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: the IFCT-1102 BUCiL study (a Better Use of Cisplatin in Lung cancer)

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ABSTRACT

Introduction This single-arm phase II trial aimed to evaluate a stop-and-go strategy with cisplatin-based chemotherapy and bevacizumab in advanced non-squamous non-small cell lung cancer (NSCLC).

Methods Patients were initially treated with three cycles of pemetrexed, cisplatin plus bevacizumab (sequence 1) followed by bevacizumab maintenance and after progression, re-introduction of three cycles of pemetrexed, cisplatin plus bevacizumab (sequence 2) and pemetrexed plus bevacizumab maintenance. The primary endpoint was the proportion of patients with advanced non-squamous NSCLC receiving the complete sequence 2 without platinum dose reduction (hypothesis ≥75%).

Results 120 patients with performance status ≤1 were included. Of 113 patients evaluable for efficacy, 65 (57.5%) entered in sequence 2 and 56 (86%) received the three planned cycles including 37 (56.9%, 95% CI 45.1 to 73.6) without platinum dose reduction. The median progression-free survival 1 (PFS1; inclusion to progression 1) was 5.6 months (95% CI 5.0 to 6.3) and median PFS2 (progression 1 to progression 2) was 6.8 months (95% CI 5.8 to 8.8). The median disease control duration (PFS1+PFS2; n=65) was 12.4 months (95% CI 11.2 to 14.9). The median overall survival was 17.7 months (95% CI 13.1 to 21.6) and 20.5 months (95% CI 16.9 to 26.9) for patients reaching the sequence 2 (n=65).

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

INTRODUCTION

Within the last years, the identification of genetic alterations in non-squamous (nsq) non-small cell lung cancer (NSCLC) has positioned this tumour pathology as a model for therapeutic innovation in oncology, and the search of actionable genomic alteration is now entered in routine practice.1 2 Taken together, epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase rearrangements are present in about 16% of cases while about half of nsqNSCLC did not exhibit any molecular alteration.1 That being said, platinum-based chemotherapy, combined or not with bevacizumab, remains a standard therapy in the management of advanced NSCLC.3–6 More recently, the anti-PD-1 antibody, pembrolizumab, has modified first-line strategy by becoming the standard for advanced NSCLC with PD-L1 expression on ≥50% of tumour cells.7 In second line, efficacy findings with pemetrexed monotherapy were disappointing in

Key questions

What is already known about this subject?
► No clinical data are available about the re-introduction of pemetrexed+cisplatin following the first progression after three cycles of the same regimen in advanced non-squamous cell lung cancer (NSCLC).

What does this study add?
► This phase II study underlines the feasibility of the stop-and-go strategy with bevacizumab continuation beyond progression.

How might this impact on clinical practice?
► The stop-and-go strategy in advanced NSCLC should be re-evaluated in the era of immunotherapy+chemotherapy combination.
patients with advanced nsqNSCLC with a median overall survival (OS) of 9.3 months and a median progression-free survival (PFS) of 3.1 months.\textsuperscript{8} One study reported that the median PFS on such patients receiving pemetrexed–carboplatin combination after disease progression following a cisplatin-based regimen had a median PFS of 4.2 months compared with 2.8 months with pemetrexed alone (p=0.005). Nevertheless, no impact on OS was observed.\textsuperscript{9} Based on these results, the BUGIL (a Better Use of Cisplatin in Lung cancer) trial was designed to evaluate a stop-and-go strategy in advanced nsqNSCLC, introducing a therapeutic break with bevacizumab maintenance after a first three-cycle-sequence platinum-based chemotherapy with pemetrexed, followed with a similar chemotherapy sequence at disease progression. Thus, such strategy will make theoretically possible to delay the introduction of the second-line chemotherapy, with satisfactory safety.

