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2022 NRDL Pricing Implementation and Access Outcomes in China

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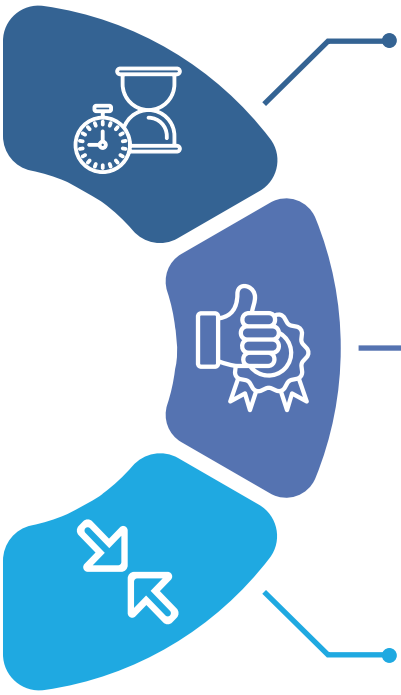
Key Takeaways of the 2022 NRDL update



Timely NRDL Inclusion:
The 2022 National Reimbursement Drug List (NRDL) update observed a faster NRDL listing compared to the prior round of NRDL updates, with a higher percentage of drugs entering the NRDL in the same year of receiving regulatory approval compared to previous NRDL updates.

Value Recognition:
Despite aggressive price cuts, novel products launched in high unmet need therapeutic areas with significant clinical benefit and robust trial data (e.g., RCT and RWE) were still able to achieve premium pricing.

Fixed Informal Threshold:
The annual price ceilings of CNY 500K (USD 69K) for negotiation eligibility and CNY 300K (USD 41K) for NRDL inclusion remain applicable across all therapeutic areas; however, lower price potential was observed for products with high budget impact.

NRDL Access Landscape

The pricing and market access (P&MA) landscape in China has been rapidly evolving as the country continuously attempts to balance rewarding innovation and sustainability of healthcare funding. China represents a unique and dynamic market archetype for manufacturers especially in terms of P&MA strategies.

China's aging population (≥60 years) is estimated to exceed 400 million by 2035 driving a significant rise in government healthcare expenditure and medical insurance subsidies in the future. As such, the Chinese government has acknowledged the important role of multi-national companies to drive innovation as seen in the Healthy China 2030 policy and an increase in the National Reimbursement Drug List (NRDL) negotiation success rate for international branded drugs.

Since the first NRDL negotiation back in 2017, the NRDL has maintained an important presence in China's market access pathway, providing broad coverage and significant market uptake opportunities for listed products. In the last 5 years, the NRDL has been updated annually with a notable > 75% reduction in the time taken between reimbursement and regulatory approval for innovative therapies.

With the intention to strive for equitable access across regions and increase single-payer negotiation power, payers in China have removed the provincial autonomy to adjust the reimbursement drug list and consolidated to one unified public reimbursement pathway. Therefore, staying informed on the NRDL changes is more critical than ever. The 2022 NRDL update represented the sixth consecutive year of negotiation, with five key significant updates observed; all updates intended to facilitate an optimized review process.

Key changes in NRDL process & rules in the 2022 update

Prioritization on Rare Disease Drugs

In the past, the NRDL primarily focused on orphan drugs launched within a five-year timeframe. However, the 2022 NRDL negotiation saw the removal of this timeframe limitation and expanded the eligibility to drugs launched beyond the five-year limit, with a notable increase in rare disease drugs being included in the NRDL list compared to previous years.

Enhanced Transparency & Evidence Requirement

To strive for enhanced transparency, manufacturers were requested to submit a value dossier summary in the form of a PowerPoint presentation. Information within the evidence package should encompass clinical data, comments on innovation and fairness, three-year sales prediction, and international reference prices based on the latest annual selected reference countries.* The non-confidential information within the dossier was then published.

Optimized Appraisal Process

As part of optimizing the review process, the responsibilities of the NRDL expert panel were further defined in 2022 with the establishment of a joint evaluation. The group of experts was comprised of individuals associated with clinical, policy, health economics and outcomes research (HEOR) alongside national and provincial fund managers to increase the efficacy and comprehensiveness of the appraisal process.

Simplified Renewal for Indication Expansion

As an effort to facilitate manufacturers' launch strategy and indication prioritization, a simplified methodology for contract renewal and indication expansion was proposed as a new pricing rule in 2022 NRDL. The rule introduced a formulaic approach to calculate price erosion upon indication expansion / contract renewal based on the expected budget impact.

New Bidding Rule for Non-exclusive Products

For the first time, non-exclusive/non-branded drugs were allowed to enter the NRDL through a bidding process with price levels determined simultaneously** – the first product listed in the NRDL through this new process is IBRANCE; however, the bidding price from at least one manufacturer must be lower than the pre-determined willingness to pay for the molecule to be included on NRDL. This update promoted an increase in access opportunities for products facing generic threats either prior to or after the loss of exclusivity.

*There is no formally defined reference basket; reference countries are typically revised every year.**The bidding price must be lower than provincial tendering price and the list price at launch; all products under the same molecule will be listed in the NRDL at the same price as long as if there is one product with a bidding price less than or equal to the envelop price (NHSA's net willingness-to-pay); the final price will be set at the lower of the lowest bidding price or 70% of the envelop price.

Key features of 2022 NRDL update

During an in-depth analysis of the 2022 NRDL update, a few notable key outcomes emerged: improved negotiation success rates with consistent price discounts similar to previous years, a continued focus on innovative therapy inclusion, a growing presence of multinational manufacturers and expanded coverage across diverse therapeutic areas.

1. In 2022, there was a modest uptick in the rate of successful negotiations, reaching 82.3%, while the average discount remained at ~60%.

