BeiGene (BGNE US)

Harvest season for a global leading biopharma company

- **Global R&D platform as a cornerstone of commercial approvals worldwide.** BeiGene has demonstrated strong ability in conducting large-scale MRCTs, which is one of the most important competitive advantages of BeiGene as compared to other China biotech companies. BeiGene has a predominately CRO-free R&D and medical affairs team of 3,200+ staff, with 1,000+ people outside China. BeiGene has initiated 100+ clinical trials in 45 countries and regions for over 30 medicines and drug candidates since 2013 (including 30+ pivotal or potentially registration-enabling trials), and has enrolled 16,000+ subjects, with around half from outside of China.

- **Rich portfolio of highly innovative assets**. With superior response rate, improved PFS and less cardiotoxicity as evidenced by head-to-head studies, zanubrutinib (BTK) has received 22+ global approvals in 50 countries and regions, including the US, China, Europe and others. Tislelizumab (PD-1) was approved in China for nine indications with large indications such as 1L sq-/nsq-NSCLC and 2L HCC covered by the NRDL. Tislelizuamb is also well-positioned for global commercialization thanks to its broad global trials - 11 of tislelizumab's 20+ pivotal trials are conducted globally. BeiGene has 11 clinical-stage internally discovered drug candidates, including the late-stage asset ociperlimab (TIGIT) and early-stage clinical assets such as BGB-11417 (BCL-2), surzebiclimab (BGB-A425, TIM-3), BGB-A445 (OX40), BGB-10188 (PI3K delta), BGB-15025 (HPK1), BGB-16673 (BTK-targeted CDAC), etc. Ociperlimab is one of the most advanced TIGIT inhibitors with intact Fc function currently in pivotal stage trials. BGB-11417 appears to be more potent than venetoclax (the only marketed BCL-2 inhibitor globally) and shows the potential to overcome resistance to venetoclax.

- **Entered into harvest season.** Powered by a sizable global commercial team of 3,400+ staff, BeiGene maintained a strong revenue growth momentum. We believe BeiGene has entered into the harvest season, as its product revenue growth outpaces that of its operating expenses (product revenue CAGR of 69% vs operating expense CAGR of 41% during 2018-2021), indicating improving operating cash flows in coming years.

- **Initiate at BUY with TP of US$248.52**. We expect zanubrutinib and tislelizumab will continue to be major revenue drivers in coming years. We derive our target price of US$248.52 based on a DCF valuation (WACC: 9.20%, terminal growth rate: 3.0%).

Earnings Summary

(YE 31 Dec)	FY20A	FY21A	FY22E	FY23E	FY24E
Revenue (US$ mn)	309	1,176	1,398	2,206	3,340
Attributable net loss (US$ mn)	(1,597)	(1,413)	(1,648)	(1,136)	(272)
EPS (US$ per ADS)	(22.9)	(19.1)	(15.2)	(16.0)	(11.0)
Consensus EPS (US$ per ADS)	NA	NA	(11.6)	(10.6)	(5.1)
R&D expenses (US$ mn)	(1,295)	(1,459)	(1,503)	(1,533)	(1,548)
SG&A expenses (US$ mn)	(600)	(990)	(1,238)	(1,337)	(1,417)
Capex (US$ mn)	(118)	(263)	(320)	(100)	(100)
Current ratio (x)	4.6	4.8	3.5	2.6	2.3

Source: Company data, Bloomberg, CMBIGM estimates

BUY (Initiation)

Target Price	US$248.52
Up/Downside	+85.77%
Current Price	US$133.78

China Healthcare Sector

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Stock Data

Mkt Cap (US$mn)	15,347
Avg 3mths t/o (US$mn)	50.78
52w High/Low (US$)	426.56/118.18
Total Issued Shares (mn)	103

Source: Bloomberg

Shareholding Structure

Amgen	18.45%
Baker Bros	11.42%
HHLR Advisor	11.02%
Capital	8.01%
Others	51.10%

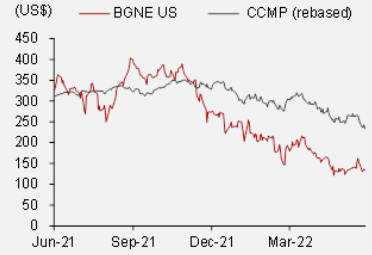
Source: Company data

Share Performance

	Absolute	Relative
1-mth	3.6%	13.5%
3-mth	-27.0%	-7.9%
6-mth	-51.0%	-30.1%

Source: Bloomberg

12-mth Price Performance



Source: Bloomberg

Auditor: Ernst & Young
Web-site: https://www.beigene.com/

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Investment Thesis

Incorporated in 2010 in Beijing, China, BeiGene has developed into a global, commercial-stage biotechnology company. The Company is the first triple-listed biotechnology company, completed listing on NASDAQ, HKEx and Shanghai STAR Market.

Global R&D platform as a cornerstone of commercial approvals worldwide

BeiGene has demonstrated strong ability in conducting large-scale MRCTs, which is one of the most important competitive advantages of BeiGene as compared to other China biotech companies. BeiGene has 3,200+ R&D and medical affairs staff, including one of the world's largest oncology research team of 800+ scientists, and an internal clinical development and medical affairs team of 2,400+ staff worldwide, which is predominately CRO-free. BeiGene's R&D and medical affairs team maintains a global operating model, with 1,000+ people outside China. Supported by the world-class global research platform, BeiGene has initiated 100+ clinical trials in 45 countries and regions for over 30 medicines and drug candidates since 2013 (including 30+ pivotal or potentially registration-enabling trials), and has enrolled 16,000+ subjects, with around half from outside of China.

Strong revenue growth powered by expanding global commercial network

With a growing global commercial team of over 3,400 staff, BeiGene is strengthening its global commercial capabilities. BeiGene currently has three approved in-house developed medicines, including zanubrutinib, tislelizumab and pamiparib. Zanubrutinib has received approvals in 50 countries, including the US, China, EU, UK, Canada, Australia, etc. Additionally, BeiGene is marketing tislelizumab and pamiparib and 13 approved in-licensed medicines in China. BeiGene has built a strong, science-based commercial team with over 3,100 staff in China to support a commercial portfolio of 3 in-house developed medicines and 13 in-licensed products. In the US, BeiGene has a commercial team focused on blood cancer market, with an opportunity to expand into solid tumors. BeiGene is also establishing its in-house commercial team in Europe and expanding into Canada, Latin America and other markets through affiliates/partnerships.

Thanks to the fast growing commercial portfolio and network, we expect BeiGene to maintain strong product revenue growth momentum in coming years. The Company's product revenue rallied at a CAGR of 69% during 2018 and 2021. In 1Q22, BeiGene's product revenue reached US$261.6mn, up 146% YoY, mainly driven by the strong sales ramp up of tislelizumab and zanubrutinib. We believe BeiGene has entered into the harvest season after many years of investment, as its product revenue growth outpaces that of its operating expenses (revenue CAGR of 69% vs operating expense CAGR of 41% during 2018-2021), indicating improving operating cash flows in coming years.

Broad BD collaborations paving the way for global success

BeiGene partners broadly with global pharmaceutical and biotech companies to develop and commercialize innovative therapies. The Company's collaboration partners include Novartis, BMS, Amgen, Zymeworks, Mirati, Bio-Thera, etc. The collaborations include out-licenses of internally developed products to other parties and in-licenses of products and drug candidates from other parties.

For out-license collaborations, BeiGene granted Novartis rights for tislelizumab in North America, Europe and Japan through a blockbuster deal in Jan 2021 with a total upfront and milestone payment up to US$2.2bn. In Dec 2021, BeiGene expanded the collaboration with Novartis to include ociperlimab. BeiGene granted Novartis an exclusive time-based option under which, upon exercise prior to late 2023, the two companies have agreed to jointly develop ociperlimab. The total upfront and milestone payment of the deal was up to US$2.9bn. Through out-license collaborations, BeiGene is able to accelerate the global development and broaden market access of its innovative drugs. More importantly, collaborations with the world leading pharmaceutical companies validated the strength of BeiGene's internal R&D capabilities and will provide sufficient financial support for BeiGene's further development.

Rich portfolio of highly innovative assets

Powered by strong internal R&D capabilities and successful business development efforts, BeiGene has established a rich innovative product portfolio of around 50 clinical and commercial assets, including 3 approved internally developed products, 13 approved in-licensed medicines, 11 clinical-stage internally developed drug candidates, and the remaining of in-licensed drug candidates.

Highly differentiated assets developed internally

Zanubrutinib, a second-generation BTK inhibitor, is equally or more selective than any approved BTKi, with fewer off-target effects and less cardiotoxicity. Zanubrutinib was shown to have a superior response rate, an improved PFS and a lower rate of atrial fibrillation/flutter compared with ibrutinib in two head-to-head phase 3 studies. As of May 2022, zanubrutinib has received 22+ approvals for CLL, MZL, MCL, and WM, covering 50 countries and regions, including the US, China, Europe, the UK, Canada, Australia, and others. Zanubrutinib has been recommended by both the NCCN and CSCO guidelines.

With the broadest Chinese patient coverage, tislelizumab (PD-1) has been approved in China for nine indications, including 1L sq-NSCLC, 1L nsq-NSCLC, 2/3L NSCLC, 2L cHL, 2L+ PD-L1 positive UC, 2L HCC, 2L/3L MSI-H/dMMR solid tumors, 2L ESCC and 1L NPC. Tislelizumab is well-positioned for global commercialization thanks to its broad global clinical trials – 11 out of tislelizumab's 20+ pivotal trials are conducted globally. As of Feb 2022, tislelizumab's clinical studies have enrolled over 9,000 subjects in 35 countries and regions, with over 2,800 from outside of China. Global filings of tislelizumab to the US FDA and EU EMA are currently under review.

As of May 2022, BeiGene has 11 clinical-stage internally discovered drug candidates, including the late-stage asset ociperlimab (TIGIT) and early-stage clinical assets such as BGB-11417 (BCL-2), surzebiclimab (BGB-A425, TIM-3), BGB-A445 (OX40), BGB-10188 (PI3K delta), BGB-15025 (HPK1), BGB-16673 (BTK-targeted CDAC), etc. Ociperlimab is one of the most advanced TIGIT inhibitors with intact Fc function currently in pivotal stage trials. BGB-11417 appears to be more potent than venetoclax (the only marketed BCL-2 inhibitor globally) and shows the potential to overcome resistance to venetoclax. BeiGene aims to start pivotal trials for BGB-11417 in 2022.

BeiGene consistently strengthens its in-house R&D capabilities by investing in new modalities, such as CDAC, BsAb/TsAb, ADC, Pro-Cytokine, cell therapy, mRNA, etc. Besides the 50 clinical and commercial assets, BeiGene has more than 50 preclinical programs, half with global best-in-class or first-in-class potentials. The Company aims to progress over 10 preclinical candidates to clinical stage within the next 24 months. We expect the Company's internal discovered pipelines to continue to expand in coming years.

Rich portfolio of in-licensed products

Leveraging its China commercial capabilities, BeiGene has licensed in 13 commercial medicines and around two dozen clinical-stage drug candidates. The rich commercial-stage in-licensed product portfolio has become an important revenue growth engine for BeiGene. We estimate that in-licensed products delivered approximately US$155mn revenue in 2021, growing by c. 50% YoY and contributing c. 25% of BeiGene's total sales.

Around two dozen in-licensed drug candidates are currently under development, among which, sitravatinib, zanidatamab and sotorasib are at late-clinical stage. Sitravatinib is a multi-kinase inhibitor from Mirati. BeiGene is evaluating sitravatinib in multiple clinical trials including a Ph3 trial combining sitravatinib with tislelizumab in 2/3L NSCLC. Zanidatamab (HER2-targeted BsAb) is currently in late-stage clinical development. BeiGene is investigating zanidatamab in three ongoing clinical studies with Zymeworks, including a global Ph3 clinical trial examining zanidatamab + chemotherapy +/- tislelizumab in HER2-positive gastroesophageal cancer. Sotorasib (first-in-class KRAS G12C inhibitor) is the only marketed KRAS G12C inhibitor globally, which was approved in nearly 40 countries. Sotorasib was

approved in the US for 2L treatment of KRAS G12C-mutated NSCLC. In China, sotorasib was granted Breakthrough Therapy Designation.

Initiate at BUY with TP of US$248.52

We expect zanubrutinib and tislelizumab will continue to drive the revenue growth in coming years. We estimate BeiGene's risk-adjusted revenue of US$1,398mn/ US$2,206mn/ US$3,340mn in FY22E/ 23E/ 24E, and net losses of US$1,648mn/ US$1,136mn/ US$272mn in FY22E/ 23E/ 24E. We derive our target price of US$248.52 based on a DCF valuation (WACC: 9.20%, terminal growth rate: 3.0%).

Investment risks

1) Failure of clinical development or regulatory approvals of drug candidates.

2) Intense competition of approved products both in China and overseas markets.

Growing into world leading biopharma company with a well-established global platform

Incorporated in 2010 in Beijing, China, BeiGene has developed into a global, commercial-stage biotechnology company. The Company is the first triple-listed biotechnology company, completed listing on NASDAQ in Feb 2016, HKEx in Aug 2018, and the Shanghai STAR Market in Dec 2021. BeiGene raised RMB22.2bn (or US$3.5bn) from the IPO of the Shanghai STAR Market, bringing sufficient capital for the Company's future development.

Through many years of development, BeiGene has established a fully integrated global organization of over 8,400 employees in 23 countries and regions, including the US, China, Europe, Australia, etc. BeiGene has built state-of-the-art biologic and small molecule manufacturing facilities in China and plans to build a commercial-stage biologics manufacturing and clinical R&D center in New Jersey.

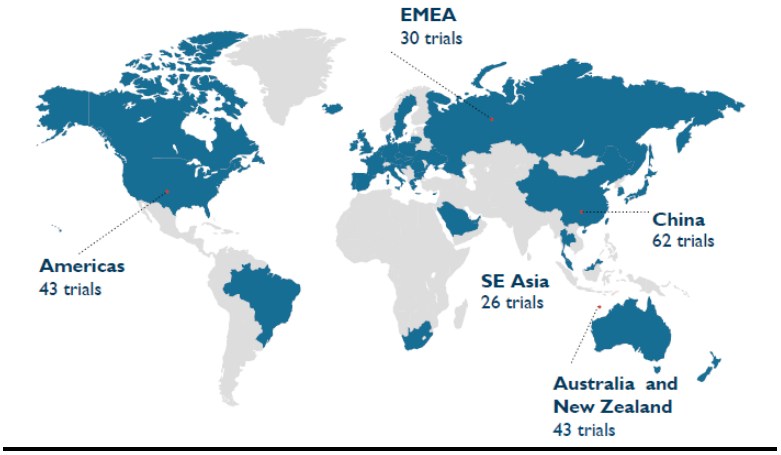
Global R&D platform as a cornerstone of wide commercial approvals

Given the US FDA has recently rejected several BLAs of drug candidates with China-only clinical data, we believe stringent MRCTs will be essential for approvals in the US and other major countries. BeiGene has demonstrated the strong ability in conducting large-scale MRCTs, which is one of the most important competitive advantages of BeiGene as compared to other China biotech companies, in our view.

BeiGene has 3,200+ R&D and medical affairs staff, including one of the world's largest oncology research teams (800+ scientists in Beijing and Shanghai research centers), and an internal clinical development and medical affairs team of 2,400+ staff worldwide, which is predominately CRO-free. BeiGene's R&D and medical affairs team maintains a global operating model, with 1,000+ people outside China.

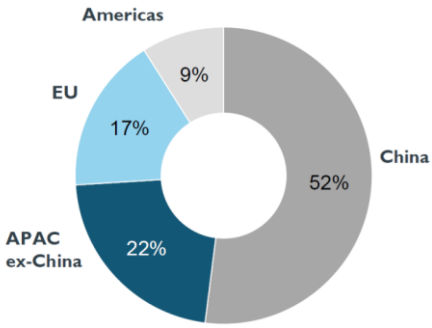
Supported by the world-class global research platform, BeiGene has initiated 100+ clinical trials in 45 countries and regions for over 30 medicines and drug candidates since 2013 (including 30+ pivotal or potentially registration-enabling trials), and has enrolled 16,000+ subjects, with around half from outside of China.

Figure 1: Clinical trials of BeiGene worldwide



Source: Company data, CMBIGM

Figure 2: Breakdown of subjects in all trials

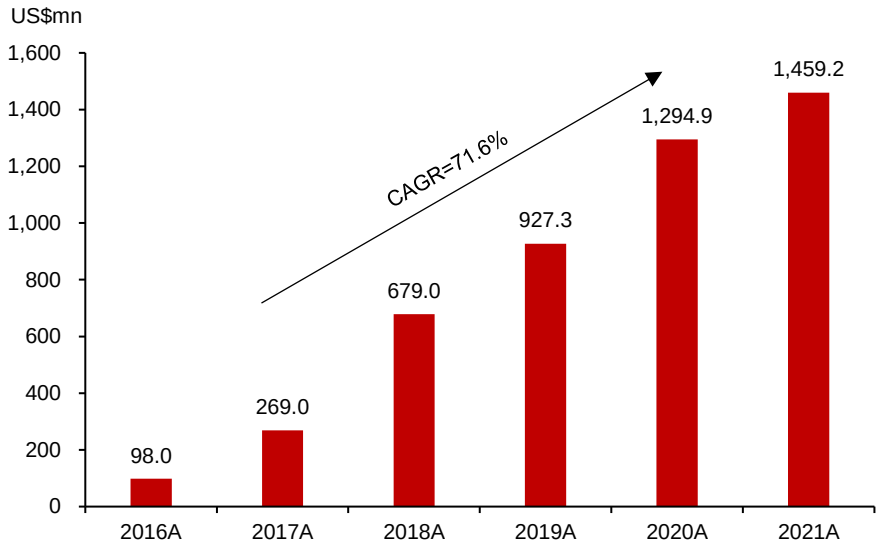


Source: Company data, CMBIGM. Notes: Inclusive of all subjects ever enrolled in all studies as of 31 Dec 2021.

In order to establish its global R&D platform and to conduct multiple MRCTs worldwide, BeiGene has maintained large amount of R&D spending in past years. In 2021, BeiGene's R&D expenditure reached US$1.46bn, ranking the first among China-based biotech and pharmaceutical companies. However, BeiGene's R&D investment amount is largely in line with global biotech companies with similar market

cap with BeiGene. More importantly, as a global company with a strong presence in China, BeiGene enjoys significant advantages in R&D efficiencies thanks to the large patient pool in China and relatively cheaper clinical costs in China.

Figure 3: BeiGene's R&D expenses



Source: Company data, CMBIGM

Figure 4: Comparison of R&D expenses of global biotech companies

(US$mn)	Market cap (2022.06.14)	R&D expenses		Revenue		R&D/Revenue		R&D/Market cap	
		2021	2020	2021	2020	2021	2020	2021	2020
BeiGene	15,162	1,479	1,295	1,177	309	126%	419%	10%	9%
Biogen	28,438	2,501	3,991	10,982	13,445	23%	30%	9%	14%
Seagen	26,625	1,229	827	1,574	2,176	78%	38%	5%	3%
Incyte	14,659	1,458	2,216	2,986	2,667	49%	83%	10%	15%
Argenx	17,650	581	423	497	47	117%	899%	3%	2%
Genmab	18,076	665	481	1,349	1,549	49%	31%	4%	3%

Source: Company data, CMBIGM

Expanding global commercial network to pursue higher sales from markted products

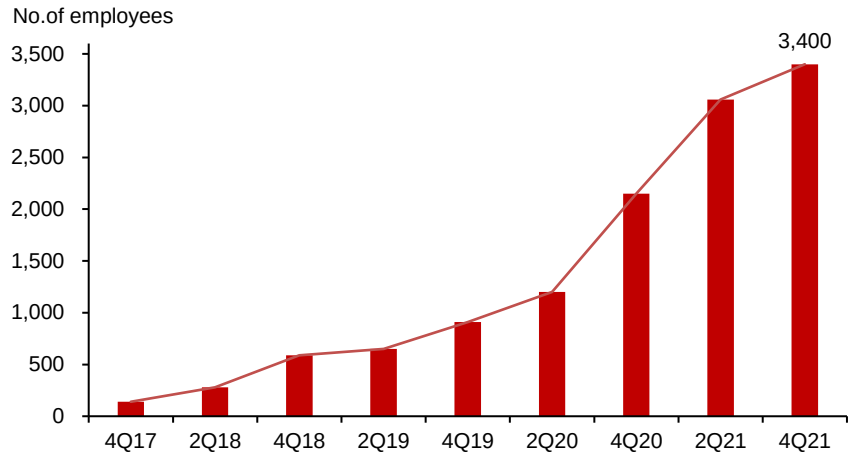
With a broad portfolio of over 50 clinical and commercial stage drug assets and a growing global commercial team of over 3,400 staff, BeiGene is strengthening its global commercial capabilities. BeiGene currently has three approved in-house developed medicines, including BRUKINSA (zanubrutinib), tislelizumab and pamiparib. BRUKINSA has received approvals in 50 countries, including the US, China, EU, UK, Canada, Australia, etc. Additionally, BeiGene is marketing tislelizumab and pamiparib and 13 approved in-licensed medicines in China.

Thanks to the fast growing commercial portfolio, BeiGene is also expanding its global commercial network to pursue higher sales growth of its products. As of May 2022, BeiGene has a sizable commercial team of 3,400+ staff, with over 3,100 people in China and 200+ in North America and Europe.

In China, BeiGene has built a strong, science-based commercial team with over 3,100 staff to support a commercial portfolio of 3 in-house developed oncology medicines and 13 in-licensed products. In the US, BeiGene has a commercial team focused on blood cancer market, which currently mainly focuses on the

marketing of zanubrutinib, with an opportunity to expand into solid tumors. Zanubrutinib sales have grown strongly in the US thanks to the continued label expansion in new indications. In Europe, BeiGene is establishing its in-house commercial team which is mainly responsible for the marketing of zanubrutinib in many European countries. In addition, BeiGene's commercial capabilities have also expanded into Canada through its affiliate and into Latin America through a distribution partner.

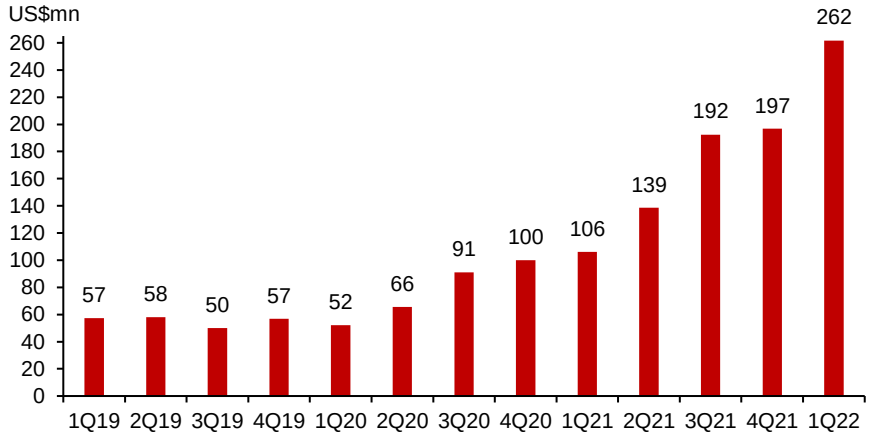
Figure 5: BeiGene's growing commercial team



Source: Company data, CMBIGM

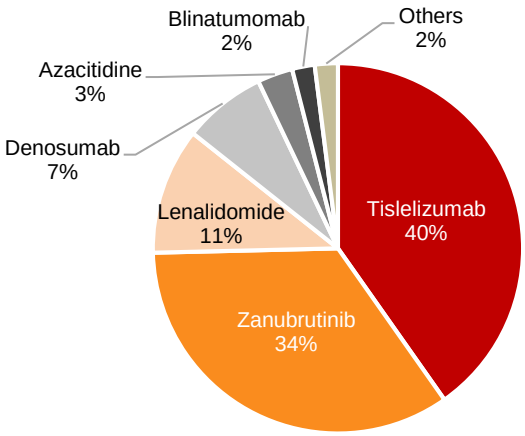
Thanks to the fast growing commercial portfolio, BeiGene will continue to maintain its strong product revenue growth momentum in coming years, in our view. BeiGene's product revenue rallied at a CAGR of 69% during 2018 to 2021. In 1Q22, BeiGene's product revenue reached US$261.6mn, up 146% YoY, which was mainly driven by the strong sales ramp up of tislelizumab and zanubrutinib.

Figure 6: Quarterly revenue of BeiGene's marketed products (1Q19-1Q22)



Source: Company data, CMBIGM. Notes: 1) 3Q19 revenue negatively impacted by temporary supply disruptions of ABRAXANE. 2) 1Q20 revenue negatively impacted by the COVID-19 pandemic, increased generic competition, and the suspension of ABRAXANE sales in China by the NMPA in March 2020. 3) FY2021 sales included negative adjustments of US$7.9mn and US$45.6mn for zanubrutinib and tislelizumab, respectively, for distributor channel inventory compensation as a result of inclusion in the Mar 2021 and Jan 2022 NRDL lists.

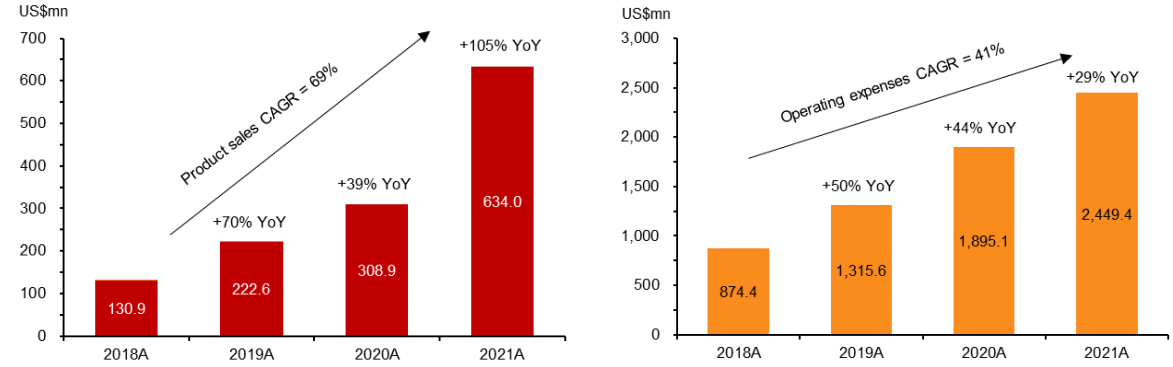
Figure 7: BeiGene's product revenue breakdown (2021)



Source: Company data, CMBIGM

We believe BeiGene has entered into the harvest season after many years of investment, as its product revenue growth outpaces that of its operating expenses (product revenue CAGR of 69% vs operating expense CAGR of 41% during 2018-2021), indicating improving operating cash flows in coming years.

Figure 8: Growth rate of BeiGene's product revenue and operating expenses



Source: Company data, CMBIGM. Notes: Operating expenses include R&D and SG&A expenses.

Building global manufacturing facilities to secure product supply

BeiGene manufactures its medicines and drug candidates internally and in some cases with the help of high-quality third-party CMOs such as Boehringer Ingelheim and Catalent. BeiGene currently has manufacturing facilities in Beijing, Guangzhou, and Suzhou, China and plans to build a commercial-stage biologics manufacturing and clinical R&D center in New Jersey, the US. BeiGene is also constructing a new small molecule manufacturing campus in Suzhou, China.

Figure 9: BeiGene's in-house manufacturing facilities

Source: Company data, CMBIGM

BeiGene continues to invest in the commercial-scale biologics manufacturing facility in Guangzhou. The Phase 1 facility with 8,000L single use disposable capacity has been approved for the commercial production of tislelizumab for the China market. The construction of Phases 2 facility was completed in Dec 2020 with 16,000L of single use disposable capacity, while the Phase 3 facility completed construction in Dec 2021 with an additional 40,000L of capacity. Upon the construction completion and GMP-ready by the end of 2022, the Guangzhou facility will have a total capacity of 64,000L.

The manufacturing facility in Suzhou has an annual production capacity of 100mn tablets/capsules of small molecule drugs and 2 x 500 liters capacity of biologics candidates for clinical supply. The facility has received a manufacturing license to produce commercial volumes of zanubrutinib and pamiparib for the China market. To meet the growing commercial and clinical demands, BeiGene has started to build a new small molecule manufacturing facility in Suzhou with the capability to produce up to 600mn solid oral dosages annually, with the construction to be completed in 2023.

In the US, BeiGene is also building a biologics manufacturing facility and a clinical R&D campus in New Jersey. Construction of the initial phase with up to 16,000L biologics manufacturing capacity has commenced in Mar 2022 and is expected to be completed in late-2023 or 2024.

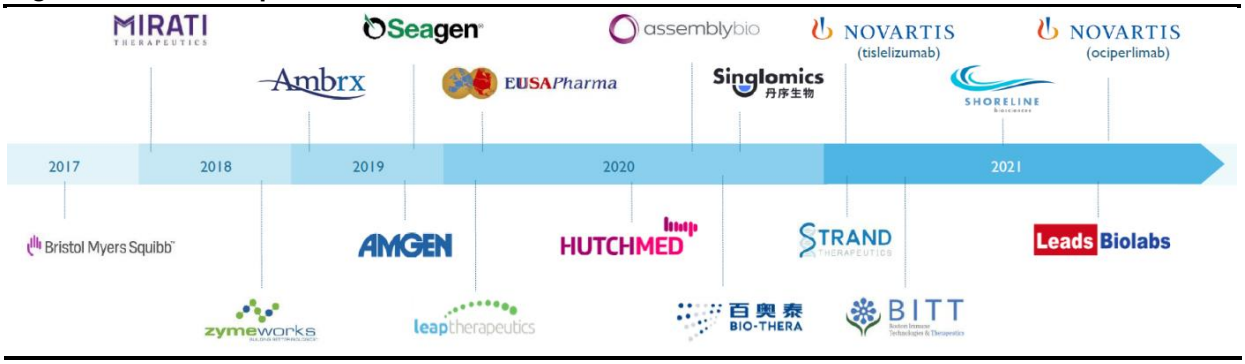
In addition to in-house manufacturing, the Company also works with high-quality CMOs to manufacture the internally developed clinical and commercial products. BeiGene entered into a commercial supply agreement with Catalent to produce zanubrutinib for the US and other overseas countries, with the current capacity of 15mm doses and the expansion to ~50mm in process. For tislelizumab, BeiGene collaborates with Boehringer Ingelheim in Shanghai, China.

Broad BD collaborations paving the way for global success

BeiGene partners broadly with global pharmaceutical and biotech companies to develop and commercialize innovative therapies. The Company's collaboration partners include Novartis, BMS, Amgen, Zymeworks, Mirati, Bio-Thera, etc. The collaborations include out-licenses of internally developed products to other parties and in-licenses of products and drug candidates from other parties. Through out-license collaborations, BeiGene is able to accelerate the global development and broaden market access

of its innovative drugs. More importantly, collaborations with the world leading pharmaceutical companies such as Novartis validated the strength of BeiGene's internal R&D capabilities and will provide sufficient financial support for BeiGene's further development (through cash payments and cost-sharing).

Figure 10: Selected partners of BeiGene



Source: Company data, CMBIGM

Figure 11: BeiGene's major BD deals

Partner	Product	Deal nature	Deal terms	Date	Territory
Out-Licensing Arrangements					
Novartis	Ociperlimab (TIGIT)	Out-license	US$300mn upfront; US$600mn or US$700mn additional payment upon option exercise, US$745mn regulatory milestones, US$1,150mn sales milestones; royalties on net sales	Dec 2021	North America, Europe, and Japan
Novartis	Tislelizumab (PD-1)	Out-license	US$650mn upfront; US$1,300mn regulatory milestones; US$250mn sales milestones; royalties on net sales	Jan 2021	North America, Europe, and Japan
SpringWorks	BGB-3245 (B-RAF)	Co-development	BeiGene and SpringWorks formed MapKure to co-develop BGB-3245 discovered by BeiGene. SpringWorks made an equity investment into MapKure.	Jun 2019	Outside of Asia, Japan
Celgene (BMS)	Tislelizumab	Out-license (Terminated in Jun 2019)	US$263mn upfront; up to US$980mn payments in milestones; royalties on net sales	Jul 2017	US, Europe, Japan and the rest of world other than Asia
In-Licensing Arrangements					
Novartis	TAFINLAR®, MEKINIST®, VOTRIENT®, AFINITOR®, and ZYKADIA®	In-license		Dec 2021	China Broad Markets
Leads Biolabs	LBL-007 (LAG-3)	In-license	US$30mn upfront; up to US$742mn payments in milestones; tiered royalties on net sales	Dec 2021	Ex-China
Shoreline Biosciences	A portfolio of natural killer (NK)-based cell therapeutics for four targets	In-license	US$45mn upfront; additional R&D funding and milestone payments; royalties on development, regulatory, and commercial milestones	Jun 2021	Worldwide (Shoreline has an option to retain rights in the US and Canada for two targets)
Bio-Thera Solutions	POBEVCY® (a biosimilar to Avastin® (bevacizumab)	In-license	US$20mn upfront; up to US$145mn payments in milestones; tiered royalties on net sales	Aug 2020	China
Assembly Biosciences	Three inhibitor for HBV infection (ABI-H0731, ABI-H2158 and ABI-H3733)	In-license	US$40mn upfront; up to US$500mn payments in milestones; tiered royalties on net sales	Jul 2020	China
EUSA Pharma	SYLVANT® (siltuximab), QARZIBA® (dinutuximab beta)	In-license	US$40mn upfront; up to US$120mn payments in milestones; tiered royalties on product sales	Jan 2020	China (siltuximab), Mainland China (dinutuximab beta)
Leap Therapeutics	DKN-01 (DKK1)	In-license, option	US$3mn upfront; up to US$132mn payments in milestones upon option exercise; tiered royalties on net sales	Jan 2020	Asia (except Japan), Australia, and New Zealand

Seagen	SEA-CD70 (CD70)	In-license	US$20mn upfront; additional payments in milestones; tiered royalties on product sales	Nov 2019	Asia (except Japan) and the rest of the world (except Americas and Europe)
Amgen	XGEVA®, KYPROLIS®, and BLINCYTO®, and a portfolio of oncology assets in Amgen's pipeline, including sotorasib (KRAS G12C), tarlatamab (DLL3), etc.	In-license	To co-fund global development costs up to a total cap of US$1,250mn	Oct 2019	Mainland China
BioAtla	BA3071 (CAB-CTLA-4)	In-license	US$20mn upfront; additional payments in milestones; tiered royalties on product sales	Apr 2019	Worldwide
Zymeworks	Zanidatamab (HER2 BsAb), ZW49 (ADC), Azymetric™ and EFECT™ platforms	In-license	US$40mn upfront for Zanidatamab and ZW49, US$20mn upfront for Azymetric™ and EFECT™ platforms; additional payment in milestones; tiered royalties on product sales	Nov 2018	Asia (excluding Japan), Australia, and New Zealand
Mirati Therapeutics	Sitravatinib	In-license	US$10mn upfront; up to US$123mn payments in milestones; significant royalties on product sales	Jan 2018	Asia (excluding Japan), Australia, and New Zealand
BMS	ABRAXANE® (terminated), REVLIMID®, and VIDAZA®	In-license		Jul 2017	Mainland China

Source: Company data, CMBIGM

Collaboration summary with Novartis

BeiGene granted Novartis rights for tislelizumab in North America, Europe and Japan through a blockbuster deal in Jan 2021 with a total upfront and milestone payment up to US$2.2bn, which includes US$650mn upfront payment, US$1.3bn regulatory milestone payment, US$250mn sales milestone payments, as well as high-teens to high-twenties percentage of tiered sales royalties.

