# Highlights from IMS 20th meeting 2023

## *Strategie Terapeutiche nel Paziente «Difficile-da-trattare»: Leucemia Plasmacellulare*


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# Primary Plasma Cell Leukemia

- ***< 1-4% of all Multiple Myelomas (MM)** (crude incidence: 0.04-0.05 /100.000 persons per year in EU)*
- ***Distinct entity (vs MM) previously** operatively defined by the presence of **20% and/or an absolute number >2×10⁹/L of clonal plasma cells in the peripheral blood,** without a previous history of MM*
- ***New IMWG criteria:** circulating plasma cell **higher than 5%***
- ***PPCL** (50-70% of PCL) **should be distinguished from secondary PCL (SPCL)** (30-50% of PCL), which constitutes the leukemic evolution of **a pre-existing, progressing MM** (1% of all MM, 12% of those with high tumor burden), with median **time to leukemic transformation of approximately 2 years** and a median **survival of only 1-2 months***
- *PPCL should be also **distinguished from extra-medullary myeloma** (both **para-skeletal or soft tissues**) that, by definition, **excludes peripheral blood dissemination***
- ***Prognosis** of PPCL still remains **significantly poorer than that of MM***

**Table 1.** Clinical presentation features of PCL and NDMM patients enrolled in the study.

| | pPCL n = 25 | sPCL n = 19 | NDMM n = 965 | *p* Value NDMM vs. pPCL | *p* Value NDMM vs. sPCL | *p* Value pPCL vs. sPCL |
|---|---|---|---|---|---|---|
| age (years) | 60 (45–81) | 65 (42–80) | 68 (29–92) | <0.01 | n.s. | n.s. |
| male sex (%) | 11/25 (44%) | 10/19 (52.6%) | 523/965 (54.2%) | n.s. | n.s. | n.s. |
| lytic lesions | 10/22 (45.4%) | 11/16 (68.8%) | 276/410 (67.3%) | 0.04 | n.s. | n.s. |
| extramedulary involvement | 4/20 (20%) | 4/15 (26.7%) | 23/301 (7.6%) | 0.07 | 0.03 | n.s. |
| hemoglobin (g/dL) | 8.5 (5.8–13.6) | 9.1 (6.8–11.2) | 10.4 (4–18) | <0.001 | 0.002 | n.s. |
| platelets ($\times 10^9$/L) | 108 (10–250) | 100 (30–300) | 244 (22–585) | <0.0001 | <0.0001 | n.s. |
| WBC ($\times 10^9$/L) | 15 (3.5–40) | 15 (4.7–34.5) | 6.1 (2.2–70) | <0.0001 | <0.0001 | n.s. |
| BM infiltration (%) | 70 (30–100) | 80 (35–100) | 55 (5–100) | <0.001 | <0.0001 | n.s. |
| PB plasmacytosis ($\times 10^9$/L) | 5.4 (0.9–72) | 6.1 (1.2–65) | - | - | - | n.s. |
| calcium (mg/dL) | 9.4 (8.3–14.4) | 9.6 (6.5–12.5) | 9.5 (6.3–15.5) | n.s. | n.s. | n.s. |
| LDH (U/L) | 330 (100–690) | 232 (120–550) | 175 (68–860) | <0.0001 | <0.001 | 0.01 |
| serum albumin (g/dL) | 3.7 (2.7–4.4) | 3.6 (2.5–4.9) | 3.9 (1.8–5.1) | n.s. | n.s. | n.s. |
| creatinine >2 mg/dL | 9/25 (36%) | 4/19 (21.1%) | 101/708 (14.3%) | <0.007 | n.s. | n.s. |
| b-2 microglobulin (mg/L) | 7.3 (1.4–11.2) | 3.8 (1.7–7.8) | 3.3 (0.38–70) | <0.0001 | n.s. | <0.0001 |
| M-protein | | | | | | |
| IgG | 13/25 (52%) | 10/19 (52.6%) | 482/965 (49.9%) | | | |
| IgA | 3/25 (12%) | 4/19 (21.1%) | 221/965 (22.9%) | n.s. | n.s. | n.s. |
| IgD | 1/25 (4%) | 1/19 (5.3%) | 33/965 (3.4%) | | | |
| light chain only | 5/25 (20%) | 4/19 (21.1%) | 150/965 (15.5%) | | | |
| non-secretory | 3/25 (12%) | 0/16 | 79/965 (8.2%) | | | |
| kappa light chain | 12/20 (60%) | 7/15 (46.7%) | 569/965 (58.9%) | n.s. | n.s. | n.s. |
| Phenotype | | | | | | |
| 19+ | 0/11 | N/A | 12/445 (2.7%) | n.s. | | |
| 45+ | 2/11 (18.2%) | N/A | 80/445 (18%) | n.s. | N/A | N/A |
| 56+ | 5/11 (45.4%) | N/A | 281/445 (63.1%) | n.s. | | |
| 117+ | 1/11 (9.1%) | N/A | 181/445 (40.7%) | 0.03 | | |

All values shown for continuous variables are median with ranges in parentheses. pPCL, primary plasma cell leukemia; sPCL, secondary plasma cell leukemia; NDMM, newly-diagnosed Multiple Myeloma; n.s., non-significant; N/A, not applicable; WBC, white blood cells; BM, bone marrow; PB, peripheral blood, LDH, lactate dehydrogenase.

Papadhimitriou et al, Biomedicine, 2022

**3399 Primary or Secondary Plasma Cell Leukemia: Dismal Outcome Despite Modern Treatments.Camille Tessier et al. Quebec, Canada**

- Rretrospective, multicenter study of 99 eligible PCL patients, of whom **33 were pPCL and 66 were sPCL** diagnosed between 2005 and 2020 in eight institutions in the Province of Québec, **focusing,** in particular, **to characteristic of MM patients evolving toward SPCL, according to «old» IMWG 2013 criteria)**
- **At MM diagnosis**, patients who eventually **progressed to sPCL were much younger** (median 61.8 years) than a typical MM cohort and many of them already demonstrated **markers of poor prognosis,** including elevated LDH, elevated ß2-microglobulin and complex cytogenetics
- **Median time** between **initial MM** diagnosis and **sPCL progression was 27.3 months.**
- Median number of **lines of treatment prior to transformation** was **2** (range 1 – 7).
- **ASCT;** n = 28) or **tandem ASCT-alloSCT**; n = 4) **did not result in longer time to sPCL progression** when compared to those who received chemotherapy alone (31.6 vs 22.9 months, p = 0.164).
- Median **OS for pPCL and sPCL** were respectively **18.3 and 1.2 months** (p < 0.001).
- Median **OS** From **MM diagnosis to death, for sPCL, was 30.2 months.**

**Table I. Patient characteristics at diagnosis of MM, sPCL or pPCL.** All patients included in the MM category correspond to patients who eventually progressed to sPCL.

| PARAMETERS | MM (n = 66) | sPCL (n = 66) | pPCL (n = 33) |
|---|---|---|---|
| Age at diagnosis, years, median (range) | 61.8 (35.7 - 83.4) | 64.2 (37.8 - 85.3) | 59.5 (40.7 - 86.3) |
| Male sex, n (%) | | 32 (48.5) | 19 (57.6) |
| ISS stage, n (%) | | | |
| I | 11/46 (23.9) | 4/31 (12.9) | 3/27 (11.1) |
| II | 12/46 (26.1) | 6/31 (19.4) | 7/27 (25.9) |
| III | 23/46 (50.0) | 21/31 (67.7) | 17/27 (63.0) |
| R-ISS stage, n (%) | | | |
| I | 4/27 (14.8) | 0/25 (0) | 2/23 (8.7) |
| II | 16/27 (59.3) | 10/25 (40.0) | 9/23 (39.1) |
| III | 7/27 (25.9) | 15/25 (60.0) | 12/23 (52.2) |
| Paraprotein isotype, n (%) | | | |
| IgG | 29 (43.9) | 29 (43.9) | 10 (30.3) |
| IgA | 19 (28.8) | 18 (27.3) | 3 (9.1) |
| IgM | 0 (0) | 0 (0) | 1 (3.0) |
| Light chain only | 18 (27.3) | 19 (28.8) | 19 (57.6) |
| Light chain isotype, n (%) | | | |
| Kappa | 34 (51.5) | 34 (51.5) | 21 (63.6) |
| Lambda | 32 (48.5) | 32 (48.5) | 12 (36.4) |
| Biclonal gammopathy, n (%) | 5 (8.1) | 10/62 (16.1) | 3/30 (10.0) |
| CRAB features, n (%) | | | |
| Hypercalcemia | 22 (34.4) | 30 (45.5) | 22 (66.7) |
| Renal failure | 25 (38.5) | 37 (56.1) | 23 (69.7) |
| Anemia (Hb < 100 g/L) | 24 (36.4) | 56 (84.8) | 30 (90.9) |
| Bone lesions | 42/64 (65.6) | 25/39 (64.1) | 21/32 (65.6) |
| Other clinical features, n (%) | | | |
| Thrombopenia (Plt < 100 x $10^9$/L) | 6 (9.1) | 54 (81.8) | 16 (48.5) |
| Leucocytosis (total WBC > 10 x $10^9$/L) | 7 (10.6) | 22 (33.3) | 27 (81.8) |
| Elevated LDH | 14/52 (26.9) | 46/63 (73.0) | 20/30 (66.7) |
| Elevated $\beta_2$-microglobulin | 35/51 (68.6) | 30/31 (96.8) | 23/27 (85.2) |
| Positive Bence Jones | 39/52 (79.0) | 20/25 (80.0) | 13/15 (86.7) |
| Immunoparesis | 52/56 (92.9) | 53/55 (96.4) | 27/30 (90.0) |
| Splenomegaly | 4/35 (11.4) | 12/25 (48.0) | 11/27 (40.7) |
| Cytogenetic abnormalities, n (%) | | | |
| Normal FISH | 10/25 (40.0) | 0/13 (0) | 2/24 (8.3) |
| Standard risk abnormalities | | | |
| Trisomy | 5/25 (20.0) | 3/13 (23.1) | 5/24 (20.8) |
| t(11;14) | 0/6 (0) | 2/4 (50.0) | 4/7 (57.1) |
| High risk abnormalities | | | |
| t(4;14) | 3/17 (17.6) | 2/9 (22.2) | 2/21 (9.5) |
| t (14;16) | 2/11 (18.2) | 2/7 (28.6) | 2/12 (16.7) |
| Del17p | 3/21 (14.3) | 3/11 (27.3) | 5/21 (23.8) |
| Gain 1q | 0/3 (0) | 4/6 (66.7) | 10/13 (76.9) |
| Del1p | 2/4 (50.0) | 2/6 (33.3) | 4/8 (50.0) |
| Complex cytogenetic (≥ 3 abnormalities) | 5/25 (20.0) | 5/13 (38.5) | 9/24 (37.5) |
| Immunophenotype, n (%) | | | |
| CD56+ | 11/14 (78.6) | 12/21 (57.1) | 9/21 (42.9) |
| CD19 and/or CD20 + | 4/21 (19.0) | 3/23 (13.0) | 7/22 (31.8) |

Abbreviations: *BM* bone marrow, *FISH* fluorescent in situ hybridization, *Hb* Hemoglobin, *LDH* lactate dehydrogenase, *ISS* international staging system, *Plt* Platelets, *R-ISS* revised ISS, *WBC* white blood cells

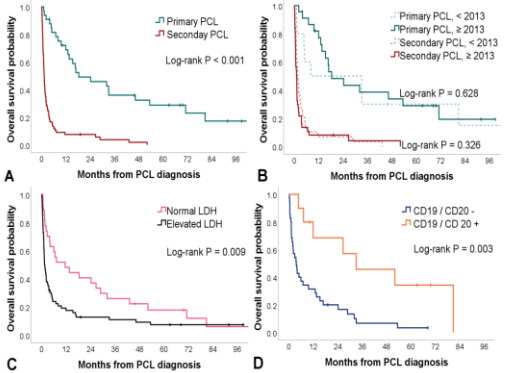


**Figure 1. Kaplan-Meier curves for OS in PCL patients based on type of PCL (A), type of PCL and year of diagnosis (B), serum LDH levels (C) and expression of CD19 and/or CD20 (D)**

## 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,[6] Joan Bladé[2] and Carlos Fernández de Larrea,[2] on behalf of GEMMAC (Grup per l'estudi del mieloma i l'amiloidosi de Catalunya)

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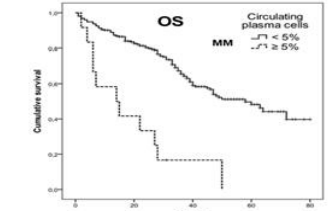


Figure 1. Overall survival according to the circulating plasma cells (PCs) group in patients with multiple myeloma (P<0.001).

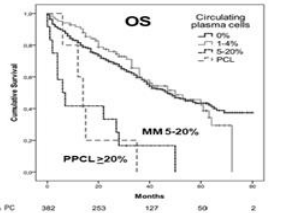


Figure 2. Overall survival according to the circulating plasma cells (PCs) in patients with multiple myeloma and plasma cell leukemia (PCL) treated with novel drugs upfront (P<0.001).

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### Revised diagnostic criteria for plasma cell leukemia: results of a Mayo Clinic study with comparison of outcomes to multiple myeloma

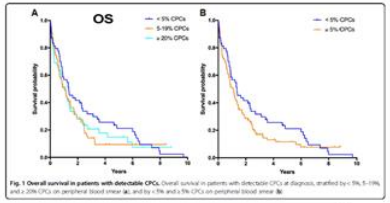


Fig. 1 Overall survival in patients with detectable CPCs. Overall survival in patients with detectable CPCs at diagnosis, stratified by < 5%, 5–19%, and ≥ 20% CPCs on peripheral blood smear (A), and by < 5% and ≥ 5% CPCs on peripheral blood smear (B).

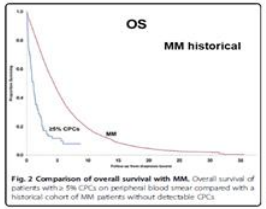


Fig. 2 Comparison of overall survival with MM. Overall survival of patients with ≥ 5% CPCs on peripheral blood smear compared with a historical cohort of MM patients without detectable CPCs.

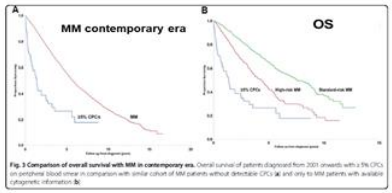


Fig. 3 Comparison of overall survival with MM in contemporary era. Overall survival of patients diagnosed from 2001 onwards with ≥ 5% CPCs on peripheral blood smear in comparison with similar cohort of MM patients without detectable CPCs (A) and only to MM patients with available cytogenetic information (B).

