A phase II study assessing the benefit of cisplatin re-introduction (stop and go strategy) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): The IFCT-1102 BUCiL study (a Better Use of Cisplatin in Lung cancer).

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ABSTRACT

Background: Pemetrexed (Pem) + Cisplatine (Cis) + Bevacizumab (Bev) followed with maintenance therapy (Bev and/or Pem) is a therapeutic standard in advanced non-squamous NSCLC.

Methods: A single arm phase II trial aimed to evaluate a stop and go strategy: Sequence 1: 3 cycles Pem 500 mg/m² + Cis 75 mg/m² + Bev 7.5 mg/kg q3 weeks, followed by maintenance Bev 7.5 mg/kg/3 week until progression ; sequence 2: reintroduction Pem + Cis + Bev, 3 cycles, Pem + Bev maintenance until progression. Primary endpoint: at least 75% of patients in the sequence 2 received the 3 cycles without cisplatin/carboplatin dose modification.

Results: from Dec. 2012 to Aug. 2014, 120 patients (77 males) were included in 14 French hospitals: PS 0 (50%); median age 60.6 y (38.0 – 77.3). Of 113 eligible patients, 65 (57.5 %) were treated in sequence 2. 37 patients (56.9%, IC95% [45.1%-73.6%]) received the 3 cycles (sequence 2) at full dose; 86 % (n = 56) with or without dose reduction. At sequence 2, specific bev-induced grade 3 – 4 toxicity was reported in 7 (10.3%) patients (1 grade 5 haemoptysis). Median follow-up was 27.1m [24.7-29.6]. Secondary objectives showed a median Progression-Free Survival 1 (PFS1) (inclusion – progression 1) 5.8 m (IC95%:5.0 – 6.3); median PFS2 (progression 1 – progression 2) 6.6 m (IC95%:5.7 – 8.4); median duration of disease control (PFS1 + PFS 2) (n = 65) 11.4 m (IC95:10.1 – 13.4). Objective response rate after sequence 2 was 15.4% (IC95%: 6.6-24.2) with 60% of stable disease. The median overall survival for eligible population was 17.7 m (IC95% 13.1 – 21.6) and 20.5 m (16.9 – NR) for patients who reached the sequence 2 (n = 65).

Conclusions: Although the stringent primary endpoint was not met, this study highlighted that a 'stop and go' strategy using a platinum-based chemotherapy with bevacizumab continuation beyond progression, compares favourably with standard schedule, deserving to be further studied in non-squamous advanced NSCLC.

Clinical trial information: NCT01705184

BACKGROUND

Pemetrexed plus cisplatin combination is now recognized as standard treatment in patients with advanced non-squamous NSCLC (Scagliotti GV et al, 2008). Moreover, adding bevacizumab increases objective response rate (ORR) and progression free survival (PFS) (Sandler A et al, 2006; Reck M et al, 2009, Soria et al, 2013).
Efficacy results observed in second line chemotherapy with pemetrexed are disappointing (Hanna N et al, 2004). In patients with advanced NSCLC and progressing after cisplatin-based chemotherapy, a randomised phase II study compared a monotherapy with pemetrexed to a combination of pemetrexed plus carboplatin (Smit EF et al, 2009). The median PFS was in favour of the carboplatin-based chemotherapy arm (4.2 months vs 2.8 months ; HR 0.65 : 0.49 – 0.85).

Based on these results, we propose to evaluate an original therapeutic schedule in non-squamous NSCLC as described in figure 1 (study design). With the BUCiL trial, our goal is to offer another therapeutic strategy for patient with advanced nonsquamous NSCLC : 3 cycles with cisplatin-based chemotherapy followed by a break (bevacizumab maintenance) and a new sequence of cisplatin-based chemotherapy at progression. By this way, the introduction of the second-line chemotherapy (defined as the use of different drugs from pemetrexed-cisplatine + bevacizumab) could be delayed.

