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# SELECT-3: a phase I study of selumetinib in combination with platinum-doublet chemotherapy for advanced NSCLC in the first-line setting

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**Background:** We investigated selumetinib (AZD6244, ARRY-142886), an oral, potent, and highly selective, allosteric MEK1/2 inhibitor, plus platinum-doublet chemotherapy for patients with advanced/metastatic non-small cell lung cancer.

**Methods:** In this Phase I, open-label study (NCT01809210), treatment-naïve patients received selumetinib (50, 75, 100 mg BID PO) plus standard doses of gemcitabine or pemetrexed plus cisplatin or carboplatin. Primary objectives were safety, tolerability, and determination of recommended Phase II doses.

**Results:** Fifty-five patients received treatment: selumetinib 50 or 75 mg plus gemcitabine/cisplatin ( $n=10$ ); selumetinib 50 mg plus gemcitabine/carboplatin ( $n=9$ ); selumetinib 50, 75 or 100 mg plus pemetrexed/carboplatin ( $n=21$ ); selumetinib 75 mg plus pemetrexed/cisplatin ( $n=15$ ). Most frequent adverse events (AEs) were fatigue, nausea, diarrhoea and vomiting. Grade  $\geq 3$  selumetinib-related AEs were reported in 30 (55%) patients. Dose-limiting toxicities (all  $n=1$ ) were Grade 4 anaemia (selumetinib 75 mg plus gemcitabine/cisplatin), Grade 4 thrombocytopenia/epistaxis and Grade 4 thrombocytopenia (selumetinib 50 mg plus gemcitabine/carboplatin), Grade 4 febrile neutropenia (selumetinib 100 mg plus pemetrexed/carboplatin), and Grade 3 lethargy (selumetinib 75 mg plus pemetrexed/cisplatin). Partial responses were confirmed in 11 (20%) and unconfirmed in 9 (16%) patients.

**Conclusions:** Standard doses of pemetrexed/carboplatin or pemetrexed/cisplatin were tolerated with selumetinib 75 mg BID. The selumetinib plus gemcitabine-containing regimens were not tolerated.

Despite advances in the diagnosis, imaging, staging, and treatment of non-small cell lung cancer (NSCLC), the estimated overall 5-year survival rate for patients in Europe is only 11% (D'Addario *et al*, 2010). A number of molecular abnormalities have been shown to be characteristic of certain lung cancers and are used to

guide first-line treatment. Patients with tumours harbouring activating epidermal growth factor receptor (EGFR) mutations receive particular benefits from selective treatment with an EGFR tyrosine kinase inhibitor, while patients with tumours that contain the fusion oncogene *EML4-ALK* will benefit from targeting its

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tyrosine kinase activity using an ALK inhibitor, such as crizotinib (Novello *et al*, 2016). However, there are no approved targeted therapies for the majority of advanced NSCLC patients that have no known or characterised molecular abnormalities and platinum-based doublet chemotherapy is the first-line treatment for the vast majority of patients.

Activation of the RAS/RAF/MEK/ERK (RAS-ERK) mitogen-activated protein kinase pathway is implicated in cellular proliferation and is central to driving cancer growth and progression (Davies *et al*, 2002; Roberts and Stinchcombe, 2013). Activation of this pathway can be driven by somatic mutations, and *KRAS* mutations are found in up to 34% of NSCLC (Shepherd *et al*, 2013). MEK1/2 are critical components of the RAS-ERK pathway and therefore inhibition of MEK1/2 may be effective in patients with NSCLC. Selumetinib (AZD6244, ARRY-142886) is an oral, potent, and highly selective, allosteric MEK1/2 inhibitor (Yeh *et al*, 2007), with a short half-life (Banerji *et al*, 2010; Denton and Gustafson, 2011). In a prospective study, selumetinib in combination with docetaxel, as second-line treatment for patients with *KRAS*-mutant (*KRAS*<sub>m</sub>) advanced NSCLC, improved progression-free survival (PFS) and objective response rate compared with placebo combined with docetaxel (Jänne *et al*, 2013). The combination safety profile was consistent with those of the individual components and adverse events (AEs) were manageable with appropriate guidance and clinical practice (Shepherd *et al*, 2000; Hanna *et al*, 2004; Hainsworth *et al*, 2010; Jänne *et al*, 2013). Following these results, selumetinib was evaluated in combination with docetaxel as second-line treatment in patients with *KRAS*<sub>m</sub> NSCLC in the Phase III SELECT-1 study (NCT01933932) (Jänne *et al*, 2016c).

Following the promising Phase II results of second-line selumetinib, and in parallel to the Phase III SELECT-1 study, the potential use of selumetinib in the first-line setting was investigated in patients unselected for *KRAS* mutation status, to test the hypothesis of MEK inhibition in the context of other non-*KRAS*<sub>m</sub> modes of pathway activation. To do this, the appropriate treatment combinations of selumetinib plus chemotherapy were investigated using platinum-doublet regimens that are standard of care for treatment-naïve patients, namely cisplatin or carboplatin, in combination with either pemetrexed or gemcitabine (Reck *et al*, 2014). Here we report results from a dose-finding Phase I study (NCT01809210), which assessed the safety, tolerability, and preliminary efficacy of selumetinib in combination with first-line chemotherapy regimens, in patients with NSCLC, unselected for *KRAS* mutation status.

