PROTOCOL LAP 07

RANDOMIZED MULTICENTER PHASE III STUDY IN PATIENTS WITH LOCALLY ADVANCED ADENOCARCINOMA OF THE PANCREAS: GEMCITABINE WITH OR WITHOUT CHEMORADIOOTHERAPY AND WITH OR WITHOUT ERLOTINIB

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INTERNATIONAL INTERGROUP STUDY
France: GERCOR- FFCD- FNCLCC- SFRO
Germany: AIO
USA: to be defined
Australia: to be defined
Belgium: to be defined

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Je soussigné, Pr Pascal HAMMEL, après lecture du présent protocole, certifie que je mènerai la présente étude selon les règles européennes, conformément à la Déclaration d'Helsinki et aux principes de Bonnes Pratiques Cliniques.

Je m'engage :
- à obtenir de chaque patient un consentement éclairé écrit, donné de son plein gré, après lui avoir fait prendre connaissance de la fiche d'information destinée au patient ;
- à procéder à la déclaration de tous les événements indésirables graves dans les 24 heures après qu’ils auront été portés à ma connaissance ;
- à respecter les critères d'inclusion et de non-inclusion ainsi que les dates de début et de fin de l'étude ;
- à remplir intégralement toutes les rubriques du cahier d'observation ;
- à répondre aux demandes de rectifications ou d'éclaircissements en rapport avec l’eCRF ;
- à accepter des visites de contrôle régulières ;
- à archiver et conserver les documents de l'essai pendant 15 ans.

L'accord de l'investigateur:

Date : 12 novembre 2007
PLAN

1- PROTOCOL SUMMARY ........................................................................................................... 6
2. SCIENTIFIC BACKGROUND ................................................................................................. 8
3. RESULTS IN THE LITERATURE ............................................................................................ 9
   A- Chemotherapy vs Chemoradiotherapy .............................................................................. 9
   3.1. Chemotherapy .................................................................................................................. 9
   3.2. Chemoradiotherapy .......................................................................................................... 12
   B- Potential interest of combining erlotinib with gemcitabine then erlotinib as maintenance treatment in LA cancers of the pancreas ....................................................... 14
   C- Prognostic biological factors of response to the proposed treatments ......................... 14
4. OBJECTIVES OF THE STUDY .............................................................................................. 15
   4.1. Hypotheses tested ............................................................................................................. 15
   4.2 Primary objective .............................................................................................................. 15
   4.3 Secondary objectives ....................................................................................................... 15
5. EXPERIMENTAL PLAN ....................................................................................................... 16
   5.1. Choice of experimental plan and justification ............................................................... 16
   5.2. Study plan ....................................................................................................................... 18
   5.3. Randomization and treatment arms .............................................................................. 19
      5.3.1. Randomization procedure ...................................................................................... 19
      5.3.2. Treatments arms ....................................................................................................... 19
   5.4. Treatments, products used, mode of administration .................................................. 20
      5.4.1. Gemcitabine ............................................................................................................. 20
      5.4.2. Erlotinib .................................................................................................................. 22
      5.4.3. Capecitabine .......................................................................................................... 22
      5.4.4. Radiotherapy .......................................................................................................... 23
   5.5. Duration and termination .............................................................................................. 26
   5.6. Stopping rules or discontinuation criteria ..................................................................... 26
   5.7. Recruitment .................................................................................................................... 27
6. SELECTION AND WITHDRAWAL OF PATIENTS................................................................. 28
   6.1. Inclusion criteria ............................................................................................................ 28
   6.2. Exclusion criteria .......................................................................................................... 29
   6.3. Patients withdrawal criteria ......................................................................................... 29
7. MANAGEMENT AND SCHEDULES ..................................................................................... 29
   7.1 Patient management .................................................................................................... 29
      7.1.1. Scheduling and content of visits .......................................................................... 29
      7.1.2. Medical acts, tests and analyses .......................................................................... 30
      7.1.3. Location of medical acts, tests and analyses ....................................................... 31
   7.2. Follow-up for patients on treatment ........................................................................ 33
8. DRUGS EVALUATED & DOSE MODIFICATIONS ............................................................. 36
   8.1. Administration schedule ............................................................................................ 36
   8.2. Dose modifications .................................................................................................... 37
      8.2.1. Treatment modifications for gemcitabine ......................................................... 37
      8.2.2. Treatment modifications for capecitabine ......................................................... 37
      8.2.3. Radiotherapy dose modification ........................................................................ 37
      8.2.4. Treatment modification for erlotinib ................................................................. 38
9. Data in the e-CRF .............................................................................................................. 40
# Table of Contents

10. **EFFICACY PARAMETERS** ................................................................. 41
    10.1. Overall survival ........................................................................... 41
    10. 2. Progression Free Survival .......................................................... 41
    10. 3. Definition of Response ................................................................. 41

11. **ASSESSMENT OF SAFETY** ............................................................. 42
    11.1. Safety Parameters ........................................................................ 42
    11.2. Methods and evaluations ............................................................... 43
    11.3. Recording and Reporting SAE ....................................................... 43
        11.3.1. Recording data .................................................................... 43
        11.3.2. Reporting SAE .................................................................. 44
    11.4. Follow-up of patients with SAE ...................................................... 45
    11.5. Declaration to authorities .............................................................. 45
    11.6. Expected adverse events .............................................................. 47
        11.6.1. Negative side effects of gemcitabine ................................. 47
        11.6.2. Negative side effects of erlotinib ...................................... 47
        11.6.3. Negative side effects of capecitabine ............................... 47
        11.6.4. Negative side effects of radiotherapy .............................. 48

12. **DATA MANAGEMENT AND STATISTICAL ANALYSIS** .................... 48
    12.1. Strategy for data analysis ............................................................. 48
    12.2. Number of planned patients and justification .............................. 49
    12.3. Planned Interim Analysis .............................................................. 49
    12.4. Management of data analysis and software .................................. 50

13. **ETHICAL AND REGULATORY CONSIDERATIONS (FOR FRANCE)** ...... 50
    13.1. Responsibilities of the sponsor .................................................. 50
    13.2. Patient information and Informed consent ................................. 50
    13.3. Patient Insurance ....................................................................... 50
    13.4. CNIL Declaration ....................................................................... 51
    13.5. Ethical Committee (EC) ............................................................... 51

14. **DATA HANDLING AND RECORD KEEPING** .................................... 51
    14.1. eCRF Handling ........................................................................... 51
    14.2. Investigator site file and archiving ............................................. 51
    14.3. Modifications to the study protocol ........................................... 52
    14.4. Extending the study ................................................................. 52
    14.5. Study documentation ............................................................... 52
    14.6. Reviewing procedures .............................................................. 52
    14.7. Transcribing data ....................................................................... 52
    14.8. Final report ................................................................................ 53
    14.9. Ownership of results .............................................................. 53
    14.10. Notice of informed consent .................................................... 53

15. **INDEPENDENT COMMITTEE** ....................................................... 53

16. **PUBLICATION** ............................................................................. 53
    16.1. Main paper ................................................................................. 53
    16.2. Oral communications ............................................................... 54

17. **REFERENCES** .................................................................................. 55

**APPENDICES** .................................................................................... 61
    APPENDIX 1. Objective Tumor Response Criteria ............................. 62
    APPENDIX 2. ECOG Performance Status ........................................ 66
| APPENDIX 3. | List of Participating Centres and Investigators for France | 67 |
| APPENDIX 4. | NCI - Common Terminology Criteria for Adverse Events (version 3.0) | 73 |
| APPENDIX 5. | Declaration of Helsinki | 77 |
| APPENDIX 6. | Adverse Event declaration form | 81 |
| APPENDIX 7. | Opinion of CPP | 83 |
| APPENDIX 8. | Insurance Policy | 84 |
1- PROTOCOL SUMMARY

TITLE Randomized multicenter phase III study in patients with locally advanced adenocarcinoma of the pancreas: gemcitabine with or without chemoradiotherapy and with or without erlotinib

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RATIONALE Survival in patients with adenocarcinoma of the pancreas is ≤ 4 % at 5 years. Median survival in cases with a locally advanced, non-resectable, non-metastatic tumor is no more than 10-12 months with conventional treatment. We recently showed (Huguet F et al. J Clin Oncol 2007;25:326-31) that the administration of radiotherapy with 5-fluorouracil in patients with a controlled tumor after three months of chemotherapy with gemcitabine (CT) resulted in 15 months survival while it was only 11.7 months in those who received continued CT alone (p=0.0009). Otherwise, a study by Moore et al has suggested a potential role of erlotinib combined with gemcitabine which needs confirmation.

OBJECTIVES OF THE STUDY:

Primary: To assess whether administering a chemoradiotherapy in patients whose tumor is controlled after 4 months of induction chemotherapy (CT) increases survival compared to continue the same CT.

Secondary:
- To assess whether erlotinib combined with gemcitabine and administered as maintenance treatment increases progression free survival compared to gemcitabine alone and without maintenance.
- To evaluate the response rate in the CT and CRT arms.
- To evaluate tolerance to erlotinib as maintenance treatment after the end of CT or CRT.
- To study the predictive molecular factors (survivin, K-ras, EGFR, PTEN, AKT) on survival.

TYPE OF STUDY Phase III multicenter prospective randomized international study.

STUDY POPULATION MAIN ELIGIBILITY CRITERIA
Eligibility criteria:
- Histologically proven adenocarcinoma of the pancreas
- De novo locally advanced non-resectable tumor (stage III according to the UICC 2002 classification),
- Measurable disease or evaluable (RECIST criteria)
- No prior abdominal radiotherapy nor chemotherapy for any reason
- Performance Status ECOG 0-2,
- Adequate biological tests (blood, liver and renal).

METHODS AND NUMBER OF PATIENTS:
First randomization: gemcitabine vs gemcitabine plus erlotinib (followed by erlotinib maintenance in patients with controlled tumor).
Second randomization in patients with controlled tumor: two additional cycles of chemotherapy vs chemoradiotherapy
Stratification criteria:
- first randomization: center, PS (0-1 vs 2),
- second randomization: center, initial arm (A vs B)
To increase median survival with CRT from 9 to 12 months, 600 patients are needed for second randomization. Taking into account that 30% of patients will progress before second randomization and 5% lost to follow-up, a total number of 820 patients are required for first randomization. Recruitment will be competitive among different countries (expected to be around 260 in France and 560 in the other participating countries).

| ADMINISTRATION SCHEDULE | First randomization:  
|                         | Arm A :  
|                         | - Gemcitabine 1000 mg/m² 30 minutes infusion on D1-D8-D15-D22-D29-D36-D43. Then, after 1st evaluation continue gemcitabine 6 infusions on D57-D64-D71-D85-D92-D99.  
|                         | Arm B :  
|                         | - Gemcitabine: 1000 mg/m² 30 minutes infusion on D1-D8-D15-D22-D29-D36-D43. Then, after 1st evaluation continue gemcitabine 6 infusions on D57-D64-D71-D85-D92-D99.  
|                         | - Erlotinib 100 mg dose per day at least one hour before or two hours after meals, during 4 months  
|                         | - Erlotinib 150 mg dose per day as maintenance therapy (see below)  
| 2nd randomization in patients whose tumor is controlled:  
| Arm 1: continue chemotherapy  
| Arm 2: chemoradiotherapy after a 1-month rest period (erlotinib must be suspended during CRT)  
| Resulting in:  
| Arm A1  
| - continue gemcitabine on every week, 6 infusions D113-D120-D127- and D141-D148-D155 (2 months). Then stop until progression.  
| Arm A2  
| - Chemoradiotherapy (ideally D127): radiation 54 Gy and concomitant capecitabine per os at a total dose of 1600 mg/m² (BID, 5 days per week ). Then stop until progression.  
| Arm B1  
| - continue gemcitabine on every week, 6 infusions D113-D120-D127- and D141-D148-D155 (2 months).  
| - erlotinib:  
| - with gemcitabine: 100 mg dose per day at least one hour before or two hours after meals, during 2 months  
| - After D155 continue with erlotinib alone 150 mg/day until progression  
| Arm B2  
| - Chemoradiotherapy (ideally D127): radiation 54 Gy and concomitant capecitabine per os at a total dose of 1600 mg/m² (BID, 5 days per week ).  
| - Reintroduction of erlotinib alone 150 mg/day within 15 days after CRT completion and until progression (or limiting toxicity)  
| At progression, further treatment is at investigator’s discretion. When feasible, secondary surgical resection is open at any evaluation in each arm.  
| STUDY PERIOD :  
| Theoretical beginning of the study: september 2007  
| Theoretical end of inclusion: march 2010  
| Theoretical end of the study: january 2011  

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2. SCIENTIFIC BACKGROUND

Adenocarcinoma of the pancreas represents 2% of all cancers and 10% of gastrointestinal cancers. In 2000, 217,000 new cases were diagnosed worldwide and 212,000 deaths were registered (1, 2). The standardized incidence of this cancer is 5.8/100,000 in men and 3.2/100,000 in women. In France there are approximately 5000 new cases per year. Between 1980 and 2000, a yearly increase of 1.7% in men and 2.07% in women was recorded. Estimated survival in Europe is 16% at 1 year, 6% at 3 years and 4% at 5 years. In France it is 16.6% at 1 year and 3.2% at 5 years (1).

Most of these cancers are not resectable at diagnosis because of the presence of nearby metastases or invasion of nearby structures of the pancreas, in particular the arterial axes (celiac trunk, hepatic artery and/or superior mesenteric artery) (locally advanced form: LA).

Certain differences between LA and metastatic cancers justify studying these patients separately in therapeutic trials:

- 1) median survival in the metastatic form is 6-8 months, in non-metastatic LA tumors this survival is significantly longer (9-12 months) (3);
- 2) strategy is different as metastatic forms only required systemic chemotherapy, while non-resectable, non-metastatic LA forms may be « locally » treated by radiotherapy and in very favorable cases (good response to chemoradiotherapy as a first line treatment) by secondary surgical resection.

The present trial only includes patients with LA adenocarcinoma of the pancreas.

1) Comparison of CT and CRT: the available therapeutic options to manage LA pancreatic cancers are systemic chemotherapy (CT) or chemoradiotherapy (CRT) but the choice of one or the other of these treatments is controversial (4-9). Moreover, it is difficult to have a clear opinion because in most series, patients with LA and metastatic carcinomas have not been studied separately. The administration of CRT as a first line treatment in patients with cancer of the pancreas has the following drawbacks: it is administered in certain cases to patients in poor condition at diagnosis (ECOG PS 2) who cannot tolerate an aggressive treatment; moreover it is well known that metastases may rapidly occur (< 3-4 months) in 20%-30% of patients receiving CT.

In a retrospective study (4), the GERCOR group has proposed a different strategy: initial treatment with CT for three months and if the tumor is controlled (partial response or stabilization), administration of CRT to finalize treatment. This strategy should however be validated prospectively.

2) Role of erlotinib: one study has shown that the association of this tyrosine kinase inhibitor with gemcitabine resulted in modest but significant increased survival; in this study, only 12% had LA disease (21). Thus, a prospective validation of erlotinib efficacy is mandatory for this particular population. Furthermore, erlotinib could also have a role as maintenance therapy when CT or CRT is completed with always persistant disease.

3) Ancillary study:
There are very few studies on the prognostic value of genetic modifications in the response to treatment with gemcitabine and erlotinib. This study will evaluate the status of the pro-apoptotic genes (survivin, bcl-2) and the signalling pathways PI3K/AKT/mTOR (K-ras, EGFR and AKT) to try and define prognostic factors (delay before development of metastases) and response to proposed treatments.

