Sponsor: Spanish Oncology Genito-Urinary Group

CLINICAL TRIAL
NO. SOGUG2011/02

Confidential

Sponsor:
Spanish Oncology Genito-Urinary Group
Conde Aranda, 20
28001 Madrid

Study product: vinflunine

Clinical trial protocol

A randomized phase II study of vinflunine in monotherapy as maintenance therapy in patients with advanced or metastatic urothelial (transitional cell) cancer who obtain clinical benefit with first-line cisplatin + gemcitabine

Study code: SOGUG2011/02

EudraCT Number: 2011-001271-39

Coordinating investigators:

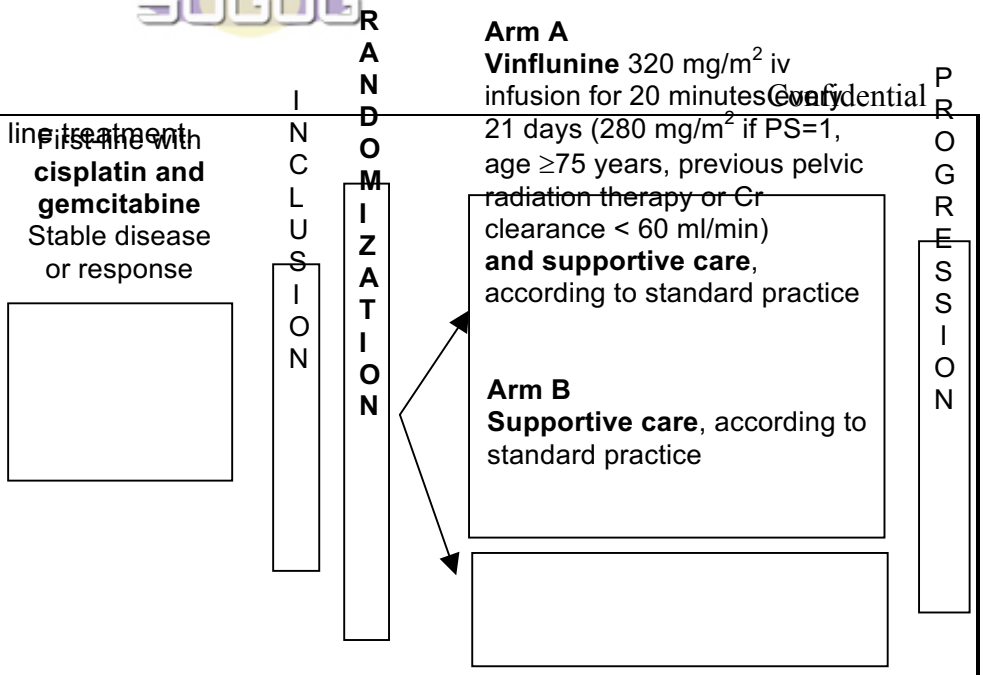
- **Coordinator #1: Jesús García-Donas**
- **Coordinator #2: Albert Font**
- **Coordinator #3: Joaquim Bellmunt**

