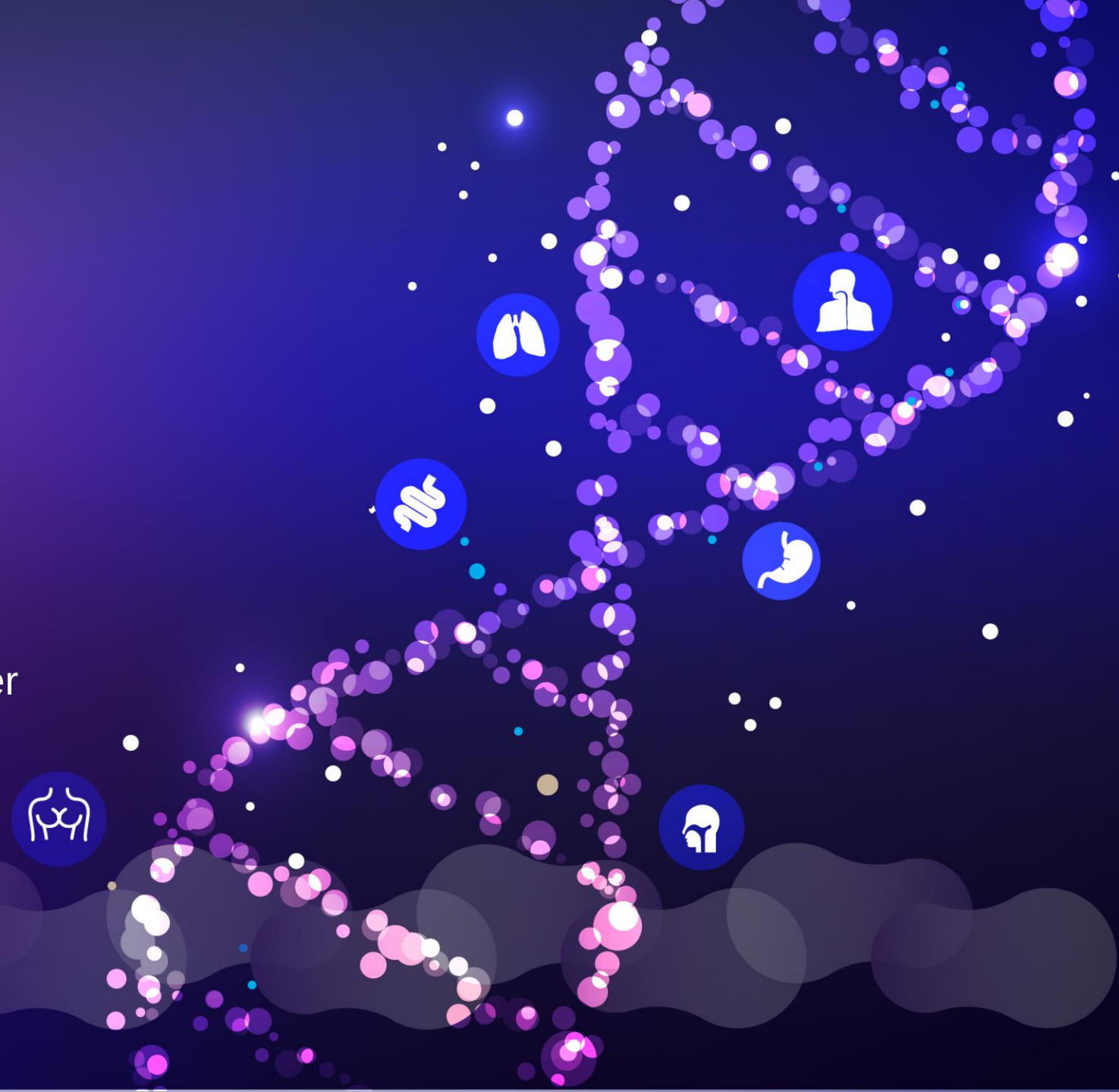
Henlius

Leading Innovation· Global Vision

Dr. Jason Zhu
Executive Director, Chief Executive Officer



Collaborate to Create

2025 Henlius Global R&D Day

Henlius

Aims to be the most trusted in biopharma, providing innovative and affordable medicine for patients worldwide

6
Products Launched

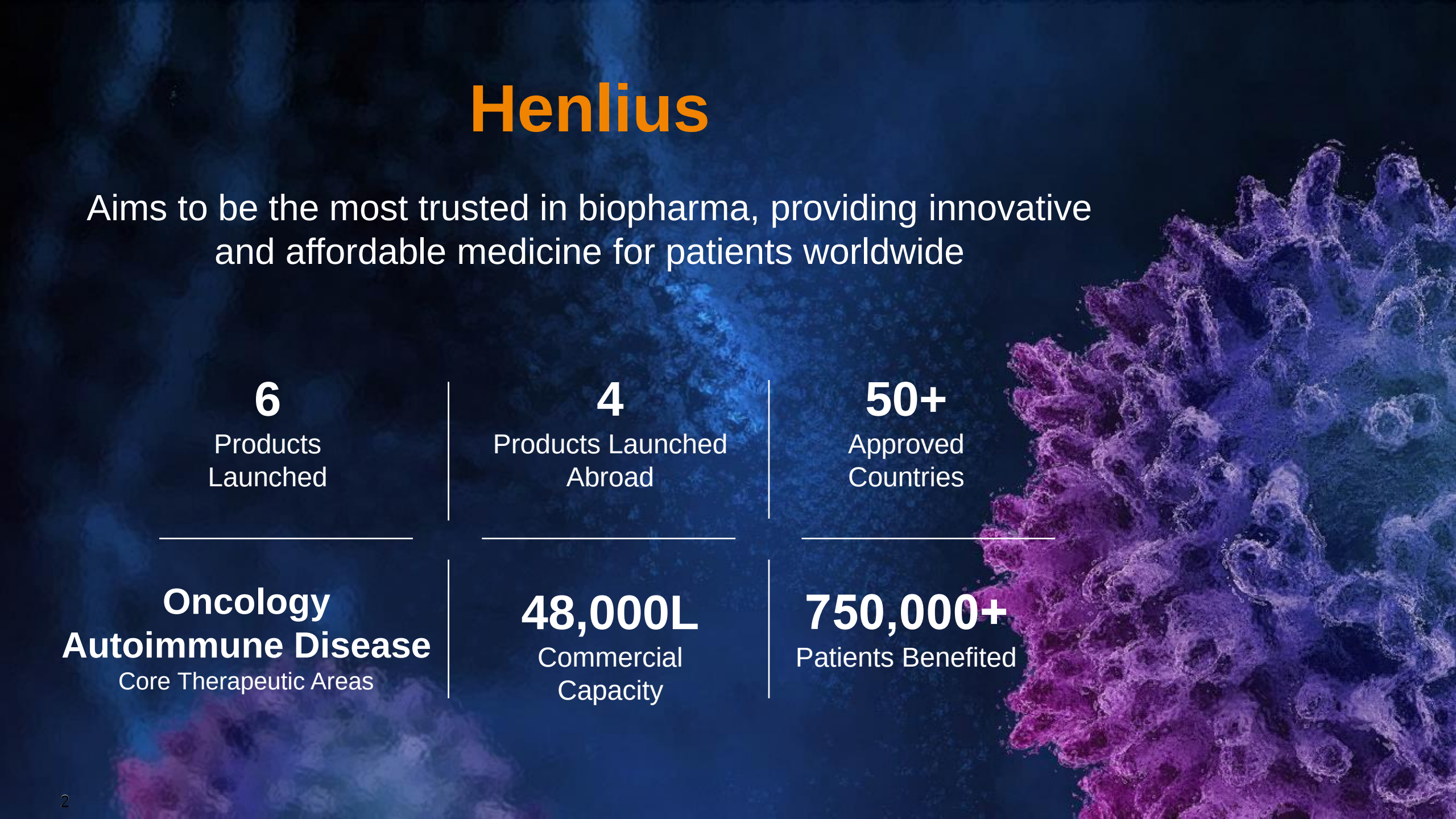
4
Products Launched Abroad

50+
Approved Countries

Oncology
Autoimmune Disease
Core Therapeutic Areas

48,000L
Commercial Capacity

750,000+
Patients Benefited



Commercial Products Fueling Sustainable Growth

RMB 5.72 billion Revenue

Core products continue to grow rapidly with 6.1% YoY

RMB 0.82 billion Net Profit

Consecutive full-year profit growth with 50.3% YOY

RMB 1.24 billion Operating Cash Flow

Continuous positive operational cash flow, with strong ability to generate cash

RMB 1.84 billion R&D Expenditure

Increase investment in R&D to spur growth

注射用曲妥珠单抗 汉曲优

1st Chinese mAb biosimilar approved in China, EU and U.S.

Launched in 53 countries and regions, including CN, US, EU, etc.

马来酸奈拉替尼 汉奈佳

Synergize with HANQUYOU, reducing the risk of recurrence for patients with early-stage HER2-positive breast cancer

Launched in CN

汉斯状 斯鲁利单抗注射液 SERPLULIMAB

Global & EU 1st approved anti-PD-1 mAb for 1L ES-SCLC

Launched in 34 countries and regions, including CN, EU, SEA etc.

汉贝泰 贝伐珠单抗注射液

The only bevacizumab biosimilars with phase 3 clinical data on mCRC in China

Launched in 2 countries including CN and Bolivia

汉利康 利妥昔单抗注射液

1st Chinese biosimilar
1st Chinese rituximab

Launched in 4 countries, including CN and Latin America

汉达远 阿达木单抗注射液

1st phase 3 clinical study of adalimumab biosimilar for psoriasis patients in China

Launched in CN

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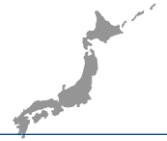
Globalization Milestone in 2024

USA

- HANQUYOU received BLA approval and completed the first commercial shipment to the U.S.
- FDA accepted Biologics License Application (BLA) for HLX14 (denosumab) and HLX11 (pertuzumab)
- HLX22 (HER2) combo therapy received Ph 3 MRCT IND approval from the U.S. FDA
- HLX15 (daratumumab) out-licensed to Dr. Reddy's in the U.S.
- Songjiang 1st Plant obtained GMP certification from the U.S.

Europe

- HANSIZHUANG got approval in the EU and entered UK's Innovation Licensing and Access Pathway (ILAP)
- EMA validated marketing authorization applications (MAA) for HLX14 (denosumab)
- HLX15 (daratumumab) out-licensed to Dr. Reddy's in 42 European countries and regions
- HANQUYOU marketed in around 20 countries in Europe, including UK, German, France and etc.
- Initiating clinical trials in more than 9 countries in the EU
- Xuhui Site and Songjiang 1st Plant obtained GMP certification from the EU



Japan

- HANSIZHUANG received approval in Japan for Ph 3 MRCT on first-Line mCRC and completed first patient dosed
- HLX22 (HER2) combo therapy received Ph 3 MRCT IND approval from PMDA, and successfully held first in-person investigator meeting in Japan
- Building in-house regulatory affairs and clinical development capacity in Japan

Southeast Asia

- HANSIZHUANG approved to launch in the Indonesia, Cambodia and Thailand; completed the first commercial shipment to Indonesia, being the 1st China anti-PD-1 mAb approved for marketing in Southeast Asia
- HANQUYOU approved to launch in Singapore, Philippines, Thailand, and Myanmar
- Initiating clinical trials in Southeast Asia, including Singapore, Philippines, Thailand and etc.

Middle East

- HANQUYOU made the first commercial shipment to Saudi Arabia and became the first Chinese monoclonal antibody to enter the Middle Eastern market
- Henlius and SVAX forged strategic partnership in MENAT Market. Two parties will establish JV in Saudi Arabia to integrate Henlius' leading capabilities in the R&D and manufacturing of biologics with SVAX's local expertise in registration, market access, and commercialization

Latin America

- HANBEITAI received approval from Bolivia's AGEMED, being Henlius' 4th self-developed product approved overseas
- HANLIKANG received marketing approval in Peru
- HANQUYOU received marketing approval in mainstream market in South America including Argentina and Brazil
- Entered out-license agreements with Abbott and Eurofarma to accelerate commercialization in LA market

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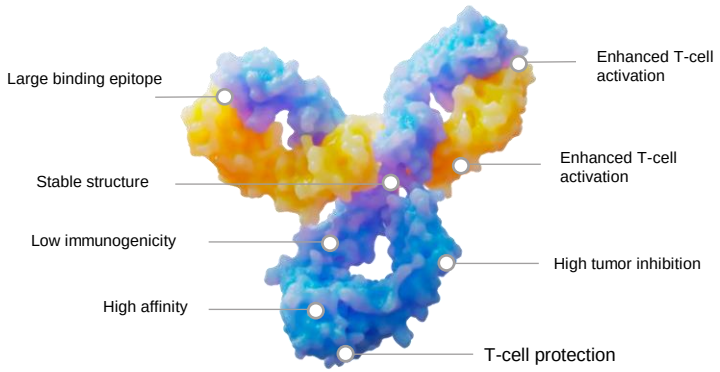
Blockbuster Pipelines Fueling Future Growth

HLX10 (HANSIZHUANG)

Expected to become the first approved PD-(L)1 for 1L mCRC.

Global Terminal Market Potential[1] >5B USD

- **Being the world's first anti-PD-1 mAb approved for first-line treatment of ES-SCLC, with 3-year OS rate 24.6% (Control group: 9.8%)**
- **Multiple Ph III MRCTs are in process, covering GC, LS-SCLC, mCRC**

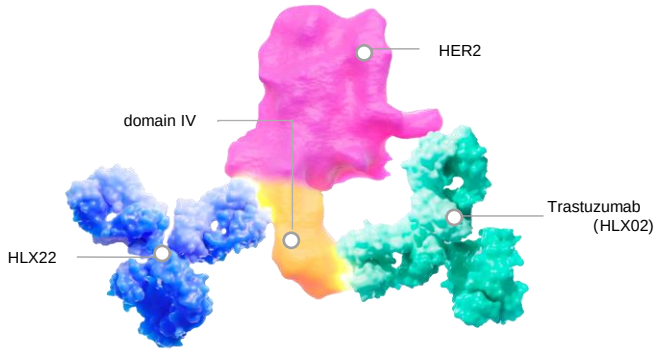


HLX22 (HER2)

Expected to change the SOC of 1L GC, aiming at a broader BC market.

Global Terminal Market Potential[1] >10B USD

- **Targets at different epitopes within domain IV of Her2**
- **Phase 2 study data shows HLX22 has clear benefits for patients, leading to great potential to change the SOC**
- **Initiating exploration in HER2 low breast cancer**

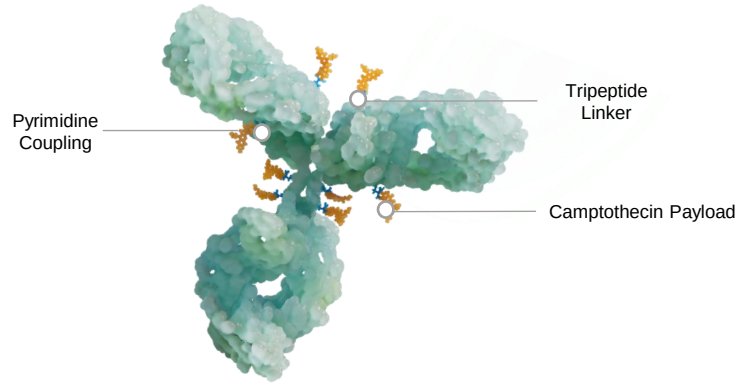


HLX43 (PD-L1 ADC)

Covering NSCLC, HCC and other high-incidence cancers.

Global Terminal Market Potential[1] >15B USD

- **An anti-PD-L1 ADC with TAMLIN linker and TOPO1i Payload**
- **Presented superior preclinical data on ESMO**
- **Showed effective tumor inhibition and controllable safety profile in Ph I study**
- **Multiple Ph II trials are ongoing**
- **Has potential to become BIC**



[1]The terminal market potential value is calculated as the eligible patients for product-related indications * the estimated annual treatment cost.

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Henlius Long-term R&D Strategy

We are committed to providing medicines and treatments that improve the quality of life for patients.

Post-PD-1 era

- **T-Cell Engager**
  HLX3901, HLX3902, …
- **ADC**
  HLX43, HLX42, HLX48, HLX***, …
- **Sialidase + TAA**
  HLX316, …
- **Cytokines**
  HLX***, …
- **PD-1+ VEGR for tumor microenvironment**
  HLX37, …

Double breakthrough

- **Continuously exploring blockbuster pipelines in autoimmune and metabolic areas**
  HLX79, ****, …
- **Continue to develop new formulations to offer patients more convenient options**
  HLX***, HLX15, HLX208, …

Continuous expansion

- **Accelerate the expansion of new indications and increase the value of individual products**
- **Accelerate global expansion of pipeline to build multi-polar growth**

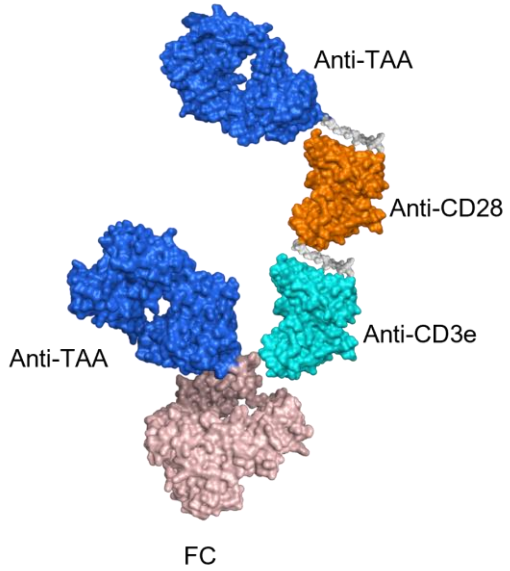
  HLX22, expect to change the SOC of 1L GC and aiming at a broader BC market

  HLX43, covering NSCLC, HCC and other high-incidence cancer

  HLX10 (HANSIZHUANG), multiple Ph III MRCTs are in process, covering GC, LS-SCLC, mCRC

Advanced Pre-clinical Platforms

Hinova TCE Platform

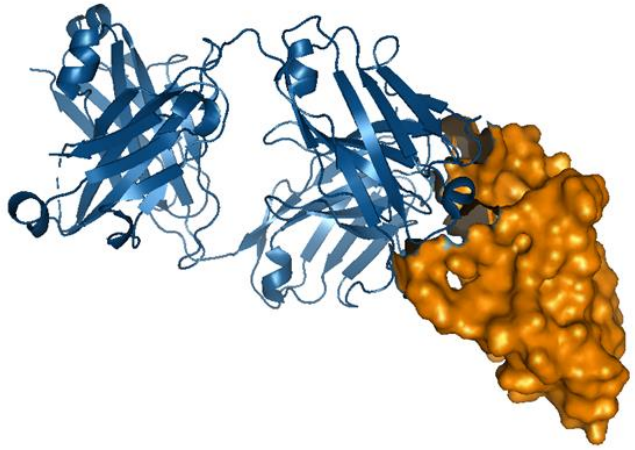


- **Longer persistence of Activated T Cell**
- **Greater Efficacy in solid tumor Treatment**
- **Enhanced Safety with lower CRS Risks**

Hanjugator™ ADC Platform

- **Expanded clinical therapeutic window**
- **Overcome resistance to widely used payloads**
- **Combination of multiple payload mechanisms**

HAI Club Platform



- **Identification of Novel drug targets**
- **Cost effective Research & Development**
- **Improved Successful rate in drug discovery**

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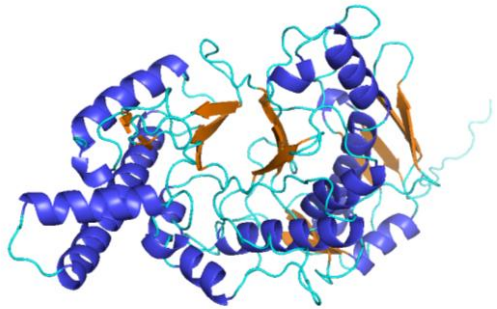
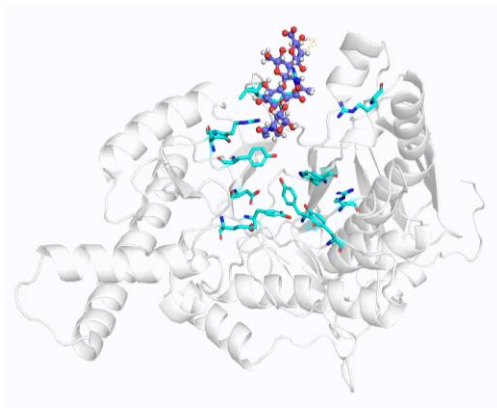
Henlius Self-Developed Hyaluronidase Platform

rHuPH20 1.0



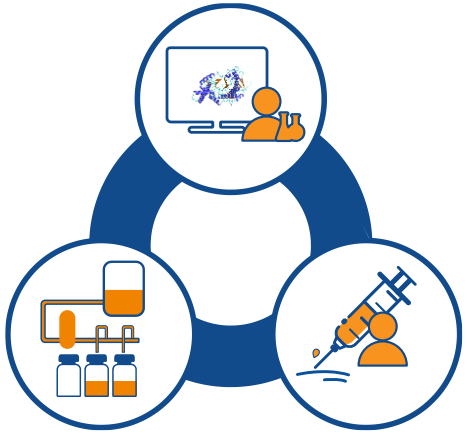
- The sequence is identical with Halozyme HYLENEX
- Ideal choice for both biosimilar and innovations
- Will file in US and CN in 2025Q3

rHuPH20 2.0



- Henlius' proprietary rHuPH20
- Excellent stability and adaptable for multiple complex scenarios
- Ideal for Innovations
- Will have GMP production in 2025 H2

SC Formulation Development



- Database + in silico tool + DoE
- High concentration and co-formulation development
- Expertise in subcutaneous drug product development.

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Product Portfolio and Pipeline

Pre-IND / IND	Phase 1	Phase 2	Phase 3	NDA	In-Market
HLX79[1] Sialidase Fc Fusion Protein Active Glomerular Diseases	HLX6018 GARP/TGF-β1 IPF	HLX10 [5] (serplulimab) + HLX07 [6] PD-1+EGFR HNSCC, NPC, sqNSCLC, etc.	HLX10 [5] (serplulimab) + Chemo PD-1 ES-SCLC 1L	HLX14 (denosumab) [12] RANKL Osteoporosis, etc.	HANSIZHUANG (serplulimab) [5] PD-1 sqNSCLC, ES-SCLC, ESCC, nsNSCLC
HLX17 (pembrolizumab) PD-1 NSCLC, TNBC, etc.	HLX42 [2] EGFR ADC Solid tumours	HLX10 [5] (serplulimab) + HLX26 + Chemo PD-1+LAG-3 NSCLC 1L	HLX10 [5] (serplulimab) + Chemo PD-1 Neo/adjuvant treatment for GC	HLX11 (pertuzumab) [13] HER2 BC	HANLIKANG (rituximab) [14] CD20 NHL, CLL, RA[15]
HLX316 Fusion protein Solid tumor	HLX43 [7] + HLX10 [5] (serplulimab) PD-L1 ADC + PD-1 Solid tumours	HLX07 [6] EGFR Solid tumors (cSCC)	HLX10 [5] (serplulimab) + Chemo + Radio PD-1 LS-SCLC 1L		HANQUYOU (trastuzumab) [16] HER2 BC, mGC
HLX105 Fusion protein Solid tumor	HLX05 [3] (cetuximab) EGFR mCRC, HNSCC	HLX53 + HLX10 [5] (serplulimab) + bevacizumab TIGIT + PD-1 + VEGF HCC	HLX10 [5] (serplulimab) + bevacizumab + Chemo PD-1+VEGF mCRC 1L		HANDAYUAN (adalimumab) [17] TNF-α RA, AS, Ps, UV, pJIA, pediatric Ps, CD, pediatric CD
HLX37 PD-L1 x VEGF Bispeciifc Solid tumors	HLX15 [4] (daratumumab) CD38 Multiple myeloma	HLX43 [7] PD-L1 ADC Solid tumours	HLX04-O [9] VEGF Wet AMD		HANBEITAI (bevacizumab) [18] VEGF mCRC, advanced, metastatic or recurrent NSCLC, GBM, etc.
HLX3901 Trispecific SCLC	HLX13 (ipilimumab) CTLA-4 Melanoma, HCC, etc.	HLX208 [8] BRAF V600E LCH/ECD, MEL, NSCLC, etc.	HLX22[10] + trastuzumab + Chemo HER2+HER2 GC		HANNAIJIA (neratinib) [19] HER1/HER2/HER4 Extended adjuvant treatment of BC
HLX3902 Trispecific PCa		HLX208 [8] + HLX10 [5] (serplulimab) BRAF V600E + PD-1 NSCLC	HLX78 (lasofoxifene) [11] SERM BC		
HLX41 ADC BC					
HLX48 Bispecific ADC NSCLC, CRC					
HLX97 KAT6A/B ERα⁺ Breast Cancer					

(1) Exclusive license obtained in China. Phase 1/2 conducting in the U.S. (2) IND approvals obtained in China/the U.S. and granted FDA Fast Track Designation. (3) Business partner: Shanghai Jingze. (4) Business partner: Dr. Reddy's, etc. (5) Approved in China, the EU and several SEA countries. trade name: Hetronifly® in Europe. partners: KGbio/Fosun Pharma/Intas. (6) IND approvals obtained in China/the U.S. (7) IND approvals obtained in China/the U.S. (8) Exclusive license obtained in China. (9) IND approvals obtained in China/Australia/the U.S./Singapore/EU countries, etc. Business partner: Essex. (10) IND approvals obtained in China/the U.S./Japan. (11) Exclusive license obtained in China. Phase 3 MRCT enrolling globally. IND approval obtained in China. (12) Marketing applications under review in the EU and the U.S. (13) Marketing applications under review in China, the U.S. and the EU Business partner: Organon. (14) Approved in countries such as China and Peru. The first biosimilar approved in China. Business partners: Fosun Pharma/Farma de Colombia/Eurofarma/Abbott/Boston Oncology. (15) The first rituximab approved for the indication in China. (16) Approved in 50+ countries, including China, U.S., the UK, Germany, France and Australia, trade name registered in U.S.: HERCESSI™. trade name registered in Europe: Zercepac®. Business partners: Accord/ Cipla/ Jacobson/ Elea/ Eurofarma/ Abbott/ KGbio/ Getz. (17) Business partners: Fosun Wanbang/Getz Pharma. (18) Business partner: Eurofarma. (19) Exclusive license obtained in China.

Innovative mAb · Innovative fusion protein · Biosimilar mAb
Innovative ADC · small molecule · Innovative multi-specific antibody
Bridging study in U.S. · BLA under FDA review · MAA under EMA review
Global MRCT · Approved in Global markets

Clinical Pipeline Milestones: Expected in 2025

	2025H1	2025H2
NDA/BLA/MAA Submission	**HLX10** ES-SCLC[1] 1L (Hong Kong SAR, MENA, Turkey, LATAM) **HLX10** sq-NSCLC[2] 1L (the Philippines) **HLX10** nsq-NSCLC[3] 1L (Indonesia, Thailand) **HLX04 HANBEITAI** mCRC, advanced, metastatic or recurrent NSCLC, GBM, etc. (Saudi Arabia) **HLX11** Breast cancer Neoadjuvant therapy (EU, Canada) **HLX14** PMOP[4] etc. (CN) **HLX04-O** Wet AMD[5] (CN)	**HLX04-O** Wet AMD[5] 1L (US) **HLX14** PMOP[4] , etc. (UK) **HLX10** ESCC[8] 1L (EU) **HLX10** nsq-NSCLC[1] 1L (Cambodia, EU) **HLX10** sq-NSCLC[1] 1L (EU, India, Singapore, Myanmar, Malaysia) **HLX10** MSI-H Later line (EU)
NDA/BLA/MAA Approval	**HLX10** ES-SCLC[1] 1L (Myanmar, the Philippines, UK) **HLX03 HANDAYUAN** RA, AS, Ps, UV, pJIA, pediatric Ps, CD, pediatric CD,etc (Pakistan) **HLX02 HANQUYOU** Breast cancer, mGC (SEA, LATAM)	**HLX10** ES-SCLC[1] 1L (Swit, India, Malaysia，Singapore) **HLX10** sq-NSCLC[2] 1L (Cambodia) **HLX11** Breast cancer Neoadjuvant therapy (US) **HLX14** PMOP[4] , etc. (EMA & US & CAN) **HLX01 HANLIKANG** NHL, CLL, RA （LATAM, Saudi Arabia） **HLX02 HANQUYOU** Breast cancer, mGC (SEA, LATAM)
Key Clinical Data Readouts	**HLX10** nsq-NSCLC[3] 1L（Pivotal） **HLX10+HLX04** mCRC[6] 1L（PoC） **HLX14** PMOP[4] etc. (Pivotal) **HLX22+HLX02** GC[7] 1L (PoC) **HLX43** PD-L1 ADC NSCLC-PoC	**HLX10** Nsq-NSCLC 1L (Pivotal)-OS **HLX07+HLX10** NPC[9] 1L (China PoC) **HLX43** PD-L1 ADC NSCLC-PoC

The Company's internal planning time is subject to the actual situation, and shareholders and potential investors of the Company are advised to exercise caution when trading the Company's shares.

Innovative mAb | mAb biosimilar | Innovative fusion protein | Innovative ADC

1. Extensive stage small cell lung cancer 2. Squamous non-small cell lung cancer 3. Non-squamous non-small cell lung cancer 4. Postmenopausal osteoporosis 5. Age-related macular degeneration 6. Metastatic colorectal cancer 7. Gastric cancer 8. Esophageal squamous cell carcinoma 9. Nasopharyngeal carcinoma

Henlius

An International Leader in Manufacturing and Quality Management

- **“Henlius Quality” with international standard:** obtained GMP certifications from China, the EU and US, products supply covering China, the US, the EU, Brazil, Indonesia, Saudi Arabia and Singapore.
- Intelligent Drug Manufacturing 2.0, completed installation and validation of new high speed PFS line; completed HANQUYOU G2.1 process technology validation.
- Advance the SJ2 – I & II projects and equipment construction: Main buildings construction of phase I already completed, with manufacturing capacity covering drug substance, liquid filling, pre-filled syringes, and ADC conjugation.

Manufacturing Capacity	Commercial GMP batches	Production success rate
84KL+60KL	**1050+**	**≥ 98%**


Xuhui Site（24,000L）


Songjiang 1st Plant（24,000L）


Songjiang 2nd Plant
(36,000L+60,000L)

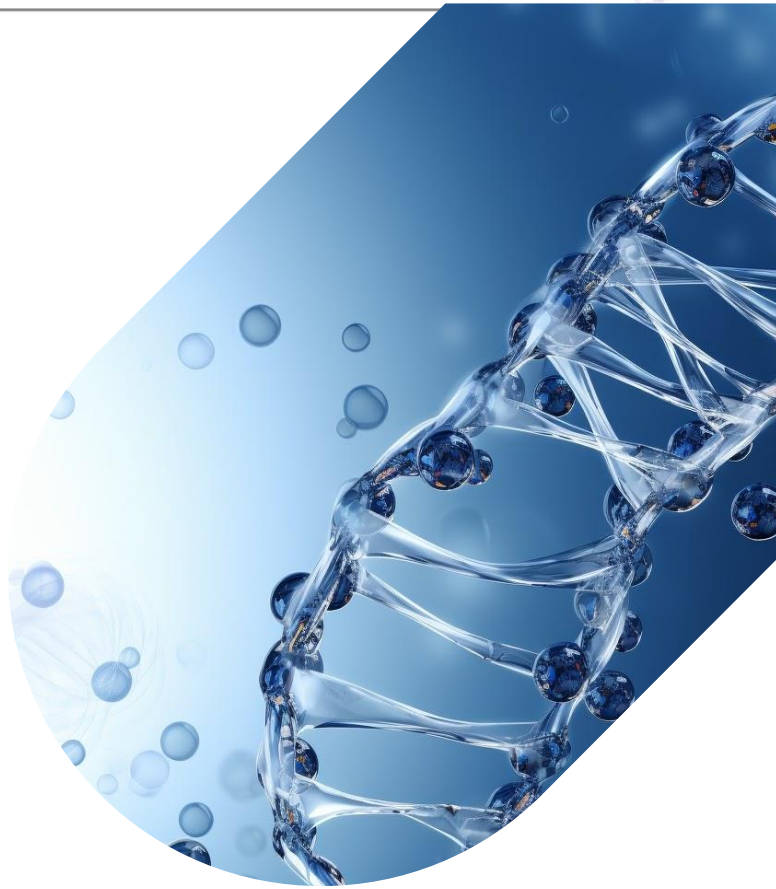
Our Commitment

Innovation

- Harness R&D strengths and cultivate differentiated competitive edges
- Focus on blockbuster pipelines with high unmet need indications

Globalization

- Build in-house end-to-end global capacity
- Forge Henlius international brand



Patient- centered

- Anchor all initiatives in patient needs and clinical value
- Dedicated to developing life-changing therapies that positively impact patients' well-being

Henlius

Innovation-Driven:

Henlius' R&D Strategy and Vision

Dr. Jijun Yuan
CSO of Henlius

Collaborate to Create

2025 Henlius Global R&D Day

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01 Henlius Portfolio and Pipeline Landscape

Henlius

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Innovative ADC · small molecule · Innovative multi-specific antibody
Bridging study in U.S. · BLA under FDA review · MAA under EMA review
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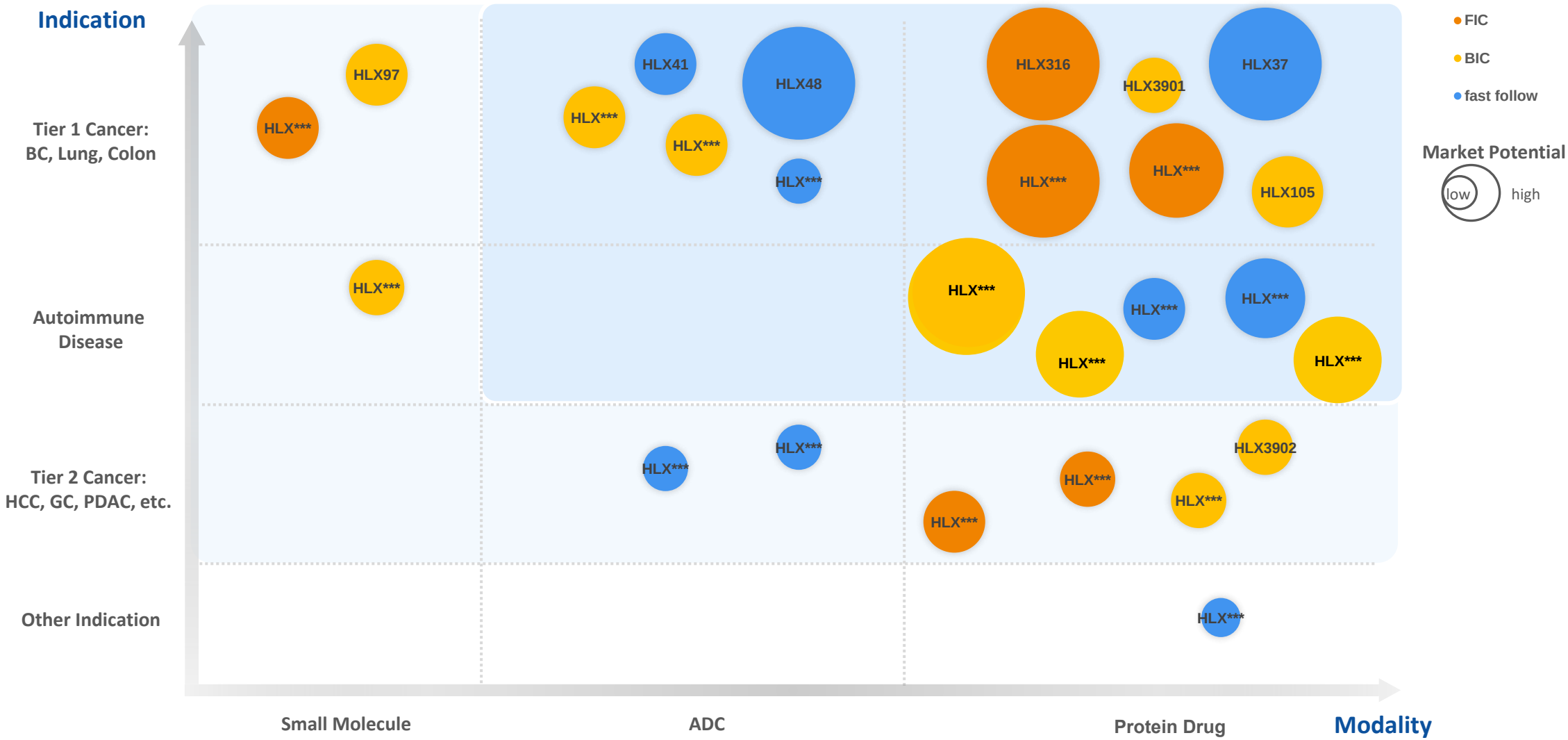
Henlius Preclinical Pipeline Landscape



Market Potential is evaluated based on epidemiology data of target indication and adjusted by target/MOA potential, market size estimation from Globaldata database. Due to the uncertainty of future clinical development plan, the evaluation shown here is a rough version.

