Safety and efficacy of copanlisib, a novel PI3K inhibitor, for the treatment of relapsed/refractory T-cell lymphoma

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INTRODUCTION

- The phosphoinositide 3-kinases (PI3Ks) are a family of lipid kinases with key roles in intracellular signaling cascades regulating many cellular processes
- PI3K-mediated activation of downstream effectors, including the serine/threonine kinase (AKT) and mammalian target of rapamycin (mTOR) pathways, is aberrantly activated in a variety of human cancers, and is key to promoting cell survival proliferation and differentiation (Figure 1)[1,2]

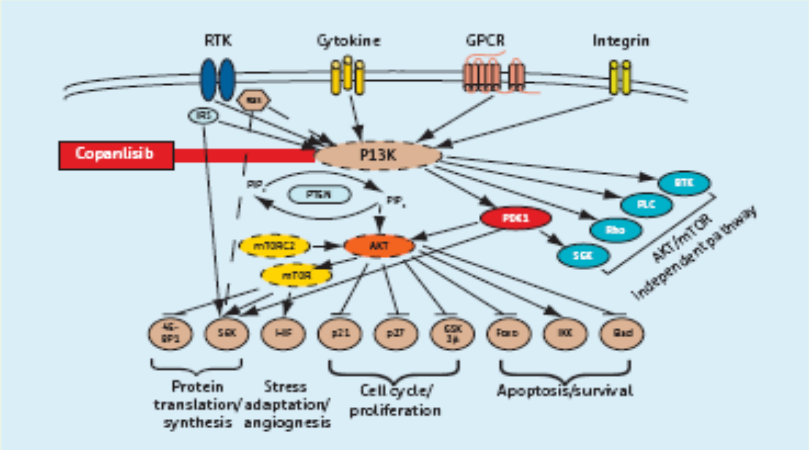


Figure 1. The PI3K/AKT/mTOR signaling cascade (modified from Steelman et al 2008)[3]

- Activation of the PI3K/AKT pathway is one of the major mechanisms by which tumors escape negative control of proliferation and become resistant to chemotherapy, targeted agents, and radiation. Therefore, PI3K inhibitors are expected to be effective not only in PI3K pathway-driven tumors but also in combination with other chemotherapy agents[4]
- Copanlisib (BAY 80-6946) is a potent pan-class I reversible PI3K inhibitor with significant activity against the PI3K δ and α isoforms. Copanlisib demonstrated efficacy in preclinical tumor models: *PIK3CA* mutation; *PTEN* deletion; over-expression of human epidermal growth factor receptor[5]
- T-cell lymphomas are a heterogeneous group of aggressive malignancies currently lacking effective therapy

METHODS

Study design

This open-label Phase II study was conducted to assess the preliminary efficacy and safety of copanlisib in patients with histologically confirmed indolent or aggressive non-Hodgkin's lymphoma relapsed/refractory to >2 prior lines of treatment

We will show the results of 4 patients with T-cell lymphoma receiving therapy with copanlisib progressing after standard therapy

PATIENTS AND TREATMENT

- Inclusion criteria were: histologically confirmed relapsed/refractory non-Hodgkin's lymphoma; Eastern Cooperative Oncology Group performance status 0-2; ≥18 years of age
- Exclusion criteria included: known involvement of the central nervous system; type 1 or type 2 diabetes mellitus; uncontrolled hypertension despite optimal medical management; concurrent treatment with CYP3A4 inducers or strong inhibitors or systemic corticosteroids[6]
- Copanlisib was administered as a 1-h intravenous infusion on days 1, 8, and 15 of every 28-day cycle at the maximum tolerated dose of 0.8 mg/kg (maximum 65 mg)[6]
- Dose reductions could be made to 0.6 mg/kg (maximum 48 mg) and 0.4 mg/kg (maximum 32.5 mg) if required
- Treatment continued until disease progression (PD), unacceptable toxicity, or withdrawal of consent

ASSESSMENTS

- Response evaluation was conducted according to the Cheson[7] or international workshop on chronic lymphocytic leukemia[8] criteria
- Primary endpoint: objective response rate up to 16 weeks after the last patient initiated treatment
- Secondary endpoints: safety; progression-free survival; duration of response; overall survival; pharmacokinetics; potential biomarkers

Patient 1

- A 69-year-old female with stage IVA peripheral T-cell lymphoma NOS; diagnosed in June 2012

Previous therapy

1. CHOP × 4: July - September 2012 PR
2. GEMOX × 2: October - November 2012 PD

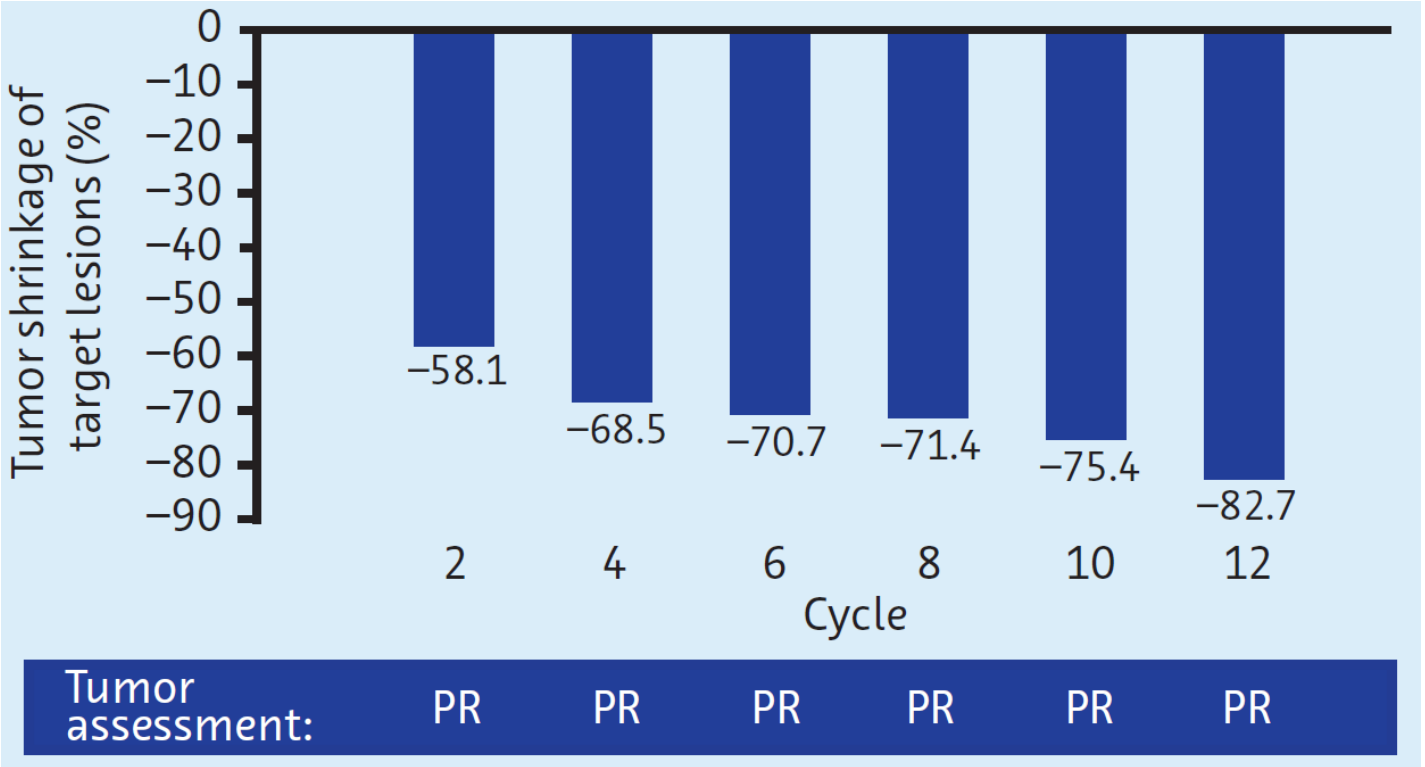
- Her most recent relapse occurred in December 2012 (refractory to last chemotherapy treatment)

