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« Randomized clinical trial comparing a web-mediated follow-up via patient-reported outcomes (PRO) vs. routine surveillance following treatment for lung cancer »

NCT 02361099

Phase 3 Multicentric Randomized Study Assessing Self-reported Symptoms Transmitted Via an Internet Web-application "Sentinel " Versus Conventional Follow-up in Patients With High Risk Lung Cancer

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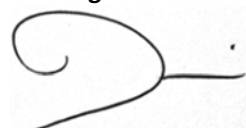

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SIGNATURE FOR PROTOCOL

SPONSOR SIGNATURE


| | | |
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INVESTIGATOR SIGNATURE

I have read all the pages of the protocol of the clinical trial of which WEPROM is the sponsor. I confirm that it contains all the informations necessary to conduct the study. I undertake to perform the clinical trial in accordance with the protocol and the terms and conditions set out therein. I undertake to carry out the study by respecting:

- ❖ the principles of the "Helsinki Declaration",
- ❖ the rules and recommendations of Good Clinical Practice on an international level (ICH-E6) and in France (rules of good clinical practice for biomedical research involving products for human use - Decisions of 24 November 2006),
- ❖ national laws and regulations relating to clinical trials,
- ❖ Law No. 2012-300 of 5 March 2012 as amended by Decree 2016-800 of 16 June 2016

I further agree that the investigators and other qualified members of my team will have access to the copies of this protocol and the documents relating to the conduct of the study, allowing them to work in accordance with the provisions contained in these documents.

| | | | |
|--------------------------------------|---|--|---|
| Coordinating investigator | Nom : Dr Fabrice DENIS | Date : January 03, 2018 | Signature :  |
|--------------------------------------|---|--|---|

LIST OF ABBREVIATIONS

| | |
|-----------|--|
| ANSM | Agence Nationale de Sécurité du Médicament et des Produits de Santé [French National Agency for Medicines and Health Products Safety] |
| AE | Adverse Event |
| CNIL | Commission Nationale de l'Informatique et des Libertés [French Data Protection Authority] |
| CNRS | <i>Centre National de Recherches Scientifiques</i> [National Centre for Scientific Research] |
| CRA | Clinical Research Associate |
| CPP | Comité de Protection des Personnes [French Ethic Committee] |
| CT scan | Scanner |
| EC | Ethic Committee |
| e-CRF | Electronic Case Report Form |
| FACT-L | Functional Assessment of Cancer Therapy-Lung |
| FDG | FluoroDesoxyGlucose |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IFCT | <i>Intergroupe Francophone de Cancérologie Thoracique</i> [French Thoracic Oncology Intergroup] |
| MRI | Magnetic Resonance Imaging |
| NCI CTCAE | National Cancer Institute – Common Terminology Criteria for Adverse Events |
| NEJM | New England Journal of Medicine |
| NPV | Negative Predictive Value |
| NSCLC | No Small Cell Lung Cancer |
| OS | Overall Survival |
| PET | Positron Emission Tomography |
| PPV | Positive Predictive Value |
| PS | Performance Status |
| QOL | Quality of Life |
| SAE | Serious Adverse Event |
| SCLC | Small Cell Lung Cancer |
| TKI | Tyrosine-Kinase Inhibitor |
| WHO | World Health Organization |

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1. STUDY RATIONALE

1.1. LUNG CANCER

Lung cancer is the leading cause of cancer death in the world with 6 million deaths per year (1). In France, the incidence of lung cancer is estimated at 39,500 new cases in 2011. It represents each year nearly 11% of all new cases of cancer (11). It is the second most common cancer for men and the third for women. With a 5-year survival of around 15%, lung cancer is a cancer with a very poor prognosis. About 70 to 75% of cancers are diagnosed at advanced stages. Relapses are frequent and rarely curable. In France in 2011, more than 29,000 deaths are attributable to it, which represents nearly 20% of cancer deaths (11).

1.2. POST-THERAPEUTIC SURVEILLANCE

At least 75% of relapses are symptomatic and there is no standard follow-up after curative treatment or not (2-7). Currently, the most common surveillance strategy consists of performing a clinical examination every 3 to 6 months associated with chest x-ray or CT scan. Intensive clinical and imaging follow-up has not yet shown more advantage on survival, but symptom monitoring appears to have a significant medico-economic advantage in comparison to imaging follow-up (12).

This non-personalized approach is a source of anxiety (useless in the absence of relapse) for patients, especially as the imaging date approaches, or even weeks before the exams. In contrast, this surveillance may leave symptomatic patients with untreated relapse for several weeks because many symptomatic patients wait for the date of this assessment to consult (8). This sometimes rapid deterioration of the general condition can reduce the accessibility to specific therapies and compromise the prognosis in the short or medium term.

However, there is currently no evidence to suggest that earlier detection of relapse provides a benefit in survival.

1.3. “SENTINEL” TOOL FOR EARLY DETECTION OF LUNG CANCER RELAPSE

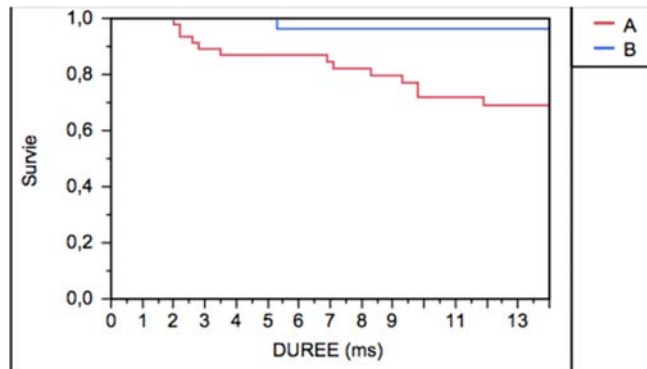
We developed a score based on the dynamic and the association of clinical signs to alert the physician of a possible relapse of lung cancer. The concerned variables are loss of weight, loss of appetite, dyspnea, asthenia, cough, pain, fever, hemoptysis, subcutaneous nodules, dysphonia and superior vena cava syndrome. These symptoms are self-assessed by patients each week and sent by their smartphone or computer via the Internet and are analyzed by software that determines a high or low probability of relapse (8, 9).

The referring physician is thus early alerted and summons the patient for a checkup.

The prospective study of this application showed interesting results on these patients with a sensitivity of 100%, a specificity of 89%, a PPV of 81% and a NPV of 100% with 11 symptoms studied. In the initial study which aim is to establish an algorithm (validated by Pr Letellier's team, CNRS CORIA-Rouen) for detection from only 6 symptoms, a NPV of 93% was already noted (8). In addition, relapses were detected on average 5 weeks before the planned follow-up assessment (imaging every 3 months) (9)

An overall survival analysis (monocentric and non-randomized) in our center also suggests a survival gain of nearly 24% at 1 year ($p = 0.02$) (F Denis et al, Supportive Care in Cancer, 2014) .

In the follow-up of the patients, it appeared that the algorithm was more sensitive if the patients were not much symptomatic at the inclusion and had an initial score lower than 7 (by adding the scores of 0 to 3 for the symptoms concerning the cough, dyspnea, pain, anorexia and asthenia: no problem = 0, slight problem = 1, medium problem = 2, major problem = 3 points)



Arm A: classic follow-up of patients between 2011 and 2012, Arm B, patients followed by SENTINEL between 2012 and 2013, $p = 0.017$). Age, sex, histology, stage and comparable treatments received.

