1. RESUME DE LA RECHERCHE

PROMOTEUR	GFPC (groupe français de pneumo-cancérologie)
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TITLE	Multicentric, retrospective study evaluating the epidemiologic characteristics and outcomes of patients aged 80 years old or older with non-small cell lung cancer harboring EGFR mutations treated by EGFR-TKI.
JUSTIFICATION / CONTEXTE	Epidemiology of non-small cell lung cancer (NSCLC) : Lung cancer is the most common cancer worldwide and the leading cause of cancer death in Western countries (1). NSCLC is the most common form (80-85% of lung cancers). Unfortunately, at the time of diagnosis, most patients present with metastatic or advanced disease. The improvement in life expectancy of the general population, associated with higher risk of developing cancer with age has led to an increased incidence of lung cancer in the older population. About 50% of new cases of NSCLC are diagnosed in patients over 65 years and 30 to 40% in patients over 70 years (2). This situation is likely to continue or even increase. Data on patients aged 80 and over are still limited in number. The latest recommendations from ESMO (3) for the treatment of elderly subjects with advanced NSCLC(4) are in favor of the use of a carboplatin based-doublet for fit elderly patients. For less fit subjects, the use of a monochemotherapy (VINORELBINE, GEMCITABINE, or TAXANE) (5, 6, 7) are a valid option. Very limited data are available for patients older than 80 years, that's why no firm recommendations can be used for this group of patients. The use of EGFR – TKI : ERLOTINIB is the first EGFR - TKI to have obtained its registration in advanced stage NSCLC after failure of first-line chemotherapy with platinum in an unselected population. The BR21 study (8) has shown that the use of ERLOTINIB whatever age <or at least 70 years after failure of first-or second-line treatment, bringing a significant overall survival benefit, progression-free survival and quality of life compared to placebo. However, older patients developed more grade 3-5 toxic effects (35% for patients ≥70 years versus 18% for patients <70 years, p <0.001). Highlighting EGFR mutations that confer sensitivity to EGFR TKI therapy : In this unselected population, a subpopulation of patients presented

impressive and rapid responses to EGFR - TKI. These patients were mainly of Asian origin, had adenocarcinoma, were more frequently women and formers or non-smokers.
In 2004, Lynch and coll demonstrated that EGFR mutations were predictors to response to EGFR TKI (9).
IPASS study (10) enrolled an Asian population enriched with patients harboring EGFR mutations and compared a treatment by GEFITINIB (EGFR - TKI) to a standard chemotherapy by CARBOPLATINE - PACLITAXEL. The study met its primary endpoint by demonstrating a significant improvement in PFS in favor to the GEFITINIB arm.
Many other studies (10, 11, 12, 13, 14, 15, 16: Table 1) have shown that EGFR - TKI was superior to a carboplatin based-doublet in terms of PFS in patients with advanced NSCLC harboring an activating EGFR mutation in first line setting.
Tableau 1

phase III trials	Number of patients harboring EGFR mutations	HR PFS EGFR-TKI /CT	CI 95% p	Median age	Limits of age
I PASS (gefitinb /carbo-taxol) [10]	N=261	0,48	0,36-0,64 p<0,001	57	24-84
First signal (gefitinib/cis-gem) [11]	N=96	0,377	0,21-0,674 p=0,001	57	32-74
Maemondo (gefitinib/carbo-taxol) [12]	N=230	0,3	0,22-0,41 p<0,001	63,9	43-75
OPTIMAL (erlotinib/carbo-gem) [13]	N=165	0,16	0,1-0,26 p<0,0001	57	31-74 (23%> 65 ans)
EURTAC (erlotinib/cis-doc ou cis-gem)[14]	N=174	O,37	0,25-0,54 p<0,001	65	24-82
LUX LUNG 3 (afatinib /cis-pemertrexed)[15]	N=230	0,58	0,43-0,78 p=0,01	61,5	28-86
LUX LUNG 6 (afatinib/cis-gem) 16	N=346	0,28	0,20–0,39 p<0,0001	58	49–65

According to these results: GEFITINIB, ERLOTINIB and more recently AFATINIB obtained their registration for the treatment of patients with advanced NSCLC harboring an activating EGFR mutation in first line setting.

