In Vivo Pre-Clinical Evaluation of LOXO-305 Alone and in Combination with Venetoclax, R-CHOP or Obinutuzumab on Human Xenograft Lymphoma Tumor Models in Mice

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In Vivo Pre-Clinical Evaluation of LOXO-305 Alone and in Combination with Venetoclax, R-CHOP or Obinutuzumab on Human Xenograft Lymphoma Tumor Models in Mice

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Presenting Author Disclosures

All authors are full time employees of Loxo Oncology, a wholly owned subsidiary of Eli Lilly
Background

• Bruton’s Tyrosine Kinase (BTK) is an essential component of normal and malignant B-cell receptor signaling

• Covalent BTK inhibitors have transformed the treatment of B-cell malignancies

• Despite the marked efficacy of covalent BTK inhibitors, their activity may be limited by suboptimal pharmacology (low oral bioavailability, high protein binding, and short half-life)
  • We hypothesized that their shared covalent binding mechanism may not sufficiently compensate for these liabilities, resulting in suboptimal target coverage: i) towards the end of the dosing interval; ii) in rapidly proliferating tumors with high BTK protein turnover; and iii) in the setting of BTK cysteine binding site (C481) mutations1-5

• To address these limitations, LOXO-305, a highly selective, non-covalent BTKi that inhibits both WT and C481-mutated BTK with equal low nM potency was developed
  • Proof-of-concept Phase I results demonstrated LOXO-305’s anti-tumor activity across patients with heavily pretreated B-cell malignancies6
  • We previously showed pre-clinical data demonstrating that LOXO-305 potently inhibited wild-type (WT) BTK and different variants of the BTK mutation C481 with nanomolar potency and caused regression in BTK-dependent lymphoma mouse xenograft models7,8

## In Vivo Studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Test Compound 1 /Frequency</th>
<th>Test Compound 2 /Frequency</th>
<th>Cell line</th>
<th>BTK status</th>
<th>Disease</th>
<th>Mouse strain</th>
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<tbody>
<tr>
<td>1</td>
<td>LOXO-305/BID</td>
<td></td>
<td>TMD8</td>
<td>WT</td>
<td>DLBCL</td>
<td>Balb/c SCID</td>
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<tr>
<td></td>
<td>Ibrutinib/BID</td>
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<td></td>
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<tr>
<td>2</td>
<td>LOXO-305/BID</td>
<td></td>
<td>REC-1</td>
<td>WT</td>
<td>MCL</td>
<td>Hsd:Athymic Nude-Foxn1&lt;sup&gt;nu&lt;/sup&gt;</td>
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<tr>
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<td>Venetoclax/QD</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>LOXO-305/BID</td>
<td>Rituximab + CHO/Q7D + P/QD(3/7)</td>
<td>TMD8</td>
<td>WT</td>
<td>DLBCL</td>
<td>Balb/c SCID</td>
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<tr>
<td>6</td>
<td>LOXO-305/BID</td>
<td>Obinutuzumab/Q7D</td>
<td>TMD8</td>
<td>WT</td>
<td>DLBCL</td>
<td>Balb/c SCID</td>
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</tbody>
</table>

*BID, twice a day; QD, once a day; Q7D, every 7 days; DLBCL, Diffuse large B cell lymphoma; MCL, Mantle cell lymphoma; CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone*
LOXO-305 shows superior potency in inhibiting tumor growth in DLBCL and MCL xenograft models versus ibrutinib

(A) TMD8 xenograft tumor growth profiles for groups of treated mice from day 19 to day 34 post cell injection.

(B) REC-1 xenograft tumor growth profiles for groups of treated mice with the indicated doses for 3 weeks.

Effects of LOXO-305 dosed as single agent versus ibrutinib on tumor growth in TMD8 and REC-1 xenograft model
LOXO-305 in combination with venetoclax shows a significant improvement in efficacy in DLBCL and MCL xenograft tumor models versus LOXO-305 or venetoclax stand alone.

**Effects of LOXO-305 and venetoclax dosed alone or in combination on tumor growth in TMD8 and REC-1 xenograft tumor models**

(A) TMD8 xenograft tumor growth profiles for the six groups of treated mice from day 20 to day 37 post cell injection.

(B) REC-1 xenograft tumor growth profiles for groups of treated mice with the indicated doses for 3 weeks.

Note: an intermediate dose of LOXO-305 was used in both studies so that combination effects could be observed.
LOXO-305 in combination with R-CHOP shows improvement in efficacy in a TMD8 xenograft tumor model vs LOXO-305 and R-CHOP stand alone, and displays similar anti-tumor activity as the combination of ibrutinib and R-CHOP.

Effects of R-CHOP dosed in combination with LOXO-305 or Ibrutinib on tumor growth and body weight in a TMD8 xenograft model

(A) TMD8 xenograft tumor growth profiles for the eight groups of tumor bearing mice from day 20 to day 33 post cell injection. The mice were dosed with the indicated treatments.

(B) Individual tumor weight (mg) of the 7 treated groups at day 33 post cell injection, end point of the study.

(C) Mean of body weight of each treated groups of mice from day 20 to day 33 post cell injection.
LOXO-305 in combination with obinutuzumab shows greater tumor regression in a TMD8 xenograft tumor model versus LOXO-305 and obinutuzumab stand alone

Effects of obinutuzumab dosed in combination with LOXO-305 on tumor growth and body weight in a TMD8 xenograft model

(A) TMD8 xenograft tumor growth profiles for the six groups of tumor bearing mice from day 20 to day 37 post cell injection. The mice were dosed with the indicated treatments.

(B) Individual tumor weight (mg) and mean of the 6 treated groups at day 37 post cell injection, end point of the study.

(C) Mean of body weight of each treated groups of mice from day 19 to day 37 post cell injection.

Vehicle
Obinutuzumab 30 mg/kg
LOXO-305 15mg/kg
LOXO-305 30mg/kg
Obinutuzumab 30mg/kg + LOXO-305 15mg/kg
Obitutuzumab 30mg/kg +LOXO-305 30mg/kg
Conclusions

• Results show that LOXO-305 potently inhibited the growth of BTK WT driven xenograft tumors from MCL and DLBCL cells. In all combinations tested, greater tumor growth inhibition was observed in groups where LOXO-305 was co-administered with clinically approved agents.

• All treatments were well tolerated without any significant clinical signs being observed on the mice. The only treatments that showed significant weight loss were the combination treatments of LOXO-305 or ibrutinib with R-CHOP.

• These data suggest that the co-administration of LOXO-305 with venetoclax, R-CHOP or obinutuzumab may have increased benefits for patients with B-cell malignancies compared to stand-alone treatments and warrants further investigation.