Krascendo-170 Lung: A phase Ib/II study of divarasib + pembrolizumab ± platinum-based chemotherapy and pemetrexed in untreated *KRAS G12C+*advanced non-small cell lung cancer (NSCLC).

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Background: The *KRAS* G12C mutation, present in ~12% of NSCLC patients, drives oncogenic signaling and cancer formation and is associated with poor prognosis. The current first-line treatment for advanced *KRAS* G12C+ NSCLC is checkpoint inhibitor (CPI) ± chemotherapy (CT). Novel combinations using a more targeted, biomarker-directed approach are supported by pre-clinical evidence and may further improve outcomes. Divarasib is an oral KRAS G12C inhibitor with potent pre-clinical and clinical anti-tumor activity. We hypothesize that divarasib + CPI ± CT may improve outcomes for patients with *KRAS* G12C+ NSCLC. **Methods:** Krascendo-170 Lung (NCT05789082) is a phase Ib/II, open-label study evaluating the safety and activity of divarasib + pembrolizumab in patients with PD-L1 tumor cell expression ≥1% (Cohort A) and of divarasib + pembrolizumab with platinum-based CT and pemetrexed in patients with any PD-L1 tumor cell expression level (Cohort B). Patients must be ≥18 years old with untreated unresectable/metastatic non-squamous NSCLC (measurable per RECIST v1.1), a confirmed *KRAS*G12C mutation, and an Eastern Cooperative Oncology Group performance status 0/1. Each cohort will have two stages: divarasib combination dose finding and dose expansion, with two planned dose levels of divarasib (Table). Tumor assessments will be performed at baseline and every 6 weeks for 48 weeks, then every 9 weeks thereafter. Plasma samples will be taken at various timepoints before and after divarasib and pembrolizumab dosing to characterize pharmacokinetics. Patients will be treated until disease progression per RECIST v1.1 or unacceptable toxicity. The co-primary endpoints are adverse events and change from baseline in targeted safety parameters. Key secondary endpoints include objective response rate, progression-free survival and duration of response (all investigator assessed per RECIST v1.1). Enrollment into the combination dose finding stage of Cohort A has been completed without dose-limiting toxicities and enrollment into the dose expansion stage is continuing. Clinical trial information: NCT05789082. Research Sponsor: F. Hoffmann-La Roche Ltd.

Cohort	PD-L1 Tumor Cell Expression	Dose Finding*	Dose Expansion†
A	≥1%	Divarasib + Pembrolizumab	Divarasib + Pembrolizumab
B	Any	Divarasib + Pembrolizumab + CT‡ + Pemetrexed	Divarasib+ Pembrolizumab + CT‡ + Pemetrexed

*Participants will receive one of two doses of divarasib. †Dose expansion will depend on pre-specified safety parameters during the dose-finding stage; ‡CT: 4 cycles of carboplatin (intravenously, every 3 weeks, AUC5) or cisplatin (intravenously, every 3 weeks, 75 mg/m^2) per investigator's choice. Drug administration schedule: Divarasib: orally once daily; Pemetrexed: 500 mg/m^2 intravenously every 3 weeks; Pembrolizumab: 200 mg intravenously every 3 weeks.