Abstract # PD23

# Initial results from a Phase I trial of OKI-179, an oral class 1-selective depsipeptide HDAC inhibitor, in patients with advanced solid tumors

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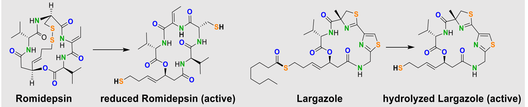
## Background

- Epigenetic escape contributes to cancer progression and treatment resistance in many tumor types. There remains a clinical need for a potent, selective, orally bioavailable histone deacetylase (HDAC) inhibitor.
- OKI-179 is a first-in-class, oral depsipeptide HDAC inhibitor with a biochemical profile similar to romidepsin.
- OKI-179 is a synthetic congener of the natural product largazole and a pro-drug.
- OKI-006 (active metabolite) potently inhibits HDAC 1,2,3 ($IC_{50}$ = 1.2, 2.4, 2.0 nM, respectively), with no significant inhibition of Class IIa HDACs.
- OKI-179 is active in preclinical models of triple-negative breast cancer and colorectal cancer and enhances the activity of nivolumab in a humanized mouse model[1].

### Figure 1: Structures of Romidepsin and Largazole




## Methods - Study Design

- First-in-human phase I, single center, dose-escalation study (NCT03931681) at the University of Colorado Cancer Center.
- OKI-179 administered orally, to fasted patients, once daily, on days 1-4 every 7 days, repeatedly with no break.
- Accelerated titration design dose escalation using single evaluable patient cohorts until grade 2 treatment-related toxicity observed. Subsequently, at least 3 evaluable patients per cohort with expansion to 6 evaluable patients if dose-limiting toxicity (DLT) is observed.
- Key DLT criteria: Grade 4 neutropenia > 5 days; grade 4 thrombocytopenia or any grade associated with bleeding; febrile neutropenia; Grade ≥ 3 non-hematologic AE except nausea, vomiting or diarrhea unless > 3 days despite max supportive care; omission of < 75% planned dosing in cycle 1 due to AE.
- Treatment continued until unacceptable toxicity, disease progression or withdrawal for other reason.
- Data reported here as of September 25, 2020.

## Methods – Patient Eligibility

**Key Inclusion Criteria**

- Histologically confirmed advanced or metastatic solid tumors refractory to standard therapies
- Measurable disease by RECIST v. 1.1; ECOG PS 0-1
- Adequate hematopoietic, hepatic and renal function, including: ANC ≥ 1.5 × $10^9$/L, no recent G-CSF; Platelet count ≥ 100 × $10^9$/L, no recent platelet transfusion

**Key Exclusion Criteria**

- Cytotoxic therapy within 21 days (capecitabine within 14 days)
- Prior HDAC, pan-deacetylase, or HSP90 inhibitors
- Symptomatic, active brain metastasis or leptomeningeal disease
- QTc ≥ 480 msec or taking medications leading to significant QT prolongation

## Results

### Table 1. Baseline Patient Characteristics

| Characteristic | All Patients N=20 |
|---|---|
| Median age (range), years | 63 (41-83) |
| Gender, n (%) | |
| Male | 6 (30) |
| Female | 14 (70) |
| Race, n (%) | |
| White | 15 (75%) |
| Black | 3 (15%) |
| Asian | 0 |
| Other | 2 (10%) |
| Ethnicity, n (%) | |
| Hispanic or Latino | 1 (5%) |
| Non-Hispanic or Latino | 19 (95%) |
| Tumor type | |
| NSCLC | 4 |
| Pancreatic cancer | 4 |
| Breast, ER+ HER2- | 3 |
| Colorectal cancer | 2 |
| Ovarian cancer | 2 |
| Endometrial | 2 |
| TNBC | 1 |
| Cholangiocarcinoma | 1 |
| Adenoid cystic carcinoma | 1 |
| No. of prior systemic therapies, n (%) Median (range) | 5 (1-11) |
| ECOG PS | |
| 0 | 9 (45) |
| 1 | 11 (55%) |

### Table 2. Dose Escalation and DLTs

| Cohort | Dose | Patients | DLTs |
|---|---|---|---|
| 1 | 30 mg | 1 | 0 |
| 2 | 60 mg | 2[1] | 0 |
| 3 | 90 mg | 1 | 0 |
| 4 | 120 mg | 1 | 0 |
| 5 | 150 mg | 1 | 0 |
| 6 | 180mg | 1 | 0 |
| 7 | 210mg | 1 | 0 |
| 8 | 270 mg | 3[2] | 0 |
| 9 | 350 mg | 3[2] | 0 |
| 10 | 450 mg | 6 | 1[3] |

