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# Growing Pains: Charting The Rapid Rise Of Chinese IO

*Recent events in the Chinese IO space and what this might suggest for the future*

by James Drew

Immuno-oncology therapies have revolutionized the treatment of many cancers over the last decade. This period has also witnessed a dramatic growth in China's domestic pharmaceutical industry, and significant changes in the interaction between this industry and international pharma. This coalescence has led to excitement about the role that Chinese IO could play on the global stage, tempered by regulatory set-backs and revised marketing timelines.

The past decade has seen an unprecedented rise in Immuno-oncology therapies, driven by the success of immune checkpoint inhibitors (ICIs), such as PD-(L)1 antibody therapies. In 2021, the ICI market alone was valued at $34bn – 20% of the total oncology market – and is expected to increase to $64bn by 2027, according to Cowen Research. China is an important part of this story and has emerged as a rapidly growing but still maturing IO ecosystem.

From humble beginnings, China has grown to become a critical player in the IO space, see Exhibit 1. In the early years of IO development, the US dwarfed China in trial volume, with five times as many IO trials initiated in the US in 2016 compared to China (384 vs 84). However, while US trial volume plateaued after 2017, the near-exponential growth in the Chinese sector has led to a turning of the tables. 2020 represented a tipping point where IO trial initiations in China outpaced that the US for the first time (650 vs 473). This disparity continued into last year with almost twice as many trials initiated in China than the US (877 vs 466).


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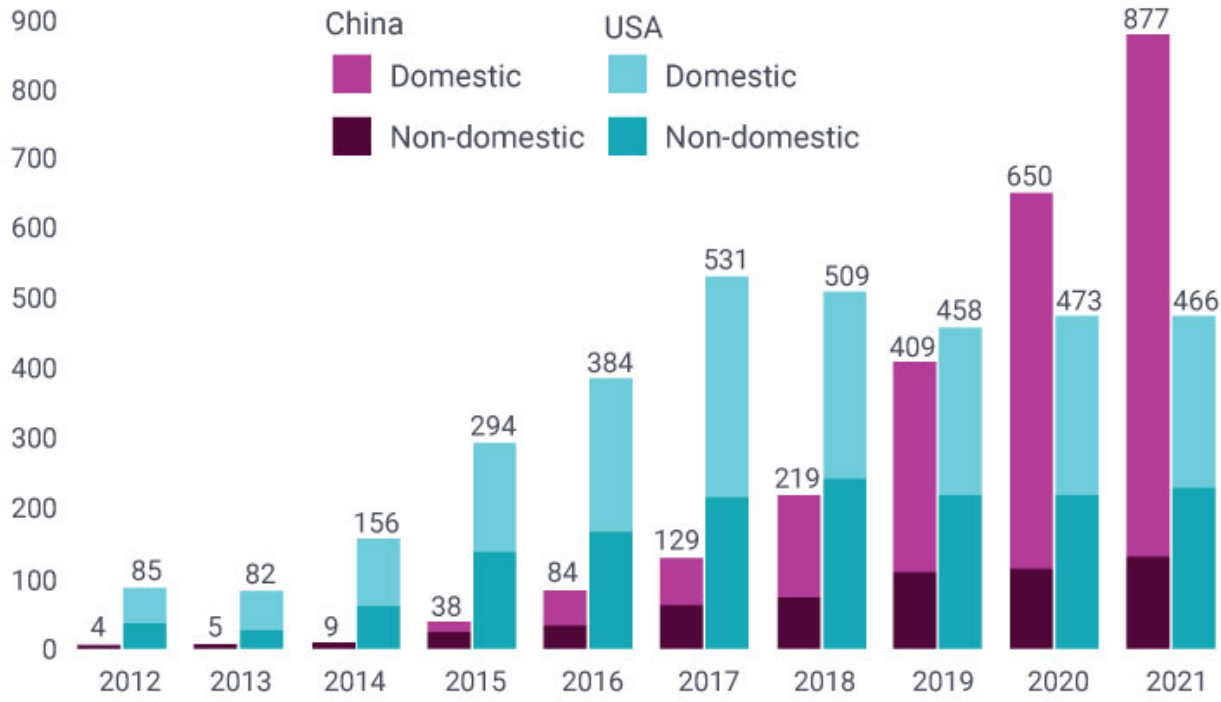
## Exhibit 1: IO Trial Initiations In China And US, Split By Sponsor Origin




