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PHASE I STUDIES

Canadian Cancer Trials Group (CCTG) IND215: A phase Ib study of Selumetinib in patients with untreated advanced or metastatic NSCLC who are receiving standard chemotherapy regimens

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Summary

Introduction Selumetinib (AZD6244, ARRY-142886) is a potent inhibitor of MEK1/2, thereby inhibiting phosphorylation of ERK2. We investigated the toxicity and the recommended phase II dose of the combination of selumetinib with two platinum based first line chemotherapy combinations in non-small cell lung cancer. *Methods* This was a phase I trial of escalating doses of selumetinib with carboplatin (AUC 6), paclitaxel (200 mg/m^2) (cohort 1) or pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) (cohort 2) in patients with chemotherapy naïve, advanced or metastatic NSCLC. Patients enrolled on cohort 2 had non-squamous histology. Dose escalation of selumetinib proceeded using a 3 + 3 design: 50 mg b.i.d. days 2–19 (dose level 1); 75 mg b.i.d. days 2–19 (dose level 2); and 75 mg b.i.d. continuously. Adverse events were evaluated using CTC AE v4 and response by RECIST 1.1. *Results* Thirty-nine patients were enrolled (cohort 1 n = 16; cohort 2, n = 23). There were no dose limiting toxicities in either cohort and the recommended phase II dose for both regimens was standard doses of carboplatin, paclitaxel or pemetrexed and cisplatin with continuous selumetinib at a dose of 75 mg b.i.d. Most adverse events were grade 1 or 2 and were predominantly diarrhea, nausea, stomatitis, peripheral edema, neutropenia, and skin rash. Response rate was 37.5% for cohort 1 and 30.4% for cohort 2. *Conclusion* Selumetinib at a dose of 75 mg b.i.d continuously can be safely combined with paclitaxel and carboplatin or pemetrexed and cisplatin in patients with advanced or metastatic NSCLC. This trial provided the dose for the regimens used in a randomized phase II trial in NSCLC (CCTG IND.219).

Keywords Selumetinib · MEK inhibitor · Non-small cell lung cancer · Phase I

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Introduction

Lung cancer causes the most cancer deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of cases [2]. In NSCLC conventional cytotoxic treatments have produced median survival around 12 months, although gains have been seen in those patients eligible for immunotherapy [3, 4]. Despite improvements, new therapies are needed.

The RAS/RAF/MEK/ERK pathway is activated by a variety of signals and has downstream effects on proliferation, survival, migration, angiogenesis, and even drug resistance [5, 6]. As such, it has been the target of oncologic interventions. Significant success in lung cancer was achieved by targeting upstream EGFR in individuals with activating EGFR mutations [7]. Conversely, while KRAS mutations

may be present in almost 30% of NSCLC [8], RAS-specific agents have not shown clinical benefit to date [9].

MEK serves as a potential downstream target in this pathway. Selumetinib (AZD6244, ARRY-142886) is a potent inhibitor of MEK1/2, thereby inhibiting phosphorylation of ERK2 [10, 11]. In vitro studies showed higher sensitivity of cell lines harbouring *BRAF* or *RAS* mutations [12]. Preclinical work has shown increased tumour control when using selumetinib in combination with EGFR inhibitors [13, 14]. In mouse xenografts, selumetinib has been shown to be additive with irinotecan and synergistic with docetaxel [12]. In a *KRAS*-dependent mouse model of lung cancer, selumetinib increased cisplatin activity through inhibition of cisplatin induced Bcl2-like 11 (BIM) suppression [15]. Conversely, other data suggest that MEK inhibitors may block apoptotic death by preventing cisplatin-induced activation of caspase-3 through the MEK/ERK pathway, discouraging simultaneous administration [16].

Single agent selumetinib has shown modest clinical activity, although a prolonged response was seen in a patient with melanoma and a *BRAF* mutation [11, 17]. A phase II study combining selumetinib with docetaxel in *KRAS*-mutated NSCLC in the second line setting showed very promising results [9], although gastrointestinal side effects such as diarrhea, nausea, vomiting and stomatitis were more common with docetaxel and selumetinib, as were skin rash, peripheral edema, and neutropenia. The subsequent phase III study, while demonstrating an improved response rate with selumetinib and docetaxel (20.1% versus 13.7%, $p = 0.05$), did not demonstrate an improvement in progression free survival or overall survival (hazard ratio [HR] PFS 0.93, 95% confidence interval [CI] 0.77–1.12 and OS HR 1.05, 95% CI 0.85–1.30, $p = 0.64$) [18].