Study therapy

- 14 cycles received

CHOP, cyclophosphamide; doxorubicin, vincristine, prednisone; GEMOX, gemcitabine plus oxaliplatin; NOS, not otherwise specified; PD, progressive disease; PR, partial response

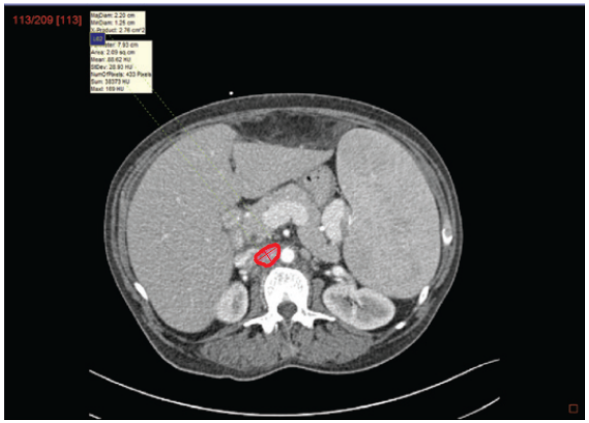
Patient 1: response to treatment



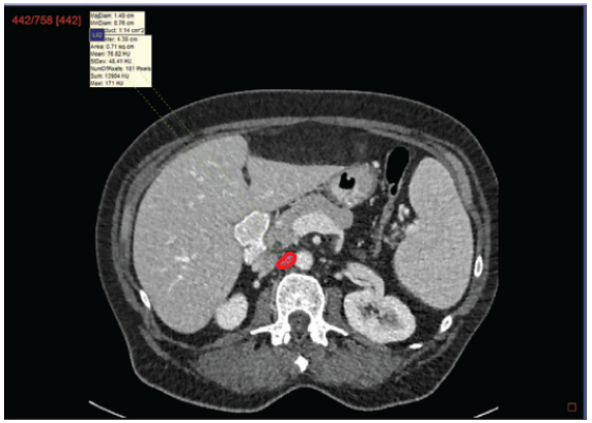
- The nodal lesion and liver had returned to normal size, with persistent splenomegaly

Patient 1: tumor assessment

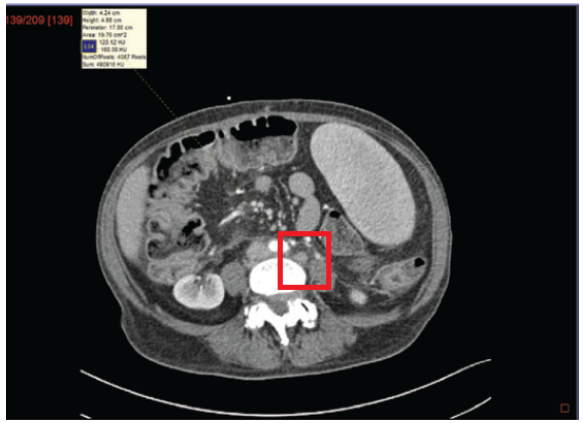
Target lesion (para-aortic lymph node) at baseline