In Dec 2021, BeiGene expanded the collaboration with Novartis to include ociperlimab. BeiGene granted Novartis an exclusive time-based option under which, upon exercise prior to late 2023, the two companies have agreed to jointly develop ociperlimab. The total upfront and milestone payment of the deal was up to US$2.9bn, including US$300mn upfront cash payment, additional US$600 or $700mn payment upon exercise of the option prior to late 2023, US$745mn regulatory milestone payment and US$1.15bn sales milestone payments. BeiGene can also receive high-teens to mid-twenties percentage of tiered sales royalties. Meanwhile, BeiGene obtained the rights to market and promote five Novartis' approved and nationally reimbursed oncology products in Broad Markets in China, namely TAFINLAR (dabrafenib), MEKINIST (trametinib), VOTRIENT (pazopanib), AFINITOR (everolimus) and ZYKADIA (ceritinib).

Collaboration summary with Amgen

In Oct 2019, BeiGene entered into a collaboration with Amgen for the commercialization and development of Amgen's XGEVA, KYPROLIS, and BLINCYTO in mainland China. Amgen and BeiGene share equally in the China commercial profits/losses during the commercialization period (five or seven years). Following the commercialization period, BeiGene has the right to retain one product, and is entitled to receive tiered mid-single to low-double digit percentage royalties on sales in China of the remaining products for an additional five years. In addition, BeiGene and Amgen have agreed to collaborate on the global clinical development and commercialization of a portfolio of Amgen's oncology pipeline products. BeiGene is responsible for co-funding global clinical development costs for the pipeline assets up to a total cap of US$1.25bn. BeiGene will receive commercial rights for seven years and share 50% of profits and losses from the products in China. BeiGene will have the right to retain approximately one of every three approved products, up to six, other than sotorasib, to commercialize in China.

Amgen also purchased US$2.78bn worth of shares of BeiGene in Oct 2019, which made Amgen the largest shareholder of the Company. As of Mar 2022, Amgen holds 18.45% stake in BeiGene, followed by Baker Brothers of 11.42% stake, Hillhouse of 11.02% and Capital of 8.01%.

Figure 12: Major collaboration terms with Novartis and Amgen

Source: Company data, CMBIGM

Rich portfolio of highly innovative assets

Powered by strong internal R&D capabilities and successful business development efforts, BeiGene has established a rich innovative product portfolio of around 50 clinical and commercial assets, including 3 approved internally developed products, 13 approved in-licensed medicines, 11 clinical-stage internally developed drug candidates, and the remaining of in-licensed drug candidates.

Highly differentiated assets developed internally

BeiGene's internally developed assets are highly differentiated with large global market potential. As of May 2022, BeiGene's inhouse discovery engine has delivered 14 molecules into clinical phase, including 3 commercialized medicines and 11 clinical-stage drug candidates. The three approved internally developed medicines are BRUKINSA (zanubrutinib), tislelizumab and pamiparib.

Zanubrutinib is a second-generation small-molecule inhibitor of Bruton's tyrosine kinase (BTK) discovered by BeiGene that is equally or more selective than any approved BTKi, with fewer off-target effects and less cardiotoxicity. Zanubrutinib has been recommended by both the NCCN and CSCO guidelines. Zanubrutinib was shown to have a superior response rate, an improved PFS and a lower rate of atrial fibrillation/flutter compared with ibrutinib in two head-to-head Ph3 studies, including the ASPEN study in WM patients and the ALPINE study in CLL/SLL patients. Initially approved in the US by FDA in Nov 2019, zanubrutinib is positioned to have the most comprehensive labels as a next-generation BTK inhibitor. As of May 2022, zanubrutinib has received 22+ approvals for CLL, MZL, MCL, and WM, covering 50 countries and regions, including the US, China, Europe, the UK, Canada, Australia, and others. In the US, zanubrutinib received accelerated approval for relapsed or refractory (r/r) MCL in Nov 2019 and has later been approved for WM and r/r MZL. In addition, an sBLA has been accepted by the US FDA for CLL/SLL, with a PDUFA date of 20 Jan 2023. In China, zanubrutinib has received conditional approvals for 2L MCL, 2L CLL/SLL, and r/r WM, all indications covered by the China NRDL.

Tislelizumab is a differentiated humanized IgG4 anti-PD-1 mAb mechanistically designed to minimize binding to Fc receptor gamma (FcγR) on macrophages to minimize its negative impact on T effector cells. With the broadest Chinese patient coverage, tislelizumab has been approved in China for nine indications, including 1L sq-NSCLC, 1L nsq-NSCLC, 2/3L NSCLC, 2L cHL, 2L+ PD-L1 positive UC, 2L HCC, 2L/3L MSI-H/dMMR solid tumors, 2L ESCC and 1L NPC. Except for 2/3L NSCLC, 2L/3L MSI-H/dMMR solid tumors, 2L ESCC and 1L NPC, which were approved in 2022, all the other 5 indications have been

included in China NRDL. Tislelizumab is also well-positioned for global commercialization thanks to its broad global clinical trials. 11 out of tislelizumab's 20+ pivotal trials are conducted globally. As of Feb 2022, tislelizumab's clinical studies have enrolled over 9,000 subjects in 35 countries and regions, with over 2,800 from outside of China. For global filings, BeiGene and Novartis have filed a BLA with the US FDA for 2L ESCC with a PDUFA date of 12 Jul 2022. In Europe, the BLAs of tislelizumab for 1L sq-NSCLC, 1L nsq-NSCLC, 2L NSCLC, and 2L ESCC have been accepted by the EMA in Apr 2022.

Pamiparib is a selective small-molecule inhibitor of PARP1 and PARP2 enzymes. In China, pamiparib received conditional approval for 3L treatment of germline BRCA mutation associated ovarian cancer in May 2021, which was included in the NRDL. BeiGene expects to release topline results from pamiparib's China Ph3 trial (NCT03519230) as a maintenance treatment of platinum-sensitive recurrent ovarian cancer in 2022.

Figure 13: Commercial products developed internally

PRODUCT	LEAD INDICATIONS	MECHANISM OF ACTION	REGULATORY STATUS	BEIGENE COMMERCIAL RIGHTS	PARTNER
Brukinsa zanubrutinib	U.S.: R/R MCL[1], WM & R/R MZL[1]; China: R/R MCL[2], R/R CLL/SLL[2] & R/R WM[2]; EU[3]: WM	BTK inhibitor	Approved in the U.S., China, EU and other markets	Global	N/A
tislelizumab	1L Squamous and Non-Squamous NSCLC; 2/3L NSCLC; R/R classical Hodgkin's lymphoma ; 2/3L HCC; R/R PD-L1+ UC; 2L/3L MSI-H/dMMR solid tumors; 2L ESCC	Anti-PD-1 antibody	Approved in China; BLA accepted in US and EU[4]	Outside North America, Japan, EU and six other European countries	NOVARTIS
pamiparib	3L BRCA-mutated ovarian cancer[2]	PARP inhibitor	Approved in China	Global	N/A

Source: Company data, CMBIGM. Notes: 1. Approved under accelerated approval. 2. Conditionally approved. 3. The approval is applicable to all 27 EU member states, plus Iceland, Lichtenstein and Norway. 4. 2L ESCC in the US and EU, NSCLC in EU.

As of May 2022, BeiGene has 11 clinical-stage internally discovered drug candidates, including the late-stage asset ociperlimab (TIGIT inhibitor) and early-stage clinical assets such as surzebiclimab (BGB-A425, TIM-3), BGB-11417 (BCL-2), BGB-A445 (OX40), BGB-10188 (PI3K delta), BGB-15025 (HPK1), lifirafenib (BRAF Dimer), BGB-23339 (TYK2), BGB-16673 (BTK-targeted CDAC), etc.

Additionally, thanks to BeiGene's proprietary biology research platform, the Company has more than 50 preclinical programs, with half of these candidates with global best-in-class or first-in-class potential. As such, we expect the Company's internal discovered pipelines to continue to expand in coming years.

Figure 14: BeiGene's global internal discovery pipeline (as of May 2022)

Asset	Program	Phase		
		Phase 1	Phase 2	Phase 3
Zanubrutinib (BTK inhibitor)	monotherapy	1L and R/R WM		
		B-cell malignancies		
		R/R CLL/SLL		
		Previously treated B-cell malignancies		
		R/R MZL		
	Zanubrutinib + Rituximab	1L MCL		
	Zanubrutinib +/- Venetoclax‡ (Bcl-2 inhibitor)	1L CLL/SLL		
	Obinutuzumab (anti-CD20) + Zanubrutinib	R/R FL		
Tislelizumab (anti-PD-1)	monotherapy	2L advanced ESCC, 1L HCC, 2L/3L NSCLC		
		Previously treated unresectable HCC,R/R cHL		
	Tislelizumab + chemotherapy	1L advanced ESCC, 1L GC/GEJC		
	Zanidatamab (anti-HER2 bi-specfic antibody) + Chemotherapy +/- tislelizumab	GEA		
	Tislelizumab + surufatinib (VEGFR, FGFR, CSF-1R inhibitor)	Advanced solid tumors		
	Tislelizumab + fruquintinib (VEGFR)*	Advanced, refractory TNBC		
Ociperlimab *(anti-TIGIT)*	Ociperlimab (anti-TIGIT) + tislelizumab	1L PD-L1 high advanced NSCLC		
		2L PD-L1+ advanced ESCC		
		Advanced solid tumors		
	Ociperlimab + tislelizumab + chemotherapy	1L NSCLC		
	Ociperlimab + tislelizumab + concurrent chemoradiotherapy	LA NSCLC		
		Previously untreated LS-SCLC		
Surzebiclimab (BGB-A425, anti-TIM-3)	monotherapy + tislelizumab	Advanced solid tumors		
BGB-A445 (anti-OX40)	monotherapy + tislelizumab	Advanced solid tumors		
BGB-10188 (PI3K inhibitor)	monotherapy + tislelizumab	Advanced solid tumors		
BGB-15025 (HPK1 inhibitor)	monotherapy + tislelizumab	Advanced solid tumors		
Pamiparib *(PARP 1/2 inhibitor)*	monotherapy	1L maintenance platinum-sensitive GC		
	Pamiparib + temozolomide	Advanced solid tumors		
BGB-3245 (BRAF inhibitor)	monotherapy	Advanced solid tumors with BRAF mutations		
Lifirafenib (RAF inhibitor)	+ mirdametinib (MEK inhibitor)	Advanced solid tumors		
BGB-10188 (PI3K inhibitor)	+/- zanubrutinib	B-cell lymphoid malignancies		
	+/- tislelizumab	B-cell malignancies		
BGB-11417 (Bcl-2 inhibitor)	monotherapy	Mature B-cell malignancies		
	+ azacitidine +/- posaconazole	Myeloid malignancies		
	+ dexamethasone +/- carfilzomib	R/R multiple myeloma with t(11;14)		
BGB-16673 (BTK-targeted CDAC)	monotherapy	B-cell malignancies		
BGB-23339 (TYK2 inhibitor)**	monotherapy	Inflammation and immunology		

Source: Company data, CMBIGM. Notes: *Enrolling in the US; **First-in-human trial, healthy subjects

Among BeiGene's rich in-house developed clinical stage assets, we would like to highlight the ociperlimab and BGB-11417 with large market potential.

1) Ociperlimab (TIGIT antibody) is one of the most advanced TIGIT inhibitors with intact Fc function current in pivotal stage trials. BeiGene is evaluating ociperlimab in comprehensive clinical programs in combination with tislelizumab, including two global Ph3 clinical trials and five Ph2 PoC studies. In Dec 2021, BeiGene entered into an option, collaboration and license agreement with Novartis for ociperlimab with a total upfront and milestone payment up to US$2.90bn and lucrative sales royalties of high-teens to mid-twenties of net sales in the licensed territory.

2) BGB-11417 (Bcl-2 inhibitor) demonstrated potent activity and high selectivity against the pro-apoptotic protein Bcl-2 according to preclinical and IND-enabling studies. The molecule appears to be more potent than venetoclax (the only marketed Bcl-2 inhibitor globally which was co-developed by AbbVie and Roche) and shows the potential to overcome resistance to venetoclax. BeiGene has an ongoing Ph1 trial (NCT04277637) in Australia and the US investigating BGB-11417 and its combination with zanubrutinib in patients with mature B-cell malignancies. BeiGene aims to start pivotal trials for BGB-11417 in 2022.

Rich portfolio of in-licensed products

Supported by its global clinical development and commercial capabilities, BeiGene collaborates with world-leading biopharma such as Amgen and Novartis to develop and commercialize innovative medicines. By leveraging its China commercial capabilities, BeiGene has in-licensed 13 commercial medicines and around two dozen clinical-stage drug candidates.

The rich commercial in-licensed product portfolio has become an important revenue growth engine for BeiGene. We estimate that in-licensed products delivered approximately US$155mn revenue in 2021, growing by c. 50% YoY and contributing c. 25% of BeiGene's total sales.

Figure 15: In-licensed commercial products (as of May 2022)

PRODUCT	LEAD INDICATIONS	MECHANISM OF ACTION	REGULATORY STATUS	BEIGENE COMMERCIAL RIGHTS	PARTNER
XGEVA® (denosumab) injection	Giant cell tumor of bone[2] / Skeletal Related Events (SREs)[2]	Anti-RANK ligand antibody	Approved in China	Mainland China	AMGEN
BLINCYTO® (blinatumomab) for injection 35 mcg single-dose vial	R/R Acute lymphocytic leukemia[2]	Anti-CD19 x anti-CD3 bispecific T-cell engager (BiTE)	Approved in China	Mainland China	AMGEN
Kyprolis® (carfilzomib) for injection	R/R Multiple myeloma[2]	Proteasome inhibitor	Approved in China	Mainland China	AMGEN
Revlimid® (lenalidomide) capsules	R/R adult multiple myeloma, newly diagnosed multiple myeloma, previously treated follicular lymphoma	Anti-angiogenesis, immuno-modulation	Approved in China	Mainland China	Bristol Myers Squibb
Vidaza® azacitidine for injection	Myelodysplastic syndromes, acute myeloid leukemia, chronic myelomonocytic leukemia	DNA hypomethylation	Approved in China	Mainland China	Bristol Myers Squibb
sylvant® siltuximab	Idiopathic multicentric Castleman disease	IL-6 antagonist	Approved in China	Greater China	EUSAPharma
Qarziba® Dinutuximab beta	High-risk neuroblastoma[2]	Anti-GD2 antibody	Approved in China	Mainland China	EUSAPharma
POBEVCY® (Avastin biosimilar)	Colorectal and lung cancers	Anti-VEGF antibody	Approved in China	Greater China	百奥泰 BIO-THERA
TAFINLAR® (dabrafenib)	Melanoma[5]	BRAF inhibitor	Approved in China	China Broad Markets[7]	NOVARTIS
MEKINIST® (trametinib)	Melanoma[5]	MEK inhibitor	Approved in China	China Broad Markets[7]	NOVARTIS
VOTRIENT® (pazopanib)	Advance renal cell carcinoma	VEGFR inhibitor	Approved in China	China Broad Markets[7]	NOVARTIS
AFINITOR® (everolimus)	Advanced renal cell carcinoma[6]	mTOR inhibitor	Approved in China	China Broad Markets[7]	NOVARTIS
ZYKADIA® (ceritinib)	ALK + NSCLC	ALK inhibitor	Approved in China	China Broad Markets[7]	NOVARTIS

Source: Company data, CMBIGM. Notes: 2. Conditionally approved. 5. TAFINLAR and MEKINIST are being investigated in combination by Novartis for NSCLC indications. 6. Following progression on or after vascular endothelial growth factor (VEGF)-targeted therapy. 7. Rights to promote and market in China's broad markets pursuant to a Market Development Agreement with Novartis dated 19 Dec 2021.

BeiGene also has around two dozen in-licensed drug candidates currently under development, among which, zanidatamab, sitravatinib and sotorasib are at late-clinical stage.

Zanidatamab (ZW25, bispecific HER2-targeted antibody) is currently in late-stage clinical development with Zymeworks. BeiGene has the rights of zanidatamab in Asia (excluding Japan), Australia, and New Zealand. BeiGene is participating in three ongoing clinical studies of zanidatamab. BeiGene initiated a global Ph3 clinical trial (NCT05152147) examining zanidatamab in combo with chemotherapy with and without tislelizumab in HER2-positive gastroesophageal cancer in late 2021. BeiGene also aims to complete enrollment of its pivotal Ph2 study (NCT04466891) evaluating zanidatamab in 2L biliary tract cancer in 2022.

Sitravatinib is a multi-kinase inhibitor in-licensed from Mirati. Sitravatinib is being evaluated by Mirati in multiple clinical trials for treatment of patients who are refractory to prior immune checkpoint inhibitor therapy, including a Ph3 SAPPHIRE trial of sitravatinib in NSCLC initiated in 2019. BeiGene is evaluating

sitravatinib in multiple clinical trials including a Ph3 trial combining sitravatinib with tislelizumab in 2/3L sq- and nsq- NSCLC.

Sotorasib (global first-in-class KRAS G12C inhibitor), in-licensed from Amgen, is the only marketed KRAS G12C inhibitor globally, which was approved in nearly 40 countries. Sotorasib was approved in the US in May 2021 for the 2L treatment of KRAS G12C-mutated locally advanced or metastatic NSCLC. In China, sotorasib was granted Breakthrough Therapy Designation (BTD).

Figure 16: BeiGene's in-licensed drug candidates (as of May 2022)

	Molecule/Asset	Indications	Phase	Commerical Rights
AMGEN	Sotorasib (KRAS G12C)	Solid tumors, CRC, NSCLC	Phase 3	China
	tarlatamab^^ (DLL3)	SCLC	Phase 2	China
	pavurutamab^^ (BCMA)	MM	Phase 1	China
	AMG 176 (Mcl-1, SM)	Hematologic malignancies	Phase 1	China
	AMG 427^^ (FLT3)	AML	Phase 1	China
	acapatamab^^ (PSMA)	Prostate cancer	Phase 1	China
	AMG 509^ (STEAP1 XmAb)	Prostate cancer	Phase 1	China
	AMG 199^^ (MUC17)	GC/GEJC	Phase 1	China
	AMG 650 (oral small molecule)	Solid tumors	Phase 1	China
	AMG 506 (FAP x 4-1BB, DARPin®)	Solid tumors	Phase 1	China
	AMG 994 (bispecific antibody)	Solid tumors	Phase 1	China
	AMG 256 (Anti-PD-1 x IL21 mutein)	Solid tumors	Phase 1	China
MIRATI THERAPEUTICS	Sitravatinib‡ (multi-kinase inhibitor) + Tislelizumab	NSCLC, RCC, OC, MEL	Phase 3	Asia ex-Japan, Australia, New Zealand
	Sitravatinib‡ (monotherapy) + Tislelizumab	HCC, GC/GEJC	Phase 2	Asia ex-Japan, Australia, New Zealand
	Sitravatinib‡ (monotherapy) + Tislelizumab	Advanced solid tumors	Phase 1	Asia ex-Japan, Australia, New Zealand
zymeworks	Zanidatamab†† (HER2, bispecific antibody) + Chemotherapy + Tislelizumab	GEA	Phase 3	Asia ex-Japan, Australia, New Zealand
	Zanidatamab†† (monotherapy)	BTC	Phase 2	Asia ex-Japan, Australia, New Zealand
	Zanidatamab†† + Chemotherapy +/- Tislelizumab	BC, GC, GEA	Phase 2	Asia ex-Japan, Australia, New Zealand
	ZW49 (HER2, bispecific ADC)	HER2 expressing cancers	Phase 1	Asia ex-Japan, Australia, New Zealand
SpringWorks THERAPEUTICS	BGB-3245[1] (BRAF)	Solid tumors	Phase 1	Asia ex-Japan
Seagen	SEA-CD70 (anti-CD70)	MDS, AML	Phase 1	Asia ex-Japan, Australia, New Zealand
leaptherapeutics	DKN-01(DKK1) + Tislelizumab ± Chemotherapy	GC/GEJC	Phase 2	Asia ex-Japan, Australia, New Zealand
Leads Biolabs	LBL-007 (LAG-3) + Tislelizumab	Advanced solid tumors	Phase 2	Ex-China
assemblybio	Vebicorvir (ABI-H0731) (HBV core inhibitor)*	Chronic hepatitis B virus	Phase 2	China
	ABI-H3733 (HBV core inhibitor)	Chronic hepatitis B virus	Phase 1	China

Source: Company data, CMBIGM

Next wave of innovation driven by new technology platforms

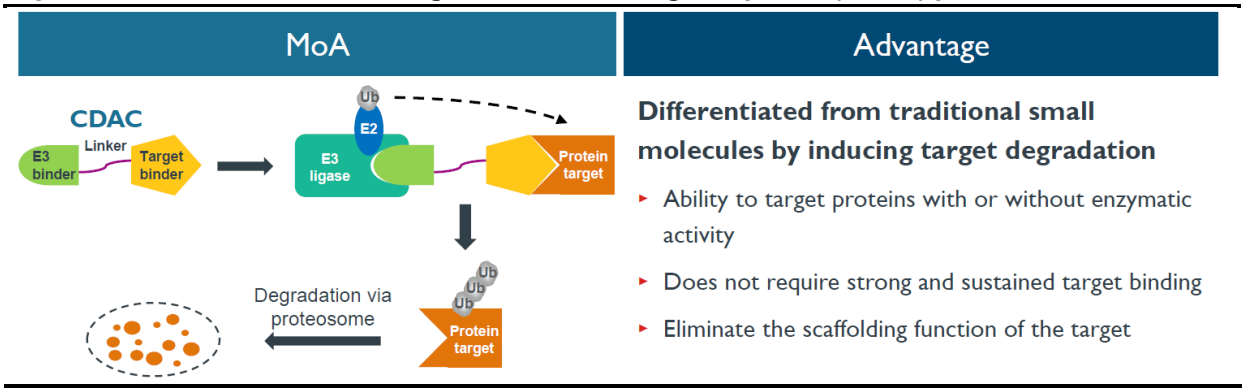
BeiGene emphasizes its strategic focus on consistently strengthening its in-house R&D capabilities. BeiGene aims to enhance its next wave of drug discovery by investing in new modalities, such as CDAC, BsAb/TsAb, ADC, Pro-Cytokine, cell therapy, mRNA, etc. BeiGene has more than 50 preclinical programs, with half of these candidates with global best-in-class or first-in-class potential. The Company aims to progress over 10 preclinical candidates to clinical stage within the next 24 months.

Figure 17: BeiGene's pipeline trend at a glance

Source: Company data, CMBIGM. Notes: SM, Small Molecule; mAb, Monoclonal Antibody; ADC, Antibody Drug Conjugate; TAA, Tumor Associated Antigen; CDAC, Chimeric Degradation Activating Compound (targeted protein degradation); BsAb, Bispecific Antibody; TsAb, Trispecific Antibody; CAR-NK, Chimeric Antigen Receptor-Natural Killer Cell

We would like to highlight BeiGene's in-house developed chimeric degradation activating compound (CDAC) platform (also called PROTAC). Differentiated from traditional small molecules, CDAC platform has the potential to drug the undruggable, thanks to 1) its ability to target proteins with or without enzymatic activity, 2) not requiring strong and sustained target binding, and 3) eliminating the scaffolding function of the target.

Figure 18: BeiGene's chimeric degradation activating compound (CDAC) platform

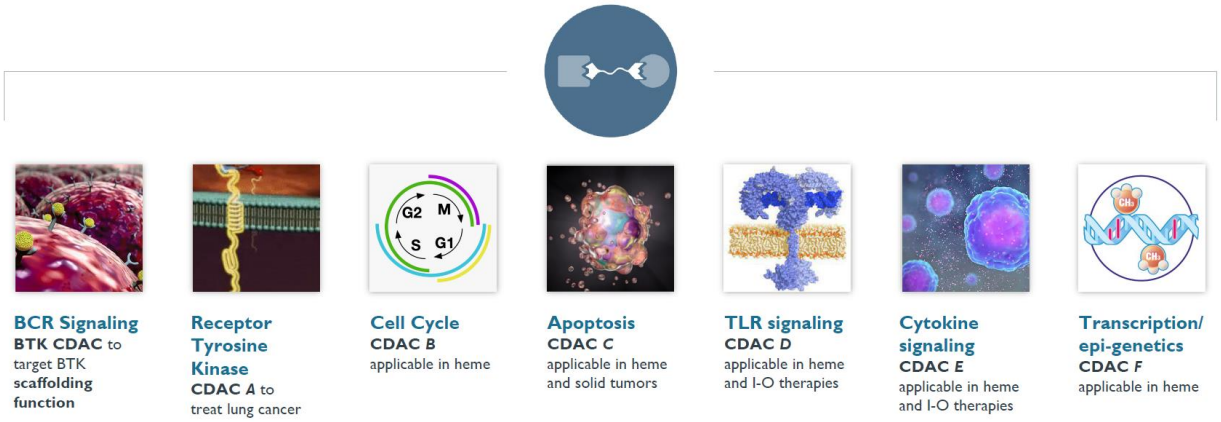


Source: Company data, CMBIGM

The CDAC (PROTAC) molecule comprises an E3 binder to recruit the E3 ligase, a warhead to bind the protein target, and a linker to connect them. When the CDAC molecule draws the protein target and E3 ligase close, E3 will employ an E2 ubiquitin-conjugating enzyme to transfer ubiquitin to the surface of the protein target. Then the proteasome will recognize the polyubiquitination signal and degrade the targeted protein. At the same time, the CDAC molecule will separate from the ternary complex and participate in another degradation cycle.

BeiGene has built-up strong capability to leverage a wider spectrum of both ubiquitous and tissue specific E3 ligases, which will potentially reduce dose-limiting toxicities, overcome E3-relevant drug resistance and broaden substrate spectrum. BeiGene is investigating CDAC in multiple programs, including BTK CDAC, receptor tyrosine kinase CDAC, apoptosis CDAC, cytokine signaling CDAC, etc.

Figure 19: BeiGene's CDAC programs

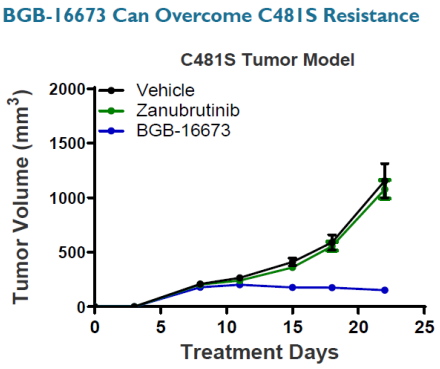


Source: Company data, CMBIGM

BGB-16673 is BeiGene's first CDAC molecule moved into clinical stage, which is an investigational BTK targeted CDAC candidate. BGB-16673 is designed to overcome zanubrutinib and other BTKi resistance. In preclinical studies, BGB-16673 showed good pharmacological properties with high potency and selectivity, good oral bioavailability and long half-life. BeiGene has initiated two Ph1 trials of BGB-16673 in B-cell malignancies in the US & Australia (NCT05006716) and in China (NCT05294731), respectively.

Irreversible BTK inhibitor has emerged as a transformative treatment option for CLL and other B-cell malignancies, yet >80% of CLL patients develop resistance due to C481S mutation. Preclinical studies show that BGB-16673 can potentially overcome C481S resistance caused by irreversible BTK inhibitors.

Figure 20: BeiGene's BTK CDAC can potentially overcome C481S resistance

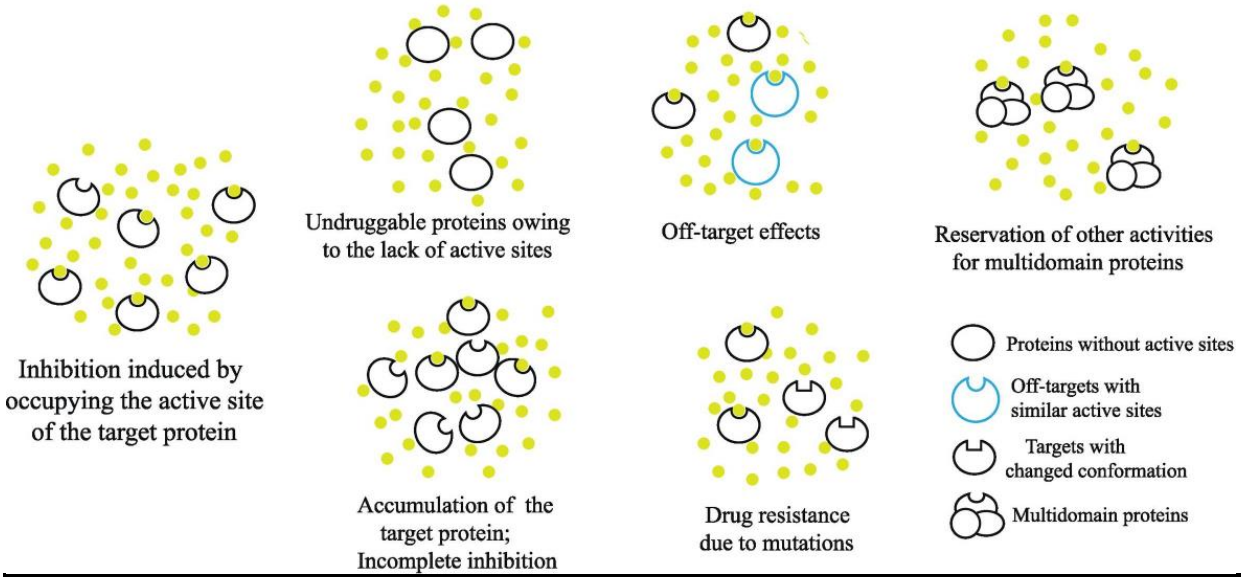


Source: Company data, CMBIGM

PROTAC (CDAC) is a promising technology for targeted therapies

Small molecule inhibitors have manifested several limitations as a type of targeted therapies. For example, the target proteins of small molecular inhibitors are usually enzymes and receptors that have pockets or active sites, while about 85% of the human proteome lack active sites and are thus undruggable in this strategy. Meanwhile, many cancer genes are highly mutated, which may lead to the conformational changes of protein productions and thus lead to drug resistance.

Figure 21: Limitations of small molecular inhibitors



Source: EBioMedicine Journal, CMBIGM

A PROTAC (CDAC) molecule has the potential to overcome these limitations with its unique advantages. (1) Event-driven mechanism. PROTACs act as catalysts to initiate degradation event of target protein in a repeatable manner (called event-driven mechanism), which allows the dosage, administration frequency and toxicity of PROTACs lower than those of small-molecule drugs. (2) Degrading undruggable targets. PROTACs could use the low-affinity small-molecule ligands or the oligonucleotides as protein decoys to release the dependence on the well-defined targetable pockets or active sites, providing opportunities to degrade undruggable proteins. (3) Avoiding compensatory protein expression. Targeted therapies may trigger compensatory protein expression after administration, which decreases drug efficacy and increases side effects. PROTAC can potently downregulate targeted protein through accelerating Ubiquitin-Proteasome System (UPS) mediated degradation, thus offering a pathway to prevent compensatory protein expression. (4) Overcoming drug resistance. A number of proof-of-concept studies have shown that PROTACs could be utilized in cases of resistant cancers where traditional inhibitors have failed to be effective.

Figure 22: Comparison of different types of drug mechanism

	PROTAC	Small-molecule inhibitor	CRISPR/Cas9	RNA interfering	Monoclonal antibody
Requirement of active sites	No	Yes	No	No	Yes
Elimination of pathogenic proteins	Yes	No	Yes	Yes	No
Undruggable targets	Yes	No	Yes	Yes	Yes
Tissue penetration	Moderate	Yes	Poor	Poor	Poor
Intracellular targets	Yes	Yes	Yes	Yes	No
Systemic delivery	Yes	Yes	Poor	No	Yes
Catalytic mechanism of action	Yes	No	Yes	Yes	No
Route of administration	PO/IV/SC	PO/IV/SC	IV	IV/SC	IV/SC

Source: CMBIGM. Notes: IV intravenous injection, PO peros, SC Subcutaneous injection.

Clinical development of PROTAC molecules

According to data from Pharmcube, there're 17 PROTAC molecules at early clinical stage worldwide, targeting a wide range of targets including ER, BRD9, AR, BTK, Bcl-xl, STAT3, IRAK4, etc. ARV-471 and ARV-110 developed by Arvinas are currently at Ph2 development for breast cancer and prostate cancer, respectively. CFT8634 developed by C4 Therapeutics is at Ph2. In China, BeiGene, Kintor and Haisco are investigating their PROTAC molecules in Ph1 studies. BGB-16673 from BeiGene and HSK29116 from Haisco both target BTK, similar to Nurix's NX-2127.

Figure 23: PROTAC molecules under clinical-stage development (as of May 2022)

Drug Name	Company	Development phase	Target	Target indications
ARV-471	Arvinas, Pfizer	PhI/II	ER	breast cancer
ARV-110	Arvinas	PhI/II	AR	castration-resistant prostate cancer (CRPC)
CFT8634	C4 Therapeutics	PhI/II	BRD9	synovial sarcoma
BGB-16673	BeiGene	PhI	BTK	CLL, SLL, MZL, WM, FL, MCL; B-cell malignancies
GT20029	Kintor Pharmaceuticals	PhI	AR	acne, androgenic alopecia (AGA)
HSK29116	Haisco Pharmaceutical	PhI	BTK	B-cell lymphoma; B-cell malignancies
ARV-766	Arvinas	PhI	AR	castration-resistant prostate cancer (CRPC)
DT2216	Dialectic Therapeutics	PhI	Bcl-xl	hematologic malignancies, solid tumor
FHD-609	Foghorn Therapeutics	PhI	BRD9	synovial sarcoma
HP518	Hinova Pharmaceuticals	PhI	AR	castration-resistant prostate cancer (CRPC)
KT-333	Kymera Therapeutics	PhI	STAT3	T-cell large granular lymphocyte leukemia (T-LGLL), solid tumor, NHL, peripheral T cell lymphoma (PTCL), cutaneous T cell lymphoma (CTCL)
KT-413	Kymera Therapeutics	PhI	IRAK4	diffuse large B-cell lymphoma (DLBCL)
KT-474	Kymera Therapeutics, Sanofi	PhI	IRAK4	suppurative hidrosadenitis, atopic dermatitis, rheumatoid arthritis (RA)
NX-2127	Nurix Therapeutics	PhI	BTK,IKZF3	B-cell malignancies
NX-5948	Nurix Therapeutics	PhI	BTK	DLBCL, primary central nervous system lymphoma (PCNSL), CLL, graft-versus-host disease (GVHD), SLL, MZL, WM, FL, MCL
AC0176	Accutar Biotechnology	PhI	AR	castration-resistant prostate cancer (CRPC)
AC0682	Accutar Biotechnology	PhI	ERα	hormone receptor positive breast cancer

Source: Pharmcube, CMBIGM

PROTAC has become a hot area of BD cooperation in recent years. In Jul 2021, Pfizer in-licensed the PROTAC estrogen receptor protein degrader ARV-471 from Arvinas with a total upfront and milestone payment of US$2.05bn and 50% profit sharing on this product. In Jul 2020, Sanofi entered into a partnership with Kymera Therapeutics to advance Kymera's PROTAC therapies, for which Kymera received US$150mn upfront and is eligible to receive more than US$2.0bn in potential milestones plus royalty payments. The partnerships validate the potential value of the PROTAC space and accelerate the clinical development of PROTAC molecules.

