White Paper

In the Eye of the Storm: PD-(L)1 Inhibitors Weathering Turbulence

Challenges and opportunities as the immune checkpoint inhibitor market matures

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MERCK EX1222
Merck Sharp & Dohme LLC v. The Johns Hopkins University
IPR2024-00647

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Introduction

Harnessing the power of the body's immune system for the fight against cancer has been one of the most remarkable success stories of the past decade. PD-1/PD-L1 checkpoint inhibitors were among the first cancer immunotherapies to be approved and they have transformed the oncology treatment landscape, offering hope to patients as new options for hard-to-treat tumours. Their universal mechanism of action enabled the rapid expansion of products across multiple indications and created blockbusters in the process, most notably Keytruda and Opdivo.

However, the checkpoint inhibitor market is facing strong headwinds. Its commercial promise has attracted numerous players, all vying for a share of the opportunity, and resulted in an increasingly crowded market and frantic development activity. With globally over 5,600 clinical trials investigating PD-1/PD-L1 inhibitors, the future immunotherapy landscape is heading for overwhelming complexity and opportunity fragmentation, which is alarming both regulators and payers. At the same time, low-cost fast followers such as EQRx and Chinese innovators are seeking to disrupt the market by aggressively competing on price. These trends are rewriting the fundamentals for achieving success as a PD-1/PD-L1 player.

In this white paper, we will review the competitive dynamics and emerging innovation landscape for PD-1/PD-L1 inhibitors, examine the challenges the market is facing and explore future opportunities and considerations for capturing these.

PD-1/PD-L1 checkpoint inhibitors significantly outperformed the global oncology market, growing at 5-year CAGR of 45%, or three times the rate of oncology overall, and are expected to reach $58 billion globally by 2025.

Competitive dynamics in the PD-1/PD-L1 market

The PD-1/PD-L1 checkpoint inhibitors represent one of the most dynamic market segments and significantly outperformed the global oncology market over the past 5 years, growing at 5-year CAGR of 45%, or three times the rate of oncology overall, to reach $36 billion globally in 2021, at ex-manufacturer prices. Future growth is expected to slow to 5-year CAGR of 15% as the PD-1/PD-L1 market matures, and IQVIA forecasting sales to reach $58 billion globally by 2025.[1] However, this lower growth rate still exceeds the expected future 5-year CAGR of 10% for the total oncology market.

The U.S. accounted for 47% of PD-1/PD-L1 global sales in 2021. Its share declined from 60% over the past 5 years as Europe is catching up, with EU4/UK now representing a quarter of the global market. Including Japan, the top 7 developed markets contribute 79% of global PD-1/PD-L1 sales. Despite rapid adoption, Europe and Japan are trailing behind the U.S. in per capita use of checkpoint inhibitors and thus provide a greater opportunity for unlocking latent demand to expand the PD-1/PD-L1 market. In 2020, combined use of all approved checkpoint inhibitors as measured in defined daily doses (DDD) per 100,000 people was 3,039 in the U.S. vs. 2,144 and 2,376 in the EU4/UK and Japan, respectively.[2]

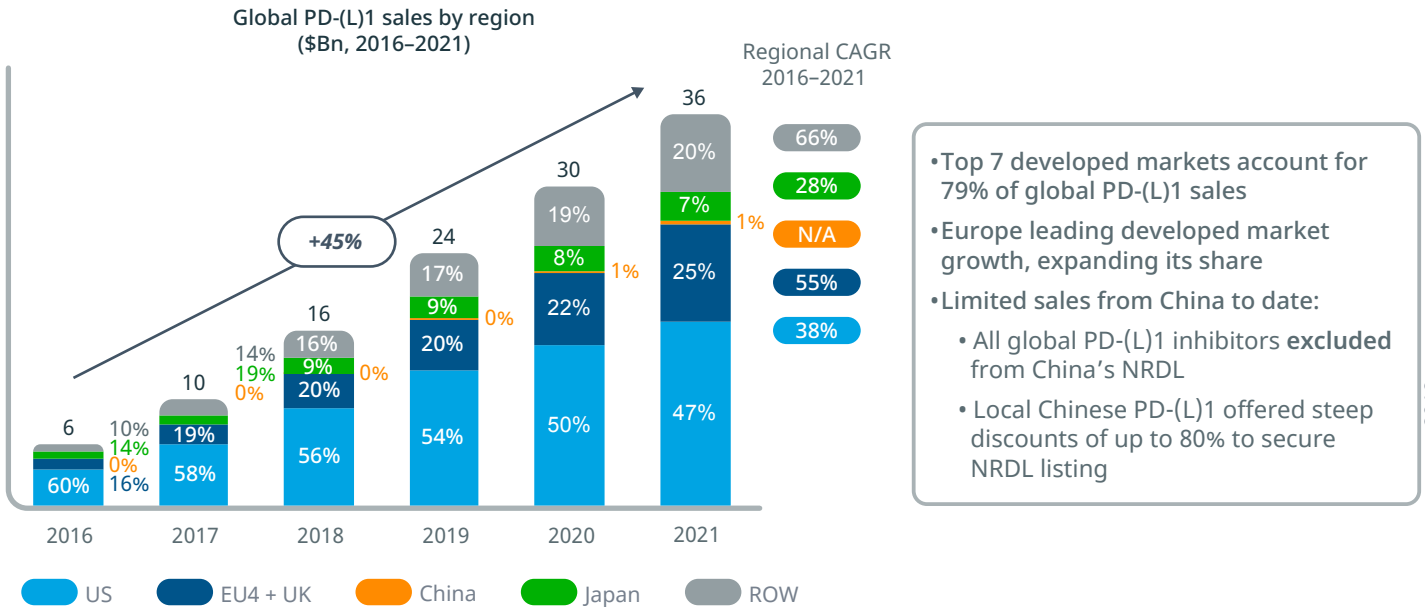
Notably, sales contributions from China have been limited to date because all global PD-1/PD-L1 inhibitors are excluded from China's National Reimbursement Drug List (NRDL), while domestic Chinese manufacturers offered steep discounts of up to 80% to secure NRDL listing for their local products.[3]

BRAND-LEVEL DYNAMICS

The dynamics of the PD-1/PD-L1 market are shaped by four defining themes which also create barriers for late and new entrants:

1. **Multi-indicationality:** Given their universal mechanism of action, PD-1/PD-L1 inhibitors represent a 'pipeline in a product'. To unlock their full commercial potential, rapid indication expansion and the strategic sequencing of indications are key to success.

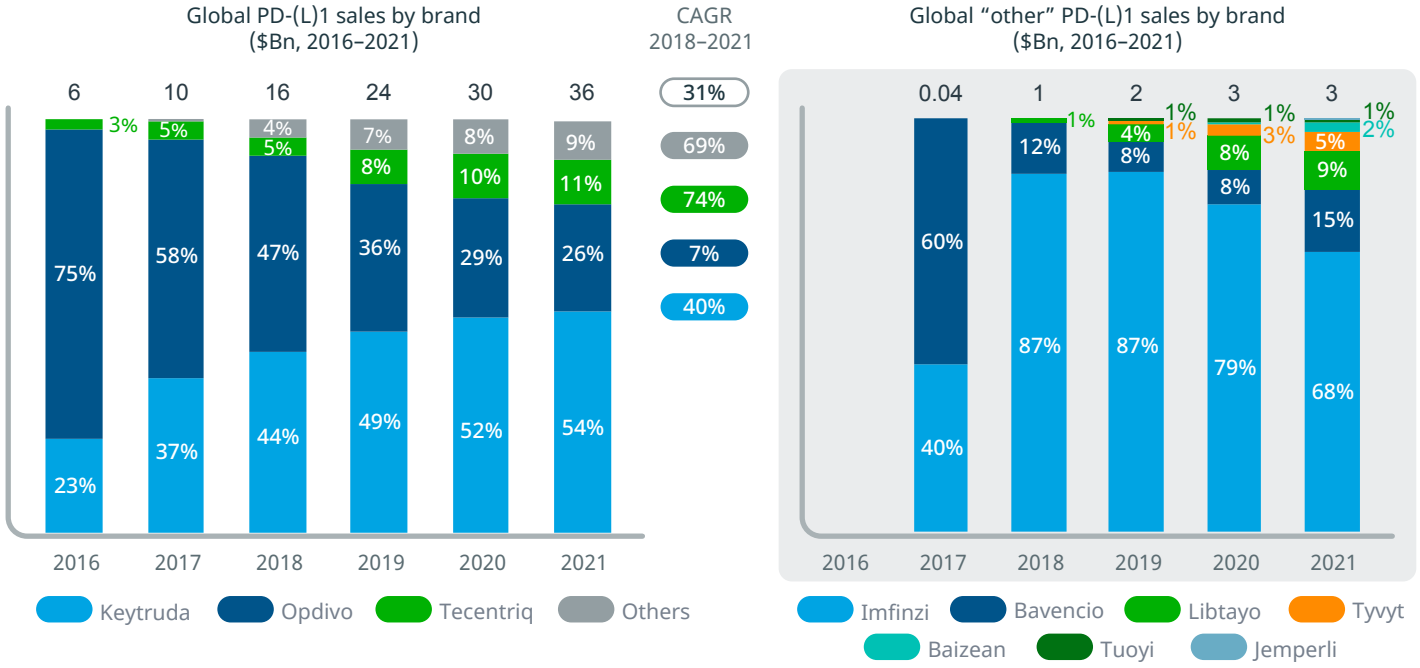
Figure 1: The global PD-(L)1 inhibitor market has enjoyed fast growth



- Top 7 developed markets account for 79% of global PD-(L)1 sales
- Europe leading developed market growth, expanding its share
- Limited sales from China to date:
  - All global PD-(L)1 inhibitors **excluded** from China's NRDL
  - Local Chinese PD-(L)1 offered steep discounts of up to 80% to secure NRDL listing

Source: IQVIA MIDAS MAT Q4 2021, Notes: Rx only; IQVIA European Thought Leadership; CAGRs are calculated using constant exchange rates.
Note: PD-(L)1 includes 7 FDA approved molecules and 3 China approved molecules

Figure 2: Keytruda dominates; top 3 brands hold 91% market share



Source: IQVIA MIDAS Q4 2021, Notes: Rx only; IQVIA European Thought Leadership; CAGRs are calculated using constant exchange rates.

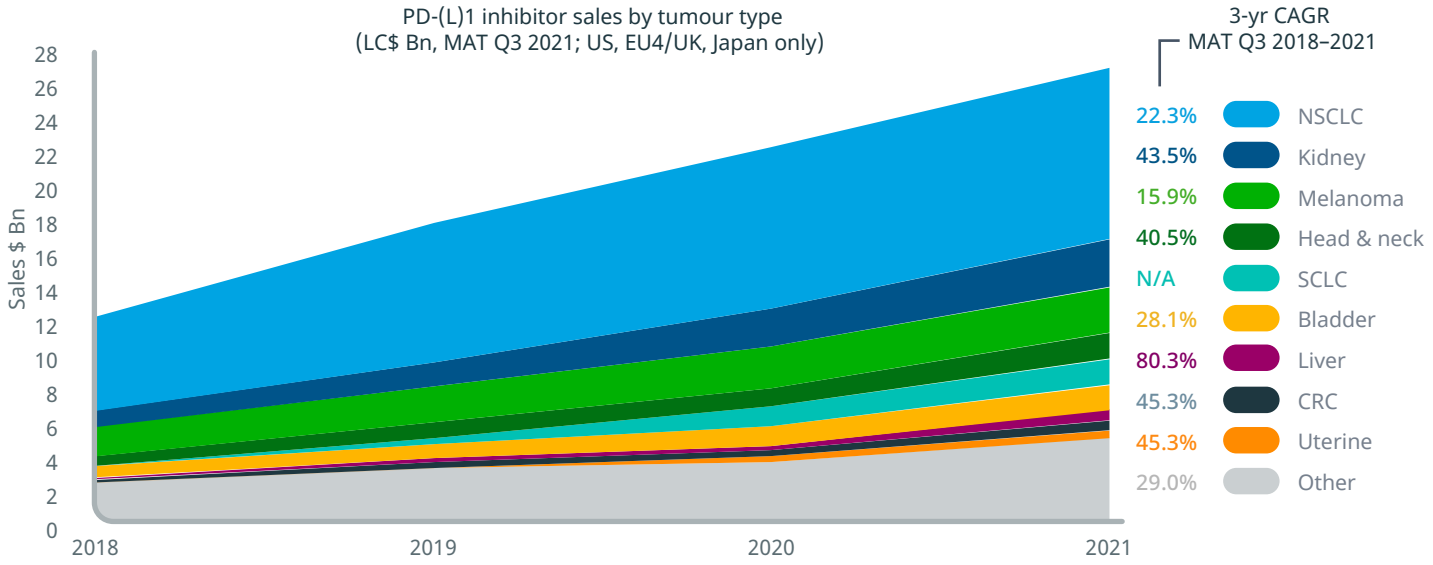
2. **Biomarkers** are critical for navigating the complex PD-1/PD-L1 therapy landscape, e.g. to pinpoint responders or to reassure payers about the size of the eligible population and patient outcomes. Consequently, the success of checkpoint inhibitors is inextricably linked to biomarker innovation, their adoption and testing rates in routine clinical practice.[4]

