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Next-Generation Targeted Therapy: The Evolving Role of Taletrectinib in Fusion-Positive Malignancies

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Abstract The discovery of ROS1 and NTRK gene fusions has transformed treatment strategies for a specific group of cancers, particularly non-small cell lung cancer (NSCLC). First-generation tyrosine kinase inhibitors (TKIs) such as crizotinib displayed significant early reactions but faced challenges due to restricted central nervous system (CNS) penetration and mutation resistance, while entrectinib and larotrectinib expanded treatment options but also experienced resistance. Taletrectinib (DS-6051b, AB-106) is an orally bioavailable, next-generation selective inhibitor of ROS1 and NTRK kinases, designed to tackle these issues. Preclinical assessments demonstrated its strong efficacy against both wild-type and resistant kinases, including the clinically challenging ROS1 G2032R mutation, alongside good CNS penetration and prolonged intracranial responses. Clinical studies, like the notable TRUST and TRUST-II trials, have demonstrated elevated objective response rates in TKI-naïve NSCLC patients (often exceeding 85–90%) and substantial effectiveness in groups pretreated with crizotinib. Basket trials are expanding their evaluation to include NTRK fusion–positive solid tumors, confirming a tumor-agnostic strategy. Safety data shows an acceptable toxicity profile, mainly featuring gastrointestinal and hepatic adverse effects, with fewer neurocognitive side effects compared to lorlatinib. Regardless of these advancements, challenges remain, including the possibility of new resistance mutations, limited patient enrollment in early-phase trials, and the critical need to enhance the management of long-term toxicities. Current trials and regulatory activities in China, the U.S., and other locations demonstrate taletrectinib's growing clinical significance. Taletrectinib's well-rounded pharmacological attributes of systemic action, intracranial effectiveness, resistance range, and tolerability render it an intriguing enhancement to the framework of precision oncology.

Keywords NSCLC, TKIs, ROS1 and NTRK kinases, TRUST and TRUST-II studies

1. Introduction

The emergence of targeted therapy has transformed the treatment approach in oncology. Unlike conventional chemotherapy, which affects all dividing cells, targeted therapies focus on specific molecular triggers of tumor development. The discovery of oncogenic ROS1 and NTRK gene fusions over the past ten years has provided both mechanistic understanding and a treatment option. These genetic alterations are rare yet clinically important, playing a notably significant role in non–small cell lung cancer

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(NSCLC) and a growing number of solid tumors

In NSCLC, ROS1 rearrangements happen in approximately 1–2% of individuals, typically seen in young, never-smokers with adenocarcinoma histology. Although they are rare, their identification carries important therapeutic implications. NTRK fusions occur in a wide range of tumor types, spanning from common cancers like lung and thyroid cancer to rare varieties such as secretory breast carcinoma and infantile fibrosarcoma. These fusions result in the persistent activation of the kinases, driving oncogenesis via continuous stimulation of downstream targets such as MAPK, PI3K/AKT, and JAK/STAT. Tumors exhibiting these changes become reliant on unusual signaling and are vulnerable to kinase inhibition[1,2].

The clinical importance of targeting ROS1 and NTRK fusions was first demonstrated with crizotinib, a multitargeted TKI initially created for ALK-positive NSCLC. Crizotinib demonstrated remarkable efficacy in NSCLC with ROS1 rearrangements, leading to regulatory approvals in various regions. Despite the high initial response rates, the long-term advantage is limited by various obstacles. Initially, crizotinib does not have effective penetration into the central nervous system (CNS), resulting in frequent intracranial progression alongside untreated brain metastases in numerous patients. Secondly, resistance mutations such as ROS1 G2032R may evolve over time, leading to disease recurrence. Third, side effects such as gastrointestinal issues and visual problems may necessitate dose adjustment or termination[3,4].

To overcome these limitations, the new generation of inhibitors was developed. Entrectinib, a drug targeting ROS1 and NTRK fusions, demonstrated improved CNS efficacy compared to crizotinib and received approval for ROS1+ NSCLC as well as tumor-agnostic indications in NTRK fusion+ cancers. Larotrectinib, an NTRK-specific inhibitor, provided additional treatment with excellent tolerability, particularly in pediatric patients and uncommon tumors. Nevertheless, resistance mutations, especially solvent-front substitutions in ROS1 and NTRK kinases, limit their prolonged efficacy. Moreover, entrectinib and larotrectinib face comparable challenges with toxicities that limit treatment and eventual disease progression, underscoring the need for additional therapeutic strategies[5,6].

