Hong Kong

ADD *(initiation)*

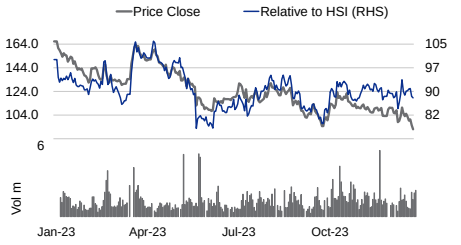
Consensus ratings*: Buy 19 Hold 2 Sell 0

Current price:	HK$91.95
Target price:	HK$169.7
Previous target:	*HK$*
Up/downside:	84.5%
CGI / Consensus:	-2.0%
Reuters:	6160.HK
Bloomberg:	6160 HK
Market cap:	US$16,565m
	HK$129,488m
Average daily turnover:	US$21.53m
	HK$168.2m
Current shares o/s:	1,341m
Free float:	60.6%

*Source: Bloomberg

Key changes in this note

N/A



Source: Bloomberg

Price performance	1M	3M	12M
Absolute (%)	-10.9	-2.9	-44.7
Relative (%)	-2.4	10	-12.6

Major shareholders	% held
Amgen	17.9
Baker Brothers Life Sciences	11.1
HHLR Fund	10.4

Analyst

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BeiGene Ltd

Leading domestic biopharmaceutical company

- We think BeiGene's near-term revenue growth momentum is supported by sales ramp-up for Brukinsa and tislelizumab, and future new indication approvals globally.
- Meanwhile, its long-term prospects are underlined by its deep innovative pipeline with multiple potential blockbuster candidates and global marketing capability, in our view.
- We forecast FY23F/24F/25F revenue growth of 70%/23%/29% and we think BeiGene could reach net profit breakeven in 2026F.
- Initiate coverage with an Add rating and TP of HK$169.7, using a DCF-based valuation method (WACC: 9.8%, terminal growth rate: 3%).

Emerging leader in haematology

Thanks to its superior efficacy and reduced cardiotoxicity vs. Ibrutinib, which is developed by Abbvie (ABBV. US, NR, CP: US$162.4) and is the biggest competitor for zanbrutinib, according to ALPINE clinical results in 2021, BeiGene's zanubrutinib (sold under the brand name Brukinsa) has received approvals in over 65 markets for the treatment of various types of lymphomas; we believe the drug is a strong FY24F revenue growth catalyst for BeiGene. BeiGene also manufactures a BCL-2 inhibitor candidate, called sonrotoclax, and BTK CDAC, a chimeric degradation activation compound, which could overcome acquired resistance observed with BTK inhibitors. With the efficacy synergy between zanubrutinib, sonrotoclax and BTK CDAC, we think BeiGene will emerge as a haematology industry leader and gain market share in the haematology treatment market globally.

Building up a solid tumour drug pipeline

BeiGene is developing a comprehensive tumour drug portfolio centred around tislelizumab, an anti-PD-1 antibody. Tislelizumab has obtained approvals in China for 12 indications. In Dec 2023, it was approved by the European Commission (EC) for esophageal squamous cell carcinoma (ESCC) treatment and is pending approval in the US for ESCC; Tislelizumab will drive BeiGene's overseas market revenue growth, in our view. We also believe tislelizumab shows promise as a valuable combination therapy partner in pan-tumour immune-oncology. BeiGene has a range of innovative candidates, including mono antibodies, bispecific antibodies and antibody-drug conjugates, that can combine with tislelizumab for enhanced efficacy. We believe future approval of these candidates will support BeiGene's long-term prospects.

Competitive advantages

We think BeiGene's competitive advantages are: a) ability to run global multi-centre clinical trials to support global marketing approvals; b) large commercial teams in China and overseas to promote its medications, and c) a deep and innovative oncology R&D pipeline with multiple blockbuster candidates.

Initiate coverage with an Add rating, TP of HK$169.7

We initiate coverage on BeiGene with an Add rating due to its solid revenue growth momentum. Our TP is derived using a DCF-based valuation (WACC: 9.8%, terminal growth rate: 3%). Near-term catalysts include new indications for zanubritinib and overseas approval of tislelizumab. Its long-term growth momentum could be driven by the continued delivery of innovative medications and global market expansion. We forecast 70%/23%/29% revenue growth for FY23F/24F/25F, with net loss of US$904m/US$853m/US$219m. We think BeiGene will break even in 2026F. As at 18 Jan, the P/S of BeiGene's A share (688235.CH), H share (6160.HK) and US share (BGNE.US) stood at 18.2x, 7.9x and 7.8x, respectively. Therefore, we think its H share and US share are cheaper than its A share. Downside risks: 1) new drug R&D may fail, which may hurt revenue growth; 2) failure to obtain marketing approvals, impacting revenue; and 3) intense competition.

Financial Summary	Dec-21A	Dec-22A	Dec-23F	Dec-24F	Dec-25F
Revenue (US$m)	1,176	1,416	2,414	2,958	3,814
Operating EBITDA (US$m)	(1,314)	(1,618)	(999)	(620)	26
Net Profit (US$m)	(1,413)	(2,004)	(904)	(853)	(219)
Normalised EPS (US$)	(1.17)	(1.49)	(0.66)	(0.63)	(0.16)
Normalised EPS Growth	(20.6%)	27.6%	(55.5%)	(5.6%)	(74.4%)
FD Normalised P/E (x)	NA	NA	NA	NA	NA
DPS (US$)	-	-	-	-	-
Dividend Yield	0%	0%	0%	0%	0%
EV/EBITDA (x)	NA	NA	NA	NA	545.9
P/FCFE (x)	NA	NA	NA	NA	NA
Net Gearing	(103%)	(99%)	(79%)	(66%)	(61%)
P/BV (x)	2.27	3.60	4.23	4.95	4.83
ROE	(28.0%)	(37.7%)	(22.1%)	(24.3%)	(6.7%)
CGI/consensus EPS (x)			0.99	0.95	0.42
% Change In Normalised EPS Estimates					
Normalised EPS/consensus EPS (x)			0.99	0.95	0.42

SOURCES: CGIS RESEARCH, COMPANY DATA, BLOOMBERG

Leading domestic biopharmaceutical company

Investment highlight

Emerging leader in haematology

With the approval of multiple indications for zanbrutinib globally and given its several promising candidates for treatment of haematological malignancies, we think BeiGene is emerging as one of the leading players in the global field of haematology. One of its most notable achievements is the approval of zanbrutinib in numerous countries for various indications, including relapsed or refractory (R/R) mantle cell lymphoma (MCL), Waldenström's macroglobulinemia (WM), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and relapsed or refractory (R/R) follicular lymphoma (FL). The R/R FL indication was approved by the European Commission (EC) in Nov 2023, making zanbrutinib the only approved Bruton's Tyrosine Kinase (BTK) inhibitor (BTKi) for this indication.

Zanbrutinib (sold under the brand name Brukinsa) has shown promising results in phase 3 head-to-head clinical trials, outperforming ibrutinib (sold under the brand name Imbruvica by AbbVie) in terms of overall response rate (ORR) and progression-free survival (PFS) in CLL/SLL patients, according to the result of the head-to-head clinical trial ALPINE. For WM patients, zanbrutinib has demonstrated a consistent trend of deeper and more durable responses compared with ibrutinib. This positive clinical data has contributed to significant revenue growth for zanbrutinib, which reached US$877m in 9M23 (+126% yoy).

We think revenue growth momentum for zanbrutinib will continue in FY24F, driven by a ramp-up of approvals for the drug both in China and international markets, particularly the US market. BeiGene has also submitted a supplemental New Drug Application (sNDA) for zanbrutinib for the treatment of FL to the US Food and Drug Administration (FDA) and ongoing trials are evaluating its efficacy in diffusing large B-cell lymphoma (DLBCL). Potential approvals for FL and DLBCL indications could serve as FY25F-FY26F revenue growth drivers, in our view. We think Brukinsa has the potential to capture market share from ibrutinib, made by AbbVie (ABBV. US, NR, CP: US$162.4) and Johnson & Johnson (JNJ. US, NR, CP: US$161.2), which together generated global sales of US$8bn in 2022, according to Abbvie and Johnson & Johnson's annual reports.

In addition to zanbrutinib, BeiGene has other promising candidates in its haematology portfolio. Sonrotoclax, a B-cell lymphoma 2 (BCL2) inhibitor, is one of the most clinically advanced BCL2 inhibitor candidates currently available, in our view, with expected approval in 2025F, in our opinion. BeiGene has initiated a phase 3 trial in treatment-naïve (TN) CLL, with combination therapy of sonrotoclax and Brukinsa. Additionally, BeiGene has two phase 2 chinical trials underway for the treatment of MCL and WM, and has registered trials for the development of therapies in acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and multiple myeloma (MM). Venclexta (venetoclax), the world's first BCL-2 inhibitor, developed by AbbVie, was approved by the US FDA in 2016. Its global annual sales reached US$2bn in 2022. Hence, we think the approval of sonrotoclax would create a new revenue growth catalyst for BeiGene.

BeiGene has also developed a BTK chimeric degradation activation compound (CDAC) to address the issue of acquired resistance observed with first-generation BTK inhibitors. BTK-CDAC is lined up to be evaluated in phase 3 studies for MCL and CLL, according to BeiGene. We think it has the potential to become a backbone treatment for patients who developed resistance after using BTK inhibitors for some time, and also has the potential to be approved as an earlier line of therapy for lymphomas.

We believe the potential efficacy synergy between Brukinsa (zanbrutinib), sonrotoclax and BTK-CDAC brightens BeiGene's prospects considerably in the

field of haematology. In our view, the haematological medication revenue of BeiGene is driven a) in FY24F by the ramp-up of zanbrutinib for approved indications globally; b) by additional approval for FL and DLBCL indications for zanbrutinib globally in FY25F-26F; and c) the approval of sonrotoclax and BTK-CDAC beyond FY26F.

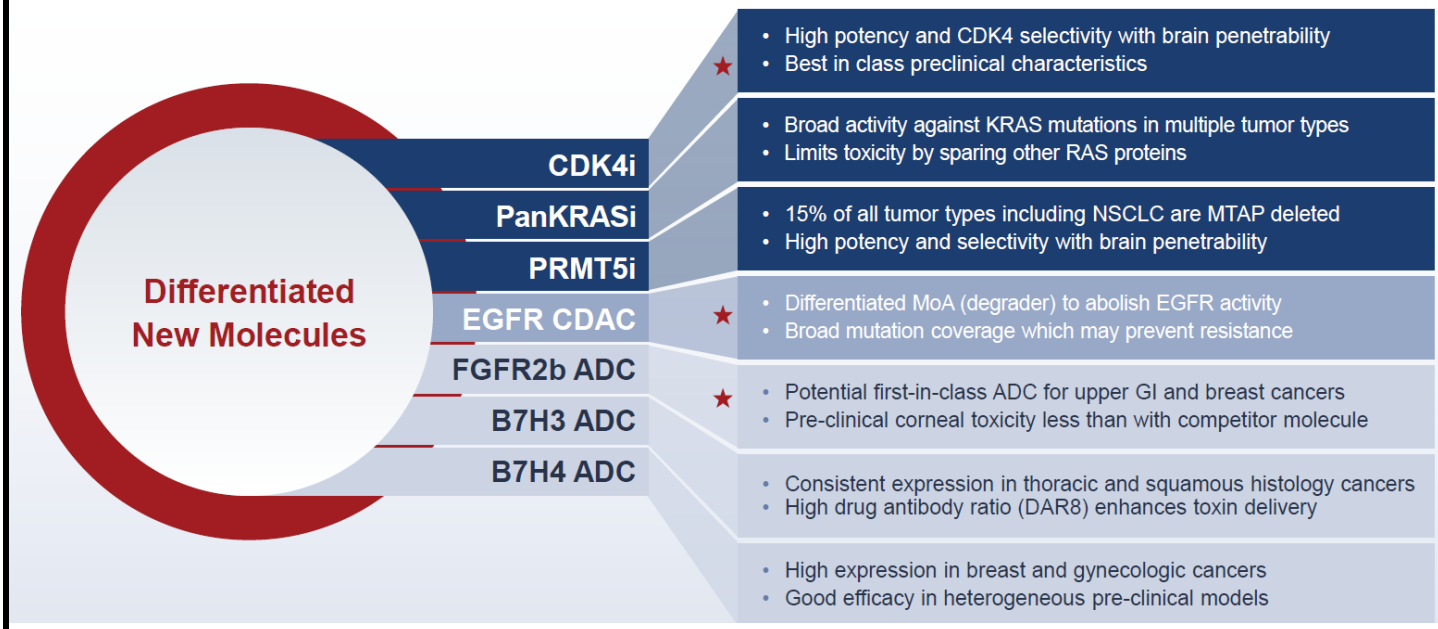
Building up a solid tumour therapy pipeline

According to the company, BeiGene is also building a comprehensive solid tumour portfolio centred around tislelizumab, an anti-PD-1 antibody marketed under the brand Tevimbra. Tevimbra has already received approvals in China and the European Union (EU), with pending approval in the US. In China, Tevimbra has been approved for 12 indications since 2019, nine of which have been included in the National Reimbursement Drug List (NRDL). The multiple indication approvals in China and the inclusion in the NRDL significantly contributed to tislelizumab's sales growth, which reached US$409m (+27% yoy) in 9M23.

Furthermore, the recent approval of tislelizumab by the EC in Sep 2023 for esophageal squamous cell carcinoma (ESCC) patients, along with its pending approval in the US for first-line (1L) treatment in ESCC with target action date in 2H24F, serves as a new near-term sales growth driver in 2024F and 2025F, in our view.

In the long term, Tevimbra holds promise as a valuable combination therapy partner for pan-tumour immuno-oncology, in our view. BeiGene has a robust pipeline of immunotherapies and antibody-drug conjugate (ADC) candidates that can synergise with tislelizumab in multiple solid tumour indications. Several promising candidates for the treatment of pan-solid tumour have the potential to become blockbuster drugs, in our view. We think BeiGene's deep and innovative pipeline will be the cornerstone for its long-term growth in the field of solid tumour therapy, with its pipeline of new drugs becoming new revenue growth drivers upon approvals.

Figure 1: BeiGene's solid tumour therapy portfolio



CDK4i: Cyclin Kinase 4 Inhibitor, KRASi: Kirsten rat sarcoma virus inhibitor, PRMT5i: Protein arginine methyltransferase 5, EGFR: Epidermal growth factor receptor, CDAC: Chimeric degradation activating compound, FGFR2b: Fibroblast growth factor receptor 2b, ADC: Antibody drug conjugate, MoA: Mechanism of action, RAS: Guanosine-nucleotide-binding protein, NSCLC: Non-small cell lung cancer, MTAP: Methylthioadenosine phosphorylase

SOURCES: CGIS RESEARCH, COMPANY DATA

Robust market expansion in overseas market

In 9M23, BeiGene's US revenue was US$816m (+135% yoy) while its China revenue was US$831m (+31% yoy). US revenue accounted for 45% of total 9M23 revenue while China accounted for 46%. The market acceptance of Brukinsa has helped drive product revenue growth, resulting in a diversified geographic and

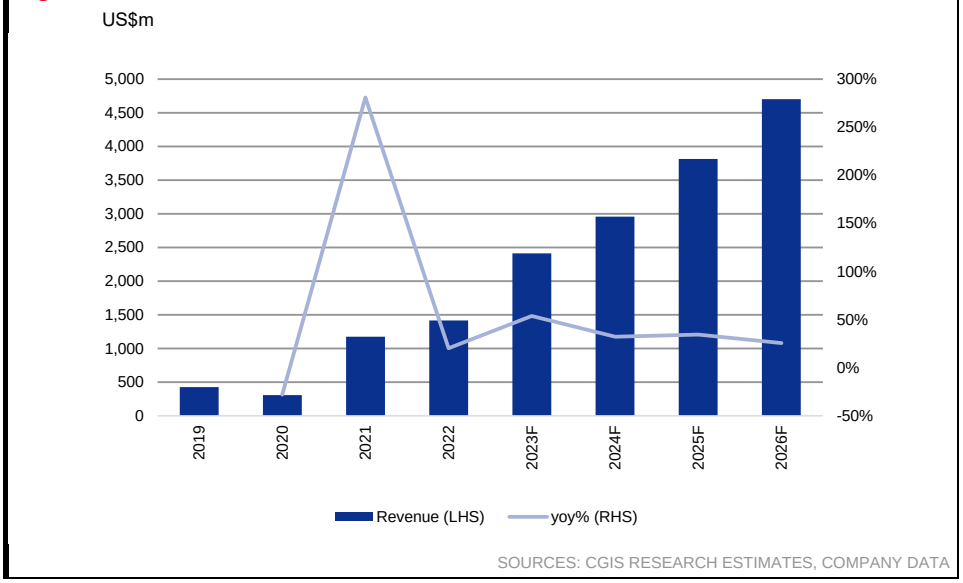
product mix, and establishing BeiGene as an international bio-pharmaceutical company, in our view. This global market expansion has been supported by: a) the company's ability to run global multi-centre clinical trials to support global marketing approval, thanks to its over-3,000 clinical development employees in 48 regions; and b) over 3,500 commercial team members in China and overseas.

Financial analysis and forecasts

Robust revenue growth led by jump in Brukinsa's sales

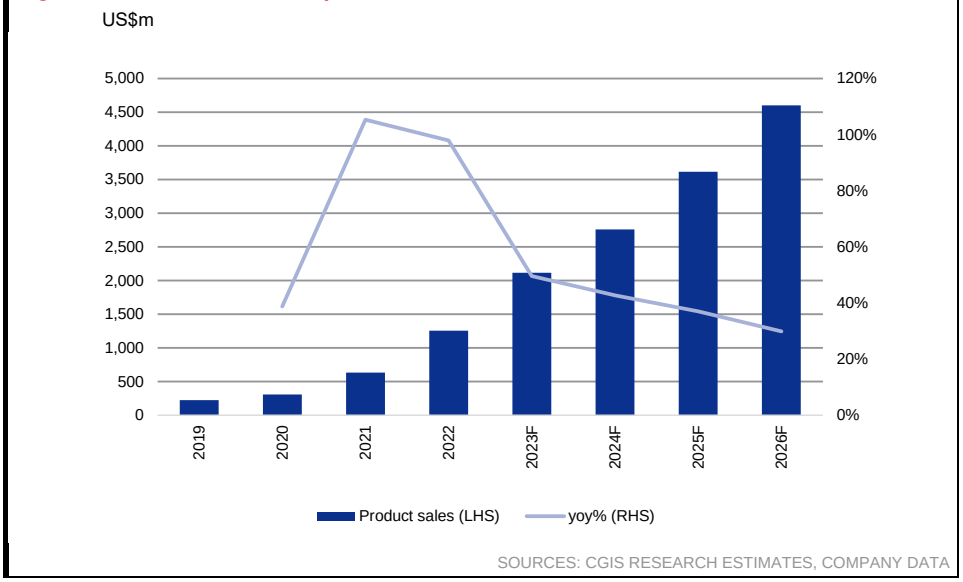
BeiGene's revenue can be divided into two major parts: product sales and collaboration revenue. 9M23 revenue amounted to US$1,824m (+76% yoy), with product sales of US$1,559m (+70% yoy) accounting for 85% of total revenue. Its 3-year total revenue CAGR for FY19-22 was 49% and 3-year FY19-22 product sales CAGR was 78%. The revenue growth was led by zanubrutinib (Brukinsa) and tislelizumab.

Figure 2: BeiGene's historical revenue and forecasts



SOURCES: CGIS RESEARCH ESTIMATES, COMPANY DATA

Figure 3: BeiGene historical product sales and forecasts



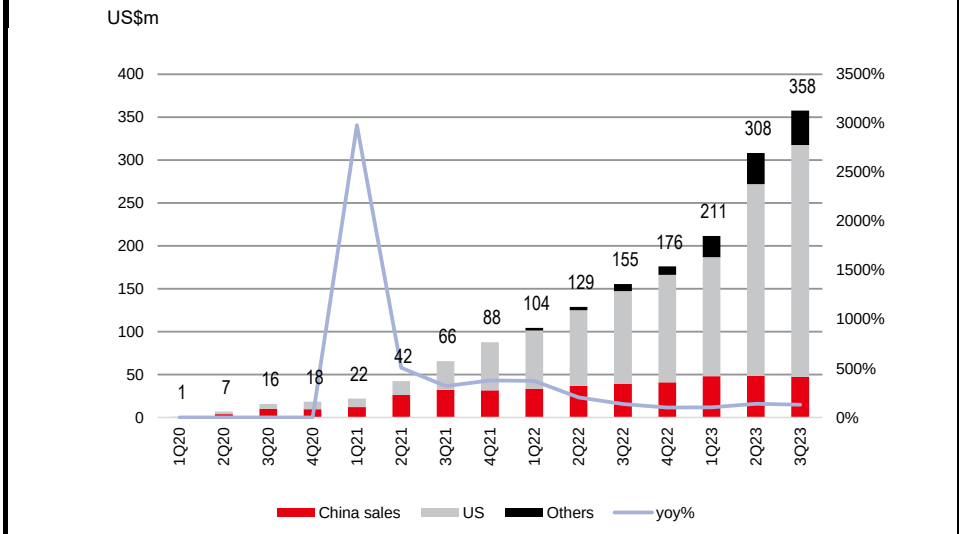
SOURCES: CGIS RESEARCH ESTIMATES, COMPANY DATA

We forecast 70%/23%/29% yoy revenue growth in FY23F/24F/25F as we expect product sales to grow steadily, driven by the visible growth outlook for Brukinsa and tislelizumab.

Brukinsa sales remain growth driver

One of the key drivers of BeiGene's product sales in the past few years has been zanubrutinib, sold under the brandname of Brukinsa. Since it was first approved in Nov 2019, zanubrutinib has experienced robust sales growth, especially in the overseas markets. Sales of zanubrutinib came in at US$877m in 9M23 (+126% yoy), with US leading the charge. The two-year CAGR for zanubrutinib sales in FY20-FY22 was 268%; the drug's 2-year CAGR for US sales was 363% and that for China was 153%.

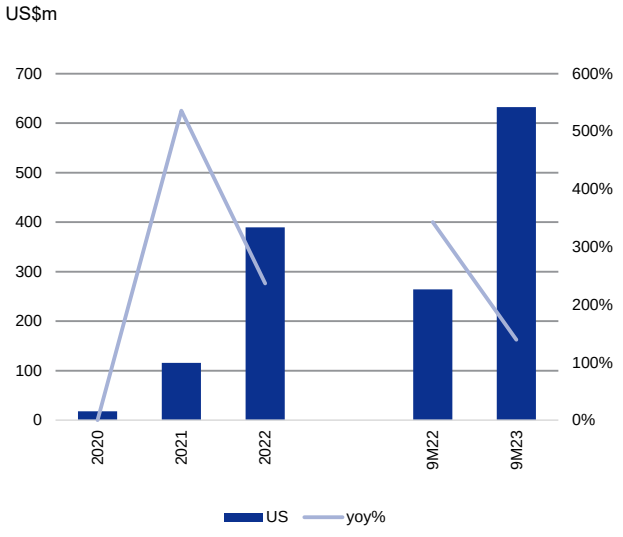
Figure 4: Historical sales of zanubrutinib (LHS) and its yoy growth (RHS)



SOURCES: CGIS RESEARCH, COMPANY DATA

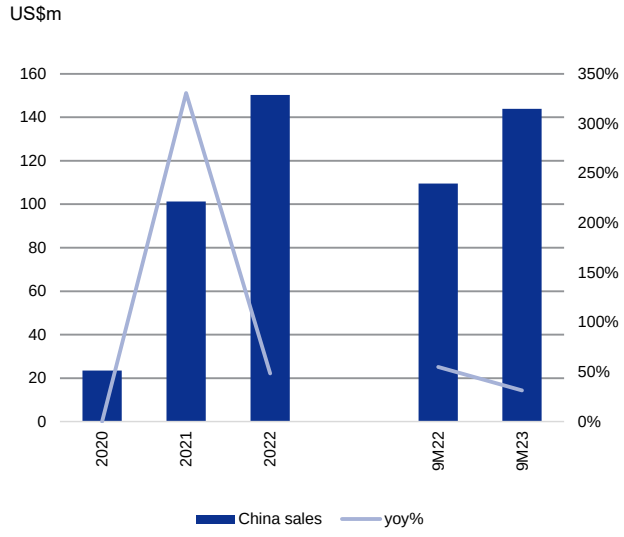
9M23 US sales of zanubrutinib were US$632m (+139% yoy), accounting for 72% of its total 9M23 sales, while that from China amounted to US$144m (+31% yoy), accounting for 16% of total sales. We believe the drug's robust growth can be attributed to market share gains across both treatment-naïve (TN) and R/R adult patients with CLL/SLL as well as expanding adoption for other FDA-approved indications. 9M23 zanubrutinib revenue accounted for 48% of the total revenue.

Figure 5: Historical US sales of zanubrutinib (LHS) and its yoy growth (RHS)



SOURCES: CGIS RESEARCH, COMPANY DATA

Figure 6: Historical China sales of zanubrutinib (LHS) and its yoy growth (RHS)

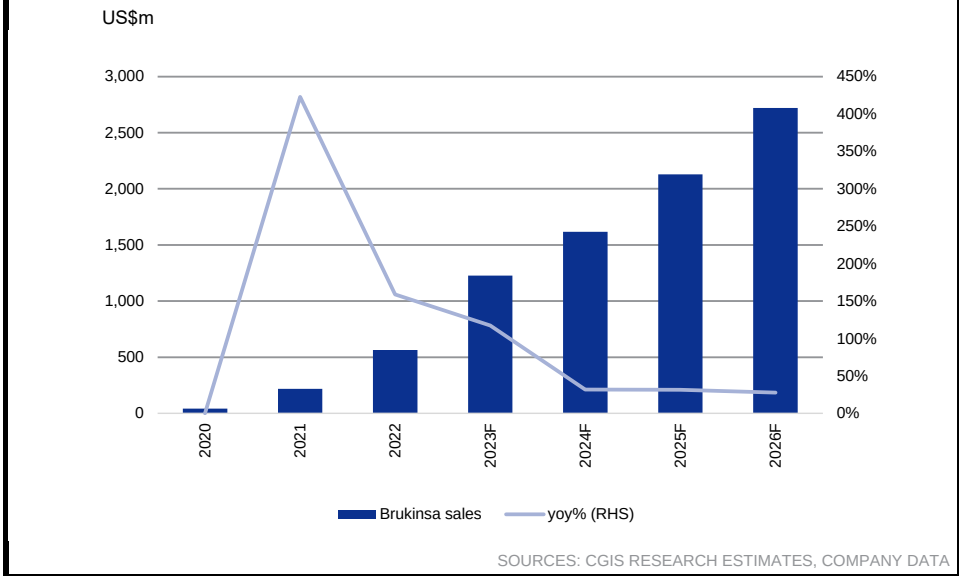


SOURCES: CGIS RESEARCH, COMPANY DATA

Currently, Brukinsa has been approved for multiple indications: R/R MCL, TN or R/R WM, MZL, and CLL/SLL. The EC granted marketing authorisation for Brukinsa in R/R FL in Nov 2023 while the US FDA has accepted an sNDA for R/R FL. In addition, BeiGene has launched clinical trials for Brukinsa for treatment of

DLBCL. Therefore, we think Brukinsa's future growth drivers include: a) sales ramp-up in already-approved indications, b) future approval for FL indications, and c) clinical results read-outs of DLBCL which should lead to its marketing approval. We forecast yoy sales growth of 117%/32%/32% for Brukinsa in FY23F/24F/25F with sales proportion of the drug growing from 40% in FY22 to approximately 58% of the total 2023F revenue.

Figure 7: Historical and forecast sales of zanubrutinib

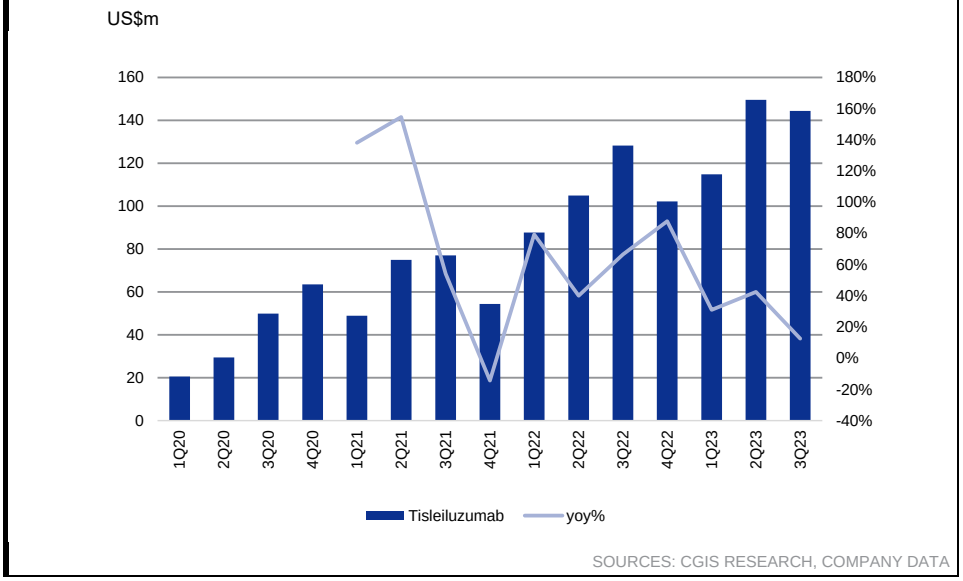


SOURCES: CGIS RESEARCH ESTIMATES, COMPANY DATA

Stable growth of tislelizumab

Sales of tislelizumab in China amounted to US$409m (+27% yoy) in 9M23, contributed by new patient demand from new indications and increased market penetration. In 9M23, tislelizemab sales accounted for 22% of total revenue, with two-year sales CAGR in FY20-22 of 61%.

Figure 8: Historical sales of tislelizumab (LHS) and its yoy growth (RHS)



SOURCES: CGIS RESEARCH, COMPANY DATA

China has approved the use of tislelizumab for 12 indications since 2019; nine of them were included in the NRDL as at the end of 2023. We think domestic sales of tislelizumab will remain steady in 2024F and 2025F on the back of BeiGene's marketing activities to promote the drug in China and the inclusion of tislelizumab in the NRDL, which makes it more affordable and accessible. Furthermore, we believe sales will ramp up in overseas markets; in Sep 2023, the EC approved tislelizumab for ESCC patients while the US FDA has accepted for review a biologics license application (BLA) for tislelizumab as a first-line treatment for

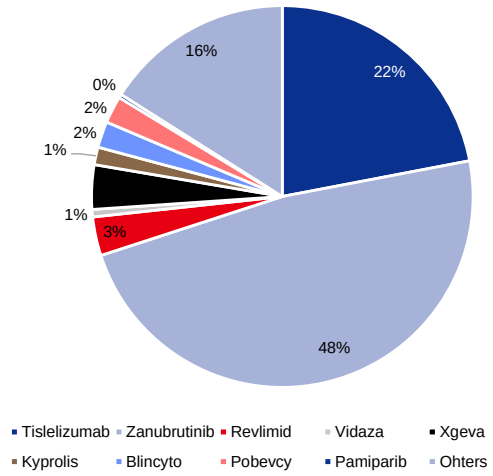
patients with unresectable, recurrent, locally advanced, or metastatic ESCC. We forecast yoy sales growth for tislelizumab at 45%/30%/20% in FY23F/24F/25F, with FY23F sales of the drug accounting for approximately 22% of total revenue.

Stable growth of other revenue contributors

BeiGene has collaborated with a) Amgen (AMGN.US, NR, CP:US$306.5) since 2019 to commercialise Amgen's Xgeva, Blincyto and Kyprolis drugs in China; b) Bio-Thera (688177.CH, NR, CP: Rmb38.3) since 2020 for the commercialisation of Pobevcy, and is c) on a licensing deal with Bristol Myers Squibb (BMS)-Celgene (BMY.US, NR, CP: US$50.3) for Revlimid and Vidaza since 2017. BeiGene and BMS mutually agreed to terminate their collaboration in Dec 2023. BeiGene has the right to continue to sell all its BMS inventory till 31 Dec 2024 or until the inventory is sold out, whichever comes earlier. BeiGene's 9M23 sales of Xgeva, Blincyto and Kyprolis totalled US$136m (+58% yoy) while its 9M23 sales of Pobevcy were US$42m (+41% yoy). Its 9M23 sales of Revlimd and Vidaza slipped 2% yoy to US$71m due to the termination of the collaboration with BMS.