MATERIALS AND METHODS
Patients and regulatory issues
Adult patients with previously untreated documented advanced nsqNSCLC were eligible to the BUGIL study if they presented with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumours (RECIST V.1.1). Patients had to be in good health condition (Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤1) with adequate haematological, liver and renal functions. Patients should not present with EGFR mutation, symptomatic brain metastases, neither history of malignant tumours for less than 5 years except for in situ cervical tumours and basal cell carcinoma, nor common contraindication of bevacizumab in NSCLC. This study (EUDRACT 2012-002647-18) was approved by a local Ethic Committee and complied with French legislation, Good Clinical Practices and the principles outlined in the latest version of the Declaration of Helsinki.

Study design
This single-arm, multicentre, phase II clinical trial was conducted in patients with advanced nsqNSCLC who received a stop-and-go strategy (figure 1). At inclusion, patients started SEQUENCE 1 treatment with 3-week cycles of cisplatin (75 mg/m\textsuperscript{2})–pemetrexed (500 mg/m\textsuperscript{2}) chemotherapy combined with bevacizumab (7.5 mg/kg). Afterwards, non-progressing patients received bevacizumab alone (7.5 mg/kg every 3 weeks) as maintenance}

![Figure 1 Study design.](image-url)
therapy until progression or unacceptable toxicity. At disease progression, patients resumed similar platinum-based regimen (SEQUENCE 2) followed by pemetrexed–bevacizumab maintenance. Cisplatin could be switched to carboplatin according to investigator decision in case of unacceptable cisplatin toxicity.

**Assessments**

At inclusion, patient’s characteristics, CT-scan assessments, relevant medical history, concomitant treatments, disease history, EGFR status and laboratory tests to confirm selection criteria were collected. At each follow-up visit, clinical data, disease evolution, regimens of bevacizumab and chemotherapy, and other concomitant treatments were reported. At each cycle, clinical examination and all the laboratory tests were performed, including haematological, liver and renal function tests. Adverse events (AEs) were reported including AEs of special interest for bevacizumab (hypertension, pulmonary embolism, proteinuria, haemorrhages). AE severity was assessed using WHO Handbook for Reporting Results of Cancer Treatment 4-grade classification. CT-scan assessments were performed at the end of the induction chemotherapy (three cycles) and every two cycles during maintenance treatments using RECIST V.1.1.

**Statistical methods**

Using a single-step Fleming method, a sample size of 59 assessable patients was required to make possible to estimate with an alpha risk of 5% (one-sided) and a power of 95% the proportion of those receiving three cycles of chemotherapy without dose reduction of platinum-based chemotherapy during SEQUENCE 2 (null hypothesis H0: p≤p0=55%; alternative hypothesis H1: p≥p1=75%). Assuming that 10% of patients may not be assessable and 55% of patients were expected to enter SEQUENCE 2, a total of 118 patients had to be enrolled in the study.

Patient and disease characteristics were analysed for all the included patients. The primary efficacy criterion was the percentage of eligible patients who received the three-cycle SEQUENCE 2 chemotherapy without platinum dose reduction or switch to carboplatin after the first disease.

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**Figure 2**  Study flowchart. EGFR, epidermal growth factor receptor. C, cycle.
progression. OS was defined as the time between patient’s inclusion and the death from any cause. PFS1 was defined as the time from inclusion to the first disease progression (as assessed by the investigator, using RECIST V.1.1) or death from any cause, whatever came first. The time taken into account for PFS2 was between first and second disease progressions or death. Disease control duration (DDC) was the sum of PFS1 and PFS2. Median OS, PFS and DDC were estimated using the Kaplan-Meier method with associated 95% CI.

Safety data were analysed all over the study period in included patients, with a focus on study treatment-related AEs and AEs of special interest related to bevacizumab.

Statistical analyses were performed using SAS software V.9.3 (SAS Institute, Cary, North Carolina, USA), and two-sided tests with type I error \( \alpha = 0.05 \) were applied for all analyses.

