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Preliminary results of ASTX660, a novel non-peptidomimetic cIAP1/2 and XIAP antagonist, in 118 patients with solid tumors or lymphoma

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BACKGROUND

Due to their roles in the evasion of apoptosis and immune modulation, Inhibitor of Apoptosis Proteins (IAPs) are considered attractive targets for anti-cancer therapy.

ASTX660 is an oral, novel non-peptidomimetic, small-molecule antagonist of cellular/X-linked inhibitor of apoptosis proteins (cIAP1/2 and XIAP) discovered using fragment-based drug design[1-4]. ASTX660 is currently being evaluated in a first-in-human phase 1–2 study in patients (pts) with advanced solid tumors or lymphoma (ClinicalTrials.gov NCT02503423).

In the phase 1 part of the study, the recommended phase 2 dose (RP2D) was identified with a manageable safety profile and initial evidence of clinical activity in a pt with mycoses fungoides[3]. In the ongoing phase 2 part of the study, clinical activity was observed in the relapsed/refractory peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL) cohorts[5]. Here, we report preliminary efficacy and safety data from the Phase 2 solid tumors and lymphoma cohorts.

METHODS

- Open-label, multi-center, Phase 1-2 study.
- In the Phase 2 part of the study, ASTX660 is administered orally at the RP2D of 180 mg/day on Days 1 to 7, and 15 to 22 in a 28-day cycle (5).
- The primary endpoint of the Phase 2 part is response rate as assessed by the investigator according to the RECIST 1.1 (solid tumors); Lugano 2014 Classification (DLBCL; PTCL) or Global Response (CTCL).
- In the first stage of Phase 2, 14 evaluable pts were enrolled in each of the 6 cohorts with the option to expand the cohort if activity was observed.
- Evaluable pts in Phase 2 are those who had tumor evaluation at baseline and at least 1 post-treatment tumor assessment, died, or stopped treatment earlier due to clinical deterioration or toxicity.
- Adverse events (AE) are assessed per CTCAE V4.03.

PATIENT CHARACTERISTICS

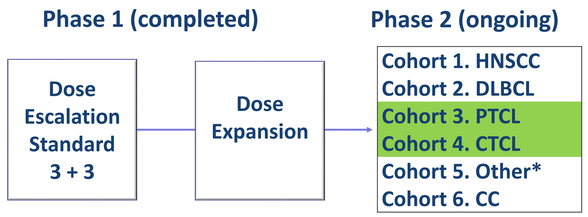
- As of 5 Sep 2019, 118 pts have received ASTX660 in the ongoing Phase 2 part of the study.

	1. HNSCC (N=14)	2. DLBCL (N=16)	3. PTCL (N=35)	4. CTCL (N=25)	5. Other* (N=14)	6. CC (N=14)
Age (yr), median	62.0	66.0	62.0	60.0	56.5	51.5
range	44-82	39-81	23-80	28-75	30-71	23-84
Male, n (%)	12 (86)	6 (38)	26 (74)	15 (60)	3 (21)	0
ECOG PS n (%)						
0	2 (14)	3 (19)	8 (23)	13 (52)	3 (21)	6 (43)
1	12 (86)	13 (81)	22 (63)	11 (44)	11 (79)	8 (57)
2	0	0	4 (11)	1 (4)	0	0
N of prior regimens, median	4	4	3	5	5	2.5
Prior RT, n (%)	14 (100)	9 (56)	6 (17)	10 (40)	7 (50)	12 (86)

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; RT, Radiotherapy

*Other solid tumor types with a potential molecular rationale

STUDY SCHEMA



*Other solid tumor types with a potential molecular rationale

PTCL and CTCL expansion ongoing. The other cohorts are closed to enrolment.

SAFETY

- 118 pts have received ASTX660 in the ongoing Phase 2 part of the study.
- Overall, the median number of cycles was 2 (range 1-19); 20% of pts required a dose delay and 30% of pts required a dose reduction.

AEs (Any Grade) related to ASTX660 in ≥10% of pts

Adverse Event	n=118(%)
Number of subjects who reported at least one TEAE	94 (78)
Rash	40 (34)
Lipase increased	38 (32)
Amylase increased	33 (28)
ALT increased	19 (16)
AST increased	16 (14)
Fatigue	16 (14)
Diarrhea	15 (13)
Nausea	15 (13)
Anemia	13 (11)

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; TEAE, Treatment-Emergent Adverse Event

AEs ≥ G3 related to ASTX660 in ≥2 of pts

Adverse Event	N=118(%)
Number of subjects who reported at least one TEAE	56 (48)
Rash	19 (16)
Lipase increased	18 (15)
Amylase increased	10 (9)
Fatigue	4 (3)
Anemia	3 (3)
Pneumonitis	3 (3)
ALT increased	2 (2)
Dyspnea	2 (2)
Lymphocyte count decreased	2 (2)
Neutropenia	2 (2)
Pancreatitis	2 (2)

