

**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**

Presented at: 2020 ASH Annual Meeting

Date: December 7, 2020

***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

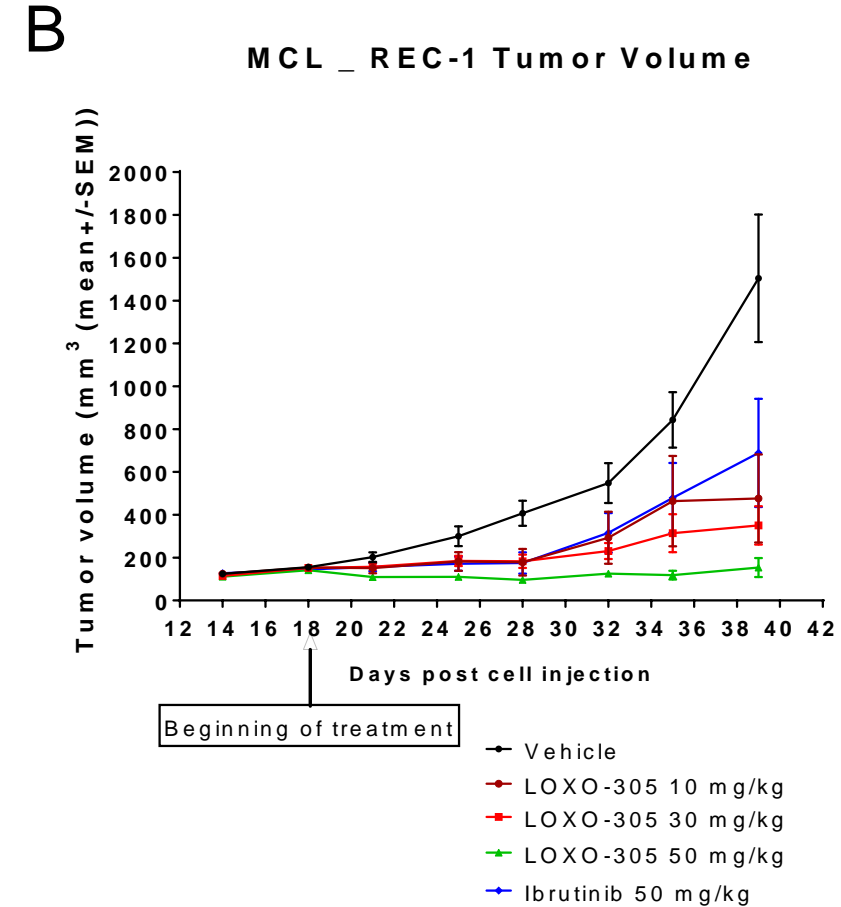
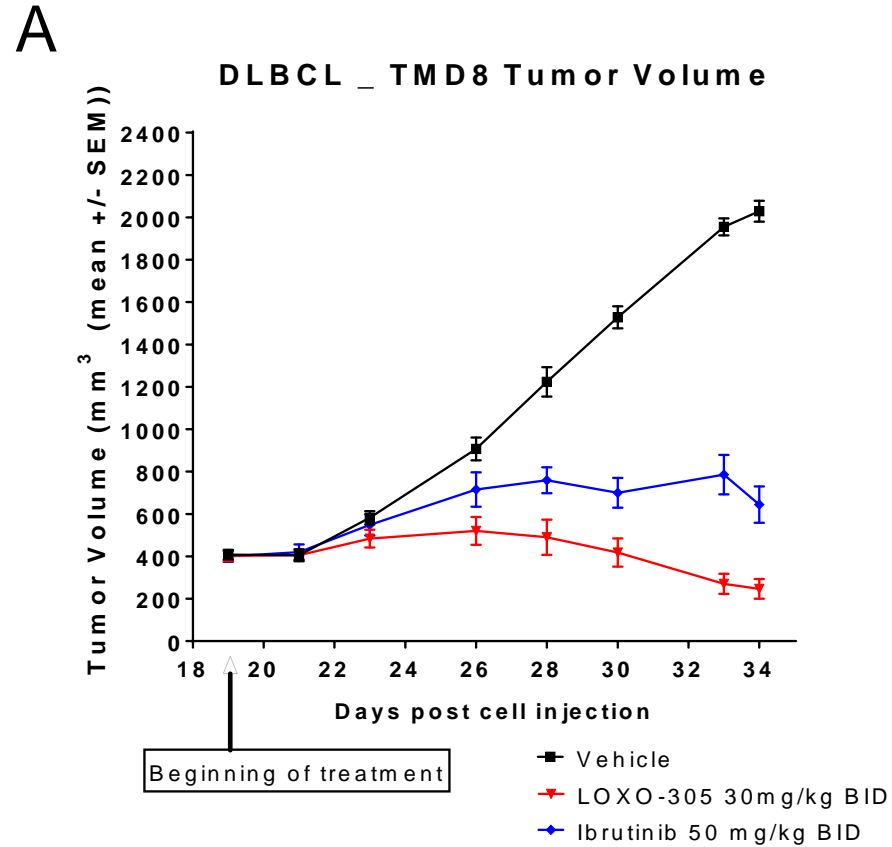
- Bruton's Tyrosine Kinase (BTK) is an essential component of normal and malignant B-cell receptor signaling
- Covalent BTK inhibitors have transformed the treatment of B-cell malignancies
- Despite the marked efficacy of covalent BTK inhibitors, their activity may be limited by suboptimal pharmacology (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 models^{7,8}

