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Preliminary Results of ASTX660, a Novel Non-Peptidomimetic cIAP1/2 and XIAP Antagonist, in Relapsed/Refractory Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma

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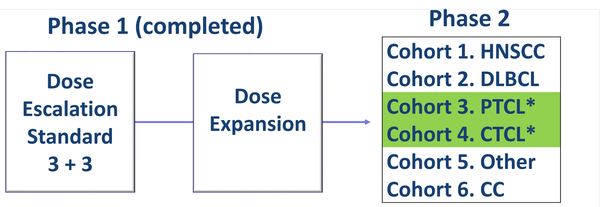
BACKGROUND

Due to their roles in the evasion of apoptosis, immune mediate and death receptor pathways, inhibitor of apoptosis proteins (IAPs) are considered attractive targets for anti-cancer therapy. ASTX660 is a potent, non-peptidomimetic, antagonist of cIAP1/2 and XIAP, discovered using fragment-based drug design (1-3). In the phase 1 part of the ASTX660-01 study, the recommended phase 2 dose (RP2D) was identified with a favourable safety profile and initial evidence of clinical activity in a subject with mycoses fungoides (4). Herein we report preliminary activity and safety data from the relapsed/refractory (r/r) peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL) Phase 2 cohorts.

METHODS

- Open-label, multi-center, Phase 1/2 study to determine the RP2D and regimen of ASTX660, and to evaluate preliminary clinical activity, pharmacokinetics (PK), and pharmacodynamics (PD) of ASTX660 in subjects with advanced solid tumors or lymphoma.
- In the Phase 2 part of the study ASTX660 was administered orally at the RP2D of 180mg/day on Days 1 to 7, and 15 to 22 in a 28-day cycle.
- The primary endpoint of the Phase 2 part is overall response rate (ORR) as assessed by the investigator according to the Lugano 2014 Classification (PTCL) or Global Response (CTCL).
- Evaluable subjects in Phase 2 are those who had tumor evaluation at baseline and at least 1 post-treatment tumor assessment, or died or stopped treatment earlier due to clinical deterioration or toxicity.
- Adverse events (AE) are assessed per CTCAE V4.03.

ASTX660-01 Study Schema



CC, cervical carcinoma; CTCL, r/r Cutaneous T-Cell Lymphoma; DLBCL, r/r Diffuse Large B-Cell Lymphoma; HNSCC, head and neck squamous cell carcinoma; PTCL, r/r Peripheral T-Cell Lymphoma

*Enrollment ongoing

PATIENT CHARACTERISTICS

Characteristics	PTCL N=22	CTCL N=21
Age (yr), median (range)	63 (39-81)	59 (23-80)
Male n (%)	16 (73)	13 (62)
ECOG PS, n (%)		
0	5 (23)	12 (57)
1	14 (64)	7 (33)
2	3 (13)	2(10)
Number of Prior Regimens Median (range)	3 (1-7)	3 (1-12)
Prior radiotherapy, n (%)	4 (18)	8 (38)

SAFETY

- As of 1 May 2019, 22 PTCL and 21 CTCL subjects have received ASTX660.
- Median number of cycles was 2 (1-13) in the PTCL cohort and 3 (1-9) in the CTCL cohort.
- 13 subjects (59%) in the PTCL cohort and 13 subjects (62%) in the CTCL cohort have discontinued study treatment.
- In the PTCL cohort 12 subjects (55%) discontinued ASTX660 due to progressive disease (PD) and 1 (4%) due to drug-related AE (G3 pneumonitis); 6 subjects (27%) required dose reduction.
- In the CTCL cohort 10 subjects (47%) discontinued ASTX660 due to PD, 1 (5%) due to AE (5%) (G2 fatigue and G1 muscle weakness), and 1 (5%) due to withdrawal by subject; 5 subjects (24%) required dose reduction.
- Serious Adverse Events (SAE) were reported in 10 subjects (46%) in the PTCL cohort and 8 subjects (38%) in the CTCL cohort; SAEs related to study drug were reported in 3 (14%) and 2 (10%) of subjects, respectively. No fatal AEs were reported in either of these 2 cohorts.