Version number 5 **12/11/2015**

STUDY SYNOPSIS

SPONSOR NAME:	Spanish Oncology Genito-Urinary Group (SOGUG)	
NAME OF FINISHED PRODUCT:	JAVLOR®	
NAME OF ACTIVE INGREDIENT (DCI):	Vinflunine ditartrate	
Study Title	**A randomized phase II study of vinflunine in monotherapy as maintenance therapy in patients with advanced or metastatic urothelial (transitional cell) cancer who obtain clinical benefit with first-line cisplatin + gemcitabine** **Short title: MAJA study** (**MA**intenance with **JA**vlor) Study code: SOGUG2011/02 EudraCT: 2011-001271-39	
Investigators coordinators	1. Dr. Jesús García-Donas 2. Dr. Albert Font 3. Dr. Joaquim Bellmunt	
Study sites	21 hospitals in Spain	
Study period	Start date: 2 April 2012 Date of completion of recruitment: December 2014 or until the inclusion of the last patient needed to reach the sample size of 86 patients.	**Clinical phase:** Randomized phase II
Justification	Advanced or metastatic urothelial (transitional cell) cancer (UC) is currently incurable. This disease represents a considerable health problem, with an incidence of 71,000 cases/year (all stages) in the United States, yet advances in treatment in recent years have been very limited. Indeed, there have been no significant advances in first-line treatment since 2000, when the combination of cisplatin and gemcitabine was adopted as the standard treatment, after it demonstrated similar efficacy but less toxicity than the MVAC (methotrexate, vinblastin, adriamycin and cisplatin) regimen (Von der Maase 2000). Two strategies have been employed in the attempt to improve outcomes in this disease. - One approach has been to reduce the toxicity of the regimen by replacing cisplatin with a better tolerated analogue, carboplatin, or a non-platinum-based product, paclitaxel. However substitution with either of the agents appears to reduce the proportion of objective responses (Dogluiotti 2007 and Calabro Cancer 2009), so they are only used in patients with comorbidities or contraindications for the use of cisplatin. - The other approach has been to try to improve the efficacy of the cisplatin-gemcitabine doublet with the addition of a third drug, generally paclitaxel. Paclitaxel is an antimicrotubule agent which has shown activity in monotherapy both in first line (Roth JCO 1994) and second line UC (Vaughn et al JCO 2002). However, while the 3-drug combination appears to improve the percentage of responses, toxicity is greater and no improvement in overall survival is obtained, so this approach is still not considered standard. New strategies, then, must be developed, if advances are to be made in the first line treatment of this tumor. One option would be the early inclusion of low-toxicity antimicrotubule agents, given their proven efficacy in UC. If maintenance therapies can be developed using drugs without	

	accumulative toxicity, progression-free survival may be extended, while improving quality of life, disease control, and, secondarily, overall survival. Vinflunine is a drug with antimicrotubule activity that was recently approved by the EMA for the treatment of advanced or metastatic UC after failure to a prior platinum based chemotherapy. In the pivotal phase III study, it showed an improved survival compared to supportive care. The toxicity profile was also favorable, particularly as it does not induce the appearance of neutropenia or other cumulative toxic effects. We therefore aim to study the viability, in terms of tolerability and efficacy, of single-agent treatment with vinflunine in patients who, after completing their first-line cisplatin-based treatment for UC, have achieved stable disease or objective response. In order to generate an appropriate control group, the proposed design consists of a randomized phase II study in which one of the groups will receive standard treatment (follow-up until disease progression). The results obtained in this study will be used as the basis for a possible phase III trial in the same setting.
Objectives	**Primary objective:** • To evaluate progression-free survival (PFS) with vinflunine in monotherapy in the maintenance of patients with advance urothelial (transitional cell) cancer who have achieved stable disease or objective response after completing a minimum of 4 cycles of combined first-line cisplatin + gemcitabine. **Secondary objectives:** • To evaluate the objective response rate (ORR) and the disease control rate (DCR) (defined according to RECIST evaluation criteria, version 1.1), median duration of response (MDR), median duration of disease control (MDDC), time to response (TTR), and overall survival (OS) in patients receiving vinflunine plus the best supportive care. • To compare overall survival of patients randomized to receive treatment in Arm A (vinflunine), compared to that of patients randomized to Arm B (best supportive care). • To compare progression-free survival of patients randomized to receive treatment in Arm A, compared to that of patients randomized to Arm B. • To compare objective response rates between the 2 treatment arms. • To compare duration of response and disease control between the 2 treatment arms. • To compare time to response rates between the 2 treatment arms. • To evaluate the safety, toxicity, and tolerability of vinflunine maintenance treatment. • To compare safety, toxicity and tolerability between the 2 treatment arms. • To perform a pharmacogenomic analysis.
Study design	**Phase II, randomized, open-label study in 2 arms** First-line treatment with gemcitabine + cisplatin does not form part of the clinical trial. Randomization and inclusion of the patient in the trial will only occur after completion of at least 4 cycles and up to 6 cycles of gemcitabine + cisplatin (cisplatin may be switched to carboplatin in cycles 5 and/or 6), and confirmation of stable disease or response after this first-



