Abstract
CT108

A first-in-human, Phase 1 study of ASTX029, a dual-mechanism inhibitor of ERK1/2, in relapsed/refractory solid tumors

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BACKGROUND

Aberrant activation of the mitogen-activated protein kinase (MAPK) pathway is a common occurrence, with roughly 20% of all cancers bearing mutations in the KRAS gene leading to constitutive pathway activation.[1] Targeting of the MAPK pathway has been clinically validated, with approval of multiple agents in mutant-BRAF indications. However, despite recent advances in direct targeting of the mutant KRAS-G12C protein, there are currently no approved agents targeting the MAPK pathway for patients bearing mutations in RAS proteins. An attractive therapeutic option in this setting is targeting of the extracellular signal-regulated kinase 1/2 (ERK1/2) proteins as a downstream node in the MAPK pathway.[2] We have recently reported the discovery of ASTX029, a novel, potent, dual-mechanism ERK1/2 inhibitor.[3] ASTX029 is currently being evaluated in an open-label Phase 1/2 study in subjects with relapsed/refractory solid tumors (NCT03520075). Here, we report the Phase 1A study results leading to the identification of a dose level of 200 mg daily of 21-day cycles for investigation in the Phase 1B study.

METHODS

- ASTX029-01 is a first-in-human, open-label, multicenter, Phase 1/2 study to evaluate safety, pharmacokinetics, and activity of ASTX029 in subjects with relapsed/refractory solid tumors
- The primary objectives for the Phase 1A study are to identify a maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D)
- The secondary objectives include pharmacokinetic profiling, preliminary efficacy analyses, and pharmacodynamic and biomarker evaluation of target engagement and clinical activity
- Subjects in Phase 1A (dose-escalation) were not required to have documented genetic perturbations of the RAS-RAF-MEK-ERK pathway
- ASTX029 was administered orally daily of 21-day cycles as powder in bottle (PiB) or as tablets
- Dose escalation occurred according to a "3+3 design" based on dose-limiting toxicity (DLT) events
- Disease response was evaluated according to RECIST v1.1 and exploratory indicators, including tumor variant allele frequency changes detected by plasma cell-free DNA (cfDNA) quantitation

STUDY OVERVIEW

Figure 1: Study design and dose escalation

Subjects with relapsed/refractory solid tumors, without regard to genetic aberrations of the RAS-RAF-MEK-ERK pathway

Phase 1A: dose escalation
ASTX029 daily dose administration, 21-day cycles

PiB/fed	Tablet/fed	Tablet/fasting	Total dosed
1/10 mg			3
2/20 mg			3
3/60 mg			3
4/120 mg			5
5/200 mg[a]			10
	6T/80 mg		6
	7T/120 mg		3
		8TF/40 mg	3
		9TF/80 mg	3
		10TF/120 mg	3
		11TF/200 mg	7
		12TF/280 mg[b]	7
			56

[a]DLT: Grade 3 maculopapular rash
[b]DLT: Grade 2 retinopathy

Primary objective: MTD and/or RP2D

ASTX029 200 mg daily, 21-day cycles selected for Phase 1B: dose expansion

Table 1: Patient Characteristics

	All Subjects (N=56)
Age	
Mean, Median	61.0, 61.5
Min-Max	39, 78
Sex	
Male n (%)	19 (33.9%)
Female n (%)	37 (66.1%)
Race, n (%)	
Asian	3 (5.4%)
Black or African American	5 (8.9%)
White	46 (82.1%)
Other	2 (3.6%)
Mutation Status Known, n (%)	
Yes	46 (82.1%)
RAS mutation	35 (76.1%)
BRAF mutation	4 (8.7%)

