Kanceras Drug development projects

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kancera

Contents list

This is Kancera

Kancera develops drugs against inflammatory diseases and cancer. Demonstrated effect on the Fractalkine system in humans has strengthened the basis for continued clinical development in a Phase II study.

Kancera develops drugs that counteract damage during acute and chronic inflammation. The Fractalkine blocker KAND567 has primarily been developed to effectively and selectively reduce inflammation of the heart and vessels following a heart attack and is expected to enter the clinical phase II study in 2019. Since scientific studies have shown elevated levels of Fractalkine not only in heart attacks, but also in inflammatory diseases and some forms of cancer, there are several possible development opportunities for a Fractalkine inhibitor such as KAND567.

Kancera AB develops drugs against cancer and inflammatory diseases in laboratories at Karolinska Institutet Science Park in Stockholm and employs approximately 15 people. The share is traded on NASDAQ First North Premier. The number of shareholders as of 30 June 2019 to approximately 7400. FNCA Sweden AB is the company's Certified Adviser. FNCA can be reached at info@fnca.se and on 08-528 00 399. MD PhD Charlotte Edenius, MD PhD Anders Gabrielsen, Professor Carl-Henrik Heldin and Professor Håkan Mellstedt are all scientific advisors and board members of Kancera AB.

Business model

To develop patent-protected drugs, which can extend life and reduce healthcare costs, for sales to the international pharmaceutical industry and further clinical trials.

Out-licensing of drug candidates is expected to take place against partial payments on signing and milestones in product development (typically when initiating clinical phase I, II, III and when registering) and royalty income.

Background

Kancera's team has extensive experience in drug research from discoveries of new disease processes to clinical development within AstraZeneca, Biovitrum (formerly Pharmacia) and Karolinska Institutet. Kancera has mainly focused on inflammatory diseases and cancer, both for its own drug development and as research consultants. As research consultants, Kancera's team has carried out projects for both pharmaceutical companies and biotech companies in the US and Europe. These assignments include the development of the chemistry that laid the foundation for Enasidenib, a drug that has been marketed by Celegene for the treatment of lymphoma (AML) since 2017.

NASDAQ approved Kancera AB for admission to trading on First North with the first day of trading on February 25, 2011. In March 2013, Kancera AB acquired a complete development laboratory, since when drug development has taken place in-house at Karolinska Institutet Science Park, Stockholm. In connection with listing on the Nasdaq First North Premier list on October 28, 2016, the subsidiary Kancera Förvaltning AB was formed, after which Kancera AB from the beginning of the second quarter of 2016 moved over to accounting in accordance with IFRS in the Group and RFR2 in the Parent Company.

Upcoming reports:

- Interim report January-September 2019
  22 November 2019
- Year-end report January-December 2019
  21 February 2020

Significant events in brief

Previous 12 months

Inhibitors of the Fractalkine receptor

The Fractalkine receptor, CX3CR1, controls the immune system and cancer cells. The goal is to prevent cancer and immune cells from infiltrating healthy tissues

- Kancera reported on milestones and time plans for the preparation and implementation of a clinical study in cardiovascular inflammation linked to myocardial infarction.
- Kancera has announced that the research project in the field of cancer financed by SWElife has been completed and that the final report has been approved.
- Kancera has reported that the clinical biomarker study in lymphoma patients is proceeding according to plan.
- Within the framework of the EU research program Horizon2020, Kancera has been awarded a research grant totaling approximately EUR 250,000 for the funding of a doctoral student with the aim of exploring how the Fractalkine system controls a type of immune cells called macrophages, which are believed to cause pain in, amongst other things, rheumatism.
- A new efficacy study in an animal model of myocardial infarction showed that lower doses than expected give a significant cardio-protective effect.
- Preliminary results from the GLP toxicological study showed that the calculated effective dose of KAND567 was safe (final results from this study are expected in January).
- The Phase 0 study in lymphoma patients ends in December, and the analyses are expected to be completed in January 2019.
- Kancera announces that two milestones have been achieved prior to the planned start of clinical studies with the drug candidate KAND567 to show reduced tissue damage in connection with heart attack. In a recent preclinical toxicological study, KAND567 has shown a favorable safety profile, while significant progress has been made in the development of a large-scale production method.
- The results of a study of lymphoma patient's immune cells show that the Fractalkine system is activated in chronic lymphocytic leukemia, diffuse large cell B cell lymphoma and Hodgkin's lymphoma. In view of this discovery, the company will now deepen the study of how drug candidates that interact with the Fractalkine system, such as KAND567, may play a role in future treatments of these diseases.
- Kancera has announced that the Medical Products Agency and the Ethics Committee have approved the application for a Phase Ib study with the drug candidate KAND567. A supplement will be submitted to the Medical Products Agency regarding additional information on a standardized method for intravenous administration of KAND567. After approval of this supplement, the study can start, which is expected to take place in June.
- Kancera has reported that the company's project portfolio was further strengthened by nominating the drug candidate KAND145. KAND145, which is covered by a patent application from July 2018, together with the clinical drug candidate KAND567, forms the basis of a new concept for the treatment of acute and chronic inflammation.