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3. RESULTS IN THE LITERATURE

A- Chemotherapy vs Chemoradiotherapy

3.1. Chemotherapy

3.1.1. Main negative trials
Generally, the response rate obtained with CT is no more than 10% (3). Moreover it is very difficult to evaluate LA tumors by scan because of the desmoplastic nature of these lesions. Numerous molecules have been tested in these cancers but with little success. High expression of the MDR gene is one of the explanations for these failures. Nevertheless, the phase III study by Burris et al (10) showed that gemcitabine significantly increased median survival (5.61 months vs 4.41 months) as well as one year survival (18 % vs 2 %), compared to 5-fluorouracile (5-FU) and also resulted in improvement in the patient’s general condition (23.8 % vs 4.8 %) according to the so-called « clinical benefit » criteria (analogical visual scale of pain, reduction in consumption of analgesics, weight gain) (11-13). Thus, since 1997 gemcitabine has been a standard treatment for cancer of the pancreas. The non-randomized study by Storniolo et al. (14), including 3013 patients with metastatic cancer of the pancreas showed a response rate of 12% and a median survival of 4.8 months.
Since then, numerous phase II and III trials have tried to increase the efficacy of CT by combining gemcitabine with other molecules (3, 15-29). The main results are shown in table 1.
Table 1. Main results of associations with gemcitabine *(from Hochster, ref 3)*

<table>
<thead>
<tr>
<th>Products</th>
<th>Reference</th>
<th>n patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(% LA cancers)</td>
<td>Association</td>
</tr>
<tr>
<td>5-FU</td>
<td>Berlin</td>
<td>326 (10 %)</td>
</tr>
<tr>
<td>5-FU (continu)</td>
<td>Riess</td>
<td>466 (23 %)</td>
</tr>
<tr>
<td>5-FU (continu)</td>
<td>DeConstanzo</td>
<td>91 (27-33%)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Herrmann</td>
<td>315 (20-21%)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Heinemann</td>
<td>195 (NA)</td>
</tr>
<tr>
<td>Oxaliplatin*</td>
<td>Louvet</td>
<td>313 (30-32%)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Moore</td>
<td>569 (24-25%)</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Rocha-Lima</td>
<td>195 (20-21%)</td>
</tr>
<tr>
<td>Exatecan</td>
<td>O’Reilly</td>
<td>349 (21-22%)</td>
</tr>
<tr>
<td>Permetrexed</td>
<td>Richards</td>
<td>330 (NA)</td>
</tr>
<tr>
<td>Tipifarnib</td>
<td>van Custem</td>
<td>688 (23-24%)</td>
</tr>
<tr>
<td>PEFG*</td>
<td>Reni</td>
<td>99 (29-30%)</td>
</tr>
<tr>
<td>Gemox/Gem FDR*</td>
<td>Poplin</td>
<td>833 (12%)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Cunningham</td>
<td>533 (12%)</td>
</tr>
</tbody>
</table>

*gemcitabine fixed dose (10 mg/m²/mn) **cisplatin, epirubicine, 5-fluorouracil and gemcitabine

In a phase III study comparing gemcitabine with the combination gemcitabine-oxaliplatin (GemOx : 1000 mg/m² continuous perfusion with oxaliplatin 100 mg/m² in 2 hours), we showed a non-significant improvement in survival with the combination therapy (9 months vs 7.3 months, p = 0.13) (20). A meta-analysis of this study with a study by our German colleagues who used a different platine salt (cisplatine), showed a significant tendency in favor of the gemcitabine-platine salt combination for improved progression free survival (6 months vs 3.75 months, HR: 1.34, p = 0.03) and for overall survival (9.0 months vs 7.25 months, HR = 1.23, p =0.0031)(27). However, an American study (E6201) presented at the ASCO meeting in June 2006 by Poplin et al. (28) did not confirm these results. These authors randomized 833 patients with LA (20 %) or metastatic cancer (80 %) to receive one of the three following treatments: a “standard” perfusion of gemcitabine 1000 mg/m² for 30 mn, a continuous perfusion of 1500 mg/m²mg/mn or a combination therapy as in the GemOx schedule that we used previously. A total of 280, 277 and 276 patients were treated in each arm and the median survival was 4.96, 6.01 and 6.47 months, respectively, with no statistical difference. As a result, the GemOx schedule was not retained as the new standard for the treatment of non-resectable pancreatic cancer.

Finally, two recently reported combinations with gemcitabine appear to be more effective than gemcitabine alone: erlotinib and capecitabine (Table 1).
3.1.2 Combination gemcitabine-capecitabine (Xeloda®):
In the study by Cunningham et al (29), 533 patients were randomized to receive gemcitabine alone or in combination with capecitabine at a dose of 1600 mg/m² D1-D21. Thirty percent of these patients had LA cancer. The response rate (14.2% vs 7.1%) and median survival (8.4 months vs 7.3 months, HR: 0.80, IC95 %: 0.65-0.98) showed better results with the gemcitabine-capecitabine combination. These results contradicted those of a previous study by Herrman et al. (18) which did not show that this combination was more effective (Table 1).

3.1.3 Combination gemcitabine-erlotinib (Tarceva ®)

3.1.3.1 Rationale for administering erlotinib in cancer of the pancreas

The epidermal growth factor receptor (EGFR) plays an important role in the development and progression of different human cancers (30-45). This transmembrane glycoprotein is composed of a single polypeptide chain of 1186 amino acids, with extracellular, transmembrane and intracellular regions (30-32). The binding of ligands (TGF-α, ...) initiates a cascade of events starting with receptor dimerization then auto-phosphorylation by a tyrosine kinase. EGFR is overexpressed in adenocarcinoma of the pancreas. (38).

Erlotinib selectively inhibits intracellular phosphorylation of type 1 EGFR (HER1), which is normally expressed on the surface of cancer cells. A quinazoline analogue causes reversible inhibition of the EGFR-TK expressed on the surface of normal and tumor cells. In in vitro models, EGFR-phosphotyrosine inhibition results in arrested cell growth and/or tumor cell death.

EGFR over-expression is present in 30-60% of pancreatic cancers (33-39). Xion et al. (39) summarized the role of EGFR in the Raf-MEK-ERK signalling pathway, and in the control of proliferation and resistance to apoptosis in cancer of the pancreas. Tan et al. (40) like Uegaki et al. (41) confirmed the role of EGFR in cancers of the pancreas via the activation of MEK/ERK.

This EGFR over-expression was the rationale for studying erlotinib for the treatment of cancer of the pancreas.

3.1.3.2 Therapeutic trials

Porterfield et al. (42) performed a phase II study in 14 patients who were treated with combination gemcitabine-erlotinib. The rate of tumor control was 70%. The most frequent toxic reactions included: skin rash, neutropenia, fatigue, nausea and diarrhoea.

The study by Moore et al. (21) randomized 569 patients to receive gemcitabine with a placebo (n = 284, 282 patients were finally evaluated) or a combination of gemcitabine-erlotinib (100 mg/d) (n = 285 patients, 280 patients were finally evaluated). Patient characteristics were similar in the two groups. The rate of LA cancers was 25%. The gemcitabine-erlotinib combination was more effective than gemcitabine alone for tumor control (57.5% vs 49.2%) and overall survival (6.37 months vs 5.91 months, HR=0.81; IC 95%: 0.69-0.99; p=0.025). Toxicity was acceptable and the reasons for dose reduction were similar in both treatment arms (skin rash 4% v 0%), diarrhoea (2% vs <1%), intercurrent diseases, (2% vs <1%), compliance (3% vs 0%), hematological toxicity (<1% vs 0%), or other (5% vs 3%).

The notion of maintenance treatment with erlotinib was hardly discussed in any previous studies. (43-45).

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3.2. Chemoradiotherapy

In the 1980’s, CRT with 5-FU was shown to be more effective than radiotherapy alone in the treatment of adenocarcinoma of the pancreas (46). Two randomized studies comparing CRT and CT showed contradictory results: the first from the ECOG group did not show any difference in the two types of treatment (47) while the second, published by the GastroIntestinal Study Group (GITSG), showed that CRT was more effective than CT (48).

Although CRT was shown to reduce pancreatic tumor mass (49), reported response rates (0-59%) and secondary resectability (0-64%) varies markedly from one study to the other. Interesting median survival rates were reported in patients with a good tumor response after CRT, allowing secondary surgical resection (50, 51). In the study by Snady et al. (50), 159 patients with resectable pancreatic cancer (n = 91) or nonresectable LA cancer (n = 68) were treated. The patients in the first group were operated directly while the second group underwent CRT. Twenty nine percent of the latter patients were able to undergo secondary tumor resection and their survival was better than the former, surgically treated group (23.6 months vs 14 months). In a second study by Sa Cunha et al. (51), 21 % of patients with inoperable tumors due to arterial invasion were able to undergo a secondary cephalic pancreaticoduodenectomy (PD), with a median survival after surgery of 40 months.

Nevertheless, the administration of CRT as a first line treatment in patients with cancer of the pancreas has the following drawbacks: it is administered in certain cases to patients in poor condition at diagnosis (OMS 2) who cannot tolerate an aggressive treatment; moreover it is well known that 20%-30% of patients receiving CT will develop metastases during the first three months of treatment.

The French FFCD-SFRO prospective study by Chauffert et al. (52) presented at the ASCO 2006 meeting compared gemcitabine chemotherapy to CRT with 5-FU and cisplatin for the first time in patients with LA cancer of the pancreas. The study was discontinued after including 119 patients because an intermediate analysis showed poorer survival in the CRT arm– which was not the initial hypothesis - (8.4 months for CRT vs 14.3 months for gemcitabine, p = 0.014). More in depth analysis of the results is ongoing. The toxicity of the CRT schedule may partially explain these results.

In a retrospective study recently published by GERCOR, Huguet et al. (4) studied the effect of CRT on survival in 181 patients with LA cancer of the pancreas, who had been treated in phase II and III chemotherapy studies. Fifty three (29.3 %) of these patients progressed to metastatic disease after three months of CT and therefore did not receive CRT. The investigators were given the choice to continue CT or administer CRT with 5-FU in the 128 remaining patients whose disease did not progress with CT. A total of 72 patients (56%) received final CRT (group A) and 25 (44%) continued CT. The two groups had similar clinical characteristics, and results of initial CT. The results showed that CRT improved progression free survival (10.8 months vs 7.4 months, p = 0.005) and median overall survival (15 months vs 11.7 months (p = 0.0009) (4).

In a phase II trial Mishra et al. (52) administered CT (gemcitabine and irinotecan) to 20 patients with LA adenocarcinoma of the pancreas. Thirty five percent of these patients had disease progression after two cycles of CT. The others received CRT (with gemcitabine as the radiosensitization agent) and their survival was 9.6 months.

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In their series, Epelbaum et al. (54) proposed initial treatment with gemcitabine, and if the tumor was controlled, secondary CRT (sensitizing agent: gemcitabine 400 mg/m² three times per week), then maintenance treatment with gemcitabine. Ten of the twenty treated patients (50 %) showed a clinical improvement with gemcitabine and received CRT. Four of them (20 %) had a partial response and three others (15 %) were able to undergo a secondary pancreatic resection, two of these patients had negative histological results, while the third only had a residual fibrous mass after surgery. Median survival for the 20 patients was 8 months and in patients who received CRT, the limit had not yet been attained at publication. (54).

**Rationale for using capecitabine in association with radiotherapy**

Since 2000, 13 studies have been published including a total of 433 patients who have received radiotherapy-capecitabine treatment (55). Blanquicett et al. (56) treated athymic mice that received injections of pancreatic cancer cell lines (BxPC-3) 28 days before the study. The protocol included CRT with capecitabine (2 Gy 5 days in a row, D0 and D24). Only one thigh was radiated. Capecitabine (350 mg/kg) was administered from D0 to D13 and from D24 to D37, associated with celecoxib. Results showed a synergic effect with the CRT-celecoxib association on the treated thigh, while tumor growth (+ 23 %) was noted on the non-radiated thigh (p<0.001). No total tumor response occurred with this treatment. Thymidine phosphorylase, dihydropyrimidine dehydrogenase and cyclooxygenase-2 mRNA were not modified in the tumors, whether they were radiated or not, suggesting that these markers are not predictive of response to treatment. On the other hand the immunohistochemical Ki-67 response to treatment was correlated to tumor response, whatever the treatment (capecitabine alone or with radiotherapy).

Saif et al. (57) treated 15 patients with LA cancer of the pancreas with 50.4 Gy radiation and capecitabine (dose increased from 600 to 1 250 mg/m2 with twice daily administration, 5 days per week). After CRT, patients with a controlled tumor (objective response or stabilization) received 2000 mg/m² of capecitabine in two daily doses for 14 days every three weeks. A grade 3 incapacitating diarrhoea was observed in 2 of the 6 patients treated with capecitabine at the 1000 mg/m² dose associated with radiotherapy. Three patients (20%) had a partial response. The recommended dose of capecitabine with CRT in a phase II study is 800 mg/m² twice a day, Monday through Friday.

In a study by Vaishampayan et al (58), 32 patients received an association of radiotherapy (45-64 Gy) and capecitabine. The response rate was 36% and tumor control (objective response + stability) was obtained in 64% of these cases. Hematological or gastrointestinal grade 3 or 4 toxicity was observed in 9% and 7% of cases respectively; the other adverse toxic reactions (diarrhoea, fatigue) were rare (< 5 %). In another study by Hashem et al., 21 patients received 54 Gy radiation with capecitabine. The response rate and tumor stability was 35 % and 43 %, respectively. Grade 3 or 4 neutropenia occurred in 10% and 5% of cases, respectively.

In a study by Ben Josef et al (59), 15 patients received CRT for LA cancer (n=18) or as part of adjuvant pancreatic resection (n=7). The median dose of radiation was 54 Gy. Capecitabine was administered at a dose of 1600 mg/m² per day divided in two doses. Only one patient (7 %) had grade 4 gastrointestinal toxicity, in the form of a gastric ulcer which responded to medical treatment. Two of the 8 patients with a LA tumor were able to undergo secondary resection and their actuarial survival at one year was 69%.

Capecitabine has been associated with CRT in other tumor locations with good results, in particular cancer of the rectum (55, 60, 61).
B- Potential interest of combining erlotinib with gemcitabine then erlotinib as maintenance treatment in LA cancers of the pancreas.

Erlotinib-gemcitabine combination

The combination gemcitabine-erlotinib was more effective than gemcitabine alone in the study by Moore et al. (21) described above. Marketing approval was obtained in the USA in 2005. It was obtained in France in December 2006, for the indication of metastatic cancer only.

As a result a study re-evaluating the effect of erlotinib in a large series of patients with LA cancer to determine the possible beneficial role of this molecule for this indication is needed. Erlotinib will be administered in two of the 4 treatment arms combined with gemcitabine for the four first months (100 mg/d by oral route), then as maintenance treatment (150 mg/d) in patients who have completed CT or CRT in the protocol. This maintenance treatment will be continued until there is disease progression. Thus, we can evaluate both tolerance to the drug and its possible role in delaying tumor progression.

Maintenance treatment

The idea of maintenance treatment by a targeted therapy has been investigated, in particular in lung cancers, with gefitinib and erlotinib with varying results (43-45). Only one study by Ianitti et al. (45) mentions its use in adenocarcinoma of the pancreas, but the small number of patients in this phase I-II study makes it impossible to draw conclusions about the efficacy of this option.