Blood Cancer Journal www.nature.com/bcj

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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[7], 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 María Victoria Mateos[10]



Primary plasma cell leukemia (PCL) has a consistently ominous prognosis, even after progress in the last decades. PCL deserves a prompt identification to start the most effective treatment for this ultra-high-risk disease. The aim of this position paper is to revisit the diagnosis of PCL according to the presence of circulating plasma cells in patients otherwise meeting diagnostic criteria of multiple myeloma. We could identify two retrospective series where the question about what number of circulating plasma cells in peripheral blood should be used for defining PCL. The presence of ≥5% circulating plasma cells in patients with MM had a similar adverse prognostic impact as the previously defined PCL. Therefore, PCL should be defined by the presence of 5% or more circulating plasma cells in peripheral blood smears in patients otherwise diagnosed with symptomatic multiple myeloma.

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### 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.

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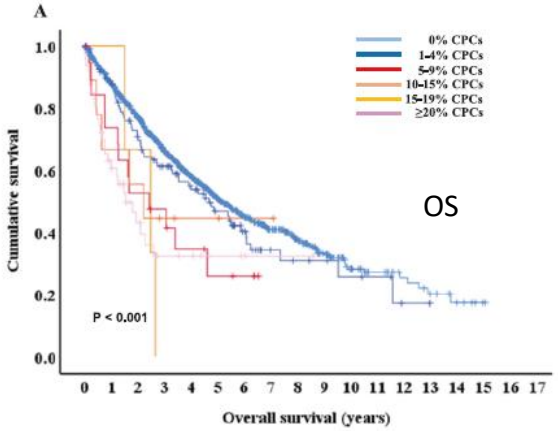
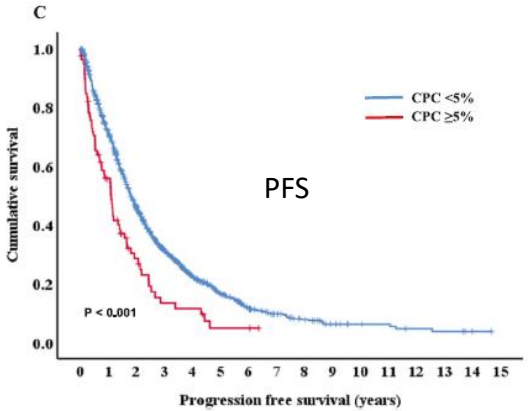
# Validation of the revised diagnostic criteria for primary plasma cell leukemia by the Korean Multiple Myeloma Working Party

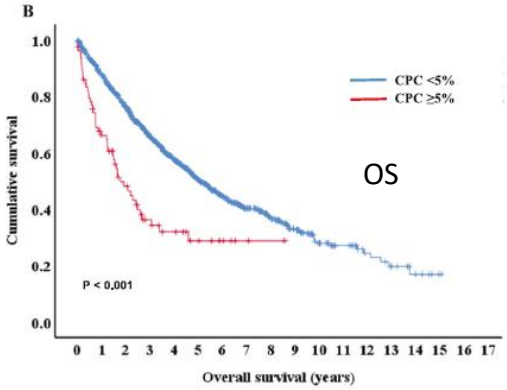
Sung-Hoon Jung[1], Kihyun Kim[2✉], Sang Eun Yoon[2], Joon Ho Moon[3], Dajung Kim[4], Hyo Jung Kim[5], Min Kyoung Kim[6], Kyoung Ha Kim[7], Hyun Jung Lee[8], Ji Hyun Lee[9], Sung-Hyun Kim[9], Kawi Han Yoo[10], Jae Hoon Lee[10] and Je-Jung Lee[1✉]



- **1357 MM** patients, 187 (13.8%) had CPCs at diagnosis, 79 **(5.8%) had ≥ 5% CPCs.**
- The median **OS of patients with CPCs ≥ 5% and ≥ 20% was similar,** but **PFS and OS were significantly inferior than (MM) those with CPCs < 5%** (13.1 vs. 21.5 months, P < 0.001, and 21.5 vs. 60.9 months, P < 0.001, respectively).
- **Primary PCL** diagnosed using the **revised criteria** presented with **higher total calcium** and **serum creatinine** levels**, lower platelet counts** and **frequent organomegaly** and **plasmacytoma at diagnosis.**
- Univariate and **multivariate analyses** demonstrated that the presence of **plasmacytoma** and **elevated serum β2-microglobulin** were significantly **associated with OS in primary PCL.**
- In conclusion, the revised criterion of **CPCs ≥ 5%** in a peripheral blood smear is **appropriate for PCL diagnosis.**



***P-431 Clinical characteristics, prognostic factors and treatment outcomes in patients diagnosed with primary plasma cell leukemia based on the revised criteria (KMM2204)***

*Sung-Hoon Jung et al., South Korea*

- *Retrospective study evaluating the clinical characteristics, prognostic factors and treatment outcomes in patients diagnosed with primary PCL based on the revised criteria.*
- *127 patients diagnosed with primary PCL; 70 (55%) had CPCs ≥ 20%, and 57 (45%) had CPCs 5-19%.*
- *The study found no significant difference in PFS and OS between the two groups (CPCs≥ 20% and 5-19%).*
- *Patients with CPCs≥20% had significantly higher white blood cell counts, LDHs and extramedullary plasmacytoma*
- *Patients who achieved CR after induction therapy showed significantly improved PFS and OS*
- *CR rate was the highest in daratumumab-based quadruplets than in other induction therapies including PIs and IMIDs based combination,*

***P-430 Incidence of primary plasma cell leukemia with the new diagnostic criteria***

*Virginia Jano et al. University Hospital of Leon, Spain*

- *Descriptive, retrospective study in which a search was conducted for patients meeting the new criteria for pPCL between January 2021 and May 2023.*
- *The average peripheral blood plasma cell count was 19.6%, with a count higher than 5% in all cases (42.9% exceeding 20% and 57.1% between 5% and 20%)*
- *Currently, the incidence of pPCL with the new diagnostic criteria is unknown, but in our case series, the cumulative incidence is 2 cases per 100,000 inhabitants in two years and five months, much higher than those reported in other series (4 cases per 10 million inhabitants).*
- *This could reflect that the disease has been underdiagnosed for years, and the modification of diagnostic criteria will allow early identification of these patients.*

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# Clinical and cytogenetic characteristics of primary and secondary plasma cell leukemia under the new IMWG definition criteria: a retrospective study

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**ABSTRACT**

**Background:** Plasma cell leukemia (PCL) is a rare and aggressive plasma cell disorder, exhibiting a more unfavorable prognosis than multiple myeloma. PCL is classified into pPCL and sPCL. Recently, the IMWG has recommended new PCL definition criteria, which require the presence of ≥5% circulating plasma cells in peripheral blood smears. Due to its low incidence, research on pPCL and sPCL is limited.

**Methods:** We conducted a retrospective study and analyzed clinical and cytogenetic data of pPCL and sPCL patients. Overall survival (OS) and progression-free survival (PFS) were assessed by the Kaplan-Meier method, and survival distributions were compared using the log-rank test.

**Results:** This is a small cohort comprising 23 pPCL and 9 sPCL patients. Notably, sPCL patients showed a higher incidence of extramedullary infiltration and a higher percentage of bone marrow plasma cells ($p = 0.015$ and 0.025, respectively). Although no significant difference was found between the two groups in OS and PFS, a trend emerged suggesting a superior survival outcome for pPCL patients, with a higher cumulative 1-year PFS rate (38.3% vs. 13.3%) and a lower early mortality rate (mortality rate at 3 months: 15% vs. 33%). We also suggested that pPCL patients carrying t(11;14) may have a longer median survival time than individuals with other cytogenetic abnormalities, but this was not confirmed due to the small sample size.

**Conclusion:** Our study revealed clinical and cytogenetic features of pPCL and sPCL patients according to the new diagnostic criteria. The findings suggested a generally better prognosis for pPCL than sPCL and the likelihood of t(11;14) translocation acting as a favorable prognostic factor in pPCL. It is important to note that our study had a limited sample size, which may lead to bias. We hope well-designed studies can be conducted to provide more results.

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**KEYWORDS**
Primary plasma cell leukemia; secondary plasma cell leukemia; cytogenetics; prognosis; treatment

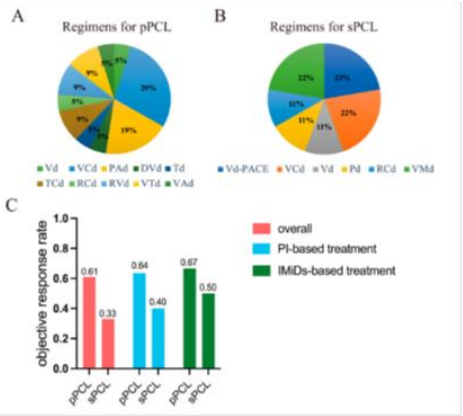



**Table 1.** Clinical and biological characteristics of patients with pPCL or sPCL.

| | pPCL, median (range) or number (%) | sPCL, median (range) or number (%) | *p* |
|---|---|---|---|
| Age at diagnosis (years) | 63 (45–73) | 63 (47–76) | 0.570 |
| Male sex | 11/23 (47.8) | 5/9 (55.6) | 1.000 |
| M protein | | | 0.926 |
| IgG | 13/23 (56.5) | 5/9 (55.6) | |
| IgA | 3/23 (13.0) | 1/9 (11.1) | |
| IgG IgA | 1/23 (4.3) | 0/9 (0) | |
| Light chain | 5/23 (21.7) | 3/9 (33.3) | |
| Non-secretory | 1/23 (4.3) | 0/9 (0) | |
| Durie-Salmon stage | | | 0.147 |
| I | 1/23 (4.3) | 0/9 (0) | |
| II | 0/23 (0) | 2/9 (22.2) | |
| III | 22/23 (95.7) | 7/9 (77.8) | |
| International staging system | | | 0.055 |
| I | 1/22 (4.5) | 4/8 (50.0) | |
| II | 7/22 (31.8) | 1/8 (12.5) | |
| III | 14/22 (63.6) | 3/8 (37.5) | |
| First symptoms | | | 0.348 |
| Renal dysfunction | 1/23 (4.3) | 0/9 (0) | |
| Anemia | 2/23 (8.7) | 0/9 (0) | |
| Bone pain or fracture | 10/23 (43.5) | 2/9 (22.2) | |
| Extramedullary tumor | 3/23 (13.0) | 4/9 (44.4) | |
| Others | 7/23 (30.4) | 3/9 (33.3) | |
| Hemoglobin (g/l) | 87 (50–121) | 86 (63–170) | 0.801 |
| Platelets ($\times 10^9$/l) | 99 (14–221) | 139 (15–239) | 0.542 |
| WBC count ($\times 10^9$/l) | 6.70 (1.87–53.15) | 6.01 (2.13–9.57) | 0.276 |
| Calcium (mmol/l) | 2.22 (1.75–3.23) | 2.29 (1.99–3.31) | 0.468 |
| Serum albumin (g/l) | 33.8 (15.0–40.8) | 34.1 (26.9–46.9) | 0.116 |
| Creatinine (μmol/l) | 113 (22–700) | 108 (73–214) | 0.950 |
| β2-microglobulin (mg/l) | 9.59 (1.83–63.70) | 6.75 (1.52–12.40) | 0.114 |
| Elevated LDH level | 10/23 (43.5) | 4/9 (44.4) | 1.000 |
| BMPCs (%) | 46.8 (18.4–93.6) | 66.8 (43.2–94.4) | **0.025** |
| PBPCs (%) | 11 (5–81) | 14 (6–31) | 0.614 |
| Extramedullary infiltration | 6/23 (26.1) | 7/9 (77.8) | **0.015** |
| Lytic lesions | 21/23 (91.3) | 9/9 (100) | 1.000 |

IgG: immunoglobulin G, IgA: immunoglobulin A, WBC: white blood cell, LDH: lactate dehydrogenase, BMPCs: bone marrow plasma cells, PBPCs: peripheral blood plasma cells.

**Table 2.** Cytogenetic characteristics of patients with pPCL or sPCL.

| | pPCL, *N* (%) | sPCL, *N* (%) | *p* |
|---|---|---|---|
| Del(13q) | 9/18 (50.0) | 3/8 (37.5) | 0.683 |
| Del(17p) | 2/19 (10.5) | 3/8 (37.5) | 0.136 |
| 1q21+ | | | 0.275 |
| Gain | 6/20 (30.0) | 5/8 (62.5) | |
| Amplification | 3/20 (15.0) | 1/8 (12.5) | |
| t(4;14) | 2/18 (11.1) | 3/8 (37.5) | 0.281 |
| t(14;16) | 1/18 (5.6) | 0/8 (0) | 1.000 |
| t(11;14) | 7/15 (46.7) | 2/7 (28.6) | 0.648 |
| t(14;20) | 2/15 (13.3) | 0/7 (0) | 1.000 |
| HRCA | | | **0.042** |
| 0 | 9/18 (50.0) | 3/8 (37.5) | |
| 1 | 6/18 (33.3) | 0/8 (0) | |
| 2 | 3/18 (16.7) | 5/8 (62.5) | |
| Risk stratification | | | 1.000 |
| High-risk | 14/20 (70.0) | 5/8 (62.5) | |
| Standard-risk | 6/20 (30.0) | 3/8 (37.5) | |
| Karyotype | | | 1.000 |
| Normal | 11/17 (64.7) | 3/4 (75.0) | |
| Hypodiploid | 2/17 (11.8) | 0/4(0) | |
| Pseudo/diploid | 2/17 (11.8) | 0/4(0) | |
| Hyperdiploid | 2/17 (11.8) | 1/4 (25.0) | |

HRCA: high-risk cytogenetic abnormalities.

**Table 3.** Cytogenetic abnormalities and prognosis of pPCL and sPCL patients.

| | Median OS (month) | | | Median PFS (month) | | |
|---|---|---|---|---|---|---|
| | pPCL | sPCL | *P* | pPCL | sPCL | *p* |
| Del(13q) | 12 | 15 | 0.6 | 12 | 15 | 0.87 |
| Del (17p) | 9 | 12 | 0.61 | 7 | 9 | 0.59 |
| 1q21+ | 9 | 6.5 | 0.22 | 8 | 5.5 | 0.27 |
| t(11;14) | 12 | 6.5 | 0.51 | 12 | 5 | 0.3 |
| t(4;14) | NR | 3 | 0.16 | NR | 3 | 0.16 |
| At least 1 HRCA | 12 | 8 | 0.085 | 12 | 7 | 0.13 |
| High-risk stratification | 12 | 6.5 | 0.095 | 13 | 5.5 | 0.18 |

NR: not reached, HRCA: High-risk cytogenetic abnormalities.

