CanBas Co., Ltd

(4575 TSE Mothers) Date: August 16, 2018

CanBas Shows Renewed Promise

The company's approach likely to benefit from a paradigm shift in cancer treatment

CanBas Co., Ltd. is an R&D focused drug discovery company which employs its own approach focusing on cell behaviour to develop novel cancer drug therapies. This does not involve high-throughput screening targeting specific molecules or antigens, but rather uses a unique approach in which the whole cell is a black box and cell behaviour is targeted using "cell phenotype screening". In the recent past there has been a paradigm shift in the area of cancer therapies. As the cancer microenvironment has become better understood, the relationship between tumor and immunity has been clarified and immune checkpoint antibodies such as Opdivo have assumed increasing importance. Furthermore, R&D on new cancer drug candidates is being carried out for cancer types and environments where immune-checkpoint antibodies are less effective. CanBas's own specialised approach provides another option in this new area for the development of promising cancer drug candidates.

Company aiming to make cancers more sensitive to Opdivo with CBP501

The company has two major products under development. The more important of these is CBP501 (a calmodulin modulator), from which three effects are anticipated. (1) Reduced production of cytokines that cause immunosuppressive action in the cancer microenvironment, and reduction in cancer stem cells. (2) inhibited migration and epithelial-to-mesenchimal transition of cancer cells, etc. (3) Increased immunogenic cell death and generation of an environment conducive to immune reactions against cancer, improving the efficacy of immunity checkpoint inhibitors such as Opdivo. The other is CBS9106, a candidate cancer drug with a novel XPO 1 (exportin 1) inhibitor mechanism. This product has been licensed out to the American company, Stemline Therapeutics, which is conducting Phase 1clinical trials in the United States. The development of both candidate products is reported to be making good progress.

We model a value of JPY6.9-43.1 billion for the company's product pipeline

In July CanBas announced a finance raising exercise valued at a maximum JPY810 million, which is expected to more or less cover the company's development costs for the next 18 months. Our figures are necessarily tentative since the drugs are still at Phase 1 in terms of development, but the combined value of the company's two pipeline drugs comes to JPY6.9-43.1 billion, exceeding by a considerable margin the company's combined market value and value of its recent financing (JPY4.2 billion). If we extend the valuation to include its development platform of cancer drugs with novel mechanisms it could even achieve a valuation similar to that of a platform company like PeptiDream. Progress in drug development and success in licensing-out will, it is expected, provide the opportunity for a change in investor attitudes.

Basic Report

Fair Research Inc.

Tsuyoshi Suzuki

Company Information	
Location	Shizuoka
President	Kawabe Takumi
Established	Jan. 2000
Capital	JPY4,171 mil.
Listed	Sept. 2009
U R L	www.canbas.co.jp
I n d u s t r y	Pharmaceuticals
No. of employees	12
Main indicators (Aug. 14 2018)	
Share Price	613 yen
Year High	880 yen
Year Low	607 yen
Shares Outstanding	5,505,000
Trading Unit	100 shrs
Market Value	JPY3,375 mil.
Dividend (est)	0
EPS (est)	-154.4 yen
Forecast PER	NA
BPS (actual)	62.93 yen
PBR (actual)	9.74X

Note: Calculated on the basis of total shares outstanding, excluding treasure shares

Results	Revenue JPY mil	YoY %	Op. Income JPY mil	YoY %	RP Income JPY mil	YoY %	Net Income JPY mil	YoY %	EPS JPY	Share Price-JPY High	Share Price-JPY Low
June 2015 Actual	60	NM	-283	NM	-265	NM	-266	NM	-62.5	2730	701
June 2016 Actual	105	72.6	-399	NM	-413	NM	-414	NM	-85.8	1088	643
June 2017 Actual	109	4.4	-406	NM	-400	NM	-419	NM	-83.4	851	595
June 2018 Actual	110	0.1	-539	NM	-547	NM	-532	NM	-96.7	880	615
Q2 2019 Forecast	60	9.9	-305	NM	-305	NM	-306	NM	-55.5		
June 2019 Forecast	115	5.0	-851	NM	-851	NM	-852	NM	-154.4		

Company Outline & Philosophy

<Business Model>

CanBas is an R&D oriented drug discovery company which creates novel cancer drug therapies using its own approach focusing on cell behaviour

CanBas Co., Ltd. started out conducting basic research into the cell cycle before creating candidate cancer drugs with a novel action mechanism using a unique approach focusing on cell behaviour. Subsequently, using feedback from R&D on these candidate drugs the company is currently known as a drug discovery company involved in multi-layered R&D on cancer drugs closely related to the immune system.

Drug discovery companies around the world tend to use two approaches for the suppression of specifically cancer cells. One is the molecular target drug approach which targets molecules characteristically related to cancer, and the other is the antibody drug approach, which uses antibodies to react to specific antigens present on cancerous cells. Hence the starting point for both is the targeting of a specific molecule. Recently, attention is also being paid to the exploration and development of immuno-checkpoint inhibitors, such as Opdivo, that are antibodies which bind to a molecule that serves as an immunity switch.

CanBas's approach does not involve screening for specific molecules or antigens, but treats the whole cell as a black box and uses its own cell phenotype screening, targeting cell behaviour

However, the CanBas approach does not pick out specific molecules or antigens by high throughput screening but rather focuses on the fact that there is a clear difference between the behaviour of normal and cancerous cells in the presence of DNA damage. Intracellular phenomena are black box and screening of cell behaviour itself is targeted using the company's distinctive cell phenotype screening.

