EHA EUROPEAN HEMATOLOGY ASSOCIATION

Encore Presentation

EHA2022 HYBRID VIRTUAL

PRELIMINARY ANALYSIS OF THE PHASE II STUDY USING TOLINAPANT (ASTX660) MONOTHERAPY IN 98 PERIPHERAL T-CELL LYMPHOMA AND 51 CUTANEOUS T-CELL LYMPHOMA SUBJECTS WITH RELAPSED REFRACTORY DISEASE

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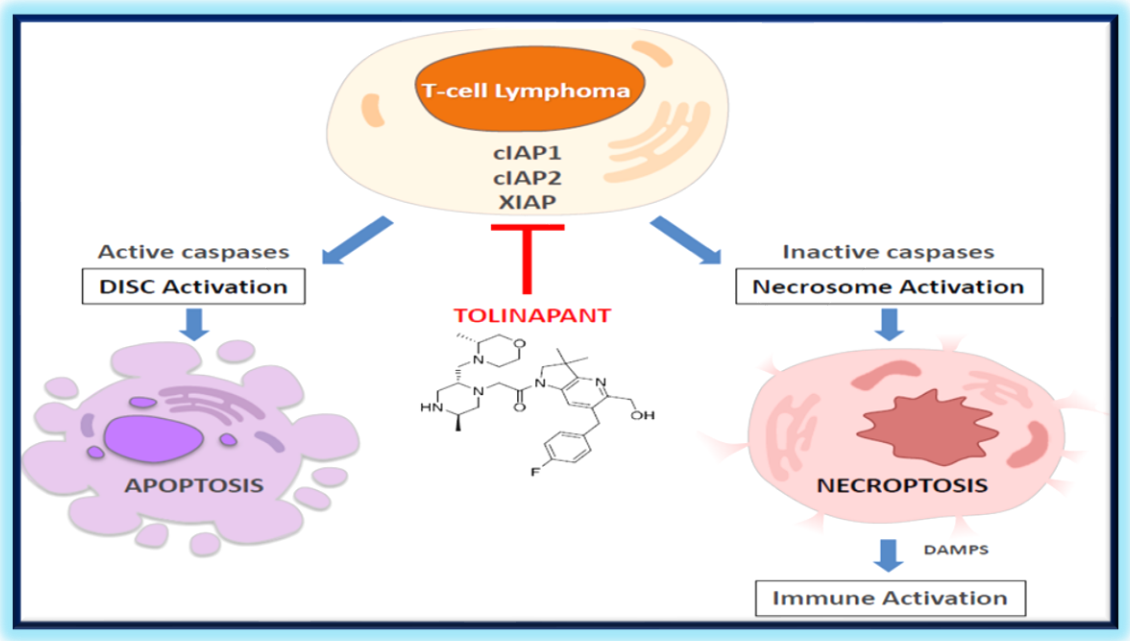
Background

- **Limited treatment options exist for patients with PTCL and CTCL, especially after front line therapy has failed. NCCN recommends clinical trials for these patients.**

ASTX660 (Tolinapant)

- **Novel Mechanism of Action[1]**
  - Oral non-peptidomimetic antagonist of inhibitor of apoptosis proteins (IAPs), cIAP1, cIAP2 and XIAP
  - Recent data demonstrates both apoptosis and immunomodulation
- Phase 1: low efficacy in other tumour types, recommended phase 2 dosing (RP2D) achieved
- >250 subjects dosed with tolinapant to date
- Manageable safety profile
  - Minimal myelosuppression



1: Ferrari N *et al*, *Blood Advances, 2021;* Johnson C *et al,* J Med Chem 2018; Ward G *et al*, Mol Cancer Ther 2018

