Bruton Tyrosine Kinase (BTK) Protein Degrader BGB-16673 Is Less Apt To Cause, And Able To Overcome Variable BTK Resistance Mutations Compared To Other BTK Inhibitors

Xiaoyu Feng,1 Yangyang Wang,1 Tao Long,1 Lanyue Bai,1 Xiaojiao Yang,1 Ailing Yang,1 Xiangmei Chen,1 Oscar Puig1, Yangbo Yue1,†, Zhifong Shen1,†
1Translational Discovery, Research and Medicine, BeiGene (Beijing) Co., Ltd., Beijing, China. *Correspondence author.

INTRODUCTION

• Bruton tyrosine kinase (BTK) plays a critical role in the B-cell antigen receptor signaling pathway and the pathogenesis of multiple B-cell malignancies 1.
• Irreversible covalent BTK inhibitors (BTKi) have been instrumental in the management of B-cell malignancies 1, but mutations in BTK can lead to BTK resistance and limit therapeutic effectiveness due to reduction binding capacity to BTK, scaffold function leading to BTK kinase hyperactivation 2,3,4,5.
• Although on-target resistant mutations emerging from covalent BTKi have been described, less is known about resistance mutations caused by reversible non-covalent BTKi, and very little is known regarding resistance to BTK degraders.
• BGB-16673 is an orally available chimeric degradation activating compound (CDAC) with demonstrated preclinical BTKi activity (Figure 1). It is under the evaluation in two clinical phase I trials (NCT05006716 and NCT05294731) 6.

OBJECTIVES

• To characterize the profile and tendency of BGB-16673 to cause on-target BTK resistance mutations as compared with non-covalent BTKi.
• To determine its ability to overcome clinically emergent BTK mutations and compare this activity to other covalent and non-covalent BTKi.

METHODS

• ENU mutagenesis screen (Figure 2)
  • BTK-sensitized TMD8 lymphoma cells were treated with N-ethyl-N-nitrosourea (ENU, a highly mutagenic) for 18h. Mutant cells were treated with serial doses of either BGB-16673, compound-ED (an E3 ligase dead control with the same warhead as BGB-16673; binds BTK reversibly, but cannot degrade it), or pirtobrutinib (a non-covalent BTKi).
  • BTK CDNA from resistant clones was sequenced to identify and calculate the frequency of BTK mutations.

RESULTS

• In ENU mutagenesis screens, fewer resistant clones and lower BTK mutation frequency were seen with BTK CDAC treatment as compared to non-covalent BTKi treatment (Figure 3 and Table 1).

Table 1. BTK mutation frequencies in the ENU mutagenesis screens

<table>
<thead>
<tr>
<th>Compound</th>
<th>BGB-16673 (BTK CDAC)</th>
<th>Compound-ED (E3 dead non-covalent control)</th>
<th>Pirtobrutinib (non-covalent-selective inhibitor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK mutation Freq.</td>
<td>12.7% (7 out of 55)</td>
<td>100% (80 out of 80)</td>
<td>100% (144 out of 144)</td>
</tr>
</tbody>
</table>

• BGB-16673 appears to have a unique BTK resistance mutation profile vs. pirtobrutinib. Much fewer BTK inactivating mutations appeared in BGB-16673 resistant clones.

• No BTK mutations with frequency >10% were observed in the BGB-16673 arm. In comparison, more clones resistant to pirtobrutinib had mutations in BTK, many of which arose in the kinase domain. Among the pirtobrutinib clinically derived BTK mutations, V416L and T474I were identified in high frequent mutations, and one L528W clone was detected (Figure 4A).

• BGB-16673 was more potent against BTK mutations derived from compound-ED and pirtobrutinib screens (Figure 4B).

• BGB-16673 could overcome all BTK mutations from both covalent and non-covalent BTKi, except A428D which was tested to be resistant to all BTKi (Figure 5).

CONCLUSIONS

• Relative to other BTKi, the BTK CDAC BGB-16673 is less apt to cause on-target resistance mutations, demonstrated a unique on-target resistance mutation profile. Further studies exploring the dominant BGB-16673 resistance mechanisms not reliant on BTKi are in progress.

• BGB-16673 could overcome a wide variety of BTK resistance mutations derived from both ENU mutagenesis screens and relapsed patients.

• These findings suggest that BGB-16673 is a promising novel BTK degrader that could benefit patients who develop BTKi on-target resistances.

ACKNOWLEDGMENTS

• We sincerely thank Jinhong Ren and Shifan Ma (BeiGene Molecular Science department) for the valuable inputs on the structure predictions of BTK protein and drug interactions, Lisa McCraw (Medical Writing, Translational Discovery, Research and Medicine, BeiGene USA, Inc) for the fantastic support on manuscript development, and Jason Paik (Medical lead of BGB-16673 clinical trial) for insightful scientific discussions and manuscript review.

DISCLOSURE

• All authors have no conflicts of interest to disclose.

CONTACT INFORMATION

• yangbo.yue@beigene.com; zhirong.shen@beigene.com

REFERENCES


Figure 1. CDAC mechanism of action

Figure 2. Procedure of the ENU mutagenesis screen

Table 1. BTK mutation frequencies in the ENU mutagenesis screens

Figure 3. Resistance clone rates in the ENU mutagenesis screens

Figure 4. BTK mutation spectrums in the ENU mutagenesis screens

Figure 5. Degradation of the BTK mutants by BGB-16673

Figure 6. Degradation of the BTK mutants by BGB-16673 (MR-12)