A Phase I study of the MEK1/2 inhibitor selumetinib in combination with first-line chemotherapy regimens for NSCLC

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Introduction

- MEK1/2 forms an integral part of the Ras/Raf/MEK/ERK pathway, the dysregulation of which is implicated in tumourigenesis via aberrant upstream growth factor signalling[1] or the direct activation of Ras and Raf.[1–3]
- Selumetinib (AZD6244, ARRY-142886) is an orally available, potent and selective, non-ATP-competitive MEK1/2 inhibitor, with activity in combination with docetaxel in the second-line setting for *KRAS*-mutant advanced non-small cell lung cancer (NSCLC).[4]
- This Phase I study (NCT01809210) was undertaken to assess the safety, tolerability and recommended Phase II combination dose (RP2D) of selumetinib when administered in combination with first-line chemotherapy regimens in patients with advanced/metastatic NSCLC (primary objective). Secondary objectives included assessment of the pharmacokinetics (PK) and activity of the combination.
- This is the first study to assess selumetinib in combination with standard first-line chemotherapy for NSCLC. The study is ongoing and here we present preliminary data.

Methods

- Patients ≥18 years with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC and World Health Organization performance status 0–1 who were eligible for standard first-line treatment for NSCLC and unsuitable for radical treatment were eligible for inclusion.
- Study design is shown in Figure 1.
  - Part A evaluated escalating doses of selumetinib to determine the maximum tolerated dose (MTD) in combination with standard first-line chemotherapy regimens.
  - Patients were enrolled into dose-finding cohorts to receive orally administered selumetinib (50 mg twice daily [bid] [sel50], 75 mg bid [sel75], 100 mg bid [sel100]) in combination with standard doses of gemcitabine (gem) or pemetrexed (pem) plus cisplatin (cis) or carboplatin (carb). Chemotherapy was administered on Day 1 (and Day 8 for gemcitabine) of each 3-week cycle.
  - On completion of chemotherapy, patients had the option of maintenance selumetinib.
- Adverse events (AEs) were reported and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
- For decisions on cohort tolerability, an evaluable patient was defined as having received ≥75% of the specified dose of selumetinib from Cycle 1 or having experienced a dose-limiting toxicity (DLT) as defined in the protocol.
- DLTs were defined as any toxicity not attributable to the disease, which was considered related to the combination of chemotherapy+selumetinib, which occurred any time in Cycle 1 and was dose limiting as per standard DLT criteria as defined in the protocol.
- Tumour response was evaluated using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Patients must have had a measurable lesion at baseline scan to be eligible for study entry. Scans were conducted every 6 weeks from baseline.
- Blood samples to determine the pharmacokinetics (PK) of selumetinib, selumetinib metabolites and chemotherapy agents were collected on Cycle 1, Day 8 (C1D8) and Cycle 2, Day 1 (C2D1).

Figure 1. Study overview*

Selumetinib (50 mg bid) Gemcitabine (1250 mg/m²) Cisplatin (75 mg/m²)	Selumetinib (75 mg bid) Gemcitabine (1250 mg/m²) Cisplatin (75 mg/m²)	Selumetinib (50 mg bid) Gemcitabine (1250 mg/m²) Carboplatin (AUC=5)	Selumetinib (50 mg bid) Pemetrexed (500 mg/m²) Carboplatin (AUC=5)	Selumetinib (75 mg bid) Pemetrexed (500 mg/m²) Carboplatin (AUC=5)	Selumetinib (100 mg bid) Pemetrexed (500 mg/m²) Carboplatin (AUC=5)	Selumetinib (75 mg bid) Pemetrexed (500 mg/m²) Cisplatin (75 mg/m²)
N=3 enrolled	N=5 enrolled	N=9 enrolled	N=3 enrolled	N=6 enrolled	N=0 enrolled	N=6 enrolled
No DLTs	Grade 4 anaemia, n=1	Grade 4 thrombocytopenia, n=2	No DLTs	No DLTs		
TOLERATED	ONGOING†	NOT TOLERATED	TOLERATED	TOLERATED	ONGOING†	ONGOING†

*Cohorts enrolled in parallel. Patients are still ongoing on treatment in the following cohorts: sel50+gem+carb, n=1; sel75+gem+cis, n=2; sel75+pem+carb, n=1 (partial response case)
†The cohort is still open to recruitment; patients are still undergoing treatment and sufficient patients have not completed the safety evaluation to assess for DLTs
AUC, area under the curve

Results

- This study is ongoing. Here we present the preliminary, unvalidated results (data cut-off: 1 August 2014).
- In total, 26 patients have received treatment across five cohorts (Figure 1). At the time of data cut-off, no patients had been enrolled onto the cohort evaluating sel100+pem+carb. Data from the sel75+pem+cis cohort are not presented as patients were ongoing in Cycle 1 at the time of data cut-off.
- Baseline characteristics were as expected in patients with advanced NSCLC (Table 1, safety analysis set).
- Data on treatment discontinuation and reasons (all patients) are presented in Table 2.

Table 1. Baseline demographic and disease characteristics (safety analysis set)

Characteristic	Sel50, gem, cis (n=3)	Sel75, gem, cis* (n=5)	Sel50, gem, carb (n=9)	Sel50, pem, carb (n=3)	Sel75, pem, carb (n=6)	Total (n=26)
Age (median), years	57	56	69	61	58	62
Sex, n (%)						
Male	2 (67)	3 (60)	4 (44)	2 (67)	2 (33)	13 (50)
Female	1 (33)	2 (40)	5 (56)	1 (33)	4 (67)	13 (50)
WHO PS, n (%)						
0	0 (0)	3 (60)	1 (11)	2 (67)	0 (0)	6 (23)
1	3 (100)	2 (40)	7 (78)	1 (33)	6 (100)	19 (73)
Histology, n (%)						
Non-squamous	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)
SCC (NOS)	3 (100)	3 (60)	6 (67)	0 (0)	0 (0)	12 (46)
ADC (NOS)	0 (0)	0 (0)	3 (33)	3 (100)	5 (83)	11 (42)
ND	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	1 (4)
Stage, n (%)						
IIIB	0 (0)	0 (0)	2 (22)	0 (0)	1 (17)	3 (12)
IV	3 (100)	4 (80)	7 (78)	3 (100)	5 (83)	22 (85)

*Disease characteristic information was not recorded for one patient
ADC, adenocarcinoma; ND, not determined; NOS, not otherwise specified; SCC, squamous cell carcinoma; WHO PS, World Health Organization performance status

Table 2. Summary of discontinuations (all patients)

	Selumetinib (n=26)*	Cisplatin (n=8)*	Gemcitabine (n=17)*	Carboplatin (n=18)*	Pemetrexed (n=9)*
Total discontinuations,† n (%)	20 (77)	4 (50)	11 (65)	13 (72)	6 (67)
Reason for discontinuation, n (%)					
Adverse event	8 (31)	2 (25)	4 (24)	3 (17)	1 (11)
Disease progression	7 (27)	2 (25)	3 (18)	2 (11)	1 (11)
Other‡	5 (19)	0 (0)	4 (24)	8 (44)	4 (44)

*Number of patients who received specific treatment as part of a combination therapy
†Discontinuation of investigational product/chemotherapy regimen: data captured for each therapy
‡Includes development of patient-specific discontinuation criteria; severe non-compliance with protocol, patient decision; patient lost to follow-up; other reasons; maximum cycles of chemotherapy reached (chemotherapy regimens only)

Safety and tolerability

- To date:
  - Sel50+gem+carb was not tolerated.
  - Sel50+gem+cis, sel50+pem+carb and sel75+pem+carb were tolerated dose combinations.
  - Sel75+gem+cis, sel100+pem+carb and sel75+pem+cis cohorts are ongoing (Figure 1).
- Median actual selumetinib exposure across all cohorts was 87 days (range 1–229), but varied between cohorts (Table 3).
- DLTs were reported in the sel75+gem+cis (Grade 4 anaemia, n=1) and sel50+gem+carb (Grade 4 thrombocytopenia, n=2) cohorts.
- AEs were reported in 26 patients (100%); events were considered by the investigator to be causally related to selumetinib in 22 patients (85%), to gemcitabine in 18 patients (69%), to cisplatin in eight patients (31%), to carboplatin in 15 patients (58%) and to pemetrexed in six patients (23%).
- Overall, the most commonly reported AEs were nausea, thrombocytopenia, anaemia, vomiting and diarrhoea (Table 4).
- AEs of CTCAE Grade ≥3 were reported in 18 patients (69%).
  - Haematological AEs of CTCAE Grade ≥3 that were reported in more than a single patient were:
    - neutropenia (n=4, all sel50+gem+carb)
    - thrombocytopenia (n=6, all sel50+gem+carb)
    - leukopenia (n=3, all sel50+gem+carb)
    - anaemia (n=2, sel50+gem+carb/sel75+gem+cis)
  - Non-haematological AEs of CTCAE Grade ≥3 reported in more than a single patient were:
    - nausea (n=2, both sel75+gem+cis)
    - fatigue (n=2, both sel50+gem+carb)
    - alanine aminotransferase increases (n=2, sel50+pem+carb/sel75+pem+carb)
    - infection (n=2, both sel50+gem+carb).
- Serious AEs were reported in 13 patients (50%). These were considered related to selumetinib by the investigator in seven patients (27%): thrombocytopenia (n=4) and single cases of febrile neutropenia, neutropenia, vomiting, pyrexia, infection, epistaxis and haemoptysis (some patients experienced multiple causally related serious AEs).
- Four patients (15%, safety analysis set) experienced an AE leading to discontinuation of selumetinib; all were receiving sel50+gem+carb (two cases of periorbital oedema, one neutropenia, one myocardial infarction, one peripheral oedema).
- Two patients died during the study due to AEs. One patient died due to colonic perforation with necrotising enterocolitis (sel50+gem+cis); one patient died due to myocardial infarction (sel50+gem+carb); these deaths were not considered by the investigators to be causally related to selumetinib dosing. The case of colonic perforation with necrotising enterocolitis was considered by the investigators to be causally related to gemcitabine+cisplatin.

