IMMUNE CHECKPOINT INHIBITOR EFFECTIVENESS SIGNIFICANTLY IMPROVED WHEN USED IN COMBINATION WITH INV043

Highlights:

- **Combination therapy of INV043 and immune checkpoint inhibitors ("ICI") shown to be more effective compared to standalone ICI therapy, resulting in ~65% reduction of tumour size in mice**
- **Despite widespread clinical use as a monotherapy, ICI's effectiveness is typically limited to a smaller proportion of the cancer patient population**
- **Results provide compelling rationale for use of INV043 in combination with ICI therapies**
- **Expands partnership opportunities to collaborate on combination therapies and develop new IP to extend patent life of ICI's**
- **Global ICI market forecast to grow at 16.8% CAGR to reach US$141 billion by 2030[1]**
- **Opens a potential additional pathway for Invion to commercialise INV043**

MELBOURNE (AUSTRALIA) 30 May 2022: Invion Limited (ASX: IVX) ("**Invion**" or the "**Company**") is pleased to announce the findings from the third Proof-of-Concept (PoC) study undertaken by its research partner, Hudson Institute of Medical Research (**Hudson Institute**).

The PoC was specifically designed to evaluate whether INV043 can be used in combination with immune checkpoint inhibition targeting PD-1 to improve outcomes in mice with triple negative breast cancer (TNBC).

Unlike previous PoC studies, administration was restricted to a small portion of the tumour to specifically probe the combination approach and immune-mediated changes following therapy in an animal model.

The results showed that the combination of INV043 with anti-PD-1:

- Led to a circa 65% reduction in tumour size in mice treated with the combination therapy
- Achieved clear tumour stabilisation and regression despite the restricted treatment protocol
- Tumours were also significantly smaller than those in mice that received monotherapy

Dr Andrew Stephens, Research Group Head, Ovarian Cancer Biomarkers at Hudson Institute commented: "As INV043 induces both direct cell death in the tumour microenvironment as well as the release of tumour neoantigens, we hypothesised that INV043 would combine with checkpoint inhibition to enhance the anti-tumour efficacy compared to either monotherapy alone."

Significance of the results

The results provide compelling rationales for the use of INV043 in combination with ICI.

Firstly, ICI therapies have limited effectiveness against several cancer types as a monotherapy despite its widespread clinical use[2]. Combining INV043 with ICI could enhance clinical

[1] https://www.alliedmarketresearch.com/immune-check-point-inhibitors-market

[2] Adel Naimi et al, (2022). Tumor immunotherapies by immune checkpoint inhibitors (ICIs); the pros and cons: Cell Communication and Signaling

response in "cold" tumours (a tumour that is unlikely to trigger a strong immune response) like TNBC.

Further, this opens up partnership possibilities as INV043 may provide potential for pharmaceutical companies with ICI drugs to improve clinical outcomes, develop new intellectual property, and extend the patent life of their ICI therapies[3].

The global ICI market is estimated to be worth US$29.8 billion in 2020 and is forecast to grow at a 16.8% compound annual growth rate (CAGR) to US$141 billion by 2030[1].

"These findings demonstrate the potential of INV043, in combination with immunotherapies like immune checkpoint inhibitors, to both improve patient outcomes and broaden its potential applications," said Invion's Executive Chairman and Chief Executive Officer, Thian Chew.

"Opportunities for strategic collaboration may also provide avenues to develop new combined IP and open up additional pathways to commercialise the Photosoft™ technology."

Details of the study

The mice were separated into eight groups with four mice in each group. Treatment groups included mice treated with single therapy anti-PD-1 or restricted PDT alone; or the combination of both. Controls included no treatment; INV043 (without activation) alone; laser alone (without INV043 drug); an antibody isotype control; and PDT plus antibody isotype control.

Statistical significance between groups was calculated using one-way ANOVA with Tukey's multiple comparisons test. A P value of <0.05 was considered significant (although it should be noted that with such small sample size, the P value should be considered representative only).

Further details of the tests and results are outlined in the presentation attached to the end of this announcement.