Figure 24: Major deals in the PROTAC space

Licensor	Licensee	Date	Product	Deal size (US$ mn)	Upfront payment (US$ mn)	Milestone payment (US$ mn)	Additional payments
Lycia Therapeutics	Eli Lilly	2021-08	Products based on Lycia's LYTAC platform (up to five targets)	1,635	35	1,600	Mid-single to low double-digits royalties
Arvinas	Pfizer	2021-07	ARV-471 (ER PROTAC)	2,050	650	1,400	50% profit sharing, additional $350mn investment in Arvinas
Kymera Therapeutics	Sanofi	2020-07	IRAK4 PROTAC, a second undisclosed program	2,150	150	2,000	Royalty payments
Nurix Therapeutics	Gilead	2019-06	Products based on Nurix's platform (up to five targets)	2,345	45	2,300	Low double-digit tiered royalties
Vividion Therapeutics	Bayer	2021-08	Acquisition of Vividion	2,000	1,500	500	N/A

Source: Company news release, CMBIGM

Zanubrutinib: potential BIC BTK inhibitor to unlock global opportunities

Diverse registration approvals worldwide

Zanubrutinib (BRUKINSA) is a second-generation Bruton's tyrosine kinase (BTK) inhibitor discovered by BeiGene that is equally or more selective than any approved BTKi, with fewer off-target effects and less cardiotoxicity. BTK is a key component of the B-cell receptor (BCR) signaling pathway and is an important regulator of cell proliferation and cell survival in various lymphomas. BTK inhibitors block BCR-induced BTK activation and its downstream signaling, leading to growth inhibition and cell death in certain malignant white blood cells called B-cells. Zanubrutinib is an orally active inhibitor that covalently binds to BTK, resulting in irreversible inactivation of the enzyme.

First approved by the US FDA in Nov 2019, zanubrutinib is positioned to have the most comprehensive label as a second-generation BTK inhibitor. As of Jun 2022, zanubrutinib has received 22+ approvals for CLL, MZL, MCL, and WM covering 50 countries and regions, including the US, China, Europe, the UK, Canada, Australia and other markets.

Zanubrutinib is recommended by authoritative clinical guidelines. In Jan 2022, NCCN changed its guidelines recommending zanubrutinib as a Category 2A preferred therapy for first-line treatment and second-line /subsequent treatment of patients with CLL/SLL, with or without the deletion(17p) / TP53 mutation, even though zanubrutinib has not been approved for CLL/SLL in overseas markets. The guideline changes improve the importance of zanubrutinib in treating CLL/SLL. Additionally, NCCN guidelines have added zanubrutinib as a preferred regimen for WM, r/r MCL, and r/r MZL. In China, zanubrutinib is recommended by CSCO for r/r CLL/SLL and r/r MCL.

Figure 25: Approved indications of zanubrutinib (as of May 2022)

Indication	Region & time of approval	Supporting registration-enabling trials
r/r CLL/SLL	China 2020.06 (FDA and EMA filings for 1L CLL/SLL accepted in Feb 2022)	NCT03206918 (single-arm pivotal Ph2 in China)
r/r MZL	US 2021.09; CA 2022.03; Uruguay 2022.04	NCT03846427/MAGNOLIA (global single-arm pivotal Ph2); NCT02343120 (global single-arm Ph1/2)
r/r MCL	US 2019.11; China 2020.06; Israel 2021.01; UAE 2021.02; CA 2021.07; Chile 2021.07; Brazil 2021.08; Singapore 2021.10; Australia 2021.10; Russia 2021.10; Saudi Arabia 2021.11; Ecuador 2021.12; South Korea 2022.02; Uruguay 2022.04	NCT03206970 (single-arm pivotal Ph2 in China); NCT02343120 (global single-arm Ph1/2)
WM (1L or r/r)	CA 2021.03; China 2021.06; US 2021.08; Australia 2021.10; EU plus Iceland, Lichtenstein, and Norway 2021.11; UK 2021.12; Switzerland 2022.02; South Korea 2022.02; Uruguay 2022.04	NCT03332173 (for China approval; single-arm pivotal Ph2 in China); NCT03053440/ASPEN (for overseas approval; Ph3 trial comparing zanubrutinib with ibrutinib in patients with r/r or treatment-naïve WM who harbor a MYD88 mutation)

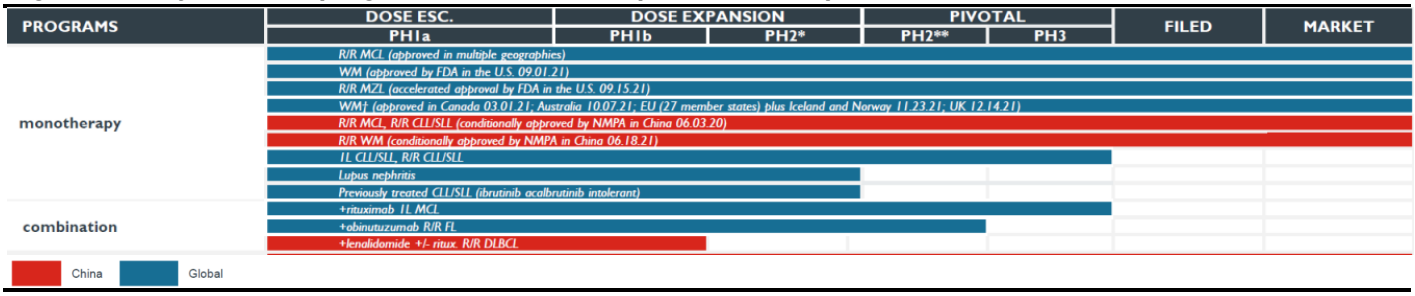
Source: Company data, CMBIGM

Additionally, as of Jun 2022, zanubrutinib has more than 40 global filings under review for various indications. In Feb 2022, zanubrutinib's sBLAs for CLL, the most common form of leukemia in Western countries, were accepted by the US FDA (PDUFA date in Jan 2023) and the EMA. In addition, an sNDA of zanubrutinib for treatment of 1L CLL/SLL has been accepted for review by the China NMPA. We expect zanubrutinib to further expand its registration approvals in new regions/indications, including potential launch in more than 10 markets in 2022.

The wide approvals of zanubrutinib are supported by broad global clinical programs. BeiGene has initiated or completed 35 trials for zanubrutinib (incl. 9 registration-enabling trials) across 28 markets in 12 indications. Particularly, two Ph3 head-to-head studies comparing zanubrutinib with ibrutinib in CLL/SLL and WM are ongoing with promising data released, demonstrating the better response and less toxicity

of zanubrutinib. As of Mar 2022, around 4,000 subjects have been enrolled in zanubrutinib's clinical trials, with over 3,500 subjects from outside China.

Figure 26: Major clinical program of zanubrutinib (as of Feb 2022)



Source: Company data, CMBIGM. Note: † R/R or not suitable for chemo-immunotherapy

Best-in-class BTKi evidenced by head-to-head studies

Zanubrutinib is a next-generation BTKi with potent efficacy and superior safety

Ibrutinib, the global first-in-class BTKi, has an issue of off-target inhibition which likely contributes to the toxicities reported in patients treated with ibrutinib, such as atrial fibrillation, hypertension, diarrhea and rash, and bleeding or bruising (link). The label for ibrutinib has been recently updated to include information about the uncommon risk of cardiac arrhythmias, cardiac failure and sudden death, which has occurred in 1% of patients, warning the safety issues of ibrutinib (link). As a selective next-generation BTK inhibitor designed to have high specificity for BTK and minimize off-target effects, zanubrutinib demonstrated complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes, and was associated with durable clinical responses in patients with CLL/SLL (link). Zanubrutinib is equally or more selective than any approved BTKi, like ibrutinib, with fewer off-target effects and less cardiotoxicity.

Zanubrutinib demonstrated best-in-class potential in head-to-head studies compared with ibrutinib and standard treatments. Zanubrutinib was shown to have a superior response rate, an improved PFS and a lower rate of atrial fibrillation/flutter as compared with ibrutinib, proven in the head-to-head ALPINE trial comparing zanubrutinib vs ibrutinib in patients with r/r CLL/SLL. In the interim analysis, ORR was significantly higher with zanubrutinib (78.3% vs 62.5%), as was overall 12-mo PFS (94.9% vs 84.0%). On the safety side, results confirmed that zanubrutinib was far more tolerable than ibrutinib with an improved cardiac profile. The rate of atrial fibrillation/flutter, a pre-specified safety endpoint in interim analysis, was significantly lower with zanubrutinib vs ibrutinib (2.5% vs 10.1%). Rates of cardiac disorders of any grade were lower with zanubrutinib (13.7% vs 25.1%) as well. Based on results from ALPINE and other studies, zanubrutinib's BLA fillings for CLL/SLL have been accepted by the FDA and EMA in Feb 2022.

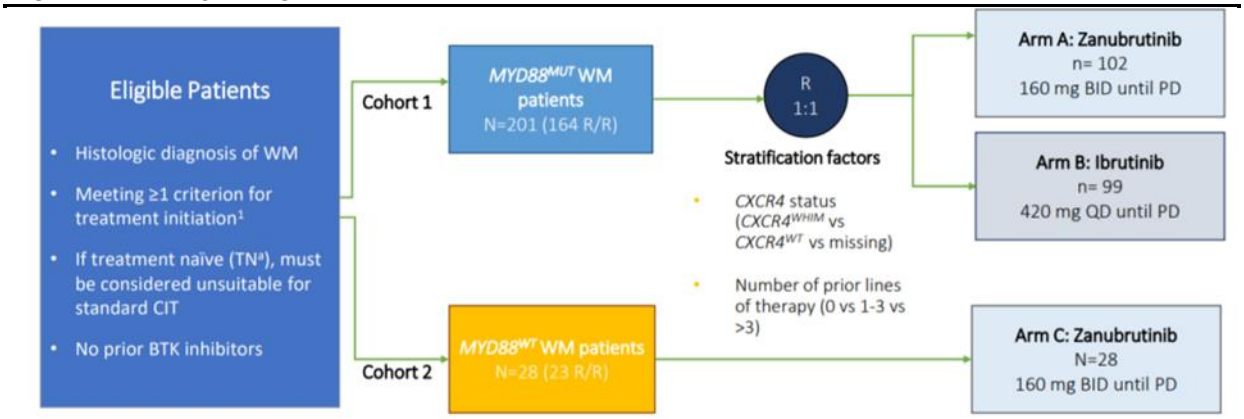
In the ASPEN trial, which compared zanubrutinib head-to-head with ibrutinib in WM patients, zanubrutinib achieved numerically higher very good partial response (VGPR) rates (28% vs 19%), although the difference was not statistically significant. In this study, zanubrutinib demonstrated a more favorable safety profile compared with ibrutinib with a lower frequency of adverse events, especially atrial fibrillation or flutter (2% vs 15%) and major hemorrhage (6% vs 9%).

Head-to-head ASPEN trial in WM

ASPEN (NCT03053440) is a Ph3 randomized, open-label, multicenter trial comparing zanubrutinib to ibrutinib in WM patients. Based on results from the ASPEN trial, zanubrutinib has been approved in multiple markets for treatment of WM, including in the US (1L), Canada (1L), EU (2L), UK (2L), Australia (2L), etc. Zanubrutinib was approved in China for treatment of r/r WM in Jun 2021, while the BLA of zanubrutinib for 1L WM was submitted to the China NMPA in Jan 2022 based on the ASPEN trial results.

In the ASPEN trial, patients were assigned to Cohort 1 (MYD88 mutation) or Cohort 2 (MYD88 wild-type or mutation unknown). WM patients with MYD88 mutation (Cohort 1) were randomly assigned 1:1 to receive ibrutinib or zanubrutinib. All Cohort 2 patients received zanubrutinib 160 mg twice daily until disease progression (link1, link2). The primary endpoint of the trial was the CR or VGPR by independent review committee (IRC).

Figure 27: Study design of ASPEN trial

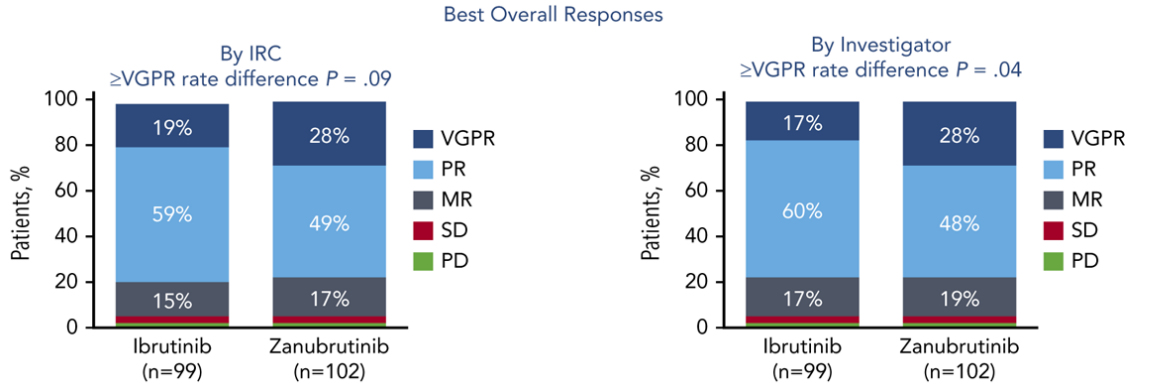


Source: Company data, CMBIGM

A total of 201 patients were enrolled in Cohort 1 of the trial (164 r/r and 37 treatment-naive). At a median follow-up of 19.4 months (link), the IRC-assessed VGPR rate was higher among zanubrutinib treated patients (28%) than ibrutinib treated (19%) patients (p=0.09). Investigator-assessed rates of VGPR were 28% and 17% in the zanubrutinib and ibrutinib arms, respectively (p=0.04). The difference in VGPR rate was not statistically significant. Major response rates (MRRs) among zanubrutinib and ibrutinib patients were 77.5% and 77.8%, respectively.

In Cohort 1 at the follow-up of 19.4 months, zanubrutinib demonstrated a favorable safety profile compared to ibrutinib with lower frequency of atrial fibrillation or flutter (2% vs 15%), major hemorrhage (6% vs 9%) and diarrhea (21% vs 32%). In the zanubrutinib arm, four (4.0%) patients discontinued treatment due to AEs and there was one (1.0%) fatal AE; in the ibrutinib arm, nine patients (9.2%) discontinued due to AEs and there were four (4.1%) fatal AEs.

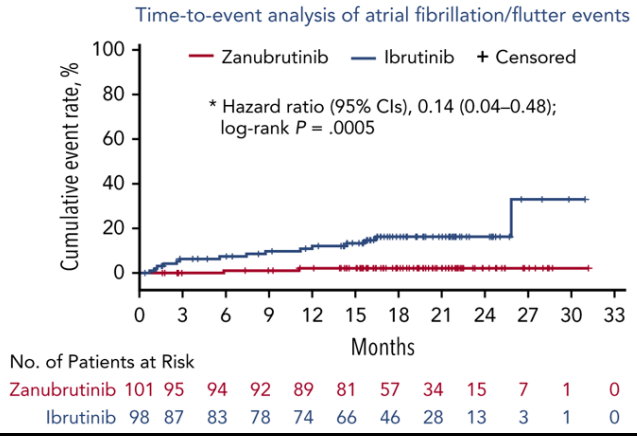
Figure 28: Results of ASPEN trial (median follow-up of 19.4 months)



AE Categories, n (%) (Pooled Terms)	All Grades	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	15 (15.3)	2 (2.0)
Diarrhea (PT)	31 (31.6)	21 (20.8)
Hemorrhage	58 (59.2)	49 (48.5)
Major hemorrhage	9 (9.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)
Neutropenia*	13 (13.3)	30 (29.7)
Infection	66 (67.3)	67 (66.3)

*Descriptive 2-sided $P < .05$

Data cutoff 31Aug2019



Source: Company data, CMBIGM

The 43 months long-term follow-up results of the ASPEN trial were reported at the 2022 ASCO meeting (link), which further demonstrated clinically meaningful advantages of zanubrutinib vs ibrutinib in WM patients. The CR+VGPR rate by investigator was 36% with zanubrutinib vs 22% with ibrutinib (p=0.02) in Cohort 1. In patients with wild type or mutant CXCR4 from Cohort 1, CR+VGPR rates with zanubrutinib vs ibrutinib were 45% vs 28% (p= 0.04) and 21% vs 5% (p=0.15), respectively. Exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension were lower with zanubrutinib vs ibrutinib (0.2 vs 0.8 and 0.5 vs 1.0 persons per 100 person-months, respectively; p<0.05). Rate of neutropenia was higher while rate of grade ≥3 infection was lower with zanubrutinib vs ibrutinib.

Figure 29: Cross-trial compassion of BTK inhibitors in r/r WM

	Zanubrutinib		Acalabrutinib
Trial ID	NCT03053440 (BeiGene's head-to-head trial to compare zanubrutinib to ibrutinib)		NCT02180724
Trial phase	Phase 3		Phase 2
Indication	r/r WM		r/r WM
Study design	Randomized 1:1 to receive zanubrutinib or ibrutinib		Single arm
Subject number	164		92
Trial location	US, China, Europe etc.		US, Europe, etc
Follow-up time	19.4 months		27.4 months
Primary endpoint	CR and VGPR rate		ORR
Efficacy*	**zanubrutinib**	**ibrutinib**	**acalabrutinib**
MRR	78%	80%	78%
CR	0%	0%	
VGPR	29%	20%	
PR	49%	61%	

MR	16%	14%	
ORR	94%	94%	93%
SD	4%	3%	
DCR	98%	97%	
Safety**			
Grade ≥3 AEs	58%	63%	
Grade ≥3 hypertension	6%	11%	3%
Grade ≥3 pneumonia	1%	7%	7%
Grade ≥3 neutropenia	20%	8%	16%
Most common serious AE	Pneumonia (1 patients in zanubrutinib arm vs 9 patients in ibrutinib arm), neutropenia and febrile neutropenia (each 3 vs 0), influenza (3 vs 1), and pyrexia and sepsis (each 2 vs 3)		Lower respiratory tract infection (7%), pneumonia (7%), pyrexia (4%), cellulitis (3%), fall (3%), and sepsis (3%)
Grade ≥3 atrial fibrillation	0%	4%	1%
Data sources	Link		Link

Source: Company data, CMBIGM. Notes: * efficacy data of treatment-naïve WM patients were not included for both trials. ** Safety profile was based on the whole trial.

Head-to-head ALPINE trial in r/r CLL/SLL

ALPINE study is a global, randomized, Ph3 study comparing zanubrutinib vs ibrutinib in patients with r/r CLL/SLL. The interim analysis were presented at EHA Meeting in Jun 2021 (link1, link2). Patients with r/r CLL/SLL were randomized 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily until disease progression. The primary endpoint was ORR (PR+CR) non-inferiority and superiority as determined by investigators. The interim analysis included 415 patients, with 207 in zanubrutinib arm and 208 in ibrutinib arm. At a median follow-up of 15.3 months, as assessed by investigator, zanubrutinib achieved an ORR of 78.3%, a statistically significant improvement compared to 62.5% with ibrutinib (p=0.0006), achieving superiority in the primary endpoint. As assessed by Independent Review Committee (IRC), zanubrutinib achieved an ORR of 76.3%, numerically higher but not statistically significant compared to 64.4% with ibrutinib (p=0.0121), achieving non-inferiority. In del17p patients, the ORR was 83.3% in the zanubrutinib arm, compared to 53.8% in the ibrutinib arm. In addition, zanubrutinib showed 94.9% 12-months PFS rate vs. 84.0% for ibrutinib (descriptive p=0.0007; descriptive HR=0.40), and 97.0% 12-month OS rate vs. 92.7% for ibruitinib (descriptive p=0.1081; descriptive HR=0.54).

Figure 30: Summary of interim efficacy data of ALPINE trial

	Zanubrutinib (n=207), n (%)	Ibrutinib (n=208), n (%)
Primary endpoint: ORR (PR+CR)	162 (**78.3**) 95% CI: 72.0, 83.7	130 (**62.5**) 95% CI: 55.5, 69.1
	Superiority 2-sided *P*=0.0006 compared with pre-specified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L+PR+CR)	*183 (88.4)*	*169 (81.3)*
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to 1st assessment	6 (2.9)	9 (4.3)

	del(17p) (n=24), n (%)	del(17p) (n=26), n (%)
ORR (PR+CR)	20 (83.3)	14 (53.8)

Source: Company data, CMBIGM. Notes: PR-L, partial response with lymphocytosis.

In the interim analysis, zanubrutinib demonstrated a statistically significant lower risk of atrial fibrillation or flutter and advantages in the overall cardiac safety profile, compared to ibrutinib. The rate of atrial fibrillation/flutter, a pre-specified safety endpoint, was significantly lower with zanubrutinib vs ibrutinib (2.5% vs 10.1%, 2-sided P=0.0014). In addition, zanubrutinib showed superior safety in Grade ⩾3 cardiac disorders (zanubrutinib vs. ibrutinib: 2.5% vs. 6.8%), major hemorrhage (2.9% vs. 3.9%), and adverse events leading to discontinuation (7.8% vs 13.0%).

Figure 31: Summary of interim safety data of ALPINE trial

Safety Analysis Population	Zanubrutinib (n=204) n (%)	Ibrutinib (n=207) n (%)
Any AE	195 (95.6)	205 (99.0)
Any grade ≥3 AE	114 (55.9)	106 (51.2)
Serious AEs	56 (27.5)	67 (32.4)
Fatal AEs	8 (3.9)	12 (5.8)
AEs leading to dose reduction	23 (11.3)	25 (12.1)
AEs leading to dose interruption	81 (39.7)	84 (40.6)
AEs leading to treatment discontinuation	16 (7.8)	27 (13.0)

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage Major hemorrhage[b]	73 (35.8) 6 (2.9)	6 (2.9) 6 (2.9)	75 (36.2) 8 (3.9)	6 (2.9) 6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies Skin cancers	17 (8.3) 7 (3.4)	10 (4.9) 3 (1.5)	13 (6.3) 10 (4.8)	4 (1.9) 2 (1.0)

Source: Company data, CMBIGM

The topline data of the final response analysis of the ALPINE trial was released in Apr 2022 (link). After achieving superiority in ORR as assessed by investigator in the interim analysis, zanubrutinib further demonstrated superiority versus ibrutinib in ORR as assessed by IRC in final analysis. In the final analysis, a total of 652 r/r CLL/SLL patients were enrolled across Europe (60%), the US (17%), China (14%), New Zealand and Australia (9%) with a median follow-up of 24.2 months. The ORR was 80.4% in the zanubrutinib arm as compared to 72.9% in ibrutinib arm (2-sided p=0.0264). BeiGene expects to further analyze the PFS data of this trial. Zanubrutinib continued to demonstrate superior safety than ibrutinib. The rate of atrial fibrillation or flutter at 24.2 months of median follow-up was 4.6% (n=15) in the zanubrutinib arm and 12.0% (n=39) in the ibrutinib arm. Among 324 patients in each arm, 13.0% (n=42) of patients who received zanubrutinib discontinued treatment due to adverse events compared to 17.6% (n=57) of patients who received ibrutinib.

These final results were submitted to FDA as a major amendment to the sNDA originally accepted by FDA in Feb 2021. As a result, the FDA has extended the PDUFA date of the sNDA from Oct 2022 to Jan 2023 to allow more time to review the additional clinical data.

In the ALPINE trial, the effects of zanubrutinib and ibrutinib on health-related quality of life (HRQoL) was examined based on the patient-reported outcomes (PROs) and the results were presented at the EHA Meeting in Jun 2022 (link). Patients with r/r CLL/SLL who received zanubrutinib monotherapy reported improvements in key HRQoL endpoints compared with patients who received ibrutinib monotherapy. Estimated mean treatment differences and 95% CI in key PRO endpoints demonstrated treatment differences, in favor of zanubrutinib, in global health status, physical functioning, and fatigue in Cycle 7, and diarrhea in Cycle 13. Mean change from baseline showed greater improvement with zanubrutinib compared with ibrutinib at both Cycle 7 and Cycle 13.

Additionally, BeiGene plans to announce the final analysis data of the ALPINE trial including PFS in 2H22.

Figure 32: Cross-trial compassion of BTK inhibitors in r/r CLL/SLL

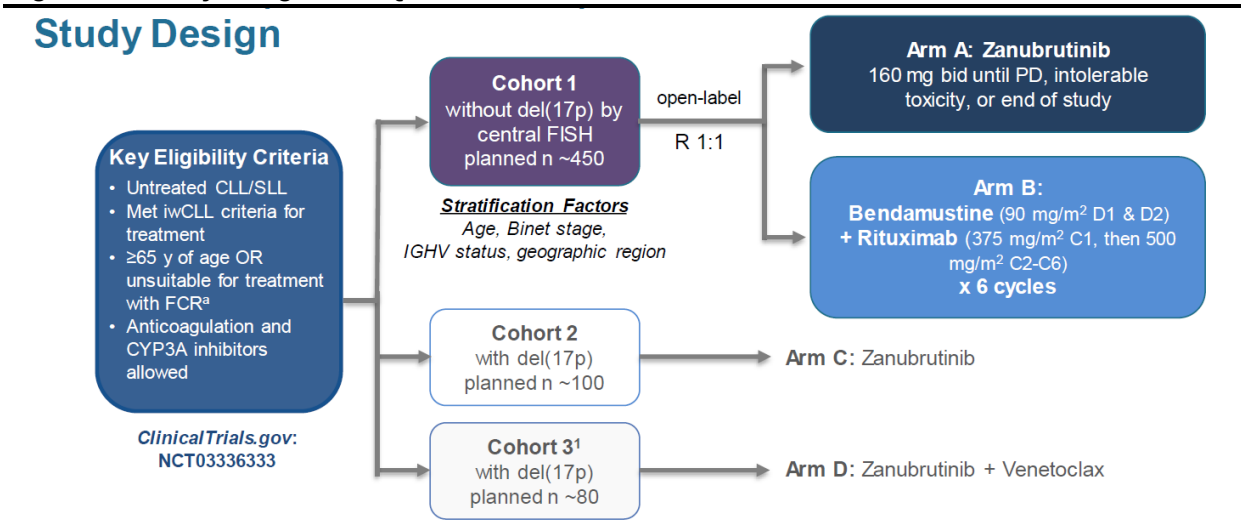
	zanubrutinib		acalabrutinib	
Trial ID	NCT03734016 (BeiGene's head-to-head trial to compare zanubrutinib to ibrutinib)		NCT02477696 (AZ's head-to-head trial to compare acalabrutinib to ibrutinib)	
Trial phase	Phase 3		Phase 3	
Indication	r/r CLL/SLL		r/r CLL/SLL	
Study design	Randomized 1:1 to receive zanubrutinib 160 mg BID or ibrutinib 420 mg QD		Randomized 1:1 to receive acalabrutinib 100 mg BID or ibrutinib 420 mg QD	
Subject number	415 (Interim data)		533	
Trial location	US, China, Europe etc.		US, Europe etc.	
Follow-up time	15 months		40.9 months	
Primary endpoint	ORR		PFS	
Efficacy	**zanubrutinib**	**ibrutinib**	**acalabrutinib**	**ibrutinib**
ORR	88.4%	81.3%		
CR/CRi	1.9%	1.4%		
nPR (nodular PR)	0.5%	0.0%		
PR	75.8%	61.1%		
PR-L	10.1%	18.8%		
DOR				
PFS	12 month PFS rate 94.9%	12 month PFS rate 84.0%	38.4 months	38.4 months
OS	12 month OS rate 97.0%	12 month OS rate 92.7%	Median OS not reached	Median OS not reached
Safety				
Atrial fibrillation/flutter	2.5%	10.1%	9.4%	16.0%
Cardiac disorders of any grade	13.7%	25.1%	24.1%	30.0%
Cardiac disorders (Gr≥3)	2.5%	6.8%	8.6%	9.5%
Hypertension (Gr≥3)	10.8%	10.6%	4.1%	9.1%
Infections (Gr≥3)	12.7%	17.9%	30.8%	30.0%
Data sources	Link		Link	

Source: Company data, CMBIGM

SEQUOIA trial in 1L CLL/SLL

SEQUOIA (NCT03336333) is an open-label, global, randomized Ph3 trial comparing zanubrutinib with standard treatment (bendamustine plus rituximab, BR) for patients with untreated CLL/SLL. The trial consists of three cohorts: Cohort 1: randomized 1:1 to receive zanubrutinib or BR in patients not harboring del(17p); Cohort 2: patients with del(17p) receiving zanubrutinib as a monotherapy; and Cohort 3: patients with del(17p) or pathogenic TP53 variant receiving zanubrutinib in combination with venetoclax.

Figure 33: Study design of SEQUOIA trial in 1L CLL/SLL



Source: Company data, CMBIGM

In Cohort 1 of the SEQUOIA trial (NCT03336333), zanubrutinib demonstrated statistically significant improvement in PFS compared to BR. 479 patients without del(17p) were randomized to zanubrutinib (n=241) and BR (n=238) (link1, link2). At the interim analysis, with a median follow-up of 26.2 months, the 24-month PFS rate assessed by IRC was 85.5% for zanubrutinib arm vs 69.5% for BR arm (HR=0.42, P<0.0001). AEs of interest of any grade included anemia (zanubrutinib arm vs. BR arm: 4.6% vs. 19.4%), arthralgia (13.3% vs. 8.8%), atrial fibrillation (3.3% vs. 2.6%), bleeding (45.0% vs. 11.0%), diarrhea (13.8% vs. 13.7%), hypertension (14.2% vs. 10.6%), infections (62.1% vs. 55.9%), myalgia (3.8% vs. 1.3%), neutropenia (15.8% vs. 56.8%), other cancers (12.9% vs. 8.8%), and thrombocytopenia (4.6% vs. 17.6%).

Figure 34: Summary of SEQUOIA Cohort 1 interim analysis

SEQUOIA Cohort 1 Summary	BRUKINSA (n=241)	Bendamustine + Rituximab (n=238)
Efficacy Results		
IRC-Assessed 24-month PFS (Primary Endpoint)	85.5% (95% CI: 80.1, 89.6)	69.5% (95% CI: 62.4, 75.5)
	Hazard Ratio=0.42 (95%CI: 0.27, 0.63)	
	2-sided *p* <0.0001	
Overall Safety Results		
AEs of any grade	93.3%	96.0%
Grade ≥3 AEs	52.5%	79.7%
Serious AEs	36.7%	49.8%
AEs leading to dose reduction	7.5%	37.4%
AEs leading to dose interruption or delay	46.3%	67.8%
AEs leading to treatment discontinuation	8.3%	13.7%
Fatal AEs	4.6%	4.8%

Adverse Events of Interest (Any Grade)		
Anemia	4.6%	19.4%
Neutropenia	15.8%	56.8%
Thrombocytopenia	4.6%	17.6%
Arthralgia	13.3%	8.8%
Atrial fibrillation	3.3%	2.6%
Bleeding	45.0%	11.0%
Diarrhea	13.8%	13.7%
Hypertension	14.2%	10.6%
Infections	62.1%	55.9%
Myalgia	3.8%	1.3%
Other cancers	12.9%	8.8%

Source: Company data, CMBIGM

The health-related quality of life (HRQoL) outcomes from the interim analysis of the SEQUOIA Cohort 1 also demonstrated improvements with zanubrutinib vs BR in global health status, physical functioning, role functioning as well as greater reductions in diarrhea, fatigue, and nausea/vomiting, according to the patient-reported outcome (PRO) analysis reported at the EHA 2022 Meeting (link) .

The non-randomized Cohort 2 (Arm C) of SEQUOIA trial included treatment-naïve CLL/SLL patients with del(17p), representing high-risk patients treated with zanubrutinib monotherapy. As presented at the ASH Meeting in Dec 2020 (link), at the data cutoff on 10 Aug 2020, all 109 patients enrolled were evaluable for efficacy. With a median follow-up time of 21.9 months, the investigator-assessed ORR was 94.5%, including 5.5% CR, 0.9% CR with incomplete bone marrow recovery, 0.9% nodular PR, 86.2% PRs, and 0.9% PR with lymphocytosis. The 18-month PFS rate was 90.6% as assessed by investigator. The efficacy results with an extended follow-up of 30.5 months were reported at ASH in Dec 2021, indicating a 24-month PFS rate of 88.9% (link).

The non-randomized Cohort 3 of SEQUOIA (enrollment ongoing) was designed to examine the hypothesis that the addition of venetoclax to zanubrutinib can drive tumors into deeper remission, in patients with del(17p) and/or pathogenic TP53 mutation variant. The results were presented at ASH Meeting in Dec 2021 (link1, link2). At the data cutoff on 7 Sep 2021, 49 patients were enrolled. Preliminary results showed that among the 14 patients who received the combination treatment for more than 12 months, five patients (36%) achieved a confirmed CR or CR with incomplete bone marrow recovery (CRi) and four additional patients met the criteria for CR or CRi but not confirmed in bone marrow assessment due to COVID-19 restrictions. In all 36 patients evaluable for efficacy, the ORR was 97.2% and the CR/CRi rate was 13.9% (all CRs or CRis were in patients who received combination treatment for more than 12 months).

Strong sales ramp up driven by BeiGene's solid global commercial capability

Favorable competitive landscape of BTKi market

To date, six BTK inhibitors have been approved across the globe. In China, three BTK inhibitors are available, including ibrutinib, zanubrutinib, and orelabrutinib. In the US and EU, ibrutinib, acalabrutinib, and zanubrutinib are marketed. Zanubrutinib is one of the only two BTK inhibitors in the world both approved in China, US and EU, which are the largest pharmaceutical markets in the world.