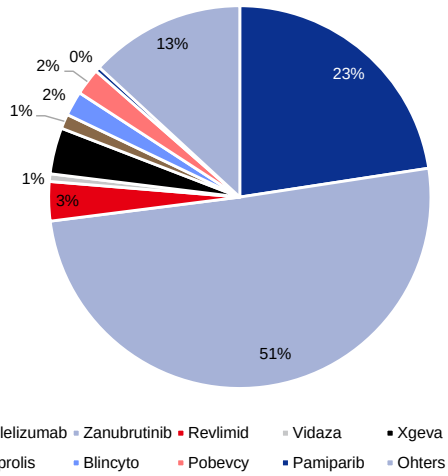
We think BeiGene's sales of the Xgeva, Blincyto, Kyprolis and Pobevcy will maintain steady growth in 2024F and 2025F but, with the termination of the collaboration between BeiGene and BMS, sales of Revlimid and Vidaza should gradually decrease.

Figure 9: 9M23 revenue breakdown by type of drug



SOURCES: CGIS RESEARCH, COMPANY DATA

Figure 10: 2023F revenue breakdown by type of drug



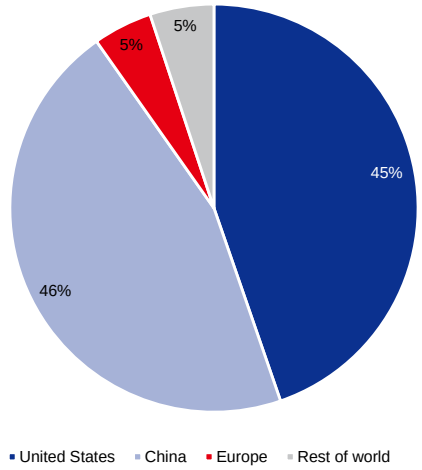
SOURCES: CGIS RESEARCH, COMPANY DATA

BeiGene's 9M23 collaboration revenue was US$265m (+120% yoy). We believe the yoy jump was mainly contributed by the recognition of the deferred revenue from the collaboration agreements with Novartis (NOVN.US, NR, CP: US$94.4) for tisleizumab and ociperlimab. Please refer to "Collaborative and licensing arrangement-Novartis" on Page 50 for details of this arrangement.

Overseas markets: a key growth driver

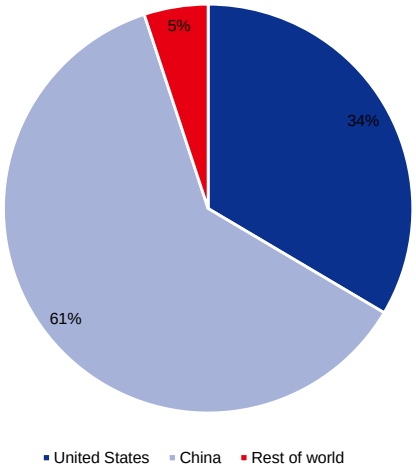
In 9M23, BeiGene's US revenue came to US$816m (+135% yoy) while its China revenue amounted to US$831m (+31% yoy). US revenue accounted for 45% of total 9M23 revenue while China made up 46% (vs. 34% and 61%, respectively, in 9M22). We think the momentum in overseas markets should remain high in FY24F, driven by increased sales for Brukinsa and tislelizumab.

Figure 11: BeiGene's 9M23 revenue breakdown by region (US$ m)



SOURCES: CGIS RESEARCH, COMPANY DATA

Figure 12: BeiGene's 9M22 revenue breakdown by region (US$ m)



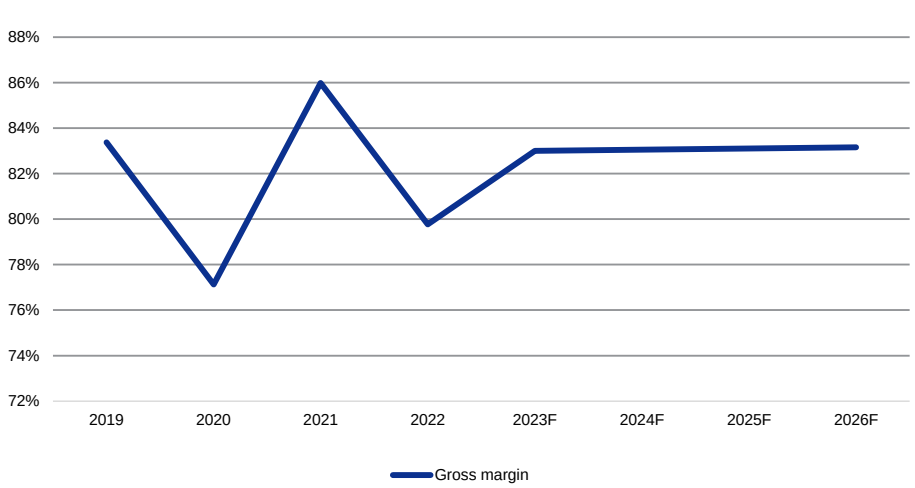
SOURCES: CGIS RESEARCH, COMPANY DATA

Steady improvement in gross profit margin

BeiGene's gross margin widened 7.4% pts yoy to 87.7% in 3Q23 (3Q22: 80.3%), primarily due to a) an increase in collaboration revenue; b) proportionally higher global sales mix of Brukinsa (46% of 3Q23 revenue) compared with other products in its portfolio and the lower-margin in-licensed products; as well as c) lower cost per unit for tislelizumab (18% of 3Q23 revenue) due to increased production volume.

Gross margin widened 5.5% pts to 85.0% in 9M23 (9M22: 79.4%). With the further expansion of sales for Brukinsa and tislelizumab, we think the product gross margin (excluding collaboration revenue) should gradually improve as in-house medications have much higher GPM than in-license products. We forecast FY23F/24F/25F gross margin of 83.0%/83.1%/83.1%.

Figure 13: The historical and forecast gross margin of BeiGene



SOURCES: CGIS RESEARCH ESTIMATES, COMPANY DATA

Enough cash to cover R&D and SG&A

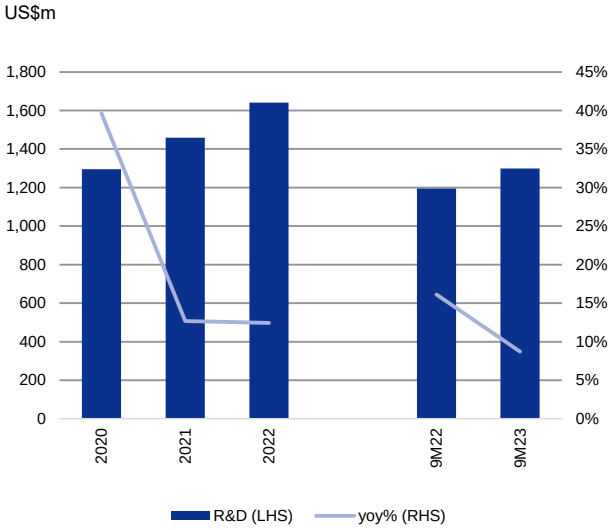
BeiGene's R&D expenses increased 9% from US$1.2bn in 9M22 to US$1.3bn in 9M23. The two-year R&D expense CAGR in FY20-22 was 13%. We think the R&D expense will stay on a mild increasing trend in the next few years as more of its drug candidates move to later clinical stages, which cost more. However, we believe BeiGene has good R&D efficiency, thanks to its large pool of scientists in China, who are paid less than in those in many other countries, and BeiGene had an R&D team of 2,300 people as at end-2022, allowing the company to run clinical

trials in-house without reliance on third-party contract research organisations (CROs).

BeiGene's SG&A expenses rose 15% yoy to US$1.1bn in 9M23. Its two-year FY20-22 SG&A expense CAGR was 46% because of the establishment of the large global commercial team for sales and distribution. As at end-2022, BeiGene had an international commercial organisation of over 3,500 employees. We think the SG&A expense should inch up in FY24F-25F, as the company is still promoting the newly-approved indications for Brukinsa and tislelizumab globally.

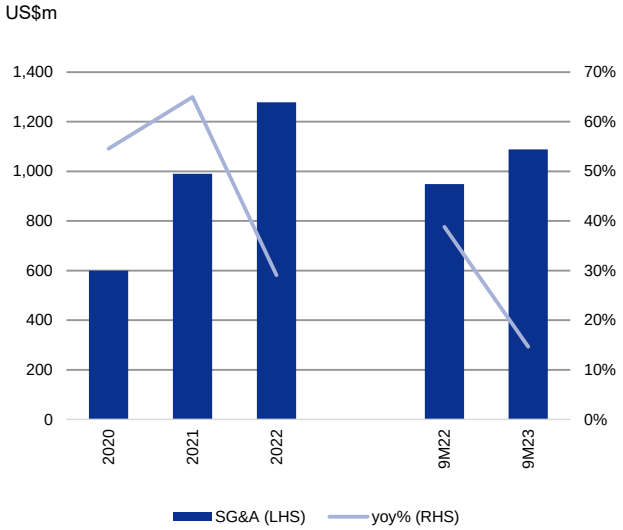
We think the revenue increase will be much larger than the increase in R&D and SG&A fees because of the strong sales outlook for Brukinsa and tisleiluzmb. Therefore, we think its operating profit margin should improve. We forecast yoy growth of R&D cost to be 7%, 3% and 3% in FY23F/24F/25F and yoy growth of SG&A cost to be 12%, 5% and 3% in FY23F/24F/25F.

Figure 14: Historical R&D expense of BeiGene and its yoy growth (%)



SOURCES: CGIS RESEARCH, COMPANY DATA

Figure 15: Historical SG&A expense of BeiGene and its yoy growth (%)



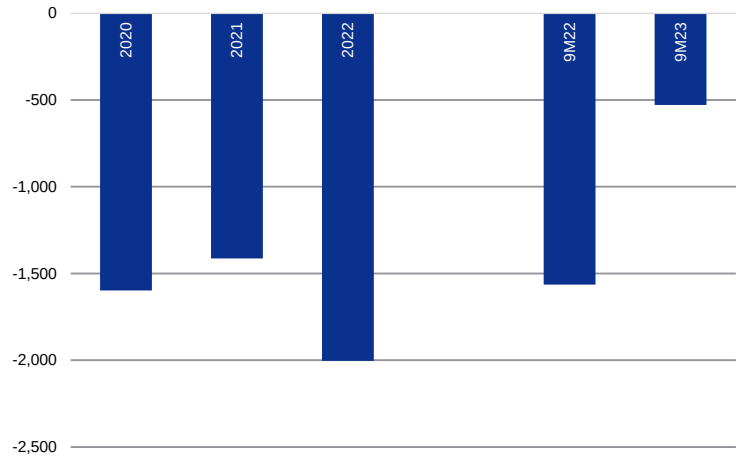
SOURCES: CGIS RESEARCH, COMPANY DATA

Narrowing net loss

BeiGene's net loss narrowed from US$1,564m in 9M22 to US$528m in 9M23. The company booked a non-operational gain of US$362.9m related to the BMS arbitration settlement in 3Q23 and the reacquisition of full global commercial rights for ociperlimab and Tevimbra from Novartis (please refer to the "Collaborative and licensing arrangements-Novartis" on Page 50 part for more details), which resulted in the recognition of the remaining deferred collaboration revenue, pushing up BeiGene's 9M23 total revenue. Nevertheless, we believe the narrowing of operating loss was mainly due to strong product sales and expense management.

We estimate net losses of US$904m/US$853m/US$219m for FY23F/24F/25F. BeiGene is cash-rich, with US$3bn cash and cash equivalents as at the end-9M23, which we believe would be more than sufficient to support the company's expenses in FY23F-FY25F.In addition, we expect the company to start to make profit beginning in 2026F on the back of a) rapid topline growth contributed by market expansion of Brukinsa and zanubrutinib, b) new approval for BGB-11417 and ociperlimab in 2025F, which will create a new revenue growth driver, and c) a higher topline growth rate than that for expenses. As BeiGene's net profit grows, the pressure to raise funds will be reduced, in our view.

Figure 16: The historical net loss of BeiGene (US$ m)



SOURCES: CGIS RESEARCH, COMPANY DATA

Valuation

We initiate coverage on BeiGene with an Add rating and a TP of HK$169.68 given its visible revenue growth momentum, driven by sales of tislelizumab and Brukinsa. We derive our target price from a DCF-based method (WACC: 9.8%, terminal growth rate: 3%). We assume a 3% terminal growth rate because of the sustained demand for oncology medication globally, especially with an ageing population. We forecast yoy revenue growth of 70%/23%/29% for FY23F/24F/25F, driven by increased sales for zanubrutinib and tislelizumab, and narrowing net losses of US$904m/US$853m/US$219m in FY23F/24F/25F. We expect BeiGene to break even in 2026F.

The P/S of BeiGene's A share (688235.CH), H share (6160.HK) and US share (BGNE.US) stood at 18.2x, 7.9x and 7.8x, respectively, as of 18 Jan 2024. Therefore, we think its H and US shares are relatively cheaper compared with its A shares.

Figure 17: DCF valuation

US$m	2023F	2024F	2025F	2026F	2027F	2028F	2029F	2030F	2031F	2032F
EBIT adjusted	(1,183.8)	(854.8)	(241.7)	394.8	1,110.7	1,738.7	2,275.0	2,650.4	2,879.6	2,988.9
Add: shared-based compensation	303.2	303.2	303.2	303.2	303.2	303.2	303.2	303.2	303.2	303.2
Less: Tax	72.4	34.2	9.7	59.2	166.6	260.8	341.3	397.6	431.9	448.3
Add: D&A	184.6	234.9	267.3	307.3	355.6	411.4	473.8	541.1	612.0	685.1
Less: Capex	362.1	295.8	190.7	235.0	284.2	328.3	367.0	396.2	416.8	430.4
less: Working capital	(159.3)	(16.2)	7.2	33.5	167.3	63.7	191.3	53.6	66.9	80.4
FCF	(1,289.9)	(662.9)	135.7	744.5	1,486.0	1,927.9	2,535.0	2,754.5	3,012.9	3,178.9
Terminal value										48,363.7
PV of FCF	(1,289.9)	(603.9)	112.6	562.9	1,023.5	1,209.7	1,449.0	1,434.3	1,429.3	22,274.8
Corporate value	27,602.3		Assumptions							
Debt & preferred stock	562.2		Risk free rate		2.5%					
Cash	3,205.2		Company Beta		1.00					
Equity value	30,245.3		Equity Risk premium		10.0%					
Divided by: # of shares outstanding	1,390.3		Cost of equity		12.5%					
NPV per share to equity shareholders US$	21.8		Pre-tax Cost of debt		4.0%					
US$/HK$	7.8		Tax rate		15.0%					
NPV per share to equity shareholders HK$	**169.7**		After-tax cost of debt		3.4%					
			Target Debt/equity		30%					
			WACC		9.8%					
			Terminal growth		3.0%					

SOURCES: CGIS RESEARCH ESTIMATES, COMPANY DATA

Figure 18 shows the sensitivity of our DCF-based valuation to variations in the terminal growth rate and WACC.

Figure 18: Sensitivity analysis

		Terminal growth				
		2.0%	2.5%	3.0%	3.5%	4.0%
	8.8%	181.37	192.10	204.68	219.65	237.75
	9.3%	166.50	175.41	185.75	197.87	212.30
WACC	9.8%	153.60	161.09	**169.68**	179.65	191.34
	10.3%	142.32	148.66	155.89	164.17	173.78
	10.8%	132.37	137.80	143.92	150.89	158.88

SOURCES: CGIS RESEARCH ESTIMATES

Our Add rating is premised on our positive view on BeiGene, based on our SWOT analysis of the company and its potential. The weaknesses and threats listed below also pose downside risks to our Add call.

- **BeiGene's strengths**

1) BeiGene is emerging as one of global haematology therapy leaders supported by a) a clear sales expansion outlook in FY24F for Brukinsa as it gains approval for multiple indications globally, b) expected further approval for new indications (FL and DLBCL) for Brukinsa, which should drive the drug's sales growth since new indication approval means access to a new pool of patients; c) the company's new BTK-CDAC candidate that could synergise with Brukinsa due to its potential to overcome acquired BTKi resistance – approval of BTK-CDAC in the future should also drive revenue; and d) approval for sonrotoclax, which will also be a new revenue growth catalyst, in our view.
2) BeiGene has a deep solid tumour therapy pipeline centred on tislelizumab. The near-term growth drivers for BeiGene's solid tumour therapy portfolio are a) the ramp-up of tislelizumab sales for 12 indications in China, b) the ESCC's recent approval of tislelizumab in the EU, which we expect will catalyse its sales growth in 2024F, and c) further approval for other indications in other countries. Furthermore, as tislelizumab is one of the cornerstones of cancer immune-therapy, combination therapies that include immunotherapies and antibody-drug conjugate (ADC) partnered with tislelizumab can deliver better efficacy, in our view. BeiGene has multiple drug candidates, including CDK4i, PanKRASi, PRMT5i, EGFR CDAC, FGFR2b ADC, BTH3 ADC, and B7H4 ADC, that can partner with tislelizumab to provide treatment solutions to pan-solid cancer patients. We believe this deep pipeline should support BeiGene's revenue growth beyond FY26F.
3) Strong R&D capability is the foundation of the successful launch of new drugs, in our view. BeiGene had a research team of approximately 1,100 scientists and 3,000 clinical development employees as of 30 Jun 2023. We believe this large global team provides the right support for BeiGene's deep R&D pipeline and global multicentre clinical trials, which are important for global marketing approval.
4) Apart from R&D capability, a biotech company needs to have a knowledgeable and motivated commercial team to promote its products. BeiGene has approximately 3,500 commercial team members globally and is currently focused on the market penetration of Brukinsa, tislelizumab and in-licence products, according to management.
5) We also believe its clear overseas market expansion outlook is a strong revenue growth catalyst. Promising clinical results from the global head-to-head ALPINE trial comparing Brukinsa and ibrutinib makes Brukinsa well-accepted globally as an effective and safe treatment option for lymphomas, in our view. This has allowed the company to chart global inroads, which will be crucial for the marketing and approval process for its future drugs.

- **BeiGene's weaknesses**

1) Every new drug research and development process carries a possibility of failure. Failure in the R&D process means expenses have already been accrued but without a product to be launched.
2) A drug candidate may not be able to obtain market approvals as the evaluation standards for clinical designs and results may differ between the various countries' drug approval authorities.

- **Opportunities**

1) The multiple indication approvals for Brukinsa in 65 countries and regions globally have given BeiGene the reputation as an innovation-driven pharmaceutical company; we believe this will pave the way for international expansion for its future drugs.

2) Some indications for Brukinsa and tislelizumab have been included in the China National Reimbursement Drug List (NRDL) and more may be included in the future. Inclusion in the NRDL means the drugs become more affordable and accessible to patients, hence lifting the sales volume of BeiGene's drugs.

- **Threats**

1) In order to be included in the NRDL, pharmaceutical companies need to undergo a negotiation process with the Chinese government, which usually involves price cuts. Too large a price cut could hurt the company's profit margin. Please refer to our published note for details on NRDL negotiations (link).

2) Each drug molecule has a patent protection period (generally 20 years). After the patent expires, BeiGene will face intense competition from generic drugs or biosimilars.

Figure 19: BeiGene's SWOT analysis

Strengths • Establishing a leading position in haematology supported by Brukinsa, and promising candidates (BTK-CDAC and sonrotoclax). • Deep pipeline of treatments for solid tumour centred around tislelizumab supports long-term growth. • Strong R&D capability supported by ~3,000 clinical development staff. • Strong commercialisation capability supported by ~3,500 commercial staff. • Global brand recognition brought by Brukinsa.	**Opportunities** • Global approval of Brukinsa brings BeiGene global brand awareness, which paves the way for international expansion for future drugs. • National reimbursement drug list (NRDL) inclusion in China make drugs more accessible, which may increase future sales volume.
Weaknesses • New drug R&D carries the possibility of failure. • Drug candidates may not be able to receive marketing approval due to different regulation requirements in different countries.	**Threats** • NRDL inclusion in China requires a price reduction, which may hurt BeiGene's gross margin. • Increased competition from generic drugs and biosimilars after patent protection expiration.

SOURCES: CGIS RESEARCH

Key downside risks:

1) BeiGene's R&D efforts may not deliver effective clinical outcomes. This could lead to diminished confidence in BeiGene's R&D ability.

2) BeiGene may not receive market approval due to countries' differing regulations and rules.

3) After the expiration of patent protection for each drug molecule, BeiGene may face intense competition from generic drugs or biosimilars.

Figure 20: Peer comparison table

Ticker	Company	Rating	Target price	Last price	Market Cap	P/E			P/Sales				P/BV		ROE		ROA		Share Price Performance				
						2023F	2024F	2025F	2022	2023F	2024F	2025F	2022	2023F	2022	2023F	2022	2023F	1M	3M	6M	12M	YTD
			Lcy	Lcy	US$m	x	x	x	x	x	x	x	x	x	%	%	%	%	%	%	%	%	%
1801 HK	Innovent Biologics Inc	NR	na	35.4	7,332.6	na	na	136.2	9.9	9.0	7.2	5.5	4.6	5.0	-28.6	-11.2	-8.0	-7.1	-7.7	-19.8	7.8	-18.0	-17.3
1877 HK	Shanghai Junshi Bioscience-H	NR	na	14.4	3,797.3	na	na	na	10.6	15.5	10.8	8.2	1.6	1.7	-10.4	-20.5	-20.8	-15.5	-20.2	-19.8	-42.5	-66.6	-26.0
9926 HK	Akeso Inc	NR	na	41.9	4,501.8	17.4	na	70.4	7.4	6.7	10.6	6.7	6.2	7.3	-33.9	48.6	28.4	30.3	-0.2	10.9	12.5	-12.4	-9.8
2696 HK	Shanghai Henlius Biotech I-H	NR	na	14.1	981.5	15.0	13.2	11.0	1.6	1.3	1.2	1.0	3.7	3.3	-35.8	25.3	-2.3	na	20.7	41.3	11.7	-4.7	1.6
6160 HK	Beigene Ltd	Add	169.7	95.5	17,186.0	na	na	na	7.5	1.8	2.2	2.8	4.5	4.6	-28.0	-22.1	-15.6	-20.6	-7.5	0.9	-19.3	-42.6	-13.3
HSI Index	Hang Seng Index																		-5.8	-10.3	-19.3	-30.1	-9.7
HSCEI Index	Hang Seng China Ent Indx																		-5.9	-12.1	-19.5	-31.0	-10.5
SHCOMP Index	Shanghai Se Composite																		-5.3	-6.1	-12.9	-15.5	-7.3
MXCN Index	Msci China																		-8.0	-11.5	-20.1	-33.2	-12.2
HSHKBIO Index	Hang Seng Bio Tech Index																		-10.2	-12.8	-19.5	-43.6	-16.4

SOURCES: CGIS RESEARCH ESTIMATES, COMPANY DATA, BLOOMBERG
Note: Estimates for Non-rated (NR) companies are based on Bloomberg consensus estimates, Data as at Jan 23 2024

Company background

BeiGene was co-founded by John V. Oyler and Xiaodong Wang in 2010. It has since become a global organisation with over 9,000 employees in 29 countries and regions, including the US, China, Europe, and Australia, as at the end of 2023. BeiGene is a global biotechnology company involved in the discovery and development of innovative oncology treatments. It currently has three approved medicines discovered and developed internally: zanubritinib marketed as Brukinsa, tislelizumab marketed as Tevimbra, and pamiparib. In addition, BeiGene has in-licence rights to distribute 14 approved medicines in the China market. BeiGene also collaborates with Amgen and Novartis to develop and commercialise innovative medications.

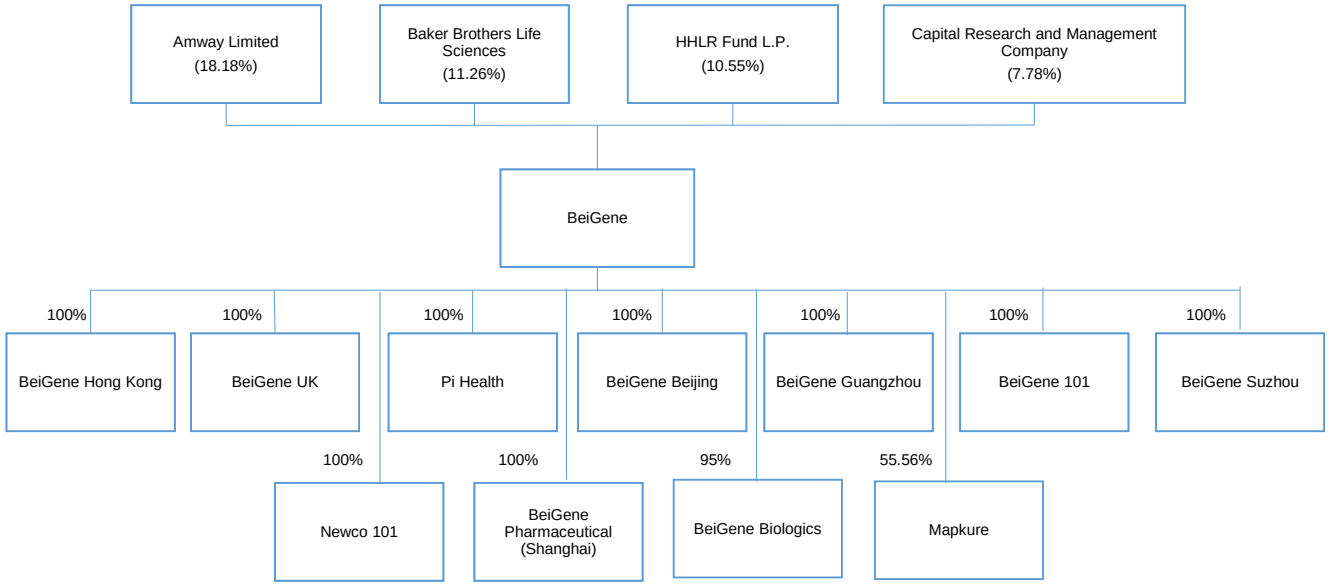
Figure 21: Management profile

Name	Position	Education Background	Experience
John V. Oyler	Co-Founder, Chairman and CEO	B.Sc. in mechanical engineering from the Massachusetts Institute of Technology; MBA from Stanford University	Management consultant at McKinsey & Company (1996-1997); Co-Chief Executive Officer of Genta Incorporated (1997-1998); President and Founder of Telephia, Inc. (1997-2002); CEO of Galenea Corp. (2002-2004); President and CEO of BioDuro, LLC (2004-2010)
Xiaodong Wang, Ph.D.	Co-Founder, Chairman of Scientific Advisory Board	B.Sc. in biology from the Beijing Normal University; Ph.D. in biochemistry from the University of Texas Southwestern Medical Center	Howard Hughes Medical Institute Investigator (1997-2010); George L. MacGregor Distinguished Chair Professor in Biomedical Sciences at the University of Texas Southwestern Medical Center in Dallas, Texas (2001-2010); founding Director of the National Institute of Biological Sciences in Beijing (since 2003) and Director and Investigator (since 2010)
Xiaobin Wu, Ph.D.	President, Chief Operating Officer, and General Manager of China	Master's degree in molecular biology and Ph.D. in biochemistry and pharmacology from the University of Konstanz in Germany	Sales and marketing with Bayer in Germany (1992-2001); General Manager of Bayer Healthcare in China (2001-2004); President and Managing Director of Wyeth China and Hong Kong (2004-2009); Country Manager of Pfizer China and the Regional President of Pfizer Essential Health for Greater China (2009-2018)
Lai Wang, Ph.D.	Global Head of R&D	B.Sc. from Fudan University; Ph.D. from the University of Texas Health Science Center at San Antonio	Post-doctorate training with Dr. Xiaodong Wang at Howard Hughes Medical Institute; Director of research at Joyant Pharmaceuticals in Dallas, Texas
Julia Wang	Chief Financial Officer	MBA from Fudan School of Business at Duke University	Led finance teams at several operating companies of Johnson & Johnson, including Xian-Hanssen Pharmaceutical, J&J's pharmaceutical business in China; various leadership roles at Quest Diagnostics; Senior Vice President, Global Business Finance, Corporate Finance and Corporate FP&A at Alexion Pharmaceuticals

SOURCES: CGIS RESEARCH, COMPANY DATA

BeiGene was incorporated on 28 Oct 2010 and listed on the Nasdaq (BGNE.US, CP: US$165.4); it was then listed on the Hong Kong stock exchange on 8 Aug 2018 (6160. HK, CP: HK$95.4) and listed on the Shanghai stock exchange on 15 Dec 2021 (688235.CH, CP: Rmb127.3).

Figure 22: Shareholding structure as at Jun 30 2023

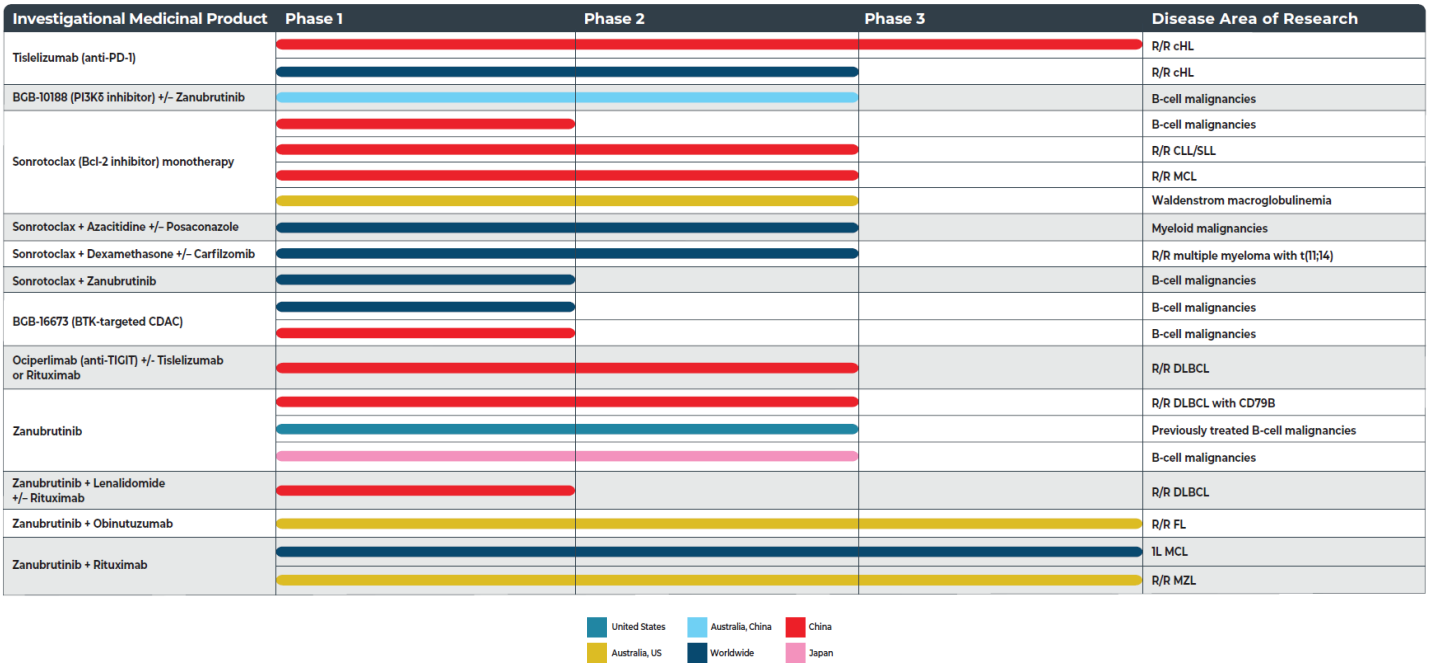


SOURCES: CGIS RESEARC, COMPANY DATA, WIND

A deep oncology innovation-driven R&D pipeline

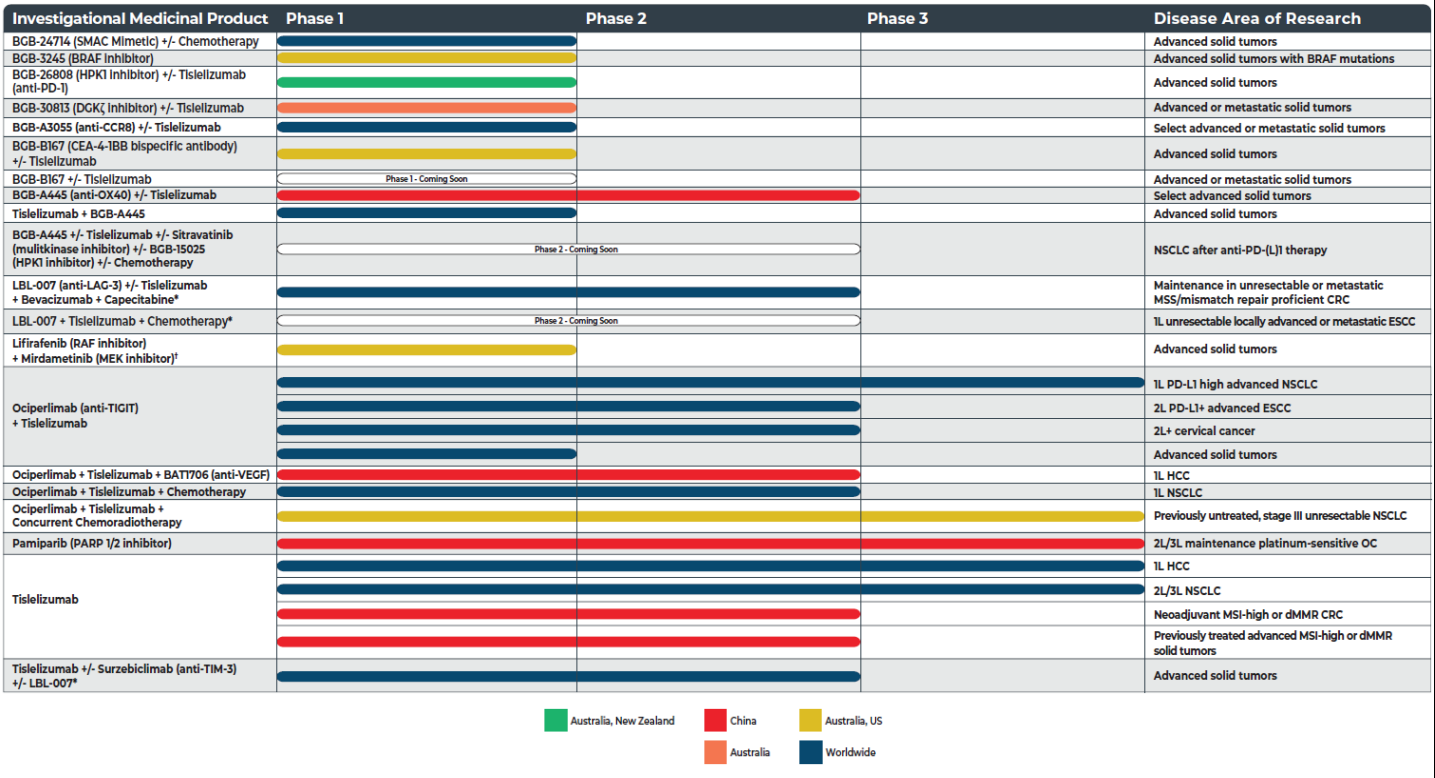
BeiGene has a diverse pipeline of novel therapeutics and, as at Sep 2023, had conducted more than 120 clinical trials in-house, with over 21,000 subjects enrolled in c.45 regions.