AEs (All Grades) Related to ASTX660 in ≥2 subjects

Adverse Event Term	PTCL (N=22) n(%)	CTCL (N=21) n(%)
Number of subjects who reported at least one TEAE	18 (82)	15 (71)
Lipase increased	11 (50)	6 (29)
Amylase increased	9 (41)	4 (19)
Diarrhoea	6 (27)	5 (24)
Rash	5 (23)	5 (24)
ALT increased	4 (18)	4 (19)
AST increased	3 (14)	4 (19)
Fatigue	3 (14)	3 (14)
ALP increased	0	4 (19)
Nausea	2 (9)	2 (10)
Pneumonitis	2 (9)	1 (5)
Thrombocytopenia	2 (9)	1 (5)
Anaemia	1 (5)	2 (10)
Headache	1 (5)	2 (10)
Hyperglycaemia	1 (5)	1 (5)
Pyrexia	1 (5)	1 (5)
Stomatitis	1 (5)	1 (5)
Dizziness	0	2 (10)
Tumor flare	0	2 (10)

ALP, Alkaline Phosphatase; ALT, alanine aminotransferase; AST, Aspartate aminotransferase; TEAE, Treatment-emergent Adverse Event

AEs ≥ G3 Related to ASTX660 in ≥2 subjects

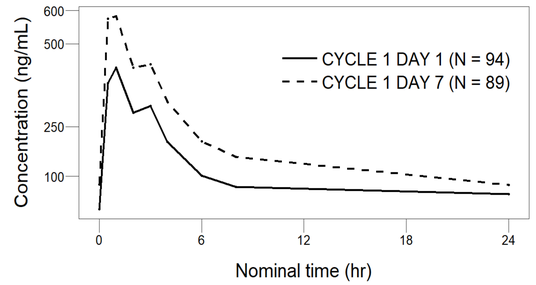
Adverse Event Term	PTCL (N=22) n(%)	CTCL (N=21) n(%)
Number of subjects who reported at least one TEAE	7 (32)	10 (48)
Lipase increased	4 (18)	3 (14)
Rash	2 (9)	5 (24)
Amylase increased	0	2 (10)

TEAE, Treatment-emergent adverse event

PHARMACOKINETICS

- ASTX660 was rapidly absorbed following oral administration, with maximum concentration (C_{max}) achieved at ~0.5–1.0 hour and terminal half-life ($T_{1/2}$) of ~ 12 hours.
- Mean plasma ASTX660 concentration-time curves exhibited biphasic profiles with secondary peaks. The cause and nature of these secondary peaks are being investigated.
- Accumulation (~ 2-fold) in AUC exposures was observed on Cycle 1 Day7 (C1D7) vs Cycle 1 Day1 (C1D1); no continuous accumulation in exposures cycle over cycle was observed.
- At the clinical RP2D of 180 mg, ASTX660 AUC exposures reached the target active range from preclinical models.

ASTX660 PK profile



ASTX660 PK Parameters on C1D7

COHORT	N	AUC_{last} (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
CTCL	19	3152.7 (82)	574.5 (87)	1 (0.5 – 4.0)	12.2 (42)
PTCL	15	2851.1 (54)	641.5 (81)	1 (0.5 – 3)	12.9 (33)
MEAN (all cohorts)	89	4291.7 (94)	776.6 (93)	1 (0.5 – 6.0)	12.1 (47)

Data are presented as Mean (%CV), except for T_{max} presented as Median (range)

