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Krascendo 1: Efficacy and safety of divarasib (diva) vs sotorasib (soto) or adagrasib (ada) in previously treated locally advanced or metastatic KRAS G12C-mutated NSCLC

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Background

Divas is an oral, next-generation KRAS G12C inhibitor that is more potent and selective for KRAS G12C *in vitro* than soto or ada. We report the primary analysis of Krascendo 1 (NCT06497556), a phase 3, global, randomised, open-label trial of diva vs soto or ada in advanced/metastatic KRAS G12C-mutated NSCLC.

Methods

Eligible patients (pts) aged ≥18 years had an ECOG PS of 0/1 and ≥1 prior systemic treatment (tx; including anti-PD-1/PD-L1 and platinum-based chemotherapy) for advanced/metastatic KRAS G12C-mutated NSCLC. Pts were randomised 1:1 to diva (400 mg PO QD) or investigator’s choice of soto (960 mg PO QD) or ada (600 mg PO BID). Stratification factors: KEAP1 status, history of CNS metastases and intended KRAS G12C inhibitor (soto/ada). Tx continued until unacceptable toxicity, clinical benefit loss, consent withdrawal or death. Primary endpoint: PFS per blinded independent committee review (BICR). Secondary endpoints included OS, confirmed ORR per BICR (RECIST 1.1), patient-reported outcomes, DoR and safety.

Results

In total 338 pts were randomised to diva (n=167) or control (n=171); baseline characteristics were generally balanced. At data cutoff (19 May 2026), median follow up was 14.3 months. A statistically significant benefit in PFS (HR: 0.58; 95% CI: 0.44–0.76) and OS (HR: 0.56; 95% CI: 0.41–0.78) was observed for the diva vs control arm (Table). A statistically significant improvement in ORR was seen for diva (58.4%) vs control (32.3%; table). Diva had a manageable safety profile consistent with previous reports for diva and other KRAS G12C inhibitors (Table). Tx duration was twice as long in the diva vs control arm, and discontinuation rates due to TRAEs were lower with diva vs control (Table).Table: LBA5

	Divas n=167	Control* n=171
Efficacy		
Median PFS,† mos (95% CI)	9.8 (8.1–12.9)	5.7 (4.2–6.8)
HR‡ (95% CI)	0.58 (0.44–0.76)	

	Diva n=167	Control* n=171
<i>p</i> value‡	<0.0001	
Median OS, mos (95% CI)	17.7 (16.3–NE)	12.0 (10.0–15.2)
HR‡ (95% CI)	0.56 (0.41–0.78)	
<i>p</i> value‡	0.0005	
Confirmed ORR,† %	58.4	32.3
n/n§	94/161	54/167
95% CI	50.4–66.1	25.3–40.0
Safety		
Median tx duration, mos (range)	11.3 (0–19.8)	5.0 (0–19.8)
AE/TRAE, n (%)		
All grade	166 (99.4)/155 (92.8)	167 (97.7)/137 (80.1)
Grade 3–4	72 (43.1)/41 (24.6)¶	88 (51.5)/59 (34.5)¶
Serious	51 (30.5)/13 (7.8)	70 (40.9)/26 (15.2)
Leading to discontinuation	12 (7.2)/8 (4.8)	25 (14.6)/20 (11.7)

*Soto: n=156; ada: n=15. †Per BICR. ‡Stratified. §Response-evaluable set per BICR. ¶No Grade 5 TRAEs.

Conclusions

Diva significantly improved PFS and OS vs control with a manageable safety profile, establishing diva as a new standard of care for pts with previously treated advanced/metastatic *KRAS G12C*-mutated NSCLC.

Clinical trial identification

NCT06497556.

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