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Phase I clinical trials in patients with advanced non-small cell lung cancer treated within a Drug Development Unit: What have we learnt?

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ABSTRACT

Objectives: Despite advances in novel drug development for patients with advanced non-small cell lung cancer (NSCLC), there are still only a limited number of approved treatments. We therefore evaluated the clinical outcomes of patients with advanced NSCLC referred to a dedicated phase I clinical trials unit assessed baseline clinical factors associated with successful enrollment onto phase I trials.

Material and methods: We conducted a retrospective study involving patients with advanced NSCLC referred to the Drug Development Unit at the RMH between January 2005 and December 2013.

Results: 257 patients with advanced NSCLC were referred for consideration of phase I trials, of which only 89 (35%) patients successfully commenced phase I trials. The commonest reasons for not entering study included poor ECOG performance status and rapid disease progression. A multivariate analysis identified that ECOG performance status (0–1) and RMH prognostic score (0–1) were associated with successful enrollment onto phase I trials ($p < 0.001$).

Single agent therapies included novel agents against the phosphatidylinositol-3 kinase pathway, insulin growth factor-1 receptor and pan-HER family tyrosine kinases. These trial therapies were well tolerated and mainly associated with grade 1–2 adverse events, with a minority experiencing grade 3 toxicities. Nine (10%) patients, 4 with known *EGFR* or *KRAS* mutations, achieved RECIST partial responses. Median time to progression was 2.6 months and median overall survival was 8.1 months for patients enrolled.

Conclusions: Phase I trial therapies were generally well tolerated with potential antitumor benefit for patients with advanced NSCLC. Early referral to drug development units at time of disease progression should be considered to enhance the odds of patient participation in these studies.

1. Introduction

Lung cancer is the main cause of cancer mortality worldwide and has a five-year survival rate of less than 15% [1,2]. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers and is histologically classified into adenocarcinoma and squamous cell carcinoma, which account for 50% and 30% of NSCLC, respectively. NSCLC is a molecularly heterogeneous disease and may harbor different putative driver aberrations [3,4]. The landscape of therapeutic options for patients diagnosed with advanced NSCLC has changed dramatically over the past decade, especially with recent advances in the development of immunotherapies and next generation molecularly targeted agents [5–9]. Novel immune checkpoint inhibitors have demonstrated longer overall survival (OS) and better toxicity profiles compared to platinum-based chemotherapy in patients whose tumors have ≥ 50% PD-L1 expression in the first-line setting, and to docetaxel in patients with advanced NSCLC who had progressed during or after platinum-based chemotherapy [5–7,10,11]. Phase III trials have demonstrated that first

Abbreviations: ALK, Anaplastic Lymphoma Kinase; DDU, Drug Development Unit; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EPR, electronic patient record; HDAC, histone deacetylase; IGF-1R, insulin growth factor-1 receptor; LDH, lactate dehydrogenase; NSCLC, non-small cell lung cancer; OS, overall survival; PARP, poly(ADP-ribose) polymerase inhibitor; PI3K, phosphatidylinositol-3 kinase; PFS, progression-free survival; PR, partial response; RMH, poyal Marsden Hospital; SD, stable disease; TKI, tyrosine kinase inhibitor; TTP, time to progression