Latest events

- Kancera announced that two patent applications within the Fractalkine project are now entering international phase. The patent

applications include a new production method and a new series of blockers of the Fractalkine system, including KAND145.

- Kancera announced that the European Society of Cardiology selected Kancera's research for its "outstanding quality", which will result in an oral presentation as part of the session for "New treatments for acute heart conditions" at the major ESC 2019 meeting in September.
- On June 20, Kancera announced positive interim results from the ongoing Phase Ib study of KAND567. The first exploratory part of the study shows that KAND567 has a good safety profile in the short-term intravenous infusion and that the calculated effective plasma concentration can be achieved according to plan. To achieve the required tolerability for long-term infusion, the ratio of infusion rate to concentration of KAND567 in the infusion solution will be adjusted. This adjustment implies that estimated reporting of the results will be in November this year.
- Kancera has announced that the third and final installment payment for the Fractalkine project and KAND567 has been made in accordance with the acquisition agreement. The payment that has been activated in connection with the ongoing Phase Ib study is made through a new issue of two million of the company's shares to Acturum AB.
- Kancera has announced that the company's clinical Phase Ib study according to plan will start again today. The aim is to report the study in November 2019..

PFKFB3- inhibitors

Block the energy supply to solid tumors, and reduce the ability of cancer cells to repair their DNA. Together, these effects can increase the tumor's sensitivity to other cancer therapies.

- The discovery of how Kancera's PFKFB3 inhibitor works against cancer has been published in Nature Communications.

HDAC6- inhibitors

Aim to kill blood cancer cells by preventing cancer cells from spreading and supporting the patient's immune system in recognizing and eliminating cancer cells.

- Kancera announced that the company has entered into a Research and Option agreement with Grünenthal, a leading pharmaceutical company within pain research and treatment. Under this agreement, Grünenthal is responsible for all preclinical research to develop drug candidates from Kancera's series of HDAC inhibitors and is entitled to acquire these substances. Through the agreement, Grünenthal will be able to accelerate its ongoing efforts in this area, with the aim of developing new and potentially disease-modifying treatments for neuropathic pain.

Kanceras project portfolio

Kancera's project portfolio comprises five drug projects.
One project is in clinical phase and four are in preclinical phase.

The drug candidate KAND567 is now being prepared for a Phase II clinical trial to test an entirely new treatment strategy to protect heart function after infarction. Although myocardial infarction is still one of the most common causes of life-threatening chronic disease, there has been a real lack of innovation in the area, until now.

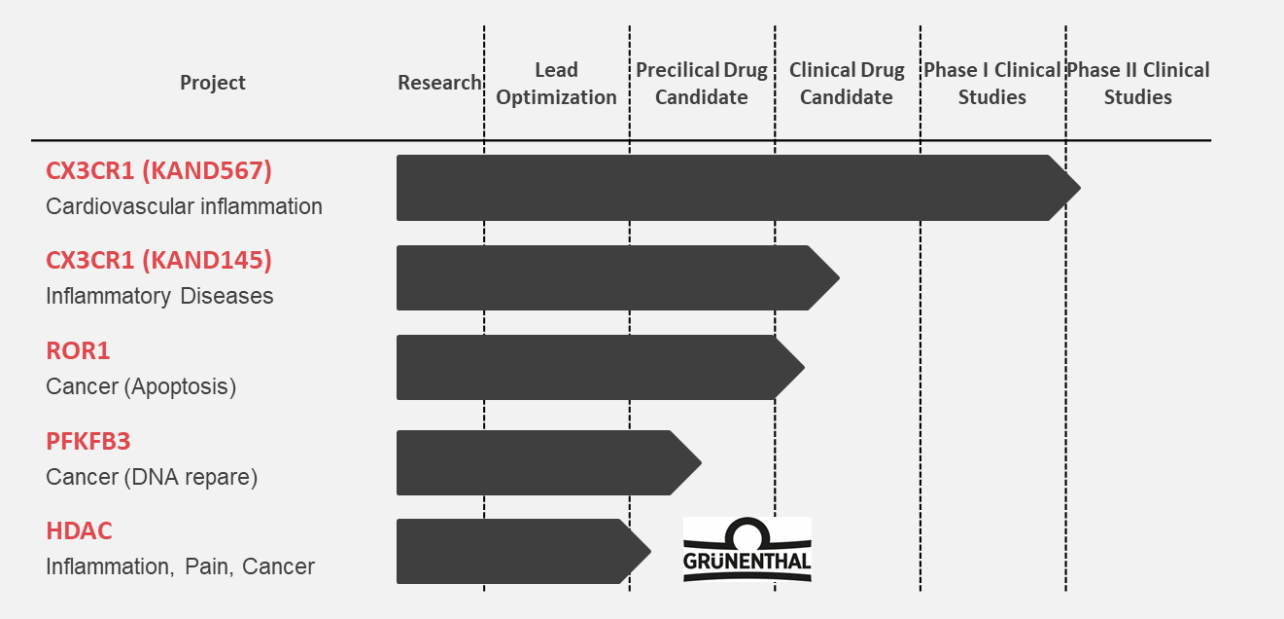
New knowledge suggests that an overreaction by the immune system is behind several types of cardiovascular diseases and that KAND567 can block this disease process. Since scientific studies have also shown that similar immunologic over-reactions lie behind several forms of inflammatory diseases and certain cancers, there is significant potential for expansion of Kancera's Fractalkine-inhibiting drug candidates.