Figure 23: Clinical pipeline – haematology, as of Nov 2023



SOURCES: CGIS RESEARCH, COMPANY DATA

Figure 24: Clinical pipeline – therapies for solid tumour part 1, as of Nov 2023



SOURCES: CGIS RESEARCH, COMPANY DATA

Figure 25: Clinical pipeline – therapies for solid tumour part 2, as of Nov 2023

Investigational Medicinal Product	Phase 1	Phase 2	Phase 3	Disease Area of Research
Tislelizumab +/- Surzebiclimab +/- LBL-007*				1L recurrent or metastatic HNSCC
Tislelizumab +/- Ociperlimab +/- LBL-007*				Resectable stage II/IIIA NSCLC
Tislelizumab +/- BGB-A445 +/- LBL-007 +/- Chemotherapy*				1L advanced, unresectable, or metastatic NSCLC
Tislelizumab + BGB-10188 (PI3Kδ inhibitor)				Advanced solid tumors
Tislelizumab + BGB-15025 (HPK1 inhibitor)				Advanced solid tumors
Tislelizumab + Chemoradiotherapy				Localized ESCC
Tislelizumab + Chemotherapy/ Chemoradiotherapy				Resectable ESCC
Tislelizumab + Chemotherapy				1L advanced ESCC
				1L GC/GEJC
				Resectable stage II or IIIA NSCLC
				1L advanced nasopharyngeal cancer
				1L advanced UBC
				1L ES-SCLC
Tislelizumab + DKN-01 (anti-DKK1) + Chemotherapy†				1L/2L GC/GEJC
Tislelizumab + Fruquintinib (VEGFR inhibitor)‡				Advanced GC/GEJC, CRC, and NSCLC
				Advanced triple negative BC, EC, and CRC
Tislelizumab + Lenvatinib (VEGFR kinase inhibitor)				1L HCC
				Advanced solid tumors
Tislelizumab + Sitravatinib (multikinase inhibitor)				Advanced NSCLC after anti-PD-(L)1 therapy
				Advanced ESCC after anti-PD-(L)1 therapy
Tislelizumab + Surufatinib (VEGFR, FGFR, CSF-1R inhibitor)‡				Advanced solid tumors
Zanidatamab (anti-HER2 bispecific antibody)§				2L+ HER2+ BTC
Zanidatamab + Chemotherapy +/- Tislelizumab§				1L HER2+ BC and 1L HER2+ GC/GEJC
				1L HER2+ advanced/metastatic GC/EC

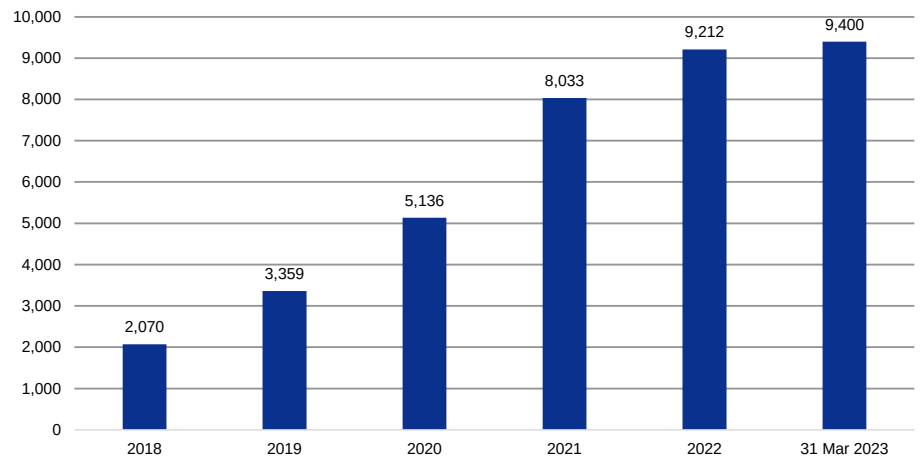
Australia, China, US | China | Australia, China | China, Thailand
United States | Worldwide | China, S. Korea

SOURCES: CGIS RESEARCH, COMPANY DATA

Up to 9,400 employees globally

The company has administrative offices in Basel, Beijing, and Cambridge in the US and had up to 9,400 global employees as at 31 Mar 2023.

Figure 26: BeiGene's number of employees



SOURCES: COMPANY DATA, CGIS RESEARCH

According to the company, BeiGene has more than 950 scientists to support its innovative oncology research, including the successful development of Brukinsa and tislelizumab. In addition, BeiGene has built a global development team of 2,300 people on five continents, allowing the company to run clinical trials without reliance on third party CROs.

BeiGene built a strong commercial portfolio, centred on two cornerstone medicines, Brukinsa and tislelizumab. The company's haematological franchise is led by Brukinsa. BeiGene had an international commercial team of over 3,500 employees as at 31 Mar 2023 (part of its team of 9,400 employees).

Manufacturing facilities and partners

BeiGene manufactures medicines and drug candidates internally or collaborates with third-party CMOs. BeiGene has manufacturing facilities for small molecule drugs and large molecule biologics in Suzhou and Guangzhou, respectively.

According to the company, its Suzhou facility is over 13,000 square metres and, as at end-2022, consisted of a manufacturing base for small molecule drug products, with an annual production capacity of about 100m tablets and capsules, and a biologics clinical development production facility, with 2 x 500 litre capacity, to produce biologics candidates for clinical supply. This facility has received a manufacturing licence to produce commercial volumes of Brukinsa and pamiparib for the China market. In order to meet the growing sales volume, BeiGene is also establishing a new small molecule manufacturing facility nearby in Suzhou that will have the capability to produce up to 600m solid oral dosages annually. Meanwhile, the Guangzhou facility is approximately 100,000 square metres for the manufacturing of large molecule biologics. The plant's capacity as at end-2023 was 64,000 litres. BeiGene is also establishing a commercial-stage manufacturing and clinical R&D campus in New Jersey, US.

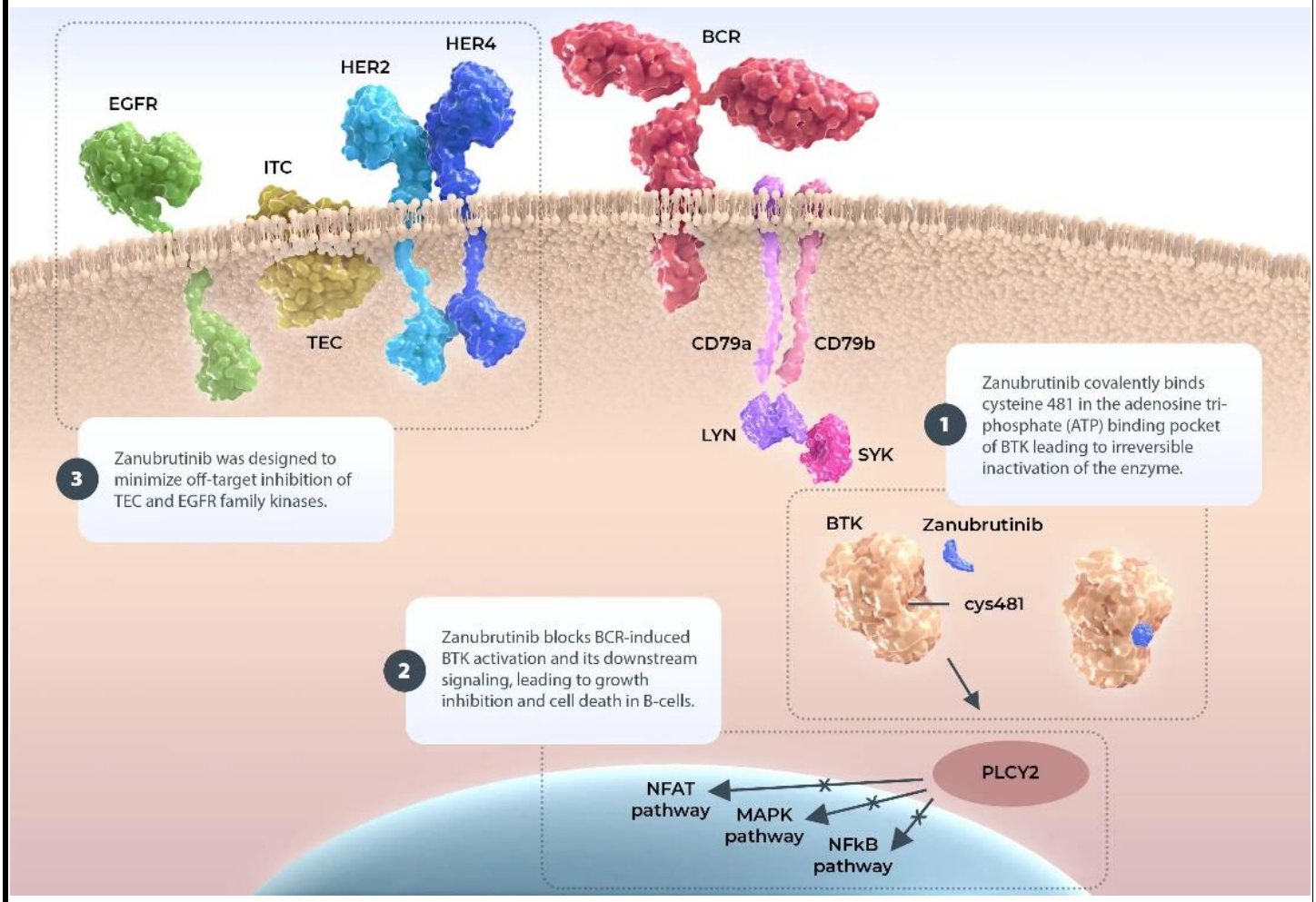
Apart from internal manufacturing, BeiGene collaborates with third-party CMOs for the production of some drug products and drug substances as well as the supply of raw materials. BeiGene's CMO and CRO partners include Catalent (for Brukinsa) (CTLT. US, NR, CP: US$49.3), and Boehringer Ingelheim Biopharmaceuticals (for tislelizumab).

Pipeline of drugs

Zanubrutinib

Brukinsa, the brand name for BeiGene's zanubrutinib (BGB-3111), is a small-molecule orally-administered second-generation Bruton's tyrosine kinase inhibitor (BTKi). Zanubrutinib binds covalently at the cysteine residue 481 (cys481) of Bruton's tyrosine kinase inhibitor (BTK), limiting its enzyme activities, leading to a slowdown of B cell proliferation (please refer to Appendix 1: BTK and BTKi for more information regarding the BTK pathway and BTKi.)

Figure 27: Mechanism of action (MOA) of zanubrutinib



SOURCES: CGIS RESEARCH, COMPANY DATA

Zanubrutinib was first approved in Nov 2019 by the US FDA. As at 30 Jun 2023, zanubrutinib had been approved in over 65 markets for multiple lymphoid malignancies, including R/R MCL, TN or R/R WM, MZL and CLL/SLL. Meanwhile, the EC granted marketing authorisation for Brukinsa in R/R FL in Nov 2023. In addition, the US FDA has accepted an sNDA for Brukinsa for R/R FL, with the assigned target action date in 1Q24F. BeiGene has also started clinical trials to test the efficacy and safety of Brukinsa for R/R diffuse large B-cell lymphoma (DLBCL) (please refer to Appendix 2: Lymphoma for more information on different lymphoma subtypes.)

Figure 28: Indications of zanubrutinib (as of 30 Jun 2023)

Indication	Region and time of approval	Supported trials and description	
R/R MCL	US Nov 2019; China (conditional approval) Jun 2020; United Arab Emirates Sep 2021; Israel Apr 2021; Canada Jul 2021; Chile Jul 2021; Brazil Aug 2021; Singapore Oct 2021; Australia Oct 2021; Russia Oct 2021; Saudi Arabia Nov 2021; Ecuador Dec 2021; South Korea Feb 2022; Uruguay Apr 2022; Kuwait Jun 2022; Bahrain Jun 2022; Qatar Jun 2022; Argentina Oct 2022; El Salvador Oct 2022; Mexico Oct 2022; Paraguay Oct 2022; European Union (EU) plus Iceland and Norway Nov 2022, China (regular approval) Apr 2023	BGB-3111-AU-003 (NCT02343120)[1]	A global multicentre, open-label, phase I/II study of zanubrutinib in patients with B-cell malignancies (n=32).
		BGB-3111-206 (NCT03206970)[2, 3, 4]	A single-arm, open-label, multicentre phase II study of zanubrutinib in subjects with R/R MCL in China (n=86).
TN or R/R CLL/SLL	China (conditional approval, R/R) Jun 2020; EC (CLL) Nov 2022; US Jan 2023; UK Jan 2023; South Korea Jul 2023; China (TN and regular approval for R/R) May 2023; Canada (CLL) May 2023	SEQUOIA[5, 6] BGB-3111-304 (NCT03336333)	An open-label, global multicentre, randomised phase III study of zanubrutinib in TN patients with CLL/SLL.
		ALPINE[7] (NCT03734016)	A global, randomised, open-label, head-to-head phase III trial of ibrutinib vs. zanubrutinib in patients with R/R CLL/SLL.
		CTR20160890 (NCT03206918)[8]	An open-label, single-arm phase II study of zanubrutinib in Chinese patients with R/R CLL/SLL.
R/R or TN WM	Canada Mar 2021; China (conditional approval, R/R) Jan 2021; US Aug 2021; Australia Oct 2021; EU plus Iceland, Lichtenstein, and Norway Nov 2021; UK Dec 2021; Switzerland Jan 2022; South Korea Feb 2022; Israel Mar 2022; Uruguay Apr 2022; Chile Oct 2022; Ecuador Oct 2022; El Salvador Oct 2022; Brazil Nov 2022, China (TN and regular approval for R/R) Apr 2023	ASPEN[9, 10] (NCT03053440)	A randomised, open-label, global multicentre, phase III study comparing ibrutinib and zanubrutinib in patients with WM.
		BGB-3111-AU-003 (NCT02343120)[11]	A study that included 24 TN and R/R BTki-naïve WM patients.
		NCT03332173[12]	A pivotal, single-arm, open-label, multicentre, phase II study of zanubrutinib in Chinese patients with R/R WM.
R/R MZL	US Sep 2021; Canada Mar 2022; Uruguay Apr 2022; Chile Oct 2022; Ecuador Oct 2022; El Salvador Oct 2022; Paraguay Oct 2022; EU plus Iceland and Norway Nov 2022; Brazil Nov 2022; South Korea; UK Jan 2023	MAGNOLIA[13, 14] BGB-3111-214 (NCT03846427)	A single-arm, open-label, global multicentre, phase II study of zanubrutinib in patients with R/R MZL.
		BGB-3111-AU-003 (NCT02343120)[15]	
R/R FL	EC Nov 2023; US accepted sNDA Jan 2023F	ROSEWOOD (NCT03332017) (BGB3111212)	A global randomised, open-label, phase II study comparing Brukinsa plus obinutuzumab alone in patients with R/R FL.
		BGB-3111_GA101_Study_001 (NCT02509476)[16]	A 2-part, open-label, phase 1b clinical trial designed to determine the safety, tolerability, and recommended phase 2 doses (RP2D) of zanubrutinib in part 1 and preliminary anti-tumour activity of zanubrutinib in indication-specific expansion cohorts in parts.

R/R: relapsed or refractory, MCL: mantle cell lymphoma, TN: treatment naïve , CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma, WM: Waldenström's macroglobulinemia, MZL: marginal zone lymphoma, FL: follicular lymphoma

SOURCES: CGIS RESEARCH, COMPANY DATA

1. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma.
2. Treatment of patients with relapsed or refractory mantle–cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine kinase.
3. Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study.
4. Long-term outcomes of second-line vs later-line zanubrutinib treatment in patients with relapsed/refractory MCL: an updated pooled analysis.
5. Zanubrutinib versus bendamustine and rituximab in untreated CLL and SLL (SEQUOIA): a randomised, controlled, phase 3 trial.
6. Zanubrutinib monotherapy for patients with treatment naïve CLL and 17p deletion.
7. Zanubrutinib or ibrutinib in relapsed or refractory CLL.
8. Treatment of relapsed/refractory CLL/SLL with the BTK inhibitor zanubrutinib: phase 2, single-arm, multicentre study.
9. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study.
10. Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial.
11. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: 3 years of follow-up.
12. A Phase II Trial of the Bruton Tyrosine-Kinase Inhibitor Zanubrutinib (BGB-3111) in patients with relapsed or refractory Waldenström macroglobulinemia.
13. The Magnolia trial: Zanubrutinib, a next-generation bruton tyrosine kinase inhibitor, demonstrates safety and efficacy in R/R MZL.
14. Long-term efficacy and safety of zanubrutinib in patients with R/R MZL: Final analysis of the Magnolia (BGB-3111-214) trial.
15. Zanubrutinib monotherapy in relapsed/refractory indolent non-Hodgkin lymphoma.
16. Zanubrutinib (BGB-3111) plus obinutuzumab in patients with CLL and follicular lymphoma.

1. **Zanubrutinib for relapsed or refractory (R/R) mantle cell lymphoma (MCL)**

The US FDA approved the use of zanubrutinib as a treatment for MCL in adult patients who have received at least one prior therapy in Nov 2019, based on efficacy results from NCT03206970 and NCT02343120. The China National Medical Products Administration (NMPA) approved it for the same indication in Jun 2020. Across both trials, zanubrutinib achieved an objective response rate (ORR) of 84%. The combined safety analysis showed a favourable safety and

tolerability profile. The incidence of grade ≥ 3 adverse event (AE) was 21.8%, and the most common AE was pneumonia.

Figure 29: Efficacy data of zanubrutinib for R/R MCL

	NCT03206970		NCT02343120
	Initial (18 months) n=86	Long term (35 months exploratory analysis)	Initial (18 months) n=32
	Independent review committee (IRC) assessed	Investigator assessed	IRC assessed
Efficacy			
Objective response rate (ORR), % (95% confidence interval/CI)	84 (74, 91)	84 (74, 91)	84 (67, 95)
Best response, n (%)			
Complete response (CR)	59 (68.6)	67 (77.9)	8 (25.0)
Partial response (PR)	13 (15.1)	5 (5.8)	19 (59.4)
Stable disease (SD)	14 (16.3)	1 (1.2)	2 (6.3)
Progressive disease (PD)		8 (9.3)	2 (6.3)
Discontinued before first assessment		5 (5.8)	1 (3.1)
Median duration of response (mDOR), months (95% CI)	19.5 (16,6, not estimable/NE)	NE (24.9, NE)	18.5 (12.6. NE)
Median Progression free survival (mPFS), months (95% CI)	22.1 (17.4, NE)	33.0 (19.4, NE)	21.1 (13.2, NE)

SOURCES: CGIS RESEARCH, COMPANY DATA

Figure 30: Combined adverse reactions in ≥10% of patients with MCL (N=118)

Adverse Reaction	All Grades (%)	Grade ≥3 (%)
Upper respiratory tract infection	39	0
Rash	36	0
Diarrhea	23	0.8
Pneumonia	15	10
Musculoskeletal pain	14	3.4
Bruising	14	0
Constipation	13	0
Hypertension	12	3.4
Cough	12	0
Hemorrhage	11	3.4
Urinary tract infection	11	0.8

SOURCES: CGIS RESEARCH, COMPANY DATA

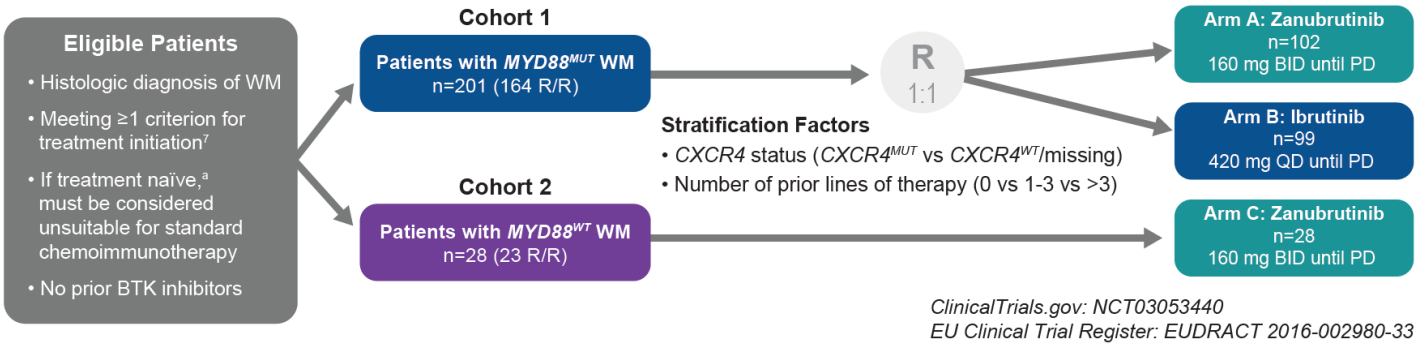
In summary, the above clinical trial results showed consistent efficacy responses and good safety of zanubrutinib in R/R MCL. As we discuss in further detail in the "Appendix 2: Lymphoma", MCL accounted for 3-10% of non-Hodgkin's lymphoma (NHL) and NHL was responsible for 544,352 global new cases in 2020. We think the good efficacy and safety profile of zanubrutinib makes it a viable treatment option for MCL patients and the penetration of zanubrutinib among existing and new MCL patients should create steady market demand for the drug.

2. Zanubrutinib for relapsed or refractory (R/R) Waldenström's macroglobulinemia (WM)

Brukinsa received conditional approval in China for the treatment of adult patients with WM who have received at least one prior therapy in Jun 2021. The US FDA granted the use of Brukinsa for WM in Sep 2021 based on data from NCT03332173 and ASPEN.

ASPEN is a phase III, head-to-head randomised clinical trial to evaluate zanubrutinib vs. ibrutinib in patients with R/R or treatment naïve (TN) waldenström's macroglobulinemia (WM). It consisted of two cohorts, based on MYD88 genotype. Cohort 1 included 201 patients with MYD88 mutations, randomised 1:1 to receive either zanubrutinib or ibrutinib. Cohort 2 included 28 patients without MYD88 mutations receiving zanubrutinib to evaluate its efficacy among patients lacking the known ibrutinib-sensitive MYD88 variant. In a previous study, BKTi had been shown to be an effective therapeutic strategy in WM, but MYD88 wild type (Wt) has been associated with poor outcomes when treated with ibrutinib.

Figure 31: ASPEN study design: zanubrutinib vs. ibrutinib in WM

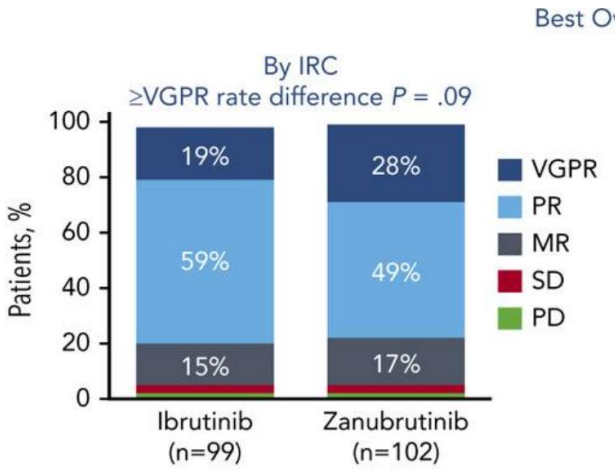


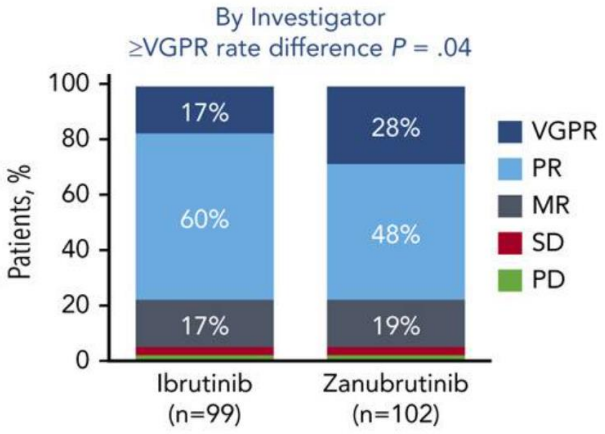
BTK: Bruton tyrosine kinase, R/R: relapsed or refractory, WM: Waldenström's macroglobulinemia, QD: Once a day, BID: Twice a day, CXCR4: C-X-C chemokine receptor type 4, MyD88: Myeloid differentiation primary response protein 88

SOURCES: CGIS RESEARCH, COMPANY DATA (ASPEN STUDY)

The very good partial response (VGPR) rate was 28% with Brukinsa, compared to 19% with ibrutinib. Adverse events (AEs), especially cardiovascular AEs, were less common in the Brukinsa arm.

Figure 32: ASPEN study results

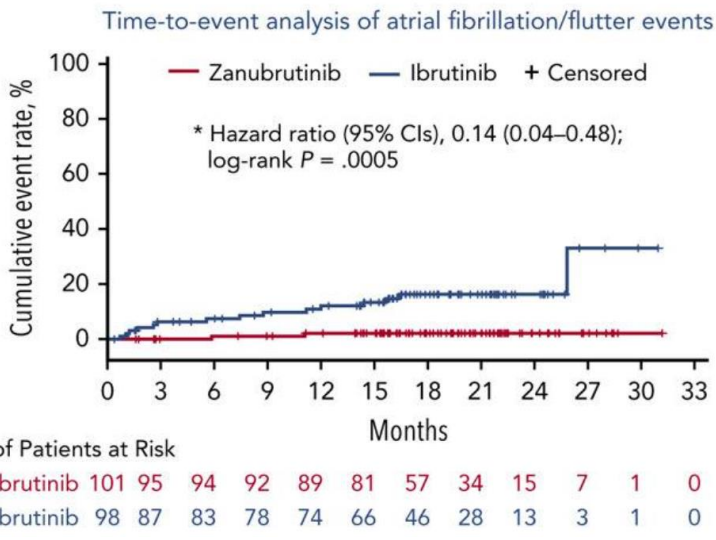




AE Categories, n (%) (Pooled Terms)	All Grades	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	15 (15.3)	2 (2.0)
Diarrhea (PT)	31 (31.6)	21 (20.8)
Hemorrhage	58 (59.2)	49 (48.5)
Major hemorrhage	9 (9.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)
Neutropenia*	13 (13.3)	30 (29.7)
Infection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

*Descriptive 2-sided $P < .05$

Data cutoff 31Aug2019



AE: Adverse event, PR: Partial response, MR: Minimal responses, SD: Stable disease, PD: Progressive disease, IRC: Independent review committee, VGPR: Very good partial response, CI: Confidence interval, n: Number

SOURCES: CGIS RESEARCH, COMPANY DATA

In summary, the above results demonstrated that zanubrutinib and ibrutinib are highly effective in the treatment of WM, but the zanubrutinib treatment was associated with a trend towards better response quality and less toxicity, particularly cardiovascular toxicity. The results of this head-to-head clinical trial comparing zanubrutinib and ibrutinib present zanubrutinib as a better treatment option over ibrutinib for WM patients. We think that, based on this clinical result, zanubrutinib will continue to gain market share from ibrutinib. As we introduced in detail in the "Appendix 2: Lymphoma", WM accounts for less than 2% of NHL and NHL was responsible for 544,352 global new cases in 2020. Although the incidence rate of WM is lower compared with other lymphoma subtypes, they still create demand for zanubrutinib, in our view.

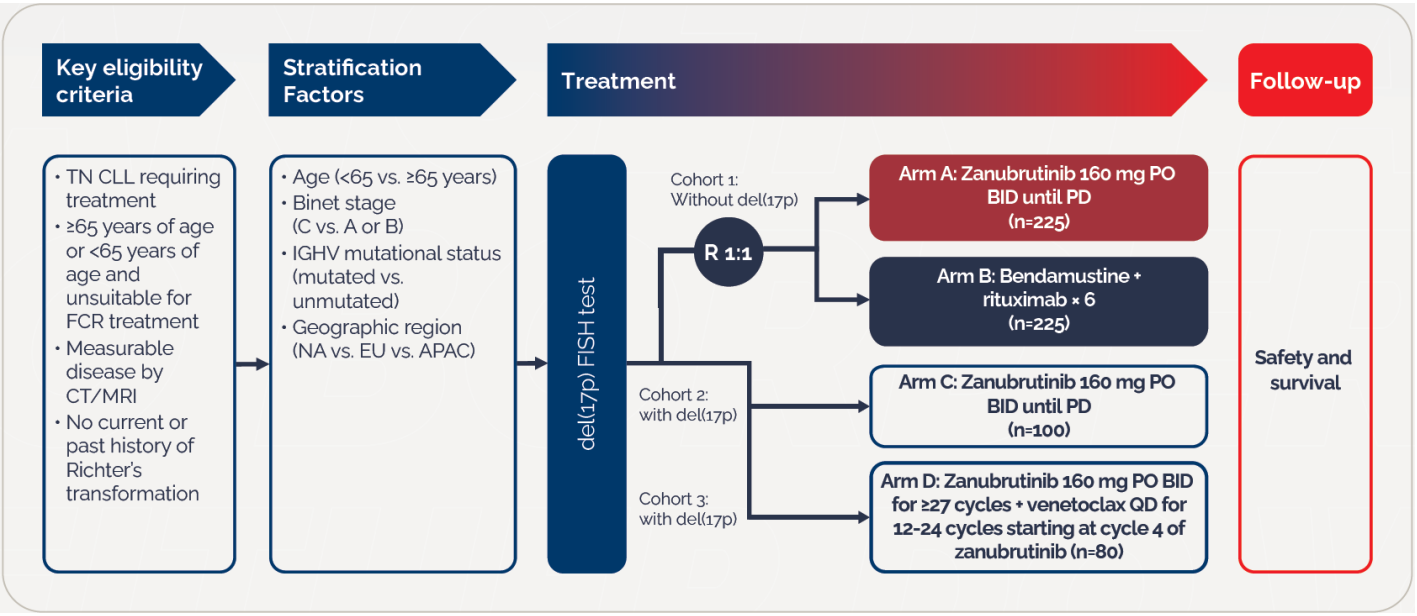
3. Zanubrutinib for relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)

Zanubrutinib received NMPA approval for R/R CLL/SLL in Jun 2020 and for CLL/SLL in May 2023. The US FDA approved the use of zanubrutinib for CLL/SLL treatment in Jan 2023 based on results of two global phase III clinical trials, ALPINE and SEQUOIA.