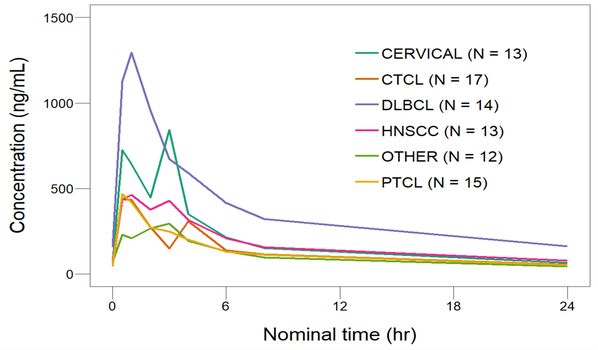
ALT, alanine aminotransferase; TEAE, Treatment-Emergent Adverse Event

- Serious Adverse Events (SAE) related to study drug were reported in 22 pts and included G3 pancreatitis (n=2), G3 Rash (n=3), G2-3 pneumonitis (n=5), G3 cytokine release syndrome (n=1), G2 facial nerve disorder (n=1) and fatal events of pneumonia (n=1) and sepsis (n=1).

PHARMACOKINETICS

- Preliminary pharmacokinetic (PK) data were available from 54 pts on C1D1 and 84 pts on C1D7 (steady state).
- Similarly to what was observed in Phase 1[3], ASTX660 plasma concentrations were higher on C1D7 vs C1D1 due to mild accumulation.
- The exposures varied among cohorts, with the highest exposures observed in the DLBCL cohort.
- ASTX660 exhibited a biphasic profile with secondary peaks, most prominent in the cervical cohort. The cause of the secondary peak is currently being investigated.

ASTX660 mean PK profile by cohort (C1D7)



Cohort (N)	AUC_{0-24h} (ng*hr/mL)[a]	C_{max} (ng/mL)[a]	T_{max} (h)[b]	$t_{1/2}$ (h)[a]
CERVICAL (13)	4359 (3705)	954 (687)	0.5 (0.5 - 4)	9.0 (5.4)
CTCL (17)	3164 (2582)	635 (495)	1 (0.5 - 4)	12 (5.1)
DLBCL (14)	8851 (6790)	1583 (1133)	1 (0.5 - 3)	12 (5.0)
HNSCC (13)	4169 (1938)	661 (355)	1 (0.5 - 6)	15 (9.4)
OTHER (12)	2513 (950)	420 (184)	2 (0.5 - 3)	11 (2.3)
PTCL (15)	2851 (1533)	642 (521)	1 (0.5 - 3)	13 (4.2)

Data presented as Mean (SD), except for Tmax, Median (Range)

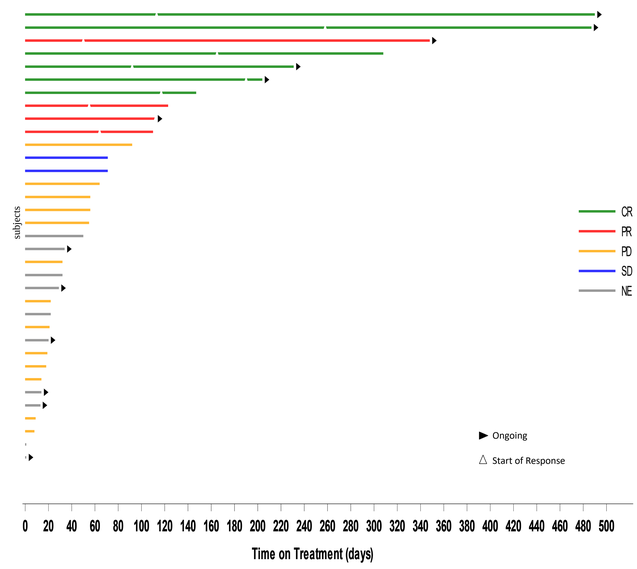
CLINICAL ACTIVITY

- As of Sep 5th, the overall response rate (Complete Response [CR] + Partial Response [PR]) was 40% in the PTCL cohort and 12% in the CTCL cohort. One PR was also reported in a patient with metastatic melanoma enrolled in Cohort 5. No responses were reported in the HNSCC, DLBCL or cervical cohorts. Exploratory biomarker analyses are ongoing.
- Responses were reported in 10 (6 CR; 4 PR) of 25 evaluable PTCL pts, as assessed by the investigators.
- 7 pts in the CTCL cohort had a skin PR, as assessed by the investigator (mSWAT score). A global PR was achieved in 3 of 23 evaluable CTCL pts; 16 pts had a best global response of stable disease (SD).
- 1 pt with metastatic BRAF wild-type melanoma, who is still receiving treatment, achieved a PR after 12 cycles of treatment that is still maintained at cycle 18.

Mycosis Fungoides with Large Cell Transformation

Screening — Cycle 2 Day 1

PTCL Cohort: Best Response and Time on Tx



CTCL Cohort: Global Response and Time on Tx

CONCLUSIONS

- In ongoing Phase 2 cohorts, ASTX660 has shown activity against heavily pre-treated PTCL and CTCL. These early data support continued development of ASTX660 for the treatment of T-Cell Lymphoma.
- PTCL and CTCL Phase 2 Cohorts expansion is ongoing in North America and Europe (NCT02503423).
- Correlative biomarker studies aimed at identifying potential predictors of response are ongoing.

References

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5. Metha A. et al (2019). 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. Presented at the EHA Annual Conference 2019, abs # PS1073.

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Poster can be downloaded from www.astx.com

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