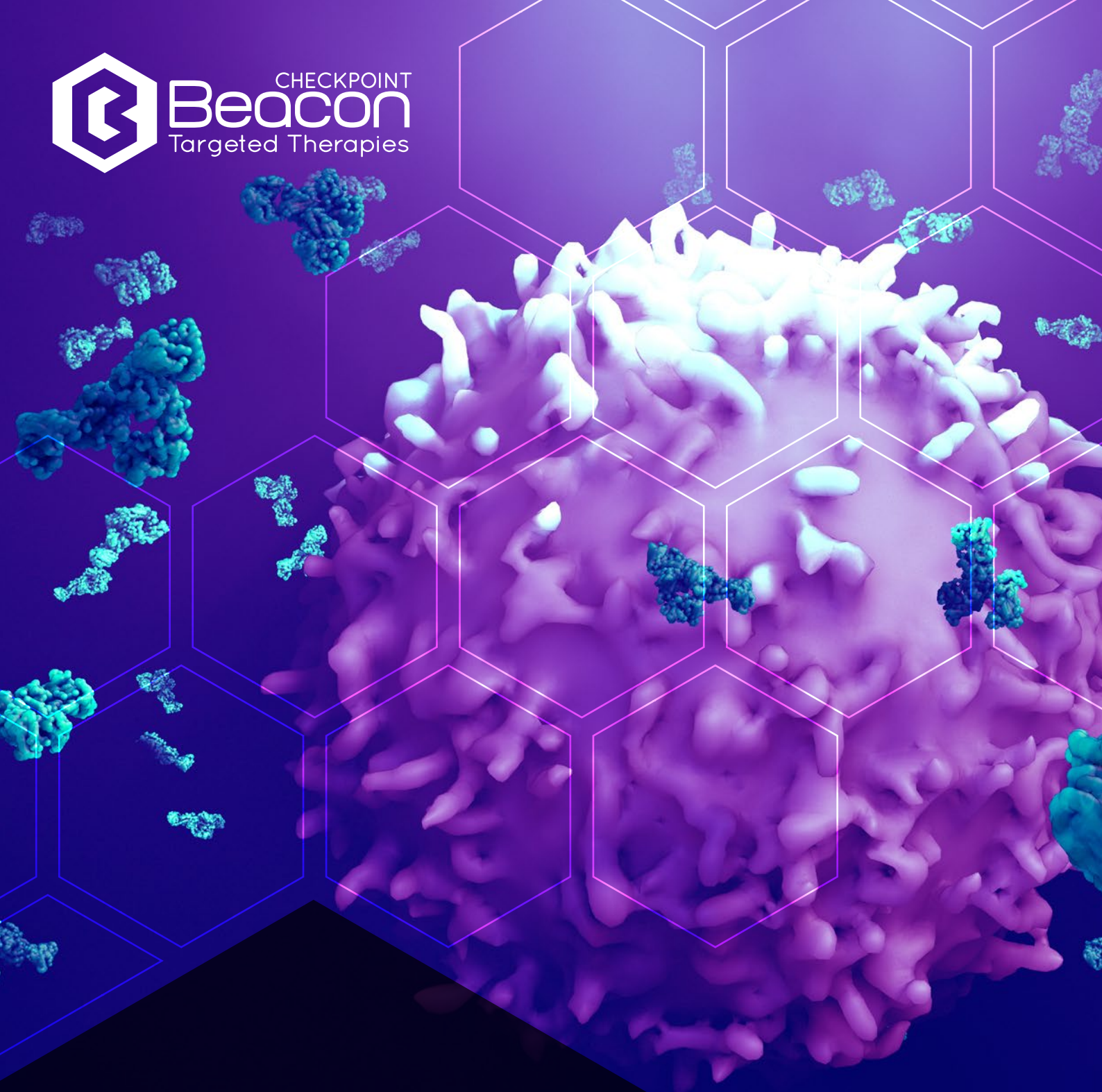
CHECKPOINT Beacon Targeted Therapies



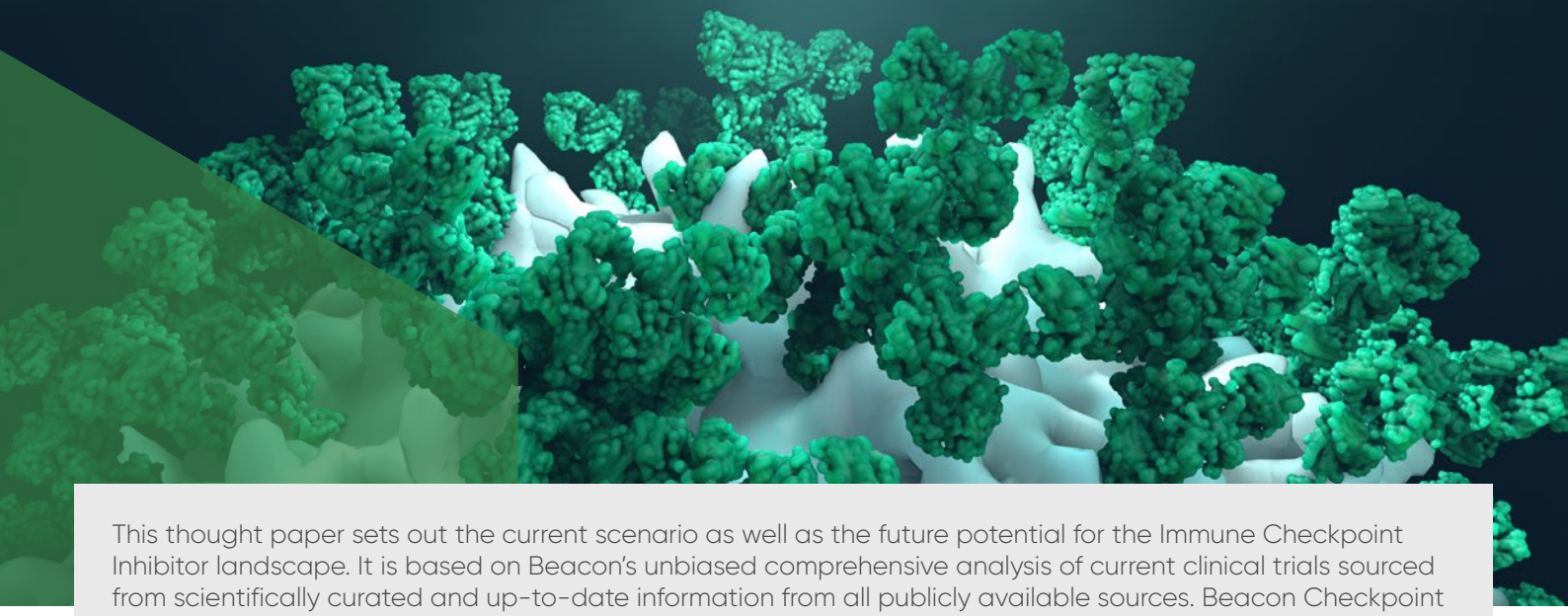
THE NEW IMMUNE-ONCOLOGY CHECKPOINT THERAPY TRIAL PARADIGM

www.beacon-intelligence.com

CHECKPOINT Beacon Targeted Therapies

THE NEW IMMUNE-ONCOLOGY CHECKPOINT THERAPY TRIAL PARADIGM

COVID-19 disruption is, for now, curbing innovation in the immune-oncology (IO) checkpoint space and driving a reorientation of clinical trial priorities. Are we now at a turning point for the next generation of these promising cancer therapies?



This thought paper sets out the current scenario as well as the future potential for the Immune Checkpoint Inhibitor landscape. It is based on Beacon's unbiased comprehensive analysis of current clinical trials sourced from scientifically curated and up-to-date information from all publicly available sources. Beacon Checkpoint is a sector-specific database that includes trial and drug records for preclinical, active, approved, and discontinued Immune Checkpoint Modulator Combinations and Monotherapies across 28 checkpoint targets.

There can be few clinical research areas more laden with therapeutic promise than that of novel immuno-oncological drugs through Immune Checkpoint Inhibitors (ICIs).

The past decade has seen a deluge of advancements, giving way to optimism that more progress is ahead as our understanding grows about how immuno-oncology treatments work, both as monotherapies and in combination.

