# Highlights from IMW 2019

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Bologna
Royal Hotel Carlton

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# La leucemia plasmacellulare: Meccanismi biologici

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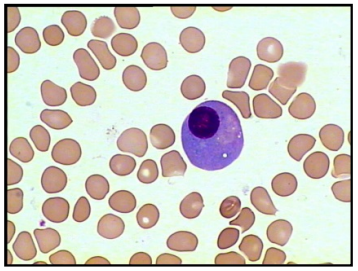
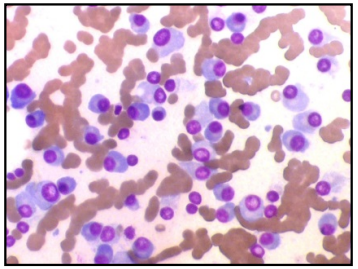
# PLASMA CELL LEUKEMIA (PCL): definition

**≥ 20% monoclonal plasma cells in peripheral blood and/or absolute plasma cell count ≥ $2x10^9$/L**

- **PRIMARY PLASMA CELL LEUKEMIA (pPCL):**
  - no previous history of MM
  - 60% of all PCL (crude incidence 0.04-0.05/100.000 persons per year in EU)



- **SECONDARY PLASMA CELL LEUKEMIA (sPCL)**
  - Leukemic transformation of Relapsed/Refractory MM
  - 40% of all PCL, about 1% of chemio-resistent MM with high tumor burden



**DIFFERENTLY FROM MM AND sPCL, IN WHICH MANY UNFAVORABLE GENOMIC ABERRATIONS GRADUALLY ACCUMULATE DURING PROGRESSION, MULTIPLE GENETIC LESIONS ARE ALREADY PRESENT IN pPCL AT ONSET OR DIAGNOSIS**


Mosca L, et al. AJH 2013
Simeon V, et al. Int. J. Mol. Sci. 2015
An G, et al. Annals of Hematology. 2015
Gonsalves WI, et al. Leukemia. 2014

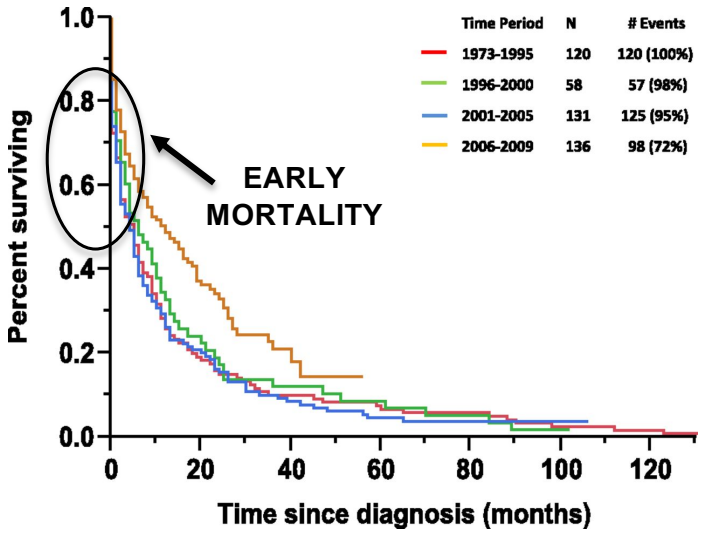
Musto P. J Clin Oncol. 2016
Musto P, et al. Leukemia. 2014
Gavriatopoulou M. et al. Leukemia 2018

van de Donk NW, et al. Blood. 2012
Fernandez de Larrea C, et al. Leukemia. 2013
Touzeau C, et al. Blood. 2016

Musto P, et al. Curr Treat Options Oncol. 2016
Tiedemann RE, et al. Leukemia. 2008
Neri A. et al. Expert Rev Hematol. 2016

# pPCL: prognosis and overall survival (OS)

## SURVIVAL TRENDS OF pPCL PATIENTS IN DIFFERENT TIME INTERVALS



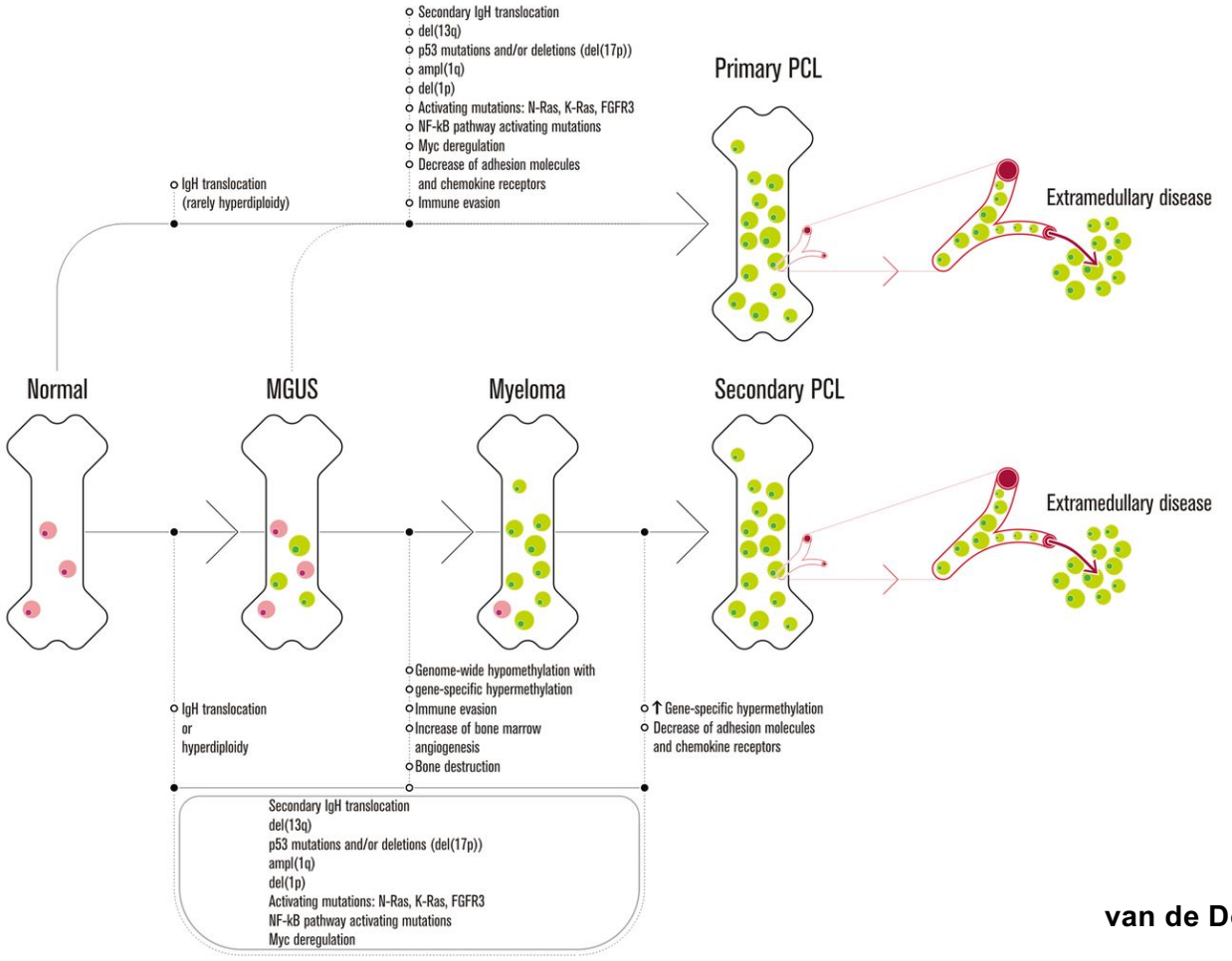

| Time interval (years of diagnosis | Median OS (months) | Early mortality (>1 month) |
|---|---|---|
| 1973-1995 | 5 | 28% |
| 1996-2000 | 6 | =23% |
| 2001-2005 | 4 | 27% |
| 2006-2009 | 12 (p< 0.001) | 15% (p=0.043) |

novel agents

Still high rate of early mortality due to:
- Disease aggressiveness
- High-risk of complications

Gonsalves WI et al. Blood 2014

# Biology of Plasma Cell Leukemia




**van de Donk NWCJ, et al. Blood 2012**

# Major biological features of Plasma Cell Leukemia

- Initial immortalizing events (genetic aberrations)
- Secondary (epi)genetic events
- Adhesion molecules and chemokine receptors
- Immune evasion

van de Donk NWCJ, et al. Blood 2012

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**van de Donk NWCJ, et al. Blood 2012**

