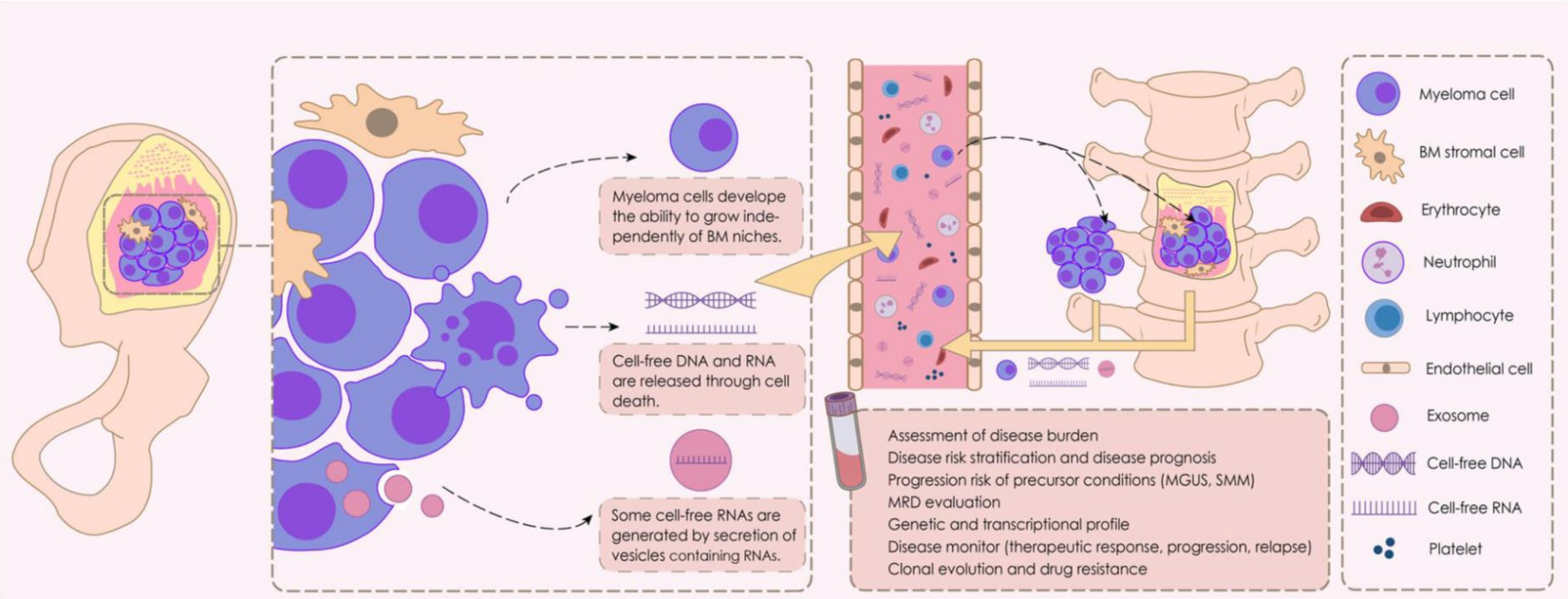
# Highlights from
# IMS 20th meeting 2023

Nicola Giuliani, MD, PhD

## Plasmacellule circolanti

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

# Circulating Plasma cells (CPCs) in multiple myeloma (MM)




Shuchan Li, et al. Biomarker Research 2023

## Mechanisms explaining PCs trafficking through peripheral blood (PB) dissemination: immunophyenotype.

✓ The mechanisms underlying the migration of PCs from the bone marrow (BM) to the circulation and extramedullary (EM) spread through PB dissemination remained unclear.

✓ Circulating PCs displayed overlapping immunophenotypic with BM tumor PCs, but there are minor but consistent differences between MM cells in the PB and BM that could indicate hallmarks associated with cell translocation and disease dissemination.

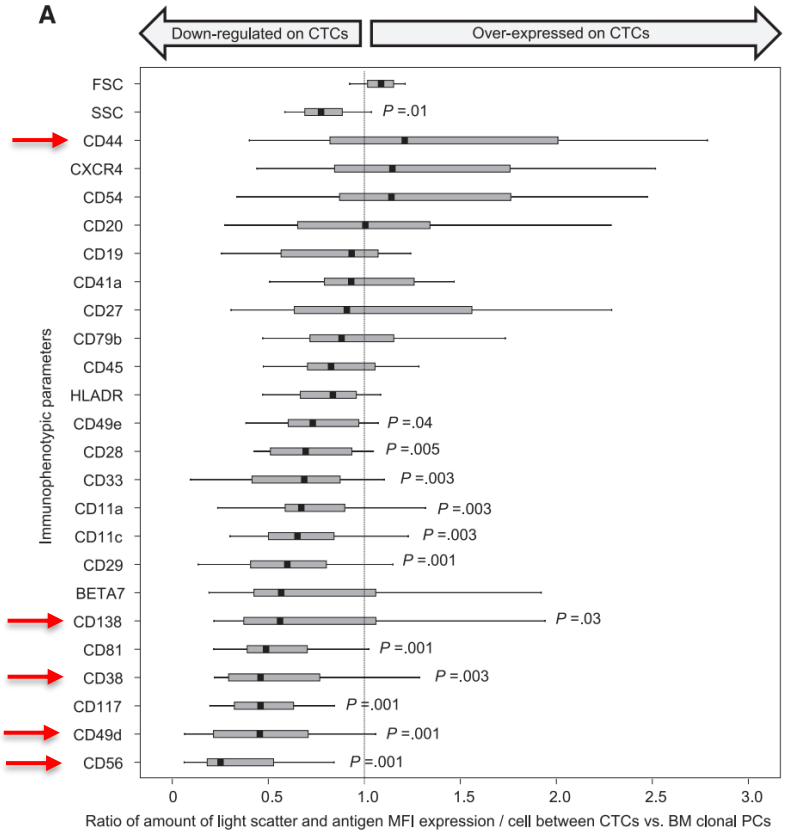
✓ A more immature and less proliferative immunophenotype was displayed on circulating PCs.

✓ Circulating PCs displayed lower expression of integrin and adhesion molecules which potentially enhanced its capacity to exit into the PB.

✓ The expression of some adhesion-related molecules (CD44 and galectin 1) and the pathway involved in epithelial–mesenchymal transition (EMT) were significantly upregulated in Circulating PCs compared to BM PCs.

*Sanoia-Flores L et al Cancers 2020; Li S et al. Biomarker Res 2023*

# CPCs in MM patients: immunophenotypic profile



## Mechanisms explaining PCs trafficking through peripheral blood (PB) dissemination: genomic.

- ✓ PCs with distinct genomic features are more prone to spread the disease.
- ✓ Some data indicated that the Circulating PCs population represented a more genetically abnormal subclone than the BM clonal PCs .
- ✓ An appreciable number of mutations that were identified in EM clones although absent in BM clones were identified in Circulating PCs.
- ✓ Circulating PCs 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 force their migration into the PB and invasion of other niches.

*Sanoia-Flores L et al Cancers 2020; Li S et al. Biomarker Res 2023*

Leukemia (2020) 34:589–603
https://doi.org/10.1038/s41375-019-0588-4

ARTICLE

Multiple myeloma gammopathies

# Transcriptional profiling of circulating tumor cells in multiple myeloma: a new model to understand disease dissemination

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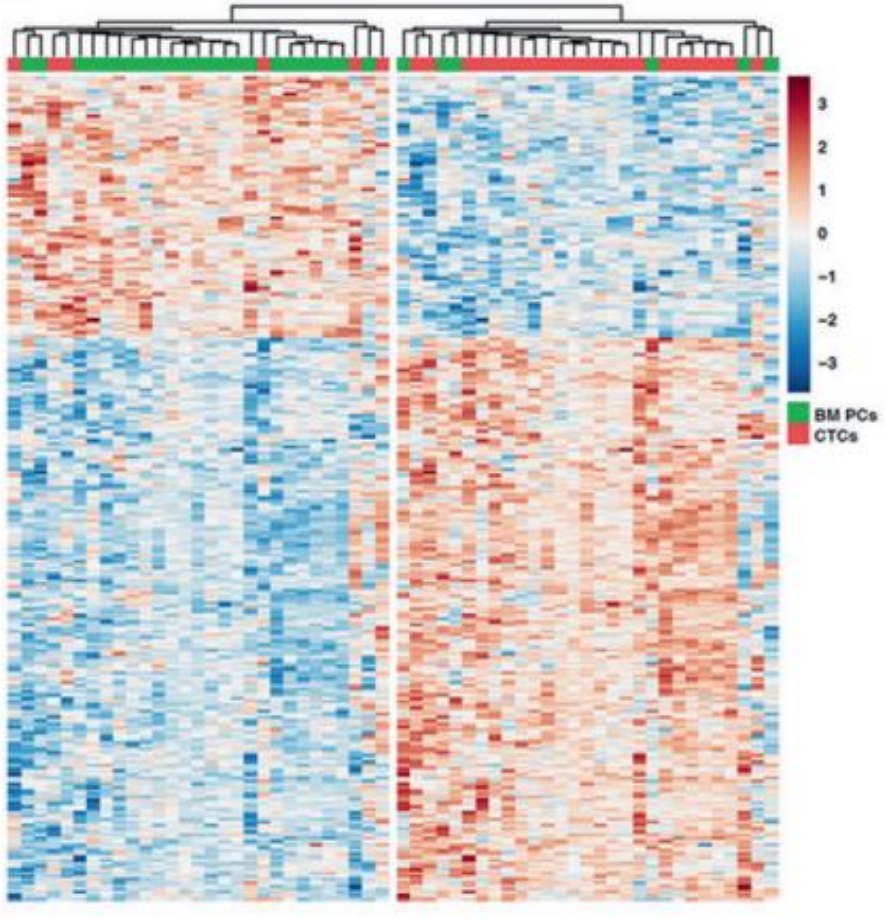
# CPCs in MM patients: molecular hallmark