In revolutionizing the oncology field – with spectacular clinical outcomes for some patients – checkpoint therapies have simultaneously driven a re-evaluation of cancer management to encompass not only the cancer cells to be targeted and destroyed, but also the tumor microenvironment.

Combination ICI therapies, to overcome resistance and broaden clinical utility, are now the main drivers of growth in frontline and second-line research for a range of specific disease indications. The top five of these being: Non-Small Cell Lung, Head and Neck, Bladder, Breast and Skin Cancers.

It is hoped that as more biomarkers for predicting ICI efficacy and toxicity are identified – together with pharmacodynamics parameters – ICI regimens can be further optimized to help treat more cancer types and more patients.

Immune checkpoint inhibitors (ICIs) explained

What are ICIs?
ICIs consist of inhibitory and stimulatory pathways that maintain self-tolerance and assist with immune response. In cancer, immune checkpoint pathways are often activated to inhibit the nascent anti-tumor immune response.

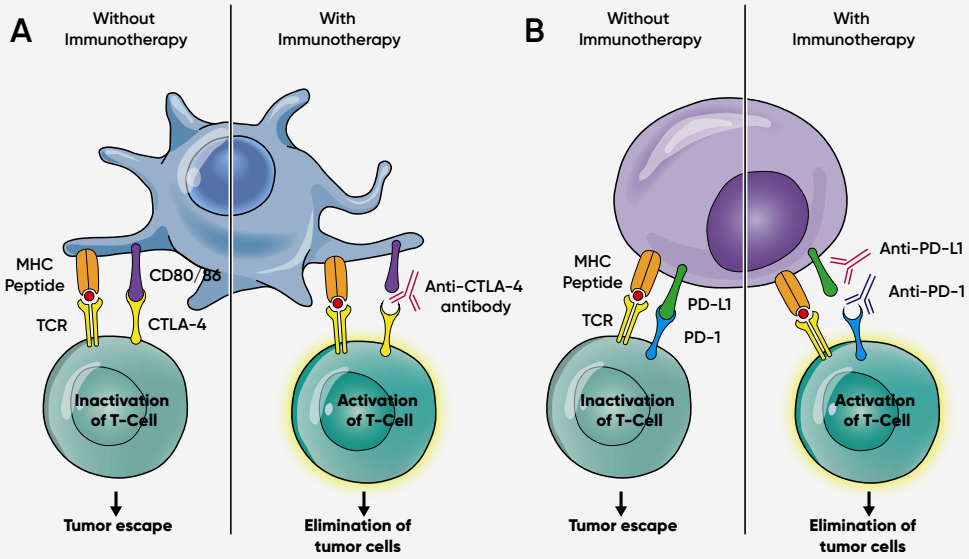
What is the mechanism of checkpoints?
Checkpoint inhibitors work by releasing a natural brake on the immune system so that immune cells recognize and attack tumors and enhance the body's immunological activity.