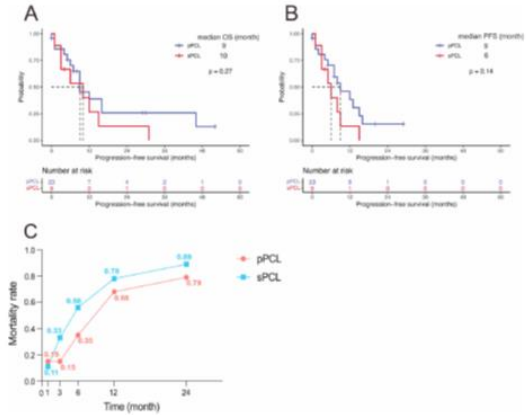



**Figure 1.** Survival outcomes of pPCL and sPCL. Overall survival (OS) (A) and progression-free survival (PFS) (B) between pPCL and sPCL patients. (C) Mortality rates of pPCL and sPCL at 1, 3, 6, 12, and 24 months after diagnosis were shown.

original reports

abstract

# High Levels of Circulating Tumor Plasma Cells as a Key Hallmark of Aggressive Disease in Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma

Luca Bertamini, MD[1]; Stefania Oliva, MD, PhD[1]; Delia Rota-Scalabrini, MD[2]; Laura Paris, MD[3]; Sonia Morè, MD[4]; Paolo Corradini, MD[5]; Antonio Ledda, MD[6]; Massimo Gentile, MD[7]; Giovanni De Sabbata, MD[8]; Giuseppe Pietrantuono, MD[9]; Anna Pascarella, MD[10]; Patrizia Tosi, MD[11]; Paola Curci, MD[12]; Milena Gilestro, BSc[1]; Andrea Capra, MScEng[1]; Piero Galieni, MD[13]; Francesco Pisani, MD[14]; Ombretta Annibali, MD, PhD[15]; Federico Monaco, MD[16]; Anna Marina Liberati, MD[17]; Salvatore Palmieri, MD[18]; Mario Luppi, MD, PhD[19]; Renato Zambello, MD[20]; Francesca Fazio, MD[21]; Angelo Belotti, MD[22]; Paola Tacchetti, MD, PhD[23]; Pellegrino Musto, MD[12,24]; Mario Boccadoro, MD[1]; and Francesca Gay, MD, PhD[1]

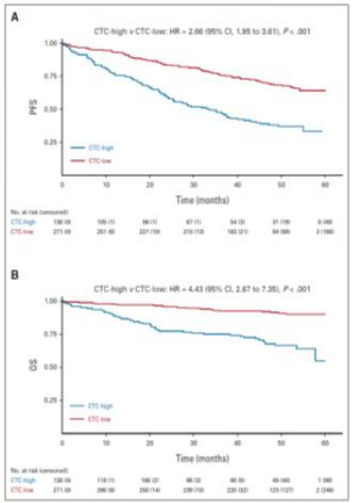



FIG 2. Kaplan-Meier estimates of (A) PFS and (B) OS according to CTC cutoff discriminating CTC-high and CTC-low patients (> 0.07% v ≤ 0.07%). CTC, circulating tumor plasma cells; CTC-high, CTC > 0.07%; CTC-low, CTC ≤ 0.07%; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

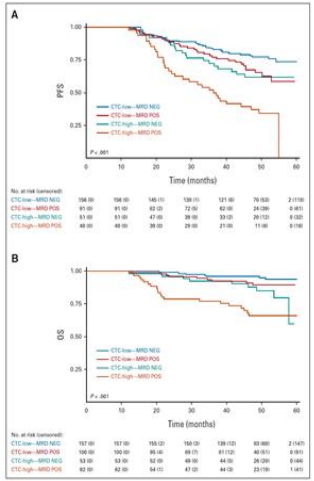



FIG 4. Kaplan-Meier estimates of (A) PFS and (B) OS according to CTC status at baseline and the achievement of pre-maintenance MRD negativity. CTC, circulating tumor plasma cells; CTC-high, CTC > 0.07%; CTC-low, CTC ≤ 0.07%; MRD, minimal residual disease; NEG, negativity; OS, overall survival; PFS, progression-free survival; POS, positivity.

J Clin Oncol, 2022

original reports

abstract

# 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[8]; 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[6]; Lucie Rihova, PhD[2]; and Roman Hajek, MD, PhD[1]

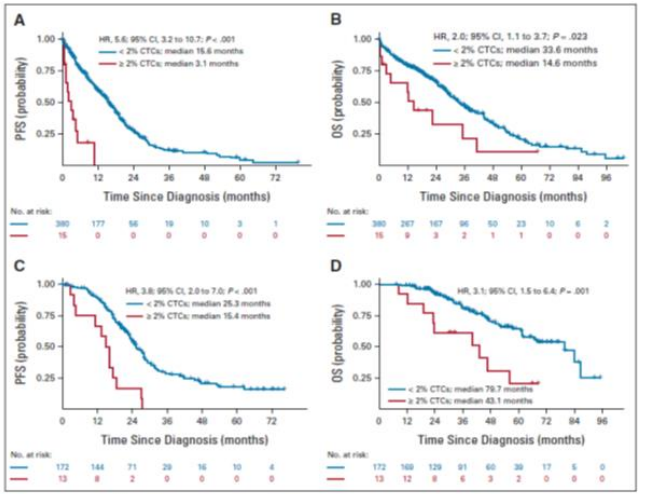
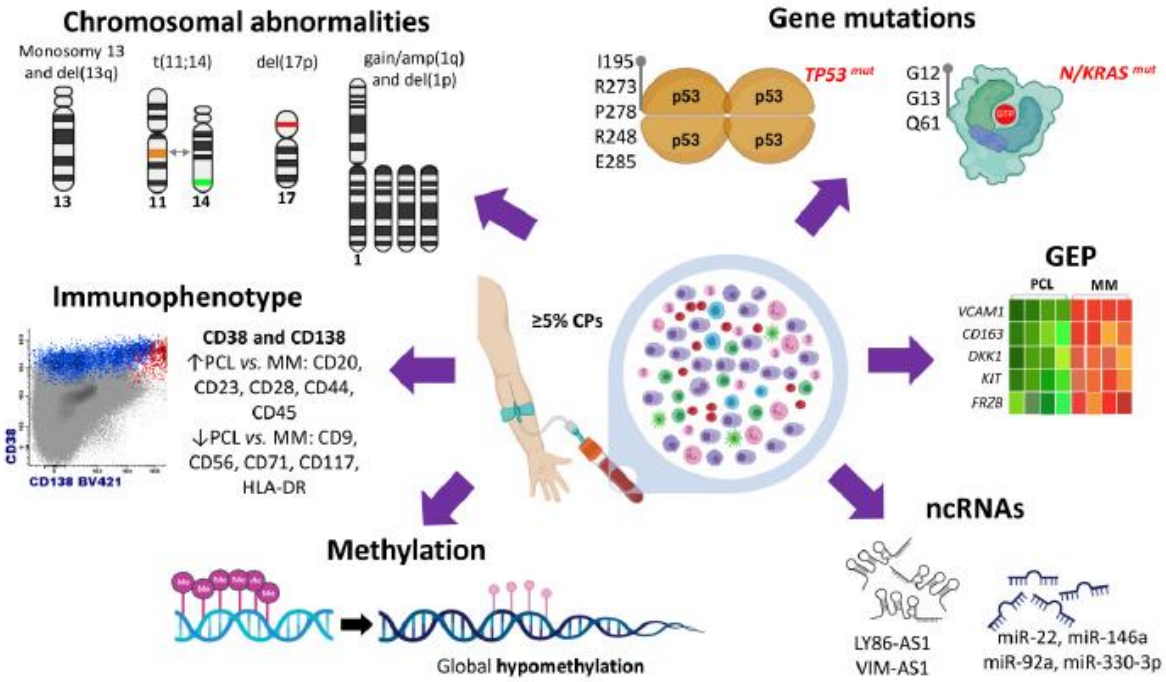



FIG 1. The optimal cutoff for identification of ultra-high-risk PCL-like multiple myeloma is 2% of CTCs. Kaplan-Meier curves for (A) PFS and (B) OS for transplant-ineligible patients with NDMM (N = 395); and (C) PFS and (D) OS for transplant-eligible patients with NDMM (N = 185) with < 2% (blue line) and 2%-20% (red line) of CTCs. CTC, circulating tumor plasma cell; HR, hazard ratio; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PCL, plasma cell leukemia; PFS, progression-free survival.

J Clin Oncol, 2022

# Phenotypic, cytogenetic and genomic characteristics of PPCL




*Cancers* **2022**, *14*, 1594. https://doi.org/10.3390/cancers14061594

- Immunophenotyping of plasma cells reveals expression of **CD38 and CD138** in both pPCL and MM, although **higher expression of CD20,** CD23, CD28, CD44, and CD45 and **lower expression of CD56, CD117,** CD9, CD71, and HLA-DR may be found in pPCL compared to MM.
- Cytogenetic studies by FISH show **predominance of monosomy and deletions of chromosome 13, t(11;14), del(17p), gain/amp(1q) and del(1p) and reduction of hyperdiploidy**
- Mutation studies by conventional DNA sequencing, WES, and targeted NGS detect a **high frequency of mutations in TP53 and K/NRAS genes.** The amino acids most frequently mutated in TP53 are I195, R273, P278, R248, and E285. Activating mutations of K/NRAS most frequently found in pPCL patients affect codons 12, 13, and 61 (G12, G13, and Q61).
- Gene expression profiling in pPCL has shown **downregulation of genes associated** with bone marrow **microenvironment and bone diseases in MM,** such as **DKK1, KIT, and NCAM1 genes.**
- **A global hypomethylation profile** has been found in pPCL samples.
- **Non-coding RNAs (miRNAs and lncRNAs)** are **dysregulated in pPCL,** and some of them are **associated with survival of patients**

# Highlights from IMS 20th meeting 2023

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

cancers
MDPI

Article

## Transcriptomic Analysis in Multiple Myeloma and Primary Plasma Cell Leukemia with t(11;14) Reveals Different Expression Patterns with Biological Implications in Venetoclax Sensitivity

Katia Todoerti [1,2], Elisa Taiana [1,2], Noemi Puccio [1], Vanessa Favasuli [1,2], Marta Lionetti [1,2], Ilaria Silvestris [1,2], Massimo Gentile [3], Pellegrino Musto [4,5], Fortunato Morabito [6,7], Umberto Gianelli [8,9], Niccolò Bolli [1,2], Luca Baldini [1,2], Antonino Neri [1,2,*] and Domenica Ronchetti [1,2,*]

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Citation: Todoerti, K.; Taiana, E.; Puccio, N.; Favasuli, V.; Lionetti, M.; Silvestris, I.; Gentile, M.; Musto, P.; Morabito, F.; Gianelli, U.; et al. Transcriptomic Analysis in Multiple Myeloma and Primary Plasma Cell Leukemia with t(11;14) Reveals Different Expression Patterns with Biological Implications in Venetoclax Sensitivity. *Cancers* **2021**, *13*, 4898. https://doi.org/10.3390/cancers13194898

**Simple Summary:** The growing interest in BCL2 inhibitors for the treatment of multiple myeloma (MM) has led to the need for biomarkers that are able to predict patient's sensitivity to the drug. The presence of the chromosomal translocation t(11;14) in MM is mainly associated with sensitivity to

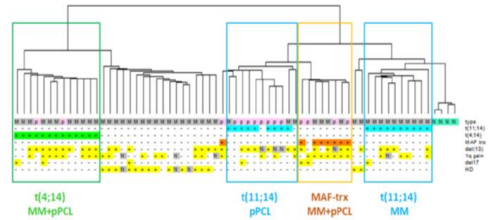


**Figure 1.** Hierarchical clustering analysis of gene-expression profiles of 50 MM (grey), 15 pPCL (pink) and 4 N samples (green). Samples are grouped according to the expression levels of the 2402 most variable transcripts (varying at least 2-fold in expression levels from the mean across the dataset). Main molecular alterations are shown; N indicates data not available. The specific types (N = normal control, M = MM, *p* = pPCL) are enriched by colored sub-branches, also highlighted by the appropriately colored box (see text).

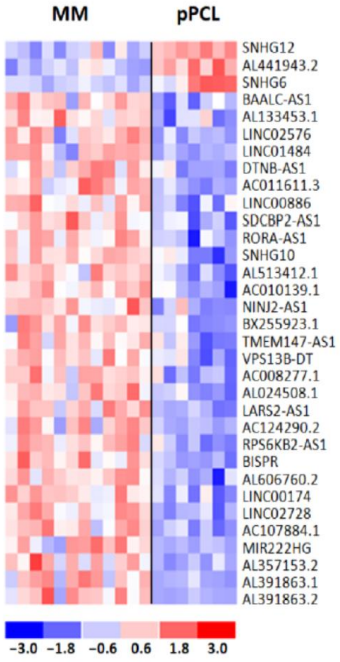


**Figure 5.** Heatmap of the 33 differentially expressed lncRNAs in 12 MM and 7 pPCL patients with t(11;14) chromosomal translocation. The colored scaled bar represents standardized rows by subtracting the mean and divided by the standard deviation.


LYMPHOID NEOPLASIA

## Primary plasma cell leukemias displaying t(11;14) have specific genomic, transcriptional, and clinical features

Tiziana Cazzaboi,[1,2] Xavier Leleu,[3] Aurore Perrot,[3,4] Salomon Manier,[5] Laure Buisson,[3,4] Sabrina Mahler,[3,4] Laura Do Souto Ferreira,[3,4] Romain Lannes,[3,4,7] Luka Pavageau,[3,4] Cyrille Hulin,[3] Jean-Pierre Marolleau,[6] Laurent Voillat,[6] Karim Belhadj,[10] Marion Divoux,[11] Borhane Slama,[12] Sabine Brechignac,[13] Margaret Macro,[14] Anne-Marie Stoppa,[15] Laurence Sanhes,[16] Frédérique Orsini-Piocelle,[17] Jean Fontan,[18] Marie-Lorraine Christen,[19] Hélène Demarquette,[20] Mohamad Mohty,[21] Anais Schavgoulidze,[22] Hervé Avet-Loiseau,[3,4] and Jill Corre[3,4]

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**KEY POINTS**

- Primary PCL displays a specific genomic and transcriptomic profile when compared with newly diagnosed myeloma.
- Primary PCL with t(11;14) is a distinct genomic and transcriptional entity, with better overall survival.

