IFCT-1201 MODEL Protocol

Maintenance *vs*. **O**bservation after in**D**uction chemotherapy
in non-progressing **E**lderly patients with advanced non-small cell **L**ung cancer

Maintenance chemotherapy versus follow-up after carboplatin and weekly paclitaxel doublet chemotherapy in elderly patients with advanced nonsmall cell lung cancer (NSCLC): IFCT-1201 MODEL randomised phase 3 trial

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Project code

IFCT-1201 MODEL Protocol

Sponsor

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APPROVAL AND SIGNATORIES TO THE IFCT-1201 MODEL PROTOCOL

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I hereby acknowledge that I have read the entire protocol

EUDRACT:

and undertake to conduct this trial in accordance with Good Clinical Practice, the Biomedical Research Law (4 August 2004) and as described in this document.

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Name: Elisabeth QUOIX Date: 20/12/2012

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1. Study Rationale

1.1. Epidemiology of Non-Small Cell Lung Cancer

The incidence of primary lung cancer was over 39,000 new cases in 2011 with a death rate of 29,100 in the same year (1). The incidence increases with age due to the significant increase in life expectancy at least in developed countries, with a median age at diagnosis currently close to 70 years (2,3).

In most epidemiological studies, the threshold at which the elderly are referred to is 65 years of age (4). In therapeutic trials for the elderly, the lower limit is generally set at 70 years of age, which corresponds to the fact that no therapeutic adaptation is required in the majority of cases between 65 and 70 years of age. Most therapeutic trials for the elderly and subgroup analyses in trials not dedicated to the elderly have used this threshold (5,6,7,8,9).

The treatment of patients over 70 years of age with lung cancer has therefore become a public health issue. Despite this, until the end of the 20th century, very few phase 3 trials specifically devoted to the elderly were carried out. Their participation in trials remains well below their representativeness in the general population of patients with primary lung cancer (2). Furthermore, a certain nihilism has meant that chemotherapy is rarely offered to elderly people with metastatic non-small cell lung cancer (NSCLC), at least in the United States (4) whereas a recent survey in France does not seem to show the same reluctance (10).

1.2. Treatment of elderly patients with advanced NSCLC

1.2.1. Chemotherapy

Since the randomized study published in 1999 by the Italian group (5) showing both survival and quality of life benefit in patients aged 70 years and over treated with vinorelbine as monotherapy, compared to supportive care, the indication for chemotherapy in elderly patients with NSCLC stage IV is no longer disputed. Several other trials dedicated to the elderly have since been published. These trials first showed that single-agent chemotherapy was preferable to dual-agent therapy without platinum salts (6). The European guidelines published in 2010 were therefore to propose a single-agent therapy that could be vinorelbine, gemcitabine or even docetaxel (11). However, these guidelines mentioned that trials comparing a platinum salt doublet with single-agent chemotherapy were essential. Indeed, the analyses in subgroups of some Phase III trials suggest a benefit to the addition of a platinum salt in the elderly, of the same order as that in the general population (8,7,12). It is clear that the selection biases in such trials are significant, and that these results observed in specifically selected elderly patients could not be transposed to the entire elderly population. It is for this reason that the IFCT initiated in

2006 a trial comparing the combination of carboplatin (AUC 6 every 4 weeks) + weekly paclitaxel (90 mg/m², D1, 8, 15), with gemcitabine monotherapy (1150 mg/m², D1, D8 with D1 = D22) or vinorelbine (25 mg/m² D1, D8 with D1 = D22). The doublet had previously demonstrated its feasibility in a Phase II trial, demonstrating both efficacy and good tolerability (13).

This Phase III trial showed a very significant and highly significant gain in overall survival and progression-free survival in patients aged 70 to 89 years, performance status (PS) 0 to 2 with locally advanced non-irradiable or metastatic locally advanced NSCLC (14). The median age of 451 patients enrolled was 77 years. Median survival was 10.3 months in the doublet arm *versus* 6.2 months in the monotherapy arm (RR=0.64, 95% CI=0.52-0.78). The probability of survival at 1 year was 44.5% (95% CI=37.9-50.9) *versus* 25.4% (95% CI=19.9-31.3).

This trial dedicated to the elderly therefore confirmed the hypothesis resulting from the subgroup analyses, namely that elderly patients can benefit from a carboplatin-based doublet, in this case in combination with weekly paclitaxel. Current recommendations are therefore to administer a carboplatin-based doublet to elderly patients with advanced NSCLC (15).

1.2.2. EGF-R TKI inhibitors in the second- or third-line in elderly patients

There have been no therapeutic trials evaluating targeted therapies specifically for elderly patients. Subgroup analysis of the BR 21 trial evaluating erlotinib as a second- or third-line therapy after using a platinum salt doublet showed that the benefit obtained in patients 70 years of age and older was similar to that obtained in younger patients (9). In the previously mentioned IFCT randomised study (14), the second-line therapy was erlotinib, at a dose of 150 mg/day. The median progression-free survival observed with erlotinib was 2.6 months in the dual-agent arm compared to 2.2 months in the single-agent arm. Median survival from the start of erlotinib therapy was 6.8 and 4.6 months, respectively. The survival rates observed in the dual-agent arm were therefore very similar to those reported in the BR21 study (16).

1.2.3. Maintenance treatment with cytotoxic therapy in the elderly

Until very recently, therapeutic recommendations from learned societies (17) for patients with NSCLC in the metastatic stage, whose tumour is devoid of EGFR activating mutation, remained based on the "stop and go" or "watch and wait" strategy after a 1st line of chemotherapy (including a platinum salt and a 3rd generation cytotoxic agent), administered at a maximum number of 4 cycles in "stable" patients or 6 cycles in "responder" patients. Treatment was interrupted and resumed in the form of a second line (docetaxel, pemetrexed, erlotinib) only when disease progression was observed. The main risk of this strategy is to be confronted with a rapid progression of the disease during the free interval of any treatment, which may lead to clinical deterioration incompatible with

the initiation of a new treatment. In fact, about one-third of patients whose disease is controlled after induction treatment do not receive any additional treatment with this type of strategy (18).

The concept of therapeutic maintenance therefore seeks to optimize the use of active treatments in advanced NSCLCs over time to avoid these drawbacks of the "stop and go" therapeutic strategy. It is based on maintaining continuous therapeutic pressure on tumour disease, thereby delaying the emergence of chemoresistant clones, increasing progression-free survival, with the gain in PFS expected to translate into overall survival gains. Maintenance therapy can thus be defined as the continuation of treatment after obtaining the maximum response to 1st line chemotherapy until disease progression. (19,20,21,22). This strategy is made possible by the availability of better-tolerated treatments, cytotoxic molecules or targeted biotherapies, that can be administered over a long period of time, without cumulative toxicity. The aim of maintenance therapy is to preserve the benefit obtained by the 1st line therapy, to increase the duration of disease control and thus to prolong patients' survival without deteriorating their quality of life. The maintenance strategy seems all the more justified as the disease being treated is rapidly progressive, which is usually the case in advanced NSCLCs.

Two maintenance options (20,21) were evaluated in advanced NSCLCs, after four cycles of chemotherapy combining a platinum salt and a 3rd generation cytotoxic agent: *i)* "true" or "continuation" maintenance, consisting in continuing the cytotoxic agent initially used in combination with the platinum salt until disease progression; *ii)* "switch" maintenance based on the introduction of a new treatment (generally a second-line validated efficacy monotherapy), upon the end of induction chemotherapy. This second option also aims to avoid the risk of disease progression that is inaccessible to any subsequent treatment and allows all patients to benefit from validated second-line treatment. These two maintenance options contribute to improving the treatment of advanced NSCLCs by optimizing the 1st treatment line with continuation maintenance on the one hand, or by optimizing patients' exposure to several different treatments with the maintenance switch on the other.

Some clinical trials have shown that continuation maintenance and switch maintenance statistically and clinically significantly increase the duration of disease control, (23,24,25), others have not (26). However, survival benefit has only been demonstrated in three trials, 2 with pemetrexed for non-squamous carcinomas (25,27), the other with erlotinib (23).

However, a meta-analysis of 8 maintenance trials, either switch or continuous, showed a significant benefit, both in progression-free survival and overall survival (28).

This has led to the development of new ASCO guidelines available since September 2011 that recognize "Switch maintenance" as a possibility for patients who respond or are stable after 4 cycles: immediate treatment with another monotherapy such as pemetrexed

for non-squamous cell carcinomas or erlotinib (or even docetaxel) for all histological types, is considered an alternative therapeutic option validated for patients whose disease has been controlled by induction chemotherapy (29).

The "PARAMOUNT" trial (25) evaluating continuation maintenance with pemetrexed confirmed an increase in progression-free survival. Thanks to its potency, this study was able to measure the real impact of this strategy on overall survival. At the recent ASCO congress, Paz-Ares et al. confirmed the overall survival gain from 11 months after randomization in the control arm to 13.9 months in the maintenance arm. The Marketing Authorization (MA) of pemetrexed has therefore recently been extended to maintenance, of course in non-squamous cell carcinomas.

Like pemetrexed, gemcitabine has a safety profile that makes its use in a maintenance strategy possible; the absence of early cumulative toxicity other than haematological in nature allows for prolonged administration.

Gemcitabine was studied in "continuation" maintenance in three phase 3 trials (24,30,31). In the first trial, 352 patients were treated with 4 cycles of cisplatin-gemcitabine combination; 206 patients considered stable or responders were randomized between the continuation of gemcitabine (1250 mg/m^2 at D1 and D8 of 3-week cycles) and simple monitoring, with TTP (Time To Progression) as the endpoint (24). Gemcitabine in maintenance therapy significantly prolongs the TTP with a quantitatively high but non-significant survival benefit due to the lack of potency of the test (median survival of 13 months in the maintenance arm versus 11 months in the "monitoring" arm, p=0.195; HR = 0.84 [0.52-1.38]). Toxicity was moderate, particularly without any episodes of febrile neutropenia, despite 15% of cycles involving grade 3-4 neutropenia. The French IFCT-GFPC 0502 trial (30) confirmed the significant impact of continuing gemcitabine in terms of PFS in patients controlled with cisplatin-gemcitabine chemotherapy (HR=0.56 [0.44-0.72]), without significant impact on overall survival (median survival increased from 10.8 to 12.1 months; HR, 0.89 [0.69 to 1.15]), since the trial was not designed to evaluate an overall survival benefit. Nevertheless, the exploratory subgroup analysis shows that the survival gain appears to be limited to patients "responding" to cisplatin-gemcitabine induction chemotherapy, this benefit being quantitatively significant (median survival increased from 10.8 to 15.2 months, HR=0.72 [0.51-1.04]) especially since almost all patients in the control arm received second-line treatment. The American maintenance trial with gemcitabine after induction therapy with carboplatin-gemcitabine, on the other hand, is entirely negative, but two-thirds of patients had a PS ≥ 2 at the time of randomization (31), confirming that continuation maintenance should only be offered to patients who maintain a correct general condition after induction chemotherapy. However, Trial 0501 showed that the benefit of induction therapy with a doublet was also observed in the 27% of patients with PS=2 at baseline, with no clear deterioration in quality of life, which

encourages these patients to remain in a maintenance strategy with “light” therapy compared to induction treatment.