Which are the most widely studied inhibitory checkpoint pathways?
These include Cytotoxic T lymphocyte-associated molecule-4 (CTLA-4), programmed cell death receptor-1 (PD1), and programmed cell death ligand-1 (PDL1).

What indications are they utilized for?
Drugs blocking these pathways are now utilized for a wide variety of malignancies. They have demonstrated durable clinical activities in a subset of cancer patients.

What other pathways are under investigation?
This approach is rapidly extending beyond CTLA-4 and PD(L)1. New inhibitory pathways are now being researched, and drugs blocking LAG-3, TIM-3, TIGIT, VISTA, or B7/H3 are being explored. Furthermore, agonists of stimulatory checkpoint pathways such as OX40, ICOS, GITR, 4-1BB, CD40, or molecules targeting tumor microenvironment components like IDO or TLR are also under investigation.

What are the immune-mediated adverse effects of ICIs and their management in cancer?
While ICIs lead to benefits for numerous cancer patients with disease control and sometimes improved survival outcomes, toxicity and safety problems do occur. Immune-mediated adverse effects have the potential to affect any organ system. The skin, joints, endocrine glands and gastrointestinal tract are most commonly affected.



The binding together of MHC-peptide and TCR activates the anti-cancer pathway of T-cell–mediated immune response. The binding of CTLA-4 to its ligand and PD1 to PDL1, on the contrary, inhibit the anti-cancer pathway. The binding of monoclonal antibodies, such as ICIs, to CTLA-4, PD1 or PDL1, prevent the deactivation of the anti-cancer pathway. (CTLA-4= cytotoxic T-lymphocyte-associated antigen 4; PD1= programmed death 1; PDL1= programmed death ligand 1 APC: Antigen Presenting Cell, TCR: T-Cell Receptor, MHC: Major Histocompatibility Complex). Image taken from:: "Soularue E, Lepage P, Colombel JF, et al Enterocolitis due to immune checkpoint inhibitors: a systematic review Gut 2018;67:2056-2067" - https://gut.bmj.com/content/67/11/2056

Overview: The IO Market

Global checkpoint market growth is expected to expand due to the increasing prevalence of cancer and a continued rise in drug launches against a backdrop of robust pipelines.

Who are the major players operating in the global immune checkpoint inhibitors market?
They include Merck & Co, Bristol-Myers Squibb, Regeneron Pharmaceuticals, Genentech., EMD Serono, Novartis, Pfizer, F. Hoffmann-La Roche, AstraZeneca, ImmunOs Therapeutics, Immutep, NewLink Genetics and Ono Pharmaceutical, among others.

What is the IO market size?
According to the new market research report Immunotherapy Drugs Market by Type (Monoclonal Antibodies, Check Point Inhibitors, Interferons, and Interleukins), Therapy Area (Cancer, Autoimmune diseases & Inflammatory, Infectious Diseases), End User (Hospitals, Clinics) - Global Forecast to 2025, published by MarketsandMarkets™, the Immunotherapy Drugs Market is projected to reach USD 274.6 billion by 2025 from USD 163.0 billion in 2020, at a CAGR of 11% during the forecast period.

COVID-19 Implications for Trial Registrations

With the unprecedented number of new investigational agents and companies in IO, it is difficult to track the current agents in clinical development and their clinical trials progress. Yet more challenging is making an assessment of the likely impact of the coronavirus pandemic.

Driven by the scale of the IO treatment market and high unmet patient need, the pipeline currently comprises no fewer than 28 checkpoint targets tracked by Beacon. This comprises 738 assets that are active or in preclinical development.

Covid-19 has severely disrupted pharma R&D across the board and the ICI space is no exception. This impact is clear from the checkpoints trials statistics compiled by Beacon. These show that the rapid pace of new clinical ICI studies starts has come – if not to a halt – to a hiatus.

New Trial Starts Go on Hold

In 2018 and 2019 respectively, the overall number of newly registered ICI trials soared by 18% (1,034) and 19% (1,228) year on year.

Fast forward to 2020, however, and the number of started trials registered in 2020 has slumped, growing by a mere 4.4% (1,282) since 2019. Thus far, for 2021, only 12 new trials have been registered.

This is a clear indication that we are now experiencing a 'new normal' for R&D in IO in response to the pandemic. Disruptions are happening in both new enrollment and in keeping existing patients on therapies.

