IMUGENE
Developing Cancer Immunotherapies

ASX Announcement

FDA clears Imugene IND to commence onCARlytics first-in-class clinical study

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SYDNEY, Australia, 19 May 2023: Imugene Limited (ASX:IMU), a clinical stage immuno-oncology company, is pleased to announce it has received US Food and Drug Administration (FDA) Investigational New Drug (IND) clearance to initiate a Phase 1 clinical study of its oncolytic virotherapy candidate, onCARlytics (on-CAR-19, CF33-CD19, HOV4).

The FDA clearance of the IND allows Imugene to start patient recruitment and dosing in a first-in-class Phase 1 clinical study for the onCARlytics platform in patients with solid tumours: "A Phase I, Dose Escalation and Dose Expansion, Safety and Tolerability Study of onCARlytics (CF33-CD19), Administered Intravenously or Intratumorally in Combination with Blinatumomab in Adults with Advanced or Metastatic Solid Tumors (OASIS)."

Imugene's CF33-CD19 oncolytic virus, when combined with the CD19 targeting bispecific monoclonal antibody blinatumomab (Blincyto®), has the potential to target and eradicate solid tumours that otherwise cannot be treated with Blincyto® therapy alone.

Imugene MD & CEO Leslie Chong said "Imugene receiving this IND clearance for onCARlytics from the FDA is a crucial step forward. The start of our onCARlytics study, which is first-in-class, is a significant milestone for clinicians treating patients faced with the challenge of solid tumour cancers, which to date have been untreatable with CD19-targeting biological drugs. Accomplishing this goal speaks to the perseverance and dedication of Imugene's and City of Hope's research and development teams as we continue to build on our clinical and commercial potential."

For more information please contact:

Leslie Chong
Managing Director and Chief Executive Officer
info@imugene.com

Investor Enquiries
shareholderenquiries@imugene.com

Media Enquiries
Matt Wright
matt@nwrcommunications.com.au

Follow us on Twitter and Instagram @TeamImugene
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About the onCARlytics Study

CF33-CD19 (onCARlytics, HOV4) is a live, attenuated oncolytic orthopox (vaccinia) virus engineered to encode a truncated human CD19 (Cluster of Differentiation 19) transgene, resulting in expression of de novo CD19 at the tumour cell surface before virus-mediated tumour cell lysis. It is being developed for the treatment of advanced or metastatic solid tumours, to be used in combination with a CD19 targeting agent. In a first-in-human (FIH) study in adult patients with advanced or metastatic solid tumours, Imugene aims to evaluate the safety and efficacy of two routes of administration of CF33-CD19, intratumoral (IT) injection and intravenous (IV) infusion, either alone or in combination with blinatumomab (a bispecific CD19-directed CD3 T-cell engager [BiTE] specific to CD19 and CD3). The study is designed as a Phase 1, dose escalating study to be conducted in the United States.

