Kelun-Biotech (6990 HK)

A trailblazer in ADC arena

BUY (Initiation)

Target Price	**HK$152.26**
Up/Downside	**30.4%**
Current Price	**HK$116.80**

- **Kelun-Biotech, a trailblazer in biotech innovation, boasts a diverse ADC pipeline with strategic backing from MSD.** Leveraging a robust integrated ADC platform, the company has developed several differentiated clinical-stage ADCs - including SKB264 (TROP2 ADC), A166 (HER2 ADC), SKB315 (CLDN18.2 ADC), and SKB410 (Nectin-4 ADC) - and numerous preclinical candidates. This pipeline's potential is underscored by a strategic partnership with MSD, which includes the out-licensing of select ex-China rights for seven ADC assets in deals potentially worth up to US$11.8bn. MSD, also the company's second-largest shareholder with a 6.1% stake, is currently progressing SKB264 through multiple global Ph3 trials, showcasing confidence in Kelun-Biotech's drug development expertise.
- **SKB264 emerges as a potential BIC TROP2-targeting ADC for challenging cancers such as TNBC and HR+/HER2- BC.** Standing out for its efficacy and safety, SKB264 has shown promising results against competitors like Trodelvy and Dato-DXd in later-line treatments. Notably, SKB264 may offer similar or superior performance to Enhertu in HR+/HER2- BC without the associated risk of interstitial lung disease (ILD). Kelun-Biotech had secured a priority review for its BLA submission to the NMPA for 3L+ TNBC as of December 2023.
- **Strategic alliances with MSD are crucial for SKB264's global journey, with ongoing trials for NSCLC, particularly EGFR-TKI resistant cases.** While competitors like Trodelvy and Dato-DXd are still early in clinical development in EGFR-TKI resistant NSCLC, SKB264 is advancing with a Ph3 trial in this setting. SKB264's preliminary results indicate potentially better efficacy compared with other innovative regimens, including sintilimab, AK112, HER3-DXd, amivantamab and others. For the first-line setting, Kelun-Biotech is planning a Ph3 trial of SKB264+A167 for 1L NSCLC in China in 2024, while MSD has already started a global Ph3 trial of SKB264+Keytruda vs Keytruda for 1L PD-L1+ NSCLC patients. Moreover, MSD has initiated a Ph3 trial of SKB264 in pretreated EGFR-mutated nsq-NSCLC and a Ph3 trial in endometrial carcinoma. These advancements are key in positioning SKB264 as a worldwide treatment option.
- **Initiate at BUY with TP of HK$152.26**. We estimate SKB264 to be the major revenue driver of the company. We anticipate SKB264 to commence commercial rollout in China by 2025E for TNBC treatment, followed by HR+/HER2- BC and NSCLC in 2026E. We estimate Kelun-Biotech's total risk-adjusted sales from products and licenses of RMB1,351mn/ RMB1,039mn/ RMB1,079mn, and net losses of RMB337mn/ RMB440mn/ RMB653mn in FY23E/24E/25E, respectively. We expect Kelun-Biotech to turn profitable in FY27E. We derive our TP of HK$152.26 based on a DCF model (WACC: 10.47%, terminal growth rate: 3.0%).

Earnings Summary

(YE 31 Dec, RMB mn)	FY21A	FY22A	FY23E	FY24E	FY25E
Revenue	32	804	1,351	1,039	1,079
YoY growth (%)		2,387	68	(23)	4
Net profit	(890)	(616)	(337)	(440)	(653)
EPS (Reported) (RMB)	(9.62)	(6.45)	(1.54)	(2.01)	(2.98)
R&D expenses	(728)	(846)	(931)	(977)	(1,026)
Admin expenses	(96)	(95)	(160)	(192)	(230)
CAPEX	(94)	(34)	(50)	(200)	(200)

Source: Company data, Bloomberg, CMBIGM estimates

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Stock Data

Mkt Cap (HK$ mn)	25,602.0
Avg 3mths t/o (HK$ mn)	18.3
52w High/Low (HK$)	60.60/115.50
Total Issued Shares (mn)	219.2

Source: FactSet

Shareholding Structure

Kelun Pharma	68.5%
MSD	6.1%

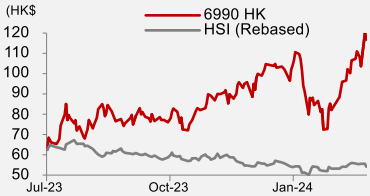
Source: Company data, as of Dec 2022

Share Performance

	Absolute	Relative
1-mth	60.7%	54.2%
3-mth	23.0%	24.3%
6-mth	50.8%	72.2%

Source: FactSet

12-mth Price Performance



Source: FactSet

Auditor:
Web-site: https:// kelun-biotech.com

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Investment thesis

Established in 2016 by Kelun Pharmaceutical (002422 CH), Kelun-Biotech has established an integrated ADC R&D platform and become a market leader in developing ADC therapies, and it has achieved multiple blockbuster deals with MSD (MRK US). The company was listed on the HKEX in Jul 2023.

Differentiated ADC pipelines led by TROP2 ADC

Over the past decade, Kelun-Biotech has honed an advanced ADC platform that integrates a comprehensive toolbox of ADC components, a streamlined process for screening linker-payload combinations, and proprietary linker and conjugation technologies. This platform enables the bespoke engineering of ADCs tailored to specific targets and diseases. Utilizing this sophisticated platform, Kelun-Biotech has generated a portfolio of distinct ADCs in clinical development - SKB264 (TROP2 ADC), A166 (HER2 ADC), SKB315 (CLDN18.2 ADC), and SKB410 (Nectin-4 ADC) - alongside several preclinical ADC candidates.

As one of the three front-runners in the global TROP2 ADC market (the other two being Trodelvy and Dato-DXd), Kelun-Biotech's TROP2 ADC asset **SKB264** is well-positioned to target the hard-to-treat cancers, including TNBC, HR+/HER2- BC, NSCLC and others. In the treatment of later-line TNBC and HR+/HER2- BC - which represent approximately 15% and 60-70% of breast cancer cases, respectively - SKB264 has shown superior efficacy and a distinct safety profile compared to other TROP2-targeting ADCs, such as Trodelvy and Dato-DXd. The therapeutic promise of SKB264 in HR+/HER2- BC is potentially on par with or exceeds that of Enhertu, with the added advantage of not being associated with interstitial lung disease (ILD). In Dec 2023, Kelun Biotech filed for a BLA with the NMPA for SKB264 for third-line or beyond TNBC, receiving priority review status. Additionally, Kelun-Biotech is gearing up to launch a Ph3 trial for SKB264 in first-line TNBC in 1H24, while a Ph3 trial for SKB264 in second-line or beyond HR+/HER2- BC is ongoing since Nov 2023.

Within the NSCLC therapeutic landscape, no TROP2 ADC has yet secured approval. SKB264 stands out amongst its peers with a robust suite of ongoing NSCLC trials, particularly for those with EGFR-TKI resistance. Kelun-Biotech initiated a Ph3 trial for SKB264 in this patient group in Jul 2023, and the early trial results are promising. While other TROP2 ADCs like Trodelvy and Dato-DXd are still in the early stages for EGFR-TKI resistant NSCLC, preliminary data suggests SKB264 could outperform existing innovative treatments such as sintilimab, AK112, HER3-DXd, and amivantamab. However, its efficacy awaits further confirmation in ongoing Ph3 trials both in China and globally. For first-line NSCLC, SKB264 is poised to enter Ph3 trials in 2024, aiming to treat EGFR wild-type patients in China. Concurrently, MSD has started a global Ph3 trial evaluating SKB264 in combination with Keytruda versus Keytruda monotherapy for PD-L1+ NSCLC patients. Additionally, MSD's initiation of multiple international Ph3 trials, including for previously treated non-squamous NSCLC with EGFR mutations and endometrial carcinoma, underscores the value of SKB264. These efforts by MSD are significant steps towards the international recognition and adoption of SKB264.

A166 (HER2 ADC) has met the primary endpoints of its pivotal Ph2 trial for 3L+ advanced HER2+ BC, based on which an NDA had been submitted to the NMPA in May 2023 and a confirmatory Ph3 trial for 2L+ advanced HER2+ BC is ongoing. A166 is poised to be a trailblazer as the first domestically developed HER2-targeting ADC for breast cancer therapy. With its clinical performance in 3L+ HER2-positive breast cancer potentially matching that of DS-8201 and surpassing Aidixi and T-DM1, A166 stands on the cusp of significant market penetration. As a potential frontrunner in the domestic HER2-positive breast cancer space, A166 may carve out a substantial niche within the competitive HER2 ADC arena, in our view.

SKB315 is a CLDN18.2 ADC currently at Ph1 stage of development. Currently there is no CLDN18.2-targeting therapies approved globally. Kelun-Biotech has strategically partnered with MSD, granting them the worldwide rights to SKB315 through a monumental collaboration agreement valued at up to $936mn. This alliance not only encompasses SKB264 and SKB315 but also extends to SKB410 (Nectin-4 ADC) and four other ADC assets in the preclinical phase, showcasing the breadth and potential of Kelun-Biotech's innovative pipeline.

Strategic collaborations with MSD paving the way for globalization

Kelun-Biotech has established extensive alliances with prestigious biopharmaceutical entities both globally and domestically, including MSD, Ellipses, and Harbour BioMed. The clinical prowess of Kelun-Biotech's ADC portfolio, along with its drug development acumen, has been notably recognized through the strategic partnership with MSD. Kelun-Biotech has adeptly out-licensed certain ex-China rights for seven of its ADC assets to MSD, through three landmark deals with cumulative upfront and milestone payments reaching an impressive US$11.8bn. MSD is not only a key strategic partner but also a significant investor, being the second-largest shareholder with approximately 6.1% of Kelun-Biotech's equity as of Jan 2024.

Initiate at BUY with TP of HK$152.26

We anticipate that SKB264 will commence its commercial rollout in China by 2025E for TNBC treatment, followed by HR+/HER2- BC and NSCLC in 2026E, with its growth trajectory in the Chinese market being predominantly propelled by the robust demand for NSCLC therapies. SKB264 is projected to become the company's cornerstone for revenue generation. In international markets, the commercial success of SKB264 is expected to be driven largely by its utilization in NSCLC and HR+/HER2- BC treatments. By 2030E, we forecast that SKB264 will contribute approximately RMB4.3bn in revenues from the China market and an additional RMB1.2bn from global markets, including milestone payments. We estimate Kelun-Biotech's total risk-adjusted sales from products and licenses of RMB1,351mn/RMB1,039mn/ RMB1,079mn in FY23E/24E/25E, respectively. In 2023, considering the upfront payment of around RMB1.2bn from MSD regarding the collaboration on multiple preclinical ADC assets and the relevant income recognition, we expect the company to narrow its net loss to RMB337mn. We expect the company to incur net losses of RMB440mn/ RMB653mn in FY24E/25E, and to turn profitable in FY27E. We derive our target price of HK$152.26 based on a DCF valuation (WACC: 10.47%, terminal growth rate: 3.0%).

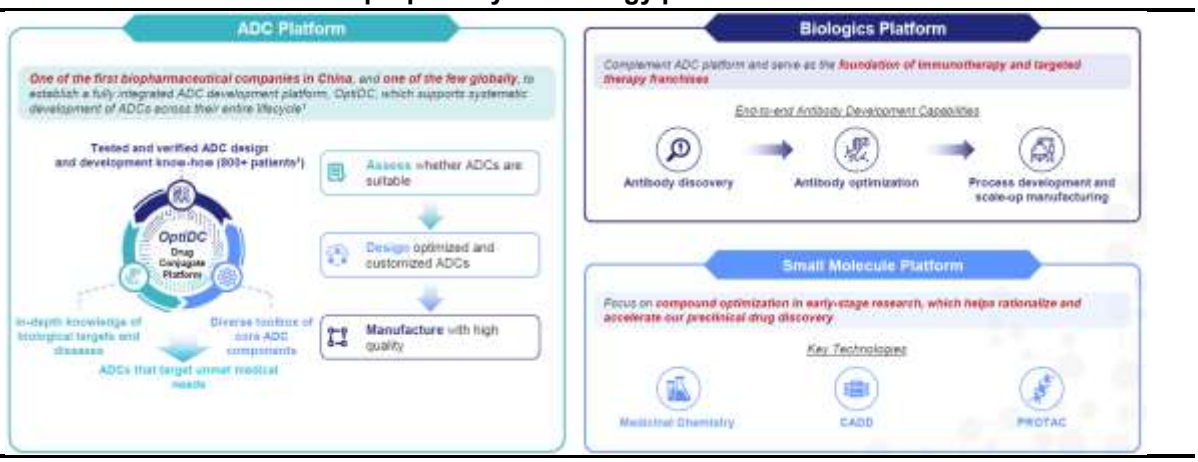
Investment risks

1) Failure of clinical development or regulatory approvals of drug candidates.
2) Competition of approved products both in China and overseas markets.
3) Uncertainties in the collaboration with MSD and other strategic partners.

A leader in ADC development

Since its incorporation in 2016 by Kelun Pharmaceutical (002422 CH), Kelun-Biotech (6990 HK) has established three proprietary technology platforms, covering ADCs, biologics (mAbs and bsAbs) and small molecule drugs, and has become a leader in ADC development. Kelun-Biotech was listed on the HKEX in Jul 2023, and raised net proceeds of HK$1.45bn. It has established a rich pipeline of 33 assets, including 14 in clinical stage. Especially, the company has established an integrated ADC R&D platform and has become a market leader in ADC R&D, and it has achieved multiple blockbuster deals with MSD (MRK US).

Figure 1: Kelun-Biotech's three proprietary technology platforms



Source: Company data, CMBIGM

Figure 2: Kelun-Biotech's ADC pipeline (as of Aug 2023)

Source: Company data, CMBIGM

Figure 3: Kelun-Biotech's non-ADC pipeline (as of Aug 2023)

Source: Company data, CMBIGM

Figure 4: Milestones of Kelun-Biotech

Time	Milestones
2023	NDA of SKB264 for TNBC (3L+) accepted by CDE
2023	Successful listing on the main board of the HKEx
2023	Completed series B financing
2023	Submitted an NDA to the NMPA for A166 for advanced HER2+ BC
2022	Entered into exclusive license and collaboration agreements with MSD including SKB264, SKB315 and 7 preclinical ADC assets
2022	Commenced a pivotal phase 3 trial in China for SKB264 in advanced TNBC patients
2021	Completed series A financing
2021	Commenced a pivotal phase 2 trial in China for A166 to treat HER2+ BC
2021	Entered into a license and collaboration agreement with Ellipses for A400
2021	Submitted an NDA to NMPA for A167 for RM-NPC
2019	Received IND approvals from FDA for initiation of the global phase 1/2 clinical trial of SKB264
2019	Launched pivotal phase 2 clinical trial of A167 for RM-NPC
2018	Two 2,000L single-use bioreactors and 300L ADC conjugation tank were put into operation
2018	Entered into strategic agreement with Harbour Biomed for A167
2017	A167 (PD-L1) received IND approval
2016	Company established

Source: Company data, CMBIGM

Kelun-Biotech's controlling shareholder Kelun Pharmaceutical holds 68.5% of Kelun-Biotech as of 22 Jan 2024. Kelun-Biotech is building up its core internal commercial team focusing on the major oncology hospitals in China. We expect Kelun-Biotech will expand its commercialization infrastructure and market access by leveraging Kelun Pharmaceutical's strong commercial capabilities in China in the near future. Kelun Pharmaceutical is a leading pharmaceutical manufacturer in IV (intravenous) fluids solution products, antibiotics intermediates and finished drugs. In 2022, Kelun Pharmaceutical recorded RMB18.9bn in revenue and RMB1.6bn in attributable profit. Kelun Pharma has established a wide distribution network in China covering oncology and other therapeutic areas, which we think may offer strong synergies with Kelun-Biotech's commercial network in China.

Differentiated ADC pipelines

Kelun-Biotech has developed an integrated ADC platform, OptiDC, which is supported by three pillars of capability, including deep understanding of biological targets and diseases, validated ADC design and development expertise, and a toolbox of ADC core components. Through over a decade of development, the company has developed a toolbox of core ADC components, a smooth workflow to screen linker-payload combinations, and a set of proprietary linker and conjugation technologies, which offer versatility to engineer customized ADCs optimized for different targets and indications. Based on the platform, the company has developed differentiated ADC pipelines, including SKB264 (TROP2 ADC), A166 (HER2 ADC), SKB315 (CLDN18.2 ADC), and SKB410 (Nectin-4 ADC) at clinical stage, as well as a couple of ADC molecules at preclinical stage.

The clinical value of Kelun-Biotech's ADC pipeline and its drug development capabilities are endorsed by its strategic partnership with MSD. The company has successfully out-licensed certain ex-China rights of its seven ADC assets to MSD through three blockbuster deals with the upfront and milestone payments totaling up to US$11.8bn. As a major strategic collaborator, MSD is also the company's second-largest shareholder, holding around 6.1% of the company as of Jan 2024.

As one of the three front-runners in the global TROP2 ADC market, Kelun-Biotech's TROP2 ADC asset **SKB264** is well-positioned to target the hard-to-treat cancers, including TNBC, HR+/HER2- BC, NSCLC and others. For later-line TNBC and HR+/HER2- BC (accounting for around 15% and 60-70% of total BC patients, respectively), SKB264 demonstrated better efficacy and differentiated safety profile in cross-trial compared with other TROP2 ADCs (Trodelvy and Dato-DXd). SKB264's potential in HR+/HER2- BC could be comparable or better than Enhertu, while SKB264 may not lead to Interstitial Lung Disease (ILD). Kelun-Biotech filed BLA of SKB264 to the NMPA for 3L+ TNBC in Dec 2023 with priority review granted by the NMPA. It also plans to initiate a Ph3 trial of SKB264 in first-line TNBC in 1H24, and a Ph3 trial of SKB264 in 2L+ HR+/HER2- BC is ongoing since Nov 2023.

For NSCLC, no TROP2 ADC drug has been approved so far. SKB264 is differentiated from other competitors with a series of clinical trials in NSCLC ongoing, especially in EGFR-TKI resistant NSCLC. Kelun-Biotech is conducting a Ph3 study of SKB264 in EGFR-TKI resistant NSCLC patients with FPI in Jul 2023, and promising early trial results in this setting has been released. Other TROP2 ADCs (Trodelvy and Dato-DXd) are still in early clinical stage for EGFR-TKI resistant NSCLC. SKB264's preliminary results in this treatment setting indicate potentially better efficacy compared with other innovative regimens, including sintilimab, AK112, HER3-DXd, amivantamab and others, even though the efficacy needs to be further validated in the ongoing Ph3 trials in China and globally. For 1L NSCLC indication, the TROP2 ADC competitors Trodelvy and Dato-DXd both have Ph3 trials ongoing. The Company is planning to start Ph3 trials of SKB264+A167 in EGFR wild-type NSCLC in China in 2024, while MSD has started a Ph3 trial of SKB264+Keytruda vs Keytruda for 1L PD-L1+ NSCLC patients in late 2023. In the overseas market, MSD has started multiple global Ph3 trials of SKB264 including 1L PD-L1+ NSCLC (combo Keytruda vs Keytruda mono), previously treated nsq-NSCLC with EGFR mutations, and endometrial carcinoma, which in our view, indicates the importance of SKB264 valued by MSD and will pave the way for the globalization of SKB264.

A166 (HER2 ADC) has met the primary endpoints of its pivotal Ph2 trial for 3L+ advanced HER2+ BC, based on which an NDA had been submitted to the NMPA in May 2023 and a confirmatory Ph3 trial for 2L+ advanced HER2+ BC is ongoing. A166 has the potential to become the first domestic HER2 ADC drug approved for breast cancer treatment. A166's efficacy in treating 3L+ HER2-positive BC could be comparable to DS-8201 and potentially better than Aidixi and T-DM1. As a potential domestic first mover in HER2-positive BC, we expect A166 to gain a meaningful share in the crowded HER2 ADC market.

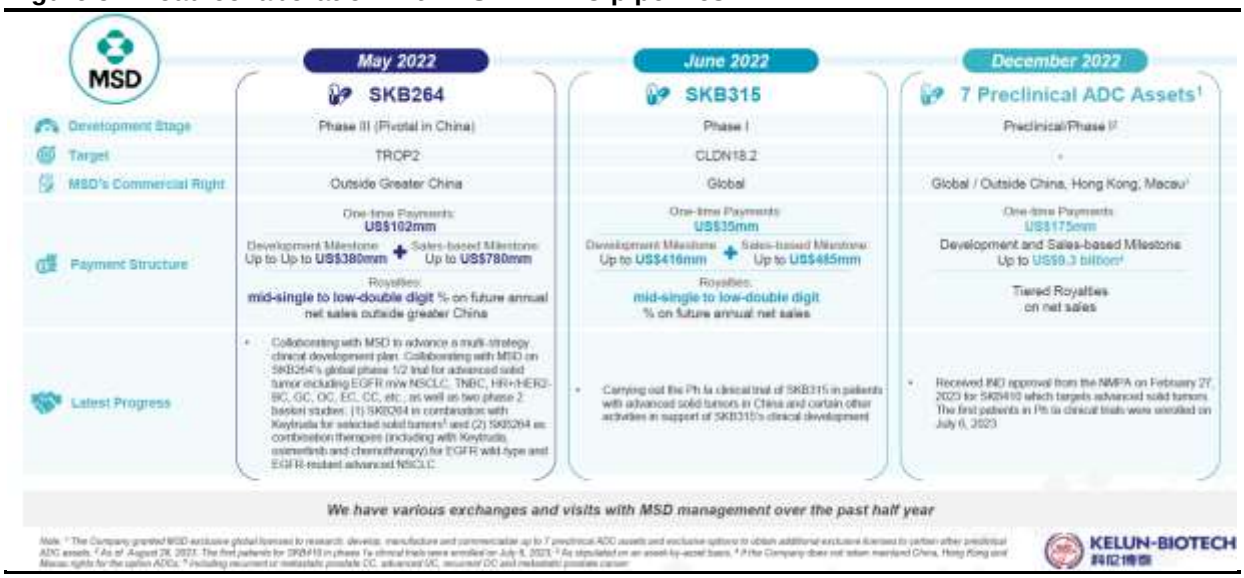
SKB315 is a CLDN18.2 ADC currently at Ph1 stage of development. Currently there is no CLDN18.2-targeting therapies approved globally. Kelun-Biotech has out-licensed the global rights of SKB315 to MSD through a blockbuster collaboration deal with the deal size up to US$936mn. Besides SKB264 and SKB315, MSD is also collaborating with Kelun-Biotech on SKB410 (Nectin-4 ADC) and other four preclinical-stage ADC assets.

