Beyond Geography: A Former Regulator's Perspective on Multiregional Oncology Trials

Harpreet Singh, M.D.
Chief Medical Officer, Precision for Medicine

About the Author

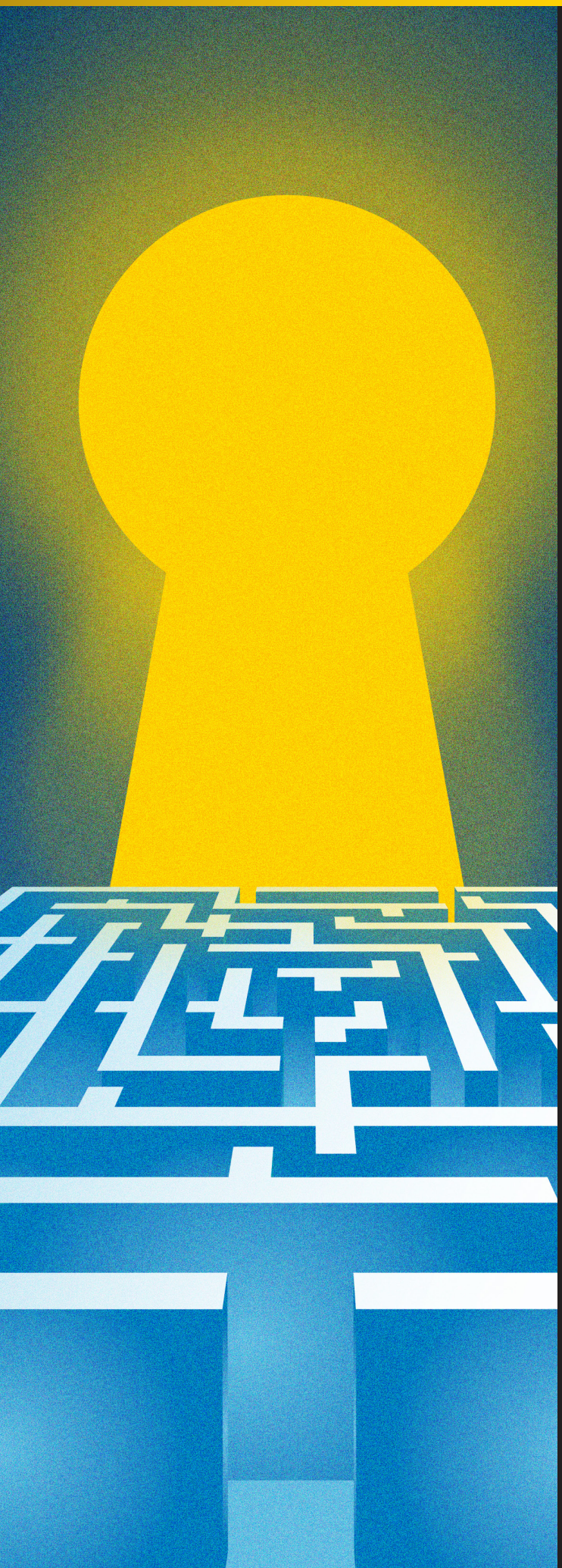
Harpreet Singh, M.D.
Chief Medical Officer, Precision for Medicine
Former Division Director, FDA Oncology

I have spent my career making hard decisions in service of patients and the science that changes their lives. For nearly a decade at the U.S. Food and Drug Administration, I presided over development programs for oncology and rare diseases, including over 50 FDA approvals. That work demanded rigor, clarity, and a deep respect for the evidence. It also demanded urgency, because patients cannot wait.

My path began at the National Cancer Institute and has taken me across academia, industry, and global regulatory bodies. I have built teams that deliver, partnered with innovators who challenge convention, and shared lessons on stages around the globe. Today at Precision for Medicine I bring that experience to sponsors who are navigating complex development programs and who share my belief that excellence in science must translate into access for patients.

This whitepaper reflects that belief. Multi regional clinical trials promise speed and scale, yet recent decisions show that compelling global efficacy is not enough on its own. What matters to FDA is whether results are applicable to patients in the United States. I will examine how regulators are approaching MRCTs, how sponsors can design with applicability in mind, and how to avoid costly missteps that delay therapies. The aim is practical guidance with strategic vision so that global data truly serves the populations we intend to help.

Table of Contents



Introduction

The path to US Food and Drug Administration (FDA) approval for oncology drugs has become increasingly complex as pharmaceutical companies seek to leverage global clinical trial data to support their regulatory submissions. While conventional wisdom suggests that multiregional clinical trials (MRCTs) with compelling efficacy results are a surefire path to FDA approval, recent regulatory decisions reveal a more nuanced reality: FDA's assessment hinges not only on the trial's geography, but the applicability of the results to the US population.

