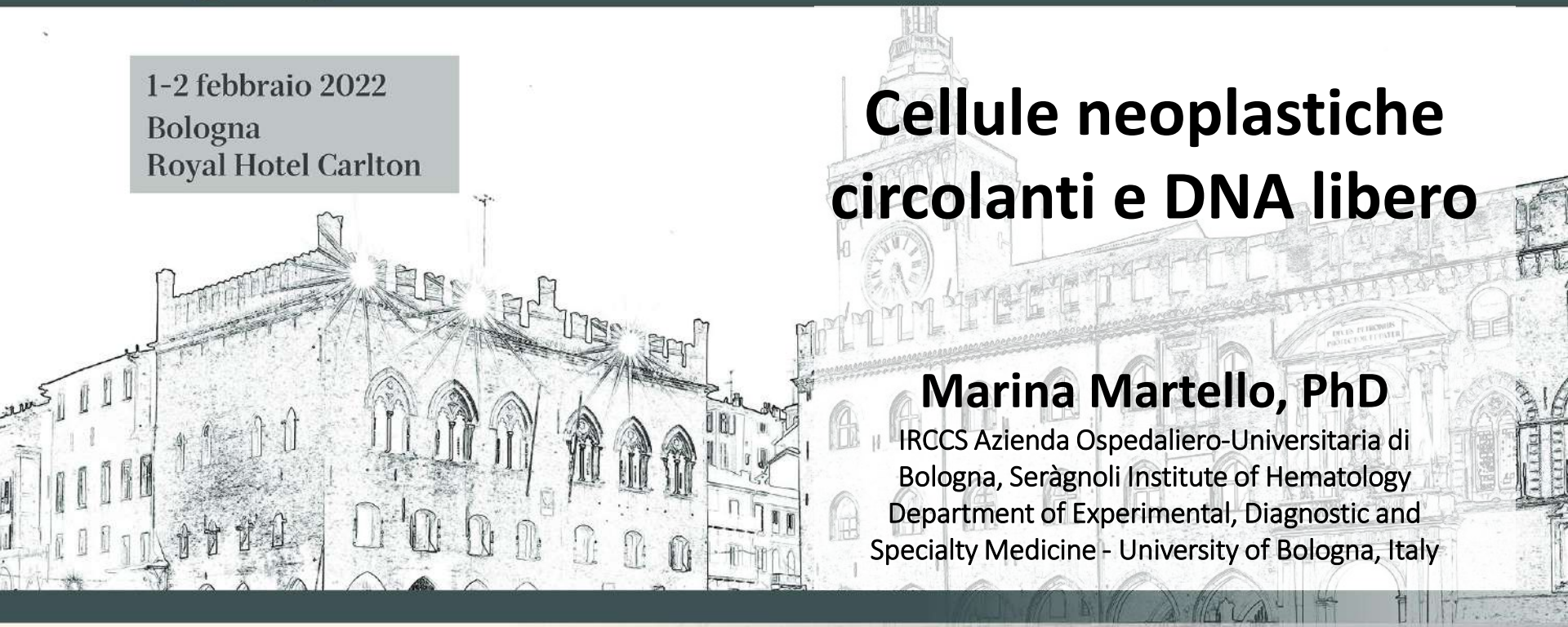
Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton



Cellule neoplastiche circolanti e DNA libero

Marina Martello, PhD

IRCCS Azienda Ospedaliero-Universitaria di Bologna, Seràgnoli Institute of Hematology Department of Experimental, Diagnostic and Specialty Medicine - University of Bologna, Italy

Coordinatore Scientifico
Michele **CAVO**

Comitato Scientifico
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Maria Teresa **PETRUCCI**

No relevant conflict of interest to disclose

International Myeloma Society

SUMMARY

Some insights from IMW 2021

- ✓ **Bruno Paiva** – Plenary session *"Circulating tumor cells and tumor DNA for response assessment"*
- ✓ **Rosalinda Termini** – Oral session *"Minimally invasive profiling of tumor and immune cells to stratify risk in smoldering multiple myeloma (SMM): the iMMunocell study"*
- ✓ **Camila Guerrero** – Oral session *"A machine learning model based on tumor and immune biomarkers to predict undetectable measurable residual disease (MRD) in transplant-eligible multiple myeloma (MM)"*
- ✓ **Cathelijne Fokkema** – Oral session *"Newly diagnosed Multiple Myeloma patients with high levels of circulating tumor cells are distinguished by increased bone marrow plasma cell proliferation"*

CTCs

- ✓ **Marina Martello** – Oral session *"Towards a comprehensive multimodal minimal residual disease assessment in multiple myeloma: the role of circulating cell-free DNA to define the extent of disease spreading"*

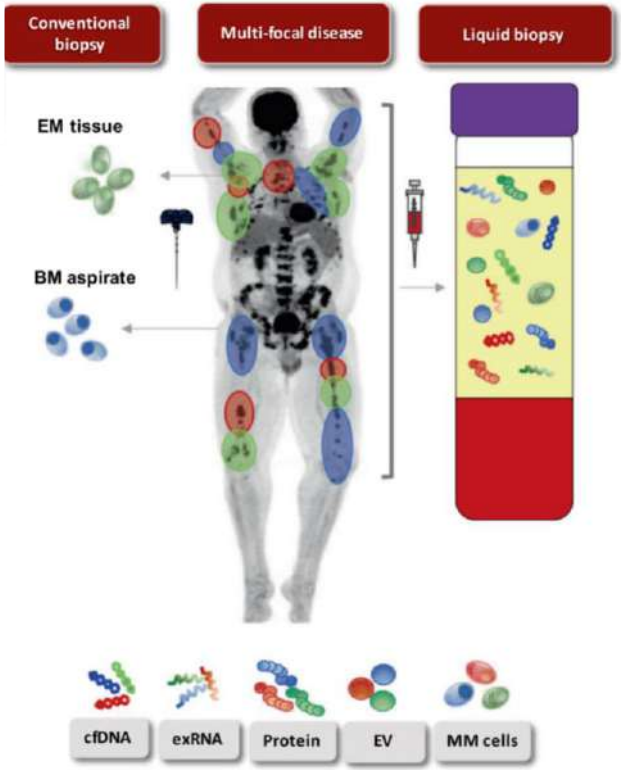
cfDNA

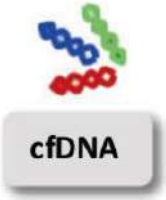
- ✓ **Dave Murray** – Plenary session *"Mass-spec to monitor the treatment response"*

