Highlights from IMW 2019

19-20 novembre 2019
Bologna
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Dipartimento Interaziendale di Ematologia della Basilicata
IRCCS-CROB, Centro di Riferimento Oncologico di Basilicata,
Rionero in Vulture (Pz)

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DIPARTIMENTO INTERAZIENDALE DI EMATOLOGIA DELLA BASILICATA

IRCCS
CROB

Leucemia plasmacellulare (primitiva): opzioni terapeutiche

Updated results (1973-2009) of SEER US PPCL 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]

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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)

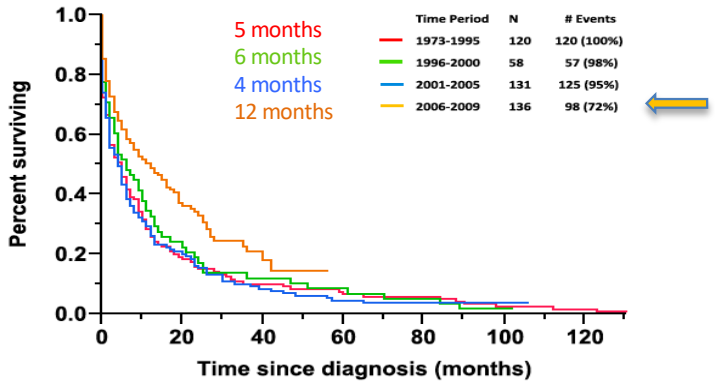

Figure 1. Kaplan-Meier Curve for OS in pPCL patients based on period of diagnosis.

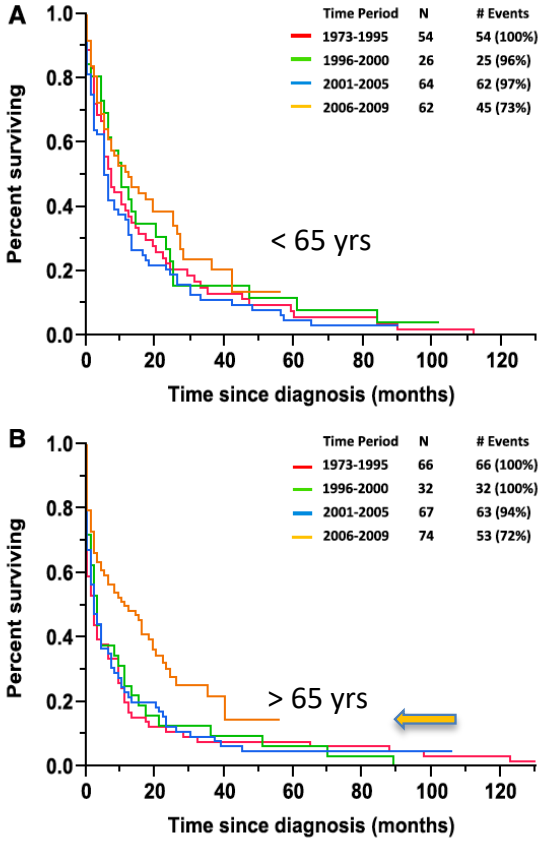

Figure 2. Kaplan-Meier curves. (A) Kaplan-Meier curve for OS in pPCL patients based on period of diagnosis in patients younger than 65 years of age. (B) Kaplan-Meier curve for OS in pPCL patients based on period of diagnosis in patients 65 years of age or older.

Outcomes for PPCL and non-PPCL patients enrolled in TT1, TT2, or TT3 programs

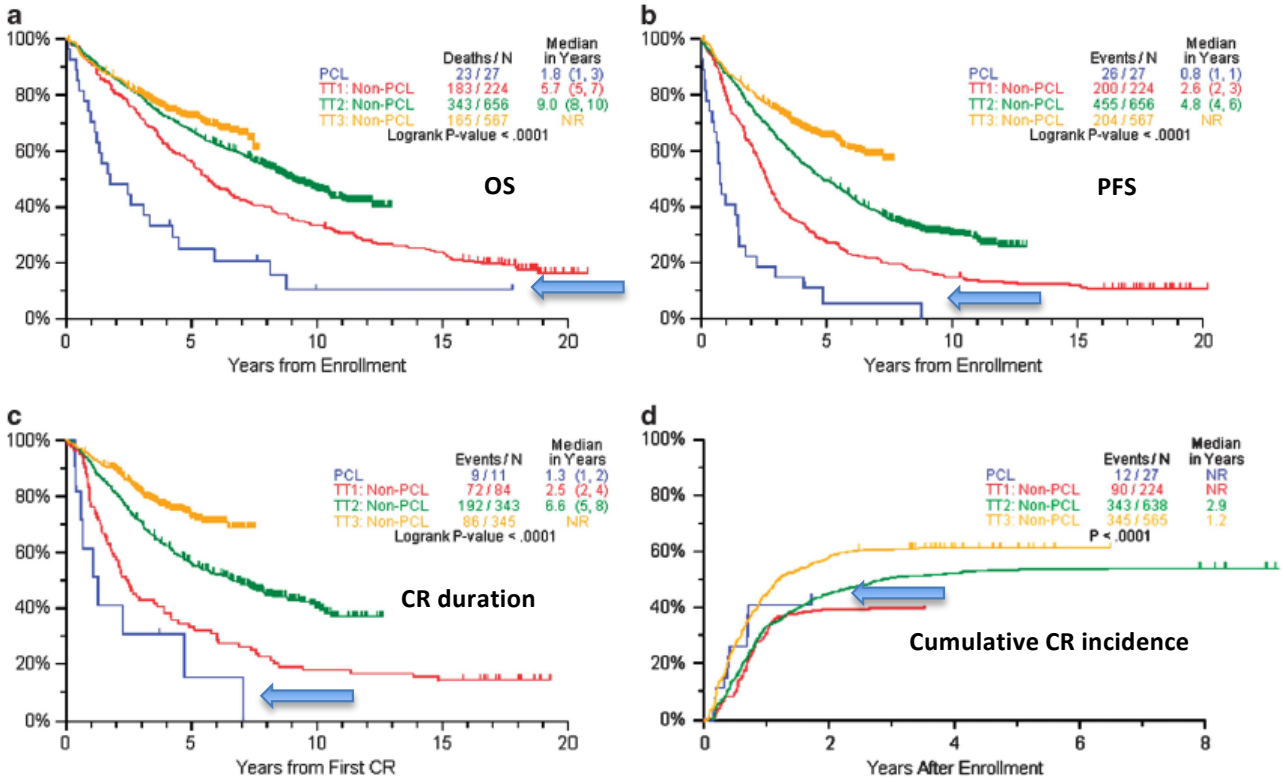

Figure 1. Clinical outcomes for PPCL and non-PPCL patients enrolled in TT1, TT2 or TT3. Although clinical outcomes improved in non-PPCL patients with successive TT protocols (TT1, TT2 and TT3), PPCL patients as a group continued to have significantly inferior OS (**a**) and PFS (**b**), CRD* (**c**) and cumulative incidence of CR (**d**). Because of small sample size, PPCL outcomes are not shown according to TT protocol. Note: seven patients enrolled in TT1 that achieved CR after disease progression were excluded from CRD, but were included in time-to-CR analyses. Blue, PPCL; red, TT1 non-PCL; green, TT2 non-PCL; yellow, TT3A/TT3B/TT3 like non-PCL.

