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## Progress report

# **SOCRATE-PRODIGE 55 trial: a randomized phase II study to evaluate second-line ramucirumab alone or with paclitaxel in older patients with advanced gastric cancer**

Emeric Boisteau (1), Eric François (2), Thomas Aparicio (3), Karine Le Malicot (4), Rabia Boulahssass (5), Thierry Lecomte (6,7), Pierre Laurent-Puig (8), Boris Guiu (9), Elena Paillaud (10), Marie-Pierre Galais (11), Daniel Lopez-Trabada Ataz (12), David Tougeron (13), Louis-Marie Dourthe (14), Rosine Guimbaud (15), Emmanuelle Samalin (16), Marie Moreau (17), Christophe Louvet (18), Côme Lepage (19), Astrid Lièvre (1)

<sup>1</sup> Service des Maladies de l'Appareil Digestif, CHU Pontchaillou; Université de Rennes 1, INSERM U1242, Rennes, France

<sup>2</sup> Service d'Oncologie, Centre Antoine Lacassagne, Nice, France

<sup>3</sup> Service de Gastroentérologie, Hôpital Saint Louis, APHP, Université de Paris, Paris, France

<sup>4</sup> FFCD EPICAD INSERM LNC-UMR 1231, Université de Bourgogne Franche-Comté  
Dijon, France

<sup>5</sup> Service de Gériatrie, CHU de Nice, Nice, France

<sup>6</sup> Service d'Hépatogastroentérologie, CHU de Tours, Tours, France

<sup>7</sup> Inserm UMR 1069, "Nutrition, Croissance et Cancer", Université de Tours

<sup>8</sup> INSERM U 775 - Faculté des Sciences Fondamentales et Biomédicales, Centre Universitaire des Saints-Pères, Université des Saints Pères, Paris Descartes, Paris, France

<sup>9</sup> Département de Radiologie, CHU St-Eloi, Montpellier, France

<sup>10</sup> APHP, Paris Cancer Institute CARPEM, Hôpital Européen Georges Pompidou, Service de Gériatrie, Paris 75015, France

<sup>11</sup> Département d'Oncologie Médiale, Centre François Baclesse, Caen, France

<sup>12</sup> Département d'Oncologie Médiale, Hôpital Saint-Antoine, Paris, France

<sup>13</sup> Service d'Hépatogastroentérologie, CHU de Poitiers, La Milétrie, et l'Université de Poitiers, Poitiers, France

<sup>14</sup> Service d'Oncologie Médicale, Clinique St Anne, Strasbourg, France

<sup>15</sup> Département d'Oncologie Médicale, Pôle Digestif, CHU Toulouse, Toulouse, France

<sup>16</sup> Département d'Oncologie Médicale, Institut du Cancer de Montpellier, Université de Montpellier, Montpellier, France

<sup>17</sup> Fédération Francophone de Cancérologie Digestive (FFCD), Dijon, France

<sup>18</sup> Service d'Oncologie Médicale, Institut Mutualiste Montsouris, Paris, France

<sup>19</sup> Service d'Hépatogastroentérologie, CHU de Dijon, Dijon, France

**Corresponding author:**

**Pr. Astrid Lièvre**

**Service des Maladies de l'Appareil Digestif, Hôpital Pontchaillou, CHU de Rennes  
35033 RENNES Cedex 9**

**Tel: +33 299 289 972**

**E-mail: astrid.lievre@chu-rennes.fr**

## **Abstract**

**Introduction:** Patients  $\geq 70$  years old constitute 40% of patients with advanced gastric cancer (GC). Ramucirumab plus Paclitaxel is a therapeutic option validated in the second-line treatment of advanced GC, but as older patients are at higher risk of severe toxicity, due to comorbidities and/or frailty, we aimed to evaluate second-line Ramucirumab alone or combined with Paclitaxel in terms of overall survival (OS) and quality of life (QoL) in patients  $\geq 70$  years-old with advanced GC.

**Methods:** In this multicenter, randomized, open-label, non-comparative, prospective phase II clinical trial, the main inclusion criteria are: patients  $\geq 70$  years old, with advanced GC having progressed after first-line chemotherapy or in the six months following the last administration of adjuvant chemotherapy, with WHO performance status  $<2$ . They are randomized to receive either Ramucirumab alone (arm A) or Ramucirumab plus Paclitaxel (arm B). The primary endpoint is 6-month OS and QoL evaluated with the EORTC QLQ-ELD14 questionnaire. The secondary endpoints include other parameters of QoL, time to definitive deterioration (TTDD) in QoL and TTDD in autonomy, treatment toxicities, other parameters of survival and disease control, identification of geriatric and nutritional prognostic scores and predictive factors of treatment safety and efficacy. OS of 60% is expected at 6 months ( $H_0:40\%$ ). Using a Simon-minimax design, with one-sided  $\alpha$  risk of 2% and 80% power for OS, and considering 5% lost to follow-up, it is necessary to randomize 56 patients in each arm.

