Carfilzomib and lenalidomide-based treatment for younger and elderly newly diagnosed primary plasma cell leukemia patients

A European Intergroup Trial of the European Myeloma Network EMN (EMN12/HO129 PCL)

PROTOCOL

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9-jan-2017

Signature of Principal Investigator Date

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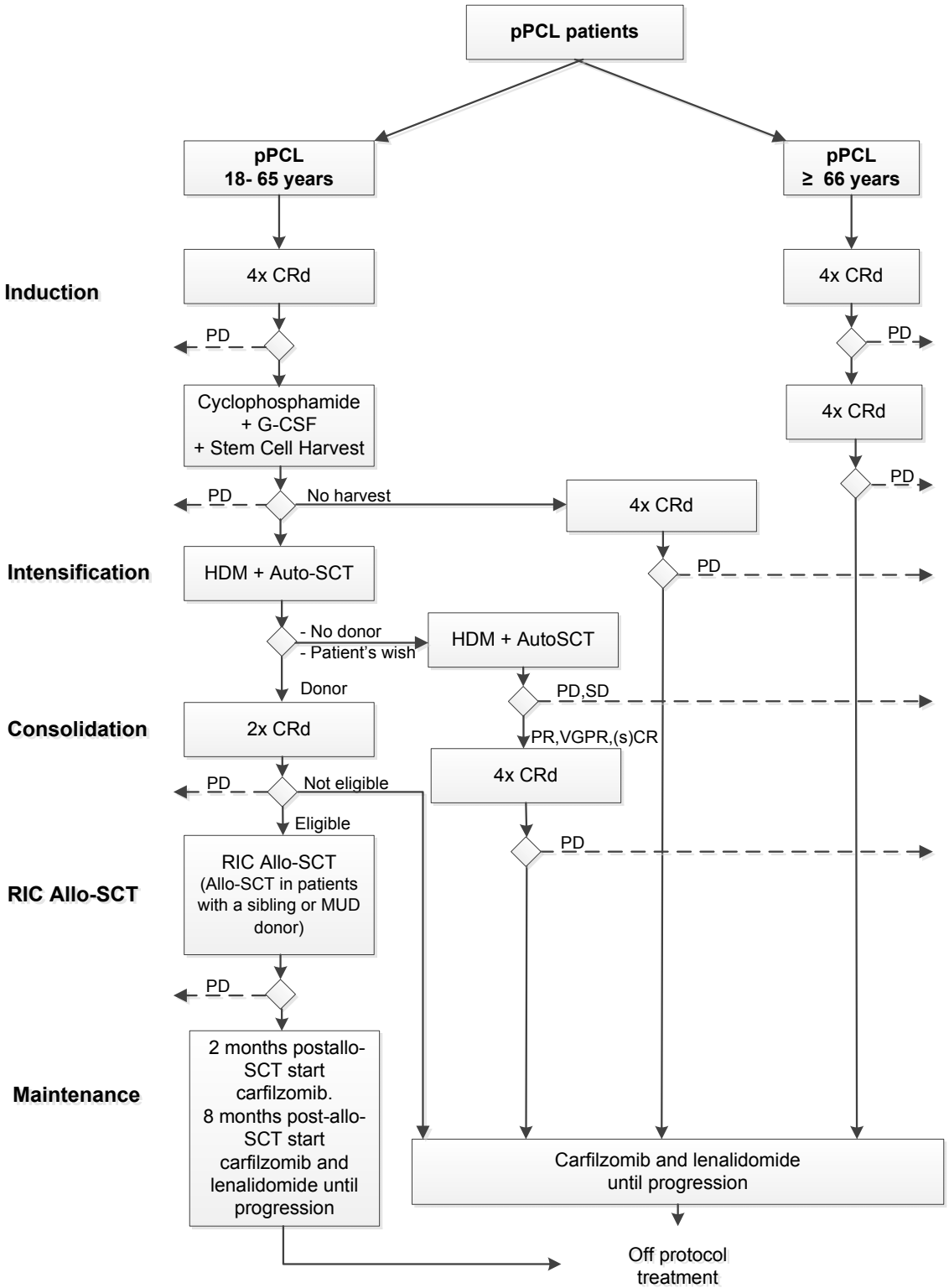
By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the EU directive Good Clinical Practice (2001-20-EG), and local regulations governing the conduct of clinical studies.

1 Scheme of study



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3 Synopsis

Rationale	Lenalidomide with carfilzomib and dexamethasone (CRd) is a regimen that combines high efficacy with low rate of polyneuropathy and is therefore an attractive combination for induction treatment in patients with primary plasma cell leukemia (pPCL). Carfilzomib and lenalidomide will also be used for consolidation and maintenance treatment after high-dose therapy and allogeneic stem cell transplantation in younger patients, and as maintenance for elderly patients after induction therapy. Altogether, the aim of this treatment strategy is to improve the outcome of pPCL patients (pPCL).
Study objectives	All analyses will be done separately for younger (18-65 years) and elderly (≥ 66 years) patients. Primary objective: • To evaluate progression-free survival in adult pPCL patients by incorporation of carfilzomib and lenalidomide in induction, consolidation, and maintenance therapy Secondary objectives: • To assess overall response rate and (s)CR + VGPR ((stringent) complete and very good partial response) rate after induction therapy, after HDM, after CRd consolidation, after RIC allo-SCT or a second HDM, and during maintenance • To evaluate overall survival • To assess safety and toxicity • To assess the prognostic value of risk factors at diagnosis, including β2-microglobulin, LDH, FISH abnormalities del1p, ampli 1q, t(4;14), t(14;16), t(11;14), ampli 9, del13q/13-, del17p as analyzed in purified bone marrow plasma cells with respect to progression-free survival • To analyze the prognostic value of myeloma gene

	expression profiles • To analyze the prognostic value of minimal-residual disease negativity • To assess the prognostic value of mutations as determined by sequencing • To establish the frequency of second primary malignancies (SPM)
Study design	Phase 2, prospective, multicenter, intergroup
Patient population	Patients with symptomatic pPCL, previously untreated, ISS stages I-III, age ≥18 years
Intervention	Patients with age 18-65 years will receive 4 cycles of CRd followed by HDM and auto-SCT, then consolidation therapy with 2 cycles of CRd, and subsequently if eligible and a suitable donor is available then allo-SCT, the latter involving semi-intensive conditioning with busulfan + fludarabine. After allo-SCT patients will receive carfilzomib maintenance. Eight months after allo-SCT lenalidomide will be added to carfilzomib maintenance. The immunomodulatory agent lenalidomide is added at a later stage after allo-SCT in order to prevent the development of GvHD. In case no donor can be identified OR if patient is ineligible to proceed with allo-SCT after the first auto-SCT OR if patient does not want to undergo allo-SCT, a second course of high dose melphalan and auto-SCT will be administered between 2 and 3 months after the first course when the patient achieved at least PR. This will be followed by 4 cycles CRd consolidation and subsequently carfilzomib-lenalidomide maintenance. Patients with age ≥66 years will receive 8 cycles of CRd followed by carfilzomib-lenalidomide maintenance until progression.
Duration of treatment	Patients 18-65 years (allo-SCT): Induction 4 months, stem cell collection and Intensification

	with HDM and auto-SCT 3 months, consolidation with CRd 2 months, and allogeneic stem cell transplant 1 month. Maintenance therapy with carfilzomib followed by carfilzomib + lenalidomide will be given until progression. Patients 18-65 years (no allo-SCT): Induction 4 months, stem cell collection and Intensification with two times HDM and auto-SCT 6 months, and consolidation with CRd 4 months. Maintenance therapy with carfilzomib + lenalidomide will be given until progression. Patients ≥66 years: Induction is 8 months. Maintenance therapy with carfilzomib + lenalidomide will be given until progression. All patients will be followed until a maximum of 5 years after registration or until completion of maintenance therapy for patients who are still on maintenance at 5 years after registration.
Target number of patients	116 patients registered (61 younger patients and 55 elderly patients)
Expected duration of accrual	3 years
Main study endpoints	To assess the efficacy of carfilzomib and lenalidomide-based treatment separately in younger (18-65 years inclusive) and elderly (≥66 years) patients with previously untreated pPCL, as measured by the progression-free survival from registration.
Benefit and nature and extent of the burden and risks associated with participation	Patients will be treated with a highly effective combination of drugs during induction, consolidation, and maintenance phases. Toxicity will be mainly hematologic.
Planned interim analysis and DSMB (if applicable)	A DSMB will be installed to advise about the continuation of the trial, see chapter 12.9

4 Investigators and study administrative structure

This is an Intergroup study coordinated by the HOVON. The present protocol is written according to the HOVON procedures, and is fully applicable to all HOVON investigators. The scientific content is also fully applicable to investigators from all other collaborative groups. For administrative matters and logistic procedures, non HOVON investigators should refer to their Group specific addendum that will supersede the contents of applicable chapters in this protocol.

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5 Introduction and rationale

Primary plasma cell leukemia (pPCL) is the most aggressive form of the plasma cell dyscrasias. It is defined by the presence of >2x10^9/L peripheral blood plasma cells or plasmacytosis accounting for >20% of the differential white cell count, and does not arise from pre-existing multiple myeloma (MM)[1,2]. Secondary PCL (sPCL), however, is a leukemic transformation of end-stage MM. The first case of pPCL was described by Gluzinski and Reichenstein in 1906[3]. In contrast to the clonal plasma cells in PCL, reactive plasmacytosis associated with bacterial or viral infections, autoimmune disorders, and serum sickness is polyclonal in nature. Primary PCL is rare with only 1-4% of MM patients presenting as pPCL[4-9]. In addition, <1% of patients presenting with extreme leucocytosis (>50x10^9/L) are diagnosed with PCL[10]. Compared to classical MM, pPCL has both a different biological background, as well as distinct clinical and laboratory features. The prognosis of pPCL is very poor, with a median overall survival (OS) of only 7 months with standard chemotherapy. The introduction of autologous stem cell transplantation (auto-SCT) and the novel agents, especially bortezomib, has recently improved outcome of patients with pPCL, but the outcome remains inferior when compared to MM. Therefore innovative treatment approaches which incorporate various modalities are required to improve outcome.

5.1 Clinical and laboratory features of PCL

Primary PCL patients have a younger age at presentation when compared to MM or sPCL patients [4;5;7]. However, their performance status at diagnosis is usually worse[6], which may be related to the more advanced stage of disease (Durie-Salmon stage III: ~80-96%; ISS stage III: ~63-80%)[4;6;11-15]. Extramedullary involvement such as hepatomegaly, splenomegaly, lymphadenopathy, leptomeningeal infiltration, or extramedullary plasmacytomas is more frequent in pPCL[1;5-9;12;14;15], with extensive bone disease being more common in patients with MM[6;16].

Various laboratory characteristics reflect a high tumor load. For example, median percentage of BM plasma cells is significantly higher in pPCL than in MM[5;6;15]. Also renal failure is more common in pPCL, which can be partly explained by the higher incidence of light-chain disease[5;6;9]. Furthermore, hypercalcemia, anemia, thrombocytopenia, elevated plasma cell labeling index, increased LDH, and GEP-defined high-risk disease are more frequent at presentation in pPCL when compared to MM[5;6;8;11;12;14]. Consistent with higher tumor burden and an increased incidence of renal impairment, significantly elevated beta-2 microglobulin levels in pPCL are seen when compared to MM[5;6;9;11].

5.2 Treatment modalities in pPCL

There is a paucity of literature on the treatment of pPCL and no randomized trials have been reported exclusively for patients with pPCL.

5.2.1 Conventional chemotherapy

The prognosis of pPCL following conventional chemotherapy without novel agents is poor, with median OS of about 7 months[6-8;17]. There appears to be limited benefit in terms of survival for multi-agent conventional chemotherapy such as vincristine, adriamycin, and dexamethasone (VAD)-based regimens, when compared to regimens containing only an alkylating agent plus a corticosteroid[5-8;12].

5.2.2 Novel agents

The introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors has significantly improved survival of MM patients[18]. Increasing evidence suggests that these agents also improve outcome of pPCL, but the benefit may be less pronounced when compared to classical MM. A retrospective analysis performed by the IFM showed that pPCL patients treated with novel agents had a survival of 15 months, as compared to 8 months for patients that did not receive novel agents as part of their treatment. Also a retrospective analysis performed by GIMEMA showed improved survival for those patients that received bortezomib and/or thalidomide at any stage of their treatment[12]. In contrast, a SEER database analysis failed to show enhanced survival of pPCL patients in the period 1973 to 2004, but information on treatment changes over time were lacking in this study[19]. There remain a limited number of prospective studies evaluating novel agents in pPCL, with several retrospective studies providing additional information on the efficacy of these drugs.

5.2.3 Bortezomib

Up till now bortezomib is probably the most important drug in pPCL, since bortezomib-based therapy rapidly reduces tumor load and reverses complications including renal failure and hypercalcemia. Bortezomib also overcomes the poor prognosis conferred by del(13q) or t(4;14), and mitigates the adverse outcome associated with del(17p)[20;21]. Several case reports and small case series suggest that bortezomib, alone or in combination with other agents, is effective in newly diagnosed pPLC and may also be active in refractory pPCL or sPCL[17;22-25].

The largest retrospective analysis of newly diagnosed pPCL patients treated with bortezomib-based regimens (n=29) comes from the Italian GIMEMA MM Working Party, with an overall response rate of 79%, and 38% ≥VGPR[23]. Importantly, there was improvement or normalization of renal function in 10

of 11 patients presenting with renal failure. Two-year PFS was 40% and 2-year OS 55%, with the best long-term results achieved in patients who received SCT after bortezomib induction[23].
In another retrospective analysis, Musto et al showed that response rate to bortezomib or bortezomib-based combinations in 8 newly diagnosed or relapsed pPCL patients was 100%, with median PFS and OS not reached after 21 months[17].
A single center retrospective analysis of all pPCL and sPCL patients has shown a survival advantage for bortezomib-treated patients as compared to a non-bortezomib treated group[26]. This is in line with a retrospective analysis of 73 pPCL patients treated with different regimens, which showed best results for patients treated with bortezomib followed by auto-SCT[12]. In contrast, a retrospective analysis performed by the IFM showed no improvement in overall survival for patients treated with relatively short courses of bortezomib[4]. Although the number of patients is small, the Arkansas group showed that Total Therapy 3 (which incorporates both bortezomib and thalidomide) did not result in an improved survival when compared to the preceding Total Therapy regimens which incorporated thalidomide alone[9].

5.2.4 Thalidomide

Efficacy of single agent thalidomide is limited in pPCL when compared to the activity of this agent in MM[27]. Although some reports with small numbers of patients showed that thalidomide may result in durable responses in sPCL or pPCL, its decreased activity in extramedullary MM makes its use less attractive[28;29]. Conversely, addition of thalidomide to dexamethasone, conventional chemotherapy, or bortezomib may result in enhanced activity in pPCL[30].

5.2.5 Lenalidomide

Lenalidomide is less toxic and more potent than thalidomide. The combination of lenalidomide with dexamethasone has been effective in newly diagnosed pPCL[31]. In a prospective phase 2 study, 23 newly diagnosed pPCL patients were treated with lenalidomide and dexamethasone: 14 patients completed the initial 4 planned cycles and PR was achieved in 61%, with ≥VGPR in 35%. Five patients underwent auto-SCT and 1 received tandem auto-allo-SCT, following lenalidomide plus dexamethasone treatment. After a median follow-up of 34 months median OS and PFS were 28 and 14 months, respectively[31]. Lenalidomide-based therapies also appear promising in the setting of relapsed/refractory disease, especially in combination with bortezomib.

5.2.6 Combinations of novel agents

In pPCL, the efficacy of combinations of novel agents such as lenalidomide, bortezomib, and dexamethasone (VRD), bortezomib, thalidomide, and dexamethasone (VTD)[17;23], or melphalan,

prednisone, bortezomib, and thalidomide (VMPT)[23] appears very promising. Studies describing these regimens invoke only small numbers of patients, but are based upon the biological and clinical features seen.

5.2.7 Autologous stem cell transplantation (auto-SCT)

McElwain and Powles were the first to describe the efficacy of high-dose melphalan in a pPCL patient, who survived more than 30 months following melphalan 140 mg/m^2 [32]. Since then other case reports and small case series suggest that high-dose therapy with hematopoietic stem cell support improves overall survival[4;5;12].

The largest retrospective analysis to date was performed by the European Group for Blood and Marrow Transplantation (EBMT)[11], who compared 272 pPCL patients with 20844 MM patients undergoing auto-SCT between 1980 and 2006[11]. Although CR rates before and after autologous SCT were higher in pPCL patients, median PFS (14.3 vs. 27.4 months) and OS (25.7 vs. 62.3 months) were significantly longer in MM patients. Conversion to CR following auto-SCT was associated with improved PFS and OS[11]. Treatment-related mortality (TRM) was higher in the pPCL group. Importantly, this study lacked information regarding type of induction regimen, which is likely critical based upon current data.