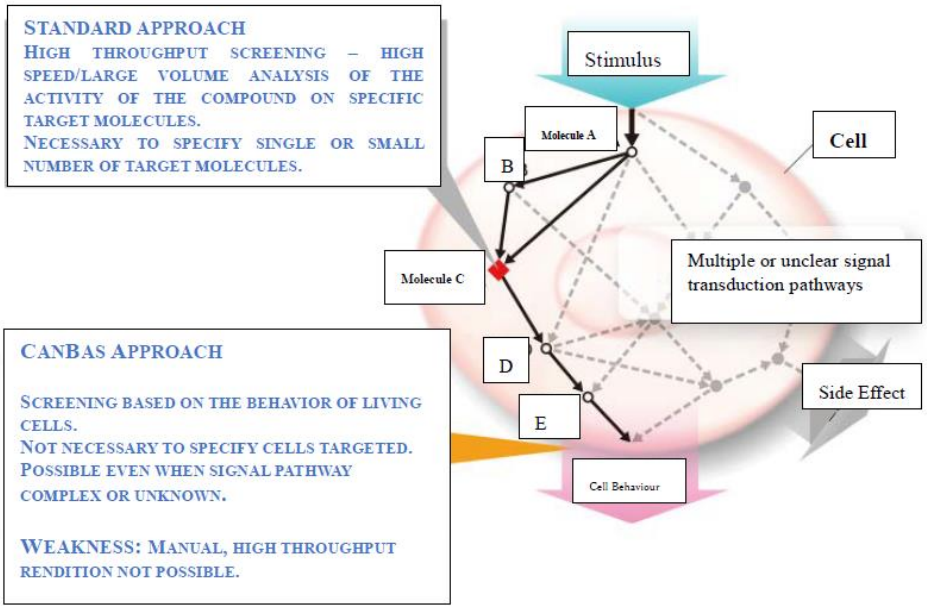
This approach may look at first glance somewhat inefficient but with the advances made in cancer research the company is increasingly confident that this approach will actually be extremely effective.

The expectation is that, as progress is made in research into the cancer microenvironment, the CanBas approach will lead to the discovery of promising new drugs

It is certainly the case that the high throughput screening method used by most drug discovery companies is regarded as a more efficient method of analysing the activity of compounds, in large volumes and at high speed, on specifically targeted molecules and antigens. However, advances in the behavioural analysis of cancers have shown that what used to be thought of as simple one-signal transmission pathways can, in fact, have numerous bypasses and branches. The specific molecule being targeted can mutate when the drug is administered and all medicinal effect lost. What has also come to light is the sheer complexity: the same cancer type can be caused not only by the mutation of the same genes but by a multiplicity of mutation combinations.

Research into the cancer micro-environment has also revealed that cancer cells interfere with the immune system by a variety of mechanisms. Since cancer cells consume large amounts of oxygen and nutrients, cancer tissue is low in oxygen and nutrient, creating an environment inhospitable to the vigorous operation of effector memory T cells, which attack cancer cells. Again, cancer cells release a variety of proteins called cytokines and chemokines, summoning regulatory T cells that suppress immune responses, in addition to which cancer cells alter the properties of macrophages that phagocytize bacteria and viruses, promoting the growth of the cancer or proliferation of new blood vessels and accelerating metastasis. Furthermore, the cancer tissue is surrounded by a tissue called "interstitium" composed of fibroblasts and new blood vessels, making it difficult for immune cells to approach cancer cells. In other words, the whole cancer mechanism is intertwined in complex ways. On the basis of clinical tests and research, CanBas believes its leading product, CBP501, can function effectively in this complex cancer micro-environment, and has therefore directed its entire R&D effort to closely correlate with immunology.

Cell Phenotype Screening



Source: CanBas home page

Brief History

Started out doing research on G2 checkpoint inhibitors in the cell cycle

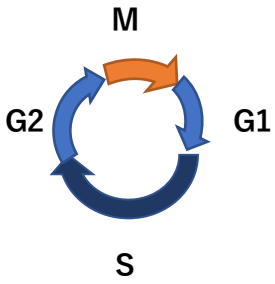
CanBas Co., Ltd. was established in January 2000 by the current CEO, Takumi Kawabe, on the basis of results produced by his research on the cell cycle. Dr. Kawabe practised internal medicine after graduating from the medical department of Kyoto University in 1983, and then moved in a new direction to engage in basic research on cancer drugs in the postgraduate school of the same university. In 1991 he studied the carcinogenic mechanism of gene translocation and cell death at Washington University in St. Louis, before returning to Japan in 1996 with the idea of G2 checkpoint inhibitors in the cell cycle. After undertaking research at the Nagoya City University Medical School's Institute of Molecular Medicine he established CanBas Co., Ltd in 2000, becoming President and Representative Director in May 2003. Dr. Kawabe remains at the forefront of drug discovery and development.

Note 1: Checkpoint inhibitors

The cell cycle is the process of cell division consisting of G1 phase => S phase (replication phase) => G2 phase => M phase (cell division phase). There are checkpoints at the end of phases G1 and G2 to repair damage to the DNA or, if it cannot be repaired, to initiate programmed cell death. In normal cells, the G1 phase checkpoint preceding the replication phase (S phase) is the main area of activity ensuring that cell division is correctly carried out by accurate replication of the DNA, whereas the G2 checkpoint is rarely active in the case of normal cells.

However, since in cancer cells the G1 checkpoint is rendered inoperable, the G2 phase checkpoint is activated to control the cell cycle. If the G2 checkpoint does not work, additional and irreparable damage is done to the DNA of the cancer cell, which is then subject to programmed cell death, an event whose repercussions are limited since the G1 phase checkpoint is effective in normal cells. From around 2000 to 2005 a lot of work worldwide went into the development of a G2 inhibitor for a cancer drug which had little effect on normal cells. So far, however, success has proven elusive.