1.4. QUALITY OF LIFE / SURVIVAL AND EARLY SUPPORTIVE CARE

One of the explanations that could demonstrate this gain in survival is the possibility offered by the use of the SENTINEL application to treat relapses earlier and thus to avoid an excessive deterioration of the general condition between two monitoring visits more or less spaced out. This deterioration of the general state can, in only one month, make a patient, initially accessible to a specific care, in situation of not being able to receive specific treatment. In addition, the early management of symptoms reported by patients (pain, anorexia, dyspnea, depressive signs ...) via this Internet application is consistent to the results obtained in the study by Dr. Temel (NEJM 2010). In this study, patients with metastatic non-small cells lung cancer were randomized between standard first-line treatments to the same treatments plus monthly follow-up by a supportive care team. This study showed a benefit in quality of life AND in survival, with a significant gain of 3 months of survival (10).

1.5. BENEFITS AND RISKS FOR STUDY SUBJECTS

1.5.1. Benefits

1.5.1.1. Individual benefits

The benefit expected for patients with the SENTINEL application will be mainly an earlier diagnosis of relapse and therefore more rapid specific treatment beginning which could have an impact on their survival but also on their quality of life via an early implementation of supportive care

1.5.1.2. Community benefits

Beyond the benefit for patients in terms of survival and quality of life, the use of the SENTINEL application makes it possible to space out imaging follow-up and thus to reduce the costs brought about compared to the standard follow-up of the patients treated for lung cancer.

1.5.2. Risks

1.5.2.1. Individual risks

➤ Constraints

Constraints are negligible and involved:

- to fill a quality of life questionnaire in at inclusion then at 3, 6 and 12 months,
- to fill a depression questionnaire in at inclusion then at 3, 6 and 12 months,
- for patients randomized in the "SENTINEL follow-up" arm, to fill a specific questionnaire in weekly via a computer or smartphone.

There are no additional exams.

➤ Risks related to the disease

The risks of natural evolution of the disease are not modified by this study.

1.5.2.2. Community risks

None

1.5.3. Benefit/risk balance

Standard follow-up would have been proposed to all patients included in this study.

Given the study already carried out, it is unlikely that the relapse of cancer is diagnosed later with the SENTINEL application than during a standard follow-up. Indeed, in the preliminary studies all relapses were symptomatic and the negative predictive value was 100%. It must be remembered that there is no standard of frequency and type of imaging in the monitoring of lung cancers. Indeed, in the "intensive follow-up" arm of the IFCT 0302 study, imaging assessments were performed only every 6 months.

It is therefore expected that the use of the application SENTINEL will be beneficial for patients by allowing to detect earlier the relapse of lung cancer of patients included in the arm "SENTINEL".

1.6. DESCRIPTION AND JUSTIFICATION OF THE METHOD STUDIED

It is therefore a study which evaluate the optimization of the patients' follow-up with lung cancer in order to extend the survival of the patients by improving their quality of life and reducing the anxiety generated by the realization of imaging exam. The spacing out of imaging exams during follow-up would also reduce the cost of this follow-up.

2. OBJECTIVES AND ENDPOINTS

2.1. PRIMARY OBJECTIVE AND ENDPOINT

2.1.1. Primary objective

The primary objective of the study is to evaluate overall survival.

2.1.2. Primary endpoint

Overall survival will be defined as the period from the date of random assignment to the date of death from any cause.

In this context, we will also evaluate the overall survival defined between the date of diagnosis and the date of death, in order to know more precisely the duration of the disease.

2.2. SECONDARY OBJECTIVES AND ENDPOINTS

2.2.1. Secondary objectives

We will evaluate too:

- the quality of life,
- the depression,
- the relapse detection time
- the PS at the relapse detection time,
- the cost of the monitoring,
- the patient's compliance,
- the type of treatment begun at the relapse.

2.2.2. Secondary endpoints

Quality of life will be evaluated by FACT-L questionnaire at inclusion, 3, 6 and 12 months. Scores will be calculated by the scoring guidelines of Facit.org.

Depression will be evaluated by PHQ9 questionnaire at baseline, 3, 6 and 12 months. Scores will be calculated by the scoring guidelines.

The relapse detection time is defined by the time between the date of the diagnosis and the date of the first detected disease progression by imaging.

The Performance Status will be evaluated by the WHO's recommendations.

Cost-effectiveness will be evaluated, first between the random assignment and the first event (a progression, a relapse or a death) or the last report for non-relapsing living patients, we reported the number of (scheduled and unscheduled) visits to the oncologist and imaging for the two groups.

The compliance rate in the experimental arm will be evaluated (use of web-application) by the ratio between the number of forms filled by the participants and the theoretical number of forms that the patients included should have filled.

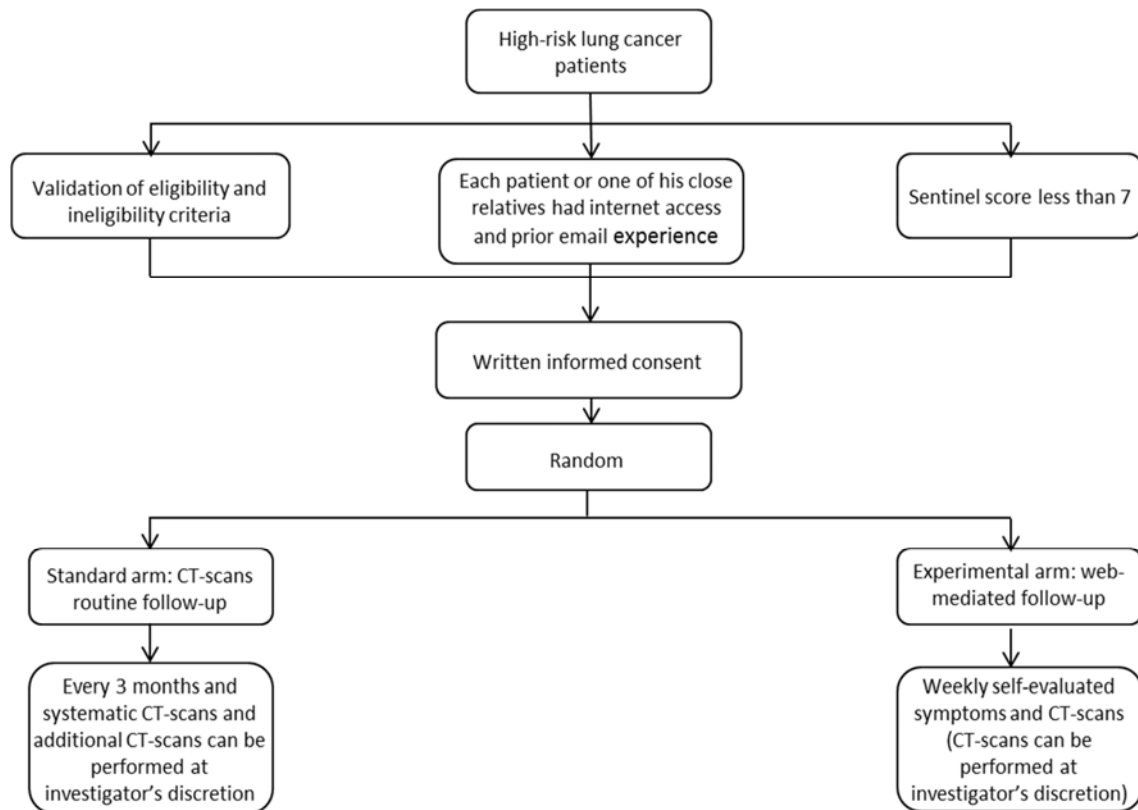
The rate of optimal or non-optimal treatment against this relapse will be reported by the investigator. An optimal treatment corresponds to a prescription for a patient with a PS equal to 0 or 1; a non-optimal treatment is a reduced prescription due to poor physical conditions.