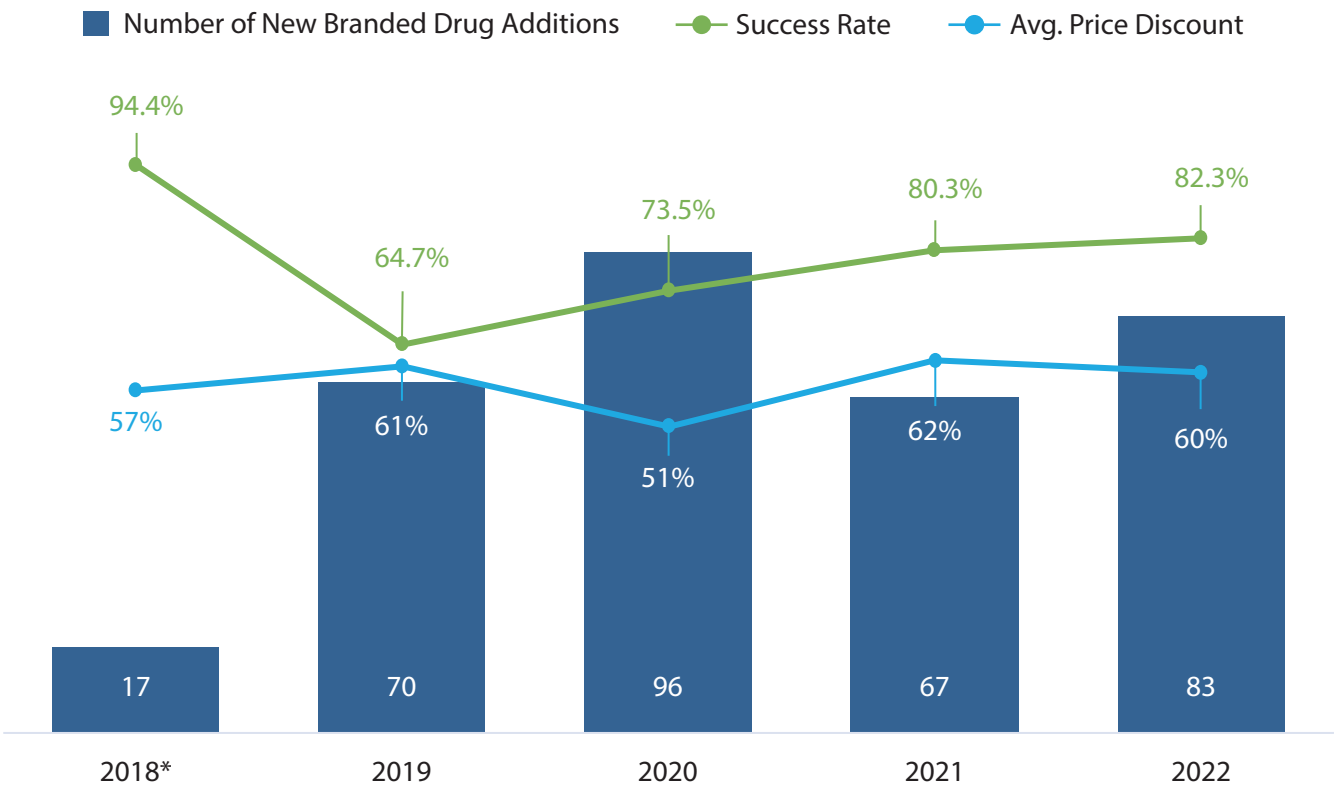


Figure 1 | 2018 - 2022 NRDL New Branded Drug Additions, Negotiation Success Rates and Pricing Discount

The number of newly included branded drugs increased from 67 in 2021 to 83 in 2022. These drugs exhibited an average price reduction of around 60%, which closely mirrored the price cuts seen in 2019 and 2021 (61% in 2019 and 62% in 2021). To demonstrate their willingness and readiness for negotiation, multinational manufacturers have voluntarily reduced their product prices before the NRDL discussions. For instance, Roche decreased the cost of EVRYSDI by 77% in preparation for the NRDL negotiations, subsequently offering an additional 17% reduction during the negotiation process.

Manufacturers that opted for voluntary price reductions before entering NRDL negotiations also met an informal eligibility criterion of the NRDL negotiation. This requirement stipulated that the annual treatment cost of innovative therapies should not exceed CNY 500K (USD 69K) per year to qualify for negotiations.

*2018 was a special negotiation for oncology drugs only.