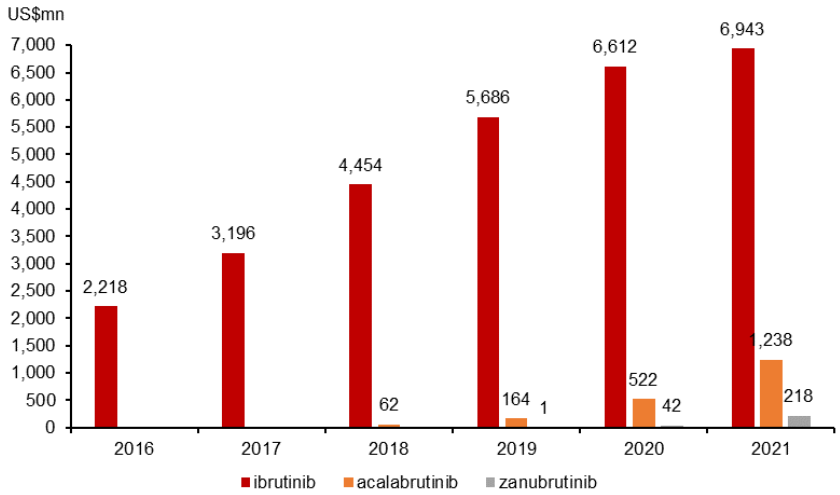
Figure 35: Major approved BTK inhibitors

Drug	Company	Initial approval time			Approved indications		
		China	US	EU	China	US	EU
Ibrutinib	J&J; AbbVie	2017/8	2013/11	2014/10	CLL/SLL (1L), CLL/SLL (2L), MCL (2L), WM (1L), WM (2L)	MCL (2L), CLL/SLL (1L), CLL (2L), WM (1L), MZL (2L), cGVHD(2L)	CLL (1L), CLL (2L), WM (1L), MCL (2L)
Acalabrutinib	AstraZeneca ; Astellas	NA	2017/10	2020/11	NA	MCL (2L), CLL/SLL (1L)	CLL (1L), CLL (2L)
Zanubrutinib	BeiGene	2020/6	2019/11	2021/11	CLL/SLL (2L), MCL (2L), WM (2L)	MCL (2L), WM (1L), MZL (2L)	WM (2L)
Orelabrutinib	InnoCare; Biogen	2020/12	NA	NA	MCL (2L), CLL/SLL (2L)	NA	NA

Source: PharmCube, CMBIGM

The global BTK market is dominated by ibrutinib in terms of revenue, because of its first mover advantage. Due to the superior efficacy and favorable safety profile of zanubrutinib as a next-generation of BTK inhibitor, we expect zanubrutinib to continue to gain market shares from ibrutinib in the global market.

Figure 36: Sales of major BTK inhibitors (2016-2021)



Source: Company data, CMBIGM. Notes: Ibrutinib's revenue refers to the sum of J&J's sales revenue outside of the US and AbbVie's sales revenue in the US.

According to Frost & Sullivan (F&S), the global BTK inhibitor market reached US$7.2bn in 2020 and the market is expected to grow at a 22.7% CAGR from 2020 to 2025. In the US, the BTK inhibitor market reached US$4.8bn in 2020 according to F&S, and is expected to grow at a 20.3% CAGR to US$12.1bn by 2025. In China, the BTK inhibitor market reached RMB1.3bn in 2020, and may expand at a 58.6% CAGR to RMB13.1bn by 2025.

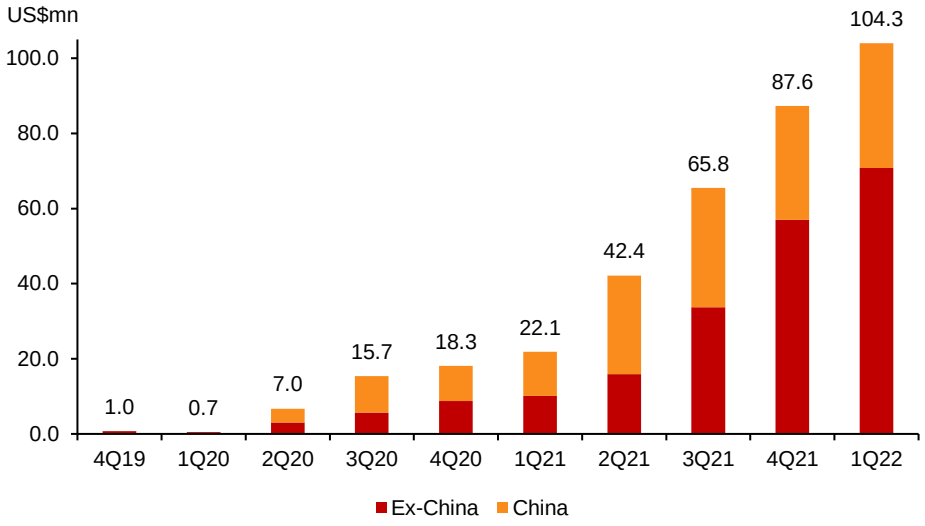
Strong growth momentum of zanubrutinib to continue

BRUKINSA (zanubrutinib) has received approvals in 50 countries, including the US, China, EU, UK, Canada, Australia, etc. Zanubrutinib is recommended by both NCCN and CSCO guidelines, which serves as a strong foundation for the drug's global commercialization. Leveraging its strong commercial team of 3,400+ employees globally, BeiGene realized strong sales growth for zanubrutinib. Zanubrutinib generated US$218.0mn revenue in 2021 (+423% YoY), with US$115.7mn revenue from the ex-China and US$101.2mn from China. In 1Q22, the global sales of zanubrutinib totaled US$104.3mn, representing a 372% YoY growth. In 1Q22, zanubrutinib sales in the US was US$67.9mn, +570% YoY, driven by expanded uptake across all approved indications - MCL, WM and MZL. Zanubrutinib sales in China

totaled US$33.5mn in 1Q22 (+180% YoY), driven by significant sales increase in all approved indications, including CLL.

Additionally, as of Jun 2022, zanubrutinib has more than 40 global filings under review for various indications, especially the BLAs for CLL/SLL accepted by the US FDA (PDUFA date in Jan 2023) and the EMA. With continuous label expansion in global markets, we expect sales of zanubrutinib to ramp up fast in coming years.

Figure 37: Quarterly sales of zanubrutinib (4Q19-1Q22)



Source: Company data, CMBIGM

In China, zanubrutinib is covered by the NDRL for all the NMPA approved indications, namely 2L CLL/SLL, 2L MCL, and 2L WM. The reimbursement for 2L CLL/SLL and 2L MCL was included in NDRL since Mar 2021. The newly approved 2L WM indication was added to the updated NDRL list since Jan 2022 with a mild price cut of 14.1% during the negotiation.

Currently, three BTK inhibitors are marketed in China, including ibrutinib by J&J/ AbbVie, zanubrutinib by BeiGene, and orelabrutinib by InnoCare. Zanubrutinib is priced more affordably than competitors in China, which is 5% cheaper than orelabrutinib (daily cost of RMB340 vs RMB356), 33% cheaper than ibrutinib for CLL/SLL and WM indications (daily cost of RMB340 vs RMB507), and 50% cheaper than ibrutinib for MCL indication (daily cost of RMB340 vs RMB676). We believe the favorable pricing, better product quality and wide NRDL coverage will help to secure a sizable market share for zanubrutinib in China's BTKi market. Similarly, zanubrutinib is priced more affordably than competitors in the US (4% cheaper vs acalabrutinib, 10% cheaper vs ibrutinib).

Figure 38: NRDL coverage of BTK inhibitors in China

Drug	NRDL reimbursed indications	Retail price	Dose	Daily treatment cost	NRDL pricing effective period
Ibrutinib	CLL/SLL (1L), CLL/SLL (2L), MCL (2L), WM (1L), WM (2L)	RMB169/140mg	560mg/day (MCL); 420mg/day (CLL/SLL, WM)	RMB676 (MCL); RMB507 (CLL/SLL, WM)	2021.03.01-2022.12.31
Zanubrutinib	CLL/SLL (2L), MCL (2L), WM (2L)	RMB85/80mg	320mg/day	RMB340	2022.01.01-2023.12.31
Orelabrutinib	MCL (2L), CLL/SLL (2L)	RMB118.68/50 mg	150mg/day	RMB356	2022.01.01-2023.12.31

Source: Company data, CMBIGM

Irreversible BTKi may continue to dominate the first-line market

A number of irreversible BTK inhibitors, ibrutinib, acalabrutinib, zanubrutinib and orelabrutinib have been developed for the treatment of B-cell malignancies. Even though next-generation BTK inhibitors like zanubrutinib outperform ibrutinib with fewer off-target effects, all of these agents interact with the target via covalent bonding, a feature which, while affording impressive efficacy, has also been associated with drug resistance.

One strategy currently being investigated to address this issue is the non-covalent binding BTK inhibitors. Non-covalent BTK inhibitors may be able to overcome drug resistance of irreversible BTK inhibitors, due to a lack of dependence on binding to C481 mutations which are a major mechanism for acquired resistance. Several reversible, non-covalent BTK inhibitors, such as pirtobrutinib, fenebrutinib, and rilzabrutinib, are under development for B-cell malignancies.

Figure 39: Reversible BTK inhibitors under clinical development

Drug	Company	Latest development phase	MoA	Target indications
Fenebrutinib	Roche	PhIII	BTK C481S inhibitor	MS, SLE, CLL, NHL, RA
Pirtobrutinib	Redx Pharma, Eli Lilly	PhIII	BTK C481S inhibitor	DLBCL, CLL, SLL, MZL, WM, MCL
Rilzabrutinib	Sanofi	PhIII	BTK inhibitor	IgG4-RD, pemphigus, CSU, immune thrombocytopenia, WAIHA, atopic dermatitis, asthma
BMS-986142	BMS	PhII	BTK inhibitor	RA
PRN473	Sanofi	PhII	BTK inhibitor	pemphigus, atopic dermatitis
Nemtabrutinib	Merck	PhII	BTK C481S inhibitor	CLL, Richter's syndrome, FL
Vecabrutinib	Biogen, Viracta	PhI/II	BTK C481S inhibitor, ITK inhibitor	WM, MCL, GVHD, FL, SLL, MZL, CLL, DLBCL

Source: PharmCube, CMBIGM

Noncovalent BTK inhibitors has the potential to treat patients who are resistant to covalent BTK inhibitors. Nevertheless, the application of noncovalent BTK inhibitors to BTKi-naïve patients remain to be investigated, because of the possible acquired new mutations that may lead to resistant to other covalent BTK inhibitors. We expect noncovalent and covalent BTK inhibitors will complement each other, while covalent (irreversible) BTK inhibitors will continue to dominate the first-line market thanks to their lower drug resistance risks and potent efficacy.

Reversible BTKi could be a good treatment option for irreversible BTKi resistance

Pirtobrutinib (LOXO-305) is a late-clinical stage non-covalent BTK inhibitor developed by Eli Lily and LOXO Oncology, and is designed to reversibly bind BTK with the potential to preserve activity in the presence of the C481 acquired resistance mutations. Pirtobrutinib is currently being studied in multiple clinical trials, including two Ph3 head-to-head studies in 1L CLL/SLL (BRUIN CLL-314) and r/r MCL (BRUIN MCL-321), respectively. In Mar 2022, Innovent Biologics obtained from Eli Lily a right of first negotiation for potential future commercialization of pirtobrutinib in Mainland China.

Figure 40: Pirtobrutinib's late-stage clinical trials (as of May 2022)

Indications	Regimen	Control	Trial ID	Stage
CLL/SLL	pirtobrutinib	ibrutinib	BRUIN CLL-314	PhIII
r/r MCL (BTK naïve patients)	pirtobrutinib	ibrutinib, acalabrutinib, or zanubrutinib	BRUIN MCL-321	PhIII
1L CLL/SLL	pirtobrutinib	bendamustine plus rituximab (BR)	BRUIN CLL-313	PhIII
r/r CLL/SLL	pirtobrutinib plus venetoclax and rituximab (PVR)	venetoclax and rituximab (VR)	BRUIN **CLL**-322	PhIII
r/r CLL/SLL (BTK treated patients)	pirtobrutinib	idelalisib plus rituximab or bendamustine plus rituximab	BRUIN **CLL**-321	PhIII
Previously treated CLL/ SLL or NHL	pirtobrutinib mono or combo with venetoclax and rituximab (VR)	-	BRUIN	PhII
Lymphoma and chronic leukemia (Chinese patients)	pirtobrutinib	-	NCT04849416	PhII

Source: Eli Lilly, CMBIGM. Notes: Rolling BLA submission to the FDA for r/r MCL initiated in Oct 2021.

Clinical studies showed that pirtobrutinib demonstrated promising efficacy in patients with CLL/SLL regardless of prior therapy, number of prior lines of therapy, or BTK C481 mutation status. At the ASH meeting in Dec 2021, LOXO Oncology announces updated data from the Ph1/2 BRUIN trial (link). As of 16 Jul 2021, 618 patients were enrolled in the study, including 296 with CLL/SLL, 134 with MCL, and 188 with other B-cell malignancies. The study showed that pirtobrutinib demonstrated promising efficacy and safety in patients with CLL/SLL previously treated with BTK inhibitors. The efficacy was independent of BTK C481 mutation status, the reason for prior BTKi discontinuation (progression versus intolerance), or other classes of prior therapy received (including covalent BTK inhibitors, BCL2 inhibitors, and PI3K-delta inhibitors).

(1) **CLL/SLL cohort** (link): among the 296 CLL/SLL patients enrolled, 261 were previously treated with a BTK inhibitor and are the subject of this analysis. The median number of prior lines of therapy was three with 100% receiving a prior BTK inhibitor. The ORR was 68% among the 252 efficacy-evaluable patients with 2 CR (1%), 137 PR (54%), 32 PR with lymphocytosis (13%), and 62 with SD (25%). Responses continue to deepen over time, with the ORR rising to 73% for those followed 12 months or more, and ORR remains consistent regardless of reason for prior BTK discontinuation, type or number of prior therapies or BTK C481 or PCLG2 mutational status. In patients who received prior BTKi and BCL2 inhibitor therapy, median PFS was 18 months. PFS was similar in patients with CLL/SLL with BTK C481 mutations and wild-type who progressed on a prior BTK inhibitor.

(2) **MCL cohort** (link): pirtobrutinib demonstrated promising efficacy as well in MCL patients previously treated with BTK inhibitors. The 134 patients with MCL received a median of three prior lines of therapy, with 90% receiving a prior BTK inhibitor. Of the 100 efficacy-evaluable patients with BTK pre-treated MCL, 51 responded including 25 CRs and 26 PRs resulting in an ORR of 51%. Among 11 BTK naïve MCL patients, 9 responded including 2 CRs and 7 PRs resulting in an ORR of 82%. Median follow-up for all responding MCL patients was 8.2 months with 60% (36/60) of responses ongoing as of the data cut-off.

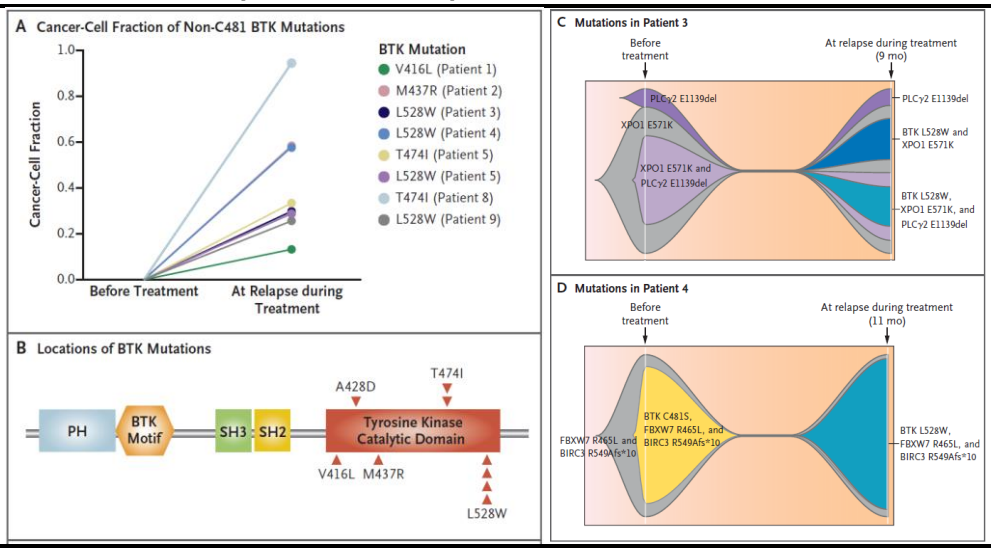
Reversible BTKi has complicated mechanisms of resistance which may prevent the drug from substituting covalent BTKi in first line treatment

An research article published at NEJM in Feb 2022 revealed the mechanisms of resistance to noncovalent BTK Inhibitors (link). The researchers performed genomic analyses of pretreatment specimens as well as specimens obtained at the time of disease progression from patients with CLL who had been treated with the noncovalent BTK inhibitor pirtobrutinib. Structural modeling, BTK-binding assays, and cell-based assays were conducted to study mutations that confer resistance to noncovalent BTK inhibitors.

Among 55 treated patients, the researchers identified 9 patients with r/r CLL and acquired mechanisms of genetic resistance to pirtobrutinib. The researchers found mutations (V416L, A428D, M437R, T474I, and L528W) that were clustered in the kinase domain of BTK and that conferred resistance to both noncovalent BTK inhibitors and certain covalent BTK inhibitors. Mutations in BTK or phospholipase C gamma 2 (PLCγ2), a signaling molecule and downstream substrate of BTK, were found in all 9 patients.

Transcriptional activation reflecting B-cell–receptor signaling persisted despite continued therapy with noncovalent BTK inhibitors.

Figure 41: Mutations in CLL patients with acquired resistance to noncovalent BTK Inhibitors



Source: NEJM, CMBIGM. Notes: 1) Panel A shows non-C481 BTK mutations found at the time of relapse during treatment, as revealed by serial targeted gene sequencing of specimens from patients with CLL treated with the noncovalent BTK inhibitor pirtobrutinib. The timing of specimen collection is shown on the x axis, and the cancer-cell fraction of the non-C481 BTK mutations is shown on the y axis. 2) Panel B shows BTK mutations outside the BTK C481 residue found in patients with resistance to pirtobrutinib. Each individual occurrence of a mutation is depicted as an arrowhead. PH denotes pleckstrin homology domain, and SH Src homology domain. 3) Panels C and D are fishplot representations of single-cell mutational data from Patient 3 (Panel C) and Patient 4 (Panel D) before pirtobrutinib therapy and at relapse during treatment. Patient 3 had a phospholipase C gamma 2 (PLCγ2) mutation before pirtobrutinib therapy and was found to have acquired BTK L528W mutations at relapse after 9 months of treatment. Patient 4 had the BTK C481S mutation before pirtobrutinib therapy, and it was suppressed during treatment; this patient was found to have acquired BTK L528W at relapse after 11 months of treatment. Mutations in XPO1 (exportin 1), FBXW7 (F-box and WD repeat–containing protein 7), and BIRC3 (baculoviral IAP repeat–containing protein 3) were also found.

Thus, we think the complicated mechanisms of resistance of reversible BTKi may limit its use in first line treatment. However, we believe reversible BTKi could become an important therapy for irreversible BTKi resistance. Meanwhile, we think new modalities such as BTK-targeted CDAC BGB-16673, also has potential to become a new treatment option for irreversible BTKi resistance.

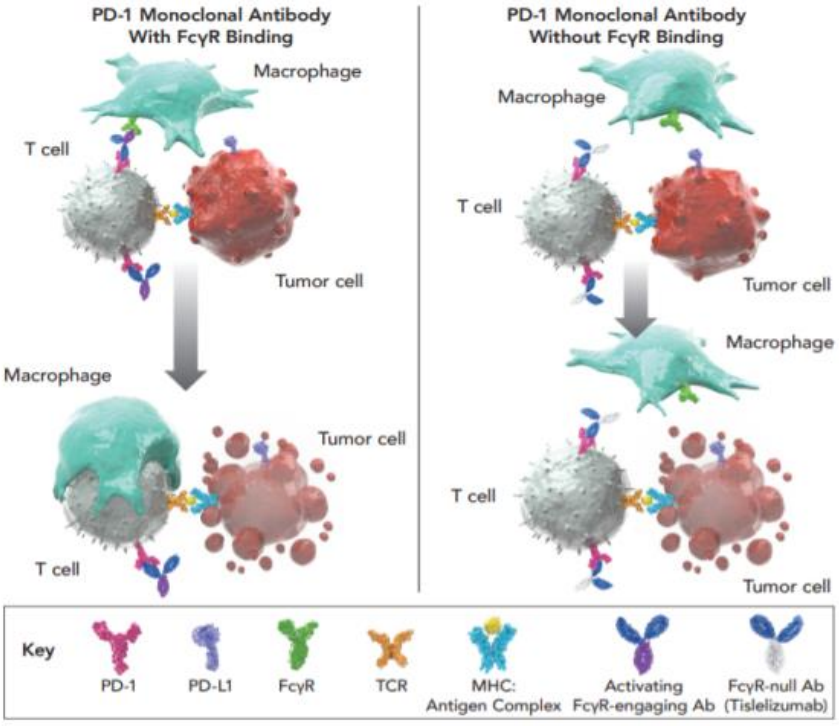
Tislelizumab: globally developed PD-1 inhibitor with broad labels

Differentiated molecule with broad labels

Differentiated MoA to minimize FcγR binding

Tislelizumab is a humanized IgG4 anti-PD-1 mAb with a differentiated mechanism compared to the currently approved PD-1 antibodies – it is designed to minimize binding to Fc receptor gamma ("FcγR") on macrophages to minimize its negative impact on T effector cells. In pre-clinical studies, binding to FcγR on macrophages has been shown to compromise the anti-tumor activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T effector cells.

Figure 42: Lack of FcγR binding helps prevent macrophage-mediated T-cell clearance



Source: Company data, CMBIGM

Broad indications approved / under review in China

To date, tislelizumab has nine indications approved in China. To be specific, tislelizumab's approved indications by the NMPA include 1) 1L sq-NSCLC in combo with chemotherapy, 2) 1L non-squamous NSCLC in combo with chemotherapy, 3) 2/3L NSCLC, 4) 2L ESCC, 5) 2L cHL, 6) 2L PD-L1+ UC, 7) 2L HCC, 8) 2L/3L MSI-H/dMMR solid tumors, and 9) 1L NPC. In addition, the global Ph3 trial for 1L ESCC has met the primary endpoint of OS at the interim analysis in Apr 2022.

Tislelizumab has nine NPMA-approved indications, covering the most common cancers in China including lung, liver, gastric, and esophageal cancers. Driven by the broad labels and wide NRDL coverage, tislelizumab has been gaining market share in China's PD-1 market and became the top 3 player as of 1Q22.

From Jan 2022, tislelizumab has three large indications added into the NRDL, including 1L sq-NSCLC, 1L nsq-NSCLC and 2L HCC. The latest retail price of tislelizuamb is RMB1,450/100mg, indicating an annual treatment cost of approximately RMB50,267.

Figure 43: Tislelizumab's approved indications in China

Indication	Regimen	Approval status	Approval/ BLA date	Clinical trial ID	Time of initial NRDL inclusion	NRDL valid period
2L cHL	Mono	Approved	2019-12-27	NCT03209973	2021-03	2022.01.01-2023.12.31
2L UC	Mono	Approved	2020-04-10	NCT04004221	2021-03	2022.01.01-2023.12.31
1L sq-NSCLC	+Chemo	Approved	2021-01-13	NCT03594747	2022-01	2022.01.01-2023.12.31
1L nsq-NSCLC (EGFR- / ALK-)	+Chemo	Approved	2021-06-23	NCT03663205	2022-01	2022.01.01-2023.12.31
2L HCC	Mono	Approved	2021-06-23	NCT03419897	2022-01	2022.01.01-2023.12.31
2L NSCLC	Mono	Approved	2022-01-05	NCT03358875	N	-
2L/3LMSI-H/dMMR solid tumor	Mono	Approved	2022-03-11	NCT03736889	N	-
2L ESCC	Mono	Approved	2022-04-13	NCT03430843	N	-
1L NPC	+Chemo	Approved	2022-06-10	NCT03924986	N	-

Source: Company data, CMBIGM

BeiGene is also evaluating tislelizumab in combination with other innovative drugs. For instance, tislelizumab is under evaluation in combo with ociperlimab (anti-TIGIT), pamiparib (anti-PARP), zanubrutinib (anti-BTK), sitravatinib, zanidatamab and other molecules for treatment of multiple cancers.

Figure 44: Summary of key clinical trials of tislelizumab

PROGRAMS	DOSE ESC.	DOSE EXPANSION		PIVOTAL		FILED	MARKETED
	Phase 1a	Phase 1b	Phase 2*	Phase 2**	Phase 3		
monotherapy	*R/R cHL (conditionally approved 12/26/2019), 2L + UC (conditionally approved 4/10/2020), 2L/3L HCC (conditionally approved 6/23/2021), 2L/3L NSCLC (approved 1/6/2022), 2L/3L MSI-H or dMMR solid tumors (conditionally approved 3/11/2022); 2L/3L NSCLC also under review by EU EMA since Apr 2022*						
	2L ESCC (approved 4/13/2022)						
	2L ESCC (filing accepted by the US FDA and EU EMA)						
	1L HCC						
	R/R NK/T-cell lymphoma						
+ chemo	*1L Sq. NSCLC (approved 1/13/2021), 1L non-Sq. NSCLC (approved 6/23/2021); The two indications also under review by EU EMA since Apr 2022*						
	1L NPC (approved 6/10/2022)						
	1L SCLC, Stage II/IIIA NSCLC, Localized ESCC, 1L UC						
	1L GC, 1L ESCC						
+ pamiparib (PARP)	*Solid tumors*						
+ zanubrutinib (BTK)	*B-cell malignancies*						

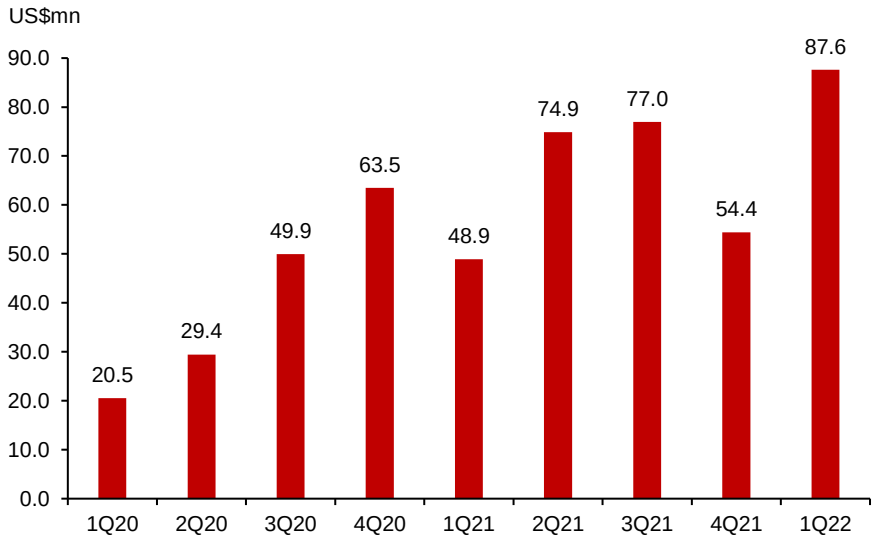
China Global

Source: Company data, CMBIGM

Becoming a top 3 PD-(L)1 player in China thanks to wide NRDL coverage and strong commercial capability

Leveraging a sizable commercial team of 3,100+ people in China, BeiGene has achieved a strong revenue growth for tislelizumab since the drug's initial approval in Dec 2019. In 2021, the sales of tislelizumab was US$255.1mn (c. RMB1.63bn), which represented a 56% YoY increase. In 2021, sales of tislelizumab was impacted by the negative adjustments totaling US$45.6mn for distributor channel inventory compensation as a result of price cuts of tislelizumab for additional indications include by the NRDL effective in the Mar 2021 and Jan 2022, respectively. In 1Q22, tislelizumab's sales further accelerated to 79% YoY growth to US$87.6mn (c. RMB560mn), which was mainly driven by strong new patient demand from broader NRDL reimbursement in approved indications. We estimate that tislelizumab has ranked top 3 in China's PD-(L)1 market in terms of revenue as of 1Q22.

Figure 45: Quarterly sales of tislelizumab (1Q20-1Q22)



Source: Company data, CMBIGM

Competition of PD-(L)1 market in China is very fierce. We estimate 2022 China PD-(L)1 market (net revenue) will amount to approximately US$2.4 bn.

As of May 2022, there are 13 PD-(L)1 antibodies approved in China, including four foreign brands and nine domestic brands. BeiGene's tislelizumab has obtained the largest number of approved indications (9 indications) in China, followed by MSD's pembrolizumab (Keytruda) and Hengrui's camrelizumab (8 indications for each of the drugs), and BMS's nivolumab (5 indications).

Figure 46: Approved PD-(L)1 antibodies in China (as of Jun 2022)

Company	Drug	Target	Indications	Regimen	Status	Approval Date	NRDL in China	NRDL Period
BMS	Nivolumab	PD-1	2L NSCLC (EGFR- / ALK-)	Mono	Approved	2018-06-15	N	
			2L PD-L1+ HNSCC	Mono	Approved	2019-09-30	N	
			2L GC	Mono	Approved	2020-03-13	N	
			1L Pleural Mesothelioma	+Yervoy	Approved	2021-06-10	N	
			1L GC	+Chemo/Yervoy	Approved	2021-08-30	N	
Merck	Pembrolizumab	PD-1	2L Melanoma	Mono	Approved	2018-07-26	N	
			1L nsq-NSCLC	+Chemo	Approved	2019-04-02	N	
			1L sq-NSCLC	+Chemo	Approved	2019-11-26	N	
			1L PD-L1+ NSCLC	Mono	Approved	2019-09-30	N	
			2L PD-L1+ ESCC	Mono	Approved	2020-06-19	N	
			1L PD-L1+ HNSCC	Mono	Approved	2020-12-11	N	
			1L CRC	Mono	Approved	2021-06-15	N	
			1L GC	+Chemo	Approved	2021-09-07	N	
AstraZeneca	Durvalumab	PD-L1	1L maintenance stage III NSCLC	Mono	Approved	2019-12-06	N	
			1L ES-SCLC	+Chemo	Approved	2021-07-19	N	
Roche	Atezolizumab	PD-L1	1L SCLC	+Chemo	Approved	2020-02-13	N	
			1L HCC	+Avastin	Approved	2020-10-29	N	
			1L NSCLC	Mono	Approved	2021-04-29	N	
			1L NSCLC	+Chemo	Approved	2021-06-23	N	
			Adj. Stage II/IIIA NSCLC	Moni	Approved	2022-03-16	N	
Junshi	Toripalimab	PD-1	2L Melanoma	Mono	Approved	2018-12-21	Y	2022.01.01-2023.12.31
			2L NPC	Mono	Approved	2021-02-19	Y	2022.01.01-2023.12.31
			2L UC	Mono	Approved	2021-04-12	Y	2022.01.01-2023.12.31
			1L NPC	+Chemo	Approved	2021-11-29	N	
			1L ESCC	+Chemo	Approved	2022-05-12	N	
Innovent	Sintilimab	PD-1	2L cHL	Mono	Approved	2018-12-24	Y	2022.01.01-2023.12.31
			1L nsq-NSCLC (EGFR- / ALK-)	+Chemo	Approved	2021-02-03	Y	2022.01.01-2023.12.31
			1L sq-NSCLC	+Chemo	Approved	2021-06-03	Y	2022.01.01-2023.12.31
			1L HCC	+Avastin	Approved	2021-06-27	Y	2022.01.01-2023.12.31
Hengrui	Camrelizumab	PD-1	2L cHL	Mono	Approved	2019-06-03	Y	2021.03.01-2022.12.31
			2L HCC	Mono	Approved	2020-03-04	Y	2021.03.01-2022.12.31
			1L nsq-NSCLC (EGFR- / ALK-)	+Chemo	Approved	2020-06-19	Y	2021.03.01-2022.12.31
			2L ESCC	Mono	Approved	2020-06-19	Y	2021.03.01-2022.12.31
			2L NPC	Mono	Approved	2021-04-29	N	
			1L NPC	+Chemo	Approved	2021-06-10	N	
			1L Esophageal Cancer	+Chemo	Approved	2021-12-10	N	
			1L sq-NSCLC	+Chemo	Approved	2021-12-10	N	
BeiGene	Tislelizumab	PD-1	2L cHL	Mono	Approved	2019-12-27	Y	2022.01.01-2023.12.31
			2L UC	Mono	Approved	2020-04-10	Y	2022.01.01-2023.12.31
			1L sq-NSCLC	+Chemo	Approved	2021-01-13	Y	2022.01.01-2023.12.31
			1L nsq-NSCLC (EGFR- / ALK-)	+Chemo	Approved	2021-06-23	Y	2022.01.01-2023.12.31
			2L HCC	Mono	Approved	2021-06-23	Y	2022.01.01-2023.12.31
			2L NSCLC	Mono	Approved	2022-01-05	N	
			2L/3L MSI-H/dMMR solid tumors	Mono	Approved	2022-03-11	N	
			2L ESCC	Mono	Approved	2022-04-13	N	
			1L NPC	+Chemo	Approved	2022-06-07	N	
Gloria Pharma /WuXi Bio	Zimberelimab	PD-1	2L cHL	Mono	Approved	2021-08-30	N	
Akeso / CTTQ	Penpulimab	PD-1	2L cHL	Mono	Approved	2021-08-05	N	
Alphamab/3D Med	Envafolimab	PD-L1	2L MSI-H/dMMR CC and other tumors	Mono	Approved	2021-11-25	N	
CStone	Sugemalimab	PD-L1	1L NSCLC	+Chemo	Approved	2021-12-21	N	
			Adj. Stage III NSCLC	Mono	Approved	2022-05-31	N	
Henlius	Opucolimab	PD-1	MSI-H/dMMR solid tumors	Mono	Approved	2022-03-25	N	

Source: Company data, CMBIGM

To date, none of the four foreign brands approved in China has been covered by the NRDL, while four domestic PD-1 antibodies are included in the list, namely tislelizumab, toripalimab (Junshi), sintilimab (Innovent), and camrelizumab (Hengrui).

PD-(L)1 drugs have experienced significant price cuts in past years during NRDL price negotiations. BeiGene's tislelizumab was initially priced at RMB10,688/100mg with aggressive PAP discounts when it was launched in China in early 2020. The price was cut to RMB2,180/100mg in Mar 2021 for the inclusion of tislelizumab for treatment of 2L CHL and 2L UC indications into the NRDL. In Jan 2022, the price further went down to RMB1,450/100mg with additional NRDL inclusion of 1L sq-NSCLC, 1L nsq-NSCLC and 2L HCC indications for tislelizumab. We think the further downside in tislelizumab's price will be limited given large indications such as NSCLC and HCC have already been added into the NRDL after significant price cuts.

Thanks to the wide NRDL coverage of large indications such as NSCLC, HCC and UC, tislelizumab is more affordable than other competing products, which also leads to the fast increasing penetration of

tislelizumab in China. Thus, we believe tislelizumab will continue to gain market share and to maintain its leading position in China's PD-(L)1 market.

Figure 47: Comparison of treatment cost of major PD-(L)1 drugs in China (as of May 2022)

Drug	NRDL valid period	NRDL reimbursed indications	Dose	Latest annual treatment cost (RMB, PAP Adj)	Annual treatment cost in 2021 (RMB, PAP Adj)	Price cut (%)
Nivolumab	N/A	None	Q2W	110,544	110,544	0%
Pembrolizumab	N/A	None	Q3W	143,344	143,344	0%
Durvalumab	N/A	None	Q2W	144,924	144,924	0%
Atezolizumab	N/A	None	Q3W	131,200	131,200	0%
Toripalimab	2022.01.01-2023.12.31	2L Melanoma, 2L NPC, 2L UC	Q2W	64,350*	70,674*	-9%
Sintilimab	2022.01.01-2023.12.31	2L cHL, 1L nsq-NSCLC (EGFR- / ALK-), 1L sq-NSCLC, 1L HCC	Q3W	37,440	39,802	-6%
Camrelizumab	2021.03.01-2022.12.31	2L cHL, 2L ESCC	Q2W	76,128	76,128	0%
		2L HCC, 1L nsq-NSCLC (EGFR- / ALK-)	Q3W	50,752	50,752	0%
Tislelizumab	2022.01.01-2023.12.31	2L cHL, 2L UC, 1L sq-NSCLC, 1L nsq-NSCLC (EGFR- / ALK-), 2L HCC	Q3W	50,267	75,573	-33%

Source: Company data, CMBIGM; Notes: * Toripalimab treatment cost, estimated based on the price of 80mg/2ml/vial, is only for NRDL reimbursed indications. Treatment cost for non-reimbursed indications is different due to different dose schedule.

