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Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: protocol for a randomized phase III trial

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Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: a randomized phase III trial

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ABSTRACT

Introduction: Palliative care (PC) has been usually offered at end-life stage, although the World Health Organization recommends providing PC as earlier as possible in the course of the disease. A recent study has shown that early PC (EPC) provides a meaningful effect on quality of life and surprisingly on overall survival (OS) over standard treatment to patients with metastatic lung cancer. Whether EPC benefit also applies to patients with metastatic upper gastrointestinal (GI) cancers is unknown.

Methods and analysis: EPIC is a randomized phase III trial comparing EPC plus standard oncologic care versus standard oncologic care in the setting of metastatic upper GI cancers. Its primary objective is to evaluate the efficacy of EPC in terms of OS. Secondary objectives are to assess the effect of EPC in terms of patient-reported outcomes (quality of life, depression and anxiety), and the number of patients receiving chemotherapy in their last 30 days of life. Assuming an exponential distribution of survival time, 381 deaths are required to ensure an 80%-power for an absolute difference of 10% in one-year OS (40% vs 50.3%, HR=0.75; logrank test two-sided alpha=5%), leading to a planned sample size of 480 patients enrolled over 3 years, with a final analysis at 4 years. The main analysis will be performed on the intention-to-treat dataset.

Ethics and dissemination: The study was approved by the "Comité de Protection des Personnes Nord-Ouest I" (April 4th, 2016) and complies with the Helsinki declaration and French laws and regulations, and follows the International Conference on Harmonisation E6 (R1) Guideline for Good Clinical Practice. The trials results, even inconclusive, will be presented at international oncology congresses, and published in peer-reviewed journals.

Trial registration numbers: EudraCT number: 2015-A01943-46; ClinicalTrials.gov number: NCT02853474.

Strenghts and limitations of this study

- Multicentric, nation-wide, academic trial with a randomized design
- Overall survival as a primary outcome
- Providing an extra survival benefit with early palliative care would be a considerable contribution for patients, as would be the same the implementation of these practices within the continuum of care of oncology

INTRODUCTION

Medical care in the metastatic setting

Medical oncology aims to increase patient's survival, even at metastatic stage, in addition to reduce disease-related and treatment-related symptoms. However, providing palliative care (PC), which includes symptoms management, nutritional support, psychosocial support, as well as assistance on end-of-life preferences in order to improve quality of life, may be as important as survival issues in such settings. Actually, decades ago, PC services were initiated in France in order to provide a medical alternative to the use of questionable medical practices regarding the end of life period: abandonment, euthanasia, and inappropriate aggressive therapy. According to the French society of palliative care,[1] PC is an approach aimed to provide active care, in a holistic approach to the person with a serious, progressive or terminal illness. The objective of PC is to relieve pain and other distressing symptoms, but also to take into account the psychological, social and spiritual suffering. PC offers an interdisciplinary support system to help patients and their relatives.[1] PC has been, in France (but also in the US),[3] usually offered late, at end-life stage, although the World Health Organization recommends providing PC as earlier as possible in the course of the disease, in order to increase quality of life.[2] Actually, PC access became a right guaranteed by the law, for patients and their families in 1999 in France.[4] This context explains why even nowadays, PC often means « end of life » not only for the lay-man but also for caregivers, and many doctors. The last World Health Organization recommendations are less restrictive than the outdated 1996 French recommendations, as it is stated that PC should be offered as early as possible in the course of the disease, in order to increase quality of life, and to positively influence the course of illness.[2] The World Health Organization recommendations add that PC is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.[2]

The concept of Early Palliative Care (EPC)

In a recent randomized study, 151 patients with newly diagnosed metastatic non–small-cell lung cancer were enrolled to receive either early PC (EPC) integrated with standard oncologic care or standard oncologic care alone.[5] It was hypothesized that patients, who received EPC would have a better quality of life (primary endpoint) compared with patients who received standard oncologic care only. In the EPC group, the first visit with the PC services (board-certified PC physicians and advanced-practice nurses) was planned within 3 weeks after enrollment and at least monthly thereafter; all patients but one had the first visit by the 12th week, with a mean number of visits of 4. In this study, the authors referred the PC package to the recommendations of the National Consensus Project for Quality Palliative Care.[6] In this setting of metastatic non–small-cell lung cancer, EPC led to significant improvements in quality of life and in mood. In addition, EPC led to a significantly

longer survival (median survival, 11.6 vs. 8.9 months; HR=0.60, p=0.02), despite less aggressive end-of-life care.[5] Following the publication of Temel and colleagues,[5] the American Society of Clinical Oncology recommended that "combined standard oncology care and PC should be considered earlier in the course of the illness for any patient with metastatic cancer….".[7] However, it appears that a gap exists (not only in France) between these recommendations and current practice. Moreover, there is no consensus on how early PC should be integrated into oncologic services, as a randomized trial reported recently a non-significant better survival favoring early (30 to 60 days after diagnosis) versus delayed (3 months later) initiation of PC in 207 patients diagnosed with an advanced cancer of various types.[3] The results of the Temel's study have modified the perception of many oncologists about the objectives of PC. However, additional clinical studies seem necessary before considering EPC as an additional survival input in other advanced malignancies than metastatic non-small-cell lung cancers.

Metastatic upper gastrointestinal cancers

The median survival of metastatic upper gastrointestinal (GI) cancers such as pancreatic cancers, esogastric cancers, and biliary tract cancers did not exceed 10-11 months, which is as poor as reported with metastatic lung cancers. Standard of care in metastatic upper GI cancers are well described in European Society of Medical Oncology guidelines.[8-10] Briefly, standard of care in metastatic pancreatic cancer in the first-line setting lies on the combination of fluorouracil, irinotecan, and oxaliplatin (folfirinox regimen) for patients without any cholestasis and in good performance status, and on gemcitabine monotherapy in frail patients.[8] In metastatic biliary tract cancers, standard of care lies on gemcitabine-based regimen (gemcitabine monotherapy, gemcitabine plus cisplatin, or gemcitabine plus fluorouracil).[9] Besides HER2 positive metastatic gastric/esogastric patients who present with much better prognosis, and should be treated with trastuzumab-based regimen, most of patients with metastatic HER2 negative tumors have poor prognosis, with similar survival rates than patients with other upper GI malignancies.[10] In that setting, various combinations of cytotoxics (fluoropyrimidins, taxanes, platinum compounds) may be offered to patients.[10] Several experimental treatments (antiangiogenics, MET inhibitors, modulators of immune check points, new cytotoxics, etc...) may be offered to patients in that setting, but these are restricted to patients in good health condition who accept to participate in clinical trials, and none have produced meaningful survival benefit yet. To make short, patients with metastatic upper GI cancers do not benefit much from currently available systemic therapies. Providing an extra survival benefit with EPC would be a considerable contribution for these patients, as would be the same the implementation of these practices within the continuum of care of oncology, in France.

Aim of the study

We designed a randomized controlled trial, called EPIC, aiming to demonstrate that the use of EPC provides a clinical benefit over standard practice to a population of patients with

metastatic upper GI cancers. Overall survival (OS) will be used as a primary endpoint. The content of palliative care visits will be studied through a specific checklist. Patient-reported outcomes (quality of life, depression and anxiety) will be also investigated through dedicated and validated questionnaires.

METHODS AND ANALYSIS

Study design

This study was designed as a randomized, open-label, multicenter phase III trial. It is aimed to estimate the survival benefit of EPC combined with standard oncologic care (experimental arm) over standard oncology care only (standard arm), in patients with metastatic upper GI cancers (esogastric/gastric cancer, pancreatic cancer, biliary tract cancers). After the participant's eligibility is established, informed consent has been obtained and stratification factors are defined, the participant will be enrolled in the study and the treatment will be centrally allocated using the on-line CS randomization Clinsight software module (Ennov, San Francisco, CA, USA) ensuring the concealment of the next patient allocation. Treatments will be randomized in a 1:1 ratio, and a minimization procedure will be used to balance patients according to: center, performance status (0-1 versus 2) and tumor location (esogastric/gastric, pancreas, and biliary tract). Patients will be recruited nationwide, in 17 university hospitals or cancer centers in France. Written informed consent will be obtained by an investigator from the patient before any screening and inclusion procedure. Patient will remain on study until one of the following condition applies: study withdrawal (patient or sponsor or investigator's decision), death.

Outcome measures

Study objectives

The primary objective of this study is to evaluate the efficacy of EPC in terms of OS curves (intent-to-treat analysis). The secondary objectives are to assess (a) the efficacy in terms of 1-year OS (intent to treat and as per protocol analysis) and OS curves (as per protocol analysis), (b) the patient-reported outcomes (quality of life, depression and anxiety) and the Time Until Definitive Deterioration (TUDD) for Quality of Life, (c) the number of patients receiving chemotherapy in their last 30 days of life, (d) the actual description of the PC package, and (e) the presence or lack of advanced directives in patient files.

Measurement tools

OS is defined as the time between the date of randomization and the date of death, whatever the cause. Patients alive at cut-off date are censored at that date. Quality of Life is assessed with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. QLQ-C30 is aimed to measure the overall quality of life, physical conditions, and limits to the ability to carry out everyday activities, cognitive, emotional and social functioning and the appearance of symptoms frequently associated with cancer or its

treatment. Patients are asked to check a scale of one to four (not at all, a little, quite a lot, a lot) or seven points (from 1 – very bad – to 7 – excellent). For each dimension, QLQ-C30 score is considering definitive deterioration if the score decreases by more than 10 points as compared with the score at baseline, without later improvement superior to 10 points as compared with baseline or if the patient dropped out of the study resulting in missing data. Thus, TUDD for Quality of Life scores is defined as the time from randomization to the first observation of a definitive deterioration of QLQ-C30 score or death. Depression is assessed with the HADS scale (Hospital Anxiety and Depression Scale). HADS is aimed to detect anxiety and depressive disorders. It contains 14 items graduated from 0 to 3: 7 items in relation with anxiety (score A) and 7 items in relation with depression (score D). The maximum note of each score is 21. The number of patients treated with chemotherapy in their last 30 days before death will be recorded. PC visits will be performed by PC physicians. In both arms, the content of PC visits will be described through a specific check-list filled by the PC physician after each visit. The number of patients whom advanced directives are identified in medical records will be recorded.

Patient selection criteria

Inclusion criteria

Patients must:

- Have an upper gastrointestinal metastatic cancer pancreatic, biliary tract or gastric (including junctional Siewert 2 and 3 cancers) cancers.
- Be aged 18 or older
- Have an Eastern Cooperative Oncology Group performance status ≤2
- Be planned for treatment with first-line chemotherapy
- Have a life expectancy of greater than 4 weeks
- Have a good understanding of French language
- Have an health insurance coverage
- Have signed and dated a written informed consent

Exclusion criteria

Patients identified with any of the following conditions or characteristics are excluded from the study:

- Locally advanced cancer
- Junctional Siewert 1 esogastric cancer
- Gastric or junctional esogastric cancer with dysphagia m
- Gastric or junctional esogastric cancer with unknown or positive HER2 status
- Compression of the biliary tract without any bypass procedure

Study description

Intervention (figure 1)

Medical oncologists are in charge of the patient for CT administration and for supportive care, in accordance with professional practices. PC specialists are in charge of PC/EPC visits.

In the standard arm (CT alone), a PC visit can be performed, anytime, if needed. In the experimental arm (CT + EPC), 5 PC visits are scheduled. The first visit (V1) will be scheduled within the first 3 weeks after randomization. V2, V3, V4, and V5 visits will be scheduled every month. The content of each of the 5 PC visits will be described by the PC physician, by filling a specific check-list built by PC physicians. Briefly, the latter will focus on the following items:

- Discussion with the patient focusing on its understanding of its disease, its treatment, and the palliative care process
- Evaluation of clinical status and symptoms
- Evaluation of psychological status
- Evaluation of the social environment including its way of living
- Stakeholder needs : psychologist, physiotherapist, dietician, social worker …
- Caring for the patient and his family
- Discussion about the identification of the "person of trust" and about advanced directives
- Coordination and continuum of care

The choice of first-line CT is left to the choice of the each investigator, but should refer to national or international guidelines. If, for any reasons (toxicity, disease progression, or deterioration of health status), CT is stopped, the patient remains in the study.

Data collection

At baseline, before randomization, patients have to fill the EORTC-QLQ-C30 and the HADS questionnaires. During the study, the EORTC-QLQ-C30 and the HADS questionnaires have to be filled by patients every 8 weeks since randomization. Then, 24 weeks after randomization, the EORTC-QLQ-C30 questionnaire only has to be filled by patients, every 8 weeks until the end of the study. In both arms, the number of PC/EPC visits performed will be collected. The number of patients whom advanced directives are identified in medical records will be recorded.

Statistical considerations

Three hundred eighty-one (381) deaths are required to show with an 80%-power a significant difference in OS curves if there is an absolute difference of 10% in one-year OS (40% vs 50.3%, HR=0.75; two-sided alpha=5%, logrank test), assuming proportional hazards over time. Assuming an exponential distribution of survival time, with accrual duration of 3 years, a 1 year minimum follow-up and a final analysis at 4 years, it is necessary to randomize 480 patients (240 in each group). This calculation takes into account a yearly 2% loss to follow-up rate. An efficacy interim analysis is planned when approximately 190 deaths are observed (which is expected to occur 27 months since the start of the study). The significance level is fixed at p=0.003 for the interim analysis and p=0.049 at the final analysis (Lan de Mets alpha-spending function,[11] with an O'Brien Fleming efficacy stopping rule.[12] No futility analysis is planned as the proportional hazards assumption may not be respected, with possibly a larger treatment effect with longer follow-up than in the first part of the survival curves. The interim analysis will also evaluate whether the sample size of the

EPIC trial should be increased, considering the observed OS curve in the control group.

OS curves will be estimated using Kaplan-Meier method. After check of proportional hazards assumption, the treatment effect of the experimental arm compared to the control arm in terms of OS will be based on the estimation of the Hazard Ratio of death in a Cox model (HR-death, based on the comparison of the OS curves between the two treatment groups), tested against the null hypothesis of no treatment effect using a logrank test with a two-sided alpha of 5%. The proportional hazards assumption underlying the HR estimate in Cox models will be evaluated, using graphic methods and models including interaction with time. Appropriate methods for treatment effect estimates will be used if the proportional hazard assumption appears violated or questionable (use of restricted mean survival as published by Royston and Parmar.[13] Heterogeneity of treatment effect by the stratification factors will be evaluated using forest plots and interaction tests. The main analysis will be performed on the intention-to-treat dataset, including data of all patients in the treatment group allocated by randomization until their last follow-up visit. A sensitivity analysis is also planned on the per protocol dataset where patients in the standard arm who got more than a PC visit within the first 6 months of treatment since randomization will be censored at the date of their second PC visit, and patients in the interventional arm who actually got less than 5 EPC visits within the first 6 months since randomization will be censored at the date of first missing EPC visit. One year survival rates with their 95% confidence interval will also be estimated and compared, both on the intent-to-treat and per protocol datasets.

Quality of life will be analyzed according to EORTC manual recommendations. For each dimension, patients with at least one score are included in the analysis. Patients without follow-up QLQ-C30 score are censored just after baseline. Patients without baseline are censored at baseline. TUDD curves for both arms are calculated using the Kaplan-Meier method and described using median and 95% confidence interval.

An Independent Data Monitoring Committee will meet when the results of the planned interim analysis are available (i.e. when 190 patients will be dead) to review the results of the first efficacy interim analysis, and to re-estimate the sample size if the baseline overall survival rate differs from the protocol assumptions.

ETHICS AND DISSEMINATION

Ethical considerations

This clinical trial is being conducted in accordance to the Declaration of Helsinki [14] or the laws and regulations of the country, whichever provides the greater protection to the patient. The study follows the International Conference on Harmonization E6 Guideline for Good Clinical Practice, reference number CPMP/ICH/135/95.[15] The protocol has been examined by the Patient Committee of the National League against Cancer, paying particular attention to the quality of the information letter, to the monitoring plan, and to suggestions implemented into the protocol to improve the comfort of the patients. An independent data

monitoring committee for the trial will be set, in order to guarantee protection of the patients, to ensure that the trial is conducted in an ethical fashion, and to evaluate the risk/benefit ratio of the trial by reviewing the interim results of the trial. The study protocol has been approved by our local ethics committee (CPP Nord-Ouest I, April 4th, 2016).

Dissemination

The study is registered in clinicaltrials.gov (NCT02853474).The protocol and the trial results, even inconclusive, will be presented at international oncology congresses, and published in peer-reviewed journals.

Trial financing

This study is supported by unrestricted public grants from Conseil Régional du Nord Pas-de-Calais and from caregivers Ligue National contre le Cancer.

DISCUSSION

This EPIC trial set up in September 2016. It is a randomized trial primarily designed to detect an OS benefit with EPC in addition to standard oncologic care over standard oncologic care only, in patients with metastatic upper GI cancer. The design of EPIC differs from the one of the seminal trial from Temel and colleagues,[5] which demonstrated first that EPC not only improves quality of life (the primary objective of their trial) but may also improve OS (a secondary objective) in patients with advanced cancers.

One may argue that the main motivation of many oncologists to engage with EPC surely is to enhance the quality of life of their patients throughout the whole cancer journey. This is precisely what did Temel et al.[5] With the choice of OS as the primary endpoint of EPIC, as we did, there is a theoretical danger that if this study does not meet its OS endpoint it will be interpreted as meaning that EPC has “failed” and should be discarded. Our point is clearly different. Our country has a strong culture of integrating PC into oncology services. However despite efforts of many PC professionals, PC is frequently offered to patients at a late stage of their metastatic disease. Some components of PC visit such as visits with a dietician and/or with psychologists are usually offered at an earlier stage, but maybe not as systematically as it should be. With OS as the primary endpoint of EPIC, we postulate that without a strong “signal” such as a survival benefit, sent to medical oncologists and colleagues in charge of metastatic patients with upper GI malignancies, it would take, *stricto sensu* sometime before the concept of EPC be implemented in our country. Furthermore, the benefit of EPC has not been validated yet in the population of patient with metastatic upper GI cancers. Obviously, patients with metastatic upper GI malignancies are different from patients with metastatic lung cancers; they do not present the same, and we assume that their co-morbidities as well as their treatment-related symptoms are also different. The difference in terms of reduction of risk of death (-25%) that we had chosen for primary

outcome derived from one reported by Temel et al. (-40%) in the setting of metastatic lung cancers.[5] Reducing this expected reduction of risk of death to 25% should lower the theoretical danger that this study does not meet its OS endpoint.

In the Temel's trial, the content of the EPC package,[10] in fact rather vague, was adapted from American guidelines for the palliative care visits.[6] There are no such recommendations in our national context. In order to overcome this, PC specialists have built a check-list of all the items that could be addressed within PC coverage. Hence, one of the secondary endpoints of this EPIC trial will be to make an actual description of each EPC/PC visit, as well as the description of the whole EPC/PC package. At the end, the material we will collect in that setting should help us in drafting guidelines for PC in France.

To conclude, we expect that this study will lead to an earlier integration of PC in oncologic care of metastatic GI cancers.

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Contributors AA, AD, EH, MCL designed the study; AA, AD, MCL, EH, SL contributed to the drafting of the manuscript; AA, SL, EH, SD contributed to the trial set-up, SD is responsible for data collection and for administrative support, EB will contribute to statistical analysis, MCL is responsible for data management and statistical analysis; AA, EH, AD, MCL will contribute to data interpretation. All authors contributed to the revision of the manuscript, and approved it for submission.

