NOVOTECH
The Asia Pacific CRO

Accelerating Immunotherapy Clinical Trials in Asia-Pacific

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Contents

Introduction and Executive Summary

Since the first Immuno-Oncology (IO) drug, ofatumumab, was approved in 2010, the clinical development of immunotherapies has accelerated dramatically.

Checkpoint inhibitors (CPIs) and chimeric antigen receptor (CAR) T-cells therapies have become the cornerstone of cancer treatment across a broad variety of haematological and solid tumour indications. Immuno-Oncology drugs stimulate the immune system to eradicate malignant cells. This unique mechanism requires specific considerations when designing clinical trials and selecting sites.

Cancers with high somatic mutations such as melanoma, lung, bladder, stomach or oesophageal cancer are known to be more responsive to immunotherapies. These cancers are highly prevalent in the Asia-Pacific region.

Most Asian countries lack systematic reimbursement of IO standard of care which means clinical trials are often the only channel that patients can access these treatments. This ultimately stimulates recruitment rates and encourages patient adherence to research therapies.

Over 600 sites across Asia-Pacific have been involved in the clinical development of now approved IO drugs, and hundreds more are experienced in managing clinical trials with immunotherapies for both monotherapy and combination therapies. This report aims at highlighting the main considerations for biotechnology companies when planning for IO drug clinical trials, and why Asia-Pacific is a key destination to conduct such trials.

1. Overview and landscape of immunotherapy drugs

The clinical development of immunotherapies has accelerated dramatically over the past few years. Since the first Immuno-Oncology (IO) drug, ipilimumab, was approved in 2011 for the treatment of melanoma, many other drugs have entered clinical trials, with many securing marketing approval. As of December 2019, over 6,000 clinical trials evaluating IO drugs were active globally. About 40% of these clinical trials involved at least one location in the Asia-Pacific region. [1]

Immunotherapy, especially checkpoint inhibitors (CPIs) and chimeric antigen receptor (CAR) T-cells therapies have become the cornerstone of cancer treatment across a broad variety of haematological and solid tumour indications. IO drugs stimulate the immune system to eradicate malignant cells. This specific mechanism leads to generally more durable clinical progress when compared with traditional chemotherapies.[2]

Immunotherapies may have hundreds of potential cellular targets, the most well-known being PD-1 and PD-L1. Immunotherapies can be classified into five main categories regarding their profile:

- Specific mAb
- Cell therapies
- Oncolytic virus
- Vaccines
- Others

Table 1. Major FDA Approved Immunotherapies *(as of December 2019)*

Name	Type
atezolizumab	Checkpoint Inhibitor
avelumab	Checkpoint Inhibitor
axicabtagene ciloleuce	CAR T-Cell Therapy
camrelizumab	Checkpoint Inhibitor
cemiplimab	Checkpoint Inhibitor
durvalumab	Checkpoint Inhibitor
ipilimumab	Checkpoint Inhibitor
nivolumab	Checkpoint Inhibitor
pembrolizumab	Checkpoint Inhibitor
sintilimab	Checkpoint Inhibitor
toripalimab	Checkpoint Inhibitor
tisagenlecleucel	CAR T-Cell Therapy

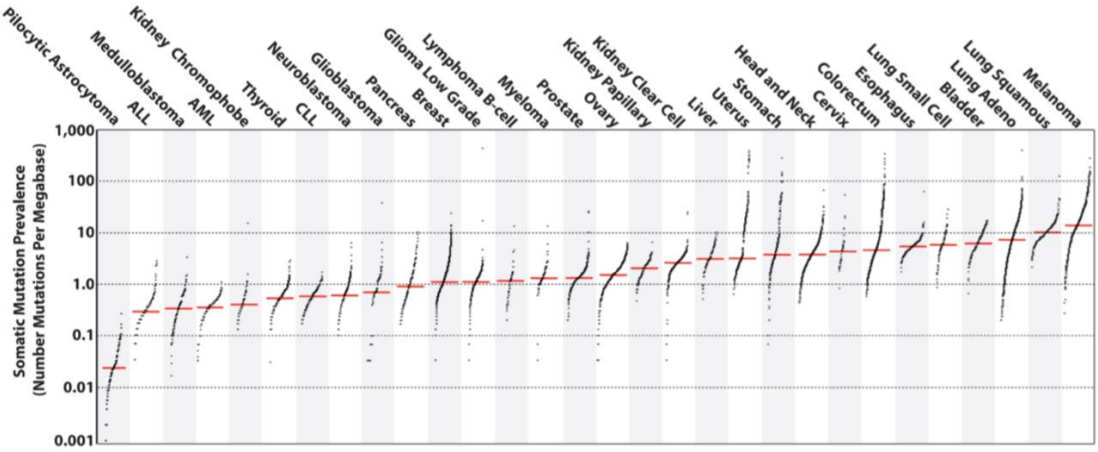
When it comes to immunotherapies, the use and understanding of biomarkers is critical. Numerous IO therapies failed in clinical development because of poor biomarker-based patient stratification. For each indication and for each patient, the interaction between the immune system, cancer cells and therapy unique. It has been shown that tumours with high mutation burden (or high somatic mutation prevalence) are more responsive to immunotherapies. The cancers with the highest levels of these mutations are melanoma, lung, bladder, stomach and oesophagal cancer, all of which are highly prevalent in the Asia-Pacific region.

