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Selumetinib in patients receiving standard pemetrexed and platinum-based chemotherapy for advanced or metastatic *KRAS* wildtype or unknown non-squamous non-small cell lung cancer: A randomized, multicenter, phase II study. Canadian Cancer Trials Group (CCTG) IND.219

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ABSTRACT

Introduction: Activation of the RAS/RAF/MEK/ERK pathway may confer resistance to chemotherapy in non-small cell lung cancer (NSCLC). Selumetinib (AZD6244, ARRY142886), a MEK1/2 inhibitor combined with chemotherapy in patients with NSCLC was evaluated in two schedules to evaluate efficacy and toxicity.

Methods: IND.219 was a three-arm study of first line pemetrexed/platinum chemotherapy with two schedules of selumetinib (Arm A: intermittent given on days 2–19; Arm B: continuous given on days 1–21) versus chemotherapy alone (Arm C). The primary endpoint was objective response rate (ORR); secondary objectives were tolerability, progression-free survival (PFS), overall survival (OS). The trial was stopped at the planned interim analysis.

Results: Arms A/B/C enrolled 20/21/21 patients, ORR was 35% (95% CI 15–59% median duration 3.8 months), 62% (95% CI 38–82%; median duration 6.3 months), 24% (95% CI 8–47%; median duration 11.6 months) respectively. The PFS (months Arm A, B, C) was 7.5, 6.7, 4.0 respectively (hazard ratio (HR) PFS Arm A over Arm C: 0.76 [95% CI, 0.38–1.51, 2-sided p = 0.42]; Arm B over Arm C 0.75 [95% CI 0.37–1.54, p = 0.43]. Skin and gastrointestinal adverse events were more common with the addition of selumetinib. A high incidence of venous thromboembolism was seen in all arms.

Conclusions: Selumetinib combined with chemotherapy was associated with a higher response rate. Continuous selumetinib appeared to be superior to an intermittent schedule. PFS was prolonged with the addition of selumetinib, however this was not statistically significant.

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1. Introduction

Lung cancer is the leading cause of world-wide cancer related mortality [1]. With the introduction of new agents such as tyrosine kinase inhibitors and checkpoint inhibitors, the treatment paradigm for patients with metastatic non-small cell lung cancer (NSCLC) is rapidly changing [2,3]. Despite significant advances, prognosis for lung cancer patients is still poor and new treatment approaches are necessary.

Platinum based pemetrexed combinations and pemetrexed maintenance therapy are beneficial for NSCLC patients with adenocarcinoma histology [4–6]. Chemotherapy agents may activate the RAS/RAF/MEK/ERK pathway, which may influence cell proliferation, survival, migration and angiogenesis and may contribute to drug resistance [7,8]. Treating drug resistant cells with a mitogen activated protein kinase (MEK) inhibitor may help mitigate this resistance and combining a MEK inhibitor with chemotherapy may be particularly efficacious.

Selumetinib (AZD6244, ARRY-142886) is a potent and selective inhibitor of MEK1/MEK2, and inhibits phosphorylation of ERK2 (Mitogen-activated protein kinase 1) [9,10]. *In vitro* studies demonstrated that cell lines harboring *BRAF* or *RAS* mutations were more sensitive to selumetinib [11]. A randomized phase II study in patients with *KRAS* mutation-positive NSCLC compared selumetinib plus docetaxel to placebo plus docetaxel, and showed promising results [12]. Although there was not a statistically significant difference in the primary overall survival (OS) endpoint, secondary endpoints of progression-free survival (PFS), objective response rate (ORR), and patients alive and progression free at six months each showed a statistically significant improvement in favor of selumetinib. Although a subsequent phase III trial did not confirm these results [13].

Response to MEK inhibitors may not be restricted to *KRAS* mutation positive disease, with preclinical data demonstrating MEK sensitivity gene signatures in both *KRAS* mutation and wildtype (WT) NSCLC [14–16]. Furthermore, preclinical data suggests a strong scheduling dependence, where combined treatment with chemotherapy and MEK inhibitors may be more active following a 48 h interruption in dosing with a MEK inhibitor, rather than dosing concurrently [17]. To address the question of schedule and explore efficacy in a population that was not selected for by *KRAS* mutation, we performed an open-label randomized phase II clinical trial of selumetinib administered in an intermittent or continuous schedule, in patients with advanced or metastatic *KRAS* WT or unknown status, non-squamous non-small cell lung cancer (NSCLC) who received pemetrexed combined with cisplatin or carboplatin as a first line palliative treatment.