1.3. Rationale of the proposed trial

No maintenance trials specifically dedicated to the elderly have been conducted to date. Sub-group analysis of the Paramount trial (25) in the 34% of individuals over 65 years of age (92 patients aged 70 and over and 97 patients aged 65 to 69 years) shows that they benefit at least as much from continuation maintenance with pemetrexed as younger patients.

In the JMEN trial (27), where 35% of patients were 65 years of age or older, there is no information available on survival by age. Finally, the IFCT-GFPC 0502 trial enrolled only patients under 70 years of age (30). As a result, there is only very limited data on maintenance treatment in the elderly. Thus, it is essential to verify whether maintenance strategies can be applied to elderly patients.

It is likely that pemetrexed in maintenance is well tolerated in the elderly subject since the analysis of the elderly subjects (32) in Hanna study (33) comparing pemetrexed with docetaxel in patients 70 years of age and older in the second line, shows that there are 12.5% of grade 3 to 4 cases of neutropenia (compared to 29.7% in the docetaxel arm) and only 2.5% of grade 3 to 4 cases of febrile neutropenia, comparable to what is observed in younger subjects. Gemcitabine was used in the Brodowicz (24) and Pérol maintenance trials (30). However, it should be noted that in the first trial, although the extreme ages are 77 years, the median age is 57 years, showing that there were probably few elderly people and it should be recalled that, in the second trial, the upper limit was 70 years (30).

The overall efficacy and favourable safety data of the medicinal products proposed for this trial (paclitaxel, carboplatin, pemetrexed, gemcitabine, erlotinib) justify evaluating this maintenance strategy in elderly patients with stage IV non-small cell lung cancer.

2. Study Objectives

2.1. Primary objective

To compare the overall survival of patients whose disease is controlled after induction chemotherapy with 4 cycles of carboplatin and paclitaxel weekly from randomization maintenance versus observation.

2.2. Secondary objectives

- To investigate the feasibility of maintenance (median number of maintenance cycles that can be administered without unbearable toxicity)
- To investigate progression-free survival
- To determine the duration of the response or stabilisation obtained from the maintenance therapy.
- To evaluate tolerance and quality of life during induction treatments (carboplatin + weekly paclitaxel), maintenance (gemcitabine, pemetrexed)
- To describe the percentage of patients who are randomised in each of the two arms accessing the second line with erlotinib and the efficacy of the second line (response rate according to RECIST 1.1, progression-free survival time, overall survival time from the time erlotinib is initiated).
- To identify clinical prognostic survival factors
- To evaluate the prognostic impact of the expression of DNA repair-regulating proteins and targets of administered cytotoxics (MSH2, RRM1, BRCA1, TS), or genetic or epigenetic markers (K-Ras mutation, RASSF1A methylation), already evaluated in previous IFCT studies. The predictive impact will be analysed in an exploratory manner.

3. Study Design

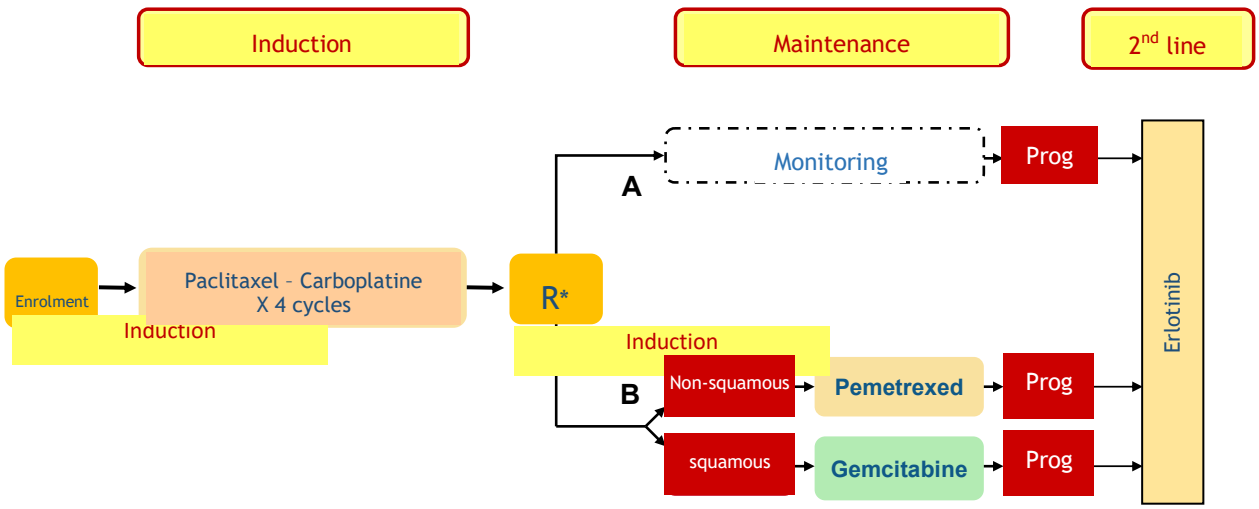
3.1. Experimental plan

This is a randomised, multicentre, open-label phase 3 trial to evaluate two management options in patients with controlled disease, one being monitoring and the other being maintenance with pemetrexed or gemcitabine with a second line fixed with erlotinib.

Patients will be randomised by minimisation according to a 1:1 scheme and a random factor and with the following stratification:

- Response after 4 cycles of induction chemotherapy (objective response versus stabilisation)
- PS at the time of randomisation: 0-1 *versus* 2
- Histology (non-squamous *versus* squamous)
- Age (< or ≥ 80 years)
- Site

Figure 1: study design



3.2. Measures taken to avoid bias

Centralized randomisation to limit screening bias. The intention-to-treat analysis will avoid attrition bias.

Evaluation bias will be limited by the objectivity of the primary endpoint, overall survival.

Finally, concomitant treatments, as well as treatment discontinuation and protocol deviation will be documented in order to avoid follow-up bias.

4. Study Population

4.1. Inclusion criteria

1. Histologically or cytologically proven Non-Small Cell Lung Cancer (NSCLC) with the greatest possible emphasis on obtaining histological evidence (detection of a mutation in the EGF-R gene and biomarker analysis).
2. Non-operable and non-irradiable Stage III or Stage IV (7th UICC TNM classification 2009 [33]). Previously operated NSCLC metastatic relapses are included only in the absence of prior perioperative chemotherapy.
3. No EGFR activating mutation (LREA deletion in exon 19, L858R or L861X mutation in exon 21, G719A/S mutation in exon 18) or mutation status of EGFR not determined.
4. No EML4-ALK translocation or ALK status not determined.
5. Presence of at least one measurable lesion in CT scan (RECIST v1.1): target over 10 mm in its largest diameter (15 mm of small axis for adenopathies), not previously irradiated and analysable by CT scan.
6. Age ≥ 70 years and < 90 years.
7. Mini-Mental Test Status (MMS) > 23.
8. WHO performance index from 0 to 2.
9. Normal liver function: bilirubin < LSN, GOT, GPT < 2.5 x LSN or < 5 x LNS in case of liver metastases.
10. Renal function with creatinine clearance calculated ≥ 45 mL/min (MDRD formula).
11. Normal haematological function (neutrophils ≥ 1.5 giga/l, platelets ≥ 100 giga/l, haemoglobin ≥ 10 g/dl).
12. Estimated life expectancy > 12 weeks.
13. Written and signed informed consent.

4.2. Exclusion criteria

1. Carcinoma, small cell (including mixed), neuroendocrine carcinoma.
2. Knowledge of an EGFR activating mutation or rearrangement of the ALK gene. The presence of a K-RAS mutation is not an exclusion criterion
3. Progressive or symptomatic metastases of the central nervous system. Patients with a history of symptomatic metastases in the central nervous system or spinal cord compression may be enrolled if they have been treated (surgery or radiotherapy) and have become asymptomatic. Oral corticosteroids are allowed, subject to a stable dose for at least 4 weeks prior to the start of treatment.
4. Superior vena cava syndrome except if they have been treated by placement of a superior vena cava prosthesis.
5. Serum calcium > 2.70 mmol/l. Use the corrected serum calcium according to the formula: Corrected Ca (mmol/l= Measured Ca (mmol/l) + 0.02x(40-albuminaemia in g/l).
6. Previous anti-tumour treatment (any chemotherapy or EGFR inhibitor).
7. MMS ≤ 23.
8. Other concomitant severe conditions: congestive heart failure, unstable angina, significant arrhythmia or a history of heart attack within 6 months before entering the trial.
9. Interstitial pulmonary pathology existing prior to lung cancer.
10. Neurological or psychiatric disorders that prevent understanding of the trial.
11. Uncontrolled infectious condition.
12. Severe or uncontrolled systemic diseases, considered by the investigator to be incompatible with the proposed protocol.
13. Grade ≥2 peripheral neuropathy.
14. History or concomitance of any other cancer except basal cell skin cancer or *in situ* carcinoma of the treated cervix or any other cancer that has received curative treatment without chemotherapy and in remission for more than 5 years.

    Patients with a history of prostate cancer under 5 years of age may be enrolled:
    - If the lung cancer is an undifferentiated adenocarcinoma or positive TTF1 undifferentiated large cell carcinoma: in case of localized prostate cancer with a good prognosis according to Amico classification (≤ T2a and Gleason's Score: ≤ 6 and PSA value (ng/ml): ≤ 10), and treated curatively (surgery or radiotherapy) without chemotherapy,
    - If the lung cancer is an undifferentiated adenocarcinoma or negative TTF1 large cell carcinoma but PSA immunohistochemical labelling on the lungs is negative or if the same anatomopathologist confirms that the morphology is different (written report required): in case of prostate cancer with a good prognosis according to Amico classification (≤ T2a and Gleason Score: ≤ 6 and

PSA value (ng/ml): ≤ 10) treated curatively (surgery or radiotherapy) without chemotherapy,

- If the lung cancer is a squamous cell cancer: in case of prostate cancer considered as cured (≤ T2a and Gleason Score: ≤ 6 and PSA value (ng/ml): ≤ 10 and treated curatively by surgery or radiotherapy), without chemotherapy.

