Advanced patients with a history of ALK TKI treatments show a high incidence of CNS metastases (>60%).

Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>ALK vs TRKB</th>
<th>ALK G1202R vs TRKB</th>
<th>ALK G1202R/G1269A vs TRKB</th>
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<tbody>
<tr>
<td>Crizotinib</td>
<td>43x</td>
<td>4x</td>
<td>4x</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>43x</td>
<td>4x</td>
<td>4x</td>
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<tr>
<td>Alectinib</td>
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<td>4x</td>
<td>4x</td>
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<tr>
<td>Brigatinib</td>
<td>43x</td>
<td>4x</td>
<td>4x</td>
</tr>
<tr>
<td>Lorlatinib</td>
<td>43x</td>
<td>4x</td>
<td>4x</td>
</tr>
</tbody>
</table>

NUV-655 shows a good human brain-to-plasma partition coefficient (Kp) = 0.1 ± 0.1 and a high CSP-to-TRKB plasma partition coefficient (0.1 ± 0.2) at a single oral dose of 20 mg/kg in Wistar Haris. The values are comparable to that of lorlatinib (0.11 and 0.47, respectively) in a similar experiment performed in parallel. TRKB plays crucial neurological functions, and sparing TRKB may be beneficial. Other kinases that are plotted with red circles whose size corresponds to the IC50 relative to ALK. Kinases with IC50 < 30% of ALK are not plotted.

Figure 3. Results of kinase selectivity screen for NUV-655 (Wild Type Kinase Panel, Reactrobio, Germany), displayed on a kinome tree. The cyan circle indicates NUV-655 is selective for ALK and ALK G1202R+ mutations over TRKB, indicating the potential to minimize TRKB-related adverse events. NUV-655 was designed to selectively inhibit ALK while sparing TRKB, showing 43- to 484-fold selectivity over TRKB (see Figure S5).

Cellular Activity

NUV-655 has been reported for CNS-penetrant TRK inhibitors and include cognitive impairment, mood disorders, sleep disturbances, distonias, ataxia, and weight gain.

In vivo Antitumor Activity

NUV-655 is efficacious in a Ba/F3 xenograft model harboring EML4-ALK v1 or G1202R/L1198F. In the same study, lorlatinib only modestly inhibited tumor growth, consistent with this detection of the G1202R/L1198F compound mutation in patients at progression on lorlatinib. Both compounds were well tolerated in this study.

Quantitative PCR supports ALK inhibition in tumor lines through reduced expression of MAP kinase pathway transcripts Spry, Dap4, and Dap5.

Figure 4. (Left and middle) NUV-655 induces regression in a xenograft model of Ba/F3 EML4-ALK v1 or G1202R/L1198F. Cells implanted in Balb/c nude mice. Lorlatinib is tested in the same study at 30 mg/kg, a dose selected to approximate the exposure of the human dose of 100 mg QD. Vehicle is 20% HP-β-Cyclodextrin. (Right) pharmacokinetic analysis by qPCR showing expression of 1 gene (Spry, Dap4, Dap5) relative to G0. In vivo Antitumor Activity

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