Out-licensing collaborations to pave the way for globalization

Kelun-Biotech has forged broad collaborations with global and domestic biopharma companies, including MSD, Ellipses, and Harbour BioMed. Especially, the company entered into three license and collaboration agreements with MSD in 2022 to develop up to nine ADC assets for cancer treatment, including three assets which have proceeded to clinical stage (SKB264/MK-2870, SKB315/MK-1200 and SKB410/MK-3120), and up to six preclinical ADC assets. The upfront payment of these three agreements totaled US$247mn, and the total milestone payment could reach US$11.6bn. The three consecutive out-licensing of ADC assets to MSD and the blockbuster deal size proved Kelun-Biotech's strong R&D capabilities in ADC drugs.

In Oct 2023, MSD terminated the collaboration with Kelun-Biotech on two undisclosed preclinical ADC assets. We think part of the reasons could be related to MSD's collaboration with Daiichi Sankyo in Oct 2023 on three ADC assets, targeting HER3, B7-H3 and CDH6 (patritumab deruxtecan, ifinatamab deruxtecan and raludotatug deruxtecan). However, the collaborations of SKB264, SKB315, SKB410 and the other four preclinical ADC assets have progressed smoothly.

Figure 5: Broad collaboration with MSD in ADC pipelines



Source: Company data, CMBIGM.
Note: for the 7 preclinical ADC assets entered into collaboration with MSD in Dec 2022, SKB410 (Nectin-4 ADC) has entered Ph1 study, and MSD has terminated the collaboration on two undisclosed preclinical ADC assets.

Figure 6: License and collaborations of Kelun-Biotech

Type	Asset	Partner	Date	Upfront payment	Milestone payment	Royalty	Rights	Notes
Out license	SKB264 (TROP2 ADC)	MSD	May 2022	US$47mn	Up to US$1.36bn	Tiered royalties	Ex-China	
Out license	SKB315 (Claudin18.2 ADC)	MSD	Jul 2022	US$35mn	Up to US$901mn	Tiered royalties	Ex-China	
Out license	Up to seven preclinical ADC	MSD	Dec 2022	US$175mn	Up to US$9.3bn	Tiered royalties	Ex-China	Collaboration on two asses has terminated; SKB410 has entered clinical stage to date
Out license	A400 (RET inhibitor)	Ellipses	Mar 2021	US$3.22mn (preclinical development, tech transfer fee)		Tiered royalties as low-teen percentages	All countries excluding China, North Korea, South Korea, Singapore, Malaysia and Thailand	
Out license	A167 (PD-L1 mAb)	Harbour BioMed	Aug 2018	US$6mn	Up to US$351mn	Tiered royalties as a high single-digit to low double-digit	Ex-China	
Co-develop	SKB378 (TSLP mAb)	Harbour BioMed	May 2019	--	--	--		Clinical trials in China, North America and certain APAC countries led by Harbour BioMed. SKB leads the marketing approvals in China and EU. Harbour BioMed leads the marketing approvals in North America and ex-China APAC countries
In license	A166 (HER2 ADC)	Levena	Mar 2014	License fees up to RMB9.5mn		To pay Levena low single-digit royalties for 10 years	Global	SKB takes a leading role in the R&D, manufacturing and commercialization of A166.
In license	TBM-001 (radionuclide-drug conjugate, RDC drug)	Affiliated Hospital of SMU	Sep 2023	RMB38.5mn (upfront, milestone)		Royalties	Global	

Source: Company data, CMBIGM

SKB264 (TROP2 ADC), a global front-runner with BIC potential

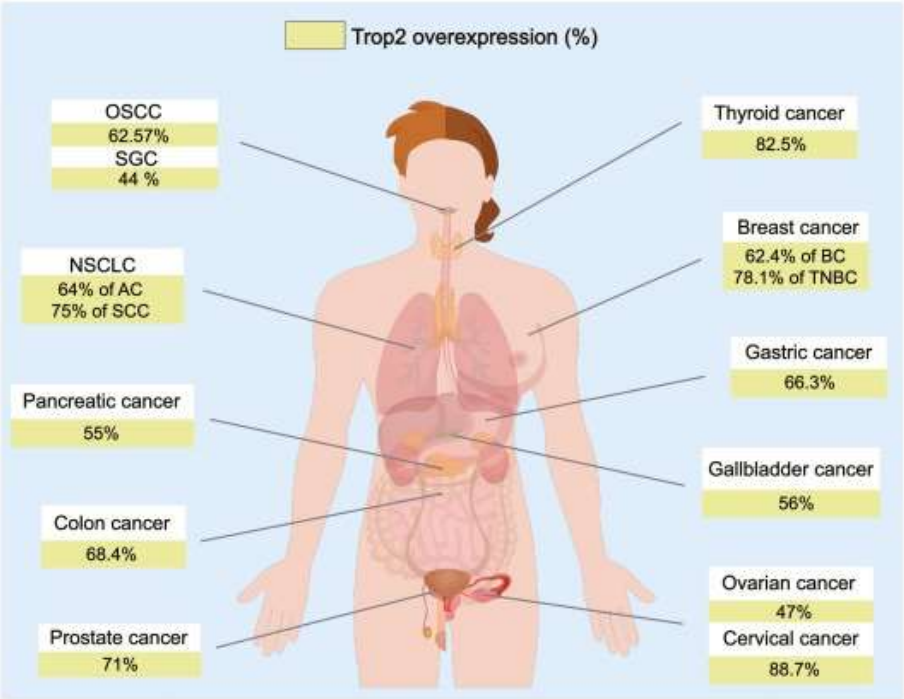
Differentiated design of SKB264

TROP2 is a transmembrane glycoprotein and calcium signal transducer with limited expression in normal human tissues. It is consistently overexpressed in a variety of malignant tumors and participates in several oncogenic signaling pathways that lead to tumor development, invasion, and metastasis. As a result, TROP2 has become an attractive therapeutic target in cancer treatment. The globally first anti-Trop2 antibody-drug conjugate (Trodelvy, sacituzumab govitecan) developed by Gilead (GILD US) has been approved by the US FDA for treatment of metastatic triple-negative breast cancer (TNBC), HR+/HER2-BC and mUC.

Trodelvy, Dato-DXd and SKB264 are global front-runners of TROP2 ADCs. Gilead's Trodelvy is currently the only FDA-approved TROP2 ADC, while AZ/Daiichi Sankyo's Dato-DXd and MSD/Kelun-Biotech's SKB264 are TROP2 ADCs in late-stage of clinical development, both focusing on TNBC, HR+/HER2- BC, NSCLC and other indications.

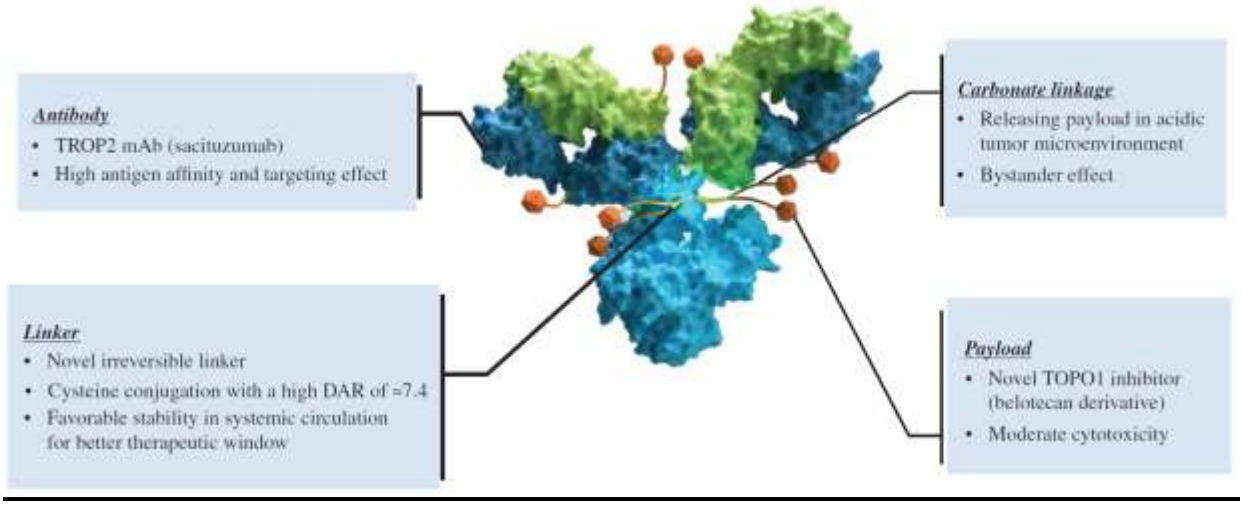
Kelun-Biotech is developing SKB264 for the treatment of BC, NSCLC and other cancers, as a later-line monotherapy and part of early-line combination therapies. SKB264 is positioned to be the first domestically developed TROP2 ADC in China.

Figure 7: TROP2 overexpression in multiple tumors



Source: ScienceDirect, CMBIGM

Figure 8: Structure of SKB264



Source: Company data, CMBIGM

SKB264 features a moderate payload toxicity-high DAR design, in which KL610023, a belotecan-derivative topoisomerase I (TOPO1) inhibitor with moderate cytotoxicity, is conjugated at a high DAR to sacituzumab, a clinically proven TROP2 mAb. The company's proprietary drug-linker strategy, Kthiol, is used to improve ADC stability and reduce off-target and on-target off-tumor toxicity. The use of a novel carbonate linkage, which connects the antibody and payload, exploits the acidic tumor microenvironment to selectively release cytotoxic payloads in tumor tissues, thereby facilitating internalization of payloads by tumor cells and subsequent intracellular tumor killing, as well as bystander killing when payloads permeate out of ADC-targeted cells and diffuse into neighboring tumor cells.

Figure 9: Design of TROP2 ADCs (SKB264, Trodelvy and Dato-DXd)

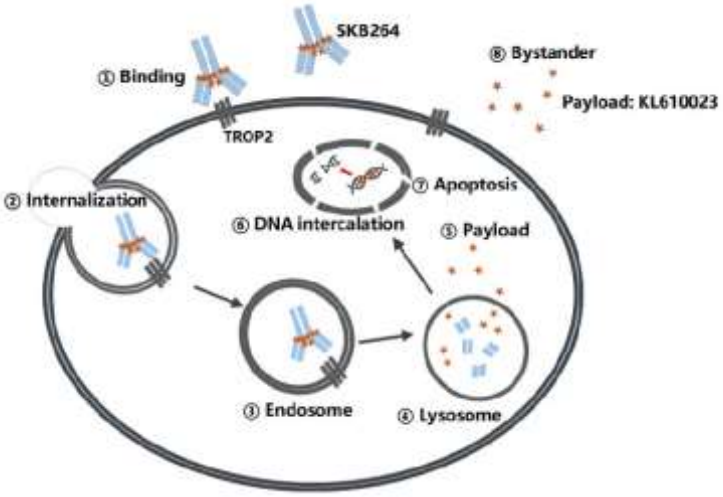
	SKB264	Trodelvy	Dato-DXd
Antibody	Sacituzumab	Sacituzumab	Datopotamab
Linker	2-methylsulfonyl pyrimidine containing CL2A linker	Maleimide containing CL2A linker	GGFG linker
Half-life	36 hrs	11-14 hrs	110 hrs
Payload	KL610023, a belotecan derivative	SN-38, a watersoluble metabolite of irinotecan	Deruxtecan, an Exatecan derivative
Payload Topo I inhibition (IC50)	Moderate (0.7 μmol/L)	Moderate (1.1-2.78 μmol/L)	High (0.31 μmol/L)
Conjugation	Irreversible site-specific methylsulfonyl pyrimidine-thiol conjugation	Reversible site-specific maleimide-thiol conjugation	Reversible sites-elective maleimide-thiol conjugation
Overall DAR	7.4	7.6	4
Bystander effect	Yes	Yes	Yes
Major differentiation of SKB264 vs Trodelvy/Dato-DXd		Compared to Trodelvy, SKB264 has improved plasma stability due to irreversible linker mAb conjugation and differentiated payload structure, preventing the payload from falling off easily from the ADC in circulation	Compared to Dato-DXd, SKB264 has favorable ADC hydrophilicity even at a higher DAR value due to the more hydrophilic CL2A linker; SKB264 also has minimal risk of ILD toxicity associated with KL610023

Source: Company data, CMBIGM.

SKB264 has differentiated molecule design compared to other late-stage TROP2 ADC drug or drug candidates. For instance, compared with Trodelvy, SKB264's improved plasma stability due to irreversible linker mAb conjugation and differentiated payload structure, are able to prevent the payload from falling off easily from the ADC in circulation, potentially leading to an improved safety profile. Compared to Dato-DXd, SKB264's demonstrated minimal risk of interstitial lung disease (ILD) toxicity associated with its payload KL610023. We think the three TROP2 ADCs are designed very differently, implying potentially variant clinical performance – a) Trodelvy having moderately potent payload and moderately stable linker;

b) SKB264 having slightly more potent payload and slightly more stable linker than Trodelvy; and c) Dato-DXd having potent payload and highly stable linker.

Figure 10: MoA of SKB264



Source: Company data, CMBIGM

Mechanistically, the TROP2 mAb (sacituzumab) directs SKB264 to TROP2-expressing tumor cells. The acid-cleavable linker then exploits the acidic pH to release the payload (KL610023) both intracellularly once it is internalized by the tumor cells and extracellularly to the tumor microenvironment. The high membrane permeability of KL610023 allows KL610023 to permeate into bystander cells to which SKB264 has not bound, regardless of their TROP2 expression status. Intracellularly, KL610023 inserts itself into the DNA structure, and inhibits TOPO1, an enzyme essential to DNA replication. Inhibition of TOPO1 leads to DNA damage during the replication process, causing apoptosis. SKB264 elicits both targeted killing in TROP2-expressing tumor cells and bystander killing in TROP2-negative tumor cells, which helps overcome heterogeneity in tumors where there is uneven expression of TROP2.

Broad global market potential of TROP2 ADCs

Trodelvy, Dato-DXd and SKB264 are globally three TROP2 ADC front-runners, all of which focus on TNBC, HR+/HER2- BC and NSCLC. Trodelvy, as the global first TROP2 ADC drug, has been approved by the US FDA for the treatment of metastatic TNBC, HR+/HER2- BC and mUC. Gilead is also exploring Trodelvy's potential in NSCLC and other solid tumors. SKB264 and Dato-DXd are globally the only two TROP2 ADCs in Ph3 studies, followed by SHR-A1921 in Ph2/3 trial.

Figure 11: Targeted indications of TROP2 ADCs (SKB264, Trodelvy and Dato-DXd)

Drug or drug candidate	Major targeted indications	Approved indications
SKB264	TNBC (3L+ mono, 1L combo), HR+/HER2- BC (2L+ mono), NSCLC (2L+ mono EGFR-TKI resistant, 1L combo)	-
Trodelvy	TNBC (3L+ mono), HR+/HER2- BC (3L+ mono), NSCLC (1L combination)	China: TNBC (3L+) The US: TNBC (3L+), HR+/HER2- BC (3L+), UC (post PD-(L)1+chemo)
Dato-DXd	TNBC (1L mono), HR+/HER2- BC (2L+ mono), NSCLC (2L+ mono); and 1L combo for BC and NSCLC	-

Source: Company data, CMBIGM.

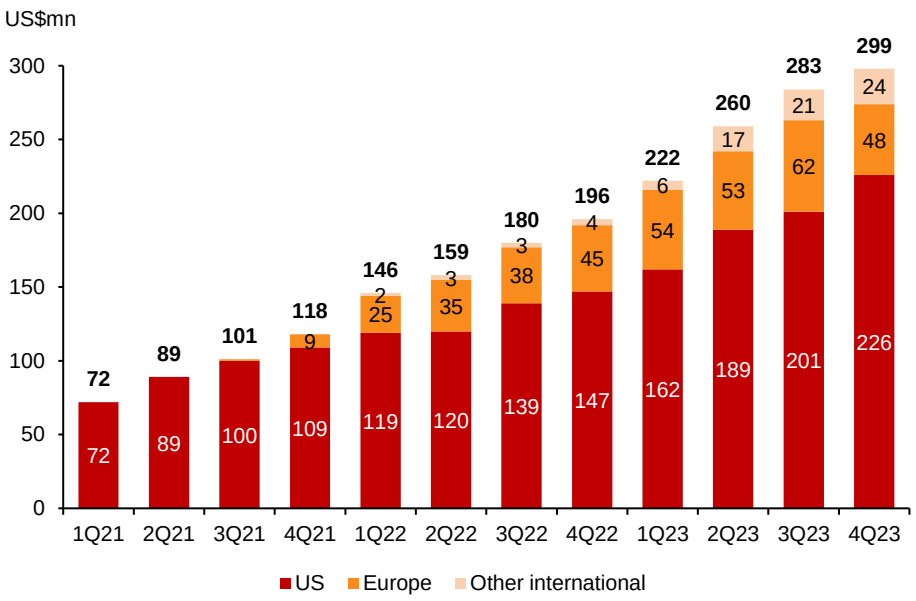
Figure 12: Global development landscape of TROP2 ADCs

Drug Name	Company	Latest China stage	Latest overseas stage
Trodelvy	Gilead	Approved	Approved
Dato-DXd	Daiichi Sankyo, AstraZeneca	Phase III	NDA filed
SKB264	MSD, Kelun-biotech	NDA filed	Phase III
SHR-A1921	Hengrui Medicine	Phase II/III	Phase I
9MW2921	Mabwell Bioscience	Phase I/II	Preclinical
BIO-106	BiOneCure Therapeutics	Preclinical	Phase I/II
BL-M02D1	Systimmune	Phase I/II	Preclinical
DB-1305	BioNTech, DualityBio	Phase I/II	Phase I/II
ESG401	Escugen, Levena Biopharma	Phase I/II	Preclinical
HS-20105	Hansoh Pharmaceutical	Phase I	Preclinical
IBI130	Innovent Biologics	IND	Phase I/II
LCB84	Mediterranea, J&J, Orion	Preclinical	Phase I/II
MHB036C	Minghui Pharmaceutical	Phase I/II	Phase I/II
BAT8003	Bio-Thera Solutions, Insud Pharma	Phase I	Preclinical
BAT8008	Bio-Thera Solutions	Phase I	Preclinical
DAC-002	DAC Biotech, Junshi Biosciences	Phase I	Preclinical
FDA018	Fudan-Zhangjiang	Phase I	Preclinical
FZ-AD004	Fudan-Zhangjiang	Phase I	Preclinical
PF-06664178	Pfizer	Preclinical	Phase I

Source: Pharmcube, CMBIGM.
Note: as of Mar 2024

Trodelvy has been approved by the US FDA for treatment of 1) 3L mTNBC, 2) HR+/HER2- BC post endocrine-based therapy and at least two additional systemic therapies, and 3) mUC post a platinum-containing chemotherapy and PD-1/PD-L1 inhibitor. Trodelvy has received NCCN Category 1 recommendation for both 2L mTNBC and pre-treated HR+/HER2- mBC. Trodelvy's global sales reached US$1.06bn (+56% YoY) in FY23, thanks to increased uptake in pre-treated HR+/HER2- mBC. However, Trodelvy carried boxed warning from the US FDA for risks of severe neutropenia and severe diarrhea.

Figure 13: Quarterly sales of Trodelvy



Source: Gilead data, CMBIGM.

Trodelvy was approved by the NMPA in Jun 2022 for treatment of 3L+ TNBC and has not been included in China's NRDL yet. The treatment cost of Trodelvy in China was approximately RMB96,000 per month, if not considering PAP price discount.

Figure 14: Treatment costs of Trodelvy

Drug name	Regions	Indications	Approval date	Unit cost	Monthly cost estimate	China NRDL
Trodelvy	US	TNBC (3L+)	Apr 2020	US$2,479/ 180mg	US$28,331 (assuming 65kg patient weight)	-
		UC (post PD-(L)1+chemo)	Apr 2021			
		HR+/HER2- BC (3L+)	Feb 2023			
	China	TNBC (3L+)	Jun 2022	RMB8,400/ 180mg	RMB96,000 (assuming 65kg patient weight)	N (failed the NRDL negotiation in late 2023)

Source: Company data, CMBIGM

Kelun-Biotech out-licensed the outside Greater China right of SKB264 to MSD in May 2022, together with other TROP2 ADC candidates the company may develop in the future. Kelun-Biotech is eligible to receive four one-time payments totaling up to US$102mn, including US$47mn upfront payment. MSD agrees to make quarterly payments in connection with SKB264's ongoing R&D activities. Kelun-Biotech is eligible to receive additional US$380mn development milestone payments and US$780mn sales milestone payments, as well as tiered royalties ranging from mid-single-digit to low-double-digit percentage on future annual net sales of SKB264 outside the Greater China.

SKB264 has received 4 BTDs from the NMPA, including for the treatment of (1) locally advanced or metastatic TNBC, (2) locally advanced or metastatic EGFR-mutated NSCLC which has failed EGFR-TKI therapy, (3) the treatment of locally advanced or metastatic HR+/HER2- BC which has received at least second-line systemic therapy, and (4) newly diagnosed unresectable PD-L1 negative TNBC.

TNBC accounts for around 15% of BC patients and has limited treatment options. Based on the results of the pivotal Ph3 trial of SKB264 in advanced TNBC (3L+), Kelun-Biotech has submitted an NDA to the NMPA in Dec 2023 with priority review status granted by the NMPA. In addition, Kelun-Biotech aims to move SKB264 to front-line treatment with a Ph2 trial assessing SKB264 with or without A167 for 1L TNBC ongoing, and plans to initiate a Ph3 trial in 1L TNBC in 1H24.

HR+/HER2- BC accounts for around 60-70% of all newly diagnosed BC. The company is advancing the global Ph1/2 dose expansion study of SKB264 in advanced HR+/HER2- BC (2L+). A Ph3 study of SKB264 in HR+/HER2- BC is enrolling since Nov 2023.