- SEQUOIA

SEQUOIA is an open-label, global randomised phase III trial, initiated in 2017, to evaluate the superiority of Brukinsa vs. the standard treatment, bendamustine plus rituximab (BR), in first-line CLL/SLL. It consisted of three cohorts. Cohort 1 included patients without the deletion of chromosome17 (del[17p]) and randomly assigned to zanubrutinib (arm A) or BR (arm B). Cohorts 2 and 3 included patients with del[17p] because patients with CLL/SLL whose tumours exhibited del[17p] had an unfavourable prognosis and responded poorly to standard chemoimmunotherapy. Patients with del(17p) mutations were assigned to receive BRUKINASA in a separate single-arm exploratory analysis. Patients in cohort 2 (arm C) received treatment with zanubrutinib while patients in cohort 3 (arm D) received zanubrutinib and venetoclax.

Figure 33: SEQUOIA study design



FCR: chemotherapy regimen of fludarabine, cyclophosphamide, and rituximab; CT: computed tomography; MRI: magnetic resonance imaging; IGHV: immunoglobulin heavy chain variable region gene; NA: North America; APAC: Asia/Pacific; PO: per oral; BID: twice a daily; PD: progressive disease; QD: once a day

SOURCES: CGIS RESEARCH, COMPANY DATA

With a follow-up of 24 months, Brukinsa demonstrated significant progression free survival (PFS) benefit vs. chemo-immunotherapy with BR (HR 0.42, [95% CI: 0.28, 0.63], P<0.0001). Zanubrutinib also induced a high ORR and showed a better safety profile.

Figure 34: Key efficacy findings of SEQUOIA

	Cohort 1		Cohort 2	Cohort 3
	Arm A, Brukinsa	Arm B, BR	Arm C	Arm D
	N=241	N=238	N=110	N=49
24 months PFS	85.5% (95% CI: 80.1, 89.6)	69.5% (95% CI: 62.4, 75.5)	88.9% (95% CI: 81.3, 93.6)	
Hazard ratio (HR)	0.42 (95% CI: 0.27, 0.63), p<0.0001			
ORR	94.6% (228/241; 95% CI: 91.0-97.1)	85.3% (203/238; 95% CI: 80.1-89.6)	90.0% (99/110; 95% CI 82.8-94.9)	97.2% (95% CI 85.8-99.9) 12 months
mDoR	Not reached (95% CI NE-NE)	30.6mo (95% CI 25.5-NE)	Not reached (95% CI NE-NE)	
24 months OS	94.3% (95% CI 90.4-96.7)	94.6% (95% 96.6-96.9)	93.6% (95% CI 87.1-96.9)	

SOURCES: CGIS RESEARCH, COMPANY DATA

Figure 35: Combined adverse reactions in ≥10% of patients with MCL (N=118)

AE, n (%)	Arm A Zanubrutinib (n=240[a])		Arm B Bendamustine + Rituximab (n=227[a])	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	11 (4.6)	1 (0.4)	44 (19.4)	4 (1.8)
Neutropenia[b]	38 (15.8)	28 (11.7)	129 (56.8)	116 (51.1)
Thrombocytopenia[c]	11 (4.6)	5 (2.1)	40 (17.6)	18 (7.9)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Atrial fibrillation	8 (3.3)	1 (0.4)	6 (2.6)	3 (1.3)
Bleeding[d] Major bleeding[e]	108 (45.0) 12 (5.0)	9 (3.8) 9 (3.8)	25 (11.0) 4 (1.8)	4 (1.8) 4 (1.8)
Diarrhea	33 (13.8)	2 (0.8)	31 (13.7)	5 (2.2)
Hypertension[f]	34 (14.2)	15 (6.3)	24 (10.6)	11 (4.8)
Infections[g]	149 (62.1)	39 (16.3)	127 (55.9)	43 (18.9)
Myalgia	9 (3.8)	0	3 (1.3)	0
Other cancers Dermatologic other cancers	31 (12.9) 16 (6.7)	17 (7.1) 2 (0.8)	20 (8.8) 10 (4.4)	7 (3.1) 2 (0.9)

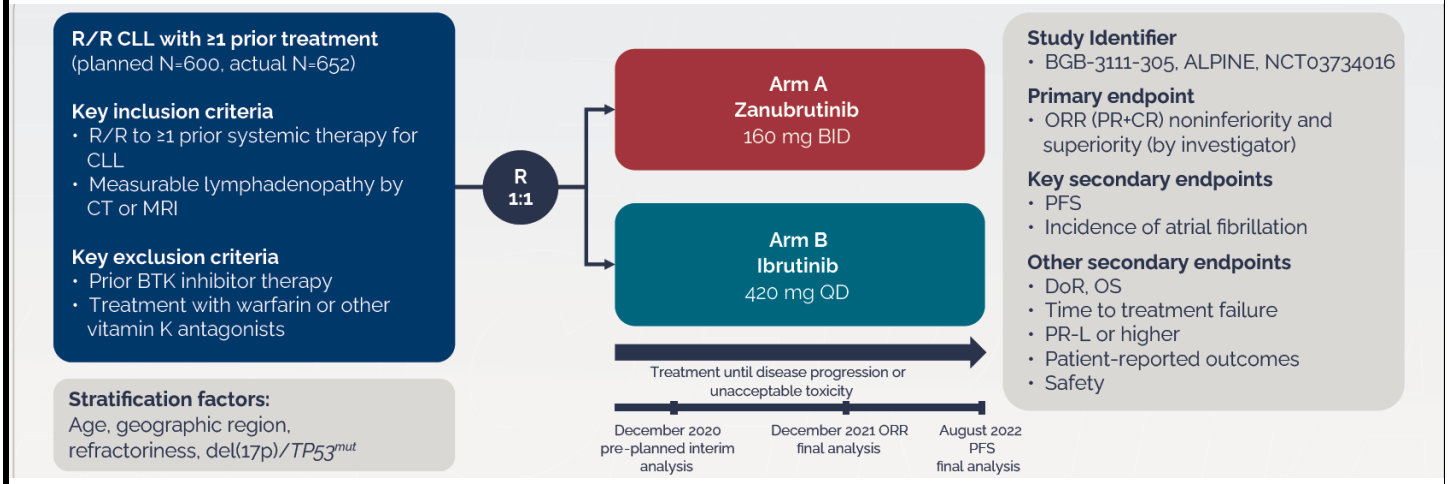
Safety was accessed in patients who received ≥1 doses of treatment: 1 patient in arm A and 11 in arm B did not receive treatment

SOURCES: CGIS RESEARCH, COMPANY DATA

- ALPINE

The ALPINE trial was designed to evaluate the superiority of Brukinsa vs. ibrutinib in second-line CLL. From 1 Nov 2018 through 14 Dec 2020, a total of 652 patients across 15 countries in the North America, Europe, and Asia Pacific regions were randomly assigned to receive zanubrutinib (160mg, twice a day, 327 patients) or ibrutinib (420mg, once daily, 325 patients). Statistical analysis for PFS and ORR were initially conducted for noninferiority. When noninferiority was met, superiority was tested.

Figure 36: ALPINE trial design



R/R: relapsed or refractory, CLL: chronic lymphocytic leukemia, MRI: Magnetic resonance imaging, DOR: Duration of response, PR: Partial response, CR: Complete response, PFS: Progression free survival, OS: Overall survival, CT: computed tomography, BID: Twice a day, QD: Once a day

SOURCES: CGIS RESEARCH, COMPANY DATA

PFS in the zanubrutinib arm was superior to PFS in the ibrutinib arm. Independent review committee (IRC)-assessed PFS rates were 79.5% and 67.3% in the zanubrutinib and ibrutinib groups (two-sided, p=0.0024), respectively. PFS favoured zanubrutinib over ibrutinib across all major subgroups, including patients with del(17p)/TP53 mutation. Zanubrutinib demonstrated a significant higher ORR vs. ibrutinib by IRC (86.2% vs. 75.7%, two-sided, p=0.007). In the final analysis, fewer deaths were reported in the zanubrutinib group than in the ibrutinib group (48 and 60). In the comparison between zanubrutinib with ibrutinib, the hazard ratio for death was 0.76 (95% CI, 0.51-1.11). The median overall survival was not reached in either treatment group.

Figure 37: Results of ALPINE trial, IRC-accessed

	ITT population		del(17p)/TP53 Mutation	
Best response, n (%)	Zanubrutinib (n=327)	Ibrutinib (n=325)	Zanubrutinib (n=75)	Ibrutinib (n=75)
ORR, % 95% CI	86.2 82.0-89.8	75.7 70.7-80.3	85.3 75.3-92.4	70.7 59.0-80.6
CR or Cri	22 (6.7)	19 (5.8)	6 (8.0)	4 (5.3)
PR or nPR	260 (79.5)	227 (69.8)	58 (77.3)	49 (65.3)
PR-L	18 (5.5)	24 (7.4)	4 (5.3)	7 (9.3)
SD	16 (4.9)	34 (10.5)	3 (4.00	8 (10.7)
PD	3 (0.9)	7 (2.2)	1 (1.3)	4 (5.3)
Discontinue prior to first assessment, NA or NE	8 (2.4)	14 (4.3)	3 (4.0)	3 (4.0)
Number of responders	282	246		
Events, n (%)	60 (21.3)	69 (28.0)		
Progressive Disease	40 (14.2)	52 (21.1)		
Death	20 (7.1)	17 (6.9)		
mDoR, mo (95% CI)	NE (31.3, NE)	33.9 (32.2, 41.4)		
24-month event-free rate, % (95%)	77.4 (71.0-82.5)	67.8 (60.1-74.3)		

ITT: intent to treat, CR: Complete response, Cri: CR with incomplete bone marrow recovery; PR-L: partial response with lymphocytosis; NA: not accessed; mo: month

SOURCES: CGIS RESEARCH, COMPANY DATA

Adverse events that occurred in at least 20% of the patients in either treatment group were diarrhoea, hypertension, neutropenia, coronavirus disease 2019, and upper respiratory tract infection. Overall, a lower incidence of cardiac disorders was reported in the zanubrutinib group (21.3%) than in the ibrutinib group (29.6%). Cardiac disorders leading to treatment discontinuation occurred in 1 patient (0.3%) in the zanubrutinib group and 14 patients (4.3%) in the ibrutinib group.

Figure 38: Adverse events in ALPINE trial (safety population)

Event, number of patients (%)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 adverse event	318 (98.1)	321 (99.1)
Grade ≥3 adverse events	218 (67.3)	228 (70.4)
Grade ≥3 adverse events reported in >2% of the patients in either trial group		
Neutropenia	52 (16.0)	45 (13.9)
Hypertension	48 (14.8)	36 (11.1)
Covid-19–related pneumonia	23 (7.1)	13 (4.0)
Covid-19	22 (6.8)	16 (4.9)
Pneumonia	19 (5.9)	26 (8.0)
Decreased neutrophil count	17 (5.2)	14 (4.3)
Syncope	9 (2.8)	4 (1.2)
Thrombocytopenia	9 (2.8)	12 (3.7)
Anemia	7 (2.2)	8 (2.5)
Atrial fibrillation	6 (1.9)	12 (3.7)
Increased blood pressure	4 (1.2)	10 (3.1)
Serious adverse events		
All serious adverse events	136 (42.0)	162 (50.0)
Events leading to dose reduction	40 (12.3)	55 (17.0)
Events leading to dose interruption	162 (50.0)	184 (56.8)
Events leading to treatment discontinuation	50 (15.4)	72 (22.2)
Events leading to death	33 (10.2)	36 (11.1)

SOURCES: CGIS RESEARCH, COMPANY DATA

In summary, the ALPINE and SEQUOIA are hallmark clinical trials for Brukinsa, especially the ALPINE trial, which directly compared the efficacy and safety of Brukinsa and ibrutinib. The superior PFS in the zanubrutinib arm indicated higher

efficacy of zanubrutinb over ibrutinib in CLL/SLL patients. Some patients using ibrutinib suffered from cardiac disorders and have had to discontinue their treatments. The ALPINE study showed a lower incidence of cardiac disorders was reported in the zanubrutinib group than in the ibrutinib group. This means patients are less likely to develop cardiac disorders using zanubrutinib.

As we discuss in “Appendix 2. Lymphoma”, CLL/SLL is one the most common types of adult leukaemia, which means a large patient pool for BeiGene to penetrate. Given its superior efficacy and safety, zanubrutinib should continue to gain market share from ibrutinib, in our view.

4. Zanubrutinib for marginal zone lymphoma (MZL)

In Sep 2021, Brukinsa was granted accelerated approval for the treatment of adult patients with R/R MZL who have received at least one anti-CD20-based regimen by the US FDA based on two open-label, multicentre, single-arm trials: Magnolia, which evaluated 66 patients with R/R MZL, and BGB311AU003, which included 20 patients with R/R MZL.

The median follow-up time was 15.7 months for Magnolia. The IRC-assessed ORR was 68.2% (95% CI, 55.56-79.11), and 25.8% patients achieved CR. The IRC-assessed duration of response (DOR) rate at 12 months was 93.0%, and IRC-assessed PFS rate was 82.5% at both 12 and 15 months. Treatment was well tolerated with the majority of AE being grade 1 or 2. The most common Aes were diarrhoea (22.1%), contusion (20.6%), and constipation (14.7%). The results from Magnolia were consistent with the results from the MZL patient group of BGB311AU003.

Figure 39: Analysis of response in Magnolia study, IRC-assessed

Response	R/R MZL (n = 66)
Median study follow-up, (range), months	15.7 (1.6–21.9)
Response rates	
ORR, *n* (%; 95% CI)	68.2 (55.56–79.11)
CR, *n* (%)	17 (25.8)
PR, *n* (%)	28 (42.4)
Stable disease, *n* (%)	13 (19.7)
Non-PD, *n* (%)	1 (1.5)
PD, *n* (%)	6 (9.1)
Discontinued study prior to first assessment	1 (1.5)
Median time to response (≥PR; range), months	2.8 (1.7–11.1)
Median and event-free rate	
Median DOR, months (range)	NE (NE–NE)
12-month DOR, % (95% CI)	93.0 (79.8–97.7)
15-month DOR, % (95% CI)	NE (NE–NE)
Median PFS, months (range)	NE (NE–NE)
12-month PFS, % (95% CI)	82.5 (70.55–89.93)
15-month PFS, % (95% CI)	82.5 (70.55–89.93)
Median OS, months (range)	NE (NE–NE)
12-month OS, % (95% CI)	95.3 (86.0–98.4)
15-month OS, % (95% CI)	92.9 (81.9–97.3)

ORR: Objective response rate, CR: Complete response, PR: Partial response, DOR: Duration of response, CI: Confidence interval, PD: Progressive disease, OS: Overall survival, NE: Not estimable

SOURCES: CGIS RESEARCH, COMPANY DATA

Figure 40: Analysis of response with zanubrutinib treatment in BGB311AU003

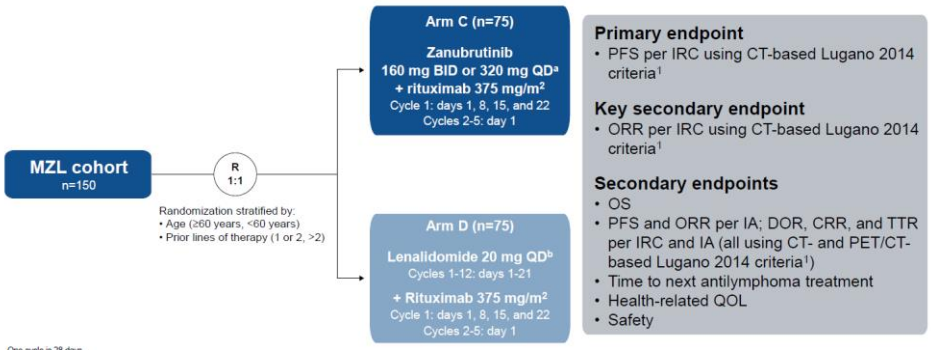
	R/R MZL (n=20)	R/R FL (n=33)
Response	IRC assessed	Investigator assessed
Median (range) study follow-up time, months	35.2 (8.3-59.2)	32.8 (1.8-58.7)
Best overall response, n (%)	16 (80) (56.3–94.3)	12 (36.4) (20.4–54.9)
ORR, n (%) (95% CI)	4 (20)	6 (18.2)
CR	12 (60)	6 (18.2)
PR	2 (10)	13 (39.4)
SD	1 (5)	5 (15.2)
PD	1 (5)	0
NE	0	3 (9.1)
Discontinued study prior to first assessment	16 (80) (56.3–94.3)	12 (36.4) (20.4–54.9)
Median (range) TTR (≥PR), months	2.8 (2.6–23.1)	2.7 (1.6–5.6)
Median and event-free rate		
Median DOR, months (95% CI)	NE (8.4–NE)	NE (8.3–NE)
6-month DOR, % (95% CI)	87.5 (58.6–96.7)	100 (NE–NE)
12-month DOR, % (95% CI)	71.6 (40.3–88.4)	74.1 (39.1–90.9)
24-month DOR, % (95% CI)	71.6 (40.3–88.4)	64.8 (31–85.2)
36-month DOR, % (95% CI)	71.6 (40.3–88.4)	64.8 (31–85.2)
Median PFS, months (95% CI)	NE (20.3–NE)	10.4 (7.7–22.9)
6-month PFS, % (95% CI)	90 (65.6–97.4)	70 (50.2–83.1)
12-month PFS, % (95% CI)	84 (57.9–94.6)	38.2 (20.9–55.3)
24-month PFS, % (95% CI)	72 (45–87.4)	30.1 (14.4–47.5)
36-month PFS, % (95% CI)	72 (45–87.4)	25.8 (11.2–43.2)
Median OS, months (95% CI)	NE (NE–NE)	NE (37.3–NE)
6-month OS, % (95% CI)	100.0 (NE–NE)	90.3 (72.7–96.8)
12-month OS, % (95% CI)	100.0 (NE–NE)	86.8 (68.5–94.8)
24-month OS, % (95% CI)	83.9 (59.7–94.5)	76.1 (56.1–87.9)
36-month OS, % (95% CI)	83.9 (59.7–94.5)	76.1 (56.1–87.9)
Median OS, months (95% CI)	NE (NE–NE)	NE (37.3–NE)

ORR: Objective response rate, CR: Complete response, PR: Partial response, DOR: Duration of response, CI: Confidence interval, PD: Progressive disease, OS: Overall survival, NE: Not estimable

SOURCES: CGIS RESEARCH, COMPANY DATA

According to BeiGene, currently, a randomised, open-label, phase 3 study called Mahogany (NCT05100862, BGB3111308; further details below) is underway, comparing the efficacy and safety of zanubrutinib + rituximab vs. lenalidomide + rituximab in R/R FL or MZL patients. In the MZL cohort, patients are randomised 1:1 to receive zanubrutinib plus rituximab (n=75) or lenalidomide plus rituximab (N=75).

Figure 41: Mahogany study design, MZL cohort



ORR: Objective response rate, CR: Complete response, PR: Partial response, DOR: Duration of response, CI: Confidence interval, PD: Progressive disease, OS: Overall survival, BID: Twice a day, QD: Once a day, MZL: Marginal zone lymphoma, R: Randomised, TTR: Time to response, PET: Positron emission tomography, IRC: Independent review committee, CT: Computed tomography, IA: Investigator analysis

SOURCES: CGIS RESEARCH, COMPANY DATA

In summary, the preliminary clinical trial results of Magnolia and BGB311AU003 show that zanubrutinib is a good treatment option for MZL patients. Although MZL is a rare type of lymphoma, which means the patient pool is small (detailed information in “Appendix 2. Lymphoma”), rare disease treatments are supported by many governments, in our opinion.

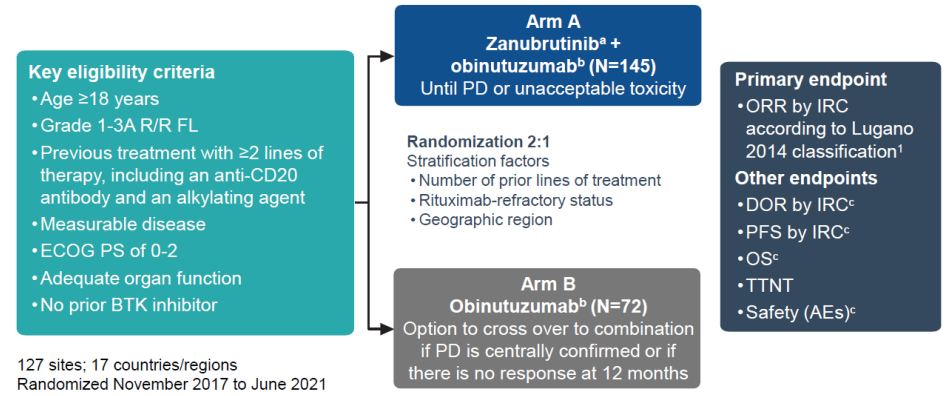
5. Zanubrutinib for relapsed or refractory (R/R) follicular lymphoma (FL)

On 12 Jul 2023, the US FDA accepted for review BeiGene's sNDA application for Brukinsa in combination with obinutuzumab (Gazyva), which is an anti-CD20 mAb, for the treatment of adult patients with R/R FL after at least two prior lines of therapy. The sNDA filing is based on results from the phase 2 Rosewood study released in 2023. BeiGene also submitted Brukinsa for review in R/R FL to regulatory authorities in the EU and China. The Canada, Switzerland, and UK submissions are part of the Access Consortium New Active Substance Work-sharing Initiative (NASWSI).

- Rosewood

Rosewood included 217 patients (145 receiving zanubrutinib plus obinutuzumab, and 72 patients receiving obinutuzumab monotherapy). At the median study follow-up of 20.2 months, the ORR by IRC was 69.0% (95% CI, 60.8-76.4) for zanubrutinib plus obinutuzumab (ZO) arm vs. 45.8% (95% CI, 34.0-58.0) for obinutuzumab arm. The CR rate for the ZO arm was 39.3% vs. 19.4% for obinutuzumab alone. The median DOR by IRC was 14.0 months with obinutuzumab and was not reached in the ZO arm. The median PFS was longer with ZO (28.0 months vs 10.4 months). The median time to next treatment (TTNT) was 12.2 months with obinutuzumab and was not reached in the ZO arm. The estimated OS rate at 24 months was numerically higher with ZO vs. obinutuzumab (77.3% vs. 71.4%). There were no expected safety findings with ZO. Among common treatment-emergent adverse events (TEAEs) of any grade, pyrexia and infusion-related reactions occurred more frequently with obinutuzumab (>5% difference vs. ZO).

Figure 42: Study design of Rosewood



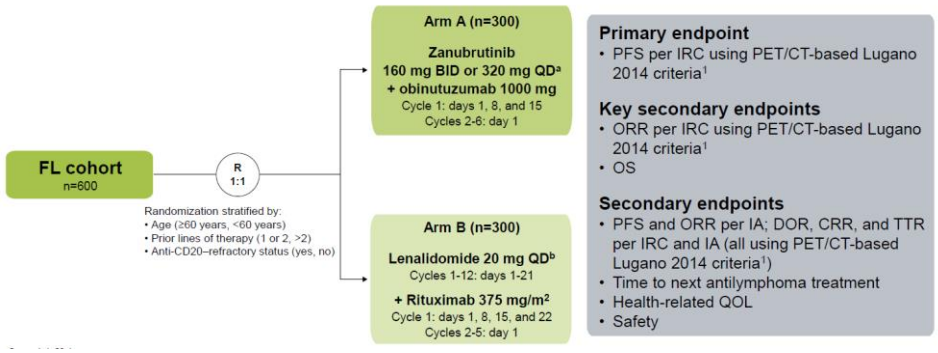
R/R: Relapsed or refractory, FL: Follicular lymphoma, ECOG: Eastern cooperative oncology group, PS: Performance status, IRC: Independent review committee, TTNT: Time to next treatment, ORR: Objective response rate, DOR: Duration of response, CI: Confidence interval, PD: Progressive disease, OS: Overall survival

SOURCES: CGIS RESEARCH, COMPANY DATA

- Mahogany

Mahogany (NCT05100862, BGB3111308) is a randomised, open-label, phase 3 study that is underway comparing the efficacy and safety of ZO vs. lenalidomide plus rituximab in R/R FL or MZL patients. In the FL cohort, patients are randomised 1:1 to receive ZO (n=300) and lenolidomide plus rituximab (n=300). The enrolment for Mahogany began in Mar 2022 and the study is currently recruiting for an estimated enrollment of 750 patients, with c.300 study sites in 25 countries planned.

Figure 43: Mahogany study design, FL Cohort



PET: positron emission tomography; IA: investigator assessment; QOL: quality of life; R: randomised; TTR: time to response, BID: Twice a day, PFS: Progression free survival, ORR: Objective response rate, OS: Overall survival, IRC: Independent review committee, QD: Once a day

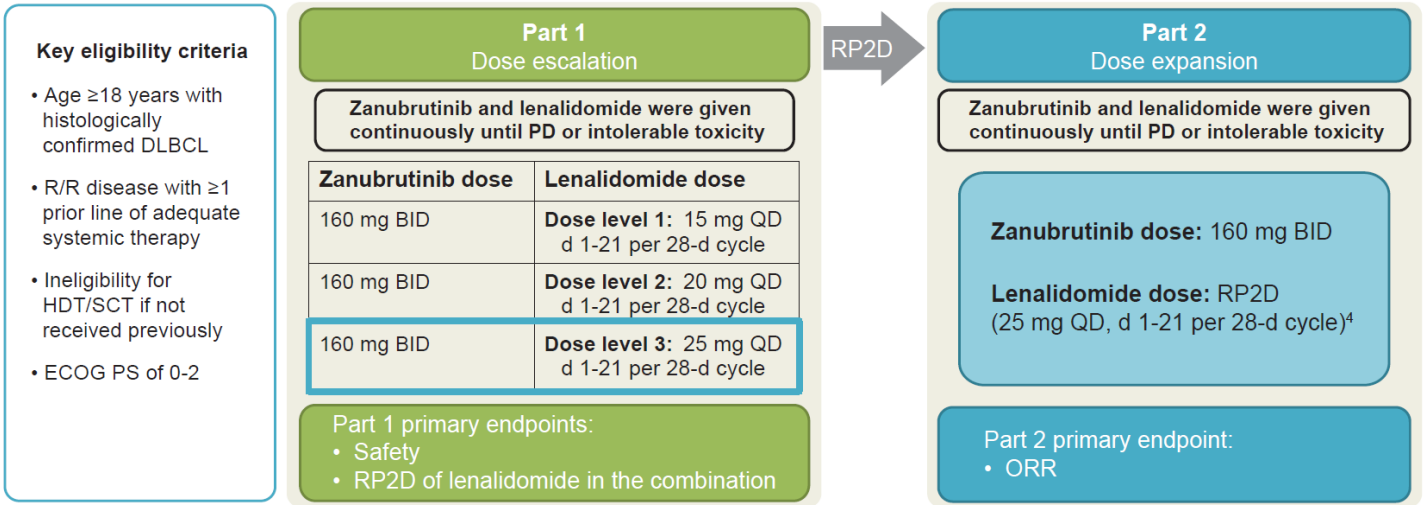
SOURCES: CGIS RESEARCH, COMPANY DATA

In summary, zanubrutinib was approved by the EC for the treatment of FL in Nov 2023 and the US FDA has already accepted the sNDA application for zanubrutinib in FL. We think the results from Rosewood will be strong support of the approval of zanubrutinib by the FDA and other countries in the future. As mentioned in "Appendix 2. Lymphoma", FL is the second-most common type of NHL, which makes it an important indication for pharmaceutical companies. Therefore, we think the future approval of FL will be a growth driver for BeiGene because of the large patient pool for FL.

6. Zanubrutinib for diffusing large B-cell lymphoma (DLBCL)

BeiGene presented the first interim analysis of a phase 1 (NCT04436107, BGB-3111-110) study of zanubrutinib plus lenalidomide in patients with R/R DLBCL at the American Society of Clinical Oncology's (ASCO) annual meeting and European Haematology Association (EHA) congress in 2023. NCT04436107 is an ongoing phase 1, open-label, dose escalation/expansion study of zanubrutinib plus lenalidomide in R/R DLBCL.

Figure 44: Study design of NCT04436107



ECOG PS: Eastern Cooperative Oncology Group performance status; HDT/SCT: high-dose therapy/stem cell transplant; RP2D: recommended part 2 dose

SOURCES: CGIS RESEARCH, COMPANY DATA (NCT04436107 STUDY)

As of 8 Nov 2022, 46 patients were treated and included in the interim analysis (27 in part 1, 19 in part 2, 30 at recommended phase 2 doses (RP2D). Median follow-up was 6.6 months (range 0.5-25.5). ORR was 46% overall (95% CI: 30.9-61.0%; CR: 24%) and 57% for recommended part 2 dose (RP2D; (95% CI: 37.4-74.5%; CR: 30%). RP2D ORR for patients with non-GCB disease was 61% (95%

CI: 38.5-80.3%; CR: 35%) and 50% for patients with GCB (95% CI: 11.8-88.2%; CR: 17%). Overall, the DOR was not reached and the 6-month event-free rate was 63.5% (95% CI: 32.8-83.0%). For RP2D, DOR was not reached and the 6-month event-free rate was 59% (95% CI: 23.8-82.8%). Overall, median PFS was 5.5 months (95% CI: 2.8–8.3 months), with a 9-month event-free rate of 31.1% (95% CI, 16.4-47.0%). At RP2D, the median PFS was 5.5 months (95% CI: 2.8-NE), with a 9-month event-free rate of 37% (95% CI: 17.6-57.4%). Overall, 46% of patients experienced ≥1 TEAE while 60% of patients experienced grade ≥3 TEAEs, the most common of hematologic toxicities.

There is also an ongoing, single-arm, multicentre phase 2 study called BGB-3111-213 (NCT03520920) to evaluate the efficacy and safety of zanubrutinib in combination with rituximab in R/R non-GCB DLBCL, FL and MZL patients. Four sites in China enrolled and treated 41 patients (20 non-GCB DLBCL, 16 FL, and five MZL). In the non-GCB cohort, the median DOR was 8.8 months (95% CI: 0.72-14.8 months) and the median PFS was 3.38 months. The estimated 12-month PFS event-free rates were 17.4%, 66%, and 75% for the non-GCB DLBCL, FL, and MZL cohorts, respectively. The most frequently reported treatment-emergent adverse events (TEAEs) were neutrophil count decrease (24.4%), and white blood cell count decrease (22%).

The BGB-3111-207 (NCT03145064) study was an ongoing multicentre single phase 2 study. 41 patients with R/R non-GCB DLBCL, across 11 centres in China, enrolled and received zanubrutinib. The median follow-up was 6.8 months, ORR was 29.3%, and CRR was 17.1%. Median DOR, PFS, and OS were 4.5, 2.8, and 8.4 months, respectively. Aes were reported in 48.8% of patients. Zanubrutinib demonstrated modest anti-tumour activity in non-GCB DLBCL, like other BTK inhibitors, as well as a safety profile consistent with previous studies.

In summary, as mentioned in “Appendix 2. Lymphoma”, DLBCL is the most common type of NHL, therefore DLBCL is one of most important indications for zanubrutinib because of the large global patient pool. The early results from the above clinical trials show an improved efficacy and safety profile for zanubrutinib. Therefore, we think the final results of these clinical trials could provide key data for the future approval of zanubrutinib in DLBCL. Because of the high incidence rate of DLBCL, we think the future approval for zanubrutinib will definitely be a strong revenue growth driver for BeiGene.

Tislelizumab

Tislelizumab (Tevimbra, BGB-A317) is a monoclonal anti-PD-1 antibody. It is an IgG4, a humanised antibody targeted to minimise binding to Fc gamma receptors (FcγR) on macrophages to lower the negative impact on T effector cells. In pre-clinical studies, binding to FcγR on macrophages has been shown to compromise the anti-tumour activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T effector cells, according to a journal titled “The binding of an anti-PD-1 antibody to Fc has a profound impact on its biological functions” (please refer to Appendix 3: Immune oncology, and Appendix 4: PD-1/PD-L1 therapy, for more information on the mechanism of action.)