C- Prognostic biological factors of response to the proposed treatments

The following molecular markers could influence response to treatment with EGFR inhibitors:
1) the PI3K/AKT/mTOR signalling pathway (phosphorylated AKT, phosphorylated S6K1 4E-BP1, EGFR),
2) markers reflecting a deficiency in certain signalling apoptosis pathways (Bcl-2, Bcl-Xl, p53, Ki67), in the cell cycle (cyclin D1) and annex signalling pathways (MAPK, Fas, FasL...).

The presence of alterations in the EGFR gene (mutations or deletions of exons 19 and 21 in particular) seem to influence response to treatment with erlotinib or gefitinib, which has thus far been mainly studied in patients with non-small cell lung adenocarcinoma (62-70). The effect on survival is controversial; results differ between studies of erlotinib alone and those combined with chemotherapy (63, 70, 71). Non-smokers seem to have a better response to treatment (71), in particular those with an EGRF mutation in the tyrosine kinase domain (62, 73).

The presence of K-ras gene mutations, on the other hand, seems to be correlated to a poorer response to erlotinib treatment (62, 70, 72, 73). The induction of survivin appears to reduce the efficacy of erlotinib (74).
4. OBJECTIVES OF THE STUDY

4.1. Hypotheses tested

- Our main hypothesis is that CRT could increase survival in patients with LA cancer of the pancreas compared to CT alone.

- Erlotinib may be useful in locally advanced tumors with an acceptable tolerance.

- Biological factors may influence the response to CT, erlotinib and CRT.

4.2 Primary objective

To assess whether administrating a chemoradiotherapy in patients whose tumor is controlled after 4 months of induction chemotherapy (CT) increases survival compared to continue the same CT.

4.3 Secondary objectives

- To assess whether erlotinib combined with gemcitabine and administered as maintenance treatment increases progression free survival compared to gemcitabine alone and without maintenance.
- To evaluate the response rate in the CT and CRT arms.
- To evaluate tolerance to erlotinib as maintenance treatment after the end of CT or CRT.
- To study the predictive molecular factors (survivin, K-ras, EGFR, PTEN, AKT) on survival.
5. EXPERIMENTAL PLAN

This is a prospective international multicenter phase III study in patients with locally advanced, non-resectable, non-metastatic cancer of the pancreas.

The inclusion period is 30 months and patient follow up at least 10 months.

5.1. Choice of experimental plan and justification

- Very few studies have been performed to specifically study locally advanced cancer of the pancreas, and there are no prospective studies on the therapeutic strategy proposed in this protocol in a large number of patients to evaluate the influence of CRT on survival in patients who have been selected by initial CT.
- Although the role of CRT on survival is the main objective of this study, we will also obtain information on the role of combination of gemcitabine and erlotinib in tumor control in non-metastatic cancers, and on tolerance to and the possible use of erlotinib in maintenance therapy to delay disease progression after CT or CRT.
- The addition of erlotinib to gemcitabine could result in a different control rate before CRT or CT continuation allocation. To avoid a possible imbalance, a second randomization is proposed.
- In such a multicenter prospective study, our hypotheses on median survival (9 months for CT alone, 12 months for CRT) were lowered compared to that reported in our retrospective study (4).
- The ancillary study will evaluate some genes involved in tumor growth, response to treatments and survival.
  1) Anti-apoptotic genes that play a role in reduced survival and chemoresistance (survivin, bcl-2) and the K-ras gene which is mutated in 80% of cases and provokes a “proliferation signal” increasing tumor growth.

EGFR and the genes involved in the downstream signalling pathway (ADT, PTEN) have rarely been studied in adenocarcinoma of the pancreas. Although the immunohistochemical expression of EGFR does not seem to make it possible to predict the response to anti-EGFR targeted therapies, certain mutations of this gene in the kinase domain seem to affect treatment efficacy.

For feasibility and cost, immunocytochemistry will be used to study certain genes (survivin, bcl-2, EGFR, AKT and PTEN) because some commercial antibodies are available and this technique is relatively easy. It is not realistic to use complex molecular biology techniques on a large scale in this study, because numerous centers will be participating. On the other hand, the search for mutations by RT-PCR in certain key genes for the response to treatment (EGFR and K-ras) will be performed by Pr Buscail (Toulouse, INSERM U531, France) on investigators request.
The difficulty of obtaining pancreatic tumor tissue in non-surgical patients is a specific problem in adenocarcinoma of the pancreas. The samples obtained from a fine needle are often paucicellular.

As a result, techniques such as RNA microchips cannot be developed in this study. On the other hand, it will be possible to perform immunohistochemical studies, and in selected centers, search for mutations in certain genes.
5.2. Study plan

1: Chemotherapy (no RT)
- A1 Gemcitabine 2 months, then stop until progression
- B1 Gemcitabine + Erlotinib (100 mg/d) 2 months, then erlotinib maintenance (150 mg/d) until progression

2: Chemoradiotherapy (CRT)
- A2 CRT then stop until progression
- B2 CRT then erlotinib maintenance (150 mg/d) until progression

At progression: further treatment at investigator discretion
Surgical resection can be considered at any evaluation.
5.3. Randomization and treatment arms

5.3.1. Randomization procedure
5.3.1.1. First randomization (R1)
An initial randomization will be carried out using a minimization technique, center, ECOG PS (0-1 versus 2). The patients will be randomized between gemcitabine alone and gemcitabine + erlotinib followed by erlotinib maintenance.

A central randomization by eCRF will provide treatment allocation as soon as inclusion criteria and exclusion criteria are fulfilled as well as responsible physician name, patient anonymous identification (initials), birthdate, sex, and minimization factors.

5.3.1.2. Second randomization (R2)
After the completion of the 13 weeks of chemotherapy (with or without erlotinib), a second evaluation will be performed to decide the following treatment for patients with stable disease or responders, and whom PS ≤ 2: chemotherapy or chemoradiotherapy. Patients will be stratified according to the centre and initial arm (A or B).

5.3.2. Treatments arms

First randomization:

Arm A:
- **Gemcitabine**: 1000 mg/m² 30 minutes infusion on D1-D8-D15-D22-D29-D36-D43. Then, after 1st evaluation continue gemcitabine 6 infusions on D57-D64-D71-D85-D92-D99.

Arm B:
- **Gemcitabine**: 1000 mg/m² 30 minutes infusion on D1-D8-D15-D22-D29-D36-D43. Then, after 1st evaluation continue gemcitabine 6 infusions on D57-D64-D71-D85-D92-D99.
- **Erlotinib**: 100 mg dose per day at least one hour before or two hours after meals, during 4 months
- **Erlotinib**: 150 mg dose per day as maintenance therapy (see below)

2nd randomization in patients whose tumor is controlled:

Arm 1: continue chemotherapy

Arm 2: chemoradiotherapy after a 1-month rest period (erlotinib must be suspended during CRT)

Resulting in:

Arm A1
- Continue gemcitabine on every week, 6 infusions D113-D120-D127- and D141-D148-D155 (2 months). Then stop until progression.

Arm A2
- **Chemoradiotherapy (ideally D127)**: radiation 54 Gy and concomitant capcitabine per os at a total dose of 1600 mg/m² (in two divided doses of 800 mg/m² 5 days per week). Then stop until progression.
Arm B1
- continue gemcitabine on every week, 6 infusions D113-D120-D127- and D141-D148-D155 (2 months).
- erlotinib:
  - with gemcitabine: 100 mg dose per day at least one hour before or two hours after meals, during 2 months
  - after D155 continue with erlotinib alone 150 mg/day until progression

Arm B2
- Chemoradiotherapy (ideally D127): radiation 54 Gy and concomitant capecitabine per os at a total dose of 1600 mg/m² (in two divided doses of 800 mg/m², 5 days per week).
- Reintroduction of erlotinib alone 150 mg/day within 15 days after CRT completion and until progression (or limiting toxicity)

At progression, further treatment is at investigator’s discretion.
When feasible, secondary surgical resection is open at any evaluation in each arm.

Assessments are planned at months M2, M4, M7, M9, M11, then every two months. If the tumor has progressed, the above mentioned treatment will be stopped and the next treatment will be discussed by the investigators in a pluridisciplinary meeting.

5.4. Treatments, products used, mode of administration

5.4.1. Gemcitabine

- **Commercial name**:
  GEMZAR® 1000 mg, lyophilized powder for parenteral use (IV).
  GEMZAR® 200 mg, lyophilized powder for parenteral use (IV).

- **Common International Name (DCI)**
  Gemcitabine hydrochloride.

- **Chemical name**
  2'-deoxy-2' chlorydrate, 2'-difluorocytidine (dFdc).

- **Chemical formula**
  C₉H₁₁F₂N₃O₄. Hcl

- **Experimentation code**
  LY 188011

- **Pharmacological class**
  Gemcitabine, with a chemical structure close to cytosine arabinoside (Ara-C), is a cytotoxic antineoplastic belonging to a group of anti-metabolites, obtained by synthesis of cytosine, a nucleotide analogue.
  Gemcitabine is a difluoride nucleotide, analogue of deoxycytidine

Form and presentation
GERCOR - LAP 07 v1.1 – 12th November 2007
• **Pharmaceutical form**
  Lyophilized powder for parenteral use (IV)

• **Packaging and doses**
  - Vial containing 200 mg of gemcitabine base (capacity 10 ml).
  - Vial containing 1000 mg of gemcitabine base (capacity 50 ml). Type I sterile vial (Ph. Eur.), closed with a rubber stopper and sealed with an aluminium band, associated with a polypropylene cap.

**Physico-chemical characteristics**

Gemcitabine comes in the form of white or beige sterile lyophilized powder.

The pH of the aqueous solution of 1% gemcitabine hydrochloride is between 2 and 3.

**Stability and incompatibility**

• **Stability of the lyophilized powder**
  Shelf life: 2 years
  Storage conditions: the lyophilized powder should be stored at less than 30°C.

• **Stability of the prepared solution**
  Shelf life: 24 hours.
  Storage conditions: the reconstituted solution should be stored at between +8° and +30°. Refrigeration is not recommended, because it could lead to crystallization. Unused solution should be discarded.

**Incompatibilities**

Although no incompatibilities have been identified, it is recommended not to mix gemcitabine solutions with other medications.

**Mode of administration**

Intravenous route only. Gemcitabine is well tolerated by parenteral infusion and is generally easy to administer. Cases of reaction at the injection site are rare; no case of cutaneous necrosis has been reported.

**Instructions for use and handling**

The usual precautions for handling anticancer drugs should be respected.

The only solution recommended to reconstitute gemcitabine powder is 0.9% sterile Sodium Chloride Injection without added preservatives. Although no incompatibility has been identified, it is still recommended not to mix gemcitabine solutions with other medications. For problems of solubility, the upper limit gemcitabine concentration after preparation is 40mg/ml. Drug preparations above 40mg/ml should be avoided because they may not be completely dissolved.

• **Reconstitution:**
  Add at least 5 ml of 0.9% Sodium Chloride Injection to the 200 mg bottle or at least 25 ml of 0.9% Sodium Chloride Injection to the 1000 mg vial. Shake until the product is fully
dissolved. Gemcitabine solutions can be administered as prepared above or be further diluted with 0.9% Sodium Chloride Injection.

Before administration, preparations for IV administration should be visually inspected to detect particulate matter or discoloration.

Like any cytostatic product, gemcitabine hydrochloride should be handled with caution. The unused products should be destroyed according to hospital procedures for cytotoxic products.

5.4.2. Erlotinib

- **Commercial name**: Tarceva®
- **DCI**: erlotinib hydrochloride
- **Composition**
  - Active ingredient: erlotinib hydrochloridum.
  - Excipients: excipiens pro compresso obducto.

- **Pharmaceutical form and quantity of the active ingredient by unit.**
  - 25 mg film coated tablets (round, biconvex; with name « Tarceva 25 » and yellowish brown logo printed on one side; white to yellowish), 100 mg (round, biconvex; with the name « Tarceva 100 » and the grey logo on the front; white to yellowish) or 150 mg (round, biconvex; with the name « Tarceva 150 » and the brown logo on the front; white to yellowish): Boxes of 30 tablets, in PVC sealed blister packs.

- **Code ATC**: L01XX34

- **Mechanism of action/Pharmacodynamics**
  Erlotinib is a tyrosine kinase inhibitor of the epidermic growth factor (EGFR, HER1). The HER1/EGFR is expressed on the surface of normal cells and cancer cells. In non clinical models, HER1/EGFR tyrosine kinase inhibition results in arrested cell growth and/or cell death. There are no existing studies on the affect of this product on tumor tissue.

- **List of common excipients**
  - **Tablet core**: lactose monohydrate, cellulose microcrystalline (E460), sodium starch glycolate type A, sodium laurilsulfate, magnesium stearate (E470b). **Tablet coating**: hydroxypropyl cellulose (E 463), titanium dioxide (E 171), macrogol, hypromellose (E 464). **printing ink yellow**(cp 25 mg) : shellac (E 904), yellow iron oxide (E 172). **printing ink grey** (cp 100 mg) : shellac (E 904), iron oxide yellow (E 172), iron oxide black (E 172), (E 171). **printing ink brown** (cp 150 mg) : shellac (E 904), iron oxide yellow (E 172), iron oxide black (E 172), iron oxide red (E 172).

- **Posology**: in between meals (≥ 1h before or ≥ 2h after meals) with 200 mL of water.

- Concomitant use of CYP3A4 substrates and modulators may require dose adjustments.

5.4.3. Capecitabine

- **Commercial name**: XELODA®
• **Common international name** (DCI)  
  Capecitabine

• **Chemical name**  
  5'-déoxy-5-fluoro-N-[(pentyloxy)carbonyl]-cytidine

• **Chemical formula**  
  C₁₅H₂₂FN₃O₆

• **Experimentation codes**  
  L01BC

• **Pharmacological class**  
  Cytostatic agent (anti-metabolite), precursor of the cytotoxic fraction of 5-FU administered by oral route.

**Pharmacodynamic properties**  
Capecitabine is a non-cytotoxic fluoropyrimidine carbamate administered by oral route which acts as a precursor to the cytotoxic fraction of 5-FU. Activation of capecitabine follows several enzymatic steps. The enzyme involved in the final conversion into 5-FU, thymidine phosphorylase is located in tumor tissue but also in healthy tissue at lower doses.

**Form and presentation**

• **Pharmaceutical form**  
  Film coated tablets for oral intake

• **Packaging and doses**  
  - 150 mg film coated tablets (box of 60)  
  - 500 mg film coated tablets (box of 120)  
  Excipients: microcristalline cellulose, croscarmellose sodium, hypromellose, anhydrous lactose, magnesium stearate.  
  Film coating: hypromellose, talc, titanium oxide, yellow and red iron oxide.

  Unused products should be destroyed according to hospital procedures for the treatment of cytotoxic waste products.

5.4.4. **Radiotherapy**

5.4.4.1. **Introduction**  
Concomitant chemoradiotherapy will begin 4 weeks (ideally D127) after the last cycle of chemotherapy and less than 6 weeks in patients who are assessed as being without disease progression and with a performance index of less than 2.
5.4.4.2. Definition of target volumes
To define target volumes, a simulation scan must be performed in the treatment position. Injection of contrast medium is recommended for better definition of anatomical structures, in particular the celiac trunk and the superior mesenteric artery. Slices should be obtained every 3–5 mm. Frontal and sagittal reconstructions will then be made.