Given the potential for combination therapy, the Canadian Cancer Trials Group conducted a phase Ib study in NSCLC to assess the use of selumetinib with standard first line platinum combination therapy. Both continuous and intermittent schedules of selumetinib were tested given the inconclusive data regarding cisplatin selumetinib interactions with respect to both efficacy and toxicity.

Methods

This trial was a phase I study to determine the recommended phase II dose of two schedules of selumetinib combined with standard first line chemotherapy platinum based regimens and a second line single agent pemetrexed regimen as follows:

- cohort 1 for treatment naïve patients with squamous or non-squamous non-small cell lung cancer to be treated with carboplatin, paclitaxel, and selumetinib
- cohort 2 for treatment naïve patients with non-squamous non-small cell lung cancer to be treated with cisplatin, pemetrexed, and selumetinib
- cohort 3 for patients being treated with 2nd line pemetrexed and selumetinib. Due to a change in the pattern of practice in Canada, there was no accrual over 9 months, and cohort 3 was closed.

Chemotherapy was delivered in standard doses (cisplatin 75 mg/m^2, pemetrexed 500 mg/m^2, carboplatin AUC 6, paclitaxel 200 mg/m^2) in 21 day cycles. There were 3 planned dose levels of selumetinib: 50 mg b.i.d. given on days 2 through 19 of the cycle (dose level 1); 75 mg b.i.d. on days 2 through 19 of the cycle (dose level 2); and 75 mg b.i.d. on days one through 21 of the cycle (continuous, dose level 3).

Patients were enrolled in a standard 3 + 3 design with an expansion cohort of 10 patients at the recommended phase II dose level for each treatment arm. Dose limiting toxicities were defined as

- Grade 2 diarrhea or rash requiring a dose hold for >5 days or a dose reduction
- Grade 4 myelosuppression for >4 days, febrile neutropenia or thrombocytopenic bleeding
- Grade 3 organ toxicity including QTc prolongation (> 500 msec)
- Grade 4 toxicity,
- Other toxicities of concern to the investigators and CCTG including selumetinib toxicities requiring >14 days hold.

Full eligibility criteria are listed on clinicaltrials.gov (NCT 02337530). In summary, eligible patients were adults with pathologically confirmed NSCLC who were not candidates for curative therapy and who had received no prior systemic treatment for their incurable disease. Patients were of ECOG performance status 0 or 1 with an expected life span of at least 12 weeks. Patients with brain metastases were excluded, as were patients with other malignancies treated within 2 years. Patients were also excluded if they had a current or past history of significant heart disease, central serous retinopathy, retinal vein occlusion, high intraocular pressure, or uncontrolled glaucoma. Measurable disease by RECIST 1.1 criteria was required. On the basis of emerging pharmacokinetic data suggesting greater plasma exposure, patients of Asian heritage were excluded from the dose escalation phase of the study, though they were eligible for the expansion cohort. Patients enrolled to the expansion cohorts of arms 1 and 2 were required to have a tissue sample sent for KRAS screening prior to registration, although the presence of a KRAS mutation was not required.

Serum and plasma were collected from all patients at baseline for correlative studies. Patients were required to have

tissue available for KRAS and EGFR mutation testing, as well as other correlative studies.

Toxicity was assessed using the Common Terminology Criteria for Adverse Events version 4.0. Response was assessed by investigators every other cycle using RECIST 1.1. Severe adverse events (SAEs) were defined as those adverse events that are fatal, life-threatening, result in new or prolonged hospitalization, cause persistent or significant disability, or are congenital anomalies or birth defects.

