Kancera's drug development projects November 2017

Contents

Important events over the last 12 months – in short

Antagonists of the Fractalkine receptor

The Fractalkine receptor, CX3CR1, controls cancer cells and the immune system. The goal is to prevent tumor growth and spread, and counteract cancer pain.

- Kancera AB has reported that the Fractalkine blocker KAND567, in a preclinical model, can counteract nerve damage/inflammation in chemotherapy and eliminate pain in inflammation of the pancreas.
- Independently of Kancera, the drug company Eisai has shown that blocking the Fractalkine system with an antibody produces the desired effect against autoimmune diseases, such as Crohn's disease and rheumatoid arthritis, in severely treated patients. These clinical results also mean that the probability increases for Kancera's KAND567 to achieve clinical and commercial success in the treatment of hard-to-treat common diseases
- Kancera announced that the company completed the acquisition by Acturum Real Estate AB of the Fractalkine project against autoimmune diseases and cancer
- In April 2017, Kancera applied to the relevant authorities in the Netherlands for authorization for clinical trials and has entered into an agreement with the clinical contract company QPS for the implementation of clinical Phase I study with KAND567
- As a consequence of Kancera AB's having applied for a clinical trial approval, Kancera will issue 2 million shares as a payment to Acturum Life Science AB
- The Medical Ethics Committee (METC) at the University Medical Center in Groningen, The Netherlands, has given approval for the initiation of clinical Phase I study by KAND567. The clinical study aims at mapping the safety, tolerability and pharmacokinetics of KAND567 in healthy subjects
- The clinical phase I study of KAND567 began in May 2017.
- Kanceras Fractalkine project has been awarded a total of MSEK 1 by the Swedish Innovation Authority, VINNOVA, targeted at projects with "a very high level of innovation and commercialization potential".

Most recent events

- The second part, the multiple dose study, of the ongoing clinical phase I study of KAND567 commenced in September 2017.
- Kancera and Recipharm have concluded an agreement on the manufacture of a pharmaceutical product for clinical trials.

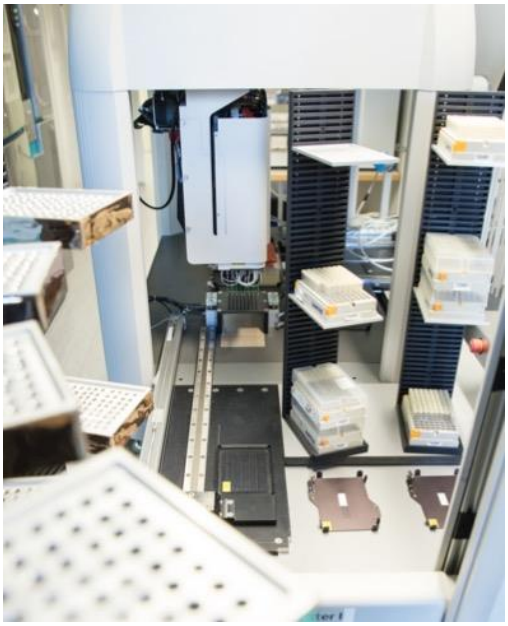
ROR-inhibitors

Reprogram the cancer cells to destroy themselves by apoptosis.

- Kancera has shown that the company's ROR1 inhibitors kill cancer cells from Richter's syndrome that express ROR1. Thus, the potential clinical use of ROR1 inhibitors may be widened
- Kancera has reported that the production method has been developed in such a way that it can be implemented easily and effectively to pave the way for further development of the compound towards clinical trials and commercial production
- One example of Kancera's new generation of ROR inhibitors, KAN0441571, has been shown to inhibit ROR over 24 hours, opening up opportunities for the treatment of several cancers

Most recent events

- Kancera has reported that the company's ROR1 inhibitor KAN0441571 effectively eliminates ROR1-bearing leukemic cells in a mouse model of human chronic lymphocytic leukemia.



PFKFB3-inhibitors

Strangles supply of glucose to solid tumors and reduces ability of cancer cells to repair their DNA, which together increase the tumor's sensitivity to other cancer therapies.

- Kancera announced that the company, within the framework of the EU research program SYNTRAIN, has hired two international industry graduates to strengthen the company's research on disruption of DNA repair in cancer cells - a new way of tackling the disease. The first three years of research are funded entirely by the EU through a grant of approximately 500 000 Euro
- New data on how PFKFB3 inhibitors appear to be more effective in cancer-transformed cells has been gathered together with Thomas Helleday's research team
- Studies in collaboration with Thomas Helleday's research team show that cancer cells resilient to the PARP inhibitor Veliparib become sensitive to treatment when Veliparib is combined with one of Kancera's PFKFB3 inhibitors
- Kancera has received prior notice from patent authorities in the EU and the US that patents on the PFKFB3 inhibitor KAN0438757 will be granted

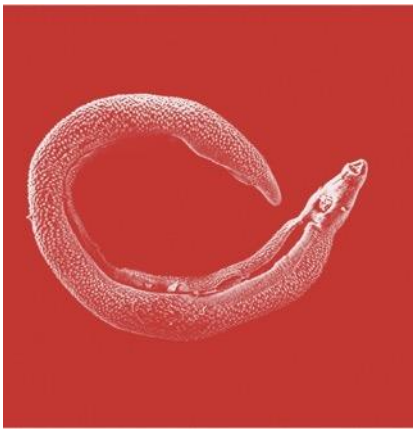
HDAC6 – inhibitors

Aim to kill leukemia cells by preventing the ability of cancer cells to spread, as well as supporting the patient's immune system to recognize and eliminate cancer cells.

- Kanceras HDAC6 inhibitors have reduced the amount of PD-L1 (Programmed death ligand 1) more effectively than the competing substance ACY-1215 in cancer cells. Researchers have shown that reducing the amount of PD-L1 has the potential to help the patient's own immune system to more easily attack and eliminate cancer cells
- A crystal structure has been developed for Target 2 in a complex with Kancera substances. With the help of information from the crystal structure, new substances have been developed which appear to be highly effective against Target 2
- Vinnova has part-financed the HDAC6 project for two years with a grant of SEK 2 million up to 30th June 2017. Kancera's final report has been submitted and approved

Anti-parasite project

Small molecule inhibitors of epigenetic processes in the parasite to develop new treatments, for example against malaria and schistosomiasis (snail fever).



- Within the framework of the project, Kancera has developed inhibitors of several epigenetic enzymes from parasites, including sirtuin 2. Kancera hereby reports that the company's inhibitor of sirtuin 2 (KAN0441411) has shown a significant effect in an animal model for Chagas Disease caused by infection by the parasite Trypanosoma cruzi. Kancera has thereby achieved its ambitious goals for the project
- The experimental part of the EU-funded anti-parasite project was completed at Kancera on January 31st, 2017
- The final report for the project was submitted to the EU on March 31st, 2017

Pharmaceutical development

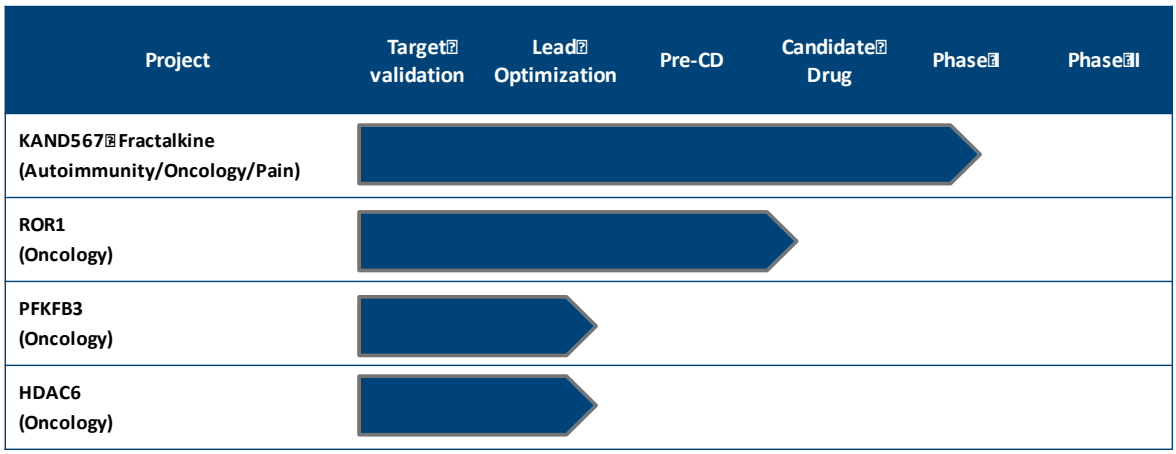
Kancera is engaged in the development of four drugs for cancer and autoimmune diseases that begin in a new treatment concept and end with a patented drug candidate offered for sale to major pharmaceutical and biotech companies in late pre-clinical or early clinical development.

