APO010 sensitivity in relapsed Multiple Myeloma patients

A.J. Vangsted[1], H. Jandu[2], P.B. Jensen[2], M.W. Madsen[2], P. Gimsing[1], T. Jensen[3], A. Hansen[3], A. Rasmussen[2], A. Nielsen[2], U. Buhl[2], N. Brunner[2], B. Pratt[2], U.C. Frølund[4], C. Hellebergs[5], N. Abildgaard[6], S. Knudsen[2]
[1]Haematology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, DK, [2]Oncology, Oncology Venture, Hørsholm, DK, [3]Biology, Medical Prognosis, Scottsdale, AZ, US, [4]Haematology, Roskilde Hospital, Roskilde, DK, [5]Oncology, University Hospital Herlev, Herlev, DK, [6]Haematology, Odense University Hospital, Odense C, DK

Introduction

Multiple Myeloma is the second most common hematological malignancy and represents a continuous medical challenge since all patients eventually progress despite of many new, recently approved drugs. The incidence of Multiple Myeloma is about 6 to 8 out of 100.000 in Western Countries [1]. Given the current lack of lasting therapeutic benefit for Multiple Myeloma patients, there is a need for new and personalized treatment options.
We aim to address this issue by introducing a new immunotherapy drug **(APO010)** in the treatment of Multiple Myeloma combined with an advanced Drug Response Predictor analysis in order to select the patients with the highest likelihood of benefit from APO010 treatment.

Drug Response Predictor (DRP™)

A validated response prediction method is used in the evaluation of prediction of sensitivity to APO010. As shown in Fig. 1, the method is based on in vitro sensitivity data and cell line microarray results in a model that also incorporates clinical variables. The DRP™ Biomarker profiles have previously been developed for a number of other drugs [2].

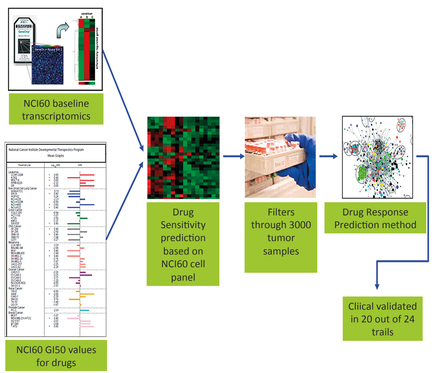

Figure 1: The principle behind the drug response prediction method Drug Response Predictor

APO010

APO010 is a completely new immuno-oncology drug. It is the first-in-class of a recombinant form of **FAS-ligand** which mimics cytotoxic T-lymphocyte (CTL) signaling to induce cancer cell apoptosis. The CTLs bind to the cancer cell via the Fas ligand to a receptor (CD95) on the tumor cell. APO010 is synthesized as a mega FasL consisting of six FasL and mimics a CTL that binds to the cancer cells hence inducing apoptosis.
This unique and differentiated cytotoxic mechanism of action has the potential of being a breakthrough immunotherapy product in Multiple Myeloma as these cells express **CD95** (FAS-receptor).

OPM-2 model of Multiple Myeloma

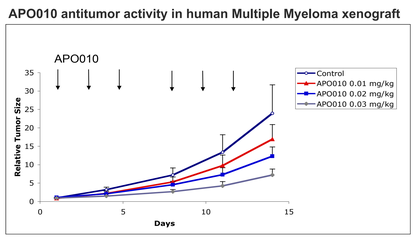

Figure 2. Dose-dependent reduction of s.c. tumor growth

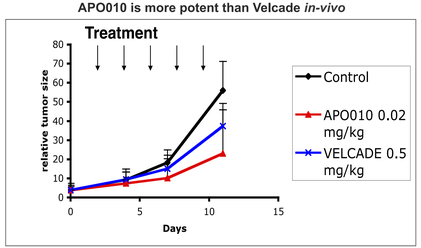

Figure 3. Dose-dependent reduction of s.c. tumor growth

Methods

APO010 response predictor **(APO010-DRP™)**, is based on gene expression clusters obtained by comparing associations between gene expression profiles and growth inhibition by APO010 in a panel of cell lines. A second step has included filtering the identified gene expression profile against mRNA expression from a collection of 3200 human tumors, thereby making a predictive profile for APO010 responsiveness (Fig.1). We have initiated screening relapsed/ refractory Multiple Myeloma patients by isolating CD138 positive myeloma cells from the bone marrow and applying APO010-DRP™ in order to select the patients with the highest likelihood of benefit from APO010 treatment.