Statistical analyses and endpoints

The primary end point of the trial was the recommended phase II dose in each arm, as well as documentation of toxicity and maximum administered dose. Secondary outcomes included gene expression and KRAS codon subtypes in tumour that may influence response, the use of plasma as a potential source of circulating free tumour DNA for analysis of KRAS mutational status, serum exploratory markers that may predict response to selumetinib, and preliminary assessment of efficacy in all patients and in expansion cohort patients with KRAS mutant NSCLC.

The study was approved by the research ethics boards of the participating institutions. All patients provided written informed consent.

Results

From June, 2013, to October, 2015, 39 patients were recruited, including 16 to cohort 1 (paclitaxel/carboplatin/selumetinib) and 23 to cohort 2 (pemetrexed/cisplatin/selumetinib). All 39 patients were assessable for both response and toxicity (Table 1).

In cohort 1, 3 patients were enrolled to DL1, 4 patients to DL2, and 9 patients to DL3, of whom 6 comprised the RP2D expansion cohort at DL3. There were no dose limiting toxicities. The RP2D expansion cohort was closed due to slow accrual before reaching the planned ten patients.

In cohort 2, 3 patients were enrolled to DL1, 4 patients to DL2, and 16 patients to DL3, including 10 patients enrolled to the RP2D expansion cohort at DL3. It was decided to expand DL3 to six patients after one patient had grade three vomiting and other gastrointestinal adverse events in cycle 1. This was not dose limiting, but was a toxicity of concern.

Chemotherapy dosing

The median number of cycles (range) of paclitaxel/carboplatin (cohort 1) was as follows: DL1, 4 cycles (range 2–4); DL2, 5 cycles (range 3–6); DL3, 4 cycles (range 2–6). Dose reductions occurred in 5 patients for reasons of nausea, neuropathy, thrombocytopenia, elevated creatinine, and investigator choice, and delays occurred in 4 patients, including for elevated CPK, neuropathy, dyspnea, and a bed shortage. Two patients in cohort 1 stopped paclitaxel/carboplatin due to adverse events (one for fatigue and sensory neuropathy related to paclitaxel/carboplatin and one for grade 5 lung infection and neutropenia at least possibly related to all drugs).

The median number of cycles (range) of pemetrexed/cisplatin (cohort 2) was as follows: DL1, 5 cycles (range 4–6); DL2, 5 cycles (range 4–6); DL3, 4 cycles (range 1–6). Dose reductions occurred in 6 patients, including for neutropenia, nausea, fatigue, and tinnitus. Dose delays in 10 patients were due to neutropenia, fatigue, nausea, bed shortages (in 4), and institutional error (1). Four patients in cohort 2 stopped pemetrexed/cisplatin due to adverse events related to pemetrexed/cisplatin (one for stroke, one for fatigue, and two for nausea and vomiting, with one of the episodes of nausea and vomiting also possibly related to selumetinib).

Discontinuation of protocol paclitaxel/carboplatin or pemetrexed/cisplatin was due to progressive disease in 14 patients (5 in cohort 1, 9 in cohort 2), completion of treatment in 14 patients (8 in cohort 1, 6 in cohort 2), patient refusal in 2 patients (both cohort 2), investigator discretion in 2 patients (both in cohort 2), and due to 1 patient stopping selumetinib (cohort 1, with discontinuation of selumetinib leading to a technical discontinuation of all on-protocol therapy).

Selumetinib dosing

The median number of cycles (range) of selumetinib in cohort 1 was as follows: DL1, 10 cycles (range 2–12); DL2, 5 cycles (range 3–10); DL3, 6 cycles (range 1–20). In cohort 1, selumetinib dose reductions occurred in 4 patients, for reasons of fatigue, hand foot syndrome, and elevated creatine phosphokinase. Only 1 patient had a dose delay, for peripheral ischemia. Selumetinib was discontinued for drug toxicity in 4 patients in cohort 1, for reasons of anorexia, nausea, fatigue, facial and limb edema, rash, and grade 5 lung infection.

The median number of cycles (range) of selumetinib in cohort 2 was as follows: DL1, 7 cycles (range 6–13); DL2, 7 cycles (range 5–14); DL3, 8 cycles (range 1–23). In cohort 2, selumetinib dose reductions occurred in 8 patients, for reasons of rash, hypertension, elevated creatine phosphokinase, fatigue, diarrhea, dehydration, mucositis, and rash. Selumetinib was discontinued for drug toxicity in 5 patients in cohort 2, for reasons of retinal vein occlusion, edema, pruritus, nausea and vomiting, diarrhea, pneumonitis, and fatigue.