MS

Conventional vs Liquid biopsy

Less invasive and more comprehensive





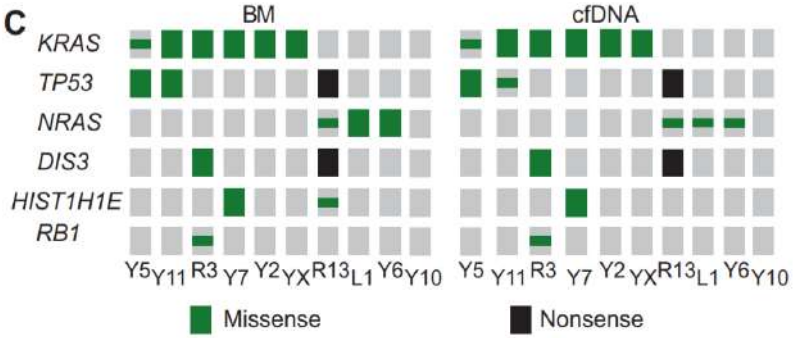
170-190 or >10.000 bp
DNA fragments
From apoptosis, necrosis, secretion
It might derived from BM neoplastic clone (ctDNA)

Plasma cells that egresses from BM neoplastic clone
Between 0-20 % in SMM, MM and RRMM

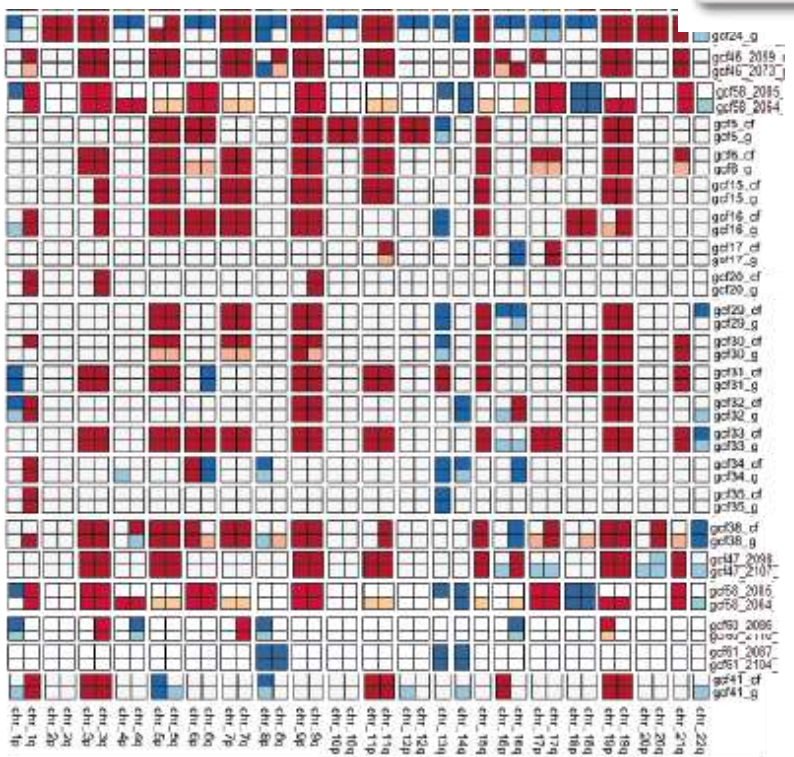
cfDNA

ctDNA for genetic characterization

High concordance with BM tumor genome



- **A median of 90.5% (CNV) and 91% (clonal mutations) were concordant between BM and cfDNA [***Guo et al., Leukemia 2018***]**
- **96% concordance with BM profiling [***Kis et al., Nat Comm 2017***]**

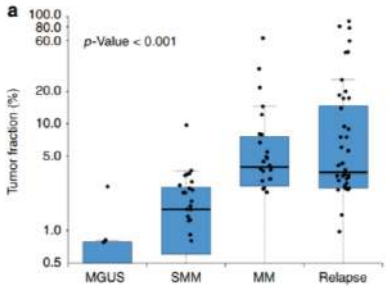


130/139 (93,5%) cfDNA genomic profiles are identical to BM clone in most of the patients