This standard has been tested through a series of high-profile regulatory decisions that have shaped the current landscape, and its concepts are articulated in the recent FDA draft guidance on multiregional oncology clinical development programs. We explore recent examples demonstrating how the standard has been applied in practice, with critical insights for pharmaceutical companies navigating the complexities of oncology drug development.

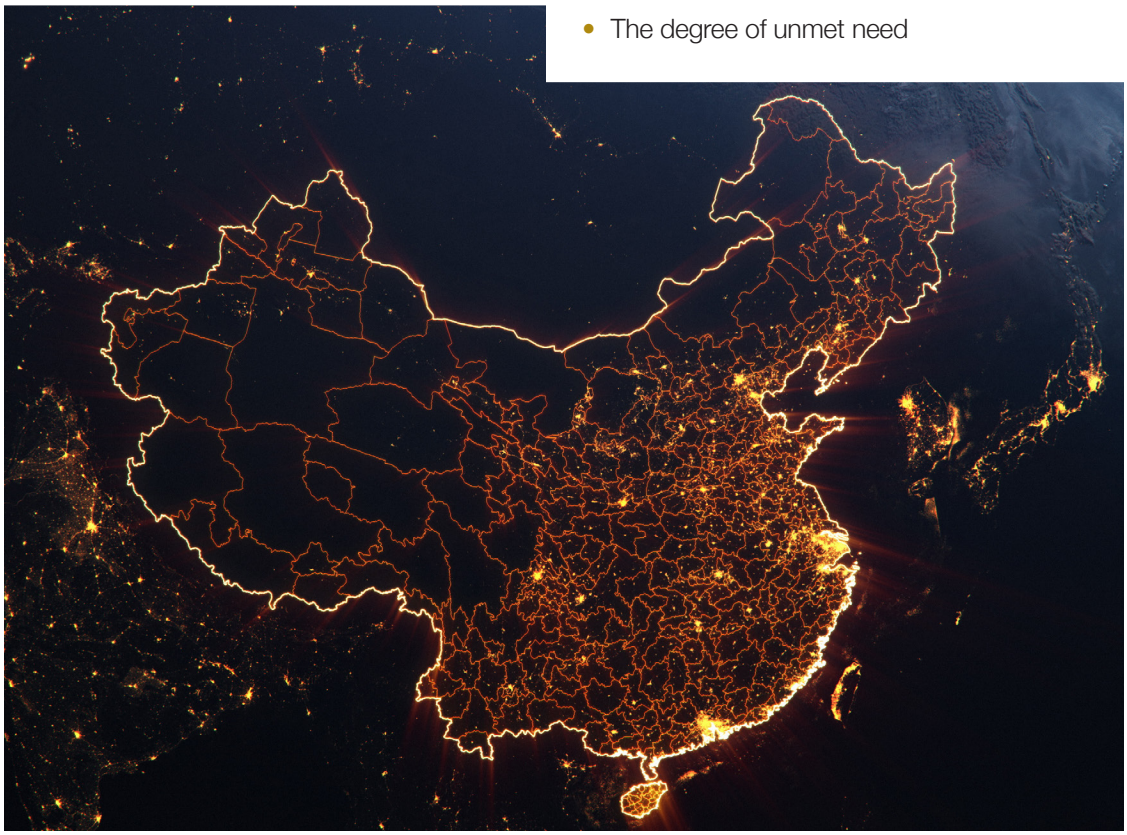
When Geography Becomes a Barrier

Over the past decade, the number of single-country clinical trials in oncology has increased, with China surpassing the US for single-country trials in 2018 and for total trials in 2021. Of the 543,694 studies registered on ClinicalTrials.gov as of July 3, 2025, 56% were conducted entirely ex-US.

A 2021 Lancet Oncology piece, *Importing oncology trials from China: a bridge over troubled waters?*, delineates concerns regarding the use of data from a single foreign country to support US approval and the generalizability of the data to the US population. The authors note that, historically, regulatory flexibility in accepting "bridging studies" was justified for drugs that had few alternatives.