Discontinuation of selumetinib ($n = 39$) was related to disease progression in 26 patients (12 in cohort 1, 14 in cohort 2), patient refusal in one patient (cohort 2), investigator discretion in 2 patients (both cohort 2), and intercurrent illness in one patient (cohort 2). For the latter patient, a grade 3 stroke was considered related to pemetrexed and cisplatin but not selumetinib, leading to discontinuation of protocol treatment.

Table 1 Patient demographics

Patient characteristics		Cohorts		
		Cohort 1 (P/C/S) N = 16	Cohort 2 (Pe/Ci/S) N = 23	Total population N = 39
Median Age	(range)	61 (50–74)	64 (51–79)	62 (50–79)
Sex	Female	7 (44%)	16 (70%)	23 (59%)
ECOG PS	0	4 (25%)	9 (39%)	13 (33%)
	1	12 (75%)	14 (61%)	26 (67%)
Histology	Adenocarcinoma	11 (69%)	23 (100%)	34 (87%)
	Squamous Carcinoma	5 (31%)	0 (0%)	5 (13%)
Cigarette smoking	Current	10 (63%)	16 (70%)	26 (67%)
	Former	6 (38%)	6 (38%)	12 (31%)
	Never	0 (0%)	1 (4%)	1 (3%)
Prior Therapy	Adjuvant chemotherapy	0	2 (9%)	2 (5%)
	Combined chemo-radiation	1 (6%)	2 (9%)	3 (8%)
	Radiation therapy	7 (44%)	10 (43%)	17 (44%)
Sites of Disease	Lung	15 (94%)	20 (87%)	35 (90%)
	Locoregional lymph nodes	14 (88%)	17 (73%)	31 (79%)
	Distant lymph nodes	1 (6%)	7 (30%)	8 (21%)
	Pleural effusion	7 (44%)	9 (39%)	16 (41%)
	Bone	8 (50%)	9 (39%)	17 (44%)
	Adrenal	2 (13%)	6 (26%)	8 (21%)
	Liver	5 (31%)	2 (9%)	7 (18%)

Abbreviations: P = paclitaxel; C = carboplatin; S = selumetinib; Pe = pemetrexed; ci = cisplatin; PS = performance status

Toxicity

Toxicities attributed to cisplatin/pemetrexed or to carboplatin/paclitaxel were typical for these well-known regimens. The most common adverse events attributable to selumetinib were gastrointestinal and skin toxicities, most of them grade 1–2. Those adverse events which occurred in at least 10% of patients, regardless of attribution, can be found in Table 2. Selected adverse of interest that occurred in fewer than 10% of patients are described in Table 3.

Laboratory values were not recorded as adverse events. The percentage of patients with grade 3 or 4 neutropenia at any time during treatment was 50.0% in cohort 1, and 34.8% in cohort 2. The rates of grade 3 or 4 thrombocytopenia in the two cohorts were 18.8 and 8.7%, respectively. Within cohorts, hematologic parameters did not differ substantially across dose levels. Rates of selected biochemical adverse events can be found in Table 4.

There was no obvious difference in selumetinib-related adverse events between doses of 50 mg b.i.d. or 75 mg b.i.d., although this analysis is limited by the small numbers of patients who received the 50 mg dose (3 in cohort 1, 3 in cohort 2). Similarly, there is no apparent toxicity difference between interrupted and continuous and schedules at 75 mg b.i.d. (dose levels 2 and 3, respectively).

In cohort 1, 8 of 16 patients experienced toxicity of at least grade 3 that was attributed to selumetinib. These eight patients had fatigue (2 patients); stroke (grade 5), confusion and epistaxis; rash and photosensitivity; fatigue and weight loss; fatigue and febrile neutropenia; febrile neutropenia (grade 4) with lung infection (grade 5); palmar-plantar erythrodysesthesia syndrome (all grade 3 unless otherwise indicated).