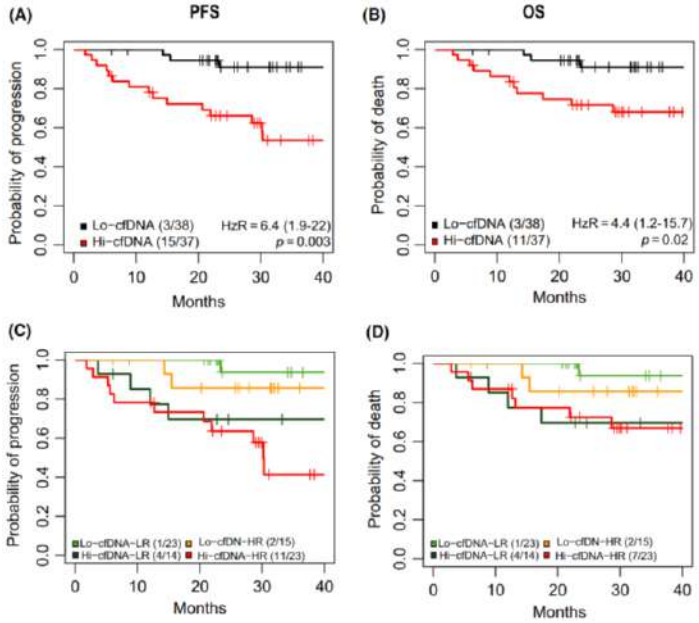
cfDNA

ctDNA for prognostication in NDMM

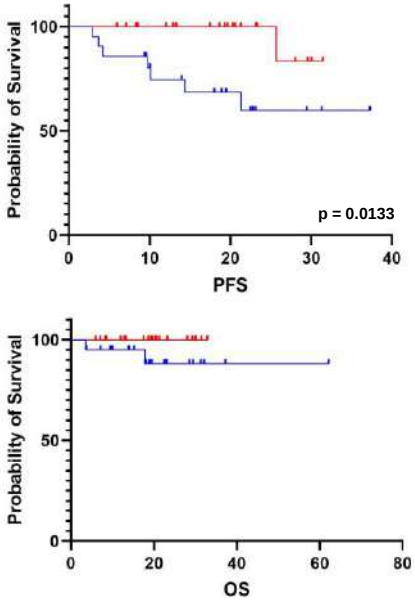
Prognostic value is defined in small study cohorts



Disease phase and R-ISS
[Manier S et al., Nat Comm 2018]



PFS and OS LR vs HR
[Deshpande S et al., EJH 2020]

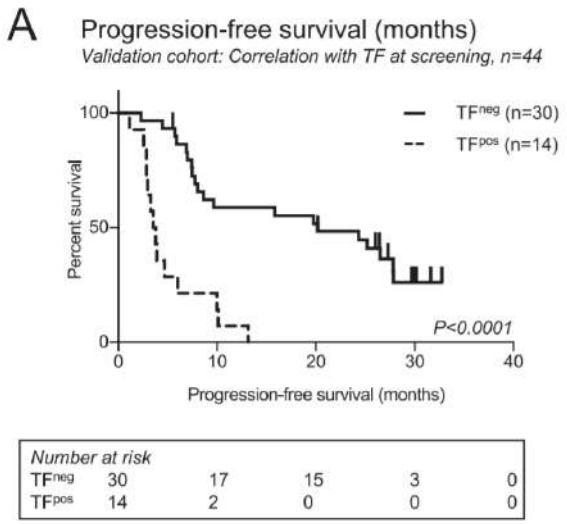


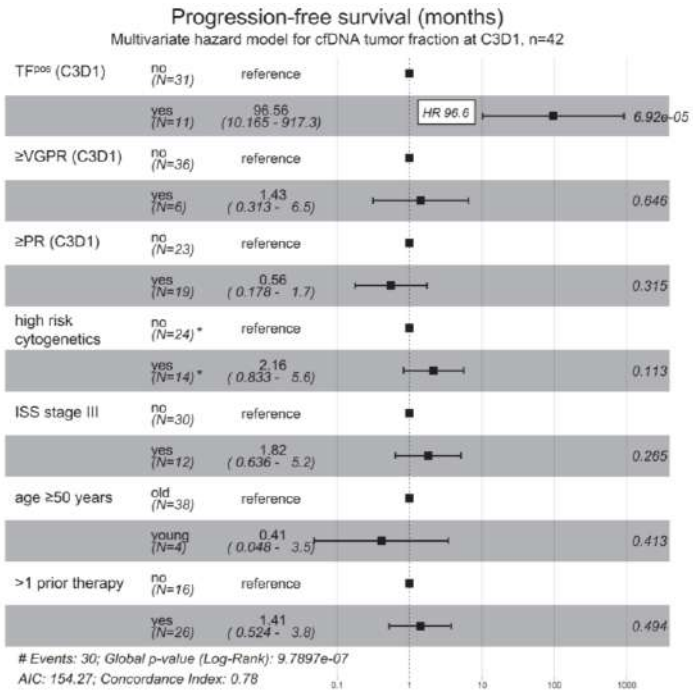
High cfDNA TF (M = 10.65%; range: 3,2-40,6) vs. patients with low cfDNA TF (M = 1,2%; range: 0,4-3,2)

cfDNA

ctDNA for prognostication in RRMM

ctDNA as independent risk factor





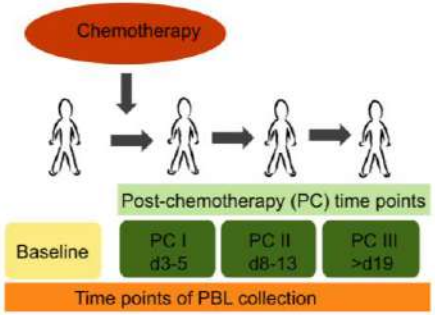
Detectability of MM-derived cfDNA, as a measure of substantial tumor burden with therapy, independently predicts poor PFS and may provide refinement for standard-of-care response parameters to identify patients with poor response to treatment earlier than is currently feasible

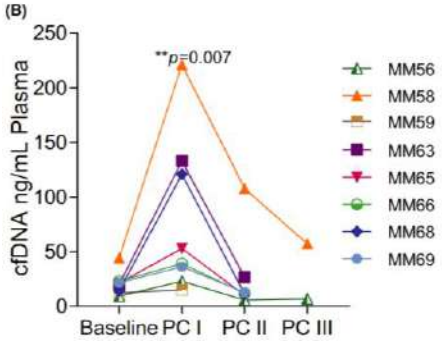
[Waldschmidt et al., Leukemia 2022]