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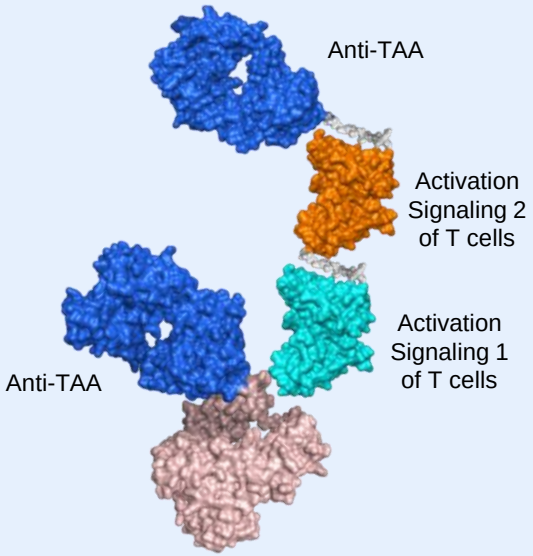
Henlius Advanced Pre-clinical Platforms

Hinova TCE Platform



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Hanjugator™ ADC Platform

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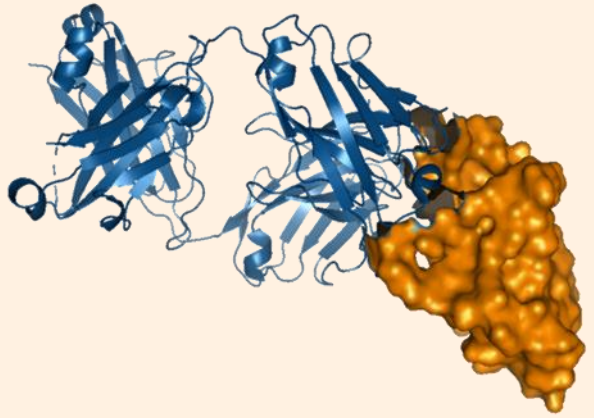
- Combination of multiple payload mechanisms

HAI Club Platform



- Identification of Novel drug targets
- Cost-effective Research & Development
- Improved Success rate in drug discovery

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02

A Next-generation TCE Platform Powered by AI-driven Design

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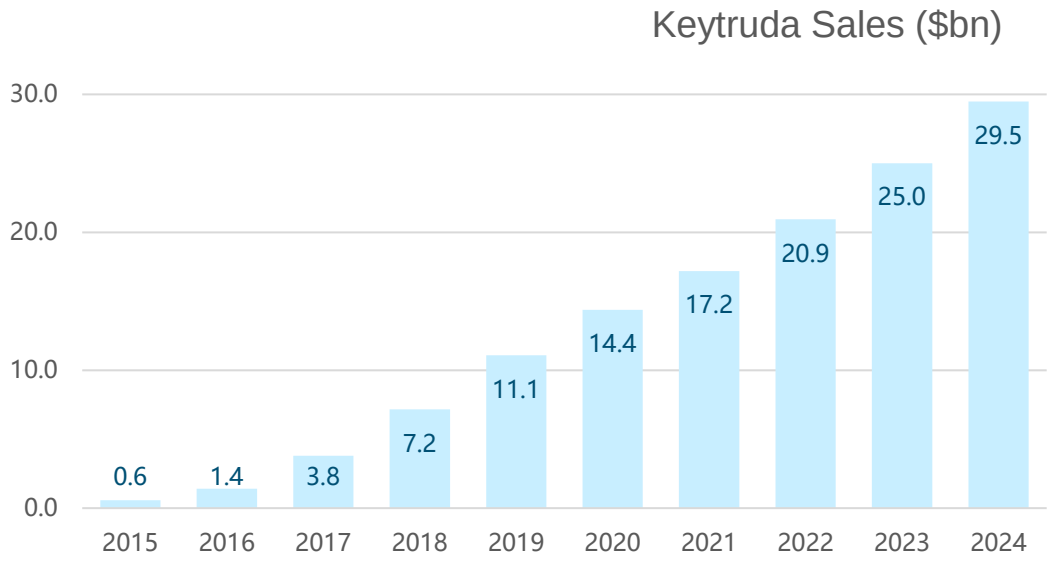
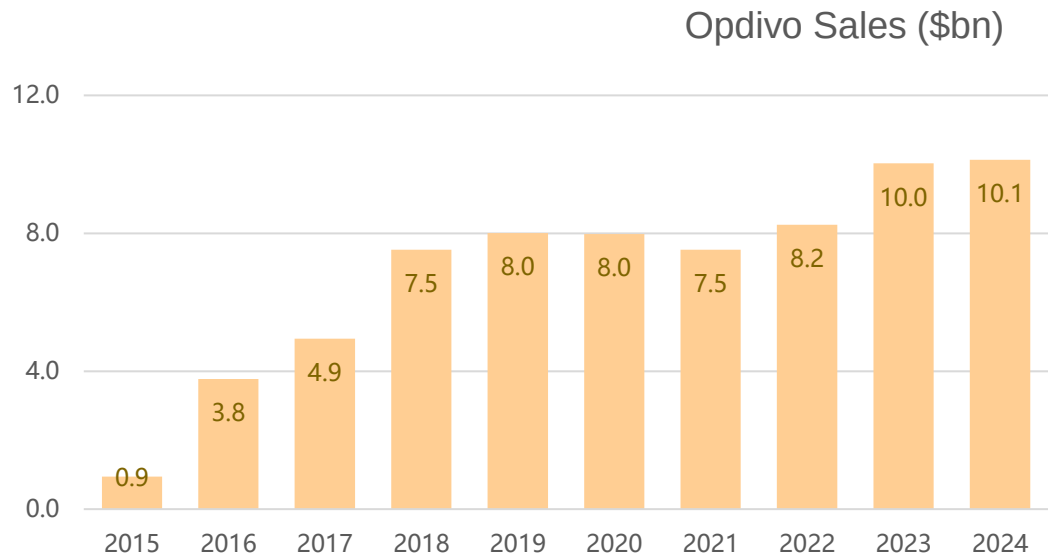
Successful PD1/PD-L1 ICIs in Treating Tumors As an I/O Therapy

KEYTRUDA® (pembrolizumab)



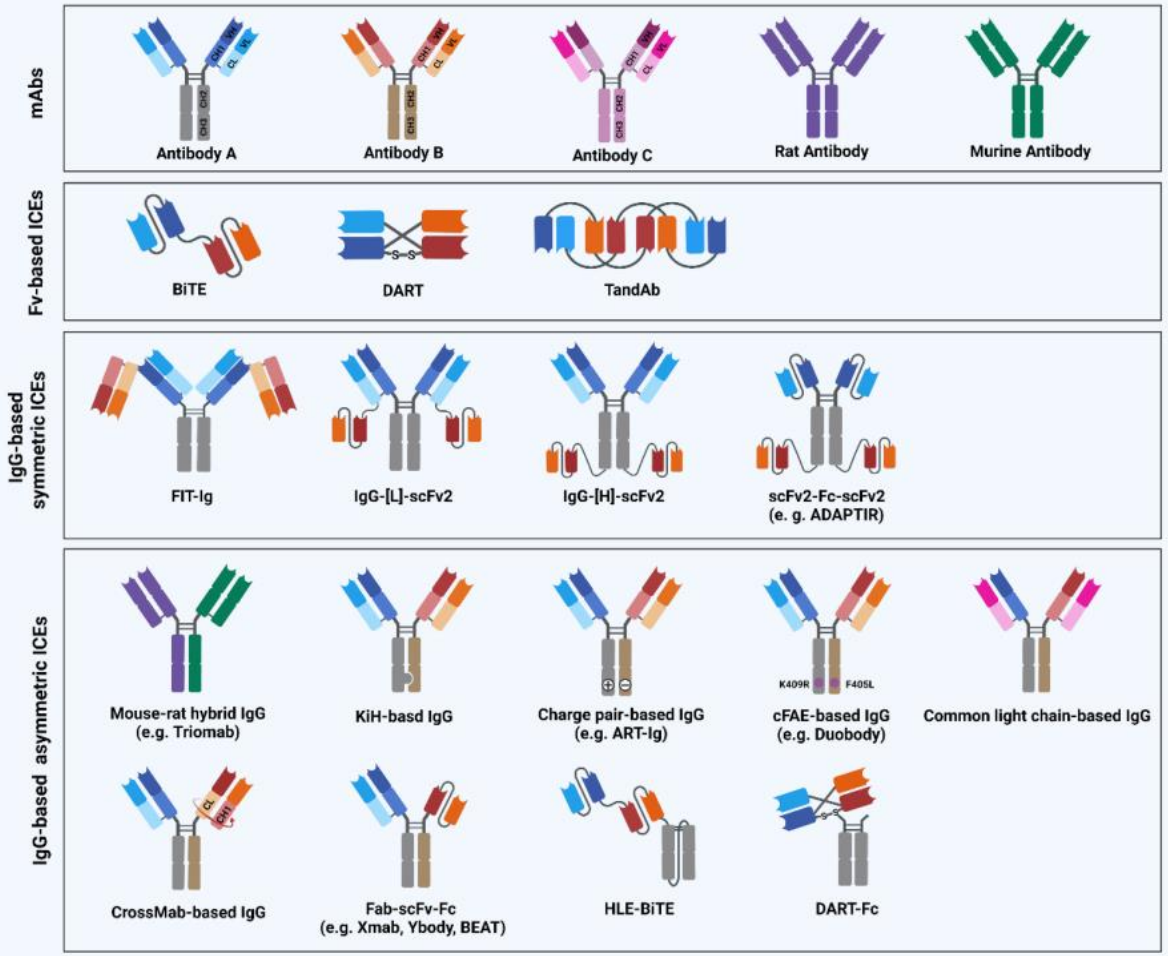
- **KEYNOTE-024:** First-line treatment for NSCLC with PD-L1-high（TPS≥50%), Median OS was 30.0 months in the pembrolizumab arm vs 14.2 months in the chemotherapy arm.
- **KEYNOTE-189:** First-line treatment for Previously Untreated Metastatic Nonsquamous NSCLC, Median OS was 22.0 months in the pembrolizumab-combination group vs 10.7 months in the placebo-combination group.
- **KEYNOTE-407**: First-line treatment in patients with metastatic squamous NSCLC, Pembrolizumab plus chemotherapy continued to exhibit a clinically meaningful improvement over placebo plus chemotherapy in OS 17.1 months versus 11.6 months

OPDIVO® (nivolumab)



- **CheckMate-017/057:** Second-line treatment for NSCLC，Median OS was 9.2 months in Opdivo vs 6.0 months in Docetaxel.
- **CheckMate-227:** First-line treatment for NSCLC with PD-L1≥1%, Median OS was 17.1 months in Opdivo plus Ipi arm vs 14.9 months in Chemo arm.
- **CheckMate-141:** Second-line treatment for Recurrent or metastatic HNSCC，Median OS was 7.5 months in Opdivo vs 5.1 months in the chemotherapy arm.
- **CheckMate-032:** Third-line treatment for SCLC, ORR of monotherapy was 10% and Median OS was 4.4 month.

TCE: Next-generation I/O Based on CD3 Bispecific Ab



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Limited Immune Cell Infiltration Hinders the Application of CD3-bispecific Antibody in Solid Tumors

Multiple TCE products have been applied in blood tumors, but only one product has been approved due to low T-cell infiltration in solid tumors

7 approved TCE products in hematology

Drug Name	Target	Indications	First Approved Date and Country	Primary Endpoint	Company
Blinatumomab	CD3/CD19	r/r B-ALL	December 2014 (USA)	CRR: 78%	Amgen
Mosunetuzumab	CD3/CD20	r/r FL	June 2022 (EU)	CRR: 60%	Roche/Chugai/Biogen
Glofitamab		DLBCL	March 2023 (Canada)	CRR: 39%	Roche/Chugai
Epcoritamab		DLBCL	May 2023 (USA)	ORR: 63%	AbbVie/Genmab
Teclistamab	CD3/BCMA	r/r MM	August 2022 (EU)	ORR: 63%	Janssen
Elranatamab		r/r MM	August 2023 (USA)	ORR: 61%	Pfizer
Talquetamab	CD3/GPRC5D	r/r MM	August 2023 (USA)	ORR: 70% *, 64% **	Janssen

TCE: T cell engager, r/r B-ALL: relapsed or refractory precursor B-cell acute lymphoblastic leukemia, r/r FL: relapsed or refractory follicular lymphoma, DLBCL: diffuse large B-cell lymphoma, r/r MM: relapsed/refractory multiple myeloma, CRR: complete response rate, ORR: overall response rate, *: subcutaneous talquetamab, 405 μg weekly; **: subcutaneous talquetamab, 800 μg every 2 weeks.

1 approved TCE product in solid tumors

Drug Name	Target	Indications	First Approved Date and Country	Primary Endpoint	Company
Tarlatamab	CD3/DLL3	SCLC	May 2024 (USA)	ORR: 40.0%; mPFS: 4.3 mon; mOS: 15.2 mon	Amgen

SCLC: small cell lung cancer.

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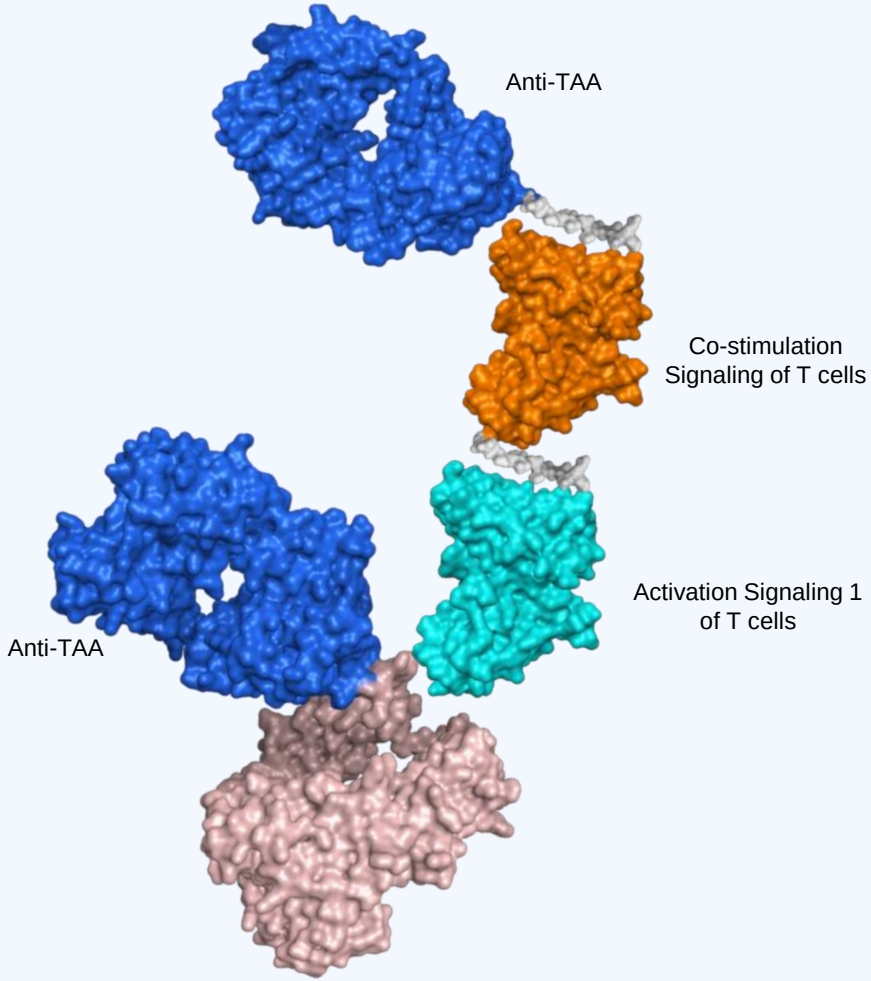
Henlius Advanced Tri-specific TCE Platform



Advantages of Tri-specific TCE Platform

Longer persistence of Activated T Cell

Greater Efficacy in solid tumor Treatment

Enhanced Safety with lower CRS Risks

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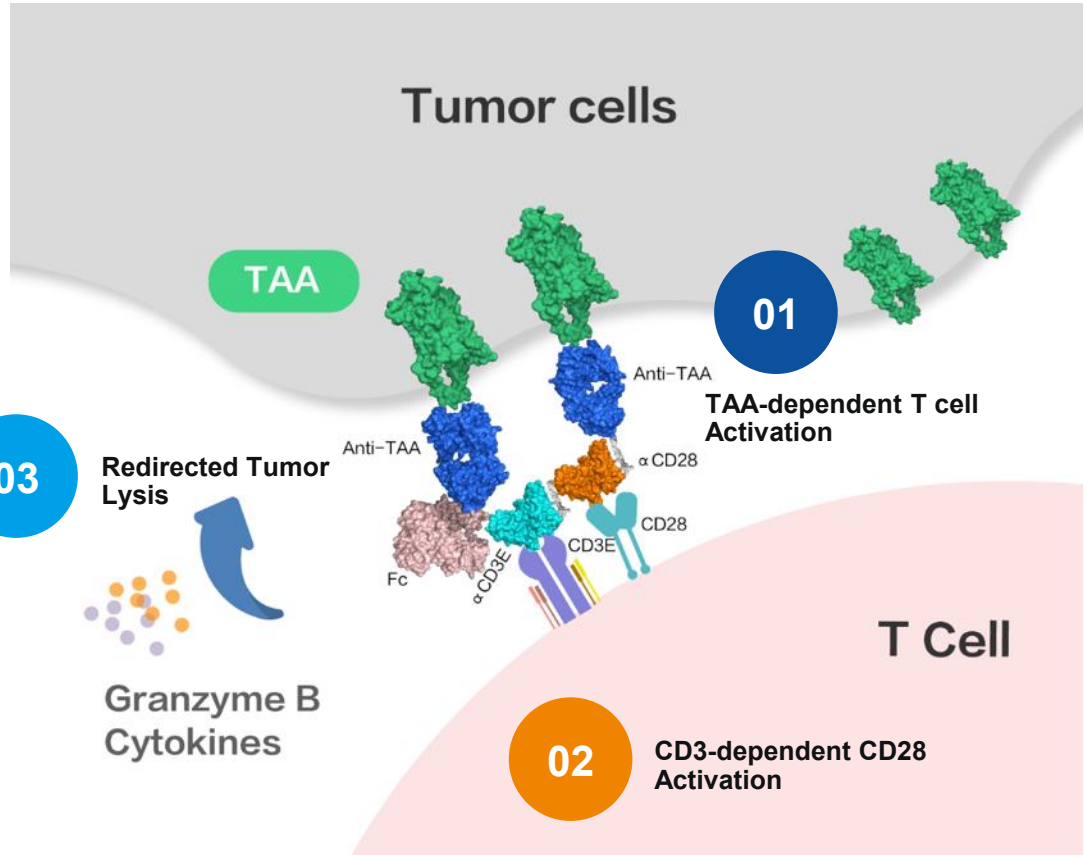
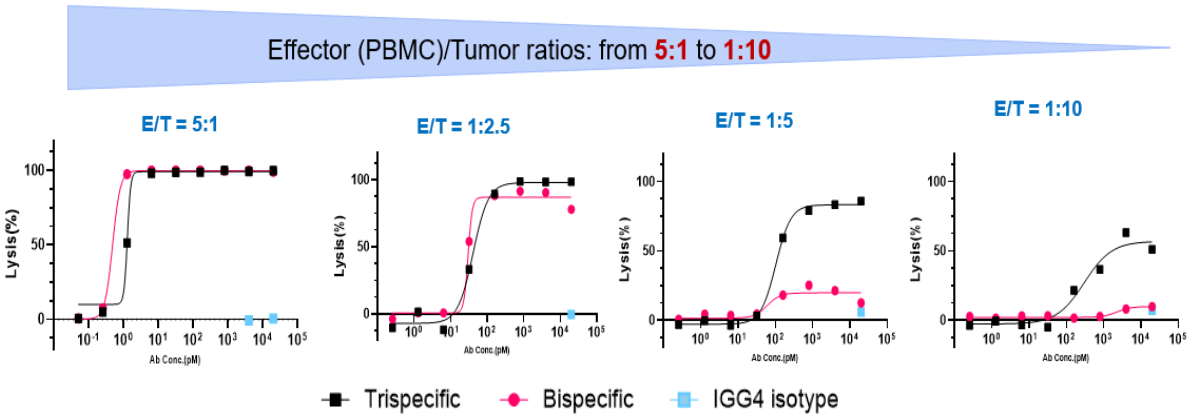
Henlius Has Established a Safer and More Efficient Tri-specific T-cell Engager Platform

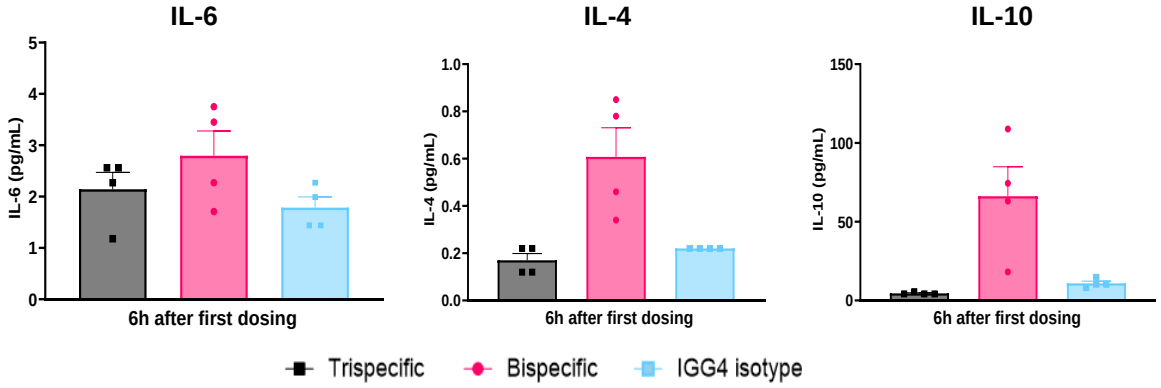


TAA: Tumor associated antigen

Better efficacy with low T-cell infiltration



Lower cytokine release



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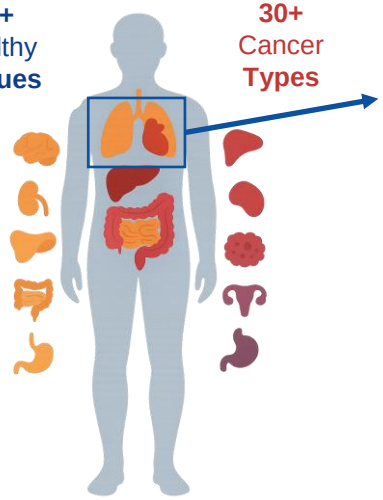
DLL3 Target Validation by Henlius Internal Database

Henlius internal multi-omics database

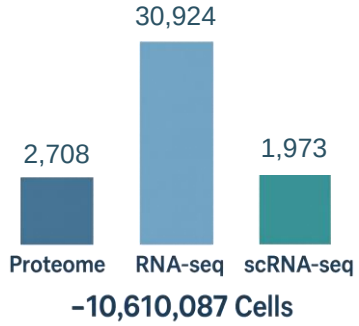
30+ Healthy Tissues

30+ Cancer Types



Small Cell Lung Cancer

Cohort: Proteomics, RNA-seq (200+ samples)
Single cell RNA-seq (48 samples, 174,000+ cells)



~10,610,087 Cells

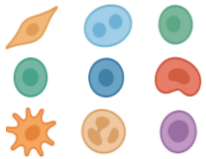
Adjacent vs. Tumor

Primary vs. Metastasis

SCLC subtypes

Untreated vs. Treated

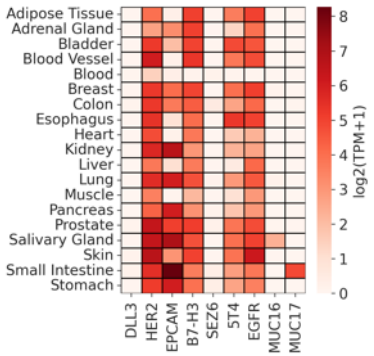
Cancer cells



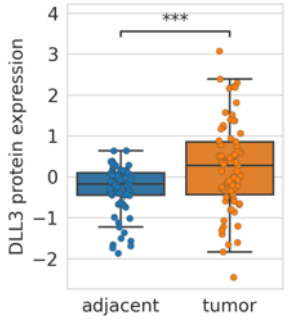
TME cells

- **DLL3 expression is lowly expressed in normal tissues and highly expressed in all SCLC subtypes**

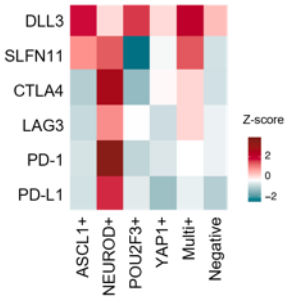
RNA data from GTEx



Protein data from SCLC cohort

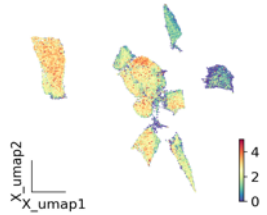


Spatial proteomics data from SCLC cohort

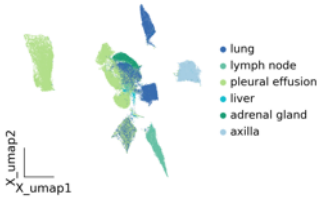


- **DLL3 is ubiquitously expressed during SCLC progression. According to single cell studies, it is expressed in various metastatic tissues, as well as after several lines of treatments.**

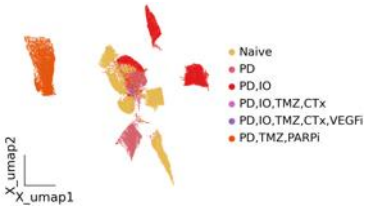
DLL3 expression in tumor cells



Primary or metastasis



Previous treatment



TMZ: temozolomide
PD: Platinum Doublet
IO: Immunotherapy
CTx: Chemotherapy
VEGFi: VEGF inhibitor
PARPi: PARP inhibitor

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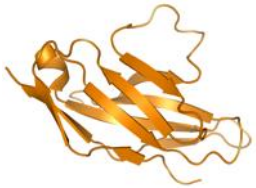
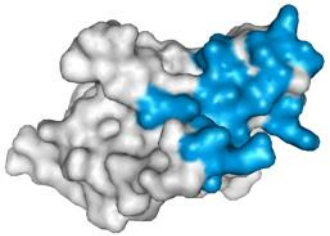
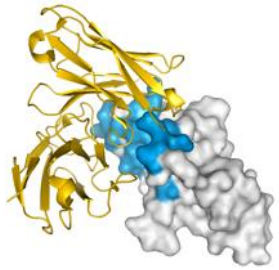
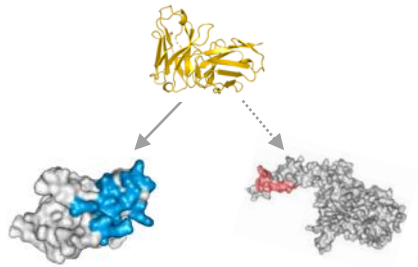
AI Drug Discovery Platform Accelerates Antibody Development









Structure

- Predict antigen structure
- Predict binding region

Epitope

- Predict antigen - antibody binding epitope
- Binding probability prediction
- mAb/bsAb epitope selection and optimization

Affinity

- Binding affinity prediction
- In silico. screening

Specificity

- Non-specific binding prediction
- Species crossing validation
- Protein family binding specificity prediction

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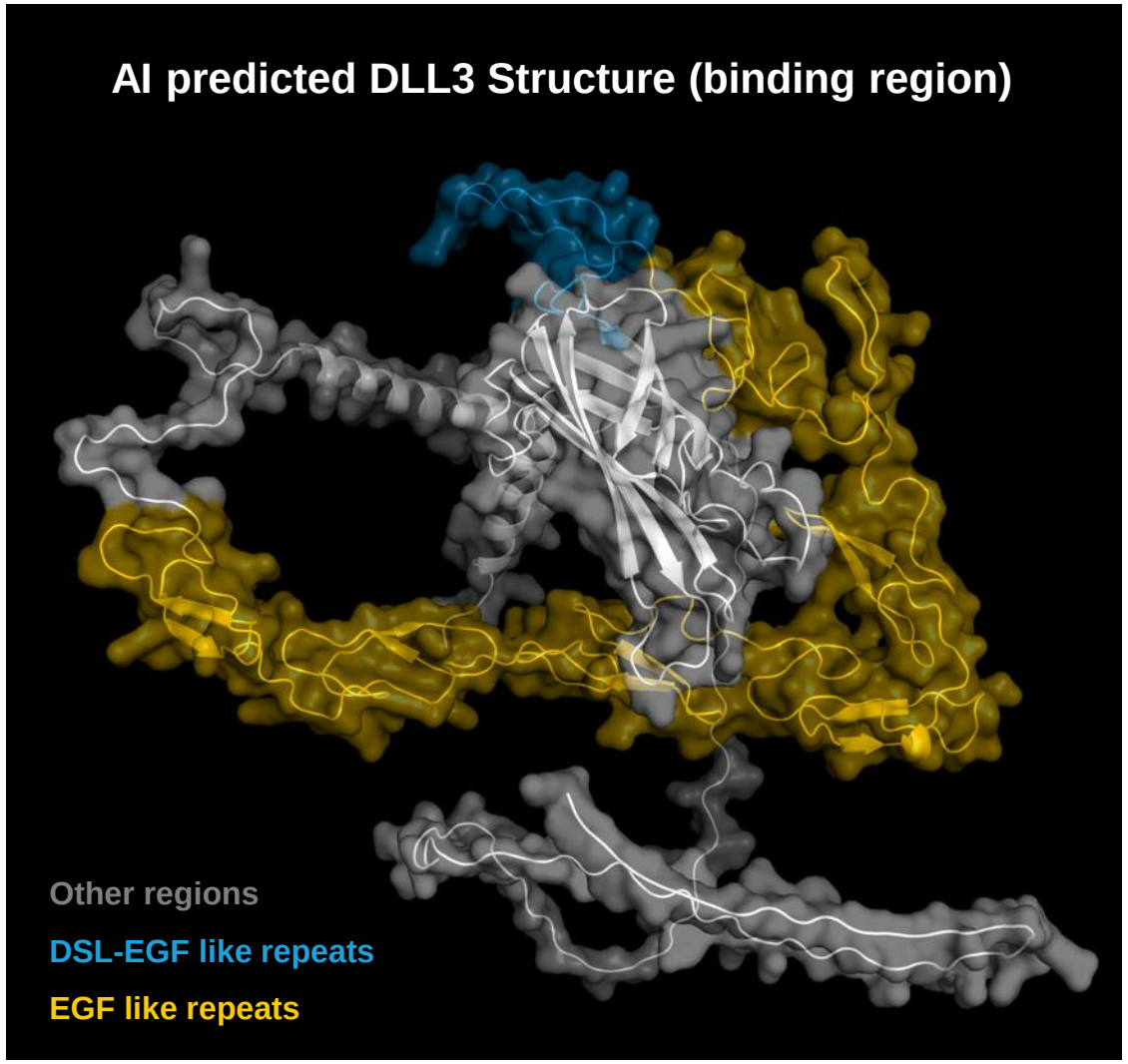
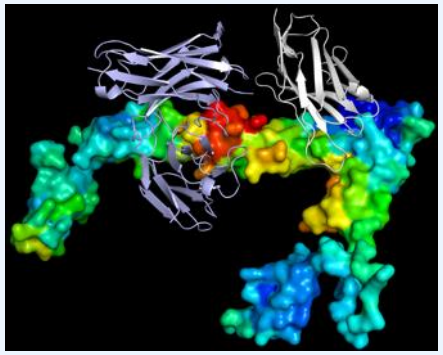
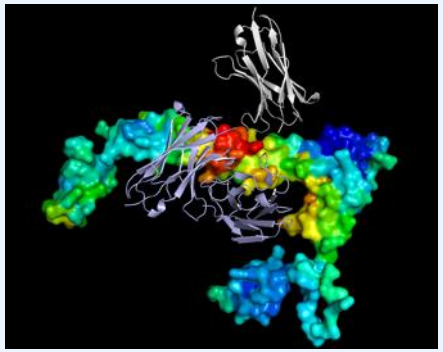
DLL3 Structure Prediction by HAI Club Platform



- DLL3 structure prediction by HAI Club platform
- We choose EGF - like repeats which is close to the cell membrane as binding domain
- Further more, we use AI to design preferable epitope for biparatopic anti-DLL3 TCE to enhance the binding affinity and accelerate the development

Examples of different epitope candidates





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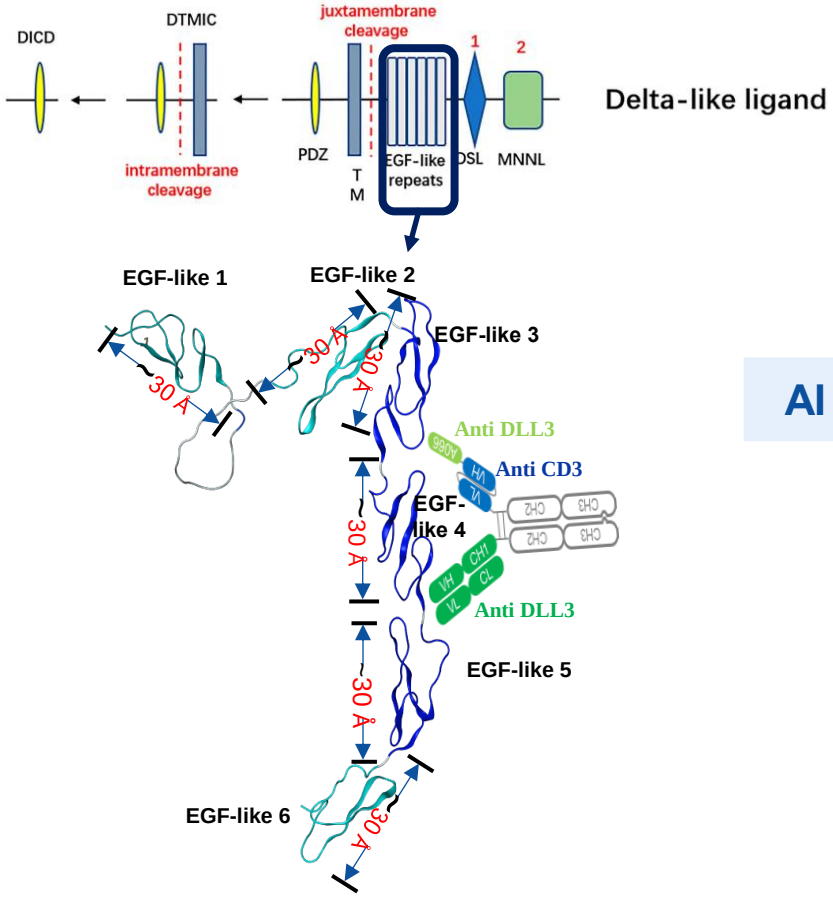
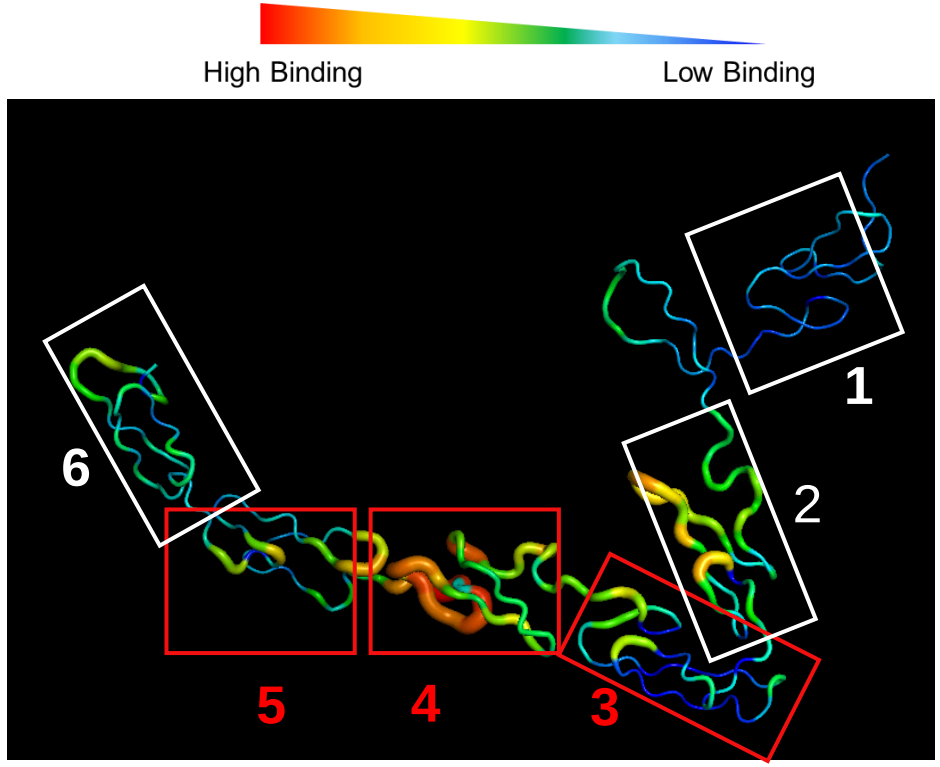
Epitope Design / Optimization by AI

- According to predicted structure, six EGF-like domains have similar length. (~ 30Å)
- Considering the most reasonable distance for biparatopic antibody, we choose adjacent repeats to target

- In order to choose the best epitope among all six repeats, we use structure based deep learning method, which predicts the binding probability between antibody and antigen.
- According to the results, repeat 4 has the highest binding probability. Repeat 4 can also forms a well-defined binding interface with both repeat 3 and 5.