**Primary plasma cell leukemia (pPCL) is an aggressive form of multiple myeloma (MM) that has not benefited from recent therapeutic advances in the field. Because it is very rare and heterogeneous, it remains poorly understood at the molecular level. To address this issue, we performed DNA and RNA sequencing of sorted plasma cells from a large cohort of 90 newly diagnosed pPCL and compared with MM. We observed that pPCL presents a specific genomic landscape with a high prevalence of t(11;14) (about half) and high-risk genomic features such as del(17p), gain 1q, and del(1p32). In addition, pPCL displays a specific transcriptome when compared with MM. We then wanted to characterize specifically pPCL with t(11;14). We observed that this subentity displayed significantly fewer adverse cytogenetic abnormalities. This translated into better overall survival when compared with pPCL without t(11;14) (39.2 months vs 17.9 months, *P* = .002). Finally, pPCL with t(11;14) displayed a specific transcriptome, including differential expression of BCL2 family members. This study is the largest series of patients with pPCL reported so far.**

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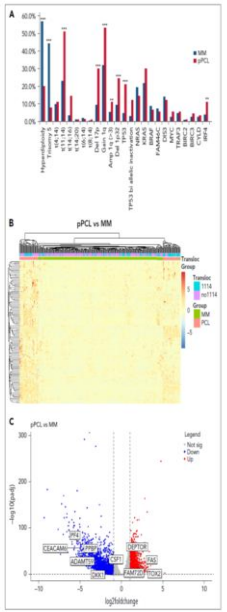


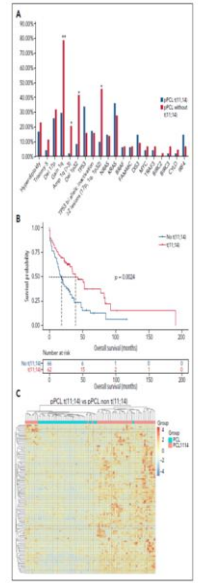


**Figure 2. Genomic and transcriptome of malignant plasma cells from primary PCL displaying t(11;14) compared with primary PCL without t(11;14).** (A) Incidence of main cytogenetics abnormalities and mutations in 90 primary PCL compared with 487 newly diagnosed MM; ****P* < .0001, ***P* < .001, **P* < .01. (B) Unsupervised clustering of 90 primary PCL and 288 newly diagnosed MM based on the expression levels of the 100 most variable genes. (C) Gene expression profiling comparing differentially expressed genes between primary PCL and newly diagnosed MM, with an least twofold change (*P* < .05, FDR<0.05). (D) GSEA from 90 primary PCL compared with 288 newly diagnosed MM.

**Figure 1. Genomic and transcriptome of malignant plasma cells from primary PCL compared with newly diagnosed multiple myeloma.** (A) Incidence of main cytogenetics abnormalities and mutations in 90 primary PCL compared with 487 newly diagnosed MM; ****P* < .0001, ***P* < .001, **P* < .01. (B) Unsupervised clustering of 90 primary PCL and 288 newly diagnosed MM based on the expression levels of the 100 most variable genes. (C) Gene expression profiling comparing differentially expressed genes between primary PCL and newly diagnosed MM, with an least twofold change (*P* < .05, FDR<0.05). (D) GSEA from 90 primary PCL compared with 288 newly diagnosed MM.

# 3349 Distinct Genetic Features in Peripheral Blood Represent the Characteristics of Circulating Plasma Cells in Primary Plasma Cell Leukemia

**Youngeun Lee et al. Seongnam, Korea, Republic of (South)**

- Targeted sequencing using the **NGS panel of 647 genes** related to hematologic malignancies.
- Three **truly unique variants** were identified in each pPCL (MED12, VPS13B variant from PB, and ZMYM3 variant from BM) and sPCL group (ARID1A, FANCE, and TP53).
- **In pPCL, PB variants had higher VAF than BM variants**, and some unique variants were identified only in the PB samples.
- Conversely, **in sPCL, more diverse variants were detected mainly in BM samples,** and VAF was also higher in BM than PB.
- This study shows that **CPCs in pPCL are not simply part of the malignant plasma cells shed from the BM** but have **characteristics distinct** from them.

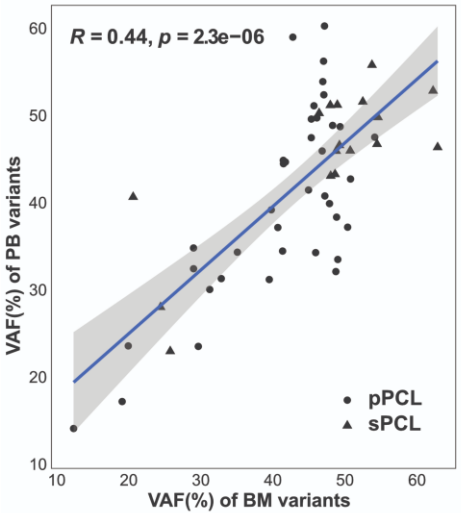


**Figure 1. Scatterplots presenting distribution of variant allele frequency (VAF) by specimen types in pPCL and sPCL patients.** The blue line is the regression line representing the correlation between paired peripheral blood and bone marrow variants.

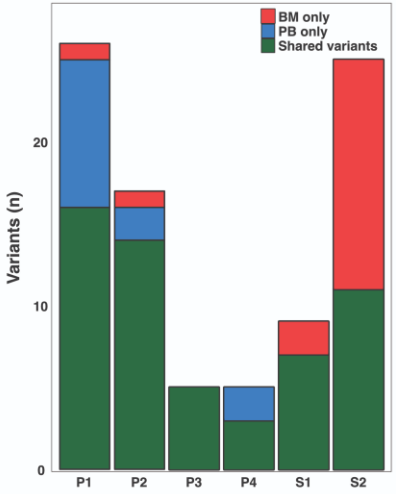


**Figure 2. Shared and unique variants between paired samples.** P and S represent the results with pPCL and sPCL patients, respectively.

bjh research paper

**Prognostic indicators in primary plasma cell leukaemia: a multicentre retrospective study of 117 patients**

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[1]Jagiellonian University Medical College, Cracow,

We report a multicentre retrospective study that analysed clinical characteristics and outcomes in 117 patients with primary plasma cell leukaemia (pPCL) treated at the participating institutions between January 2006 and December 2016. The median age at the time of pPCL diagnosis was 61 years. Ninety-eight patients were treated with novel agents, with an overall response rate of 78%. Fifty-five patients (64%) patients underwent upfront autologous stem cell transplantation (ASCT). The median follow-up time was 30 months (95% confidence interval [CI] 33; 76), with a median overall survival (OS) for the entire group of 23 months (95% CI 15; 34). The median OS time in patients who underwent upfront ASCT was 35 months (95% CI 24-3; 46) as compared to 13 months (95% CI 6-3; 35-8) in patients who did not receive ASCT ($P = 0{\cdot}001$). Multivariate analyses identified age ≥60 years, platelet count ≤100 × $10^9$/l and peripheral blood plasma cell count ≥20 × $10^9$/l as independent predictors of worse survival. The median OS in patients with 0, 1 or 2–3 of these risk factors was 46, 27 and 12 months, respectively ($P < 0{\cdot}001$). Our findings support the use of novel agents and ASCT as frontline treatment in patients with pPCL. The constructed prognostic score should be independently validated.

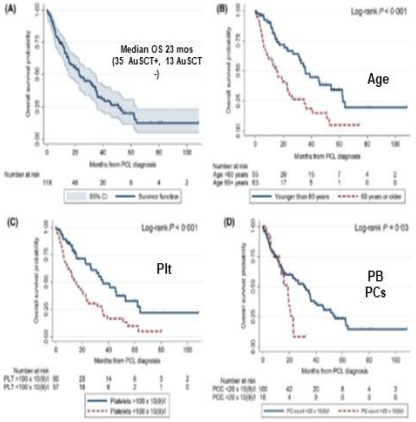



Fig 1. Overall survival estimates in 117 primary plasma cell leukaemia patients for the entire cohort (A), by age (B), platelet count (C) and plasma cell count in peripheral blood (D). 95% CI, 95% confidence interval; PCC, plasma cell count; PCL, plasma cell leukaemia; PLT, platelet count. [Colour figure can be viewed at wileyonlinelibrary.com]

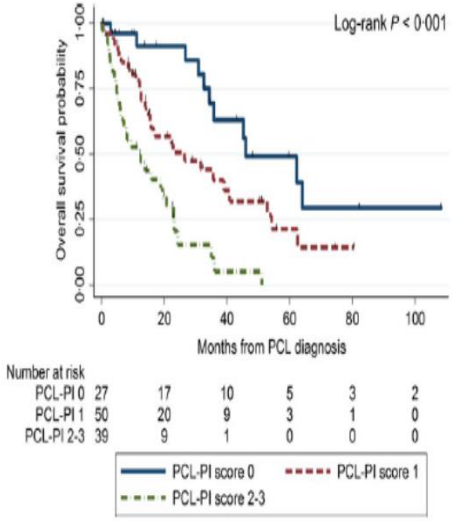



Fig 2. Overall survival estimates in 117 patients with primary plasma cell leukaemia by pPCL Prognostic Index. PCL, plasma cell leukaemia; PCL-PI, plasma cell leukaemia prognostic index. [Colour figure can be viewed at wileyonlinelibrary.com]

 doi: 10.1111/bjh.15092

**TABLE. Univariate and Multivariate Analysis of Clinical and Laboratory Characteristics Predictive of OS and TTNT[a]**

| | OS | | | | TTNT | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate Analysis | | Multivariate Analysis | | Univariate Analysis | | Multivariate Analysis | |
| Characteristic | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age ≥75 y | 1.68 (0.77-3.64) | .19 | — | — | 0.57 (0.20-1.60) | .29 | — | — |
| CR w/first-line therapy | 0.43 (0.22-0.83)[b] | .01[b] | 0.47 (0.23-0.96)[b] | .04[b] | 0.29 (0.16-0.55)[b] | <.001[b] | 0.29 (0.16-0.55)[b] | <.001[b] |
| High-risk cytogenetics | 2.66 (1.35-5.24)[b] | .01[b] | 2.95 (1.37-6.26)[b] | .01[b] | 1.54 (0.81-2.91) | .19 | — | — |
| Elevated serum LDH | 0.67 (0.30-1.49) | .33 | — | — | 0.76 (0.35-1.62) | .47 | — | — |
| PCLI >2% | 2.62 (0.92-7.55) | .07 | — | — | 1.31 (0.45-3.85) | .62 | — | — |
| Platelets <100k per μl | 1.40 (0.67-2.93) | .38 | — | — | 1.45 (0.71-2.97) | .31 | — | — |
| ≥20% cPCs by PB smear | 1.12 (0.60-2.08) | .72 | — | — | 0.97 (0.54-1.76) | .93 | — | — |

[a]HR, hazard ratio; cPC, clonal plasma cell; CR, complete response; LDH, lactate dehydrogenase; OS, overall survival; PB, peripheral blood; PCLI, plasma cell labeling index; TTNT, time to next therapy.
[b]Statistically significant.

# Updated results (1973-2009) of SEER US Registry: the impact of transplant and novel agents

CLINICAL TRIALS AND OBSERVATIONS

## Trends in survival of patients with primary plasma cell leukemia: a population-based analysis

Wilson I. Gonsalves,[1] S. Vincent Rajkumar,[1,2] Ronald S. Go,[1] Angela Dispenzieri,[1] Vinay Gupta,[1] Preet P. Singh,[1] Francis K. Buadi,[1] Martha Q. Lacy,[1] Prashant Kapoor,[1] David Dingli,[1] John A. Lust,[1,2] Steven R. Zeldenrust,[1] Suzanne R. Hayman,[1] Robert A. Kyle,[1] Morie A. Gertz,[1] and Shaji K. Kumar[1]

[1]Division of Hematology, [2]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

**Key Points**

- Survival of patients with primary plasma cell leukemia has improved in recent years, but is still inferior to those patients with multiple myeloma.
- This survival benefit appears to be mainly in patients older than 65 years of age.

Primary plasma cell leukemia (pPCL) is a rare malignancy with an aggressive course and poor outcome. There has been significant improvement in the survival of multiple myeloma patients over the past decade as a result of incorporating autologous stem cell transplantation (ASCT) and novel agents into treatment regimens. However, it is unknown whether these therapies have had a similar impact on the survival of patients with pPCL. We conducted an analysis of the Surveillance, Epidemiology, and End Results database to evaluate the trends in survival of 445 patients with pPCL between 1973 and 2009. The widespread availability of ASCT and use of novel agents in the upfront setting of multiple myeloma and pPCL began after 1995 and 2006, respectively. The median overall survival based on periods of diagnosis were 5, 6, 4, and 12 months for those diagnosed during 1973-1995, 1996-2000, 2001-2005, and 2006-2009, respectively ($P = .001$). Thus, the current study confirms the recent survival improvement in pPCL within a large US population that may be associated with the use of better therapeutic strategies. (*Blood*. 2014;124(6):907-912)

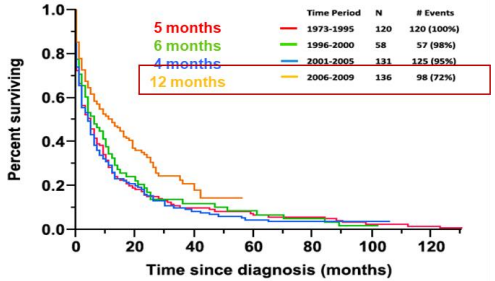



**Figure 1. Kaplan-Meier Curve for OS in pPCL patients based on period of diagnosis.**

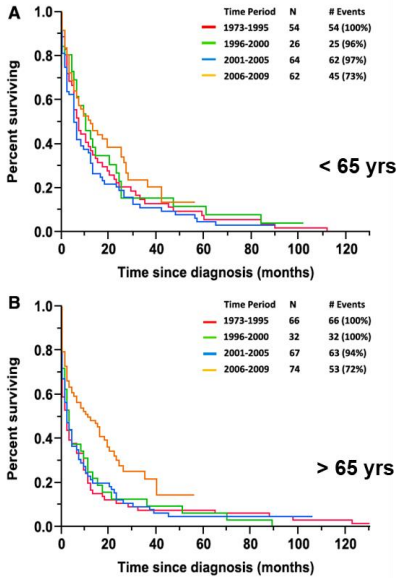



**Figure 2. Kaplan-Meier curves.** (A) Kaplan-Meier curve for OS in pPCL patients based on period of diagnosis in patients younger than 65 years of age. (B) Kaplan-Meier curve for OS in pPCL patients based on period of diagnosis in patients 65 years of age or older.

LETTER

MULTIPLE MYELOMA, GAMMOPATHIES

## Real world analysis on the determinants of survival in primary plasma cell leukemia in the United States

Ludovic Saba[1], Kevin S. Landau[1], Hong Liang[2], Chieh-Lin Fu[1] and Chakra P. Chaulagain[1]



*Leukemia*; https://doi.org/10.1038/s41375-023-02100-x

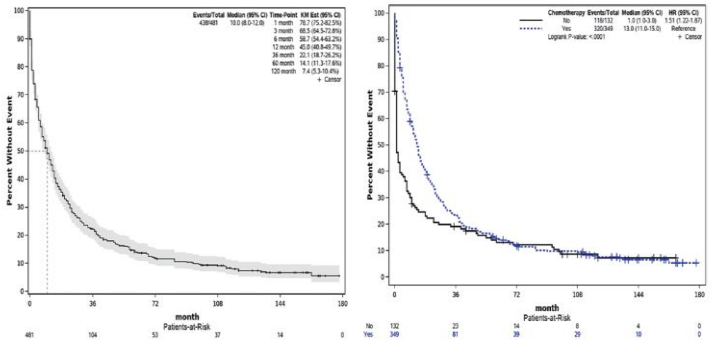



**Fig. 1 Kaplan-Meier Analysis for Patient Survival. a** Kaplan–Meier survival curve for whole cohort of plasma cell leukemia patients ($N = 481$). **b** Kaplan–Meier survival curves for plasma cell leukemia patients who received chemotherapy vs. plasma cell leukemia patients who did not receive chemotherapy.