cfDNA

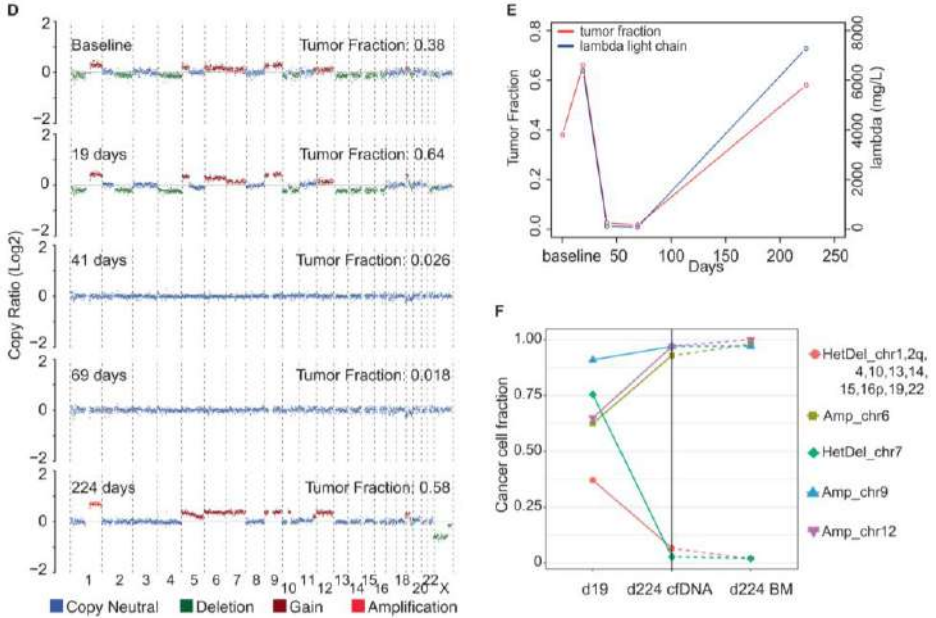
ctDNA for therapeutic monitoring

To be determined





High cfDNA release in few days after TT starting
[Deshpande S et al., EJH 2020]

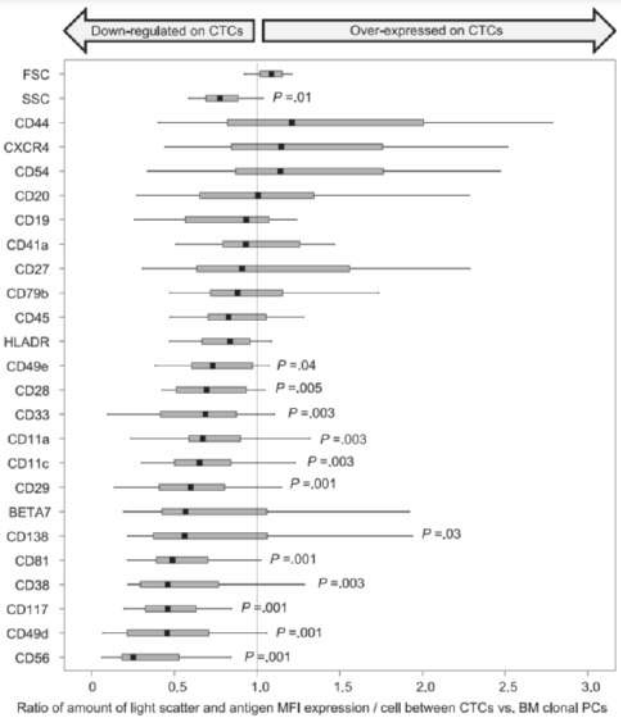


Tumor fraction cfDNA monitoring
[*Guo et al., Leukemia 2018*]

CTCs

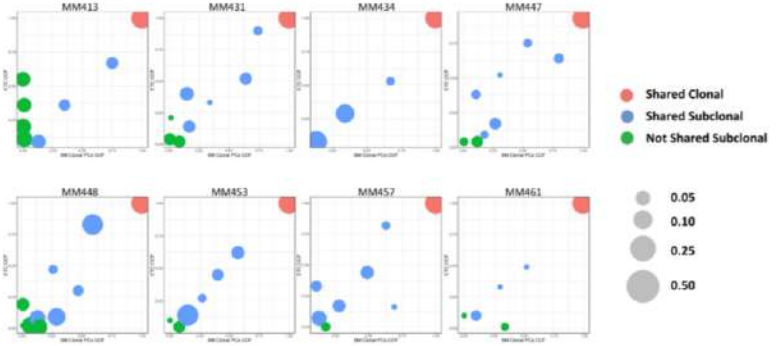
Circulating Tumor Cells (CTCs) for genetic characterization

Understanding disease dissemination



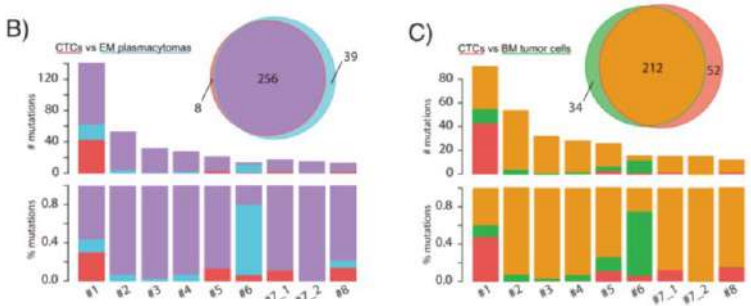
CTCs display a peculiar immunophenotype

[Paiva B et al., Blood 2013]



CTCs vs BM PCs subclonal mutations

[Mishima et al., Cell Rep 2017]



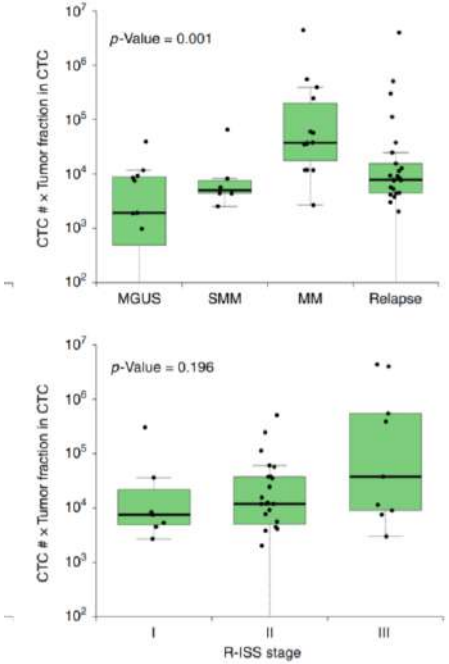
CTCs and EM plasmocytomas

[Garces JJ et al., Leukemia 2020]