AI prediction



Tubiana, Jérôme, Dina Schneidman-Duhovny, and Haim J. Wolfson. "ScanNet: an interpretable geometric deep learning model for structure-based protein binding site prediction." *Nature Methods* 19.6 (2022): 730-739.

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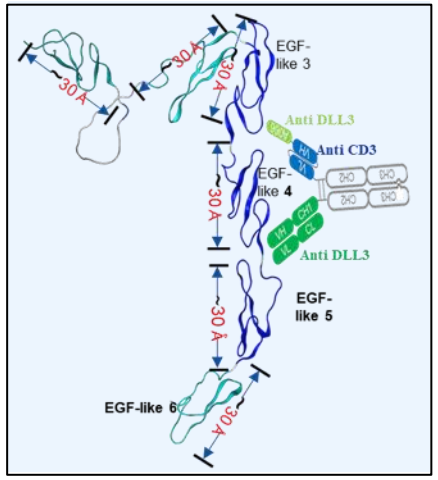
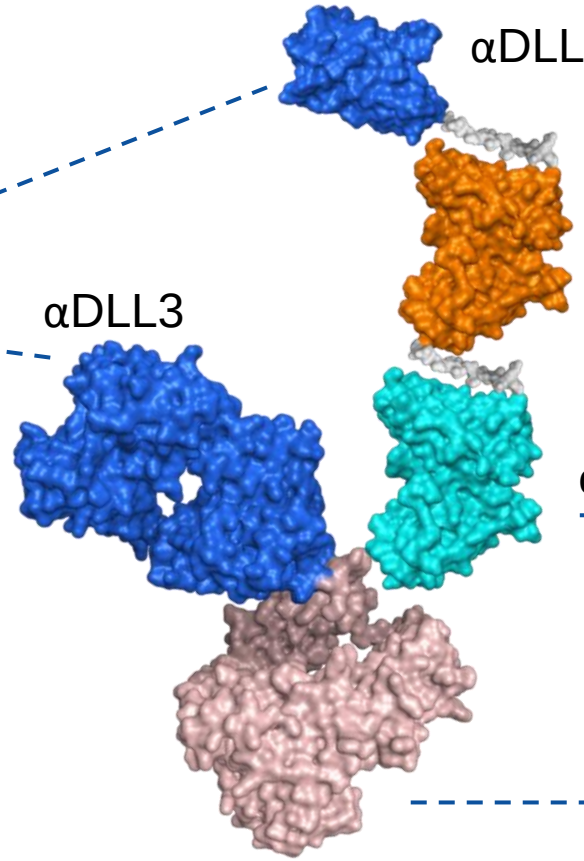
Developed a First-in-class DLL3xCD3xCD28 Tri-specific Ab for The Treatment of SCLC

Biparatopic design enhances specificity towards tumors





CD3-dependent activation

Adjusted activation potency

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HLX43: a PiP in Transforming, Advance is Accelerating

Henlius' ADC Workman Piece: Vision, Strategy, and Practice

Lixin Feng, PhD

April 2025

Collaborate to Create

2025 Henlius Global R&D Day

CONTENTS

01

HLX43 Key Attributes

Molecule By Design

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HLX43: Molecule Features and Development Process

- Target: **Programed Death Ligand 1 (PD-L1)**
- Ab, HLX20, **anti-PD-L1 hIgG1**
- **LP:** TMALIN, **novel linker-payload,** MediLink.

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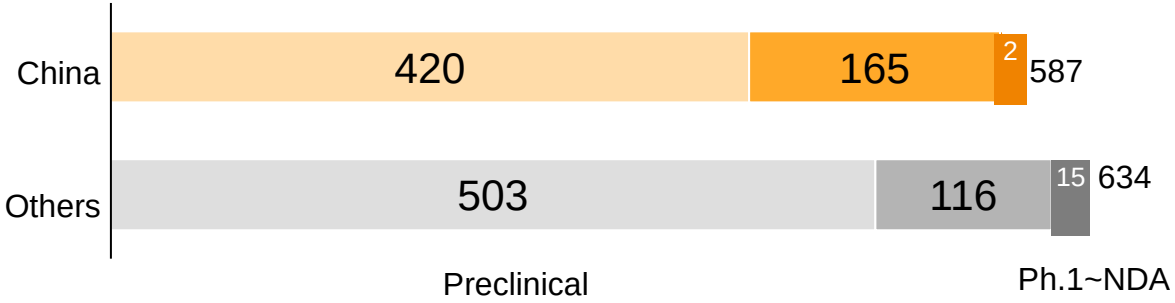
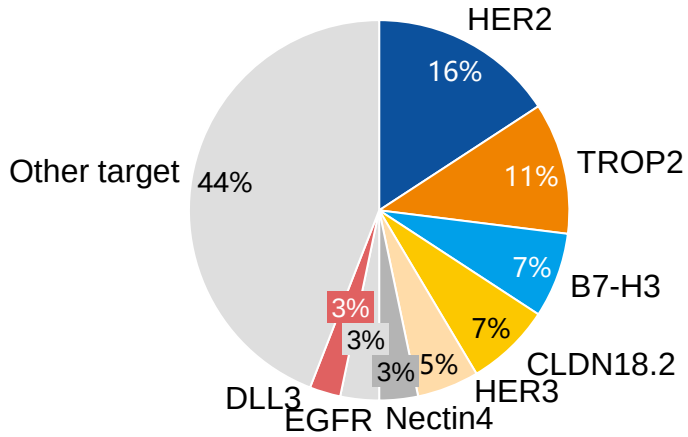
HLX43, a PD-L1 ADC: 1st in China, 2nd Globally

Almost half of global ADC molecules are developed by Chinese companies

ADC molecules launched or under development by originator's location



Targets of China-Originated ADCs

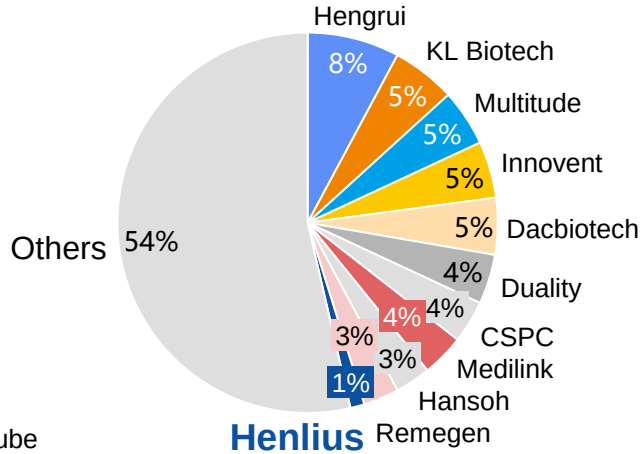


~60 companies in China have ADC products in development pipeline

Distribution of Pipelines:

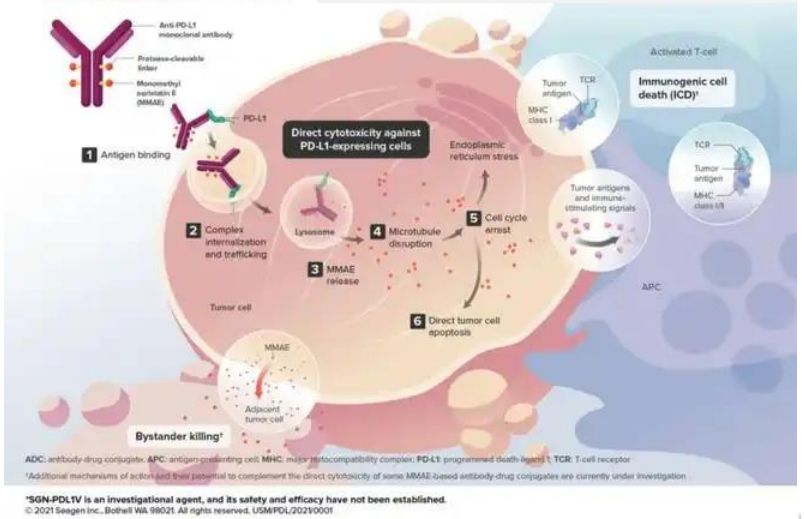
Ph.1~Launched ADCs

Owned by Chinese originators



Data Source: Globaldata Pharmcube

SGN-PDL1V — Globally 1st PD-L1 ADC



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HLX43: a Drug By Design with a Bold Vision

Pipeline-In-a-Pill

Drug By Desire:

Henlius' Vision: a new PiP

Drug By Design:

Blueprint Crafted Through Workmanship

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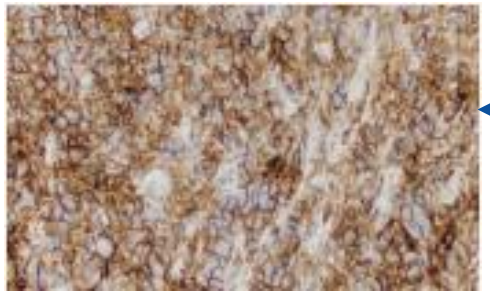
HLX43: A Pan Solid Tumor TAA

§ PD-L1 is a trans-membrane protein with internalization capability

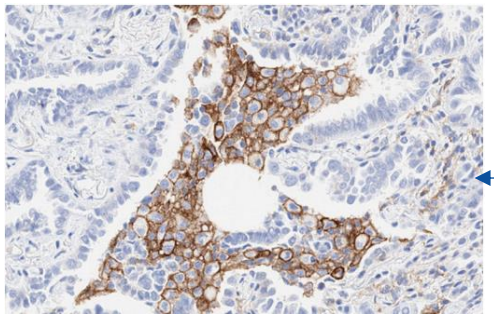
§ PD-L1 expression is observed in a broad spectrum of solid tumors

§ Normal tissue expression low/negligible, limited to primarily immune cells

Cancer Type	n	Prevalence (TPS >1%)
Total	15486	63.4% (TPS>50% High expression 29.5%)
Metastatic	1208	61.5% (High Expression 30.7%)
Lung	1695	70.2% (High Expression 36.5%)
Gastric	545	50.3% (High Expression 20%)
Esophageal	384	49.2% (High Expression 12%)
Colon	1142	31.5% (High Expression 5.3%)
Melanoma	555	56% (High Expression 14%)



NSCLC



PD-L1 positive staining in luminal macrophages not in tumor

O'Malley DP, et al. Mod Pathol. 2019;32(7):929-42.
*TPS: tumor proportion score

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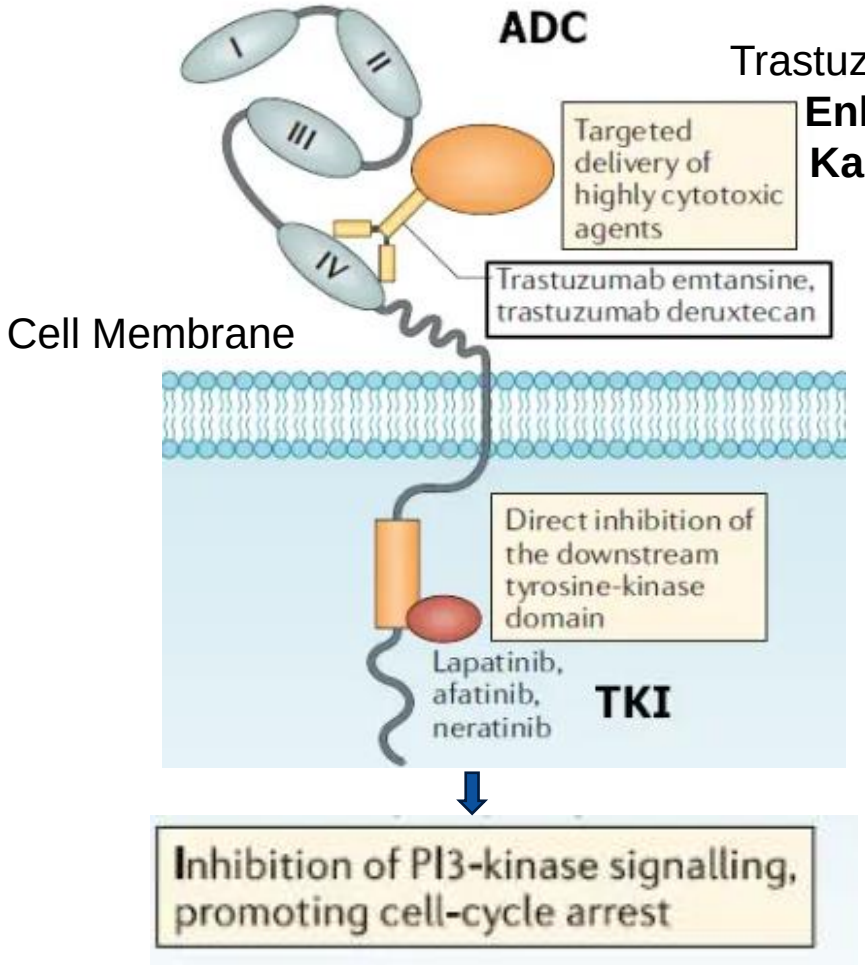
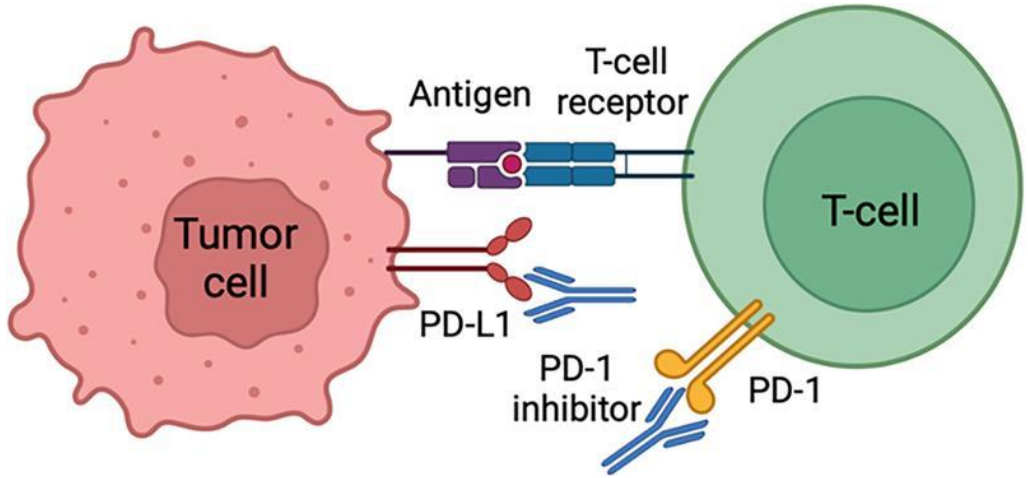
PD-L1: Functions Beyond a Tumor Target

HER2: regulates key cascades for cell proliferation



https://www.nature.com/articles/s41571-019-0268-3

- PD-1/PD-L1: the Immune Checkpoint
- PD-L1 Inhibitors: successful IO Therapies



https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1084873/full

- **Atezolizumab (Tecentriq):** UC, NSCLC, SCLC, TNBC, HCC
- **Durvalumab (Imfinzi):** UC, NSCLC, SCLC etc.
- **Avelumab (Bavencio):** MCC, UC, RCC, etc

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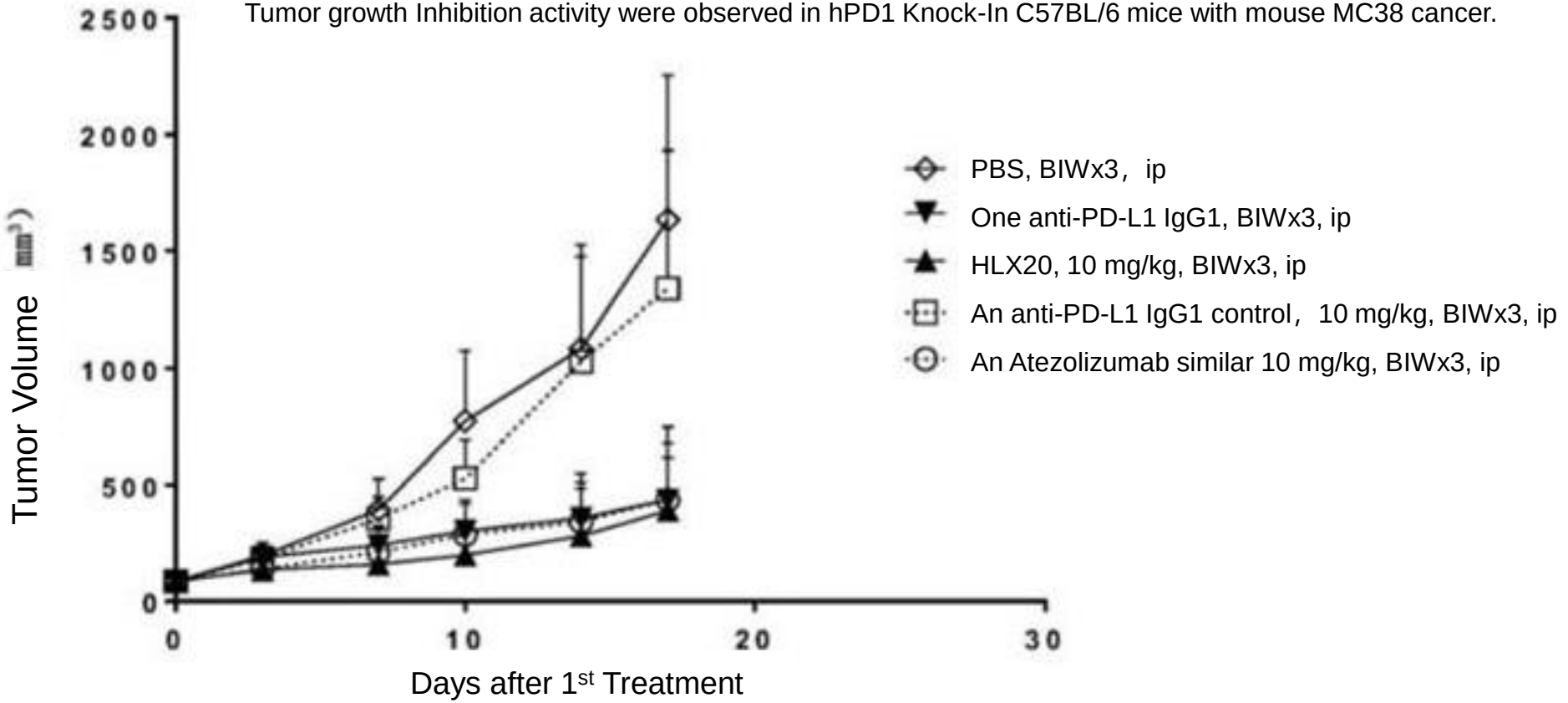
HLX20: the Backbone for HLX43 to fly

Tumor growth Inhibition activity were observed in hPD1 Knock-In C57BL/6 mice with mouse MC38 cancer.



HLX20 showed similar tumor grow Inhibition efficacy as that of an Atezolizumab similar

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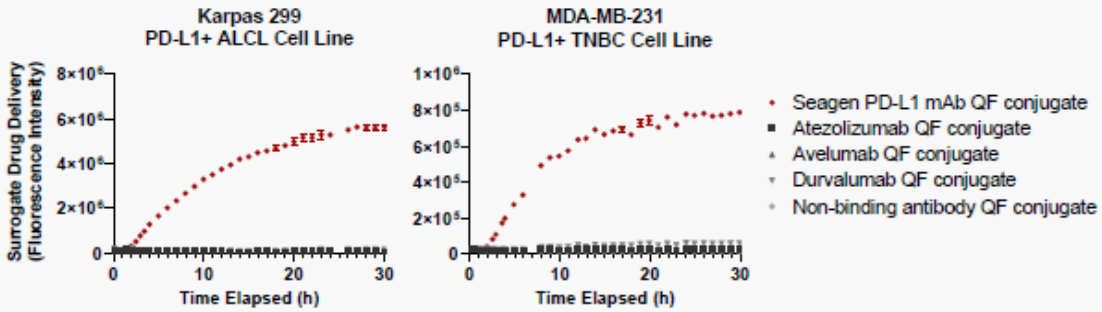
HLX20 Engaging TMALIN: Equip the ADC with Wings

PD-L1: a TAA with low internalization capacity

- PD-L1 offers limited intrinsic internalization capacity
- SGNPDL1V mAb was engineered for fast internalization, but its internalization rates varied largely among tumor cell lines, might impact the efficacy to different tumors.

SGN-PDL1V is engineered for rapid internalization into cells

- Seagen PD-L1 mAb achieves faster internalization and proteolytic cleavage compared to other approved PD-L1 mAbs.

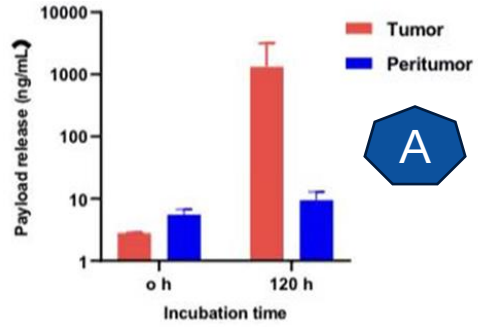


Quenched fluorophore (QF) conjugates incorporate a specialized fluorophore containing the same linker found in SGN-PDL1V, and only emit fluorescence upon cleavage of the linker. QF conjugates allow for quantitation of internalization and proteolytic cleavage, serving as a surrogate for drug delivery. PD-L1-expressing cell lines were incubated with indicated QF conjugates at 37°C and fluorescent signal was quantified using the Incucyte Live-Cell Analysis System.

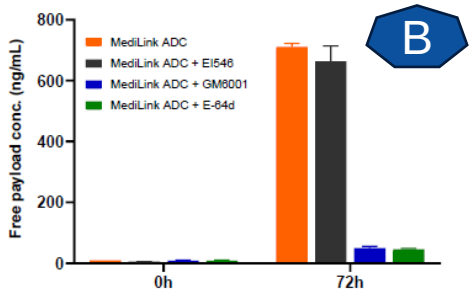
(SGNPDL1V SITC 2021 Poster)

Tumor Microenvironment Activable LINker-payload, TMALIN

ADC incubation in human breast cancer homogenate



ADC incubation with inhibitor in CDX tumor homogenate

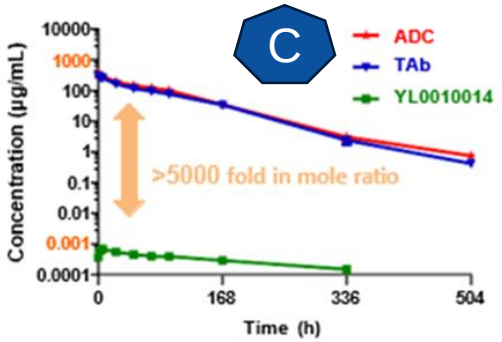


- GM6001: pan-MMP inhibitor
- E-64D: cysteine protease inhibitor
- E1546: Elastase inhibitor).

Dual Release of Payload: intra- and extracellular

A. Payload release specifically in tumor
B. Release of payload is mediated by multiple proteases, expressed in lysosome and TME
C. TMALIN offers high *in vivo* stability of ADC

PK profiles of ADC in monkey



Cancer Res 1 April 2023; 83 (7_Supplement): 596.

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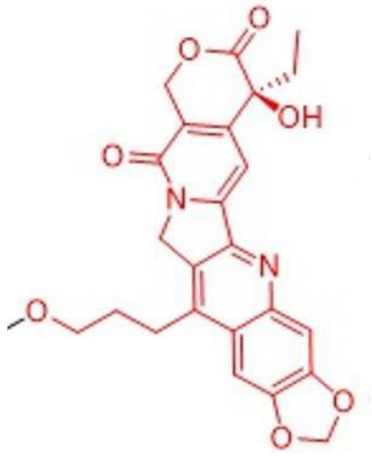
C24, TMALIN Payload, Arms ADC with Potent Warhead

- C24 is a Topoisomerase 1 inhibitor
- Potency is 4-10x of DXd in vitro
- t1/2 is shorter than DXd

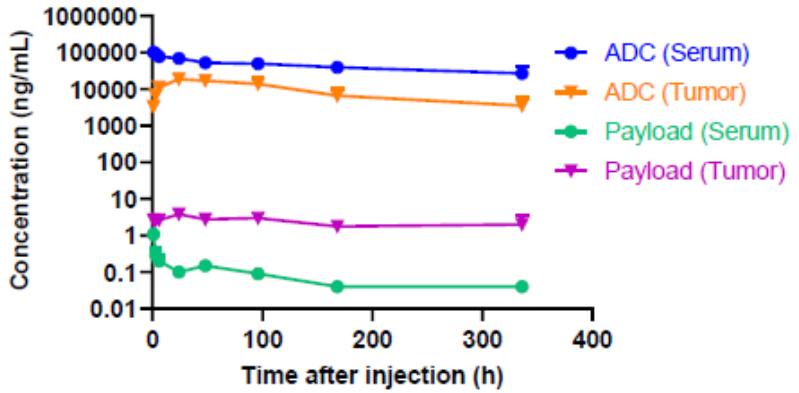
Cell Line	Cell Type	Payload IC_{50} nM	DXd IC_{50} nM
NUCG-4	Gastric Cancer	8.73	43.32
PC-9	Lung Cancer	2.06	16.69
HT29	Colorectal Cancer	20.32	210.5
NCI-H358	NSCLC	46.2	261.6
KYSE520	Esophageal Cancer	49.62	398.5
A431	Epidermal Carcinoma	5.71	25.08
A549	NSCLC	65.86	262.2



C24 or
YL0010014

- ADC concentration, plasma > tumor
- C24 concentration, Tumor >> plasma
- High bystander effects of C24

PK in mice receiving ADC of 10 mg/kg



- C24 has high potency with strong bystander effects and a short systemic half-life.
- This profile ensures enriched payload delivery to tumors upon LP release, while minimizing systemic exposure due to rapid clearance.
- As a payload in ADC,C24 demonstrates potent tumor-killing efficacy with low systermatic toxicity.

Cancer Res 1 April 2023; 83 (7_Supplement): 596.

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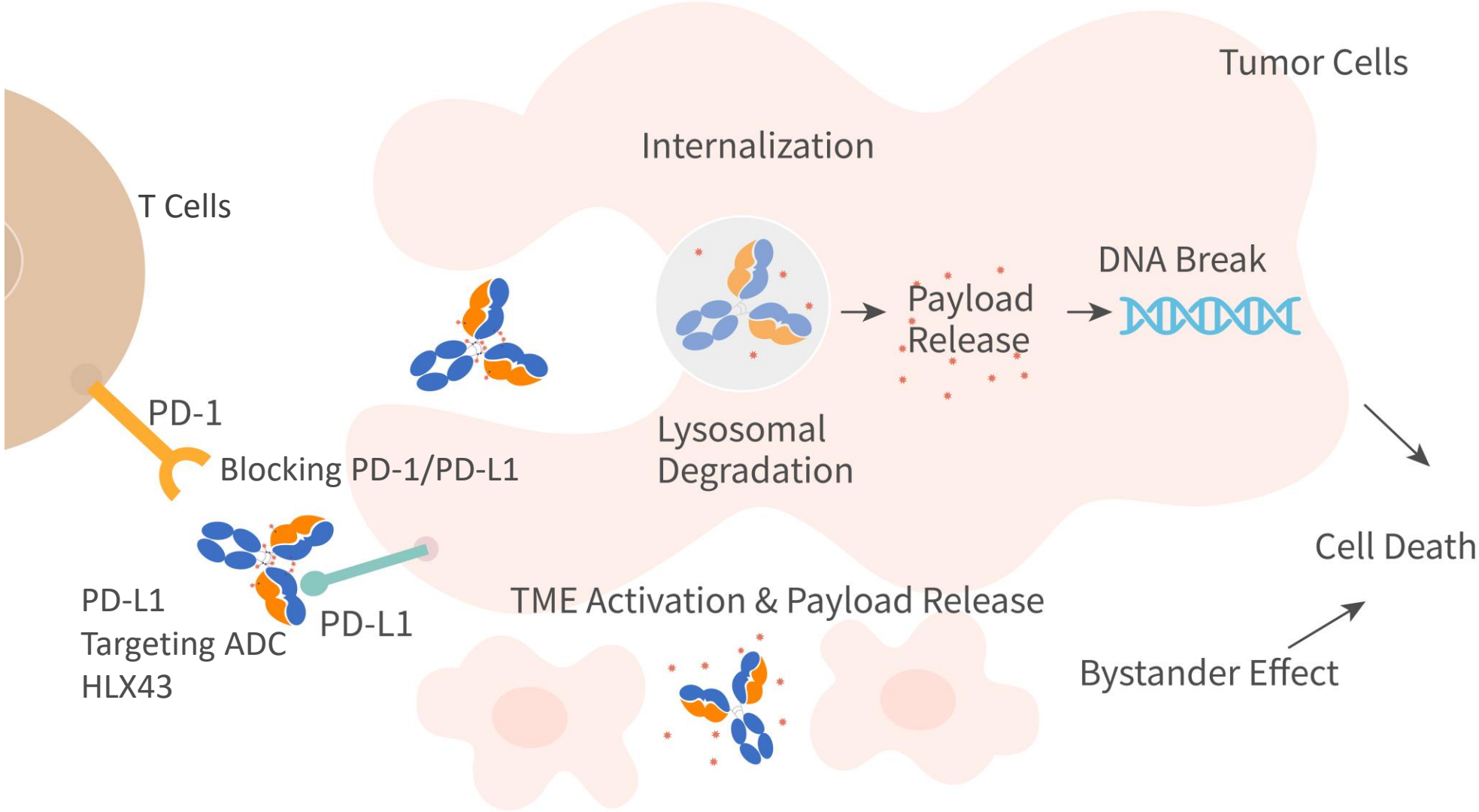
HLX43 MoA: Killing Tumor Cells with chemo and IO



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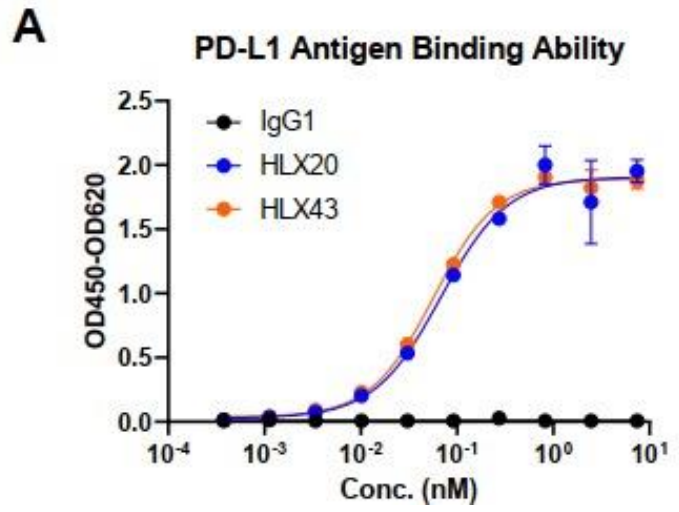
02

Preclinical Summary

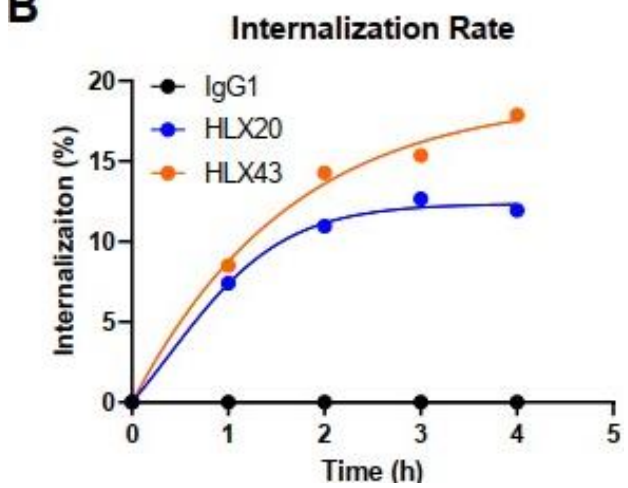
Preclinical Profiling

In vitro: Affinity, Internaltzation, Potency, Stability, By-Stander Effects

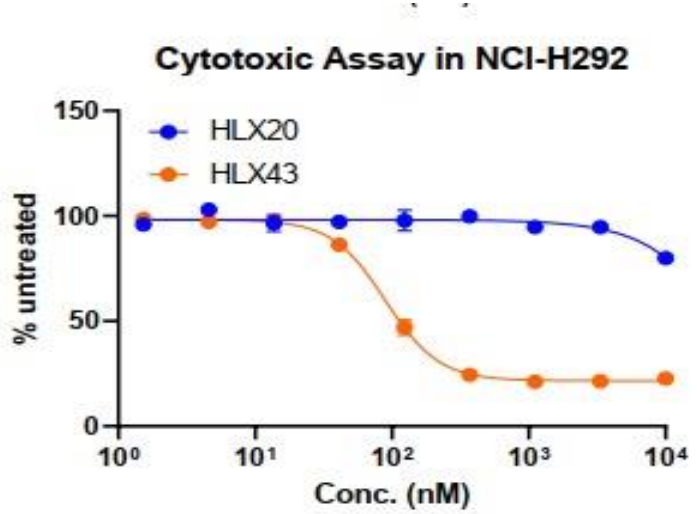
Binding Ability to PD-L1 Antigen



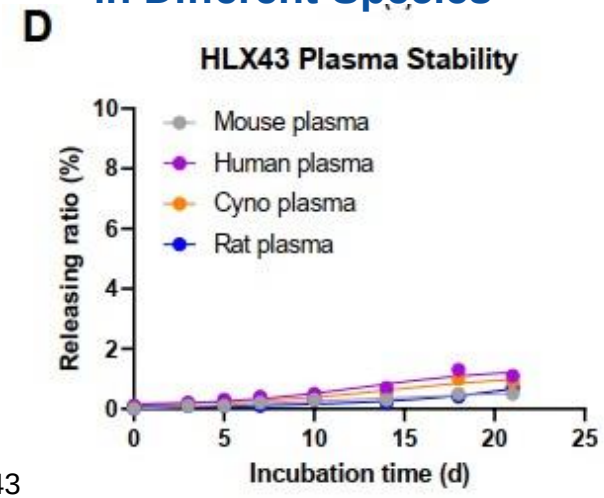
Internalization in NCI-H292 cells (human lung cancer cell line)



