Abstract # CT066

Phase 1 study of MDM2 antagonist ASTX295 in patients with solid tumors with wild-type *TP53*

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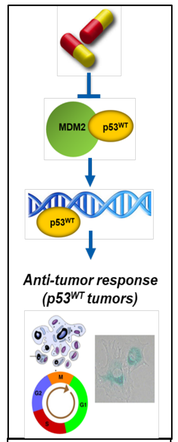
BACKGROUND

- p53 is a tumor suppressor that induces cell cycle arrest and/or apoptosis in response to cellular stress. The p53 pathway is frequently inactivated in tumors by *TP53* mutation or MDM2 amplification or MDM2 overexpression.
- Disrupting the MDM2-p53 protein-protein interaction has been pursued as a promising strategy for cancer therapy (see right), however, MDM2 antagonists have shown only modest anti-tumor activity in the clinic being hampered by dose-limiting hematological toxicities, notably thrombocytopenia and neutropenia[1,2]
- ASTX295 is a potent, next generation MDM2 antagonist with a shorter half-life aimed at reducing on-target bone marrow toxicity (see other AACR abstracts on ASTX295 #6588, #3333, #666, #667).
- Here we report the safety and preliminary efficacy of ASTX295 investigated in the phase I dose escalation and expansion portions of the ASTX295-01 clinical study.

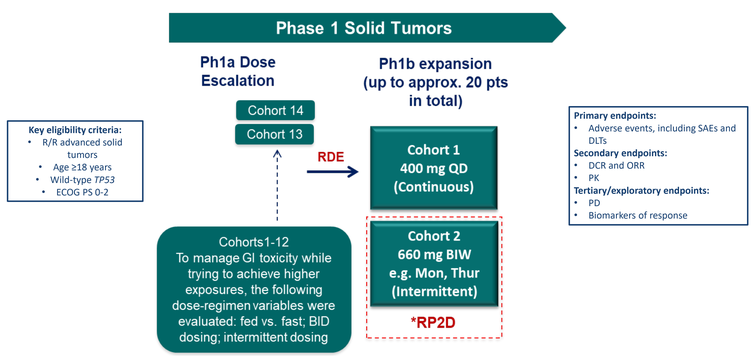


Targeting the MDM2-p53 interaction

STUDY METHODS

- This is a first-in-human, open-label, multicenter, Phase 1-2 study to assess the safety, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary clinical activity of ASTX295 in subjects with wild-type *TP53*.
- Standard "3+ 3" approach for dose-escalation was used with additional cohorts to examine impact of fed vs. fasted and once-daily, twice daily, and intermittent dosing schedules on tolerability.
- Safety was assessed by adverse events and dose-limiting toxicity (DLT).
- PK was assessed by a validated method.
- PD was assessed by measurements of pathway-relevant markers GDF-15 protein (plasma) and MDM2 and p21 gene expression (PBMCs).
- Clinical activity was assessed clinically and using RECIST1.1.

Study Design



ECOG – Eastern Cooperative Oncology Group; PS – performance status; AUC – are under the curve; NGS – next-generation sequencing; RP2D- recommended phase 2 dose; QD- daily dosing; BIW- bi-weekly dosing

ASTX295-01 STUDY PATIENT CHARACTERISTICS

- A total of 106 subjects enrolled and received at least one dose of ASTX295.
- General demographics were Age 59 (average; range 20-87), 54 (51%) Female, 52 (49%) Male; Median 3 prior treatments.