Randomization will be stratified by (minimization procedure):

- Initial planned dose of vinflunine (320 versus 280 mg/m^2)
- Liver metastasis (yes versus no).
- Cisplatin-gemcitabine cycles (4 cycles versus 5 or 6 cycles)

At the start of the study, full cancer and non-cancer medical history will be collected and a full physical examination will be performed, including vital signs, weight, blood pressure, body surface area, and performance status. Baseline serum biochemistry parameters and a complete blood count (CBC) will be obtained before randomization and before all administrations of the cytotoxic agent.
Patients who discontinue chemotherapy with no signs of progressive disease (PD) will continue in follow-up until progression. All patients will be followed up periodically until death or study completion.

Patient numbers	39 evaluable patients in each study arm, for a total of 78 patients: it is calculated that 86 patients will be included (allowing for 10% unevaluable patients).
Eligibility criteria	**Inclusion criteria:** 1. Men and women aged ≥ 18 years and < 80 years. 2. Written informed consent signed before performing any study-related procedure. 3. Histological confirmation of unresectable locally advanced or metastatic urothelial (transitional cell) cancer (bladder, kidney, renal pelvis, urethra or ureter). 4. At least 1 measurable or evaluable target lesion at baseline before starting treatment with cisplatin and gemcitabine (RECIST criteria, version 1.1). If the only tumor site is bone metastases, with no measurable soft tissue involvement, patients will be considered eligible if no new bone lesions are detected after completion of first-line treatment. 5. ECOG performance status 0 or 1. 6. Life expectancy of at least 12 weeks. 7. Patient who, after completing first-line treatment with a minimum of 4 cycles and a maximum of 6 cycles with a standard* cisplatin and gemcitabine combination (cisplatin may be switched to carboplatin

* Cisplatin administered every 21 days, or every 28 days in line with NCCN guidelines, version 2.2012 will be considered standard.

	in cycles 5 and 6, at the criteria of the investigator), have achieved documented stable disease or objective response according to RECIST criteria, version 1.1. 8. Patients may have received cisplatin in monotherapy or in combination in a neoadjuvant or adjuvant setting after initial surgery for urothelial cancer, provided at least 6 months have elapsed between the last dose of (neo)adjuvant chemotherapy and the first dose of chemotherapy for advanced or metastatic disease. 9. Last administration of cisplatin (or carboplatin) and gemcitabine (last day of administration of both drugs) ≤6 weeks before inclusion. 10. Recovery from any toxicity derived from previous treatment to grade I or less according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0. 11. Appropriate bone marrow, kidney and liver function, confirmed by: - Absolute neutrophil count ≥ 1,500/mm^3 (≥ 1.5 x 10^9/l) - Hemoglobin ≥ 10 g/dl - Platelet count ≥100,000/mm^3 - Total bilirubin in serum ≤ 1.5 x upper limit of normal (ULN†) - AST and ALT ≤ 2.5 x ULN [≤ 5 times ULN only in the case of liver metastasis] - Alkaline phosphatase ≤ 5 x ULSN - Calculated creatinine clearance ≥ 40 ml/min (Cockcroft-Gault formula). 12. Absence of psychological disease, or family, sociological or geographical circumstances that might interfere with compliance with the study protocol and follow-up timing; these aspects will be evaluated with the patient before study inclusion. 13. Sexually active women of childbearing potential must use a medically acceptable contraceptive method (which includes sexual abstinence) to avoid pregnancy during the 2 months before starting study treatment, during the study period, and for 3 months after the last dose of study treatment, to minimize the risk of pregnancy; women of childbearing potential must have a negative pregnancy test in serum or urine within 72 hours before starting treatment. 14. Sexually active men must use an effective contraceptive method (which includes sexual abstinence) during the study and for a period of 6 months after the last dose of study treatment, if their partner is a woman of childbearing potential.
Eligibility criteria (continued)	**Exclusion criteria:** 1. ECOG performance status ≥ 2. 2. Patients ≥ 80 years. 3. Patients with a histological evidence of small cell carcinoma, lymphoma or bladder sarcoma. 4. Patients who have received 7 or more cycles of a combination of cisplatin and gemcitabine as first-line treatment for metastatic disease, or who have received this combination on a fortnightly schedule. 5. Women who are pregnant or breast-feeding or who have a positive pregnancy test at admission; sexually active women of