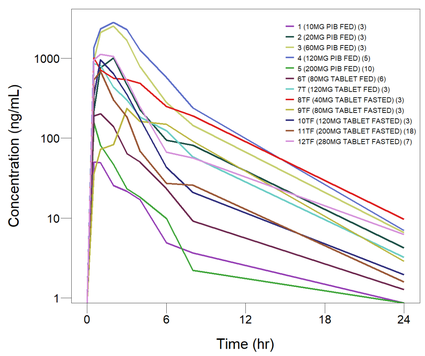
	All Subjects (N=56)
Diagnosis, n (%)	
Colorectal	16 (28.6%)
Pancreatic	11 (19.6%)
NSCLC/Lung	8 (14.3%)
Gynecological	5 (8.9%)
Head and Neck	4 (7.1%)
Melanoma	3 (5.4%)
Other*	9 (16.1%)
Prior treatment, n/known (%)	
Cytotoxic chemotherapy	50/56 (89.3%)
Anti-PD1, -PDL1, or -CTLA-4	21/55 (38.2%)
MEK inhibitor	6/54 (11.1%)
BRAF inhibitor	0/54 (0.0%)

*Other: bile duct, gallbladder, gastric, GI stromal tumor, liver, sarcoma, thyroid, unknown primary

RESULTS

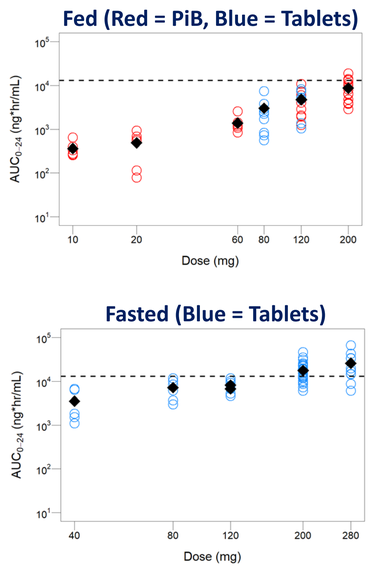
Figure 2: Pharmacokinetics data

A: C1D1 mean concentration (semi-log) vs. time



- PK profiles of ASTX029 were characterized by fast absorption: median T_{max} in plasma of 0.5-1 hour (PiB under fed conditions), 1-3 hours (tablets under fed conditions), and 1-2 hours (tablets under fasted conditions)
- The terminal half-lives were 1.4-3.8 hours (PiB under fed conditions), 2.4-4.4 hours (tablets under fed conditions), and 3.0-3.4 hours (tablets under fasted conditions)
- No accumulation in AUC0-24 or C_{max} was observed

B: AUC (log-scale) vs. dose



Dashed line = target therapeutic AUC from mouse translational studies
◆ = mean AUC for each cohort

- Tablets had higher exposures than PiB administered under fed conditions
- Tablets administered under fasted conditions have higher and less variable exposures than tablets administered under fed conditions
- 200mg tablets under fasted conditions was selected for Phase 1b expansion, which is in the biologically active range

Figure 3: Mutation analysis of tissue and plasma cfDNA

A: Variants identified in subject with colorectal CA

Variants detected in a subject from Cohort 7T (120mg)

Archival tissue		Plasma (cfDNA, screening)
Local Laboratory	**PGDx** -CancerSelect125	**Foundation Medicine** FoundationOneLiquid (% MAF)
NRAS Q61R	**ERBB4** S1263N NRAS Q61R **POLD1** S1052L **CCND2, KRAS, RUNX1** (amplification indeterminate)	NRAS Q61R (19.2) **APC** A1582fs*68 (16.37) **APC** Y973*(19.64) **BRCA2** L901R (0.26) **FGFR2** P458T (0.21) **AR** L548V (0.15)