Usmani et al, Leukemia 2012

Retrospective Italian and Greek experiences

original article

Annals of Oncology
doi:10.1093/annonc/mdr480

Frontline chemotherapy with bortezomib-containing combinations improves response rate and survival in primary plasma cell leukemia: a retrospective study from GIMEMA Multiple Myeloma Working Party

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Blood Cancer Journal

ARTICLE Open Access

Real-world data on prognosis and outcome of primary plasma cell leukemia in the era of novel agents: a multicenter national study by the Greek Myeloma Study Group

Eirini Katodritou[1], Evangelos Terpos[2], Sossana Delimpasi[3], Maria Kotsopoulou[4], Eurydiki Michalis[5], Chrysanthi Vadikolia[6], Marie-Christine Kyrtsonis[7], Argiris Symeonidis[8], Nikolaos Giannakoulas[9], Chrissa Vadikolia[10], Michalis Michael[11], Christina Kalpadakis[12], Theodora Gougopoulou[13], Chrystalla Prokopiou[14], Georgia Kaiafa[15], Dimitrios Christoulas[16], Maria Gavriatopoulou[2], Evlampia Giannopoulou[1], Vasiliki Labropoulou[8], Evgenia Verrou[1], Efstathios Kastritis[2], Pavlina Konstantinidou[1], Achilles Anagnostopoulos[5] and Meletios A. Dimopoulos[2]

Abstract
We have studied the efficacy and the prognostic impact of novel agents in 50 primary plasma cell leukemia (pPCL) patients registered in our database. Eighty percent of patients were treated upfront with novel agent-based combinations; 40% underwent autologous stem cell transplantation (ASCT). Objective response rate was 76; 38% achieved at least very good partial response (≥vgPR) and this correlated significantly with bortezomib-based therapy plus ASCT. At the time of evaluation, 40 patients had died. Early mortality rate (≤1 month) was 6%. Median progression-free survival (PFS) and overall survival (OS) were 12 months and 18 months respectively, both significantly longer in patients treated with bortezomib-based therapy + ASCT vs. others (PFS: 18 vs. 9 months; $p = 0.004$, OS: 48 vs. 14 months; $p = 0.007$). Bortezomib-based therapy + ASCT predicted for OS in univariate analysis. In multivariate analysis, achievement of ≥vgPR and LDH ≥ 300 U/L were significant predictors for OS. These real-world data, based on one of the largest reported national multicenter series of pPCL patients treated mostly with novel agents support that, among the currently approved induction therapies, bortezomib-based regimens are highly effective and reduce the rate of early mortality whereas in combination with ASCT consolidation they prolong OS.

Table 1. Response and survival

29 patients

Overall response rate	79%
Complete remission	8 (28%)
Very good partial remission	3 (10%)
Partial remission	12 (41%)
Alive patients[a]	16 (55%)
In remission	12
Relapsed	4
Transplanted patients	12
Alive	10 (83%)
Not-transplanted patients	17
Alive	6 (35%)

[a]Median follow-up: 24 months.

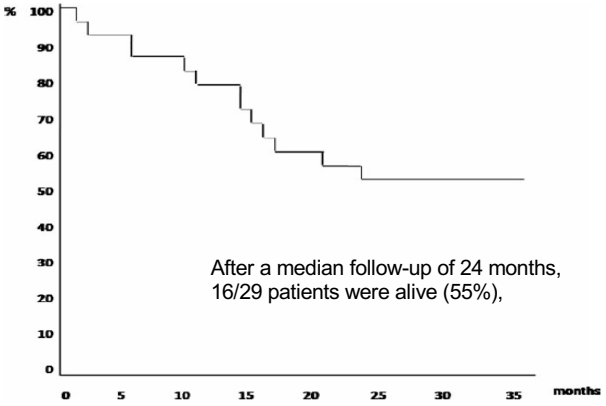

Figure 1. Overall survival in all patients with PPCL. PPCL, primary plasma cell leukemia.

Table 2 Response according to treatment

50 patients

Therapy	Patients, *n*	≥vgPR%	ORR%	vgPR, *n*	CR, *n*	PR, *n*	SD, *n*	PD, *n*
All treatments	50	38	76	11	8	19	3	9
Bortezomib-based, no ASCT	23	26	70	4	2	10	2	5
Bortezomib-based, +ASCT	15	73	100	6	5	4	-	-
Conventional treatment (including 2 MPT)	12	17	58	1	1	5	1	4

vgPR very good partial response, *ORR* objective response rate, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ASCT* autologous transplantation, *MPT* melphalan, prednisone, thalidomide

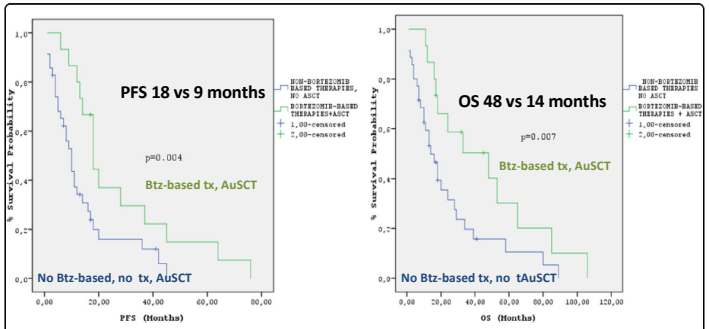

Fig. 2 a Progression-free survival (PFS) in patients treated with non-bortezomib based therapies, without autologous transplantation (blue curve) and patients treated with bortezomib-based regimens and autologous transplantation (green curve). **b** Overall survival (OS) in patients treated with treatments non- bortezomib based therapies without autologous transplantation (blue curve) and patients treated with bortezomib-based regimens and autologous transplantation (green curve)

Retrospective Israeli and US experiences

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Research paper

Primary plasma cell leukemia in the era of novel agents for myeloma – a multicenter retrospective analysis of outcome

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37 patients

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Immunomodulatory drugs (IMIDs)

ABSTRACT

Primary plasma cell leukemia (PPCL) is a rare form of multiple myeloma with a dismal prognosis. This retrospective multi-center study examines the national experience of PPCL in the era of novel agents. During 2002–2016, thirty-nine patients with PPCL were identified in 11 Israeli centers. One-fifth of them died in the first 2 months after diagnosis. The overall survival (OS) of those who survived the first 3 months was 22.5 months. About 70% of patients received at least one type of immunomodulatory drug (IMID) and similarly proteasome inhibitor (PI) during treatment. There was a survival advantage for those who received IMID but not for those who received PI or other type of standard dose chemotherapy. In multivariate analysis, low performance status and increased uric acid were also associated with shorter OS. In conclusion, this study demonstrates favorable impact of treatment with IMIDs and hematopoietic cell transplantation on the survival of PPCL patients.

Bone Marrow Transplantation
https://doi.org/10.1038/s41409-018-0392-1

ARTICLE

Primary plasma cell leukemia: autologous stem cell transplant in an era of novel induction drugs

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23 patients

Abstract
Primary plasma cell leukemia (pPCL) is a rare and aggressive variant of multiple myeloma (MM) with poor long-term survival after cytotoxic chemotherapy. Many novel drugs have revolutionized the treatment algorithms for MM. The impact of targeted therapy, both pre- and post-autologous stem cell transplant (auto-HCT) remains an area of ongoing interest. In this study, we report outcomes post auto-HCT for pPCL and the impact of maintenance therapy posttransplant with novel agents.

Table 2
Treatment and response.

Variable/group	Index	PPCL
Induction:		
Treatment at induction – novel agents	n (%)	
Bortezomib		25 (64)
Thalidomide.		3 (8)
Bortezomib + Thalidomide		5 (13)
No novel agents		6 (15)
Treatment at induction – chemotherapy		
Cyclophosphamide		26 (67)
Melphalan		6 (15)
Anthracycline		10 (26)
Best response to induction (N = 37)	n (%)	
PD		11 (30)
SD + MR		5 (14)
VGPR + PR		13 (35)
CR + SCR		8 (22)
ORR		21 (57)
Treatment during the entire course:	n (%)	
> PI		30 (77)
Bortezomib		28 (72)
Carfilzomib		6 (15)
Ixazomib		1 (3)
IMiD		26 (67)
Thalidomide		17 (44)
Revlimide		13 (33)
Pomalidomide		4 (10)
Lines of treatment (not include HSCT)	Median	2 (1–4)
HSCT	n (%)	19 (49)
Autologous		13 (35)
Allogeneic		1 (3)
Autologous + Autologous		1 (3)
Autologous + Allogeneic		4 (11)

