A TWO STAGE PROSPECTIVE CLINICAL TRIAL WITH IROFULVEN TREATMENT TARGETING A SELECTED SUBGROUP OF CASTRATION-AND DOCETAXEL RESISTANT PROSTATE CANCER PATIENTS

Steen Knudsen1, Thomas Jensen1, Anker Hansen1, Ulla Buhl2, Annie Rasmussen1,2, Bruce Pratt3, Arun Asaithambi3, James G Cullem2, Nils Brünner2,4 and Peter Buhl Jensen1,2.

ABSTRACT

IROFULVEN, a DNA damaging semi-synthetic analog of illudin S (phytoalexin from Omphalotus illudens, jack-o’-lantern mushroom) which in the body is activated by prostaglandin reductase, has shown promising clinical activity in a range of cancer forms but the objective response rates were too low to justify further clinical development.

Of particular interest is that irofulven may not be a substitute of the mdr-1 drug efflux pump and therefore potentially active in prostate cancer patients with acquired resistance to docetaxel. We have now developed an irofulven responsive predictor which is based on gene expression data by comparing associations between gene expression profiles and growth inhibition in a panel of cell lines treated with irofulven.

A second step has included filtering the identified gene expression profile against mRNA expression from a collection of 3000 human tumors. Only genes being differentially expressed in the primary clinical tumor material were retained in the model. A total of 205 mRNAs were selected for the final irofulven responsive profile. The profile can be converted to a single score of predicted irofulven responsiveness.

We are now initiating a prospective clinical trial (Simon’s two stage design) in selected patients with castration- and docetaxel resistant prostate cancer and with a favorable irofulven responsive profile. We are screening 600 prostate cancer samples (FFPE tissue) in order to select the 10% of patients with”.

INTRODUCTION

Oncology Venture A/S is developing the promising phase II cytotoxic drug candidate irofulven. Irofulven technology (DRP®) is designed to identify patients likely to respond to specific anticancer agents. The predictive irofulven companion diagnostic is derived from the Drug Response Predictor (DRP®) Platform of Medical Prognosis Institute (MPI). Previous substantial clinical investigation of irofulven by US biotech company MGX Pharmas and pharmaceutical companies led to objective responses in subsets of patients, including for a range of hard to treat cancers, such as prostate, colorectal and pancreatic cancer. However, a lack of understanding of response mechanisms led to small several overall response rates (Fig. A) in phase I/II clinical trials conducted at the MPI Drug Response Predictor Platform. Oncology Venture has now identified the genetic signature associated with irofulven’s response to irofulven, and has secured rights to the drug for focused development in patient populations with a high likelihood of response. Oncology Venture is currently enrolling patients, and will soon commence a focused phase I trial of irofulven in likely patients) respondents with hormone refractory prostate cancer (HRPC) as the next step toward the commercialization of irofulven as an precision therapy for a range of hard to treat cancers.

OPPORTUNITY

Key attributes of the opportunity include:

• An expansive irofulven data and regulatory dossier, spanning 1300 patients for >17 cancer types, preclinical characterisation and 38 clinical trials (19 published)(Figure 1A)

• A TWO STAGE PROSPECTIVE CLINICAL TRIAL WITH IROFULVEN TREATMENT TARGETING A SELECTED SUBGROUP OF CASTRATION-AND DOCETAXEL RESISTANT PROSTATE CANCER PATIENTS

• Predictive DNA adducts, leading to 5 phase cell-cycle arrest, independent only by the transcriptional coupled repair (TCR) pathway

• Inhibits RNA polymerase II, an essential enzyme of the TCR pathway

• Inhibits topoisomerase I

• Inhibits the RNA polymerase II, an essential enzyme of the TCR pathway

• Leverages the proven capability of the MPI DRP® Platform to objectively respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy.