Supplementary Online Content

Jänne PA, van den Heuvel MM, Barlesi F, et al. Effect of selumetinib plus docetaxel compared with docetaxel alone and progression-free survival in patients with KRAS-mutant advanced non–small cell lung cancer: the SELECT-1 randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.3438

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Censoring of Patients

For PFS, patients who had not progressed or died at the time of the analysis were censored at the time of the latest assessment date from their last evaluable RECIST 1.1 assessment. However, if the patients experienced disease progression or died after two or more missed visits, they were censored at the time of the latest evaluable RECIST 1.1 assessment. For OS, any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive, prior to the time of data cut-off. For duration of response, if a patient did not progress following a response, then their duration of response was be censored at the PFS censoring time. For time to symptom progression, patients whose symptoms (as measured by ASBI) had not shown a clinically meaningful deterioration (defined as a decrease in the ASBI from baseline as ≥10) and who were alive at the time of the analysis were censored at the time of their last LCSS assessment where ASBI could be evaluated. Also, if symptoms progressed or the patient died after two or more missed LCSS assessment visits, the patient was censored at the time of the last LCSS assessment where ASBI could be evaluated. Two missed visits were defined as no assessments within 8 weeks (56 days) of randomization or the previous evaluable assessment. If a patient had no evaluable visits or did not have baseline data they were censored at day 1.

eTable 1. Most Frequently Reported Adverse Events Causally Related to selumetinib/placebo

Preferred term, No. (%) participants with an event	Selumetinib + docetaxel n=251		Placebo + docetaxel n=254	
	All grades	CTCAE grade ≥3	All grades	CTCAE grade ≥3
Diarrhea	125 (50)	16 (6)	64 (25)	6 (2)
Rash	79 (32)	8 (3)	23 (9)	1 (1)
Nausea	53 (21)	3 (1)	29 (11)	0
Fatigue	47 (19)	4 (2)	43 (17)	4 (2)
Stomatitis	46 (18)	7 (3)	20 (8)	0
Edema peripheral	43 (17)	3 (1)	13 (5)	0
Vomiting	41 (16)	6 (2)	17 (7)	1 (1)
Asthenia	33 (13)	12 (5)	24 (9)	2 (1)
Decreased appetite	32 (13)	3 (1)	28 (11)	2 (1)
Dermatitis acneiform	29 (12)	4 (2)	1 (1)	0
Dry skin	24 (10)	0	12 (5)	0
Neutropenia	18 (7)	14 (6)	8 (3)	4 (2)
Anemia	17 (7)	2 (1)	8 (3)	0
Dyspnea	13 (5)	4 (2)	4 (2)	0
Face edema	16 (6)	0	3 (1)	0

Population: safety analysis set, data cut-off 7 June 2016
Adverse events causally related to selumetinib/placebo reported during randomized treatment in ≥5% of patients in either treatment group, by frequency in selumetinib + docetaxel group.
CTCAE, Common Toxicity Criteria for Adverse events; No., number of participants

eTable 2. PD-L1 Subgroup Analysis of Progression-Free Survival and Overall Survival Events

Subgroup	No. with event/Total No. (%) in selumetinib + docetaxel group	No. with event/Total No. (%) in placebo + docetaxel group	HR (95% CI)
PFS			
PD-L1 <5%	94/112 (84)	101/112 (90)	0.89 (0.67, 1.18)
PD-L1 ≥5%	65/79 (82)	71/82 (87)	0.70 (0.50, 0.99)
PD-L1 unknown	59/63 (94)	57/62 (92)	1.24 (0.86, 1.79)
OS			
PD-L1 <5%	73/112 (65)	74/112 (66)	0.94 (0.68, 1.30)
PD-L1 ≥5%	55/79 (70)	58/82 (71)	0.89 (0.61, 1.28)
PD-L1 unknown	48/63 (76)	38/62 (61)	1.57 (1.02, 2.41)

CI, confidence interval; HR, hazard ratio; No., number of participants; PD-L1, Programmed death-ligand 1; PFS, progression-free survival; OS, overall survival

Submitted as part of an abstract published in the IASLC WCLC 2016 abstract book[1]

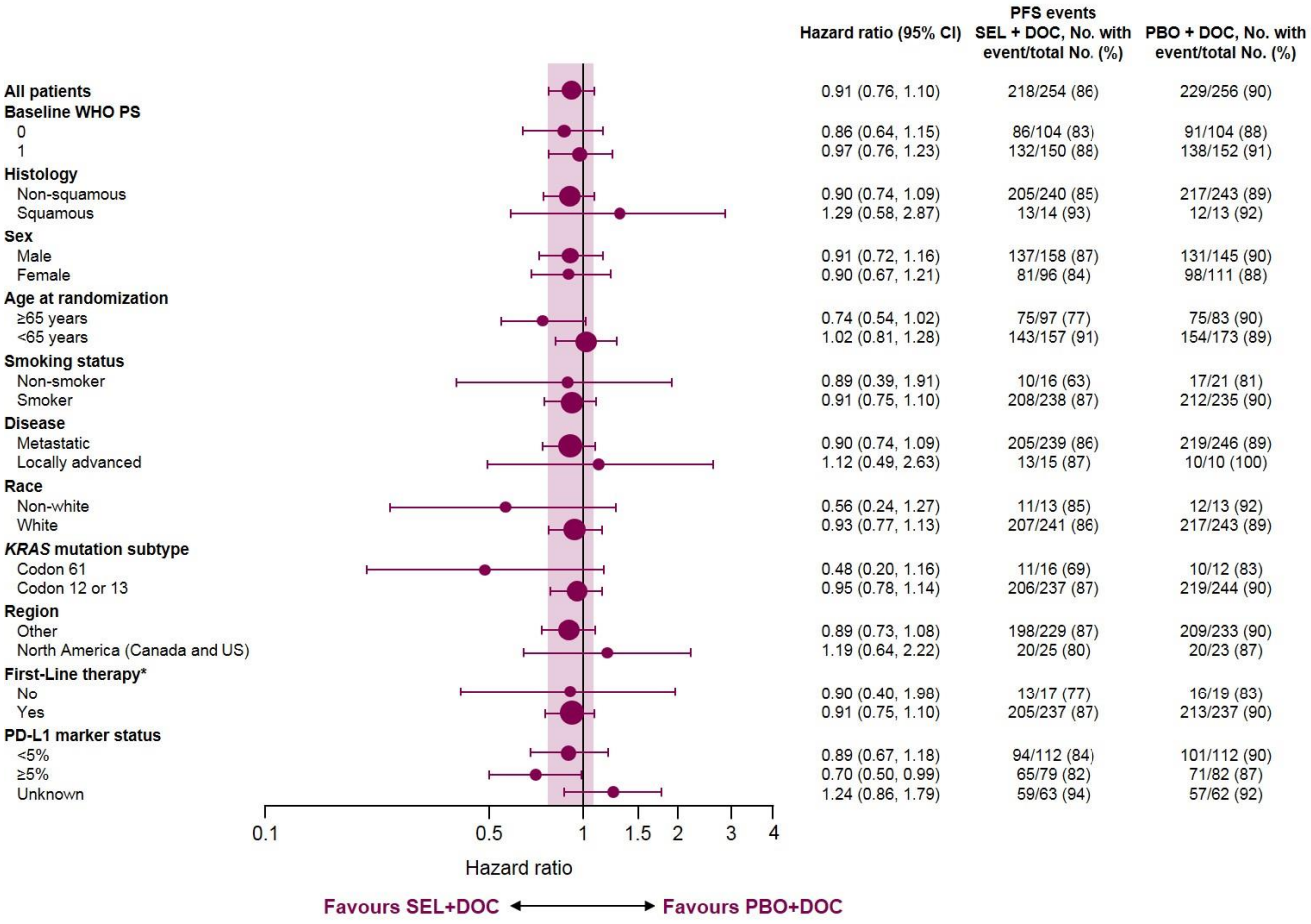
eTable 3. Objective Response Rate Analysis by *KRAS* Mutation Group Status (Next-Generation Sequencing Data)

Mutation group	Patients with response, No. with event/Total No. (%)		Difference between groups in ORR, % (IQR)	Odds ratio (95% CI)
	Selumetinib + docetaxel	Placebo + docetaxel		
Mutation group 1	35/152 (23)	18/149 (12)	11 (1.9-19.9)	2.27 (1.22, 4.34)
Mutation group 2	13/94 (14)	16/101 (16)	-2 (-12.7-8.9)	0.83 (0.37, 1.86)