The implication for biotechnology companies is the need to partner with central laboratories with the ability to adapt to the specific requirements of IO drug trials. Central laboratories must support sponsors' biomarker development from both a strategic standpoint but also from an operational aspect. Central laboratories in the Asia-Pacific have this ability.

[1] GlobalData

[2] Kaufman, H.L., Atkins, M.B., Subedi, P. et al. The promise of Immuno-oncology: implications for defining the value of cancer treatment. j. immunotherapy cancer 7, 129 (2019) doi:10.1186/s40425-019-0594-0

Figure 1. Prevalence of somatic mutations across various cancer types
(Alexandrov et al 2013)



2. Consideration for clinical trials

Immunotherapies have unique pharmacokinetic properties and clinical effect. This results in very specific treatment length, durability of response as well as side effects when compared with traditional chemotherapy. While adverse events remain infrequent, immune checkpoint inhibitors for example can be associated with inflammatory adverse events while CAR T-cell therapies can be linked to cytokine release syndrome, neutropenia and neurological disorders. Adverse events can appear long after the therapy was administered, so it is critical the sites involved are experienced in using these therapies. Patients should be aware of these pharmacokinetic properties, and the site must have a well-trained medical team with a structured lab and testing plan in place.

The bottom line for sponsors looking at entering the clinic with an IO drug candidate, is that clinical trial designs and protocols need to consider this uniqueness when planning dose escalation schemes. Given IO drugs are usually slower to act, the maximum tolerated dose is hard to evaluate, and patient follow-up needs to be adapted accordingly. Some other considerations for biotechnology sponsors when planning to enter the clinic for their IO drug candidate include:

- Sites should have experience in IO trials and more specifically regarding the management of adverse events such as cytokine release syndrome management.
- Biomarker assessment vendors and capabilities.
- Patient profile and prior immunotherapeutic treatment.
- Genetically modified products require additional considerations such as institutional biosafety committee (IBC) review.
- Determine the tool(s) which will be used to define and measure adverse events. A variety of tools exist such as CTCAE, ASBMT, as well as other GVHD Criteria evaluation tools such as MAGIC, IBMTR, Modified Glucksberg criteria.
- The primary endpoint of overall survival is not always the best endpoint due to the large number of patients who usually need to be enrolled.

3. Site experience in the Asia-Pacific region

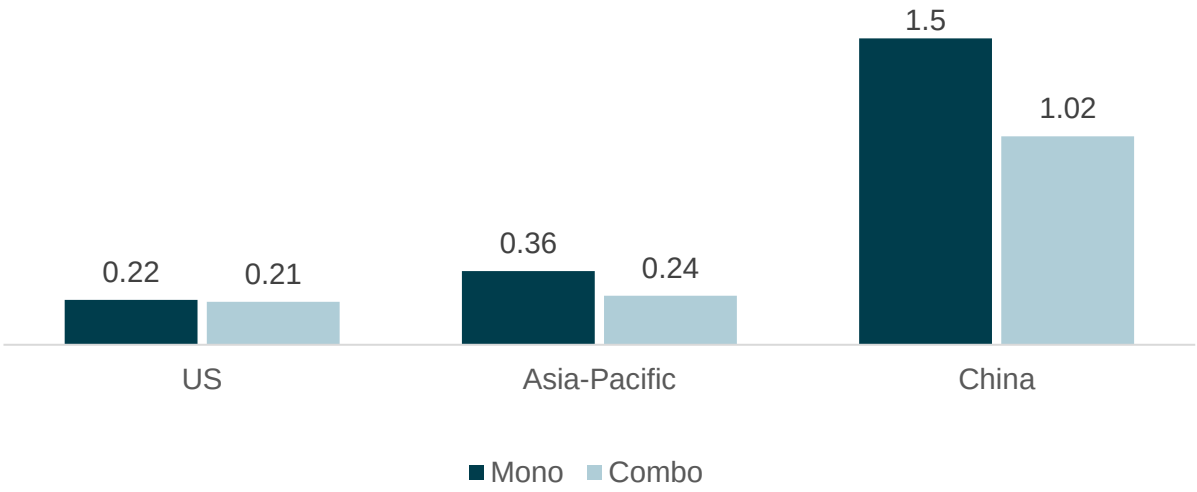
Many sites across Asia-Pacific have developed a strong track-record in managing clinical trials with immunotherapies. Countries such as China, Australia and South Korea are the main locations for these trials with 205, 189 and 76 sites respectively that have been involved in trials for FDA approved Immunotherapies. (Source GlobalData).