2. Materials and methods

2.1. CCTG IND.219 study design and patients

The Canadian Cancer Trials Group (CCTG) conducted this randomized phase II study at 10 sites across Canada. Patients included were aged ≥18 years with *KRAS* confirmed histologically or cytologically as wild type or unknown non-squamous NSCLC that was stage IIIB or IV and for which standard curative measures did not exist. Eligible patients were of ECOG 0 or 1, had adequate bone marrow, renal and liver function, and measurable disease by RECIST 1.1 criteria. Prior surgery or radiotherapy was permitted. Prior adjuvant platinum-based chemotherapy or combined chemo-radiotherapy with curative intent was permitted provided it was completed at least one year prior to enrolment. Prior treatment with MEK or tyrosine kinase (including EGFR) inhibitors of any kind was not permitted, nor was any type of prior cytotoxic chemotherapy for advanced or metastatic disease. Patients with symptomatic brain metastasis or spinal cord compression were excluded, as were patients with a history of other untreated malignancies or malignancies which required therapy within the past 2 years. Also excluded were patients with significant cardiac disease, active infection, active bleeding diatheses or renal transplant, including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus, neuropathy, significant gastrointestinal disease, those on potent inhibitors or inducers of CYP3A4/5, CYP2C19 and CYP1A2, those with current or past history of central serous retinopathy or retinal vein occlusion, high intraocular pressure (IOP) or uncontrolled glaucoma (irrespective of IOP level).

All patients provided written informed consent and the study was done in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review board at each study site and complied with local country regulations.

2.2. Objectives

The primary objective of this study was to determine the ORR of selumetinib either administered in an intermittent or continuous schedule combined with pemetrexed/ platinum chemotherapy versus pemetrexed/ platinum chemotherapy alone. Secondary objectives included PFS and OS the tolerability of the different schedules and whether *KRAS* mutation status, the presence of other common mutations, or tumor based molecular signatures are predictive of selumetinib effect.

2.3. Randomization

Eligible patients were randomized 1:1:1 to one of the three treatment arms (Table 1): Intermittent oral selumatinib (Arm A) or continuous oral selumetinib (Arm B) combined with pemetrexed and platinum or pemetrexed and platinum chemotherapy alone (Arm C) stratified by *KRAS* status (WT versus unknown) and planned platinum treatment (cisplatin versus carboplatin). An interim analysis was planned after 20 patients had been randomized to each treatment arm, following which one of the selumetinib arms would be discontinued if the trial proceeded to full accrual. If at the interim analysis either Arm A and B had < 4 responses, that arm would be discontinued, if both Arm A and B had ≥4 responses, one arm would be selected based on response efficacy and toxicity data. If neither Arm A nor Arm B had ≥4 responses, the trial would be discontinued.

2.4. Procedures

Patients on all three treatment arms were to receive standard pemetrexed plus cisplatin or carboplatin for 4–6 cycles followed by maintenance pemetrexed if at least stable disease after the doublet chemotherapy (Table 1). Patients on Arms A and B were to take oral selumetinib. Treatment was discontinued if one or more of the following occurred: (1) intercurrent illness which would affect

Table 1
Treatment Schedules.

Arm	Selumetinib (oral)	Chemotherapy (Intravenous [i.v.])
A	selumetinib 75 mg twice a day on days 2-19	Pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) or carboplatin (AUC 6) by i.v. on day 1 every 21 days (for 4-6 cycles, followed by maintenance pemetrexed if at least stable disease after combination chemotherapy
B	selumetinib 75 mg twice continuously	Standard premedication including B12, folic acid and anti-emetics were administered according to product monograph and local and provincial formulary guidelines
C	No selumetinib	

Table 2
Baseline Patient Characteristics.

	Arm A N = 20	Arm B N = 21	Arm C N = 21	Total N = 62
Baseline Patient Characteristics				
Gender				
Female	10 (50%)	11 (52%)	11 (52%)	32 (52%)
Male	10 (50%)	10 (48%)	10 (48%)	30 (48%)
Median Age (range)	68 (50–80)	66 (53–82)	65 (42–85)	66 (42–85)
> 65	11 (55%)	12 (57%)	10 (48%)	33 (53%)
< 65	9 (45%)	9 (43%)	11 (52%)	29 (47%)
Smokers				
Present	1 (5%)	4 (19%)	3 (14%)	8 (13%)
Past	17 (85%)	14 (66%)	17 (80%)	48 (77%)
Never	2 (10%)	3 (14%)	1 (5%)	6 (10%)
ECOG Performance Status:				
0	4 (20%)	3 (14%)	3 (14%)	10 (16%)
1	16 (80%)	18 (86%)	18 (86%)	52 (84%)
Histology: Adenocarcinoma	19 (95%)	18 (86%)	18 (86%)	55 (89%)
Not otherwise specified	0 (0%)	2 (10%)	1 (5%)	3 (5%)
Other	1 (5%)	1 (5%)	2 (10%)	4 (6%)
Brain Metastasis				
No	11 (55.0%)	10 (47.6%)	10 (47.6%)	31 (50.0%)
Yes	0 (0.0%)	4 (19.0%)	1 (4.8%)	5 (8.1%)
Missing	9 (45%)	7 (33.3%)	10 (47.6%)	26 (41.9%)
KRAS status analyzed after enrollment				
WT	11 (55%)	7 (33%)	9 (43%)	27 (44%)
Mutation +	6 (30%)	11 (52%)	10 (48%)	27 (44%)
Assessment not successful	2 (10%)	1 (5%)	2 (10%)	5 (8%)
Missing sample	1 (5%)	2 (10%)	0 (0 %)	3 (5%)
EGFR status analyzed after enrollment				
WT	14 (70%)	14 (67%)	17 (81%)	45 (73%)
Mutation +	3 (15%)	4 (19%)	2 (10%)	9 (15%)
Assessment not successful	2 (10%)	1 (5%)	2 (10%)	6 (10%)
Missing sample	1 (5%)	2 (10%)	0 (0%)	3 (5%)
Previous Anticancer treatment at baseline				
Prior surgery				
Yes	2 (10%)	2 (10%)	1 (5%)	5 (8.1%)
No	18 (90%)	19 (90%)	20 (95%)	57 (92%)
Prior radiotherapy				
Yes	11 (55%)	11 (52.4%)	9 (42.9%)	31 (50%)
No	9 (45%)	10 (47.6%)	12 (57.1%)	31 (50%)
At least one prior systemic therapy	5 (25.0%)	1 (4.8%)	1 (4.8%)	7 (11.3%)
Therapy setting/intent[a]				
Adjuvant	2 (10.0%)	1 (4.8%)	0 (0.0%)	3 (4.8%)
Combination chemotherapy-radiation (with curative intent)	3 (15.0%)	0 (0.0%)	1 (4.8%)	4 (6.5%)
Prior systemic drug /agent[b]				
Carboplatin	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (1.6%)
Cisplatin	5 (25.0%)	1 (4.8%)	0 (0.0%)	6 (9.7%)
Docetaxel	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (1.6%)
Vinorelbine	4 (20.0%)	1 (4.8%)	0 (0.0%)	5 (8.1%)