2. Focus on oncology and rare disease and infectious diseases

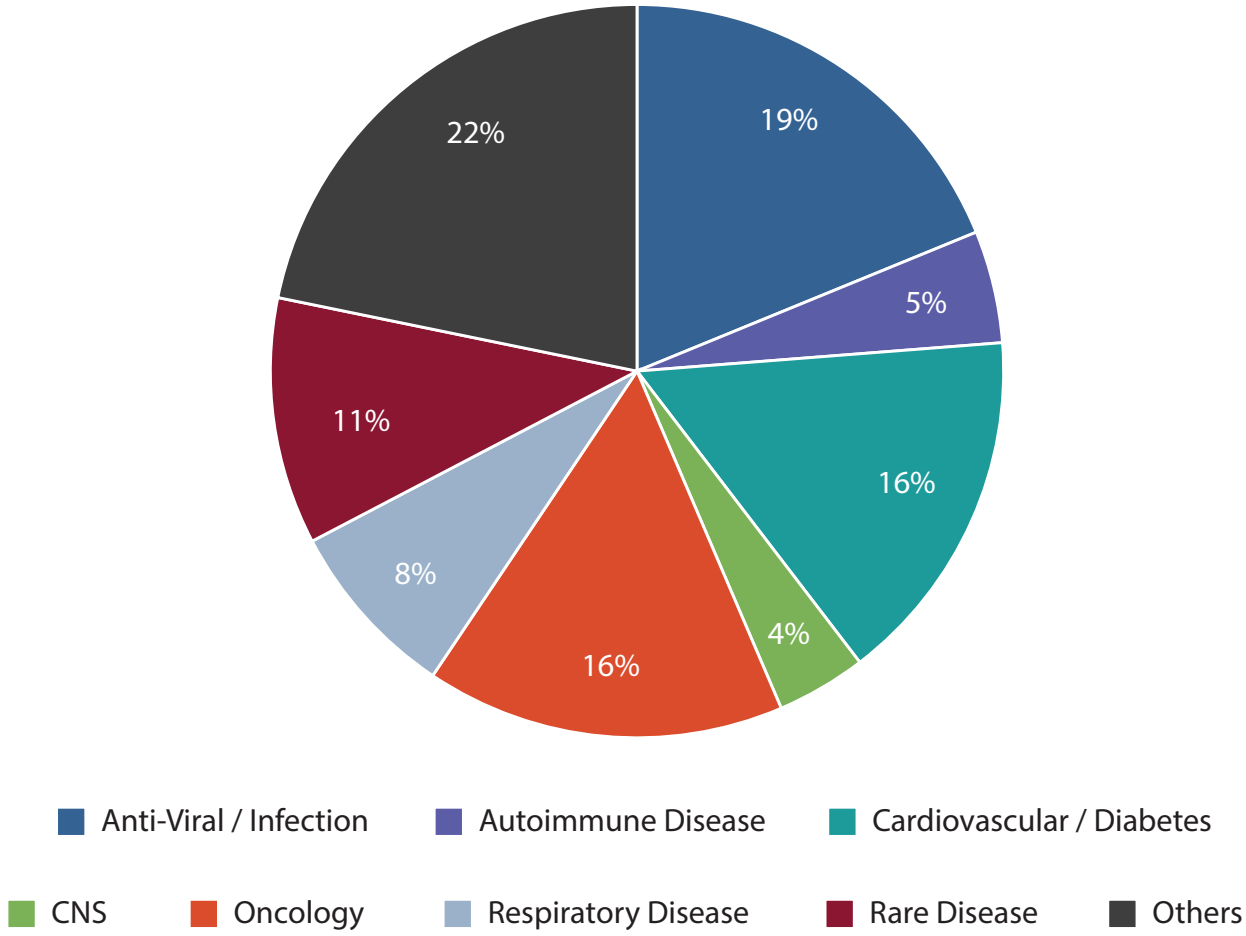


Figure 2 | Therapeutic Area Distribution and Focus

Through the dedication of resources to addressing diseases with significant unmet needs and emphasis on fostering innovation, therapeutic areas such as oncology and rare diseases are anticipated to remain at the forefront of priorities for inclusion in the NRDL. Among the 83 newly added Western drugs, oncology and infectious diseases stood out as the primary therapeutic domains to reap the benefits. Additionally, the incorporation of antiviral medications aligned with the National Healthcare Security Administration's (NHSA) commitment to eradicating COVID-19.

3. Strong presence of multinational manufacturers

The Chinese government's focus on driving innovation in healthcare will facilitate multinational manufacturers' efforts to achieve early and broader access to innovative treatment. Out of the 83 new drugs listed, approximately half were from multinational manufacturers resulting in an equilibrium between the presence of local and multinational manufacturers. Back in 2021, local manufacturers dominated the NRDL listing with a 61% share compared to the 39% multinational manufacturers, but in contrast by 2022, the NRDL listing consisted of 49% multinational manufacturers, with 51% from local manufacturers. Takeda, Merck, and Novartis took the lead with four new listings each, followed by Roche and Pfizer, each securing two listings.

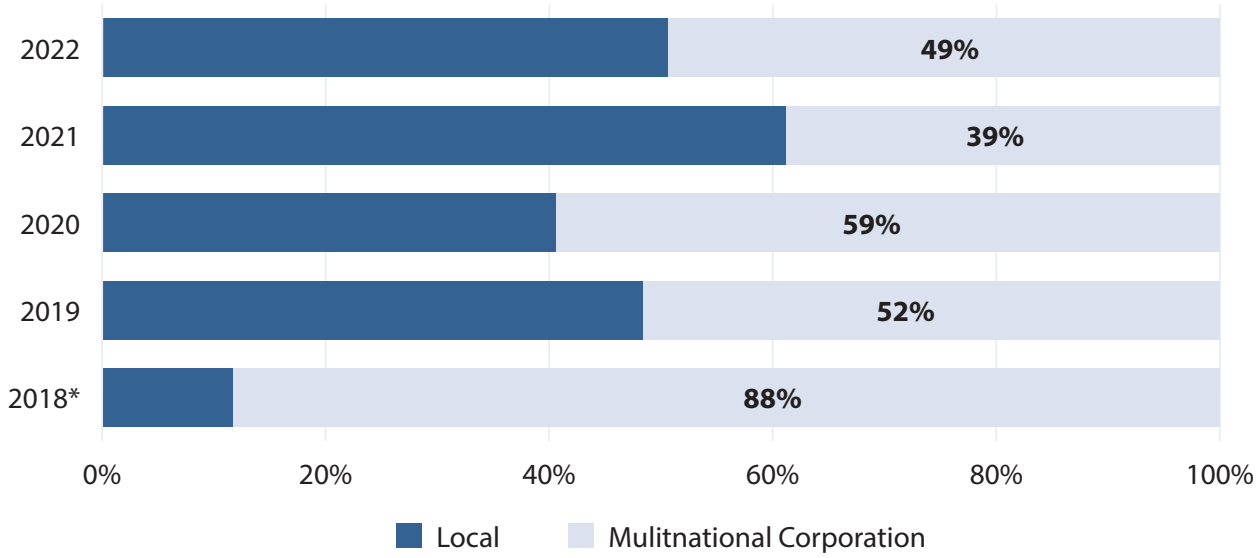


Figure 3 | 2018 - 2022 NRDL Distribution of Local and Multinational Corporations

4. Reduced time lag for NRDL inclusion post-launch

A notable update for 2022 was the timeframe required for innovative therapies to achieve NRDL inclusion post-approval, with the average timeline in 2022 being approximately two years. The shortened timeframe between regulatory approval and NRDL inclusion resulted in more opportunities for newly launched drugs to be included through negotiation.