Another large retrospective analysis of 97 pPCL patients who received upfront auto-SCT between 1995 and 2006 was generated by the Center for Instrumental Blood and Marrow Transplant Research (CIBMTR)[33]. In contrast to the EBMT results, three-year PFS (34%) and OS (64%) were similar to that observed in MM, and there was a trend towards superior OS in patients who received a tandem auto-SCT compared with those receiving a single transplant. Non-relapse mortality at 3 years was 5%. The use of novel agents as part of the induction therapy was very low, which may explain the absence of any major difference in outcome.

Moreover, when comparing both studies, PFS is almost identical, whereas OS was significantly longer in the CIBMTR study. This outcome may be related to greater availability of novel agents for relapse treatment in the CIBMTR study (>60% transplanted after 2000). Altogether, these studies show an encouraging survival after auto-SCT with acceptable toxicity. However, in both series it is unclear which proportion of patients planned to undergo auto-SCT did not receive this treatment, due to either early progression or death. This selection bias may lead to an overestimation of the effectiveness of auto-SCT in pPCL; nonetheless integration of novel therapies into induction, consolidation, and maintenance around auto-SCT would seem justified.

5.2.8 Allo-SCT

Since response duration after auto-SCT is relatively short, other strategies are needed as a consolidation treatment, including allogeneic stem cell transplantation (allo-SCT), under the auspices of a clinical trial. Although TRM is high, several case reports and case series reported successful results and long-term survival following allo-SCT in pPCL[34].

The retrospective CIBMTR analysis also compared the outcome of the 97 patients that received auto-SCT with 50 patients that received allo-SCT between 1995 and 2006[33]. Most patients (68%) received a myeloablative conditioning regimen prior to allo-SCT, while 32% received a non-myeloablative or reduced-intensity conditioning regimen (NMA/RIC). Only 4 patients received tandem auto-allo-SCT. Although the cumulative incidence of relapse at 3 years was significantly lower in the allogeneic group (allo-SCT: 38% vs. auto-SCT: 61%), TRM at 3 years was considerably higher in patients that received an allogeneic transplant (allo-SCT: 41% vs. auto-SCT: 5%). This resulted in a 3-year OS of 64% and 39% for the auto-SCT and allo-SCT group, respectively[33]. Relapse risk was lower and PFS was superior in patients who were transplanted within 6 months of diagnosis. Importantly, the use of novel agents as part of the induction regimen remained low. Furthermore, this analysis covers a long time span, during which TRM of allo-SCT has decreased due to better supportive care and use of other reduced intensity conditioning regimens.

Importantly, Kröger et al recently demonstrated that upfront auto-allo tandem SCT overcomes the negative prognostic value of del(17p) and t(4;14) in myeloma patients (Kroger BMT 2013 398). Similarly, a retrospective analysis from France showed that after allo-SCT del(17p) and t(4;14) had no impact on outcome (Roos-Weil Haem 2011 1504). Since these high-risk cytogenetic abnormalities are more frequently observed in pPCL than in myeloma, pPCL patients may especially benefit from the tandem of auto-allo-SCT.

5.3 Maintenance/consolidation

Post-transplantation consolidation and/or maintenance strategies with novel agents have not been extensively studied in pPCL, with only case reports and small case series describing prolonged remissions after maintenance treatment with thalidomide, lenalidomide, and bortezomib.

In multiple myeloma, there is increasing evidence that consolidation and/or maintenance treatments increase the quality of response, which is associated with improved OS and PFS, and this may be especially important in high-risk disease, such as pPCL. In particular, achievement of a minimal residual disease-negative status is predictive of improved outcome, especially in the presence of high-risk cytogenetics. The generally short PFS after auto-SCT (also for patients achieving CR) seen in pPCL is indicative of the persistence of a substantial burden of (minimal) residual disease. Altogether, this provides strong rationale for the use of post-transplantation therapies in pPCL to improve depth of response, maintain remission, and prolong survival.

5.4 Carfilzomib combined with lenalidomide

Carfilzomib is an irreversible inhibitor of the chymotrypsin-like activity of the proteasome and has recently received FDA-approval for the treatment of patients with relapsed and refractory myeloma previously treated with lenalidomide and bortezomib. A phase 1b dose-escalation study showed that carfilzomib combined with lenalidomide-dexamethasone (CRd) is an effective combination in relapsed patients. This led to a phase 3 trial, which is currently evaluating lenalidomide and low-dose dexamethasone with or without carfilzomib for relapsed/refractory myeloma (ASPIRE).
Based on the high efficacy of carfilzomib and the favorable side effect profile, especially the low incidence of treatment-emerging peripheral neuropathy also after prolonged treatment, makes it an attractive agent to incorporate in treatment protocols for newly diagnosed patients. In this respect, carfilzomib combined with lenalidomide and low-dose dexamethasone as a frontline treatment is very active with rapid induction of high-quality responses and a favorable toxicity profile in multiple myeloma. Up till now this combination has not been tested in pPCL.

5.5 Prognostic factors

Various unfavorable prognostic factors for newly diagnosed MM also have prognostic value in pPCL. However, the prevalence of these risk factors in pPCL is significantly higher. Prognostic parameters include low serum albumin[12], elevated β2-microglobulin[6], hypercalcemia[12], elevated serum LDH[15], advanced age[19], worse performance status[15], and increased percentage of S-phase plasma cells[6]. Response to treatment is also of great prognostic value in pPCL. Patients presenting with disease that is resistant to initial therapy have a very poor prognosis, with survival estimates of a few months[12]. The failure of blood plasma cells to decline by 50% within 10 days or to be cleared within 4 weeks have been proposed as criteria identifying patients with unresponsive disease[8].
Since most studies performed in pPCL are small and retrospective in nature with heterogeneous treatments, the value of the cytogenetic abnormalities with prognostic impact in MM remains unclear in pPCL. The presence of hypodiploidy, complex karyotype, del(13q), del(17p), del(1p), or ampl(1q) were associated with reduced OS in a retrospective study performed in Italy[12]. Survival in a cohort of both primary and secondary PCL patients was negatively affected by the presence of t(4;14) and del(1p21)[16]. Avet-Loiseau et al showed that pPCL patients with t(11;14)[35] had a longer OS and Tiedemann et al[5] found that *MYC* rearrangements predicted for shorter OS. Larger prospective studies with standardized treatments are needed to establish the prognostic value of the diverse cytogenetic abnormalities in PCL overall.

5.6 Rationale for the trial

Based on 1) the improvement in survival of both younger and elderly pPCL patients by incorporation of novel agents (especially proteasome inhibitors and lenalidomide) and 2) improvement in survival for younger patients by using auto-SCT in treatment schedules, combined with the lower relapse rate with allo-SCT in pPCL, we here propose a new study to further improve the outcome of both transplant eligible (younger) and non-transplant eligible (elderly) pPCL patients.

In this prospective European Myeloma Network (EMN) study, newly diagnosed pPCL patients (both elderly and younger patients) will be treated with the combination of carfilzomib-lenalidomide-dexamethasone (CRd).

5.6.1 Rationale of CRd

Lenalidomide and bortezomib combined with dexamethasone are now recognized as the most active drugs for remission induction in both younger and elderly patients with multiple myeloma including those patients with high-risk cytogenetics. Bortezomib has the disadvantage of inducing peripheral polyneuropathy which is dose limiting in 50% of patients and leads to premature termination of treatment in 25%. Replacing bortezomib by carfilzomib would associate effective proteasome inhibition with lack of neuropathy, thereby improving the proportion of patients who are able to complete the planned treatment and reducing the rate of serious adverse events, in particular polyneuropathy. In view of the recently reported high response rates with bortezomib plus lenalidomide-containing regimens (VRD), a regimen consisting of lenalidomide with carfilzomib which combines less polyneuropathy with similar efficacy would be a likely candidate for standard induction in the future. Equally, such regimen could be used for consolidation and maintenance treatment after high-dose therapy for younger patients, and as maintenance for elderly patients after induction therapy.

5.6.2 Dose rationale of CRd

Jakubowiak et al showed in a phase 1/2 study that carfilzomib combined with lenalidomide and low-dose dexamethasone (CRd) as a frontline treatment is very active with rapid induction of high-quality responses and a favorable toxicity profile in multiple myeloma[36]. Carfilzomib is also combined with thalidomide and dexamethasone (Carthadex study) with carfilzomib doses safely given up to a dose of 56 mg/m^2 [37]. There is preliminary evidence that higher doses of carfilzomib are more effective in reducing myeloma tumor load[37]. Up till now the CRd regimen has not been tested in pPCL. We will evaluate CRd in pPCL at the same lenalidomide and dexamethasone dose as previously used by Jakubowiak et al in the phase 2 part of that study[36].

5.6.3 Rationale for design

All patients will receive the potent CRd regimen in different phases of the treatment schedule, since CRd is currently the most effective regimen in plasma cell dyscrasias. To consolidate the response, younger, transplant-eligible patients, will also receive auto-SCT, since multiple studies have shown that auto-SCT improves survival in pPCL. Younger patients will also receive allo-SCT in case of an available donor, since this treatment modality reduces relapse risk and overcomes poor-risk conferred by cytogenetic abnormalities.

In more details, younger patients (18-65 years inclusive) will receive 4 cycles of CRd followed by high-dose melphalan (HDM) and auto-SCT, then consolidation therapy with 2 cycles of CRd, and subsequently allo-SCT, the latter involving semi-intensive conditioning with busulfan + fludarabine. After allo-SCT patients will receive carfilzomib maintenance. Eight months after allo-SCT lenalidomide will be added to carfilzomib maintenance. The immunomodulatory agent lenalidomide is added at a later stage after allo-SCT in order to prevent the development of Graft versus Host Disease (GvHD).

We expect that for about 80% of the pPCL patients a suitable donor can be selected (HLA-identical sibling or unrelated donor (at least 9/10 allele-matched donor)).

A meta-analysis recently demonstrated that multiple myeloma patients with high-risk cytogenetics and treated with bortezomib-based induction regimens benefit from double auto-SCT compared to single transplant (Cavo ASH 2013 767). Therefore, in case no donor can be identified OR if patient is ineligible to proceed with allo-SCT after the first auto-SCT OR if patient does not want to undergo allo-SCT, a second course of HDM and auto-SCT will be administered between 2 and 3 months after the first course when the patient achieved at least PR otherwise the patient will go off protocol treatment). This will be followed by CRd consolidation and subsequently carfilzomib-lenalidomide maintenance.

Elderly patients (≥66 years) will receive 8 cycles of CRd. Since there is increasing evidence that maintenance therapy prolongs response duration and survival in myeloma as well as pPCL (van de Donk Blood), CRd induction will be followed by carfilzomib-lenalidomide maintenance until progression.

6 Study objectives

The objectives will be separately studied in younger (18-65 years) and elderly (≥66 years) patients.

6.1 Primary Objective

- To evaluate progression-free survival in adult pPCL patients by incorporation of carfilzomib and lenalidomide in induction, consolidation, and maintenance therapy

6.2 Secondary objectives

- To assess overall response rate and (s)CR + VGPR ((stringent) complete and very good partial response) rate after induction therapy, after HDM, after CRd consolidation, after RIC allo-SCT or a second HDM, and during maintenance
- To evaluate overall survival
- To assess safety and toxicity
- To assess the prognostic value of risk factors at diagnosis, including β2-microglobulin,LDH, FISH abnormalities del1p, ampli 1q, t(4;14), t(14;16), t(11;14), ampli 9, del13q/13-, del17p as analyzed in purified bone marrow plasma cells with respect to progression-free survival
- To analyze the prognostic value of myeloma gene expression profiles
- To analyze the prognostic value of minimal residual disease negativity
- To assess the prognostic value of mutations as determined by sequencing
- To establish the frequency of second primary malignancies

7 Study design

Details of all treatments (dose and schedule) are given in paragraph 9.

7.1 Younger patients (18-65 years inclusive):

Patients between 18-65 years with pPCL will be registered on entry and treated with 4 induction cycles CRd, followed by cyclophosphamide for stem cell mobilization and collection. After induction patients will be treated with the intensification regimen (HDM). When patients are eligible for transplant they will be treated with 2 cycles of CRd as consolidation. This will be followed by RIC allo-SCT and carfilzomib-lenalidomide maintenance.

In case no donor can be identified OR if patient does not want to undergo allo-SCT, a second course of HDM will be administered between 2 and 3 months after the first course when the patient achieved at least PR(otherwise patient will go off protocol). This will be followed by CRd consolidation and subsequently carfilzomib-lenalidomide maintenance.

7.2 Elderly patients (≥66 years)

Elderly patients (≥66 years), will be treated with 8 induction cycles with CRd, followed by carfilzomib-lenalidomide maintenance.

8 Study population

8.1 Eligibility for registration

All pPCL patients who fulfill the eligibility criteria below have to be registered before start of treatment.

8.1.1 Inclusion criteria

- Patients with diagnosis of symptomatic pPCL (see appendix A)
- Measurable disease as defined by the presence of M-protein in serum or urine (serum M-protein > 5 g/l or urine M-protein > 200 mg/24 hours or abnormal FLC ratio with involved free light chain (FLC) > 100 mg/l) or proven plasmacytoma by biopsy)
- Age ≥18 years
- WHO-performance status 0-3 (but WHO=3 is allowed only when caused by pPCL and not by co-morbid conditions)
- Written informed consent
- Patient capable of giving informed consent (patient is legally, physically and mentally capable of giving consent)
- All men and women of childbearing potential should use adequate contraception during the study. Sperm could be frozen from men with child wish before start of treatment
- Negative pregnancy test at entry (if applicable)
- Patient is willing and able to adhere to the requirements of the lenalidomide Pregnancy Prevention Program (PPP)

8.1.2 Exclusion criteria

- Any current CNS involvement with disease refractory to intrathecal chemotherapy.
- Female patients who are pregnant or breast feeding.
- HIV positive patients
- Active malignancy other than pPCL requiring treatment, or a malignancy that has been treated with chemotherapy currently affecting bone marrow capacity
- Patients with active, uncontrolled infections
- Severe neurological or psychiatric disease

- Severe cardiac dysfunction (NYHA classification II-IV, see appendix E) - Myocardial infarction within 6 months, unstable angina, and cardiac arrhythmias which are not controlled by conventional treatment (including medications and cardiac devices)
- Severe pulmonary dysfunction
- Significant hepatic dysfunction (serum bilirubin or transaminases ≥ 3.0 times normal level), unless related to pPCL
- Patients with GFR < 15 ml/min
- Known history of allergy to Capsidol (a cyclodextrin derivative used to solubilize carfilzomib)
- Hypersensitivity to the active substances or to any of the excipients of the drug products
- Previous chemotherapy or radiotherapy except local radiotherapy in case of local myeloma progression or corticosteroids maximum 7 days for symptom control or stabilization(this includes dexamethasone 40 mg daily) or inthrathecal chemotherapy in case of CNS involvement
- Systemic AL amyloidosis
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Note: like in acute myeloid leukemia and acute lymphoblastic leukemia studies, pPCL patients will not be excluded from participation in this study based on platelet or neutrophil counts. pPCL frequently presents with low blood counts due to high tumor load. Rapid and effective initiation of anti-pPCL treatment will result in improvement in blood cell counts.

9 Treatment

9.1 Younger patients (18-65 years inclusive):

Treatment plan

Patients will receive 4 courses of CRd, cyclophosphamide/G-CSF mobilized PBSC collection and standard autologous transplant with melphalan at 200 mg/m^2. This is followed by 2 courses of CRd consolidation treatment cycles and RIC allo-SCT for patients with an HLA-identical sibling or a suitable unrelated donor (at least 9/10 allele-matched donor) allocated to a planned nonmyeloablative/reduced-intensity allograft. Two months after the allo-SCT patients will start with carfilzomib maintenance. Eight months after allo-SCT low-dose lenalidomide is added to carfilzomib. Maintenance is given until progression.

In case no donor can be identified OR if patient does not want to undergo allo-SCT, a second course of high dose melphalan will be administered between 2 and 3 months after the first course when the

patient achieved at least PR. This will be followed by 4 cycles of CRd consolidation, and subsequent carfilzomib-lenalidomide maintenance (see paragraph 9.3).

9.1.1 CRd induction phase

9.1.1.1 Treatment schedule

All patients will receive 4 cycles of CRd, according to the schedule in Table 1:

Table 1: CRd induction treatment schedule for patient's ≤65 years

Agent	Dose/day	Route	Days
Carfilzomib	36 mg/m^2 #	i.v.	1,2,8,9,15,16
Lenalidomide†	25 mg†	p.o.	1-21
Dexamethasone	20 mg	p.o.	1,2,8,9,15,16,22,23

Carfilzomib will be given at a dose of 20 mg/m^2 on days 1 and 2 of cycle 1

† The start dose of lenalidomide will be reduced depending on renal function. Patients with impaired renal function (calculated or measured creatinine clearance < 50 mL/minute) will have lenalidomide dose reduction as outlined in chapter 9.1.1.3, otherwise they will receive full dose lenalidomide (25 mg).

Cycles will be given every 28 days. The next cycle will start at day 29 of the previous cycle.

Patients will be evaluated for response after cycle 4 as described in chapter 10.1 and appendix B. In case of progressive disease after cycle 4 patients will go off protocol treatment.