## PATIENTS AND METHODS

**Patients.** Patients aged 18 years or older with histologically or cytologically confirmed, locally advanced (stage IIIB) or metastatic (stage IV) NSCLC, eligible for standard first-line platinum-doublet treatment for NSCLC but unsuitable for radical treatment were included in the study. Other eligibility criteria included World Health Organization performance status (WHO-PS) of 0–1 and radiologically measurable disease. Patients were not selected based on *KRAS* mutation status, but local *KRAS* test results were recorded if known.

Patients were excluded if they had received prior systemic anti-cancer treatment for advanced NSCLC. Previous adjuvant chemotherapy, prior surgery, or radiotherapy for curative intent was permitted if they occurred >6 months prior to starting study treatment. Other exclusion criteria included: treatment with potent inhibitors or inducers of cytochrome P450 (CYP) 3A4/5, CYP2C19 and CYP1A2 within 2 weeks of the first dose of study treatment; symptomatic brain metastases or spinal cord compression; history

of central serous retinopathy or retinal vein occlusion; uncontrolled glaucoma or intraocular pressure >21 mm Hg.

**Study design and treatment.** This was a Phase I/Ib, open-label, multicentre study of selumetinib in combination with platinum-doublet chemotherapy regimens, following a ‘rolling six’ design with cohorts of at least three and up to six evaluable patients. The study was designed to allow an investigation of the optimal combination dose while ensuring the safety of patients with intensive safety monitoring.

The primary study objective was to investigate the safety and tolerability, and to determine the recommended Phase II dose (RP2D) of selumetinib when administered in combination with first-line chemotherapy regimens. Secondary objectives included assessment of pharmacokinetics (PK) of selumetinib, its metabolite *N*-desmethyl selumetinib, gemcitabine/pemetrexed and cisplatin/carboplatin when administered in combination and evaluation of tumour response to assess preliminary efficacy of the treatment combinations using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

Selumetinib was administered orally twice-daily (BID) in continuous 21-day cycles. The starting dose of selumetinib was chosen as 50 mg being two-thirds of the combination dose used in two Phase II studies (Kirkwood *et al*, 2012; Jänne *et al*, 2013), increasing in 25 mg increments. Doses administered were selumetinib 50 or 75 mg BID plus standard doses (for first-line treatment of NSCLC) of gemcitabine (1250 mg m<sup>-2</sup>) or pemetrexed (500 mg m<sup>-2</sup>) plus cisplatin (75 mg m<sup>-2</sup>) or carboplatin (AUC = 5). Only patients with non-squamous histology received pemetrexed as per the approved indication. An additional dose-finding cohort of selumetinib 100 mg BID plus pemetrexed and carboplatin was included. Primary prophylactic use of granulocyte colony stimulating factors (G-CSF) was not permitted, but G-CSF was permitted after Cycle 1.

Treatment was continued until a treatment or study discontinuation criterion was met. Patients who discontinued one, or both, chemotherapy agents were able to continue receiving selumetinib monotherapy if there was evidence of continuing clinical benefit as assessed by the investigator. The study was designed to include an optional dose expansion study at the recommended Phase II combination dose. The safety review committee recommended that the pemetrexed/cisplatin cohort be expanded to ascertain the safety and tolerability of this regimen, in combination with the recommended Phase II dose of selumetinib 75 mg BID.

The study followed the principles of the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation. All patients provided written informed consent prior to their participation in the study. Approval was obtained from the local institutional review board at each participating site and complied with local country regulations.

**Assessments.** Safety was assessed in terms of AEs, laboratory data, vital signs, electrocardiogram changes, physical examinations, echocardiogram/multigated acquisition scan, and ophthalmologic examinations. AEs were graded using the National Cancer Institute CTCAE version 4.0. Dose-limiting toxicity (DLT) was assessed during the first treatment cycle (a full definition of DLT is provided in Supplementary Digital Content 1, Supplementary Methods). Patients were followed up for 28 ± 7 days following discontinuation of selumetinib.

Plasma samples were collected for PK assessments at baseline and on Cycle 1 Day 8 and Cycle 2 Day 1 for selumetinib and its metabolite *N*-desmethyl selumetinib, gemcitabine and its metabolite deoxy-1,1-difluorouridine (dFdu), pemetrexed, cisplatin (total and/or unbound platinum) and carboplatin (total and/or unbound platinum) (full details of the PK analysis are given in

Supplementary Digital Content 1, Supplementary Methods) (Severin *et al*, 2016).

Tumour response to treatment was assessed using RECIST v1.1 assessment of computed tomography or magnetic resonance imaging scans at screening and then every 6 weeks for 6 months and every 12 weeks thereafter until discontinuation of selumetinib.

**Statistical analyses.** Safety data were summarised for all patients who received at least one dose of selumetinib. The PK analysis was summarised for all patients with sufficient samples to provide an adequate profile, with no important AEs or protocol deviations that may have impacted PK. Plasma PK parameters were derived using standard non-compartmental methods and actual elapsed time from dosing. Efficacy data were summarised for all patients who received at least one dose of selumetinib with a baseline tumour assessment. Statistical analyses were performed by Phastar (London, UK) under the direction of the Biostatistics Group, AstraZeneca, (London, UK) using SAS software Version 9.1.3 or later (SAS Institute, Inc. Cary, NC, USA).

