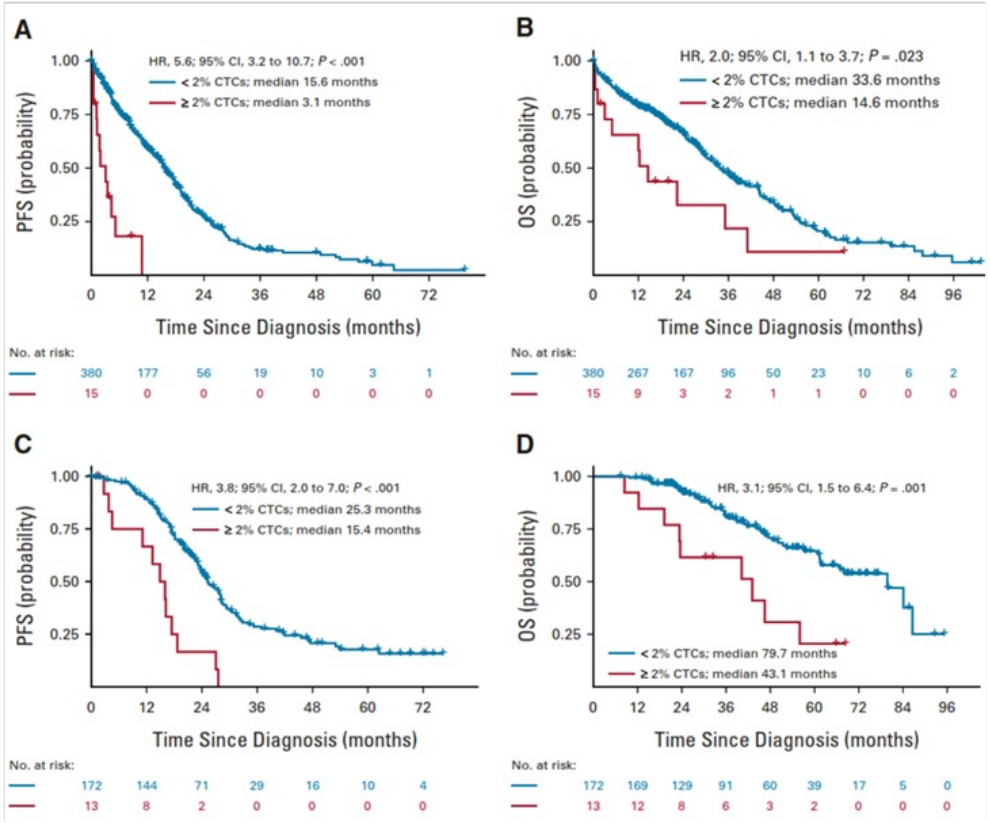

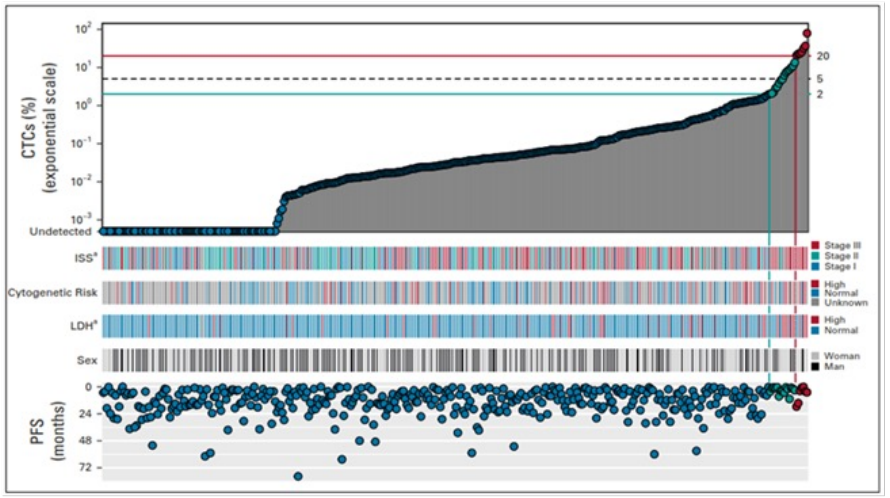

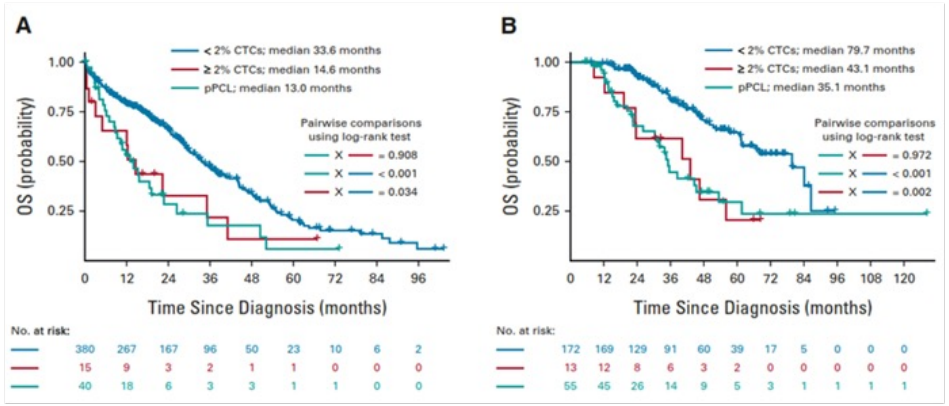

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CTCs in trasplanted patients

TRANSPLANTATION

Flow cytometric detection of circulating myeloma cells before transplantation in patients with multiple myeloma: a simple risk stratification system

David Dingli, Grzegorz S. Nowakowski, Angela Dispenzieri, Martha Q. Lacy, Suzanne R. Hayman, S. Vincent Rajkumar, Philip R. Greipp, Mark R. Litzow, Dennis A. Gastineau, Thomas E. Witzig, and Morie A. Gertz

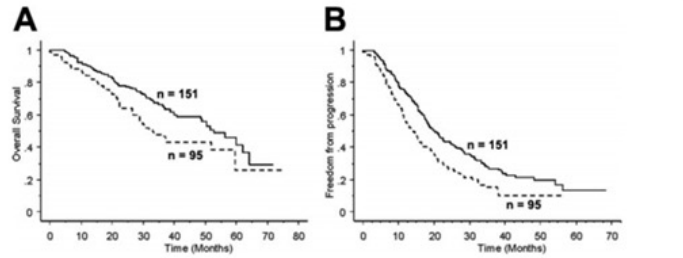

Figure 2. Kaplan-Meier plots based on the presence or absence of circulating myeloma cells detected by flow cytometry. (A) Overall survival (OS). (B) Time to progression (TTP). The presence of circulating myeloma cells is associated with an adverse outcome with respect to both OS and TTP ($P = .005$ and $P < .001$, respectively).