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Competing interests None.

Ethics approval (CPP Nord-Ouest I, April 4th, 2016)

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This is original materials without any unpublished data, but the full results of this ongoing trial

FIGURE LEGEND

Figure 1 – Study design

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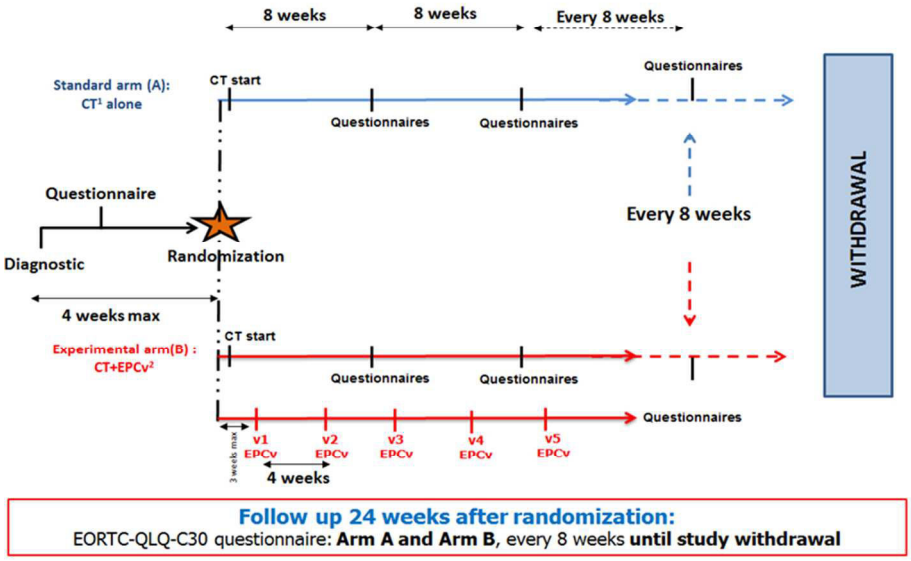
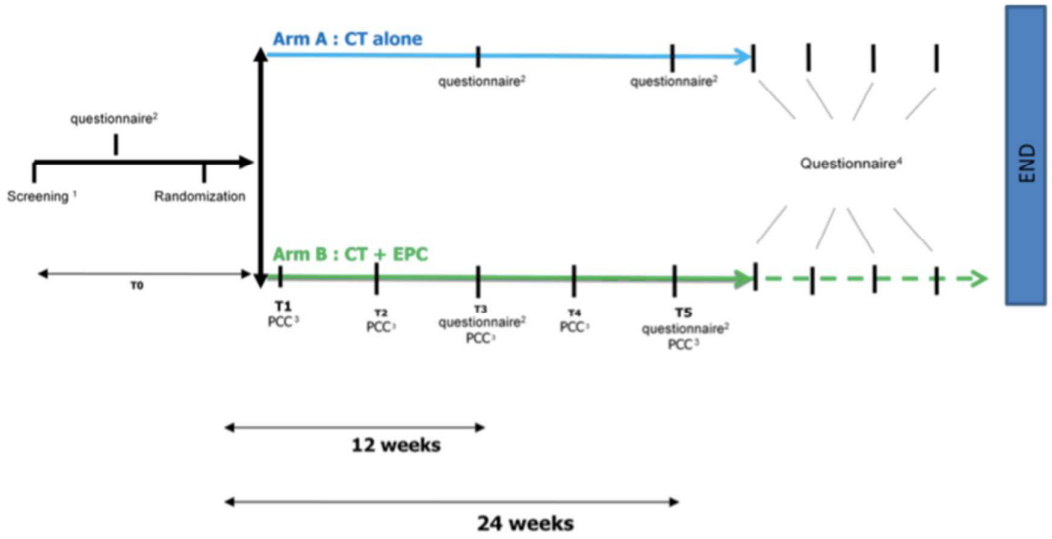


Study design

254x190mm (96 x 96 DPI)

Appendix 1- Study plan



¹: Information - Signature of consent– verification inclusion criteria/ exclusion criteria
²: self assessment of quality of life(QLQ-C30) and of depression (HADS)
³ : PCC : palliative care consultation
⁴ : self assessment of quality of life(QLQ-C30) every 8 weeks until withdrawal study

CLINICAL STUDY PROTOCOL

Study number: 1511

Protocol title:

Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers, treated with first-line chemotherapy: a randomized phase III trial

Study code: EPIC-1511

N° IdRCB N°: 2015-A01943-46

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Confidentiality

Version 2.2 approved by «CPP Nord-Ouest I» on December 16th, 2016 and by ANSM on December 26th, 2016

1. APPROVAL AND PROTOCOL SIGNATURE

Study code: EPIC-1511

SPONSOR REPRESENTATIVE		
	Date	Signature
Pr Eric LARTIGAU Director-General *Centre Oscar Lambret – Lille – France*		
COORDINATING INVESTIGATOR FOR STUDY		
	Date	Signature
Pr Antoine ADENIS Coordinator		
Dr Arlette DA SILVA Co-Coordinator		

Principal investigator / Site

Investigator name and address:

I have read the present protocol.

I agree:

- To obtain approval of my Institution to lead the study in the establishment;
- To maintain confidentiality regarding the contents of this protocol;
- To conduct the study as outlined in the protocol and in compliance with GCP and with applicable regulatory requirements ;
- To provide the protocol and all drug information provided to me by the sponsor, to all physicians responsible to me who participate in this study. I will discuss the material with them to ensure that they are fully informed regarding the drug and the conduct of the study;
- To direct and assist appropriately the staff under my responsibility, who will be involved in the study;
- To use the trial material only according to the instructions of the protocol;
- To permit monitoring, auditing and inspection;
- To keep the trial-related essential documents until the sponsor indicates that these documents are no longer needed.

Investigator signature: **Date:**

2. LIST OF TRIAL SITES AND COORDINATING STUDY PERSONNEL

The list of trial sites will be attached to the protocol.

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3. SYNOPSIS

See attached documents.

4. BACKGROUND AND RATIONALE OF THE STUDY

Medical care in the metastatic setting

Medical oncology is aimed to increase patient's survival, even at metastatic stages, in addition to disease-related and treatment-related symptoms. However, providing palliative care (PC) which includes symptoms management, nutritional support, psychosocial support, as well as assistance on end-of-life preferences, may be as important as survival issues to improve quality of life in such setting. In France, PC has been traditionally offered late, at end-life stage, although the World Health Organization recommends providing PC as earlier as possible in the course of the disease, in order to increase quality of life [1].

Palliative care

Decades ago, PC services were initiated in France in order to provide a medical alternative to the use of questionable medical practices regarding the end of life period: abandonment, euthanasia, and inappropriate aggressive therapy. According to the French society of palliative care (Société Française d'Accompagnement et de Soins Palliatifs, 1996) [2], PC is an approach aimed to provide active care, in a holistic approach to the person with a serious, progressive or terminal illness. The objective of PC is to relieve pain and other distressing symptoms, but also to take into account the psychological, social and spiritual suffering. PC offers an interdisciplinary support system to help patients and their relatives [2]. As mentioned previously, PC has been in France (but also in the US) [3] usually offered late, at end-life stage. Actually, PC access became a Right guaranteed by the Law, for patients and their families in 1999 (Kouchner law and 1st Program for PC implementation in 1999-2001) [4]. This context should explain why even nowadays, PC often means « end of life » not only for the lay-man for the general public but also for caregivers, and some doctors.

The last World Health Organization (WHO) recommendations are less restrictive than the rather dated 1996 French recommendations, as it is stated that PC should be offered as earlier as possible in the course of the disease, in order to increase quality of life, and to positively influence the course of illness [1]. The World Health Organization recommendations add that PC is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications [1].

The concept of Early Palliative Care (EPC)

In a recent randomized study, 151 patients with newly diagnosed metastatic non–small-cell lung cancer were randomized to receive either early PC (EPC) integrated with standard oncologic care or standard oncologic care alone (Temel JS, N Engl J Med 2010) [5]. It was hypothesized that patients, who received EPC, compared with patients who received standard oncologic care only, would have a better quality of life (primary endpoint). The first visit with the PC service set up within the first 12 weeks, and the median number of visits in the EPC group was 4. In this study, the authors referred to the recommendations of the National Consensus Project for Quality Palliative Care [6]. Among patients with metastatic non–small-cell lung cancer, EPC led to significant improvements in quality of

life. In addition, EPC led to significant improvements in mood, as well as in overall survival (median survival, 11.6 vs. 8.9 months; HR=0.60, p = 0.02)), despite less aggressive end-of-life care [5].
Following the publication of Temel et al. [5], the American Society of Clinical Oncology recommends nowadays that "combined standard oncology care and PC should be considered earlier in the course of the illness for any patient with metastatic cancer…." [7]. However, it is clear that a gap exists (not only in France) between this recommendation and current practice, and that there is no consensus on how early PC should integrated in oncologic services, even though an underpowered small randomized trial reported recently an insignificant better survival favoring early versus delayed (3 months later) initiation of PC [3].
The results of study of Temel et al. [5], although formally restricted to the field of metastatic non-small-cell lung cancers, have modified the perception of many oncologists about the objectives of PC. However, additional clinical studies should be done before considering EPC as an additional survival input in other advanced malignancies.

Metastatic upper gastrointestinal cancers

The median survival of metastatic upper gastrointestinal (GI) cancers such as pancreatic cancers, gastric cancers, and biliary tract cancers did not exceed 10-11 months, which is as poor as reported with metastatic lung cancers. Standard of care in the metastatic setting in upper GI cancers are described in *ad hoc* French guidelines, i.e.: "Thésaurus National de Cancérologie Digestive" [8]. Briefly, standard of care in metastatic pancreatic cancer in the first-line setting lies on the combination of fluorouracil, irinotecan, and oxaliplatin (folfirinox regimen) for patients without any cholestasis and in good performance status, and on gemcitabine monotherapy. In metastatic biliary tract cancers, standard of care in terms of chemotherapy lies on gemcitabine-based regimen (gemcitabine monotherapy, gemcitabine plus cisplatin, or gemcitabine plus fluorouracil). Besides HER2 positive metastatic gastric/esogastric patients who present with much better prognosis, and should be treated with trastuzumab-based regimen, most of patients with metastatic HER2 negative patients (IHC + or IHC ++ with negative fish/sish) have poor prognosis, with similar survival rates than patients with other upper GI malignancies. In that setting, several regimens may be offered to patients, such as the following: Folfox, EOX/ECX, Folfiri, LV5FU2-cisplatin, Capecitabine-platinum salt or docetaxel-based regimen ...) [8]. Several experimental treatments (antiangiogenics, met inhibitors, modulators of immune check points, etc...) are currently tested in metastatic gastric/esogastric cancers, but these treatments are restricted to patients in good health condition who accept to participate to clinical trials, and none have yet produced meaningful survival benefit in the first-line setting.
To summarize, therapeutic progresses in the setting of metastatic upper GI cancers are infrequent, and often modest. Providing an extra survival benefit for these patients with EPC, may contribute to deeply modify the practice of care of oncology in France.

Why did we choose OS as the primary endpoint of this trial?

One may argument that the main motivation of oncologists to engage with EPC surely should be to enhance the quality of life of their patients throughout the whole cancer journey. This is precisely what did Temel et al. [5]. Moreover, there is a theoretical danger that if this study does not meet its OS endpoint it will be interpreted as meaning that EPC has "failed" and should be discarded.

Our point is clearly different. Our country has a strong culture of integrating PC into oncology services. However despite efforts of many PC professionals, PC is frequently offered to patients at a late stage of their metastatic disease. Some components of PC visit such as visits with a dietician and/or with psychologists may be offered at an earlier stage, but maybe not as systematically as it should be. We postulate that without a strong "signal" such as a survival benefit, sent to medical oncologists and colleagues in charge of metastatic patients with upper GI malignancies, it would take some time before the concept of EPC be implemented in our country. Furthermore, and *stricto sensu*, the benefit of EPC has not been validated yet in the population of patient with metastatic upper GI cancers. Obviously, patients with metastatic upper GI malignancies are different from patients with metastatic lung cancers; they do not present the same, and we assume that their co-morbidities as well as their treatment-related symptoms are also different. The difference in terms of reduction of risk of death (-25%) that we had chosen for primary outcome derived from one reported by Temel et al. (-40%) in the setting of metastatic lung cancers [5]. Reducing this expected reduction of risk of death to 25% should lower the theoretical danger that this study does not meet its OS endpoint.
Finally, as we believe that quality of live is also an important goal in the setting of metastatic upper GI cancers, and as we anticipate that EPC may have a positive effect in lowering the quality of life degradation, we add to the classical QLQC30 questionnaire, the study of Time Until Definitive Degradation (TUDD) of Quality of Life.

5. OBJECTIVES

5.1. Primary objective

- Efficacy in term of overall survival (intent-to-treat analysis)

5.2. Secondary objectives

- Efficacy in term of 1-year survival (intent to treat and as per protocol analysis) and overall survival (as per protocol analysis)
- Patient-reported outcomes (Quality of life, depression and anxiety, …)
- TUDD (Time Until Definitive Deterioration) for Quality of Life
- Number of patients on chemotherapy, in their last 30 days of life
- Description of the content of Palliative Care (PC)

6. STUDY DESIGN

6.1. Overview

This prospective, randomized, open-label and multicenter phase III study is aimed to estimate the survival benefit of Early Palliative Care (EPC) combined with standard oncology care (including first-line chemotherapy) (experimental arm) over standard oncology care only (standard arm), in patients with metastatic upper gastrointestinal cancers (gastric cancer, pancreatic cancer, biliary tract cancers). Patients will be stratified by minimization according to:

- center,
- performance status (0-1 versus 2),
- localization (esogastric/gastric, pancreas, and biliary tract).

6.2. Inclusion criteria

- Patients with an upper gastrointestinal metastatic cancer: pancreatic, biliary tract or gastric (including junctional Siewert 2 and 3 cancers) cancers.

  NB: Esogastric junctional cancers with dysphagia and/or gastric/esogastric cancers with unknown or positive HER2 status are not eligible.
- Patients planed to be treated with first-line chemotherapy for metastatic disease.
- Age ≥ 18 years
- Life expectancy ≥ 1 month
- Performance status (OMS) ≤ 2
- Good understanding of French language
- Signed and dated informed consent
- Patients covered by government health insurance

6.3. Non inclusion criteria

- Locally advanced cancer
- Junctional Siewert 1 esogastric cancer
- Gastric or junctional esogastric cancer with dysphagia
- Gastric or junctional esogastric cancer with unknown or positive HER2 status (IHC: +++ or IHC ++ and FISH/SISH +)
- Compression of the biliary tract requiring a bypass
- Patients included in a clinical trial with an anticancer agent

6.4. Patient enrolment

The following procedures should be performed before the registration of the patient:

- Informed consent leaflet should be signed by both patient and investigator before starting any study procedure ;
- All selection procedures should be performed as per protocol ;

A randomization request form is to be filled in by the investigator in order to ensure that the patient meets ALL the selection criteria. BEFORE STARTING TREATMENT, the investigator must fax the randomization request form to the Sponsor:

Clinical Research Integrated Unit / Sponsor Unit

Centre Oscar Lambret – Lille - France

Tel: 33 (0)3 20 29 59 18 - Fax: 33 (0)3.20.29.58.96

After checking all the inclusion and non-inclusion criteria, an identification number will be allocated to the patient. This number will then be retained for the whole duration of the trial. A confirmation of inclusion and the arm to which the patient has been randomly assigned will be sent to the investigator.

After patient registration, the patient identification number and treatment arm allocated will be retained within the study even if the patient is withdrawn from the study before the first study drug administration.

6.5. Withdrawal from study

The study will continue until one of the following applies:

- Patient's choice
- Investigator's decision
- Sponsor's decision
- Patient's death

➢ **AT ANY TIME DURING THE STUDY TREATMENT:**

- ***Patient's death should be immediately notified to the sponsor in order to plan the interim analysis.***

7. ENDPOINTS

7.1. Primary endpoints

- **Overall survival (as intent-to treat analysis)**

The overall survival is defined as the time between the date of randomization and the date of death, whatever the cause.

7.2. Secondary endpoints

a. One year survival rate (intent-to treat and per protocol analyses), and overall survival (per protocol analysis)

One year survival rates with their 95% confidence interval in both intent-to-treat and per protocol analyses, as well as OS curves in per protocol analysis will be given.

b. Quality of life

The Quality of Life is assessed with the QLQ-C30 questionnaire at baseline, 8and 16 weeks after inclusion, as well as every 8 weeks thereafter.

The **QLQ-C30** by EORTC (European Organization for Research and Treatment of Cancer) measures the quality of life of patients suffering from cancer. It includes 30 items with measure the overall quality of life, physical conditions, and limits to the ability to carry out everyday activities, cognitive, emotional and social functioning and the appearance of symptoms frequently associated with cancer or its treatment. The participants reply on a scale of one to four (not at all, a little, quite a lot, a lot) or seven points (from 1 – very bad – to 7 – excellent).

c. Depression assessed with the HADS score

The depression is assessed with the HADS scale (Hospital Anxiety and Depression Scale) at baseline, and then 8 and 16 weeks after inclusion.

HADS is a tool which detects anxiety and depressive disorders. It contains 14 items graduated from 0 to 3: 7 items in relation with anxiety (score A) and 7 items in relation with depression (score D). The maximum note of each score is 21.

d. TUDD (Time Until Definitive Deterioration)

For each dimension, QLQ-C30 score is considering definitive deterioration if the score decreased by more than 10 points as compared with the score at baseline, without later improvement superior to 10

points as compared with baseline or if the patient dropped out of the study resulting in missing data. Thus, TUDD for Quality of Life scores was defined as the time from randomization to the first observation of a definitive deterioration of QLQ-C30 score or death. Median TUDD and 95% confidence interval are given for both arms.

e. Presence or lack of advanced directives

The number of patients whom advanced directives are written in their medical records will be recorded.

f. Actual contain of PC visits

A PC visit is a visit done by a PC physician. *Any kind of visits done by other professionals (i.e: dieticians, nurses, social workers, psychologists, pain specialists, etc.) IS NOT a PC visit.*

In both arms, some specific items will be collected:

- Actual number of PC visits within the first six months since randomization
- Actual timing of PC visits within the first six months since randomization
- Total number of PC visits until death

Only in Arm B (interventional arm), the content of each PC visit will be described by the PC physician at the end of the visit, by filling a specific check-list (*Cf.* appendix 3) built by an *ad hoc* working-group of PC physicians. Briefly, the latter will focus on the following items:

- Discussion with the patient focusing on its understanding related to its disease, its treatment, and the palliative care process.
- Evaluation of clinical status and symptoms
- Evaluation of psychological status
- Evaluation of the social environment including its way of living
- Stakeholder needs : psychologist, physiotherapist, dietician, social worker …
- Caring for the patient and his family
- Discussion about the identification of the "person of trust" and about advanced directives
- Coordination and continuum of care

g. Chemotherapy in the last 30 days before death

The number of patients treated with chemotherapy in their last 30 days before death will be recorded.

8. EVALUATION ASSESSMENT

8.1. Baseline assessment (T0)

Patients are included by a medical oncologist within 4 weeks after the diagnosis disclosure.