The following volumes will be defined based on the ICRU 50 report:
- The macroscopic volume (Gross Tumor Volume, GTV) should be drawn on the simulation scan slice by slice using 3D planning software or simulation scan software;
- the anatomoclinical target volume (Clinical Target Volume, CTV) is defined as the GTV as well as the peripancreatic lymph nodes, second order lymph node relays (mesenteric, transverse mesocolon, hepatic), and third order (celiac lymph nodes, interaorticocaval, left pararenal);
- the initial planning target volume (PTV1, Planning Target Volume 1) includes the CTV with a 2 cm margin in all directions. The PTV1 should follow the following standardized limits unless there are specific anatomical requirements: the upper limit at the level of disks D10-D11; the lower limit at disks L3-L4; the posterior limit passing in between disks D11 to L3; the anterior limit 2cm in front of the CTV anterior limit. For tumors of the head of the pancreas, at least 2/3 of the left kidney should be protected when calculating, because approximately half the right kidney will be radiated. For tumors of the body and tail of the pancreas, half of the left kidney is often radiated, so at least 2/3 of the right kidney should be protected.
- the reduced planning volume (PTV2) is limited to the GTV and para-aortic retroperitoneal lymph nodes between the celiac trunk and the superior mesenteric artery with a safety margin of 2cm in all directions. The PTV2 is included in the PTV1.

5.4.4.3. Organs at risk
The organs at risk are the kidneys, the spine and the liver. They should all be drawn on the simulation scan so that a 3D dosimetric study can be performed with the Dose Volume Histogram (DVH), to confirm that maximum-tolerated doses are not exceeded. The maximum-tolerated doses are the following:
- kidneys: an entire kidney should receive a dose of less than 20 Gy. Otherwise, 2/3 of the other kidney should be outside the radiated volume. If there is only one kidney, 2/3 of the kidney must be outside the radiated volume. If one of the two kidneys is completely outside the radiation beam, the other can receive 30 Gy over 2/3 of its volume, or even the entire prescribed dose over 1/3 of its volume. If there is any doubt about renal function, or if radiation of a large part of the kidney is inevitable because of the location of the tumour, a
bilateral renal isotopic scintigraphy is recommended to evaluate function in each kidney separately.

- spine: the maximum-tolerated dose for the spinal is 45 Gy in a conventional fractionated schedule (1.8 to 2 Gy per session, 5 sessions per week).
- liver: the maximum-tolerated dose for the liver is 30 Gy over 3 weeks for the entire liver, 35 Gy over 3.5 weeks for 2/3 of the liver, 50 Gy in 5 weeks for one third of the liver.

5.4.4.4. Radiation technique
An isocentric technique with a linear accelerator generating X photons of at least 6MV of energy will be used. On each day of treatment, PTV1 will be radiated with four isocentric beams, one anterior, one posterior, and two lateral. PTV2 will be radiated with two opposed beams, which may or may not be isoweighted, one anterior, one posterior, but which may also be oblique to reduce the dose received by the organs at risk, in particular the kidneys. Personalized shields or shields from a laminated collimator will be used to reduce the maximum dose.

The Dose Volume Histogram (DVH) of the GTV, PTV1 PTV2, as well as the kidneys, liver, and spine must be obtained to define the optimized dose distribution. The Beam Eye View (BEV) or digital reconstructions (Digitally Reconstructed Radiographs, DRR) of each beam will be printed out for quality control and planning. Dosimetry will be performed with software allowing 3D study of dose distribution. To reduce intestinal toxicity, hot points of more than 105% should be avoided.

5.4.4.5. Dose specification
The total prescribed dose at the reference point (isocenter) of the PTV is 54 Gy in 5 fractions of 1.8 Gy per week. At a dose of 45 Gy, the PTV will be reduced as defined above (PTV2). The total cycle should be administered in 6 weeks. A difference of ± 5% of the prescribed dose is authorized. The isodose 95% should completely surround the PTV. Hot points outside the PTV should be avoided. Minimum and maximum doses within the PTV should be determined and recorded.

5.4.4.6. Quality control
Throughout the entire radiotherapy schedule, the position of the isocenter should be checked at least once a week on portal images or validation photos by comparing it to the DRR or the simulation images.
5.4.4.7. Radiotherapy toxicity
In general, patients have more or less marked asthenia during radiotherapy. Radiation of one part of the stomach and of the celiac region can result in the following symptoms: nausea, loss of appetite, weight loss, and stress ulcers. A preventive anti-emetic treatment 1 hour before each radiation session is recommended. Radiation of one part of the large intestine can cause an increase in the frequency of bowel movements. To diagnose and manage side effects, patients will be monitored once a week throughout radiation therapy. During this weekly consultation, a clinical examination will be performed including the patient’s weight, performance status and consumption of analgesics as well as any new symptoms or side effects. Moreover, the patients will undergo a blood count, creatinine level and liver tests (AST, ALT, alkaline phosphatases (AP), γGT, bilirubin) to evaluate hematological and liver tolerance to treatment. All clinical or biological side effects will be graded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (http://ctep.cancer.gov/reporting/ctc_v30.html). If necessary, anti-emetic or anti-diarrhoea treatment can be prescribed to treat symptoms. The systematic prescription of anti-gastric secretion medicine (anti-H2 or PPI) is highly recommended during radiation as well as six months afterwards to reduce gastric acid secretion and prevent the risk of upper gastrointestinal ulcer.

5.4.4.8. Concomitant chemotherapy
During radiotherapy, capecitabine will be administered by tabs at a total dose of 1600 mg/m² (in two divided doses of 800 mg/m², 5 days a week).

5.4.4.9. Reintroduction of erlotinib
For patients in arm B2, erlotinib 150 mg/d will be reintroduced within 15 days after CRT completion until disease progression.

5.5. Duration and termination

5.5.1. Inclusion duration planned: 30 months
- First inclusion planned: September 2007
- Last inclusion planned: March 2010

5.5.2. Follow-up duration: 10 months

5.6. Stopping rules or discontinuation criteria
The decision to discontinue the study will be taken by the scientific council. An extraordinary meeting may be requested by the principal investigator or the methodologist, if serious adverse events or results occur which could require discontinuation of the protocol.

The following may also justify ending the study:
- Insufficient recruitment
- Publication of the results of a trial giving answer to the debated question

The decision to stop the study will be taken by the scientific council with advice of the independent committee. An extraordinary meeting can be requested by the principal investigator or the methodologist if serious adverse events or results occur which could require discontinuation of the protocol.

Rules for premature discontinuation due to toxicity:
(i.e. § 8.2. Dose modifications »)

5.7. Recruitment

Patient recruitment and selection will be performed in the Gastroenterology, Cancer and Radiotherapy units mentioned in the appendix 3. This list is subject to modification depending on later requests for participation by centers not mentioned on the list.

This is an intergroup trial with GERCOR, FFCD, FNCLCC and SFRO for France, the German group A.I.O., and American, Belgium and Australian groups to be defined for the international study. Other countries could join the trial.

All patients who are diagnosed with LA cancer of the pancreas in one of the participating centers will be evaluated for inclusion in the study. The decision to include eligible patients will be made during pluridisciplinary meetings including all participating centers. Patients will be informed by the gastroenterologist or oncologist co-investigators of the study who will obtain their informed consent. Informed consent will be obtained during the first meeting, once the diagnosis has been confirmed by biopsy.
6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Inclusion criteria

1. Age older than $\geq 18$

2. Patients with *de novo* locally advanced, histologically proven adenocarcinoma of the pancreas without distant metastases (stage III according to the UICC classification) and not considered for curative resection after pluridisciplinary discussion.

3. ECOG Performance Status $\leq 2$ (Appendix 2)

4. Estimated life expectancy $\geq 12$ weeks

5. No prior radiotherapy nor chemotherapy for any reason

6. Signed informed consent form

7. Polynuclear neutrophils $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L and hemoglobin $\geq 9$ g/dL

8. Total bilirubin $\leq 1.5$ N (N: upper limit of normal). In patients who have had a recent biliary drain and whose bilirubin is descending, a value of $\leq 3$ N (50 μmole/L) is acceptable.

9. AST and ALT $\leq 2.5$ N, alkaline phosphatase $\leq 5$ N

10. Albumin $\geq 25$ g/L

11. Creatinin $\leq 177$ μmol/L (2 mg/dL)

12. Female patients who are not menopausal and their partners must accept to use effective contraception throughout treatment and for 3 months after the end of treatment. All patients who are capable of becoming pregnant must take a pregnancy test which is negative within 72 hours before beginning treatment. The definition of effective contraception is left up to the decision of the investigator.
6.2. Exclusion criteria

1. Localized stage IA to IIB or metastatic cancer (stage IV) according to UICC
2. Previous chemotherapy for any reason
3. Previous abdominal radiotherapy
4. Allergy to one of ingredients in erlotinib
5. Prior treatment with an anti-EGFR
6. Cancer within the 5 years before inclusion, except for in situ cancer of the neck of the uterus or basal cell skin cancer.
7. Severe infection
8. Ophthalmic disease (inflammation, keratopathy or infection)
9. Symptomatic coronary or cardiac insufficiency, myocardial infarction or stroke within the last 6 months.
10. Unable to take oral treatments or with gastrointestinal disorders that could be associated with absorption disorders, untreated gastric or duodenal ulcer.
11. Pregnancy or breast feeding
12. Unable to follow for psychological, familial or geographic reasons.
13. Not affiliated with a social security regime.
14. Diarrhea ≥ grade 2 and/or uncontrolled diarrhoea

6.3. Patients withdrawal criteria

- Disease progression during treatment. FOLFOX is suggested as a second line therapy
- Limiting toxicity
- Patient refusal
- Investigator’s decision
- Lost to follow up
- Treatment delayed for more than 14 days for patients receiving gemcitabine alone or in association with erlotinib
- When toxicity is due to radiotherapy with a stop more than 7 consecutive days, except for patients who did already receive 5 consecutive weeks of radiotherapy who stop the treatment but remain included in the study

7. MANAGEMENT AND SCHEDULES

7.1 Patient management
7.1.1. Scheduling and content of visits
7.1.1.1. Pre-inclusion visit:
The aim of this visit is to confirm patient eligibility. It must be performed within the 14 days before first infusion of chemotherapy.

- Questions on the patient’s medical history, including a history of cancer, present or past tobacco addiction (to be quantified in pack-years), associated diseases such as cardiovascular disease, high blood pressure, atherosclerosis, stroke, as well as any other treatments the patient is taking.
- Clinical examination
- Biological tests
- Imaging tests (at most 3 weeks before inclusion).
- Information and signed written informed consent obtained from the patient

7.1.1.2. Weekly visits on each day of gemcitabine perfusion.

- Clinical assessment: clinical examination and details of side effects of CT that have occurred during the inter-treatment period as well as any other treatments the patient is taking.
- Biological tests performed within the three days before the clinical assessment.

7.1.1.3. Visit after CT or CRT completion:
End of treatment assessment must be performed within 14 days after the last CT or CRT session.

- Clinical assessment: clinical examination, details of any side effects of CT that have occurred during the inter-treatment period as well as any other treatments the patient is taking
- Biological assessment
- Imaging

7.1.1.4. Visit during maintenance therapy with erlotinib or follow-up:
Clinical, biological and imaging assessment every two months until tumor progression.

7.1.2. Medical acts, tests and analyses

7.1.2.1. Clinical assessment
Complete clinical examination including weight, height, ECOG Performance Status, vital signs, abdominal and skin examination.

7.1.2.2. Biological assessment
- Blood count, platelet count,
- Blood ionogram, calcemia, protidemia, albumin, creatinin, liver tests with bilirubin, AST, ALT, alkaline phosphatase
- CA 19-9

7.1.2.3. Imaging
- Thoracoabdominal scan with injection of contrast medium
- Other imaging tests (bone scintigraphy…): in case of clinical or biological signs.

7.1.2.4. Biopsy of the pancreas before treatment
Biopsy of the pancreas will either be endoscopic ultrasonography guided biopsies (EUS-FNA) or ultrasound or CT scan guided if the centers do not have the former expertise, or surgical biopsy when the non resectability due to local extension is assessed during laparotomy.

GERCOR - LAP 07 v1.1 – 12th November 2007
7.1.3. Location of medical acts, tests and analyses

7.1.3.1. Blood tests at local laboratory

7.1.3.2. Thoracoabdominal CT scan as usual for investigators

7.1.3.3. EUS fine needle aspiration in centers practicing this technique

7.1.3.4. Cytological/histological analyses at the usual pathological laboratory of investigators

Biopsy samples will be frozen and first sent to the pathological laboratory at the center that is managing the patients.

7.1.3.5. Blank Slides (mandated for all included patients)

Samples will be centralized and managed by Dr Couvelard at the Centre de Ressource Biologique (CRB) of the Beaujon Hospital (Pr Bedossa).

Dr Anne Couvelard
Service d’Anatomie Pathologique, Hôpital Beaujon
100 boulevard Leclerc
92110 CLICHY
tel : + 33 1 40 87 54 62
anne.couvelard@bjn.aphp.fr

7.1.3.6. K-ras and EGFR gene mutations (optional)

Samples will be taken by gastroenterologists who do the EUS-FNA and who are participating in this part of the ancillary study.

Specific informed consent for the ancillary study should be obtained before sending the samples.

Procedure after EUS tumor aspiration:

a- Put the sample in the tube for regular histological/cytological examination

b- Push what remains in the needle into two separate tubes with a (20 cc) pump syringe:

i. Sterile Eppendorf for DNA extraction (« transparent » cap)

ii. Eppendorf with the red cap for freezing containing 500μL of RNAlater (preservation solution to be kept at 4°C)

iii. Put a sticker on the two tubes

iv. Immediately freeze the tubes in a refrigerator at – 20 °C
The samples will be sent to Pr. Buscaill’s team in Toulouse at the following address:

Pr Buscaill  
INSERM U531, Hôpital Rangueil  
1 av. Jean Poulhès, TSA 50032  
31059 Toulouse cedex  
tel : 05 61 32 30 55  
buscail.l@chu-toulouse.fr
7.2. Follow-up for patients on treatment

7.2.1. Follow-up for patients with chemotherapy only (i.e. figure 1 below)

7.2.2. Follow-up for patients with chemoradiotherapy (i.e. figure 2 below)
EVALUATION SCHEDULE of DIFFERENT TREATMENT ARMS

Fig. 1: Follow-up for patients with Chemotherapy only

- **Liver tests (every 2 weeks)**
- **Clinical assessment**
  - Blood count
  - Toxicity (weekly)
- **CA 19.9 CT scan**
- **M2**
- **M4**
- **M7**

**Complete biological assessment (D0)**

**Post treatment follow-up:**
- Clinical examination
- Biological tests
- Ca 19.9; D28, W16, W28, W40
- CT scan

every 2 months until progression
Liver tests (every 2 weeks)

Clinical assessment
- Blood count
- Toxicity
  (weekly)

Complete biological assessment (D0)

M2

E V A L U A T I O N

Liver tests

Irradiation

E V A L U A T I O N

Capecitabine

E V A L U A T I O N

Clinical assessment
- Blood count
- Toxicity
  (weekly)

D7, D15, D28, after CRT

M7

Post treatment follow-up:
- Clinical examination
- Biological tests
- Ca 19.9; D28, W16, W28, W40
- CT scan
  every 2 months until progression

M9

CA 19.9

CT scan

Liver tests

E V A L U A T I O N

Fig. 2: Follow-up for patients with Chemoradiotherapy
8. DRUGS EVALUATED & DOSE MODIFICATIONS

Drug and radiotherapy doses will have been previously validated. We based erlotinib doses on the studies by Moore (21) and Ianitti (45) who used 100mg/d in combination with gemcitabine and 150 mg/d as maintenance therapy.