# Initial immortalizing events (genetic aberrations)

**Primary IgH translocations and hyperdiploidy are considered to be early oncogenic events necessary for the immortalization of the plasma cell clone but insufficient for the development of symptomatic disease**

**Table 3** Ploidy in PCL and MM tumors (%)[a]

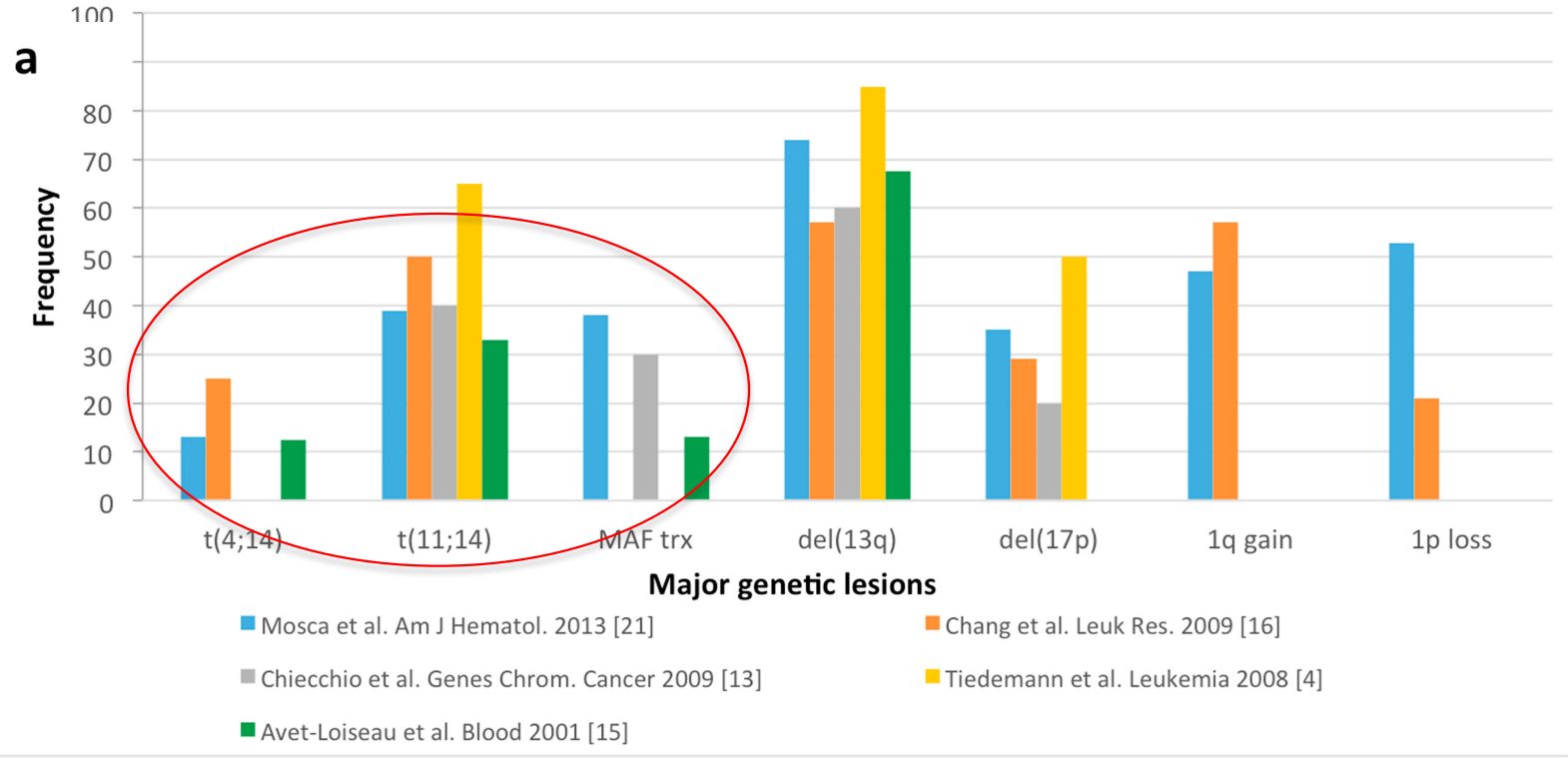
| *Ploidy* | *MM* | *sPCL* | *pPCL* |
|---|---|---|---|
| Hypodiploid (<45, >75) | }40 | 42 | 60 |
| Pseudo/diploid (45–47) | | 42 | 40 |
| Hyperdiploid (48–75) | 60 | 17 | 0 |

Abbreviations: MM, multiple myeloma; PCL, plasma cell leukemia.
[a]Percentages derived from abnormal karyotypes only.

Tiedemann et al, Leukemia 2008

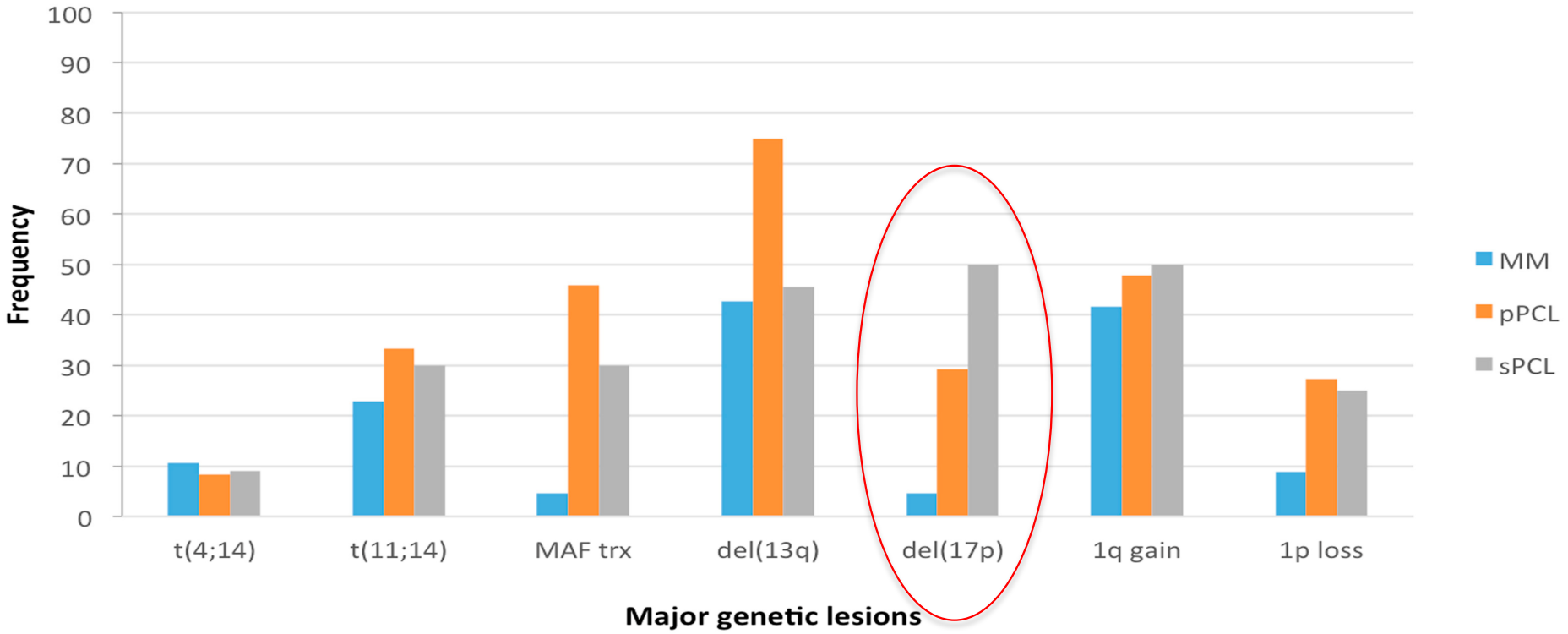
- In **pPCL:**
  - hyperdiploidy is observed in only 0%-8.8% of the cases, whereas it is observed in ~ 50% of NDMM.
  - incidence of hypodiploidy and IgH translocations is significantly increased.
- similar pattern is observed in **sPCL**, with the exception that hyperdiploidy is slightly more prevalent in sPCL (~ 17%) compared with pPCL.

