Prospective multicenter study MYRE

Treatment of myeloma cast nephropathy – MYRE
P081226

Indication	Renal failure and monoclonal gammopathy
Study name	MYRE
Type of study	Prospective multicenter study
Version and date	Version n°7-0, May 05, 2013
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Page de SIGNATURE D'UN PROTOCOLE de recherche biomédicale
par l'investigateur COORDONNATEUR et le représentant du PROMOTEUR

Recherche biomédicale N° P081226

Titre : Traitement de la néphropathie à cylindres myélomateux Etude MYRE

Version N° Version n°7-0, 13/05/2013

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STUDY SUMMARY

PROSPECTIVE MULTICENTER STUDY MYRE:
Treatment of myeloma cast nephropathy

STUDY OBJECTIVES	In patients with multiple myeloma (MM) complicated with inaugural renal failure secondary to myeloma cast nephropathy (MCN), to evaluate the effect on renal function of: - bortezomib (Velcade ®) plus dexamethasone (Neodex®) (BD), compared with cyclophosphamide (Endoxan ®) plus bortezomib and dexamethasone (C-BD), in patients not requiring hemodialysis - an intensive hemodialysis regimen using either a dialyzer with very high permeability to proteins (Theralite™), or a conventional high-flux dialyzer, combined with chemotherapy with BD, in patients requiring hemodialysis
Coordinating Investigator	**Prof Jean Paul FERMAND** **Department of Clinical Immunology, Hôpital Saint Louis, Paris**
Associate Coordinating Investigator	**Prof Frank BRIDOUX** **Department of Nephrology, University Hospital Poitiers**
EXPERIMENTAL PLAN	Prospective randomized multicenter controlled trial with two parallel groups stratified according to the requirement of hemodialysis
NUMBER OF PATIENTS	284 patients (including 93 x 2 not requiring dialysis and 49 x 2 requiring hemodialysis)
NUMBER OF CENTRES	125
CRITERIA OF RANDOMIZATION	1) Renal failure (serum creatinine >170 µmol/l and estimated glomerular filtration rate (eGFR) calculated using the MDRD equation <40 ml/min/1.73m^2. 2) Secondary to MCN, probable (albuminuria <30% of total urine proteins, with albuminuria <500 mg/24h and et urine albumin/creatinine ratio <300 mg/g), or biopsy-proven (kidney biopsy is mandatory for patients randomized in the hemodialysis part of the study). 3) Established diagnosis of multiple myeloma, with measurable serum monoclonal Ig by conventional electrophoresis, and/or Bence Jones proteinuria >0.5g/24h, and/or serum free LC level >2 x upper limit of normal (ULN), with abnormal kappa/lambda ratio. 4) Absolute neutrophil count ≥1.0 x 10^9/L and platelet count ≥70 x 10^9/L. 5) Written informed consent.
CRITERIA OF NON-RANDOMIZATION	1. Any nephropathy other than MCN (ex: amyloidosis). 2. MCN associated with another LC-related renal disorder (ex: MCN + AL amyloidosis) except for MCN associated with amorphous linear peritubular LC deposits (i.e. LCDD without nodular glomerulosclerosis). 3. Any uncontrolled medical condition, co-morbidity, psychiatric disorder or biological abnormality that might interfere with subject's participation or ability to sign an informed consent form. 4. Severe pre-existing chronic kidney disease with eGFR <30 ml/min/1.73 m^2, whatever its origin; patient on chronic dialysis or renal transplanted patient. 5. Patients who received more than 7 hemodialysis sessions prior to randomization. 6. Patients who were started on hemodialysis more than 15 days prior to the date of randomization

	7. Patients who received more than one session of hemofiltration or hemodiafiltration before randomization. 8. Patients who received plasma exchanges before randomization. 9. Concomitant severe disease, including cancer or non-malignant conditions. 10. Positive HIV serology, active hepatitis B or hepatitis C infection, or active herpes/VZV viral infection. 11. Patient treated with more than one course of anti-myeloma chemotherapy, and/or who received corticosteroid treatment with a total dose equivalent to more than 160 mg of Dexamethasone, or more than 1 mg/kg/day of Prednisone during 1 month. 12. Patient who received more than 4 IV or SC injections of bortezomib (Velcade®) before the inclusion/screening phase. 13. Hepatic insufficiency, AST (SGOT) and ALT (SGPT) >10 x ULN and/or persistent cholestasis (alkaline phosphatases or gammaGT >5 x ULN) 14. Severe preexisting peripheral neuropathy 15. Any contraindication to high-dose steroids 16. Any contraindication to bortezomib treatment 17. Patient without affiliation to the French National Security system. 18. Inability to comply with study procedures 19. In women of child bearing potential, a positive pregnancy test or breast feeding
PRIMARY ENDPOINT	Improvement in renal function after 3 cycles of chemotherapy (at the latest 3 months after randomization), as evaluated by: - in patients requiring hemodialysis: the rate of hemodialysis independence - in patients not requiring hemodialysis: the rate of renal response defined by achievement of serum creatinine level ≤170 µmol/l or estimated glomerular filtration rate (GFR) calculated using the modified MDRD equation ≥40 ml/min/1.73m^2 (i.e., renal function compatible with eligibility for intensive treatment of MM)
SECONDARY ENDPOINTS	• Improvement in renal function (same criteria) after 1 cycle of chemotherapy, after completion of the studied chemotherapy protocol, at 6 months and 1 year after randomization. • Complete renal recovery, defined by return to baseline level of serum creatinine or eGFR (if known), or by eGFR ≥60 ml/min/1.73m^2 after 1 and 3 cycles of chemotherapy, after completion of the studied chemotherapy protocol, at 6 months and 1 year after randomization. • Renal function, as evaluated by calculation of eGFR after 1 and 3 cycles of chemotherapy, after completion of the studied chemotherapy protocol, at 6 months and 1 year after randomization • Hematologic response, after 1 and 3 cycles of chemotherapy, after completion of the studied chemotherapy protocol, at 6 months and 1 year after randomization • Relapse-free survival, event-free survival and time to subsequent myeloma therapy, measured from randomization • 12 month-overall survival • Tolerance to treatment, particularly incidence of hematologic and peripheral nerve complications
DURATION OF STUDY	Total duration: 4 years Duration of the inclusion period: 3 years Duration of participation and follow-up: 1 year

1. RATIONALE

Renal failure is a severe and frequent complication in multiple myeloma (MM), occurring in nearly half of the patients during the course of the disease (Rayner 1991, Rota 1987). In more than two third of the cases, renal failure results from myeloma cast nephropathy (MCN) due to cast precipitation in the renal distal tubule lumens, secondary to the interaction of monoclonal immunoglobulin (Ig) light chains (LC) with uromodulin (Tamm-Horsfall protein) (Pirani 1987, Rota 1987, Sakhuja 2000). Ig LC, which are freely filtered through the glomerulus, are physiologically reabsorbed in the proximal tubular cells, through a mechanism of endocytosis mediated by a tandem of receptors (cubilin and megalin), and then degraded in the lysosomal compartment of the proximal tubular cell (Birn 2006). Therefore, MCN is nearly always observed in the context of high-grade MM, with production of large amounts of Ig LC, exceeding the capacity of proximal tubular catabolism. Renal failure in MCN results not only from tubular obstruction by LC casts, but also from severe tubulo-interstitial inflammation, characterized by infiltrates of macrophages, mononuclear cells and giant cells around casts, resulting in major damage of the tubulo-interstitial compartment (Pirani 1987). Tubulo-interstitial inflammation is enhanced by massive proximal tubular reabsorption of monoclonal LC, leading to phosphorylation of MAP kinases (p38 MAPK) and activation of transcription factors (NF-κB, AP-1) that generate local production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin 6 and 8, and monocyte-chemoattractant protein (MCP)-1 (Batuman 2007). Cellular injury is accompanied by morphologic and functional alterations of proximal tubular cells, including epithelial-mesenchymal transition (Li 2008). MCN is usually triggered by various facilitating factors, namely dehydration, hypercalcemia, infections, contrast media, or nephrotoxic drugs (non-steroidal anti-inflammatory agents, diuretics, angiotensin conversing-enzyme inhibitors, or angiotensin receptor antagonists). The risk of MCN is also influenced by the amount of monoclonal LC excreted in the urine, and it is particularly high in MM patients with Bence Jones proteinuria over 2 g/day (Cohen 1984, Ronco 2001).

MCN usually presents as acute or sub-acute renal failure, isolated or sometimes associated with general symptoms related to high tumour mass MM, such as skeletal pains related to lytic bone lesions.

Renal prognosis of MCN remains poorly defined, with sometimes inconsistent data in the literature, mainly due to the lack of histopathological confirmation of renal lesions in most series. Furthermore, some of these series are old and in most cases, chemotherapy regimens varied greatly, including low or high-dose steroids. Moreover, renal response was usually not correlated with hematologic response assessed using modern tools, such as nephelometric assays for serum free LC. It is usually considered that renal function improves with treatment of MM in 50 to 60% of patients (Knudsen 2000), and in only 20 to 40% of those who require dialysis support (Clark 2005, Chanan-Khan 2007). Recent data suggest that these results might be significantly improved with the use of modern chemotherapy agents such as bortezomib or thalidomide, combined with high-dose dexamethasone (Tosi 2004, Ludwig 2007, Kastritis 2007). It is generally assumed that persistence of renal failure despite chemotherapy is predictive of poor patient survival in MM. Indeed, in a retrospective series published in 1998, median survival was only 4 months in patients with persistent renal impairment, compared to 28 months in patients who experienced renal recovery after chemotherapy (Bladé 1998).

Treatment of MCN relies on symptomatic measures and on the introduction of chemotherapy aiming at rapidly controlling the production of monoclonal LC by malignant plasma cells.

A) SYMPTOMATIC TREATMENT

Symptomatic treatment is a key step in the management of MCN. It is based on the correction of precipitating factors (vigorous rehydration, correction of hypercalcemia and treatment of infections) with administration of sodium bicarbonate to obtain a urine pH ≥7. Indeed, acidic urine promotes the formation of myeloma casts, by enhancing homotypic aggregation of Tamm-Horsfall protein, and its interaction with urine free LC. Some reducing agents such as colchicine might theoretically inhibit the aggregation of Tamm-Horsfall protein with monoclonal LC but their benefit in clinical use remains unproven (Sanders 1992, Ronco 2001).

Rapid removal of circulating monoclonal LC, through plasmapheresis or intensive hemodialysis using new protein-leaking dialyzers with high permeability to proteins, could also represent an interesting treatment strategy in MCN. In a randomized controlled study of 107 patients with acute renal failure (which type was not confirmed histologically) contemporary to the diagnosis of MM, plasmapheresis (5 to 7 exchanges of 50 ml/kg body weight) coupled with a chemotherapy regimen based on VAD (vincristine-adriamycine-dexamethasone), or melphalan plus prednisone, did not show a significant effect on a composite criterion defined by death, or dialysis-dependent renal failure, or severe renal failure with a glomerular filtration rate <30ml/min/1.73 m^2, compared to chemotherapy alone (Clark 2005). Recently, Leung et al. have suggested that histological confirmation of MCN is critical to correctly interpret the effects of therapy in MM patients with renal failure. In a retrospective series of 40 patients, kidney biopsy, performed in 28 cases, showed pure MCN in 18 patients. Only in patients with biopsy-proven MCN, the combination of plasmapheresis with high-dose dexamethasone based chemotherapy induced improvement in renal function in 45% of patients and in 75 % of those whose serum free LC levels decreased by more than 50% with treatment. By contrast, no correlation between renal response and reduction in serum free LC levels was observed in patients without biopsy-proven MCN (Leung 2008). These data indicate that pathological confirmation of the nature of renal lesions is important to evaluate the impact of therapy in MM patients with renal failure.

Recently, it was shown that an extended hemodialysis protocol, using a new generation dialyzer with very high permeability to proteins (Gambro HCO 1100™), was highly efficient in removing circulating free LC (with 35 to 70% reduction of serum free LC levels after 2 hours of hemodialysis) in patients with MM and severe renal failure. The authors tested a daily hemodialysis treatment strategy using this membrane as a complementary therapy in 5 patients with biopsy-proven MCN. Duration of dialysis sessions ranged between 2 to 12 hours, and in some cases, 2 or 3 dialyzers in series were used after the first or second dialysis sessions. Among the 5 patients who all received various chemotherapy regimens containing dexamethasone, improvement of renal function with subsequent dialysis withdrawal was achieved in 3. Clinical tolerance of extended dialysis with the protein-leaking dialyzer HCO 1100™ was good, despite the fact, that, on account of the high membrane permeability to large molecules, a perfusion of 20 to 40 g of albumin was required at the end of each dialysis session (Hutchison 2007). In a subsequent series of 19 patients, a similar hemodialysis regimen associated with conventional chemotherapy based on cyclophosphamide (7 patients), thalidomide (14 patients), vincristine/doxorubicin (1 patient), and high-dose dexamethasone (all patients), induced a significant reduction in the concentration of serum free LC in 13 patients (median reduction rate of 85%, range: 50 to 97%). In these 13 patients, hemodialysis was withdrawn after 4 weeks (median time 27 days, range: 13 to 120 days). In 6 patients, chemotherapy was stopped because of recurrent infectious complications: renal recovery occurred in one patient at day 105, whereas the 5 remaining patients were still dialysis-dependent. Survival of patients free of dialysis was significantly higher in this series (Hutchison 2009).

Preliminary data from case reports indicate that daily dialysis sessions of 4 to 6 hours, using a single HCO 1100™ dialyzer instead of 2 dialyzers in series, might be sufficient to obtain efficient removal of circulating LC and improvement in renal function (Bachmann 2008). The real benefit of this

novel dialysis strategy in patients remains to be confirmed in large randomized trials dedicated to MM patients with severe renal failure and biopsy-proven MCN.

B). CHEMOTHERAPY

The choice and modalities of initial chemotherapy in patients with MCN remain poorly defined. Rapid introduction of treatment, immediately after diagnostic confirmation, is essential to obtain a swift and profound reduction in the rate of production of monoclonal LC and to induce a renal response, a key prognostic factor for patient survival.

In young patients, improvement or recovery of renal function is also mandatory for consideration of eligibility for high-dose therapy, which is currently considered as the standard of care of symptomatic MM in this population. Intensive therapy usually consists of few courses of « classical » chemotherapy, followed by bone marrow stem cell mobilization through injections of growth factor with or without chemotherapy, stem cell collection, and then high-dose chemotherapy (usually based on an injection of 200 mg/m^2 of melphalan) and re-injection of bone marrow stem cells. In patients over 65 years in age, who are not eligible to intensive therapy, the reference treatment consists either in classical 4-day monthly courses of melphalan plus prednisone per-os associated with daily low-dose thalidomide (Facon 2007), or in the oral melphalan plus prednisone regimen reinforced by bortezomib (San Miguel 2008).

Most randomized controlled studies that demonstrated a benefit of intensive treatment compared to standard chemotherapy did not include patients with impaired renal function (usually defined as a serum creatinine level >150 µmol/L). Small series have shown that intensive treatment is feasible in myeloma patients with chronic renal failure, even in patients requiring chronic hemodialysis, but with significantly higher morbidity and mortality rates (Badros 2001, Knudsen 2005). In patients with dialysis-dependent renal failure, high dose therapy allows recovery of renal function in only few cases (Lee 2004). To date, the benefit over risk ratio of intensive therapy in myeloma patients with persistent renal failure remains uncertain and its indication and modalities are far from being established. Furthermore, even the choice of first-line chemotherapy in patients with multiple myeloma and inaugural renal failure is still poorly defined. Because of its anti-inflammatory properties, high-dose dexamethasone is considered as mandatory (Kastritis 2007). However, little attention has been paid to the agents that should be associated with high-dose steroids in this situation. Renal elimination of many agents used in the treatment of MM limits their use in patients with renal failure: for example, if an alkylating agent is considered, cyclophosphamide should be preferred to melphalan. The VAD regimen (Vincristine, Doxorubicin, Dexamethasone) has been widely employed, despite cardiac toxicity associated with doxorubicin and peripheral nerve complications with vincristine (Haubitz 2006).

The recent introduction of novel agents, initially thalidomide, then the proteasome-inhibitor bortezomib, and, more recently, lenalidomide (Revlimid®), has modified the strategy of initial chemotherapy in MM with renal failure. Metabolism of thalidomide in patients with renal failure is poorly defined. Due to the risk of central nervous system side-effects, including seizures, thalidomide dose should not exceed 200 mg/day. Moreover, serum potassium levels should be closely monitored, as severe hyperkalemia has been described in thalidomide-treated myeloma patients with advanced renal failure (Fakhouri 2004). Bortezomib may be used without dose adaptation for the treatment of MM with renal failure, even in patients requiring hemodialysis, with safety and efficacy profiles similar to MM patients with preserved renal function (Jagannath 2005, Chanan-Khan 2007, San Miguel 2008). Bortezomib-related side effects mainly involve gastro-intestinal tract, bone marrow (thrombocytopenia) and peripheral nerve. The risk of peripheral neuropathy is decreased when bortezomib is injected subcutaneously, without loss of efficacy (Moreau 2011). Because of its potent inhibitory effect on Nf-κB mediated production of pro-inflammatory cytokines, which is likely to play a central role in tubulointerstitial inflammation in MCN, bortezomib appears as the molecule of choice as first-line therapy in MM with renal failure, in association with high-dose dexamethasone.

Lenalidomide, which is mainly eliminated through the kidney, should be used with reduced dose adapted to the severity of renal failure. All these new drugs, commonly used in combination with high-dose dexamethasone, have proven to be efficient in the treatment of myeloma in patients with preserved renal function, by inducing hematologic remission in most cases, usually within the first month. Moreover, a complete hematologic response is achieved in a significant proportion of patients, reaching 30% when these drugs are used in combination with dexamethasone and an alkylating agent (Mateos 2006). The impact on renal function of rapid very good hematologic responses obtained with novel agents has not been investigated in prospective controlled studies.

Given these data, the combination of bortezomib and dexamethasone is currently the standard of care in MM with renal failure, even if it has not been evaluated prospectively, particularly regarding the duration of hematologic responses. It is likely that the duration of hematologic remission could be increased with the adjunction of an alkylating agent, which may further improve renal prognosis without inducing higher frequency of adverse events (San Miguel 2008).

To address these issues, we have designed a prospective multicenter study that will evaluate the benefit of reinforcing the current reference regimen bortezomib-dexamethasone with cyclophosphamide. Cyclophosphamide is the most commonly used alkylating agent in patients with renal failure, and is part of the CTD (Cyclophosphamide-Thalidomide-Dexamethasone) regimen, currently given as first line therapy in MM in the UK (Kyriakou 2005, Sidra 2006). In a retrospective study, the Cyclophosphamide-Bortezomib-Dexamethasone (C-BD) regimen resulted in hematologic response rate of 75% (including complete responses), higher than that obtained with BD and with similar tolerance profile (Davies, 2007). In a prospective phase II study, Reeder et al have confirmed the efficacy of the C-BD regimen, with cyclophosphamide given orally, which produced a hematologic response rate of 88% and complete response or very good partial response rate of 39% (Reeder, 2009). The optimal dose of intravenous cyclophosphamide in association with BD was determined in another recent study (Kropff, 2009).