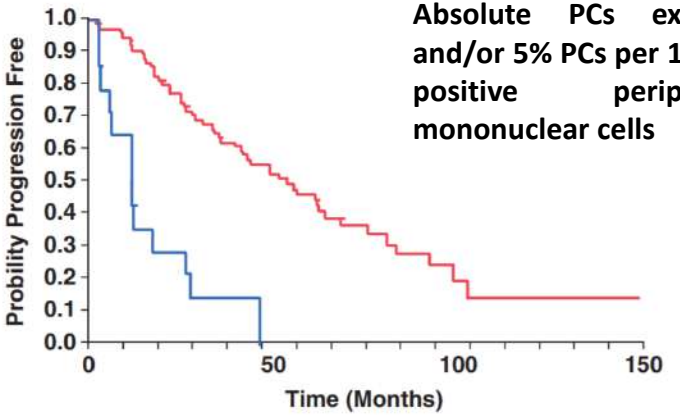
CTCs

Circulating Tumor Cells (CTCs) for risk stratification

In Smouldering Myeloma



Disease phase and R-ISS
[Manier S et al., Nat Comm 2018]



Absolute PCs exceeding $5x10^6$/L and/or 5% PCs per 100 cytoplasmic Ig-positive peripheral blood mononuclear cells

	Median TTP (months)
High circ PC	12
Low circ PC	57

P value: <0.001

High CTC risk progression SMM to MM
[Bianchi G et al., Leukemia 2013]

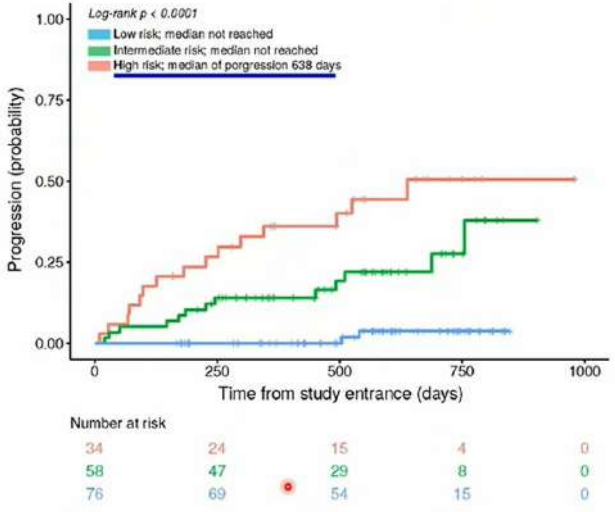
CTCs

Circulating Tumor Cells (CTCs) for risk stratification

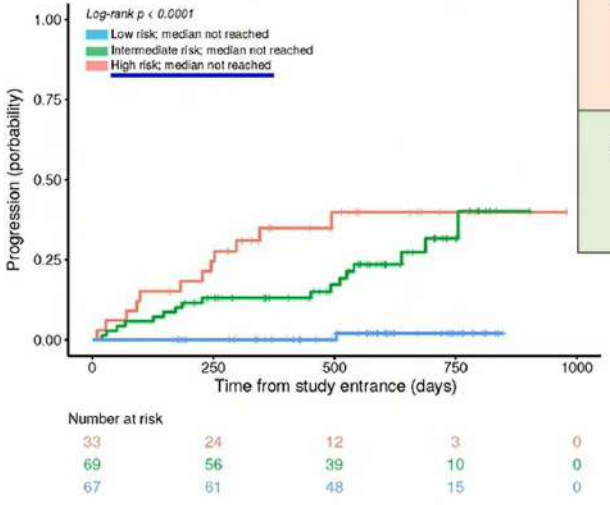
Towards a minimally invasive SMM risk stratification

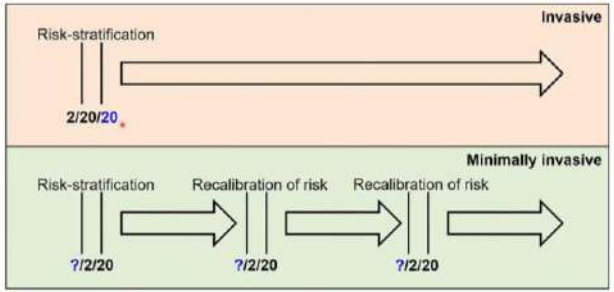
CTCs/uL>0.7, serum M spike >2g/dL and FLC ratio>20 (0.7/2/20)

0.7/2/20 Model (CTC/µL >0.7)



2/20/20 Model (BMPC >20%)



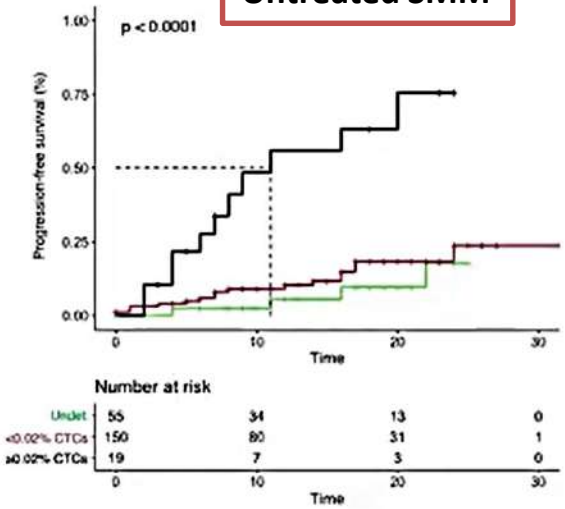


[Termini R et al, IMW 2021]