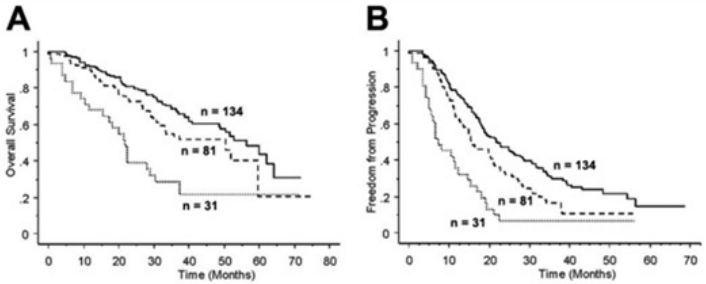

Figure 3. Kaplan-Meier plots based on the risk stratification combining cytogenetics and presence of circulating myeloma cells. (A) OS. (B) TTP. Patients with normal cytogenetics and no circulating myeloma cells have a superior OS and TTP compared with patients with one or both of these parameters.

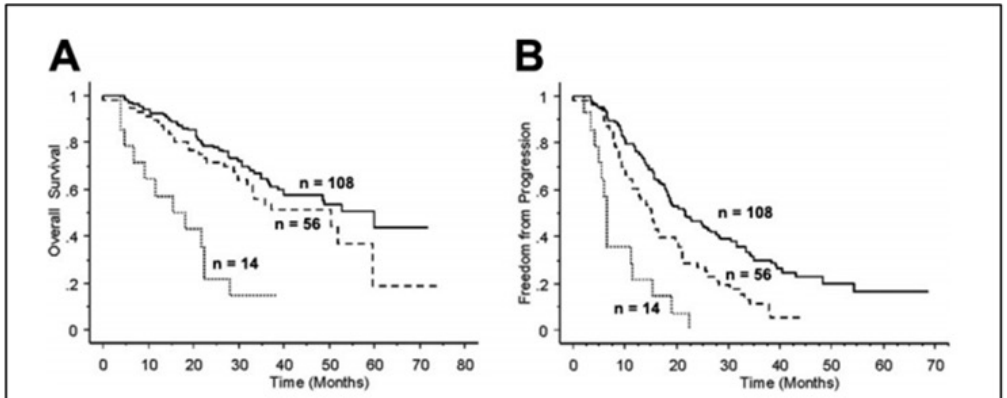

Figure 4. Kaplan-Meier plots for patients who received transplants, either in plateau phase or with chemotherapy-sensitive disease, stratified on the scoring system developed. (A) OS. (B) TTP. In this group of patients, both OS and TTP are inferior for patients with either or both risk factors.

Table 4. Overall survival and time to progression in the 3 risk groups based on cytogenetics and circulating myeloma cells

Risk group	n	OS, mo	TTP, mo
Low	134	55	21.8
Intermediate	81	48	15.4
High	31	21.5	6.5

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CTCs for MM staging

editorials

Circulating Tumor Cell Burden as a Component of Staging in Multiple Myeloma: Ready for Prime Time?

Rajshekhar Chakraborty, MD[1] and Suzanne Lentzsch, MD, PhD[1]

TABLE 1. Characteristics of Studies Assessing CTCs as a Prognostic Factor in Newly Diagnosed Myeloma

Characteristic	Garcés et al[12]	Bertamini et al[13]	Hofste op Bruinink et al[14]
RCTs	GEM2012MENOS65 and GEM2014MAIN (referred to as GEM trial)	FORTE	EMN12/HO129, CASSIOPEIA, and HO143
Treatment schema	VRd × 6 → HDT-AHCT (MEL200 *v* BUMEL) → VRd × 2 → Rd *v* IRd	First random assignment: Arm A: KRd × 4 → HDM-AHCT → KRd × 4 Arm B: KRd × 12 Arm C: KCd × 4 → HDM-AHCT → KCd × 4 Second random assignment: KR *v* R	EMN12/HO129: KRd × 4 → HDM-AHCT → KRd × 2, followed by allo-HCT or second HDM-AHCT → KR consolidation and maintenance CASSIOPEIA: Dara-VTd *v* VTd × 4 → HDM-AHCT → Dara-VTd *v* VTd × 2 → Dara *v* Observation HO-143: IDd × 9 → ID
Median follow-up	5 years	4.2 years	4.8 years in the pooled survival cohort[a] used for validation of the prognostic impact of PCL-like status
Methodology used for CTC detection	MFC	MFC	MFC
Sensitivity (limit of detection)	2×10^{-6} (NGF)	4×10^{-5}	2×10^{-6} (NGF)
Proportion of newly diagnosed patients with CTCs, %	92	67	87
Correlation between CTC and BMPC burden	$\rho = 0.41$ ($P < .001$)[b]	$r = 0.382$ ($P < .01$)[b]	Adjusted $R^2 = 0.16$ ($P < .001$)[c]
CTC cutoff for risk stratification	≥ 0.01%	≥ 0.07%	No specific cutoff provided for prognostication

On the basis of the consistency of evidence, we are confident that the CTC burden is a strong, negative, and independent prognostic factor in newly diagnosed transplant-eligible myeloma. In our opinion, centers with access to NGF can consider quantification of CTCs at baseline for risk stratification. These findings also have important implications in the design of high-risk enrichment trials where a high CTC burden on NGF or PCL-like transcriptome can potentially be used as an inclusion criterion even in the absence of clinical PCL with >5% CTCs on morphology. However, before formal incorporation in staging and routine clinical practice, the ≥0.01% cutoff for CTC burden using NGF needs to be validated in external data sets of transplant-eligible and transplant-ineligible patients receiving anti-CD38 monoclonal antibody–based frontline combination therapies.

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CTCs for a new R-ISS

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Enhancing the R-ISS Classification of Newly Diagnosed Multiple Myeloma by Quantifying Circulating Clonal Plasma Cells

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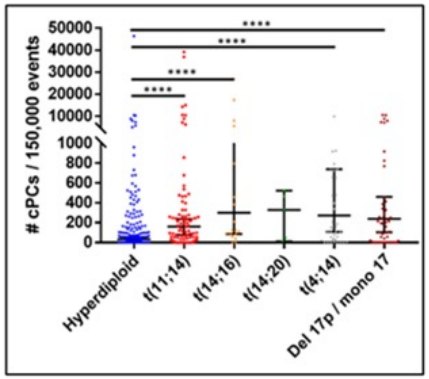