*These **US registry studies** , updated **up to 2009,** however, suffer from **several problems** mainly related to the **limited quality of data collected** and a **reduced access to appropriate therapies** (novel agents and transplant procedures, likely due to **insurance questions).***

*Overall, the introduction of* ***bortezomib and lenalidomide as initial therapy and, particularly, their integration within transplant programs,*** *have produced* ***(in retrospective studies):***

- *A* ***marked increase in rate and quality of response*** *(ORR 54%-90%; CR 12%-47%)*
- *A* ***moderate, but significant improvement in the clinical outcome*** *of PPCL, particularly reducing the rate of early deaths and allowing* ***OS of approximately 1 year in elderly*** *patients, and* ***3 years in patients undergoing transplant procedures***
- *A positive impact on PFS and OS by* ***maintenance therapy, low-risk cytogenetics and achievement of CR after auto-SCT.***

*Three registry studies of 780 PPCL patients transplanted* ***(AutoSCT)*** *between 1980 and 2009 (limited use of new drugs!):*

- ***Higher rates of CR than in MM.***
- ***Less effective than in MM in the long term*** *(increased non relapse-related mortality and short duration of post-transplantation response): median* ***PFS 14.3 months, median OS 25.7 months.***
- ***Trend toward superior 3-year OS*** *in patients who underwent* ***double versus single AuSCT (84% vs 56%).***

***Two registry studies (CBMTR and EBMT) comparing AlloSCT*** *in 135 patients between 1984 and 2009, with* ***similar populations treated with AuSCT:***

- ***Lower relapse rate for AlloSCT,*** *but* ***much higher risk of NRM*** *compared with AuSCT,* ***without evidence of survival benefits*** *(OS 39% and 32% at 3 and 4 years, respectively).*
- ***OS at 5 years 19%*** *for reduced-intensity conditioning* ***(RIC)*** *and* ***27%*** *for myeloablative conditioning* ***(MAC)*** *AlloSCT.*
- ***Plateau at approximately 20%,*** *as seen in MM, but at a lower level.*

*Musto P and Walsch R. Plasma cell leukemia: another piece of the puzzle. Haematologica 2022*

Leukemia
https://doi.org/10.1038/s41375-020-0830-0

ARTICLE

Stem cell biology

# Hematopoietic cell transplantation utilization and outcomes for primary plasma cell leukemia in the current era

Binod Dhakal[1] · Sagar Patel[2] · Saulius Girnius[3] · Lohith Bachegowda[4] · Raphael Fraser[1,5] · Omar Davila[1] · Abraham S. Kanate[6] · Amer Assal[7] · Amr Hanbali[8] · Asad Bashey[9] · Attaphol Pawarode[10] · César O. Freytes[11] · Cindy Lee[12] · David Vesole[13] · Robert Frank Cornell[14] · Gerhard C. Hildebrandt[15] · Hemant S. Murthy[16] · Hillard M. Lazarus[17] · Jan Cerny[18] · Jean A. Yared[19] · Jeffrey Schriber[20,21] · Jesus Berdeja[22] · Keith Stockerl-Goldstein[23] · Kenneth Meehan[24] · Leona Holmberg[25] · Melhem Solh[26] · Miguel Angel Diaz[27] · Mohamed A. Kharfan-Dabaja[16] · Nosha Farhadfar[28,29] · Qaiser Bashir[30] · Reinhold Munker[31] · Richard F. Olsson[32,33] · Robert P. Gale[34] · Ruthlee-Lu Bayer[35] · Sachiko Seo[36] · Saurabh Chhabra[1] · Shahrukh Hashmi[37,38] · Sherif M. Badawy[39,40] · Taiga Nishihori[41] · Wilson Gonsalves[42] · Yago Nieto[30] · Yvonne Efebera[43] · Shaji Kumar[42] · Nina Shah[30] · Muzaffar Qazilbash[4] · Parameswaran Hari[1] · Anita D'Souza[1]

Table 3 Multivariate analysis of factors predicting outcomes after auto-HCT.

| Characteristic | Progression-free survival | | Relapse/Progression | | Overall survival | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *p* value | HR (95% CI) | *p* value | HR (95% CI) | *p* value |
| Disease status at transplant | | <0.001 | | <0.001 | | <0.001 |
| ≥VGPR | Reference | | Reference | | Reference | |
| PR | 1.53(1.11–2.11) | 0.008 | 1.4 (1.01–1.96) | 0.04 | 1.55 (1.09–2.2) | 0.01 |
| SD/PD/relapse | 3.6 (2.3–5.8) | <0.001 | 3.3 (2.04–5.45) | <0.001 | 4.3 (2.6–7.2) | <0.001 |
| Missing | 1.8 (0.63–5.22) | 0.26 | 1.4 (0.44–5.8) | 0.53 | 2.7 (0.99–7.8) | 0.05 |
| Melphalan dose | | 0.04 | | 0.08 | – | – |
| 140 mg/m$^2$ | Reference | | Reference | | | |
| 200 mg/m$^2$ | 0.65 (0.44-0.98) | | 0.68 (0.45–1.04) | | | |
| Karnofksy performance status | – | | – | | | 0.0018 |
| ≥90 | | | | | Reference | |
| <90 | | | | | 1.80 (1.3–2.49) | 0.004 |
| Missing | | | | | 1.79 (0.43–7.3) | 0.41 |

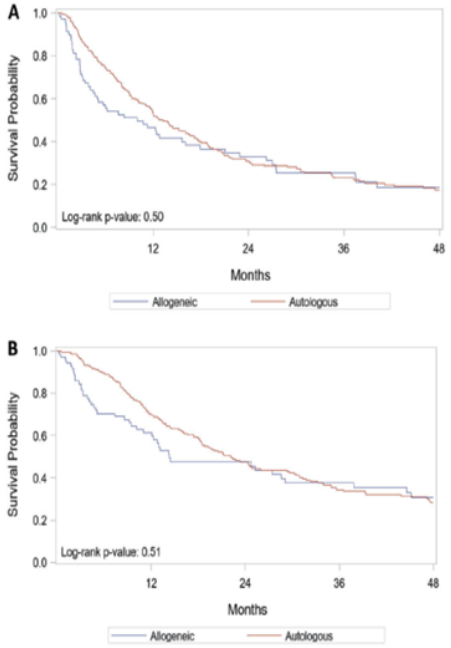



Fig. 1 Survival of plasma cell leukemia after HCT. a Probability of progression-free survival after HCT—by transplant type. b Probability of overall survival after HCT—by transplant type.

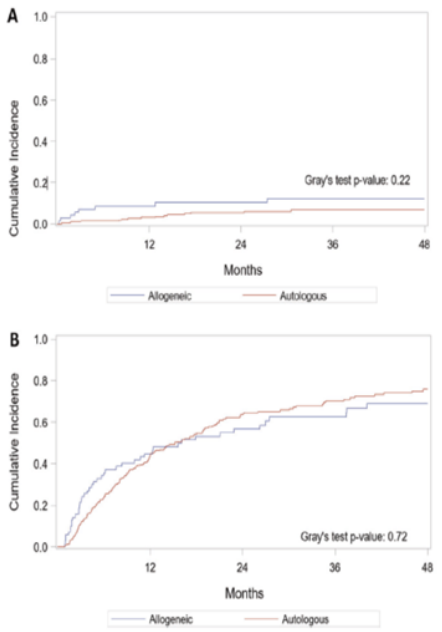



Fig. 2 Non-relapse mortality and relapse of plasma cell leukemia after HCT. a Cumulative incidence of non-relapse mortality after HCT—by transplant type. b Cumulative incidence of relapse after HCT—by transplant type.

*This more recent survey of 71 patients undergoing Allo-SCT compared to 277 patients receiving AuSCT between 2008 and 2015 **confirmed no differences in outcome** and **a high percentage of relapse** in both procedures*

haematologica
Journal of The Ferrata Storti Foundation

## Comparison of autologous and allogeneic hematopoietic cell transplantation strategies in patients with primary plasma cell leukemia, with dynamic prediction modelling

by Sarah Lawless, Simona Iacobelli, Nina Simone Knelange, Patrice Chevallier, Didier Blaise, Noel Milpied, Robin Foà, Jan J. Cornelissen, Bruno Lioure, Reuben Benjamin, Xavier Poiré, Monique C. Minnema, Matthew Collin, Stig Lenhoff, John A. Snowden, Stella Santarone, Keith M.O. Wilson, Fernanda Trigo, Peter Dreger, Lara H. Bölmer, Hein Putter, Laurent Garderet, Nicolaus Kröger, Ibrahim Yakoub-Agha, Stefan Schönland, and Curly Morris

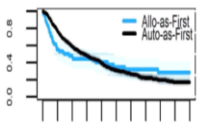
*Received: December 21, 2021.*
*Accepted: May 27, 2022.*

**Table 2. Characteristics of patients according to transplant strategy**

| | | Single Auto | Tandem Auto-Auto | Tandem Auto-Allo | Allo-first |
|---|---|---|---|---|---|
| | Nr of patients | 442 | 117 | 122 | 70 |
| Age at 1st transplant (years) | Median (min-max) | 58.7 (25,79) | 58.7 (37,75) | 51.6 (33,70) | 47.2 (20-68) |
| Sex | Male | 224 (50.7%) | 64 (54.7%) | 46 (37.7%) | 44 (62.9%) |
| | Female | 218 (49.3%) | 53 (45.3%) | 76 (62.3%) | 26 (37.1%) |
| Time from diagnosis to 1st transplant | ≤12 months | 403 (91.2%) | 114 (97.4%) | 120 (98.4%) | 59 (84.3%) |
| | >12 months | 39 (8.8%) | 3 (2.6%) | 2 (1.6%) | 11 (15.7%) |
| Disease status at 1st transplant | Complete response | 155 (35.1%) | 28 (23.9%) | 38 (31.1%) | 26 (37.1%) |
| | Partial response | 268 (60.6%) | 79 (67.5%) | 80 (65.6%) | 33 (47.1%) |
| | Stable disease | 19 (4.3%) | 10 (8.5%) | 4 (3.3%) | 11 (15.7%) |
| Karnofsky performance status at 1st transplant* | ≥70 | 366 (95.1%) | 99 (98.0%) | 106 (99.1%) | 61 (96.8%) |
| | <70 | 19 (4.9%) | 2 (2.0%) | 1 (0.9%) | 2 (3.2%) |
| | (missing) | (57, 13%) | (16, 14%) | (15, 12%) | (7, 10%) |
| Calendar period of 1st transplant | 1998-2003 | 92 (20.8%) | 27 (23.1%) | 13 (10.7%) | 21 (30.0%) |
| | 2004-2007 | 77 (17.4%) | 32 (27.4%) | 22 (18.0%) | 12 (17.1%) |
| | 2008-2010 | 85 (19.2%) | 14 (12.0%) | 34 (27.9%) | 11 (15.7%) |
| | 2011-2012 | 96 (21.7%) | 19 (16.2%) | 21 (17.2%) | 13 (18.6%) |
| | 2013-2014 | 92 (20.8%) | 25 (21.4%) | 32 (26.2%) | 13 (18.6%) |
| Disease status at 2nd transplant | CR/PR | *Not Applic* | 116 (99.1%) | 119 (97.5%) | *Not Applic* |
| | SD/MR | *Not Applic* | 1 (0.9%) | 3 (2.5%) | *Not Applic* |

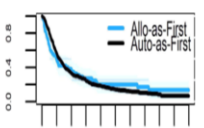
*Percentages computed among non-missing cases.

OS by first trx



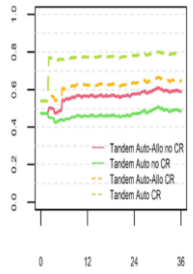

months since trx1

PFS by first trx



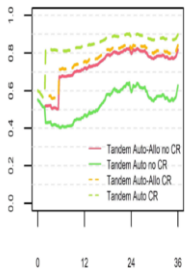

months since trx1

A
3-yrs OS prediction (55-yo). Role of CR



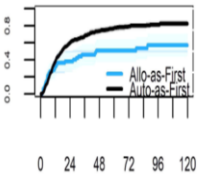

months since trx1

B
1-yr PFS prediction (55-yo). Role of CR



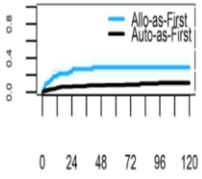

months since trx1

CIR by first trx



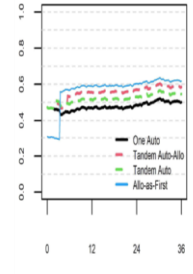

months since trx1

NRM by first trx



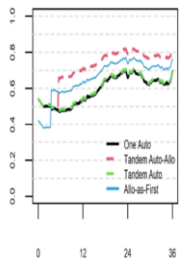

months since trx1

A
3-yrs OS prediction (55-yo noCR)




months since trx1

B
1-yr PFS prediction (55-yo noCR)

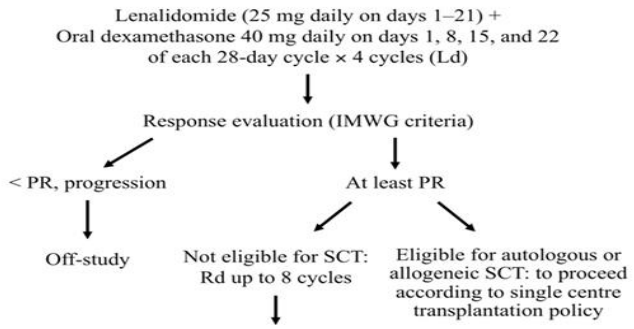



months since trx1

**Table 4. Cox models for comparison of transplant strategies**

| | OS | | | PFS | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | p-value | HR | 95%CI | p-value |
| Age: Effect of +1 yr | 1.01 | 1.00-1.02 | 0.064 | 1.01 | 1.00-1.02 | 0.146 |
| Disease status: No CR vs CR | 1.31 | 1.06-1.62 | 0.014 | 1.31 | 1.08-1.58 | 0.005 |
| Allo-first, effect within 100 days | 5.74 | 2.66-12.4 | <0.001 | 2.84 | 1.57-5.15 | 0.001 |
| Allo-first, effect after 100 days | 0.92 | 0.61-1.38 | 0.677 | 0.83 | 0.57-1.20 | 0.317 |
| Tandem auto-allo, effect within 100 days | 0.89 | 0.45-1.79 | 0.751 | 1.01 | 0.62-1.64 | 0.967 |
| Tandem auto-allo, effect after 100 days | 0.80 | 0.59-1.08 | 0.148 | 0.69 | 0.52-0.92 | 0.012 |
| Tandem auto-auto | 0.81 | 0.60-1.08 | 0.144 | 0.86 | 0.67-1.11 | 0.254 |
| In a model with interactions[1]: | | | | | | |
| - Tandem auto-auto, No CR | 0.94 | 0.68-1.28 | 0.678 | 1.08 | 0.82-1.42 | 0.602 |
| - Tandem auto-auto, CR | 0.44 | 0.21-0.91 | 0.026 | 0.39 | 0.21-0.73 | 0.003 |

[1]Models with interaction terms: only the HR for Tandem Auto combined with Disease status are shown. The p-value for the interaction was 0.060 for OS and 0.003 for PFS.