This announcement was approved for release by Thian Chew, Chairman of the Board.

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About Invion

Invion is a life-science company that is leading the global research and development of the Photosoft™ technology for the treatment of a range of cancers, atherosclerosis and infectious diseases. Invion holds the exclusive Australia and New Zealand license rights and exclusive distribution rights to Asia Pacific excluding China (other than Hong Kong, which is included in the Territory), Macau, Taiwan, Japan and South Korea to the Photosoft™ technology for all cancer indications. It also holds the exclusive rights to the technology in Asia Pacific (excluding Greater China) for atherosclerosis and infectious diseases. Research and clinical cancer trials

[3] https://www.fiercepharma.com/special-report/top-15-blockbuster-patent-expirations-coming-decade

are funded by the technology licensor, RMW Cho Group Limited, via an R&D services agreement with the Company. Invion is listed on the ASX (ASX: IVX).

About Photodynamic Therapy (PDT)

Invion is developing Photosoft™ technology as a novel next generation Photodynamic Therapy (PDT). PDT uses non-toxic photosensitisers and light to selectively kill cancer cells and promote an anti-cancer immune response. Less invasive than surgery and with minimal side effects, PDT offers an alternative treatment option aimed at achieving complete tumour regression and long-lasting remission.

About Hudson Institute of Medical Research

A global bioscience medical research leader, Hudson Institute's sole focus is on powering breakthrough scientific discoveries into improved health care that will transform lives. We strive to improve human health through ground-breaking, collaborative, medical research discoveries and the translation of these to real world impact.

Our scientists research five areas of medical need

- Inflammation
- Reproductive health and pregnancy
- Infant and child health
- Cancer
- Hormones and health

To learn more, please visit: hudson.org.au

FINDINGS:
PROOF OF CONCEPT III

Combination with Immune Checkpoint Inhibitors (ICI)

May 2022

INVION™

PoC III: COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS

ADDITIVE BENEFITS COMBINING INV043 WITH CHECKPOINT INHIBITORS

BACKGROUND

- Previously announced Proof of Concept II, performed on immunocompetent *in vivo* models, demonstrated complete tumour regression in a mouse model of triple negative breast cancer (TNBC) following optimal treatment using INV043.
- Subsequent Proof of Concept work has been focused on characterising the immune response, which will ultimately help in optimising treatment protocols for clinical applications.
- One study conducted evaluated whether INV043-PDT could be used as an immune-stimulatory therapy to enhance immune checkpoint efficacy. It was designed to monitor tumour regression from immune checkpoint inhibitor ("ICI") therapy, and the impact of combining this with INV043 (administered on a restricted basis).

FINDINGS

- There was a clear additive effect when INV043-PDT and immune checkpoint inhibition targeting the PD-1 / PD-L1 axis were combined. This resulted in significantly enhanced tumour regression *in vivo* vs the ICI treatment alone
- Mice treated with combination therapy had ~65% reduction in tumour size at endpoint; and tumours were also significantly smaller than those in mice that received standalone therapy.

CONCLUSION AND NEXT STEPS

- These results provide a compelling rationale for the use of INV043 in combination approaches, to prime the tumour microenvironment and enhance the efficacy of checkpoint inhibition in immunologically "cold" tumours such as TNBC.
- Moreover, the already established applicability of INV043 against multiple cancer types suggests broad clinical relevance for the treatment of established, drug-resistant disease.
- Ongoing data analyses will identify the key features of induced immunity following INV043 treatment, and how these are influenced by the combination with anti PD-1. Specific biomarkers to assess treatment response will also be identified, necessary to guide clinical decision making around treatment protocols as INV043 moves towards clinical trials.

