Healthcare at a distance

Ben Faircloth and Klaus Boehncke from L.E.K. Consulting examine how telemedicine is globalising healthcare

Eastern promise

Medii co-founder Lynzi Wang talks about the emerging Chinese private patient market

In peak health

We report from the Private Healthcare Summit 2019

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HealthcareMarkets

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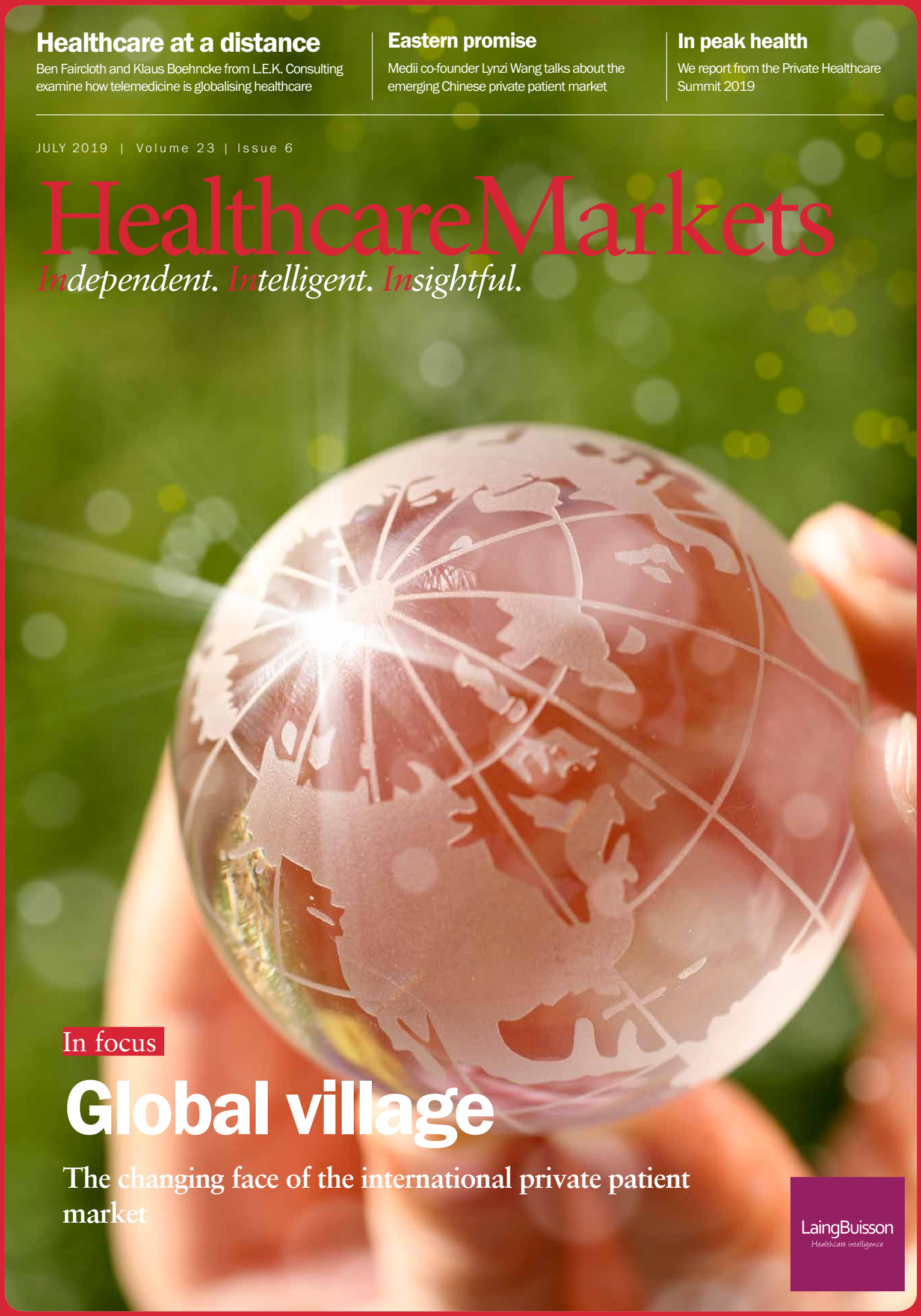