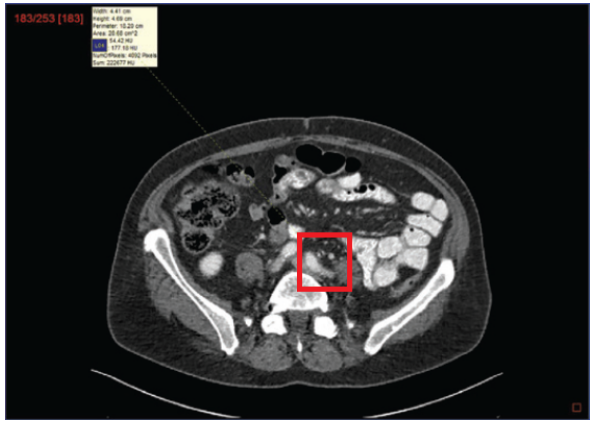
Target lesion at endpoint



Non-target lesion (group of lymph nodes) at baseline



Non-target lesion at endpoint



Patient 1: tolerability

Toxicity

- SAEs: none
- CTC grade 3 TEAEs: arthritis; hypertension; decreased neutrophil count (all drug-related)
- Arthritis and hypertension were already present in the patient's medical history
- CTC grade 4 TEAEs: none

Dose modification

- 1 drug interruption was required due to CTC grade 3 decreased neutrophil count
- 2 drug interruptions for CTC grade 3 arthritis
- 1 dose reduction to 0.6 mg/kg on cycle 14, day 8 for CTC grade 3 arthritis

CTC, Common Terminology Criteria; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Patient 2

- A 63-year-old male with stage IVB angioimmunoblastic T-cell lymphoma; diagnosed in August 2012

Previous therapy

1. CHOP + romidepsin × 4: August - November 2012 PD
2. DHAOX × 1: November - December 2012 PD
3. Gemcitabine + masitinib × 2: December 2012 - February 2013 PD

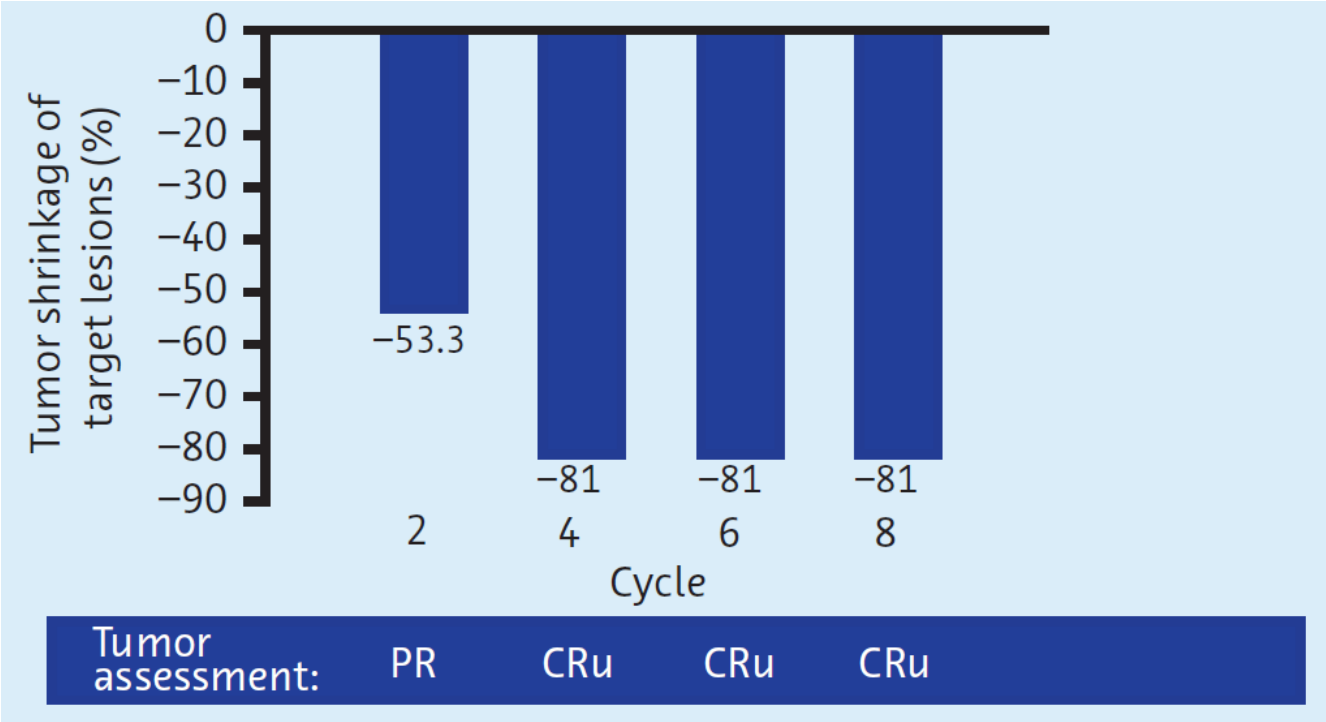
- His most recent relapse occurred in February 2013 (refractory to last chemotherapy treatment)