Eleven of 23 patients in cohort 2 suffered grade 3 toxicity related to selumetinib. There were no selumetinib-related grade 4 or 5 toxicities in cohort 2. Affected patients experienced hypertension; retinal vein occlusion; venous thromboembolism; vomiting; nausea and vomiting; fatigue; fatigue with rash; syncope; periorbital edema and hypertension; diarrhea, dehydration, and mucositis; diarrhea, dehydration and hypertension.

Efficacy

All patients were evaluable for best response, as shown in the waterfall plot in Fig. 1. In cohort 1, confirmed partial response was observed in 6 patients (37.5%) and stable disease in 6 (37.5%) (Table 5). The median duration of response was 5.1 months (range 4.2–8.5). In cohort 2, confirmed partial response was observed in 7 patients (30.4%) and stable disease in 13 (56.5%). The median duration of response was 5.6 months (range 2.7–41.3). Although numbers were small, no discernible difference in response rate was seen between dose levels (data not shown). Progression-free survival in

Table 2 Adverse events, All grades and attributions, occurring in >10% of patients

Adverse event	All adverse events occurring in >10% of patients in at least one cohort regardless of attribution										
	Cohort 1 (P/C/S)						Cohort 2 (Pe/Ci/S)				
	Grade						Grade				
	1	2	3	4	5	Total % N = 16	1	2	3	4	Total % N = 23
Gastrointestinal Disorders											
Abdominal pain	2	2				25.0	3	2	1		26.1
Constipation	10	1				68.8	15	5			87.0
Diarrhea	13	2				93.8	10	5	2		73.9
Dry Mouth	1					6.3	3				13.0
Dyspepsia	1					6.3	5	2			30.4
Flatulence	1					6.3	3				13.0
Gastroesophageal reflux	2	1				18.8	2	4			26.1
Oral mucositis	3	2				31.3	7	2	1		43.5
Nausea	9	5				87.5	10	10	1		91.3
Vomiting	12	1				81.3	14	5	2		91.3
Skin/subcutaneous Disorders											
Alopecia	1	12				81.3	5				21.7
Dry skin	6	1				43.8	8	2			43.5
Palmar-plantar erythrodysesthesia		1	1			12.5	2	1			13.0
Edema, face	4	1				31.3	9	5	1		65.2
Edema, limbs	5	4				56.3	12	3			65.2
Pruritus	2	1				18.8	2	1			13.0
Rash	12	1	1			87.5	14	7	1		95.7
General Disorders											
Anorexia	7	4				68.8	8	9	1		78.3
Chills	2	1				18.8	5				21.7
Dehydration		1				6.3	1	4	2		30.7
Dizziness	5	1				37.5	5				21.7
Dysgeusia	2					12.5	4	2			26.1
Fatigue	4	7	4			93.8	5	13	5		100
Fever	5					31.3	5	1			26.1
Insomnia	3	3				37.5	3				13.0
Weight Loss			1			6.3	2	2			17.4
Pain											
Arthralgia	3	6				56.3		1			4.3
Back pain	3	3				37.5	9	1			43.5
Chest Wall Pain						0	4	1			21.7
Headache	2					12.5	7	2			39.1
Myalgia	4	3				43.8					0
Non-Cardiac Chest Pain	1					6.3	2	1			13.0
Pain, extremity/NOS	4	7				68.8	4	3			30.4
Pelvic Pain	1	1				12.5		3			13.0
Tumour Pain	1	1				12.5		2			8.7
Respiratory Tract Disorders											
Allergic Rhinitis						0	4				17.4
Cough	9	4				81.3	11	3			60.9
Dyspnea	8	8				100	7	6	1		60.9
Epistaxis	6		1			43.8	6				26.1

Table 2 (continued)

Adverse event	All adverse events occurring in >10% of patients in at least one cohort regardless of attribution										
	Cohort 1 (P/C/S)						Cohort 2 (Pe/Ci/S)				
	Grade						Grade				
	1	2	3	4	5	Total % N = 16	1	2	3	4	Total % N = 23
Lung Infection		2			1	18.8		4			17.4
Upper Respiratory Infection		2				12.5		2			8.7
Neurologic Disorders											
Peripheral Neuropathy	6	4	1			68.8	7	1			34.8
Tinnitus	2					12.5	5	1			26.1
Syncope						0			4		17.4
Other Disorders											
Blurred Vision	2					12.5	1	1			8.7
Hypertension		1	1			12.5		1	3		17.4
Other Infection	3					18.8	2				8.7
Thromboembolism		1	2		1	25.0		2	3		21.7
Watering Eyes						0	4				17.4

