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ABSTRACT

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

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ABSTRACT

IROFULVEN, a DNA damaging semi-synthetic analog of Illudin S (phytotoxin from Omphalotus illudins, 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 substrate of the mdr-1 drug efflux pump and thereby 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 3200 human tumors. Only genes being differentially expressed in the clinical tumor material were retained in the model. A total of 205 mRNA's 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 the highest likelihood of benefit from irofulven treatment. Primary end-points are objective response rate and changes in serum PSA.

INTRODUCTION

Oncology Venture ApS is developing the promising phase II cytotoxic drug candidate irofulven, together with a companion diagnostic technology (Irofulven DRP®) to identify patients highly likely to respond to irofulven therapy. The Irofulven DRP® 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 MGI Pharma and pharmaceutical company Eisai led to objective responses in subsets of patients, including for a range of hard to treat cancers; such as prostate, ovarian, liver and pancreatic cancer. However, a lack of understanding of response biomarkers led to small overall response rates and failure to achieve suitable efficacy endpoints. Utilising the DRP® Platform, Oncology Venture has now identified the genetic signatures associated with likely response to irofulven, and has secured rights to the drug for focused development in patient populations with a very high likelihood of response. Oncology Venture is currently recruiting patients, and will soon commence a focused phase II trial of irofulven in likely patient responders with hormone refractory prostate cancer (HRPC) as the next step towards the commercialisation of irofulven as a precision therapy for a range of hard to treat cancers.

OPPORTUNITY

Key attributes of the opportunity includes:

- An expansive irofulven data and regulatory dossier, spanning preclinical characterisation and 38 clinical trials (19 published) in 1300 patients for >17 cancer types,
- The Irofulven DRP® companion diagnostic to stratify likely responder patients, facilitating focused trial design and patient recruitment to achieve clinical success,
- Addressing significant unmet medical need in patients with refractory cancers for which irofulven is highly likely to be efficacious,
- Enduring intellectual property coverage (>20+yrs) through strategic patent filings claiming the use of irofulven in combination with the Irofulven DRP® companion diagnostic, together with US FDA Orange Book exclusivity,
- Leveraging the proven capability of the MPI DRP® Platform to identify likely responder patients, validated in 26 clinical trials to date.

DETAIL

A pro-drug, irofulven requires catalysis by prostaglandin reductase 1 to become active[1].

Discovered at the University of California, San Diego, irofulven was exclusively licensed to US biotech company MGI Pharma, which was acquired by Eisai in 2007. Lantern Pharma licensed irofulven from Eisai in 2015, and subsequently sub-licensed irofulven to Oncology Venture to access the Irofulven DRP® companion diagnostic for investigation in likely responder patients.

Irofulven treatment leads to three primary anti-tumour mechanisms of action [2,3]:

- Produces DNA adducts, leading to S phase cell cycle arrest, repairable only by the transcriptional coupled repair (TCR) pathway,
- Inhibits the RNA polymerase II, an essential enzyme of the TCR pathway,
- Inhibits topoisomerase 1;

Irofulven is more active *in vitro* against tumour cells of epithelial origin and is more resistant than other alkylating agents to deactivation by p53 loss and MDR1[4]. Irofulven exhibits impressive anti-cancer results in xenograft models *in vivo* [5–7], and has demonstrated activity against cell lines that are resistant to other therapies[8,9]. Irofulven has significant scope for combination with other therapies, including standard chemotherapeutic regimes.

Irofulven has been studied in 38 clinical trials (19 published)(Figure 1A) between 1995 and 2007, for which it has demonstrated promising single agent activity in a range of indications, including HRPC, ovarian, liver and pancreatic cancer, and clinical activity in combination treatments targeting HRPC, colorectal and tyroid cancers[10,11]. For example, Irofulven demonstrated:

- a 10% response rate in prostate cancer patients pre-treated with docetaxel[12],
- a 13% response rate in ovarian cancer patients relapsing between 6 and 12 months after standard treatment with carboplatin and paclitaxel[3].

Whilst these clinical responses indicate activity, a lack of knowledge about response biomarkers led to uninformed recruitment of trial participants, and resulted in a failure to achieve required clinical efficacy endpoints. The Irofulven DRP® has now idenfied genetic signatures associated with likely response to irofulven, optimally positioning Oncology Venture to select patients for focused clinical trials to achieve objective response rates required for regulatory approval.

