A novel small molecule inhibitor of inactive and active forms of oncogenic mutant KRAS promotes tumor regression in KRAS^{mutated} cancer models

ABSTRACT 103

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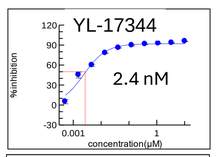
BACKGROUND

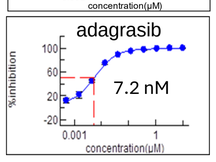
KRAS, a significant oncogenic driver of many cancers, is an important target for drugs, with an objective of blocking the KRAS^{mutated} oncoprotein selectively, and inhibiting KRAS-specific functions that cause tumor growth and metastasis. Several KRAS mutations, namely KRAS$^{G12C, V, and D}$ mutations, occur at high frequencies in major cancers, such as NSCLC, colorectal, pancreatic and others, underscoring the need for identifying inhibitors directed to these oncogenic proteins.

RESULTS

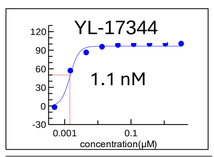
YL-17344 Lead candidate demonstrates selective growth inhibition for key KRAS^{mutant} cancer cells

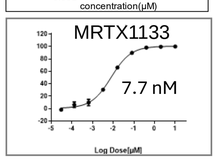
NCI-H358 KRAS^{G12C}



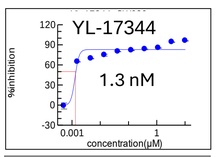


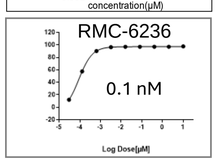
LS513 KRAS^{G12D}





SW620 KRAS^{G12V}



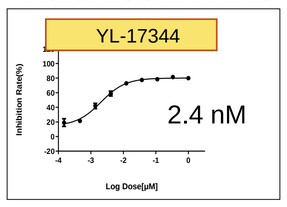


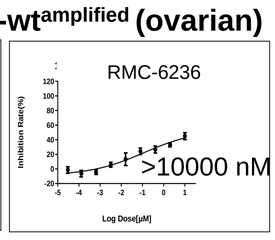
Cell line	Tumor	KRAS mutation	IC50 (nM)
H358	Lung	G12C	2.4
AGS	Stomach	G12D	<1.5
LS513	Colon	G12D	1.1
SW620	Colon	G12V	1.3
NCI-H441	Lung	G12V	3.6
LoVo	Colon	G13D	7.8
NCI-H460	Lung	Q61H	119
A375	Skin	KRAS WT	> 3330
SK-MEL-2	Skin	KRAS WT	5467
NCI-H2126	Lung	KRAS WT	5270

Benchmark inhibitors for comparisons :
-- adagrasib (MRTX849), a covalent G12C-selective inhibitor
-- MRTX1133, a non-covalent G12D-selective inhibitor
-- RMC-6236, a panKRAS tricomplex inhibitor
[refs. Wei 2024 CCR 30(4):655-662; Jiang 2024 Canc Discovery 14: 994-1017]

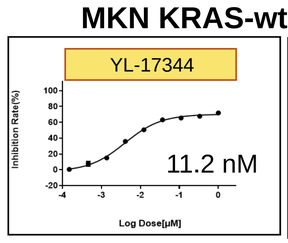
KRAS-wt^{amplified} cell proliferation is inhibited by YL-17344

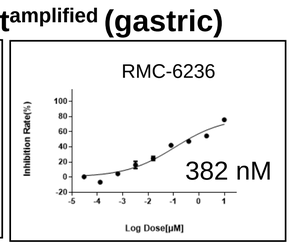
Kuramochi KRAS-wt^{amplified} (ovarian)





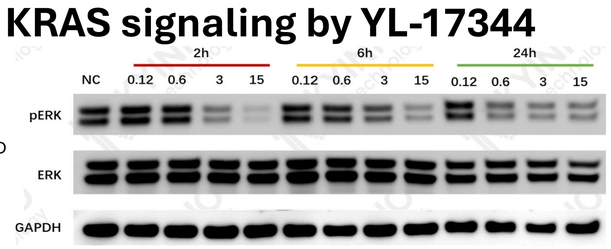
MKN KRAS-wt^{amplified} (gastric)