For each patient, *before randomization (T0):*

- EORTC-QLQ-C30 questionnaire
- HADS questionnaire

8.2. Assessment during study procedure

For both arms (Arm A and Arm B):

- ***every 8 weeks (T3 and T5)*** **:** EORTC-QLQ-C30 questionnaire and HADS questionnaire

For Arm B only:

- ***every 4 weeks (T1, T2, T3, T4, T5):*** PC visit

The content of each PC visit will be described by the PC physician at the end of the visit, by filling a specific check-list (Cf. appendix 3: PC grid):

- *Discussion with the patient focusing on its understanding related to its disease, its treatment, and the palliative care process.*
- *Evaluation of clinical status and symptoms*
- *Evaluation of psychological status*
- *Evaluation of the social environment including its way of living*
- *Stakeholder needs : psychologist, physiotherapist, dietician, social worker …*
- *Caring for the patient and his family*
- *Discussion about the identification of the "person of trust" and about advanced directives*
- *Coordination and continuum of care*

8.3. Follow-up assessment (after 24 weeks)

For both arms (Arm A and Arm B), every 8 weeks until the end of the study

- EORTC-QLQ-C30 questionnaire

9. STUDY DESCRIPTION

9.1. Scheme

See appendix 2.

9.2. Chemotherapy

The choice of first-line CT is left to the choice of the each investigator, but should refer to regional, national or international guidelines.

The treatment begins within 10 days after the inclusion of the patient. If, for any reasons (toxicity, disease progression, or deterioration of health status), the first-line CT has to be stopped, the patient remains in the study.

9.3. Study arms

a. Arm A: CT alone (standard arm)

The medical oncologists (or gastroenterologist physician) are in charge of the patient for chemotherapy administration, and for the management of symptoms related to the disease and/or the treatment, in accordance with professional practices.

If needed (any time), a PC visit could be performed.

b. Arm B: CT + EPC (Early Palliative Care) (interventional arm)

Again, medical oncologists (or gastroenterologist physician) are in charge of the patient for CT administration, and for the management of symptoms related to the disease and/or the treatment, in accordance with professional practices. In addition, PC visits will be scheduled.

PC visits at times T1, T2, T3, T4 and T5: **PC visits will be performed by a PC physician.**

The first visit (T1) will be scheduled within the first 3 weeks after randomization. The following visits (T2, T3, T4, T5) will be scheduled approximately every month. At best, these visits will be organized at the same time as standard medical oncology visits.

All these visits will be recorded (cf. §15 annex 2).

If needed, a dedicated visit could be scheduled with other professionals (i.e.: dieticians, nurses, social workers, psychologists, pain specialists, etc.) but will not be considered as a PC visit.

NB: There is no equivalent in the French context to the recommendations of the National Consensus Project for Quality in Palliative Care [6]. Therefore, in our study, the content of each PC visit will be described by the PC physician at the end of the visit, by filling a specific check-list (built by an *ad hoc* working-group of PC physicians).

9.4. Concomitant treatment

Non-authorized treatment

None

Authorized treatment

Any therapy deemed to be necessary for the patient's well-being.
All concomitant prescription will be documented in the eCRF.

10. PATIENT'S SAFETY AND SAFETY REPORTING

Only adverse events related to clinical research (PC visits, questionnaires) will be collected in the eCRF according to CTCAE version 4.0.

10.1. Definition

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical trial subject and which does not necessarily have a causal relationship with this clinical investigation.
A serious adverse event (SAE) is defined as any AE which results in death, is life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalization, is a congenital anomaly / birth defect.
The following events do not have to be reported as SAE:
- Hospitalization planned before the beginning of the trial and/or planned by the protocol;
- Hospitalization in accordance with standard procedures of the site;
- Hospitalization for pre-existing conditions in absence of worsening;
- Hospitalization or prolonged hospitalization for administrative or social reasons, in absence of an AE.

An event which is part of the natural course of the disease (i.e. progressive disease or hospitalization related to progressive disease) or related without doubt to a concomitant treatment (chemotherapy) should not be reported as a SAE.
However, AT ANY TIME DURING THE STUDY TREATMENT, patient's death whatever the cause should be immediately notified to the sponsor in order to plan the interim analysis.

10.2. Investigator's responsibilities

The investigator must evaluate for each adverse event reported during the study:

- its seriousness
- its causal relationship with the clinical investigation.

- Notification to the sponsor of serious adverse events (SAE)

In the event of the occurrence of any SAE between signature of informed consent form and the end of the 28-day follow up period after last sampling, the Investigator informs the Sponsor's Safety Desk immediately, i.e. within 24 hours of awareness of the event(s) by e-mail or by fax.

Clinical Research Unit – Sponsor Unit - Safety Desk
Tél. : **03 20 29 59 18** - Fax : **03 20 29 58 96**
E-mail: **vigilanceEC@o-lambret.fr**

- Follow-up of SAE

The investigator has to follow each SAE until its resolution and to transmit follow-up information (detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports, or other relevant documents) to the Sponsor's Safety Desk.

The investigator has to answer to additional information requested by the Sponsor's Safety Desk or the monitor.

10.3. Sponsor's responsibilities

- Determination of expectedness/unexpectedness of SAE

Expected Serious Adverse Events

The risk for apparition of Expected Serious Adverse Events related to study procedures is low.

Unexpected Serious Adverse Events (SUSAR)

Suspected Unexpected Serious Adverse Events are all adverse events not listed above. Nevertheless, all expected adverse event which differs on intensity, evolution or frequencies will be considered as unexpected.

- Recording of vigilance data and immediate reporting of Suspected Unexpected Serious Adverse Events (SUSAR)

The sponsor will update and store all vigilance data regarding the study. He will also notify all Suspected Unexpected Serious Adverse Events to regulatory authorities (National Competent Authority and Ethic Committee) and inform all investigators, in accordance with applicable laws and regulations.

- Periodic Safety Reports

The Sponsor will prepare and submit appropriate periodic safety reports to regulatory authorities (National Competent Authority and Ethic Committee), in accordance with applicable laws and regulations.

11. STATISTICAL ANALYSIS AND SAMPLE SIZE

11.1. Sample size

Three hundred eighty-one (381) deaths are required to show an absolute difference of 10% in one year overall survival (40% vs 50.3%, HR=0.75; two-sided alpha=5%) with an 80%-power, assuming proportional hazards over time. Assuming an exponential distribution of survival time, with an accrual duration of 3 years, a 1 year minimum follow-up and a final analysis at 4 years, it is necessary to randomize **480 patients** (240 in each group), corresponding to an accrual of 13 patients per month. This calculation takes into account a yearly 2% loss to follow-up rate. An interim analysis is planned when approximately 190 deaths are observed (which is expected to occur 27 months since the start of the study). The significance level is fixed at p=0.003 for the interim analysis and p=0.049 at the final analysis (Lan de Mets alpha-spending function, with an O'Brien Fleming efficacy stopping rule).

Patients will be stratified by minimization technical according to:

- Center

- Performance status (0-1 versus 2)
- Tumor location (esogastric or gastric versus pancreas versus biliary tract)

As the expected baseline overall survival is uncertain in the control group, the sample size will be re-estimated at the interim analysis, blinded to the observed effect size

11.2. Statistical analysis

Baseline characteristics will be presented as summary tables. Categorical variables will be presented as frequencies and percentages. Continuous variables will be presented as medians (range) and means (standard deviation) if justified. Missing data will be indicated.
Overall survival corresponds to the time interval between date of randomization and date of death. All causes of deaths are considered as events. Patients alive at cut-off date are censored at that date.

After check of proportional hazards assumption, the treatment effect of the experimental arm compared to the control arm will be based on the estimation of the Hazard Ratio of death in a Cox model (HR-death, based on the comparison of the OS curves between the two treatment groups), tested against the null hypothesis of no treatment effect using a logrank test with a two-sided alpha of 5%.
The proportional hazards assumption underlying the HR estimate in Cox models will be evaluated, using graphic methods and models including interaction with time. Appropriate methods for treatment effect estimates will be used if the proportional hazard assumption appears violated or questionable (use of restricted mean survival as published by Royston and Parmar).

Heterogeneity of treatment effect by the stratification factors will be evaluated using forest plots and heterogeneity tests.

The main analysis will be performed on the intention-to-treat dataset, including all patients included the treatment group allocated by randomization until their last follow-up visit.

A sensitivity analysis is also planned on the per protocol dataset where patients in the standard arm who got more than a PC visit within the first 6 months of treatment since randomization will be censored at the date of their second PC visit, and patients in the interventional arm who actually got less than 5 PC visits within the first 6 months since randomization will be censored at the date of first missing PC visit.

Quality of life will be analyzed according to EORTC manual recommendations.

TUDD is defined as the time interval between date of randomization and date of first definitive deterioration or death. For each dimension, patients with at least one score are included in the analysis. Patients without follow-up QLQ-C30 score are censored just after baseline. Patients without baseline are censored at baseline. TUDD curves for both arms are calculated using the Kaplan-Meier method and described using median and 95% confidence interval.

The IDMC will meet when the results of the planned interim analysis are available (i.e. when 190 patients will be dead) to review the results of the first efficacy interim analysis, and to re-estimate the sample size if the baseline overall survival rate differs from the protocol assumptions. No futility analysis is planned as the proportional hazards assumption may not be respected, with possibly a larger treatment effect with longer follow-up than in the first part of the survival curves

11.3. Data management

Data Management will be undertaken by the data management team of the North-West Cancéropôle Data Treatment Centre situated in Caen, France at the François Baclesse Cancer Centre, where the database will be located.

A trial-specific database will be created, tested and validated before the start of data capture. This database will be developed using Clinsight (ENNOV), which is a software package designed for the overall management of clinical studies, and which meets the regulatory requirements for clinical trials. A data validation plan will be developed and will describe in detail the checks to be performed for each significant variable and a list of obvious authorized corrections.

The essential data necessary for monitoring the primary and secondary endpoints will be identified and managed at regular intervals throughout the trial in collaboration with the coordinator and the COL Sponsorship Unit.

The electronic case report forms (eCRF) will be subjected to data entry at each investigator site.

The data will be monitored by the team responsible for data management by using the error messages from validation programs. Obvious errors will be corrected. Other errors, omissions or inconsistencies will be listed on data correction forms (DCF) to be sent to the medical investigator for resolution. When the UMB receives the medical investigator's reply, the corrections will be included in the database. A statistical data analysis plan will be established in collaboration between the data-management, the Sponsorship Unit and the trial coordinator.

The database will be frozen after final quality control, and then exported to the STATA statistical software by an automated and validated procedure.

12. LEGAL AND ETHICAL ASPECTS

This clinical trial will be conducted in accordance with the protocol, the ethical principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies; the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (CPMP/ICH/135/95), and all applicable laws and regulations.

This clinical trial will be recorded in the public registry website clinicaltrials.gov before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients (and their healthcare practitioners) how to enroll in the trial.

12.1. Investigator's responsibilities

The principal investigator of each concerned center undertakes to manage the clinical trial in accordance with the protocol approved by the local ethic committee and the national competent authority. The investigator must not make any modification to the protocol without the sponsor's

authorization and without the local ethic committee and the national competent authority approving the proposed modifications.

The investigator is responsible:

- for providing the sponsor with his/her curriculum vitae, along with those of his/her co-investigators,
- for identifying the members of his/her team who are to take part in the trial and for defining their responsibilities,
- for initiating patient recruitment after receiving the sponsor's authorization,
- for making all necessary efforts to include the required number of patients, within the limits of the defined enrolment period.

Each investigator is responsible:

- for obtaining informed consent, personally dated and signed by the patient, prior to any trial-specific selection procedure,
- for regularly updating the case report forms (CRF) for each patient included in the trial and for providing the Clinical Research Associate (CRA) with direct access to the source documents to validate the CRF data,
- for dating, correcting and signing any CRF corrections for each patient included in the study,
- for welcoming regular visits from the CRA and, if applicable, those of auditors mandated by the sponsor, or by regulatory authority inspectors.

The study will be conducted in accordance with the protocol. Study personnel involved in conducting this trial will qualified by education, training and experience to perform their respective task(s).

All documentation relative to the study (protocol, consent forms, CRF, investigator's files, etc…) along with original documents (laboratory results, x-ray, consultation reports, clinical examinations reports, etc.) must be kept in a safe place and considered confidential.

The investigator is responsible for data archiving in accordance with current legislation. The latter must keep the data along with a patient identification list, for at least 15 years after the end of the study.

12.2. Ethic Committee

The clinical study protocol, along with its various amendments, is submitted by the study sponsor, or its representative, to an ethic committee according to the national legislation.

12.3. Participant information and consent

Prior to performing biomedical research on an individual, the latter's **voluntary written informed** consent must be obtained, after having been informed of the aims of the research, of the progress and duration of the study, of the potential study benefits, risks and requirements of the study, along with the type of product under study and the opinion given by the local ethic committee and the national competent authority.

The consent form must be personally dated and signed by the patient and investigator, or by the physician representing the investigator (original filed by the investigator, a copy shall be issued to the patient or his/her legal representative).

The rights safety and well-being of the trial patients are the most important considerations and should prevail over interests of science and society.
The patient information sheet will include all elements required by ICH, GCP and applicable regulatory requirements.
The investigator or his/her designee must provide the patient with a copy of the consent form and written full information about the study in a language that is non-technical and easily understood. The investigator should allow enough time for the patient or his/her legally acceptable representative to inquire about the details of the study. Then, the informed consent must be freely signed and personally dated by the patient and by the person who conducted the informed consent discussion before the beginning of the study. The patient should receive a copy of the signed informed consent and any other written information provided to the patient prior to participation in the trial.
During his/her participation in the trial, any updates to the consent form and to the written information will be provided to the patient.
If a new consent needs to be obtained from the patients, the investigator or his/her designee should inform the patient of any new information relevant to his/her willingness to continue participation in the study before obtaining the written consent.

12.4. Patients Committee

The protocol will be examined by the Patient Committee of the National League against Cancer (LNCC) paying particular attention to the quality of the information letter, the availability of a treatment and monitoring plan and suggestions for measures to improve the comfort of the patients.

12.5. Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) for the trial will be established in order to guarantee protection of the patients, to ensure that the trial is conducted in an ethical fashion, to evaluate the risk/benefit ratio of the trial by reviewing the scientific results during the trial. In fact, the IDMC will meet when the results of the planned interim analysis are available (i.e. when 190 patients will be dead) to confirm or not the statistical hypotheses. This committee will be composed of a medical oncologist in charge of gastrointestinal oncology, a biostatistician and a PC physician.

12.6. Confidentiality

In accordance with the Public Health Code, the investigators and all individuals are required to collaborate in the study shall be held to professional secrecy concerning, in particular, the nature of the products used, the study itself, the test subjects and the results obtained. The investigator must ensure that his/her patients remain anonymous. The investigator shall keep a confidential patient identification list.

12.7. Archiving

The archiving of all study relevant documents at the trial site, at the trial offices and the coordinating investigator's site will be handled according to the requirements of the ICH-GCP, the EU Commission Directive 2005/28/EC of 8th April 2005 and national laws.

13. OPERATIONAL MANAGEMENT OF THE STUDY

13.1. Study organization

This study is sponsored by Centre Oscar LAMBRET (COL), Lille, France.

- Administrative and regulatory, project management, data monitoring (monitoring): Integrated Clinical Research Unit / Sponsorship cell Centre Oscar Lambret - LILLE (S CLISANT, M VANSEYMORTIER)
- Data management and analysis : Data Processing Center "Cancéropôle" Northwest - Biostatistics and Methodology Unit Centre Oscar Lambret - LILLE (E BOGART)

13.2. Research costs and additional costs

Any additional cost as stated in the Public Health Code is covered by an agreement negotiated between the COL and the centre representative, with consideration for the COL's financial means in the context of its sponsoring activity.

The COL shall, however, organize the study and shall provide the following materials (protocol, case report forms, investigator file) required for managing the study.

13.3. Case reports forms - Monitoring

Data are collected in a case report form (CRF) under the investigator's responsibility. These data are entered and validated in accordance with the study specifications. The Clinical Research Associate (CRA) assists the investigator in conducting the study. The CRA mandated by the sponsor makes a series of setup, follow-up and closure visits, in accordance with GCP.

13.4. Quality assurance

The sponsor is responsible for implementing and maintaining a quality assurance system, as described in the COL procedures, in order to ensure that the study is conducted in accordance with the protocol and with GCP.

13.5. Use of information and publication

At the end of the study, a report will be written by the study coordinator and statistician. No publication or presentation of the results of this trial will be done without the permission of the sponsor.

The sponsor is interested in the publication of the results of every study it performs. All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator/institution. The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

14. REFERENCES

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7. Schnipper LE, Smith TJ, Raghavan D, Blayney DW, Ganz PA, Mulvey TM, Wollins DS. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. J Clin Oncol. 2012 May 10;30(14):1715-24. doi: 10.1200/JCO.2012.42.8375.
8. http://www.tncd.org

15. APPENDIX

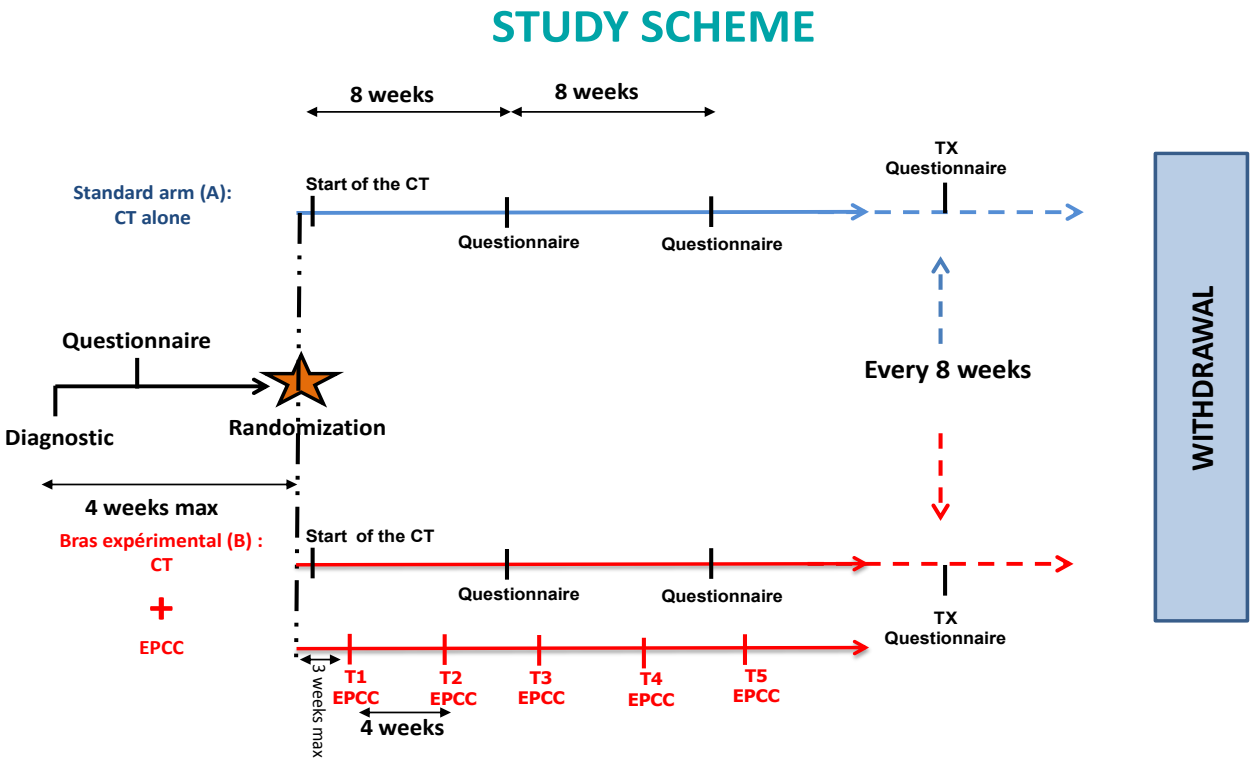
15.1. Appendix 1 – Flowchart

	Baseline < 4 weeks before randomization	RANDOMIZATION < 4 weeks after the diagnosis	Arm A (Standard arm)	Arm B (Interventional arm)
Informed consent	X		-	-
Inclusion/exclusion criteria	X		-	-
Prior medical/surgical history & cancer history Prior medication history	X		-	-
Standard treatment (first-line chemotherapy for metastatic disease)	-		X [(a)]	X [(a)]
Quality of life: questionnaire QLQ-C30	X		X[(b)]	X[(b)]
Depression : questionnaire HADS	X		X[(c)]	X[(c)]
PC visit			- [(d)]	X[(e)]

a) The chemotherapy should begin **within 10 days after randomization**.
b) **Every 8 weeks** after randomization (**T3, T5)** and then **every 8 weeks** until the end of study.
c) **Every 8 weeks** after randomization **(T3 and T5)**.
d) **Only if needed.** The number of PC visits will be recorded but the check-list will not be completed.
e) The first PC visit should be performed **within the first 3 weeks after randomization (T1)** and then every 4 weeks **(T2, T3, T4, T5)** and the check-list will be completed for these 5 visits. After T5, the number of PC visits will be recorded but the check-list will not be completed.

AT ANY TIME DURING THE STUDY, patient's death, whatever the cause, should be immediately notified to the sponsor in order to plan the interim analysis.

15.2. Appendix 2 – Study scheme



Follow up 24 weeks after randomization:
Questionnaire EORTC-QLQ-C30: **Arm A and Arm B**, every 8 weeks **until the withdrawal** from the study

15.3. Appendix 3 – PC grid

Grille de recueil de données – Consultation de Soins Palliatifs

Date : ..... Médecin : ..... Cs n° : .....

Autres intervenants présents : ☐ Infirmière ☐ Psychologue ☐Autre : .....

Le patient était accompagné d'un proche : ☐oui ☐non

INFORMATION

Lors de la consultation les éléments suivants ont été abordés :

- ☐ Compréhension du patient de sa pathologie en termes d'évolution et de pronostic
- ☐ Compréhension du patient des traitements (notamment traitement carcinologique) en cours et des objectifs
- ☐ Explications sur la prise en charge palliative

EVALUATION CLINIQUE

- Score OMS du patient : .....
- Evaluation de l'état psychique : ☐oui ☐non
- Un examen clinique a été réalisé : ☐oui ☐non

	Les symptômes suivants ont été recherchés ?		**Des propositions thérapeutiques ont été réalisées ?**	
	Oui	Non	Oui	Non
Douleur				
Troubles de l'Alimentation				
Troubles digestifs				
Effets secondaires de la chimiothérapie				
Troubles du Sommeil				
Troubles respiratoires				
Anxiété				
Dépression				
Autres :				

MODE DE VIE

Evaluation du contexte familial : ☐oui ☐non

Evaluation du contexte socio professionnel : ☐oui ☐non

Evaluation des besoins humains et matériels dans le lieu de vie : ☐oui ☐non

Propositions/Informations sur les aides possibles au domicile : ☐oui ☐non

- ☐ Mise en place d'aides humaines et matérielles à domicile
- ☐ Mise en place d'un réseau de soins à domicile
- ☐ Mise en place d'une hospitalisation à domicile
- ☐ Autres : .....

PRISE EN CHARGE GLOBALE MULTIDISCIPLINAIRE : le recours aux intervenants suivants a été proposé

- ☐ Algologue
- ☐ Assistante sociale
- ☐ Diététicienne
- ☐ Infirmière
- ☐ Intervenant religieux
- ☐ Kinésithérapeute
- ☐ Psychiatre
- ☐ Psychologue
- ☐ Stomathérapeute
- ☐ Autres : .....

ACCOMPAGNEMENT DU PATIENT :

Lors de la consultation les éléments suivant ont été abordés :

- ☐ Projet de vie
- ☐ Anticipation des complications médicales possibles
- ☐ Directives anticipées
- ☐ Personne de confiance
- ☐ Aide aux prises de décisions thérapeutiques concernant :
  - Traitements à visée carcinologique
  - Autres traitements
  - Limitation / arrêt de traitement mettant en jeu le pronostic vital
- ☐ Souhaits de fin de vie

ACCOMPAGNEMENT DE LA FAMILLE / DES PROCHES :

Lors de la consultation les éléments suivant ont été abordés :

- ☐ Compréhension par la famille/les proches de la pathologie en termes d'évolution et de pronostic
- ☐ Compréhension par la famille/les proches des traitements en cours et des leurs objectifs
- ☐ Explications à la famille/aux proches de la prise en charge palliative
- ☐ Discussion sur l'annonce du pronostic de la maladie aux proches (enfants, parents...)
- ☐ Evaluer les ressources et repérer les situations d'épuisement chez l'aidant principal
- ☐ Orientation de la famille/des proches vers :
  - ☐ Assistante Sociale
  - ☐ Psychologue
  - ☐ Autres : .....

COORDINATION ET CONTINUITE DES SOINS :

- Lien avec le médecin traitant : ☐ par courrier ☐ par appel téléphonique

- Lien avec les services de soins à domicile : ☐ par courrier ☐ par appel téléphonique

- identification des personnes/services recours en cas de complications : ☐ oui ☐ non

Commentaires :.....
.....
.....
.....
.....
.....
.....
.....

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	none
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	none
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	not applicable

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7-8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	not applicable
Recruitment	14a	Dates defining the periods of recruitment and follow-up	not applicable
	14b	Why the trial ended or was stopped	not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	not applicable
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	not applicable
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	not applicable
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	not applicable
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	not applicable
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	not applicable
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	not applicable
Other information			
Registration	23	Registration number and name of trial registry	9
Protocol	24	Where the full trial protocol can be accessed, if available	9
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: a randomized phase III trial

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Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: a randomized phase III trial

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ABSTRACT

Introduction: Palliative care (PC) has usually been offered at the end-of-life stage, although the World Health Organization recommends providing PC as early as possible in the course of the disease. A recent study has shown that early PC (EPC) provides a more meaningful effect on quality of life and, surprisingly, on overall survival (OS) than standard treatment for patients with metastatic lung cancer. Whether EPC benefits also apply to patients with metastatic upper gastrointestinal (GI) cancers is unknown.

Methods and analysis: EPIC is a randomized phase III trial comparing EPC plus standard oncologic care versus standard oncologic care in patients with metastatic upper GI cancers. Its primary objective is to evaluate the efficacy of EPC in terms of OS. Its secondary objectives are to assess the effects of EPC on patient-reported outcomes (quality of life, depression and anxiety) and the effect of EPC on the number of patients receiving chemotherapy in their last 30 days of life. Assuming an exponential distribution of survival time, 381 deaths are required to ensure an 80% power for an absolute difference of 10% in one-year OS rates (40% vs 50.3%, HR=0.75; log rank test two-sided alpha=5%), leading to a planned sample size of 480 patients enrolled over 3 years and a final analysis at 4 years. The main analysis will be performed on the intent-to-treat dataset.

Ethics and dissemination: This study was approved by the "Comité de Protection des Personnes Nord-Ouest I" (April 4th, 2016), complies with the Helsinki declaration and French laws and regulations, and follows the International Conference on Harmonisation E6 (R1) Guideline for Good Clinical Practice. The trial results, even if they are inconclusive, will be presented at international oncology congresses and published in peer-reviewed journals.

Trial registration numbers: EudraCT number: 2015-A01943-46; ClinicalTrials.gov number: NCT02853474.

Strengths and limitations of this study

- Multicentric, nationwide, academic trial with a randomized design
- Overall survival as a primary outcome, as it is a reliable and precise endpoint which has never been previously challenged in such setting
- Providing an extra survival benefit with early palliative care would be a considerable contribution for patients, as would the implementation of these practices within the continuum of oncological care

INTRODUCTION

Medical care in the metastatic setting

Medical oncology aims to increase the survival rates of patients, even at metastatic stages, in addition to reducing disease-related and treatment-related symptoms. However, providing palliative care (PC), which includes symptom management, nutritional support, psychosocial support, and assistance with end-of-life preferences to improve quality of life, may be as important as survival issues at metastatic stages. Decades ago, PC services were initiated in France to provide a medical alternative to questionable medical practices regarding the end-of-life period: abandonment, euthanasia, and inappropriate aggressive therapy. According to the French Society of Palliative Care,[1] PC is a holistic approach that aims to provide active care to a person with a serious, progressive or terminal illness. The objective of PC is to relieve pain and other distressing symptoms; moreover, PC also accounts for psychological, social and spiritual suffering. PC offers an interdisciplinary support system to help patients and their relatives.[1] In both France and in the US,[3] PC is usually offered late, at the end-of-life stage, although the World Health Organization recommends providing PC as early as possible in the course of the disease to increase quality of life.[2] In 1999, PC access became a right guaranteed by the law for patients and their families in France.[4] This context explains why even now, PC often means “end-of-life” not only for the patient but also for caregivers and many doctors. The last World Health Organization recommendations are less restrictive than the outdated 1996 French recommendations that stated that PC should be offered as early as possible in the course of the disease to increase quality of life and to positively influence the course of the illness.[2] The World Health Organization recommendations add that PC is applicable early in the course of illness in conjunction with other therapies that are intended to prolong life, such as chemotherapy (CT) or radiation therapy; the recommendations also state that investigations are necessary to better understand and manage distressing clinical complications.[2]

The concept of Early Palliative Care (EPC)

In a recent randomized study, 151 patients newly diagnosed with metastatic non-small-cell lung cancer were assigned to receive either early PC (EPC) integrated with standard oncologic care or standard oncologic care alone.[5] It was hypothesized that patients who received EPC would have a better quality of life (primary endpoint) compared with patients who received standard oncologic care only. In the EPC group, the first visit with the PC services (board-certified PC physicians and advanced practice nurses) was planned within 3 weeks after enrollment and at least monthly thereafter; all but one patient had the first visit by the 12th week, with a mean of four total visits. In this study, the authors referred to the PC package presented in the recommendations from the National Consensus Project for Quality Palliative Care.[6] For patients with metastatic non-small-cell lung cancer, EPC led to significant improvements in quality of life and in mood. Additionally, EPC led to a

significantly longer survival (median survival, 11.6 vs. 8.9 months; HR=0.60, p=0.02), despite less aggressive end-of-life care.[5] Several hypotheses for the effect of EPC on survival have been raised by Pirl et al. [7], such as improving the management of medical comorbidities including depression, and aiding in the discontinuation of inappropriate and possibly detrimental cancer treatments at the end of life.

Following the publication of Temel and colleagues,[5] the American Society of Clinical Oncology recommended that "combined standard oncology care and PC should be considered earlier in the course of the illness for any patient with metastatic cancer….".[8] However, it appears that a gap exists between these recommendations and current practice in France and elsewhere. Moreover, there is no consensus on how early PC should be integrated into oncologic services; a randomized trial recently reported a non-significant increase in survival rate for early (30 to 60 days after diagnosis) versus delayed (3 months later) initiation of PC in 207 patients diagnosed with various types of advanced cancer.[3] The results of Temel's study have modified the perception of many oncologists about the objectives of PC. However, additional clinical studies seem necessary before considering EPC as an additional survival input in advanced malignancies other than metastatic non-small-cell lung cancers.

Metastatic upper gastrointestinal cancers

The median survival time of patients with metastatic upper gastrointestinal (GI) cancers, such as pancreatic cancers, esogastric cancers, and biliary tract cancers, does not exceed 10-11 months [9-11], which is as poor as survival rates reported for metastatic lung cancer patients. The standard of care for metastatic upper GI cancers is well described in the European Society of Medical Oncology guidelines.[12-14] Briefly, the standard of care for metastatic pancreatic cancer in the first-line includes a combination of fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX regimen) for patients without any cholestasis who are in good performance status; the standard of care includes gemcitabine monotherapy for frail patients.[12] For metastatic biliary tract cancers, the standard of care includes a gemcitabine-based regimen (gemcitabine monotherapy, gemcitabine plus cisplatin, or gemcitabine plus fluorouracil).[13] Most patients with metastatic HER2-negative tumors have a poor prognosis with survival rates similar to those of patients with other upper GI malignancies; HER2-positive metastatic gastric/esogastric patients present with a much better prognosis and should be treated with a trastuzumab-based regimen.[14] For patients with upper GI malignancies, various combinations of cytotoxics (fluoropyrimidines, taxanes, platinum compounds) may be offered to patients [12-14]. Several experimental treatments (antiangiogenics, MET inhibitors, modulators of immune check points, new cytotoxics, etc.) may be offered to these patients, but these treatments are restricted to patients in good health who are willing to participate in clinical trials; none of these treatments have produced a meaningful survival benefit thus far. In summary, patients with metastatic upper GI cancers do not benefit from currently available systemic therapies. Providing an extra survival benefit with EPC would be a considerable contribution for these patients, as would

the implementation of these practices within the continuum of care of oncology in France.

Aim of the study

We designed a randomized controlled trial, called EPIC, which aims to demonstrate that the use of EPC provides greater clinical benefits than standard practice for a population of patients with metastatic upper GI cancers. Overall survival (OS) will be used as a primary endpoint. The content of palliative care visits will be studied through a specific checklist. Patient-reported outcomes (quality of life, depression and anxiety) will also be investigated using dedicated and validated questionnaires.

METHODS AND ANALYSIS

Study design

This study was designed as a randomized, open-label, multicenter phase III trial. It aims to estimate the survival benefits of EPC combined with standard oncologic care (experimental arm) compared with standard oncology care only (standard arm) for patients with metastatic upper GI cancers (esogastric/gastric cancer, pancreatic cancer, biliary tract cancer). After the participant's eligibility is established, informed consent has been obtained and stratification factors are defined, the participant will be enrolled in the study and the treatment will be centrally allocated using the online CS randomization module from Clinsight software (Ennov, San Francisco, CA, USA), ensuring the concealment of the next patient allocation. Treatments will be randomized in a 1:1 ratio, and a minimization procedure will be used to balance patients according to center, Eastern Cooperative Oncology Group (ECOG) performance status [15] (0-1 versus 2) and tumor location (esogastric/gastric, pancreas, or biliary tract). Patients will be recruited nationwide from 17 university hospitals or cancer centers in France. Written informed consent will be obtained from the patient by an investigator before any screening or inclusion procedures. The patient will remain in the study until one of the following conditions applies: study withdrawal (patient or sponsor or investigator's decision) or death.

Outcome measures

Study objectives

The primary objective of this study is to evaluate the efficacy of EPC in terms of OS curves (intent-to-treat analysis). The secondary objectives are to assess the following: (a) the efficacy of EPC in terms of 1-year OS (intent-to-treat and per protocol analyses) and OS curves (per protocol analysis), (b) the patient-reported outcomes (quality of life, depression and anxiety) and the Time Until Definitive Deterioration (TUDD) for Quality of Life, (c) the number of patients receiving chemotherapy in their last 30 days of life, (d) the actual description of the PC package, and (e) the presence or absence of advanced directives in patient files.

Measurement tools

OS is defined as the time between the date of randomization and the date of death, no matter the cause of death. Patients who are alive at the cut-off date will be censored at that date. Quality of Life will be assessed with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. The QLQ-C30 aims to measure a person's overall quality of life, physical conditions, and limits to the ability to carry out everyday activities; the questionnaire also assesses cognitive, emotional and social functioning as well as the appearance of symptoms frequently associated with cancer or its treatment. Patients are asked to check a scale that ranges from one to four (not at all, a little, quite a lot, a lot) or from one to seven (from 1 – very bad – to 7 – excellent). For each dimension, the QLQ-C30 score indicates definitive deterioration if the score decreases by more than 10 points compared with the score at baseline, without later improvement that is greater than 10 points compared with baseline unless the patient dropped out of the study, resulting in missing data. Thus, TUDD for the Quality of Life scores is defined as the time from randomization to the first observation of a definitive deterioration of the QLQ-C30 score or the time from randomization to death. Depression will be assessed with the HADS scale (Hospital Anxiety and Depression Scale). HADS aims to detect anxiety and depressive disorders. It contains 14 items with response options ranging from 0 to 3: 7 items assessing anxiety (score A) and 7 items assessing depression (score D). The maximum score for a patient is 21. The number of patients treated with chemotherapy in their last 30 days before death will also be recorded. PC visits will be performed by PC physicians. In both arms, all the dates of PC visits will be recorded in the data base. The content of PC visits will be described through a specific checklist that will be completed by the PC physician after each visit. The number of patients in whom advanced directives are identified in medical records will be recorded.

Patient selection criteria

Inclusion criteria

Patients must:

- Have an upper gastrointestinal metastatic cancer, including pancreatic cancer, biliary tract cancer or gastric cancer (including junctional Siewert 2 and 3 cancers) (An amendment is being submitted to our ethic committee in order to include other oesophageal cancers, too)
- Be 18 years of age or older
- Have an ECOG performance status ≤2
- Be planned for treatment with first-line CT
- Have a life expectancy of more than 4 weeks
- Have a good understanding of the French language
- Have health insurance coverage
- Sign and date a written informed consent form

Exclusion criteria

Patients with any of the following conditions or characteristics are excluded from the study:

- Locally advanced cancer
- Junctional Siewert 1 esogastric cancer (An amendment is being submitted to our ethic committee in order to include these cancers together with other oesophageal cancers)
- Gastric or junctional esogastric cancer with dysphagia
- Gastric or junctional esogastric cancer with unknown or positive HER2 status
- Compression of the biliary tract without any bypass procedure

Study description

Intervention (Figure 1)

Medical oncologists will be in charge of the patient for CT administration and for supportive care, in accordance with professional practices. PC specialists will be in charge of PC/EPC visits. In order to match with standard practice in France, participants allocated to the standard arm (CT alone) are not scheduled to meet with the PC service, but a PC visit can be performed anytime if requested by the patient, the family, or the oncologist. . In the experimental arm (CT + EPC), 5 PC visits are scheduled. The first visit (V1) will be scheduled within the first 3 weeks after randomization. The remaining four visits will be scheduled every month. The content of each of the 5 PC visits will be described by the PC physician and documented in the data base following a specific check-list developed by PC physicians. In part, the visits will focus on the following items:

- Discussion with the patient, focusing on his/her understanding of the disease, its treatment, and the palliative care process
- Evaluation of clinical status and symptoms
- Evaluation of psychological status
- Evaluation of the social environment, including the patient's way of living
- Stakeholder needs: psychologist, physiotherapist, dietician, social worker, etc.
- Caring for the patient and his/her family
- Discussion about the identification of the "person of trust" and about advanced directives
- Coordination and continuum of care

The choice of first-line CT will be decided by each investigator but should adhere to national or international guidelines. If CT is stopped for any reason (toxicity, disease progression, or deterioration of health status), the patient will remain in the study.

Data collection

At baseline, before randomization, patients will have to complete the EORTC-QLQ-C30 and the HADS questionnaires. During the study, the EORTC-QLQ-C30 and the HADS questionnaires will be completed by patients every 8 weeks after randomization. Then, 24 weeks after randomization, only the EORTC-QLQ-C30 questionnaire will be completed by patients every 8 weeks until the end of the study. In both arms, the number and the dates of

PC/EPC visits that are performed will be recorded. The number of patients in whom advanced directives are identified in medical records will also be recorded.