In Vivo Studies

STUDY	Test Compound 1 /Frequency	Test Compound 2 /Frequency	Cell line	BTK status	Disease	Mouse strain
1	LOXO-305/BID		TMD8	WT	DLBCL	Balb/c SCID
	Ibrutinib/BID		TMD8		DLBCL	Balb/c SCID
2	LOXO-305/BID		REC-1	WT	MCL	Hsd:Athymic Nude-Foxn1 ^{nu}
	Ibrutinib/BID		REC-1		MCL	Hsd:Athymic Nude-Foxn1 ^{nu}
3	LOXO-305/BID	Venetoclax/QD	TMD8	WT	DLBCL	Balb/c SCID
4	LOXO-305/BID	Venetoclax/QD	REC-1	WT	MCL	Hsd:Athymic Nude-Foxn1 ^{nu}
5	LOXO-305/BID	Rituximab + CHO/Q7D + P/QD(3/7)	TMD8	WT	DLBCL	Balb/c SCID
	Ibrutinib/BID	Rituximab + CHO/Q7D + P/QD(3/7)	TMD8		DLBCL	Balb/c SCID
6	LOXO-305/BID	Obinutuzumab /Q7D	TMD8	WT	DLBCL	Balb/c SCID

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



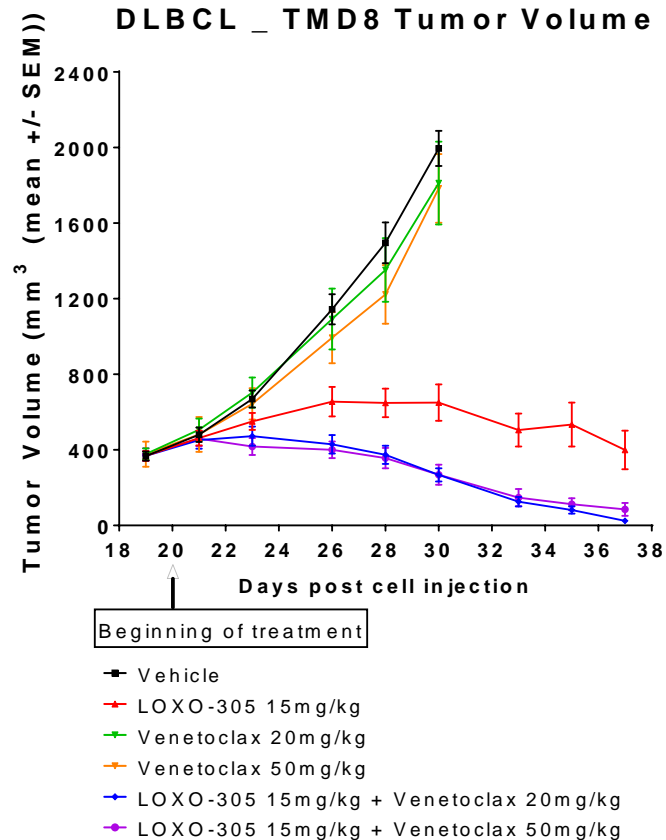
Effects of LOXO-305 dosed as single agent versus ibrutinib on tumor growth in TMD8 and REC-1 xenograft model