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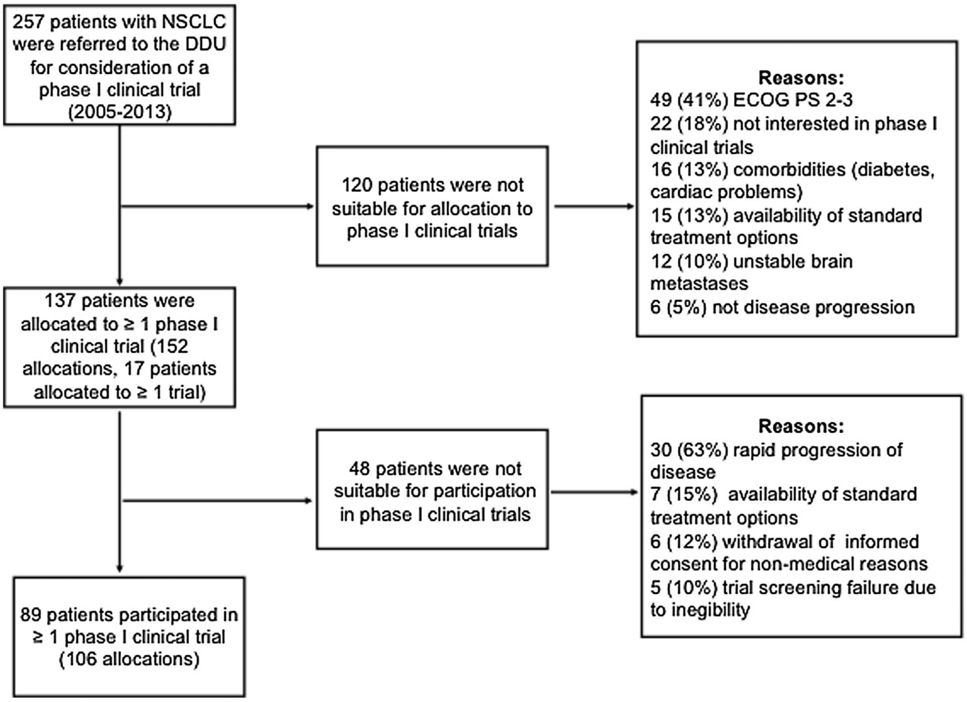

Fig. 1. Flow chart of advanced NSCLC patients participating in phase I clinical trials in the DDU at the RMH (2005–2013).

and second generation tyrosine kinase inhibitors (TKIs), such as erlotinib (Roche), gefitinib (AstraZeneca) and afatinib (Boehringer Ingelheim) in patients with epidermal growth factor receptor (EGFR) mutant NSCLC improve progression-free survival (PFS), but not OS when compared with platinum-based chemotherapy in the first and second-line settings [8,12–14]. Phase III studies performed in patients with Anaplastic Lymphoma Kinase (ALK) fusion rearrangements, which accounts for approximately 4% of NSCLC, when treated with crizotinib (Pfizer) have shown improvements in PFS compared with platinum chemotherapy [9,15].

Despite advances in the development of antitumor therapies, there are still only a limited number of approved lines of treatment available for patients with advanced NSCLC. Patients are typically considered for clinical trials within specialist lung cancer units upon the exhaustion of conventional treatment options. Such trials are often limited by protocol restrictions on patient eligibility and number of prior lines of treatments received. Patients who remain fit with acceptable organ function may then be referred to specialist drug development units for consideration of phase I trials of novel experimental therapies, including first-in-human studies. However, to the best of our best knowledge, there are currently no published data on the outcomes of patients with advanced NSCLC treated within the context of phase I clinical trials in dedicated drug development units, including treatment-related toxicities and antitumor activity. Such data will be important to establish the extent of benefit which may be anticipated from experimental phase I trials are *bona fide* antitumor treatment options for patients with advanced NSCLC.

A critical aspect of phase I trials is the selection of suitable patients, especially those with NSCLC who are at high risk of rapid clinical deterioration. Olmos and colleagues developed and validated the Royal Marsden Hospital (RMH) prognostic score – comprising serum albumin levels, number of metastatic sites and lactate dehydrogenase (LDH) levels – as a predictor of 90-day mortality to optimize the selection of appropriate patients for participation in phase I trials [16,17].

The main aim of this retrospective study was to evaluate the clinical outcomes of patients with advanced NSCLC referred to the Drug Development Phase I Unit at the Royal Marsden Hospital (RMH) for consideration of novel therapies, and to explore the outcomes of patients treated with molecularly targeted agents. The second aim was to identify baseline clinical factors associated with successful enrollment onto phase I clinical trials.

