Optical genome mapping of myeloma at Versailles Hospital

CENTRE HOSPITALIER DE VERSAILLES
CHV

Hippolyte GUERINEAU

FrOGG French-speaking OGM Group-GFCH

GFCH Groupe Francophone de Cytogénétique Hématologique

Workflow

- Collection of **1 EDTA & 1 heparinized bone marrow samples (4 mL)**
- **If less than 80% plasma cells infiltration → plasma cells isolation**
- Mix EDTA and heparinized samples
- At least 0,5M cells, otherwise no OGM and 3 FISH (*FGFR3*-IGH, *TP53* and 1p/1q)
- Between 0,5M and 1M cells, dilution with negative fraction to obtain at least 50% plasma cells
- If more than 1M cells, no dilution with negative fraction and if more than 2M cells, backup sample

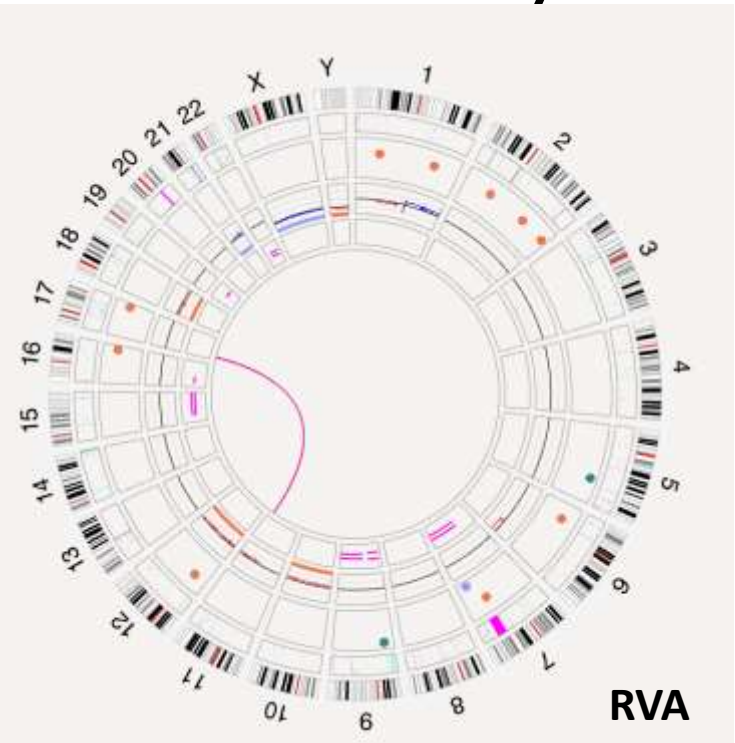
Workflow

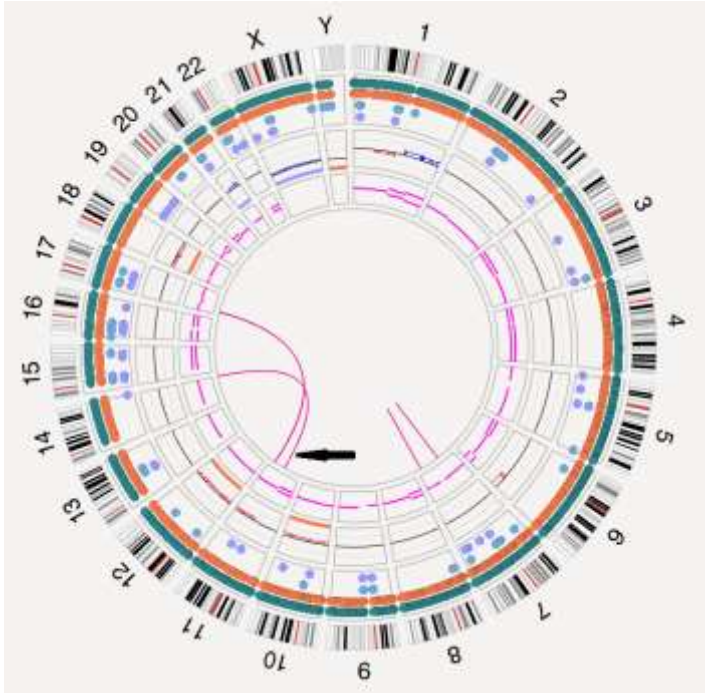
During the first 3 months :