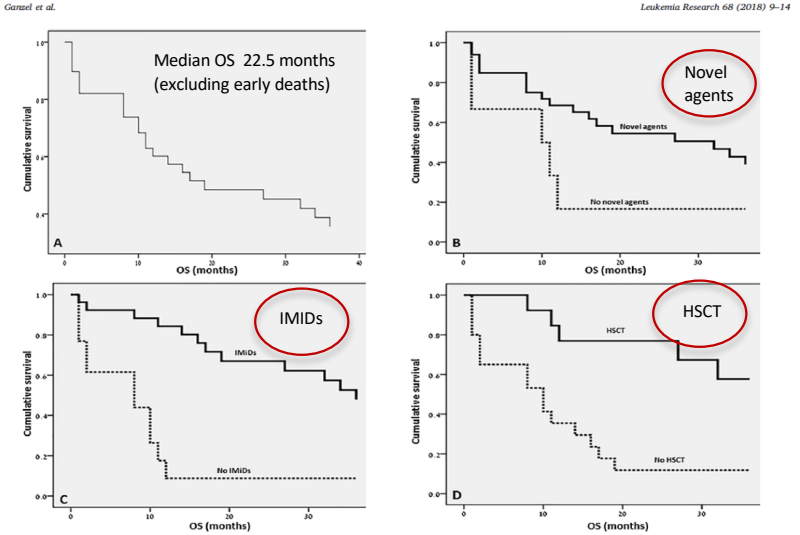
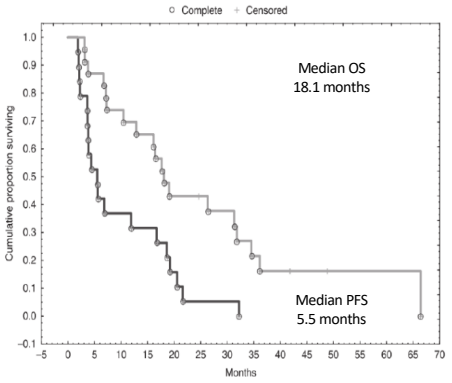
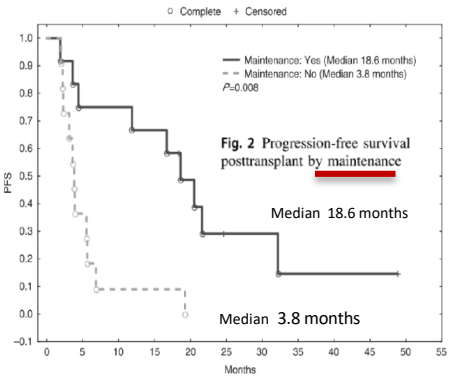
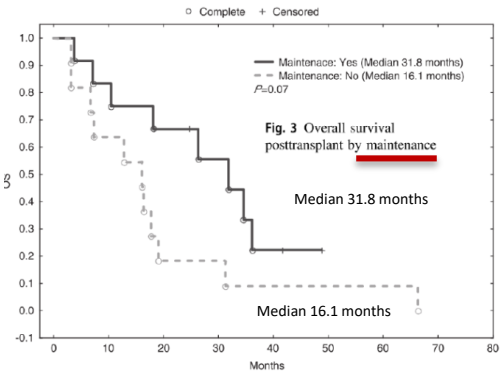


Fig. 1. Survival curves; the entire cohort (A), with vs. without novel agents (B), with vs. without IMiDs (C), with vs. without HSCT (D).







Winship Cancer Institute Emory University experience

Original Article

Survival Outcomes of Patients With Primary Plasma Cell Leukemia (pPCL) Treated With Novel Agents

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TABLE 1. First-Line Treatment

Regimen	No. of Patients (%)
Induction, n = 38	
VTD-PACE	16 (42)
RVD	15 (40)
VD-CEP	2 (5)
VTD	2 (5)
RVD-PACE	1 (2)
VTD-C	1 (2)
VD	1 (2)
Consolidation	
ASCT	28 (74)
Maintenance, n = 23	
RVD	14 (37)
KPd	3 (8)
KRd	1 (2)
PVd	1 (2)
IRd	1 (2)
Rd	1 (2)
Lenalidomide	1 (2)
Thalidomide	1 (2)

TABLE 2. Best Response to First-Line Treatment, n = 38

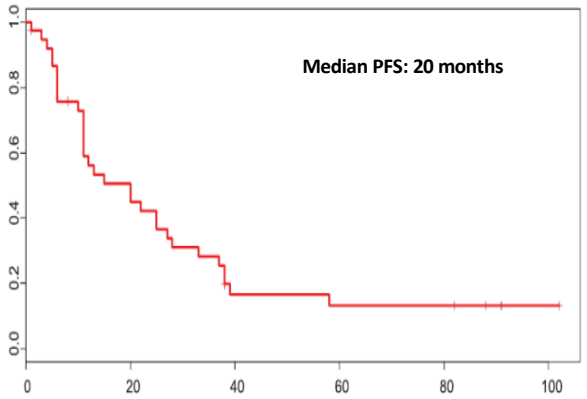
Response	No. of Patients (%)	
	After Induction	Best Response
sCR	—	7 (18)
CR	7 (18)	10 (26)
VGPR	10 (26)	9 (24)
PR	14 (37)	7 (18)
SD	4 (10)	2 (5)
PD	2 (5)	2 (5)
NA	1 (2)	1 (2)
ORR	31 (82)	33 (87)
≥VGPR	15 (45)	26 (68)

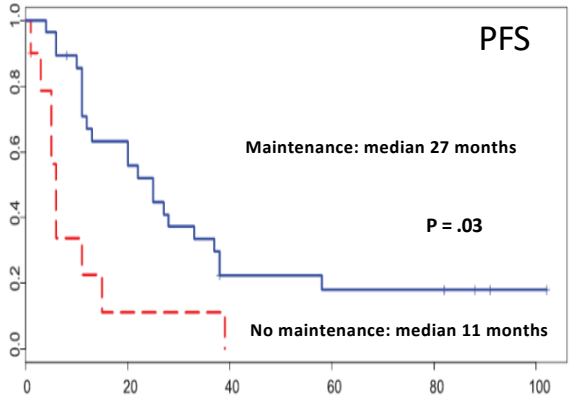
Abbreviations: CR, complete response; NA, not available; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

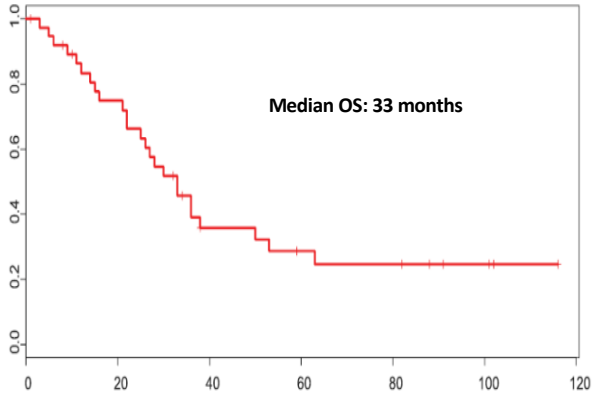
38 patients

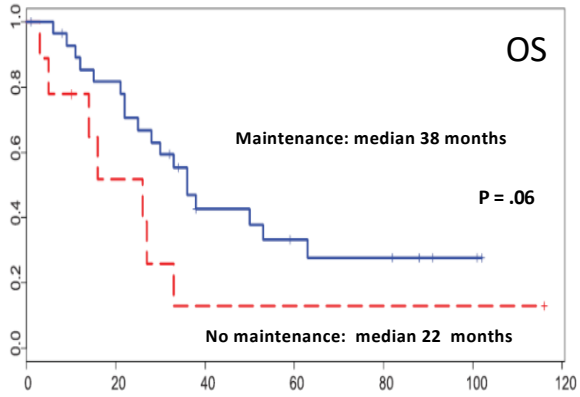
100% patients received a bortezomib-based induction regimen, 92% received both bortezomib and an IMIDs, 74% of patients underwent AuSCT, 61% received maintenance therapy.

- PFS was prolonged in patients who underwent ASCT compared with those who did not undergo ASCT (25 vs 6 months; P = .004)
- The achievement of ≥CR was a predictor for prolonged PFS and OS.









Mina et a, Cancer 2019

EBMT and CIBMTR Transplant studies in PPCL (1980-2009: limited use of novel agents)

Musto et al, Exp Rev Hematol 2019

Table 1. Registry studies with transplant procedures in PPCL

Author	Type of transplant	Number of subjects (median age, years)	Study group (period of analysis)	Conditioning regimen	Disease status at transplant	NRM	PFS and OS
Drake et al. [47]	AuSCT	272 (55)	EBMT (1980–2006)	Unspecified (TBI = 9 %)	CR = 25 %; PR = 59 %; NR/MR = 9 %; REL/PROG = 7 %	Reported increased with respect to registered myeloma patients undergoing AuSCT, but unspecified.	Median PFS = 14.3 months; Median OS = 25.7 months; 1-year OS = 69.3 %; 2-years OS = 54.1 %; 3-year OS = 39.5 %; 5-year OS = 27.2 %
Mahindra et al. [48••]	AuSCT	97 (56)	CIBMTR (1995–2006)	Melphalan-based = 91 %; TBI = 11 %	CR = 20 %; PR = 56 %; MR/SD = 14 %; REL/PROG = 1 %, Missing = 9 %	3-year = 5 %	3-year PFS = 34 %; 3-year OS = 64 %; 3-year PFS: single AuSCT = 36 %; double AuSCT = 37 %; 3-year OS: single AuSCT = 56 %; double AuSCT = 84 %
Morris et al. [50]	AuSCT	411 (56)	EBMT (1984–2009)	N/A	N/A	Reported lower than in 62 similar PPCL patients undergoing AlloSCT, but unspecified	12-month PFS = 51 %; 60-month PFS: 10 %; 12-month OS at 12 = 73 %; 60-month OS = 25 %
Mahindra et al. [48••]	AlloSCT	50 (48)	CIBMTR (1995–2006)	MAC = 68 %, NMA/RIC = 32 %	CR = 18 %; PR = 46 %; MR/SD = 8 %	MAC 3-year = 41 %, NMA/RIC 3-year = 42 %	3-year PFS = 20 %; 3-year OS = 39 %; 3-year PFS: MAC = 21 %; NMA/RIC = 18 %; 3-year OS: MAC = 32 %; NMA/RIC = 56 %
Morris et al. [50]	AlloSCT	85 unselected (N/A); MAC (46), RIC (53)	EBMT (1984/1998–2009)	MAC = 45, RIC = 17	N/A	Reported higher than in 411 similar PPCL patients undergoing AuSCT, but unspecified	12-month PFS: MAC = 39 %; RIC = 43 %: 60-month PFS : MAC = 19 %; RIC = 11 %; 12-month OS: MAC = 46 %; RIC = 59 %; 60-month OS: MAC = 27 %; RIC = 19 %. Plateau phase seen at 20 %

