LIST OF SUPPLEMENTAL FILES

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Supplemental Table Legends

Supplemental Table 1. Dose limiting toxicity events

Supplemental Table 2. Clinical activity of selumetinib combined with chemotherapy in patients with NSCLC

Supplemental Table 3: Cycles of chemotherapy received

SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1. Supplemental Methods

Dose-limiting Toxicity and Dose Cohorts

A DLT was defined as any toxicity that was not attributable to the disease under investigation, was considered related to the combination of selumetinib plus chemotherapy, occurred at any time from the first dose on Cycle 1 Day 1, up to dosing on Cycle 2 Day 1, was dose limiting and included: a hematological toxicity of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥4 present for more than 4 days; a non-hematological toxicity of CTCAE Grade ≥3 (including febrile neutropenia and QTc prolongation); any toxicity that resulted in a disruption of selumetinib or chemotherapy dosing for more than 14 continuous days; any other toxicity that was greater than that at baseline, was clinically significant/unacceptable, did not respond to supportive care and was judged as a DLT by the safety review committee.

If no DLT was observed within a cohort of three to six evaluable patients, then dose escalation was permitted. If 1 patient experienced a DLT in a group of ≥3 evaluable patients, the cohort was expanded to include 6 evaluable patients and dose escalation was permitted if only 1 DLT was observed amongst the 6 evaluable patients. If ≥2 patients experienced DLTs in a cohort of up to 6 patients, the combination dose was considered non-tolerated and dose escalation ceased.

Pharmacokinetic Evaluations

Plasma samples were collected at specified time points during the treatment period and were assayed using a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantification of 2.00 ng/ml for selumetinib and N-desmethyl selumetinib. Parameters included $C_{ss,max}$, t_{max}, $t_{ss,max}$, time of the last quantifiable plasma concentration at steady state ($t_{ss,last}$), AUC_T and apparent oral plasma clearance (CL/F, selumetinib only).