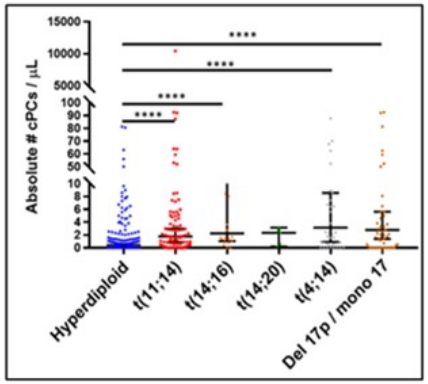

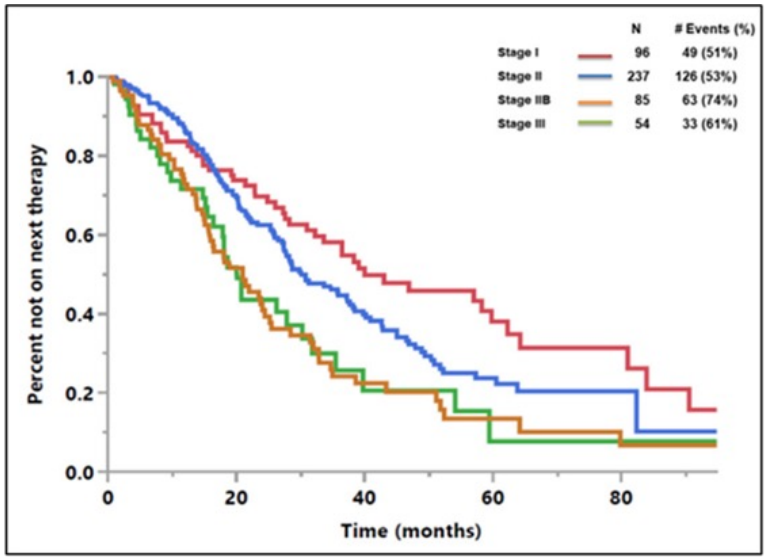

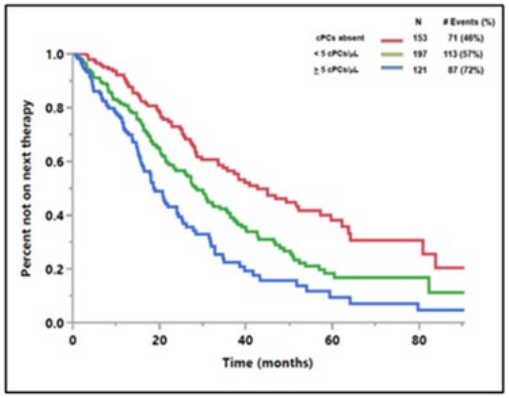

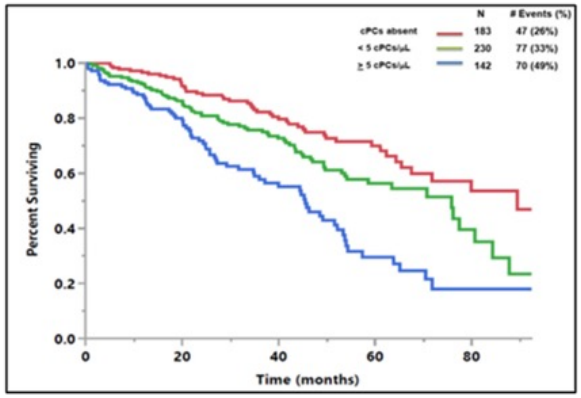

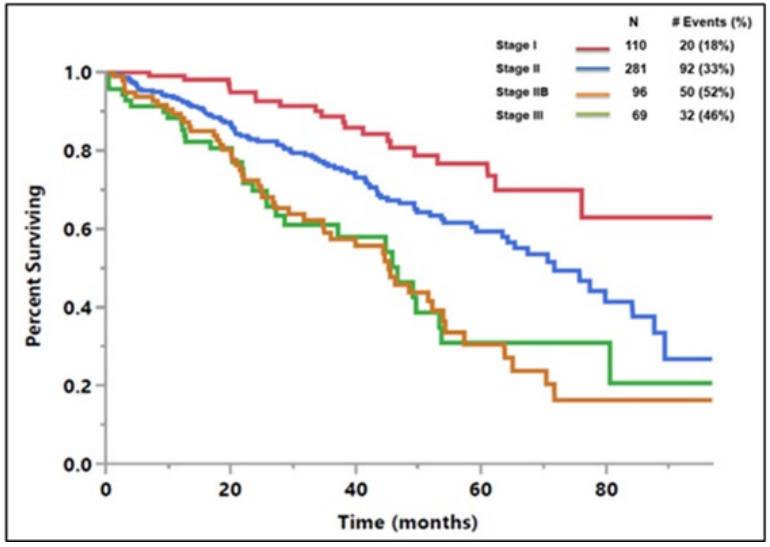

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Comparison of MRD evaluation in the BM and PB

Sample	Method	Results
CMMC n=122	MRD in BM: 5-color MFC MRD in PB: MACS (CD138) combined with 5-color MFC	1. MRD-positive BM samples were accompanied by PB-MRD-positive results in 88% of corresponding PB samples 2. 100% of MRD-negative BM samples were accompanied by MRD negative PB samples in NDMM, RRMM and MM achieved PR
CMMC n=45	MRD in BM and PB: 8-color MFC	1. 100% of PB-MRD-positive patients were BM-MRD-positive 2. 56% of PB-MRD-negative patients were BM-MRD-negative
CMMC n=137	MRD in BM and PB: NGF	1. 100% of PB-MRD-positive patients were BM-MRD-positive 2. 46/101 of PB-MRD-negative patients were BM-MRD-negative
CMMC n=42	MRD in BM and PB: RT-qPCR of IGH rearrangements	1. 100% of BM-MRD-negative patients were PB-MRD-negative before/after transplantation 2. 47% of BM-MRD-positive patients were PB-MRD-positive before transplantation 3. 33% of BM-MRD-positive patients were PB-MRD-positive after transplantation

CTCs for MRD evaluation

original reports

Measurable Residual Disease by Next-Generation Flow Cytometry in Multiple Myeloma

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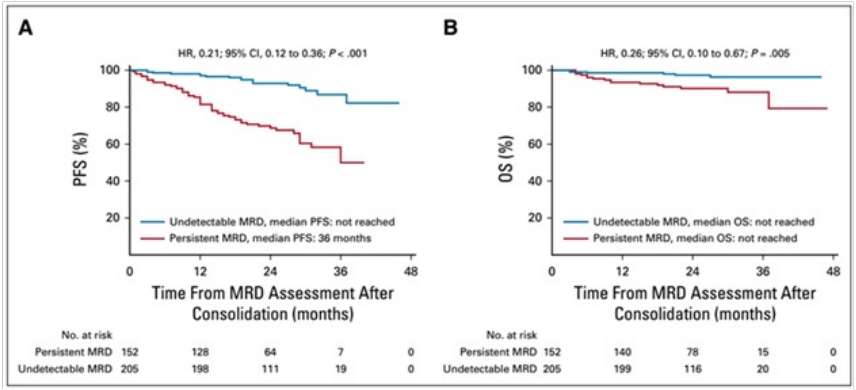

