SymBio Pharmaceuticals Ltd.

(4582 JASDAQ) Issued: December 6, 2021

SymBio's JPY1.3 Billion Operating Profits Target Achievable

2021 operating profit in the JPY1.3 billion range within reach

Due to inventory consolidation following the switch to in-house sales and as a result of the COVID-19 pandemic, cumulative sales of Treakisym®, the company's key product, were somewhat lacklustre in the first three quarters, reaching only 60.7% of full-year expectations. However, with the approval of the r/r DLBC indication in March 2021, there has been steady progress in the expansion of indications, and the company's new in-house sales structure has made a good start. On the other hand, the switch to an RTD formulation has not been as rapid as the company had planned and the effect this would have had on reducing unit costs has been delayed somewhat. For this reason, third quarter unit costs stood at 26.4%, only 0.3 points below the second quarter level. Even so, the operating margin rose to 25.7% in the third quarter, and cumulative operating profits for quarters 1-3 were positive, totaling JPY424 million. SymBio Pharmaceuticals estimates the RTD switch is around 3 months behind the original schedule, which means fourth quarter unit costs could fall to 22-24%, and next year to around 20%. Even assuming annual sales come in at JPY8.35 billion, missing the company's target of JPY9.15 billion, if fourth quarter unit costs fall to 24% and SG&A remains at the level of the third quarter, it is quite possible that the company will secure annual operating profits of JPY1.3 billion or above, in line with its forecast. A further decline in unit costs and annual sales close to the company forecast of JPY9.1 billion would make it likely for operating profits to exceed the company's expectations.

New therapies will not alter Treakisym's status for the time being

The main areas in which Treakisym® is competing are malignant lymphomas and r/r DLBCL, areas for which a lot of antibody and immunotherapies are being developed. Antibody drug conjugates (ADC's) such as Polivy® have appeared, as has the high-response rate CAR-T therapy, in addition to which there is the promising area of Bi-specific T-cell engagers (BiTEs). Some of these can be used in combination with Treakisym® (the Pola-BR therapy) or Treakisym® can be used in a pretreatment (CAR-T). In the case of BiTEs, there have not yet been any trials of Treakisym® in combination mode, but the possibility is there. In any case, since there are not yet enough results available for r/r DLBCL therapies, it is quite possible that various combinations of treatments will be considered using the combined therapies and usages that have been overviewed so far. We think Treakisym's position is assured for the interim unless a therapy is developed that challenges the B-R therapy's established position and effectiveness.

Development of rigosertib and brincidofovir

SymBio has now begun a review of its pipeline strategy. That is, while rigosertib was originally developed to treat myelodysplastic syndromes, at present the focus is on its function as a RAS inhibitor. Its development as a cancer drug is ongoing at Onconova Therapeutics, which was the original licensor. SymBio is now seeking to elucidate other modes of action in collaboration with academia. As for brincidofovir (BCV), focusing on viral infections contracted after hematopoietic stem cell transplantation in blood cancer patients, Phase-2 trials on children with adenovirus infections are now underway, and it is likely that in the second half of 2022 a plan to extend trials to global Pivotal will evolve. Further, development is underway to use BCV to treat viral infections following kidney transplantations and, further down the line, plans are in hand to develop a treatment for malignant brain tumours.

Follow-Up Report

Fair Research Inc

Tsuyoshi Suzuki

Company Outline	
Location	Tokyo
President	Fuminori Yoshida
Established	March 2005
Capital	JPY17,152 mil
Listed	October 2011
URL	www.symbiopharma.com
Industry	Pharma
Employees	144 (non-consol)
Key Indicators (Dec. 3, 2021)	
Stock Price	JPY1,236
52-week high	JPY2,423
52-week low	JPY387
Shares outstanding	38,449 thousand
Trading Unit	100 shares
Market Cap	JPY47,523 mil
Dividend (est)	0.0
Forecast EPS	JPY 30.0
Forecast PER	41.19X
Actual BPS	JPY117.60
Actual PBR	10.51X

Note: EPS, PER, BPS、and PBR calculated on the basis of shares outstanding excl. treasury shares

Results	Revenues JPY mil.	YoY %	Op. Income JPY mil	YoY %	Rec. Profit JPY mil	YoY %	Net Income JPY mil	YoY %	EPS JPY	Stock Price High	Stock Price Low
2018/12 Actual	3,835	11.4	-2,656	NA	-2,748	NA	-2,752	NA	-165.5	335	196
2019/12 Actual	2,837	-26.0	-4,301	NA	-4,376	NA	-4,376	NA	-189.0	275	150
2020/12 Actual	2,987	5.3	-4,506	NA	-4,615	NA	-4,090	NA	-124.1	653	243
2020/1Q-3Q Actual	2,332	16.2	-3,142	NA	-3,220	NA	-2,694	NA	-84.6	644	264
2021/1Q-3Q Actual	5,553	138.1	424	NA	414	NA	324	NA	8.48	2,423	387
2021/12 Forecast	9,151	206.4	1,361	NA	1,350	NA	1,149	NA	30.0		