**RESULTS**

**Patients’ disposal and characteristics**

From December 2012 to August 2014, 14 hospital centres from the French Cooperative Thoracic Intergroup included 120 patients. Among these patients, 113 were evaluable for efficacy at SEQUENCE 1 and 65 of them for SEQUENCE 2 (figure 2). Otherwise, the safety analysis was initially performed for 118 patients because two patients were never treated in the protocol (one contraindication to bevacizumab and one rapid progression disease). For the SEQUENCE 2, 68 patients were considered for safety. Most of the patients were men (64%), less than 70 years old (88%) at inclusion, current smokers (83%), with adenocarcinoma without bronchioloalveolar component (94%) and metastasis (99%) (table 1). ECOG-PS was scored ‘1’ for half of them.

**Efficacy results**

Out of the 65 patients entered in the SEQUENCE 2, 37 patients (56.9%; 95% CI 45.1 to 73.6) received all the three cycles of chemotherapy without dose reduction of cisplatin or switch for carboplatin (primary criterion, figure 3). Otherwise, for 16 patients, cisplatin has been switched for carboplatin during SEQUENCE 2, and 56 patients (86%) completed this sequence disregarding platinum-salt dose reduction or not. Overall, 47 patients received pemetrexed plus bevacizumab in maintenance therapy after sequence 2.

At the time of analysis, five patients (4%) were still treated in SEQUENCE 1 bevacizumab maintenance at the end of the study. After a median follow-up of 31.6 months (95% CI 29.7 to not reached), the median PFS1 (defined as the time from inclusion to the first disease progression or death) was 5.6 months (95% CI 5.0 to 6.3) in the 113 eligible patients. The median PFS2 (defined as the time from first to second disease progression or death) was 6.8 months (95% CI 5.8 to 8.8) for the 65 eligible patients entered in SEQUENCE 2. The median DDC (PFS1+PFS2) was 12.4 months (95% CI 11.2 to 14.9). After SEQUENCE 2, 75.4% of the patients (49/65) reached a disease control with 10 of these 65 patients having reached RECIST objective response (15.4%; 95% CI 6.6 to 24.2).

From inclusion, the median OS was 17.7 months (95% CI 13.1 to 21.6) in the 113 patients evaluable for efficacy (figure 4). For the 65 patients eligible for SEQUENCE 2, it was 20.5 months (95% CI 16.9 to 26.9) and 14.1 months (95% CI 11.6 to 20.0) from the introduction of the SEQUENCE 2 (at first disease progression).

**Safety results**

Over the study period, at least one chemotherapy-related or bevacizumab-related AE was reported in 100% of the patients of the safety population (n=118) and at least one grade ≥3 AE related to study treatments was reported in 50 patients (42.4%).

At least one study treatment-related AE was reported in 66 patients (97.1%) of SEQUENCE 2 safety population (n=68), and at least one grade ≥3 AE related to study treatments was reported in 41 patients (60.3%) (table 2). Two patients (2.9%) had at least one fatal study treatment-related AE (one haemoptysis and one sepsis). Thus, 33.8% of the 68 patients experienced at least one grade ≥3 study treatment-related haematological AE (mainly neutropenia, 26.5% of the patients) and 11.8% at least one grade ≥3 AE.
of special interest related to bevacizumab (mainly hypertension, 7.4% of the patients).

DISCUSSION
The identification of actionable genomic alterations has entered in routine practice to select the appropriate patients for target therapy. Similarly, immune checkpoint inhibitors, promoting the restoration of host immunity against tumours, are making possible a durable response for patients in several cancers. Thus, more predictive biomarkers for immunotherapy response will be integrated in the guide therapeutic decision-making, as many patients respond to such treatment. However, for patients not eligible for tailored treatment, platinum-based chemotherapy, combined or not with bevacizumab, remains a major issue in advanced NSCLC as established in several experimental and real-life studies.

Figure 3 Proportion of patients receiving three cycles of chemotherapy without dose reduction of cisplatin or switch to carboplatin during the second sequence of chemotherapy (primary criterion). C, cycle; EGFR, epidermal growth factor receptor.

