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BACKGROUND

30–40% of advanced NSCLC patients are over 70 years old at diagnosis. In 2014, the EORTC recommends the use of carboplatin-based doublets in fit elderly patients. For less fit patients, single-agent treatment represents a valid option and no specific recommendations can be made for octogenarians. Unfortunately no clear definition of fit, or less fit patients exists. Comprehensive geriatric assessment (CGA) is a multidisciplinary and global approach exploring different aspects of the elderly population, including functional status, cognitive abilities, emotional conditions, comorbid conditions, nutritional status, polypharmacy, social and environmental situation, and potential geriatric syndrome. CGA can predict morbidity and mortality in elderly patients with cancer and can be useful to adapt the cancer treatment to their frailty. CGA's use is recommended by the International Society of Geriatric Oncology (SIOG) task force, the National Comprehensive Network (NCCN) and the EORTC. However to date, firm recommendations for implementing geriatric assessment and the type of geriatric assessment in routine clinical practice await additional studies in more homogeneous and larger population of patients because the effectiveness of geriatric assessment in improving patient outcomes remains unclear. The main objective of this study was to show that, compared to a standard strategy based on PS and age, the use of a CGA can improve the management of elderly patients with advanced NSCLC in first line.

METHODS

Randomized, multicentric, prospective phase III study

Arm A chemotherapy allocation based on PS and age

Arm B treatment allocation based on CGA (details are given in table 1).

Eligibility criteria : age ≥70 years, histologically or cytologically documented stage IV NSCLC with measurable disease according to RECIST 1.0, ECOG PS 0-2. Adequate haematological, renal, hepatic functions and a life expectancy of at least 12 weeks were required.

Exclusion criteria : severe concurrent disorders during the prior six months before enrollment, active malignancy within the past 5 years, any previous chemotherapy grade ≥2 neuropathy, presence of symptomatic brain metastases.

Patients were randomly assigned in a 1:1 ratio to arm A and B and stratified by center. Details are given study design (figure 1).

Four cycles of chemotherapy were to be given every three weeks. The primary endpoint was Time to Failure Free Survival (TFFS), secondary endpoints were Overall Survival (OS), Overall Response Rate (ORR), toxicity, QoL and life expectancy adjusted on QoL.

QoL was assessed during treatment by EQ-5D health questionnaire at baseline, week 6, 12, 20, 28, 36. Taking into account the longitudinal nature of the data, a mixed-effects model was used, to compare the utility score and therefore the quality of life between arms A and B.

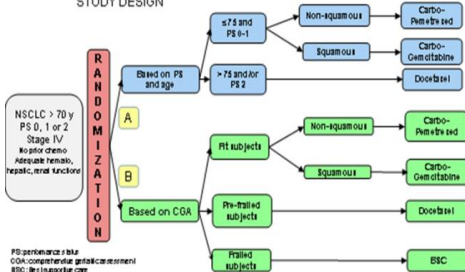
Planned sample size : 490 patients for an expected hazard ratio of 1.30, a power of 80%, a two-sided overall type I error of 5%, assuming 5% of dropout patients

Table 1: Definition of the 3 groups of patient according to CGA in arm B

GERIATRIC PARAMETERS	Fit Katz index = 1	Pre-frail Katz index = 2	Frail Katz index = 3
Activities of daily living (ADL) (8-14)	14	12	10
Instrumental ADL (IADL) (8-14)	14	12	10
Weighted Lyden's scale	0	1	2
Cognitive function (Schulz-Lewis mini-MMS (0-12) Patients < 65 years old (0-12))	10	12	12
Repetitive falls	No	No	Yes
Urinary or fecal incontinence	No	No	Yes
Charlson's comorbidity index score	low	Moderate	Severe
Geriatric Depression Scale G-15 (0-15)	0-5	6-9	10-15

Figure 1

STUDY DESIGN



RESULTS

PATIENTS AND DISEASE CHARACTERISTICS

Between Jan 2010 and Jan 2013, 494 patients were enrolled onto 45 centers in France and Spain, 251 in arm A, 243 in arm B. Table 2

GENERAL CHARACTERISTICS	ARM A (PS, Age) N=251	ARM B (CGA) N=243	P
Median age	76 [70-91]	77 [70-87]	0.19
Gender : male	74.5%	74.0%	0.91
Histology			
Non-squamous	72.9%	71.2%	0.67
Squamous	27.1%	28.8%	
Never smokers	20.8%	19.6%	0.94
ECOG PS 0-1/2	100/119/1%	81/5/18.5%	0.86
GERIATRIC CHARACTERISTICS			
MMSE score ≥25	16.3%	14.4%	0.55
ADL score ≥55	82.1/17.9%	89.3/10.7%	0.02
IADL score 0/1/2	71/7/16.3/12.0%	71/2/20.8/6.4%	0.31
Charlson 0/1/2	38/7/37/23.5%	48/6/27/2/24.2%	0.03
GDS 0-1/2-3/4-5	85/6/12/8/1.6%	83/5/12/0/4.5%	0.16
BMI ≥20	17.5%	14.3%	0.37