会社概要･経営理念

＜Business Model＞ The company is a specialty pharma engaged in drug discovery without the risks presented by laboratories or manufacturing, employing a niche strategy to secure high returns	SymBio Pharmaceuticals Ltd. is a global specialty pharma with a focus on rare conditions with high medical need in the areas of cancer and hematology, to which the major pharmaceutical companies have paid little attention. Its involvement extends from clinical trials, rather than the high-risk area of drug discovery, through to sales activity. The company's business model has three characteristics: ① Post-POC strategy The company does not itself undertake drug discovery research but investigates candidates developed by drug discovery ventures and pharmaceuticals companies around the world. Usually, proof of concept has already been established. By insisting on prior evidence of efficacy and safety in human subjects the company reduces the development risks of new drug candidates. ② SymBio is a specialty pharma operating a high return, high market share niche strategy. The company focuses its efforts on drugs for relatively rare indications in, for example, cancer and hematology, where the need is high, but where the major pharmaceuticals companies are relatively unrepresented. Using this niche strategy, the company seeks high market share and high returns. Until 2020, The company's business model involved entering into licensing agreements covering new drug candidates it has selected, developing them in Japan and then licensing out to other pharmaceuticals companies. However, it has now set up its own sales function in Japan and has established itself as a pharma specialising in hematology. ③ Global licensor Further, in September 2019, SymBio acquired exclusive rights (development, production and sales) to brincidofovir (BCV), a product with global applications. SymBio has thus evolved from a company seeking licenses in Japan to one providing licenses around the world, firstly in Asia, including China, and also the US and Europe.
The key to returns is the company's network of drug discovery companies and its own expertise	The success or failure of this business model is dependent on the company's network of pharma-collaborators around the world and the company's own expertise. Hence, the company's track record. Normally, it takes some 10-20 years to bring a drug from basic research to the market. In terms of the probability of success, some estimates suggest that, counting from the chemical compound stage, it is less than 1/30,000, and even from the POC stage, only around 7-8%.
SymBio is an unusual bio-venture in that it already has a product on the market, which took only five years from inception to regulatory approval Treakisym® selected as a standard therapy in 2018 Successful expansion of approved indications	In the case of SymBio's first product, Treakisym® (generic name: bendamustine) it took only five years or so to go from licensing-in (in 2005) to manufacturing and sales approval (in 2010). The first approved indications were relapsed/refractory low-grade non-Hodgkin's lymphoma and mantle cell lymphoma. Additional indications then came one after the other. In August 2016, chronic lymphocytic leukemia (CLL) became an additional approved indication, as did untreated low-grade NHL/MCL in December of the same year. Additionally, in July 2018, with respect to all approved indications, Treakisym® was newly listed in the Guidelines for Clinical Practice in Hematopoietic Tumours for 2018 (edited by the Japanese Society of Hematology) as a standard treatment option. In March 2021, the company succeeded in acquiring authorisation for relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL).

Note: malignant lymphoma types

Lymphoma is a blood disease caused by the cancerisation of immunity cells called lymphocytes (a type of leukocyte). There are two major types: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Most Japanese cases of malignant lymphoma are NHL, which can be classified into three types depending on speed of disease progression (Treakisym® is indicated for the NHL type). The most frequently occurring medium-grade malignant NHL in Japan is diffuse large B-cell lymphoma (DLBCL).

Types of malignant lymphoma (Japan)

(%)

Non-Hodgkin Lymphoma	**DLBCL**	**45.3**
	Focular Lymphoma	13.5
	MZBCL	7.2
	CLL/SLL	3.2
	MCL	2.0
	Burkitt Lymphoma	1.3
	T/NK Cell Lymphoma	18.1
Hodgkin Lymphoma		5.9
Others		3.8

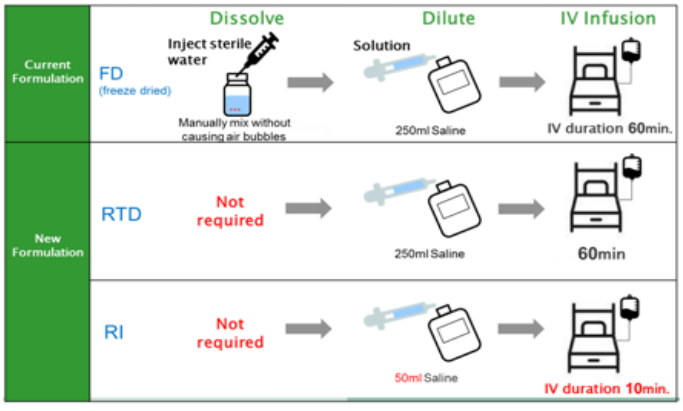
Low grade
Medium-high grade

Source: Chihara D et al "Differences in incidence and trends of haematological malignancies in Japan and the United States", British Journal of Haematology, 2014

Progress in life-cycle management through formulation changes

Additionally, the company has been working on managing the product's life cycle by making changes to the formulation. To this end it has promoted the development of a liquid formulation, which is easier to use than the existing freeze-dried formulation, and in September 2020 it acquired authorisation for an RTD formulation. In May 2021 the company additionally submitted an application for approval of an even more convenient RI formulation, which it expects to receive in the first half of 2022. This should extend product life-cycle to the end of 2031.

Comparison of the FD, RTD and RI formulations



Source: SymBio results meeting

SymBio's network and expertise are enhanced by an outstanding workforce and company organisation	Reference: Having launched a freeze-dried formulation in 2014, the US company, Teva Pharmaceuticals Industries, in January 2016 launched an RI preparation (product name: Bendeka®, licensed in from Eagle Pharmaceuticals) which is more easily administered). In only two years Bendeka® came to account for 97% of the Treakisym® market. We believe SymBio's track record has been made possible by the expertise of the company's staff and by the way the company is organised. SymBio has a staff of 155, of whom 55 are involved in R&D (figures as of end of 2020). The drug search function is supported by a Scientific Advisory Board (SAB) of experts (including Nobel Prize candidates). Needless to say, a major role has been played by the company founder and CEO, Fuminori Yoshida, who developed the network and contributes his expertise. In the 15 years since the company was founded, it has introduced six products. It is currently promoting the development of three drugs, the first of which is Treakisym®, whose various modes of action it is elucidating to further expand the product's area of utility. The second is rigosertib, a RAS pathway inhibitor licensed in from the US firm, Onconova Therapeutics. And the third is brincidofovir (BCV), a highly active multiviral drug for treating infections, licensed in from the US firm, Chimerix. It can be used to fight various infections contracted by blood cancer patients after hematopoietic stem cell transplantation in the interval until the patient's own immunity recovers. It can also be used to fight viral infections in organ transplant patients.