BeiGene applies a dual strategy for the manufacturing of tislelizumab. The Company collaborates with Boehringer Ingelheim, one of the leading biologics manufacturers, for manufacturing tislelizumab in Shanghai. Meanwhile, BeiGene has built a manufacturing facility in Guangzhou with a current capability of 24,000L, of which 8,000L has been approved for production of tislelizumab. An additional facility extension is currently in progress to bring the total capacity in Guangzhou from 24,000L to 64,000L, with the construction expected to be completed by the end of 2022. The construction of a biologics manufacturing facility with an initial capacity of 16,000L in New Jersey, the US started in Mar 2022, and is expected to be completed in late-2023 or 2024.

Collaborating with Novartis to explore tislelizumab's global potential

Multiple global MRCTs provide a solid foundation for global regulatory approvals

Tislelizumab is the only Chinese PD-1 drug assessed in many MRCTs, which we believe paves the way for tislelizumab's global regulatory approvals. BeiGene has initiated or completed more than 20+ potentially registration-enabling clinical trials for tislelizumab in 35 countries and regions, including 17 Ph3 trials (incl. 8 global Ph3 trials) and 4 pivotal Ph2 trials (incl. 3 global pivotal Ph2 trials). As of Feb 2022, the global tislelizumab clinical development program has enrolled more than 9,000 subjects (incl. ~3,000 outside of China).

BeiGene has filed a BLA to the US FDA for tislelizumab as a treatment for 2L ESCC, with a PDUFA target action date of 12 Jul 2022. However, we think the regulatory approval for tislelizumab may be delayed because the required on-site inspections have been hindered by travel restrictions related to the COVID-19 pandemic in China. BeiGene also plans to support additional BLA filings by Novartis in 1L NPC and NSCLC in the US in 2022.

In Apr 2022, the European Medicines Agency (EMA) accepted the marketing authorization applications submitted by Novartis for tislelizumab for the treatments of 2L ESCC, 2L NSCLC, 1L sq-NSCLC and 1L nsq-NSCLC (EGFR- / ALK-).

To date, four domestic PD-1 brands are currently under review or have received feedback from the US FDA, namely tislelizumab (2L ESCC), toripalimab (1L/2L NPC), penpulimab (3L NPC), and sintilimab (1L nsq-NSCLC). The FDA rejected the BLA of sintilimab in Mar 2022, and recommended additional study, specifically an MRCT designed to compare the experimental regimen with SoC, with a noninferiority design that includes OS as an endpoint. For the BLAs of toripalimab, FDA issued a CRL in early May 2022 to require quality process change. Junshi and Coherus plan to resubmit the BLA by mid-summer 2022.

Figure 48: Domestic PD-1 antibodies under review by the US FDA

Company	Drug	Indications	Regimen	Approval Status	Clinical Trial ID
BeiGene	Tislelizumab	2L ESCC	Mono	PDUFA date Jul 2022	NCT03430843
Junshi	Toripalimab	1L NPC; 2L NPC	+Chemo (1L); Mono (2L)	To resubmit BLA in mid-summer 2022	NCT03581786 (1L); NCT02915432 (2L)
Akeso / CTTQ	Penpulimab	3L NPC	Mono	BLA filed in Sep 2021	NCT03866967
Innovent	Sintilimab	1L nsq-NSCLC	+Chemo	Rejected	NCT03607539

Source: Company data, PharmCube, CMBIGM

As the US FDA has taken a prudent view on China-only clinical data, tislelizumab enjoys significant advantages in US registration thanks to its widely conducted MRCTs. The BLA of tislelizumab's 2L ESCC was based on clinical results of a MRCT study (NCT03430843) which enrolled 21% of the total patients from North America and Europe.

Figure 49: Comparison of registration trials of 2L ESCC in the US

Drug	FDA status	Regimen	Trial ID	Trial regions	Primary endpoint	Patient number	OS in all pts (vs chemo)	OS in PD-L1+ pts (vs chemo)	Link
KEYTRUDA	Approved for PD-L1+ pts in 2019.07	Mono	NCT02 564263	Multiregion	OS	628	7.1 vs 7.1 mo; HR=0.89 (not meet)	9.3 vs 6.7 mo; HR=0.69	Link
Opdivo	Approved regardless of PD-L1 level in 2020.06	Mono	NCT02 569242	Multiregion	OS	419	10.9 vs 8.4 mo; HR=0.77	-	Link
Tislelizumab	BLA filed in 2021.07	Mono	NCT03 430843	Multiregion	OS	512	8.6 vs 6.3 mo; HR=0.70	10.3 vs 6.8 mo; HR=0.54	Link

Source: Company data, CMBIGM

Novartis to play an important role in tislelizumab's global registration and commercialization

In Jan 2021, BeiGene granted Novartis rights to develop, manufacture, and commercialize tislelizumab in North America, the EU, Japan, and six other European countries (Novartis Territory). BeiGene retained worldwide rights to commercialize outside of the Novartis Territory and with its proprietary products in combination with tislelizumab. We think Novartis will help to smoothly progress the global registration of tislelizumab and to efficiently drive the sales ramp up of tislelizumab if approved in the US and other regions.

Besides tislelizumab, four other domestic PD-(L)1 antibodies also completed out-licensing deals with global partners, while tislelizumab recorded the highest upfront payment of US$650mn and the highest milestone fee of US$1.55bn.

Figure 50: Major domestic PD-(L)1 license-out deals

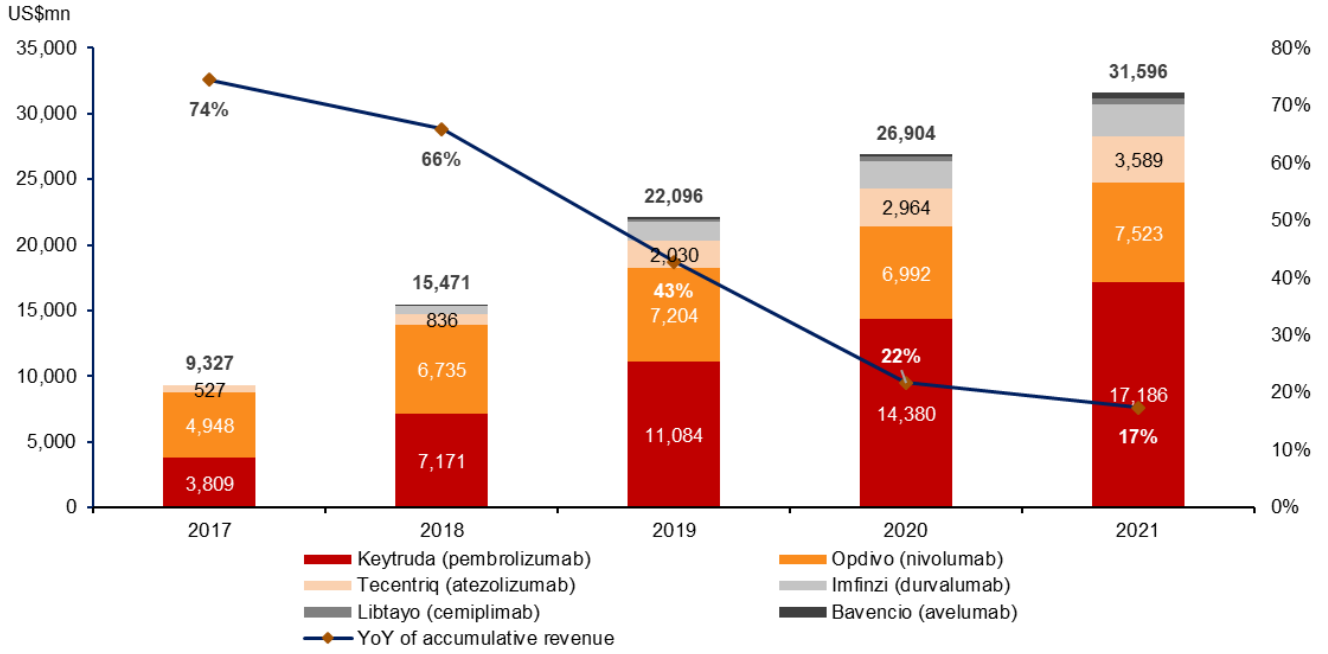
Drug	Company	Partner	License regions	Upfront fee	Milestone fee	Date	Royalty
Toripalimab	Junshi	Coherus BioSciences	US, Canada	US$150mn	US$380mn	2021-02	20%
Tislelizumab	Beigene	Novartis	US, Canada, Mexico, EU, UK, Norway, Switzerland, Iceland, Liechtenstein, Russia, and Japan	US$650mn	US$1,550mn	2021-01	double-digit
Sugemalimab (PD-L1) and CS1003 (PD-1)	CStone	EQRx	ex-Greater China	US$150mn	US$1,150mn	2020-10	separate tiered
Sintilimab	Innovent	Eli Lilly	ex-China	US$200mn	US$825mn	2020-08	double-digit
Camrelizumab	Hengrui	Crystal Genomics	South Korea	US$1.5mn	US$85.75mn	2020-04	10-12%

Source: Companies' data, CMBIGM

As of Mar 2022, seven PD-1 or PD-L1 antibody medicines have been approved by the US FDA, including Merck's KEYTRUDA, BMS's OPDIVO, Roche's TECENTRIQ (atezolizumab), AstraZeneca's IMFINZI (durvalumab), Pfizer and Merck Sereno's BAVENCIO (avelumab), Regeneron and Sanofi's LIBTAYO (cemiplimab), and GSK's JEMPERLI (dostarlimab). In 2021, the above-mentioned PD-(L)1 antibodies had a total revenue of approximately US$31.6bn (+17% YoY). KEYTRUDA generated US$17.2bn revenue in 2021, growing at a CAGR of 33.8% between 2018 and 2021.

We expect the global PD-(L)1 market to be more than US$50bn by 2025E, driven by multiple factors including indication expansion, approvals and adoptions in earlier lines of therapies, further market penetration, and extension of duration of therapy.

Figure 51: Global sales of FDA-approved PD-(L)1 antibodies (2017-2021)



Source: Companies' annual reports, CMBIGM

Ociperlimab: one of the global most advanced anti-TIGIT antibodies

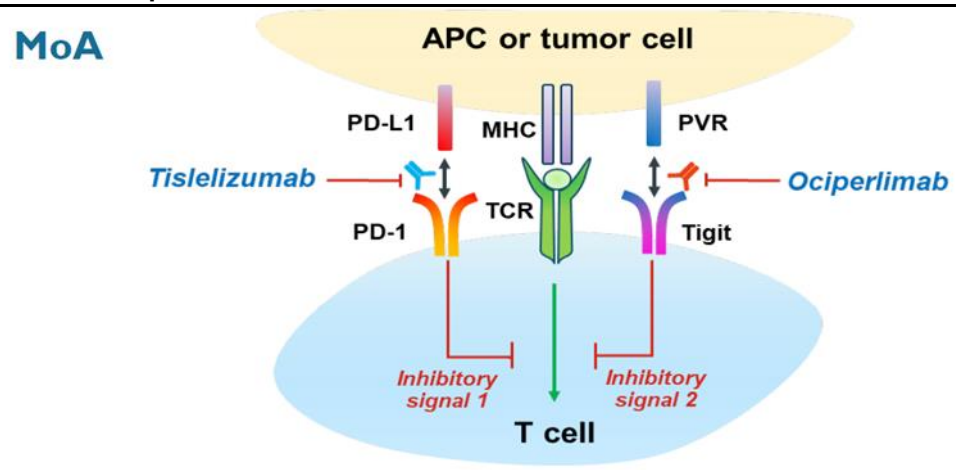
Ociperlimab has differentiated design with intact Fc function

Competent Fc function is critical for the anti-tumor activity of ociperlimab

Ociperlimab is an investigational humanized IgG 1 monoclonal antibody discovered and being developed globally by BeiGene. As one of the most advanced anti-TIGIT antibodies, ociperlimab has intact Fc function which can potentially lead to high potency of the drug.

Ociperlimab is designed to mechanistically synergize with PD-1 and is positioned to be combined with tislelizumab in PD-1 sensitive tumors. The TIGIT pathway cooperates with PD-1 to maximize the suppression of effector tumor infiltrating immune cells as well as to promote resistance to anti-PD-1 therapy. Targeting TIGIT provides a potential mechanism to rescue immune cells (e.g., T cells, NK cells, and dendritic cells) from the immunosuppressive tumor microenvironment to induce an efficient antitumor immune response. Ociperlimab binds to the extracellular domain of TIGIT with high affinity and specificity, and efficiently blocks the interaction between TIGIT and its ligands PVR or PVR-L2. Preclinical studies have demonstrated dual targeting with ociperlimab (TIGIT) and tislelizumab (PD-1) produces synergistic immune cell activation and enhanced antitumor activity.

Figure 52: MoA of ociperlimab



Source: Company data, CMBIGM. Notes: T cells use surface receptor (T cell receptor, TCR) to recognize peptides presented by major histocompatibility complex (MHC) molecules on tumor cell. PVR (poliovirus receptor) is a ligand of TIGIT.

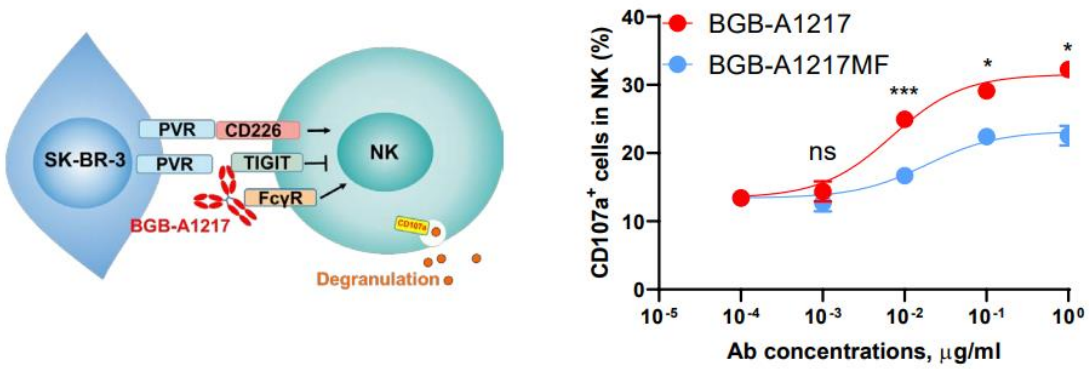
With an effector function competent Fc region, ociperlimab induces antibody dependent cellular cytotoxicity (ADCC) against Treg cells, activates NK cells and monocytes, and removes TIGIT from T cell surfaces in an Fc-dependent manner. In vivo, ociperlimab, either alone or in combination with an anti-PD-1 mAb elicits strong immune responses and potent anti-tumor efficacy in pre-clinical models. Moreover, the Fc effector function is critical for the anti-tumor activity of ociperlimab in a syngeneic human TIGIT-knock-in mouse model (link).

Among the TIGIT antibodies under development, the majority of TIGIT candidates has Fc-competent backbone (tiragolumab, ociperlimab, vibostolimab, EOS-448, etc.), while some TIGIT antibodies have inactivated Fc domain (domvanalimab, BMS-986207, etc.). Although currently it's not clear which modality works better, we believe competent Fc function is important to promote the effector function of CD8+ T and NK cells, and to enhance therapeutic effects of TIGIT combination therapies as proved in a number of preclinical experiments.

It's also worth noting that Agenus is advancing two Fc enhanced anti-TIGIT antibodies, including a TIGIT monospecific (AGEN1327) and a bispecific (AGEN1777). In May 2021, BMS obtained the global exclusive

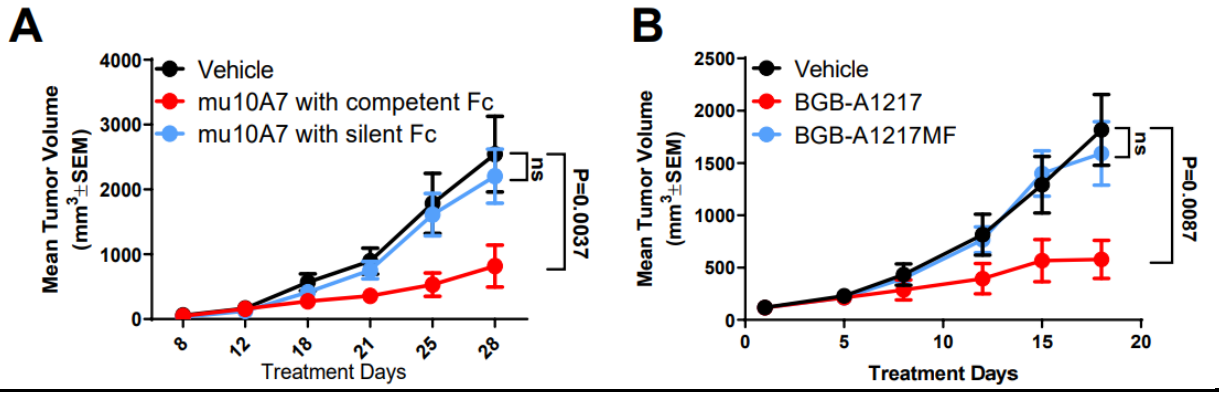
license to AGEN1777 which was at preclinical stage and agreed to pay US$200mn upfront payment and up to US$1.36bn milestones in addition to tiered double-digit sales royalties. This is interesting given BMS already has BMS-986207, an Fc-inactivated TIGIT antibody, at clinical development. Thus, the deal may further indicate the importance of competent Fc function for TIGIT antibodies.

Figure 53: Ociperlimab (BGB-A1217) activates human NK cells *in vitro*



Source: Company data, CMBIGM. Notes: The indicated anti-TIGIT antibodies, BGB-A1217 or BGB-A1217MF (MF: mutant Fc with Fc effector function abolished), were incubated with SK-BR-3 human breast cancer cell line (5x104/well), and NK cells isolated from PBMC of healthy donors (5x104/well). NK cells were pre-stimulated with 25 U/ml IL-2 overnight before the co-culture assay. CD107a expression on NK cells was measured by FACS. Data are shown as mean ± SD. N=2. *p<0.05, ***p<0.001, ns: no significant difference.

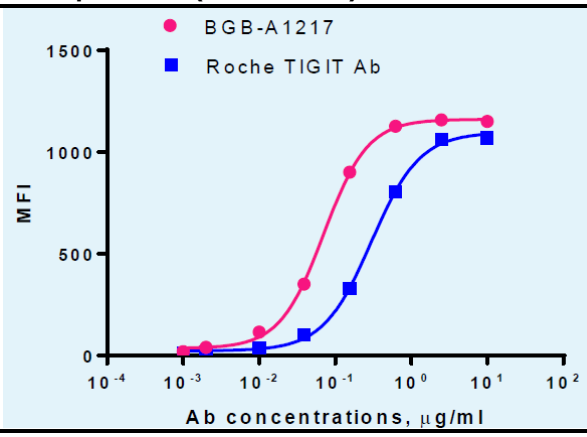
Figure 54: Fc effector function is required for anti-tumor efficacy of TIGIT blockade Ab *in vivo*



Source: Company data, AACR 2021, CMBIGM. Notes: (A) murine TIGIT blockade antibody mu10A7 with indicated Fc was administered to CT26WT tumor-bearing mice (5 mg/kg, QW). N=13. (B) CT26WT tumor-bearing humanized TIGIT knock-in mice were treated with indicated antibodies (10 mg/kg, Q5D), N=10. Data shown as mean ± SEM.

According to BeiGene's preclinical data, ociperlimab's binding affinity to TIGIT is significantly better than that of tiragolumab (IC50=0.037 nM for ociperlimab vs 0.16 nM for tiragolumab).

Figure 55: Ociperlimab (BGB-A1217) binds to human TIGIT with high affinity



	IC50
BGB-A1217	0.037 nM
Roche TIGIT Ab	0.16 nM

Source: Company data, CMBIGM. Notes: Ociperlimab also named BGB-A1217.

Ociperlimab is well-tolerated with observed early efficacy

Ociperlimab is generally well-tolerated in patients with advanced solid tumors, with no additional safety signals when administrated with tislelizumab. Early anti-tumor efficacy was observed in Ph1 study. The results of Ph1 AdvanTIG-105 study (NCT04047862) was presented at 2021 ASCO Meeting (link1, link2). The trial assessed the safety and preliminary antitumor activity of ociperlimab + tislelizumab in advanced solid tumors.

As data cut-off of 21 Feb 2021, 26 patients from Australia were enrolled in this trial and received ociperlimab ranging from 50-900mg dose plus fixed 200mg dose of tislelizumab. Ociperlimab + tislelizumab was well tolerated. The types and severity of adverse events observed were consistent with tislelizumab monotherapy, and no DLTs were observed. At the data cut-off, 25 (96.2%) of the 26 patients had ⩾1 TEAE. Fifteen (57.7%) patients experienced at least one immune-related TEAE. No DLTs were observed and recommended Ph2 dose is ociperlimab 900mg IV + tislelizumab 200mg IV Q3W.

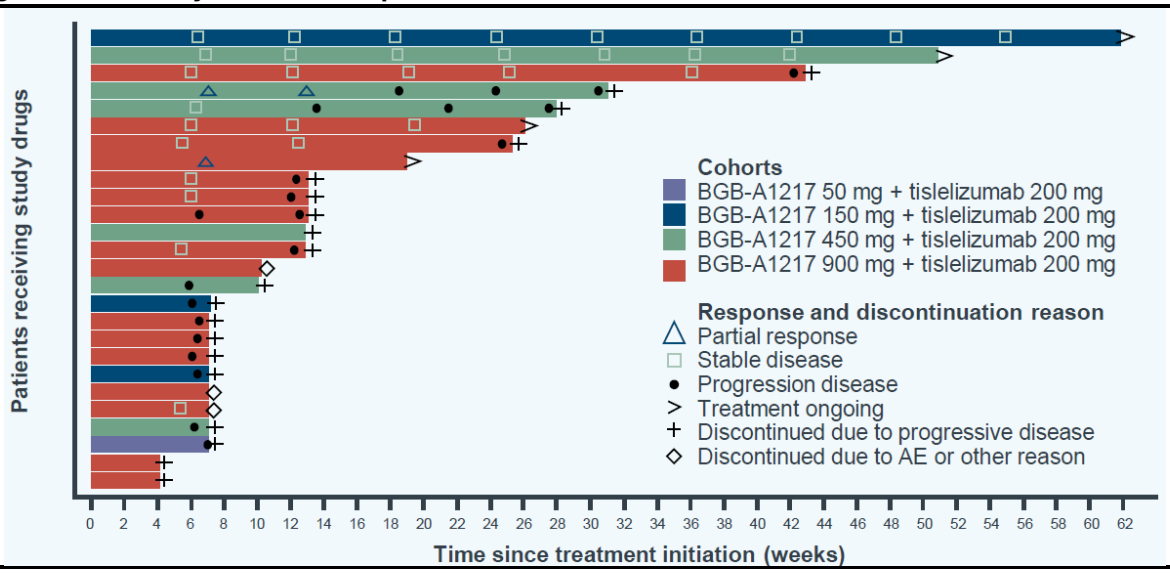
Figure 56: Safety results of ociperlimab's Ph1 trial

	OCI 50 mg plus TIS 200 mg, n (%) (n=1)	OCI 150 mg plus TIS 200 mg, n (%) (n=3)	OCI 450 mg plus TIS 200 mg, n (%) (n=6)	OCI 900 mg plus TIS 200 mg, n (%) (n=16)	Total, n (%) (N=26)
Patients with ≥1 TEAE	1 (100.0)	3 (100.0)	6 (100.0)	15 (93.8)	25 (96.2)
Any treatment-related TEAE	1 (100.0)	1 (33.3)	5 (83.3)	10 (62.5)	17 (65.4)
Serious TEAE	1 (100.0)	1 (33.3)	2 (33.3)	9 (56.3)	13 (50.0)
Serious treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	4 (25.0)	4 (15.4)
Grade ≥ 3 TEAE	1 (100.0)	1 (33.3)	3 (50.0)	11 (68.8)	16 (61.5)
Grade ≥ 3 treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	4 (25.0)	4 (15.4)
Immune-related TEAEs	1 (100.0)	1 (33.3)	5 (83.3)	8 (50.0)	15 (57.7)
Serious immune-related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	3 (11.5)
Grade ≥ 3 immune-related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	3 (11.5)

Source: Company data, CMBIGM

Preliminary anti-tumor activity was observed in the Ph1 study. At the data cut-off, partial response was observed in two patients (one patient at 450 mg ociperlimab, and one patient at 900 mg ociperlimab). Stable disease was observed in nine patients (one at 150 mg, three at 450 mg, and five at 900 mg ociperlimab).

Figure 57: Efficacy results of ociperlimab's Ph1 trial



Source: Company data, CMBIGM

Ociperlimab is assessed in broad clinical studies

As one of the most advanced anti-TIGIT antibodies, ociperlimab is being investigated in broad clinical programs, including two global Ph3 trials and five Ph2 proof of concept studies. As of May 2022, more than 1,000 subjects have been enrolled in 25 countries and regions across the development programs of ociperlimab.

Figure 58: Ongoing global trials of ociperlimab

	Phase Ia	Phase Ib	Phase 2	Phase 3
Untreated, locally advanced, unresectable NSCLC	*AdvanTIG-301*, Ociperlimab + Tislelizumab + CRT			Global
1L PD-L1+ NSCLC	*AdvanTIG-302*, Ociperlimab + Tislelizumab			Global
1L All-Comer NSCLC	*AdvanTIG-205*, Ociperlimab + Tislelizumab + Chemo		Global	
1L LS-SCLC	*AdvanTIG-204*, Ociperlimab + Tislelizumab + CRT		Global	
2/3L CC	*AdvanTIG-202*, Ociperlimab + Tislelizumab		Global	
2/3L ESCC	*AdvanTIG-203*, Ociperlimab + Tislelizumab		Global	
1L HCC	*AdvanTIG-206*, Ociperlimab + Tislelizumab + bevacizumab biosimilar		China	
NSCLC (sq, non-sq, PD-L1+, CPI), ES-SCLC, ESCC, EAC, HNC, GC	*BGB-900-105*, Ociperlimab +Tislelizumab ± chemo	Global		

Source: Company data, CMBIGM. Notes: AdvanTIG-205 has started enrollment. AdvanTIG-202 has completed patient enrollment.

Ociperlimab is currently being investigated in two global Ph3 clinical trials in NSCLC. The global Ph3 AdvanTIG-301 trial (NCT04866017) compares ociperlimab plus tislelizumab to durvalumab (PD-L1 mAb) when co-administered with concurrent chemoradiotherapy (cCRT) in previously untreated, locally advanced, unresectable NSCLC. The trial has started enrollment in Jun 2021.

The global Ph3 AdvanTIG-302 trial (NCT04746924) compares ociperlimab + tislelizumab to Keytruda for the first-line treatment of locally advanced, unresectable, or metastatic NSCLC patients whose tumors exhibit high PD-L1 expression and do not harbor EGFR-sensitizing mutations or ALK translocations. The first patient was enrolled in Jun 2021. Although it is risky to directly challenge Keytruda in 1L PD-L1 high NSCLC, ociperlimab + tislelizumab will have the chance to replace Keytruda as a new SoC in this indication if succeed.

TIGIT is a promising IO target despite of setbacks of tiragolumab

Globally, four anti-TIGIT antibodies have entered into Ph3 stage, including tiragolumab (Roche), ociperlimab (BeiGene), vibostolimab (Merck) and domvanalimab (Arcus/Gilead). Ociperlimab is among the most advanced TIGIT inhibitors worldwide with two Ph3 trials in NSCLC ongoing.

Figure 59: Major TIGIT inhibitors under late-stage development

Phase 3 molecules	Company	# of ongoing Ph3 trials	Fc function	Phase 3 indications
Tiragolumab	Roche	5	Intact	NSCLC; ES-SCLC; ESCC
Ociperlimab	BeiGene	2	Intact	NSCLC
Vibostolimab	Merck	2	Intact	NSCLC
Domvanalimab	Arcus/Gilead	2	Null	NSCLC

Source: Company data, CMBIGM

Many global MNCs have recognized TIGIT as a promising IO target and has completed sizable deals to acquire TIGIT-targeted assets. To date, the total transaction size of TIGIT candidates have passed US$7.9bn, indicating the promising outlook of this asset class.

In Dec 2021, BeiGene granted Novartis an exclusive time-based option under which, upon exercise prior to late 2023, the two companies have agreed to jointly develop ociperlimab. Novartis' territories include North America, Europe, Japan, etc. The total upfront and milestone payment of the deal was up to US$2.9bn, including US$300mn upfront cash payment, additional US$600 or $700mn payment upon exercise of the option prior to late 2023, US$745mn regulatory milestone payment and US$1.15bn sales milestone payments. BeiGene can also receive high-teens to mid-twenties percentage of tiered sales royalties. We believe the cooperation with Novartis will expedite the global development of ociperlimab. Novartis' strong global commercial capabilities will also accelerate sales ramp up of ociperlimab if approved.

Figure 60: Major cooperation deals of TIGIT-targeted assets

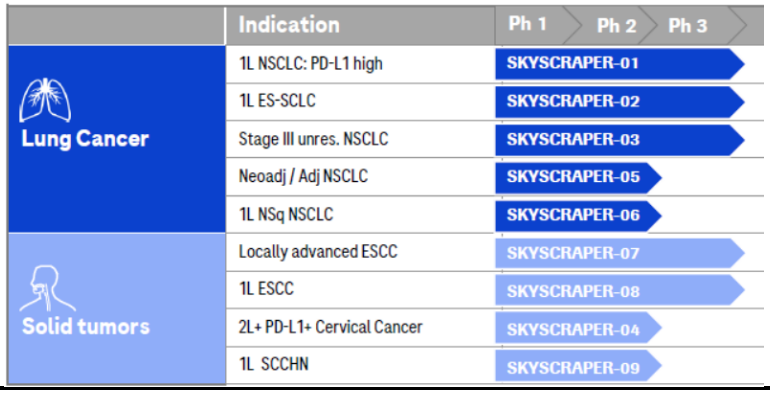
Licensor	Licensee	Product	Date	Deal size (upfront + milestones)
Agenus	BMS	AGEN1777	2021-05	US$1,560mn
iTeos Therapeutics	GSK	EOS-448	2021-06	US$2,075mn
Arcus Biosciences	Gilead	Domvanalimab (AB154), AB308	2021-11	US$1,100mn*
BeiGene	Novartis	Ociperlimab	2021-12	US$2,895mn
Junshi	Coherus	JS006	2022-01	US$290mn

Source: Company data, CMBIGM. Note: * CMBIGM estimate.

Tiragolumab still has chance to hit the OS endpoint in SKYSCRAPER-01 study

Roche has initiated 9 pivotal trials for tiragolumab (TIGIT mAb) since 2020, including five Ph3 trials evaluating tiragolumab + atezolizumab in lung cancer (SKYSCRAPER-01, SKYSCRAPER-02, SKYSCRAPER-03) and oesophageal cancer (SKYSCRAPER-07, SKYSCRAPER-08). Tiragolumab was granted Breakthrough Therapy Designation by the FDA in Jan 2021 for the initial treatment of PD-L1+ metastatic NSCLC.

Figure 61: Pivotal trials of Roche's tiragolumab



Source: Company data, CMBIGM

As the global most advanced TIGIT inhibitor, tiragolumab has experienced some setbacks in its clinical studies. In Mar 2022, Roche announced that the Ph3 SKYSCRAPER-02 (NCT04256421) study of tiragolumab in 1L ES-SCLC didn't meet the co-primary endpoints of PFS and OS in the interim analysis, and the co-primary endpoint of OS was unlikely to reach statistical significance at the planned final analysis (link). The trial evaluated tiragolumab + atezolizumab + chemotherapy vs placebo + atezolizumab + chemotherapy for 1L treatment of ES-SCLC in 490 patients. The findings of the SKYSCRAPER-02 study was presented at the 2022 ASCO meeting (link). With a median follow-up of 14.3 months, the median PFS in the primary analysis set (397 patients) was 5.4 months vs 5.6months in the placebo group (stratified HR 1.11; P=0.3504). The interim OS in the primary analysis set was 13.6 months in both groups (stratified HR 1.04; P=0.7963). The ORR in the full analysis set was numerically higher with the tiragolumab arm vs placebo arm (70.8% vs 65.6%), but not meaningfully so. Roche expects to continue to complete the planned primary OS analysis of the SKYSCRAPER-02 study. In our view, as less than 20% of SCLCs express PD-L1 in >1% of tumor cells, the efficacy of tiragolumab + atezolizumab in the PD-L1-low SCLC is uncertain.

In May 2022, Roche announced results from its Ph3 SKYSCRAPER-01 study (NCT04294810), evaluating the investigational anti-TIGIT immunotherapy tiragolumab plus Tecentriq (atezolizumab) vs Tecentriq alone as an initial treatment for PD-L1-high NSCLC (link). The study did not meet its co-primary endpoint of PFS. At this first analysis, the other co-primary endpoint of OS was immature, and the study will continue. A numerical improvement was observed in both co-primary endpoints. Although missing the PFS endpoint is disappointing, there's still chance for the study to hit the OS endpoint given Roche has allocated most of the alpha to the OS endpoint. We expect the interim OS readout of SKYSCRAPER-01 study to happen in 2023.

BeiGene's global Ph3 AdvanTIG-302 trial (NCT04746924) followed the design of SKYSCRAPER-01 study. However, BeiGene still have the opportunity to adjust its study protocol based on the results from SKYSCRAPER-01. Thus, as a second mover, BeiGene's AdvanTIG-302 trial has a better chance of success, in our view.

Tiragolumab's SKYSCRAPER-01 study was based on the overwhelmingly positive results from the Ph2 CITYSCAPE trial (NCT03563716). At the ESMO meeting in Dec 2021, Roche presented updated data (link) of the Ph2 CITYSCAPE trial investigating tiragolumab + atezolizumab compared with atezolizumab alone as 1L treatment for people with PD-L1-positive metastatic NSCLC. The co-primary endpoints were investigator-assessed ORR and PFS. After 2.5 years of median follow-up, tiragolumab + atezolizumab continued to show an improvement in the intention-to-treat (ITT) population (n=67), driven by the PD-L1-high population (TPS $\geqslant$ 50%) (n=29). In the ITT population, the tiragolumab + atezolizumab combination reduced the risk of PFS by 38% (median PFS=5.6 vs 3.9 months; HR=0.62) and improved ORR (38.8% vs 20.6%) compared with atezolizumab alone. A predefined exploratory analysis in the PD-L1-high

population showed a 71% reduction in the risk of disease worsening or death (median PFS=16.6 vs 4.1 months; HR=0.29) and a clinically meaningful improvement in ORR (69.0% vs 24.1%) with the combination compared with atezolizumab alone. The analysis also showed that tiragolumab plus Tecentriq improved OS in the ITT population, which was driven by the PD-L1-high population. Median OS was 23.2 vs 14.5 months (HR=0.69) in the ITT population and NE vs 12.8 months (HR=0.23) in the PD-L1-high population.