The goal for the development of Kancera AB's product portfolio is to complete the Phase 1 study for KAND567 within the Fractalkine project before the end of Q4 2017. In parallel, we will also complete the evaluation of a broader use of KAND567 in order to reduce the risk inherent in continued product development and to demonstrate the full commercial potential for cancer, autoimmune diseases and pain. Operational goals also include selecting a substance in the ROR Project for regulatory toxicology studies (which are required to be performed before clinical studies), as well as delivering drug candidates from the HDAC6 and PFKFB3 projects.

The company has five drug development projects in the portfolio.

- **Antagonists of the Fractalkine Receptor CX3CR1 for the treatment of autoimmune diseases, pain and cancer.** Blocking the CX3CR1 receptor counteracts inflammation and metastasis by preventing cancer and immune cells from infiltrating healthy tissues.
- **ROR inhibitors for treatment of cancer.** Inhibitors of ROR reprogram the cancer cells so that they destroy themselves. In the laboratory, the ROR technology has been shown to work in both solid tumors and leukemia.
- **Inhibitors of PFKFB3 for treatment of cancer.** Inhibitors of PFKFB3 strangle the energy supply from glucose to solid tumors and decrease the ability of the cancer cells to repair their DNA. The combined effect may increase the tumor's sensitivity to other cancer therapies.
- **HDAC6 inhibitors for treatment of cancer.** HDAC6 inhibitors primarily aim at increasing the patient's immune system's capacity to recognize and eliminate cancer cells, as well as to prevent the ability of cancer cells to spread.
- **Small molecule inhibitors of epigenetic processes in parasites.** The goal of this EU-funded project has been to develop new treatments against human parasitic diseases such as Malaria and schistosomiasis (snail fever).

Figure 1. Kancera´s cancer project portfolio



See page 24 for more information on the commercial prospects for Kancera AB's products.

The Fractalkine project
– controls the immune system in cancer and alleviates severe pain

Product profile – Fractalkine-antagonist

Property	Summary of "Target Product Profile" (TPP)
Primary indication	Autoimmune disease
Secondary indication	Pancreatic cancer and metastasizing breast/prostate cancer. Inflammatory diseases and pain.
Treatment regime	Mono-therapy or in combination with other drugs, one to two times per day.
Administration	Peroral
Biomarker	Markers for cell migration and invasion in blood.
Product differentiation	*Effect:* a) Autoimmune disease: remission of anti-TNF resistant disease, b) Cancer: increased progression-free survival, c) Pain: Efficient pain relief when opiates are not efficient. *Safety:* Low level of mechanism related side effects is expected. Therapeutic window is under investigation. *New mechanism of action:* Expected to be the first small molecule antagonist of the Fractalkine receptor.

Kancera AB has entered into an agreement with Acturum Life Science AB for the purpose of evaluating and further developing the unique Fractalkine Blocker KAND567 (AZD8797, for example, KAN0440567). The agreement with Acturum Life Science gives Kancera AB the right to evaluate KAND567 in preclinical studies and then acquire the project. In view of the effects shown in disease models that are relevant for the treatment of cancer pain, Kancera AB announced in April 2016 the decision to acquire the Fractalkine project after successful transfer of know-how and data from AstraZeneca and Acturum. Payment for the Fractalkine project is made through a three-stage offset issue with a total of 6 million shares in Kancera AB. Part payments are made as the project progresses successfully until the first clinical study has been completed. This payment model means that the two companies share the risk of product development until the first study has been conducted in humans. Kancera AB intends to strengthen the protection of the Fractalkine blocker by applying for immune system is needed. However, animal studies show that the Fractalkine receptor is not essential for survival and that important immune functions are

Orphan drug designation with the aim of ensuring at least 10 years of market exclusivity in Europe and 7 years in the United States.

KAND567 is a perorally available small molecule that blocks CX3CR1, the Fractalkine receptor. Fractalkine is an immune-modulating factor, called a chemokine, which transmits signals via the CX3CR1 receptor, thereby controlling the function of immune cells and cancer cells. The amount of Fractalkine and its receptor CX3CR1 has been shown to be elevated in several inflammatory diseases, in cancer and in chronic pain conditions.

Kancera's drug candidate KAND567 is the most advanced drug candidate against CX3CR1 and has been shown to be effective against inflammation and pain in multiple preclinical disease models.

In the healthy individual, Fractalkine and its receptor, CX3CR1, control the migration of immune cells from the blood across the vessel wall to areas where the retained intact despite the

absence of the receptor. Effectively combatting local

inflammation while maintaining a well-functioning immune system is expected to be the basis for successful development of KAND567.

Autoimmune diseases and cancer can both be caused and aggravated by a dysfunctional immune system. The human immune system consists essentially of a specific immune system that is taught to attack foreign structures in the body, and a non-specific immune system that can quickly, and without learning, attack foreign structures. The Fractalkine system belongs to the latter.

The majority of today's powerful anti-inflammatory drugs block either major parts of the immune system (eg cortisone, anti-TNF, cyclosporin, anti-VLA4) or target the specific immune system (eg, JAK inhibitor, PD1 / L1 inhibitor). These drugs are successful, but in a significant proportion of patients they are not effective enough. In addition, a strong inhibition of the immune system involves an increased risk of serious infections and cancer.

New drugs, such as Fractalkine blockers, are now being sought to effectively and selectively target the non-specific immune system in humans to achieve better therapeutic effects and lower side effects risk. The immune system, through immune cells called macrophages, has been linked to several severe diseases including cancer and chronic inflammatory diseases of the gastrointestinal tract, joints, nerves and blood vessels.

Blocking of the Fractalkine system has been shown in clinical trials to produce the desired effect against autoimmune diseases such as Crohn's disease and rheumatoid arthritis in hard-to-treat patients. These positive studies have been conducted by the drug company Eisai with a monoclonal antibody (E6011) directed against the ligand Fractalkine, preventing it from binding to receptor CX3CR1. The results of the studies increase the likelihood for Kancera's drug candidate KAND567 to achieve clinical and commercial success as the first small molecule drug acting through the Fractalkine system.

The two drug candidates against the Fractalkine system, the E6011 and KAND567 antibody, behave as two sides of the same coin, i.e. one affects the Fractalkine system transmitter and the other affects the receiver of the signal. Both the antibody and KAND567 are expected to act in the bloodstream to prevent immune cells from penetrating tissues and creating or maintaining inflammation. The antibody is given via injections while KAND567 can be given as a tablet or capsule orally. KAND567 is expected to have an advantage over the antibody since, being a small molecule, it can more easily penetrate into tissues outside the blood vessels to exert its effect. Blockage of the Fractalkine system may prove to be the basis for a whole new class of drugs for the treatment of multiple common diseases.

Previous results in a multiple sclerosis disease model (PNAS, 2014, Vol. 111, pp. 5409-5414) also indicate that Kanceras KAND567 treatment produces the desired effect against autoimmune disease. This research study further supports the idea that desired effects against the disease can be achieved without significant side effects on the specific immune system. If this can be repeated in humans, it represents a competitive advantage over other drugs acting through the immune system.

Kancera's studies have also shown that KAND567 can reduce nerve damage associated with chemotherapy, which may enable more effective treatment for cancer by counteracting dose-limiting side effects. Today there is no effective treatment for this type of nerve damage.

In addition, there is reason to test whether Fractalkine-blocking drugs can directly attack cancer cells. The reason for this is that several types of cancer cells have acquired abilities possessed by the unspecific immune system. One of these abilities is to use the Fractalkine system to spread, like the immune system, into the body. If KAND567 can block this ability in cancer cells, the possibility exists for preventing or reducing metastasis.

Independent research groups have studied Fractalkine signaling and its biological and clinical role have reported data supporting that an antagonist of the Fractalkine-receptor may:

- facilitate the immune system’s attack on cancer
- prevent cancer cells from spreading to nerves and bone marrow
- reduce cancer pain caused by the tumor itself and side effects of chemotherapy

Although the drug candidate KAND567 was originally developed by AstraZeneca more than 10 years ago, the

compound is still the leading small molecule antagonist of the Fractalkine receptor CX3CR1. There are other projects that develop small molecule drug candidates against CX3CR1. Kerberos Biopharma (USA) develops small

molecule antagonists of the CX3CR1 and their candidate JMS-17-2 has shown interesting effects against breast cancer metastasis in animal models (AACR; Cancer Res 2015; 75 (15 Suppl): Abstract No.4116. doi: 10.1158/1538-7445. AM2015-4116). However, public information indicates that JMS 17-2 does not have the desired pharmaceutical properties, which is supported by the fact that the compound was administered to the animal model by injection in the abdomen. As mentioned above, the pharmaceutical company Eisai Co. Ltd. develops a monoclonal antibody that captures Fractalkine and makes Fractalkine unavailable to its receptor CX3CR1. Recently, Eisai Co. Ltd published that they have developed a small molecule CX3CR1 modulator called E6130 which has shown effect in two colitis mouse models (Wakita et al., Mol Pharmacol. 2017 Nov;92(5):502-509). Earlier this year, a single-ascending dose (SAD) phase 1 clinical study of E6130 was completed in healthy volunteers (https://www.clinicaltrials.gov/ct2/show/NCT02902978?term=E6130&rank=1).