All other patients who meet the inclusion criteria for Cyclophosphamide and stem cell collection (see chapter 9.1.2.1) will continue with mobilization of stem cells with cyclophosphamide + G-CSF, independent from the response after CRd.

9.1.1.2 Initiation of a new CRd cycle

In order to initiate a new cycle of CRd, the following parameters must be met:

- ANC ≥ 0.75 x 10^9/L (growth factor support is strongly recommended if ANC< 1.0 x 10^9/L)
- Platelet count ≥ 30 x 10^9/L (platelet transfusion support is allowed)
- All non-hematologic side effects must be resolved to ≤ CTCAE grade 2 or the patient's baseline condition.

If those parameters are not satisfied, then delay the start of treatment until toxicity is resolved (follow instructions for dose modification). The next cycle may be held for a maximum of 28 days until recovery to the specified levels.

9.1.1.3 Lenalidomide dosing for patients with impaired renal function

Table 2: Lenalidomide dosing for patients with impaired renal function

Renal function (CrCl)	**Lenalidomide dose**
Mild (CrCl ≥ 50 ml/min)	25 mg once a day (full dose)
Moderate (CrCl ≥ 30 to <50 ml/min)	10 mg once a day Dose may be escalated to 15 mg once a day after 2 cycles if patient is not responding to treatment
Severe (CrCl < 30 ml/min, *not* requiring dialysis)	15 mg once per 48 hrs.
ESRD (CrCl <30 ml/min, requiring dialysis)	5 mg once daily. On the day of dialysis lenalidomide will be administered following dialysis

9.1.1.4 Special management in conjunction with carfilzomib during CRd therapy

Patients may be treated on an outpatient basis. The appropriate amount of carfilzomib will be drawn from the injection vial and administered intravenously. Vials are for single use administration. The patient should be considered clinically stable by their physician before discharge.
Before each carfilzomib dose, the patient will be evaluated for possible thrombocytopenia and neuropathy that may have occurred after the previous dose(s).

Tumor-lysis prophylaxis is required in induction treatment cycle 1, see chapter 9.6.1.4 for details.

See chapter 9.8 for anti-bacterial prophylaxis, prophylaxis to reduce the risk of Herpes Zoster (HZ) infection, and thrombosis prophylaxis.

See chapter 9.5 for dose modifications of carfilzomib / lenalidomide in case of toxicities.

9.1.2 Stem cell mobilization and collection

All eligible patients will be given cyclophosphamide followed by G-CSF for stem cell collection. Cyclophosphamide will start 4-6 weeks after start of the fourth CRd cycle.

9.1.2.1 Eligibility criteria for cyclophosphamide and stem cell collection

- WHO performance 0-2
- Absence of severe pulmonary, neurologic, or psychiatric disease
- Bilirubin and transaminases of less than 3 times the upper limit of normal values
- No progressive disease

9.1.2.2 Stem cell mobilization with cyclophosphamide and G-CSF

Stem cell collection will be performed after priming with cyclophosphamide and G-CSF, according to Table 3 or according to local protocols.

Table 3 Stem cell mobilization schedule

Agent	Dose/day	Route	Days
Cyclophosphamide	2000 mg/m^2	i.v.	1
G-CSF (filgrastim)	10 µg/kg (divided in 2 gifts daily, according to local rules)	s.c.	day 5 until last leucopheresis

9.1.2.3 Special management orders in conjunction with cyclophosphamide

Selective gut decontamination may be performed according to local protocols.

9.1.2.4 Stem cell collection

Stem cell collection will be performed as soon as CD34+ cells are present in peripheral blood, which is usually between 9-14 days after cyclophosphamide. In case double intensification is planned a minimum of 5 x 10^6 CD34+ cells/kg is required. Otherwise 2.5 x 10^6 CD34+ cells/kg can be considered. In case insufficient stem cells are collected the procedure may be repeated or alternatively bone marrow stem cell collection may be performed.

All patients who meet the eligibility criteria for high-dose melphalan and autologous stem cell rescue (see 9.1.3.1) will continue with HDM + autologous stem cell rescue.

All other patients will go off protocol treatment with the exception of:

Patients who fulfil the criteria in 9.1.3.1 except the criterium for successful stem cell harvest will be treated with 4 additional CRd cycles (total of 8) followed by carfilzomib-lenalidomide maintenance (see chapter 9.3.3).

9.1.3 Intensification with High Dose Melphalan and auto-SCT

All patients who meet the eligibility criteria for intensification will be treated with High Dose Melphalan 200 mg/m² total (given in two days) followed by autologous stem cell reinfusion. All eligible patients will start intensification with High Dose Melphalan between 4 and 6 weeks after stem cell collection.

9.1.3.1 Eligibility criteria for high dose melphalan intensification

- WHO performance 0-2
- Bilirubin and transaminases < 3 times the upper limit of normal values
- A suitable stem cell graft containing at least 2.0 x 10^6 viable CD34+ cells/kg (or according to national guidelines)
- Absence of severe pulmonary, neurologic, or psychiatric disease
- No progressive disease

9.1.3.2 High Dose Melphalan followed by stem cell reinfusion

Patients will be treated with High Dose Melphalan followed by autologous stem cell reinfusion according to Table 4.

Table 4: HDM and auto-SCT treatment schedule

Agent	Dose/day	Route	Days
Melphalan	100 mg/m²	i.v. rapid infusion	-3, -2*
Stem cell infusion	2 x 10^6 $CD34^+$ cells/kg	i.v.	0

* Patients with renal insufficiency (creatinine clearance ≤ 40 ml/min) 100 mg/m² only at day –3.

Although melphalan pharmacokinetics are not adversely affected by impaired renal function, the general toxicity of Melphalan 200 mg/m^2 total may be increased in patients with a creatinine clearance ≤ 40 ml/min. For patients with a creatinine clearance ≤ 40 ml/min, Melphalan dose should be reduced to 100 mg/m^2 total, given only at day -3.

A hydration regimen will be started 30 minutes before administration of Melphalan and consists of 500 ml NaCl 0.9 % and 40 mmol KCl over 1 hour. Diuretics must be administered when needed.
On day 0 the stem cells are thawed at the bedside and infused without washing steps. The procedure will be performed according to the local standard protocols.

9.1.3.3 Supportive care during Melphalan 200 mg/m² induced aplasia

- Placement of an indwelling central venous catheter
- Anovulatory drugs for menstruating females
- Antibacterial and antifungal prophylactic antibiotics
- Antistreptococcus prophylaxis is recommended from day +4 until day +14
- G-CSF 3 µg/kg/d from day +5 until hematological recovery is optional

9.2 Younger patients with donor

After HDM and stem cell infusion, patients with a suitable donor will receive CRd consolidation. Patients without a donor or unwilling to undergo allo-SCT will receive a second course of HDM (see chapter 9.3.1).

9.2.1 Consolidation therapy with CRd

All patients who meet the eligibility criteria for CRd consolidation will continue with CRd consolidation. Two cycles of CRd will be administered starting 8-12 weeks after the end of the last course of HDM. Eligibility for CRd consolidation should also be checked prior to the next CRd consolidation cycle.

9.2.1.1 Eligibility criteria for CRd consolidation

- Bilirubin and transaminases <3 times the upper limit of normal values;
- ANC ≥ 0.75 x 10^9/l and platelets ≥ 30 x 10^9/l;
- No progressive disease

9.2.1.2 Treatment schedule

All patients will receive 2 cycles of CRd, according to the schedule in Table 5.

Table 5: CRd consolidation treatment schedule

Agent	Dose/day	Route	Days
Carfilzomib	36 mg/m^2	i.v.	1,2,8,9,15,16

Lenalidomide	25 mg	p.o.	1-21
Dexamethasone	20 mg	p.o.	1,2,8,9,15,16,22,23

Cycles will be given every 28 days. The next cycle will start at day 29 of the previous cycle.

Patients will be evaluated for response after the 2nd course of CRd. Patients with progressive disease will go off protocol treatment.

All patients who meet the eligibility criteria for allo-SCT will continue with allo-SCT. Patients who do not meet the eligibility criteria for RIC allo-SCT, may continue with carfilzomib PLUS lenalidomide maintenance (see section 9.3.3 for details).

9.2.2 Allogeneic stem cell transplant

Preferably, one month after the last course of CRd patients proceed to reduced-intensity allo-SCT. However, in case of logistic issues such as donor availability or slow recovery of the patient, pPCL patients may proceed to reduced-intensity allo-SCT between one and three months after the last course of CRd.

Patients can only proceed to allogeneic stem cell transplantation when the eligibility criteria for allo-SCT are met:

9.2.2.1 Inclusion criteria

- HLA-identical sibling or an unrelated donor (at least 9/10 allele-matched donor) available
- WHO performance status 0-2

9.2.2.2 Exclusion Criteria

- Progressive disease
- Patients who achieved less than PR
- Life expectancy severely limited by diseases other than pPCL
- Any current CNS involvement with disease refractory to intrathecal chemotherapy
- HIV positive patients
- Patients with active, uncontrolled infections
- Severe neurological or psychiatric disease
- Severe cardiac dysfunction (NYHA classification II-IV, see appendix E)

- Severe pulmonary dysfunction
- Significant hepatic dysfunction (serum bilirubin or transaminases ≥ 3.0 times normal level)
- GFR < 30 mL/min

9.2.2.3 Conditioning

The conditioning regimen consists of the combination of busulfan and fludarabine i.v.. Recommendations for the scheme are given below. Slight variations may be possible according to local protocols.

Table 6: Allo-SCT conditioning treatment schedule

Agent	**Dose/day**	**Route**	**Days**
Busulfan	3.2 mg/kg/day	i.v.	Day-5,-4,-3,-2
Fludarabine	40 mg/m²/day	i.v.	Day-5,-4,-3,-2
Stem cell infusion	According to local guidelines	i.v.	Day 0

9.2.2.4 Graft versus Host Disease Prophylaxis

GvHD prophylaxis consists of Cyclopsporin-A combined with Mycophenolate Mofetil (MMF). In patients with a 9/10 sibling donor or an unrelated donor Anti-Human Thymocyte Globulin (ATG) is added to the conditioning regimen. Recommendations for the prophylaxis scheme are given below. Slight variations may be possible according to local protocols.

Table7: GvHD prophylaxis treatment schedule

Agent	**Dose/day**	**Route**	**Days**
Cyclosporine	5 mg/kg q12hrs or 1.5 mg/kg q12 hrs	p.o. i.v.	From -3 to +80 then tapered. STOP at +180
Mycophenolate Mofetil			
Sibling donor	15 mg/kg q8hrs	p.o. (or i.v.)	From 0 to +40 then tapered. STOP at +96
Unrelated donor	15 mg/kg q8hrs	p.o. (or i.v.)	From 0 to +40 then tapered. STOP at +96
Anti-Human Thymocyte Globulin			

Unrelated donor or 9/10 sibling donor	2.5 mg/ kg	i.v.	Day -3 and day -2

9.2.3 Maintenance therapy with carfilzomib, followed by carfilzomib-lenalidomide

Two months after the allo-SCT patients will start with carfilzomib maintenance, according to the schedule in table 8. Lenalidomide will be added at a minimum of 8 months post-allo transplant.

9.2.3.1 Eligibility criteria for maintenance therapy with carfilzomib

- Absolute neutrophil count ≥ 0.75 x 10^9/L
- Platelet count ≥ 30 x 10^9/L
- Calculated or measured creatinine clearance: ≥ 20 mL/minute
- Bilirubin and transaminases <3 times the upper limit of normal values
- No progressive disease

9.2.3.2 Eligibility criteria for maintenance therapy with carfilzomib-lenalidomide

Lenalidomide will be started at a minimum of 8 months post-allo transplant (combined with carfilzomib), if the following conditions are present:

- No immune suppressive drugs for at least the past 4 weeks
- Absence of CTCAE grade 3 toxicity
- No signs of any grade of acute GvHD or extensive chronic GvHD with the exception of oral GvHD that is manageable with local therapy
- Absolute neutrophil count ≥ 0.75 x 10^9/L
- Platelet count ≥ 30 x 10^9/L
- Calculated or measured creatinine clearance: ≥ 20 mL/minute
- Bilirubin and transaminases <3 times the upper limit of normal values
- No progressive disease

Maintenance is given until progression.

Table 8: Maintenance dosing and schedule

Agent	**Dose/day**	**Route**	**Days**
Carfilzomib (start 2 months after allo-SCT)	27 mg/m^2	i.v.	1,2,15,16
Lenalidomide (added to	5 mg cycle 1 and 2	p.o.	1-21

carfilzomib 8 months after allo-SCT)	10 mg in the next cycles		

Lenalidomide once daily will be given for 21 consecutive days of a 28 day cycle .
Lenalidomide will be stopped immediately at any sign of acute extensive GvHD or chronic GvHD with the exception of oral GvHD that is manageable with local therapy.
Lenalidomide may be restarted with 5 mg every other day after complete disappearance (minimal 1 month) of GvHD.
Cycles will be repeated at day 29 until progression.
See chapters 9.5.1 and 9.5.2 for dose modifications in case of toxicities

9.3 Younger patients without donor or not willing to undergo allogeneic SCT

Treatment plan

In case no donor can be identified OR if patient is ineligible to proceed with allo-SCT after the first auto-SCT OR if patient does not want to undergo allo-SCT, patients will receive a second HDM and auto-SCT followed by 4 cycles of CRd consolidation and then maintenance treatment with carfilzomib and lenalidomide until progression. If there are not enough stem cells collected for a second HDM, patients will receive 4 cycles of CRd consolidation and then maintenance treatment with carfilzomib and lenalidomide until progression.

9.3.1 Second course of Melphalan 200 mg/m^2 total followed by stem cell reinfusion

The second course of high dose melphalan will be administered between 2 and 3 months after the first course when the patient achieved at least PR. In case not at least a PR is achieved after first course of HDM and auto-SCT, the patients will go off protocol treatment.

Patients have to meet the eligibility criteria of paragraph 9.1.3.1 for HDM before starting the second course.

Patients will be evaluated for response after each course of High Dose Melphalan. Patients with progressive disease and stable disease will go off protocol treatment.

9.3.2 Consolidation therapy with CRd

All patients who meet the eligibility criteria for CRd consolidation will continue with CRd consolidation. Four cycles of CRd will be administered starting 8-12 weeks after the end of the last course of HDM.

9.3.2.1 Eligibility criteria for CRd consolidation

- Bilirubin and transaminases <3 times the upper limit of normal values;
- ANC ≥ 0.75 x 10^9/L and
- Platelets ≥ 30 x 10^9/L
- No progressive disease

9.3.2.2 Treatment schedule

All patients will receive 4 cycles of CRd, according to the schedule in Table 9.

Table 9: CRd consolidation treatment schedule

Agent	Dose/day	Route	Days
Carfilzomib	36 mg/m^2	i.v.	1,2,8,9,15,16
Lenalidomide	25 mg	p.o.	1-21
Dexamethasone	20 mg	p.o.	1,2,8,9,15,16,22,23

Cycles will be given every 28 days. The next cycle will start at day 29 of the previous cycle. Patients will be evaluated for response after the 4th course of CRd, or earlier in case of progressive disease. Patients with progressive disease will go off protocol treatment.

9.3.3 Maintenance therapy after consolidation with carfilzomib-lenalidomide

Maintenance will start immediately after the end of the last course of consolidation.
Maintenance is given until progression, according to the schedule in Table 10.

Carfilzomib-lenalidomide maintenance can only start if (see chapter 9.5):

- ANC ≥ 0.75 x 10^9/L;
- Platelets ≥ 30 x 10^9/L
- No progressive disease

Table 10: Maintenance treatment schedule

Agent	Dose/day	Route	Days
Carfilzomib	27 mg/m^2	i.v.	1,2,15,16
Lenalidomide	10 mg	p.o.	1-21

Cycles will be given every 28 days. The next cycle will start at day 29 of the previous cycle. Cycles will be repeated until progression.
See chapter 9.5 for dose modifications of carfilzomib and lenalidomide in case of toxicities.

9.4 Elderly patients (≥66 years)

9.4.1 CRd induction phase

9.4.1.1 Treatment schedule

All patients will receive 8 cycles of CRd, according to the schedule in Table 11.

Table 11: CRd induction treatment schedule

Agent	Dose/day	Route of administration	Days
Carfilzomib[#]	36 mg/m^{2} [#]	i.v.	1,2,8,9,15,16
Lenalidomide[†]	25 mg	p.o.	1-21
Dexamethasone	20 mg	p.o.	1,2,8,9,15,16,22,23

[#] Carfilzomib will be given at a dose of 20 mg/m^{2} on days 1 and 2 of cycle 1.

[†] The start dose of lenalidomide will be reduced depending on renal function. Patients with impaired renal function (calculated or measured creatinine clearance < 50 mL/minute) will have lenalidomide dose reduction as outlined in paragraph 9.1.1.3, otherwise they will receive full dose lenalidomide (25 mg).

Cycles will be given every 28 days. The next cycle will start at day 29 of the previous cycle. See chapter 9.4.1.2.

Patients will be evaluated for response after cycle 4 and 8 as described in chapter 10.1 and appendix B.
In case of progressive disease after cycle 4 or 8 patients will go off protocol treatment.