ASTX660-01 Phase 2 Design and Expansion

Phase 2: Open Label Non-Randomized Basket Trial

RP2D and Dosing Regimen Identified in Phase 1

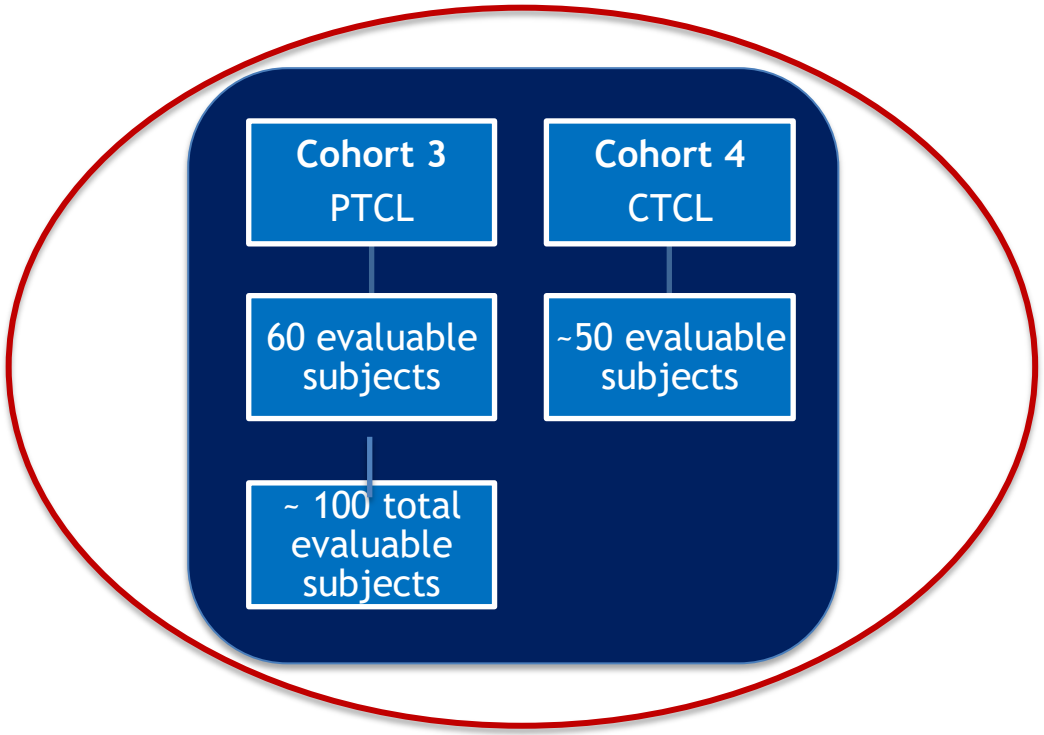
Approximately 14 evaluable subjects to be enrolled into each of (up to 6) specific tumor-type cohorts at the RP2D

- Cohort 1 HNSCC (n=30)
- Cohort 2 DLBCL (n=30)
- Cohort 3 PCTCL (n=30)
- Cohort 4 CTCL (n=30)
- Cohort 5 Other Cell Tumor Type (n=30)
- Cohort 6 Cervical Carcinoma (n=30)

Subject Expansion (conditional)

Decision to expand enrollment in a specific cohort based on response

Further expansion of the PTCL and CTCL cohorts were undertaken in subjects that received at least 2 previous systemic lines of therapy



RP2D 180 mg/day on Days 1 to 7, and 15 to 22 in a 28-day cycle

HNSCC = Head and Neck Squamous Cell Carcinoma; DLBCL = Diffuse Large B cell Lymphoma

Key Study Entry Criteria

- **Key Inclusion Criteria**
  - Subjects with PTCL or CTCL with evidence of documented progressive disease who received at least two prior systemic therapies
  - Those with CD30-positive lymphoma must have received, be ineligible for, or intolerant to brentuximab vedotin
  - Those with Mycosis Fungoides or Sezary syndrome must have received, be ineligible, or intolerant to mogamulizumab
  - Subjects with PTCL must have measurable disease by CT
  - Subjects must have adequate organ function
- **Key Exclusion Criteria**
  - Cardiac disease (EF<50%, NYHA >3, unstable disease, prolonged QTc)
  - Recent systemic therapy, including CAR-T cells (within 2-6 weeks of study treatment)
  - Systemic steroids >20 mg prednisone equivalent

Study Objectives

- **Primary Objective**
  - To assess preliminary efficacy, as determined by response rate (determined by investigator)
    - PTCL: 2014 Lugano classification: radiologic-based criteria
    - CTCL: Global Assessment: Olsen *et al*. Blood, 2007 and Olsen *et al.* J Clin Oncol., 2011
- **Secondary Objectives**
  - To determine the pharmacokinetic (PK) parameters of orally administered ASTX660
    - Previously presented as part of the Phase 1 results (Mita e*t al*. Clin Cancer Res, 2020)
  - To evaluate other efficacy parameters, such as duration of response (DOR) and progression-free survival (PFS)
  - To evaluate relevant pharmacodynamic (PD) targets and potential biomarkers of ASTX660 activity