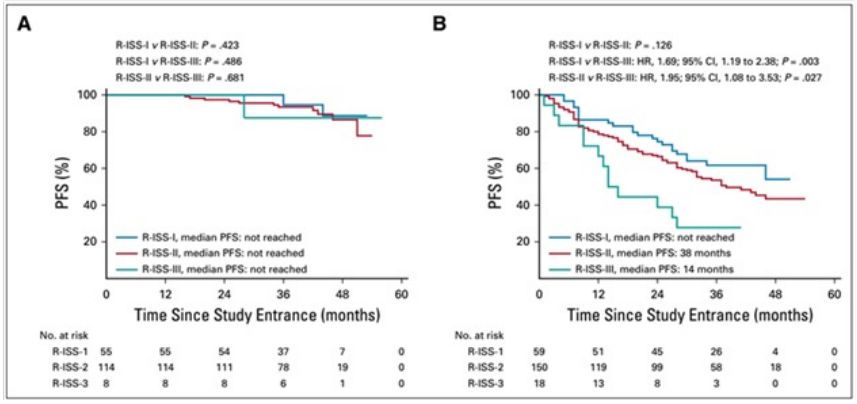

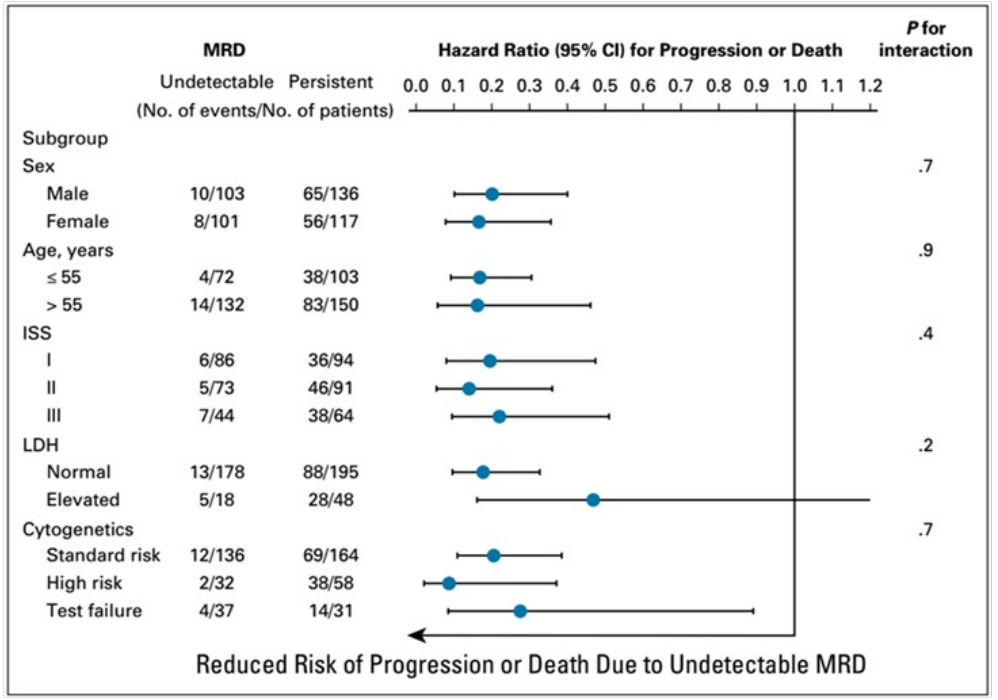

Model	PFS HR	PFS 95% CI	PFS P	OS HR	OS 95% CI	OS P
First regression						
Undetectable *v* persistent MRD	0.12	0.07 to 0.21	< .001	0.09	0.04 to 0.23	< .001
Second regression						
Undetectable *v* persistent MRD	0.12	0.07 to 0.21	< .001	0.09	0.04 to 0.23	< .001
R-ISS I/II *v* III	0.46	0.26 to 0.80	.006	0.29	0.15 to 0.55	< .001

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Roberto Ria, MD

CTCs in relapsed MM

bjh research paper

Quantification of clonal circulating plasma cells in relapsed multiple myeloma

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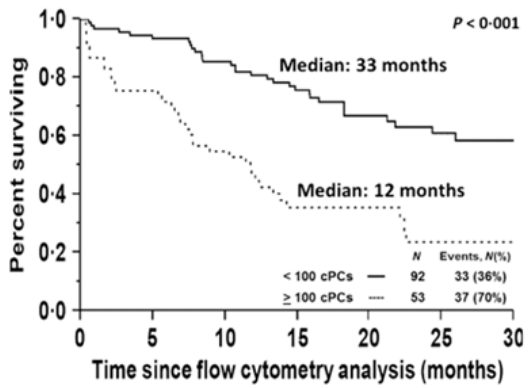

Fig 2. Shows the Kaplan–Meier Curve for survival from the time of peripheral blood flow cytometry analysis in all previously treated patients with actively relapsing disease based on the presence of circulating plasma cells (cPCs) based on the presence of 100 or more cPCs.

Table II. Univariate and Multivariate analysis of factors predicting worse overall survival.

	Overall survival			
	Univariate		Multivariate	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
≥100 clonal cPCs detected	**3·32 (2·05–5·41)**	**<0·0001**	**2·67 (1·37–5·17)**	**0·0041**
Number of prior lines of therapy	**1·15 (1·05–1·26)**	**0·0027**	**4·09 (1·56–10·14)**	**0·0048**
Serum creatinine	**1·56 (1·23–1·88)**	**0·0008**	**1·29 (0·89–1·87)**	0·1723
β2-microglobulin	**1·12 (1·07–1·16)**	**<0·0001**	1·05 (0·97–1·12)	0·2165
Elevated LDH (>222 u/l)	**1·02 (1·01–1·03)**	**<0·0001**	**2·93 (1·67–5·08)**	**0·0003**
High bone marrow PC%	1·00 (0·99–1·02)	0·0785	–	–
High risk status by FISH	1·64 (0·88–2·95)	0·1138	–	–

Bolded *P*-values and HRs represent statistically significant variables (i.e. $P < 0·05$).

cPCs, circulating plasma cells; LDH, lactate dehydrogenase; PC%, plasma cell percentage; FISH, fluorescent *in-situ* hybridization; HR, Hazard ratio; 95% CI, 95% confidence interval.

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CTCs for MM monitoring

blood Letters to *Blood*

TO THE EDITOR:

Blood monitoring of circulating tumor plasma cells by next generation flow in multiple myeloma after therapy

