White Paper

# Evolving Landscape of Immuno-Oncology

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# Evolving landscape of Immuno-Oncology — India perspective

The incidence of cancer cases in India is expected to increase by 12.8% by 2025, highlighting a pressing need for advancements in oncology management. Lung and breast cancers are the most common among both sexes, with one in nine individuals likely to develop cancer in their lifetime. Addressing this health crisis demands innovative and effective solutions. The unmet needs in diagnostic and treatment strategies evolve in parallel with oncology advances. Oncologists now face increasingly complex decisions, balancing newly approved treatments with investigational agents. Ongoing clinical trials underscore a rise in immunotherapy approvals for early-stage cancers. The future of cancer immunotherapy hinges on combination therapies, such as immune checkpoint inhibitors (ICIs) paired with other checkpoint inhibitors, with chemotherapy, targeted therapy, and Tumor Infiltrating Lymphocytes (TIL), cell therapy like chimeric adoptive antigen receptor (CAR)-engineered immune cells — all FDA approved.

Incorporating India into these global trials could broaden patient access to these emerging therapies. Yet, achieving a universal approach presents challenges due to diverse immune-escape mechanisms. Furthermore, the high costs of these novel treatments restrict accessibility within India. To ensure that Indian patients have access to the latest treatment options, India is making significant strides in aligning its healthcare infrastructure and clinical practices with global standards. This progress includes enhancing the availability of novel treatments and facilitating access to cutting-edge clinical trials.

To understand oncologists' perspectives on crucial clinical questions and to narrow the disparity in cancer care between India and other countries, IQVIA Asia's Oncology division organized an advisory board meeting in Mumbai on November 24, 2023. The board consisted of six prominent oncologists from diverse regions of India, in conjunction with IQVIA's medical advisors from its Oncology and BIosimilar Center of Excellence (COE). This advisory board played a pivotal role in identifying the latest treatment opportunities in India, given the country's large population and increasing incidence of cancer.

The advisory board evaluated emerging treatments for various oncology indications, including combination therapies and biomarker-driven approaches. It also examined the future of Immuno-Oncology (IO) therapies with the goal of enhancing patient support through clinical trials and ensuring the availability of treatments aligns with global standards. This includes incorporating patient perspectives via standard-of-care (SOC) questionnaires to understand the real-world impact of drugs.

With the increasing number of cancer patients, particularly those with solid tumors, there is a growing need for more clinical trials and access to the latest treatments. To achieve this, it is crucial to inform stakeholders about the strengths of India's healthcare system, medical expertise, and advancements in clinical trials and regulations. Clinical cancer research must align more closely with the country's healthcare needs and burden of disease, focusing on common and lethal cancers, as well as making clinical trials accessible across all regions and to underserved communities.

In this white paper, we will explore the evolving landscape of immuno-oncology from both global and India's perspectives. We will delve into the significant progress of CAR T-cell therapy in India, examining the development and manufacturing challenges faced and the promising results from recent clinical trials. We will also cover the opportunities of biosimilars trials and their potential to improve healthcare in India. Furthermore, we will address the present challenges for rare cancers in India, highlighting the unique epidemiology and the urgent need for innovative research models and funding to tackle these uncommon yet devastating diseases.

