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Abstract CT266: D3S-001, a next generation GDP-bound KRAS G12C inhibitor, as monotherapy in KRAS G12C inhibitor resistant non-small cell lung cancer FREE

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Abstract

Background:

Resistance mechanisms to first-generation (1G) KRAS G12C inhibitors (G12Ci) are diverse, with previous data revealing a heterogeneous pattern characterized by multiple subclonal events emerging after treatment (Tx). Incomplete G12C target engagement (TE) and G12Ci induced G12C amplification contributed to the resistance mechanisms against 1G G12Ci. D3S-001, a next-generation KRAS G12Ci, has demonstrated potent, faster and complete TE to effectively deplete active KRAS mutated protein. In pre-clinical studies, D3S-001 resulted in tumor regression in xenograft models that are resistant to sotorasib (soto) and adagrasib (ada). Phase 1 results demonstrated favorable safety and promising early efficacy across NSCLC, CRC and PDAC; Here, we present findings in G12Ci resistant NSCLC patients (pts) from the ongoing Phase 2 trial (NCT05410145).

Methods:

Pts of locally advanced or metastatic NSCLC with historically confirmed KRAS G12C mutation were eligible for inclusion if they had radiologically or clinically documented PD following TX of 1 prior KRAS G12Ci achieving CR/PR or SD for >= 6 months. In this cohort, D3S-001 was administered as monotherapy at 600mg once daily. The key objectives included safety, efficacy, and ctDNA kinetics by liquid biopsy.

Results:

As of 14 Feb 2024, a total of 20 pts were enrolled. Prior G12Ci Tx included FDA approved and experimental G12Cis. 7 pts had soto, 1 pt had ada and 12 pts had other experimental G12Cis. During their prior G12Ci Tx, 8 pts (40%) achieved PR, 7 pts (35%) achieved SD, and 5 pts (25%) were unknown as the BOR. 14 pts (70%) were enrolled into this study immediately after PD from

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prior G12Ci. Median study follow-up was 4.7 months (range: 1.3-12.8 months), and 9 pts (45%) remain on-study Tx. TRAE of any grade occurred in 18 pts (90%). Of which, 2 (10%) were Grade 3 (no >=G4). PR was achieved in 6 pts (30%). Median DOR was 8.2 months. DCR was 80% and tumor shrinkage was observed in 12 of the 20 (60%) pts. Of the 20 pts, 14 (70%) were KRAS G12C ctDNA positive at baseline [bG12C(+)]. Notable baseline co-mutations included secondary KRAS alterations (A146V, R68S and three G12C amplification), BRAF, EGFR, NTRK1/2/3, TP53, etc. Of the 14 bG12C(+) pts, 11 achieved >90% G12C MAF reduction including 8 with complete clearance. All 6 radiological responders were bG12C(+) and 5 of 6 had complete clearance of G12C MAF. Remarkably, of the 3 pts with KRAS amplification, 2 achieved PR and 1 SD with D3S-001 Tx. Conversely, pts who had immediate PD to D3S-001 carried baseline gene alterations of switch II pocket mutation (KRAS R68S), BRAF V600E, MYC amplification, NTRK2, CDKN2A and PIK3CG. These findings align with preclinical observation that D3S-001 was effective in G12Ci resistant xenograft model including those with KRAS G12C gene amplification.

Conclusions:

These findings highlight the potential of D3S-001 to overcome the limitations of earlier KRAS G12Ci and address unmet needs in G12Ci resistant NSCLC, offering a promising therapeutic option for pts with KRAS G12C-mutant cancers.

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