Although tiragolumab + atezolizumab showed astonishing efficacy in PD-L1-high NSCLC patients, the data was from a small group of 29 patients. Thus, the results of CITYSCAPE study could be misleading which has led to the aggressive trial design of the Ph3 SKYSCRAPER-01 study. We believe that TIGIT antibodies have clear efficacy in PD-L1-high NSCLC patients, as proved in multiple clinical trials including CITYSCAPE and SKYSCRAPER-01. However, a rationally designed clinical study is necessary to prove the efficacy of TIGIT antibodies.

Figure 62: Efficacy results of the Ph2 CITYSCAPE trial in NSCLC

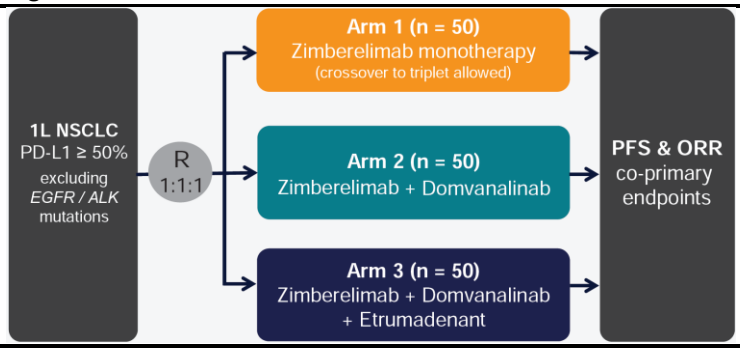
	ITT		PD-L1 TPS ≥ 50%		PD-L1 TPS 1-49%	
	Placebo plus Tecentriq	Tiragolumab plus Tecentriq	Placebo plus Tecentriq	Tiragolumab plus Tecentriq	Placebo plus Tecentriq	Tiragolumab plus Tecentriq
N	68	67	29	29	39	38
ORR, %	20.6	38.8	24.1	69.0	17.9	15.8
mDOR, mo (95% CI)	10.7 (6.0-18.8)	17.6 (9.1-26.1)	8.2 (5.6-10.4)	15.7 (9.1-NE)	18.8 (15.9-22.8)	17.8 (8.3-24.2)
mPFS, mo (95% CI)	3.9 (2.7-4.5)	5.6 (4.2-10.4)	4.1 (2.1-6.8)	16.6 (5.5-22.3)	3.6 (1.4-5.5)	4.0 (1.6-5.6)
HR (95% CI)	0.62* (0.42-0.91)		0.29† (0.15-0.53)		1.07† (0.67-1.71)	
mOS, mo (95% CI)	14.5 (9.6-20.4)	23.2 (14.1-31.5)	12.8 (4.7-24.2)	NE (30.3-NE)	14.5 (8.3-25.6)	13.3 (8.0-20.7)
HR (95% CI)	0.69* (0.44-1.07)		0.23† (0.10-0.53)		1.16† (0.70-1.94)	

Source: Company data, CMBIGM. Notes: *Stratified; †Unstratified; NE: non-evaluable.

Furthermore, domvanalimab from Arcus/Gilead is an Fc-silent anti-TIGIT antibody currently in Ph2/3 trials. Meanwhile, Arcus/Gilead is also assessing AB308, an Fc-enabled anti-TIGIT antibody, in Ph1 trials. Domvanalimab's Ph2 ARC-7 study (NCT04262856) is going to have data readout in 2H22, which will provide a new evidence for the efficacy of TIGIT inhibitors.

The ARC-7 study is an ongoing open-label randomized Ph2 study evaluating patients randomly allocated to domvanalimab + zimberelimab vs zimberelimab alone vs domvanalimab + zimberelimab + etrumadenant as first-line treatment for PD-L1 high NSCLC. The primary endpoints are ORR and PFS. In Nov 2021, Arcus released the results of a second interim analysis for the ARC-7 trial (link). Both domvanalimab-containing arms of the ARC-7 trial demonstrated differentiated clinical activity compared to that of zimberelimab alone.

Figure 63: Study design of the ARC-7 trial



Source: Company data, CMBIGM

Internally developed drug candidates to drive the second wave of innovation

BGB-11417, a potential BIC BCL-2 inhibitor which synergizes with zanubrutinib

BCL-2 is a challenging field for drug development

Inhibitors of antiapoptotic proteins of the BCL-2 family can successfully restart the deregulated process of apoptosis in malignant cells. Venetoclax (brand name Venclexta), co-developed by AbbVie and Roche, is currently the only marketed BCL-2 selective inhibitor globally. Venetoclax was firstly approved by the US FDA in Apr 2016 as a second line therapy for CLL with 17p deletion. As of May 2019, venetoclax has expanded its approved indication to 1) in combination with obinutuzumab as a first-line treatment of CLL/SLL and 2) in combination with azacytidine or decitabine or low-dose cytarabine as a first-line treatment of newly-diagnosed AML in adults who aged 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

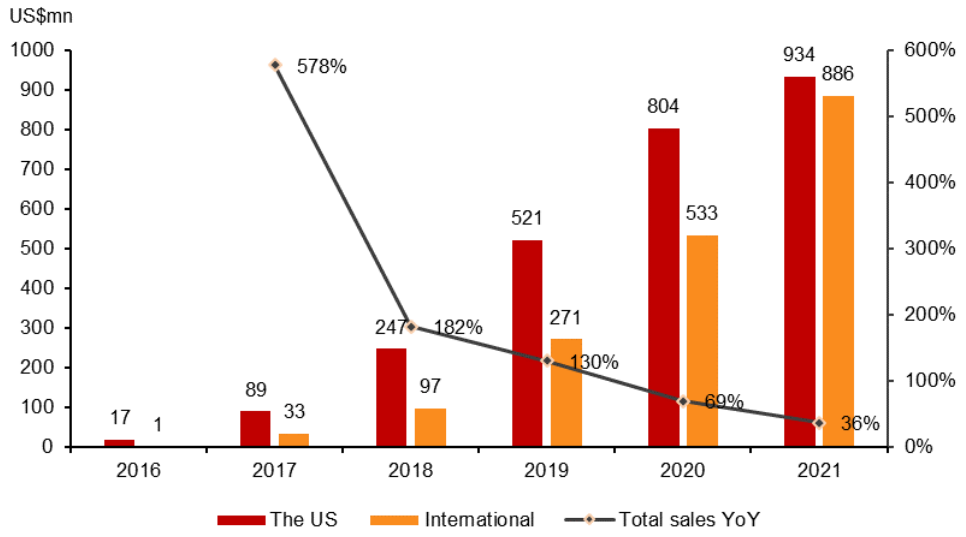
Figure 64: Venetoclax's indication expansion in past years

Date of FDA approval	Indications approved by FDA
2016-04-11	2nd line treatment of CLL with 17p deletion
2018-06-08	2nd line treatment of CLL/SLL, with or without 17p deletion In combination with rituxan as a 2nd line treatment of CLL/SLL, with or without 17p deletion
2018-11-21	In combination with azacitidine or decitabine or low-dose cytarabine as 1st line therapy for AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy
2019-05-15	In combination with obinutuzumab as a 1st line treatment of CLL/SLL

Source: FDA, CMBIGM

Venetoclax has received 6 FDA Breakthrough Therapy Designations. Abbvie and Roche are close to complete the registrational programs of venetoclax in MM and MDS. Initially approved by the US FDA in 2016, venetoclax achieved US$1.82bn sales worldwide in 2021, up 36% YoY.

Figure 65: Sales revenue of venetoclax (2016-2021)

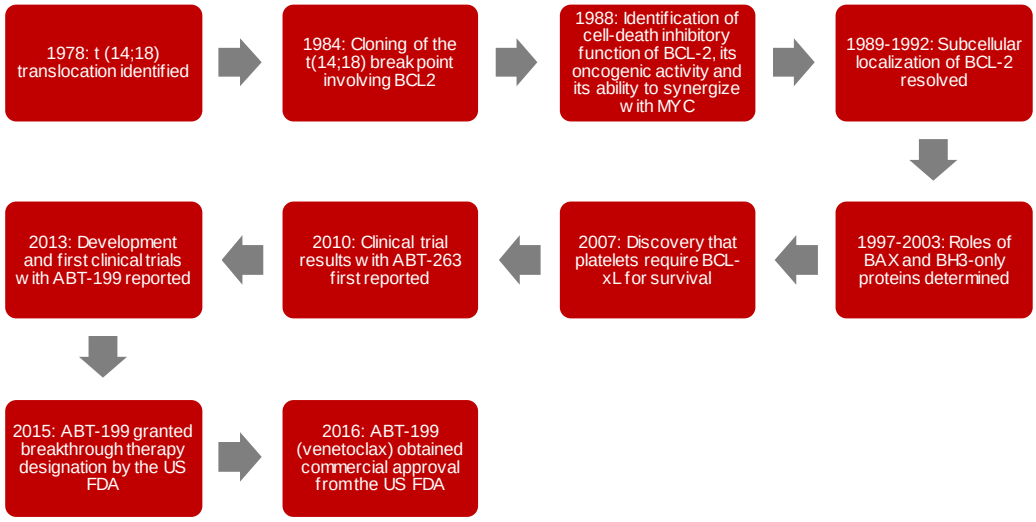


Source: AbbVie annual reports, CMBIGM

Development of BCL-2 targeted drug is very difficult. The intracellular localization of the BCL-2 family proteins on the mitochondrial membrane prevents the use of antibodies and other large molecules to target these anti-death BCL-2 family proteins. Moreover, the very large and hydrophobic interfaces involved in BCL-2 PPIs makes BCL-2 family proteins difficult targets for small molecule drugs.

ABT-737 was the first small molecule targeting BCL-2 family proteins that has entered into clinical phase. Nevertheless, ABT-737 can only be administered via injection. Abbott Laboratories has ceased the development of ABT-737. ABT-263 (navitoclax) is a successor of ABT-737 and can be orally administered. ABT-263 started clinical trials in 2006 but was found to cause severe thrombocytopenia which limits the dosing of ABT-263. This was because BCL-xL is crucial for the survival of platelets. ABT-199 (venetoclax), developed by AbbVie (ABBV US) and Genetech, only targets BCL-2 but not BCL-xL and is therefore better tolerated than ABT-263. In 2016, venetoclax became the firstly approved BCL-2 inhibitor worldwide.

Figure 66: Timeline of key discoveries related to BCL-2 family members



Source: "30 years of Bcl-2: translating cell death discoveries into novel cancer therapies" published at Nature, 29 Jan 2016, CMBIGM

Many companies are currently exploring the BCL-2 target, while the development of many drug candidates are inactive due to the unencouraging clinical results. For selective BCL-2 inhibitors at clinical stage, Ascentage Pharma's lisaftoclax (APG-2575), BeiGene's BGB-11417, Eli Lily/ Fochon Pharma's FCN-338/ LOXO-338, Novartis' VOB560 and Zentalis Pharma's ND-d5 are among the most advanced candidates.

Figure 67: Development landscape of BCL-2 inhibitors

Drug	Company	Development status	Latest development phase	Target	Targeted indications
Venetoclax	Roche/ AbbVie	**Active**	Approved	BCL-2	AML, CLL/SLL, RS, WM, FL, breast cancer, SCLC, AML, DLBCL, MCL, MM, MDS
Navitoclax	Roche/ AbbVie	**Active**	PhIII	BCL-2, BCL-xL	myelofibrosis (MF), AML, OC, DLBCL, CLL/ALL, SCLC
ABT-737	AbbVie	Inactive	PhII	BCL-2, BCL-xL	ovarian cancer
Oblimersen	Genta	Inactive	BLA filed	BCL-2	AML, CLL, CRPC, NHL, MEL, SCLC, MM
Obatoclax	Teva	Inactive	PhIII	BCL-2, Mcl-1	AML, CLL, MCL, SCLC, MEL, MF, MDS, NSCLC
AT-101	Ascentage	Inactive	PhII	BCL-2, BCL-xL, Mcl-1	GBM, SCCHN, CLL, HSPC, CRPC, ACC, SCLC, MM, NSCLC
Lisaftoclax (APG-2575)	Ascentage	**Active**	PhII	BCL-2	AML, CLL, SLL, WM, T-PLL, breast cancer, MM
Rosomidnar	Sierra Oncology	Inactive	PhII	BCL-2	DLBCL, RS, solid tumor

AZD0466	AstraZeneca/ Starpharma	**Active**	PhI/II	BCL-xL,BCL-2	NHL
BGB-11417	BeiGene	**Active**	PhI/II	BCL-2	AML, MDS, MM, B-cell malignancies
FCN-338/ LOXO-338	Eli Lily/ Fochon Pharma	**Active**	PhI/II	BCL-2	CLL/SLL, Leukemia, B-Cell Lymphoma, MM
VOB560	Novartis/ Servier	**Active**	PhI/II	BCL-2	AML, NHL, MM
ZN-d5	Zentalis Pharma	**Active**	PhI/II	BCL-2	AML, AL amyloidosis, NHL
Palcitoclax (APG-1252)	Unity Biotech/ Ascentage	**Active**	PhI/II	BCL-2,BCL-xL	gastric cancer, NET, NHL, SCLC, MF, NSCLC

Source: PharmCube, CMBIGM

BCL-2 inhibitors show excellent efficacy in hematologic malignancies

We believe venetoclax and other selective BCL-2 inhibitors have potential to become a foundational therapy in multiple hematologic malignancies, allowing patients to achieve more durable, deeper responses, including the option for some patients to stop treatment.

Venetoclax has shown strong efficacy in combination with ibrutinib (BTK inhibitor) and obinutuzumab (anti-CD20 antibody). These combination therapies achieve very high rates of complete response and high rates of minimal residual disease-negativity. Venetoclax is currently assessed in multiple clinical trials covering major hematologic oncology indications, such as CLL/SLL, AML, MM, MDS, ALL, etc. We expect venetoclax to further expand indications to major hematologic cancer types.

In July 2021, AbbVie announced that the FDA granted Breakthrough Therapy Designation to venclexta in combination with azacitidine for the potential treatment of adult patients with previously untreated intermediate-, high- and very high-risk MDS.

Figure 68: Abbvie/ Roche is exploring venetoclax for hematologic cancers

Indications	Regimen	Control	Trial ID	Stage
1L CLL	ibrutinib plus venetoclax	chlorambucil plus obinutuzumab	GLOW	Ph3
1L CLL	venetoclax plus obinutuzumab	fludarabine plus cyclophosphamide plus rituximab or bendamustine plus rituximab (FCR/BR)	CRISTALLO	Ph3
r/r MCL	ibrutinib plus venetoclax	ibrutinib plus placebo	SYMPATICO	Ph3
AML Maintenance	venetoclax plus azacitidine	placebo plus azacitidine	VIALE-M	Ph3
r/r t(11;14)-positive MM	venetoclax plus dexamethasone	pomalidomide plus dexamethasone	CANOVA	Ph3
1L high-risk MDS	venetoclax plus azacitidine	placebo plus azacitidine	Verona	Ph3

Source: AbbVie/ Roche presentations, CMBIGM

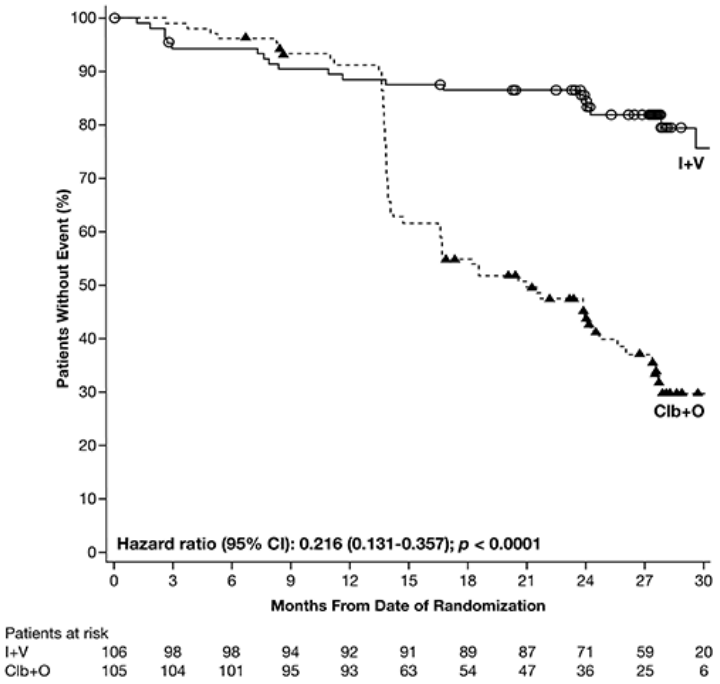
In June 2021, AbbVie announced results from its Ph3 GLOW study (NCT03462719) comparing the efficacy and safety of ibrutinib in combination with venetoclax versus chlorambucil plus obinutuzumab for first-line treatment of CLL/SLL met its primary endpoint (link).

The GLOW study is a randomized, open label Ph3 trial evaluating fixed-duration ibrutinib plus venetoclax (I+V) compared to chlorambucil plus obinutuzumab (C+O) for first-line treatment of elderly or unfit patients with CLL/SLL. Patients with del(17p) or known TP53 mutations were excluded. There were 211 patients randomly assigned in a 1:1 ratio to receive either I+V (106) and or C+O (105) and the median age was 71 years. Patients assigned to I+V received treatment for 15 cycles (1 cycle is 28 days), starting with three cycles of ibrutinib monotherapy lead-in followed by the combination of I+V for 12 cycles. Patients assigned to C+O were treated for six cycles.

The GLOW study demonstrated superior PFS of a once-daily, all-oral, fixed-duration regimen of I+V versus C+O as first-line treatment of CLL/SLL. With median follow-up of 27.7 months, IRC-assessed PFS for I+V was superior to C+O (HR=0.216; $p < 0.0001$). Median PFS was not reached for I+V and 21.0 months for C+O. The GLOW study also showed improved duration of remission and significantly improved

depth of remission. At 3 months after end of treatment (EOT+3), rate of undetectable minimal residual disease (uMRD) was significantly higher for I+V vs C+O in bone marrow (51.9% vs 17.1%; p < 0.0001) and peripheral blood (54.7% vs 39.0%; p = 0.0259). With I+V, uMRD in peripheral blood was sustained in 84.5% of patients one year after end of treatment. CR rate (including CRi) was significantly higher for I+V vs C+O by IRC (38.7% vs 11.4%; p < 0.0001). The safety profile of I+V was generally consistent with the safety profile of the single agents.

Figure 69: PFS assessed by IRC in the Ph3 GLOW study



Source: EHA 2021, CMBIGM

In comparison, ibrutinib monotherapy can reach 87% ORR with a median follow-up of eight years while most responses were partial with persistent disease typically in the bone marrow and complete remission was uncommon. We believe the oral combination of BCL-2 inhibitor and BTK inhibitor could potentially become the golden standard for first-line treatment of CLL/SLL given as it can significantly improve the depth and duration of remission compared with existing therapies.

Figure 70: Comparison of efficacy between therapies for 1L CLL/SLL

	Venetoclax + Ibrutinib	Venetoclax + Ibrutinib	Venetoclax + Obinutuzumab	Obinutuzumab + chlorambucil	Ibrutinib + Rituximab	Ibrutinib	Venetoclax + Ibrutinib	Obinutuzumab + chlorambucil
Source	JCO Journal	JAMA	JCO Journal		NEJM	Blood Journal	AACR Journal	
Trial ID	NCT02910583	NCT02756897	NCT02242942		NCT02048813	NCT01105247, NCT01109069	GLOW (NCT03462719)	
Administration	Oral	Oral	Oral + Intravenous		Oral + Intravenous	Oral	Oral	
Trial stage	Phase II	Phase II	Phase III		Phase III	Phase Ib/II	Phase III	
Line of treatment	1st line	1st line	1st line		1st line	1st line	1st line	
Median follow-up	31.3 mos	38.5 mos	52.4 mos		33.6 mos	8 years	27.7 mos	
Patient number	164	80	216	216	354	31	106	105
PFS		3-year PFS 93%	Not reached	36.4 mos	3-year PFS 73%	7-year PFS was 83%	Not reached	21.0 mos
			HR=0.33, P<0.0001				HR 0.22, P<0.0001	
MRD-negativity in bone marrow	68% (best response)	75% (best response)	74% (at EoT+3)	33% (at EoT+3)	-	-	51.9% (at EoT+3)	17.1% (at EoT+3)
CR	46%	69%	-	-	17%	35%	39%	11%
ORR	97%	87%	-	-	96%	87%	-	-
Data source	Link	Link	Link		Link	Link	Link	

Source: PudMed, CMBIGM

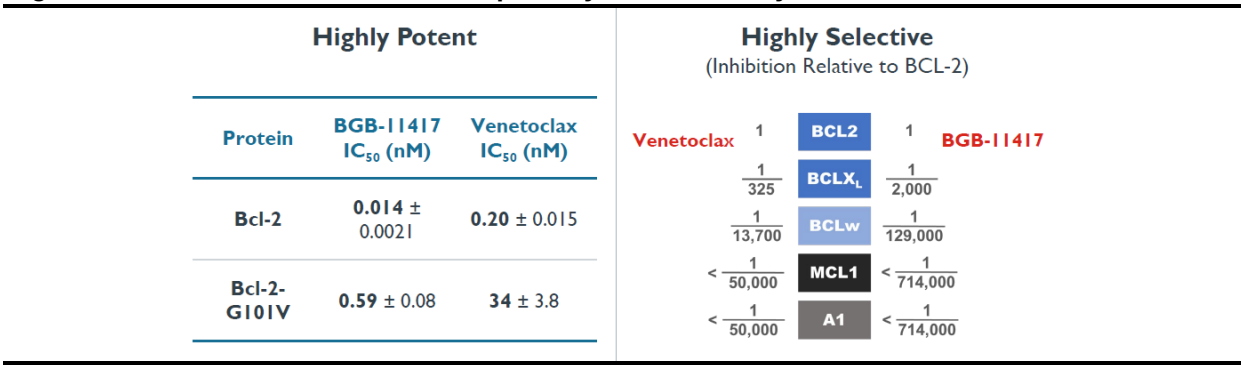
BGB-11417 showed potent activity and high selectivity in preclinical studies

Venetoclax has demonstrated improved clinical outcomes in indicated patients with hematological malignancies, while it is associated with common gastrointestinal toxicities and neutropenia. With the recent expansion in the applications of venetoclax, some cases of venetoclax resistance have appeared (link). Unique toxicities of venetoclax also include tumor lysis syndrome (TLS) due to the rapid apoptotic effect by BCL-2 inhibition. TLS is the uncontrolled release of phosphorus, nucleic acids, potassium and inflammatory cytokines into the bloodstream, which leads to renal insufficiency, seizures and death due to cardiac arrythmias and multiorgan failure.

Venetoclax requires an inconvenient 5-week ramp-up dosing schedule to gradually reduce tumor burden (debulk) and mitigate the risk of TLS - dosing is increased weekly according to a schedule of 20 mg, 50 mg, 100 mg, 200 mg, reaching a target dose of 400 mg daily in Week 5. Moreover, given the severity of TLS, inpatient hospitalization during initial venetoclax dose ramp up is usually required, which causes extra medical expenses for patients. Thus, a more convenient ramp-up schedule becomes an unmet need, especially for patients with very aggressive diseases. For instance, patients who progress on ibrutinib may need expedited dose ramp-up of venetoclax to rapidly achieve the therapeutic dose of venetoclax. Due to the above-mentioned limitations of venetoclax, we believe a better BCL-2 inhibitor with higher selectivity and lower toxicities, the potential to avoid drug resistance, and a more convenient dose ramp-up schedule will address the significant unmet medical need.

Internally developed by BeiGene, BGB-11417 has shown antitumor activity superior to venetoclax in AML, MCL, and DLBCL xenograft models. In-vitro evaluation has shown that BGB-11417 is >10-fold more potent than venetoclax at inhibiting BCL-2 (IC50: 0.014nm with BGB-11417 vs 0.20nM with venetoclax). Moreover, the potency of BGB-11417 for inhibiting the BCL-2-G101V mutant protein, which can induce resistance to venetoclax on continued treatment, was >50-fold higher than that of venetoclax (IC50: 0.59nM with BGB-11417 vs 34nM with venetoclax), showing the potential of BGB-11417 to avoid drug resistance. BGB-11417 demonstrated ⩾2,000-fold selectivity for BCL-2 compared to BCL-xL, BCL-W, MCL-1, and BCL-2A1 in vitro, which illustrates its high selectivity.

Figure 71: In vitro studies show better potency and selectivity of BGB-11417 than venetoclax



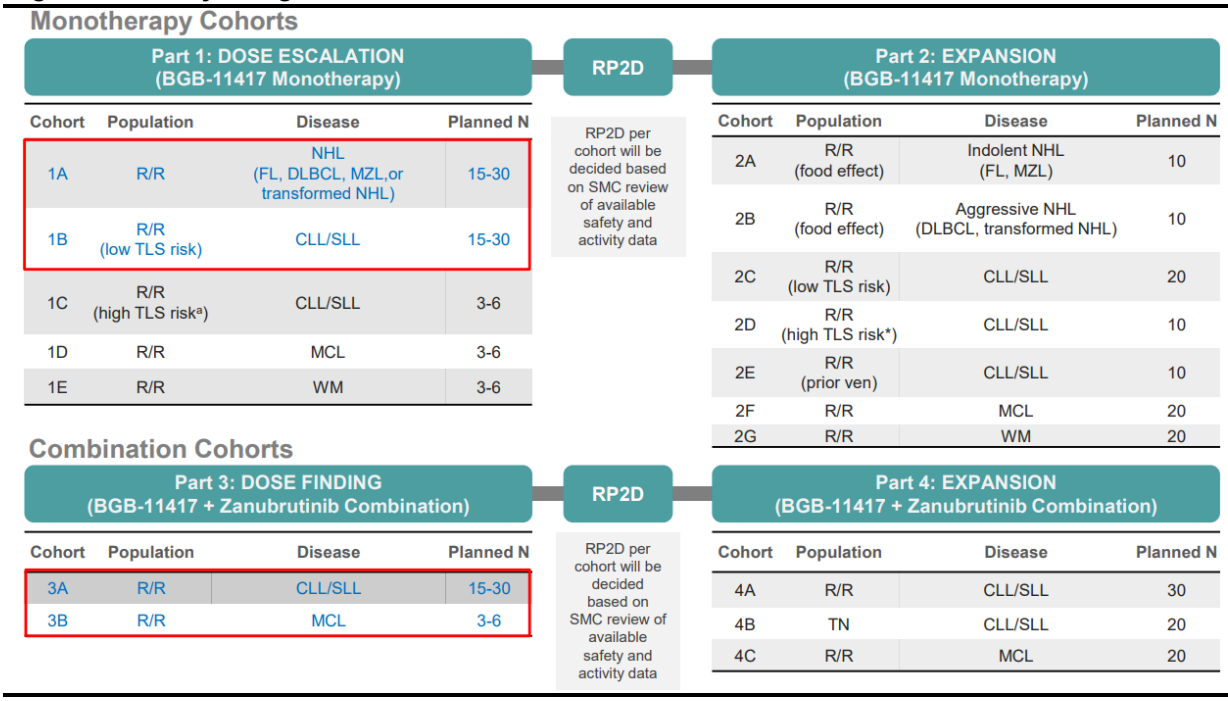
Source: Company data, CMBIGM

Preliminary safety and efficacy data released

Ph1 trial in r/r B-cell malignancies

At the 2021 ASH meeting, BeiGene shared preliminary safety and efficacy data of the Ph1 trial (NCT04277637) of BGB-11417 in monotherapy or in combination with zanubrutinib in r/r B-cell malignancies conducted in the US, Australia and other overseas countries (link1, link2).

Figure 72: Study design of BGB-11417's Ph1 trial

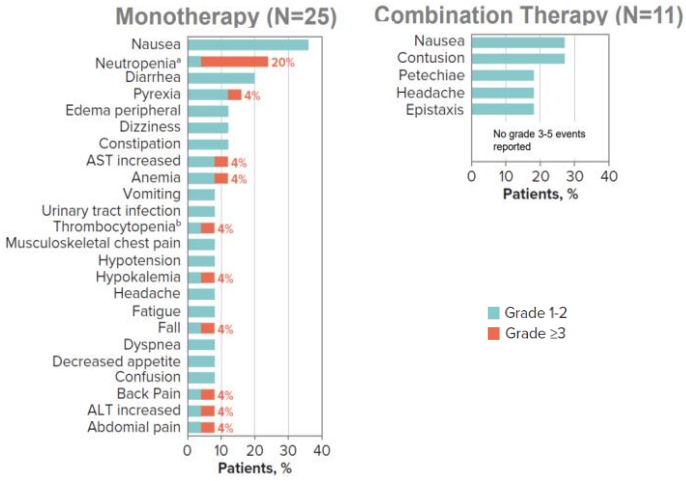


Source: Company data, CMBIGM. Notes: As of 25 Sep 2021, Cohorts 1A, 1B, 3A, and 3B have opened and enrolled patients.

As of 25 Sep 2021, 36 patients had been treated, including 25 patients treated with monotherapy (NHL n=19, CLL/SLL n=6) and 11 patients treated with combination treatment (CLL n=10, MCL n=1). In the monotherapy arm, the most common treatment-emergent AEs were nausea and neutropenia (including decreased neutrophil count). Grade ⩾3 AEs have been infrequent and manageable, with none seen in combination cohorts. Laboratory TLS (Howard Criteria) was seen in 1 patient with CLL in the monotherapy group while no change in management was required.

Figure 73: Safety data of BGB-11417's Ph1 trial

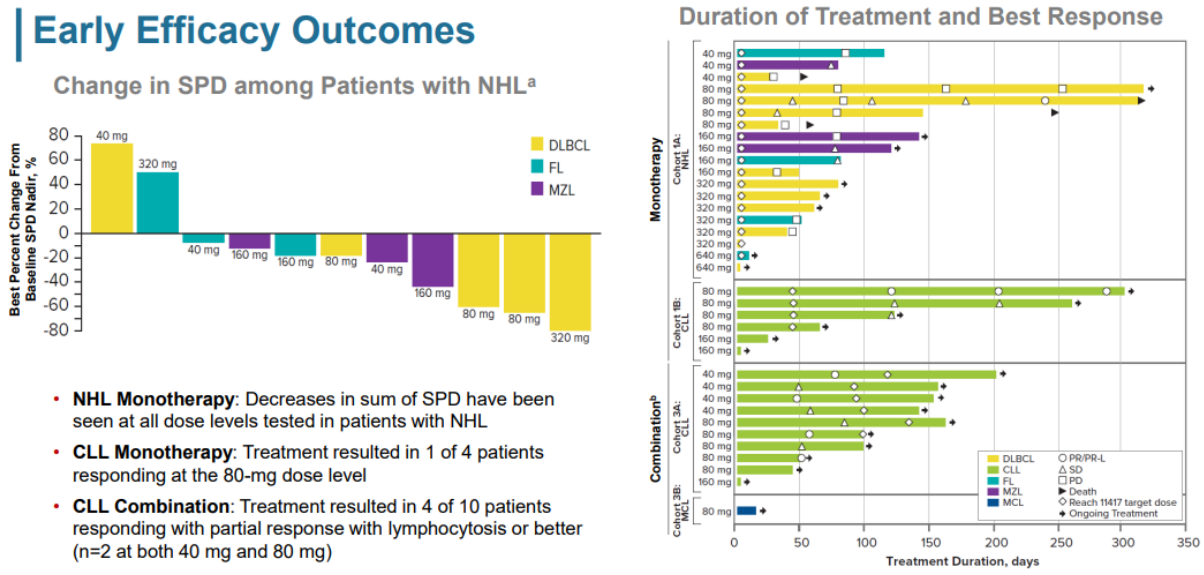
AEs, n (%)	BGB-11417 Monotherapy (N=25)	BGB-11417 + Zanubrutinib Combination (N=11)	All Patients (N=36)
Any AE	22 (88)	9 (82)	31 (86)
Grade ≥3 AEs	11 (44)	0	11 (30)
Serious AEs	9 (36)	0	9 (25)
Leading to death	2 (8)	0	2 (6)[a]
AEs leading to hold of BGB-11417	4 (16)	0	4 (11)[b]
AEs leading to dose reduction of BGB-11417	0	0	0
AEs leading to discontinuation of BGB-11417	1 (4)	0	1 (3)[c]



Source: Company data, CMBIGM

Efficacy data are limited as dose escalation is not complete for any cohort and not all patients have reached their first response assessment, but responses have been observed at preliminary dose levels. For CLL/SLL patients received combination treatment, 4 of 10 patients responded with partial response with lymphocytosis or better (n=2 at both 40 mg and 80 mg). Significant reduction in absolute lymphocyte count (ALC) was noted among all patients with CLL during ramp-up, with reduction in lymphocytes noted at dose levels as low as 1 mg.

Figure 74: Efficacy data of BGB-11417's Ph1 trial



Source: Company data, CMBIGM. Notes: SPD, sum of the product of greatest diameter.

The updated results of the above Ph1 trial was released at the EHA Meeting in Jun 2022 (link1, link2). As of Feb 2022, 78 patients received BGB-11417 (34 with monotherapy, 44 in combination with zanubrutinib). The trial consistently demonstrated the generally well-tolerated safety profile of BGB-11417 monotherapy and in combination with zanubrutinib. Dose escalation was concluded for monotherapy patients with NHL (cohort 1A), with 1 DLT of grade 3 febrile neutropenia seen at 160 mg, and no MTD reached at doses as high as 640mg. One patient with CLL receiving monotherapy with high baseline TLS risk had a marked tumor flare on BTK inhibitor withdrawal and developed laboratory TLS in a late ramp-up. The patient experienced no sequelae from laboratory TLS and resolved by the next day and BGB-11417 did not need

to be withheld. Neutropenia was observed in 8 patients receiving monotherapy (n=6 grade ≥3; n=5 received growth factor) and 6 patients receiving combination therapy (n=3 grade ≥3; n=4 received growth factor). All cases were resolved without the need for dose reduction.