15. Allergy to any of the treatments or excipients.
16. Combination with yellow fever vaccine (pemetrexed) or CYP3A4 inducers (erlotinib)
17. Sexually active male, with a partner in genital activity who refuses to use an effective contraceptive method during the study and for 6 months after the last dose of the treatment.
18. Impossibility to submit to the medical follow-up of the trial for geographical, social or psychological reasons.
19. Patient under legal protection.

4.3. Maintenance Treatment Eligibility Criteria

1. Patients with objective or stabilised response (according to RECIST 1.1) after 4 cycles of first-line chemotherapy with carboplatin AUC 6 every 4 weeks and paclitaxel 90 mg/m^2 weekly.
2. PS 0, 1 or 2 after induction chemotherapy.
3. Normal liver function: bilirubin < LSN, GOT, GPT < 2.5 x LSN or < 5 x LNS in case of liver metastases.
4. Creatinine clearance ≥ 45 ml/min (MDRD).
5. Recovery of sufficient haematological function (polynuclear neutrophils ≥ 1.5 giga/l, platelets ≥ 100 giga/l).
6. No concomitant radiotherapy, except in the case of localized bone radiation therapy for palliative purposes, other than spinal, with a 2-week delay between the administration of gemcitabine and the start of the radiation therapy or the end in the case of radiation therapy before treatment begins, this period may be reduced to eight days if the patient's clinical condition so requires. In the case of spinal irradiation, any irradiation should be avoided as much as possible within 4 weeks of gemcitabine administration.

4.4. Concomitant Treatments

4.4.1. Cancer treatments

No other cancer treatment (including bevacizumab) is allowed during the trial period, except for the use of analgesic radiation therapy on bone damage. This radiation therapy should only be performed within a two-week period between the administration of gemcitabine and the start or end of the radiation therapy and the administration of gemcitabine. Only an emergency such as spinal cord compression can be considered to reduce this period to 8 days.

4.4.2. Other Concomitant Treatments

The use of other symptomatic medications (steroids, anti-emetics, analgesics) will be at the discretion of the physician in charge of the patient. Any need for a significant increase in symptomatic treatment should be investigated and documented for possible disease progression.

The use of non-steroidal anti-inflammatory agents is not recommended on the days before and two days after the administration of pemetrexed.

Hematopoietic Growth Factors will not be used in primary prevention. However, they can be used as secondary prevention or curative measures.

Erythropoiesis Stimulating Agents may be used during chemotherapy, provided that the haemoglobin is < 10 g/dl, with a maximum therapeutic target of 11 g/dl haemoglobin levels, as recommended in each study site. In addition, an iron profile (including, in addition to the blood count, the determination of ferritin, serum iron and transferrin saturation coefficient associated with an inflammation marker: CRP) will be performed in principle before the start of treatment and at the time of randomisation.

Concomitant administration of nephrotoxic drugs (e.g., aminoglycosides, loop diuretics, NSAIDs) may potentially decrease the clearance of pemetrexed or potentiate the nephrotoxicity of chemotherapy. These combinations should be used with caution. Creatinine clearance will be evaluated before each chemotherapy treatment course.

Concomitant administration of substances also secreted at the tubular level (e.g., probenecid, penicillin) may decrease the clearance of pemetrexed. Precautions should be taken when these drugs are combined with pemetrexed.

4.5. Criteria for Early Discontinuation and Withdrawal from Trial

4.5.1. Withdrawal

The study is conducted with the intention-to-treat (ITT) and therefore, a patient is followed whether or he is *per*-protocol or not. Withdrawal from a trial is not synonymous with the end of the study.

The reasons for withdrawing from the trial are:

-withdrawal of consent,

Patients have the right to withdraw their consent and ask to leave the study at any time and for any reason (which they are not required to explain). This should not in any way affect their right to subsequent care. However, the investigator should make every effort to ensure that the non-medically justified withdrawal of patients is avoided.

4.5.2. Early discontinuation of treatment

In case of:

- tumour progression during treatment,

- toxicity requiring discontinuation of the study treatments,

- intercurrent disease,

- protocol violation

- non-compliance,

- administrative reasons

- patient’s decision.

5. Schedule of Assessments and Procedures

5.1. Patient inclusion

- Complete physical examination (weight, height, body surface area, SP, history collection, geriatric assessment (MMS, IADL, geriatric depression scale, INCA G8 oncode score) within 7 days.
- Biological assessment carried out within 7 days prior to enrolment: blood count and platelets, CRP, serum electrolytes, serum calcium, serum albumin, serum creatinine with calculation according to MDRD of creatinine clearance, GOT, TGP, alkaline phosphatases, serum bilirubin, ferritin and transferrin saturation coefficient.
- Tumour imaging performed within 4 weeks prior to enrolment: chest x-ray, chest CT with sections on adrenal areas, abdominal ultrasound and/or abdominal CT, CT or brain MRI.
- In case of pain suggestive of bone metastases, if access to PET scan is not possible, standard X-ray, MRI or CT and/or bone scan imaging will be performed.
- Electrocardiogram (ECG), cardiac ultrasound if there is a history of heart disease that may impair left ventricular function.

5.2. Patient Randomisation

- Complete physical examination (weight, height, body surface area, SP, history collection, geriatric assessment (geriatric depression scale, CNIB G8 oncode score).
- Biological assessment: blood and platelet count, CRP, serum electrolytes, blood calcium, albuminemia, creatinine with calculation according to MDRD of creatinine clearance, GOT, PGT, alkaline phosphatases, serum bilirubin, ferritin and transferrin saturation coefficient.
- Tumour imaging: chest CT with adrenal sections, abdominal ultrasound and/or abdominal CT, brain CT or MRI.

5.3. Treatment period

5.3.1. Evaluation before each cycle

- Complete physical examination (weight, height, BMI, body surface area, PS).
- Biological assessment: blood count and platelet count, serum creatinine with clearance calculation according to MDRD, AST, ALT, serum bilirubin and alkaline phosphatase.
- Collection of adverse events and follow-up of these events until adequate resolution or explanation is provided, even if the patient has completed the study treatment.

5.3.2. Evaluation on D8, D15 of each cycle and D21 during induction

- Biological assessment: blood and platelet count, serum creatinine levels.

5.3.3. Evaluation imaging examinations

During the 1st line (induction and maintenance), an evaluation report will be prepared after 2 cycles, after 4 cycles. Every two cycles for the first two maintenance evaluations (EVA4 and EVA5). Then the evaluations will be done every 3 cycles in both arms.

- A chest CT with adrenal sections is the minimum required for each evaluation.
- repetition of examinations to determine the initial measurable lesion(s).
- any examination necessary to confirm the appearance of a new lesion in the event of clinical suspicion of disease progression.
- The PET scan will only be repeated before randomisation if it was performed before induction because of the risk of qualifying any lesion first revealed by the PET scan as a progression.

5.3.4. Evaluation of quality of life

This will be done during randomisation and then at each evaluation assessment after randomisation.

The scale used is the Lung Cancer Symptom Scale of Quality of Life (LCSS, Appendix 6)

5.3.5. Minimum and maximum time limits

The maximum time between enrolment and the start of induction therapy is 2 weeks.

The maximum time between D1 of the 4th induction treatment cycle and D1 of maintenance is 42 days.

The 2nd line must start no later than 3 weeks after the evaluation showing progression.

5.3.6. Second-line treatment

During the second line, an evaluation report will be prepared (similar to that done during induction treatment) every 2 cycles for the first 3 evaluations and then every 3 cycles:

- repetition of examinations to determine the initial measurable lesion(s).
- any examination necessary to confirm the appearance of a new lesion in the event of clinical suspicion of disease progression.

5.4. Follow-up period

A follow-up will be carried out after the study is completed:

- Collection of subsequent cancer treatments.
- Collection of tolerance and adverse events (only target AEs and SAEs that may be related to the study treatments or the research) and follow-up of these events until adequate resolution or explanation is provided, even if the patient has completed the study treatment.

Summary table of investigations (Flow-Chart)

		Induction						Maintenance/Monitoring							
	Enrolment	Cycle 1	Cycle 2	VAS2	Cycle 3	Cycle 4	VAS3	Cycle 1	Cycle 2	VAS4	Cycle 3	Cycle 4	VAS5	Every cycle	Every three cycles
Informed consent signed	X														
Demographic data	X														
Medical history	X														
Physical examination	X	X	X		X	X		X	X		X	X		X	
Adverse events	X	X	X		X	X		X	X		X	X		X	
Concomitant treatments	X	X	X		X	X		X	X		X	X		X	
Geriatric assessment (IADL, MMS)	X														
Geriatric depression scale	X						X								
Oncodage Questionnaire	X						X								
LCSS questionnaire							X						X		X
Haematological assessment	X	X[1]	X[1]		X[1]	X[1]		X[1]	X[1]		X[1]	X[1]		X[1]	
Biochemical assessment	X	X[2]	X[2]		X[2]	X[2]		X[2]	X[2]		X[2]	X[2]		X[2]	
Hepatic assessment	X	X	X		X	X		X	X		X	X		X	
Iron profile and CRP	X						X								
Chest and supramesocolic CT scan	X			X			X			X			X		X
Abdominal and pelvic CT scan or ultrasound	X			X[3]			X			X[3]			X[3]		X[3]
Brain CT or MRI	X			X[3]			X			X[3]			X[3]		X[3]
PET scan (optional)	X						X[4]								

[1] To be performed also on D8 and D15 of each cycle as well as on D21 during induction except for patients under supervision

[2] Serum creatinine (MDRD) to be performed also on D8 and D15 of each cycle as well as on D21 during induction except for patients under supervision

[3] If target initially present or in case of a clinical sign

[4] To be performed if PET scan performed during the inclusion assessment

6. Study Treatments

Patients will be enrolled before the 1st cycle of induction chemotherapy but randomisation will only take place after induction treatment in responders or stabilised patients after the 4 cycles.

Premedication with pemetrexed will be in accordance with its MA:

- Corticosteroid therapy the day before, the day after and the day after administration with a dosage equivalent to 50 mg of prednisolone per day.
- Oral folic acid (350 to 1000 µg/day) at least 5 doses within 7 days before the first injection, then throughout the treatment and for 21 days after the last dose.
- Intramuscular vitamin B12 (1000 µg) in the week before the 1st dose and then once every 3 cycles.

Primary preventive treatment of the emetic risk should be implemented during induction chemotherapy. The choice of treatment is left to the investigator's discretion.

Since the protocol uses medicinal products used in routine practice, chemotherapy products will not be provided. The reconstitution of cytotoxic products must be carried out in a centralised reconstitution unit.