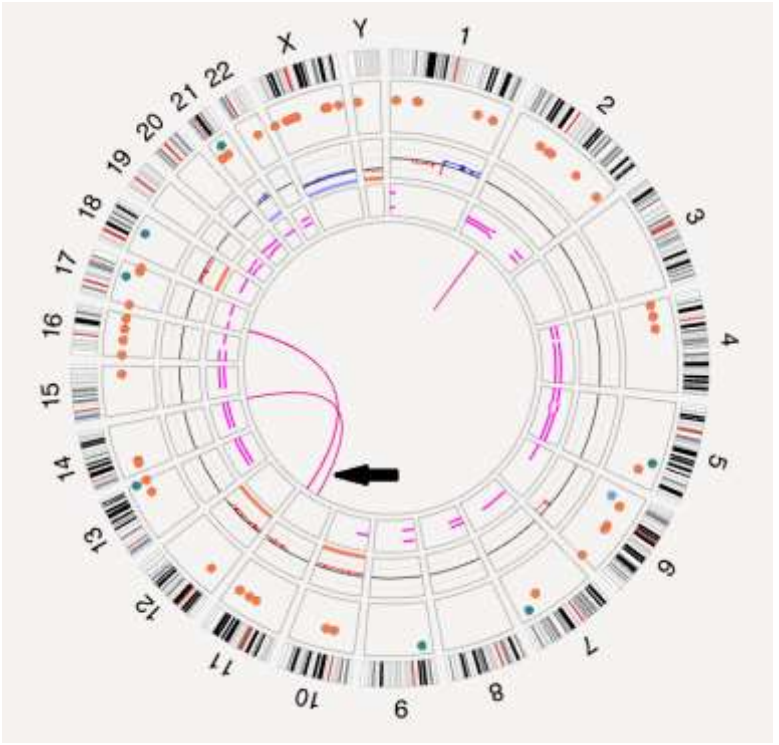
- **OGM analysis + *TP53*, 1p1q and IGH-*CCND1* FISH**
- **RVA and De Novo** because t(11;14) not always visible and asses ploidy

Now :

- **OGM analysis + *TP53* FISH**
- **Guided assembly** and De Novo if ploidy issue







De Novo and Guided assembly

Workflow

- Risk stratification of myeloma by IFM and IMWG 2023 scores

IFM score

Trisomy 5 → -0.3
Trisomy 21 → 0.3
t(4;14) → 0.4
1q gain → 0.5
del(1p32) → 0.8
del(17p) → 1.2

Score ≤ 0 : Low risk
Score > 0 et < 1 : Intermediate risk
Score ≥ 1 : High risk

Perrot et al, J Clin Oncol 2019

IMWG 2023 score

High risk if :

- Del17p > 20% of sorted plasma cells
- Biallelic del1p32
- TP53 mutation (no threshold VAF)
- Association of 2 lesions among : t(4;14), t(14;16), t(14;20), 1q gain (at least 3 copies), monoallelic del1p32

- **BED by FROGG (myeloma group)**
- **Duplicate analysis by 2 operators**
- **Only prognostic abnormalities are reported**
- **DNA UHMW sent to molecular biology department to test for *TP53* mutation**

Myeloma at Versailles hospital

124 NDMM between october 2024 and march 2025

- **113 were analysed (91%)**
- 11 not enough cells (less than 0,5M cells) (9%)

Among 113 analyzed :

- **86 with plasma cells isolation with no dilution (76%)**
- 21 with plasma cells isolation with negative fraction dilution (19%)
- 6 with no plasma cells isolation (5%)

- **101 optimal metrics (89%)**
- 6 sub-optimal (5%)
- 6 non-optimal (5%)

Cytogenetic abnormalities

113 samples

Primary events

Abnormalities	Number of samples	Reported frequency	p-value (z-test*)
IGH r	47 **(42%)**	40%	0,80
• **t(11;14) *CCND1***	32 **(28%)**	20%	0,04
• **t(4;14) *NSD2***	3 **(3%)**	10%	0,01
• **t(14;16) *MAF***	3 **(3%)**	4%	0,62
• **t(14;20) *MAFB***	2 **(2%)**	<1%	
• **t(6;14) *CCND3***	4 **(4%)**	5%	0,63
• **t(8;14) *CMYC***	4 **(4%)**		