The year 2018 began with the reporting of Kancera's first clinical study with KAND567 in healthy subjects. In addition, an agreement was entered into between Kancera and the pharmaceutical company Grünenthal on the further development of Kancera's HDAC project in the field of neuritis.

During the first half of 2019, the second phase I study (Phase Ib) was initiated with KAND567 to determine intravenous dosing strategy for the planned Phase IIa study in myocardial infarction patients. The first exploratory part of the Phase Ib study shows that KAND567 has a good safety profile in the short-term intravenous infusion and that the calculated effective plasma concentration can be achieved as planned.

The goals for the development of Kancera's product portfolio over the next 12-24 months are to:

- conduct a clinical Phase IIa study with KAND567 against inflammatory damage in myocardial infarction.
- advance Kancera's second drug candidate KAND145 through clinical preparatory steps.
- evaluate opportunities to expand the indication area for KAND567 and KAND145 in inflammatory niche diseases and cancer.



Kancera has five drug projects in the portfolio with the main resources being invested in the two Fractalkine projects. The further development of the HDAC project is externally financed through agreement with the pharmaceutical company Grünenthal. The PFKFB3 project is funded through an EU Horizon2020 project and ROR1 mainly through academic collaborations.

Project in clinical phase

- Inhibitors of the Fractalkine receptor CX3CR1. Kancera is developing the small molecule drug candidates KAND567 and KAND145, both of which block the Fractalkine receptor and thus specific parts of the immune system. The first indication for Kancera's Fractalkine inhibitor is treatment for heart injury after myocardial infarction. Expansion possibilities for the inhibitors of the Fractalkine system are also being evaluated in inflammatory diseases and cancer.

Projects in pre-clinical phase

- Kancera's HDAC project is being evaluated and developed in partnership with Grünenthal for nerve inflammation and pain.
- ROR inhibitors for the treatment of cancer. Inhibitors of ROR re-program cancer cells to destroy themselves. In the laboratory, ROR inhibitors have been shown to work on cells from both solid tumors and blood cancer (leukemia and lymphoma).
- PFKFB3 inhibitor for the treatment of cancer. Inhibitors of PFKFB3 throttle the energy supply to solid tumors, and reduce the ability of cancer cells to repair their DNA, which together can increase the tumor's sensitivity to other cancer therapies.

Fractalkine project

Steers the immune system against inflammation and cancer.

Property	Summary of Target Product Profile (TPP)
Primary indication	Acute inflammatory damage to the heart during and after treatment for myocardial infarction
Secondary indication	Inflammatory heart muscle disease
Treatment regime	Intravenous treatment in acute phase Oral treatment for chronic state
Biomarker	*Myocardial infarction:* ECG *Inflammatory heart muscle disease:* *Inflammation biomarkers*
Product differentiation	Increased protection against heart damage compared to current treatment of heart attack

In connection with myocardial infarction, inflammatory processes cause tissue death and Kancera has shown that the so-called Fractalkine inhibitor, KAND567 has positive effects on this in disease models. The results of a recent Phase I clinical trial confirm that KAND567 also blocks the human Fractalkine system at doses well tolerated in healthy subjects. The company thus sees a strong foundation for further development of KAND567 in clinical phase II studies against inflammatory diseases, including heart attacks.

Myocardial infarction is still one of the most common causes of life-threatening chronic disease. At the same time, there is a great lack of innovation and new drugs in this area. New knowledge now indicates that acute myocardial infarction starts an overreaction in the immune system that leads to inflammation of the heart muscle with the accumulation of specific immune cells (lymphocytes). It has also been shown that this correlates with impaired possibilities for the body to heal the injury and increased risk of acute complications, chronic heart disease and death. A significant proportion of the accumulated immune cells in the injured area carry the Fractalkine receptor. KAND567, which has the capacity to block the Fractalkine receptor and the accumulation of these immune cells, is now being prepared for a clinical Phase II study which will test a completely new treatment strategy to protect the function of the heart.