## RESULTS

**Patient disposition.** Between 4 April 2013 and 30 September 2015, 76 patients were enrolled; 21 failed to meet the eligibility criteria and 55 received study treatment with selumetinib and first-line chemotherapy regimens across seven dose escalation cohorts (Figure 1). Ten patients were treated with gemcitabine and cisplatin; nine with gemcitabine and carboplatin; 21 with pemetrexed and carboplatin and 15 with pemetrexed and cisplatin. Median treatment duration of selumetinib was 84 days (range, 4–266); median number of cycles of chemotherapy received are displayed in Supplementary Table 1. All patients discontinued selumetinib, due to the following reasons: AE (23 patients, 41.8%), condition under investigation worsened (21 patients, 38.2%), subject decision (11 patients, 20.0%). Nine patients died during the study; two deaths were attributed to serious AEs of myocardial infarction, two to disease progression and AEs (both colonic perforation; one considered to be causally related to gemcitabine and cisplatin) and five to disease progression alone. No deaths were considered related to selumetinib.

**Demographics and baseline disease characteristics.** Overall, demographics were as expected in patients with advanced NSCLC and were generally balanced between treatment groups (Table 1),

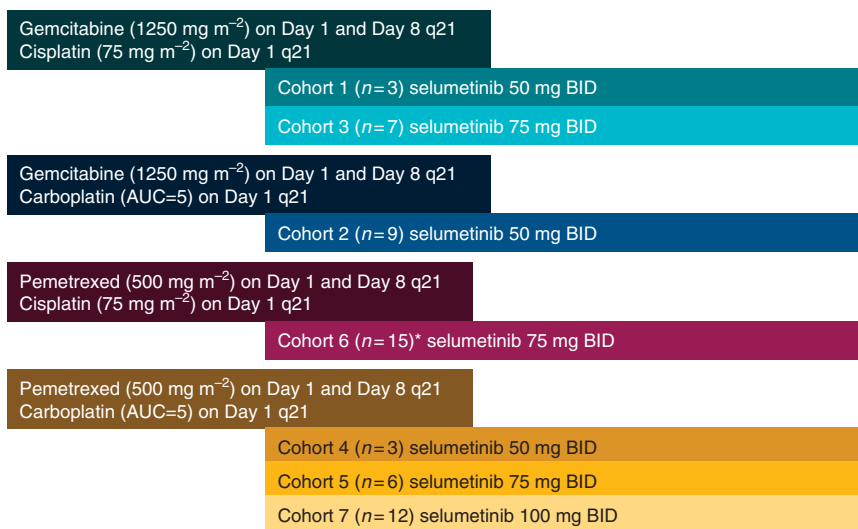
with the exception of the male:female ratio of patients treated with pemetrexed-cisplatin (2 : 1;  $n = 15$ ). This was due to the sequential enrolment process and the variable number of patients assigned to each cohort. Most patients (66%) had a WHO-PS of 1 and the majority had adenocarcinoma (67%). Fifty patients (91%) had metastatic disease. *KRAS* mutation status was determined retrospectively using archival tumour samples in 28 patients (51%); six (11%) had confirmed *KRAS*<sup>m</sup> NSCLC. Of these six patients, five had adenocarcinoma histology and for one patient the histology could not be determined.

**Safety.** In total, five DLTs were reported (Supplementary Table 2). The gemcitabine and cisplatin combination was tolerated at selumetinib 50 mg dose level. In the selumetinib 75 mg plus

**Table 1. Patient demographics**

Characteristic	Total (n = 55)
<b>Age (years)</b>	
Mean (range)	61.5 (39–76)
<b>Gender, n (%)</b>	
Female	26 (47)
Male	29 (53)
<b>Racial origin, n (%)</b>	
White	50 (91)
Black or African American	3 (6)
Other	2 (4)
<b>Histology type, n (%)</b>	
Not determined	2 (4)
Squamous cell carcinoma	13 (24)
Adenocarcinoma	37 (67)
Adenocarcinoma: bronchiolo-alveolar	1 (2)
Other	2 (4)
<b>KRAS mutation status, n (%)</b>	
Mutant	6 (11)
Mutation not detected	12 (22)
Unknown	37 (67)
<b>Disease classification, n (%)</b>	
Locally advanced	5 (9)
Metastatic	50 (91)
<b>WHO-PS, n (%)</b>	
0	19 (35)
1	36 (66)

Abbreviation: WHO-PS = World Health Organization performance status.