*Source: Pharmaprojects, Trialtrove*

China's expanding IO trial landscape has been fuelled by a rapidly growing domestic drug development sector. In the 5-year period from 2015 to 2020, the proportion of trial initiations in China sponsored by domestic biotech rose from 34% to 82%. This is particularly staggering given that non-domestic sponsors were still ramping up involvement in the region over this period (2015: 25 trials, 2020: 115 trials). The US, by comparison, has maintained a relatively stable proportion of domestic sponsor activity of around 50% over the past decade.

### Supporting Homegrown Success

What is driving this rapid rise? Chinese leadership's awareness of the growing importance of oncology treatments to national health is a key part of the story. Cancer represents an immense and growing burden on China's healthcare system, and oncology was one of 5 high priority disease areas in the government's Health China Action Plan for 2019–30. The cancer landscape in China is also unique, with the country having significantly higher proportions of gastric, esophageal and nasopharyngeal cancers compared to US and EU markets. This creates clear incentives for the government to support a homegrown industry that can meet the specific demands of its population.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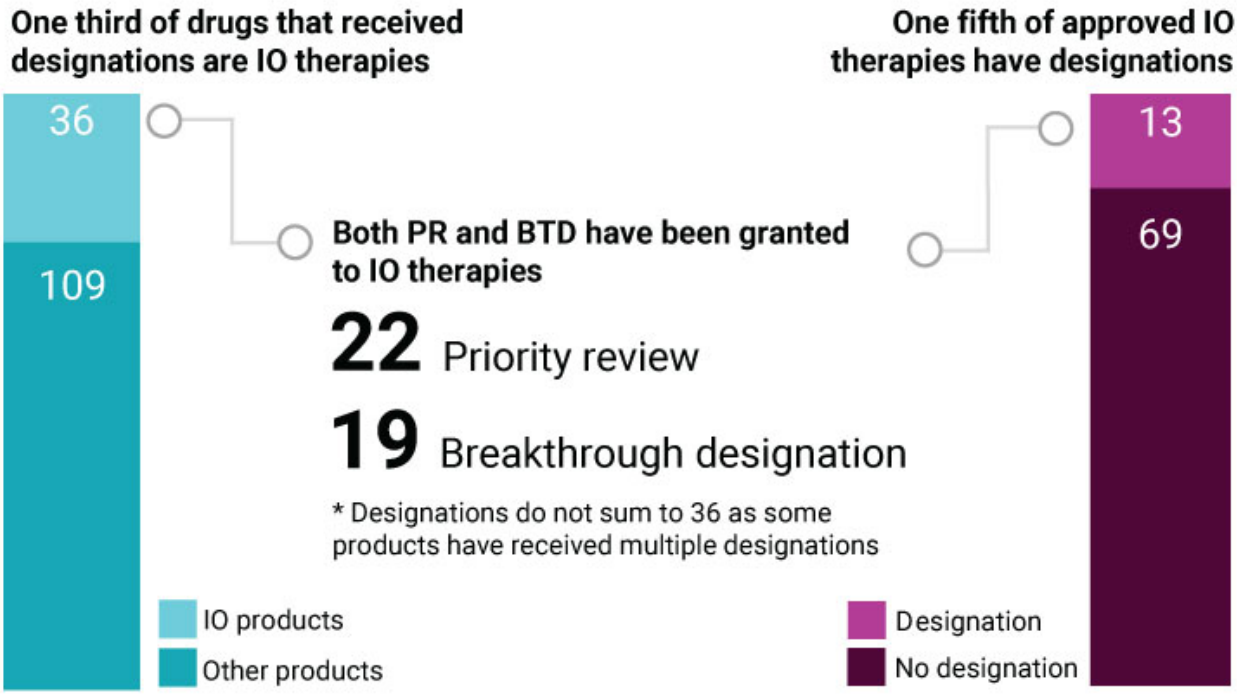
To address this challenge, China has made a concerted effort to support the domestic biotech ecosystem. From a regulatory perspective, the National Medical Products Administration (NMPA) introduced fast-track programs including Breakthrough Therapy (BT) and Priority Review (PR) designations in 2015, aimed to accelerate approval timelines and align itself with its US and EU counterparts. Fiscal reforms such as increasing access to capital for biopharma (via opening of HK capital market to pre-revenue companies) have also helped create a booming investment sector. (Also see "*Hong Kong Ushers in 'New Era' For Bioventures As Listing Rules Eased*" - Scrip, 1 May, 2018.)