# Major genetic alterations in pPCL series




**Simeon et al, Int J Mol Sci 2015**

# Major genetic alterations in PCL vs MM




Simeon et al, Int J Mol Sci 2015

# Cytogenetic features of pPCL (prospective studies)

## Frequency of the major genomic aberrations by FISH and/or SNP array

| Genomic aberration | GIMEMA study PPCL cases pos/tested (%) | IFM study PPCL cases pos/tested (%) |
|---|---|---|
| t(11;14) | 9/23 (39%) | 16/32 (50%) |
| t(4;14) | 3/23 (13%) | 2/32 (6%) |
| t(14;16) | 7/23 (30%) | 5/32 (16%) |
| del(13q) | 17/23 (74%) | 19/32 (59%) |
| del(17p) | 8/23 (35%) | 9/32 (28%) |
| 1q gain | 10/21 (48%) | 17/32 (53%) |
| 1p loss | 8/21 (38%) | 5/32 (16%) |
| MYC locus rearrangement | 2/15 (13%) | 9/32 (28%) |

FISH: fluorescence *in situ* hybridization; SNP: single-nucleotide polymorphism; PPCL: primary plasma cell leukemia; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; IFM: Intergroupe Francophone du Myélome; pos: positive; del: deletion.

Neri et al, Exp Rev Hematol 2016

# Summary of pPCL cytogenetic features

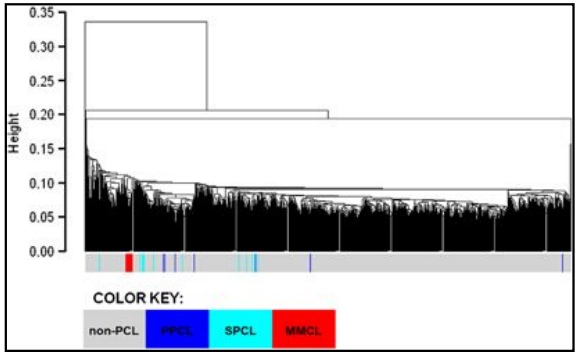
- **Hyperdiploidy very rare in pPCL: 0-8.8 % vs 50% in MM**
- **Relative occurrence of changes differs between pPCL and MM**

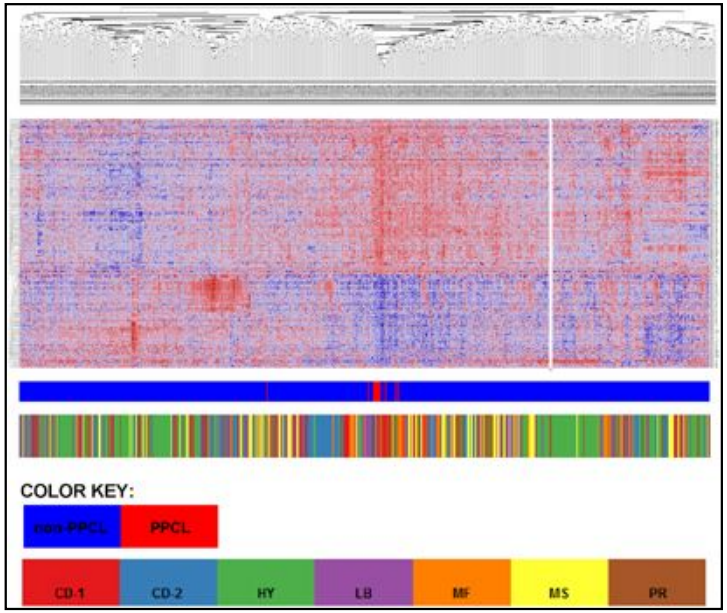
| FISH abnormalities | pPCL | MM |
|---|---|---|
| Del (17p) | 40% | =10% |
| t(11,14) | 25-65% | =15% |
| t(14,16) | 20% | 4% |
| t(4,14) | 14% | 14% |

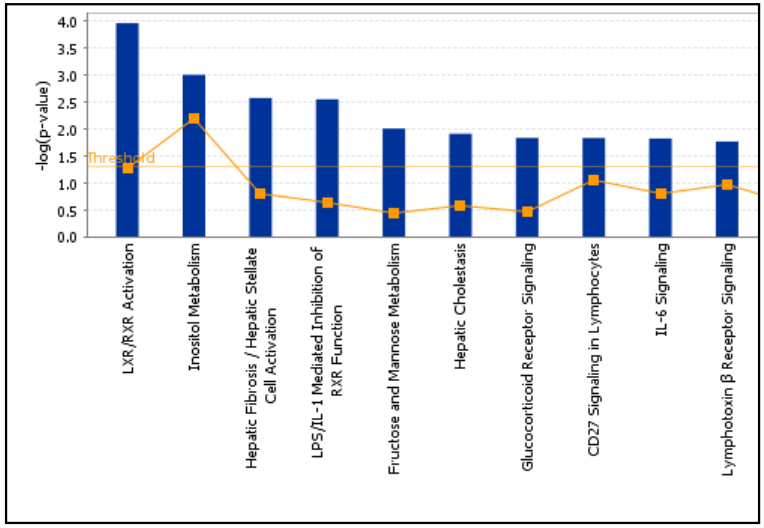
- **Poor prognosis of t(11;14) bearing pPCL (in contrast with the more favourable prognosis associated with this abnormality in MM).**
- **t(11,14) may predicts sensibility to the bcl2 inhibitor, venetoclax**

**……..Altogether, this suggests that non-hyperdiploid tumors are less dependent on the BM microenvironment than hyperdiploid tumors.**