The cell cycle



M phase:	Mitosis
Phase G1/interphase:	G1/S G2 checkpoint checks for DNA damage
S phase:	DNA synthesis
Phase G2: interphase	G2/M checkpoint checks for DNA damage

Source: Prepared by Fair Research Inc.

Note 2: Why the checkpoint inhibitor does not succeed

There is no universally accepted opinion but according to CanBas there are two broad possibilities: 1. Due to the toxicity peculiar to each development compound it seems the concentration provided is insufficient for a medicinal effect. That is why candidate compounds have different toxicity levels from each other. In other words, the toxicity does not seem to be specific to the action mechanism; and 2, more prosaically, the cell cycle of the cancer cell is not as rapid in the human body as it is in the laboratory.

CanBas signed an agreement with Takeda Pharmaceutical for joint development of G2 checkpoint inhibitor CBP501 in 2007, with US Phase 2 trials starting in 2008

The company's promising cancer drug candidate CBP501 was developed at the time of the company's founding as a G2 checkpoint inhibitor. From May 2005 it began Phase 1 testing in the US and in October 2006 began Phase 1 testing in combination with cisplatin. Subsequently, in March 2007, CanBas signed a joint development agreement with Takeda Pharmaceutical covering CBP501 and its backup compounds with a view to achieving a higher profile and accelerated development. In May 2008 the company began Phase 1 tests in the US of CBP501 in combination with cisplatin and pemetrexed, in November of the same year clinical Phase 2 trials targeting malignant pleural mesothelioma, and in the US in June began Phase 2 trials targeting non-small cell lung cancer. In September 2009 it listed on the T.S.E Mothers market.

Although the company was listed on the stock market in 2009 the joint development agreement and development was dissolved in 2010 and development of a G2 checkpoint inhibitor came to a standstill in 2013

However, in June 2010 the collaboration with Takeda Pharmaceutical was terminated. The reason for this, according to CanBas, was that Takeda at that time had made cancer a priority area for its business but as a result of its acquisition of Millennium Pharmaceuticals, Inc. in 2008 the focus within the broad cancer area became blood cancer (Millennium was the company that developed Velcade, a therapy for the blood cancer, multiple myeloma).

The development of CBP501 as a checkpoint inhibitor then ran aground. In November 2011the Phase 2 targeting of malignant pleural mesothelioma showed promising results, but the final report on Phase 2 targeting of non-small cell lung cancer in July 2013 showed it could not achieve its main endpoint, progression-free survival (PFS). Nevertheless, among sub-groups there was a remarkable effect on overall survival (OS) in the group of subjects with normal white blood cell count.

However, after steady analysis and additional research the company came up with the idea of using calmodulin modulator to develop a unique cancer drug with a new mechanism.

There then began a period of steady analysis and additional research by CanBas. It had already been known that there is an effect of increasing the intracellular influx of cisplatin within cancer cells through the calmodulin mechanism which is activated at a concentration lower than that showing G 2 checkpoint inhibitory activity. The company has continued its research, seeking an hypothesis and verification that can explain the sub-group analysis consistently and unambiguously

Note: Findings from the sub-group analysis

CBP501 suppresses the phagocytosis function by acting on the calmodulin of macrophages. When an anticancer agent is administered to a patient with abnormally high number of leukocytes, the DNA may be released from neutrophils, a type of leukocyte, which is not phagocytosed and remains, thus increasing the

	tendency to thrombosis. Therefore, thrombosis is likely to occur in a group of patients with high leukocyte concentration, and overall survival time (OS) is considered to be worse than for a group of patients with normal number of leukocytes.
Currently under development (Phase 1b) as a drug to improve the effectiveness of immunity checkpoint agent	And, as a result of solid research, CanBas is continuing to develop CBP501, not as a G2 checkpoint inhibitor but as a calmodulin modulator, providing a unique anticancer agent with a new mechanism (explained in the main pipeline section below). Since the improved effectiveness of the immunity checkpoint inhibitor agent was also anticipated, Phase 1b tests of CBP501, cisplatin, and three immunosuppressant inhibitors in combination was started from October 2017 with plans now in hand to expand the number of cases.
Another cancer drug candidate born of the company's own screening approach has been licensed out to the American company Stemline Therapeutics, Inc. and is at the Phase 1 stage	CanBas has used its cell phenotype screening approach to develop another cancer drug candidate called CBS9106. This has a novel action mechanism and in December 2014 was the subject of a licensing agreement with Stemline Therapeutics, Inc. in the US. Phase 1 tests targeting solid tumours were begun in May 2016 and are currently ongoing.
	In addition to the two products mentioned above CanBas is also developing two successor candidates of CBP501. Moreover, the company is pursuing joint research on IDO/TDO inhibitors with University of Shizuoka, and has signed an agreement (June 2017) on joint research with Fujifilm Co., Ltd. with the aim of developing a novel immunological cancer drug. It is also engaged on collaborative research with the University of Tokyo School of Medicine Hospital, the Pharma Valley Project (Fujinokuni Jokamachi Medical Promotion Organisation – formerly the Shizuoka Prefectural Industrial Promotion Foundation).