Of all the negotiated drugs in the 2022 NRDL all were approved within the last 5 years compared to only 71% approval back in 2020. Furthermore, 53% of the approved drugs achieved NRDL inclusion in the same year as their regulatory approval, compared to only 40% observed in 2021.

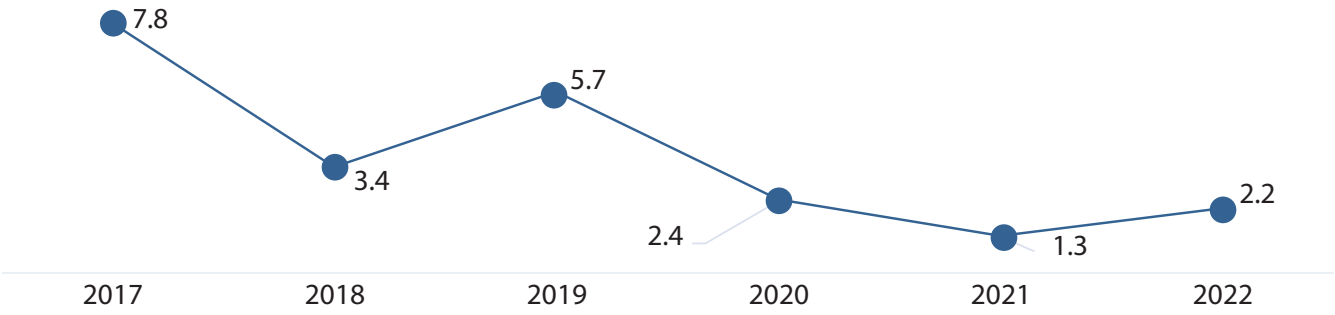


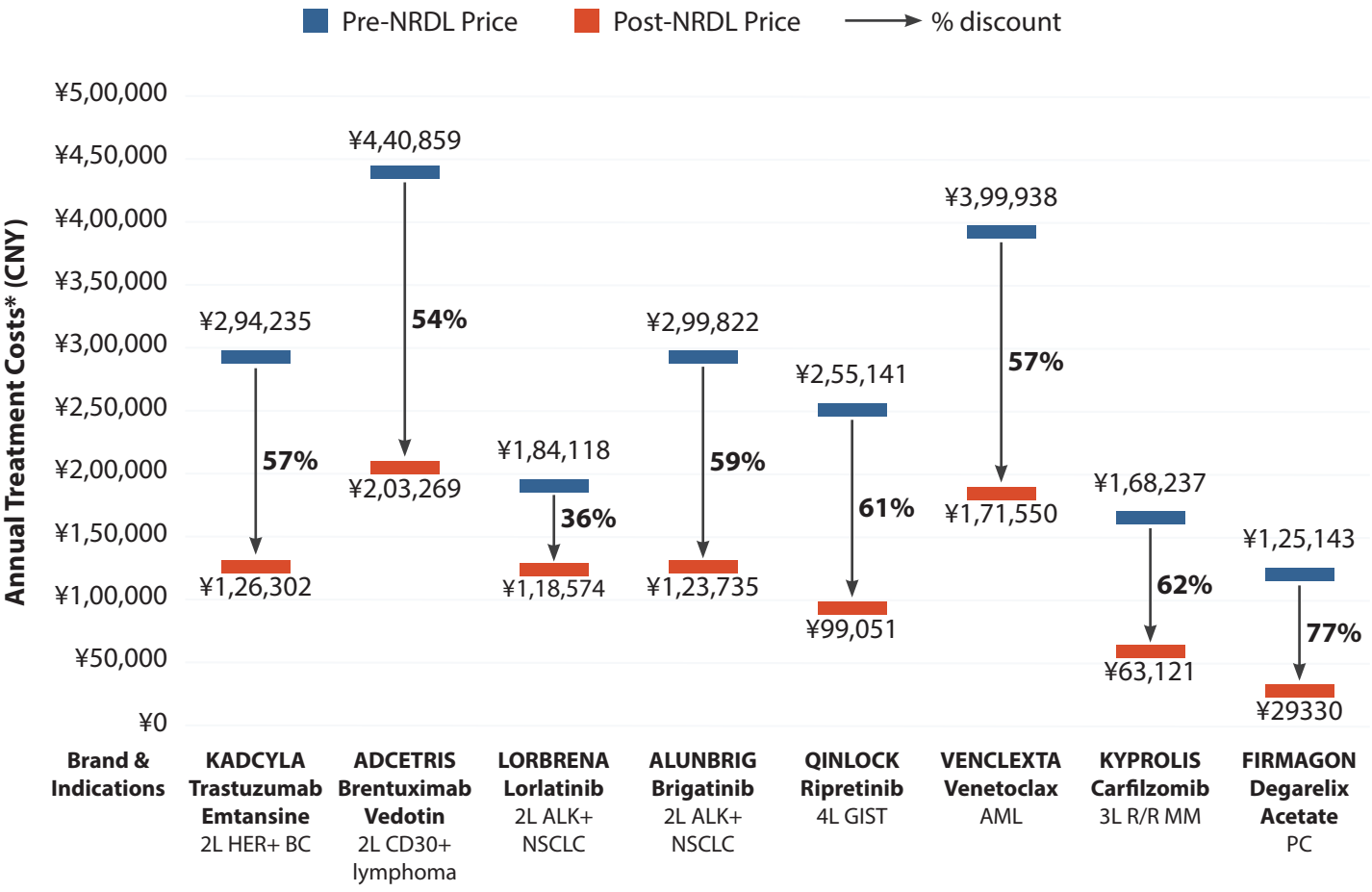
Figure 4 | Average Timeline Reported in Years Between Regulatory Approval and NRDL Inclusion

Oncology Deep Dive

In 2022, oncology remained the primary focus for payers and manufacturers, with an average discount of 58%; products in smaller indications or later treatment lines maintained high prices.