Reference: SymBio's product pipelines

[TREAKISYM®]

Pipeline	Indication(s)	Clinical Trial Phase 1	Phase 2	Phase 3	NDA*1	MA*2
SyB L-0501 Anti-cancer agent	r/r Low-grade NHL/MCL	Approved October, 2010				
	CLL	Approved August, 2016				
	1st line Low-grade NHL/MCL	Approved December, 2016				
	r/r DLBCL	Approved March, 2021				
SyB L-1701 (RTD)※	All except for r/r DLBCL	Approved September, 2020				
	r/r DLBCL	Approved April, 2021				
SyB L-1702 (RI)※	All	Submitted a partial change application				

※ On September 20, 2017, SymBio obtained the exclusive rights from Eagle Pharmaceuticals, Inc. (New Jersey) for its patent-protected bendamustine liquid formulations (RTD and RI). SymBio plans to market the RTD formulation on January ,2021 and launch the RI formulation on the subsequent date.

RTD: Ready-To-Dilute; RI: rapid infusion

[Rigosertib]

Pipeline	Indication(s)	Clinical Trial Phase 1	Phase 2	Phase 3	NDA*1	MA*2
SyB L-1101 Anti-cancer agent (IV)	Relapse/ refractory high risk MDS monotherapy	Global phase III study additional analysis				
SyB C-1101 Anti-cancer agent (oral)	Relapse/ refractory high risk MDS	Japan study completed				
	1st line high risk MDS Combination with AZA	Global phase I / II study completed				

Note: The company is now studying multiple modes of action prior to deciding future strategy direction

[Brincidofovir]

Pipeline	Indication(s)	Clinical Trial Phase 1	Phase 2	Phase 3	NDA*1	MA*2
SyB V-1901 Antiviral Drug (IV)	Adenoviral disease of immunocompromised patients including post hematopoletic stem cell transplantation (pediatric/ adult) (Global)	Start of global study				
SyB V-1901 Antiviral Drug (oral)	Formulation development (Global)	Beginning in 2020				

Source: SymBio Pharmaceuticals web site

*1: NDA: Filing for New Drug Approval

*2: MA: Approval

	Insights from the company's Q3/2021 results
Operating revenues finally achieve profitability in the third quarter	SymBio Pharmaceuticals released its third-quarter results on November 11, 2021. The company has at last achieved a cumulative profit surplus for the three quarters January-September, recording JPY424 million on an operating basis. Looking at individual quarters, the April-June second quarter had already produced a small positive result.
Sales are on a recovery track but are lagging the company's full-year forecast However, unit costs are down significantly, and profitability up, due to the in-house sales change and the switch to a liquid formulation	Preparations for the in-house sales structure continued until the middle of last year and became operational in December. However, there was an adverse impact from the inventory adjustments necessitated by the switch from Eisai to doing its own sales, and also from the effect on sales activities of COVID-19. These factors led to a slightly sluggish start, with sales in the first quarter coming to JPY1.42 billion and in the second quarter JPY1.726 billion. However, due to the addition of r/r DLBCL as an approved indication in March 2021, sales recovered to JPY2.4 billion in the third quarter. Elsewhere, because of the change to in-house sales and the switch to an RTD formulation, unit costs fell sharply from 71% in 2020 to 28.9% in the first quarter of 2021 and 26.7% in the second quarter, leading to a profit surplus.
But the introduction of a liquid formulation is behind schedule	Nevertheless, the switch to the RTD formulation is proceeding less smoothly than originally expected (around 20% in the first quarter and 91% by the end of 2021) and consequently the decline in unit costs is lagging expectations, by 0.3 points to 26.4% in the third quarter. All the same, third quarter operating revenues reached 25.7% in the third quarter.
The switch to a liquid formulation is running some 3 months behind the company's schedule Unit costs expected to fall to 22-24% in the fourth quarter	The reason why the switch to an RTD formulation has not proceeded as planned is that, while the conventional freeze-dried formulation comes in lots of 100mg and 25mg, the RTD formulation is 100mg only. This caused problems at medical facilities which had become accustomed to using the 25mg lots. In addition, it has taken some time to make improvements to the device used for extracting the drug solution from the vials. SymBio believes it is about 3 months behind schedule in the switching process, meaning that fourth quarter unit costs should come in at about 22-24%, and fall next year to around 20%.
It therefore seems likely that while sales may not meet the company's projections, operating profits should	In the fourth quarter, the effect of adding r/r DLBCL to approved indications is expected to keep sales on a growth trend. However, even if sales in the fourth quarter were to stall at JPY2.8 billion yen and annual sales came to JPY8.353 billion, short of the company's forecast of JPY9.151 billion, the unit cost rate in the fourth quarter would drop to 24%. Thus, if SG&A expenses remain at the same level as in the third quarter, it is quite possible that annual operating income will reach the mid-JPY1.3 billion level, on a par with the company's forecast (JPY1.361 billion). If the unit cost rate drops further and sales approach the company's forecast of JPY9.1 billion yen, then operating profit is likely to exceed the company expectations. (It should be noted that Eagle Industries, the source of the liquid formulation, does not receive milestone payments from SymBio in 2021.)