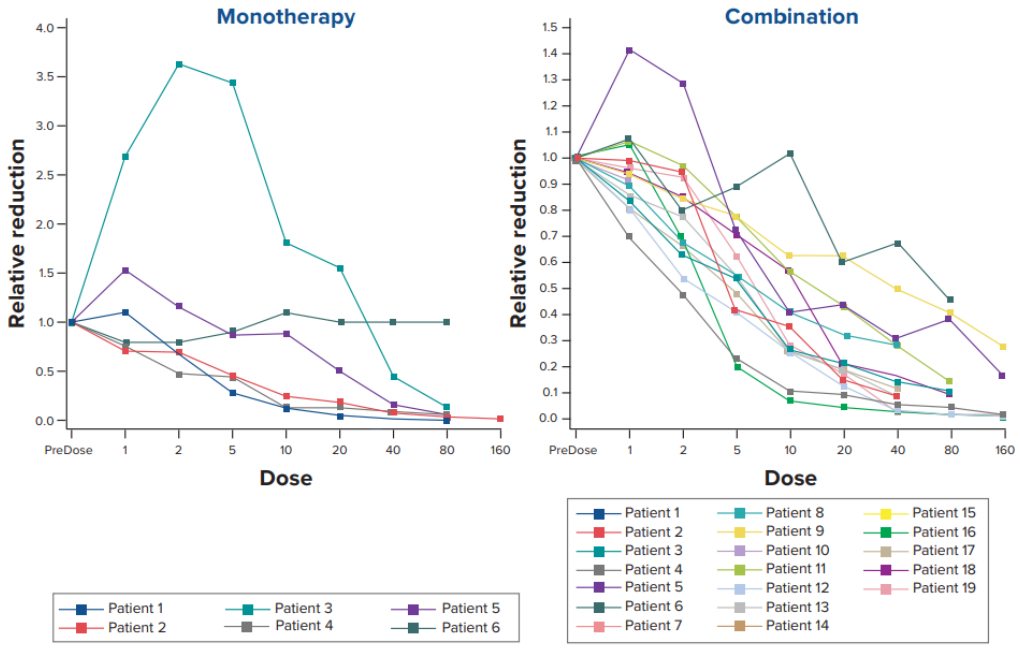
Figure 75: Overall adverse events of BGB-11417's Ph1 trial

AEs, n (%)	BGB-11417 monotherapy (n=34[a])	BGB-11417 + zanubrutinib combination (n=44[b,c])	All patients (N=78)
Any AEs	32 (94.1)	34 (77.3)	66 (84.6)
Grade ≥3 AEs	14 (41.2)	7 (15.9)	21 (26.9)
Serious AEs	11 (32.4)	5 (11.4)	16 (20.5)
Leading to death	2[d] (5.9)	1 (2.3)[e]	3 (3.8)
Leading to hold of BGB-11417	5[f] (14.7)	1[g] (2.3)	6 (7.7)
Leading to dose reduction of BGB-11417	0	0	0
Leading to discontinuation of BGB-11417	1[h] (2.9)	0	1 (1.3)

Source: EHA 2022, CMBIGM

The efficacy data were early, while responses were observed at the preliminary dose levels. A reduction in ALC (absolute lymphocyte count) was noted among all patients with CLL during ramp-up. 16 of 20 (80%) r/r CLL/SLL patients receiving BGB-11417 + zanubrutinib achieved PR-L or better across dose levels ranging from 40 - 320 mg.

Figure 76: Activity of BGB-11417: reduction in ALC over ramp-up in CLL patients



Source: EHA 2022, CMBIGM

Ph1b/2 trial in AML

The preliminary data of BGB-11417 in combination with azacitidine in patients with AML (NCT04771130) were released at the EHA Meeting in Jun 2022 (link). This is an ongoing global Ph1b/2 study evaluating the combination of BGB-11417 and azacitidine in patients with AML (TN unfit for chemotherapy or r/r) or MDS. For patients with AML, the 10-day regimen consisted of BGB-11417 at 40 mg (Cohort 1), 80 mg (Cohort 2), or 160 mg (Cohort 3) in combination with azacitidine. In Cycle 1, a 4-day ramp-up of BGB-11417 was utilized starting at 1/8 of the target dose.

At a median follow-up of 3.06 months, 2 of 26 (7.7%) evaluable patients experienced DLTs (grade 4 neutropenia/ thrombocytopenia). Laboratory TLS was observed in 1 patient (3.2%) with a known history of chronic kidney disease in Cohort 3, while the patients was asymptomatic and the TLS resolved within 4 days. Neutropenia was the most common grade ≥3 AE (54.8%) and was manageable with growth factor support and dose modification.

Figure 77: Dose-limiting toxicity and tumor lysis syndrome of BGB-11417's Ph1b/2 trial in AML

	BGB-11417			
	40 mg × 10 d (n=5)	80 mg × 10 d (n=15)	160 mg × 10 d (n=6)	Total[b] (N=26)
DLT,[a] n (%)	0	2 (13.3)	0	2 (7.7)
Hematologic	0	2 (13.3)	0	3 (11.5)
Grade 4 neutropenia	0	1 (6.7)	0	1 (3.8)
Grade 4 thrombocytopenia	0	2 (13.3)	0	2 (7.7)
Nonhematologic (grade ≥3)	0	0	0	0
Hy's Law	0	0	0	0
Laboratory TLS,[c] n (%)	0	0	1 (16.7)[d]	1 (3.2)

Source: EHA 2022, CMBIGM

CR/CRh achieved in 58% TN and 55% r/r AML patients, with most CRs achieved by the end of cycle 1. Thirteen patients met CR/CRi with evaluable flow cytometry MRD results, while 5 (38.5%) of the 13 evaluable patients achieved MRD negativity (malignant AML <0.1% per ELN 2018), and 2 of 5 were MRD negative after 1 cycle of treatment. Most patients had ≥80% reduction in bone marrow blast.

Figure 78: Best overall response of BGB-11417's Ph1b/2 trial in AML

	40 mg × 10 d		80 mg × 10 d		160 mg × 10 d		Total	
	TN (n=4)	R/R (n=3)	TN (n=11)	R/R (n=6)	TN (n=4)	R/R (n=2)	TN (n=19)	R/R (n=11)
CR+CRh, n (%)	2 (50)	2 (67)	7 (64)	2 (33)	2 (50)	2 (100)	11 (58)	6 (55)
CR+CRh after 1 cycle	2 (50)	1 (33)	5 (45)	1 (17)	2 (50)	0	9 (47)	2 (18)
CR+CRi, n (%)	2 (50)	2 (67)	7 (64)	3 (50)	2 (50)	2 (100)	11 (58)	7 (64)
MRD evaluable[a]	2	1	6	2	1	1	9	4
MRD negative	1	0	3	1	0	0	4	1
CR	2 (50)	0	6 (55)	1 (17)	1 (25)	1 (50)	9 (47)	2 (18)
CRi	0	2 (67)	1 (9)	2 (33)	1 (25)	1 (50)	2 (11)	5 (46)
ORR (CR+CRi+MLFS+PR), n (%)	2 (50)	2 (67)	10 (91)	3 (50)	2 (50)	2 (100)	14 (74)	7 (64)
MLFS	0	0	2 (18)	0	0	0	2 (11)	0
PR	0	0	1 (9)	0	0	0	1 (5)	0
Time to CR, median, mo	1.31	N/A	1.36	3.75	0.95	1.94	1.31	2.84
Response assessment not done, n (%)	1 (25)	0	1 (9)	0	1 (25)	0	3 (16)	0
BGB-11417 treatment duration, median (range), mo	1.31 (0.3-4.8)		2.96 (0.3-9.2)		1.95 (0.3-3.7)		2.40 (0.3-9.2)	

Source: EHA 2022, CMBIGM

Efficient clinical development of BGB-11417

Besides the above-mentioned ongoing Ph1 trial in r/r B-cell malignancies and Ph1b/2 trial in AML, BeiGene is also conducting another Ph1b/2 trial of BGB-11417 + dexamethasone + carfilzomib in r/r MM (NCT04973605). BeiGene aims to start pivotal trials for BGB-11417 in 2022.

Figure 79: Clinical trials of BGB-11417

DRUG CANDIDATES	PROGRAMS	DOSE ESC.	DOSE EXPANSION		PIVOTAL		FILED	MARKETED
		Phase 1a	Phase 1b	Phase 2*	Phase 2**	Phase 3		
BGB-11417 (Bcl-2)	monotherapy & + zanubrutinib	*B-cell malignancies*						
	+ dexamethasone & + carfilzomib	*R/R Multiple Myeloma*						
	+ azacytidine	*AML, MDS*						

Source: Company data, CMBIGM

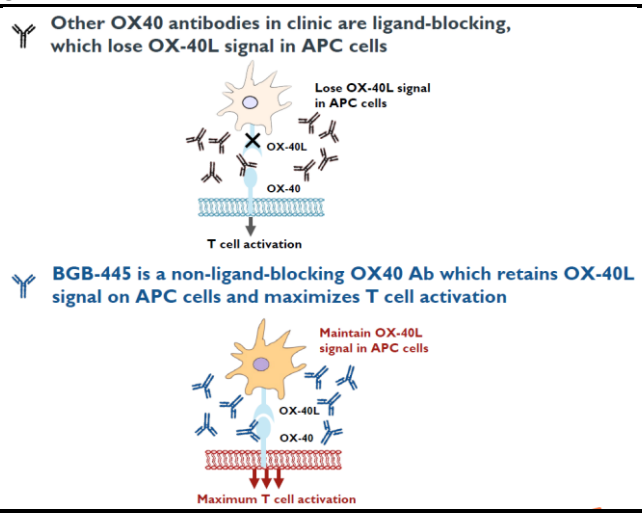
BGB-445, a differentiated non-ligand competing OX-40 agonist

OX40 is a member of the tumor necrosis factor receptor super family (TNFRSF, 肿瘤坏死因子受体超家族) primarily expressed on activated CD4+ and CD8+ T cells, as well as natural killer T and NK cells. It is an immune costimulatory receptor which binds to its ligand OX40L and activates downstream NF-κB pathway to induce immune cell activation, proliferation, and survival.

The existing clinical stage OX40 agonistic antibodies, which are mostly ligand-competitive antibodies, showed limited clinical responses, mainly at lower doses. Blockade of OX40-OX40L interaction might limit the efficacy of these ligand-competitive antibodies at higher doses, as OX40-OX40L interaction is essential for enhancing effective anti-tumor immunity.

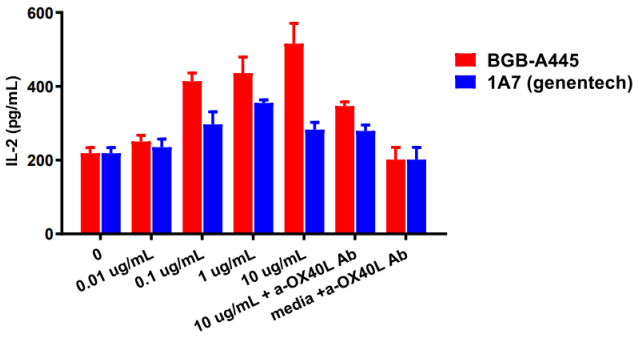
BGB-A445 (OX40 antibody) is a non-ligand competing agonistic OX40 antibody that does not disrupt OX40 to OX40 ligand engagement (link). BGB-A445 interacts with the CRD4 region of OX40 which is distant from OX40L binding region, therefore BGB-A445 did not interfere with the binding of OX40 to OX40L even at high concentrations, which was proved in preclinical studies. In contrast, MOXR0916, an OX40 agonistic antibody developed by Genentech, completely blocked OX40 binding to OX40L. Preclinical experiments showed that BGB-A445 has increasing effectiveness at higher doses versus MOXR0916 (a ligand-competing antibody), with the latter showing falling effectiveness at higher doses. In preclinical tests, BGB-A445 has also demonstrated the combination potential with several agents, such as tislelizumab, a TLR9 agonist, a PI3Kδ inhibitor, sitravatinib, and chemotherapy.

Figure 80: MoA of BGB-A445



Source: Company data, CMBIGM

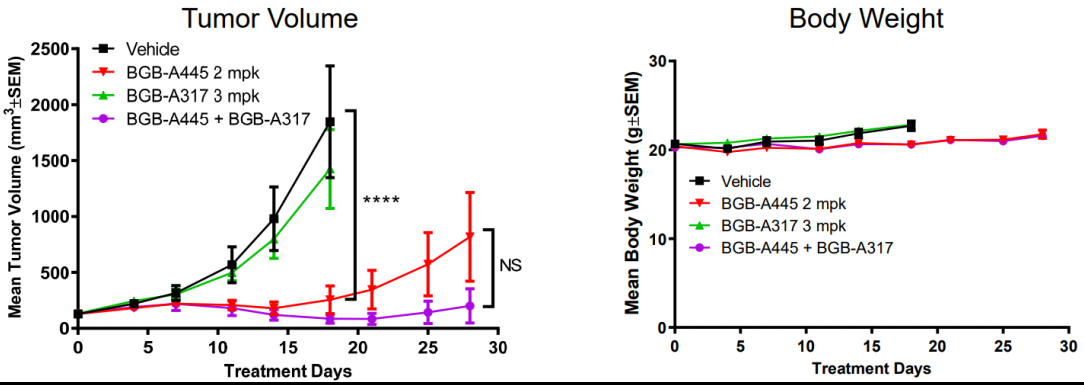
Figure 81: BGB-A445 promotes immune responses



Source: Company data, CMBIGM. Notes: 1A7, analog of pogalizumab developed by Genetech.

BeiGene has an ongoing Ph1 trial (NCT04215978) assessing BGB-A445 combined with tislelizumab in advanced solid tumors and expects to initiate dose expansion for BGB-A445 in 1H22.

Figure 82: BGB-A445 + PD-1 mAb reveals better antitumor activity in CT26WT colon tumor model



Source: Company presentation, CMBIGM. Notes: BGB-A317 (anti-human PD-1 Ab tislelizumab)

Many OX40 antibodies are at clinical development while most of the candidates are at early clinical stage. BGB-A445 has potential to become a FIC/BIC OX40 agonist with differentiated non-ligand competing mechanism, in our view.

Figure 83: OX40 agonists under clinical development

Drug	Company	Latest development phase	Target	Targeted incidations
INCAGN1949	Incyte, Agenus	PhI/II	OX40	solid tumor
BMS-986178	Bristol-Myers Squibb	PhI/II	OX40	solid tumor
ATOR-1015	Alligator Bioscience	PhI	CTLA4, OX40	solid tumor
INBRX-106	Elpiscience Biopharma, Inhibrx	PhI	OX40	solid tumor
BAT6026	Bio-Thera Solutions	PhI	OX40	solid tumor
BGB-A445	BeiGene	PhI	OX40	solid tumor
HFB301001	HiFiBiO Therapeutics	PhI	OX40	SCCHN, renal cell carcinoma (RCC), uterine carcinosarcoma, HCC, soft tissue sarcoma
Cudarolimab	Adimab, Innovent Biologics	PhI	OX40	hepatitis B, solid tumor
ATOR-1015	Alligator Bioscience	PhI	CTLA4, OX40	solid tumor
Revdofilimab	AbbVie	PhI	OX40	SCCHN,TNBC,NSCLC
FS120	F-star Therapeutics	PhI	OX40, 4-1BB	cancer
EMB-09	EpimAb Biotherapeutics	PhI	PDL1, OX40	solid tumor
YH-002	Eucure Biopharma (Biocytogen)	PhI	OX40	solid tumor
KN052	Alphamab	PhI	PDL1, OX40	solid tumor
Cudarolimab/ IBI-101	Innovent	PhI	OX40	solid tumor
Revdofilimab	Abbvie	PhI	OX40	TNBC, NSCLC, HNSCC

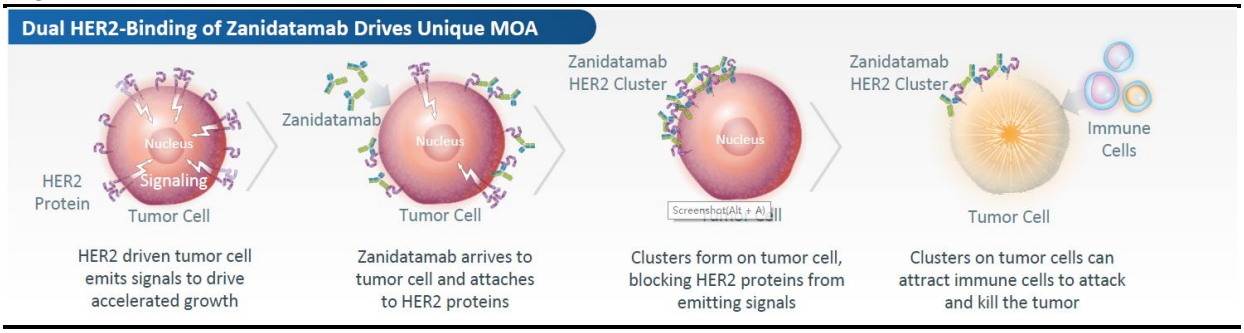
Source: Pharmacube, CMBIGM

Key in-licensed drug candidates at late clinical stage

Zanidatamab, a dual HER2-binding bispecific antibody

Developed based on Zymeworks's Azymetric platform, zanidatamab can simultaneously bind two non-overlapping epitopes of HER2, ECD2 (trastuzumab binding domain) and ECD4 (pertuzumab binding domain). Zanidatamab has increased tumor cell binding and enhanced HER2 internalization compared with trastuzumab, and is superior to trastuzumab and pertuzumab in preclinical studies. In Nov 2018, BeiGene and Zymeworks entered into collaboration and license agreements whereby BeiGene acquired licenses to develop and commercialize Zymeworks' clinical-stage candidate zanidatamab (ZW25) and preclinical-stage bispecific ADC ZW49 in Asia (excluding Japan), Australia, and New Zealand.

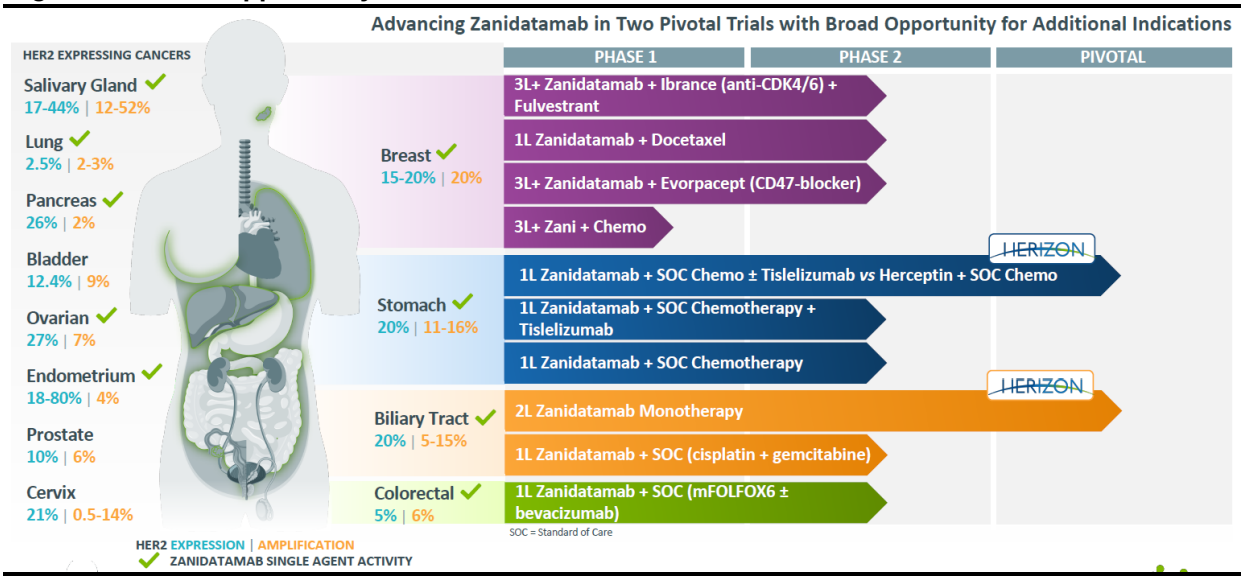
Figure 84: MoA of zanidatamab



Source: Zymeworks presentation, CMBIGM

In clinical trials, zanidatamab has been well tolerated with promising antitumor activity in patients with treatment-naive and heavily pretreated HER2-expressing cancers, including individuals whose disease had progressed on multiple prior treatment regimens that included HER2-targeted agents. Zanidatamab has been granted Breakthrough Therapy Designation by the FDA for patients with previously-treated HER2 gene-amplified BTC as well as two Fast Track designations, one for previously treated or recurrent HER2-positive BTC and another for first-line GEA in combination with standard of care chemotherapy.

Figure 85: Broad opportunity for zanidatamab in HER2 cancers



Source: Zymeworks presentation, CMBIGM

Zymeworks is currently evaluating zanidatamab in two pivotal clinical trials, one for the first-line treatment of advanced or metastatic HER2-positive gastroesophageal adenocarcinoma (HERIZON-GEA-01), and

the other for previously treated HER2-amplified biliary tract cancer (HERIZON-BTC-01). BeiGene also participates in the above-mentioned two studies.The HERIZON-GEA-01 study (NCT05152147) is a Ph3 trial to assess zanidatamab in combination with chemotherapy +/- tislelizumab for 1L treatment of HER2-positive gastroesophageal cancer (GEA). BeiGene, in conjunction with its partner Zymeworks, is expected to release clinical data of this trial in 1H22. The HERIZON-BTC-01 study (NCT04466891) is a Ph2b pivotal study evaluating zanidatamab as a monotherapy in previously treated patients with advanced or metastatic HER2-amplified biliary tract cancers (BTC). BeiGene has completed the enrollment of this trial by May 2022, and expects to announce efficacy and safety results from the trial by early 2023 in collaboration with Zymeworks.

BeiGene also initiated a Ph1/2 trial (NCT04276493) of zanidatamab combined with docetaxel/ tislelizumab + chemo in HER2-positive breast/ gastric cancer, respectively.

Figure 86: BeiGene's clinical trials of zanidatamab

<table>
<tr><th rowspan="2">COMPOUND</th><th rowspan="2">(TARGET) / PROGRAM</th><th>DOSE ESC.</th><th colspan="2">DOSE EXPANSION</th><th colspan="2">PIVOTAL</th><th rowspan="2">COMM. RIGHTS</th><th rowspan="2">PARTNER</th></tr>
<tr><th>Phase 1a</th><th>Phase 1b</th><th>Phase 2*</th><th>Phase 2**</th><th>Phase 3</th></tr>
<tr><td rowspan="3">zanidatamab
††</td><td>(HER2, bispecific antibody) + chemo + tislelizumab</td><td colspan="5">GEA</td><td rowspan="3">Asia ex-Japan, AU, NZ</td><td rowspan="3">zymeworks</td></tr>
<tr><td>Monotherapy</td><td colspan="4">Bilary tract cancers</td><td></td></tr>
<tr><td>+ chemo, +/- tislelizumab</td><td colspan="2">Breast cancer, GC, GEA</td><td colspan="3"></td></tr>
</table>

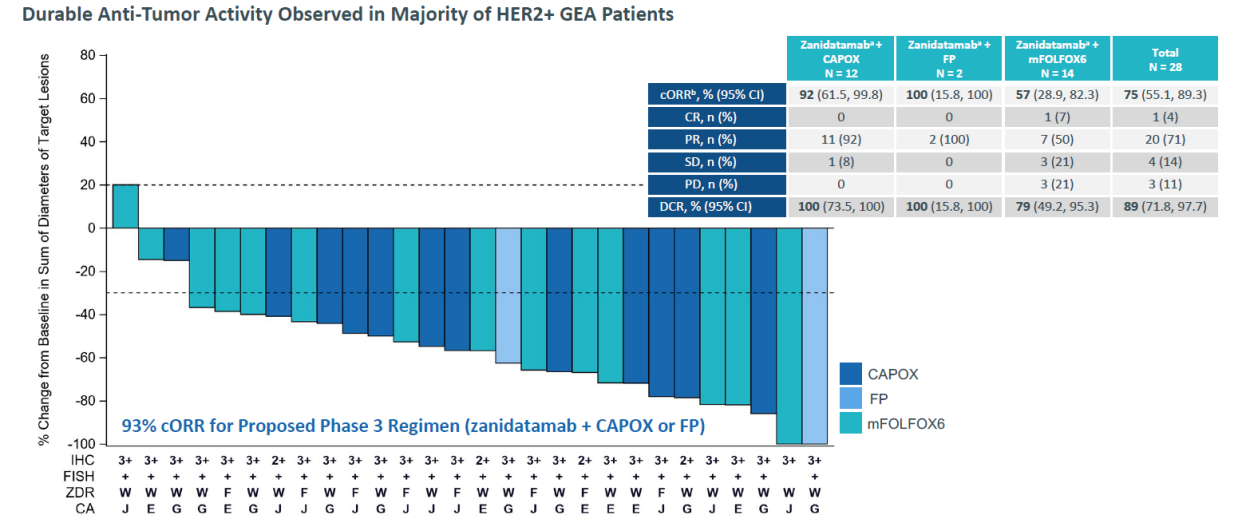
Source: Company presentation, CMBIGM

Promising clinical data of zanidatamab in multiple indications

Gastroesophageal adenocarcinoma (GEA)

The ZWI-ZW25-201 (NCT03929666) study is an ongoing multicenter, global, Ph2, open-label study to investigate zanidatamab + standard first-line combination chemotherapy regimens in subjects with locally advanced, unresectable, or metastatic HER2-expressing gastrointestinal cancers, including GEA. The data of this study (NCT03929666) for zanidatamab in combination with chemotherapy in first-line HER2-positive GEA was presented at the ESMO meeting in Sep 2021 (link). The study enrolled 36 patients with HER2-expressing GEA who received zanidatamab in combination with either CAPOX (capecitabine/oxaliplatin; n=14), FP (5FU/cisplatin; n=2), or mFOLFOX6 (5FU/leucovorin/oxaliplatin; n=20), while none of the patients had received prior HER2-targeted therapies. For the 28 evaluable patients with metastatic HER2-positive GEA, at a median follow-up of 6.9 months, zanidatamab plus chemotherapy resulted in a confirmed ORR (cORR) of 75% and DCR of 89%, with a cORR of 93% and DCR of 100% in the proposed Ph3 regimen of zanidatamab + CAPOX/FP. All patients except one experienced a decrease in their tumor size. The mDOR was 16.4 months and the mPFS was 12.0 months across all treatment regimens with 61% of patients still on study at the time of data cutoff.

Figure 87: Efficacy of the Ph2 trial of zanidatamab in first-line HER2+ GEA



Source: Zymeworks presentation, CMBIGM

In addition, the data demonstrate that zanidatamab plus chemotherapy is generally well tolerated, with the majority of TRAEs considered mild to moderate in severity (Grade 1 or 2). The most common grade ⩾ 3 TRAE was diarrhea which was manageable in the outpatient setting; introduction of prophylactic loperamide reduced the incidence in cycle 1 from 44% to 18%. No severe (grade ⩾ 3) infusion-related reactions or cardiac events were observed.

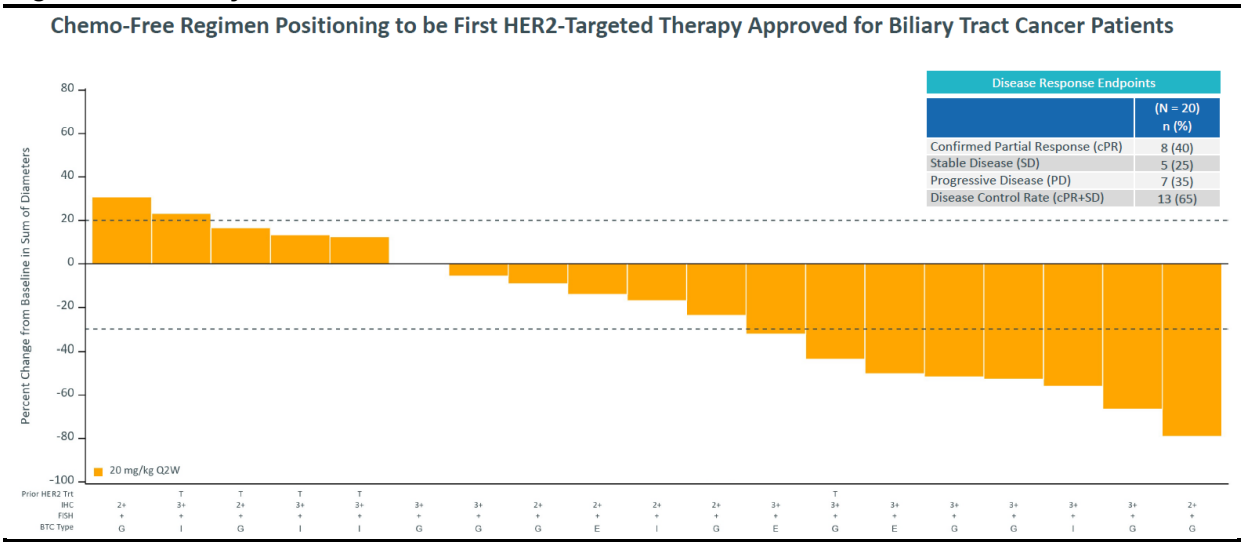
Zanidatamab in combination with chemotherapy exhibited promising response rates and durability and, overall, was well tolerated. Based on the Ph2 data, Zymeworks initiated a randomized pivotal Ph3 HERIZON-GEA-01 trial.

Biliary tract cancer (BTC)

ZW25-101 trial (NCT02892123) is a Ph1 study that evaluates zanidatamab in HER2-expressing cancers, including BTCs. The updated results of zanidatamab in HER2-amplified BTC patients as a second line treatment were released at the ASCO GI meeting in Jan 2021 (link).

Data were from 21 patients diagnosed with HER2-amplified BTC who received zanidatamab at the recommended dose of 20 mg/kg every two weeks. The median number of prior systemic therapies was 2 (range 1-8), including five patients who had received prior HER2-targeted therapy (trastuzumab). Zanidatamab was well tolerated and demonstrated durable antitumor activity in these patients. All zanidatamab-related AEs were mild or moderate in severity (Grade 1 or 2). The confirmed ORR in trastuzumab-naïve patients was 47% (7/15) and overall ORR was 40% (8/20). The overall disease control rate was 65% (13/20), and median duration of response was 7.4 months with several patients still on study at the time of data cut-off.

Figure 88: Efficacy of the Ph1 trial of zanidatamab in second-line HER2+ BTC



Source: Zymeworks presentation, CMBIGM

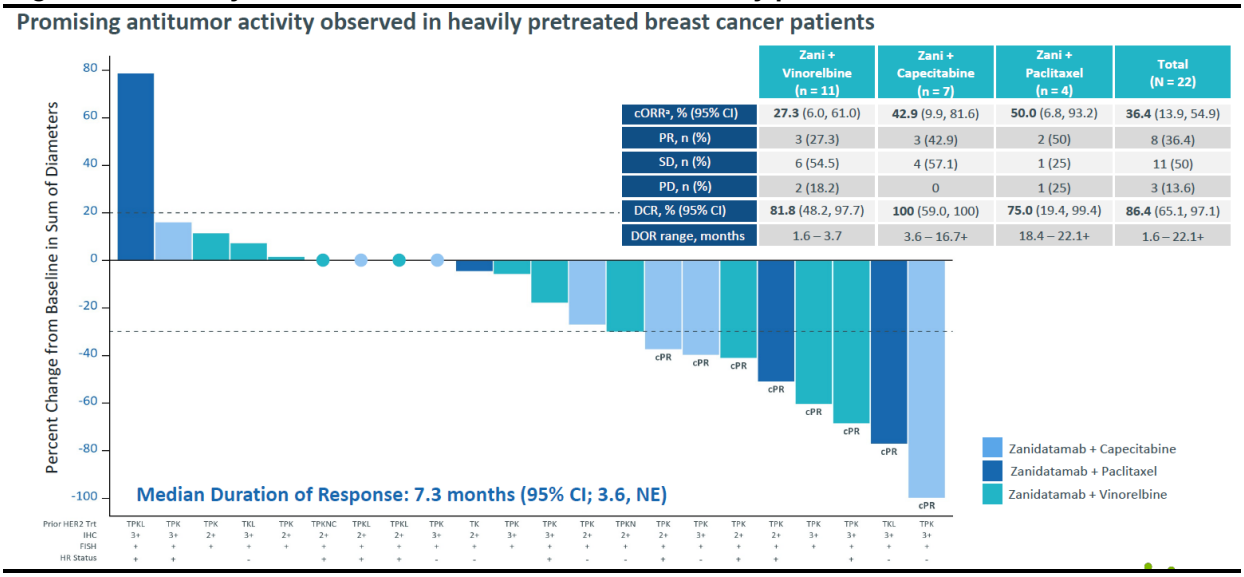
Based on the data, zanidatamab obtained a Breakthrough Therapy Designation from the FDA for patients with previously treated HER2 gene-amplified BTC. Zymeworks initiated a global pivotal Ph2b trial (HERIZON-BTC-01) of zanidatamab monotherapy in patients with HER2-amplified BTC.

Breast Cancer (BC)

In Part 3 of the Ph1 trial ZW25-101 (NCT02892123), zanidatamab was evaluated in combination with chemotherapy in patients with HER2-positive metastatic BC. The data was presented at the SABCS meeting in Dec 2021 (link). The data were from 24 patients with heavily pretreated HER2-positive BC who received zanidatamab in combination with either vinorelbine (n=12), capecitabine (n=8), or paclitaxel (n=4). Patients received multiple prior regimens containing HER2-targeted agents including trastuzumab (96%), pertuzumab (96%), and T-DM1 (96%), and many also received a tyrosine kinase inhibitor.

In 22 efficacy-evaluable patients, treatment with zanidatamab and chemotherapy resulted in a cORR of 36.4% and DCR of 86.4%, and the majority of patients experienced a decrease in their tumor size. The mPFS is 7.3 months across all treatment regimens with 42% of patients still on study at the time of data cutoff. Zanidatamab in combination with single agent chemotherapy is well tolerated, with the majority of TRAEs considered mild to moderate in severity (Grade 1 or 2). These data support further investigation of zanidatamab plus chemotherapy as a novel therapeutic option for patients with HER2-positive metastatic breast cancer after three or more lines of prior therapy.

Figure 89: Efficacy of the Ph1 trial of zanidatamab in heavily pre-treated HER2+ BC



Source: Zymeworks presentation, CMBIGM

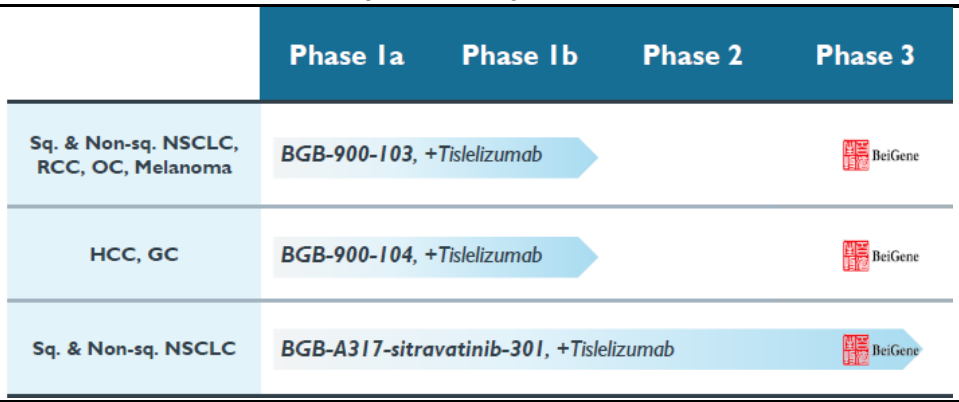
Sitravatinib, a multi-kinase inhibitor at late clinical stage

Sitravatinib (multi-kinase inhibitor) is an investigational spectrum-selective kinase inhibitor, which potently inhibits several closely related receptor tyrosine kinases (RTKs), including RET, TAM family receptors (TYRO3, Axl, MER), and split family receptors (VEGFR2, KIT). BeiGene is developing sitravatinib in collaboration with Mirati Therapeutics. In Jan 2018, BeiGene entered into an exclusive in-license agreement with Mirati to develop, manufacture, and commercialize sitravatinib in Asia (excluding Japan and certain other countries), Australia, and New Zealand.