All other patients will continue with carfilzomib-lenalidomide maintenance if blood values are recovered (see chapter 9.4.2).

9.4.1.2 Initiation of a new CRd cycle

In order to initiate a new cycle of CRd, the following parameters must be met:

- ANC ≥ 0.75 x 10^{9}/L (growth factor support is strongly recommended if ANC< 1.0 x 10^{9}/L)
- Platelet count ≥ 30 x 10^{9}/L (platelet transfusion support is allowed)

- All non-hematologic side effects must be resolved to ≤ CTCAE grade 2 or the patient's baseline condition.

If those parameters are not satisfied, then delay the start of treatment until toxicity is resolved (follow instructions for dose modification). The next cycle may be held for a maximum of 28 days until recovery to the specified levels.

9.4.1.3 Lenalidomide dosing for patients with impaired renal function

Table 12: Lenalidomide dosing for patients with impaired renal function

Renal function (CrCl)	**Lenalidomide dose**
Mild (CrCl ≥ 50 ml/min)	25 mg once a day (full dose)
Moderate (CrCl ≥ 30 to <50 ml/min)	10 mg once a day Dose may be escalated to 15 mg once a day after 2 cycles if patient is not responding to treatment
Severe (CrCl < 30 ml/min, *not* requiring dialysis)	15 mg once per 48 hrs.
End-stage renal disease **(**ESRD) (CrCl <30 ml/min, requiring dialysis)	5 mg once daily. On the day of dialysis, lenalidomide will be administered following dialysis

9.4.1.4 Special management in conjunction with carfilzomib during CRd therapy

Patients may be treated on an outpatient basis. The appropriate amount of carfilzomib will be drawn from the injection vial and administered intravenously. Vials are for single use administration. The patient should be considered clinically stable by their physician before discharge.
Before each carfilzomib dose, the patient will be evaluated for possible thrombocytopenia and neutropenia that may have occurred after the previous dose(s) (see chapter 9.4.1.2).

Tumor-lysis prophylaxis is required in induction treatment cycle 1, see chapter 9.6.1.4 for details.

See chapter 9.8 for anti-bacterial, prophylaxis to reduce the risk of Herpes Zoster (HZ) infection, and thromboprophylaxis.
See chapter 9.5 for dose modifications of carfilzomib / lenalidomide in case of toxicities.

9.4.2 Maintenance therapy with carfilzomib/lenalidomide

Carfilzomib-lenalidomide maintenance will start immediately after the end of the last course of CRd according to the schedule in Table 13.
Carfilzomib-lenalidomide maintenance can only start if ANC ≥ 0.75 x 10^9/L, platelets > 30 x 10^9/L and no progressive disease. Otherwise postpone start of maintenance until these criteria are met.

Table 13: Maintenance therapy treatment schedule

Agent	Dose/day	Route	Days
Carfilzomib	27 mg/m^2	i.v.	1,2,15,16
Lenalidomide	10 mg	p.o.	1-21

Cycles will be repeated every 28 days until progression. The next cycle will start at day 29 of the previous cycle.
See chapter 9.5 for dose modifications of carfilzomib / lenalidomide in case of toxicities.

9.5 Dose modification guidelines

The following sections and tables summarize dosing modifications of carfilzomib, lenalidomide, and dexamethasone to manage possible toxicity. Administration of carfilzomib or lenalidomide will be discontinued in the event of a treatment-related toxicity that, in the opinion of the Investigator, warrants discontinuation. The subject will be considered still on protocol treatment as long as at least one of the specified drugs in the regimen is being administered.

Dose reduction levels of carfilzomib and lenalidomide for toxicity management of individual subjects are provided in Table 14 and Table 15, respectively:

Table 14: Dose decrements for carfilzomib

Nominal dose	Reduced carfilzomib doses		
	Dose -1	Dose -2	Dose -3
36 mg/m^2	27 mg/m^2	20 mg/m^2	15 mg/m^2

Table 15: Dose decrements for lenalidomide

Nominal dose	Reduced lenalidomide doses		
	Dose -1	Dose -2	Dose -3
25 mg	15 mg	10 mg	5 mg

Treatment guidelines for specific hematologic toxicities are outlined in chapter 9.5.1 and nonhematologic toxicities in chapter 9.5.2.
If either the lenalidomide or carfilzomib dose is reduced during the previous cycle, the reduced dose level will be continued on Day 1 of the new cycle. If the reduced dose level is well tolerated for a complete cycle, the subject may, at the Investigator's discretion, be rechallenged with the dose level prior to the reduction at the start of the next cycle.

Two dose reduction levels are defined for dexamethasone, as illustrated in Table 16.

Table 16: Dose decrements for dexamethasone

Nominal dose	**Reduced dexamethasone dose**	
	Dose -1	**Dose -2**
20 mg	10 mg	5 mg

Dexamethasone will be permanently discontinued after two dose reductions in the event of additional dexamethasone-related toxicity. At the Investigator's discretion, dexamethasone may be tapered prior to complete discontinuation according to institutional practice. The subject may continue on treatment with the other protocol-specified drug(s). Guidelines for dexamethasone dose modifications are summarized in Table 20.

9.5.1 Hematological toxicity

Guidelines for the management of thrombocytopenia are summarized in Table 17 and those for neutropenia in Table 18.

Table 17: Treatment guidelines for thrombocytopenia

Lenalidomide		**Carfilzomib**	
When platelets	**Recommended action**	**When platelets**	**Recommended action**
Fall to <30 x 10^9/L *	Hold dose, follow CBC weekly Hold prophylactic anticoagulation until platelets return to ≥30 x 10^9/L*, then resume at 1	If platelets 10-30 x 10^9/L without evidence of bleeding	Maintain full dose
		If evidence of bleeding or platelets	Hold dose until platelets return to

	dose decrement	< 10 x 10^9/L	≥10 x 10^9/L and/or bleeding is controlled, then resume at full dose
For each subsequent drop to <30 x 10^9/L *	Hold dose, follow CBC weekly, hold prophylactic anticoagulation until platelets return to ≥30 x 10^9/L*, then resume at additional dose decrement	If platelets 10-30 x 10^9/L without evidence of bleeding	Maintain full dose
		If evidence of bleeding or platelets < 10 x 10^9/L	Hold dose until platelets return to ≥10 x 10^9/L and/or bleeding is controlled, then resume at 1 dose decrement

*In case of thrombocytopenia during induction cycle 1 and plasma cell leukemia involvement in the bone marrow >50% (before start of therapy), it is allowed to continue full-dose CRd treatment with adequate transfusion support.

Furthermore, for subjects entering the study with plasma cell leukemia involvement in the bone marrow >50%, a lower threshold of 20 x 10^9/L may be applied for lenalidomide dose reductions

Table 18: Treatment guidelines for neutropenia

Lenalidomide		**Carfilzomib**	
When ANC	**Recommended action**	**When ANC**	**Recommended action**
Falls to <0.75 x 10^9/L	Hold dose, administer myeloid growth factor, follow CBC weekly; Resume at full dose when ANC ≥0.75 x 10^9/L*	If ANC 0.5-0.75 x 10^9/L	Continue at full dose
		If ANC<0.5 x 10^9/L	Hold dose; Resume at full dose when ANC ≥ 0.5 x 10^9/L
For each subsequent drop to <0.75 x 10^9/L	Hold dose, administer myeloid growth factor, follow CBC weekly; Resume at 1 dose decrement when ANC	If ANC 0.5-0.75 x 10^9/L	Continue at full dose
		If ANC<0.5 x 10^9/L	Hold dose; Resume at 1 dose decrement when ANC

	≥0.75 x 10^9/L*		≥ 0.5 x 10^9/L

*In case of neutropenia during induction cycle 1 and plasma cell leukemia involvement in the bone marrow >50%, it is allowed to continue full-dose CRd treatment with adequate supportive care including myeloid growth factor administration.

9.5.2 Nonhematological toxicity

Guidelines for the management of nonhematologic toxicities are summarized in Table 19.

Table 19: Treatment guidelines for non-hematologic toxicity

Symptom	**Recommended action**	
Renal dysfunction	**Lenalidomide**	**Carfilzomib**
CrCL ≥ 15 and <30 ml/min (NCI-CTCAE Grade 3)	Hold dose. If CrCl recovers to baseline resume dose at 1 dose decrement. If significant CrCl reduction reappears then reduce dose to 15 mg every 48 hours. Further dose modification will be based on individual subject treatment tolerance	Full dose
CrCL < 15 ml/min (NCI-CTCAE Grade 4)	Hold dose. If CrCl recovers to baseline resume dose at 1 dose decrement. If significant CrCl reduction reappears then reduce dose to 15 mg every 48 hours. If dialysis is required, reduce dose to 5 mg once daily (administer the lenalidomide after dialysis on dialysis days). Further dose modification will be based on individual subject treatment tolerance.	Hold dose. When CrCl returns to ≥ 15 ml/min, resume dose. If dialysis is required, may resume at a maximal dose of 27 mg/m^2 and administer the carfilzomib after dialysis.
Any other drug-related non-hematologic toxicity * NCI-	For lenalidomide attribution, hold dose.	For carfilzomib attribution, hold dose.

CTCAE Grade ≥3	Resume at 1 dose decrement when toxicity has resolved to grade 2 or less or to baseline grade.	Resume at full dose when toxicity has resolved to grade 2 or less or to baseline grade. If toxicity recurs, resume at 1 dose-decrement.

* In the event of a possible drug-related non-hematologic toxicity, the investigator should, to the best of his/her ability, assess its relationship to lenalidomide, carfilzomib, dexamethasone, or the combination of CRd to the extent possible. If both carfilzomib and lenalidomide are considered likely to be involved, then recommended actions for both should be instituted. For non-hematologic toxicity likely due to dexamethasone, refer to Table 20 for treatment guidelines for dexamethasone-related toxicity.

Table 20: Treatment guidelines for dexamethasone-related toxicity

Body system	**Symptom**	**Recommended action**
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis grade >grade 3	Hold dexamethasone until symptoms adequately controlled. Restart dexamethasone at 1 dose decrement along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone permanently.
Cardiovascular	Edema >grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.

Neurology	Confusion or mood alteration >grade 2 (interfering with function +/- interfering with activities of daily living	Hold dexamethasone until symptoms resolve. Restart dexamethasone at 1 dose decrement. If symptoms persist despite above measures, reduce by another dose decrement.
Musculoskeletal	Muscle weakness > grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Metabolic	Hyperglycemia ≥ grade 3	Treatment with insulin or other hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory
All other	Other nonhematologic toxicity ≥ grade 3 felt related to dexamethasone	Hold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to grade2 or less or to baseline. If toxicity recurs, discontinue dexamethasone permanently.

9.5.3 Conditions not requiring dose reduction

The following conditions are exceptions to the above guidelines. Carfilzomib, lenalidomide, and dexamethasone do not need to be held in the following cases:

- Grade 3 nausea, vomiting, or diarrhea (unless persisting more than 3 days with adequate treatment of antiemetics or antidiarrheal agents)
- Grade 3 dexamethasone-related hyperglycemia
- Grade 3 fatigue (unless persisting for > 14 days)
- Alopecia

9.5.4 Missed Doses

Missed doses of carfilzomib will be given after the last administration of a given cycle following the same weekly scheduling. The following cycle will be postponed accordingly.

9.5.5 Changes in Body Surface Area (BSA)

Dose adjustments for carfilzomib do not need to be made for weight gains/losses of ≤ 20%.
Each dose will consist of carfilzomib for Injection administered on an mg/m^2 basis and should be based on the subject's actual calculated BSA. Subjects with a BSA of 2.2 m^2 or higher receive a dose based upon 2.2 m^2 BSA.

9.6 Safety considerations concerning carfilzomib

Based upon the experience in the Phase I and II clinical studies with carfilzomib, the following observations are noted:

- A "first-dose" effect has been seen, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release. Should a "first-dose" effect occur at any point during cycle 1 or 2, treatment with high dose glucocorticoids (e.g. methylprednisolone 50-100 mg) is recommended. In addition, IV fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted as medically indicated.
- All subjects should be well hydrated. Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib during cycle 1. Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation.
- Subjects with active or suspected infections of any kind should not be dosed with carfilzomib until infection has resolved and if being treated with an anti-infective, the course of antibiotics has been completed.
- Subjects with grade 4 neutropenia should not be treated until ANC resolves to >0.5 x 10^9/L.
- Thrombocytopenia has been transient and typically resolves during the week between treatments. If evidence of bleeding or platelets < 10 x 10^9/L, carfilzomib dosing must be held until platelets return to ≥10 x 10^9/L and/or bleeding is controlled, then resume at full dose (see Section 9.4.1).
- Subjects should have anemia corrected in accordance with the Institutional guidelines.
- Drug should be withheld for all ≥ Grade 3 events until resolved to ≤ Grade 2 or return to baseline, with exceptions, as noted in Section 9.5. After resolution of the ≥ Grade 3 non-hematological toxic effects, treatment with carfilzomib will resume, according to the guidelines as summarized in Section 9.5.2.

- Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.

9.6.1 Guidelines for Monitoring, Prophylaxis, and Treatment of Tumor Lysis Syndrome (TLS)

TLS, which may be associated with multi-organ failure, has been observed in treatment cycles 1 and 2 in some patients with multiple myeloma who have been treated with carfilzomib.

The following safety measures are mandatory for all subjects. In addition, pPCL subjects with high tumor burden (e.g., ISS Stage II/III) or rapidly increasing M-protein or light chains or compromised renal function (CrCl < 50 mL/min) should be considered to be at particularly high risk.

9.6.1.1 Hydration and Fluid Monitoring

1. Oral hydration

All subjects must be well hydrated (i.e. volume replete). Begin oral hydration equal to approximately 30 mL/kg/day (~6–8 cups of liquid per day), starting 48 hours prior to the planned first dose of carfilzomib. Compliance must be reviewed with the subject and documented by the site personnel prior to initiating treatment with carfilzomib; treatment is to be delayed or withheld if oral hydration is not deemed to be satisfactory.

2. Intravenous Fluids

250–500 mL of IV normal saline (or other appropriate IV fluid formulation) must be given before and after each carfilzomib dose during cycle 1. If lactate dehydrogenase (LDH) or uric acid is elevated at cycle 2, day 1, then the recommended IV hydration should be repeated for Cycle 2. The goal of the hydration program is to maintain robust urine output, (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload.

In subjects considered to be still at risk for TLS at completion of cycle 1, hydration should be continued into cycle 2, if clinically indicated. Patients in whom this program of oral and IV fluid hydration is contraindicated, e.g. due to pre-existing pulmonary, cardiac, or renal impairment, will not be eligible to participate in the clinical trial.

9.6.1.2 Laboratory Monitoring

Obtain and review serum electrolytes and chemistries prior to each administration of carfilzomib on days 1, 2, 8, 9, 15, and 16 during cycle 1. Results of laboratory studies must be reviewed and

deemed acceptable prior to administering the carfilzomib dose. Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g., serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose. Subjects with such abnormalities should be re-evaluated again within the next 24 hours (or sooner, if clinically indicated) and then periodically as clinically indicated.

If risk factors for TLS persist after day 17 of cycle 1, monitoring of serum chemistries on days 1, 2, 8, 9, 15, 16 should be continued through cycle 2.

9.6.1.3 Clinical Monitoring

Inform subjects of signs and symptoms that may be indicative of TLS, such as fevers, chills/rigors, dyspnea, nausea, vomiting, muscle tetany, weakness, or cramping, seizures, and decreased urine output. Advise subjects to report such symptoms immediately and seek medical attention.

9.6.1.4 Management of Tumor Lysis Syndrome

If TLS occurs, cardiac rhythm, fluid, and serial laboratory monitoring should be instituted.
Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer therapeutic and supportive care, including dialysis, as clinically indicated.

All cases of TLS must be reported to EMN as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event. See chapter 12.3.1 for reporting of SAE.

9.6.1.5 Dosing carfilzomib in Subjects with Acute or Chronic Renal Insufficiency

Carfilzomib has not been fully characterized in subjects with creatinine clearance < 15 mL/min. It is critical that the subject's renal function is known at the time of dosing.
See chapters 9.1.1.3, 9.4.1.3 and 9.5 for guidance regarding dose reduction in subjects with compromised renal function.

9.6.1.6 Urate Lowering Prophylaxis

All patients must receive prophylaxis with hydration and patients should receive rasburicase during Cycle 1 to correct uric acid levels to within normal range prior to carfilzomib doses. Rasburicase 3 mg iv should be given prior to the planned first dose of carfilzomib (day 1 and day 8 and day 15, cycle 1).

If risk factors for TLS no longer exist, rasburicase may then be discontinued. Other uric acid lowering agents such as febuxostat may be substituted for rasburicase.
The use of allopurinol is not advised because of possible medication interaction with carfilzomib.

In patients considered to be still at risk for TLS at completion of cycle 1, rasburicase may be continued into cycle 2, if clinically indicated.

The dose of rasburicase should be adjusted based on renal function, if indicated, according to its package insert. Rasburicase should not be given to patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency.

9.7 Bisphosphonates

Bisphosphonates are recommended after correction of factors predisposing to renal deterioration, such as hypovolemia, except in patients with severe renal impairment, in which reversibility is anticipated.