While these are measures that encourage and incentivize R&D broadly, they are being well-utilized by the IO sector, see Exhibit 2. To date, one third of all expedited designations have been granted to IO therapies, with BT and PR designations being used in roughly equal measure. Our analysis shows that one fifth of approved IO therapies were part of a fast-track program in their approved indication, suggesting that these designations are beginning to feed through into approvals. Although the impact of these designations can sometimes be hard to capture, PR-designated drugs are leading to shorter NDA approval times (14.4 vs 22.1 mo), according to a *recent study*.

**Exhibit 2: IO Drugs Have Utilized Expedited Review Pathways For Approvals**




*Source: Pharmaprojects*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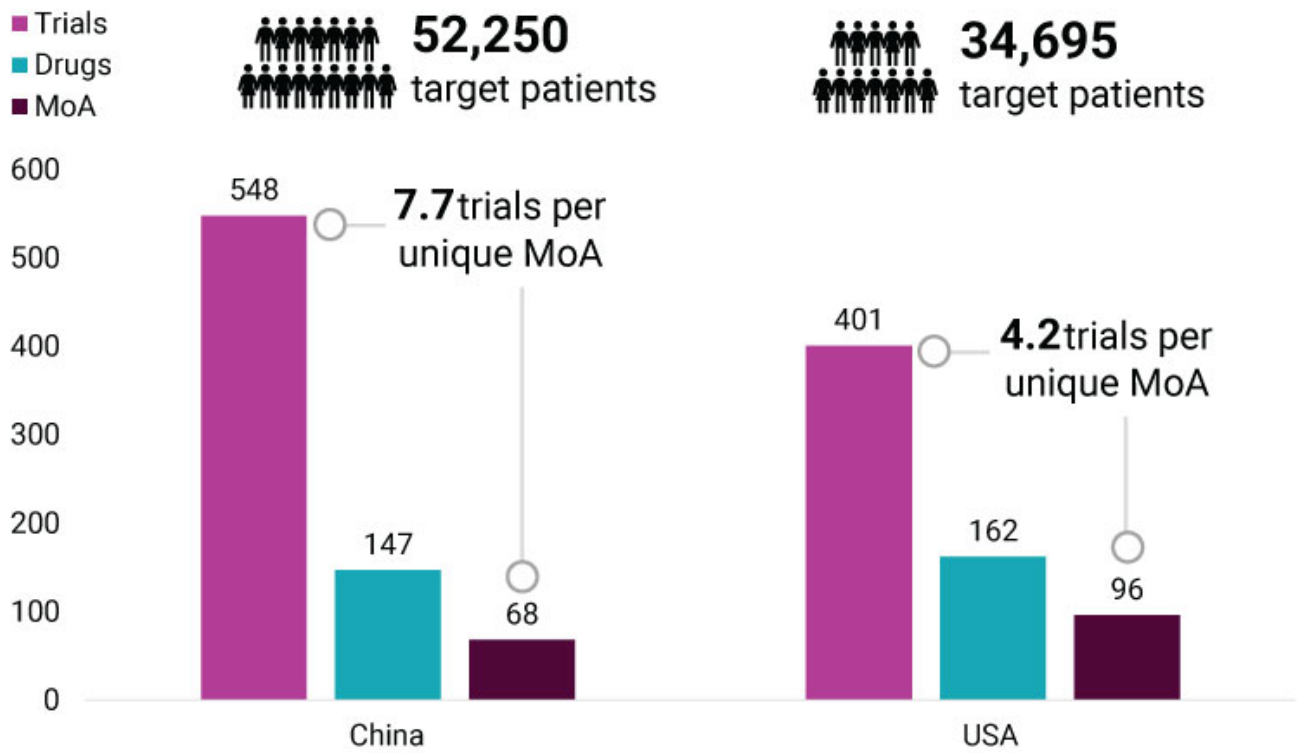
## Bigger Isn't Always Better