† ULN = upper limit of normal

	childbearing potential who were not using or who do not want to use or who are incapable of using an acceptable contraceptive method during the 2 months before starting study treatment, during the study period, and for 3 months after the last dose of study treatment; 6. Sexually active men who do not want to use a contraceptive method during the study and for a period of 6 months after the last dose of study treatment, if their partner is a woman of childbearing potential. 7. Documented brain metastases or meningeal involvement. Computed tomography (CT) scans are not required to rule this out unless central nervous system (CNS) involvement is clinically suspected. 8. Peripheral neuropathy grade ≥ 2 according to the NCI CTC version 4.0. 9. Previous radiation therapy to ≥ 30% of the bone marrow or completed < 30 days or failure to recover fully from toxic effects. 10. Other serious diseases or medical disorders such as: - Infection requiring systemic anti-infectious treatment (NCI CTC version 4.03 grades 3 or 4). - Any uncontrolled medical disorder, e.g., patients with unstable angina or myocardial infarction within 6 months before inclusion in the study or uncontrolled diabetes. 11. Progressive disease during first-line treatment of advanced or metastatic disease with systemic chemotherapy with cisplatin and gemcitabine. 12. Patients who have received more than one line of treatment for metastatic disease. 13. Patient treated with another investigational drug or anticancer treatment other than cisplatin or gemcitabine within 30 days before randomization. 14. Other invasive cancers, with the exception of successfully treated basal cell skin cancer, in situ cervical cancer, or any other tumor with a disease-free interval of ≥ 3 years. 15. Insufficient kidney function defined as calculated creatinine clearance in serum < 40 ml/min (Cockcroft-Gault formula). 16. Known hypersensitivity to the study drug or drugs of a similar chemical structure. 17. Patients needing treatment with ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, rifampicin or phenytoin (any potent CYP3A4 inhibitor or inducer). 18. Any concurrent chronic immunotherapy or previous organ allograft.
Study product, dose and method of administration	The dose of study drug and criteria for dose adjustments are those specified in the Javlor® Summary of Product Characteristics. **One cycle is defined as a 3-week treatment period.** **Treatment group (Arm A): vinflunine** will be administered on day 1, every 21 days in a 20-minute intravenous infusion**, with 2 dose options based on performance status, radiation therapy history, age or presence of renal failure:** **- Patients with PS 0, no previous pelvic radiation therapy, age < 75 years and creatinine clearance ≥ 60 ml/min: 320 mg/m^2**; treatment will continue at this dose in the absence of significant toxicity*, In case of significant hematological or non-hematological toxicity, the dose will be reduced to 280 mg/m^2 in the first episode and to 250 mg/m^2