In Sep 2023, the EC approved Tevimbra as monotherapy for the treatment of adult patients with unresectable, locally advanced or metastatic ESCC after prior platinum-based chemotherapy. In addition, the US FDA accepted for review a biologics license application (BLA) for tislelizumab as a first-line treatment for patients with unresectable, recurrent, locally advanced, or metastatic ESCC, with a target action date of 2H24F. The European Medicines Agency (EMA) is reviewing a marketing authorisation application for Tevimbra as a treatment for locally advanced or metastatic NSCLS after prior chemotherapy and in combination with chemotherapy for previously untreated locally advanced or metastatic NSCLC. Regulatory submissions for Tevimbra are also under review by authorities in the UK, Australia, China, New Zealand, Brazil, Korea, Switzerland, Israel, and Indonesia.

Tislelizumab is approved for 12 indications in China, and nine indications were included in the NRDL: classical Hodgkin (cHL) and urothelial carcinoma (UC) were included in 2020; non-squamous NSCLC, squamous NSCLC and HCC in 2021; locally advanced or metastatic NSCLC, MSI-H solid tumours, locally advanced or

metastatic ESCC following progression or intolerance to prior 1L chemotherapy, and for first-line recurrent or metastatic NPC, in 2022.

Figure 45: Approved indications of tislelizumab in China as at 15 Jan 2024

	Indication	Approval time	Clinical trials	Description
1	Conditional approval for classical Hodgkin (cHL) patients who have received at least two prior therapies.	Dec 2019	BGB-A317-203 NCT03209973	A single-arm, multi-centre, pivotal phase 2 trial.
2	Locally advanced or metastatic urothelial carcinoma (UC) with PD-L1 high expression whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	Apr 2020	NCT04004221	A single-arm, phase 2 trial for patients from China and South Korea.
3	1L treatment for advanced squamous NSCLC in combination with chemotherapy.	Jan 2021	Rationale 303 NCT03358875	A randomised, open-label, global phase 3 trial, comparing tislelizumab to docetaxel in patients with locally advanced or metastatic NSCLC who have progressed on prior platinum-based chemotherapy. A total of 805 patients in 10 countries across Asia, Europe, the Americas, and Oceania were enrolled.
4	1L treatment for advanced non-squamous NSCLC in combination with chemotherapy	Jun 2021	Rationale 304 NCT03663205	It is a phase 3 trial and a total of 334 patients in China were enrolled
5	Treatment for hepatocellular carcinoma (HCC) patients who have received at least one systemic therapy	Jun 2021	NCT03419897	A single-arm, open-label, multicentre, global pivotal phase 2 trial conducted in 249 patients from eight countries and regions in Asia and Europe.
6	2L or 3L treatment of patients with locally advanced or metastatic NSCLC with locally advanced or metastatic NSCLC who progressed on prior platinum-based chemotherapy.	Jan 2022	Rationale 303	
7	Treatment for locally advanced or metastatic ESCC who have disease progression or are intolerant to 1L standard chemotherapy.	Apr 2022	Rationale 302 NCT03430843	A randomised, open-label, multi-centre, global phase 3 clinical trial to evaluate the efficacy and safety of tislelizumab compared to chemotherapy.
8	1L treatment of patients with recurrent or metastatic nasopharyngeal cancer (RM-NPC).	Jun 2022	Rationale-309 NCT03924986	A multicentre, randomised, double-blind, placebo-controlled phase 3 clinical trial designed to evaluate the efficacy and safety of tislelizumab combined with gemcitabine and cisplatin versus placebo combined with gemcitabine and cisplatin.
9	Adult patients with advanced unresectable or metastatic microstatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours, including: patients with advanced colorectal cancer (CRC) who had been treated with fluoropyrimidine, oxaliplatin and commercial and other advanced solid tumours who develop disease progression after prior treatment and have no satisfactory alternative treatment options.	Mar 2022	NCT03736889	A single-arm, multi-centre, open-label, pivotal phase 2 clinical trial to evaluate efficacy and safety of tislelizumab as monotherapy in patients with previously treated locally advanced unresectable or metastatic MSI-H or dMMR solid tumours, with 80 patients enrolled in China.
10	1L treatment for gastric or gastroesophageal junction (G/GEJ) adenocarcinoma with high PD-L1 expression.	Feb 2023	Rationale 305 NCT03777657	A global, double-blind, phase 3 study comparing 1L tislelizumab +chemotherapy vs. placebo + chemotherapy in G/GEJ.
11	1L treatment for adult patients with unresectable locally advanced, recurrent or metastatic ESCC.	May 2023	Rationale 302	
12	1L treatment for HCC	Jan 2024	Rationale 301 NCT03412773	A global, randomised, open-label phase 3 study to compare the efficacy and safety of tislelizumab vs. sorafenib as a 1L systemic treatment in participants (n=674) with unrespectable HCC.

SOURCES: CGIS RESEARCH, COMPANY DATA

Based on released results from the above clinical trials, tislelizumab appears to safely deliver clinical improvements in survival benefits and quality of life for many cancer patients across a range of tumour types, both as a monotherapy and in combination with other regimens. There are also many ongoing tislelizumab clinical trials to treat different cancers, according to BeiGene.

Figure 46: Ongoing tislelizumab clinical trials, as of 30 Sep 2023

Indication	Clinical trial	
Lung cancer	NCT03358875	A global phase 3 trial evaluating tislelizumab as a 2L or 3L treatment compared to docetaxel in patients with locally advanced or metastatic NSCLC
	NCT03594747	Two phase 3 trials in China evaluating tislelizumab + chemotherapy versus chemotherapy in squamous NSCLC
	NCT03663205	Two phase 3 trials in China evaluating tislelizumab + chemotherapy versus chemotherapy in non-squamous NSCLC
	NCT04005716	A phase 3 trial in China in 1L SCLC evaluating tislelizumab + chemotherapy versus chemotherapy
	NCT04379635	A phase 3 trial in China of tislelizumab in combination with platinum-based doublet chemotherapy as neoadjuvant treatment for patients with NSCLC
Liver cancer	NCT03412773	A global phase 3 trial comparing tislelizumab with sorafenib as 1L treatment for patients with HCC
	NCT03419897	A global single-arm pivotal phase 2 trial in 2L or 3L unresectable HCC.
Gastric cancer	NCT03777657	A global phase 3 trial of tislelizumab combined with chemotherapy versus placebo combined with chemotherapy as 1L treatment for patients with gastric cancer.
Lymphoma	NCT04486391	A phase 3 trial in China comparing tislelizumab to salvage chemotherapy in patients with R/R cHL
	NCT03209973	A phase 2 trial in China in patients with R/R cHL
Bladder cancer	NCT03967977	A phase 3 trial in China in patients with commercial advanced or metastatic UC
	NCT04004221	A phase 2 trial in China in patients with commercial advanced or metastatic UC
ESCC	NCT03430843	A global phase 3 trial comparing tislelizumab with chemotherapy as 2L treatment for patients with advanced ESCC
	NCT03783442	A global phase 3 trial of tislelizumab in combination with chemotherapy as 1L treatment for patients with ESCC.
	NCT03957590	A phase 3 trial in China of tislelizumab versus placebo in combination with chemoradiotherapy in patients with localised ESCC
Solid tumour and nasopharyngeal cancer	NCT03736889	A phase 2 trial in China in patients with MSI-H/dMMR solid tumours
	NCT03924986	A phase 3 trial in China and Thailand of tislelizumab combined with chemotherapy versus placebo combined with chemotherapy as 1L treatment in patients with nasopharyngeal cancer.

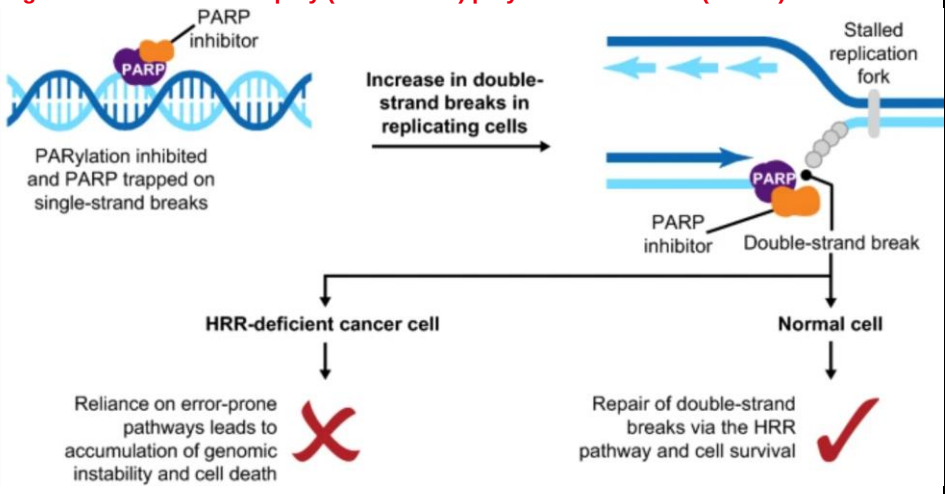
SOURCES: CGIS RESEARCH, COMPANY DATA

In summary, future growth drivers lie in more indications being approved for zanubrutinib, either as monotherapy or combination therapy. The above ongoing clinical trials will provide efficacy and safety data needed to pass the evaluations of different authorities.

Pamiparib

Pamiparib (BGB-290) is a small molecule inhibitor of PARP1 and PARP2. As members of the poly (ADP-ribose) polymerase (PARP) family, PAPR1 and PARP2 are involved in DNA replication and transcriptional regulation, and play an essential role in cell survival in response to DNA damage. RARP1 and PARP2 can bind to the site of damaged DNA and modulate a variety of proteins in DNA repair processes. PARPs inhibitors prevent the repair of common single-strand DNA breaks, which lead to the formation of double-strand breaks during DNA replication. Double-strand DNA breaks in normal cells are repaired by homologous recombination repair (HRR) pathways, therefore normal cells are relatively tolerant of PARP inhibitors. However, cancer cells which are HRR-deficient are sensitive to RARP inhibitors.

Figure 47: Mechanism of poly (ADP-ribose) polymerase inhibitor (PARPi)



SOURCES: Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Target Oncol. 2021

Pamiparib received conditional approval in May 2021 from NMPA for the treatment of patients with germline BRCA (gBRCA) mutation-associated recurrent advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more lines of chemotherapy, based on clinical results from a pivotal Phase 2 portion of the Phase ½ trial (NCT03333915). A total of 113 patients in China with high-grade, non-mucinous, epithelial ovarian cancer (including fallopian or primary peritoneal cancer), harbouring gBRCA mutations, following at least two prior lines of standard chemotherapy, were enrolled in the pivotal Phase 2 portion of the trial, including 90 patients with advanced platinum-sensitive ovarian cancer (PSOC), and 23 patients with advanced platinum-resistant ovarian cancer (PROC). For patients with PSOC, with a median follow-up time of 17.0 months, ORR was 68.3% (95% CI: 57.1, 78.1) and DoR was 13.8 months (95% CI: 10.97, 20.73). For patients with PROC, the median follow-up time was 11.6 months, the ORR was 31.6% (95% CI: 12.6, 56.6) and the median DoR was 11.1 months (95% CI: 4.21, 16.59). Grade ≥3 adverse reactions occurred in 71.7% of patients, with the most common (≥1%) being anaemia, neutropenia, leukopenia, thrombocytopenia, lymphopenia, vomiting, diarrhoea, increased gamma-glutamyltransferase, hypokalemia, abdominal pain, fatigue, upper respiratory tract infection, pancytopenia, and hypertension. Pamiparib is also undergoing a phase 3 trial as a maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer (OC) (NCT03519230), a phase 2 trial in first-line platinum-sensitive gastric cancer (GC) maintenance (PARALLEL 303, NCT03427814), and a phase 1b trial in combination with temozolomide in solid tumours (NCT03150810).

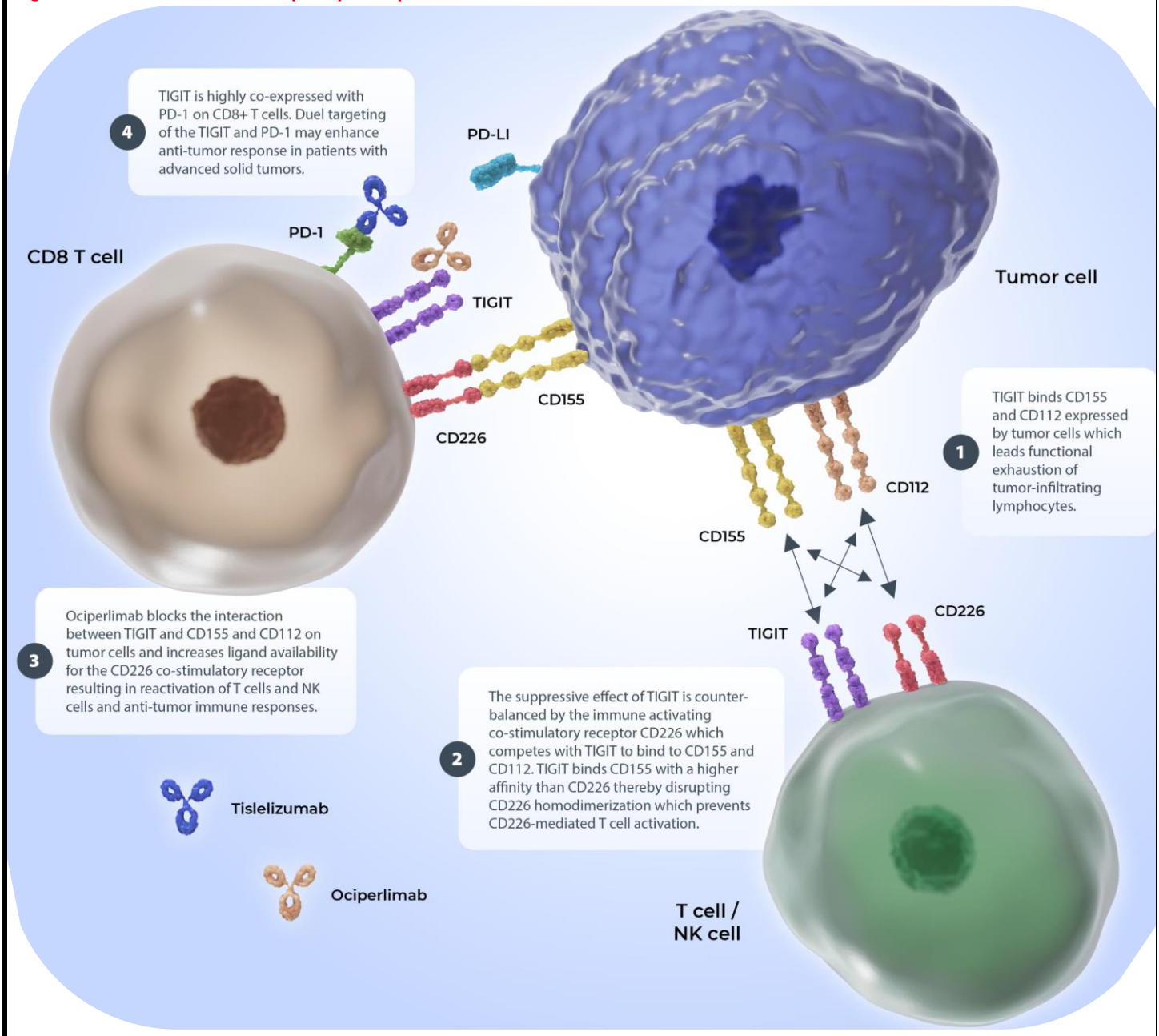
In summary, ongoing trials could provide crucial data on the effects and safety of the drug to support future approvals for use to treat other solid tumours and expand its potential customer volume.

Ociperlimab

Ociperlimab (BGB-A1217) is an investigational humanised mAb designed to bind T cell immunoglobulin and immunoreceptor tyrosine-base inhibitory motif domain (TIGIT). TIGIT is a co-inhibitory immune checkpoint receptor expressed on multiple immune cells, including regulatory T cells (Tregs), activated and exhausted T cells, and natural killer (NK) cells. TIGIT binds to two ligands, poliovirus receptor 9 (CD155) and poliovirus receptor-related 2 (CD112), expressed by tumour cells and antigen-presenting cells, which leads to inhibitory signalling in T cells. TIGIT expression is unregulated in the tumour microenvironment in multiple malignancies and it is often co-expressed with PD-1 and other inhibitory receptors, such as TIM-3 and LAG-3, on exhausted CD8+ T cells and Tregs in tumours. Ociperlimab binds to TIGIT and blocks its interactions with the CD155 and CD112 ligands on tumour cells, resulting in the activation of T cell mediated antitumour immune responses.

Ociperlimab is currently undergoing a pivotal phase 3 trial in combination with tislelizumab in 1L PD-L1 positive advanced/metastatic NSCLC and a global phase 3 trial in locally advanced NSCLC in combination with concurrent chemoradiation. Ociperlimab plus tislelizumab is further evaluated in an undergoing pivotal global phase 2 trials in combination with chemotherapy in 1L NSCLC irrespective of PD-L1 expression as well as in combination with tislelizumab and concurrent chemoradiotherapy in the previously untreated limited-stage SCLC. Novartis had paid BeiGene US$300m upfront to obtain the 31 ommercialization rights of ociperlimab in overseas market from BeiGene in 2021, but BeiGene regained the global right of ociperlimab from Novartis in Jul 2023 due to the termination of this collaboration.

Figure 48: Mechanism of action (MOA) of ociperlimab



SOURCES: CGIS RESEARCH, COMPANY DATA

BeiGene also released several progress reports of ociperlimab in American Society of Clinical Oncology's (ASCO) annual meeting in 2023. AdvanTIG-203 progress showed in the second line (2L) therapy of advanced ESCC patients, ociperlimab (O) + tislilelizumab (T) showed a tolerable safety profile and trend towards better ORR, but similar PFS compared to placebo (P) +T. The AdvanTIG-202 progress demonstrated that O + T showed promising antitumor activity and durable response, regardless of PD-L1 expression, and was well tolerated in patients with recurrent/metastatic (R/M) cervical cancer (CC). The AdvanTIG-206 results indicated that in patients with advanced hepatocellular carcinoma (HCC), T + BAT1706 (bevacizumab biosimilar) demonstrated promising ORR. AdvanTIG-105 results showed that O +T + chemotherapy was generally well tolerated and showed encouraging antitumour activity in patients with stage IV gastric/gastroesophageal adenocarcinoma (GC/GEJC). We think these clinical result updates show that the combination of O and T manifested in improved antitumour activity, making ociperlimab a promising cancer immuno-therapy candidate.

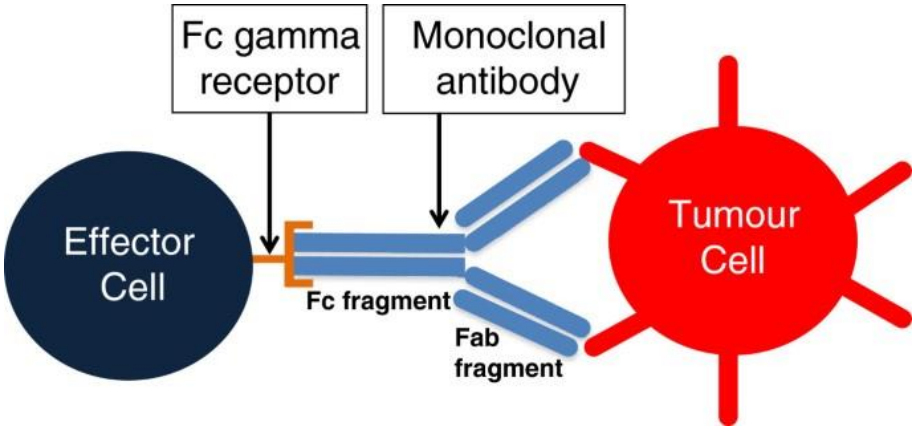
Figure 49: Ongoing clinical trials for ociperlimab as at Jun 2023

Compound	Disease area	Trial	Phase	Countries	Progress
Ociperlimab (O) + Tislelizumab (T)	1L PD-L1 positive, unresectable, locally advanced, recurrent or metastatic NSCLC	AdvanTIG-302 BGB-A317-A1217-302 NCT04746924	Randomised, multicenter phase 3 study	Globally	Enrolment complete
	2L PD-L1 positive advanced ESCC	AdvanTIG-203 BGB-A317-A1217-203 NCT04732494	Randomised, double-blind, placebo (P)-controlled, multicenter phase 2 study	Globally	Investigator-assessed ORR was 30.6% with O + T vs. 20.6% with P + T, HR of INV-assessed PFS was 0.93 (95% CI: 0.61, 1.43). Incidence of patients with ≥1 any AE was comparable between O +T (93.5%) and P + T (95.2%)
	2L+ cervical cancer	AdvanTIG-202 NCT04693234 BGB-A317-A1217-202	Randomised, multicenter, open-label study	China, South Korea	2023 ESMO poster: Link
	Advanced solid tumours	AdvanTIG-105 NCT04047862 BGB-900-105	1b dose-expansion study in patients with ESCC and EAC.	Globally	ASCO 2023 abstract: Link
Ociperlimab + Tislelizumab + concurrent chemoradiotherapy	Previously untreated, stage III unresectable NSCLC	AdvanTIG-301 BGB-A317-A1217-301 NCT04866017	Phase 3	Conducted in Australia, U .S.	
Ociperlimab + tislelizumab or rituximab	R/R DLBCL	AdvanTIG-101 NCT05267054	Phase 2	China	
Tislelizumab + Ociperlimab + BAT1706 (anti-VEGF bevacizumab biosimilar)	1L HCC	NCT04948697 AdvanTIG-206	Phase 2 randomised, multicenter, open label study.	Conducted in China	2023 ESMO poster: LinkINV-assessed ORR was 35.5% with O + T +B vs. 37.5% with T + B. For O+T+B and T+B, respectively, Grade ≥ 3 TRAEs were 50.0% and 25.8%.
Ociperlimab + Tislelizumab + Chemotherapy	1L NSCLC	AdvanTIG-205 NCT05014815	Phase 2	Worldwide	
Tislelizumab + Ociperlimab + LBL-007	Resectable stage II/IIIA NSCLC	BGB-LC-202 NCT05577702	Phase 2	China	

SOURCES: CGIS RESEARCH, COMPANY DATA

There are two types of anti-TIGIT candidates. The first kind is similar to ociperlimab and has an FC receptor function. The FC receptor, which is found on the immune cell surface, binds to antibdodies (Abs) which are attached to infected cells or invading pathogens. In pre-clinical models, ociperlimab induced antibody dependent cellular cytotoxicity (ADCC) against Treg cells, activated NK cells and monocytes, and removed TIGIT from T cell surfaces in an Fc-dependent manner, according to results presented in “An Fc-competent anti-Human TIGIT Blocking Ab ociperlimab elicits strong immune responses and potent anti-tumour efficacy in pre-clinical models” in 2022.

Figure 50: The Ab-dependent cellular cytotoxicity complex



SOURCES: Mellor JD, Brown MP, Irving HR, Zalcberg JR, Dobrovic A. A critical review of the role of Fc gamma receptor polymorphisms in the response to monoclonal antibodies in cancer. J Hematol Oncol. 2013.

Tiragolumab from Roche (ROG.US, NR, CP😊 is another anti-TIGIT candidate with an intact Fc region. Roche's TIGIT candidate failed to meet clinical endpoints in two clinical trials in 2022. In May 2022, Roche announced that phase 3 of the Skyscraper -01 study (n=534) to evaluate tiragolumab + Tecentriq (atezolizumab) vs. Tecentriq alone as an 1L treatment for people with PD-L1-high locally advanced or metastatic NSCLC, and the phase 3 Skyscraper -02 study to evaluate tiragolumab + Tecentriq and chemotherapy (carboplatin and etoposide) as an 1L treatment for people with extensive-stage SCLC, did not meet its PFS endpoint. We think this announcement of undesirable clinical results may have cast a shadow over the TIGIT target.

However, in Aug 2023, new results shed light on the tiragolumab study. The second interim analysis of Skyscraper-01, the median OS estimates of 22.9 months (95% CI: 17.5, NE) in the tiragolumab + Tecentriq arm and 16.7 months (95% CI: 14.6, 20.2) in the Tecentriq monotherapy arm, yielded HR of 0.81 (95% CI: 14.6, 20.2). The median follow-up was 15.5 months. Roche also released results from the MORPHEUS-Liver study, a phase Ib/II randomised evaluation of tiragolumab (tira) in combination with atezolizumab (atezo) and bevacizumab (bev) in patients with unresectable, locally advanced or metastatic heptocellular carcinomas, at the 2023 American Society of Clinical Oncology (ASCO) annual meeting. The tira + atezo + bev arm exhibited improved ORR and PFS. We think the promising early results from Morpheus-Liver and updated interim results of Skycraper-01 prove that TIGIT is a good target in cancer treatment.

Figure 51: Efficacy outcome of Morpheus-Liver study in Aug 2023

	Tira + atezo + bev	Atezo + bev
ITT, n	40	18
Confirmed ORR, % (n/N) (95% CI)	42.5 (17/40) (27.0–59.1)	11.1 (2/18) (1.4–34.7)
Median PFS, months (95% CI)	11.1 (8.2–NE)	4.2 (1.6–7.4)
HR (95% CI)	0.42 (0.22–0.82)	
PD-L1+, n	16	7
Confirmed ORR, % (n/N)	56.3 (9/16)	14.3 (1/7)
Median PFS, months (95% CI)	13.6 (7.1–NE)	2.8 (2.3–NE)
HR (95% CI)	0.46 (0.16–1.31)	
PD-L1–, n	18	9
Confirmed ORR, % (n/N)	27.8 (5/18)	0 (0/9)
Median PFS, months (95% CI)	9.1 (4.0–NE)	4.2 (1.5–7.4)
HR (95% CI)	0.36 (0.14–0.94)	

ITT: Intent to treat, CI: Confidence interval, PFS: Progression free survival, NE: Not estimable, ORR: Objective response rate, HR: Hazard ratio

SOURCES: AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO), CGIS RESEARCH

The second type of anti-TIGIT candidate has a mutated receptor function. One example is domvanalimab, an investigational mAb developed by Gilead Sciences (GILD.US, NR, CP:) and Arcus Biosciences (RCUS. US, NR, CP:). Gilead updated an interim analysis of its ARC-7 study in Jun 2023 that showed domvanalimab demonstrating consistent improvements in PFS in the NSCLC study. ARC-7 is a phase 2, randomised, open-label study evaluating the combinations of Fc-silent anti-TIGIT monoclonal antibody domvanalimab plus anti-PD-1 mAb zimberelimab (doublet) and domvanalimab plus zimberelimab and etrumadenant, an A2a/b adenosine receptor antagonist (triplet), versus zimberelimab monotherapy.

Figure 52: Interim result of ARC-7 study in 2022

Endpoint	Zimberelimab monotherapy (n=50)	domvanalimab + zimberelimab (n=50)	etrumadenant + domvanalimab + zimberelimab (n=50)
PFS			
Median in Months (95% CI)	5.4 (2.7, 9.7)	9.3 (4.1, NE)	9.9 (4.8, 14.6)
Hazard Ratio* (95% CI)		0.67 (0.4, 1.13)	0.72 (0.63, 1.8)
Six-month PFS rate (95% CI)	45% (30, 59)	58% (43, 72)	62% (48, 76)
12-month PFS rate (95% CI)	25% (11, 40)	41% (26, 56)	44% (29, 59)
ORR			
ORR+ Confirmed + Pending (95% CI)	15 (30%) [17.9%, 44.6%]	20 (40%)++ [26.4%, 54.8%]	22 (44%) [30%, 58.7%]
CR	1 (2%)	1 (2%)	0 (0%)
Partial Response Confirmed	14 (28%)	18 (36%)	22 (44%)
Partial Response Pending	0 (0%)	1 (2%)	0 (0%)
SD	16 (32%)	18 (36%)	16 (32%)
PD	12 (24%)	4 (8%)	7 (14%)
NE	7 (14%)	8 (16%)	5 (10%)

CI: Confidence interval, PFS: Progression free survival, NE: Not estimable, ORR: Objective response rate, HR: Hazard ratio, CR: Complete response, SD: Stable disease, PD: Progressive disease

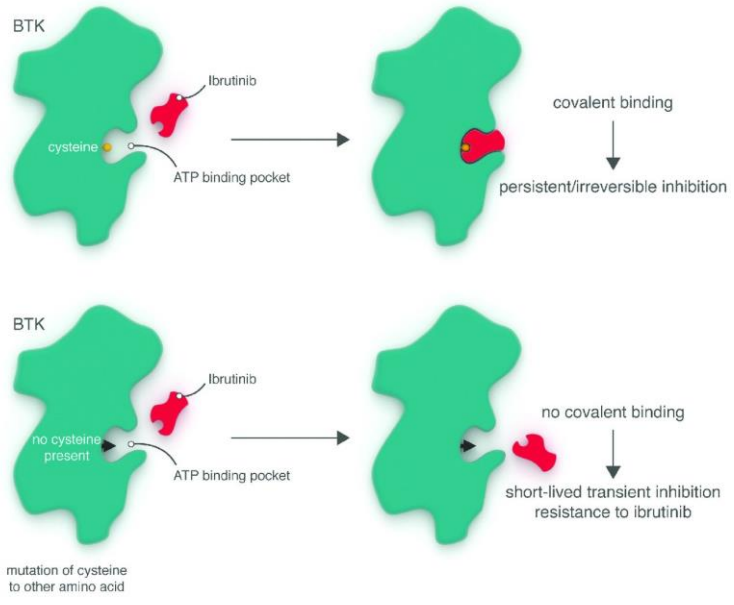
SOURCES: CGIS RESEARCH, GLIEAD

In summary, we think the promising results from multiple ociperlimab, tiragolumab and domvanalimab trials show that TIGIT is a good target for cancer immuno-therapy. The anti-TIGIT Ab and anti-PD-1 Ab can synergise to enhance antitumour response. Ociperlimab, as one of the most clinically advanced anti-TIGIT candidates in the world, has great potential to be an early and effective anti-TIGIT Ab therapy, in our view.

BGB-16673

BTK is a key component of the B cell antigen receptor (BCR) signalling pathway whose chronic activation is critical for cell proliferation and survival in various B cell malignancies. Inhibition of BTK by covalent BTKi (cBTKi), such as ibrutinib, acalabrutinib, and zanubrutinib, has revolutionised the treatment of B cell malignancies. However, one problem is that BTK resistant mutations at cysteine 481 is frequently acquired. This mutation affects the binding capacity of cBTKi to BTK which limits the long-term clinical benefit of cBTKi.

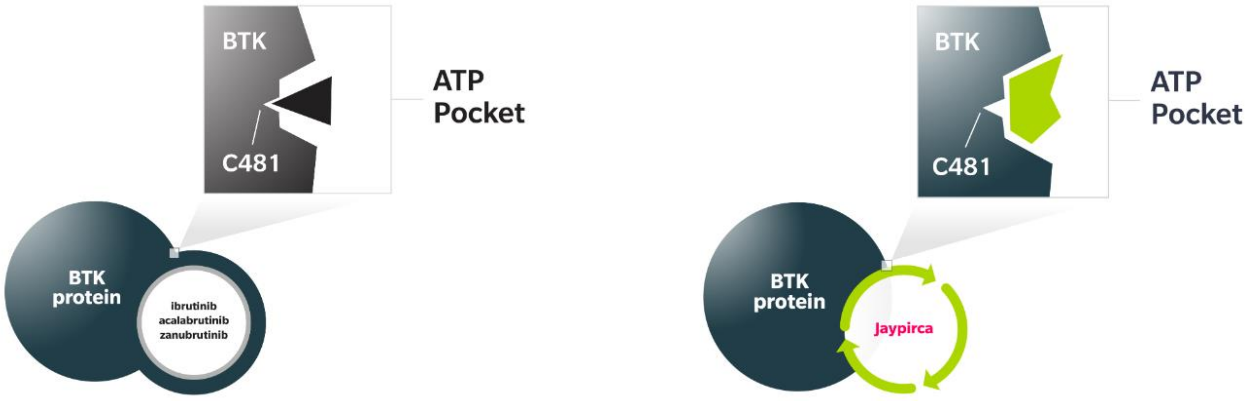
Figure 53: Mutation of cysteine



SOURCES: Wiestner A. The role of B-cell receptor inhibitors in the treatment of patients with chronic lymphocytic leukemia. Haematologica. 2015

Covalent or non-covalent BTKis and BTK-targeted degradation, which could overcome resistance mutations, may provide novel treatment options, in our opinion. One example of non-covalent BTKi is pirtobrutinib (Jaypirca) from Eli Lilly (LLY.US, NR, CP:), which was approved by the US FDA in Jan 2023 for R/R MZL, and in Dec 2023 for 3L CLL/SLL. Eli Lilly collaborated with Innovent (1801.HK, NR, CP:) for market approval in China and, Oct 2023, its application for R/R MZL was included in China's Center For Drug Evaluation (CDE) priority review of premarket submissions.