2. STUDY OBJECTIVES

The aim of the present randomized controlled phase III trial in patients with renal failure contemporary to the diagnosis of myeloma, or complicating the course of previously diagnosed but non-treated myeloma, is to evaluate the effect on renal function of:

- The association of bortezomib plus dexamethasone, reinforced or not with cyclophosphamide in patients not requiring dialysis. Randomization will be stratified according to patient age and to the severity of acute kidney injury, based on Acute Kidney Injury Network (AKIN) classification.
- An intensive dialysis regimen using either a conventional dialysis membrane, or the new generation protein-leaking HCO dialyzer 2.1 m^2 in surface (Theralite^{TM}) in patients requiring hemodialysis. Given the small number of patients potentially enrollable within a reasonable duration of inclusion period, all will receive the same chemotherapy with dexamethasone and bortezomib.

3. STUDY DESIGN

The present study is a prospective randomized multicenter controlled trial with two parallel groups stratified according to the requirement of hemodialysis at the time of inclusion. Before randomization, all eligible patients will enter a screening/inclusion phase that will serve to validate inclusion criteria.

A) INCLUSION/SCREENING PERIOD

The study starts with a screening phase that will include all potentially eligible patients presenting with acute kidney injury and monoclonal gammopathy. This inclusion period is dedicated to secure the diagnosis of MCN, and to verify that significant renal impairment persists after symptomatic

measures and correction of precipitating factors. Each patient will be considered potentially eligible when meeting the following criteria:

1. Age ≥18 years.
2. Detectable serum and/or monoclonal immunoglobulin (Ig) (whatever its isotype) and/or isolated monoclonal LC.
3. Renal failure with serum creatinine >170 µmol/L and/or eGFR <40 ml/min/1.73 m^2 (MDRD).
4. Having received no more than one course of chemotherapy usually given for the treatment of MM or other lymphoid malignancy.
5. Fully informed and did not expressed opposition.
6. Affiliation to the national Social Security system.

During the inclusion period, the following procedures are performed:

- Correction of precipitating factors, such as dehydration through saline and alkaline fluid administration, withdrawal of nephrotoxic drugs, treatment of hypercalcemia, treatment of infections with antibiotics (if applicable). Alkaline therapy should aim at achieving a urine pH >6.5. The use of bisphosphonate therapy is permitted. Loop diuretics (furosemide, bumetamide) should be avoided, and, if necessary, used only after appropriate rehydration.
- I.V. methylprednisolone (Solumedrol®) 400 mg/day, or oral dexamethasone 40 mg/day, for 4 days.
- bone marrow aspiration (or biopsy if required), including molecular studies (FISH and/or PCR) according to local practice, and all explorations required for the diagnosis of MM.
- in case of clinical suspicion of amyloidosis, a minor salivary gland biopsy, or other pertinent biopsy (abdominal fat) will be performed.
- A kidney biopsy will be required in patients with urine albumin excretion above 500 mg/day, or urine albumin over creatinine ratio >300 mg/g, or if albuminuria represents ≥30% of proteinuria on urine protein electrophoresis. A kidney biopsy will be required in all patients presenting with anuria or requiring dialysis. In the other situations, the indication of a kidney biopsy should be evaluated in each patient, according to the local investigator's judgement. It is highly recommended in patients with newly diagnosed MM revealed by AKI without any obvious precipitating factor, and in patients with IgM monoclonal gammopathy.

B) RANDOMIZATION

Randomization will be performed between day 4 and day 16 post-inclusion. However, patients with MM and renal failure who already received symptomatic measures (rehydration, correction of precipitating factors) and corticosteroid therapy equivalent to dexamethasone 40 mg or methylprednisolone (Solumedrol®) 400 mg for 4 days, can be randomized immediately.

Randomization criteria are:

1. Persistent renal failure, as defined by serum creatinine >170 µmol/L and eGFR <40 ml/min/1.73m^2.
2. Secondary to MCN, probable (albuminuria <30% of total proteinuria, with albuminuria <500 mg/day, and urine albumin over creatinine ratio <300 mg/g, or proven by a kidney biopsy (whenever required by the clinical context or analysis of proteinuria). The association of AL amyloidosis with MCN is a criterion of exclusion. However, the association of MCN with amorphous peritubular monoclonal light chain deposits is not a criterion of exclusion, providing there is no evidence of glomerular lesions (nodular glomerulosclerosis) related to light chain deposition disease.
3. Confirmed diagnosis of multiple myeloma. The diagnosis of MM implicates the presence of significant bone marrow plasma cell infiltration. MM should secrete a measurable monoclonal Ig, i.e. with detectable serum monoclonal Ig by conventional electrophoresis, and/or Bence-Jones proteinuria >0.5g/j, and/or serum free LC level >2 x ULN, with abnormal kappa/lambda ratio.
4. Signed informed consent form for participating to either the chemotherapy part of the study, or the hemodialysis part, as appropriate.

5. Absolute neutrophil count ≥1.0 x 10^9/L **and** platelet count ≥70 x 10^9/L.

Patients with any of the following exclusion criteria will not be randomized:

1. Any nephropathy other than MCN (ex: amyloidosis).
2. MCN associated with another LC-related renal disorder (ex: MCN + AL amyloidosis) except for MCN associated with amorphous linear peritubular LC deposits (i.e. LCDD without nodular glomerulosclerosis).
3. Any uncontrolled medical condition, co-morbidity, psychiatric disorder or biological abnormality that might interfere with subject's participation or ability to sign an informed consent form.
4. Severe pre-existing chronic kidney disease with eGFR <30 ml/min/1.73 m^2, whatever its origin; patient on chronic dialysis or renal transplanted patient.
5. Patients who received more than 7 hemodialysis sessions prior to randomization.
6. Patients who were started on hemodialysis more than 15 days prior to the date of randomization.
7. Patients who received more than one session of hemofiltration or hemodiafiltration before randomization.
8. Patients who received plasma exchanges before randomization.
9. Concomitant severe disease, including cancer or non-malignant conditions.
10. Positive HIV test, or active hepatitis B or C virus infection, or HSV/VZV viral infection.
11. Patient who previously received more than one course of chemotherapy for the treatment of myeloma and/or corticoid therapy equivalent to more than 160 mg of dexamethasone, or more than 1 mg/kg/day of prednisone for a month (excluding methylprednisolone pulses during the inclusion phase).
12. Patient who received more than 4 I.V. or S.C. injections of bortezomib (Velcade®) before the inclusion/screening phase.
13. Hepatic insufficiency, AST (SGOT) and ALT (SGPT) >10 x ULN and/or persistent cholestasis (alkaline phosphatases or gammaGT >5 x ULN).
14. Subjects with pre-existing severe peripheral neuropathy.
15. Any contraindication to high-dose steroids.
16. Any contraindication to bortezomib, particularly related to lung or pericardial disorders.
17. Patient without affiliation to the French National Security system.
18. Inability to comply with study procedures.
19. In women of child bearing potential, a positive pregnancy test or breast feeding.

For patients in whom MM and renal failure are diagnosed in a context that requires admission to an intensive care unit (ICU), for other reasons, such as infection:

- These patients can be screened. If they require hemodialysis, hemodialysis procedures will be performed in the ICU at the responsible physician's discretion.
- Randomization is allowed before the 16th day after screening, providing that they meet all the above criteria, including the ability to give signed informed consent, and providing that they did not receive more than 1 session of hemofiltration or hemodiafiltration.

4. RANDOMIZATION PROCEDURE

Randomization will be centralized online, through a secured internet connection. Randomization lists will be predefined in each subgroup (patients requiring or not hemodialysis) and equilibrated according to permutation blocks, the size of which will be blinded to investigators.

Two different situations will be distinguished:

1. Patients not requiring hemodialysis at the time of randomization will be randomized to receive two different chemotherapy regimens: **Bortezomib-Dexamethasone (BD), or Cyclophosphamide-Bortezomib-Dexamethasone (C-BD)**. Randomization will be equilibrated according to age (over or less than 65 years) and to stage of acute kidney injury as defined by the AKIN criteria (cf appendix 2).

2. Patients requiring hemodialysis at the time of randomization will be assigned to an intensive hemodialysis protocol using either the new generation protein-leaking dialyzer Gambro Theralite™, or a conventional high-flux membrane. Given the small number of patients potentially randomized in this part of the study, all will receive the same chemotherapy regimen with **Bortezomib-Dexamethasone**.

Randomization will be equilibrated according to age (over or less than 65 years) and, if applicable, on prior randomization of chemotherapy (i.e. patients enrolled in the first part of the study who require hemodialysis before the second course of chemotherapy will be randomized on a separate list, in order to equilibrate their repartition in the 2 arms of the hemodialysis part of the study).

5. PART 1: TREATMENT OF PATIENTS NOT REQUIRING HEMODIALYSIS

Patients who do not require hemodialysis at the time of randomization will be randomly assigned to receive either the Bortezomib-Dexamethasone regimen (BD group), or the Cyclophosphamide-Bortezomib-Dexamethasone regimen (C-BD group). Modalities of treatment administration are as defined in the Summary of product Characteristics (SmPC) (Appendix 13).

A) MODALITIES OF TREATMENT WITH BORTEZOMIB-DEXAMETHASONE (BD GROUP)

Treatment is started on the day of randomization (day 1). The BD regimen consists of:

- Bortezomib 1.3 mg/m^2 (preferentially subcutaneously) twice weekly for 2 weeks (on days 1, 4, 8, and 11), followed by a 10 day-period without treatment (days 12-21). This period of 21 days is considered as a cycle of treatment. An interval of at least 72 hours is required between two consecutive injections of bortezomib.

  The subcutaneous route should be used preferentially, without modification of the dose or administration schedule, and using the adapted dilution (2.5 mg/ml instead of 1 mg/ml for the I.V. route). The I.V. route can be used in the following conditions: i) severe obesity, ii) severe oedema iii) local skin conditions contraindicating the use of subcutaneous injections, iv) patient's refusal of subcutaneous injections. In the event of a local reaction, the following injections should be performed at other injection sites. If local reaction recurs on novel injection sites, it is recommended to use the I.V. route. The reconstituted solution of Velcade® 3.5 mg/ml is administered in thighs (left or right) or in the abdomen (left or right). The solution should be injected subcutaneously, using a 45 to 90 degree angle. It is recommended to alternate injection sites between each consecutive injection. If local reaction occurs after a subcutaneous injection of Velcade®, it is recommended to use a solution reconstituted at lower concentration (Velcade® 3.5 mg reconstituted at 1 mg/ml instead of 2.5 mg/ml) for S.C. injection, or to consider the I.V. route.

- Dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12, i.e. on the day of each injection of bortezomib, and on the day after. The use of Neodex® (dexamethasone) is recommended. In case of gastrointestinal symptoms (vomiting), steroid therapy should be administered transiently through I.V. route (using 200 mg of Solumedrol® for 20 mg of dexamethasone)

The regimen is given for 3 cycles in the absence of serious side-effect. Appropriate supportive measures should be performed, at the local investigator's discretion. It is recommended to consider prevention of gastrointestinal side-effects with proton pump-inhibitors, antibiotherapy with sulfamethoxazole-trimethoprim (Bactrim forte®), and prophylactic treatment of herpes virus infections (Zelitrex® 500mg/day). The use of nephrotoxic agents (aminoglycosides, non-steroidal anti-inflammatory agents, diuretics) and contrast media should be avoided.

Adaptation of therapy:

In patients aged over 80 years, from the beginning of the second cycle of chemotherapy, it is possible to perform 4 weekly injections of bortezomib 1.3 mg/m^2 (preferentially using the subcutaneous route), with dexamethasone given on the day and the day after each bortezomib injection. This adaptation is at the local investigator's discretion. It results in the modification of the duration of chemotherapy cycles, from 21 days to 35 days.

The dose of bortezomib is unchanged in patients with impaired renal function. The occurrence of steroid-related side effects may lead to an adaptation of the dexamethasone dose, at the local investigator's discretion.

Absolute neutrophil count must be ≥1.0 x 10^9, and platelet count must be ≥70 x 10^9 before starting each BD cycle. If not, introduction of BD should be postponed by 8 days. After this interval, if cytopenias are still present, bortezomib is reintroduced using a 25% lower dose (i.e. 1.3 mg/m^2 reduced to 1 mg/m^2; 1 mg/m^2 reduced to 0.7 mg/m^2).

Full blood count should be monitored weekly throughout the duration of chemotherapy. Once a cycle has been started, bortezomib should be interrupted if any of the following occurs:

- Non-hematologic grade 3 toxicity (cf appendix 3)
- Grade 4 hematologic toxicity (platelets <30 x 10^9/l, or neutrophils <0.5 x 10^9/l).

In this situation, Bortezomib should be stopped until the next cycle. At that time:

- If symptoms of toxicity have disappeared, bortezomib is reintroduced using a 25% lower dose (i.e. 1.3 mg/m^2 reduced to 1 mg/m^2; 1 mg/m^2 reduced to 0.7 mg/m^2)
- In case of persistent symptoms or relapsing symptoms with the lower dose, withdrawal of bortezomib should be considered.

In bortezomib-treated patients who develop neuropathic pain or peripheral neuropathy, the following measures should be applied (table 1):

Table 1: Instructions for bortezomib dose modifications in case of neuropathic pain and/or peripheral neuropathy

Severity	Dose modification
Grade 1 (paresthesias, muscle weakness and/or reduced deep tendon reflexes) without pain or incapacity	None
Grade 1 with pain, or grade 2 (not interfering with usual daily activities)	Reduce to 1 mg/m^2
Grade 2 with pain, or grade 3 (interfering with usual daily activities)	Stop bortezomib until disappearance of symptoms. Resume bortezomib at a dose of 0.7 mg/m^2 once a week.
Grade 4 (permanent sensitive loss with incapacity)	Stop bortezomib

On the basis of bortezomib dose adaptation in phase II and phase III studies in multiple myeloma

At the end of each cycle, patient survival, tolerance to treatment, renal response (i.e. serum creatinine ≤170 µmol/L and/or estimated glomerular filtration rate (GFR) calculated using the modified MDRD equation ≥40 ml/min/1.73m^2), and hematologic response (cf appendix 4) will be evaluated.

- In case of worsening renal failure requiring hemodialysis:
    - If hemodialysis is required before the second cycle of chemotherapy, the patient will be considered for randomization in the dialysis part of the study, with either the Theralite™ dialyzer, or a conventional high-flux dialyzer. The patient will be considered as non-responder in the comparison of BD versus C-BD. In case of patient refusal, hemodialysis sessions will be performed using a conventional dialyzer, at the local investigator's discretion and according to local practice. If not, the patient will be randomized in the hemodialysis part of the study. The patient will receive appropriate information using the specific information notice. Signed informed consent must be obtained before randomization in the hemodialysis part of the study.
    - If hemodialysis is required after the second cycle of chemotherapy, the patient will not be randomized for the dialysis membrane. Chemotherapy regimen will not be modified. Hemodialysis sessions will be performed using a conventional dialyzer, with dialysis modalities at local investigator's discretion and according to local practice.
- In case of side-effect leading to permanent bortezomib interruption, the patient will be withdrawn from the study and treatment of myeloma will be at the local investigator's discretion.

<u>After the third cycle of BD:</u>

1. In patients aged less than 65 years, eligible for intensive treatment, who have achieved both hematologic response (≥ PR, cf appendix 4) **<u>and</u>** renal response (serum creatinine ≤170 µmol/l or eGFR ≥40 ml/min/1.73m^2): **collection of peripheral blood stem cells (after G-CSF only), followed by high-dose melphalan (200 mg/m^2) and blood stem cell transplantation** is recommended, in the absence of contraindication.

2. In patients who have achieved hematologic response (≥PR, cf appendix 4), but who are not eligible for intensive treatment (age >65 years), or did not achieve a renal response, or who show renal progression (even requiring hemodialysis): **administration of three more courses of Bortezomib-Dexamethasone** is recommended

3. In patients who do not achieve a hematologic response (<PR, cf appendix 4), whatever the renal response, it is strongly recommended to reinforce chemotherapy with **by the adjunction of cyclophosphamide, i.e. introduction of a C-BD regimen**, for 3 cycles (cf infra).

<u>After the sixth cycle of BD</u>:

1. In patients aged less than 65 years, eligible for intensive treatment, who have achieved both hematologic response (≥PR, cf appendix 4) **<u>and</u>** renal response (serum creatinine ≤170 µmol/l or eGFR ≥40 ml/min/1.73m^2): **collection of peripheral blood stem cells (after G-CSF only), followed by high dose melphalan (200 mg/m^2) and blood stem cell transplantation** is recommended.

2. In all other situations, treatment of myeloma will be at the local investigator's discretion.

B) MODALITIES OF TREATMENT WITH CYCLOPHOSPHAMIDE-BORTEZOMIB-DEXAMETHASONE (C-BD GROUP)

Treatment is started on the day of randomization (day 1). The C-BD regimen consists of:

- Bortezomib 1.3 mg/m^2 (preferentially subcutaneously) twice weekly for 2 weeks (on days 1, 4, 8, and 11), followed by a 10 day-period without treatment (days 12-21). This period of 21 days is considered as a cycle of treatment. An interval of at least 72 hours is required between two consecutive injections of bortezomib.
- Dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12, i.e. on the day of each injection of bortezomib, and on the day after. The use of Neodex® (dexamethasone) is recommended. In case of gastrointestinal symptoms (vomiting), steroid therapy should be administered transiently through I.V. route (using for example 200 mg of Solumedrol® instead of 20 mg of dexamethasone).
- Cyclophosphamide 750 mg/m^2 on day 1, through a short I.V. infusion (30 min to 2 hours)

Treatment is delivered over this period of 21 days, which is considered as 1 cycle of treatment. The regimen is given for 3 cycles in the absence of serious side-effect. Appropriate supportive measures, including those required by the use of steroids, should be performed at the local investigator's discretion. It is recommended to consider prevention of nausea, of gastrointestinal side-effects with proton pump-inhibitors, prophylactic antibiotherapy with sulfamethoxazole-trimethoprim (Bactrim forte®) and prophylactic treatment of herpes virus infections (Zelitrex® 500mg/day). With the recommended dose of cyclophosphamide, it is not necessary to give systematic bladder protection.

The use of nephrotoxic agents (aminoglycosides, non-steroidal anti-inflammatory agents, diuretics) and contrast media should be avoided.

Adaptation of therapy:

In patients aged over 80 years, from the beginning of the second cycle of chemotherapy, it is possible to perform 4 weekly injections of bortezomib 1.3 mg/m^2 (preferentially using the subcutaneous route), with dexamethasone given on the day and the day after each bortezomib injection. This adaptation is at the local investigator's discretion. It results in the modification of the duration of chemotherapy cycles, from 21 days to 35 days.