Despite its impressive growth, China's IO market still has room to mature, see Exhibit 3. An analysis of IO trials initiated in 2022 shows that while around 37% more trials were initiated in China compared to the US (548 vs 401), the number of unique drug products and targets being studied across these trials was in fact higher in the US. Comparing the number of trials per mechanism of action (MoA), we find China has roughly twice the ratio of trials per MoA compared to the US (7.7 vs 4.2). This highlights the fact that while the trial landscape has expanded rapidly, the depth of the research base in China has not yet caught up with more mature ecosystems.

**Exhibit 3: Comparison Of IO Activity By Unique Trials, Drugs And MoAs, 2022**




*Source: Pharmaprojects, Trialtrove*

The proportion of new trials for key targets provides a striking example of the relative homogeneity of clinical activity in the Chinese IO market, see Exhibit 4. In 2022, well over half of all trial initiations were for drugs targeting the well-established PD-(L)1 axis (68.3%). Other checkpoint inhibitor targets CTLA-4, TIGIT and LAG-3 contributed 5% or less of new trials combined. By contrast, PD-(L)1 trials made up a far smaller proportion of initiations in the US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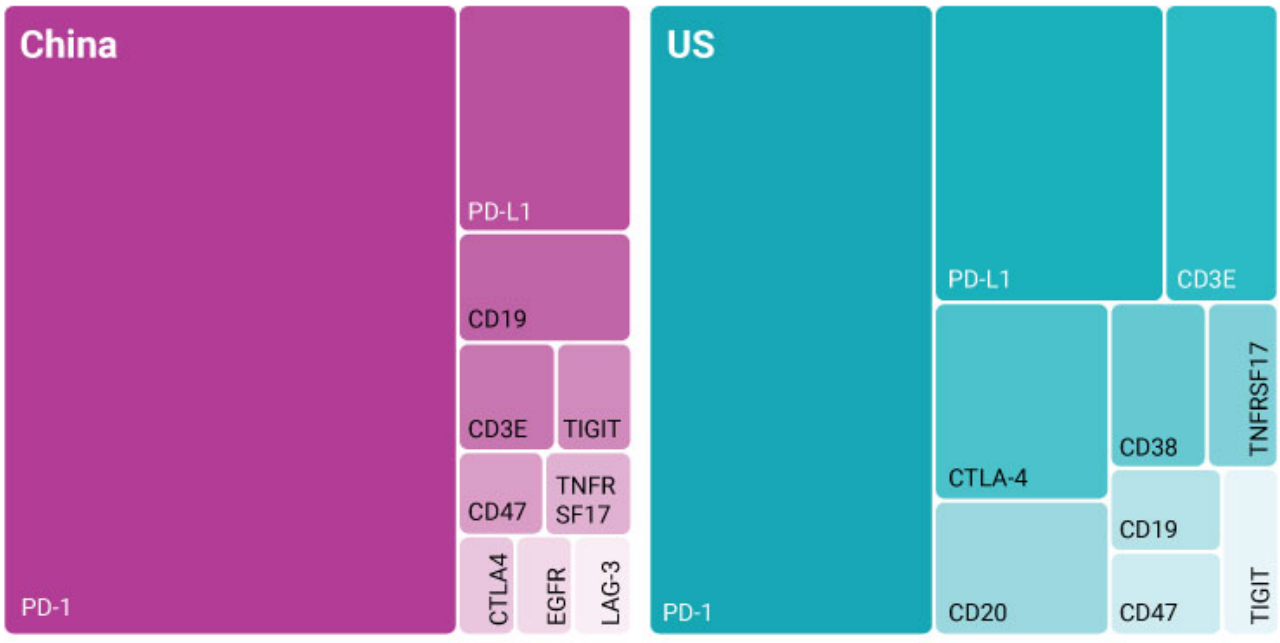
(41.2%), with greater proportions of CTLA-4 (5.6%), CD3E (5.6%) and CD20 (4.3%) trials.