Table 3. Summary of exposure to selumetinib (safety analysis set)

Treatment	Sel50, gem, cis (n=3)	Sel75, gem, cis (n=5)	Sel50, gem, carb (n=9)	Sel50, pem, carb (n=3)	Sel75, pem, carb (n=6)	Total (n=26)
Median actual selumetinib exposure, days*						
Median	39	132	82	169	61	87
Range	38–106	1–180	14–183	120–229	29–113	1–229
Selumetinib dose interruptions, reductions and/or modifications,† n (%)						
Interruptions‡	1 (33)	3 (60)	7 (78)	3 (100)	6 (100)	20 (77)
Reductions	0 (0)	0 (0)	3 (33)	0 (0)	1 (17)	4 (15)
Modifications	1 (33)	3 (60)	7 (78)	3 (100)	6 (100)	20 (77)

*Actual treatment duration = total treatment duration, excluding dose interruptions
†One patient had both a dose interruption and dose reduction, sel50+gem+carb
‡Patients may have had >1 dose interruption. Reasons for interruptions, reductions or modifications are not mutually exclusive for patients with multiple interruptions, reductions or modifications but were counted only once per category

Table 4. Summary of all-causality AEs (>20% frequency in total population) by preferred term (safety analysis set)

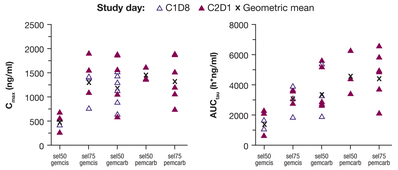
AE, n (%)	Sel50, gem, cis (n=3)	Sel75, gem, cis (n=5)	Sel50, gem, carb (n=9)	Sel50, pem, carb (n=3)	Sel75, pem, carb (n=6)	Total (n=26)
Any AE	3 (100)	5 (100)	9 (100)	3 (100)	6 (100)	26 (100)
Nausea	3 (100)	5 (100)	5 (56)	3 (100)	5 (83)	21 (81)
Thrombocyto-penia	2 (67)	1 (20)	9 (100)	1 (33)	3 (50)	16 (62)
Anaemia	2 (67)	2 (40)	7 (78)	2 (67)	2 (33)	15 (58)
Vomiting	3 (100)	3 (60)	4 (44)	1 (33)	4 (67)	15 (58)
Diarrhoea	2 (67)	2 (40)	5 (56)	1 (33)	3 (50)	13 (50)
Decreased appetite	1 (33)	2 (40)	6 (67)	0 (0)	3 (50)	12 (46)
Fatigue	2 (67)	1 (20)	6 (67)	1 (33)	2 (33)	12 (46)
Constipation	1 (33)	2 (40)	5 (56)	1 (33)	1 (17)	10 (39)
Neutropenia	1 (33)	2 (40)	5 (56)	0 (0)	2 (33)	10 (39)
Epistaxis	1 (33)	0 (0)	4 (44)	1 (33)	3 (50)	9 (35)
Rash	0 (0)	3 (60)	3 (33)	1 (33)	2 (33)	9 (35)
AST increase	0 (0)	1 (20)	3 (33)	1 (33)	3 (50)	8 (31)
Lethargy	0 (0)	3 (60)	2 (22)	1 (33)	2 (33)	8 (31)
ALT increase	0 (0)	1 (20)	2 (22)	1 (33)	3 (50)	7 (27)
Periorbital oedema	0 (0)	2 (40)	3 (33)	2 (67)	0 (0)	7 (27)
Blood alkaline phosphatase increased	1 (33)	1 (20)	1 (11)	1 (33)	2 (33)	6 (23)
Dyspnoea	1 (33)	0 (0)	2 (22)	1 (33)	2 (33)	6 (23)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Pharmacokinetics

- Selumetinib steady-state PK exposures, maximum plasma concentration (C_{max}) and AUC during dosing interval (AUC_{tau}) (Figure 2) were generally within a similar range between the different chemotherapy regimens, considering the limited data and individual variability.
- Selumetinib in combination with chemotherapy did not appear to show any marked differences in steady-state PK exposures from selumetinib monotherapy reported in a previous study.[5]
- Metabolites of selumetinib detected in combination therapy were also within the range reported for monotherapy.[5]
- Chemotherapy PK analysis is ongoing.