Bevacizumab with chemotherapy in first-line non-squamous NSCLC

Study	N	Treatment	PFS	HR (PFS)	OS	HR (OS)
Sandler E4599	444	Paclitaxel + Carbo	4.5 mo.		10.3 mo.	
	434	Pacl + Carbo + Bev 15	6.2 mo.	0,66 (0.57 – 0.77)	12.3 mo.	0.79 (0.67 – 0.92)
Reck AVAiL	347	Gem + Cis + Plac	6.2 mo.	0,75 (0.64 – 0.87)	13.1 mo.	0.93 (0.78-1.11)
	345	Gem + Cis + Bev 7.5	6.8 mo.	0.85 (0.73 – 1.00)	13.6 mo.	1.03 (0.86-1.23)
	351	Gem + Cis + Bev 15	6.6 mo.		13.4 mo.	
Niho JO19907	59	Pacl + Carbo	5.9 mo.		23.4 mo.	
	121	Pacl + Carbo + Bev 15	6.9 mo.	0,61 (0.42 – 0.89)	22.8 mo.	0.99 (0.65 – 1.50)

AVAPERL : bevacizumab + pemetrexed in maintenance

n	treatment	PFS	HR (PFS)	OS	HR (OS)
Efficacy data from induction phase					
376	+ Bevacizumab maintenance + Pemetrexed + Bevacizumab maintenance	6.6 mo. 10.2 mo.	0.58 (0.45 – 0.76)	15.8 mo. 19.8 mo.	0.88 (0.64 – 1.22)
Efficacy data from maintenance phase					
125 128	+ Bevacizumab maintenance + Pemetrexed + Bevacizumab maintenance	3.7 mo. 7.4 mo.	0.57 (0.44 – 0.75)	13.2 mo. 17.1 mo.	0.87 (0.63–1.21)

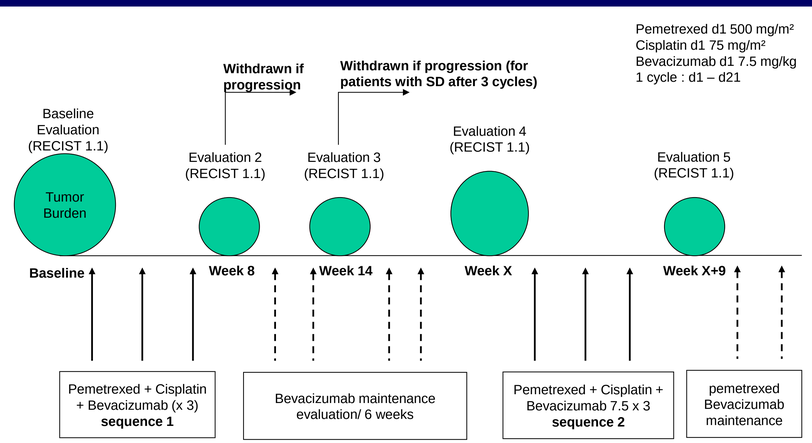
Barlesi F, et al. Ann Oncol 2014;25:1044-52.

POINTBREAK

n	treatment	PFS	HR (PFS)	OS	HR (OS)
Efficacy data for Overall population					
472 467	Pemetrexed + carboplatin + Bevacizumab Paclitaxel + Carboplatin + Bevacizumab	6.0 mo. 5.6 mo.	0.83 (0.71 – 0.96)	12.6 mo. 13.4 mo.	1.00 (0.86 – 1.16)
Efficacy data from maintenance phase					
292 298	Pemetrexed + Bevacizumab maintenance + Bevacizumab maintenance	8.6 6.9		17.7 mo. 15.7 mo.	

Patel JD, et al. J Clin Oncol 2013;31:4349-57.