# The genomic landscape of pPCL (mRNA)




**Usmani SZ. et al, Leukemia 2012**

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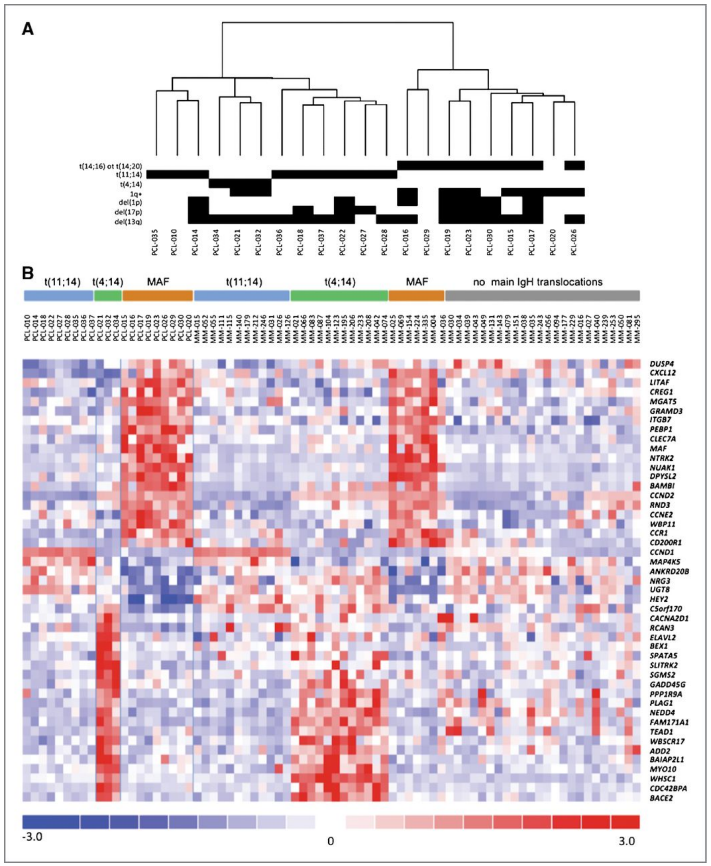
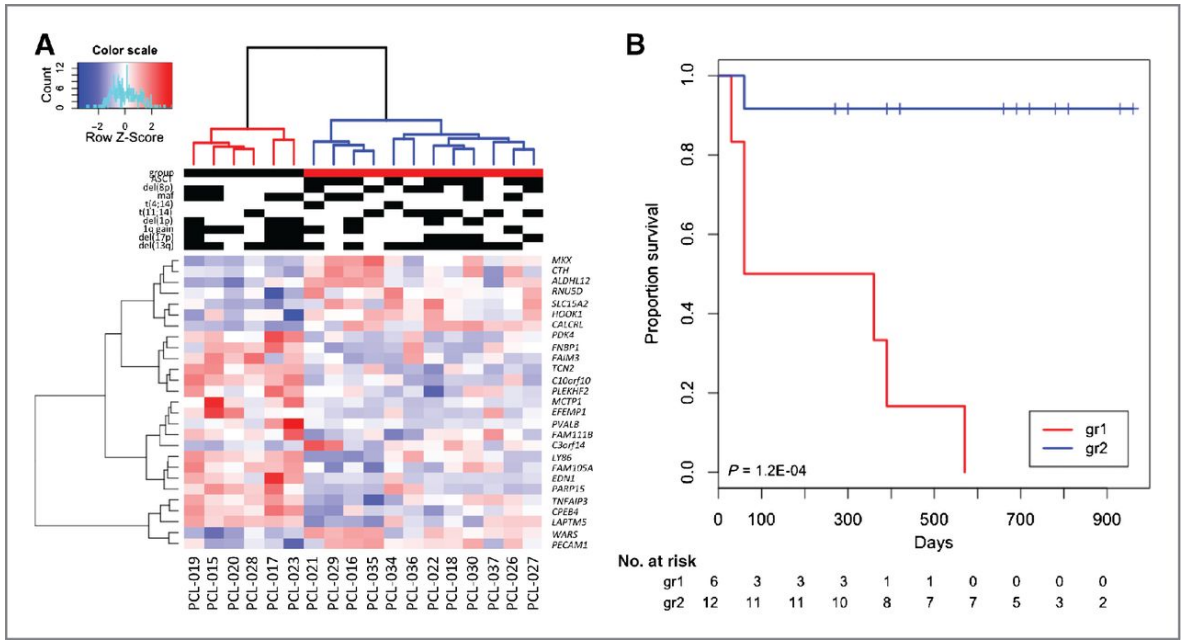
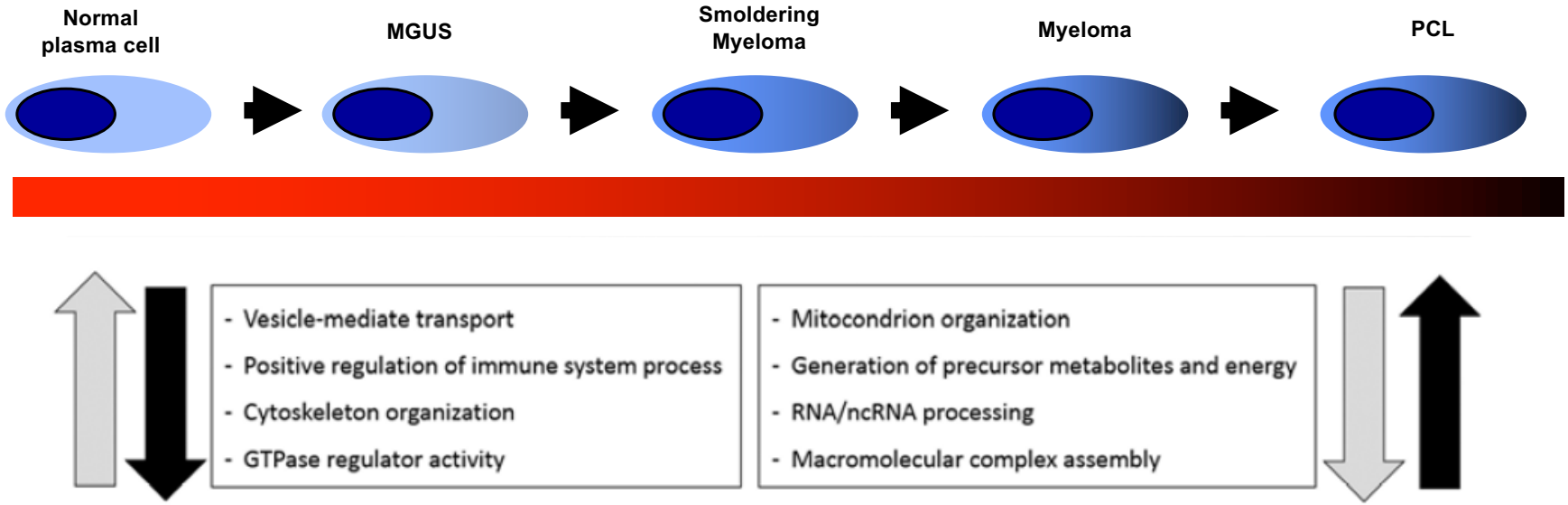


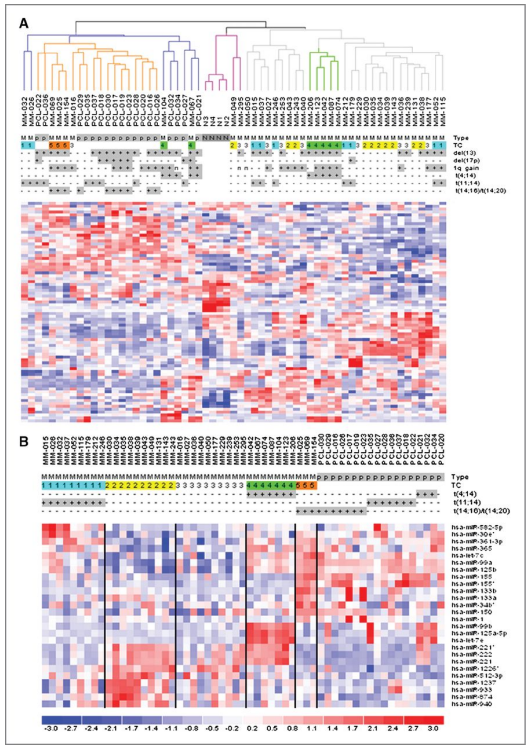

Todoerti K. et al, CCR 2013

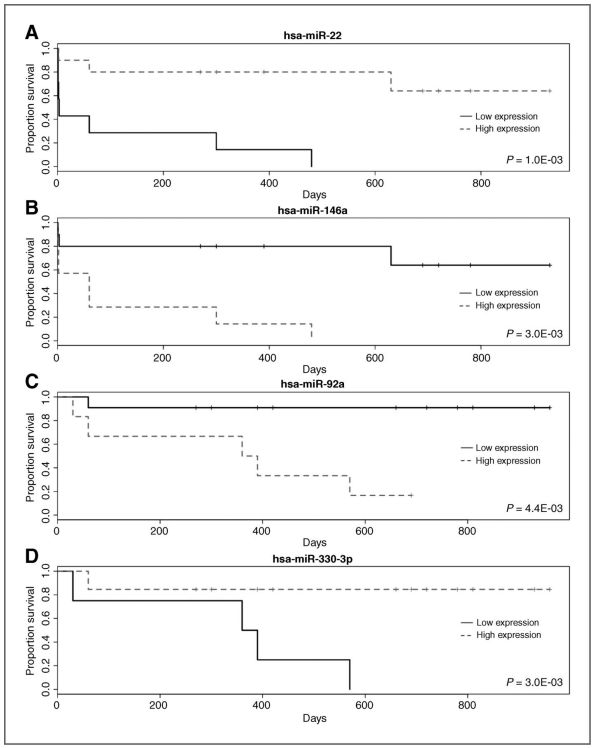
# Biological processes significantly modulated across different PC dyscrasies