3. STUDY DESIGN

3.1. GENERAL STUDY METHODOLOGY

This is a prospective, multicenter, randomized, opened phase III study.

3.2. STUDY FLOWCHART



4. PATIENTS SELECTION

4.1. STUDY POPULATION

The population concerned includes all patients treated for a lung cancer and having an access to the internet.

We plan to include 224 patients during a 36-months period.

4.2. INCLUSION CRITERIA

- 1) Patient with lung cancer (NSCLC and SCLC), histologically proven
- 2) Patient at high risk of relapse (TxN1, IIIA, IIIB, IV stages)
- 3) Age \geq 18 years
- 4) PS \leq 2 within 15 days before enrollment
- 5) Patient having:
 - a) finished his cancer treatment in the last 3 months by:
 - Surgery or
 - Surgery then adjuvant chemotherapy or
 - Concomitant radio-chemotherapy or
 - Conventional or stereotactic radiotherapy or
 - 1st or 2nd line chemotherapy
 - b) treatment with TKI (tyrosine kinase inhibitor) in 1st or 2nd line or maintenance treatment with pemetrexed and/or bevacizumab or gemcitabine well tolerated (SENTINEL's score with this treatment (TKI or maintenance) start since less than 3 month and not progressive to its latest assessment.
- 6) Patient with an initial SENTINEL score \leq 6
- 7) Patient with internet access and an e-mail box
- 8) Patient affiliated to a social security scheme
- 9) Patient has given its written consent before any specific procedure from protocol

4.3. EXCLUSION CRITERIA

- 1) Patient whose disease has progressed at the end of the specific treatment
- 2) Symptomatic brain metastases
- 3) Persons deprived of liberty or under guardianship or curatorship
- 4) Dementia, mental alteration or psychiatric pathology that can compromise informed consent from the patient and / or adherence to the protocol and the monitoring of the trial
- 5) Patient who cannot submit himself to the followed of the protocol for psychological reasons, social, family or geographical
- 6) Pregnant or breastfeeding women

- 7) Patient participating in another interventional study

5. STUDY DESCRIPTION

5.1. STUDY CALENDAR

5.1.1. Screening and enrolment

Eligible patients will sign a consent form.

For inclusion, exams results (extension assessment for example) done before the consent form signature can be used if they were done in the timeline accept by the protocol.

5.1.1.1. Clinical exam

It contains a full medical examination with :

- Medical history
- Weight and PS
- Initial SENTINEL score at the inclusion

5.1.1.2. Imaging exam

Assessment have to be done in the 4 weeks before random assignment and the beginning of the follow-up. It contains:

- At least a pulmonary CT scan (abdomen and cerebral if wanted)
- PET/CT ¹⁸FDG according to lesions if negative CT scan
- Cerebral MRI if cerebral metastasis

5.1.1.3. Paraclinical checkup

It had to be done in the maximum 15 days before random assignment and the beginning of the follow-up. Patients had to fill the following quality of life questionnaires in:

- FACT-L,
- HUMEUR PHQ9.

5.1.2. Assessment during the study

Patient follow-up will be in accordance with the random assignment.

Whatever the randomized arm of the patient, he could receive appropriate supportive care for his situation. The necessity of supportive cares can be detected by the way of the medical consultation or by the way of the web application for patients in the "SENTINEL follow-up" arm.

When questionnaire must be completed (programmed at M3, M6 or M12) but there isn't a medical visit, questionnaire had to be complete at patient's home and returned by post. These questionnaires must be always completed before imaging exam results to avoid patient to be influence by the imaging results.

5.1.2.1. Arm A : standard follow-up (control arm)

- Patients with non-treatment follow-up will visit physician every 3 months with:
 - Clinical examination with PS estimation every 3 months during 2 years with pulmonary x-ray if necessary
 - Cerebral, thorax and abdominal CT scan (or PET/CT or/and MRI according to the targets lesions saw or not in the CT scan) every 6 months during 2 years (except for patient with IIB/IV stage)
 - Fill the quality of life questionnaire in (FACT-L) at M3, M6 and M12 follow-up
 - Fill the HUMEUR PHQ9 questionnaire in (in relation with depression) at M3, M6 and M12 follow-up

For patients with a IIB/IV stage lung cancer, medical examination will be every 3 months (medical examination and PS estimation) with a cerebral, thorax and abdominal CT scan (or PET/CT or/and MRI according to the targets lesions saw or not in the scanner).

| | Inclusion | M3 | M6 | M9 | M12 | M15 | M18 | M21 | M24 |
|---|----------------------------|---------|---------|---------|---------|---------|---------|---------|---------|
| Eligibility criteria | X | | | | | | | | |
| Consent form | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Medical examination (weight and PS) | X (in the last 15 days) | X | X | X | X | X | X | X | X |
| Referring imaging exam (no progressive disease) | X (in the last 4 weeks) | | | | | | | | |
| Patient self-assessment | X | | | | | | | | |
| Imaging exam (Stage II/IIIA) | | | CT scan | | CT scan | | CT scan | | CT scan |
| Imaging exam (Stage IIB/IV) | | CT scan | CT scan | CT scan | CT scan | CT scan | CT scan | CT scan | CT scan |
| FACT-L | X | X | X | | X | | | | |
| HUMEUR PHQ9 | X | X | X | | X | | | | |

- Patients with treatment by TKI in 1st or 2nd line will visit physician every 3 months with:
- Clinical examination with PS assessment
 - Fill the quality of life questionnaire in (FACT-L) at M3, M6 and M12 follow-up
 - Fill the HUMEUR PHQ9 questionnaire in (in relation with depression) at M3, M6 and M12 follow-up
 - Cerebral, thorax and abdominal CT scan (or PET/ CT according to the targets lesions saw or not in the CT scan)

| | Inclusion | M3 | M6 | M9 | M12 | M15 | M18 | M21 | M24 |
|---|------------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|
| Eligibility criteria | X | | | | | | | | |
| Consent form | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Medical examination (weight and PS) | X (in the last 15 days) | X | X | X | X | X | X | X | X |
| Referring imaging exam (no progressive disease) | X (in the last 4 weeks) | | | | | | | | |
| Patient self-assessment | X | | | | | | | | |
| Imaging exam | | CT scan | CT scan | CT scan | CT scan | CT scan | CT scan | CT scan | CT scan |
| TKI treatment | <i>Per os</i> continuous treatment | | | | | | | | |
| FACT-L | X | X | X | | X | | | | |
| HUMEUR PHQ9 | X | X | X | | X | | | | |