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Organ/Cancer	#pts.	# trials (# pts in largest trial)
CRPC	273	8 (134)
Pancreas	168	6 (100)
Ovary	141	7 (74)
Colon	90	7 (26)
Lung (NSCLC)	59	4 (36)
Sarcoma, various	58	4 (30)
Liver	52	4 (38)
Kidney	47	5 (20)
Breast	40	3 (32)
Glioma	>35	1 (>33)
Endometrium	29	3 (25)
Thyroid	27	2 (23)
Gastric CA	23	1 (23)
Melanoma	21	2 (16)
Leukemia/MDS	20	1 (20)
Cervix	>12	1 (>12)
Solid tumour nos / others	200	11

Fig. A

CANCER TYPE	PATIENTS	DRUGS	PATENTS	PATIENTS (SEC) ENDPOINT	P VALUE
ALL	161	Methotrexate	Issued	WBC count	0.008*
AML	13	Belinostat+idarub.	Issued	ORR	0.02*
AML	88	7 combinations	Issued	CR	0.02*
AML	53	decitabine	Issued	ORR	0.01*
AML	79	HAM	Issued	CR	0.45
Breast	136	tamoxifen	Issued	DMFS	0.03*
Breast	102	16 combinations	Issued	DMFS	0.006*
Breast	244	11 combinations	Issued	pCR	8e-12*
Breast	125	TET/FEC	Issued	pCR	0.007*
Breast	268	tamoxifen	issued	RFS	0.03*
Breast	24	docetaxel	Issued	pCR	0.02*
Breast	44	Fulvestrant	Pending	CR	0.01*
Breast	24	cisplatin	Issued	Miller-Payne	0.02*
Breast	114	epirubicin	Pending	pCR (DMFS)	0.9 (0.03)
Breast	19	Anastrozole	Pending	ORR	0.9
Breast	61	Xeloda + docetaxel	Issued	pCR	0.14
Colon	40	FOLFIRI	Issued	ORR	0.04*
Colon	17	FOLFOX	Issued	ORR	0.015*
Colon, metastatic	20	FOLFIRI	Issued	ORR	0.15
Colon, metastatic	80	cetuximab	Issued	OS	0.24
Colon, stage III adj	307	5-FU	Issued	RFS (OS)	8e-06*
Colon, stage I-IV	232	5-FU	Issued	RFS (OS)	0.0005*
Colon, unresectable	83	FOLFOX	Issued	ORR	0.18
DLBCL	166	CHOP	Issued	CR (OS)	0.007*
DLBCL	414	(R)-CHOP	Issued	OS	1e-15*
DLBCL (miRNA)	116	R-CHOP/CHOEP	Issued	CR	0.03*
Hodgkin	130	ABVD	Issued	CR	0.003*
Myeloma	84	VAD	Issued	CR	0.004*
Myeloma	169	bortezomib	Issued	ORR	0.008*
NSCLC	21	Tarceva (erlotinib)	Pending	PFS	0.02*
NSCLC	50	cisplatin	Issued	OS	0.03*
Ovarian	63	cisplatin	Issued	OS	0.047*