CanBas Timeline

Date	Event
Jan. 2000	Company set up in Toyota, Aichi Pref. to develop new cancer drugs using results of cell cycle research
Sep. 2000	Applies for patents covering screening methodology and original peptide TAT-S216
Apr. 2002	Company moves to Numazu City in Shizuoka Prefecture
Jan. 2003	Applies for patent for candidate cancer compound CBP501 optimising original peptide TAT-S216
May 2005	Phase 1 trials for CBP501 begin in the US
Oct 2006	Phase 1 trials for the CBP501+cisplatin doublet therapy begin in the US
Mar. 2007	CanBas concludes a joint development agreement covering CBP501 and back-up compounds with Takeda Pharmaceutical
May 2008	Phase 1 trials start in the US for a triplet therapy involving CBP501, cisplatin and pemetrexed
Nov. 2008	Phase 2 trials start in the US for a triplet therapy involving CBP501, cisplatin and pemetrexed (target: malignant pleural mesotheloma)
May 2009	Phase 2 trials start in the US for a triplet therapy involving CBP501, cisplatin and pemetrexed (target: non-small cell lung cancer)
Sep. 2009	CanBas lists on the TSE Mothers market
June 2010	Dissolution of joint development agreement with Takeda Pharmaceutical covering CBP501 and back-up compounds
Sep. 2010	CanBas moves office within Numazu City
Dec. 2011	CBS9106 patent granted by US Patent Office
Nov. 2012	Phase 2 trials for triplet therapy involving CBP501, cisplatin and pemetrexed (target: malignant pleural mesotheloma) final report => effective =>Perhaps because target is MPM, licensing-out may prove difficult
Jul. 2013	Phase 2 trials for triplet therapy involving CBP501, cisplatin and pemetrexed (target: non-small cell lung cancer) final report => no significant difference => CanBas then started doing solid analysis and follow-up research on CBP501 => The company thereby gains insights into how CBP501 works in the cancer micro-environment
Dec. 2014	Licensing agreement on CBS9106 signed with Stemline Therapeutics, Inc.
Oct. 2015	The company is granted a special use patent for CBP501 targeting lower white blood cell counts Around this time company starts planning new clinical trials (combining immuno-checkpoint antibodies and chemotherapy)
May 2016	US Phase 1 trials begin for CBS9106 (Target: all solid cancers)
April 2017	Receives approval from FDA to commence Phase 1 trials for combined administration of CBP501, cisplatin and immuno-checkpoint inhibitor antibodies
June 2017	Signs joint research agreement with Fujifilm on the creation of a novel immunological cancer drug
Aug. 2017	Facility opened for Phase 1b trials of combined administration of CBP501, cisplatin and immuno-checkpoint inhibitor antibodies
Oct. 2017	First subjects administered combined CBP501, cisplatin and immuno-checkpoint inhibiter antibodies in CBP501 initial Phase 1b trials
Aug. 2018	Expansion of CBS9106 market territory agreed with Stemline Therapeutics, Inc.

Source: Prepared by Fair Research from corporate filings

Note: the IDO Inhibitor

The IDO inhibitor is an immunity checkpoint inhibitor. Much had been expected of it as new immunotherapy checkpoint following on from anti-PD-1antibodies (Opdivo and KEYTRUDA) and anti-CTLA-4 antibodies (YERVOY). The most advanced drug in this area was Epacadostat (developed by the US company, Incyte) but in April 2018 clinical Phase 3 trials of this drug in combination with KEYTRUDA were cancelled, sending a shock through the oncology community. However, CanBas strongly believes that “failure is the root of success” and because its own development product is a dual IDO/TDO inhibitor it has decided to continue development while analyzing the reasons for Incyte’s decision to terminate.

Main Pipeline Products

Two main drug candidates now under development

There are two main drug candidates now under development at CanBas: the calmodulin-modulator CBP501, and the Exportin-1inhibitor CBS9106. The CBP501 successors and the IDO/TDO inhibitor are still at the pre-clinical stage.

CanBas Pipeline

Compound	Mechanism	Collaborator	Development stage	Target indication
CBP501	Calmodulin Modulator		Ph2 completed / Ph1b progressing	Solid cancers
CBS9106	Reversible XPO1 Inhibitor	Stemline Therapeutics	Ph1	Solid cancers
CBP-A	CBP501 series peptide		Compound optimisation completed	
CBP-B	CBP501 series peptide		Optimisation proceeding	
IDO/TDO Inhibitor	IDO/TDO inhibitor	Shizuoka University	Optimisation proceeding	

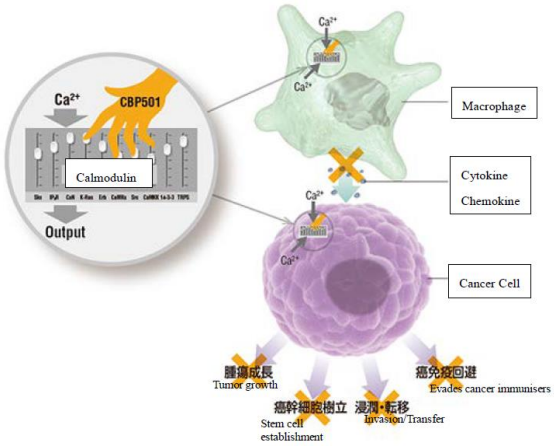
Source: CanBas home page

(1) CBP501 (calmodulin-modulator)

Calmodulin is a protein present in all cells and present in a variety of locations, such as intracellular organelles and in membranes. Since calmodulin changes its structure when calcium binds and is able to bind with specific proteins, it has a control function over a variety of proteins and has an effect on a number of cell functions. It is involved in numerous processes, including metabolism, intracellular migration, apoptosis (programmed cell death) and immune responses.

As noted in the section on company history CBP501 was originally developed as a G2 checkpoint inhibitor but subsequent research showed that it acts on calmodulin at a lower concentration than is necessary for G2 checkpoint inhibitor activity. Hence, ① the cellular influx of the platinum cancer drug cisplatin increases only in cancer cells via the effect on ion channels, and ②anti-cancer activity has been apparent via the action on calmodulin, in a broad range of areas including cancer microenvironment, cancer immunity, and cancer stem cells.