Abbreviations: WT wildtypeARM A: pemetrexed/platinum/selumetinib intermittent scheduleARM B: pemetrexed/platinum/selumetinib continuous scheduleARM C: pemetrexed/ platinum.

[a] Patients may have more than one setting/intent.

[b] Patient may have more than one drug or regimen.

assessments of clinical status and require discontinuation of protocol therapy; (2) unacceptable toxicity; (3) tumor progression; (4) or patient request.

Two selumetinib dose reductions were permitted for toxicity; from 75 mg BID to 50 mg twice a day and 50 mg once a day, patients had to discontinue selumetinib if a third dose reduction was required.

Response was evaluated every 6 weeks during protocol treatment, using the RECIST (Response Evaluation Criteria in Solid Tumors) criteria 1.1. Safety was assessed and graded using the NCI CTCAE (Version 4).

2.5. Statistical analysis

All comparisons between treatment arms were carried out using a one-sided test at an alpha level of 10% unless otherwise specified. When appropriate, discrete variables are summarized with the number and proportion of subjects falling into each category, and compared using Fisher's exact test. Continuous and ordinal categorical variables are summarized using the mean, median, standard error, minimum and maximum values and when appropriate, compared using the Wilcoxon test. All confidence intervals are computed based on normal approximations except those for rates, which will be computed based on the exact method. The time to event variables were summarized using Kaplan-Meier plots. Primary comparisons of the treatment groups are made using the stratified log-rank test. Primary estimates of the treatment differences are obtained with the hazard ratios and 95% confidence intervals from stratified Cox regression models using treatment arm as the single factor.

Percentages given in the summary tables are rounded and may therefore not always add up to exactly 100%. Listings, tabulations, and statistical analyses will be carried out using the SAS (Statistical Analysis System, SAS Institute, North Carolina, USA) software.

This study is registered with ClinicalTrials.gov, number NCT02337530.

2.6. Correlative analyses

Tumor tissue was collected from all randomized patients to evaluate KRAS expression and other molecular variants, and three gene signatures that may predict benefit from MEK inhibitors. Next generation sequencing of tumor tissue was performed using genomic DNA from baseline FFPE slides and/or tissue blocks. Targets of interest were amplified using a highly multiplexed PCR assay and sequenced using Illumina technology.

Three gene signatures were evaluated, an 18 gene signature, 13 gene signature and a lung optimized gene signature as previously been reported by Brant et al and Dry et al. [15,16]. Given the small number of available samples, a median cut point was selected for analysis.

2.7. Role of the funding source

This trial was partially funded by the AstraZeneca, but they did not provide input or oversight into how the trial was conducted, data collection and analysis or manuscript preparation. The study was designed and conducted by the CCTG under the leadership of the principal investigators and CCTG senior investigator. CCTG was responsible for data collection, data analysis, and had a role in data interpretation. This report was written by BM and PB, and was reviewed and approved for publication by all coauthors. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the publication.

3. Results

Between February 5, 2015, and November 11, 2016, 20 patients were randomized to arm A and 21 to each of Arms B and C. All 62 patients received at least one dose of protocol treatment.

Baseline characteristics were generally well balanced between the three arms (Table 2). The median age was 66 (range 42 to 85) years and 52% were female, 85% of patients had an ECOG performance status of 1. The majority of patients were prior smokers (89%), with 13% currently smoking at time of randomization. Adenocarcinoma was the

histologic type for most patients (89%). Median time from first histological diagnosis to randomisation was 1.9 months (range from 0.6 to 135.8 months).