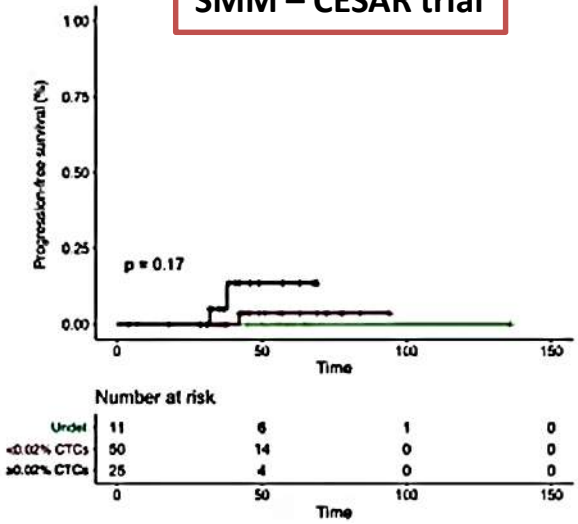
Circulating Tumor Cells (CTCs) for risk stratification

Untreated SMM patients with ≥0.02% CTCs have ultra-high risk transformation

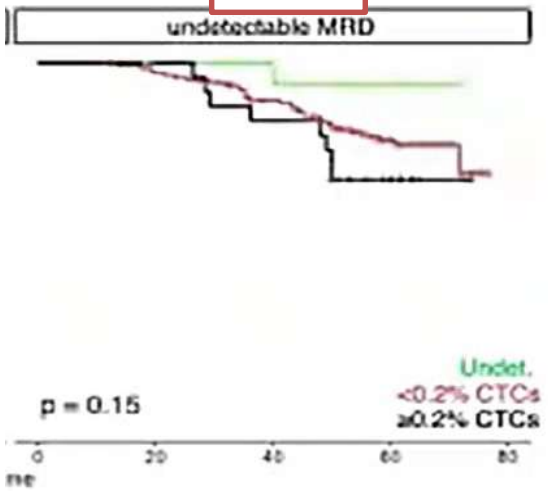
Untreated SMM



SMM – CESAR trial



NDMM



11 months with respect to <0.02% CTCs or undetectable CTCs

Early intervention in SMM and undetectable BM MRD in NDMM can abrogate dismal outcome associated with high CTCs levels

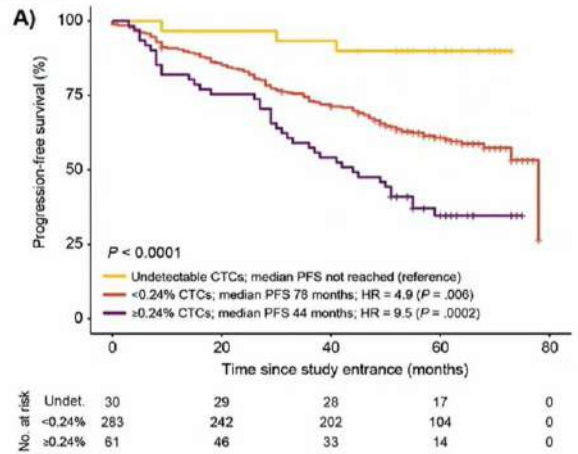
[Garces JJ et al, ASH 2021, Manuscript in review]

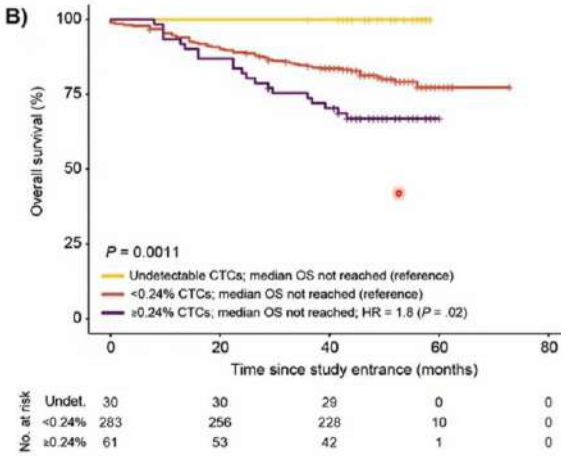
CTCs

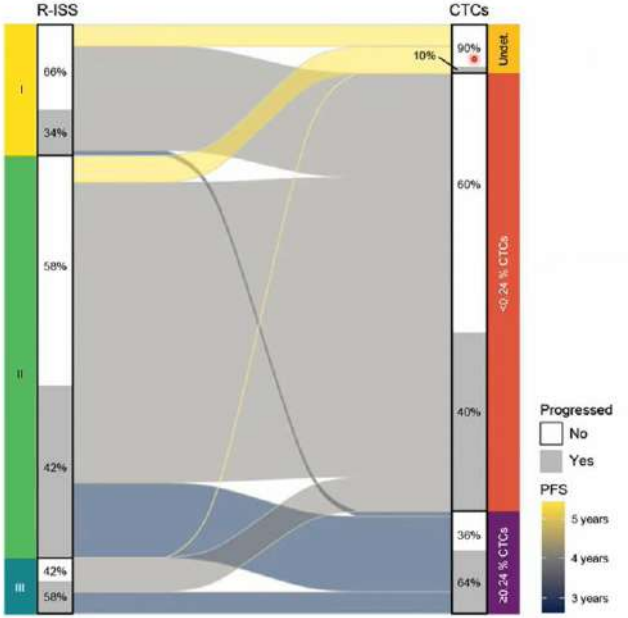
Circulating Tumor Cells (CTCs) for risk stratification

NDMM CTCs are the most relevant diagnostic biomarker in active MM

Transplant-eligible pts treated with VRD induction and consolidation







Independent prognostic value

[Garces JJ et al, ASH 2021, Manuscript in review]