Fig. C

Fig. B

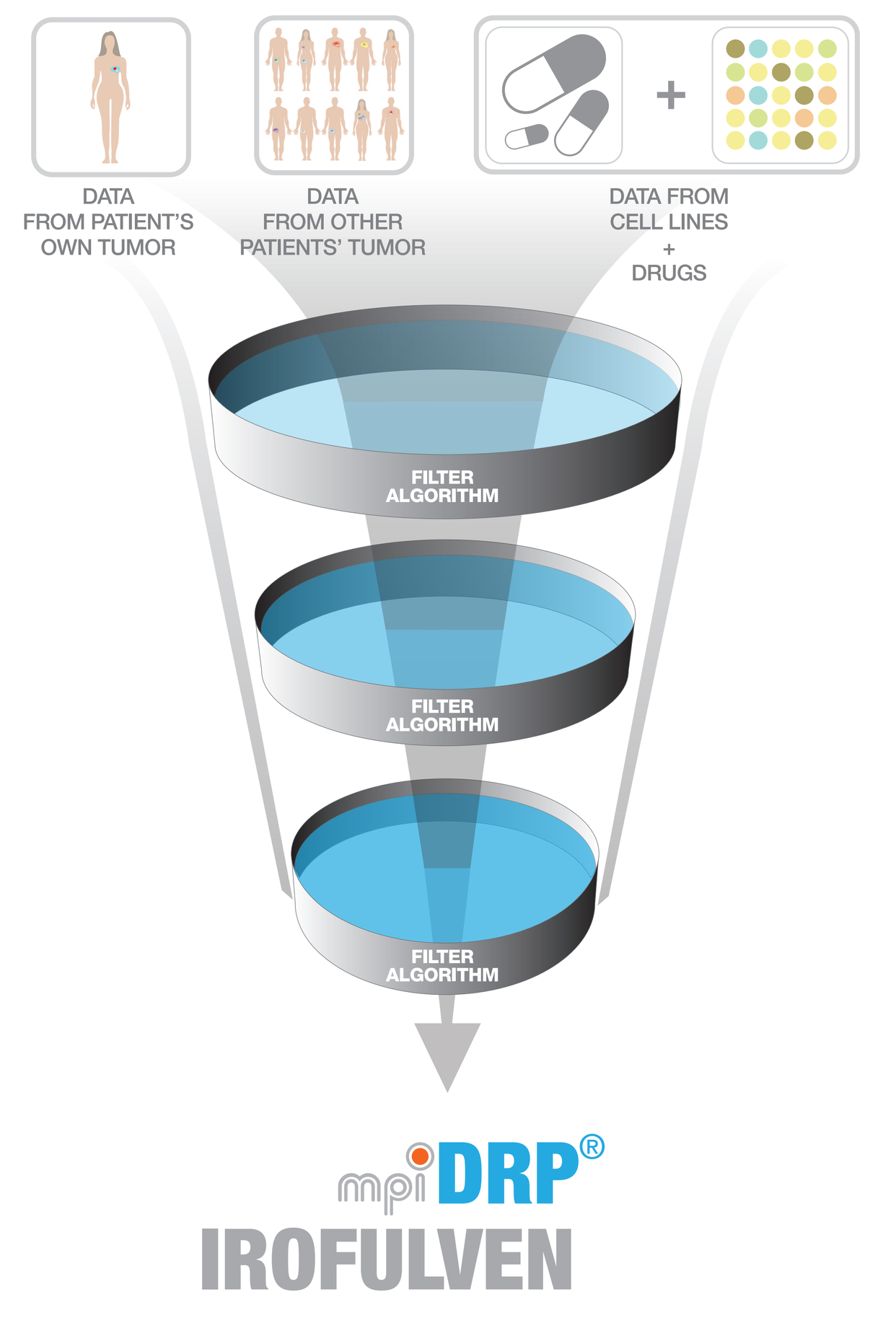
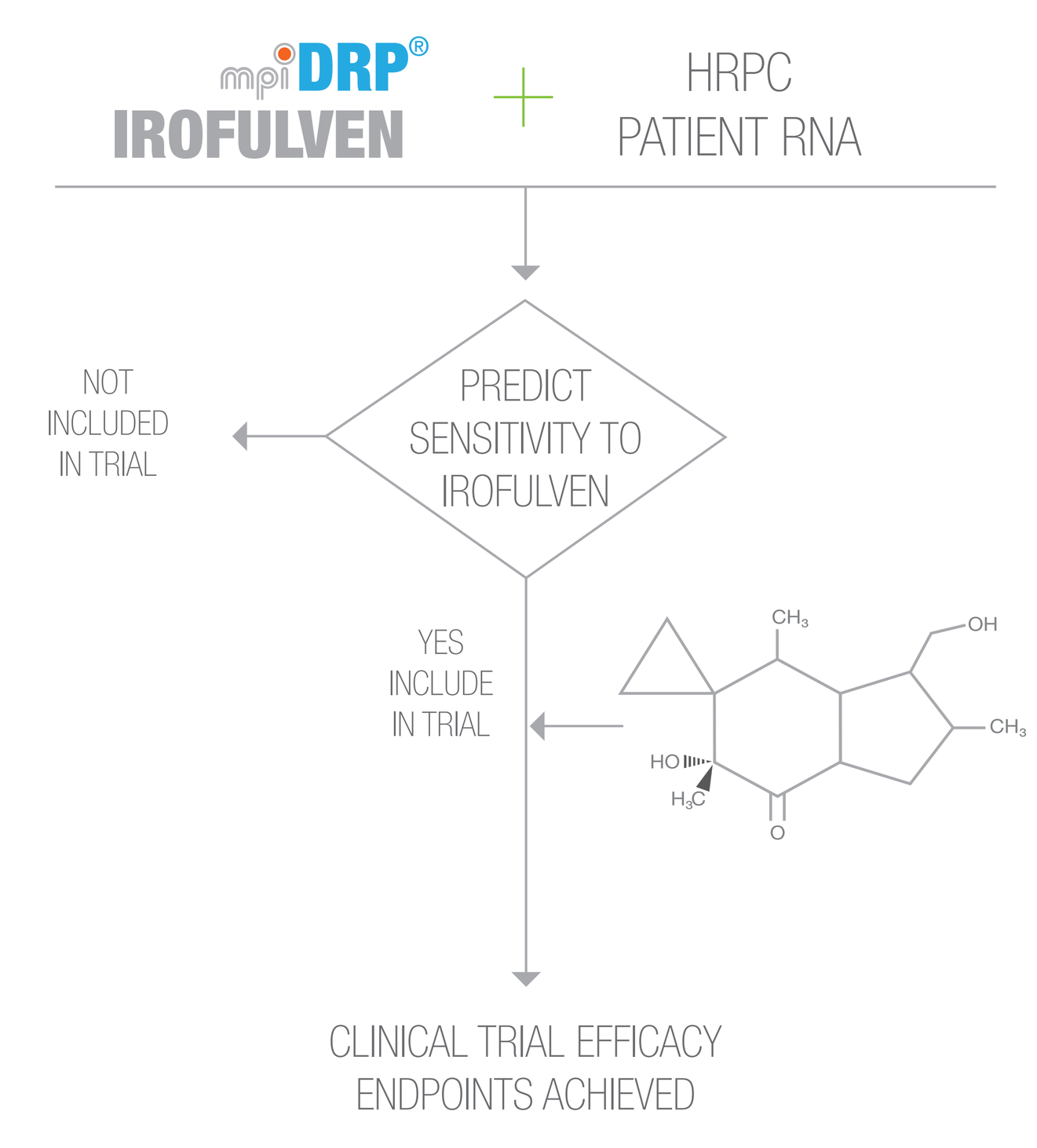