**Figure 1. Dose-escalation cohorts.** \*Includes patients from expansion cohort, after selumetinib 75 mg BID dose was declared tolerated in combination with pemetrexed and cisplatin.

gemcitabine and cisplatin group, one of four evaluable patients experienced a DLT of Grade 4 anaemia; enrolment at selumetinib 75 mg dose level was stopped by the study sponsor when two serious AEs of large bowel perforation (at selumetinib dose levels 50 and 75 mg), considered not related to selumetinib by the investigators, were reported for this combination. The combination of selumetinib 50 mg plus gemcitabine and carboplatin was declared non-tolerated, and two of seven evaluable patients experienced DLTs: one Grade 4 thrombocytopenia, and one Grade 4 thrombocytopenia plus Grade 4 epistaxis. The pemetrexed and carboplatin combination was tolerated at selumetinib 50 and 75 mg dose levels; no DLTs were reported. One of six evaluable patients in the selumetinib 100 mg plus pemetrexed and carboplatin group experienced a DLT of Grade 4 febrile neutropenia. Although DLT criteria were not reached for the selumetinib 100 mg cohort, nine (75%) patients required a dose modification and therefore this was not considered suitable for evaluation in subsequent Phase II studies. The combination of pemetrexed and cisplatin was not explored at selumetinib 50 mg dose level due to emerging data from a Phase Ib trial study (NCT01783197) investigating selumetinib (50 or 75 mg BID) in combination with cisplatin and pemetrexed or carboplatin and paclitaxel in patients with previously untreated metastatic NSCLC. The trial demonstrated that selumetinib 75 mg BID was generally well tolerated in these combinations (Nicholas *et al*, 2015). In the current study, selumetinib in combination with pemetrexed and cisplatin was found to be tolerated at 75 mg from an expanded cohort of a total of 12 evaluable patients: one patient in this group experienced a DLT of Grade 3 lethargy. The RP2Ds were identified as selumetinib 75 mg BID plus standard doses of pemetrexed/carboplatin and pemetrexed/cisplatin. No RP2Ds were defined for treatment with gemcitabine; the carboplatin combination was declared non-tolerated, and the combinations with cisplatin were discontinued due to concerns about potential tolerability of this regimen and the fatalities related to large bowel perforation.

The most commonly reported AEs overall were nausea (73%), diarrhoea (55%), fatigue (55%), and vomiting (55%) (Table 2). These were the most common AEs in each treatment arm except for selumetinib plus gemcitabine/carboplatin, in which patients reported fatigue, neutropenia, and thrombocytopenia most commonly (all 67%). In total, 44 (80%) patients experienced an AE of Grade  $\geq 3$ ; the most common, regardless of causality, were neutropenia (14, 26%), anaemia (12, 22%), and thrombocytopenia (11, 20%). Thirty (55%) patients experienced an AE of Grade  $\geq 3$  causally related to selumetinib. AEs leading to a dose interruption or discontinuation of selumetinib were observed in 29 (53%) and 23 (42%) patients, respectively. Serious AEs were observed in 33 (60%) patients. In 17 (31%) patients, serious AEs were considered causally related to selumetinib by the investigator, of which 6 (11%) were thrombocytopenia.

AEs of particular interest due to their causal relationship to selumetinib (as assessed by investigator) included facial oedema, rash, retinal events, and decreases in left ventricular ejection fraction (LVEF). Six patients experienced maculo-papular rash (all Grade 1/2) with one patient discontinuing treatment due to this AE; however, there were no cases of rash leading to a DLT. Twelve patients experienced peripheral oedema with one instance leading to treatment discontinuation; two patients experienced facial oedema. Retinal vein occlusion, retinal pigment epithelial detachment, and central serous retinopathy were each reported in one patient receiving pemetrexed and cisplatin plus selumetinib 75 mg BID. No AEs of cardiac failure were reported. Decreased LVEF causally related to selumetinib was reported in two patients (both Grade 2). One patient who received gemcitabine and cisplatin plus selumetinib 50 mg BID experienced decreased LVEF 85 days after the first dose of study treatment. LVEF was 64% at screening and selumetinib was permanently discontinued due to the event, which