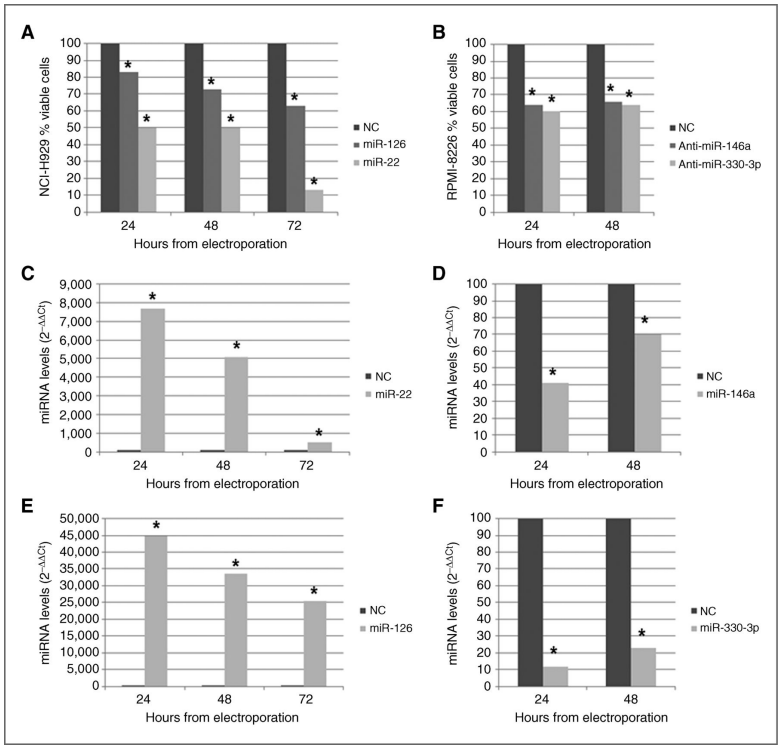



Neri A. et al, Exp. Rev. Hem. 2016

# The genomic landscape of pPCL (miRNAs)




**Lionetti M. et al. CCR 2013**

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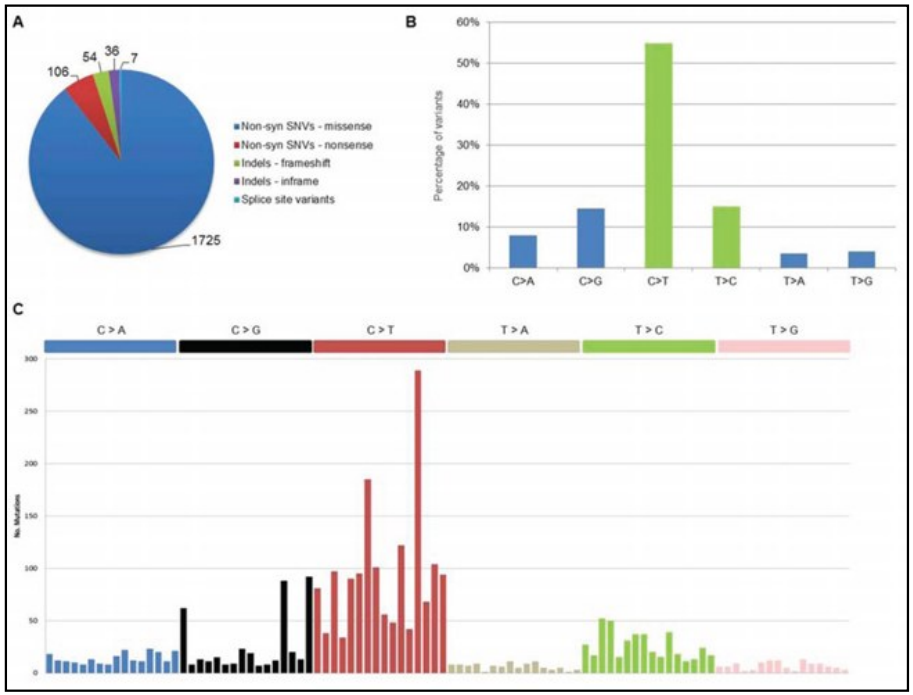
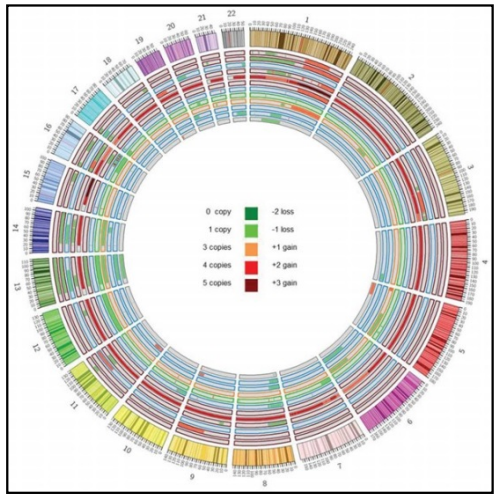
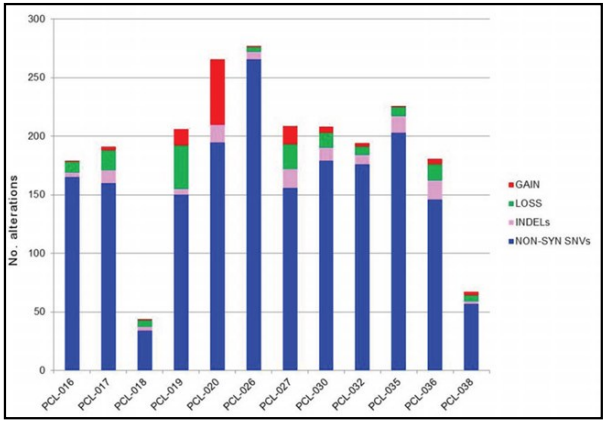
**van de Donk NWCJ, et al. Blood 2012**

# The molecular landscape of pPCL (WES)




Cifola I. et al. Oncotarget 2015

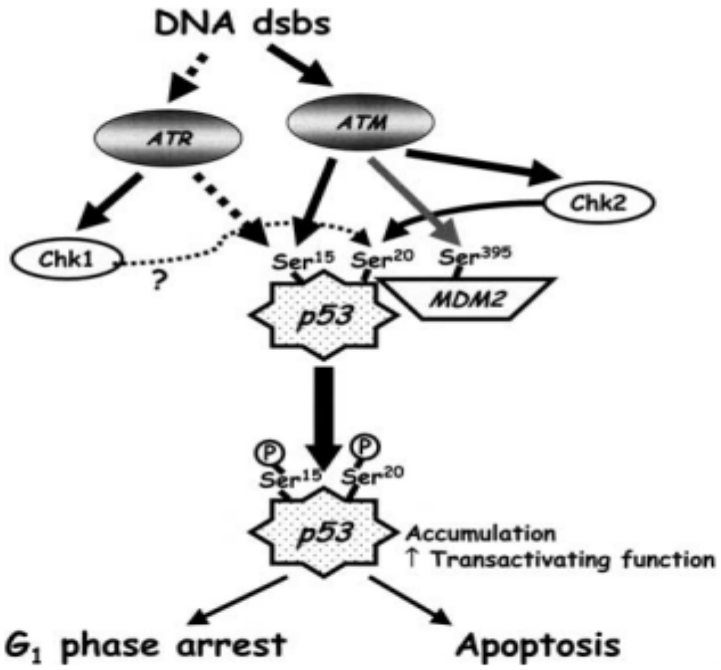
# The molecular landscape of pPCL (WES)

14 recurrently affected genes with potential driver role in pPCL have been identified:

- ✓ **cell-matrix adhesion and membrane organization (SPTB, CELA1),**
- ✓ cell cycle and apoptosis (CIDEC),
- ✓ genome stability (KIF2B),
- ✓ RNA binding and degradation (DIS3, RPL17)
- ✓ protein folding (CMYA5)
- ✓ **Immune respone (HLA-DQA1)**
- ✓ Ion transmembrane transport (UNC80, SCN9A, ZNF598)
- ✓ Unknown (FAM166B, SRRM5, CCDC144NL)

**Cifola I. et al. Oncotarget 2015**

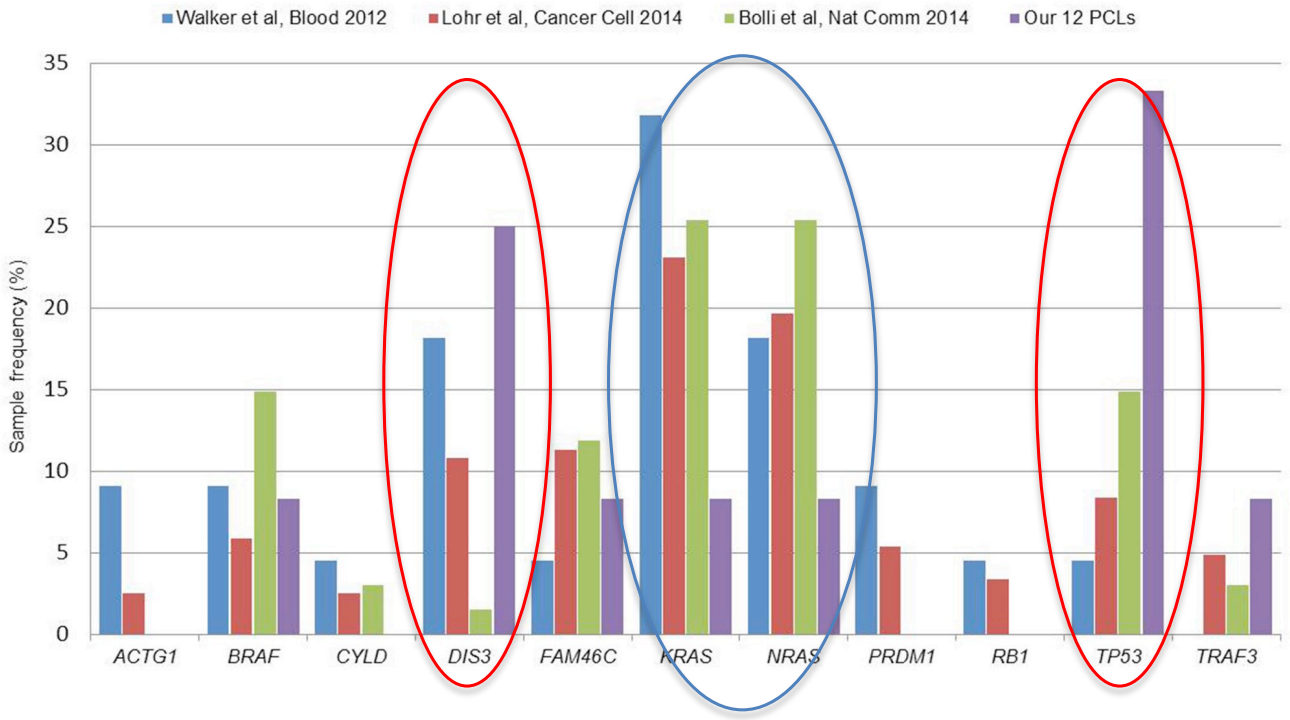
# DNA repair and cell cycle check-point genes in pPCL




| PCL-017 | PCL-018 | PCL-019 | PCL-020 | PCL-026 | PCL-027 | PCL-030 | PCL-032 | PCL-035 |
|---|---|---|---|---|---|---|---|---|
| ATM | TP53 | ATR | ATM | ATM | CDKN1A | ATM | BRCA1 | ATR |
| TP53 | | BRCA1 | ATR | EP300 | RPS6KA1 | CDC25A | | CDKN1A |
| | | | | | TP53 | CDKN1A | | |
| | | | | | | CHEK2 | | |
| | | | | | | PRKDC | | |
| | | | | | | TP53 | | |