This rationale was further supported by the results of preclinical studies, which demonstrated that taletrectinib inhibits ROS1- and NTRK-mediated signaling, suppresses tumor growth in xenograft models, and has durable intracranial responses in animal models. Clinical trials further reinforced this therapeutic promise: early-phase studies demonstrated encouraging overall response rates, with prolonged progression-free survival and notable CNS efficacy both in treatment-naïve and in TKI-pretreated patients. Importantly, to date, the safety profile of taletrectinib has been manageable, with gastrointestinal symptoms, fatigue, and liver enzyme elevations reported as the most common adverse events. Unlike lorlatinib, another next-generation ROS1 inhibitor with significant CNS activity, taletrectinib is associated with fewer neurocognitive side effects, allowing improved quality of life during treatment[3,7].

The landscape of ROS1 and NTRK inhibition is constantly changing, with multiple agents, each with distinct strengths and weaknesses. Crizotinib, while groundbreaking, is limited by CNS progression. Entrectinib and larotrectinib expanded treatment options, particularly in NTRK-positive cancers, but inevitably, resistance develops. Lorlatinib offers potent CNS penetration but introduces complex toxicity profiles. Repotrectinib, another next-generation ROS1/NTRK inhibitor, shows promise against resistance mutations but remains under clinical investigation. Within this dynamic setting, taletrectinib distinguishes itself by offering a balanced profile of systemic potency, intracranial activity, and tolerability[5].

Clinical development of taletrectinib is ongoing, including pivotal phase II studies, TRUST and TRUST-II, evaluating the role of taletrectinib in both TKI-naïve and previously treated populations with ROS1-positive NSCLC. Further basket trials assess efficacy in NTRK fusion-positive tumors, extending its use toward a tumor-agnostic framework. Preliminary results have been sufficiently promising to warrant regulatory review in select regions, suggesting taletrectinib may soon enter clinical practice as part of the expanding arsenal of precision oncology agents[5,8].

2. Chemistry of Taletrectinib

Taletrectinib (DS-6051b, AB-106) is a synthetic small-molecule tyrosine kinase inhibitor with dual selectivity for *ROS1* and *NTRK* kinases. It is structurally characterized as a heteroaryl–aryl compound optimized for ATP-competitive binding. The drug incorporates a fused aromatic ring system that enables strong hydrogen bonding and hydrophobic interactions within the ATP-binding pocket of ROS1 and TRK family kinases. Its scaffold was designed through structure-guided optimization, balancing

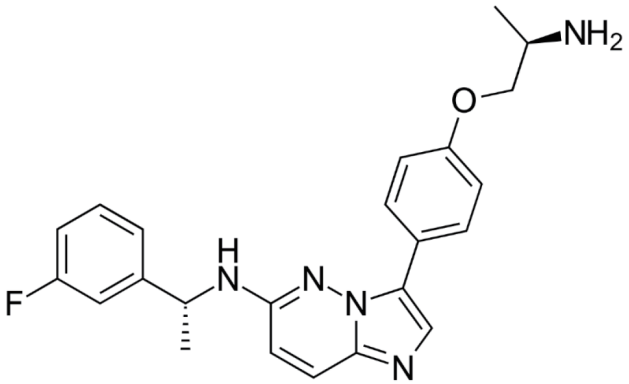

Figure 1. Structure of Taletrectinib

potency, metabolic stability, and blood–brain barrier (BBB) penetration[9].

The molecular formula of taletrectinib is $C_{26}H_{26}N_6O_2$, with a molecular weight of approximately 454.53 g/mol. It contains multiple nitrogen heterocycles that enhance kinase selectivity by forming hydrogen bonds with the hinge region of the kinase domain. Lipophilic substituents improve membrane permeability and CNS distribution, while steric modifications allow activity against solvent-front resistance mutations, such as ROS1 G2032R, by reducing steric clashes within the binding pocket[8,10].