3. **Market maturity:** Today, seven global PD-1/PD-L1 inhibitors are on the market with approvals across 17 cancer indications, many of which are served by multiple agents. As PD-1/PD-L1 inhibitors are used both as monotherapies and increasingly in combination with other cancer treatments, the market is getting crowded, more complex to navigate while opportunities start to fragment.

4. **Keytruda dominance:** Despite an increasingly crowded market, Keytruda has firmly established a dominant position, holding 54% market share in 2021. It is approved across 13 indications, has accumulated extensive data while oncologists have gained deep familiarity through hands-on experience. In many settings, Keytruda has become the standard of care and set the benchmark to beat, including in clinical trials.

The position of leading brands in today's competitive landscape still largely reflects the order of market entry. Among the seven, globally competing PD-1/PD-L1 inhibitors — Keytruda, Opdivo, Tecentriq, Imfinzi, Bavencio, Libtayo, Jemperli — early entrants Opdivo and Keytruda together still command 80% of the global checkpoint inhibitor market in 2021. However, over the past 5 years Keytruda has squeezed Opdivo and significantly expanded its share. Beyond those two leading brands, only third-to-market Tecentriq has gained sizeable share of 11%, whereas all other entrants have made limited inroads and share just 9% of the market between them. This includes three domestic PD-1/PD-L1 inhibitors that are approved in China — Tyvyt, Baizean, Tuoyi – and which to date have only been used locally.

Figure 3: Collectively, PD-(L)1 inhibitors are approved across 17 tumour types



Source: IQVIA European Thought Leadership, MIDAS Sales by Disease MAT Q3 2018 - 2021, PD-(L)1 inhibitors: Keytruda, Opdivo, Imfinzi, Bavencio, Tecentriq, Libtayo, Jemperli.

Collectively, the seven approved, global PD-1/PD-L1 inhibitors find use across 17 different tumour types, with non-small cell lung cancer (NSCLC) by far the biggest indication, representing about 40% of the market. Different indications are dominated by different checkpoint inhibitors, for example Keytruda is the leading agent in NSCLC, Opdivo dominates melanoma and renal cancer, and Tecentriq small cell lung cancer (SCLC).

BIOMARKERS: AT THE CENTRE OF SUCCESS

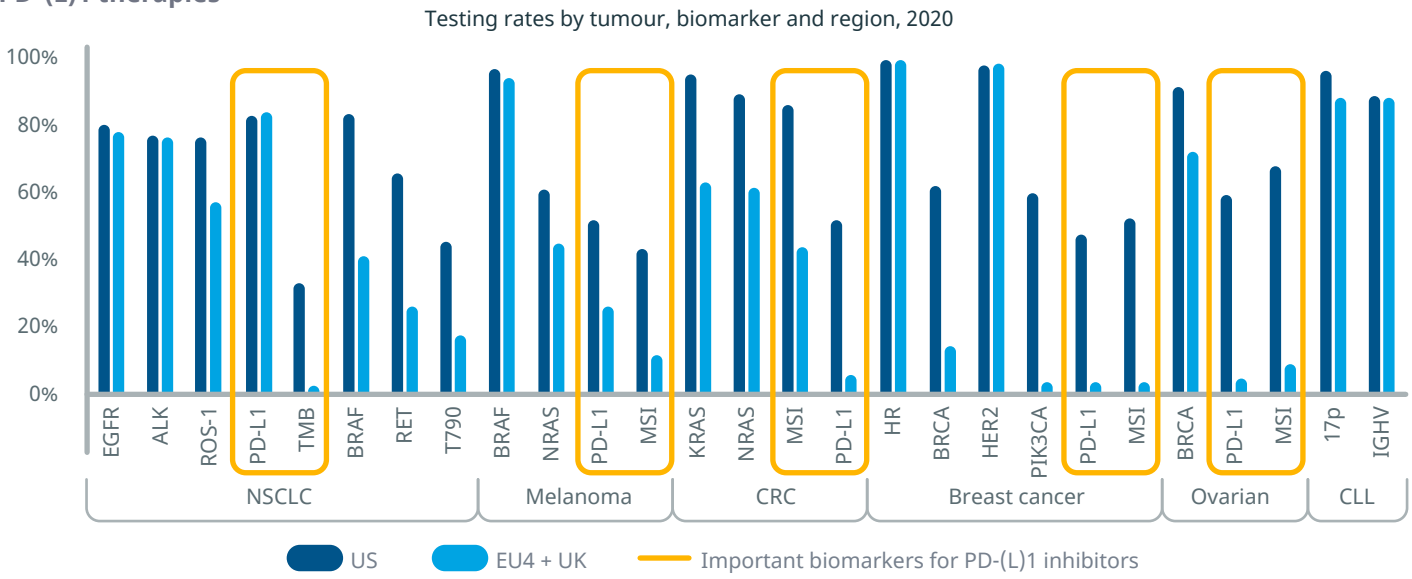
From the very beginning, biomarkers have been an integral part of the story of the PD-1/PD-L1 checkpoint inhibitors.