However, many studies conducted in single countries are for indications where there are several FDA approved drugs similar to those available. The acceptability of the data from that single country and its applicability to a new population should be balanced against the novelty of the drug. Other factors that must be considered include:[3]

- The trial's endpoint(s) compared with endpoints used to support previous FDA approvals
- The size and diversity of the trial population
- The percentage of study participants from the US
- Disease prevalence in the US compared with the country of clinical trial
- The degree of unmet need



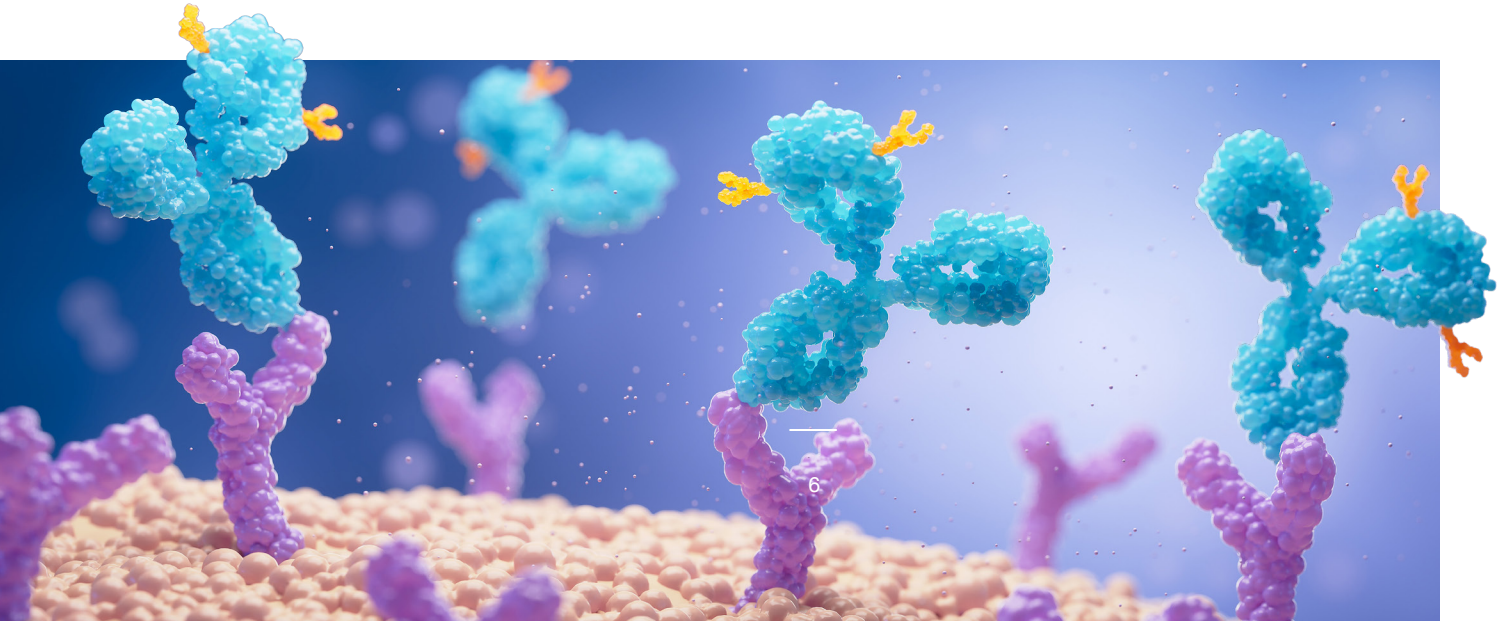
The Catalyst: ORIENT-11

The Lancet article preceded a closely-watched FDA Oncologic Drugs Advisory Committee (ODAC) meeting to discuss sintilimab (Tyvyt®), a PD-1 checkpoint inhibitor developed in combination with chemotherapy as a first-line therapy for metastatic non-squamous non-small-cell lung cancer (NSCLC). The ORIENT-11 trial conducted exclusively in China deployed a study design that closely mirrored Merck's KEYNOTE-189, which served as the cornerstone for the approval of pembrolizumab (Keytruda®) in the same indication.

In a 14-1 vote, ODAC recommended that FDA require additional data demonstrating applicability to US patients and a more direct comparison to US standard of care. Although ORIENT-11 met its primary endpoint of progression-free survival (PFS), the study could not have been conducted in the US because the comparator arm offered an outdated chemotherapy regimen. There was insufficient pharmacokinetic data to show similarity to a diverse US population with both known and unknown differences in intrinsic and extrinsic factors. Further, ODAC members raised concerns over the use of PFS rather than overall survival (OS) as the primary endpoint, given approvals based on OS.

FDA issued a Complete Response Letter (CRL) on March 24, 2022, informing the sponsor that their application had been fully reviewed and would not be approved.
The agency suggested an MRCT evaluating standard of care therapy for first-line metastatic NSCLC compared with sintilimab plus chemotherapy using a potential non-inferiority design with an OS primary endpoint.