A likely factor here is that cancer seems to be a risk factor for contracting COVID-19 and that patients with cancer could be more susceptible to poorer outcomes.

Trials that are currently active and no longer recruiting have achieved 48% of their target enrollment to date. This is a marked difference compared to trials that have been officially disrupted by COVID-19 which are only reporting only 16% of their enrollment estimate.

Phase 4 Provides Promise

But there is reason for optimism. Research is continuing apace, with continuous year-on-year growth right up to 2020 of new ICM trials registered.

Per annum, there has also been a consistent growth of ~12-13% in exploratory therapeutic phase 1/2 and phase 2 trials.

Most tellingly, even in 2020, we are seeing an expansion in phase 4 trials.

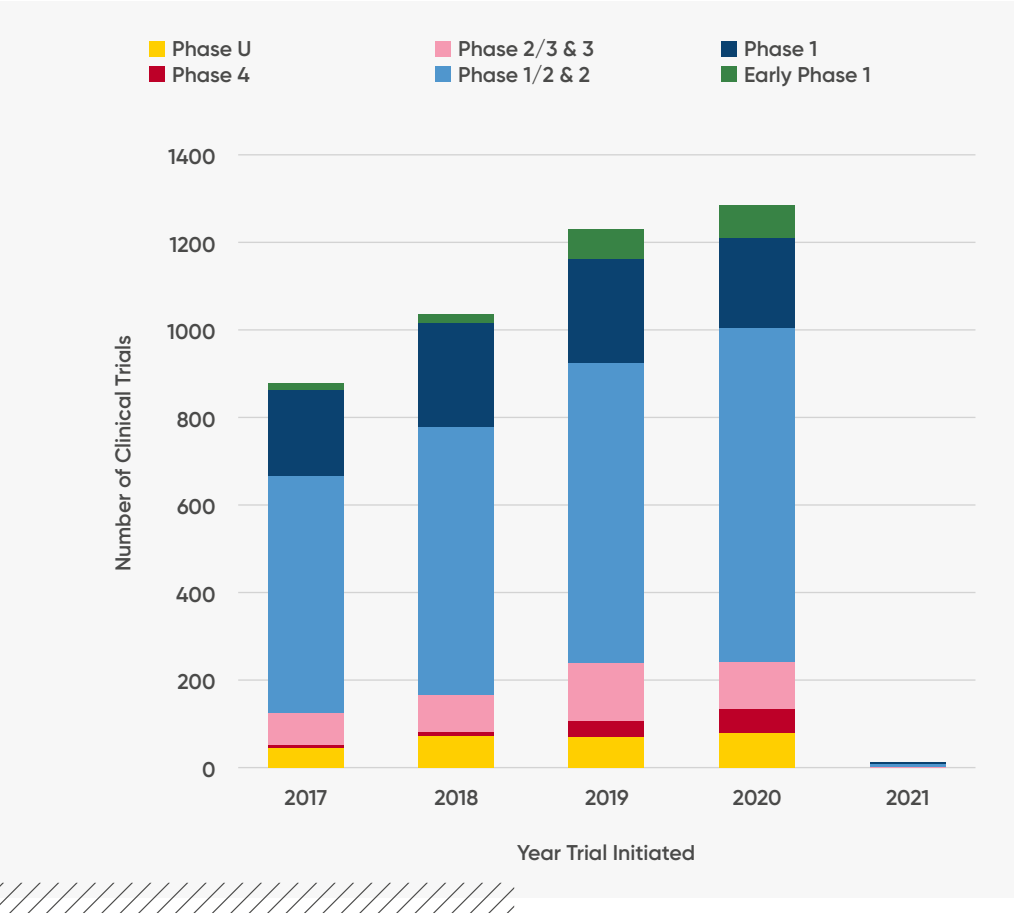
And these are on an upward trend.

There were 35 phase 4 trials reported to start in 2019 compared to 7 in 2018. This encouraging surge continued in 2020, with no sign of phase 4 trials being paused or halted. In fact, a further 54 phase 4 trials were registered to start in 2020.

The phase 4 trials registered in 2019 and 2020, whether monotherapy or combination, are likely to be the harbingers of what is to come. They should deliver approvals and data sets that will give rise to fresh innovation in late 2021 or early 2022.

They will pave the way for critical thinking for the refinement of more sophisticated trial designs to test checkpoint assets in different settings, combinations and treatment lines and improve durable efficacy rates.

Fig. 1 The eveolution of checkpoint trials for cancer indications since 2017. Both inactive and currently active trials have been used in the analysis to show the number of trials registered to start year after year. Data was collected in Oct 2020. Data sourced: Beacon Checkpoint.



ICI Key Findings and Frequency in Phase 2-3 Trials

BEACON TRACKED THE 2,378 PHASE 2-3 TRIALS FROM 2017-2020 TO HIGHLIGHT THE INVESTIGATIONAL AGENTS BEING STUDIED. OF THESE TRIALS, 88% PROVIDE LINE OF THERAPY; 19% ARE FRONTLINE STUDIES; 51% ARE SECOND-LINE OR GREATER.