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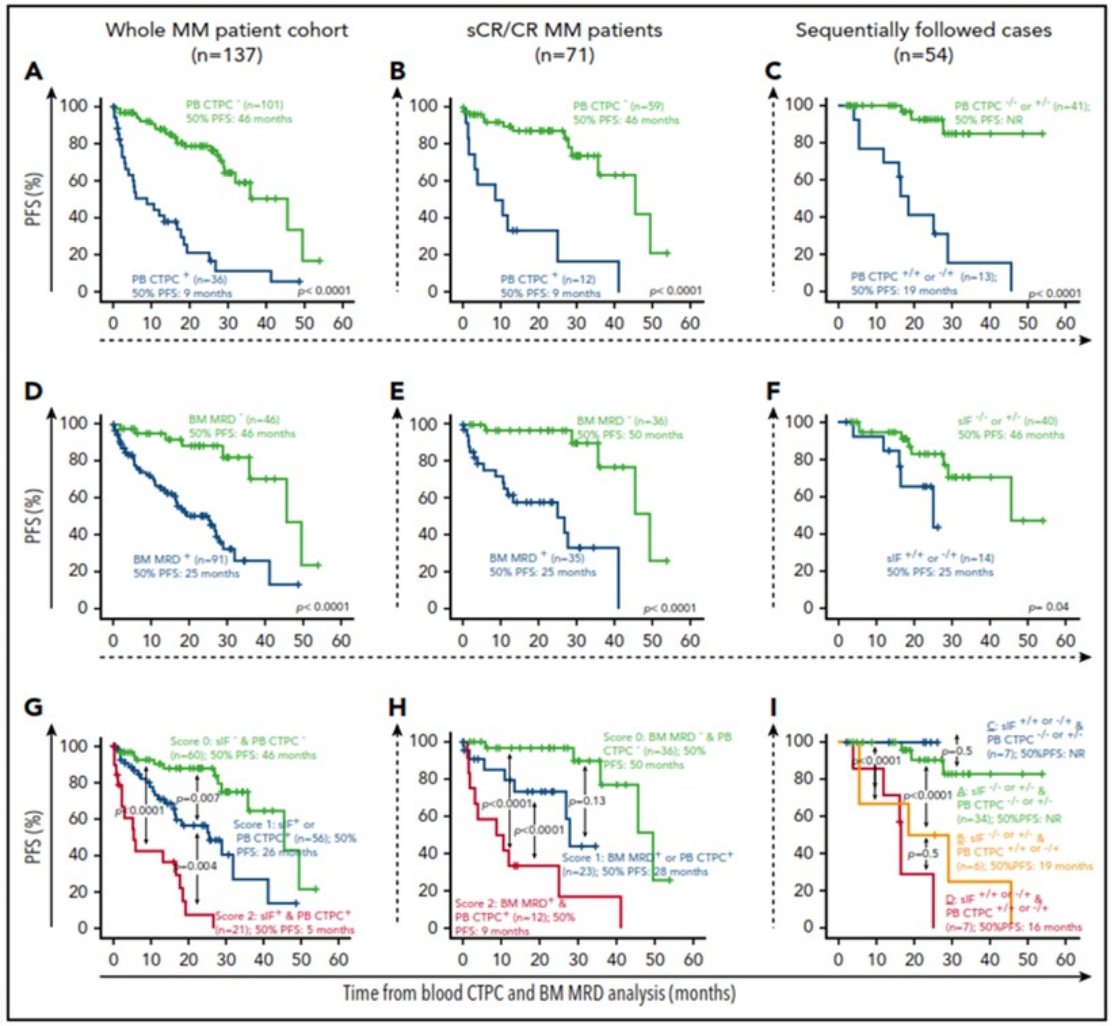
	Univariate analysis		Multivariate analysis		
	Median PFS (mo)	*P*	HR	(95% CI)	*P*
Prognostic factors for entire MM series					
Age					
<65 y	28	.3	—	—	—
≥65 y	36				
Cytogenetic profile by FISH					
Standard-risk	36	.07	—	—	—
High-risk	16				
Serum IF					
Negative	41	.001	—	—	—
Positive	18		2.4	(1.3-4.4)	.004
BM MRD status by NGF					
Negative	46	<.0001	—	—	—
Positive	25				
PB CTPC status by NGF					
Negative	46	<.0001	—	—	—
Positive	9		5.1	(2.9-8.9)	<.0001
Prognostic factors for sCR/CR cases					
Age					
<65 y	50	.5	—	—	—
≥65 y	41				
Cytogenetic profile by FISH					
Standard-risk	50	.09	—	—	—
High-risk	28				
BM MRD status by NGF					
Negative	50	<.0001	—	—	—
Positive	25		6.1	(1.5-24.4)	.01
PB CTPC status by NGF					
Negative	46	<.0001	—	—	—
Positive	9		7.4	(3.0-18.2)	<.0001



Unità per lo Studio e la Terapia delle Gammopatie Monoclonali

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DIPARTIMENTO DI MEDICINA DI PRECISIONE E RIGENERATIVA E AREA JONICA (DIMEPRE-J)

Roberto Ria, MD

Kinetics of CTCs as prognostic factor

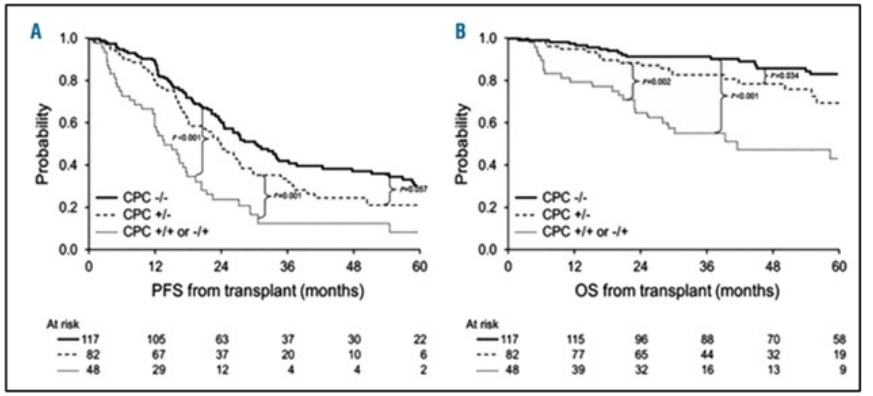
Plasma Cell Disorders ARTICLE

Serial measurements of circulating plasma cells before and after induction therapy have an independent prognostic impact in patients with multiple myeloma undergoing upfront autologous transplantation

Rajshekhar Chakraborty,[1,2] Eli Muchtar,[1] Shaji K. Kumar,[1] Dragan Jevremovic,[3] Francis K. Buadi,[1] David Dingli,[1] Angela Dispenzieri,[1] Suzanne R. Hayman,[1] William J. Hogan,[1] Prashant Kapoor,[1] Martha Q. Lacy,[1] Nelson Leung[4] and Morie A. Gertz[1]

[1]Division of Hematology, Mayo Clinic, Rochester; [2]Hospitalist Services, Essentia Health-St. Joseph's Medical Center, Brainerd, and [3]Department of Laboratory Medicine and Pathology, Division of Hematopathology, Mayo Clinic, Rochester, MN, USA

Haematologica 2017
Volume 102(8):1439-1445



Variable	N.*	Progression-free survival				Overall survival			
		Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
Age ≥65	247	0.80 (0.58-1.10)	0.178	NA	NA	0.90 (0.53-1.49)	0.902	NA	NA
High-risk cytogenetics by FISH	224	1.33 (0.89-1.93)	0.149	NA	NA	2.35 (1.31-4.04)	0.005	2.67 (1.29-5.29)	0.009
CPC kinetics	247								
CPC-/-		1 (referent)		1 (referent)		1 (referent)			
CPC+/-		1.40 (0.98-1.99)	0.060	1.63 (1.08-2.45)	0.020	1.82 (0.99-3.35)	0.053	2.68 (1.27-5.84)	0.009
CPC+/+ or -/+		2.79 (1.87-4.11)	<0.001	2.88 (1.73-4.68)	<0.001	4.53 (2.53-8.17)	<0.001	5.73 (2.53-13.12)	<0.001
≥VGPR at transplant	247	0.66 (0.48-0.90)	0.009	0.68 (0.46-0.99)	0.047	1.01 (0.61-1.04)	0.973	NA	NA
ISS stage 3 at diagnosis	226	1.03 (0.72-1.44)	0.869	NA	NA	1.36 (0.80-2.26)	0.249	NA	NA
LDH>UNL at diagnosis	210	0.87 (0.54-1.34)	0.532	NA	NA	1.63 (0.86-2.90)	0.125	NA	NA
LI>1 at diagnosis	185	1.53 (1.05-2.20)	0.028	1.57 (1.07-2.27)	0.021	2.18 (1.22-3.90)	0.009	1.91 (1.03-3.54)	0.039
PI-based induction therapy	247	1.03 (0.74-1.42)	0.846	NA	NA	1.29 (0.75-2.14)	0.344	NA	NA
IMiD-based induction therapy	247	1.06 (0.78-1.44)	0.704	NA	NA	0.59 (0.35-0.97)	0.037	0.79 (0.40-1.49)	0.466
PI- and IMiD-based induction therapy	247	0.92 (0.64-1.28)	0.618	NA	NA	1.47 (0.87-2.42)	0.145	NA	NA

NA: not applicable; HR: high-risk; FISH: fluorescence *in situ* hybridization; CPC: circulating plasma cells; VGPR: very good partial response; sCR: stringent complete response; ISS: International Staging System; LI: Labeling Index; PI: proteasome inhibitors; IMiD: immunomodulators; LDH: lactate dehydrogenase; UNL: upper normal limit. *Indicates number of patients with available data.