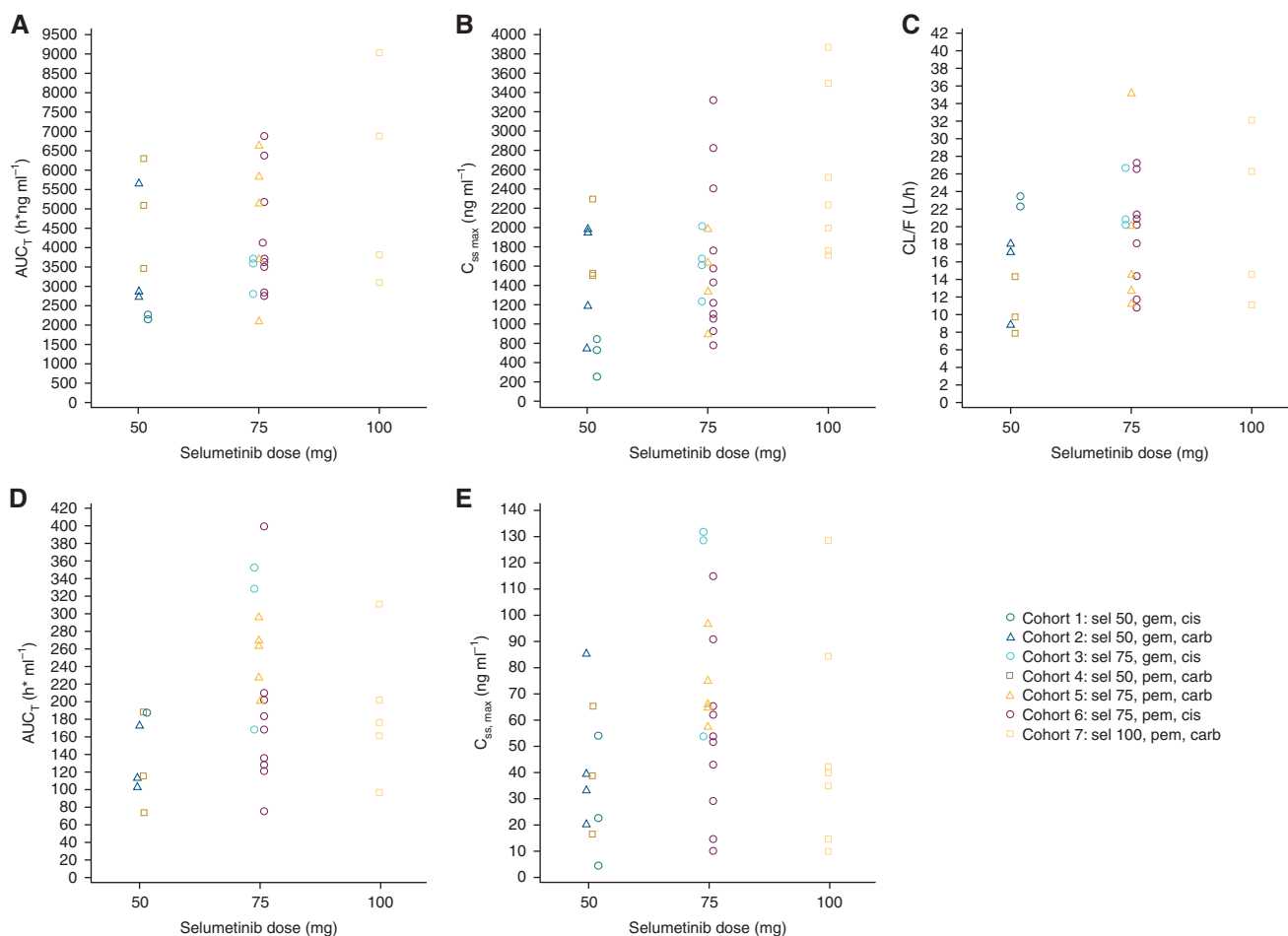
**Table 2. Most frequent AEs reported in at least 15% of patients (full analysis set)**

AE category, n (%)	Any grade	Grade 1	Grade 2	$\geq$ Grade 3 <sup>a</sup>
Patients with any AE	55 (100)	0	11 (20)	44 (80)
Nausea	40 (73)	17 (31)	15 (27)	8 (15)
Diarrhoea	30 (55)	26 (47)	3 (6)	1 (2)
Fatigue	30 (55)	13 (24)	15 (27)	2 (4)
Vomiting	30 (55)	20 (36)	9 (16)	1 (2)
Constipation	29 (53)	21 (38)	8 (15)	0
Rash	25 (46)	15 (27)	10 (18)	0
Decreased appetite	16 (29)	9 (16)	7 (13)	0
Neutropenia	16 (29)	0	2 (4)	14 (25) <sup>b</sup>
Periorbital oedema	16 (29)	12 (22)	4 (7)	0
Anaemia	15 (27)	0	3 (6)	12 (22)
Lethargy	14 (26)	7 (13)	5 (9)	2 (4)
Dyspnoea	13 (24)	4 (7)	6 (11)	3 (6)
Epistaxis	12 (22)	10 (18)	1 (2)	1 (2)
Oedema peripheral	12 (22)	7 (13)	5 (9)	0
Thrombocytopenia	12 (22) <sup>c</sup>	0	0	11 (20) <sup>d</sup>
Headache	11 (20)	8 (15)	3 (6)	0
Lower respiratory tract infection	11 (20)	3 (6)	6 (11)	2 (4)
Oral candidiasis	11 (20)	10 (18)	1 (2)	0
Stomatitis	11 (20)	3 (6)	6 (11)	2 (4)

Abbreviations: AE=adverse event; CTCAE=common terminology criteria for adverse events. Includes AEs with an onset date on or after the date of first dose and up to 35 (28  $\pm$  7) days following the date of last dose of selumetinib.  
<sup>a</sup>Patients with multiple AEs of CTCAE Grade 3 or higher are counted once for each preferred term.  
<sup>b</sup>Four patients reported Grade 4 neutropenia, two each in the gemcitabine + carboplatin plus selumetinib 50 mg and pemetrexed + carboplatin plus selumetinib 100 mg cohorts.  
<sup>c</sup>One AE of unknown grade.  
<sup>d</sup>Five patients reported Grade 4 thrombocytopenia, three in the gemcitabine + carboplatin plus selumetinib 50 mg cohort and two in the pemetrexed + carboplatin plus selumetinib 100 mg cohort.

was assessed by the investigator as causally related to selumetinib, when LVEF decreased to 51%. Another patient who received pemetrexed and carboplatin plus selumetinib 50 mg BID experienced decreased LVEF with onset 170 days after the first dose of study treatment. Echocardiography at screening showed an LVEF of 62% with atrial dilation, which decreased to 33% and selumetinib was interrupted. Selumetinib 50 mg was continued after 44 days when LVEF had increased to 41%. At the time of treatment discontinuation, LVEF was 49% and the event was recorded as ongoing (78 days after onset). Echocardiography showed a mildly dilated left ventricular cavity with mildly impaired systolic function and moderate dilation. Selumetinib was permanently discontinued due to the event which was assessed by the investigator as causally related to selumetinib.