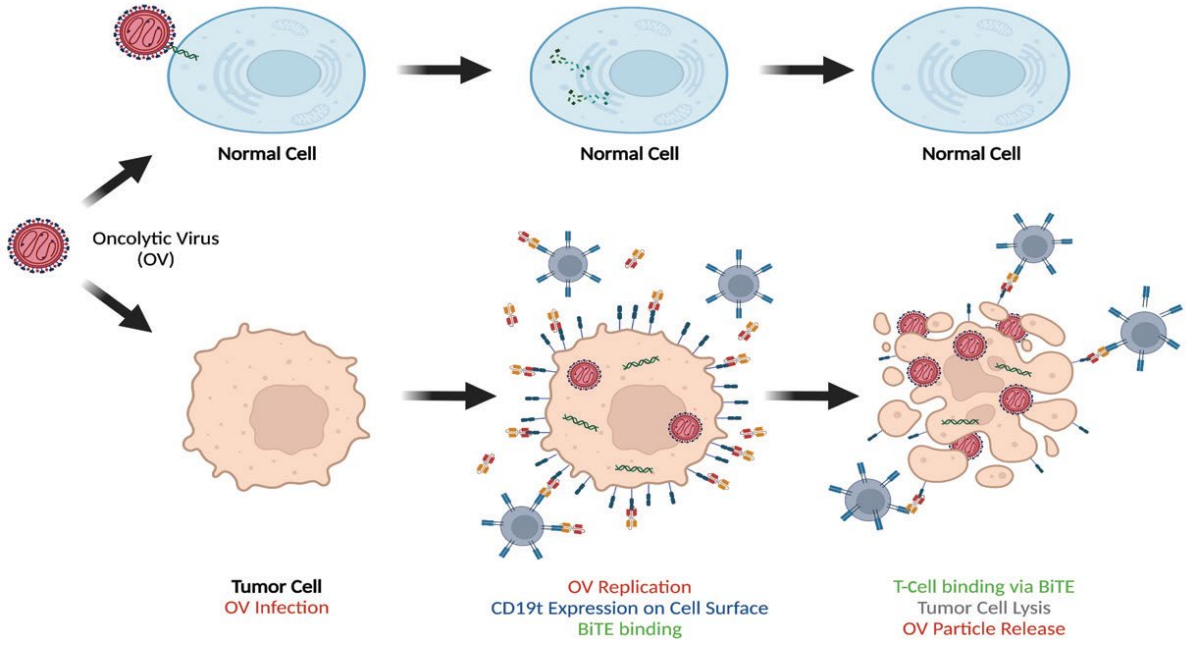
The cell surface expression of CD19 enables targeting of tumour types that do not endogenously express CD19 to be targeted by CD19-CAR T or anti-CD19 specific antibody therapies (Park et al., 2020). CF33-CD19, with its parental strain CF33 and various derivatives of the parental strain, have been extensively characterized in vitro and in vivo (Warner et al., 2019, Park et al., 2020) and have demonstrated:

- effective expression of truncated CD19 on the cell surface;
- robust anti-cancer activity in vitro and in vivo against human colon and breast cancer cells via direct cell lysis including the release of virions that can infect and lyse neighbouring cells;

- release of pathogen-associated molecular patterns (PAMS) and damage-associated molecular patterns (DAMS) inducing immunogenic cell death; and
- ability to change tumour microenvironment (TME) and recruit CD8+ lymphocytes and IFNγ+ to induce a tumour-specific immune response.

The parenteral virus CF33, which provides the backbone for CF33-CD19 and other derivatives, has been shown clinically to have an acceptable safety and tolerability profile; no DLTs have been documented to date in ongoing clinical trials. CF33-CD19 has been engineered to selectively infect and drive tumour-specific expression of a CD-19 targetable tumour antigen (a truncated non-signalling variant of CD19). Providing tumour cells with a target for anti-CD19 therapy allows for subsequent T-cell binding and ultimately tumour lysis (Figure 1).

Figure 1: CF33-CD19 Selectively Infects and Drives Tumour-Specific Expression of CD19



Park A, Fong Y, Kim SI, Yang M, Murad JP, Lu J, et al. Effective combination immunotherapy using oncolytic viruses to deliver CAR targets to solid tumors. Sci Transl Med. 2020 Sep 2;12(559).

Warner SG, et al. A Novel Chimeric Poxvirus Encoding CD19 is Tumor-Tropic, Imageable, and Synergistic with Radioiodine to Sustain Colon Cancer, Regression. Mol Ther. 2019;13(6):82-92.

About the CF33 Oncolytic Virus Platform

Oncolytic virotherapy is an emerging, novel therapeutic approach for solid tumours that selectively replicates in and destroys tumour cells while leaving normal cells undamaged.