Figure 2. Plot of C_{max} and AUC_{tau} for selumetinib



C1D8, Cycle 1, Day 8; C2D1, Cycle 2, Day 1

Preliminary activity

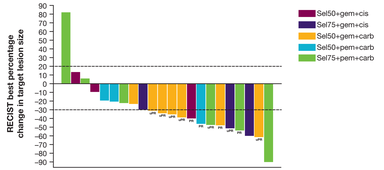
- Four confirmed partial responses were observed in: one patient receiving sel50+gem+cis; one patient receiving sel50+gem+carb; one patient receiving sel50+pem+carb and one patient receiving sel75+pem+carb (Table 5).
- Thirteen patients (52%) had stable disease ≥6 weeks (Table 5), including seven patients with a partial response unconfirmed by a follow-up scan.
- Across all cohorts, confirmed + unconfirmed objective response rate was 44% (11/25 partial responses, Table 5).
- Five patients were non-evaluable for response; four due to an incomplete post-baseline assessment; one due to stable disease <6 weeks.
- RECIST best percentage change in target lesion size is shown in Figure 3.

Table 5. Best objective tumour response (tumour response analysis set)

Objective tumour response	Sel50, gem, cis (n=3)	Sel75, gem, cis (n=4)	Sel50, gem, carb (n=9)	Sel50, pem, carb (n=3)	Sel75, pem, carb (n=6)	Total (n=25)
Complete response	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Partial response	1 (33)	0 (0)	1 (11)	1 (33)	1 (17)	4 (16)
Stable disease ≥6 weeks	0 (0)	3 (75)	6 (67)	2 (67)	2 (33)	13 (52)
- Unconfirmed complete or partial response*	-	1 (25)	5 (56)	0 (0)	1 (17)	7 (28)
- Stable disease	-	2 (50)	1 (11)	2 (67)	1 (17)	6 (24)
Progressive disease†	2 (67)	0 (0)	0 (0)	0 (0)	1 (17)	3 (12)
Not evaluable	0 (0)	1 (25)	2 (22)	0 (0)	2 (33)	5 (20)

*Partial response or complete response achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed
†RECIST progression

Figure 3. Waterfall plot of RECIST best percentage* change in target lesion size (tumour response analysis set)

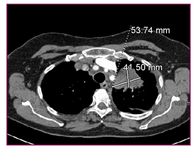


*Best percentage change only considers the best change in the sum of the diameters without considering important RECIST version 1.1 criteria, including: the presence of new lesions at the same visit; missing target lesion data; non-target lesion visit response. The majority of partial responses shown are unconfirmed (see Table 4)

PR, confirmed partial response; uPR, unconfirmed partial response

Serial scan

- Patient diagnosed with primary lung adenocarcinoma in January 2014 and enrolled onto the study March 2014.
- Received treatment with sel75+pem+carb with a partial response ongoing in Cycle 8.
- Completed six cycles of sel75+pem+carb and continued with selumetinib monotherapy (dose reduced to 75 mg once daily due to skin toxicity).
- RECIST partial response was detected at Week 6 scan; 36% reduction in target lesion. At Week 12 scan, a 47% reduction in target lesion was observed.



Baseline

Week 12

Conclusions

- The AE profile of selumetinib in combination with standard first-line chemotherapy regimens for advanced NSCLC seemed to be consistent with the known side-effect profiles of the individual components of study treatments.
- Selumetinib 75 mg bid was tolerated in combination with pem+carb; selumetinib 50 mg bid was tolerated in combination with gem+cis and dose exploration is ongoing for both combinations.
- Selumetinib was not tolerated in combination with gem+carb.
- The combination of selumetinib with first-line standard of care platinum-based chemotherapy showed signs of preliminary clinical activity in this early Phase I study.
- Based on the limited PK data, selumetinib given in combination with chemotherapy did not show distinct differences in steady state PK exposure between the different chemotherapies.
- This study is ongoing; validation and assessment of the data continues.

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