- Patients treated with bevacizumab or/and pemetrexed in maintenance therapy will have medical examination as usual by the physician for treatment validation and an assessment will be done every 4 cycles (estimated every 3 months) with:
- Clinical examination with PS assessment
 - Cerebral, thorax and abdominal CT scan (or PET/ CT or/and MRI according to the targets lesions saw or not in the CT scan)
 - Fill the quality of life questionnaire in (FACT-L) at M3, M6 and M12 follow-up
 - Fill the HUMEUR PHQ9 questionnaire in (in relation with depression) at M3, M6 and M12 follow-up

| | Inclusion | Between C4-C5 | M3 | Between C8-C9 | M6 | Between C13-C14 | M12 | Between C16-C17... Between 33-C34 |
|--|----------------------------|---------------|----|---------------|----|-----------------|-----|--------------------------------------|
| Eligibility criteria | X | | | | | | | |
| Consent form | X | | | | | | | |
| Medical history | X | | | | | | | |
| Medical examination (weight and PS) | X (in the last 15 days) | X | | X | | X | | X |
| Referring imaging exam (no progressive disease) | X (in the last 4 weeks) | | | | | | | |
| Patient self-assessment | X | | | | | | | |
| Imaging exam | | CT scan | | CT scan | | CT scan | | CT scan |
| Maintenance therapy J1-J21 | | | | | X | | | |
| FACT-L | X | | X | | X | | X | |
| HUMEUR PHQ9 | X | | X | | X | | X | |

5.1.2.2. Arm B : SENTINEL follow-up

- Patients with a stage II / IIIA lung cancer without maintenance therapy will visit physician every 3 months with:
 - Clinical examination with PS assessment with pulmonary x-ray if necessary
 - Cerebral, thorax and abdominal scanner (or PET/CT or/and MRI according to the targets lesions saw or not in the CT scan) at M6, M12 and M24.
 - Fill the quality of life questionnaire in (FACT-L) at M3, M6 and M12 follow-up
 - Fill the HUMEUR PHQ9 questionnaire in (in relation with depression) at M3, M6 and M12 follow-up

For patients with stage IIIB / IV lung cancer, medical examination will be performed every 3 months (medical examination and PS assessment), a single imaging exam will be done at M12 in the case of no SENTINEL alert or no anomaly at medical examination. An assessment can be done if wanted by the physician, even if no SENTINEL alert.

Parallel, patients will realize a weekly self-assessment by the SENTINEL web application. In order to do this, randomized patients will get an instruction mail to connect themselves in the application and an user manual of this application.

| | Inclusion | M3 | M6 | M9 | M12 | M15 | M18 | M21 | M24 |
|---|----------------------------|---|---------|----|---|---------|-----|---|---------|
| Eligibility criteria | X | | | | | | | | |
| Consent form | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Medical examination (weight and PS) | X (in the last 15 days) | X | X | X | X | X | X | X | X |
| Referring imaging exam (no progressive disease) | X (in the last 4 weeks) | | | | | | | | |
| Patient self-assessment | | | | | X* | | | | |
| Imaging exam (Stage II/IIIA) | | <i>CT scan if SENTINEL alert or medical anomaly</i> | CT scan | | <i>CT scan if SENTINEL alert or medical anomaly</i> | CT scan | | <i>CT scan if SENTINEL alert or medical anomaly</i> | CT scan |
| Imaging exam (Stage IIIB/IV) | | <i>CT scan if SENTINEL alert or medical anomaly</i> | | | | X | | <i>CT scan if SENTINEL alert or medical anomaly</i> | |
| FACT-L | X | X | X | | X | | | | |
| HUMEUR PHQ9 | X | X | X | | X | | | | |

*weekly

- Patients with treatment by TKI in 1st or 2nde line will visit physician every 3 months with:
- Clinical examination with PS assessment
 - Fill the quality of life questionnaire in (FACT-L) at M3, M6 and M12 follow-up
 - Fill the HUMEUR PHQ9 questionnaire in (in relation with depression) at M3, M6 and M12 follow-up

Parallel, patients will realize a weekly self-assessment by the SENTINEL web application. In order to do this, randomized patients will get an instruction mail to connect themselves in the application and an user manual of this application.

Imaging exam will be realized only if necessary (wishes of the physician, clinical anomaly with potential relapse, SENTINEL alert). One systematic medical imaging will be done at M12 if no SENTINEL alert or medical anomaly.

| | Inclusion | M3 | M6 | M9 | M12 | M15 | M18 | M21 | M24 |
|---|-----------------------------|--|----|----|-----|-----|-----|--|-----|
| Eligibility criteria | X | | | | | | | | |
| Consent form | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Medical examination (weight and PS) | X (in the last 15 days) | X | X | X | X | X | X | X | X |
| Referring imaging exam (no progressive disease) | X (in the last 4 weeks) | | | | | | | | |
| Patient self-assessment | X* | | | | | | | | |
| Imaging exam | | CT scan if SENTINEL alert or medical anomaly | | | X | | | CT scan if SENTINEL alert or medical anomaly | |
| TKI treatment | Per os continuous treatment | | | | | | | | |
| FACT-L | X | X | X | | X | | | | |
| HUMEUR PHQ9 | X | X | X | | X | | | | |

* : weekly

- Patients treated with bevacizumab or/and pemetrexed or gemcitabine in maintenance therapy will visit physician as usual by the physician for treatment validation and an extension assessment will be done every 4 cycles (estimated every 3 months) with:
- Clinical examination with PS assessment
 - Fill the quality of life questionnaire in (FACT-L) at M3, M6 and M12 follow-up
 - Fill the HUMEUR PHQ9 questionnaire in (in relation with depression) at M3, M6 and M12 follow-up

Parallel, patients will realize a weekly self-assessment by the SENTINEL web application. In order to do this, randomized patients will get an instruction mail to connect themselves in the application and an user manual of this application.

Imaging exam will be realized only if necessary (wishes of the physician, clinical anomaly with potential relapse, SENTINEL alert). One systematic medical imaging will be done at M12 if no SENTINEL alert or medical anomaly.

| | Inclusion | Between C4-C5 | M3 | Between C8-C9 | M6 | Between C13-C14 | M12 | Between C16-C17... Between 33-C34 | |
|---|----------------------------|---|----|---------------|----|-----------------|-----|---|--|
| Eligibility criteria | X | | | | | | | | |
| Consent form | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Medical examination (weight and PS) | X (in the last 15 days) | X | | X | | X | | X | |
| Referring imaging exam (no progressive disease) | X (in the last 4 weeks) | | | | | | | | |
| Patient self-assessment | X* | | | | | | | | |
| Imaging exam | | <i>CT scan if SENTINEL alert or medical anomaly</i> | | | | | X | <i>CT scan if SENTINEL alert or medical anomaly</i> | |
| Maintenance therapy J1-J21 | X | | | | | | | | |
| FACT-L | X | | X | | X | | X | | |
| HUMEUR PHQ9 | X | | X | | X | | X | | |

* : weekly

5.1.2.3. SENTINEL follow-up management

The investigator will consult SENTINEL application historic every day.

In case of suspected relapse (due to the patient's answers on the application), an email alert will be sent to the investigator.

More, a systematic mailing will be done the investigator if free text field is completed by the patient. If symptoms aren't seriousness, answer will be facultative, patient is informed of this possibility. But in case of a doubt, investigator will call the patient or ask patient to visit him for medical examination.

