

## **EMN12/ HOVON 129 PCL**

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)

Principal Investigator : N.W.C.J. van de Donk (patients 18-65 years inclusive)

Co-principal Investigator : P. Musto (patient's  $\geq 66$  years)

Sponsor : HOVON

### **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 ( $\geq 66$  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  $\beta 2$ -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  $\geq 18$  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 carfilzomiblenalidomide maintenance.

Patients with age  $\geq 66$  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 EMN12/ HOVON 129 PCL Version 05.1, 04-JAN-2017 Page 11 of 103 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  $\geq 66$  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 lenalidomidebased treatment separately in younger (18-65 years inclusive) and elderly ( $\geq 66$  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 EMN12/