Figure 4 Overall survival (OS) from patient inclusion—eligible population (n=113).
To improve outcome in such patients, new schedules may be explored. Recently, in metastatic colorectal cancer, a stop-and-go strategy with oxaliplatin-based chemotherapy showed limited toxicity without any pejorative impact on efficacy.21–23 On the basis of these positive findings, the aim of our study was to demonstrate the relevance of a stop-and-go strategy in patients with non-squamous advanced NSCLC with ECOG-PS ≤1, by assessing the feasibility of platinum-salt re-introduction after disease progression following bevacizumab maintenance, with a shortened first chemotherapy period (three cycles instead of four to six as usually recommended).24–26 The primary endpoint was not met: 56.9% (95% CI 45.1% to 73.6%) of the 65 patients entered in the second sequence received the three full cycles of chemotherapy without platinum-salt dose reduction, instead of 75% as expected. However, 56 patients (86%) completed all the three cycles with or without platinum-salt dose reduction. This primary endpoint could be thus considered as too stringent, and this study highlighted that a ‘stop-and-go’ strategy compares favourably with standard schedule.

The median OS from inclusion was 17.7 months, which is longer than in the PointBreak Study (patients with stage IIIB or IV non-squamous NSCLC, ECOG-PS ≤1, up to four cycles of induction therapy: 12.6 months in the pemetrexed–carboplatin–bevacizumab arm).27 It was also longer than in previous studies with other standard chemotherapies combined with bevacizumab (median OS in the SAiL study: 14.6 months).17

### Table 2

| AEs of special interest for bevacizumab | Grade 3–4 AEs n (%) | Grade 5 AEs n (%) |
|----------------------------------------|---------------------|------------------|
| Epistaxis                              | 8 (10.3)            | 1 (1.5)          |
| Hypertension                           | 12 (17.6)           | 0                |
| Other haemorrhage*                     | 5 (7.4)             | 0                |
| Haematological AEs                     | 49 (72.1)           | 23 (33.8)        |
| Anaemia                                | 46 (67.6)           | 11 (16.2)        |
| Neutropenia                            | 31 (45.6)           | 18 (26.5)        |
| Thrombocytopenia                       | 21 (30.9)           | 10 (14.7)        |
| Febrile neutropenia                    | 4 (5.9)             | 4 (5.9)          |
| Other AEs                              | 61 (89.7)           | 13 (19.1)        |
| Asthenia†                              | 54 (79.4)           | 10 (14.7)        |
| Nausea                                 | 38 (55.9)           | 2 (2.9)          |
| Vomiting                               | 14 (20.6)           | 2 (2.9)          |
| Diarrhoea                              | 13 (19.1)           | 0                |
| Constipation                           | 12 (17.6)           | 0                |
| Stomatitis‡                            | 20 (29.4)           | 4 (5.9)          |
| Renal failure                          | 6 (8.8)             | 0                |
| Anorexia                               | 22 (32.4)           | 4 (5.9)          |
| Conjunctivitis§                         | 17 (25.0)           | 0                |
| Sepsis                                 | 1 (1.5)             | 1 (1.5)          |
| Peripheral neuropathy¶                 | 8 (11.8)            | 0                |
| Alopecia                               | 4 (5.9)             | 0                |
| Hypoacusis**                           | 4 (5.9)             | 0                |

*Rectal haemorrhage, gingival bleeding and haemorrhoids.
†Asthenia, general physical health deterioration and fatigue.
‡Stomatitis, dry mouth, aphthous stomatitis and oral candidiasis.
§Lacrimation increased and conjunctivitis.
¶Paraesthesia and peripheral neuropathy.
**Tinnitus and hypoacusis.

