

# Kanceras drug development projects

# May 2018

## Contents

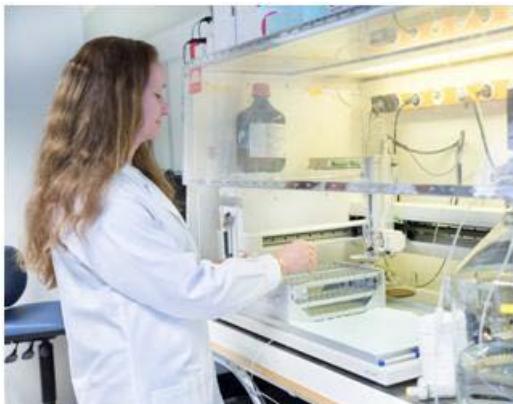
|  |           |
|--|-----------|
| <b>Important events over the last 12 months – in short .....</b> | <b>3</b>  |
| <b>Pharmaceutical development .....</b>                          | <b>5</b>  |
| Fractalkine project.....   | 6         |
| ROR-project .....  | 11        |
| PDKFB3-project.....  | 13        |
| HDAC6-project .....  | 15        |
| <b>Patent portfolio and intellectual property rights .....</b>   | <b>18</b> |
| <b>Market outlook for Kancera's products .....</b>               | <b>20</b> |

## 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.*

- The clinical phase I study of KAND567 began in May 2017.



- Kancera's Fractalkine project has been awarded a total of SEK 1M by the Swedish Innovation Authority, VINNOVA, targeted at projects with "a very high level of innovation and commercialization potential".
- The second part, the multiple dose study, of the ongoing clinical phase I study of KAND567 commenced in September 2017.
- Kancera and Recipharm have signed an agreement for the manufacture of drug products for clinical studies
- Kancera AB announced that the company has made the second installment for the Fractalkine project under an agreement with Acturum Real Estate AB.
- Kancera AB announced that rights to the Fractalkine project in the field of lung disease were acquired from AstraZeneca AB and Acturum Real Estate AB, which means that Kancera AB now has full control over the rights to the project.
- Kancera AB reported that the Phase I study in the Fractalkine project has been completed. In the study, drug properties, safety and tolerability have been documented for KAND567.
- Results from the Phase 1 study in healthy subjects show that KAND567 is safe and well tolerated up to plasma concentrations that are five to ten times higher than the calculated effective level for therapeutic

effect in humans. The results also showed that KAND567 blocks the Fractalkine system by reducing the number of Fractalkine receptors on the surface of immune cells.

- Studies on three preclinical disease models have shown cardiovascular protection properties of KAND567.
- Kancera is evaluating KAND567 against primarily cardiovascular inflammation as well as cancer. There is strong scientific support for the idea that KAND567 reduces cardiovascular injury after infarction from preclinical animal studies and from major clinical trials conducted by Novartis (CANTOS study in > 10,000 patients) and Freeman Hospital, Newcastle (1,300 heart attack patients). There is currently no effective treatment against this type of problem.

### Most recent events

- Kancera AB announced that a new patent application has been submitted describing a new synthesis pathway for KAND567 which provides an improved quality of active substance and the possibility of extended protection for a future drug. In addition, two preparations of KAND567 have been developed which can form the basis for two independent products.

### ROR-inhibitors

*Reprogram cancer cells to destroy themselves by apoptosis.*

- 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.

### Most recent events

- Research on Kancera's ROR inhibitor has been published by scientists from Karolinska Institutet and Kancera in the reputed scientific journal Leukemia.
- The company's ROR1 inhibitor KAN0441571 penetrates the bone marrow where it achieves an expected pharmacologically active concentration for several hours.

### **PFKFB3-inhibitors**

*Strangle 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.*

- 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.*

- Vinnova has part-financed the HDAC6 project for two years with a grant of SEK 2 million up to 30<sup>th</sup> June 2017. Kancera's final report has been submitted and approved.

### **Most recent events**

- Animal studies show that Kanceras HDAC6 inhibitor KAN0440262 resides in the brain at significantly higher concentrations and for longer than in the blood. This opens up opportunities to exploit the substance against brain diseases, e.g. brain tumors and neuropathic pain.
- A report from EPO (The European Patent Office) enables a faster handling of the patent application, which includes KAN0440262, due to its level of inventiveness.