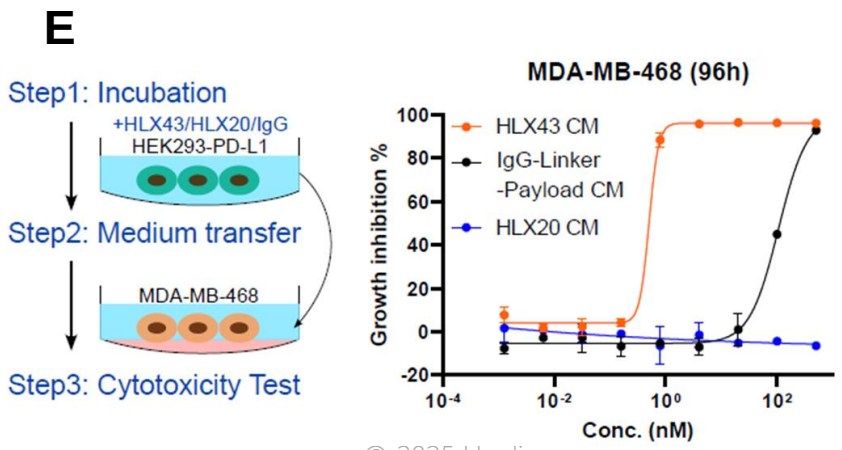
Cytotoxicity in NCI-H292 cells (human lung cancer cell line)



The Plasma Stability of HLX43 in Different Species



HLX43 exhibits bystander effects



An ADC with solid druggability

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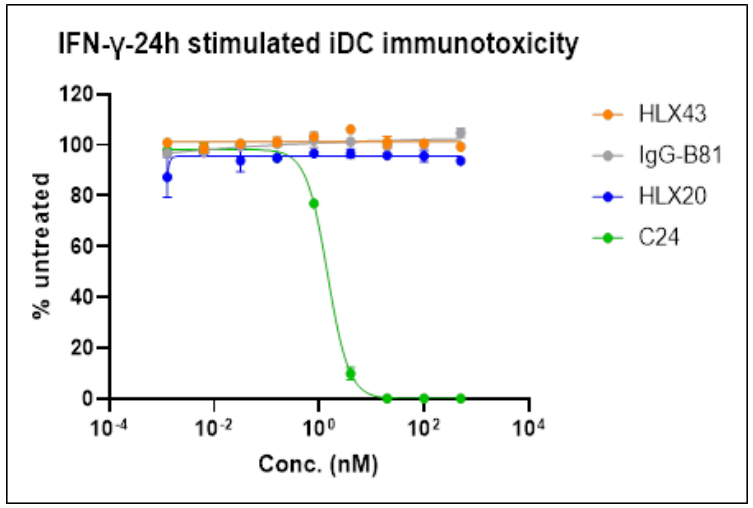
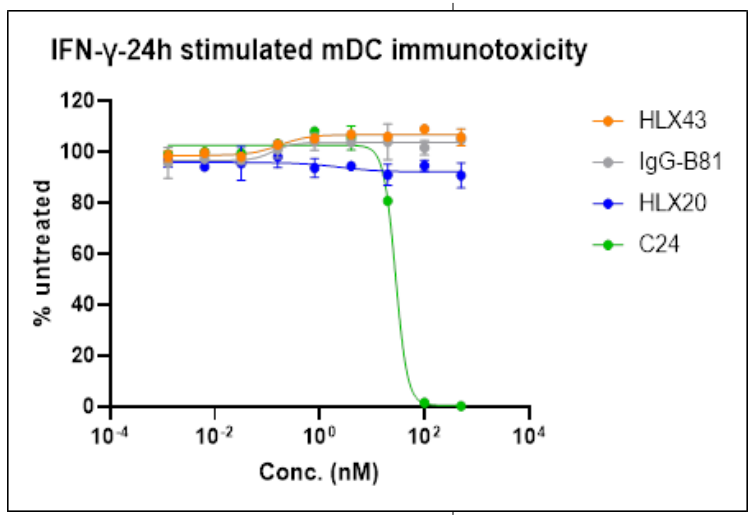
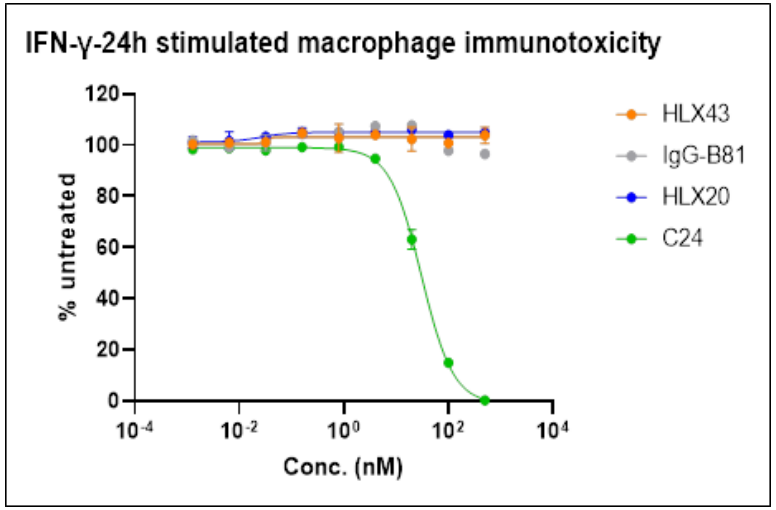
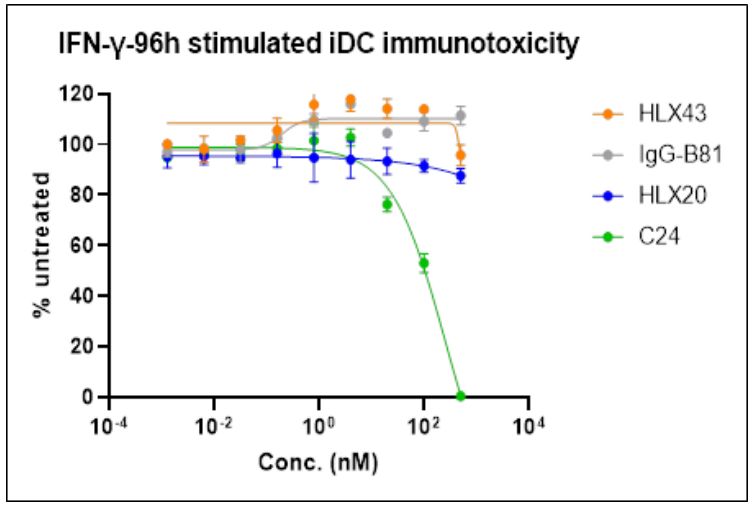
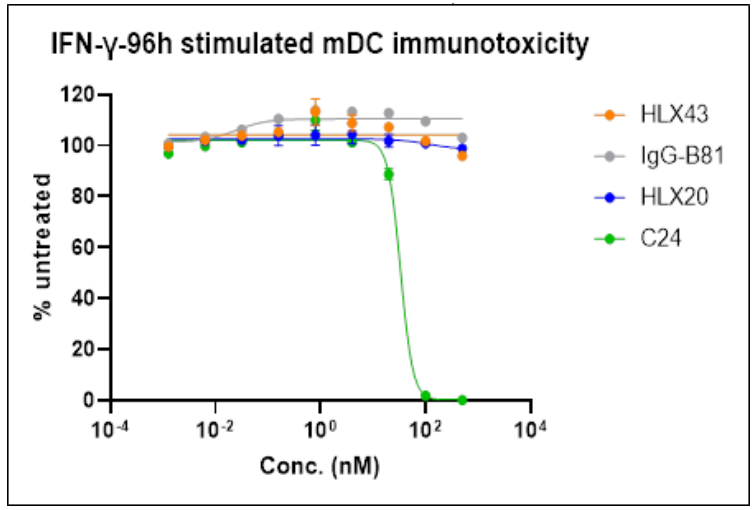
HLX43 showed no cytotoxicity to dendritic cells and macrophage by in vitro assay

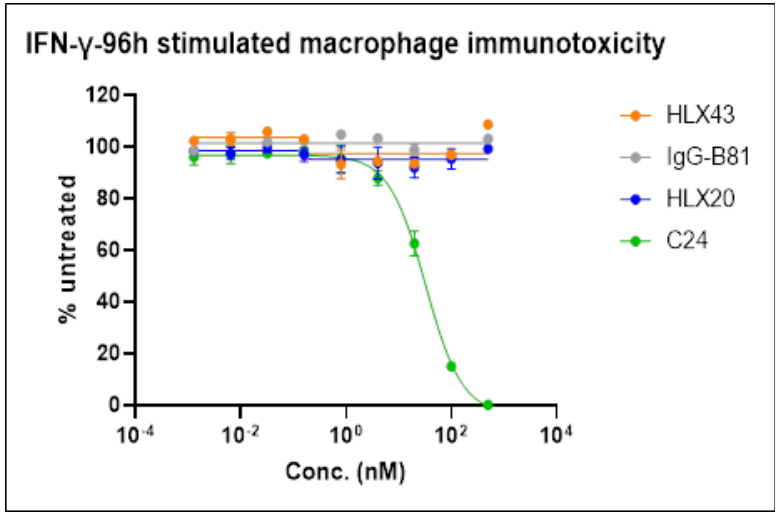












44 IFN-γ was used to stimulate PD-L1 expression

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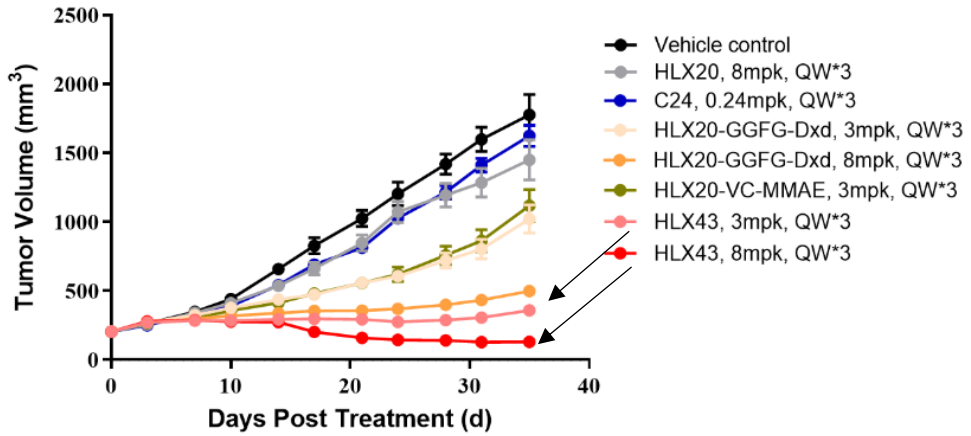
HLX43 Demonstrates Superior Efficacy In Mouse Models

MDA-MB-231 CDX model

(TNBC PD-L1 2+)

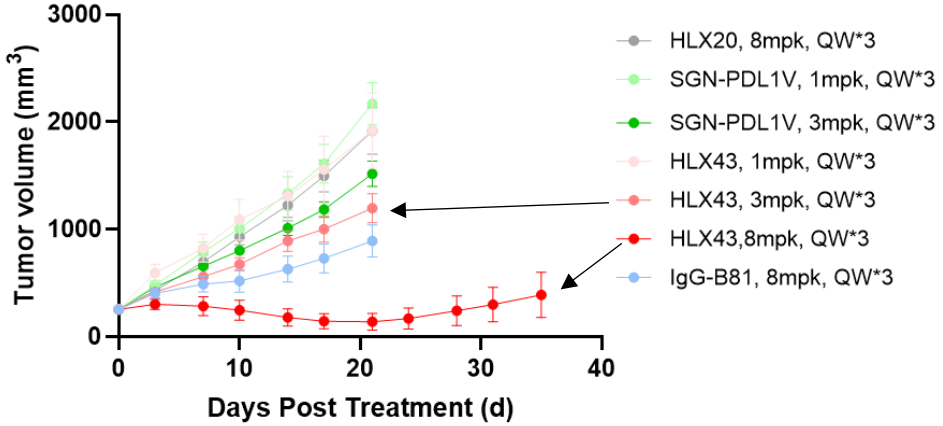


Notes: (i) C24, Payload; (ii) HLX20, Henlius in-house anti-PDL1 mAb, the antibody of HLX43; (iii) HLX20-GGFG-Dxd: Anti-PDL1-GGFG-Dxd.

- HLX43 showed more effective tumor inhibition than HLX20-GGFG-DXd in 8 mpk and 3 mpk dose, and HLX20-VC-MMAE in 3 mpk dose in MDA-MB-231 CDX model.
- HLX43 treatment at 8 mg/kg QW×3 resulted in tumor regression.

LU6437 PDX model

(sqNSCLC PD-L1 2+, HLX10 resistant)



Notes: (i) HLX20, Henlius in-house anti-PDL1 mAb, the antibody of HLX43; (ii) SGN-PDL1V: Seagen's Anti-PDL1 ADC; (iii) (iv) IgG-B81: Isotype-ADC.

- HLX43 showed more effective tumor inhibition in NSCLC PDX model than SGN-PDL1V in 3 mpk dose;
- HLX43 8 mpk showed significant tumor inhibition in the NSCLC PDX model.

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HLX43 Shows Tumor Growth Inhibition Effects Across a Broad Range of Tumor Types in Mouse Models

NO	Model	PD-L1 Expression	Type of Cancer	Any Resistant
1	**MD-MAB-231 CDX**	PD-L1 IHC 2+	TNBC	NA
2	**sqNSCLC PDX (LU6437)**	PD-L1 IHC 2+	sqNSCLC	HLX10 resistant (preclinically tested)
3	**CRC PDX+PBMC (LD1-2013-362125)**	PD-L1 IHC 3+	CRC MSI-H	Pembrolizumab resistant
4	**CRC PDX**	PD-L1 IHC 3+ TPS 100%	CRC MSI-H	PD-1/EGFR mAb, and chemo resistant
5	**CRC PDX**	PD-L1 IHC - TPS 20%	CRC MSS & $KRAS^{m}$	Chemo resistant
6	**GC PDX**	PD-L1 IHC 2+ TPS 70%	GC KRASm	Treatment naïve
7	**GC PDX**	PD-L1 IHC - TPS 20%	GC	Chemo & PD-1 mAb resistant
8	**HNSCC PDX**	PD-L1 IHC 2+ TPS 87.5%	HNSCC	Chemo & PD-1 mAb resistant
9	**Cervical Cancer PDX**	PD-L1 IHC1+ TPS 30%	Cervical Cancer	PD-1 mAb & Anlotinib resistant
10	**ESCC PDX**	PD-L1 IHC 2+ TPS 75%	ESCC	Treatment naïve
11	**HCC PDX (LD1-0011-411084)**	PD-L1 IHC -	HCC	Sintilimab resistant
12	**HCC PDX (LD1-0011-200617)**	PD-L1 IHC 1+	HCC	NA (treatment naïve)

HLX43 has a favorable PK profile in monkeys; HNSTD is 20 mg/kg Q3W in GLP-Tox Study in the monkeys

Study	Key Information of the Study	Results of the Study
PK	**Single-dose Study in Monkeys** Dose: i.v.; 3, 10, 20 mg/kg	• C_{max} and AUC_{0-t} increased with dose increase; $t_{1/2}$ = 50.8h to 82.8h. • HLX43 and total antibody exhibited similar pharmacokinetic profiles; Serum level of payload was quite low, molar ratio < $1/10^3$, mass ratio < $2.4/10^6$ (calculated by C_{max}: C24/ADC).
Tox	**Repeat-dose in Mice (GLP)** Dose: i.v.; 0, 10, 30, 60 mg/kg; QWx5 Recovery period: 8 weeks	• No death • Bone marrow, spleen and thymus were identified as target organs; recovery of adverse effects were observed. • **STD10 was 60 mg/kg.**
	Repeat-dose In Monkey (GLP) Dose: i.v.; 0, 3, 10, 20 mg/kg, Q3Wx3 3M/3F for 3 mg/kg, 5M/5F for other groups Recovery period: 8 weeks	• No Death • Bone marrow, spleen, thymus, lymph nodes were identified as target organs; epididymis and seminal vesicles could not be excluded as target organ. • **HNSTD was 20 mg/kg.**

- High stability of HLX43 in NHP PK suggested low off-target toxicity and supported dose interval of three weeks.
- Favorable safety profiles were observed in monkey GLP Tox with an HNSTD higher than therapeutic effective dose range.
- Therapeutic window suggested by combining the tolerated dose level found in monkey and efficacious dose in mouse models

03

Clinical Progress

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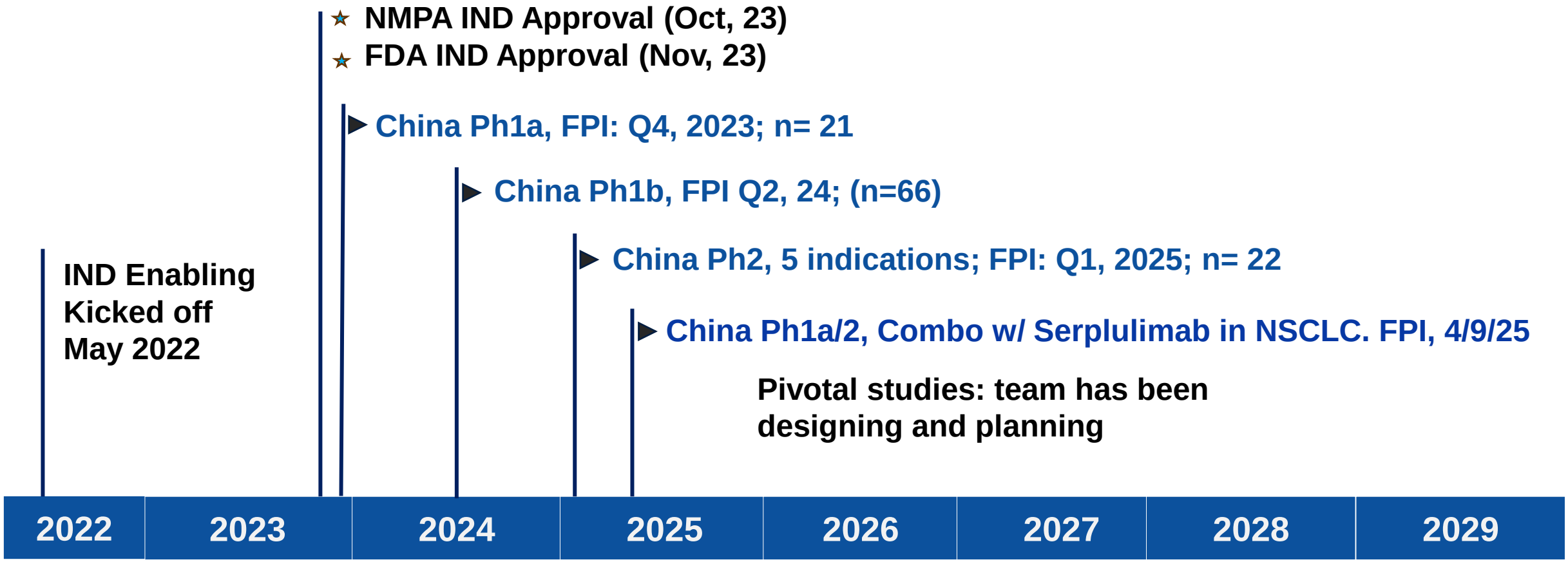
HLX43: Rapid and Steady Development Progress



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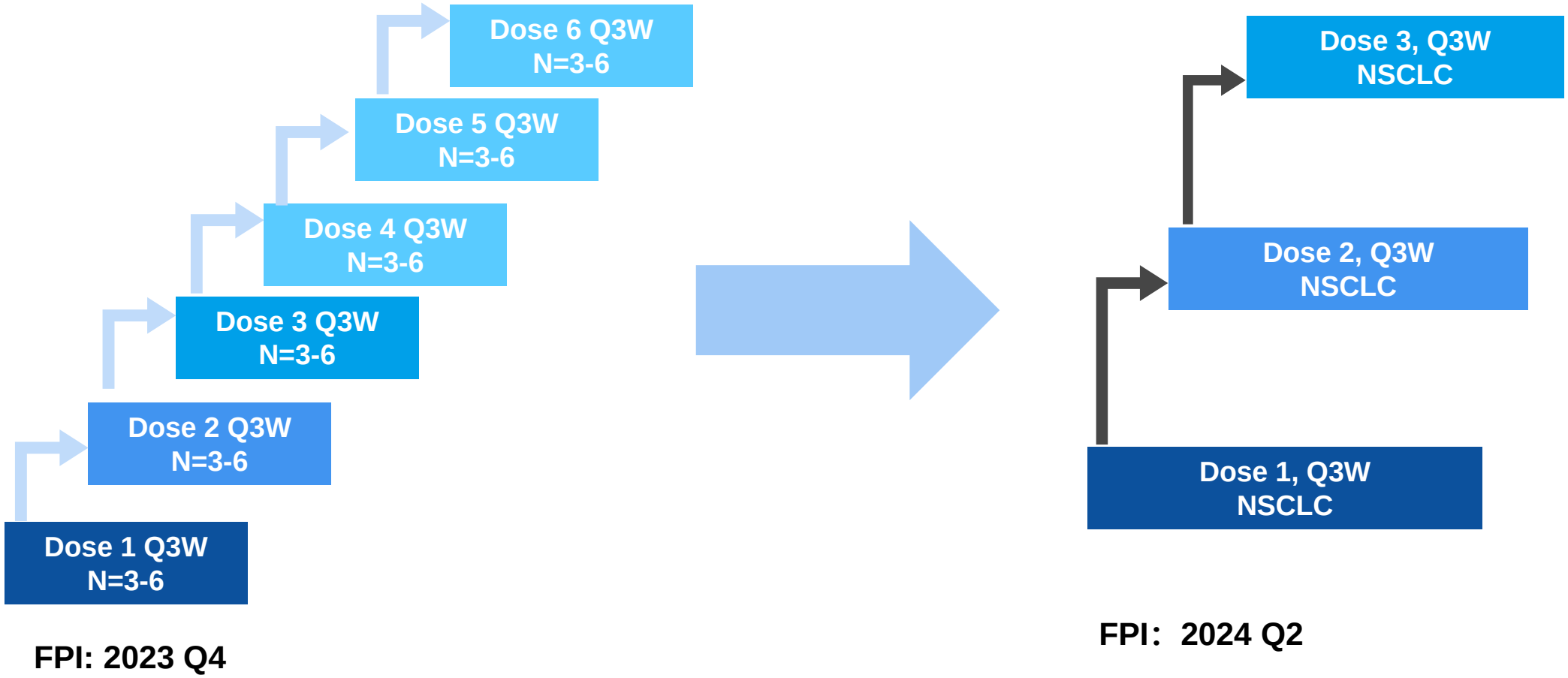
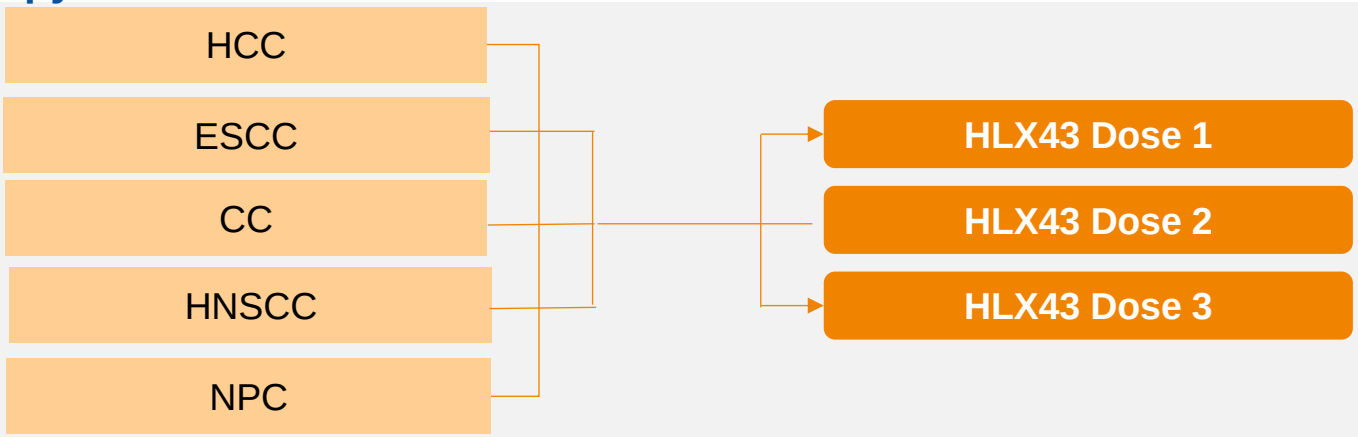
HLX43 Ph1a in solid tumors, Ph1b in NSCLC



HLX43 Ongoing POC Study Design

Ph2 monotherapy



HLX43+Serplulimab(PD-1)

Phase I in Solid Tumor Patients

- **HLX43 Dose 3 Q3w +Serplulimab 300mg Q3w N=3-6**
- **HLX43 Dose 2 Q3w + Serplulimab 300mg Q3w N=3-6**
- **HLX43 Dose 1 Q3w + Serplulimab 300mg Q3w N=3-6**

Phase II in NSCLC patients

- **HLX43 Dose 3 + Serplulimab 300mg Q3w**
- **HLX43 Dose 2 + Serplulimab 300mg Q3w**
- **HLX43 Dose 1 + Serplulimab 300mg Q3w**

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HLX43: 15 Months After Entering Clinical Ph1

- A new PiP is emerging from conceptual promise into tangible hope

- Clinical development is proceeding with deliberate strategy and steady progress

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Future Outlook for HLX43

Team Henlius holds high confidence and ambitious hope for HLX43

Our ultimate mission for HLX43 is to transform this innovative therapy into real hope for patients in need

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Clinical Development of HLX22

Dr. Shen Lin

Beijing Cancer Hospital

2025.04.15

Collaborate to Create

2025 Henlius Global R&D Day

CONTENTS

01 Background

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Introduction

- Gastric/gastroesophageal junction (G/GEJ) cancer represents a global healthcare challenge. With nearly one million new cases estimated in 2022, it ranked fifth among all cancers.[1]
- Around 12–23% of patients with gastric cancer have HER2-positive disease, whose prognosis used to be worse than patients with HER2-negative disease.[2, 3]

HLX22, a novel anti-HER2 monoclonal antibody, binding to a different epitope from trastuzumab.

Here we introduce HLX22 in combination with trastuzumab and XELOX as 1L treatment for HER2-positive locally advanced or metastatic gastric/gastroesophageal junction cancer.

1. Bray F. et al. CA Cancer J Clin 2024;74(3):229-263. 2. Ajani JA. et al. J Natl Compr Canc Netw 2022;20(2):167-92. 3. Gravalos C. et al. Ann Oncol 2008;19(9):1523-9.

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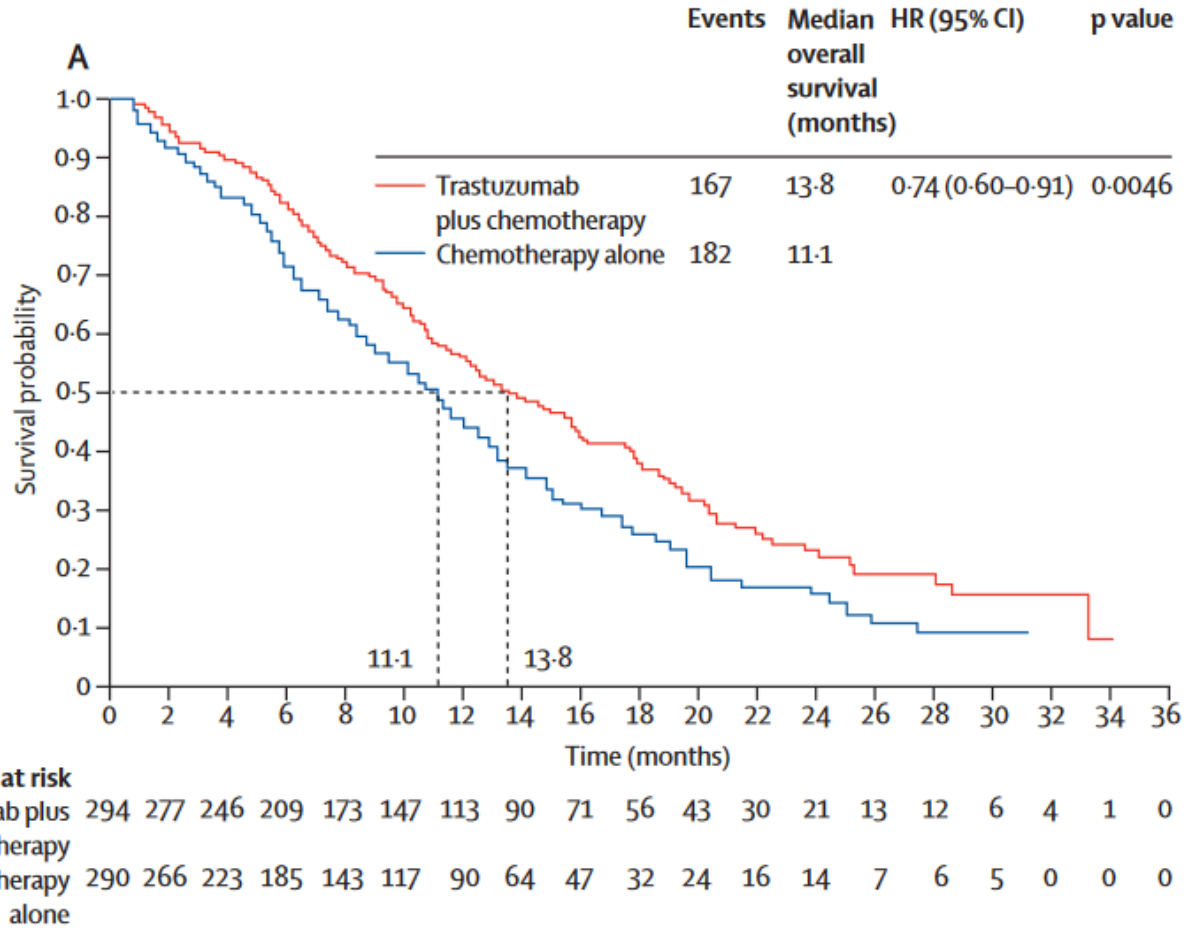
TOGA Study

Previous Results of HER2 Antibody + Chemotherapy



TOGA Study

- **Intervention**: trastuzumab + CF/CX vs CF/CX
- **Results**: improved OS

Bang Y-J, et al. Lancet 2010;376(9742):687-97.

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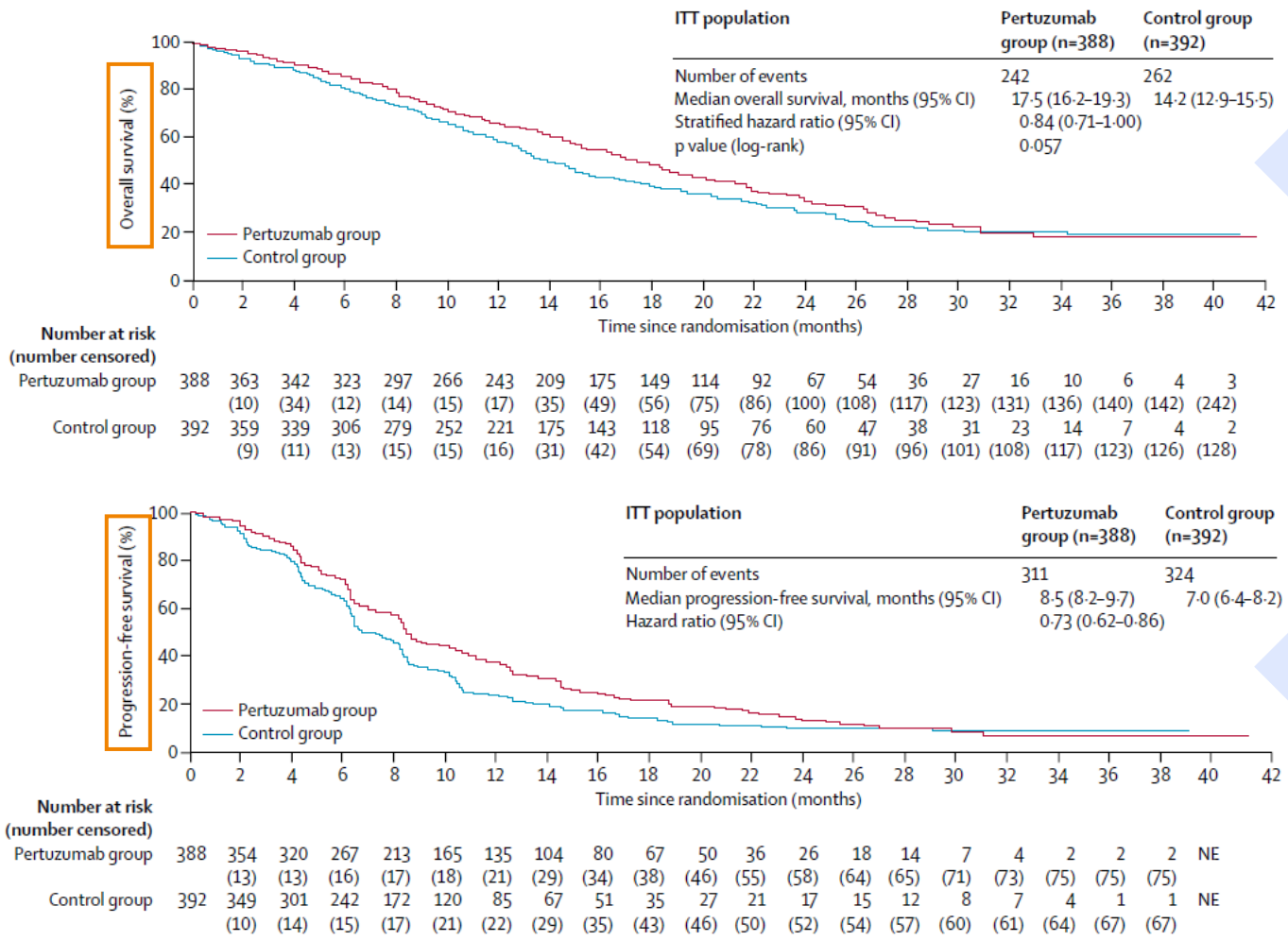
JACOB Study

Previous Results on Dual HER2 Inhibition



JACOB Study

- **Intervention**: trastuzumab + pertuzumab + chemotherapy vs trastuzumab + chemotherapy
- **Results**: failed OS, limited improvement on PFS

Tabernero J, et al. Lancet Oncol 2018;19(10):1372-1384.