**Perspectives:** As older patients are at higher risk of chemotherapy toxicity, Ramucirumab alone could be an interesting alternative to Paclitaxel plus Ramucirumab, as a second-line therapy for patients  $\geq 70$  years old with advanced GC, and needs to be evaluated.

**Keywords:** advanced gastric cancer, geriatric, Ramucirumab, Paclitaxel, quality of life

## **1. Rationale and aims:**

Gastric cancer (GC) is the fifth most frequently diagnosed cancer worldwide with 1,033,701 new cases in 2018, and it is the third cause of death by cancer<sup>1</sup>. It is more prevalent in Eastern Asia, but remains a health problem in Western countries. Though its incidence has been decreasing in recent decades in developed countries, partly because of *H. pylori* eradication<sup>2,3</sup>, 6,557 new cases and 2,794 deaths were still reported in 2018 in France<sup>4</sup>. The prognosis of GC remains poor, with 5-year overall survival (OS) rate of 30% in France, and an increase in 5-year OS of only 6 percentage points in the last 25 years (from 25% in 1990 to 31% in 2015)<sup>4</sup>. Therefore, new therapeutic strategies must be developed to improve the prognosis of GC, especially in cases of metastatic disease where survival remains poor (median OS < 1 year and 16 months in HER2-negative and positive tumors, respectively)<sup>5-7</sup>.

Furthermore, 40% of patients with GC are  $\geq 70$  years old<sup>8,9</sup>. This proportion will increase in the future due to population aging and increased life expectancy. Older patients with cancer raise therapeutic challenges, because they constitute a heterogeneous population with various combinations of comorbidities, as well as functional, nutritional and cognitive impairments, all of which contribute to frailty<sup>10,11,12</sup>. Comorbidities significantly reduce life expectancy and can therefore be a contra-indication to treatments<sup>13</sup>. Older patients are often polymedicated and more susceptible to treatment side effects and, in this population, chemotherapy may induce or exacerbate geriatric frailties. In older patients with metastatic colorectal cancer treated with first-line chemotherapy, geriatric factors such as reduced autonomy and cognitive impairments were shown to predict severe toxicity or unexpected hospitalization in the FFCD 2001-02 randomized phase III study<sup>14</sup>. A multidimensional geriatric assessment is recommended in older cancer patients to inventory health problems and tailor treatment decisions accordingly, but it requires considerable time and human resources. The G8 score has been developed in older patients with cancer, and is one of the most sensitive screening

tools for detecting frail patients requiring a complete geriatric assessment<sup>15</sup>. The management of digestive cancers in patients over 70 years remains controversial because these patients are under-represented in clinical trials despite constituting a significant proportion of cancer patients in routine clinical practice<sup>16–18</sup>. In a meta-analysis that included 28,000 patients from 55 trials, patients > 70 years old represented only 20% of participants, even though they account for 46% of overall cancer patients<sup>19</sup>. To date, no randomized study in the literature has evaluated the benefit of chemotherapy in advanced GC in older patients specifically.

In metastatic or locally advanced GC, chemotherapy based on fluoropyrimidine plus cisplatin is now considered a standard first-line treatment<sup>20–23</sup>. Cisplatin, however, is often replaced by oxaliplatin, given the renal side effects and mandatory intravenous hydration associated with the former<sup>20,24</sup>. Among patients with failed first-line chemotherapy, 62% are still able to receive a second-line treatment<sup>25</sup>. Several cytotoxic chemotherapies, including irinotecan alone or in combination with 5-FU or a taxane in monotherapy, have proved to be superior to best supportive care (BSC), and have become standards of care in second-line treatment<sup>26–30</sup>.

Ramucirumab, an anti-VEGFR2 monoclonal antibody (mAb), also provided a survival benefit compared with BSC in the second-line for patients with advanced GC, and the benefit was shown to be greater when ramucirumab was associated with paclitaxel in the REGARD and RAINBOW trials, respectively<sup>31,32</sup>. Exploratory subgroup analyses by age from these two trials showed that the beneficial effects of ramucirumab were maintained in older patients, with longer OS (median 5.2 vs 3.8 months; HR 0.72, 95% CI: 0.48–1.08 in REGARD and 10.7 vs 8.7 months; HR: 0.88, 95% CI: 0.66–1.18 in RAINBOW) and progression-free survival (PFS) (2.8 vs 1.4 months; HR: 0.48, 95% CI: 0.32–0.72 in REGARD and 4.6 vs 2.9 months; HR: 0.72, 95% CI: 0.55–0.94 in RAINBOW) in ramucirumab-treated patients aged  $\geq$  65 years compared with placebo-treated patients<sup>33</sup>. However, differences were not statistically significant due to a lack of power. Similar trends towards improved OS and PFS were