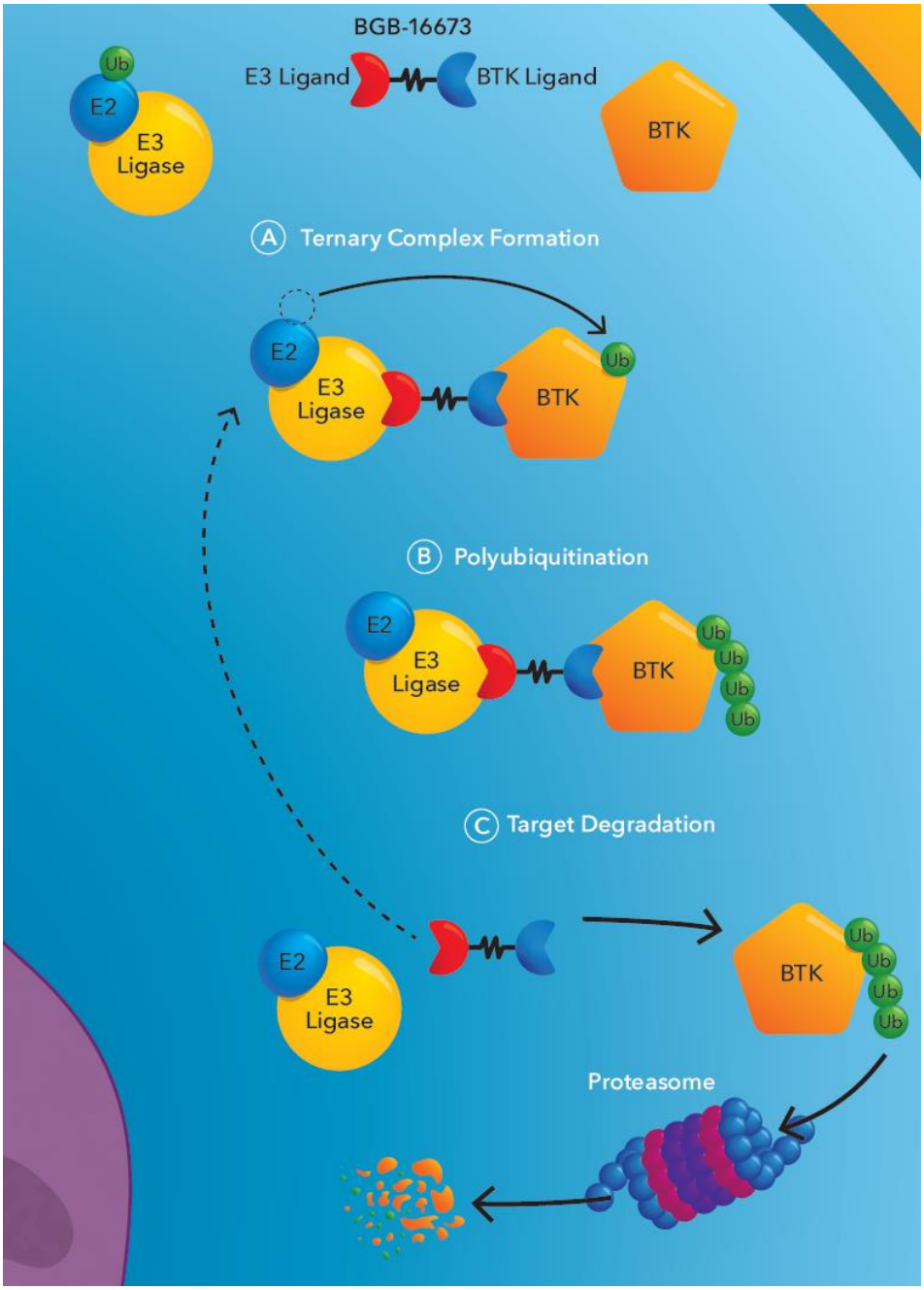
Figure 54: Mechanism of action (MOA) of Jaypirca



SOURCES: CGIS RESEARCH, ELI LILY

BeiGene's BGB-16673 is an orally-available BTK-targeting chimeric degradation activation (BTK-CDAC) compound designed to degrade wild type BTK and multiple mutant forms. It is a bivalent molecule comprising a BTK-binding site + linker + E3 ligase binder. The engagement of the drug with BTK activates the ubiquitination pathway, resulting in degradation of BTK. It is currently evaluated in two phase I studies: NCT05006716 (BGB-16673-101) and NCT05294731. Please refer to "Appendix 5: PROTAC" for more details on the mechanism of chimeric degradation.

Figure 55: Mechanism of action (MOA) of BGB-16673

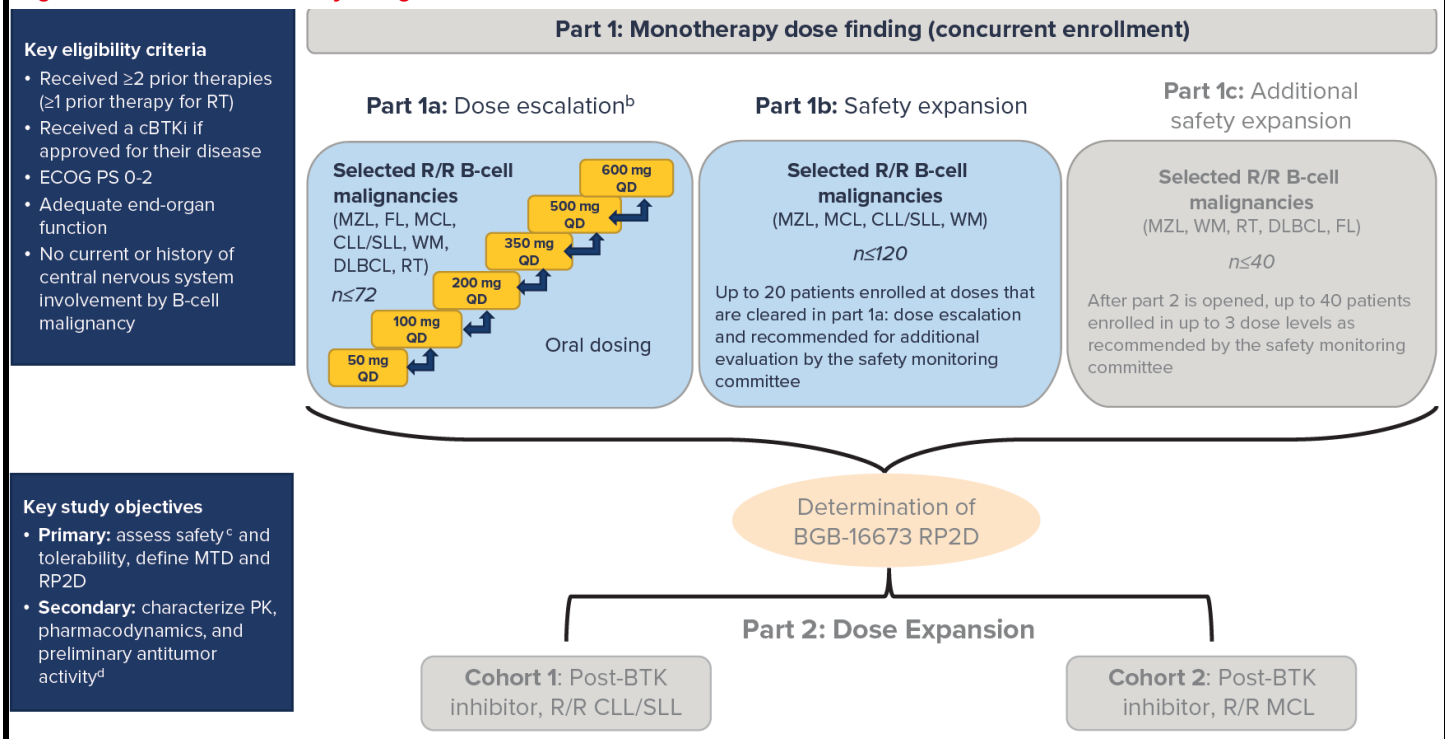


SOURCES: CGIS RESEARCH, COMPANY DATA

BeiGene presented a poster of BGB-16673 titled "BGB-16673, A BTK Degrader, Overcomes On-Target Resistance From BTK Inhibitors And Presents Sustainable Long-Term Tumour Regression In Lymphoma Xenograft Models" at the 2023 European Haematology Association (EHA) annual meeting. The preclinical results showed that BGB-16673 was less apt to cause on-target resistance mutations and could overcome a wide variety of BTK resistance mutations derived from mutagenesis screens and relapsed patients.

In addition, initial findings from phase I of the concurrent enrolment NCT05006716 trial were presented during the 2023 American Society of Haematology (ASH) annual meeting. Patients with R/R CLL/SLL, WM, MCL, MZL, non-germinal centre B-cell DLBCL, FL, or Richter transformation (RT) are eligible for this open-label, dose escalation and expansion study evaluating BGB-16673 in adults.

Figure 56: NCT05006716 study design



R/R: relapsed or refractory, MCL: mantle cell lymphoma, TN: treatment naïve , CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma, WM: Waldenstr'm's macroglobulinemia, MZL: marginal zone lymphoma, FL: follicular lymphoma, DLBCL: Diffuse large B cell lymphoma, n: number, ECOG: Eastern cooperative oncology group, PS: performance status, PK: pharmacokinetic, BTKi: bruton tyrosine kinase inhibitor, RT: radiation therapy, MTD: maximum tolerated dose, RP2D: recommended phase 2 doses

SOURCES: COMPANY DATA (NCT05006716 STUDY), CGIS RESEARCH

ORR was 57% for all efficacy-evaluable patients (n=28). Responses consisted of 1 CR, 13 PRs, 1 PR with PR-L, and 1 MR. The disease control rate (DCR) was 75%, with a median time to first response of 2.76 months. The ORR in patients with CLL/SLL was 70%, and included 6 PRs, 1 PR-L, 2 SDs, and 1 patient who discontinued treatment prior to first assessment. The DCR in this cohort was 90%, and the median time to first response was 2.83 months. In patients with WM, MCL or MZL, the ORR was 56%, with 1 CR, 7 RPs, 1 MR, 3 SDs and 3 PDs, as well as 1 patient who discontinued treatment prior to their first assessment. These patients had a DCR of 75% and a median time to first response of 2.33 months.

Figure 57: Responses by histology in evaluable patients

	CLL/SLL (n=10)	MCL/MZL/WM/ FL (n=16)	DLBCL/RT (n=2)	All (n=28)
Best overall response, n (%)				
CR	0	1 (6)	0	1 (4)
PR	6 (60)	7 (44)	0	13 (46)
PR-L	1 (10)	N/A	0	1 (4)
MR	0	1 (6)	0	1 (4)
SD	2 (20)	3 (19)	0	5 (18)
PD	0	3 (19)	2 (100)	5 (18)
Discontinued prior to first assessment	1 (10)	1 (6)	0	2 (7)
Disease control rate, n (%)[a]	**9 (90)**	**12 (75)**	**0**	**21 (75)**
ORR, n (%)[b]	**7 (70)**	**9 (56)[d]**	**0**	**16 (57)**
Median time to first response, months[c]	2.83	2.33	N/A	2.76

CR: Complete response, PR: Partial response, MR: Minimal response,sSD: Stable disease, PD: Progressive disease, PR-L: Partial response with lymphocytosis, ORR: Objective response rate

SOURCES: CGIS RESEARCH, COMPANY DATA

Across all dose levels, 92% of patients experienced any treatment emergent adverse event (TEAE), with 38% of patients experiencing grade 3 or higher toxicities and 28% experiencing serious AEs. Any-grade Treatment-related adverse event (TRAE) were observed in 64% of patients, 22% of which were grade 3 or higher and 10% of which were serious TRAEs. Two TEAEs led to death, although neither death was treatment related. Three TEAEs led to treatment

discontinuation, including 1 TRAE; 11 TEAEs led to treatment modification, including 11 dose interruptions and 2 dose reductions.

The most common TEAEs in more than 10% of all patients consisted of contusion (any-grade, 30%; grade ≥ 3, 0%), diarrhoea (24%; 0%), fatigue (20%; 0%), increased amylase (16%; 0%), neutropenia (16%; 12%), increased lipase (14%; 4%), pyrexia (14%; 0%), cough (12%; 0%), headache (10%; 0%), thrombocytopenia (10%; 4%), pneumonia (6%; 6%), and Covid-19 pneumonia (4%; 4%). Common grouped TEAEs of interest included bleeding (42%; 4%) and infection (40%; 16%). No atrial fibrillation or hypertension was reported to date.

Figure 58: Overall safety summary of NCT05006716

Patients, n (%)	50 mg (n=4)	100 mg (n=14)	200 mg (n=15)	350 mg (n=13)	500 mg (n=4)	All Doses (N=50)
Any TEAE	4 (100)	13 (93)	13 (87)	12 (92)	4 (100)	46 (92)
Any treatment-related	3 (75)	11 (79)	8 (53)	8 (62)	2 (50)	32 (64)
Grade 3 or higher	3 (75)	4 (29)	6 (40)	5 (38)	1 (25)	19 (38)
Treatment-related grade 3 or higher	2 (50)	4 (29)	2 (13)	3 (23)	0	11 (22)
Serious	1 (25)	4 (29)	5 (33)	4 (31)	0	14 (28)
Treatment-related serious	0	2 (14)	2 (13)	1 (8)	0	5 (10)
Leading to death[a]	0	0	2 (13)	0	0	2 (4)
Treatment-related leading to death	0	0	0	0	0	0
Leading to treatment discontinuation[b]	0	0	1 (7)	2 (15)	0	3 (6)
Treatment-related leading to treatment discontinuation	0	0	0	1 (8)	0	1 (2)
Leading to treatment modification	1 (25)	4 (29)	4 (27)	2 (15)	0	11 (22)
Dose interruption	1 (25)	4 (29)	4 (27)	2 (15)	0	11 (22)
Dose reduction[c]	1 (25)	1 (7)	0	0	0	2 (4)
DLT[d]	0	0	1 (7)	0	0	1 (2)

DLT: Dose limiting toxicities

SOURCES: CGIS RESEARCH, COMPANY DATA

In summary, the pre-clinical results of BGB-16673 showed deep BTK degradation activity while early clinical study results demonstrated promising efficacy and safety for the treatment of lymphoma patients. Therefore, we think BGB-16673 has the potential to become the treatment option for patients that develop resistance after taking Brukinsa as monotherapy or in combination with sonrotoclax. The mechanism of action (Moa) of CDAC also makes BGB-16673 effective in multiple indications, such as large B-cell lymphoma (LBCL). We think the approval of BGB-16673 will address the unmet clinical demand of patients that develop resistance after taking Brukinsa, and thus create a new revenue driver for BeiGene when it receives approval.

Sonrotoclax

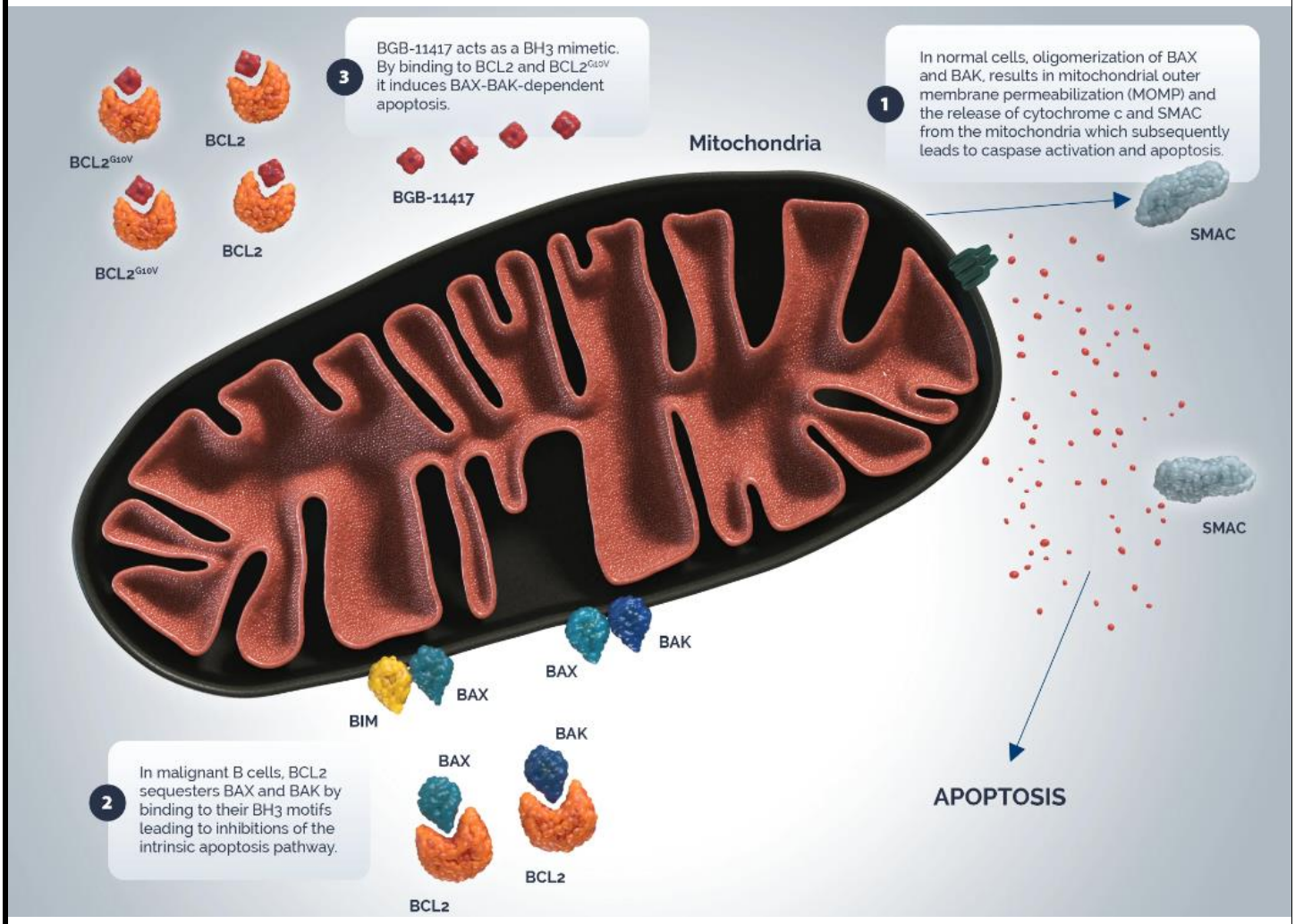
BCL2 is a key regulator of apoptosis, aberrantly expressed in many hematologic malignancies. This first globally approved BCL2 inhibitor, venetoclax from AbbVie, has been shown to be safe and effective and is approved for the treatment of patients with CLL/SLL and AML. Please refer to “Appendix 6: BCL-2 inhibitor” for more details of BCL-2 inhibitor and “Appendix 7: Leukemia” for more details on AML.

BeiGene’s sonrotoclax (BGB-11417) is a highly selective BH3 mimetic, binding to BCL2 to induce BAX-BAK-dependent apoptosis. In in vitro studies, sonrotoclax potently inhibited both wildtype and G10V-mutated BCL2, which is a known mutation of BCL2 associated with acquired resistance of venetoclax. Sonrotoclax also showed better activity against BCL2-dependent hematological tumours than venetoclax in vitro.

Phase I clinical data for NHL, CLL, AML and MM from NCT04277637 (BGB-11417-101, link), NCT04883957 (BGB-11417-102, link), NCT04771130 (BGB-11417-103), and BGB-11417-105 (NCT04973605, link) were presented by BeiGene at ASH 2022 while updated preliminary data from BGB-11417-105 (link)

and BGB-11417-101 (link) were presented in ASH 2023. BeiGene also initiated patient dosing in a Phase 2 study to evaluate BGB-11417 as monotherapy in patients with R/R MCL (NCT05471843) and R/R CLL/SLL (NCT05479994) in 2022.

Figure 59: Mechanism of action (MOA) of sonrotoclax



SOURCES: CGIS RESEARCH, COMPANY DATA

Figure 60: Potency and selectivity profile of BCB-11417

In vitro assays	BGB-11417	venetoclax
SPR binding assay K_D (nM)		
Bcl-2 WT	0.035	1.3
Bcl-2 G101V	0.28	34
TR-FRET assay IC_{50} (nM)		
Bcl-2 WT	0.014	0.20
Bcl-X_L	28	65
Mcl-1	>10000	>10000
Bcl-w	1803	2730
Bcl2A1	>10000	>10000
Cell survival assay IC_{50} (nM)		
RS4;11 cell line	0.42	3.4
Molt4 cell line	2314	2790

Abbreviation: IC_{50}, 50% inhibitory concentration

SOURCES: COMPANY DATA, CGIS RESEARCH

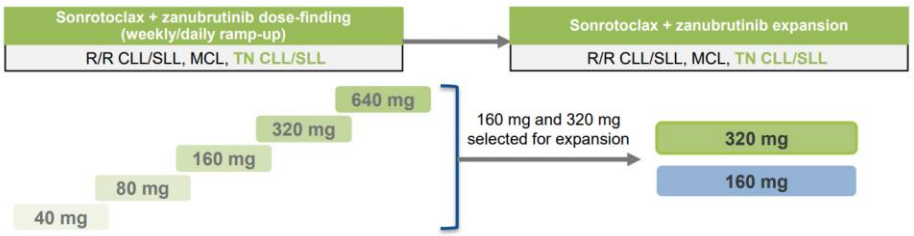
Figure 61: Ongoing sonrotoclax trials as at Jan 2023

Clinical trial	Phase	Therapy	Indication	Latest update
BGB-11417-301 (NCT06073821)	Phase 3	+ Zanubrutinib	TN CLL	
BGB-11417-203 (NCT05952037)	Phase 2	Monotherapy	r/r WM	
BGB-11417-201 (NCT05471843)	Phase 1/2	Monotherapy	r/r MCL	
BGB-11417-202 (NCT05479994)	Phase 2	Monotherapy	r/r CLL/SLL	
BGB-11417-101 (NCT04277637)	Phase 1/1b dose-escalation and dose-expansion study	monotherapy	B-cell malignancies	r/r MZL: 2023 ASH Link cn CLL/SLL: 2023 ASH Link
BGB-11417-102 (NCT04883957)	Phase 1	monotherapy	B-cell malignancies	
BGB-11417-103 (NCT04771130)	Phase 1b/2 dose-finding and expansion study	+ azacitidine	Tn or R/R AML	
BGB-11417-105 (NCT04973605)	phase 1b/2	+ dexamethasone +/- carfilzomib	R/R MM with the t(11;14)	ASH2023: Link

SOURCES: CLINICATRIALS.GOV, CGIS RESEARCH

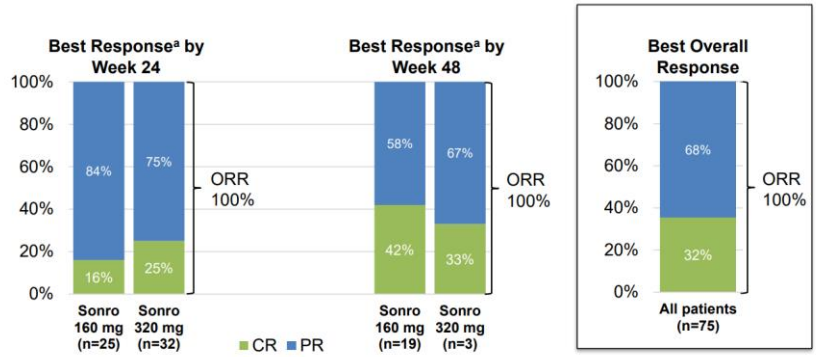
BGB-11417-101 is a phase 1/2 study evaluating sonrotoclax as monotherapy, in combination with zanubrutinib, and in combination with obinutuzumab ± zanubrutinib in patients with B-cell malignancies. Adverse events (AEs) observed with sonrotoclax + zanubrutinib combination therapy were mostly grades 1 and 2. At a median follow-up of 9.7 months, no patient experienced disease progression or died at either sonrotoclax dose level; ORR was 100%. Based on these data, sonrotoclax 320 mg was selected for the phase 3 study in combination with zanubrutinib in patients with TN CLL.

Figure 62: Clinical design of BGB-11417-101



SOURCES: COMPANY DATA (BGB-11417-101 STUDY), CGIS RESEARCH

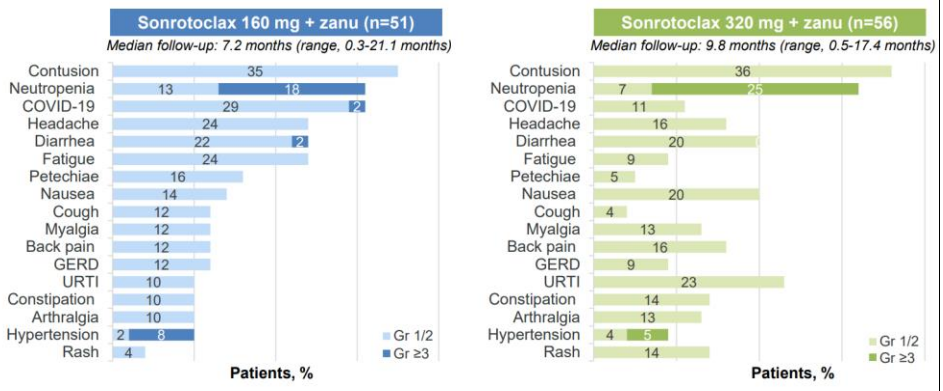
Figure 63: ORR of BGB-11417-101



Percentage of response is based on number of patients who have reached the assessment at 24 or 48 weeks after completion of ramp-up, following zanubrutinib monotherapy and sonrotoclax ramp-up to target dose.

SOURCES: COMPANY DATA (BGB-11417-101 STUDY)

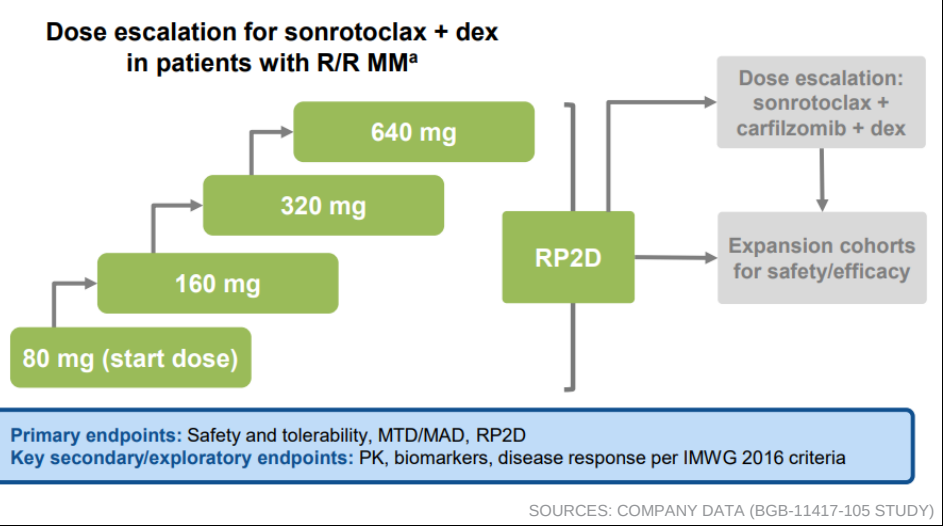
Figure 64: Most frequent AEs of BGB-11417-101 (incidence ≥5 patients)



SOURCES: COMPANY DATA (BGB-11417-101 STUDY)

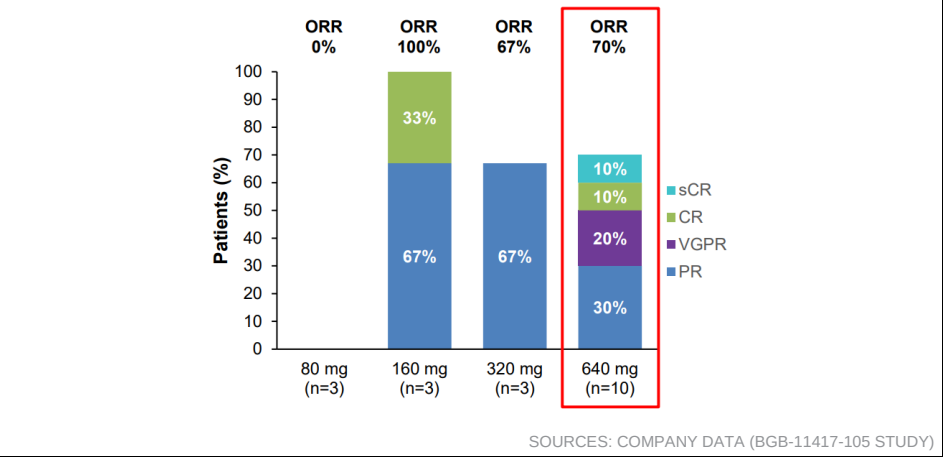
BGB-11417-105 (NCT04973605) is an ongoing phase 1b/2 study in patients with R/R MM harboring the t(11;14) translocation. Sonrotoclax + dexamethasone combination treatment was well tolerated in a heavily pretreated population (median of 4 prior lines of therapy), with no dose limiting toxicities observed at any tested dose level and the majority (74%) of patients only experiencing Grade 1 or 2 AEs. The majority of patients (70%) receiving 640 mg achieved a clinical response including ≥VGPRs of 40%.

Figure 65: Design of BGB-11417-105



SOURCES: COMPANY DATA (BGB-11417-105 STUDY)

Figure 66: Investigator-assessed response rates of BGB-11417-105



SOURCES: COMPANY DATA (BGB-11417-105 STUDY)

Figure 67: Overall safety summary and DLTs of BGB-11417-105

	Sonrotoclax 80 mg + Dex (n=3)	Sonrotoclax 160 mg + Dex (n=3)	Sonrotoclax 320 mg + Dex (n=3)	Sonrotoclax 640 mg + Dex (n=10)	All (N=19)
Treatment cycles, median (range), n	3.0 (2-4)	28.0 (11-30)	6.0 (4-6)	8.0 (4-22)	7.0 (2-30)
Serious TEAE, n (%)	0	0	1 (33)	1 (10)	2 (11)
TEAE leading to death, n (%)	0	0	1 (33)	0	1 (5)
TEAE leading to discontinuation, n (%)					
Sonrotoclax	0	0	1 (33)	2 (20)[a]	3 (16)
Dexamethasone	0	0	1 (33)	2 (20)	3 (16)
TEAE leading to dose interruption, n (%)					
Sonrotoclax	0	2 (67)	1 (33)	2 (20)	5 (26)
Dexamethasone	0	2 (67)	0	1 (10)	3 (16)
TEAE leading to dose reduction, n (%)					
Sonrotoclax	0	0	0	0	0
Dexamethasone	2 (67)	2 (67)	1 (33)	4 (40)	9 (47)

SOURCES: COMPANY DATA (BGB-11417-105)

In summary, the preclinical results show that sonrotoclax exhibited greater potency than venetoclax. Early clinical results demonstrate that sonrotoclax has had durable responses and is safe as well as tolerable. We think that with the promising preliminary results and future readouts of ongoing phase 2 and phase 3 trials, it may be easier for physicians to accept sonrotoclax, leading to gains in market share from venetoclax. As BeiGene has multiple ongoing trials for sonrotoclax, it is very possible that sonrotoclax usage could expand into other hematological malignancies, such as acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS) other than lymphoma. Approval of sonorotoclax will be a large revenue growth driver for BeiGene in the long term, in our view.

Sonrotoclax can be used as mono therapy or in combination with Brukinsa and BGB-11471. With the synergy of these three key drugs, BeiGene could well emerge as a haematology industry leader, in our view.