Calmodulin modulator



Source: CanBas home page

What exactly are the effects on calmodulin?

Three things are expected of CBP501 (calmodulin modulator): 1Suppression of the production of cytokines that generate an immune-suppressive effect in the cancer micro-environment, and reduction in cancer stem cells; 2.Inhibition of cancer cell migration and epithelial-to-mesenchymal transition; and, 3. Increase in immunogenic cell death and creation of an environment more conducive to cell death, improving the efficacy of immunolological checkpoint inhibitors such as Opdivo

(a) In the cancer micro-environment, macrophages (TAM) release cytokines (IL-6, TNF-α, IL-10) which restrain immunity to cancer. However, CBP501 acts to suppress the production of cytokines and reduces cancer cell stems.
(b) CBP501 prevents the binding of calmodulin and KRas, a cancer causing gene, and thereby inhibits the migration, infiltration and epithelial-to-mesenchymal transition of cancerous cells.
(c) CBP501increases immunogenic cell death, promotes the infiltration of effector memory T cells and improves the efficacy of immune checkpoint inhibitors such as Opdivo by creating an environment where an immune response against cancer is likely to occur.

Note: Immunogenic cell death
When the cancer cell dies the cell is destroyed and the contents of the cell are released, a signal that the cancer cell has been destroyed is received by the dendritic cell, which is one type of immune cell. Information on how to distinguish cancer cells is transmitted to the effector memory T cells and the immune system is activated. In cancer cell death by cisplatin, there are few immunogenic cell deaths. This is because endoplasmic reticulum stress is necessary to cause immunogenic cell death and almost no such ER stress occurs with the usual cisplatin amounts. It is thought that CBP501 increases the cisplatin concentration within cells and immunogenic cell death occurs due to the additional ER stress.

From the end of 2018 and into 2019 the company plans to start latter stage Phase 1b tests, narrowing down the types of cancer types and increasing the number of cases to explore efficacy

In October 2017 the first test subjects for Phase 1b in the US were administered a combination of CBP501, cisplatin and immunological checkpoint inhibitor (Opdivo). At a company presentation in April 2018 it was reported that several of the first cohort (of 3 patients) had proceeded well and that the dosages had been changed for the second and third cohorts. With the completion of dose finding portion of Phase 1b tests anticipated this summer the company expects to clear the safety confirmation hurdle and will select cancer types which clearly respond to treatment. Late this year and into next the company plans to begin latter stage Phase 1b tests, conducting extension phase examinations to examine medicinal efficacy using fewer cancer types (The company announced in July it would be raising funds to finance the extension phase examination.)

Opdivo is known to remain effective for an extended period of time but its efficacy varies greatly depending on the cancer being treated. CanBas's development strategy calls for improving the efficacy of Opdivo by combined use. However, because Opdivo's effectiveness is relatively low (≒ genetic mutation volume: TMB was low) and to restrain development costs it is anticipated that the tests will involve a relatively limited number of solid cancer cases being selected for extension phase testing. Fair Research assumes the indications will include pancreatic cancer and unresectable metastatic colorectal cancer with low microsatellite instability (≒ TMB is low).

Successors to CBP501 now being developed

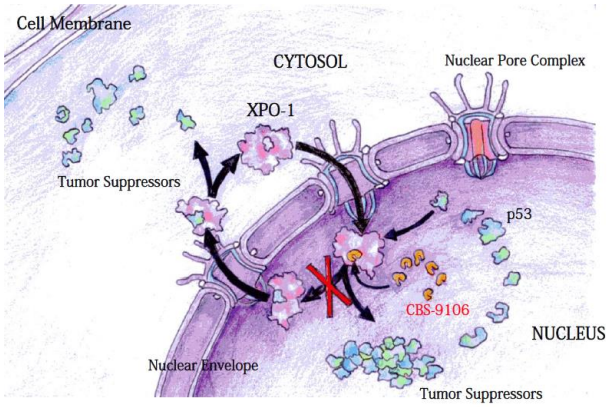
CanBas is now using the platform it used to create CBP501 to develop candidate successors. Both are now at the compound stage of development. The CBP-A series is designed to suppress histamine release to avoid infusion reaction, while the CBP-B series uses a compound which does not increase cisplatin inflow.

(2) : CBS9106: reversible XPO1 (exportin-one inhibitor – oral)

CBS9106 is an XPO1 inhibitor obtained using CanBas's own screening methodology. It has a novel mechanism and offers promise as a cancer drug candidate.

XPO1 shuttles various cargo proteins out of the nucleus, including messenger RNA coupled with the proteins and tumour suppressors, such as IκB, p53 and FOXOs. It is thought that XPO1 inhibitors suppress the transport of these outside the nucleus, inducing cell cycle arrest and apoptosis.

The action mechanism of XP01 (exportin-one inhibitor)



CBS9106 inhibits the binding of nuclear proteins (eg. Tumor Suppressors) to XPO1.

Source: Fair Research using Stemline materials and etc.

CBS9106 was licensed out to the US company, Stemline Therapeutics, in 2014 and is now undergoing Phase 1 tests.

CanBas developed the XPO1 inhibitor CBS9106 using its own screening approach. In December 2014 it concluded a licensing agreement covering CBS9106 granting exclusive worldwide (excluding Japan, China, Taiwan and South Korea) development and commercialization rights to Stemline Therapeutics, Inc. Stemline is now conducting Phase 1 trials on solid tumours (the Stemline development code is SL-801).