observed in more advanced age groups ( $\geq 70$  and  $\geq 75$  years), except for OS in patients aged  $\geq 75$  years in the RAINBOW trial (11.0 months in both treatment arms). Moreover, the toxicity profile, time to deterioration in ECOG PS  $\geq 2$  and quality of life (QoL) were comparable among patients of all age groups<sup>33</sup>. However, patients  $\geq 65$  years old represented only 36% and 37% of intention-to-treat populations in the REGARD and RAINBOW studies, respectively, and the number of older patients was even lower ( $\geq 70$  years, 22% and 20% and  $\geq 75$  years, 9% and 5% in REGARD and RAINBOW, respectively), making it impossible to draw definitive conclusions on the survival benefit of ramucirumab in older patients with advanced GC, or on its most appropriate use, as a monotherapy or in combination with paclitaxel, in this frail population.

As ramucirumab monotherapy is well tolerated in the second-line treatment of advanced GC, it could be particularly suitable for older patients, and provide a reasonable alternative to ramucirumab plus paclitaxel in terms of efficacy, tolerance and preservation of QoL. Indeed, the majority of grade  $\geq 3$  treatment-related adverse events (AE) were comparable between ramucirumab and BSC arms for both the  $< 65$  and  $\geq 65$ -year age groups in the REGARD study, with the exception of hypertension which was more common in ramucirumab-treated patients<sup>31</sup>, while higher incidences of grade  $\geq 3$  neutropenia and leucopenia were reported in patients  $\geq 65$  years than in younger patients in the two paclitaxel-based arms of the RAINBOW study<sup>32</sup>. Moreover, analyses of QLQ-C30 data in REGARD showed that the percentage of patients with an improved or stable QoL was greater in the ramucirumab-treated arm than in the placebo arm while QLQ-C30 scores were mostly comparable between paclitaxel + placebo and paclitaxel + ramucirumab arms across all age groups.

The aim of the SOCRATE-PRODIGE 55 trial is to evaluate the efficacy, safety and impact on QoL of ramucirumab (CYRAMZA, Lilly, Indianapolis, USA) alone or in combination with

paclitaxel in the second-line treatment of advanced gastric or gastro-esophageal junction (GOJ) adenocarcinoma in patients  $\geq 70$  years old.

## **2. Patients and study design**

### ***2.1. Study design***

SOCRATE is a multicenter, randomized, open-label, non-comparative phase II trial, sponsored by the FFCD and supported by the French PRODIGE intergroup (FFCD, UNICANCER GI and GERCOR), designed to evaluate the efficacy and safety of ramucirumab alone (arm A) or in combination with paclitaxel (arm B) in elderly patients ( $\geq 70$  years) with advanced GC, in whom first-line chemotherapy containing fluoropyrimidine and platinum salt or irinotecan failed.

The trial was opened to inclusion in November 2018. Overall, 79 centers are including patients in France. The end of recruitment is scheduled for August 2022, and to date 75 patients have been randomized.

### ***2.2. Inclusion and exclusion criteria***

The main inclusion and exclusion criteria are summarized in **Table 1**.

Patients are randomly assigned (ratio 1:1) to receive ramucirumab alone (arm A) or ramucirumab + paclitaxel (arm B). Randomization is done using a minimization technique. Stratification factors are center, Instrumental Activities of Daily Living (IADL) score ( $\leq 7$  or  $= 8$ ), histological type (signet-ring cell gastric adenocarcinoma ( $> 50\%$  of signet-ring cells) versus other gastric adenocarcinoma subtypes).

### ***2.3. Study treatments***



In the experimental arm (arm A), patients receive an intravenous (IV) infusion of ramucirumab at 8 mg/kg in 60 minutes at day 1 (D1) and day 15 (D15) (1 cycle) of a 28-day cycle (**Figure 1**). In the control arm (arm B), patients receive an IV infusion of ramucirumab 8mg/kg at D1 and D15, in association with a 60-minute IV infusion of paclitaxel at 80 mg/m<sup>2</sup> at D1, D8 and D15 of a 28-day cycle (**Figure 1**).

The cycles will be repeated in the two treatment arms until disease progression, unacceptable toxicity (grade 4 toxicity or grade 3 toxicity after the dose has been adjusted twice), patient refusal or upon the investigator's decision. In arm B, if the specific toxicity of either ramucirumab or paclitaxel becomes unacceptable, leading to the discontinuation of one of the two drugs, it is possible to continue with the other drug in monotherapy.