**Pharmacokinetics.** PK analyses showed that the steady-state PK of selumetinib and *N*-desmethyl selumetinib were generally similar when administered with chemotherapy across the combination regimens (Figure 2). Following oral administration of 50, 75, and 100 mg BID, selumetinib was rapidly absorbed with a median time to reach maximum plasma concentration ( $t_{max}$ ) of 1.00–1.75 h post-dose. No marked trend in time to reach maximum plasma concentration at steady state ( $t_{ss,max}$ ) was observed across selumetinib dose or combination chemotherapies. With a low number of evaluable PK parameters in some treatment groups, selumetinib inter-patient variability of systemic exposure to selumetinib was generally moderate to high, with geometric mean



**Figure 2.** Scatter plots of selumetinib (A–C) and *N*-desmethyl selumetinib (D–E) PK parameters (PK analysis set).  $AUC_{\tau}$  = area under the plasma concentration time curve in the dosing interval; Carb = carboplatin;  $C_{ss,max}$  = maximum observed plasma concentration at steady state; Cis = cisplatin; CL/F = apparent oral plasma clearance; Gem = gemcitabine; Pem = pemetrexed; Sel = selumetinib.

CV% for the area under the plasma concentration time curve in the dosing interval ( $AUC_{\tau}$ ) and the maximum observed plasma concentration at steady state ( $C_{ss,max}$ ) ranging from 15%–57% and 23%–76%, respectively, across treatment arms on Cycle 1 Day 8 and Cycle 2 Day 1. Visual assessment of PK parameters across all treatment groups did not reveal any major differences in systemic exposure, although there was a trend towards lower  $AUC_{\tau}$  and  $C_{ss,max}$  in patients receiving selumetinib 50 mg plus gemcitabine and cisplatin, with individual estimates ranging from 1590 to 2240  $ng \cdot h \cdot ml^{-1}$  and 276–686  $ng \cdot ml^{-1}$ , respectively, across both treatment cycles. However, this trend was not apparent in patients receiving selumetinib 75 mg plus gemcitabine and cisplatin. Mean metabolite:parent  $AUC_{\tau}$  ratios indicated that *N*-desmethyl selumetinib represented approximately 3–8% of selumetinib systemic exposure, with no apparent trend in PK across treatment arms. The PK of gemcitabine, dFdu, pemetrexed, cisplatin, and carboplatin were generally similar across the doses of selumetinib administered for the various combination chemotherapy regimens.

**Efficacy.** All 55 patients treated were evaluable for response, a confirmed partial response was observed in 11 (20%) patients, and an unconfirmed partial response in 9 (16%), resulting in an estimated response rate of 36%. Figure 3 shows best percentage change in tumour size. In addition, 21 (38%) patients had stable disease at  $\geq 6$  weeks (Supplementary Table 3). Confirmed partial responses were seen in: 3/10 (30%) patients receiving selumetinib plus gemcitabine/cisplatin, 2/9 (22%) patients receiving selumetinib plus gemcitabine/carboplatin (unconfirmed partial response in 3/9, 33%), 4/21 (19%) patients receiving selumetinib plus

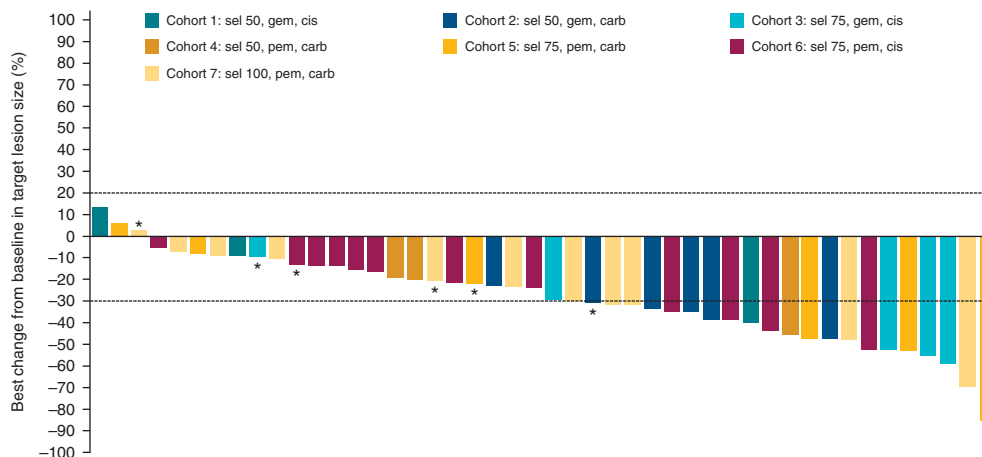
pemetrexed/carboplatin (unconfirmed complete or partial response in 4/21, 19%), and 2/15 (13%) patients in the selumetinib plus pemetrexed/cisplatin treatment arm (unconfirmed complete or partial response in 2/15, 13%). Of the six patients with *KRAS* NSCLC detected using a local test, best objective response was 1 partial response; 3 stable disease; 2 progressive disease.