Doses of cyclophosphamide and of bortezomib are unchanged in patients with impaired renal function. In patients who might require hemodialysis, cyclophosphamide and bortezomib should be administered I.V at the end of a dialysis session. The occurrence of steroid-related side effects may lead to an adaptation of the dexamethasone dose, at the local investigator's discretion.

Full blood count should be monitored weekly throughout the duration of chemotherapy.

Absolute neutrophil count must be ≥1.0 x 10^9, and platelet count must be ≥70 x 10^9 before starting each C-BD cycle. If not, introduction of C-BD should be postponed by 8 days. After this interval, if cytopenias are still present, bortezomib **AND** cyclophosphamide should be re-introduced at lower doses:

- Bortezomib: dose reduced from 1.3 mg/m^2 to 1.0 mg/m^2; or from 1.0 mg/m^2 to 0.7 mg/m^2
- Cyclophosphamide: reduced from 750 mg/m^2 to 600 mg/m^2; or from 600 mg/m^2 to 300 mg/m^2

Once a cycle has been started, bortezomib should be stopped until the next cycle, in case of:

- non-hematologic grade 3 toxicity (cf appendix 3)
- grade 4 hematologic toxicity (platelets <30 x 10^9/l, or neutrophils <0.5 x 10^9/l)

In this situation, bortezomib should be stopped until the next cycle. At that time:

1. If symptoms of toxicity have disappeared, bortezomib **and** cyclophosphamide should be re-introduced, at lower doses:

- Bortezomib: reduced from 1.3 mg/m^2 to 1.0 mg/m^2; or from 1.0 mg/m^2 to 0.7 mg/m^2

- Cyclophosphamide: reduced from 900 mg/m^2 to 600 mg/m^2; from 600 mg/m^2 to 300 mg/m^2

2. In case of persistent toxicity or if toxicity reoccurs despite lower doses of cyclophosphamide and bortezomib, cyclophosphamide should be stopped.

In Bortezomib-treated patients who develop neuropathic pain or peripheral neuropathy, appropriate measures should be applied, as described above (table 1).

At the end of each cycle, patient survival, tolerance to treatment, renal response (i.e. serum creatinine ≤170 µmol/L or estimated glomerular filtration rate (GFR) calculated using the modified MDRD equation ≥40 ml/min/1.73m^2), and hematologic response (cf appendix 4) will be evaluated.

- In case of worsening renal failure requiring hemodialysis:
  - If hemodialysis is required before the second cycle of chemotherapy, the patient will be considered for randomization in the dialysis part of the study and assigned to receive either the Theralite™ dialyzer, or a conventional high-flux dialyzer. Treatment with C-BD will be stopped, and the patient will be switched to the BD regimen, according to the modalities described above. The patient will be considered as non-responder in the comparison of BD versus C-BD. In case of patient refusal, C-BD regimen will be maintained, and hemodialysis sessions will be performed using a conventional dialyzer, with dialysis modalities at the local investigator's discretion and according to local practice.
  - If hemodialysis is required after the second cycle of chemotherapy, the patient will not be randomized for the dialysis membrane. Chemotherapy regimen (C-BD) will not be modified. Hemodialysis sessions will be performed using a conventional dialyzer, with dialysis modalities performed at local investigator's discretion, according to local practice.
- In case of side-effect leading to permanent interruption of cyclophosphamide **and** bortezomib, the patient will be withdrawn from the study and treatment of myeloma will be at the local investigator's discretion.

After the third cycle of C-BD:

1. In patients aged less than 65 years, eligible for intensive treatment, who have achieved both hematologic response (≥ PR, cf appendix 4) **and** renal response (serum creatinine ≤170 µmol/l or eGFR ≥40 ml/min/1.73m^2): **collection of peripheral blood stem cells (after G-CSF only), followed by high-dose melphalan (200 mg/m^2) and blood stem cell transplantation** is recommended, in the absence of contraindication.
2. In patients who have achieved hematologic response (≥PR, cf appendix 4), but who are not eligible for intensive treatment (age >65 years), or who did not achieve a renal response, or who show renal progression (even requiring hemodialysis): **administration of three more courses of Cyclophosphamide-Bortezomib Dexamethasone** is recommended
3. In patients who do not achieve a hematologic response (< PR, cf appendix 4), whatever the renal response, it is strongly recommended to reinforce chemotherapy with the **adjunction of thalidomide,** i.e. introduction of a C-VTD regimen (Cyclophosphamide-Bortezomib-Thalidomide-Dexamethasone), for 3 cycles (cf appendix 4). In case of any contra-indication to thalidomide, the choice of chemotherapy will be at the local investigator's discretion

After the sixth cycle of C-BD:

1.In patients aged less than 65 years, eligible for intensive treatment, who have achieved both hematologic response (≥PR, cf appendix 4) **and** renal response (serum creatinine ≤170 µmol/l or eGFR ≥40 ml/min/1.73m^2): **collection of peripheral blood stem cells (after G-CSF only), followed by high dose melphalan (200 mg/m^2) and blood stem cell transplantation** is recommended.

2. In all other situations, treatment of myeloma will be at the local investigator's discretion.

6. PART 2: TREATMENT OF PATIENTS REQUIRING HEMODIALYSIS

For patients requiring hemodialysis, 2 situations should be distinguished:

1. Patients requiring hemodialysis after the end of screening period will be randomly assigned to receive hemodialysis either with the Theralite™ dialyzer, or with a conventional high-flux dialyzer. Randomization will occur before the first hemodialysis session, or before the second dialysis session in patients needing emergency dialysis. All patients will receive the same chemotherapy regimen with Bortezomib-Dexamethasone (BD).

2. Patients not requiring hemodialysis at the end of the screening period, who have been initially randomized to receive either the BD or C-BD (see above) may secondarily require dialysis support. Only patients who received no more than 1 cycle of protocol chemotherapy (BD or C-BD) will be eligible for randomization in the use of the dialysis membrane. In patients from the C-BD group, cyclophosphamide will be interrupted and the Bortezomib-Dexamethasone regimen will be used at the second cycle of chemotherapy.

Indications of hemodialysis:

Indication for hemodialysis should be considered in any patient with eGFR $\leq$10 ml/min/1.73m^2. The decision of starting hemodialysis will be at the local investigator's discretion. The following criteria for initiation of hemodialysis are recommended:

- Severe hyperkalemia (>6 mmol/l) or rapid increase in serum potassium level
- Severe metabolic acidosis (arterial pH <7.1)
- Poor clinical tolerance of renal failure (encephalopathy, severe fluid retention)
- Anuria ≥24 hours

A). MODALITIES OF HEMODIALYSIS SESSIONS

The choice and site of insertion of the hemodialysis catheter will be at the local investigator's discretion, in accordance to local protocols.

According to their randomization arm, patients will be dialyzed using either:

- the Gambro Theralite™ dialyzer of 2.1 m^2 in surface (HCO group).
- a conventional high-flux dialyzer (control group) with an ultrafiltration coefficient >14 ml/min (Eknoyan 2002) and ≥1.8 m^2 in surface. The use of one of the following membrane types, polyacrylonitrile, polysulfone, or PMMA, is recommended.

HCO group:

a) As long as patients do not have criteria for dialysis withdrawal, 8 hemodialysis sessions will be performed over the first 10 days following randomization. The duration of each hemodialysis session will be of 5 hours. Dialysis sessions will be performed using a single Theralite™ dialyzer, with blood flow ≥250 ml/min and dialysate flow ≥300 ml/min. Fluid removal will be determined by the supervising investigator, aiming not to induce hypovolemia. Anticoagulation will be performed using heparin according to local practice (with similar dose as for hemodialysis with a conventional dialyzer, according to manufacturer's recommendation). Serum albumin levels will be measured at the beginning of each dialysis session. If serum albumin level is <25 g/l, a perfusion of 20g of albumin (100 ml of albumin 20g/100ml) will be performed at the end of the dialysis session.

b) From the 11th day, if dialysis is still indicated, 3 weekly hemodialysis sessions will be performed with the same modalities as described above. In patients who do not achieve a renal response, Theralite™ dialyzers will be provided until completion of the third cycle of chemotherapy. If the patient further

requires hemodialysis after this period, the choice of dialyzer will be at the local investigator's discretion. It is recommended to use the same hemodialysis modalities as for the control group. Duration and periodicity of hemodialysis sessions are also at the local investigator's discretion.

Control group:

Hemodialysis sessions will be performed according to local habits, using high-flux biocompatible dialyzers, as specified above. The duration of each session is 5 hours. As long as patients do not have criteria for dialysis withdrawal, 8 hemodialysis sessions will be performed over the first 10 days following randomization. From the 11th day, if dialysis is still indicated, 3 weekly hemodialysis sessions will be performed. Fluid removal will be determined by the supervising investigator, aiming not to induce hypovolemia. Anticoagulation will be prescribed according to local practice. Serum albumin levels will be measured at the beginning of each dialysis session. If serum albumin level is <25 g/l, a perfusion of 20g of albumin (100 ml of albumin 20g/100ml) will be performed at the end of the dialysis session.

B). MODALITIES OF HEMODIALYSIS MONITORING

The usual clinical surveillance will be applied, according to local practice. The following biological parameters will be measured:

- Before each dialysis session: serum Na, K, Cl, HCO3, calcium, phosphate, total protein, serum albumin, full blood count

- After each dialysis session: same parameters, except for full blood count

- Before and after the first 3 dialysis sessions, then once weekly before and after hemodialysis: serum free light chains

The monitoring of parameters for dialysis efficiency, such as percentage of urea reduction, ionic dialysance, and KT/V is recommended, as appropriate.

C). MODALITIES OF CHEMOTHERAPY IN HEMODIALYSIS PATIENTS

All patients with receive the same Bortezomib-Dexamethasone regimen, as described page 13, section 5, paragraph a) « Modalitiesof treatment with Bortezomib-Dexamethasone (BD group) ». Bortezomib injections will be systematically performed at the end of the dialysis sessions on hemodialysis days. Three cycles of BD will be administered, followed by evaluation of renal and hematologic responses after the third cycle. Modalities of treatment adaptation will be similar as described above.

Treatment is started on the day of randomization (day 1). The BD regimen consists of:

- Bortezomib 1.3 mg/m^2 (preferentially subcutaneously) twice weekly for 2 weeks (on days 1, 4, 8, and 11), followed by a 10 day-period without treatment (days 12-21). This period of 21 days is considered as a cycle of treatment. An interval of at least 72 hours is requiredbetween two consecutive injections of bortezomib.
- Dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12, i.e. on the day of each injection of Bortezomib, and on the day after. The use of Neodex® (dexamethasone) is recommended. In case of gastrointestinal symptoms (vomiting), steroid therapy should be administered transiently through I.V. route (using for example 200 mg of Solumedrol® instead of 20 mg of dexamethasone).

The regimen is given for 3 cycles in the absence of serious side-effect. Appropriate supportive measures should be performed, at the local investigator's discretion. It is recommended to consider

prevention of gastrointestinal side-effects with proton pump-inhibitors, antibiotherapy with sulfamethoxazole-trimethoprim (Bactrim forte®), and prophylactic treatment of herpes virus infections (Zelitrex® 500mg/day).

The use of nephrotoxic agents (aminoglycosides, non-steroidal anti-inflammatory agents, diuretics) and contrast media should be avoided.

Adaptation of therapy:

In patients aged over 80 years, from the beginning of the second cycle of chemotherapy, it is possible to perform 4 weekly injections of bortezomib 1.3 mg/m^2 (preferentially using the subcutaneous route), with dexamethasone given on the day and the day after each bortezomib injection. This adaptation is at the local investigator's discretion. It results in the modification of the duration of chemotherapy cycles, from 21 days to 35 days.

The dose of bortezomib is unchanged in patients on hemodialysis. The occurrence of steroid-related side effects may lead to an adaptation of the dexamethasone dose, at the local investigator's discretion.

Absolute neutrophil count must be ≥1.0 x 10^9, and platelet count must be ≥70 x 10^9 before starting each BD cycle. If not, introduction of BD should be postponed by 8 days. After this interval, if cytopenias are still present, bortezomib is reintroduced using a 25% lower dose (i.e. 1.3 mg/m^2 reduced to 1 mg/m^2; 1 mg/m^2 reduced to 0.7 mg/m^2)

Full blood count should be monitored weekly throughout the duration of chemotherapy.

Once a cycle has been started, bortezomib should be interrupted if any of the following occurs:

- non-hematologic grade 3 toxicity (cf appendix 3)
- grade 4 hematologic toxicity (platelets <30 x 10^9/l, or neutrophils <0.5 x 10^9/l)

In this situation, bortezomib should be stopped until the next cycle. At that time:

- if symptoms of toxicity have disappeared, bortezomib is reintroduced using a 25% lower dose (i.e. 1.3 mg/m^2 reduced to 1 mg/m^2; 1 mg/m^2 reduced to 0.7 mg/m^2)
- In case of persistent symptoms or relapsing symptoms with the lower dose, withdrawal of bortezomib should be considered.

In bortezomib-treated patients who develop neuropathic pain or peripheral neuropathy, adapted measures should be applied (table 1, page 14).

At the end of each cycle, patient survival, tolerance to treatment, renal response (i.e. serum creatinine ≤170 µmol/L or estimated glomerular filtration rate (GFR) calculated using the modified MDRD equation ≥40 ml/min/1.73m^2), and hematologic response (cf appendix 4) will be evaluated. In case of side-effect leading to permanent bortezomib interruption, the patient will be withdrawn from the study and treatment of myeloma will be at the local investigator's discretion.

After the third cycle of BD:

1. In patients aged less than 65 years, eligible for intensive treatment, who have achieved both hematologic response (≥PR, cf appendix 4) **and** renal response (serum creatinine ≤170 µmol/l or eGFR ≥40 ml/min/1.73m^2): **collection of peripheral blood stem cells (after G-CSF only), followed by high-dose melphalan (200 mg/m^2) and blood stem cell transplantation** is recommended, in the absence of contraindication.

2. In patients who have achieved hematologic response (≥PR, cf appendix 4), but who are not eligible for intensive treatment (age >65years), or did not achieve a renal response: **administration of three more courses of Bortezomib-Dexamethasone** is recommended

3. In patients who do not achieve a hematologic response (<PR, cf appendix 4), whatever the renal response, it is strongly recommended to reinforce chemotherapy with the **introduction of a C-BD regimen (reinforcement of BD by the adjunction of cyclophosphamide)**, for 3 cycles. Modalities of the C-BD regimen in hemodialysis patients are similar to those detailed page 15.

After the sixth cycle of BD:

1. In patients aged less than 65 years, eligible for intensive treatment, who have achieved both hematologic response (≥ PR, cf appendix 4) **and** renal response (serum creatinine ≤170 µmol/l or eGFR ≥40 ml/min/1.73m^2): **collection of peripheral blood stem cells (after G-CSF only), followed by high dose melphalan (200 mg/m^2) and blood stem cell transplantation** is recommended.

2. In all other situations, treatment of myeloma will be at the local investigator's discretion.

7. INITIAL EVALUATION, COMPLEMENTARY INVESTIGATIONS

A) INITIAL EVALUATION

Before the introduction of chemotherapy (i.e. between day 1 and day 3 post-randomization), complete clinical and biological evaluation of multiple myeloma will be performed, and renal function will be assessed with calculation of eGFR using the simplified MDRD equation (cf appendix 1).

Multiple myeloma stage will be defined, according to Durie and Salmon and to ISS systems (cf appendix 6).

Complete physical examination will be performed with collection of vital parameters, body weight, blood pressure, heart rate, 24-hour urine excretion, ECOG performans status (cf appendix 7). Significant results of baseline physical examination will be recorded.

Biological tests at baseline will include the following:

Blood:

- Full blood count.
- Coagulation profile (prothrombin time and activated cephalin time).
- Serologic tests for HIV, hepatitis B, hepatitis C, HSV and VZV infections.
- Serum creatinine and urea.
- Serum electrolytes (Na, K, Cl, HCO3).
- Total calcium, phosphate.
- Serum albumin.
- Serum protein electrophoresis.
- Serum FLC.
- Beta-2 microglobulin, LDH.
- C-reactive protein.
- Serum immunoelectrophoresis or immunofixation. Serum should be stored for the entire duration of the study.
- Hepatic tests.
- Beta HCG, in women of child bearing potential.

Urine chemistry (on 24-hour urines, if applicable)

- Urine electrolytes (Na, K, Cl), urea, creatinine.
- 24-hour proteinuria.
- Urine protein electrophoresis and immunoelectrophoresis or immunofixation.
- Urine dipstick analysis with measurement of pH.

Other:

- Bone marrow aspiration/or biopsy (if not performed before), including cytogenetics and molecular studies of malignant plasma cells, according to local practice.
- Skeleton X-ray survey if required (skull, spine, upper and lower limbs, pelvis).
- Chest radiography.

B) FOLLOW-UP EVALUATION

The following tests will be performed at the beginning of each chemotherapy cycle, after the third and sixth cycles of chemotherapy, and at 6 and 12 months post-randomization:

- Full blood count.
- Coagulation profile (prothrombin time and activated cephalin time).
- Serum creatinine and urea.
- Serum electrolytes (Na, K, Cl, HCO3).
- Total calcium, phosphate.
- Serum albumin.
- Serum uric acid.
- Serum protein electrophoresis.
- Serum FLC.
- C-reactive protein.
- Urine electrolytes (Na, K, Cl), urea, creatinine.
- 24-hour proteinuria.
- Urine dipstick analysis with measurement of pH.
- Urine protein electrophoresis.

Serum and urine immunoelectrophoresis or immunofixation will be performed at 6 and 12 months.

8. JUDGEMENT CRITERIA

A). PRIMARY OUTCOME

Improvement in renal function after 3 cycles of protocol chemotherapy (at 3 months at the latest), as evaluated by:

- In patients requiring hemodialysis: by the cumulative incidence of hemodialysis independence. Hemodialysis independence is defined by the achievement of eGFR calculated using the modified MDRD equation >15 ml/min/1.73 m^2, 15 days after the last hemodialysis session.
- In patients not requiring hemodialysis, by the achievement of a serum creatinine level ≤170 µmol/l or an estimated glomerular filtration rate (GFR) calculated using the modified MDRD equation ≥40 ml/min/1.73m^2 (i.e., renal function compatible with eligibility for intensive treatment of MM)

B). SECONDARY OUTCOMES

- Improvement in renal function (same criteria) after 1 cycle of chemotherapy, after completion of protocol chemotherapy, at 6 months and 1 year after randomization.
- Complete renal recovery, defined by return to baseline level of serum creatinine or eGFR (if known), or by eGFR ≥60 ml/min/1.73m^2 after 1 and 3 cycles of chemotherapy, after completion of protocol chemotherapy, at 6 months and 1 year after randomization.
- Renal function, as evaluated by eGFR level after 1 and 3 cycles of chemotherapy, after completion of protocol chemotherapy, at 6 months and 1 year after randomization
- Hematologic response, after 1 and 3 cycles of chemotherapy, after completion of protocol chemotherapy, at 6 months and 1 year after randomization (cf appendix 4)
- Relapse-free survival, event free survival, time to next myeloma therapy, and overall survival measured from randomization
- Tolerance to treatment, particularly the occurrence of cytopenias, infectious or haemorrhagic adverse events, and peripheral neuropathy.