Our IQVIA Launch Excellence research[5] identified Keytruda not only as an excellent launch but also as a case in point for a tremendously successful 'narrow-first' strategy, in which the PD-L1 biomarker played a crucial role. When launching Keytruda, Merck chose a highly targeted approach, focussing on second-line NSCLC patients with high PD-L1 expression who should see the greatest benefit. By demonstrating superior outcomes in that narrow population, Keytruda secured subsequent approval for first-line NSCLC patients with tumours expressing high levels of PD-L1, opening up the larger first-line market opportunity. At the same time, the FDA expanded use of Keytruda to all second-line NSCLC patients regardless of level of PD-L1 expression. Thus 'narrow-first', followed by strategic indication expansion, provided the path towards broad use of Keytruda and, ultimately, its dominant market position.

Undoubtedly, Keytruda was in the right place, at the right time, for this particular strategy to be so successful. However, the importance of biomarkers for the success of PD-1/PD-L1 inhibitors cannot be overstated, and it is only growing.

In an increasingly crowded marketplace, competitors need to demonstrate differentiated value, e.g. by targeting sub-populations with high unmet need and by 'guaranteeing' positive patient outcomes, for which diagnostic and predictive biomarkers are essential. For example, Tumour Mutational Burden (TMB) and Microsatellite Instability – High (MSI-H) are becoming increasingly important biomarkers to understand patients' response to PD-1/PD-L1 inhibitors.[6, 7]

Figure 4: Testing levels vary between biomarkers, tumour types and countries, hampering optimal adoption of PD-(L)1 therapies

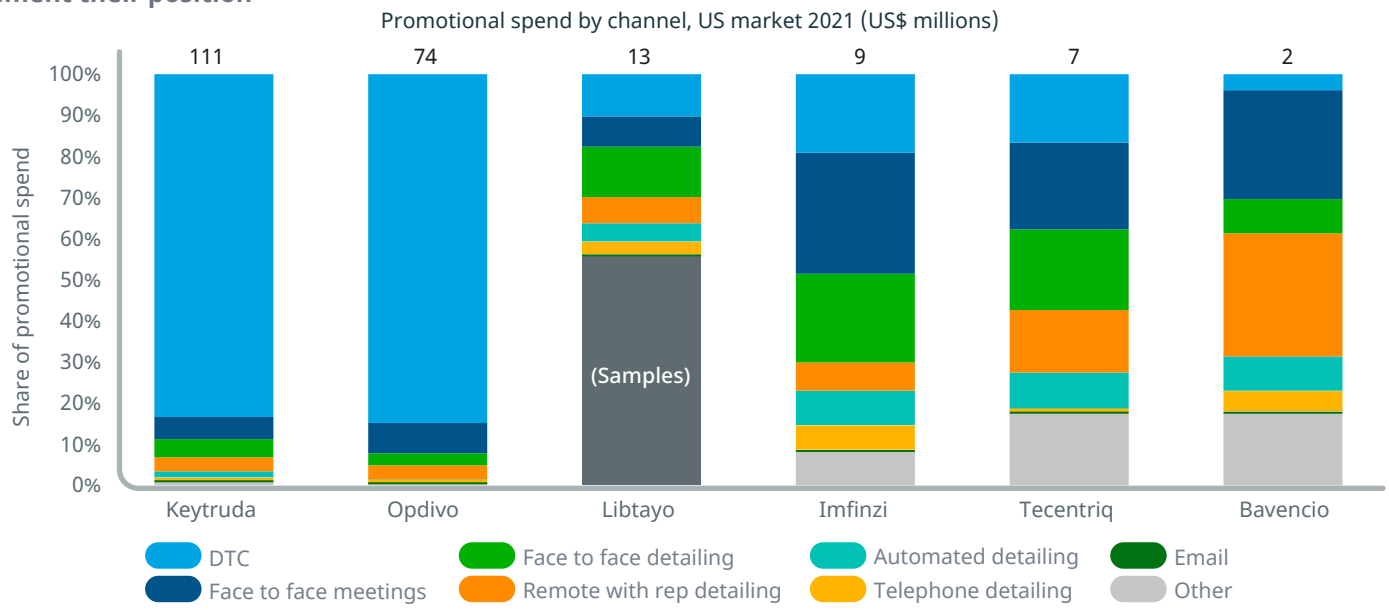


Source: IQVIA Oncology Dynamics,EU4+UK; Brand Impact, US, Dec 2020.

However, testing levels vary considerably between biomarkers, tumour types and countries, which creates barriers to the optimal adoption of PD-1/PD-L1 therapies.

Therefore, in addition to incorporating biomarkers into (co-)development and commercial strategies of checkpoint inhibitors, health systems' biomarker readiness must be a key consideration, too, for example to address practical challenges for widely embedding new biomarkers in routine clinical practice, such as testing infrastructure and capacity, impact on workflows, establishing testing standards or training of key personnel.[4]

Figure 5: Leading PD-1 inhibitors Keytruda and Opdivo aggressively spend on DTC to activate demand and cement their position



Source: IQVIA EMEA Thought Leadership; IQVIA ChannelDynamics, March 2022.
Note: * "Other" includes Live Meetings, Journal Adverts, Mailings, Automated Messages, Texts, Social Media, Web Adverts, Corporate Website, Samples.

PROMOTIONAL INVESTMENT: INTENSE COMPETITION

The PD-1/PD-L1 market is fiercely contested, with over $500 million spent globally in 2021 on promotional activities, including DTC, between the seven global checkpoint inhibitor brands. A closer look at the underlying channel mix in the U.S. reveals that leading brands Keytruda and Opdivo aggressively spent on DTC advertising to activate demand and cement their position.

The high noise level generated by the two leading PD-1/PD-L1 incumbents further raises entry barriers to the market and it demands commercial precision from later entrants with smaller checkpoint inhibitor franchises to be able to compete successfully.