AE, adverse event.
re-challenged with pemetrexed–cisplatin–bevacizumab followed by pemetrexed–bevacizumab maintenance, was 20.5 months, which is similar to the 19.8 months observed in the AVAPERL study (patients with advanced nsqNSCLC, ECOG-PS ≤2, four cycles with pemetrexed–cisplatin–bevacizumab followed by pemetrexed–bevacizumab maintenance).20 Otherwise, the median OS calculated from the start of the SEQUENCE 2 chemotherapy (14.1 months) could be compared with the second-line studies showing a median OS of about 8 months with pemetrexed monotherapy.20 Moreover, when considering the median OS of patients with advanced nsqNSCLC treated with second-line immunotherapy, it was 12.2 months in patients treated with nivolumab (and 9.4 months for the docetaxel comparator arm), but it did not exceed 10 months in both arms when PD-L1 expression <10%.10 However, the impact of immune checkpoint inhibitor is delayed and 1-year or 2-year PFS rate parameters better reflect their efficacy.

Otherwise, the median PFS from the re-introduction of chemotherapy was 6.8 months, which corresponded to a disease control in 75.4% of these patients. This proportion is higher than in the PointBreak study (65.9%). Finally, the median DDC (ie, PFS1 plus PFS2) was 12.4 months, allowing to delay the second-line therapy.

Regarding safety data of the population who entered in SEQUENCE 2 combination therapy, the proportion of patients with at least one grade ≥3 related adverse event is consistent with previous findings on bevacizumab combination therapy, without any unexpected trend.30,31 Our stop-and-go strategy (with two sequences of three-cycle platinum–pemetrexed chemotherapy combined with bevacizumab) could be compared with the PointBreak study based on four successive cycles containing the same components.26 Regarding grade ≥3 related haematological adverse events, similar results were observed apart from thrombocytopenia less frequently reported in our SEQUENCE 2 population (14.7% vs 23.3%). For grade ≥3 related clinical adverse events, no fatigue was reported in our SEQUENCE 2 patients (vs in 11% of patients in the PointBreak study), but hypertension onset was more often reported (7.4% vs 3.4% of patients). Finally, our stop-and-go strategy tends to show satisfactory safety findings in patients with advanced nsqNSCLC.

In conclusion, even though the emergence of immune checkpoint inhibitors led to postulate that therapeutic strategy in NSCLC will be fully modified in the near future as it was the case with the raising of targeted therapy, platinum-based chemotherapy will likely remain one major therapy. To patients with advanced nsqNSCLC who do not positively answer to predictive biomarkers for tailored therapy, the BUCIL study proposes a new therapeutic option with a stop-and-go strategy, which deserved to be further studied. In addition, with the emergence of immunotherapy, new therapeutic strategies are being evaluated. One schedule that can be proposed could combine two cycles of cisplatin-based chemotherapy with an immune checkpoint inhibitor (ICI). The ICI will be maintained until progression of disease. In this situation, the issue of cisplatin or carboplatin re-introduction will be raised.

**Short clinical practice points section**

A stop-and-go strategy with cisplatin or carboplatin re-introduction could be a valid option in patients with advanced NSCLC and not eligible for immunotherapy or targeted therapy.

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**Acknowledgements** The authors thank all the patients for their participation in the study as well as all the investigators. For this study, support was provided by Roche (bevacizumab supply for the second sequence of treatment and unrestricted grant), IFCT (monitoring and logistic services), IFCT (data management and statistical analyses) and AXUES (manuscript preparation).

**Funding** This work was supported by Roche, the French National Cancer Institute (INCa) and French League Against Cancer.

**Competing interests** JB: advisory board for Roche, Bristol-Myers Squibb, Boehringer-Ingelheim and Astra-Zeneca. FB: personal fees for Astra-Zeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, Clovis Oncology, Eli Lilly Oncology, F Hoffmann-La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre and Pfizer. JC: participation to boards of experts for Lilly, Roche, Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Pfizer and Novartis. OM: advisory board for Roche. EQ: advisory board for Novartis, Abbvie and Roche; travel meeting grant and honoraria for Boehringer-Ingelheim; travel meeting grant for Pfizer, Amgen and Lilly. JR: personal fees for Pierre Fabre, Bayer and Novartis. P-JS: grants and non-financial support for Roche and Lilly.

**Patient consent** Not required.

**Ethics approval** Comité de Protection des Personnes.

**Provenance and peer review** Not commissioned; internally peer reviewed.

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