Preclinical Activity of NVL-655 in a Patient-Derived NSCLC Model with Lorlatinib-Resistant ALK G1202R/T1151M Mutation

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NVL-655, 0.1 mg/kg BID
Lorlatinib, 5 mg/kg BID
Lorlatinib, 10 mg/kg QD

CONCLUSIONS

- ALK G1202R is effective in preclinical models, including those harboring ALK rearrangement or activating ALK (ALKOVE-1):

- NVL-655 is being evaluated in a Phase 1/2 clinical trial for patients with advanced NSCLC, and other clinical trials are targeting harboring ALK rearrangement or activating ALK (ALKOVE-2) at NCT05348462.

IN VITRO ACTIVITY

- NVL-655 showed strong antitumor activity against ALK G1202R/F1174L, a compound mutation identified in a patient after sequential treatment with four ALK inhibitors with or without alectinib.

- Consistent with treatment history, MR619 tumors bearing ALK G1202R mutation showed resistance to lorlatinib treatment in a patient-derived xenograft study.

- NVL-655 was efficacious against MR619, inducing regression at both doses tested (0.5 and 3 mg/kg BID) without causing significant body weight changes.

NCI-H322M-ALK-WT
NCI-H322M-ALK-G1202R
Karpas299-ALK-WT
Karpas299-ALK-G1202R
Ba/F3 EML4-ALK v1 G1202R/L1198F
Ba/F3 EML4-ALK v1 D1203N
Aska-SS ALK Ex2-17del
NB-1 ALK Ex2-3del
Kelly ALK F1174L
ALK

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- Among all inhibitors tested, NVL-655 showed the broadest activity across ALK-positive NSCLC patient after progressive disease on sequential treatment with four ALK inhibitors, including a G1202R/T1151M compound mutation model derived from a patient previously treated with crizotinib, alectinib, and lorlatinib.

- NVL-655 efficiently inhibited ALK while sparing TRKB, showing 91- to 870-fold selectivity.

- NVL-655 exhibited potent activity (IC50 < 50 nM) in many ALK cancer models shown to be resistant to previous-generation therapy.

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- NVL-655 had broader activity across models than other ALK inhibitors tested.

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- Inhibitors include ceritinib, alectinib, and brigatinib. **See Table 1.**

- Consistent with treatment history, MR648e tumors showed limited sensitivity to lorlatinib, which induced modest tumor growth inhibition at 3 mg/kg QD and tumor stasis at 5 mg/kg BID.

- NVL-655 was efficacious against MR648e, inducing regression at 1 mg/kg BID without causing significant body weight changes.

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