Sites involved in immunotherapy clinical studies need specific expertise and experience.
For cellular therapies, the FACT-JACIE standards have been established as requirements set by international teams of world-renowned experts vested in the improvement and progress of cellular therapy. Sites and organizations can voluntarily seek inspection and accreditation for hematopoietic cellular therapy and for cord blood banking. At the time this report was issued, there were 290 FACT accredited institutions globally, 20 of which are in the Asia-Pacific region (in Australia, New Zealand, Hong Kong, Taiwan, India and Singapore).

Asia, with its large treatment-naïve population pool and low trial concentration has become a preferred destination for clinical trials for immunotherapies in particular. IO drug clinical studies conducted in Asia-Pacific showed a rate of recruitment up to +60% and +15% faster than in the US for mono and combo therapies respectively.
China has over 4 million new cancer cases each year, and the patient recruitment rate in China is materially higher than in the US for both monotherapy and combination therapy studies. [3]

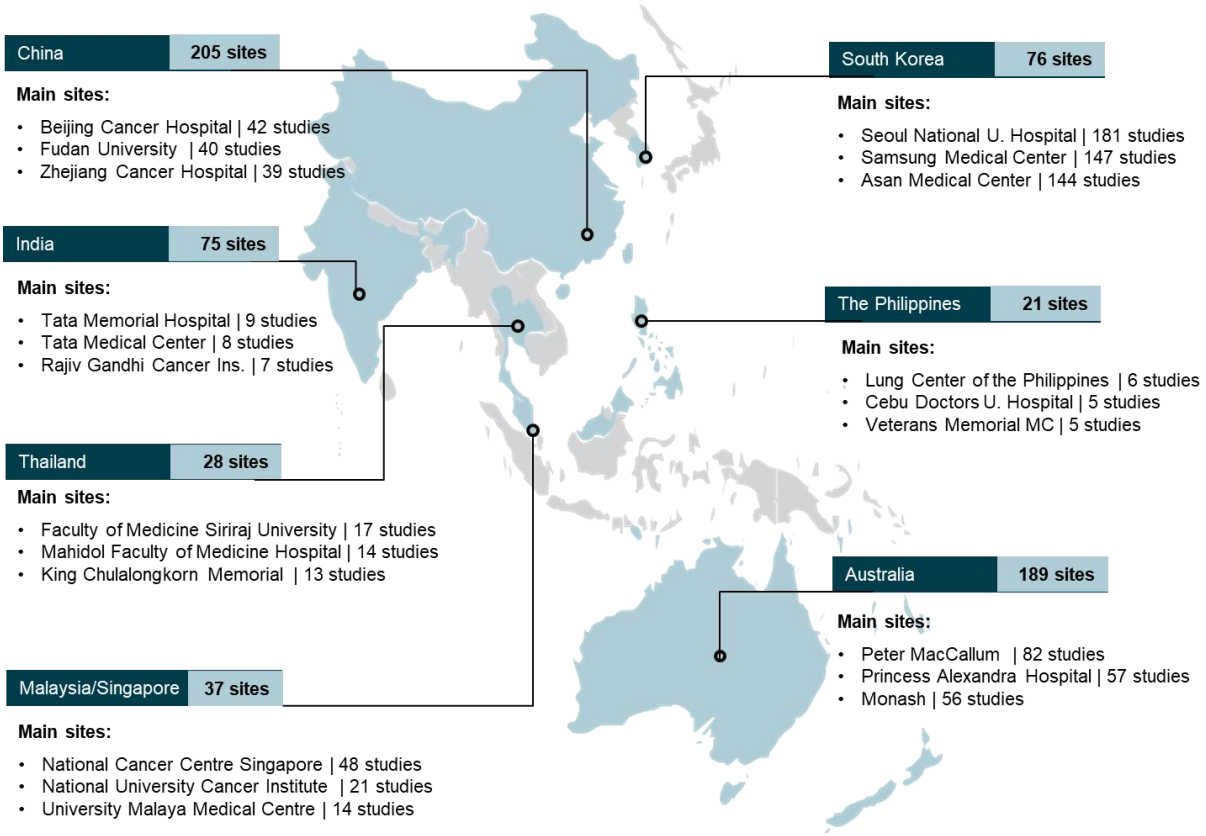
The higher recruitment rates observed can also be explained by the reimbursement status of the comparator drug. Most countries in Asia lack systematic reimbursement of IO standard of care which means clinical trials are often the only channel through which patients can access these treatments. In some Asian countries where an IO standard of care is reimbursed, sponsors will need to pay this cost, which can be an important consideration in country selection.