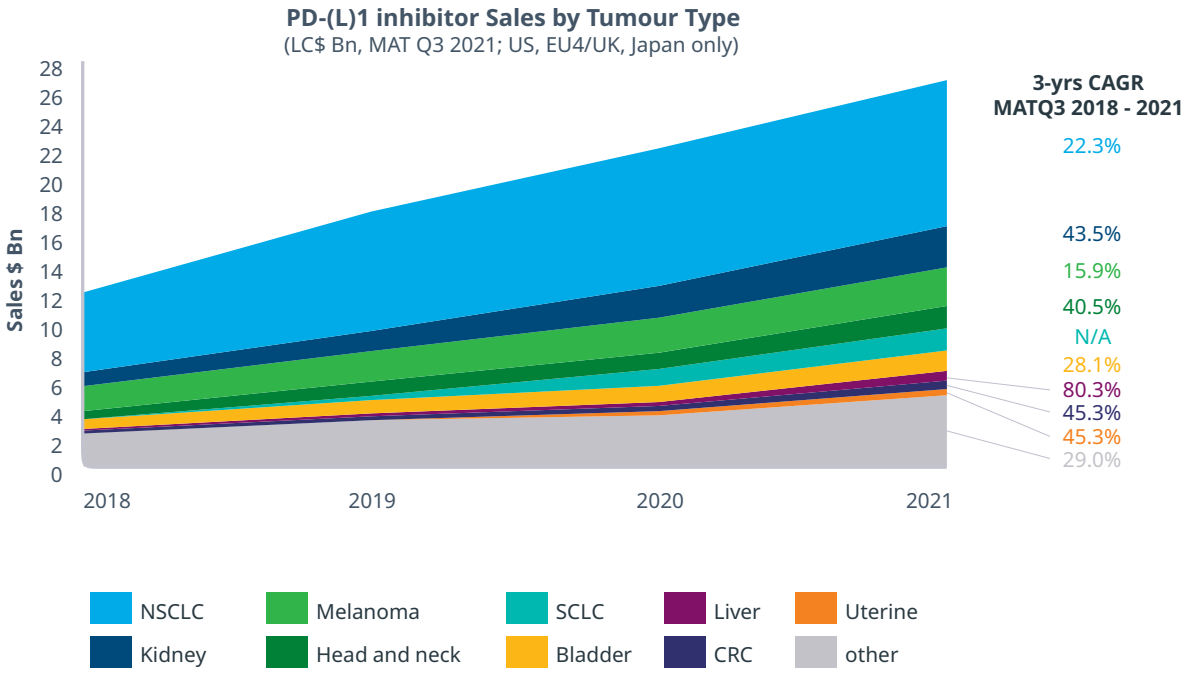
By addressing these topics, we aim to provide a comprehensive understanding of the current landscape and prospects of immuno-oncology in India, emphasizing the importance of collaboration and innovation in improving cancer care for patients across the country.

## Evolving landscape of Immuno-Oncology — global perspective

We are currently in an era of expanding oncology treatments, with immunotherapy prominently featured as a transformative approach. Immunotherapy, including vaccine therapy, CAR T cell therapy, TILs and ICIs, significantly improves cancer survival rates and is increasingly utilized across various cancer stages, particularly in early-stage tumors. According to IQVIA's analysis of published data, immunotherapy delays disease progression, enhances overall patient survival rates, and improves quality of life. Between 2018 and 2021, the application of immunotherapy expanded to include 17 additional cancer types, with non-small cell lung cancer (NSCLC) being the most prevalent. It is also being integrated with other therapies, such as in the treatment of hepatocellular carcinoma. Additionally, combining immunotherapy with other treatments such as poly adenosine diphosphate-ribose polymerase (PARP) inhibitors represents a growing area of research and practice, particularly in improving outcomes for cancers affecting women, enhancing patient survival rates and prognostic outcomes.

However, access to these drugs varies globally due to cost and reimbursement policies, with a noticeable correlation between a country's income level and the adoption of immunotherapy. Despite high costs, expanding market competition is expected to improve future accessibility as pharmaceutical companies invest more in clinical trials. This competitive landscape can potentially drive down costs and broaden the range of treatment options beyond earlier approved programmed cell death ligand (PD-(L)1) inhibitors.

**Chart 1: 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; 

In recent years, the average number of patients per clinical trial has decreased, even as the overall number of trials has increased and drug approvals have accelerated with smaller participant cohorts. This trend carries significant implications for stimulating market competition and advancing clinical research. Globally, there is a growing shift of clinical trials away from the United States of America (USA), with India emerging as a competitive destination due to its robust network of referral sites.

Moreover, there is a notable increase in single-country trials, particularly focused on PD-(L)1 agents. This trend presents both challenges and opportunities for enhancing global clinical trial diversity. Precision medicine is advancing through strides in biomarker research and next-generation sequencing (NGS). However, hurdles such as the need for improved modeling tools and more effective matching algorithms persist.