AlloSCT allogeneic stem cell transplantation; *AuSCT* autologous stem cell transplantation; *CIBMTR* Center for Instrumental Blood and Marrow Transplant Research; *CR* complete response; *EBMT* European Group for Blood and Marrow Transplantation; *MAC* myeloablative conditioning; *MR* minimal response; *N/A* not available; *NMA* non-myeloablative conditioning; *NR* no response; *NRM* non-relapse mortality; *OS* overall survival; *PFS* progression-free survival; *PPCL* primary plasma cell leukemia; *PR* partial response; *PROG* progressive disease; *RIC* reduced intensity conditioning; *REL* relapsed disease; *SD* stable disease; *TBI* total body irradiation; *VGPR* very good partial response

AuSCT

- *Three registry studies of 711 PPCL patients transplanted between 1980 and 2009 (limited use of new drugs!): higher rates of CR achived with AuSCT than in MM.*
- *AuSCT 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 OS in patients who underwent double versus single AuSCT.*

AlloSCT

- *Variable efficacy and safety of AlloSCT described in small retrospective series.*
- *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.*

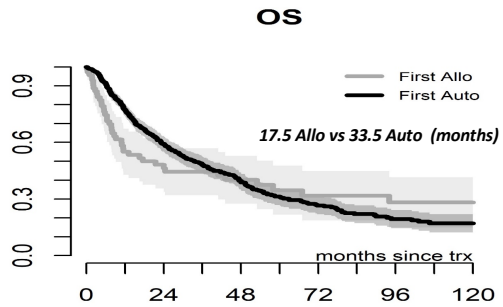
Results of Autologous and Allogeneic Transplantation in Patients with Primary Plasma Cell Leukemia: A Large Retrospective Analysis of the Chronic Malignancies Working Party of the EBMT Malignancies

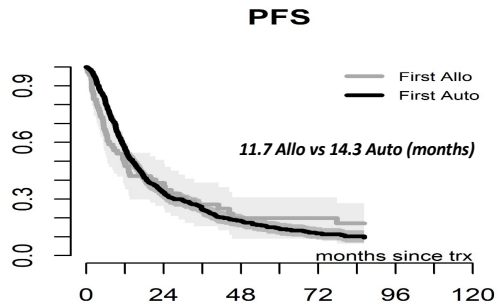
Sarah Lawless, MB BCH BAO (Hons), MRCP, FRCPath[1*], Simona Iacobelli, PhD[2*], Nina Knelange[3*], Patrice Chevallier, MD[4], Didier Blaise[5], Noel-Jean Milpied, MD[6], Robin Foà, MD[7], Jan J Cornelissen, MD, PhD[8], Bruno Lioure, MD[9*], Victoria Potter[10*], Xavier Poire, MD[11*], Eefke J. Petersen, MD, PhD[12], Matthew P. Collin, MD, PhD[13], Stig Lenhoff[14*], John Snowden[15*], Stella Santarone, MD[16*], Keith Wilson, FRCPath, MRCP, MBBS[17*], Jose E. Guimaraes, MD, PhD[18], Peter Dreger[19], Martin R. Schipperus[20*], Curly Morris[21*], Stefan Schönland[22*], Ibrahim Yakoub-Agha, MD, PhD[23], Laurent Garderet[24] and Kroger Nicolaus, MD phD[25]

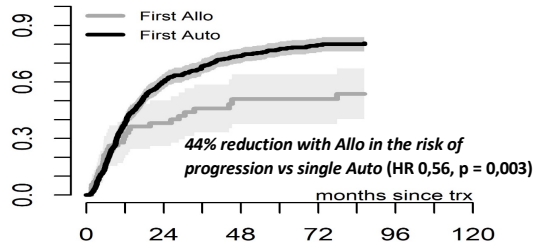
- *A retrospective analysis of EBMT of 751 patients with pPCL undergoing transplantation between 1998 and 2014.*

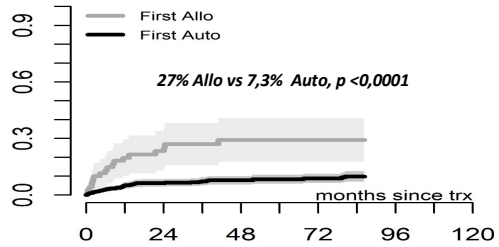
- *70 Allo as first transplant.*
- *681 Auto as first transplant*
- *239 elective double transplant:*

✓ *122 tandem Auto/Allo*
✓ *117 double Auto*









- ***AlloSCT upfront has worse outcome in the short term**, argely due to significant NRM.*
- *However, landmark analysis and dynamic prediction models indicated that the **sequence of AutoSCT followed by AlloSCT had an acceptable NRM and a lower relapse rates, translating into a better PFS, with and a favorable trend for OS with longer follow-up at 3-year,** though not statistically significant* (HR 0.78, p=0.20) with respect to single AuSCT
- **No data clear regarding the comparison of AlloSCT vs double AuSCT.**

ASH Meeting 2018 abs. 3425

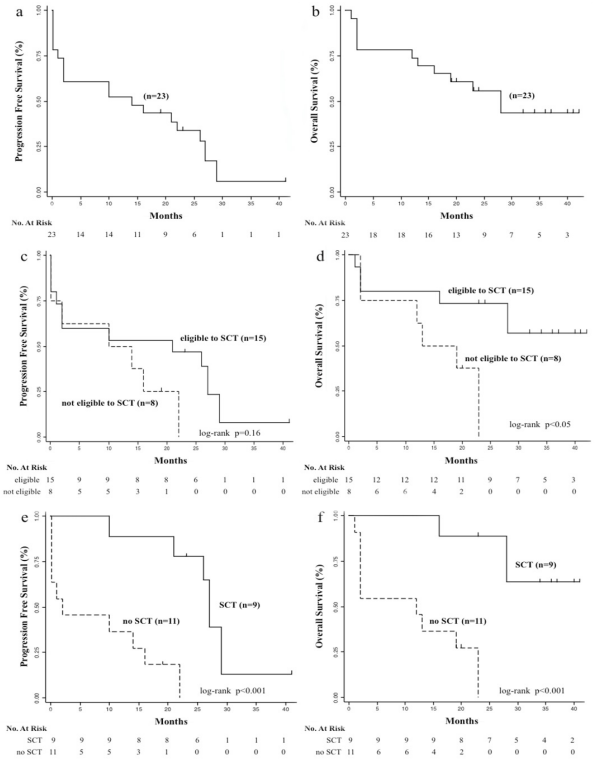
Prospective studies with novel agents and transplant procedures in PPCL

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

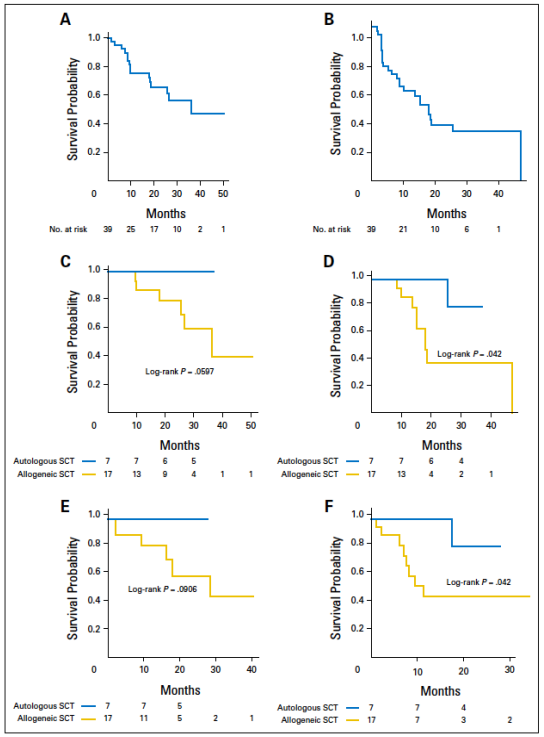
	GIMEMA study (19)	IFM study (18)
N. patients	23	40
Median age (range)	60 (44–80)	57 (27–71)
Induction	Ld (4 cycles for younger, 8 cycles for elderly patients)	PAD/VCD (2 + 2 cycles)
Consolidation	AuSCT (in eligible patients)	Double AuSCT or, in patients <66 years with a matched donor, tandem AuSCT/AlloSCT (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



OS ≥ 3 years in two prospective studies, which have integrated novel agents and AuSCT.

