Abstract # NT-009

Trial in Progress: A Study of Tolinapant in Combination With Oral Decitabine/Cedazuridine and Oral Decitabine/Cedazuridine Alone in Participants With Relapsed/Refractory Peripheral T-Cell Lymphoma (NCT05403450)

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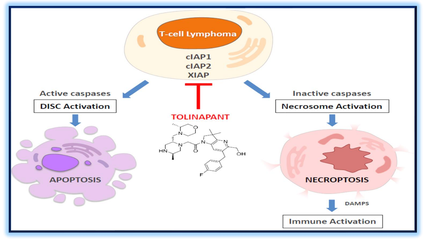
BACKGROUND

- Peripheral T-Cell Lymphoma (PTCL) and Cutaneous T-Cell Lymphoma (CTCL) are rare malignancies that comprise <10% of Non-Hodgkin Lymphoma.
- Limited treatment options exist for patients with PTCL and CTCL, especially after front line therapy has failed. NCCN recommends clinical trials for these patients.
- This study uses two oral study drugs, tolinapant and the oral hypomethylating agent (HMA) decitabine/cedazuridine, with preclinical evidence for synergy, safety profiles without overlapping toxicities, and no evidence of drug-drug interactions between the two agents
- In early clinical studies, HMAs and tolinapant have demonstrated single-agent activity in PTCL

Tolinapant

- Oral non-peptidomimetic antagonist of inhibitor of apoptosis proteins (IAPs): cIAP1, cIAP2 and XIAP; discovered by Astex via a Fragment-Based Drug Discovery approach
- Antagonism of IAPs induces intrinsic and extrinsic apoptosis via caspase activation
- Recent publications suggest IAP antagonism can also result in:
  - Necroptosis
  - Immunomodulation
- Study ASTX660-01: Phase 2 data abstract were presented as an oral presentation at the 2022 EHA Annual Congress and as an encore oral presentation at the 2022 T-Cell Lymphoma Forum. (Michot, et al.,HemaSphere, 2022; 6:(S3), S217)



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

Oral Decitabine/Cedazuridine, a hypomethylating agent (HMA)

- Decitabine is a pyrimidine nucleoside analogue inhibitor of DNA methyl-transferase (DNMTi) resulting in DNA hypomethylation, reactivation of silenced genes, and cellular differentiation. It has historically been given intravenously.
- Cedazuridine is a novel, potent, and well-tolerated inhibitor of cytidine deaminase (CDA), which, when given orally in combination with decitabine, can produce decitabine exposures similar to those following IV administration.
- There are limited clinical data with HMAs in PTCL with most reported studies being retrospective or case controlled.
- A recent prospective single arm study involving 20 subjects showed a 40% ORR in R/R PTCL with the HMA guadecitabine (Wong *et al*., Leukemia, 2022)

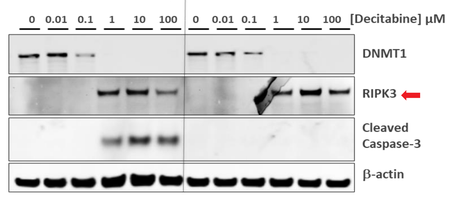
PRECLINICAL RATIONALE

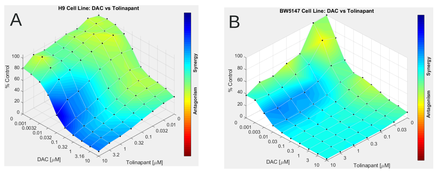
- Epigenetic silencing of necrosome genes prevents necroptosis and leads to tolinapant resistance. Decitabine can re-activate these genes, sensitize the cells to tolinapant-induced necroptosis and subsequent immune response.

Preclinical observations

- Decitabine induces re-expression of RIPK3 and/or MLKL.
- Decitabine increases cell death and necroptotic signals. This is enhanced when combined with tolinapant.
- Both agents increase IFN signalling, which could further enhance immune activation.

RIPK3-negative cell lines treated with decitabine





Synergy: H9(A) and BW5147(B) cell viability is reduced with combination of tolinapant and DAC treatment (72h proliferation assay). Synergy assessed by HSA model (Combenefit).