SymBio quarterly results and simulated forecast

(JPY-mil)

	1 Q	2 Q	3 Q	4 Q (results)	
Sales	1,420	1,726	2,407	2,800 ～	3,600
CoGS	410	461	636	672 ～	864
Gross profit	1,009	1,265	1,771	2,128 ～	2,736
SG&A	1,220	1,249	1,152	1,200 ～	1,200
R&D	473	439	374	400 ～	400
Excl R&D	747	810	778	800 ～	800
Op. profit	-210	16	618	928 ～	1,536
Rec. profit	-208	5	617	928 ～	1,536
Net profit	-209	4	529		
Cost rate	28.9%	26.7%	26.4%	24.0%	24.0%
Op. profit rate	-14.8%	0.9%	25.7%	33.1%	42.7%

(JPY-mil)

	1 Q	1Q-2Q	1Q-3Q	1Q-4Q (results)	
Sales	1,420	3,146	5,553	8,353 ～	9,153
CoGS	410	871	1,507	2,179 ～	2,371
Gross profit	1,009	2,274	4,045	6,173 ～	6,781
SG&A	1,220	2,469	3,621	4,821 ～	4,821
R&D	473	912	1,286	1,686 ～	1,686
Excl R&D	747	1,557	2,335	3,135 ～	3,135
Op. profit	-210	-194	424	1,352 ～	1,960
Rec. profit	-208	-203	414	1,342 ～	1,950
Net profit	-209	-205	324	1,149	

(Difference)	1 Q	2 Q	3 Q
Cash	-915	-607	287
Accounts receivable	455	199	777
Finished goods	83	177	-30
Semi-finished goods	-63	156	-299
Pre-paid costs	48	53	-42

(Balance)	2020Dec	2021 March	June	September
Cash	3,848	2,933	2,326	2,613
Accounts receivable	406	861	1,060	1,837
Finished goods	271	354	531	501
Semi-finished goods	672	609	765	466
Pre-paid costs	80	128	181	139

Provisional

Source: Fair Research Inc. using short-form results

Reference: SymBio's 2021 annual plan and medium-term plan

(JPYmil)

	2020 (actual)	2021 (forecast)	2022 (med. term plan)	2023 (med.term plan)
Sales	2,987	9,151	10,985	12,369
Gross profit	866	6,957		
GP margin ratio	29.0%	76.0%		
SG&A	5,373	5,596		
of which, R&D	2,266	2,019		
Operating profit	-4,506	1,361	1,738	2,099
OP margin ratio		14.9%	15.8%	17.0%
Recurring Profit	-4,615	1,350	1,727	2,088
Net profit	-4,090	1,149	1,470	1,778

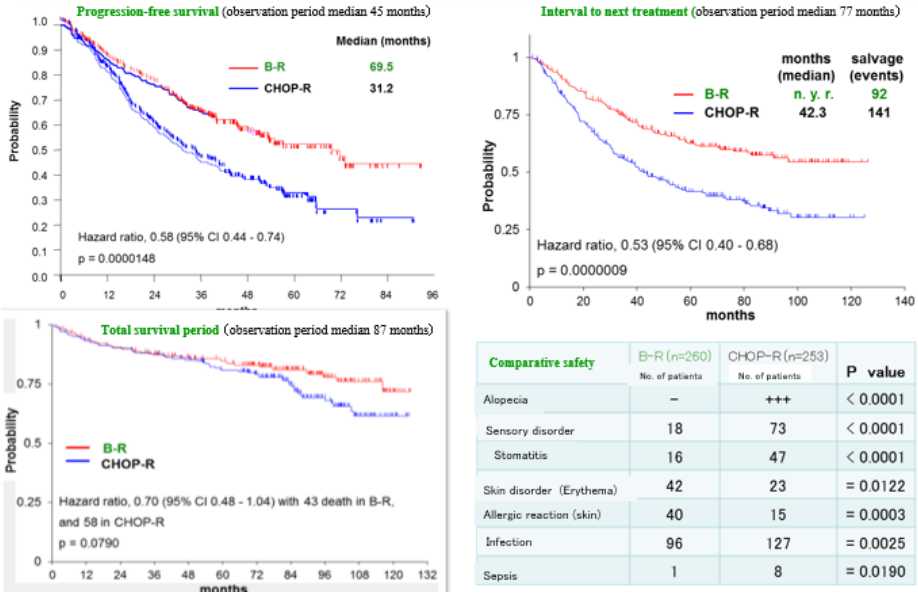
Source: Fair Research Inc. using SymBio's Medium Term Corporate Plan and securities report filings

Treakisym® in the context of new drug developments to treat DLBCL

The B-R therapy is now the standard therapy in the treatment of DLBCL, which is the main type of malignant lymphoma

Looking back briefly at the history of DLBCL therapies, until the development of multi-drug chemotherapies (e.g. the CHOP therapy) there was no effective treatment, especially for r/r DLBCL. The CHOP therapy was developed in the 1970's but, while DCBCL was thereby no longer incurable, CHOP's effectiveness fell short. However, in 1997 the use of Rituxan® (generic name: rituximab) in R-CHOP therapy was authorised and this produced a much better rate of overall survival than the CHOP therapy. Nevertheless, about one-third of patients failed to respond or suffered a recurrence, rendering them the subject of high unmet medical needs. In addition, many patients with malignant lymphoma tend to be of advanced years, for whom the there was always a risk of side-effects from the multi-drug R-CHOP therapy. In response to this, the B-R therapy was developed. This consists of Treakisym® (generic name: bendamustine) together with Rituxan® (generic name: rituximab), providing greater efficacy with fewer side-effects. It has since established itself as a standard treatment of choice.