What about current treatments in PPCL?

References	Patients (n.)	AuSCT (%)	Treated with novel agents (%)	ORR with novel agents (%)	≥ VGPR with novel agents (%)	CR with novel agents (%)	Median PFS with novel agents (months)	Median OS with novel agents (months)
Prospective trials								
Musto et al. [24]	23	39%	100%	74%	39%	13%	14 (27 with AuSCT vs 2 w/o AuSCT	28 (not reached at 34 months with AuSCT vs 12 w/o AuSCT)
Royer et al. [25]	39	100%	100%	69%	36%	10%	15.1 (not reached at 28.7 months with double AuSCT vs 17.9 with tandem AuSCT/AlloSCT)	36.3 (not reached at 28.7 months with double AuSCT vs 36.3 with tandem AuSCT/AlloSCT)
Retrospective, observational studies								
Iriuchishima et al. [39]	38	NA	61%	67%	50%	NA	NA	34.2 (53.4 with maintenance vs 34.2 w/o maintenance after AuSCT)
Jung et al. [41]	59	37%	61%	75%	42%	22% after induction, 32% after AuSCT)	12.9 (26.4 with AuSCT vs 9 w/o AuSCT)	18.5 (31.1 with AuSCT vs 12.3 w/o AuSCT)
Katodritou et al. [33]	50	32%	80%	82%	45%	18%	12 (18 with btz + AuSCT vs 9 in others)	18 (48 with btz + AuSCT vs 14 in others)
Jurczyszyn et al. [34]	106	52%	92%	79%	44%	21%	NA	23 (35 with AuSCT vs 13 w/o AuSCT)
Ganzel et al. [35]	37	51%	85%	57% (all patients)	43% (all patients)	22% (all patients)	NA	22.5 (all patients, excluding early deaths; 35.5 with AuSCT)
Nakaya et al. [36]	23	39%	87%	75%	NA	0%	NA	34 (40 with AuSCT, 55 with AlloSCT, 61 with tandem AuSCT/Allo/SCT vs 28 w/o any transplant
Mina et al. [40]	38	74%	100%	87%	68%	45%	20 (25 with AuSCT vs 6 w/o AuSCT; 27 with AuSCT and maintenance vs 11 with AuSCT w/o maintenance	33 (38 with AuSCT and maintenance vs 22 with AuSCT w/o maintenance)
Gowda et al. [42]	23	100%	100%	65%	43% after induction, 47% after AuSCT,	13% after induction, 26% after AuSCT	5.5 (18.6 with maintenance vs 3.8 w/o maintenance	18.1 (31.8 with maintenance vs 16.1 w/o maintenance)

Overall, the introduction of ***bortezomib and lenalidomide as initial therapy*** *and, particularly,* ***their integration within stem cell transplant programs,*** *have produced:*

- *A* ***marked increase in rate and quality of response*** *(ORR 57%-100%; at least VGPR 28.5%-45%)*
- ***A moderate, but significant improvement in the clinical outcome*** *of PPCL, particularly reducing the rate of early deaths and allowing OS of 12-28 months in elderly patients, and of 16-61 months in patients undergoing transplant procedures*

Musto et al, Exp Rev Hematol 2019

EMN Recommendations for the treatment of Primary Plasma Cell Leukemia

Leukemia
https://doi.org/10.1038/s41375-018-0209-7

REVIEW ARTICLE

Multiple myeloma gammopathies

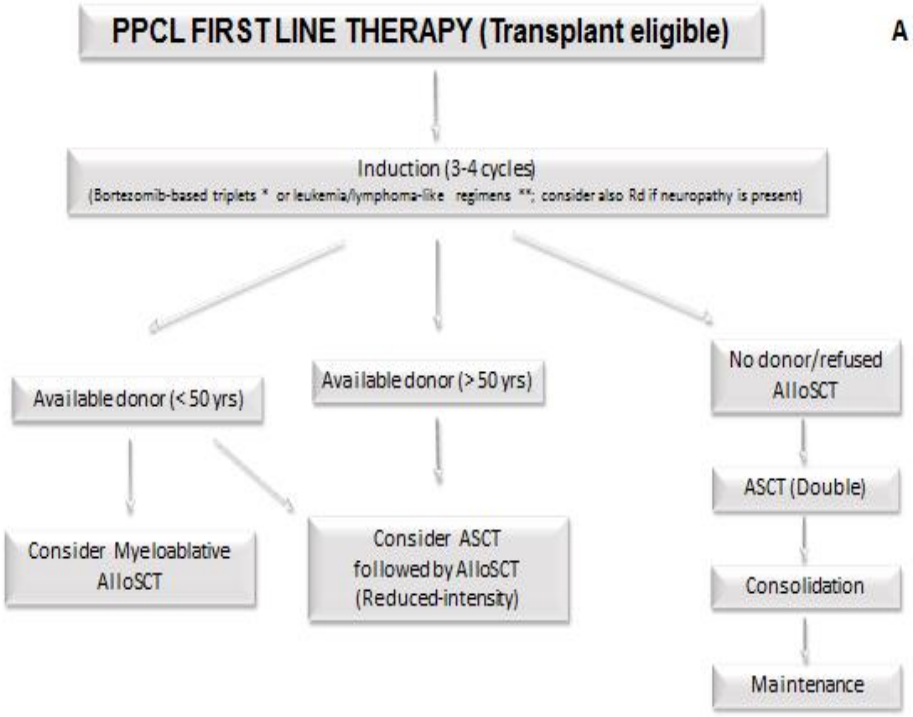
European myeloma network recommendations on diagnosis and management of patients with rare plasma cell dyscrasias

Maria Gavriatopoulou[1] · Pellegrino Musto[2] · Jo Caers[3] · Giampaolo Merlini[4] · Efstathios Kastritis[1] · Niels van de Donk[5] · Francesca Gay[6] · Ute Hegenbart[7] · Roman Hajek[8] · Sonja Zweegman[5] · Benedetto Bruno[6] · Christian Straka[9] · Meletios A. Dimopoulos[1] · Hermann Einsele[10] · Mario Boccadoro[6] · Pieter Sonneveld[11] · Monika Engelhardt[12] · Evangelos Terpos[1]

Received: 21 April 2018 / Revised: 28 May 2018 / Accepted: 7 June 2018

- *There are no precise, evidence-based guidelines for the treatment of PPCL. In particular, no randomized, phase III trials have been performed in PPCL, while only two prospective, phase II studies have been published so far.*
- *Overall, PPCL therapy should be immediate with short treatment-free intervals in order: i) to ensure rapid disease control and reduction of early deaths due to initial complications; ii) contrast clonal evolution that may induce drug resistance; and iii) have activity on residual disease by decreasing the risk of relapse.*
- *Prevention of tumor lysis syndrome, bisphosphonates and anti-infective prophylaxis are recommended in all patients.*
- *Intrathecal prophylaxis should be also considered for patients at high risk of CNS infiltration (i.e. those with a high WBC count).*
- *Thromboprophylaxis should be given in patients receiving IMIDs.*

EMN Recommendations for the treatment of Primary Plasma Cell Leukemia



* VRD (bortezomib, lenalidomide, dexamethasone); VTD (bortezomib, thalidomide, dexamethasone; PAD (bortezomib, doxorubicin, dexamethasone).