*Comparing an observed frequency to a theoretical frequency

Abnormalities	Number of samples	Reported frequency	p-value (z-test*)
Hyperdiploidy	59 **(52%)**	55%	0,61

Rajkumar et al, Am J Hematol 2024

Daudignon et al, Curr Res Transl Med 2023

Cytogenetic abnormalities

113 samples

Secondary events

Abnormalities	Number of samples	Reported frequency	p-value (z-test*)
Gain 1q21	32 **(28%)**	40%	0,01
Del1p32	16 **(14%)**		
• **Monoallelic**	15 **(13%)**	11%	0,53
• **Biallelic**	1 **(<1%)**	<1%	

Abnormalities	Number of samples	Reported frequency	p-value (z-test*)
***MYC* r**	17 **(15%)**	15%	1

Rajkumar et al, Am J Hematol 2024

Weinhold et al, Haematologica 2021

Schavgoulidze et al, Blood 2023

Daudignon et al, Curr Res Transl Med 2023

Myeloma risk stratification

113 samples

Risk according to IFM	Number of samples	Reported frequency	p-value (z-test*)
Low risk	64 **(57%)**	55%	0,80
Intermediate	36 **(32%)**	30%	0,74
High risk	13 **(12%)**	15%	0,52

Perrot et al, J Clin Oncol 2019

Risk according to IMWG 2023	Number of samples	Reported frequency	p-value (z-test*)
No High risk	92 **(81%)**	77%	0,32
High risk	21 **(19%)**	23%	0,32

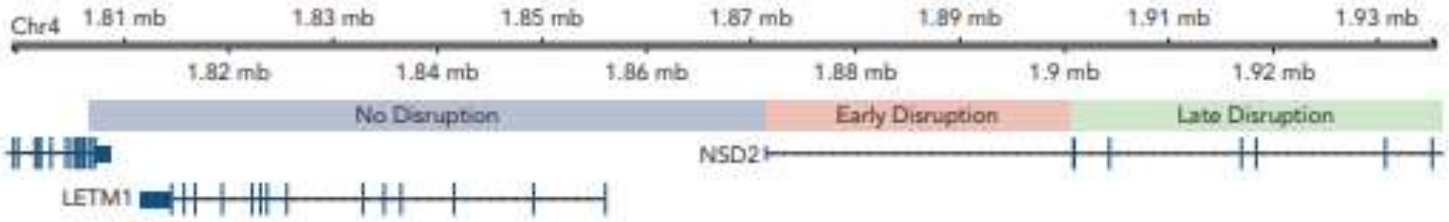
TP53

113 samples

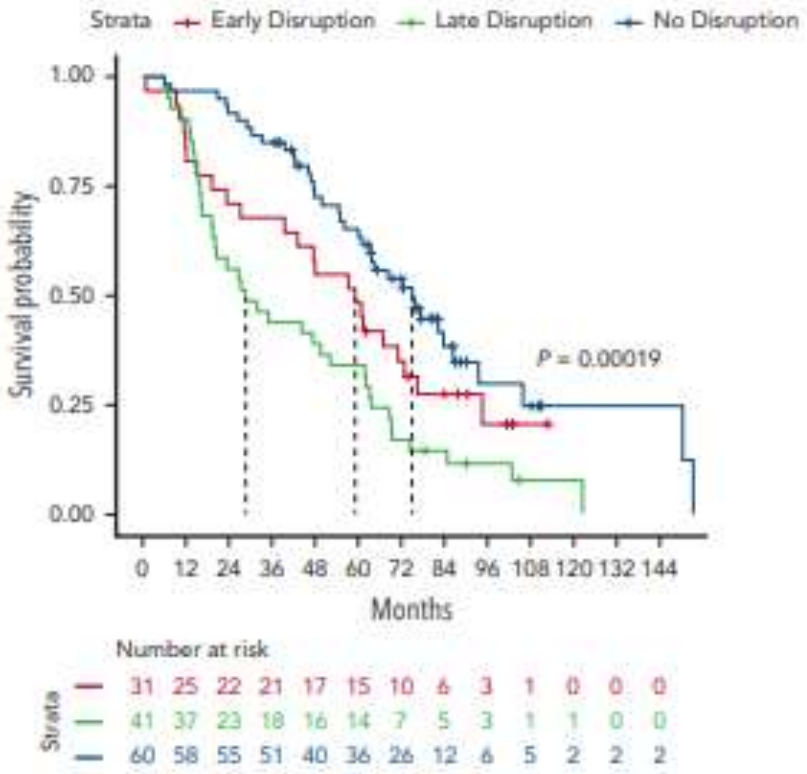
Loss of TP53 (> 20% cells) : 10 samples (9%)