Cifola I. et al. Oncotarget 2015

# Recurrence of MM genes in pPCL (WES)




Cifola I. et al. Oncotarget 2015
Lionetti M. et al. Oncotarget 2015

# Molecular features of pPCL (prospective studies)

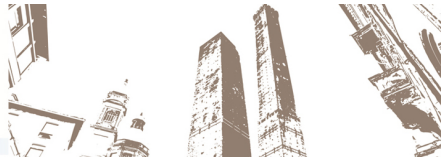
## Mutation frequency of most recurrently mutated genes by NGS

| Gene | PPCL cases pos/ tested (%) | MM cases pos/ tested (%) | SPCL cases pos/ tested (%) |
|---|---|---|---|
| TP53 | 6/24 (25%) | 4/129 (3.1%) | 2/10 (20%) |
| DIS3 | 6/24 (25%) | 24/130 (18.5%) | 3/10 (30%) |
| FAM46C | 1/24 (4.2%) | 15/128 (11.7%) | 2/10 (20%) |
| NRAS | 1/24 (4.2%) | 35/132 (26.5%) | 4/11 (36.4%) |
| KRAS | 4/24 (16.7%) | 43/132 (32.6%) | 2/11 (18.2%) |
| BRAF | 5/24 (20.8%) | 14/132 (10.6%) | 1/11 (9.1%) |

Pos: positive; PPCL: primary plasma cell leukemia; MM: multiple myeloma; SPCL: secondary plasma cell leukemia.

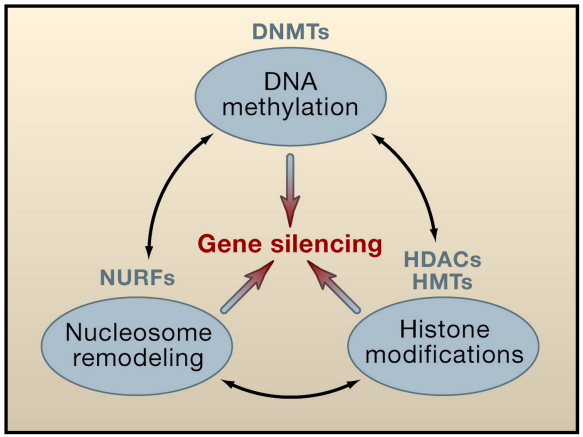
Neri et al, Exp Rev Hematol 2016

# pPCL: genetic aberrations summary

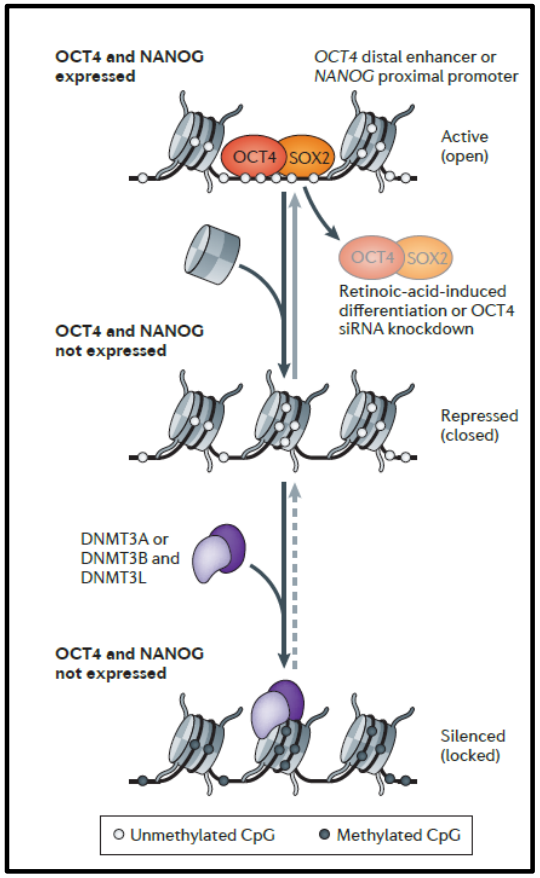


- **No mutations or / gene aberrations are specific for pPCL compared to MM**
- **Relative occurrence of changes differs between pPCL and MM**
- **NRAS, KRAS and BRAF mutations are less frequently observed in PCL than in MM**
- **TP53 and DIS3 mutations are more common in PCL than in MM-predictor of aggressive disease**
- **MYC rearrangements commonly up-regulated**
- **Very heterogenous mutations and complex genotypes-WGS**