3. Pharmacology

Taletrectinib (DS-6051b, AB-106) is a next-generation, orally available small-molecule tyrosine kinase inhibitor (TKI) designed to selectively target *ROS1* and *NTRK* fusion kinases. It functions as an ATP-competitive inhibitor, binding to the kinase domain and preventing phosphorylation of downstream substrates, thereby blocking oncogenic signaling cascades including the MAPK/ERK and PI3K/AKT pathways. This results in growth arrest and apoptosis in fusion-driven tumor cells[11].

a) Kinase Selectivity and Potency

Biochemical assays have demonstrated that taletrectinib exhibits low nanomolar inhibitory activity against ROS1 and TRK family kinases. Reported IC_{50} values are approximately 0.2–1.0 nM for ROS1, 0.9–2.0 nM for TRKA/B/C, and higher values (>100 nM) for most non-target kinases, underscoring its high degree of selectivity. This kinase selectivity profile minimizes off-target toxicities while maintaining robust anti-tumor activity[12].

b) Pharmacokinetics and Distribution

Early clinical pharmacokinetic studies indicate that taletrectinib is rapidly absorbed after oral administration, with a median Tmax of 2–4 hours and an elimination half-life of approximately 12–24 hours, allowing once-daily dosing. Exposure increases proportionally with dose, and steady-state concentrations are achieved within one week of continuous treatment. Metabolism is primarily hepatic, mediated by CYP3A enzymes, with biliary/fecal excretion as the dominant elimination pathway. Importantly, systemic exposures at clinically tolerable doses exceed the concentrations required to inhibit resistant ROS1/NTRK mutants in vitro[11].

c) Molecular Design and Safety Considerations

The structural optimization of taletrectinib emphasized kinase domain selectivity, which contributes to a more favorable safety profile compared with other next-generation inhibitors such as lorlatinib. By limiting interaction with non-target kinases, taletrectinib avoids significant neurocognitive toxicities while maintaining manageable gastrointestinal and hepatic adverse events[9].

4. Preclinical Data

Preclinical studies established that taletrectinib is a highly potent and selective dual inhibitor of ROS1 and NTRK kinases, with several features that address the shortcomings of earlier agents. It inhibits wild-type and mutant kinases at nanomolar concentrations, demonstrates robust activity in both systemic and intracranial tumor models, and retains efficacy against common resistance mutations such as ROS1 G2032R and TRK solvent-front alterations. Furthermore, taletrectinib's ability to penetrate the CNS and sustain intracranial tumor control provides a compelling rationale for its evaluation in patients with brain metastases. Collectively, these data laid the foundation for ongoing clinical trials, which are now assessing whether the preclinical promise of taletrectinib translates into meaningful clinical benefit[1,13].

5. Clinical trial data

Taletrectinib has progressed from preclinical validation into pivotal clinical studies, underscoring its potential to address unmet needs in ROS1- and NTRK-driven cancers. The TRUST (NCT04395677) and TRUST-II (NCT04919811) Phase II trials are evaluating its efficacy in advanced or metastatic ROS1-positive NSCLC, both in TKI-naïve and previously treated patients, with early results demonstrating high response rates (often exceeding 85–90% in treatment-naïve cases), activity against resistance mutations