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


C
log2FC
-0.5
0.0
0.5
1.0
CTCs
BM clonal PCs
MM-related genes
Pan-cancer genes
#genes/geneset
INFLAMMATORY_RESPONSE
TNFA_SIGNALING_VIA_NFKB
ALLOGRAFT_REJECTION
INTERFERON_ALPHA_RESPONSE
INTERFERON_GAMMA_RESPONSE
COMPLEMENT
IL6_JAK_STAT3_SIGNALING
APOPTOSIS
COAGULATION
CHOLESTEROL_HOMEOSTASIS
IL2_STAT5_SIGNALING
KRAS_SIGNALING_UP
EPITHELIAL_MESENCHYMAL_TRANSITION
HYPOXIA
APICAL_JUNCTION
P53_PATHWAY
ANGIOGENESIS
APICAL_SURFACE
TGF_BETA_SIGNALING
MYOGENESIS
MTORC1_SIGNALING
PROTEIN_SECRETION
XENOBIOTIC_METABOLISM
MYC_TARGETS_V1
DNA_REPAIR
MITOTIC_SPINDLE
MYC_TARGETS_V2
G2M_CHECKPOINT
E2F_TARGETS
AHNAK
ATP2B1
BIRC3
BMF
CD44
CDC6
CENPF
CTSS
EMP3
EZR
GBP2
GBP4
IL15
INSIG1
KLF6
LAMP3
LDLR
LGALS1
LGALS3
LGMN
MVP
NFKBIA
NUSAP1
RPS6KA3
RRAS
RRM2
SDCBP
STARD4
TNFAIP3
−2
0
2
NES

# CPCs in MM patients: Genes differentially expressed in CPCs are associated with poor prognosis

# CPCs in MM patients: implication for plasma cell leukemia definition

Plasma Cell Disorders

ARTICLE

## Prognostic impact of circulating plasma cells in patients with multiple myeloma: implications for plasma cell leukemia definition

**Miquel Granell,[1] Xavier Calvo,[2,6] Antoni Garcia-Guiñón,[3] Lourdes Escoda,[4] Eugènia Abella,[5] Clara Mª Martínez,[1] Montserrat Teixidó,[3] Mª Teresa Gimenez,[4] Alicia Senín,[5] Patricia Sanz,[1] Desirée Campoy,[3] Ana Vicent,[4] Leonor Arenillas,[6] Laura Rosiñol,[2] Jorge Sierra,[1] Joan Bladé[2] and Carlos Fernández de Larrea,[2] on behalf of GEMMAC (Grup per l'estudi del mieloma i l'amiloïdosi de Catalunya)**

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**ABSTRACT**

The presence of circulating plasma cells in patients with multiple myeloma is considered a marker for highly proliferative disease. In the study herein, the impact of circulating plasma cells assessed by cytology on survival of patients with multiple myeloma was analyzed. Wright-Giemsa stained peripheral blood smears of 482 patients with newly diagnosed myeloma or plasma cell leukemia were reviewed and patients were classified into 4 categories according to the percentage of circulating plasma cells: 0%, 1-4%, 5-20%, and plasma cell leukemia with the following frequencies: 382 (79.2%), 83 (17.2%), 12 (2.5%) and 5 (1.0%), respectively. Median overall survival according to the circulat-

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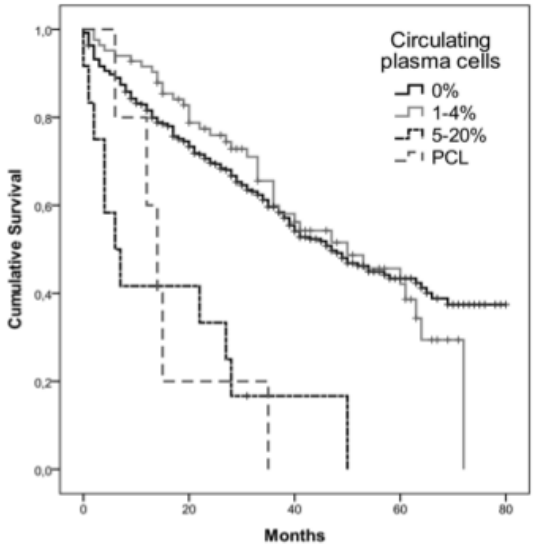
# CPCs in MM patients: implication for plasma cell leukemia definition




| | | | | | |
|---|---|---|---|---|---|
| 0% PC | 382 | 253 | 127 | 50 | 2 |
| 1-4% PCs | 83 | 62 | 31 | 13 | 0 |
| 5-20% PCs | 12 | 5 | 1 | 0 | 0 |
| PCL | 5 | 1 | 0 | 0 | 0 |

Figure 2. Overall survival according to the circulating plasma cells (PCs) in patients with multiple myeloma and plasma cell leukemia (PCL) treated with novel drugs upfront ($P<0.001$).

As highlighted in the last consensus by IMWG,[3] the diagnosis of PCL has been classically done on the basis of the presence of >20% circulating PCs and/or an absolute count >2 × $10^9$/L PCs. However, lower peripheral blood PC counts, as showed in our study (that is, ≥5% peripheral blood plasma cells), should be considered as a diagnostic criteria of PCL ("PCL-like" myeloma or early PCL), due to the independent and strong prognostic impact.

In conclusion, the presence of ≥5% circulating PCs by conventional cytology easily identifies a group of patients with myeloma with a prognosis as poor as that of PCL, suggesting that the diagnosis of PCL should be revisited. If confirmed in other series, especially in prospective studies of uniformly treated patients, such patients may benefit from a distinct and more intensified therapeutic approach.

Blood Cancer Journal

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ARTICLE OPEN

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# Primary plasma cell leukemia: consensus definition by the International Myeloma Working Group according to peripheral blood plasma cell percentage

Carlos Fernández de Larrea[1✉], Robert Kyle[2], Laura Rosiñol[1], Bruno Paiva[3], Monika Engelhardt[4], Saad Usmani[5], Jo Caers[6], Wilson Gonsalves[2], Fredrik Schjesvold[7], Giampaolo Merlini[8], Suzanne Lentzch[9], Enrique Ocio[10], Laurent Garderet[11], Philippe Moreau[12], Pieter Sonneveld[13], Ashraf Badros[14], Gösta Gahrton[15], Hartmut Goldschmidt[16], Sascha Tuchman[17], Hermann Einsele[18], Brian Durie[19], Baldeep Wirk[20], Pellegrino Musto[21], Patrick Hayden[22], Martin Kaiser[23], Jesús San Miguel[3], Joan Bladé[1], S. Vincent Rajkumar[2] and Maria Victoria Mateos[10]



## Consensus recommendation

Primary PCL is defined by the presence of 5% or more circulating plasma cells in peripheral blood smears in patients otherwise diagnosed with symptomatic MM. Careful examination of peripheral blood by conventional microscopy should be done in all patients with MM. A minimum of 100–200 nucleated cells per smear should be systematically analyzed by an experienced pathologist/hematologist. Patients with this new definition should not be excluded from clinical trials.

original reports

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

Tomas Jelinek, MD, PhD[1]; Renata Bezdekova, PhD[2]; David Zihala, PhD[1]; Tereza Sevcikova, PhD[1,3]; Anjana Anilkumar Sithara, MSc[1,3]; Lenka Pospisilova, MSc[4]; Sabina Sevcikova, PhD[5]; Petra Polackova, MSc[2]; Martin Stork, MD, PhD[6]; Zdenka Knechtova, MCs[6]; Ondrej Venglar, MSc[3]; Veronika Kapustova, MSc[1]; Tereza Popkova, MD[1]; Ludmila Muronova, MD[1]; Zuzana Chyra, PhD[1]; Matous Hrdinka, PhD[1]; Michal Simicek, PhD[1]; Juan-Jose Garcés, PhD[7]; Noemi Puig, MD, PhD[8]; Maria-Teresa Cedena, MD, PhD[9]; Artur Jurczyszyn, MD, PhD[10]; Jorge J. Castillo, MD, PhD[11]; Miroslav Penka, MD[2]; Jakub Radocha, MD, PhD[12]; Maria Victoria Mateos, MD[8]; Jesús F. San-Miguel, MD, PhD[7]; Bruno Paiva, PhD[7]; Ludek Pour, MD, PhD[5]; Lucie Rihova, PhD[2]; and Roman Hajek, MD, PhD[1]

**METHODS** We assessed the levels of CTCs by multiparameter flow cytometry in 395 patients with newly diagnosed transplant-ineligible MM to establish a cutoff for CTCs that identifies the patients with ultra-high-risk PCL-like MM. We tested the cutoff on 185 transplant-eligible patients with MM and further validated on an independent cohort of 280 transplant-ineligible patients treated in the GEM-CLARIDEX trial. The largest published real-world cohort of patients with primary PCL was used for comparison of survival. Finally, we challenged the current 5% threshold for primary PCL diagnosis.