Our assessment is that a small molecule antagonist of the Fractalkine receptor CX3CR1 has the potential to be a significantly better anti-cancer drug compared to an antibody that captures Fractalkine. This assessment is based on the fact that it is more difficult for antibodies to penetrate and affect a solid tumor compared to a small molecule and that CX3CR1 may affect cancer and immune cells independently of Fractalkine. A third aspect is that a small molecule is usually cheaper to produce than an antibody, which may lead to more extensive use of the small molecule than the antibody, if it otherwise meets the requirements for efficacy and safety.

KAND567 is a drug candidate that has undergone toxicological evaluation according to GLP and with a production method that has been proven in kg scale.

The next step in the drug development will be execution of a clinical phase I study in order to document the substance's drug properties and safety in humans.

Events during 2016

Kancera reported results from a first of a series of planned studies that will examine whether Kancera's Fractalkine receptor antagonist can become an anticancer drug. In this collaborative study with Professor Mia Phillipson (Department of Medical Cell Biology, Uppsala University), KAND567 was tested in two types of mice, one that carries a functional target for the substance (CX3CR1) and one that lacks CX3CR1. The results show that KAND567 selectively and effectively blocks the effect of Fractalkine signaling on *e.g.* macrophages, which are a type of immune cell. Independent research has shown that Fractalkine signaling in cancer contributes to the reprogramming of macrophages from being a threat to the tumor to aid the tumor. Thus, it may be desirable to block the effect of the Fractalkine signaling in cancer.

Kancera has previously announced that the company owns an option to acquire exclusive rights to the Fractalkine project (excluding the therapeutic area respiratory diseases) during an evaluation period of 24 months (from September 2015). The project has now generated positive results in multiple disease models of cancer and pain. The results show desired treatment effects that are important for Kancera´s further product development and commercialization of the project. The results will be published at a later date, in collaboration with the academic partners involved. In light of the positive results Kancera Board has decided to acquire the Fractalkine project. The acquisition will be carried out in connection with the completion of the ongoing transfer of results and know-how from Acturum and AstraZeneca to Kancera. Payment for the project to Acturum Life Science AB will be made in three steps by a total of 6,000,000 shares, of which the first payment is due at the submission of the application for authorization of a clinical trial after an approval by Kancera´s shareholders. In parallel, the company intends to validate a broader use of the drug candidate (KAND567) in order to demonstrate its full commercial potential.

Kancera AB reported that the Fractalkine antagonist KAND567 is able to eliminate pain resulting from inflammation of the pancreas. Kancera AB has previously announced that the company's goal for the Fractalkine antagonist KAND567 in cancer is to cause tumor regression and to relieve severe pain. Pain in pancreatic cancer is similar to the pain resulting from inflammation of the pancreas. For this reason, studies have been conducted to find out how effectively KAND567 can alleviate pain in animal models of inflamed pancreas. Kancera reported that the researchers and surgeons Gueralp Ceyhan and Jan D'Haese, Klinikum rechts der Isar (University Hospital at the Munich Technical University), have conducted animal studies showing that the severe pain caused by an inflamed pancreas is eliminated

by oral administration of KAND567. The study also shows that the pain signal activation through the spinal cord, which in cancer could be caused by the cancer itself or be due to side effects of chemotherapy (e.g. following treatment with Paclitaxel), is reduced by Kancera's Fractalkine antagonist. The results support Kancera's continued investment in KAND567 for clinical development. Further studies will be focused on

determination of the minimum effective dose for the treatment of cancer pain, and based on that, assess the safety of the treatment.

The company announced in May 2016 that at least one pharmaceutical project would be advanced into clinical trials in the next 18-24 months. According to plan, Kancera's Fractalkine project was taken into clinical Phase Ia study in May 2017.

Kancera has reported that the development of the Fractalkine project is making progress according to the project goals described in Kancera's prospectus from May 2016. The procurement of clinical contract companies for the execution of the clinical trial has been initiated in parallel with the procurement of the manufacture and stability testing of the Fractalkine-blocking product to be used in this study. At the same time, an application for a clinical trial is prepared to the responsible authority (the Medical Products Agency in Sweden or equivalent authority in another EU country) and for the corresponding ethical permission.

The planned clinical study aims to map out the safety, tolerability and pharmacokinetics of KAND567 in healthy subjects. KAND567 will be administered orally in increasing doses, and thereafter in multiple doses. The study will include a part that determines whether or not food intake influences the absorption of KAN0440567. Also included are biological markers that will show how KAND567 affects the mechanism in the body that is expected to provide the desired pharmaceutical effect.

Before the timetable for the clinical study is publicly communicated, Kancera intends to complete the development of at least one of the products to be used in the clinical trial and await approval from the responsible authority and the ethical committee.

Kancera reported in December 2016 that the company's Fractalkine blocker KAND567 effectively prevents pain caused by vincristine, which is used to treat cancers such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin's disease, neuroblastoma and small cell lung cancer.

A goal of treatment with KAND567 is to enable an effective cancer treatment without dose-limiting side effects due to acute pain and, in addition, to counteract persistent nerve pain and complications after successful treatment. This treatment concept is based on KAND567 achieving effective protection of nerves and reducing the amplification of pain signals that vincristine induces. Today there is no effective treatment for this type of nerve damage.

Kancera report here that treatment with KAND567 prevents immune cells (monocytes) from infiltrating the nerves and spinal cord, which also counteracts nerve damage and enhances pain sensitivity (see Figure 2).

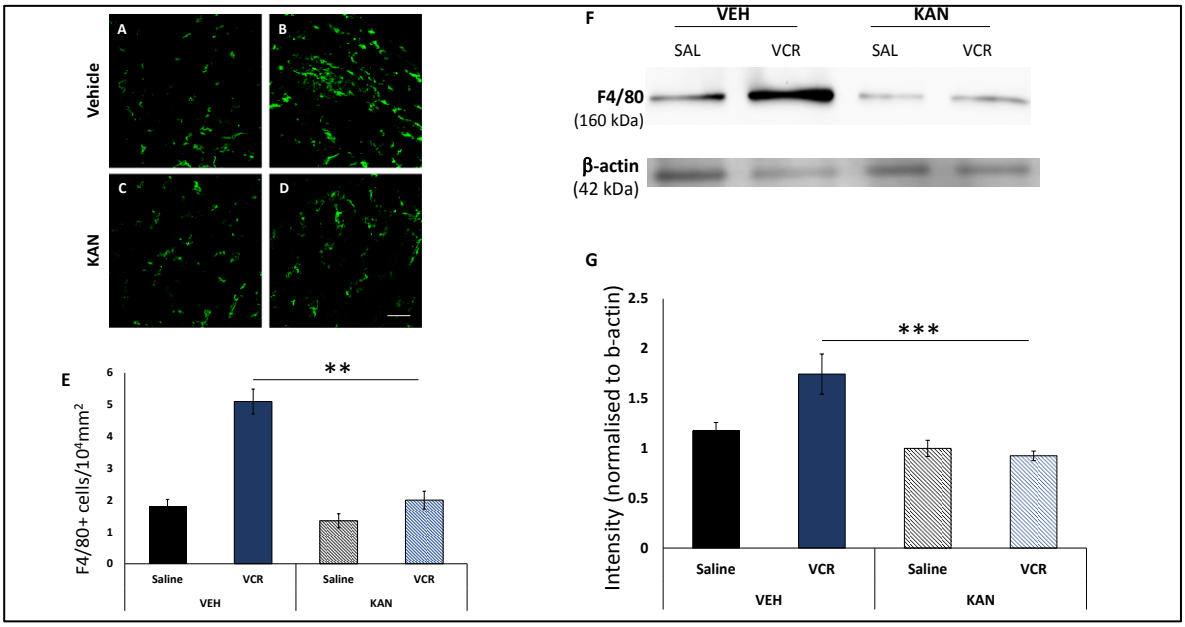
This has laid the foundation for KAND567 contributing to a more effective cancer treatment.

The immediate neuroprotective effect of KAND567 that can be seen after treatment with chemotherapy reflects the neuroprotective effect previously shown for this substance in the disease model for the autoimmune disease multiple sclerosis (PNAS, Vol 111, No.14, 5409-5414, 2014).

Overall, the findings suggest that KAND567 has the potential to significantly improve the treatment of cancer as well as autoimmune diseases.