2. Material and methods

This retrospective study included patients with advanced NSCLC who were referred to the Drug Development Unit (DDU) at the Royal Marsden Hospital (RMH), London, United Kingdom, for consideration of phase I clinical trials from 1st January 2005 to 31st December 2013. This study was approved by the Royal Marsden Hospital Committee for Clinical Research.

Clinical parameters were collected from electronic patient records (EPR) during the patients' first visit to the DDU prior to starting a clinical trial, including: stage of cancer, sites of disease, histological subtype, mutation status, prior lines of antitumor therapy, Eastern Cooperative Oncology Group performance status (ECOG PS), full blood count, biochemistry, RMH prognostic score and genetic mutation status if known. The RMH prognostic score, which comprise serum albumin, number of metastatic disease and lactate dehydrogenase (LDH) levels, is a predictor of 90-day mortality used to optimize the selection of patients for phase I clinical trials. All patients enrolled on these clinical studies had provided their written informed consent for trial participation.

The primary endpoint of this study was to evaluate patient outcomes (treatment-related toxicities and antitumor activity) of patients with NSCLC who enrolled in at least one phase I trial. Toxicity data were collected as originally reported on EPR, i.e. graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 or 4.0 depending on the study. Antitumor response rates were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 or 1.1 depending on the study. Tumor responses were confirmed by a board-certified radiologist. OS data were obtained from EPR and when necessary, by contacting the patients' family physician.

The SPSS program version 20 was used for the statistical analysis. Univariate and multivariate binary Cox logistic regression was used to identify clinical factors associated with patients being enrolled onto phase I trials. OS was defined as the interval between the day of the first administered dose of clinical trial therapy and the date of death from

Table 1
Patients demographics.

Patient characteristics	Patients enrolled n = 89 (35%)	Patients not enrolled n = 168 (65%)	All patients n = 257 (100%)
Age			
Median			
< 65 years	60 (68%)	104 (62%)	164(64%)
> 65 years	29 (32%)	64 (38%)	93 (36%)
Sex			
Male	54 (61%)	88(52%)	142 (55%)
Female	35 (39%)	80 (48%)	115 (45%)
Race			
White	82 (92%)	150 (90%)	232 (91%)
Asian	3 (3%)	11 (6%)	14 (5%)
Black	4 (5%)	3 (2%)	4 (5%)
Indian	0 (0%)	3 (2%)	3 (1%)
Smoking status			
Ex-smoker	39 (44%)	86 (51%)	125 (49%)
Smoker	11 (13%)	19 (11%)	30 (11%)
Never smoker	23 (25%)	18 (11%)	41 (16%)
Unknown	16 (18%)	45 (27%)	61 (24%)
Stage			
III	7 (8%)	7 (4%)	14 (5%)
IV	82 (92%)	161 (96%)	243 (95%)
Histology			
Adenocarcinoma	56 (63%)	111 (66%)	167 (65%)
Squamous	27 (30%)	45 (27%)	72 (28%)
Other	6 (7%)	12 (7%)	18 (7%)
Mutations			
Not available	63 (71%)	110 (65%)	173 (67%)
Available	26 (29%)	58 (35%)	84 (33%)
KRAS mutations	8 (9%)	18 (30%)	26 (31%)
EGFR mutations	3 (3%)	5 (8%)	8 (9%)
Previous lines of treatment			
1	10 (11%)	18 (11%)	28 (11%)
2	42 (47%)	67 (40%)	109 (42%)
3	25 (28%)	57 (34%)	82 (32%)
4	12 (14%)	21 (12%)	33 (13%)
5	NA	5 (3%)	5 (2%)
Chemotherapy first line doublet			
Platinum-based chemotherapy	74 (83%)	152 (91%)	226 (88%)
Other	3 (3%)	2 (1%)	5 (2%)
First line single chemotherapy	12 (14%)	14 (8%)	26 (10%)
Erlotinib	52 (58%)	83 (49%)	135 (52%)
Prior lines of targeted therapy	54 (61%)	98 (58%)	152 (59%)
ECOG PS			
0	16 (18%)	15 (9%)	31 (12%)
1	69 (77%)	100 (60%)	169 (66%)
2	4 (5%)	44 (26%)	48 (19%)
3	NA	8 (5%)	8 (3%)
RMH score			
0	19 (21%)	18 (11%)	37 (14%)
1	46 (52%)	58 (34%)	104 (41%)
2	17 (19%)	59 (35%)	76 (29%)
3	7 (8%)	33 (20%)	40 (16%)