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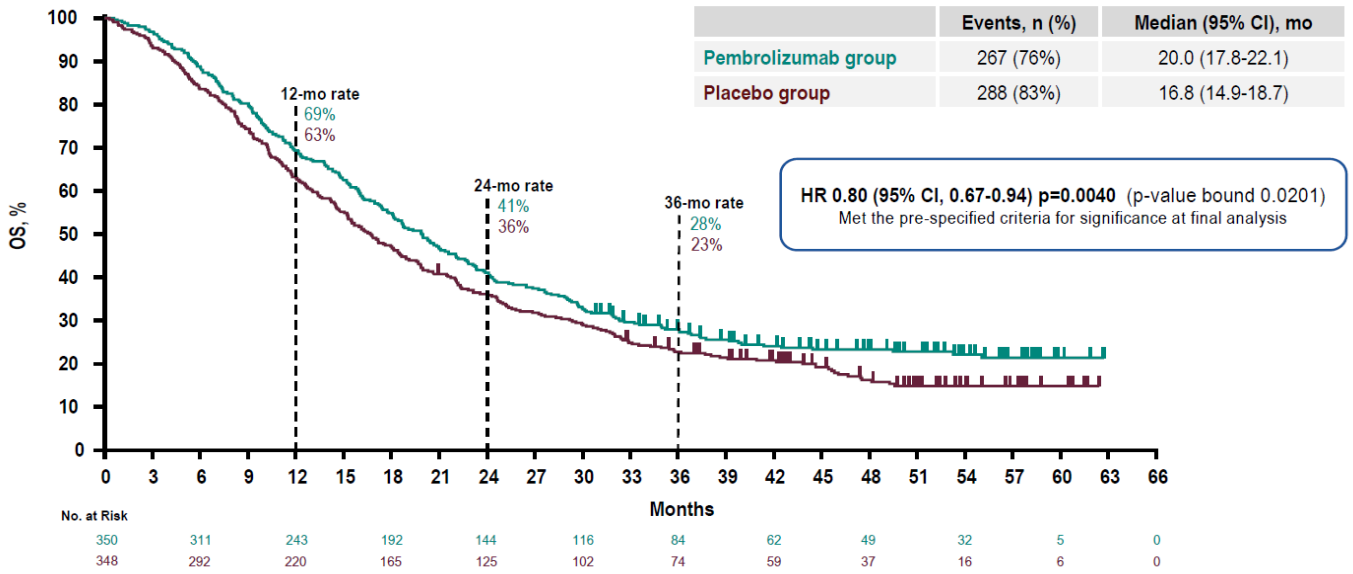
KEYNOTE-811 Study

Previous Results of HER2 Antibody + PD-1 Antibody

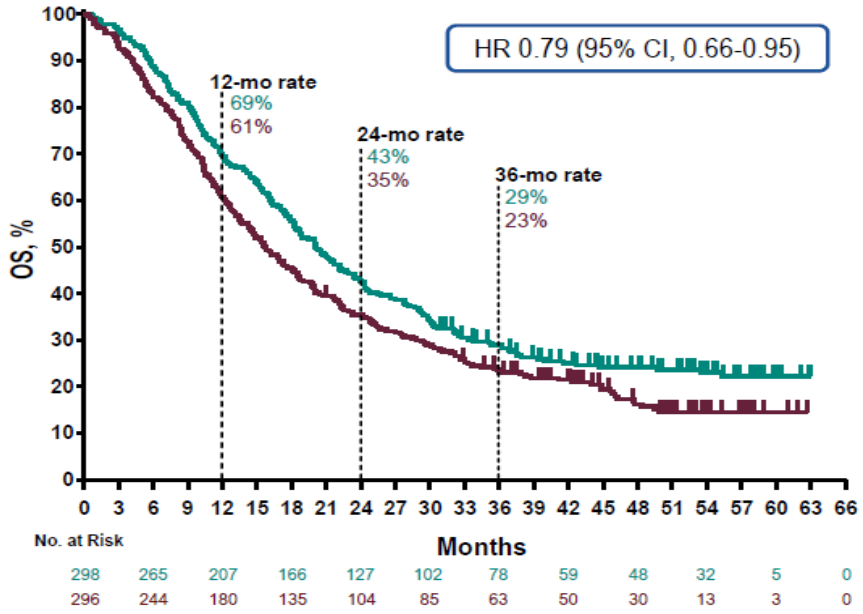
ITT Population



	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	267 (76%)	20.0 (17.8-22.1)
Placebo group	288 (83%)	16.8 (14.9-18.7)

HR 0.80 (95% CI, 0.67-0.94) p=0.0040 (p-value bound 0.0201)
Met the pre-specified criteria for significance at final analysis

CPS ≥ 1 Subgroup



KEYNOTE-811 Study

- **Intervention**: pembrolizumab + trastuzumab + CF/XELOX vs trastuzumab + CF/XELOX
- **Results**: slightly improved OS, only approved for PD-L1 CPS ≥ 1 HER2+ G/GEJ cancer

Annals of Oncology (2024) 35 (suppl_2): S878-S912.

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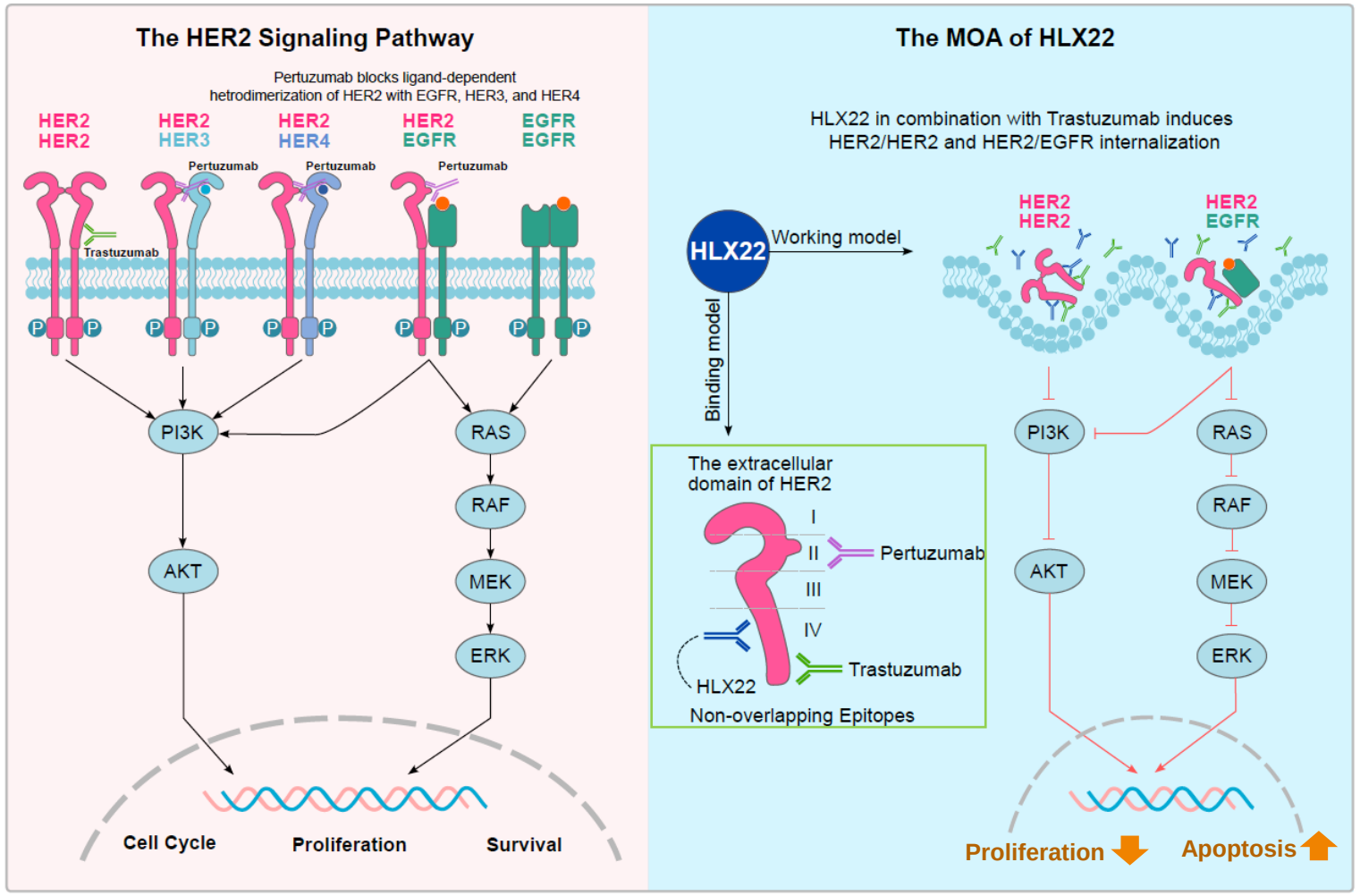
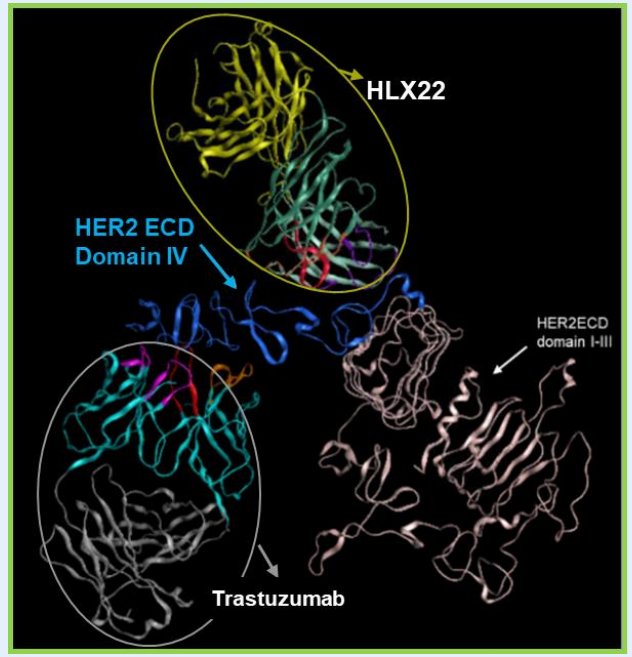
Novel MOA of HLX22





- HLX22 + trastuzumab increased internalization of HER2/HER2 homodimers and HER2/EGFR heterodimers, ultimately led to the reduction of HER2 and EGFR signaling.

MOA, mechanism of action

J Transl Med. 2024 Jul 9;22(1):641.

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02 Clinical Development of HLX22

HLX22-GC201 Study Results

Study Design

An ongoing, randomized, double-blinded, phase 2 study

Key inclusion criteria:

- Age 18–80 years; ECOG PS 0 or 1;
- treatment naïve; unresectable, locally advanced or metastatic HER2+ G/GEJ adenocarcinoma
- HER2-positive (i.e., HER2 3+ by IHC or HER2 2+ by IHC and positive by FISH).

R 1:1

HLX22 group Q3W
- HLX22[a], IV, 15 mg/kg
- Trastuzumab[a,b], IV, 6 mg/kg
- XELOX[c]

Placebo group Q3W
- Placebo[a], IV
- Trastuzumab[a,b], IV, 6 mg/kg
- XELOX[c]

- **Primary endpoints: PFS and ORR (IRRC, RECIST v1.1)**
- **Secondary endpoints:** PFS (INV), ORR (INV), OS, DOR, quality of life, safety, etc.

[a] Up to 2 years; [b] Initial loading dose of 8 mg/kg; [c] IV oxaliplatin (up to 8 cycles) + oral capecitabine (up to 2 years).

DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; IRRC, independent radiological review committee; IV, intravenous; INV, investigator; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W: every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

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Patient Disposition and Baseline Characteristics

- Between Nov. 29, 2021 and Sep. 18, 2023, 62 patients were randomized to the HLX22 and placebo groups (n = 31 each).
- As of data cutoff on June 30, 2024, the median follow-up was **24.1** months.

	HLX22 group (n = 31)	Placebo group (n = 31)
Median age (range), years	60.0 (26–78)	64.0 (28–74)
Male, n (%)	26 (83.9)	25 (80.6)
Median body mass index, kg/m^2 (range)	23.0 (16.8–29.4)	21.5 (17.5–27.5)
ECOG PS 1, n (%)	20 (64.5)	19 (61.3)
Median LVEF, % (range)	64.0 (57–74)	64.0 (60–71)
≥ 55%, n (%)	31 (100)	31 (100)
Primary tumor site, n (%)		
Gastric	22 (71.0)	23 (74.2)
GEJ	9 (29.0)	7 (22.6)
HER2 status[a], n (%)		
IHC 2+ and FISH-positive	3 (9.7)	2 (6.5)
IHC 3+	28 (90.3)	29 (93.5)

	HLX22 group (n = 31)	Placebo group (n = 31)
Histological subtype, n (%)		
Diffuse	1 (3.2)	2 (6.5)
Intestinal	6 (19.4)	4 (12.9)
Mixed or others	21 (67.7)	23 (74.2)
Stage IV disease, n (%)	30 (96.8)	30 (96.8)
Liver metastasis, n (%)	19 (61.3)	18 (58.1)
Lung metastasis, n (%)	5 (16.1)	6 (19.4)
Peritoneal metastasis, n (%)	4 (12.9)	5 (16.1)
Number of metastatic sites, n (%)		
1–2	24 (77.4)	23 (74.2)
> 2	6 (19.4)	7 (22.6)
Previous gastrectomy, n (%)	7 (22.6)	6 (19.4)
Previous chemotherapy, n (%)	4 (12.9)	2 (6.5)

[a]HER2 FISH testing was not required for patients with HER2 IHC 3+ tumors.

ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; LVEF, left ventricular ejection fraction.

Confirmed Tumor Response by IRRC

June 30, 2024 (data cutoff), median follow-up 24.1 months

	HLX22 group (n = 31)	Placebo group (n = 31)
Best overall response, n (%)		
Complete response	1 (3.2)	0
Partial response	26 (83.9)	25 (80.6)
Stable disease	3 (9.7)	3 (9.7)
Progressive disease	0	2 (6.5)
Not evaluable	1 (3.2)	1 (3.2)
ORR, % (95% CI)	87.1 (70.2–96.4)	80.6 (62.5–92.5)
Odds ratio (95% CI)	1.6 (0.4–6.5)	
ORR at Week 48 (95% CI)	38.7 (21.8–57.8)	9.7 (2.0–25.8)
Median DOR, month (95% CI)	NR (22.1–NE)	9.7 (4.6–20.0)
Hazard ratio (95% CI)	**0.1** (0.04–0.41)	
12-month DOR rate (95% CI)	78.5 (51.8–91.4)	26.3 (5.1–55.0)

CI, confidence interval; DOR, duration of response; IRRC, independent radiological review committee; NA, not applicable; NE, not evaluable; NR, not reached; ORR, objective response rate.

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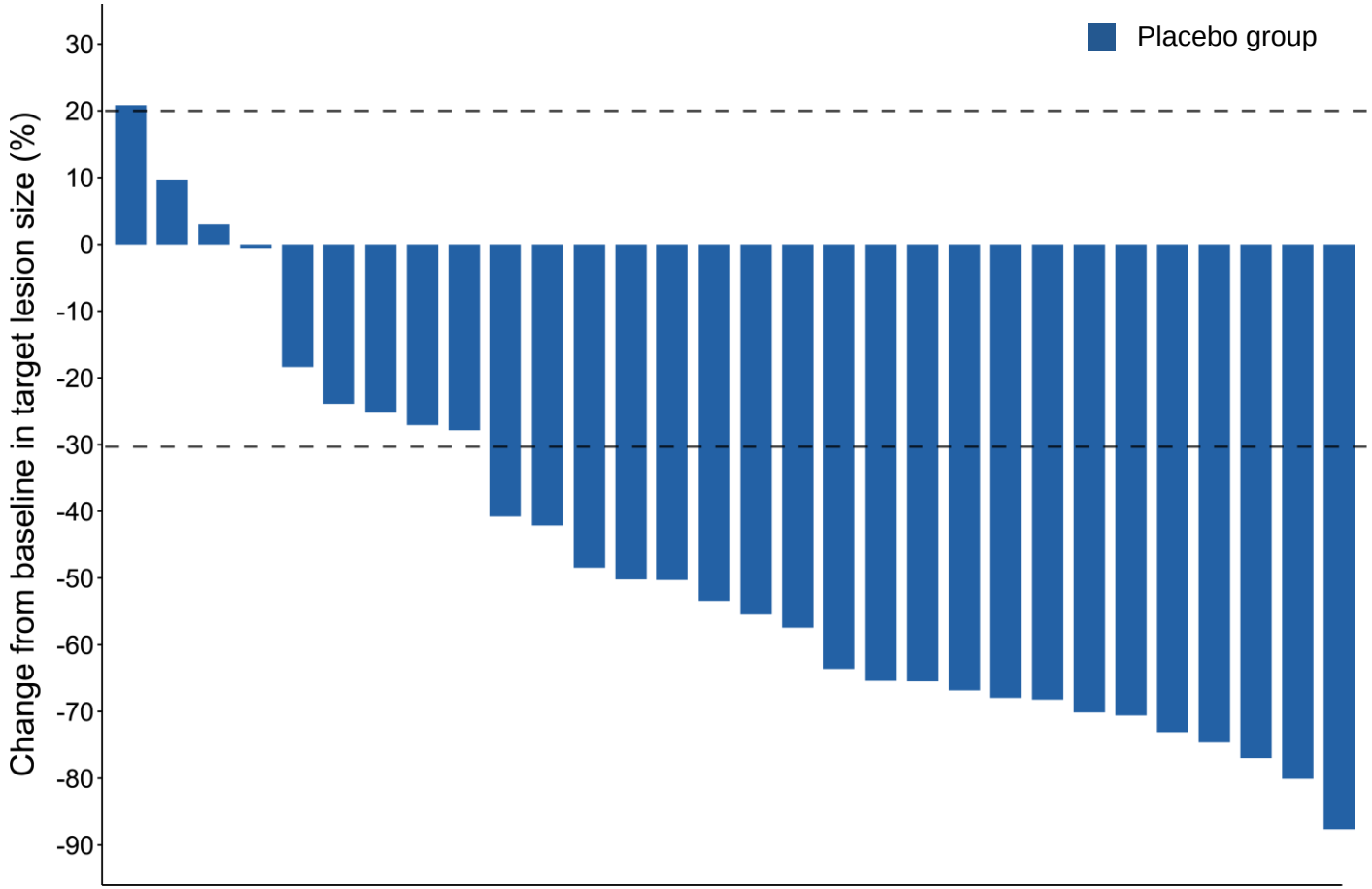
Waterfall Plot According to IRRC Assessments

June 30, 2024 (data cutoff), median follow-up 24.1 months



Excluding two patients with no post-baseline tumor assessment.
IRRC, independent radiological review committee.

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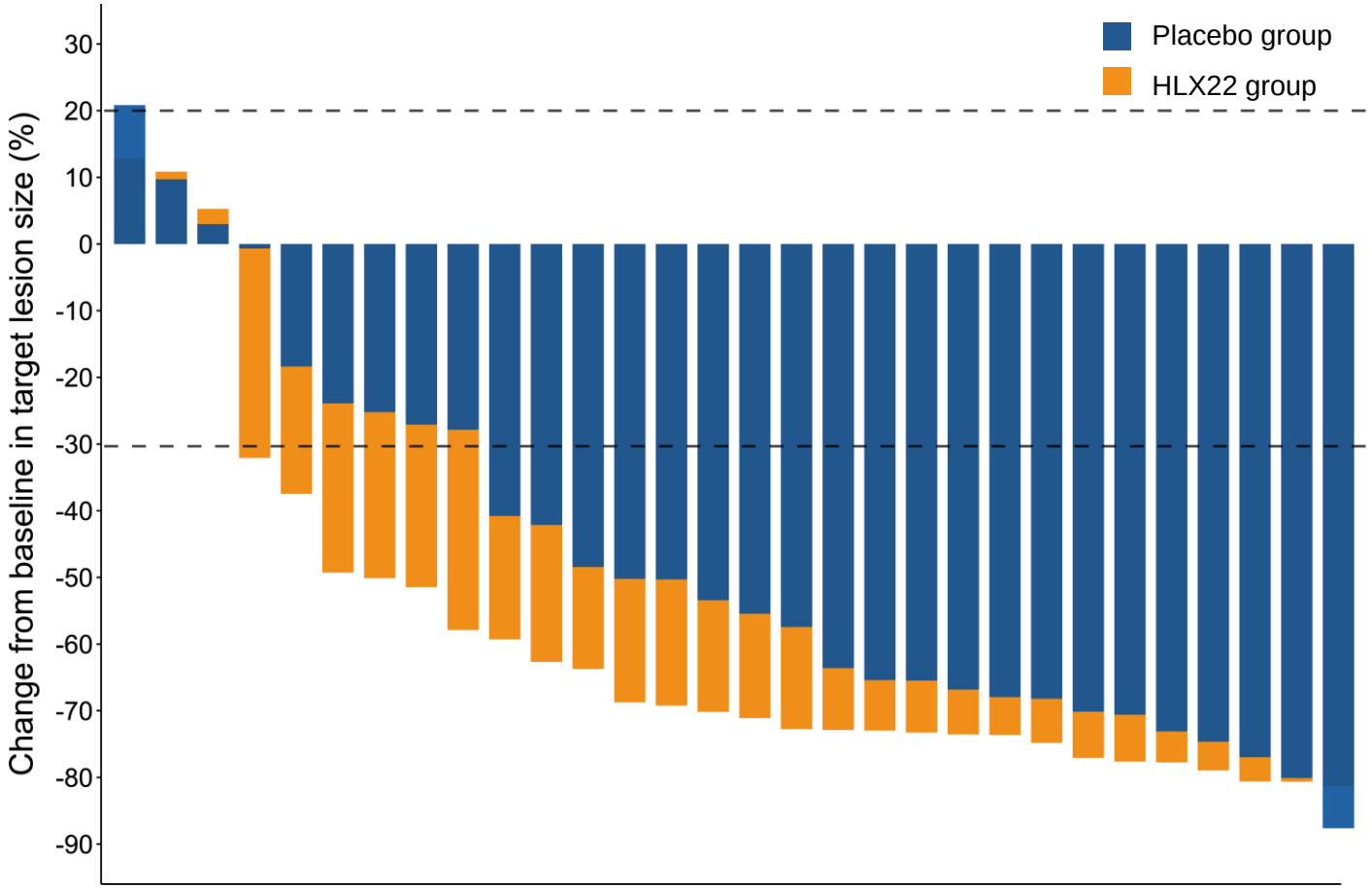
Waterfall Plot According to IRRC Assessments

June 30, 2024 (data cutoff), median follow-up 24.1 months



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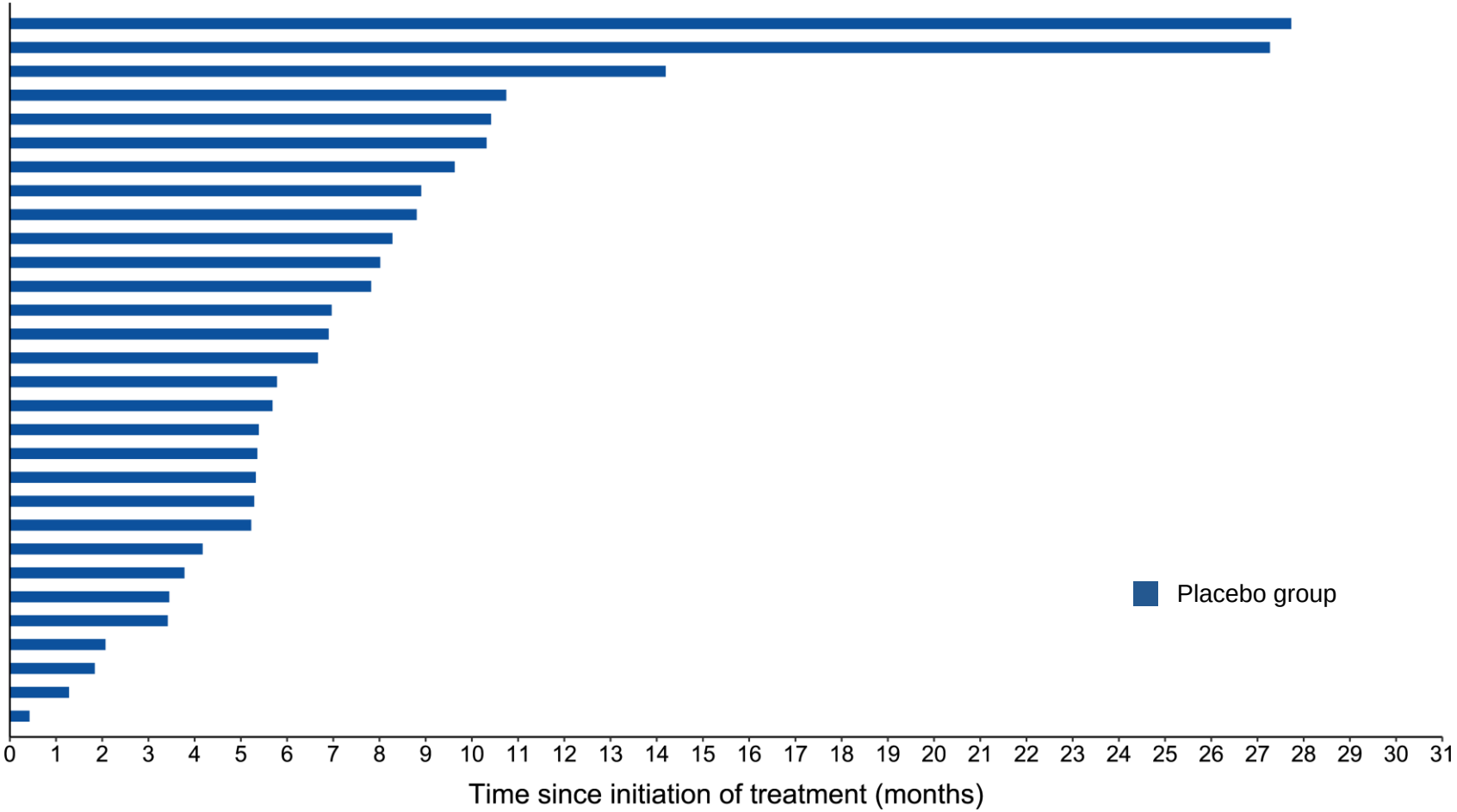
Swimmer Plot According to IRRC Assessments

June 30, 2024 (data cutoff), median follow-up 24.1 months



Excluding two patients with no post-baseline tumor assessment.
IRRC, independent radiological review committee.

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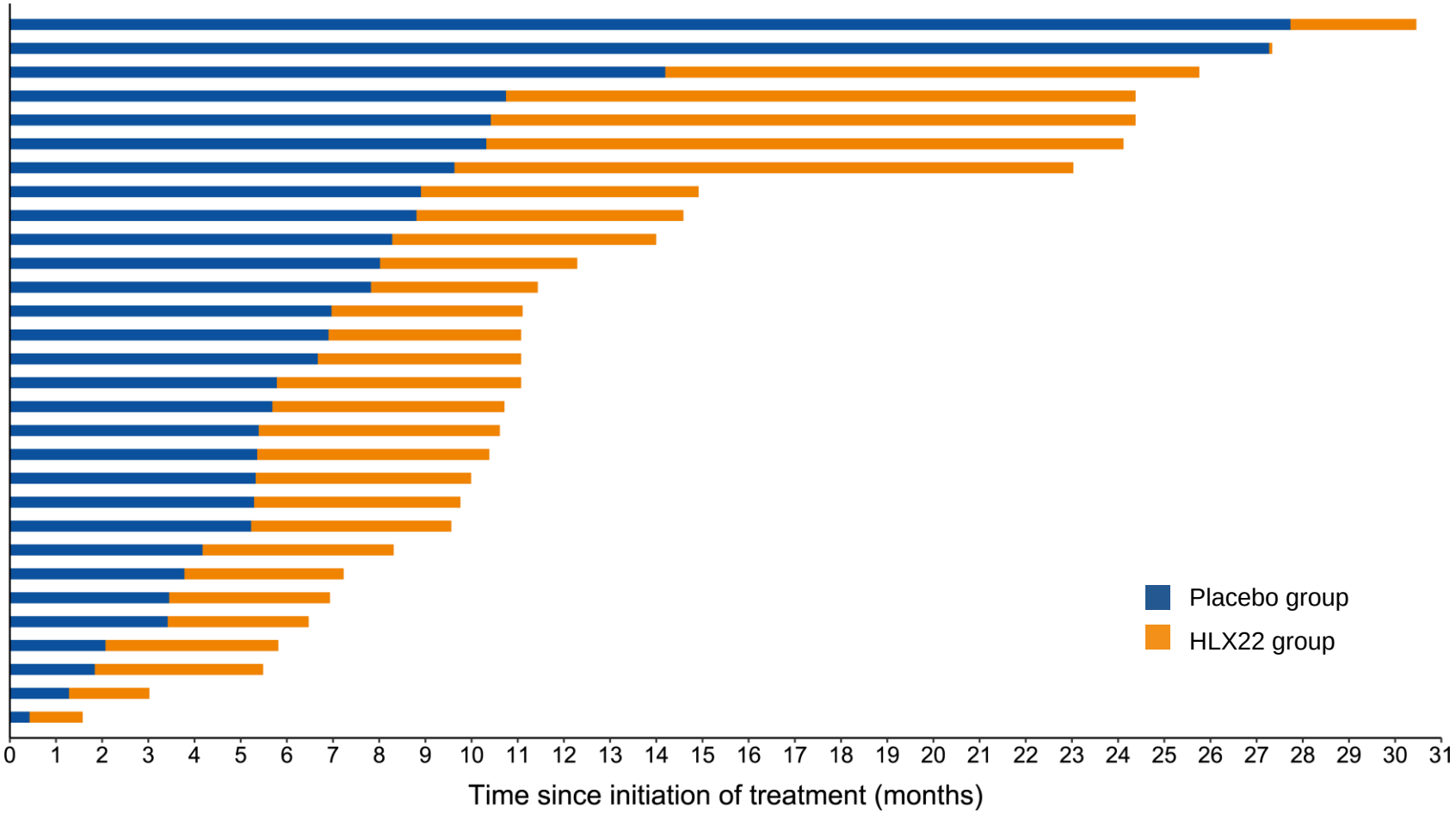
Swimmer Plot According to IRRC Assessments

June 30, 2024 (data cutoff), median follow-up 24.1 months



Excluding two patients with no post-baseline tumor assessment.
IRRC, independent radiological review committee.

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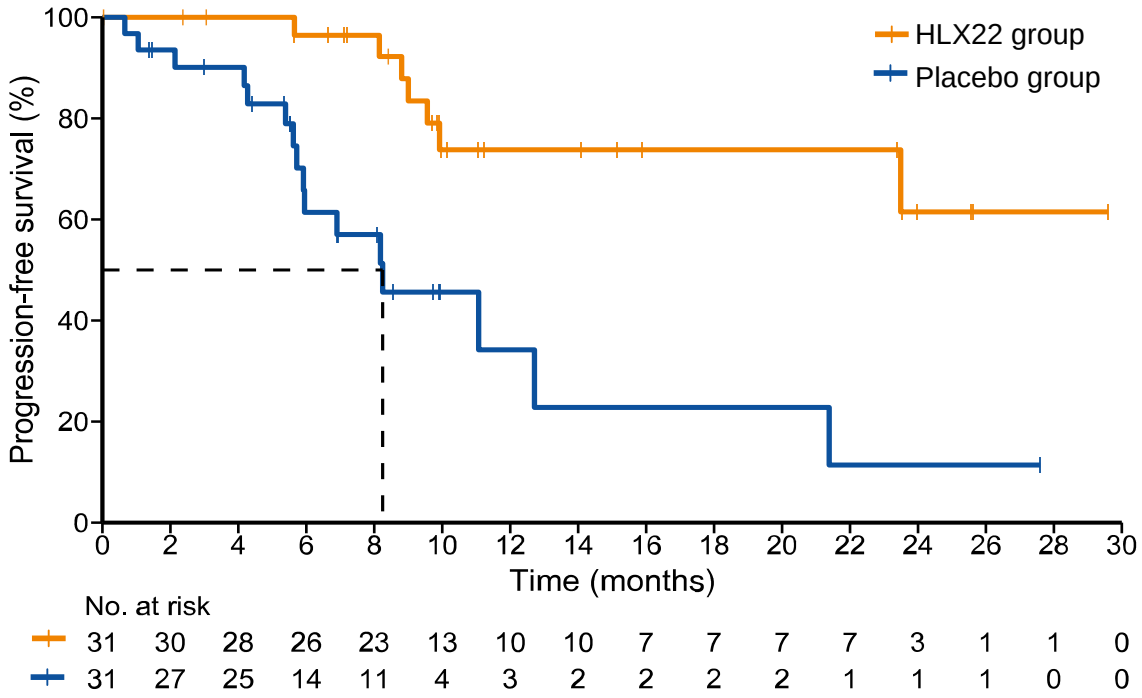
Primary Endpoint: PFS by IRRC and OS

- Median follow-up duration: 24.1 months; Median PFS and OS are not mature in the HLX22 group



	HLX22 group (n = 31)	Placebo group (n = 31)
mPFS, months (95% CI)	NR (23.5–NE)	8.3 (5.7–12.7)
HR (95% CI)	**0.2** (0.06–0.45)	p<0.0001
12-month PFS rate (95% CI)	73.8 (50.3–87.4)	34.2 (12.0–58.1)
24-month PFS rate (95% CI)	61.5 (30.4–82.0)	11.4 (0.8–38.1)
mOS, months (95% CI)	NR (17.6–NE)	22.0 (10.6–NE)
HR (95% CI)	0.5 (0.20–1.21)	p=0.1174
Subsequent anti-HER2 therapy, n (%)	3 (9.7)	13 (41.9)
Antibody-drug conjugate	3 (9.7)	8 (25.8)
Monospecific antibody	1 (3.2)	2 (6.5)
Bispecific antibody	0	3 (9.7)[a]

[a]*Including one patient in a blinded trial.*

CI, confidence interval. HR, hazard ratio. NE, not evaluable. NR, not reached. PFS, progression-free survival.

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Safety Profile

June 30, 2024 (data cutoff), median follow-up 24.1 months

	HLX22 group (n = 31)	Placebo group (n = 31)
Any TEAE	30 (96.8)	31 (100)
Grade ≥ 3	17 (54.8)	15 (48.4)
Leading to death	0	4 (12.9)
Leading to treatment discontinuation	3 (9.7)	7 (22.6)
Any AESI	14 (45.2)	6 (19.4)
Infusion-related reaction	14 (45.2)	6 (19.4)
Related to HLX22/placebo	4 (12.9)	0
Cardiac-related	1 (3.2)	0
Any TRAE	30 (96.8)	30 (96.8)
Leading to death	0	1 (3.2)
Related to HLX22/placebo	27 (87.1)	14 (45.2)
Grade ≥ 3	9 (29.0)	6 (19.4)
Leading to treatment discontinuation	2 (6.5)	2 (6.5)

Most common TEAEs (≥ 25% in either group):	HLX22 group (n = 31)	Placebo group (n = 31)
Platelet count decreased	25 (80.6)	23 (74.2)
Neutrophil count decreased	25 (80.6)	17 (54.8)
Anemia	18 (58.1)	19 (61.3)
White blood cell count decreased	18 (58.1)	18 (58.1)
Chills	14 (45.2)	4 (12.9)
Aspartate aminotransferase increased	13 (41.9)	6 (19.4)
Hypoesthesia	11 (35.5)	7 (22.6)
Vomiting	10 (32.3)	7 (22.6)
Pyrexia	10 (32.3)	5 (16.1)
Nausea	8 (25.8)	9 (29.0)
Hypokalemia	8 (25.8)	7 (22.6)
COVID-19	8 (25.8)	1 (3.2)
Hypoalbuminemia	6 (19.4)	9 (29.0)

AESI, Adverse event of special interest; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Conclusions

- Adding HLX22 to trastuzumab + XELOX was safe, and prolonged PFS and enhanced antitumor response in patients with HER2-positive G/GEJ cancer in the first-line setting. HLX22 + trastuzumab + XELOX warrants further large-scale investigation and could be a new first-line treatment option for HER2-positive G/GEJ cancers.