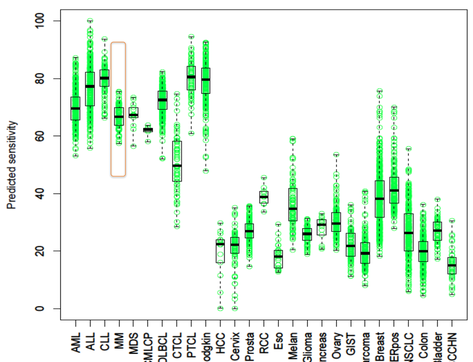

Table 1: Each green circle represents the predicted APO010 sensitivity of a Multiple Myeloma patient
The predictions are normalized to a scale of 0-100 for all 3522 patients in this plot

APO010 was tested in 25 patients with solid tumors in a phase 1 study (NCT00437736).The drug was well tolerated.
Pre-clinical studies (Fig2,3) have revealed that APO010 is highly efficient in Multiple Myeloma. Therefore, a phase 1b trial will be conducted in patients with Multiple Myeloma that have been pre-screened for sensitivity using the APO010 DRP(TM) technology

Phase 1b study in Multiple Myeloma

The study will be a phase 1b, open label, dose escalation study to investigate the tolerability and efficacy of APO010 in patients with relapsed Multiple Myeloma selected by APO010-DRP™. It will multi-center study at hematology departments in Denmark.

The screening is being done through **Oncology Venture** and will identify 15 Multiple Myeloma patients most likely to benefit from treatment with APO010. These patients will then be enrolled in a multi-center Phase 1b trial, which is planned to begin in early 2017.

Patient selection criteria

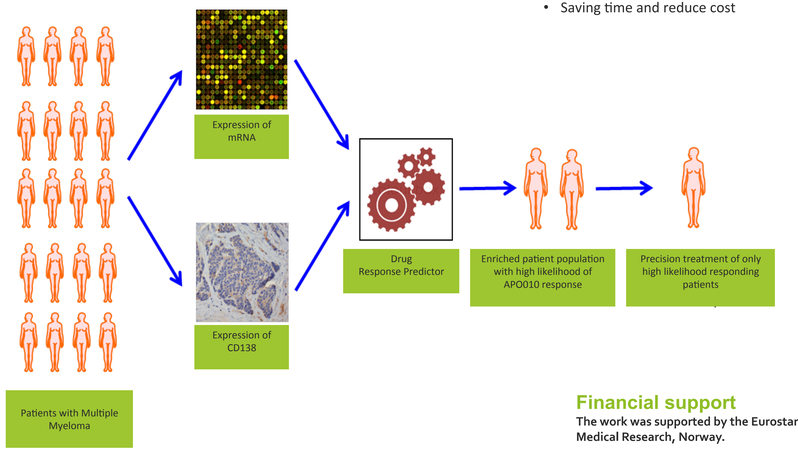

Figure 4. Strategy for inclusion of biomarker positive patients in the Phase 1b study

Conclusions

Combining APO010 with DRP™ analysis will add a precision medicine element to immuno-oncology treatment of Multiple Myeloma. This will enable us to identify patients with high likelihood of response and thereby facilitate focused future trial design and patient recruitment to achieve clinical success.

Expected achievements

- Introducing immunotherapy in the treatment of Multiple Myeloma
- The use of DRP will ensure higher response rate
- Saving time and reduce cost

Financial support

The work was supported by the Eurostars grant and Smerud Medical Research, Norway.

References

[1] Kyle R.A. & Rajkumar S.V. Blood,2008; 111:2962-72
[2] Wang W et al J Natl Cancer Inst;2013;105:1284–1291.

Corresponding author: haj@oncologyventure.com.