AE ≥ G3 Related to ASTX660 in ≥ 1% of Subjects

Most common G3 AEs: rash, lipase elevation, and amylase elevation

- Severe cutaneous toxicities occur more commonly in the CTCL cohort
- Incidence of asymptomatic pancreatic enzyme elevation is similar across cohorts

Adverse Event	PTCL (N=99) N (%)	CTCL (N=51) N (%)	Phase 2 Total (N=150) N (%)
Total Number of TEAEs	90	52	142
Number of subjects who reported at least one TEAE	41 (41.4)	27 (52.9)	68 (45.3)
Lipase increased	15 (15.2)	8 (15.7)	23 (15.3)
Rash (combined terms)	8 (8.1)	8 (15.7)	16 (10.7)
Amylase increased	6 (6.1)	4 (7.8)	10 (6.7)
Anaemia	6 (6.1)	1 (2.0)	7 (4.7)
Thrombocytopenia	6 (6.1)	1 (2.0)	7 (4.7)
Neutropenia	6 (6.1)	0	6 (4.0)
Febrile neutropenia	3 (3.0)	0	3 (2.0)
Pancreatitis	2 (2.0)	0	2 (1.3)
Tumor Flare	0	2 (3.9)	2 (1.3)
Acute kidney injury	2 (2.0)	0	2 (1.3)
Ejection fraction decrease	1 (1.0)	1 (2.0)	2 (1.3)
Hypercalcemia	2 (2.0)	0	2 (1.3)
Pruritis	0	2 (3.9)	2 (1.3)

Efficacy Endpoints

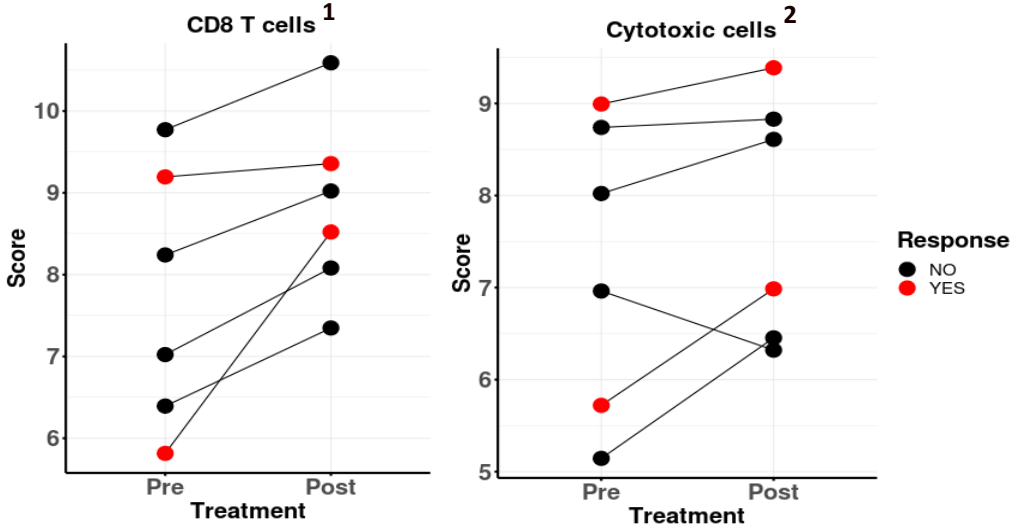
	PTCL	CTCL
– **Number of Evaluable Subjects**	**96**	**50**
– **Best Overall Response Rate (ORR)**	**22.9% (N = 22)**	**28.0% (N = 14)**
• Partial Response	13.5% (13)	24.0% (12)
• Complete Response	9.4% (9)	4.0% (2)
– **Median Duration of Response**	**6.5 months**	**8.8 months**
• Range (min, max), months	(1.5, 45.1)	(1.0, 43.0)
• Mean Duration of Response	12.2 months	11.5 months
– **Median Progression Free Survival**	**1.8 months**	**5.5 months**
• Mean Progression Free Survival	5.0 months	7.3 months
– **Median Kaplan-Meier Overall Survival**	**15.4 months**	**40.7 months**

