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Phase 1 study of the IAP inhibitor ASTX660 in adults with advanced cancers and lymphomas

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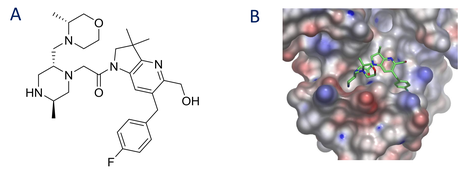
BACKGROUND

Due to their roles in the evasion of apoptosis, Inhibitor of Apoptosis Proteins (IAPs) are considered attractive targets for anti-cancer therapy. ASTX660 is a potent, next generation, non-peptidomimetic, dual antagonist of both XIAP and cIAP1, discovered using fragment-based drug design (1-3). We report here the results of the first-in-human phase 1 dose escalation and dose expansion study of ASTX660 administered orally to adults with advanced solid tumors and lymphoma.

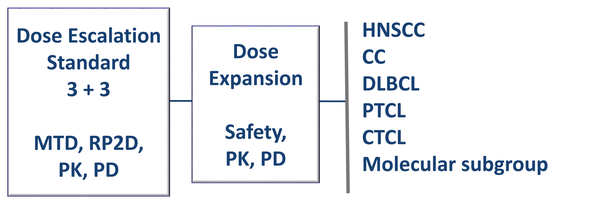


A. Chemical structure of non-peptidomimetic dual cIAP1 and XIAP antagonist, ASTX660, derived by fragment-based drug discovery. B. X-ray crystal structure of ASTX660 (in green) in complex with XIAP-BIR3.

STUDY DESIGN

- Open-label, Phase 1/2 study to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of ASTX660, and to evaluate preliminary clinical activity, pharmacokinetics (PK), and pharmacodynamics (PD), in subjects with advanced solid tumors or lymphoma.
- ASTX660 was administered orally once a day for 7 consecutive days every other week of each 28 day cycle.

ASTX660-01 Study Schema



CC, Cervical Carcinoma; CTCL, Cutaneous T Cell Lymphoma; DLBCL, Diffuse Large B Cell Lymphoma; . HNSCC, Head and Neck Squamous Cell Carcinoma, PTCL, Peripheral T Cell Lymphoma

PATIENT CHARACTERISTICS

Characteristics		All Patients N=45
Age (yr), median (range)		63 (36-77)
Gender, Male		18 (40%)
ECOG Performance Status	0	7 (15%)
	1	35 (78%)
	2	3 (7%)
Tumor type	Colorectal cancer	7 (16%)
	Head and Neck	6 (13%)
	Non-small cell lung cancer	4 (9%)
	Ovarian cancer	4 (9%)
	Renal cell carcinoma	4 (9%)
	Other	20 (44%)

SAFETY

- 45 patients received at least one dose of ASTX660 (dose ranged from 10 to 270 mg)
- DLTs were reported in 4 subjects (asymptomatic G3 lipase elevation with or without amylase elevation).
- Most DLTs resolved on dose interruption and rechallenge was successful at a lower dose.

Dose Limiting Toxicities (DLTs), MTD and RP2D

Cohort	Dose (mg QD)	Form	N pts	DLTs
1	15		3	-
2	30	Powder In	3	-
3	60	Bottle	4	-
4	120		3	-
5	180		3	-
6	180		6	-
7	270		6	3 (G3 lipase elevation)
8	210 MTD	Capsule	9	1 (G3 lipase elevation)
Dose Expansion	180 RP2D		8	-

Adverse events regardless of relationship in ≥10% subjects – Phase 1 (n=45)

Preferred Term	Grade 1-2	Grade 3-4	All
Fatigue	15 (33%)	0	15 (33%)
Anemia	8 (18%)	6 (13%)	14 (31%)
Lipase increased	8 (18%)	6 (13%)	14 (31%)
Vomiting	14 (31%)	0	14 (31%)
Nausea	13 (29%)	0	13 (29%)
Lymphocyte count decreased/lymphopenia	5 (11%)	7 (16%)	12 (27%)
Pruritus	10 (22%)	0	10 (22%)
Hypocalcaemia	9 (20%)	0	9 (20%)
ALT increased	8 (18%)	0	8 (18%)
Decreased appetite	7 (16%)	1 (2%)	8 (18%)
AST increased	7 (16%)	0	7 (16%)
Edema peripheral	7 (16%)	0	7 (16%)
Rash maculo-papular	7 (16%)	0	7 (16%)
Amylase increased	5 (11%)	1 (2%)	6 (13%)
Diarrhea	6 (13%)	0	6 (13%)
Hypokalemia	5 (11%)	1 (2%)	6 (13%)
Hyponatremia	3 (6.7%)	3 (6.7%)	6 (13%)
Cough	5 (11.1%)	0	5 (11.1%)
Headache	4 (8.9%)	1 (2.2%)	5 (11.1%)
Hypoalbuminemia	5 (11.1%)	0	5 (11.1%)
Hypotension	5 (11.1%)	0	5 (11.1%)

ASTX660 related adverse events in ≥10% of subjects treated at the RP2D 180 mg (n=17)

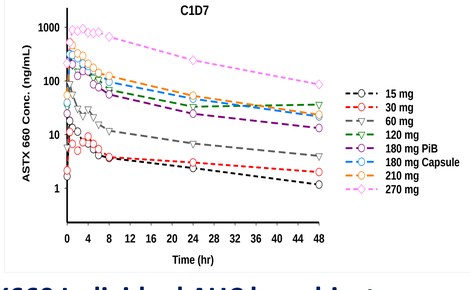
Preferred Term	Grade 1-2	Grade 3-4	All
ALT increased	4 (24%)	0	4 (24%)
Anemia	3 (18%)	1 (6%)	4 (24%)
Hypocalcaemia	4 (24%)	0	4 (24%)
Lipase increased	4 (24%)	0	4 (24%)
AST increased	3 (18%)	0	3 (18%)
Fatigue	3 (18%)	0	3 (18%)
Lymphocyte count decreased	3 (18%)	0	3 (18%)
Nausea	3 (18%)	0	3 (18%)
Pruritus	3 (18%)	0	3 (18%)
Alkaline phos. Increased	2 (12%)	0	2 (12%)
Dry mouth	2 (12%)	0	2 (12%)
Vomiting	2 (12%)	0	2 (12%)