The field of immunology provides a slew of potential molecules and pathways to target, with immunotherapy combinations optimally chosen based on biologic rationale to address the mechanisms of primary and acquired immune resistance. (Other commercial considerations – such as advancing opportunities for new regulatory approval and marketing of the combination agent – may also be deciding factors.)

With the continuous expansion of new checkpoint investigational agents, those being continually advanced to phase 2-3 trials provide us with insight into the likely shape of the landscape ahead.

Beacon tracked the 2,378 phase 2-3 trials from 2017-2020 to highlight the investigational agents being studied. Of these trials, 88% provide line of therapy; 19% are frontline studies; 51% are second-line or greater.

The Checkpoint team observed that first-generation targets, predictably, are being prioritized. But drilling down and presenting the top 8 next-generation targets and bispecific antibodies that have shown to have between 7 and 35 assets used in these trials, our research showed these five key takeaways:

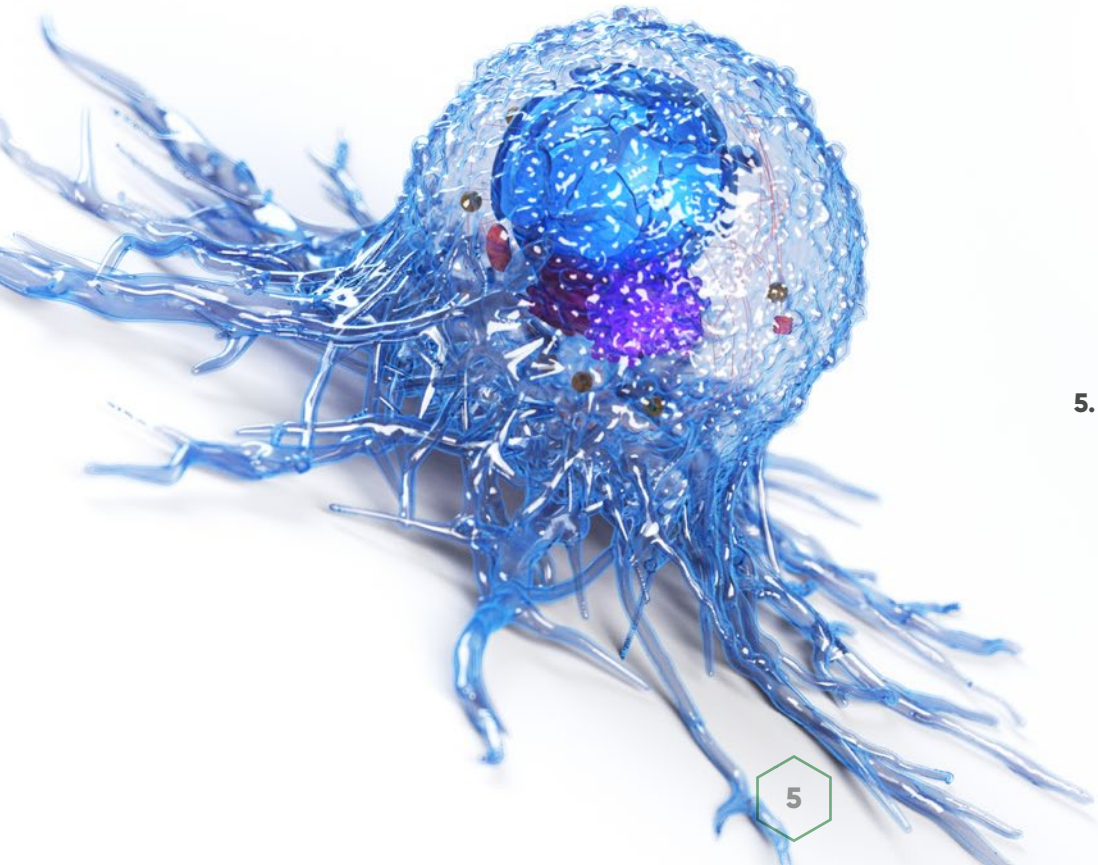
1. **First-generation targets**
   All 11 approved drugs are being utilized as a monotherapy or in combination, (most commonly with chemotherapy), with Tremelimumab being used as a combination drug with Durvalumab in 27% of trials.

2. **Next-generation targets**
   LAG-3 is shown to have multiple assets actively being utilized in combination trials. Relatlimab dominates the space and is being frequently tested with Nivolumab.

3. **Bispecifics**
   Bispecific assets are repeatedly appearing in therapies, which suggests more innovation in the way ICIs are being combined is underway.

4. **NSCLC**
   This heterogeneous disease has shown to respond well to PD(L)1 inhibitors e.g. nivolumab and pembrolizumab. Despite frequent utilization of next-generation targets, NSCLC therapies remain focused on utilizing first-gen combinations commonly with chemotherapy to address the pathophysiological characteristics.

5. **Bladder Cancer**
   Atezolizumab has demonstrated encouraging clinical activity for Bladder cancer. In trial formats for 2017-2020, it is apparent approved immune checkpoints are being investigated for their capabilities to battle bladder cancer not only at frontline, but also as an adjuvant therapy.