any cause. Time to progression (TTP) was the time elapsed between the first dose of trial therapy until radiological progression or death from any cause. The Kaplan-Meier method as used to estimate median TTP and OS.

3. Results

3.1. Patient and tumor characteristics

A total of 257 patients diagnosed with advanced NSCLC were referred to the DDU at the RMH from January 2005 to December 2013 for consideration of participation in phase I clinical trials. Eighty-nine of these 257 (35%) patients participated in at least one phase I trial, with 17 of these 89 (19%) patients in two or more phase I trial (106 trial enrollments). A total of 168 of 257 (65%) patients referred to DDU did not start a phase I trial. Of these 168 patients, a total of 120 were deemed not suitable for allocation to a Phase I trial, while 48 were allocated but did not start treatment (Fig. 1). Overall, the main reasons for patients not participating in phase I clinical trials were poor ECOG PS (49 [29%]) and rapid disease progression (30 [18%]). Other reasons included patients not interested in participating in phase I clinical trials (22 [13%]) and comorbidities such as cardiac disease and diabetes (16 [10%]). Details of other reasons are outline in (Fig. 1).

Patient demographic characteristics were similar in the enrolled versus not enrolled groups, respectively: median age (61 vs. 60 years), histology (lung adenocarcinoma [63% vs. 66%] and squamous cell lung cancer [30% vs. 27%]), ≥3 previous lines of antitumor treatment in the metastatic disease setting (42% vs. 46%), and prior use of molecular targeted agents (61% vs. 58%), respectively. 95% of enrolled patients had an ECOG PS 0–1 versus 69% in the non-enrolled group; RMH prognostic score 0–1 was 73% in the enrolled group compared with 45% in the non- enrolled group (Table 1).

Genetic aberration status (*EGFR*, *KRAS* and *BRAF* mutations; *ALK* rearrangements) was available for only 84 (33%) of 257 patients. 26 (31%) of these 84 patients referred for consideration of a phase I trial had a known *KRAS* mutation, while 8 (9%) had an *EGFR* mutation. Neither *BRAF* mutations nor *ALK* rearrangements were detected in our study (Table 1).

3.2. Univariate and multivariate analysis

Univariate and multivariate analyses were performed in order to investigate clinical factors associated with patients being enrolled versus not being enrolled onto phase I clinical trials. Clinical factors including the number of sites of disease (< 3 sites), ECOG PS (0–1), RMH prognostic score (0–1), white blood cells (WBC) < 10^9/L, neutrophils, lymphocytes, hemoglobin (> 9 g/dL), platelets (< 400,000), albumin (> 35 g/L), alkaline phosphatase (< 110) and LDH (< 192 U/L) levels were significantly associated with being enrolled onto a phase I clinical trial in the univariate analysis (Table 2).

However, the ECOG PS and RMH prognostic score were the only independent factors associated with successful patient enrollment using a multivariate analysis. Patient with ECOG PS 2–3 versus 0–1 (odds ratio (OR) 0.06 [95% CI, 0–22–0.20; $p < 0.001$]) and those with RMH prognostic score 2–3 versus 0–1 (OR 0.29 [95% CI, 0.15–0.58; $p < 0.001$]) were significantly less likely to be enrolled onto phase I trials (Table 2).