In focus

Global village

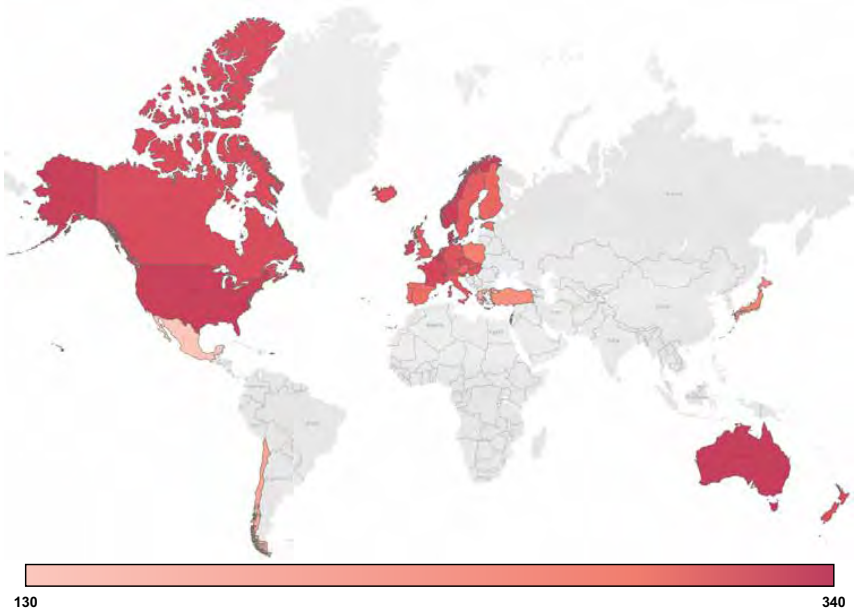
The changing face of the international private patient market

LaingBuisson
Healthcare intelligence

Dr Karen Sayal, oncology doctor and **Dr Michelle Tempest**, Candesic Partner, discuss how the growing market for cancer care, globalisation of care pathways and future treatments are opening up new opportunities for investors to make financial returns and fund life-saving care

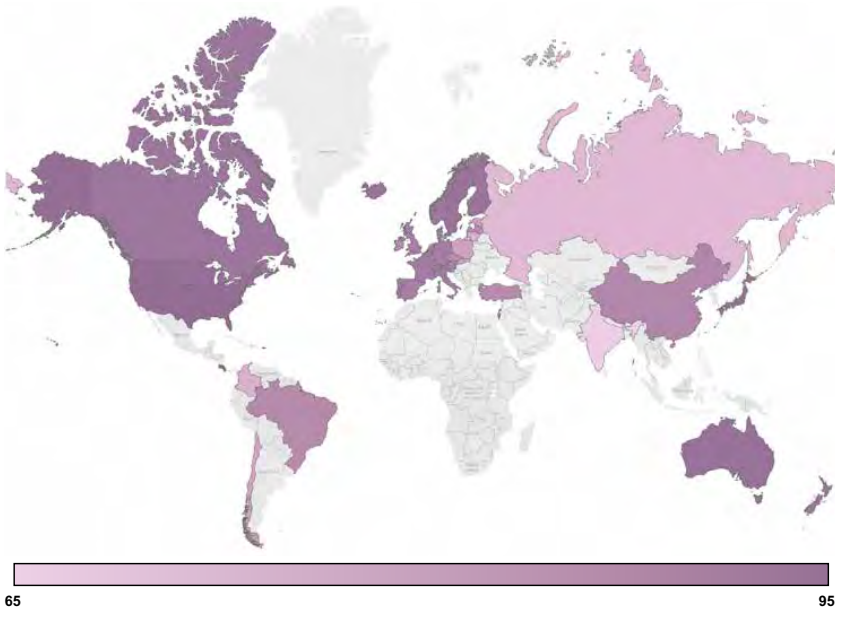
The next generation investing in cancer care