Comparative study of the R-CHOP and B-R therapies



Comparative safety	B-R (n=260) No. of patients	CHOP-R (n=253) No. of patients	P value
Alopecia	–	+++	< 0.0001
Sensory disorder	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Skin disorder (Erythema)	42	23	= 0.0122
Allergic reaction (skin)	40	15	= 0.0003
Infection	96	127	= 0.0025
Sepsis	1	8	= 0.0190

Source: SymBio company briefing (showing better results for the B-R therapy)

Note: R-CHOP therapy

Chemotherapy that combines the molecular targeted drug rituximab with the anticancer drugs cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and the steroid prednisolone.

In recent years, in the area of malignant lymphoma, much progress has been made in developing new antibody and immunotherapy modalities

Currently, in the field of malignant lymphoma, antibody/immunotherapy has progressed and is being developed as a primary therapy. It is often the case that malignant lymphoma is caused by an abnormality in the B-cells. Malignant B-cells express CD19, CD20, CD22, CD30, CD79a and CD79b on the B-cell surface, and research is progressing to develop therapies which target these.

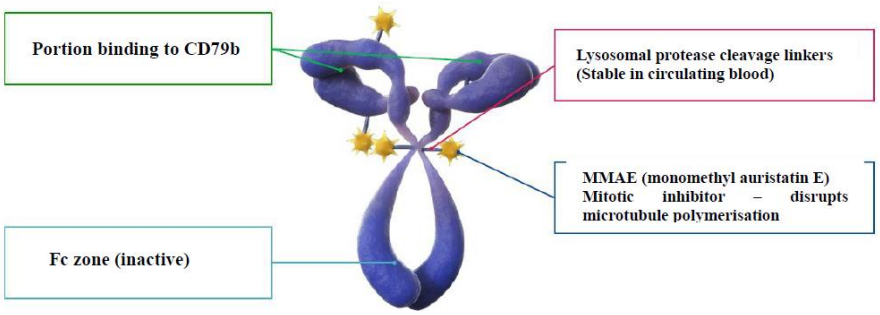
Polivy® was the first antibody drug conjugate (ADC) worldwide to receive authorisation

① Antibody drug conjugates (ADC's)

Authorised for the treatment of r/r DLBCL, Polivy® (polatuzumab vedotin) is an antibody drug conjugate (ADC) of MMAE, a mitotic inhibitor that inhibits

microtubule polymerization and binds to CD79b. The mechanism at work inhibits cell division and induces apoptosis.

The structure of Polivy®



Source: Chugai Pharmaceutical, Polivy intravenous drip information meeting materials, June 2021

Polivy® is not used alone but in combination with Treakisym® and Rituxan® (Pola+BR therapy)

Polivy® is not used alone but in combination with Treakisym® and Rituxan® (Pola+BR therapy)

Reference: Pola+BR therapy vs B-R therapy (r/r DLBCL)

There is data showing that the complete response (CR) rate for Pola+BR is 40% (GO29365 study; Phase-1b/2. Source: Sehn LH e al., J Clin Oncol, 2019). In addition, Phase-2 trials in Japan (P-DRIVE trials) produced a CR rate of 34.3%. The CR rate for the B-R therapy, whose cohort was included in the GO29365 study, was 17.5%. Elsewhere, the SymBio's Phase-3 results targeting the B-R therapy on r/rDLBCL produced a 47.4% CR rate, a 76.3% overall response rate (ORR), and a median overall survival rate (mOS) of 29.2 months. (Note: In SymBio's Phase-3, 70% of the patients on whom genetic analysis was conducted were of the non-GCB type; In the B-R therapy GO29365 study cohort, 57.5% of the patients were non-GCB).

	GO29365 Trial		Symbio
	Pola-BR (90mg/㎡)	B-R (90mg/㎡)	B-R (120mg/㎡)
ORR(%)	70.0	32.5	76.3
CR(%)	57.5	20.0	47.4
mOS (month)	12.4	4.7	29.2

( ) dose of Treakisym

Source: Sehn LH et al, J Clin Oncol 2019, and SymBio IR materials

Since the two cohorts have different backgrounds, we cannot simply compare them. Also, in the GO29365 B-R therapy trials, the Treakisym® dose administered was 90mg/m², while the Treakisym® dose administered in SymBio's Phase-3 B-R trials was 120mg/m². This means that the difference in response, for the same B-R therapy, could be due to the difference in dosage. It is not at present possible to say one is superior to the other.

Pola-BR and B-R could both become the main therapies for r/r DLBCL

It is thought that Pola-BR and B-R will become the mainstream therapies for r/r DLBCL, but whatever happens, Treakisym® (bendamustine) will be used.
For first-line DLBCL, a Pola+RCHP study is now underway, with the possibility that this could become a treatment option. However, even if Pola-RCHP is approved

for first-line DLBCL, it is thought that the size of the r/r DLBCL market for which Treakisym® is indicated will not change much in the short term. Pola-RCHP may achieve a longer progression-free survival (PFS), but it is unclear at the present time whether recurrence is reduced or not. If the rate of recurrence is reduced, then it is possible that the r/r DLBCL market will contract but the proportion of refractory patients resistant to treatment will increase. It is not thought there will a significant effect on f Treakisym® sales in first-line (off-label) treatment.

Another ADC is **Zynlonta®** (generic name: **loncastuximab**), which was authorised in the US in April 2021for the treatment of third-line DLBCL. Since this ADC is a CD19 targeting antibody and alkylating agent it is unlikely to be used in combination with Treakisym®, which also has an alkylation action, thus leaving room for competition. However, as it is a third-line therapy, this competition will be limited. Also, **brentuximab vedotin** (target:CD30) is now undergoing trials for the treatment of DLBCL in combination with Rituxan® (rituximab) and lenalidomide, and combined use with Treakisym® for the treatment of Hodgkin's lymphoma is being studied (however, this indication not authorised in Japan). A monotherapy using **coltuximab ravtansine**(target: CD19) is undergoing Phase-2 trials for DLBCL. While both could be competitive in the distant future, neither offers immense competition for the time being.