This decision marked a definitive statement from FDA regarding its standards for evaluating geographically limited clinical data, particularly in settings where regulatory flexibility may not be warranted due to available therapies. This statement was reinforced in the fall of 2022, when FDA determined that the sponsor of sugemalimab would need to complete a second phase 3 trial in NSCLC comparing the drug to an approved PD-L1 therapy with a representative, diverse US population to show OS, despite having conducted a similar trial called GEMSTONE-302 in China. Due to the increased cost of development, the sponsor concluded that there was no commercially viable path for sugemalimab in the US, but that regulatory efforts would proceed in other parts of the world using existing data.



The Exception That Proved the Rule: JUPITER-02

In October 2023, FDA approved toripalimab with cisplatin and gemcitabine for the first-line treatment of adults with metastatic or recurrent, locally advanced nasopharyngeal carcinoma (NPC) based on pivotal data generated in JUPITER-02, a randomized, multicenter, double-blind, placebo-controlled trial conducted exclusively in China. The decision hinged on critical factors that distinguished this case from sintilimab:

- **High unmet need.** Due to a dearth of dedicated NPC trials conducted by industry, US patients were left with limited treatment options despite the availability of potentially effective therapies.
- **Scientific rationale.** The disease characteristics and histological patterns of NPC differ significantly between Asian and Western populations. While non-keratinizing NPC is more common in areas with high prevalence of NPC, such as Southern China and Southeast Asia, keratinizing squamous cell carcinoma is the most prevalent type in the US. Thus, the approval came with an important caveat—a post-marketing requirement for the sponsor to conduct "a clinical trial enrolling a total sample size of 100 patients in the United States (U.S.) and Canada, that includes a sufficient representation of patients in racial and ethnic minority subgroups and is reflective of the U.S. population of patients with NPC" and to include "a sufficient number of patients with the keratinizing subtype reflecting the incidence of keratinizing NPC in the U.S. population." This requirement acknowledged the scientific uncertainty while balancing the urgent need for treatment options.

The toripalimab approval demonstrated that single-country data could be acceptable in areas of high unmet need, with sound scientific rationale and a favorable benefit risk profile.[13,14]

FDA Oncology Center of Excellence Releases DRAFT Guidance on MRCT

In September 2024, the Oncology Center of Excellence published draft guidance on Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs.[1]

The draft guidance emphasizes that the fundamental question is not geographical diversity per se, but rather whether the trial population and results can support conclusions about efficacy and safety in the intended US patient population. It also includes recommendations on site selection, data analysis, and addressing the decreasing proportion of US participants in oncology trials to produce results that are meaningful to US patients and applicable to US standards of cancer care. Embedded in the draft guidance is the principle that simply conducting an MRCT does not automatically ensure regulatory success—consistency of the data and its generalizability to patients in the US remain paramount.

When a MRCT Falls Short: The STARGLO Study

In May 2025, FDA held an ODAC to discuss the supplemental Biologics License Application (sBLA) for glofitamab (Columvi™) in combination with gemcitabine and oxaliplatin (GemOx) for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are ineligible for autologous stem cell transplant. Glofitamab was previously granted accelerated approval in June 2023 for relapsed/refractory DLBCL after two or more lines of systemic therapy, based on objective response rate (ORR).

STARGLO was a phase 3 multicenter, open-label, randomized trial that enrolled 274 patients at 62 sites across 13 countries, with 52% of patients enrolled outside of Asia. The efficacy results suggested differences between participants enrolled in Asia compared to those enrolled in non-Asian regions.

Moreover, while STARGLO was a multiregional study, only 9% (n=25) hailed from the US, making it difficult to extrapolate the results to a US population (Table 1).

Table 1. **STARGLO Patient Subgroups by Region**[17]

Region		ITT Population N=274 n (%)	Prespecified Subgroup[b]	FDA Subgroups
US		25 (9%)	North America	Non-Asian Region
Europe[a]		88 (32%)	Europe	
Australia		30 (11%)	Rest of World	
Asia	**Total** China Korea Taiwan	**131 (48%)** 80 (29%) 37 (14%) 14 (5%)		Asian Region