Scientific studies have shown that similar immunological over-reactions to the Fractalkine system underlie several forms of inflammatory diseases. Furthermore, research studies in disease models support the fact that the Fractalkine system is involved in certain tumor diseases, amongst others, breast, ovarian, prostate and pancreatic cancer. This means that there are significant expansion opportunities for Kancera's Fractalkine platform. To take advantage of these opportunities, Kancera has continued the work of identifying additional substances with the aim of being able to develop several pharmaceutical products in various disease areas. This research has resulted in another drug candidate, KAND145, which is covered by one of Kancera's three new patent applications in 2018.

Kancera's main resources are now being invested in the development of drug candidates that can stop inflammation in a new and effective way and amongst which KAND567 is the most advanced and is entering a first study in patients with acute myocardial infarction.

ROR-project

Re-programs cancer cells to self-destruct.

Property	Summary of Target Product Profile (TPP)
Primary indication	B-cell lymphoma
Secondary indication	Lung-, pancreas-, breast- and ovarian cancer
Administration	Oral with other drugs
Product differentiation	*Effect:* Induction of tumor-selective cell death in blood, bone marrow and lymph of blood cancer, as well as in various solid tumors, provides the conditions for complete remission *Safety:* ROR1 is mainly found in cancer cells, which is why a ROR1 targeted treatment should cause a lower level of side effects than broad-acting drugs. *New mechanism of action:* Add to the effect of existing drugs

Blocking ROR1 induces cancer to self-destruct

When healthy cells have suffered damage to their genetic material that is not repaired, a cellular suicide is normally initiated in order to eliminate the threat posed by these injuries to surrounding healthy cells. Cancer cells, on the other hand, have developed resistance to signals that should lead to cellular suicide when serious injuries occur in the genome. In fact, the faults in the genomes of cancer cells are a prerequisite for the aggressive and life-threatening properties of the cancer.

Cancer has shown that if the growth factor receptor ROR1 is present in the tumor then anti-ROR drugs can be developed which reprogram the cancer cells to destroy themselves by cellular suicide. This fact forms the basis for the development of Kancera's drug candidate.

The first indication is B cell lymphoma

Kancera's first drug candidate within the ROR project is aimed at lymphatic leukemia.

After decades of stagnation in the development of drugs against this disease, several new drugs have been approved such as Imbruvica from Pharmacyclics / J & J / Abbvie and Zydelig from Gilead. The introduction of these drugs has led to great progress in the treatment of patients with advanced and treatment-resistant disease. For these patients, the disease can now be stabilized for another two to three years compared to traditional treatment. However, clinical experience shows that significant medical needs remain despite these advances.

There are still no drugs for chronic lymphocytic leukemia (CLL) that in the long run bring the disease under control (complete remission) without posing a threat to the patients' normally functioning organs. Kancera inhibitors of the cancer-selective growth factor receptor ROR1 have this potential since the company and independent researchers have shown that a blockade of ROR1 leads cancer cells to suicide, including even the most treatment-resistant cancer cells. Furthermore, the fact that ROR1 is mainly targeted at cancer cells but not to healthy surrounding cells means that a drug that works with good selectivity against ROR1 has the potential to give the patient the opportunity to live a normal life with limited side effects.

The goal is to break the cancer's resistance

About 15% of patients with CLL develop a very difficult to treat form of lymphoma called Richter's syndrome. Neither the standard treatments nor the newest drugs against CLL have the desired effect on Richter's syndrome, which is why the medical need for new drugs is great against this disease. Studies have shown that tumor cells from Richter's syndrome carry ROR1 in a majority of patients studied. Kancera has also shown that the

company's ROR1 inhibitor kills cancer cells that represent Richter’s syndrome and express ROR1.

A first generation of Kancera ROR inhibitors have been shown to work quickly and effectively against CLL cells from patients, even against treatment resistant cells from patients with treatment resistant CLL. This has been demonstrated in the laboratory against isolated cancer cells and in animal studies where human disease has been recreated in mice. A first drug candidate, KAN0439834, was nominated against CLL but the substance disappears relatively quickly from the circulation and does not provide sufficient effect against solid cancer diseases.

Second generation ROR-inhibitors

Kancera's development of a second-generation ROR inhibitor aims to prolong the residence time of the substances in the blood, which is expected to enable effect on several cancers. Research groups have, independently of Kancera, demonstrated that ROR1 is involved in blood cancer forms such as acute myeloid leukemia (AML) and multiple myeloma (MM) as well as some difficult-to-treat solid cancers such as pancreatic cancer (pancreatic cancer) ovarian cancer (ovarian cancer) and triple-negative breast cancer (a particularly difficult-to-treat form of breast cancer which lacks three common targets for cancer drugs, thereby called triple negative).