8.1. Administration schedule

8.1.1. Gemcitabine
Patients will receive gemcitabine as hospital outpatients at the following schedule:
Gemcitabine : 1000 mg/m² by intravenous perfusion for 30 minutes.
The doses of gemcitabine will be re-calculated for each cycle according to the patient’s body surface. Before the protocol, the patient will receive the antiemetic which is generally used by the hospital in charge of the patient.

8.1.2. Erlotinib
One 100 mg tablet of erlotinib to be taken daily by the patient at home (during gemcitabine chemotherapy) or 150 mg (as maintenance therapy) at least one hour before, or two hours after the meal.

8.1.3. Re-treatment criteria
To begin a new cycle of treatment, the following conditions must be met:
- neutrophils > 1500 / mm³,
- platelet count > 100 000 / mm³,
- non-hematological toxicity levels (except for alopecia) returned to grade ≤ 1.

8.1.4. Delay before re-treatment
If all the conditions for re-treatment are not met, treatment can be delayed for at most 1 week. If conditions are met during this period, the treatment may, if possible, be begun again and the doses modified according to the recommendations set out below. Otherwise the patient should be excluded from the study.
If the delay is due to a cause other than treatment toxicity, the problem will be discussed with the coordinator.
8.2. Dose modifications

The following tables show dose modifications in case of toxicity. The toxicity levels taken into account should be the highest levels occurring during each cycle. Except for nausea and vomiting, dose reductions are permanent. A maximum of two dose reductions are allowed. Any patient who has two reductions and who needs a third should be excluded from the study. Anaemia should be treated according to the local practices of each managing center and no dose reduction will be made for this. Erythropoietin may be used.

### 8.2.1. Treatment modifications for gemcitabine

<table>
<thead>
<tr>
<th>Type</th>
<th>Adverse Event</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>ANC</td>
<td>100%</td>
<td></td>
<td></td>
<td>Suspend until ≤ grade 2 toxicity, then reintroduce at reduced dose 25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>100%</td>
<td></td>
<td></td>
<td>Suspend until ≤ grade 1 toxicity, then begin again at reduced dose 25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea / Vomiting</td>
<td>100%</td>
<td></td>
<td></td>
<td>Stop</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>100%</td>
<td>50%</td>
<td></td>
<td>Stop</td>
<td></td>
</tr>
</tbody>
</table>

Dose of gemcitabine
- 100% : 1000 mg/m²
- 75% : 750 mg/m²
- 50% : 500 mg/m²

### 8.2.2. Treatment modifications for capecitabine

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological &amp; non hematological</td>
<td>100%</td>
<td></td>
<td></td>
<td>Stop</td>
<td></td>
</tr>
</tbody>
</table>

For patients receiving capecitabine during radiotherapy, if capecitabine is stopped for toxicity, radiotherapy must go on.

### 8.2.3. Radiotherapy dose modification

<table>
<thead>
<tr>
<th>Type</th>
<th>Adverse Event</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>All types except for platelets</td>
<td>100%</td>
<td></td>
<td></td>
<td>Suspend until ≤ grade 2 toxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>100%</td>
<td></td>
<td></td>
<td>Suspend until ≤ grade 1 toxicity</td>
<td></td>
</tr>
</tbody>
</table>
8.2.4. Treatment modification for erlotinib

### Rash:

<table>
<thead>
<tr>
<th>NCI-CTCAE Grade</th>
<th>Dose modification</th>
<th>Management</th>
</tr>
</thead>
</table>
| Tolerable rash  | No                | Investigator’s choice:  
- Minocyclin by oral route¹,  
- Local application: tetracycline, clindamycin,  
- Oral prednisone (short term). |
| Intolerable rash| Temporary discontinuation of erlotinib.  
Discuss temporary or permanent dose reduction* if the rash continues for more than 10-14 days and/or worsens. | Same as above |
| Grade 4         | Stop erlotinib    | Same as above |

¹ Minocyclin, suggested dose: 100 to 200 mg by oral route for 30 days, then 50 to 100 mg.

*Reduction of 50 mg (with gemcitabine: from 100 to 50 mg; maintenance: from 150 mg to 100 mg)

### Pulmonary toxicity:

Discontinue erlotinib if pulmonary symptoms occur (dyspnoea, cough and/or fever) and based on the investigator’s evaluation of the patient. In case of infection discontinue erlotinib and begin appropriate antibiotic treatment.

### Gastrointestinal toxicity:

Treatment for erlotinib induced diarrhoea is as follows:

<table>
<thead>
<tr>
<th>NCI-CTCAE Grade</th>
<th>Dose modification</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>No</td>
<td>Consider loperamide (4 mg first then 2 mg every 2-4 h until diarrhoea disappears) &gt; 12 h</td>
</tr>
<tr>
<td>Grade 2</td>
<td>No Reduce* the dose of erlotinib if diarrhoea persists more than 48-72 hours despite appropriate medical treatment</td>
<td>Same as above</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Stop erlotinib until return to grade ≤ 1, then start again at reduced dose *</td>
<td>Treatment of symptoms up to investigator</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanent discontinuation of erlotinib.</td>
<td>Treatment of symptoms up to investigators.</td>
</tr>
</tbody>
</table>

* Reduction of 50 mg (with gemcitabine: from 100 to 50 mg; maintenance: from 150 mg to 100 mg)
Liver toxicity:

Erlotinib toxicity may be increased by associated treatment with CYP3A4 inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, delavirdine, cimetidine, diltiazem, fluconazole, gestodene (++), mifepristone, norfloxacin, mibefradil, amiodarone, ciprofloxacin, diethyl-dithiocarbamate, erythromycin, fluvoxamin, fruit juice, or norfluoxetin). In this case the erlotinib dose should be reduced.

Other medications to avoid: rifampicin, rifabutin, rifapentin, phenytoïne, carbamazepin, phenobarbital.
9. Data in the e-CRF

- Center and number, Managing doctor, Patient’s initials (1st letter of name – 1st letter of first name)
- Date of diagnosis of primary tumor, ECOG Performance Status,
- Biological assessment: blood count, platelet count, creatinin, alkaline phosphatase, bilirubin, AST, ALT, GGT, CA 19.9
- Disease measurable or not by scan (size according to RECIST), tumor location (head, body-tail), prior treatment
- Total administered dose of drugs
- Dose reductions (cause)
- Number of days of suspended treatment or hospitalization (cause)
- NCI/CTCAE Toxicity
- Evaluations: Date, clinical assessment (weight, ECOG PS), tumor markers, CT scan: objective response (partial, complete), stability or progression according to RECIST
- Therapeutic decision
- Unexpected or serious adverse events
- Death
10. EFFICACY PARAMETERS

10.1. Overall survival
Survival will be assessed from the date of the first randomization to the date of patient death, due to any cause, or to the last date the patient was known to be alive. Patients who were not reported as having died at the time of the analysis will be censored using the date they were last known to be alive.

10.2. Progression Free Survival
Progression-free survival (PFS) is the time from the date of the first randomization to the date of progressive disease (RECIST criteria) or death. Death will be regarded as a progression event in those patients who die before disease progression. Patients without documented objective progression at the time of the final analysis will be censored at the date of their last objective tumor assessment.

10.3. Definition of Response
The modified Response Evaluation Criteria in Solid tumors (RECIST) criteria will be used for this trial for objective tumor response assessment; details are given in Appendix 4, also see the Trial Plan for timing of the assessments. RECIST will be utilized during the treatment period but the formula will be used for rules of reintroduction.

- Complete Response (CR): disappearance of all target lesions;
- Partial Response (PR): at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter;
- Progression Disease (PD): at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions;
- Stable disease (SD): neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.
11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

11.1.1. Adverse Event (AE)
An adverse event is defined as any noxious or unexpected event that occurs in a person participating in a biomedical study, whatever the cause of this event, that is likely to be due to either a product investigated in the study or to the study in general (wash out period imposed by the protocol, diagnostic investigation performed only within the framework of the study etc…) This also includes abnormal results to additional tests that are considered clinically relevant and that may require either diagnostic tests and/or therapeutic measures or even exclusion from the study.
Lack of effect of a drug is not considered an adverse event in a clinical study.

11.1.2. Adverse Drug Reaction (ADR)
All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled.

11.1.3. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)
Any toward medical occurrence that at any dose:
- Result in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Or is a congenital anomaly/birth defect.

11.1.4. Drug Relationship
There is a reasonable possibility that the reaction or event may have been caused by the drug (i.e. a causal relationship between the reaction and the drug cannot be ruled out)

The relationship of an AE to the study drug is graded as follows:

(a) **None**: The AE is definitely not associated with the study drug administered.

(b) **Remote**: The temporal association is such that the study drug is not likely to have had an association with the observed event.

(c) **Possible**: This causal relationship is assigned when the AE: (i) follows a reasonable temporal sequence from study drug administration; (ii) could have been produced by the participant’s clinical state or other modes of therapy administered to the participant.

(d) **Probable**: This causal relationship is assigned when the AE: (i) follows a reasonable temporal sequence from study drug administration; (ii) abates upon discontinuation of the study drug; (iii) cannot be reasonably explained by known characteristics of the participant’s clinical state.

(e) **Definitely related**: This causal relationship is assigned when the AE: (i) follows a reasonable temporal sequence from study drug administration; (ii) abates upon discontinuation of the study drug; and (iii) is confirmed by reappearance of the adverse event on repeat exposure (rechallenge).

11.1.5. Serious Unexpected Adverse Drug Reaction (SUADR)
An unexpected event is any event that is not mentioned or that is of a different nature, intensity or frequency than that found in the investigator’s brochure, or in the summary of the
characteristics of the product in drugs with marketing approval. “Unexpected” refers to an adverse drug experience that has not been previously observed.

11.1.6. Other Event

In case of pregnancy and/or breast feeding during the study, the patient should be withdrawn immediately. A follow-up should continue until the end of pregnancy, and after birth.

11.2. Methods and evaluations

During each visit, any adverse events will be noted and graded according to version 3 of the NCI-CTCAE (Appendix 3). Any adverse events that persist at the end of the CTI will be followed up until they disappear. Adverse events will be identified by:

- questioning,
- clinical assessment,
- analysis of weekly biological tests. A blood count and platelet count will be performed every 2 days in case of grade 4 neutropenia or thrombopenia.

Intensity criteria:

Intensity criteria should not be confused with the criteria to determine the grade of severity for reporting obligations.

The intensity of an event will be estimated according to the NCI-CTCAE version 3 (toxicity grades 1 to 4). The intensity of adverse events that are not listed in this classification index will be evaluated based on the following terms:

- mild (grade 1): does not affect the patient’s regular daily activity,
- moderate (grade 2): upsets the patient’s regular daily activity,
- severe (grade 3): prevents the patient’s normal daily activity,
- very severe (grade 4): requires resuscitation measures/life threatening
- death related to AE (grade 5)

Toxicity limits as defined in this study are:

- Grade 4 neutropenia for more than 7 days,
- Grade 3-4 neutropenia (whatever the duration) associated with an infectious syndrome,
- Grade 3-4 thrombopenia associated with a progressive hemorrhage syndrome,
Grade ≥ 3 extra-hematological toxicity (except for alopecia and nausea-vomiting) that does not resolve at D21

11.3. Recording and Reporting SAE

This procedure is valuable for France; in other countries, to defined with local sponsors. A copy of SAE should be send in any case to the GERCOR for centralized assessment.

11.3.1. Recording data

The investigator will record the following for each event:

- Describe the event as clearly as possible using medical terminology,
- Whether the event is serious or not,
• The intensity of the event according to the grades mentioned above,
• Beginning and end dates,
• Measures taken and necessity or not of corrective measures,
• Whether the patient interrupted the study or not because of the event,
• Its outcome. If it was not fatal, the outcome should be followed up until it is resolved, the patient returns to his/her former condition, or any eventual sequella have stabilized.
• The causal relationship between this event, the treatment being studied, or a situation linked to the study (period without treatment, complementary tests requested within the framework of the study etc…).
• The possible causal relationship with the disease being treated, another disease or another treatment.

Any clinical adverse event or abnormal laboratory test value that is serious occurring during the course of the study, irrespective of the treatment received by the patient, must be reported to the sponsor within one working day of knowledge (expedited reporting).

All related SAEs or related serious lab abnormalities that occurred at any time following study discontinuation or completion are immediately reportable to the sponsor as expedited reports.

11.3.2. Reporting SAE

The investigators must immediately inform the GERCOR of any possible adverse events. The investigator must send a copy of the official form for serious adverse events from the laboratory notebook describing the serious event to the GERCOR to the attention of the project leader in charge of research by fax at (+33) 1 40 29 85 08 within 48 hours (after having made, if possible, an immediate call to (+33) 1 40 29 85 00 in case of death or a life threatening reaction).

Reporting serious adverse events to the Medical Authorities will be managed by the GERCOR.

In the case of a Serious Adverse Event the Investigator must:

• FILL IN immediately the "Serious Adverse Event" Form (which is independent of the usual Case Report Form) (Appendix 5);
• SEND immediately (within 24 hrs, preferably by fax) the signed and dated "Serious Adverse Event" Form to the Centre Monitor whose name and address is on the first page of the protocol and
• TELEPHONE immediately (day of awareness) the Centre Monitor; telephone number is on the page 1 of the protocol in the case of death or life-threatening events;
• ATTACH the photocopy of all examinations which have been carried out and the dates on which these examinations were performed. For laboratory results send also the laboratory normal ranges.

GERCOR
22, rue Malher
75004 PARIS, France
Fax : (+33) 1 40 29 85 08
11.4. Follow-up of patients with SAE

Any non-severe adverse events that occur during the study should be reported in the official form found in the laboratory notebook for the study and should be followed up by the CST during regular visits, especially in relation to the outcome and the measures taken.

The coordinator will promptly inform the pharmacovigilance specialist during their regular meetings of any non-severe adverse events that have required suspension of treatment or that are unexpected.

The coordinator will provide the pharmacovigilance specialist with a list of non-severe adverse events during the study, after the intermediate analysis and at the end of the study. All non-severe adverse events will be sent to the sponsor and will be included with the other CRF and listed in the tables in the chapter on “tolerance” in the final report.

11.5. Declaration to authorities

« Events to be declared are SAE which must be sent to AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) (French Agency for the Safety of Health Products). This includes expected or unexpected SAE which the investigator and/or the sponsor thinks may be linked to the administration of product(s) being studied (product(s) tested in comparison). »

The investigator shall inform the Unité Fonctionnelle d’Enregistrement Pharmacovigilance (UF of PV) (Pharmacovigilance Registration Unit) of any deaths, whatever the cause, including if they are a result of progression of the disease being treated, any events that are likely to be life threatening and any serious expected or unexpected side effects, whether they are due to the study or not, which occur during the study, within 30 days after the final treatment, and during the follow up period as defined in the protocol. A declaration is made by sending a signed and dated copy of the initial report that describes the adverse event as precisely as possible (appendix II of the laboratory notebook) to the UF, by fax, email or regular mail, and if this is not possible by telephone, within 48 hours (2 working days) after the event has been discovered.

Any report by telephone must be confirmed by sending a written report of the serious adverse event by fax or regular mail within the delay set out in the operating procedure.

The initial report must include at least:

1) Patient identification (initials, birth date, sex, randomization n°)
2) Identification of reporter and protocol (name, address, tel/fax/email, N°CSET protocol number)
3) Treatment(s) in the study (name, indication, treatment mode, date of administration)
4) One adverse event (beginning and ending dates, diagnosis, clinical signs, measures taken, outcome, cause according to the investigator).
Whenever possible the investigator must also include the following in the report on the serious adverse event:
- A copy of the hospital report or extended hospitalization report,
- A copy of the autopsy,
- A copy of the results of any additional tests, including relevant negative results, with normal laboratory values,
- Any other useful or relevant documents.