Doses will be capped at 400 mg/m² for carboplatin and 2 m² of body surface area in general.

In both arms, maintenance therapy should be started no later than 42 days after D1 of the last induction chemotherapy.

Patients who meet the eligibility criteria will be randomised after induction chemotherapy to one of the following 2 arms: observation or maintenance with Pemetrexed or gemcitabine depending on histology (non-squamous *vs* squamous)

6.1. Induction chemotherapy

4 cycles of carboplatin AUC6 (D1= D29) + paclitaxel 90 mg/m² D1, D8, D15; cycles repeated every 28 days.

The calculation of the dose of carboplatin will be done using the Calvert formula.

Before being infused, Paclitaxel must be diluted with aseptic techniques. The following infusion solutions may be used for dilution: 0.9% sodium chloride infusion solution, 5% glucose infusion solution, 5% glucose infusion solution containing 5% glucose and 0.9% sodium chloride, 5% glucose infusion solution in a Ringer solution, for a final concentration of 0.3 to 1.2 mg/ml.

The physicochemical stability of the diluted solutions was demonstrated at 5°C and 25°C for 7 days when diluted in 5% glucose solution and 5% glucose solution in Ringer's solution for infusion, and for 14 days when diluted in 0.9% sodium chloride solution for injection. From a microbiological point of view, the product must be used immediately. If not used immediately, the conditions and shelf life before use are the responsibility of the user and should normally not exceed 24 hours between 2° and 8°C.

During preparation, the solutions may show some turbidity attributed to the excipient of the product. This turbidity is not removed during filtration. To reduce the risk of precipitation, the dilution of Paclitaxel actavis for infusion should be used as soon as possible after dilution. A filter should be placed on the infusion line insofar as a small number of fibres (within the USP Particulate Matter Test for LVP limits) have been observed. PVC bags should be avoided as the EL* Cremophor could attack them. This consideration also applies to the equipment used during reconstitution. Only glass or polyolefin bags and polyethylene tubing have been validated.

All patients should be pre-medicated with corticosteroids, antihistamines and H2 receptor antagonists before paclitaxel is administered:

<table>
<tr><th>Medication</th><th>Dosage</th><th>Administration before paclitaxel</th></tr>
<tr><td rowspan="2">Dexamethasone</td><td rowspan="2">20 mg
per os or IV</td><td>Oral administration:
approximately 12 and 6 hours</td></tr>
<tr><td>IV Administration:
30 to 60 minutes</td></tr>
<tr><td>Diphenhydramine*</td><td>50 mg IV</td><td>30 to 60 minutes</td></tr>
<tr><td>Cimetidine</td><td>300 mg IV</td><td rowspan="2">30 to 60 minutes</td></tr>
<tr><td>or ranitidine</td><td>50 mg IV</td></tr>
</table>

* or 5 mg of DEXCHLORPHENIRAMINE

Growth factors

Given the expected dose adjustments, the use of haematopoietic growth factors is not recommended for primary prophylaxis. Their use as secondary prophylaxis or for curative purposes is possible. Administration from D3 to D5 has been described with a weekly cisplatin paclitaxel combination (34) and this regimen could be used in the context of secondary prevention (granocyte* or neupogen*).

Subsequent treatment:

- In case of disease progression (RECIST 1.1) and only in case of progression: treatment with erlotinib 150 mg/day as second-line treatment

6.2. Study design

After 4 cycles of induction chemotherapy, in case of controlled disease (RECIST 1.1) and eligibility for maintenance treatment:

- *For patients with squamous cell carcinoma:* after 4 induction cycles: **Maintenance switch with gemcitabine** monotherapy (1150 mg/m² on D1, D8, cycles repeated every 21 days) until progression or unacceptable toxicity; in case of documented disease progression, **second-line therapy with erlotinib 150 mg/day.**
- *For patients with non-squamous cell carcinoma*: after 4 induction cycles: **maintenance switch with pemetrexed** 500 mg/m² every 3 weeks until progression or toxicity; in case of documented disease progression, **second-line therapy with erlotinib 150 mg/day.**

Anti-emetic treatment will be decided by each investigator, knowing that steroids and apepritant are not recommended for this indication (corticosteroids, on the other hand, are recommended for pemetrexed for anti-allergic use).

Any patient who is required to discontinue induction or maintenance therapy for toxicity reasons is monitored in accordance with the protocol without starting second-line therapy. This is only initiated in case of objective disease progression.

The patient should receive his first course of induction chemotherapy within 14 days of enrolment.

After documented disease progression during first-line treatment, randomized patients should start second-line treatment (erlotinib) within a maximum of 3 weeks. After this time, the patient will have to be withdrawn from the study.

7. Dose adjustment

7.1. Induction chemotherapy with Paclitaxel - Carboplatin (4 cycles)

7.1.1. Dose reduction ranges for Paclitaxel/carboplatin

	0 (starting dose)	-1	-2
Paclitaxel (mg/m^2)	90	80	70
Carboplatin (AUC)	6	5	4.5

Dose adjustments on D1 depending on the greatest haematological toxicity observed during the past cycle

On D1 the doses of carboplatin and paclitaxel will be reduced by one level if the following toxicities have been observed:

-Grade 4 neutropenia (PNN < 500/mm^3) for at least 7 days

-Grade 3 or 4 febrile neutropenia (PNN < 1000/mm3 with temperature >= 38°5C) [sic]

-Grade 4 anaemia (< 6.5 g/dl)

-Grade 4 thrombocytopenia (< 25000/mm^3 or bleeding that required a transfusion

7.1.2. Time of administration on D1 based on haematological and non-haematological toxicities observed on the day of rechallenge:

To receive chemotherapy, the patient must have:

PNN >= 1500/mm^3

Platelets >=100000/mm^3

Return of all non-haematological toxicities to a grade <=1.

A period of two times a week may be proposed. If D1 cannot be administered on D43, chemotherapy is discontinued, with exceptions to be discussed with the principal investigator.

7.1.3. Changes in Paclitaxel/Carboplatin doses on D1 based on the non-haematological toxicities observed during the past cycle:

Organ or tissue	Toxicity	Grade	Action
Ear	Hearing/Internal ear	>=2	Discontinuation of carboplatin Continuation of Paclitaxel according to the investigator's choice
Cardiovascular	Asymptomatic sinus bradycardia Ventricular Arrhythmia Asymptomatic	1	No adjustment ECG before each cycle
	Symptomatic ventricular arrhythmia Atrioventricular block (except 1st degree) Other blocks	>=2	Discontinuation of chemotherapy
Gastrointestinal	Mucositis	>=3	1 reduction level for both drugs
Liver	Bilirubin > 3 x LSN AST/ALT (> 2.5 x LSN) In case of hepatic metastases: >= 5	>=3 >= 2	Discontinuation of chemotherapy
Infection	Infection without neutropenia	>=3	1 reduction level for both drugs
Nervous system	Sensory neuropathy	1 2 *2	No adjustment One reduction level for both drugs *If persistence despite dose reduction, second reduction

		>=3	level Discontinuation of chemotherapy
Pain	Arthralgia/myalgia for more than 7 days	>= 3 >=3	One level of dose reduction for Paclitaxel only Discontinuation of chemotherapy (2 drugs)
Kidneys	clearance < 30 ml/min	> 2	Discontinuation of carboplatin Continuation of paclitaxel at the investigator's discretion
Toxicity affecting other organs except nausea, vomiting and fatigue		>=3	2-level dose reduction or discontinuation of chemotherapy at the investigator's discretion

7.1.4. Dose adjustment/administration time for paclitaxel on D8 and D15

The patient must meet the following criteria to receive paclitaxel on D8 and D15:

PNN >= 1500/mm^3

Platelets >= 100000/mm^3

The dose of Paclitaxel will then be the same as on D1 unless non-haematological toxicity requiring a dose reduction had occurred between D1 and D8 or between D8 and D15.

As mentioned above, if D8 is postponed, this dose is cancelled, similarly, if D15 cannot be administered, the dose is cancelled. If D8 and D15 must be cancelled, the same procedure is repeated on D29, while respecting the dose-level reduction rules described above.

7.1.5. What to do if there is a hypersensitivity reaction

Cases of severe hypersensitivity characterised by hypotension, dyspnoea, angioedema or generalised urticaria have been described in 2% of patients receiving paclitaxel.

In the event of a hypersensitivity reaction, appropriate measures should be taken by the investigator depending on the severity of the event.

CTC Grade 1: transient rash, fever < 38°C: continued infusion, monitoring. No treatment required.

CTC Grade 2: urticaria, fever >= 38°C and/or symptomatic bronchospasm: discontinuation of paclitaxel infusion, administration of 2.5 mg of dexchlorpheniramine and methylprednisolone 60 mg. Resume paclitaxel infusion after sedation of symptoms at a slower flow rate: 20 ml/h for 15 minutes then 50 ml/h for 15 minutes then if there are no other symptoms at the initial flow rate until the end of the infusion. Special attention with controlled monitoring should be exercised during the next administration of paclitaxel.

CTC Grade 3 or 4: severe or even life-threatening symptoms: major bronchospasm requiring intravenous treatment with or without urticaria, oedema/angioedema, anaphylactic shock: discontinuation of paclitaxel infusion. Administration of diphenhydramine and methylprednisolone as above. Add adrenaline or bronchodilators by aerosol or IV route if necessary. Mention the incident as a Serious Adverse Event (SAE). Do not resume chemotherapy.

7.2. Maintenance with pemetrexed

To receive chemotherapy, the patient must have:

PNN >= 1500/mm^3

Platelets >=100000/mm^3

Dose adjustment based on haematological toxicity

Nadir	Pemetrexed dose
PNN ≥ 500/mm^3 Platelets ≥ 50,000/mm^3	100% of the preceding dose
PNN < 500/mm^3 Platelets ≥ 50,000/mm^3	75% of the preceding dose
Platelets < 50,000/mm^3 Irrespective of PMN levels	75% of the preceding dose
Platelets < 50,000/mm^3 with bleeding ≥ Grade 2 Irrespective of PMN levels	50% of the preceding dose

The occurrence of Grade 3 or 4 neutropenia or thrombocytopenia after two dose reductions results in the permanent discontinuation of pemetrexed. The patient will be monitored according to the protocol with second-line erlotinib treatment upon relapse.

The use of white-line growth factors (G-CSF) is allowed.