In case of a SENTINEL alert, investigator must:

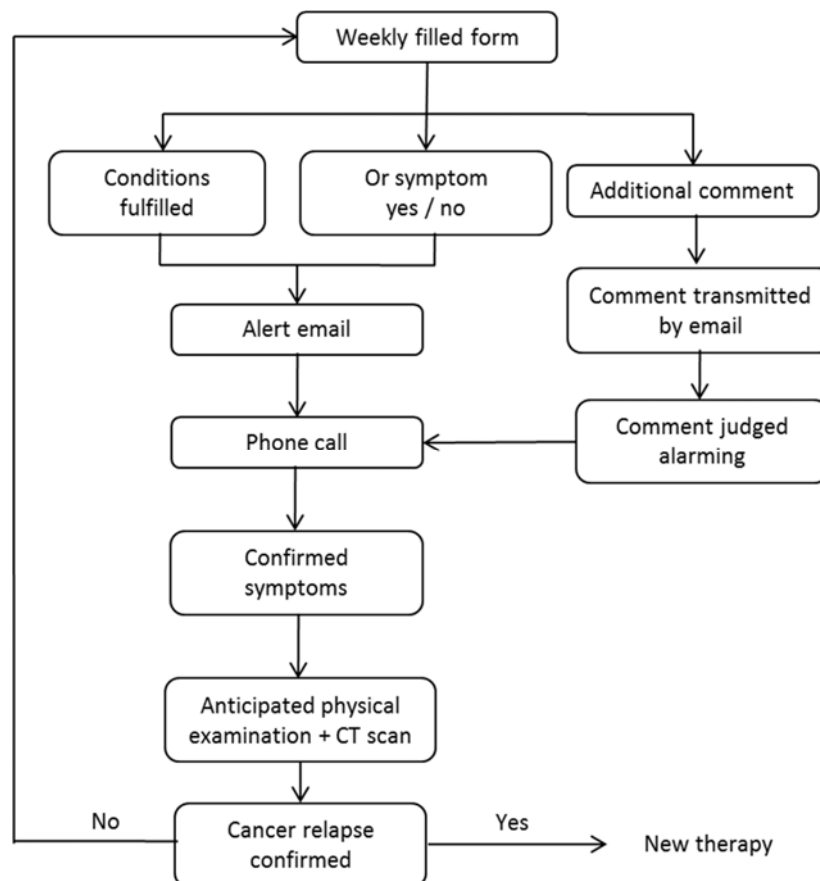
- 1) Consult symptoms historic
- 2) Call patient to check lack of mistake in the input and lack of diet if weight loss
- 3) If confirmed doubt, call in the patient in maximum 7 days with a thorax-abdominal CT scan (and cerebral if medical signs)
- 4) If negative CT scan, realize a PET (or lumbar puncture or MRI if neurologic signs or suspect pains)

If depression item is rated to 3, a psychologist consultation can be schedule. More, please note that a depressive syndrome can increase symptoms strength and weight loss and so disturb the analyze of the alert of the application.

For very significant symptoms, care supports can be suggesting, for example:

- If remain pains: alogologist consultation
- If 3 kg weight loss or more and/or anorexia: dietician consultation
- If increase of cough and dyspnea or hemoptysis: pulmonologist consultation

Decision-making tree for SENTINEL alerts



Investigator will be mailing if patients don't complete application.

5.2. TREATMENT DURING STUDY

In case of relapse, investigators will have the freedom to choose the treatment.

During the relapse treatment, whatever the randomized arm of the patient, investigator will have the freedom to program imaging exam as much as necessary.

However, for patients randomized in the SENTINEL arm, application follow-up will be kept up during and after the treatment.

Supportive cares can be proposed in accordance with the clinical examination in the two arms of the study but also in accordance with SENTINEL alerts for the SENTINEL arm randomized patients (early adaptation of supportive cares according to patient's responses in the weekly questionnaire).

After relapse treatment (for example after 4 or 6 cycles of chemotherapy), follow-up will be the same that IIIB/IV stage patients:

- Control arm, after relapse treatment, patient will get a CT scan every 3 months.
- SENTINEL arm, after relapse treatment, patient will get a CT scan only in case of SENTINEL alert or medical anomaly.

In case of maintenance therapy establishment, follow-up will be the same as inclusion maintenance therapy arm. In case of TKI treatment establishment, follow-up will be the same as inclusion TKI treatment arm.

5.3. IDENTIFICATION OF ALL DATA SOURCE NOT APPEARING IN THE MEDICAL FILE

Quality of life and depression questionnaires will not form part of the patient's source files. They will be made available in a sheet protector per patient in the investigative file so that they can be retranscribed in e-CRFs.

In addition, self-assessments completed by patients will not form part of the source files, and will be directly completed in the web application.

Other data concerning the patient, necessary for their follow-up outside of the trial, will be collected in their medical file.

5.4. RULES FOR SUBJECT WITHDRAWAL

5.4.1. Criteria for a study subject's early withdrawal

Patients may withdraw their consent and ask to leave the trial at any time and for any reason, without losing the right to be treated by their doctor.

The Investigator may also prematurely withdraw a patient from the trial for any reason which would best serve the interests of the patient, including a comorbid disease or an adverse event. In the event of early withdrawal, at any time and for any reason, the Investigator must inform the patient, if necessary, and document the reasons as fully as possible.

Withdrawals from the study must be reported, especially at the potential following reasons:

- death,
- patient refusal to continue the study,
- withdrawal of consent
- Investigator judgment,
- loss of contact.

5.4.2. Procedures for a study subject's early withdrawal

The means of medical care and follow-up in the event of early withdrawal from the study for a given patient will be the same as the usual means outside of the Protocol.

5.4.3. Study termination criteria (excluding biostatistics considerations)

The last follow-up visit of the last patient enrolled will determine the end of the study, corresponding to their follow-up visit 24 months after enrolment.

In addition, the study may be terminated for administrative reasons and/or on Sponsor's decision. If the study is terminated early or suspended, the study manager will immediately inform the Ethics Committee (EC) of the reason for termination or suspension.

In all cases, enrolled patients will be followed up within the study until the study exit visit with the Investigator.

6. DATAMANAGEMENT AND STATISTICS

6.1. STUDY DATA COLLECTION AND PROCESSING

6.1.1. Data collection

An electronic case report form (e-CRF) (ENNOV Clinical®, Floirac, France) will be created for each patient. All information required by the protocol must be provided in the e-CRF. It will include the data necessary to confirm compliance with the protocol and identify any major gaps in the protocol, but also the data necessary for statistical analysis.

The person(s) responsible for completing the e-CRFs (Investigator, technician, nurse, etc.) must be defined and identified in the table of responsibilities' delegation for each site (stored in the Investigator file).

6.1.2. Data coding

By signing this protocol, the principal investigator and all their co-investigators undertake to keep confidential the identity of patients participating in the study.

Information required by the Protocol will be collected anonymously in the e-CRF with an identification number for the site and a patient number. Only the first letters of the patient's surname and first name will appear. This code will be the only information appearing on the e-CRF, enabling the e-CRF to be correlated with the patient in retrospect.

The Investigator must ensure the anonymity of the patient. Therefore, patients must not be identified by name in the documents submitted to the Sponsor.

6.1.3. Data processing

For each patient, all the data will be collected in the e-CRF. The e-CRF will be completed by the investigator and / or a nurse that he will have designated for this task.