*India possesses the capability for biomarker testing and advanced diagnostic modalities, yet cost remains a significant barrier for patients across diverse geographic regions.*

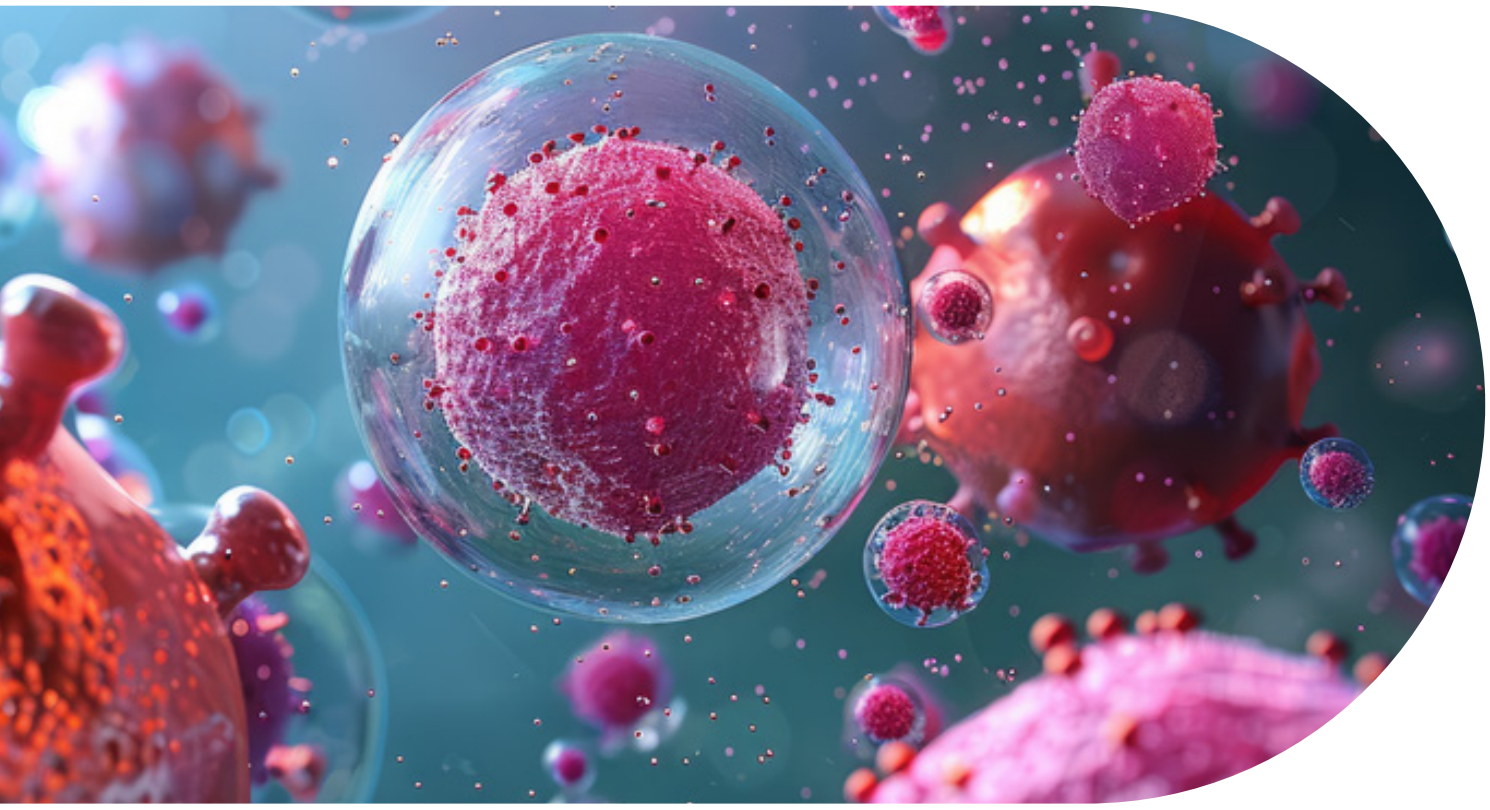
# The progress of CAR T-cell therapy in India

The development of CAR T-cell therapy in India marks a significant milestone where future trials could be conducted with clearer guidelines and reduced barriers. Pioneers in CAR T-cell therapy discussed development and manufacturing challenges in India, emphasizing the critical need for sourcing patient cells and ensuring good manufacturing practices (GMP)-grade vector production.  India has immense potential in Pediatric Trials. For example, The CAR T trial was a Pediatric trial and it is an unaddressed need.