Statistical considerations

To ensure an 80% power, three hundred eighty-one (381) deaths are required to show a significant difference in OS curves if there is an absolute difference of 10% in one-year OS rates (40% vs 50.3%, HR=0.75; log rank test two-sided alpha=5%), assuming proportional hazards over time. Assuming an exponential distribution of survival time, with an accrual duration of 3 years, a 1 year minimum follow-up and a final analysis at 4 years, it will be necessary to randomize 480 patients (240 in each group). This calculation takes into account a yearly 2% loss to follow-up rate. An efficacy interim analysis is planned for when approximately 190 deaths are observed (which is expected to occur 27 months from the start of the study). The significance level is fixed at p=0.003 for the interim analysis and p=0.049 at the final analysis (Lan-DeMets alpha-spending function),[16] with an O'Brien-Fleming efficacy boundary.[17] No futility analysis is planned as the proportional hazards assumption may not be met; there may be a larger treatment effect with a longer follow-up period than in the first part of the survival curves. The interim analysis will also evaluate whether the sample size of the EPIC trial should be increased, considering the observed OS curve in the control group.

OS curves will be estimated using the Kaplan-Meier method. After checking the proportional hazards assumption, the treatment effect of the experimental arm compared to the control arm, in terms of OS, will be based on the estimation of the hazard ratio of death in a Cox model (HR-death, based on the comparison of the OS curves between the two treatment groups) and tested against the null hypothesis of no treatment effect using a log rank test with a two-sided alpha of 5%. The proportional hazards assumption underlying the HR estimate in Cox models will be evaluated using graphic methods and models, including interaction with time. Appropriate methods for estimating treatment effect will be used if the proportional hazard assumption appears to be violated or questionable (use of the restricted mean survival as published by Royston and Parmar).[18] Heterogeneity of the treatment effect by stratification factors will be evaluated using forest plots and interaction tests. The main analyses will be performed on the intent-to-treat dataset, including data from all patients in the treatment group allocated by randomization until their last follow-up visit. A sensitivity analysis is also planned on the per protocol dataset in which patients in the standard arm who completed more than one PC visit within the first 6 months of treatment after randomization will be censored at the date of their second PC visit, and patients in the treatment arm who completed fewer than 5 EPC visits within the first 6 months after randomization will be censored at the date of the first missing EPC visit. One-year survival rates with their 95% confidence interval will also be estimated and compared between groups, considering the intent-to-treat and the per protocol datasets.

Quality of life will be analyzed according to the EORTC manual recommendations. For each dimension, patients with at least one score will be included in the analysis. Patients without

a follow-up QLQ-C30 score will be censored just after baseline. Patients without baseline scores will be censored at baseline. TUDD curves for both arms will be calculated using the Kaplan-Meier method and described using medians and 95% confidence intervals.

An Independent Data Monitoring Committee will meet when the results of the planned interim analysis are available (i.e., when 190 patients have died) to review the results of the first efficacy interim analysis and to re-estimate the sample size if the baseline overall survival rate differs from the protocol assumptions.

ETHICS AND DISSEMINATION

Ethical considerations

This clinical trial will be conducted in accordance with the Declaration of Helsinki[19] or the laws and regulations of the country, whichever provides greater protection to the patient. This study follows the International Conference on Harmonization E6 Guideline for Good Clinical Practice, reference number CPMP/ICH/135/95.[20] The protocol has been examined by the Patient Committee of the National League against Cancer, paying particular attention to the quality of the information letter, to the monitoring plan, and to suggestions implemented into the protocol to improve the comfort of the patients. An independent data monitoring committee for the trial will be formed to guarantee protection of the patients, to ensure that the trial is conducted in an ethical fashion, and to evaluate the risk/benefit ratio of the trial by reviewing the interim results of the trial. The study protocol has been approved by our local ethics committee (CPP Nord-Ouest I, April 4th, 2016).

Dissemination

The study is registered at clinicaltrials.gov (NCT02853474). The protocol and the trial results, even if they are inconclusive, will be presented at international oncology congresses and published in peer-reviewed journals.

Trial financing

This study is supported by unrestricted public grants from Conseil Régional du Nord Pas-de-Calais and from caregivers Ligue National contre le Cancer.

DISCUSSION

This EPIC trial was set up in September 2016. It is a randomized trial primarily designed to detect an OS benefit due to EPC combined with standard oncologic care compared with standard oncologic care only for patients with metastatic upper GI cancer. The design of EPIC differs from the design of the seminal trials by Temel and colleagues,[5] which demonstrated that EPC not only improves quality of life (the primary objective of their trial) but also may

improve OS (a secondary objective) for patients with advanced cancers.

One may argue that the main motivation for many oncologists to engage with EPC is to enhance quality of life for their patients throughout the cancer journey. This is precisely what Temel et al. did.[5] When using OS as the primary endpoint of EPIC, as we will, there is a theoretical danger that if a study does not meet its OS endpoint, it will indicate that EPC has "failed" and should be discarded. Our point is different. Our country has a strong culture of integrating PC into oncology services. However, despite efforts from, many PC professionals, PC is frequently offered to patients at a late stage of their metastatic disease. Some components of PC visits, such as visits with a dietician and/or with psychologists, are usually offered at an earlier stage but not as systematically as they should be. Using OS as the primary endpoint of EPIC, we postulate that without a strong "signal", such as a survival benefit, sent to medical oncologists and colleagues in charge of metastatic patients with upper GI malignancies, it would take some time before the concept of EPC is implemented in our country. Furthermore, the benefits of EPC have yet to be validated in a population of patients with metastatic upper GI cancers. Patients with metastatic upper GI malignancies are different from patients with metastatic lung cancers; they do not present the same, and we assume that their co-morbidities and their treatment-related symptoms are also different. The difference in terms of reduced risk of death (-25%) that we have chosen for the primary outcome is derived from the work reported by Temel et al. (-40%) regarding metastatic lung cancers.[5] Further reducing the risk of death to 25% should lower the theoretical danger that this study may not meet its OS endpoint.

In Temel's trial [5], the content of the EPC package, which was rather vague, was adapted from American guidelines for palliative care visits.[6] There are no such recommendations in our national context. To overcome this, PC specialists have developed a checklist of all of the items that could be addressed within PC coverage. Hence, one of the secondary endpoints of this EPIC trial will be to make an actual description of each EPC/PC visit, as well as to provide a description of the whole EPC/PC package. At the end of the study, the materials we will collect should help us in drafting guidelines for PC in France.

To conclude, we expect that this study will lead to earlier integration of PC in oncologic care for metastatic GI cancer patients.

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Contributors AA, AD, EH, and MCL designed the study; AA, AD, MCL, EH, and SL contributed to the drafting of the manuscript; AA, SL, EH, and SD contributed to the trial set-up; SD is responsible for data collection and for administrative support; EB will contribute to statistical analyses; MCL is responsible for data management and statistical analyses; AA, EH, AD, and MCL will contribute to data interpretation. All authors contributed to the revision of the manuscript and approved it for submission.

Funding This study is supported by unrestricted public grants from Conseil Régional du Nord Pas-de-Calais and from caregivers Ligue National contre le Cancer.

Competing interests None.

Ethics approval (CPP Nord-Ouest I, April 4th, 2016)

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This manuscript contains original material without any unpublished data, but the full results of this ongoing trial

FIGURE LEGEND

Figure 1 – Study design

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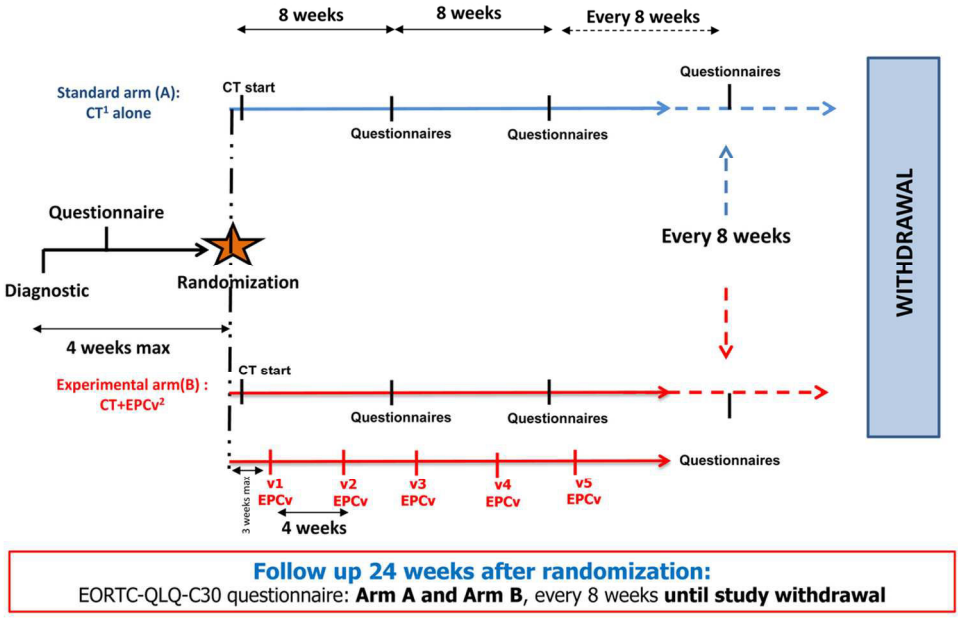
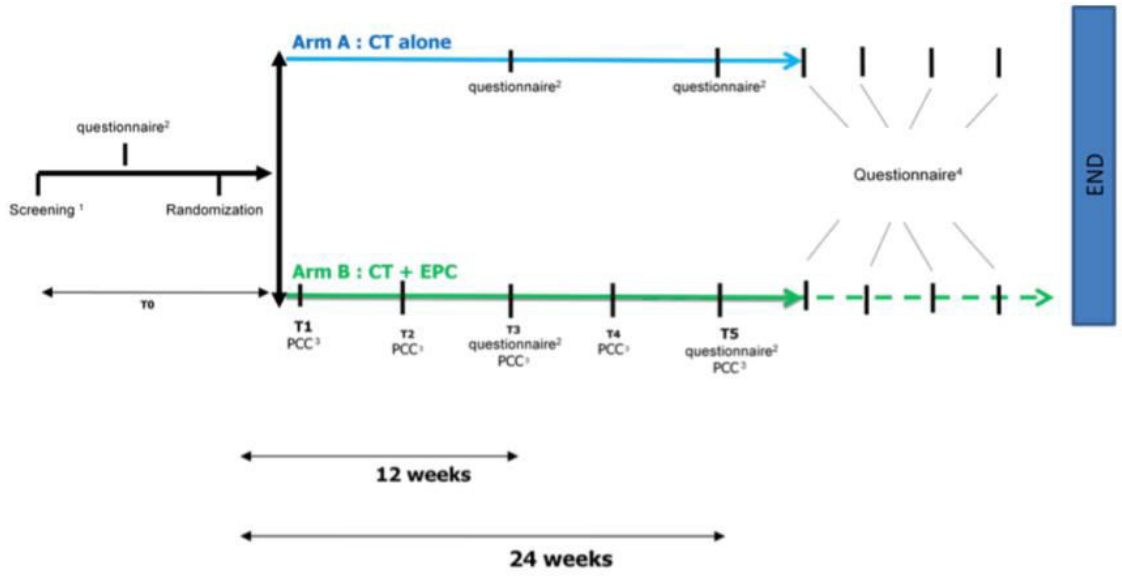


[1] **CT**: *Chemotherapy according to national or international guidelines*
[2] **EPCv**: *Early palliative care visit, 5 EPCv are scheduled at v1, v2....v5*

112x84mm (300 x 300 DPI)

Appendix 1- Study plan



¹: Information - Signature of consent– verification inclusion criteria/ exclusion criteria
²: self assessment of quality of life(QLQ-C30) and of depression (HADS)
³ : PCC : palliative care consultation
⁴ : self assessment of quality of life(QLQ-C30) every 8 weeks until withdrawal study

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	none
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	none
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	not applicable

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7-8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	not applicable
Recruitment	14a	Dates defining the periods of recruitment and follow-up	not applicable
	14b	Why the trial ended or was stopped	not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	not applicable
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	not applicable
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	not applicable
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	not applicable
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	not applicable
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	not applicable
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	not applicable
Other information			
Registration	23	Registration number and name of trial registry	9
Protocol	24	Where the full trial protocol can be accessed, if available	9
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: a randomized phase III trial

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Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: a randomized phase III trial

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ABSTRACT

Introduction: Palliative care (PC) has usually been offered at the end-of-life stage, although the World Health Organization recommends providing PC as early as possible in the course of the disease. A recent study has shown that early PC (EPC) provides a more meaningful effect on quality of life and, surprisingly, on overall survival (OS) than standard treatment for patients with metastatic lung cancer. Whether EPC benefits also apply to patients with metastatic upper gastrointestinal (GI) cancers is unknown.

Methods and analysis: EPIC is a randomized phase III trial comparing EPC plus standard oncologic care versus standard oncologic care in patients with metastatic upper GI cancers. Its primary objective is to evaluate the efficacy of EPC in terms of OS. Its secondary objectives are to assess the effects of EPC on patient-reported outcomes (quality of life, depression and anxiety) and the effect of EPC on the number of patients receiving chemotherapy in their last 30 days of life. Assuming an exponential distribution of survival time, 381 deaths are required to ensure an 80% power for an absolute difference of 10% in one-year OS rates (40% vs 50.3%, HR=0.75; log rank test two-sided alpha=5%), leading to a planned sample size of 480 patients enrolled over 3 years and a final analysis at 4 years. The main analysis will be performed on the intent-to-treat dataset.

Ethics and dissemination: This study was approved by the "Comité de Protection des Personnes Nord-Ouest I" (April 4th, 2016), complies with the Helsinki declaration and French laws and regulations, and follows the International Conference on Harmonisation E6 (R1) Guideline for Good Clinical Practice. The trial results, even if they are inconclusive, will be presented at international oncology congresses and published in peer-reviewed journals.

Trial registration numbers: EudraCT number: 2015-A01943-46; ClinicalTrials.gov number: NCT02853474.

Strengths and limitations of this study

- Multicentric, nationwide, academic trial with a randomized design
- Overall survival as a primary outcome, as it is a reliable and precise endpoint which has never been previously challenged in such setting
- Providing an extra survival benefit with early palliative care would be a considerable contribution for patients, as would the implementation of these practices within the continuum of oncological care
- Possible difficulties in recruiting participants due to the reluctance of some oncologists to talk about palliative care at diagnosis and possible screen failures due to patient refusals. Actions are on-going to communicate on this issue and overcome this hurdle.
- Compared to Temel's pivotal study, the control arm in our study may include some components of palliative care visits as this is a clinical practice in France. This may lead to a smaller relative difference between randomized groups compared to the Temel's publication. The sample size calculation has been performed targeting a hazard ratio of death of 0.75 compared to an observed HR of 0.6 in Temel's study. The study will be underpowered for a smaller effect.

INTRODUCTION

Medical care in the metastatic setting

Medical oncology aims to increase the survival rates of patients, even at metastatic stages, in addition to reducing disease-related and treatment-related symptoms. However, providing palliative care (PC), which includes symptom management, nutritional support, psychosocial support, and assistance with end-of-life preferences to improve quality of life, may be as important as survival issues at metastatic stages. Decades ago, PC services were initiated in France to provide a medical alternative to questionable medical practices regarding the end-of-life period: abandonment, euthanasia, and inappropriate aggressive therapy. According to the French Society of Palliative Care,[1] PC is a holistic approach that aims to provide active care to a person with a serious, progressive or terminal illness. The objective of PC is to relieve pain and other distressing symptoms; moreover, PC also accounts for psychological, social and spiritual suffering. PC offers an interdisciplinary support system to help patients and their relatives.[1] In both France and in the US,[2] PC is usually offered late, at the end-of-life stage, although the World Health Organization recommends providing PC as early as possible in the course of the disease to increase quality of life.[3] In 1999, PC access became a right guaranteed by the law for patients and their families in France.[4] This context explains why even now, PC often means “end-of-life” not only for the patient but also for caregivers and many doctors. The last World Health Organization recommendations are less restrictive than the outdated 1996 French recommendations that stated that PC should be offered as early as possible in the course of the disease to increase quality of life and to positively influence the course of the illness.[3] The World Health Organization recommendations add that PC is applicable early in the course of illness in conjunction with other therapies that are intended to prolong life, such as chemotherapy (CT) or radiation therapy; the recommendations also state that investigations are necessary to better understand and manage distressing clinical complications.[3]

The concept of Early Palliative Care (EPC)

In a recent randomized study, 151 patients newly diagnosed with metastatic non-small-cell lung cancer were assigned to receive either early PC (EPC) integrated with standard oncologic care or standard oncologic care alone.[5] It was hypothesized that patients who received EPC would have a better quality of life (primary endpoint) compared with patients who received standard oncologic care only. In the EPC group, the first visit with the PC services (board-certified PC physicians and advanced practice nurses) was planned within 3 weeks after enrollment and at least monthly thereafter; all but one patient had the first visit by the 12th week, with a mean of four total visits. In this study, the authors referred to the PC package presented in the recommendations from the National Consensus Project for Quality Palliative Care.[6] For patients with metastatic non-small-cell lung cancer, EPC led to significant improvements in quality of life and in mood. Additionally, EPC led to a

significantly longer survival (median survival, 11.6 vs. 8.9 months; HR=0.60, p=0.02), despite less aggressive end-of-life care.[5] Several hypotheses for the effect of EPC on survival have been raised by Pirl et al. [7], such as improving the management of medical comorbidities including depression, and aiding in the discontinuation of inappropriate and possibly detrimental cancer treatments at the end of life.

Following the publication of Temel and colleagues,[5] the American Society of Clinical Oncology recommended that "combined standard oncology care and PC should be considered earlier in the course of the illness for any patient with metastatic cancer….".[8] However, it appears that a gap exists between these recommendations and current practice in France and elsewhere. Moreover, there is no consensus on how early PC should be integrated into oncologic services; a randomized trial recently reported a non-significant increase in survival rate for early (30 to 60 days after diagnosis) versus delayed (3 months later) initiation of PC in 207 patients diagnosed with various types of advanced cancer.[2] The results of Temel's study have modified the perception of many oncologists about the objectives of PC. However, additional clinical studies seem necessary before considering EPC as an additional survival input in advanced malignancies other than metastatic non-small-cell lung cancers.

Metastatic upper gastrointestinal cancers

The median survival time of patients with metastatic upper gastrointestinal (GI) cancers, such as pancreatic cancers, esophago-gastric cancers, and biliary tract cancers, does not exceed 10-11 months [9-11], which is as poor as survival rates reported for metastatic lung cancer patients. The standard of care for metastatic upper GI cancers is well described in the European Society of Medical Oncology guidelines.[12-14] Briefly, the standard of care for metastatic pancreatic cancer in the first-line includes a combination of fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX regimen) for patients without any cholestasis who are in good performance status; the standard of care includes gemcitabine monotherapy for frail patients.[12] For metastatic biliary tract cancers, the standard of care includes a gemcitabine-based regimen (gemcitabine monotherapy, gemcitabine plus cisplatin, or gemcitabine plus fluorouracil).[13] Most patients with metastatic HER2-negative tumors have a poor prognosis with survival rates similar to those of patients with other upper GI malignancies; HER2-positive metastatic esophago-gastric patients present with a much better prognosis and should be treated with a trastuzumab-based regimen.[14] For patients with upper GI malignancies, various combinations of cytotoxics (fluoropyrimidines, taxanes, platinum compounds) may be offered to patients [12-14]. Several experimental treatments (antiangiogenics, MET inhibitors, modulators of immune check points, new cytotoxics, etc.) may be offered to these patients, but these treatments are restricted to patients in good health who are willing to participate in clinical trials; none of these treatments have produced a meaningful survival benefit thus far. In summary, patients with metastatic upper GI cancers do not benefit from currently available systemic therapies. Providing an extra survival benefit with EPC would be a considerable contribution for these patients, as would

the implementation of these practices within the continuum of care of oncology in France.