CTCs

Tumor and immune biomarkers to predict undetectable MRD

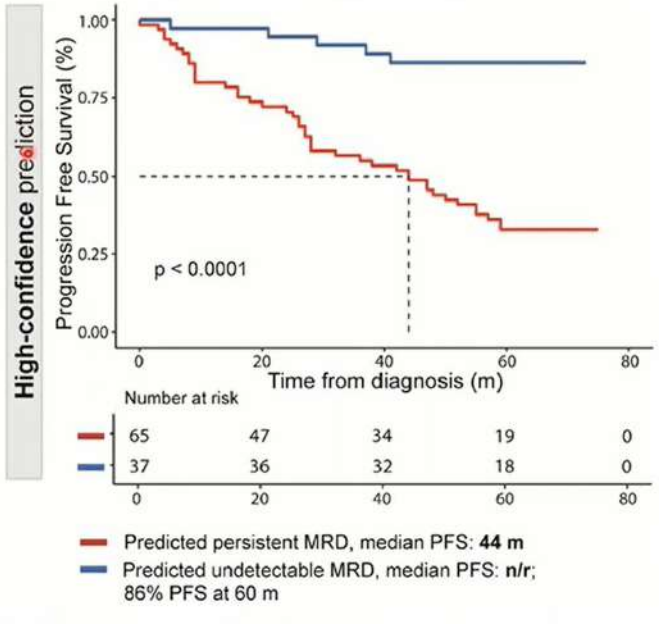
A machine learning model developed in transplant-eligible MM

Variable	Sustained und. MRD (n/N)	Non-sustained und. MRD (n/N)	Log odds [CI]	P
ISS Stage I *(vs II and III)*	36/90	62/164	0.10 [-0.4; 0.6]	0.73
ISS Stage III *(vs I and II)*	15/90	41/164	-0.51 [-1.2; 0.1]	0.13
R-ISS Stage I *(vs II and III)*	26/73	42/142	0.28 [-0.3; 0.9]	0.37
R-ISS Stage III (vs I and II)	5/73	16/142	-0.54 [-1.6; 0.5]	0.30
Elevated LDH levels	8/87	28/156	-0.78 [-1.6; 0.1]	0.07
gain(1q)	28/71	62/139	-0.21 [-0.8; 0.4]	0.48
t(4;14)	9/76	27/150	-0.49 [-1.3; 0.3]	0.23
t(14;16)	4/58	7/118	0.16 [-1.1; 1.4]	0.80
del(17p13)	4/76	21/150	-1.08[-2.2; 0.0]	0.05
del(17p13) and/or t(4;14)	13/90	41/164	-0.67 [-1.3; 0.0]	0.05
CTCs (>0.735)	39/90	102/164	-0.78 [-1.3; -0.2]	**0.004**
PC clonality (>13.39)	12/90	56/164	-1.20 [-1.9; -0.5]	**<0.001**
Myeloid precursors (>0.21)	45/90	62/164	0.50 [0.0; 1.0]	0.06
NK $CD56_{bright}$ $CD27_{neg}$ cells (>0.04)	32/90	84/164	-0.63 [-1.2; -0.1]	**0.02**
Eosinophils (>1.76)	55/90	74/164	0.65 [0.1; 1.2]	**0.02**
$CD27_{neg}$ $CD38_{pos}$ T cells (>0.61)	12/90	39/164	-0.71 [-1.4; 0.0]	0.05
Mature B cells (>1.75)	20/90	35/164	0.05 [-0.6; 0.7]	0.90
Intermediate neutrophils (>36.33)	9/90	15/164	0.10 [-0.8; 1.0]	0.80
Predicted und. MRD *(standard confidence)*	62/90	57/164	1.44 [0.9; 2.0]	**<0.001**
Predicted und. MRD *(high confidence)*	25/37	15/84	2.26 [1.4; 3.1]	**<0.001**

Increased odds of sustained undetectable MRD

-2 -1 0 1 2 3

Log odds ratio

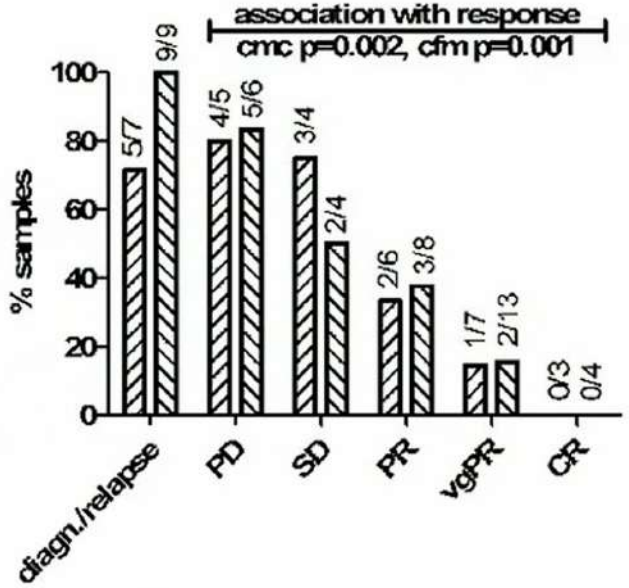


[Guerrero C et al, Clin Canc Res 2022]

cfDNA

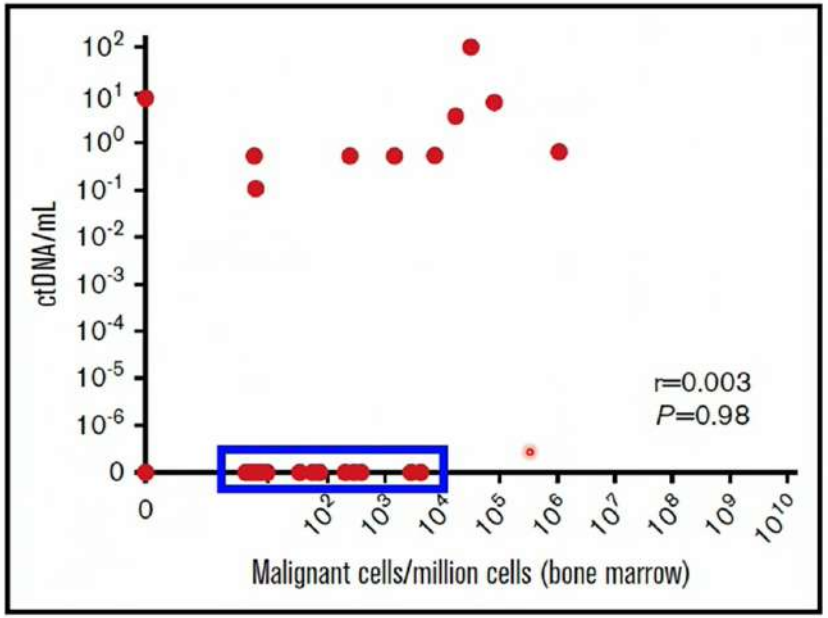
ctDNA for MRD monitoring

To be determined



NGS of VDJ from circulating myeloma cells and cfDNA
Low detection rate in patients achieving VGPR or CR