9. STATISTICS

A). COMPUTATION OF SAMPLE SIZE

In patients requiring hemodialysis: the primary end-point is the cumulative incidence of hemodialysis independence at 3 months. With the assumption of a 30% cumulative incidence of hemodialysis independence in the control group, it is necessary to recruit two groups of 49 patients to demonstrate a 30% benefit (i.e., a 60% cumulative incidence of hemodialysis independence) in the experimental arm, with a tolerable risk of type I and type II error set at 5% and 20%, respectively.

In patients not requiring dialysis: the primary endpoint is renal response after 3 cycles of chemotherapy. With the assumption of 50% of patients having achieved a renal response at 3 months in the reference group (BD), it is necessary to recruit 2 groups of 93 patients to demonstrate a 20% benefit (i.e., 70% of renal response) in the experimental arm (C-BD), with a tolerable risk of type I and type II error set at 5% and 20%, respectively.

B) STATISTICAL ANALYSIS

Statistical analysis plan.

The two parts (hemodialysis and non hemodialysis patients) of the study will be analyzed separately. Analyses will be performed in a modified intention-to-treat basis, that is, only patients who violated the eligibility criteria or those with consent withdrawal, can be excluded from the analysis. Patients not requiring dialysis will participate to the comparison of the 2 chemotherapy arms. Among these, patients secondarily requiring hemodialysis and included in the hemodialysis part of the study, will be considered as treatment failures for the comparison of the 2 chemotherapy arms, in their randomly allocated chemotherapy arm. For the calculation of event-free survival, they will be considered as events, and the duration of event-free survival will be defined as the time to the first hemodialysis session. For the calculation of renal survival, they will be censored at the time of the first hemodialysis session. Patients in the hemodialysis part of the study will participate to the comparison of the 2 hemodialysis strategies (HCO or conventional dialyzer) for all end-point criteria, whatever their outcome, from the day of randomization and in their randomly allocated hemodialysis arm.

Interim analysis

For safety and ethical concerns, an interim analysis will be performed 1 year after the date of the first randomization, or after the effective randomization of 40 patients in the chemotherapy part of the study and of 20 patients in the hemodialysis part. Interim analysis will be dedicated to the evaluation of tolerance and mortality, and results will be reported to the Data and Safety Monitoring Board (DSMB) (see page 25). Because the aim of interim analysis is not the comparison of primary or secondary endpoints, no adaptation of the type I error rate will be realized.

Statistical tests and methods

Binary outcomes measured will be estimated using punctual estimates with 95% confidence interval. Treatment effect will be measured by odds ratio estimated from logistic model. Comparisons between the randomization groups on the secondary endpoints will be based on appropriate bilateral formulation tests. The continuous criteria will be compared by Mann and Whitney rank tests; qualitative criteria by chi2 tests or exact Fisher tests; the censored criteria by log-rank tests, unless there is competition (or informative censoring) of the observations, in which case a cumulative incidence will be estimated and comparison based on Gray tests. Failure-time data (overall survival and event-free survival) will be computed from date of randomization, estimated by the Kaplan Meier method, then compared by the log-rank test, with treatment size effect measured by hazard ratios (HR) estimated from Cox models. Proportional hazards assumptions will be checked.

Safety will be evaluated by the incidence rates of reported severe adverse events by patient-years of treatment exposure. The center effect will be studied.

The threshold of significance will be set at 5% for all the tests of the statistical terminal analysis, which will therefore intervene at the end of the inclusions. All analyses will be based on SAS (SAS Inc, Cary, NC) and R (http://www.Rproject.org) packages

10. SAFETY EVALUATION

A) DESCRIPTION OF PARAMATERS OF SAFETY EVALUATION

Adverse event: Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Life-threatening adverse event or life-threatening suspected adverse reaction: an adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death.

Serious adverse event or serious suspected adverse reaction: any untoward medical occurrence or effect that at any dose results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

B). METHODS AND SCHEDULE OF SAFETY PARAMETERS MEASUREMENT, COLLECTION AND ANALYSIS

Steering committee.

It is composed of the coordinating investigators (Prof Fermand/Prof Bridoux), of investigators (Prof Attal, Prof Combe, Prof Jaccard, Prof Moulin, Prof Moreau, Prof Ronco), of the biostatistician in charge of the project (Prof Sylvie Chevret), and of representatives of the Sponsor and of the Clinical Research Unit (Hôpital Saint Louis, Paris). The committee will define general organization, conduct of research and coordination of information. It will initially determine the methodology, decide appropriate

measures in case of unexpected events, and monitor the conduct of research with focus on tolerance and adverse events.

Data and Safety Monitoring Board (DSMB):

The DSMB will be composed of experts not involved in research: Prof Saudan (nephrologist), Prof Delforge (hematologist) specialized in the studied pathology, and Prof Benichou (Biostatistician). The committee will meet once during the first year of research, then twice a year. A report will be written after each meeting and will require approbation form all members of the DSMB. The report will be signed by the DSMB president and submitted to the Sponsor (Project manager DRCD). DSMB members are encouraged to keep a detailed record of the close meeting that will be available to DSMB members only.

The DSMB may issue the following recommendations:

- Continue research without modifications
- Premature interruption of research or temporary suspension of research (because of tolerance, efficacy or pertinence)
- Proposition of modification of the research protocol (criteria of inclusion and non-inclusion, follow-up, complementary investigations….)

Recommendations issued by the DSMB will be transmitted to the Sponsor. The project manager will inform the DSMB of the Sponsor's decisions and their implementation.

Interim safety analysis.

An interim safety analysis will be organized by the DSMB based on information provided by the study biostatistician (Prof Sylvie Chevret). It will be held 1 year after the date of the first randomization, or after randomization of 40 patients in the chemotherapy part of the study (patients not requiring hemodialysis) and 20 patients in the hemodialysis part of the study. The main objective will be the evaluation of the benefit to risk ratio of the study. To this aim, all adverse events and serious adverse events will be analyzed, as well as their accountability and all appropriate measures will be decided to guarantee the securing of subjects participating to the research.

C) PROCEDURES REGARDING REGISTRATION AND REPORTING OF ADVERSE EVENTS

Adverse events should be recorded according to the above classification (see appendixes 3, 14, 16)

All adverse events occurring after the first dose of investigational product observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be reported on the CRF. Any relevant clinical or para-clinical information that may help to describe the corresponding event will be reported. Medically significant adverse events considered related to the investigational product by the investigator or the sponsor will be followed until resolved or considered stable. The following attributes must be assigned by the investigator: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, and action taken. The investigator may be asked to provide follow-up information.

Serious adverse events (SAE). Any serious adverse event, as defined above, will be immediately notified by the investigators to the Sponsor (APHP). Completed SAE report forms (see appendix 16) will be immediately sent by fax or telecopy to the Pharmacovigilance pole at the DRCD, (fax: 01 44 84 17 99). The Clinical Research Unit in Saint Louis Hospital (DBIM) in charge of research will be regularly informed through transmission of the SAE report forms. SAE will be reported to the Sponsor during the entire duration of administration of the experimental treatments and until 1 month after completion of treatment.

Data regarding SAE will be reported in the eCRF, which corresponding page will be printed and faxed to the DRCD as soon as possible, as requested by the law.

For each serious adverse event, the investigator will have to assess causality between the event and experimental and/or non-experimental treatment.

Information relative to the description and evaluation of an adverse event may be not obtained in the time allocated for the initial declaration. Thus, clinical follow-up data and results of clinical evaluation and of complementary diagnostic or laboratory investigations, or of any other information that may allow appropriate analysis of causality will be reported:

- either on the initial adverse event report form if information is readily available,

-or later and as soon as possible, by sending a novel completed SAE form by fax, specifying that it corresponds to the tracking of a declared SAE, and the tracking number.

All SAE reports by investigators should identify each participating patient by a single specific code number. In the event of the death of a participating patient, investigator will provide all relevant information to the Sponsor (hospitalization report, autopsy report…).

Any significant development during research or in the context of research, coming from data of the literature, or from other ongoing research, will be notified to the Sponsor.

Any pregnancy that would occur immediately after biomedical research will be immediately declared as a SAE to the Sponsor and specific follow-up will be organized until delivery.

SAE reporting to Regulatory Authorities and Ethics Committee

AE reporting will be undertaken by the « Pôle Vigilance » of DRCD, after evaluation of the AE severity, of the causality with experimental treatment and non-experimental treatment, and whether AE was expected or not. Unexpected AE will be reported by the Sponsor to competent regulatory authorities within legal declaration time:

- unexpected SAE responsible for death or vital threat: 7 days from the day of report to the Sponsor

- other unexpected SAE: within 15 days from the day of report to the Sponsor.

In the event of an unexpected SAE related to the research treatment or to research itself, all regulatory authorities, ethics committee, and research investigators will be informed.

D) MODALITIES AND DURATION OF SURVEILLANCE FOLLOWING THE OCCURRENCE OF ADVERSE EVENTS

Any patient in whom an adverse event has occurred should undergo clinical surveillance until resolution or stabilization of the adverse event. All patients participating to the research will undergo full evaluation at 12 months.

E) MEASURES TO PREVENT PREGNANCY

This paragraph does not apply to female subjects or to female partners of male patients aged more than 50 years and with amenorrhea for more than 1 year. It does not apply also to women with early menopause confirmed by a specialized gynecologist and to patients with a past history of gynecologic surgery (bilateral salpingectomy and ovariectomy or hysterectomy) or with congenital disorders (Mullerian agenesis, Turner syndrome).

In the other situations, a pregnancy risk cannot be definitely ruled out, which justifies the following:

- to perform a pregnancy test in case of any doubt in female patients who will receive bortezomib with or without cyclophosphamide, during initial evaluation and all along the follow-up period.

- female subjects of child bearing potential should agree to use and be able to comply with effective contraception without interruption, throughout the entire duration of study and for 3 months after the end of study.

- in the event of prescription of thalidomide, to comply with current rules regarding the use of thalidomide, which risk of teratogenicity is well established.

• *Before starting treatment:*

- complete information on the teratogenic risk of thalidomide and on the Pregnancy Prevention Program must be provided by the investigator to female subjects of child bearing potential, and, if appropriate, to male subjects.

- female subjects of child bearing potential should have a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/ml on the day of the study visit or in the 3 days prior to the study visit when thalidomide is prescribed once the subject has been on effective contraception for at least 4 weeks. This requirement also applies to women of childbearing potential who practice complete and continued abstinence. The test should ensure the subject is not pregnant when she starts treatment with thalidomide.

• *Under treatment and after the end of study treatment*

Female subjects of child bearing potential should undergo a supervised pregnancy test every 4 weeks until 4 weeks after the end of study treatment, except in the case of confirmed tubal sterilization. These pregnancy tests should be performed on the day of the study visit or in the 3 days prior to the study visit. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.

These recommendations are listed in the information material, which also includes a patient follow-up diary, pregnancy prevention and treatment follow-up measures, the patient package insert and a pregnancy report form delivered by the authorization holder (Celgene France).

H) PROCEDURES OF BORTEZOMIB ADMINISTRATION (POOR TOLERANCE OR OTHER SITUATIONS)

Bortezomib will be administered preferentially using the subcutaneous route (see appendix 13). The reconstituted solution of Velcade® 3.5 mg/ml is administered in thighs (left or right) or in the abdomen (left or right). The solution should be injected subcutaneously, using a 45 to 90 degree angle. It is recommended to alternate injection sites between each consecutive injection.

The I.V. route can be used in the following conditions: i) severe obesity, ii) severe oedema iii) local skin conditions contraindicating the use of the subcutaneous injections, iv) patient's refusal of subcutaneous injections.

An interval of 1 week should be observed before starting I.V. injections, in case of modification of the route of injection from S.C. to I.V.

11. PROCEDURES OF TEMPORARY OR PERMANENT TREATMENT INTERRUPTION

Interruption of the experimental treatment will be at the investigator's judgment, if justified by patient's interest. Causes of premature treatment interruption are serious adverse event (toxicity/tolerance) or inefficacy, leading to the introduction of treatment other than that patient received at the time of inclusion, or if the result of complementary investigations makes it necessary to stop the study. Clinical monitoring will be pursued as planned in the study design and patient data will be recorded. If treatment is stopped because of toxicity, a SAE will be declared and clinical monitoring will be maintained until resolution.

Subjects may withdraw their consent to participate in this study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. A subject's

participation in the study may be discontinued at any time at the discretion of the investigator in accordance with his/her clinical judgment. The Sponsor should be notified in a timely manner of all subject discontinuations. If asked by the subject, none of his own data will be used for research.

According to circumstances, the Sponsor (Assistance Publique-Hôpitaux de Paris) and/or regulatory authorities may decide to prematurely end the research, in the event of a modification of expected benefit over risk ratio, or because of novel data regarding the experimental treatment that may compromise patient security, or in case of a major protocol deviation.

12. CASE REPORT FORM

Data regarding research will be collected and monitored using the CleanWEB electronic CRF, according to the public contract concluded between AP-HP and TELEMEDICINE TECHNOLOGIES S.A. on November 17, 2003 (reference N° 033845) and renewed on November 21, 2006 (reference N° 063844). Data will be centralized on a server hosted by the Département des Services Opérationnels (DSO) of AP-HP, 67 boulevard Bessières, 75017 PARIS. Data will be collected in eCRF after each clinical visit by local investigators. Access will be restricted to each investigator by a personal access code and password. Each investigator will be attributed a specific profile that will allow access to part or entire system functionalities (from data entry or visualization to full access to whole study data, or ability to modify and validate data by clinical research assistants, etc…). Data storage will be done on a secure server, providing data encryption during transmission and automatic internal save on the server hosting the eCRF.

13. ETHICAL CONSIDERATIONS

Role of the study Sponsor

In accordance with the law of the French Public Health (law n°2004-806 of 9 August 2004), Assistance Publique-Hôpitaux de Paris (APHP) will be the Sponsor of the research study. The Regional Delegation for Clinic Research (Délégation Régionale à la Recherche Clinique) will monitor regulatory issues and have a decision-making role, in compliance with article L 1121-1 of the French Code of Public Health. Assistance Publique–Hôpitaux de Paris reserves the right to interrupt research at any time for medical or administrative reasons; in this event, the decision will be notified to the investigator.

Submission of the protocolto the Ethics Committee

In accordance with article L.1123-6 French Code of Public Health, the research protocol will be submitted (along with insurance certificate and receipt) to the Comité Consultatif de Protection des Personnes en Recherche Biomédicale-Ile de France, after approval of the project Sponsor. The decision of the committee will be notified in the form addressed by the study Sponsor to competent regulatory authority before the beginning of the study.

Authorization from the Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps) - French Agency for Health and Safety of Health Products.

Assistance Publique–Hôpitaux de Paris, as the study Sponsor, must obtain authorization from Afssaps for biomedical research on medicinal product for human use prior to the implementation of research, within its competences and in accordance with regulatory and legal measures in force.

Declaration to the National Commission for Data Protection and Liberties (CNIL-France)

The legislation provides that the declaration should have been filed before the effective beginning of the research.

Research documentation

Before starting research, the coordinating investigator and all study investigators will provide a signed up-to-date curriculum-vitæ as well as their registration number to the French National Medical Council (CNOM). The accepted submitted protocol version and its appendixes will be signed by the

coordinating investigator, the Sponsor representative and, if applicable, by the scientific manager. Each novel protocol version, updated after amendments and/or request from regulatory authorities, will be attributed a novel number, with updated date of issue, and same signatures will be obtained. The investigator and the Sponsor will ensure that the study is conducted in full compliance with the "Declaration of Helsinki" ICH guidelines (http://private.ich.org/LOB/media/MEDIA482.pdf), with the ICH Good Clinical Practice Guideline, and with the French laws and regulations to afford the greater protection to the subjects participating to the study. To this end, a signed scientific agreement from each investigator in each participating center will be delivered to the study Sponsor.

14. DATA PROCESSING AND STORAGE

Data transcription

Investigators participating in the study should submit all required information for each enrolled subject using the eCRF. An explanation should be given for missing data. Clinical and para-clinical data should be transferred in the eCRF as soon as they are collected.

Incorrect data identified in the eCRF will be replaced by a declared investigator, who will access the Cleanweb system using personal identification code and password. These codes are strictly confidential and can by no means be communicated to a third party; they contribute to secure data confidentiality and to authenticate interventions. Access codes are associated with an electronic signature system which validates data entered by the investigator. Each signature is time stamped and registered in the research "Audit trail". Signed data cannot be modified, but the investigator can cancel his signature if data need to be modified. Signature annulation is also recorded and time stamped.

Anonymity of participating subjects will be secured by the mention of only patient number and initials in all documents relative to research and by masking of individual-related data on source documents, by any appropriate mean. Electronic data file will be declared to CLIN-France, according to adapted procedure.

Clinical research assistants, project manager, assistant project manager, clinical trial coordinator of the Clinical Research Unit, and data manager will have habilitation to visualize CRF and to ask queries to investigators.

Protocol amendments

The Department of Clinical Research and Development (DRCD) should be informed from any modification of the study by the coordinating investigator. Modifications should be qualified as substantial or non-substantial. Any amendment to the research protocol must be notified to the Ethics Committee if it includes substantial modifications, i.e. that may in one way or another modify guarantees to persons participating to the biomedical research (medication of inclusion criteria, prolongation of the inclusion period, participation of additional investigators….).

Extension of research

Any extension of the research protocol (significant modification of the treatment schedule or of studied populations, prolongation of research treatment or medical actions not initially intended) should be considered as new research.

Retention of records

In accordance with regulations for Biomedical Research Involving Human Subjects, investigators are required to maintain all study documentation, including documents created ormodified in electronic format, for at least 15 years following the completion of the study.

Indexed archiving includes:

• All successive versions of the study protocol (identified by specific number and date of issue).

• By the coordinating investigator: certificates of authorization by regulatory authorities and ethics committee approval for the corresponding research.

• All correspondence with the Sponsor

• Signed Informed Consent Form (ICF) from each subject participating to the research (under sealed envelope for minor child with signed consent of the person who has parental authority) with the corresponding list or registry of inclusions.

• Completed and validated paper copy of the CRF from each included participating subject, dated and signed by the coordinating investigator or the local investigator.

• Audit trail.

• Data Handling Manual, with accurate description of eCRF (data, monitoring….).

• All ancillary documents specifically relevant to research.