This trial was conducted in patients who were *KRAS* wild type or unknown; after enrollment tissue samples from 59 patients were tested for KRAS mutation, which was present in 27 (44%) patients and unknown in 8 patients. Fifteen percent of patients had mutated *EGFR,* but mutation was very rare for other genes tested (1 patient or 2% for *MET*, *IDH1*, *NRAS*, *GRAS*, *PIK3CA*; and 3 patients or 5% for *BRAF*).

3.1. Protocol treatment

The median number of cycles was similar across all three arms. Dose modifications were common; 30% of patients on Arm A and 43% on Arm B received 90% or more of planned selumetinib dose and 55% of patients on Arm A, 38% on Arm B, and 52% on Arm C had 90% or higher relative dose intensity of pemetrexed (Supplementary Table 1).

Selumetinib doses were reduced at least once in 7 patients (35%) on Arm A and 9 patients (43%) on Arm B. The proportion of patients who had at least one dose reduction of pemetrexed was marginally higher on arm B (Arm A: 5 patients [25%], Arm B: 7 [33%], Arm C: 5 [24%] and a similar pattern of dose reductions for 7 patients that received carboplatin (Arm A: 2 [29%]; Arm B: 3 [43%], Arm C: 2 [33%] although similar rates of dose reductions for cisplatin (4 patients [24%] on Arm A, 4 [24%] on Arm B, and 4 [22%] on Arm C). Disease progression was the most common reason for discontinuing selumetinib and pemetrexed (Arm A: 5 [20%] and 8[40%], Arm B: 8 [38%] and 8[38%] and Arm C: 13 [62%] respectively). Selumetinib was discontinued due to adverse events in 35% of patients on Arm, A and 57% of patients on Arm B and for pemetrexed 15% on Arm A; 38% on Arm B and 9% on Arm C.

3.2. Treatment response

A total of 25 patients had a partial response on treatment, 6 on Arm A (30.0% ORR [95% CI 11.9–54.3%]), 14 on Arm B (66.7% ORR [95% CI 43.0–85.4%]), and 5 on Arm C (23.8% ORR [95% CI 8.22–47.2%]) (Table 3). P-value was respectively 0.51 for the comparison in response between Arms A and C and 0.03 between Arms B and C. After adjusting for the potential prognostic factors (gender [male vs. female], age [< = 65 vs. > 65 years], ECOG performance status [1 vs. 0], KRAS status [WT vs. mutated]), the adjusted p-value was respectively 0.68 for the comparison in response between Arms A and C and 0.003 between Arms B and C. The median duration of response was 4.2 months (95% CI 2.8–15.2 months) for patients on Arm A, 5.6 months (95% CI 3.2–7.0 months) on Arm B, and 11.6 months (95% CI 2.7 – NE) for patients on Arm C (Supplementary Table 2).

Table 3
Best response by RECIST Version 1.1.

	Number of patients (%)[a]		
	Arm A N = 20	Arm B N = 21	Arm C N = 21
Complete Response (CR)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Partial response (PR)	6 (30.0%)	14 (66.7%)	5 (23.8%)
Stable disease (SD)	11 (55.0%)	5 (23.8%)	9 (42.9%)
Progressive disease (PD)	1 (5.0%)	2 (9.5%)	5 (23.8%)
Not evaluable for response (IN)	1 (5.0%)	0 (0.0%)	2 (10.0%)
Not assessed	1	0	0

Data set includes all randomized patients.
Abbreviations: ARM A: pemetrexed/ platinum/ selumetinib intermittent schedule, ARM B: pemetrexed/ platinum/ selumetinib continuous schedule, ARM C: pemetrexed/ platinum.
[a] Percentages are calculated out of the number of randomized patients.

3.3. Progression free survival

The Kaplan-Meier curve for PFS by treatment arm is presented in Fig. 1. Median PFS was 7.2 months (95% CI 4.0–8.6 months) for patients on Arm A, 6.9 months (95% CI 4.6–8.6 months) on Arm B, and 4.0 months on Arm C (95% CI from 1.4 to 6.8 months).

The hazard ratio (HR) for median PFS of ARM A over ARM C was 0.82 (95% CI0.42–1.60, p-value of the two-sided log-rank test was 0.56). The HR adjusting for the potential prognostic factors between Arm A and Arm C was 0.65 (95% CI0.28–1.51 and p = 0.31). No significant median PFS differences between Arms A and C was found in any of the subset analyses, based on performance status, age, gender and *KRAS, EGFR* and *BRAF* mutation status.

The HR for median PFS of ARM B over ARM C was 0.77 (95% CI 0.40–1.49, p 0.44). The HR adjusting for the potential prognostic factors between Arm B and Arm C was 0.62 (95% CI 0.28 -1.35, p = 0.23). No significant differences between Arms B and C were found in any of the subset analyses.

