ONCOLOGY RESEARCH INTERNATIONAL LIMITED

NEWSLETTER

September 2015

Overview

Until mid-2014 ORIL's research and development efforts were directed to the optimisation of the lead candidate ORIL007, characterisation and understanding of the unique properties of the ORIL compounds, including the novel mode of action of inducing apoptosis (cell death), and developing a reliable source of supply through patented process of synthesis and scale-up. All these have been achieved.

Formulation efforts were directed toward the development of injectable formulations with variable success. Recognising the technical challenges associated with the injectable delivery system, R&D efforts in the past 12 months expanded to other drug delivery systems including topical and oral which are progressing well. While the cumulative scientific evidence supports that ORIL007 is safe and non-toxic, the most recent *in vivo* tests of injecting the ORIL007 compound directly into the tumour (intratumoral route) showed no efficacy.

The company has therefore decided to refocus its efforts and resources to revisit the co-administration of ORIL compounds with other anti-cancer agents where earlier *in vivo* tests showed added or better than added efficacy – an application for which ORIL holds patents in major jurisdictions (See Table 1). Work is still continuing on parenteral, oral and topical formulations

Given the recent results, clinical trials will be now deferred until more key pre-clinical data are available, with the topical (dermal) trial with TRI expected to take 9-10 months to produce results. The overall strategy can be summarized in the following key areas:

1. Work will still continue in all delivery systems of injectable (for other than solid tumours), oral, topical (and novel) formulations and in other key product pipeline areas to utilize the ORIL platform technology.

2. ORIL007 as a co-administrative anti-cancer therapy, i.e. using ORIL007 as an adjunct to other anti-cancer agents. This includes work with existing therapies as well as the investigation and evaluation of external "new" technology to complement the ORIL mode of action. To this end ORIL executives will visit Biopharm America in Boston, USA later in September to review and assess new opportunities.

3. Application of anti-angiogenic properties of ORIL007 in other (cancer-related) therapeutic applications to utilize the patents granted in major jurisdictions.

4. Application of ORIL007 in other therapeutic areas. The synthesis patent application for ORIL compounds, including ORIL007, was recently granted in Australia and is undergoing National Phase Entry in major jurisdictions. The Plant Master File for "pharmaceutical grade" ORIL007 is ready for submission to the relevant regulatory authorities when

required. This is commercially significant as it provides surety of supply of the lead candidate ORIL007.

Summary of recent scientific results:

Parenteral

A recent study to investigate the delivery of ORIL007 directly into the (solid) tumour in three cancer types showed no tumour reduction. Although a disappointing result which has effectively ended the likelihood of a successful application of ORIL007 as a single agent to solid tumours, it allows the company to focus its activities on other delivery systems and programs that have a greater likelihood of success. Development work will continue on a restricted basis.

Topical

Previous *ex vivo* test data using human skin show the ORIL007 drug penetrates the epidermis and the dermis at significant levels. The recent UK study using radiolabelled ^{3}H-ORIL007 (pig) skin structure has also shown, as expected, that the drug is not transported across the skin into the bloodstream, but does penetrate the epidermis and through to the dermis.

Oral

Testing in animals to determine the pharmacokinetic profile (how much and to what extent is the drug absorbed) of two prototypes relative to an intravenous injection, has been completed. Around 1% of ORIL007 was absorbed into the bloodstream. This is in line with other anti-cancer drugs which are therapeutically effective despite low oral bioavailability. Development work continues.

Product Pipeline

The company strategy includes building its product pipeline by the application of its platform technology to cancer-related diseases and other conditions, for example those in which angiogenesis plays a role and which are covered in the ORIL patent. Such conditions include psoriasis, diabetic retinopathy, and others that remain confidential. Background investigations and discussions with CROs to design *in vitro* and *in vivo* studies to support additional "proof-of-concept" stage have commenced.

IP Portfolio

Table 1 Status of the ORIL family of patents.

Title (Family)	Patent Application No.	Status
Methods and compositions for promoting activity of anti-cancer therapies	PCT/AU2007/001091	Granted in Australia, China, Europe, Eurasia, Mexico, Taiwan and Japan Under examination/pending in Brazil, India, USA, Canada
Methods and compositions for inhibiting angiogenesis	PCT/AU2007/001092	Granted in Australia, China, Europe, Eurasia, Taiwan, Canada, Japan, Mexico Under examination/pending in Brazil, India, USA
Improved synthesis of a class of steroid saponins	PCT/AU2013/000416	National Phase Entry November 2014. Granted in Australia, Aust Patent 2013204005
Polymorph (ORIL007)	PCT/AU2013/000417	PCT filed in April 2013, National Phase Entry June 2015. Accepted in Australia