[1] Two patients enrolled as 1 patient was not evaluable due to dosing error
[2] Cohort was expanded in order to obtain more safety and PK data
[3] <75% of dosing in C1 due to Gr 2 thrombocytopenia

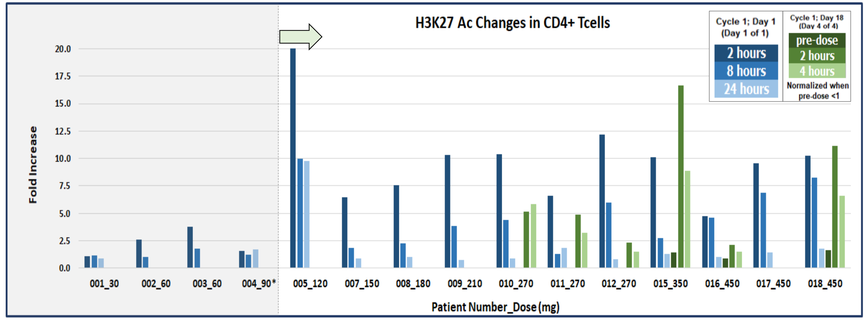
### Table 3. Treatment-emergent Adverse Events in ≥ 15% of Patients (N=20)

| | Grade 1 | Grade 2 | Grade 3 | All |
|---|---|---|---|---|
| Nausea | 9(45%) | 4 (20%) | 0 | 13 (65%) |
| Anemia | 2 (10%) | 3 (15%) | 3 (15%) | 8 (40%) |
| Fatigue | 3 (15%) | 2 (10%) | 2 (10%) | 7 (35%) |
| Vomiting | 4 (20%) | 2 (10%) | 0 | 6 (30%) |
| Anorexia | 4 (20%) | 2 (10%) | 0 | 6 (30%) |
| Diarrhea | 4 (20%) | 0 | 0 | 4 (20%) |
| Fever | 3 (15%) | 0 | 1 (5%) | 4 (20%) |
| Headache | 3 (15%) | 0 | 0 | 3 (15%) |
| Weight loss | 2 (10%) | 1 (5%) | 0 | 3 (15%) |
| Back pain | 2 (10%) | 0 | 1 (5%) | 3 (15%) |
| Cough | 2 (10%) | 1 (5%) | 0 | 3 (15%) |
| Dyspnea | 3 (15%) | 0 | 0 | 3 (15%) |
| Hypokalemia | 1 (5%) | 2 (10%) | 0 | 3 (15%) |

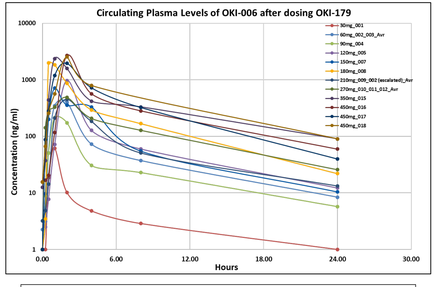
### Clinical Activity

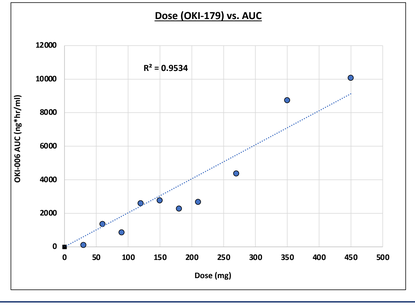
- Stable disease was best response in 5/16 (31%) evaluable for response. No PR or CR observed.
- Stable disease > 12 mos in patient with platinum-resistant ovarian cancer, 8 mos in adenoid cystic carcinoma and 5 mos in NSCLC patient.

### Figure 2. Histone Acetylation in CD4+ T cells




### Figure 3: Pharmacokinetic profile of active metabolite OKI-006




## Conclusions

- OKI-179 is an orally bioavailable, potent inhibitor of HDACs 1, 2, and 3.
- OKI-179 has well-managed toxicity with intermittent dosing, dose-proportional pharmacokinetics and on-target pharmacodynamic activity.
- OKI-006 exposure exceeds efficacy range observed in preclinical models.
- Preliminary signs of clinical benefit with prolonged stable disease.
- Ongoing dose escalation with continuous daily dosing is ongoing.

## References & Acknowledgements

1. Capasso A, Lang J, Pitts TM, et al. Characterization of immune responses to anti-PD-1 mono and combination immunotherapy in hematopoietic humanized mice transplanted with tumor xenografts. J Immunother Cancer 2019 (PMID 30736857).

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