B: Longitudinal sequencing of plasma cfDNA

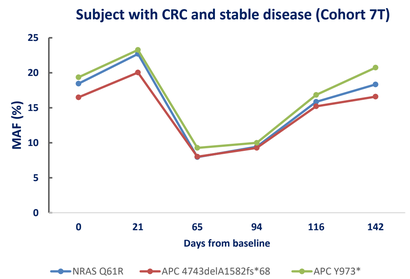
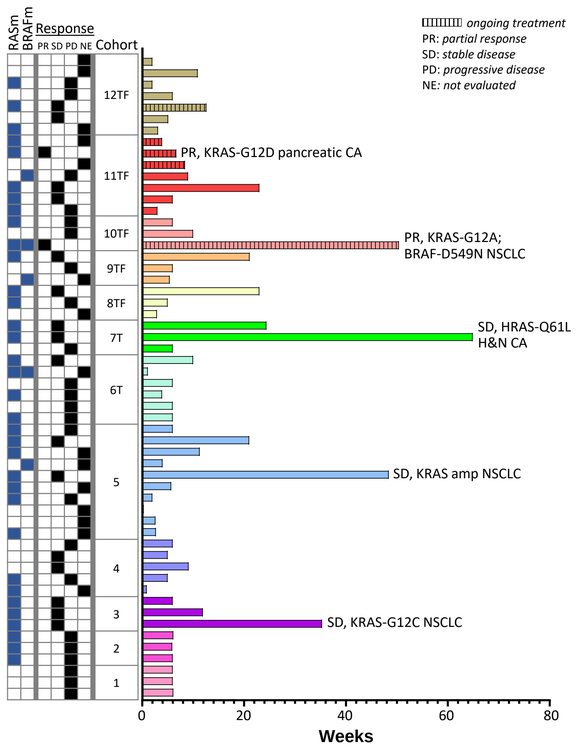


Figure 4: Patient Outcomes



SAFETY

Table 2: Adverse events occurring at >10% frequency*

Adverse event	Grade 1	Grade 2	Grade ≥3	N (%)
Nausea	16	6	2	24 (43%)
Anemia**	5	4	7	16 (29%)
AST increased	10	4	1	15 (27%)
Diarrhoea	13	2	0	15 (27%)
Rash**	13	1	1	15 (27%)
Fatigue	7	7	0	14 (25%)
Vomiting	10	2	0	12 (21%)
Alkaline phosphatase increased	5	3	2	10 (18%)
Visual disturbance**	9	1	0	10 (18%)
ALT increased	6	2	0	8 (14%)
Hyponatraemia	4	1	3	8 (14%)
Abdominal pain	4	1	1	6 (11%)
Hyperglycaemia	3	2	1	6 (11%)
Pneumonia	0	1	5	6 (11%)

*Regardless of relationship to ASTX029. There were 36 serious AEs, all were unrelated to ASTX029 except one Grade 3 malaise.
**AE terms combined: anemia (anemia and anemia of malignant disease); rash (rash, rash maculopapular, rash pruritic, dermatitis acneiform, rash pustular); visual disturbance (vision blurred, vision acuity reduced, visual field defect, visual impairment)

SUMMARY

- 56 subjects were dosed with ASTX029, a dual-mechanism, allosteric inhibitor of ERK1/2, in this Phase 1A (dose escalation) study as of December 14, 2020
- The 280 mg daily dose level was considered not tolerated due to two Grade 2 and one Grade 1 events of retinopathy
- >100% of target AUC exposure (13,022 ng*hr/ml) was achieved at 200 mg daily dose level (cohort mean was 15,681 ng*hr/ml [53% CV])
- Longitudinal monitoring of plasma cfDNA tumor variants tracked with presumed-on target ASTX029 effects and disease progression
- Two partial responses were observed: KRAS-G12A; BRAF-D549N non-small cell lung cancer (120 mg) and KRAS-G12D metastatic pancreatic cancer (200 mg)
- Adverse events were generally similar to those previously described with the MEK inhibitor class of drugs
- There were 36 serious AEs, of which, only one was assessed as related to ASTX029 (Grade 3 general malaise)
- The most common reason for treatment discontinuation was disease progression
- ASTX029 200 mg daily of 21-day cycles was selected as the dose/regimen for Phase 1B (dose expansion) based on safety, tolerability, and PK evaluation

References

1. Montagut and Settleman. Targeting the RAF-MEK-ERK pathway in cancer therapy. *Cancer Lett* 2009 283(2):125-34.
2. Kidger et al. ERK1/2 inhibitors: New weapons to inhibit the RAS-regulated RAF-MEK1/2-ERK1/2 pathway. *Pharmacol Ther* 2018 187: 45-60.
3. Munck et al. The clinical candidate, ASTX029, is a novel, dual-mechanism ERK1/2 inhibitor and has potent activity in MAPK-activated cancer cell lines and in vivo tumor models. EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Conference. 2020: Abstract No. 187.

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