STUDY DESIGN



KEY INCLUSION CRITERIA

- Histologically or cytologically documented stage IV non-squamous NSCLC, not EGFr mutated
- Measurable disease (at least one lesion) according to RECIST V1.1 (outside a previous radiation field)
- Age ≥18 years
- ECOG Performance Status : 0 or 1
- Adequate renal function: serum creatinine ≤1.25 U ; or calculated creatinine clearance ≥ 60 mL/min according to the MDRD formula; urine dipstick for proteinuria < 2+
- International Normalized Ratio (INR) ≤ 1.5 ; and activated prothrombin time (aPTT) ≤ 1.5 x ULN within 7 days prior to enrolment.
- Written informed consent

OBJECTIVES

Primary objective

Rate of patients who received 3 cycles of chemotherapy containing a platinum salt (cisplatin or carboplatin) without dose reduction during the sequence 2 with pemetrexed plus cisplatin plus bevacizumab

Secondary objectives

To assess the disease control rate (Stable disease plus OR) after the sequence 2 (reintroduction of pemetrexed and platin)
Progression Free Survival (PFS) from the sequence 1 (3 cycles with pemetrexed-cisplatin + bevacizumab) including maintenance with bevacizumab until the first progression: PFS1.
PFS from the sequence 2 (3 cycles with pemetrexed-cisplatin + bevacizumab) until the second progression: PFS2. Duration of disease control (DDC) under the first treatment line (PFS1 + PFS2)

STATISTICS

p0: proportion of patients who received 3 cycles of chemotherapy without dose reduction of cisplatin which will not be enough to justify the continuation of the study in phase III.
p1: proportion of patients who received 3 cycles of chemotherapy without dose reduction of cisplatin which will be enough to justify the continuation of the study in phase III.

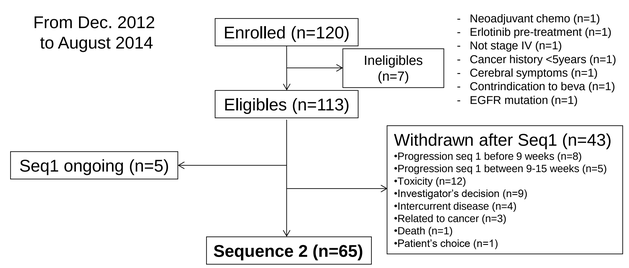
Tested hypothesis : H0 : p ≤ p0=55% versus H1 : p ≥ p1=75%

With an alpha-risk of 5% (one-sided) and a power of 95%. 59 patients should be included. By considering that 10 % of patients will not be evaluable, 65 patients will be required (for sequence 2)
→ 120 patients in total

PATIENT CHARACTERISTICS

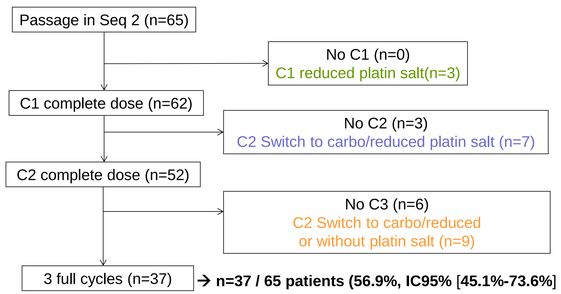
	ALL (N=120) N (%)
Sex	
Male	77 (64.2)
Female	43 (35.8)
Age	
Median	60.6
Range	[36.0-77.3]
Smoking status	
Smoker	99 (82.5)
Non Smoker	21 (17.5)
Pack-years smoked	
Median	40.0
Range	[5.0-160.0]
Performance Status	
0	60 (50.0)
1	60 (50.0)
Histology	
Adenocarcinoma	115 (95.8)
Large Cell carcinoma	5 (4.2)
Stage	
M0	1 (0.8)
M1a	39 (32.5)
M1b	80 (66.7)

FLOW-CHART



PRIMARY OBJECTIVE

« Proportion of patients receiving 3 cycles of chemotherapy without of dose reduction of cisplatin/carboplatin during of the 2nd sequence of treatment »



OVERVIEW OF TOXICITIES (sequence 2)

	ALL (N=68)
Any AE, any grade (N,%)	65 (95.6%)
Any AE, grade 3 - 4 (N,%)	36 (52.9%)
Any AE, grade 5 ‡ (N,%)	2 (2.9%)