Abbreviations: P = paclitaxel; C = carboplatin; S = selumetinib; Pe = pemetrexed; Ci = cisplatin;

cohort 1 was a median 5.4 months (95% CI 1.4 to 7.3 months) and in cohort 2 was 5.0 months (95% CI 3.0 to 6.8 months).

KRAS mutation status was assessed in all patients on the RP2D expansion cohorts. In cohort 1 ($n = 6$), two patients with a *KRAS* mutation had stable disease, with a median duration of 7.9 months. Of the four wild-type patients, three had partial responses (median duration 4.8 months) and one patient had progressive disease.

In cohort 2 ($n = 10$), there were seven patients with *KRAS* mutations and three wild-type patients. Three of the patients with *KRAS* mutation had partial response with a median duration of 12.9 months, and the other four had stable disease (median 4.7 months). All wild-type patients had stable disease (median 6.6 months duration).

Among all 25 patients with assessable tissue, genetic mutations were found for the following (with patient numbers in parenthesis): *ERBB4* (1), *PIK3CA* (6), *FGFR3* (1), *KIT* (5), *KDR* (17), *APC* (15), *EGFR* (1), *CDKN2A* (2), *RET* (1), *PTEN* (2), *ATM* (3), *KRAS* (11), *ERBB2* (1), *STK11* (2), *RB1* (1). No significant association with response was found for any biomarker in any cohort or among all patients.

Discussion

Employing targeted agents against the RAS/RAF/MEK/ERK pathway has been fruitful in several malignancies. Selumetinib, an inhibitor of MEK1/2, is supported by preclinical work showing benefit in combination with both targeted and cytotoxic agents [12–15]. The present phase Ib study was designed to define the RP2D and toxicity profile of selumetinib when given in combination with paclitaxel/carboplatin, pemetrexed/cisplatin, and pemetrexed.

Table 3 Selected Grade 3–5 adverse events

Adverse event	Selected grade 3/4/5 adverse events regardless of attribution or frequency										
	Cohort 1 P/C/S						Cohort 2 (Pe/Ci/S)				
	Grade						Grade				
	1	2	3	4	5	Total % N = 16	1	2	3	4	Total % N = 23
Febrile Neutropenia			1	1		12.5			1		4.3
Retinal Vascular Disorder						0			1		4.3
Stroke			1		1	12.5			1		4.3

Abbreviations: P = paclitaxel; C = carboplatin; S = selumetinib; Pe = pemetrexed; Ci = cisplatin;

Table 4 Selected biochemical adverse events in patients with normal pre-treatment values

Adverse Event	Selected biochemical adverse events in patients with normal pre-treatment values											
	Cohort 1 (P/C/S)						Cohort 2 (Pe/Ci/S)					
	Grade						Grade					
	1	2	3	4	n	Total %	1	2	3	4	n	Total %
Elevated Creatinine	4	1			13	38.5	10	1			22	50.0
Hypoalbuminemia	6	1			8	87.5	8	2	1		12	91.7
Elevated Alk Phos	5				12	41.7	5				20	25.0
Elevated ALT	3	2			13	38.5	8	1			20	45.0
Elevated AST	9				13	69.2	14	1			21	71.4
Elevated Serum Bilirubin	2				14	14.3	0				24	0
Elevated LDH	7				8	87.5	11				15	73.3
Elevated CK	5	3		1	15	60.0	8	3	2		23	56.5

Abbreviations: P = paclitaxel; C = carboplatin; S = selumetinib; Pe = pemetrexed; ci = cisplatin; PS = performance status

We observed the expected toxicity profile of selumetinib, with the most frequent toxicities involving the skin and gastrointestinal tract, with low-grade limb and facial edema also being notable [11, 17]. Although most toxicities were of low grade, most patients had constellations of multiple low grade toxicities, including several for whom these toxicities led to drug discontinuation, as described above. Retinal vein occlusion was seen in one patient in this study. While neutropenia appeared somewhat higher in cohort 2 than what has been noted in randomized trials, the degree of myelosuppression was otherwise as expected for these chemotherapy regimens alone [3, 19–21]. It should be noted that growth factor support was not required for this trial.