Dose adjustment based on non-haematological toxicity

The dose should be adjusted to the most significant non-haematological toxicity observed during the previous cycle as shown in the diagram below:

Toxicity	
Grade 3 or 4 diarrhoea or diarrhoea requiring hospitalisation.	75% of the preceding dose Treatment postponed until diarrhoea is resolved
Grade 3 or 4 stomatitis	50% of the preceding dose Study withdrawal after recurrence of a Grade 3-4

	after 2 dose reductions
Renal failure	Creatinine clearance (MDRD) must be > 45 ml/min before any administration of pemetrexed. The cycle can be postponed for up to 35 days. If creatinine clearance remains < 45 ml/min after this time, pemetrexed will be permanently stopped.
Any other Grade 3 or 4 toxicity	75% of the preceding dose Treatment postponed until the toxicity is resolved. Study withdrawal after a maximum of two dose reductions.

7.3. Maintenance with gemcitabine

Dose adjustment of gemcitabine on D1 of the cycle based on the blood count prior to each cycle (the day before or the day of chemotherapy)

FBC before D1 of each cycle

Polynuclear Neutrophils (/mm^3)	Platelets (/mm^3)	Dose and postponement
≥ 1,500	and ≥ 100,000	Treatment within the scheduled time, dose adjustment based on nadir
< 1,500	and/or < 100,000	Treatment postponed for one week*, dose adjusted to the nadir of the previous cycle

** maximum postponement of twice a week; beyond that, withdrawal from the trial.*

Dose adjustment based on the Nadir at each cycle

Nadir

Polynuclear Neutrophils (/mm^3)	Platelets (/mm^3)	Dose at next cycle
≥ 500	and ≥ 50,000	No adjustment
< 500 less than 5 days without fever	and ≥ 50,000	No adjustment
< 500 for > 5 days and/or febrile neutropenia	and/or < 50,000	Reduce by one dose level*

* Dose levels:

Level -1: reduction of the gemcitabine dose to 1000 mg/m$^{2.}$

Level -2: reduction of the gemcitabine dose to 750 mg/m^2

*Adjustment of gemcitabine doses **on D8** based on FBC*

Polynuclear Neutrophils (/mm^3)	Platelets (/mm^3)	Gemcitabine (% dose)
> 1,500	> 100,000	100% of the dose given on D1
1,000 to 1,500	or 75,000 to 100,000	75% of the dose given on D1
< 1,000	or < 75,000	0*

* injection cancelled and not postponed

Dose adjustment based on hepatic toxicity

Serum bilirubin (μmol/l)	NCI grade	Gemcitabine (% dose)
< ULN	0	100
> ULN-1.5 ULN	1	100
> 1.5 ULN	2, 3, 4	75

7.4. Erlotinib in second line

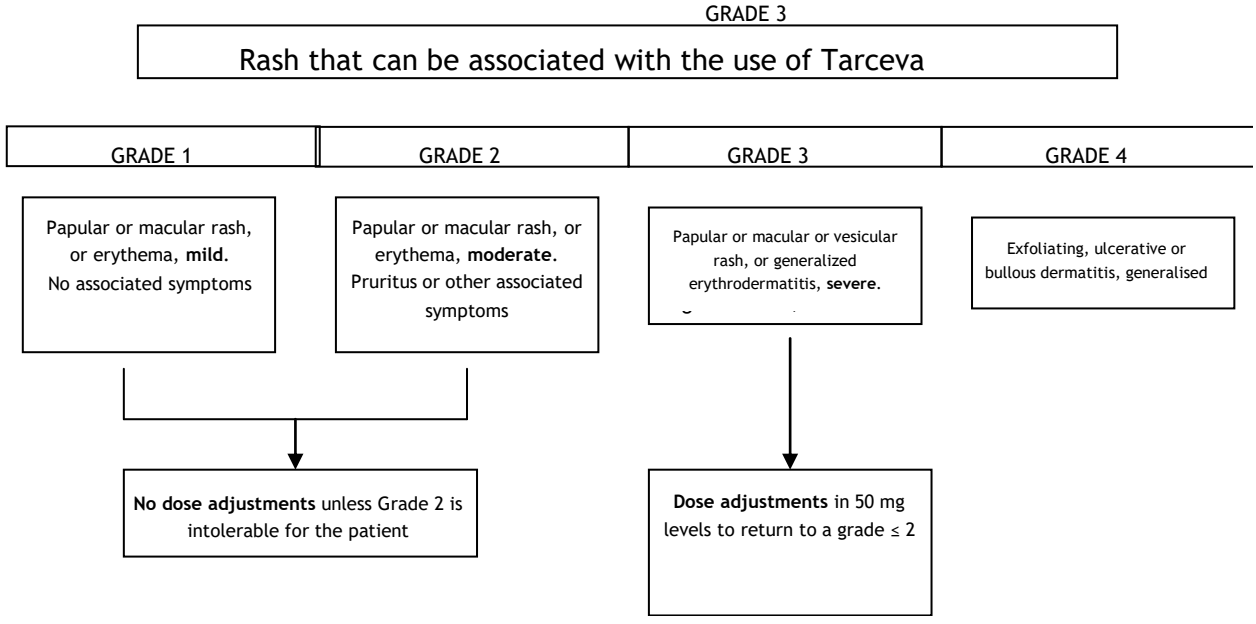
Treatment will be temporarily discontinued in the event of Grade 3 or 4 toxicity until return to Grade 2. The maximum interruption period is 14 consecutive days. When treatment is resumed, a dose reduction in 50 mg levels is envisaged (2 possible reductions). In the event of a new Grade 3 or 4 toxicity despite appropriate treatment, erlotinib treatment will be permanently stopped, the patient should be withdrawn from the study.

Dermatological toxicity

This is the most common side effect (75% of patients observed in the BR 21 trial). However, a Grade 3 or 4 toxicity was only observed in 9% of patients in the BR 21 trial.

It is important to distinguish between the rash observed during treatment with erlotinib and acne. Therefore, this rash must be treated differently from acne: retinoid ointments are not indicated.

Identification/evaluation of the grade:



Recommendations for physicians in case of rash:

Primary management of rash

Treatment option

- Consider early topical treatment (from Grade 1) with topical corticosteroids.
- An analgesic may be beneficial: consider it before reducing doses of erlotinib

- Topical retinoids and other treatments for acne **are not** recommended. They could even exacerbate the rash.
- A dermatological opinion will be sought if necessary

General Recommendations

- Evaluation of the effectiveness of the treatment after one week and continue for another week. Discontinue if there is no improvement after 2 weeks.
- Use topical agents with caution, especially in cases of severe rash: efficacy may be limited if there is little penetration into the deep layers of the skin.

Secondary management of infected rash

Treatment options

- Consider the use of local topical antibiotics.
- Consider the use of rapid treatment with oral antibiotics such as doxycycline.

Recommendations for patients in case of rash:

Make-up

- The rash can be covered with make-up without risking aggravating the symptoms. Dermatologically approved make-up is preferable.
- Use a mild make-up remover.

Moisturising cream

- Use a hypo-allergenic emollient cream to prevent and soothe dry skin, such as Dexeryl®.

Sun exposure

- Avoid exposure to the sun, or use good protection.

Other treatments

- Do not use acne treatments as this may aggravate symptoms.

Gastrointestinal toxicity

Nausea/Vomiting

Vomiting < 30 minutes after taking erlotinib: new dose of 150 mg of erlotinib

Changed doses and recommendations if diarrhoea

Grade per toxicity scale NCI-CTC v3	Adjustment of erlotinib doses	Recommendations for the management
Grade 1	No	Consider Loperamide (4 mg for the first dose, followed by 2 mg every 2 - 4 hours until diarrhoea is stopped for 12 hours) and rehydrate appropriately.
Grade 2	No	Loperamide (4 mg for the first dose, followed by 2 mg every 2 - 4 hours until diarrhoea is stopped for 12 hours) and rehydrate appropriately.
Grade 3	Discontinuation	Discontinue treatment and provide appropriate rehydration, monitor diuresis and renal function until resolution at Grade ≤ 1; resume treatment at a reduced dose.
Grade 4	Withdrawal from the study	If treatment is ineffective: withdraw the patient from the study.

Ophthalmological toxicity

Patients with dry eyes will initially be treated with artificial tears. If the symptom persists, a consultation with the ophthalmologist should be arranged.

Vascular toxicity

Elevations of the International Normalized Ratio (INR) and bleeding (including gastrointestinal) have been reported in clinical studies, in some cases in combination with warfarin or an NSAID. In patients treated jointly with warfarin or a coumarin derivative, prothrombin time or INR should be regularly monitored.

Other toxicities

Liver function monitoring with AST/ALT transaminases, bilirubin, alkaline phosphatases assay every 4 to 6 weeks is recommended. If the hepatic profile is disturbed, the benefit of continued erlotinib therapy should be reassessed.

Pulmonary toxicities found in the BR21 trial are less than 1%[31] and not significantly different from the placebo arm. As a precaution, special monitoring of respiratory symptomatology should be carried out with a chest x-ray or even a chest scan if there is any doubt, and erlotinib should be discontinued pending the results of the diagnostic assessment of respiratory symptomatology.

8. Endpoints

8.1. Eligibility and patient evaluation

Any patients enrolled will be evaluated for overall survival and progression-free survival. Any patient who has received at least one dose of one of the study treatments will be evaluated for toxicity. Response rates will be expressed in terms of intention to treat (ratio of the number of responders to the total number of patients enrolled in each arm).

8.2. Toxicity evaluation

It will be carried out according to the NCI-CTC criteria version 4.0.

8.3. Definition of evaluation targets

The evaluation will be carried out according to RECIST 1.1 [24] (See Appendix 1) by each investigator.

8.4. Evaluation of biomarkers: Bio-1201 MODEL

Biomarkers evaluated by immunohistochemistry (IFCT centralisation): MSH2 (human MutS homolog 2), TS (Thymidylate synthétase), RRM1 (Ribonucleoside-diphosphate reductase large subunit), BRCA1 (**br**east **ca**ncer **1**, early onset).

A collection of paraffin-embedded tumour blocks will be collected from all the patients enrolled in the clinical study. For each patient, the minimum requirement is 5 white slides (+1 HES slides). tumour blocks, or failing this, 5 freshly cut white slides (precise cutting date: 4 slides for IHC + 1 slide if labelling fails), whose tumour content has been verified on adjacent HES section, will be sent to IFCT (with HES section), for the performance of these IHC labelling by the IFCT teams having already performed these analyses for Bio-IFCT0002 studies (Zalcman et al. WCLC 2011) and PREDICT (Histology Laboratory of the CHU [University Hospital] of Caen, Dr Levallet; Anatomy and Pathology Laboratory of the CHU [University Hospital] of Tenon, Paris, Dr Martine Antoine). The interpretation of immunolabelling and their quantification will be carried out by the ana-pathological group of the IFCT according to the methodologies validated in the above-mentioned studies.