### **Anti-parasite project**

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

- The final report for the project was submitted to the EU on March 31st, 2017 and was approved in August 2017.
- After approval of the final project report, the EU has paid the final part of the contribution of approximately 1.4 Mkr and an additional payment of approximately SEK 180,000 as compensation for costs in excess of budget.

## Pharmaceutical development

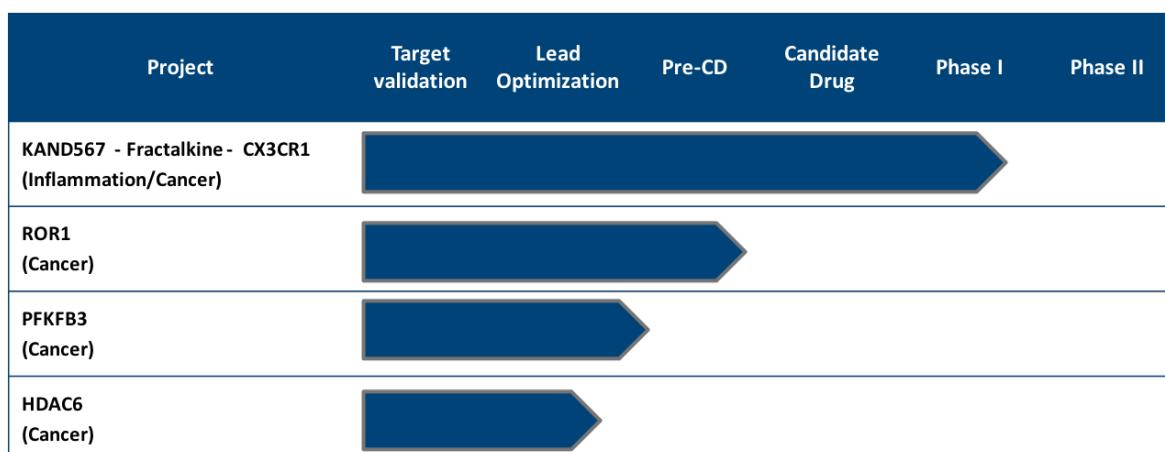
Kancera is engaged in the development of four drugs for cancer and autoimmune diseases that begin in a new treatment concept and end with a patented drug candidate offered for sale to major pharmaceutical and biotech companies in late pre-clinical or early clinical development.

The goal of completing the phase 1 study for KAND567 in the Fractalkine project before the end of Q4 2017 has been achieved. Kancera AB is now evaluating the conditions for continued clinical development of KAND567 against cancer and inflammatory cardiovascular injuries, e.g. in connection with infarction. As the largest part of Kancera's resources were used for the Fractalkine project in 2017, our other pharmaceutical projects have slowed slightly. However, studies are ongoing to identify the company's next drug candidate for clinical development in the ROR, PFKFB3 and HDAC6 projects.

The company has four drug development projects in the portfolio.

- **Antagonists of the Fractalkine Receptor CX3CR1 for the treatment of heart damage after an infarct and the most aggressive form of blood 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 cells.
- **Inhibitors of PFKFB3 for treatment of cancer.** Inhibitors of PFKFB3 strangle the energy supply from glucose to tumor cells and decrease the ability of the cancer cells to repair their DNA. The combined effect may increase the tumor's sensitivity to other cancer treatments such as radiation therapy.
- **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.

**Figure 1.** Kancera AB's cancer project portfolio



See page 20 for more information on the commercial prospects for Kancera AB's products.