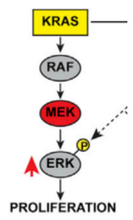




Inhibition of KRAS signaling by YL-17344

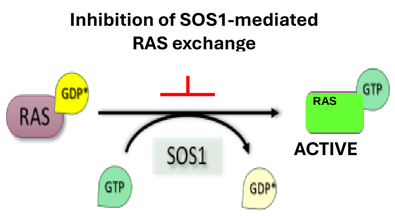
LS513 KRAS^{G12D} colorectal

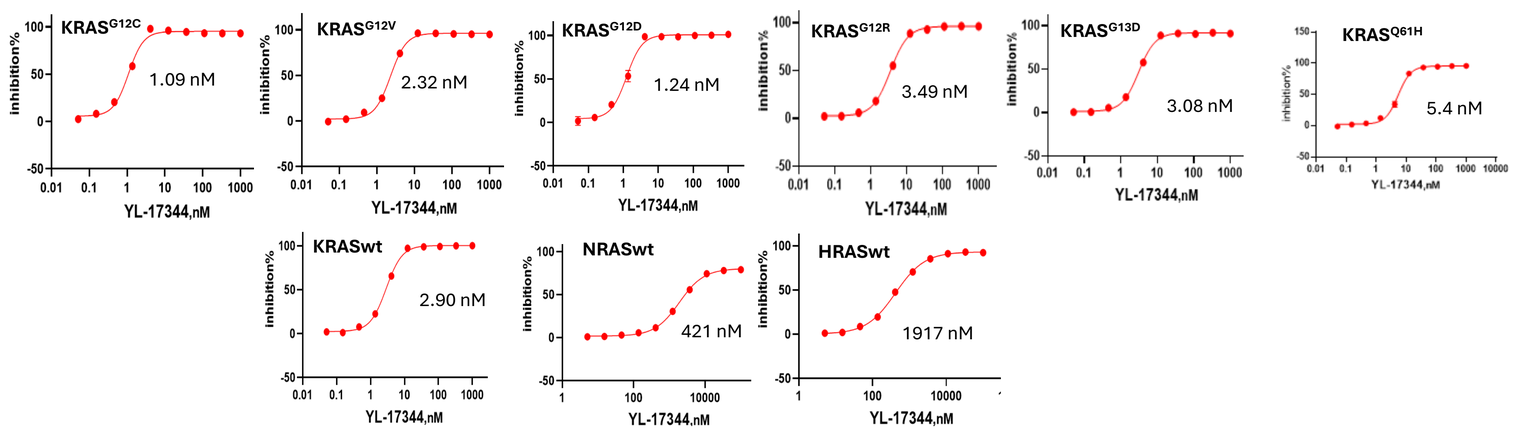




Potent and selective inhibition of KRASmutant oncoproteins in GDP/GTP exchange assays

