Abstract 9085

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 RAS-RAF-MEK-ERK pathway is common in human cancers
- This is an open-label Phase 1/2 study of ASTX029[1], a dual-mechanism extracellular signal-regulated kinase 1/2 (ERK1/2) inhibitor, in subjects with relapsed/refractory solid tumors (NCT03520075)
- ERK1/2 is a downstream node in the MAPK pathway and its inhibition may overcome resistance mechanisms reported with the use of MEK and BRAF inhibitors[2]
- Here, we report the Phase 1 data identifying 200 mg orally daily in 21-day cycles as the dose regimen for further investigation in the Phase 2 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
- An overview of the Phase 1 study design and the objectives are summarized in Figure 1
- Phase 1A is a dose escalation study according to a "3+3 design" based on dose-limiting toxicity (DLT) events
- Phase 1B is a dose expansion study to further evaluate safety and preliminary efficacy in the target RAS and BRAF mutated indications
- ASTX029 was administered orally daily in 21-day cycles as powder in bottle (PiB) or as tablets in Phase 1A and only as tablets in Phase 1B
- Disease response was evaluated according to RECIST v1.1
- Exploratory indicators, including pharmacodynamic (PD) effect on fresh tumor biopsies (Phase 1B only), were used to confirm pathway modulation

STUDY OVERVIEW

Figure 1: Study Design and Phase 1A Dose Escalation

Phase 1A (N=56)
Subjects with relapsed/refractory solid tumors, without regard to genetic aberrations of the RAS-RAF-MEK-ERK pathway

Dose escalation cohorts
ASTX029 orally daily, 21-day cycles

PiB/fed	Tablet/fed	Tablet/fast	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
			N=56

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

Phase 1A/Phase 1B Study Objectives
Primary objective: Identification of maximum tolerated dose and/or recommended Phase 2 dose
Secondary objectives: Pharmacokinetic profiling, preliminary efficacy analyses, and pharmacodynamic and biomarker evaluation of target engagement and clinical activity

Phase 1B (N=20)
Subjects with relapsed/refractory solid tumors, with RAS or BRAF mutations

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

RESULTS

Table 1: Subject Characteristics

	Phase 1A (N=56)	Phase 1B (N=20)	All Subjects (N=76)
Age (yr)			
n	56	20	76
Mean	60.9	60.3	60.8
SD	9.24	15.63	11.16
Median	61.5	63.0	62.0
Min, Max	39, 78	30, 85	30, 85
Sex, n (%)			
Male	19 (33.9)	8 (40.0)	27 (35.5)
Female	37 (66.1)	12 (60.0)	49 (64.5)
Race, n (%)			
Asian	3 (5.4)	1 (5.0)	4 (5.3)
Black or African American	5 (8.9)	2 (10.0)	7 (9.2)
White	46 (82.1)	16 (80.0)	62 (81.6)
Other	2 (3.6)	1 (5.0)	3 (3.9)
Mutational Status Known, n(%)			
Yes	46 (82.1)	18 (90.0)	64 (84.2)
RAS mutation	35 (62.5)	14 (70.0)	49 (64.5)
BRAF mutation	5 (8.9)	4 (20.0)	9 (11.8)
Diagnosis, n(%)*			
Colorectal	16 (28.6)	3 (15.0)	19 (25.0)
Pancreatic	11 (19.6)	4 (20.0)	15 (19.7)
Lung/NSCLC	8 (14.3)	4 (20.0)	12 (15.8)
Other	8 (14.3)	2 (10.0)	10 (13.2)
Melanoma	3 (5.4)	5 (25.0)	8 (10.5)
Gynecological	5 (8.9)	1 (5.0)	6 (7.9)
Head and Neck	4 (7.1)	0	4 (5.3)
Thyroid	1 (1.8)	1 (5.0)	2 (2.6)
Number of Prior Regimen, n(%)**			
1	12 (21.4)	3 (15.0)	15 (19.7)
2	9 (16.1)	5 (25.0)	14 (18.4)
3	8 (14.3)	5 (25.0)	13 (17.1)
4+	27 (48.2)	7 (35.0)	34 (44.7)