The US company, Karyopharm Therapeutics, Inc. is developing a drug, selinexor, with the same mechanism. As of 2018 development is reported to be progressing steadily and the XPO1 inhibitor drug is regarded as having established itself as a distinct area of cancer therapy.

Another drug using the same oral XPO1 inhibitor is selinexor, being clinically developed by the US company, Karyopharm Therapeutics, Inc. At the present time development is proceeding smoothly. On May 1, 2018 there was a preliminary report on 122 multiple myeloma subjects who had been resistant to five commonly used cancer drugs (Revlimid, Pomalyst, Velcade, Kyprolis and Darzalex) and were treated in a Phase 2 trial (named STORM) with a therapy combining selinexor and dexamethasone. This therapy proved effective in 25.4% of subjects.

Karyopharm believes selinexor will receive fast track approval from the FDA on the basis of the STORM tests, given that Kyprolis was so approved on a 22.9% effective rate for multiple myeloma subjects who had proved resistant to two cancer drugs. This is considered positive for CanBas as it further helps position XPO1 as a target deserving of clinical appraisal (in passing, in October 2017 the Japanese company Ono Pharmaceutical signed an agreement covering all types of cancer with Karyopharm for exclusive rights to the development and commercialization of selinexor and its successor, KPT-8602, in Japan, South Korea, Taiwan, Hong Kong and the ASEAN countries)

CanBas's CBS9106 differs from selinexor in that it has reversibility

In comparing CanBas's CBS9106 with the XPO1 inhibitor of Karyopharm, one advantage is that the targeted XPO1 itself is induced to decompose (has reversibility). The XPO1 inhibited by CBS 9106 does not linger and it is thought this suppresses side effects.

Judging from a 2018 poster publication by ASCO it appears that development is proceeding steadily

A poster presentation on 35 cases from Stemline was conducted at the American Society of Clinical Oncology (ASCO) in June 2018. Up to the present, it has been confirmed that dose-dependent rises in blood concentration, predictable manageable safety and tolerance, and disease stabilization including tumor shrinkage have been achieved in patients who have undergone multiple previous treatments. We therefore infer that development is proceeding well.

P&L and balance sheet trend

CanBas's sales consist of technical advisory fee income from Stemline, the payment of which has been extended to June 2021

CanBas's operational income (sales) is made up of technical advisory fees from Stemline amounting to approximately JPY110 million per year (however, for the period ending June 2015 the company received a one-off contract fee of JPY10 million and a half-year technical advisory fee). The territory covered by the contract with Stemline was originally global but excluding Japan, China, South Korea and Taiwan. However, in August 2018 the contract was amended to include Japan, China, Taiwan and South Korea, thus becoming truly global. With this contractual amendment came a 30-month extension, from December 2018 to June 2021) of the period during which Stemline would pay technical advisory fees. CanBas also became entitled to a lump-sum contract payment of JPY5.5 million, receivable in the June/2019 period.

Costs will rise partly because of an increase in the number of cases for the CBP501 tests, and these will generate a final loss of around JPY850 million in the June 2019 period. This loss could rise to around JPY850-900 million in the following period.

On the costs side much of the expenditures will go on general expenditures covering R&D and SG&A, with the latter fluctuating at around JPY200 million. Since the plan is for CanBas's important development drug, CBP501, to start latter-stage Phase 1b trials using an expanded number of cases in the period to June 2019, and given costs associated with pre-clinical test preparations for the development of next-generation compounds, the company is expecting total R&D expenditures to balloon to around JPY770 million p.a. in that year. In subsequent years also, continued and expanded development costs will keep total R&D expenditures at or above that level. Therefore, the final loss in the period ending June 2019 is expected to be around JPY850 million, and in June 2020 could trend around JPY850-900 million.

P&L Trend

(JPY'000)

Period ending	Jun-13	Jun-14	Jun-15	Jun-16	Jun-17	Jun-18	Jun-19(Comp.est)
Revenue	0	0	60,958	105,243	109,852	110,000	115,000
Cost of Operations	651,875	483,814	344,501	504,359	516,678	649,456	967,000
R&D	455,055	300,780	164,908	316,180	294,921	423,473	771,000
SG&A expenses	196,820	183,033	179,592	188,178	221,756	225,983	195,000
Operating Profits	-651,875	-483,814	-283,542	-399,115	-406,825	-539,456	-851,000
Non-Operating P&L	10,018	3,585	17,828	-14,624	6,173	-7,635	
Extraordinary earnings	0	105,210	0	0	-17,595	16,254	
Pre-tax net earnings	-641,857	-375,019	-265,714	-413,739	-418,248	-530,837	
Net earnings	-643,107	-376,269	-266,964	-414,989	-419,498	-532,087	-852,000

Source: Prepared by Fair Research from company filings

While at the end of June 2018 the company had only JPY460 million cash on the balance sheet, the capital raising announced in July should secure funding sufficient for the next 18 months

As of the end of June 2018 the company held cash on the balance sheet of JPY460 million. If the convertible bonds issued in July 2018 and new share subscription rights raise a total of JPY810 million, the cash outstanding will come to around JPY1.3 billion, covering the company's cash needs through to June 2019. The company made clear at the time of the capital raising that if the exercise of new share subscription rights is disappointing it would trim the scale of its testing plans. Investors should remain alert to the possibility of a new cash raising exercise.