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

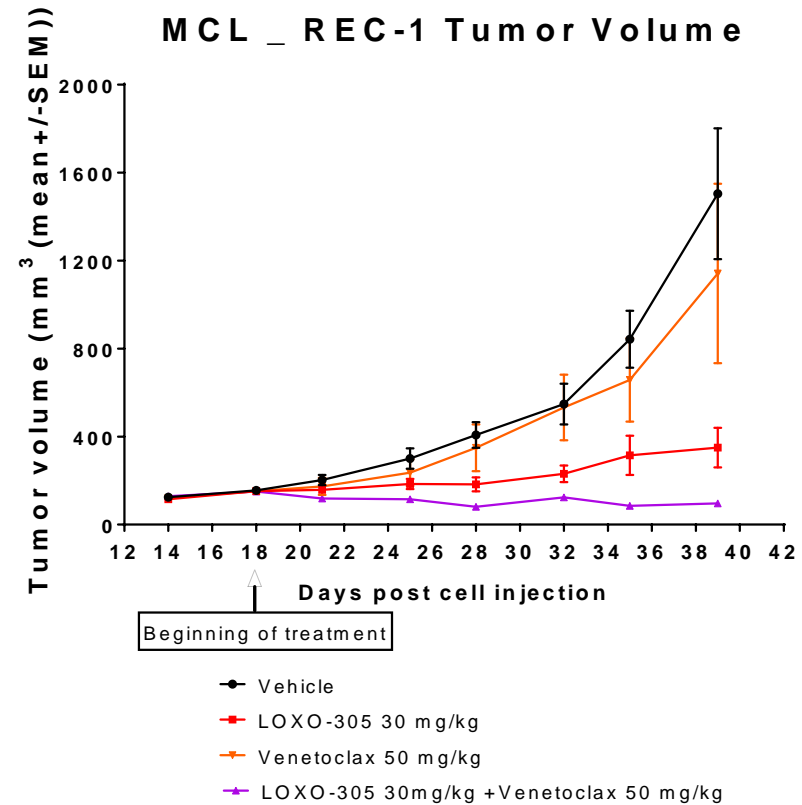
(B) REC-1 xenograft tumor growth profiles for groups of treated mice with the indicated doses for 3 weeks.

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

A



B



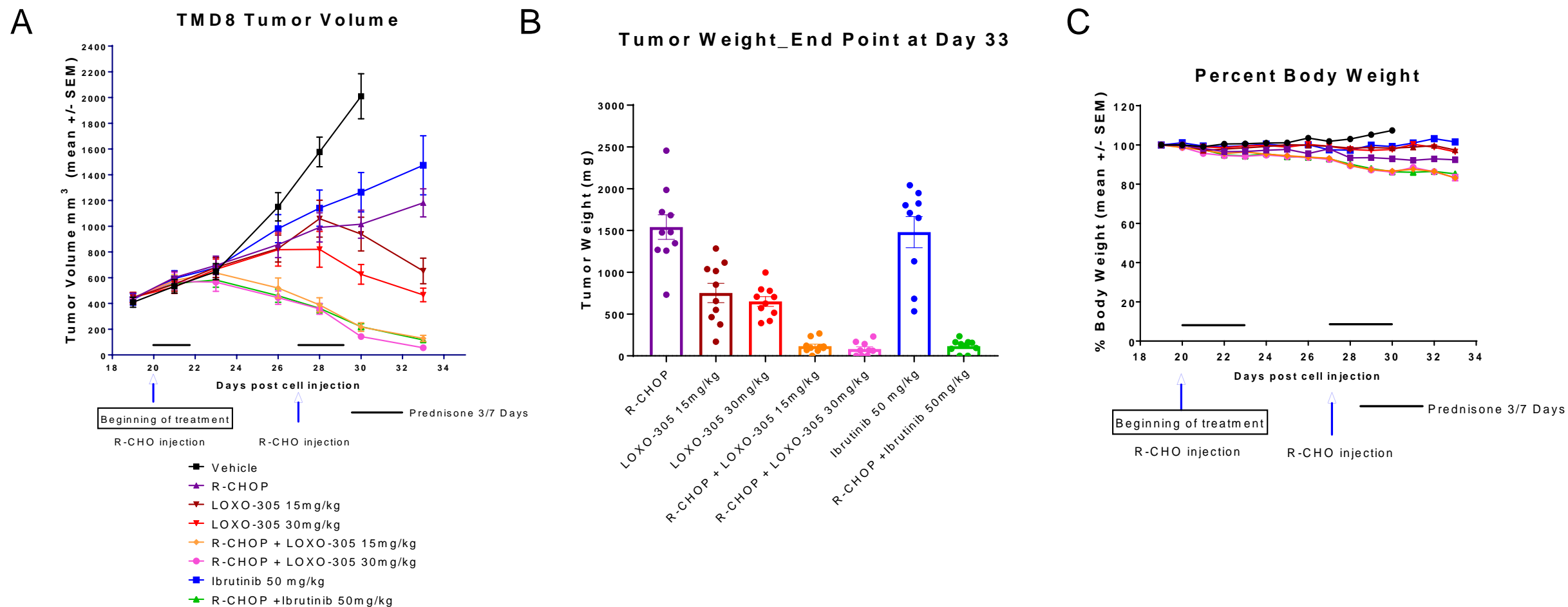
Note: an intermediate dose of LOXO-305 was used in both studies so that combination effects could be observed

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.