FIGURE ONE A
CANCER INCIDENCE RATES, (SURVIVAL RATES/100,000), 2012



NOTE RELIABLE DATA SOURCE UNAVAILABLE FOR UNSELECTED COUNTRIES; 2012 SELECTED FOR COMPLETENESS OF DATA
SOURCE OECD; CANDESIC RESEARCH AND ANALYSIS

FIGURE ONE B
BREAST CANCER SURVIVAL RATES (%), 2010-14



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SOURCE OECD; CANDESIC RESEARCH AND ANALYSIS

No matter where you are in the world, whatever class, colour or creed: one six letter word - 'cancer' - is a uniting reminder of life's fragility.

Cancer prevalence is increasing globally, but survival rates vary significantly across borders (Figures One A and One B). One thing is clear, clinical cancer protocols and care pathways are developing international standards and the paradigm shift is the introduction of immunotherapy.

Traditionally, cancer treatment has been dominated by cytotoxic agents, treatments which cause lethal DNA damage in cancer cells. However, these treatments do not just kill cancer cells, they also result in collateral damage in normal tissue and thereby cause a broad spectrum of side-effects.

Cancer immunotherapy treatments are more personalised and mechanistically distinct to traditional cytotoxic approaches. It has long been recognised that cancers dampen the immune system of a patient in order to develop and grow. Immunotherapy works by boosting the immune system to recognise and kill cancer. The outcomes observed with immunotherapy are reshaping the cancer therapeutic landscape.

To date, this transformation has been most marked in the treatment of melanoma, a lethal form of skin cancer. Historically, responses with chemotherapy were poor and survival rates in those with metastatic melanoma, where the cancer has spread beyond the skin, were low. A form of immunotherapy called 'checkpoint blockade' is now standard and offers patients the potential for control of disease. Across almost every cancer subtype, immunotherapy is now either in routine clinical use or under investigation in the research setting.

There are 3,394 therapies in the current global development pipeline, 1,287 of which are clinical studies. The implementation of these therapies is being facilitated by a previously unwitnessed

speed of approval by the international regulatory agencies.

The introduction of cancer immunotherapy in these areas of unmet clinical need also represents an area of commercial potential. In a recently published report by *Progressive Markets*, the global market for cancer immunotherapy is expected to rise from $57bn in 2017 to $166bn in 2025.

Therefore, close collaboration and partnership between commercial, academic, clinical and regulatory bodies is essential in the implementation of these therapies.

Opportunities in Cancer Immunotherapy

The current use of cancer immunotherapy is primarily centred on monoclonal antibody based treatment or checkpoint inhibitors. Monoclonal antibodies are large Y-shaped proteins which are engineered to bind to cancer cells.

Once attached to cancer cells, monoclonal antibodies signal for the immune system to destroy them and the cells they are attached to in a process called antibody-dependent cell-mediated cytotoxicity. Trastuzumab (Herceptin) is a monoclonal antibody widely used in the treatment of breast and stomach cancer.

Checkpoint inhibitors work indirectly to activate the immune response. Cancer cells can express a range of proteins to dampen the activity of immune cells. One of the most widely studied set of proteins is the PD-1/PD-L1 axis. By blocking these proteins, the immune system can be activated to kill cancer cells. Pembrolizumab (KeytrudaTM) is a PD-1 inhibitor used in the treatment of melanoma, lung cancer and Hodgkins lymphoma.