Mutation group 1, $Kras^{G12C}$ or G12V; mutation group 2, all other *KRAS* mutations. Objective response rate is the proportion of patients with at least one visit response of complete response or partial response using investigative site assessments according to RECIST 1.1

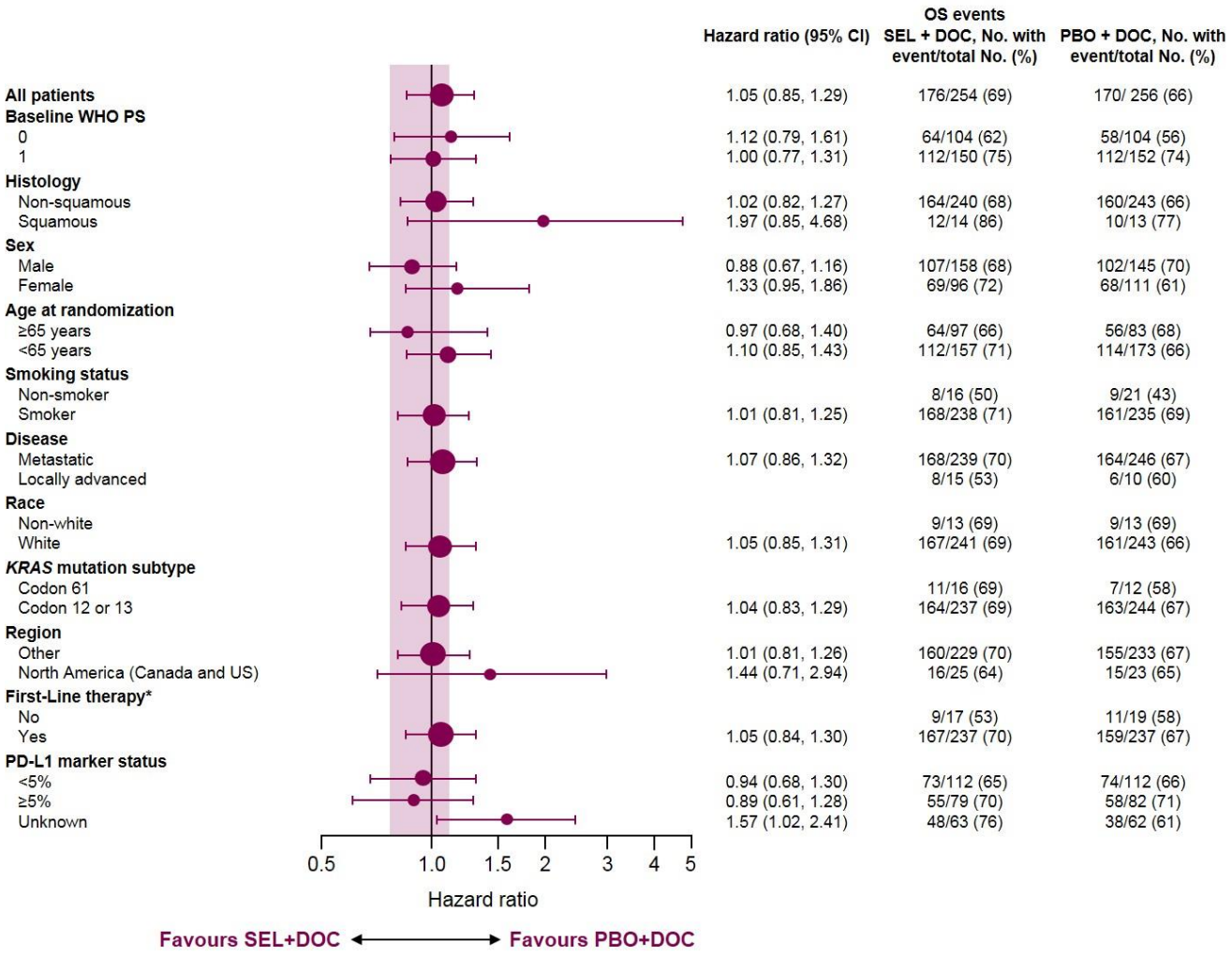
CI, confidence interval; IQR, interquartile range; No., number of participants; ORR, objective response rate; RECIST, response evaluation criteria in solid tumors