No TROP2 ADC drug has been approved for treatment of NSCLC so far. Differentiated from other late-stage TROP2 ADCs, SKB264 has started a series of clinical trials in NSCLC, especially for EGFR-TKI resistant NSCLC. A pivotal Ph3 trial (NCT05870319) of SKB264 in 2L+ EGFR-mutant advanced NSCLC patients who have failed EGFR-TKI therapy is ongoing with FPI in Jul 2023. Additionally, SKB264 is also being evaluated in EGFR wild type NSCLC, including a Ph2 trial of SKB264 + A167 +/- chemotherapy for 1L EGFR-wild type advanced NSCLC, and a global Ph1/2 trial for EGFR-wild type and EGFR-mutant advanced NSCLC. In collaboration with MSD, Kelun-Biotech is conducting a Ph2 basket study of SKB264 as combination therapies (combined with Keytruda, osimertinib, chemo) for EGFR wild type and EGFR-mutant advanced NSCLC in China. Kelun-Biotech is also planning to start Ph3 studies of SKB264 in combination with A167 in 1L NSCLC in China in 2024.

With the ex-China rights out-licensed to MSD, MSD is conducting multiple Ph3 trials of SKB264 in the overseas market. MSD has started several Ph3 studies in late 2023, including 1) a Ph3 MRCT of SKB264 in previously treated nsq-NSCLC with EGFR mutations or other genomic alterations (NCT06074588) with PFS and OS as dual primary endpoints, 2) a Ph3 trial of SKB264 in endometrial carcinoma (NCT06132958) with PFS and OS as dual primary endpoints, and 3) a Ph3 trial of SKB264+Keytruda vs Keytruda mono in 1L PD-L1 TPS ⩾50% NSCLC (NCT06170788) with OS superiority as primary endpoint.

Figure 15: Broad clinical trials of SKB264

Indications	Trial ID	Trial stage	Regimen	Region	Notes
Trials conducted by Kelun-Biotech					
TNBC (3L+)	NCT05347134	Ph3, pivotal	Mono vs chemo	China	Primary endpoint met in Aug 2023, NDA accepted in Dec 2023 with priority review
TNBC (1L)	NCT05445908	Ph2	+/- A167 (PD-L1)	China	To complete enrollment in 1H24; Ph3 to start in 1H24
HR+/HER2- BC (2L+)	NCT04152499	Ph2	Mono	China	
HR+/HER2- BC (2L+)	NCT06081959	Ph3, pivotal	Mono vs chemo	China	FPI in Nov 2023
EGFR-mutant NSCLC (TKI failure)	NCT05870319	Ph3, pivotal	Mono vs chemo	China	FPI in Jul 2023, 3L+ part to file NDA in 2H24, 2L part to have pre-NDA by end-2024
EGFR-wild type (1L) and EGFR-mutant (TKI failure) NSCLC	CTR20230825	Basket Ph2	+ Keytruda, osimertinib, chemo	China, US	FPI in China in Apr 2023, US IND filed in Jan 2023
EGFR-mutant NSCLC (1L)					
EGFR-wild type and mutant NSCLC (1L)	NCT05351788	Ph2	+ A167 (PD-L1) +/- chemo	China	FPI in China in May 2022
NPC/ NSCLC	NCT05631262	Ph2	Mono	China	
CC(2/3L)	NCT05642780	Ph2, basket	Combo Keytruda	China, US	FPI in China in Feb 2023, US IND approved in Nov 2022
UC (IL)					
OC(2L maintenance)					
CRPC (2L+)					
Trials conducted by MSD					
Previously treated nsq-NSCLC with EGFR mutations or other genomic alterations	NCT06074588	Ph3	Mono vs chemo	US, HK, AU, Israel, etc	Actual start date in Nov 2023, estimated primary completion in May 2027
1L PD-L1 TPS ⩾50% NSCLC	NCT06170788	Ph3	+ Keytruda vs Keytruda mono	US, AU, Turkey	Actual start date in Dec 2023, estimated primary completion in Jan 2028
Endometrial carcinoma	NCT06132958	Ph3	Mono vs chemo	AU, Israel, etc	Actual start date in Dec 2023, estimated primary completion in Jan 2028

Source: Company data, Pharmcube, CMBIGM

SKB264, Trodelvy and Dato-DXd all target the indications of TNBC, HR+/HER2- BC, NSCLC, etc. SKB264's indication of 3L+ TNBC has been under NDA review in China since Dec 2023, and the Ph3 trial of SKB264 for 2L+ HR+/HER2- BC is currently ongoing. Kelun-Biotech expects to start 1L Ph3 trial of SKB264 for TNBC in 1H24. For NSCLC, SKB264 differentiates itself from peers by targeting the TKI-resistant EGFR-m NSCLC patients first with a Ph3 trial ongoing since Jul 2023, with the 3L+ part of the trial to file NDA in 2H24. The global Ph3 trials of SKB264 for TKI-resistant EGFR-m NSCLC patients and 1L PD-L1+ NSCLC will pave the way for SKB264's globalization, in our view.

Trodelvy, as the first-mover in the TROP2 ADC space, has been approved for multiple indications, including 3L+ TNBC, 3L+ HR+/HER2- BC and post-platinum/IO UC. While the modest efficacy and boxed warning safety concern of Trodelvy highlight the necessity of the development of other TROP2 ADCs. For TNBC, Trodelvy has several Ph3 trials in earlier-line treatment, and we expect the ASCENT-03 trial of Trodelvy mono vs chemo in 1L mTNBC (PD-L1-) to read out in 2H24. Trodelvy's Ph3 confirmatory trial in post-platinum/IO UC is expected to read out in 1H24. For NSCLC, Trodelvy failed to meet the OS endpoint in the EVOKE-01 trial vs docetaxel for 2L NSCLC, while the trial of EVOKE-03 of Trodelvy + Keytruda vs Keytruda mono in 1L PD-L1+ NSCLC is still ongoing and expected to read out in 2025+.

For Dato-DXd, a Ph3 trial (TROPION-Breast02) of Dato-DXd mono vs chemo in 1L TNBC is expected to read out in 2H24. Dato-DXd has met the PFS endpoint in the TROPION-Breast01 trial for 2L+ HR+/HER2- mBC, while the OS endpoint was not met at the interim analysis; AstraZeneca expects to file US BLA based on this trial in 1H24 with the acceptance pending as of Feb 2024. Dato-DXd's Ph3 trial TROPION-Lung01 in 2/3L nsq-NSCLC has met the PFS endpoint but missed the OS endpoint at the interim analysis in 3Q23, and AstraZeneca has filed the BLA with FDA in Feb 2024 with PDUFA in Dec 2024. Multiple Ph3 trial of Dato-DXd combination therapies in 1L NSCLC are ongoing with the fastest AVANZAR trial to release data in 2025.

Figure 16: Major clinical trials of Trodelvy

Indications	Trial ID	Treatment line	Regimen	Stage
mTNBC	ASCENT	3L mTNBC	Mono vs chemo	Indication approved in the US in Apr 2021, and other countries ✓
	ASCENT-03	1L mTNBC (PD-L1-)	Mono vs chemo	Phase 3, data readout in 2H24
	ASCENT-04 (MSD collaboration)	1L mTNBC (PD-L1+)	+ Keytruda vs Keytruda + chemo	Phase 3
	ASCENT-05	Adjuvant mTNBC	+ Keytruda vs Keytruda mono or Keytruda + chemo	Phase 3
	SASCIA (GBG collaboration)	Adjuvant mTNBC	Mono vs chemo	Phase 3
HR+/HER2-mBC	TROPiCS-02	3L+ HR+/HER2- mBC	Mono vs chemo	Approved in the US ✓
	ASCENT-07	2L+ HR+/HER2- chemo-naïve mBC	Mono vs chemo	Phase 3 FPI in 2Q23
	SASCIA (GBG collaboration)	Adjuvant HR+/HER2-mBC	Mono vs chemo	Phase 3
Urothelial cancer	TROPiCS-04	Post-platinum/IO mUC	Mono vs chemo	Phase 3, FDA filling in 2024, data readout in 1H24
	TROPHY-U-01 (cohorts 1-3)	Post-platinum/IO mUC	Single arm: mono; + Keytruda	Phase 2, accelerated approval ✓
	TROPHY-U-01 (cohorts 4-6)	1L mUC	Single arm: mono; + chemo + PD(L)-1; PD(L)-1	Phase 2
NSCLC	EVOKE-01	2L Post-IO NSCLC	Mono vs docetaxel	Phase 3; failed to meet OS primary endpoint in Jan 2024
	EVOKE-02	1L mNSCLC (all-comers)	+ Keytruda vs + Keytruda + chemo	Phase 2; interim data released in Sep 2023, next update in 1H24
	EVOKE-03	1L mNSCLC (PD-L1⩾50%)	+ Keytruda vs Keytruda	Phase 3, data in 2025+
Endometrial cancer	TROPiCS-03	Advanced endometrial cancer	Single arm: mono	Phase 2
	GS-US-682-6769	2L metastatic endometrial cancer	--	Phase 3 FPI in 2H24

Source: Gilead data (link), CMBIGM.
Note: as of Feb 2024

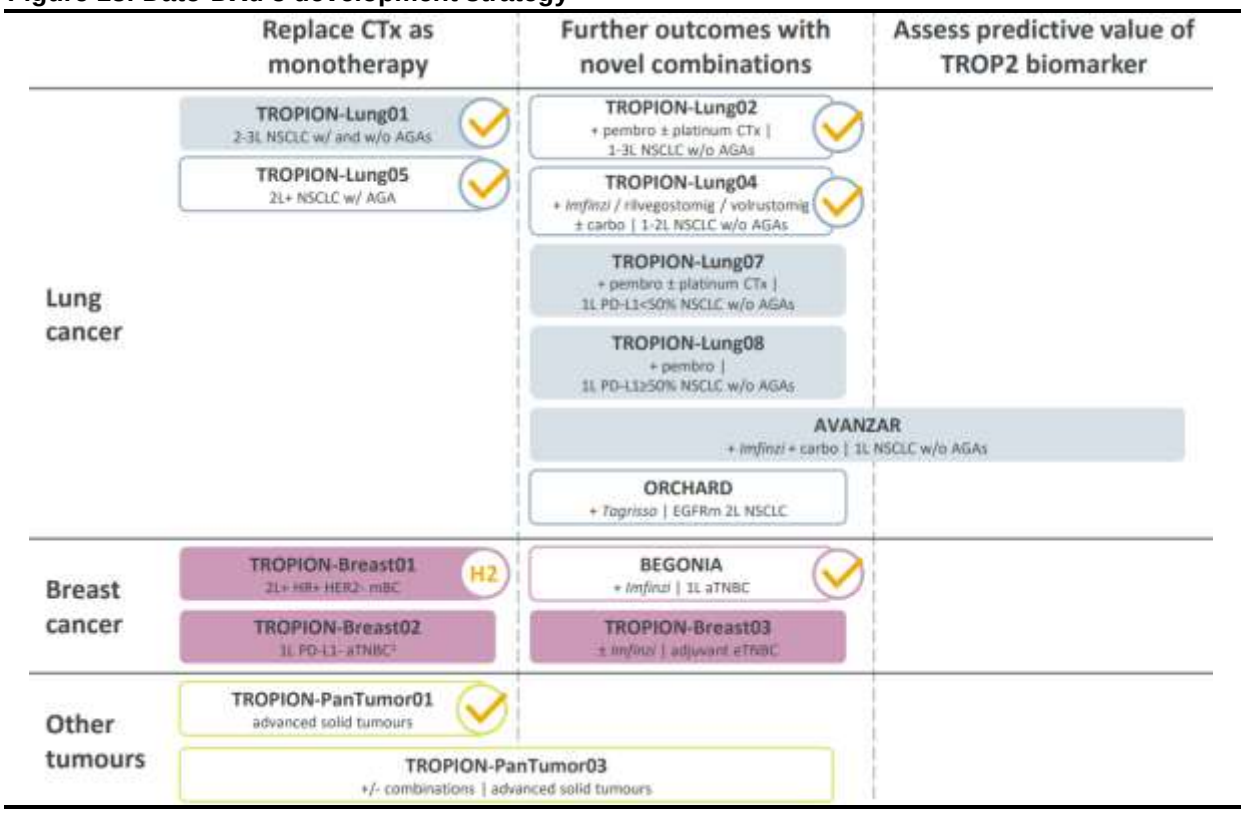
Figure 17: Major clinical trials of Dato-DXd

Indications	Trial ID	Treatment line	Regimen	Stage
NSCLC	TROPION-Lung01	2/3L w/ and w/o AGAs	Mono	Phase 3; data readout in 3Q23; dual primary endpoint PFS met, OS was immature and not significant; filed BLA in the US in Feb 2024 (PDUFA on 20 Dec 2024)
	TROPION-Lung07	1L PD-L1<50% w/o AGAs	+pembro±chemo vs +pembro vs pembro + chemo	Phase 3; data anticipated >2025
	TROPION-Lung08	1L PD-L1 ⩾ 50% w/o AGA	+pembro vs pembro	Phase 3; data anticipated >2025
	AVANZAR	1L w/o AGA	+ Imfinzi + chemo vs pembro + chemo	Phase 3; data anticipated 2025
	TROPION-Lung05	2L+ w/ AGA	Mono single-arm	Phase 2; data anticipated 2H24
Breast cancer	TROPION-Breast01	2L+ HR+/HER2- mBC	Mono vs chemo	Phase 3; data readout in 3Q23, Dual primary endpoint PFS met, OS was immature and not significant; BLA submission pending acceptance by FDA as of Feb 2024
	TROPION-Breast02	1L TNBC	Mono vs chemo	Phase 3; data anticipated 2H24
	TROPION-Breast03	Stage I-III TNBC	+ Imfinzi vs mono vs chemo	Phase 3; data anticipated >2025
	TROPION-Breast04	neoadjuvant stage II-III TNBC	+ Imfinzi	Phase 3; data anticipated >2025

	TROPION-Breast05	TNBC with PD-L1 CPS ⩾ 10	± Imfinzi	Phase 3; data anticipated >2025
Others	TROPION-PanTumor03	Endometrial cancer, GC, mCRPC, OC, CRC, bladder and BTC	multiple arms for multiple indications	Phase 2; data anticipated 2025
	TROPION-PanTumor02	NSCLC and TNBC and others (China trial)	Single arm	Phase 1/2; data readout in 4Q23

Source: AstraZeneca data (link), CMBIGM.
Note: as of Feb 2024; AGA = actionable oncogenic alterations

Figure 18: Dato-DXd's development strategy



Source: AstraZeneca data, CMBIGM

TNBC, the lead indicaiton of SKB264 with large unmet medical needs

Large unmet medical needs of TNBC

TNBC is an aggressive subtype of BC, accounting for about 15% of total BC cases. The treatment paradigm for advanced TNBC in China and the US primarily involves single-agent or doublet chemotherapy, chemoimmunotherapy that combines chemotherapy with PD-1 inhibitor (for PD-L1+ patients) and PARP inhibitor (for patients with deleterious BRCA mutations) in the front-line setting, and TROP2 ADC Trodelvy in the later-line setting. However, PD-L1 expression (20%) and BRCA1/2 mutations (10-20%) are only present in a subset of advanced TNBC patients, leaving most of the patients in need for better therapies.

TROP2 is overexpressed in about 88% of TNBC patients. TROP2 ADC may become a promising therapy for TNBC. Trodelvy was initially approved by the US FDA in Apr 2020 for the treatment of 3L+ TNBC. However, many patients were unresponsive to Trodelvy with limited ORR of 35% as observed in Trodelvy's global registrational trial for TNBC, and some patients developed resistance to Trodelvy. Additionally, the FDA issued a black box warning for Trodelvy due to side effects such as severe neutropenia and severe diarrhea. More potent therapies for TNBC with a more tolerable safety profile are needed.

SKB264 is de-risked thanks to the success in TNBC

Later-line TNBC

The hard-to-treat TNBC is expected to be the first commercial indication of SKB264. In Aug 2023, Kelun-Biotech announced that the pivotal Ph3 trial of SKB264 in advanced TNBC (3L+) met the primary endpoint. The company has filed the BLA of SKB264 to the NMPA in Dec 2023 with priority review granted by the NMPA. This Ph3 study enrolled 254 patients in China, evaluating the PFS superiority of SKB264 vs chemo in 3L+ TNBC.

The company has released promising Ph1/2 trial data of SKB264, which supports its BTD designation in China. In a Ph1/2 trial, as of Oct 2022, 59 advanced TNBC patients were enrolled (23 patients received 4 mg/kg Q2W, 36 received 5 mg/kg Q2W). 88% of these patients had experienced ⩾3 prior therapies for metastatic disease. With a median follow-up of 22.8 months, the ORR was 42.4% and the mDoR was 11.5 months. The mPFS reached 5.7 months and mOS was 16.8 months, with the 12-month and 24 months OS rate reaching 65.0% and 57.3%. For patients with high TROP2 expression (n=32), the ORR was better at 53.1%; the mDoR was 11.1 months, and the mPFS reached 5.8 months; and the preliminary OS data were encouraging with 12-month OS rate of 65.3%.

SKB264 demonstrated a manageable safety profile. With 9.6 months of follow-up (link), TRAEs of Grade ⩾3 were reported in 55.9% (33/59) of patients. The most common grade ⩾3 TRAEs were neutrophil count decreased (23.7%), anemia (20.3%) and platelet count decreased (16.9%). TRAEs led to dose reduction in 15.2% (9/59) and to discontinuation in 6.8% (4/59) of patients, while no treatment-related AEs leading to death or interstitial lung disease (ILD) were reported.

In cross-trial comparisons, SKB264 demonstrated 42.4% ORR and 5.7 months of mPFS in heavily pre-treated TNBC, which was better vs 35% ORR and 5.6 months mPFS of Trodelvy, and 32% ORR and 4.4 months mPFS of Dato-DXd. Additionally, SKB264 had lower rate of grade ⩾3 TRAEs of neutropenia (decreased neutrophil count) (23.7% vs 51%) and diarrhea (0% vs 11%) compared to Trodelvy, with the latter having a FDA boxed warning of severe neutropenia and diarrhea. We notice that SKB264 has higher rates of platelet count decreased, leukopenia and anemia compared to Trodelvy, Dato-DXd and DS-8201.

Figure 19: Cross-trial comparison of ADC drugs for late-line TNBC

Drug	SKB264	Trodelvy	Dato-DXd
Company	Kelun-Biotech	Gilead	Daiichi Sankyo / AstraZeneca
Trial ID	NCT04152499	ASCENT	TROPION-PanTumor01
Trial stage	Ph1/2	Ph3	Ph1
Regimen	SKB264, single arm	Trodelvy vs chemo	Dato-DXd, single arm
Primary endpoint		PFS	Safety
n (efficacy evaluable)	59	468 (235 vs 233) pts without brain metastases	44
Baseline	88% pts had >=3 prior treatment	All >= 2 prior treatment	Median of 3 prior treatment (range 1-10)
Median follow-up	22.8 months	17.7 months	16.6 months
PFS (month)	5.7	5.6 vs 1.7 HR=0.41, P<0.001	4.4
OS (month)	16.8	12.1 vs 6.7 HR=0.48, P<0.001	13.5
ORR	42.4%	35% vs 5%	32%
CR	--	--	2%
mDoR (month)	11.5	6.3 vs 3.6	16.8
Key Grade>=3 AEs			
diarrhea	*0*	*11% vs 1%*	--
stomatitis	--	--	*11%*
decreased neutrophil count (neutropenia)	*25.4%*	*51% vs 33%*	*2%*
platelet count decreased	*16.9%*	*1.2% vs 2.7%*	--
leukopenia (decreased in total white blood cell)	*23.7%*	*10% vs 5%*	--
anemia	*22%*	*8% vs 5%*	*2%*
ILD	0%	1 case with grade 3 ILD in Trodelvy arm	0% (2% discontinued due to pneumonitis, not ILD)
AE leading to dose reduction	15.2%	--	18%
AE leading to discontinuation	6.8%	5% vs 5%	2% (due to pneumonitis)

Approval status	BLA accepted in Dec 2023	Approved in China (3L+ TNBC) and the US (3L+ TNBC)	Not approved yet
Source	Link	Link1 Link2	Link1, Link2

Source: Company data, CMBIGM.

Front-line TNBC

Kelun-Biotech is exploring the potential of SKB264 for first-line TNBC. The Company plans to complete a Ph2 trial of SKB264 with or without A167 in 1L TNBC in 1H24 which could be followed by the initiation of a Ph3 study in 1H24.

SKB264 showed promising preliminary efficacy signals in first-line TNBC. A Ph2 trial assessing SKB264 with or without A167 in 1L TNBC is ongoing. The trial consists of two cohorts: cohort A is SKB264 5mg/kg Q2W in combination with A167 and cohort B is SKB264 monotherapy. As of Dec 2022, 8 patients were enrolled and six of the 7 evaluable patients received SKB264 + A167 treatment achieved PR and one patient had SD with target lesion shrinkage of 25% at first scan. The ORR was 85.7% (including unconfirmed response) and DCR was 100%. In cross-trial comparisons, Keytruda plus chemo only achieved 40.8% ORR in its Ph3 study in 1L TNBC (see table below).

SKB264 + A167 was generally well-tolerated. 37.5% (3/8) patients experienced grade 3 or above TRAE, and no patient experienced SKB264 or A167-related SAE. In comparison, Keytruda plus chemo demonstrated the rate of grade ⩾3 TRAEs as high as 68.1% for 1L TNBC.

Despite with data from limited number of patients, SKB264 plus immunotherapy demonstrated promising early results in front-line TNBC.