A first goal in this work has been achieved in as much as a second generation of ROR inhibitors have been developed that show an improved effect on cancer cells (lower dose is required than before to achieve the same killing effect). In addition, these ROR inhibitors are maintained in the blood circulation for such a long time that the drug substance has the potential to achieve efficacy against lymphoma and solid tumors. Second generation ROR inhibitors have shown efficacy against solid tumors in a disease model based on human triple-negative breast cancer that are implanted and studied in zebrafish, and have also been shown to eliminate ROR1 bearing leukemia cells in a human CLL human model.

The assessment is that Kancera's development of small-molecule drugs against the cancer-specific growth factor ROR is world-leading. If ROR1 is blocked, leukemia cells, for example, are re-programmed to destroy themselves. Competing groups are developing antibodies and modified immune cells that target ROR1, but Kancera's ROR inhibitor has the ability to penetrate cancer cells and kill them despite the fact that ROR1 is not on the surface of the cancer cells. Neither antibodies nor modified immune cells can do this.

PFKFB3-project

Prevents cancer cell repair ability

Property	Summary of Target Product Profile (TPP)	
Primary indication	Solid tumors, such as ovarian cancer, breast cancer and lung cancer, treated with DNA-disrupting therapy	
Secondary indication	Inflammation	
Administration	Oral/intravenous	
Product differentiation	*Effect:*	Synergistic effect with PARP-inhibitors, radiation or chemotherapy
	Safety:	PFKFB3 is primarily found in hypoxic tissue and in cancer cells, so a drug selectively acting on PFKFB3 has the potential to give a low level of side effects.
	New mechanism of action:	*Adds to the effect of existing drugs*

The project aims to develop inhibitors of the enzyme PFKFB3 in order to suppress the energy metabolism of cancer cells and thereby make them sensitive to chemo- and radiotherapy. Kancera, together with Professor Thomas Helleday and his research group at Karolinska Institutet, have made a surprising discovery that shows how the company's inhibitor of PFKFB3 enters the cancer cell's nucleus and strengthens the effect of a recently given radiation dose. This discovery has been submitted for patent protection in the United States (the patent application is owned by Kancera).

The background to this invention is the unique metabolism of the cancer. For example, cancer cells use up to 200 times as much sugar as a healthy cell for their energy supply. In recent years, both academic researchers and pharmaceutical companies have noticed that the altered metabolism contributes to cancer cells being able to survive with access to very little oxygen, which creates an environment in which aggressive cancer cells develop. By strangling the particular metabolism that cancer cells need in order to resist both chemotherapy and radiation, the tumor becomes weakened. However, healthy cells are not affected by the treatment in the same way since these have a different metabolism from the cancer cells. Thus, a new strategy for combating cancer has emerged.

PFKFB3 is an enzyme that acts as an accelerator in the conversion of sugar to energy. Kancera has developed a substance that inhibits PFKFB3 and has shown that this slows down the growth of pancreatic cancer in an animal study. Although this cancer is very difficult to treat, the slowing effect of the PFKFB3 inhibitor on the tumor was not considered strong enough to justify proceeding with the selected substance as a monotherapy. Instead, Kancera chose to start a collaboration with Professor Thomas Helleday's group at Karolinska Institutet to better understand how PFKFB3 inhibitors are best used to achieve the greatest possible effect against cancer.

The collaboration with Professor Helleday and Karolinska Institutet has led to the discovery that PFKFB3 not only regulates the conversion of sugar into energy but also accumulates in the cancer cell's nucleus to contribute to its ability to repair genetic material (DNA). As expected from this discovery, Kancera's patent-pending substance KAN0438757 also increases the damage caused by radiation in the cancer cells. These results support Kancera's continued work to further develop a drug candidate against PFKFB3 and to test this in combination with various treatments to combat resistant cancer.

Radiation therapy is an effective method for treating cancer but is challenged by adverse side effects and by cancer cells exhibiting resistance to

radiation. In order to improve the therapeutic effect and reduce side effects, it is desirable to make the cancer cells more sensitive to radiation. One of the most attractive possibilities is to make it difficult for the cancer cells to repair damage to genetic material caused by the radiation and preferably without stopping this repair in healthy cells. Healthy cells are exposed to external factors, e.g. sunlight, that cause single-strand breakdown of DNA. Gamma radiation used in cancer therapy, however, is more powerful and, in addition to single-strand breaks, also causes double-strand breaks in DNA. A drug that prevents double-strand break repair but allows single-strand break repair would do more damage to the cancer cell exposed to gamma radiation (and chemotherapy) than to the healthy cell exposed to the sun's rays. The discovery that Kancera has now made together with Prof. Thomas Helleday's research group indicates that Kancera's PFKFB3 inhibitor meets these desired criteria.