- One subject discontinued study treatment due to a study drug related AE (Grade 3 lipase elevation).
- Serious Adverse Events (SAE) were reported in 17 subjects. None of the SAEs were related to study drug
- Two subjects died on study as the result of an SAE not related to study drug (large intestinal obstruction and sepsis).

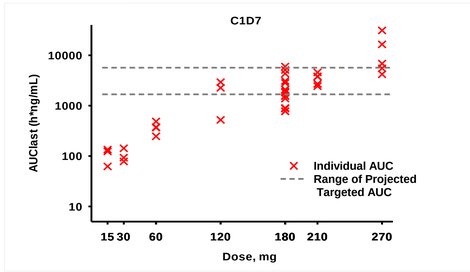
PHARMACOKINETICS

- ASTX660 AUC increased in a dose-proportional manner in the dose range of 15 to 180 mg, and supra- proportionally above 180 mg.
- Accumulation (~ 2-fold) in AUC exposures was observed on Cycle 1 Day7 (C1D7) vs Cycle 1 Day1 (C1D1); minimal for C_{max}.
- At the clinical RP2D of 180 mg, ASTX660 AUC exposures reached the target active range from preclinical models.

ASTX660 PK profile



ASTX660 Individual AUC by subjects



ASTX660 PK parameters on C1D7

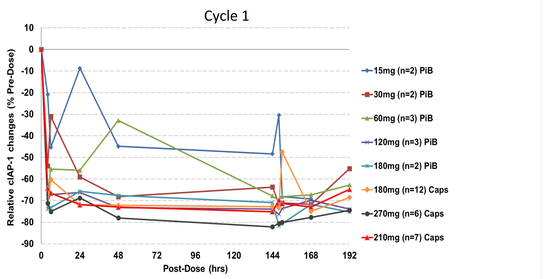
Dose (mg/day) (N)	$AUC_{0\text{-}24h}$ (ng•h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC Accum. Ratio
15 (3)	107 (38.9)	18.5 (7.34)	0.5	24.3 (2.29)	3.6
30 (3)	104 (33.7)	14.9 (3.42)	0.5	26.3 (8.02)	1.1
60 (4)	369 (97.6)	88.6 (34.1)	0.5	15.6 (4.23)	1.9
120 (3)	1900 (1240)	302 (152)	0.5	9.64 (1.47)	2.2
180 PiB (3)	1590 (1300)	388 (378)	1	14.8 (4.64)	2.1
180 Cap (11)	2580 (1770)	493 (312)	1	15.2 (5.52)	1.6
210 (6)	3330 (843)	696 (406)	1	17.9 (6.45)	2.1
270 (5)	12800 (11300)	1180 (526)	3	11.4 (3.26)	3.2

Data are presented as Mean (SD), except for T_{max} (Median)

PHARMACODYNAMICS

- Rapid and sustained cIAP-1 degradation was observed following treatment with ASTX660. Suppression was maintained in cycle 2 at doses ≥180 mg.
- Plasma levels of multiple cytokines including TNFα,IL-6, IL-8 and CRP were assessed using the Myriad RBM's Human InflammationMAP® panel. No dose-dependent changes were observed.

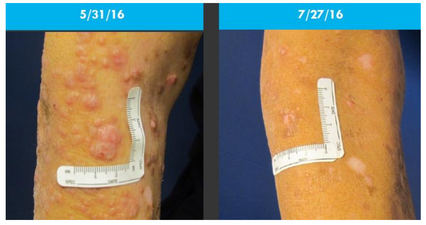
ASTX660 induced cIAP1 depletion in PBMC



CIAP-1 protein degradation was measured in PBMCs pre and post ASTX660 treatment using a custom-made Multi-Spot V-Plex Assay (MSD).

CLINICAL ACTIVITY

- One clinical response in a subject with cutaneous T cell lymphoma was observed at the 180 mg dose level.



- At data cut-off, one patient at the 210 mg dose level was still receiving ASTX660 in cycle 11.

CONCLUSIONS

- ASTX660 administered orally in a intermittent (7 days on/7 days off) schedule demonstrated a manageable safety profile.
- 180 mg dose was identified as the RP2D. This dose was well tolerated, achieved target therapeutic exposure and demonstrated biological and preliminary clinical activity.
- Enrolment to Phase 2 cohorts in lymphoma and other selected cancers is ongoing (NCT02503423).

REFERENCES

1. Tamanini , et al, (2017). Discovery of a Potent Nonpeptidomimetic, Small-Molecule Antagonist of Cellular Inhibitor of Apoptosis Protein 1 (cIAP1) and X-Linked Inhibitor of Apoptosis Protein (XIAP). J. Med. Chem 2017 60 (11).
2. Ward et al, (2014). Induction of apoptosis with a novel dual cIAP1/XIAP antagonist in models of melanoma. European Journal of Cancer 50(Suppl 6):122.
3. Ward et al, (2017). ASTX660, a novel non-peptidomimetic dual antagonist of cIAP1 and XIAP, potently induces TNF-α dependent apoptosis in cancer cell lines and inhibits tumor growth. Manuscript submitted.

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Poster can be downloaded from www.astx.com

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