Musto et al, Leukemia 2014

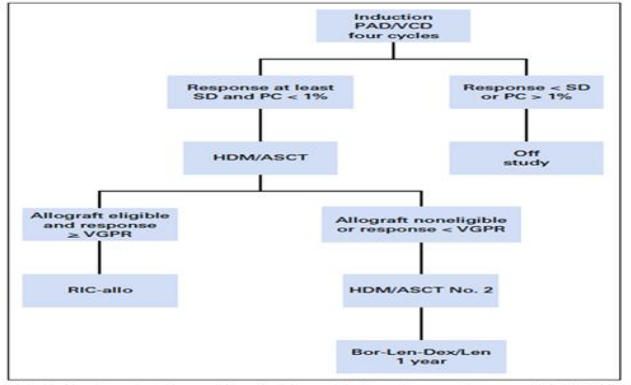



**Fig 1.** Treatment schema. Bor, bortezomib; Dex, dexamethasone; HDM/ASCT, high-dose melphalan/autologous stem cell transplantation; Len, lenalidomide; PAD, bortezomib + dexamethasone on days 1, 4, 8, and 11 + doxorubicin on day 4; PC, plasma cell; RIC-allo, reduced-intensity conditioning allograft; SD, stable disease; VCD, bortezomib + dexamethasone on days 1, 4, 8, and 11 + cyclophosphamide on days 1 and 8; VGPR, very good partial response.

## Prospective studies with novel agents in PPCL

Table 1. Results of the two prospective studies so far published in primary plasma cell leukemia.

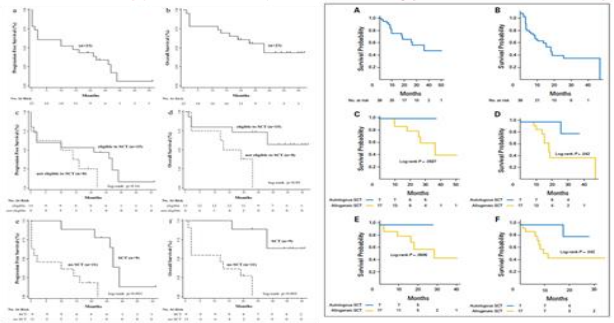
| | GIMEMA study (19) | IFM study (18) |
|---|---|---|
| N. patients | 23 | 40 |
| Median age (range) | 60 (44-80) | 57 (27-71) |
| Induction | Ld (4 cycles for younger, 8 cycles for elderly patients) | PAD/VCD (2 + 2 cycles) |
| Consolidation | AuSCT (in eligible patients) | Double AuSCT or, in patients <66 years with a matched donor, tandem AuSCT/AlloSCT (RIC) |
| Maintenance | Low-dose lenalidomide (in patients not eligible for AuSCT) | VRD/Lenalidomide (1 year) in patients undergoing double AuSCT |
| ORR (after induction) | 74% | 69% (including 10% SD with disappearance of circulating plasma cells |
| At least VGPR (after induction) | 39% (CR 13%) | 36% (CR 10%) |
| At least VGPR after the entire treatment | 56.5% | 59% (sCR/CR 33%) |
| Median follow-up | 34 months | 28.7 months |
| Median PFS | 14 months (27 months in transplanted vs. 2 months in non-transplanted patients) | 15.1 months (not reached with double AuSCT vs. 17.9 months with AutoSCT/AlloSCT) |
| Median OS | 28 months b(not reached in transplanted vs. 12 months in non-transplanted patients) | 36.3 months (not reached with double AuSCT vs. 36.3 months in AutoSCT/AlloSCT |

GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; IFM: Intergroupe Francophone du Myélome; Ld: lenalidomide and low-dose dexamethasone; PAD: bortezomib, doxorubicin, and dexamethasone; VCD: bortezomib, cyclophosphamide, and dexamethasone; AuSCT: autologous stem cell transplantation; AlloSCT: allogeneic stem cell transplantation; RIC: reduced intensity conditioning; VRD: bortezomib, lenalidomide, and dexamethasone; ORR: overall response rate; SD: stable disease; VGPR: very good partial response; CR: complete response; sCR: stringent complete response; PFS: progression-free survival; OS: overall survival.

Musto et al, Leukemia 2014 Royer et al, J Clin Oncol 2016

Royer et al, J Clin Oncol 2016

GIMEMA study (Lenalidomide-based) IFM study (Bortezomib-based + lena + SCT)



Musto et al, Leukemia 2014 Royer et al, J Clin Oncol 2016

# Treatment of primary plasma cell leukaemia with carfilzomib and lenalidomide-based therapy (EMN12/HOVON-129): final analysis of a non-randomised, multicentre, phase 2 study

Niels W C J van de Donk, Monique C Minnema, Bronno van der Holt, Fredrik Schjesvold, Ka Lung Wu, Annemiek Broijl, Wilfried W H Roeloffzen, Alain Gadisseur, Giuseppe Pietrantuono, Ludek Pour, Vincent H J van der Velden, Thomas Lund, Massimo Offidani, Mariella Grasso, Luisa Giaccone, Wida Razawy, Paola Tacchetti, Katia Mancuso, Trine Silkjaer, Jo Caers, Sonja Zweegman, Roman Hájek, Reuben Benjamin, Annette Juul Vangsted, Mario Boccadoro, Francesca Gay, Pieter Sonneveld, Pellegrino Musto

## Summary

**Background** Primary plasma cell leukaemia is a rare and aggressive plasma cell disorder with a poor prognosis. The aim of the EMN12/HOVON-129 study was to improve the outcomes of patients with primary plasma cell leukaemia by incorporating carfilzomib and lenalidomide in induction, consolidation, and maintenance therapy.

**Methods** The EMN12/HOVON-129 study is a non-randomised, phase 2, multicentre study conducted at 19 academic centres and hospitals in seven European countries (Belgium, Czech Republic, Denmark, Italy, Norway, The Netherlands, and the UK) for previously untreated patients with primary plasma cell leukaemia aged 18 years or older. Inclusion criteria were newly diagnosed primary plasma cell leukaemia (defined as >2×10⁹ cells per L circulating monoclonal plasma cells or plasmacytosis >20% of the differential white cell count) and WHO performance status 0–3. Patients aged 18–65 years (younger patients) and 66 years or older (older patients) were treated in age-specific cohorts and were analysed separately. Younger patients were treated with four 28-day cycles of carfilzomib (36 mg/m² intravenously on days 1, 2, 8, 9, 15, and 16), lenalidomide (25 mg orally on days 1–21), and dexamethasone (20 mg orally on days 1, 2, 8, 9, 15, 16, 22, and 23). Carfilzomib–lenalidomide–dexamethasone (KRd) induction was followed by double autologous haematopoietic stem-cell transplantation (HSCT), four cycles of KRd consolidation, and then maintenance with carfilzomib (27 mg/m² intravenously on days 1, 2, 15, and 16 for the first 12 28-day cycles, and then 56 mg/m² on days 1 and 15 in all subsequent cycles) and lenalidomide (10 mg orally on days 1–21) until progression. Patients who were eligible for allogeneic HSCT, could also receive a single autologous HSCT followed by reduced-intensity conditioning allogeneic HSCT and then carfilzomib–lenalidomide maintenance. Older patients received eight cycles of KRd induction followed by maintenance therapy with carfilzomib and lenalidomide until progression. The primary endpoint was progression-free survival. The primary analysis population was the intention-to-treat population, irrespective of the actual treatment received. Data from all participants who received any study drug were included in the safety analyses. The trial was registered at www.trialregister.nl (until June 2022) and https://trialsearch.who.int/ as NTR5350; recruitment is complete and this is the final analysis.

**Findings** Between Oct 23, 2015, and Aug 5, 2021, 61 patients were enrolled and received KRd induction treatment (36 patients aged 18–65 years [20 (56%) were male and 16 (44%) female], and 25 aged ≥66 years [12 (48%) were male and 13 (52%) female]). With a median follow-up of 43·5 months (IQR 27·7–67·8), the median progression-free survival was 15·5 months (95% CI 9·4–38·4) for younger patients. For older patients, median follow-up was 32·0 months (IQR 24·7–34·6), and median progression-free survival was 13·8 months (95% CI 9·2–35·5). Adverse events were most frequently observed directly after treatment initiation, with infections (two of 36 [6%] younger patients and eight of 25 [32%] older patients) and respiratory events (two of 36 [6%] younger patients and four of 25 [16%] older patients) being the most common grade 3 or greater events during the first four KRd cycles. Treatment-related serious adverse events were reported in 26 (72%) of 36 younger patients and in 19 (76%) of 25 older patients, with infections being the most common. Treatment-related deaths were reported in none of the younger patients and three (12%) of the older patients (two infections and one unknown cause of death).

**Interpretation** Carfilzomib and lenalidomide-based therapy provides improved progression-free survival compared with previously published data. However, results remain inferior in primary plasma cell leukaemia compared with multiple myeloma, highlighting the need for new studies incorporating novel immunotherapies.

**Funding** Dutch Cancer Society, Celgene (a BMS company), and AMGEN.



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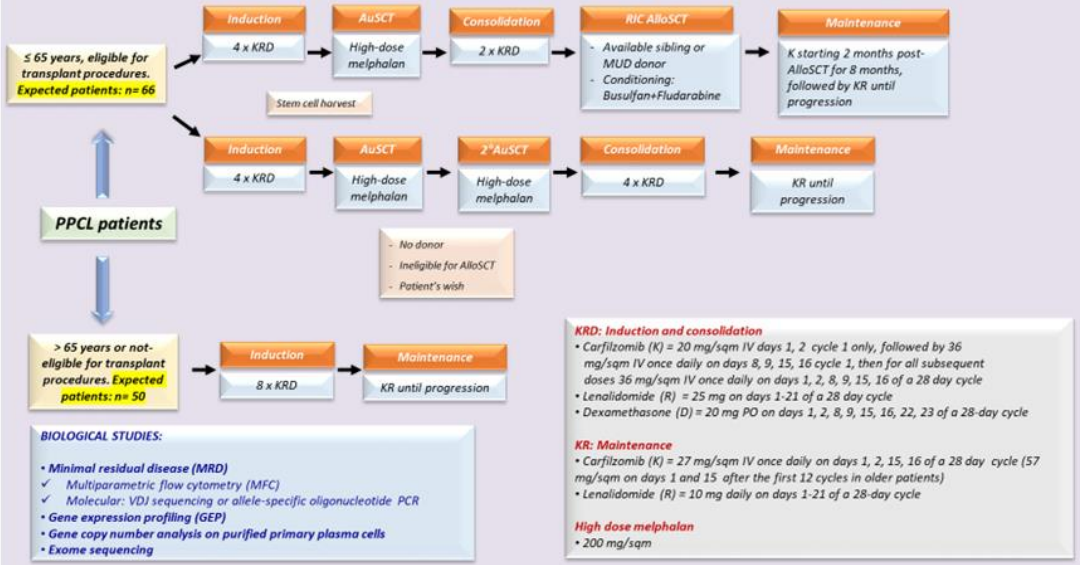
## Non-randomized, phase 2, multicenter study, patients with previously untreated PPCL (EMN12/HOVON129, www.trialregister.nl as NTR5350)




**61 PPCL pts enrolled between 2015 and 2021, 36 < 65 yrs, 25 > 65 yrs**

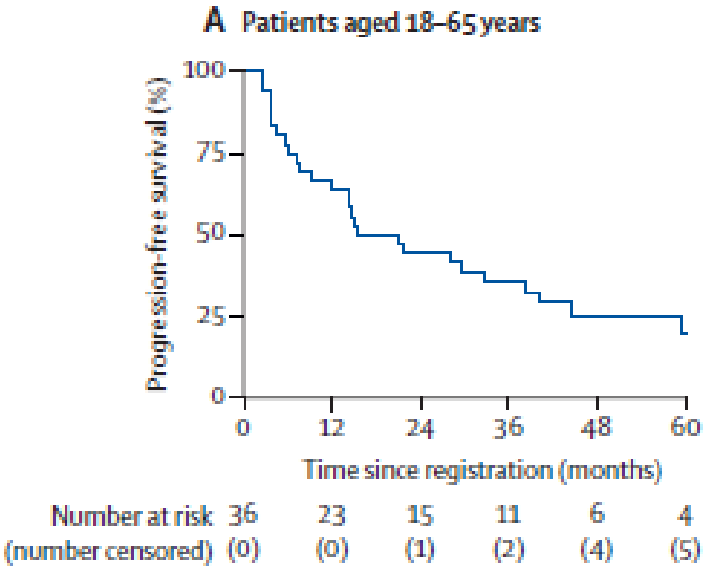
The primary endpoint was PFS, and secondary endpoints were response rate, OS, and toxicity.