Of the various possibilities for attacking the cancer's metabolism, inhibition of PFKFB3 has attracted the interest of several pharmaceutical companies. However, developing drugs against PFKFB3 is technically challenging, which has probably contributed to the fact that no drug against this enzyme has yet been tested in clinical efficacy studies (clinical phase 2). This also means that the area is not yet dominated by any company. Examples of companies that work with PFKFB3 are AstraZeneca and the American biotech company Advanced Cancer Therapeutics. Compared to AstraZeneca substances, Kancera's PFKFB3 inhibitors can have the advantage of achieving a higher degree of selectivity against cancer than the substances published by AstraZeneca due to their distinctive mechanism of action. For PFKFB3 inhibitors from Advanced Cancer Therapeutics, Kancera has not been able to demonstrate the desired effect on DNA repair that Kancera's PFKFB3 inhibitor exhibits.

HDAC6-project

Works against cancer by controlling cancer cells' ability to spread

Property	Summary of Target Product Profile (TPP)
Primary indication	Glioblastoma
Secondary indication	Pain
Administration	Oral
Product differentiation	*Effect:* a) New mechanism of action which, in combination with other drugs, can have an improved effect on the cancer cell's ability to divide b) Under investigation: Small molecule immunostimulatory effect against cancer *Safety:* Due to a high degree of selectivity for HDAC6, a lower degree of gastrointestinal effects is expected compared to less selective HDAC inhibitors currently in clinical development. *New mechanism of action:* *Combination of effect on HDAC6 and Kanceras "Target 2"*

HDAC6 is an enzyme that controls how the cell's internal fibers, a type of cell skeleton, work and thereby how cells can move in the body. An active HDAC6 affects the tumor's ability to invade surrounding healthy tissue and form metastases. HDAC6 has also been shown to be a valuable marker that gives an indication of how difficult the cancer is to treat. Together, these observations indicate that HDAC6 contributes to changes in cells leading to the formation of tumors and invasion of tumor cells into healthy tissue, making HDAC6 an attractive target for the development of novel effective anti-cancer drugs.

New research also shows that HDAC6 inhibitors can help the patient's immune system to recognize and attack cancer cells. This is done by HDAC6 inhibitors releasing a molecular brake, called PD-L1, which the cancer puts on immune cells. Thus, HDAC6 inhibitors can be an effective small molecule substitute for the new PD-L1 antibodies presently in clinical use with the benefits that the drug can be taken in tablet form rather than with syringe and can be a cheaper drug, making it available to multiple patients. It remains for Kancera to show how efficiently the company's substances can counteract the cancer's brake on the patient's immune system.

There are currently five HDAC inhibitors on the market for the treatment of acute myeloid leukemia (AML), multiple myeloma (MM) and various forms of T cell lymphoma. These inhibitors broadly affect several members of the HDAC family's enzymes, which also leads to severe side effects, including in the gastrointestinal tract. The risk of negative effects on cardiac function is also high. Cancer's discovery of selective HDAC6 inhibitors can provide a way for the healthcare system to benefit from the HDAC inhibitors' cancer-inhibiting effect without causing severe side effects for the patient.

Kancera's HDAC6 inhibitor is covered by two patent applications filed in 2015 and 2016. These substances are more potent and selective in vitro against multiple myeloma cancer cells than the most advanced competing HDAC6 inhibitor ACY-1215.

Kancera has also found that some of the company's HDAC6 inhibitors can be controlled to work through another mechanism that has not been described publicly for reasons of competition. Kancera's results show that a combined effect against HDAC6 and Target 2 more effectively prevents the cancer cell's ability to multiply.

Kancera has developed a selective HDAC6 inhibitor that combines good killing effect on cancer

cells in the laboratory with significantly better uptake and stability in the blood circulation of mice on oral administration compared to the most advanced competing HDAC6 inhibitor ACY-1215. Kancera's HDAC6 inhibitor is now being evaluated in disease models.

New animal studies show that KAN0440262 effectively passes through the blood-brain barrier and remains in the brain at significantly higher concentrations and for longer than in the blood. This combination of properties allows Kancera to exploit the substance against several diseases of the brain, including brain tumor (glioblastoma) and neuropathic pain. Kancera has also been able to show that treatment that has given relevant exposures in the brain of KAN0440262 does not lead to notable effects on the animal's behavior or general health. The previously positive safety profile of KAN0440262 is further substantiated by studies conducted without remarks on 44 safety markers in vitro. However, prior to clinical studies, extended toxicological studies are required.