With the establishment of a "Letter of Intent" with a company for the implementation of phase I clinical study, the Fractalkine project is proceeding according to plan.

Figure 2. KAND blocks the infiltration of inflammatory macrophages in spinal cord after treatment with the chemotherapy substance vincristine



The upper left graph: Microscope images showing that the number of green marked macrophages are fewer in the spinal cord in animals treated with Vincristine + KAND567 (figure D) compared with Vincristine + placebo (figure B) and are on the same level as before treatment started (figure A and C)	Top right graph: The stained areas show the protein F4/80, which marks the active macrophages. Treatment with VEH# cannot curb the increase in macrophages (greater staining of F4/80) while KAND567 (CAN) blocks this increase.
Lower left graph: Calculation of the number of macrophages (F4/80 + cells) shows that KAND567 (KAN) prevents the infiltration / increase in macrophages in the spinal cord after treatment with vincristine (VCR), unlike VEH#. The animals treated with KAND567 show the same pattern as animals that have never been treated with vincristine	Lower right graph: Same conclusion as for the graph in the lower left corner with the difference that the calculations in this graph have been compared to a control protein present at a constant level in the spinal cord. This allows more reliable calculation in this graph.

#experimental substance that is injected and totally blocks release of Fractalkine

** / *** Show that the effects of KAND567 are statistically significant

Events during 2017 up to the date of this report

Independently of Kancera, the drug company Eisai has shown that blocking the Fractalkine system with an antibody (E6011) produces the desired effect against autoimmune diseases such as Crohn's disease and rheumatoid arthritis in hard-to-treat patients. The treatment has in some cases resulted in a return to normal health. These effects have been shown in patients who do not respond to or tolerate today's best anti-autoimmune drug (anti-TNF treatment). These clinical results also mean that the probability increases for Kancera's KAND567 to achieve clinical and commercial success in the treatment of hard-to-treat common diseases. KAND567 can be the first drug to block the

Fractalkine system using a small molecule that, compared to an antibody, is easier to medicate with and easier reaches effected organs or tumors.

In April 2017, Kancera has applied to the relevant authorities in The Netherlands for permission for clinical trials and has entered into an agreement with the clinical contract company QPS for the implementation of a clinical phase I study with KAND567. The study will be conducted at the QPS facility in Groningen. QPS is an internationally established contract research company that performs clinical trials, develops drug preparations and conducts laboratory analyzes according to GLP and GCP (Good Laboratory and Clinical Practice Quality Standards).

Kancera has announced that the company has completed the acquisition of the Fractalkine project, for autoimmune diseases and cancer, from Acturum Real Estate AB.

As a result of Kancera AB applying for a clinical trial, Kancera will issue 2 million shares to Acturum as an installment for the Fractalkine project.

The Medical Ethics Committee (METC) at the University Medical Center in Groningen, The Netherlands, has given approval for the initiation of a clinical Phase I study with KAND567. The clinical study aims at mapping the safety, tolerability and pharmacokinetics of KAND567 in healthy subjects.

The clinical Phase 1 study with KAND567 was initiated in May 2017

Kanceras Fractalkine project has been awarded a total of SEK1million by the Swedish Innovation Authority VINNOVA, aimed at projects with "a very high level of innovation and commercialization potential". The purpose of the grant is to contribute to preparation for phase II studies.

The second part, the multiple-dose study, of the ongoing clinical Phase I study of KAND567, commenced in September 2017. The study is scheduled to be completed in the fourth quarter of 2017. In the clinical study, KAND567 is administered first orally and then in multiple doses to a total of 80 subjects. The purpose of the study is to evaluate KAND567 in healthy volunteers with regard to safety, tolerance and pharmacokinetics (drug absorption, exposure and excretion) as well as food interaction (how food affects the absorption of drugs in the body).

Kancera and Recipharm have concluded an agreement on the manufacture of a pharmaceutical product for clinical trials. In future clinical trials, Kancera intends to treat patients with the drug candidate KAND567 packed in capsules for oral intake. The collaboration includes the development of the formulation required for effective release of KAND567 from the capsules and production of the pharmaceutical product. The work is carried out at Recipharm's plant in Solna.

ROR-project
– reprograms cancer to self-destruct

Product profile – ROR1 inhibitor

Property	Summary of "Target Product Profile" (TPP)
Primary indication	Chronic lymphocytic leukemia, other hematological cancer forms.
Secondary indication	Lung, pancreatic, breast, and ovarian cancer
Treatment regime	Mono-therapy or in combination with other drugs, one to two times per day.
Administration	Peroral/IV/SC
Biomarker	Active ROR1, markers for anti-apoptotic signaling.
Product differentiation	*Effect:* Induction of cancer selective cytotoxicity in blood, bone marrow and lymph in blood cancer as well as in solid tumor provides opportunities for complete remission. *Safety:* ROR1 is mainly found in cancer cells why a ROR1 targeted treatment should give a lower level of side effects compared to broad-acting drugs. *New mechanism of action:* Adds effect to existing drugs.

When healthy cells suffer genetic damage that is not repaired, a cellular suicide is normally initiated in order to eliminate the threat that these injuries constitute for the surrounding healthy parts of the body. Cancer cells, in contrast, have developed a resistance to signals that should lead to cellular suicide when serious injuries occur in the genome. In fact, the genomic errors in the cancer cells are a prerequisite for the aggressive and life threatening characteristics of the cancer.

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

Kanceras first drug candidate in the ROR project is directed against lymphocytic 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 brought great progress especially in the treatment of patients with advanced and refractory disease. For these patients, the disease can now be stabilized for an additional two to three years, compared with the traditional treatment. Clinical experience shows that significant medical need persists despite these advances.

There is still a lack of a drug against chronic lymphatic leukemia, which causes a long-term control of the disease (give complete remission) without posing a threat to the patient's organs that are function normally. Kancera's inhibitors of the cancer-selective growth factor receptor ROR1 has the potential to become such a drug since the company and independent researchers have demonstrated that blocking of ROR1 leads cancer cells, even the most treatment-refractory, to destroy themselves. Also, ROR1 is selectively found in cancer cells and not in the surrounding healthy tissue and a drug that acts with a high selectivity against ROR1 has the potential to give the patient possibilities to live a normal life with limited side effects of the treatment.

Kancera's ROR inhibitors act quickly and efficiently to treatment resistant cells from patients with refractory chronic lymphocytic leukemia. This has been demonstrated in the laboratory against isolated cancer cells and in animal studies in which human

disease has been recreated in mice. Preliminary animal studies support that ROR inhibitors are well tolerated by the animals that have been studied in ten selected organs from treated animals. These studies on chronic lymphocytic leukemia were completed in early 2015. Since then Kancera's goal has been to develop a new generation of ROR inhibitors that through an extended residence time in the blood circulation is expected to provide efficacy against several cancers. Independent research groups have demonstrated that ROR1 is involved in blood cancer forms such as acute myeloid leukemia (AML) and multiple myeloma (MM) as well as certain refractory solid cancers like pancreatic cancer, ovarian cancer and triple negative breast cancer (an especially intractable form of breast cancer that lacks three common targets of cancer drugs, hence "triple negative").

A first goal in this work has been achieved since a second generation of ROR inhibitors have been developed that exhibit an improved effect against cancer cells (lower dose required to achieve the same killing effect). In addition, these ROR inhibitors are maintained in the blood circulation for a time long enough to have the potential to be efficient against lymphoma and solid tumors. Recent results show that this new generation of ROR inhibitors is effective in a first disease model for solid tumor in which triple negative breast cancer in humans has been implanted and treated in a zebra fish. In this study, the ROR inhibitors reduce both tumor size and metastasis (spread).

The assessment is that Kancera is a world leader in the development of synthetic drugs against the cancer-specific growth factor ROR. If ROR1 is blocked, then e.g. leukemia cells are reprogrammed to destroy themselves. There are competing groups that develop antibodies and modified immune cells directed against ROR1. In contrast to these, Kancera's ROR inhibitors have the ability to penetrate into cancer cells and kill these even if ROR1 is not present on the surface of the cancer cells. Neither antibodies nor modified immune cells are able to do this.

In February 2015 Kancera reported that a patent application (EP15153394.0) had been registered containing examples of approximately 100 small-molecule ROR inhibitors, including the drug candidate KAN0439834.

Events during 2016

Kancera reported that a patent application (EP15153394.0) was registered containing examples of approximately 100 small-molecule ROR inhibitors, including the drug candidate KAN0439834. This application has now entered the international stage and Kancera has strengthened the application by adding examples of a further approximately 300 substances, including substances that have shown to be more than 20 times more potent than KAN0439834 against cancer cells from CLL patients. Kancera also reported that the new series of compounds a) shows higher potency against leukemia cells and affects healthy blood cells to a lower degree, b) shows a higher metabolic stability in liver cells from both mouse and human, and c) remains in circulation during four times longer time compared to KAN0439834. Both KAN0439834 and compounds in the new series show good oral availability indicating that both can be developed to be administered in the form of pills.