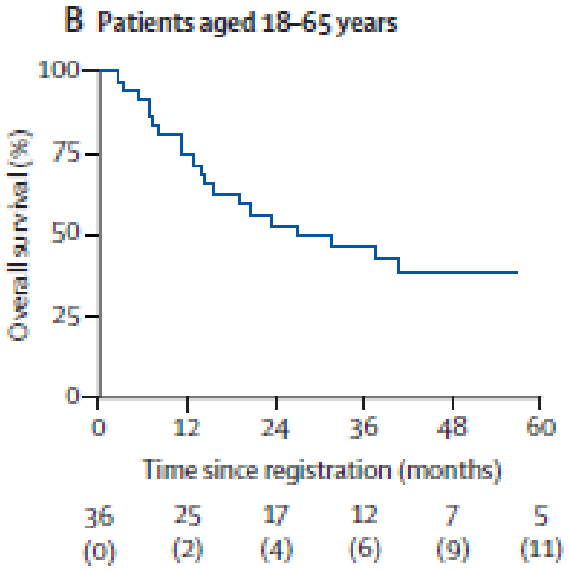
| | Patients aged 18–65 years | | | | | Patients aged 66 years or older | | |
|---|---|---|---|---|---|---|---|---|
| | Response after induction (n=36) | Response after first autologous HSCT (n=24) | Response after second autologous HSCT (n=12) | Response after allogeneic HSCT (n=5) | Best response on protocol (n=36) | Response after induction cycles 1–4 (n=25) | Response after induction cycles 5–8 (n=19) | Best response on protocol (n=25) |
| Partial response or better | 30 (83%) | 23 (96%) | 12 (100%) | 5 (100%) | 31 (86%) | 20 (80%) | 18 (95%) | 20 (80%) |
| Very good partial response or better | 27 (75%) | 23 (96%) | 12 (100%) | 5 (100%) | 30 (83%) | 17 (68%) | 17 (89%) | 17 (68%) |
| Complete response or better | 5 (14%) | 8 (33%) | 3 (25%) | 4 (80%) | 18 (50%) | 6 (24%) | 8 (42%) | 9 (36%) |
| Stringent complete response | 1 (3%) | 3 (13%) | 1 (8%) | 2 (40%) | 12 (33%) | 3 (12%) | 4 (21%) | 5 (20%) |
| Complete response | 4 (11%) | 5 (21%) | 2 (17%) | 2 (40%) | 6 (17%) | 3 (12%) | 4 (21%) | 4 (16%) |
| Very good partial response | 22 (61%) | 15 (63%) | 9 (75%) | 1 (20%) | 12 (33%) | 11 (44%) | 9 (47%) | 8 (32%) |
| Partial response | 3 (8%) | 0 | 0 | 0 | 1 (3%) | 3 (12%) | 1 (5%) | 3 (12%) |
| Stable disease | 1 (3%) | 0 | 0 | 0 | 1 (3%) | 1 (4%) | 0 | 1 (4%) |
| Progressive disease | 3 (8%) | 1 (4%) | 0 | 0 | 2 (6%) | 0 | 1 (5%) | 0 |
| Unevaluable | 2 (6%)* | 0 | 0 | 0 | 2 (6%) | 5 (20%)† | 0 | 5 (20%) |

Data are n (%).HSCT=haematopoietic stem-cell transplantation. *Two patients were not evaluable for response; one patient because of withdrawal of consent 14 days after treatment initiation and one patient went off-protocol 28 days after protocol initiation because of development of renal failure in the absence of disease progression. †Five patients were not evaluable for response because of early death in two patients (10 and 15 days after treatment initiation), excessive toxicity in two patients (protocol treatment was stopped 14 days and 19 days after its initiation), and withdrawal of consent in one patient (28 days after treatment initiation).

*Table 2:* **Response rate in patients aged 18–65 years and patients aged 66 years or older**

16/20 (80%) of younger patients and 5/8 (63%) of elderly patients in at least CR who could be evaluated for minimal residual disease (MRD) achieved MRD negativity ($10^{-5}$) by flow cytometry



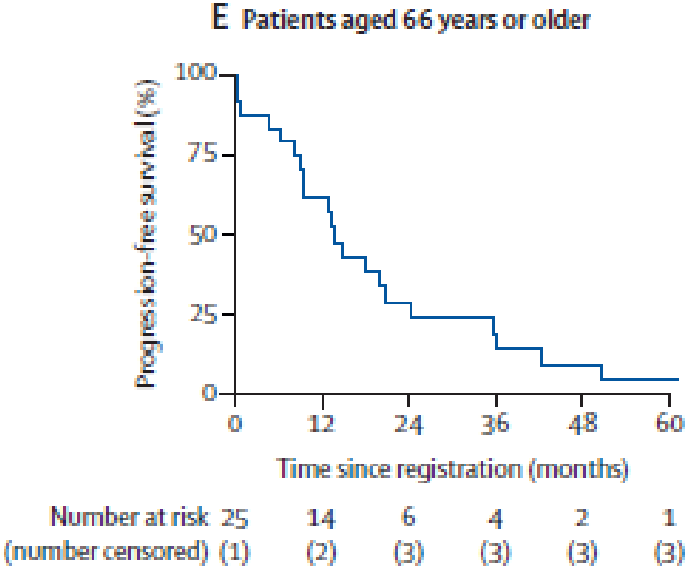

**Median PFS (primary end-point) was 15.5 months** (95% CI 9.4-38.4), **sufficient to reject initial null hypothesis of 9 months**, based on previous studies

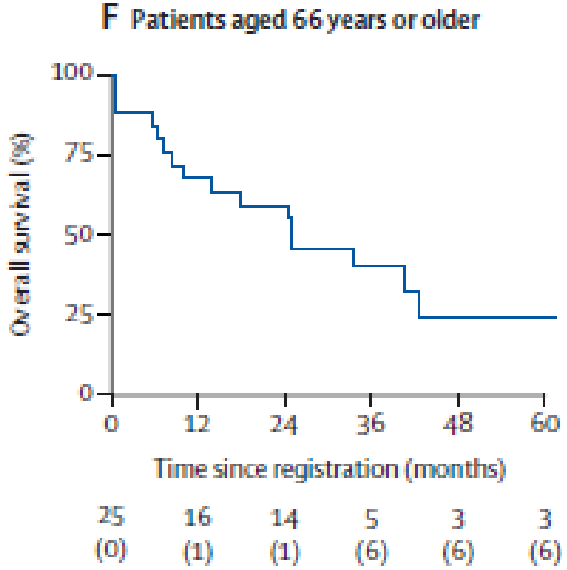
**Median OS was 28.4 months** (95% CI 15.1-NR)

**Low early mortality** (8.3% at 6 months)

- *For patients who underwent first AuSCT, median PFS and OS were 32.9 and 34.1 months from date of first AuSCT, respectively .*
- *From the date of the second transplant, median PFS was comparable for double AuASCT and tandem AuSCT-AlloSCT (31.2 vs 49.2 months, respectively; 58% at and 60% at two years, respectively)*
- *From the date of the second transplant median OS was comparable for double AuSCT and tandem AuSCT-AlloSCT (both not estimable; 82% and 63% at two years, respectively);*

Median follow-up 43.5 months




*Median OS substantially doubled compared to what has been reported in recent retrospective studies and, particularly, in the only other prospective trial (with the doublet lenalidomide-dexamethasone) so far conducted in transplant ineligible, elderly patients with PPCL (Musto P et al. Leukemia. 2014).*

**Median PFS (primay end-point was 13.8 months** (95% CI 9.2-35.5), **sufficient to reject initial null hypothesis of 6.5 months,** based on previous studies

**Median OS was 24.8 months** (95% CI 14-not reached [NR]).
**Low early mortality** (16% at 6 months)

Median follow-up 32 months

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DOI: 10.1002/ajh.26891

RESEARCH ARTICLE

AJH WILEY

# Improved survival of patients with primary plasma cell leukemia with VRd or daratumumab-based quadruplets: A multicenter study by the Greek myeloma study group

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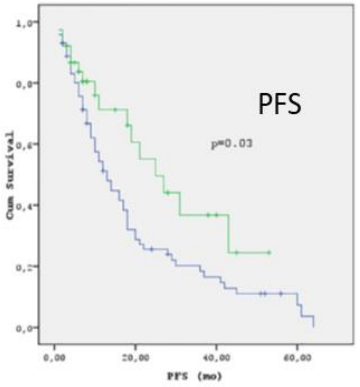
**TABLE 3** Cox regression analysis for overall survival.

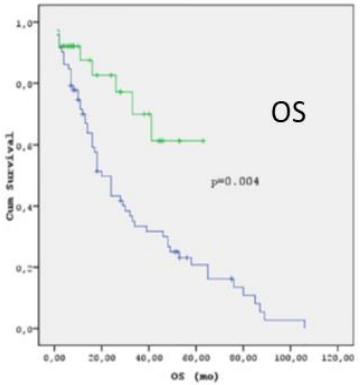
| Variable | p | HR | 95% CI |
|---|---|---|---|
| Univariate cox regression analysis | | | |
| Del17p present | .01 | 2.37 | 1.17–4.7 |
| PS (ECOG) ≥ 2 | <.001 | 2.6 | 1.6–4.4 |
| CR or less than CR | .01 | 0.42 | 0.24–0.8 |
| cPCs 5%–19% versus ≥20% | .01 | 0.45 | 0.25–0.8 |
| Type of treatment (VRd/DBQ vs. BST/CT) | .006 | 0.35 | 0.17–0.7 |
| ASCT | <.001 | 0.36 | 0.2–0.63 |
| PLT <100.000/μL | .001 | 2.35 | 1.4–3.9 |
| Multivariate cox regression analysis | | | |
| Type of treatment (VRd/DBQ vs. BST/CT) | .006 | 0.28 | 0.16–0.6 |
| Del17p present | .003 | 3.1 | 1.45–6.5 |
| Platelets <100.000/μL | .003 | 3.2 | 1.6–6.5 |

**TABLE 2** Treatment regimens.

| Treatments | |
|---|---|
| Conventional (VAD/MP/MPT) | 12 (6/3/3) |
| VCd | 32 |
| VDT | 6 |
| PAD | 11 |
| VD (T)-PACE | 9 |
| VRd | 17 |
| DaraVCd | 14 |
| DaraVRd | 4 |
| DaraVDT | 5 |
| ASCT/double ASCT | 38/2 |
| Auto-Allo SCT | 1 |

Abbreviations: Allo, allogeneic; ASCT, autologous stem cell transplantation; PAD, bortezomib, Adriamycin, dexamethasone; VAD, vincristine, adriamycin, dexamethasone; VCd, bortezomib, cyclophosphamide, dexamethasone; VDT, bortezomib, Thalidomide, dexamethasone; VDT-PACE, VDT + cisplatinum, adriamycin, cyclophosphamide, etoposide.

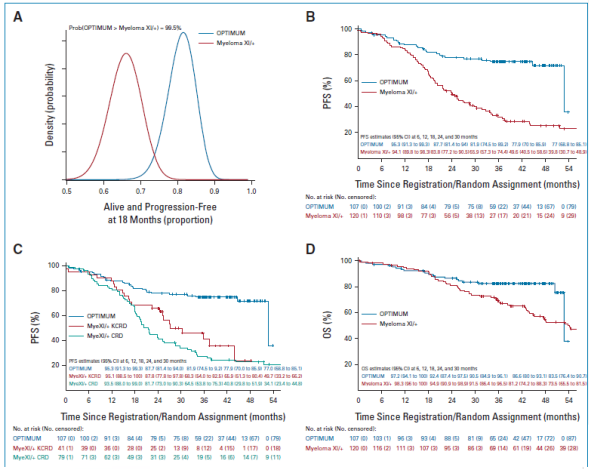


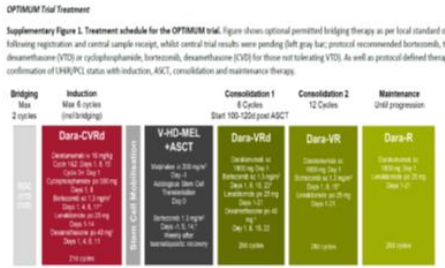




- **VRd or daratumumab-based quadruplets (DBQ)** versus **previous therapies** with bortezomib standard combinations (BSC) or conventional chemotherapy (CT),
- **110 pPCL patients,** including those with cCPS ≥5%); **37% had CPCs 5%–19%;**
- 89% received **DBQ (21%), VRd (16%)** and BSC (52%); 35% underwent ASCT).
- Treatment with **VRd/DBQ** strongly correlated with a **higher CR rate** (41% vs. 17%;p=.008).
- After a median follow-up of 51 months. **early mortality was 3.5%.**
- Median **PFS** was 16 months and significantly **longer in patients treated with VRd/DBQ** versus BSC/CT (25 months vs. 13 months, ;p=.03).
- Median **OS** was 29 months, **significantly longer in patients treated with VRd/DBQ** versus BSC/CT (not reached vs. 20 months,3-year OS:70% vs. 32%, respectively; p< .001).
- In the **multivariate analysis VRd/DBQ therapy, del17p(+) and PLT <100.000/μL,** independently predicted OS (p< .05).

## Daratumumab, Cyclophosphamide, Bortezomib, Lenalidomide, and Dexamethasone as Induction and Extended Consolidation Improves Outcome in Ultra-High-Risk Multiple Myeloma

Martin F. Kaiser, MD[1,2]; Andrew Hall, MSc[3]; Katrina Walker, MSc[3]; Amy Sherborne, PhD[3]; Ruth M. De Tute, PhD[3]; Nicola Newnham, BSc[3]; Sadie Roberts, PhD[3]; Emma Ingleson, PhD[3]; Kristian Bowles, PhD[3]; Mamta Garg, MD[3]; Anand Lokare, MD[3]; Christina Messios, MD[1,2]; Richard S. Houlston, MD, PhD[3]; Graham Jackson, MD[4]; Gordon Cook, PhD[1,2,5]; Guy Pratt, MD[6]; Roger G. Owen, MD[6]; Mark T. Drayson, PhD[3]; Sarah R. Brown, PhD[3]; and Matthew W. Jenner, MD[1,2]




## Primary Plasma Cell Leukemia: a Prospective Phase 2 Study Incorporating Daratumumab to Chemotherapy and Stem Cell Transplantation (PCL-2)

**Single-Arm phase 2 trial** evaluating efficacy of incorporating Daratumumab to treatment of newly diagnosed **primary plasma cell leukemia.** Treatment will be based on **Dara-VRd induction followed by first ASCT, Dara-VRd for first consolidation, second ASCT, Dara-VRd for 1 year as second consolidation and Lenalidomide for 1 year.**

Single-arm phase 2 trial
Estimated Study Start Date: October 2021
Estimated Primary Completion Date: June 2024
Estimated Study Completion Date: February 2028

**ClinicalTrials.gov Identifier: NCT05054478**

Principal Investigator: Bruno Royer, MD
Assistance Publique - Hôpitaux de Paris

Experimental: Experimental Arm

4 days of dexamethasone. According to local practice, one dose of doxorubicine (30 mg/m2 IV) or cyclophosphamide (750 mg/m2 IV) may also be added

Induction Treatment (4 months): Subject will receive 4 x 28 days cycles of Dara-VRD induction:

Daratumumab sc 1800 mg on D1 D8 D15 D22 for cycle1 & 2 and D1 D15 for cycle 3 & 4
Bortezomib sc 1.3 mg/m2 on D1 D4 D8 D11 for each cycle Lenalidomide po 25 mg on D1 to D21 for each cycle Dexamethasone po 20 mg on D1 D2 D8 D9 D15 D16 D22 D23 for each cycle