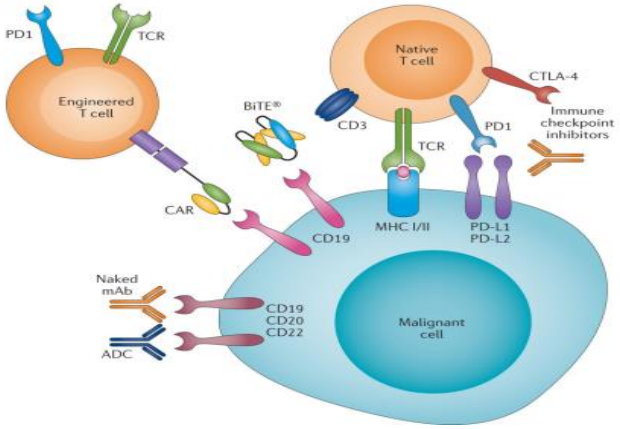
② The CAR-T cell therapy

There are many problems facing broader use of the CAR-T cell therapy

In addition to antibody drug conjugates, another therapy receiving attention is the CAR-T cell therapy. **Kymriah®, Yescarta®** and **Breyanzi®** have already been approved for use in CAR-T therapy. CAR-T is a T cell with a CAR (chimeric antigen receptor) that specifically binds to the cancer antigen CD19 on the surface of tumorised B cells. The T-cell only targets cancerous B-cells and is said to have a response rate of 70-90%. The CAR-T cell therapy is currently limited to transplant non-adaptive (mostly third-line) cases. The intention is to expand the scope to second-line cases and development is underway with the aim of achieving a higher response than autologous transplantation. However, because CAR-T cell therapy requires advanced technology, equipment, and considerable labor to create the CAR-T cells using autologous cells, it is very costly (around JPY30 million per patient) and can only be administered at medical facilities with the ability to respond to adverse events, such as cytokine release syndrome. The use of the CAR-T cell therapy is therefore extremely limited. Treakisym® is used as a pretreatment with Kymriah®, Yescarta® and Breyanzi®.

In the CAR-T therapy Treakisym® is used as pre-treatment

Conceptual depiction of CAR-T and BiTEs



Source: Batlevi CL et al "Novel immunotherapies in lymphoid malignancies", Nat Rev Clin Oncol, 2016

A promising approach is currently being developed: the bispecific T-cell engager (BiTEs)	③ **BiTEs**（Bispecific T-cell engagers） A promising therapy now being developed which has lower barriers to adoption than CAR-T is bispecific T-cell engagers (BiTEs). In this therapy, a complex of which one part binds to CD19 or CD20 that present on the surface of tumorised B cells, and one part binds to CD3 that presents on the surface of T cells. The T cells are induced to tumorise the B cells, providing cancer immunotherapy. Currently, Phase2 trials are underway involving the administration of **blinatumomab** (CD19 / CD3 BiTEs) to first-line DLBCL patients after rituximab-based immuno-chemotherapy, and good results have been reported. Also, trials are underway of **glofitamab** (CD20/CD3 BiTEs) combined with R-CHOP, G-CHOP targeting first-line DLBCL, as are trials of **mosunetuzumab** (CD20/CD3 BiTEs) targeting r/r DLBCL. None of these have been trialed in combination with Treakisym® and it is unlikely that any combination therapy would be with Rituxan®, which targets CD20. A Treakisym® combination would be possible.
Treakisym's position will not be threatened unless a therapy producing a much superior response rate to the widely used B-R therapy is developed	It is apparent that the results of various r/r DLBCL therapies are still insufficient. It seems likely that the different therapies discussed above, individually and in combination, will be the subject of consideration going forward. But the position of Treakisym® will not be challenged for the time being unless a therapy producing a much superior response rate to the widely used B-R therapy is developed.

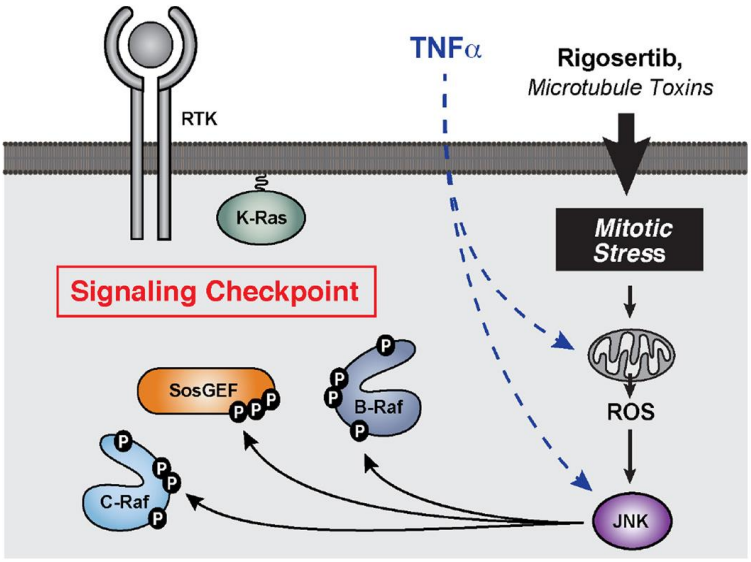
Rigosertib and Brincidofovir (BCV) – development going forward

① Rigosertib (intravenous injection and oral formulations)

Onconva Therapeutics, the original licensor of rigosertib, changes its purpose to RAS pathway inhibitor

The development of rigosertib was originally directed at the treatment of myelodysplastic syndromes (MDS). However, in joint international Phase3 trials (INPIRE trials) it failed to achieve the primary endpoint (August 2020). Currently, however, the focus is on its function as a RAS inhibitor, and the original licensor, Onconova Therapeutics, is pressing ahead with its development as a cancer drug.