Aim of the study

We designed a randomized controlled trial, called EPIC, which aims to test the hypothesis that the use of EPC provides greater clinical benefits than standard practice for a population of patients with metastatic upper GI cancers. Overall survival (OS) will be used as a primary endpoint. The content of palliative care visits will be studied through a specific checklist. Patient-reported outcomes (quality of life, depression and anxiety) will also be investigated using dedicated and validated questionnaires.

METHODS AND ANALYSIS

Study design

This study was designed as a randomized, open-label, multicenter phase III trial. It aims to estimate the survival benefits of EPC combined with standard oncologic care (experimental arm) compared with standard oncology care only (standard arm) for patients with metastatic upper GI cancers (esophago-gastric cancer, pancreatic cancer, biliary tract cancer). After the participant's eligibility is established, informed consent has been obtained and stratification factors are defined, the participant will be enrolled in the study and the treatment will be centrally allocated using the online CS randomization module from Clinsight software (Ennov, San Francisco, CA, USA), ensuring the concealment of the next patient allocation. Treatments will be randomized in a 1:1 ratio, and a minimization procedure will be used to balance patients according to center, Eastern Cooperative Oncology Group (ECOG) performance status [15] (0-1 versus 2) and tumor location (esophago-gastric, pancreas, or biliary tract). Patients will be recruited nationwide from 17 university hospitals or cancer centers in France. Written informed consent will be obtained from the patient by an investigator before any screening or inclusion procedures. The patient will remain in the study until one of the following conditions applies: study withdrawal (patient or sponsor or investigator's decision) or death.

Outcome measures

Study objectives

The primary objective of this study is to evaluate the efficacy of EPC in terms of OS curves (intent-to-treat analysis). The secondary objectives are to assess the following: (a) the efficacy of EPC in terms of 1-year OS (intent-to-treat and per protocol analyses) and OS curves (per protocol analysis), (b) the patient-reported outcomes (quality of life, depression and anxiety) and the Time Until Definitive Deterioration (TUDD) for Quality of Life, (c) the number of patients receiving chemotherapy in their last 30 days of life, (d) the actual description of the PC package, and (e) the presence or absence of advanced directives in patient files.

Measurement tools

OS is defined as the time between the date of randomization and the date of death, no matter the cause of death. Patients who are alive at the cut-off date will be censored at that date. Quality of Life will be assessed with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. The QLQ-C30 aims to measure a person's overall quality of life, physical conditions, and limits to the ability to carry out everyday activities; the questionnaire also assesses cognitive, emotional and social functioning as well as the appearance of symptoms frequently associated with cancer or its treatment. Patients are asked to check a scale that ranges from one to four (not at all, a little, quite a lot, a lot) or from one to seven (from 1 – very bad – to 7 – excellent). For each dimension, the QLQ-C30 score indicates definitive deterioration if the score decreases by more than 10 points compared with the score at baseline, without later improvement that is greater than 10 points compared with baseline unless the patient dropped out of the study, resulting in missing data. Thus, TUDD for the Quality of Life scores is defined as the time from randomization to the first observation of a definitive deterioration of the QLQ-C30 score or the time from randomization to death. Depression will be assessed with the HADS scale (Hospital Anxiety and Depression Scale). HADS aims to detect anxiety and depressive disorders. It contains 14 items with response options ranging from 0 to 3: 7 items assessing anxiety (score A) and 7 items assessing depression (score D). The maximum score for a patient is 21. The number of patients treated with chemotherapy in their last 30 days before death will also be recorded. PC visits will be performed by PC physicians. In both arms, all the dates of PC visits will be recorded in the data base. The content of PC visits will be described through a specific checklist that will be completed by the PC physician after each visit. The number of patients in whom advanced directives are identified in medical records will be recorded.

Patient selection criteria

Inclusion criteria

Patients must:

- Have an upper gastrointestinal metastatic cancer, including pancreatic cancer, biliary tract cancer or gastric cancer (including junctional Siewert 2 and 3 cancers) (An amendment is being submitted to our ethic committee in order to include other esophageal cancers, too)
- Be 18 years of age or older
- Have an ECOG performance status ≤2
- Be planned for treatment with first-line CT
- Have a life expectancy of more than 4 weeks
- Have a good understanding of the French language
- Have health insurance coverage
- Sign and date a written informed consent form

Exclusion criteria

Patients with any of the following conditions or characteristics are excluded from the study:

- Locally advanced cancer
- Junctional Siewert 1 esophago-gastric cancer (An amendment is being submitted to our ethic committee in order to include these cancers together with other esophageal cancers)
- Gastric or junctional esophago-gastric cancer with dysphagia
- Gastric or junctional esophago-gastric cancer with unknown or positive HER2 status
- Compression of the biliary tract without any bypass procedure

Study description

Intervention (Figure 1)

Medical oncologists will be in charge of the patient for CT administration and for supportive care, in accordance with professional practices. PC specialists will be in charge of PC/EPC visits. In order to match with standard practice in France, participants allocated to the standard arm (CT alone) are not scheduled to meet with the PC service, but a PC visit can be performed anytime if requested by the patient, the family, or the oncologist. In the experimental arm (CT + EPC), 5 PC visits are scheduled. The first visit (V1) will be scheduled within the first 3 weeks after randomization. The remaining four visits will be scheduled every month. The content of each of the 5 PC visits will be described by the PC physician and documented in the data base following a specific check-list developed by PC physicians. In part, the visits will focus on the following items:

- Discussion with the patient, focusing on his/her understanding of the disease, its treatment, and the palliative care process
- Evaluation of clinical status and symptoms
- Evaluation of psychological status
- Evaluation of the social environment, including the patient's way of living
- Stakeholder needs: psychologist, physiotherapist, dietician, social worker, etc.
- Caring for the patient and his/her family
- Discussion about the identification of the "person of trust" and about advanced directives
- Coordination and continuum of care

The choice of first-line CT will be decided by each investigator but should adhere to national or international guidelines. If CT is stopped for any reason (toxicity, disease progression, or deterioration of health status), the patient will remain in the study.

Data collection

At baseline, before randomization, patients will have to complete the EORTC-QLQ-C30 and the HADS questionnaires. During the study, the EORTC-QLQ-C30 and the HADS questionnaires will be completed by patients every 8 weeks after randomization. Then, 24 weeks after randomization, only the EORTC-QLQ-C30 questionnaire will be completed by

patients every 8 weeks until the end of the study. In both arms, the number and the dates of PC/EPC visits that are performed will be recorded. The number of patients in whom advanced directives are identified in medical records will also be recorded.

Statistical considerations

To ensure an 80% power, three hundred eighty-one (381) deaths are required to show a significant difference in OS curves if there is an absolute difference of 10% in one-year OS rates (40% vs 50.3%, HR=0.75; log rank test two-sided alpha=5%), assuming proportional hazards over time. Assuming an exponential distribution of survival time, with an accrual duration of 3 years, a 1 year minimum follow-up and a final analysis at 4 years, it will be necessary to randomize 480 patients (240 in each group). This calculation takes into account a yearly 2% loss to follow-up rate. An efficacy interim analysis is planned for when approximately 190 deaths are observed (which is expected to occur 27 months from the start of the study). The significance level is fixed at p=0.003 for the interim analysis and p=0.049 at the final analysis (Lan-DeMets alpha-spending function),[16] with an O'Brien-Fleming efficacy boundary.[17] No futility analysis is planned as the proportional hazards assumption may not be met; there may be a larger treatment effect with a longer follow-up period than in the first part of the survival curves. The interim analysis will also evaluate whether the sample size of the EPIC trial should be increased, considering the observed OS curve in the control group.

OS curves will be estimated using the Kaplan-Meier method. After checking the proportional hazards assumption, the treatment effect of the experimental arm compared to the control arm, in terms of OS, will be based on the estimation of the hazard ratio of death in a Cox model (HR-death, based on the comparison of the OS curves between the two treatment groups) and tested against the null hypothesis of no treatment effect using a log rank test with a two-sided alpha of 5%. The proportional hazards assumption underlying the HR estimate in Cox models will be evaluated using graphic methods and models, including interaction with time. Appropriate methods for estimating treatment effect will be used if the proportional hazard assumption appears to be violated or questionable (use of the restricted mean survival as published by Royston and Parmar).[18] Heterogeneity of the treatment effect by stratification factors will be evaluated using forest plots and interaction tests. The main analyses will be performed on the intent-to-treat dataset, including data from all patients in the treatment group allocated by randomization until their last follow-up visit. A sensitivity analysis is also planned on the per protocol dataset in which patients in the standard arm who completed more than one PC visit within the first 6 months of treatment after randomization will be censored at the date of their second PC visit, and patients in the treatment arm who completed fewer than 5 EPC visits within the first 6 months after randomization will be censored at the date of the first missing EPC visit. One-year survival rates with their 95% confidence interval will also be estimated and compared between groups, considering the intent-to-treat and the per protocol datasets.

Quality of life will be analyzed according to the EORTC manual recommendations. For each

dimension, patients with at least one score will be included in the analysis. Patients without a follow-up QLQ-C30 score will be censored just after baseline. Patients without baseline scores will be censored at baseline. TUDD curves for both arms will be calculated using the Kaplan-Meier method and described using medians and 95% confidence intervals.

An Independent Data Monitoring Committee will meet when the results of the planned interim analysis are available (i.e., when 190 patients have died) to review the results of the first efficacy interim analysis and to re-estimate the sample size if the baseline overall survival rate differs from the protocol assumptions.

ETHICS AND DISSEMINATION

Ethical considerations

This clinical trial will be conducted in accordance with the Declaration of Helsinki [19] or the laws and regulations of the country, whichever provides greater protection to the patient. This study follows the International Conference on Harmonization E6 Guideline for Good Clinical Practice, reference number CPMP/ICH/135/95.[20] The protocol has been examined by the Patient Committee of the National League against Cancer, paying particular attention to the quality of the information letter, to the monitoring plan, and to suggestions implemented into the protocol to improve the comfort of the patients. An independent data monitoring committee for the trial will be formed to guarantee protection of the patients, to ensure that the trial is conducted in an ethical fashion, and to evaluate the risk/benefit ratio of the trial by reviewing the interim results of the trial. The study protocol has been approved by our local ethics committee (CPP Nord-Ouest I, April 4th, 2016).

Dissemination

The study is registered at clinicaltrials.gov (NCT02853474). The protocol and the trial results, even if they are inconclusive, will be presented at international oncology congresses and published in peer-reviewed journals.

Trial financing

This study is supported by unrestricted public grants from Conseil Régional du Nord Pas-de-Calais and from caregivers Ligue National contre le Cancer.

DISCUSSION

This EPIC trial was set up in September 2016. It is a randomized trial primarily designed to detect an OS benefit due to EPC combined with standard oncologic care compared with standard oncologic care only for patients with metastatic upper GI cancer. The design of EPIC differs from the design of the seminal trials by Temel and colleagues,[5] which demonstrated

that EPC not only improves quality of life (the primary objective of their trial) but also may improve OS (a secondary objective) for patients with advanced cancers.

One may argue that the main motivation for many oncologists to engage with EPC is to enhance quality of life for their patients throughout the cancer journey. This is precisely what Temel et al. did.[5] When using OS as the primary endpoint of EPIC, as we will, there is a theoretical danger that if a study does not meet its OS endpoint, it will indicate that EPC has "failed" and should be discarded. Our point is different. Our country has a strong culture of integrating PC into oncology services. However, despite efforts from, many PC professionals, PC is frequently offered to patients at a late stage of their metastatic disease. Some components of PC visits, such as visits with a dietician and/or with psychologists, are usually offered at an earlier stage but not as systematically as they should be. Using OS as the primary endpoint of EPIC, we postulate that without a strong "signal", such as a survival benefit, sent to medical oncologists and colleagues in charge of metastatic patients with upper GI malignancies, it would take some time before the concept of EPC is implemented in our country. Furthermore, the benefits of EPC have yet to be validated in a population of patients with metastatic upper GI cancers. Patients with metastatic upper GI malignancies are different from patients with metastatic lung cancers; they do not present the same, and we assume that their co-morbidities and their treatment-related symptoms are also different. The difference in terms of reduced risk of death (-25%) that we have chosen for the primary outcome is derived from the work reported by Temel et al. (-40%) regarding metastatic lung cancers.[5] Further reducing the risk of death to 25% should lower the theoretical danger that this study may not meet its OS endpoint.

In Temel's trial [5], the content of the EPC package, which was rather vague, was adapted from American guidelines for palliative care visits.[6] There are no such recommendations in our national context. To overcome this, PC specialists have developed a checklist of all of the items that could be addressed within PC coverage. Hence, one of the secondary endpoints of this EPIC trial will be to make an actual description of each EPC/PC visit, as well as to provide a description of the whole EPC/PC package. At the end of the study, the materials we will collect should help us in drafting guidelines for PC in France.

To conclude, we expect that this study will lead to earlier integration of PC in oncologic care for metastatic GI cancer patients.

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Contributors AA, AD, EH, and MCL designed the study; AA, AD, MCL, EH, and SL contributed to the drafting of the manuscript; AA, SL, EH, and SD contributed to the trial set-up; SD is responsible for data collection and for administrative support; EB will contribute to statistical analyses; MCL is responsible for data management and statistical analyses; AA, EH, AD, and MCL will contribute to data interpretation. All authors contributed to the revision of the manuscript and approved it for submission. AA is responsible to submit the report of the study for publication.

Funding This study is supported by unrestricted public grants from Conseil Régional du Nord Pas-de-Calais and from caregivers Ligue National contre le Cancer. The funders have no role in study design, management, analysis, and interpretation of data, as well as no role in the writing of the final report.

Competing interests None.

Ethics approval (CPP Nord-Ouest I, April 4th, 2016)

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This manuscript contains original material without any unpublished data, but the full results of this ongoing trial

FIGURE LEGEND

Figure 1 – Study design

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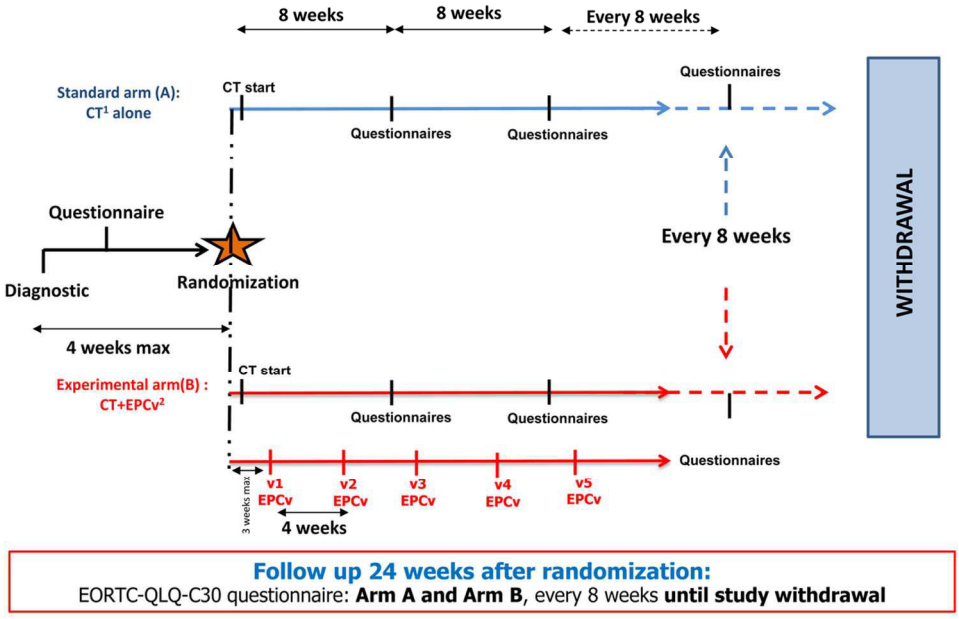

[1] ***CT***: *Chemotherapy according to national or international guidelines*
[2] ***EPCv***: *Early palliative care visit, 5 EPCv are scheduled at v1, v2....v5*

112x84mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	full protocol p.1
Protocol version	3	Date and version identifier	full protocol p.1
Funding	4	Sources and types of financial, material, and other support	_____9_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1 & 11__
	5b	Name and contact information for the trial sponsor	_____1_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____11_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	full protocol p.4

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___3 & 4 & 5__
	6b	Explanation for choice of comparators	_____3_____
Objectives	7	Specific objectives or hypotheses	_____5_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____5_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	full protocol p.4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____6 & 7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____5 & 6____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____7_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	ND
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____7_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____5 & 6_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____7_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____8 & 9____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____ND____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____5_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____ND_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____5_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____ND_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____N/A_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____5 & 6_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____ND_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	full protocol p.17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____8_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____8_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____8_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____8_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____8_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	full protocol p.14 & p.15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	full protocol p.19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____9_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	full protocol p.17 & p.19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	full protocol p.17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	full protocol p.20
	31b	Authorship eligibility guidelines and any intended use of professional writers	ND
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	ND
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	ND
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CLINICAL STUDY PROTOCOL

Study number: 1511

Protocol title:

Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers, treated with first-line chemotherapy: a randomized phase III trial

Study code: EPIC-1511

N° IdRCB N°: 2015-A01943-46

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Confidentiality

Version 2.2 approved by «CPP Nord-Ouest I» on December 16th, 2016 and by ANSM on December 26th, 2016

1. APPROVAL AND PROTOCOL SIGNATURE

Study code: EPIC-1511

SPONSOR REPRESENTATIVE		
	Date	Signature
Pr Eric LARTIGAU Director-General *Centre Oscar Lambret – Lille – France*		
COORDINATING INVESTIGATOR FOR STUDY		
	Date	Signature
Pr Antoine ADENIS Coordinator		
Dr Arlette DA SILVA Co-Coordinator		

Principal investigator / Site

Investigator name and address:

I have read the present protocol.

I agree:

- To obtain approval of my Institution to lead the study in the establishment;
- To maintain confidentiality regarding the contents of this protocol;
- To conduct the study as outlined in the protocol and in compliance with GCP and with applicable regulatory requirements ;
- To provide the protocol and all drug information provided to me by the sponsor, to all physicians responsible to me who participate in this study. I will discuss the material with them to ensure that they are fully informed regarding the drug and the conduct of the study;
- To direct and assist appropriately the staff under my responsibility, who will be involved in the study;
- To use the trial material only according to the instructions of the protocol;
- To permit monitoring, auditing and inspection;
- To keep the trial-related essential documents until the sponsor indicates that these documents are no longer needed.

Investigator signature: **Date:**

2. LIST OF TRIAL SITES AND COORDINATING STUDY PERSONNEL

The list of trial sites will be attached to the protocol.

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3. SYNOPSIS

See attached documents.