Treatment with i.v. bisphosphonates will be given 4-6 weeks for 2 years, thereafter i.v. bisphosphonates may be stopped in patients with CR or at the discretion of the treating physician. A commonly used regimen consists of zoledronate 4 mg i.v. or pamidronate (APD) 30 mg i.v. once every 4 weeks.

9.8 Special precautions and supportive care

Female subjects of child-bearing potential must agree to use dual methods of contraception for the duration of the study. Male subjects must agree to use a barrier method of contraception for the duration of the study if sexually active with a female of child-bearing potential.

Approved bisphosphonates and erythropoietic agents are allowed. Subjects may receive antiemetics and antidiarrheals as necessary, but these should not be administered unless indicated.

Pegylated filgastrim (6 mg) should be given in case of ANC drops below 1.0 x 10^9/L prior to initiating the next course of treatment and in case ANC drops below 0.75 x 10^9/L during courses. When pegylated filgastrim is started, it will be given for each successive course on day 1. As an alternative, non-pegylated filgastrim can be considered.

Subjects may receive red blood cells (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines or as described in 9.8.1and 9.8.2. Subjects may receive supportive care with erythropoietin or darbepoetin, in accordance with institutional guidelines.

During CRd treatment subjects should receive antibiotic prophylaxis with co-trimoxazol or ciprofloxacin or other fluoroquinolone. In addition, during CRd treatment and carfilzomib-lenalidomide maintenance subjects should receive acyclovir or similar (famiciclovir, valacyclovir) antivaricella (anti-herpes) agent prophylaxis. Furthermore, during CRd treatment and carfilzomib-lenalidomide maintenance patients should receive thrombosis prophylaxis with “aspirin” (acetylsalicylic acid 75 or 80 mg or carbasalate calcium 100 mg). Patients with a positive history of a venous thrombosis event will receive thrombosis prophylaxis with low molecular heparin. The treating physician might prefer LMWH instead of aspirin, also in patients other than with a positive history of venous thrombosis, which is allowed.

Palliative radiation therapy is permitted if clinically indicated.

9.8.1 Guidelines for platelet transfusions

Thrombocytopenia can occur as a consequence of bone marrow infiltration by tumor cells or may be related to study drug administration. The clinical significance of thrombocytopenia experienced by a patient should be assessed in light of its etiology (treatment or disease or both), the state of the underlying pPCL (stable versus worsening disease), and whether the patient is bleeding or being prepared for a surgical procedure.

The use of any platelet product should be considered in the following circumstances:

- As preparation for an invasive surgical procedure, transfuse in order to maintain a platelet count > 50 x 10^9/L to prevent bleeding.
- If the patient has an active infection, high fever, rapid decrease in platelet count to ≤ 20 x10^9/L and/or coagulopathy, transfuse to maintain a platelet count to > 20 x 10^9/L as prophylaxis for spontaneous bleeding.
- If the patient is actively bleeding or has a platelet count below 10 x 10^9/L, transfuse in order to maintain a platelet count > 10 x 10^9/L.

9.8.2 Guidelines for red cell transfusions

The use of any red cell product should be considered in the following circumstances:

- If the patient has hemoglobin value < 4.3 mmol/L, transfuse to maintain hemoglobin value > 5.0 mmol/L in order to reduce the risk of inadequate oxygenation.
- If the patient is asymptomatic and has a hemoglobin value between ≥ 4.3 and ≤ 5.0 mmol/L, the investigator may consider transfusion on a per-patient basis in order to maintain a hemoglobin value > 5.0 mmol/L.
- If the patient is actively bleeding or has symptomatic cardiac or pulmonary disease or other extenuating circumstances where oxygenation is impaired, the investigator may elect to transfuse on a per-patient basis. In these instances, the trigger hemoglobin value may be > 5.0 mmol/L.
- The use of erythropoietin (e.g. Eprex®/Erypo®) or darbepoetin is allowed.

9.8.3 Forbidden concomitant medication during the study

Concurrent therapy with an approved or investigative anticancer therapeutic with activity against pPCL is not allowed.
Other investigative agents (e.g., antibiotics or antiemetics) should not be used during the study.

9.9 Investigational Medicinal Product Carfilzomib

9.9.1 Summary of known and potential risks

Further details on the potential risks of carfilzomib may be found in the Investigator Brochure.

9.9.2 Preparation and labelling

Carfilzomib will be shipped to trial sites in containers labeled as an Investigational Medicinal Product. Carfilzomib will be prepared and labeled in compliance with GMP and other applicable regulatory requirements.

Carfilzomib for Injection is supplied as a lyophilized parenteral drug product in single-use vials. Each vial contains 60 mg of carfilzomib.

9.9.3 Storage and handling

The investigational medicinal product should be stored in such a manner that accidental loss or destruction or access by an unauthorized person is prevented (in a securely locked area to which access is limited to appropriate study personnel).

Lyophilized carfilzomib for injection must be stored at 2 – 8ºC under the conditions outlined in the separate Pharmacy Manual.

Prior to administration of carfilzomib, the lyophilized product is reconstituted with Water for Injection (WFI), yielding 2 mg/mL solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-b-cyclodextrin (SBE-b-CD, Captisol®).

Please refer to the Pharmacy Manual for “Instructions for Handling of Lyophilized Carfilzomib for Injection.”

Carfilzomib for Injection will be given as an IV infusion over approximately 30 minutes. The dose will be administered at a facility capable of managing hypersensitivity reactions. Subjects will remain at the clinic for at least one hour following each dose of carfilzomib for clinical observation during all of Cycle 1 and Cycle 2, Day 1.

Before and after drug administration, the line must be flushed with 20 mL of normal saline.

9.9.4 Study Drug supply

The sponsor will arrange delivery of carfilzomib to trial sites. No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available.

Carfilzomib for injection is an antineoplastic agent and will be supplied on study. Carfilzomib for injection is supplied as a lyophilized parenteral drug product in single-use vials.

9.9.5 Drug accountability

The investigator, or a pharmacist or other appropriate individual who is designated by the investigator, should maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients (if applicable). Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor. The investigator should also collect and count remaining medication, empty boxes and blisters of medication to check that the patient has taken the assigned dose.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

9.9.6 Study drug return and destruction

Partially used investigational medicinal product should not be redispensed to either the same or another patient after it has been returned.
The trial site should destroy used or partially used study drug containers after drug accountability records have been completed. Destruction should be documented.
At the end of the trial or after expiry of the product unused investigational medicinal product should be destroyed by the trial site. Destruction should be documented.

9.10 Investigational Medicinal Product Lenalidomide

9.10.1 Summary of known and potential risks

Details on known and potential risks are available in the Investigational Drug Brochure and the IND Safety Letters.

9.10.2 Preparation and labeling

Lenalidomide will be shipped to trial sites in containers labeled as an Investigational Medicinal Product. Lenalidomide will be prepared and labeled in compliance with GMP and other applicable regulatory requirements.

All study medication will be dispensed in child-resistant packaging.
Lenalidomide will be supplied as capsules of 5 mg, 10 mg, 15 mg or 25 mg in blisters/wallets.

9.10.3 Storage and handling

See the Investigators Brochure for detailed storage and handling procedures. The investigational medicinal product should be stored in such a manner that accidental loss or destruction or access by an unauthorized person is prevented.

9.10.4 Study drug supply

The sponsor will arrange delivery of lenalidomide to trial sites. No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available.

Lenalidomide (Revlimid®) is an antineoplastic agent for oral use. Patients must comply with the Lenalidomide (Revlimid®) Pregnancy Prevention Risk Management Program.

9.10.5 Drug accountability

Drug accountability should be done according to chapter 9.9.5.

9.10.6 Study drug return and destruction

Study drug return and destruction should be done according to chapter 9.9.6.
Please note that patient should return unused or partially used investigational product in their original packaging/blisters for drug accountability.

10 Study procedures

Aim of the clinical evaluation at entry is to determine eligibility, to evaluate in which ISS stage of disease the patients are classified and to determine the presence of adverse prognostic factors and establish a baseline for response evaluations. Aim of the clinical evaluation during treatment and follow up is to determine response, toxicities and eligibility for further treatment. Before start of each treatment cycle, routine investigations like blood cell count and renal function will be performed according to local policy.

10.1 Time of clinical evaluations

- At entry: before start of treatment (results from diagnostic tests may be used, provided that they are no older than 4 weeks prior to registration)
- After 4 induction treatment cycles for younger patients and after 4 and 8 induction treatment cycles for elderly patients
- After stem cell collection (if applicable): 4 weeks after start cyclophosphamide i.v.
- After each HDM (if applicable): 8 weeks after each course of HDM
- After CRd consolidation : 4 weeks after start of the 2nd CRd consolidation cycle for younger patients with donor; and after 4th CRd for younger patients without donor

- After RIC allo-SCT (if applicable): 8 weeks after RIC allo-SCT
- During maintenance/follow up: every 2 months (after progression every 6 months)

All patients will be followed until 5 years after registration. Patients who are still on maintenance at 5 years after registration will be followed until completion of maintenance therapy.

10.2 Required investigations

	At entry	After each CRd induction treatment cycle†	After 4th CRd (and after 8th CRD for elderly)	After stem cell collection	After each course HDM	After each CRd consolidation †	After 2nd CRd consolidation for patients with donor; or after 4th CRd for patients without donor	After RIC allo-SCT	During maintenance /follow up until progression every 2 months[7], thereafter every 6 months	At progression
Medical history	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Serum Immunochemistry[1)]	X	X	X	X	X	X	X	X	X	X
Urine M-protein (Bence Jones)	X	o.i.	X	X	X	o.i.	X	X	X	X
Blood chemistry[9)]	X	X	X	X	X	X	X	X	X	X
Creatinine clearance	X	X	X	X	X	X	X	X	X	X
Bone marrow aspirate[2)]	X[10)]		X		X		X	X	X	X
Bone marrow biopsy	X									
Skeletal survey	X[8)]									
MRI	o.i.		o.i.	o.i.	o.i.		o.i.	o.i.	o.i.	o.i.
Cardiac ejection fraction	o.i.									
ECG	X		X		X		X			X
X-thorax	X									

	At entry	After each CRd induction treatment cycle†	After 4th CRd (and after 8th CRD for elderly)	After stem cell collection	After each course HDM	After each CRd consolidation †	After 2nd CRd consolidation for patients with donor; or after 4th CRd for patients without donor	After RIC allo-SCT	During maintenance[7] /follow up until progression every 2 months, thereafter every 6 months	At progression
Sperm cryopreservation [3]	X									
PB cryopreservation[4]	X									X
Saliva cryopreservation[4]	X									
BM cryopreservation [5]	X									X
Pregnancy test [6]	X									
Additional studies	X									

o.i. on indication

†) On day 1 of the next cycle before start of therapy, or day 28 of last cycle

1) Includes immuno-electropheresis, immuno-fixation (if immuno-electropheresis is negative) and quantitative serum free light-chain analysis (if free-light chain is used to monitor response, or in case stringent CR is expected).

2) At diagnosis and at the first response evaluation moment when there is immunofixation negativity in serum and urine. After that when immunofixation becomes positive again.
Must be analyzed on morphology for CR and for immunophenotyping to confirm stringent CR (sCR). When there is immunofixation negativity in serum and urine, flowcytometric MRD evaluations should take place after 4th and 8th CRd induction cycle, after each course of HDM, after the 2nd CRd consolidation cycle for younger patients with donor and after 4th CRd consolidation cycle for younger patients without donor, after RIC allo-SCT, and every 6 months during maintenance treatment. (For Italian sites bone marrow will be analyzed every 6 months).

3) For male patients with active child wish.

4) For SNP analysis and paired-end whole exome sequencing (samples will be sent to central laboratory).

5) For Gene Expression Profiling, miRNA profiling and paired-end whole exome sequencing (samples will be sent to central laboratory).

6) At entry, and before and during lenalidomide treatment according to the Pregnancy Prevention Risk Management Plan.

7) During maintenance: hematology every two weeks in the first month, then every four weeks. Immuno-chemistry tested every four weeks.

8) Skeletal survey every 12 months.

9) In addition during cycle 1 and 2 TLS monitoring according to 9.6.1.2.

10) Sampling of blood and bone marrow for central lab is mandatory for enrolment.

Medical history

Standard medical history, with special attention for:

- WHO performance status
- Bone pain
- Infections
- Bleeding tendency
- Obstipation
- Polyneuropathy

Only at entry:

- Prior and present other diseases
- Antecedent hematological or oncological diseases
- Previous chemotherapy or radiotherapy
- Ethnicity

Physical examination

Standard physical examination including body weight and height, with special attention for:

- Macroglossia
- Kyphoscoliosis
- Orthostatic hypotension
- Carpal tunnel syndrome
- Polyneuropathy or other neurologic symptoms
- Edema
- Infections
- Bleeding tendency

Hematology

- Hemoglobin
- Leukocyte count, differential count
- Platelets

Cryopreservation

At Entry: PB, bone marrow and saliva cryopreservation for SNP analysis and for sequencing studies (see chapter 10.5.2)

Blood chemistry

Complete blood chemistry should be performed at entry and in case of abnormal values. Otherwise serum creatinine, albumin, calcium and total proteins are routine evaluations.

- BUN
- Creatinine
- Liver enzymes (AST and ALT)
- Total bilirubin
- Alkaline phosphatase
- Total proteins
- Albumin
- Glucose
- Serum β2-microglobulin
- LDH
- CRP
- Calcium
- Phosphate
- Sodium
- Potassium
- Uric acid

Immunochemistry

- Quantitative serum immune-electropheresis for identification and quantification of M-protein
- Immunofixation to confirm CR
- Quantitative serum light chain (for screening and to confirm (s)CR)
- The 24hr proteinuria should be determined, and in case of a positive result (>150 mg/24hrs) a urine electrophoresis should be performed (in order to distinguish between excretion of albumin (and other proteins) and paraproteins. This will allow quantification of 24hr paraproteinuria also
- Quantitative urine M-protein (Bence Jones) in 24 hrs. urine, including immunofixation to confirm CR

Only at entry or to confirm (s)CR:

- Qualitative serum M-protein
- Qualitative urine M-protein (Bence Jones)

Bone marrow

- Bone marrow biopsy
- Bone marrow aspirate at entry for:
  - Morphology, immunophenotyping (see chapter 10.4)
  - FISH analysis (see chapter 10.3) will be done locally
  - Molecular analysis (sample should be sent to central laboratory, plasma cell purification and cryopreservation for sequencing and RNA microarray analysis, see for collecting and handling of samples for RNA microarray analysis see lab manual)
- Bone marrow aspirate during treatment and follow up (when needed to confirm (s)CR) for:
  - Morphology
  - Immunophenotyping (see chapter 10.4)

Specific investigations

- Creatinine clearance if increased serum creatinine
- Radiographic skeletal survey including skull, pelvis, vertebral column and long bones
- X-Thorax
- ECG
- MRI if patient experiences pain without specific abnormalities on X-Ray
- Cardiac ejection by scintigraphy or cardiac echo; it is advised to perform a Left Ventricular Ejection Fraction (LVEF) in all patients at entry. In addition it is recommended to repeat the LVEF after stem cell collection, as part of the pre-transplantation screening prior to HDM.

Additional investigations

Only on clinical indication:

- Survey for exclusion of AL amyloidosis
- Bleeding time
- Cryoglobulins, cold agglutins
- Serum viscosity, fundoscopy
- Spirometry

10.3 Cytogenetic analysis

FISH analysis is required in all patients at diagnosis. The following cytogenetic abnormalities will be evaluated as prognostic variables del1p, ampli 1q, t(4;14), t(14;16), t(11;14), ampli 9, del13q/13-,

del17p as analyzed in purified bone marrow plasma cells. Conditions for FISH will be according to the EMN Consensus[38].

10.4 Immunophenotyping

At diagnosis, during treatment and follow-up, a bone marrow aspirate will be performed for both morphology and immunophenotyping analyses. Each responsible physician for the immunophenotyping analysis of the patients in a hospital will be notified automatically by email of the registration of a patient from that hospital in the study.
Special investigations are required in patients that achieve a CR. At the time that patients have obtained normal free light chain ratio, and are expected to be in CR, CR has to be confirmed on bone marrow morphology and additional immunophenotyping is needed to confirm ***stringent*** CR (sCR=polyclonal plasma cell phenotype). Bone marrow aspirate will be processed using a 4-color direct immunofluorescence technique. CD138/CD38/CD45 and light scatter characteristics will be assessed simultaneously in at least one tube. Sample quality, number of events and clonality assessment will be performed according to EMN Consensus (Rawstron AC et al. Haematologica 2008; 93(3) 431-438).
For the assessment of stringent CR (sCR) bone marrow samples can be collected and analyzed in the local center or in case this technique is not locally available, the samples will be sent to central laboratories in each participating country (see Appendix F).

10.5 Correlative studies

See appendix F for a detailed description of correlative studies, including a description of the management and handling of pPCL samples.