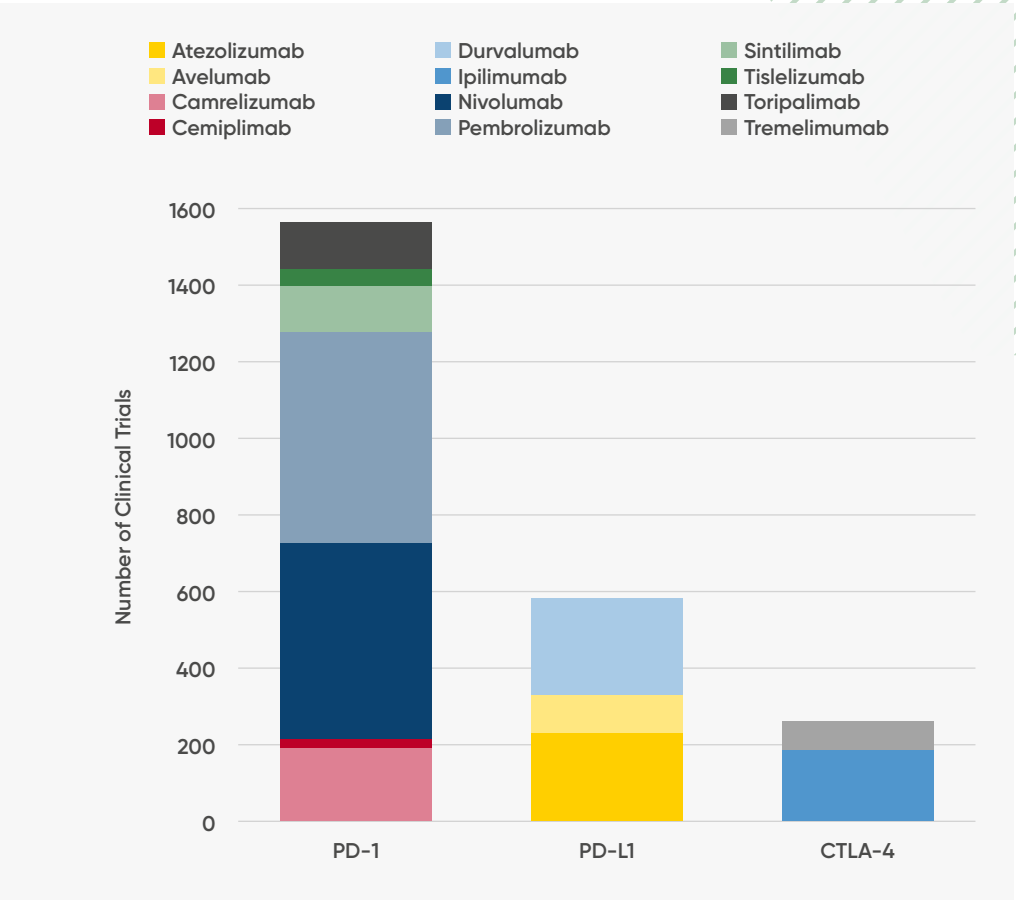
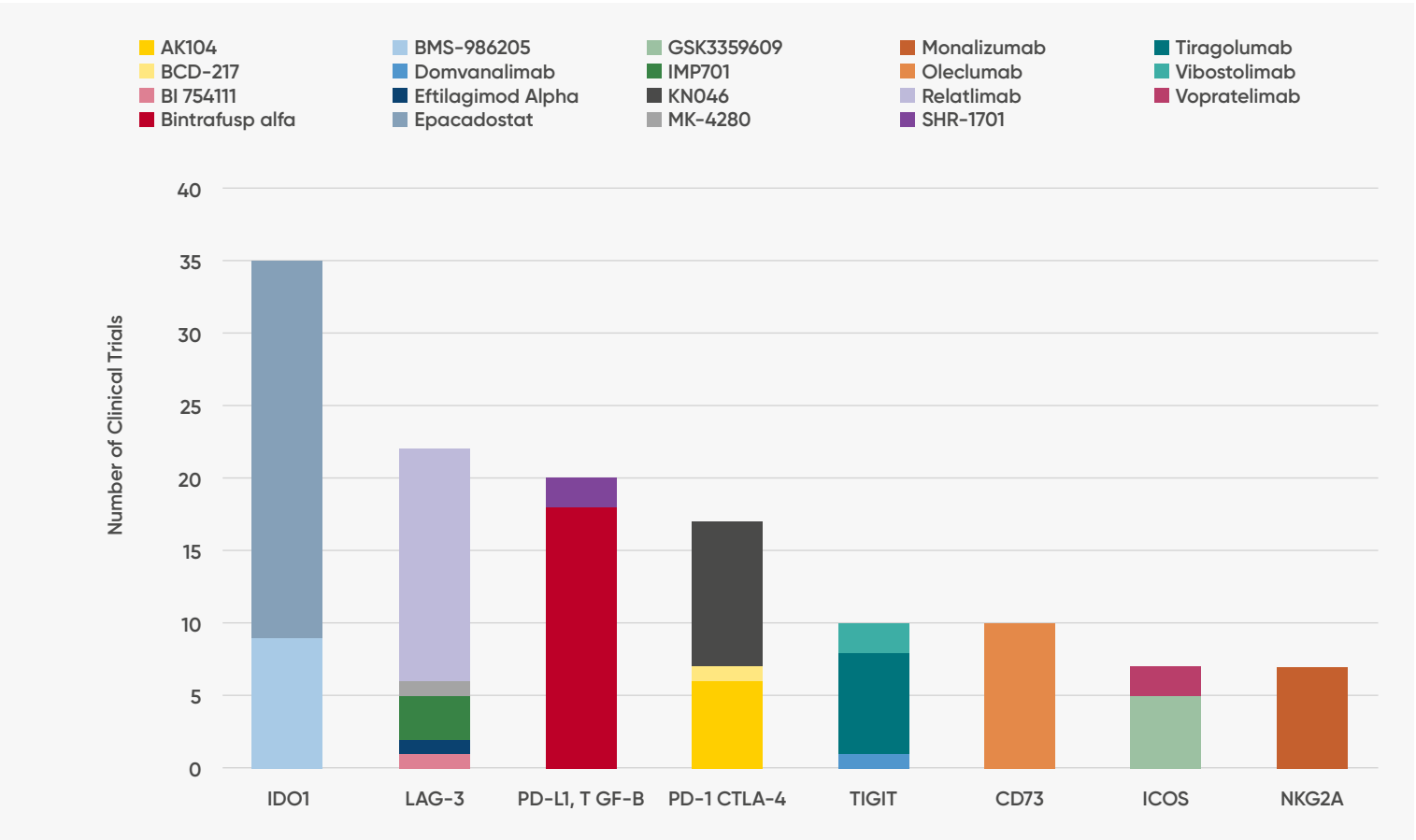