TREATMENTS ADMINISTRED by arm Table 3

Allocation of treatments	Global population (%) N=494	Arm A (%) N=251	Arm B (%) N=243
Carboplatin based-doublet	40.3	35.0	45.7
Carboplatine/Pemetrexed	30.2	25.9	34.6
Carboplatine/Gemcitabine	10.1	9.1	11.1
Docetaxel	48.4	65.0	31.3
BSC	11.3	0	23.0

KAPLAN-MEYER CURVES

Figure 2: TFFS

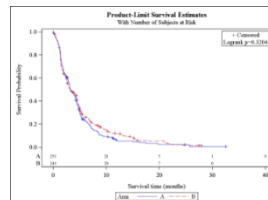


Figure 3: OS

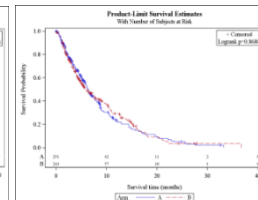


Table 4: mOS by arm and by type of treatment

	Arm A (PS, age) n=251	Arm B (CGA) n=243
Carboplatin based doublet n=88 (35%)	Doc n=163 (85%)	Doc n=111 (46%)
Carboplatin based doublet n=111 (46%)	BSC n=76 (31%)	BSC n=56 (23%)
mOS (months)	8.6	5.7
	10.0	4.9
	2.8	

Table 5:

CAUSES OF TREATMENT FAILURES	Arm A (PS, Age) n=251	Arm B (CGA) n=243	P
Progression	65.8%	69.3	0.15
Toxicity	13.8	4.8	0.006
Withdrawal of consent	3.8	3.3	0.67
Death	13.1	14.0	0.76
Investigator's decision	4.2	5.7	0.46
Intercurrent disease	0.8	1.3	0.68
missing	14	15	

TOXICITIES

	Arm A (PS, Age) N=251	Arm B (CGA) N=243	P
All grades AE	232 (92.4%)	208 (85.6%)	0.015
AE grade ≥3	179 (71.3%)	165 (67.9%)	0.409
Grade 3-4 hematological AE			
Neutropenia	28 (11.1%)	14 (5.8%)	0.386
Fatigue	14 (5.6%)	10 (4.1%)	0.141
Anemia	28 (11.2%)	10 (4.1%)	0.882
Thrombopenia	9 (3.6%)	7 (2.9%)	0.509

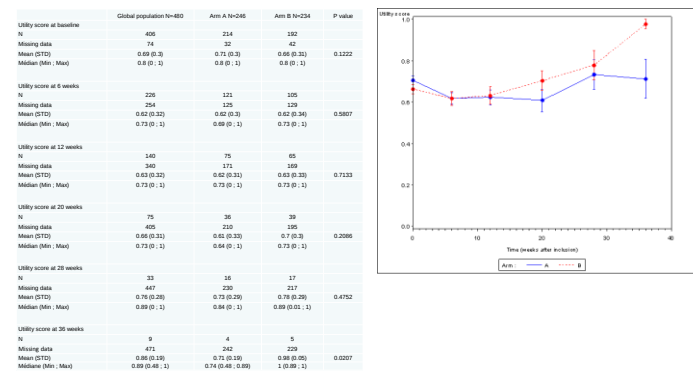
QUALITY OF LIFE - COMPLIANCE TO EQ-5D QUESTIONNAIRES Table 7

	Arm A	Arm B
	Patients drop out	Patients in the study
Time of assessments	Total	Missing questionnaires
Baseline	0	251
6 weeks	47	204
12 weeks	106	145
20 weeks	141	110
28 weeks	170	81

UTILITY SCORE

Utility score quantifies the quality of life associated to a health status. That score varies from 0 (death) to 1 (full health) and was calculated according to EQ-5D. An utility score was measured for each patient at each time an EQ5D questionnaire was performed.

Comparison by arm of the utility scores according to non parametric Wilcoxon Mann-Whitney test
Table 8: Figure 4: Evolution of utility score over time



Except at baseline, the utility score at each evaluation was always superior in arm B (CGA) than in arm A (standard), but the difference was significantly different only at week 36 (p=0.02). Using a linear mixed generalized model, the utility score tended to decrease over time and was not significantly different between the two arms (p=0.8558).

LIFE EXPECTANCY ADJUSTED ON QoL Table 9

	Mean (days) Estimated on sample	Bias Estimated by bootstrap	Standard error Estimated by bootstrap	P value Wilcoxon Mann-Whitney test
Arm A	130.12	-0.15	13.30	0.51
Arm B	133.34	-0.05	14.45	

CONCLUSION

A strategy of treatment allocation based on CGA does not improve the TFFS nor OS of elderly patients with advanced NSCLC. This strategy is able to reduce the treatment failures due to toxicity. In experimental arm, more patients received a carboplatin-based doublet, 23% of patients were considered as frail by CGA and received an exclusive BSC management, their spontaneous mOS was very low. Despite a trend in favor of CGA arm, there is no significant difference between the two arms in terms of utility scores. Life expectancy adjusted on QoL was not different between the two arms.