• The final research report after statistical analysis and quality control (with copy sent to the study Sponsor). During the closing visit to each participating center, clinical research assistants will make a CD-ROM copy of the following: pdf files of eCRF from each patient included in the centre, randomization fax, all correspondence related to research, the audit trail and electronic correction queries. This CD-ROM will be archived in the investigator site file.

The database used for statistical analysis should be also archived by the statistician in charge of final analysis (paper support or electronic file).

15. ACCESS RIGHTS AND SOURCE DOCUMENTS

In accordance with applicable laws and regulations, particularly articles L.1121-3 and R.5121-13 of the French Public Health Code, authorized persons (including investigators, persons in charge of quality control, data monitors, clinical research assistants, auditors, and all persons collaborating to the trial) are required to take all measures necessary to guarantee confidentiality of all information regarding experimental treatments, clinical trial, identity of participating subjects, and results of research. All data collected by these persons during quality controls or audits will remain anonymous.

16. QUALITY CONTROL AND ASSURANCE

Quality control and assurance will be performed by a clinical research assistant specifically recruited for this trial. Research will be framed under the Sponsor's Standard Operating Procedure (SOP). Research and management of patients in each participating center will be conducted in compliance with the principles of the Declaration of Helsinki and with Good Clinical Practice Guidelines. The Sponsor's representatives will organize regularly visitsto participating centers, according to the schedule of patient follow-up visits as defined in the study protocol, to the inclusion rate and to the protocol risk assessment.

During subsequent visits, case report files will be reviewed according to the progression of research, by clinical research assistants representing the Sponsor who will control the accuracy of data reporting and validate CRF. Primary investigator and associate investigators in each center, involved in the inclusion and follow-up of participating subjects, must consent to regularly meet the Sponsor's

representatives designated by APHP. During these on-site visits and in accordance with Good Clinical Practice Guidelines, the following items will be checked:
- Compliance with the research protocol and related procedures.
- Verification of source documents and confrontation with data reported in the CRF.
- Quality assurance of data reported in the CRF: accuracy, missing data, data consistency, in accordance with the protocol procedures.

17. FUNDING AND INSURANCE

Funding is provided according to the budget obtained by the Program Hospitalier de Recherche Clinique. Assistance Publique-Hôpitaux de Paris is the Sponsor of the present research in France. The Sponsor Assistance Publique–Hôpitaux de Paris has purchased insurance with the HGIGERLING company through BIOMEDIC-INSURE for the entire duration of the study, which guarantees its own civil liability as well as that of all persons involved in the conduction of research (medical and non-medical contributors) (law N° 2004-806 Art. L 1121-10 of the French Public Health Code). Address: Parc d'Innovation Bretagne Sud C. P. 142 56038 Vannes Cedex, France.

18. FINAL RESEARCH REPORT

In accordance with the article R1123-60 of the French Public Health Code, the final research report is established and signed by the Sponsor and the Coordinating Investigator. A report written in compliance with the reference plan of the competent regulatory authority should be transmitted to the regulatory authority and to the Ethics Committee within the first year following the end of the research, which corresponds to the end of the participation of the last subject enrolled onto the research protocol.

19. DATA PUBLICATION RULES AND INTELLECTUAL PROPERTY RIGHTS

Assistance Publique-Hôpitaux de Paris (AP-HP) retains ownership of all data related to the study. None of these data cannot be used or transmitted to a third party without the prior expressed consent of APHP. AP-HP must be identified as the financial sponsor where appropriate. The terms « Assistance Publique–Hôpitaux de Paris » must appear in the authors address. The final publication of the study should be sent for approval to all contributors before submission. According to the rate of patient recruitment in the study, contributors will be included in the author list.

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APPENDIX 1. Evaluation of renal function

MDRD (Modification of Diet in Renal Disease) – simplified equation:

1. If serum creatinine is measured using the Jaffé colorimetric assay:

Estimated GFR (ml/min/1.73m^2): **186, 3** x [serum creatinine (mg/dl)]$^{-1.154}$ x [age (years)]$^{-0.203}$ x 0.742 (if female) x 1.212 (if black).

2.: If serum creatinine is measured using an enzymatic assay

Estimated GFR (ml/min/1.73m^2): **175** x [serum creatinine (mg/dl)]$^{-1.154}$ x [age (years)]$^{-0.203}$ x 0.742 (if female) x 1.212 (if black).

Cockcroft and Gault equation:

$$\text{Creatinine clearance, ml/min:} \quad \frac{[140 - \text{age (years)}] \times \text{body weight (kgs)}}{\text{Serum creatinine (}\mu\text{mol/l)}} \times K$$

K = 1.23 if male, 1.04 if female

APPENDIX 2. AKIN (Acute Kidney Injury Network) classification/staging system for acute kidney injury

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of ≥ to 0.3 mg/dl (26.4 µmol/l) or increase to ≥ 150 to 200 % (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg/h for more than 6 hours
2	Increase in serum creatinine to more than 200 to 300% (> 2- to 3-fold) from baseline	Less than 0.5 ml/kg/h for more than 12 hours
3	Increase in serum creatinine to more than 300% (> 3-fold) from baseline, or serum creatinine of ≥ to 4.0 mg/dl (≥ 354 µmol/l) with an acute increase of at least 0.5 mg/dl (44 µmol/l)	Less than 0.3 ml/kg/h for 24 hours, or anuria for12 hours

From Mehta RL, Kellum JA, Shah SV, et al. Report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11: R31.

Only one criterion (serum creatinine or urine output) has to be fulfilled to qualify for a stage.

According to the recommendations of the ADQI workgroup (Bellono 2004), in patients in whom a baseline serum creatinine is unknown, it is possible to calculate a theoretical baseline serum creatinine value assuming a given normal GFR. By normalizing the GFR to the body surface area, a GFR of approximately 75 to 100 ml/min per 1.73 m^2 can be assumed. Thus, for a given patient, a baseline serum creatinine value can be calculated assuming a value of baseline GFR of 75 ml/min/1.73m^2, using the simplified “modification of diet in renal disease” (MDRD) formula, which provides a robust estimate of GFR relative to serum creatinine based on age, race and sex.

APPENDIX 3. Common Terminology Criteria for Adverse Events

For both AE and SAE, the investigator(s) must assess the severity of the event. The severity of the adverse events (AEs) will be graded on a scale of 1 to 5 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE). The NCI CTCAE V4.0 can be viewed on-line at the following NCI web site: http://ctep.cancer.gov/reporting/ctc.html.

If a specific event is not included in the NCI CTCAE toxicity scale, the following scale should be used to grade the event

Grade	Definition
1.	**Mild**: Awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities
2.	**Moderate**: Discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic manoeuvres
3.	**Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention. Hospitalization may or may not be required
4.	**Life-threatening:** Immediate risk of death; requires hospitalization and clinical intervention
5.	**Death**

Classification of relationship/causality of adverse events (SAE/AE) to study drug

The investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as "Not suspected" or "Suspected" as defined below:

Not suspected: The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

APPENDIX 4. Haematological response criteria

Partial Response (PR), all of the following:

- ≥ 50% reduction in involved free light chain (LC) serum level.
- Parallel improvement of the serum kappa/lambda ratio.
- Reduction in the level of monoclonal entire Ig, if present
- Reduction in the involved LC urine excretion
- No evidence of any sign of disease progression (i.e. new soft tissue plasmocytoma, new lytic bone lesions, hypercalcemia).

Very Good Partial Response (VGPR), all of the following:

- ≥ 90% reduction in involved serum free light chain (LC) level.
- Parallel improvement of the serum kappa/lambda ratio.
- Serum monoclonal Ig (if present) and urine monoclonal LC detectable by immunofixation but not on electrophoresis
- No evidence of any sign of disease progression (i.e. development of lytic bone lesions or soft tissue plasmacytoma, or hypercalcemia).

Complete Response (CR), all of the following:

- Negative immunofixation of the serum and urine monoclonal Ig
- Normal serum kappa/lambda ratio
- < 5% plasma cells in bone marrow (by aspiration or bone marrow if needed)
- No evidence of any sign of disease progression (i.e. development of lytic bone lesions or soft tissue plasmacytoma, or hypercalcemia).

Progressive Disease (PD), or relapse, at least one of the following:

- Increase of ≥ 25% from baseline in:
  - involved serum free light chain (LC) level, with parallel change in serum kappa/lambda ratio
  - serum level of entire monoclonal Ig, if present
  - % of bone marrow plasma cell infiltration (the absolute % must be ≥ 10%)
- Confirmed development of new lytic bone lesions or soft tissue plasmacytomas or confirmed 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) than can be attributed solely to the plasma cell proliferative disorder.

Relapse from complete remission, at least one of the following:

- Reappearance of the serum or urine monoclonal Ig, detectable by immunofixation or electrophoresis
- Reappearance of an abnormal serum free LC level
- Reappearance of ≥ 5%dystrophic plasma cells on bone marrow aspiration
- Any other sign of disease progression

Stable Disease (SD): not meeting criteria for PR, VGPR, CR, PD or relapse

Adapted from Durie BGM et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467-1473.

APPENDIX 5. C-VTD regimen

C-VTD (Cyclophosphamide + Bortezomib + Thalidomide+ Dexamethasone)

- Cyclophosphamide: 600 mg/m^2 through a short IV infusion on day 1. In patients requiring dialysis support, cyclophosphamide should be given at the end of a dialysis session.
- Bortezomib 1.3 mg/m^2 (S.C. or I.V.) **twice** a week for 2 weeks (days 1 and 8), followed by a 13-day period without treatment (days 9-21).
- Thalidomide: a daily single dose of 50 mg/day, given orally every evening for 15 days. If the treatment is well tolerated, thalidomide dose will be increased of 50 mg/day every 15 days, up to a daily dose of 100 mg.
- Dexamethasone 20 mg/day in the morning of days 1, 2, and 8, 9, i.e. on the day and the day after each injection of bortezomib. In case of gastro-intestinal symptoms (vomiting) steroid therapy should be administrated IV (for example, by substituting dexamethasone 20 mg by Solumedrol 200 mg).

APPENDIX 6: Durie Salmon and ISS staging systems for multiple myeloma.

Stage	Durie-Salmon	ISS
I	All of the following present: - Hb>10 g/dL - Serum IgG <50 g/L - Serum IgA <30 g/L - Normal serum calcium (<3 mmol/l) - No generalized lytic bone lesions - Urine monoclonal protein excretion < 4 g/day	Serum beta2-microglobulin <3.5 mg/l and serum albumin >35 g/l
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: - Hb< 8.5 g/dl - Serum IgG >70 g/l - Serum IgA >50 g/l - Serum calcium >3 mmol/l - Advanced lytic bone lesions - Urine monoclonal protein excretion >12 g/day	Serum Beta2-microglobulin>5.5 mg/l
A	Serum creatinine <20 mg/l (177 µmol/l)	
B	Serum creatinine >20 mg/l (177 µmol/l)	

APPENDIX 7: Eastern Cooperative Oncology Group (ECOG) performans status

Grade	Eastern Cooperative Oncology Group
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

From Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology group. Am J Clin Oncol 1982; 5: 649-655

APPENDIX 8: **New York Heart Association (NYHA) functional classification system for congestive heart failure.**

- Class I: patients with cardiac disease bur without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or angina pain.
- Class II: patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or angina pain.
- Class III: patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea, or angina pain.
- Class IV: patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX 9. List of participating centres

N° centre	SITE	Centre	Investigateur principal	Adresse
2	AMN	CHU Amiens groupe hospitalier SUD (néphro)	Pr CHOUKROUN	Service de Néphrologie Hopital Sud Avenue Laënnec - Salouël 80054 **AMIENS** Cedex 1
3	AMN	CHU Amiens groupe hospitalier SUD (hémato)	Dr ROYER	Service d'Hématologie Hopital Sud 124 Rue Camille Desmoulins 80054 **AMIENS** Cedex 1
4	ANG	CHU Angers Hôpital Hotel Dieu (nephro)	Dr AUGUSTO	Service de Néphrologie-Dialyse-Transplantation CHU Angers 4 rue Larrey 49000 **ANGERS**
5	ANG	CHU Angers Hôpital Hotel Dieu (hémato)	Dr DIB	Service d'Hématologie CHU Angers 4 rue Larrey 49000 **ANGERS**
6	AVC	Hôpital AVICENNE (hémato)	Dr BRECHIGNAC	Service d'Hématologie Hôpital Avicenne 125, rue de Stalingrad 93009 **BOBIGNY** Cedex
61	SLS	Hôpital St Louis référent néphro pour l'Hôpital AVICENNE	Pr PERALDI	Service de Néphrologie Hôpital St Louis 1 Av Claude Vellefaux 75010 **PARIS**
7	BSC	CHU Besançon Hôpital Saint Jacques (néphro)	Pr CHALOPIN	Service de Néphrologie hôpital Saint Jacques 2 pl St Jacques 25030 **BESANCON** Cedex
8	BSC	CHU Besançon Hôpital Jean Minjoz (hémato)	Pr DECONINCK	Service d'Hématologie Hôpital Jean Minjoz 3, bd Alexandre Fleming 25030 **BESANCON** Cedex

9	BCH	CHU Bichat (néphro)	Pr DAUGAS	Service de Néphrologie Hôpital Bichat 46, rue Henri-Huchard 75877 **PARIS** Cedex 18
1	SLS	Hôpital St Louis, référent hémato pour le CHU de Bichat	Pr FERMAND	Service d'hématologie Hôpital St Louis 1 Av Claude Vellefaux 75010 **PARIS**
10	BDX	CHU Bordeaux (nephro)	Pr COMBE	Service de Néphrologie Hôpital Pellegrin place Amelie Raba-Léon 33076 **BORDEAUX** Cedex
11	BDX	CHU Bordeaux (hémato)	Pr MARIT	Service d'Hématologie CHU Bordeaux Hopital Haut Leveque Av de Magellan 33604 **PESSAC**
13	BRS	CHU Brest Hôpital Morvan (nephro)	Pr LEMEUR	Service de Néphrologie CHU site de la Cavale Blanche bd Tanguy Prigent 29200 BREST
12	BRS	CHU Brest Hôpital Morvan (hémato)	Pr BERTHOU	Service d'Hématologie CHU Morvan 5 av Foch 29609 **BREST** Cedex
14	CAE	CHU Caen (hémato)	Dr MACRO	Service d'Hématologie CHU Caen Av Georges Clemenceaux 14033 **CAEN** Cedex 05
15	CAE	CHU Caen (néphro)	Dr FICHEUX	Service de Néphrologie CHU Caen Av Georges Clemenceaux 14033 **CAEN** Cedex 05

16	CCH	CHU Cochin (hémato)	Pr BOUSCARY	Service d'Hématologie Hôpital Cochin 27 rue du Faubourg St Jacques 75679 **PARIS** Cedex 14
17	NCK	CHU Necker référent néphro pour le CHU de Cochin	Pr KNEBELMANN	Service néphrologie Hôpital de Necker 149 rue de Sèvres 75015 **PARIS**
20	FRD	CHU Clermont-Ferrand Hôpital Gabriel Montpied (hémato)	Pr BAY	Service d'Hématologie CHU Gabriel Montpied 56 rue Montalembert BP 69 63003 **CLERMONT-FERRAND** Cedex
18	FRD	CHU Clermont-Ferrand Hôpital Gabriel Montpied (rhumato)	Pr SOUBRIER	Service de Rhumatologie CHU Gabriel Montpied 56 rue Montalembert BP 69 63003 **CLERMONT-FERRAND** Cedex
19	FRD	CHU Clermont-Ferrand Hôpital Gabriel Montpied (néphro)	Dr HENG	Service de Néphrologie CHU Gabriel Montpied 56 rue Montalembert BP 69 63003 **CLERMONT-FERRAND** Cedex
21	DJN	CHU Dijon Hôpital du Bocage (hémato)	Dr CAILLOT	Service d'Hématologie clinique CHU Dijon - Hôpital d'enfants 10 Bd Mal de Lattre de Tassigny 21000 **DIJON** Cedex
22	DJN	CHU Dijon Hôpital du Bocage (néphro)	Pr MOUSSON	Service de Néphrologie CHU Dijon 2 Bd Maréchal de Lattre de Tassigny BP 77908 21079 **DIJON** Cedex

23	EGP	CHU Georges Pompidou Hôpital Europeen (néphro)	Dr KARRAS	Service de Néphrologie Hôpital Européen G. Pompidou 20 rue Leblanc75015 **PARIS**
16	CCH	CH Hôtel-Dieu référent hémato pour le CHU Georges Pompidou	Pr BOUSCARY	Service d'Hématologie Hôpital Cochin 27 rue du Faubourg St Jacques 75679 **PARIS** Cedex 14
24	GRN	CHU Grenoble Hôpital Albert Michallon (hémato)	Dr PEGOURIE	Service d'Hématologie Hôpital Albert Michallon boulevard de la chantourne BP 217 38043 **GRENOBLE** Cedex 9
25	GRN	CHU Grenoble Hôpital Albert Michallon (nephro)	Pr CARRON	Service de Néphrologie Hôpital Albert Michallon boulevard de la chantourne BP 217 38043 **GRENOBLE** Cedex 9
93	HMN	CHU Henri Mondor (néphro)	Dr BOUACHI	Service de Néphrologie Hôpital Henri Mondor 51 avenue du Mal de Lattre de Tassigny 94010 **CRETEIL** Cedex
26	HMN	CHU Henri Mondor (hémato)	Dr BELHADJ	Unité Fonctionnelle : Hémopathie Lymphoïdes Hématologie Hôpital Henri Mondor 51 avenue du Maréchal de Lattre de Tassigny 94010 **CRETEIL** Cedex
27	JVR	CHU JEAN VERDIER (hémato)	Pr FAIN	Service d'Hématologie Hôpital Jean Verdier Avenue du 14 Juillet 93143 **BONDY** Cedex

61	SLS	Hôpital St Louis référent néphrologie pour le CHU JEAN VERDIER	Pr PERALDI	Service de Néphrologie Hôpital Saint Louis 1 Av Claude Vellefaux 75010 **PARIS**
28	KBC	CHU KREMLIN BICETRE (néphro)	Pr CHARPENTIER	Service de Néphrologie CHU KREMLIN BICETRE 78 rue du Général Leclerc 94275 **LE KREMLIN BICETRE**
29	KBC	CHU KREMLIN BICETRE (Rhumato)	Dr MARIETTE	Service de Rhumatologie CHU KREMLIN BICETRE 78 rue du Général Leclerc 94275 **LE KREMLIN BICETRE**
31	LIL	CHU LILLE (hémato)	Pr FACON	Service des maladies du sang CHU de Lille rue Michel Polonovski 59037 **LILLE** Cedex
30	LIL	CHU LILLE (néphro)	Dr PROVOT	Service de Néphrologie Pôle de Néphrologie Hôpital Calmette CHRU de Lille 59000 **LILLE**
32	LMG	CHU LIMOGES- Hôpital Dupuytren (néphro)	Pr ESSIG	Service de Néphrologie, Hémodialyse, Transplantation CHU Limoges 2 Av Martin Luther King 87042 **LIMOGES** Cedex
33	LMG	CHU LIMOGES- Hôpital Dupuytren (hémato)	Pr JACCARD	Service d' Hématologie Clinique et de Thérapie cellulaire CHU Dupuytren 2 avenue Martin-Luther-King 87042 **LIMOGES** Cedex
34	HEH	CHU LYON- Hôpital Edouard Herriot (HCL) (néphro)	Dr JUILLARD	Service de Néphrologie Hôpital Edouard Herriot Place d'Arsonval 69437 **LYON** Cedex 03