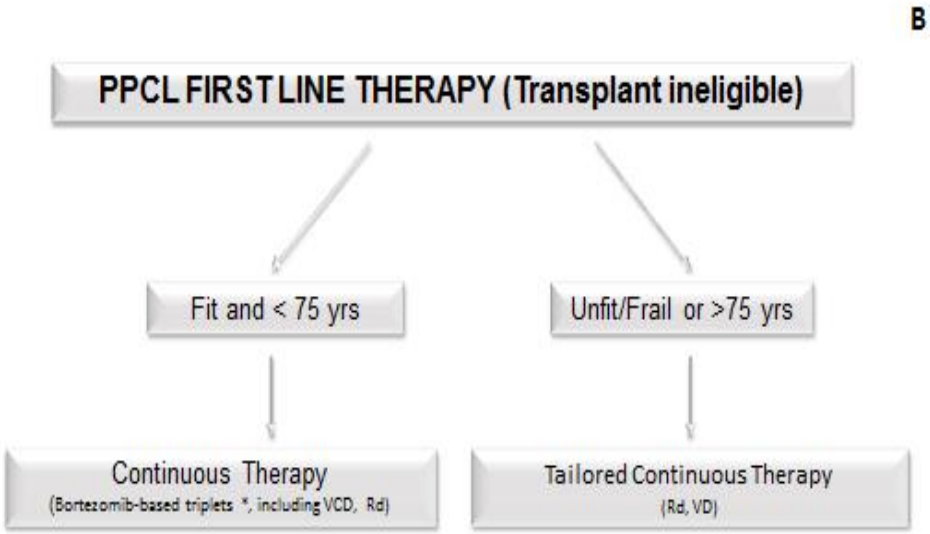
** HyperCVAD-VD (hyperfractionated cyclophosphamide, vincristine, continue-infusion doxorubicin, bortezomib, dexamethasone; VTD/VRD-PACE (bortezomib, thalidomide, lenalidomide dexamethasone, continue infusion cisplatin, doxorubicin, cyclophosphamide, etoposide).

AlloSCT: allogeneic stem cell transplantation; ASCT: autologous stem cell transplantation; Rd: lenalidomide, low-dose dexamethasone; VD: bortezomib and dexamethasone;

- *First line therapy for younger patients should be initially oriented toward a PI and IMID-based triplet as induction (1B).*
- *After induction phase, the treatment should ideally include double AuSCT, consolidation, and maintenance in all eligible patients (1B).*
- *Frontline AlloSCT should be considered in selected cases (1B).*
- *AlloSCT may be potentially curative, but the results obtained upfront do not show a clear significant OS advantage respect to AuSCT. Pros and cons of front-line Allo-SCT should be therefore carefully discussed with eligible patients (younger individuals with poor prognosis characteristics at baseline, but who have achieved a good response to first-line induction treatment).*

EMN recommendations on diagnosis and management of patients with rare plasma cell dyscrasias, Leukemia 2018

EMN Recommendations for the treatment of Primary Plasma Cell Leukemia

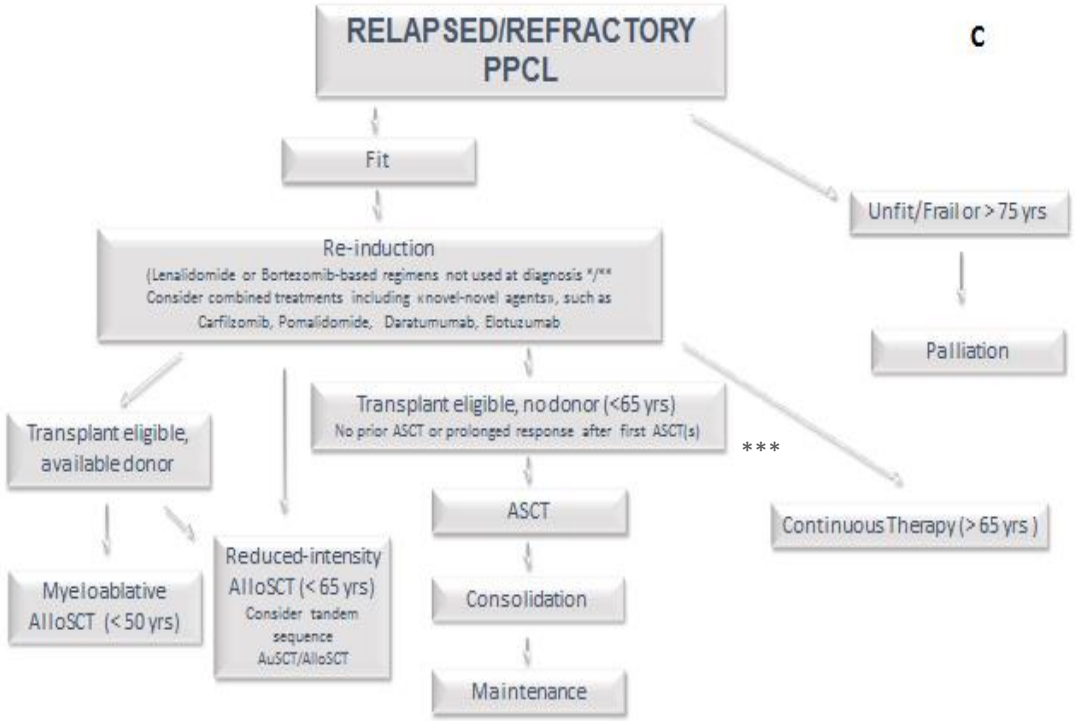


- *The expert panel suggests that aged, but still fit patients not eligible for transplant procedures, should be planned for continuous therapy, ideally until response is maintained or significant toxicities occur.*
- *In very old and/or frail individuals, personalized treatments (i.e. dose and time adjusted combinations of lenalidomide or bortezomib plus dexamethasone) should be given according to efficacy and tolerability, aiming to maintain patients on therapy as long as possible.*

* VRD (bortezomib, lenalidomide, dexamethasone); VTD (bortezomib, thalidomide, dexamethasone; PAD (bortezomib, doxorubicin, dexamethasone).,VCD (bortezomib, cyclophosphamide, dexamethasone)..

EMN recommendations on diagnosis and management of patients with rare plasma cell dyscrasias, Leukemia 2018

EMN Recommendations for the treatment of Primary Plasma Cell Leukemia



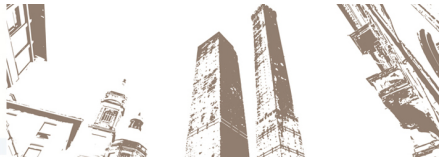
- *In relapsed/refractory PPCL a switch to drugs not used at diagnosis should be considered, favouring continuative combinations of lenalidomide or pomalidomide plus dexamethasone with carfilzomib or monoclonal antibodies (daratumumab or elotuzumab) (expert consensus).*
- *AlloSCT in relapsed and eligible patients with sensitive disease after salvage treatments is recommended (1B).*
- *Palliation*

*/** VRD (bortezomib, lenalidomide, dexamethasone); VTD (bortezomib, thalidomide, dexamethasone; PAD (bortezomib, doxorubicin, dexamethasone).,VCD (bortezomib, cyclophosphamide, dexamethasone)..

*** Also explore the feasibility of a other emerging approaches employed in multiple myeloma, such as venetoclax, particularly for PPCL with t(11;14), nuclear exportin-1 selinexor, or CAR-T cells.

EMN recommendations on diagnosis and management of patients with rare plasma cell dyscrasias, Leukemia 2018

Plasma Cell Leukemia (therapy) at IMW 2019



OAB-033

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

Authors:
Chunrui Li[1], Xiaoxi Zhou[1], Jue Wang[1], Guang Hu[2], yongkun yang[2], Li Meng[1], Zhenya Hong[1], Liting Chen[1], Jianfeng Zhou[1]

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SP-095

Consolidation following DPACE therapy improves outcomes in relapsed/refractory myeloma patients in the era of novel agents

Authors:
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Institutions:
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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

Authors:
James Berenson[1], Daisy Martinez[1], Tanya Spektor[1], Armando Sanchez[1], Matthew Ghermezi[2], Regina Swift[2], Benjamin Eades[3], Gary Schwartz[3], Shahrooz Eshaghian[4], Stephen Lim[5], Robert Vescio[6]

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SP-092

KD-PACE salvage therapy for aggressive relapsed multiple myeloma

Authors:
Shelton Harrell[1], Muhammad Khan[2], Binod Dhakal[2], Hari Parameswaran[2], Robert Cornell[1]

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OAB-062

Profound MRD negativity rates after frontline tandem autologous-allogeneic stem cell transplantation followed by bortezomib maintenance in high-risk or young myeloma patients