Product	Clinical Trial	Regimen	Sample Size	mPFS (months)	mOS (months)	mDOR (months)
HLX22	**HLX22-GC-201** (Ph2) Data cutoff: June 30, 2024	HLX22 group: HLX22 (15 mg/kg) + Tras + XELOX Placebo group: placebo + Tras + XELOX	ITT population 31 vs 31	NR vs 8.3 **HR=0.2, p<0.0001**	NR vs 22.0 **HR=0.5, p=0.1174**	NR vs 9.7 HR=0.1, p<0.0001
Pembrolizumab	**KEYNOTE-811**[1.2] (Ph3) **EMA**: approved for PD-L1+ subgroup; **FDA**: accelerate approval for PD-L1+ subgroup	A: Pembrolizumab + Tras + CF/XELOX B: Tras + CF/XELOX	ITT population 350 vs 348	10.0 vs 8.1 HR=0.73, p<0.0002	20.0 vs 16.8 HR=0.80, p=0.004	11.3 vs 9.5 HR NA, p NA
			PD-L1+ subgroup 298 vs 296	10.9 vs 7.3 HR=0.72, p<0.0002	20.1 vs 15.7 HR=0.79, p=0.0143	11.3 vs 9.5 HR NA, p NA
			PD-L1- subgroup* 52 vs 52	9.5 vs 9.5 HR=0.99, p=0.7432	18.2 vs 20.4 HR=1.10, p NA	8.9 vs 9.0 HR NA, p NA

* mDOR in PD-L1- subgroup is from IA2, other indicators are from Final analysis. *CF, cisplatin and fluorouracil; CX, cisplatin and capecitabine; DOR, duration of response; G/GEJ, gastric/gastroesophageal junction; FA, final analysis. HR, hazard ratio; ITT, intention-to-treat; IA interim analysis; m, median; NA, not available; NR, not reached; OS, overall survival; PFS, progression-free survival; Tras, trastuzumab; XELOX, capecitabine and oxaliplatin.*

1. Janjigian YY, et al. Lancet 2023;402(10418):2197-2208. 2. Annals of Oncology (2024) 35 (suppl_2): S878-S912.

03 Clinical Development of HLX22

HLX22-GC301 Study Design

HLX22-GC Ph3 Study Design

A randomized, global, double-blinded, 1L, phase 3 study

1. Age≥18Y
2. **Treatment naïve**, advanced unresectable, **HER2+** G/GEJ adenocarcinoma
3. Life expectancy ≥ 6 month
4. HER2 and PD-L1 expression status assessed by central lab

N=550

R 1:1

- HLX22 (**15mg/kg**) + SOC ± placebo(K), Q3W
- Placebo(HLX22) + SOC ± Keytruda , Q3W

- **SOC:** Trastuzumab + XELOX

Primary Endpoint
- **PFS** (IRRC，RECIST)
- **OS**

Secondary Endpoint
- PFS (INV，RECIST)
- ORR(INV/ IRRC，RECIST)
- DOR(INV/ IRRC，RECIST
- PFS2 (INV，RECIST)
- Safety

Stratification factors:
- HER2 status (3+ vs 2+)
- Region (Asia vs Europe/North America vs the rest of the world)
- Primary cancer site (GC vs GEJC)
- PD-L1 status (CPS<1 vs 1≤ CPS < 10 vs 10≤CPS)

Sample size: Based on dual primary endpoints PFS and OS，*subjects number* = 550 (275:275)

CPS, combined positive score; DOR, duration of response; GC, gastric cancer; GEJ, gastroesophageal junction; INV, investigator; IRRC, independent radiological review committee; IV, intravenous; K, Keytruda; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W: every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care.

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04 Clinical Potential of HLX22

Clinical Potential of HLX22

Larger Patient Population

- **Pembro is only approved in HER2+ G/GEJ Cancer patients with PD-L1+**

Suboptimal Clinical Outcomes with Current Treatments

- KEYNOTE-811: Pembro has limited efficacy in Asian patients
- A Single Arm Study in South Korea: Pembro showed less benefit in Asian patients.
- The combination of T-Dxd plus Pembro is not as good as expected (DS-GC03 ORR T-Dxd + Pembro + chemo vs Tras + chemo: 59% vs. 76%)

More Potential Indications

- Compared with other HER2 targeted therapy, HLX22 exhibits the potential to be a Pan-tumor treatment for all HER2+ Cancers owing to its unique MOA

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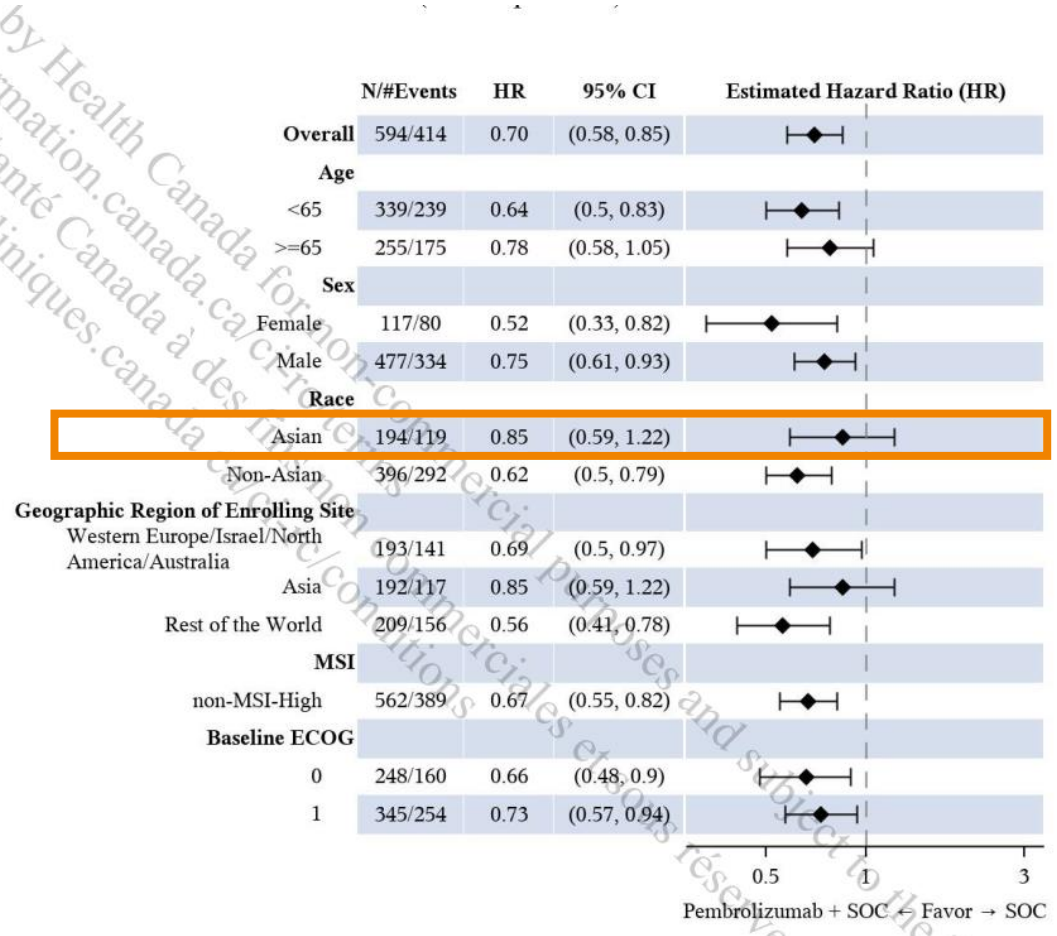
KEYNOTE-811
Pembrolizumab showed less benefit in Asian HER2+ GC subjects

PFS in ITT population(IA3)

	Events/patients, n/N		HR (95% CI)
	Pembrolizumab group	Placebo group	
Age, years			
<65	152/205	153/192	0·67 (0·54-0·85)
≥65	101/145	108/156	0·84 (0·64-1·10)
Sex			
Female	42/66	55/68	0·49 (0·32-0·74)
Male	211/284	206/280	0·83 (0·69-1·01)
Race			
Asian	76/119	80/121	0·85 (0·62-1·16)
Non-Asian	177/231	179/225	0·69 (0·56-0·84)
Geographical region			
Europe, North America, and Australia	84/113	88/111	0·73 (0·54-0·99)
Asia	75/118	78/119	0·84 (0·61-1·16)
Rest of world	94/119	95/118	0·65 (0·49-0·87)
PD-L1 status			
CPS≥1	217/298	225/296	0·71 (0·59-0·86)
CPS<1	36/52	36/52	1·03 (0·65-1·64)

PFS in PD-L1+ population (IA2)

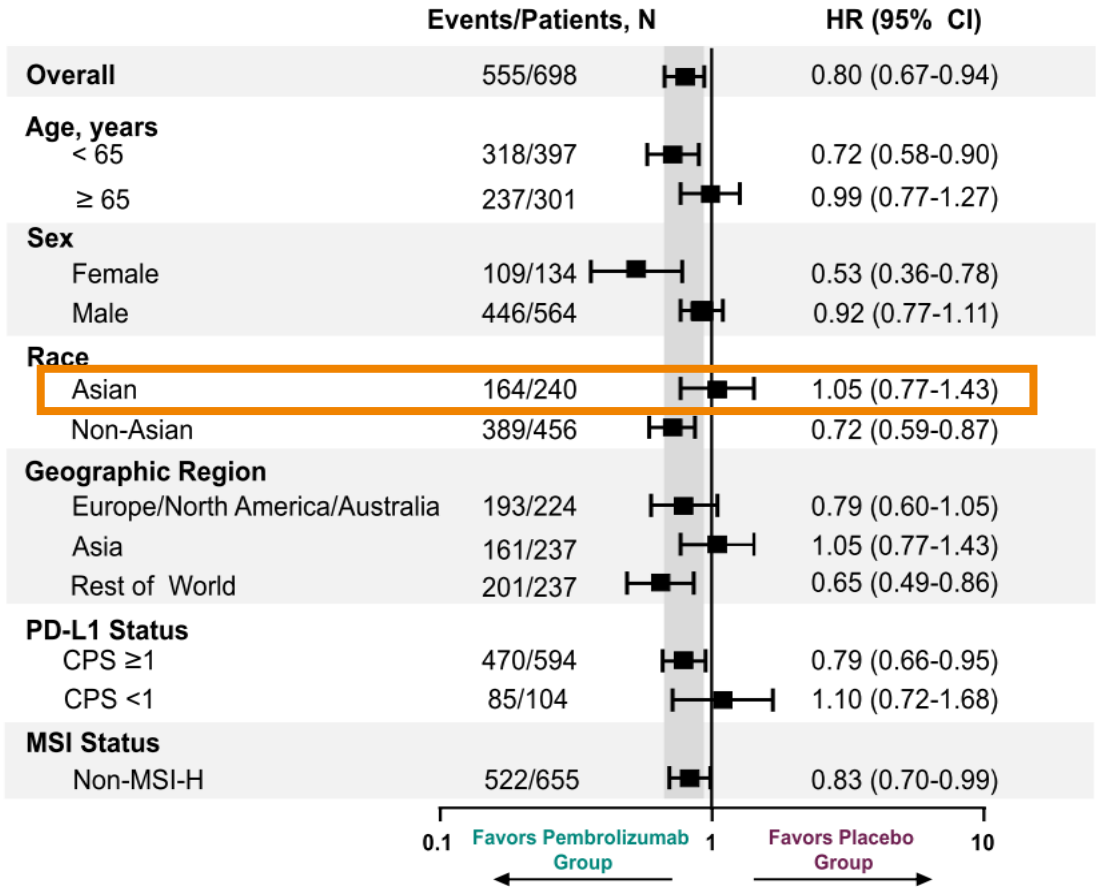


Annals of Oncology (2023) 34 (suppl_4): S1520-S1555.

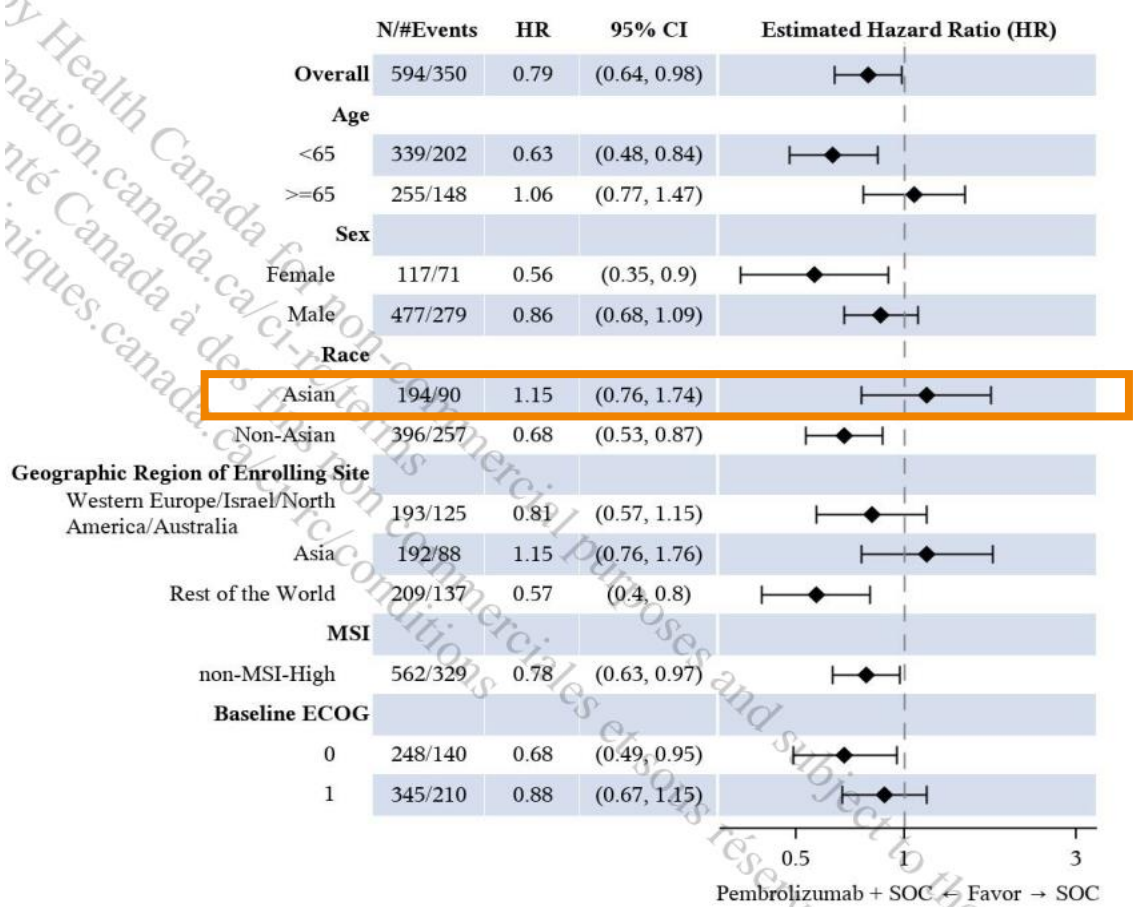
KEYNOTE-811

Pembrolizumab showed less benefit in Asian HER2+ GC subjects

OS in ITT population (FA)



OS in PD-L1+ population (IA2)



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A Single Arm Study in South Korea

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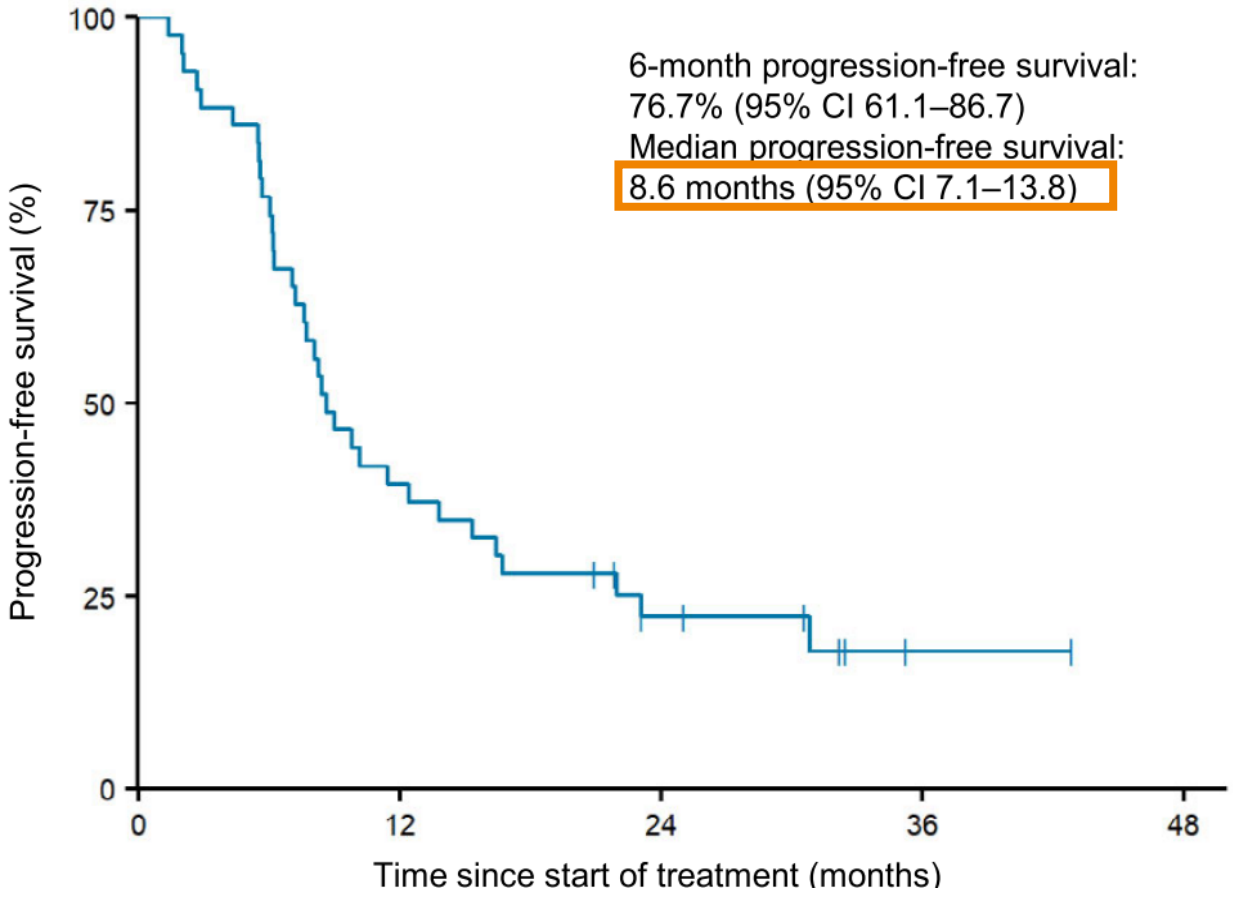

- **Intervention**: pembrolizumab + trastuzumab + cisplatin + capecitabine
- **Results**: median follow-up duration: 18.2 months, median PFS: 8.6 months

Nature communications vol. 13,1 6002. 12 Oct. 2022,

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Clinical Potential of HLX22

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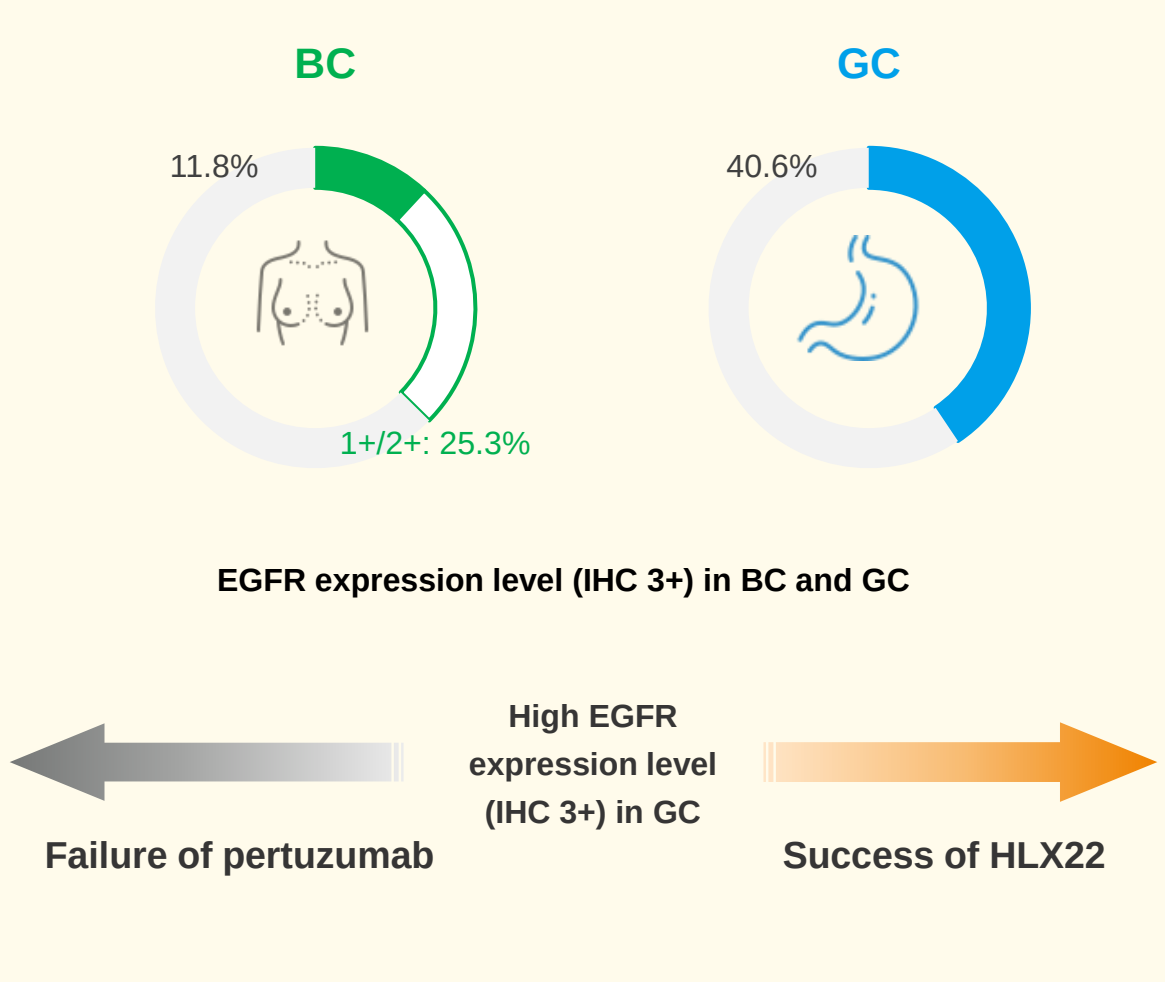
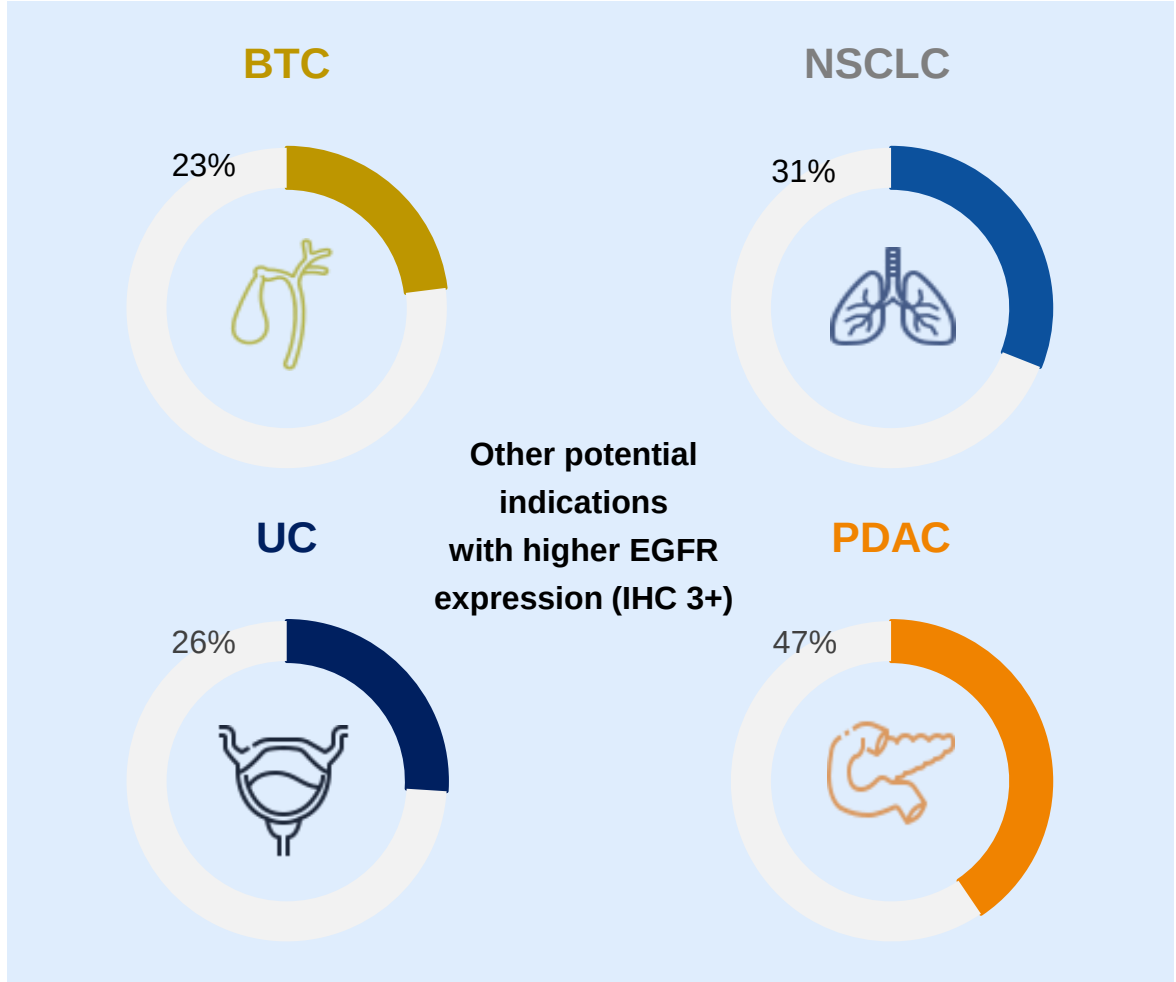
Clinical Potential of HLX22

Pan-tumor





BC, breast cancer; BTC, biliary tract cancers; GC, gastric cancer; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

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AI-Assisted Development of Proprietary Hyaluronidase and Subcutaneous Injection Products

- **Simon Hsu, PhD.**
- Henlius CTO & Senior VP

Collaborate to Create

2025 Henlius Global R&D Day

CONTENTS

01

Henozye™: AI-Assisted Development of Proprietary Hyaluronidase

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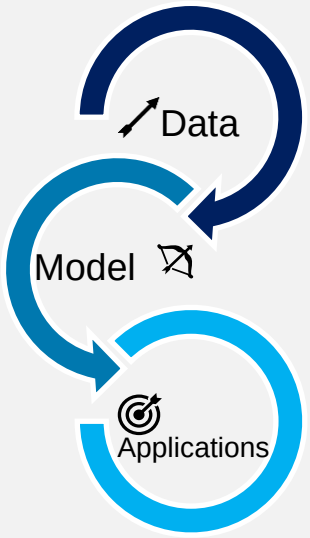
AI-Assisted Protein Development



- Pre-PCC: research data
- Pre-IND: process development data
- Late stage: scale-up data & long-term stability data
- Commercial stage: production data of multiple batches
- Others: cell culture media development data, particulate characterization data, etc.

- Machine Learning: Supervised learning, unsupervised learning, reinforcement learning, framework tools, etc.
- Deep Learning: Convolutional neural networks, recurrent neural networks, generative adversarial networks, etc.
- Large language model
- Multimodal AI

- Target Discovery
- Molecule Design
- Molecule Modification
- Developability Assessment
- Process Development & Optimization
- Production Process Control

In 2020, AI for Science platform launched.

- In silico molecule structure modeling and developability assessment (Application started in 2022, article submitted)
- In silico prescription development (Application started in 2022)
- Downstream process development based on digital twin (Biotechnology and Bioengineering, 121, 1702–1715; Patent application number 202310817446.2)
- Particle image AI recognition and characterization based on a Resnet architecture generalized from physical models (Appl. Sci. 2022, 12, 5843)
- Particulate characterization based on knowledge-driven AI models (Article in preparation)

1956
Dartmouth Conference

Perceptron
The First Neural Network Software

Logic Theorist
The First AI Software

Mathematician Ratcliffe's stern criticism of AI

Rise of the Fifth Generation Computers

Hopfield Networks & BP Algorithm

Failure of the Fifth Generation Computers
DARPA Funding Cuts

2006
Hinton's team made a breakthrough in deep learning

2012
Success of Convolutional Neural Networks (CNN) in Image Recognition

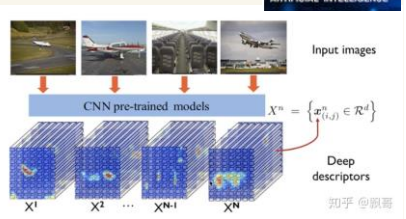
2016
AlphaGo Moment

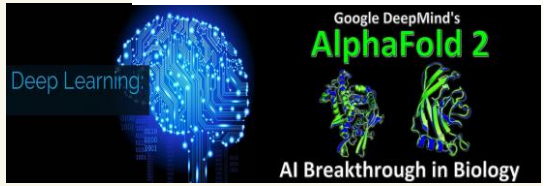
2020
AlphaFold 2

2022
ChatGPT

2024
AlphaFold 3

2025
DeepSeek





1980 2000 2020

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Henlius AI-Assisted Product Development Toolbox

Structural Modeling

MOE

SWISS-MODEL

AlphaFold

FAST. FLEXIBLE. FREE. GROMACS

AMBER MD

Henlius in-house Model

Molecule Assessment

- Affinity Prediction
- Stability Assessment
  - Conformational prediction
  - Surface properties
  - Aggregation prediction
  - Viscosity prediction
  - Degradation prediction
  - PTMs
  - Solubility prediction
- Immunogenicity Evaluation

FAST. FLEXIBLE. FREE. GROMACS MOE

Henlius in-house Model

Process Development

- **Upstream Process Development:**
  - Media optimization
  - Cell line screening
  - Cell culture process design
  - Production process control
- **Downstream Process Development:**
  - Digital Twin-based downstream process development
  - Production process control
- **Formulation Development:**
  - Formulation design
  - Image analysis-based particulate characterization

FAST. FLEXIBLE. FREE. GROMACS AMBER MD

Henlius in-house Model

Database

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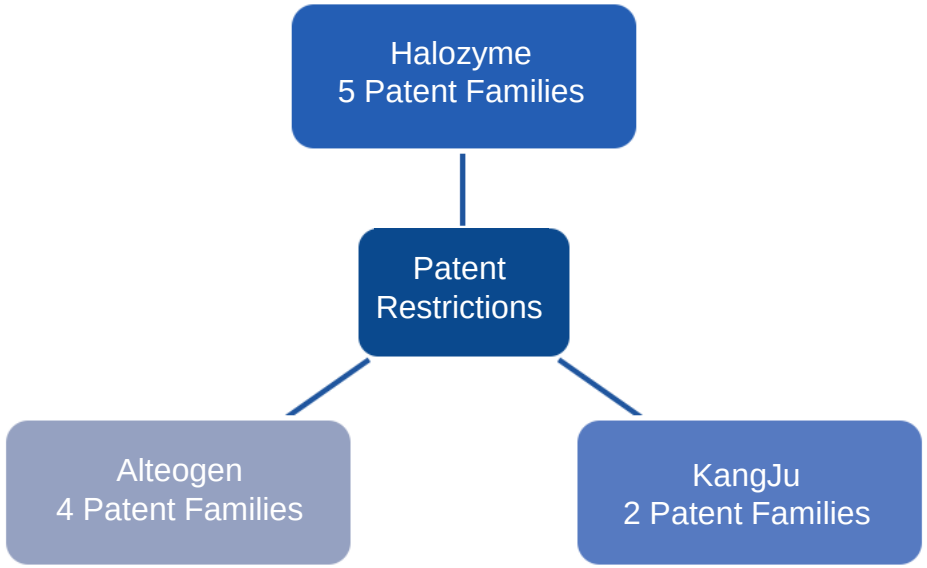
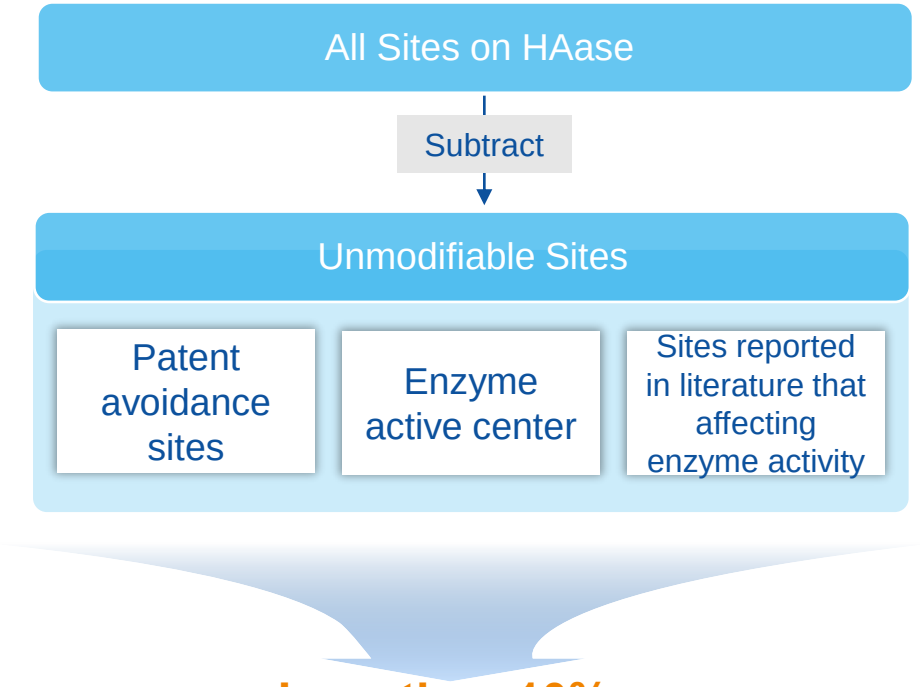
AI-Assisted Development of Henlius Proprietary Hyaluronidase Henozye ™

Challenges in Developing Henlius rHuPH20 2.0

Enhanced Patent Barriers



Limited Modifiable Space



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Successful Development of a Superior Hyaluronidase

Design Objectives

- Own Proprietary Patents
- Address Aggregation Issues
- Mitigate Degradation Issues
- Alleviate Oxidation Issues
- Enhance Producibility
- Maintain Efficacy and Safety Profiles

Development Steps

01 Structural Modeling
Construct HAase structure

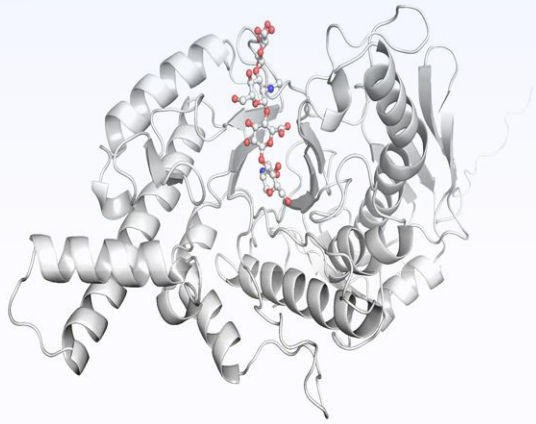
02 Modification Site Identification
Recognize key regions/sites for enzyme activity and stability

03 Molecular Design
Sequence alignment → modification of homologous proteins
Amino acid properties → specificity modification

04 Enzyme Activity Evaluation
Calculating the binding energy between HAase and HA

05 Stability Assessment
Assess molecular conformational stability/hydrophobicity/charge distribution, etc.

06 Immunogenicity Assessment
Evaluate immunogenicity



of buffer system and pH condition

Results

The Harvest enzymatic activity of rHuPH20 2.0 is:
~ 300-fold higher than the homologous enzyme of H company;
~ 4-fold higher than the homologous enzyme of A company.