	in the second, if applicable. **- Patients with PS 1, previous pelvic radiation therapy, age ≥ 75 years and < 80 years or moderate renal failure (40 ml/min ≤ creatinine clearance < 60 ml/min): 280 mg/m^2**; treatment will continue at this dose in the absence of significant toxicity (in case of significant hematological or non-hematological toxicity, the dose will be reduced to 250 mg/m^2). **Observational group (Arm B):** this group will continue regular monitoring, according to the standard hospital protocol, with evaluation every 9 weeks (RECIST criteria, version 1.1). At the time of progression, the patient will withdraw from the study but periodical follow-up will be performed to determine overall survival. **Dose reductions and administration delays:** - No dose increase is permitted after a dose reduction. - Two dose reduction steps are possible (280 mg/m^2 and 250 mg/m^2) for patients who begin by receiving a dose of 320 mg/m^2, and a single dose reduction for those who begin at 280 mg/m^2. - For a patient receiving a dose of 250 mg/m^2 who needs another dose reduction, treatment will be discontinued and the patient will be withdrawn from the study. - During the baseline period, no treatment may be administered if ANC < 1,500/m^3 or platelet count < 100,000/mm^3. After starting treatment, for subsequent cycles, the drug should not be administered on D1 if ANC < 1,500/mm^3 or platelet count < 75,000/mm^3 and dosing will be delayed until recovery; in case of grade ≥ 2 organ toxicity other than asthenia, treatment must be delayed until recovery to grade ≤ 1 or initial status. If recovery does not occur within 2 weeks, treatment must be discontinued. **Hematological toxicities requiring the use of filgastrim as secondary prophylaxis:** - Neutropenia grade 4 > 7 days - Febrile neutropenia ***Significant hematological toxicities requiring dose reduction:** - Neutropenia grade 2 > 7 days that cannot be treated with filgastrim. - Febrile neutropenia that cannot be treated with filgastrim. - Thrombocytopenia grade 3 (platelets ≥ 25 x 10^9/l and < 50 x 10^9/l) with bleeding - Thrombocytopenia grade 4 (platelets < 25 x 10^9/l). **Significant non-hematological toxicities requiring dose reduction:** - Mucositis or constipation grade 2 ≥ 5 days or grade ≥ 3 of any duration. - Any other toxicity grade ≥ 3 associated with the study drug, except grade 3 vomiting, nausea, or asthenia inappropriately treated or no previous medication. **Dose adjustments in case of renal failure are specified in section 5.5.3.3.**
Treatment duration	Patients included in Arm A (treatment) will receive at least 1 cycle and will continue on treatment until documented progressive disease, inacceptable toxicity, patient refusal or investigator's decision.
Concomitant treatment	**Concomitant administration of laxatives is recommended, and appropriate dietetic measures** for the study treatment should be

	introduced, starting on the first day of vinflunine administration (day 1) until day 5: **A/ Laxatives*:** o Mainly fecal softeners: lactulose, polyethylene glycol, docusate sodium, milk of magnesia, or mineral oil (paraffin). o Or mainly stimulants: senna derivatives or bisacodyl. *Laxative doses will be determined by the investigator. **B/ Dietetic measures, sufficient fluid and fiber intake in the diet:** o Oral hydration: at least 1.5 liters of water a day. o Pharmaceutical fiber supplements. **Standard anti-emetic prophylaxis** is recommended, starting in the first cycle before each treatment administration, with a single oral dose of 8 mg dexamethasone or the equivalent dose of methylprednisolone just before the infusion. Prophylactic measures may be adapted according to standard hospital practice. **Hematopoietic growth factors:** the **primary** prophylactic use of colony stimulating factors is not permitted, but **secondary** prophylaxis is permitted in subsequent cycles for patients who experience febrile neutropenia, asymptomatic neutropenia grade 4, for more than 7 days or neutropenic infection. If the investigator suspects a risk of significant neutropenia in the first cycle already, for example, in patients who required G-CSF support during their previous treatment with cisplatin and gemcitabine, complete blood count should be monitored according to standard hospital practice and recommendations on the prophylactic use of factors in this protocol should be applied. Prophylactic antibiotic treatment may be administered according to standard hospital practice. The use of all other investigational drugs, anticancer drugs, any other medications that are contraindicated or that should not be administered concomitantly with the study drug is prohibited throughout the study.