Authors:
Richard LeBlanc[1], Imran Ahmad[1], Rafik Terra[1], Séverine Landais[1], Céline Nkoué[1], Michael Sebag[2], Émilie Lemieux-Blanchard[3], Nadia Bambace[1], Léa Bernard[1], Sandra Cohen[1], jean-Sébastien Delisle[1], Thomas Kiss[1], Silvy Lachance[1], Denis-Claude Roy[1], Guy Sauvageau[1], Jean Roy[1]

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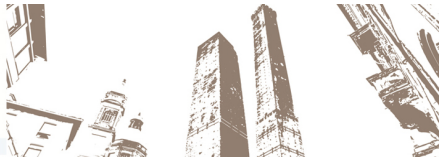
«Pre-»
61st ASH 2019
ANNUAL MEETING& EXPOSITION
7 TO 10 DECEMBER ORLANDO,FL

Primary Plasma Cell Leukemia Outcomes Remain Dismal Despite Novel Agents and Hematopoietic Cell Transplantation



- *O*utcomes of pPCL patients receiving **novel agents with autologous (AuSCT) or allogeneic (AlloSCT**) approaches as reported to the Center for International Blood and Marrow Transplant Research **(CIBMTR) from 2008 to 2015**
- **348 pPCL pts** underwent SCT (N = **277 AuSCT and 71 AlloSCT)** with 45% and 48% having research level data available, respectively
- Cumulative incidences of **non-relapse mortality (NRM)** and **relapse/progression (REL),** and probability of **progression-free survival (PFS)** and **overall survival (OS)** were calculated
- **Median follow-up in AuSCT and AlloSCT was 48 and 60 months,** respectively

AuSCT Cohort

- Median age was 60 years, 35% had high risk cytogenetics
- 93% received AuSCT within 12 months of diagnosis with 76% after a single line of induction
- 23% received bortezomib, doxorubicin, cisplatin, cyclophosphamide, and etoposide (VDPACE)
- 40% received bortezomib (BTZ) and immunomodulatory drug (IMIID)-based triplets
- Disease status at AuSCT was VGPR or better in 47%
- 27% maintenance therapy

AlloSCT Cohort

- Median age was 53 years, 42% had high-risk cytogenetics
- 89% received AlloSCT within 12 months of diagnosis
- 61% received a single AlloSCT, while 39% used AuSCT-AlloSCT tandem approach
- Use of VDPACE was at 41% in this cohort
- VGPR status at AlloSCT 48%, maintenance in 12%
- 61% received TBI, with 44% receiving myeloablative conditioning
- Grade II-IV acute GVHD occurred in 30% and chronic GVHD in 45%

Patel et al, Oral presentation ASH MEETING 2019, abstract 266

Primary Plasma Cell Leukemia Outcomes Remain Dismal Despite Novel Agents and Hematopoietic Cell Transplantation

At 4 years post-AuSCT:

- NRM 7% (4-11%)
- REL 76% (69-82%)
- PFS 17% (13-23%)
- OS 28% (22-35%)

At 4 years post-AlloSCT

- NRM 12% (5-21%)
- REL 69% (56-81%)
- PFS 19% (10-31%)
- OS 31% (19-44%

Figure 1A: Probability of progression-free survival after HCT – by transplant type

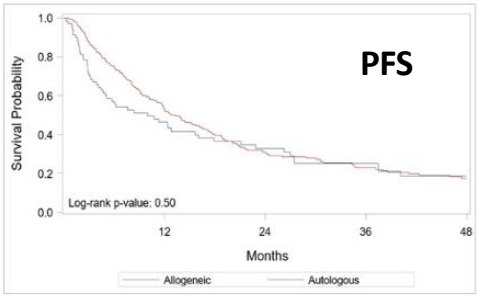
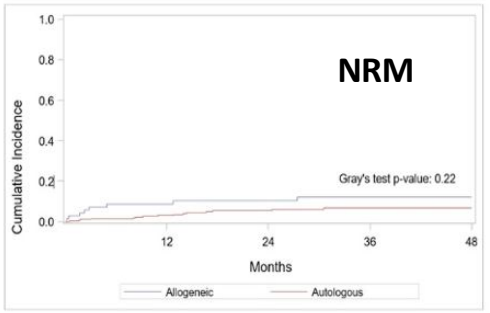


Figure 2A: Cumulative incidence of non-relapse mortality after HCT – by transplant type



- There were **no differences in outcomes based on type of HCT.**
- Disease status **≥VGPR and Karnofsky PS >90** significantly predicted superior OS after AuSCT in multivariate analysis.
- Analysis of SEER (1995-2009) and CIBMTR databases showed that use of **HCT increased** from 12% (7-21%) in 1995 to 46% (34-64%) in 2009.
- A comparison of post-HCT outcomes of CIBMTR pPCL patients from 1995 to 2006 showed that **PFS and OS outcomes are inferior despite lower NRM** in this modern cohort.

Figure 1B. Probability of overall survival after HCT – by transplant type

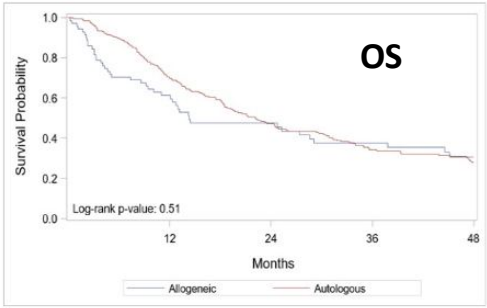
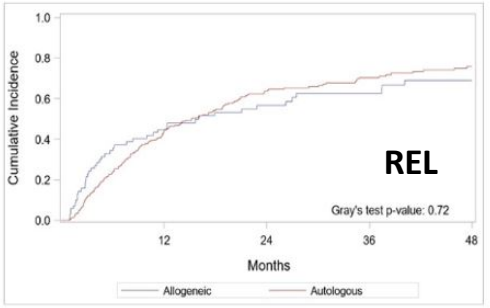
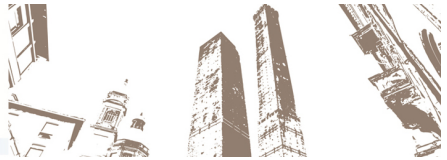


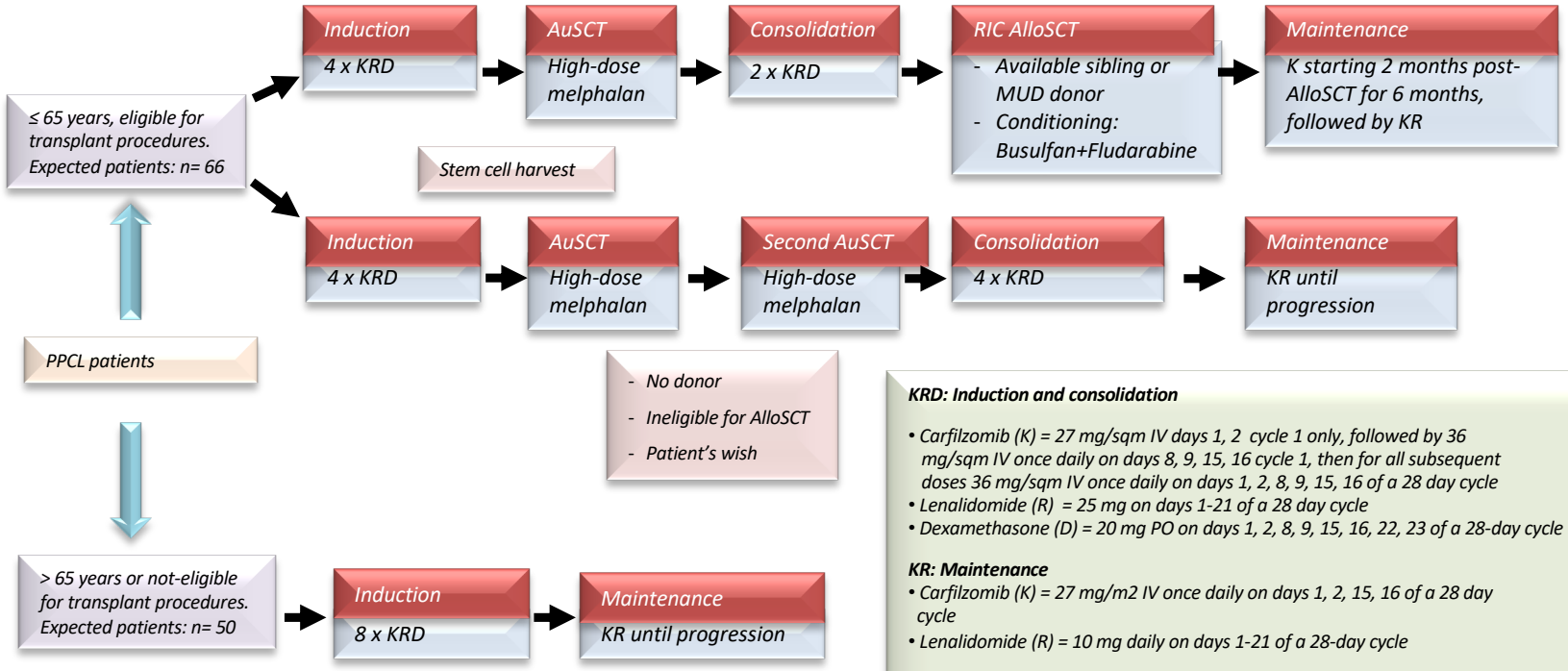
Figure 2B: Cumulative incidence of relapse after HCT – by transplant type



