Abstract # B007

OKI-179, A 1st in Class, Orally Administered HDAC Inhibitor with a Romidepsin-like Profile

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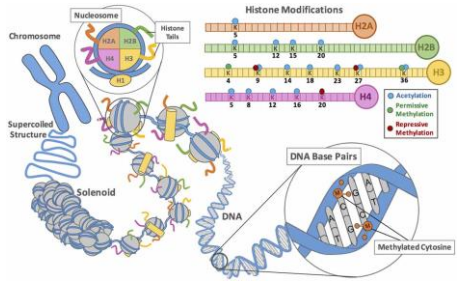
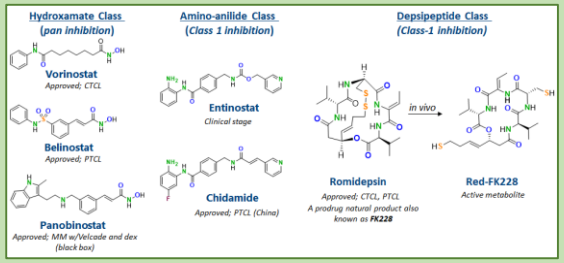
OnKure THERAPEUTICS

Background

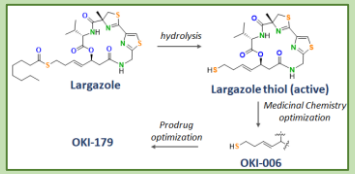


- Gene expression is controlled, in part, by histone acetylation state, and this state is critical for oncogenesis.
- Histone deacetylase inhibitors (HDACi) have been developed to target this oncogenic drive.
- To date, responses with single agent HDACi have been predominantly observed in advanced hematologic malignancies.
- By contrast, clinical trials with HDACi in the treatment of solid tumors demonstrate modest efficacy due in part to toxicity, inability to combine with other agents, and a lack of effective patient selection strategies.
- There is a need for more potent, selective, orally delivered HDACi, coupled with a targeted development plan.
- Herein we report pre-clinical and Phase 1 data for the novel, first-in-class HDACi (OKI-179) derived from the natural product Largazole, a depsipeptide of the Romidepsin type of inhibitory profile. [1,2]

Chemical Structure Strategy



Structural classes of approved and clinical stage HDACi include hydroxamic acids, amino-analides and depsipeptides. Romidepsin is highly potent, however, dose is limited by toxicity and administration requires a 4-hour i.v. infusion. Thus, there remains a clinical unmet need for an agent to address epigenetic targeting in solid tumor cancers.



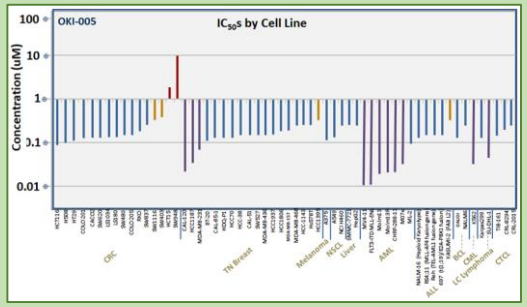
Medicinal chemistry optimization of Largazole-thiol resulted in OKI-006, a potent inhibitor of HDACs 1,2 and 3 with no inhibitory activity against the Class 2a isoforms

Pre-Clinical Results

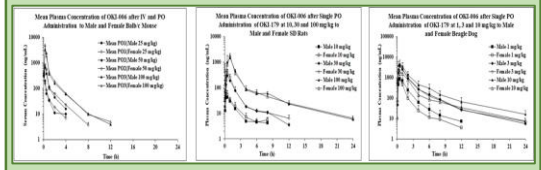
OKI-006 Biochemical inhibitory profile as compared with Reduced-FK228

Compound	HDAC by Class (IC50nM) Class 1			Class 2A				Class 2B	Class 4	
	1	2	3	8	4	5	7	9	6	10	11
Romi (Red-FK228)	0.8	1.0	1.3	>1000	647	>1000	>1000	>1000	226	0.9	0.03
OKI-006	1.2	2.4	2.0	49	>1000	>1000	>1000	>1000	46.9	2.8	2.3

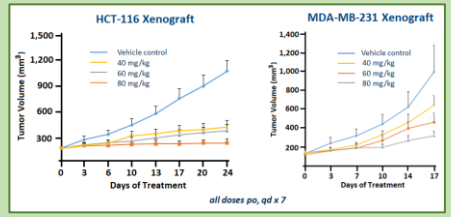
OKI-006 inhibits the proliferation of a variety of cell types at physiological achievable concentrations