In a phase I/Ib trial conducted by an expert team with twelve subjects, nine underwent infusion after multiple prior treatments. The results at day 30 showed a 66.6% complete response rate without minimal residual disease (MRD), a 25% complete response rate with MRD, and an overall response rate of 92%. Reported toxicities included cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and hypogammaglobulinemia. The discussion emphasized the need to increase the accessibility and affordability of CAR T-cell therapy in India. This can be achieved through local development, participation in global trials, and leveraging existing expertise and infrastructure.

The advisory board endorsed India's potential in conducting trials involving tumor infiltrating lymphocytes (TILs), highlighting the country's substantial patient pool, oncology expertise, and regulatory alignment. Confidence in India's capability to conduct Phase I trials, focusing on anti-tumor activity and targeted patient cohorts, has grown. Initiatives like the Network of Oncology Clinical Trials in India (NOCI), supported by the Biotechnology Industry Research Assistance Council of India (BIRAC), aim to enhance capacity, establish a multicentric registry, and prepare clinical trial sites nationwide.

Insights from the COVID-19 pandemic were also discussed, underscoring its transformative impact on global clinical trials. Key takeaways include the necessity of integrating remote monitoring and risk management strategies into research study protocols worldwide.



# Opportunities for Biosimilars competition at the end of the decade

The lead medical advisor of IQVIA Biosimilars COE initiated a discussion on the current landscape of biosimilars, their future prospects, and anticipated challenges. Legislative amendments establishing a regulatory framework for biosimilars were enacted two decades ago. Since then, biosimilars for over 20 biological medicines have been approved and launched in international markets, significantly expanding access to treatments and reducing healthcare costs. With the extensive knowledge acquired in the development and evaluation of biosimilars, there has been an active discussion about refining clinical development processes, particularly customizing efficacy and safety study requirements based on the specific characteristics of the reference biologic and proposed biosimilar product.

Several biologic drugs, including seven cancer treatments with annual global revenues exceeding $1 billion (such as Keytruda®, Opdivo®, and Tecentriq®), are expected to have their patents expire by 2030. As a result, it is anticipated that within the next four to five years, more than forty international clinical trials will be launched by various entities to introduce biosimilars for these cancer treatments into the market.

Under existing regulatory guidelines, biosimilars must demonstrate comparable pharmacokinetics (PK) and pharmacodynamics (PD), as well as effectiveness, safety, and immunogenicity through extensive comparative clinical trials involving 500 participants or more. For most biosimilars, clinical PK equivalence is evaluated in healthy volunteers to mitigate variability introduced by disease and concurrent medications. However, for biosimilars of immune checkpoint inhibitors (ICIs), PK equivalence must be determined in patients due to the potential for severe immune-mediated side effects affecting any organ or tissue. The anticipated increase in biosimilar and novel product trials, alongside the requirement to assess PK equivalence in patients, complicates the upcoming studies for ICI biosimilars.