## Fractalkine project

– controls the immune system in cancer and alleviates severe pain

Product profile – Fractalkine inhibitor

| Property                | Summary of “Target Product Profile” (TPP)   |
|-------------------------|---|
| Primary indication      | Inflammation, e.g. Cardiovascular disease   |
| Secondary indication    | Cancer  |
| Administration          | Myocardial infarction: IV, Cancer and other inflammatory diseases: Peroral  |
| Biomarker               | Markers for cell migration and invasion in blood.   |
| Product differentiation | <i>Effect:</i> a) Selective modulation of inflammation b) Cancer: increased progression-free survival<br><i>Safety:</i> Low level of mechanism related side effects is expected.<br><i>New mechanism of action:</i> 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 blocker of the Fractalkine-signalling KAND567 (AZD8797, for example, KAN0440567). The agreement with Acturum Life Science gave 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 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 an orally 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 immune system is needed. However, animal studies show that the Fractalkine receptor is not essential for survival and that important immune functions are 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 (e.g. cortisone, anti-TNF, cyclosporin, anti-VLA4) or target the specific immune system (e.g. 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 blockers of the Fractalkine signal, 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 both as an injection or 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 Kancera's 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. In the fall of 2017, Eisai Co. Ltd published a small molecule CX3CR1 modulator called E6130 which has shown effect in two mouse models of colitis (Wakita et al., Mol Pharmacol. 2017 Nov; 92 (5): 502-509). During 2017, a single-ascending dose (SAD) phase 1 clinical study of E6130 was completed in healthy volunteers, see:

(<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 the presence of the Fractalkine ligand. 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.

According to plan, Kancera's Fractalkine project was taken into clinical Phase Ia study in May 2017 and completed in December 2017. In the study, drug characteristics, safety and tolerability have been documented for KAND567 in healthy subjects. The results show that KAND567 is safe and well tolerated up to plasma concentrations that are five to ten times higher than the calculated effective level for therapeutic effect in humans. The results also showed that KAND567 blocks the Fractalkine system not only by direct interaction with the Fractalkine receptor but also by reducing the number of Fractalkine receptors on the surface of immune cells. Kancera is evaluating KAND567 primarily against cardiovascular inflammation, but also for cancer.

KAND567 has shown, in three preclinical animal models, cardiovascular-protective anti-inflammatory properties by significantly reducing infarct size, stabilizing vessel plaques that can cause infarction and counteracting reocclusion (restenosis) after expansion of the coronary artery with so-called vascular stents. These studies were carried out when the project was owned by AstraZeneca. Clinical evidence from Novartis CANTOS study in 2017 showed that anti-inflammatory treatment reduces the risk of complications following myocardial infarction. In addition, follow-up analyzes showed a strong and dose-dependent reduction of lung cancer in patients treated with anti-inflammatory drugs. Publications of independent research groups also support blocking of the Fractalkine system to protect the heart in conjunction with myocardial infarction (in animal models), and the Fractalkine system is an independent risk marker and driving factor behind the inflammation of the blood vessel and the heart muscle after myocardial infarction (shown in a study of a total of 1300 patients). Inflammatory cells from the blood infiltrate the heart after the infarction and cause complications in the aftermath. Among these disease-causing immune cells, are those identified as responsible, together with an active Fractalkine system, for complications following myocardial infarction. Together, these results provide support for KAND567 as a drug candidate for the treatment of cardiovascular disease. The results also provide information on appropriate biomarkers for the identification of patients who could benefit from such treatment.

In 2017, results were published that support the idea that the Fractalkine system in immune cells is correlated with an aggressive disease in lymphoma and suggests that a blockade of the Fractalkine system could inhibit the disease. In view of these findings, as well as the results from Kancera AB's clinical phase I study that demonstrate that KAND567 works against the identified immune cells, Kancera AB has initiated a collaboration with the Karolinska Institutet. The collaboration aims to prepare for a clinical study by evaluating biomarkers for the Fractalkine system in blood and cancer tissue and the effect of KAND567 on these biomarkers (in isolated blood from the patients), which may provide information on which patients could benefit clinically from treatment with KAND567.

#### **Events during 2017**

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 mediate 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.

Kancera AB has made the second installment for the Fractalkine project and two million of the company's shares have thus been newly issued to Acturum Real Estate AB. The second installment for the Fractalkine project became due in accordance with the agreement with Acturum Real Estate AB in connection with the fact that the drug candidate KAND567 had been given to a certain number of subjects in the Phase Ia study.