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# CPCs in MM patients: definition of plasma cell leukemia-like MM by flow cytometry

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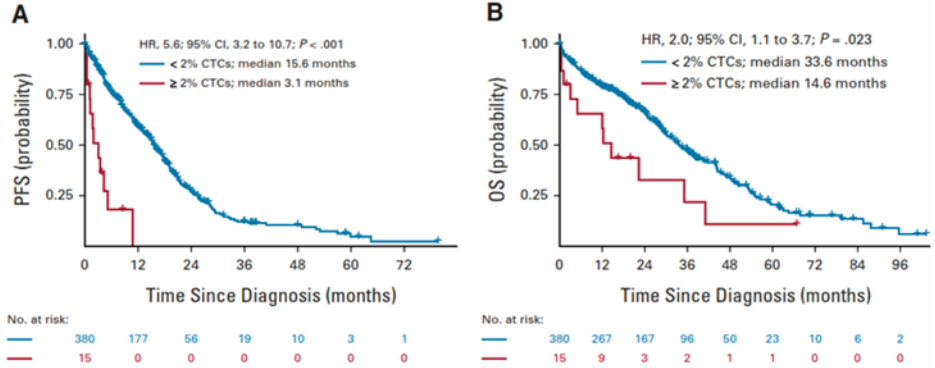


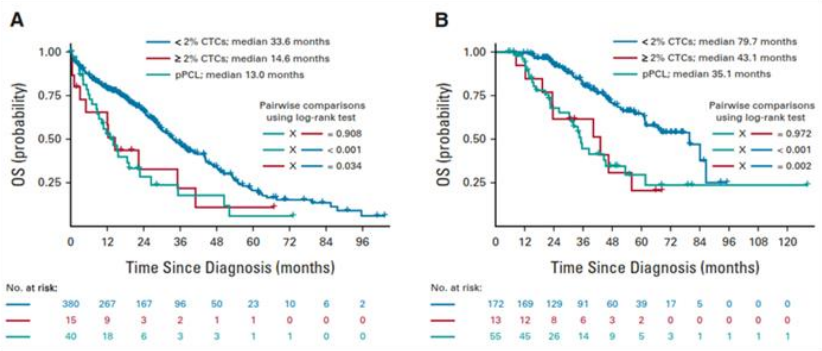


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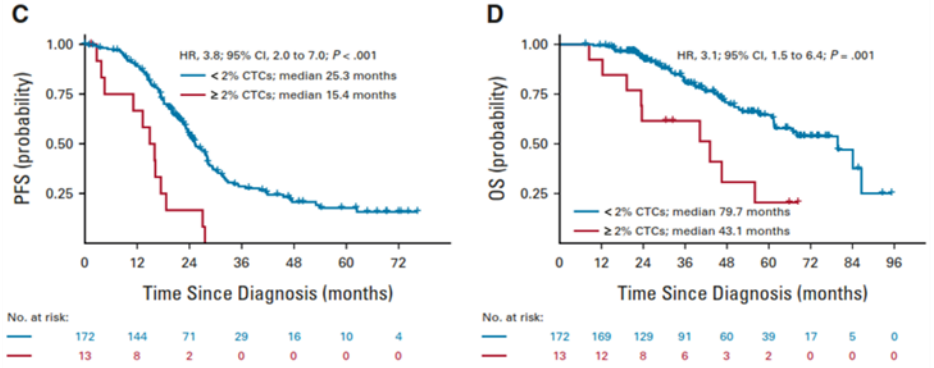
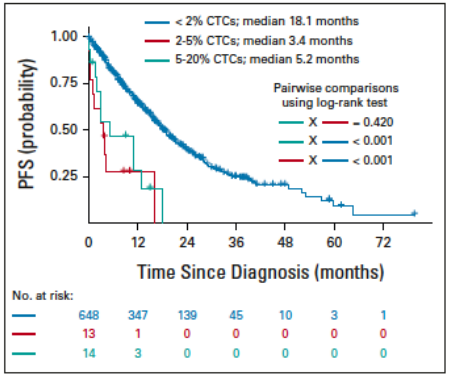
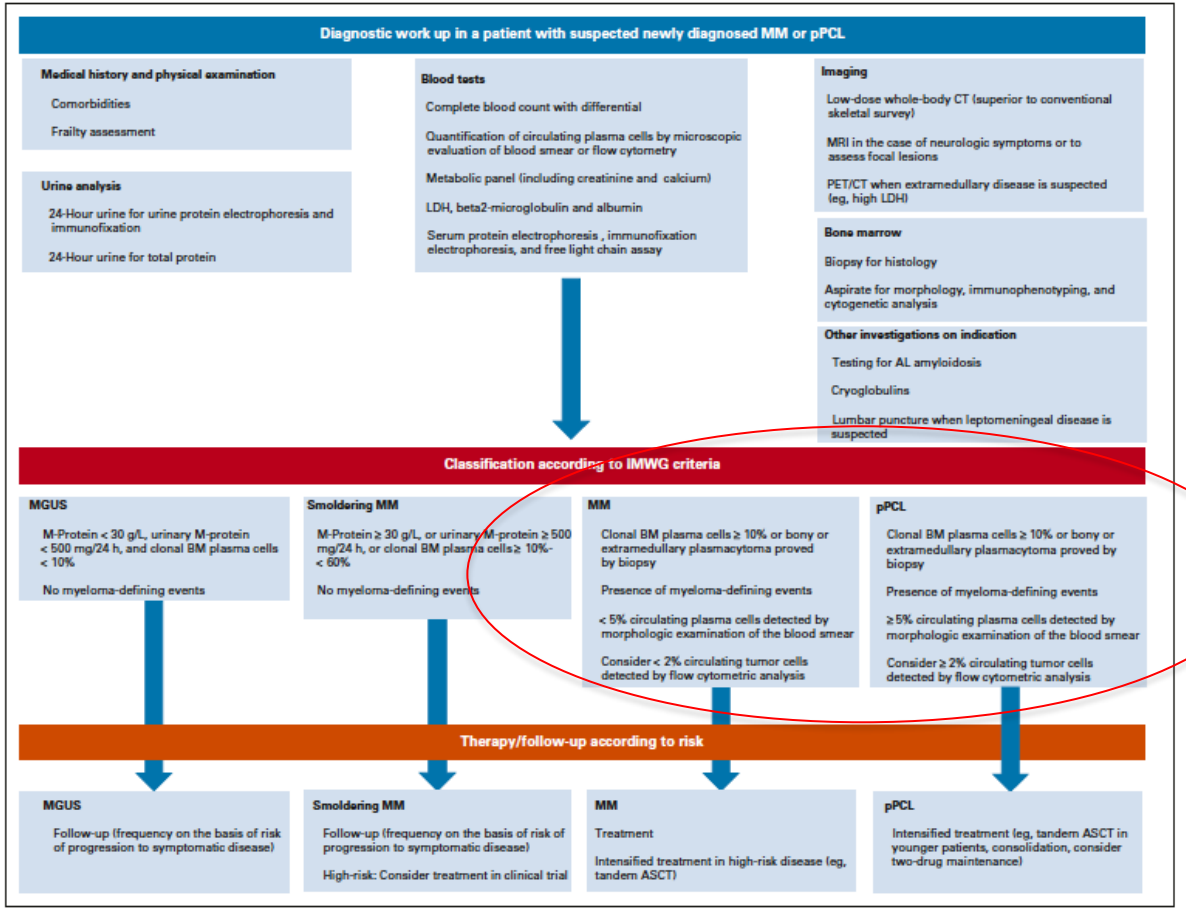


# How We Manage Newly Diagnosed Multiple Myeloma With Circulating Tumor Cells

Niels W.C.J. van de Donk, MD, PhD[1,2]




Journal of Clinical Oncology

original reports

# Identification of High-Risk Multiple Myeloma With a Plasma Cell Leukemia-Like Transcriptomic Profile

Davine Hofste op Bruinink, MD, MSc[1,2]; Rowan Kuiper, PhD[1,3]; Mark van Duin, PhD[1]; Tom Cupedo, PhD[1]; Vincent H.J. van der Velden, PhD[2]; Remco Hoogenboezem, MSc[1]; Bronno van der Holt, PhD[4]; H. Berna Beverloo, PhD[5]; Erik T. Valent, PhD[3]; Michael Vermeulen, BSc[1]; Francesca Gay, MD, PhD[6]; Annemiek Broijl, MD, PhD[1]; Hervé Avet-Loiseau, MD, PhD[7]; Nikhil C. Munshi, MD, PhD[8]; Pellegrino Musto, MD[9]; Philippe Moreau, MD[10]; Sonja Zweegman, MD, PhD[11]; Niels W.C.J. van de Donk, MD, PhD[11]; and Pieter Sonneveld, MD, PhD[1]