35	HEH	CHU LYON- Hôpital Edouard Herriot (HCL) (hémato)	Pr MICHALLET	Service Hématologie Marcel Bérard Centre Hospitalier Lyon Sud Secteur 1G 694395 PIERRE BENITE
36	LYS	CHU LYON Sud (hémato)	Dr TRAULLE	Service d'Hématologie Centre Hospitalier Lyon Sud 165, chemin du grand revoyet 69495 **PIERRE BENITE** Cedex
37	LYS	CHU LYON Sud (néphro)	Dr VILLAR	Service de Néphrologie Centre Hospitalier Lyon - Sud 165, chemin du grand Revoyet 69495 **PIERRE-BENITE** Cedex
38	MRS	CHU MARSEILLE-Hôpital de la Conception (APHM) (néphro)	Dr BURTEY	Service de Néphrologie Hôpital de la Conception 147, boulevard Baille 13385 **MARSEILLE** cedex 5
39	MRS	Institut Paoli Calmette référent hémato pour le CHU de MARSEILLE-Hôpital de la Conception (APHM)	Dr STOPPA	Service d'hématologie Institut Paoli-calmette 232, bl de sainte marguerite 13273 **MARSEILLE** cedex 5
41	NCY	CHU NANCY (néphro)	Pr FRIMAT	Service de Néphrologie CHU De Nancy Hôpital de Brabois rue de Morvan 54511 **VANDOEUVRE LES NANCY Cedex**
40	NCY	CHU NANCY (hémato)	Dr HULIN	Service d'Hématologie et de Médecine Interne CHU de Nancy Hôpital de Brabois Rue de Morvan 54511 **VANDOEUVRE LES NANCY** Cedex

43	NTE	CHU NANTES HOPITAL HOTEL DIEU (hémato)	Pr MOREAU	Service d'Hématologie CHU Hôtel Dieu Place Alexis Ricordeau 30 Bd Jean Monnet 44093 **NANTES** Cedex 01
42	NTE	CHU NANTES HOPITAL HOTEL DIEU (néphro)	Dr LAVAINNE	Service de Néphrologie CHU Hôtel Dieu Immeuble Jean Monnet 30 Bd Jean Monnet 44093 **NANTES** Cedex
17	NCK	CHU NECKER (néphro)	Pr KNEBELMANN	Service de Nephrologie Hôpital Necker 149 rue de Sévres 75015 **PARIS**
44	NCK	CHU NECKER (hémato)	Dr DELARUE	Service d'Hématologie Hôpital de Necker 149 rue de Sèvres 75015 **PARIS**
46	NIC	CHU NICE (hémato)	Pr FUZIBET	Médecine Interne - Cancerologie Hôpital de L'Archet 151 route de Saint antoine de Ginestière BP 3079 06202 **NICE** Cedex 3
45	NIC	CHU NICE (néphro)	Pr ESNAULT	Service de Néphrologie Hôpital Pasteur 30 avenue de la voie Romaine 06002 **NICE**
48	PSL	CHU PITIE SALPETRIERE (néphro)	Pr ISNARD BAGNIS	Service de Néphrologie Hôpital Pitié Salpétriere 47-83 Bd de l'Hôpital 75013 **PARIS**
47	PSL	CHU PITIE SALPETRIERE (hémato)	Dr ROOS-WEIL	Service d'Hématologie Hôpital Pitié Salpétriere 47-83 Bd de l'Hôpital 75013 **PARIS**

49	PTS	CHU POITIERS (néphro)	Pr BRIDOUX	Service de Néphrologie CHU Poitiers Hôpital Jean Bernard 2 rue de la Miletrie 86021 **POITIERS**
50	PTS	CHU POITIERS (hémato)	Dr LACOTTE	Département d'oncologie Hématologique et Thérapie Cellulaire CHRU de Poitiers 2rue de la Miletrie 86021 **POITIERS**
51	RMS	CHU REIMS (néphro)	Pr RIEU	Service de Néphrologie Centre Hospitalier Universitaire Hôpital de la Maison Blanche 45 rue Cognacq Jay 51092 **REIMS** Cedex
52	RMS	CHU REIMS (hémato)	Dr KOLB	Hôpital Robert Debré - CHU de Reims avenue du Général Koenig 51092 Reims cedex
54	RNS	CHU RENNES (médecine interne)	Dr DECAUX	Service de Médecine interne Hôpital Sud 16 Bd de Bulgarie 35203 **RENNES** Cedex
55	RNS	CHU RENNES (hémato)	Dr ESCOFFRE-BARBE	Service d'Hématologie Hôpital Pontchaillou rue Henri le Guilloux 35033 **RENNES** Cedex 09
53	RNS	CHU RENNES (néphro)	Dr VIGNEAU	Service de Néphrologie CHU Pontchaillou 2 rue Henri Le Guilloux 35000 **RENNES**
57	ROU	CHU ROUEN Hopital De Bois Guillaume (néphro)	Dr LE ROY	Service de Néphrologie Hôpital du Bois Guillaume Centre Hospitalier Universitaire 76031 **ROUEN** Cedex

56	ROU	Centre Becquerel réferent Hématologie pour le CHU deROUEN	DR LENAIN	Service d'Hématologie Centre Henri Becquerel rue d'Amiens 76038 **ROUEN** Cedex
58	SAT	CHU St ANTOINE (hémato)	Dr GARDERET	Service des maladies du sang et de thérapie cellulaire Hôpital Saint Antoine 184 rue du Fg Saint Antoine 75012 **PARIS**
95	TNN	Hopital Tenon réferent Néphro pour le CHU de St ANTOINE	Pr RONCO	Service de Néphrologie Hôpital Tenon 4 rue de la Chine 75970 **PARIS** Cedex 20
60	ENN	CHU St ETIENNE (hémato)	Dr JAUBERT	Service d'Hématologie Institut de Cancérologie de la Loire 108 Bis Av albert Raymond BP 60008 42271 **ST PRIEST EN JAREZ** Cedex
59	ENN	CHU St ETIENNE (néphro)	PR ALAMARTINE	Service de Néphrologie, Dialyse, Transplantation Rénale Hôpital Nord CHRU de Saint Etienne 42055 **SAINT ETIENNE** Cedex 2
61	SLS	CHU St LOUIS (néphro)	Pr PERALDI	Service de Néphrologie Hôpital St Louis 1 Av Claude Vellefaux 75010 **PARIS**
1	SLS	CHU St LOUIS (hémato)	Pr FERMAND	Service d'Hématologie Hôpital St Louis 1 Avenue Claude Vellefaux 75010 **PARIS**

63	SBG	CHU STRASBOURG (néphro)	Pr MOULIN	Service de Néphrologie Nouvel Hôpital Civil 1 Place de l'Hôpital BP 426 67091 **STRASBOURG**
62	SBG	CHU STRASBOURG (hémato)	Pr LIOURE	Département d'Hématologie et Oncologie CHRU Hautepierre 67098 **STRASBOURG** Cedex
64	TNN	CHU TENON (Néphro A)	Pr RONDEAU	Service des Urgences Néphrologiques et transplantation Rénale Hôpital Tenon 4 rue de la Chine 75970 **PARIS** Cedex 20
95	TNN	CHU TENON (Néphro B)	Pr RONCO	Service de Néphrologie Hôpital Tenon 4 rue de la Chine 75970 **PARIS** Cedex 20
1	SLS	Hôpital Saint Louis, référent hémato pour le CHU de TENON	Pr FERMAND	Service d'Hématologie Hôpital St Louis 1 Avenue Claude Vellefaux 75010 **PARIS**
58	SAT	CHU Saint Antoine, référent hémato pour le CHU de TENON	Dr GARDERET	Service des maladies du sang et thérapie cellulaire Hôpital Saint Antoine 184 rue du Fg Saint Antoine 75012 **PARIS**
65	TSE	CHU TOULOUSE (néphro)	Pr CHAUVEAU	Service de Néphrologie CHU de Rangueil, 1 avenue Jean Poulhès, 31059 **TOULOUSE** Cedex 9

66	TSE	CHU TOULOUSE (hémato)	Dr ROUSSEL	Service d'Hématologie CHU Purpan Place du Dr Baylac TSA 40031 31059 **TOULOUSE** Cedex 9
68	TRS	CHU TOURS-Hôpital de Bretonneau (hémato)	Dr BENBOUKER	Service d'Hématologie Hôpital de Bretonneau 2, boulevard tonnellé 37000 **TOURS**
67	TRS	CHU TOURS-Hôpital de Bretonneau (néphro)	Dr RABOT	Service de Néphrologie Hôpital de Bretonneau 2, boulevard tonnellé 37000 **TOURS**
90	MFL	Hôpital de Montfermeil, référent hémato pour le CH André Grégoire	Dr LENOBLE	Service d'Hématologie Centre Hospitalier Intercommunal 10 rue du Général Leclerc 93370 **MONTFERMEUIL**
69	MFL	CH André Grégoire (néphro)	Dr BELENFANT	Service de Néphrologie Centre Hospitalier André Grégoire 56, bd de la Boissiere 93100 **MONTREUIL**
70	AGM	CH ANGOULEME (néphro)	Dr YVER	Service de Néphrologie-hémodialyse Centre Hospitalier D'Angoulême Rond Point GIRAC 16470 **SAINT MICHEL**
50	PTS	CHU Poitiers référent hémato pour le CH d'ANGOULEME	Dr LACOTTE	Département d'oncologie Hématologique et Thérapie Cellulaire CHRU de Poitiers 2rue de la Miletrie 86021 **POITIERS**

72	AVG	CH Avignon Hôpital Henri Duffaut (hémato)	Dr SLAMA	Service d'Hématologie Hôpital Henri Duffaut 305 rue Raoul Follereau 84902 **AVIGNON** Cedex 8
71	AVG	CH Avignon Hôpital Henri Duffaut (néphro)	Dr GOBERT	Service de Néphrologie Hôpital Henri Duffaut 305 rue Raoul Follereau 84902 **AVIGNON** Cedex 8
73	TRB	CH de BIGORRE (néphro)	Dr HEMERY	Service de Néphrologie Hôpital de Tarbes Bd de lattre de Tassigny 65000 **TARBES**
91	TRB	CH de BIGORRE (hémato)	Dr DINGREMONT	Service de Médecine Interne CH Tarbes Vic-Bigorre Bd de Lattre de Tassigny BP 1330 65013 **TARBES** Cedex 09
74	BLG	CH Boulogne sur Mer (néphro)	Dr BATAILLE	Service de Néphrologie Centre Hospitalier de Boulogne sur mer BP 609 62321 **BOULOGNE SUR MER** cedex
75	BLG	CH Boulogne sur Mer (hémato)	Dr CHOUFFI-BELGHOUL	Service d'Hématologie Centre Hospitalier de Boulogne sur mer BP 609 62321 **BOULOGNE SUR MER** cedex
76	CHR	CH CHARTRES (néphro)	Dr GODART	Service de Néphrologie Hôtel Dieu 34 rue du docteur Maunoury 28018 **CHARTRES**

77	CHR	CH CHARTRES (hémato)	Dr MAIGRE	Service d'Hématologie- Oncologie médicale CH de Chartres BP 407 28018 **CHARTRES** Cedex
79	DNK	CH de Dunkerque (hémato)	Dr VETTERWALD	Service d'Hématologie Hôpital de Dunkerque 130, avenue Louis Herbeaux BP 6 367 59385 **DUNKERQUE** cedex 1
78	DNK	CH de Dunkerque (néphro)	Dr AZAR	Service de Néphrologie Hôpital de Dunkerque 130, avenue Louis Herbeaux BP 6 367 59385 **DUNKERQUE** cedex 1
81	FCH	CH Foch (hémato)	Dr GLAISNER	Service d'Hématologie Hôpital Foch 40, rue Worth 92151 **SURESNES**
80	FCH	CH Foch (néphro)	Dr DELAHOUSSE	Service de Néphrologie Hôpital Foch 40 rue Worth 92150 **SURESNES**
82	HVR	CH le Havre (rhumato)	Dr ZARNITSKY	Service de Rhumatologie CH le Havre 29, avenue Pierre Mendès France Montivilliers 76290 **LE HAVRE**
92	HVR	CH le Havre (néphro)	Dr THUILLIER-LECOUF	Service de Néphrologie CH le Havre 29, avenue Pierre Mendès France Montivilliers 76290 **LE HAVRE**

84	RSY	CHD La Roche sur Yon (hémato)	Dr TIAB	Service d'Hématologie CHD Vendée Bd Stephane Moreau 85925 **LA ROCHE SUR YON**
83	RSY	CHD La Roche sur Yon (néphro)	Dr OTTAVIOLI	Service de Néphrologie-Dialyse CHD des Oudairies Bd Stephane Moreau 85925 **LA ROCHE SUR YON** Cedex 9
85	CRB	CH Sud Francilien (hémato)	Dr JOLY	Service d'Hématologie Centre Hospitalier Sud Francilien Service Hématologie Clinique, Pôle D, 3ème étage 116 bd Jean Jaurès 91100 **Corbeil-Essonnes**
86	CRB	CH Sud Francilien (néphro)	Dr CAUDWEL	Service de Néphrologie Centre Hospitalier Sud Francilien Service Hématologie Clinique, Pôle D, 3ème étage 116 bd Jean Jaurès 91100 **Corbeil-Essonnes**
87	VLC	CH Valenciennes (néphro)	Dr Vrigneaud	Service de Néphrologie CH Valenciennes Avenue Desandrouin BP 479 59322 **VALENCIENNES** Cedex
88	VLC	CH Valenciennes (hémato)	Dr POLLET	Service d'Hématologie CH Valenciennes Avenue Desandrouin BP 479 59322 **VALENCIENNES** Cedex

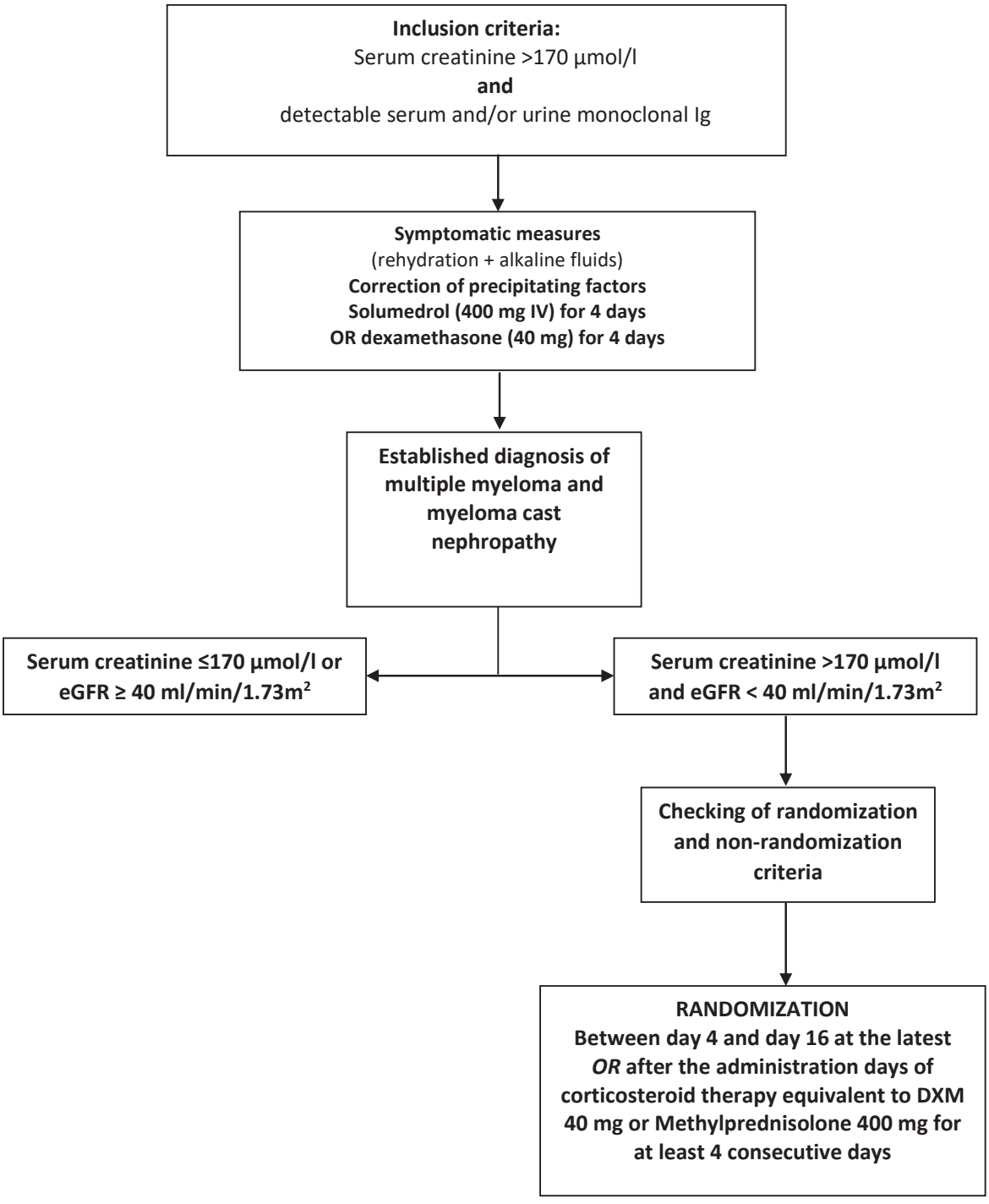
96	KBC	CHU Kremlin Bicêtre, référent néphro pour l'IGR	DURRBACH	Service de Néphrologie CHU Kremlin Bicetre 78 rue du Général Leclerc 94275 **LE KREMLIN BICETRE**
89	IGR	IGR (hémato)	Dr RIBRAG	Service d'Hématologie Institut Gustave Roussy 39 rue C desmoulins 94805 **VILLEJUIF**
97	RCH	CH La Rochelle	Dr LEROY	Service de Néphrologie et medecine interne 1 rue du Dr Schweitzer CH St Louis 17000 **LA ROCHELLE**
98	RCH	CH La Rochelle	Dr FLECK	Service d'oncologie 1 rue du Dr Schweitzer CH St Louis 17000 **LA ROCHELLE**
99	NRT	CH Niort	Dr MOTARD	Service de medecine interne hématologie CH Niort 40 avenue Charles De Gaulle 97021 **NIORT**
100	NRT	CH Niort	Dr MOUMAS	Service de néphrologie CH Niort 40 avenue Charles De Gaulle 97021 **NIORT**
101	PON	CH Pontoise	Dr BENRAMDANE	Service d'oncohématologie CH René Dubos 6 Av de l'IE de France 95000 **PONTOISE**
102	PON	CH Pontoise	Dr MONTSENY	Service de néphrologie CH René Dubos 6 Av de l'IE de France 95000 **PONTOISE**