## DISCUSSION

In the first-line setting, platinum-doublet chemotherapy represents the standard of care for patients with advanced NSCLC without *EGFR* activating mutation or *ALK* gene rearrangement, but objective response rates are low (15–31%) and median survival is generally up to approximately 10 months (Schiller *et al*, 2002; Sandler *et al*, 2006; Scagliotti *et al*, 2008). Selumetinib, given in combination with docetaxel, improved response rates and PFS in the second-line setting (Jänne *et al*, 2013); therefore, we investigated whether selumetinib could be safely and effectively combined with platinum-doublet chemotherapy in the first-line setting.

In the SELECT-3 study presented here, we identified recommended Phase II doses of selumetinib 75 mg BID when combined with standard doses of pemetrexed and cisplatin or pemetrexed and carboplatin, which were tolerated with AE profiles consistent with the individual agents. The combinations with gemcitabine were not tolerated and a recommended Phase II dose was not determined.

The overall safety profile of selumetinib in combination with pemetrexed plus carboplatin or cisplatin was acceptable, and there



**Figure 3.** Best percentage change in tumour size. Abbreviations: carb = carboplatin; cis = cisplatin; gem = gemcitabine; pem = pemetrexed; sel = selumetinib.  $n = 47$ . Eight patients were excluded due to incomplete post-baseline assessments of tumour response. Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. \*Patients with detected KRAS mutation.

were no selumetinib-related deaths in any treatment arm. Many of the AEs were those that would be anticipated from the administration of platinum-doublet chemotherapy. The safety profile presented here is consistent with a Phase Ib trial by the National Cancer Institute of Canada (NCIC) investigating selumetinib (50 or 75 mg BID) combined with cisplatin and pemetrexed or carboplatin and paclitaxel in patients with previously untreated metastatic NSCLC ( $n = 22$ ) (Nicholas *et al*, 2015). In the NCIC study, the most common selumetinib-related toxicities were mild gastrointestinal and skin-related AEs. We also observed generally mild skin and gastrointestinal toxicities, although in the current study, six patients in the cisplatin-containing treatment groups experienced  $\geq$  Grade 3 nausea (three each in gemcitabine and cisplatin plus selumetinib 75 mg, and pemetrexed and cisplatin plus selumetinib 75 mg groups). Owing to the known emetogenic properties of cisplatin, we subsequently agreed to a standardised anti-emetic regimen between participating trial centres to include 3 days of steroids, a 5-HT<sub>3</sub> receptor antagonist, and aprepitant, and this would be recommended for any subsequent studies of these combinations.

In our study the rate of Grade 3–4 neutropenia was lower than that reported in the NCIC study (25% vs 44%) (Nicholas *et al*, 2015). In a previous Phase II study of selumetinib in combination with docetaxel, rates of Grades 3–4 neutropenia were 67% in the selumetinib plus docetaxel group, and 55% in the placebo plus docetaxel group, without prophylactic GCSF treatment (Jänne *et al*, 2013). In the current study, AEs were managed using safety management guidelines according to standard clinical practice, hence commonly occurring AEs were effectively managed using specific treatment algorithms and GCSF was permitted after Cycle 1. Prophylactic GCSF was also used in the Phase III SELECT-1 study (Jänne *et al*, 2016b). In the present study, two patients experienced Grade 2 decreased LVEF considered causally related to selumetinib. Reversible, asymptomatic reductions in LVEF have been reported in a small number of patients in some studies of selumetinib (Banerji *et al*, 2010). As such, mandatory safety monitoring of LVEF with scheduled echocardiography assessments and guidance to assist in the early diagnosis and management of decreased LVEF have been incorporated into trial protocols, including that of the SELECT-3 trial.

The recommended Phase II dose was not determined for the gemcitabine-containing regimens, due to fatalities of unknown relationship to the combinations and therefore a tolerable regimen was not identified for patients with squamous NSCLC in this study. The carboplatin combination was not tolerated, while the combinations with cisplatin were discontinued due to fatalities related to

colonic perforation: two patients (one receiving selumetinib 50 mg plus gemcitabine/cisplatin; one receiving selumetinib 75 mg plus gemcitabine/cisplatin) experienced large intestine perforation leading to death 50 days and 25 days after the first dose of selumetinib, respectively. These AEs were not deemed by the investigator to be related to selumetinib in the present study, although this effect has been reported with other MEK inhibitors (Minor *et al*, 2015). By contrast, a manageable toxicity profile was reported at a dose of 75 mg BID selumetinib plus gemcitabine 1000 mg m<sup>-2</sup> and cisplatin 25 mg m<sup>-2</sup> in a Phase Ib trial in patients with advanced or metastatic biliary tract cancer (Bridgewater *et al*, 2016). However, this may be due to the lower doses of both gemcitabine and cisplatin, and the fractionated regimen of cisplatin, or the variation in comorbidities of the patients enrolled.

Combination therapy did not appear to show any marked effect on the PK profile of selumetinib or its metabolite *N*-desmethyl selumetinib. It was noted that there was a trend for lower systemic exposure to selumetinib in the selumetinib 50 mg plus gemcitabine and cisplatin treatment group, but due to the limited data in this study and high variability of selumetinib PK, no conclusions can be made regarding the significance of this finding. While the study was not designed to assess whether selumetinib affects the exposure of the chemotherapies investigated, the available data did not find any marked differences in the PK of gemcitabine, pemetrexed, cisplatin and carboplatin, across the doses of selumetinib administered for the various combination chemotherapy regimens.