CDK4 inhibitor

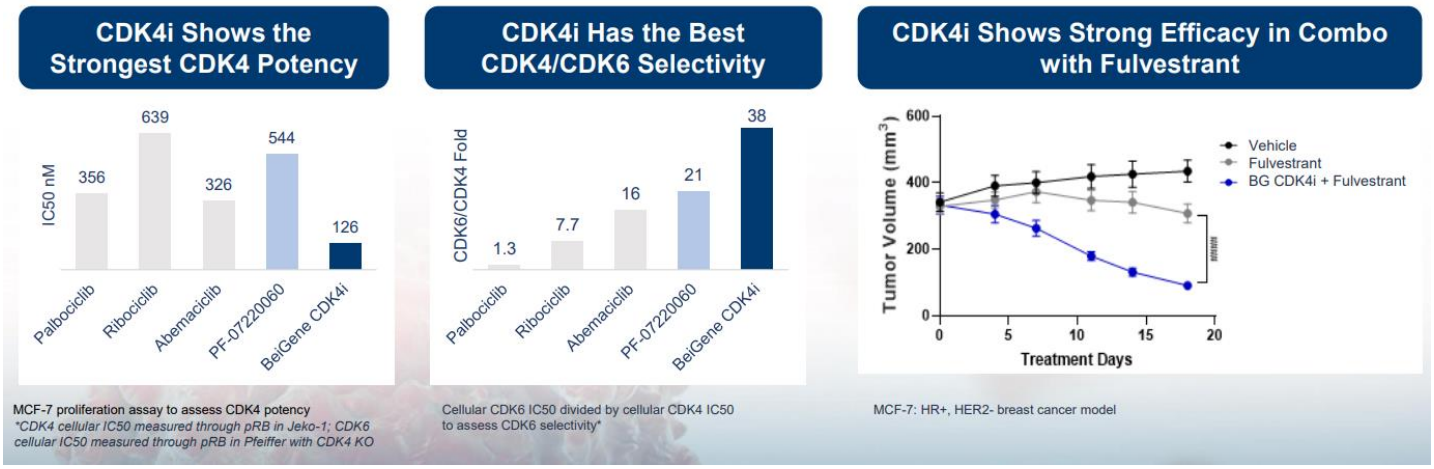
In Nov 2023, BeiGene's BGB-43395, a CDK4i, was approved by the National Medical Products Administration (NMPA) for clinical trial, having shown improved efficacy and safety profiles in pre-clinical experiments. Please refer to "Appendix 7: CDK4 and CDK6 inhibitors" for more details of the MOA of CDK4/6 inhibitor.

The initial generation of CDK inhibitors, such as favopiridol and roscovitine, exhibited potent inhibition of CDK4 but lacked selectivity, leading to the inhibition of multiple kinases. Consequently, these compounds displayed severe toxic side effects during clinical trials. To address these limitations, next-generation CDK inhibitors (CDKi) like palbociclib were developed with improved specificity towards individual CDKs.

Globally, there are five CDK4/6i approved, namely palbociclib (Ibrance) from Pfizer (PFE.US, NR, CP:), ribociclib (Kisqali) from Novartis, abemaciclib (Verzenio) from Eli Lilly, dalpiciclib from Hengrui and trilaciclib (Cosela) from G1 Therapeutics (GTHX. US, NR, CP:). China has approved 4 CKD4/6i: palbociclib, abemaciclib, robociclib and dalpiciclib.

In summary, in preclinical studies, BeiGene's CDK4 showed better CDK4 potency and CDK4/6 selectivity than palbociclib, robociclib, abemaciclib and PF-07220060 (an investigational CDK4 inhitor from Pfizer), in our view. Three CDK4/6 indictors (palbociclib, ribociclib and abemaciclib) have had huge commercial success in HR+/HER2- breast cancer in the past eight years. However, these three drugs all have on-target toxicity. We think BeiGene's CDK4 inhibitor may offer a new therapeutic option, with better efficacy and less toxicity.

Figure 68: Preclinical results of BeiGene's CDK4 inhibitor



SOURCES: CGIS RESEARCH, COMPANY DATA

Competitive landscape

Competitive landscape of Brukinsa

As of 30 Jun 2023, the US Food and Drug Administration (FDA) had approved four BTKis including Imbruvica (inbrutinib), Calquence (acalabrutinib), Brukinsa (zanubrutinib) and Jaypirca (pirtobrutinib). China NMPA approved ibrutinib, zanubrutinib, orelabrutinib from Innocare, and acalabrutinib as of 30 Jun 2023. Except acalabrutinib, all were included in the National Reimbursement Drug List (NRDL) category B. Orelabrutinib was also approved in Japan and Singapore. Japan also approved another BTKi, tirabrutinib.

Figure 69: Approved BTKi in the US as at end-Jun 2023

Name	Company	Indications	First approval data
imbruvica (ibrutinib)	Johnson & Johnson (JNJ. US, NR, CP:) and AbbVie (ABBV.US, NR, CP:)	CLL/SLL, WM, 2L chronic graft versus host disease (cGVHD)	Nov 12, 2013
calquence (acalabrutinib)	AstraZeneca (AZN.US, NR, CP:)	2L MZL, CLL/SLL	Oct 31, 2017
brukinsa (zanubrutinib)	BeiGene	2L MCL, WM, 2L MZL, CLL/SLL	Nov 14, 2019
jaypirca (pirtobrutinib)	Eli Lilly (LLY.US, NR, CP:)	3L MCL	Jan 27, 2023

SOURCES: CGIS RESEARCH, THE US FDA

Ibrutinib was the first BTKi approved by the US FDA as a breakthrough therapy in 2013. Before ibrutinib, chemotherapy was the main option for CLL/SLL. The 2021 global sales of imbruvica reached US$9.7bn, becoming the world's fourth best-selling medication for the treatment of lymphomas, according to Nature Journal, a British weekly scientific journal. In 2022, global sales of imbruvica dropped to US$8.4bn and in 1H23, the global sales of imbruvica had fallen to US$3.5bn (-20% yoy), due to competition. However, ibrutinib has off-target effects, which may influence the adverse event (AE) profile associated with the drug. The use of ibrutinib can be limited because of its AEs, especially cardiotoxicities including atrial arrhythmias, mainly atrial fibrillation and ventricular arrhythmias. Acalabrutinib and zanubrutinib are second-generation BTKi, which have reduced off-target effects, and were approved by the FDA in 2017 and 2019, respectively.

Figure 70: Annual cost of approved BTKis as at end-Jun 2023

Name	Annual cost in the US (US$)*	NMPA first approval	NRDL inclusion	Annual cost in China (Rmb)*
Imbruvica (ibrutinib)	~215m	Aug 2017	Yes	~182m
Calquence (acalabrutinib)	~189m	Mar 2023		~427m
Brukinsa (zanubrutinib)	~183m	Jun 2020	Yes	~124m
Jaypirca (pirtobrutinib)	~265m			
Yinuokai (Orelabrutinib)		Dec 2020	Yes	~130m

*Annual cost estimation did not consider any promotion discount

SOURCES: CGIS RESEARCH ESTIMATES, NMPA

We have elaborated in detail the efficacies and safety comparisons between Brukinsa and ibrutinib in “Pipeline-zanubrutinib-zanubrutinib for R/R CLL/SLL-ALPINE”. ALPINE, the head-to-head phase 3 clinical trial, is a hallmark study which directly compares the efficacy and safety of Brukinsa and ibrutinib. The results demonstrate the superior efficacy and safety profile of Brukinsa over ibrutinib. Together with other clinical results, we think Brukinsa will be well accepted globally as an effective and safer BTKi.

Note that there have been no head-to-head clinical trials directly comparing zanubrutinib and acalabrutinib. However, Elevate-RR (NCT02477696) directly compared acalabrutinib with ibrutinib.

The Elevate-RR trial was a phase III, randomised, multicentre, open-label, no-inferiority, head-to-head study comparing acalabrutinib, a competitor of zanubrutinib developed by AstraZeneca (AZN.US, NR, CP: US$69.4), and ibrutinib. A total of 533 patients (acalabrutinib, n=268; ibrutinib, n=265) were randomly assigned to receive oral acalabrutinib 100mg twice daily or ibrutinib 420mg once daily. The primary end point was IRC-assessed PFS and the median follow-up time was 40.9 months.

Figure 71: Cross-trial comparison of BTKi in R/R CLL/SLL

	ITT population		**acalabrutinib**	
Trial	ALPINE		Elevate-RR (NCT02477696)	
Follow-up time	24 months		40.9months	
Efficacy	Zanubrutinib (n=327)	Ibrutinib (n=325)	Acalabrutinib (n=268)	Ibrutinib (n=265)
ORR (95% CI)	86.2% (82.0-89.8)	75.7% (70.7-80.3)	81.0% (75.3-92.4)	77.0% (59.0-80.6)
CR/CRi	6.7%	5.8%	1.9%	3%
PR/nPR	79.5%	69.8%	79.1%	73.9%
PR-L	5.5%	7.4%	2.2%	3.0%
SD	4.9%	10.5%	10.8%	10.2%
PD	0.9%	2.2%	0.7%	2.3%
PFS	24 months PFS rate: 79.5%	24 months PFS rate: 67.3%	38.4 months	38.4 months
Safety				
Cardiac disorders (any grade)	21.3%	29.6%	24.1%	30.0%
Atrial fibrillation/flutter (any grade)	5.2%	13.3%	9.4%	16.0%
Hypertension (any grade)	14.8%	11.1%	8.6%	22.8%

SOURCES: CGIS RESEARCH, BEIGENE (ALPINE STUDY), ASTRAZENECA (ELEVATE-RR STUDY)

We did a cross-trial comparison of Brukinsa and acalabrutinib in Fig 71, and we think Brukinsa still exhibits a better efficacy and safety profile. The FY22 annual sales of acalabrutinib were US$2.1bn and its 1H23 sales were US$1.2bn (+31% yoy), according AstraZeneca.

In summary, we think the approval of Brukinsa brought fierce competition to ibrutinib and acalabrutinib given Brukinsa’s stronger efficacy and safety profile. This is consistent with the sales decline for ibrutinib, growth slowdown for acalatinib and rapid growth of Brukinsa over the past two years. We think that with the sales ramp-up for Brukinsa in light of approved indications and given potential future indication approvals, Brukinsa will continue to gain market share at the expense of ibrutinib and acalatinib.

Competitive landscape of tislelizumab

The first anti-PD-1 antibodies, Opdivo and Keytruda, were approved by the US FDA in 2014. To date, seven global PD-1/PD-L1 inhibiters are on the market with approvals across 17 cancer indications, many of which are served by multiple agents. As of 26 Dec 2023, eight PD-1/PD-L1 were approved in the US across 25 indications. As at 31 Jul 2023, China had approved 10 PD-1 inhibitors and most of them were approved with multiple indications, according to the NMPA.

Figure 72: Anti-PD-1/L1 Antibody (Ab) approvals by the US FDA as at 26 Dec 2023

SOURCES: CANCER RESEARCH INSTITUTE, CGIS RESEARCH

Figure 73: Approved anti-PD-1 Antibodies (Abs) in China, as of 31 Jul 2023

Company	Ticker	Name	Therapy	Indications	Approval time	NRDL inclusion
Junshi Biosciences	688180.CH 1877.HK	Toripalimab (Tuoyi)	Monotherapy	2L, 3L melanoma	Dec 2018	Yes
				2L, 3L NPC	Feb 2021	Yes
				2L, 3L UC	Apr 2021	Yes
			+ Chemotherapy	1L NPC	Nov 2021	No
				1L ESCC	May 2022	No
				1L non-squamous NSCLC	Sep 2022	No
Innovent Biosciences	1801.HK	Sintilimab (Tyvyt)	+ Bevacizumab, chemotherapy	Locally advanced non-squamous NSCLC	May 2023	No
			+ Chemotherapy	1L non-squamous NSCLC	Feb 2021	Yes
				1L squamous NSCLC	Jun 2021	Yes
				1L GC/GEJC	Jun 2022	Yes
				1L ESCC	Jun 2022	Yes
			+ Bevacizumab	1L HCC	Jun 2021	Yes
			Monotherapy	2L, 3L HL	Dec 2018	Yes
Hengrui Medicine	300276.CH	Camrelizumab (AiRuiKa)	+ Chemotherapy	1L non-squamous NSCLC	Jun 2020	Yes
				1L squamous NSCLC	Dec 2021	Yes
				1L ESCC	Dec 2021	Yes
				1L NPC	Jun 2021	Yes
			+ Apatinib	1L HCC	Jan 2023	No
			Monotherapy	2L, 3L HCC	Mar 2020	Yes
				2L, 3L ESCC	Jun 2020	Yes
				2L, 3L NPC	Apr 2021	Yes
				2L, 3L HL	Dec 2018	Yes
Akesobio	9926.HK	Penpulimab (Annike)	+ Chemotherapy	1L squamous NSCLC	Jan 2023	No
			Monotherapy	2L, 3L HL	Aug 2021	No
Gloria Biosciences		Zimberelimab (Yutuo)	Monotherapy	2L, 3L HL	Aug 2021	No
				2L, 3L cervical cancer	Jul 2023	No
BeiGene	688235,CH 6160.HK BGNE.US	Tislelizumab	+ Chemotherapy	1L non-squamous NSCLC	Jun 2021	Yes
				1L squamous NSCLC	Jun 2022	Yes
				1L GC/GEJC	Feb 2023	No
				1L ESCC	Apr 2022	Yes
				1L NPC	Jun 2022	Yes
			Monotherapy	2L, 3L NSCLC	Jan 2022	Yes
				2L, 3L HCC	Jun 2022	Yes
				2L, 3L colorectal cancer, CRC	Jun 2022	Yes
				2L, 3L UC	Apr 2020	Yes
				2L, 3L HL	Dec 2019	Yes
				Locally advanced MSI-H/dMMR	Mar 2022	Yes
Henlius	2696.HK	Serplulimab (Hansizhuang)	+ Chemotherapy	1L squamous NSCLC	Nov 2022	No
				1L SCLC	Jan 2023	No
			Monotherapy	2L, 3L MSI-H/dMMR	Mar 2022	No
Lepu Biopharma	2157.HK	Pucotenlimab (Purouheng)	Monotherapy	2L, 3L melanoma	Sep 2022	No
				2L, 3L MSI-H/dMMR	Jul 2022	No
Bristol-Myers Squibb	BMY.US	Nivolumab (Opdivo)	+ Chemotherapy	NSCLC neoadjuvant treatment	Jan 2023	No
				1L GC/GEJC	May 2022	No
				1L Esophageal adenocarcinoma (EAC)	Aug 2022	No
			+ Ipilimumab	1L malignant pleural mesothelioma (MPM)	Apr 2022	No
			Monotherapy	2L, 3L NSCLC	Jun 2018	No
				GC/GEJC adjuvant treatment	Jun 2022	No
				2L, 3L GC/GEJC	Oct 2020	No
				Esophageal Cancer (EC) adjuvant treatment	Jun 2022	No
				UC adjuvant treatment	Jan 2023	No
				2L, 3L Head and neck cancer (HNC)	Oct 2019	No
MSD	MRK.US	Pembrolizumab Keytruda	+ Chemotherapy	1L squamous NSCLC	Nov 2019	No
				1L non-squamous NSCLC	Nov 2019	No
				1L GC/GEJC	Sep 2021	No
				High-risk early-stage triple-negative breast cancer (TNBC) neoadjuvant or adjuvant treatment	Nov 2022	No
			Monotherapy	2L, 3L HCC	Oct 2022	No
				2L, 3L ESCC	Jun 2020	No
				1L colorectal cancer, CRC	Jun 2021	No
				2L, 3L melanoma	Jul 2018	No
				1L Head and neck squamous cell carcinomas (HNSCC)	Dec 2020	No

SOURCES: CGIS RESEARCH, COMPANY DATA, NMPA

In our view, this fierce competition has been caused by: 1) PD-1/PD-L1 revolutionising cancer immunotherapy in many cancers, leading to huge market demand, and 2) PD-1/PD-L1 antibodies acting as good partners for cancer combination therapy. Most pharmaceutical and biotech companies have developed in-house PD-1/PD-L1 antibodies, not only to meet clinical demand but also to combine with their other in-house candidates.

In China, the competitive landscape of PD-1/PD-L1 Abs is “4+4”. The domestic market is dominated by four overseas brands (BMS, MSD, Roche, AstraZeneca) and four domestic brands (Hengrui, Junshi, Innovent, and BeiGene), in our view. BeiGene’s tislelizumab was one of the earliest approved domestic PD-1 Ab in China and it had first-mover advantage. In addition, BeiGene’s tislelizumab is one of the PD-1 Ab that had been approved for the most cancer indications in China (Fig 71). Furthermore, multiple indications of tislelizumab had been included in the NRDL which makes it more accessible and affordable to patients.

The sales of tislelizumab are supported by BeiGene’s strong sales force. The 1H23 sales of tislelizumab amounted to US$264m (+37% yoy), much higher than those of its peers, including Junshi’s toripalimab (Rmb447m in 1H23), and Tyvyt whose sales were announced by Eli Lilly as US$165m in 1H23.

In summary, despite fierce competition in PD-1/PD-L1 Abs, we think tislelizumab remains one of the key players in the industry because of it has already been approved for multiple indications, supported by many clinical studies. The future growth drivers of tislelizumab include: 1) potential indication approvals, either as tislelizumab monotherapy or as combination therapy with other BeiGene drugs; 2) sales ramp-up given the approved indications in China; 3) sales ramp-up given the newly approved indication for ESCC in Europe; 4) future approval for ESCC in the US, and 5) approvals for other indications globally.

Collaborative and licensing arrangements

BeiGene engages in collaborative partnerships for various aspects of drug product and drug candidate research, development, manufacturing and commercialisation. These collaborations involve agreements such as out-licences, options for out-licensing internally developed products and drug candidates to external parties, as well as in-licensing of products and drug candidates from other entities. These collaborative arrangements may include non-refundable upfront payments, contingent obligations tied to potential development, regulatory and commercial performance milestones, cost-sharing and reimbursement agreements, royalty payments, and profit sharing, according to the company.

Amgen

In Oct 2019, BeiGene entered into a collaboration with Amgen for the commercialisation and development in China, excluding Hong Kong, Taiwan and Macau, of Amgen's XGEVA, KYPROLIS and BLINCYTO, and the joint global development of a portfolio of oncology assets in Amgen's pipeline, with BeiGene responsible for development and commercialisation in China.

BeiGene has been responsible for the commercialisation of XGEVA, KYPROLIS and BLINCYTO in China since 2019, while Amgen is responsible for manufacturing the products globally. Following the commercialisation period, BeiGene has the right to retain one product and is entitled to receive royalties on sales in China for an additional five years on the products not retained.

XGEVA was approved in China in 2019 for patients with giant cell tumour of the bone and in Nov 2020 for the prevention of skeletal-related events in cancer patients with bone metastases. In Dec 2020, BLINCYTO was approved in China for injection for the treatment of adult patients with R/R B-cell precursor acute lymphoblastic leukemia (ALL). In Jul 2021, KYPROLIS was conditionally approved in China for injection in combination with dexamethasone for the treatment of adult patients with R/R MM. In Apr 2022, BLINCYTO was conditionally approved for injection for the treatment of paediatric patients with R/R CD19-positive B-cell precursor ALL.

Figure 74: Commercial product collaborations with Amgen as of 27 Feb 2023

PRODUCT	LEAD INDICATIONS	MECHANISM OF ACTION	REGULATORY STATUS	BEIGENE COMMERCIAL RIGHTS	PARTNER
XGEVA (denosumab) injection	Giant cell tumor of bone[8]/Skeletal Related Events (SREs)[8]	Anti-RANK ligand antibody	Approved in China	Mainland China	AMGEN
BLINCYTO (blinatumomab) for injection 35 mcg single-dose vial	R/R Acute lymphocytic leukemia[8]	Anti-CD19 x anti-CD3 bispecific T-cell engager (BiTE)	Approved in China	Mainland China	AMGEN
Kyprolis (carfilzomib) for injection	R/R Multiple myeloma[8]	Proteasome inhibitor	Approved in China	Mainland China	AMGEN

SOURCES: CGIS RESEARCH, COMPANY DATA

Amgen and BeiGene are also jointly developing a portfolio of Amgen oncology pipeline assets. BeiGene is responsible for conducting clinical development activities in China and co-funding global development costs by contributing cash and development services up to a total cap of US$1,250,000. Amgen is responsible for all development, regulatory and commercial activities outside of China. For each pipeline asset that is approved in China, BeiGene will receive commercial rights for seven years from approval. The company has the right to retain approximately one out of every three approved pipeline assets.

Novartis

In Jan 2021, BeiGene entered into a collaboration and license agreement with Novartis, granting Novartis rights to develop, manufacture and commercialise tislelizumab in the US, Canada, Mexico, member countries of the EU, UK, Norway, Switzerland, Iceland, Liechtenstein, Russia and Japan. BeiGene received an upfront cash payment of US$650m from Novartis and was eligible to receive up to US$1.3bn upon the achievement of regulatory milestones, US$250m upon the achievement of sales milestones, and royalties on future sales of tislelizumab in the licensed territory. However, in Sep 2023, BeiGene and Novartis agreed to mutually terminate the license agreement for tislelizumab.

In Dec 2021, BeiGene expanded its collaboration with Novartis by entering into an option, collaboration and licence agreement to develop, manufacture and commercialise ociperlimab. However, in July 2023, the BeiGene and Novartis mutually agreed to terminate the ociperlimab option, collaboration and licence agreement.

In addition, BeiGene and Novartis entered into an agreement in 2019 granting BeiGene rights to market, promote and detail five approved Novartis oncology products – TAFINLAR (dabrafenib), MEKINIST (trametinib), VOTRIENT (pazopanib), AFINITOR (everolimus) and ZYKADIA (ceritinib).

Figure 75: Commercial product collaborations with Novartis as of 27 Feb 2023

PRODUCT	LEAD INDICATIONS	MECHANISM OF ACTION	REGULATORY STATUS	BEIGENE COMMERCIAL RIGHTS	PARTNER
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

SOURCES: CGIS RESEARCH, COMPANY DATA

BMS and Bio-Thera

According to the company, BeiGene sells Revlimid and Vidaza in China under a licence from Bristol Myers Squibb (BMS). Revlimid (lenalidomide) is an oral immunomodulatory medication initially approved in China in 2013 for the treatment of MM in combination with dexamethasone. This approval was specifically for adult patients who had received at least one prior therapy. Subsequently, in Feb 2018, Revlimid obtained additional approval from the NMPA for a new indication for the treatment of previously untreated MM in combination with dexamethasone, specifically for adult patients who were not eligible for transplant. In Jun 2017, Revlimid was listed on the National Reimbursement Drug List (NRDL) in China. In Nov 2019, the formal inclusion of Revlimid on the NRDL for R/R MM was announced. Additionally, in Nov 2020, the NMPA approved the sNDA for the use of Revlimid in combination with rituximab for adult patients with previously treated FL.

Vidaza (azacitidine for injection) is a pyrimidine nucleoside analog with the ability to reverse DNA hypermethylation and promote gene re-expression. It received approval in China in Apr 2017 for the treatment of intermediate-2 and high-risk MDS, chronic myelomonocytic leukemia (CMML), and AML with 20% to 30% blasts and multilineage dysplasia. Subsequently, in Jan 2018, Vidaza became commercially available in China. However, BMS-Celgene and BeiGene agreed to

terminate the in-licences of Revlimid and Vidaza on 31 Dec 2023. BeiGene has the right to continue to sell all its inventory of the two drugs till 31 Dec 2024 or until they are sold out, whichever comes earlier.

In collaborated with Bio-Thera, BeiGene has the rights to develop, manufacture, and commercialise Pobevcy in China. Pobevcy is a biosimilar to bevacizumab injection for the treatment of patients with advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) and metastatic colorectal cancer.

Figure 76: Commercial products with BMS as of 27 Feb 2023

PRODUCT	LEAD INDICATIONS	MECHANISM OF ACTION	REGULATORY STATUS	BEIGENE COMMERCIAL RIGHTS	PARTNER
Revlimid (lenalidomide)	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
POBEVCY® (Avastin biosimilar)	Colorectal and lung cancers	Anti-VEGF antibody	Approved in China	Greater China	百奥泰 BIO-THERA

SOURCES: CGIS RESEARCH, COMPANY DATA

In-licensed candidates

Besides in-licensed drugs that are already approved, there also many in-licensed drug candidates from BeiGene's in-licensed clinical and late-preclinical-stage drug candidates from its collaboration partners. BeiGene said it will have the right to commercialise these products when they are approved in China.

Figure 77: In-licensed drug candidates as of 27 Feb 2023

Partner	Molecule/Asset	Indications	Phase	Commercial Rights
AMGEN	Sotorasib	Solid tumors, CRC, NSCLC	Phase 3	China
	tarlatamab ^^	SCLC	Phase 2	China
	acapatamab ^^	Prostate cancer, NSCLC	Phase 1	China
	AMG 176	Hematologic malignancies	Phase 1	China
	AMG 427 ^^	AML	Phase 1	China
	AMG 509	Prostate cancer	Phase 1	China
	AMG 199 ^^	GC/GEJC	Phase 1	China
	AMG 650	Solid tumors	Phase 1	China
	AMG 256	Solid tumors	Phase 1	China
MIRATI THERAPEUTICS	Sitravatinib † + Tislelizumab	NSCLC	Phase 3	Asia, Australia, New Zealand
	Sitravatinib † + Tislelizumab	HCC, GC/GEJC	Phase 2	Asia, Australia, New Zealand
	Sitravatinib † + Tislelizumab	Solid tumors	Phase 1	Asia, Australia, New Zealand
zymeworks	Zanidatamab + chemo + Tislelizumab	GEA	Phase 3	Asia, Australia, New Zealand
	Zanidatamab (monotherapy)	BTC	Phase 2	Asia, Australia, New Zealand
	Zanidatamab	BC, GC, GEA	Phase 2	Asia, Australia, New Zealand
	ZW49	HER2 expressing cancers	Phase 1	Asia, Australia, New Zealand
SpringWorks THERAPEUTICS	BGB-3245[1]	Solid tumors	Phase 1	Asia
Seagen	SEA-CD70	MDS, AML	Phase 1	Asia, Australia, New Zealand
leaptherapeutics	DKN-01 + Tislelizumab + Chemo	GC/GEJC	Phase 2	Asia, Australia, New Zealand
Leads Biolabs	LBL-007 + Tislelizumab	Advanced solid tumors	Phase 2	Ex-China
assemblybio	ABI-H3733	Chronic hepatitis B virus	Phase 1	China

SOURCES: CGIS RESEARCH, COMPANY DATA

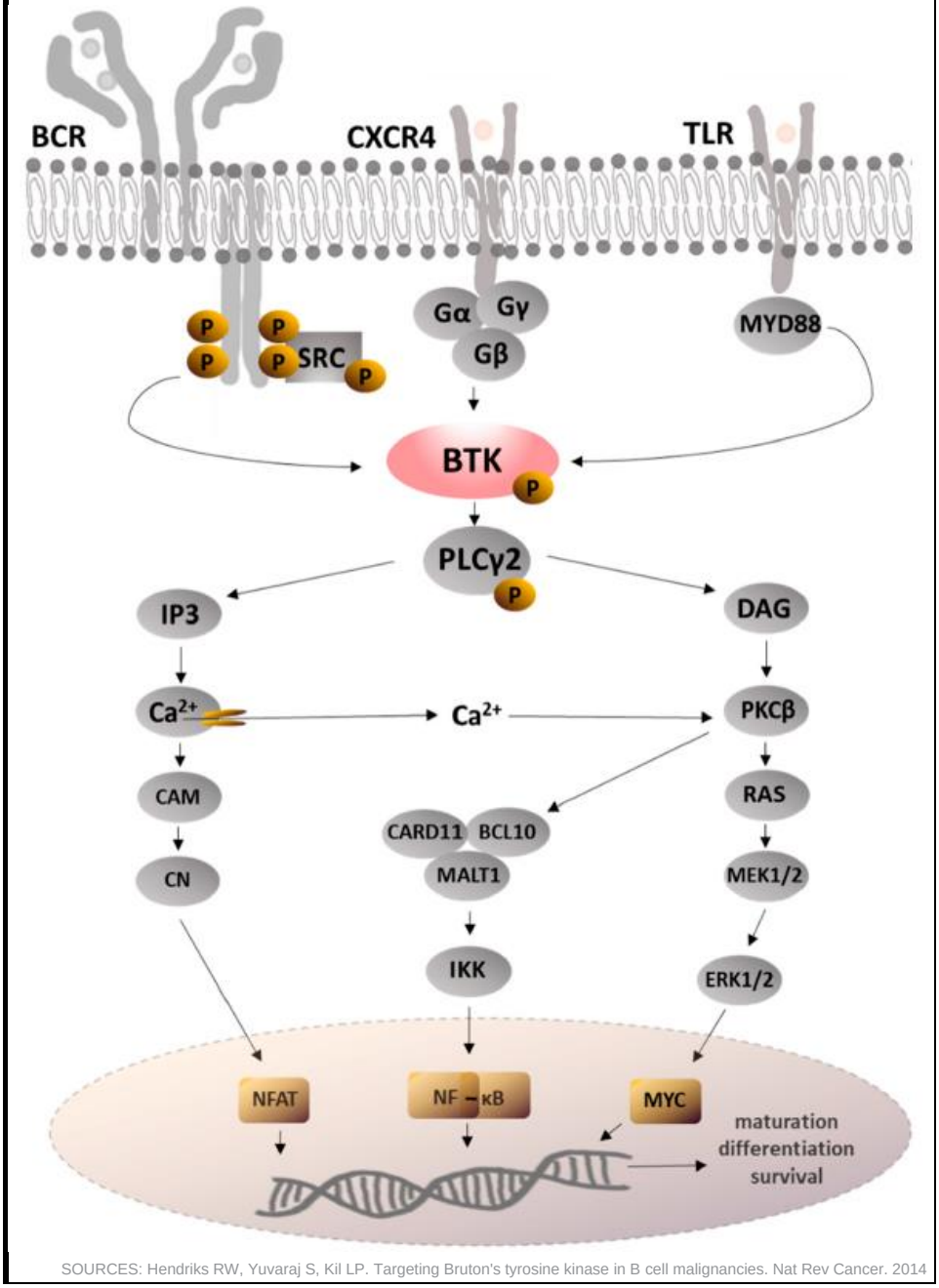
Appendix

1. BTK and BTKi

BTK plays a crucial role in B cell development by being in the B cell antigen receptor (BCR) signalling pathway. BCRs are specifically expressed on the cell surface of B cells. They are activated by antigen recognition results in translocation and phosphorylation of BTK which initiate signal cascade involving transcription factor nuclear factor kappa B (NFkb) which is necessary for B cell proliferation and survival, according to “Targeting Bruton's tyrosine kinase in B cell malignancies” published in 2014. However, unregulated activation of BTK can result in various B cell malignancies. BTKi blocks BCR-induced BTK activation and its downstream signalling, resulting in controlling of B-cell proliferation, differentiation and survival.

First- and second-generation BTKi bind covalently to the cysteine 481 (C481) BTK and they are susceptible to resistance mutations at C481. The third-generation BTKi, pirtobrutinib, a noncovalent BTKi, was developed to overcome the C481 resistance mutations.

Figure 78: BTK pathway



SOURCES: Hendriks RW, Yuvaraj S, Kil LP. Targeting Bruton's tyrosine kinase in B cell malignancies. Nat Rev Cancer. 2014

2. Lymphoma

Lymphoma is a general term for a group of blood cancers that originate in the lymphatic system. Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are the two main types of lymphoma. According to World Health Organization (WHO) Global Cancer Observatory (GLOBOCAN), NHL was responsible for 544,352 new cases as well as 259,793 new deaths worldwide in 2020 while HL was responsible for 83,087 new cases and 23,376 new deaths in 2020 worldwide.

There were an estimated 136,960 new cases of lymphoma with an age-standardised incidence rate of 34.4 per 100,000 population in the US in 2016, according to WHO. The new cases and age-standardised incidence rate per 100,000 population were 8,500 and 2.7 for HL, and 125,850 and 31.1 for NHL, respectively. During the same period, there were an estimated 6,900 and 68,500 incident cases with an age-standardized incidence rate of 0.46 and 4.29 per 100,000 population for HL and NHL in China, according to the same journal.

HL is B cell origin and can further divided into classical HL (cHL) and nodular lymphocyte predominant HL (NLPHL), according to WHO's classification of heamatolymphoid tumours (2017). According to China's clinical oncology guidelines for lymphoma (2022), 90% of HL are cHL, which can be further divided into nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted.

NHL are mostly classified into three different categories: indolent, aggressive, and very aggressive. NHL can also be divided into B-cell NHL or T-cell NHL, according to its origin. According to the Leukemia & Lymphoma Society, most (80-85%) NHL arise from B lymphocytes and the remainder arise from T lymphocytes or NK cells.

Diffuse large B cell lymphoma (DLBCL) is the most common type of NHL. The condition originates from B-cells and accounted for 30-40% of adult NHL cases in the US and 35-50% of adult NHL cases in China in 2020, according to the "China clinical oncology guidelines for lymphoma (2022)" published by the Chinese government. DLBCL is a clinical aggressive lymphoma and often arises in the lymph nodes but can also present anywhere else in the body.

Follicular lymphoma (FL) is an indolent lymphoma and is the second-most common type of NHL, accounting for 20-30% of NHL in the US and Europe according to "China clinical oncology guidelines for lymphoma (2022)". The incidence rate of FL is lower in Asians, including in China ,and is less than 10% of NHL, according to "China clinical oncology guidelines for lymphoma (2022)". It originates from the follicular cells in the germinal centre of the lymph node. The tumour cells have overexpression of the anti-apoptotic protein B-cell lymphoma 2 (BCL-2), due to translocation of the BCL-2 gene on chromosome 14 to the immunoglobulin or B-cell receptor gene on chromosome 18. It can transform into more aggressive DLBCL in some cases.