eFigure 1. Prespecified Subgroup Analysis of Progression-Free Survival



Population: full analysis set, data cut-off 7 June 2016; HRs were not calculated for sub-groups with fewer than 10 events; all analyses were performed using a Cox proportional hazards model. Progression includes deaths in the absence of RECIST progression. Progression events occurring 14 weeks after last evaluable assessment (or randomization) are censored and therefore excluded
Data-marker size reflects number of patients analyzed; error bars indicate 95% confidence limits for HR; vertical band corresponds to 95% confidence limits for the HR for all patients
*First-line therapy was included as an eligibility criterion, however patients who received adjuvant/neoadjuvant chemotherapy and developed a recurrence, with evidence of Stage IIIB to IV disease within 6 months of completing chemotherapy, could be eligible
CI, confidence interval; DOC, docetaxel; HR, hazard ratio; *KRAS*, v-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog; No., number of participants; PBO, placebo; PD-L1, Programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; SEL, selumetinib; WHO PS, World Health Organization performance status

eFigure 2. Prespecified Subgroup Analysis of Overall Survival



Population: full analysis set, data cut-off 7 June 2016; HRs were not calculated for sub-groups with fewer than 10 events; all analyses were performed using a Cox proportional hazards model
Data-marker size reflects number of patients analyzed; error bars indicate 95% confidence limits for HR; vertical band corresponds to 95% confidence limits for the HR for all patients
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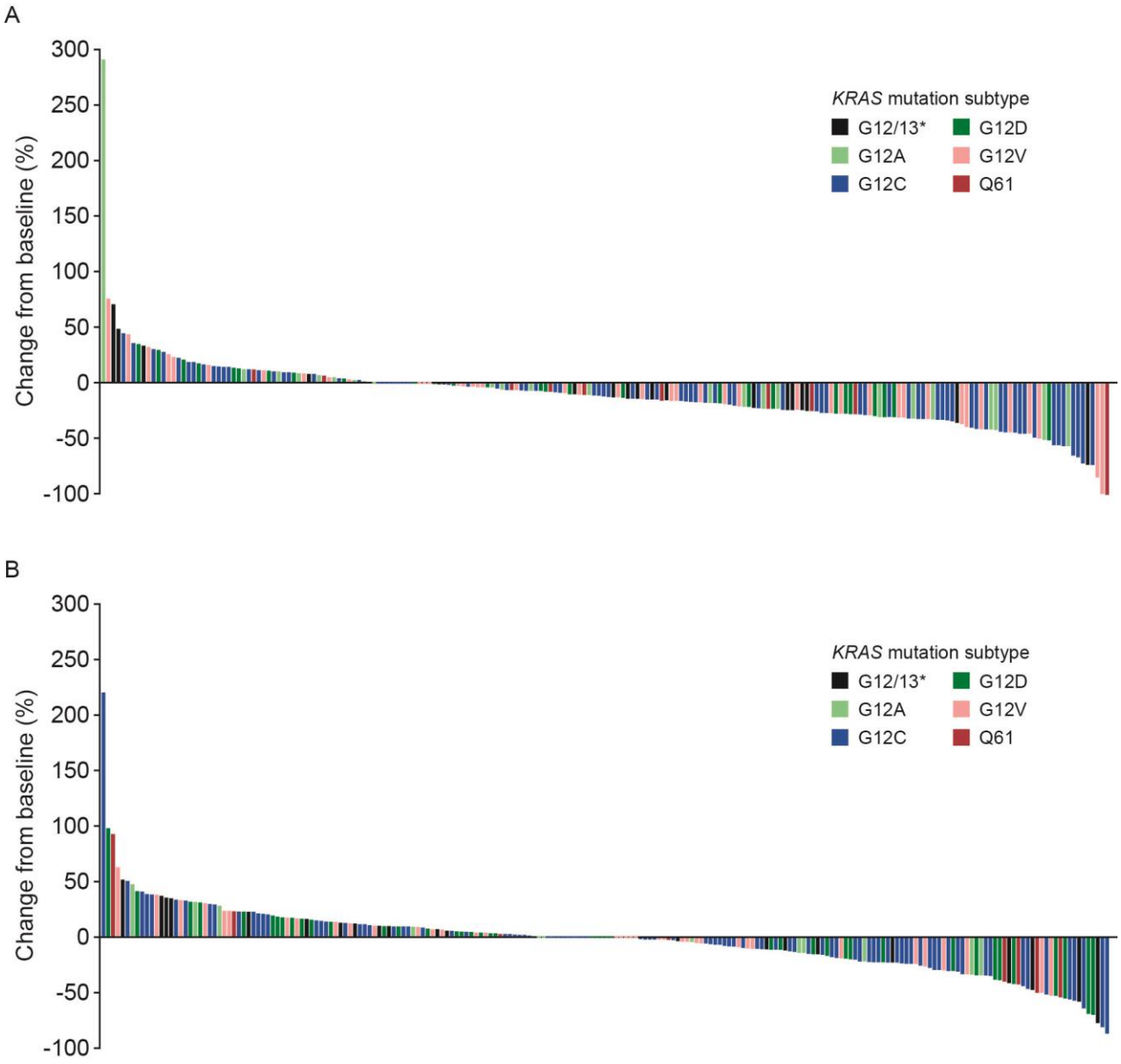
CI, confidence interval; DOC, docetaxel; HR, hazard ratio; *KRAS*, v-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog; No., number of participants; OS, overall survival; PBO, placebo; PD-L1, Programmed death-ligand 1; SEL, selumetinib; WHO PS, World Health Organization Performance Status

