# CLINICAL STUDY REPORT
# (Synopsis)

## CESAR C-II-004/ EUDRACT 2007-005022-71

## Prospective randomized phase II trial with Gemcitabine plus Sunitinib versus Gemcitabine alone in first-line therapy of metastatic or locally advanced pancreatic cancer

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| **Study protocol No:** | CESAR C-II-004 / EUDRACT 2007-005022-71 |
| **Document status:** | FINAL 2.0 |
| **Investigational product:** | Sutent® (Sunitinib), Gemzar® (Gemcitabine) |
| **Sponsor** | CESAR Central European Society for Anticancer Drug Research-EWIV<br>Hanglüssgasse 4/1-3, 1150 Vienna, Austria |
| **Study Chairman:** | Prof. Dr. Lothar Bergmann,<br>Cancer Center, Medical Clinic II, University Hospital,<br>Theodor-Stern-Kai 7, 60590 Frankfurt, Germany |
| **Development phase:** | Phase II |
| **Study initiation date:** | 16-Apr-2008 (first patient in) |
| **Study termination date:** | 06-Feb-2012 (last patient out) |
| **CESAR Central Office (Sponsor Signatory)** | Dr. Max Roessler<br>Hanglüssgasse 4/1-3, 1150 Vienna, Austria<br>phone: +43 1 522 30 9316, fax: +43 1 522 30 93 14<br>email: max.roessler@cesar.or.at |
| This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents<br>Date of the report: 23 September 2013 (revised on 25 November 2013, 2nd revision 05 March 2019) | |
| Date: 6/3/19 | Signature Sponsor: |

## SYNOPSIS

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| Name of Company: CESAR Central European Society for Anticancer Research-EWIV | C-II-004 / EUDRACT 2007-005022-71 | (For National Authority Use Only) |
| Name of Finished Product: Sutent ®, Gemzar ® | | |
| Name of Active Ingredient: Sunitinib, Gemcitabine | | |
| Title of Study: Prospective randomized phase II trial with Gemcitabine plus Sunitinib versus Gemcitabine alone in first-line therapy of metastatic or locally advanced pancreatic cancer<br>Protocol Versions:<br>1.0 (20-10-2007)<br>2.0 (20-02-2008): Implemented prior to enrolment. Implementation of dose modifications, addition of effective contraception, blinding of statistician to the treatment assignment until SAP.<br>3.0 (25-03-2009): Implementation of further safety measures, based on the Annual Safety Report (23 March 2009).<br>4.0 (29-03-2010): Implementation of further safety measures, based on SMPC of Sunitinib (Version August 2009), change of study statistician, inclusion of biomarker sub-study to increase scientific value of the study.<br>The study was not interrupted and ended as defined in the study protocol (No premature termination of study). | | |
| Study Chair: Lothar Bergmann, MD | | |

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Study Site(s) and Principal Investigators:

<u>Germany</u>

- Site 01 / Prof. Dr. Lothar Bergmann (LKP), Klinikum der J.W. Goethe Universität, Zentrum der Inneren Medizin, Theodor Stern-Kai 7, 60590 Frankfurt, DEUTSCHLAND – **14 patients**
- Site 02 / Prof. Dr. Walter-Erich Aulitzky, Robert-Bosch-Krankenhaus, Hämatologie, Onkologie, Klinische Immunologie, Auerbachstrasse 110, 70376 Stuttgart, DEUTSCHLAND – **4 patients**
- Site 03 / Dr. Hans Jörg Cordes, Internistisches Facharztzentrum Stresemannalle – IFS, Stresemannallee 3, 60596 Frankfurt, DEUTSCHLAND – **0 patients**
- Site 04 / Prof. Dr. Max E. Scheulen, Universitätsklinikum Essen, Innere Klinik und Poliklinik (Tumorforschung), Hufelandstrasse 55, 45122 Essen, DEUTSCHLAND – **45 patients**
- Site 07 / Dr. Karin Weigang-Köhler, Klinikum Nürnberg Nord, 5. Med. Klinik, Prof.-Ernst-Nathan-Strasse 1, 90419 Nürnberg, DEUTSCHLAND – **2 patients**
- Site 08 / Dr. med. Stefan Fuxius, Praxis für Hämatologie und Onkologie, Kurfürstenanlage 34a, 69115 Heidelberg, DEUTSCHLAND – **5 patients**
- Site 09 / Dr. Jörn Rüssel (before Dr. Dirk Arnold), Martin-Luther-Universität Halle-Wittenberg, Medizinische Fakultät, Ernst-Grube-Strasse 40, 06097 Halle (Saale), DEUTSCHLAND – **10 patients**
- Site 10 / Prof. Dr. Gerhard Heil, Märkische Kliniken GmbH, Klinikum Lüdenscheid, Klinik für Hämatologie und Onkologie, Paulmannshöher Strasse 14, 58516 Lüdenscheid, DEUTSCHLAND – **11 patients**
- Site 14 / Prof. Dr. Elke Jäger, Krankenhaus Nordwest, II. Medizinische Klinik Onkologie – Hämatologie, Steinbacher Hohl 2-26, 60488 Frankfurt, DEUTSCHLAND – **9 patients**
- Site 15 / Dr. Gisela Fritsch (before Prof. Dr. Bernhard Wörmann), Medizinische Klinik III, Städt. Klinikum Braunschweig gGmbH, Celler Str. 38, 38114 Braunschweig, DEUTSCHLAND – **4 patients**
- Site 16 / Dr. Silke Schumann-Binarsch (before PD Dr. Gernot Hartung, Dr. Anja Urbigkeit), Klinikum Oldenburg gGmbH, Klinik für Onkologie und Hämatologie, Rahel-Strauss-Str. 10, 26133 Oldenburg, DEUTSCHLAND – **3 patients**
- Site 17 / PD Dr. Michael Flaßhove, Krankenhaus Düren gem. GmbH, Abteilung für Innere Medizin / Hämatologie und Internistische Onkologie, Roonstr. 30, 52351 Düren, DEUTSCHLAND – **0 patients**