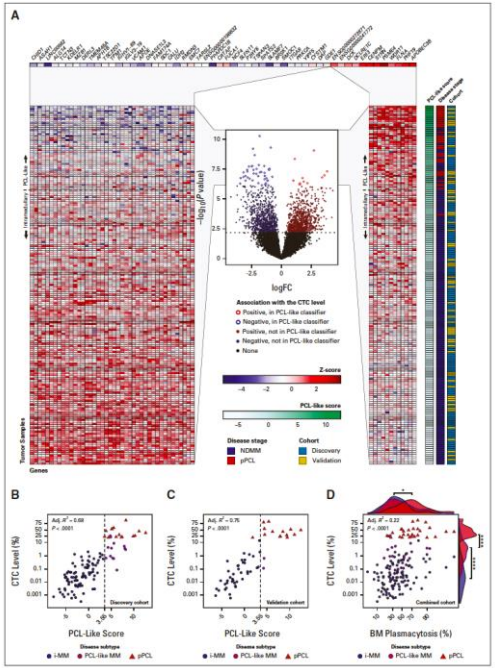



TABLE 3. Multivariate Analyses of PCL-Like Status in Combination with Conventional Prognostic Factors for PFS and OS in NDMM

| | PFS | | OS | |
|---|---|---|---|---|
| Prognostic Factor | HR (95% CI) | P | HR (95% CI) | P |
| PCL-like classifier: PCL-like MM *v* i-MM | 1.64 (1.30 to 2.07) | < .0001 | 1.89 (1.42 to 2.50) | < .0001 |
| R-ISS | | | | |
| R-ISS II *v* R-ISS I | 1.63 (1.33 to 2.00) | < .0001 | 2.28 (1.64 to 3.17) | < .0001 |
| R-ISS III *v* R-ISS I | 2.67 (2.03 to 3.52) | < .0001 | 5.50 (3.75 to 8.04) | < .0001 |
| Age: ≤ 65 years *v* > 65 years | 0.70 (0.55 to 0.91) | .007 | 0.44 (0.30 to 0.65) | < .0001 |

| | PFS | | OS | |
|---|---|---|---|---|
| Prognostic Factor | HR (95% CI) | P | HR (95% CI) | P |
| PCL-like classifier: PCL-like MM *v* i-MM | 1.78 (1.51 to 2.11) | < .0001 | 1.86 (1.53 to 2.26) | < .0001 |
| ISS | | | | |
| ISS II *v* ISS I | 1.49 (1.30 to 1.70) | < .0001 | 1.64 (1.36 to 1.97) | < .0001 |
| ISS III *v* ISS I | 1.83 (1.59 to 2.11) | < .0001 | 2.65 (2.20 to 3.18) | < .0001 |
| Age: ≤ 65 years *v* > 65 years | 0.83 (0.71 to 0.97) | .02 | 0.73 (0.59 to 0.90) | .003 |

| | PFS | | OS | |
|---|---|---|---|---|
| Prognostic Factor | HR (95% CI) | P | HR (95% CI) | P |
| PCL-like classifier: PCL-like MM *v* i-MM | 1.64 (1.33 to 2.01) | < .0001 | 1.89 (1.48 to 2.41) | < .0001 |
| FISH: high-risk *v* standard-risk | 1.37 (1.18 to 1.59) | < .0001 | 1.67 (1.39 to 2.01) | < .0001 |
| Age: ≤ 65 years *v* > 65 years | 0.72 (0.59 to 0.87) | .0008 | 0.55 (0.42 to 0.71) | < .0001 |

| | PFS | | OS | |
|---|---|---|---|---|
| Prognostic Factor | HR (95% CI) | P | HR (95% CI) | P |
| PCL-like classifier: PCL-like MM *v* i-MM | 1.49 (1.26 to 1.77) | < .0001 | 1.52 (1.25 to 1.85) | < .0001 |
| SKY92 classifier: high-risk *v* standard-risk | 2.10 (1.85 to 2.38) | < .0001 | 2.79 (2.40 to 3.24) | < .0001 |
| Age: ≤ 65 years *v* > 65 years | 0.76 (0.65 to 0.89) | .0005 | 0.65 (0.53 to 0.80) | < .0001 |

| | PFS | | OS | |
|---|---|---|---|---|
| Prognostic Factor | HR (95% CI) | P | HR (95% CI) | P |
| PCL-like classifier: PCL-like MM *v* i-MM | 1.63 (1.38 to 1.93) | < .0001 | 1.62 (1.33 to 1.98) | < .0001 |
| UAMS70 classifier: high-risk *v* standard-risk | 2.17 (1.87 to 2.53) | < .0001 | 3.05 (2.57 to 3.63) | < .0001 |
| Age: ≤ 65 years *v* > 65 years | 0.75 (0.65 to 0.88) | .0003 | 0.65 (0.53 to 0.80) | < .0001 |

Abbreviations: FISH, fluorescence in situ hybridization; HR, hazard ratio; i-MM, intramedullary multiple myeloma; ISS, International Staging System; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PCL-like MM, plasma cell leukemia-like multiple myeloma; PFS, progression-free survival; R-ISS, Revised International Staging System.

# CPCs in MM patients: the detection efficiency and sensitivity of different method of 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%<br>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%<br>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%<br>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%)<br>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%<br>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%<br>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%<br>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<br>(2-tube/8-color) | Sensitivity: 0.0001%<br>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%<br>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%<br>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%<br>1. CMMCs were detected in 78% of patients with MM using DNA assay and 96% of patients with MM using DNA and RNA assays<br>2. ctDNA was detected in 83% of patients with MM using DNA assay<br>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%<br>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%<br>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<br>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%<br>≥ 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 |

Shuchan Li, et al. Biomarker Research 2023

# CPCs in MM patients: prognostic value

| 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<br>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<br>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<br>2. CMMC (+/+) or (−/+) was an independent factor for inferior PFS and OS<br>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<br>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<br>2. A factor for inferior PFS and OS independent of ISS, cytogenetics, and LDH level<br>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<br>2. A prognostic factor for inferior PFS, independent of ISS stage, cytogenetics, and maintenance therapy<br>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<br>2. A factor for SMM of higher incidence of progression to MM in 2 years<br>3. A factor for MM of inferior PFS and OS independent of CR status or MRD status |

# CPCs in MM patients: prognostic value

| Sample | Detection time | Method | Cut-off | Prognostic value |
|---|---|---|---|---|
| Treated MM | After therapy | NGF | 1. Presence of CMMC<br>2. Kinetics of CMMCs | 1. An independent prognostic factor for inferior PFS<br>2. The presence of CMMC enhanced the stratifcation of CR/sCR<br>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<br>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<br>2. Three months after HDT for ASCT: a prognostic factor for inferior EFS and OS |

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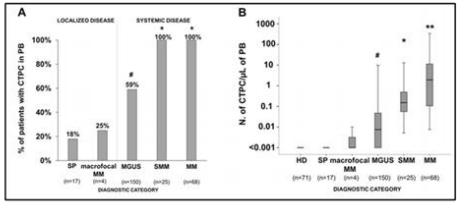
Sanoja-Flores et al. *Blood Cancer Journal* (2018)8:117
DOI 10.1038/s41408-018-0153-9

Blood Cancer Journal

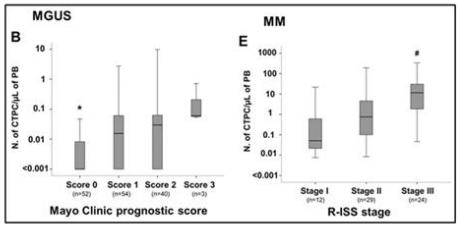
ARTICLE Open Access

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

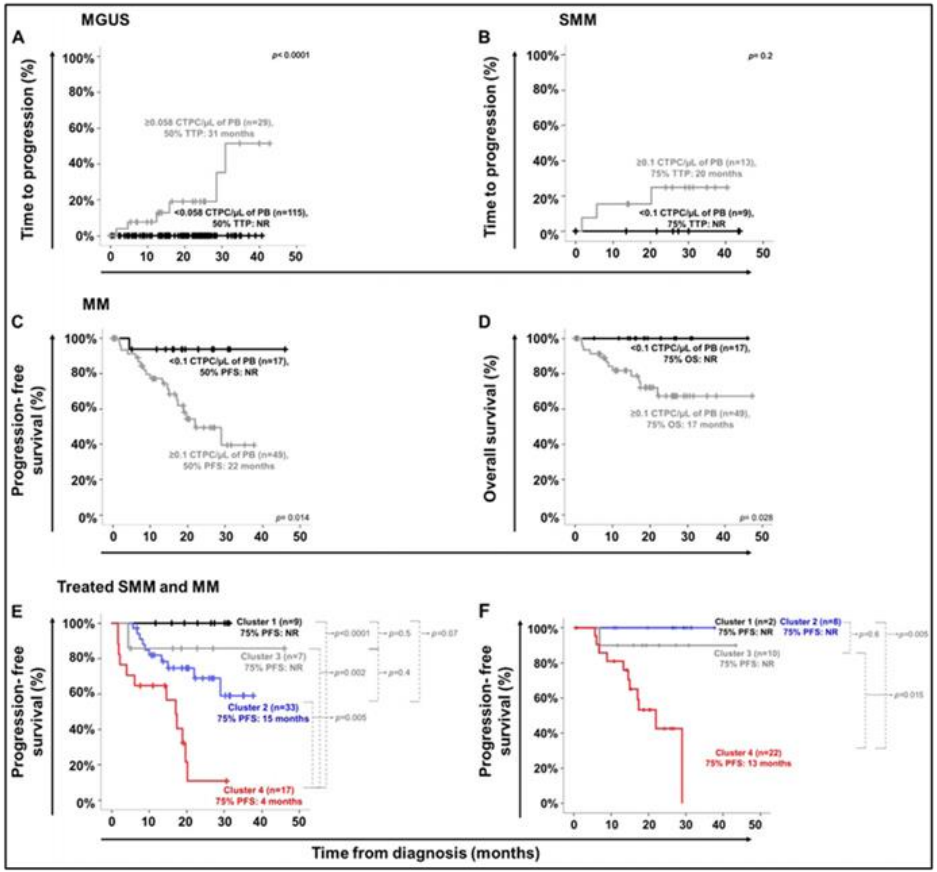
L. Sanoja-Flores[1,2], J. Flores-Montero[1,2], J. J. Garcés[3], B. Paiva[3], N. Puig[4], A. García-Mateo[5], O. García-Sánchez[4], A. Corral-Mateos[1,2], L. Burgos[3], E. Blanco[1,2], J. Hernández-Martín[3], R. Pontes[6], M. Díez-Campelo[4], P. Millacoy[7], P. Rodríguez-Otero[3], F. Prosper[3], J. Merino[3], 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[1,2], 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**

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

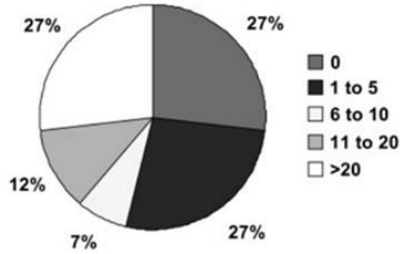



**Figure 2. Distribution of circulating PCs in 302 study patients.** Patients were divided into 5 groups based on the number of PCs.