All other NHL subtypes have a frequency of less than 10%, according to "Non-Hodgkin's lymphoma: a review (published in 2020)". CLL/SLL is a type of indolent mature B-cell malignancy in which abnormal leukemic B lymphocytes arise from the bone marrow and flood peripheral blood, bone marrow, and lymphoid tissues. CLL/SLL accounts for 7-10% of NHL in the US and Europe, according to World Health Organization (WHO), making it one of the most common types of adult leukemia. The frequency of CLL/SLL is lower in Asians, including in China, accounting for 1-3% of NHL. CLL and SLL are considered different manifestations of the same disease. When most of the cancer cells are located in the bloodstream and the bone marrow, the disease is referred to as CLL but, if the cancer cells are located mostly in the lymph nodes, the disease is called SLL.

Waldenström Macroglobulinemia (WM) is a rare, slow-growing lymphoma that occurs in less than 2% of patients with NHL. The disease usually affects older adults and is primarily found in the bone marrow, although it may also impact lymph nodes and the spleen. According to "China clinical oncology guidelines for lymphoma (2022)", in China, there are an estimated 88,200 patients diagnosed with lymphoma each year; approximately 91% of these cases are classified as NHL, amounting to 1,000 newly diagnosed WM patients per year in China.

Mantle cell lymphoma (MCL) accounts for 3-10% of NHL, which is an aggressive form of NHL that arises from B-cells originating in the mantle zone. Patients usually have a poor prognosis and it is often diagnosed at the later stages of the

disease. MZL is another type of indolent NHL which is a rare disease, happening when B-cells in the marginal zone mutate.

Figure 79: Lymphoma classification

HL	cHL	
	NLPHL	
NHL	Indolent	FL
		CLL / SLL
		WM
		MZL
		Natural killer/T-cell lymphoma (NTKL)
	Aggressive	MCL
		Multiple myeloma (MM)
		DLBCL
		Peripheral T-cell lymphoma
	Very Aggressive	Burkitt's lymphoma
		Lymphoblastic lymphoma

SOURCES: WHO, CGIS RESEARCH

3. Immune oncology

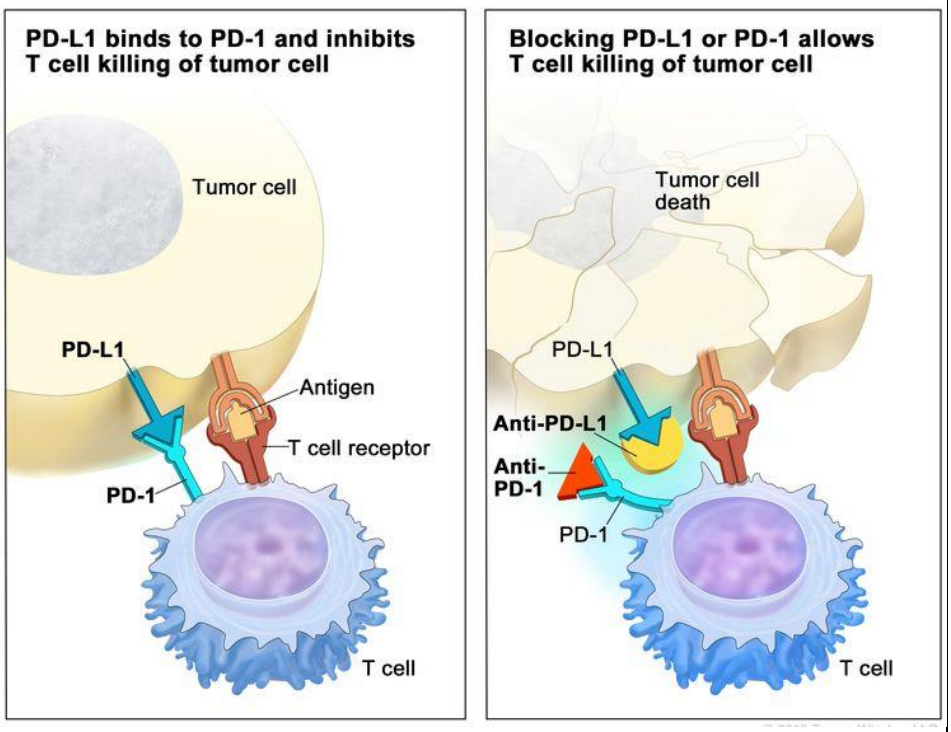
Immunotherapy is a treatment that uses the patient's immune system to fight cancer. Substances made by the body or made in a laboratory are used to boost, direct, or restore the body's natural defences against cancer. This cancer treatment is a type of biologic therapy. There are different types of immunotherapy: a) mAb and immune checkpoint inhibitors; b) non-specific immunotherapies, such as cytokines; c) oncolytic virus therapy; d) chimeric antigen receptor T-cell (CAR-T) therapy; and e) cancer vaccines.

Some mAbs are used to block protein activities in cancer cells to inhibit their growth. This is also considered as cancer targeted therapy. For more details about targeted therapy, please refer to our previously published report (link). Other types of mAb specialise in inhibiting immune checkpoints. Immune checkpoints are naturally present on the T cell surface. Their function is to tune down the immune response to prevent damage to healthy cells. Cancer cells can activate immune checkpoints to hide from the immune system. Checkpoint inhibitors prevent the binding of tumour cells and immune checkpoints, which allows the T cells to kill cancer cells. There are two types of immune checkpoint inhibitor therapy approved globally: CTLA-4 inhibitor therapy and PD-1/PD-L1 inhibitor therapy.

4. PD-1/PD-L1 therapy

Programmed cell death protein 1 (PD-1) is expressed on the surface of the T cells. Programmed cell death ligand 1 (PD-L1) is a trans-membrane protein that can bind with PD-1 to stop the T cell from killing cancer cells. PD-1/PD-L1 inhibitors can block the binding between PD-1 and PD-L1.

Figure 80: Mechanism of PD-1/PD-L1 therapy



SOURCES: National Cancer Institute, CGIS RESEARCH

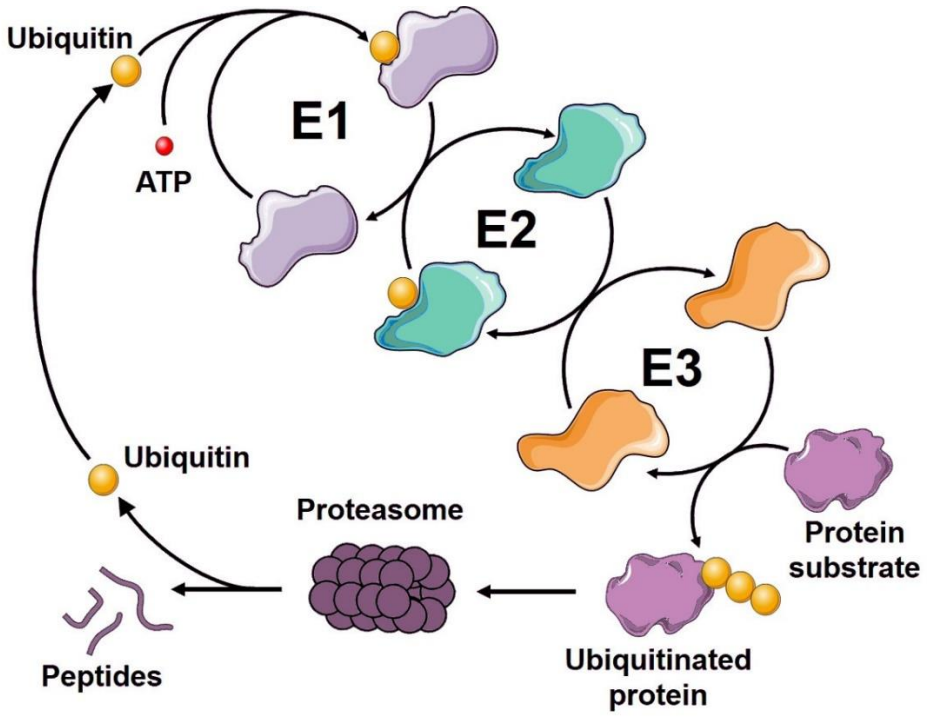
PD-1/PD-L1 inhibitors emerged as a pioneering cancer inmmunotherapy in the early 2000s, revolutionising the field of cancer treatment. The most notable PD-1 are Keytruda (pembrolizumab) from Merck, and Opdivo (nivolumab) from Bristol Myers Squibb (BMS). Both were first approved by the US FDA in 2014 and soon became blockbusters. Since then, the number of PD-1/PDL-1 inhibitors and their indications have expanded.

5. PROTAC

Proteolysis targeting chimera (PROTAC) is a proteomic platform to identify off-target proteins. They are heterobifunctional degraders that specifically eliminate targeted proteins by hijacking the ubiquitin-proteasome system (UPS). A PROTAC is composed of two ligands, one to a protein of interest and the other recruiting an E3 ubiquitin ligase, connected by a linker. PROTACs achieve target degradation via the proteasome mediated ubiquitination machinery. Contrary to protein inhibition, this technology benefits from the cell's own protein degradation pathway, UPS, to specifically remove labelled proteins.

UPS is a highly complex, temporally controlled and conserved pathway that plays a major role in a myriad of cellular functions because UPS has a large hand in determining the fate of cells and proteins. The purpose of the UPS is to conjugate a ubiquitin molecule to a protein that is destined for degradation. The UPS pathway is a three-step process that ends with the ubiquitin conjugation to a protein. Enzymes involved are ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and substrate-specific ligases (E3).

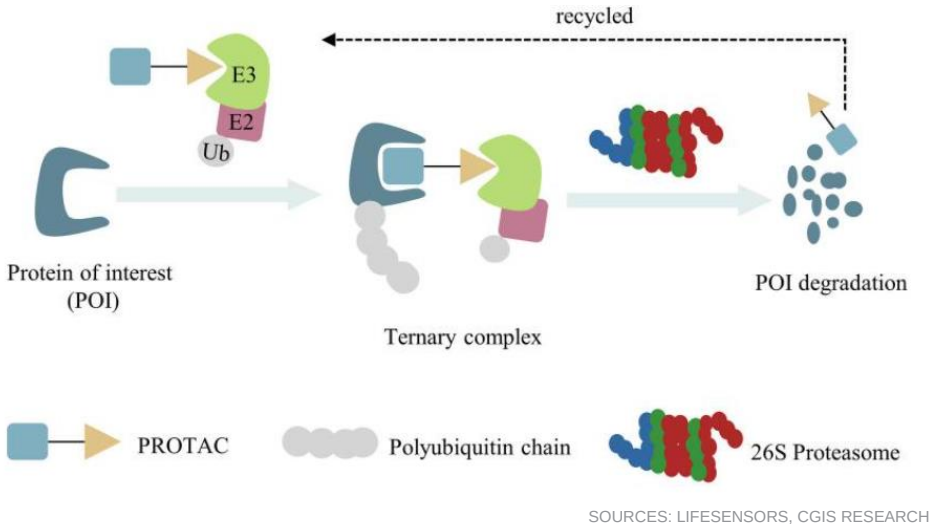
Figure 81: The ubiquitin-proteasome system



SOURCES: LIFESENSORS, CGIS RESEARCH

PROTACs simulate specific recognition of substrate by E3 and then hijack the intracellular protein destruction mechanism to degrade protein of interests (POIs) from cells. PROTACs theoretically have several advantages. PROTACs do not require the existence of active pockets like traditional small-molecule inhibitors, which make them suitable for previously undruggable targets. In addition, PROTACs can initiate the degradation of POI catalytic, which means they can be used at lower doses with longer intervals.

Figure 82: Mechanism of PROTAC



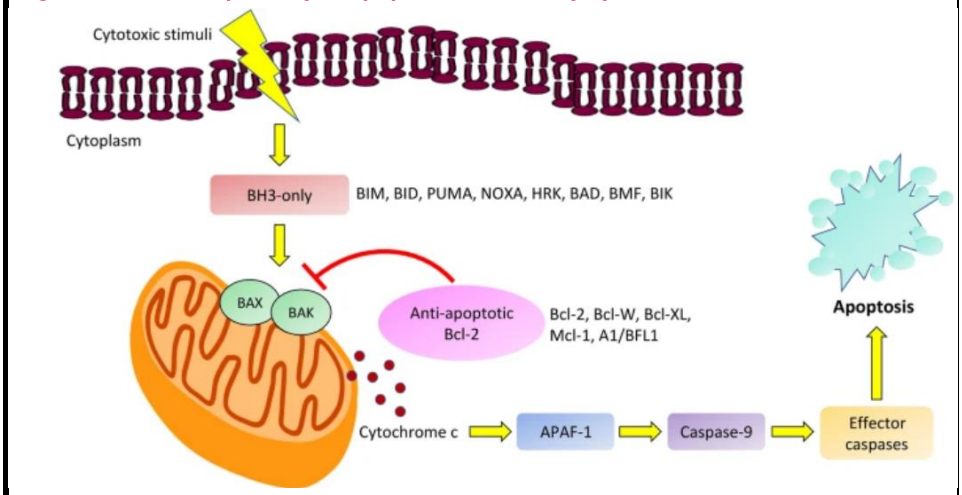
SOURCES: LIFESENSORS, CGIS RESEARCH

6. BCL-2 inhibitor

Apoptosis serves as a form of programmed cell death that acts in response to various physiological processes, abnormal stimuli or cellular stress. Therefore, apoptosis can prevent a defective cell from growing into cancer cell. It can be initiated through two distinct pathways: the intrinsic pathway, which is triggered by the release of apoptogenic factors in the mitochondria, and the extrinsic pathway, which is activated when specific death receptors on the plasma membrane are bound with its ligand.

A critical regulator of the intrinsic pathway is the BCL-2, a family of regulatory proteins. BCL-2 can be categorised into different groups based on their morphology and BCL-2 homology (BH) domain. BH3-only proteins play a crucial role in activating BAC and BAK, which subsequently form pores in the outer mitochondrial membrane. This pore formation leads to the release of cytochrome c, initiating the caspase cascade pathway and ultimately resulting in cell apoptosis. Anti-apoptotic proteins primarily inhibit BAX, BAK, and BH3-only proteins by binding to BH-3 domain, thus preventing the apoptotic process. Therefore, BCL-2 are fundamental regulators that balance cell survival and cell death.

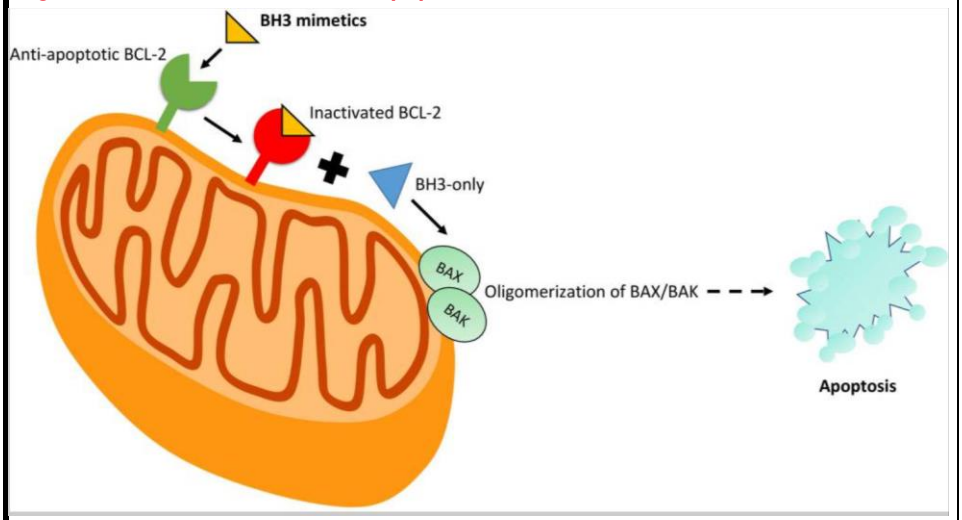
Figure 83: Intrinsic pathway of apoptosis initiated by cytotoxic stimuli



SOURCES: Ploumaki I, Triantafyllou E, Koumprentziotis IA, Karampinos K, Drougkas K, Karavolias I, Trontzas I, Kotteas EA. Bcl-2 pathway inhibition in solid tumors: a review of clinical trials. Clin Transl Oncol. 2023

In many types of cancer, there is an up-regulation of anti-apoptotic proteins and a down-regulation of pro-apoptotic members of the BCL-2 family because prevention of apoptosis is one mechanism through which cancer cells continue to service. Venetoclax is a first-of-class selective BCL2 inhibitor, also known as a BH3-mimetic, approved by the US FDA in 2016 for treatment of CLL/SLL and AML.

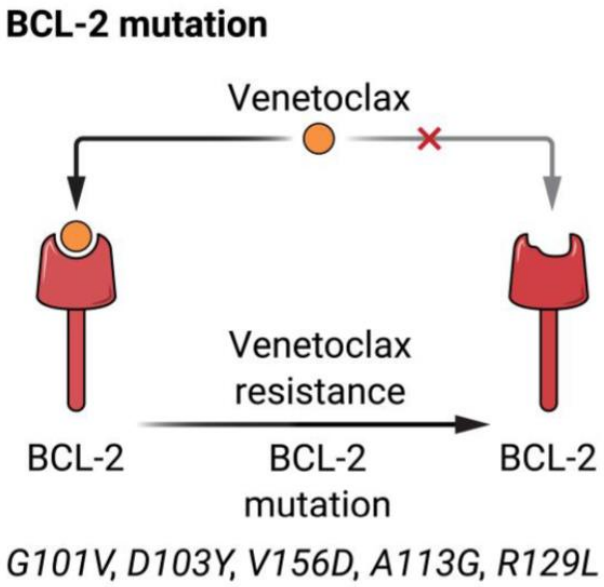
Figure 84: BH3 mimetic activates apoptosis



SOURCES: Ploumaki I, Triantafyllou E, Koumprentziotis IA, Karampinos K, Drougkas K, Karavolias I, Trontzas I, Kotteas EA. Bcl-2 pathway inhibition in solid tumors: a review of clinical trials. Clin Transl Oncol. 2023

However, treatment with venetoclax can be limited by common gastrointestinal toxicities, neutropenia, and the emergence of resistance. Mutations in drug binding sites are a common mechanism by which malignant cells evade therapies. One main genetic mutation driving venetoclax resistance is point mutations in the BH3-binding site. One common mutation is the substitution of a valine for the glycine residue at position 101 (G101V) in BCL-2. This mutation reduces the binding affinity of venetoclax to BCL-2.

Figure 85: Resistance of venetoclax



SOURCES: Sullivan GP, Flanagan L, Rodrigues DA, Ní Chonghaile T. The path to venetoclax resistance is paved with mutations, metabolism, and more. Sci Transl Med. 2022

6. Leukemia

Leukemia is a heterogeneous group of hematologic malignancies characterised by the abnormal proliferation of leukocytes in the bone marrow. It can be classified as acute or chronic, based on the rapidity of proliferation, and as myelocytic or lymphocytic, based on the cell of origin.

The most common subtypes of leukemia are acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), involving the myeloid lineage, as well as acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL), involving the lymphoid chain. There are also rarer variants, such as mature B-cell and T-cell leukemias, as well as NK cell-related leukemias, which arise from mature white blood cells.

Acute leukemias are characterised by a rapid onset of symptoms and the presence of more than 20% immature and dysfunctional cells, called blasts, in the peripheral blood or bone marrow. Normally, blasts only account for 1% to 5% of marrow cells. In contrast, chronic leukemias have a slower onset and fewer than 20% blasts. The accelerated/blast phase represents a transformation of chronic leukemia into an acute phase with a significantly higher number of blasts.

ALL primarily affects B and T cells and is the most common type of leukemia in children, accounting for up to 80% of cases in this age group (20% of leukemia cases in adults). AML is characterised by the presence of more than 20% myeloid blasts and is the most common type of acute leukemia in adults. It is an aggressive cancer with a variable prognosis depending on the molecular subtypes.

CLL arises from the proliferation of monoclonal lymphoid cells and primarily affects individuals aged 60-70. CLL is considered an indolent disease, meaning that not all patients with a diagnosis will require immediate treatment unless they develop symptoms. CML is typically caused by a specific chromosomal translocation known as the Philadelphia (Ph) chromosome, resulting in the fusion of the BCR on chromosome 22 and ABL1 on chromosome 9. This leads to the production of a dysregulated tyrosine kinase that causes the overproliferation of granulocytes, primarily neutrophils, basophils and esinophils.

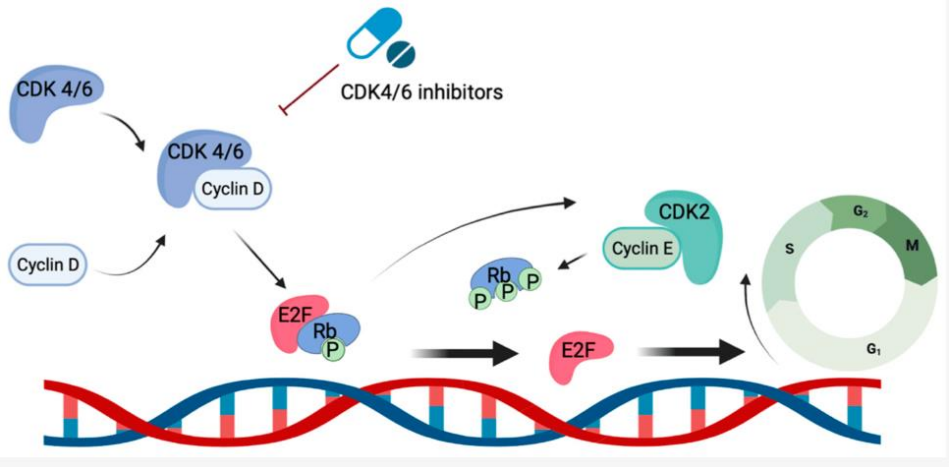
7. CDK4 and CDK6 inhibitors

CDK4/6 inhibitors are compounds that specifically target and inhibit the activity of cyclin-dependent kinase 4 and 6 (CDK4/6). CDK4/6 is a crucial regulator of the cell cycle, particularly in the G1 phase when cells prepare for DNA synthesis. By blocking CDK4/6, these inhibitors can disrupt cell cycle progression and inhibit

cell proliferation. The emergence of CDK4/6 inhibitors has revolutionised the treatment landscape for hormone receptor-positive breast cancer where CDK4/6 is dysregulated.

These inhibitors work by binding to the active site of CDK4 and preventing its interaction with cyclin D, its regulatory partner. This prevents the formation of the CDK4/cyclin D complex, which is required for the phosphorylation of retinoblastoma (RB). The phosphrylation of RB protein releases E2F transcription factors, causing the cell cycle to progress from G1 to S phase and resulting in cancer cell proliferation.

Figure 86: Signalling pathway of CKD4/6-cycle D complex and mechanism of action of SDK4/6 inhibitors



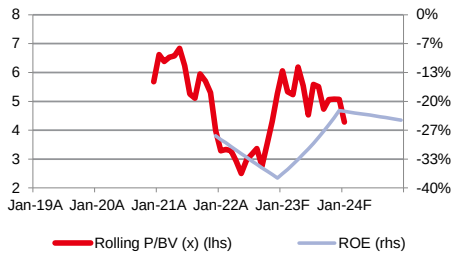
SOURCES: Lee JS, Hackbart H, Cui X, Yuan Y. CDK4/6 Inhibitor Resistance in Hormone Receptor-Positive Metastatic Breast Cancer: Translational Research, Clinical Trials, and Future Directions. Int J Mol Sci. 2023

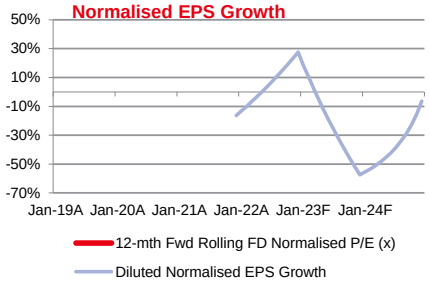
The development of the CDK4/6 inhibitors, of which three (palbociclib, ribociclib and abemaciclib) have become widely clinically used over the past eight years, has been a major success, according to the review “The CDK4/6 inhibitor revolution-a game-changing era for breast cancer treatment”. The use of these inhibitors in HR+ breast cancer patients have dramatically improved clinical outcomes. However, these drugs have on-target toxicities and develop acquired resistance.

Abbreviations

BTK: Bruton tyrosine kinase
RP2D: Recommended phase 2 doses
ORR: Objective response rate
CR: Complete response
PR: Partial response
PR-L: Partial response with lymphocytosis
MR: Minimal responses
SD: Stable disease
PD: Progressive disease
DOR: Duration of response
PFS: Progression free survival
OS: Overall survival
IRC: Independent review committee
NE: Not estimable
CI: Confidence interval
VGPR: Very good partial response
HR: Hazard ratio
AE: Adverse event
DLT: Dose limiting toxicities
Wt: Wild type
PO: Per oral
BID: Twice a day
PD: Progressive disease
QD: Once a day
ITT: Intent to treat
CRi: CR with incomplete bone marrow recovery
PR-L: Partial response with lymphocytosis
TTNT: Time to next treatment
TEAEs: Treatment-emergent adverse events
R/R: Relapsed or refractory
MCL: Mantle cell lymphoma
TN: Treatment naïve
CLL/SLL: Chronic lymphocytic leukemia/small lymphocytic lymphoma
WM: Waldenström's macroglobulinemia
MZL: Marginal zone lymphoma
FL: Follicular lymphoma
DLBCL: Diffuse large B cell lymphoma
PET: Positron emission tomography
IA: Investigator assessment
QOL: Quality of life
R: Randomised
TTR: Time to response
AML: Acute myelogenous leukemia
MRI: Magnetic resonance imaging
CT: Computed tomography
PET: Positron emission tomography
ECOG: Eastern cooperative oncology group
PS: Performance status

BY THE NUMBERS





Profit & Loss

(US$m)	Dec-21A	Dec-22A	Dec-23F	Dec-24F	Dec-25F
Total Net Revenues	**1,176**	**1,416**	**2,414**	**2,958**	**3,814**
Gross Profit	**1,011**	**1,129**	**2,004**	**2,457**	**3,169**
Operating EBITDA	**(1,314)**	**(1,618)**	**(999)**	**(620)**	**26**
Depreciation And Amortisation	(124)	(171)	(185)	(235)	(267)
Operating EBIT	**(1,439)**	**(1,790)**	**(1,184)**	**(855)**	**(242)**
Financial Income/(Expense)	0	(171)	332	34	31
Pretax Income/(Loss) from Assoc.	0	0	0	0	0
Non-Operating Income/(Expense)	0	0	0	0	0
Profit Before Tax (pre-EI)	**(1,439)**	**(1,961)**	**(852)**	**(821)**	**(210)**
Exceptional Items					
Pre-tax Profit	**(1,439)**	**(1,961)**	**(852)**	**(821)**	**(210)**
Taxation	25	(43)	(52)	(33)	(8)
Exceptional Income - post-tax					
Profit After Tax	**(1,413)**	**(2,004)**	**(904)**	**(853)**	**(219)**
Minority Interests					
Preferred Dividends					
FX Gain/(Loss) - post tax					
Other Adjustments - post-tax					
Net Profit	**(1,413)**	**(2,004)**	**(904)**	**(853)**	**(219)**
Normalised Net Profit	(1,413)	(2,004)	(904)	(853)	(219)
Fully Diluted Normalised Profit	**(1,413)**	**(2,004)**	**(904)**	**(853)**	**(219)**

Cash Flow

(US$m)	Dec-21A	Dec-22A	Dec-23F	Dec-24F	Dec-25F
EBITDA	(1,314)	(1,618)	(999)	(620)	26
Cash Flow from Invt. & Assoc.					
Change In Working Capital	(444)	266	(159)	(16)	7
(Incr)/Decr in Total Provisions					
Other Non-Cash (Income)/Expense					
Other Operating Cashflow	471	(130)	(0)	(0)	0
Net Interest (Paid)/Received	(16)	0	0	0	0
Tax Paid	5	(14)	(11)	(14)	(14)
Cashflow From Operations	**(1,299)**	**(1,497)**	**(1,170)**	**(650)**	**19**
Capex	0	0	(362)	(296)	(191)
Disposals Of FAs/subsidiaries					
Acq. Of Subsidiaries/investments					
Other Investing Cashflow	641	1,077	0	0	0
Cash Flow From Investing	**641**	**1,077**	**(362)**	**(296)**	**(191)**
Debt Raised/(repaid)					
Proceeds From Issue Of Shares					
Shares Repurchased					
Dividends Paid					
Preferred Dividends					
Other Financing Cashflow	3,637	(19)	0	0	0
Cash Flow From Financing	**3,637**	**(19)**	**0**	**0**	**0**
Total Cash Generated	2,979	(438)	(1,532)	(946)	(172)
Free Cashflow To Equity	**(658)**	**(419)**	**(1,532)**	**(946)**	**(172)**
Free Cashflow To Firm	**(642)**	**(419)**	**(1,532)**	**(946)**	**(172)**

SOURCES: CGIS RESEARCH, COMPANY DATA, BLOOMBERG

BY THE NUMBERS… cont'd

Balance Sheet

(US$m)	Dec-21A	Dec-22A	Dec-23F	Dec-24F	Dec-25F
Total Cash And Equivalents	6,618	4,535	3,205	2,342	2,219
Total Debtors	483	173	637	756	891
Inventories	243	282	337	412	530
Total Other Current Assets	270	217	227	239	251
Total Current Assets	**7,614**	**5,207**	**4,407**	**3,748**	**3,890**
Fixed Assets	588	846	901	1,147	1,305
Total Investments	0	0	0	0	0
Intangible Assets	47	41	41	41	41
Total Other Non-Current Assets	398	286	286	286	286
Total Non-current Assets	**1,032**	**1,172**	**1,228**	**1,473**	**1,631**
Short-term Debt					
Current Portion of Long-Term Debt	0	0	0	0	0
Total Creditors	820	762	1,132	1,321	1,593
Other Current Liabilities	779	706	192	141	84
Total Current Liabilities	**1,600**	**1,469**	**1,325**	**1,462**	**1,678**
Total Long-term Debt	202	209	209	209	209
Hybrid Debt - Debt Component					
Total Other Non-Current Liabilities	601	318	318	318	318
Total Non-current Liabilities	**803**	**527**	**527**	**527**	**527**
Total Provisions	0	0	0	0	0
Total Liabilities	**2,403**	**1,996**	**1,852**	**1,989**	**2,205**
Shareholders' Equity	6,243	4,383	3,782	3,232	3,317
Minority Interests					
Total Equity	**6,243**	**4,383**	**3,782**	**3,232**	**3,317**

Key Ratios

	Dec-21A	Dec-22A	Dec-23F	Dec-24F	Dec-25F
Revenue Growth	281%	20%	70%	23%	29%
Operating EBITDA Growth	(17.0%)	23.1%	(38.3%)	(38.0%)	N/A
Operating EBITDA Margin	(112%)	(114%)	(41%)	(21%)	1%
Net Cash Per Share (US$)	5.32	3.23	2.20	1.57	1.48
BVPS (US$)	5.18	3.27	2.78	2.38	2.44
Gross Interest Cover	(91.31)	N/A	N/A	N/A	N/A
Effective Tax Rate	0%	0%	0%	0%	0%
Net Dividend Payout Ratio	NA	NA	NA	NA	NA
Accounts Receivables Days	84.33	84.59	61.26	86.16	78.80
Inventory Days	367.3	334.4	275.6	273.5	266.7
Accounts Payables Days	547.1	355.0	406.1	501.4	488.9
ROIC (%)	1147%	(418%)	(315%)	(77%)	(17%)
ROCE (%)	(27.4%)	(31.5%)	(26.6%)	(22.1%)	(6.0%)
Return On Average Assets	(19.8%)	(24.4%)	(20.6%)	(16.4%)	(4.7%)

Key Drivers

	Dec-21A	Dec-22A	Dec-23F	Dec-24F	Dec-25F
Tislelizumab (yoy%)	56.2%	65.8%	30.0%	25.9%	22.4%
Zanubrutinib (yoy%)	422.7%	159.0%	117.3%	31.9%	31.6%

SOURCES: CGIS RESEARCH, COMPANY DATA, BLOOMBERG

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	Rating Distribution (%)	Investment Banking clients (%)
Add	67.5%	1.3%
Hold	22.5%	0.0%
Reduce	10.1%	0.2%

Spitzer Chart for stock being researched (2 year data)

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