All toxicities requiring dose adjustment will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 and managed as usually recommended.

#### ***2.4. Trial objectives and endpoints***

The co-primary endpoints of the SOCRATE study are i) the proportion of patients alive at 6 months (OS defined as the time between randomization and the date of death from any cause) and ii) the patients' QoL at 4 months evaluated according to the three key dimensions of the EORTC QLQ-ELD14 questionnaire (mobility, burden of illness, worries about the future) (**Table 2**). Mobility is derived from items 31, 33 and 34, worries about the future from items 38, 39 and 40 and burden of illness from items 44 and 45 of the QLQ-ELD14 questionnaire. The smallest clinically meaningful difference in QoL is defined as a difference of at least 10 points for each dimension between the score at 4 months and baseline score.

The secondary endpoints include: other dimensions of QoL (EORTC QLQ-C30 and other items of the QLQ-ELD14 questionnaire), time to definitive deterioration (TTDD) in QoL

(defined as the time between randomization and the date of a decrease in the EORTC QLQ-C30 and QLQ-ELD14 scores of 10 points from the baseline score), TTDD in autonomy (defined as the time between randomization and the date of a decrease in the IADL score of at least 1 point from the baseline score), OS, toxicity according to the NCI-CTCAE 4.0, dose-intensity of each drug administered, time to treatment failure (defined as the time between randomization and disease progression, treatment interruption or death), PFS (defined as the time between randomization and the time of first disease progression or death from any cause) by local assessment using RECIST 1.1 and by central review, objective response rate according to RECIST 1.1 (in case of measurable disease), identification of geriatric predictive factors of patient outcome and treatment efficacy and tolerance (the following geriatric parameters will be assessed before the start of treatment and during the follow-up: social status, ADL and IADL<sup>34</sup>, G8 score<sup>35</sup>, cognitive test (3 words test, clock test), thymic state (mini-Geriatric Depression Scale<sup>36</sup>), comorbidities according to the adjusted Charlson index<sup>37</sup>, and mobility according to the Timed Get Up and Go Test<sup>38</sup>), and identification of nutritional predictive factors of patient outcome and tolerance to treatment (the following nutritional parameters will be assessed before the start of treatment and during the follow-up: weight loss (i.e.  $\geq 5\%$ , between 5 and 10% and  $\geq 10\%$ ), analogic visual nutritional scale of ingesta (from 0 to 10, a value  $<7$  indicating anorexia that requires nutritional supplementation), serum albumin and pre-albumin).

### ***2.5. Monitoring of patients***

The baseline evaluation should take place within 2 weeks prior to randomization. It includes clinical (medical history, weight, percentage of weight loss, height and body surface, body mass index (BMI), blood pressure, WHO performance status, ingesta verbal/visual analogue scale (VVAS), QLQ-C30 and QLQ-ELD14 questionnaires), biological (complete blood

count, creatinine, serum electrolytes, liver function, coagulation tests, Lactate Dehydrogenase (LDH), proteins, albumin, pre-albumin, C-reactive protein (CRP), dipstick urinalysis, CEA and CA 19.9 tumor markers) and geriatric assessments (as described above). The initial tumor assessment should be carried out within 4 weeks prior to randomization, with a chest-abdomen-pelvis CT-scan.

Evaluations are done every 8 weeks until progression. These evaluations include a clinical evaluation, biological tests, QoL questionnaires, chest-abdomen-pelvic CT-scan and geriatric assessments.

## ***2.6. Statistical analysis***

This is a non-comparative trial. For the first co-primary endpoint, OS, the clinical hypothesis is an increase in 6-month OS from 40% (H0: the percentage of patients alive at 6 months of 40% or less is not useful) to 60% (H1: the percentage of patients alive at 6 months of 60% is expected). Using a 2-stage Simon Minimax design, with a one-sided  $\alpha$  risk of 2% and 80% power, it is necessary to randomize 53 patients in each treatment arm. For the experimental arm (arm A), the following rules are being used. In the first stage, 18 patients are included. If at least eight patients or more are alive at 6 months, the trial will continue until 53 patients have been randomized in each arm. At the last stage, if at least 29 patients are alive at 6 months in arm A, the treatment will be considered effective. Anticipating that 5% of patients will be lost to follow-up, a total of 56 patients per arm will be randomized, for a total of 112 patients. For the second co-primary endpoint, QoL, the clinical hypothesis for the three dimensions analyzed is an improvement in the targeted QoL dimensions (mobility, disease burden, worry about the future) from no improvement (H0: no improvement or improvement < 10 points) to an improvement of at least 10 points; (H1: improvement  $\geq$  10 points between the baseline and the QLQ-ELD14 scores at 4 months, with a standard error of 20). Using a

one-sided paired series Student T-test with an  $\alpha$  risk of 1% and 85% power, it is necessary to randomize 46 patients in each arm. If an improvement in QoL occurs in one of the three targeted dimensions with no deterioration in any other dimension, the QoL will be considered improved. Considering that 5% of patients will be lost to follow-up, a total of 48 patients per arm have to be randomized, for a total of 96 patients.