**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 |

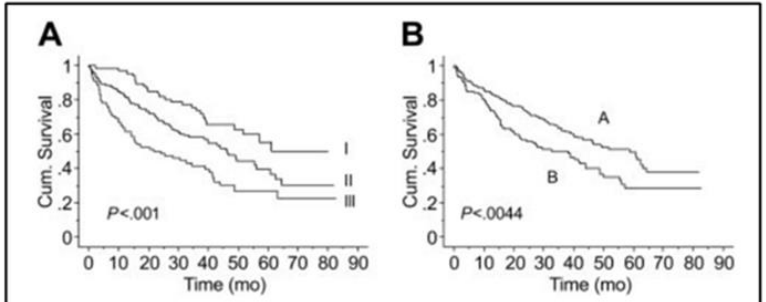



**Figure 3. Kaplan-Meier estimates of OS.** (A) Survival by ISS (ISS 1-I, ISS 2-II, ISS 3-III). (B) Survival by number of circulating PCs (A, 10 or less; B, more than 10).

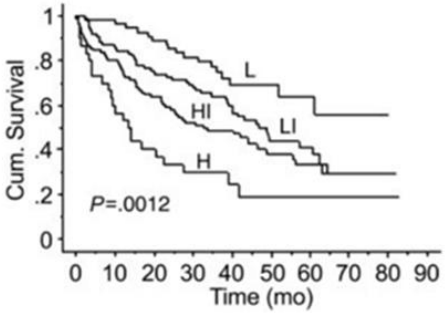



**Figure 4. Kaplan-Meier estimates of OS in the risk stratification model using B2M, albumin levels, and circulating PCs.** L indicates low-risk group; LI, low-intermediate risk group; HI, high-intermediate risk group; H, high-risk group.

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]

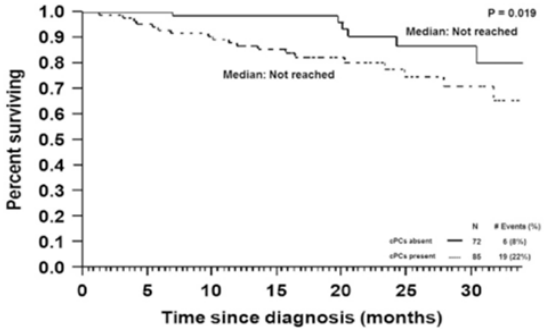



**Figure 2.** The Kaplan–Meier curve for OS in patients based on the presence of cPCs is shown.

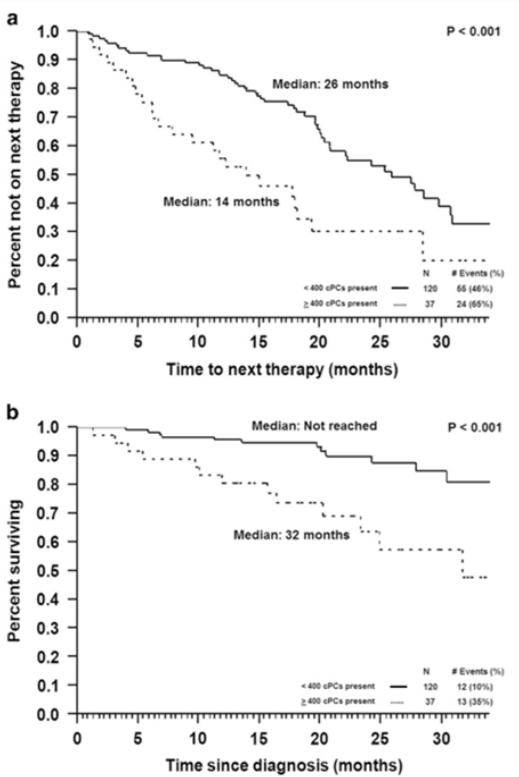



**Figure 3.** The Kaplan–Meier curve for TTNT (**a**) and OS (**b**) in patients based on the presence of ⩾400 cPCs is shown.

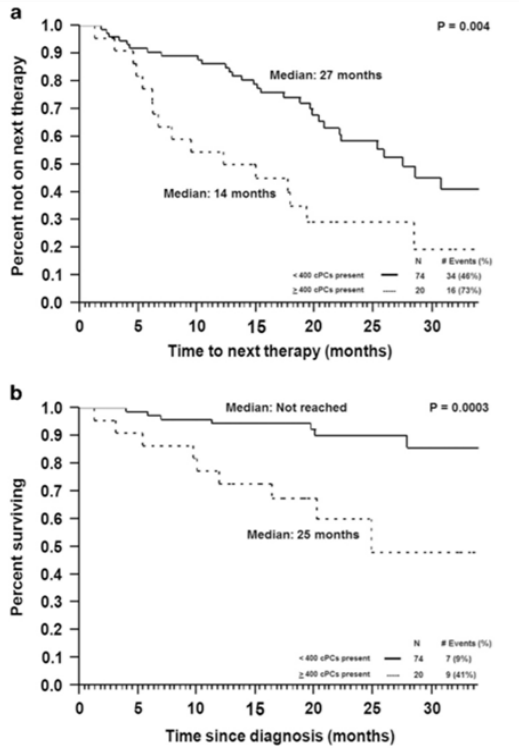



**Figure 4.** The Kaplan–Meier curve for TTNT (**a**) and OS (**b**) in patients with standard risk disease by FISH cytogenetics based on the presence of ⩾400 cPCs.

Citation: Blood Cancer Journal (2016) 6, e512; doi:10.1038/bcj.2016.117
www.nature.com/bcj

ORIGINAL ARTICLE

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

R Chakraborty[1,2], E Muchtar[1], SK Kumar[1], D Jevremovic[3], FK Buadi[1], D Dingli[1], A Dispenzieri[1], SR Hayman[1], WJ Hogan[1], P Kapoor[1], MQ Lacy[1], N Leung[1] and MA Gertz[1]

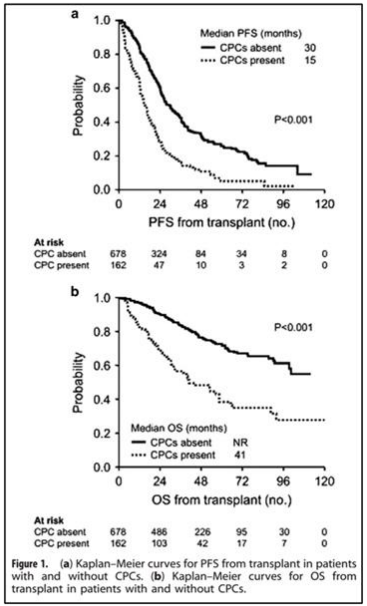



**Figure 1.** (**a**) Kaplan–Meier curves for PFS from transplant in patients with and without CPCs. (**b**) Kaplan–Meier curves for OS from transplant in patients with and without CPCs.

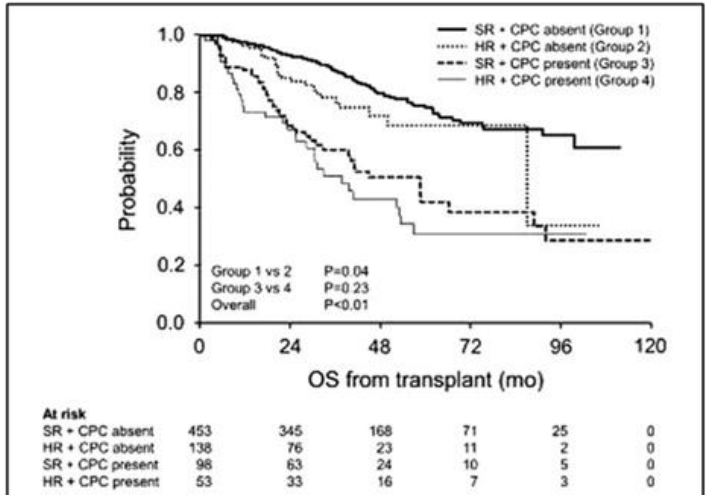



**Figure 2.** Kaplan–Meier curves for OS in patients stratified by the presence of CPCs and HR cytogenetics by FISH.

**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.

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

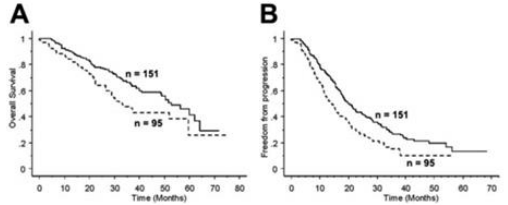



**Figure 2. Kaplan-Meier plots based on the presence or absence of circulating myeloma cells detected by flow cytometry.** (A) Overall survival (OS). (B) Time to progression (TTP). The presence of circulating myeloma cells is associated with an adverse outcome with respect to both OS and TTP ($P = .005$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

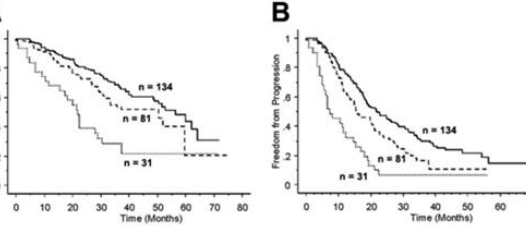



**Figure 3. Kaplan-Meier plots based on the risk stratification combining cytogenetics and presence of circulating myeloma cells.** (A) OS. (B) TTP. Patients with normal cytogenetics and no circulating myeloma cells have a superior OS and TTP compared with patients with one or both of these parameters.