Study therapy

- 10 cycles received

DHAOX, dexamethasone, high-dose cytarabine, oxaliplatin

Patient 2: response to treatment



- The nodal lesions had returned to normal size; bone marrow was undetermined

CRu, unconfirmed complete response

Patient 2: tolerability

Toxicity

- SAEs: none
- CTC grade 3 TEAEs: hyperglycemia; decreased white blood cell; decreased neutrophil count; febrile neutropenia; diarrhea (all drug-related)
- CTC grade 4 TEAEs: decreased neutrophil count; hypokalemia (both drug-related)

Dose modification

- 1 drug interruption was required due to CTC grade 4 decreased neutrophil count

Patient 3

- A 61-year-old female with stage IVB peripheral T-cell lymphoma NOS; diagnosed in September 2007

Previous therapy

1. CHOP × 6: October 2007 - February 2008 CR
2. IVAM × 6: May - October 2011 CR
3. Dexa-BEAM: February 2012 PR
4. Gemcitabine: May - July 2012 PR

- Her most recent relapse occurred in January 2013 (refractory to last chemotherapy treatment)

Study therapy

- 2 cycles received
  - After the second cycle, the patient discontinued from study treatment due to radiologic PD

CR, complete response; Dexa-BEAM, dexamethasone, carmustine, etoposide, cytarabine, melphalan; IVAM, ifosfamide, etoposide, cytarabine, methotrexate

Patient 3: tolerability

Toxicity

- SAEs: none
- CTC grade 3-4 TEAEs: none

Dose modification

- None

Patient 4

- A 65-year-old male with stage IVB peripheral T-cell lymphoma NOS; diagnosed in November 2010

Previous therapy

1. CHOP × 6 + ASCT (BEAM): December 2010 - May 2011 CR
2. DHAP × 4: March - June 2012 CR

- His most recent relapse occurred in January 2013

Study therapy

- Only 1 infusion received (on cycle 1, day 1); no tumor assessment was made
- Patient discontinued from study treatment due to CTC grade 4 thrombocytopenia caused by progressive bone marrow infiltration (clinical progression)

ASCT (BEAM), autologous stem cell transplantation (carmustine, etoposide, cytarabine, melphalan);
DHAP, dexamethasone, cytarabine, cisplatin

Patient 4: tolerability

Toxicity

- SAEs: influenza
- CTC grade 3 TEAEs: hypertension; anemia; hypokalemia; hypophosphatemia (all drug-related)
- CTC grade 4 TEAEs: hyperuricemia; decreased neutrophil count; decreased platelet count
- CTC grade 5 TEAEs: multiple organ failure

Dose modification

- Not applicable

STUDY SUMMARY

We showed the effects of the use of copanlisib in 4 patients with T-cell lymphoma

- PR in 1 patient with stage IVA peripheral T-cell lymphoma NOS
- CR in 1 patient with stage IVB angioimmunoblastic T-cell lymphoma
- Radiologic PD in 1 patient with peripheral T-cell lymphoma NOS
- Clinical PD (progressive bone marrow infiltration) in 1 patient with stage IVB peripheral T-cell lymphoma NOS

OVERALL CONCLUSIONS

- The novel PI3K inhibitor copanlisib demonstrated encouraging single-agent antitumor activity and an acceptable toxicity profile consistent with toxicities seen in other non-Hodgkin's lymphoma subtypes
- Additional T-cell lymphoma patients are now being enrolled in this trial to further expand and confirm these results