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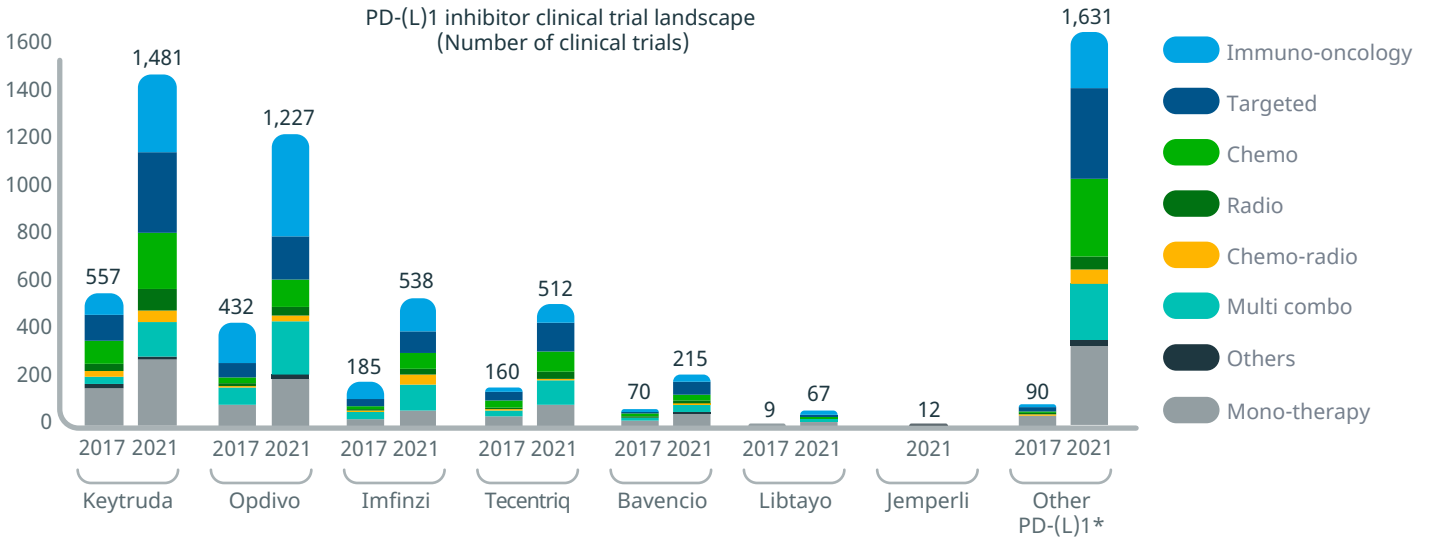
Emerging innovation landscape for PD-1/PD-L1 inhibitors

Despite the extraordinary impact PD-1/PD-L1 checkpoint inhibitors have had on transforming the treatment landscape and improving the prognosis and outcomes for many patients in different malignancies, unmet needs still exist.

For example, patients' response to treatment is variable in both depth and duration. Durable sensitivity to PD-1/PD-L1 inhibition only occurs in a relatively small proportion of patients, with many patients not responding at all to PD-1/PD-L1 therapies; others develop resistance eventually via a range of mechanisms, e.g. tumour-intrinsic, related to the tumour microenvironment or patient-specific factors.[8] PD-1/PD-L1 therapies have also been associated with immune-related toxicities that can affect all organ systems and tissues and, depending on their severity, may require discontinuation of therapy. Furthermore, such immune-related adverse events may occur months or even years after completing treatment.[9]

Figure 6: PD-(L)1 combination trials explore a broad range of modalities



Source: Upadhaya S., Neftelinov S., Hodge J., Campbell J.: Challenges and opportunities in the PD1/PDL1 inhibitor clinical trial landscape, Nature Reviews Drug Discovery, February 2022

Note: * Includes PD-(L)1 inhibitors without FDA approval

This level of unmet need combined with the potential of PD-1/PD-L1 therapies to expand into earlier settings, including neo-adjuvant, as well as opportunities to enter new indications, is fuelling frantic development activity. In 2021, 5,683 clinical trials globally were investigating PD-1/PD-L1 inhibitors, of which 4,897 trials were active, an increase of 278% over the past 5 years.[10]

THE RISE OF COMBINATIONS

The vast majority, 83%, of those clinical trials test combinations of PD-1/PD-L1 inhibitors with a broad range of modalities, spanning other immunotherapies, targeted therapies, chemotherapies and radiotherapies.[10]

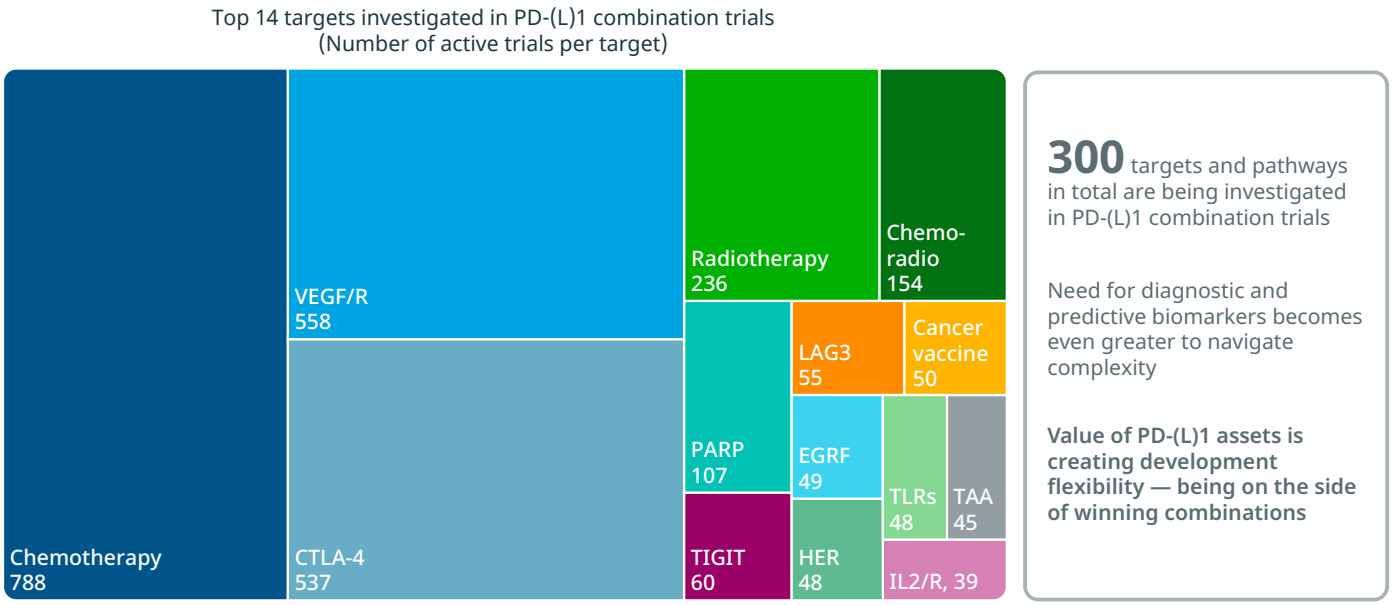
There is a plausible rationale for exploring combinations to overcome resistance and achieve a deep and durable response, including stimulating a stronger T-cell response, e.g. by blocking other inhibitory checkpoints; the direct modification of tumour immunogenicity, e.g. via chemotherapy, radiotherapy or oncolytic viruses; or a multi-pathway attack using other targeted therapies, e.g. VEGF or PARP inhibitors. The current development landscape reflects this thinking: Nearly 300 targets and pathways in total, excluding PD-1/PD-L1, are being investigated in combination trials.[10]