Genetic biomarkers: The findings of the K-Ras mutation research carried out by the regional molecular genetics platform labelled by the iNCA will be collected by the IFCT. In case of any remaining DNA material after the mandatory genetic study of the platforms, a DNA collection will be carried out by the IFCT from the platforms for the centralized methylation research of RASSF1A using the MS-PCR technique validated in bio-IFCT 0002 study (35) by the Inserm de Caen [*Institut*

national de la santé et de la recherche médicale (French National Institute for Health and Medical Research)] UMR 1086 team (Dr G. Levallet, Prof. G. Zalcman)

9. Pharmacovigilance

9.1. Toxicity evaluation

All the patients who received the protocol treatment regardless of the duration of the treatment will be evaluable for toxicity.

9.2. Non-serious adverse events

An adverse event is defined as a harmful and unintended event in a clinical trial participant, regardless of whether the event is related (effect) or not to the research or product being investigated.

This may be a symptom, a group of symptoms, a laboratory abnormality or a temporarily associated intercurrent disease.

9.3. Serious adverse events

9.3.1. Regulatory definition

A serious adverse event is defined as an event occurring in a patient participating in a clinical study, whether therapeutic or not, regardless of whether it is related to the purpose of the clinical study (in particular a medicinal product under analysis) and which corresponds to the following definition:

- death
- life-threatening
- hospitalisation or prolongation of hospitalisation (a scheduled hospitalisation is not a SAE, for whatever reason)
- persistent handicap/disability or severe temporary disability
- congenital abnormality/malformation or abortion
- a medically significant event or new fact (clinical event or laboratory result considered serious by the investigator and that does not meet the severity criteria defined above).

Examples: overdose, second cancers, significant increase in the frequency of a known adverse event, etc.

Deaths related to the obvious progression of the cancer disease will not be reported as a SAE. The cause of death must be carefully recorded in the source file. If the patient dies during unscheduled hospitalisation, the hospitalisation will be reported as a SAE.

A serious adverse event is also not considered to be hospitalisation < 24 hours unless it is a life-threatening event resulting in death on the same day (cause other than cancer).

9.3.2. Time limit for notification to the sponsor

All SAEs must be reported to the study sponsor. This reporting is a legal requirement. Serious adverse events should be reported on a special form (see Appendix 2) within 24 business hours from the time the investigator becomes aware of them, by fax to the trial coordination (IFCT fax: **01.44.83.01.51**). They will be updated if necessary (monitored until the event is resolved).

Any serious adverse event occurring within 30 days of the end of the administration of any of the study treatments should be subject to the above procedure. After this period, only events for which a causal link to any of the study products is suspected (late toxicity) will be reported as SAEs.

9.3.3. Unexpected serious adverse events

An unexpected serious adverse event is considered to be any event not mentioned or different in nature, intensity or frequency from the reference document. The reference document is the investigator's brochure (IB) or the summary of product characteristics (SmPC) for medicinal products with a marketing authorisation.

In this study, the reference documents will be the SmPC for cisplatin, pemetrexed and gemcitabine since they all have the MA.

The sponsor will inform investigators about the occurrence of all unexpected serious adverse events within the notification time described above.

10. Statistical methodology

10.1. Calculation of the number of subjects required

The median survival rate of patients who received 4 cycles of carboplatin + paclitaxel in the IFCT-0501 study and had control of their disease at the end of these 4 cycles was 10.2 months from the end of the induction treatment.

To demonstrate a 4-month gain in overall survival in the maintenance arm (median survival at 14 months from baseline (or 10 months from randomisation) in the maintenance arm with a 5% bilateral alpha risk and a 20% beta risk, with a 4-year baseline period and a minimum 3-year follow-up period), 328 patients should be randomised, i.e., enrol 546 patients, assuming that 60% will be responders or stabilised.

Randomisation will be carried out via extranet using a minimisation technique already widely used in our previous trials.

10.2. Analysis population

Any patients enrolled will be evaluated for progression-free survival and survival. Any patient who has received at least one dose of one of the study treatments will be evaluated for toxicity. Response rates will be expressed in terms of intention to treat (ratio of the number of responders to the total number of patients enrolled in each arm).

- The tolerance analysis population will be defined as all patients who received one dose of treatment.

- The Intention-to-Treat (ITT) population will include all enrolled and randomised patients.

- The population of eligible patients will be ITT patients who do not have any deviations considered as major on the inclusion and non-inclusion criteria.

Deviations from the protocol will be reviewed by the principal investigators, then classified as minor or major deviations, and listed.

10.3. Analysis of study data

Analyses will be carried out on the ITT population and on the population of eligible patients if relevant for the analysis of the primary endpoint. The safety analysis will be carried out on the safety population.

10.3.1. Analysis of the primary endpoint

Overall survival is defined as the time between the date of randomisation and death from any cause. It will be estimated using the Kaplan-Meier method. The number of patients who died during the study will be described by arm. The comparison between the 2 arms

will be carried out using a bilateral Log-Rank test. The median overall survival and its 95% confidence interval will be presented. The overall survival curves will be tracked.

10.3.2. Analysis of secondary endpoints

- The feasibility of maintenance will be studied and reported according to the median number of maintenance cycles that can be administered without unacceptable toxicity.
- Progression-free survival is defined as the time between the date of randomisation and progression or death from any cause. It will be estimated using the Kaplan-Meier method. The number of patients who progressed will be described. The comparison between the 2 treatment arms will be carried out using a bilateral Log-Rank test. The median progression-free survival and its 95% confidence interval will be presented. The progression-free survival curves will be tracked.
- The response (complete+partial) will be measured according to RECIST 1.1. The duration of the maintenance response will be defined as the time between the evaluation date of the EVA3 response and progression on maintenance. The duration of the control (response+stabilisation) will also be analysed.
- Tolerance will be analysed on induction, maintenance treatments (gemcitabine, pemetrexed) and relapse (erlotinib). Adverse events will be coded using MedDRA coding. The number of patients for whom at least one adverse event has been reported will be presented in each arm, as well as the number of events itself, depending on the relationship to the treatment, the intensity, and the cycle of onset.
- Exposure to treatments will be evaluated by the length of time the study treatments were taken in each arm.
- The percentage of patients randomised in each of the 2 arms accessing the second line with Erlotinib will be presented with its 95% confidence interval.
- The efficacy of the second will be analysed according to response rate, overall survival and progression-free survival.
- The response will be evaluated after 2 and 4 maintenance cycles. Patients for whom the response is not evaluable will be considered as failures. Response rates will be compared using the exact Fisher test.
- Overall survival and progression-free survival of the second line will be based on the first dose of erlotinib and will be analysed in the same way as in the first line.

10.3.3. Investigation for prognostic and predictive factors

A multivariate analysis using the Cox proportional risk model will be performed to investigate prognostic factors for survival. A procedure for selecting the step-by-step downward variables will be used to keep the independent survival factors in the model. All statistically significant basal variables at the 20% threshold will be introduced into the initial model.

An exploratory analysis will study the effect of treatments in each of the modalities of the variables selected in the final model.

An exploratory analysis of the prognostic value of the biomarkers studied will be performed with a multivariate analysis using the same methodology. The prognostic model that may be identified will be validated by a bootstrap technique that reproduces all the steps of this analysis. The predictive value of biomarkers will be investigated using interaction tests between the maintenance arm (overall for MSH2, BRCA1, K-Ras) and the observation arm, and for RRM1 between patients receiving gemcitabine and patients in the observation arm, for TS between patients receiving pemetrexed and those in the observation arm.

10.4. Monitoring analysis

A monitoring analysis will be performed after enrolling half of the randomised patients, i.e. 164 patients. The objective of the monitoring analysis will be to ensure the overall quality of the trial, i.e. enrolment rate, treatment compliance, protocol deviations, as well as adverse event monitoring. In particular, the feasibility of maintenance treatment in this elderly population will be analysed and reported according to the median number of maintenance cycles that can be administered without unacceptable toxicity.

The Independent Data Monitoring Committee will be composed of one statistician and three physicians qualified in oncology.

Its operating rules will be formalised in the IDMC charter drawn up by the IFCT and the Steering Committee and submitted to the IDMC for approval.

The charter will cover administrative, operational and methodological aspects and will be finalised before the enrolment of the first patient in the trial.

11. Administrative section

11.1. Obligations of the sponsor

11.1.1. Before the trial

The sponsor:

- shall complete the regulatory formalities prior to the conduct of the trial;
- shall ensure all administrative procedures with the management of each associated institution
- shall provide the complete protocol and its appendices, the adverse event report form, the positive opinion of the EC, the certificate of insurance and the authorisation of the Competent Authority (ANSM).

The sponsor or its representatives:

- shall provide the research sites with the necessary instructions and documents for the proper conducting of the trial (protocol, case report forms, investigator's brochure),
- shall organise an introductory meeting to train investigators and study coordinators (during this meeting, all the sections of the protocol will be discussed, how to complete the case report forms will be explained, as will the study procedures)

11.1.2. During the trial

The sponsor or its representatives:

- shall conduct regular visits to the research sites
- shall be available at any time for consultation and shall remain in contact with research site personnel by letter, telephone and/or fax.
- shall review and evaluate the data in the case report forms and investigate potential data collection errors

In consultation with the principal investigator, the sponsor shall provide the investigators involved in the study with any new information likely to interfere in the conducting of the trial.

11.1.3. At the end of the trial

The sponsor is responsible for ensuring that the end of trial procedures are carried out.

11.2. Obligations of the investigator

The investigator undertakes to conduct the study in accordance with the 1974 version of the Declaration of Helsinki, revised in 1975 and 1989, Good Clinical Practice, and the applicable laws and regulations.

Regarding the latter, the investigator at each site undertakes to collect the informed written consent of each patient included in the trial. A copy of the written consent shall be given to the patient, and another will be kept in the patient's medical file. Patients must be able to give their informed consent and therefore not be under guardianship or suffering from a neuropsychic pathology that affects their judgement.

They also undertake to complete the case report forms required for the monitoring of the study.

Furthermore, the investigator undertakes to:

- Report any serious or unexpected adverse events occurring during the trial to the sponsor within the time frame described in Chapter 7.1 using the appropriate form.
- Agree to the monitoring with access to source documents to validate the data in the case report forms and, if necessary, to accept an internal or external audit requested by the sponsor or a representative of the regulatory authorities.
- Archive the trial documents (copy of the case report form pages, informed consent) for a period of at least 15 years.
- Include at least one patient during the first six months following the implementation of the trial.
- Ensure no interference with another trial with the same indications.
- Respect the confidentiality of documents that are provided.