Breadth over depth has also created an extremely crowded market for approved drugs in the IO space. Of the 14 PD-(L)1 antibodies approved in China, 9 are homegrown. Currently, newcomers are still gaining market share through targeting less competitive indications, aggressive label expansion and vying for inclusion in China's National Reimbursement Drugs List (NRDL). However, it seems that a plateau in activity will be inevitable without a shift away from me-too products and towards development of truly novel therapies.

We are starting to see evidence of this taking place. A particular area of focus is in IO combination therapies, which would enable sponsors to leverage existing assets while bringing new ones to market. The approval of *Akeso Inc.*'s PD-1/CTLA-4 bi-specific antibody cadonilimab earlier this year is a positive sign that Chinese biopharma is fully capable of developing world-leading innovations. (Also see "*China Approves World's First Bispecific IO Drug Amid PD-1/L1 Glut*" - Scrip, 1 Jul, 2022.) Chinese firms including *BeiGene, Ltd.* and *Shanghai Junshi Biosciences Co., Ltd.* are also racing to bring a TIGIT/PD-(L)1 combination market, another world first that would represent a watershed moment for Chinese biotech. (Also see "*BeiGene Is Keeping The Faith In IO/IO Combinations*" - Scrip, 31 Aug, 2022.)

## Exhibit 4: Share Of Trial Initiations For Top 10 IO Targets, 2022




*Source: Pharmaprojects, Trialtrove*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The next five to 10 years will represent a new phase in China's IO development, from a fast-follower to an innovator of novel IO therapeutics. To achieve this Chinese firms will need to:

- improve access – leveraging China's vast patient population will enable more large-scale trials that are needed to properly assess efficacy of therapies, particularly as new standards of care (SOC) necessitate IO vs IO comparator trials

- diversify pipelines – in order to mature into an IO innovation leader, Chinese biopharma will need to heavily invest in the next generation of immune checkpoint inhibitors, other IO targets, and novel IO/IO combinations

- build trust abroad - as Chinese pharma looks to bring IO products to international markets, it will be important to actively engage with other regulators to show that domestic trials results are both applicable and reliable. Integration into multi-regional clinical trial (MRCT) networks and continued domestic regulatory stringency will be important here

## International Deal-Making

From its inception, China's IO market has had interest from multinational pharmaceutical companies (MNPCs) – highlighted by the prevalence of non-domestic IO drugs in the early years, see Exhibit 1. As China's domestic pharmaceutical ecosystem has grown, there has also been substantial interest from MNPCs in out-licensing of IO products to international markets. In the ICI field, there have been 9 out-licensing deals worth over $100m between Chinese biotech and international pharma [Exhibit 5]. It is worth noting that there has also been significant activity outside of ICI therapies, with *Janssen Pharmaceuticals Inc.*'s deal with *Legend Biotech Corp.* for the BCMA-targeted CAR-T product LCAR-B38M being valued at $1.7bn in 2017.