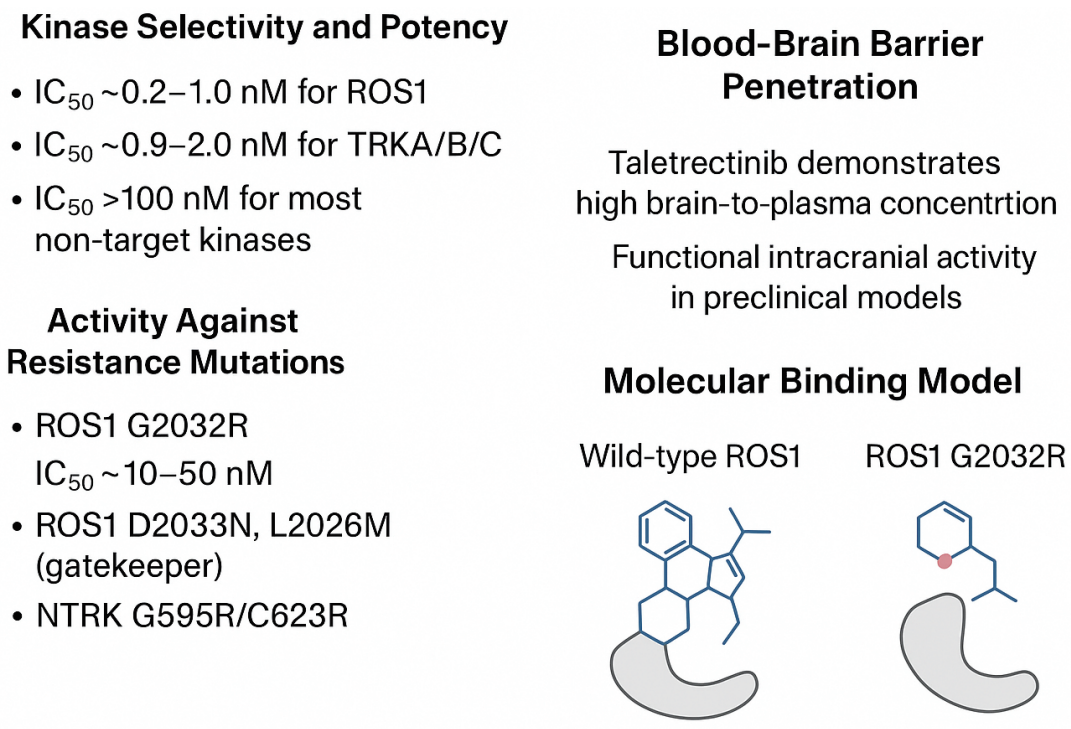

Figure 2. Summary of Pharmacology

Table 1. Preclinical Data of Taletrectinib

Category	Key Findings
Kinase Potency (IC_{50})	ROS1: 0.2–1.0 nM; TRKA/B/C: 0.9–2.0 nM; high selectivity over non-target kinases (>100 nM)
Cellular Activity	Suppresses proliferation of ROS1- and NTRK-fusion cell lines; inhibits MAPK/PI3K/AKT signaling
Resistance Mutation Coverage	Active against ROS1 G2032R, D2033N, L2026M; TRKA G595R; TRKC G623R
CNS Penetration	Brain-to-plasma ratio >0.25; active in intracranial tumor models; sustained brain tumor regression
In Vivo Efficacy	Tumor regression in ROS1- and NTRK-driven xenografts; active in patient-derived G2032R models
Pharmacokinetics	Oral bioavailability; Tmax 2–4 h; half-life 12–20 h; exposures exceed required inhibitory concentrations

such as G2032R, and durable intracranial responses. Beyond NSCLC, basket trials are assessing its activity in NTRK fusion–positive solid tumors, reflecting a tumor-agnostic development strategy similar to entrectinib and larotrectinib. Regulatory submissions are already under review in China, with exploratory filings in the U.S. and other regions, supported by presentations at international meetings such as ASCO and ESMO. Collectively, these efforts highlight taletrectinib's balanced clinical profile—combining systemic efficacy, CNS penetration, and manageable safety—and position it as a promising next-generation therapy for ROS1- and NTRK-driven malignancies[14,15].

• **Maximum Tolerated Dose (MTD)** established in Phase I US study: 800 mg once daily. Doses above (1,200 mg) had unacceptable toxicity (transaminase elevations).

• **Dose reduction or interruptions** were implemented in various studies when elevated liver enzymes or gastrointestinal side effects occurred.

• **Response in resistance mutation subgroups**, especially ROS1 G2032R: TRUST-I showed responses in pretreated cohort (~8/12) with G2032R.

• **Intracranial responses** have been consistently

high across studies, including both naïve and pretreated cohorts.

• **Follow-up durations** varied: TKI-naïve patients in TRUST-I with longer follow-up (≈ 23-24 months) had PFS and DOR not yet reached; pretreated cohorts had shorter follow-ups[16].