Figure 20: Cross-trial comparison of therapies for 1L TNBC

Drug	SKB264	Dato-DXd	Keytruda
Company	Kelun-Biotech	Daiichi Sankyo / AstraZeneca	MSD
Trial ID	NCT05445908	BEGONIA	KEYNOTE-355
Trial stage	Ph1/2	Ph1b/2	Ph3
Regimen	SKB264 + A167 (PDL-1)	Dato-DXd + Imfinzi (PDL-1)	Pembro + chemo vs chemo
Primary endpoint	Safety, ORR	Safety	PFS, OS
n (efficacy evaluable)	7	62	847
median Follow up (month)	As of Dec 2022; FPI in Sep 2022	11.7	44.1
PFS (month)	-	13.8	7.5 vs 5.6 HR=0.82 (0.70-0.98)
OS (month)	-	-	17.2 vs 15.5 HR=0.89 (0.76-1.05)
ORR	85.7%	79%	40.8% vs 37.0%
CR	-	10%	-
TRAEs Grade>=3	37.5%	36%	68.1% vs 66.9%
Key any grade TRAEs			
nausea	*NA*	*55%*	*39% vs 41%*
stomatitis	*62.5%*	*51%*	*NA*
diarrhea	*NA*	*13%*	*NA*
anemia	*37.5%*	*8.5%*	*41% vs 46%*
neutropenia	*62.5%*	*2.1%*	*41% vs 38%*
ILD	0	*5%*	pneumonitis 2.5% vs 0
Discontinuation due to AE		16%	
Source	Link	Link1; Link2	Link1; Link2

Source: Company data, CMBIGM.

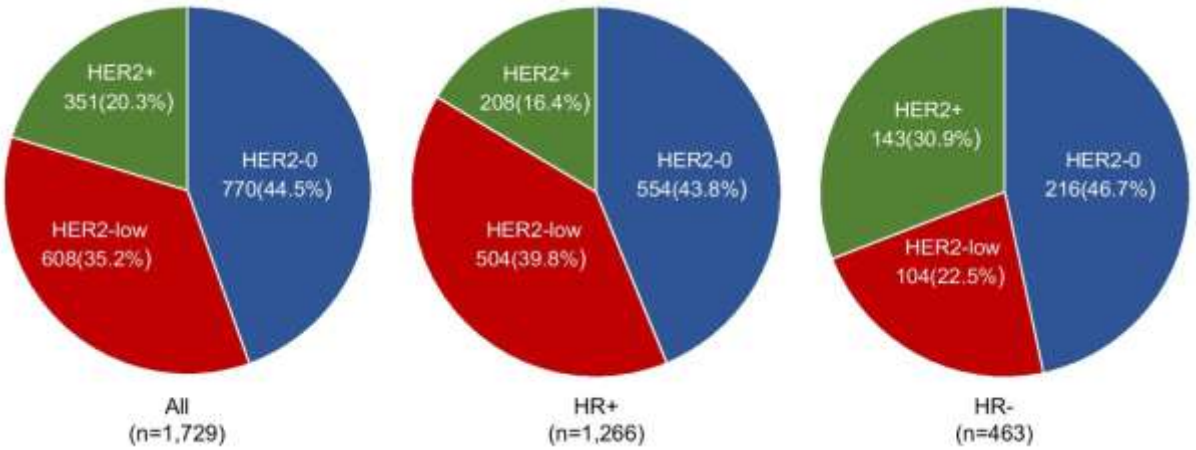
HR+/HER2- BC, Ph3 study ongoing supported by promising early clinical data

Treatment paradigm of HR+/HER2- BC

Research suggests among all BC patients, approximately 80% are HER2-low (IHC 1+ or IHC 2+/ISH-) and HER2 negative. HR-positive, HER2-low or negative BC is the most prevalent subtype of BC, accounting for about 60-70% of all BC cases. Endocrine therapy such as aromatase inhibitors (AIs) and a selective ER degrader (SERD) represents the cornerstone treatment for advanced HR+/HER2- BC in the US and China.

According to the article "Landscape of HER2-low metastatic breast cancer (MBC): results from the Austrian AGMT_MBC-Registry" published on *Breast Cancer Research* (14 Dec 2021) , HR+/HER2- BC patients account for approximately 32% of total BC patients, HR+/ HER2 low BC patients account for c. 29% of the total, and TNBC patients account for c. 12% of the total.

Figure 21: Frequencies of HER2 expression in dependency of HR status



Source: Link, CMBIGM
Note: HER2+ = HER2-positive (IHC 3+ or IHC 2+ and ISH+); HER2-low = low HER2 expression (IHC 1 or IHC 2+ and ISH−); HER2-0 = completely HER2-negative (IHC 0).

In the US, the 1L and 2L treatment options for advanced HR+/HER2- BC include various endocrine therapy regimens, such as AI + CDK4/6 inhibitor or SERD +/- CDK4/6 inhibitor, or combination regimens such as an endocrine therapy + either a PI3K inhibitor or a mammalian target of rapamycin inhibitor for patients with PIK3CA mutations. The treatment paradigm in China is similar to that of the US with an additional 2L option containing an AI plus chidamide, an epigenetic modulator. However, approximately 40-50% of advanced HR+/HER2- BC patients are resistant to endocrine therapy, leaving a need for effective non-endocrine therapy-based treatment. Trodelvy was approved in the US for treating advanced 3L+ HR+/HER2- BC in Feb 2023. Gilead is conducting a Ph3 study (CTR20210096/NCT04639986) in China in 3L+ HR+/HER2- BC with patient recruitment completed in Dec 2022, and a Ph3 study in China in 2L HR+/ HER2- or HER2-low BC with FPI in Jun 2023 (CTR20233370/ NCT05840211/ ASCENT-07).

SKB264 has moved to registration study in HR+/HER2- BC

Kelun-Biotech is conducting a global Ph1/2 trial of SKB264 in 2L+ HR+/HER2- BC and a Ph3 study in 2L+ HR+/HER2- BC in China. The updated Ph1/2 data of SKB264 in HR+/HER2- BC was presented at the ESMO 2023 meeting (link). With 8.2 months of follow-up, 38 patients with HR+/HER2- mBC treated with SKB264 were evaluable for response assessment. 79% of patients had ⩾2 prior chemotherapies, and prior taxane and CDK4/6. The ORR was 36.8%, and the mDoR was 7.4 months. The mPFS reached 11.1 months, which was quite promising in cross-trial comparisons (see Figure 22).

Globally, Enhertu (DS-8201) has been approved for HER2-low (IHC 1+ or IHC 2+/ISH-) BC regardless of HR status in the US and China based on the DESTINY-Breast04 trial. Enhertu demonstrated strong efficacy in HR+/HER2-low BC with ORR of 52.6% and mPFS of 10.1 months. Nevertheless, Enhertu carried a boxed warning issued by the US FDA for ILD and embryo-fetal toxicity. For HR+/HER2- mBC, endocrine therapy along with CDK4/6 inhibitors remained as the 1L SoC. In later lines, Enhertu is expected to become the first ADC of choice in HER2-low (IHC 1+ or IHC 2+/ISH-) setting and Trodelvy in HR+/HER2 low/negative (IHC 0, IHC 1+ or IHC 2+/ISH–) setting based on TROPiCS-02 study. Additionally, Enhertu started a Ph3 study in HER2 low and negative BC (including both HR+ and HR-) in late 2023 (NCT05950945), which will expand the indications of Enhertu upon approval. Nevertheless, Trodelvy's efficacy is modest in this setting (21.0% ORR and 5.5 months of mPFS, vs 36.8% ORR and 11.1 months of mPFS of SKB264 in cross-trial comparison, see Figure 22), leaving large unmet need for a better TROP2 ADC.

In Sep 2023, AstraZeneca/ Daiichi Sankyo announced that in Ph3 TROPION-Breast01 study, Dato-DXd demonstrated statistically significant and clinically meaningful PFS benefit in HR+/ HER2-low or negative (IHC 0, IHC 1+ or IHC 2+/ISH-) BC patients previously treated with endocrine-based therapy and at least one systemic therapy (link). The detailed data were released at the ESMO 2023 meeting (link). In the study, 732 patients were randomized 1:1 receiving Dato-DXd or chemo. The mPFS was 6.9 months in Dato-DXd arm vs 4.9 months in chemo arm (HR=0.63, p<0.001), and the ORR was 36.4% vs 22.9%, respectively. The OS primary endpoint was not met at the interim analysis (HR=0.84, CI 0.62-1.14) and the trial is still ongoing. AstraZeneca is going to file BLA in the US based on this trial (BLA submission pending acceptance by FDA as of Feb 2024). The safety profile in the Dato-DXd was better than the chemo arm, with the rate of Grade ⩾3 TRAEs of 21% vs 45%. In the Dato-DXd arm, the all-grade interstitial lung disease (ILD) rate was 3% and there was one grade 5 ILD event related to drug treatment.

In cross-trial comparisons, the 11.1 months of mPFS observed in SKB264's Ph1/2 study was much better than the efficacy showed in the Ph3 studies of Trodelvy and Dato-DXd (mPFS of 5.5 months and 6.9 months, respectively). Meanwhile, SKB264's preliminary 11.1 months mPFS in 3L+ HR+/HER2- BC was comparable to the 10.1 months of mPFS of DS-8201 observed in the Ph3 DESTINY-Breast04 study in 3L+ HER2-low BC. On the safety side, DS-8201 has a concern on serious pneumonitis/ILD event, while SKB264 is free from the ILD issue. To summarize, compared to Trodelvy and Dato-DXd's modest profile in HR+/HER2- patients, Enhertu demonstrated quite promising results, and we foresee SKB264 to show comparable results to Enhertu for these patients based on the early Ph1/2 data.

Figure 22: Cross-trial comparison of therapies for late-line treatment of HR+/HER2- BC

	SKB264	Trodelvy	Dato-DXd		DS-8201
MoA	TROP2 ADC	TROP2 ADC	TROP2 ADC		HER2 ADC
Company	Kelun-Biotech	Gilead	Daiichi Sankyo/ AZ		Daiichi Sankyo / AZ
Regimen	Mono	Mono vs chemo	Mono	Mono vs chemo	Mono vs chemo
Trial	NCT04152499	TROPiCS-02	TROPION-PanTumor01	TROPION-Breast01	DESTINY-Breast04
Trial stage	Ph1/2	Ph3	Ph1	Ph3	Ph3
Primary endpoint		PFS		PFS, OS	PFS in HR+/HER2 low cohort
Treatment line	79% pts had ⩾2 prior therapies	Median of 3 prior chemo regimens in the metastatic setting	Median of 5 prior regimens	62% previously treated with 1 line of chemo, 38% treated with 2 lines	HR+/HER2 low pts received a median of 3 prior lines of therapy
Patient number	38	543	41	732 (1:1)	331 vs 163 (HR+/HER2 low cohort)
HER2 or HR level	HR+/HER2-low or negative	HR+/HER2-low or negative	HR+/HER2-low or negative	HR+/HER2-low or negative	HR+/HER2-low (no HER-negative pts)
ORR	36.8%	21.0% vs 14.0%	29%	36.4% vs 22.9%	52.6% vs 16.3% (HR+/HER2 low cohort)
CR					3.6% vs 0.6%
mDoR (mo)	7.4	8.1 vs 5.6			10.7 vs 6.8
mPFS (mo)	**11.1**	5.5 vs 4.0, HR=0.66, p=0.0003	8.9	6.9 vs 4.9 HR=0.63, p<0.0001	10.1 vs 5.4, HR=0.51, p<0.001
mOS (mo)		14.4 vs 11.2, HR=0.79, p=0.02		Interim OS didn't reach significance with HR=0.84, trial still ongoing	23.9 vs 17.5, HR=0.64, P=0.003
Safety	No drug-related ILD/pneumonitis	No patients treated with Trodelvy experienced ILD	One case of grade 3 treatment-related ILD	3% all grade ILD. One grade 5 drug related ILD event, with death primarily due to disease progression	12.1% pts in the DS-8201 arm had drug-related ILD or pneumonitis. 5 Gr3 ILD and 3 ILD-related deaths were reported
AEs **Grade>=3**	48.8% (TRAE)	*NA*	*NA*	20.8% vs 44.7% (TRAE)	*NA*
Diarrhea	*NA*	*10% vs 1%*	*0%*		*1.1% vs 1.7%*
Stomatitis	*NA*	*NA*	*10%*	*6% vs 3% (TRAE)*	
Decreased leukocyte count	*22% (TRAE)*	*38% vs 26%*	*15%*		*6.5% vs 19.2%*
Decreased neutrophil count	*36.6% (TRAE)*	*53% vs 40%*		*1% vs 31% (TRAE)*	*13.7% vs 40.7%*
Decreased lymphocyte count		*21% vs 14%*			*6.5% vs 19.2%*
Anemia	*14.6% (TRAE)*			*1% vs 2% (TRAE)*	
Decreased platelet count	*9.8% (TRAE)*	*1% vs 4%*		*5.1% vs 0.6% (TRAE)*	
Approval status	Ph3 trial ongoing in China	HR+/HER2- BC approved in the US, not in China yet		Not approved yet	3L HER2-low BC approved in the US and China
Data source	Link	Link	Link1, Link2	Link1, Link2	Link

Source: Company data, Pubmed, CMBIGM

Note: DS-8201 was approved with a boxed warning for the risk of ILD and embryo-fetal toxicity. Trodelvy has a boxed warning for severe or life-threatening neutropenia and severe diarrhea. HER2-low: IHC1+ or IHC2+/ISH-. HER2-negative: IHC0.

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NSCLC to become a major market for SKB264

Treatment paradigm of NSCLC

The treatment paradigm of advanced NSCLC in the US and China can be broadly classified based on the presence or absence of actionable driver mutations. For driver mutation-positive advanced NSCLC, targeted therapies directed against specific actionable driver mutations, typically TKIs, are usually considered in the 1L setting. For patients who have failed TKIs, platinum-based doublet chemotherapy with or without anti-angiogenic mAb bevacizumab, single-agent chemotherapy, or PD-(L)1 inhibitor monotherapy is usually considered. For driver mutation-negative advanced NSCLC, the 1L treatment options include chemo-immunotherapy with or without bevacizumab, doublet chemotherapy with or without PD-(L)1 inhibitor, and monotherapy with PD-(L)1 inhibitor (for PD-L1+ patients). 2L+ treatment options include PD-(L)1 inhibitor monotherapy, single-agent chemotherapy, and multi-targeting TKI anlotinib (for patients who have failed two chemotherapy regimens).

Although the recent addition of PD-(L)1 to standard treatments has improved the survival of patients with driver mutation-negative NSCLC, many patients remain unresponsive. Meanwhile, each TKI is only clinically relevant for a subset of advanced NSCLC patients with a specific driver mutation. Consequently, there is a need for innovative treatments that are potentially effective for a broader patient population regardless of driver mutation status. TROP2 overexpression is reported in about 64% to 75% of patients with NSCLC, indicating the potential of TROP2-targeted therapies for the treatment of NSCLC.

SKB264 showed promising preliminary efficacy in NSCLC

No TROP2 ADC drug has been approved for treatment of NSCLC so far. SKB264 is targeting the NSCLC treatment through various treatment settings. Differentiated from other TROP2 ADCs, SKB264 initially focuses on EGFR-TKI resistant NSCLC patients, with a pivotal China Ph3 trial ongoing in EGFR-mutant advanced NSCLC patients who have failed EGFR-TKI therapy. SKB264 is also being evaluated in a global Ph1/2 trial for advanced NSCLC, including EGFR-wild type and EGFR-mutant advanced NSCLC. Kelun-Biotech is also conducting a Ph2 trial of SKB264 in combination with A167 with or without chemotherapy for EGFR-wild type advanced NSCLC. Additionally, in collaboration with MSD, Kelun-Biotech has initiated a Ph2 basket study of SKB264 as combination therapies (including combined with Keytruda, osimertinib and chemo) for EGFR-wild type and EGFR-mutant advanced NSCLC in Mar 2023 in China. Kelun-Biotech is also planning to start Ph3 studies of SKB264 in combination with A167 in 1L NSCLC in China in 2024.

MSD owns the ex-China rights of SKB264/ MK2870, and plans to start multiple global Ph3 trials of SKB264. MSD has started 1) a Ph3 MRCT of SKB264 vs chemo in previously treated nsq-NSCLC with EGFR mutations or other genomic alterations (NCT06074588) with PFS and OS as dual primary endpoints, 2) a Ph3 trial of SKB264 vs chemo in post platinum and post Immunotherapy endometrial carcinoma with PFS and OS as dual primary endpoints (NCT06132958), and 3) a Ph3 trial of SKB264+Keytruda vs Keytruda in 1L PD-L1 TPS ⩾50% NSCLC (NCT06170788) to test the OS superiority.

SKB264 has released promising early results in NSCLC. As of Feb 2023, in the NSCLC cohort of a Ph1/2 study, 43 NSCLC patients were enrolled and treated with SKB264 5mg/kg Q2W. With a median follow-up of 11.5 months (link), of the 39 response-evaluable patients, the ORR was 43.6% (17/39, 2 pending confirmation), and the mDoR was 9.3 months. Among the two subgroups, SKB264 showed much better efficiency in the EGFR-TKI resistant EGFR-mutant patients than that in the EGFR wild-type patients. For the EGFR wild-type NSCLC subgroup (N=21, previously received median 2 lines of therapy including anti-PD-(L)1 therapy), the ORR was 26.3%, median PFS was 5.3 months and 9-month OS rate was 80.4%. For the TKI-resistant EGFR-mutant NSCLC subgroup (N=22, among which 50% also failed at least one line of chemotherapy), the ORR was 60.0% (12/20), median PFS was 11.1 months and 9-month PFS rate was 66.7%. Based on the promising Ph1/2 results of SKB264 in EGFR-TKI resistant NSCLC, we are positive on its ongoing Ph3 study in this treatment setting.

Figure 23: Efficacy of SKB264 in a Ph1/2 study in late-line NSCLC

	All NSCLC (N=43)	EGFR mutant (N=22)	EGFR wild-type (N=21)
ORR, %	43.6%	60.0%	26.3%
Confirmed ORR (cORR), %	38.5%	55.0%	21.1%
DCR, %	94.9%	100%	89.5%
DoR, median (95% CI), mo	9.3 (3.7, NE)	9.3 (2.0,NE)	9.6 (3.5, NE)
PFS, median (95% CI), mo	6.2 (5.3, 11.3)	11.1 (5.7, 13.1)	5.3 (3.5, 6.2)
9-mo PFS rate (95% CI), %	46.7 (30.2, 61.6)	66.7 (40.4, 83.4)	27.7 (10.3, 48.5)
OS, median (95% CI), mo	NR (NE, NE)	NR (NE, NE)	NR (10.7, NE)
12-mo OS rate (95% CI), %	70.6 (53.9, 82.1)	80.7 (56.3, 92.3)	60.6 (36.1, 78.2)

DCR, disease control rate; DoR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; PFS, progression-free survival; OS, overall survival.
*Based on response evaluable patients who have had at least on post-baseline scan (N=39).

Source: Company data, CMBIGM

In the Ph1/2 study, 67.4% (29/43) of patients had grade ⩾3 TRAEs. The most common grade ⩾3 TRAEs were neutrophil count decreased (32.6%), anemia (30.2%), white blood cell count decreased (23.3%), stomatitis (9.3%), rash (7.0%), and lymphocyte count decreased (7.0%). Grade 4 TRAEs occurred only for neutropenia and WBC decreased. 23.3% (10/43) of the patients experienced dose reduction due to TRAEs. No neuropathy or drug-related ILD/pneumonitis was reported. No TRAEs led to treatment discontinuation or death.

Treatment options are limited for EGFR-mutated NSCLC patients after failure with EGFR-TKIs. However, R&D competition in later-line EGFR-mutant NSCLC is intense, with various novel therapies under development, including PD(L)-1, TROP2 ADC, HER3 ADC, EGFR/HER3 ADC, PD-1/VEGF bsAb, and EGFR/MET bsAb. We have summarized the major clinical results of the above-mentioned therapies in NSCLC as below.

Figure 24: Cross-trial comparison of therapies for EGFR-TKI resistant NSCLC

Drug	SKB264	Dato-DXd		Trodelvy	BL-B01D1	HER3-DXd	AK112	amivantamab		sintilimab	tislelizumab
MoA	TROP2 ADC	TROP2 ADC		TROP2 ADC	EGFR/HER3 ADC	HER3 ADC	PD1/VEGF	EGFR/MET bsAb		PD1	PD1
Company	Kelun-Biotech	Daiichi Sankyo/ AstraZeneca		Gilead	Baili Pharm	Daiichi Sankyo/ AstraZeneca	Akeso/Summit	Janssen/ Genmab		Innovent	BeiGene
Trial ID	NCT04152499 (n=20)	TROPION-PanTumor01 (n=50)	TROPION-Lung05 (n=78, EGFRm pts)	NCT01631552 (n=54)	NCT05194982 (n=40)	HERTHENA-Lung01 (n=225)	NCT04736823 (n=19)	MARIPOSA-2 (n=657)	CHRYSALIS-2 (n=20)	ORIENT-31 (n=476)	NCT04405674 (n=62)
Trial stage	Ph1/2	Ph1	Ph2	Ph1/2	Ph1	Ph2, pivotal	Ph2	Ph3	Ph1b/2	Ph3	Ph2
Baseline	All with mEGFR; post EGFR-TKI and 50% post chemo	10 pts with AGAs; median 3 prior treatments; 18% pts treated with TKI	137 pts enrolled; 78 with EGFRm; 71.5% with ⩾3 prior therapies; at least 1 targeted therapy and chemo	4 pts with EGFR mutations; median 3 prior treatments; 32% pts treated with EGFR TKI	Post EGFR-TKI; Median 3 lines of prior treatment	Post EGFR TKI and post chemo (**3L**); 63% and 36% of pts had either ex19del or L858R; Median 3 lines of prior treatment	Post EGFR-TKI; 37% had brain metastasis; All nsq	Post osimertinib; pts with EGFR ex19del or L858R;	Post osimertinib; pts with EGFR ex19del or L858R;	Post EGFR-TKI; 51% and 44% of pts had ex19del or L858R; median 3 prior treatment	Post EGFR-TKI; all nsq
Regimen	SKB264 mono	Dato-DXd mono (at the recommended 6mg/kg Q3W)	Dato-DXd mono (at the recommended 6mg/kg Q3W)	Trodelvy mono	BL-B01D1 mono	HER3-DXd mono	AK112 + chemo	amivantamab+chemo+lazertinib vs amivantamab+chemo vs chemo	amivantamab + lazertinib + chemo	sintilimab+ beva+chemo vs sintilimab+ chemo vs chemo	tislelizumab + chemo
Median follow up (month)	11.5	13.3	15.2	9.0		18.9	25.8	8.7	13.1	12.9	8.2
ORR	60.0%	26%	43.6%	17%	52.5%	29.8%	68.4%	63% vs 64% vs 36%	50.0%	43.9% vs 33.1% vs 25.2%**	50.0%
mPFS (month)	11.1	6.9		5.2	5.6	5.5	8.5	8.3 vs 6.3 vs 4.2	14.0	7.2 vs 5.5 vs 4.3	7.6
mOS (month)	-	11.4		9.5		11.9	22.5			21.1 vs 20.5 vs 19.2	
12-month OS rate	80.7%						73.7%	Around 68% vs 66% vs 62%			
24-month OS rate							40.9%				
Grade 3–5 TRAEs	67.4%	26%	47.4%	-		45.3%	36.8%			56% vs 41% vs 49%	41% (Gr ⩾3 TEAEs)
Treatment discontin-uation	0	14%	9.5%	2%		7.1%		34% vs 18% vs 4%			
Others		2% drug-related Gr>=3 ILD	0.7% drug-related Gr>=3 ILD	Gr>=3 neutropenia occurred in 28% pts		5.3% ILD					
Source link	Link	Link	Link	Link	Link1, Link2	Link1, Link2	Link1, Link2, Link3	Link	Link	Link1, Link2	Link

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Latest progress on post EGFR-TKI NSCLC	Ph3 trial ongoing (FPI in Jul 2023)	Ph2 TROPION-Lung05 ongoing	Ph3 EVOKE-01 in 2L post-IO NSCLC ongoing	Ph2 ongoing	BLA in Dec 2023 based on the above pivotal Ph2 (PDUFA date Jun 2024); Ph3 (2L) ongoing	NDA submitted in China in Aug 2023; Ph3 MRCT trial ongoing	The Ph3 met primary endpoint, and is still ongoing	Approved in China in May 2023	-

Source: Company data, Pubmed, CMBIGM.