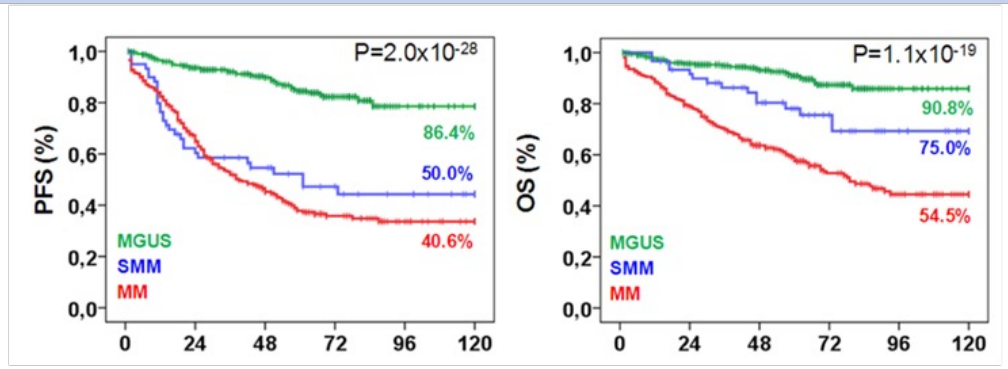
CTCs for premalignant disease stratification

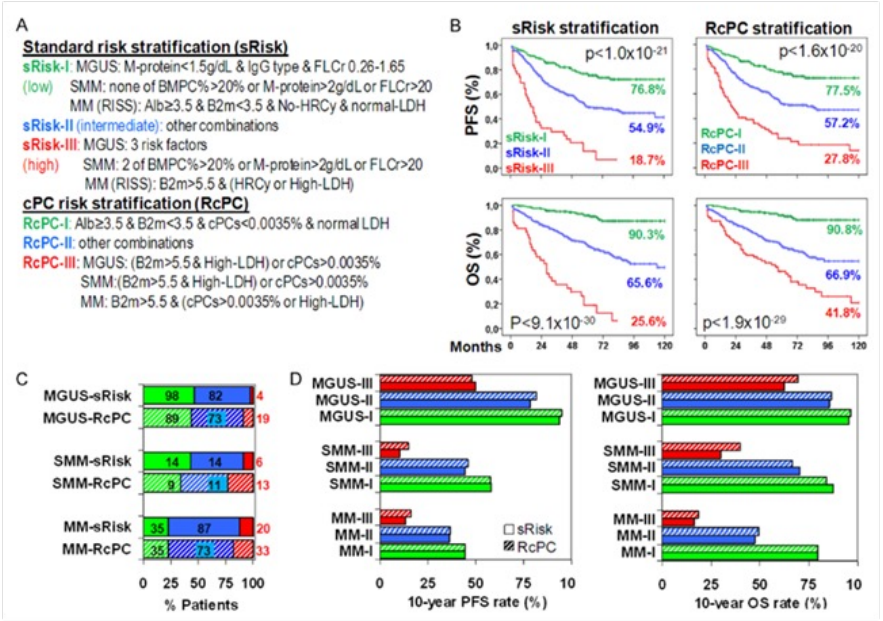
Am J Cancer Res 2021;11(6):2736-2753
www.ajcr.us /ISSN:2156-6976/ajcr0133903

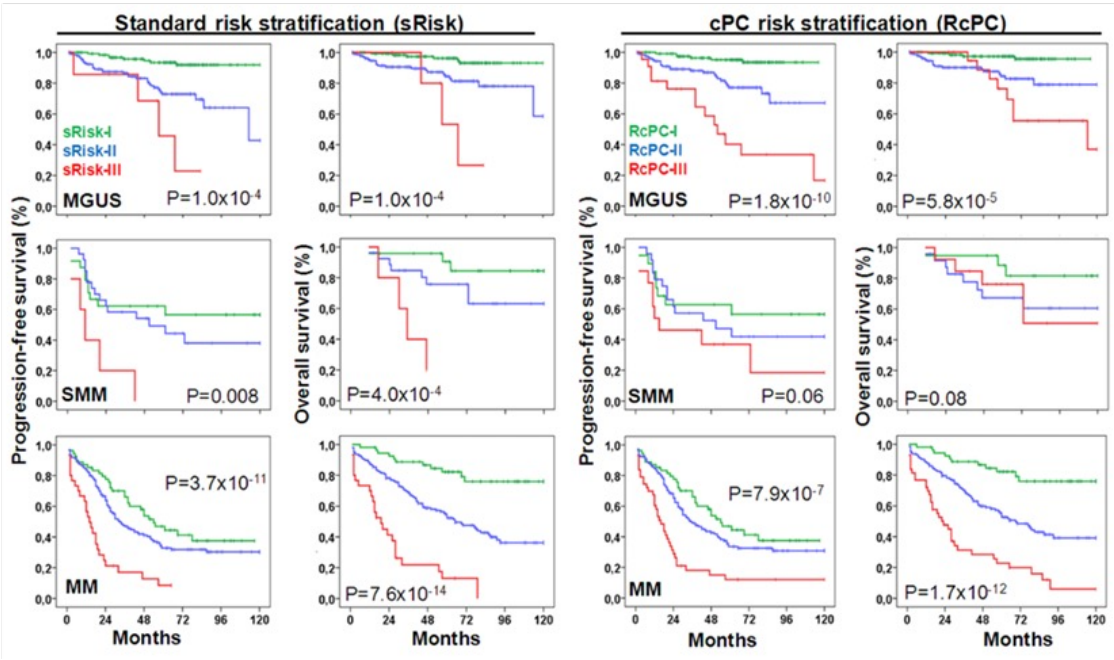
Original Article

Blood-based risk stratification for pre-malignant and symptomatic plasma cell neoplasms to improve patient management

María A Vasco-Mogorrón[1], José A Campillo[1], Adela Periago[2], Valentin Cabañas[3], Mercedes Berenguer[4], María C García-Garay[3], Lourdes Gimeno[1,5], María F Soto-Ramírez[1], María D Martínez-Hernández[1], Manuel Muro[1], Alfredo Minguela[1]