Balance Sheet Trend

(JPY '000)

Period Ending	Jun-13	Jun-14	Jun-15	Jun-16	Jun-17	Jun-18
Liquid assets	548,023	343,178	953,097	923,428	973,558	546,469
Cash	463,109	323,354	885,355	815,110	889,368	466,277
Fixed assets	139,048	54,301	44,762	43,844	19,723	31,819
Tangible fixed	44,561	31,411	23,449	23,025	0	
Total assets	687,072	397,480	997,859	967,273	993,281	578,289
Liquid liabilities	52,128	26,166	33,083	38,135	66,187	156,352
Fixed liabilities	0	36,645 CB issue No.1	0	0	0	0
Total liabilities	52,128	62,811	33,083	38,135	66,187	156,352
Shareholders equity	615,859	308,176	945,720	902,535	866,913	346,468
Warrants	19,084	26,492	19,054	26,602	60,180	75,468
Total net assets	634,943	334,668	997,859	967,273	927,094	421,936

(Ref) (JPY mil)

Period Ending	Jun-13	Jun-14	Jun-15	Jun-16	Jun-17	Jun-18
Cash from finance activities	377	110	856	375	381	7
of which, income from CB's, warrants, share issues	375	109	856	375	381	7
New equity issue	Warrants no. 8 (JPY300 mil)	CB issue No.1 Warrants no.9 (JPY974 mil))	(Conversion ends)	Warrants no. 10 (JPY1,268 mil)		

Status of outstanding warrants as of July 2 2018:
Warrants No.8 – No.10: rights exercised or lapsed
Outstanding rights limited to stock options for executive officers
No. of latent shares 312,500, or 5.7% of total shares outstanding

Status of No. 2 CB and No, 14 warrants issued July 18 2018:
No.2 CB: Amount raised: JPY209.22 million, initial conversion price: JPY634
Initial latent shares: 330,000, dilution 6.0%
Third-party allotment to Milestone Capital Management Ltd.

No. 14 warrants maximum amount: JPY603.25 million
Initial conversion price: JPY634
Latent shares: 950,000, Dilution 17.3%
Third-party allotment to Milestone Capital Management Ltd.

Source: prepared by Fair Research Inc. using company filings

Considering pipeline value

Since there are no products on the market with the same action mechanisms as those in the company's pipeline, and since the development is still at Phase 1, any estimation of pipeline value presents difficulties. The following, therefore, is intended only as an indication based on some demanding assumptions.

We estimate pipeline value based on a number of demanding assumptions

(1) CBP501

① Discounted cash flow (DCF) of individual candidate development products

The following assumptions made in calculating value:

(a) Development and commercialization schedule

Our calculation of CBP501 market size is for MSI-low patients with pancreatic cancer and unresectable metastatic colon cancer

Latter-stage Phase 1b trials (reduced number of cancers, increased number of cases) assumed to take place in 2019-2020. In 2021, on the basis of results will proceed to Phase 2/3 (Pivotal) trials and simultaneously conclude a licensing-out agreement. Application for approval around 2024, approval and commercialization around 2025. (This is not a forecast but simply a possible timeline).

We posit a market size of around JPY100-500 billion

(b) Market size at peak

For pancreatic cancer and unresectable and metastatic colon cancer that are MSI-low, the number of patients (USA) is assumed to be 45,000 and 240,000 people respectively. Using as a benchmark the price of existing drugs such as dexamethasone (trade name LENADEX), which suppresses tumour cell proliferation, and assuming a prescription administration cost of JPY 300,000 yen / month/per person and a 6-months administration cycle, the maximum market scale models out at approximately JPY500 billion yen. Modelling in a 20% market penetration rate gives the market a size of JPY100 billion.

Assumed probability of success: 10-30%

(c) Various parameters

Since CBP501 is still at Phase 1 we estimate a 10-30% probability of success. Total milestone payments for a JPY100 billion market we posit at JPY10 billion, and for a JP500 billion market, JPY30 billion. If the product is licensed out at Phase 2/3 ((Pivotal) we posit a royalties rate on sales of 12%. Since CanBas is a bio-venture with continuous losses we set the discount rate at a relatively high 12%.

As a result we model a value of JPY3.4-36.4 billion for CBP501

On the basis of the foregoing parameters we estimate a value for CBP501 as summarized in the table below. Even at peak market size of JPY100 billion and with a 10% probability of success we model a value of JPY3.4 billon. Should the market for CBP501 grow to a scale comparable to Avastin (sales of around JPY500 billion) with a 30% probability of success we would posit a value of JPY36.4 billion.

CBP501 value

(JPY mil)

		Peak sales	
		JPY100 bil	JPY500 bil
Success	10%	3,390	14,921
Probability	30%	7,913	36,438

The above assumes a discount rate of 12%, total milestone income of JPY10 billion on peak sales of JPY100 billion, JPY30 billion on peak sales of JPY500 billion, and royalties at 12%

Source: Fair Research, Inc.

② The drug discovery platform concept

It is possible that the company will conclude joint development agreements covering not only a single drug but a drug discovery platform based on CanBas's calmodulin modulator technology

CanBas is planning to create not only CBP501 but a series of drugs using its calmodulin modulator based on CBP501. If the calmodulin modulator technology itself is recognized as a breakthrough in cancer drug development by major global pharmaceutical companies it is thought that it can conclude joint development agreements covering not only a single development candidate but a drug discovery platform using the calmodulin modulator. A precedent exists in the form of PeptiDream's tie-ups with Janssen Pharma or Bayer AG covering the development of the company's special peptide drug discovery platform. The platform agreement would have the advantage for CanBas of providing income at an early stage without interruption. Thus, technical fees would be payable immediately after the conclusion of the agreement, and success fees at stepped intervals determined by development progress. The expected value of calmodulin modulator platform technology could, it is thought, be a function of the value of the drug discovery platform joint development agreement multiplied by the number of contracting companies.