6.2. STATISTICS

6.2.1. Description of planned statistical methods

According to a phase II trial, the OS should be greater for patients in the experimental arm than for those in the standard arm; a one-sided test is thus ethical to assess the OS. The sample size is computed using the R function "powersurvct.func". We assess that, at nine months, the OS rate could be equal to 82% with the web-mediated follow-up and 70% with the standard follow-up. Thus, with the same number of patients in the two arms, the present study is designed to have 80% power to detect (with a type I error of 5%) a hazard ratio for death equal to 0.556. It is therefore required to observe 73 deaths.

An intermediate analysis is planned at the 37th recorded death allowing to stop the trial for ethical reasons if the p-value is less than or equal to 0.006 (logrank test).

Analyses will be performed on an intention-to-test basis. All patients found to be ineligible after random assignment will be excluded of the analysis.

The baseline characteristics of the two groups will be presented with the effective and percentage for qualitative variables and continuous variables will be presented with median and range [Min-Max]. Patients in the two arms will be compared with a Chis-square test for categorical data and a non-parametric Wilcoxon test for continuous variables.

The Kaplan-Meier methodology will be used to summarize time-to-event variables. The number of patients with events and the number of censored patients will also be presented. Plots of Kaplan-Meier product limit estimates of time-to-event will be drawn, medians will be presented in addition to confidence intervals, set at 95 percent.

Hazards ratio will be calculated using the univariate Cox proportional hazard model.

A univariate analysis of variance was performed at baseline and at the second and third follow-up for quality of life score, and depression score.

Quality of life scores will be calculated following the Facit.org guidelines in using the FACT-L questionnaire.

Questionnaire completion rates will be calculated as a percentage of all patients who completed a questionnaire at a given time point. Completion rates and baseline quality of life scores (PWB, FWB, SWB, EWB, TOI, LCS, FACT-G, FACT-L) will be compared according to treatment arm.

The FACT-L scores (PWB, FWB, SWB, EWB, TOI, LCS, FACT-G, FACT-L) will be described with mean, standard deviation, median and range. The ceiling and floor effect will be evaluated with frequency. Comparison at the baseline will be done, Wilcoxon non parametric test will be used. A longitudinal study with the help of mixed variance analyses to measure repetitions will be realized .

Statistical analyses will be performed using SAS 9.3 software (SAS Institute Inc, Cary, NC).

6.2.1. Healthcare cost

The main objective of the clinical study is to evaluate the overall survival of patients in both arms. The medico-economic study conducted will be a cost-effectiveness study (Drummond et al, 1987). Its objective is to compare the costs of the two types of surveillance from the perspective of the Health Insurance. The cost items evaluated mainly correspond to consultations, imaging and, for the SENTINEL arm, the time mobilized for the management of the web-application for the healthcare team.

6.2.2. Sample size

Based on the results from our earlier phase II trial, we hypothesized that the web-mediated follow-up would improve OS at nine months by 12% compared with standard follow-up (82% vs 70%). Consequently, with a 1:1 random assignment, we planned to enroll 224 patients for detecting a hazard ratio for the OS equal to 0.55 (corresponding to 73 deaths) with a power of 80% and a one-sided type I error of 5%.

6.2.3. Random assignment

Random assignment 1 : 1 will be perform according to a minimization with stratification on gender, age, PS, center, initial stage of the disease, treatment indication (adjuvant, 1st line, 2^d line) and type of the taking care of (surveillance, maintenance, treatment by TKI).

Random assignment is performed directly on the e-CRF (ENNOV Clinical[®], Cenon, France).

The patient's arm of monitoring will be displayed instantly on the e-CRF after performing the random assignment. A random assignment confirmation email will also be sent to the investigator.

7. VIGILANCE AND MANAGING OF ADVERSE EVENTS

7.1. DEFINITIONS

7.1.1. Adverse events

An adverse event is defined as any occurrence harmful to a patient or participant in a clinical trial. The adverse event is not necessarily related to the study.

The severity of adverse events will be rated according to the NCI CTCAE criteria, v. 4.0. For any event not referred to in the selected classification, the rating will be as follows:

- 1 = benign
- 2 = moderate
- 3 = severe
- 4 = life-threatening

7.1.2. Adverse effects

An adverse effect is considered to be suspected for any adverse event where a causal link with the trial may be envisaged, regardless of its extent (doubtful, plausible, possible, certain).

7.1.3. Unexpected adverse effects

An unexpected adverse effect is an effect the nature, severity, frequency or development of which are inconsistent with the information relating to the actions taken and methods used during the trial.

As part of this research no AE are expected with the use of the SENTINEL application. The AEs expected during this study are those related to the evolution of the disease (weight change, anorexia, dyspnea, asthenia, cough, pain, fever, hemoptysis, subcutaneous nodules, dysphonia and superior vena cava syndrome) or injection of contrast material during CT (allergic, cardiovascular, neurosensory, digestive, respiratory, renal, thyroid reactions or local effects).

7.1.4. Serious adverse events or effects

An AE is considered as an SAE when it:

- results in death,
- is life-threatening,
- results in disabilities or temporary or permanent invalidity,
- requires or prolongs the patient's admission to hospital,
- results in a congenital or neonatal abnormality.

The following types of admissions to hospital are not considered SAEs:

- for the treatment of a previous medical condition,
- as an outpatient, not resulting in inpatient admission,
- for the relapse or progression of the lung cancer,
- for the cancer's treatment.

7.2. ADVERSE EVENTS HANDLING

7.2.1. SAE reporting

All SAEs (except as specified in section 7.1.4) require a SAE occurrence report (available in the e-CRF) to be completed, whether the SAE is expected or unexpected. The Investigator must check that the information provided in the form is accurate and clear (with no abbreviations, etc.).

The SAE must be reported immediately (within 24 hours of the Investigator observing the SAE) to the Sponsor via the e-CRF, then by fax at +33 2 41 68 29 79.

7.2.2. Independent Data Monitoring Committee

An IDMC with expertise and experience in the pathology, and without direct involvement in the conduct of the trial, will be set up, specifically to guarantee effective protection of patients, insure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial.

The IDMC will be composed of :

- Dr Pierre-Etienne CAILLEUX (Oncologist, TOURS, France)
- Dr Bruno MINAUD (Pulmeunologist, LE MANS, France)
- Mr Marc ETTAICHE (Statistician, NICE, France)

The charter of the IDMC is presented in annex.

7.3. TERMS AND DURATION OF SUBJECT FOLLOW-UP AFTER THE OCCURRENCE OF ADVERSE EVENT

All enrolled patients will be followed up until the end of follow-up appointment (corresponding to the follow-up appointment taking place 24 months after enrolment).

8. ADMINISTRATIVE AND REGULATORY ASPECTS

8.1. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

Before the start of the study, the Investigator is required to sign a Protocol signature page confirming his/her agreement to conduct the study in accordance with all the instructions and procedures appearing in this Protocol, and to provide access to all relevant data saved to the monitor CRAs, the auditors and the representatives of the regulatory authorities.

The medical data concerning each patient will only be sent to the Sponsor, the partner company developing the application or any person duly authorized thereby, and where applicable to the authorized health authorities, under conditions guaranteeing the confidentiality of the data.

The Sponsor and the supervisory authorities may request direct access to medical records to verify the clinical trial procedures and/or data, without breaching confidentiality and to the extent permitted by the laws and regulations.

Data collected during the trial may be subject to computer processing in accordance with the CNIL requirements (conformity to the reference methodology 001).