Table 2. Clinical study details of Taletrectinib

Study/Phase	Population	Dose/Regimen	Key Efficacy Endpoints	Safety/Key Adverse Events
Phase I, U.S. first-in-human (DS-6051b/ AB-106)	Advanced solid tumors including ROS1- or NTRK-fusion positive; some ROS1+ NSCLC patients, including crizotinib-refractory. Total n ≈ 46.	Dose-escalation: 50-1,200 mg once daily or 400 mg twice daily. MTD determined.	• Confirmed Objective Response Rate (cORR): ~33.3% in the subgroup of 6 ROS1+ NSCLC patients resistant to crizotinib. • In one TPM3-NTRK1 thyroid cancer patient, partial response maintained for ~27 months as of cutoff.	• Dose-Limiting Toxicity (DLT): Grade 3 transaminase increase at 1,200 mg once-daily. • Most common treatment-related AEs: nausea (~47.8%), diarrhea (~43.5%), vomiting (~32.6%). • MTD: 800 mg once daily.
Phase I pooled analysis (U.S. & Japan)	ROS1+ NSCLC patients from Phase I dose-escalation cohorts (total ROS1+ NSCLC ≈22)	Various doses tested: 400, 600, 800, 1,200 mg once daily; 400 mg twice daily in some cohorts.	• ORR by RECIST 1.1: among the 22 patients, responses observed; data cutoff median follow-up ~14.9 months. (Exact ORR %: see study) • Additional follow-up time for durability, safety assessments.	• Safety profile consistent with Phase I: gastrointestinal AEs, transaminase elevation etc. • No unexpected severe toxicity beyond that seen in first-in-human study.
Phase II: TRUST-I (China, pivotal study, NCT04395677)	ROS1+ NSCLC in China; both TKI-naïve patients (no prior ROS1 TKI) and crizotinib-pretreated patients. Total enrolled ~173 patients (106 naive, 67 pretreated).	Taletrectinib 600 mg once daily; 21-day cycles. Majority patients in each stratum; some prior chemotherapy in both arms.	**TKI-naive:**- Confirmed ORR by independent review committee (IRC): ≈ 90.6-91% in TKI-naive cohort. - Intracranial cORR in patients with measurable brain metastases: ~87.5% (in TKI-naïve) - Median duration of response (DOR) & progression-free survival (PFS) not reached at ~23.5 month follow-up in TKI-naïve cohort. Two-year PFS ~70.5% etc. **Crizotinib pretreated:**- cORR ~51.5% in pretreated cohort. - Intracranial cORR ~73.3% in pretreated patients with measurable CNS disease. - Median DOR ~10.6 months; median PFS ~7.6 months for pretreated cohort. - In subset with ROS1 G2032R mutation: 8/12 responded (~66-67%) in pretreated cohort.	• TEAEs (any grade): elevated AST (~76%), diarrhea (~70%), elevated ALT (~68%) in TRUST-I; most grade 1-2. • Neurologic TEAEs were relatively low: dizziness (~23%), dysgeusia (~10%), mostly grade 1. • Discontinuation rate due to TEAEs ~5%; dose reductions ~19%.

Phase II: TRUST-II (Global, interim data)	Global ROS1+ NSCLC patients: both TKI-naïve (Cohort 1) and ROS1 TKI-pretreated (Cohort 2); various sites in Asia, Europe, North America. Interim cohorts: ~53 naive, ~46 pretreated in registrational cohorts.	Taletrectinib 600 mg once daily.	**Cohort 1 (TKI-naive):** - cORR ~87% (95% CI: 74-94%) - Intracranial ORR ~75% (95% CI: 35-97%) for those with baseline brain metastasis. - Median PFS: not reached (at interim follow-up) **Cohort 2(pretreated):**- cORR ~55% (95% CI: 39-70%) - Intracranial ORR ~56% (95% CI: 30-80%) in patients with brain metastases at baseline. - Median PFS ~11.9 months in pretreated cohort.	• Common AEs: Increased ALT, AST (~65-66%), diarrhea (~50-52%) in both cohorts; most events grade 1-2; <10-15% higher grade in some. • Low incidence of neurological adverse events; generally tolerable safety profile.

6. Comaprison with existing therapy

The clinical management of ROS1- and NTRK-fusion cancers has evolved rapidly, and several TKIs are now used or under investigation. Below I compare the principal attributes of crizotinib, entrectinib, lorlatinib, and repotrectinib with taletrectinib, focusing on systemic potency, resistance-mutation coverage, central nervous system (CNS) activity, and tolerability. Key, load-bearing statements are cited[6,10,17].