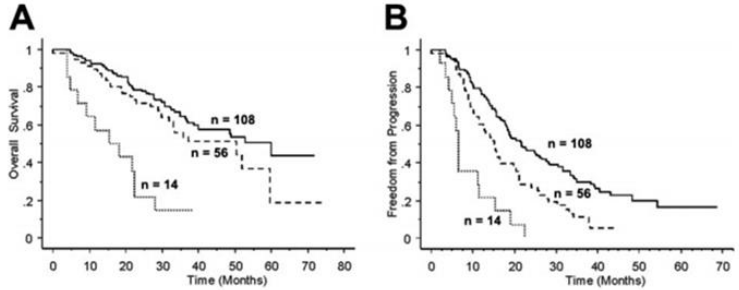



**Figure 4. Kaplan-Meier plots for patients who received transplants, either in plateau phase or with chemotherapy-sensitive disease, stratified on the scoring system developed.** (A) OS. (B) TTP. In this group of patients, both OS and TTP are inferior for patients with either or both risk factors.

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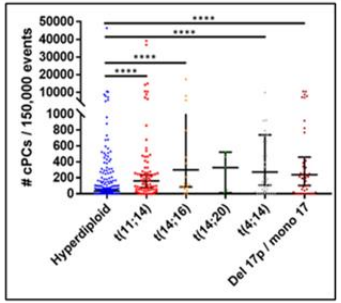
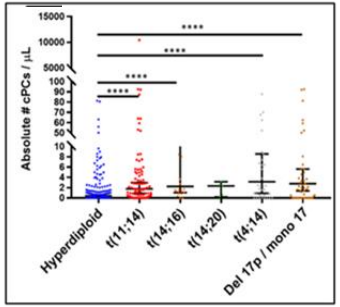
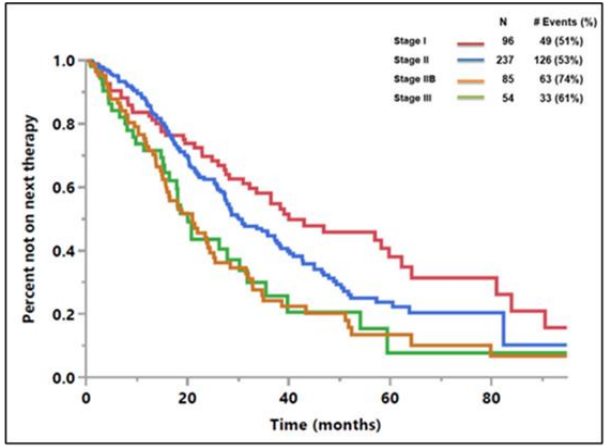
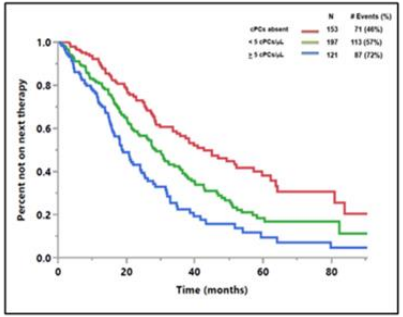
## Enhancing the R-ISS Classification of Newly Diagnosed Multiple Myeloma by Quantifying Circulating Clonal Plasma Cells

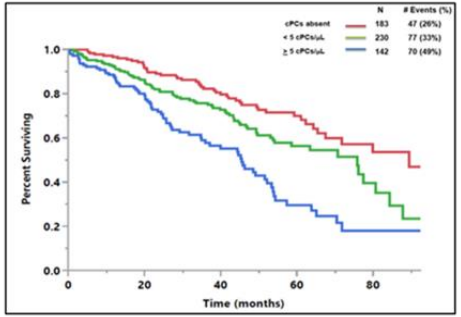
Wilson I. Gonsalves, MD[1], Dragan Jevremovic, MD[2], Bharat Nandakumar, MBBS[1], Angela Dispenzieri, MD[1], Francis K. Buadi, MD[1], David Dingli, MD, PhD[1], Martha Q. Lacy, MD[1], Suzanne R. Hayman, MD[1], Prashant Kapoor, MD[1], Nelson Leung, MD[1,3], Amie Fonder, PA-C[1], Miriam Hobbs, DNP[1], Yi Lisa Hwa, DNP[1], Eli Muchtar[1], Rahma Warsame, MD[1], Taxiarchis V. Kourelis, MD[1], Stephen Russell, MD, PhD[1], John A. Lust, MD, PhD[1], Yi Lin, MD, PhD[1], Ronald S. Go, MD[1], Mustaqeem A. Siddiqui, MD[1], Robert A. Kyle, MD[1], Morie A. Gertz, MD[1], S. Vincent Rajkumar, MD[1], Shaji K. Kumar, MD[1]

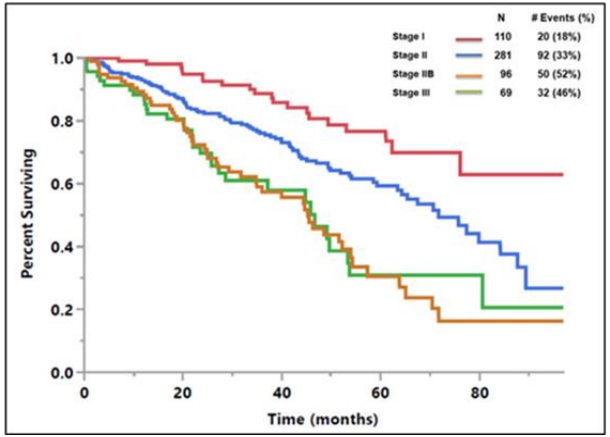


original reports

# Circulating Tumor Cells for the Staging of Patients With Newly Diagnosed Transplant-Eligible Multiple Myeloma

Juan-Jose Garcés, MSc[1]; Maria-Teresa Cedena, MD[2]; Noemi Puig, MD, PhD[3]; Leire Burgos, PhD[1]; Jose J. Perez, PhD[3]; Lourdes Cordon, PhD[4]; Juan Flores-Montero, MD, PhD[5,6]; Luzalba Sanoja-Flores, PhD[7]; Maria-Jose Calasanz, PhD[1]; Albert Ortiol, MD[8]; María-Jesús Blanchard, MD[9]; Rafael Rios, MD, PhD[10]; Jesus Martin, MD[7]; Rafael Martínez-Martinez, PhD[11]; Joan Bargay, MD, PhD[12]; Anna Sureda, MD, PhD[8,13]; Javier de la Rubia, MD[4,14,15]; Miguel-Teodoro Hernandez, MD, PhD[16]; Paula Rodriguez-Otero, MD, PhD[1]; Javier de la Cruz, MD[2]; Alberto Orfao, MD, PhD[5,6]; Maria-Victoria Mateos, MD, PhD[3]; Joaquin Martinez-Lopez, MD[2,17]; Juan-Jose Lahuerta, MD[2]; Laura Rosiñol, MD, PhD[18]; Joan Blade, MD, PhD[18]; Jesus F. San-Miguel, MD, PhD[1]; and Bruno Paiva, PhD[1]