8.2. STUDY MONITORING

The study will be monitored by the Sponsor (by ICO until December 03, 2017 thus by Weprom following the sponsoring transfer) . The Sponsor will regularly conduct quality control on the data reported in the e-CRFs.

The monitoring will take place as follows, with visits to each site at least once then regularly according to the site enrolment numbers with monitoring of the following data :

- 1) The existence of the included patients
- 2) The collection of signed informed consents and their archiving
- 3) Respect of the eligibility criteria (inclusion and non-inclusion)
- 4) The presence of the primary endpoint
 - Collection of imaging reports
- 5) Reporting and Monitoring of Adverse Events
 - Serious Adverse Events (SAE)
 - New facts

The CRAs must be able to consult:

- the data collection forms for enrolled patients,
- patients' medical and nursing records,
- the Investigator's file.

Additional remote visits may be made.

The Investigator must devote the necessary time for these visits. S/he must also ensure that the monitor has free access to the source documents (i.e. the patient clinical record, original laboratory and radiology tests, etc.) that support the data contained in the case report form

8.3. *INSPECTIONS / AUDIT*

As part of this study, an inspection or audit may take place. The Sponsor will be responsible for preparing this audit or inspection, for ensuring access to all the study data and for verifying all the source data.

8.4. *ETHICAL ASPECTS*

8.4.1. Written informed consent

The Investigator undertakes to inform patients clearly and fairly of the Protocol and to request from them a written informed consent form (the information sheet and consent collection form are attached below).

The Investigator must give the patient one copy of the information sheet and one copy of the consent form. The patient may only be enrolled in the study after having read the information sheet and having signed and dated the consent collection form. The Investigator must also sign and date the consent collection form. The Investigator's original copy will be archived in the Investigator file.

The means of obtaining informed consent must be documented in the patient's medical records.

8.4.2. Ethics committee

The study draft must be submitted in advance for authorization from an EC. The information provided relates to both the terms and type of the study, and to the safeguards for patients participating in this trial.

The Ethics Committee (CPP Ouest II, ANGERS, France) issued a favorable opinion on this study on April 04, 2014.

8.5. *AMENDMENTS TO THE PROTOCOL*

Substantial amendment applications must be made by the Sponsor for authorization from or information to the EC in question, pursuant to Law 2004-806 of August 9, 2004 and its application Decree.

An updated and dated version of the amended Protocol must be submitted.

The patient information and consent collection forms may be subject to amendment if required

8.6. *DECLARATION TO THE COMPETENT AUTHORITIES*

The ANSM granted authorization to conduct this study on May 02, 2014.

8.7. FUNDING AND INSURANCE

The Sponsor has made a partnership for funding the study. The Sponsor has taken out an insurance policy with the SHAM (policy n°138926) guaranteeing the financial consequences of their civil liability in accordance with the regulations.

8.8. RULES FOR PUBLICATION

All the information resulting from this trial is considered confidential, at least until appropriate analysis and checking by the Sponsor, the Coordinating Investigator and the trial statistician have been completed.

All publications, abstracts or presentations including the results of the trial must be submitted for approval to the Sponsor (WeproM) and to SIVAN Innovation.

Furthermore, all communications, manuscripts or presentations must include a section referring to WeproM, all the institutions, Investigators, cooperative groups and academic societies that contributed to the conduct of the trial, and to the organization that financially supported the study.

For the main publication, in French or in English, the authors are: *(to be confirmed depending on the trial and the partners participating in the study)*.

For example:

- the study coordinator (first author or last author);
- the Investigators who recruited the most patients (cited in order of recruitment numbers), regardless of the cooperative group of which they are members;
- the Study statistician;
- a representative of the Sponsor.

Similarly, the publication of annex results must include the name of the person who performed the complementary work and the name of any other person concerned by this work.

In the event of a dispute, the order of the authors will be arbitrated by the Promoter (WeproM).

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LIST OF APPENDICES

- *APPENDIX 1* *Initial SENTINEL score*
- *APPENDIX 2* *HUMEUR PHQ9 questionnaire*
- *APPENDIX 3* *FACT-L quality of life questionnaire*
- *APPENDIX 4* *Ethics Committee favorable opinion*
- *APPENDIX 5* *Insurance certificate*
- *APPENDIX 6* *Charter of IDMC*

APPENDIX 1 : INITIAL SENTINEL SCORE

| | | |
|--|--------------------------|-----------------|
| | SENTINEL Protocol | Patient's label |
| | INITIAL SCORE | |

We care about you and your health. Rate all your symptoms by circling the number that best matches your situation. There is no “right” or “wrong” answer. This information is strictly confidential.

| | No trouble | Low trouble | Medium trouble | Major trouble |
|-----------------|------------|-------------|----------------|---------------|
| Asthenia | 0 | 1 | 2 | 3 |
| Loss of appetit | 0 | 1 | 2 | 3 |
| Cough | 0 | 1 | 2 | 3 |
| Dyspnea | 0 | 1 | 2 | 3 |
| Pain | 0 | 1 | 2 | 3 |

Total :

APPENDIX 2 : HUMEUR PHQ9 QUESTIONNAIRE

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?
(Use "✓" to indicate your answer)

| | Not at all | Several days | More than half the days | Nearly every day |
|---|------------|--------------|-------------------------|------------------|
| 1. Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| 2. Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| 3. Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| 4. Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| 5. Poor appetite or overeating | 0 | 1 | 2 | 3 |
| 6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down | 0 | 1 | 2 | 3 |
| 7. Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| 8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |
| 9. Thoughts that you would be better off dead or of hurting yourself in some way | 0 | 1 | 2 | 3 |

For office coding: 0 + + +
=Total Score:

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

| Not difficult at all | Somewhat difficult | Very difficult | Extremely difficult |
|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

APPENDIX 3 : FACT-L QUESTIONNAIRE

FACT-L (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

| <u>PHYSICAL WELL-BEING</u> | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|-----------------------------------|---|------------|--------------|-----------|-------------|-----------|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed..... | 0 | 1 | 2 | 3 | 4 |

| <u>SOCIAL/FAMILY WELL-BEING</u> | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|--|---|------------|--------------|-----------|-------------|-----------|
| GS1 | I feel close to my friends..... | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends..... | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness..... | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | <i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i> | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

FACT-L (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING

| | | Not at all | A little bit | Some- what | Quite a bit | Very much |
|-----|--|---------------|-----------------|---------------|----------------|--------------|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness..... | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness..... | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous..... | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying..... | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse..... | 0 | 1 | 2 | 3 | 4 |

FUNCTIONAL WELL-BEING

| | | Not at all | A little bit | Some- what | Quite a bit | Very much |
|-----|---|---------------|-----------------|---------------|----------------|--------------|
| GF1 | I am able to work (include work at home)..... | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling..... | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life..... | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness..... | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now..... | 0 | 1 | 2 | 3 | 4 |

APPENDIX 4 : ETHICS COMMITTEE FAVORABLE OPINION

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COMITE de PROTECTION des PERSONNES

CPP OUEST II - ANGERS

Angers, le 4 avril 2014

Le Comité a été saisi le 11 mars 2014 d'une demande d'avis pour le projet de recherche intitulé :