Rigosertib action mechanism



Source: Daniel A. Ritt et al, "Inhibition of Ras/Raf/ MEK/ERK Pathway Signalng by a Stress-induced Phospho-regulatory Circuit" Mol Cell 2016 Dec

It is thought that rigosertib's microtubule inhibition action activates JNK and acts on the Ras/Raf/MEK/ERK pathway

Confirmed response in combination with OPDIVO® (anti-PD-1 antibody) targeting NSCLC with KRAS mutations

In September 2021, Onconova Therapeutics disclosed interim partial results for Phase-1/2a trials combining rigosertib (oral formulation) and the anti-PD-1 antibody nivolumab (OPDIVO®), targeting KRAS-mutated non-small cell lung cancer (NSCLC).

Since OPDIVO® does not always evoke a response, even in some patients with a high PD-L1 rate of expression, drug companies are concentrating on the development of combination drugs

The target patients in these trials were KRAS-mutation NSCLC patients who had at least one treatment with anti-PD-1 antibodies. In the case of NSCLC patients, anti-PD-1 antibodies such as OPDIVO® are targeted at patients with a PD-L1 expression rate of 50% or higher, but among patients with a PD-L1 expression rate of 50% or higher, the response rate of anti-PD-1 antibodies is only about 45%. In other words, even if genetic testing indicates treatment with the anti-PD-1 antibody (OPDIVO®), it is ineffective in 55% of patients at the initial treatment stage. There is thus an unmet medical need here, and drug companies are competing vigorously with each other to fill the need.

In terms of the interim results, two of the 12 subjects had not yet reached the evaluation stage and 3 withdrew due to side-effects. Of the seven patients who were eligible for evaluation, 2 registered a partial response (PR), 1 recorded disease

stabilisation (SD) and the disease control rate was 43%. Partial response was observed in patients with G12C mutations as well as G12V mutations. No unexpected serious side effects were observed.

Other KRAS inhibitors bind directly to the mutation location, acting on specific mutations

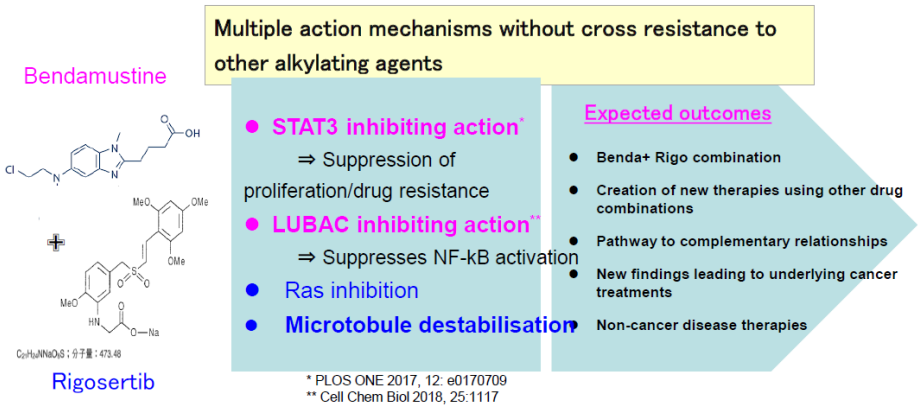
Among NSCLC patients, around 20% have KRAS mutations, the most common (13%) of which are G12C mutations. The first KRAS inhibitor worldwide to receive authorisation was **LUMAKRAS®** (generic name **sotorasib**; Amgen Inc. received accelerated approval in May 2021), a G12C inhibitor. The US firm, Mirati Therapeutics, is developing **adagrasib**, a KRAS (G12C) inhibitor targeting NSCLC, and also a KRAS (G12D) inhibitor targeting pancreatic and other cancers. However, both the Amgen and Mirati drugs bind with specific KRAS mutation and are only effective against those mutations. On the other hand, rigosertib has several potential action mechanisms, including RAS signaling inhibition and microtubule destabilisation, so can elicit responses despite the differences in KRAS mutations noted above, making it more widely applicable.

Rigosertib elicits a response notwithstanding differences in mutation

SymBio Pharmaceuticals is now collaborating on research with academia (Tokyo University's Institute of Medical Science and Gunma University) to elucidate novel mechanisms of rigosertib and Treakisym® (bendamustine). The future strategy for rigosertib should become apparent in mid-2022.

SymBio Pharmaceuticals is now considering the way forward for rigosertib

Potential combinations for rigosertib and Treakisym® (bendamustine)



Source: SymBio Pharmaceuticals company briefing

② Brincidofovir new developments

The primary target is AdV infections following hematopoietic stem cell transplantation for blood cancer treatment

On August 16, 2021, SymBio succeeded in registering its first patient (FPI) for Phase-2 joint international trials of the anti-viral brincidofovir intravenous preparation (BCV IV) for treatment of child adenovirus infections (AdV infections). These trials are directed at an area of extreme medical needs for which there is currently no effective treatment, i.e. disseminated AdV infections and AdV infections from immunodeficiency in children (infections acquired following hematopoietic stem cell transplantation as part of blood cancer therapy). The object is to evaluate safety, tolerability and effectiveness and to decide on recommended dose volumes for subsequent trials. Looking ahead, with more medical facilities contributing in the US, we believe the brincidofovir trials will steadily move ahead, and medical facilities in the UK are scheduled to participate in trials in 2022. The plan is to complete the joint international trials in the second half of 2022 and move ahead to global Pivotal trials. Further, planning is in hand to direct development of brincidofovir at AdV infections of immuno-deficient adults. In addition, a joint