Of the 13 newly negotiated multinational corporation (MNC) oncology branded drugs in the 2022 NRDL, 8 were launched by multinational manufacturers (KADCYLA, ADCETRIS, LORBRENA, ALUNBRIG, VENCLEXTA, KYPROLIS, FIRMAGON), while QINLOCK was a collaboration between MNC (Deciphera Pharma) and a local manufacturer (Zai Lab). Consistent with previous years, the informal annual treatment cost ceiling remained applicable as all oncology MNC drugs fell under CNY 500K (USD 69K) for negotiation eligibility and CNY 300K (USD 41K) for NRDL inclusion. Nevertheless, 2022 witnessed smaller price reductions in contrast to prior years.

Multinational oncology drugs that were newly manufactured were offering an average discount of 58%, which was lower than the 67% discount seen in 2021. This trend was especially noticeable for products with smaller indications or those positioned in later lines of treatment.



*Based on mPFS if dosed until disease progression and the duration of treatment does not exceed 12 months. Abbreviations: CNY: Chinese Yuan; NRDL: National Reimbursement Drug List; MNC: Multinational Corporation; NSCLC: Non-Small Cell Lung Cancer; GIST: Gastrointestinal Stromal Tumor; AML: Acute Myeloid Leukemia; BC: Breast Cancer; R/R MM: Relapsed or Refractory Multiple Myeloma; PC: Prostate Cancer.

Figure 5 | First Year Treatment Costs of 2022 NRDL-Listed MNC Oncology Branded Drugs

Oncology Case Study - LORBRENA

LORBRENA gains premium price by emphasizing innovation, added clinical benefits vs. standard of care (SoC), and willingness to discount.

LORBRENA is an example of a successful multinational oncology drug listed in the NRDL. LORBRENA only had a minor price cut of 36% and was priced at a ~50% premium to other ALK inhibitors attributed to factors such as its first-to-market status for non-small cell lung cancer (NSCLC) in China, FDA breakthrough therapy designation, strong clinical evidence with the longest progression-free survival (PFS) and high complete response rate. The proactivity and commitment to discounting demonstrated a 39% price reduction in Q3 2022 before the NRDL formal review.

- **FDA Breakthrough Designation:** With LORBRENA being the first-to-market third generation ALK inhibitor to be launched for non-small cell lung cancer (NSCLC) in China status, as well as its FDA breakthrough therapy designation, LORBRENA was granted for priority review.
- **FDA Accreditation:** Chinese clinical key opinion leaders (KOLs) highly valued the recommendations from the U.S. clinical guidelines and FDA accreditation to support the clinical benefits of LORBRENA.
- **Robust Clinical Evidence:** LORBRENA's robust evidence demonstrated substantial clinical advantages in 2L ALK+NSCLC. Two randomized controlled trials (RCTs) comparing it to crizotinib, along with a meta-analysis indicated that LORBRENA achieved the longest progression-free survival (PFS) of over three years among all ALK inhibitors.

Oncology Case Study - Antibody Drug Conjugates (ADCs)

In 2022, two ADC drugs - KADCYLA and ADCETRIS, successfully secured listing, despite previous NRDL setbacks, thanks to substantial voluntary price reductions.

Two ADCs, KADCYLA and ADCETRIS, were included in the 2022 NRDL and underwent significant voluntary discounts to lower their prices below the informal annual cost threshold to be eligible for the NRDL negotiation in 2022. KADCYLA lowered its price by another 57% following the previous negotiation failure in 2021, while ADCETRIS lowered the price by 54% following unsuccessful listing in both 2020 and 2021.

The two ADC drugs both demonstrated statistically significant OS improvement vs. comparators in relevant therapeutic areas.

- KADCYLA demonstrated significant PFS and OS benefits vs. chemotherapy in HER2+ breast cancer (PFS 9.6 s 6.4 months, OS 30.9 vs. 25.1 months).
- Meanwhile, ADCETRIS demonstrated significant OS (40.5 months) in R/R cHL and PFS improvement vs. physician's choice in R/R systemic Anaplastic Large Cell Lymphoma (sALCL) (16.7 vs. 3.5 months).

Oncology Case Study – IBRANCE (palbociclib)

Pfizer's IBRANCE successfully secured NRDL listing in China via a new bidding process, which provides a new access route for branded drugs facing generic competition.

- Back in 2019, IBRANCE failed NRDL negotiations and as a result, IBRANCE struggled to achieve significant growth in volume and overall sales in China. But by 2021, three branded CDK4/6i competitors (MNC: VERZENIO, KISQUALI; domestic: dalpiciclib) had launched in China for breast cancer, and several domestic palbociclib generics were expected to launch at the time of IBRANCE's loss of exclusivity in January 2023. As a result, IBRANCE risked losing its market share and experienced intense competition from incoming competitors and generic entry.
- Fast forward to 2022, Pfizer's IBRANCE became the first and only multinational manufactured product successfully listed in the NRDL via the new bidding process. With a successful listing on the NRDL before expected generics entry, the risks associated with market share and competitors were mitigated, allowing Pfizer additional time to establish the market share and strengthen presence before IBRANCE's loss of exclusivity (LoE).
- The new bidding process required NRDL experts to set a confidential willingness-to-pay price and manufacturers could bid for NRDL inclusion if one of the bidding prices was lower than the benchmark; this allowed for NRDL inclusion by molecule name and provided a new access pathway for branded drugs with upcoming LoE.