However, mechanistic plausibility is not the same as demonstrating actual efficacy in patients. Numerous potential combination therapies that appeared promising a priori have suffered setbacks in clinical trials, for example PD-1/IL-2 in melanoma,[11] PD-L1/paclitaxel in triple negative breast cancer (TNBC),[12] PD-1/BTK in urothelial carcinoma,[13] PD-1/PARP in prostate cancer[14] or PD-L1/CTLA-4 in NSCLC,[15] to name a few. The inherent complexity of the immune system renders development of checkpoint inhibitor combination therapies a highly unpredictable, and risky, endeavour for innovators.

Beyond combination therapies, several novel approaches are pushing the innovation frontier in inhibiting the PD-1/PD-L1 pathway, e.g. bi-specific antibodies simultaneously directed at PD-1/PD-L1 and a wide range of other targets, with over 90 such bi-specific antibodies currently tested in trials;[10] small molecule, oral PD-1/PD-L1 inhibitors in early development;[16] or masking technologies for the conditional activation of PD-1/PD-L1 agents once they reach the target tissue to minimise toxicity.[17]

For all the uncertainty surrounding individual innovation efforts, collectively, the ongoing frantic development activity will lead to overwhelming complexity of the

Figure 7: Frantic innovation activity is leading to overwhelming complexity and opportunity fragmentation



Source: Upadhaya S., Neftelinov S., Hodge J., Campbell J.: Challenges and opportunities in the PD1/PDL1 inhibitor clinical trial landscape, Nature Reviews Drug Discovery, February 2022

future PD-1/PD-L1 treatment landscape. This goes beyond the sheer number of available therapies and raises many practical questions for oncologists and payers alike, for example: How and when to combine different agents? How many agents to combine, e.g. double or triple stacked treatments? How to sequence such combinations? How to assess the differential value of different combinations against which standard of care, and against each other? And how to pay for this huge wave of innovation hitting the market?

The challenges caused by such overwhelming complexity drive an even greater need for diagnostic and predictive biomarkers to diagnose and treat patients with ever greater precision, e.g. accurately identifying high responders for a given treatment regimen and predicting the occurrence of adverse events, to enable the optimal use of the emerging, vast armamentarium of future PD-1/PD-L1 therapies.

Research into potential predictive biomarkers has evolved from focussing on factors within tumour cells, e.g. tumour mutation burden (TMB), deficiency in DNA mismatch repair (dMMR) and microsatellite instability (MSI), to understanding the tumour microenvironment (TME), e.g. via an immune-score to capture the immune status of the TME or characterising the phenotype of tumour infiltrating lymphocytes. Recent focus has expanded into exploring circulating factors, such as plasma exosomes or circulating tumour DNA (ctDNA), as well as host systemic biomarkers, including the role of a patient's gut microbiome.[18] Given the complexity of the immune system and the multitude of organs, cells, tissues and interactions involved, the likely outcome is the need for a holistic interpretation of multiple, possibly dynamic biomarkers to characterise patients and accurately predict their response to PD-1/PD-L1 therapies.

REGULATOR CONCERNS AND CRITICISM

The frantic innovation activity we are witnessing has prompted the FDA to express concern and lament the 'The Wild West of Checkpoint Inhibitor Development'.[19]

In its criticism directed at manufacturers, the FDA called out the uncoordinated expansion of PD-1/PD-L1 development by the industry which is putting growing pressure on patient recruitment; the lack of consensus on biomarkers and companion diagnostics; and the increasing reliance on non-randomized, single arm trials and the use of the accelerated approval pathway.

A particular criticism focused on sponsors seeking regulatory approval exclusively on the basis of non-U.S. data, especially those generated in Chinese studies. Consequently, several late-stage PD-1/PD-L1 candidates that rely on Chinese data are facing a moment of truth: How will the FDA regard their regulatory submissions?

In March 2022, the FDA rejected Lilly's and Innovent's application for Tyvyt (sintilimab) in non-squamous NSCLC, arguing the submitted data which were exclusively generated in China were not generalisable to the U.S. population and also citing the lack of comparison vs. the standard of care (SoC), which the FDA defined as Keytruda.[20]

A number of other innovators with late-stage checkpoint inhibitor assets reliant on Chinese data, exclusively or partially, will find out later in 2022 how the FDA will view their respective submissions: Akeso/Sino with Annik (penpulimab); Coherus/Shanghai Junshi with Tuoyl (toripalimab); and Novartis/Beigene with Baizean (tislelizumab).

The FDA's demand for U.S. data and comparison against SoC has serious implications for aspiring PD-1/PD-L1 players pursuing a low-cost strategy, for example disruptors like EQRx[21] or big pharma late-comers. To be able to (aggressively) compete on price with incumbent PD-1/PD-L1 category leaders, their model depends on development cost arbitrage (e.g. U.S. vs China) to be financially viable. To satisfy FDA requirements, their clinical trial costs will soar as a result, as some of the data generation shifts to the U.S., while comparisons against SoC will add further cost, e.g. where Keytruda is the SoC, sponsors will need to acquire the comparator at expensive commercial list price.