3.3. Phase I clinical trial therapies

We classified the individual drugs tested in the 26 phase I clinical trials into four categories: single agent targeted therapies (51 events [55%]), targeted therapy-chemotherapy combinations (18 events [19%]), targeted–targeted therapy combinations (14 events [15%]) and novel chemotherapies (10 events [11%]). Single agent targeted therapies included inhibitors against histone deacetylase (HDAC), the phosphatidylinositol-3 kinase (PI3K) pathway, insulin growth factor-1 receptor (IGF-1R), pan-HER family tyrosine kinase, antiangiogenic agents, poly(ADP-ribose) polymerase (PARP) inhibitors, integrins, aurora kinase inhibitors, PIM kinase inhibitors, monocarboxylase inhibitors and intravenous reovirus (Table 4).

Table 2
Factor associated with enrollment onto phase I clinical trials.

Variable	Univariate analysis OR	95% CI	P value	Multivariate analysis OR	95% CI	P value
Histology (Adenocarcinoma vs. others)	0.98	0.55–1.77	0.967	NA	NA	NA
Platinum sensitive vs. resistant/refractory	0.66	0.35–1.25	0.213	NA	NA	NA
Number of prior lines of treatment ≥ 3	0.71	0.40–1.25	0.240	NA	NA	NA
Kras mutation	1.09	0.34–3.45	0.873	NA	NA	NA
Number of sites of disease ≥ 3	0.51	0.29–0.92	0.026	NA	NA	NA
ECOG (2–3 vs. 0–1)	0.05	0.20–0.17	0.001	0.06	0–22–020	< 0.001
RMH prognostic score (2–3 vs. 0–1)	0.26	0.14–0.48	0.001	0.29	0.15–0.58	< 0.001
WBC > 10^9/L	0.87	0.21–0.73	0.003	NA	NA	NA
Neutrophils	0.87	0.80–0.94	0.001	NA	NA	NA
Lymphocytes	1.29	0.86–1.92	0.214	NA	NA	NA
Hemoglobin > 9 g/dL	1.42	1.11–1.71	0.001	NA	NA	NA
Platelets > 400,000	0.99	0.99–1.00	0.611	NA	NA	NA
Albumin > 35 g/L	3.39	1.73–6.63	0.001	NA	NA	NA
Alkaline phosphate > 110 u/L	0.26	0.12–0.58	0.001	NA	NA	NA
LDH > 192 U/L	0.53	0.29–0.97	0.040	NA	NA	NA

Table 3
Main drug related toxicities according to CTCAE.

Toxicities	G1 (n, %)	G2 (n, %)	G3 (n, %)	G4 (n, %)	All grades
Fatigue	14(13%)	14 (13%)	5 (5%)	NA	33 (31%)
Skin rash	12 (12%)	12 (13%)	5 (5%)	NA	31 (29%)
Diarrhea	13(12%)	8 (8%)	6 (6%)	NA	27 (26%)
Nausea	16 (15%)	10 (9%)	NA	NA	26 (24%)
Mucositis	15 (15%)	6 (6%)	1 (1%)	NA	22 (20%)
Vomiting	9 (9%)	1 (1%)	1 (1%)	NA	11 (10%)
Allergic reactions	NA	1 (1%)	4 (4%)	NA	5 (5%)
Liver transaminase elevation	1 (1%)	1 (1%)	3 (3%)	NA	5 (5%)

Note: Adverse events during the trial, i.e., exceeding dose-limiting toxicity period.

3.4. Phase I trial therapy-related toxicities

We assessed the therapy-related adverse events collected during the duration of trial treatment of 106 patient enrollments. Overall, phase I trial therapies were well tolerated, with mainly grade 1–2 adverse events. The most common toxicities at any grade included fatigue (33 patients [31%]), skin rash (31 [29%]), diarrhea [27 (26%]) and nausea (26 [24%]). The most common grade 3 or worse toxicities included diarrhea (6 patients [6%]), skin rash (5 [5%]), fatigue (5 [5%]) and acute allergic reactions (4 [4%]). The acute allergic reactions were observed in patients treated with chemotherapy and monoclonal antibodies. Grade 3 trial-related toxicities were observed in 25 patients (24%), leading to 12 (11%) patients discontinuing trial therapy. No grade 4–5 toxicities were observed (Table 3).