- Demonstrates superior stability over the homologous enzymes of H and A company.
- Broad formulation flexibility: compatible with a broad range of buffer system and pH conditions.
- Preservative tolerance
- Universal protein compatibility

Animal study demonstrate:

rHuPH20 2.0 has good safety and efficacy

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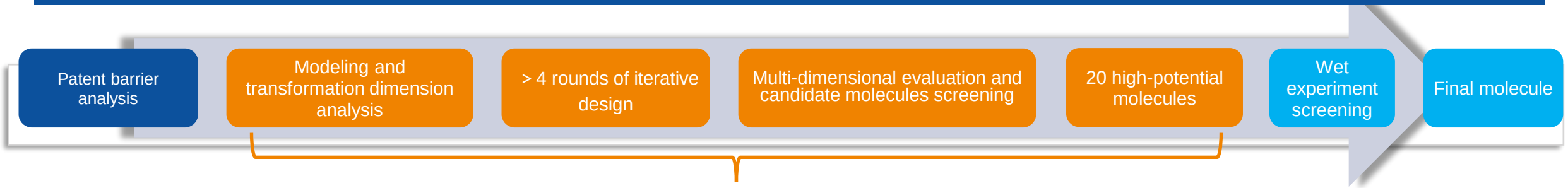
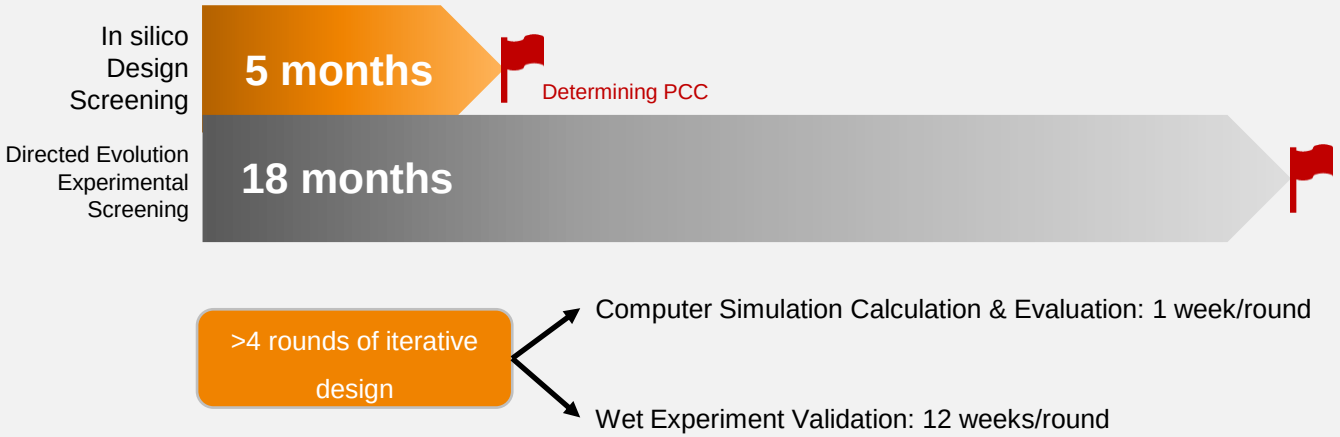
Development Time Shorten from 18 Months to 5 Months

Development Process

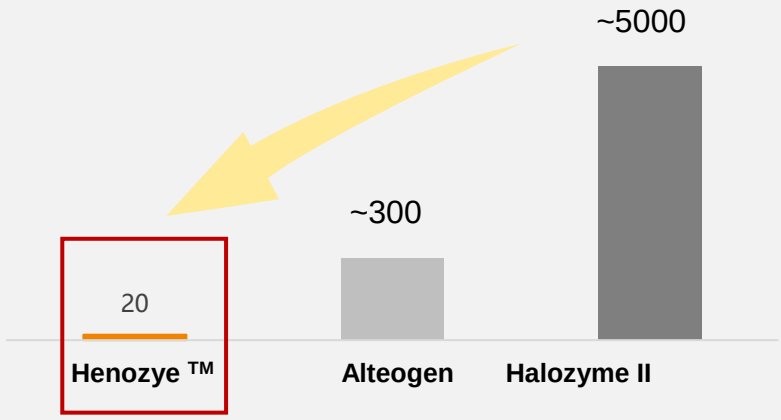


Development Cycle Timeline



Data Source: Industry Technical Consultancy

Molecules Number Screened in Wet Experiments



Data source: Patents CN104244968B & CN113840921A

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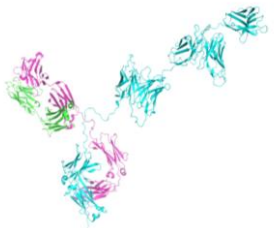
Henlius AI-Assisted Product Development Platform

Molecule Design, Modification & Evaluation



Affinity/Activity
Immunogenicity
Physicochemical Properties
Developability
…

QVQLV
QSGGG
VVQPG
RSLRL
SCAAS
…

Applicable Molecular Types:
Monoclonal Antibody, Bispecific Antibody, Multispecific Antibody, Enzyme, Fusion Protein, ADC …

Commercial Algorithms
&
In house Algorithms

Henlius in-house Database

Training

Process Development AI Model

Process Development, Production & Control

- Upstream Process Design
  - Medium Optimization
  - Cell Culture Process
  - Cell Line Screening
  - Production Process Control
- Downstream Process Design
  - Digital Twin-based downstream process development
  - Production Process Control
- Formulation Process Design
  - Computational Simulation-based formulation design
  - Image analysis-based particulate characterization

Applied | Trial Phase | Proof of Concept (POC)

02

Subcutaneous Injection Technology Platform Based on Hyaluronidase

Hyaluronidase Significantly Increases S.C. Injection Volume

Injection volume
Hyaluronic acid impedes the diffusion and absorption of liquids in subcutaneous tissue; the conventional subcutaneous injection volume is ≤ 2 mL.

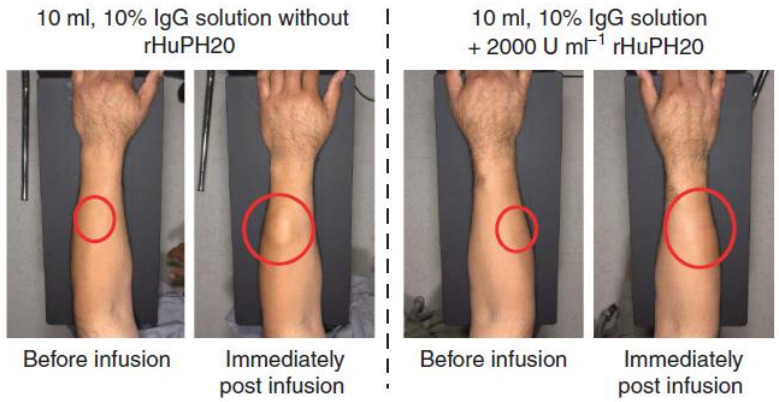
+

Protein concentration
The highest concentration of marketed biologics is 200 mg/mL. Higher the protein concentration brings greater process development difficulty and risk.

→

High-dose subcutaneous biologics injections
These dual restrictions of volume and concentration fail high-dose subcutaneous injection.

Hyaluronidase degrades hyaluronic acid in subcutaneous tissue, accelerating the diffusion and absorption rate of subcutaneous injection drugs, thereby enabling larger volume drug delivery.



BJC, 2013, 109: 1556-1561.

Injection volume of marketed drugs using hyaluronidase

Drug	Injection volume
Darzalex Faspro®	**15 mL**
Herceptin Hylecta®	**5 mL**
Phesgo®	**15 mL** loading **10 mL** maintenance
Rituxan Hycela®	**11.7 mL** (NHL) **13.4 mL** (CLL)
Tecentriq®	**15 mL**
Ocrevus Zunovo™	**23 mL**

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Halozyme Hyaluronidase Market Expectation in 3 Years

Expected sales of approximately $20 billion in 2028

2013-2020 Launches

- DARZALEX Faspro® (daratumumab and hyaluronidase-fihj) Injection for subcutaneous use | 1,800mg/30,000units
- PHESGO® pertuzumab/trastuzumab/hyaluronidase-zzxf SUBCUTANEOUS INJECTION
- HyQvia Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase
- RituxanHYCELA rituximab/hyaluronidase human subcutaneous injection | 1,400 mg/23,400 Units | 1,600 mg/26,600 Units
- Herceptin HYLECTA™ trastuzumab and hyaluronidase-oysk INJECTION FOR SUBCUTANEOUS USE | 600 mg/10,000 units

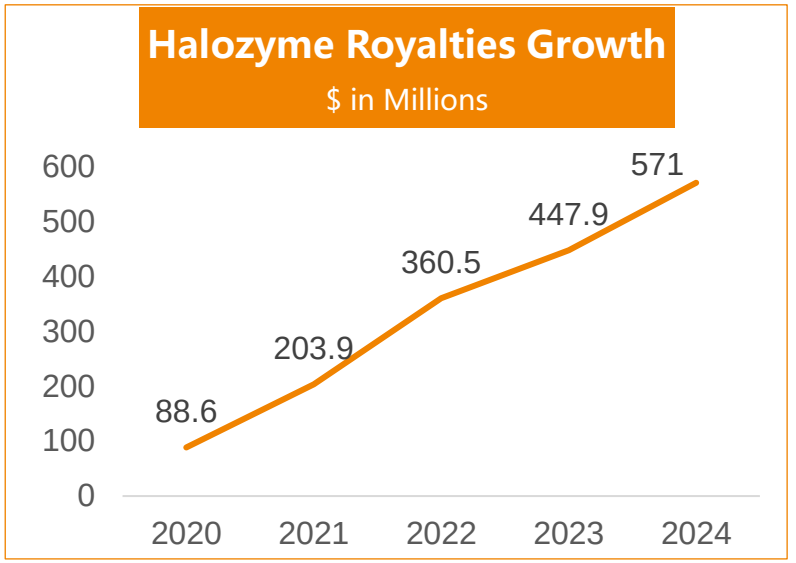
Expected sales of approximately $35 billion in 2028

2023-2024 Launches

- VYVGART® Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) Subcutaneous Injection 180 mg/mL and 2000 U/mL vial
- OCREVUS® ocrelizumab
- TECENTRIQ® SC atezolizumab subcutaneous
- OPDIVO® (nivolumab)

Projected Launches

Amivantamab SC - JnJ



The sales of the 9 marketed products are expected to reach approximately 50 billion USD by 2028, bringing about 1 billion USD royalty revenue to Halozyme. Expected royalty revenue growth YOY at 27-31%. Assuming the royalty percentage remains, the expected total revenue is about 1.8 billion USD in 2028.

Data source: Halozyme 2022-2024 report

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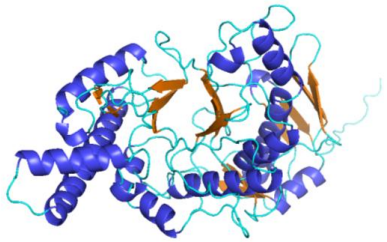
Henlius Technology Platform Based on Hyaluronidase

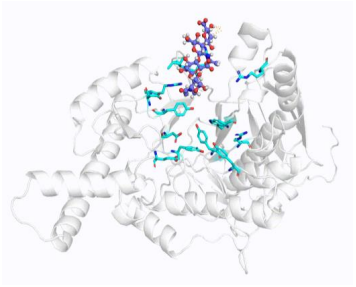
rHuPH20 1.0



- Identical sequence as Halozyme HYLENEX®
- Ideal choice for biosimilars and innovative drugs

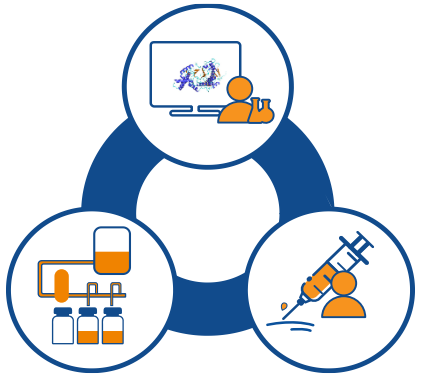
rHuPH20 2.0

HENOZYE



- Henlius propretairy hyaluronidase.
- Excellent stability and adaptable for multiple complex scenarios
- Ideal choice for innovative drugs

Formulation Development



- Development platform based on AI+ technology
- High concentration formulation development
- Co-formulation development with different types of hyaluronidase

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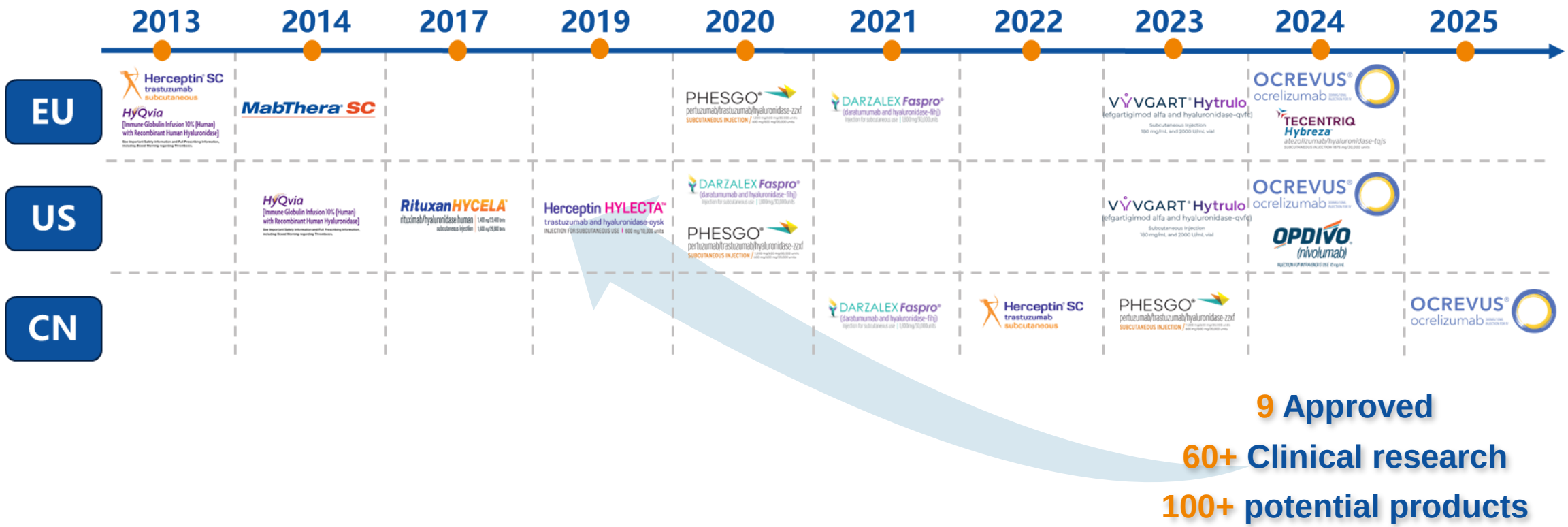
rHuPH20 1.0 - the Ideal Choice for Biosimilars

Currently, nine products utilizing Halozyme Hylenex® hyaluronidase have been commercialized. The combined intravenous (IV) and subcutaneous (SC) administration market is valued at approximately $40 billion, reflecting a sustained upward growth trajectory. To date, no biosimilars have been approved for any of these SC-based therapeutics.

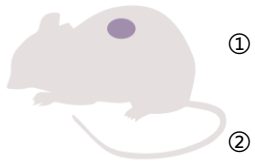


Data sources: Roche, Argenx, Takeda, BMS, and Janssen 2024 reports; desk research

rHuPH20 1.0 Comparable to Hylenex® in Mice & Mini Pigs

Head-to-head animal studies with Hylenex® and the original co-formulation drug show that rHuPH20 1.0 is comparable to Hylenex® regarding efficacy and safety.

01 Mouse subcutaneous Trypan blue diffusion assay



a. rHuPH20 1.0 VS Hylenex®

① Pure enzyme sequential injection: HAase → Trypan blue

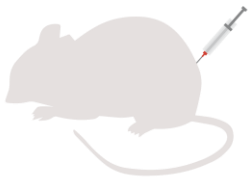
② Injection dose: 150 U

b. HLX15 VS Darzalex Faspro®

① Co-formulation sequential injection: co-formulation → Trypan blue

② Enzyme activity concentration: 2000 U/mL

02 Mouse subcutaneous injection pressure test

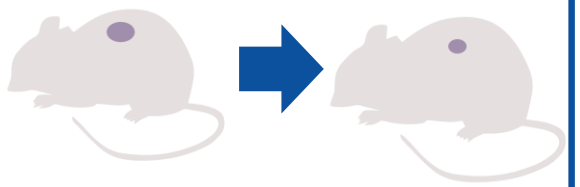


HLX15 vs Darzalex Faspro ®

① Co-formulation injection

② Enzyme activity concentration: 2000 U/mL

03 Mouse skin reconstruction assay



HLX15 vs Darzalex Faspro®

① Enzyme activity concentration: 2000 U/mL

04 PK and tissue resistance studies in mini pigs

HLX15 vs Darzalex Faspro®

a. PK parameters: AUC, Cmax, Tmax, T1/2, MRT, CL/F, CL, Vss etc.

b. Tissue resistance study:
- Erythema and edema/hardness scores
- Swelling volume
- Injection pressure

Henozye ™ - Versatile and Adaptable

	rHuPh20 1.0 Halozyme HYLENEX ® identical sequence enzyme	Henozye ™ (rHuPH20 2.0) New generation of enzyme with proprietary patents
Stability of enzyme	★★★	★★★★★
Stability of enzyme in coformulations	★★	★★★★★
Compatibility with different molecules	★★	★★★★★
Compatibility with different formulations	★★	★★★★★
Compatibility with preservatives	★	★★★★
Efficacy	★★★★★	★★★★★
Patent	None	Applied
Application Scenarios	• Biosimilars • Innovative drugs with simple formulations	• Innovative drugs (patent barriers & product lifecycle management) • Complex formulations • Products used in special scenarios (e.g., Cold chain-free)

Henlius

Henozye ™ - Functional Equivalence to Reference Products

In head-to-head animal studies with Hylenex® homologous enzyme and Alt-B4 homologous enzyme, Henozye™ exhibits equivalent efficacy to references.

01 Mouse subcutaneous trypan blue diffusion test

a. Hylenex® VS Alt-B4 sequence enzyme VS Hylenex®

① Pure enzyme sequential injection: HAase → Trypan blue

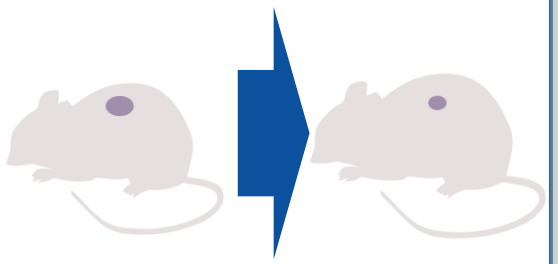
② Injection dose: 150 U

b. HLX15+ Hylenex® VS Darzalex Faspro®

① Co-formulation sequential injection: co-formulation → Trypan blue

② Enzyme activity concentration: 2000 U/mL

02 Mouse skin reconstruction test



Hylenex® VS Alt-B4 Same Sequence Enzyme VS Hylenex®

Enzyme Activity Concentration: 150 U/mL

03 Immunogenicity Test

Hylenex® VS Alt-B4 Same Sequence Enzyme VS Hylenex®

Immunotoxicity: Cellular Immune Response, Immune Factors, Organ-related

04 PK and tissue resistance study in mini pigs

Hylenex® VS Alt-B4 sequence enzyme VS Hylenex®

a. PK: AUC, Cmax, Tmax, T1/2, MRT, CL/F, CL, Vss etc.

b. Tissue resistance study:
- Erythema edema/firmness score
- Swelling volume
- Injection pressure

On-going

Henlius

Henozye ™ – the Ideal Choice for Global Drug Development and Commercialization

01

AI+ Technology

- Significantly shortens development time, reduces costs, and increases the success rate of molecule screening

03

Formulation Stability

- Stability superior to other hyaluronidases.
- Suitable for scale-up production and storage

05

Animal Experiments

- No efficacy difference compared to H enzyme and A homologous enzyme.
- Faster skin reconstruction.

02

Process Developability

- Strong process developability
- Good process robustness

04

Co-formulation Stability

- Enhanced stability
- Compatible to preservatives
- Broad formulation flexibility

Henlius

03

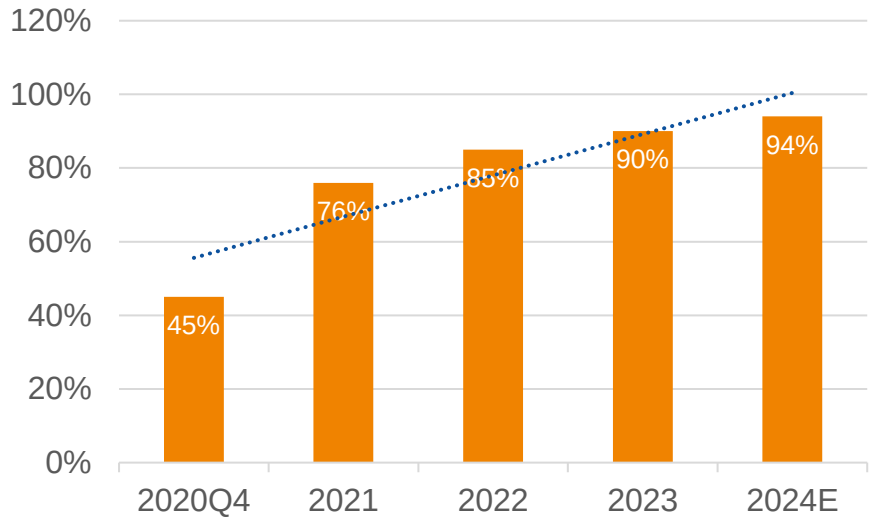
Market Demand for Subcutaneous Drug Delivery

Improved Treatment Experience to Patients

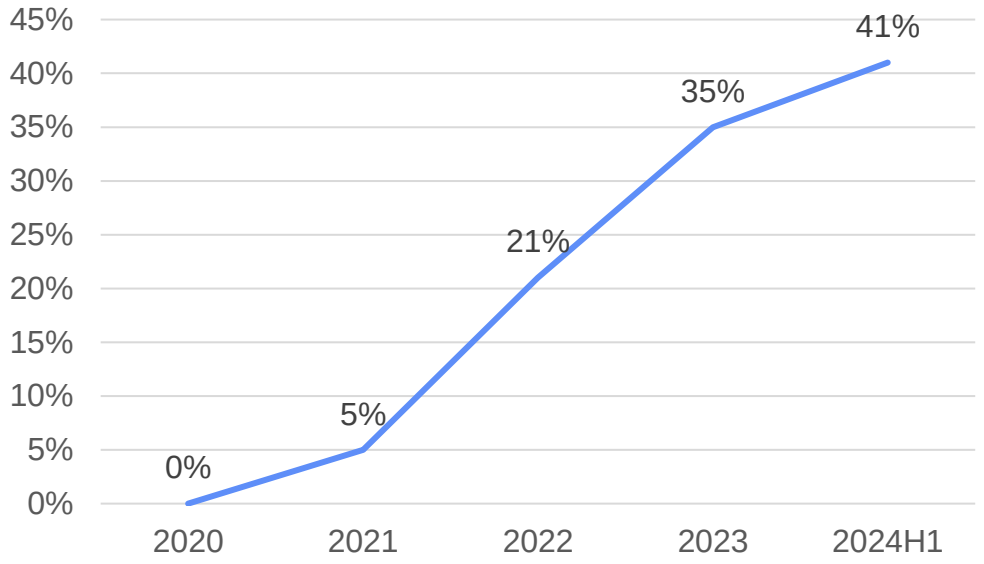
Patients in the US and Europe prefer the treatment route:

Access to health care, respect for patient values and preferences, coordination of medical services, emotional and psychological support, physical comfort, etc.

DARZALEX FASPRO® (SC) Sales Share of Total DARZALEX (SC/SC+IV) in US



Global Phesgo ® Conversion Rate



Data source: Halozyme, Roche H1 2024 report, Delveinsight, IQVIA，案头研究

Phesgo®conversion rate is based on volumes (vials) and includes all launch countries after the 2nd quarter after the launch (25 countries) in 2020 Q4..

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Favorable to Payers

https://www.tigerless.com/blogde/american-health-insurance/cn

High demand for cost control in healthcare in Europe and America, with all parties eager to reduce medical expenses.

- In 2025, the health insurance costs for American employees are projected to increase by 7%-8%, potentially marking the highest rise in decades. The main reasons include inflation, increased medical claims, and the widespread use of GLP-1 drugs (for the treatment of diabetes and obesity) driving up overall healthcare costs.
- The annual Medicare prescription drug out-of-pocket cap has been reduced to $2,000, which alleviates the burden on patients but results in higher expenditures for the government.
- According to data from the Kaiser Family Foundation (KFF), 25% of Americans delay or forego necessary medical services due to financial stress, and 21% of adults fail to purchase prescription medication on time because of high costs.

Data source: CBS News, KFF reports

Friendly to Environmental Protection Regulations

EU and US environmental protection regulations drive drug delivery optimization.

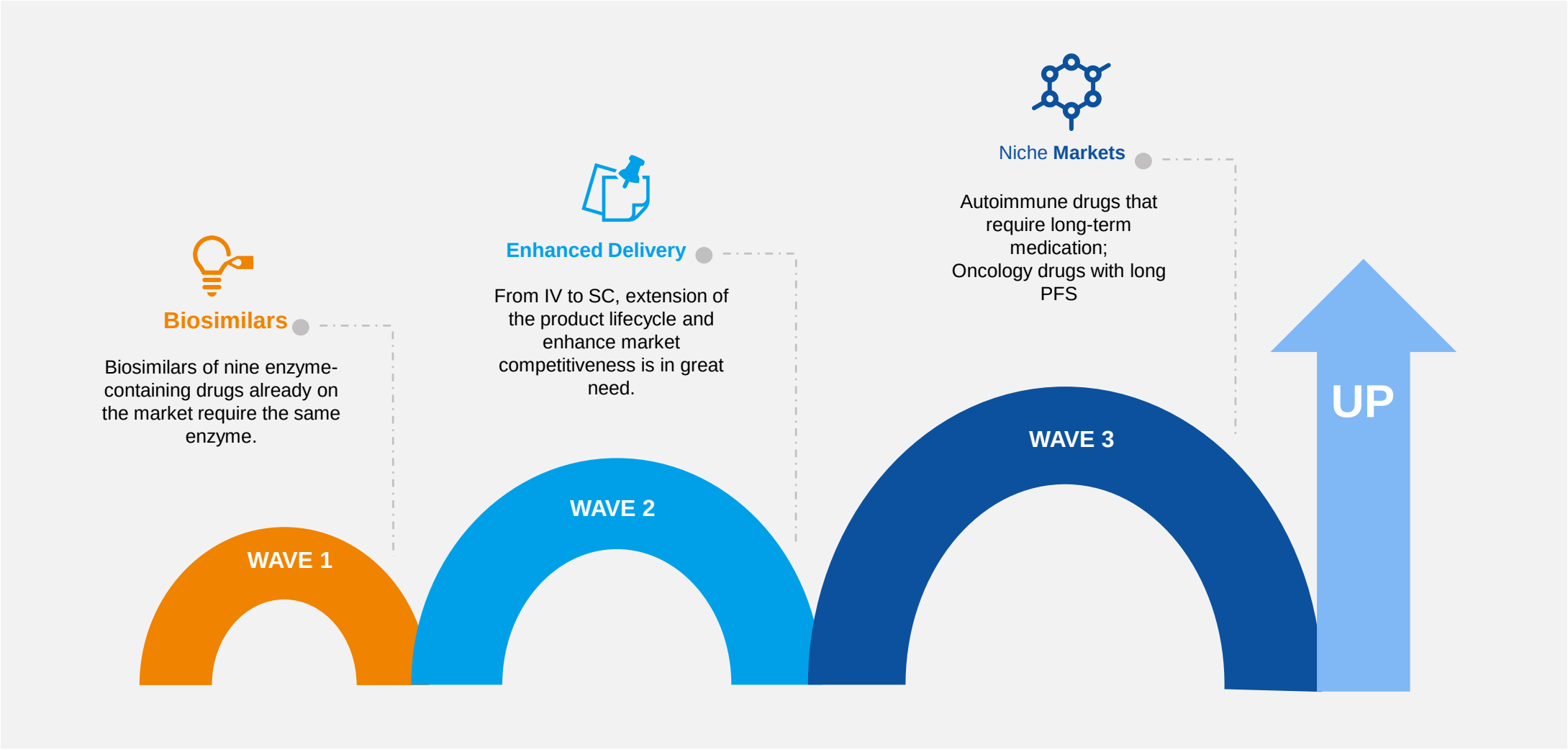
01

- The EU plans to reduce the waste generated by half by 2030.
- The US Environmental Protection Agency (EPA) is promoting the reduction of medical waste through the Resource Conservation and Recovery Act (RCRA).
- The World Health Organization continues to advance the reduction and proper disposal of medical waste.

02

- All parties aim to develop high-concentration injection to reduce the use of infusion packaging materials, syringes and needles, thereby lowering transportation costs and easing medical waste disposal pressures.
- Pharmaceutical companies should respond more to ESG requirements.

Market Expectations for Henozye ™



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Globalization 2.0

Strategic Entrance into the Japanese Market

Jin Li

Regulatory Affairs Vice President

Collaborate to Create

2025 Henlius Global R&D Day

CONTENTS

01

1.0 Key Achievements

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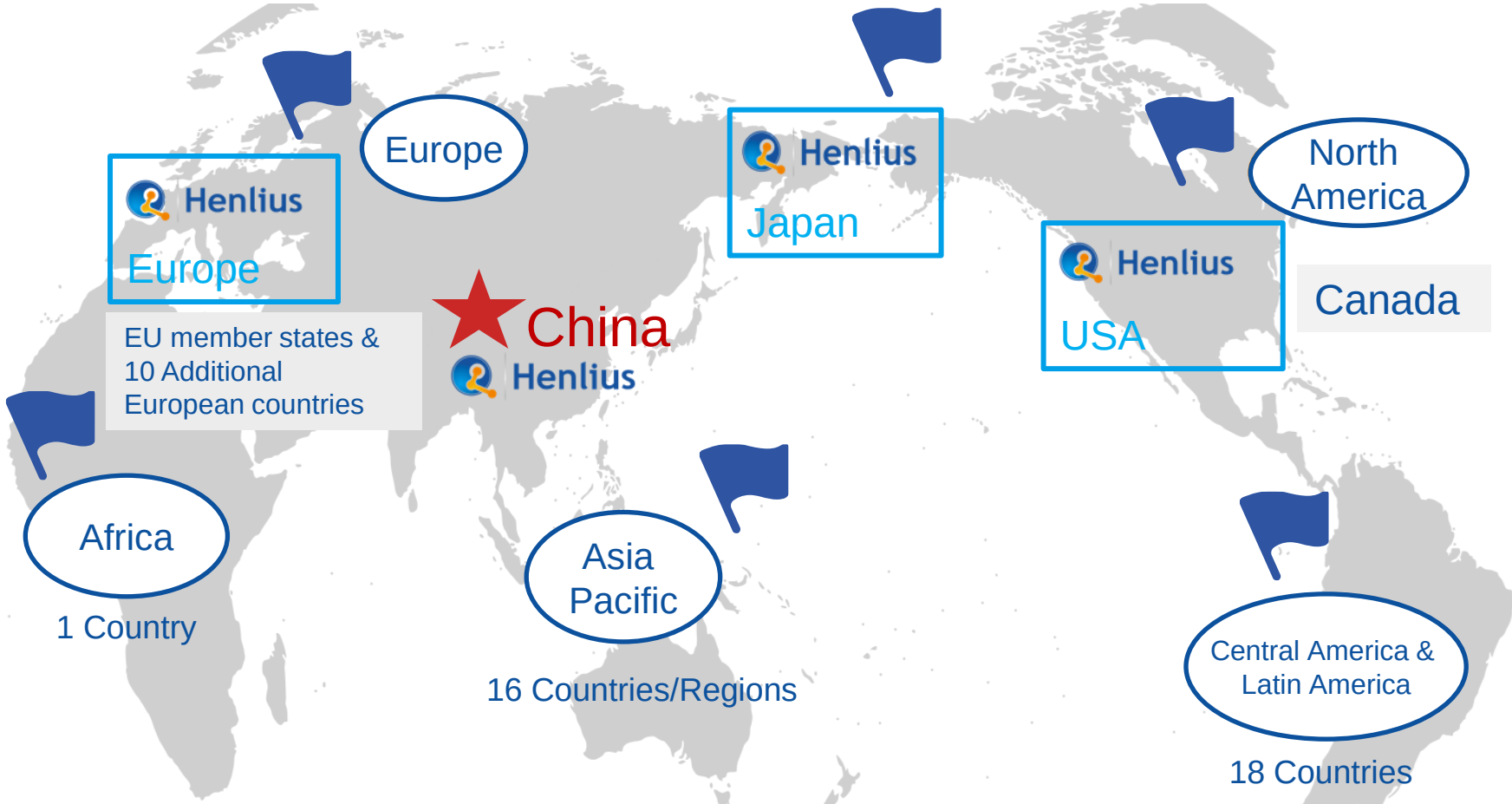
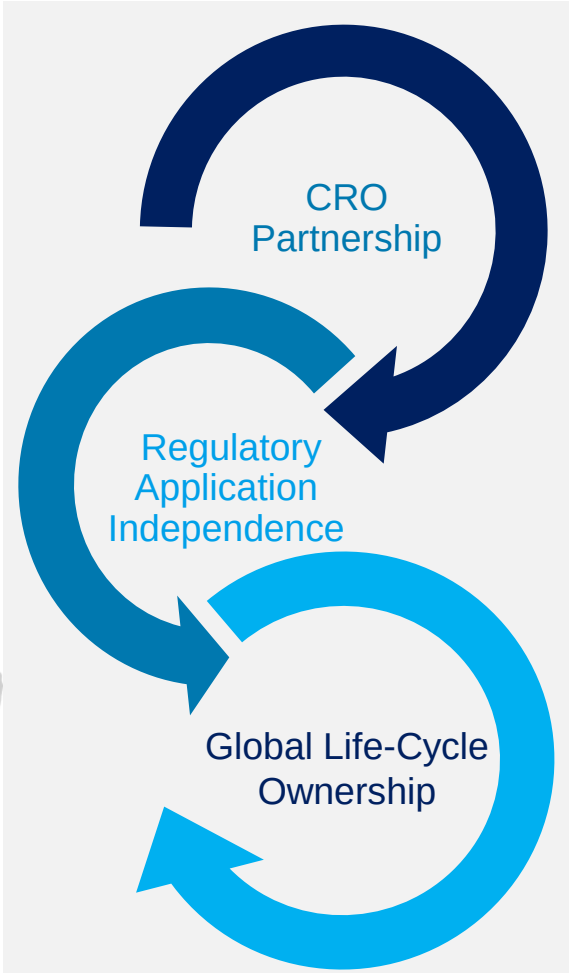
A Globalization Journey in Regulatory Affairs

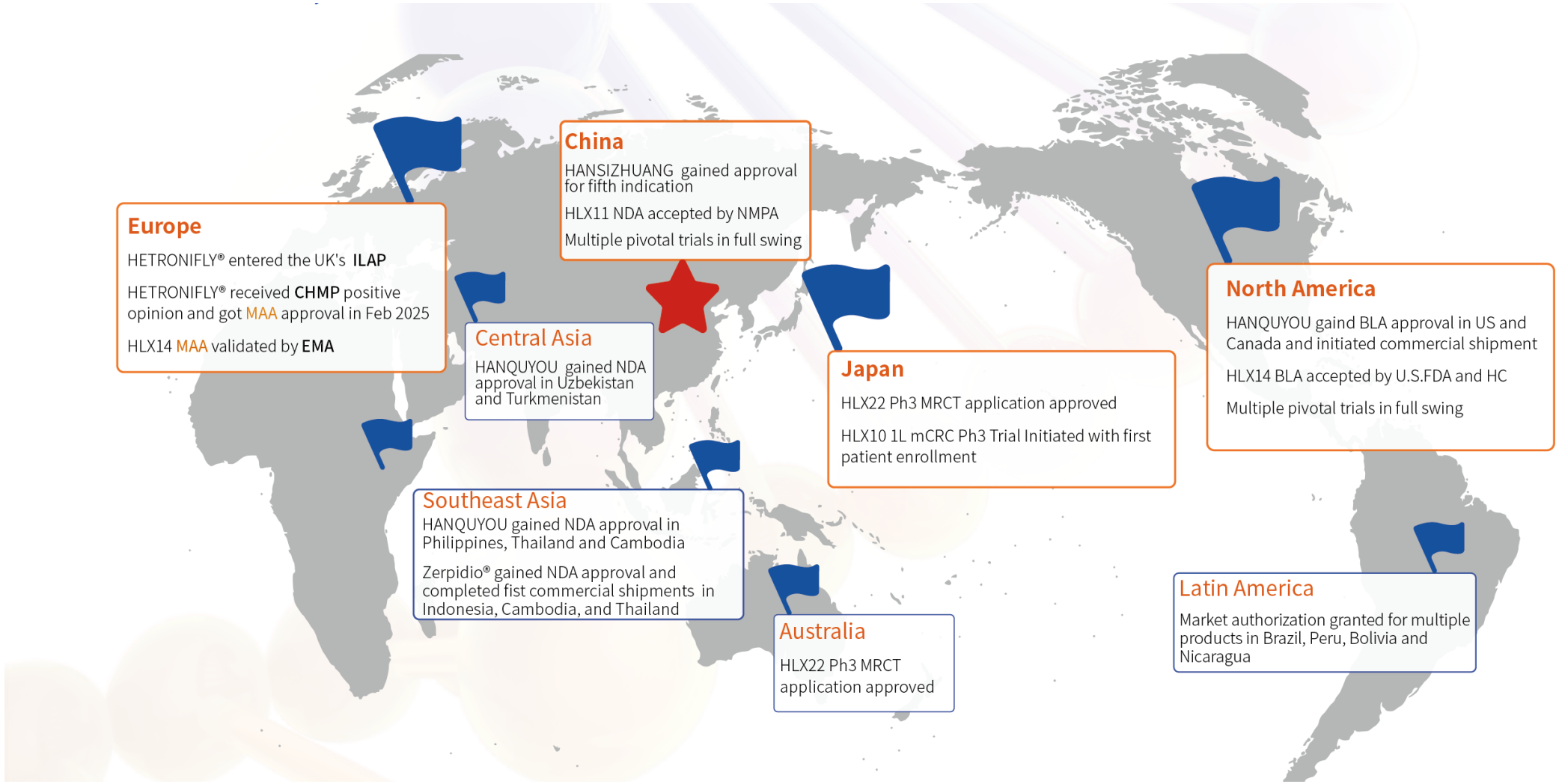




Approval number: GS (2016) 1561
Produced by the Department of Natural Resources

Henlius

2024: New Peaks in Quality and Quantity



Approval number: GS (2016) 1561
Produced by the Department of Natural Resources

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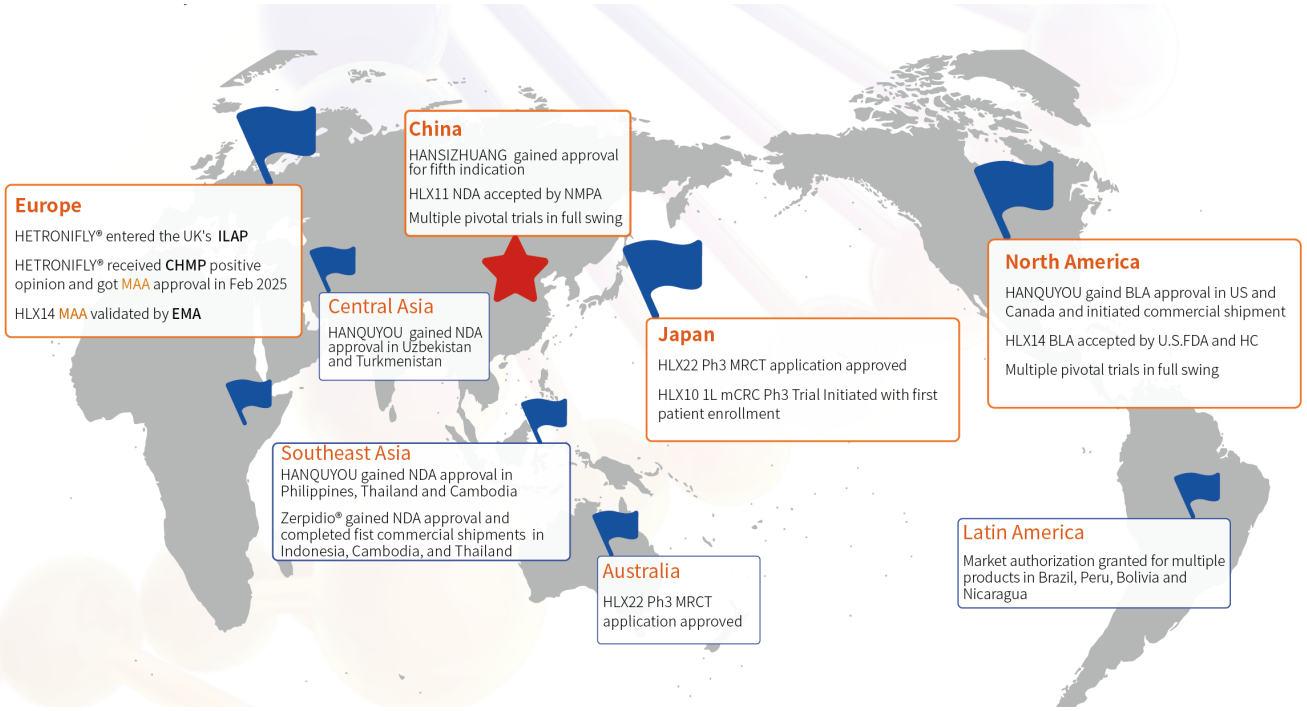
2024: New Peaks in Quality and Quantity



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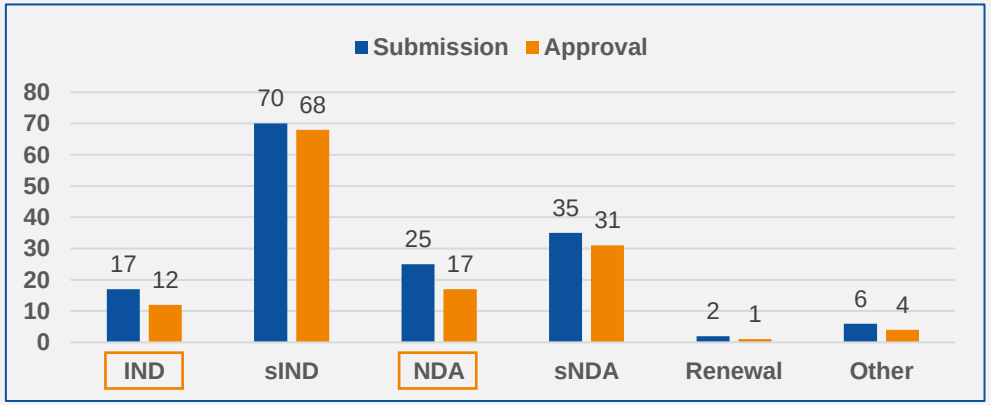

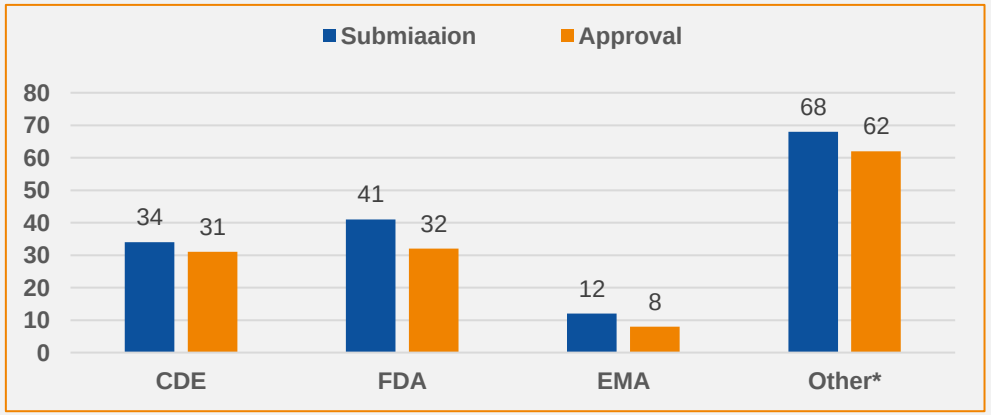

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Drug Innovations
Sustaining Momentum

Biosimilar Breakthrough

Zercepac®

01

2020
Approval

Hetronifly ®

02

2022
ODD Submission

03

2023
MAA Submission

04

2024
ODD Granted

2025 Feb
Approval

05

EU

U.S.A

FDA Inspection

GXP

- Application Rejection
- Warning Letters **&** Market Suspension
- Reputational Damage **&** Financial Losses
- High Remediation Costs

U.S.A

FDA Inspection Review

GMP

HLX02
2023.7.26-8.4

GCP

HLX02
2023.9.5-15
1 site

GMP

HLX02
2023.10.25-27

GCP

HLX02
2024.3.11-15
1 site

GCP

HLX02
2024.1.22-26
2 sites

Henlius 1.0 Summary

From Local Leadership to Global Excellence

Domestic Leadership, Global Coverage

- Unmatched track record, industry-leading submission & approval rates among domestic peers.
- Dual assurance for global expansion: Robust local operations underpin submissions in key global markets

Zero-Failure Benchmark

- Flawless execution in 2024: **Zero submission/approval failures**
- No clinical holds or CRLs due to quality/compliance issues in the U.S. or EU, validating our cross-department synergy.

Quality Culture: End-to-End Integration

- Deep collaboration among manufacturers, clinical and regulatory teams for rapid adaptation to regional technical requirements, forging a **"Core Triad"**
- Global R&D and regulatory teams align efficiently with strict adherence to international standards，driving Henlius' **Competitive Advantage**

02

2.0 Strategic Considerations

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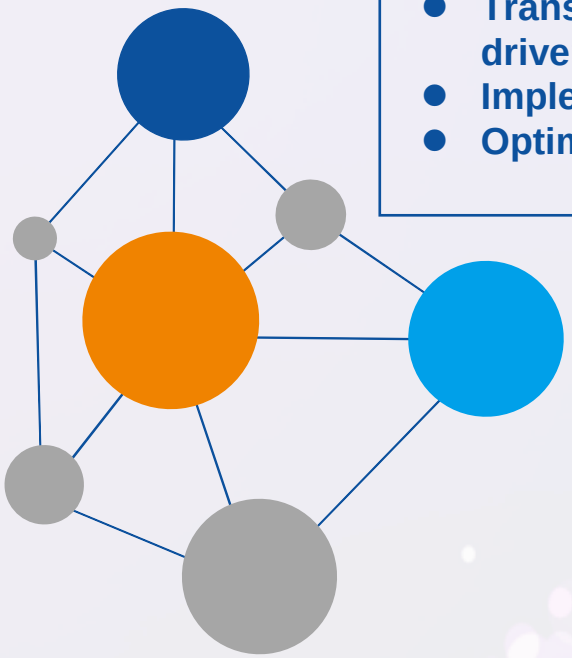
Multi-dimensional Approach to Globalization 2.0

AI Empowerment

- **Develop a database to track real-time regulatory changes across countries.**
- **Transition from manual compliance to AI-driven predictive compliance.**
- **Implement forward-looking pilot projects.**
- **Optimize clinical trial designs.**

Ecosystem Collaboration & Localization

- To address logistics costs and localization needs for overseas supply, regional supply chain hubs are established in markets like Europe and Southeast Asia. Logistics and tariff costs are reduced in regions such as the Middle East and Africa by aligning with their epidemiological profiles.
- Collaborate with multinational pharmaceutical companies to build a global commercialization network, reducing single-market risks and distribution costs while accelerating penetration into emerging markets through technology licensing.



Regionalized Clinical Design

- Indication strategies are customized and tailored to the epidemiological profiles of regions like the Middle East and Africa. For example, HANSIZHUANG (serplulimab) received prioritized approval for small cell lung cancer (SCLC) in Indonesia.
- Specific bridge studies designed in US and JP of HLX 10.These strategy enable Henlius to adapt to diverse regulatory and market environments, reducing global operational risks.

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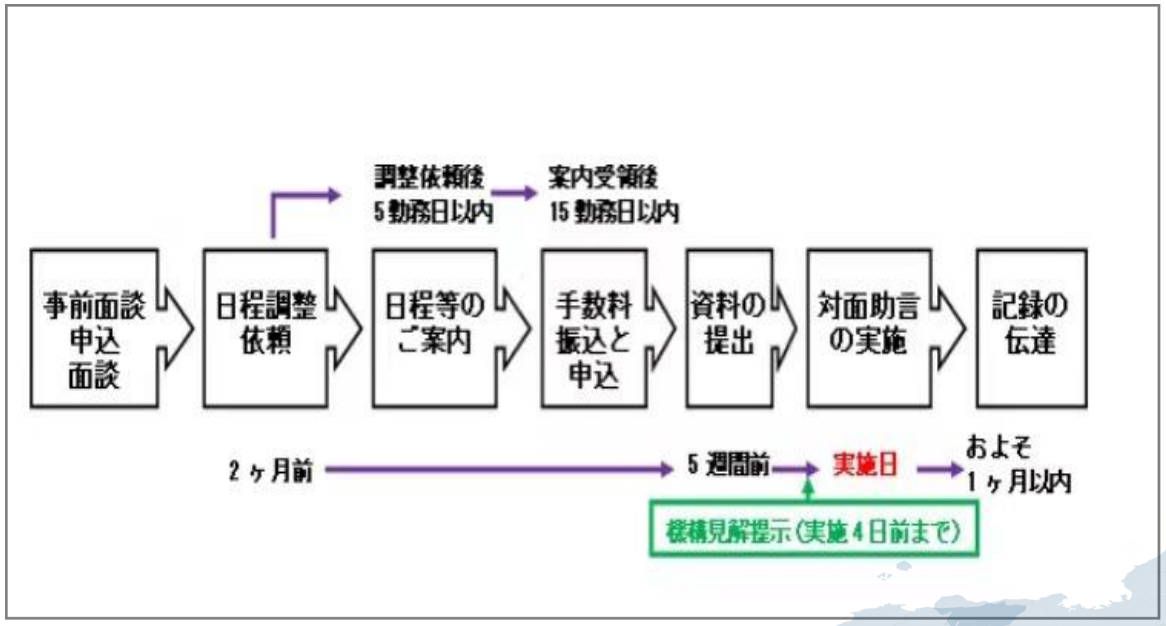
Regulatory Opportunities and Challenges: Entering the Japanese Market



Category	Objective	Consultant	Style	Period from application to consultation	Duration	Fee	Minutes
General Consultation	Introduction of general information on: -Consultation system -Pharmaceutical regulatory system -Related guidelines	Technical Experts	F2F / Online	1 to 3 weeks	20min	Free	Not shared
Pre-consultation meeting	Clarification of discussion points, consultation dossiers	Technical Experts and Reviewers	F2F / Online	2 to 5 weeks	30min	Free	Not shared
Consultation	Scientific discussion	Technical Experts and Reviewers	F2F / Online	2 to 3 months	Max. 2hr	Charged	Shared

Language barriers — **Multinational collaborators** — **Cultural differences** — **Documentation overload & process complexity** — **Regulatory compliance alignment (FDA/EMA)**

Patient population & pharmaceutical market potential

- **International mainstream pharmaceutical regulation**
- **ICH founding members**
- **Patient population & pharmaceutical market potential**
- **High-standard & quality clinical trial management**
- **Comprehensive regulatory framework**

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Aging population and high healthcare benefits in Japan, the world's third-largest pharmaceutical market

Market scale in 2024

$ 61,4 billion

JPY ¥ 9.2 trillion

(USDJPY=150)

3-yr CAGR: 2.7% (Local exchange rate)

The growth rate ranks at the bottom among the top 10 countries in the market, but the prescription volume has increased more than sixfold over 30 years.

Possesses a universal health insurance system based on the National Health Insurance Act, covering all groups, with the government bearing approximately 40% of the costs.

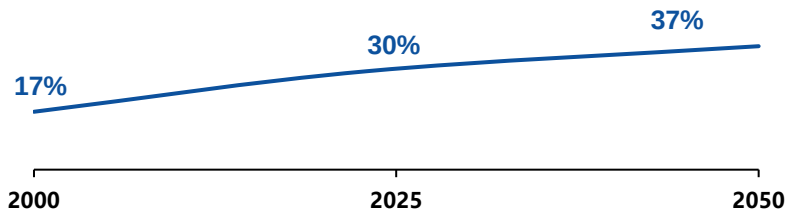
The longevity and aging population drive a substantial demand in the pharmaceutical market

Japan is one of the countries with the highest average life expectancy in the world, as well as one of the most severely aging nations.

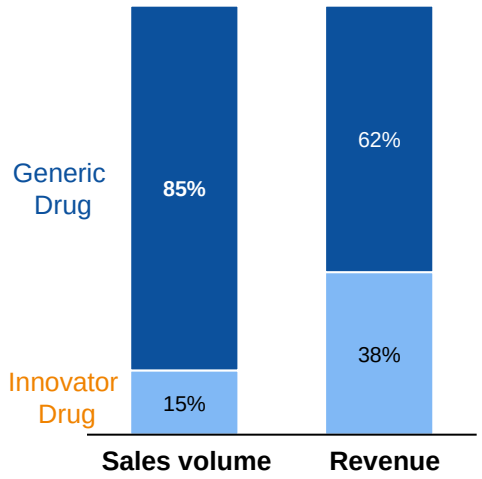
Comparison of Average Life Expectancy in 2023[2] (years)

	Japan	France	Germany	UK	US	China
♂	81.1	80.0	78.3	78.6	74.8	73.6
♀	87.1	85.8	83.8	82.6	80.2	79.4

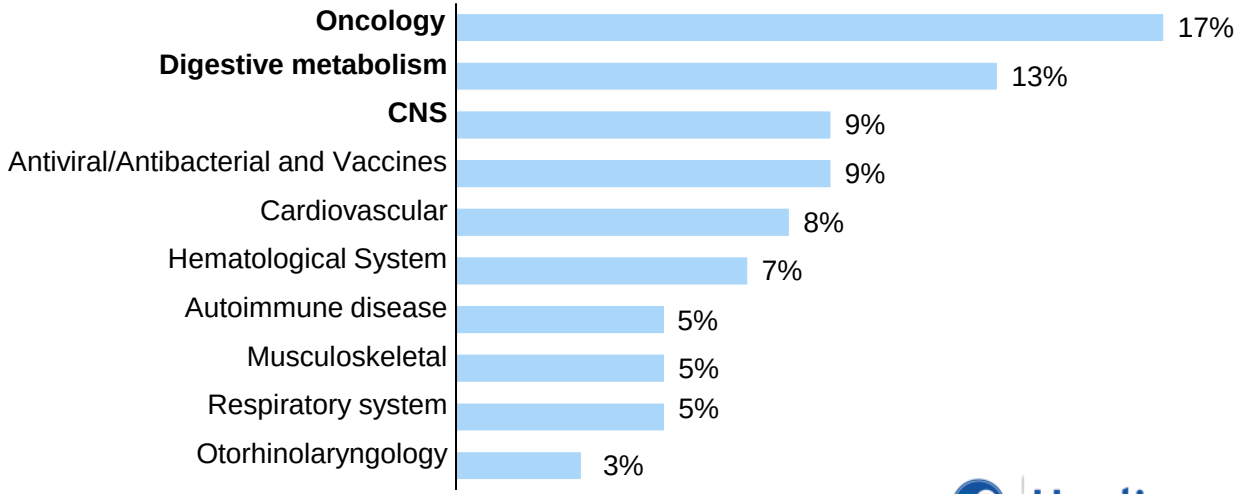
Aging rate[2]



High market share of generic drugs[1]



Leading the market in the fields of oncology and chronic diseases



Data Source: IQVIA MIDAS、Securities Firm Report

- https://www.mhlw.go.jp/content/10808000/001344742.pdf
- https://www8.cao.go.jp/kourei/whitepaper/w-2024/zenbun/pdf/1s1s_01.pdf

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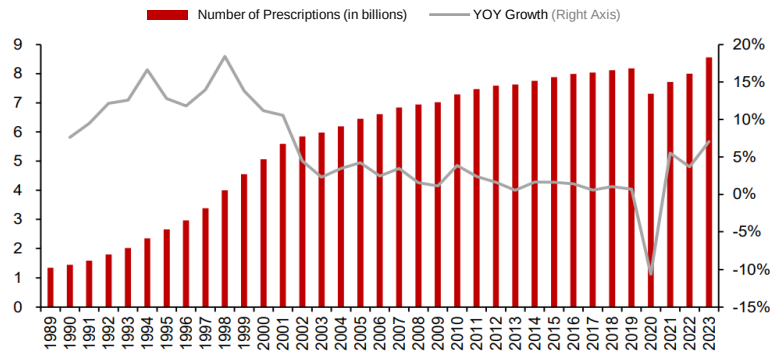
New Opportunities: Supply-Demand Imbalances in Japan's Pharma Market

Continuous Growth in Medical Needs

- The gradual economic recovery and the accelerated aging process are driving the sustained growth in overall medical and pharmaceutical demand in Japan. Market is characterized by long-term insufficiency in allocation of medical resources and the continuous expansion of pharmaceutical demand.

1989-2023 Japan Prescription Volume[1] (Hundred million)

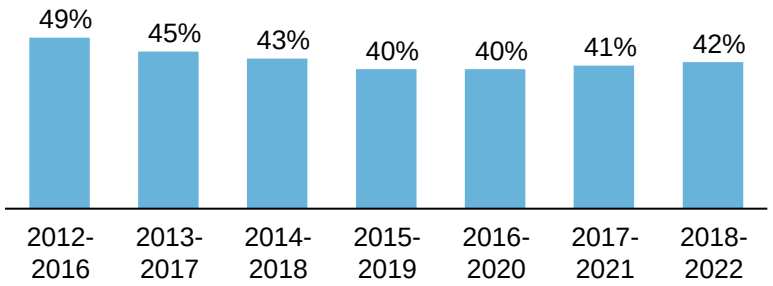


VS.

Insufficient Momentum for Innovative Drugs Development

- Since 2016, Japan's stricter drug pricing and cost control measures led to limitations on drug pricing and profits, affecting companies' willingness for research and development as well as the launch of new products, resulting in a temporary decline in innovative product launches in Japan.

The percentage of new drugs launched in Japan over the past five years in relation to global new drugs[2]



Opportunities in the Japanese Market

High-quality, affordable generic drugs/biosimilars

Rapid market replacement after the exclusivity period of the innovator drug

Innovative drugs targeting unmet needs

Differentiated indications and independent global pricing

- https://www.ewitkey.cn/szyy/show-31127.html
- https://www.phrma-jp.org/wordpress/wp-content/uploads/2024/04/2024-04-03press-conference-slides_eng.pdf

Regulatory Reform in Japan to Address Delays in Innovative Drug Approvals

Delay in the Marketed Authorization of Innovative Drugs in Japan

The proportion of drugs approved by the FDA each year between 2016 and 2022 that were not approved by PMDA within two years.

63~65%

Data source: IQVIA Institute, Oct 2024.

The primary causes of delayed early market entry[1, 2]

High threshold for MAA

MAA in Japan requires clinical data from Japanese patients

Before the release of ICH E5, PMDA hardly accepted overseas clinical data.

Low willingness of enterprises for MAA

Drug price restrictions affect corporate profits, reducing the motivation for development and market launch in Japan

Clinical delay

Early clinical trials did not include the Japanese population; Supplementary Phase I/bridging studies delayed Phase III MRCT

Further reduction in investment returns

The cost of IND in Japan is not low, additional trials increase development costs

To address challenges, Japan is gradually lowering the clinical registration threshold for innovative drugs

Reduction of Phase I/PK clinical trials before MRCT proposed by MHLW in December 2023[1]

- In Phase I clinical trials prior to the initiation of MRCT, it is not mandatory to conduct separate studies based on different races, ethnicities, countries, or regions. Safety evaluations for Japanese trial participants can be conducted using existing data, and, **in principle, additional studies are not required except in necessary circumstances**.
- From the perspective of providing information to medical institutions, if Phase I clinical trials are also global multi-center trials and Japan is involved, it is advisable to **collect as much information as possible regarding the pharmacokinetics (PK) of Japanese individuals**.

The clinical exemption pathway for market approval in Japan

proposed by MHLW in October 2024[2]

- Cases in which **key clinical trials have been appropriately conducted** outside Japan (including cases where interim analyses have been completed, provided that the interim analysis results can be regarded as primary evaluation outcomes).
- Due to the extremely small number of patients, it is difficult to conduct additional clinical trials
- Based on existing efficacy and safety data, the overall benefit for Japanese patients is expected to outweigh the risks

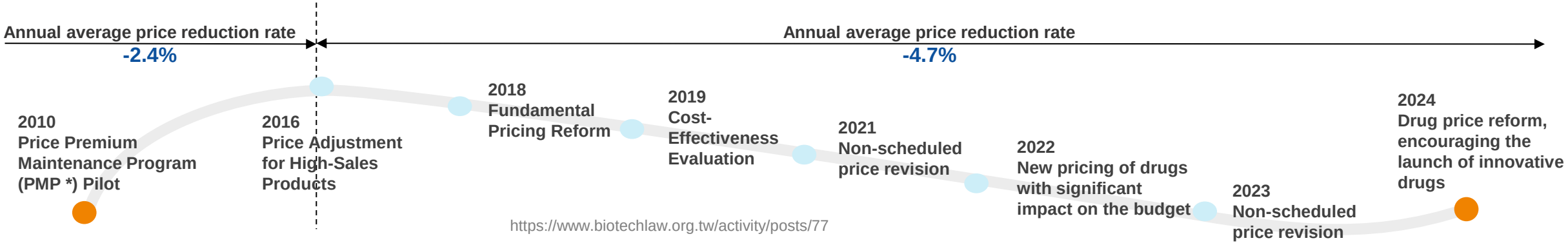
- Positive Ph.3 in US
- Rare disease orphan drugs in Japan
- Topical administration or cell therapy

http://atdd-frm.umin.jp/slide/35/matsukura.pdf
https://www.linical.com/white-papers/regulatory-update-in-japan-new-regulation-allows-nda-filing-without-japanese-data

From Strict Price Control to Encouraging Premiums, Optimized Pricing to Promote New Drug Innovations

Under the universal healthcare system, the listing price of prescription drugs is determined by MHLW , known as the reimbursement price[1]

The drug price reform initiated by MHLW after 2016 significantly suppressed the prices of pharmaceuticals in Japan[2]



https://www.biotechlaw.org.tw/activity/posts/77

2024 Drug Price Reform Focuses on Mechanism Optimization and Encouraging Drug Innovation [3]

Provide a 5-10% premium to enable earlier product launches in Japan

- Japanese clinical trials (global multi-center or standalone Japanese clinical trials) should not be later than other markets
- The Japanese NDA is submitted earlier than in Europe and the US, or the Japanese NDA is applied within 6 months of the European and US NDA
- Products eligible for priority review

Grant premium qualification to products that improve efficacy and meet unmet needs

- Provide additional premiums for products with significant differences in development and manufacturing processes compared to similar drugs, targeting areas lacking new mechanism drugs, refractory diseases and rare diseases, significant improvement in efficacy compared to existing therapies, and notable improvement in secondary endpoints.

Expand the scope of PMP* and exempt certain disease indication extension price adjustments

- The PMP rules have been expanded to include "early-launch products in Japan" and "pediatric drugs"
- Price adjustments accompanying the addition of indications may be exempted in specific disease areas
- Premiums are granted for newly added indications, and additional premiums can also be obtained for other indications

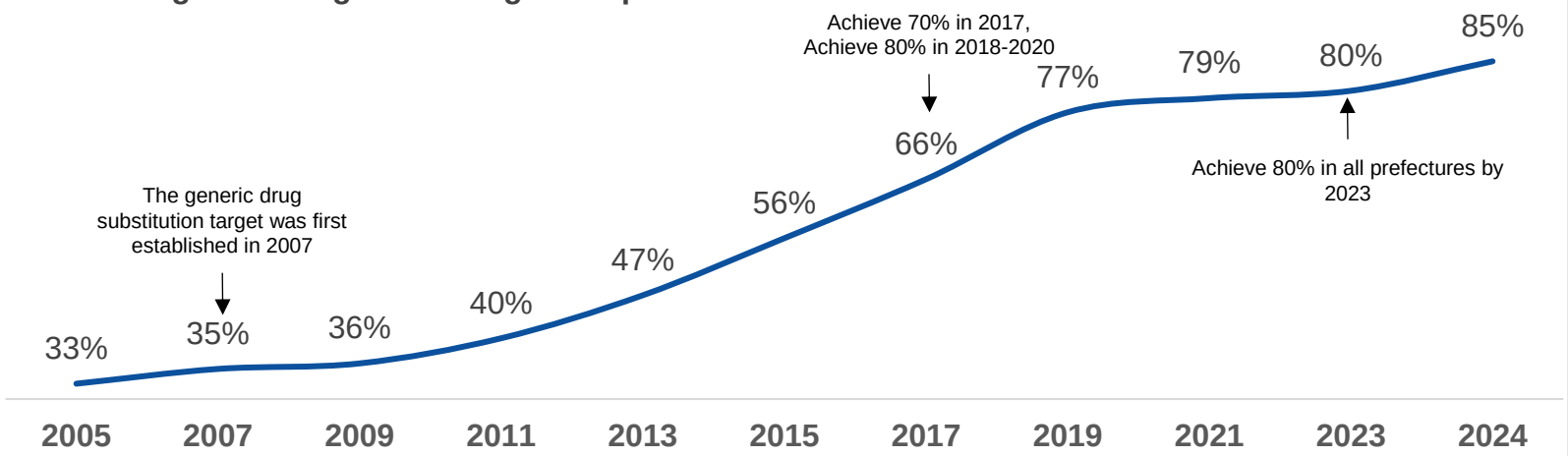
- http://journal.healthpolicy.cn/html/20200411.htm
- https://www.phrma-jp.org/wordpress/wp-content/uploads/2024/04/2024-04-03press-conference-slides_eng.pdf
- Https://www.mhlw.go.jp/stf/shingi2/0000212451_00051.html

Henlius

Set an 80% Generic Drug Substitution Target, Benefiting The Long-term Development of High-quality Generics and Biosimilars

MHLW has set clear generic drug substitution targets since 2007

Actual usage ratio of generic drugs in Japan[1]



Setting 2029 Goals in 2024<Reiwa 6>

- Main Objective: Ensure stable supply of medications while increasing the share of generic drugs to over 80% in all prefectures by the end of fiscal year **2029**.
- Secondary Objective①: By the end of fiscal year 2029, **60%** of biological drug types will achieve an 80% biosimilar substitution rate.
- Secondary Objective②: Increase the market share of generic drugs to over 65% by the end of fiscal year 2029 (currently approximately 62%).

Examples of Initiatives

Implement prescription system reform

- **Pharmacist automatic substitution:** Since 2008, Japan has added a checkbox labeled "Can be substituted with generic drugs" in prescriptions. If the physician does not explicitly check "Do not choose generic drugs," pharmacists are authorized to automatically substitute with generic drugs to encourage their use[2]
- **Encourage the use of generic drugs:** Subsidies and rewards based on the proportion of generic drug usage, incentives for medical institutions to establish a generic drug utilization system, and the formulation of guidelines for medical insurance pharmacists and doctors to guide patients in the use of generic drugs[3]

Enhancing the confidence of patients and healthcare providers in the use of generic drugs[6]

- **Adequate patient education and information disclosure:** Lead by MHLW, the equivalence and cost-effectiveness of generic drugs are promoted through media and medical institutions, gradually changing the public's preference for brand-name drugs.
- **Quality and supply assurance:** Strict consistency evaluation and drug quality supervision, statistical compilation and public disclosure of data related to the generic drug industry for public oversight, and ensuring stable supply of generic drugs through capacity building and platform coordination.

- https://www.mhlw.go.jp/content/001379914.pdf
- https://www.yyjjb.com.cn/yyjjb/201912/201912181712341234_6589.shtml
- https://finance.sina.com.cn/jjxw/2025-01-17/doc-inefhrny3248841.shtml
- https://answers.ten-navi.com/pharmanews/17740/
- https://www.yyjjb.com.cn/yyjjb/202410/20241028160417417_20237.shtml
- https://ewb-c.infocreate.co.jp/ewbc7_pt_pdf.html?siteId=031_mhlw&id=0.4500456063092837#!lang=zh-cn&file=https%3A%2F%2Fwww.mhlw.go.jp%2Fbunya%2Firyou%2Fkouhatu-iyaku%2Fdl%2Froadmap03.pdf

Expansion in Japan: Building Full-Cycle In-House Capabilities from Clinical to Commercialization

- Establishing Henlius Japan Subsidiary: Integrated Full-Cycle Capabilities to Position as the Leading Chinese Biopharma in the Japanese Market
- Advancing Overseas Commercialization Through Core Pipeline-Driven Strategy

Capability Development

- **Product Introduction:** Innovative products including HLX10 (anti-PD-1 mAb) and HLX22 (anti-HER2 mAb) Initiation of Registration
- Preparations for Japan Subsidiary

Action Items:

- Launch: Onboarding of key personnel for Japan entity and partner engagement
- Capability: Leveraging Henlius' pipeline to establish end-to-end regulatory submission capabilities in Japan
- MAH: Implementation of Marketing Authorization Holder frameworks, including pharmacovigilance and quality Release

Business Development

Strategic Focus: Targeting High-Prevalence Malignancies in Japan (Gastric Cancer, NSCLC, Liver Cancer) with HLX10 (anti-PD-1) and HLX22 (anti-HER2)

Action Items:

- Regulatory Capability: Submit HLX10 (PD-1 inhibitor) for PMDA approval
- Commercialization: Build integrated in-house and partner commercialization capabilities to drive the launch of biosimilars and HLX10.
- Explore and pilot optimal commercialization models for Henlius through in-house development or external partnerships.

Global Competencies

- Align with international standards to forge Henlius' global footprint through dual-track pipeline development (self-developed + BD-licensed assets).
- Explore Local Financing and Strategic Partnership Opportunities

Action Items:

- Pursue Operational Excellence: Establish quality management system in line with international standards that cover the entire product lifecycle
- Explore additional collaboration opportunities in the Japanese market, including BD partnerships for innovative pipelines and strategic financing initiatives
- Financing Capability: Secure local financing in Japan through innovative drug pipelines and apply for government funding programs (e.g., METI's R&D subsidies, PMDA orphan drug incentives) to offset clinical trial costs.

Thanks!

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PATIENT CENTRICITY

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Affordable Innovation