Patent portfolio and immaterial rights

Patent work is an integral part of the business and is based on extensive experience of establishing and implementing patent strategies.

The basis for commercial opportunities for new drugs is a broad patent protection. Patent work is an important and integral part of Kancera's business, especially in the early preclinical phases. Kancera's management has extensive experience of establishing patent strategies and building competitive patent portfolios even in highly competitive areas.

For Kancera's projects, patent strategies and patent portfolios are being developed together with internationally established patent agencies. Time plans for the first patent applications are determined on a case-by-case basis depending on competitor activity. When Kancera sells drug candidates, a negotiation regarding whether the company's patent or patent applications are to be licensed or sold, directly or through option.

Kancera currently has 12 patent families for small molecule substances: four for Fractalkine blockers, two for ROR inhibitors, three for PFKFB3 inhibitors and three for HDAC6 inhibitors. In addition to these, Kancera has two patent families covering anti-bodies against ROR1. However, these are not currently being developed commercially.

Kancera's patent portfolio is presented in the table on the following two pages.

Project/ Patent family	Description	Status	Application/Patent-number	Date of application	Patent bureau
Fractalkine	Substance patent 1	Granted patent in: China Germany France UK Italy Japan Sweden USA	US 7947693	2006-04-03	Swea IP Law
Fractalkine	Substance patent 2	Granted patent in: China Germany France UK Italy Japan Sweden USA	US 7960395	2007-09-27	Swea IP Law
Fractalkine	Process patent	International application	GB1807898.0	2018-05-15	Potter Clarkson
Fractalkine	Substance patent 3	International application	P66314GB	2018-07-06	Potter Clarkson
ROR1	Substance patent 1	Patent application in: Australia Brazil Europe Hongkong India Israel Japan Canada China Mexico New Zealand South Africa South Korea USA	PCT/EP2016/052091	2016-02-01	Brann
ROR1	Substance patent 2	Patent application in: Europe USA HongKong India Japan China South Korea	PCT/EP2017/067262	2017-07-10	Brann
ROR1	Antibodies from mouse	Granted patent in: Europe China USA Patent application in: Indien	PCT/EP2010/007524	2010-12-10	Novitas Patent

Project/ Patent family	Description	Status	Application/Patent-number	Ansöknings-datum	Patent bureau
ROR1	Human antibodies	Granted patent in: Europe China USA Patent application in: India	PCT/EP2011/072490	2011-12-12	Novitas Patent
PFKFB3	Patent family "Sulphonamide compounds"	Granted patent in: Europe USA Patent application in: Hongkong India	PCT/EP2011/066250	2011-09-19	Brann
PFKFB3	Patent family"Bisarylsulphonamides"	Granted patent in: Australia Europe Hongkong Japan China Mexico New Zealand South Africa USA Patent application in: Brazil India Israel South Korea	PCT/EP2012/076836	2012-12-21	Brann
PFKFB3	Patent family "Biarylsulphonamides in combination with radiation therapy".	Patent application in: USA (Continuation-in - Part)	PCT/EP2012/076836	2012-12-21	Brann
HDAD6	Substance patent 1	Patent application in: Australia Europe Canada New Zealand USA	PCT/EP2015/0603293	2015-05-11	Brann
HDAC6	Substance patent 2	Patent application in: Australia Europe India Japan Canada China New Zealand South Africa USA Russia South Korea Hongkong	PCT/EP2016/077914	2016-11-16	Brann
HDAC6	Substance patent 3	Patent application in: Europe	18205819.8.	2018-11-13	Brann

Market prospects for Kancera's products

Kancera's project addresses medical needs in inflammation and cancer in a growing market.
Accelerated testing of new drugs for life-threatening illnesses contributes to the increased number of approved drugs.

2017 was a strong year for the industry with a 19% increase in the Biotech index on Nasdaq. This trend continued during the first three quarters of 2018, after which the stock market fell generally and significantly during the fourth quarter. However, during the beginning of 2019, the stock market recovered and the Biotech index internationally went up 18% during the first two months of 2019. The number of acquisitions and the total size of these has been comparable during the period 2016-18. The IPO market as well as venture investments in early R&D companies continue to be strong.

In the PWC report Global Pharma & Life Sciences Deals Insights Year-end 2018, Glenn Hunzinger, US PLS Deals Leader, PwC comments: "we expect 2019 to be a robust year for M&A in the biotech sector, as underlying market forces have never been better". The market for IPOs and investments of risk capital in early R&D remains strong.