10.5.1 MRD analysis

In this trial the importance of flowcytometric Minimal Residual Disease (MRD) negativity will be investigated in a correlative study. Patients who are immunofixation negative in serum and urine need to undergo a bone marrow puncture in order to confirm flowcytometric MRD negativity. A bone marrow puncture needs to be performed at every response evaluation moment at which there is immunofixation negativity (after 4th and 8th CRd induction cycle, after each course of HDM, after the 2nd CRd consolidation cycle for younger patients with donor and after 4th CRd consolidation cycle for younger patients without donor, after RIC allo-SCT, and every 6 months during maintenance treatment). Flowcytometric MRD analyses are typically performed regionally with an 8 color FACS machine using the EMN-02 MRD protocol. At the 2-monthly examinations mandatory serum immunofixation and serum free light levels will be repeatedly performed, in order to mark the point

when a patient turns from MRD-negative (=immunofixation-negative) to MRD-positive (=immunofixation-positive), i.e. before a clinical relapse has occurred. These immunofixations and serum-free light assessments can be performed locally. (See appendix F).
When there is immunofixation negativity in serum and urine, flowcytometric MRD evaluations should take place after 4th and 8th CRd induction cycle, after each course of HDM, after the 2nd CRd consolidation cycle for younger patients with donor and after 4th CRd consolidation cycle for younger patients without donor, after RIC allo-SCT, and every 6 months during maintenance treatment.

10.5.2 Gene-expression profiling, miRNA-profiling, paired-end whole-exome sequencing& single nucleotide polymorphism (SNP) analysis

Gene expression profiling, miRNA profiling, paired-end whole exome sequencing and SNP analysis will be performed to further characterize MM subgroups at the molecular level, to find new biomarkers with prognostic value, to elucidate mechanisms of drug resistance & disease progression and identify SNPs related to treatment outcome and side-effects. Bone marrow samples, peripheral blood and saliva will be drawn before start of treatment and at relapse/progression. Samples are handled according to the procedure described in the lab manual.

Since there are inter-ethnic differences in frequency of SNPs, it is necessary to document the ethnicity of patients included in the trial. This will allow us to perform multivariate analysis to find whether a certain SNP is an independent prognostic factor.

10.6 Response Evaluation

Response will be evaluated after 4 CRd induction treatment cycles for younger patients and after 4 and 8 CRd induction treatment cycles for elderly patients, after stem cell collection, after each HDM, 4 weeks after start of the 2nd CRd consolidation cycle for younger patients with donor and after 4th CRd for younger patients without donor, 8 weeks after RIC allo-SCT (if applicable) and at 2 months intervals during maintenance and follow up. Response will be evaluated according to the modified IMWG criteria for pPCL[39](see appendix B). Progression-free survival will be calculated from registration until progression or death.

11 Withdrawal of patients or premature termination of the study

11.1 Withdrawal of individual patients from protocol treatment

Patients should be withdrawn from protocol treatment if any of the following criteria for withdrawal are met:

- Death
- No compliance of patient: patient is unable or unwilling to adhere to the treatment schedule and/or procedures required by the protocol (e.g. lenalidomide pregnancy prevention program)
- Patient not eligible in hindsight
- Progression at evaluation moments
- Pregnancy (of female patient)

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can also decide to withdraw a patient from protocol treatment for other reasons than the criteria described above. Examples of reasons for withdrawal from protocol treatment are:

- Excessive toxicity
- Refusal of patient to continue protocol treatment
- No compliance of the patient: patient is unable or unwilling to adhere to the treatment schedule and/or procedures required by the protocol

Patients who are withdrawn from protocol treatment will receive medical care according to local practice

11.2 Follow up of patients withdrawn from protocol treatment

Patients who are withdrawn from treatment for other reasons than death will be followed as described in chapter 10.1 for follow up.
For patients who are withdrawn from treatment because in hindsight they did not fulfill the eligibility criteria (see chapter 8.1) at time of enrolment, data will be collected until 30 days after the last protocol treatment given. SAE information will be collected as described in chapter 12.3.

11.3 Withdrawal of informed consent

If a patient states he or she withdraws their consent to participate in the trial, the investigator should attempt to verify the patient's intent and record this in the patient's medical file:

- The patient can refuse further treatment and/or procedures according to protocol, while still consenting with further follow up data collection.
- The patient can refuse further treatment and/or procedures according to protocol, and withdraw consent for further follow up data collection.
- The patient can refuse further treatment and procedures according to protocol, withdraw consent for further follow up data collection and withdraw consent to use any data in the trial.

If the patient's intent is to withdraw consent for further data collection or to withdraw consent to use his or her data in the trial, the investigator should inform EMN Research Italy so appropriate actions can be taken.
If the patient's intent cannot be verified, further follow up data will be collected for this patient as described in chapter 10.1 for follow up.

11.4 Premature termination of the study

The sponsor may decide to terminate the study prematurely based on the following criteria:

- There is evidence of an unacceptable risk for study patients (i.e. safety issue)
- There is reason to conclude that it will not be possible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue enrolment of more patients; for example insufficient enrolment that cannot be improved
- The DSMB recommends to end the trial based on viable arguments other than described above

The sponsor will promptly notify all concerned investigators, the Ethics Committee(s) and the regulatory authorities of the decision to terminate the study. The sponsor will provide information regarding the time lines of study termination and instructions regarding treatment and data collection of enrolled patients.

12 Safety

12.1 Definitions

Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject administered a medical product and which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious adverse event (SAE)

A serious adverse event is defined as any untoward medical occurrence that at any dose results in:

- Death
- A life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Significant / persistent disability or incapacity
- A congenital anomaly / birth defect
- Any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above, including suspected transmission of infectious agents by a medicinal product).

Suspected unexpected serious adverse reaction (SUSAR)

All **suspected** Adverse Reactions which occur in the trial and that are both **unexpected** and **serious**. Suspected adverse reactions (AR) are those AEs of which a reasonable causal relationship to any dose administered of the investigational medicinal product and the event is suspected. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorized medicinal product).

12.2 Adverse event

12.2.1 Reporting of adverse events

Adverse events will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier.

Adverse events occurring after 30 days after the last dose of any study drug should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.

Adverse Events have to be reported on the Adverse Events CRF. Adverse Events will be scored according to the NCI Common Terminology Criteria for Adverse Events, version 4.0 (see appendix D).

Comorbidities will be entered at baseline on the electronic CRF.

All Adverse Events have to be reported, with the exception of:

- A pre-existing condition that does not increase in severity; the pre-existing condition should be reported on the baseline concomitant diseases CRF
- AEs of CTCAE grade 1
- Abnormal laboratory values that have been recorded as being not clinically significant by the investigator in the source documents
- Alopecia
- Nausea/vomiting
- Relapse/Progression of the disease under study; complications as a result of disease progression remain reportable Adverse Events
- AEs due to HDM and auto-SCT treatment
- AEs occurring during the planned hospitalization for the allo-SCT

12.2.2 Follow up of adverse events

All adverse events will be followed clinically until they have been resolved, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
Follow up information for grade 3 or 4 adverse events considered at least possibly related to the investigational medicinal product by the investigator should be reported on the AE CRF until recovery or until 6 months after the last dose of IMP, whichever comes first.
Follow up information for all other adverse events should be reported on the AE CRF until recovery or until 30 days after the last dose of any drug from the protocol treatment schedule, whichever comes first.

12.3 Serious Adverse Events

12.3.1 Reporting of serious adverse events

Serious Adverse Events (SAEs) will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier.
Serious Adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.
All cases of TLS must be reported as SAE. Second primary malignancies must be reported as described in chapter 12.6.

SAEs must be reported to EMN Research Italy by fax **within 24 hours** after the event was known to the investigator, using the SAE report form provided. This initial report should contain a minimum amount of information regarding the event, associated treatment and patient identification, as described in the detail in the instructions for the SAE report form. Complete detailed information should be provided in a follow-up report within a further 2 business days, if necessary.

The following events are not considered to be a Serious Adverse Event:

- Relapse/Progression of the disease under study; death or complications as a result of disease progression remain reportable Serious Adverse Events
- Hospitalization for protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a Serious Adverse Event
- Hospitalization for diagnostic investigations (e.g., scans, endoscopy, sampling for laboratory tests, bone marrow sampling) that are not related to an adverse event. Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- Hospitalization for a procedure that was planned prior to study participation (i.e. prior to registration). This should be recorded in the source documents. Prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.

12.3.2 Causality assessment of Serious Adverse Events

The investigator will decide whether the serious adverse event is related to trial medication, i.e. any of the products from the protocol treatment schedule. The decision will be recorded on the serious adverse event report. The assessment of causality is made by the investigator using the following:

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship.

12.3.3 Follow up of Serious Adverse Events

All serious adverse events will be followed clinically until they are resolved or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
Follow up information on SAEs should be reported monthly until recovery or until a stable situation has been reached. The final outcome of the SAE should be reported on a final SAE report.

12.3.4 Processing of serious adverse event reports

The EMN Research Italy will forward all SAE reports within 24 hours of receipt to the Principal Investigator, Amgen and Celgene.
EMN Research Italy will evaluate if the SAE qualifies as a suspected unexpected serious adverse reaction (SUSAR).
The IB will be used for carfilzomib as a reference document for expectedness assessment.
The IB will be used for lenalidomide as a reference document for expectedness assessment.
EMN Research Italy will ensure that a six-monthly line listing of all reported SAE's is provided to the Ethics Committee(s) if this is required by national laws or regulations or by the procedures of the Ethics Committee.

12.4 Reporting Suspected Unexpected Serious Adverse Reactions

EMN Research Italy, on behalf of the sponsor, will ensure the reporting of any SUSARs to the Ethics Committees (EC), the Competent Authorities (CA), Amgen and Celgene and the investigators in compliance with applicable laws and regulations, and in accordance with any trial specific agreements between the sponsor and a co-sponsor or Amgen and Celgene. Each participating country will ensure the reporting of any SUSAR to the Ethics Committee (EC)

Expedited reporting of SUSARs will occur no later than 15 days after EMN Research Italy had first knowledge of the serious adverse event. For fatal or life-threatening cases this will be no later than 7 days for a preliminary report, with another 8 days for a complete report.
The manner of SUSAR reporting will be in compliance with the procedures of the Ethics Committees and Health Authorities involved.

12.5 Pregnancies

Pregnancies or suspected pregnancies (including positive pregnancy tests regardless of age or disease state) occurring in female patients or female partners of male patients while the patients are still treated with the Investigational Product or within 28 days of the patients' last dose of Investigational Product ,must be reported to EMN Research Italy immediately by fax after the event was known to the investigator, using the pregnancy report form provided.

The investigator will follow the female subject until completion of the pregnancy, and must notify the sponsor and Celgene's Drug Safety Department of the outcome of the pregnancy (including false-positive pregnancy tests) within 24hours of having knowledge of the event or as specified below. The investigator will provide this information as a follow-up to the initial pregnancy report. If the outcome of the pregnancy meets the criteria for classification as a SAE (i.e., spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly – including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs. In the case of a live "normal" birth, the sponsor should be informed as soon as the information is available. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the investigator suspects is related to the in utero exposure to the investigational medicinal product(s) should also be reported.
The investigator is encouraged to provide outcome information of the pregnancy of the female partner of a male subject, if this information is available to the investigator and the female partner gives her permission.

12.6 Second Primary Malignancies

Second primary malignancies (SPMs) will be monitored until 3 years after the last administration of lenalidomide as events of interest and must be reported as SAEs. This includes any SPM, regardless of causal relationship to any study drug, occurring at any time during treatment and during the follow up period.

Events of second primary malignancy are to be reported using the SAE report form and must be considered an “Important Medical Event” even if no other serious criteria apply. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g. pathology report).

The incidence of second primary malignancies is also monitored via a separate form (Second Primary Malignancy Report Form). This form should be filled out, dated and signed by the responsible investigator and returned to the EMN by fax within 24 hours after establishment of a second primary malignancy.

SPMs must also be documented in the other appropriate page(s) of the CRF (e.g. Adverse Event Form and Follow up Form).

12.7 Reporting of safety issues

The sponsor will promptly notify all concerned investigators, the Ethics Committee(s) and the regulatory authorities of findings that could affect adversely the safety of patients, impact the conduct of the trial, increase the risk of participation or otherwise alter the EC’s approval to continue the trial. In the occurrence of such an event the sponsor and the investigators will take appropriate urgent safety measures to protect the patients against any immediate hazard. The accredited Ethics Committee will suspend the study pending further review, except insofar as suspension would jeopardize the patient’s health. The local investigator will inform the patients and local ethics or review committees according to hospital policy. The sponsor will inform any other parties that are involved in the trial.

12.8 Annual safety report

The sponsor will submit once a year throughout the clinical trial, a safety report to the Ethics Committees and Competent Authorities of the concerned Member States, Amgen and Celgene. The content of the annual safety report will be according to the EU guidance document ‘*Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use’.*

12.9 Data Safety and Monitoring Board

The DSMB will advise the Chair of the HOVON working group, Principal Investigator and Co-investigators in writing about the continuation of the trial. The DSMB will evaluate the general progress and feasibility of the study, the quality and completeness of the data, adverse events and safety, and differences between the arms.

The DSMB consists of at least three members, among whom (at least) one statistician and minimal two physicians. The members of the DSMB are invited on personal title on the basis of their expert knowledge of the disease involved or the research methodology. Members of the DSMB will have ample experience with clinical trials. The members of the DSMB will not be involved in the study, work at the HOVON Data Center, EMN Research Italy, be a member of the HOVON board, or work in a hospital department participating in the study. The members will not have a conflict of interest due to ties with a company involved in the study. The DSMB reports their written recommendations to the trial statistician. The report may consist of a confidential and a public part, where the confidential part contains references to unblinded data. The trial statisticians forward the public part of the DSMB recommendation to the Principal Investigator. The DSMB recommendations are not binding.

Details of the DSMB constitution and tasks are documented in the trial specific DSMB chapter.

The DSMB will receive at least the following reports from the trial statistician for review:

- Interim analysis report (as described in chapter 14.3)
- Annual safety data listing the incidence of (serious) adverse events, (serious) adverse reactions and SUSARs
- Annual progress report and annual safety report

13 Endpoints

The endpoints will be separately studied in younger (18-65 years inclusive) and elderly (≥ 66 years) patients.

13.1 Primary endpoint

♦ Progression-free survival (PFS, i.e. time from registration until progression or death, whichever comes first)

13.2 Secondary endpoints

- Safety and toxicity as defined by type, frequency and severity of adverse events as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4
- Overall response rate (at least PR) after the different phases of treatment
- (s)CR + VGPR ((stringent) complete and very good partial response) after the different phases of treatment
- Overall survival, defined as time from registration until death from any cause. Patients still alive at the date of last contact, will be censored
- Toxicity and tolerability of the different phases of treatment
- Explore the value of prognostic factors including FISH abnormalities, β2-microgloublin, LDH, MRD-negativity, pPCL gene expression profiles and sequencing results on the overall response, overall survival and progression–free survival
- Frequency of second primary malignancies

14 Statistical considerations

14.1 Patient numbers and power considerations

This is a prospective phase 2 study to evaluate the efficacy of the combination of carfilzomib-lenalidomide-dexamethasone in both younger (age 18-65 years inclusive) and elderly (≥66 years) newly diagnosed pPCL patients. Data for these two age groups will only be analyzed separately.

We expect that for about 80% of the younger patients a suitable donor can be selected. In addition, we expect that 20% of the patients with a donor will not proceed to allo-SCT because of progressive disease, refusal, or development of complications.

Prior data indicate that the median PFS for younger patients on the historical treatment is 12 months.[39]
A true median PFS on the experimental treatments of (at least) 18.3 months (intention to treat) would imply that the current schedule is sufficiently promising for further investigation in clinical trials. Assuming uniform accrual for 3 years and an additional follow up of 1 year after the last patient has been registered, then in order to have power $1 - \beta = 0.80$ to detect this improvement, with 2-sided significance level $\alpha = 0.05$, a total of 61 patients need to be registered[40].

For elderly patients, median progression-free survival is about 10 months (based on historical treatment of non-transplant eligible patients [39] For an improvement of PFS to median 15.3 months,

we would require 55 registered patients (assuming uniform accrual 3 years, additional follow up of 1 year, 2-sided significance level $\alpha = 0.05$ and power $1 - \beta = 0.80$)[40]

14.2 Statistical analysis

All analyses will be according the intention to treat principle, irrespective the actual treatment received. However, patients initially included in the study but considered ineligible afterwards based on information that should have been available before registration, will be excluded from the respective analyses. All analyses will only be done separately for younger patients (by B. van der Holt, HOVON) and for elderly patients (by R. Passera, GIMEMA).

14.2.1 Efficacy analysis

The main endpoint is the progression-free survival, defined as time from registration until progression or death, whichever comes first. Actuarial survival curves for PFS, separately for younger and elderly patients, will be computed using the Kaplan-Meier method, and 95% CI will be constructed. Estimates for median PFS including 95% CI's will also be determined, as these are the primary endpoints. The data of patients in a specific age group will be analyzed when for each patient validated data are available indicating that he is known to be alive without progression after more than 18 months after randomization, or had progression or died within 18 months.
For the younger patients, the null hypothesis will be rejected when the lower limit of the 95% CI of the estimated median PFS is larger than 12 months. For the elderly patients, the null hypothesis will be rejected when the lower limit of the 95% CI of the estimated median PFS is larger than 10 months.