3.4. Overall survival

The median OS was 10.0 months (95% CI from 5.9 - NE) for patients on Arm A, 10.1 months (95% CI 8.0–13.3 months) on Arm B, and 15.3 months (95% CI from 3.8 -NE) on Arm C. The Kaplan-Meier curve for OS by treatment arm is presented in Fig. 1.

The HR for OS of ARM A over ARM C was 1.56 (95% CI0.66 - 3.69, two-sided log-rank test p = 0.31). The HR adjusting for the potential prognostic factors between Arm A and Arm C was 1.43 (95% CI 0.54–3.82, p = 0.47). No significant differences between Arms A and C was found in any of the subset analysis.

The HR for OS of ARM B over ARM C was 1.72 (95% CI 0.74–3.98, two-sided log-rank test p = 0.20). The HR adjusting for the potential prognostic factors between Arm B and Arm C was 1.78 (95% CI0.65 - 4.86, p = 0.26). No significant differences between Arms B and C were found in any of the subset analysis.

3.5. Safety

Table 4 summarises all causality adverse events experienced by > 20% patients. Gastrointestinal adverse events including diarrhea, dry mouth, abdominal pain, mucositis and vomiting were more common in the selumetinib combinations, particularly for Arm B. Skin toxicities including skin rash and dry skin was also more common in the selumetinib arms compared with chemotherapy alone, as was peri-orbital edema. The incidence of venous thromboembolism was high across all arms, but higher in the selumetinib arms (Arm A: 45%, Arm B 38%, versus Arm C 24%).

3.6. MEK signature

Three MEK signatures were evaluated MEK, MEK CR, MEK Lung (Table 5). Given the small number of patients, a median cut-point was selected for analysis. Patients randomized to the selumetinib containing arms, with the high value of each of the three signatures trended to superior PFS from selumetinib (intermittent or continuous) treatment, while the patients with low value of signatures had smaller or no benefits. This was especially evident for MEK CR signature (interaction p = 0.055), although none were statistically significant.

4. Discussion

The CCTG IND.215 clinical trial demonstrated selumetinib at a dose of 75 mg twice a day, combined with standard dose platinum based combination chemotherapy was tolerable, and with a response rate of > 30% in a patients with NSCLC without selection for KRAS, lead to this randomized phase II trial (IND.219) to further explore efficacy and