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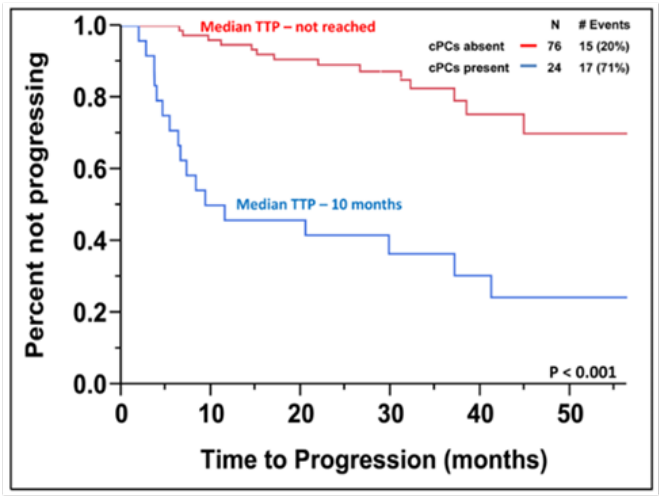
CTCs for SMM risk stratification

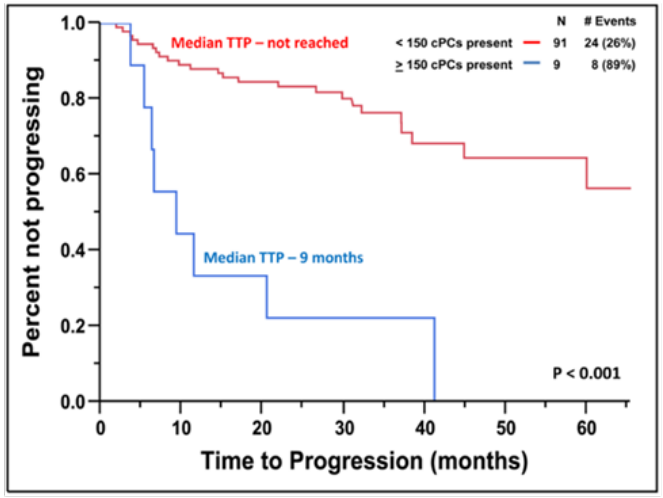
Leukemia. 2017 January ; 31(1): 130–135. doi:10.1038/leu.2016.205.

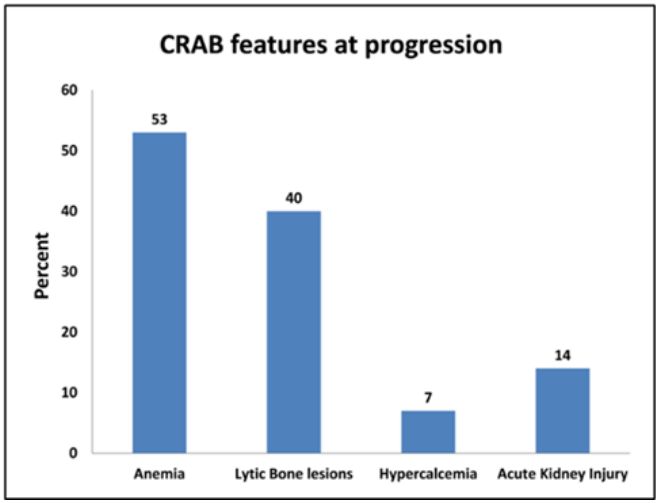
Quantification of Circulating Clonal Plasma Cells via Multiparametric Flow Cytometry Identifies Patients with Smoldering Multiple Myeloma at High Risk of Progression

Wilson I. Gonsalves, S. Vincent Rajkumar, Angela Dispenzieri, David Dingli, Michael M. Timm, William G. Morice, Martha Q. Lacy, Francis K. Buadi, Ronald S. Go, Nelson Leung, Prashant Kapoor, Suzanne R. Hayman, John A. Lust, Stephen J. Russell, Steven R. Zeldenrust, Lisa Hwa, Taxiarchis V. Kourelis, Robert A. Kyle, Morie A. Gertz, and **Shaji K. Kumar**

Divisions of Hematology and Blood and Marrow Transplantation, Mayo Clinic, Rochester, MN







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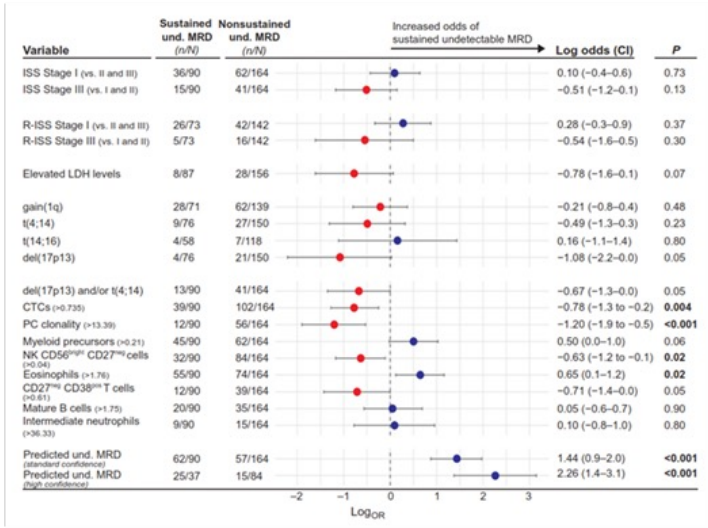
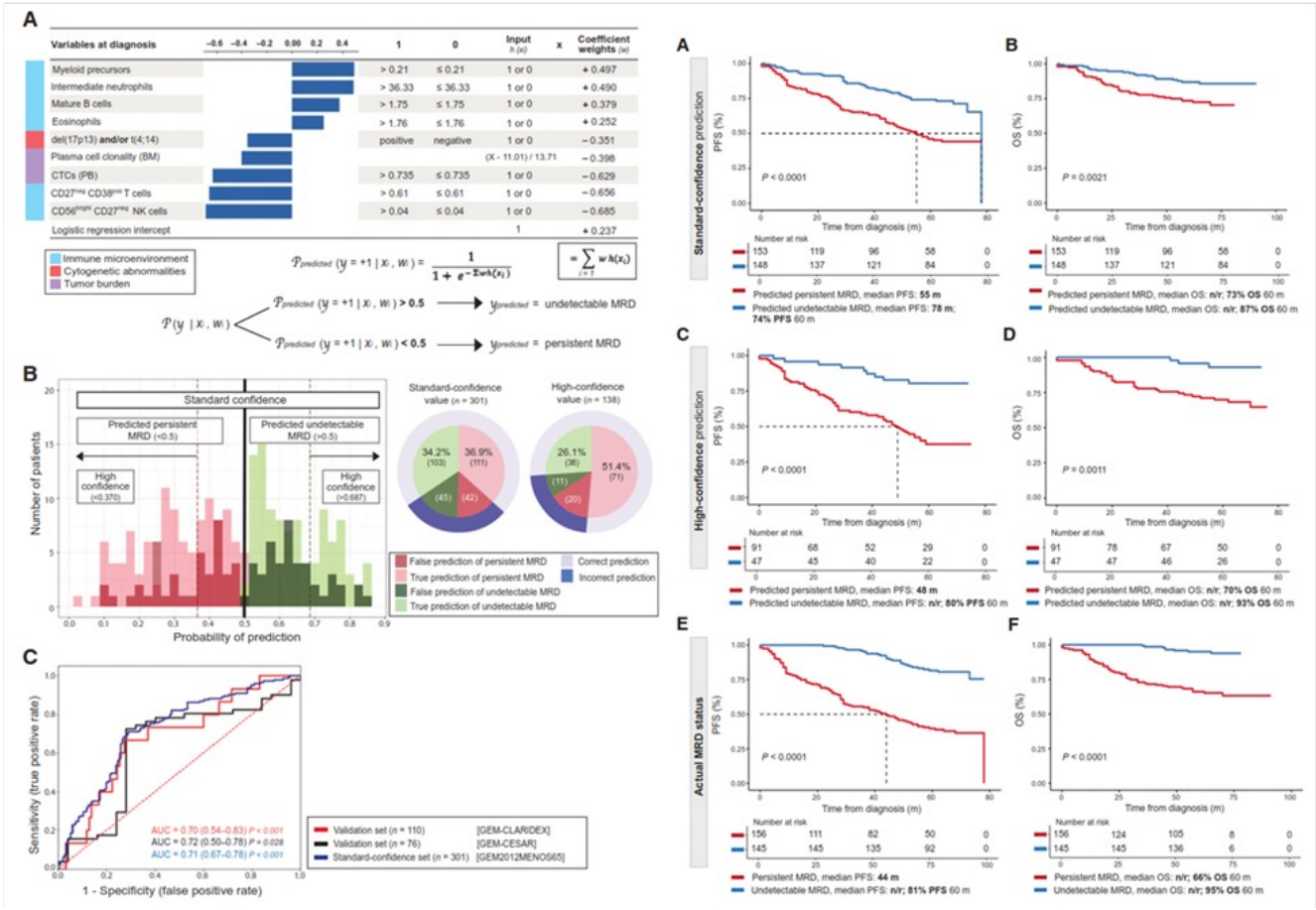
Can Artificial Intelligence help us?