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PD(L)1 in EGFR-mutant NSCLC: mild efficacy in EGFR-TKI resistant NSCLC.

Opdivo and Keytruda failed for EGFR-TKI resistant NSCLC patients in combination with chemo vs chemo alone, according to the CheckMate-722 study (mPFS 5.6 vs 5.4 months) and KeyNote-789 study (mPFS 5.6 vs 5.5 months), respectively. However, sintilimab in combination with bevacizumab and chemo demonstrated PFS benefit in EGFR-TKI resistant nsq-NSCLC in the Orient-31 study (mPFS 7.2 vs 4.3 months) and was approved in China for this indication. Nevertheless, there are still huge unmet medical needs in the EGFR-resistant NSCLC market, in our view.

Trodelvy in NSCLC: failed in later-line NSCLC, exploring potential in 1L PD-L1 high NSCLC.

In Jan 2024, Gilead announced that the Ph3 EVOKE-01 study of Trodelvy vs docetaxel in pre-treated NSCLC patients who had progressed on or after platinum-based chemo and checkpoint inhibitor therapy failed to meet the OS endpoint (link). The detailed data was not released yet. Gilead plans to continue to review the data and discuss results from this trial with regulators. Nevertheless, based on promising data from Ph2 EVOKE-02 trial in 1L NSCLC, Gilead remains confident in its ongoing Ph3 EVOKE-03 study in 1L PD-L1 high NSCLC, which is currently enrolling patients, with the data readout expected in 2025+.

The Ph2 EVOKE-02 study of Trodelvy + Keytruda demonstrates satisfying efficacy signals in 1L NSCLC (link) in both subgroups. In Cohort A (PD-L1 TPS ⩾50%, n=29), the confirmed and unconfirmed ORR was 69%. In Cohort B (PD-L1 TPS <50%, n=32), the confirmed and unconfirmed ORR was 44%. Across both cohorts, the ORR was 56%. Median DoR was not reached at the time of data cut-off, and DoR rate at six months was 88% in both cohorts. A Ph3 EVOKE-03 study of Trodelvy + Keytruda vs Keytruda mono in 1L PD-L1-high NSCLC is ongoing, with data readout expected in 2025+. The trial expects to enroll ~614 untreated NSCLC patients with no AGAs and with PD-L1 TPS ⩾50%. The dual primary endpoints of the trial are PFS and OS.

Recall that Keytruda mono was approved for 1L treatment of PD-L1-positive NSCLC, and recommended by NCCN and CSCO for patients with PD-L1 TPS ⩾1% and without EGFR activating mutations/ALK fusions, based on the KEYNOTE-042 (TPS ⩾1%) and KEYNOTE-024 (TPS ⩾50%) trial. In the KEYNOTE-042 (link), for the TPS ⩾50% subgroup, the ORR was 39.1% vs 32.3% in the Keytruda vs chemo arms, way below Trodelvy's 69% ORR shown above in cross-trial comparison. In the KEYNOTE-024 trial (link), the ORR was 44.8% vs 27.8% in the Keytruda vs chemo arms for 1L NSCLC patients with PD-L1 TPS ⩾50%, again way below Trodelvy's 69% ORR in cross-trial comparison. Meanwhile, to compare with the current SoC of 1L NSCLC, Trodelvy's efficacy seems to be promising while not overwhelming, in our view. Recall that in the KEYNOTE-189 trial for 1L nsq-NSCLC (link), Keytruda + chemo showed 61% ORR for patients with TPS ⩾ 50% patients, 48% ORR for patients with TPS of 1-49%, and 32% ORR for patients with TPS <1%. We look forward to the readout of Gilead's Ph3 EVOKE-03 study in 2025+.

Dato-DXd in NSCLC: uncertainty in all-comer later-line NSCLC while waiting for results of Ph3 studies in 1L NSCLC; attention to ILD risk.

Dato-DXd has shown promising clinical benefits in the first-line treatment of NSCLC. However, there are still uncertainties regarding its potential efficacy in later-line NSCLC treatment.

In a Ph2 TROPION-Lung05 study (link), Dato-DXd was evaluated in NSCLC patients with actionable genomic alterations such as EGFR, ALK, and ROS1 mutations. These patients had progressed on or after at least one targeted therapy and chemotherapy. In the study, a total of 137 patients were enrolled, with 71.5% of them having received three or more prior therapies, and 57% had EGFR mutations. The cORR in patients with EGFR mutations was 43.6%. It is important to note that one patient experienced ⩾Grade 3 drug-related interstitial lung disease (ILD). These results suggest the potential of Dato-DXd in the treatment of NSCLC patients with EGFR mutations who have progressed on previous therapies. However, further studies are necessary to confirm the efficacy and safety profile of Dato-DXd in this patient population.

In the Ph3 TROPION-Lung01 study, Dato-DXd demonstrated an improvement in PFS compared to docetaxel in later-line NSCLC patients (link). The study included patients in the second-line or later settings who had received chemotherapy, PD-(L)1 inhibitors, or targeted therapies, regardless of genomic

alterations. The trial included a total of 604 patients in the full analysis set, with 43.1% of them having undergone two or more prior therapies. At baseline, 13% of patients in the Dato-DXd arm and 15% in the docetaxel arm had EGFR mutations. Dato-DXd demonstrated a median PFS of 4.4 months compared to 3.7 months in the docetaxel arm, with a HR of 0.75 (p=0.004). The confirmed objective response rate (cORR) was 26.4% for Dato-DXd and 12.8% for docetaxel. The PFS benefit with Dato-DXd was observed in almost all patients, except those with squamous histology who had a median PFS of 2.8 months in the Dato-DXd arm compared to 3.9 months in the docetaxel arm. At interim analysis, the improvement in overall survival (OS) with Dato-DXd was not statistically significant, with a median OS of 12.4 months in the Dato-DXd arm compared to 11.0 months in the docetaxel arm (HR=0.90).

Regarding safety, the rate of grade ⩾3 TRAEs was lower in the Dato-DXd arm (25%) compared to the docetaxel arm (41%). However, three patients in the Dato-DXd arm and two patients in the docetaxel arm died due to TRAEs. Grade 3 or higher ILD was observed in 3.4% of the Dato-DXd arm compared to 1.4% in the docetaxel arm. Notably, seven patients in the Dato-DXd arm developed drug-related grade 5 ILD, and four of the 7 ILD resulted deaths were primarily due to disease progression. There is a strong need for careful monitoring and adherence to ILD management guidelines.

These findings suggest that Dato-DXd provides a significant improvement in PFS compared to docetaxel in later-line NSCLC patients. However, further analysis is needed to determine the impact on overall survival. Safety considerations, particularly regarding ILD, should also be carefully considered and managed in patients receiving Dato-DXd. Even though the OS endpoint was not met at the interim analysis, AstraZeneca and Daiichi Sankyo submitted a BLA of Dato-DXd for nsq-NSCLC patients post prior systemic therapy in Feb 2024 based on the above TROPION-Lung01 trial with a PDUFA date in Dec 2024. The OS results in the final analysis are expected in 2024.

The ongoing trials of Dato-Dxd plus Keytruda or durvalumab in first-line NSCLC have shown positive results. In the Ph1b TROPION-Lung04 trial (link), in 1L NSCLC patients without actionable genomic alterations, Dato-DXd + durvalumab (PD-L1) (doublet; n=14) demonstrated an ORR of 50%, Dato-DXd + durvalumab + chemo (triplet; n=13) which demonstrated an ORR of 77%. Similarly, in the TROPION-Lung02 Ph1b study (link), Dato-Dxd + Keytruda +/- chemo showed ORRs of 50% and 57% in the doublet (n=34) and triplet (n=53) cohorts respectively in previously untreated NSCLC patients without actionable genomic alterations (AGAs).

AstraZeneca and Daiichi Sankyo are conducting three Ph3 trials to evaluate Dato-DXd as a potential first-line treatment option for NSCLC. These trials include TROPION-Lung07, which is evaluating Dato-Dxd + Keytruda +/- chemo in nsq-NSCLC patients with PD-L1 expression of less than 50%; TROPION-Lung08, which is evaluating Dato-Dxd + Keytruda in NSCLC patients with PD-L1 expression of 50% or greater; and AVANZAR, which is evaluating Dato-Dxd plus Imfinzi (durvalumab) and chemo in patients regardless of PD-L1 expression.

Further investigation of Dato-DXd's potential in NSCLC is required in the ongoing Ph3 studies for both front and later-line settings. The safety profile of Dato-DXd is noteworthy, particularly considering the observation of multiple drug-related grade 5 ILD events.

HER3-DXd in NSCLC: BLA accepted by FDA for EGFR TKI-resistant patients based on positive pivotal Ph2 results.

MSD and Daiichi Sankyo's HER3 ADC, HER3-DXd, has shown promising responses in EGFR-mutant NSCLC patients who have previously received EGFR-TKI and chemotherapy. The pivotal Ph2 HERTHENA-Lung01 trial (link) demonstrated a confirmed ORR of 29.8%, an mPFS of 5.5 months, and an mOS of 11.9 months. It is important to note that these results were observed in patients who had undergone a median of three prior treatments. However, it is worth mentioning that 5.3% of patients experienced treatment-related ILD events, including two grade 3 events and one grade 5 event. In comparison, real-world data for EGFR TKI and chemo failed NSCLC patients showed a median PFS of only 3.3 months, an mOS of 8.6 months, and an ORR of only 14.1% (link).

MSD and Daiichi Sankyo submitted a BLA for HER3-DXd in the US in Dec 2023. This submission is for the treatment of EGFR-mutant NSCLC patients who have previously received two or more systemic therapies. The PDUFA date for the BLA is expected in June 2024.

In addition to the HERTHENA-Lung01 trial, MSD and Daiichi Sankyo are conducting the HERTHENA-Lung02 trial, a confirmatory Phase 3 study comparing HER3-DXd to platinum-based chemotherapy in second-line patients with EGFR-mutated NSCLC who experienced disease progression after treatment with a third-generation EGFR TKI. HER3-DXd was granted a BTD by the US FDA in 2021 for EGFR TKI-resistant NSCLC, indicating its potential as a promising treatment option.

MSD also collaborated with Kelun-Biotech in developing SKB264 for treatment of EGFR-TKI resistant NSCLC. MSD has started three Ph3 studies, including 1) a Ph3 MRCT of SKB264 in previously treated nsq-NSCLC with EGFR mutations or other genomic alterations (NCT06074588), 2) a Ph3 trial of SKB264 in endometrial carcinoma (NCT06132958), and 3) a Ph3 trial of SKB264+Keytruda vs Keytruda mono in 1L PD-L1 TPS ⩾50% NSCLC (NCT06170788) with OS as primary endpoint.

Amivantamab (EGFR/MET bsAb) in NSCLC: could be a competitive player in both EGFR-TKI resistant and front-line settings for EGFR mutant patients.

Amivantamab (EGFR/MET bsAb) developed by J&J was approved by the FDA in May 2021 for the treatment of post-chemo NSCLC patients with EGFR exon 20 insertion mutations. J&J further filed the sBLA for amivantamab plus chemo in the treatment of EGFR-m NSCLC post osimertinib to the FDA in Nov 2023 based on the MARIPOSA-2 trial. Additionally, there are two sBLAs of amivantamab for first-line NSCLC, one in combination with lazertinib for patients with EGFR ex19del or L858R substitution mutations based on the MARIPOSA trial (BLA in Dec 2023), and the other in combination with chemo for patients with EGFR exon 20 insertion mutations based on the PAPILLON trial (BLA in Aug 2023), which are currently under FDA review.

The Ph3 studies mentioned (MARIPOSA-2, MARIPOSA, and PAPILLON) did include patients enrolled in China, which may potentially pave the way for amivantamab approvals in the Chinese market. In Oct 2023, the BLA for amivantamab in China was accepted by the CDE, with the indication likely being for post-chemo NSCLC patients with EGFR exon 20 insertion mutations. Furthermore, in Dec 2023, amivantamab's new indication for treating osimertinib-post EGFR-m NSCLC was also submitted to the NMPA in China. In Jan 2024, the indication for 1L NSCLC patients with EGFR ex19del or L858R substitution of amivantamab + lazertinib was filed for BLA in China as well.

For TKI-resistant patients, the Ph3 trial (MARIPOSA-2, link) of amivantamab + chemo +/- lazertinib (3rd-gen EGFR TKI) compared to chemo alone in NSCLC patients with EGFR ex19del or L858R substitution, who progressed on osimertinib as either the first or second line of treatment, met its dual primary endpoint of PFS. The data was released at ESMO 2023 meeting (link1, link2). With 8.7 months of follow-up, the median PFS by IRC was 8.3, 6.3, and 4.2 months in the amivantamab+chemo+lazertinib (n=263), amivantamab+chemo (n=131), and chemo-only arms (n=263), respectively. The hazard ratios for the two amivantamab arms compared to chemo alone were 0.44 and 0.48, both statistically significant. Notably, the median intracranial PFS was 12.8 months (HR=0.58, p <0.001) vs 12.5 months (HR=0.55, P=0.001) vs 8.3 months, respectively. Grade ⩾3 adverse events occurred in 92%, 72%, and 48% of patients in the three arms, respectively, and the rates of adverse event-led discontinuation were 34%, 18%, and 4%. EGFR ex19del or EGFR L858R mutations are the most common types of EGFR mutations, accounting for approximately 90% of the cases (link). Considering efficacy, safety and intracranial PFS, amivantamab plus chemo shows promise as a potential therapy for EGFR mutant patients post-osimertinib. J&J filed the sBLA of amivantamab plus chemo for EGFR-m NSCLC patients post-osimertinib to the FDA in Nov 2023.

For first-line treatment, the Ph3 trial (MARIPOSA) evaluates amivantamab+lazertinib compared to osimertinib in 1L NSCLC patients with EGFR ex19del or L858R substitution mutations. The trial has met its endpoint, with an mPFS of 23.7 months for amivantamab+lazertinib compared to 16.6 months for osimertinib (HR=0.7, p<0.001). The data was released at ESMO in Oct 2023 (link1, link2). In an interim OS analysis, there was a favourable trend for amivantamab+lazertinib over osimertinib (HR 0.80; 95% CI 0.61–1.05; p=0.11). TRAEs leading to discontinuations of all agents occurred in 10% of patients treated with amivantamab plus lazertinib and 3% with osimertinib. Any venous thromboembolism (VTE) occurred in 37% of patients in the amivantamab+lazertinib group and 9% on osimertinib, leading the investigators to recommend prophylactic anticoagulation for the first 4 months of treatment in ongoing trials of amivantamab+lazertinib. Based on the results of MARIPOSA trial, J&J has filed a sBLA to the FDA

seeking approval of amivantamab+lazertinib for the first-line treatment of EGFR mutant NSCLC in Dec 2023.

In a similar vein, there is an ongoing Ph3 PAPILLON trial that examines the efficacy of amivantamab in combination with chemotherapy versus chemotherapy alone as a first-line treatment for patients with EGFR exon 20 insertions in NSCLC. The trial has achieved its intended outcome, demonstrating a mPFS of 11.4 months for the group receiving amivantamab plus chemotherapy, compared to 6.7 months for those receiving chemotherapy alone (HR = 0.4, p< 0.001, link). Based on these promising results, J&J has submitted a sBLA to the FDA for the accelerated approval of amivantamab plus chemotherapy in the first-line treatment of NSCLC patients with EGFR exon 20 insertions in Aug 2023.

SKB264 in NSCLC: promising early efficacy in EGFR-TKI resistant patients, but needs to expedite the development in front-line NSCLC.

SKB264 mono demonstrated promising median mPFS results of 11.1 months in EGFR-mutated NSCLC patients who had previously failed EGFR-TKI therapy, outperforming AK112 + chemo (8.5 months), sintilimab + beva + chemo (7.2 months), and amivantamab + chemo (6.3 months) in cross-trial comparisons. Notably, SKB264 showed better efficacy in EGFR-mutated patients (mPFS 11.1 months) compared to wild-type patients (mPFS 5.3 months), indicating its potential for treating EGFR mutant patients, although further biomarker analysis is required. However, given the limited proportion of EGFR-mutated patients in the early trials of Dato-DXd and Trodelvy, additional follow-up data are necessary to compare SKB264 with Dato-DXd/Trodelvy in EGFR-TKI resistant NSCLC patients.

SKB264 was granted Breakthrough Therapy designation by the NMPA in Jan 2023 for the treatment of advanced NSCLC that has failed to respond to EGFR-TKI therapy. In China, Kelun-Biotech has started a Ph3 clinical trial of SKB264 as a monotherapy compared to chemotherapy in patients with EGFR-TKI resistant NSCLC. The trial began enrolling patients in Jul 2023 (CTR20231535, NCT05870319). In addition to the monotherapy study, Kelun-Biotech is also conducting a Ph2 clinical trial of SKB264 in combination with A167, with or without platinum-based chemotherapy, for various types of NSCLC (CTR20220980, NCT05351788). Looking ahead, Kelun-Biotech plans to initiate Ph3 studies China in 2024 to assess the combination therapy of SKB264 and A167 as a first-line treatment for EGFR wild-type NSCLC.

In March 2023, in collaboration with MSD, Kelun-Biotech initiated a Ph2 basket study of SKB264 as a combination therapy in China. This study involves combining SKB264 with Keytruda, osimertinib, and chemotherapy for advanced NSCLC in patients with both EGFR-wild type and EGFR-mutant tumors (CTR20230825).

MSD is also conducting a comprehensive clinical development program for SKB264, known as MK-2870, with Ph3 trials planned globally. These trials will focus on lung cancer and other tumor types. One of the Ph3 trials started by MSD is comparing SKB264 monotherapy to chemotherapy in previously treated NSCLC patients with EGFR or other genomic mutations. This trial is registered under the trial number NCT06074588, with PFS and OS as dual primary endpoints.

Additionally, MSD has started another Ph3 trial (NCT06170788) comparing the combination of SKB264 and Keytruda to Keytruda monotherapy as a first-line treatment for NSCLC patients with a PD-L1 TPS of 50% or higher. The aim of this trial is to evaluate the OS superiority of the combination therapy.

Safety profile is another key concern

Dato-DXd has been associated with a specific set of AEs, such as interstitial lung disease (ILD). For instance, in the TROPION-Breast01 trial for HR+/ HER2- BC, one grade 5 drug-related ILD death was observed, and in the TROPION-Lung01 trial of Dato-DXd vs docetaxel for later-line NSCLC, seven patients in the Dato-DXd arm died due to drug-related grade 5 ILD. There is a strong need for careful monitoring and adherence to ILD management guidelines.

In the case of Trodelvy, isolated cases of ILD or pneumonitis (a type of ILD) have been reported in clinical trials such as ASCENT study for TNBC, the basket study IMMU-132-01, and TROPHY-U-01 study for metastatic urothelial cancer (mUC) (link).

No cases of ILD have been reported yet with SKB264, which suggests a favorable safety profile for this drug. SKB264 also appears to have decreased incidence of neutropenia compared to Trodelvy, which may be attributed to a more stable linker in SKB264's composition. However, SKB264 seems to have a worse adverse effect profile regarding anemia, potentially due to the more toxic payload it carries. While SKB264's gastrointestinal (GI) profile has been improved compared to Trodelvy, it still exhibits a relatively high incidence of stomatitis as an adverse effect.