4. BACKGROUND AND RATIONALE OF THE STUDY

Medical care in the metastatic setting

Medical oncology is aimed to increase patient's survival, even at metastatic stages, in addition to disease-related and treatment-related symptoms. However, providing palliative care (PC) which includes symptoms management, nutritional support, psychosocial support, as well as assistance on end-of-life preferences, may be as important as survival issues to improve quality of life in such setting. In France, PC has been traditionally offered late, at end-life stage, although the World Health Organization recommends providing PC as earlier as possible in the course of the disease, in order to increase quality of life [1].

Palliative care

Decades ago, PC services were initiated in France in order to provide a medical alternative to the use of questionable medical practices regarding the end of life period: abandonment, euthanasia, and inappropriate aggressive therapy. According to the French society of palliative care (Société Française d'Accompagnement et de Soins Palliatifs, 1996) [2], PC is an approach aimed to provide active care, in a holistic approach to the person with a serious, progressive or terminal illness. The objective of PC is to relieve pain and other distressing symptoms, but also to take into account the psychological, social and spiritual suffering. PC offers an interdisciplinary support system to help patients and their relatives [2]. As mentioned previously, PC has been in France (but also in the US) [3] usually offered late, at end-life stage. Actually, PC access became a Right guaranteed by the Law, for patients and their families in 1999 (Kouchner law and 1st Program for PC implementation in 1999-2001) [4]. This context should explain why even nowadays, PC often means « end of life » not only for the lay-man for the general public but also for caregivers, and some doctors.

The last World Health Organization (WHO) recommendations are less restrictive than the rather dated 1996 French recommendations, as it is stated that PC should be offered as earlier as possible in the course of the disease, in order to increase quality of life, and to positively influence the course of illness [1]. The World Health Organization recommendations add that PC is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications [1].

The concept of Early Palliative Care (EPC)

In a recent randomized study, 151 patients with newly diagnosed metastatic non–small-cell lung cancer were randomized to receive either early PC (EPC) integrated with standard oncologic care or standard oncologic care alone (Temel JS, N Engl J Med 2010) [5]. It was hypothesized that patients, who received EPC, compared with patients who received standard oncologic care only, would have a better quality of life (primary endpoint). The first visit with the PC service set up within the first 12 weeks, and the median number of visits in the EPC group was 4. In this study, the authors referred to the recommendations of the National Consensus Project for Quality Palliative Care [6]. Among patients with metastatic non–small-cell lung cancer, EPC led to significant improvements in quality of

life. In addition, EPC led to significant improvements in mood, as well as in overall survival (median survival, 11.6 vs. 8.9 months; HR=0.60, p = 0.02)), despite less aggressive end-of-life care [5].
Following the publication of Temel et al. [5], the American Society of Clinical Oncology recommends nowadays that "combined standard oncology care and PC should be considered earlier in the course of the illness for any patient with metastatic cancer…." [7]. However, it is clear that a gap exists (not only in France) between this recommendation and current practice, and that there is no consensus on how early PC should integrated in oncologic services, even though an underpowered small randomized trial reported recently an insignificant better survival favoring early versus delayed (3 months later) initiation of PC [3].
The results of study of Temel et al. [5], although formally restricted to the field of metastatic non-small-cell lung cancers, have modified the perception of many oncologists about the objectives of PC. However, additional clinical studies should be done before considering EPC as an additional survival input in other advanced malignancies.

Metastatic upper gastrointestinal cancers

The median survival of metastatic upper gastrointestinal (GI) cancers such as pancreatic cancers, gastric cancers, and biliary tract cancers did not exceed 10-11 months, which is as poor as reported with metastatic lung cancers. Standard of care in the metastatic setting in upper GI cancers are described in *ad hoc* French guidelines, i.e.: "Thésaurus National de Cancérologie Digestive" [8]. Briefly, standard of care in metastatic pancreatic cancer in the first-line setting lies on the combination of fluorouracil, irinotecan, and oxaliplatin (folfirinox regimen) for patients without any cholestasis and in good performance status, and on gemcitabine monotherapy. In metastatic biliary tract cancers, standard of care in terms of chemotherapy lies on gemcitabine-based regimen (gemcitabine monotherapy, gemcitabine plus cisplatin, or gemcitabine plus fluorouracil). Besides HER2 positive metastatic gastric/esogastric patients who present with much better prognosis, and should be treated with trastuzumab-based regimen, most of patients with metastatic HER2 negative patients (IHC + or IHC ++ with negative fish/sish) have poor prognosis, with similar survival rates than patients with other upper GI malignancies. In that setting, several regimens may be offered to patients, such as the following: Folfox, EOX/ECX, Folfiri, LV5FU2-cisplatin, Capecitabine-platinum salt or docetaxel-based regimen ...) [8]. Several experimental treatments (antiangiogenics, met inhibitors, modulators of immune check points, etc...) are currently tested in metastatic gastric/esogastric cancers, but these treatments are restricted to patients in good health condition who accept to participate to clinical trials, and none have yet produced meaningful survival benefit in the first-line setting.
To summarize, therapeutic progresses in the setting of metastatic upper GI cancers are infrequent, and often modest. Providing an extra survival benefit for these patients with EPC, may contribute to deeply modify the practice of care of oncology in France.

Why did we choose OS as the primary endpoint of this trial?

One may argument that the main motivation of oncologists to engage with EPC surely should be to enhance the quality of life of their patients throughout the whole cancer journey. This is precisely what did Temel et al. [5]. Moreover, there is a theoretical danger that if this study does not meet its OS endpoint it will be interpreted as meaning that EPC has "failed" and should be discarded.

Our point is clearly different. Our country has a strong culture of integrating PC into oncology services. However despite efforts of many PC professionals, PC is frequently offered to patients at a late stage of their metastatic disease. Some components of PC visit such as visits with a dietician and/or with psychologists may be offered at an earlier stage, but maybe not as systematically as it should be. We postulate that without a strong "signal" such as a survival benefit, sent to medical oncologists and colleagues in charge of metastatic patients with upper GI malignancies, it would take some time before the concept of EPC be implemented in our country. Furthermore, and *stricto sensu*, the benefit of EPC has not been validated yet in the population of patient with metastatic upper GI cancers. Obviously, patients with metastatic upper GI malignancies are different from patients with metastatic lung cancers; they do not present the same, and we assume that their co-morbidities as well as their treatment-related symptoms are also different. The difference in terms of reduction of risk of death (-25%) that we had chosen for primary outcome derived from one reported by Temel et al. (-40%) in the setting of metastatic lung cancers [5]. Reducing this expected reduction of risk of death to 25% should lower the theoretical danger that this study does not meet its OS endpoint.
Finally, as we believe that quality of live is also an important goal in the setting of metastatic upper GI cancers, and as we anticipate that EPC may have a positive effect in lowering the quality of life degradation, we add to the classical QLQC30 questionnaire, the study of Time Until Definitive Degradation (TUDD) of Quality of Life.

5. OBJECTIVES

5.1. Primary objective

- Efficacy in term of overall survival (intent-to-treat analysis)

5.2. Secondary objectives

- Efficacy in term of 1-year survival (intent to treat and as per protocol analysis) and overall survival (as per protocol analysis)
- Patient-reported outcomes (Quality of life, depression and anxiety, …)
- TUDD (Time Until Definitive Deterioration) for Quality of Life
- Number of patients on chemotherapy, in their last 30 days of life
- Description of the content of Palliative Care (PC)

6. STUDY DESIGN

6.1. Overview

This prospective, randomized, open-label and multicenter phase III study is aimed to estimate the survival benefit of Early Palliative Care (EPC) combined with standard oncology care (including first-line chemotherapy) (experimental arm) over standard oncology care only (standard arm), in patients with metastatic upper gastrointestinal cancers (gastric cancer, pancreatic cancer, biliary tract cancers). Patients will be stratified by minimization according to:

- center,
- performance status (0-1 versus 2),
- localization (esogastric/gastric, pancreas, and biliary tract).

6.2. Inclusion criteria

- Patients with an upper gastrointestinal metastatic cancer: pancreatic, biliary tract or gastric (including junctional Siewert 2 and 3 cancers) cancers.

  NB: Esogastric junctional cancers with dysphagia and/or gastric/esogastric cancers with unknown or positive HER2 status are not eligible.
- Patients planed to be treated with first-line chemotherapy for metastatic disease.
- Age ≥ 18 years
- Life expectancy ≥ 1 month
- Performance status (OMS) ≤ 2
- Good understanding of French language
- Signed and dated informed consent
- Patients covered by government health insurance

6.3. Non inclusion criteria

- Locally advanced cancer
- Junctional Siewert 1 esogastric cancer
- Gastric or junctional esogastric cancer with dysphagia
- Gastric or junctional esogastric cancer with unknown or positive HER2 status (IHC: +++ or IHC ++ and FISH/SISH +)
- Compression of the biliary tract requiring a bypass
- Patients included in a clinical trial with an anticancer agent

6.4. Patient enrolment

The following procedures should be performed before the registration of the patient:

- Informed consent leaflet should be signed by both patient and investigator before starting any study procedure ;
- All selection procedures should be performed as per protocol ;

A randomization request form is to be filled in by the investigator in order to ensure that the patient meets ALL the selection criteria. BEFORE STARTING TREATMENT, the investigator must fax the randomization request form to the Sponsor:

Clinical Research Integrated Unit / Sponsor Unit

Centre Oscar Lambret – Lille - France

Tel: 33 (0)3 20 29 59 18 - Fax: 33 (0)3.20.29.58.96

After checking all the inclusion and non-inclusion criteria, an identification number will be allocated to the patient. This number will then be retained for the whole duration of the trial. A confirmation of inclusion and the arm to which the patient has been randomly assigned will be sent to the investigator.

After patient registration, the patient identification number and treatment arm allocated will be retained within the study even if the patient is withdrawn from the study before the first study drug administration.

6.5. Withdrawal from study

The study will continue until one of the following applies:

- Patient's choice
- Investigator's decision
- Sponsor's decision
- Patient's death

➢ **AT ANY TIME DURING THE STUDY TREATMENT:**

- ***Patient's death should be immediately notified to the sponsor in order to plan the interim analysis.***

7. ENDPOINTS

7.1. Primary endpoints

- **Overall survival (as intent-to treat analysis)**

The overall survival is defined as the time between the date of randomization and the date of death, whatever the cause.

7.2. Secondary endpoints

a. One year survival rate (intent-to treat and per protocol analyses), and overall survival (per protocol analysis)

One year survival rates with their 95% confidence interval in both intent-to-treat and per protocol analyses, as well as OS curves in per protocol analysis will be given.

b. Quality of life

The Quality of Life is assessed with the QLQ-C30 questionnaire at baseline, 8and 16 weeks after inclusion, as well as every 8 weeks thereafter.

The **QLQ-C30** by EORTC (European Organization for Research and Treatment of Cancer) measures the quality of life of patients suffering from cancer. It includes 30 items with measure the overall quality of life, physical conditions, and limits to the ability to carry out everyday activities, cognitive, emotional and social functioning and the appearance of symptoms frequently associated with cancer or its treatment. The participants reply on a scale of one to four (not at all, a little, quite a lot, a lot) or seven points (from 1 – very bad – to 7 – excellent).

c. Depression assessed with the HADS score

The depression is assessed with the HADS scale (Hospital Anxiety and Depression Scale) at baseline, and then 8 and 16 weeks after inclusion.

HADS is a tool which detects anxiety and depressive disorders. It contains 14 items graduated from 0 to 3: 7 items in relation with anxiety (score A) and 7 items in relation with depression (score D). The maximum note of each score is 21.

d. TUDD (Time Until Definitive Deterioration)

For each dimension, QLQ-C30 score is considering definitive deterioration if the score decreased by more than 10 points as compared with the score at baseline, without later improvement superior to 10

points as compared with baseline or if the patient dropped out of the study resulting in missing data. Thus, TUDD for Quality of Life scores was defined as the time from randomization to the first observation of a definitive deterioration of QLQ-C30 score or death. Median TUDD and 95% confidence interval are given for both arms.

e. Presence or lack of advanced directives

The number of patients whom advanced directives are written in their medical records will be recorded.

f. Actual contain of PC visits

A PC visit is a visit done by a PC physician. *Any kind of visits done by other professionals (i.e: dieticians, nurses, social workers, psychologists, pain specialists, etc.) IS NOT a PC visit.*

In both arms, some specific items will be collected:

- Actual number of PC visits within the first six months since randomization
- Actual timing of PC visits within the first six months since randomization
- Total number of PC visits until death

Only in Arm B (interventional arm), the content of each PC visit will be described by the PC physician at the end of the visit, by filling a specific check-list (*Cf.* appendix 3) built by an *ad hoc* working-group of PC physicians. Briefly, the latter will focus on the following items:

- Discussion with the patient focusing on its understanding related to its disease, its treatment, and the palliative care process.
- Evaluation of clinical status and symptoms
- Evaluation of psychological status
- Evaluation of the social environment including its way of living
- Stakeholder needs : psychologist, physiotherapist, dietician, social worker …
- Caring for the patient and his family
- Discussion about the identification of the "person of trust" and about advanced directives
- Coordination and continuum of care

g. Chemotherapy in the last 30 days before death

The number of patients treated with chemotherapy in their last 30 days before death will be recorded.

8. EVALUATION ASSESSMENT

8.1. Baseline assessment (T0)

Patients are included by a medical oncologist within 4 weeks after the diagnosis disclosure.

For each patient, *before randomization (T0):*

- EORTC-QLQ-C30 questionnaire
- HADS questionnaire

8.2. Assessment during study procedure

For both arms (Arm A and Arm B):

- ***every 8 weeks (T3 and T5)*** **:** EORTC-QLQ-C30 questionnaire and HADS questionnaire

For Arm B only:

- ***every 4 weeks (T1, T2, T3, T4, T5):*** PC visit

The content of each PC visit will be described by the PC physician at the end of the visit, by filling a specific check-list (Cf. appendix 3: PC grid):

- *Discussion with the patient focusing on its understanding related to its disease, its treatment, and the palliative care process.*
- *Evaluation of clinical status and symptoms*
- *Evaluation of psychological status*
- *Evaluation of the social environment including its way of living*
- *Stakeholder needs : psychologist, physiotherapist, dietician, social worker …*
- *Caring for the patient and his family*
- *Discussion about the identification of the "person of trust" and about advanced directives*
- *Coordination and continuum of care*

8.3. Follow-up assessment (after 24 weeks)

For both arms (Arm A and Arm B), every 8 weeks until the end of the study

- EORTC-QLQ-C30 questionnaire

9. STUDY DESCRIPTION

9.1. Scheme

See appendix 2.

9.2. Chemotherapy

The choice of first-line CT is left to the choice of the each investigator, but should refer to regional, national or international guidelines.

The treatment begins within 10 days after the inclusion of the patient. If, for any reasons (toxicity, disease progression, or deterioration of health status), the first-line CT has to be stopped, the patient remains in the study.

9.3. Study arms

a. Arm A: CT alone (standard arm)

The medical oncologists (or gastroenterologist physician) are in charge of the patient for chemotherapy administration, and for the management of symptoms related to the disease and/or the treatment, in accordance with professional practices.

If needed (any time), a PC visit could be performed.

b. Arm B: CT + EPC (Early Palliative Care) (interventional arm)

Again, medical oncologists (or gastroenterologist physician) are in charge of the patient for CT administration, and for the management of symptoms related to the disease and/or the treatment, in accordance with professional practices. In addition, PC visits will be scheduled.

PC visits at times T1, T2, T3, T4 and T5: **PC visits will be performed by a PC physician.**

The first visit (T1) will be scheduled within the first 3 weeks after randomization. The following visits (T2, T3, T4, T5) will be scheduled approximately every month. At best, these visits will be organized at the same time as standard medical oncology visits.

All these visits will be recorded (cf. §15 annex 2).

If needed, a dedicated visit could be scheduled with other professionals (i.e.: dieticians, nurses, social workers, psychologists, pain specialists, etc.) but will not be considered as a PC visit.

NB: There is no equivalent in the French context to the recommendations of the National Consensus Project for Quality in Palliative Care [6]. Therefore, in our study, the content of each PC visit will be described by the PC physician at the end of the visit, by filling a specific check-list (built by an *ad hoc* working-group of PC physicians).

9.4. Concomitant treatment

Non-authorized treatment

None

Authorized treatment

Any therapy deemed to be necessary for the patient's well-being.
All concomitant prescription will be documented in the eCRF.

10. PATIENT'S SAFETY AND SAFETY REPORTING

Only adverse events related to clinical research (PC visits, questionnaires) will be collected in the eCRF according to CTCAE version 4.0.

10.1. Definition

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical trial subject and which does not necessarily have a causal relationship with this clinical investigation.
A serious adverse event (SAE) is defined as any AE which results in death, is life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalization, is a congenital anomaly / birth defect.
The following events do not have to be reported as SAE:
- Hospitalization planned before the beginning of the trial and/or planned by the protocol;
- Hospitalization in accordance with standard procedures of the site;
- Hospitalization for pre-existing conditions in absence of worsening;
- Hospitalization or prolonged hospitalization for administrative or social reasons, in absence of an AE.

An event which is part of the natural course of the disease (i.e. progressive disease or hospitalization related to progressive disease) or related without doubt to a concomitant treatment (chemotherapy) should not be reported as a SAE.
However, AT ANY TIME DURING THE STUDY TREATMENT, patient's death whatever the cause should be immediately notified to the sponsor in order to plan the interim analysis.

10.2. Investigator's responsibilities

The investigator must evaluate for each adverse event reported during the study:

- its seriousness
- its causal relationship with the clinical investigation.

- Notification to the sponsor of serious adverse events (SAE)

In the event of the occurrence of any SAE between signature of informed consent form and the end of the 28-day follow up period after last sampling, the Investigator informs the Sponsor's Safety Desk immediately, i.e. within 24 hours of awareness of the event(s) by e-mail or by fax.

Clinical Research Unit – Sponsor Unit - Safety Desk
Tél. : **03 20 29 59 18** - Fax : **03 20 29 58 96**
E-mail: **vigilanceEC@o-lambret.fr**

- Follow-up of SAE

The investigator has to follow each SAE until its resolution and to transmit follow-up information (detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports, or other relevant documents) to the Sponsor's Safety Desk.

The investigator has to answer to additional information requested by the Sponsor's Safety Desk or the monitor.

10.3. Sponsor's responsibilities

- Determination of expectedness/unexpectedness of SAE

Expected Serious Adverse Events

The risk for apparition of Expected Serious Adverse Events related to study procedures is low.

Unexpected Serious Adverse Events (SUSAR)

Suspected Unexpected Serious Adverse Events are all adverse events not listed above. Nevertheless, all expected adverse event which differs on intensity, evolution or frequencies will be considered as unexpected.

- Recording of vigilance data and immediate reporting of Suspected Unexpected Serious Adverse Events (SUSAR)

The sponsor will update and store all vigilance data regarding the study. He will also notify all Suspected Unexpected Serious Adverse Events to regulatory authorities (National Competent Authority and Ethic Committee) and inform all investigators, in accordance with applicable laws and regulations.

- Periodic Safety Reports

The Sponsor will prepare and submit appropriate periodic safety reports to regulatory authorities (National Competent Authority and Ethic Committee), in accordance with applicable laws and regulations.