<u>Few data are available in subjects 80 years and older :</u>
However, these studies included very few elderly patients. The age limit for inclusion was 75 years for some studies (Maemondo (12) and Zhou (13)), 65 years for Lux Lung 6 (16). The median age was 65 years for EURTAC (14). These activating mutations are a powerful predictor of response which is often intense and fast (ORR 58% (14) 73.7% (13)) to EGFR – TKIs. Moreover their safety

	profile is favorable even if some differences exist between the three compounds. Inoue and al (17) demonstrated that elderly patients or with poor performance status with advanced NSCLC harboring EGFR mutation, can impressively benefit from EGFR-TKI. These patients who were considered ineligible to chemotherapy because of their age or because of PS 3 or 4 may thus regain a PS 0 or 1 and even become eligible for part of them to a second line chemotherapy treatment beyond progressive disease. Maemondo (18) reported, in a prospective study, 31 cases of elderly Asian patients 75 years and older (median age 80.3 years (75-89 years) with advanced NSCLC with activating mutations of EGFR treated in first line by GEFITINIB. The overall response rate was 75%, median PFS was 12.3 months and the rate of toxic effects is considered acceptable. Another Asian study published in January 2013 (18) retrospectively analyzed the efficacy and safety of GEFITINIB in 55 patients aged 75 years and older (median age 81.1 years (75-94 years). The overall disease control rate was 72.7%, the PFS and OS were 13.8 and 29.1 months respectively. Tolerance also appears satisfactory. <u>Data concerning patients older than 80 years are quantitatively very limited and concern almost exclusively an asian population.</u> In addition, old age often hinders the realization of diagnostic investigations and prescription of specific treatments for fear of doctors, patients and / or caregivers of excess toxicity and efficiency often considered insufficient. The results of retrospective data from the current practice regarding this particular population of patients 80 years and older with NSCLC harboring activating EGFR mutation could lead to better identify their epidemiological profile, the benefits that could provide EGFR – TKIs in terms of survival, their toxicity profiles and modify in some cases diagnostic and therapeutic practices.
OBJECTIVES	• **Primary** : Better knowledge of the clinical characteristics, socio-demographic characteristics of patients with NSCLC harboring activating EGFR mutations and their evolution under treatment with EGFR-TKI • **secondary** :

	- Analyze treatment modalities: molecules used, dose, duration of treatment, dose adaptations. - Analysis of best response according to RECIST 1.1 criteria (17) - Toxicities reported with treatment Subsequent treatment Overall survival Progression-free survival
DIAGRAM OF RESEARCH	Observational retrospective multicenter study
INCLUSION CRITERIA	NSCLC patients with activating EGFR mutations aged 80 or over
EXCLUISION CRITERIA	Patients with small cell lung cancer No EGFR activating mutation
treatment / strategies / procedures research	Recording on a crf data:: - Socio-demographic information, PS, regular ongoing treatments - Characteristics of NSCLC - Histology, technique for obtaining - Type EGFR mutation - detection technique - TNM - Number of metastases at diagnosis and localization - geriatric assessment - first-line treatment - Treatment at progression - Response to treatment with EGFR TKI by RECIST 1.1 [19] - Progression-free survival - Overall survival - Toxicities on treatment - Adjustments treatment - treatment after disease progression under EGFR TKI
END POINTS	• **Primary end point** Analysis of the characteristics of the population of NSCLC patients with activating EGFR mutation: socio-demographic, tumor, risk factors data, Progression-free survival, survival Overall, treatment toxicity
STUDY SIZE	100 patients

NUMBER OF CENTERS	30
TIME OF RESEARCH	*12 months*
STATISTICAL ANALYSIS	Qualitative data will be described by their frequency, percentage and confidence interval of 95%. Quantitative data will be described by their mean and standard deviation or median and interquartile range. For quantitative variables, means and standard deviations are presented, comparisons will be made using an analysis of variance or comparison of average: Student t test or U-test and Mann Whitney , depending on the variables studied. For qualitative variables, the sizes and the percentages will be mentionned and comparisons will used Chi-2 test or exact Fischer's test. The number of missing data is presented. - Analysis of overall survival and progression-free survival will be conducted using the Kaplan-Meier method. The base time will be the time between the start date of the first-line treatment and the date of the event (progression or death) for PFS and OS.
EXPECTED ADVANCES	Improved knowledge of the clinical characteristics, tumor, response and tolerance to EGFR-TKI's of patients 80 years or more with advanced NSCLC harboring activating EGFR mutation. Enable the access of elderly patients to EGFR-TKI's in accordance to their registration in first line setting.

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