Figure 25: Cross-trial comparison of safety profile of major TROP2 ADC drugs

	SKB264 5mg/kg	Trodelvy 10mg/kg	Trodelvy 10mg/kg	Dato-DXd 6mg/kg	Dato-DXd 6mg/kg
Trials	Ph1/2 in solid tumors (TNBC, BC, NSCLC)	Ph3 in TNBC (ASCENT)	Ph3 in HR+/HER2- BC (TROPiCS-02)	Ph1 in NSCLC	Ph1 in TNBC
	n=188	n=258	n=268	n=50	n=44
Adverse effects	>=Gr 3	>=Gr 3	>=Gr 3	>=Gr 3	>=Gr 3
Decreased neutrophil count (neutropenia)	26%	49%	53%	6%	2%
Decreased hemoglobin (anemia)	23%	9%	8%	4%	2%
Decreased platelet count	8%	1%	1%	NA	NA
Decreased leukocyte count	17%	41%	38%	NA	NA
Decreased lymphocyte count	4%	31%	21%	6%	7%
Lung-related AEs					
ILD	0%	0% ILD (1 patient had Gr 3 pneumonitis)	NA	8% potential Gr>=3 ILD, 2% drug-related	0% ILD (2% discontinued due to pneumonitis, not ILD)
Gastrointestinal AEs					
Diarrhea	0%	11%	10%	0%	0%
Stomatitis	9%	2%	NA	2%	11%
Nausea	1%	3%	1%	4%	2%
Vomiting	1%	2%	1%	2%	5%
Rash	4%	0%	NA	0%	NA
Alopecia	0%	0%	0%	0%	0%

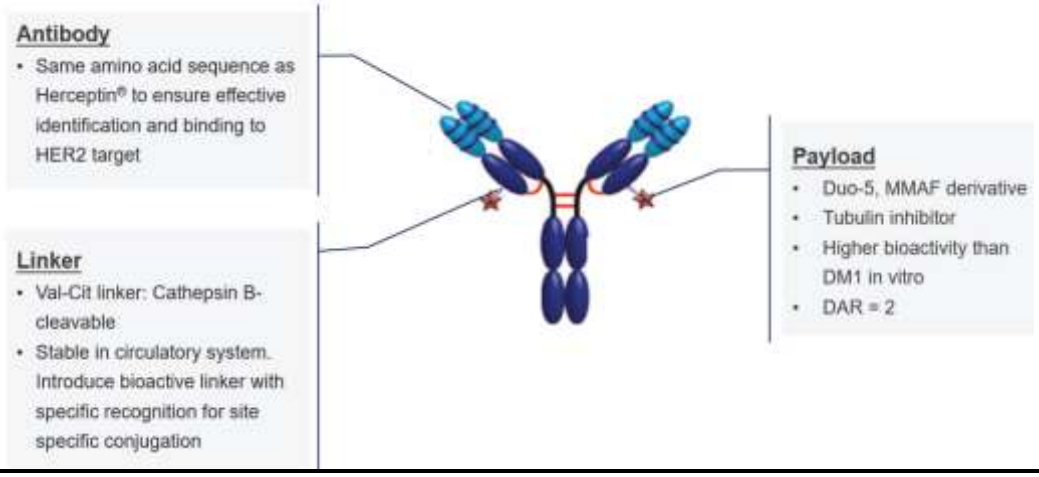
Source: Company data, Pubmed, CMBIGM.

A166 (HER2 ADC), potentially the first domestically developed HER2 ADC for breast cancer

MoA advantage of A166

With license granted from Levena, Kelun-Biotech is co-developing A166, which is a differentiated HER2 ADC in NDA registration stage to treat advanced HER2+ solid tumors, including BC, GC, CRC, and OC. A166 is positioned to be the first domestically developed ADCs for HER2+ BC in China.

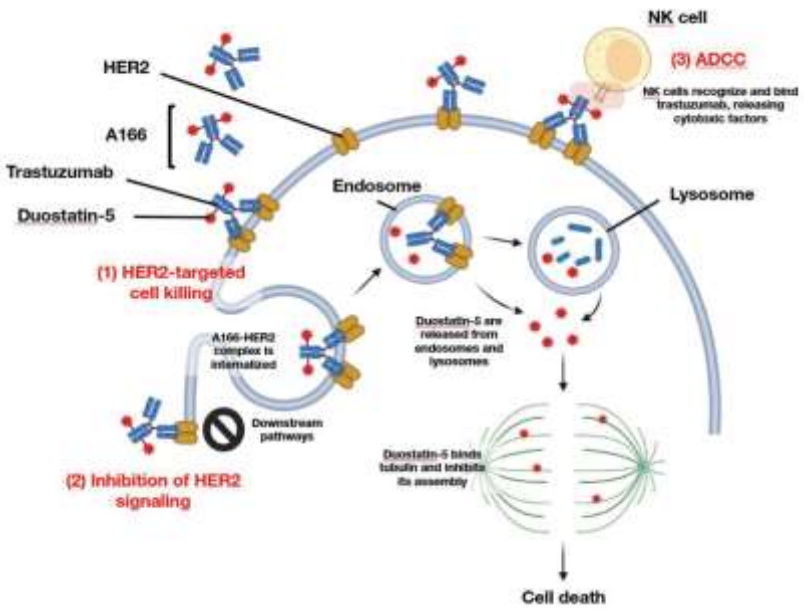
Figure 26: Molecular structure of A166



Source: Company data, CMBIGM

A166 employs a high payload toxicity-low DAR design, in which a novel, highly cytotoxic tubulin inhibitor, duostatin-5, is conjugated at a low DAR via an enzyme-cleavable linker to a HER2 mAb, which has the same amino acid sequence as Herceptin (trastuzumab), to ensure effective identification of and binding to HER2. Coupled with a homogeneously low DAR, achieved via site-specific conjugation technology, this design potentially ensures the safety of A166 by enhancing ADC stability and reducing premature payload release in blood circulation, while maintaining robust anti-tumor potency.

Figure 27: MoA of A166



Source: Company data, CMBIGM

As illustrated above, the design of A166 potentially enables strong anti-tumor activity through (1) HER2-targeted cell killing, (2) inhibition of HER2 signalling and (3) antibody-dependent cellular cytotoxicity (ADCC). Following its binding to the HER2 receptor via trastuzumab, the A166-HER2 complex is internalized and transported via the endosome-lysosome pathway. This releases duostatin-5, which then binds to and inhibits the assembly of tubulin, a major protein required for the maintenance of cellular architecture, thereby interfering with the cell division cycle and triggering apoptosis that kills the tumor cells.

Moreover, trastuzumab, the mAb component of A166, can block HER2 from propagating oncogenic signals to downstream signalling molecules, thereby inhibiting the major signalling route that HER2+ tumor cells rely on for growth and expansion. Further, trastuzumab can trigger ADCC, an immune-mediated attack, in which trastuzumab is recognized and bound by natural killer (NK) cells, which can release cytotoxic factors that kill the A166-bound tumor cells.

Figure 28: ADC design of HER2 ADCs (A166, Kadcyla, Aidixi and Enhertu)

	A166	Kadcyla	Aidixi	Enhertu
Company	Kelun Biotech	Roche	RemeGen	AZ / Daiichi Sankyo
Antibody	Trastuzumab	Trastuzumab	Disitamab	Trastuzumab
Linker	Val-Cit linker	MCC linker	Val-Cit linker	GGFG linker
Payload	Duo-5, a MMAF derivative and a highly toxic tubulin inhibitor	DM1, a maytansine derivative and a highly toxic tubulin inhibitor	MMAE, a highly toxic tubulin inhibitor	Deruxtecan, an Exatecan derivative and a moderately toxic TOPO I inhibitor
Conjugation	Stable site-specific lysine conjugation	Stochastic lysine conjugation	Reversible non-site-specific cysteine conjugation	Reversible site-specific cysteine conjugation
Overall DAR	2	3.5	4	8
Major differentiation of A166	--	A166's bystander effect due to enzyme-cleavable linker with cell membrane permeable payload A166's greater ADC homogeneity due to site-specific conjugation	A166's greater ADC homogeneity due to site-specific conjugation A166's improved plasma stability due to stable linker mAb conjugation	A166's minimal risk of ILD toxicity associated with Duo-5 A166's improved plasma stability due to stable linker mAb conjugation

Source: Company data, CMBIGM.
Note: Genentech's Kadcyla (T-DM1), Remege's Aidixi (RC48) and and Daiichi Sankyo's Enhertu (DS-8201) are the three HER2 ADCs approved in China.

HER2+ BC to be the first commercial indication of A166

A166 demonstrated promising efficacy in heavily pretreated advanced HER2+ BC and GC patients with a differentiated safety profile, based on preliminary results from a Ph1 dose expansion study and a Ph1b trial in China. A166 has met the primary endpoints of its pivotal Ph2 trial for 3L+ advanced HER2+ BC, based on which an NDA was submitted to the NMPA in May 2023. In addition, Kelun-Biotech is conducting a confirmatory Ph3 trial of A166 in China for 2L+ advanced HER2+ BC, and multiple Ph1b trials in China for other advanced solid tumors, including 2L+ HER2+ GC and 3L+ HER2+ CRC.

Figure 29: Clinical trials of A166

Indications	Stage	Trial ID	Region	Status
HER2+ BC (3L+)	Ph2 pivotal	CTR20212088	China	Met primary endpoint, NDA filed in May 2023
HER2+ BC(2L+)	Ph3 confirmatory	CTR20231740	China	Started in Jun 2023 (head-to-head vs TDM-1 HER2+ BC post trastuzumab and docetaxol)
HER2+ GC(2L+)	Ph1b	CTR20213396	China	To complete in 1H24
HER2+ CRC (3L+)	Ph1b	CTR20212950	China	To complete in 1H24

Source: Company data, CMBIGM

Unmet medical needs of HER2+ BC

The treatment paradigm for HER2+ BC patients in China primarily involves combination chemotherapy with two HER2 mAbs, trastuzumab and pertuzumab, or doublet chemotherapy with trastuzumab in the first-line setting, combination chemotherapy with TKI pyrotinib or HER2 mAb in the 2L setting, and triple-combination therapy involving a HER2 mAb pertuzumab or TKIs, and other chemotherapy in the 3L setting. For advanced HER2+ BC patients not eligible for trastuzumab, the treatment paradigm in China primarily involves combination chemotherapy with TKI pyrotinib in the first-line setting, HER2 ADC Kadcyla monotherapy and combination chemotherapy with TKI lapatinib in the 2L setting, and combination chemotherapy with TKI neratinib, TKI pyrotinib monotherapy and other TKI/HER2 mAb-chemotherapy combinations in the 3L setting. HER2 ADC Enhertu monotherapy is approved in China for treatment of 2L+ HER2+ BC and 2L+ HER2 low BC. Notably, Kadcyla and Enhertu carry notable safety concerns, including black box warning issued by the FDA for hepatic, cardiac and embryo-fetal toxicities for Kadcyla, and interstitial lung disease and embryo-fetal toxicity for Enhertu.

Promising efficacy of A166 in HER2+ BC with differentiated safety profile

Kelun-Biotech filed a NDA of A166 in China in May 2023, based on the pivotal Ph2 trial of A166 in 3L+ HER2+ BC. The pivotal trial is an open-label, single-arm trial in China with 123 adult subjects enrolled, receiving 4.8mg/kg of A166 injection once every 21 days. The primary endpoint is ORR assessed by IRC. With all enrolled patients having undergone a follow-up period of at least six months, the trial met its primary endpoint, while the detailed data of this trial has not been released.

The preliminary data from a single-arm, open-label Ph1 trial (CTR20181301) of A166 in HER2+ solid tumors has been released. The results, reported at the ASCO 2022 meeting, provided an update up to the cutoff date of Dec 2021 (link). The updated results, as of Jul 2022, are summarized below.

The Ph1b trial consists of both dose escalation and dose expansion parts. The dose escalation part was completed in Apr 2020, with a total of 25 patients enrolled and receiving A166 at doses ranging from 0.1 to 6.0 mg/kg. The dose expansion part of the trial is still ongoing, with the targeted 71 patients fully enrolled in Jan 2023, receiving A166 at the RP2D dose of either 4.8 or 6.0 mg/kg Q3W. Among the 25 patients enrolled in the dose escalation study, five achieved PR, indicating a positive treatment outcome.

In the dose expansion study, at the cut-off date of Jul 2022, 58 patients were enrolled and evaluable for efficacy. All the patients had prior HER2-targeted therapy with a median 4 lines of prior treatment, of which 100% (58/58) received trastuzumab, 95% (55/58) received anti-HER2 TKIs, 33% (19/58) received pertuzumab, and 21% (12/58) received anti-HER2 ADCs (eight received T-DM1, three received ARX-788 and one received TAA-013). A166 achieved an overall ORR of 70.7% (41/58), with an ORR of 73.9% (17/23) in the 4.8 mg/kg cohort and 68.6% (24/35) in the 6.0 mg/kg cohort. The mPFS was 12.3 months in the 4.8 mg/kg cohort and 9.4 months in the 6.0 mg/kg cohort, and the mDOR was 11.0 months in the 4.8 mg/kg cohort and 8.3 months in the 6.0 mg/kg cohort.

Figure 30: A166's best responses for HER2+ BC patients in a Ph1 study

	4.8 mg/kg, Q3W N=23	6.0 mg/kg, Q3W N=35	Total N=58
ORR	73.9%	68.6%	70.7%
DCR	82.6%	80.0%	81.0%
mPFS (months)	12.3	9.4	10.2
mDOR (months)	11.0	8.3	8.5

Source: Company data, CMBIGM.

Figure 31: Cross-trial comparison of HER2 ADC therapies for 3L treatment of HER2-positive BC

	A166	RC48	DS-8201		T-DM1	SHR-A1811
Company	Kelun-Biotech	RemeGen	AstraZeneca		Roche	Hengrui
Regimen	Mono, single arm	Mono, single arm	Mono, single arm	Mono, vs T-DM1	Mono, vs lapatinib plus capecitabine	Mono
Trial	CTR20181301	NCT02881138, NCT03052634	DESTINY-Breast01 (registrational)	DESTINY-Breast03 (head-to-head)	NCT00829166	NCT04446260
Trial stage	Phase 1	Phase 1/1b	Phase 2	Phase 3	Phase 3	Phase 1
Primary endpoint	Safety, RP2D	Safety, RP2D	ORR	PFS	PFS, OS, safety	DLT, safety, RP2D
Treatment line	Median 4 lines of prior treatment	78.6% pts received prior ⩾ 2 lines of chemo	Pts previously treated with T-DM1	Pts previously treated with trastuzumab and taxane	Pts previously treated with trastuzumab and a taxane	A median of 3 prior treatment lines in the metastatic setting
Patient number	58	70	184	524	991	108
Biomarker status	HER2 IHC3+ or IHC2+&FISH+	HER2 IHC3+ or IHC2+&FISH+	HER2 IHC3+ (83.7%), IHC1+/2+&FISH+ (15.2%)	HER2 IHC3+ (88.9%), IHC2+&FISH+ (10.5%)	HER2 IHC3+ or FISH⩾2	HER2-positive
ORR	**73.9%** (4.8 mg/kg, Q3W cohort)	42.9%	60.9%	**79.7%** vs 34.2%	43.60%	**81.5%**
mPFS (mo)	**12.3** (4.8 mg/kg, Q3W cohort)	6.0	**16.4**	Not reached (18.5, NE) vs 6.8 (12mo PFS rate 75.8% vs 34.1%)	9.6 vs 6.4	-
mOS (mo)	-	-	-	-	30.9 vs 25.1	-
Grade ⩾3 TRAEs	61.0% (47/77)	41.4%	48.4%	45.1% vs 39.8%	41% vs 57%	52.4% (131/250)
Interstitial lung disease	2.6% (2/77)	-	13.6%	10.5% vs 1.9%	-	1.2% (3/250)
Approval status in US and China	BLA in China in May 2023	Not approved for BC yet	Approved for 2L in the US and in China for both HER2 positive and HER2 low BC		Approved in the US and China for HER2 positive BC	Not approved yet, two Ph3 ongoing for HER2 positive BC and HER2 low BC
Data source	Link	Link	Link	Link	Link	Link

Source: Company data, Pubmed, CMBIGM.
Note: DS-8201 was approved in the US with a boxed warning for the risk of interstitial lung disease (ILD) and embryo-fetal toxicity.

In cross-trial comparison, the ORR of A166 in 3L+ HER2+ BC (73.9% ORR) were comparable to DS-8201 (60.9%~79.7% ORR) and SHR-A1811 (81.5% ORR).

TRAEs were primarily ocular and peripheral nerve-related and reversible. Grade ⩾3 TRAEs were reported in 61.0% (47/77) of patients in A166's Ph1 trial. The most common Grade ⩾3 TRAEs were corneal epitheliopathy, blurred vision, dry eyes and peripheral neuropathy, happening in 36.4%, 24.7%, 15.6% and 6.5% of the patients. All ocular-related AEs were reversible and occurred approximately after two cycles of A166 treatment. Following a protocol assigned eye examination, ocular-related AEs was generally manageable and reversible.

In cross-trial safety comparison, the 61.0% Grade ⩾3 TRAEs of A166 was higher than that of Aidixi (41.4%), Enhertu (48.4%), and Kadcyla (41%), while A166 showed a differentiated safety profile from other HER2 ADC drugs, with lower incidence of haematological, GI and lung toxicities in non-head-to-head cross-trial comparisons. However, A166 demonstrated higher incidences of ocular and peripheral nerve-related toxicities, which were reversible and generally manageable.

Figure 32: Grade ⩾3 AEs of HER2 ADC therapies for 3L treatment of HER2-positive BC

Grade>=3 AEs	A166 (4.8 and 6.0 mg/kg, Q3W, N=77)	Aidixi (RC48) (2.5 mg, Q2W, N=350)	Enhertu (DS-8201) (5.4 mg/kg, Q3W, N=234)	Kadcyla (TDM-1) (3.6 mg/kg, Q3W, N=490)
Anemia	3.9	2.6	7	4.1
Decreased platelet count	0	1.1	3.4	17
Decreased neutrophil count	1.3	16.9	16	3
Decreased white blood cell count	4.2	10.9	7	N/A
Nausea	0	0.3	7	0.8

Vomitting	0	0.6	3.8	0.8
Diarrhea	0	0.3	1.7	1.6
Elevated aspartate aminotransferase	0	16	0.9	<8
Elevated alanine aminotransferase	0	1.7	0.4	<6
Peripheral neuropathy	6.5	1.1	N/A	2.2
Corneal disease	36.4	N/A	N/A	0
Dry eye	15.6	N/A	0.4	0
Blurred vision	24.7	N/A	N/A	0
ILD (grade>=3)	0	N/A	2.6	N/A
ILD (all grade)	*2.6*	*N/A*	*10*	*N/A*

Source: Company prospectus, drug labels.
Note: This table summarizes the common drug adverse reactions and laboratory abnormalities (>=2% grades 3 or 4) for A166, Aidixi, Enhertu and Kadcyla.

Exploring opportunities of A166 in HER2+ GC and HER2+ CRC

Treatment paradigm of HER2+ GC

In China, the early-line treatments for HER2+ GC primarily involve combination chemotherapy with HER2 mAb trastuzumab and single-agent chemotherapy (in the 2L setting), with HER2 ADC Aidixi (RC48), an anti-angiogenic TKI, PD-1 inhibitors and single-agent chemotherapy available as 3L+ treatments. The use of trastuzumab + chemo in early-line HER2+ GC patients generally improves patient outcome vs conventional chemotherapy. However, a significant proportion of patients do not respond to trastuzumab and the majority of patients who initially benefit from trastuzumab develop drug resistance. These patients have limited effective 2L+ treatment options, with Aidixi being the only HER2-directed drug available in the 3L+ setting. This underscores a need for novel HER2-directed drugs to overcome trastuzumab resistance and widen the treatment options for 2L+ HER2+ GC patients. Aidixi is currently the only HER2 ADC approved in China for advanced HER2+ GC, and Enhertu submitted the sBLA for HER2+ GC in Dec 2023 in China.

Satisfying data of A166 in HER2+ GC

The Ph1b trial of A166 in 2L+ HER2+ GC completed enrollment in Dec 2022. As of Feb 2023, 16 patients were dosed at 4.8 mg/kg of A166 injection Q3W, with a median follow-up of 6.7 months. The ORR was 31.3% (5/16) and the mPFS was 4.6 months. On the safety side, the most frequent TRAEs in the 16 evaluable patients were blurred vision (68.8%), corneal epitheliopathy (68.8%), dry eye (50.0%), neutropenia (25.0%), lymphopenia (25.0%), anemia (25.0%) and weight loss (25.0%). Grade 3 or higher TRAEs were reported in 37.5% of patients. Enhertu will be a strong competitor for A166 in the HER2+ GC market in China, in our view.

Figure 33: Cross-trial comparison of therapies for 2/3L GC treatment

	A166	RC48	DS-8201	T-DM1	Apatinib	Nivolumab
Regimen	Mono	Mono, single arm	Mono, vs chemo	Mono, vs chemo	Mono, vs placebo	Mono, vs placebo
Trial	CTR20213396	RC48-C008	DESTINY-Gastric01	GATSBY	NCT01512745	ATTRACTION-2
Trial stage	Phase 1b	Phase 2	Phase 2	Phase 2/3	Phase 3	Phase 3
Primary endpoint	RP2D, ORR	ORR	ORR	OS	OS, PFS	OS
Treatment line	2L+	All pts had ⩾2 lines prior regimens	All pts had ⩾2 lines prior regimens	Progressed during or after first-line therapy	All pts had ⩾2 lines prior regimens	All pts had ⩾2 lines prior regimens
Patient number	16	125	187	345	267	493
Biomarker status	HER2 IHC2+/ISH+ or IHC 3+	HER2 IHC2+/3+	HER2 IHC2+/ISH+ or IHC 3+	HER2-positive	-	-
ORR	**31.3%**	24.8%	**51.3% vs 14.3%**	20.6% vs 19.6%	2.8% vs 0%	11.9% vs 0%
mPFS (mo)	**4.6**	4.1	**5.6** vs 3.5	2.7 vs 2.9	2.6 vs 1.8	1.6 vs 1.5
mOS (mo)		7.9	12.5 vs 8.4	7.9 vs 8.6 (not superior)	6.5 vs 4.7	5.3 vs 4.1
Grade ⩾3 TRAEs/TEAEs		56.8%	85.6% vs 56.5%	60% vs 70%	69% vs 43%	11.8% vs 4.3%

Approval status in US and China for GC	Not approved yet	Approved in China for 3L+ HER2+ GC	Approved in the US (2L+ HER2+ GC); sBLA in China submitted in Dec 2023	Not approved due to clinical trial failure	Approved in China for 3L+ GC	Approved in China (mono for 3L+ GC, +chemo for adjuvant and 1L GC) and in the US (+chemo for adjuvant and 1L GC)
Data source	Link	Link	Link	Link	Link	Link

Source: Company data, Pubmed, CSCO GC guideline, CMBIGM.