- **8 cases with a clone size similar between OGM and FISH**
  - 2 cases with loss of TP53 only apparent by removing all filters (loss of TP53 in around 20% plasma cells)
- **2 cases with different clone size between OGM and FISH**
  - larger clone size with FISH than OGM but both > 55% plasma cells

t(4;14) breakpoints



- **No-disruption** : no high risk
- **Early disruption** : intermediate risk
- **Late disruption** : high risk



Stong et al, Blood 2023

t(4;14) breakpoints

- **BED myeloma from FROGG**

Stong et al, Blood 2023

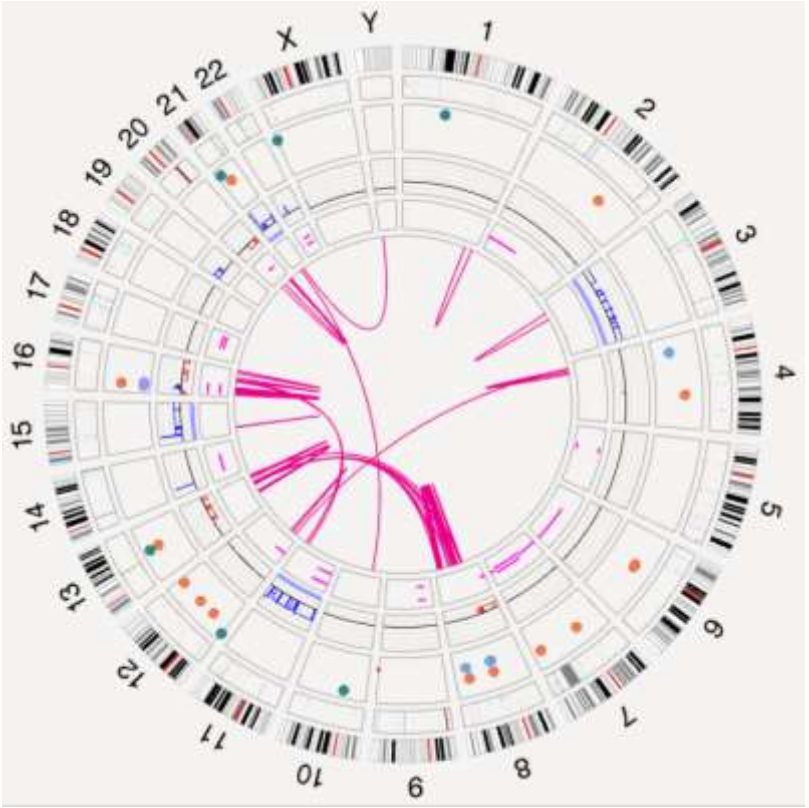
Complex events

- **Complex structural variants including chromoanagenesis** in 41 samples (40%)
  - Chromothripsis : adverse risk, definition ?
  - Chromoplexy