High dose melphalan 200mg/m2 as conditioning therapy and first ASCT

First consolidation : 2 cycles of Dara-VRd

Daratumumab 1800 mg s.c D1 D15

Bortezomib 1.3 mg/m2 s.c D1 D8 D15 D22

Lenalidomide 25 mg p.o from D1 to D21

Dexa 20 mg p.o D1 D8 D15 D22

High dose melphalan 200mg/m2 as conditioning therapy and second ASCT Second consolidation : 6 cycles of Dara-VRd (every 2 months for 2 years) Then maintenance: Lenalidomide every 28 days (25 mg from D1 to D21) for 1 year

## 573 Bortezomib-Decp Alternating with Daratumumab-Vpd Plus Stem Cell Transplantation, Followed By Maintenance with VP in Ultra-High Risk (UHIR) Newly Diagnosed Multiple Myeloma (NDMM) and Primary Plasma Cell Leukemia (pPCL): A Multicenter, Prospective Phase 2 Pilot Trial (DRAGON CATCHER TRIAL)

*Jin Lu, MD[1], **Yang Liu, PhD[2]**, Jian Hou[2] and Juan Li, PhD[3]*
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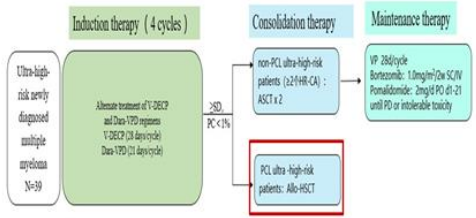
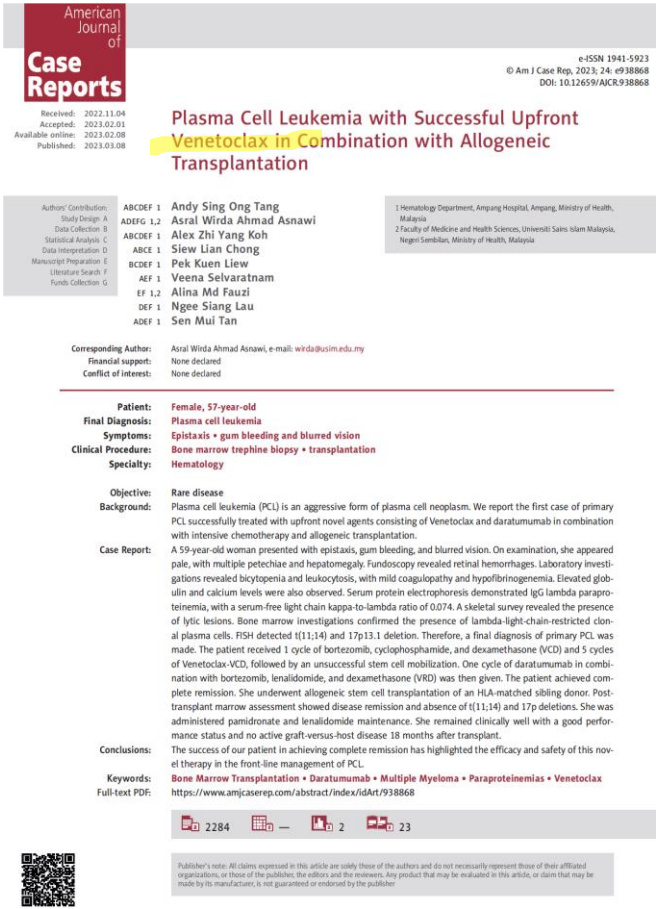



- Primary endpoint: ≥VGPR ( after 4 cycles of induction therapy )
- Secondary endpoints: Iy-PFS, MRD Negative Rate (NGF, $10^{-5}$) 、ORR、safety



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# Plasma Cell Leukemia with Successful Upfront Venetoclax in Combination with Allogeneic Transplantation

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Financial support: None declared
Conflict of interest: None declared

Patient: Female, 57-year-old
Final Diagnosis: Plasma cell leukemia
Symptoms: Epistaxis • gum bleeding and blurred vision
Clinical Procedure: Bone marrow trephine biopsy • transplantation
Specialty: Hematology

Objective: Rare disease
Background: Plasma cell leukemia (PCL) is an aggressive form of plasma cell neoplasm. We report the first case of primary PCL successfully treated with upfront novel agents consisting of Venetoclax and daratumumab in combination with intensive chemotherapy and allogeneic transplantation.
Case Report: A 59-year-old woman presented with epistaxis, gum bleeding, and blurred vision. On examination, she appeared pale, with multiple petechiae and hepatomegaly. Fundoscopy revealed retinal hemorrhages. Laboratory investigations revealed bicytopenia and leukocytosis, with mild coagulopathy and hypofibrinogenemia. Elevated globulin and calcium levels were also observed. Serum protein electrophoresis demonstrated IgG lambda paraproteinemia, with a serum-free light chain kappa-to-lambda ratio of 0.074. A skeletal survey revealed the presence of lytic lesions. Bone marrow investigations confirmed the presence of lambda-light-chain-restricted clonal plasma cells. FISH detected t(11;14) and 17p13.1 deletion. Therefore, a final diagnosis of primary PCL was made. The patient received 1 cycle of bortezomib, cyclophosphamide, and dexamethasone (VCD) and 5 cycles of Venetoclax-VCD, followed by an unsuccessful stem cell mobilization. One cycle of daratumumab in combination with bortezomib, lenalidomide, and dexamethasone (VRD) was then given. The patient achieved complete remission. She underwent allogeneic stem cell transplantation of an HLA-matched sibling donor. Post-transplant marrow assessment showed disease remission and absence of t(11;14) and 17p deletions. She was administered pamidronate and lenalidomide maintenance. She remained clinically well with a good performance status and no active graft-versus-host disease 18 months after transplant.
Conclusions: The success of our patient in achieving complete remission has highlighted the efficacy and safety of this novel therapy in the front-line management of PCL.
Keywords: Bone Marrow Transplantation • Daratumumab • Multiple Myeloma • Paraproteinemias • Venetoclax
Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/938868

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NCT05870917
A Study of Ve-VRD or S-VRD Combined With CART-ASCT-CART2 Treatment in Patients With Primary Plasma Cell Leukemia
Tianjin, China
RECRUITING

Ve =Venetoclax
S = Selinexor

NCT05979363
A Study of Bortezomib, Lenalidomide and Dexamethasone (VRd) Followed by BCMA CAR-T Therapy in Transplant-Ineligible Patients With Primary Plasma Cell Leukemia
Locations
Tianjin, China
RECRUITING

***P-049 Safety and efficacy of standard of care ciltacabtagene autoleucel (Cilta-cel) for relapsed/refractory multiple myeloma (RRMM): real world experience***

*Surbhi Sidana et al. Stanford University, USA*

- *Outcomes of patients treated with intended standard of care ciltacel at 14 US academic centers by September, 15, 2022, and April 1, 2023.*
- *Compared to CARTITUDE-1 study, this cohort (n. 143 patients) had higher incidence of extramedullary disease (31% vs 13%) and high-risk cytogenetics (41% vs 24%).*
- *57% of the patients would not have met eligibility criteria for CARTITUDE-1 due to cytopenias (17%), prior BCMA therapy (15%), organ dysfunction (12%), poor performance status (11%) and plasma cell leukemia (7%).*
- *CRS was seen in 80% (≥ grade 3: 5%), ICANS in 18% (≥ grade 3: 6%) and hemophagocytic lympho-histiocytosis (HLH)-like syndrome in 3% of patients.*
- *Delayed neurotoxicity (NT) was seen in 12% (mainly cranial nerve palsy and Parkinsonism); 3 patients died with ongoing delayed NT. Infections were seen in 37% of patients.*
- *Best response rates were: ≥ PR 89%; VGPR 77%; CR 56%, respectively.*
- *With a median follow-up of 6 months, median PFS was not reached, with 6-month estimate being 79%.*
- *22 patients died (10%) due to non-relapse mortality (mainly infections, CRS, ICANS, delayed NT, HLH).*

# A EUROPEAN MYELOMA NETWORK PROSPECTIVE PHASE II CLINICAL TRIAL PROPOSAL FOR NEWLY DIAGNOSED MYEIOMA PATIENTS WITH UNMET MEDICAL NEED: MYELOMA WITH EXTRA-MEDULLARY PLASMACYTOMA AND PRIMARY PLASMA CELL LEUKEMIA

Niels van de Donk, Meral Beksac, Pellegrino Musto, Mario Boccadoro, and Pieter Sonneveld

Date: october 2023
Version: 4

**Proposed study:**

- Patients will be treated with **dara-VRD induction (4 cycles) followed by auto-SCT.**
- Next, patients will receive **consolidation treatment consisting of combination treatment with teclistamab+talquetamab (for a duration of 2 years** (26 cycles;)
- **After the 2-year consolidation treatment, lenalidomide maintenance** can be adminsitered as per local standard-of-care.
- **Alternatively,** if PERSEUS study shows advantage of adding daratumumab to induction/consolidation/maintenance, then **daratumumab+lenalidomide maintenance will be maintenance of choice.**

**Patient population**

- **Newly diagnosed, transplant eligible pPCLpatients (currently defined by the presence of ≥ 5% circulating plasma cells);**

**Endpoints**

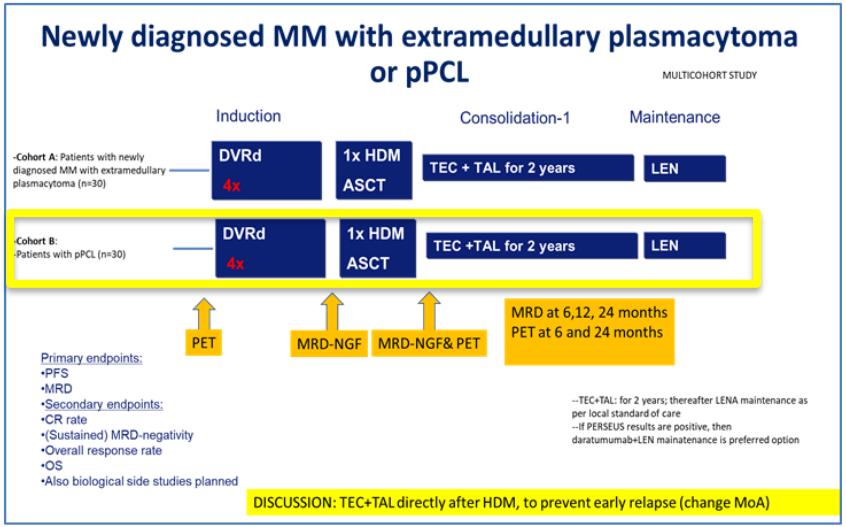
- **Primary endpoints:** PFS
- **Secundary endpoints:** CR rate, sustained MRD-negativity, overall response rate, OS, safety

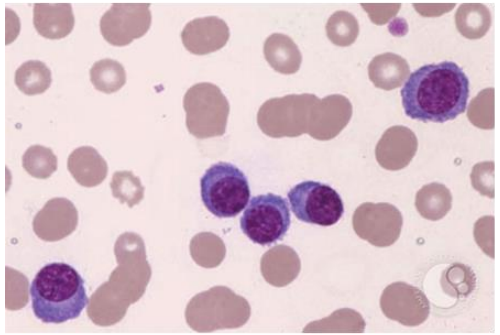
**Sample size**

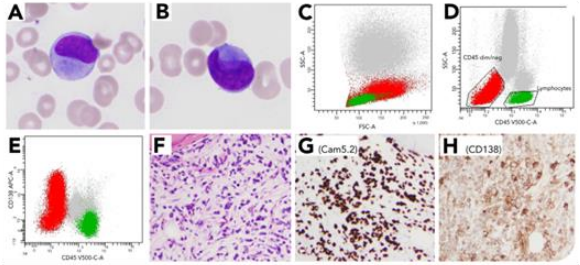
- **30 patients**
- **MRD** samples will be taken prior to transplant (after induction), after transplant, and during consolidation after 6, 12, and 24 months.
- **PET scans** will be performed to assess extramedullary disease (as per IMWG criteria) at screening, after transplant, and at 6 and 24 months during consolidation.
- **Correlative studies** will include molecular profiling, immune profiling, and assessment of circulating tumor cells.

**Countries, sites & recruitment:**

- **Czechia** (3 sites), Greece (2 sites), **Italy** (2 sites), **The Netherlands** (5 sites), **Norway** (1 site) & **Turkey** (4 sites).
- **24 month recruitment** period








CD138⁺ carcinocythemia mimicking plasma cell leukemia by flow cytometry. Byron Barksdale,Catherine P. Leith, Blood, 2020,

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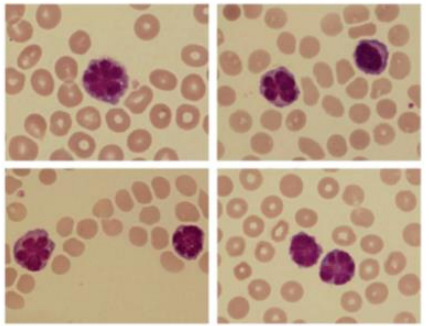
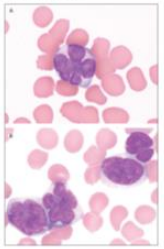
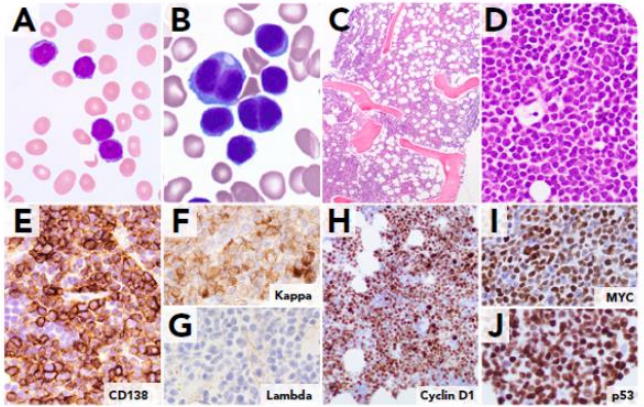
**Primary plasma cell leukaemia presenting with flower-shaped nuclei**



**Plasma cell leukaemia presenting as flower-shaped plasma cells mimicking adult T-cell leukaemia or lymphoma**



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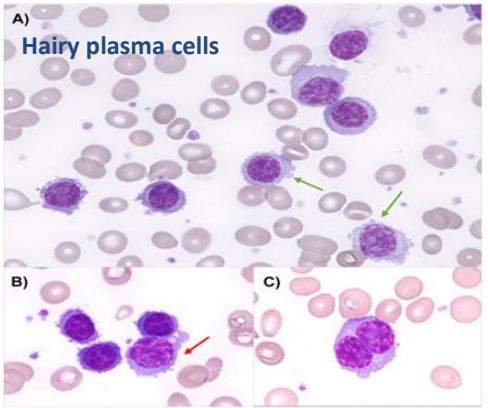
Plasma cell leukemia with small cell morphology

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