Treatment paradigm of HER2+ CRC

Kelun-Biotech is also conducting a Ph1b trial in HER2+ CRC since Dec 2021. In China, the early-line treatments for HER2+ CRC primarily involve chemotherapy with or without EGFR mAb cetuximab or anti-angiogenic mAb bevacizumab. To date, there have been no HER2-directed drugs approved by the NMPA for advanced HER2+ CRC. The response rates of advanced HER2+ CRC patients to current non-HER2-directed standard treatments are only between 10.0% to 35.3%, leaving many patients with limited clinical benefit and highlighting the need for novel HER2-directed drugs to improve the survival of advanced HER2+ CRC patients. We look forward to Kelun-Biotech to release data of A166 in HER2+ CRC.

Gain a foothold in the crowded HER2 ADC market

The HER2 ADC market is crowded with three medicines already approved, followed by multiple drug candidates at Ph3 stage trials. Roche/Genentech's Kadcyla (T-DM1), Remegen's Aidixi (RC48) and Daiichi Sankyo's Enhertu (DS-8201) are currently the three HER2 ADCs approved in China.

In Aug 2023, the NMPA released draft rules on drug conditional approval (link). According to these rules, once certain drugs receive full approval, drug candidates with the same mechanism of action (MoA) and targeting the same indications may not be eligible for conditional approval. This has raised concerns in the market regarding the regulatory uncertainty surrounding the NDA of A166 for HER2+ BC based on Ph2 results. This uncertainty is due to the full approval of Enhertu in China for 2L and beyond HER2+ BC, as well as 3L and beyond HER2- BC, and the full approval of T-DM1 in China for HER2+ BC in advance. However, it is important to note that these new rules are still in the draft stage and are open for comments. As A166 represents a potential first domestic HER2 ADC for the treatment of breast cancer, it still enjoys regulatory favor, in our view. Moreover, the confirmatory Ph3 trial of A166 in HER2+ BC is progressing smoothly, with the first patient enrollment achieved in Jun 2023.

Figure 34: Approved HER2 ADCs in China

Drug	Indications	Approval date	Dose	Price (RMB)	Monthly cost (RMB)	Annual cost (RMB)	NRDL	NRDL period
Aidixi (RC48)	3L+ HER2+ GC	2021.06	2.5 mg/kg, Q2W (GC)	3,800/60mg	24,429*	293,143*	3L+ HER2+ GC; 2L+ HER2+ UC	2024.01-2025.12
	2L+ HER2+ UC	2021.12	2.0 mg/kg, Q2W (UC)		16,286*	195,429*		
Kadcyla (T-DM1)	Early-stage HER2+ BC; late-stage/m HER2+ BC	2020.01 2021.06	3.6 mg/kg, Q3W	3,580/100mg 5,130/160mg	12,443	149,314	Early-stage HER2+ BC; late-stage/m HER2+ BC	2023.03-2024.12
Enhertu (DS-8201)	2L+ HER2+ BC; 3L+ HER2- BC	2023.02 2023.07	5.4 mg/kg, Q3W	9,432/100mg	25,152**	301,824**	--	--

Source: CMBIGM
Note: *Aidixi renewed the NRDL in late 2023 with the updated price available since Jan 2024; RemeGen has not officially released the latest NRDL price of Aidixi as of Feb 2024; the price of Aidixi in the table was the price prior Jan 2024. ** PAP of Enhertu: buy two, get one free.

Figure 35: Anti-HER2 ADC molecules at late clinical stage

Drug	Company	China development phase	Overseas development phase	Targeted indications
Enhertu (DS-8201)	Daiichi Sankyo, AstraZeneca	Approved	Approved	HER2-positive BC (2L+)
		Approved	Approved	HER2-low BC (3L+ approved, 2L data readout in 1H24)
		BLA filed	Approved	HER2-positive GC (2L+)
		Phase III	Approved	HER2-mutated NSCLC (2L+)
		--	NDA filed, Phase II	HER2+ tumour-agnostic indication (PDUFA in 2Q24, link)
		Phase III	Phase III	HER2-positive BC (1L, +/- Keytruda)
		Phase III	Phase III	HER2-positive early BC
		Phase III	Phase III	HR+/HER2-low early BC
		Phase III	Phase III	HER2-mutated NSCLC (1L)
		Phase II	Phase III	Biliary tract cancer
		--	Phase II	CRC, bladder cancer, osteosarcoma, TNBC, UC, OVC, cervical cancer, endometrial cancer, pancreatic cancer
Kadcyla (T-DM1)	ImmunoGen, Roche	Approved	Approved	HER2-positive BC (3L+ and adjuvant)
		Phase II/III	Phase II/III	HER2-positive GC, GEJC
		--	Phase II	Salivary gland cancer, OVC, lung cancer
Aidixi (RC48)	RemeGen, Seagen	Approved	Phase III (1L)	HER2-expressing UC (2L+)
		Approved	--	HER2-positive GC, GEJC (3L+)
		Phase III	--	HER2-low BC
		Phase II/III	--	HER2-positive BC
		Phase II	--	BTC, melanoma, MIBC, NSCLC
Kadcyla biosimilar	Zydus Lifesciences	--	Approved	Similar to the reference product
A166	**Levena, Kelun-biotech**	**NDA filed**	**--**	**HER2+ BC (3L+)**
		Phase III	**--**	**HER2+ BC (2L+)**
		Phase Ib	**--**	**HER2 positive GC (2L+), CRC (3L+)**
SHR-A1811	Hengrui	Phase III	--	HER2-positive BC
		Phase III	--	HER2-low BC
		Phase III	--	GC
		Phase III	--	CRC
		Phase II	--	BC, TNBC, HER2-expressing NSCLC, salivary gland cancer
trastuzumab duocarmazine (SYD985)	Byondis, medac	--	BLA, while suspended by FDA	HER2-positive BC (FDA CRL was issued in May 2023 to require additional info that requires time and resources)
		--	Phase II	HER2-expressing endometrial cancer
		--	Phase I	UC, OVC, bladder cancer, BC
BAT8001	Bio-Thera	Phase III	--	HER2-positive BC
DB-1303	BioNTech, DualityBio	Phase III	Phase III	HER2-positive BC
		Phase III	Phase III	HER2-low BC
DP303c	CSPC	Phase III	--	HER2-positive BC
		Phase II	--	OVC, HER2 positive BC, GC, GEJC
JSKN-003	Alphamab	Phase III	--	HER2-low BC
LCB14-0110	LegoChem, Iksuda, Fosun	Phase III	Phase II	HER2-positive BC
		Phase II	Phase I	GC, GEJC, CRC, NSCLC
TAA013	TOT Biopharm	Phase III	--	HER2-positive BC
MRG002	Lepu Biopharma	Phase III	--	UC
		Phase II/III	--	HER2-positive BC
		Phase II	Phase I/II	BTC, UC, HER2-low BC, HER2-positive BC, GC, GEJC, NSCLC
ARX788	Ambrx, Novocodex	Phase II/III	--	HER2-positive BC
		Phase II/III	--	HER2-positive GC
		Phase II	Phase II	TNBC, NSCLC, BTC, CRC

Source: PharmCube (as of Mar 2024), CMBIGM

The global HER2 ADC market is grow rapidly, led by the growth of Enhertu. Excluding Japan, Enhertu's global in-market sales, recorded by Daiichi Sankyo and AstraZeneca, amounted to US$1,173mn (+175% YoY) in FY22 (vs US$426mn in FY21). The combined sales of Enhertu, recorded by Daiichi Sankyo and AstraZeneca, amounted to US$1,169mn in 1H23, representing 168% YoY growth vs US$436mn. The recent approval of Enhertu for HER2-low BC should further expand the HER2 ADC market. We expect A166 to be able to gain reasonable share in the HER2 ADC market in China.

The global market for HER2 ADCs is experiencing rapid growth, largely driven by the success of Enhertu. In FY23, the combined global sales of Enhertu recorded by Daiichi Sankyo and AZ amounted to US$2.57bn (+105% vs US$1.25bn in FY22). Furthermore, the recent approval of Enhertu for the

treatment of HER2-low breast cancer expands the potential market for HER2 ADCs. With this in mind, we anticipate that A166 has the potential to capture meaningful market share in the HER2 ADC market, particularly in China.

Other clincial oncology pipelines

SKB315, early-stage CLDN18.2 ADC that has outlicensed to MSD

SKB315 is a novel CLDN18.2 ADC targeting advanced solid tumors, currently in Ph1 clinical development. There is no CLDN18.2-targeting therapies approved globally, while Astellas' zolbetuximab(mAb) is leading the development with BLAs filed in both China and the US in Jul 2023. For ADC development, the CLDN18.2 targeted ADC development is still at early stage globally.

Compared with mAbs, targeting CLDN18.2 via ADC is potentially a more efficacious therapeutic strategy as ADCs exert anti-tumor effects primarily via cytotoxic payloads and bystander effect, which may overcome low or heterogeneous CLDN18.2 expression in tumors that traditionally limits the efficacy of mAbs. With a differentiated payload-linker design and an in-house developed humanized CLDN18.2 antibody, SKB315 has demonstrated encouraging efficacy and safety across various preclinical in vivo tumor models with heterogeneous CLDN18.2 expression, indicating its promising therapeutic potential.

Due to the selective expression in prevalent and lethal cancers that have limited effective treatment, such as gastric cancer (GC) and pancreatic cancer (PC), CLDN18.2 has been a promising therapeutic target pursued by multiple companies for in-house development and licensing deals. In Jun 2022, Kelun-Biotech out-licensed the global development and commercialization rights for SKB315 to MSD, coded as MK-1200. MSD paid an upfront of US$35mn, and is committed to future milestone payments of up to US$416mn and sales milestone payments of up to US$485mn, together with future tiered royalties.

Figure 36: Development of CLDN18.2 ADC globally

Drug Name	Company	Latest stage in China	Latest overseas stage	MoA	Drug Classification
IBI343	Innovent, Synaffix	Phase II in GC	--	CLDN18.2 ADC, Top I inhibitor camptothecin	--
CMG901	Keymed, Lepu, AstraZeneca	Phase II in GC, pancreatic cancer	Phase II in GC, pancreatic cancer	Anti-microtubule/CLDN18.2 ADC, auristatin derivative	Payload [MMAE], cleavable linker
LM-302	LaNova,Turning Point (BMS)	Phase II in GC, pancreatic cancer biliary tract cancer, solid tumor	Phase I in solid tumor	Anti-microtubule/CLDN18.2 ADC, auristatin derivative	Payload [MMAE], cleavable linker
SKB315	**MSD, Kelun-Biotech**	**Phase I in solid tumor**	**--**	**CLDN18.2 ADC, Top I inhibitor camptothecin**	**Payload [belotecan], cleavable linker**
RC118	RemeGen	Phase I/II in solid tumor	Phase I in solid tumor	Anti-microtubule/CLDN18.2 ADC, auristatin derivative	Payload [MMAE], cleavable linker
SHR-A1904	Hengrui, MSD	Phase I in pancreatic cancer	Phase I/II in solid tumor	CLDN18.2 ADC	Payload [TOPOi]
SO-N102	Sotio	--	Phase I/II in gastric cancer, pancreatic cancer	CLDN18.2 ADC	Payload [PNU-159682], non-cleavable linker
XNW27011	Evopoint	Phase I in solid tumor	Phase I in solid tumor	CLDN18.2 ADC	--
ATG-022	Antengene	Phase I in solid tumor	Phase I in solid tumor	Anti-microtubule/CLDN18.2 ADC, auristatin derivative	Payload [MMAE], cleavable linker
JS107	Junshi Biosciences	Phase I in solid tumor, pancreatic cancer	--	Anti-microtubule/CLDN18.2 ADC, auristatin derivative	Payload [MMAE]
PR301	Boan Biotech	Phase I in solid tumor	--	CLDN18.2 ADC	--
SYSA1801	CSPC,Elevation Oncology	Phase I in solid tumor	Phase I in solid tumor	Anti-microtubule/CLDN18.2 ADC, auristatin derivative	Payload [MMAE], cleavable linker
TORL-2-307	TORL	--	Phase I/II in gastric cancer, pancreatic cancer	CLDN18.2 ADC	--
TQB2103	Chia Tai Tianqing	Phase I	Phase I	CLDN18.2 ADC	--

Source: PharmCube (as of Mar 2024), CMBIGM

Figure 37: Development of major CLDN18.2 therapies (excluding ADC) globally

Drug Name	Company	Latest stage in China	Latest overseas stage	Type of drug
zolbetuximab	Ganymed (Astellas Pharma)	Filed BLA for 1L CLDN18.2 positive GC in China in Jul 2023	FDA issued a CRL to decline the BLA due to manufacturing issues in Jan 2024; Ph2 in pancreatic cancer	CLDN18.2 mAb
osemitamab	Transcenta (创胜集团)	Phase III in GC; Phase II in BTC, cholangiocarcinoma	Phase II in GC, PC	CLDN18.2 mAb
ASKB589	AskGene Pharma	Phase III in GC; Phase I/II in PC	--	CLDN18.2 mAb
M108	Futuregen Biopharm	Phase III in GC	--	CLDN18.2 mAb
IBI389	Innovent	Phase II in PC	--	CLDN18.2/CD3 bispecific
CT041	CARsgen Therapeutics	Phase II in GC	Phase II in GC	CLDN18.2 CART
AZD5863	AstraZeneca, Harbour	Phase I/II in solid tumor	Phase I/II in solid tumor	CLDN18.2/CD3 bispecific
LB1904	Legend Biotech	Phase I in PC	--	CLDN18.2 CART
IMC002	Immunofoco	Phase I/II in GC, PC	--	CLDN18.2 CART
MIL93	Mabworks Biotech	Phase I in GC, PC	--	CLDN18.2 mAb
NBL-015	Leap Therapeutics,CSPC	Phase I in solid tumor	--	CLDN18.2 mAb
PM1032	Biotheus,GeneChem	Phase I/II in solid tumor	--	4-1BB,CLDN18.2 bsAb
Q-1802	QureBio	Phase I/II in GC	--	CLDN18.2,PDL1 bsAb
ZL-1211	ZAI Lab	Phase I/II in solid tumor	Phase I/II in solid tumor	CLDN18.2 mAb

Source: PharmCube (as of Mar 2024), CMBIGM

Astellas' zolbetuximab is leading the development of CLDN18.2 targeted therapies, as a mAb, with BLAs filed both in the US and China in Jul 2023 for 1L CLDN18.2 positive GC. In Jan 2024, the US FDA issued a CRL to decline the BLA due to manufacturing issues, while no additional clinical data or studies were requested to affirm the agent's efficacy or safety. The BLAs were based on the SPOTLIGHT and GLOW registrational MRCT trials, both with patients enrolled in the China. In the SPOTLIGHT trial, zolbetuximab plus mFOLFOX6 demonstrated statistically significant improvements in PFS and OS compared with the mFOLFOX6 arm, with mPFS of 10.61 vs 8.67 months (HR=0.75, p=0.0066, link). In the GLOW study, zolbetuximab plus CAPOX demonstrated a statistically significant improvement in PFS compared with CAPOX only, with mPFS of 8.21 vs 6.80 months (HR=0.69, p=0.0007, link). To note, nivolumab plus chemo realized 7.7 months of mPFS (vs 6.9 months in the chemo arm, HR=0.79) as observed in its registrational Checkmate-649 trial for 1L GC, regardless of CLDN18.2 expression.

Osemitamab, a mAb developed by Transcenta (创胜集团), is also at late-stage of development. Osemitamab plus CAPOX realized 68% (27/45) ORR as observed in Ph1/2a study for 1L GC (link). The mPFS and mOS were immature at the cutoff date. Osemitamab plus nivolumab is currently in a global Ph3 MRCT trial for 1L GC.

A167, a PD-L1 mAb with potential to combo with ADCs for cancer treatment

A167 (PD-L1 mAb) is expected to be Kelun-Biotech's first commercialized product with an NDA submitted to the NMPA for 3L+ RM-NPC in Nov 2021 and conditional marketing approval expected in 2024. The approval will be conditional partially upon the company's commitment to complete a Ph3 trial of A167+chemotherapy for 1L RM-NPC. The Ph3 study completed patient enrollment in Jun 2023 and the data of the trial was submitted to CDE in early 2024.

The company is proactively investigating the prospects of A167 as a foundational component in early-line therapies, synergizing with its ADC offerings. Currently, two Ph2 trials are in progress: (1) a trial assessing the combination of SKB264 with A167, with or without chemotherapy, as a first-line treatment for advanced NSCLC with EGFR-wild type, and (2) another examining SKB264 with or without A167 as an initial treatment for advanced TNBC.

The PD(L)-1 landscape in China is saturated, with a multitude of PD(L)-1 inhibiting antibodies authorized for treating diverse cancers. Nonetheless, A167 holds promise for innovative combination treatments with ADC assets such as SKB264. Following the completion of patient enrollment in the Ph3 confirmatory trial for first-line NPC, we anticipate that A167 stands a strong chance of receiving approval in China, upon a favorable outcome from the Ph3 trial.

A140, a potential front-runner in the cetuximab biosimilar space in China

A140 has potential to be the first cetuximab biosimilar in China with an NDA filed in Sep 2023 (link) for RAS wild-type mCRC and head and neck cancer (HNSCC), providing increased accessibility and affordability for a widely used therapy targeting a key pathway in many cancers, starting with rat sarcoma virus (RAS) wild-type mCRC.

Driven by its high demand in China and NRDL inclusion, cetuximab (Erbitux, EGFR mAb) posted annual sales of approximately EUR441mn in the Asia-Pacific region in 2022. A140 demonstrated PK equivalence to cetuximab in a Ph1 trial, with clinical equivalence being evaluated in a pivotal Ph3 trial (CTR20202451). To note, Mabpharma/Simcere filed NDAs for their EGFR mAb CMAB009 in Mar 2023.

In 2022, Merck KGaA recorded EUR1.02bn (+4% YoY) in sales from Erbitux in the global market and Eli Lilly recorded additional US$567mn (+3%) in the North America market. In the Asia-Pacific region, the sales of Erbitux grew faster at a YoY rate of 13% in 2022, reaching EUR441mn.

A400, a second-generation selective RET inhibitor designed to combat drug resistance

A400 is positioned to be the first domestically developed second-generation selective RET inhibitor for NSCLC, medullary thyroid cancer (MTC) and other solid tumors with a high prevalence of RET alterations. RET alterations have been reported to be a major oncogenic driver in about 2% of all cancers, most notably in NSCLC and MTC.

Two first-generation selective RET inhibitors, pralsetinib from Blueprint and selpercatinib from Eli Lilly / Innovent, have been approved in China and in the US for RET+ NSCLC and MTC. However, there could be acquired RET drug-resistant mutations and safety issues such as hypertension and hematological toxicity with the first-generation RET inhibitors, underscoring the need for novel selective RET inhibitors with improved safety and efficacy against drug resistant mutations.

Kelun-Biotech has designed A400 with a novel proprietary molecular structure to potentially address selective RET inhibitor resistance while maintaining target selectivity, efficacy and safety with reduced manufacturing cost and difficulty.

According to Kelun-Biotech's prospectus, in a Ph1/2 trial, A400 demonstrated promising anti-tumor efficacy in patients with advanced RET+ solid tumors, highlighted by an ORR of 74% and 66.7% at RP2D (90mg QD) for 1L and 2L+ advanced RET+ NSCLC, respectively. Notably, A400 demonstrated therapeutic potential in selective RET inhibitor-resistant patients with an ORR of 33% and DCR of 83% at RP2D.

Figure 38: Cross-trial comparison of RET inhibitors in NSCLC

Drug	A400	Selpercatinib	Pralsetinib
Company	Kelun-Biotech / Ellipses	Eli Lilly / Innovent	Blueprint / Cstone
Trial ID	NCT05265091, Ph1/2	LIBRETTO-001, Ph1/2	ARROW, Ph1/2
Patient No.	57	316	237
Baseline	For later line: median prior 2 treatments, 28% pretreated with PD(L)1	For later line: 43% pts received >=3 prior treatment	For later line: median prior 2 treatments, 42% pretreated with PD(L)1
ORR	76% for 1L pts (n=25); 63% for pre-treated pts (n=32)	84% for 1L pts (6% CR, n=69); 61% for pre-treated pts (7% CR, n=247)	78% for 1L pts (7% CR, n=107); 63% for pre-treated pts (6% CR, n=130)
mPFS		22.0 mos for 1L pts; 24.9 mos for pre-treated pts	
TRAE (Gr>=3)	24.1%		
TRAEs led to dose reduction	4.6%	30.0%	
TRAEs led to treatment discontinuation	6.9%	2.0%	
Hypertension	Rare (<5%) and low-grade	14% Gr 3 or 4	18% Gr 3 or 4
QT interval prolongation	Rare (<5%) and low-grade		
Platelets decrease	Rare (<5%) and low-grade		5% Gr 3 or 4
Lymphocytes decrease	Rare (<5%) and low-grade		32% Gr 3 or 4
Others	-	Warnings for hepatotoxicity, ILD, hypertension, QT interval prolongation, hemorrhagic events, etc in the label	Warnings for ILD, hypertension, hepatotoxicity, hemorrhagic events, etc in the label
Source	Link	Link1, Link2	Link

Source: Company data, FDA labels, Pubmed, CMBIGM

A400 demonstrated a potentially favorable safety profile, with no incidence of grade 3 or above lymphopenia and thrombocytopenia, and had substantially lower incidence of grade 3 or above cardiovascular AEs (e.g., hypertension), hematological toxicity and electrolyte abnormalities, based on cross-trial comparisons with approved first-generation selective RET inhibitors.

Overall, A400's efficacy in NSCLC could be comparable to the first-generation RET inhibitors, while it is expected to have an improved safety profile, in our view. We expect A400 to be a reasonable alternative to the first-generation RET inhibitors upon its approval. Based on the promising preliminary results of A400 in advanced RET+ NSCLC patients, Kelun-Biotech completed CDE clinical consultation and initiated a pivotal trial for 2L+ advanced RET+ NSCLC in May 2023. The company also initiated a pivotal trial for 1L advanced RET+ NSCLC in 2H23. Additionally, in Mar 2021, the company granted to Ellipses an exclusive license of A400 outside Greater China and certain Asian countries (link).