<u>Switzerland</u>

- Site 11 / Dr. Dieter Köberle, Kantonsspital St. Gallen, Department Innere Medizin, Onkologie / Hämatologie, Rorschacherstrasse 95, 9007 St. Gallen, SCHWEIZ – **6 patients**

Publication (reference): N/A

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| Study Dates:<br>First Patient In: 16-Apr-2008<br>Last Patient Completed: 06-Feb-2012 | Phase of Development: Clinical Phase II |

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| Name of Active Ingredient: Sunitinib, Gemcitabine | | |

Objectives:

Primary objective: to evaluate whether the addition of sunitinib to gemcitabine (arm A) prolongs the progression-free survival (PFS) compared to gemcitabine alone (arm B) in patients with advanced pancreatic cancer.

Secondary objectives: characterization of safety and additional efficacy outcomes in the experimental arm A and their exploratory comparison with arm B.

- safety assessment using CTCAE v3.0 - safety assessed according to reported SAEs
- objective response (OR) assessed using RECIST criteria Version 1.0
- time-to-progression (TTP)
- overall survival (OS)

Methodology: This was an open-label, randomized (1:1), parallel group, multicenter, international Phase-II study. The randomization was stratified by center. Patients with metastatic or locally advanced pancreatic cancer who were chemo-naïve were eligible for the trial. Patients meeting the inclusion/exclusion criteria and having signed the Informed Consent were randomly allocated to one of the two treatment arms: Arm A - gemcitabine plus sunitinib (SUNGEM), Arm B - gemcitabine therapy alone (GEM) (dosage and mode: see below). Patients visited the investigational site after each cycle and assessment of tumor response (RECIST) was done at baseline, 6 weeks and 12 weeks after treatment start, thereafter every 8 weeks until disease progression. Patients received therapy until disease progression or intolerable toxicity whichever came first. Patients got further treatment according to best local practice. If disease progression was documented, the patient was followed every 3 months for survival.

No of patients: 113 randomized, 106 received study treatment

No of planned patients: 86 evaluable patients, 96 patients in total

No of analyzed patients: 106

Diagnosis: metastatic or locally advanced pancreatic cancer

Main Criteria for Inclusion: First Line gemcitabine chemotherapy in adult males and females: over 18 years of age with locally advanced or metastatic pancreatic cancer

Test Product: Stutent ®

Dose and Mode: Arm SUNGEM: Sunitinib 50 mg orally 1x/day for 2 weeks followed by 1 week of rest added to gemcitabine therapy (1.000 mg/m², IV, on day 1 and 8 of a 21 day cycle).

Batch Numbers:

12.5mg 06-042994, 07-056426, M022AJ, N215S, E793A

25mg 05-033391, 07-056427, 09-076363, K727P, E793A, P023S, L080A, N347M, K0135

50mg HB478 / 6778A

Test Product: Gemzar ®

Dose and Mode: Arm GEM: Gemcitabine therapy (1,000 mg/m²) will be given on day 1, 8 and 15 of a 28 day cycle.

Batch Numbers:

Gemcitabine was supplied as a lyophilized powder in sterile vials containing 200 mg or 1,000 mg of gemcitabine. It was provided by the institution where the patient was treated and prepared by the pharmacy at the very institution. Gemcitabine administration was documented in the source documentation and the electronic CRF. Specific drug accountability procedures were not applied.

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Duration of Treatment: until disease progression, intolerable toxicity or other reasons to end treatment as defined in the protocol

Reference Therapy, Dose and Mode: Gemcitabine: 1.000 mg/m², IV, given on day 1, 8 and 15 of a 28-day cycle.