Regarding these two criteria, it is necessary to randomize 112 patients, 56 per treatment arm.

The proportion of patients alive at 6 months and secondary endpoints will be analyzed on the basis of intention-to-treat (ITT), and modified-ITT 1 (= all the patients included having received at least one dose of treatment, and analyzed according to the treatment attributed at randomization). The primary endpoint based on QoL will be analyzed on the basis of modified ITT 2 (all patients included having an EORTC QLQ-C30 and QLQ-ELD14 scores completed at baseline and at 4 months, and analyzed according to the treatment arm at randomization). Safety criteria will be analyzed for all included patients having received at least one dose of treatment, according to the real treatment intake. A statistical plan for the analysis will be written before each analysis. Continuous variables will be reported as means, standard-deviations, medians (range), inter-quartile intervals, minima and maxima, and qualitative variables will be reported as frequencies and percentages. For efficacy criteria, the proportion of patients alive at 6 months will be described by treatment arm, with a 98% confidence interval (CI). For QoL, the three dimensions will be considered, the number of patients experiencing improvements at 6 months will be described by treatment arm, with a 1% one-sided CI. Times to events (PFS, OS etc.) will be estimated using a Kaplan-Meier method, and will be described as the median values and rates at specific times with the corresponding 95% CI. Median follow-up will be calculated with a reverse Kaplan-Meier method. For safety criteria, the time of treatment for each treatment, and the total duration of treatment will be described using descriptive statistics. Dose-intensity for each treatment will

also be described. Toxicities will be described by treatment arm and by grade of severity according to NCI-CTCAE v4.0. SAS version 9.4 or more (Cary, North-Carolina, USA) will be used for all analyses.

### ***2.7 Administrative and ethical considerations***

This study (ClinicalTrials.gov Identifier: NCT03760822) is being conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Practice Guidelines (ICH-E6 17/07/96). The trial was approved by an Institutional Review Board (Comité de Protection des Personnes (CPP) Sud-Est V, Ref 18-FFCD-01) on April 4, 2018 and by the French National Safety Drug Agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, Ref 170666A-12) on January 12, 2018. All of the patients have to provide written and oral informed consent before joining the study.

### ***2.8. Ancillary studies***

All patients enrolled in the trial are being invited to participate in two optional biological ancillary studies, one on circulating tumor DNA (ctDNA) and the other on the pharmacokinetics (PK) of ramucirumab. We will investigate the prognostic value of the detection and quantification of ctDNA at baseline, and also the prognostic impact of an early decrease in the amount of ctDNA. ctDNA is analyzed before the first cycle of treatment and before the second cycle of treatment (at 4 weeks). The serum concentration of ramucirumab will be centrally assessed by an enzyme-linked immunosorbent assay <sup>39</sup>. Blood samples for PK analysis are being collected at the following time points:

- at cycle 1: D1 hour 0 (H0), D15 H0 and D15 H2 (end of infusion) in arm A; D1 H0, D8 H0, D15 H0 and D15 H2 in arm B
- at cycle 2: D1 H0, D1 H2, D15 H0 and D15 H2 (arms A and B)

In addition to these two biological ancillary studies, two other ancillary studies are planned. The first one is a radiological study including the evaluation of prognostic and predictive CT-scan factors of response to treatment, based on density- and/or size-based criteria (RECIST, CHOI and CHUN criteria). Visceral fat area, total fat area and subcutaneous fat area will also be tested as predictive factors of the response to ramucirumab. In addition, sarcopenia, also assessed on CT-scan images at L3 vertebra, will be correlated with the occurrence of adverse events (grade 3-4 NCI-CTCAE 4.0) and survival. The second study will assess the prognostic value of nutritional parameters (percentage of weight loss, BMI, ingesta VVAS, albumin, pre-albumin, CRP, Nutritional Risk Index) and their ability to predict treatment toxicity and efficacy.