The first patient for joint international Phase-2 trials targeting AdV infections in children was registered in August 2021

The schedule is for joint

international trials to be completed, and global Pivotal trials to begin, in the second half of 2022	research agreement has been signed with the National Cancer Center of Singapore to search for antitumor effects and their mechanisms against Epstein-Barr virus-positive lymphoma.
There is also promising treatment development in the areas of viral infections following kidney transplants	Consideration is also being given to other indications for brincidofovir. Particularly promising is development targeting BK viral infections which are a frequent occurrence worldwide following kidney transplants. There could be an announcement of a new development plan in the first half of 2022.
There are also plans to go beyond viral diseases into the area of oncology Cytomegalovirus is related to malignant brain tumours	SymBio Pharmaceuticals also plans to expand beyond viral diseases into the area of oncology. In September 2021, the company began pre-clinical studies of the antitumor effect on brain tumors at the Brain Tumor Center in the Department of Neurological Surgery at the University of California in San Francisco. BCV can cross the blood-brain barrier (BBB). In almost all cases of malignant brain tumours a large amount of cytomegalovirus (CMV) is present (Nikkei Science magazine, March 2009). It has been established that CMV creates the protein which turns off the genetic switch preventing defective cell growth, which is necessary for tumor growth.
In order to expedite the development and commercialisation of brincidofovir, the company's US subsidiary has brought a key person on board	In October 2021, the company's wholly-owned subsidiary, SymBio Pharma USA, appointed Dr. Carolyn Yanavich as Deputy CEO and Head of Clinical Operations to start operations in earnest. Looking ahead, using this as the strategy base for global specialty pharma operations, the company plans to accelerate the development of the brincidofovir injection formulation in Europe and the United States and realise commercialization.

Conclusions

The operational plan is being implemented with a view to achieving a positive profit figure

SymBio Pharmaceuticals has set up is own in-house sales structure and acquired a new drug, brincidofovir, for which it has a global license. In so doing it has laid the groundwork for growth as a haematology specialist pharma and embarked on a new corporate life. While sales of its main product, Treakisym®, have been slightly lacklustre as a result of inventory adjustments in the switch to in-house sales, and because of the COVID-19 pandemic, there has been progress in expanding indications and changing formulations, and in preparing for the introduction of a new sales structure. In the company's 3Q2021 results released in November 2021 it was reported that cumulative operating profits for the three quarters to date were at last showing a surplus. In results for the full year 2021 there may be a shortfall in sales compared to the company's projections but expectations for operating profit should be amply met.

The company could achieve an operating surplus of JPY1.3-1.4 billion in the full year 2021

Various new modalities in the key r/r DLBCL area

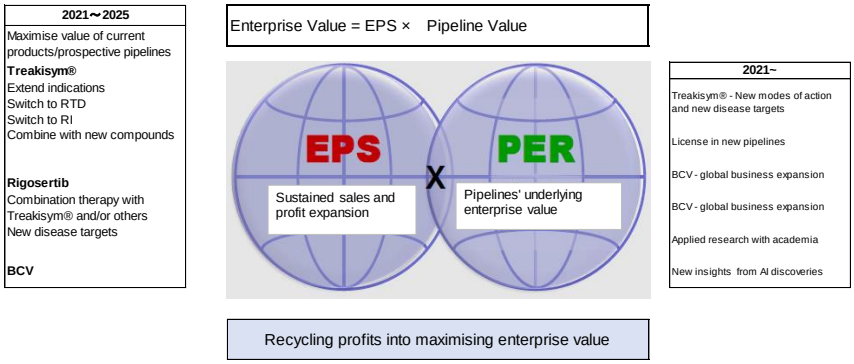
The main challenge for the company's key product, Treakisym®, is in the area of malignant lymphomas, notably r/r DLBCL, where antibody therapies and immunotherapies have made advances. Polivy® and other ADCs (antibody drug conjugates) have arrived, as has the high-response CAR-T therapy. There is also optimism for the development of bispecific T-cell engagers (BiTEs). However, many of these are used in combination with Treakisym®, such as in the POLA-BR therapy, or as preliminary treatment in CAR-T. No trials have been conducted withBiTEs but the possibility is there. Whatever the case, it is apparent that the results of various r/r DLBCL therapies are still insufficient. It seems likely that the different therapies discussed above, individually and in combination, will be the subject of consideration going forward. But Treakisym's position will not be threatened for the time being unless a therapy producing a much superior response rate to the widely used B-R therapy is developed.

The established status of Treakism® is assured unless a therapy with a superior response rate to the B-R therapy appears

New developments of rigosertib and brincidofovir also emerging

As SymBio is now entering its second corporate existence it will pause to review its pipeline strategy. That is to say, while rigosertib has opened the way as a RAS inhibitor there are now other mechanisms of action whose elucidation is under study. Similarly, Phase-2 trials have started on BCV for pediatric adenovirus subjects as a prelude to viral infections in blood cancer patients following hematopoietic stem cell transplantation. It is expected that global Pivotal trials will take place in the second half of 2022. Finally, researchers are now looking at developing therapies for infections following liver transplants for treating malignant brain tumours.

SymBio advancing to its second stage



Source: SymBio results meeting materials

Note: Please see our Basic Report, released on June 1st, 2021, for details on pipeline values

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