



Fondation du Centre
Pluridisciplinaire d'Oncologie

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ZOOM SAKK 65/08

Indication	Advanced hematologic malignancies (multiple myeloma, acute myeloid leukemia, acute lymphoblastic leukemia, malignant lymphoma)
Title	Phase I trial of nelfinavir and bortezomib in advanced hematologic malignancies
Protocol ID	SAKK 65/08
Phase	Phase I
Sponsor	SAKK (Swiss Group for Clinical Cancer Research)
Local Principal Investigator	Dr. J. Bauer
Primary Objective	The objective of the trial is to assess the safety of nelfinavir in combination with bortezomib in patients with advanced hematologic malignancies, to establish the recommended dose for phase II, and to detect signs of activity.
Inclusion/exclusion criteria	<p>Inclusion Criteria include the following :</p> <ul style="list-style-type: none"> ○ Patient must give written informed consent before registration. ○ The trial includes patients with hematologic malignancies (restricted to the entities detailed below), whose disease has either relapsed following, or progressed through, standard therapy; and where standard intensive therapy is not feasible, or who have a current disease state for which there is no standard effective therapy; or who have refused standard therapy in cases where no curative option exists. <p>Patients with the following disease entities may be included in the trial:</p> <ul style="list-style-type: none"> · multiple myeloma: after having received at least two lines of prior chemotherapy (induction chemotherapy followed by high dose chemotherapy and autologous stem cell transplant ± maintenance therapy is considered one line of therapy) · acute myeloid leukemia, acute lymphoblastic leukemia · malignant lymphoma: <ul style="list-style-type: none"> - diffuse large B cell lymphoma - Hodgkin lymphoma - mantle cell lymphoma - mature T- and NK-cell neoplasms, restricted to the following WHO-defined entities: T-cell prolymphocytic leukemia, T-cell large granular lymphocytic leukemia, aggressive NK cell leukemia, adult T-cell leukemia/lymphoma, extranodal NK/T cell lymphoma (nasal type), mycosis fungoides, Sézary syndrome, primary CD30 positive T-cell lymphoproliferative disorders, primary cutaneous anaplastic large cell lymphoma, primary cutaneous gamma-delta T-cell lymphoma, peripheral T-cell lymphoma NOS, angioimmunoblastic T-cell lymphoma,

anaplastic large cell lymphoma (ALK positive/ALK negative)
- follicular lymphoma (grade 3B)

- WHO performance status ≤ 2
- Life expectancy ≥ 3 months
- Age ≥ 18 years.
- Women are not breastfeeding. Women with child-bearing potential are using effective contraception, are not pregnant, and agree not to become pregnant during participation in the trial and during the 12 months thereafter. A negative pregnancy test before inclusion into the trial is required for all women with child-bearing potential.
- Men agree not to father a child during participation in the trial or during the 12 months thereafter.
- Patient demonstrates willingness and capability to comply with an oral regimen.
- Patient has capability to understand information given by the investigator on the trial.
- Patient adherence and geographic proximity allow proper staging, treatment, and followup.
- Measurable disease defined as:
 - for myeloma: measurable serum monoclonal protein >1 g/dL for IgG, or >0.5 g/dL for IgA, IgM or IgD, or difference between involved and uninvolved free light chain levels in serum is >100 mg/L
 - for lymphoma: presence of at least one lesion measurable by CT (longest diameter minimum 15 mm)
 - for acute leukemia: at least 20% blasts in bone marrow or in peripheral blood (minimum of at least 200/mL blasts in peripheral blood)
- Adequate hematological values:
 1. Patients with **acute leukemia** must have:
 - platelets $>50 \times 10^9/L$
 - hemoglobin >80 g/L (may be achieved by transfusion)
 2. All other patients must have:
 - a) in case **no bone marrow impairment** due to the underlying malignancy is known:
 - absolute neutrophils $>1.5 \times 10^9/L$
 - platelets $>75 \times 10^9/L$
 - hemoglobin >80 g/L (may be achieved by transfusion)
 - b) in case of known **bone marrow involvement**:
 - absolute neutrophils $>0.5 \times 10^9/L$. In addition, for neutrophils $<1.0 \times 10^9/L$: no decline by $>0.5 \times 10^9/L$ during 7 days prior to registration (e.g. from $1.2 \times 10^9/L$ to $0.6 \times 10^9/L$ not allowed)
 - platelets $>50 \times 10^9/L$
 - hemoglobin >80 g/L (may be achieved by transfusion)
- Adequate hepatic function: total bilirubin $\leq 1.5 \times ULN$ (for patients with suspected hemolysis: direct bilirubin $\leq 1.5 \times ULN$), ALT $\leq 2.5 \times ULN$

- Adequate renal function: calculated creatinine clearance >30 mL/min, according to the formula of Cockcroft-Gault

Exclusion criteria include the following :

- Previous non-hematologic malignancy within 5 years with the exception of adequately treated cervical carcinoma in situ or localized non-melanoma skin cancer.
- More than 4 prior lines of chemotherapeutic regimens (induction chemotherapy followed by high dose chemotherapy and autologous stem cell transplant ± maintenance therapy is considered one line of therapy).
- Any concurrent antineoplastic therapy with chemotherapeutic or biologic agents or radiation therapy.
- Chemotherapy or biologic agents received in the last 30 days prior to entering the trial, with one exception: in patients with acute leukemia, hydroxyurea may be given up to 48h before first administration of the trial treatment, and low dose AraC (up to 20 mg/m²) and mitoxantrone up to 20 mg up to 14 days before first dosing.
- Treatment in a clinical trial within 30 days prior to trial entry.
- Concurrent treatment with other experimental drugs.
- Known chronic hepatitis B or C, known HIV infection. HIV-associated lymphoma.
- Any serious underlying medical condition (at the judgment of the investigator) which impairs the ability of the patient to participate in the trial (e.g. active autoimmune disease, uncontrolled diabetes, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, psychiatric disorder).
- Myocardial infarction in the last six months prior to enrollment.
- Polyneuropathy > grade 1 significantly interfering with activities of daily living, or painful polyneuropathy.
- Patients who are on the following CYP3A4 modulators and cannot replace these medications with other equivalent medications at least one week before the first dose of trial drug and for the period of the trial: antiarrhythmics (amiodarone, quinidine), neuroleptics (pimozide), sedative/hypnotic agents (midazolam, triazolam), ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), HMG-CoA reductase inhibitors (lovastatin, simvastatin, atorvastatin), rifampicin, rifabutin, felodipine, nifedipine, HIV protease inhibitors (amprenavir, saquinavir, indinavir, ritonavir); cannabinoids, cimetidine, clarithromycin, clotrimazole, cyclosporin, delavirdine, diltiazem, ethinylestradiol, erythromycin, fluconazole, fluoxetine, fluvoxamine, itraconazole, ketoconazole, metronidazole, miconazole, nefazodone, nifedipine, norfloxacin, propafol, quinine, sertraline, troleandomycin, verapamil, zafirlukast, carbamazepine, ethosuximide, glutethimide, nevirapine,

	<p>phenobarbital, phenytoin, primidone, St. John's Wort, sulfadimidine, sulfipyrazone, troglitazone, troleandomycin, bergamottin (constituent of grapefruit juice), Echinacea.</p> <ul style="list-style-type: none">○ Known hypersensitivity to trial drugs or hypersensitivity to any other component of the trial drugs.
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