"Making crucial progress in combination therapy with ICI is of paramount importance given that only a small proportion of patients respond to ICI therapy, and many will relapse"[1]

[1]Adel Naimi et al, (2022). *Tumor immunotherapies by immune checkpoint inhibitors (ICIs); the pros and cons*: Cell Communication and Signaling

PoC III: COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS

SUBSTANTIAL RESTRICTION OF TUMOUR GROWTH

BACKGROUND AND APPROACH

- Immune checkpoint inhibition ("ICI"), despite widespread clinical use, has limited objective response as a monotherapy[1].
- We hypothesised the immune-stimulatory nature of INV043 – previously observed to provide protective immunity against tumour re-implantation – could be used to potentiate the efficacy of ICI, particularly where monotherapy is less effective.
- **Purpose of study**
  - To monitor tumour regression following the restricted administration of INV043 (i.e., limiting treatment to a small portion of the tumour).
  - To determine whether the combination of PDT using INV043 with anti-PD-1 antibody has an additive effect to restrict tumour growth and improve overall survival.
  - To evaluate whether INV043-PDT could be used as an immune-stimulatory therapy to prime the tumour microenvironment and enhance immune checkpoint efficacy.

[1]Whilst immune checkpoint inhibitors are used extensively for the treatment of lung cancers and melanoma, objective response rates are typically between 30-40%[2]. In fact, single-agent monoclonal anti PD-1 therapy in breast cancer only achieves clinical response rates between 12-19%[3], highlighting the immunologically "cold" nature of breast cancers

[2] Vafaei, S. *et al.* Combination therapy with immune checkpoint inhibitors (ICIs); a new frontier. *Cancer cell international* **22**, 2 (2022).

[3] Vonderheide, R.H., Domchek, S.M. & Clark, A.S. Immunotherapy for Breast Cancer: What Are We Missing? *Clinical cancer research : an official journal of the American Association for Cancer Research* **23**, 2640-2646 (2017).

FINDINGS

A combination of INV043 with anti PD-1 substantially enhanced restriction of tumour growth, with clear tumour regression despite the sub-optimal INV043 treatment protocol used.

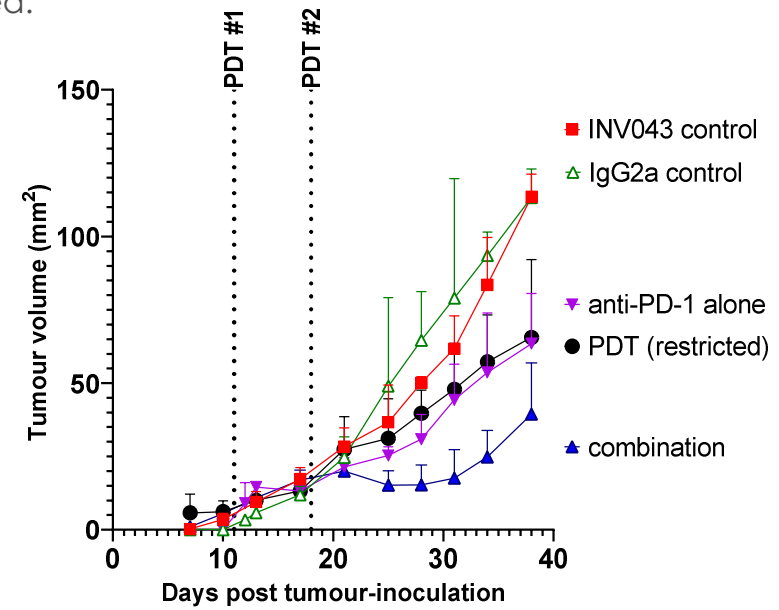

Figure 1. INV043-PDT combines with immune checkpoint inhibition to regress and stabilise tumour mass. Mice with established 4T1 breast tumours were treated using a restricted administration INV043 PDT protocol and/or anti PD-1 antibody over a 14 day period. Tumour size was monitored until endpoint (tumour size ≥100mm²). Monotherapies restricted tumour growth by ~40% compared to untreated controls; combination therapy regressed and stabilised tumours and achieved a ~65% reduction in tumour size at endpoint. INV043 control, no light activation; IgG2a control, isotype antibody control; combination, PDT+ anti PD-1. Additional control groups have been omitted for clarity. *mean +/- SD, n=4/group.*

The research activities involving the use of animals were carried out in accordance with relevant guidelines and regulations as well as with appropriate Animal Ethics Committee approval.