Evaluation criteria - Efficacy evaluation	• Efficacy variables: - Efficacy will be determined according to RECIST criteria (version 1.1) as follows: lesion assessment (measurable and non-measurable) at baseline and every 9 weeks. - Investigators will evaluate progression and tumor response in all randomized patients. - Response and disease control rates and their duration will be evaluated in all patients who respond and who show disease control, respectively. - Progression-free survival will be evaluated with assessments every 9 weeks, and subsequently, overall survival will be evaluated every 3 months.
- Safety evaluation	• Safety variables: physical examination and vital signs, performance status, complete blood count, serum biochemistry, clinical safety, adverse events using the NCI CTC (version 4.0).
- Pharmacogenomic evaluation	• Pharmacogenomic study: each patient will have 2 blood draws (patients included in both treatment groups), one on the day of randomization and another at the time of tumor progression. If possible, paraffin-embedded tumor tissue samples obtained from the transurethral resection, the cystectomy resection, or from a biopsy of a metastatic lesion will be collected. Genetic markers related with DNA repair pathways and antimicrotubule agent activity will be determined. Markers to be analyzed will be BRCA1, RAP80 and AEG-1 (astrocyte elevated gene-1) expression and DAB2IP (DOC-2/DAB2 interactive protein) methylation, for example.
Statistical methods	This study is designed to evaluate median progression-free survival. In the vinflunine (Javlor®) phase III registrational study, the subgroup which presented stable disease or response after first-line treatment with gemcitabine-cisplatin (n = 115) was analyzed. On the basis of data from this subgroup, the expected PFS on maintenance treatment is 4.7 months. The sample size was calculated on the basis of the following clinical suppositions: we consider a median PFS in the experimental arm of 4 months (p0) to be inacceptable and a PFS of 6.5 to be quite acceptable (p1). With a 12-month recruitment period and minimum follow-up of 12 months, and a type I error of 0.05 (α, single-tailed test), and with a type II error of 0.1 (β), the required sample size was 39 evaluable patients per arm. This figure will be increased by 10% to cover possible loss of evaluable patients. The final number will be 43 patients per arm. A total of 86 patients will need to be included. Statistical analysis of the primary objective: to evaluate the efficacy of the experimental treatment, after a minimum follow-up of 12 months after the end of recruitment, the study hypothesis will be considered positive if the median PFS is greater than 5.29 months and negative otherwise. To be included in the evaluable population for the evaluation of efficacy, patients must be eligible, evaluable and treated in the arm to which they were randomized. All baseline lesions must have been evaluated at least once since cycle 3 (9 weeks), with the same measuring techniques as used in the baseline period, in accordance with standard hospital practice. For cases with suspected progressive disease or if considered clinically indicated, disease evaluation may be performed before the specified 9 weeks, in accordance with standard hospital practice. Patients included in the observation arm will be followed up with radiological examinations every 9 weeks, in accordance with standard

	hospital practice. Overall responses will also be expressed with their corresponding confidence intervals. Progression-free survival, duration of response, duration of disease control, time to response and overall survival will be analyzed using the Kaplan-Meier method. Safety analyses will be performed in all patients treated. NCI-CTC version 4.0 will be used to classify toxicities. Analyses of the maximum grades will be performed by cycle and by patient. **Interim safety analysis:** An interim safety analysis will be performed when the first 12 patients in the experimental arm have received at least 2 treatment cycles, unless progressive disease, unacceptable toxicity or refusal by the patient is documented. The calculation of the sample size for this objective is not based on any statistical test, since it is a purely descriptive evaluation of safety that will be used to confirm that the experimental treatment is safe enough to continue treating patients. Data will be analyzed using descriptive tables by patient and by cycle, according to treatment arm. For comparisons of these qualitative variables, we will use the Chi-squared test or Fisher's exact test, as appropriate. Comparisons will be made using a two-tailed test with a level of significance of 5%.
Follow-up	The follow-up period is the time between 30 days after the last administration of study treatment and death in cases included in Arm A. In Arm B (observation), follow-up will be the time between inclusion in the trial and death. In both cases, survival data will be collected every 9 weeks approximately until progressive disease and then every 3 months until death or decision to conclude the study.