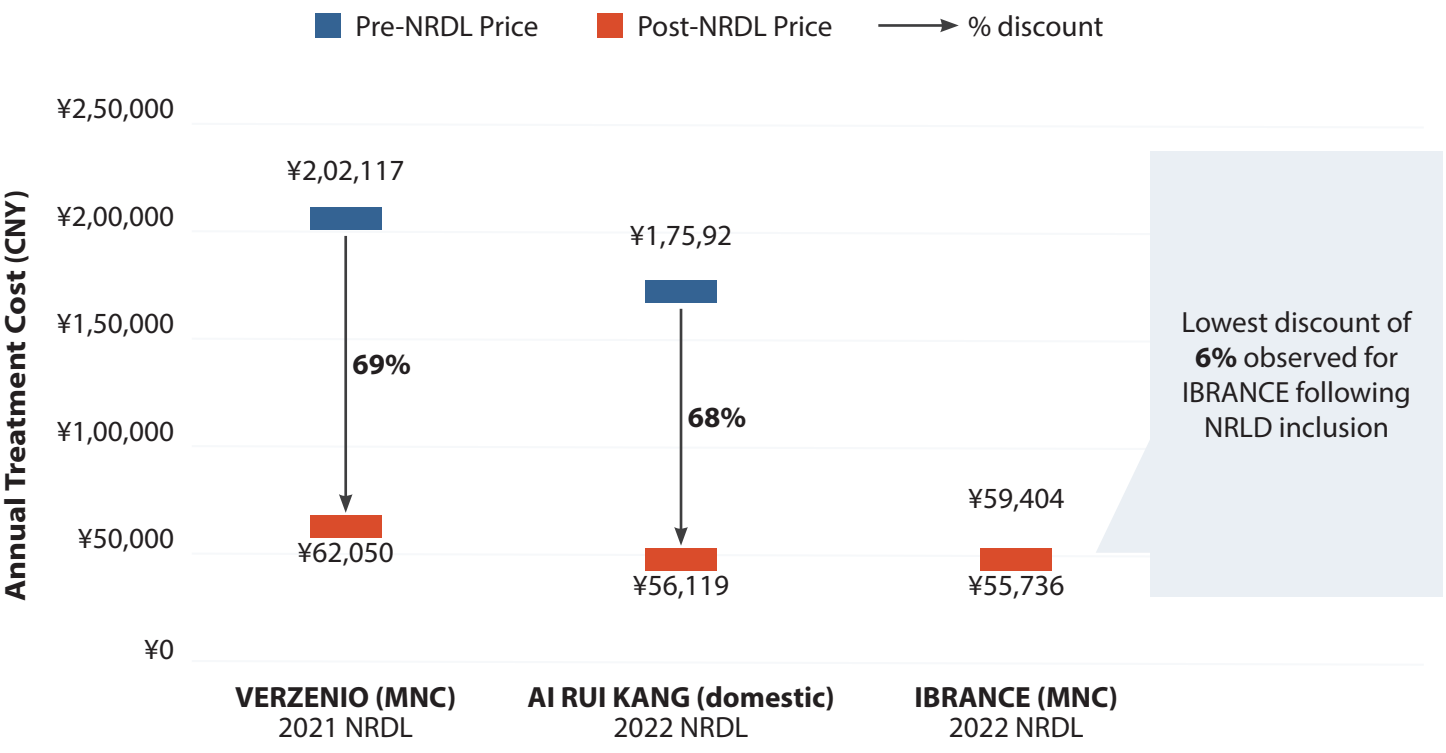


Figure 6 | Annual Treatment Cost of 2022 NRDL-listed CDK4/6 Inhibitors

Oncology Case Study – CAR-Ts

YESCARTA and CARTEYVA did not enter NRDL but have explored private market access pathways.

YESCARTA and CARTEYVA failed to enter the 2022 NRDL as both therapies surpassed the annual price threshold for NRDL negotiation eligibility; however, both therapies entered many cities' public-private health insurance schemes (Hui Min Bao), which provided coverage of treatment costs of up to CNY 500K (USD 69K) with a low premium. Both manufacturers collaborated with various private medical insurers to increase access in the private sector to build physician and patient experience. FOSUN Kite engaged early on, with top-tier hospitals and experts to develop a CAR-T nascent market and established collaborations with 70+ hospitals in 2022.

In China, innovative contracting and payment models are still under development; pay-for-performance and per-patient cap are two types of contracting that are currently under discussion for cell and gene therapy products.

	YESCARTA (Axi-Cel)	CARTEYVA (Rema-Cel)
Manufacturer	FosunKite	JW Therapeutics
China Launch	June 2021	Sep 2021
Approved Indication	» Adult 2nd line r/r LBCL » Adult 3rd line r/r indolent NHL (exp.)	» Adult 2nd line r/r LBCL » Adult 3rd line r/r indolent NHL (exp.)
Key Efficacy	PFS: 5.9 months; ORR: 79.2%[3]	PFS: 7 months[1]; ORR: 77.6%[2]
Annual Treatment Price	**¥1,200 K**	**¥1,290 K**
Uptake Post Launch	> 200 patients since launch	64 patients in Jan-June 2022
Commercial Insurance Coverage	52 Huiminbao[4] listing	28 Huiminbao listing

Figure 7 | Overview of Two CAR-Ts That Did Not Enter NRDL

Source:

1. Axi-Cel clinical trial is ZUMA-1, a single-arm, multicentre, phase 1-2 trial in refractory large B-cell lymphoma, with N=101 patients and 27.1 months of follow up.
2. Axi-Cel's ORR is derived from a bridge study in Chinese population for ZUMA -1.
3. Relma-cel clinical trial is RELIANCE study for Chinese r/r LBCL patients, with N=59 patients and 17.9 months of follow up.
4. Huiminbao: government-backed inclusive product, an initiative between commercial insurance and local government to supplement national medical insurance

Rare Diseases Deep Dive

The 2022 NRDL witnessed the inclusion of eight new rare disease drugs, with the majority manufactured by multinational companies, and all eight new rare disease drugs received a lower discount compared to 2021.