CTCs for Risk Stratification of Newly Diagnosed MM

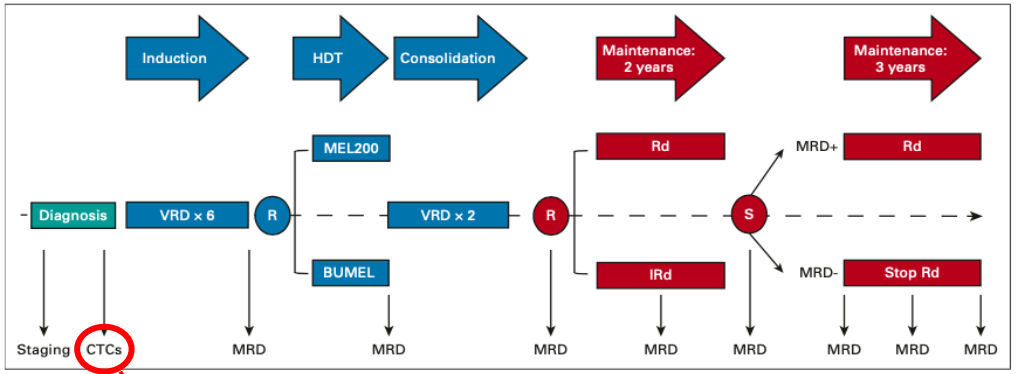


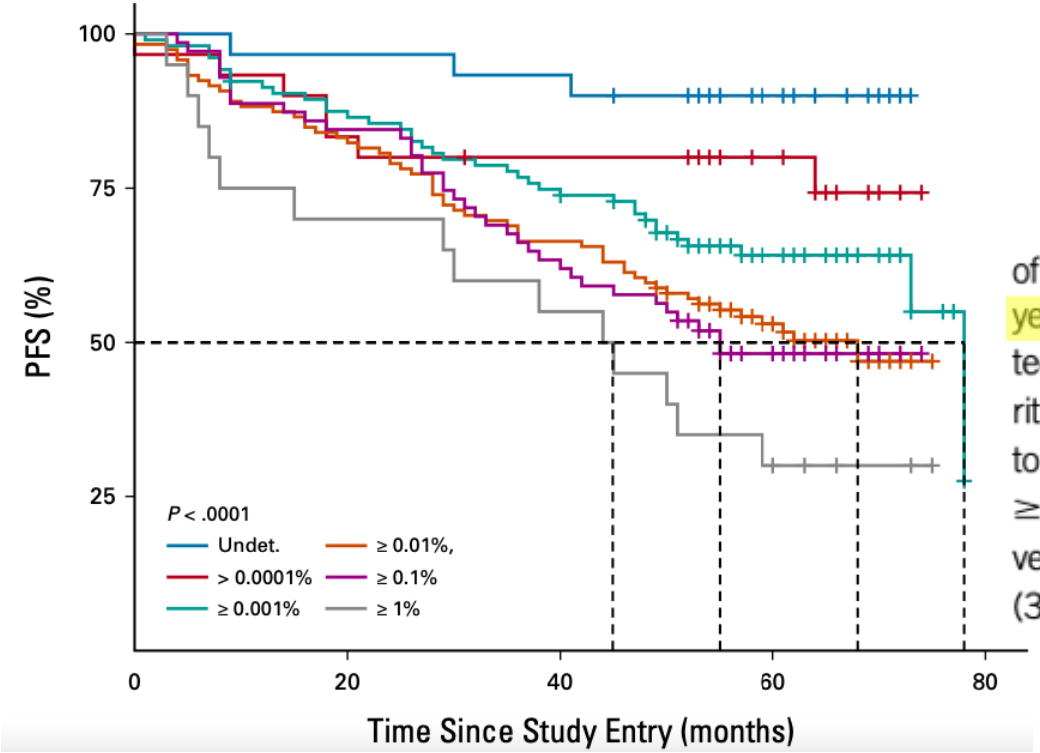

**FIG 1.** Treatment schema and laboratory examinations in the PETHEMA GEM2012MENOS65 and GEM2014MAIN clinical trials. BUMEL, busulfan/melphalan; CTCs, circulating tumor cells; HDT, high-dose therapy; IRd, ixazomib, lenalidomide, and dexamethasone; MEL, melphalan; MRD, measurable residual disease; R, randomization; Rd, lenalidomide and dexamethosone; S, stratification; VRD, bortezomib, lenalidomide, and dexamethasone.

## Laboratory Examinations

Assessment of CTCs in PB at diagnosis and MRD in BM aspirates collected in EDTA was performed using the EuroFlow NGF methodology.[22] After counting, volumes of

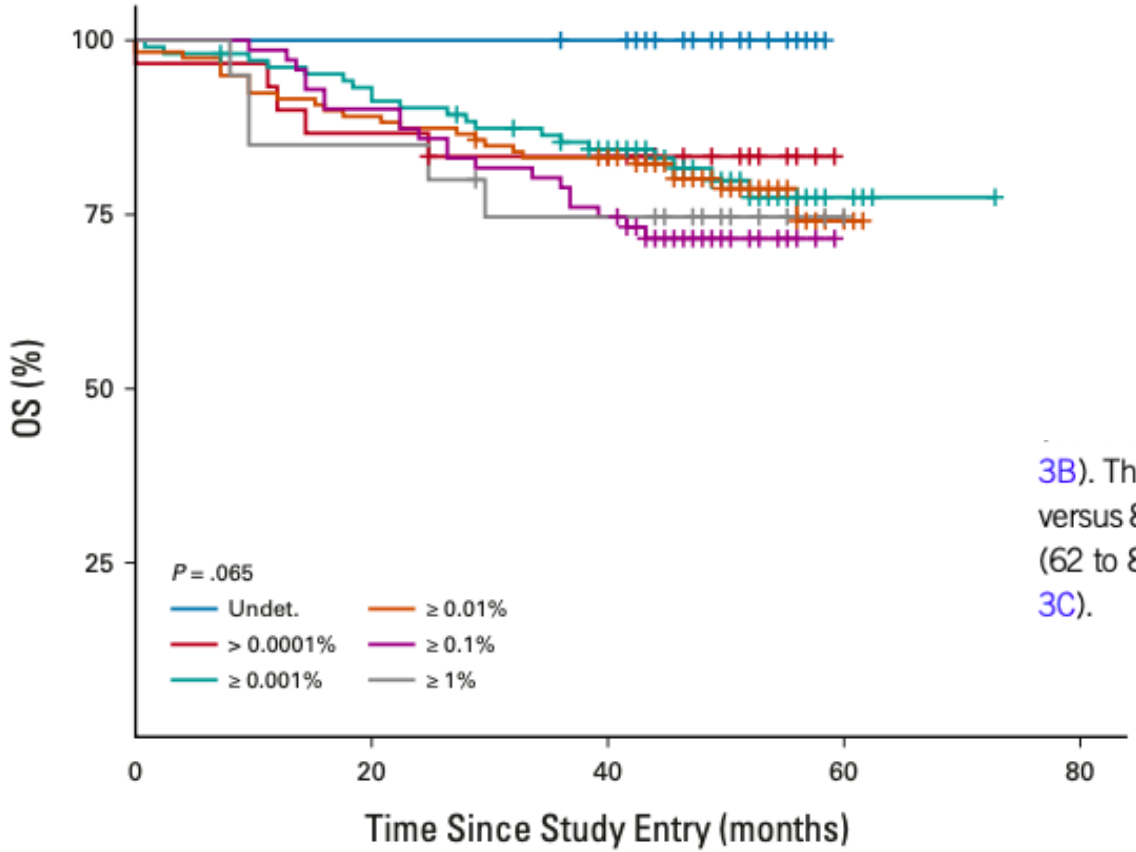
Journal of Clinical Oncology

**B**




of relapse with higher CTC levels (Data Supplement). Thus, 5-year rates of PFS progressively worsen in cases with undetectable CTCs versus those with increasingly higher logarithmic percentages of CTCs (ie, intervals from > 0.0001% to < 0.001%, ≥ 0.001% to < 0.01%, ≥ 0.01% to < 0.1%, ≥ 0.1% to < 1%, and ≥ 0.1%): 90% (95% CI, 80 to 100) versus 80% (67 to 96), 64% (55 to 74), 53% (45 to 63), 48% (38 to 62), and 30% (15 to 59), respectively ($P < .0001$; Fig

C




3B). The OS rates at 5 years were 100% (95% CI, 100 to 100) versus 83% (71 to 98), 82% (74 to 90), 80% (73 to 88), 72% (62 to 83), and 75% (58 to 97), respectively ($P$ = .065; Fig 3C).

Open access Original research

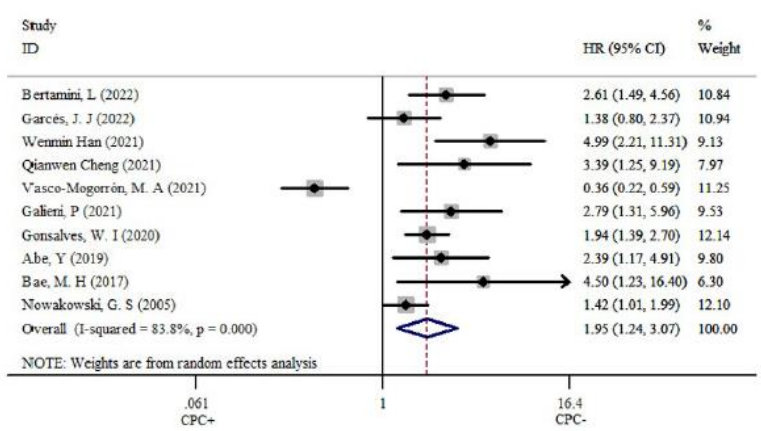
BMJ Open

# Prognostic value of circulating plasma cells detected by flow cytometry in newly diagnosed multiple myeloma patients: a systematic review and meta-analysis

Xiaoyan Liu,[1] Feifei Wu,[1] Wu Ye,[2] Jili Deng,[3] Mengmeng Zhang,[1] Congli Zhang,[1] Qingfeng Yu,[1] Li Cao,[1] Silin Gan,[1] Jie Ma [1]

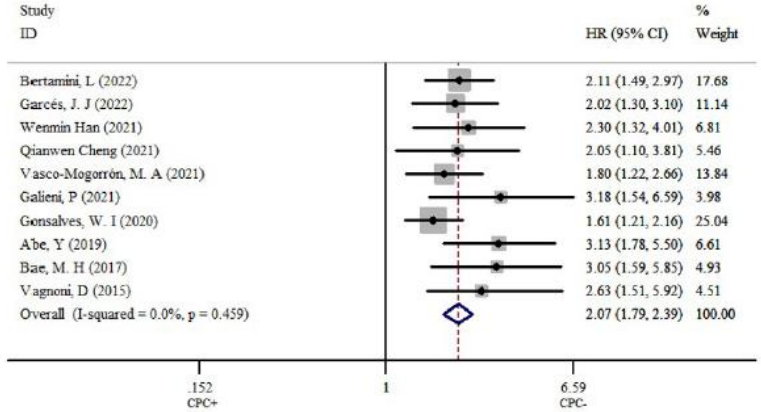
A

OS




B

PFS



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) | $2 \times 10^{-6}$ (NGF) | $4 \times 10^{-5}$ | $2 \times 10^{-6}$ (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.