**Chart 2: Biosimilars pipeline 2022 — 2030: Biologics with Global Sales >1 Bn USD only**

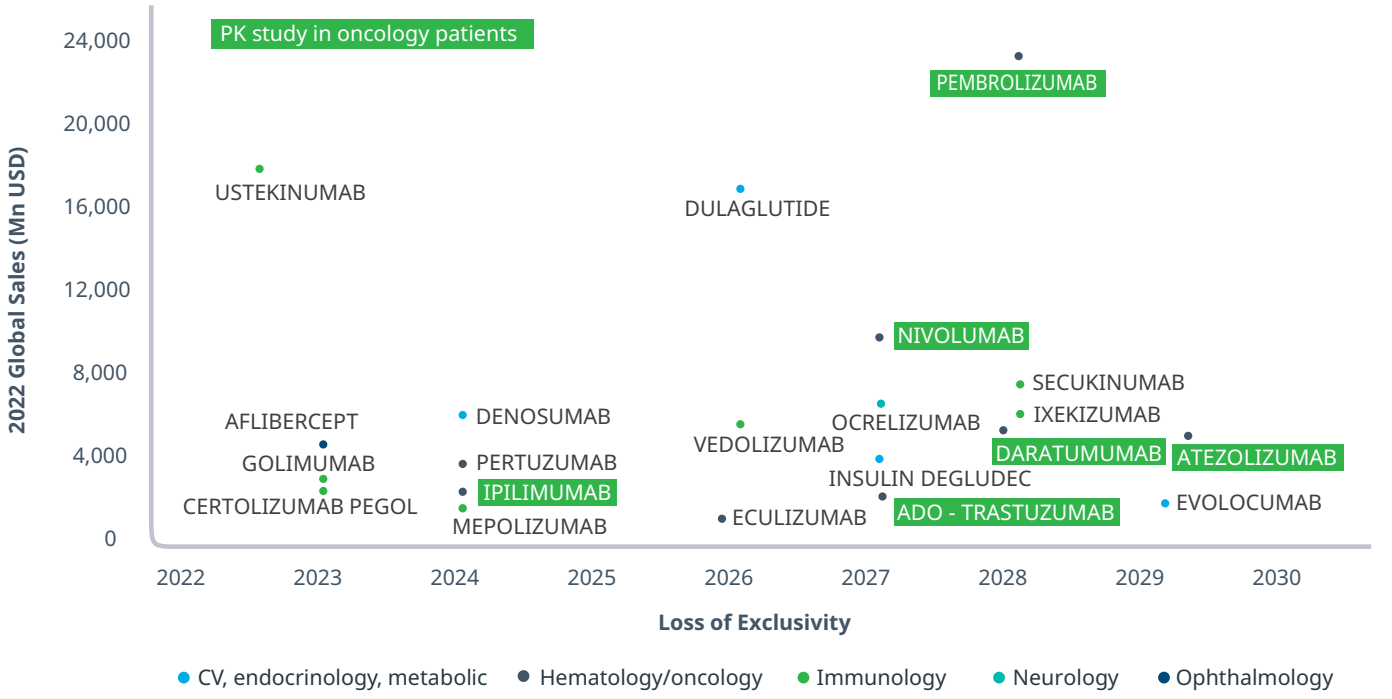



Chart: Several biologics with global revenues exceeding $1 billion are expected to lose patent protection by 2030, potentially paving the way for biosimilars to enter the market for cancer treatments.

Despite these challenges and competitive pressures, ICI biosimilar trials present a valuable opportunity for patients in regions with limited or no access to these medications. Participants in these trials receive standard care throughout the study and can continue treatment for an additional year post-study. Moreover, these trials typically compare the biosimilar candidate directly against the reference biologic, ensuring all patients receive active treatment and are not assigned to a placebo group. Before entering clinical trials, biosimilar candidates undergo rigorous physicochemical and biological activity assays against their reference biologics. These evaluations confirm the biosimilars' identity, structure, and biological activity are sufficiently similar, providing confidence in their quality and minimizing risks to participants.

It is crucial for potential investigators and ethics committees to understand established regulatory standards for biosimilar quality and preclinical evaluation. In countries like India, the anticipated increase in ICI biosimilar trials in the coming years offers significant opportunities for local patients to access standard-of-care treatments with minimal risk.

## Present challenges for Rare Cancers in India

The epidemiology of rare cancers in India differs significantly from that in other countries. Unlike the USA, where prevalent cancers listed among the top 19 include those like breast and prostate cancers, India sees higher incidences of cancers affecting the head and neck, cervix, gallbladder, and bile duct. Conversely, melanomas and other non-melanoma skin cancers are less common in India. In contrast, cancers considered rare in the USA, such as adenocarcinomas of the esophagus and stomach, squamous cell carcinoma of the esophagus and head and neck, cervical carcinoma, and Hodgkin lymphoma, are relatively more frequent in India.

