TPS8656 **Poster Session**

Krascendo 2: A phase III study of divarasib and pembrolizumab vs pembrolizumab and chemotherapy in patients with previously untreated, advanced or metastatic, *KRAS* G12C-mutated non-small cell lung cancer (NSCLC).

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Background: *KRAS G12C* mutations are found in ~12% of NSCLC cases. The recommended first-line treatment for patients (pts) with advanced or metastatic non-squamous *KRAS G12C*-mutated (*G12C*+) NSCLC is immunotherapy (most commonly pembrolizumab [pembro]) ± chemotherapy (chemo); however, there is an unmet need in this pt population for more efficacious therapies with tolerable and manageable safety profiles. Divarasib is a potent KRAS G12C inhibitor that has shown efficacy and safety as a monotherapy in pts with previously treated, advanced or metastatic *KRAS G12C*+ NSCLC. Previous reports suggest that combinations of KRAS G12C inhibitors and pembro have promising anti-tumor activities with manageable safety profiles. We hypothesize that divarasib plus pembro may be an effective and well tolerated first-line chemo-free treatment option in pts with advanced or metastatic *KRAS G12C*+ NSCLC. **Methods:** Krascendo 2 (CO45042; NCT06793215) is a randomized, open-label, multicenter, global, phase III study, evaluating the efficacy and safety of first-line treatment with divarasib and pembro vs pembro and chemo (pemetrexed + carboplatin/cisplatin), in pts with advanced or metastatic *KRAS G12C*+ NSCLC. Eligible pts (≥18 years old) must have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, measurable disease per RECIST version 1.1, and histologically/cytologically confirmed advanced or metastatic, non-squamous NSCLC that is not eligible for curative surgery and/or definitive chemoradiotherapy and is previously untreated. Pts must also have known programmed death-ligand 1 (PD-L1) expression status and *KRAS G12C*+ status. Asymptomatic individuals with stable and treated central nervous system (CNS) metastases are eligible. Pts will be randomized 1:1 to receive either oral divarasib daily and intravenous (IV) pembro (in 21-day cycles), or IV pembro, pemetrexed and four cycles of platinum-based chemo (in 21-day cycles), until disease progression, or unacceptable toxicity. Pts will be stratified by PD-L1 expression status (tumor proportion score or tumor cell <1% vs 1–49% vs ≥50%), ECOG PS (0 vs 1), and history of CNS metastases (yes vs no). Pts who show clinical benefit per investigator judgment may continue study treatment after disease progression at the investigator's discretion. Primary endpoints are progression-free survival by blinded independent central review (BICR) and overall survival. Secondary endpoints include confirmed objective response rate and duration of response by BICR, changes in patient-reported symptoms and functioning from baseline to Cycle 5 assessed via questionnaires, and safety. Tumor assessments will occur at screening, every 6 weeks (±7 days) for the first 72 weeks after randomization, and then every 9 weeks (±7 days). Clinical trial information: NCT06793215. Research Sponsor: This study is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of the authors, was provided by Tahmina S. Alam, MA, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.