Increasing number of approved drugs

In 2018, the European Medicines Agency (EMA) approved 84 new drugs, of which 42 of a completely new class. The US Medicines Agency (FDA), approved 60 new drugs in 2018, surpassing the record of 46 pharmaceuticals in 2017. Small molecule drugs still dominate with 38 approved drugs compared to 17 protein drugs. A significant proportion of new approved drugs have benefited from the European and US drug agencies' (EMA and FDA) offer of accelerated testing and strengthened counseling aimed at projects that can improve the care of life-threatening diseases.

Kancera has contributed to the development of one of the small-molecule drugs that was approved in 2017: Enasidenib against acute myeloid leukemia (AML), which also received an accelerated trial by the FDA. Kancera's achievement in this development was, as a paid consulting firm, to develop the chemistry that underlies the drug marketed by Agios Inc. and Celgene Inc. In 2018, Kancera entered into an option agreement with Grünenthal to develop another small-molecule drug, this time against nerve inflammation and pain. The project is still in early preclinical phase.

Kancera's primary market is based on sales of business-to-business pharmaceutical candidates for further clinical development and marketing by internationally established pharmaceutical companies. The prioritized type of transaction is based on an option model in which Kancera signs agreements in preclinical or early clinical phase, with a selected international partner who has the resources and capacity for effective clinical development and marketing on an international basis. The option model gives Kancera a cash flow under more costly parts of the project's development, while the collaboration gives the partner the opportunity to influence the project's focus during the critical phase between late preclinical development and clinical development to form the basis for registration. This also increases opportunities for effective clinical development. A quick and successful transition from Kancera's preclinical and early clinical development to the partner's further registration-aimed clinical development also increases the likelihood that the timetable for milestone payments to Kancera will be kept.

Synergy between biotech and Pharma

There are several reasons why development projects in the late preclinical or early clinic attract increased interest from the large pharmaceutical companies. The development departments of the pharmaceutical companies themselves want to be able to influence the choice and design of an active substance, product formulation and indication. It

could be devastating if a substance that reaches phase III proves to be suboptimal or insufficiently adapted to its task. Time and money are lost if a clinical study needs to be taken back to the beginning. Historically, there are many examples of projects that need to be corrected and where the clinical trial needs to be re-started. At the same time, pharmaceutical companies sometimes choose to run several parallel exploratory clinical trials to ensure that several different patient groups and diseases are covered, as well as schedules for treatment, in order to optimally position the product prior to expensive clinical phase III studies.

The underlying demand for Kancera's drug candidates is driven by a medical need to make the fight against inflammatory diseases, including cardiovascular inflammation and cancer, more effective.

Kancera's clinical development against inflammatory diseases

Kancera's clinical drug candidate and inhibitors of the Fractalkine system (KAND567) have shown a potent effect against both acute and chronic inflammatory conditions. Inhibitors of the Fractalkine system have also been proven by others to be an effective means of treating autoimmune inflammatory diseases. All in all, this means that Kancera is faced with the possibility of developing this type of drug against a variety of diseases, acute and chronic, major diseases and niche diseases.

For such a long-term expansion, several drug candidates are needed that can meet different technical and commercial conditions, including the fact that products that are used in large volumes (e.g. against cardiovascular inflammation) are priced differently than products against niche indications that are sold in smaller volumes. It is against this background that we see a great advantage in now having two drug candidates in the Fractalkine project: KAND567 and KAND145. The first indication for KAND567 is cardiovascular inflammation associated with myocardial infarction. Decisions have not yet been taken regarding the first indication for KAND145.

Myocardial infarction is still the driving force behind heart failure and premature death, which is also the diseases with the greatest cost to society. For example, it is expected that the drug costs for heart failure treatment will increase by 15% annually to 2026 up to $ 16 billion.

Global data for heart failure can be found on the following web site:

https://www.globaldata.com/store/report/gdhc146pidr--pharmapoint-heart-failure-global-drug-forecast-and-market-analysis-to-2026/

Myocardial infarction affects approximately 7 million people a year worldwide. Approximately 25% of these suffer from an additional serious cardiovascular event or die within five years of the first infarction. The medical need is therefore very large. Despite this, few new drugs are being developed in the cardiovascular area. This large gap between needs and innovation is probably largely dependent on the lack of knowledge of the disease factors that are drive the complications. New knowledge (which has been generated by the CANTOS study: N Engl J Med 2017; 377: 1119-1131) shows that inflammation and the innate immune system is an underestimated disease-inducing factor during the chronic phase after myocardial infarction. During the acute phase after myocardial infarction, a more fundamental study in over 1300 STEMI patients (ST elevation Myocardial Infarction, which is a major infarction in the left ventricle) has shown that the Fractalkine system is closely linked to complication and survival (Hazard ratio 2.4: J Clin Invest. 2015; 125 (8): 3063-3076). The fact that heart and vessels can be protected by inhibition of the Fractalkine system by treatment with KAND567 has also been demonstrated by Kancera in several disease models.

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