General Session

# OA-13: Increased levels of circulating tumor cells correlate with adverse clinical outcomes and distinct biological features in newly diagnosed patients with multiple myeloma

Saturday, September 30, 2023 11:55 AM – 12:05 PM EEST

Location: Trianti

## Speaker(s)

IK

**Ioannis V Kostopoulos, n/a**

Post doctoral research fellow
Section of Animal and Human Physiology, Department of Biology, School of Sciences, National and Kapodistrian University of Athens, Athens, Greece, Greece

## IMS 20° meeting 2023: Circulating Tumor cells (CTCs) in MM patients

**Methods:**

- 550 NDMM pts; 210 (38%) were TE and 340 (62%) were TI.
- NGF was used for the detection of clonal cells in both BM and PB.
- To define the optimal clinical cutoff of CTCs, we performed various multivariable regression models including CTCs, ISS (or R-ISS), cytogenetic status and LDH, and selected the one with the best performance.
- The median follow-up period was 41 months (range: 5-66 months).

## IMS 20° meeting 2023: Circulating Tumor cells (CTCs) in MM patients

**Results:**

- CTCs were detected in 493/550 (89.6%) pts with a median value of **0.01%** of all nucleated cells. Increased levels of CTCs correlated with advanced ISS stage (0.002%, 0.007% and 0.037% for pts with ISS-I, ISS-II and ISS-III respectively, p< 0.0001), high risk cytogenetics (median: 0.038% vs. 0.006% in standard risk, p< 0.0001), and higher levels of b2-microglobulin and BM infiltration.
- **The optimal clinical cut-off of CTCs was defined at 0.02%, stratifying pts in two different prognostic groups with high and low CTCs [median PFS: 40 months vs. not reached (NR), HR: 2.59, 95% CI:1.71-3.91, p< 0.0001].**
- In the multivariable analysis the 0.02% cut-off was independent from ISS and/or cytogenetics and was clinically relevant for both TI (median PFS: 47 vs. 23 months, p< 0.0001) and TE pts (median PFS: NR in both categories, p< 0.01).

## IMS 20° meeting 2023: Circulating Tumor cells (CTCs) in MM patients

**Conclusions:**

- The presence of CTC at a level of >0.02% confers an adverse prognostic factor for NDMM pts, irrespective of their transplant status.
- Since the liquid biopsy is a better representative of the entire tumor load than a tissue biopsy sample, the analysis of CTCs may serve as the new hallmark for the real-time evaluation of a patient's disease and immune status.

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[1] and Morie A. Gertz[1]

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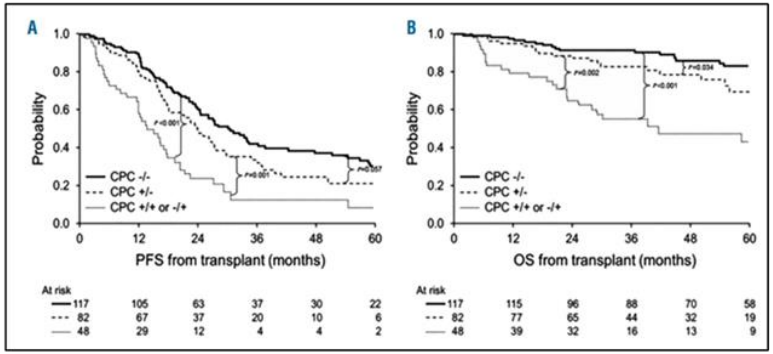



| Variable | N.* | Progression-free survival | | | | Overall survival | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Univariate HR (95% CI) | P | Multivariate HR (95% CI) | P | Univariate HR (95% CI) | P | Multivariate HR (95% CI) | P |
| Age ≥65 | 247 | 0.80 (0.58-1.10) | 0.178 | NA | NA | 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.

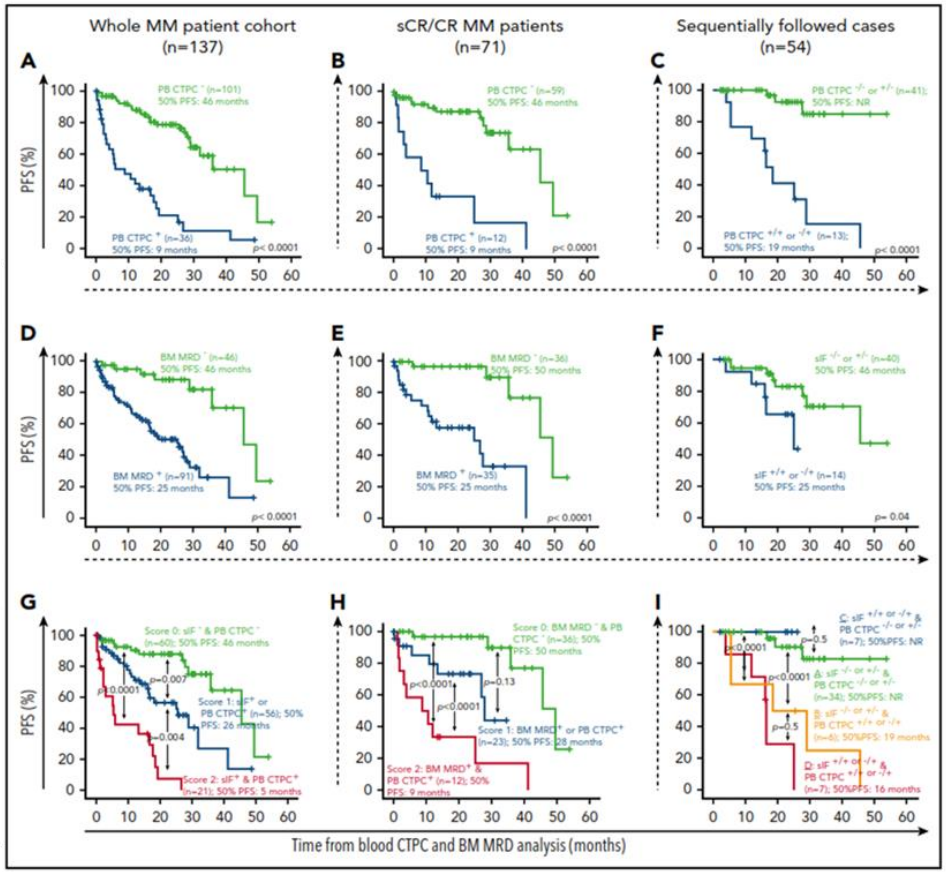
blood
Letters to *Blood*

TO THE EDITOR:

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

Luzalba Sanoja-Flores,[1-3] Juan Flores-Montero,[1-3] Noemi Puig,[1,4-6] Teresa Contreras-Sanfeliciano,[7] Roberia Pontes,[8] Alba Corral-Mateos,[1-3] Omar García-Sánchez,[1,4-6] María Díez-Campelo,[1,4-6] Roberto José Pessoa de Magalhães,[9] Luis García-Martín,[10] José María Alonso-Alonso,[11] Aranzazú García-Mateo,[12] Carlos Aguilar-Franco,[13] Jorge Labrador,[14] Abelardo Barez-García,[15] Angelo Maiolino,[8] Bruno Paiva,[4,16] Jesús San Miguel,[4,16] Elaine Sobral da Costa,[8] Marcos González,[1,4-6] María Victoria Mateos,[1,4-6] Brian Durie,[17] Jacques J. M. van Dongen,[18] and Alberto Orfao,[1-3] on behalf of the EuroFlow Consortium

| | 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 |



## TAKE HOME MESSAGE AND CONCLUSIONS…

- ✓ The presence of the more than 2% of CPCs detected by flow cytometry is considered a new cut-off MM patients with plasma cell-like leukemia and ultra high-risk disease.
- ✓ The CPCs burden is a new independent adverse prognostic factor in transplant eligible MM patients.
- ✓ The cut-off of CPCs by NGF should be yet defined: ≥0.01%?, ≥0.02%?, ≥0.07% ?

- ✓ The evaluation of CPCs would be incorporated in the risk stratification risk of MM patients
- ✓ The liquid biopsy would improve disease evaluation in MM patients and 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.

# Highlights from
# IMS 20th meeting 2023

*Grazie per l'attenzione…*

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

bjh research paper

## Quantification of clonal circulating plasma cells in relapsed multiple myeloma

Wilson I. Gonsalves,[1] William G. Morice,[2] Vincent Rajkumar,[1] Vinay Gupta,[1] Michael M. Timm,[2] Angela Dispenzieri,[1] Francis K. Buadi,[1] Martha Q. Lacy,[1] Preet P. Singh,[1] Prashant Kapoor,[1] Morie A. Gertz[1] and Shaji K. Kumar[1]

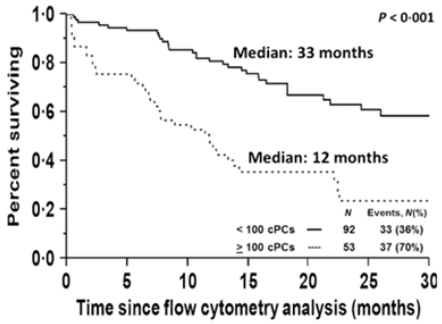



Fig 2. Shows the Kaplan–Meier Curve for survival from the time of peripheral blood flow cytometry analysis in all previously treated patients with actively relapsing disease based on the presence of circulating plasma cells (cPCs) based on the presence of 100 or more cPCs.

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.