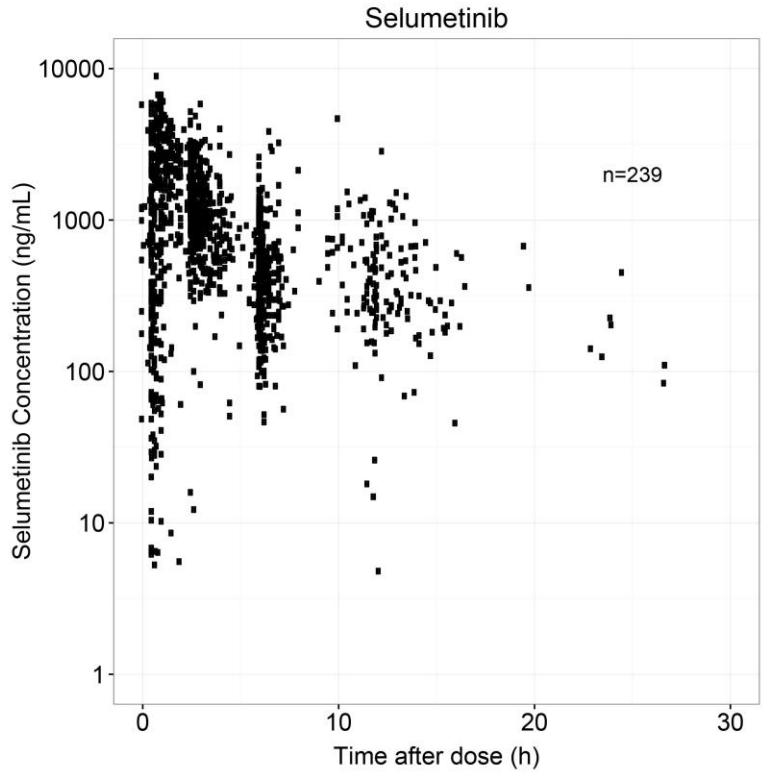
eFigure 3. Waterfall Plots of Best Percentage Change in Tumor Size for Target Lesions by Patient in (A) Selumetinib + Docetaxel, and (B) Placebo + docetaxel Groups