Table 3. Comaprison of taletrectinib existing therapy

Drug	Systemic Efficacy	CNS Penetration/ Intracranial Activity	Resistance Mutation Coverage	Key Toxicities	Overall Clinical Profile
Crizotinib	High initial ORR in ROS1+ NSCLC; durable in some patients	Poor CNS penetration; frequent brain progression	Limited; no activity against solvent-front (e.g., ROS1 G2032R)	GI upset, visual disturbances, hepatotoxicity	First-generation benchmark; limited by CNS and resistance
Entrectinib	High ORR; approved for both ROS1+ NSCLC and NTRK+ solid tumors	Good CNS penetration; durable intracranial responses	Susceptible to solvent-front resistance (ROS1 G2032R, TRK G595R/ G623R)	Fatigue, dizziness, weight gain, edema	Balanced systemic + CNS activity; loses potency to solvent-front mutations
Lorlatinib	High ORR in both treatment-naïve and resistant settings	Excellent CNS penetration; robust intracranial responses	Active against multiple ROS1 resistance mutations, but limited NTRK data	Neurocognitive AEs, mood effects, dyslipidemia	Potent CNS agent; toxicity often limits tolerability
Repotrectinib	Strong ORR; effective in crizotinib-pretreated patients	Good CNS activity; intracranial responses reported	Active against solvent-front mutations (ROS1 G2032R, TRK G595R/ G623R)	Dizziness, dysgeusia, fatigue	Promising next-gen agent; long-term data still emerging
Taletrectinib	High ORR (≥90% in TKI-naïve); durable systemic responses	Robust CNS penetration; sustained intracranial control	Retains activity against G2032R, D2033N, L2026M, TRK solvent-front mutations	GI events, transaminitis; fewer neurocognitive AEs vs lorlatinib	Balanced profile: systemic potency, CNS activity, resistance coverage, and manageable safety

7. Challenges and Limitations

Despite the significant promise of taletrectinib as a next-generation ROS1 and NTRK inhibitor, several challenges and limitations remain that will influence its clinical development, regulatory approval, and eventual integration into standard care. These include the risk of emerging resistance mutations, the limitations of early-phase trial data, and the need for optimized management of chronic toxicities[18].

Challenge	Description	Implications
Resistance mutations	Potent against known mutations (e.g., ROS1 G2032R, TRK solvent-front), but novel/compound mutations and bypass pathways may emerge with prolonged use.	Risk of relapse; need for molecular profiling and future combination strategies.
Limited trial populations	Early-phase studies (TRUST/TRUST-II, basket trials) have modest patient numbers and geographic concentration, limiting generalizability.	Uncertainty in rare tumor types and global populations; larger, randomized, international trials required.
Chronic toxicities	Hepatotoxicity (elevated transaminases), GI effects (nausea, diarrhea) reported; long-term safety profile not fully known.	May affect adherence and quality of life; requires optimized toxicity management and monitoring.
Clinical positioning	Competing agents (crizotinib, entrectinib, lorlatinib, repotrectinib) already established; unclear if taletrectinib is best used first-line or in resistant disease.	Need to demonstrate added clinical value; positioning depends on ongoing and future trial results.
Future directions	Combination therapy, improved trial diversity, and long-term follow-up essential for maximizing benefit.	Defines future development strategy and regulatory acceptance.

8. Conclusion

Taletrectinib has emerged as one of the most promising next-generation inhibitors in the management of ROS1- and NTRK-driven cancers. Its development was guided by the critical limitations of earlier agents—poor CNS penetration, limited efficacy against solvent-front mutations, and tolerability concerns. Preclinical data established its potency against wild-type and resistant kinases, while demonstrating durable intracranial efficacy, laying the foundation for its advancement into clinical trials. Early-phase studies, particularly the TRUST and TRUST-II programs, have reinforced these findings, showing consistently high response rates in TKI-naïve patients, clinically meaningful benefit in crizotinib-pretreated populations, and encouraging activity against the G2032R mutation, a recognized barrier to first-generation therapies.

Despite this progress, challenges remain. Resistance mechanisms outside taletrectinib's inhibitory spectrum are likely to emerge with long-term use, necessitating ongoing molecular profiling and the exploration of combination approaches. The relatively small patient populations studied to date also limit the generalizability of outcomes across tumor types and geographies, underscoring the need for larger, randomized, and globally representative trials. Furthermore, while its toxicity profile appears manageable, chronic hepatic and gastrointestinal events warrant careful monitoring and optimization of supportive care strategies to ensure treatment adherence and long-term tolerability.

Looking ahead, taletrectinib's clinical impact will hinge on its ability to demonstrate durable benefit across broader populations, achieve regulatory approvals in multiple regions, and establish its place among other next-generation ROS1/NTRK inhibitors. Comparative data against agents such as lorlatinib and repotrectinib will be particularly important for defining its role in treatment sequencing. In addition, tumor-agnostic development for NTRK fusion–positive cancers, supported by biomarker-driven patient selection, may significantly expand its utility. Collectively, taletrectinib represents not only an incremental advance but also a potentially transformative therapy within the precision oncology era, poised to improve outcomes for patients with oncogenic fusion–driven malignancies.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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