«**Etude randomisée évaluant l'impact sur la survie et la qualité de vie de la surveillance par web-application des patients atteints d'un cancer bronchique par rapport à un suivi classique. Etude SENTINEL** »

n° identification de l'A.C : **2014-A00263-44**

n° identification CPP : **2014/06**

Promoteur : Institut de Cancérologie de l'Ouest Paul Papin, 2 rue Moll, 49933 Angers Cedex 9

Investigateur principal : Dr Fabrice Denis, Institut de Cancérologie Libérale, Centre Jean Bernard, 9 rue Beauverger, 72000 Le Mans

La délibération a été conduite le mardi 18 mars 2014 sur les documents suivants :

- le courrier de soumission du projet, daté du 25 février signé,
- le formulaire de demande d'autorisation, daté du 25 février 2014 signé,
- le document additionnel daté du 25 février 2014 et signé,
- le résumé du protocole, version française n° 1.0 en date du 24 février 2014,
- le protocole de recherche et ses annexes, version française n° 1.0 en date du 24 février 2014,
- la liste des investigateurs, version du 24 février 2014,
- le curriculum vitae des investigateurs,
- la lettre d'information au patient, version française n° 1.0 en date du 24 février 2014,
- le formulaire de consentement du patient, version française n° 1.0 en date du 24 février 2014,
- le bordereau d'enregistrement de la recherche daté du 14 février 2014.
- l'attestation d'assurance datée du 28 février 2014.

Ont participé les membres suivants mais seuls les membres titulaires ont délibéré :

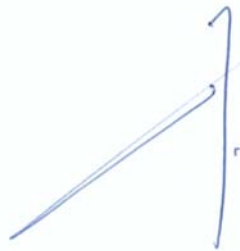
- **Recherche biomédicale** : Messieurs Audran (T), Diquet (T), Lasocki (S) et Sentilhes (S).
- **Médecin généraliste** : Monsieur Jousset (T).
- **Pharmacien** : Madame Daniel (S).
- **Infirmière** : Madame M.R. Poirier (S).
- **Ethique** : Monsieur Moriceau (T).
- **Psychologue** : Mesdames Courtillié (T) et Roquand (S).
- **Travailleur social** : Madame Malgras (T).
- **Juriste** : Monsieur Rangé (T).
- **Association agréée de malades** : Madame Cartron-Launay (T).

Le comité a émis un **AVIS FAVORABLE à la mise en oeuvre de cette étude après réception le 1er avril 2014 des documents suivants :**

- le courrier de réponses de l'investigateur principal aux remarques du comité daté du 31 mars 2014,

- la lettre d'information au patient, version française n°1.1 en date du 31 mars 2014,
- le formulaire de consentement du patient, version française n°1.1 en date du 31 mars 2014.

Pr Maurice Audran
Président du CPP Ouest II



APPENDIX 5 : INSURANCE CERTIFICATE



ATTESTATION D'ASSURANCE

RESPONSABILITÉ CIVILE PROMOTEUR DE RECHERCHES BIOMÉDICALES

(Loi n° 2004-806 du 9 août 2004 et textes d'application subséquents)

SOCIÉTÉ HOSPITALIÈRE D'ASSURANCES MUTUELLES
18, rue Édouard Rochet - 69372 LYON CEDEX 08

atteste que l' INSTITUT DE CANCEROLOGIE DE L'OUEST
2 RUE MOLL
49933 ANGERS CEDEX 09

A souscrit sous le n° **138926** un contrat d'assurance de la Responsabilité Civile Promoteur de Recherche Biomédicale conforme aux dispositions du décret 2006-477 du 26 avril 2006, afin de couvrir les obligations mises à sa charge en application de l'article L.1121-10 du Code de la Santé Publique.

« Etude randomisée évaluant l'impact sur la survie et la qualité de vie de la surveillance par web-application des patients atteints d'un cancer bronchique par rapport à un suivi classique » (DR DENIS)

La garantie prend effet au plus tôt le **01/03/2014**, et est automatiquement acquise en cas notamment de modifications affectant le nombre de sujets ou la durée de la recherche.

La présente attestation ne constitue toutefois qu'une présomption d'assurance à la charge de la Société avant validation par les autorités compétentes.

Fait et Certifié, à LYON, le 28 février 2014


Elsa DAVAUX-PUIG
Souscription et Vie des contrats
Direction Etablissements privés et professionnels de santé

APPENDIX 6 : CHARTER OF IDMC

| <i>Phase 3 multicentric randomized study assessing self-reported symptoms transmitted via an Internet Web-application « sentinel » versus conventional follow-up in patients with high risk lung cancer.</i> | |
|--|-----------------------------------|
| Abbreviated title | SENTINEL |
| SPONSOR | ICO-Paul Papin thus Weprom |
| Coordinating investigator | Dr Fabrice DENIS |
| ICO Ref / Weprom ref | ICO-A-2014-03 / WP-2018-01 |
| Registration n° | 2015-A00263-44 |

Definition of the Independent Data Monitoring Committee:

The IDMC is an advisory committee made up of competent persons in clinical trials (pathology, methodology ...), not involved in the study. This Committee is responsible for advising the sponsor and the principal coordinator / investigator of the benefit / risk study and the conduct of a clinical trial. It takes into account any information resulting from the study and related to the criteria for pursuit of the study. It makes recommendations as to the future of the study (pursuit, amendment, stop ...)

Missions of the IDMC in the SENTINEL study

The Independent Data Monitoring Committee will be established to ensure that the trial is conducted in an ethical manner, to evaluate the benefit / risk ratio of the trial and to ensure independent review of scientific results in progress or at the end of the study.

The committee will meet by conference call and email following the planned interim analysis and at the end of the study or in case of major event. The Committee will be composed of a radiotherapist, a pulmonologist and a methodologist.

The role of this committee is advisory to the sponsor who is responsible for making the final decision on the implementation of the recommendations proposed by this committee.

Composition of the IDMC

| Name | Specialty | Healthcare center | Email |
|-------------------------------|----------------|--|--|
| Dr Pierre-Etienne CAILLEUX | Radiotherapist | Pôle Santé Léonard de Vinci – TOURS, France | pe.cailleux@cort37.fr |
| Dr Bruno MINAUD | Pulmonologist | Pôle Santé Sud – LE MANS, France | Bruminaud@laposte.net |
| Mr Marc ETTAICHE | Methodologist | Centre Antoine Lacassagne – NICE, France | marc.ettaiche@nice.unicancer.fr |

The agreement of the participants has already been obtained.

To ensure the operation of the IDMC, with the help of the sponsor, members must:

| |
|--|
| Define the provisional schedule of the meetings (annual meeting or meetings for the interim analyze if envisaged in the protocol, the final analyze) |
| Name a president, provide a session secretary |
| Anticipate the type of meeting and the logistical needs (phone, room ...) |
| For each meeting : Complete the list of present person, represented person (obtain written comments from absent person) Confirm the agenda : Update on the version of the current protocol State of inclusions Monitoring report (deviation ...) Analysis of available statistical data Analysis of SAE and AE ASR Analysis Specific point according to need Additional information (alerts, bibliography, other studies ...) Conclusion, (vote if necessary) and opinion on the future of the protocol |
| Forward the opinion to the sponsor and study coordinator. This opinion is included in the reports to the competent authorities. |
| In case of obligation to modify the composition of the IDMC (replacement) or impossibility of meeting, the president of the IDMC (or the concerned member) must inform the sponsor. |