MNPCs are clearly still very serious about this approach. *Eli Lilly and Company* was out of the blocks early with its partnership with *Innovent Biologics, Inc.* to commercialize sintilimab in 2015. However, four out of five of deals valued at over $1bn were struck in the past two years. BeiGene has been the main beneficiary, with *Novartis AG* signing deals worth over $5bn for tislelizumab (anti-PD-1) and ociperlimab (anti-TIGIT). (Also see "*BeiGene Ties Up With Novartis To Take PD-1 Global In $2.2bn+ Deal*" - Scrip, 12 Jan, 2021.) (Also see "*Novartis Expands BeiGene Tie-Up To TIGIT Inhibitor In $1bn-Plus Option Deal*" - Scrip, 21 Dec, 2021.) Having only been founded in 2011, BeiGene has been at the forefront of IO development in China and pursuing global ambitions. In 2019, it became the first Chinese firm to successfully break into the US market with the launch of the BTK inhibitor Brukinsa. (Also see "*Keeping Track Of User Fee Decisions And Filings: Adakveo, Brukinsa And Fetroja Mark Massive Week Of Novel Approvals*" - Pink Sheet, 17 Nov, 2019.) The company will now be looking to replicate this success with its IO products in the near future.


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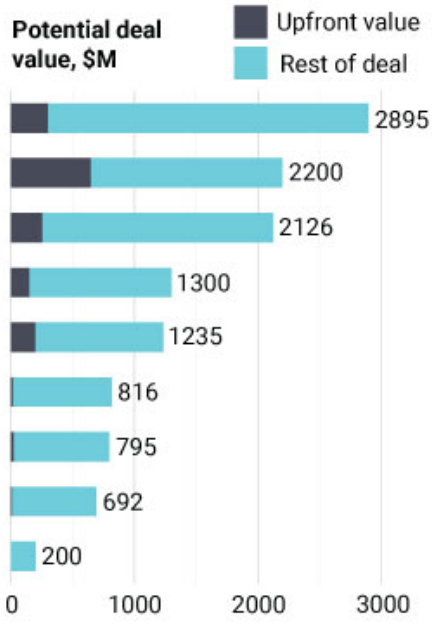
## Exhibit 5: Top ICI Out-Licensing Deals Between Chinese Are International Pharma

| Year | Licensor | Licensee | Assets (MoA) | Potential deal value, $M |
|---|---|---|---|---|
| 2021 | BeiGene | Novartis | ociperlimab (TIGIT) | 2895 |
| 2021 | BeiGene | Novartis | tislelizumab (PD-1) | 2200 |
| 2015 | Innovent Bio | Eli Lilly | sintilimab (PD-1), IBI321 (PD -1/TIGIT) | 2126 |
| 2020 | CStone | EQRx | nofazinlimab (PD-1), sugemalimab (PD-L1) | 1300 |
| 2021 | Shanghai Junshi | Coherus | toripalimab (PD-1), JS-006 (TIGIT) | 1235 |
| 2017 | WuXi AppTec | Arcus | Zimberelimab (PD-1) | 816 |
| 2015 | Jiangsu Hengrui* | Incyte | camrelizumab (PD-1) | 795 |
| 2019 | Shanghai Henlius | Kalbe-Genexine | serplulimab (PD-1) | 692 |
| 2015 | Akeso Inc. | Merck | quavonlimab (CTLA-4) | 200 |




* Deal terminated in 2018

*Source: Biomedtracker*

From a strategic perspective, the logic of these deals is clear. MNPCs view arrangements with Chinese firms as a way to simultaneously jumpstart their IO pipeline and integrate themselves into the China ecosystem. From the standpoint of a company like BeiGene, there is perhaps even greater incentive. In many ways the FDA is as much an unknown entity to Chinese companies as the NMPA may seem to international pharma, and local support in submissions is highly valuable. Access to the US market will also open key revenue streams that can be leveraged to support innovative R&D initiatives at home. The success of these arrangements will likely determine how quickly Chinese biopharma can rise to the stature of the likes of Novartis and *Merck & Co., Inc.*.