All documents will be anonymous.

In addition to filling out the official form, if necessary, the investigator should write a report on the SAE, in particular if death has occurred or if the event is unexpected and life threatening, within 72 hours after sending the official form (in accordance with existing legislation) which should include the following information:
- Patient’s initials, age, sex.
- The diagnosis or differential diagnoses considered, or the clinical and/or biological signs of the SAE, history of the disease for which the patient was included in the study.
- Medical background and other existing diseases.
- Concomitant treatments at the time of the adverse event.
- The inclusion arm (except if it is a blind study) and the dates of administration.
- The number of cycles received and if they were well tolerated. The date and test results with accompanying normal values, including negative results if they are relevant.
- Therapeutic measures undertaken and/or planned
- Attitude towards the study treatment.
- Patient’s condition on the date of the report (in the event of specific sequella, describe them and their severity, in case of death provide the date as well as the causes and circumstances of death.)
- The reporter’s opinion about any link between the event and the study treatment or another aspect of the study, on one hand, and the treated disease, another disease or another treatment, on the other hand.

Additional information may be requested (by fax, telephone or during a visit) by the monitor and/or the pharmacovigilant specialist.

The UF of the PV must notify AFSSAPS of any serious adverse events that are likely to have been caused by biomedical research and that fall under the Loi Huriet for trials sponsored by AP-HP or in which AP-HP is responsible for pharmacovigilance.

Any disagreement between the investigator and the sponsor concerning a link between the adverse event and the drug being studied will be specified in the report, in accordance with the recommendations of the loi HURIET.

The investigator must provide appropriate medical follow-up of patients until the event has resolved or stabilized or until death. This may require following the patient after he/she has been excluded from the study.

The investigator must inform the pharmacovigilance service of any additional information about the SAE within 48 hours after receiving it, using an SAE report form (by filling in the square « Follow-up N° » to explain that this is a follow up report and not the initial report). The final report on the resolution or stabilization of the SAE should be sent to the same authorities. The investigator should keep all original documents concerning the presumed adverse event so that further information can be provided to the authorities upon request.
investigator must respond to requests for further information from the pharmacovigilant specialist and provide full documentation to complete the initial report and implement decisions on the SAE from the DRT and the PV committee.

11.6. Expected adverse events

Any events whose occurrence cannot reasonably be attributed to a cause other than the study are considered « likely to be caused by the study ».

11.6.1. Negative side effects of gemcitabine
- Frequent:
  - Nausea
  - Vomiting
  - Diarrhoea
  - Flu-like syndrome
  - Neutropenia, thrombopenia
- Rare:
  - Anaemia
  - Thrombotic microangiopathy
  - Alopecia
  - Rash, pruritis

11.6.2. Negative side effects of erlotinib
- Frequent:
  - Rash, pruritus
  - Diarrhoea
  - Infections
  - Respiratory disorders: dyspnoea, cough +/- fever
  - Mucitis
  - Fatigue
  - Nausea
  - Vomiting
  - Deshydratation
  - Ophthalmologic disorders (conjunctivitis, keratitis, and lowered visual acuity). Wearing contact lenses is not recommended. Increased transaminase and bilirubin levels
  - Haemorrhage due to interaction with oral anticoagulants (with increased INR)

11.6.3. Negative side effects of capecitabine
- Frequent:
  - Diarrhoea
  - Nausea
  - Vomiting
  - Hand-foot syndrome
  - Fatigue
  - Loss of appetite
  - Elevated bilirubin levels
  - Anaemia, neutropenia, thrombopenia
- Rare
  - Constipation
11.6.4. Negative side effects of radiotherapy
- Alopecia
- Headache
- Oedema of the lower limbs

12. DATA MANAGEMENT AND STATISTICAL ANALYSIS

12.1. Strategy for data analysis

*Primary objective:*
- The Kaplan-Meier method will be used to evaluate overall survival. It will be calculated from the first day of treatment until death.

- Comparisons on survival will be made with the log-rank test. The $\chi^2$ or the Fischer exact test will be used, if necessary, for comparison of qualitative variables. The Student t test will be used for quantitative variables.

*Secondary objectives:*
- The Kaplan-Meier method will be used to evaluate progression free survivals. It will be calculated from the first day of treatment until evidence of progressive disease or death.

- Relationships will be investigated between biological markers and resistance to treatment. Expression of these markers in initial biopsies will be compared in resistant and non-resistant subjects. These comparisons will also be calculated with the Student t test or Fisher exact test to 5% depending on the variables.

To calculate tolerance, adverse events will be reported and only descriptive statistics will be provided.

These statistical analyses will be performed in intent-to-treat.
12.2. Number of planned patients and justification

The number of patients planned for inclusion was based on three elements:

1) The results of a recent study by our group (4).

2) The fact that the results of that retrospective study could overestimate survival.

3) A certain proportion of patients will not participate in the second randomization (continued CT or CRT) because of tumor progression observed in the first or second evaluation (after 2 or 4 months of treatment).

Overall expected accrual is 30 patients/month. Among them 20 would have controlled illness

Calculation of the number of patients by intent-to-treat:

- Hypothesis: CRT increases median survival from 9 to 12 months (hazard ratio: 0.75)
- With an alpha risk of 0.025% and a beta risk of 80%, 467 deaths could occur
- With a monthly accrual of 20 patients during 30 months, 600 patients must be included
- The minimal follow up for the last included patient is 10 months
- Total duration of the study is 40 months - 3.3 years (accrual 30 months + 10 months of follow up for overall survival)
- With estimation of 30% of progressive patients in the first 4 months of initial chemotherapy and who could not undergo the second randomization, 780 patients are required (4 x 195)
- In consideration of 5% of patients lost during the follow up, 39 additional patients are required, that is 820 total patients (4 x 205)

12.3. Planned Interim Analysis

When 230 deaths will be observed, an intermediate analysis is planned, that is 24 months after randomization of the first patient. The aim of this analysis is to stop prematurely the trial if superiority of treatment is clearly shown, or if a demonstration of a clinically significant difference is not probable. The p value for significant statistical intermediate analysis (p=0.00084) and final analysis (0.05) is obtained by EAST software, using alpha spending function (Lan and Demetz, 1983). Limits are established with Obrien’s and Fleming’s methods, (1979).

All analysis are treated in intent-to-treat method and per protocol.
12.4. Management of data analysis and software

- The statistical analysis will be performed by GERCOR statisticians.
- Data recorded for the study will be electronically treated, stored and reported to the Commission Informatique et Libertés (Freedom and Electronic Information Commission) (CNIL).
- SAS software will be used for all statistical analyses.

13. ETHICAL AND REGULATORY CONSIDERATIONS (FOR FRANCE)

13.1. Responsibilities of the sponsor

This role is defined by Law N°2004-806 dated August 9, 2004. GERCOR is the study’s sponsor.

The Sponsor agrees to be solely responsible for the study, and as such the Sponsor guarantees that the study will be implemented in accordance with the applicable laws and regulations in France. The Sponsor will submit all individual and periodic reports on Serious Adverse Events which occur during the Study to the Medical Authorities in accordance with local and European regulations. It is the Sponsor’s responsibility to inform investigators and Ethical Committees in accordance with existing regulations. The reference texts used by the Sponsor for the evaluation of the unexpected/expected nature of adverse events will be summarized for this study in the Summary of Product Characteristics.

The GERCOR reserves the right to stop the study at any moment for medical or administrative reasons, and in this case, the investigator will be so informed.

13.2. Patient information and Inform consent

This trial should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki (Appendix VI), and that are consistent with GCP and the applicable regulatory requirement(s).

Prior to participation to the trial, the patient or the subject’s legally acceptable representative should receive a copy of the signed and dated written informed consent form, and any other information provided to the patient. During a patient’s participation in the trial, the patient or the subject’s legally acceptable representative should receive a copy of the signed and dated written consent form updates and a copy of any amendments to the written information provided to the patient.

13.3. Patient Insurance

The Sponsor will forward a copy of the insurance, covering his and any other participating party's liabilities.
In accordance with the law on biomedical research, GERCOR has taken insurance with the GERLING FRANCE company (n° 1680 90712) for the entire study, guaranteeing its civil liability as well as that of all study personnel (physicians or personnel involved in the study) (loi n°2004-806, Art L.1121-10 du CSP). (Appendix 8)

13.4. CNIL Declaration

CNIL : Commission Nationale Informatique et Liberté

The law states that a report must be made before the study begins.
- If the study must be submitted to quality control of data by an ARC (risks B,C and D) and falls within the scope of the simplified procedure, the sponsor, must send a report to the CNIL in association with the electronic data manager, as part of its simplified annual report.
- The following are excluded: genetic, epidemiological or behavioural research, results that include confidential data, (complete identity of patients or social security numbers). In these cases, as well as for unmonitored research, the electronic data manager will provide the report to the Consulting committee on the treatment of medical research data, then to the CNIL.

13.5. Ethical Committee (EC)

The sponsor of the study will submit this protocol to a Comité de Protection des Personnes (CPP) de l’Île de France (Advisory committee for the Protection of Subjects in Biomedical Research, Ile de France) pursuant to article L.1123-6 of the Public Health Code when he/she has received a favourable response from the sponsor (with a copy of the insurance policy, and receipt of payment of any inscription fees). The response from this advisory committee will be included in the letter of intent and sent to the Minister by the sponsor before the study begins. (Appendix 7)

14. DATA HANDLING AND RECORD KEEPING

14.1. eCRF Handling

Data will be entered directly in an electronic CRF available from a web site (eCRF). A personal identification code will be delivered to each investigator.
All data to be controlled or to be completed will be listed for further verification at site of investigation by the trial monitor.
After this last verification, the concerned data will be updated and locked into the database. Any further modification will be documented in an audit file before the statistical analysis is initiated. Data will be extracted from the database directly into data files for statistical analysis.

14.2. Investigator site file and archiving

Filing
The Investigator will keep the study documents, the medical records, the laboratory reports, the informed consent forms, the drug distribution rosters, the adverse event reports, the
information concerning patients that prematurely went off-study and all other pertinent
information, such as letters and administrative documents exchanged between the Sponsor
and the center.
All the study documents must be kept by the Investigator for the maximum period of time
allowed by the hospital, the institution or the practice where he/she works. However, as far as
Europe is concerned, the patients' identification codes must be kept for at least 15 years after
the end of the trial.
In order to avoid possible errors, the Investigator will contact the Sponsor before destroying
trial documents or if he is going to leave the institution where the study was conducted.
Furthermore, he will inform the Sponsor in the event of the loss or destruction of any
document concerning the study.

14.3. Modifications to the study protocol
The GERCOR must be informed if the coordinator plans to modify the study protocol. The
CPP must be informed of any modifications to the study protocol by the coordinator if
substantial changes are made, that is if the changes could in any way modify the guarantees
provided to the participants in the biomedical research (modification of inclusion criteria,
extended inclusion, and participation by new investigators).

14.4. Extending the study
Any extension of the study (prolonging treatment or therapeutic acts that were not initially
planned in the protocol) will be considered a new study.

14.5. Study documentation
Before the study begins, the coordinator will provide a copy of his/her résumé, as well as
those of all the other investigators, to a sponsor representative. Each investigator agrees to
respect the obligations of the loi Huriet (or if applicable law 2004-800 dated August 6, 2004)
and to perform the study in accordance with the GCP, and the terms of the Declaration of
Helsinki (Appendix 5). A copy of the signed and dated statement of scientific commitment
will be sent to the sponsor signed in each center by each investigator.

14.6. Reviewing procedures
The scientific committee will review the eCRF to make sure that they have been filled in and
to validate data. The investigator and co-investigators agree to meet regularly with official
GERCOR sponsor representatives.
During the on-site visits and pursuant to Good Clinical Practice, the following points will be
reviewed:
- Respect of the study protocol and the procedures as defined.
- Quality assurance of the data in the laboratory notebook: accuracy, missing data, coherence
  of data
- Validation of source documents.
During these on site visits, review procedures will correspond to the level of risk associated
with the protocol.

14.7. Transcribing data
All information obtained in the protocol must be entered in the eCRF by the investigator’s
representant or by himself, and the investigator must provide an explanation for any missing
data.
Data should be entered as soon as it is obtained, whether it is clinical or paraclinical.
Subjects’ identities will be kept anonymous by mentioning initials’ patient (1st initial of the
name, and 1st initial of the first name) on all documents necessary for the study and to be included in the study data.
Electronic data files will be declared to the CNIL.

14.8. Final report
The final study report will be written by the study coordinator and the biostatistician. This report will be submitted to each of the investigators for comment. Once a consensus has been reached, the final draft will be signed by each of the investigators and sent to the sponsor in a timely manner after the end of the study.

14.9. Ownership of results
The GERCOR owns the results to the study and these results may not be transferred or used by any third party without obtaining prior approval from GERCOR.

14.10. Notice of informed consent
Subjects can only participate in this study if they freely provide informed consent in writing. The informed consent of the patient must be obtained before any investigation or consultation can be undertaken specifically for biomedical research (eg, laboratory tests for patient selection for study inclusion).
The patients will have received prior information from the physician about the following:
- the purpose of the study,
- the duration of their participation in the study,
- the procedures that will be followed,
- possible advantages, foreseeable risks, disadvantages of the study treatment,
- confidentiality of data,
- insurance coverage,
- and the fact that their participation is voluntary.
All of this information will be summarized in a letter of information provided to each patient. Three copies of the consent form will be signed by the subject and the investigating physician. It will mention that an electronic file will be created on the study data and the patient’s legal rights as defined by the law « Informatique et Libertés » (Freedom and Electronic Information) with respect to data concerning them.
A copy of this document will be provided to the person participating in the study. The investigator must keep a second copy in the archives for at least 15 years. The sponsor will place the third copy in its archives.

15. INDEPENDENT COMMITTEE
Considering that the safety of the drugs used in this study is recognized, the implementation of an independent Data Monitoring Committee is not necessary.

16. PUBLICATION

16.1. Main paper
First author: Coordinator.
Next authors: each group will propose 1 to 3 co-authors, and the number of co-authors per group will depend on the number of patients included. A group will be represented only if it included at least 3% of patients.

All the participants who do not figure in the authors are cited at the end of the publication. The data manager is also cited. He can be cited in the authors if the coordinator considers it as justified.

The partnerships will be thanked.

The authors and the sponsor receive the manuscript for review before the submission to the journal. They undertake to answer within 15 working days so that their opinion will be taken into account (30 days in summer period).

16.2. Oral communications

An investigator can, with the agreement of the coordinator, presents all or a part of the results in oral presentations after the inaugural communication. The authors are the same as for the written publication, but the order of the authors for the publications and communications could vary.
17. REFERENCES


GERCOR - LAP 07 v1.1 – 12th November 2007


56-Blanquicett C, Saif MW, Buchsbaum DJ, Eloubeidi M, Vickers SM, Chhieng DC, Carpenter MD, Sellers JC, Russo S, Diasio RB, Johnson MR. Antitumor efficacy of capecitabine and


APPENDIX 1. Objective Tumor Response Criteria

Objective tumor response criteria (RECIST)

1. MEASURABILITY OF TUMOR LESIONS AT BASELINE

1.1. Definitions
At baseline, tumor lesions will be categorized as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as 20 mm with conventional techniques or as 10 mm with spiral CT scan [see section 2.2]) or nonmeasurable (all other lesions, including small lesions [longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan] and truly nonmeasurable lesions). The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

Lesions considered to be truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

(Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.)