3.5. Antitumor activity

Of the 106 patient enrollments, 93 patients were evaluable for response assessment according to RECIST; the remaining 13 patients were not evaluable as they discontinued the trial early (11 because of toxicity and 2 because of non drug-related reasons). Nine (10%) patients achieved a RECIST partial response (PR), 37 (40%) achieved clinical benefit (PR + stable disease [SD]) at 3 months and 15 (15%) at 6 months. Among the nine patients who achieved a RECIST PR, 8 patients had lung adenocarcinoma, while 1 had lung squamous cell carcinoma. All patients received at least 2 prior lines of antitumor treatment in the metastatic setting and five out of nine patients had previously received a targeted therapy (Table 5).

Median TTP for all novel therapies was 2.6 months (95% CI, 0.2–35.5). Patients who received a combination of drugs, especially targeted therapy-chemotherapy combinations had the longest median TTP of 4.7 months (0.2–35.5) and the highest rates of PR (Table 4). The median OS for the patients enrolled onto phase I trials was 8.1 In addition, at 6 months after their first consultation in the Phase I DDU, 61% (95% CI, 51.11–71.89) of patients enrolled onto phase I trials were alive.

An actionable mutation was detected in four of 9 (44%) patients who achieved a PR on phase I trials; all four patients were treated with matched targeted therapies. Two never-smoker female patients with *EGFR* mutant NSCLC achieved a median TTP of 18 and 36 months with a single agent pan-HER family tyrosine kinase inhibitor and a combination of paclitaxel chemotherapy and a pan-HER family tyrosine kinase inhibitor, respectively. Two ex-smoker patients with *KRAS* mutations had progressed on four lines of treatment, including platinum-doublet chemotherapy, docetaxel, pemetrexed and erlotinib. Both patients were treated with a combination of a selective MEK inhibitor and AKT inhibitor. One patient achieved a RECIST PR lasting four months and the other patient discontinued trial after 3.3 months because of non-trial related pneumonia; restaging imaging at the time of trial discontinuation showed RECIST PR (Table 5).

4. Discussion

Treatment strategies for advanced NSCLC remain limited, thus novel experimental therapies within the context of early phase clinical trials may provide additional therapeutic approaches for these patients. In this study, we assess the outcomes of patients with advanced NSCLC treated on phase I trials within a dedicated drug development unit, including therapy-related toxicities and response rates. We also investigate clinical factors, which predict for successful enrollment onto phase I trials. In our retrospective study, novel therapies were generally well tolerated, with only 12 (11%) patients discontinuing trial because of adverse events. The rates of phase I trial-related grade 3 toxicities of 24% were lower than the docetaxel-related grade 3 toxicity rates of 40%–70% [18,19], but higher compared with grade 3–4 toxicities reported in phase III studies with the immune checkpoint inhibitors nivolumab and pembrolizumab of 7%–10% [5,6,10].

The identification of suitable patients for phase I trials remains challenging, especially in patients with advanced NSCLC who have a high risk of clinical deterioration. We therefore evaluated the RMH prognostic score – which comprises serum albumin level, number of metastatic sites and lactate dehydrogenase levels – and other potential clinical factors that may be associated with being enrolled onto phase I clinical trials. The RMH prognostic score 0–1 and ECOG PS 0–1 were the only clinical factors found to be significantly associated with being

Table 4
Antitumor activity.