The results of the evaluation of peptide sequences for vaccine development have confirmed that they do not generate an immune response that is effective enough against leukemia cells in comparison to that achieved with Kancera's small molecules. Against this background, Kancera has now chosen to terminate the vaccine product development and return it to academic research. Thus, Kancera will concentrate the ROR-project investments to small molecule inhibitors.

Kancera has previously reported that a new generation of ROR inhibitors (*e.g.* the compound KAN0440550) have been developed and these show a high level of efficacy and selectivity against cancer cells compared with healthy cells at the same time as they reach a concentration in the blood after oral administration that is expected to be sufficient to achieve efficacy against several cancers such as lymphoma and solid tumors. Kancera has now examined the effect of a representative of this new generation of ROR inhibitors against solid tumor in a disease model based on a human triple negative breast cancer implanted and studied in zebra fish. The results show that a three-day treatment with a ROR inhibitor results in both reduced tumor growth and reduced metastasis (spread). The study also shows that KAN0440550 is well tolerated at the effective concentration of the compound.

KAN0440550 and related ROR inhibitors are now being tested against solid cancers and lymphomas in preclinical disease models for the selection of a candidate drug complementary to KAN0439834, which is a compound that is more suited for effect against blood cancer such as chronic lymphatic leukemia (CLL).

Multiple myeloma (MM) is manifested in the bone marrow and is an essentially incurable chronic

disease today. Cancer cells from both CLL and MM patients carry ROR1 and are driven by a cancer stimulating signaling called "Wnt". Kancera now reports that the company's ROR inhibitors block both the pathways that "Wnt" conveys in cancer cells. In line with these results, Kancera together with Professor Håkan Mellstedt at the Karolinska Institute and University Hospital has also shown that resistant cells from the bone marrow of MM patients are effectively killed by Kancera's ROR inhibitor KAN0439834. Further studies are now focused on translating these findings to effects in animal models of MM, which will provide a basis for decisions on future clinical trials evaluating Kancera's ROR inhibitors.

15% of patients with chronic lymphocytic leukemia (CLL) develop an intractable type of lymphoma, called Richter's syndrome. Neither standard treatments nor the newest drugs for CLL have the desired effect on Richter's syndrome, so there is a great medical need for new drugs against this disease.

Studies together with Dr. Georgios Rassidakis at the Karolinska Institute and MD Anderson Cancer Center (USA) have shown that tumor cells from Richter's syndrome carry ROR1 in a majority of patients examined. Kancera has also shown that its ROR1 inhibitors are active against cancer cells of the same type as in Richter's syndrome. Thus, the potential clinical use of ROR1 inhibitors may be broadened.

The further development of KAN0439834 depends on a large-scale synthesis and purification (production) of the substance. Kancera has reported that the production method for KAN0439834 has been further developed and is now implemented in a straightforward and efficient way. The company believes that this paves the way for the further development of the substance towards clinical development and commercial production. Toxicology and safety studies under GLP still remain before a decision is made to initiate a clinical trial.

Events during 2017 up to the date of this report

In the ROR project a substance (KAN0441571) has been developed that can inhibit ROR during 24 hours by administering oral doses twice daily. This now provides the opportunity to test Kancera ROR inhibitors against both hematological and solid cancers. The latter have been shown to be resistant to Kancera's first drug candidate KAN0439834.

Kancera reported that the company's ROR1 inhibitor KAN0441571 effectively eliminates ROR1-bearing leukemic cells in a mouse model of human chronic lymphocytic leukemia. Human leukemia cells were allowed to infiltrate the lymphatic system in mice to mimic the situation in humans. After 13 days (and four treatment days), the number of ROR1-bearing human cancer cells in the lymphatic system (spleen sample) decreased by about 50% compared to control-treated animals. This effect is statistically significant ($P < 0.0005$) as well as the desired decrease in the spleen weight ($P < 0.0002$). The results provide further evidence for satisfactory toleration of KAN0441571 and its long-acting effect against chronic lymphocytic leukemia in this disease model that closely resembles human disease.

Kancera has been able to verify that the combined effect of KAN0441571, in addition to an inhibition of ROR1, also includes regulation of mechanisms that control cell division and inflammation signals. This effect pattern can lead Kancera to identify cancers that are particularly sensitive to the substance.

PFKFB3-project
- blocks glycolysis in solid tumors and weakens cancer cells

Product profile – PFKFB3-inhibitor

Property	Summary of "Target Product Profile" (TPP)
Primary indication	Solid tumors treated with DNA-damaging therapy such as ovarian and lung cancer
Secondary indication	Inflammation
Treatment regime	Mono-therapy or in combination with other drugs that damages or counteract DNA repair, one to two times per day.
Administration	Peroral/IV/SC
Biomarker	Markers for the cancer's ability to repair DNA, including expression of BRCA. PET-scanning with labelled glucose (2FDG) to identify glucose consuming tumors.
Product differentiation	*Effect:* Synergistic effect with PARP-inhibitors, radiation or chemotherapy. *Safety:* PFKFB3 is mainly found in hypoxic tissue and in cancer cells why a PFKFB3 selective drug can be expected to give a low level of side effects. *New mechanism of action:* Adds effect to existing drugs.

The project aims to develop PFKFB3 enzyme inhibitors to strangle the energy metabolism in cancer cells, thereby rendering the cancer cells more sensitive to chemotherapy and radiotherapy. Kancera has, together with Professor Thomas Helleday and his research group at Karolinska Institutet, made a surprising discovery that shows how Kancera's PFKFB3 inhibitor enters the cancer cell's nucleus and enhances the effect of a recently given radiation dose. This discovery has been claimed in a US patent application owned by Kancera.

The background to this invention is the unique metabolism of cancer. Cancer cells consume *e.g.* up to 200 times more sugar compared to healthy cells. In recent years, both academic researchers and pharmaceutical companies have paid attention to that the altered metabolism contributes to that cancer cells can survive with very little oxygen available, creating an environment where aggressive cancer cells develop. By strangulating the special metabolism that cancer cells need to resist both chemotherapy and radiation, the tumor becomes weakened. Healthy cells, on the other hand, are not affected by the treatment in the same way since they have a different metabolism than the cancer cells. Thus, a new strategy for fighting cancer has emerged.

Kancera's drug discovery project directed against cancer metabolism targets PFKFB3, which is an enzyme that acts to accelerator the metabolism of sugar to energy. Kancera has already developed a compound that inhibits PFKFB3 and shown that this slows the growth of pancreatic cancer in an animal study. Although this cancer is very difficult to treat, the assessment was that the effect of the PFKFB3 inhibitor was not strong enough to proceed with the selected compound as a mono-therapy. Instead Kancera started a collaboration with Professor Thomas Helleday's group at Karolinska Institutet to better understand how PFKFB3 inhibitors are to be used to achieve maximum effect against cancer.

The collaboration with Professor Helleday and Karolinska Institutet has now led to the discovery that PFKFB3 not only regulates the metabolism of sugar to energy but also migrates into the cancer cell's nucleus where PFKFB3 contributes to the cell's ability to repair genetic material (DNA). As can be expected from this discovery, Kancera's patent pending compound KAN0438757 increases the damage that radiation causes cancer cells. These results, together with the knowledge that patients suffering from radiation resistant acute leukemia (ALL) have an elevated level of PFKFB3, support that Kancera continues the work to develop a drug candidate against PFKFB3 and test it in combination with radiation treatment to combat resistant cancers.

Radiation therapy is one of the most effective methods to treat cancer. However, radiation therapy is challenged by the fact that cancer cells exhibit resistance and due to the adverse side effects of the radiation itself. To improve the therapeutic effect and reduce the side effects it is desirable to make cancer cells more sensitive to radiation. One of the most attractive ways to achieve this is to make it difficult for cancer cells to repair the genetic damage produced by radiation preferably without hindering healthy cells to repair their DNA. Healthy cells are exposed to external factors that cause single-strand DNA breaks, e.g. by sunlight. However, gamma radiation is stronger and causes, in addition to single-strand breaks, also double-strand breaks in the DNA. A drug that blocks repair of double-strand breaks but allows the repair of single-strand breaks could thus do more damage to cancer cells exposed to gamma radiation (and chemotherapy) compared to the healthy cell that has been exposed to sunlight. The discovery by Kancera together with Prof. Thomas Helleday's research group points to that Kancera's PFKFB3 inhibitor meets the requirements of a therapy that increases sensitivity to gamma radiation in a cancer-selective manner.