### **3. Discussion**

To date, there have been no randomized studies dedicated to older patients with advanced GC, especially in the second-line setting where several standard treatments exist, including cytotoxic chemotherapies (irinotecan alone or combined with 5-FU, paclitaxel or docetaxel) and ramucirumab alone or in combination with paclitaxel. Older patients represent a heterogeneous population in which a significant proportion of patients are frail due to comorbidities and disabilities, as well as nutritional and functional impairments, all of which may affect treatment tolerance and outcomes<sup>40</sup>. This is why the results of therapeutic trials carried out in the general population, whether in terms of efficacy or toxicity, cannot necessarily be extrapolated to older patients. Moreover, in palliative settings such as the second-line treatment of advanced GC, QoL takes on a greater importance in older patients, in whom more frequent side effects may counteract the efficacy of a treatment. For this reason, the most appropriate (effective, low toxicity and QoL-preserving) treatment for older patients remains to be determined.

As ramucirumab monotherapy is one of the best-tolerated second-line treatments of advanced GC, it could be particularly suitable for older patients, and be a reasonable alternative to cytotoxic chemotherapy or ramucirumab plus paclitaxel in terms of efficacy, tolerance and preservation of QoL in this population. This is what we seek to demonstrate in the SOCRATE study.

Other therapies could also be interesting in the second-line treatment of advanced GC in elderly patients ineligible for standard cytotoxic chemotherapy. Tipiracil/trifluridine and the anti-PD-1 nivolumab have recently proved their superiority to BSC in terms of survival in the third-line treatment of advanced GC, with few side effects<sup>41,42</sup>. However, to date, tipiracil/trifluridine has not been evaluated and compared with second-line chemotherapy, and other anti-PD-1 inhibitors, such as avelumab and pembrolizumab, failed to demonstrate their superiority over second-line cytotoxic chemotherapy in unselected patients from the JAVELIN GASTRIC 300<sup>43</sup> and KEYNOTE-061<sup>44</sup> trials, respectively. For the moment, therefore, immunotherapy should be reserved for patients with microsatellite instability-high tumors, and continue to be evaluated in this situation in patients selected on the basis of biomarkers such as PD-L1 or EBV status or tumor mutational burden, as their favorable safety profile as a single agent could be of particular interest in those patients, such as older patients, who are not eligible for cytotoxic chemotherapy. However, the recent demonstration of the benefit of immunotherapy combined with chemotherapy in the first-line treatment of advanced GC<sup>45</sup> will change the therapeutic strategy for these cancers and probably make the question of second-line immunotherapy obsolete, while the place of ramucirumab will remain relevant.

ctDNA is a potential surrogate of a solid biopsy for detecting important theranostic genetic alterations, but also a potential early predictor of treatment efficacy. Very few data are available on ctDNA in GC<sup>46,47</sup>. ctDNA evaluated on the detection of mutation or gene

amplifications is present in 30% to 70% of stage IV GC. The SOCRATE trial provides an opportunity to test the prevalence of ctDNA in a large series of advanced GC and to test the prediction of treatment efficacy based on the early decrease in ctDNA after one cycle of chemotherapy.

Several studies on the PK profile of ramucirumab have shown large inter-individual variations of PK parameters. An exposure-response relationship has been observed in randomized trials of ramucirumab in lung, colorectal and gastric cancers<sup>48-50</sup>. In advanced GC, a low ramucirumab concentration before the second injection is associated with significantly lower PFS and OS<sup>50</sup>. The PK of monoclonal antibodies is dependent on multiple factors, such as age, sex, albuminemia or antigenic mass<sup>51,52</sup>. The PK and concentration-effect relationships of therapeutic monoclonal antibodies remain poorly studied in elderly patients. Greater knowledge of the inter-patient variability of ramucirumab PK parameters in older patients is required. The PK ancillary study will enable us to build individual pharmacokinetics/pharmacodynamics (PK/PD) models to investigate the relationships between the individual serum concentrations and clinical effects of ramucirumab. These models could then be used as a tool to refine ramucirumab dosages so as to ensure maximum efficacy in patients with advanced GC.

#### **4. Conclusion**

SOCRATE-PRODIGE-55 is a randomized trial evaluating second-line ramucirumab alone compared with ramucirumab plus paclitaxel in patients  $\geq 70$  years with advanced GC. It is the first randomized therapeutic trial dedicated to elderly patients with advanced GC. The geriatric analyses and ancillary studies of this trial will provide data to better define which patients are likely to be the best candidates for ramucirumab alone or combined with



paclitaxel and to identify potential relevant predictive biomarkers of efficacy and tolerance to treatment.

