An Oral Combination Study of Novel Nucleoside Analogue Sapacitabine and BCL2 Inhibitor Venetoclax to Treat Patients with Relapsed or Refractory AML or MDS

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BACKGROUND

AML and MDS occur primarily in older patients

- No effective therapies for persistent or progressive disease after standard chemotherapy and hypomethylating agents (HMA)

Nucleoside analogues are active against AML and MDS

- Ara-C is most active anti-leukemic agent
- Decitabine and azacitidine are active against AML and MDS; their anti-leukemic activities are enhanced by combining with venetoclax
- Sapacitabine, an orally bioavailable nucleoside analogue, has induced complete remission (CR), CR with incomplete platelet count recovery (CRp), partial remission (PR), and major hematological improvement (HI) in patients with AML and MDS who were previously treated with other nucleoside analogues (Kantarjian H *et al.*, ASH, 2013)

The combination of sapacitabine and venetoclax, two oral drugs, may demonstrate synergistic activity and translate into improved outcomes for patients with these diseases

SAPACITABINE

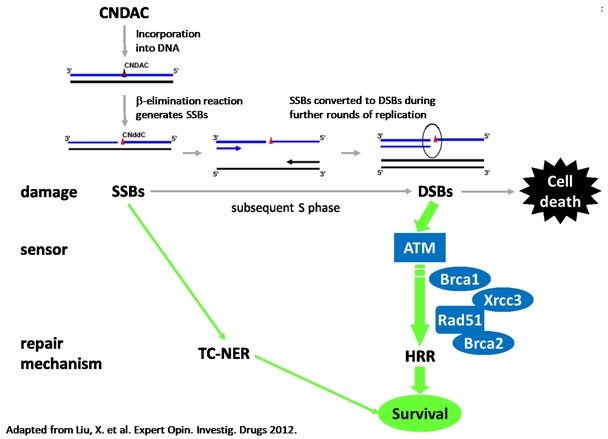
Orally available 2'-deoxycytidine analogue, converted to CNDAC *in vivo*

Incorporated into DNA during replication or repair, resulting in ssDNA breaks via a covalent rearrangement

During further rounds of replication, ssDNA breaks converted to dsDNA breaks, resulting in cell death

Active in solid tumors (BRCA mutated breast, ovarian, and pancreatic cancers) and hematological malignancies (AML, MDS)

Predominant dose-limiting toxicities (DLTs) in patients with advanced leukemias or MDS were gastrointestinal toxicities including abdominal pain/small bowel obstruction, diarrhea and neutropenic colitis. Non-hematological toxicities were generally mild to moderate.



Adapted from Liu, X. et al. Expert Opin. Investig. Drugs 2012.

SAPACITABINE-VENETOCLAX COMBINATION IN AML AND MDS

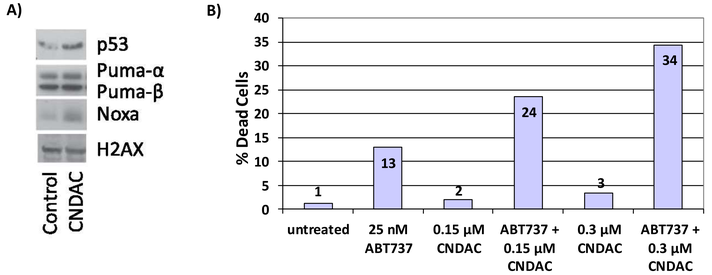
Two clinical studies have demonstrated synergistic activity of venetoclax in combination with hypomethylating agents or low-dose ara-C in newly diagnosed AML

Synergy between venetoclax and cytotoxic therapy in AML models is mediated by combined targeting of anti-apoptotic BCL2 and MCL1 mechanisms (Teh T-C *et al.*, Leukemia, 2018)

- Cytotoxic drugs, such as nucleoside analogues, induce apoptosis through genotoxic damage, p53 activation and increased expression of pro-apoptotic NOXA and PUMA (Villunger A *et al.*, Science, 2003) which can inactivate MCL1, a key anti-apoptotic protein in the BCL2 family. These features have also been demonstrated for sapacitabine (Green S *et al.*, Br J Cancer, 2010) .