‡ Haemoptysis, Sepsis

	Any grade (N=68)	Grade 3 - 4 (N=68)
Hematological AEs	49 (72.1%)	23 (33.8%)
Anaemia	40 (58.8%)	10 (14.7%)
Neutropenia	28 (41.2%)	16 (23.5%)
Thrombocytopenia	20 (29.4%)	9 (13.2%)
Febrile neutropenia	3 (4.4%)	3 (4.4%)

	Any grade (N=68)	Grade 3 - 4 (N=68)	Grade 5 (N=68)
Epistaxis	20 (29.4%)	0 (0%)	0 (0%)
Hypertension	16 (23.5%)	5 (7.4%)	0 (0%)
Haemoptysis	3 (4.4%)	0 (0%)	1 (1.5%)
Pulmonary embolism	1 (1.5%)	1 (1.5%)	0 (0%)
Proteinuria	7 (10.3%)	0 (0%)	0 (0%)
Other haemorrhage	4 (5.9%)	1 (1.5%)	0 (0%)

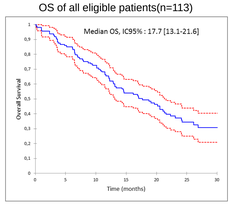
	Any grade (N=68)	Grade 3 - 4 (N=68)	Grade 5 (N=68)
Asthenia	52 (76.5%)	9 (13.2%)	0 (0%)
Nausea	37 (54.4%)	2 (2.9%)	0 (0%)
Vomiting	13 (19.1%)	2 (2.9%)	0 (0%)
Diarrhoea	12 (17.6%)	0 (0%)	0 (0%)
Constipation	11 (16.2%)	0 (0%)	0 (0%)
Stomatitis	19 (27.9%)	4 (5.9%)	0 (0%)
Renal failure	30 (44.1%)	3 (4.4%)	0 (0%)
Anorexia	21 (30.9%)	4 (5.9%)	0 (0%)
Conjunctivitis	13 (19.1%)	0 (0%)	0 (0%)
Sepsis	1 (1.5%)	0 (0%)	1 (1.5%)
Neuropathy peripheral	6 (8.8%)	0 (0%)	0 (0%)
Alopecia	4 (5.9%)	0 (0%)	0 (0%)
Hypoacusis	4 (5.9%)	0 (0%)	0 (0%)

With support of Roche France: unrestricted grant + supply of bevacizumab (Seq2)

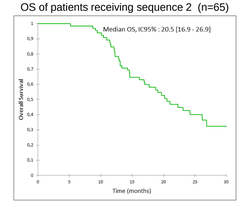
SURVIVAL

Median Follow-up : 31.6 months [29.7-NR]

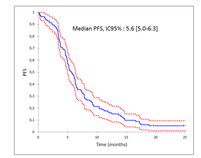
OS of all eligible patients(n=113)



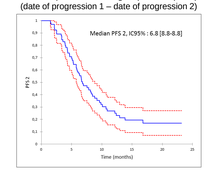
OS of patients receiving sequence 2 (n=65)



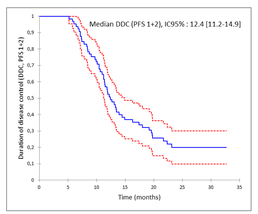
PFS of all eligible patients (n=113)
(inclusion date - date of progression 1)



PFS 2 of patients receiving sequence 2 (n=65)
(date of progression 1 – date of progression 2)



Duration of disease control (DDC : PFS1+2)
(n=65) (inclusion date - date of progression 2)



N=65	n	Response at sequence 2 (after 3 cycles) (%, IC95%)
Objective response	10	15.4 [6.6-24.2]
Stable	39	60.0 [48.1-71.9]
Disease Control	**49**	**75.4 [64.9-85.6]**
Progression	7	10.8 [3.2-18.3]
Not evaluable	9	13.8 [5.4-22.2]

CONCLUSIONS

Although the stringent primary endpoint was not met, this study highlighted that a 'stop and go' strategy using a platinum-based chemotherapy with bevacizumab continuation beyond progression, compares favourably with standard schedule, deserving to be further studied in non-squamous advanced NSCLC.

Poster online
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