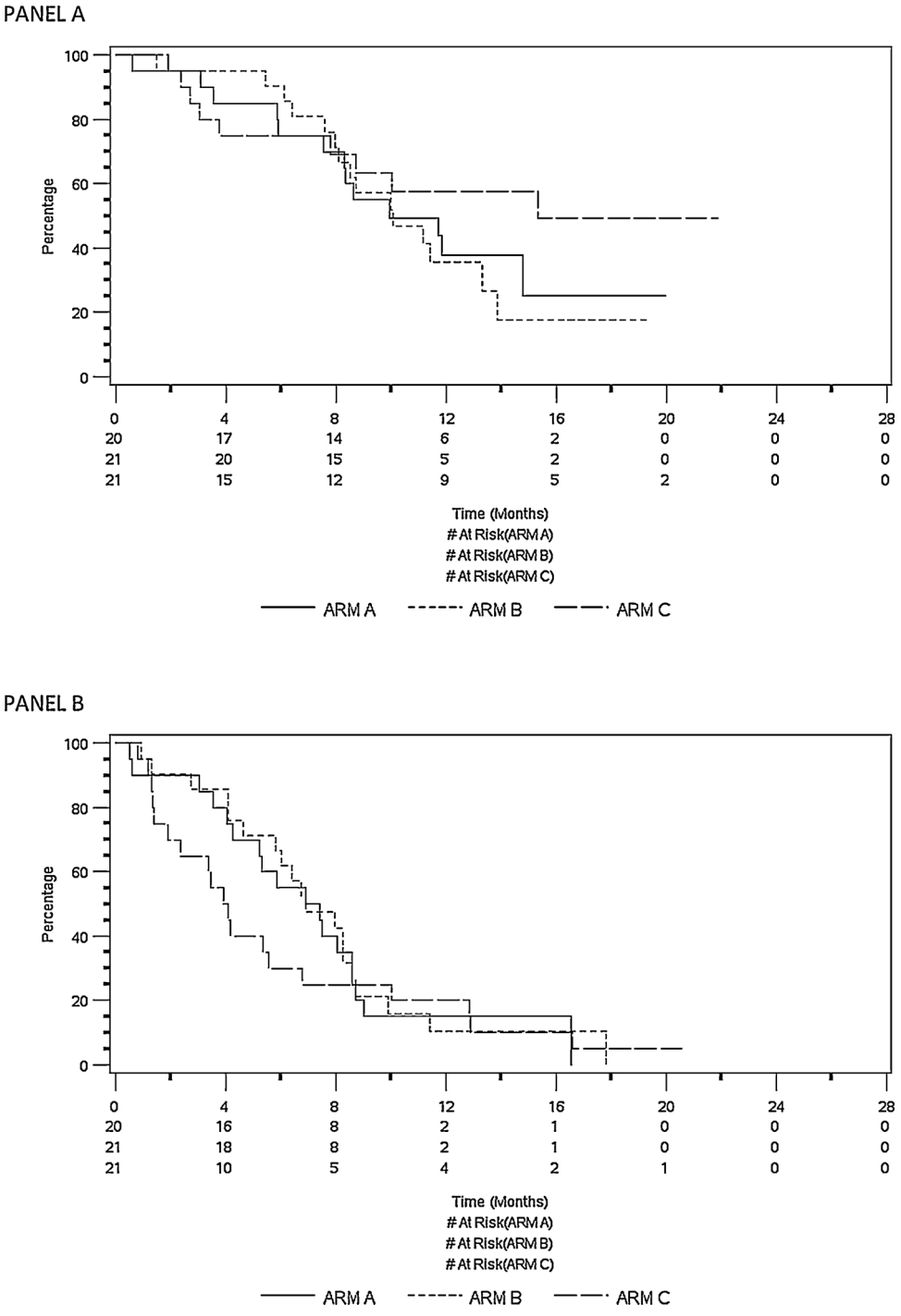

Fig. 1. Kaplan-Meier Curves for PFS and OS.
Panel A: Arm A versus Arm C: PFS 7.2 months versus 4.0 months HR 0.82 (0.42–1.60) p = 0.56.
Arm B versus Arm C: PFS 6.9 months versus 4.0 months HR 0.77 (0.40–1.49) p = 0.44. Panel B: Arm A versus Arm C: OS 10.0 (5.9 – not evaluable (NE)) months versus 15.3 (3.8-NE) months HR 1.56 (0.66–3.69) p = 0.31. Arm B versus Arm C: OS 10.1 (8.0–13.3) months versus 15.3 (3.8-NE) months HR 1.72 (0.74–3.98) p = 0.20.

two selumetinib regimens [18]. IND.219 demonstrated that superior response rates and a non-significant trend for improved PFS are associated with selumetinib combined with chemotherapy as compared to platinum-based chemotherapy alone. The continuous schedule appeared to have superior efficacy compared with the intermittent schedule, with no evidence to suggest there was an antagonistic effect of combining selumetinib on the same days as chemotherapy administration. Based on the protocol specified criteria, the achieved efficacy would have enabled the trial to move forward to complete accrual; however, after review by the trial committee, and given the large number of competing trials and the likelihood that standard or care would change with checkpoint inhibitors moving into the first line setting, a decision was made to not proceed with the second stage of the trial.

During the conduct of this trial, results became available from the phase III SELECT-1 study of selumetinib plus docetaxel versus docetaxel and placebo in patients with *KRAS* mutated NSCLC in the second line setting [12]. There was no improvement in either PFS or OS (PFS HR

Table 4
Adverse events in patients.