### Regulatory Pitfalls

To paraphrase Robert Burns, even the best-laid schemes of pharma CEOs and biotech often go awry. Decisions by the FDA earlier this year have thrown some cold water on those expecting a smooth entry of China-developed IO therapies into the US market. The Covid pandemic and strict response by the Chinese authorities has also led to delays in site inspections required for approval. Finally, political uncertainty continues to rock investor confidence, impacting company bottom lines. (Also see "*US-Listed China Biotechs Tank As Xi Takes Third Term*" - Scrip, 25 Oct, 2022.)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In February, the FDA's ODAC determined by a 14-1 vote that Eli Lily/Innovent Bio's PD-1 antibody, sintilimab, could not be approved based on results from the pivotal phase 3 ORIENT-11 trial conducted solely in China. (Also see "*Casualty Of Change? Innovent/Lilly's Chinese PD-1 Inhibitor Sintilimab Falls Hard At US FDA Panel*" - Pink Sheet, 10 Feb, 2022.) The agency strongly stated a preference of MRCTs with US SOC control arms and overall survival endpoints. Novartis/BeiGene's decision to halt a planned BLA submission for tislelizumab in 2L NSCLC was a direct reaction to this, Novartis's CEO Vas Narasimhan stating that "FDA is making it very clear now that any studies to be filed are global in nature" during an investor call in the summer. (Also see "*Novartis/BeiGene Opt For PD-1/TIGIT Combo For NSCLC In US*" - Scrip, 21 Jul, 2022.)

A look at the pivotal trial data available for ICI therapies that are approved in China and have out-licensing deals with US/EU companies suggests that there may be a long way to go before these therapies reach US patients, see Exhibit 6. Our analyses show that one third of pivotal trials had an overall survival endpoint, while less than one fifth were MRCTs. Taken together, only 12% of trials met these high-level criteria, raising the question of whether the bulk of data used for approvals in China will be valid for FDA submissions. As already highlighted, a move towards large-scale, multi-regional trials will be necessary for Chinese biotech to make a lasting impact on the markets outside of Asia.


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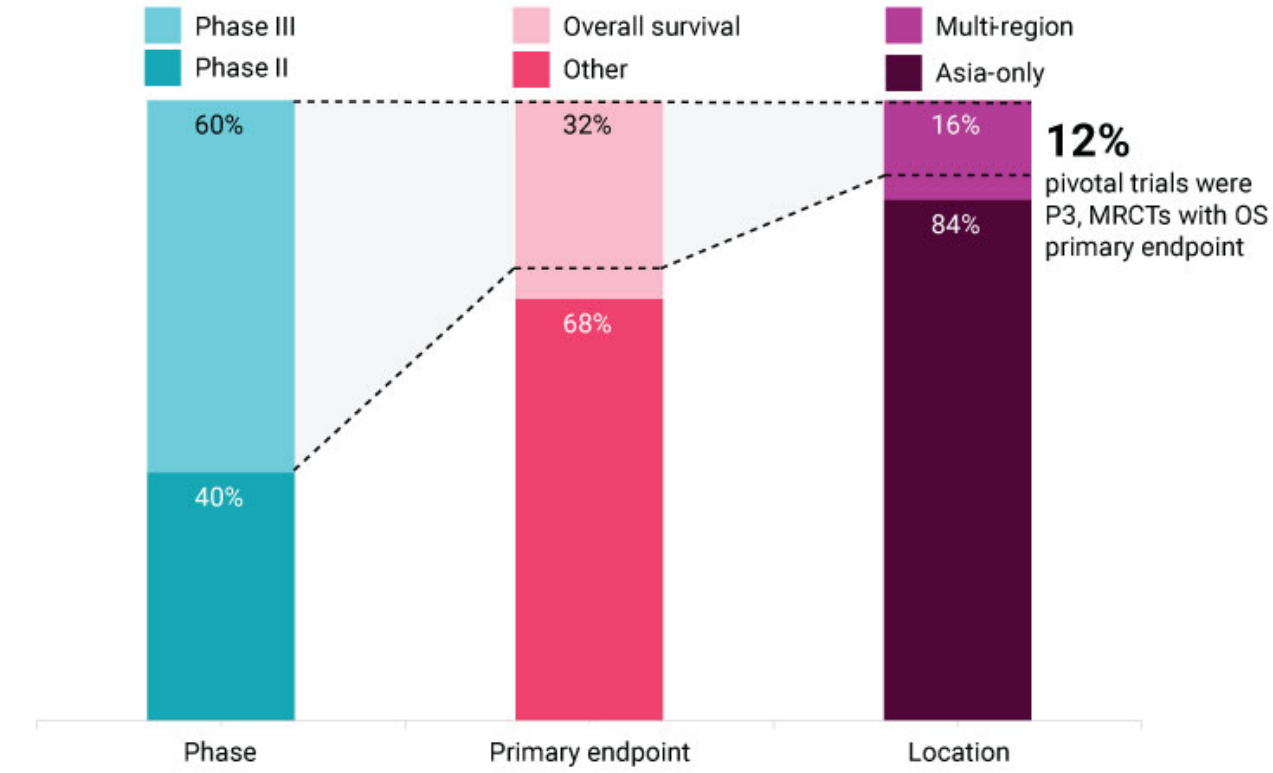
## Exhibit 6: Pivotal Trial Characteristics Of IO Drugs With Out-Licensing Agreements