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

A Machine Learning Model Based on Tumor and Immune Biomarkers to Predict Undetectable MRD and Survival Outcomes in Multiple Myeloma

Camila Guerrero[1], Noemi Puig[2], Maria-Teresa Cedena[3], Ibai Goicoechea[1], Cristina Perez[1], Juan-José Garcés[1], Cirino Botta[4], Maria-Jose Calasanz[1], Norma C. Gutierrez[2], Maria-Luisa Martin-Ramos[3], Albert Oriol[5], Rafael Rios[6], Miguel-Teodoro Hernandez[7], Rafael Martinez-Martinez[8], Joan Bargay[9], Felipe de Arriba[10], Luis Palomera[11], Ana Pilar Gonzalez-Rodriguez[12], Adrian Mosquera-Orgueira[13], Marta-Sonia Gonzalez-Perez[13], Joaquin Martinez-Lopez[3], Juan-José Lahuerta[3], Laura Rosiñol[14], Joan Blade[14], Maria-Victoria Mateos[2], Jesus F. San-Miguel[1], and Bruno Paiva[1]; on behalf of the Programa para el Estudio de la Terapéutica en Hemopatías Malignas (PETHEMA)/Grupo Español de Mieloma (GEM) cooperative study group





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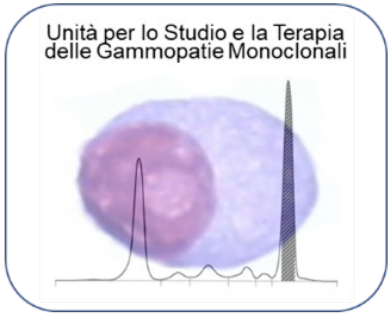
Take home messages

- ✓ Liquid biopsy allows for the minimally invasive detection of disease burden and molecular alterations in MM;
- ✓ The use of liquid biopsy would improve disease evaluation, also in patients with precursor diseases, EM diseases, or serologically nontrackable diseases;
- ✓ The introduction of liquid biopsy into the disease evaluation of MM would provide a tool for the comprehensive and real-time assessment complementary to conventional methods, promoting the development of new risk stratification systems and individual therapy options;
- ✓ Liquid biopsy in MM should be standardized to establish consistency to compare clinical trial data;
- ✓ To date, the sensitivity of liquid biopsy in MRD evaluation remains lower than that of BM-based MRD assay in MM;
- ✓ Methods with high sensitivity of liquid biopsy for MRD evaluation need to be further explored.

Head

Prof. Angelo Vacca

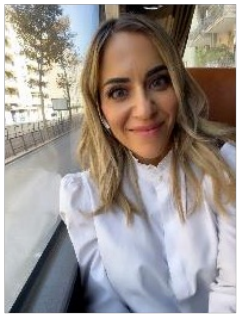
Prof. Roberto Ria



Dr. Antonio G. Solimando

Laboratorio: I. Saltarella, A. Lamanuzzi, V. Desantis

Data Manager
Study Nurse:
R. Acquaviva



Dr.ssa Giuditta De Fazio

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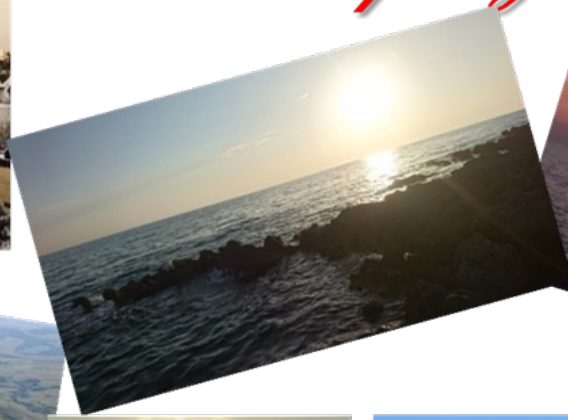
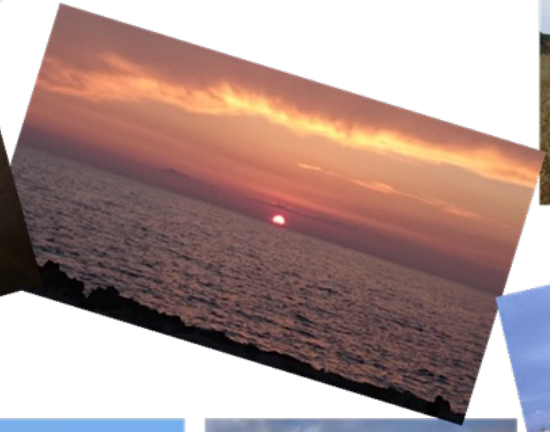
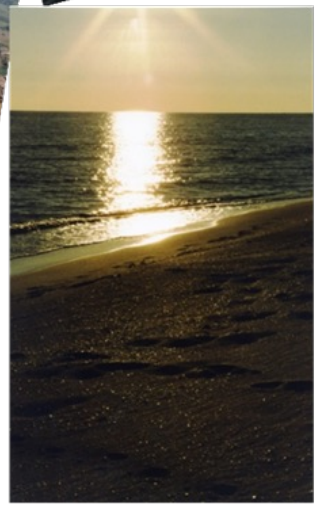
Thanks for your attention







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