Table 1: Study schedule

Evaluations required		Screening period	Treatment period Scheduled cycle = 21 days		End of study	Follow-up	
Schedule		**D–28 to D–1**	**D1 of each cycle**	**Every 9 weeks**	**D30 after last infusion**	**Every 9 weeks ≤PD**	**Every 3 months > PD**
Signed informed consent (before any specific study procedure)		**X**					
Demographic data/history		X					
Tumor history		X					
Documentation of histological diagnostic		X					
Pregnancy test in serum or urine		X[1]					
Calculated creatinine clearance		X[2,5]	X[5]				
Physical examination: weight/body surface/BP/ Vital signs/ECOG performance status		X[2]	X		X	X	
Eligibility/randomization		**X**					
Treatment							
ARM A	Vinflunine		X				
ARM B	Observation						
Safety							
ECG (if indicated)		X					
Hematology (complete blood count)		X[2,5]	X[5]		X[7]		
Biochemistry with calculated CrCl		X[2,5]	X[5]		X[7]		
Concomitant medications		X	X		X[7]	X[6]	X[6]
Signs and symptoms/adverse events		X	X		X[7]	X[12]	X[12]
Efficacy[8]							
CT or MRI (chest, abdomen, pelvis, brain, if indicated)[9]		x		x		x[11]	
Clinical tumor evaluation		X		X	x	x[11]	
Bone scintigraphy[9,10]		x		x[10]		x[10]	
Standard Rx, CT or MRI of sites with hyper-uptake on scintigraphy in which malignancy is suspected[9,4]		x				x[4,11]	
Survival data						x[3]	x[3]
Other imaging techniques[9]		x		x	x	x[4,11]	
Pharmacogenomics							
Peripheral blood sample		x[13]				x[15]	
Paraffin-embedded tissue sample		x[14]					

[1]72 hours before inclusion, if applicable
[2]Within up to 7 days before the first administration of study drug; body surface area need only be calculated at study start, and then only if required.
[3]Every 9 weeks until progressive disease (PD) (± 7 days) and then every 3 months (± 15 days) after progression until death or study completion
[4]If necessary, according to standard clinical practice, bone radiographs or CTs (bone window) or MRI will be performed of the most significant sites of bone lesions observed on bone scintigraphy and at symptomatic sites.
[5]Blood samples must be collected within 24 hours before the administration of each dose of study drug, and up to 48 hours maximum for biochemistry analyses, except for the baseline determination of biochemistry, which may be performed up to 7 days before (creatinine clearance must be recorded in the randomization form for determination of the initial dose).
[6]Main treatment regimens, anticancer drugs if applicable.
[7]Within 30 days following the last administration of study drug
[8]The most appropriate test for studying and monitoring tumor sites (CT or MRI) as determined by the investigator, according to standard hospital practice.
[9]The same evaluation techniques as used during screening must be used throughout the study to ensure comparability. Baseline evaluations performed within 28 days before randomization are acceptable.
[10]Baseline bone scintigraphy is needed only in patients with confirmed or suspected bone metastases. Repeat in the following cases:
• In patients with bone lesions at the start of the study: to document overall complete response
• In all patients: if progression of bone lesions is suspected due to bone-related episodes, such as increase in pain intensity or use of analgesics or alkaline phosphatase or calcium levels; or new pathological pain symptoms requiring palliative treatment or spinal cord compression or pathological bone fracture
[11]Every 9 weeks until progressive disease (PD) (± 7 days)
[12]Only if related with study treatment
[13]On the day of randomization
[14]If available
[15]At the time progressive disease is determined or end of study
Note: Creatinine clearance will be calculated using the Cockcroft-Gault formula.