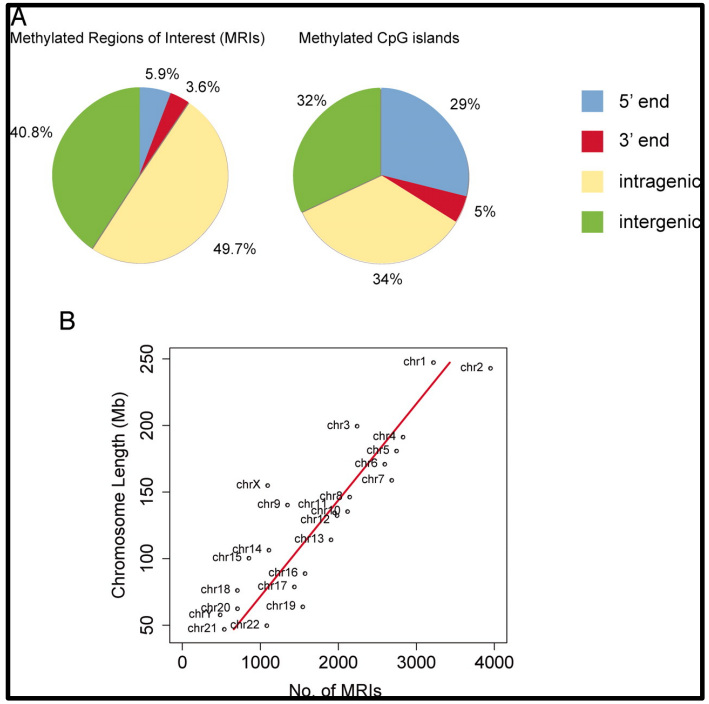
# The Epigenomics of Cancer




Jones P.A. et al. Cell 2007

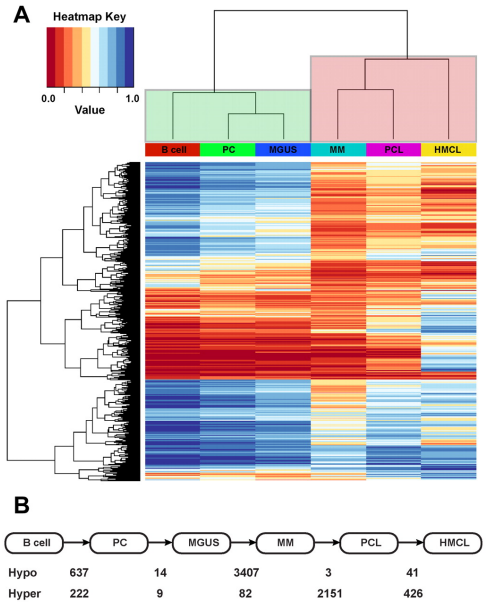


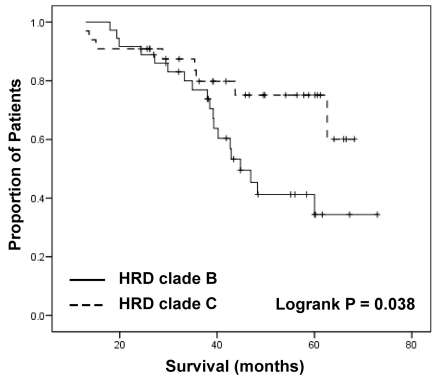

Jones P.A. Nat. Rev. Genet. 2012



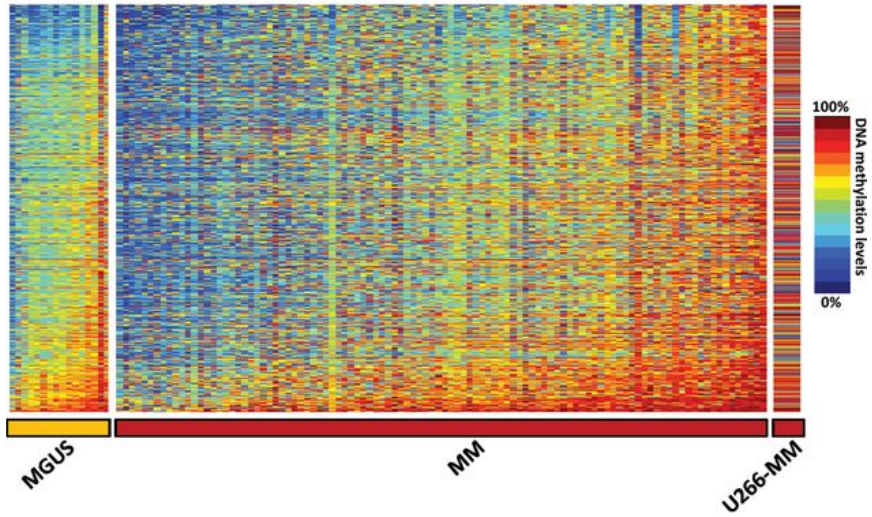

Tibor A. Rauch et al. PNAS 2009

# Aberrant global methylation in PC dyscrasias



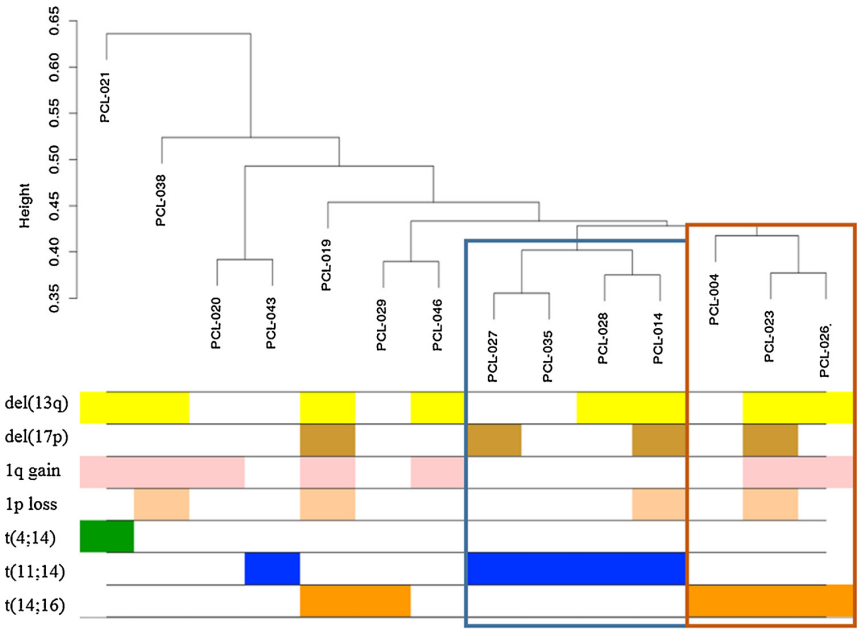



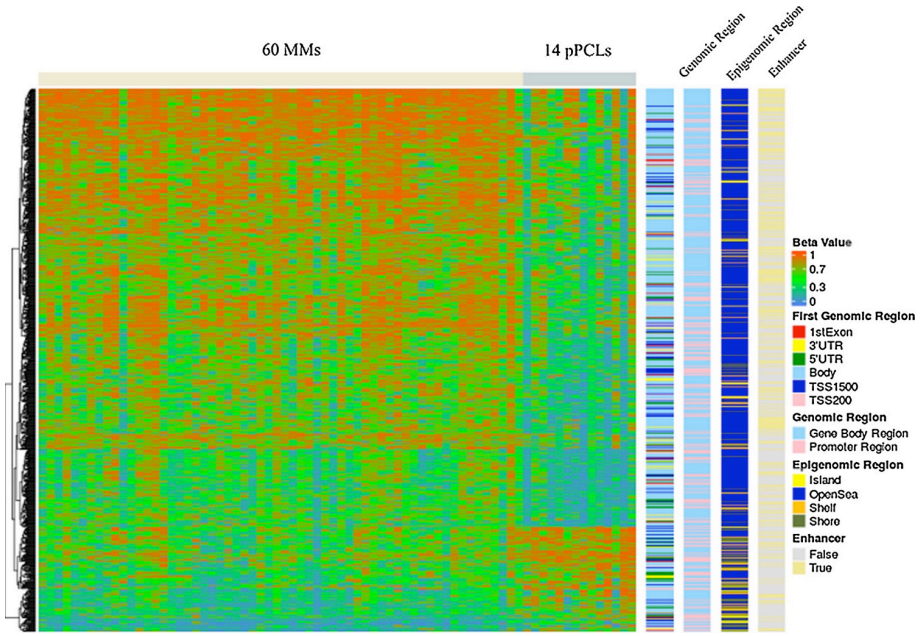

Walker BA. et al. Blood 2011




Agirre X. et al. Genome Res. 2015

# Global methylation patterns in pPCL




**Todoerti K. et al. Leuk Res 2018**

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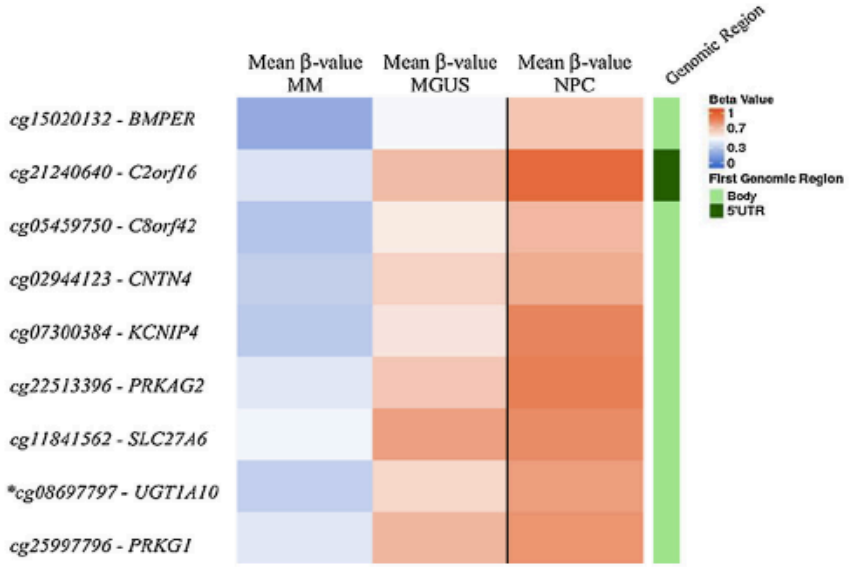


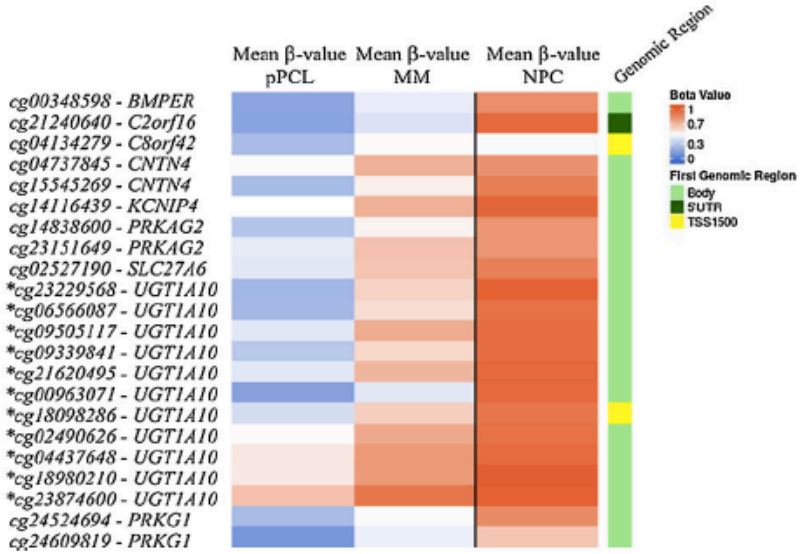


**Todoerti K. et al. Leuk Res 2018**

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van de Donk NWCJ, et al. Blood 2012