11.3. Ethical considerations

11.3.1. Participant information and consent

Prior to the conduct of this biomedical research on a human subject, the **free**, **informed** and **express** consent of the latter must be obtained after having been informed of the objective of the research, the conduct and duration of the study, the benefits, potential risks and constraints of the study as well as the nature of the study product and the opinion given by the Ethics Committee (Art. L. 1122-1 of the French Public Health Code (CSP)).

The consent form shall be dated and signed personally by the patient and the investigator or the physician representing them (original archived by the investigator, a copy will be given to the patient or their legal representative).

11.3.2. Request for CNIL (Commission Nationale de l'Informatique et des Libertés [French Data Protection Authority]) authorisation to process computerised data:

This biomedical research shall result in the production of information for scientific purposes. This directly or indirectly personal and encoded information is covered by a legal framework for the use of files (Law no. 78-17 of 6 January 1978 and Law no. 94-548 of 1st July 1994).

The sponsor (IFCT) has an authorisation (*No. 1227585*) relating to the processing of personal data for the purpose of biomedical research on medicinal products and pathologies pursuant to the law of 20 December 1988 as amended by law No. 2004-806 of 9 August 2004.

Insofar as this biomedical research is conducted within the framework of strict legislative and regulatory requirements ("Huriet-Sérusclat" law of 20 December 1988 as amended by law No. 2004-806 of 9 August 2004) in accordance with standardised methodologies. The CNIL has adopted a reference methodology (MR001 in accordance with Article 54 of the amended law of 6 January 1978) which now covers all processing of personal data carried out in the context of biomedical research - including pharmacogenetic trials.

11.3.3. Procedures for amendments and addenda

Any substantial amendment to the protocol shall be proposed by the study sponsor. This will have to be the subject of an amendment submitted to the EC and the ANSM. The amendment may only be made with the agreement of the EC and the ANSM (if applicable). The sponsor shall inform each investigator and send them the amendment and related authorisations.

11.4. Quality control and assurance

eRegulatory considerations: The medical procedures in this trial are consistent with the most recent recommendations of the Declaration of Helsinki and public health law No. 2004-806 from 9 August 2004 on the protection and safety of human subjects.

Confidentiality: The Protocol and its appendices, as well as all data, shall be confidential as indicated at the beginning of the Protocol.

Data monitoring: The IFCT Clinical Research Unit will monitor this trial to ensure the collection of accurate, complete and reliable data, as well as logistical support for the research sites. An inspection mandated by the Regulatory Authorities by employees who are bound by professional secrecy may be required to ensure that all the necessary source documents are available, and that the clinical trial is conducted in accordance with Good Clinical Practice and the law of 09/08/2004.

11.5. Study schedule

The protocol is expected to start in May 2013, with a projected recruitment period into the trial of 4 years, and a follow-up of 3 years, with the trial expected to be completed in April 2020.

Early termination of the study

Any early termination of the study will be made by the sponsor in contact with the coordinating investigator. It will be notified in writing by the sponsor. This letter will be sent to the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) and to each investigator as well as to the EC.

11.6. Commitment Statement

New investigators

Investigators may only participate in the trial after a written request to the sponsor. It should consist of the following elements:

- the estimated number of patients he/she will be able to include in the protocol per year,
- a recent *curriculum vitae* with medical board number.

Site opening

Before starting the inclusions, a site must be officially opened, i.e., the name of the investigator, his/her institution, phone number, fax number, email address, must be duly submitted to the sponsor, the EC, and the ANSM. The investigator must be in possession of all the documents necessary for the proper conducting of the trial (protocol, investigator's

brochure, case report forms). He/she must have obtained the agreement of the institution's pharmacist for the distribution of treatments and, in case of difficulty, resolve the problem with the study coordinator. They must have, by means of a letter, informed their institution's director of their participation. An agreement shall be signed between the director of their institution and the sponsor.

11.7. Organisation of the study

The Steering Committee takes all decisions concerning the implementation, execution, analysis and report of the study. It will meet 2 times per year, and periodically send information on the conducting of the study to the investigators.

It is composed of members of the editing committee, study statisticians, and a representative of the sponsor.

The Coordinating Site shall be the Clinical Research Unit (CRU) of the IFCT, located at "10 rue de la Grange-Batelière, 75009 PARIS". Its role is to ensure the proper conduct of the trial as provided for in the protocol: inclusion management, data collection, data management, SAE management, organization of investigator and various committee meetings. It shall inform the Steering Committee of all elements concerning the conduct of the trial.

Furthermore, the Steering Committee reserves the right of regularly organising an investigators' meeting where the files of the included patients will be reviewed. The purpose of this review panel will be to jointly check that the eligibility criteria and therapeutic modalities required by the protocol are respected and properly understood.

12. Final Report and Publication

Once the study ends, a clinical trial report will be published by the principal investigators and the statistician responsible for the study. The coordinating investigator will sign the final version of the clinical trial report for this study, hereby indicating their agreement with the analyses, the results, and the conclusions of the report.

The key players in a clinical study are the coordinating investigator, investigators, members of the IFCT staff team and members of the boards of directors and scientists, all of whom collaborate to varying degrees from the design of the trial to the final writing of the findings. The order of signatories will be governed by the IFCT rules (http://www.ifct.fr):

1. The coordinating investigator has the choice between first and last place. In both cases, he or she must have been extensively involved in the design of the trial, inclusions and drafting of the article.
2. If he/she chooses the first place, the last place is reserved for the President, one of the secretaries or one of the other elected members of the Board of Directors (BOD) or the Secretary of the Scientific Council (SC). The latter must be chosen on the basis of his or her participation in the design of the trial, inclusions and the drafting of the article. In the event of any difficulty in choosing this person, a secret ballot of the Board of Directors will determine the outcome.
3. If he/she chooses the last place, the second to the last place goes to the Chairperson, one of the Secretaries or one of the other elected members of the Board or the Secretary of the SC under the same conditions, unless the latter takes the first place if, in agreement with the principal investigator, he/she drafts the article. In the event of any difficulty in choosing this person, a secret ballot of the Board of Directors will determine the outcome.
4. Investigators are listed in order of inclusion of eligible patients. All other investigators should be listed in an appendix.
5. Two members of the same team may not sign the same article unless one of them appears as the coordinating investigator or member of the Board or secretary of the signatory SC as such in first, last or second last place.
6. IFCT staff team members play an essential role in clinical studies. As such, those involved in the design of the trial, its management or the drafting of the article must systematically appear in the acknowledgements or as signatories. Their names will be listed by the Director to the Coordinating Investigator. If they appear as signatories, they must not appear in the first 6 or last 2 positions. They may not exceed two if the number of signatories is above 10, 1 if it is equal to or below 10.

7. If a university statistician has collaborated in the development and processing of trial data, he/she may sign in agreement with the principal investigator (coordinator) at a position defined between them by consensus (usually 3rd or 4th position).
8. Under no circumstances shall anyone request a signature for having provided care for a patient for routine care that is not research-related.
9. all investigators (1 per IFCT research site) will be listed following each article in a table that may also include anatomopathologist, surgeon, radiotherapist from the site depending on the article, so that this citation induces a Medline occurrence.
10. For ancillary studies (biological, radiological or other), in the case of an article or abstract with a maximum of 10 signatures, the principal investigator (coordinator) of the biological study has the choice between the first and the last place. In both cases, he or she must have been extensively involved in the design of the trial, its funding, inclusions and drafting of the article. The above rules apply for the last place if he or she chooses the first place. The second-to-last place may be reserved for the head of the research laboratory that made the most decisive contribution to the study. The third-to-last place may be reserved for the Principal Investigator (coordinator) of the clinical study if he/she is not the PI (CI) of the biological research study. The first four places may be occupied by the scientists or physicians, members or not of the IFCT, who have contributed the most to the ancillary study, including, where applicable, the university statistician upon proposal by the CI and the Board Bureau and validation by the Board. If a maximum of 10 signatories, 3 to 4 central places will be reserved for the best 3 to 4 clinicians (in the sense that they have contributed most in terms of anatomical/pathological sampling). In the case of articles with 20 signatures, 2 to 3 places will be reserved for the pathologists who contributed most to the study (either in the collection of specimens or in the review of the IFCT Anapath Panel). All biology labs participating in the study should be represented by one signatory, the remaining signatory places should be reserved for clinicians according to the above rules, including 1 member of the IFCT permanent team who contributed most to the study (Decision of the CI + Director+ Chairperson), and the clinical study CI.
11. All articles shall be marked "...on behalf of IFCT" at the end of the list of signatories and shall include the acronym IFCT-XXYY in their title of the clinical trial from which the ancillary study was derived.
12. IFCT may need to be assisted in the formatting of an article in English, but shall under no circumstances delegate the actual writing to an agency or industry.

These rules were developed and validated by the IFCT Board of Directors in September 2010

13. A BIO-IFCT-1201 Ancillary study (Bio-MODEL)

13.1. Biological samples (tumour block)

This trial proposes a design to test 4 of the biomarkers determined on the tumour samples taken at baseline:

- biomarkers of sensitivity or resistance to the platinum salt used in the induction phase doublet (MSH2, BRCA1),
- biomarkers of sensitivity or resistance to compounds used during the RRM1 maintenance phase for gemcitabine (M1 subunit of ribonucleotide reductase), TS (thymidylate synthetase) and folate carriers for pemetrexed,
- biomarker of sensitivity or general resistance to chemotherapy (or poor prognosis: K-Ras mutation,
- biomarkers of poor prognosis and sensitivity or resistance to paclitaxel used in induction: RASSF1A methylation.

A collection of paraffin-embedded tumour blocks will be performed on all patients enrolled in the clinical study. For each patient, the minimum requirement is to obtain 5 white slides (4 antibody labels + 1 in case of failure) centralised with the adjacent locally produced HES slides.

The detection of K-Ras mutations tumour biopsy is now routinely performed by molecular genetic platforms. In order not to carry out this analysis in duplicate, the case report form includes an item to specify the result obtained from the platform. Any remaining residue at the platform level will be collected by IFCT for the centralised search for RASSF1A methylation by MS-PCR, and the unused DNA will then be returned to the platform.

13.2. Statistics

13.2.1. Statistical power consideration

Statistical power considerations were made for a univariate logistic regression modelling the probability of death at 1 or 2 years based on a dichotomised biomarker score.

It is assumed that biomarker results will be collected for 80% of the patients enrolled, i.e. 437 patients.

The following assumptions are based on the results of IFCT-0002 trial: Randomized trial comparing two preoperative chemotherapy regimens in clinical Stage I and II NSCLC. Since patients aged 70 and older in this trial represent only 15%, the results are based on the entire biological sample.

For the RRM1 biomarker, it is assumed that the proportion of patients who will die within one year of starting treatment will be 12%.