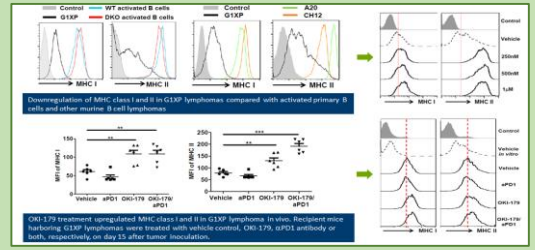
OKI-179 displays favorable oral pharmacokinetic properties in mouse, rat and dog



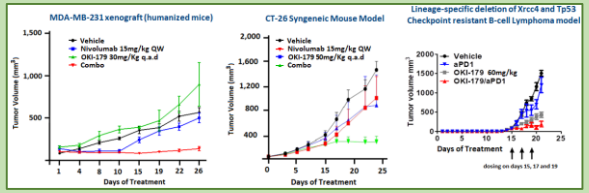
OKI-179 displays, dose-dependent, single-agent activity in CRC and TNBC xenograft models



OKI-179 promotes upregulation of MHC Class 1 & 2 at physiologically achievable concentrations



Epigenetic priming with OKI-179 overcomes immune-tolerance of PD1 blockade in humanized mouse, syngeneic and genetic cancer models



Phase 1 Clinical Study Design

Ongoing phase 1, dose escalation, single center (University of Colorado Cancer Center), adaptive design study of OKI-179 in patients with advanced solid tumor (NCT03931681)

Eligibility	Advanced solid tumors, ECOG 0-1, normal organ function
Dosing	Oral, fixed dose, days 1-4, 8-11, 15-18 in repeated 21-day cycles N=1 per cohort until G2 AE, then 3+3 design
AEs	No dose limiting toxicities observed up to 120 mg. To-date, well-tolerated without grade ≥ 2 drug-related AEs
PK	PK assessments on Days 1, 2 and 15, 16 of cycle 1
PD	Global H3, H4 in PBMCs; H3K9, H3K27 in CD4+, CD8+ T-cells

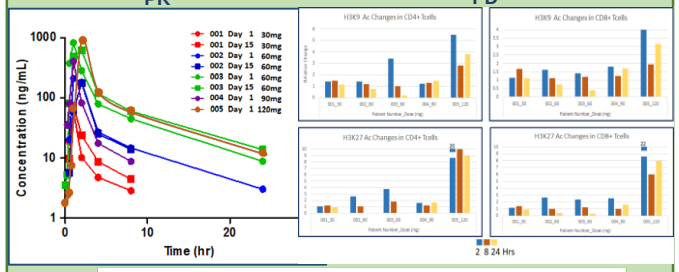
Primary Endpoints
Safety & Tolerability
Recommended P2 dose

30 mg → 60 mg → 90 mg → 120 mg → 150 mg Open

Secondary Endpoints
PK & PD profile
Preliminary evidence of efficacy

Clinical Data To-date

OKI-179 PK-PD profile, with demonstrated target engagement, with on 4 days on, 3 days off dosing schedule



Highest Blood Levels Achieved to Date

Subject	Dose (mg)	Matrix	OKI-006	Cycle	Day	Tmax (hr)	Cmax (ng/ml)	T1/2 (hr)	T last (hr)	AUC Last (hr*ng/ml)	AUC Inf (hr*ng/ml)
001-003	60	Plasma	Total	1	1	1	824	6.5	24	1940	2020
001-005	120	Plasma	Total	1	1	2	968	4.3	24	2590	2670

Conclusions

- OKI-179 is a potent inhibitor of Class 1 HDAC enzymes 1,2 and 3
- OKI-006, the active parent drug is structurally and biochemically similar to the active form of Romidepsin, Reduced-FK228
- OKI-179 is delivered orally and is active in several pre-clinical cancer models
- The phase 1 first-in-human dose escalation clinical study of OKI-179 is currently enrolling patients at the University of Colorado Cancer Center
- To date, OKI-179 is well-tolerated with no DLTs observed up to 120 mg, exhibits favorable PK and has on-target PD effects at tolerable doses
- Dose escalation will continue until MTD is determined
- Cohort expansions are planned in specific patient populations:
  - T-Cell Lymphoma
  - ER+ / Her2- Breast Cancer, combination with ERi
  - Small Cell Lung Cancer with CREBBP Mutations, with SoC
  - N-Ras Melanoma, combination with MEKi

References & Acknowledgements

1. Taori et al., Structure and activity of largazole, a potent antiproliferative agent from the Floridian marine cyanobacterium Symploca sp. J Am Chem Soc. 130(6):1806-7, 2008.
2. Ying et al., Total synthesis and molecular target of largazole, a histone deacetylase inhibitor. J Am Chem Soc. 130(26):8455-9, 2008.

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