Dual Targeted Therapy with the AKT Inhibitor Perifosine and the Multikinase Inhibitor Sorafenib in Patients with Relapsed/Refractory Lymphomas: Final Results of a Phase II Trial


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Background

- Significant proportions of high-risk NHL (20 – 30%), and relapsed HL (50 – 60%) are not cured with currently available therapeutic strategies
- Perifosine (Eisma Zentaris GmbH, Germany) is an AKT inhibitor with clinical activity in a variety of solid tumors
- Sorafenib (Nexavar, Bayer) is an oral multikinase inhibitor with clinical activity in a variety of cancers
- Perifosine and Sorafenib targets pathways which are activated in a substantial proportion of NHL and HL
- Preclinical data show that the combination of Perifosine and Sorafenib results in a synergistic antilymphoma activity

Objectives of the Study

- Primary - Objective response rate
- Secondary - Safety and tolerability; TTP, PFS, OS
- Evaluation of predictive and prognostic biomarkers

Inclusion Criteria

- Patients for whom no other treatment options are available
- At least one lesion measurable by CT-scan or MRI
- ECOG Performance Status of 0 or 1
- Adequate bone marrow, liver and renal function
- Written informed consent

Exclusion Criteria

- Active bacterial or myocytic infections
- Anticancer CT or RT within 4 weeks of study entry
- Investigational drug therapy within 4 weeks of study entry
- Clinically significant cardiovascular disease

Treatment Plan

- Perifosine (50 mg BID, PO) n = 40
- Sorafenib (400 mg BID, PO) n = 40
- Perifosine (50 mg BID, PO) + Sorafenib (400 mg BID, PO) n = 24
- Perifosine (50 mg BID, PO) or Sorafenib (400 mg BID, PO) n = 24

Biomarkers Analysis

- Peripheral blood lymphocytes (PBL) collected prior to therapy initiation and monthly during therapy were analyzed for pERK and pAKT expression by flow cytometry
- Unstimulated or phorbol myristate acetate (PMA)-stimulated PBL were fixed with paraformaldehyde, permeabilized with methanol and stained with Alexa Fluor-conjugated Anti-ERK1/2 (pT202/p204) and anti-AKT (pS473) monoclonal antibodies (MoAbs) or the appropriate isotype controls (all from Becton-Dickinson).

Conclusions

- Peri/Sor therapy has a good toxicity profile and is well tolerated by heavily pretreated patients
- Combination therapy has promising anti-lymphoma activity in relapsed/refractory HL
- No response other than SD observed in NHL patients
- Early reduction of pERK and pAKT has a significant predictive value of clinical response

pERK and pAKT Analysis

- A significant correlation between reduction of values of pERK and pAKT during therapy and clinical response was demonstrated by logistic regression model (p<0.003 and p<0.005 for pERK and pAKT)