*Other category: ampullary adenocarcinoma, gallbladder (2), gastric, gastrointestinal stromal tumor, intrahepatic bile duct carcinoma, liver (hepatic metastasis), spindle cell sarcoma, unknown primary, ureter
**For all subjects, median number of prior regimen is 3.0 (minimum 1, maximum 7)

Table 2: Adverse Events ≥10% Frequency*

Adverse event	All Subjects (N=76), n (%) Grade 1/2	Grade ≥3	All
Nausea	31 (40.8)	2 (2.6)	33 (43.4)
Diarrhoea	26 (34.2)	1 (1.3)	27 (35.5)
Rash**	25 (32.9)	2 (2.6)	27 (35.5)
Anaemia**	14 (18.4)	9 (11.8)	23 (30.3)
Fatigue	23 (30.3)	0	23 (30.3)
Visual disturbance**	20 (26.3)	0	20 (26.3)
Aspartate aminotransferase increased	18 (23.7)	1 (1.3)	19 (25.0)
Vomiting	17 (22.4)	1 (1.3)	18 (23.7)
Abdominal pain	10 (13.2)	2 (2.6)	12 (15.8)
Hyponatraemia	6 (7.9)	6 (7.9)	12 (15.8)
Alanine aminotransferase increased	11 (14.5)	0	11 (14.5)
Blood alkaline phosphatase increased	8 (10.5)	2 (2.6)	10 (13.2)
Constipation	7 (9.2)	1 (1.3)	8 (10.5)
Decreased appetite	8 (10.5)	0	8 (10.5)
Dry mouth	8 (10.5)	0	8 (10.5)
Urinary tract infection	8 (10.5)	0	8 (10.5)

*Regardless of relationship to ASTX029. There were 52 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, rash macular); visual disturbance (all SOC equal to eye disorder)

Table 3: Pharmacokinetics Data

Cycle 1 Day 1 mean pharmacokinetic parameters

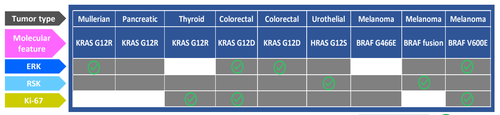
Cohort (N)	DOSE	$AUC_{0\text{-}24H}$ (NG*HR/ML)[1]	C_{max} (NG/ML)[1]	T_{max} (HR)[2]	%AUC TARGET[4]
1 (3)	10MG PIB FED	323 (22)	109 (48)	1 (0.5 – 3)	2%
2 (3)	20MG PIB FED	342 (209)	217 (165)	0.5 (0.5 – 0.5)	3%
3 (3)	60MG PIB FED	1168 (8)	469 (9)	0.5 (0.5 – 1)	9%
4 (5)	120MG PIB FED	4024 (83)	1646 (57)	0.5 (0.5 – 1)	31%
5 (10)	200MG PIB FED	7382 (63)	1845 (67)	0.75 (0.5 – 4)	57%
6T (6)	80MG TAB FED	1882 (127)	496 (128)	3 (1 – 6)	14%
7T (3)	120MG TAB FED	3365 (138)	1493 (142)	1 (1 - 3)	26%
8TF (3)	40MG TAB FASTED	2193 (120)	742 (302)	1 (1 - 4)	17%
9TF (3)	80MG TAB FASTED	6417 (64)	2840 (31)	1 (0.5 - 2)	49%
10TF (3)	120MG TAB FASTED	5809 (30)	2057 (50)	2 (0.5 - 2)	45%
11TF+EXP[3] (27)	200MG TAB FASTED	13130 (48)	5218 (61)	2 (0.5 - 6)	101%
12TF (7)	280MG TAB FASTED	18176 (85)	6044 (58)	2 (1 - 4)	140%

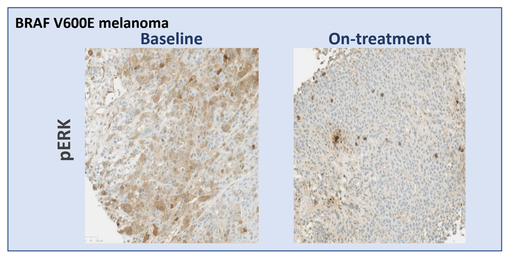
[1]Geometric mean (%CV); [2]Median (range); [3]11TF + Phase 1b Expansion; [4]Based on mouse translational study; PiB = powder in bottle; TAB = tablet

- The ASTX029 PK profiles are characterized by fast absorption and monophasic elimination.
- Exposures were low with PiB under fed conditions but improved after the switch to tablets under fasted conditions.
- Exposures were higher with tablets than PiB and less variable under fasted conditions.
- No accumulation in $AUC_{0\text{-}24H}$ or C_{max} was observed.
- At the RP2D (200 mg/day tablets under fasted conditions), exposure levels reached the biologically active range.