103	HAG	CH HAGUENAU	Pr DIMITROV	Service de néphrologie 64 Avenue Prof Leriche, 67504-**Haguenau**
62	SBG	CHU STRASBOURG Référent hémato pour le CH HAGUENAU	Pr LIOURE	Département d'Hématologie et Oncologie CHRU Hautepierre 67098 **STRASBOURG** Cedex
38	MRS	CHU MARSEILLE- Hôpital de la Conception (APHM) (néphro)	Dr BURTEY	Service de Néphrologie Hôpital de la Conception 147, boulevard Baille 13385 **MARSEILLE** cedex 5
104	MRS	CHU MARSEILLE- Hôpital de la Conception (APHM) (hémato)	Dr COSTELLO	Service d'hématologie Hôpital de la Conception 147, boulevard Baille 13385 **MARSEILLE** cedex 5
105	LNS	Centre Hospitalier de Lens (hémato)	Dr MOREL	Service d'hématologie Centre Hospitalier de Lens 99, Route de la Bassée 62300 **LENS**
106	LNS	Centre Hospitalier de Lens (néphro)	Dr MAC NAMARA	Service d'hémodialyse Centre Hospitalier de Lens 99, Route de la Bassée 62300 **LENS**
107	LNS	Centre Hospitalier de Béthune (néphro)	Dr MAC NAMARA	Service d'hémodialyse Centre hospitalier de **Béthune** rue Delbecque 62660 BEUVRY
108	LMN	CH LE MANS (hémato)	Dr LARIBI	CH LE MANS Service d'oncologie-hématologie 194 avenue Rubillard 72000 LE MANS
109	LMN	CH LE MANS (néphro)	Dr COINDRE	CH LE MANS Service de néphrologie 194 avenue Rubillard 72000 LE MANS
110	ORL	CHR Orléans	Dr BENBRAHIM	CHR Orléans

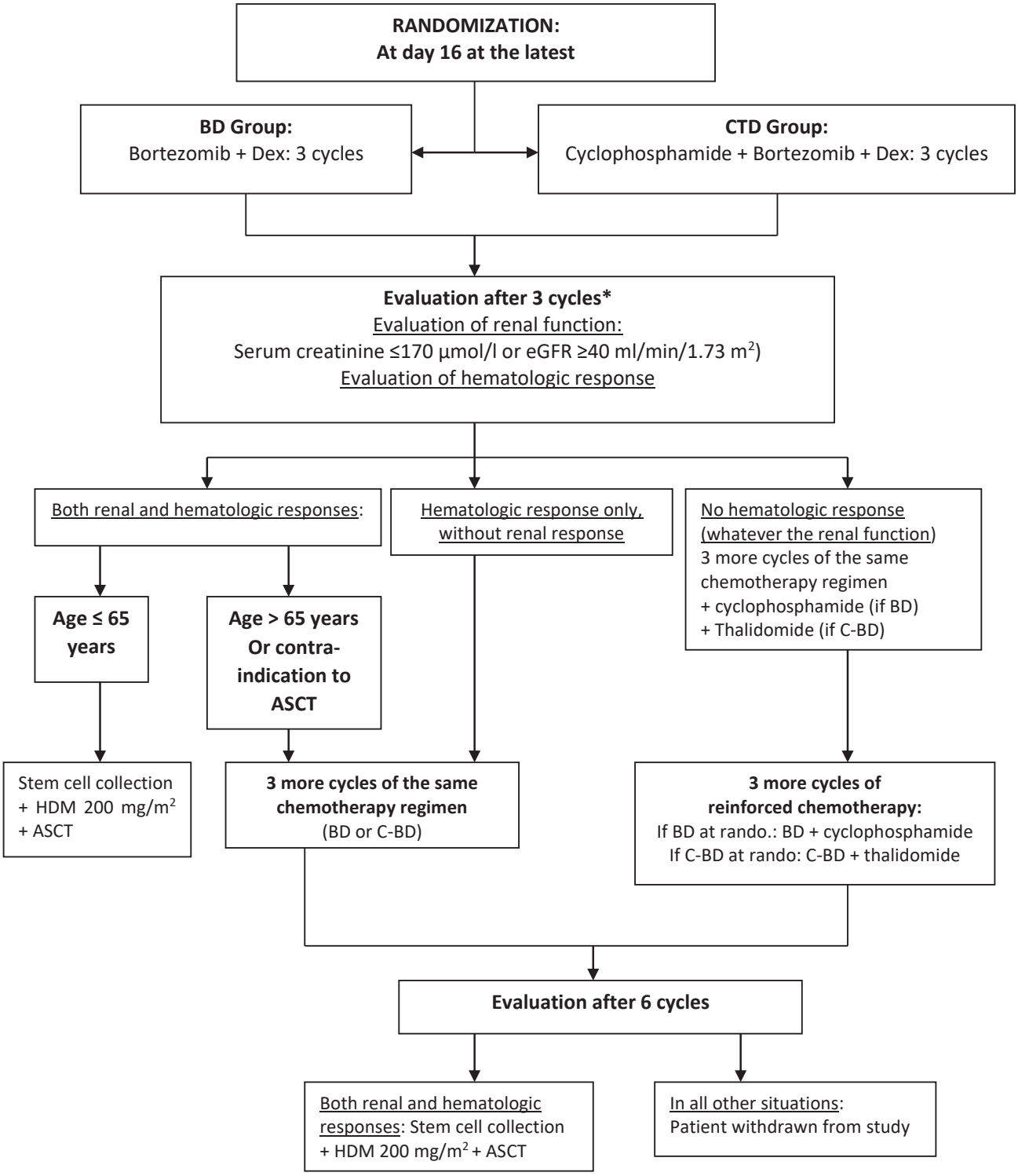
		(hémato)		Service d'onco-hématologie 14 avenue de l'Hôpital 45100 ORLEANS
111	ORL	CHR Orléans (néphro)	Dr EL KHOURU-HANNA	CHR Orléans Service de néphrologie 14 avenue de l'Hôpital 45100 ORLEANS
112	PPG	CH de Perpignan (hémato)	Dr SANHES	CH St Jean Service d'Hématologie Clinique Avenue du Languedoc 66 000 Perpignan
113	PPG	CH de Perpignan	Dr VELA	CH St Jean Service de néphrologie Avenue du Languedoc 66 000 Perpignan
114	QPR	CH de Cornouaille (Médecine interne)	Dr HUTIN	CH de Cornouaille Service de médecine interne Maladies infectieuses-Maladies du sang 14 av Yves Thépot 29107 QUIMPER
115	QPR	CH de Cornouaille (néphro)	Dr SIOHAN	CHG Laennec Service de néphrologie 14 av Yves Thépot 29107 QUIMPER
116	MEX	Centre hospitalier de Meaux (hémato)	Dr FOUILLARD	Service d'hématologie et de thérapie cellulaire Centre hospitalier de Meaux 6-8 rue Saint Fiacre 77100 Meaux
117	MEX	Centre hospitalier de Meaux (néphro)	Dr FARAH	Service de néphrologie Centre hospitalier de Meaux 6-8 rue Saint Fiacre 77100 Meaux
118	STB	Centre Hospitalier de St Brieuc	Dr BOULAHROUZ	Hopital Yves le Foll Service de néphrologie 10 r Marcel Proust 22027 ST BRIEUC CEDEX 1
119	STB	Centre Hospitalier de St Brieuc	Dr ALLANGBA	Hopital Yves le Foll Service d'hématologie 10 r Marcel Proust 22027 ST BRIEUC CEDEX 1

120	LIC	Hôpital St Vincent GH-ICL	Dr CLIQUENNOIS	Hôpital St Vincent GH-ICL Service d'onco-hématologique Boulevard de Belfort 59020 LILLE
121	LIC	Hôpital St Vincent GH-ICL	Dr HOFFMANN	Hôpital privé La louvière Service de néphrologie 69 rue de la Louvière 59000 LILLE
122	BRG	CH de BOURGES	Dr MAAKAROUN	CH de BOURGES Hôpital Jacques-Cœur Unité d'hématologie Clinique 145, avenue François Mitterrand 18020 BOURGES Cedex
123	BRG	CH de BOURGES	Dr RIFARD	CH de BOURGES Hôpital Jacques-Cœur Service de néphrologie-Hémodialyse 145, avenue François Mitterrand 18020 BOURGES Cedex
124	ANC	CH de la région d'ANNECY	Dr ORSINI-PIOCELLE	CHRA Service d'hématologie BP 90074 1 avenue de l'hôpital METZ-TESSY 74374- PRINGY Cedex
125	ANC	CH de la région d'ANNECY	Dr TURC-BARON	CHRA Service de néphrologie BP 90074 1 avenue de l'hôpital METZ-TESSY 74374- PRINGY Cedex

APPENDIX 10. Study synopsis: inclusion/screening period prior to randomization

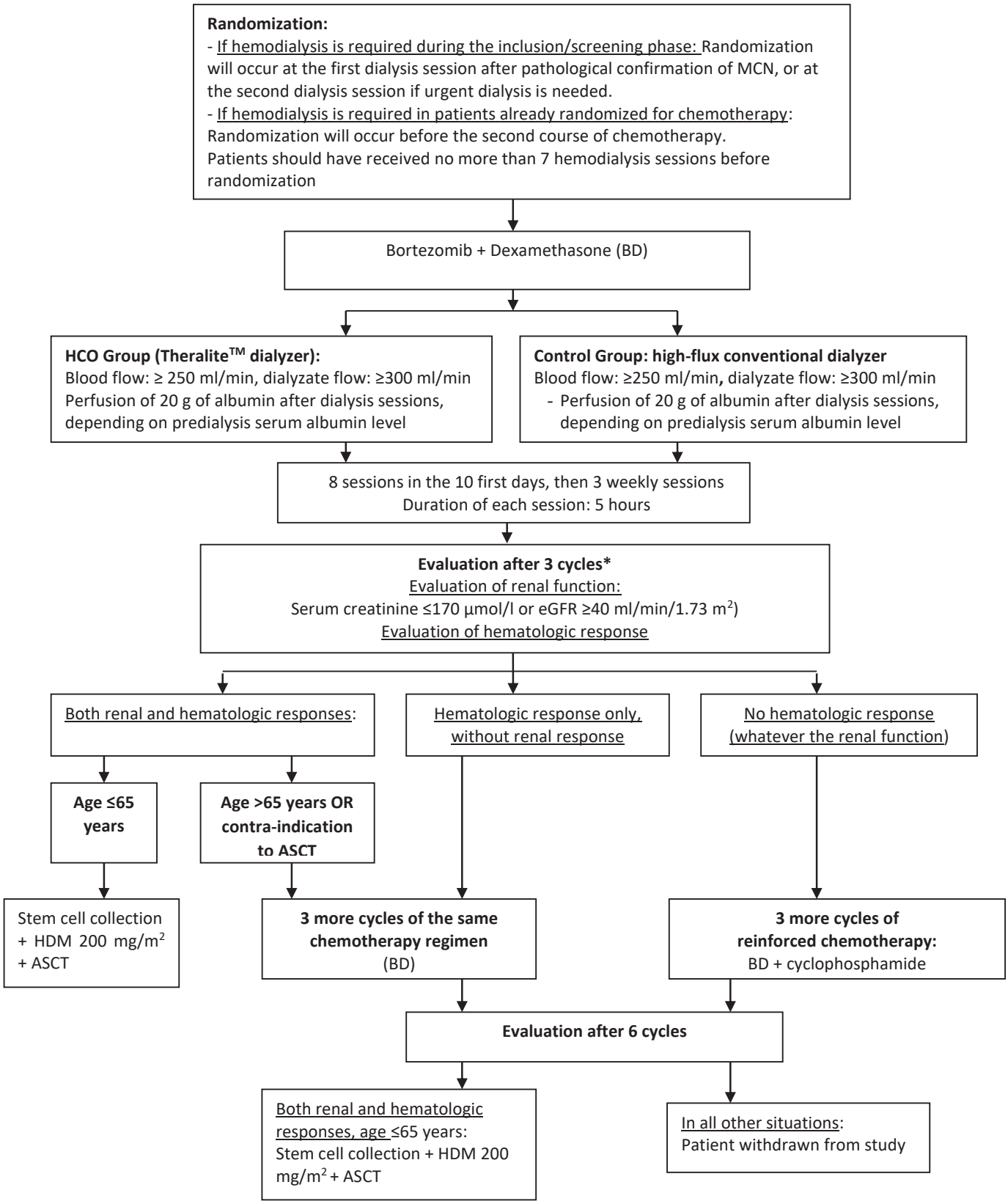


Appendix 11. Study synopsis - Patients not requiring dialysis: randomization for chemotherapy



* For patients requiring hemodialysis before the second course of chemotherapy, and who are randomized for the dialysis membrane, B-CD is stopped and replaced by BD.

APPENDIX 12. Study synopsis - Patients requiring hemodialysis: randomization for the hemodialysis membrane



APPENDIX 13. Summary of Product Characteristics (SmPC)

Bortezomib (Velcade®) (http://www.ema.europa.eu/docs/fr_FR/document_library/EPAR_-_Product_Information/human/000539/WC500048471.pdf)

Thalidomide (http://www.ema.europa.eu/docs/fr_FR/document_library/EPAR_-_Product_Information/human/000823/WC500037050.pdf)

Dexamethasone (Neodex®) (https://ec.europa.eu/health/documents/community-register/2016/20160316134053/anx_134053_fr.pdf)

Methylprednisolone Hemisuccinate (Solumedrol®) (http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0165262.htm)

Cyclophosphamide (Endoxan ®) (http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0139134.htm)

Theralite™ operating instructions

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Événements pouvant être graves mais non liés aux médicaments expérimentaux (bortezomib, cyclophosphamide, methylprednisolone, thalidomide), ni au dispositif médical expérimental (membrane Theralite™), ni aux actes et procédures ajoutés par la recherche	**Effets Indésirables (EI) Non Graves ATTENDUS** Connus pour être liés aux médicaments expérimentaux, au dispositif médical expérimental ou aux actes et procédures de la recherche (Réf : CTCAE v4.0)	**Evénements Indésirables Graves (EIG) ATTENDUS** (Réf : CTCAE v4.0)	**Effets Indésirables Graves (EIG) INATTENDUS (SUSARs)**
• **Tout ce qui est en rapport avec l'évolution naturelle et habituelle de la pathologie** : - Insuffisance rénale sévère - Anurie - Syndrome d'hyperviscosité - Hypercalcémie - Hyperkaliémie - Autres signes traduisant l'évolution de la maladie - Hospitalisation programmée ou non pour suivi de la pathologie • Effets indésirables éventuellement graves mais bien connus, très fréquents et bien maîtrisés dont la déclaration n'apporterait rien à la sécurité des patients (à ne pas notifier sauf si aggravation) : Aplasie médullaire post-chimiothérapie de grade ≤ 3 sans complication. • **Tout effet indésirable grave susceptible d'être lié aux traitements prescrits dans le cadre du soin pendant le suivi de la recherche.** • **Tout autre évènement médical en dehors de la pathologie.**	**Liés au bortezomib** • **Infections et infestations** - Rhino-pharyngite. - Grade ≤ 2 : bronchite, sinusite, pneumonie infection en relation avec un cathéter, bactériémie, infections des voies respiratoires supérieures et inférieures, infection pleurale, infection fongique, infection urinaire. • **Affectations hématologiques et du système lymphatique** - Grade ≤ 2 : anémie, thrombocytopénie, purpura thrombocytopénique, neutropénie, lymphopénie, leucopénie. • **Affections du système nerveux** - Grade ≤ 2 : neuropathie périphérique, paresthésies, encéphalopathie, étourdissement (à l'exclusion des vertiges), troubles de l'attention, augmentation de l'activité somnolence, troubles cognitifs, vertiges orthostatiques, sciatique, mono névrite, dysesthésie, vertiges orthostatiques, sciatique, mouvements saccadés, hémorragie intracrânienne, syndrome de leuco encéphalopathie postérieure réversible, hypotension orthostatique. • **Affections gastro-intestinales** - Stomatite, selles trop liquides, flatulences, saignement gingival, douleur buccale, haut-le-cœur, pétéchies de la muqueuse buccale, langue décolorée, langue saburrale, colite liée aux antibiotiques, modification du transit, gêne abdominale, éructation, hypersialorrhée, entérite, douleur splénique. - Grade ≤ 2 : distension abdominale, douleur abdominale, diarrhées, vomissements, nausées, constipation, douleur de l'abdomen supérieur, sécheresse buccale, dyspepsie, ulcération buccale, douleur gingivale, douleur pharyngo-laryngée, colite ischémique, colite, hémorragie gastro-intestinale, hémorragie rectale, gastrite, reflux gastro-œsophagien, douleur gastro-intestinale, dysphagie, hoquet, trouble de la motilité gastro-intestinale. • **Troubles généraux et anomalies au site d'administration** - Syndrome pseudo-grippal, malaise, faiblesse, frissons, léthargie, chute, sensation de froid, sensibilité au toucher, sensation d'oppression thoracique, gêne pectorale, oppression thoracique, inflammation des muqueuses. - Grade ≤ 2 : fatigue, douleur, douleur de l'aine, douleur thoracique, pyrexie, asthénie, névralgie, phlébite au point d'injection, érythème au site d'injection. (Liste non exhaustive : se reporter au RCP de Velcade® en vigueur).	**Liés au bortezomib** • **Infections et infestations** - Zona, herpès, septicémie, méningo-encéphalite herpétique, pneumopathie à pneumocoques, névralgie post herpétique, candidose orale, blépharite, infection à *Haemophilus*, zona, infection à *cytomégalovirus*, infection à *Candida*, mononucléose infectieuse, varicelle. - Grade ≥ 3 : choc septique, sepsis. • **Affectations hématologiques et du système lymphatique** - Anémie hémolytique, pancytopénie, lymphadénopathie. - Grade ≥ 3 : thrombocytopénie, neutropénie fébrile, anémie, leucopénie, lymphopénie, purpura thrombocytopénique. • **Affections du système nerveux** - Syndrome des jambes sans repos, polynévrite, hypoesthésie, paraplégie, hémorragie sous-arachnoïdienne, convulsions, neuropathie autonome, parésies, mono névrite, dysgueusie, agueusie, migraine, troubles cognitifs - Grade ≥ 3 : encéphalopathie, étourdissement, neuropathie sensitive périphérique, troubles de l'attention, augmentation de l'activité somnolence, dysesthésie, mouvements saccadés, neuropathie périphérique aggravée, encéphalopathie, hémorragie intracrânienne, syndrome de leuco encéphalopathie postérieure réversible, neuropathie motrice périphérique, céphalées, paresthésies, syncope, tremblement, hypotension orthostatique. • **Affections gastro-intestinales** - Diarrhée hémorragique, œsophagite, hernie hiatale, hématémèse, fécalome, syndrome du côlon irritable. - Grade ≥ 3 : hoquet, douleur de l'abdomen supérieur, ulcération buccale, douleur pharyngo-laryngée, saignement gingival, diarrhées, vomissements, constipation, colite ischémique, pancréatite aiguë, iléus paralytique, colite, hémorragie gastro-intestinale, hémorragie rectale, gastrite, reflux gastro-œsophagien, douleur gastro-intestinale, dysphagie, distension abdominale, nausées, douleur abdominale, sécheresse buccale, dyspepsie, douleur gingivale, oesophagite, gastrite, trouble de la motilité gastro-intestinale. • **Affections de la peau et du tissu sous- cutané** - Nécrolyse épidermique toxique, syndrome de Stevens-Johnson. • **Troubles généraux et anomalies au site d'administration** - Œdème, inflammation extravasée, œdème périphérique, hémorragie muqueuse. - Grade ≥ 3 : fatigue, douleur, douleur de l'aine, douleur thoracique, pyrexie, asthénie, névralgie. • **Tumeurs bénignes et malignes (y compris kystes et polypes)** - Grade ≥ 3 : syndrome de lyse tumorale. • **Affections du système immunitaire** - Réactions potentiellement médiées par les complexes immuns telles que des réactions à types maladie sérique, polyarthrite avec éruption, et glomérulonéphrite proliférative.	Notifier tous les événements présentant l'un des critères de gravité noté ci-dessous, à l'exception de ceux recensés dans le protocole comme ne devant pas être notifiés : **1-** Décès **2-** Mise en jeu du pronostic vital **3-** Nécessite ou prolonge l'hospitalisation **4-** Séquelles durables **5-** Anomalie ou malformation congénitale **6-** Evénement jugé grave par l'investigateur (raison à préciser) **ATTENTION :** toute découverte d'une GROSSESSE au décours d'une recherche biomédicale doit être immédiatement déclarée au promoteur et fera l'objet d'un suivi jusqu'à l'accouchement.