Irrespective of their individual circumstances, the extraordinary level of ongoing innovation activity poses both strategic and operational challenges for all existing

and emerging PD-1/PD-L1 players. These range from questions about differentiation and carving out a unique value proposition for their asset(s), pursuing the co-development of biomarkers and companion diagnostics alongside their asset(s), to practical questions such as competition for patients and trial feasibility or access to key investigators and trial sites.

Furthermore, challenges are not limited to generating evidence in clinical trials. As we have shown in previous IQVIA research,[22] real world evidence (RWE) has played a critical role in the success of the first two PD-1 market entrants. They used RWE both to develop a deep market understanding to inform their respective strategies and to polish their value propositions through a continuous stream of evidence generated over the product lifecycle. As competition intensifies and the pace of change accelerates, it will be imperative to win the evidence battle, thus raising the cost of playing in the PD-1/PD-L1 market further still.

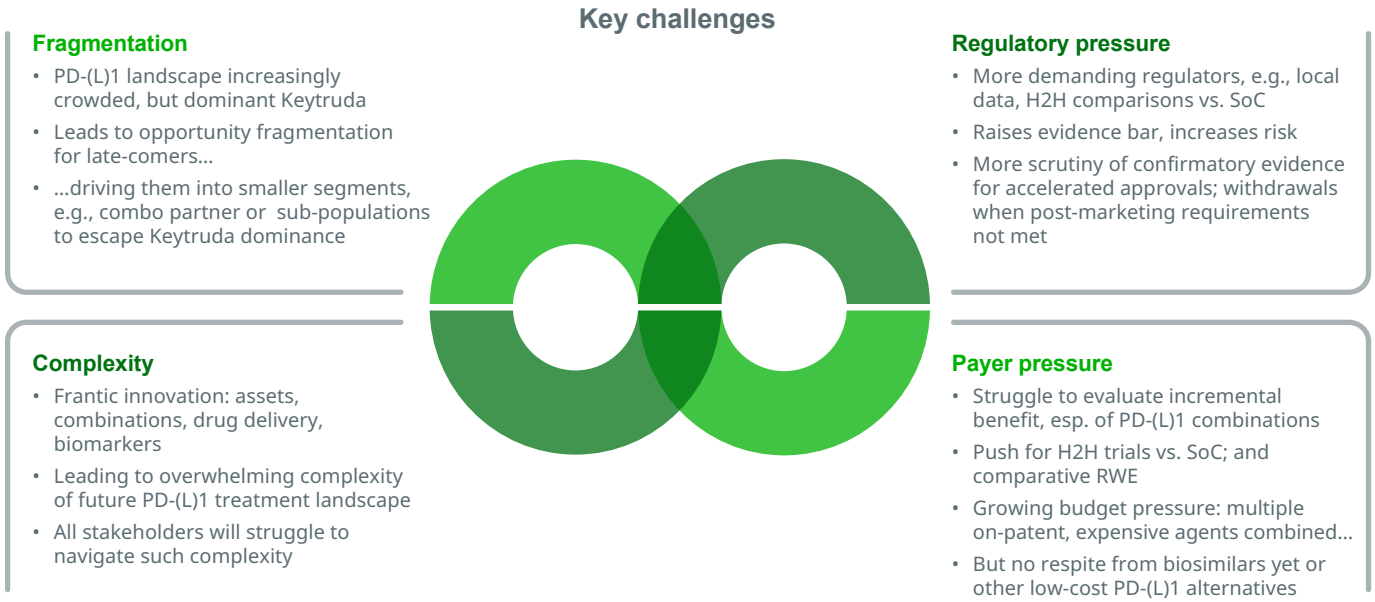
How the collective answers to those challenges play out will determine the shape of the future PD-1/PD-L1 therapy landscape.

Future outlook: Considerations for innovators

The confluence of intense competitive dynamics and a surge in innovation creates strong headwinds for the future PD-1/PD-L1 market.

- **Complexity:** Frantic innovation activity spanning novel assets, combination therapies, enhanced drug delivery technologies and biomarkers is creating an impossibly complex future PD-1/PD-L1 treatment landscape which all stakeholders, including manufacturers, regulators, payers, healthcare professionals and patients, will struggle to navigate.
- **Fragmentation:** As the PD-1/PD-L1 market becomes increasingly crowded while Keytruda is deeply entrenched and maintains its dominant position across many indications, late-comers will face opportunity fragmentation that will drive them into smaller market segments, e.g. as partner in combination regimens or being forced to target patient sub-populations to escape the dominance of Keytruda.

Figure 8: In the eye of the storm – The future PD-(L)1 inhibitor market is facing strong headwinds



Source: IQVIA European Thought Leadership

- **Regulatory pressure:** The FDA's criticism of current trends in PD-1/PD-L1 development and its stance in recent reviews are indicative of growing regulatory scrutiny. Demand for local data and head-to-head comparisons vs. the latest standard of care are raising the evidence bar that innovators will have to clear for regulatory success, and thus driving up cost and increasing development risk. Furthermore, the FDA is likely to scrutinise confirmatory evidence more rigorously for products approved via the accelerated pathway and revisit its original decisions. For example, between December 2020 and March 2021 four manufacturers, BMS, AstraZeneca, Merck and Roche, voluntarily withdrew specific indications for their respective PD-1/PD-L1 inhibitors amid an industry-wide review by the FDA's Oncology Center of Excellence of accelerated approvals with confirmatory trials that did not meet their post-marketing requirements.[23] This may well be a harbinger of things to come.
- **Payer pressure:** Faced with the overwhelming complexity of the emerging PD-1/PD-L1 landscape, payers are increasingly struggling to evaluate the incremental benefit of new PD-1/PD-L1 therapies, in particular combinations. They will therefore also push for head-to-head trials vs. a relevant standard of care, possibly even against competing, novel PD-1/PD-L1 regimens to compare differential value. Demand for comparative real-world evidence (RWE) for both effectiveness and safety will also increase to help payers understand benefits in routine practice. Overall, payer scrutiny of value will intensify because of growing budget pressures, with many of the combination regimens including multiple, often on-patent and expensive agents, while in the near- to medium-term there will be no respite from biosimilars or other low-cost PD-1/PD-L1 alternatives.