Figure 2: Pharmacodynamic Data

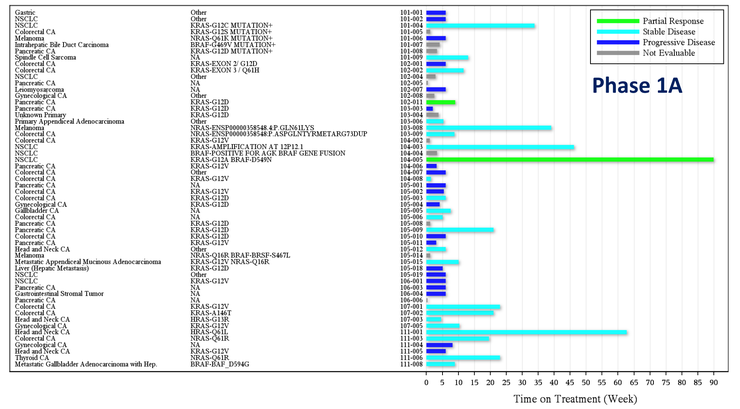
- Pharmacodynamic effect of ASTX029 was assessed by IHC in paired biopsies from 9 subjects
- Markers assessed were phospho-ERK (pERK), total ERK, phospho-RSK (pRSK), total RSK, and Ki-67
- Reduction in pERK and pRSK, but not total ERK or RSK, indicated pathway modulation via the dual-mechanism of action of ASTX029
- PD effect was observed in 7 out of 9 evaluable paired samples

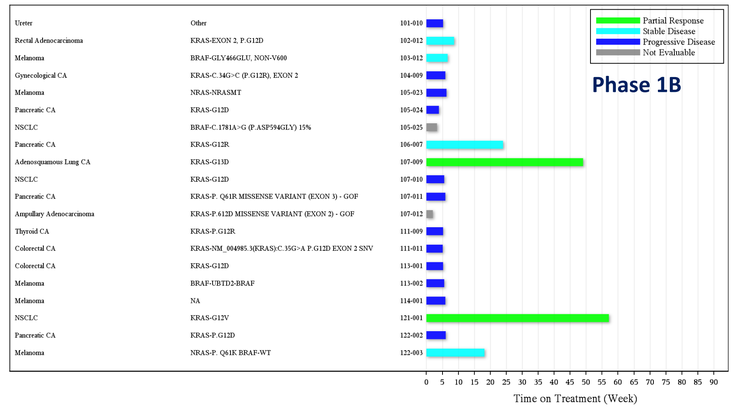




RESULTS

Figure 3: Subject Outcomes





SUMMARY

- At 200 mg orally daily dose level, AUC exposures of ASTX029 exceeded the target exposures (101%) defined by mouse translational studies
- Pharmacodynamic studies evaluating phospho-ERK1/2, phospho-RSK, and Ki-67 demonstrated ASTX029 pathway modulation in 7 of 9 evaluable paired fresh biopsy samples
- Three durable partial responses were observed in KRAS-mutated NSCLC – one subject in Phase 1A (120 mg, lasting 28 cycles), and two subjects in Phase 1B (200 mg), one lasting 16 cycles and one lasting 20 cycles and ongoing
- Adverse events were generally similar to those previously described with the MEK inhibitor class of drugs
- There were 56 serious AEs, of which, only a Grade 3 malaise was related to ASTX029
- The most common reason for treatment discontinuation was disease progression
- ASTX029 200 mg orally daily given continuously of 21-day cycles was selected as the dose regimen for further evaluation in Phase 2 based on safety, tolerability, PK, and PD evaluation

REFERENCES

1. Munck et al., Mol Cancer Ther, 2021. 20(10): 1757-1768.
2. Hazar-Rethinam et al., Cancer Discovery, 2018. 8(4): 417-427.

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