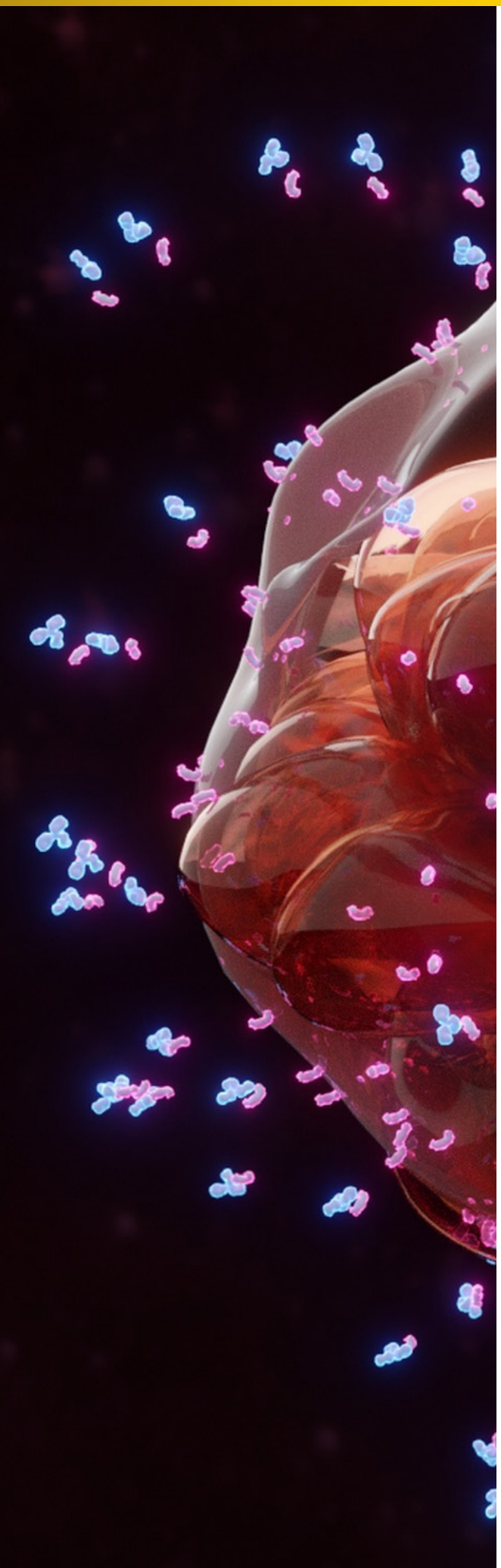
Although the combination therapy demonstrated a statistically significant OS benefit, ODAC members expressed concerns over the limited US patient population enrolled, imbalances in prior therapies that did not align with US-based clinical practice, and inconsistent treatment effects for different regional subgroups. Several subgroup analyses performed by FDA suggested that patients from Asia showed a differential treatment effect versus those from non-Asian regions, across all major efficacy measures—including OS, PFS, and overall response rate (ORR) (Table 2). Thus, despite showing an OS benefit in the total population, the data suggested that these results were being driven by the Asian regional subgroup and that the magnitude of benefit for patients in the US was likely limited and further constrained by the low US enrollment.

Table 2. **STARGLO Summary of Regional Differences**

Factors	Difference		Asian Region (48% ITT)	Non-Asian Region (52% ITT)
Treatment effect on outcomes	OS HR		0.39 (0.25, 0.63)	1.06 (0.61, 1.84)
	PFS HR		0.25 (0.15, 0.14)	0.81 (0.48, 1.35)
	CR Difference		44% (27, 60)	22% (4, 41)
	ORR difference		46% (28, 63)	9% (-10, 28)
Patient and Disease Factors	Demographics	Age	Median age 62y, 21%>65y	Median Age 71y, 55%>65y
		Race/ Ethnicity	100% Asian/2% Hispanic	80% White/4% Asian/ 9% Hispanic
	Disease	Early Relapse	81%	64%
		ABC-DLBCL	70% (49% tested)	42% (68% tested)
	Treatment History	Prior Therapy	2% CART, 13% lenalidomide, 15% other	13% CART, 3% lenalidomide, 2% other
		Transplant Refusal	65%	7%
Healthcare system and trial factors	Treatment Duration (R-GemOx)		1.1 months	3.1 months
	Early Assessments (R-GemOx)		56%	22%
	"Novel" NALT (R-GemOx)		24% (7% CAR-T)	40% (21% CAR-T)

*Adapted from FDA ODAC

The ODAC voted 8-1 that the results of the STARGLO trial were not applicable to the US population, underscoring the FDA's inability to reliably extrapolate the STARGLO results to a US patient population. While demonstrating statistically significant benefit in OS in the setting of a MRCT would in most circumstances assure regulatory success, the STARGLO example highlights that geographic diversity in enrollment alone is not enough—the underlying scientific and clinical applicability to US patients must be demonstrated.16 Genentech has issued a CRL citing that the STARGLO data did not provide sufficient evidence to support the proposed second-line DLBCL indication in the US patient population.[19]



The Application of the Standard: TRUST-I and TRUST-II

The approval of the tyrosine kinase inhibitor (TKI) taletrectinib (Ibtrozi™) for adults with locally advanced or metastatic ROS1-positive NSCLC illustrates the overwhelming efficacy. Taletrectinib was initially granted breakthrough therapy designation based solely on single-country data from China in August 2022, just a few months after FDA issued the CRL on sintilimab.