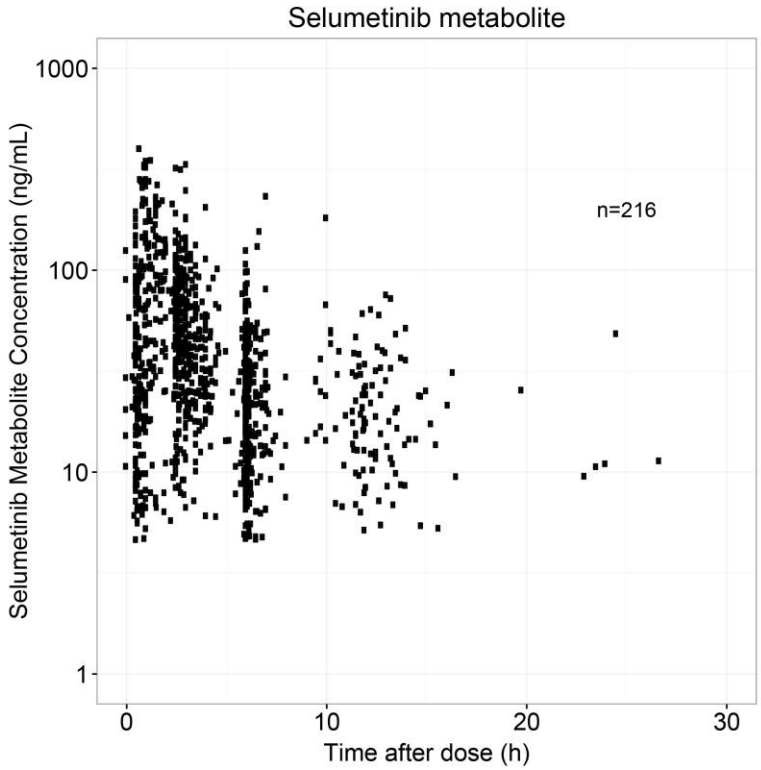
Population: patients with measurable disease at baseline who underwent follow-up scan, and had specific *KRAS* mutation sub-type determined by NGS analysis (selumetinib + docetaxel, n=206; placebo + docetaxel, n= 212); data cut-off 7 June 2016. Patients with indeterminate *KRAS* mutation subtypes were excluded.
RECIST 1.1 partial response: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters; complete response: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
*includes all other G12 and G13 *KRAS* mutation sub-types other than G12A, G12C, G12D, and G12V
NGS, next-generation sequencing; RECIST: response evaluation criteria in solid tumors

eFigure 4. Selumetinib (A) and N-desmethyl Selumetinib Metabolite (B) Plasma Concentration over Time

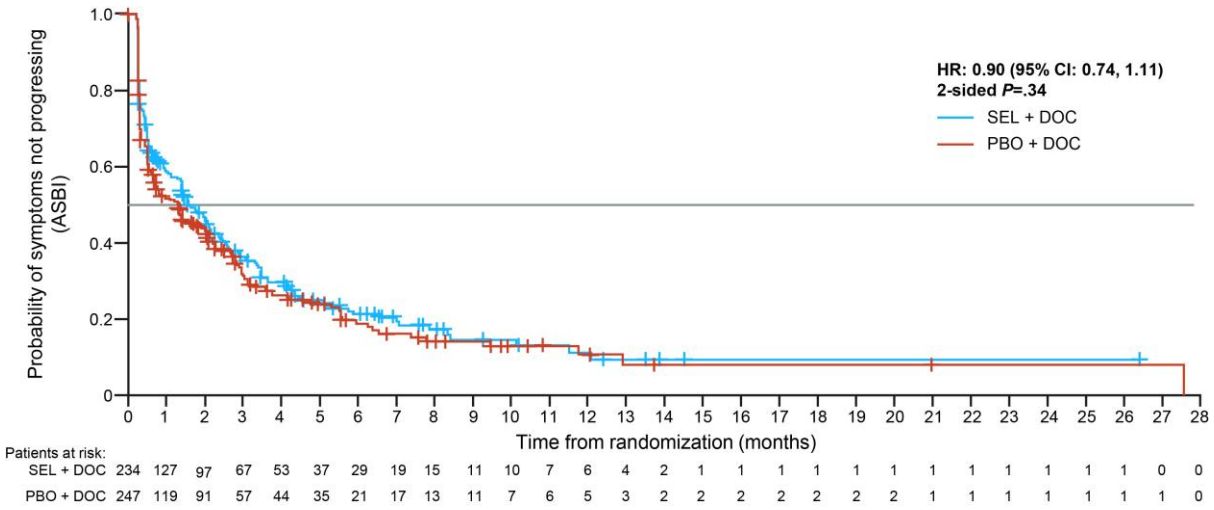
(A)



(B)