1.2. Specifications by methods of measurements
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

CT and MRI.
CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis, while head and neck tumors and those of the extremities usually require specific protocols.

2. TUMOR RESPONSE EVALUATION

2.1. Baseline evaluation
2.1.1. Assessment of overall tumor burden and measurable disease.
To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary end point. Measurable disease is defined by the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

GERCOR - LAP 07 v1.1 – 12th November 2007
2.1.2 Baseline documentation of "target" and "nontarget" lesions.

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response. All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

2.2. Response criteria

2.2.1 Evaluation of target lesions.

This section provides the definitions of the criteria used to determine objective tumor response for target lesions. The criteria have been adapted from the original WHO Handbook, taking into account the measurement of the longest diameter only for all target lesions: complete response—the disappearance of all target lesions; partial response—at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease—at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

2.2.2 Evaluation of nontarget lesions.

This section provides the definitions of the criteria used to determine the objective tumor response for nontarget lesions: complete response—the disappearance of all nontarget lesions and normalization of tumor marker level; incomplete response/stable disease—the persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker level above the normal limits; and progressive disease—the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions. (Note: Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel [or study chair]).

2.2.3 Evaluation of best overall response.

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 3.3.1). Table provides overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions.

Notes:
- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be
classified as having "symptomatic deterioration." Every effort should be made to document the objective disease progression, even after discontinuation of treatment.

- Conditions that may define early progression, early death, and inevaluability are study specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity).
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine-needle aspiration/biopsy) before confirming the complete response status.

2.2.4 Frequency of tumor re-evaluation.
Tumor re-evaluation should be performed after cycle 4 and cycle 6 (confirmation of response), then every 6 cycles or 3-month interval.

Table 1: Overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions

<table>
<thead>
<tr>
<th>Target lesions</th>
<th>Nontarget lesions</th>
<th>New lesions</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Incomplete response/SD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or no</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or no</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

*CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. See text for more details.

2.2.5 Duration of overall response.
The duration of overall response is measured from the time that measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete response is measured from the time measurement criteria are first met for complete response until the first date that recurrent disease is objectively documented.

2.2.6 Duration of stable disease.
Stable disease is measured from the start of the treatment until the criteria for disease progression is met (taking as reference the smallest measurements recorded since the treatment started). The clinical relevance of the duration of stable disease varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of stable disease. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

3. REPORTING OF RESULTS
All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). (Note: GERCOR - LAP 07 v1.1 – 12th November 2007)
By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.
All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.
All conclusions should be based on all eligible patients.
### APPENDIX 2. ECOG Performance Status

#### ECOG PERFORMANCE STATUS SCORING SYSTEM

<table>
<thead>
<tr>
<th>STATUS</th>
<th>ECOG PERFORMANCE STATUS SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, asymptomatic</td>
</tr>
<tr>
<td>1</td>
<td>Ambulatory; capable of carrying out work of a light or sedentary nature, eg: light house work, office work.</td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt; 50% of the time: capable of self-care but not work</td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt; 50% of the time: capable of only limited self-care.</td>
</tr>
<tr>
<td>4</td>
<td>Completely bedridden; incapable of self-care</td>
</tr>
</tbody>
</table>
APPENDIX 3. List of Participating Centres and Investigators for France

<table>
<thead>
<tr>
<th>N°centre</th>
<th>Investigateurs</th>
<th>Adresse</th>
<th>Co-investigateurs</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>HAMMEL Pascal</td>
<td>Hôpital Beaujon&lt;br&gt;Service de Gastroentérologie&lt;br&gt;100, bd du Général Leclerc&lt;br&gt;92 118 CLICHY Cedex</td>
<td>DREYER&lt;br&gt;HENTIC&lt;br&gt;HENNEQUIN&lt;br&gt;Christophe</td>
</tr>
<tr>
<td>1</td>
<td>ANDRE Thierry</td>
<td>Hôpital Tenon&lt;br&gt;Service d’Oncologie Médicale&lt;br&gt;4, rue du Fbg St-Antoine&lt;br&gt;75970 PARIS Cedex 20</td>
<td>ABBAS Fadi&lt;br&gt;HUGUET Florence&lt;br&gt;TOUBOUL Emmanuel</td>
</tr>
<tr>
<td>22</td>
<td>LOUVET Christophe</td>
<td>Hôpital St Antoine&lt;br&gt;Service d’Oncologie Médicale&lt;br&gt;184, rue du Fbg St-Antoine&lt;br&gt;75571 PARIS Cedex 12</td>
<td>MAINDRAULT&lt;br&gt;CHIBAUDEL&lt;br&gt;AFCHAIN&lt;br&gt;HUGUET Florence&lt;br&gt;TOUBOUL Emmanuel</td>
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<tr>
<td>67</td>
<td>CRETIN Jacques</td>
<td>ONCOGARD Clinique Valdegour&lt;br&gt;772, chemin de Valdegour CS&lt;br&gt;22017 30907 NIMES CEDEX 02</td>
<td>ALCARAZ Laurent</td>
</tr>
<tr>
<td>92</td>
<td>ELLIS Stephen</td>
<td>Centre Catalan d’Oncologie&lt;br&gt;80, rue Pascal Marie Agasse&lt;br&gt;66000 PERPIGNAN</td>
<td></td>
</tr>
<tr>
<td>86</td>
<td>TAIÈB Julien</td>
<td>Hôpital de La Pitié Salpêtrière&lt;br&gt;Service de Gastroentérologie&lt;br&gt;47-83, bd de l’Hôpital&lt;br&gt;75651 PARIS Cedex 13</td>
<td>ASNACIOS&lt;br&gt;LOUAFI&lt;br&gt;BONYHAY&lt;br&gt;TOUBIANA&lt;br&gt;SIMON Jean-Marc</td>
</tr>
<tr>
<td>64</td>
<td>BONICHON LAMICHHANE</td>
<td>Clinique Tivoli&lt;br&gt;220, rue Mandron&lt;br&gt;33000 BORDEAUX</td>
<td>JAUBERT Dominique</td>
</tr>
<tr>
<td>13</td>
<td>DUTEL Jean-Luc</td>
<td>CH de Beauvais&lt;br&gt;40 av Léon Blum&lt;br&gt;60021 BEAUVAIS</td>
<td>N’GUYEN Suzanne&lt;br&gt;Ozanne Fabienne</td>
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<tr>
<td>90</td>
<td>LOUËT Estelle</td>
<td>Clinique du Tonkin&lt;br&gt;26-36 rue du Tonkin&lt;br&gt;69100 VILLEURBANNE</td>
<td>COQUARD Régis</td>
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<tr>
<td>93</td>
<td>LECOMTE Thierry</td>
<td>Hôpital Trouseau CHRU de Tours&lt;br&gt;Service d’Hépato-gastroentérologie&lt;br&gt;37000 Cedex 09 Tours</td>
<td>DORVAL Etienne&lt;br&gt;VIGUIER Jérôme&lt;br&gt;ASSOR Philippe&lt;br&gt;CHAPET Sophie</td>
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<tr>
<td>54</td>
<td>PAITEL Jean-François</td>
<td>CH de La Rochelle&lt;br&gt;Service d’Oncologie médicale&lt;br&gt;17019 LA ROCHELLE Cedex</td>
<td>FLECQ&lt;br&gt;BERNARD</td>
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<tr>
<td>N°centre</td>
<td>Investigateurs</td>
<td>Adresse</td>
<td>Co-investigateurs</td>
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<td>97</td>
<td>DEPLANQUE Gaël</td>
<td>GH St Joseph 33, rue Olivier de Serres</td>
<td>LEVASSEUR</td>
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<tr>
<td></td>
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<td>75015 PARIS</td>
<td>GATINEAU</td>
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<td>REBISHUNG Christine</td>
<td>CHU de GRENOBLE Hôp Nord BP 217 Dpt de</td>
<td>PHELIP</td>
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<tr>
<td></td>
<td></td>
<td>Cancéro et d'hématologie 38043 GRENOBLE</td>
<td>BALOSSO</td>
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<tr>
<td>75</td>
<td>DURANDO Xavier</td>
<td>Centre Jean Perrin 58 r Montalembert</td>
<td>MOURET REYNIER</td>
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<td>63011 CLERMONT-FERRAND Cedex 11</td>
<td>DILLIES LE GRAIN</td>
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<tr>
<td>52</td>
<td>VIRET Frédéric</td>
<td>IPC 232 Bd Ste Marguerite BP 156 13273</td>
<td>GIOVANNINI Marc</td>
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<tr>
<td></td>
<td></td>
<td>Marseille Cedex 9</td>
<td>MOUREAU-ZABOTTO Laurence</td>
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Two modifications of address in November 2007

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Change of principal investigator in November 2007 at an existing site

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APPENDIX 4.  NCI - Common Terminology Criteria for Adverse Events (version 3.0)

Publish date: August, 2006


INSTRUCTIONS
1. Be aware that some definitions provided under grading include seriousness criteria. Such events must always be reported on the SAE form (eg: hemorrhage Grade 4: life threatening → SAE form).
2. Toxicity grade should reflect the most severe degree occurring during the evaluation period, not an average.
3. When two criteria are available for similar toxicities, the more severe grade should be used.
4. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
5. An accurate baseline prior to start of therapy is necessary.
6. Toxicities related to muscle, oesophagus, gallbladder or unspecified (end of table) have been added by SANOFI for internal reasons.