Figure 2. Median recruitment rates of Immuno-Oncology clinical trials for different study locations *(p/s/m)* [4]



[3] https://www.nature.com/articles/d41573-019-00182-w (accessed on December 13th 2019)

Figure 3. Overview map of APAC sites involved in trials for FDA-approved Immunotherapies
Source GlobalData



Appendix. FACT accredited organizations in the Asia-Pacific region *(as of December 2019)*

Organization	Location
Sydney Cord Blood Bank	Australia
Queensland Cord Blood Bank at the Mater	Australia
BMDI Cord Blood Bank	Australia
Blood and Marrow Transplant Program, Sydney Children's Hospital	Australia
The Children's Hospital at Westmead Blood and Marrow Transplant Service	Australia
Royal Brisbane and Women's and Queensland Children's Hospital	Australia
The Royal Children's Hospital Children's Cancer Centre	Australia
Cell & Tissue Therapies WA	Australia
WA Paediatric and Adolescent Cellular Therapies Program	Australia
Fiona Stanley Hospital Blood and Marrow Transplant Program	Australia
Hong Kong Red Cross Blood Transfusion Service Cord Blood Bank	Hong Kong
HealthBaby Biotech (HK) Co., Ltd.	Hong Kong
StemCyte India Therapeutics Private Limited	India
Auckland City and Starship Children's Hospitals Stem Cell Transplant	New Zealand
Christchurch Hospital	New Zealand
Cordlife Group Limited	Singapore
Singapore Cord Blood Bank	Singapore
StemCord Pte Ltd	Singapore
National University Health System Hematopoietic Progenitor Cell	Singapore
StemCyte Taiwan Cord Blood Bank	Taiwan

4. Case study

Phase 1/2 study of oral checkpoint inhibitor in patients with solid tumors

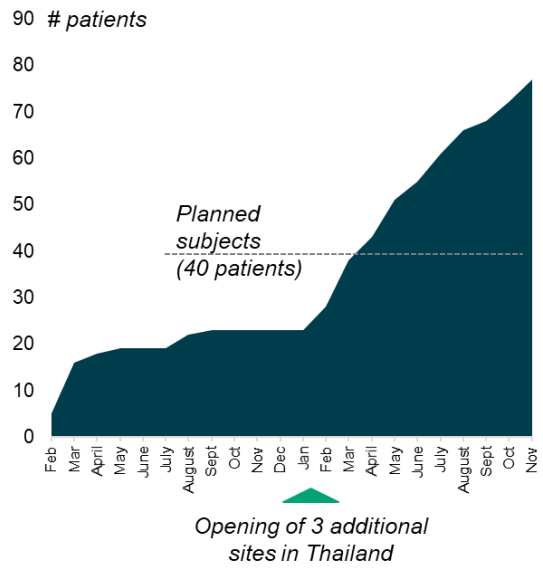
12 sites in Australia, New Zealand and Thailand

Asia's availability of vast treatment-naïve patient pool can speed up recruitment.

Portfolio of selected countries can meet multiple strategic objectives e.g. FPI/Trial Volume/ KOLs/Commercial.

- US-based sponsor looking to take advantage of Asia-Pacific rapid clinical trial environment for their IO drug first-in-man study.
- Sponsor was looking specifically for treatment naïve patients, and those with specific mutation prevalent in Asian population
- Involving sites in Australia and NZ allowed to take advantage of fast regulatory streams and the lucrative R&D cash refund….
- …while involving sites in Thailand allowed to accelerate patient recruitment rates at lower costs.
- 77 patients were recruited over 21 months across 12 sites in ANZ and Thailand.

Cumulative patient recruitment over time



Let's continue the discussion

Over the last 25 years, Novotech has partnered with numerous biotechnology companies and completed hundreds of projects in Oncology. Novotech has consistently provided high quality Oncology CRO services through a flexible approach that suits the need of small and medium biotechnology companies.

To learn more or talk to our experts about your clinical trial, visit https://novotech-cro.com/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