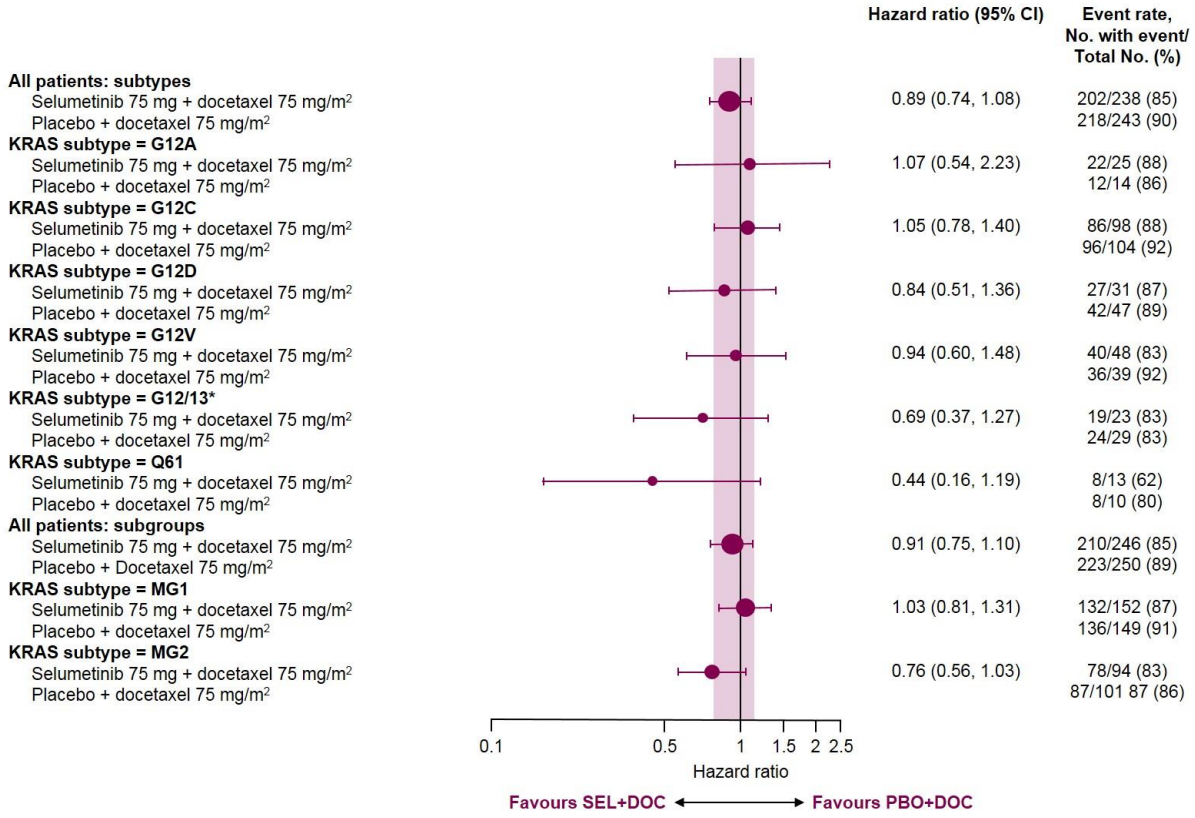


eFigure 5. Kaplan-Meier Estimates of Time to Symptom Progression (ASBI)



Only patients with a baseline ASBI score of ≤90 are included.
This analysis was performed using stratified log-rank test with factors for World Health Organization performance status; crosses denote censored observations. HR, CI, and two-sided p-value are calculated using the stratified log-rank test
ASBI, average symptom burden index; DOC, docetaxel; PBO, placebo; SEL, selumetinib

eFigure 6. Progression-Free Survival Analysis by *KRAS* mutation Subgroup (All Patients with Available Next-Generation Sequencing Data)



*Includes all G12 and G13 *KRAS* subtypes other than G12A, G13C, G12D and G12V
Data-marker size reflects number of patients analyzed; error bars indicate 95% confidence limits for HR; vertical band corresponds to 95% confidence limits for the HR from the SELECT-1 primary analysis (HR: 0.93, 95% CI: 0.77, 1.12)
Mutation group 1, *KRAS* G12C or G12V; mutation group 2, all other *KRAS* mutations
CI, confidence interval; DOC, docetaxel; HR, hazard ratio; *KRAS*, v-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog; No., number of participants; PBO, placebo; SEL, selumetinib

eReferences

1. Jänne P, Van den Heuvel M, Barlesi F, et al. Impact of PD-L1 Status on Clinical Response in SELECT-1: Selumetinib + Docetaxel in KRASm Advanced NSCLC. *Journal of Thoracic Oncology.* 2016;12(1; supplement):S952–S953.