# Biology of pPCL: Immunophenotype

**CD38, 138+**

**Myeloma** cells are strongly dependent on the bone marrow microenvironment which regulates their proliferation and survival

≠

**pPCL** malignant plasma cells tend to eggress to the peripheral blood stream and are more immature cells

## DIFFERENT PATTERNS OF EXPRESSION ADHESION MOLECULES: ROLE OF CD56/NCAM

**Higher CD56 expression anchorage of plasma cells to bone marrow stroma**

**Lower CD56 expression migration to extramedullary sites**

**Higher CD20 expression**

# Comparison of immunophenotypic markers in pPCL vs. in MM

| | CD19+ PCs | CD56+ PCs | CD20+ PCs | CD27+ PCs | CD28+ PCs | CD117+ PCs | CD44+ PCs | nestin+ PCs |
|---|---|---|---|---|---|---|---|---|
| **Relative expression of markers on CD38+ CD138+ PCs** | | | | | | | | |
| **MM BM** (n = 110) median of relative expression [%] (min–max) | 38 (0.0–66.0) | 96.3 (0.5–100.0) | 0.2 (0.0–90.8) | 16.8 (0.6–99.7) | 3.1 (0.1–98.9) | 4.5 (0.0–99.4) | 84.8 (1.0–99.6) | 5.3 (0.0–99.4) |
| **pPCL PB** (n = 11) median of relative expression [%] (min–max) | 0.1 (0.0–94.7) | 19.4 (0.4–99.9) | 2.5 (0.0–94.4) | 0.4 (0.0–50.6) | 0.1 (0.0–99.6) | 0.1 (0.0–30.2) | 98.1 (2.3–100.0) | 21.8 (0.1–99.1) |
| **pPCL BM** (n = 10) median of relative expression [%] (min–max) | 0.1 (0.0–92.6) | 48.9 (0.2–99.3) | 2.4 (0.0–92.8) | 0.6 (0.0–18.5) | 1.8 (0.0–99.9) | 0.0 (0.0–37.5) | 77.0 (49.8–99.7) | 53.6 (0.2–99.1) |
| **Positivity of expressed markers on CD38+ CD138+ PCs** | | | | | | | | |
| **MM BM** (n = 110) positivity [%] | 6.4 (7/110) | 75.5 (83/110) | 8.2 (9/110) | 31.8 (35/110) | 20.9 (23/110) | 31.8 (35/110) | 84.3 (43/51) | 30.5 (18/59) |
| **pPCL PB** (n = 11) positivity [%] | 18.2 (2/11) | 45.5 (5/11) | 18.2 (2/11) | 18.2 (2/11) | 18.2 (2/11) | 9.1 (1/11) | 83.3 (5/6) | 50.0 (3/6) |
| **pPCL BM** (n = 10) positivity [%] | 20.0 (2/10) | 60.0 (6/10) | 30.0 (3/10) | 0.0 (0/10) | 33.3 (3/9) | 11.1 (1/9) | 100.0 (4/4) | 75.0 (3/4) |

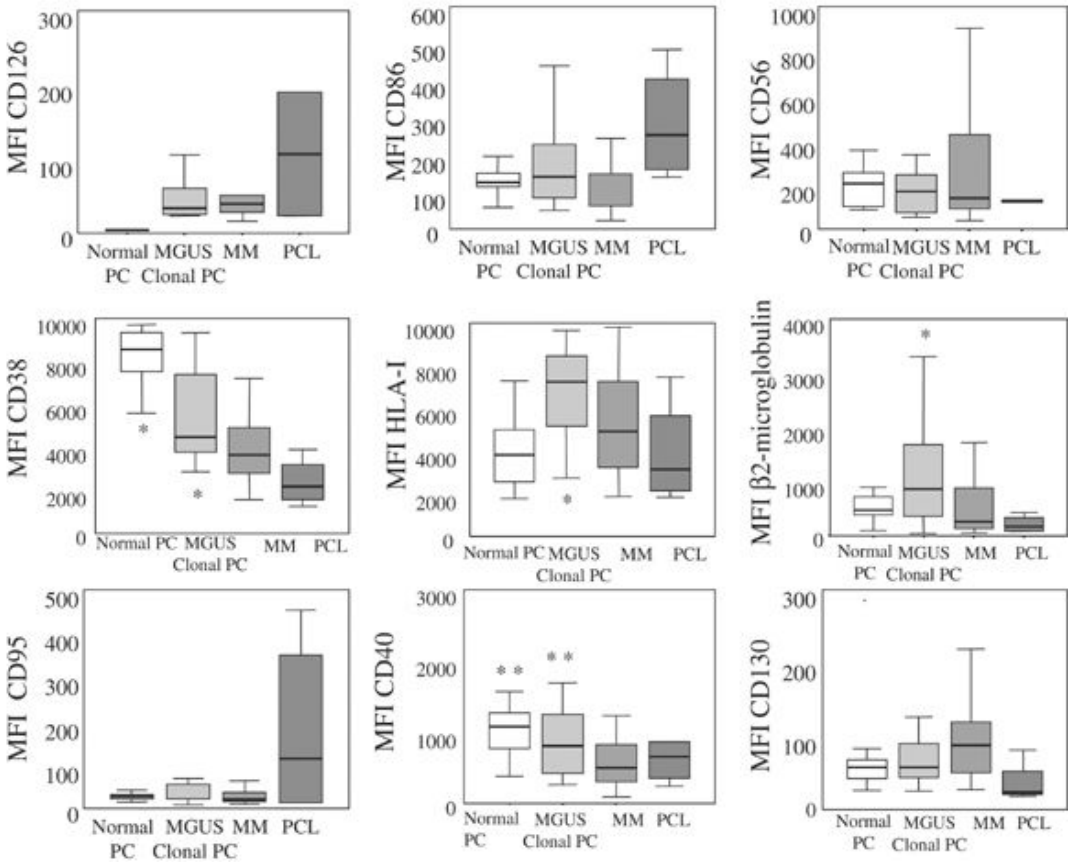
Jelinek et al. EJH 2015

# Major biological features of Plasma Cell Leukemia

- Initial immortalizing events (genetic aberrations)
- Secondary (epi)genetic events
- Adhesion molecules and chemokine receptors
- **Immune evasion**

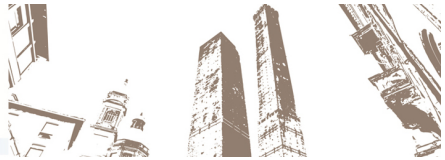
**van de Donk NWCJ, et al. Blood 2012**

# Immune evasion: different phenotype from MGUS to MM and PCL




Perez-Andres M. et al. Leukemia, 2005

# pPCL: current and future directions



- It is a rare variant of multiple myeloma, which differs from secondary PCL and shows peculiar epidemiology, clinical, phenotypic and genotypic characteristics

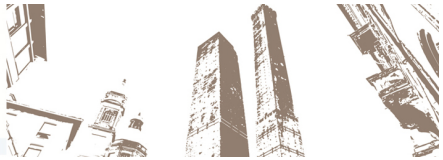
- Prognosis remains generally poor, especially in patients who are not eligible for stem cell transplantation, though during the last five years some advances have been reached using new drugs

- Better understanding of biology of the disease

- Plasma cell leukemia prognostic index

- **Improve pPCL outcome:**

  - **Reduce early mortality rate**
  - **New therapeutic targets  t(11;14) and venetoclax therapy**



**SP-092**

## KD-PACE salvage therapy for aggressive relapsed multiple myeloma

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## Primary Plasma Cell Leukemia: a retrospective series from a tertiary care center in India

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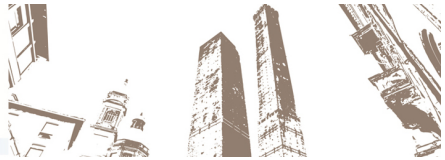

## OAB-033

### Clinical Responses and Pharmacokinetics of fully human BCMA Targeting CAR T Cell Therapy in Relapsed/Refractory Multiple Myeloma

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## SP-021

### Over 10 years relative median survival in MM patients ≤ 65 years with VGPR or better on 1st line treatment. Population-based data on patients diagnosed 2008-2018 from the Swedish Myeloma Registry

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## SP-087

### A Phase 2 Trial of the Efficacy and Safety of Elotuzumab in Combination with Pomalidomide, Carfilzomib and Dexamethasone for High Risk Relapsed/ Refractory Multiple Myeloma Patients

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## SP-092

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## SP-191

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