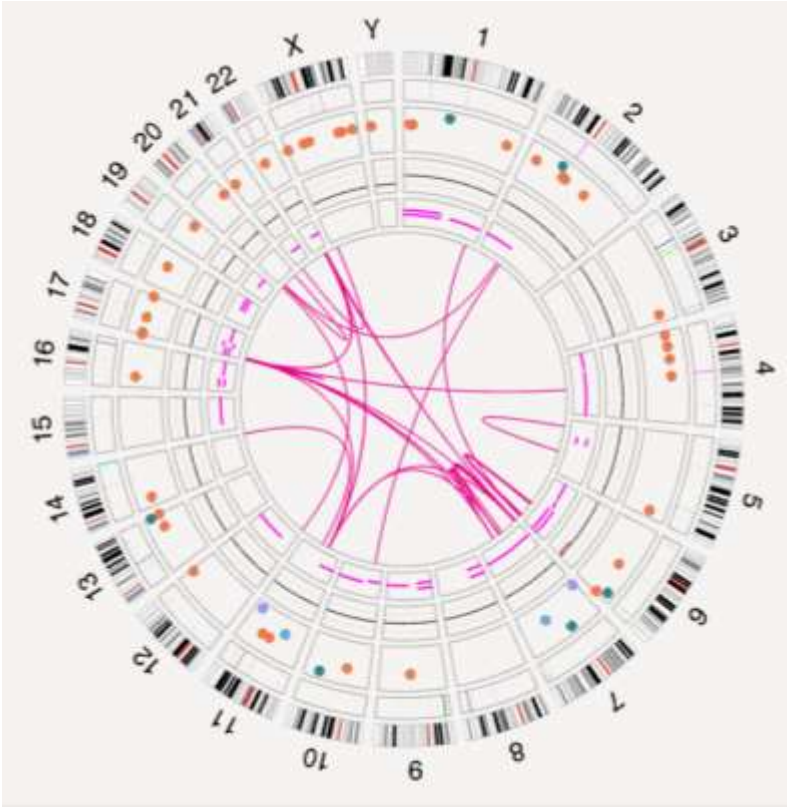
Magrangeas et al, Blood 2011

Daudignon et al, Curr Res Transl Med 2023

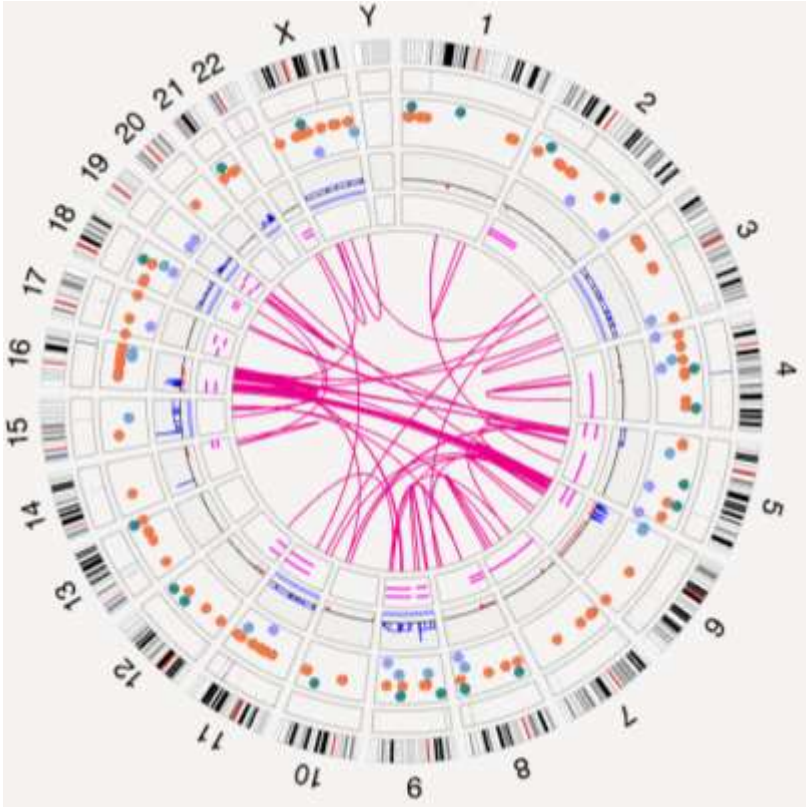
Complex events



Chromothripsis



Chromoplexy



Complex structural variants

Conclusion

In Multiple Myeloma :

- **OGM is consistent with FISH**
- **OGM provides more abnormalities without multiple FISH tests**
  - Breakpoint analysis and chromoanagenesis
- **OGM is sucessfully implemented in the workflow for MM**

- **Versailles hospital** : Christine TERRE, Victoria RAGGUENEAU
- **GFCH** and **FROGG** : Agnès DAUDIGNON, Helene GUERMOUCHE

  Myeloma group : Catherine GERVAIS, Isabelle RAYMOND-BOUCHARD, Baptiste GAILLARD
- **Bionano**

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