Ward *et al.*, ASH 2021

STUDY OBJECTIVES

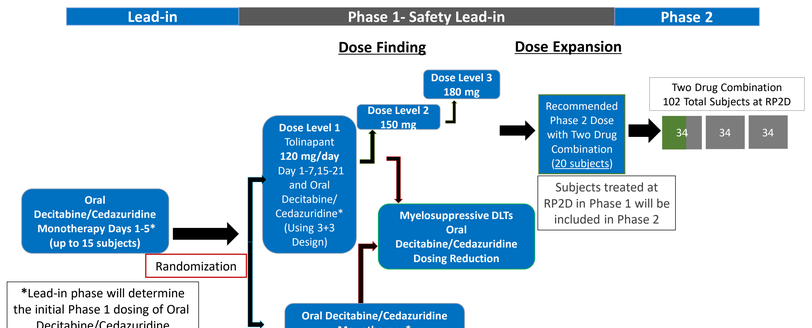
Primary Objectives

- Phase 1: To assess safety, and to identify the recommended Phase 2 dose (RP2D) of tolinapant in combination with oral decitabine/cedazuridine.
- Phase 2: To assess preliminary efficacy in relapsed/refractory (R/R) PTCL, as determined by Overall Response Rate (ORR) using Lugano criteria as assessed by the investigator

Secondary Objectives

- Phase 1: To determine the pharmacokinetic (PK) parameters of both tolinapant and oral decitabine/cedazuridine.
- Phase 2
  - To evaluate other efficacy parameters, including duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) for tolinapant in combination with oral decitabine/cedazuridine.
  - To assess preliminary efficacy for tolinapant in combination with oral decitabine/cedazuridine by overall response rate (ORR) with the assessment for pseudoprogression.

STUDY SCHEMA



STUDY DESIGN

- **Lead-in phase:** Ensure that the approved treatment dosing of oral decitabine/cedazuridine is tolerated in this population, with dosing decreases for DLTs if needed.
- **Phase 1:** Randomized to oral decitabine/cedazuridine alone or in combination with tolinapant. The combination arm will have escalation of tolinapant in ranges that have shown activity in PTCL. The oral decitabine/cedazuridine only arm will enroll ~20-24 subjects. Once the combination arm reaches RP2D or MTD there will be a dose expansion of 20 subjects in the combination arm
- **Phase 2:** will be the combination of tolinapant with oral decitabine/cedazuridine
- **Statistical considerations**: There will be no formal analysis in Phase 1. In Phase 2, there will be analysis after every 34 subjects, without a pause in enrollment.
- **Study opened May 2022:**
  - Anticipated period of enrollment of 36 months
  - Total enrollment goal of 137 subjects
  - Multicenter international study involving sites in the US, Australia, and Europe

ENROLLMENT CRITERIA

Key Inclusion Criteria

- Men and women 18 years of age or older.
- Expected life expectancy of > 12 weeks.
- Subjects must have histologically confirmed R/R PTCL as defined by 2016 World Health Organization (WHO) classification. The following subtypes are eligible:
  - Extranodal natural killer (NK)/T-cell lymphoma nasal type
  - Enteropathy-associated T-cell lymphoma
  - Monomorphic epitheliotropic intestinal T-cell lymphoma
  - Hepatosplenic T-cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS)
  - Angioimmunoblastic T-cell lymphoma
  - Follicular peripheral T-cell lymphoma
  - Nodal peripheral T-cell with T-follicular helper (THF) phenotype
  - Anaplastic large-cell lymphoma (ALCL)
- Subjects must have evidence of progressive disease and must have received at least two prior systemic therapies.
- Subjects must have measurable disease by contrast-enhanced diagnostic CT
- Subjects with CD30-positive disease must have received, be ineligible for, or intolerant to brentuximab vedotin. If an investigator determines that the subject will have a minimal likelihood of benefiting from brentuximab vedotin, this should be discussed with the medical monitor and can be approved on a case-by-case basis.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
- Acceptable organ function
- Women of childbearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening.

Key Exclusion Criteria

- Prior treatment with tolinapant, or any hypomethylating agent.
- Cardiac disease (EF<50%, NYHA >3, unstable disease, prolonged QTc)
- Recent systemic therapy, including CAR-T cells (within 2-12 weeks of study treatment)
- Known history of human immunodeficiency virus (HIV) infection; or seropositive results consistent with active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection.
- Grade 3 or greater neuropathy.
- Concurrent second malignancy currently requiring active therapy, except breast or prostate cancer stable on or responding to endocrine therapy or superficial bladder cancer.
- Subjects with a history of allogenic transplant are excluded from this study.
- Autotransplant within 100 days of the first dose of the study drug(s).
- Systemic corticosteroids > 10 mg prednisone equivalent within 7 days of the first dose of study drug(s)
- Anti-T-cell directed therapy:
  - Lymphotoxic agents (e.g., anti-CD52) in the past 12 months
  - Inhibitory drugs (e.g., calcineurin inhibitors) within 4 weeks of the first dose of study drug(s)
- Use of a concomitant medication which is a moderate or strong CYP3A4 inhibitor/inducer within 2 weeks of study start.
- Use of any vaccine within 10 days of the first dose of the study drug(s).

CONTACT INFORMATION

For more information on this study:

- Scan the QR code to ClinicalTrials.gov Identifier NCT05403450 at https://clinicaltrials.gov/ct2/show/ NCT05403450
- Email: clinicaltrials@astx.com

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