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« TRAITEMENT DE LA NEPHROPATHIE A CYLINDRES MYELOMATEUX »

A NE PAS NOTIFIER AU PROMOTEUR **Evénements recensés dans le protocole comme ne devant pas être notifiés mais qui pourront être recueillis dans le cahier d'observation (CRF)**		**A NOTIFIER SANS DELAI** AU PROMOTEUR **Envoi du formulaire de notification d'EIG par fax au 01 44 84 17 99 et à recueillir dans le CRF**	
Événements pouvant être graves mais non liés aux médicaments expérimentaux (bortezomib, cyclophosphamide, methylprednisolone, thalidomide), ni au dispositif médical expérimental (membrane Theralite™), ni aux actes et procédures ajoutés par la recherche	**Effets Indésirables (EI) Non Graves ATTENDUS** Connus pour être liés aux médicaments expérimentaux, au dispositif médical expérimental ou aux actes et procédures de la recherche (Réf : CTCAE v4.0)	**Evénements Indésirables Graves (EIG) ATTENDUS** (Réf : CTCAE v4.0)	**Effets Indésirables Graves (EIG) INATTENDUS (SUSARs)**
• **Tout ce qui est en rapport avec l'évolution naturelle et habituelle de la pathologie** : - Insuffisance rénale sévère - Anurie - Syndrome d'hyperviscosité - Hypercalcémie - Hyperkaliémie - Autres signes traduisant l'évolution de la maladie - Hospitalisation programmée ou non pour suivi de la pathologie • Effets indésirables éventuellement graves mais bien connus, très fréquents et bien maîtrisés dont la déclaration n'apporterait rien à la sécurité des patients (à ne pas notifier sauf si aggravation) : Aplasie médullaire post-chimiothérapie de grade ≤ 3 sans complication. • **Tout effet indésirable grave susceptible d'être lié aux traitements prescrits dans le cadre du soin pendant le suivi de la recherche.** • **Tout autre évènement médical en dehors de la pathologie.**	**Liés au dispositif médical expérimental** (Membrane Théralite ™) - Fuite externe de sang - Fuite interne de sang dans le compartiment dialysat - Pénétration d'air dans le circuit du sang extra corporel n'entrainant pas d'embolie gazeuse - Coagulation à l'intérieur du dialyseur n'entraînant pas de thrombose **Liés aux gestes de mise en œuvre du dispositif médical** - Crampes musculaires - Sensations de brûlure, d'engourdissement et fourmillements - Infections locales n'entraînant pas de septicémie… - Fuite externe de sang - Pénétration d'air dans le circuit sang extracorporel n'entraînant pas d'embolie gazeuse **Liés à la dialyse** - Nausées, impression de « mal de mer » - Grade ≤ 2 : maux de tête, hypertension, hypotension	• **Affections cutanées** Nécrolyse épidermique toxique, syndrome Stevens-Jonhson • **Risque tératogène** **Liés au dispositif médical expérimental** (Membrane Théralite ™) - Pénétration d'air dans le circuit du sang extra corporel entrainant une embolie gazeuse - Coagulation à l'intérieur du dialyseur entrainant une thrombose **Liés aux gestes de mise en œuvre du dispositif médical** - Infections locales entraînant une septicémie, sepsis… - Pénétration d'air dans le circuit sang extracorporel entraînant une embolie gazeuse **Liés à la dialyse** - Réactions anaphylactiques (rash, collapsus …) - Grade ≥ 3 : maux de tête, hypertension, hypotension **Information ANSM du 06/03/2012** : - Réaction allergique aigue pendant une séance de dialyse	gravité noté ci-dessous, à l'exception de ceux recensés dans le protocole comme ne devant pas être notifiés : **1-** Décès **2-** Mise en jeu du pronostic vital **3-** Nécessite ou prolonge l'hospitalisation **4-** Séquelles durables **5-** Anomalie ou malformation congénitale **6-** Evénement jugé grave par l'investigateur (raison à préciser) **ATTENTION :** toute découverte d'une GROSSESSE au décours d'une recherche biomédicale doit être immédiatement déclarée au promoteur et fera l'objet d'un suivi jusqu'à l'accouchement.

APPENDIX 15: SCHEDULE OF ASSESSMENTS

	Inclusion	Randomisation	Cycle 1 (J21)	Cycle 2 (J21)	Cycle 3 (J21)	Cycle 4 (J21)	Cycle 5 (J21)	Cycle 6 (J21)	Bilan 6 mois	Bilan 1 an
Examen Clinique										
Pouls	x	x	x	x	x	x	x	x	x	x
Pression artérielle	x	x	x	x	x	x	x	x	x	x
Diurèse des 24 heures	x	x	x	x	x	x	x	x	x	x
Poids	x	x	x	x	x	x	x	x	x	x
Examens biologiques										
NFS, plaquettes	x	x	x	x	x	x	x	x	x	x
Créatininémie, urée, Uricémie	x	x	x	x	x	x	x	x	x	x
Ionogramme sanguin (Na, K, Cl, HCO3)	x	x	x	x	x	x	x	x	x	x
Calcémie, phosphorémie	x	x	x	x	x	x	x	x	x	x
Albuminémie, CRP	x	x	x	x	x	x	x	x	x	x
Bilan hépatique	x	x	x	x	x	x	x	x	x	x
Ionogramme urinaire (Na, K, Cl), urée, créatinine urinaires	x	X	x	x	x	x	x	x	x	x
Protéinurie des 24 heures	x	X	x	x	x	x	x	x	x	x
Bandelette urinaire (pH)	x	X	x	x	x	x	x	x	x	x
Electrophorèse des protides (EP) sériques	x	x	x	x	x	x	x	x	x	x
Dosage des chaînes légères libres sériques	x	x	x	x	x	x	x	x	x	x
Electrophorèse des protides (EP) urinaire	x		x	x	x	x	x	x	x	x
Immunofixation (IF) urinaire	x								x	x
β2 microglobuline	x									
LDH	x									
Immunoélectrophorèse (IEP) ou immunofixation (IF) sérique*	x								x	x
IEP ou IF urinaires	x								x	x
Sérologies (HIV, hépatite B et C, herpes-varicelle-zona)	x								x	x
Test de grossesse (betaHCG) pour les femmes en âges de procréer	x	x	x	x	x	x	x	x	x	x
Autres examens										
Myélogramme ou biopsie ostéo-médullaire	x								x	x
Radiographies du squelette **	x								X	X
Radiographie du poumon	x									
Ponction biopsie rénale ***	x									

* Serum should be stored for the entire duration of the study.
** skull, spine, upper and lower limbs, pelvis
*** Kidney biopsy is mandatory for patients randomized inthe hemodialysis part of the study

MODALITIES OF HEMODIALYSIS MONITORING

The usual clinical surveillance will be applied, according to local practice. The following biological parameters will be measured:

- Before each dialysis session: serum Na, K, Cl, HCO3, calcium, phosphate, total protein, serum albumin, full blood count

- After each dialysis session: same parameters, except for full blood count

- Before and after the first 3 dialysis sessions, then once weekly before and after hemodialysis: serum free light chains

The monitoring of parameters for dialysis efficiency, such as percentage of urea reduction, ionic dialysance, and KT/V is recommended, as appropriate.

APPENDIX 16: SEVERE ADVERSE EVENT REPORTING FORM

FORMULAIRE DE DECLARATION D'UN EVENEMENT INDESIRABLE GRAVE (EIG) SURVENANT AU COURS D'UNE RECHERCHE BIOMEDICALE SUR UN MEDICAMENT OU PRODUIT ASSIMILE EN HEMATOLOGIE

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

PARTIE RESERVEE AU PROMOTEUR : NE PAS REMPLIR
|__|__|-|__|__|- *DRCD* -|__|__|__|__|-|__|__|__|__|

Cette fiche doit être retournée dûment complétée (3 pages) au DRCD par fax : +33 (0)1 44 84 17 99
A l'attention de *Damien Vanhoye et de Marie Castera*

Date de notification : |__|__| |__|__| |__|__|__|__| (jj / mm / aaaa)

Code de la Recherche : P081226

N° EudraCT : EUD2009-017926-38 **Déclaration initiale** ☐ **Suivi d'EIG déclaré** ☐ **N° du suivi** |__|

Titre de la Recherche Biomédicale :

Traitement de la néphropathie à cylindres myelomateux - Etude MYRE

1) Nom et adresse du centre : _____

Centre n° : |__|__|__| Investigateur (Qualité - Nom - Prénom) : _____

2) Identification du patient :

Identifiant patient : |__|__|__| |__|__|__|__| |__||__|
(site + n° inclusion + initiales)

Sexe : Masculin ☐ Féminin ☐

Date de naissance : |__|__| |__|__| |__|__|__|__|

Poids : |__|__|__| kg

Taille : |__|__|__| m

Date d'inclusion : |__|__| |__|__| |__|__|__|__|

Date de randomisation |__|__| |__|__| |__|__|__|__|

3) Evénement indésirable grave :

Décès ☐

Nécessite ou prolonge l'hospitalisation : ☐
Du |__|__| |__|__| |__|__| *au* |__|__| |__|__| |__|__| ☐ *en cours*

Incapacité ou invalidité ☐

Anomalie congénitale ☐

Autre(s) critère(s) médicalement significatif(s) (préciser) : ☐
_____
_____
_____

Arrêt prématuré des traitements : oui ☐ non ☐

Date d'arrêt : |__|__| |__|__| |__|__|__|__|

Cause :
_____
_____

4) Stratégie thérapeutique

A l'inclusion :

Pas d'épuration extra-rénale ☐

Epuration extra-rénale ☐

Bras de randomisation :

BD ☐ C-BD ☐

HCO ☐ Classique ☐

Changement de stratégie oui ☐ non ☐

Seconde randomisation oui ☐ non ☐

Si oui, préciser la date : |__|__| |__|__| |__|__|__|__|

HCO ☐ Classique ☐

Antécédents (allergie, insuffisance rénale …) : _____
_____
_____

Identification du patient : |__|__|__| |__|__|__|__| |__||__| **Centre n° :** |__|__|__| **Code de la Recherche : P081226 -MYRE**

5) Description complète de l'événement indésirable (diagnostic retenu, localisation anatomique, critères permettant de considérer l'événement comme grave) :

Période d'apparition de l'événement	Date de début	Date de fin	En cours
Cure N° |__|__|	|__|__| |__|__| |__|__|	|__|__| |__|__| |__|__|	☐

Descriptif détaillé de l'événement indésirable grave	Grade 1)	Date et Heure de début	Evolution 2) et Date et heure de fin
	|__|	|__|__| |__|__| |__|__| jj mm aa |__|__| |__|__| hh min	|__| évolution |__|__| |__|__| |__|__| jj mm aa |__|__| |__|__| hh min Mesures symptomatiques prises : non ☐ oui ☐ *Si oui, (préciser)* ____________ ____________
	|__|	|__|__| |__|__| |__|__| jj mm aa |__|__| |__|__| hh min	|__| évolution |__|__| |__|__| |__|__| jj mm aa |__|__| |__|__| hh min Mesures symptomatiques prises : non ☐ oui ☐ *Si oui, (préciser)* ____________ ____________
	|__|	|__|__| |__|__| |__|__| jj mm aa |__|__| |__|__| hh min	|__| évolution |__|__| |__|__| |__|__| jj mm aa |__|__| |__|__| hh min Mesures symptomatiques prises : non ☐ oui ☐ *Si oui, (préciser)* ____________ ____________
	|__|	|__|__| |__|__| |__|__| jj mm aa |__|__| |__|__| hh min	|__| évolution |__|__| |__|__| |__|__| jj mm aa |__|__| |__|__| hh min Mesures symptomatiques prises : non ☐ oui ☐ *Si oui, (préciser)* ____________ ____________

1) Grade de toxicité/sévérité :	*2) Evolution :*
1 = léger 2 = modéré 3 = sévère 4 = mise en jeu du pronostic vital 5 = décès lié à l'effet indésirable Selon la classification du NCI (CTAE version 3.0)	1 = guérison sans séquelle 2 = guérison avec séquelle 3 = aggravation de la sévérité/grade de la toxicité 4= amélioration de la sévérité/grade de la toxicité 5= en cours, sans traitement 6 = en cours, avec traitement 7= décès dû à l'effet indésirable 8 = décès sans rapport avec l'effet indésirable

Commentaires : si possible joindre une copie du compte rendu d'hospitalisation ou tout résultat pertinent de tests diagnostics

____
____
____

6) Médicament(s) expérimental (aux) administré(s) avant la survenue de l'événement indésirable :

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie	Dose/24h	Date de début	En cours	Date de fin	Indication	Causalité * (1,2,3 ou 4)
			|__|__| |__|__| |__|__|	☐	|__|__| |__|__| |__|__|		
			|__|__| |__|__| |__|__|	☐	|__|__| |__|__| |__|__|		
			|__|__| |__|__| |__|__|	☐	|__|__| |__|__| |__|__|		
			|__|__| |__|__| |__|__|	☐	|__|__| |__|__| |__|__|		

** 1 = Probable 2 = Possible 3 = Non liée 4 = Inconnue*

7) Médicament(s) concomitant(s) à l'exclusion de ceux utilisés pour traiter l'événement indésirable :

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie	Dose/24h	Date de début	En cours	Date de fin	Indication	Causalité * 1,2,3 ou 4)
			|__|__| |__|__| |__|__|	☐	|__|__| |__|__| |__|__|		
			|__|__| |__|__| |__|__|	☐	|__|__| |__|__| |__|__|		
			|__|__| |__|__| |__|__|	☐	|__|__| |__|__| |__|__|		
			|__|__| |__|__| |__|__|	☐	|__|__| |__|__| |__|__|		

** 1 = Probable 2 = Possible 3 = Non liée 4 = Inconnue*

8) Description du dispositif médical (DM) impliqué, le cas échéant :

Nature	Modèle /type/référence	N° de série ou de lot	Nom du fournisseur	Nom du fabricant	**Si DM stérile :** Date de stérilisation et Date de péremption	Causalité * 1,2,3 ou 4)
					|__|__| |__|__| |__|__| et |__|__| |__|__| |__|__|	

** 1 = Probable 2 = Possible 3 = Non liée 4 = Inconnue*

Si accessoire, consommable :

Désignation	Modèle	N° de série ou de lot	Nom du fabricant	Date de péremption
				|__|__| |__|__| |__|__|

9) Autre(s) étiologie(s) envisagée(s) : non ☐ oui ☐ *Si oui, préciser :*

_____

_____

_____

10) Examen(s) complémentaire(s) réalisé(s) : non ☐ oui ☐ *Si oui, préciser date, nature et résultats :*

_____

_____

_____

11) Traitements de la Recherche Biomédicale :

Ré-administration du (des) médicament(s) : non ☐ oui ☐ non applicable ☐ date : |__|__| |__|__| |__|__|__|__|

Si oui, le(s) quel(s) : _____

Récidive après ré-administration : non ☐ oui ☐ non applicable ☐ date : |__|__| |__|__| |__|__|__|__|

12) Selon l'investigateur, l'événement indésirable grave semble plutôt lié :

☐ au(x) médicament(s) de la recherche : le(s)quel(s) : _____ ☐ à une maladie intercurrente

☐ au(x) médicament(s) concomitant(s) : le(s)quel(s) : _____ ☐ à la progression de la maladie

☐ aux procédures de la recherche biomédicale ☐ au dispositif médical de la recherche

☐ autre : _____

Date : |__|__| |__|__| |__|__| **Tampon du service :** **Nom de l'Investigateur:** _____
Signature :

Nom et fonction du Notificateur: _____ **Téléphone** _____ **Signature :**

PARTIE RESERVEE AU PROMOTEUR : NE PAS REMPLIR
Numéro d'identification de l'événement : **EV |__|__|__|**

Date de réception par le promoteur : |__|__| |__|__| |__|__|__|__|

Date de ce rapport : |__|__| |__|__| |__|__|__|__| ☐ initial ☐ suivi n° |__|__|

Selon le promoteur, l'événement indésirable semble plutôt lié :

☐ au(x) médicament(s) de la recherche : le(s)quel(s) : _____ ☐ à une maladie intercurrente

☐ au(x) médicament(s) concomitant(s) : le(s)quel(s) : _____ ☐ à la progression de la maladie

☐ aux procédures de la recherche biomédicale ☐ au dispositif médical de la recherche

☐ autre : _____

Si selon le promoteur, l'événement semble plutôt lié au médicament ou au dispositif médical de la recherche

☐ L'événement indésirable grave est attendu ☐ L'événement indésirable grave est inattendu

Commentaires du promoteur :

_____

_____

_____

_____

Nom et qualité du représentant du promoteur : **Signature :**