Novel therapies	n (%)	PR	SD	CB (PR + SD) for 4 months	CB (PR + SD) for 6 months	Median TTP (months) (range)
Single targeted therapies						
HDAC inhibitor	14 (15%)	NA	7 (50%)	2 (14%)	2 (14%)	2.4 (1.5–3.5)
PI3K pathway inhibitor	9 (10%)	NA	4 (45%)	2 (22%)	2 (22%)	1.7 (0.9–9.5)
IGF-1R inhibitor	7 (8%)	NA	3 (37%)	1 (12%)		1.8 (0.7–7.8)
Virotherapy	4 (4%)	NA	3 (75%)	1 (25%)		2.5 (1.8–4.8)
Pan-HER family tyrosine kinase inhibitor	9 (10%)	2 (18%)	5 (46%)	3 (27%)	2 (18%)	3.5 (0.6–19.4)
PARP inhibitor	1 (1%)		1 (100%)	1 (100%)		4.1
Anti-angiogenic inhibitor	1 (1%)		1 (33%)			1.4
Integrin inhibitor	1 (1%)					1.4
Aurora Kinase inhibitor	1(1%)		1 (100%)	1(100%)		5.8
Monocarboxylate transporter inhibitor	1(1%)					2.6
PIM kinase inhibitor	1 (1%)		1 (50%)			0.3
c-MET inhibitor	1 (1%)					0.9
DNA methyltransferase 1	1 (1%)					1.6
Overall	51 (55%)	2 (4)	26 (50%)	11 (22%)	6 (12%)	3.2 (2.4–4.3)
Targeted therapy- chemo chemotherapy combinations	18 (19%)	4	10 (55%)	9 (50%)	6 (33%)	4.7 (0.2–35.5)
Targeted-targeted therapy combinations	14 (15%)	3	7 (47%)	5 (33%)	2 (13%)	3.33 (0.3–14.0)
Novel chemotherapies	10 (11%)		5 (50%)	2 (18%)	1 (9%)	1.4 (0.6–7.8)
All drugs	93 (100%)	9 (10%)	48 (52%)	27 (29%)	15 (14%)	2.6 (0.2–35.5)

Table 5
Characteristics of the patients who achieved a PR.

Patient	Age	Sex	Histology	Mutation	ECOG PS	Prior lines mtx	Prior TT	Type of drug	TTP (months)
1	73	F	Adeno	EGFR	0	2	No	Paclitaxel + Pan-HER family tyrosine kinase inhibitor	35.5
2	45	F	Adeno	EGFR	2	2	Yes	Pan-HER family tyrosine kinase inhibitor	18.4
3[a]	62	M	Adeno	KRAS	0	4	Yes	MEK inhibitor + AKT inhibitor	3.3
4	62	F	Adeno	KRAS	2	4	No	Mek-inhibitor + AKT inhibitor	4.2
5[a]	56	M	Squamous	No	2	2	No	Paclitaxel + TORC1/2 inhibitor	4.7
6	59	F	Adeno	No	0	2	No	MEK inhibitor + PI3 K inhibitor	14
7	64	F	Adeno	Unknown	1	2	Yes	Docetaxel + BCL2 inhibitor	6
8	59	F	Adeno	Unknown	0	3	Yes	Pan-HER family tyrosine kinase inhibitor	11.2
9	68	M	Adeno	Unknown	1	2	Yes	Docetaxel + BCL2 inhibitor	7.5

M: male; F: female; Adeno: adenocarcinoma; mtx: metastatic; TT: targeted therapy.
[a] Note: Patients 3 and 5 discontinued treatment because of non-disease related reasons (bilateral pneumonia and pneumothorax, respectively).

successfully enrolled onto phase I trials in a multivariate analysis [16,17]. The ECOG PS and RMH prognostic score should therefore be used to identify suitable patients with NSCLC for phase I clinical trials. In addition, the early referral of patients with advanced NSCLC to dedicated phase I units should be considered so as to preserve both ECOG PS and RMH prognostic scores and to improve the odds of patients being successfully enrolled onto phase I studies.