ROS1-positive NSCLC is a rare cancer and though there were several FDA approved therapies for this indication, each had its limitations. Data supporting the breakthrough therapy designation included results from the China-only TRUST-I study, which demonstrated overall and intracranial response rates as high as 90% in treatment-naïve patients. These data provided preliminary clinical evidence of improvement over available therapy, and broader population representation was still warranted.

The sponsor subsequently conducted TRUST-II, a phase 2 study where 47% of the participants were from Asia and 56% were from the rest of the world, including the US. Multiple analyses of the efficacy outcomes from TRUST-I and TRUST-II revealed consistent response rates and safety profiles regardless of race or geographic origin, providing clinical rationale that the efficacy observed in the predominantly Chinese cohort would translate to US patients.[17]

This consistency of taletrectinib across populations, combined with the compelling nature and magnitude of the efficacy data in a rare disease with limited treatment options, supported its June 2025 FDA approval.

Strategic Insights for Oncology Drug Development

These regulatory decisions illuminate several key principles that guide FDA evaluation of clinical trial data:

- Population representativeness. The critical question is not whether a clinical trial includes patients from multiple countries, but whether the study population is representative of the patients for whom the therapy is intended. This includes consideration of relevant intrinsic and extrinsic factors, such as genetics, disease characteristics, regional standards of care, and sociocultural variables that might influence treatment response.
- Consistency across subgroups. When multiregional data are available, FDA expects to see consistent treatment effects across geographic regions. Significant heterogeneity in response raises questions about which populations will truly benefit from the therapy and FDA is obligated to closely review available data for US patients.
- Biological plausibility. The mechanism of action and expected patient response must be biologically plausible across different populations. Drugs and biologics targeting rare mutations with clear biomarkers may be more likely to show consistent effects across populations than those relying on more complex biological pathways.
- Unmet medical need. Regulatory flexibility may be considered in diseases with higher unmet need, particularly in rare diseases where conducting large MRCTs may be impractical.

Risk-benefit assessment. The agency's evaluation rests on whether the available data support a favorable risk-benefit profile for US patients.Practical Implications for Oncology Drug Development

- Engage with regulatory agencies early. Sponsors should engage with FDA early in development to discuss their global strategy and understand the agency's expectations for their specific indication and patient population.
- Prioritize quality over quantity. Simply including multiple countries in a clinical trial does not guarantee regulatory success. Companies must ensure that their study design will generate high-quality, consistent data that support conclusions about efficacy and safety in the intended population.
- Plan for subgroup analyses. MRCTs should be designed with sufficient power to evaluate treatment effects in relevant subgroups, particularly if there are known biological or epidemiological differences between populations.
- Consider disease epidemiology. The acceptability of regional data may vary significantly based on disease characteristics, prevalence patterns, and available treatment options in different regions.
- Develop strong scientific justification. Sponsors must be prepared to provide robust scientific justification for why their data is generalizable to US patients and US medical practice.

Key Takeaway

The evolving global clinical trial landscape serves to reaffirm FDA's commitment to ensuring that approved therapies provide meaningful benefit to US patients while recognizing the realities of drug development. Rather than defaulting to a specific geographic strategy, drug developers must carefully consider the specific characteristics of their drug, indication, and target population to design development programs that will generate the most clinically meaningful and relevant data.

The FDA's guidance on MRCTs provides a framework for these decisions, but the real-world application of these principles—as demonstrated through the cases discussed here—shows that regulatory success ultimately depends on the scientific rigor and consistency of the data and its applicability to US patients and medical practice.

Navigating these nuanced regulatory waters requires more than understanding the published guidance. It demands deep insight into the scientific rationale that drives FDA decision-making and the application of regulatory principles into practice. At Precision for Medicine, we bring firsthand experience from FDA's hematology and oncology divisions, with experts who have been directly involved in shaping policies and precedents. A successful global development strategy requires more than checking boxes—it requires partnered thinking about study design, population selection, and scientific justification that will resonate with regulators. Whether it is a rare indication with high unmet need or a multiregional strategy for a broader population, our unique expertise can help sponsors navigate the complexities of modern drug development and position their programs for technical and regulatory success.

References

1. US Food and Drug Administration. FDA Issues Draft Guidance on Conducting Multiregional Clinical Trials in Oncology, September 16, 2024. Available at https://www.fda.gov/news-events/press-announcements/fda-issues-draft-guidance-conducting-multiregional-clinical-trials-oncology.