In line with the increased focus on rare disease, the 2022 NRDL included eight new rare disease drugs. Most were manufactured by MNC players and include ROMIPLATE, REBLOZYL, TAKHZYRO, KESEMPTA, UPLIZNA, TECIFEDRA, EVRYSDI, and TIGLUTIK. These products on average underwent 52% price cut upon NRDL negotiation, and this represented a lower discounts level vs. 2021 (68.9%). Despite the high launch prices of rare disease products, the annual treatment cost ceiling of CNY 300K (USD 41K) per year for NRDL inclusion remained applicable. For instance, TAKHZYRO's price was significantly reduced due to patient access program (PAP) allowing it to meet the ceiling despite a launch price of CNY 1.1M (USD 151K).

Both SMA and MS were included in China's 121 National Rare Disease List and were perceived to have high clinical burden and payer awareness. Following last year's inclusion of SPINRAZA in the NRDL, the 2022 NRDL included the addition of EVRYSDI for SMA; the 2021 NRDL included FAMPYRA for MS in the 2021 NRDL, TECIFEDRA and KESEMPTA for MS was subsequently included in the 2022 NRDL.

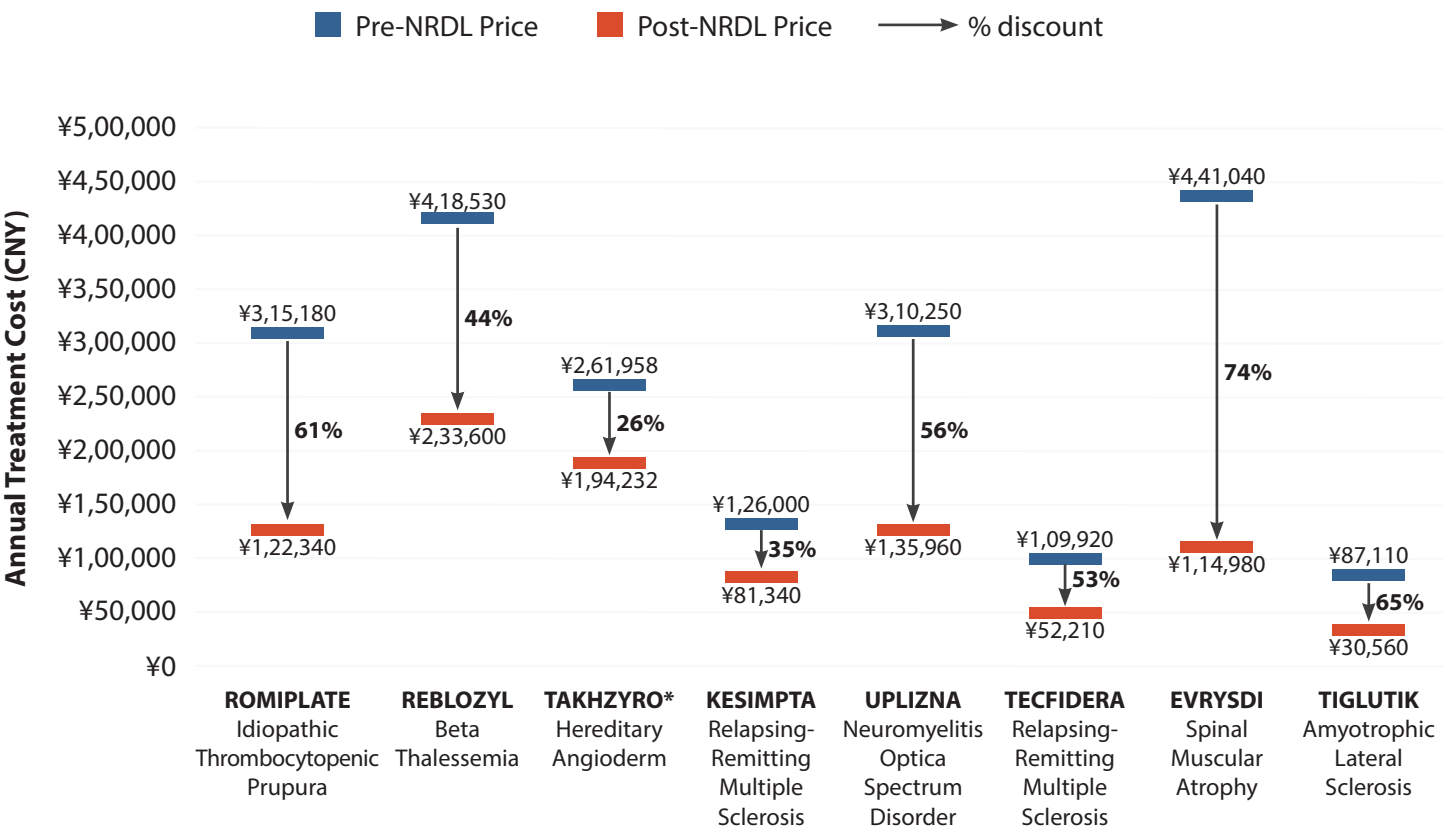


Figure 8 | Annual Treatment Costs of 2022 NRDL-listed Rare Disease Drugs

*There is no pre-NRDL price available for TAKZHYRO

Chronic Disease Deep Dive

Chronic disease drugs typically face significant pricing discount due to the implications of budget impact; however, with robust clinical data, premium pricing is achievable.

Chronic disease drugs typically had a significant discount of ~70%, this was likely due to the large patient population and the implications on budget impact. However, with strong and robust clinical data, premium pricing was still feasible as seen in the case for GLP-1 competitors: The NRDL currently consists of 6 GLP-1 receptor agonists for the treatment of diabetes with Novo Nordisk's XULTOLPY achieving a premium price of CNY 18K (USD 2.5K) in 2022 NRDL vs. its in-class branded competitors listed in prior years of NRDL based on robust clinical profile.