CNDAC (2'-*C*-cyano-2'-deoxy-1-β-D-arabino-pentafuranosylcytosine), the active metabolite of sapacitabine, was synergistic with BCL2 inhibitor ABT737 in inducing apoptosis in AML cell line MV4-11 (Frame S *et al.*, 14th EHA, 2009, Abs 0761)

SAPACITABINE COMBINES SYNERGISTICALLY WITH BCL2 INHIBITORS



CNDAC treatment increases p53, Puma and Noxa protein levels and combines synergistically with BCL2 inhibitor ABT737 in AML cell line MV4-11

A) Western blot of MV4-11 cells following 24 h treatment with DMSO (control) or 1 x IC_{50} concentration of CNDAC (Green S *et al.*, Br J Cancer, 2010)

B) Induction of MV4-11 cell death following 48 h treatment with ABT737 (25 nM), CNDAC (0.15 or 0.3 μM), or both. Cell death determined as sub-G1 DNA content assessed by flow cytometry. (Frame S *et al.*, 14th EHA, 2009, Abs 0761)

SAPACITABINE-VENETOCLAX COMBINATION (CYC682-11): NCT01211457

Primary objective

Determine maximum tolerated dose (MTD) of sapacitabine administered in combination with venetoclax

Secondary objective

Assess durations of clinical benefit response (CR, CRp, PR, or major HI), transfusion requirements, number of hospitalized days and overall survival

Planned accrual (n=25): approximately 12 patients in each cohort

Cohort 1: sapacitabine b.i.d. x 5 days/venetoclax q.d. x 14 days

Cohort 2: sapacitabine b.i.d. x 3 days/week x 2 weeks/venetoclax q.d. x 14 days

KEY ELIGIBILITY CRITERIA AND DLT DEFINITION

Inclusion

- Relapsed or refractory AML and MDS with ≥10% blasts in bone marrow or peripheral blood
- Total bilirubin ≤ 1.5 mg/dL, ALT ≤ 2 x ULN
- Creatinine ≤ 1.5 x ULN
- At least 2 weeks from prior chemotherapy, radiation therapy, major surgery or other investigational anticancer therapy

Exclusion

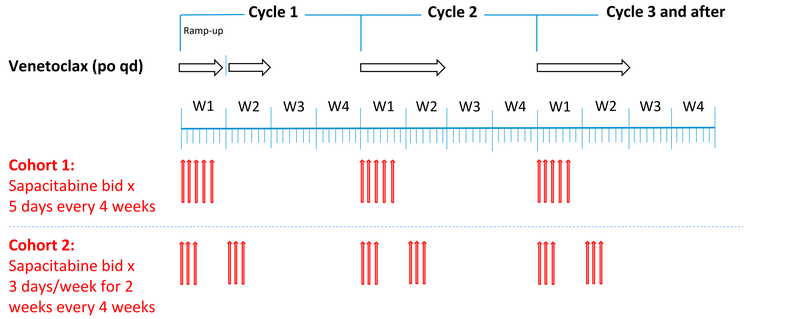
- APL or extramedullary myeloid tumor without bone marrow involvement

Dose Limiting Toxicity (DLT)

- Grade 3/4 nausea, vomiting, or diarrhea despite maximum supportive care
- Other Grade 3/4 non-hematological toxicity with exception of alopecia
- Pancytopenia with hypocellular bone marrow (≤ 5% cellularity) and no evidence of leukemia, lasting longer than 42 days

Maximum Tolerated Dose (MTD) = RP2D: Dose level at which ≤ 2 of 6 patients experienced a dose-limiting toxicity during the first 2 treatment cycles

DOSING SCHEDULE



ENROLLMENT

Cohort 1

Sapacitabine 250 mg b.i.d. x 5 days/venetoclax q.d. x 14 days

- 3 patients dosed
- Prior therapies included liposomal ara-C/ daunorubicin, azacitidine, venetoclax

Cohort 2

Sapacitabine 300 mg b.i.d. x 3 days/week x 2 weeks/venetoclax q.d. x 14 days

- 2 patients dosed
- Prior therapies included ara-C/daunorubicin, cladribine, decitabine, azacitidine, venetoclax

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