There are various possibilities to attack the metabolism of the cancer, and inhibition of PFKFB3 has attracted several pharmaceutical companies. However, the development of drugs against PFKFB3 is technically challenging, which is likely to have contributed to that no drug against this enzyme has been tested in clinical efficacy studies (Phase 2) yet. This also means that the area is not yet dominated by any company. Examples of companies working with PFKFB3 are AstraZeneca and the American biotech company Advanced Cancer Therapeutics. In comparison with AstraZeneca's compounds, Kancera's PFKFB3 inhibitors may have the advantage to be more cancer-selective due to another mechanism of action, as compared to the compounds that AstraZeneca have published. Regarding the PFKFB3 inhibitors from Advanced Cancers Therapeutics, Kancera has not been able to demonstrate that they have the desired effect on DNA repair that Kancera's PFKFB3 inhibitor shows.

Kancera has three patent applications (one granted in the US) in the PFKFB3 project. Two of these cover new PFKFB3 inhibitors (registered in 2010 and 2012) and one of these (registered in 2016) covers the combination therapy with PFKFB3 inhibitors and radiation.

Events during 2016

Kancera reported that a patent for small molecule inhibitors of PFKFB3 has been approved in the USA. Kancera´s PFKFB3 inhibitor (KAN0438757) has previously been shown to be effective against triple negative breast cancer. An additional zebrafish study verified the effect of Kancera's PFKFB3 inhibitor in monotherapy (treatment with substance without combining it with another therapy). Kancera's PFKFB3 inhibitor was well tolerated at the active concentration of the compound. Kancera has previously reported a discovery, made together with Professor Thomas Helleday's research team at the Karolinska Institute, that treatment with Kancera´s PFKFB3 inhibitor enhances the effect of radiation on cancer cells in laboratory studies. This discovery has now been claimed in the United States by complementing the company's earlier patent application, which protects the PFKFB3-inhibiting compounds. Kancera is the owner also of this new patent application.

Within the framework of the EU research program Horizon 2020, Kancera has been awarded a research grant of approximately EUR 500,000 over three years for the financing of two Ph.D. students in order to explore how resistance in cancer cells arises and how it can be broken. The two Ph.D. students' research will be performed in close collaboration with Prof. Thomas Helleday at Karolinska Institutet. One of these students will focus his/her research on PFKFB3.

Kancera is part of a consortium, along with nine internationally recognized research groups that will explore the area of DNA damage response (DDR) in tumor cells. DDR is one of the most promising research areas for the development of new drugs against currently incurable cancers.

An example of the type of drugs that act through the DDR are the new so-called PARP inhibitors against treatment-resistant mutated ovarian cancer, a treatment strategy that Prof. Thomas Helleday was

the first to discover. Over the past year, Kancera, together with Prof. Thomas Helleday's scientists, has shown that even PFKFB3 is part of cancer cells' DDR system and represents a promising target for the treatment of treatment-resistant cancer. Kancera is now developing drugs that inhibit PFKFB3.

In light of the success of PARP inhibitors the company and research groups are now searching for new targets that can benefit from the same type of action against cancer. Among these targets being evaluated for cancer treatment are proteins ATM, ATR and PFKFB3.

Kancera reported, together with Helleday's research group, that the impact of the company's PFKFB3 inhibitors (KAN0438757) increases in conjunction with radiation when a cell transforms from healthy to cancerous using the cancer gene RAS (RAS is activated in about 20% of all cancers and 90% of pancreatic cancer).

Competing inhibitors that act against the ATR and ATM do not exhibit this favorable ratio between activity against cancer cells and normal cells. These results support the idea that PFKFB3 has a significant role in the RAS-driven ability of cancer cells to survive and KAN0438757 can counteract this function of RAS in cancer cells.

Events during 2017 up to the date of this report

Kancera in collaboration with Thomas Helleday's research team has shown that cancerous cells resistant to the PARP inhibitor Veliparib become sensitive to treatment when Veliparib is combined with one of Kancera's PFKFB3 inhibitors. This means that Kancera's PFKFB3 inhibitor in combination with PARP inhibitors can fight more difficult-to-treat cancers than PARP inhibitors individually. The reason that Kancera's PFKFB3 inhibitor increases the efficacy of Veliparib is that it blocks the cancer cell's ability to repair DNA. Since healthy cells are not recombination deficient and are not dependent on PFKFB3 for a functioning DNA repair, such combination therapy may prove to be well tolerated with few side effects.

HDAC6-project
– acts against cancer by controlling the cancer cell's ability to spread

Product profile – HDAC6-inhibitor

Property	Summary of "Target Product Profile" (TPP)
Primary indication	Multipel myeloma
Secondary indication	T-cell lymphoma, Breast cancer, Fibrotic diseases
Treatment regime	Combination with other drugs, one to two times per day.
Administration	Peroral/IV/SC
Biomarker	Remains to be identified in biopsy and circulating tumor cells.
Product differentiation	*Effekt:* a) new mechanism of action that in combination with other drugs may give an increased effect on the ability of the cancer cell to divide. b) under investigation: immuno-stimulating effect against cancer by small molecule. *Safety:* Due to high selectivity for HDAC6, a lower degree of gastro-intestinal effects is expected compared to the less selective HDAC inhibitors that are currently in clinical development. *New mechanism of action:* Combination of effect on HDAC6 and Kancera's "Target 2".

HDAC6 is an enzyme that controls the interior cell fibers, a type of cell skeleton, functions and thereby how cells can move in the body. Active HDAC6 affects the tumor's ability to invade surrounding healthy tissue and form metastases. HDAC6 has also been shown to be a useful marker providing an indication on how difficult the cancer is to treat. Taken together, these observations point to that HDAC6 contributes to cell changes that lead to tumor formation and invasion of tumor cells into healthy tissue making HDAC6 an attractive target for the development of new effective drugs against cancer.

Recent research also shows that HDAC6 inhibitors can help the patient's immune system to recognize and attack cancer cells. The HDAC6 inhibitors relieve a molecular brake, called PD-L1, which is applied on the immune cells by the cancer. Thus, HDAC6 inhibitors may constitute an effective small molecule replacement of the new PD-L1 antibodies which are in clinical use today, with the advantages that the small molecule drug can be taken in pill form instead of via syringe and will be cheaper to produce, which can make the drug available to more patients. However, it remains for Kancera to show how effectively the company's compounds can counteract the ability of the cancer to slow down the patient's immune system.

There are currently five HDAC inhibitors on the market for the treatment of various forms of T-cell lymphomas, AML and multiple myeloma. These inhibitors are active against several members of the HDAC family of enzymes leading to severe side effects on e.g. the gastrointestinal tract. Also, the risk of significant negative impact on cardiac function is considered to be high. Kancera's discovery of selective HDAC6 inhibitors may provide a solution to how the health care can take advantage of the HDAC inhibitor's effect on cancer without causing the patient severe side effects.

Kancera's HDAC6 inhibitors are covered by two patent applications submitted in 2014 and 2015. These compounds are more potent and selective in vitro against cancer cells from multiple myeloma than the furthest developed competing HDAC6 inhibitor ACY-1215.

Kancera has also discovered that the company's HDAC6 inhibitors can be designed to operate also through an additional mechanism, which has not been described publicly for competitive reasons. Kancera's results show that a combined effect against HDAC6 and Target 2 in a more efficient manner stops the cancer cell's ability to proliferate.

The company estimates the project with adequate resources could deliver a drug candidate in approximately 12 months. In a next step Kancera intends to evaluate how the new mechanism can be combined with inhibition of HDAC6 to combat intractable cancer.

In June 2015, VINNOVA announced that SEK 2 million had been granted Kancera to support the further development of HDAC6 inhibitors against cancer.

Events during 2016

Kancera reported that new series of potent compounds that only inhibit HDAC6 have been developed and a patent application has been filed.

Kancera has previously reported that the company's substance KAN0439782, which acts by inhibiting both HDAC6 and "Target 2" (the identity of the target is not published), selectively prevents the ability of cells that normally surrounds and helps tumors (so-called cancer-associated fibroblasts) to migrate by disrupting the cytoskeleton (the cytoskeleton is composed of protein fibers that affect the cell's ability to *e.g.* divide, send hormone signals, invade and migrate to other locations in the body).

These studies have now been extended to cancer cells, which have a strong ability to use the cytoskeleton to adhere to surrounding healthy tissues, invade and metastasize. KAN0439782 can affect the cytoskeleton so that aggressive prostate cancer cells detach and die while treatment with the competing HDAC6 inhibitor ACY-1215 allows a portion of the cancer cells to survive and spread out on the surface.

VINNOVA has paid Kancera's HDAC6 project the third installment of the grant from the Strategic Innovation Agenda of common diseases (SWElife). The payment of SEK 358,451 followed VINNOVA's approval of Kancera's progress report for the project.