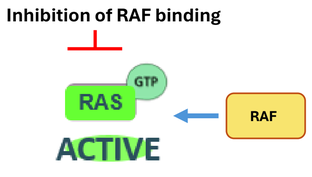
Probing the RAS inactive form

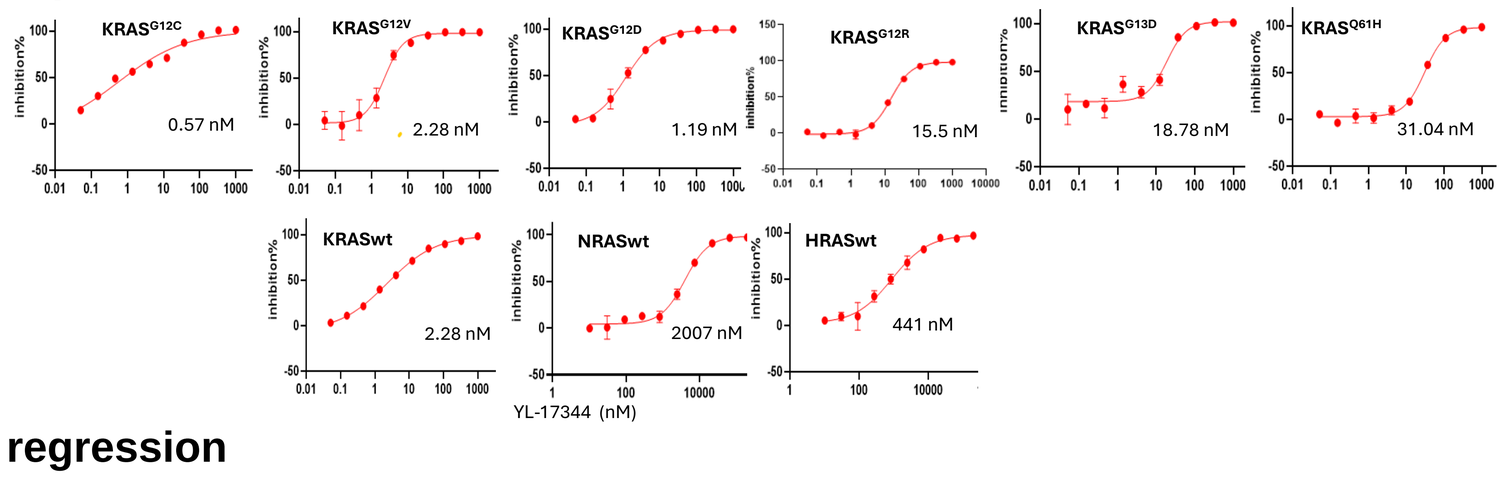




Inhibition of KRAS^{active} binding to Raf by YL-17344

Probing the RAS active form

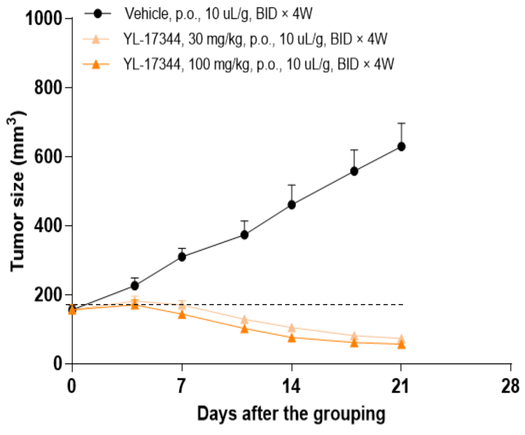


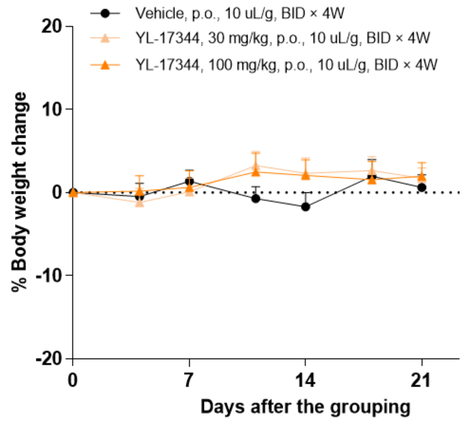


Oral inhibitor YL-17344 drives tumor regression

LS513 KRAS^{G12D} colorectal xenograft

YL-17344 TGI:
30mg/kg 118%
100mg/kg 121%





CONCLUSIONS

- A Lead Series was discovered, including YL-17344, a highly potent oral small molecule inhibitor of KRAS
- YL-17344 inhibits inactive and active forms of KRAS in vitro
- YL-17344 has selective inhibitory tumor cell proliferation activity towards the KRAS^{G12D,C,V} tumor cell lines, as well as inhibiting KRAS-wt^{amplified}
- YL-17344 potently drives tumor regression in the LS513 KRAS^{G12D} colorectal tumor xenograft model
- A novel KRAS-selective inhibitor with this profile warrants clinical investigation for treating patients with KRAS^{mutated} cancers

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