These combined headwinds make the PD-1/PD-L1 market an unforgiving place, especially for late-comers and new entrants. Nevertheless, opportunities in the future PD-1/PD-L1 market continue to exist.

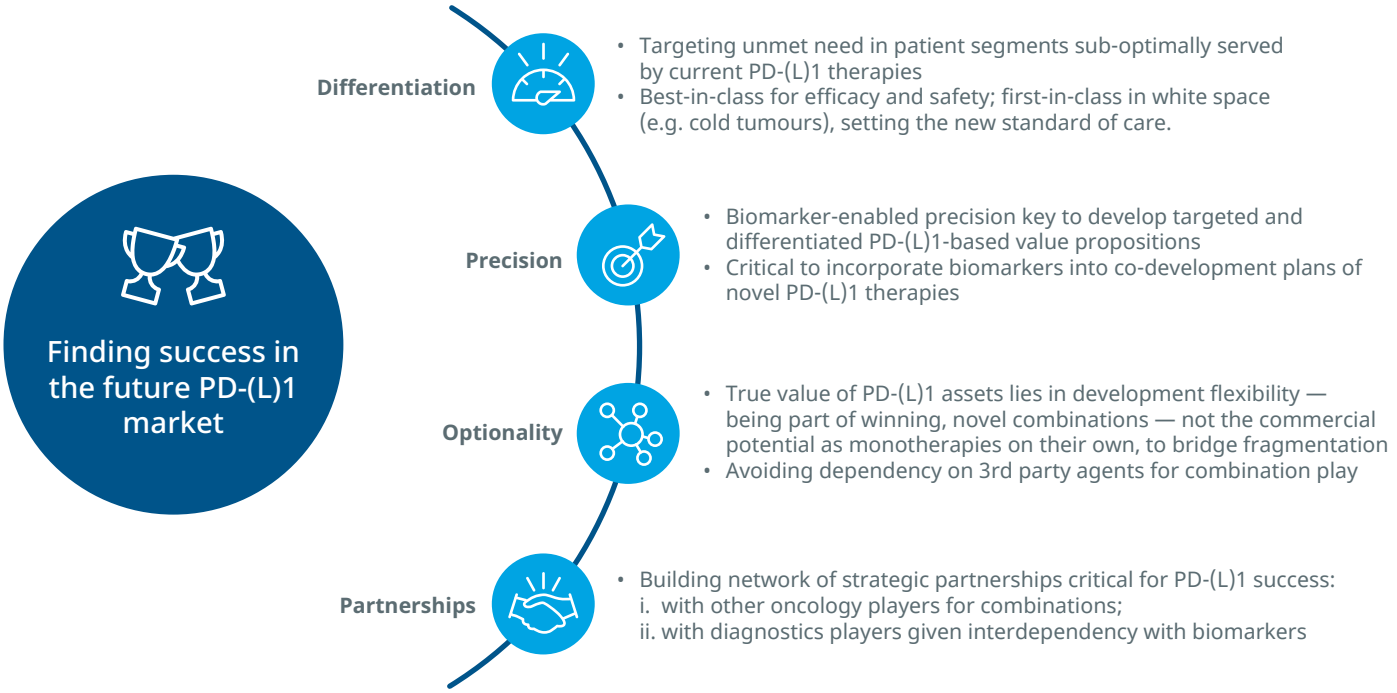
Finding differentiation is paramount for success in the crowded PD-1/PD-L1 landscape with its prevailing competitive dynamics. This means targeting unmet need, for example as the best-in-class option in efficacy and safety for a patient segment served sub-optimally by current PD-1/PD-L1 therapies, or even being first-in-class when going after white space, e.g. turning cold tumours that have eluded immunotherapies to date into hot ones, with the aim of setting the new standard of care.

Biomarker-enabled precision will play a key role for creating such targeted and differentiated value propositions. In this context, the competitive dynamics among diagnostics companies matter as several players are driving testing innovation to enable precision medicine, for example Illumina/Grail, Guardant Health, Exact Sciences, Adaptive, Natera, Foundation Medicine, to name a few. How these dynamics play out will shape the future biomarker testing landscape, e.g. which specific biomarker test will become the standard for a given tumour type, or what role will broad, pan-tumour tests play in future? Therefore, not only is it important to incorporate biomarkers into (co-)development of novel PD-1/PD-L1 therapies, innovators must also establish a network of strategic partnerships with key diagnostics players, given the interdependencies between biomarker adoption and testing standards, and commercial success in the PD-1/PD-L1 market.

With the rise of combination approaches shaping the future treatment landscape, the true value of PD-1/PD-L1 assets lies in providing development optionality and flexibility – being part of winning, novel combinations — not in the commercial potential as monotherapies in their own right. This will allow innovators to overcome opportunity fragmentation by playing in multiple patient sub-segments to achieve scale.

Arguably, the PD-1/PD-L1 market may be viewed as a microcosm of where oncology is headed as a whole, but with the key drivers and challenges intensified.

Figure 9: Considerations for PD-(L)1 innovators



Source: IQVIA European Thought Leadership.

As immuno-therapies establish themselves as a mainstay of cancer treatment, players with a broader oncology portfolio must also consider the risk to their oncology ambitions from a dependency on third-party checkpoint inhibitors for participating in the opportunity of combination therapies. This risk of a potential dependency will persist for the time being, as no off-patent PD-1/PD-L1 inhibitors will become available as backbone alternatives any time soon, with Keytruda likely to maintain exclusivity until late into the second half of the decade.

When Keytruda loss of exclusivity (LoE) eventually does happen, the entry of pembrolizumab biosimilars will likely be a seismic event for the PD-1/PD-L1 market. While there are many uncertainties around the extent and speed of the impact, innovators should think ahead to the Keytruda post-LoE era and consider the role of their launches between now and then to position themselves with next generation immuno-therapies in a world where Keytruda biosimilars co-exist.

The PD-1/PD-L1 market is not for the faint-hearted. However, despite the strong headwinds the market is facing, with the right strategy and an open mindset for embracing partnerships, shrewd innovators will continue to capture attractive opportunities and find success with novel PD-1/PD-L1 therapies.

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05.2022.NEMEA