CF33 is a "chimeric poxvirus" derived through recombination among multiple strains of vaccinia virus strains, that has been engineered to be far superior to a virus based on a single strain. CF33 efficiently shrinks injected tumours and distant non-injected tumours in human triple negative breast cancer, colon, ovarian, lung, pancreatic and liver cancer models in mice. This was demonstrated without adverse effects at a dose that is 2-5 orders of magnitude lower than doses used for oncolytic viruses under current clinical testing. As well as being able to shrink multiple types of cancers at an extremely low dose, CF33 importantly also shrinks non-injected distant tumours (abscopal effect).

Imugene is developing three forms of CF33, all of which contain an identical genetic sequence resulting in equal tumour targeting and killing potential.

CF33 is a modern-day cancer fighting soldier specifically trained to target and destroy tumour cells with precision. CF33 is armed with "specialised weapons" that either help detect the tumour (via marking the tumour with a target flag) or assist the immune system to complete the elimination of the tumour. The scientific term is to insert a "transgene" into CF33, which provides the soldier with instructions to generate and use the weapons.

VAXINIA / CF33-hNIS

VAXINIA is being used for the ongoing MAST clinical study where CF33 is treating patients with metastatic solid tumours of various types. The hNIS ("human sodium iodide symporter") transgene provides instructions for displaying a flag on the tumour cell which attracts radioactive molecules such as its natural ligand iodine used in imaging of tumours. It provides the ability to see in real time where the CF33 virus is and therefore where the tumour is. This is an extremely powerful weapon not only to detect the tumour, but also converts CF33 into a synergistic radiotherapy drug.

CHECKvacc / CF33-hNIS-anti-PDL1

CHECKvacc also adds a precision weapon that, when released by the virus after infecting the tumour, releases the brakes on the localised immune response generated within the tumour microenvironment. This additional weapon, an immune checkpoint inhibitor, enables CHECKvacc to kill tumours systematically and comprehensively in multiple ways. Imugene is currently testing CHECKvacc in the very hard to treat triple negative breast cancer.

On-CAR-19 / onCARlytics / CF33-CD19

Imugene is developing a new weapon to eradicate tumours that has never been seen nor utilised in the fight against cancer. Still based on the same tumour targeting CF33, on-

CAR-19 adds a weapon which creates a paradigm shift in the war against solid tumours. Cell therapies such as chimeric antigen receptor T-cell therapy (CAR T) have resulted in cures for the first time in liquid or blood tumours such as lymphoma. These liquid tumour weapons target a flag on the liquid tumour cells called CD19. This flag is specific for liquid tumours only and isn't found on solid tumours, which represent 90% of all tumour types. Until now, these modern weapons that have been so successful in curing liquid tumours, have been useless in the fight against solid tumours. Imugene's new CF33 platform onCARlytics changes this. While CF33 is the same efficient tumour infecting and killing machine, adding the CD19 flag transgene to the CF33 soldiers' weaponry completely changes the fight against all cancer types by flagging the solid tumour cells with CD19 for eradication.

About Imugene (ASX:IMU)

Imugene is a clinical stage immuno-oncology company developing a range of new and novel immunotherapies that seek to activate the immune system of cancer patients to treat and eradicate tumours. Our unique platform technologies seek to harness the body's immune system against tumours, potentially achieving a similar or greater effect than synthetically manufactured monoclonal antibody and other immunotherapies. Our product pipeline includes multiple immunotherapy B-cell vaccine candidates and an oncolytic virotherapy (CF33) aimed at treating a variety of cancers in combination with standard of care drugs and emerging immunotherapies such as CAR T's for solid tumours. We are supported by a leading team of international cancer experts with extensive experience in developing new cancer therapies with many approved for sale and marketing for global markets.

Our vision is to help transform and improve the treatment of cancer and the lives of the millions of patients who need effective treatments. This vision is backed by a growing body of clinical evidence and peer-reviewed research. Imugene is well funded and resourced, to deliver on its commercial and clinical milestones. Together with leading specialists and medical professionals, we believe Imugene's immuno-oncology therapies will become foundation treatments for cancer. Our goal is to ensure that Imugene and its shareholders are at the forefront of this rapidly growing global market.

Release authorised by the Managing Director and Chief Executive Officer