Multiple early-stage oncology assets to support future innovation

Kelun-Biotech is also advancing several early-stage oncology assets. SKB337 is a differentiated PD-L1/CTLA-4 bsAb in Ph1 stage, with a potentially better safety and efficacy profile demonstrated in preclinical studies than monospecific PD-L1 and CTLA4 mAbs. A289 is a Ph1 stage mAb targeting LAG3 and has demonstrated its potential to synergize with PD-(L)1 mAbs and chemotherapy to promote anti-tumor response. A296, a novel second-generation small molecule STING agonist with a differentiated molecular design, has the potential to invigorate anti-tumor immunity in cold tumors that are unresponsive to existing immune checkpoint inhibitors and is positioned as a combination therapy to be used with the company's other immunotherapy assets.

Financial analysis

Product sales to ramp up fast

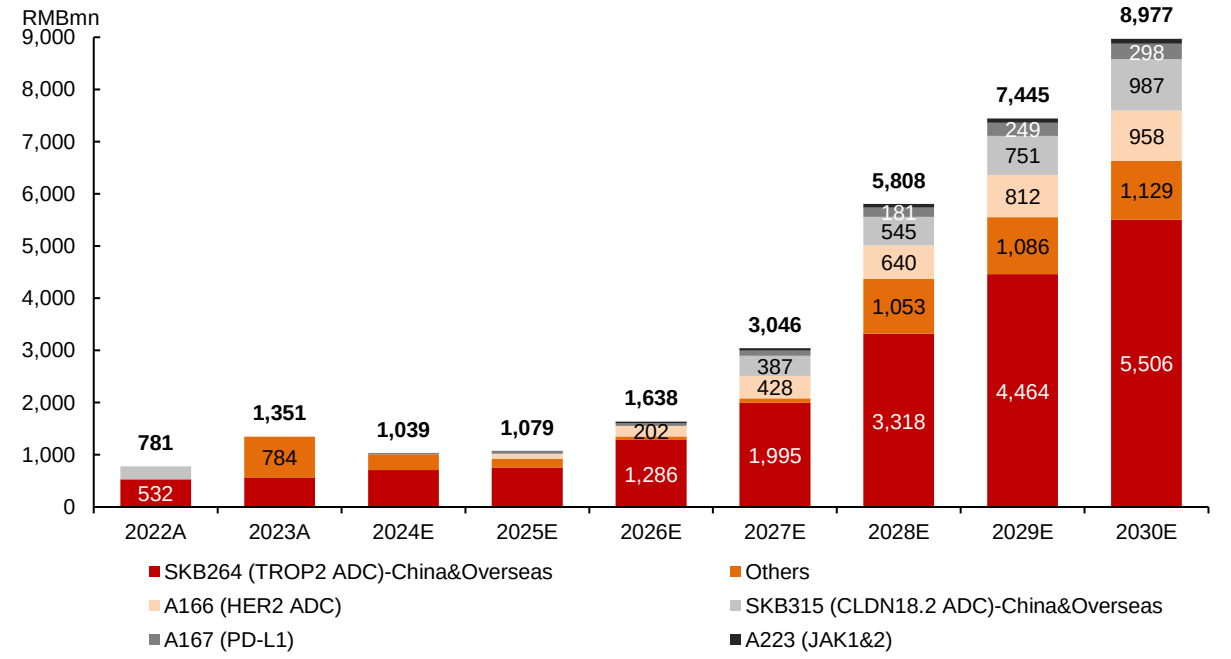
We anticipate that SKB264 will commence its commercial rollout in China by 2025E for TNBC treatment, followed by HR+/HER2- BC and NSCLC in 2026E, with its growth trajectory in the Chinese market being predominantly propelled by the robust demand for NSCLC therapies. SKB264 is projected to become the company's cornerstone for revenue generation. In international markets, the commercial success of SKB264 is expected to be driven largely by its utilization in NSCLC and HR+/HER2- BC treatments. By 2030E, we forecast that SKB264 will contribute approximately RMB4.3bn in risk-adj revenues from the China market, and an additional RMB1.2bn risk-adj revenue from global markets including milestone payments. We estimate Kelun-Biotech's total risk-adj sales from products and licenses of RMB1,351mn/RMB1,039mn/ RMB1,079mn in FY23E/24E/25E, respectively.

Figure 39: Risk-adjusted sales and license income forecasts

YE Dec 31 (RMB mn)	2022A	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Product sales – risk adj.	**0**	**0**	**27**	**249**	**928**	**2,254**	**3,841**	**5,223**	**6,470**
SKB264 (TROP2 ADC, China)	0	0	0	44	576	1,523	2,615	3,508	4,267
A166 (HER2 ADC)	0	0	0	93	202	428	640	812	958
SKB315 (CLDN18.2 ADC, China)	0	0	0	0	0	67	224	428	662
A167 (PD-L1)	0	0	27	61	53	103	181	249	298
A223 (JAK1&2)	0	0	0	0	31	49	71	83	99
Other products	0	0		50	65	85	110	143	186
License and collaboration – risk adj.	**781**	**1,351**	**1,011**	**830**	**710**	**792**	**1,967**	**2,222**	**2,507**
SKB264 (TROP2 ADC, Overseas)	532	568	710	710	710	472	703	956	1,239
SKB315 (CLDN18.2 ADC, Overseas)	248	0	0	0	0	320	321	323	325
Other license (i.e. preclincial assets to MSD)	0	784	301	121	0	0	943	943	943
Total revenue – risk adj.	**781**	**1,351**	**1,039**	**1,079**	**1,638**	**3,046**	**5,808**	**7,445**	**8,977**
YoY		*73%*	*-23%*	*4%*	*52%*	*86%*	*91%*	*28%*	*21%*

Source: Company data, CMBIGM estimates

Figure 40: Risk-adjusted sales and license income forecasts



Source: Company data, CMBIGM estimates

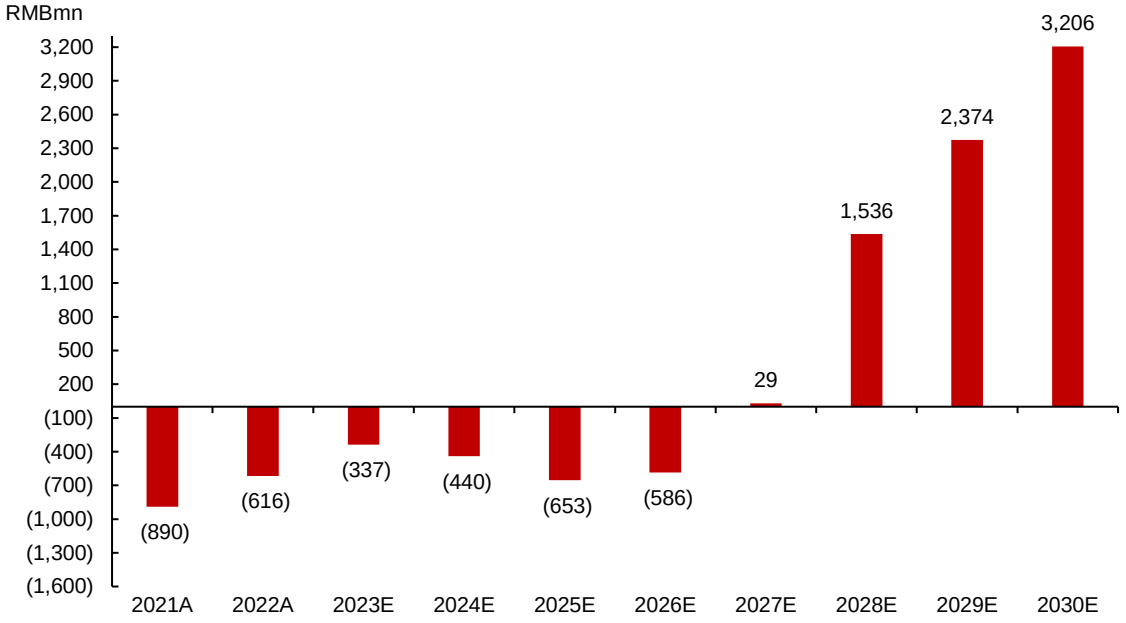
Kelun-Biotech recorded attributable net loss of RMB890mn/RMB616mn in FY21A/22A. In 2023, considering the upfront payment of around RMB1.2bn from MSD regarding the collaboration on multiple preclinical ADC assets and the relevant income recognition, we expect the company to narrow its net loss to RMB337mn. We expect the company to incur net losses of RMB440mn/ RMB653mn in FY24E/25E, and to turn profitable in FY27E.

Figure 41: P&L forecasts

YE Dec 31 (RMB mn)	2021A	2022A	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Revenue	**32**	**804**	**1,351**	**1,039**	**1,079**	**1,638**	**3,046**	**5,808**	**7,445**	**8,977**
YoY		*2387%*	*68%*	*-23%*	*4%*	*52%*	*86%*	*91%*	*28%*	*21%*
Cost of sales	(21)	(277)	(473)	(309)	(260)	(292)	(547)	(809)	(1,051)	(1,290)
Gross profit	**12**	**527**	**878**	**729**	**819**	**1,346**	**2,499**	**4,999**	**6,393**	**7,687**
GPM	*36%*	*66%*	*65%*	*70%*	*76%*	*82%*	*82%*	*86%*	*86%*	*86%*
R&D expenses	(728)	(846)	(931)	(977)	(1,026)	(1,077)	(1,066)	(1,452)	(1,489)	(1,616)
% of revenue	*2251%*	*105%*	*69%*	*94%*	*95%*	*66%*	*35%*	*25%*	*20%*	*18%*
Selling and marketing expenses	0	0	0	(27)	(224)	(557)	(902)	(1,152)	(1,410)	(1,553)
% of revenue	*0%*	*0%*	*0%*	*3%*	*21%*	*34%*	*30%*	*20%*	*19%*	*17%*
Administrative expenses	(96)	(95)	(160)	(192)	(230)	(276)	(451)	(538)	(679)	(776)
% of revenue	*298%*	*12%*	*12%*	*18%*	*21%*	*17%*	*15%*	*9%*	*9%*	*9%*
Profit/(loss) before tax	**(890)**	**(567)**	**(265)**	**(440)**	**(653)**	**(586)**	**34**	**1,807**	**2,793**	**3,772**
% of revenue	*-2753%*	*-71%*	*-20%*	*-42%*	*-61%*	*-36%*	*1%*	*31%*	*38%*	*42%*
Income tax expense	0	(49)	(72)	0	0	0	(5)	(271)	(419)	(566)
Attributable net profit/(loss)	**(890)**	**(616)**	**(337)**	**(440)**	**(653)**	**(586)**	**29**	**1,536**	**2,374**	**3,206**
NPM	*-2753%*	*-77%*	*-25%*	*-42%*	*-61%*	*-36%*	*1%*	*26%*	*32%*	*36%*

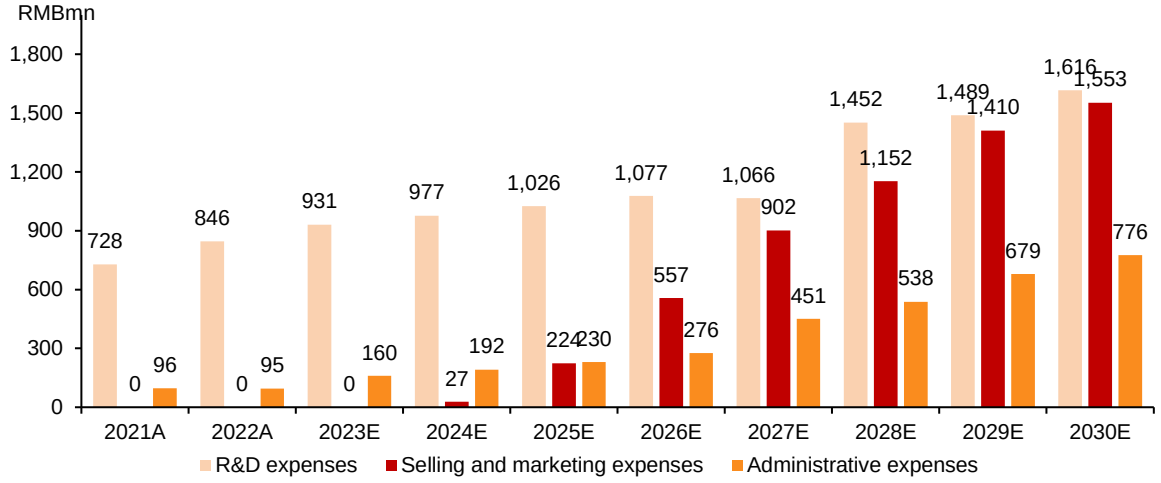
Source: Company data, CMBIGM estimates

Figure 42: Net profit (loss) forecasts



Source: Company data, CMBIGM estimates

Figure 43: Operating expense forecasts



Source: Company data, CMBIGM estimates

Valuation

Initiate at BUY with TP of HK$152.26

We derive our target price of HK$152.26 based on a DCF valuation (WACC: 10.47%, terminal growth rate: 3.0%).

Figure 44: Risk-adjusted DCF valuation

DCF Valuation (RMB mn)	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E
EBIT	**(437)**	**(631)**	**(535)**	**111**	**1,887**	**2,845**	**3,772**	**4,478**	**5,073**	**5,434**	**5,590**	**5,475**
Tax rate	*0%*	*0%*	*0%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
EBIT*(1-tax rate)	(437)	(631)	(535)	94	1,604	2,419	3,206	3,806	4,312	4,619	4,751	4,654
+ D&A	37	44	51	61	72	73	74	76	77	78	79	80
- Change in working capital	(91)	(87)	(173)	(263)	(305)	(246)	(203)	(93)	(22)	33	91	87
- Capex	(200)	(200)	(200)	(300)	(300)	(100)	(100)	(100)	(100)	(100)	(100)	(100)
FCFF	**(692)**	**(874)**	**(857)**	**(408)**	**1,071**	**2,146**	**2,978**	**3,689**	**4,267**	**4,630**	**4,822**	**4,721**
Terminal value												**65,087**
FCF + terminal value	**(692)**	**(874)**	**(857)**	**(408)**	**1,071**	**2,146**	**2,978**	**3,689**	**4,267**	**4,630**	**4,822**	**69,808**

Present value of enterprise (RMB mn)	28,920
Net debt (RMB mn)	(1,450)
Equity value (RMB mn)	**30,370**
No. of shares (mn)	219
DCF per share (RMB)	**138.55**
DCF per share (HK$)	**152.26**
Terminal growth rate	**3.0%**
WACC	**10.47%**
Cost of equity	14.1%
Cost of debt	4.5%
Equity beta	1.1
Risk-free rate	2.5%
Market risk premium	10.5%
Target debt to asset ratio	35.0%
Effective corporate tax rate	15.0%

Source: CMBIGM estimates

Figure 45: Sensitivity analysis (HK$)

	WACC				
Terminal growth rate	**9.47%**	**9.97%**	**10.47%**	**10.97%**	**11.47%**
4.0%	209.98	187.49	168.63	152.59	138.81
3.5%	196.59	176.73	159.85	145.36	132.79
3.0%	185.27	167.51	**152.26**	139.04	127.49
2.5%	175.58	159.52	145.61	133.46	122.77
2.0%	167.18	152.54	139.75	128.51	118.55

Source: CMBIGM estimates

Investment risks

1) Failure of clinical development or regulatory approvals of drug candidates.
2) Intense competition around approved products both in China and overseas markets.
3) Uncertainties in the collaboration with MSD and other strategic partners.

Appendix

Figure 46: Major shareholders

Shareholder	% of stake
Kelun Pharma	54.5%
ESOP	13.7%
MSD	6.1%
IDG Capital	2.1%
Wellington	1.8%

Source: Wind (as of Aug 2023), CMBIGM.

Figure 47: Management profile

Name	Position
Mr. LIU Gexin	Chairman of the Board and non-executive drector
Dr. GE Junyou	Executive director and general manager; Responsible for overall corporate and business strategies and making key business and operational decisions
Dr. WANG Jingyi	Executive director; Responsible for overall strategic planning and development
Mr. FENG Yi	Deputy general manager, chief strategy officer and senior vice president; Responsible for management of strategic planning of R&D and clinical development
Dr. ZHANG Yiwei	Deputy general manager; Responsible for management of manufacturing, quality analysis and control
Dr. TAN Xiangyang	Deputy general manager and chief scientific officer; Responsible for management of preclinical research and business development
Dr. JIN Xiaoping	Deputy general manager and chief medical officer; Responsible for management of clinical development
Mr. ZHOU Zejian	Chief financial officer and the secretary of the Board; Responsible for management of finance, capital market and securities affairs
Mr. GUO Yong	Deputy general manager and chief commercial officer; Responsible for management of sales, marketing, medical affairs and commercial operations

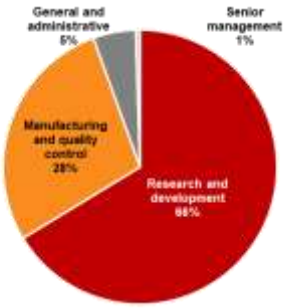
Source: Company data, CMBIGM

Figure 48: Employee structure

Function	# of staff	% of Total
Research and development	766	66%
Manufacturing and quality control	325	28%
General and administrative	58	5%
Senior management	6	1%
Total	**1,155**	**100%**

Source: Company annual report (as of Dec 2023), CMBIGM

Figure 49: Employee number breakdown



Source: Company annual report (as of Dec 2023), CMBIGM

Financial statements

INCOME STATEMENT	2021A	2022A	2023E	2024E	2025E
YE 31 Dec (RMB mn)					
Revenue	**32**	**804**	**1,351**	**1,039**	**1,079**
Cost of goods sold	(21)	(277)	(473)	(309)	(260)
Gross profit	**12**	**527**	**878**	**729**	**819**
Operating expenses	**(789)**	**(946)**	**(1,047)**	**(1,138)**	**(1,430)**
Selling expense	0	0	0	(27)	(224)
Admin expense	(96)	(95)	(160)	(192)	(230)
R&D expense	(728)	(846)	(931)	(977)	(1,026)
Others	35	(4)	44	59	51
Operating profit	**(777)**	**(419)**	**(168)**	**(409)**	**(610)**
Net Interest income/(expense)	**(113)**	**(149)**	**(97)**	**(32)**	**(43)**
Pre-tax profit	**(890)**	**(567)**	**(265)**	**(440)**	**(653)**
Income tax	0	(49)	(72)	0	0
After tax profit	**(890)**	**(616)**	**(337)**	**(440)**	**(653)**
Minority interest	0	0	0	0	0
Net profit	**(890)**	**(616)**	**(337)**	**(440)**	**(653)**

BALANCE SHEET	2021A	2022A	2023E	2024E	2025E
YE 31 Dec (RMB mn)					
Current assets	**298**	**332**	**2,486**	**1,744**	**1,383**
Cash & equivalents	82	93	2,242	1,548	1,151
Restricted cash	37	26	26	26	26
Account receivables	79	99	0	7	59
Inventories	79	53	156	102	85
Financial assets at FVTPL	0	0	0	0	0
Other current assets	23	62	62	62	62
Non-current assets	**515**	**661**	**681**	**845**	**1,001**
PP&E	432	530	556	724	885
Right-of-use assets	42	117	112	107	102
Intangibles	0	3	3	3	3
Other non-current assets	40	10	10	10	10
Total assets	**813**	**993**	**3,167**	**2,589**	**2,384**
Current liabilities	**3,445**	**4,167**	**1,361**	**1,223**	**1,671**
Short-term borrowings	2,388	2,891	1	1	501
Account payables	185	243	327	189	137
Other current liabilities	761	787	787	787	787
Lease liabilities	2	82	82	82	82
Contract liabilities	109	164	164	164	164
Non-current liabilities	**12**	**52**	**52**	**52**	**52**
Deferred income	11	11	11	11	11
Other non-current liabilities	1	41	41	41	41
Total liabilities	**3,457**	**4,219**	**1,413**	**1,275**	**1,723**
Share capital	107	107	107	107	107
Other reserves	(2,751)	(3,334)	1,647	1,207	553
Total shareholders equity	**(2,644)**	**(3,226)**	**1,754**	**1,314**	**661**
Total equity and liabilities	**813**	**993**	**3,167**	**2,589**	**2,384**

CASH FLOW	2021A	2022A	2023E	2024E	2025E
YE 31 Dec (RMB mn)					
Operating					
Profit before taxation	**(890)**	**(567)**	**(265)**	**(440)**	**(653)**
Depreciation & amortization	23	67	29	37	44
Tax paid	0	(49)	(72)	0	0
Change in working capital	279	35	80	(91)	(87)
Others	102	195	97	32	43
Net cash from operations	**(486)**	**(320)**	**(132)**	**(463)**	**(654)**
Investing					
Capital expenditure	(94)	(34)	(50)	(200)	(200)
Net proceeds from disposal of short-term	0	1	0	0	0
Others	(1)	1	0	0	0
Net cash from investing	**(94)**	**(32)**	**(50)**	**(200)**	**(200)**
Financing					
Dividend paid	0	0	0	0	0
Net borrowings	155	318	(390)	0	500
Proceeds from share issues	534	0	2,818	0	0
Others	(42)	(5)	(97)	(32)	(43)
Net cash from financing	**647**	**313**	**2,331**	**(32)**	**457**
Net change in cash					
Cash at the beginning of the year	16	82	93	2,242	1,548
Exchange difference	(1)	1	0	0	0
Cash at the end of the year	**82**	**44**	**2,242**	**1,548**	**1,151**

GROWTH	2021A	2022A	2023E	2024E	2025E
YE 31 Dec					
Revenue	na	2,387.3%	68.1%	(23.1%)	3.9%
Gross profit	na	4,368.1%	66.6%	(17.0%)	12.4%

PROFITABILITY	2021A	2022A	2023E	2024E	2025E
YE 31 Dec					
Gross profit margin	36.5%	65.6%	65.0%	70.2%	75.9%
Operating margin	(2,404.6%)	(52.1%)	(12.5%)	(39.3%)	(56.6%)
Return on equity (ROE)	na	na	na	(28.7%)	(66.2%)

GEARING/LIQUIDITY/ACTIVITIE	2021A	2022A	2023E	2024E	2025E
YE 31 Dec					
Current ratio (x)	0.1	0.1	1.8	1.4	0.8

VALUATION	2021A	2022A	2023E	2024E	2025E
YE 31 Dec					
P/B	na	na	13.4	17.9	35.7

Source: Company data, CMBIGM estimates. Note: The calculation of net cash includes financial assets.

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