Mirati is evaluating sitravatinib in multiple clinical trials to treat patients who are refractory to prior immune checkpoint inhibitor therapy, including a Ph3 SAPPHIRE (NCT03906071) trial of sitravatinib in NSCLC initiated in 2019.

Meanwhile, BeiGene is also evaluating sitravatinib in multiple studies, including a Ph1b study (BGB-900-103, NCT03666143) assessing sitravatinib + tislelizumab in advanced solid tumors, a Ph1/2 study (BGB-900-104, NCT03941873) evaluating sitravatinib +/- tislelizumab in HCC and GC, and a Ph3 trial (BGB-A317-sitravatinib-301, NCT04921358) combining sitravatinib with tislelizumab in 2/3L NSCLC).

Figure 90: Clinical trials of sitravatinib sponsored by BeiGene



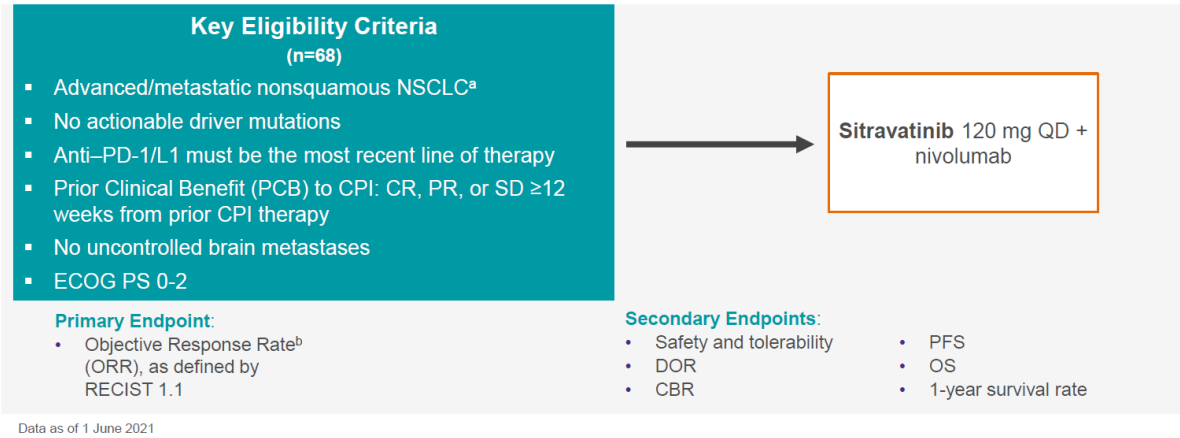
Source: Company presentation, CMBIGM; Note: Mirati is conducting other studies for sitravatinib

Sitravatinib in combination with tislelizumab showed a manageable safety profile and demonstrated preliminary antitumor activity in patients with r/r melanoma previously treated with a PD-(L)1 inhibitor, and in patients with advanced platinum-resistant ovarian cancer (PROC). At ESMO IO Congress in Dec 2021, BeiGene presented data of two cohorts from a Ph1b trial (BGB-900-103, NCT03666143) of sitravatinib in combination with tislelizumab in patients with metastatic melanoma who were r/r to PD-(L)1 inhibitors and in patients with PROC. In the PD-(L)1 resistant metastatic melanoma cohort (link), at the median follow-up of 9.6 months, the confirmed ORR was 36% (1 CR and 8 PRs), DCR was 88.0% and the median PFS was 6.7 months. In the PROC cohort (link), at the follow-up of 8.9 months, ORR was 28.8% (17 PR in the 59 efficacy evaluable patients), DCR was 79.7%, and median PFS was 4.1 months.

Encouraging OS data reported in a Ph2 trial in 2/3L nsq-NSCLC

MRTX-500 study (NCT02954991), conducted by Mirati, is an open-label Ph2 study, which includes a cohort of sitravatinib + nivolumab (OPDIVO) as a 2L or 3L treatment in patients with non-squamous NSCLC who have experienced clinical benefit on a prior checkpoint inhibitor (CPI) and subsequent disease progression. The primary endpoint of the study was ORR. Secondary endpoints include OS, PFS, and safety.

Figure 91: Study design of Ph2 MRTX-500 study in nsq-NSCLC conducted by Mirati

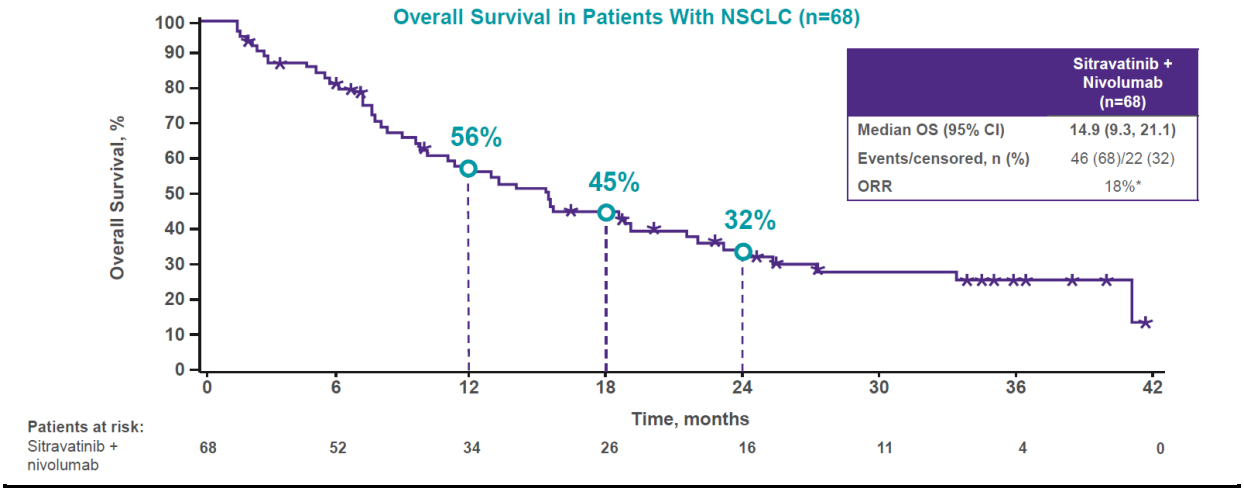


Source: ESMO 2021, CMBIGM

The updated data of MRTX-500 trial was presented at ESMO meeting in Sep 2021 (link). 68 patients with prior clinical benefit on a CPI were treated with sitravatinib + nivolumab as of Jun 2021. At a follow-up of 33.6 months, the median PFS was 5.7 months and the median OS was 14.9 months, with 56% and 32% of these patients alive at one year and two years, respectively. The ORR was 18%, with 3% of patients achieving a CR and 15% of patients achieving a PR. The median DOR was 12.8 months. Sitravatinib plus nivolumab was well-tolerated with no unexpected safety signals observed, and AEs were manageable. Grade 3/4 TRAEs were reported in 66% of patients. The rate of TRAEs leading to study treatment discontinuation was 22%.

The encouraging OS of 14.9 months and durable responses in 2/3L patients who progressed on a CPI supports Mirati's ongoing Ph3 SAPPHIRE study, and demonstrated the potential to establish sitravatinib + nivolumab as new standard of care after checkpoint inhibitor failure.

Figure 92: OS in nsq-NSCLC patients with prior clinical benefit from CPI therapy



Source: ESMO 2021, CMBIGM. Note: Median follow up in PCB cohort: 33.6 months; data as of 1 June 2021.

Sotorasib, a first-in-class KRAS G12C inhibitor

Sotorasib /Lumakras (KRAS G12C), in-licensed from Amgen, is the first and only marketed KRAS G12C inhibitor globally, which has been approved in nearly 40 countries around the world for treatment of KRAS G12C-mutated NSCLC.

KRAS G12C is the most common KRAS mutation in NSCLC. About 13% of patients with NSCLC in the US harbor the KRAS G12C mutation. Unmet medical need remains high and treatment options are limited for NSCLC patients with the KRAS G12C mutation. The outcomes with other approved therapies are suboptimal, with a median PFS of approximately four months following second-line treatment of KRAS G12C-mutated NSCLC.

In Oct 2019, BeiGene and Amgen agreed to jointly develop a portfolio of oncology assets in Amgen's pipeline, with BeiGene responsible for development and commercialization in China. Sotorasib is included as one of the most advanced assets in this portfolio to be co-developed by the two parties. Upon sotorasib's approval in China, BeiGene will receive commercial rights for seven years from approval and share 50% of profits and losses for the product in China. After the seven-year commercialization period, sotorasib will be transitioned to Amgen, and BeiGene will be eligible to receive tiered mid-single to low-double-digit royalties on net sales in China for an additional five years.

Amgen is investigating sotorasib as a treatment for a variety of solid tumors, including NSCLC, colorectal cancer and other solid tumor and is exploring more than 10 sotorasib combination regimens, including triplets, with clinical trial sites spanning five continents. As of Apr 2022, over 4,000 patients worldwide have received sotorasib through the clinical development program and commercial use.

Sotorasib was initially approved in the US in May 2021 based on the CodeBreaK 100 study for the 2L treatment of KRAS G12C-mutated NSCLC, representing the first approved targeted therapy for a KRAS mutation tumor. The CodeBreaK 100 study (NCT03600883) is a Ph1/2 trial evaluating sotorasib monotherapy in advanced solid tumors With KRAS p.G12C mutation and sotorasib combination therapy in advanced NSCLC with KRAS p.G12C mutation. In April 2022, Amgen announced long-term efficacy and safety data from the CodeBreaK 100 study in patients with KRAS G12C-mutated advanced NSCLC at the AACR 2022 meeting (link). At a median follow-up of 24.9 months, in the 174 heavily pre-treated patients, sotorasib demonstrated a centrally confirmed ORR of 40.7%, disease control rate of 83.7% and median duration of response of 12.3 months. The results also showed median PFS of 6.3 months and overall survival of 12.5 months, with 32.5% of patients still alive at two years.

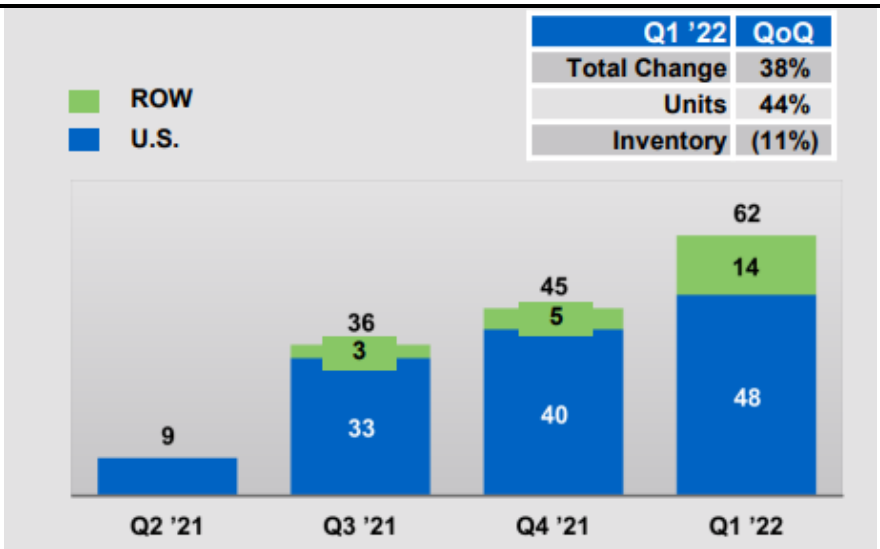
Amgen has completed the enrollment of 345 patients in the CodeBreaK 200 study (NCT04303780), a global Ph3 randomized active-controlled study comparing sotorasib to docetaxel in 2L KRAS G12C-mutated NSCLC. Amgen is also conduting a Ph2 randomized study evaluating sotorasib as a first line treatment for patients with stage IV KRAS G12C-mutated NSCLC (CodeBreaK 201 study).

In addition to NSCLC, sotorasib has demonstrated satisfying results in pancreatic cancer. In Feb 2022, Amgen presented the data from the CodeBreaK 100 Ph1/2 trial in patients with KRAS G12C-mutated advanced pancreatic cancer (link). Sotorasib demonstrated a centrally confirmed ORR of 21% and DCR of 84% across 38 heavily pre-treated advanced pancreatic cancer patients. Nearly 80% of patients received sotorasib as a third-line or later therapy. Median duration of response was 5.7 months with a median follow-up of 16.8 months. The results also show a median PFS of 4 months and a median OS of almost 7 months. There is a high unmet need for patients with advanced pancreatic cancer that has progressed after first-line treatment, where FDA-approved second-line therapy has provided survival of about six months and a response rate of 16%. After progression on first- and second-line chemotherapy, there are no therapies with a demonstrated survival benefit. Approximately 90% of patients with pancreatic cancer harbor a KRAS mutation with KRAS G12C accounting for approximately 1-2% of these mutations.

In Sep 2021, Amgen announced the results from the Ph1b/2 CodeBreaK 101 study evaluating sotorasib combined with panitumumab (anti-EGFR antibody) in patients with KRAS G12C-mutated advanced colorectal cancer (CRC) (link). The ORR was 27% (confirmed and unconfirmed) among 26 patients in the efficacy analysis set (which included 5 patients who had progressed with prior sotorasib monotherapy). The DCR was 81%. In the expansion cohort of sotorasib-naïve patients with refractory CRC (n=18), ORR was 33% (confirmed and unconfirmed). Based on the encouraging results, Amgen initiated a new Ph3 trial with the combination therapy in KRAS G12C mutation CRC (NCT05198934).

As the FIC KRAS inhibitor, sales of sotorasib ramped up fast since its first approval by the FDA in May 2021. In 1Q22, sotorasib recorded US$62mn sales revenue worldwide. In the US, sotorasib has been prescribed to approximately 2,500 patients by over 1,500 physicians in both academic and community settings.

Figure 93: Global sales of sotorasib



Source: Amgen presentation, CMBIGM. Notes: sotorasib was initially approved in the US in May 2021; Inventory represents wholesaler inventories

In China, sotorasib was granted Breakthrough Therapy Designation for the treatment of KRAS G12C-mutated NSCLC in Jan 2021. In 3Q21, BeiGene has secured approval by the Hainan BoAo government for early access to sotorasib in designated hospitals in the province. Nevertheless, the applications to the Human Genetic Resources Administration of China (HGRAC) to obtain approval to conduct clinical

studies in China for sotorasib is currently delayed. Approval from the HGRAC is required to initiate clinical trials involving the collection of human genetic materials in China.

The second KRAS G12C inhibitor potentially to be approved in the US is adagrasib developed by Mirati (China rights granted to Zai Lab). The NDA of adagrasib for patients with previously treated KRAS G12C positive NSCLC is under review by the FDA with a PDUFA date of Dec 2022. Adagrasib also showed very potent efficacy in clinical studies.

Figure 94: Cross-trial comparison of sotorasib and adagrasib

Indication	Drug	Trial	No. of patients	ORR	Source
NSCLC	sotorasib	Codebreak 100	172	41%	Link
	adagrasib	Krystal-1	116	43%	Link
Pancreatic cancer	sotorasib	Codebreak 100 (data cutoff Feb 2022)	38	21%	Link
	adagrasib	Krystal-1 (data cutoff Sep 2021)	10	50%	Link
CRC	sotorasib	Codebreak 100 (data cutoff Mar 2021)	62	10%	Link
	sotorasib + panitumumab	Codebreak 101 (data cutoff Sep 2021)	26	27%	Link
	adagrasib	Krystal-1 (data cutoff May 2021)	45	22%	Link
	adagrasib + cetuximab	Krystal-1 (data cutoff Jul 2021)	28	43%	

Source: Company data, CMBIGM

Financial Analysis

Strong product revenue growth to continue

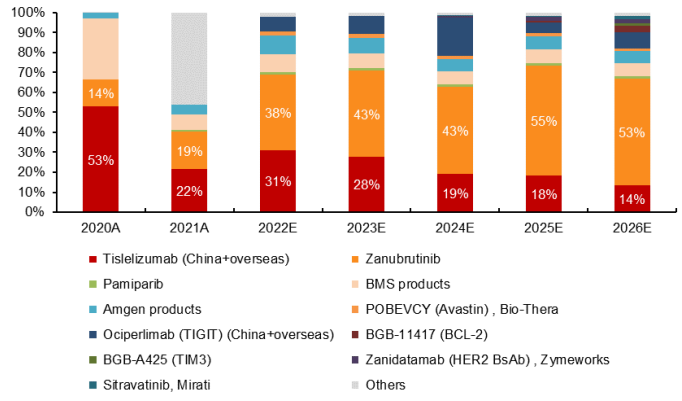
We expect zanubrutinib and tislelizumab will continue to be the major revenue driver of in coming years. We estimate BeiGene's risk-adjusted product revenue of US$2,613mn in FY24E, representing a 60% CAGR in FY21-24E. We forecast a total risk-adjusted revenue of US$1,398mn/ US$2,206mn/ US$3,340mn in FY22E/ 23E/ 24E, respectively.

Figure 95: Risk-adjusted revenue forecasts

(YE 31 Dec, US$mn)	2020A	2021A	2022E	2023E	2024E	2025E	2026E
- Tislelizumab China sales	163	255	385	513	518	561	585
YoY	*N/A*	*56%*	*51%*	*33%*	*1%*	*8%*	*4%*
- Zanubrutinib	42	218	527	949	1,450	2,149	2,629
YoY	*3,914%*	*423%*	*142%*	*80%*	*53%*	*48%*	*22%*
- Pamiparib	0	12	17	28	43	52	70
- REVLIMID (lenalidomide), BMS	47	70	98	132	172	215	258
- VIDAZA, BMS	30	20	26	34	43	53	64
- ABRAXANE, BMS	18	0	0	0	0	0	0
- XGEVA, Amgen	8	46	60	75	90	103	115
- BLINCYTO, Amgen	0	13	55	69	83	95	106
- KYPROLIS, Amgen	0	0	20	30	41	53	66
- Sotorasib (KRAS G12C) , Amgen	0	0	0	0	1	9	18
- POBEVCY (Avastin) , Bio-Thera			30	38	46	54	63
- Ociperlimab (TIGIT) China sales	0	0	0	0	43	150	317
- BGB-11417 (BCL-2)	0	0	0	0	0	36	161
- BGB-A425 (TIM3)	0	0	0	0	0	0	49
- Zanidatamab (HER2 BsAb) , Zymeworks	0	0	0	0	30	68	120
- Sitravatinib, Mirati	0	0	0	0	4	22	73
- Others	0	0	30	39	51	65	84
Product revenue	**309**	**634**	**1,248**	**1,906**	**2,613**	**3,686**	**4,777**
YoY	*39%*	*105%*	*97%*	*53%*	*37%*	*41%*	*30%*
- Tislelizumab overseas income	0	0	50	100	124	154	90
- Ociperlimab (TIGIT) overseas income	0	0	100	200	603	65	87
- Others	0	542	0	0	0	0	0
Collaboration revenue	**0**	**542**	**150**	**300**	**727**	**219**	**177**
YoY	*-100%*	*N/A*	*-72%*	*100%*	*142%*	*-70%*	*-19%*
Total revenue	**309**	**1,176**	**1,398**	**2,206**	**3,340**	**3,905**	**4,954**
YoY	*-28%*	*281%*	*19%*	*58%*	*51%*	*17%*	*27%*

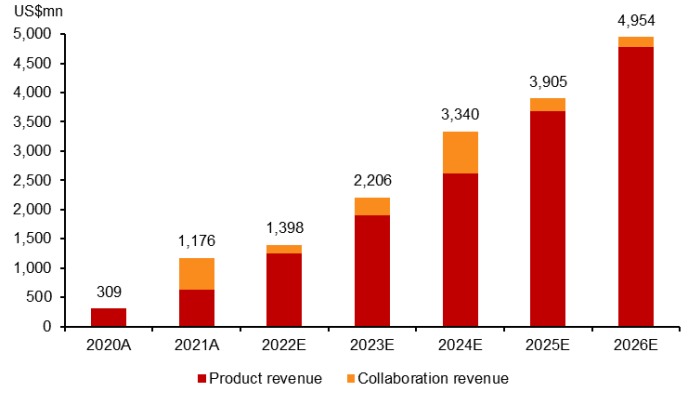
Source: Company data, CMBIGM estimates

Figure 96: Revenue breakdown



Source: Company data, CMBIS estimates

Figure 97: Risk-adjusted revenue forecasts



Source: Company data, CMBIS estimates

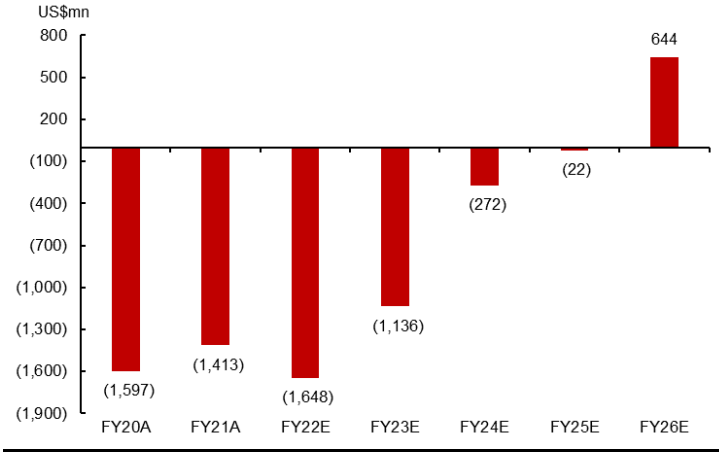
BeiGene recorded net losses of US$1,597mn/ US$1,413mn in FY20A/ 21A. We expect the Company to continue to incur net losses of US$1,648mn / US$1,136mn/ US$272mn in FY22E/ 23E/ 24E, and to turn profitable in FY26E.

Figure 98: P&L forecasts

YE Dec 31 (US$ mn)	FY19A	FY20A	FY21A	FY22E	FY23E	FY24E	FY25E	FY26E
Revenue	**428**	**309**	**1,176**	**1,398**	**2,206**	**3,340**	**3,905**	**4,954**
YoY		*-28%*	*281%*	*19%*	*58%*	*51%*	*17%*	*27%*
Cost of sales	(71)	(71)	(165)	(312)	(473)	(643)	(899)	(1,156)
% of revenue		*-23%*	*-14%*	*-22%*	*-21%*	*-19%*	*-23%*	*-23%*
Gross profit	**(71)**	**238**	**1,011**	**1,086**	**1,734**	**2,697**	**3,006**	**3,798**
GPM		*77%*	*86%*	*78%*	*79%*	*81%*	*77%*	*77%*
R&D expenses	(927)	(1,295)	(1,459)	(1,503)	(1,533)	(1,548)	(1,548)	(1,533)
% of revenue		*-419%*	*-124%*	*-108%*	*-69%*	*-46%*	*-40%*	*-31%*
SG&A expenses	(388)	(600)	(990)	(1,238)	(1,337)	(1,417)	(1,474)	(1,503)
% of revenue		*-194%*	*-84%*	*-89%*	*-61%*	*-42%*	*-38%*	*-30%*
Operating profit	**(1,388)**	**(1,658)**	**(1,439)**	**(1,656)**	**(1,137)**	**(269)**	**(17)**	**761**
% of revenue		*-537%*	*-122%*	*-118%*	*-52%*	*-8%*	*0%*	*15%*
Interest income (expense), net	9	2	(16)	(2)	(9)	(13)	(15)	(14)
Other income, net	7	37	16	10	10	10	10	10
Loss before tax	**(1,372)**	**(1,618)**	**(1,439)**	**(1,648)**	**(1,136)**	**(272)**	**(22)**	**757**
% of revenue		*-524%*	*-122%*	*-118%*	*-51%*	*-8%*	*-1%*	*15%*
Income tax benefit (expense)	(7)	18	25	0	0	0	0	(114)
Net loss	**(1,379)**	**(1,601)**	**(1,413)**	**(1,648)**	**(1,136)**	**(272)**	**(22)**	**644**
Non-controlling interests	(2)	(4)	0	0	0	0	0	0
Net loss attributable to BeiGene	**(1,377)**	**(1,597)**	**(1,413)**	**(1,648)**	**(1,136)**	**(272)**	**(22)**	**644**
NMP	*-322%*	*-517%*	*-120%*	*-118%*	*-51%*	*-8%*	*-1%*	*13%*

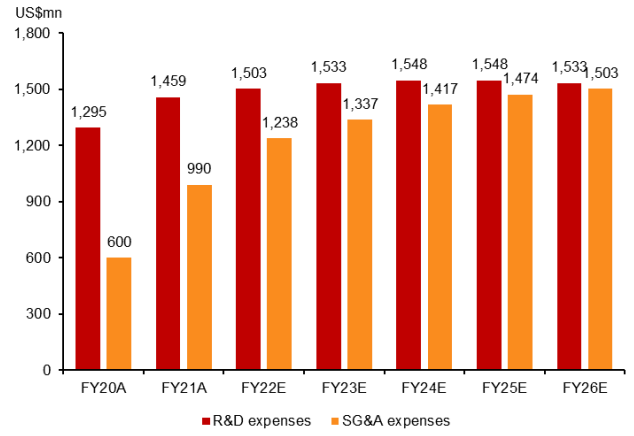
Source: Company data, CMBIGM estimates

Figure 99: Net profit forecasts



Source: Company data, CMBIGM estimates

Figure 100: Operating expenses forecasts



Source: Company data, CMBIGM estimates

Valuation

Initiate at BUY with TP of US$248.52

We derive our target price of US$248.52 based on a DCF valuation (WACC: 9.20%, terminal growth rate: 3.0%).

Figure 101: Risk-adjusted DCF valuation (terminal growth rate: 3.0%)

DCF Valuation (US$ mn)	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E
EBIT	**(1,646)**	**(1,127)**	**(259)**	**(7)**	**771**	**1,477**	**2,087**	**2,686**	**3,042**	**3,194**	**3,341**	**3,464**	**3,511**	**3,606**
Tax rate	*0%*	*0%*	*0%*	*0%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
EBIT*(1-tax rate)	(1,646)	(1,127)	(259)	(7)	656	1,255	1,774	2,283	2,586	2,715	2,840	2,944	2,985	3,065
+ D&A	67	70	72	74	76	78	79	81	82	84	85	86	87	88
- Change in working capital	275	(94)	(97)	(146)	(142)	(97)	(84)	(67)	(22)	14	19	25	38	31
- Capex	(320)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)
FCFF	**(1,623)**	**(1,251)**	**(384)**	**(179)**	**489**	**1,136**	**1,669**	**2,197**	**2,546**	**2,713**	**2,844**	**2,956**	**3,010**	**3,084**
Terminal value														**51,259**
FCF + Terminal value	**(1,623)**	**(1,251)**	**(384)**	**(179)**	**489**	**1,136**	**1,669**	**2,197**	**2,546**	**2,713**	**2,844**	**2,956**	**3,010**	**54,343**

PV of enterprise (US$ mn)	21,218
Net debt (US$ mn)	(4,370)
Equity value (US$ mn)	**25,588**
No. of ADS (mn)	103
DCF per ADS (US$)	**248.52**

Terminal growth rate	**3.0%**
WACC	**9.20%**
Cost of Equity	11.5%
Cost of Debt	4.5%
Equity Beta	0.9
Risk Free Rate	2.5%
Market Risk Premium	10.0%
Target Debt to Asset ratio	30.0%
Effective Corporate Tax Rate	15.0%

Source: CMBIGM estimates

Figure 102: Sensitivity analysis (US$)

			WACC		
Terminal growth rate	**8.20%**	**8.70%**	**9.20%**	**9.70%**	**10.20%**
4.0%	357.72	313.56	278.15	249.17	225.07
3.5%	330.44	292.81	262.03	236.44	214.86
3.0%	308.41	275.71	**248.52**	225.60	206.06
2.5%	290.25	261.36	237.02	216.28	198.41
2.0%	275.02	249.16	227.12	208.16	191.70

Source: CMBIGM estimates

Financial Statements

Income statement

YE 31 Dec (US$ mn)	FY20A	FY21A	FY22E	FY23E	FY24E
Revenue	**309**	**1,176**	**1,398**	**2,206**	**3,340**
Cost of sales	(71)	(165)	(312)	(473)	(643)
Gross profit	**238**	**1,011**	**1,086**	**1,734**	**2,697**
R&D expenses	(1,295)	(1,459)	(1,503)	(1,533)	(1,548)
SG&A expenses	(600)	(990)	(1,238)	(1,337)	(1,417)
Operating profit	**(1,658)**	**(1,439)**	**(1,656)**	**(1,137)**	**(269)**
Interest income (expense), net	2	(16)	(2)	(9)	(13)
Other income, net	37	16	10	10	10
Loss before tax	**(1,618)**	**(1,439)**	**(1,648)**	**(1,136)**	**(272)**
Income tax benefit (expense)	18	25	0	0	0
Net loss	**(1,601)**	**(1,413)**	**(1,648)**	**(1,136)**	**(272)**
Non-controlling interests	(4)	0	0	0	0
Net loss attributable to BeiGene	**(1,597)**	**(1,413)**	**(1,648)**	**(1,136)**	**(272)**

Cash flow summary

YE 31 Dec (US$ mn)	FY20A	FY21A	FY22E	FY23E	FY24E
Net loss	**(1,601)**	**(1,413)**	**(1,648)**	**(1,136)**	**(272)**
Depreciation and amortization	**32**	**46**	**67**	**70**	**72**
Change in working capital	151	(118)	275	(94)	(97)
Others	135	187	0	0	0
Net cash from operating	**(1,283)**	**(1,299)**	**(1,305)**	**(1,160)**	**(298)**
PP&E	(118)	(263)	(320)	(100)	(100)
Purchases of investments	(5,690)	(2,191)	0	0	0
Proceeds from disposal of available-for-sale securities	2,751	3,147	0	0	1,000
Other investing activities	(112)	(52)	0	0	0
Net cash from investing	**(3,168)**	**641**	**(320)**	**(100)**	**900**
Net proceeds from shares	4,232	3,443	0	0	0
Net bank borrowing	290	102	0	0	0
Proceeds from option exercises	93	93	0	0	0
Other financing activities	588	0	0	0	0
Net cash from financing	**5,203**	**3,637**	**0**	**0**	**0**
FX changes	18	14	0	0	0
Net change in cash	**769**	**2,993**	**(1,625)**	**(1,260)**	**602**
Cash at the beginning of the	621	1,390	4,383	2,758	1,498
Cash at the end of the year	**1,390**	**4,383**	**2,758**	**1,498**	**2,100**

Balance sheet

YE 31 Dec (US$ mn)	FY20A	FY21A	FY22E	FY23E	FY24E
Cash and cash equivalences	1,382	4,376	2,758	1,498	2,100
Short-term investments	3,269	2,242	2,242	2,242	1,242
Accounts receivable	60	483	274	418	573
Inventories	89	243	256	382	511
Prepaid expenses and other current	160	270	270	270	270
Total current assets	**4,961**	**7,614**	**5,800**	**4,810**	**4,696**
Properties and equipment, net	358	588	840	871	899
Other non-current assets	282	444	438	438	438
Total non-current assets	**640**	**1,032**	**1,278**	**1,308**	**1,336**
Accounts payable	232	262	342	518	704
Accrued expenses and other payables	346	558	558	558	558
Short-term debt	335	428	428	428	428
Other current liabilities	162	352	352	352	352
Total current liabilities	**1,075**	**1,600**	**1,679**	**1,855**	**2,042**
Long-term bank loan	184	202	202	202	202
Operating lease liabilities	29	43	43	43	43
R&D cost share liability	375	270	270	270	270
Other long-term liabilities	68	289	289	289	289
Total non-current liabilities	**656**	**803**	**803**	**803**	**803**
Additional paid-in capital	7,415	11,191	11,191	11,191	11,191
Accumulated deficit	(3,553)	(4,966)	(6,614)	(7,750)	(8,022)
Total BeiGene shareholders' equity	**3,869**	**6,243**	**4,595**	**3,459**	**3,187**
Non-controlling interest	0	0	0	0	0
Total equity	**3,869**	**6,243**	**4,595**	**3,459**	**3,187**

Key ratios

YE 31 Dec	FY20A	FY21A	FY22E	FY23E	FY24E
Profit & loss ratios (%)					
Gross margin	77	86	78	79	81
EBITDA margin	(514)	(117)	(113)	(48)	(6)
Net margin	(517)	(120)	(118)	(51)	(8)
Effective tax rate	0	0	0	0	0
Balance sheet ratios					
Current ratio (x)	4.6	4.8	3.5	2.6	2.3
Inventory turnover days	304	367	300	295	290
Trade receivables turnover days	78	84	80	80	80
Trade payables turnover days	915	547	400	400	400
Total debt to asset ratio (%)	31	28	35	43	47
Returns (%)					
ROE	(41)	(23)	(36)	(33)	(9)
ROA	(29)	(16)	(23)	(19)	(5)
Per share data					
EPS (US$)	(22.9)	(19.1)	(15.2)	(16.0)	(11.0)
DPS (US$)	0.00	0.00	0.00	0.00	0.00
BVPS (US$)	3.57	5.18	3.43	2.58	2.38

Source: Company data, CMBIGM estimates

Investment Risks

1) Failure of clinical development or regulatory approvals of drug candidates.

2) Intense competition of approved products both in China and overseas markets.

Appendix: Company Profile

Figure 103: Major shareholders (as of 31 Mar 2022)

Shareholder	% of stake
Amgen Inc	18.45%
Baker Bros Advisors LP	11.42%
HHLR Advisor Ltd	11.02%
Capital Research and Management Company	8.01%
John Olyer	5.45%
Xiaodong Wang	1.58%

Source: Company financial report, CMBIGM

Figure 104: Management profile

Name	Age	Position
Mr. John V. Oyler	54	Executive Director, Chairman and Chief Executive Officer
Dr. Xiaodong Wang	59	Non-executive Director
Mr. Anthony C. Hooper	67	Non-executive Director
Xiaobin Wu, Ph.D.	60	President, Chief Operating Officer and General Manager of China
Julia Wang	51	Chief Financial Officer
Lai Wang, Ph.D.	45	Global Head of R&D

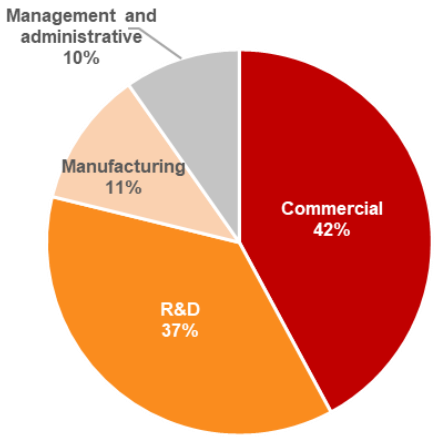
Source: Company data, CMBIGM

Figure 105: Employee structure

Function	# of staff	% of Total
Manufacturing	918	11%
Commercial	3,383	42%
R&D	2,949	37%
Management and administrative	783	10%
Total	**8,033**	**100%**

Source: Company annual report (as of 31 Dec 2021), CMBIGM

Figure 106: Employee number breakdown



Source: Company annual report (as of 31 Dec 2021), CMBIGM

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