Tumor Types		
Sarcoma		59
	De-diff Liposarcoma	22
	Well-diff Liposarcoma	23
	Other sarcoma subtypes	11
	Chordoma	3
Gastrointestinal*		10
Lung (Small-cell and Non-small Cell)		7
CNS (Glioblastoma multiforme)		5
Head & Neck		5
Gynecological**		4
Breast		2
Melanoma		2
Other¥		12

*Gastrointestinal included colorectal, esophageal, pancreatic and anal cancer;**Gynecological included endometrial, cervical, and ovarian cancer ¥Other includes peripheral nerve sheath tumor, myoepithelial tumor, mesothelioma, GIST and bladder

- Subjects were dosed over 14 cohorts with daily dosing levels ranging from 15 mg-800 mg/day on various regimens, including daily, twice daily, fasted, fed, 5 days on/2 days off, 3 days on/4 days off, and twice weekly in the dose escalation phase (n=82), see pharmacokinetic results.
- Based on safety, pharmacokinetic exposure, PD, and preliminary activity, 2 cohorts were selected for expansion as possible recommended Phase 2 dose (RP2D):
  - 400 mg daily
  - 660 mg twice weekly

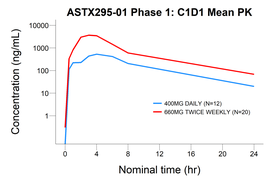
SAFETY SUMMARY

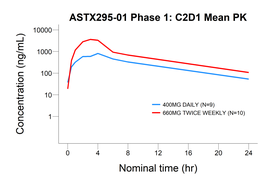
- Across all dose regimens, observed DLTs included: nausea, vomiting, diarrhea, fatigue
- For regimens selected for expansion, treatment related adverse events were as follows:
  - 400 mg QD - most common: nausea 76.2%, diarrhea 76.2%, vomiting 33.3%; Grade 3 GI AEs 14.3%; no grade ≥4
  - 660 mg BIW - most common: nausea 71.4%, diarrhea 47.6%, vomiting 33.3%; Grade 3 GI AEs 9.5% ; no grade ≥ 4 (selected schedule); One subject with grade 2 thrombocytopenia

PHARMACOKINETICS RESULTS

COHORT	DOSE (MG)	N	$AUC_{0\text{-}24H}$[1] (NG*HR/ML)	C_{MAX}[1] (NG/ML)	T_{MAX}[2] (HR)	%AUC TARGET
1	15	1	30 (NA)[3]	17 (NA)[3]	1 (1 – 1)	0.1 - 0.4%
2	45	3	163 (64)	33 (66)	2 (0.5 – 4)	0.6 - 2.0%
3	120	4	1452 (125)	350 (128)	1.5 (1 – 4)	5 - 18%
4	240	4	2153 (76)	663 (75)	2 (1 – 4)	8 - 26%
5	420	10	4061 (123)	1083 (189)	3 (2 – 4)	15 - 49%
6	520	8	3000 (168)	564 (294)	3 (3 – 4)	11 - 37%
7	415 (FED)	4	3836 (176)	930 (575)	4 (1 – 4)	14 - 47%
8	200 BID	5	3304 (37)	408 (70)	3 (2 – 6)	12 - 40%
9	320 BID	7	5632 (189)	1071 (177)	3 (2 – 4)	20 - 69%
10[4]	520 (5 days on/2 days off)	7	9680 (142)	2253 (152)	3 (0.5 – 6)	35 - 118%[5]
11	520 (3 days on/4 days off)	4	3426 (70)	921 (75)	2 (1 – 3)	12 – 42%
Combined 6, 10, 11	520	19	4804 (213)	1145 (222)	3 (0.5 – 6)	17 – 59%
12	660 (twice weekly)	10	13097 (118)	2580 (127)	3 (1 – 6)	47 – 160%
13	660 (3 DAYS ON, 4 DAYS OFF)	4	9680 (218%)	2200 (236%)	3.5 (2 – 6)	35-118%
14	800 (TWICE WEEKLY)	2	11539 (NA)[3]	2834 (NA)[3]	4 (4 – 4)	41-141%

[1]Geometric mean (%CV); [2]Median (range); [3]%CV NA due to limited number of patients; [4]included two patients with very high exposures





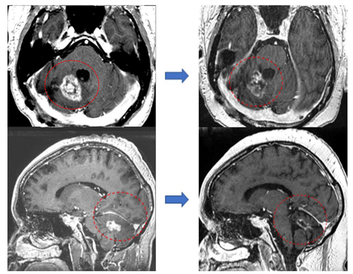
- Higher daily doses produced higher exposures. A positive trend between AUC and severity of nausea/vomiting was observed. $T_{1/2}$ ~ 4-6 hours.
- The 660 mg dose given twice weekly achieved target levels associated with biological activity and was selected as the optimal RP2D.