	All toxicities occurring in > 20% of patients regardless of attribution																
	Arm A N = 20						Arm B N = 21						Arm C N = 21				
NCI CTCAE grade	1	2	3	4	5	N (%)	1	2	3	4	5	N(%)	1	2	3	4	5	N(%)
Eye disorders																		
Watering eyes	4					4(20)	3					3(14)	4	2				6(29)
Gastrointestinal Disorders																		
Abdominal pain	2	1	1			4(20)	4	3				7(33)	2	1				3(14)
Bloating	4					4(20)	0					0(0)	0					0(0)
Constipation	10	2				12(60)	9	5	1			15(71)	12	5	1			18 (86)
Diarrhea	9	2				11(55)	12	1				13(62)	4	3	2			9(43)
Dry mouth	4					4(20)	2					2(10)	0					0(0)
Dyspepsia	2	3				5(25)	2	3				5(24)	4	3	2			9(43)
Gastroesophageal reflux	1	1				2(10)	3	1				4(19)	2					2(10)
Oral mucositis	2		1			3(15)	5	2	2			9(43)	3	3				6(29)
Nausea	9	3	2			14(70)	5	10	1			16(76)	10	6	1			17(81)
Vomiting	9	2	2			13(65)	8	7	1			16(76)	11	2				13(62)
General disorders																		
Edema, face	3	1				4(20)	4	1				5(24)	4					4(19)
Edema, limbs	5	4	2			11(55)	11	5				16(76)	8	3				11(52)
Fatigue	5	13	1			19(95)	6	9	5			20(95)	4	8	6			18(86)
Non-cardiac chest pain	1	3				4(20)	2	1				3(14)	2	2	1			5(24)
Pain	2	2				4(20)	4	1				5(24)	1	3				4(19)
Infections																		
Lung infection		3	1			4(20)			2			2(10)		1	2			3(14)
Metabolism and nutrition disorders																		
Anorexia	4	6	1			11(55)	3	12				15(71)	7	4				11(52)
Dehydration		3	2			5(25)		3	4			7(33)		1				1(5)
Hypomagnesemia	3		1			4(20)	2	1	1			4(19)	2					2(10)
MSK and connecting tissue																		
Arthralgia	3	1				4(20)	3					3(14)	0					0(0)
Back pain	8					8 (40)	1	3				4(19)	2	6	3			11(52)
Pain, extremity	5					5(25)	5	2				7(33)	3	2				5(24)
Nervous system and psychiatric disorders																		
Anxiety	1	2				3(15)	1	2				3(14)	4	2				6(29)
Dizziness	1					1(5)	10					10(48)	4	1				2(10)
Headache	5	1				6(30)	8	1				9(43)	5	2				7(33)
Peripheral sensory neuropathy	6					6(30)	4					4(19)	5					5(24)
Insomnia	7	2				9 (45)	6	3				9(43)	5	1				6(29)
Respiratory																		
Cough	9	4	1			14(70)	12	3				15(71)	14	2				16(76)
Dyspnea	6	3	1			10(50)	9	6	1			16(76)	8	5	1			14(67)
Hoarseness	4					5(20)	1					1(5)	3					3(14)
Sore throat	2					2(10)	4	1				5(24)	1					1(5)
Skin and subcutaneous																		
Dry skin	4	1				5(25)	4	2				6(29)	2					2(10)
Periorbital edema	2	2				4(20)	3	4				7(33)	2					2(10)
Pruritus	3	1				4(20)	2	1				3(14)	0					0(0)
Rash acneiform	8	2	1			11(55)	5	3	1			9(43)	1	1				2(10)
Rash maculo-papular	3	1				4(20)	6	1				7(33)	1					1(5)
Vascular disorders																		
Hypotension	1					1(5)	3		3			6(29)	0					0(0)
Thromboembolic event		1	6	1	1	9(45)	1	2	5			8(38)	2		3			5(24)
Haematology[a]																		
Neutropenia		7	3	1		11 (55%)	2	7	4	3		16 (76%)	3	2	6	2		13 (62%)
Anemia	6	10	3	1		20(100%)	6	11	3	1		21 (100%)	6	10	5			21 (100%)
Thrombocytopenia	4	2	1	2		9 (45%)	8	3	2	2		15 (71%)	6	3		1		10 (48%)
Serum Creatinine	6	3				9(45%)	11	2				13 (62%)	9	2				11 (52%)
Elevated Alk Phos	7					7 (35%)	5					5 (24%)	6	1				7 (33%)
Elevated AST	10	1				11 (55%)	14	2	1			17 (81%)	8					8 (38%)
Elevated ALT	5		2			7 (35%)	10	2	1			13 (62%)	9					9 (43%)
Hypoalbuminemia	6	8	3			17 (85%)	8	9	1			18 (71%)	7	8				18 (71%)
Elevated LDH	18	1				19 (95%)	19	2				21 (100%)	18					18 (86%)

Abbreviations: ARM A: pemetrexed/ platinum/ selumetinib intermittent schedule, ARM B: pemetrexed/ platinum/ selumetinib continuous schedule, ARM C: pemetrexed/ platinum.

[a] Note that not all the patients were tested for each laboratory test. Abbreviations: ALK phos, alkaline phosphatase; AST, Aspartate amino-transferase; ALT; Alanine amino-transferase; LDH, Lactic dehydrogenase.

Table 5
Progression Free Survival Analysis of Patients with High and Low Mek Signature (MEK, MEK CR, and MEK Lung).

Signature	Subgroup[a]	N	Arm A Median PFS (95% C.I.)	N	Arm C Median PFS (95% C.I.)	Hazard Ratio (95% CI) [p-value]	Interaction Hazard Ratio (95% CI) [p-value]
Arm A to C							
MEK	> 7.5	3	6.9 (0.5– 8.6)	6	2.4 (0.8–10.0)	0.96 (0.21–4.50, p = 0.96)	0.91 (0.11– 7.47, p = 0.93)
	≤7.5	4	6.4 (4.0– 16.6)	4	5.5 (4.0–12.9)	0.67 (0.15– 3.02, p = 0.60]	
MEK CR	> 6.6	4	7.8 (0.5– 16.6)	5	2.9 (0.8– 4.2)	0.18 (0.02– 1.72, p = 0.14)	0.09 (0.01–1.05, p = 0.06)
	≤6.6	3	4.3 (4.0- 8.6)	5	6.8 (1.3- 12.9)	1.85 (0.37- 9.28, p = 0.46)	
MEK Lung	> 7.5	2	7.8 (6.9– 8.6)	5	2.9 (0.8– 10.0)	0.71 (0.11– 4.45, p = 0.96)	0.66 (0.08– 5.86, p = 0.71)
	≤7.5	5	4.3 (0.5– 16.6)	5	4.2 (1.3– 6.8)	0.75 (0.20– 2.82, p = 0.67)	
Arm B to C							
MEK	> 7.5	5	8.6 (2.8– 17.8)	6	2.4 (0.8– 10.0)	0.34 (0.08– 1.46, p = 0.15)	0.25 (0.02– 2.50, p = 0.24)
	≤7.5	2	7.3 (4.6– 9.9)	4	5.5 (4.0– 12.9)	0.95 (0.15– 5.77, p = 0.95)	
MEK CR	> 6.6	3	8.6 (6.9– 17.8)	5	2.9 (0.8– 4.2)	0.00 (0.00– NA, p = 1.00)	0.07 (0.01– 0.95, p = 0.05)
	≤6.6	4	7.3 (2.8– 9.9)	5	6.8 (1.3– 12.9)	1.31 (0.26– 6.55, p = 0.74)	
MEK Lung	> 7.5	5	8.6 (2.8- 17.8)	5	2.9 (0.8- 10.0)	0.39 (0.09- 1.82, p = 0.23)	0.37 (0.04- 3.71, p = 0.40)
	≤7.5	2	7.3 (04.6– 9.9)	5	4.2 (1.3– 6.8)	0.77 (0.14– 4.30, p = 0.77)	