Kancera AB has evaluated a selection of the company's patent-pending HDAC6 inhibitors for properties that determine how efficiently the compound is taken up in the body and the concentration in the blood. These properties will normally determine the ability to achieve the desired treatment effect. In Kancera's studies, compounds have been given orally to mice after which the concentration of the substance has been determined in circulation. The experiments led to the identification of HDAC6 inhibitors that are significantly better with respect to uptake and stability in the circulation as compared to Acetylon's HDAC inhibitor ACY-1215. This is expected to enhance the effect of the substance against cancer cells.

Laboratory studies at Kancera have shown further support to that a combined effect against HDAC6 and Target 2 may provide an advantage over other HDAC6 inhibitors in cancer treatment by stopping the division of cancer cells *via* a dual mechanism of action. Further, Kancera reported that its HDAC6 inhibitors in studies of multiple myeloma cells reduce the amount of PD-L1 (Programmed Death Ligand 1) more effectively than the competing substance ACY-1215 (see Figure 3). Cancer researchers have previously shown that a reduction in the amount of PD-L1, which can be achieved with HDAC6 inhibitors, has the potential to contribute to an increased immune response against cancer. An observed positive effect of treatment with antibodies against the receptor of PD-L1, PD1, in malignant melanoma, lung and kidney cancer supports this (see studies with nivolumab, *e.g.* Ther Adv Med Oncol. 7 (2): 85-96). Additional studies are needed to determine if also Kancera's HDAC6 inhibitors can achieve the desired immune stimulatory effect against cancer cells.

Events during 2017 up to the date of this report

Kancera has also reported that the company in collaboration with SARomics Biostructures has succeeded in determining the crystal structure of Target 2 bound to Kancera's combined HDAC6/Target 2 inhibitors. Through this structural determination at atomic level, Kancera obtains information on how drugs can be designed in a more optimal way to inhibit both HDAC6 and Target 2.

Kancera has previously reported on the company's unique substances that exert a combined inhibition on HDAC6, and a yet unspecified mechanism, called Target 2. The combined effect is expected to be an advantage in the treatment of breast cancer. With the ambition to enhance the activity on Target 2, a crystal structure has been developed for this target (protein) in the cancer cell. Using information from the crystal structure new compounds have now been developed that act with great efficiency on Target 2.

Thus, Kancera has achieved the milestones in the Vinnova-funded project HDAC6 up to January 2017 as documented in a Vinnova-approved report. For this milestone, the company has received an interim payment of 454 706 SEK from VINNOVA. The final reporting of this Vinnova project takes place during the month of July 2017.

Vinnova has part-financed the HDAC6 project for two years through a grant of SEK 2 million up until 30th June 2017.

Kancera's final report has been submitted and was approved in July 2017.

Vinnova has part-financed the HDAC6 project for two years, through a grant of 2 MSEK. 2017-06-30. Kancera's final report has been submitted and approved in July 2017.

The effect of two Kancera substances is currently being studied in a first in vivo study in a multiple myeloma mouse model.

Anti Parasite Project - an EU-funded international cooperation against deadly diseases

The EU-financed project (A-PARADDISE (Anti-Parasitic Drug Discovery in Epigenetics) is coordinated by the Institut Pasteur and includes collaborations with epigenetic experts from Germany, France, UK, Italy, Australia and Brazil.

The project focuses on target proteins in the following diseases (parasites): Malaria (*Plasmodium falciparum*), Schistosomiasis (*Schistosoma mansoni*), Leishmaniasis (*Leishmania*) and Chagas disease (*Trypanosoma cruzi*).

Kancera is the only pharmaceutical development company in the A PARADDISE consortium and is well positioned to commercialize the drug candidates that the company develops and owns together with its partners. For clinical development and commercialization of drugs for neglected diseases, it is likely that Kancera will seek cooperation with internationally established pharmaceutical companies and nonprofit organizations that have chosen to take social responsibility by investing in the development therapies against diseases that primarily affect poor countries in tropical and subtropical areas. Since countries that currently suffer from serious parasitic diseases have an increasing financial capacity to invest in drugs, the project´s future drug candidates may also have a commercial potential.

Kancera has continued the optimization of anti-parasitic compounds, which Kancera successfully initiated during the completed EU funded project SETTREND. The project work mainly focused on the further development of anti-parasitic compounds that the company previously developed. More than 150 new substances against parasitic target proteins have been synthesized since the start of the project. The academic groups in the consortium are continuously testing the effect of synthesized compounds against various types of parasites. Further, Kancera together with partners in the consortium have established an experimental plan for the selection of anti-parasitic drug candidates that can come from Kancera´s chemistry development or from other partners in the consortium. Exchange of substances has been initiated in order to identify the epigenetic mechanisms that are appropriate to target in the four studied parasitic diseases.

Events during 2016

In January, 300 000 € (ca SEK 2.8m) was paid to Kancera by the EU for the continuing operation of the project until its end in January 31, 2017.

During the period, the project has commenced efficacy studies of a substance that has been developed by an academic partner within the consortium, for the treatment of schistosomiasis in a disease model in mice. Kancera

has contributed with analyses of the drug properties of the substance, and established the formulation of the substance used in the present efficacy study. Thus, the consortium has taken a decisive step towards achieving the final goal of the A-PARADDISE project, which is to demonstrate the therapeutic efficacy of a substance developed within the project in a validated disease model for one of the world´s largest parasitic diseases.

Events during 2017 up to the date of this report

Within the framework of the project, Kancera has developed inhibitors of several epigenetic enzymes from parasites, including sirtuin 2. Kancera reports that the company's inhibitor of sirtuin 2 (KAN0441411) has shown a significant effect in an animal model of Chagas disease caused by infection with the parasite Trypanosoma cruzi. Kancera has thus achieved its ambitious goals for the project. Approximately 8 million people are expected to carry Chagas disease which, in the chronic phase, leads to heart failure. Patients are mainly in Central and South America.

The experimental part of this EU-funded anti-parasitic projects was completed at Kancera on January 31st, 2017. The final report was submitted to the EU in March 2017. Kancera is willing to cooperate with non-profit organizations and pharmaceutical companies to further develop the project through external financing.

Patent portfolio and intellectual property rights

The basis for the commercial potential of new drugs is a broad patent protection. Patent work is an important and integral part of Kancera's operations, especially in the early preclinical phases. Kancera's management has extensive experience in establishing patent strategies and build competitive patent portfolios even in highly competitive fields. For Kancera's projects, patent strategies and patent portfolios are developed together with internationally established patent law firms with which Kancera's management has a long-lasting relationship. Timelines for the first patent application is determined from case to case depending e.g. on competitor activity. When Kancera sells drug candidates, there is a negotiation on whether the Company's patents or patent applications are to be licensed or sold, directly or through option.

Kancera currently owns eight patent families of small molecules (including the exclusive option to acquire the patents from the Fractalkine project), one for ROR inhibitors, two for Fractalkine receptor antagonists, three for PFKFB3 inhibitors and two for HDAC6 inhibitors. In addition to these Kancera owns two patent families covering antibodies against ROR1. However, these are not being commercially developed at the moment.

Project/ Patent family	**Description**	**Status**	**Application-/ Patent number**	**Filing date** (YYYY-MM-DD)
Fractalkine*	Substance patent 1	Approved international patent	US 7947693	2006-04-03
Fractalkine*	Substance patent 2	Approved international patent	US 7960395	2007-09-27
ROR1	Substance patent	International application	15201842.2	2016-02-01
ROR1	Antibodies from mouse	Approved international patent	US 9150647	2010-12-10
ROR1	Human antibodies	Approved international patent	US 9266952	2011-12-12
PFKFB3	Patent family "Sulphoneamide compounds"	Approved international patent	9233946	2011-09-19
PFKFB3	Patent family "Biarylsulfoneamides"	Approved international patent	12806515.8	2012-12-21
PFKFB3	Patent family "Biarylsulfoneamides". Divisional application in the United States. Combination of biarylsulfoneamides with radiation therapy.	Divisional application in the US	15/078502	2016-03-23
HDAD6	Substance patent 1	International application	PCT/EP2015/0603293	2015-05-11
HDAC6	Substance patent 2	International application	PCT/EP2015/077914	2015-12-22

* Kancera has an exclusive option to acquire these patents by Acturum AB.

Market outlook for Kancera's products

While 2015 was a strong year for the industry, 2016 was a year of weaker share price performance, lower level of investment and Phase III clinical trials that have failed in inflammation and cancer. In 2016, we still see 326 contracts in the industry and a Biotech Index, which has been stronger in Europe than in the United States in 2016 (in which the Nasdaq fell 22%) (Bloomberg, BioCentury). Even if the investment rate was significantly lower in 2016 compared with the previous year, it was still the fourth highest since 1994 (BioCentury). The need for improved drugs persists and the valuation of pharmaceutical companies are still driven by the ability to develop innovative medicines, and these two factors together support a continued strong demand for biotech companies best drug projects. It is also welcome to see that the proportion of options that are really used to acquire projects in the period 2010-2013 is 40% and the duration is 2-3 years, suggesting that many collaborations relatively quickly leads to the decision to continue product development, (Thomson Reuters Life Sciences Report 2015).

