LB204

The class I-targeting, oral HDAC inhibitor OKI-179 increases tumor regressions when combined with the MEK inhibitor binimetinib in models of NRAS melanoma

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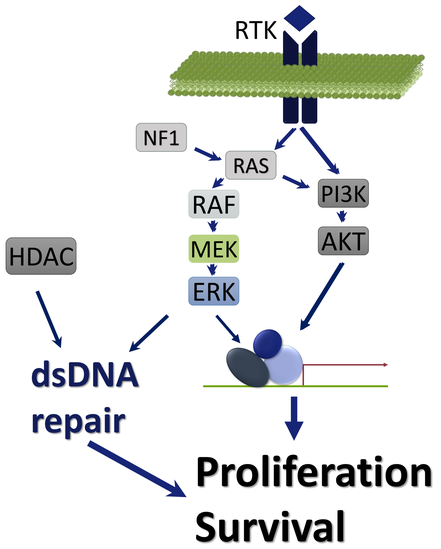
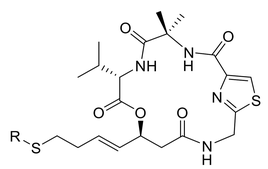
HDAC inhibition shows chemical synthetic lethality with MEK and BRAF inhibitors in RAS-pathway mutated cancers[1]



- RAS pathway mutations drive aberrant DNA repair, including activation of HRR[2]
- Inhibition of RAF pathway alone through BRAF or MEK inhibitors) is often insufficient to drive apoptosis in cancers with mutations in RAS or upstream pathways[3]
- Inhibition of HDACs (HDAC3) cooperates with MEK or BRAF inhibitors to fully inhibit dsDNA repair, via suppression of ELK1 resulting in significantly increased double strand breaks and cell death, representing a novel therapeutic approach in RAS-mutated cancers[1]

OKI-179 is a novel, clinical-stage Class I-targeting HDAC inhibitor



R = octanoate thioester = OKI-005
R = H = OKI-006
R = l-valine thioester benzesulfonic acid salt = OKI-179

Compound IC50 (nM)				
Class	HDAC	OKI-006	Red-FK228*	Vorinostat
I	1	1.2	0.8	75.5
I	2	2.4	1.0	362
I	3	2.0	1.3	57.4
I	8	49.0	>1000	1069
IIa	4	>1000	647.0	>1000
IIa	5	>1000	>1000	163
IIa	7	>1000	>1000	>1000
IIa	9	>1000	>1000	78.1
IIb	6	47.0	226.0	27.1
IIb	10	2.8	0.9	88.4
IV	11	2.3	0.3	109.0

OKI-179 is an orally-bioavailable prodrug, rapidly converting to the active parent, OKI-006 *in vivo*.

OKI-005 is a research tool prodrug that also converts to OKI-006 in vitro.

OKI-006 shows low nM activity on Class I HDACs, with high-selectivity relative to Class IIa.

OKI-179 has completed Ph1 clinical trials as a single agent.
OKI-179 has good PK and PD activity at the proposed RP2D* with a well-tolerated safety profile[4]

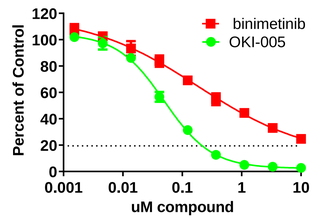
* RED_FK226 is active metabolite of romidepsin

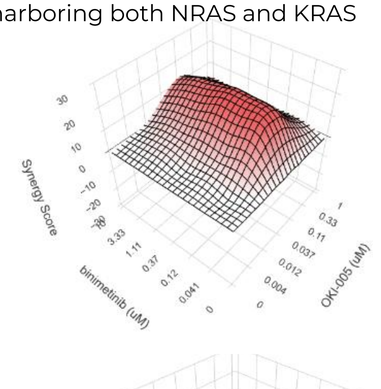
OKI-005 shows Synergy with binimetinib in SKMEL2 and AGS cell lines in vitro

Both OKI-005 and binimetinib show anti-proliferative activity as single-agents in cell lines harboring RAS mutations

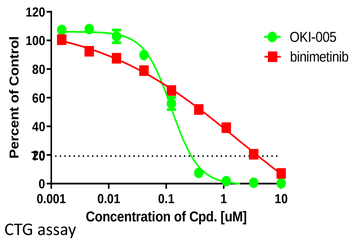
- OKI-005 combined with binimetinib shows strong synergy as assessed by the Loewe additivity model[5]
- Synergy was observed in models harboring both NRAS and KRAS mutations

SKMEL2 (NRAS Melanoma)

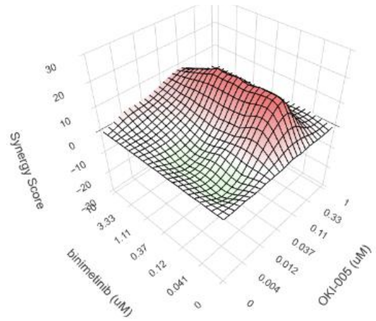




AGS (KRAS^{G12D} Gastric)