In the future, the main areas of growth are likely to arise from:

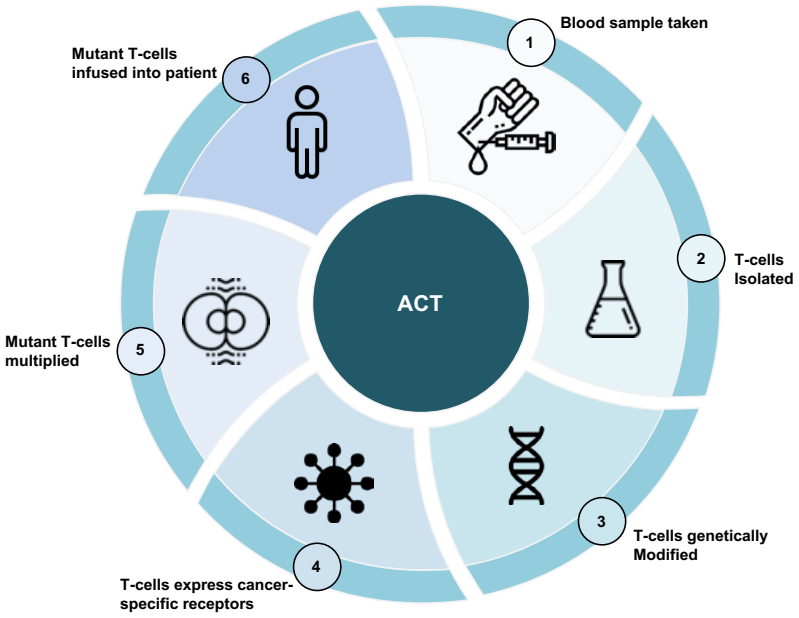
- Novel combinations of check point inhibitors
- Cellular based immunotherapy

Novel checkpoint inhibitors

Cancer cells express a range of surface proteins to mediate suppression of the immune response.

Ongoing research is investigating novel targets for checkpoint inhibition. Targets under investigation include T-cell immunoglobulin and mucin domain 1 and 3 (TIM-1 or TIM-3) and lymphocyte-activa-

FIGURE TWO
BREAST CANCER SURVIVAL RATES, 2010-14



SOURCE CANDESIC RESEARCH AND ANALYSIS

FIGURE THREE
CAR-T MARKET LEADERS

SOURCE CANDESIC RESEARCH AND ANALYSIS

tion gene 3 (LAG-3). These proteins are co-expressed with PD-1 on exhausted T cells. Combined inhibition may then restore T cells to full activity.

Several biotechnology firms have developed promising LAG-3 inhibitors and Bristol-Myers Squibb, Novartis and Boehringer Ingelheim all have products in early clinical development.

There is also promising preclinical data supporting the potential of TIM-1/TIM-3 inhibitors, either as single agent therapy or in combination with existing PD-1/PD-L1 inhibitors.

Curis/Aurigene have exclusive licenses to dual small molecule antagonists of TIM-3 and PD-1. Novartis has developed a novel TIM-3 inhibitor, MBG453, which is in early phase clinical trials for several cancer types.

The commercial potential with checkpoint inhibitors is believed to have an annual growth rate of 14.4%, rising from $14.9bn in 2018 to $29.3bn by 2023. Although, judicious scientific, clinical and commercial validation will be essential to translate such potential into tangible gains.

THE COMMERCIAL POTENTIAL WITH CHECKPOINT INHIBITORS IS BELIEVED TO HAVE AN ANNUAL GROWTH RATE OF 14.4%

Cellular based immunotherapy

Cellular immunotherapy utilises immune cells as a direct form of treatment. The most promising area of cellular immunotherapy is adoptive cell transfer (ACT) (see Figure Two).

ACT involves the isolation of specific immune cell populations from the patient, in a lab setting, manipulation and expansion of the harvested cells followed by re-infusion back into the patient.

Most work to date has focused on the use of genetically modified T cells called CAR T-cells.

CAR T-cell therapy involves taking a blood sample from the patient and isolating the T-cells. Using a disarmed virus, the genetic structure of the T-cell is modified in order to produce Chimeric Antigen Receptors (CARs). CARs are synthetic proteins expressed on the T-cell surface which enable it to recognise and bind antigens (specific proteins) on cancer cells. In the lab, these modified T-cells are expanded hundreds of millions of times and then re-infused into the patient.