2. Clinical Trials Arena. OCT West Coast 2025: China surpasses US for annual number of clinical trials, February 12, 2025. Available at https://www.clinicaltrialsarena.com/news/china-surpasses-us-for-annual-trials/.

3. ClinicalTrials.gov. Trends and Charts on Registered Studies. Available at https://clinicaltrials.gov/about-site/trends-charts. Accessed July 4, 2025.w

4. Singh H, Pazdur R. Importing oncology trials from China: a bridge over troubled waters? *Lancet Oncol*. 2022;23(3):323-325.

5. Primm KM, Zhao H, Hernandez DC, Chang S. Racial and Ethnic Trends and Diparities in NSCLC. JTO Clin Res Rep. 2022;3(8):100374,

6. BioSpace. FDA's ODAC Says Lilly & Innovent Must Run U.S. Trial, February 10, 2022. Available at https://www.biospace.com/fda-adcom-says-lilly-and-innovent-must-run-u-s-trial.

7. OncLive. ODAC Recommends New Trial Data of Sintilimab in US Population of Frontline NSCLC, February 10, 2022. Available at https://www.onclive.com/view/odac-votes-against-frontline-sintilimab-chemo-for-nonsquamous-nsclc.

8. BioSpace. In Expected Decision, FDA Rejects Lilly's Sintilimab in NSCLC, March 24, 2022. Available at https://www.biospace.com/fda-rejects-lilly-s-sintilimab-in-lung-cancer.

9. Fierce Biotech. From $4.2B deal to a desperate search for buyers: How EQRx's low-cost drug dream unraveled, October 5, 2023. Available at https://www.fiercebiotech.com/biotech/unraveling-eqrxs-low-cost-drug-dream.

10. Targeted Oncology. FDA Grants Breakthrough Therapy Designation to Toripalimab Combination in Nasopharyngeal Carcinoma, August 12, 2021. Available at https://www.targetedonc.com/view/fda-grants-breakthrough-therapy-designation-to-toripalimab-combination-in-nasopharyngeal-carcinoma.

11. US Food and Drug Administration. FDA approves toripalimab-tpzi for nasopharyngeal carcinoma. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-toripalimab-tpzi-nasopharyngeal-carcinoma.

12. US Food and Drug Administration. BLA 761240 Approval Letter for Loqtorzi (toripalimab-tpzi). Coherus BioSciences, Inc.; 2023. Reference ID 5268318. Available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/761240Orig1s000ltr.pdf. Accessed July 7, 2025.

13. US Food and Drug Administration. FDA approves penpulimab-kcqx for non-keratinizing nasopharyngeal carcinoma. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-penpulimab-kcqx-non-keratinizing-nasopharyngeal-carcinoma.

14. US Food and Drug Administration. Approval Letter_761258, April 29, 2025. Available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2025/761258Orig1s000correctedltr.pdf.

15. US Food and Drug Administration. FDA grants accelerated approval to glofitamab-gxbm for selected relapsed or refractory large B-cell lymphomas. Available at https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-glofitamab-gxbm-selected-relapsed-or-refractory-large-b-cell.

16. Goldberg P, Ed. The Cancer Letter, Volume 51, No 20. Washington, DC: *The Cancer Letter Inc,*; May 23, 2025.

17. US Food and Drug Administration. Oncologic Drugs Advisory Committee Meeting, May 20, 2025. Available at https://www.fda.gov/media/186557/download.

18. Applied Clinical Trials. FDA Panel Votes Against Columvi-GemOx sBLA for R/R DLBCL Over Regional Data Concerns from STARGLO Trial, May 21, 2025. Available at https://www.appliedclinicaltrialsonline.com/view/fda-panel-columvi-dlbcl-starglo-trial.

19. Roche. Roche provides update on supplemental Biologics License Application for Columvi combination for people with relapsed or refractory diffuse large B-cell lymphoma. Available at https://www.roche.com/investors/updates/inv-update-2025-07-18.

20. CancerNetwork. FDA Grants Breakthrough Therapy Designation to Taletrectinib for ROS1+ Non–Small Cell Lung Cancer, August 5, 2022. Available at https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-designation-to-taletrectinib-for-ros1-non-small-cell-lung-cancer.

21. Pérol M, et al. Taletrectinib in ROS1+ Non-Small Cell Lung Cancer: TRUST. J Clin Oncol. 2025;43(16);1920-1929.

22. Li W, et al. Efficacy and Safety of Taletrectinib in Chinese Patients With ROS1+ Non-Small Cell Lung Cancer: The Phase II TRUST-I Study. *J Clin Oncol.* 2024;42(22):2660-2670.