In our study, a large number of patients were heavily pretreated with 42% having had 3 or 4 prior lines of treatment in the metastatic setting. Overall, nine (10%) patients achieved RECIST PR, with median TTP of 2.6 months (95% CI, 0.2–35.5) and median OS of 8.1 months. These results are comparable with single agent chemotherapies, such as docetaxel and pemetrexed given in the second line treatment setting, which has an overall response rate of $\leq$10% and a TTP of 2–3 months [18,19]. The main limitation of our study is that patients with advanced NSCLC were treated with different novel drugs or therapeutic combinations with different mechanisms of action. Some patients may also have been treated with subtherapeutic or ineffective drug doses during these phase I studies. This may explain the wide variability in the median TTP.

Genetic aberration status (*EGFR*, *KRAS* and *BRAF* mutations; *ALK* rearrangements) was only available for only 84 (33%) of 257 patients. This may be explained by the fact that molecular characterization of patients with advanced NSCLC was not routinely tested during the early to middle parts of our study period between 2005 and 2013 and that very often, only limited amounts of tissue are available in diagnostic lung biopsies. National efforts such as the Cancer Research UK Stratified Medicine Program-2 are now ongoing to molecularly characterize patients with advanced NSCLC prospectively for enrollment onto the National Lung Matrix Trial [20].

In our study, 26 of 84 (31%) patients with available genetic aberrations were found to harbor a known *KRAS* mutation while 8 (9%) had an *EGFR* mutation, which are consistent with the proportion of *KRAS* and *EGFR* mutations described in the literature of 20%–30% and 10%, respectively [21]. It should be noted that 4 of nine patients who achieved confirmed PRs had known putative driver mutations, and were treated with matched molecularly targeted therapies. Two patients with known sensitizing *EGFR* mutations were treated with a pan-HER family tyrosine kinase inhibitor, achieving median TTPs of 18 and 36 months. The patient in our study who achieved a median TTP of 36 months had a known deletion in chromosome 19 EGFR; according to the LUX3 and LUX6 studies, patients with del19 EGFR aberrations treated with afatinib had the longest OS lasting over 30 months [22].

The other two patients who achieved RECIST PRs had known *KRAS* mutations and were treated with a combination of MEK and AKT inhibitors. Jänne and colleagues reported a randomized phase II study assessing the combination of docetaxel plus the MEK inhibitor selumetinib (AZD6244; AstraZeneca) versus docetaxel plus placebo in patients with *KRAS* mutant NSCLC in the second-line setting [23]. The selumetinib group showed a median PFS of 5.3 months (95% CI, 4.6–6.4) versus 2.1 months (95% CI, 1.4–3.7) in the placebo group (HR 0.58, $p < 0.014$) [23]. Based on data from this phase II trial and our study, it appears that patients with *KRAS* mutant NSCLC may benefit more from the combination of a MEK inhibitor either with chemotherapy or a PI3K pathway inhibitor, than MEK inhibitor monotherapy [24]. The rationale for the latter combination strategy is because of the potential development of signaling crosstalk between the PI3K and the RAS/RAF/MEK pathways and subsequent drug resistance [25,26]. These early phase clinical trial findings suggest that such combination strategies are promising in *KRAS* mutant NSCLC where there are currently no approved targeted therapies.

The management of patients with advanced NSCLC has changed dramatically in recent years, partly because of the development of novel immunotherapeutic approaches, including the FDA approval of novel immune checkpoint inhibitors, such as nivolumab and pembrolizumab in patients with squamous and non-squamous NSCLC [5–7]. In addition, third generation EGFR mutation specific inhibitors, such as osimertinib are highly active in patients with *EGFR* T790M mutations who have progressed on first and second-generation EGFR inhibitors [27,28]. Signals of antitumor activity in NSCLC in molecular subpopulations of patients with these agents were first observed in phase I trials, stressing the importance of such studies in accelerating drug development through the use of hypothesis-testing, biomarker-driven studies [29,30].

Conflict of interest

The final manuscript has been read and approved by all authors.

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