Fig. 2 Analysis of first (left) and next (below)-generation targets being used in clinical trials from 2017 to 2021. Includes bispecific immune checkpoint modulators. Data sourced: Beacon Checkpoint



COVID-19 Caution in the Clinic

While the trend for combination trials shows no sign of slowing at present, the impact of the pandemic for R&D cannot be ignored.

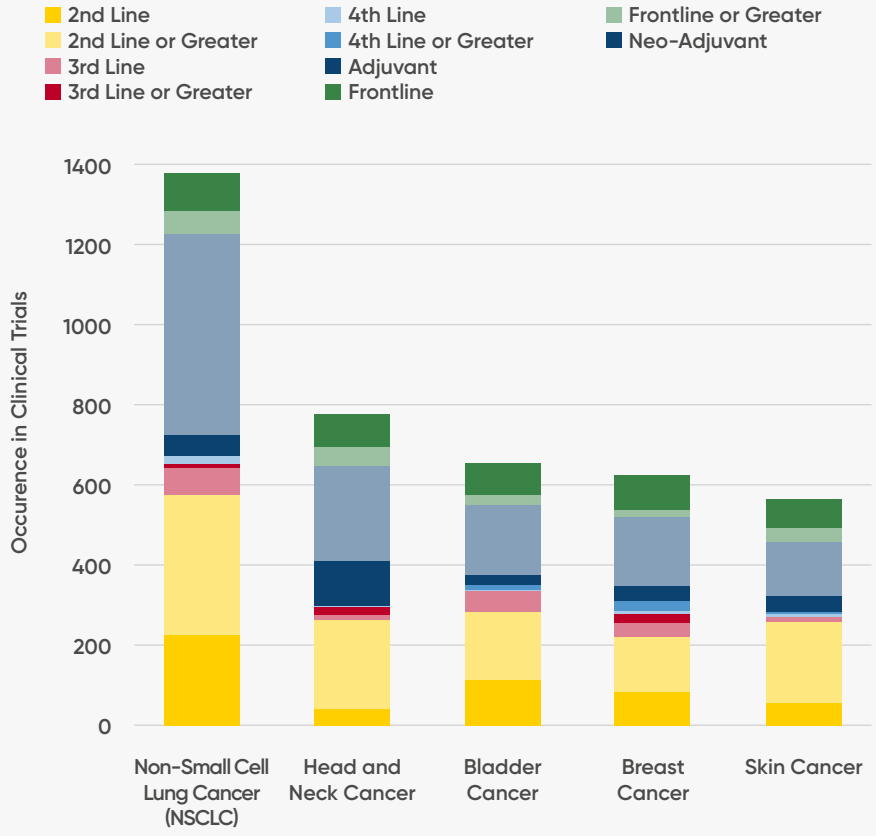
Pre-COVID-19, combination therapies under consideration for future investigation in a clinical setting – such as the interaction of PD(L1) and chemotherapy – were being widely explored.

Post-COVID-19, and the attainment of synergy with such assets now appears more complex due to the risk of immune-mediated adverse effects. This main factor here is that the interplay of COVID-19 and the immune system has been associated with the development of Acute Respiratory Distress Syndrome (ARDS).

Oncologists, consequently, are now taking a more cautious treatment approach to ensure immune-suppressive treatment is only used when it is felt safe to do so.

While we remain under pandemic conditions, this is likely to result in a more conservative stance in the investigation of new targets for various indications due to unknown toxicities and autoimmune side effects.

Fig. 4 The top 5 cancer indications studied in trials registered to start 2017 - 2021, together with the lines of therapy which they are being investigated.



CHECKPOINT Beacon Targeted Therapies

The COVID conundrum for ICIs and NSCLC

Protocols for the utilization of ICIs with NSCLC – a heterogeneous indication accounting for over 80% of all lung cancers – are, for now, changing.