Secondary efficacy endpoints are response rate and overall survival. Response rates will be described as percentages with 95% CI. Actuarial survival curves for OS, separately for younger and elderly patients, will be computed using the Kaplan-Meier method, and 95% CI will be constructed.

14.2.2 Toxicity analysis

The analysis of treatment toxicity will be done primarily by tabulation of the incidence of adverse events CTCAE grade 2 or more (Appendix C) by treatment arm and cycle. Data from all subjects who receive any study drug will be included in the safety analyses. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events will be summarized by worst CTCAE grade.

14.2.3 Additional analyses

Additional analyses may involve the analysis of prognostic factors, especially FISH abnormalities, ISS stage and molecular profiles (GWAS, GEP, mutations) with respect to PFS, response rate, and OS. Logistic and Cox regression analysis may be used for this purpose. To include all patients in (multivariate) analyses, a multiple imputation algorithm will be used to impute missing covariate values if applicable. In addition, an exploratory analysis evaluating the prognostic value of gene expression profiles on overall response will be performed. At the time of analysis of this microarray data an appropriate tool will be used to overcome the problem of over fitting.
Flow cytometry for detection of neoplastic plasma cells will be performed in patients achieving CR to confirm sCR in patients with normal free light chain. Results will be correlated with PFS and OS. It should be stressed that these additional analyses should be considered as exploratory, and therefore only as hypothesis-generating.

14.2.4 Statistical analysis plan

Before the final analysis will be performed, a Statistical Analysis Plan (SAP) will be written, which will describe in more detail all the analyses as described in paragraphs 14.2.1-14.2.3 to be performed. Deviations from the analysis plan will be discussed with the study coordinators and can only affect the additional (exploratory) analyses, but not the primary (confirmatory) analyses on which the sample sizes for both age groups is based.
The SAP for the younger patients will be prepared by B. van der Holt (HOVON) in close cooperation with R. Passera (GIMEMA), while R. Passera will prepare the SAP for the elderly patients in close cooperation with B. van der Holt.

14.3 Interim analysis

For each of the two age groups, one interim analysis is planned, primarily to describe adverse events observed during induction therapy with CRd. This will be done when complete data of the first 20 registered patients (elderly and younger patients separately) regarding CRd cycles 1-4 are available. The accrual will however not be discontinued while waiting for these data. Results of the interim analysis will be presented confidentially to an independent data and safety monitoring board (DSMB). Only if the DSBM recommends that the study should be stopped or modified, the results will be made public to the principal investigators for further decisions. The DSMB is free in its public recommendations to the study coordinators and the confidential recommendations to the study statisticians. For the interim analysis a detailed report will be generated and presented to the DSMB. It will include the number of entered patients and at that time evaluable patients, treatment given, and incidence of SAE’s and other adverse events and infections by grade. Adverse events will be

described by summary table broken by site, CTCAE grade and relation to trial treatment. The study will be closely and sequentially monitored before the interim analysis. Monitoring will be based on the reported SAE's, which are not subjected to data delay. In addition, a separate report on the incidence of SAE's and other adverse events and infections, as described before, will be sent to the DSMB once a year. Again, the DSMB is free in her public recommendations to the study coordinators and the confidential recommendations to the study statisticians.

15 Registration

15.1 Regulatory Documentation

Before shipment of study drug to the investigational site and before enrollment of the first patient the following documents must be provided to HOVON Data Center, unless specified differently in the country/group specific addendum.

By the principal investigator or study coordinator for all sites within their country:

- name and address of the (central) Ethical Committee including a current list of the members
- Co-sponsor contract
- EC and CA approval
- Insurance certificate
- CV coordinating investigator
- any other documentation required by local regulations.

By the local investigator for each investigational site:

- Local Contact Form, signed and dated by the local investigator;
- a copy of the dated and signed (central) Ethical Committee approval of the protocol, any amendments and informed consent form for the investigational site. This approval must clearly identify the specific protocol by title, number and version date and must be signed by the chairman or authorized designee. The approval must also clearly identify the site(s) the approval applies to;
- a copy of the approved local version of the Patient Information and Informed Consent form;
- approval of participation by site's Board of Directors, if required by local regulations;
- CV of local investigator;
- Any other documentation required by local regulations.

15.2 Registration

The patient should be registered immediately after diagnosis and before the start of protocol treatment.

Patients will be registered at EMN Research Italy by web http://www.emntg.org. Investigators who do not have an account yet should register at this website to obtain an account after consultation of HDC.

The following information will be requested at registration:

- Protocol number
- Institution name
- Name of responsible investigator
- Age on inclusion
- Date of informed consent
- Date of sample shipment (optional)
- Date of diagnosis of pPCL
- Criteria for measurable disease
- Serum β2-microglobulin
- Serum albumin
- Eligibility criteria

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number.

16 Data collection and quality assurance

16.1 Case Report Forms

Data will be reported on electronic Case Report Forms (CRF) which will be completed and submitted using Remote Data capture (RDC). Guidelines on how to use RDC will be provided to all centers. All RDC forms (CRF forms) will be specifically designed by EMN Research Italy for this study. These electronic forms will be used by all participants.

Data will be collected to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data collected on the CRF are derived from the protocol and will include at least:

- Inclusion and exclusion criteria;
- Baseline status of patient including medical history and stage of disease;
- Timing and dosage of protocol treatment;
- Baseline concomitant diseases and adverse events;
- Parameters for response evaluation;
- Any other parameters necessary to evaluate the study endpoints;
- Survival status of patient;
- Reason for end of protocol treatment.

The forms must be electronically completed according to the schedule defined in the CRF guidelines through the EMN web based Remote Data Capture (RDC) system that can be accessed at http://www.emntg.org. The list of staff members authorized to enter forms (with a sample of their signature) must be identified on the signature log and sent to the HOVON Data Center by the responsible investigator before the start of the study.
In all cases, it remains the responsibility of the investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

Each page can be changed and saved whenever necessary until it is submitted; once the CRF is submitted, the center that wants to change the data can unlock the CRF by sending an e-mail to EMN Research Italy. All changes will be tracked: the database of the web site will keep track of the first version with the date of validation, and of the second version with the date of correction.

All CRF entries must be based on source documents.
SAE, SPM and Pregnancy Notification forms will be sent by fax to EMN Research Italy, where they will be entered in the database.

16.2 Data quality assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator before the study, and site visits by the sponsor.
Data collected on the CRF will be verified for accuracy. If necessary, queries will be sent to the investigational site to clarify the data on the CRF. The investigator should answer data queries within the specified time line.

16.3 Monitoring

This trial is part of the HOVON Site Evaluation Visit program. For other groups the EMN regulations will apply and deviations of the monitoring will be described in the addendum.
Site evaluation visits will be performed for HOVON trials to review the quality of the site and not specifically the quality of a certain trial. It will enable HOVON to collect quality data and facilitate improvement of the participating sites. Data cleaning or monitoring of the performance of specific trials is not the goal of the site evaluation visits. Site evaluation visits will be performed according to the site evaluation visit plan.
A fundamental ingredient of the site evaluation visit is the interview with an investigator regarding the site's organization and trial procedures. The site documents from a randomly selected HOVON trial will serve as a guide to review the results of these procedures: the rights and well-being of patients are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).
Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. The sponsor expects that during site visits the relevant investigational staff will be available, the source documentation will be available and a suitable environment will be provided for review of study-related documents.

16.4 Audits and inspections

The investigator will permit site-visits to carry out an audit of the study in compliance with regulatory guidelines. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected.
Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17 Ethics

17.1 Accredited ethics committee

An accredited Ethics Committee will approve the study protocol and any substantial amendment.

17.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines, the EU Clinical Trial Directive (2001/20/EG), and applicable regulatory requirements. The local investigator is responsible for the proper conduct of the study at the study site.

17.3 Patient information and consent

Written informed consent of patients is required before enrolment in the trial and before any study related procedure takes place.
The investigator will follow ICH-GCP and other applicable regulations in informing the patient and obtaining consent. The investigator should take into consideration if the patient is capable of giving informed consent. Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient.
There is no set time limit for the patient to make a decision. The investigator should inform each patient if there is a specific reason why he/she must decide within a limited time frame, for example if patients condition necessitates start of treatment or if the trial is scheduled to close for enrolment.

The content of the patient information letter, informed consent form and any other written information to be provided to patients will be in compliance with ICH-GCP and other applicable regulations and should be approved by the Ethics Committee in advance of use.
The patient information letter, informed consent form and any other written information to be provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent. Any revised informed consent form and written information should be approved by the Ethics Committee in advance of use. The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

17.4 Trial insurance

Prior to the start of the trial, the sponsor will ensure that adequate insurance for patients is in place covering losses due to death or injury resulting from the trial, in accordance with applicable laws and regulations in each country where the trial is conducted. The sponsor will take out an insurance policy or delegate this responsibility to a national co-sponsor. Proof of insurance will be submitted to the Ethics Committee.

In addition, the sponsor will ensure that adequate insurance is in place for both investigator(s) and sponsor to cover liability pertaining to death or injury resulting from the trial.

18 Administrative aspects and publication

18.1 Handling and storage of data and documents

18.1.1 Patient confidentiality

Each patient is assigned a unique patient study number at enrolment. In trial documents the patient's identity is coded by patient study number as assigned at enrolment. In some cases date of birth is also listed.
The local investigator will keep a subject enrolment and identification log that contains the key to the code, i.e. a record of the personal identification data linked to each patient study number. This record is filed at the investigational site and should only be accessed by the investigator and the supporting site staff, and by representatives of the sponsor or a regulatory agency for the purpose of monitoring visits or audits and inspections.

18.1.2 Filing of essential documents

Essential Documents are those documents that permit evaluation of the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).
The investigator should file all essential documents relevant to the conduct of the trial on site. The sponsor will file all essential documents relevant to the overall conduct of the trial. Essential documents should be filed in such a manner that they are protected from accidental loss and can be easily retrieved for review.

18.1.3 Record retention

Essential documents should be retained for 15 years after the end of the trial. They should be destroyed after this time.
Source documents (i.e. medical records) of patients should be retained for at least 15 years after the end of the trial. Record retention and destruction after this time is subject to the site's guidelines regarding medical records.

18.1.4 Storage of samples

Biological samples should only be stored for the purpose of additional research if the patient has given consent. If no informed consent was obtained, samples should be destroyed after the patient has completed all protocol treatment and procedures.
Storage of biological samples on site is subject to the site's guidelines; samples may be labeled with the patients identifying information (e.g. name, hospital record number)
Samples that are shipped to another facility (e.g. a central laboratory) for a purpose as described in this protocol or for additional scientific research, should be stripped from any identifying information and labeled with a code (trial name or number and patient study number as assigned at enrolment).

18.2 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the Ethics Committee application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be submitted to the Ethics Committee and to the Competent Authority.

Non-substantial amendments will not be submitted, but will be recorded and filed by the sponsor.

18.3 Annual progress report

The sponsor will submit a summary of the progress of the trial to the accredited Ethics Committee once a year. Information will be provided on the date of inclusion of the first patient, numbers of patients included and numbers of patients that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

18.4 End of study report

The sponsor will notify the accredited Ethics Committee and the Competent Authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited Ethics Committee and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the sponsor will submit an end of study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethics Committee and the Competent Authority. Upon request of the accredited Ethics Committee or the Competent Authority the sponsor will submit an updated version of the end of study report within one year after the last patient's last visit.

18.5 Publication policy

Final publication of trial results

Trial results will always be submitted for publication in a peer reviewed scientific journal regardless of the outcome of the trial – unless the trial was terminated prematurely and did not yield sufficient data for a publication.

The final publication of the trial results of the younger patients will be written by the Principal Investigator, the Co-investigators and the trial statisticians on the basis of the statistical analysis performed at the HOVON Data Center by B. van der Holt (HOVON) in close cooperation with R. Passera (GIMEMA). A draft manuscript will be submitted for review to:

- All co-authors
- The chair of the relevant HOVON working group, who is entitled to share and discuss the manuscript with working group members.

After revision the final manuscript is submitted to the HOVON secretary for review of compliance with this policy. After approval by the HOVON board the manuscript will be sent to a peer reviewed scientific journal.

The final publication of the trial results of the elderly patients will be written by the Principal Investigator, the Co-investigator and the trial statisticians on the basis of the statistical analysis performed at EMN Research Italy by R. Passera (GIMEMA) in close cooperation with B. van der Holt (HOVON). A draft manuscript will be submitted for review to:

- All co-authors
- The chair of the relevant GIMEMA working group, who is entitled to share and discuss the manuscript with working group members

After revision the final manuscript is submitted to the GIMEMA secretary for review of compliance with this policy.
After approval by the GIMEMA board the manuscript will be sent to a peer reviewed scientific journal.

Authorship

Authors of the main manuscripts will include the Principal Investigator, the Co-investigators, investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion rate), the trial statisticians and the trial manager. Others who have made a significant contribution to the trial may also be included as author, or otherwise will be included in the acknowledgement.

Authors of correlative manuscripts (e.g. results of side studies) will include the Principal Investigator, the Co-investigator(s), and those persons who have made a significant contribution to the published results.

The Principal Investigators should discuss and decide on the matter of authorship of the main manuscript prior to the start of the trial – with the exception of authors included on account of inclusion rate. The Principal Investigators are urged to use the maximum number of authors allowed by the journal to the full extent.

Interim and partial publications

Interim publications, abstracts or presentations of the study may include demographic data, overall results and prognostic factor analyses, results for secondary endpoints, but no comparisons for the primary endpoint may be made publicly available before the recruitment is discontinued.

The proposed publication policy regarding various manuscripts will be as follows:

Study question	**1st author**	**2nd author**	**Last author**
Younger patients**	HOVON	Based on inclusion	GIMEMA
Elderly patients*	GIMEMA	Based on inclusion	HOVON
Sequencing			
GEP			

**For younger publication first author: HOVON, second: GIMEMA, third: HOVON; third to last: GIMEMA, second to last: HOVON, last: GIMEMA; all other investigators will be included based on recruitment.

For elderly publication first author: GIMEMA, second: HOVON, third: GIMEMA; third to last: HOVON, second to last: GIMEMA, last: HOVON; all other investigators will be included based on recruitment.

Investigators participating in the trial have a right to publish results from data they collected for the study. The Principal Investigator, the Co-investigator(s) and the trial statisticians must approve any such publication, abstract or presentation based on patients included in this study. This is applicable

to any individual patient or any subgroup of the trial patients. Such a publication cannot include an analysis of any of the study endpoints unless the final results of the trial have already been published.

All clinical and study data will be the property of the cooperative tumor groups. Patents and intellectual properties will belong to the cooperative tumor groups or will be subject to a decision made by the principal investigators.

Abstracts and presentations

Abstracts and presentations at public meetings will represent the trial as a project under HOVON affiliation (younger patients) or GIMEMA affiliation (elderly patients). The abstract or presentation should not be represented under affiliation of the working group or a specific hospital.

Slides will be designed using the HOVON style template and any other presentation materials will show the HOVON logo.

Since the trial is conducted in partnership with GIMEMA (co-sponsor), the abstract and presentation should represent the co-sponsor contribution and slides should also show the co-sponsor logo in addition to the HOVON logo.

Prior to its public use, the abstract or presentation is submitted to the HOVON and GIMEMA secretary for review of compliance with this policy.

Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
Auto-SCT	Autologous Stem Cell Transplantation
Allo-SCT	Allogeneic Stem Cell Transplantation
AL	Amyloid Light-chain
ANC	Absolute Neutrophil Count
BJ	Bence Jones
BM	Bone Marrow
BM	Bone Marrow Transplant
BRDU	Bromo Deoxy Uridine
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
Ca	Calcium
CA	Competent Authority
CIBMTR	Center for Instrumental Blood and Marrow Transplant Research
CNS	Central Nervous System
CR	Complete Remission
CRd	Carfilzomib, Revlimid (lenalidomide), dexamethasone
CRF	Case Report Form
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebro Vascular Accident
DFS	Disease-Free Survival
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EBMT	European Group for Blood and Marrow Transplantation
EFS	Event Free Survival
EORTC	European Organization for Research and Treatment of Cancer
ESRD	End Stage Renal Disease
FISH	Fluorescence In Situ Hybridization
FLC	Free Light Chain
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular Filtration Rate

GI	Gastro-intestinal
GvDH	Graft versus Host Disease
Hb	Hemoglobin
HDM	High-Dose Melphalan
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte histocompatibility Antigen
HOVON	Dutch-Belgian Hematology-Oncology Cooperative Group
HZ	Herpes Zoster
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IFM	Intergroup Français de Myelome
IMiDs	Immunomodulatory Drugs
IMP	Investigational Medicinal Product
ISS	International Staging System
ITT	Intention To Treat
IU	International Units
KCl	Potassium chloride
LDH	Lactate Dehydrogenase
METC	Medical Ethical Review Committee
MM	Multiple Myeloma
MRD	Minimal Residual Disease
NaCl	Sodium Chloride
NCI	National Cancer Institute
NMA	Non Myeloablative
NMSG	Nordic Myeloma Study group
NYHA	New York Heart Association
OS	Overall Survival
PB	Peripheral Blood
PBSC	Peripheral Blood Stem Cell(s)
PCL	Plasma cell leukemia
PD	Progressive Disease
PFS	Progression-Free Survival
pPCL	Primary Plasma Cell Leukemia
PO	Per Os
PR	Partial Response
RBC	Red Blood Cells

RIC	Reduced Intensity Conditioning
SAE	Serious Adverse Event
SC	Subcutaneous
sCR	Stringent Complete Response
SD	Stable Disease
SNP	Single Nucleotide Polymorphism
sPCL	Secondary Plasma Cell Leukemia
SPEP	Serum Protein Electro-Phoresis
SPM	Second Primary Malignancy
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLS	Tumor Lysis Syndrome
TRM	Treatment-Related Mortality
TTP	Time to Progression
ULN	Upper Limit of Normal
UPEP	Urine Protein Electro-Phoresis
UTI	Urinary Tract Infection
VAD	Vincristine, Doxorubicin (Adriamycin), Dexamethasone
VGPR	Very Good Partial Response
VMPT	Bortezomib, Melphalan, Prednison, Thalidomide
VTD	Bortezomib, Thalidomide, Dexamethasone
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen

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A. Criteria for diagnosis

Criteria for primary plasma cell leukemia

Primary plasma cell leukemia is defined by the presence of >2x10^9/L peripheral blood plasma cells or plasmacytosis accounting for >20% of the differential white cell count, and does not arise from pre-existing multiple myeloma (MM)

Criteria for symptomatic pPCL

Presence of a M-protein and/or abnormal free light chain ratio in serum

In case no M-protein or free light chain in serum urine parameter might be used

AND

Clonal plasma cells in bone marrow or plasmocytoma

AND

Presence of >2x10^9/L peripheral blood plasma cells or plasmacytosis accounting for >20% of the differential white cell count, and does not arise from pre-existing multiple myeloma (MM)

AND

At least 1 myeloma-related dysfunction* (CRAB criteria):

- calcium > 2.65 mmol/l
- renal insufficiency (creatinine > 177umol/l)
- anemia (Hb < 6.2 mmol/l or > 1,25 mmol/l below normal limit)
  (HB < 10 g/dl or > 2.1 g/dl below normal limit)
- bone disease (lytic lesions or osteopenia)

* must be attributable to the underlying plasma cell disorder

Criteria for measurable disease

Serum M-protein > 5 g/l

OR

Urine M-protein > 200 mg/24 hours

OR

Abnormal FLC ratio with involved free light chain (FLC) > 100 mg/l

OR

Proven plasmacytoma by biopsy

Staging according to ISS criteria

Stage I: Serum β_2-microglobulin < 3.5 mg/l AND
Serum albumin ≥ 3.5 g/dl (≥ 35 g/l)

Stage II: Patients who qualify for neither Stage I nor III

Stage III: Serum β_2-microglobulin ≥ 5.5 mg/l

B. Response criteria

Response subcategory	Criteria
MRD-negative CR[a]	sCR as defined below plus ▪ MRD-negative bone marrow[b] by multicolor flow cytometry or allele-specific oligonucleotide PCR[c] and ▪ MRD-negative peripheral blood by multicolor flow cytometry or allele-specific oligonucleotide PCR[c]
sCR[a]	CR as defined below plus ▪ Normal FLC ratio (0.26 – 1.65) and ▪ Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[d] and ▪ Absence of clonal cells in peripheral blood by immunofluorescence
CR[a]	▪ Negative immunofixation on the serum and urine and ▪ Disappearance of any soft tissue plasmacytomas and ▪ <5% plasma cells in bone marrow[b] and ▪ No plasma cells in blood smear
VGPR[a]	▪ Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ▪ ≥ 90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h and ▪ No plasma cells in blood smear
PR[a]	▪ ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h ▪ If the serum and urine M-protein are unmeasurable[#], a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria ▪ If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% ▪ In addition to the above listed criteria, a ≥90% reduction of peripheral blood plasma cells is required and peripheral blood plasma cells must be ≤5% of the differential white cell count, and if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD[a]	Not meeting criteria for CR, VGPR, PR or progressive disease

[†] Criteria are based on International Myeloma Working Group (IMWG) criteria[41] with some modifications and inclusion of the response subcategory MRD-negative CR[39].

[#] Measurable disease: Serum M-protein ≥0.5 g/dl (≥5 g/l); urine M-protein ≥200 mg/24 h; involved FLC level ≥10 mg/dl (≥100 mg/l) provided serum FLC ratio is abnormal.

[a] All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b] Confirmation with repeat bone marrow biopsy not needed.

[c] Sensitivity attainable with eight-color multiparameter flow cytometry and allele-specific oligonucleotide PCR is10^{-6}.

[d] Presence/absence of clonal cells is based upon the *κ/λ* ratio. An abnormal *κ/λ* ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is *κ/λ* of >4:1 or <1:2.

NOTE: Once (s)CR is established, response remains (s)CR until relapse is documented

Relapse Criteria

Relapse subcategory	Criteria
PD[e] To be used for calculation of TTP and PFS end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one or more of the following: Increase of ≥ 25% from baseline/nadir in • Serum M-component (the absolute increase must be ≥0.5 g/dl)[f] • Urine M-component (the absolute increase must be ≥200 mg/24 h) • Peripheral blood plasma cells (with at least $2x10^9$ cells per L or >20% of the differential white cell count) • Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dl. • Bone marrow plasma cell percentage: the absolute % must be ≥10%[g] • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Relapse from CR[e] (To be used only if the end point studied is DFS)[h]	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Reappearance of peripheral blood plasma cells in blood smear

	• Development of ≥5% plasma cells in the bone marrow[g] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see above)

[e] All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.

[f] For progressive disease, serum M-component increases of ≥1 g/dl (10 g/l) are sufficient to define relapse if starting M-component is ≥5 g/dl (50 g/l).

[g] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

[h] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease

PRACTICAL DETAILS OF RESPONSE EVALUATION

Laboratory tests for measurement of M-protein

- Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable such as in patients with IgA monoclonal proteins migrating in the beta region. If SPEP is not available or felt to be unreliable (e.g., in some cases of IgA myeloma) for routine M-protein quantitation during therapy, then quantitative immunoglobulin levels on nephelometry or turbidometry can be accepted. However, this must be explicitly reported, and only nephelometry can be used for that patient to assess response and SPEP and nephelometric values cannot be used interchangeably.
- Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended

Definitions of measurable disease

- Response criteria for all categories and subcategories of response except CR are applicable only to patients who have 'measurable' disease defined by at least one of the following four measurements:
  - Serum M-protein ≥ 0.5 g/dl (≥ 5 g/l)
  - Urine M-protein ≥ 200 mg/24 h
  - Serum FLC assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) provided serum FLC ratio is abnormal
  - Proven plasmacytoma by biopsy

- Response criteria for CR are applicable for patients who have abnormalities on one of the four measurements.

Follow-up to meet criteria for PR or SD

- It is recommended that patients undergoing therapy be tracked monthly for the first year of new therapy and every other month thereafter
- Patients with 'measurable disease' as defined above need to be followed by both SPEP and UPEP for response assessment and categorization
- Except for assessment of CR, patients with measurable disease restricted to the SPEP will need to be followed only by SPEP; correspondingly, patients with measurable disease restricted to the UPEP will need to be followed only by UPEP[a]
- Patients with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these two tests and not by the FLC assay. FLC response criteria are only applicable to patients without measurable disease in the serum or urine, and to fulfill the requirements of the category of stringent CR
- To be considered CR, both serum and urine immunofixation must be carried out and be negative regardless of the size of baseline M-protein in the serum or urine; patients with negative UPEP values pretreatment still require UPEP testing to confirm CR and exclude light chain or Bence–Jones escape
- Skeletal survey is not required for assessment of response unless clinically indicated, but is recommended once a year in clinical practice; bone marrow is required only for categorization of CR, and for patients with non-secretory disease

[a] For good clinical practice patients should be periodically screened for light chain escape with UPEP or serum FLC assay

C. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

2 Some bed time, but to be in bed less than 50% of normal daytime

3 Needs to be in bed more than 50% of normal daytime

4 Unable to get out of bed

5 Death

D. Common Terminology Criteria for Adverse Events

The grading of adverse events will be done using the NCI Common Terminology Criteria for Adverse Events, CTCAE version 4.0. A complete document may be downloaded from the HOVON website:

http://www.hovon.nl (under Trials > General information about studies)

E. NYHA scoring list

The New York Heart Association functional and therapeutic classification applied to dyspnea

Grade 1	No breathlessness
Grade 2	Breathlessness on severe exertion
Grade 3	Breathlessness on mild exertion
Grade 4	Breathlessness at rest

F. Correlative studies: Management and handling of pPCL samples

Bone marrow and plasma cryopreservation

EMN biobank laboratories will collect bone marrow cells, peripheral blood cells and saliva which are stored according to biobank laws in the separate countries. See the lab manual for details on collection and sending of bone marrow, peripheral blood and saliva. This material will be used for additional investigations in order to determine prognostic factors.

These will include:

A. Cytogenetic analysis

In case FISH analysis has not been performed at entry, FISH analysis will be either performed on cryopreserved bone marrow samples or bone marrow slides for del1p, ampli 1q, t(4;14), t(14;16), t(11;14), ampli 9, del13q/13-, del17p

B. Minimal residual disease (MRD)

Since with the currently used therapies the rate of complete remission, as defined by the International Myeloma Working Group (IMWG) criteria, has significantly increased in both multiple myeloma as well as pPCL, there is a need for more sensitive methods to assess response. In multiple myeloma achievement of minimal residual disease (MRD)-negative status, as determined by multiparameter flow cytometry or molecular techniques, is associated with improved outcome both in the setting of standard-risk and high-risk cytogenetics. MRD-negative disease will probably become an important endpoint in clinical studies and a surrogate marker for survival.

In this pPCL study, we will also determine the prognostic role of minimal residual disease (MRD) in pPCL. MRD will be detected by multiparametric flow cytometry (MFC), and by molecular techniques such as VDJ sequencing or allele-specific oligonucleotide PCR. Patients with evidence of immunofixation negative CR at a response evaluation moment will be studied for MRD.

Serum samples will be tested for free-light chain. In addition to measuring the absolute levels of free-light chain, the free-light chain ratio will be considered (normal reference range, 0.26 to 1.65). Patients with a k/l FLC ratio <0.26 are typically defined as having a monoclonal lambda free light chain and those with ratios >1.65 are defined as having a monoclonal kappa free light chain. Bone marrow samples will be tested by 8-colour flowcytometry for the presence of monoclonal plasma cells according to the methods described in the EMN-02 MRD Protocol. The outcome of patients in stringent CR or MFC remission will be compared with those in immunofixation negative CR or VGPR.

C. Whole genome gene expression profiling

Whole genome transcriptional profiling will be used to establish the level of over 47,000 transcripts, representing 38,500 genes. Aim of this exploratory analysis is to further develop a molecular classification of plasma cell leukemia patients, validation of prognostic markers identified in previous studies and identification of novel candidate markers that predict patient's response to the specific treatment used in the current study by correlations with clinical outcome.

Bone marrow samples for gene expression profiling will be collected centrally at the EMN-02 biobank laboratories, where plasma cells will be purified within 24 hours after sampling using a CD138 positive selection kit. Performance of the purification will be monitored using FACS analysis of the original bone marrow sample and the final purified plasma cell fraction with CD38, CD138 and CD45 antibodies. The viability of the cells will be measured using annexin and 7AAD.

Purified plasma cells will be stored in RLT Plus buffer with β-mercaptoethanol at -80°C and shipped to the laboratory of the Erasmus MC EMN-02 biobank laboratory badgewise, where these will be further processed and analyzed as outlined below.

Total RNA will be isolated using the RNeasy kit (Qiagen). RNA levels and quality will be assessed with the RNA6000 Nano assay on the Agilent 2100 Bioanalyzer. Samples of which the 28S/18S ratio is <1,7 or with a RIN number <7.0 will be excluded from further analysis.
Total RNA will be used to prepare antisense biotinylated RNA using the genechip ® 3"IVT express kit (Affymetrix). The biotinylated RNA will be hybridized to the Affymetrix U133 Plus 2.0 array. Staining, washing and scanning procedures, as well as hybridization controls provided by Affymetrix will be used and GeneChips will be visually inspected for irregularities.

The global method of normalization will be used and the mean difference between all GeneChips will be used as indicator of assay-quality. In addition, the variations in percentage of genes present, the 3'/5' ratio of Actine and the 3'/5' ratio of GAPH will be assessed to verify the quality of the array.

The Omniviz package will be used to perform and visualize the results of unsupervised cluster analysis, whereas all supervised analyses will be performed using SAM software. For supervised class-prediction analyses, PAM software in R will be applied.

D. Single Nucleotide Polymorphism (SNP) analysis in patients with pPCL

Anti-cancer treatment is associated with a wide variety of side effects, which also vary considerably between patients. Bortezomib induces painful neuropathy, thrombocytopenia and gastro-intestinal symptoms. Lenalidomide induces neutropenia and thrombocytopenia. The proportion of patients

experiencing these side effects in trials ranges from 10 to 50%. The most likely explanation for the inter-individual variation in response and toxicity may be found in the genetic heterogeneity of genes involved in detoxification processes, DNA repair, myeloma biology and neuropathy.

It is known that such single nucleotide polymorphisms (SNPs) are observed in many genes that are important for multiple myeloma biology and/or are involved in metabolism of anti-cancer drugs. Furthermore, it is anticipated that these SNP's play an important role in outcome (OS and DFS) and toxicity in patients treated with conventional agents, while little is known about their relevance for the effects of novel agents.

The novel agents carfilzomib and lenalidomide are now moving to up-front therapy of multiple myeloma. Therefore it is of critical importance to investigate which gene(s) are involved in the drug metabolism and anti-tumor effect of these agents.

The involvement of inherited genetic polymorphisms will be investigated prospectively in this trial, using in a high through-put system with a Genome-Wide Human SNP array 6.0 (Affymetrix) platform of DNA isolated from white blood cells. The presence of inherited genotype polymorphisms will be correlated to response, progression-free survival and toxicity.

Blood samples will be taken before start of treatment. About 6 ml of EDTA blood divided over two tubes, is needed to obtain a reasonable amount of DNA, necessary for the analyses.

Blood samples will be stored at room temperature immediately after collection. The samples should be sent to the central laboratory at room temperature by overnight mail within one day after sampling to maintain a good quality of DNA. The centers will be provided with special envelopes for the sending of diagnostic samples. The central laboratories for participating countries will contact the hospitals for instructions and to make arrangements for shipping of samples (see lab manual).

E. Gene copy number analysis on purified pPCL cells

The development of microarray technology has enabled high-resolution, genome-wide analysis based on single-nucleotide polymorphisms (SNPs). This technology scans the genome and is able to reveal gains and losses as well as regions of loss of heterozygosity (LOH).

In our study we will perform high-density 6.0 SNP array to search for genetic lesions that may be involved in development of pPCL, or that have prognostic relevance. We will compare the abnormalities observed in pPCL with those observed in active symptomatic multiple myeloma,

asymptomatic smoldering myeloma, or monoclonal gammopathy of undetermined significance (MGUS) as described in the literature.

F. Exome sequencing

Another very powerful way to understand the molecular basis of cancer is to sequence the protein-coding exome, and to compare tumor to normal from the same patient to identify the acquired somatic mutations. Recent reports have described the sequencing of whole genomes and exomes from patients with multiple myeloma. These data have greatly contributed to a better understanding of the pathogeneis of multiple myeloma. It has also resulted in the identification of targetable mutations in multiple myeloma such as BRAF.

In pPCL, exome sequencing of the tumor genome of a large number of cases will permit the identification of biologically relevant patterns that would not otherwise be evident. We will compare the mutated genes in pPCL, with those mutated in multiple myeloma.

However, sequencing of the pPCL genome will not only contribute to a better knowledge of pPCL biology, but may also result in the identification of molecular aberrations with important prognostic value. This technique may also lead to the identification of new targets for therapy.

Furthermore, recent studies have shown that in myeloma tumors there is frequently considerable intraclonal heterogeneity with shifting predominant subclones under the selective pressure of therapy. Increased knowledge of the clonal heterogeneity at the time of diagnosis as well as relapse will provide information in order to select a combination of drugs that will target all individual subclones. This will prevent the rapid outgrowth of an already present resistant subclone. There is currently no data on clonal evolution in pPCL. We will also collect bone marrow at the time of relapse, and perform exome sequencing of the tumor genomes.
Comparing the results obtained at diagnosis with those obtained at the time of relapse will provide information on clonal development during treatment.

G. Additional molecular analyses of MM samples

Other analyses may appear to be relevant at a later stage and the EMN-02 biobank is left open to interested groups. The procedure and what analyses to be performed will be decided later. In addition to cryopreserved bone marrow cells and DNA of peripheral blood cells, peripheral blood plasma and saliva will be stored.

REQUIRED BONE MARROW AND PERIPHERAL BLOOD AND LOGISTICS

Note 1: This section is discussed in the lab manual.