XULTOLPY was able to achieve premium pricing due to two main factors:

- The randomized controlled trials (RCTs) involving Chinese patients observed that among inpatients who were unresponsive to oral hypoglycemic agents and those using basal insulin, there was a substantial reduction in HbA1c levels ranging from 60% to 90% when comparing deglutide or liraglutide. Additionally, the reduction in gastrointestinal adverse events (GI AEs) by 40% to 61% was noted when comparing these individuals to those using GLP-1.
- Both clinical trial data and real-world evidence were leveraged to demonstrate clinical benefits. The global Phase 3 DUAL studies demonstrated that patients who had previously failed other treatments experienced a further reduction in HbA1c levels ranging from 1.3% to 1.9% after being treated with XULTOPHY while real-world studies indicated that HbA1c levels were lowered by 0.6% to 1.0% compared to existing standard of care (e.g., monotherapy & combination therapy of GLP-1RA and basal insulin).

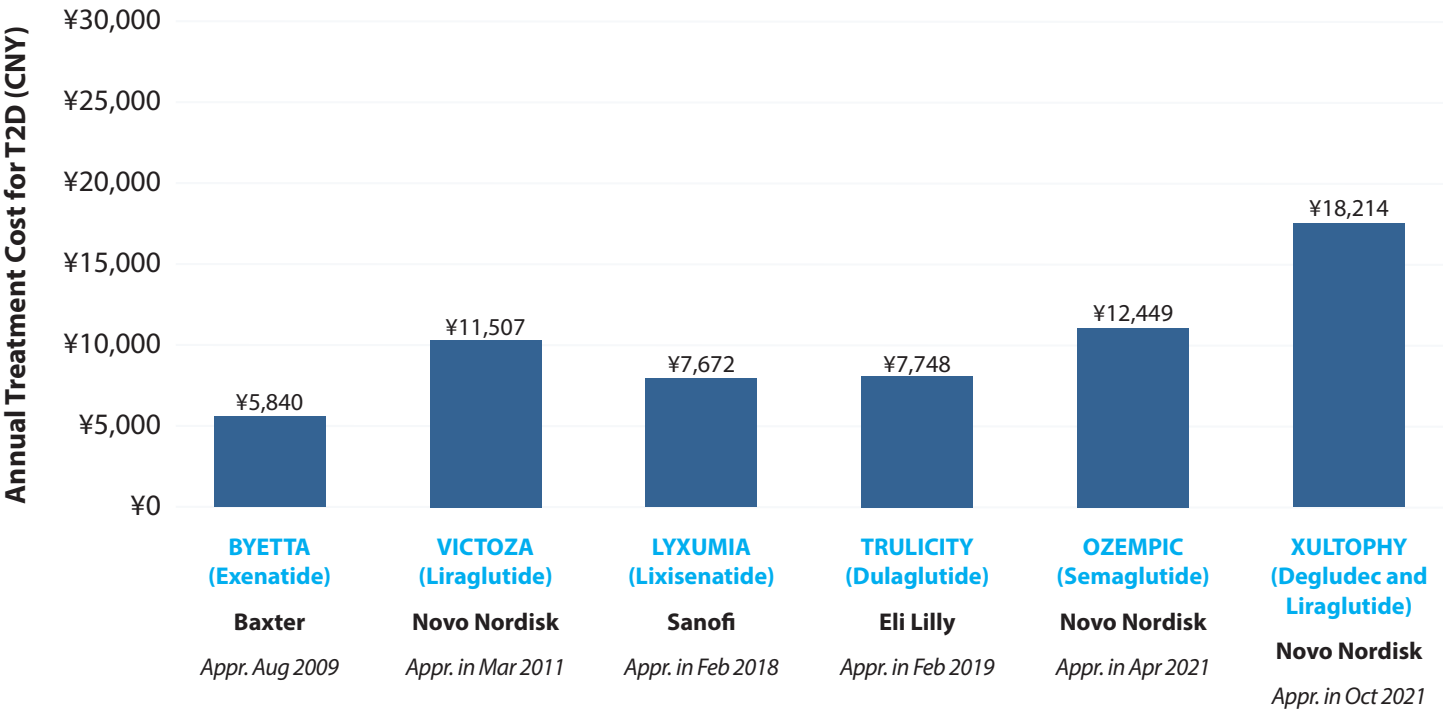


Figure 9 | Annual Treatment Costs of 2022 NRDL-Listed GLP-1 Receptor Agonists

Key Learnings

Challenges

There was a consistent pattern of price discounts and an informal annual price ceiling observed in the 2022 NRDL update in comparison to previous years. This suggests continuous pricing pressures and a focus on budget impact. The price limits of CNY 500K (USD 69K) for negotiation eligibility and CNY 300K (USD 41K) for NRDL inclusion remained consistent across all disease areas.

Furthermore, despite the perceived high clinical value of cell and gene therapies, their annual price cap remains consistent with that of other novel therapies. This underscores the importance of cell and gene therapies exploring alternative funding pathways in order to attain commercial success.

Opportunities

Consistent with the previous year, the 2022 NRDL update placed significant emphasis on innovation, particularly in the areas of rare diseases, oncology, and pediatric medications. In 2022, the NRDL included drugs more quickly after regulatory approval compared to previous updates, with a higher percentage of therapies entering the list in the same year.

Despite price reductions and the focus on budget impact, products targeting therapeutic areas with high unmet needs and backed by robust clinical evidence have the potential to achieve premium prices compared to in-class competitors.

Forward Looking for the 2023 NRDL

Some changes in negotiation rules are anticipated for the 2023 NRDL. Firstly, there will be a shift in the eligibility deadline from January 1st, 2017 to January 1st, 2018, considering recent approvals for assessment. Moreover, the evaluation criteria for NRDL-listed drugs will emphasize clinical unmet needs and delivering benefits to patients as key considerations to allow a more comprehensive assessment of product value. Lastly, for products undergoing indication expansion or contract renewals, the new formulaic approach will apply based on budget impact increase, leading to an expectation of lower pricing pressures compared to previous method of renegotiations.

In light of the insights gleaned from the 2022 NRDL update, the outlook of China's healthcare heads towards more promising access and pricing opportunities, especially for innovative drugs with high added clinical value. This is primarily driven by a heightened focus on evaluating product value comprehensively and a decrease in pricing pressure for NRDL renewals.

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