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**Declaration of competing interest:**

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**Figure legend:**

**Figure 1:** study design of the SOCRATE trial.

D = day, C = cycle, R= randomization

**Table legends:**

**Table 1:** Main inclusion and exclusion criteria.

**Table 2:** EORTC QLQ-ELD14

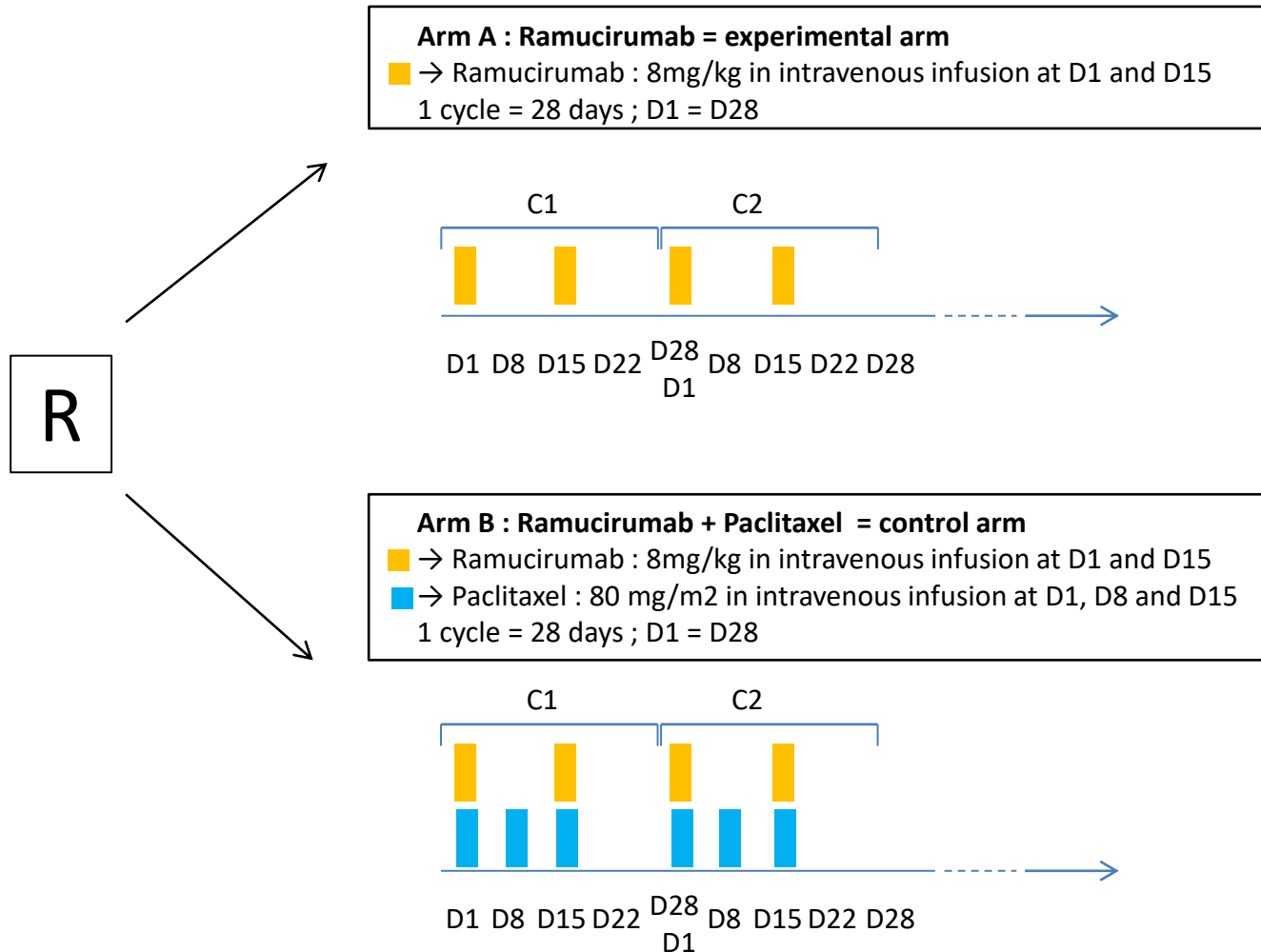


Figure 1

**Table 1:** Main inclusion and exclusion criteria.

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**Inclusion criteria**

- Histologically confirmed, unresectable, locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, whatever the HER2 status
- Aged  $\geq 70$  years
- WHO performance status  $< 2$
- Estimated life expectancy  $> 3$  months
- Measurable or non-measurable disease according to RECIST 1.1 criteria
- Documented progression during first-line fluoropyrimidine- and platinum- or irinotecan-containing chemotherapy (with or without anthracycline), or during the 4 months following the last cycle of such chemotherapy administered for metastatic or locally advanced disease, or during the 6 months following the last dose of adjuvant therapy containing fluoropyrimidine and platinum (treatment by immunotherapy is allowed)
- Adequate hepatic, renal and hematologic function:
  - Absolute neutrophil count  $\geq 1\,500 / \text{mm}^3$ , platelets  $\geq 100\,000 / \text{mm}^3$ , hemoglobin  $\geq 9$  g/dL
  - Blood creatinine  $\leq 1.5 \times \text{ULN}$  and creatinine clearance (MDRD formula)  $\geq 40$  mL/min
  - Total bilirubin  $\leq 1.5 \times \text{ULN}$ , AST and ALT  $\leq 3 \times \text{ULN}$  ( $\leq 5 \times \text{ULN}$  if hepatic metastasis)
  - INR  $\leq 1.5$  or INR  $\leq 3$  for patients taking AVK and PTT  $\leq 5$  seconds above the ULN
  - Dipstick proteinuria  $\leq 1+$  or 24 hours proteinuria  $< 1$  g in total
- EORTC QLQ-C30 + QLQ-ELD14, completed
- IADL geriatric questionnaire, completed
- Signed informed consent

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**Exclusion criteria**

- Known cerebral metastasis
  - Prior treatment with taxanes
  - Prior treatment with an antiangiogenic agent
  - Grade  $\geq 2$  neuropathy (NCI-CTCAE 4.0)
  - Unresolved partial or total bowel obstruction, inflammatory bowel disease (such as Crohn's disease or ulcerative colitis) or extensive gastrointestinal (GI) resection combined with chronic diarrhea
  - GI perforation and/or fistulae in the 6 months preceding randomization.
  - Grade  $\geq 3$  GI bleeding within the last 3 months (NCI-CTCAE 4.0)
  - Chronic use of antiplatelet drugs (including aspirin, but a daily intake of  $\leq 325$  mg/day is accepted), non-steroidal anti-inflammatory drugs (ibuprofen, naproxen),
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dipyridamole, clopidogrel or similar agents

- Any arterial thromboembolic event (such as myocardial infarction, unstable angina, cerebrovascular accident or transient ischemic attack) in the 6 months preceding randomization