11. STATISTICAL ANALYSIS AND SAMPLE SIZE

11.1. Sample size

Three hundred eighty-one (381) deaths are required to show an absolute difference of 10% in one year overall survival (40% vs 50.3%, HR=0.75; two-sided alpha=5%) with an 80%-power, assuming proportional hazards over time. Assuming an exponential distribution of survival time, with an accrual duration of 3 years, a 1 year minimum follow-up and a final analysis at 4 years, it is necessary to randomize **480 patients** (240 in each group), corresponding to an accrual of 13 patients per month. This calculation takes into account a yearly 2% loss to follow-up rate. An interim analysis is planned when approximately 190 deaths are observed (which is expected to occur 27 months since the start of the study). The significance level is fixed at p=0.003 for the interim analysis and p=0.049 at the final analysis (Lan de Mets alpha-spending function, with an O'Brien Fleming efficacy stopping rule).

Patients will be stratified by minimization technical according to:

- Center

- Performance status (0-1 versus 2)
- Tumor location (esogastric or gastric versus pancreas versus biliary tract)

As the expected baseline overall survival is uncertain in the control group, the sample size will be re-estimated at the interim analysis, blinded to the observed effect size

11.2. Statistical analysis

Baseline characteristics will be presented as summary tables. Categorical variables will be presented as frequencies and percentages. Continuous variables will be presented as medians (range) and means (standard deviation) if justified. Missing data will be indicated.
Overall survival corresponds to the time interval between date of randomization and date of death. All causes of deaths are considered as events. Patients alive at cut-off date are censored at that date.

After check of proportional hazards assumption, the treatment effect of the experimental arm compared to the control arm will be based on the estimation of the Hazard Ratio of death in a Cox model (HR-death, based on the comparison of the OS curves between the two treatment groups), tested against the null hypothesis of no treatment effect using a logrank test with a two-sided alpha of 5%.
The proportional hazards assumption underlying the HR estimate in Cox models will be evaluated, using graphic methods and models including interaction with time. Appropriate methods for treatment effect estimates will be used if the proportional hazard assumption appears violated or questionable (use of restricted mean survival as published by Royston and Parmar).

Heterogeneity of treatment effect by the stratification factors will be evaluated using forest plots and heterogeneity tests.

The main analysis will be performed on the intention-to-treat dataset, including all patients included the treatment group allocated by randomization until their last follow-up visit.

A sensitivity analysis is also planned on the per protocol dataset where patients in the standard arm who got more than a PC visit within the first 6 months of treatment since randomization will be censored at the date of their second PC visit, and patients in the interventional arm who actually got less than 5 PC visits within the first 6 months since randomization will be censored at the date of first missing PC visit.

Quality of life will be analyzed according to EORTC manual recommendations.

TUDD is defined as the time interval between date of randomization and date of first definitive deterioration or death. For each dimension, patients with at least one score are included in the analysis. Patients without follow-up QLQ-C30 score are censored just after baseline. Patients without baseline are censored at baseline. TUDD curves for both arms are calculated using the Kaplan-Meier method and described using median and 95% confidence interval.

The IDMC will meet when the results of the planned interim analysis are available (i.e. when 190 patients will be dead) to review the results of the first efficacy interim analysis, and to re-estimate the sample size if the baseline overall survival rate differs from the protocol assumptions. No futility analysis is planned as the proportional hazards assumption may not be respected, with possibly a larger treatment effect with longer follow-up than in the first part of the survival curves

11.3. Data management

Data Management will be undertaken by the data management team of the North-West Cancéropôle Data Treatment Centre situated in Caen, France at the François Baclesse Cancer Centre, where the database will be located.

A trial-specific database will be created, tested and validated before the start of data capture. This database will be developed using Clinsight (ENNOV), which is a software package designed for the overall management of clinical studies, and which meets the regulatory requirements for clinical trials. A data validation plan will be developed and will describe in detail the checks to be performed for each significant variable and a list of obvious authorized corrections.

The essential data necessary for monitoring the primary and secondary endpoints will be identified and managed at regular intervals throughout the trial in collaboration with the coordinator and the COL Sponsorship Unit.

The electronic case report forms (eCRF) will be subjected to data entry at each investigator site.

The data will be monitored by the team responsible for data management by using the error messages from validation programs. Obvious errors will be corrected. Other errors, omissions or inconsistencies will be listed on data correction forms (DCF) to be sent to the medical investigator for resolution. When the UMB receives the medical investigator's reply, the corrections will be included in the database. A statistical data analysis plan will be established in collaboration between the data-management, the Sponsorship Unit and the trial coordinator.

The database will be frozen after final quality control, and then exported to the STATA statistical software by an automated and validated procedure.

12. LEGAL AND ETHICAL ASPECTS

This clinical trial will be conducted in accordance with the protocol, the ethical principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies; the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (CPMP/ICH/135/95), and all applicable laws and regulations.

This clinical trial will be recorded in the public registry website clinicaltrials.gov before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients (and their healthcare practitioners) how to enroll in the trial.

12.1. Investigator's responsibilities

The principal investigator of each concerned center undertakes to manage the clinical trial in accordance with the protocol approved by the local ethic committee and the national competent authority. The investigator must not make any modification to the protocol without the sponsor's

authorization and without the local ethic committee and the national competent authority approving the proposed modifications.

The investigator is responsible:

- for providing the sponsor with his/her curriculum vitae, along with those of his/her co-investigators,
- for identifying the members of his/her team who are to take part in the trial and for defining their responsibilities,
- for initiating patient recruitment after receiving the sponsor's authorization,
- for making all necessary efforts to include the required number of patients, within the limits of the defined enrolment period.

Each investigator is responsible:

- for obtaining informed consent, personally dated and signed by the patient, prior to any trial-specific selection procedure,
- for regularly updating the case report forms (CRF) for each patient included in the trial and for providing the Clinical Research Associate (CRA) with direct access to the source documents to validate the CRF data,
- for dating, correcting and signing any CRF corrections for each patient included in the study,
- for welcoming regular visits from the CRA and, if applicable, those of auditors mandated by the sponsor, or by regulatory authority inspectors.

The study will be conducted in accordance with the protocol. Study personnel involved in conducting this trial will qualified by education, training and experience to perform their respective task(s).

All documentation relative to the study (protocol, consent forms, CRF, investigator's files, etc…) along with original documents (laboratory results, x-ray, consultation reports, clinical examinations reports, etc.) must be kept in a safe place and considered confidential.

The investigator is responsible for data archiving in accordance with current legislation. The latter must keep the data along with a patient identification list, for at least 15 years after the end of the study.

12.2. Ethic Committee

The clinical study protocol, along with its various amendments, is submitted by the study sponsor, or its representative, to an ethic committee according to the national legislation.

12.3. Participant information and consent

Prior to performing biomedical research on an individual, the latter's **voluntary written informed** consent must be obtained, after having been informed of the aims of the research, of the progress and duration of the study, of the potential study benefits, risks and requirements of the study, along with the type of product under study and the opinion given by the local ethic committee and the national competent authority.

The consent form must be personally dated and signed by the patient and investigator, or by the physician representing the investigator (original filed by the investigator, a copy shall be issued to the patient or his/her legal representative).

The rights safety and well-being of the trial patients are the most important considerations and should prevail over interests of science and society.
The patient information sheet will include all elements required by ICH, GCP and applicable regulatory requirements.
The investigator or his/her designee must provide the patient with a copy of the consent form and written full information about the study in a language that is non-technical and easily understood. The investigator should allow enough time for the patient or his/her legally acceptable representative to inquire about the details of the study. Then, the informed consent must be freely signed and personally dated by the patient and by the person who conducted the informed consent discussion before the beginning of the study. The patient should receive a copy of the signed informed consent and any other written information provided to the patient prior to participation in the trial.
During his/her participation in the trial, any updates to the consent form and to the written information will be provided to the patient.
If a new consent needs to be obtained from the patients, the investigator or his/her designee should inform the patient of any new information relevant to his/her willingness to continue participation in the study before obtaining the written consent.

12.4. Patients Committee

The protocol will be examined by the Patient Committee of the National League against Cancer (LNCC) paying particular attention to the quality of the information letter, the availability of a treatment and monitoring plan and suggestions for measures to improve the comfort of the patients.

12.5. Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) for the trial will be established in order to guarantee protection of the patients, to ensure that the trial is conducted in an ethical fashion, to evaluate the risk/benefit ratio of the trial by reviewing the scientific results during the trial. In fact, the IDMC will meet when the results of the planned interim analysis are available (i.e. when 190 patients will be dead) to confirm or not the statistical hypotheses. This committee will be composed of a medical oncologist in charge of gastrointestinal oncology, a biostatistician and a PC physician.

12.6. Confidentiality

In accordance with the Public Health Code, the investigators and all individuals are required to collaborate in the study shall be held to professional secrecy concerning, in particular, the nature of the products used, the study itself, the test subjects and the results obtained. The investigator must ensure that his/her patients remain anonymous. The investigator shall keep a confidential patient identification list.

12.7. Archiving

The archiving of all study relevant documents at the trial site, at the trial offices and the coordinating investigator's site will be handled according to the requirements of the ICH-GCP, the EU Commission Directive 2005/28/EC of 8th April 2005 and national laws.

13. OPERATIONAL MANAGEMENT OF THE STUDY

13.1. Study organization

This study is sponsored by Centre Oscar LAMBRET (COL), Lille, France.

- Administrative and regulatory, project management, data monitoring (monitoring): Integrated Clinical Research Unit / Sponsorship cell Centre Oscar Lambret - LILLE (S CLISANT, M VANSEYMORTIER)
- Data management and analysis : Data Processing Center "Cancéropôle" Northwest - Biostatistics and Methodology Unit Centre Oscar Lambret - LILLE (E BOGART)

13.2. Research costs and additional costs

Any additional cost as stated in the Public Health Code is covered by an agreement negotiated between the COL and the centre representative, with consideration for the COL's financial means in the context of its sponsoring activity.

The COL shall, however, organize the study and shall provide the following materials (protocol, case report forms, investigator file) required for managing the study.

13.3. Case reports forms - Monitoring

Data are collected in a case report form (CRF) under the investigator's responsibility. These data are entered and validated in accordance with the study specifications. The Clinical Research Associate (CRA) assists the investigator in conducting the study. The CRA mandated by the sponsor makes a series of setup, follow-up and closure visits, in accordance with GCP.

13.4. Quality assurance

The sponsor is responsible for implementing and maintaining a quality assurance system, as described in the COL procedures, in order to ensure that the study is conducted in accordance with the protocol and with GCP.

13.5. Use of information and publication

At the end of the study, a report will be written by the study coordinator and statistician. No publication or presentation of the results of this trial will be done without the permission of the sponsor.

The sponsor is interested in the publication of the results of every study it performs. All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator/institution. The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

14. REFERENCES

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15. APPENDIX

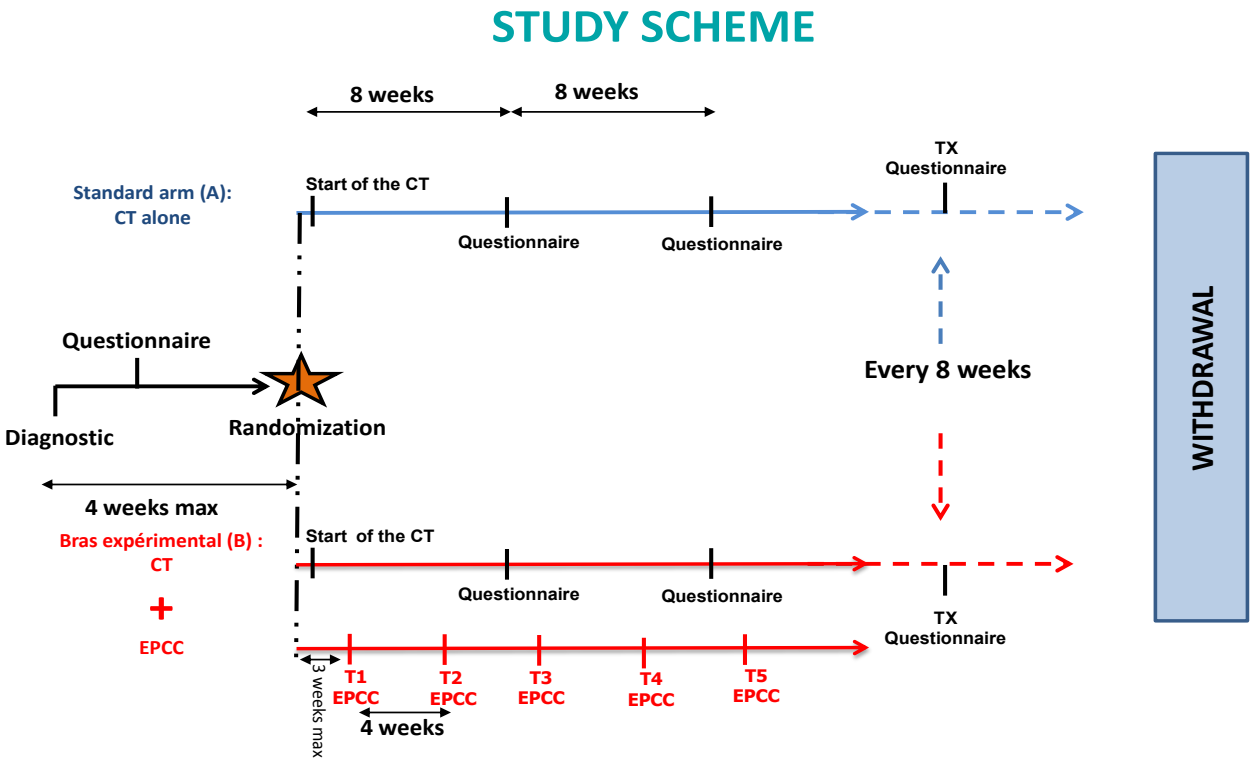
15.1. Appendix 1 – Flowchart

	Baseline < 4 weeks before randomization	RANDOMIZATION < 4 weeks after the diagnosis	Arm A (Standard arm)	Arm B (Interventional arm)
Informed consent	X		-	-
Inclusion/exclusion criteria	X		-	-
Prior medical/surgical history & cancer history Prior medication history	X		-	-
Standard treatment (first-line chemotherapy for metastatic disease)	-		X [(a)]	X [(a)]
Quality of life: questionnaire QLQ-C30	X		X[(b)]	X[(b)]
Depression : questionnaire HADS	X		X[(c)]	X[(c)]
PC visit			- [(d)]	X[(e)]

a) The chemotherapy should begin **within 10 days after randomization**.
b) **Every 8 weeks** after randomization (**T3, T5)** and then **every 8 weeks** until the end of study.
c) **Every 8 weeks** after randomization **(T3 and T5)**.
d) **Only if needed.** The number of PC visits will be recorded but the check-list will not be completed.
e) The first PC visit should be performed **within the first 3 weeks after randomization (T1)** and then every 4 weeks **(T2, T3, T4, T5)** and the check-list will be completed for these 5 visits. After T5, the number of PC visits will be recorded but the check-list will not be completed.

AT ANY TIME DURING THE STUDY, patient's death, whatever the cause, should be immediately notified to the sponsor in order to plan the interim analysis.

15.2. Appendix 2 – Study scheme



Follow up 24 weeks after randomization:
Questionnaire EORTC-QLQ-C30: **Arm A and Arm B**, every 8 weeks **until the withdrawal** from the study

15.3. Appendix 3 – PC grid

Grille de recueil de données – Consultation de Soins Palliatifs

Date : ..... Médecin : ..... Cs n° : .....

Autres intervenants présents : ☐ Infirmière ☐ Psychologue ☐Autre : .....

Le patient était accompagné d'un proche : ☐oui ☐non

INFORMATION

Lors de la consultation les éléments suivants ont été abordés :

- ☐ Compréhension du patient de sa pathologie en termes d'évolution et de pronostic
- ☐ Compréhension du patient des traitements (notamment traitement carcinologique) en cours et des objectifs
- ☐ Explications sur la prise en charge palliative

EVALUATION CLINIQUE

- Score OMS du patient : .....
- Evaluation de l'état psychique : ☐oui ☐non
- Un examen clinique a été réalisé : ☐oui ☐non

	Les symptômes suivants ont été recherchés ?		**Des propositions thérapeutiques ont été réalisées ?**	
	Oui	Non	Oui	Non
Douleur				
Troubles de l'Alimentation				
Troubles digestifs				
Effets secondaires de la chimiothérapie				
Troubles du Sommeil				
Troubles respiratoires				
Anxiété				
Dépression				
Autres :				

MODE DE VIE

Evaluation du contexte familial : ☐oui ☐non

Evaluation du contexte socio professionnel : ☐oui ☐non

Evaluation des besoins humains et matériels dans le lieu de vie : ☐oui ☐non

Propositions/Informations sur les aides possibles au domicile : ☐oui ☐non

- ☐ Mise en place d'aides humaines et matérielles à domicile
- ☐ Mise en place d'un réseau de soins à domicile
- ☐ Mise en place d'une hospitalisation à domicile
- ☐ Autres : .....

PRISE EN CHARGE GLOBALE MULTIDISCIPLINAIRE : le recours aux intervenants suivants a été proposé

- ☐ Algologue
- ☐ Assistante sociale
- ☐ Diététicienne
- ☐ Infirmière
- ☐ Intervenant religieux
- ☐ Kinésithérapeute
- ☐ Psychiatre
- ☐ Psychologue
- ☐ Stomathérapeute
- ☐ Autres : .....

ACCOMPAGNEMENT DU PATIENT :

Lors de la consultation les éléments suivant ont été abordés :

- ☐ Projet de vie
- ☐ Anticipation des complications médicales possibles
- ☐ Directives anticipées
- ☐ Personne de confiance
- ☐ Aide aux prises de décisions thérapeutiques concernant :
  - Traitements à visée carcinologique
  - Autres traitements
  - Limitation / arrêt de traitement mettant en jeu le pronostic vital
- ☐ Souhaits de fin de vie

ACCOMPAGNEMENT DE LA FAMILLE / DES PROCHES :

Lors de la consultation les éléments suivant ont été abordés :

- ☐ Compréhension par la famille/les proches de la pathologie en termes d'évolution et de pronostic
- ☐ Compréhension par la famille/les proches des traitements en cours et des leurs objectifs
- ☐ Explications à la famille/aux proches de la prise en charge palliative
- ☐ Discussion sur l'annonce du pronostic de la maladie aux proches (enfants, parents...)
- ☐ Evaluer les ressources et repérer les situations d'épuisement chez l'aidant principal
- ☐ Orientation de la famille/des proches vers :
  - ☐ Assistante Sociale
  - ☐ Psychologue
  - ☐ Autres : .....

COORDINATION ET CONTINUITE DES SOINS :

- Lien avec le médecin traitant : ☐ par courrier ☐ par appel téléphonique

- Lien avec les services de soins à domicile : ☐ par courrier ☐ par appel téléphonique

- identification des personnes/services recours en cas de complications : ☐ oui ☐ non

Commentaires :.....
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Correction: *Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: a randomised phase III trial*

Hutt E, Da Silva A, Bogart E, *et al*. Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: a randomised phase III trial. *BMJ Open* 2018;8:e015904. doi: 10.1136/bmjopen-2017-015904

This article was previously published with an error.

The funding information in the published article was incomplete. The complete funding details are as follows:

This study is supported by unrestricted public grants from Conseil Régional du Nord Pas-de-Calais and from caregivers Ligue National contre le Cancer. The EPIC trial (NCT02853474.) is also supported by public grants from the French National Cancer Institute, INCa (INCa-DGOS_11170). The funders have no role in study design, management, analysis and interpretation of data as well as no role in the writing of the final report.

These errors did not affect the design or results of the study.

BMJ Open 2019;**9**:e015904corr1. doi:10.1136/bmjopen-2017-015904corr1