IMS Health reports that the forecast for the use of drugs and the society's investment in the use of drugs will increase by 4-7% per year until 2018, which is an increased rate compared to the previous five years. The driving factors behind this growth are the increased availability of good new proprietary specialty pharmaceuticals (such as cancer drugs) for an increasing number of patients and the fact that a growing proportion of the world population is over 65 years.

In 2016, the European Medicines Agency (EMA) approved 81 new drugs of which about 33% constituted a new class and 20% were orphan drugs. The US Food and Drug Administration (FDA), approved 22 new drugs in 2016 which is lower than the average of about 30 new drugs per year during the period 2006 to 2015. Of these 81 new drugs, 36% constituted a new class and 41% were orphan drugs. The number of new applications to FDA for approval of drugs has remained at the same level during 2006-2016, indicating a lower fraction of approvals during 2016. Of the 22 drugs approved in the USA in 2016, the proportion that acquired the status of so-called "Break-through therapy" was 73%. Both in the USA and in Europe, cancer was the disease with most new registered drugs (4 new cancer drugs approved in the USA and 8 in Europe) (Source: EMA and FDA).

Kancera's primary market is based on business-to-business sales of drug candidates for further clinical development and marketing by internationally established pharmaceutical companies.

The prioritized deal is based on an option model where Kancera signs agreements in the preclinical phase or early clinical phase, with a selected international partner possessing the resources and capacity for effective clinical development and marketing internationally. The option model provides Kancera with a cash flow during the more expensive parts of the project's development, and at the same time the cooperation gives partners the opportunity to influence the direction of the project during the critical phase between late pre-clinical development and clinical development that forms the basis for registration. This also increases the possibility of a rapid start of a clinical program. A quick and successful transition from Kancera´s preclinical to the partner´s further clinical development also increases the likelihood that the schedule for milestone payments to Kancera is kept.

There are several reasons for late preclinical or early clinical projects to be met with increased interest from large pharmaceutical companies. The development departments at pharmaceutical companies want to influence the selection and design of an active substance, the product formulation and indication. It could be disastrous if a substance that has reached phase II or phase III proves to be suboptimal or insufficiently suited to its task. Time and money will be lost if a clinical trial needs to be redone from the beginning. Historically, there are many examples of projects that need to be corrected and where the clinical trial needs to be repeated from the start. Sometimes pharmaceutical companies also choose to run several explorative clinical studies to ensure that they cover several different patient populations and diseases, as well as schedules for treatment, and thereby position the product optimally for the costly phase III clinical trials.

The underlying demand for Kancera´s drug candidates is driven by the medical need to make the combat against cancer more efficient.

The trend is towards

- diagnostic methods that provide genetic information about exactly what factors in the individual patient's cancer drive the disease and whether there are mutations that render a traditional drug inactive

- drugs that attack the driving mechanisms of the cancer, that overcome causes of resistance and act

selectively against cancer to reduce the side effects that would otherwise contribute to increased mortality and high medical costs

Consequently, more patients will be offered a personalized cancer treatment resulting in a longer and better life. The number of drug development projects within the cancer area has steadily increased, but many of them follow the same path as others (Source: lifescivc.com/2012/06/cancer-drug-targets-the-march-of-the-lemmings) which is why pharmaceutical companies now focus their search for drug candidates that distinguish themselves from the mainstream and have the potential to fundamentally change the situation for the treatment of life-threatening diseases.

Kancera´s focus is on target molecules in the cancer that opens opportunities to break the resilience of life-threatening cancer forms as well as the development of diagnostics that allow early identification of patients who benefit from the new treatment.

Currently Kancera evaluates applications of future drugs against the Fractalkine-receptor, ROR, PFKFB3, and HDAC6 in

- Solid tumors in the pancreas, ovary, lung, bowel and breast. These forms of cancer are among the types of cancer that causes most deaths.
- Chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML), which are the most common chronic and acute form of leukemia respectively in adults, as well as multiple myeloma (MM).
- Inflammation driven by our innate immune system and that causes cancer related pain and autoimmune diseases.

These cancer indications and inflammatory diseases each represent a world market in the range of SEK 3.5 to >10 billion annually (Source: GlobalData). According to the Dental and Pharmaceutical Benefits Agency (TLV), in Sweden the society is willing to pay for drugs that treat life-threatening and other serious diseases up to SEK 1 million per year of life with full quality of life (so-called quality adjusted life year, QALY. Two extra years' survival with an estimated 50% level of full quality of life corresponds to one QALY). Although there are no definitive requirements to show prolonged survival of new drugs, TLV means that in practice it will be difficult to justify subsidization of new drugs that prolong survival less than 6 months since this level of prolongation of survival implies a low pricing to cope with the cost per QALY. There exist similar principles for society's willingness to pay in the rest of the world. For example, in England drugs with a cost per QALY in excess of £ 30,000 are not subsidized. However, exceptions are made for life-threatening conditions where the boundary is moved up to £ 50,000 in accordance with the Agency's (NICE) "end-of-life criteria" (at the time of registration of the drug results in terms of overall survival is often lacking, so it is assumed that a longer period of stable disease translates into equally long prolongation in survival).

In addition, the industry's interest in rare diseases, so-called Orphan diseases, has increased in recent time given that they represent significant unmet medical need and that the patient group often is clearly defined thus facilitating clinical studies. This has led the authorities to facilitate the development of, and the protection of products against these diseases. New approved drugs by both the European Medicines Agency EMA and the American FDA include a high proportion of drugs to treat rare diseases (see the introduction for 2015 statistics). Kancera's projects have in preclinical studies been shown to be a possible way to treat several forms of cancer that precisely meet the requirements for designation as an Orphan disease (the definition of Orphan disease in the United States is diseases affecting fewer than 200,000 individuals).

The need for improved treatments is exemplified below for two of the cancer forms that Kancera addresses with its drug projects and that qualify as Orphan diseases.

Cancer of the pancreas annually affects more than 100 000 patients in Europe and the U.S. The survival of these patients is less than two percent five years after diagnosis. A combination of chemotherapy and radiotherapy is used to enable removal of the tumor by surgery. The life sustaining drug treatment mainly consists of various types of cell poisons (Gemcitabine and FOLFIRINOX which contain combinations of Fluorouracil, Irinotecan, and Oxaliplatin). Today, there is no recommended drug targeting pancreatic cancer. In recent years, more specific enzyme-inhibiting drugs have been approved for the treatment of pancreatic cancer, such as erlotinib (EGFR inhibitor mainly) and Sutent (a broad-acting inhibitor of many kinase enzymes, including

VEGF, PDGF and SCF (Kit)). However, these drugs have shown limited therapeutic efficacy and the medical need for new drugs against this disease remains very high. The market for pancreatic cancer in the United States in 2009 totaled USD 781 million and the expected growth was -4 to +8% in 2017, (Source: Global Data Healthcare).

Chronic lymphocytic leukemia (CLL) annually affects approximately 30 000 patients in Europe and the U.S., which makes CLL to the most common chronic form of leukemia. The traditional treatment of cancers such as CLL is currently not sufficiently effective and selective. The most common type of treatment of CLL is a combination of the antibody Rituximab and chemotherapy such as Fludarabine and Cyclophosphamid. This combination of drugs is used in 19% of the treatments in the seven countries that represent the largest pharmaceutical markets. Following the initial treatment of patients approximately 85% are symptom free, but only after four years' freedom from symptoms of cancer the disease had returned for 80% of the patients. New and better treatments are required in this phase of the disease. New drugs with other effects on refractory CLL are now being introduced, such as ibrutinib and idelalisib. Ibrutinib and Idelalisib have clearly improved the treatment of CCL, and give effect in 70-80% of the patients with this disease. However, so-called complete remission (the symptoms have disappeared) has only been reached in a small number of these patients. Since complete remission in cancer is generally linked to a longer survival, there is a need for drugs that work in a new way.

Kancera has previously shown that the candidate drug KAN0439834 effectively kills CLL cells from blood and lymph taken from patients in-vitro and also in animal models of the human disease. Also, Kancera in collaboration with Prof. Håkan Mellstedt's group at the Karolinska Institute, has demonstrated that Kancera's ROR inhibitor is also effectively killing CLL cells from bone marrow which is a characteristic sought as a complement to today's registered drugs against CLL.

The market for CLL is estimated at 800 million USD in 2017 (Source: Global Data Healthcare 2013). Kancera also expects that there are good opportunities to expand into other cancers, given that ROR-1 is found in at least eight other blood cancers and several solid tumors (ovarian cancer, lung cancer, breast cancer, pancreatic cancer).

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