23. IASLC Lung Cancer News. Taletrectinib Shows Promising Results in Patients with ROS1-Positive NSCLC, November 26, 2024. Available at https://www.ilcn.org/taletrectinib-shows-promising-results-in-patients-with-ros1-positive-nsclc/.

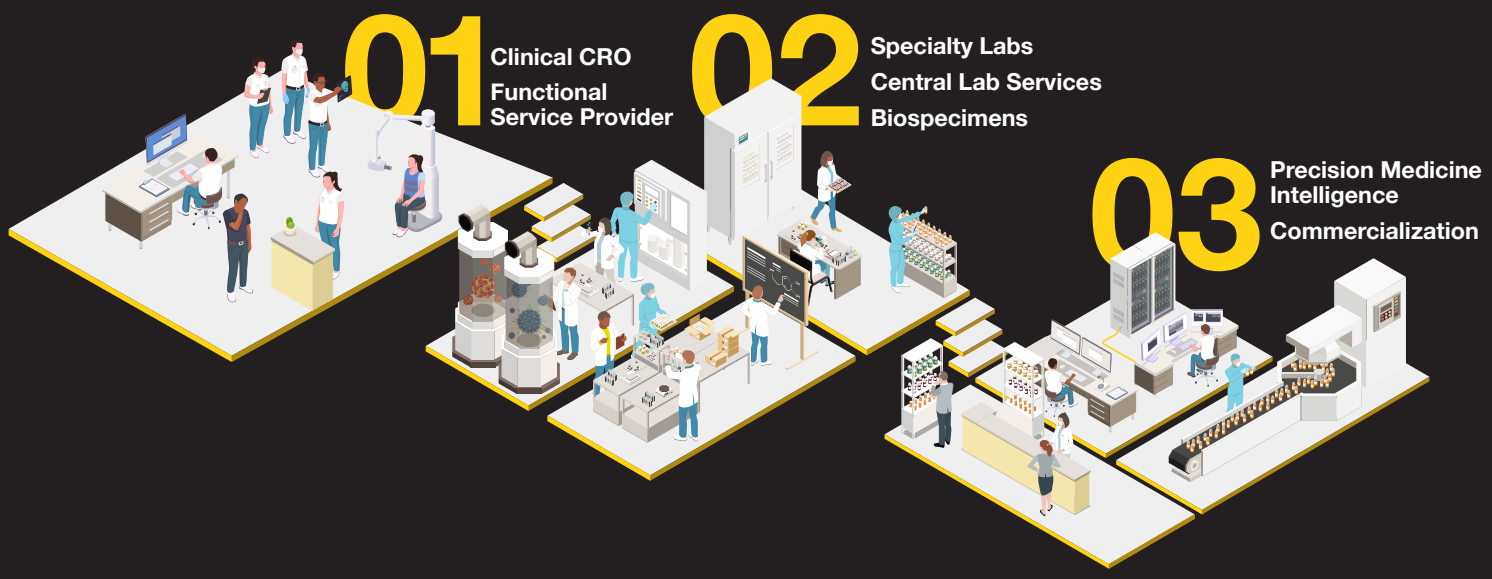
24. US Food and Drug Administration. FDA approves taletrectinib for ROS1-positive non-small cell lung cancer. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-taletrectinib-ros1-positive-non-small-cell-lung-cancer.

Life-changing Therapies Without a Lifetime of Development

Precision for Medicine is a next-generation global clinical research organization (CRO) purpose-built to streamline the development of innovative therapies.

Leading-edge research deserves more than a generalist approach. As oncology and rare disease specialists, Precision reliably accelerates development, reduces unnecessary cost, and increases the probability of approval for advanced therapies.

Whether you need comprehensive development support or functional expertise that integrates with your team, you get the specialized knowledge your program requires without coordinating multiple vendors.



Expertise and Efficiency
Integrated into Every Stage

With integrated capabilities, responsive operations, and deep scientific expertise, Precision is the CRO partner who understands both the science and your ideal pathway to approval.

75% of clinical trials are in oncology

600+ clinical trials

2000+ lab projects

5 specialty labs in the US and Europe

Recognized for Excellence

CRO LEADERSHIP AWARDS 2024 CAPABILITIES

CRO LEADERSHIP AWARDS 2024 COMPATIBILITY

CRO LEADERSHIP AWARDS 2024 EXPERTISE

CRO LEADERSHIP AWARDS 2024 QUALITY

CRO LEADERSHIP AWARDS 2024 RELIABILITY

FIERCE Biotech CRO Awards WINNER 2025

Download your digital copy

For more information please visit us at:

precisionformedicine.com

Rev. 01

PRECISION for medicine®