MEK: DUSP6; PHLDA1; ETV5; SPRY2; DUSP4; ETV4; ELF1; LGALS3; KANK1; TRIB2; MAP2K3; LZTS1; PROS1; ZNF106; S100A6; SERPINB1; SLCO4A1; FXYD5
MEK CR: BASP1; CD274; CLU; COL12A1; COL5A1; CRIM1; FZD2; G0S2; GPR176; IL6; LOX; SERPINE1; STAC
MEK LUNG: PHLDA1; SPRY2; DUSP6; DUSP4; ETV4; ETV5

Abbreviations: ARM A: pemetrexed/ platinum/ selumetinib intermittent schedule, ARM B: pemetrexed/ platinum/ selumetinib continuous schedule, ARM C: pemetrexed/ platinum.

[a] Cutpoint defining the subgroup for each signature was determined by median of all values.

0.93 [95% CI, 0.77–1.12]; P = .44); OS HR, 1.05 [95% CI, 0.85–1.30]; P = .64), although response rate favored the addition of selumetinib.

The IND219 trial was designed to evaluate efficacy in a population with *KRAS* WT or unknown in order to confirm that MEK inhibitors may not be restricted to *KRAS* mutation positive disease [14–16]. *KRAS* testing was not routine across Canada when this trial was activated. Overall 44% of patients were KRAS mutation positive, with some imbalance across the arms with, almost 50% of patients in arm B and C had *KRAS* mutation positive disease with 30% in Arm A. However, there was no apparent association between *KRAS* status and efficacy. Although some *KRAS* mutation subtypes are hypothesized to preferentially benefit from selumetinib, the subset analysis of *KRAS* mutations in SELECT-1 did not support this. Three MEK signatures were evaluated based on prior published work by Brant et al and Dry et al. [15,16]. Patients with higher signature values trended toward an improved PFS, but given small numbers of patients, interpretation is limited.

The addition of selumetinib was associated with skin and some gastrointestinal adverse events compared to chemotherapy alone. One notable finding of our trial, was the high rate of venous thromboembolism (VTE) in all three arms and highest in the selumetinib arms. A previous study reported the incidence of VTE in CCTG trials [19] was < 8% in patients with advanced NSCLC receiving first line chemotherapy, however in our trial we found VTE rates of 24% on the chemotherapy arm and 45% and 38% on the intermittent and continuous selumetinib arms respectively. Ades et al. [20] reported similar rates of VTE in patients with KRAS mutation positive colorectal cancer, which was substantially higher than that of patients with WT *KRAS* disease. Given the small numbers of patients we were not able to assess the association between KRAS status and VTE in this trial. Furthermore, there did not appear to be a high rate of VTE in the SELECT-1 trial which enrolled patients with advanced KRAS mutation positive NSCLC [13]. Alternatively, dehydration secondary to diarrhea may have increased the VTE risk of this population.

There are limitations to this trial. The trial only enrolled approximately 20 patients to each arm, preventing definitive conclusions regarding the efficacy of the combination in first line NSCLC. Furthermore, while the trial was intended to address the question of efficacy in patients with KRAS WT or unknown NSCLC, a high proportion of patients were subsequently found to have KRAS mutation positive disease. Proceeding to the planned second phase of the trial would have enabled more definitive conclusions; however, the landscape was rapidly changing with multiple trials evaluating the role of checkpoint inhibitors in patients with advanced NSCLC. Checkpoint inhibitors either as single agents or in combination with chemotherapy have demonstrated OS benefits compared to standard chemotherapy for patients with advanced NSCLC in the first line setting [3].

In summary, this study did not show an appreciable difference in toxicity or efficacy between an intermittent or continuous schedule of selumetinib. The trial was stopped at the interim analysis, which demonstrated the combination of selumetinib and platinum-based chemotherapy in the first line setting was associated with higher ORR. Progression free survival was numerically prolonged with the combination, but at the expense of increased gastrointestinal and skin toxicities, but this was not statistically significant.

Previous presentation of results

Interim results from study IND.219 were presented at the IASLC (International Association for the Study of Lung Cancer) 18th World Conference on Lung Cancer, held in Yokohama, Japan, October 15–18, 2017.

Transparency document

The Transparency document associated with this article can be found in the online version.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the

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