In the US, the FDA has approved CAR T-cell therapy in specific settings for haematological cancers. Axicabtagene ciloleucel (YescartaTM) has been approved for diffuse large B-cell lymphoma and tisagenlecleucel (KymriahTM) is now available for a subtype of acute lymphocytic leukaemia (ALL).

According to clinicaltrials.gov, there are 519 ongoing or completed trials exploring

CAR T-cell therapy in a range of cancer types.

The CAR-T market is gaining rapid momentum with a predicted annual growth rate of 46% from 2017 to 2028 and expected to reach $3bn by 2025. At present, the key global players in CAR T-cell therapy are Novartis International, Kite Pharmaceuticals, Juno Therapeutics and Pfizer. In August 2017, Gilead bought Kite Pharmaceuticals for $11.9bn. Likewise, Celgene took over Juno Therapeutics in January 2018 for $9bn.

Investment has also been high in CAR T-cell start-ups with many investors keen to explore the overlap of this technology in regenerative medicine. By the end of 2018, the market capitalisation from CAR T-cell companies amounted to $20bn. (See Figure Three for examples of market leaders).

To date, most innovation has been driven by academic institutions. However, industry interest has grown significantly over the last several years. There are now several R&D collaborations between pharmaceutical companies and academia.

The most notable and successful partnership has been between Novartis and the University of Pennsylvania. KymriahTM, one of the two FDA approved CAR T-cell therapies, resulted out of a five-year collaboration from this partnership. Kite pharmaceuticals, which developed YescartaTM, has a research agreement with the National Cancer Institute (Maryland, USA) to develop ACT-based therapies.

Challenges in cancer immunotherapy

Cancer immunotherapy is unquestionably changing the field of oncology. It is likely that the developments seen in this field will translate into related domains of medicine. However, multiple challenges remain from both the clinical and commercial perspective. Unlike traditional cancer treatments, cancer immunotherapy does not have the same correlation between efficacy and toxicity.

Increasing the dose of treatment will not necessarily result in improved outcomes and there is potential for severe toxicity with single dose or low dose approaches. At present, there is a paucity of predictive biomarker panels to guide patients and clinicians on the benefits and risks of treatment.

Immunotherapy toxicity, when it arises, can result in long-term morbidity, thereby increasing the costs associated with such treatment and creating additional demands on healthcare services.

Cancer immunotherapy is expensive. A one-time dose of YescartaTM costs $373,000 and for KymriahTM is $475,000. Therefore, a high threshold of efficacy will be expected in order to justify such costs.

It is unlikely that state-funded health services will ever be in a position to fund widespread implementation of such therapies, unless pharmaceutical companies offer outcomes based pricing (which is being discussed) which payers can use to do cost of care calculations.

CANCER IMMUNOTHERAPY IS EXPENSIVE... THEREFORE, A HIGH THRESHOLD OF EFFICACY WILL BE EXPECTED IN ORDER TO JUSTIFY SUCH COSTS

Improvements in the R&D process; hypothesis-driven exploration of biological targets; efficiencies in the production streams and better stratification of patients will be required to curtail burgeoning costs.

The largest market lies in the treatment of solid cancers. Solid tumours are particularly challenging from a biological perspective since they are typically surrounded by an immunosuppressive environment. These therapies need to be modified accordingly to account for these additional obstacles.

In the case of CAR T-cell therapy, Juno pharmaceuticals and Novartis are exploring CAR T-cells with additional modifications to boast responses. These therapies are currently in preclinical development.

Conclusion

Cancer immunotherapy is reshaping the international market in oncology so now is the time to invest in this nascent market. The prerequisite to investing in cancer immunotherapy treatment is leveraging a deep clinical expertise to be confident that the therapy works and understanding the route to the internationalised and increasingly personalised care. At the end of the day, the person with the diagnosis of cancer is at the heart of it all. The aim of all those involved is to widen the horizon of effective therapies and safeguard patients from unnecessary risks. This journey has only just started and it will contribute to advancing the cancer care global market.


Dr Karen Sayal


Dr Michelle Tempest, partner, Candesic