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<td>WBC (10^9/L)</td>
<td>≥ 4.0</td>
<td>3.0 - 3.9</td>
<td>2.0 - 2.9</td>
<td>1.0 - 1.9</td>
<td>&lt; 1.0</td>
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<td>PLT (10^9/L)</td>
<td>WNL</td>
<td>75.0 - Normal</td>
<td>50.0 - 74.9</td>
<td>25.0 - 49.9</td>
<td>&lt; 25.0</td>
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<td>Hgb (g/100ml)</td>
<td>WNL</td>
<td>10.0 - Normal</td>
<td>8.0 - 9.9</td>
<td>6.5 - 7.9</td>
<td>&lt; 6.5</td>
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<td>Granulocytes/Bands (10^9/L)</td>
<td>≥ 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt; 0.5</td>
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<td>Lymphocytes (x 1000/mL)</td>
<td>≥ 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
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<td>Hemorrhage (Clinical)</td>
<td>None</td>
<td>Mild, no transfusion</td>
<td>Gross, 1 to 2 units transfusion per episode</td>
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<td>Massive, &gt; 4 units transfusion per episode</td>
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<td>Nausea</td>
<td>None</td>
<td>Able to eat, reasonable intake</td>
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<td>Vomiting</td>
<td>None</td>
<td>1 episode in 24 hours</td>
<td>2 - 5 episodes in 24 hours</td>
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<td>Diarrhoea</td>
<td>None</td>
<td>Increase of 2 - 3 stools/day over pre-therapy</td>
<td>Increase of 4 - 6 stools/day, or nocturnal stools, or moderate cramping</td>
<td>Increase of 7 - 9 stools/day or incontinence, or severe cramping</td>
<td>Increase of &gt; = 10 stools / day or grossly bloody diarrhoea, or need for parenteral support</td>
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<td>Stomatitis</td>
<td>None</td>
<td>Painless ulcers, erythema, or mild soreness</td>
<td>Painful erythema, edema, or ulcers, but can eat</td>
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<td>Requires parenteral or enteral support</td>
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WNL = within normal limits
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<td>Transaminase (SGOT, SGPT)</td>
<td>WNL</td>
<td>&lt; 2.5 x N</td>
<td>2.6 - 5.0 x N</td>
<td>5.1 - 20.0 x Normal</td>
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<td>Alkaline Phosphatase or 5’ Nucleotidase</td>
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<td>&lt; 2.5 x N</td>
<td>2.6 - 5.0 x N</td>
<td>5.1 - 20.0 x N</td>
<td>&gt; 20.0 x N</td>
</tr>
<tr>
<td>Liver (Clinical)</td>
<td>No change</td>
<td>——</td>
<td>——</td>
<td>Pre-coma</td>
<td>Hepatic coma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KIDNEY/BLADDER</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>WNL</td>
<td>&lt; 1.5 x Normal</td>
<td>1.5 - 3.0 x Normal</td>
<td>3.1 - 6.0 x Normal</td>
<td>&gt; 6.0 x Normal</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>No change</td>
<td>1+ or &lt; 0.3 g% or &lt; 3 g/L</td>
<td>2 - 3+ or 0.3 - 1.0 g% or 3 - 10 g/L</td>
<td>4+ or &gt; 1.0 g% or &gt; 10 g/L</td>
<td>Nephrotic syndrome.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HAIR</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>No loss</td>
<td>Mild hair loss.</td>
<td>Pronounced or total hair loss.</td>
<td>——</td>
<td>——</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PULMONARY</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>None or o change</td>
<td>Asymptomatic with abnormality in pulmonary function tests</td>
<td>Dyspnea on significant exertion.</td>
<td>Dyspnea at normal level of activity.</td>
<td>Dyspnea at rest.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CARDIAC</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Dysrhythmias</td>
<td>None</td>
<td>Asymptomatic, transient, requiring no therapy.</td>
<td>Recurrent, or persistent, no therapy required</td>
<td>Requires treatment.</td>
<td>Requires monitoring, or hypotension, or ventricular tachycardia, or fibrillation.</td>
</tr>
<tr>
<td>Cardiac Function</td>
<td>None</td>
<td>Asymptomatic, decline of resting ejection fraction by &lt; 20% of baseline value.</td>
<td>Asymptomatic, decline of resting ejection fraction by &gt; 20% of baseline value.</td>
<td>Mild congestive heart failure responsive to therapy.</td>
<td>Severe or refractory congestive heart failure</td>
</tr>
<tr>
<td>Cardiac Ischemia</td>
<td>None</td>
<td>Non-specific T-wave flattening.</td>
<td>Asymptomatic ST and T-wave changes suggesting ischemia.</td>
<td>Angina without evidence for infarction.</td>
<td>Acute myocardial infarction.</td>
</tr>
<tr>
<td>Cardiac - Pericardial</td>
<td>None</td>
<td>Asymptomatic effusion, no intervention required.</td>
<td>Pericarditis (rub, chest pain, ECG changes).</td>
<td>Symptomatic effusion; drainage required.</td>
<td>Tamponade; drainage urgently required.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BLOOD PRESSURE</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>No change or None</td>
<td>Asymptomatic, transient increase by &gt; 20 mm Hg (D), or to &gt;150/100 if previously WNL. No treatment required.</td>
<td>Recurrent or persistent increase by &gt; 20 mm Hg (D), or to &gt;150/100 if previously WNL. No treatment required.</td>
<td>Requires therapy.</td>
<td>Hypertensive crisis.</td>
</tr>
<tr>
<td>Hypotension</td>
<td>No change or None</td>
<td>Changes requiring no therapy (i.e., transient orthostatic hypotension).</td>
<td>Requires fluid replacement or other therapy, but not hospitalization.</td>
<td>Requires therapy and hospitalization, resolves within 48 hours of stopping the agent.</td>
<td>Requires therapy and hospitalization for &gt; 48 hours after stopping the agent.</td>
</tr>
<tr>
<td>NEUROLOGIC</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Neuro-Sensory</td>
<td>No change or None</td>
<td>Mild paresthesias, loss of deep tendon reflexes.</td>
<td>Mild or moderate objective sensory loss, moderate paresthesias.</td>
<td>Severe objective sensory loss or paresthesias that interfere with function.</td>
<td>---------</td>
</tr>
<tr>
<td>Neuro-Motor</td>
<td>No change or None</td>
<td>Subjective weakness, no objective findings.</td>
<td>Mild objective weakness without significant impairment of function.</td>
<td>Objective weakness with impairment of function.</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Neuro-Cortical</td>
<td>None</td>
<td>Mild somnolence or agitation.</td>
<td>Moderate somnolence or agitation.</td>
<td>Severe somnolence, agitation, confusion, disorientation or hallucinations.</td>
<td>Coma, seizures, toxic psychosis.</td>
</tr>
<tr>
<td>Neuro-Mood</td>
<td>No change</td>
<td>Mild anxiety or depression.</td>
<td>Moderate anxiety or depression.</td>
<td>Severe anxiety or depression.</td>
<td>Suicidal ideation.</td>
</tr>
<tr>
<td>Neuro-Headache</td>
<td>None</td>
<td>Mild</td>
<td>Moderate or severe but transient.</td>
<td>Unrelenting and severe.</td>
<td>---------</td>
</tr>
<tr>
<td>Neuro-Constipation</td>
<td>No change or None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Ileus &gt; 96 hrs</td>
</tr>
<tr>
<td>Neuro-Hearing</td>
<td>None or no change</td>
<td>Asymptomatic hearing loss on audiometry only.</td>
<td>Tinnitus</td>
<td>Hearing loss interfering with function but correctable with hearing aid</td>
<td>Deafness not correctable.</td>
</tr>
<tr>
<td>Neuro-Vision</td>
<td>None or no change</td>
<td>-</td>
<td>-</td>
<td>Symptomatic sub-total loss of vision.</td>
<td>Blindness</td>
</tr>
<tr>
<td>SKIN</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Skin</td>
<td>No change or None</td>
<td>Scattered macular or papular eruptions, or asymptomatic erythema.</td>
<td>Scattered macular or papular eruptions, or erythema with puritus, or other associated symptom(s).</td>
<td>Generalized symptomatic macular, papular, or vesicular eruption(s).</td>
<td>Exfoliative dermatitis or ulcerating dermatitis.</td>
</tr>
<tr>
<td>ALLERGY</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Allergy</td>
<td>None</td>
<td>Transient rash, drug fever &lt; 38°C (100.4°F).</td>
<td>Urticaria, drug fever ≥ 38°C (100.4°F), mild bronchospasm.</td>
<td>Serum sickness, bronchospasm, requires parenteral medications.</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>FEVER</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Fever (absence of infection)</td>
<td>None</td>
<td>37.1° - 38.0° C (98.7° - 100.4°F)</td>
<td>38.1° - 40.0° C (100.6° - 104.0°F) F for &lt; 24 hours</td>
<td>&gt; 40.0° C (104.0°F) for &gt; 24 hours accompanied by hypotension.</td>
<td>&gt; 40.0° C (104.0°F) for &gt; 24 hours accompanied by hypotension.</td>
</tr>
<tr>
<td>LOCAL</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Local</td>
<td>None</td>
<td>Pain</td>
<td>Pain and swelling with inflammation or phlebitis.</td>
<td>Ulceration</td>
<td>Plastic surgery indicated.</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>------------------</td>
<td>---------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain/Loss</td>
<td>&lt; 5.0 %</td>
<td>5.0 - 9.9 %</td>
<td>10.0 - 19.9%</td>
<td>≥ 20 %</td>
<td>-</td>
</tr>
<tr>
<td>METABOLIC</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Hyperglycemia (mg/dl)</td>
<td>&lt; 116</td>
<td>116 - 160</td>
<td>161 - 250</td>
<td>251 - 500</td>
<td>&gt; 500 or ketoadosis</td>
</tr>
<tr>
<td>Hypoglycemia (mg/dl)</td>
<td>&gt; 64</td>
<td>55 - 64</td>
<td>40 - 54</td>
<td>30 - 39</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Amylase</td>
<td>WNL</td>
<td>&lt; 1.5 x Normal</td>
<td>1.5 - 2.0 x Normal</td>
<td>2.1 - 5.0 x Normal</td>
<td>&gt; 5.0 x Normal</td>
</tr>
<tr>
<td>Hypercalcemia (mg/dl)</td>
<td>&lt; 10.6</td>
<td>10.6 - 11.5</td>
<td>11.6 - 12.5</td>
<td>12.6 - 13.5</td>
<td>≥ 13.6</td>
</tr>
<tr>
<td>Hypocalcemia (mg/dl)</td>
<td>&gt; 4.4</td>
<td>8.4 - 7.8</td>
<td>7.7 - 7.0</td>
<td>6.9 - 6.1</td>
<td>≤ 6.0</td>
</tr>
<tr>
<td>Hypomagnesemia (mg/dl)</td>
<td>&gt; 1.4</td>
<td>1.4 - 1.2</td>
<td>1.1 - 0.9</td>
<td>0.8 - 0.6</td>
<td>≤ 0.5</td>
</tr>
<tr>
<td>COAGULATION</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>WNL</td>
<td>0.99 - 0.75 x Normal</td>
<td>0.74 - 0.50 x Normal</td>
<td>0.49 - 0.25 x Normal</td>
<td>≤ 0.24 x Normal</td>
</tr>
<tr>
<td>Prothrombin Time (PT)</td>
<td>WNL</td>
<td>1.01 - 1.25 x Normal</td>
<td>1.26 - 1.50 x Normal</td>
<td>1.51 - 2.00 x Normal</td>
<td>&gt; 2.00 x Normal</td>
</tr>
<tr>
<td>Partial Thromboplastin Time (APTT)</td>
<td>WNL</td>
<td>1.01 - 1.66 x Normal</td>
<td>1.67 - 2.33 x Normal</td>
<td>2.34 - 3.00 x Normal</td>
<td>&gt; 3.00 x Normal</td>
</tr>
<tr>
<td>MUSCLE</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cramping</td>
<td>None</td>
<td>Requires stretching and massage; no interference with activities of daily living.</td>
<td>May temporarily interfere with activities of daily living (&lt; 24 hours).</td>
<td>Substantially interferes with activities of daily living (&gt; 24 hours).</td>
<td>Unresponsive to medication; unable to perform activities of daily living.</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>None</td>
<td>Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing.</td>
<td>Unable to take solid food normally; swallowing semi-solid food; dilatation may be indicated.</td>
<td>Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required.</td>
<td>Necrosis; perforation; fistula.</td>
</tr>
<tr>
<td>GALLBLADDER</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>No symptoms; no abnormality by ultrasound (US)</td>
<td>No symptoms; changes by ultrasound</td>
<td>No symptoms; changes by ultrasound including stones</td>
<td>Stones or other changes by ultrasound with symptoms lasting &gt; 6 hours or leading to treatment</td>
<td>Stones or other changes by ultrasound with symptoms leading to surgery, hospitalization or in-tense medical intervention</td>
</tr>
<tr>
<td>UNSPECIFIED</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Local scales used at a particular site may be used as a guideline for grading toxicity, provided the grading is consistent with this standard scale.</td>
<td>No change from baseline</td>
<td>Asymptomatic signs or mild symptoms not requiring any intervention and not interfering with daily activities.</td>
<td>Moderate symptoms; may require intervention with mild medications; may interfere with normal activities.</td>
<td>Severe symptoms interfering significantly with daily activities and requiring intervention with potent medications.</td>
<td>Life-threatening symptoms or symptoms threatening permanent severe disability; requires immediate, major intervention.</td>
</tr>
</tbody>
</table>
APPENDIX 5. Declaration of Helsinki

DECLARATION OF HELSINKI
Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, and the 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World Medical Assembly, Hong Kong, September 1989

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical or mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding, of the etiology, and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research, a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying, direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future; It must
be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I - BASIC PRINCIPLES

1) Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and a thorough knowledge of the scientific literature.

2) The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3) Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4) Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objectives is proportionate to the inherent risk to the subject.

5) Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6) The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7) Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8) In publishing, the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9) In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her
consent of participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10) When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case, the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11) In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12) The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II - MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (clinical research)

1) In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering,

2) The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3) In any medical study, every patient - including those of the control group, if any - should be assured of the best proven diagnostic and therapeutic method.

4) The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5) If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).

6) The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.
III - NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS
(non-clinical biomedical research).

1) In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2) The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3) The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4) In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.
APPENDIX 6. Adverse Event declaration form

(Art L.209-12, Alinéa, Public Health Code)

**I – INFORMATION ABOUT THE EVENT**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>day mo year</td>
<td>day mo year</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. Mark the corresponding choice (serious adverse event)

- O… Death
- O… Apt to be life threatening
- O… Invalidity or incapacity
- O… Hospitalization or extended hospital stay
- O… Other, describe

* in case of a follow up report or the end of an event, indicate the corresponding date

**II – INFORMATION ON SUSPECTED MEDICATION(S)**

9. SUSPECTED MEDICATIONS 15-POSOLOGY 16-ROUTE OF ADMINISTRATION

<table>
<thead>
<tr>
<th>10. THERAPEUTIC INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>o YES            o NO              o…  S.O</td>
</tr>
</tbody>
</table>

11. DATE OF TREATMENT

<table>
<thead>
<tr>
<th>12. DURATION OF TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA (=not applicable)</td>
</tr>
</tbody>
</table>

15. Medication administered: was the randomization code revealed?

- o Yes, result:…………………………
- o NO
- o  NOT APPLICABLE

**III – ASSOCIATED MEDICATION(S) AND PREVIOUS HISTORY**

16. ASSOCIATED MEDICATIONS and ADMINISTRATION DATES (except for those used to treat the observed event)

17. RELEVANT HISTORY (for eg : diseases, allergies, pregnancy or the date of the last period).

**IV – INVESTIGATOR**

<table>
<thead>
<tr>
<th>18. Name and Address :</th>
</tr>
</thead>
<tbody>
<tr>
<td>19. Relationship between the event and the study product:</td>
</tr>
<tr>
<td>o no</td>
</tr>
<tr>
<td>o improbable</td>
</tr>
<tr>
<td>o possible</td>
</tr>
<tr>
<td>o probable</td>
</tr>
<tr>
<td>o impossible to evaluate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>20. Date :</th>
<th>Signature :</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><strong>/</strong></em><strong>/</strong>___</td>
<td></td>
</tr>
</tbody>
</table>

**V – SPONSOR**

| 21a. NAME AND ADDRESS OF THE SPONSOR |
| 21b. IDENTIFICATION N° of the EVENT by SPONSOR : |
| n° |

| 21c. DATE OF RECEPTION BY THE SPONSOR |
| 21d. ORIGIN OF THE REPORT |
| ___/_____/_____ |
| o Biomedical Research. In this reference of the investigator: Center N° |
| o Study o Literature o Health profession o Other |

<table>
<thead>
<tr>
<th>22. TYPE OF REPORT :</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Initial o Follow up n°</td>
</tr>
<tr>
<td>23a. If the sponsor feels the adverse event is related to the drug being studied:</td>
</tr>
<tr>
<td>o the event is expected</td>
</tr>
</tbody>
</table>

| 23b. Sponsor’s comments |

DATE ____/_____/_____

Name and title of sponsor representative: ________________________________

Signature: ________________________________
APPENDIX 7.  Opinion of CPP

CPP - Ile-de-France VI
Groupe Hospitalier Pitié-Salpêtrière

CPP n° 46-07          A Paris, le 25 juin 2007
EudraCT : 2007-001174-81

le comité a été saisi le : 30 mai 2007
d'une demande d'avis pour le projet de recherche intitulé :

"Randomized multicenter phase III study in patients with locally advanced adenocarcinoma of the pancreas: gemcitabine with or without chemoradiotherapy and with or without erlotinib" Protocol LAP 07

donc le promoteur est : GERCOR
donc le coordinateur est : Professeur P. HAMMEL

Le comité a examiné les informations relatives à ce projet lors de sa séance du :

19 juin 2007

Ont participé à la délibération :
Claude ANDRE - Allergologue (T)
Odile BALAND - Infirmière (T)
Laurent CAPELLE - Neurochirurgien (T)
Christophe DEMONFACON - Représentant des associations agréées de malades (T)
Marie-Hélène FIEVET - Pharmacien hospitalier (T)
Marie GICQUEL-BENADE - Travaillieur social (T)
Jean-Louis GOLMARD - Biostatisticien (T)
Thierry HERGUETA - Psychologue hospitalier (T)
Annie LE FRANC - Représentante des associations agréées de malades (T)
Fabienne LEVASSEUR - Qualifiée en matière juridique (T)
Marie-Cécile MASURE - Psychologue hospitalier (S)
Michèle MEUNIER-ROTIVAL - Chercheur en génétique (S)
Anne-Laure MORIN - Qualifiée en matière juridique (T)
Corinne TAIROG - Représentante des associations agréées de malades (S)
Martin THIBIERGE - Neuroradiologue (S)

LE COMITE A ADOPTE LA DELIBERATION SUIVANTE : AVIS FAVORABLE

Motivation : Le comité a estimé que le rapport bénéfice/risque est acceptable pour les sujets participant à la recherche.

Le Président de séance

Docteur Jean-Louis GOLMARD

CPP IDF VI 47, Boulevard de l'Hôpital 75013 PARIS
Tel : 01 42 16 16 85 Fax : 01 42 16 27 15

APPENDIX 8. Insurance Policy

Biomedicinsure
Société de courtage d’Assurances
SAS au capital de 48,000 €
RCN VANNESS 147 351 308 - APR 672
PARC D’INNOVATION BRETAGNE SUD
C.P. 141 - 56088 VANNESS CEDEX
Tél. : 33 2 97 69 19 19 - Fax : 33 2 97 69 11 11
E-mail : info@biomedicinsure.com

GERLING FRANCE

ATTESTATION D’ASSURANCE
RESPONSABILITÉ CIVILE
PROMOTEUR DE RECHERCHE BIOMÉDICALE
ADHÉSION n°
200700069

Nous, soussignés GERLING FRANCE - 111, rue de Longchamp 75116 PARIS, agissant en qualité d’assureur, attestons par la présente que :

GERCOR
22, rue Malher
75004 PARIS

a souscrit un contrat de Responsabilité Civile sous le n° (1680) 90712


Description précise de la recherche assurée :

RANDOMIZED MULTICENTER PHASE III STUDY IN PATIENTS WITH LOCALLY ADVANCED ADENOCARCINOMA OF THE PANCREAS: GEMCITABINE WITH OR WITHOUT CHEMORADIOTHERAPY AND WITH OR WITHOUT ERLOTINIB.
Protocole n° LAP 07

La garantie est conforme à l’obligation d’assurance instituée par les textes de la loi précitée, article L. 1121-10 du Code de la Santé Publique, à la charge du promoteur, tant pour sa responsabilité que pour celle des intervenants.

La garantie prévue au contrat restera acquise à l’Assuré en cas de modification affectant la prise d’effet du protocole.

La présente attestation est valable pour la durée de la recherche concernée et sa présentation vaut présomption de garantie à la charge de l’assureur.

Fait le 17 avril 2007

Le Courtier

Biomedicinsure
Société de courtage d’Assurances
SAS au capital de 48,000 €
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PARC D’INNOVATION BRETAGNE SUD
C.P. 141 - 56088 VANNESS CEDEX
Tél. : 33 2 97 69 19 19 - Fax : 33 2 97 69 11 11
E-mail : info@biomedicinsure.com

L’Assureur

GERLING
Allgemeine Versicherungs-AG
147/2007

Direction pour la France
111, rue de Longchamp 75116 PARIS

Complément péréi rôye par le Code des Assurances
Capitale 234 769 483 €
R.C.S. Paris B 375 746 419