Fig. D



DRUG RESPONSE PREDICTION

Oncology Venture has an exclusive license to MPI's DRP® Platform and the Irofulven DRP® companion diagnostic for the development and commercialisation of irofulven. The DRP® Platform (Fig. B) comprises an undisclosed proprietary systems biology and big-data algorithm that inputs publicly available transcriptomics data from the NCI-60 panel of tumour cell lines and genomics data from >3,000 patient biopsies, to identify tumour-derived genetic signatures that are highly likely responders to a given anticancer product.

The DRP® Platform also allows for identification of tumour types that have the highest fractions of responders. A DRP® companion diagnostic designed and validated for a particular drug candidate can be applied to identify likely responders in any cancer type. DRP® technology has been validated as a powerful diagnostic tool for a diverse range of oncology drugs (including cytotoxic and targeted), providing a statistically significant prediction of clinical outcomes from drug treatment in cancer patients in 26 of 32 clinical studies (Fig. C).

(Fig. A) Irofulven has been investigated in 38 clinical trials, including 1300 patients, >2200 cycles and 6200 doses; (Fig. B) The DRP® Platform incorporates a proprietary systems biology and big-data algorithm that inputs publicly available transcriptomics data from the NCI-60 panel of tumour cell lines and genomics data from >3,000 patient biopsies to interrogate individual patient tumour data to predict likelihood of drug response; (Fig. C) The DRP® Platform has been validated by successfully predicting patient response for a broad range of oncology drugs, P values represent statistically significant prediction of patient response; (Fig. D) Oncology Venture will achieve clinical trial efficacy endopoints by pre-screening prospective HRPC patients with the Irofulven DRP® companion diagnostic to selectively recruit patients with a high likelihood of response.

The DRP® platform has been externally validated and published in collaboration with leading statisticians at the MD Anderson Cancer Center[13], other academic partners[14,15] and industry, for example with AstraZeneca in the study of breast cancer patient response to Fulvestrant[16]. Companies that have publically disclosed licenses to the DRP® Platform for their internal drug candidate development include LiPlasome Pharma ApS (LiPlaCis®, pI/II metastatic breast cancer) and Nemucore Medical Innovations (NMI-900, pII ovarian cancer; NMI-8000, pI ovarian cancer / solid tumours).

CLINICAL STRATEGY

Oncology Venture will utilise the Irofulven DRP® companion diagnostic to initally focus irofulven clinical development on likely responder patients with HRPC. Based on MPI's experience with the DRP® Platform and existing evidence of clinical activity in certain patients (Fig. 1A), the risk of not achieving regulatory endpoints is regarded as low.

Hormone Refractory Prostate Cancer
150 HRPC patients will be screened using the Irofulven DRP® companion diagnostic to identify a minimum of 15 patients that have a very high likelihood of responding to Irofulven treatment (Fig. D). The clinical trial will be run at two sites in Denmark during 2016, with the goal of demonstrating a significant increase in the irofulven objective response rate to at least 30%. Clinical endpoints will be based on the tumour response rate, progression free survival and prostate-specific antigen (PSA) level.

Subsequent clinical investigations may include larger studies aimed at regulatory approval with advanced patients, and/or focus on establishing irofulven as a frontline HRPC therapy. The DRP® Platform also allows for stratification of patients that are likely to respond to irofulven and unlikely to respond to the standard of care (e.g., docetaxel for frontline HRPC therapy[17]), thus allowing the design of clinical trials to secure frontline regulatory approval.

Other indications
Once clinically validated, the Irofulven DRP® will be applicable to predicting likely responders in all cancer types. This will position irofulven for clinical investigation in a range of other cancer indications for which it previously demonstated promise (Fig. A), including ovarian cancer and hepatic cell carcinoma.

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