Abstract #2627

The small molecule KRAS inhibitor, TEB-17231, blocks tumor progression and overcomes KRAS G12C inhibitor mediated resistance

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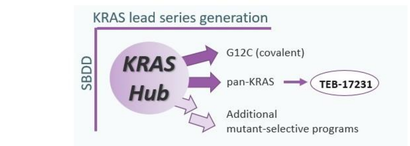
Background

KRAS signaling is frequently upregulated in cancers owing to oncogenic KRAS mutations or other signaling modifications. Also, resistance to KRAS^{G12C} inhibitors and other KRAS/RAF/MEK pathway drugs is commonly observed in the treated cancer patients. A significant unmet need is the development of agents that potently and safely inhibit the activated KRAS signaling in these settings.
TEB-17231（YL-17231), a novel small molecule pan-KRAS inhibitor, is described in a series of in vitro and in vivo pre-clinical models.

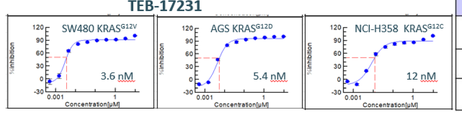
Results

1. TEB-17231, a novel pan-KRAS inhibitor

Rational drug design, medicinal chemistry, and cell growth inhibition methodologies were applied in a '***KRAS target hub***' program to differentiate pan-KRAS small molecule inhibitors. Chemical and structure-based drug design (SBDD) launch points and binding features of the KRAS^{G12C} inhibitors (YL-15293 and others) were utilized. Through extensive pharmacophore screening at specific subdomains, a lead series was discovered with potent and selective cell proliferation inhibition in KRAS^{G12V}, KRAS^{G12D} and KRAS^{G12C} tumor cell lines. A number of compounds from this lead series consistently indicated a 5- to 6-fold selectivity of inhibition for KRAS^{mutant} over KRAS^{wildtype} cell lines.



TEB-17231



TEB-17231 Lead series

Selectivity Ratio	KRAS^{G12V}/ KRAS^{WT}
Cmpd 21	5X
Cmpd 55	5X
TEB-17231	6X
Cmpd 100	6X
Cmpd 101	5X
Cmpd 111	3X

2. TEB-17231 inhibits cell growth of various KRAS and RAS mutation tumor cells and under conditions of KRAS^{G12C} drug-resistance

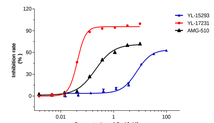
Cell growth inhibition properties of TEB-17231 were evaluated in tumor cell lines containing various KRAS, NRAS or HRAS mutations (A). Also, TEB-17231 inhibition was shown in two conditions of KRAS^{G12C} inhibitor mediated resistance (B)

A. Other KRAS and RAS mutations

Cell Line	IC_{50} (nM)
NCI-H1734 KRAS G13C	6.5
MDA-MB-231 KRAS G13D	11.2
RPMI-8226 KRAS G12A	11.3
Calu-6 KRAS Q61K	19.8
KP-2 KRAS G12R	24.1
LS123 KRAS G12S	21.0
NCI-H1915 HRAS	11.5
NCI-H1299 NRAS	10.8
KURAMOCHI KRAS^{ampl}	12.4

B. KRAS^{G12C} inhibitor resistance

Sotorasib-resistant Miapaca-2



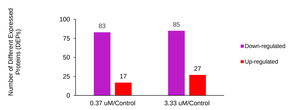
Ba/F3: engineered to express patient KRAS secondary mutations combined with KRAS^{G12C}

Expressed KRAS^{mutant} form	IC_{50} (nM)
KRAS-G12C	14.0
KRAS-G12C-H95Q	31.8
KRAS-G12C-H95D	39.7
KRAS-G12C-Y96C	38.6
KRAS-G12C-Y96D	20.0
KRAS-G12C-R68S	21.6

3. Lead series induces cell proliferation/cell cycle gene downmodulation, G2 arrest, and apoptosis

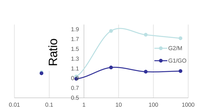
A. Quantitative proteomics:

HPAC KRAS^{G12D}/ Cmpd 55



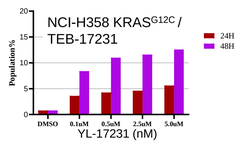
B. G2/M cell cycle arrest:

AGS KRAS^{G12D}/ Cmpd 55

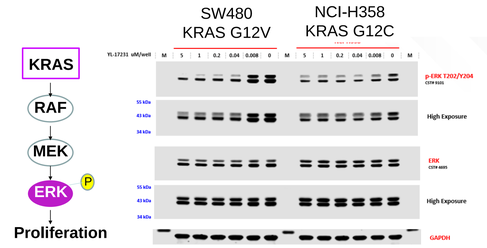


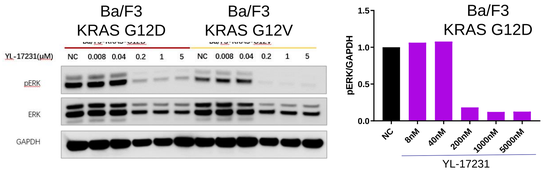
C. **Apoptosis**:

NCI-H358 cells seeded at 300,000 cells/ml, were treated for 24 or 48 hours with TEB-17231, evaluated by flow cytometry with 7-AAD and AnnexinV-FITC. TEB-17231 significantly induced apoptosis of NCI-H358 cells and the effect was enhanced with the increase of concentration and time.

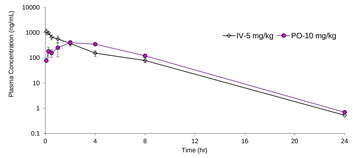


4. TEB-17231 inhibits phosphoERK downstream signaling in KRAS^{mutated} tumor cell lines





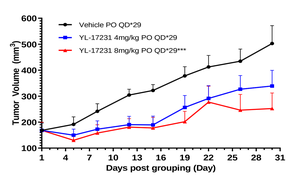
5. TEB-17231 demonstrates satisfactory pharmacokinetics with high bioavailability in mice

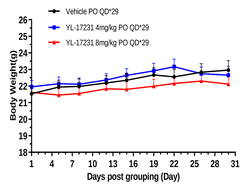


After single IV and PO administrations of TEB-17231 in male C57BL/6 mice (N=3 / time point), plasma concentration were measured, and mean PK values computed by the non-compartmental model

	AUC_{INF} (hr*ng/mL)	$t_{1/2}$ (hr)	CL (L/hr/kg)	V_{ss} (L/kg)
IV Dose 5mpk	2527	2.50	1.98	6.36
	AUC_{INF} (hr*ng/mL)	C_{max} (ng/mL)	T_{max} (hr)	F%
PO Dose 10mpk	2776	407	2	54.9

6. TEB-17231 is well tolerated and inhibits tumor growth of human SW480 colorectal tumor xenograft





Following subcutaneous injections into female BALB/c nude mice, the human colorectal SW480 xenograft tumors were expanded. Treatment with TEB-17231 or Vehicle controls were initiated as tumor sizes reached ~168 mm^3; tumor size and body weight were monitored for n=8 animals per group.

Summary

- A novel series of potent, reversible inhibitors of KRAS were identified.TEB-17231 showed robust activity with in vitro and in vivo pre-clinical tumor models
- TEB-17231 exhibits cell growth inhibition with tumor cell lines containing various KRAS mutations
- KRAS G12C drug-resistant cell lines are effectively inhibited by TEB-17231
- TEB-17231 blocks phosphoERK downstream of KRAS in KRAS mutant cell lines and induces late apoptosis
- With satisfactory pharmacokinetics and oral bioavailability, TEB-17231 demonstrates antitumor efficacy at QD dosing of 4-8 mg/kg PO without body weight loss
- Investigation of TEB-17231 as a clinical drug candidate is planned, and the IND-enabling process is underway

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