- Cytokine storm syndrome and acute respiratory distress syndrome (ARDS) are factors causing deterioration of COVID-19 patients.
- The severity of COVID-19 has shown to be high in lung cancer patients.
- Although tumor-specific characteristics in data from a limited sample size* did not appear to impact the severity, patient-specific features did.
- Uncertainty remains as to whether the vulnerability of lung cancer patients could lead to the potentiation of ARDS through treatment with immune checkpoints.

Many questions remain. Not least -

- Whether immuno-modulation is beneficial or harmful in patients with cancer and COVID-19?
- How will the disease characteristics of COVID/ cancer patients differ, and what impact will this have for the inclusion of these patients in interventional trials?
- How will trial protocols be adapted to meet the new challenges in light of new guidance from the FDA and EU regulators providing greater flexibilities for use of, for example, decentralized and virtual trials and telehealth platforms?
- What will be the impact for population sizing?

** https://www.esmo.org/oncology-news/severity-of-covid-19-in-lung-cancer-patients*

The 'Next Normal' for the Checkpoint Trial Space

The specific trial issues caused by the COVID-19 pandemic are likely to continue providing researchers with obstacles to navigate for the short to medium term – or at least until widespread adoption and availability of authorized COVID-19 vaccines heralds a resumption of normal activities.

But, while many checkpoint trials have been halted or not initiated on their proposed dates for late 2020 and early 2021 – most likely due to COVID-related patient safety and enrolment hurdles – encouragingly, other cancer therapeutics such as cell therapy, cancer vaccines and oncolytic viruses have continued to initiate trials.

This indicates that if, for now, ICI developers are being forced to adapt their operations, backlogged clinical trial activity will likely restart once the crisis has passed.

Certainly, delays from regulatory bodies to review results and progress trials due to COVID-19 are to be expected. But it is to be hoped that this will be mitigated following the FDA's stated commitment to help advance trials about to start or in the clinic.

It is also possible that manufacturing of ICIs may be impacted in the near future. COVID-19 could affect supply and demand for two reasons. The first is that pharma is redirecting its resources towards the pandemic. The second is that many ICIs are administered by physician practices that are seeing pandemic-induced declines in patient volume.

Nonetheless, despite the dark cloud of COVID-19 undoubtedly proving a challenge for checkpoint R&D (and indeed for pharma across the board), there are brighter horizons ahead.

Concluding checkpoint trials are in the majority providing positive ORR and PFS from trial data that Beacon is tracking closely at major conferences such as ASCO, AACR, ESMO, ASH and others.

These endpoints are illuminating the way towards a 'next normal', which – if still in flux – offers plenty of inspiration for the field.

So, while the future of the immune-oncology (IO) checkpoint trial space may, for now, be unclear, what is clear is this.

The full story of its potential is yet to be told. ■

This thought paper is insight and analysis that has been manually curated and conducted by Beacon's Checkpoint Expert, Navneet Kaur Bhogal, PhD. She has utilized Beacon Checkpoint database, which exhaustively and comprehensively covers immune checkpoint inhibitor or stimulator clinical trials and drugs across all publicly available sources in real time.

To find out more about how we can help you leverage this insight and information to suit your drug development programs, please do get in touch by visiting ***www.beacon-intelligence.com/checkpoint***

FDA-APPROVED CHECKPOINT IMMUNOMODULATORS OVERVIEW

Atezolizumab (Tecentriq®):
A checkpoint inhibitor that targets the PD(L)1 pathway; approved for subsets of patients with bladder cancer, breast cancer, liver cancer, lung cancer, and melanoma

Avelumab (Bavencio®):
A checkpoint inhibitor that targets the PD(L)1 pathway; approved for subsets of patients with bladder cancer, kidney cancer, and Merkel cell carcinoma, a type of skin cancer

Cemiplimab (Libtayo®):
A checkpoint inhibitor that targets the PD(L)1 pathway; approved for subsets of patients with cutaneous squamous cell carcinoma, a type of skin cancer

Durvalumab (Imfinzi™):
A checkpoint inhibitor that targets the PD(L)1 pathway; approved for subsets of patients with bladder cancer and lung cancer

Ipilimumab (Yervoy®):
A checkpoint inhibitor that targets the CTLA-4 pathway; approved for subsets of patients with melanoma, liver cancer, and lung cancer

Nivolumab (Opdivo®):
A checkpoint inhibitor that targets the PD(L)1 pathway; approved for subsets of patients with bladder cancer, colorectal cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, lymphoma, and melanoma

Pembrolizumab (Keytruda®):
A checkpoint inhibitor that targets the PD(L)1 pathway; approved for subsets of patients with bladder cancer, cervical cancer, colorectal cancer, cutaneous squamous cell carcinoma, esophageal cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, lymphoma, melanoma, Merkel cell carcinoma, and stomach cancer. It is also approved to treat subsets of patients with cancers of any type that present with certain genetic mutations (MSI-H or TMB-H).

Contact us:
Beacon@hansonwade.com

Follow us:
Beacon Targeted Therapies @beaconintel

www.beacon-intelligence.com