- RMM1 biomarker:

  Proportion of patients who will have negative RRM1 labelling (first quartile threshold Q1, <Q1): 23%

  Proportion of patients who will die within the year knowing that they will have a negative RRM1 label: 19%

  Under these assumptions, this would correspond to an Odds Ratio of 2.1, 95% CI [1.2; 3.9].

  For the MSH2 and BRCA1 biomarkers, it is assumed that the proportion of patients who will die within two years of starting treatment will be 26%.

- for the MSH2 biomarker, the parameters are as follows:

  Proportion of patients who will have a positive biomarker value (median threshold Q2, ≥Q2): 53%

  Proportion of patients who will die within 2 years knowing they will have a positive biomarker: 30%

  Under these assumptions, this would correspond to an Odds Ratio of 1.6, 95% CI [1.0; 2.4].

- for the BRCA1 biomarker, the parameters are as follows:

  Proportion of patients who will have a negative biomarker value (median threshold Q2, <Q2): 42%

  Proportion of patients who will die within 2 years knowing they will have a negative biomarker: 33%

  Under these assumptions, this would correspond to an Odds Ratio of 1.9, 95% CI [1.2; 2.9].

For TS markers whose positivity threshold appears to be more variable and random in comparison with past studies, such as RASSF1A methylation (positive in 21% of patients with early stage NSCLC (35)) whose study will depend on the availability of unused DNA on genetic platforms and whose size cannot therefore be predicted with reliability (possibly less than 50% of the initial size), the study will be purely exploratory and will not allow for the development of power assumptions *a priori*.

13.2.2. Statistical analysis plan

The main objective of the ancillary study is to assess the prognostic value of biological markers using Cox's survival model, adjusted to the clinical and biological factors of the trial.

The secondary objective is to evaluate the predictivity of these markers: RRM1 versus gemcitabine, TS versus pemetrexed, and the remaining markers versus one of the two treatments.

Descriptive analysis

Biological markers will be analysed in a quantitative and qualitative manner (dichotomisation according to a threshold defined by past studies).

Their association with clinical and biological factors will be assessed using Chi2 and ANOVA tests, or using the Fisher and Mann-Whitney non-parametric tests if necessary.

Prognostic analysis of response and survival

The prognostic value of biological markers will be evaluated using a logistic model and a Cox model.

The markers will be analysed continuously and discretely.

As a second step, clinical factors associated with response and overall survival will be identified, using univariate logistic and Cox models, significant variables at $p<0.2$ will be entered in multivariate models to which a variable selection procedure will be applied.

Markers with a p of less than 0.2 will be entered into the clinical model to determine an optimal model.

Validation study

In order to confirm the prognostic role of the biological markers identified in this trial, a validation study will be carried out using a bootstrap method.

Predictive analysis of response and survival

The predictivity of biological markers will be evaluated using an interaction test between each marker and treatment in both the logistic and Cox models.

The markers will be analysed continuously and discretely.

The following strategy will limit the number of analyses:

The predictive value of the markers will be tested in a logistic and Cox model each containing the treatment, the marker and the treatment* marker interaction term.

The second step will be to identify the clinical factors associated with response and overall survival. To do this, univariate logistic and Cox models will be performed and the significant variables at $p<0.2$ will be entered in the multivariate models to which a variable selection procedure will be applied.

Finally, markers for which the p of the interaction term is less than 0.2 will be entered into the clinical model to determine an optimal model.

14. References

1. HCL/InVS/INCa/Francim/Inserm. Projection de l'incidence et de la mortalité par cancer en France en 2011

2. Jennens RR, Giles GG, Fox RM. Increasing underrepresentation of elderly patients with advanced colorectal or non-small-cell lung cancer in chemotherapy trials. Intern Med J. 2006 avr;36(4):216-20.

3. Blanchard EM, Arnaoutakis K, Hesketh PJ. Lung cancer in octogenarians. J Thorac Oncol. 2010 juin;5(6):909-16.

4. Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. J. Clin. Oncol. 2010 mai 1;28(13):2191-7.

5. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J. Natl. Cancer Inst. 1999 janv 6;91(1):66-72.

6. Gridelli C, Perrone F, Gallo C, Cigolari S, Rossi A, Piantedosi F, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J. Natl. Cancer Inst. 2003 mars 5;95(5):362-72.

7. Lilenbaum RC, Herndon JE 2nd, List MA, Desch C, Watson DM, Miller AA, et al. Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: the cancer and leukemia group B (study 9730). J. Clin. Oncol. 2005 janv 1;23(1):190-6.

8. Ansari RH, Socinski MA, Edelman MJ, Belani CP, Gonin R, Catalano RB, et al. A retrospective analysis of outcomes by age in a three-arm phase III trial of gemcitabine in combination with carboplatin or paclitaxel vs. paclitaxel plus carboplatin for advanced non-small cell lung cancer. Crit. Rev. Oncol. Hematol. 2011 mai;78(2):162-71.

9. Wheatley-Price P, Ding K, Seymour L, Clark GM, Shepherd FA. Erlotinib for advanced non-small-cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J. Clin. Oncol. 2008 mai 10;26(14):2350-7.

10. Quoix E, Monnet I, Scheid P, Hamadouche A, Chouaid C, Massard G, et al. [Management and outcome of French elderly patients with lung cancer: an IFCT survey]. Rev Mal Respir. 2010 mai;27(5):421-30.

11. Pallis AG, Gridelli C, van Meerbeeck JP, Greillier L, Wedding U, Lacombe D, et al. EORTC Elderly Task Force and Lung Cancer Group and International Society for Geriatric Oncology (SIOG) experts' opinion for the treatment of non-small-cell lung cancer in an elderly population. Ann. Oncol. 2010 avr;21(4):692-706.

12. Belani CP, Fossella F. Elderly subgroup analysis of a randomized phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for first-line treatment of advanced nonsmall cell lung carcinoma (TAX 326). Cancer. 2005 déc 15;104(12):2766-74.

13. Pujol J-L, Milleron B, Molinier O, Quoix E, Depierre A, Breton J-L, et al. Weekly paclitaxel combined with monthly carboplatin in elderly patients with advanced non-small cell lung cancer: a multicenter phase II study. J Thorac Oncol. 2006 mai;1(4):328-34.

14. Quoix E, Zalcman G, Oster J-P, Westeel V, Pichon E, Lavolé A, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet. 2011 sept 17;378(9796):1079-88.

15. Ganti AK, deShazo M, Weir AB 3rd, Hurria A. Treatment of non-small cell lung cancer in the older patient. J Natl Compr Canc Netw. 2012 févr;10(2):230-9.

16. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N. Engl. J. Med. 2005 juill 14;353(2):123-32.

17. Azzoli CG, Baker S Jr, Temin S, Pao W, Aliff T, Brahmer J, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J. Clin. Oncol. 2009 déc 20;27(36):6251-66.

18. Gerber DE, Rasco DW, Le P, Yan J, Dowell JE, Xie Y. Predictors and impact of second-line chemotherapy for advanced non-small cell lung cancer in the United States: real-world considerations for maintenance therapy. J Thorac Oncol. 2011 févr;6(2):365-71.

19. Stinchcombe TE, Socinski MA. Maintenance therapy in advanced non-small cell lung cancer: current status and future implications. J Thorac Oncol. 2011 janv;6(1):174-82.

20. Pérol M, Arpin D. [Maintenance therapy in advanced non-small cell lung cancer: A new paradigm?]. Presse Med. 2011 avr;40(4 Pt 1):404-14.

21. Fidias P, Novello S. Strategies for prolonged therapy in patients with advanced non-small-cell lung cancer. J. Clin. Oncol. 2010 déc 1;28(34):5116-23.

22. Socinski MA. Re-evaluating duration of therapy in advanced non-small-cell lung cancer: is it really duration or is it more about timing and exposure? J. Clin. Oncol. 2009 juill 10;27(20):3268-70.

23. Coudert B, Ciuleanu T, Park K, Wu Y-L, Giaccone G, Brugger W, et al. Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. Ann. Oncol. 2012 févr;23(2):388-94.

24. Brodowicz T, Krzakowski M, Zwitter M, Tzekova V, Ramlau R, Ghilezan N, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer. 2006 mai;52(2):155-63.

25. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol J-L, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012 mars;13(3):247-55.

26. Westeel V, Quoix E, Moro-Sibilot D, Mercier M, Breton J-L, Debieuvre D, et al. Randomized study of maintenance vinorelbine in responders with advanced non-small-cell lung cancer. J. Natl. Cancer Inst. 2005 avr 6;97(7):499-506.

27. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet. 2009 oct 24;374(9699):1432-40.

28. Zhang X, Zang J, Xu J, Bai C, Qin Y, Liu K, et al. Maintenance therapy with continuous or switch strategy in advanced non-small cell lung cancer: a systematic review and meta-analysis. Chest. 2011 juill;140(1):117-26.

29. Azzoli CG, Temin S, Aliff T, Baker S Jr, Brahmer J, Johnson DH, et al. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J. Clin. Oncol. 2011 oct 1;29(28):3825-31.

30. Perol, M, Chouaid C, Milleron BJ. Maintenance with either gemcitabiene or erlotinib versus observation with predefined second-line tretament after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC : IFCT-GFPC 0502 phase III study. J Clin Oncol. 28(Suppl 15):540S.

31. Belani CP, Waterhouse DM, Ghazal H, Ramalingam S, Bordoni R, Greenberg R et al. Phase III study of maintenance gemcitabine and best supportive care versus best supportive care following standard combination therapy with gemcitabine-carboplatin for patients with advanced non-small cell lung cancer. J Clin Oncol. 28(18S):A7506.

32. Weiss GJ, Langer C, Rosell R, Hanna N, Shepherd F, Einhorn LH, et al. Elderly patients benefit from second-line cytotoxic chemotherapy: a subset analysis of a randomized phase III trial of pemetrexed compared with docetaxel in patients with previously treated advanced non-small-cell lung cancer. J. Clin. Oncol. 2006 sept 20;24(27):4405-11.

33. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J. Clin. Oncol. 2004 mai 1;22(9):1589-97.

34. Frasci G, Comella P, D'Aiuto G, Budillon A, Barbarulo D, Thomas R, et al. Weekly paclitaxel-cisplatin administration with G-CSF support in advanced breast cancer. A phase II study. Breast Cancer Res. Treat. 1998 mai;49(1):13-26.

35. De Fraipont F, Levallet G, Creveuil C, Bergot E, Beau-Faller M, Mounawar M, et al. An apoptosis methylation prognostic signature for early lung cancer in the IFCT-0002 trial. Clin. Cancer Res. 2012; 18(10): 2976-86.