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

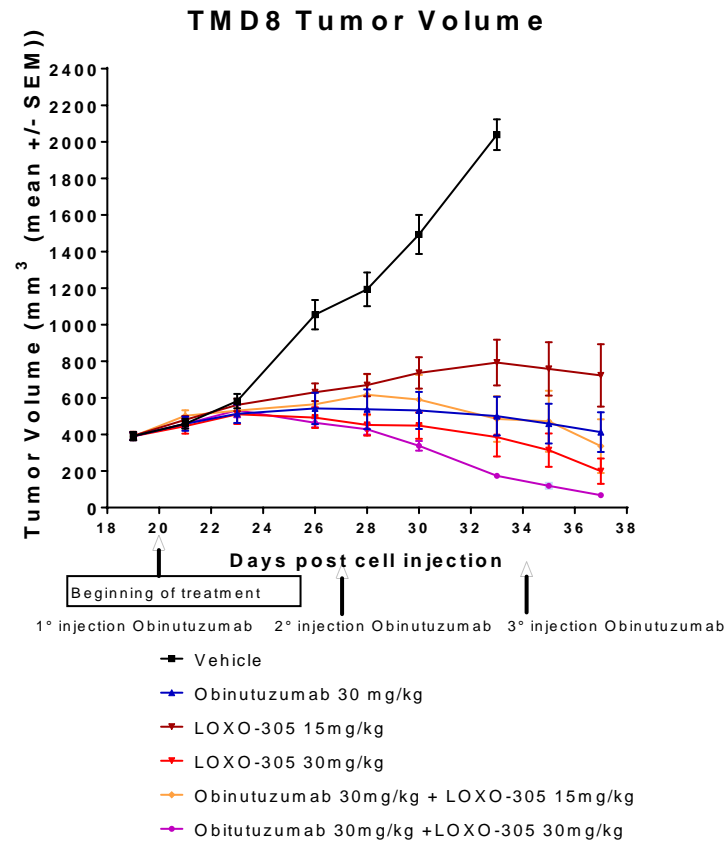


Effects of R-CHOP dosed in combination with LOXO-305 or Ibrutinib on tumor growth and body weight in a TMD8 xenograft model

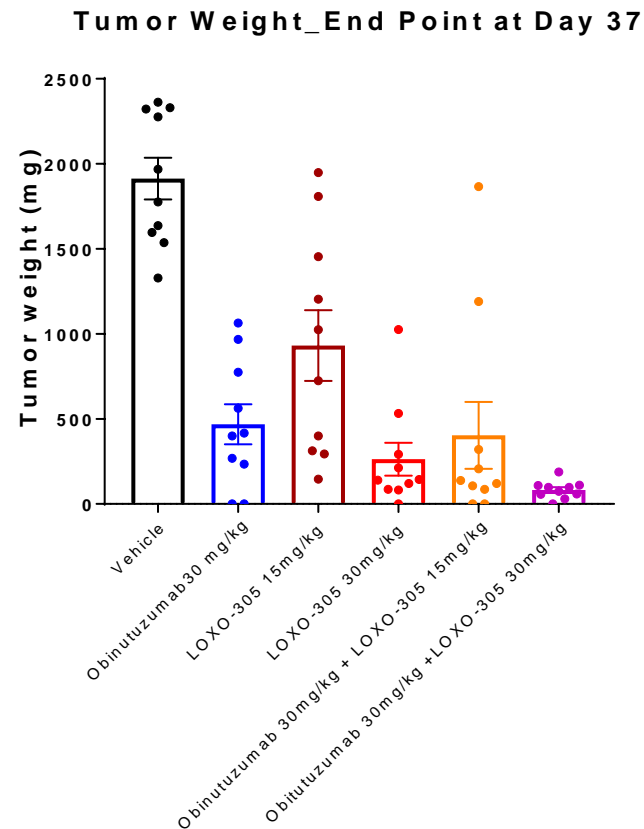
- (A) TMD8 xenograft tumor growth profiles for the eight groups of tumor bearing mice from day 20 to day 33 post cell injection. The mice were dosed with the indicated treatments.
- (B) Individual tumor weight (mg) of the 7 treated groups at day 33 post cell injection, end point of the study.
- (C) Mean 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

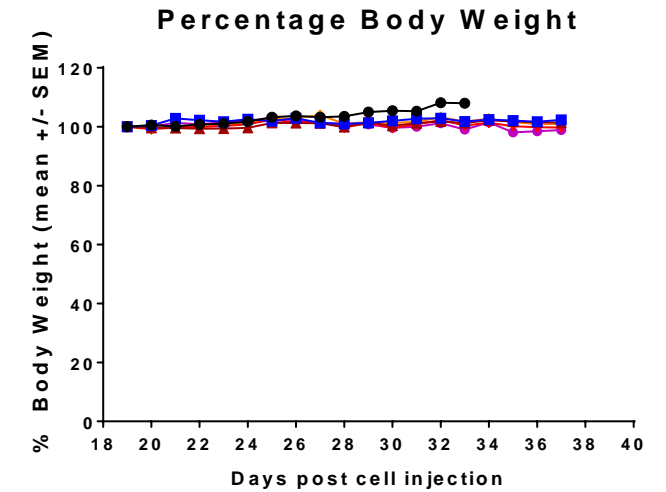
A



B



C



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.

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.