Source: Trialtrove

There is evidence that these issues are being addressed. At the recent ESMO 2022 conference, Chinese sponsors revealed results from several pivotal Phase III trials that seemed to acknowledge the FDA's current stance. (Also see "*ESMO: Positive Results Buoy Chinese Oncology Developers' Global Hopes*" - Scrip, 11 Sep, 2022.) The HCC market in particular looks to be heating up, with positive results from both *Hengrui Therapeutics, Inc.*'s camrelizumab and BeiGene's tislelizumab as 1L therapy versus sorafenib, currently 1L SOC. The FDA has also hinted at flexibility for therapies targeting indications of high unmet need in the US. *Coherus BioSciences, Inc.*'s toripalimab and BeiGene's tislelizumab may fit this bill, both of which are approved in China for nasopharyngeal carcinoma – an indication without an IO therapy option in the US.

For Coherus and BeiGene, it has been inspection delays that have hampered approval decisions by the FDA. BeiGene/Novartis's tislelizumab application for esophageal cancer is in limbo while travel restrictions restrict US inspectors. (Also see "*BeiGene/Novartis's Tislelizumab Faces US Delay Over China Inspection Challenges*" - Pink Sheet, 18 Jul, 2022.) Coherus/Shanghai Junshi Biosciences Co., Ltd.'s toripalimab received a CRL from the FDA back in February requesting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“quality process” changes. While the sponsors have made quick work addressing this, their resubmission in the summer was given a six-month decision timeline to allow for likely delays to on-site inspections. (Also see "*Keeping Track: Longer US FDA Reviews For Tislelizumab, Toripalimab, Olipudase; Perrigo Wants OC To Go OTC*" - Pink Sheet, 18 Jul, 2022.) Sponsors are generally confident that these hold-ups represent bumps in the road rather than symptoms of failure, although they highlight the added difficulties in moving beyond domestic markets.

## Key Takeaways

China’s IO industry has undergone a radical transformation over the last decade. From a trailing start, it is rapidly catching up with more established regions. This has been driven by a combination of a decisive national investment strategy as well as growing integration and involvement of MNPCs. Looking ahead, further integration of China into international trial networks and continued regulatory support will be required. From a company perspective, biological innovation will help transition China from a me-too industry to a world leader of innovative IO therapies.

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