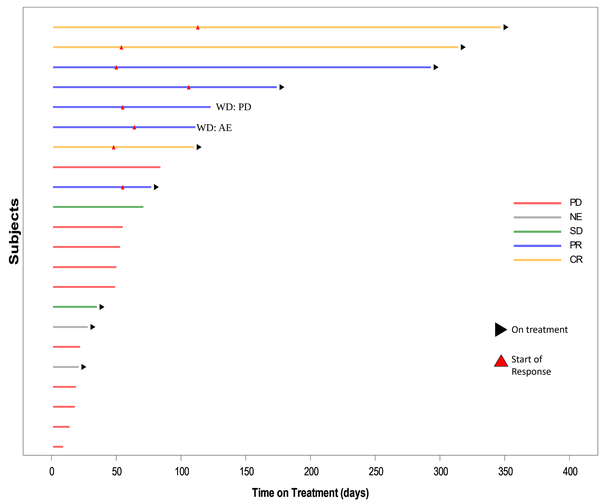
CLINICAL ACTIVITY

- As of the data cut-off, the ORR was 40% in the PTCL cohort and 22% in the CTCL cohort.
- Responses were reported in 8 (3 CR; 5 PR) of 20 evaluable PTCL subjects, as assessed by the investigators. Responses were observed in multiple subtypes.
- The median duration of response (DoR) in the PTCL cohort was 171 days.
- A best overall global response was achieved in 4 of 18 evaluable CTCL subjects; 2 were confirmed >4 weeks after. Responses were observed in subjects with large cell transformation, Sezary Syndrome and visceral metastases.

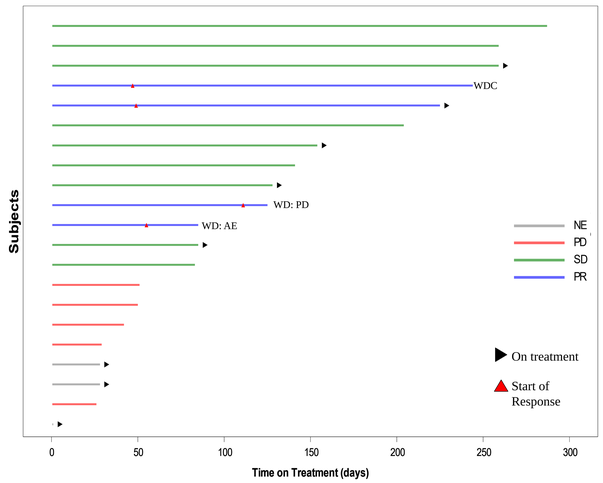
Mycosis Fungoides with Large Cell Transformation

Screening | Cycle 2 Day 1

PTCL Cohort: Best Response and Time on Treatment



CTCL Cohort: Global Response and Time on Treatment



CONCLUSIONS

- In ongoing Phase 2 cohorts, ASTX660 has shown activity against highly pre-treated PTCL and CTCL. These early data support continued development of ASXT660 for the treatment of r/r PTCL and CTCL.
- Enrollment into the PTCL and CTCL Phase 2 Cohorts is ongoing (NCT02503423).

References

1. Ward G. et al, (2018). ASTX660, a novel non-peptidomimetic antagonist of cIAP1/2 and XIAP, potently induces TNF-α dependent apoptosis in cancer cell lines and inhibits tumor growth. Mol Cancer Ther. 2018 Jul;17(7):1381-1391.
2. Johnson CN et al, (2018). A Fragment-Derived Clinical Candidate for Antagonism of X-Linked and Cellular Inhibitor of Apoptosis Proteins: 1-(6-[(4-Fluorophenyl)methyl]-5-(hydroxymethyl)-3,3-dimethyl-1 H,2 H,3 H-pyrrolo[3,2- b]pyridin-1-yl)-2-[(2 R,5 R)-5-methyl-2-[[(3R)-3-methylmorpholin-4-yl]methyl)piperazin-1-yl]ethan-1-one (ASTX660). J Med Chem. 2018 Aug 23;61(16):7314-7329
3. Ward G. et al (2019) ASTX660, a non-peptidomimetic antagonist of cIAP1/2 and XIAP, induces apoptosis in T cell lymphoma by enhancing immune mediated and death receptor dependent killing. Presented at the EHA Annual Conference 2019, abs # PS1322.
4. Mita et al, presented at the AACR-NCI-EORTC Conference 2017, abs #A091

Poster presented at: 24th Congress of European Hematology Association (EHA), Amsterdam, The Netherlands June 13 – 16, 2019

Poster can be downloaded from www.astx.com