Patel et al, Oral presentation ASH MEETING 2019, abstract 266

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





KRD: Induction and consolidation

- *Carfilzomib (K) = 27 mg/sqm IV days 1, 2 cycle 1 only, followed by 36 mg/sqm IV once daily on days 8, 9, 15, 16 cycle 1, then for all subsequent doses 36 mg/sqm IV once daily on days 1, 2, 8, 9, 15, 16 of a 28 day cycle*
- *Lenalidomide (R) = 25 mg on days 1-21 of a 28 day cycle*
- *Dexamethasone (D) = 20 mg PO on days 1, 2, 8, 9, 15, 16, 22, 23 of a 28-day cycle*

KR: Maintenance

- *Carfilzomib (K) = 27 mg/m2 IV once daily on days 1, 2, 15, 16 of a 28 day cycle*
- *Lenalidomide (R) = 10 mg daily on days 1-21 of a 28-day cycle*

High dose melphalan

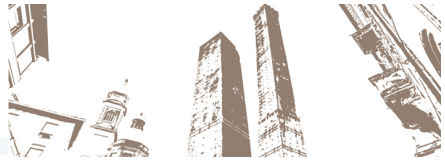
- *200 mg/sqm*

BIOLOGICAL STUDIES

- *Minimal residual disease (MRD):: Multiparametric flow cytometry (MFC) and molecular: VDJ sequencing or allele-specific oligonucleotide PCR*
- *Gene expression profiling (GEP)*
- *Gene copy number analysis on purified primary plasma cells*
- *Exome sequencing*

A total of 42 patients have been registered in the trail up to November, 11, 2019, 15 aged 66 years and 27 in the other group (18-65 years);

Treatment of primary plasma cell leukemia with carfilzomib and lenalidomide-based therapy: Results of the first interim analysis of the phase 2 EMN12/HOVON129 study



- *First planned interim analysis for **patients aged ≤ 65 years** to describe ORR and toxicity of induction therapy for the first 15 registered patients*
- ***14/15 patients received the planned 4 cycles of KRD** induction treatment, one patient had progressive disease after cycle 3*
- *After 4 KRd induction cycles, **≥ PR was achieved by 14 pts (93%), at least VGPR by 12 (80%), (stringent) CR by 5 (33%)***
- ***Adverse events mainly occurred during the first cycle** and decreased thereafter*
- ***Two grade 3** (1 infection, 1 myocardial infarction; one grade 2 (heart failure); **hematological toxicity was limited and manageable***
- ***No patient discontinued because of toxicity, mortality during induction was 0%***

Van De Donk et al, Oral presentation ASH MEETING 2019, abs. 693

Treatment of primary plasma cell leukemia with carfilzomib and lenalidomide-based therapy: Results of the first interim analysis of the phase 2 EMN12/HOVON129 study

- *First planned interim analysis for **patients aged > 65 years** to describe ORR and toxicity of induction therapy (four cycles) for the first 15 registered patients*
- **Four patients went off protocol (27%):** three during cycle 1, due to toxicity (2) and death (1); one during cycle 3 due to withdrawal of consent
- **SAEs occurred in 13/15 patients: 5 SAEs were fatal;** one during cycle 1, one during cycle 7, two on maintenance and one within 30 days from date of discontinuation
- ITT respone rates are promising **(ORR 80% during the cycle 1-4): 2 patients achieved PR (13%), 4 sCR (27%), 6 VGPR (40%)**

6 Efficacy analysis

6.1 Best response on induction cycles 1-4

Response	number	percentage
Total	15	100
Best response on CRd 1-4		
sCR	4	27
VGPR	6	40
PR	2	13
Not Available	3	20
At least VGPR on CRd 1-4		
no	5	33
yes	10	67
At least PR on CRd 1-4		
no	3	20
yes	12	80

3 patients went off protocol during first cycle before response evaluation

Key messages

- *Novel agents and, above all, their integration within stem cell transplant programs have recently produced a marked increase in rate and quality of response and a moderate, but significant improvement in OS in PPCL patients*

- *These results, however, still remain unsatisfactory, so patients with PPCL should always be considered for clinical trials, preferably in prospective studies designed for MM, with a dedicate plan to extrapolate specific data, end points and ad hoc analyses.*

ClinicalTrials.gov Search Results 09/16/2019

NCT Number	Title	Status	Study Results	Characteristics
NCT04008888	a Clinical Trial of Efficacy and Safety of the Holistic Treatment of Young High-risk Multiple Myeloma Patients	Recruiting	No Results Available	Phase: Not Applicable
NCT02858999	Treatment of Primary Plasma Cell Leukaemia in Subjects Under the Age of 70	Completed	No Results Available	Phase: Phase 2
NCT02547662	Pomalidomide, Ixazomib Citrate, and Dexamethasone in Treating Patients With Previously Treated Multiple Myeloma or Plasma Cell Leukemia	Recruiting	No Results Available	Phase: Phase 2
NCT02506959	Panobinostat, Gemcitabine Hydrochloride, Busulfan, and Melphalan Before Stem Cell Transplant in Treating Patients With Refractory or Relapsed Multiple Myeloma	Recruiting	No Results Available	Phase: Phase 2
NCT02504359	Combination Chemotherapy and Donor Stem Cell Transplant Followed by Ixazomib Citrate Maintenance Therapy in Treating Patients With Relapsed High-Risk Multiple Myeloma	Active, not recruiting	No Results Available	Phase: Phase 1
NCT02334865	SVN53-67/M57-KLH Peptide Vaccine in Treating Patients With Newly Diagnosed Multiple Myeloma Receiving Lenalidomide Maintenance Therapy	Recruiting	No Results Available	Phase: Phase 1
NCT01729091	Umbilical Cord Blood-Derived Natural Killer Cells, Elotuzumab, Lenalidomide, and High Dose Melphalan, Followed by Stem Cell Transplant in Treating Patients With Multiple Myeloma	Active, not recruiting	No Results Available	Phase: Phase 2
NCT01658904	Carfilzomib and Stem Cell Transplant for Plasma Cell Myeloma	Terminated	Has Results	Phase: •Phase 1 •Phase 2
NCT01372540	Filanesib and Carfilzomib in Treating Patients With Relapsed or Refractory Multiple Myeloma or Plasma Cell Leukemia	Completed	No Results Available	Phase: Phase 1
NCT01248923	A Study of ARRY-520 and Bortezomib Plus Dexamethasone in Patients With Relapsed/ Refractory Multiple Myeloma	Completed	No Results Available	Phase: Phase 1
NCT01163357	Bortezomib, Total Marrow Irradiation, Fludarabine Phosphate, and Melphalan in Treating Patients Undergoing Donor Peripheral Blood Stem Cell Transplant For High-Risk Stage I or II Multiple Myeloma	Active, not recruiting	No Results Available	Phase: Phase 1

NCT Number	Title	Status	Study Results	Characteristics
NCT00821249	A Study of ARRY-520 in Patients With Relapsed or Refractory Multiple Myeloma	Completed	No Results Available	Phase: •Phase 1 •Phase 2
NCT00615589	Stem Cell Transplantation To Treat High Risk Multiple Myeloma With Reduced Toxicity Myeloablative Conditioning Regimen	Terminated	Has Results	Phase: Phase 2
NCT00307086	Bortezomib Followed by High-Dose Melphalan and Bortezomib as Conditioning Regimen for Tandem Stem Cell Transplants	Completed	Has Results	Phase: Phase 2
NCT00258245	Arsenic Trioxide and Ascorbic Acid Combined With Bortezomib, Thalidomide, and Dexamethasone in Treating Patients With Relapsed or Refractory Multiple Myeloma or Plasma Cell Leukemia	Completed	No Results Available	Phase: Phase 1