[Oberle A et al, Haematologica 2017]



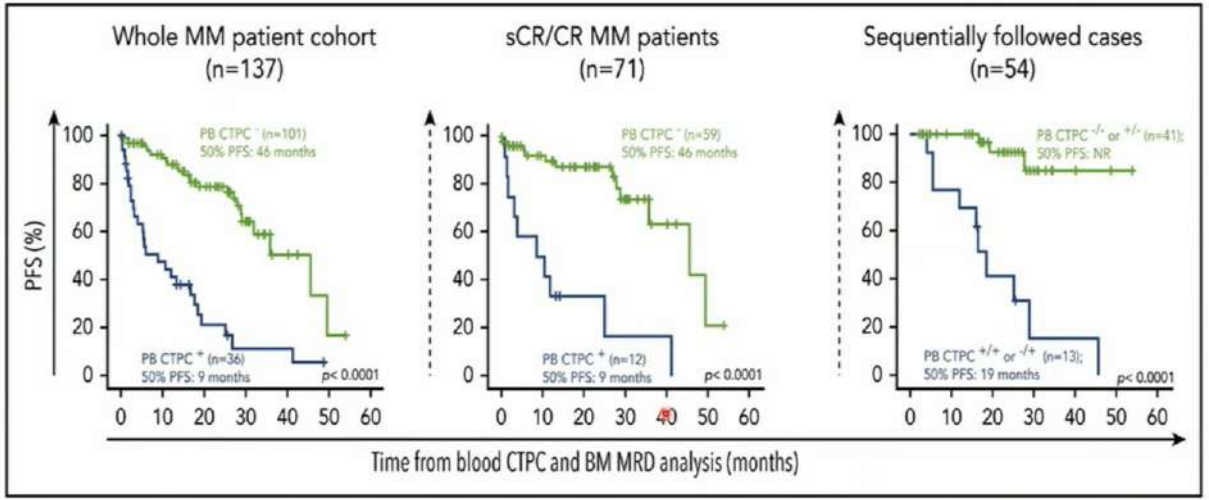
MRD assessment by NGS in paired marrow vs blood samples
Partial correlation with false negative results in blood (44%)

[Mazzotti C et al, Blood 2018]

CTCs

MRD assessment by NGF in paired marrow vs blood samples

Partial correlation with false negative results in blood (40%)



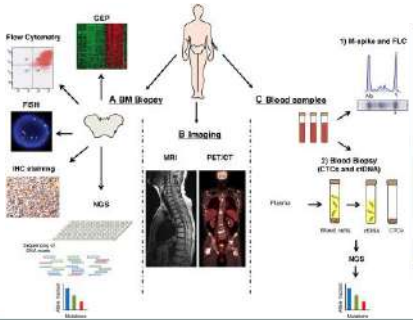
Despite the greater sensitivity and rate of positivity for CTPC reported here, a significant proportion of MM cases that were BM MRD⁺ or sIF⁺ still had undetectable CTPC in (paired) blood samples: 55/137 (40%) and 41/137 (30%), respectively

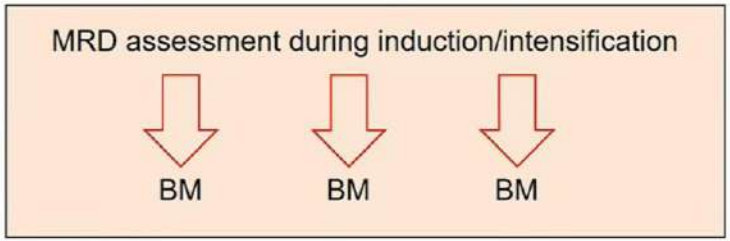
[Sanoja Flores L et al., Blood 2019]

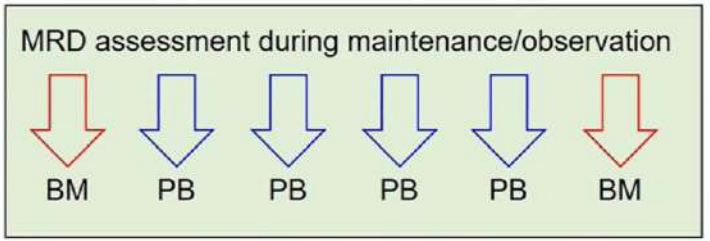
Summary

CTCs and cfDNA

- Genetic characterization using <u>minimally invasive ctDNA and CTCs</u> is possible, but in the short-term it is unlikely that these will replace bone marrow biopsies
- Both ctDNA and CTCs hold information about <u>tumor egression and dissemination</u>
- When compared to the quantification of the tumor burden in the marrow, the <u>enumeration of CTCs may have superior prognostic value in SMM and active MM</u>
- ctDNA has shown limited sensitivity for MRD detection, but there has been <u>remarkable improvement</u> (e.g. targeted sequencing of phased variants in lymphoma)
- NGS of VDJ rearrangements and NGF can detect MRD in blood, but <u>greater sensitivity</u> is warranted to make it clinically useful.







- Greater standardization is needed

Highlights from IMW 2021

1-2 Febbraio 2022
Bologna
Royal Hotel Carlton