CLINICAL ACTIVITY

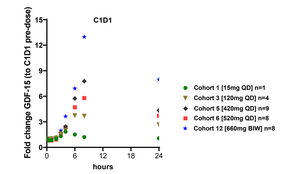
- Objective responses by RECIST1.1 were seen in 1 patient with NSCLC and 3 patients with liposarcoma (LPS)
- De-diff LPS: ORR was 7.7%, PFS 7.95 months, and 16 wk DCR was 69.2%.
- Well-diff LPS: ORR was 8.0%, PFS 9.66 months, and 16wk DCR was 72%.
- 4 Glioblastoma (GBM) with *MDM2*[amp] were enrolled, 3 with evidence of tumor regression; 1 on study for >34 cycles (see below).

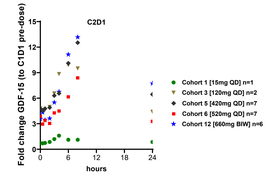
MDM2 amp
CDK4 amp
PDGFRA amp
KDR amp
KIT amp
CDK12 mut

↓ enhancing tumor

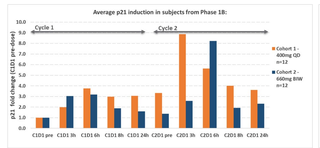


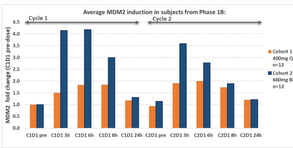
PHARMACODYNAMICS RESULTS





GDF-15 analysis in EDTA plasma samples (run by Frontage Laboratories, Inc.) using an MSD Assay (Meso Scale Diagnostics, LLC.). Samples taken during Cycle 1 Day 1 and Cycle 2 Day 1. Induction profile of GDF-15, a transcriptional target of p53, indicates a shorter pulsatile pathway modulation.





MDM2 and p21 gene expression analysis in PBMCs using quantitative and high-sensitivity probe-based Droplet Digital PCR (ddPCR) Technology (Bio-Rad Laboratories, Inc.).

Samples taken during Phase 1B Cycle 1 Day 1 and Cycle 2 Day 1. Induction profiles of MDM2 and p21, transcriptional targets of p53, are also consistent with a shorter pulsatile pathway modulation.

SUMMARY/CONCLUSIONS

- ASTX295 was well tolerated at clinically effective doses while avoiding significant thrombocytopenia and neutropenia.
  - GI adverse events (nausea, vomiting, etc.) were dose-limiting rather than myelosuppression.
- PK exposures increased with dose escalation and exposures produced were above those active in non-clinical cancer models.
  - Intermittent dosing appeared to achieve higher peak exposure on dosing days. Half-life was 4-6 hours.
- Shorter pulsatile modulation of the p53 pathway was observed consistent with the desired PK profile.
- The 660 mg twice weekly regimen achieved target level exposures and was selected as RP2D
- Objective clinical responses were seen, including in heavily pre-treated subjects, including liposarcoma and lung cancer
  - Suggestion of clinical activity was observed in some GBM patients and warrants further investigation.
- The lack of myelosuppression observed suggests that ASTX295 may be well used in combination therapy, particularly in settings where the partner compound may impact bone marrow.

REFERENCES/RELATED WORK

1. Italiano A: Cancer Discov 2023;13:1765-7.
2. Ray-Coquard I, et al: Lancet Oncology 2012; 13:1133-40

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Willmore E, et al.: Poster #3333 at AACR Annual Meeting 2024.

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This study is sponsored by AstexPharmaceuticals, Inc. and is registered at ClinicalTrials.gov: https://classic.clinicaltrials.gov/ct2/show/NCT03975387

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