Note: 1 month = 30.4 days

Pharmacodynamic Studies: Clinical PTCL Samples Show Evidence of Immune Modulation

Biopsies

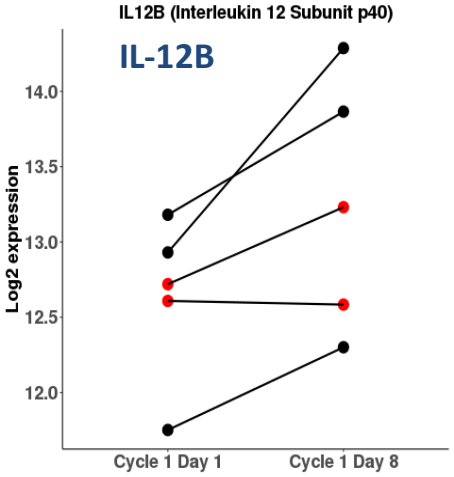
CD8 and cytotoxic cell recruitment



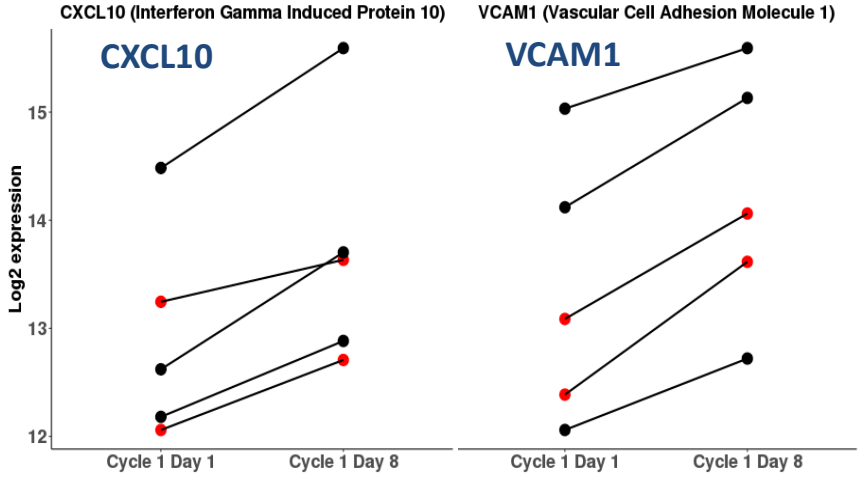
- **Consistent with preclinical models, post-treatment PTCL samples show evidence of increased immune cell recruitment and soluble immune mediators**

Plasma

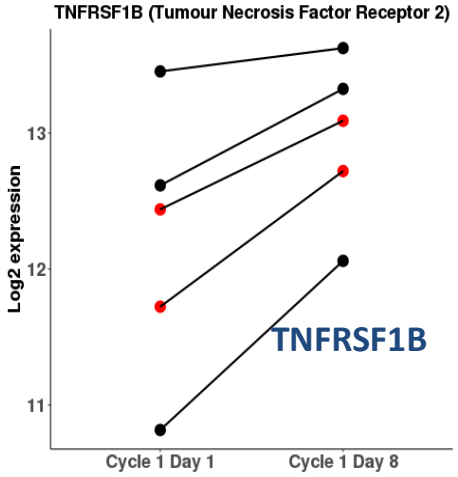
T cell differentiation



Mediators of leukocyte recruitment



TNF pathway modulation



1: Gene expression associated with CD8⁺ T cell
2: Gene expression associated with cytotoxic CD8⁺ T cells and NK cells

Ferrari N *et al.*, *Blood Advances, 2021*

Summary

- ASTX660 has a manageable safety profile with most common AEs being asymptomatic increases of lipase and amylase as well as rash
- ASTX660 shows encouraging single agent activity:
  - PTCL ORR of 22.9% with a median DoR of 6.5 months
  - CTCL ORR of 28.0% with a median DoR of 8.8 months
- Preliminary PD data demonstrates immune modulation (Data shown at EHA)
- A new study is underway combining ASTX660 with an oral HMA (decitabine/cedazuridine) in R/R PTCL (NCT05403450)
  - Preclinical rationale on the combination synergy presented at EHA in posters P1293 and P1278