72h CTG assay



OKI-179 is super-additive in combination with binimetinib in NRAS^{MT} melanoma and with binimetinib + encorafenib in BRAF^{MT} CRC *in vivo*

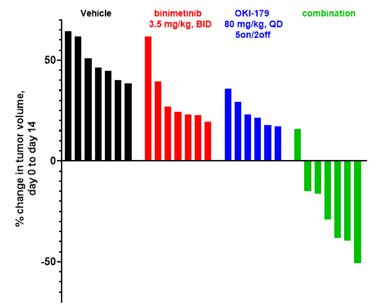
Model	RAS Pathway Mutation	Treatment	Max % BW loss	% Tumors with Regression (D14)
MEL278 (Melanoma)	NRAS	bini	1.7	0%
		OKI-179	8.7[1]	0%
		OKI-179 + bini	15.6[2]	**86**
MM415 (Melanoma)	NRAS	bini	5.5	25%
		OKI-179	7.7	0%
		OKI-179 + bini	8.1	**75%**
SKMEL2 (Melanoma)	NRAS	bini	13.1	0%
		OKI-179	16.7[3]	0%
		OKI-179 + bini	20[4]	**86%**
HT29 (CRC)	BRAF	bini + enco	4.2	13%
		OKI-179	7.8	0%
		OKI-179 + bini/enco	6.1[5]	**71%**

Binimetinib: 3.5 mg/kg PO BID. Encorafenib: 20 mg/kg PO QD, OKI-179: 80 mg/kg PO D1-4 QW

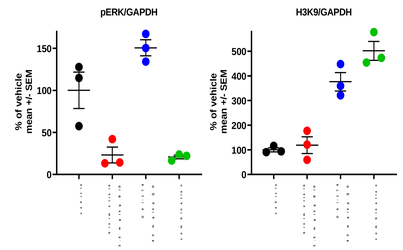
binimetinib: 3.5 mg/kg PO BID. OKI-179: 80 mg/kg PO D1-5 QW
Mice received a drug dosing holiday if weights dropped by 15% (SKMEL2) or 10% (MEL278, MM415)
[1] 1/8 mice found dead day 12
[2] 1/8 mice found dead day 7, all mice received dosing holiday days 8-9
[3] 1/7 mice found dead day 11, 2/7 mice received dosing holiday days 11-13
[4] 4/7 mice received dosing holiday days 11-13
[5] 2/8 mice received dosing holiday D11, 12

- OKI-179, binimetinib and encorafenib were administered at doses and schedules that model clinically approved or tolerated exposures.
- Both binimetinib and OKI-179 show strong on-target PD activity (increased AC-H3K9 or decreased pERK) at these doses.
- OKI-179, or binimetinib as single agents, or binimetinib + encorafenib combination show tumor growth delay, but few regressions.
- OKI-179 combined with binimetinib in SKMEL2 NRAS melanoma or combined with binimetinib + encorafenib in HT29 BRAFV600E colorectal xenografts shows significantly increased regressions compared to either single agent following 2 weeks of dosing.

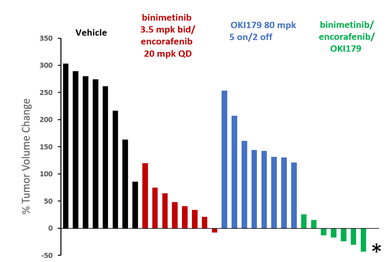
SKMEL2 Xenografts



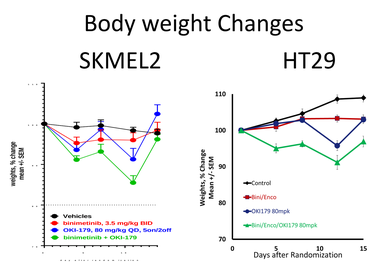
Changes in SKMEL2 tumor pERK (MEKi PD) and Ac-H3K9 (HDACi PD) at 2h post dose



HT29 Xenografts (BRAFV600E CRC)



Body weight Changes



* No data (animal death)

Summary

- OKI-179 is a clinical-stage, Class I-targeting, oral HDAC inhibitor
- OKI-005 shows synergy with binimetinib in the SKMEL2 NRAS^{MT} melanoma and AGS KRAS^{G12D} gastric lines in vitro
- OKI-179 is super-additive in combination with binimetinib or binimetinib + encorafenib in models of NRAS^{MT} melanoma or BRAF^{MT} colorectal cancer
- Collectively these data support combining OKI-179 with binimetinib in RAS pathway-mutated tumors in multiple indications, including in tumors less sensitive to RAS pathway inhibition alone
- OKI-179 is currently being investigated in a Ph1b/2 trial in combination with binimetinib in NRAS^{MT} melanoma

[1] Maertens et al. Cancer Discovery (2019), 9, 526-45 [2] Jinesh et al Oncogene (2018) 37, 839–46. [3] Blumenschein et al Ann Oncol. (2015) 26, 894–901 [4] Kagihara et al J Clin Oncol 39, no. 15_suppl (May 20, 2021) 3075-3075 [5] Loewe S. (1953) The problem of synergism and antagonism of combined drugs. ArzneimiettelForschung,3, 286-290. * RP2D Recommended Phase 2 Dose

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