The administration of the platinum doublet agents was as expected in terms of dose modifications. This study did not show an appreciable difference in toxicity according to the interrupted or continuous schedule of selumetinib.

The observed response rate (37.5% in cohort 1, 30.4% in cohort 2) was somewhat higher compared to previous randomized trials with these platinum doublets, while PFS was similar [3, 20, 21]. Despite supportive preclinical data [12], no signal of increased activity was seen among individuals having a *KRAS* mutated cancer, although analysis is limited by small numbers of patients. In our wider biomarker screen, no signal of enhanced activity was seen with other mutations. Similarly, no clear benefit was seen in the phase III SELECT-1 study of selumetinib plus docetaxel in patients with *KRAS* mutated NSCLC [18]. Despite the common pathway of RAS and MEK, it is hypothesized that mutational subtypes or other factors mitigate selumetinib benefit. Jänne et al. did not find benefit among subsets of *KRAS* mutations in SELECT-1. Preclinical study suggests that inactivation of the tumour suppressor gene *LKB1* (also known as *STK11*) could diminish the efficacy of selumetinib, possibly through decreased ERK phosphorylation and greater growth input from other signaling pathways [22]. Our study had insufficient numbers to evaluate this; two patients had an *STK11* mutation and neither had a response.

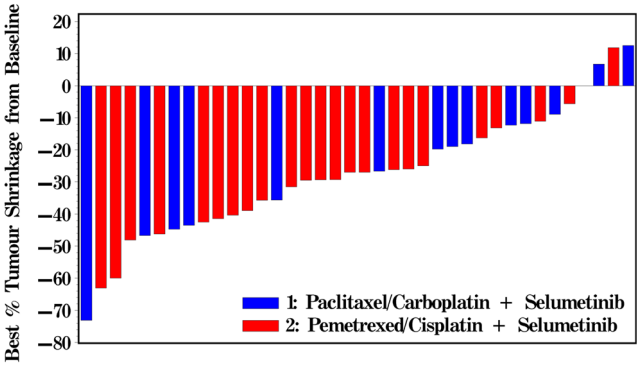

Fig. 1 Best response by patient ($n = 38$ evaluable patients)

Table 5 Tumour response

Best Response	Cohort 1 (n = 16) (P/C/S)	Cohort 2 (n = 23) (Pe/Ci/S)
Complete Response	0	0
Partial Response	6	7
Stable Disease	6	13
Progressive Disease	4	3
Response Rate All patients	6/16 = 37.5%	7/23 = 30.4%

Abbreviations: P = paclitaxel; C = carboplatin; S = selumetinib; Pe = pemetrexed; ci = cisplatin; PS = performance status

Study IND 215 demonstrates that selumetinib can be safely administered concurrently with either cisplatin/pemetrexed or carboplatin/paclitaxel in selected patients with metastatic non-small cell lung cancer which is KRAS wild-type or unknown. Although patient numbers are small, the response rates compare favorably to published trials with cisplatin/pemetrexed and carboplatin/paclitaxel [3, 20]. This trial provided the RP2D for a randomized phase II trial of pemetrexed and platinum chemotherapy alone or in combination with intermittent or continuous selumetinib in *KRAS* wild type or unknown non-squamous NSCLC (CCTG IND.219).

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Compliance with ethical standards

Conflict of interest Dr. Seymour received funding for the Canadian Cancer Trials Group from AstraZeneca to support this trial. Dr. Goffin has received honorarium from Amgen, Boehringer Ingelheim, and Bristol-Myers Squibb and conference travel support from AstraZeneca. Dr. Juergens has consulted for and has received grant funding from AstraZeneca. All other authors had no conflicts to report.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. The study was approved by the research ethics boards of the participating institutions.

Informed consent Informed consent was obtained from all individual participants included in the study.

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