Advancements in targeted therapies offer significant opportunities for improving the management of rare cancers. However, several challenges persist in rare cancer research, including conducting clinical trials with small patient populations, adopting innovative trial methods, and securing adequate research funding. Additionally, comprehensive data on the histology of rare cancers is essential. The unique epidemiology of rare cancers in India and other South Asian Association for Regional Cooperation (SAARC) countries underscores the need for distinct recognition of these cancers in the region. This recognition should be based on realistic definitions and thresholds, emphasizing the importance of tailored approaches in diagnosis, treatment, and research initiatives. Molecular technologies and new research models are exploring the genetic profiles of various rare cancers and seeking actionable mutations. The use of checkpoint inhibitors, immunotherapy, and targeted therapies is expanding across different cancer types. In the context of India, it is essential to establish a national consortium focused on tackling rare cancers. The primary objective of this consortium would be to meticulously document the incidence of rare cancer. This data collection would be pivotal in defining rare cancers, assessing the disease's burden, categorizing rare cancers specific to India, and planning for future challenges. Well-structured clinical trials are also a crucial path ahead in cancer research, thus the International Rare Cancers Initiative will act as a crucial platform for initiating new international clinical trials targeting rare tumors that India might consider as it seeks to become part of the worldwide clinical trial landscape.

# Conclusion

1. India faces significant challenges in cancer with a high annual diagnosis rate, thus requiring more treatment options, support, and clinical trials.
2. The immunotherapy market is expanding rapidly due to increased clinical trials and pharmaceutical interest. As competition grows, costs are decreasing, leading to a wider range of treatment options beyond PD-(L)1 blockers.
3. Current oncology research focuses on solid tumors and advanced biotherapeutic approaches. Inclusion of a country in clinical trials depends on research quality, efficiency, and availability of the patient population.
4. Enhancing accessibility and affordability of CAR T-cell therapy in India is crucial. This involves promoting local manufacturing, participating in global and regional research, and leveraging existing knowledge and infrastructure.
5. The COVID-19 pandemic has significantly reshaped global clinical trial conduct. Lessons learned underscore the value of virtual or decentralized monitoring and risk reduction strategies now integrated into research protocols.
6. Over the next four to five years, more than forty global clinical trials are projected to launch to support the approval of potential biosimilars for established anticancer biologics.
7. Aspiring researchers and ethics boards must understand regulatory standards for biosimilar integrity and preclinical assessments. The anticipated increase in ICI biosimilar studies in India presents an opportunity for local patients to access standard treatments with low risk.
8. Precision medicine advancements offer substantial potential for improving rare cancer treatment. Research challenges include conducting studies with limited patient numbers, adopting novel methodologies, and securing funding.
9. The unique epidemiology of rare cancers in India and the SAARC region underscores the need for a customized approach to identify these cancers. Establishing a network and consortium for data collection could enhance global and regional clinical trials and treatments.
10. The advisory board unanimously agreed on promising future prospects for India, contingent upon resolving identified issues. Collaboration among oncology professionals and stakeholders in the public and private sectors is essential to increase patient access to the latest diagnostic and treatment options in India.

# Key opinion leaders

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Dr. Anju Gopan has been with IQVIA for over 5 years, serving as a therapeutic medical expert in medical oncology and hematology. With a career spanning 18 years, she has facilitated oncology advisory boards, presented at webinars and conferences, authored whitepapers, and co-authored articles in oncology. Dr. Gopan is an expert in oncology clinical trials, including the latest evolving oncology therapeutic drugs classes such as CAR T-cells,antibody-drug conjugates, biomarker-driven treatments, and immunotherapy agents. Since 2006, she has served as sub-investigator for multiple international oncology clinical trials and has been a therapeutic medical expert for numerous clinical trials in clinical research organizations for more than 12 years. Dr. Gopan is also a proficient guest speaker in discussions on clinical trials based in India, regulatory issues concerning medical devices, and various oncology panel discussions under both government-sponsored and private programs.

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Dr. Jaime Enrique Hilado completed his specialty training in medical oncology last 2013 and served as a sub-investigator in numerous clinical trials in that period. Following his training, he worked in the medical affairs division of a leading global pharmaceutical company in oncology before joining IQVIA 6 years ago. Now, Dr. Hilado serves as a therapeutic medical expert in medical oncology and hematology, conducting advisory boards and committee meetings. Currently, his field of interest includes leukemias, lymphomas, and a wide variety of solid tumors.

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