Batch Number: N/A (commercial product was administered)

Criteria for Evaluation:

Efficacy: Antitumor activity as assessed by progression free survival time (PFS) in arm A compared to arm B; PFS12 (proportion of patients progression free for at least 12 weeks); OR (objective response) based on Response Evaluation Criteria in Solid Tumors (RECIST v1.0); Best Response based on Response Evaluation Criteria in Solid Tumors (RECIST v1.0); TTP (time-to-progression); OS (overall survival)

Safety: Adverse events assessed according to the National Cancer Institute Common Toxicity Criteria CTCAE v3.0

Statistical Methods:

Sample Size Calculation: The study is designed as a one-stage randomized (1:1) non-blinded phase II trial to show a sufficient superiority of arm A over the standard treatment arm B by testing the null hypothesis H0: PFS-A = PFS-B (expected = 3) versus the alternative H1 : PFS-A > PFS-B (in A expected >= 5) at the significance level of alpha= 10%.

A total of N=86 patients evaluable for PFS is to be recruited (n= 43) in each arm. We expect about 10% of the patients recruited to be not evaluable for PFS. As a consequence a total of N=96 patients are planned to be recruited in this trial.

Interim Analysis: not planned/performed.

Analysis Methods: Confirmatory statistical analysis of the primary endpoint PFS is based on the ITT (intention-to-treat) population and is done using a one-sided logrank-test. Secondary analyses of the primary endpoint, secondary endpoints and subgroup analyses are all of explorative nature and are reported using descriptive analysis methods. For sensitivity reasons, an analysis of primary and secondary efficacy endpoints is additionally performed based on the per protocol population (PPP).

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Summary of Safety Results:

| | SUNGEM | GEM | SUM TOTAL |
|---|---|---|---|
| No of patients | 52 | 54 | 106 |
| Adverse Events | 937 | 673 | 1610 |
| Pre-existing Events | 55 | 48 | 103 |
| AEs minus pre-existing | 882 in 51 pts | 625 in 54 pts | 1507 in 105 pts |
| Suspected Adverse Reactions | 462 in 49 pts | 252 in 50 pts | 714 in 99 pts |
| Total No SAEs | 97 in 71.2% pts | 77 in 53.7% pts | 174 in 62.3% pts |
| Definitely related SAEs | 2 | 5 | 7 |
| Probably related SAEs | 13 | 0 | 13 |
| Possibly related SAEs | 10 | 7 | 17 |
| Unlikely related SAEs | 9 | 19 | 28 |
| Unrelated SAEs | 63 | 46 | 109 |
| Fatal SAEs (within 4 weeks of treatment) | 9 | 7 | 16 |
| SUSARs | 3 | 0 | 3 |

Most frequently documented adverse drug reactions: Fatigue (50%), Nausea (47.2%), Vomiting (38.7%)

Fatal events reported as SUSARs: Cardiac Shock (pt 11-001, Switzerland), Multiple Organ Dysfunction Syndrome (pt 09-001, Germany), Sudden Death (pt 09-010, Germany)

Significant differences at the 5 % significance level were obtained for neutropenia with a higher observed incidence of 48.1 % for the SUNGEM arm compared to 27.8 % for the GEM arm (p=0.045).

Efficacy Results:

| | SUNGEM | GEM | Sum TOTAL |
|---|---|---|---|
| 6-month PFS rate (in 106 evaluable patients) | 25.0% | 26.8% | |
| Objective response rate (confirmed response between 8 and 24 weeks in 61 evaluable patients) | 7.1% | 6.1% | 6.6% |
| Partial remissions (between 8 and 24 weeks after start of treatment) | 2 of 28 pts | 2 of 33 pts | 4 of 61 pts |
| Median time-to progression (TTP) | 18.0 weeks | 14.0 weeks | |
| Median Overall survival | 30.4 weeks | 36.7 weeks | |

As primary test for the treatment comparison the one-sided logrank test (for PFS) testing superiority of SUNGEM compared to GEM was performed and revealed that the null hypothesis could not be rejected at the 10 % significance level (p=0.78) as set in the protocol. The two-sided log-rank test (for TTP and OS) revealed that the null hypothesis of equal TTP Kaplan-Meier functions could not be rejected at the 5 % significance level (p=0.60 for TTP; p=0.44 for OS).

Conclusions:

Advanced and metastatic pancreatic cancer is still associated with a poor prognosis with a 5-year overall survival of only about 15%.

The combination of gemcitabine plus sunitinib (SUNGEM) did not significantly improve progression free survival (PFS) or overall survival (OS) in patients with locally advanced or metastatic pancreatic cancer compared to gemcitabine alone.

Despite the lower dose intensity of gemcitabine in the SUNGEM arm (667 mg/m²/week) compared to the GEM arm (750 mg/m²/week), SUNGEM caused significantly more neutropenia than GEM. In general, more AEs did occur in the SUNGEM arm. The safety profile in both arms was as expected in this type of clinical studies.

Date of Report: 23 September 2013 (revised on 25 November 2013, 2nd revision 05 March 2019)