- A life-threatening episode of pulmonary embolism in the 6 months preceding randomization
- Deep-vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to first dose of protocol therapy
- Uncompensated congestive heart failure or uncontrolled arrhythmia
- Uncontrolled hypertension ( $\geq 140/90$  mm Hg for  $> 4$  weeks) despite properly observed antihypertensive therapy
- Child-Pugh B or C cirrhosis; or cirrhosis (any degree) with a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis
- Serious or unhealed wound, peptic ulcer or fracture within 28 days of randomization
- Radiotherapy or major surgery within 28 days prior to first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement within 7 days prior to the first dose of protocol therapy
- Known allergy to paclitaxel or ramucirumab
- Another concomitant cancer or a history of cancer in the last 5 years, except cervical carcinoma in situ, cutaneous basal-cell or squamous-cell carcinoma, or any other carcinoma in situ deemed to be successfully treated
- Lack of effective contraception in patients (man and/or women) of childbearing age
- Persons deprived of liberty or under supervision
- Impossibility of undergoing medical monitoring during the trial for geographic, social or psychological reasons

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WHO = World Health Organization, ULN = upper limit of normal, AVK= Anti-vitamin K, PTT = Prothrombin Time, NCI-CTCAE= National Cancer Institute Common Terminology Criteria Adverse Event

**Table 2: EORTC QLQ-ELD14**

<b>Dimension</b>	<b>During the past week</b>	<b>Not at all</b>	<b>A little</b>	<b>Quite a bit</b>	<b>Very much</b>
Mobility	31. Have you had difficulty with steps or stairs?	1	2	3	4
Single item: joint stiffness	32. Have you had trouble with your joints (e.g. stiffness and pain)?	1	2	3	4
Mobility	33. Did you feel unsteady on your feet?	1	2	3	4
Mobility	34. Did you need help with household chores such as cleaning or shopping?	1	2	3	4
Single item: family support	35. Have you felt able to talk to your family about your illness?	1	2	3	4
Worries about others	36. Have you worried about your family coping with your illness and treatment?	1	2	3	4
Worries about others	37. Have you worried about the future of people who are important to you?	1	2	3	4
Future worries	38. Were you worried about your future health?	1	2	3	4
Future worries	39. Did you feel uncertain about the future?	1	2	3	4
Future worries	40. Have you worried about what might happen towards the end of your life?	1	2	3	4
Maintaining purpose	41. Have you had a positive outlook on life in the last week?	1	2	3	4
Maintaining purpose	42. Have you felt motivated to continue with your normal hobbies and activities?	1	2	3	4
Burden of illness	43. How much has your illness been a burden to you?	1	2	3	4
Burden of illness	44. How much has your treatment been a burden to you?	1	2	3	4