(We should note in passing that the maximum amount receivable under PeptiDream's April

PeptiDream Ltd. has already concluded several joint development agreements related to its drug discovery platform

2017 agreement with Janssen Pharma is set at JPY126 billion, and with Bayer AG (November 2017) at JPY124.5 billion. Since we assume that these sums include large amounts for sales milestones and expanded applications* they should be treated as maximum amounts and the actual platform values discounted accordingly).

*Application expansion: Including the development of novel small molecule drugs based on the analysis of special peptide behaviour

（2）CBS9106: Trial DCF calculation

For the trial calculation we made the following assumptions

(a) Development and commercialiation schedule

We are assuming expansion cohort of Phase 1 will take place in 2019-2020, and that Phase 2/3 (Pivotal) trials will start in 2021. Application for approval we assume will occur in 2024, with approval and marketing taking place in around 2025 (this is not a forecast but a set of assumptions for the purpose of the trial calculation).

For CBS9108 we model a value for the market targeting multiple myeloma, an indication for which the development of XPO1 inhibitor is progressing. We posit peak sales at JPY100 billion

(b) Market size (for multiple myeloma)

It is hoped that XPO1 inhibitor can be used on all cancers, including solid tumours, but since Karyopharm's Selinexor is already ahead in development for multiple myeloma, we here consider the market size for this condition. According to Karyopharm, there are 30,000 new cases of multiple myeloma in the US each year and 12,500 deaths (2016 figures). Moreover, in 2015 the value of the market for drugs to treat this condition totaled USD11 billion and by 2023 is expected to grow to USD22 billion (Source: Global Data). Drugs on the market for this condition include the standard therapy, lenalidomide (marketed as REVLIMID) combined with dexamethasone (LENADEX). It is surmised that this therapy can command peak sales of USD7 billion. Second-line and subsequent therapies include (commercial names) VELCADE (peak sales of USD2.5 billion) KYPROLIS (USD1 billion), POMALYST (USD2 billion), and DARSALEX (USD2 billion). Karyopharm expects second-line selinexor, now under development, to achieve peak sales of USD1-2 billion because it will be the first single-agent oral drug. Bearing in mind the competition with selinexor, Stemline's peak sales of CBS9108 we have assumed will be in the area of USD1 billion (JPY100 billion market).

(c) Various parameters

Since it is now at Phase 1 we are positing the probability of success at 10-30%. Stemline will pay CanBas technical advisory fees, milestone payments and royalties in line with sales. It has been revealed that the upper limit for advisory fees and royalties combined will be JPY10.7 billion (assuming a forex rate of USD1=JPY120). The royalties payout rate has not been disclosed but given the product's pre-Phase 1 licensing we are assuming it will be 8%. We are positing the discount rate at a relatively high 12% given CanBas's status as a bio-venture running at a loss.

Assuming probability of success at 10-30%. The royalties payout rate has not been disclosed but assuming close to 10%

On the basis of the foregoing parameters we model a value of value as shown in the chart below. If peak market size is JPY100 billion and probability of success is 10%, the value of CBS9106 comes to around JPY3.4 billion. Further, positing a success probability of 30% yields a value of JPY6.7 billion. Needless to say, if the cancer types are expanded to include solid cancers then the market size increases and the trial values changes.

Therefore modelling the value of CBS9106 at JPY3.5-6.7 billion

Value of CBS9106

(JPYmil)

		Peak sales JPY100 bil
Success	10%	3,486
Probability	30%	6,718

Note: Does not take accunt of any new tie-ups in Asia

Source: Fair Research

Reference:
Under the terms of the October 2017 licensing agreement between Ono Pharmaceutical and Karyopharm, Ono was to pay Karyopharm a lump sum contractual payment of JPY2.5 billion and a maximum of JPY19.15 billion for milestone payments in line with progress made in development and progress in sales. The royalties rate on sales was set at a double digit level. Ono received the rights for Japan, South Korea, Taiwan, Hong Kong and ASEAN. Selinexor and its successor product KPT-8602 were targeted at all cancer types.

Conclusion

Since this drug is still at Phase 1 our calculations are only for reference but the total trial value of CanBas's two pipeline drugs significantly exceeds the total for CanBas's market value and the proceeds of July's financing operation. Further, it should be noted that pipeline value and corporate value differ.

As the paradigm shift in cancer treatment advances it is looking more likely that CanBas's day has arrived

The trial value of CanBas's two products, CBP501 (JPY3.4-36.4 billion) and CBS9106 (JPY3.5-6.7 billion) total out at JPY6.9-43.1 billion. This is considerably in excess of the total (JPY4.19 billion) for sum of Canbas's market value of JPY3.38 billion (as of August 14) and the proceeds of its July financing operation (JPY810 million). However, the it should be borne in mind that the above trial calculations are based on various suppositions. In addition, it should be remembered that corporate value is not just the value of a company's product lineup but should also include a consideration of the company's basic research costs, SG&A, tax and other expenses. Also worth remembering is the fact that the company may need to tap the market for funds if development requirements so demand.

Our understanding of the cancer micro-environment is growing, such that there has been a paradigm shift in cancer therapies since 2010, when Opdivo and other immunological checkpoint antibodies made their appearance. However, we realise that the efficacy of such checkpoint antibodies depends on the cancer in question. As for CBP501, the possibility that the efficacy of immunological checkpoint antibodies can be improved is recognised, and we look forward to seeing those improvements reflected in the company's value. In addition, CBS9106 is an oral cancer drug with a novel mechanism and we look forward to advances in its development. CanBas's "phenotype cell screening" represents a platform built on basic research into the cancer micro-environment and could well mean the company's day is coming.

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