Preliminary anti-tumour activity was observed across all treatment arms. Confirmed partial responses were detected in 20% of patients and 38% of patients had stable disease at  $\geq$ 6 weeks. Data for each arm were consistent with previous reports of chemotherapy alone (Karampeazis *et al*, 2016; Langer *et al*, 2016; Park *et al*, 2017a,b). Six patients (40%) in the pemetrexed plus cisplatin group opted to continue with the standard maintenance therapy of pemetrexed. Maintenance therapy with selumetinib was not robustly explored in this study.

This trial was initiated before immunomodulatory therapies were approved for the treatment of patients with NSCLC in the second-line setting. Based on encouraging results from studies of these agents (Besse *et al*, 2015; Gettinger *et al*, 2016; Rizvi *et al*, 2016), several Phase III trials are currently evaluating immunotherapies in the first-line setting as monotherapy, in combination with different immunotherapies, or with platinum-based chemotherapy. The Keynote-024 study has shown higher response rate, PFS and overall survival for pembrolizumab when compared with standard platinum-based doublet chemotherapy as first-line treatment for patients with advanced NSCLC with high levels

(>50%) of PD-L1 expression (Reck *et al*, 2016). Despite the rapidly changing treatment landscape, it is not anticipated that all patients will benefit from immunotherapy, particularly those patients whose tumours are PD-L1 negative or low (Qin *et al*, 2016). Therefore, it is expected that platinum-doublet chemotherapy will continue to be used in the first-line setting for certain patient populations, especially if PD-L1 testing becomes more widely used, and will likely be used in relapse for patients following first-line immunotherapy. However, it should be noted that the efficacy and safety profile of subsequent treatments may be altered following first-line immune checkpoint inhibition. Selumetinib is being investigated in combination with the PD-L1 inhibitor durvalumab for patients with advanced solid tumours, including lung cancer, in the Phase I SELECT-4 trial (NCT02586987).

A limitation of the present study is that patients were not prospectively evaluated for *KRAS* mutation status, therefore subpopulations of patients deriving clinical benefit could not be identified. Limited *KRAS* mutation information was obtained from local test results using different methodologies with various limits of detection and coverage. The rate of *KRAS*m in adenocarcinoma and squamous NSCLC is approximately 34% and 6%, respectively (Shepherd *et al*, 2013), with a higher incidence in Western compared with Asian populations (Dogan *et al*, 2012; Dearden *et al*, 2013). Although many agents have been developed to target this element of the RAS-ERK pathway, clinical efficacy data have been mixed (Kempf *et al*, 2016). Direct inhibition of RAS activation using salirasib failed to show clinical efficacy in patients with stage IIIB/IV lung adenocarcinoma *KRAS* mutations (Riely *et al*, 2011). In patients with NSCLC who were treated with the multitarget tyrosine sorafenib in the third or fourth-line setting, *post-hoc* analyses found that *KRAS* mutation status was not predictive of efficacy (Mok *et al*, 2012).

The Phase I NCIC study has been expanded into a Phase II trial investigating selumetinib in patients receiving pemetrexed and platinum-based chemotherapy in advanced or metastatic non-squamous NSCLC without a detected *KRAS* mutation or with an unknown *KRAS* mutation status (NCT02337530). Selumetinib has also been explored in combination with docetaxel as a second-line treatment in patients with *KRAS*m advanced NSCLC in the SELECT-1 trial. However, no difference in PFS (primary endpoint), overall survival, or objective response rate was observed (Jänne *et al*, 2016c). Owing to the large number of co-mutations in patients with *KRAS*m NSCLC, the specific patient subgroup that may derive benefit from selumetinib remains to be determined. Consequently, no further clinical trials are currently planned with selumetinib in this setting. Exploratory analyses from the SELECT-1 trial demonstrated that there was no evidence that treatment effect on PFS differed by specific *KRAS* mutation status (determined by next-generation sequencing) (Jänne *et al*, 2016a). Similarly, PD-L1 status did not significantly impact PFS, overall survival, or objective response rate in either the selumetinib plus docetaxel or docetaxel alone treatment groups (Jänne *et al*, 2016a). However, selumetinib monotherapy has demonstrated clinical benefit in patients with neurofibromatosis type 1 (Dombi *et al*, 2016), which may warrant investigation of the utility of selumetinib for neurofibromatosis type 1 mutant NSCLC tumours (Redig *et al*, 2016).

In conclusion, our study demonstrates that selumetinib can be combined with standard doses of pemetrexed plus carboplatin or cisplatin in the first-line setting with an AE profile consistent with the individual agents.

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## CONFLICT OF INTEREST

AG received consultancy fees from AstraZeneca. KS, DG and AWD are employees of AstraZeneca, and DG and AWD hold stock options. FB received a grant and personal fees from, and is a Board Member for AstraZeneca. NS has received travel costs from AstraZeneca for her attendance at AstraZeneca-funded meetings. RC, RP and YS have received honorarium for advisory boards from AstraZeneca. H-TA, NMD, CRL, SH and MV have no conflicts of interest to declare.

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