Kancera AB has acquired rights to the Fractalkine project in the field of lung diseases from AstraZeneca AB and Acturum Real Estate AB, which means that Kancera AB now has full control over the rights to the project. The agreement means, on the one hand, that AstraZeneca AB is entitled to be the first company offered the opportunity to acquire, on commercial terms, a possible right of first refusal for a product from the Fractalkine Project for the treatment of lung diseases and, on the other hand, that Kancera AB pays a low level of royalties on net income from such product to Acturum Real Estate AB. Kancera AB's above commitments do not apply to products outside the area of lung diseases. The fact that Kancera AB hereby controls full rights to the Fractalkine project facilitates the company's future commercialization of the drug candidate KAND567.

According to plan, the clinical Phase Ia study of Kancera's Fractalkine project was finalized in December 2017. In the study, drug characteristics, safety and tolerability have been documented for KAND567 in healthy subjects. KAND567 has been given orally, i.e. by mouth, in increasing single doses and then in repeated doses. The study has also included a subset that aims to show whether food affects the absorption of KAND567. The purpose of the study is to demonstrate opportunities and limitations for the further development of this drug candidate. All data will

now be quality-controlled, compiled and analyzed and, according to the present plan, the results of the study are expected to be communicated in February 2018.

***Events during the first quarter of 2018 and up to the date of this report***

On February 19<sup>th</sup> 2018, Kancera AB reported results from a Phase I study in healthy subjects with the immunoregulating drug candidate KAND567. The study has shown that KAND567 is safe and well tolerated up to plasma concentrations that were five to ten times higher than the calculated effective level for therapeutic effect in humans. Upon further increase of the dose, a reversible increase in markers for liver effect was noted. The results also showed that KAND567 blocks the Fractalkine system by reducing the number of Fractalkine receptors on the surface of immune cells.

Kancera has also reported results from three preclinical disease models showing cardiovascular protection properties of KAND567. Kancera evaluates KAND567 primarily against cardiovascular inflammation but also against cancer.

Kancera AB announced that a new patent application has been submitted describing a new synthesis pathway for KAND567 which provides an improved quality of active substance and the possibility of extended protection for a future drug. In addition, two preparations of KAND567 have been developed which can provide the basis for two independent products that can be targeted at various diseases and buyers.

## ROR-project

### – reprograms cancer to self-destruct

*Product profile – ROR1 inhibitors*

| Property                | Summary of “Target Product Profile” (TPP)  |
|-------------------------|--|
| Primary indication      | B cell lymphoma  |
| Secondary indication    | Lung, pancreatic, breast, and ovarian cancer   |
| Administration          | Peroral with other drugs   |
| Product differentiation | <p><b>Effect:</b> Induction of tumor-selective cell death in blood, bone marrow and lymph in blood cancer as well as in solid tumors provides opportunities for complete remission.</p> <p><b>Safety:</b> ROR1 is mainly found in cancer cells, which is why a ROR1 targeted treatment should give a lower level of side effects compared to broad-acting drugs.</p> <p><b>New mechanism of action:</b> Adds effect to existing drugs.</p> |

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 Zydelfig 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 (CLL), 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.

About 15% of patients with CLL develop a very hard-treated form of lymphoma called Richter's syndrome. Neither the standard treatments nor the newest drugs against CLL have the desired effect against Richter's syndrome which is why there is a great medical need for new drugs against this disease. Studies have shown that tumor cells in Richter's syndrome carry ROR1 in a majority of subjects studied. Kancera has also shown that the company's ROR1 inhibitor kills cancer cells that represent Richter's syndrome and expresses ROR-1.

A first generation of Kancera's ROR inhibitors has been shown to work rapidly and efficiently against CLL cells from

patients, even against treatment-resistant cells from patients with treatment-resistant CLL. This has been demonstrated in the lab against isolated cancer cells and in animal studies where human disease has been recreated in mice. A first drug candidate, KAN0439834, was selected against CLL, but the substance disappears relatively quickly from blood circulation and does not provide sufficient effect against solid cancer.

Kancera's development of a second generation of ROR inhibitors has been to extend the retention time in the blood circulation which 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 retained in the blood circulation for a time long enough to have the potential to be efficient against lymphoma and solid tumors. This second generation of ROR inhibitors have been shown to be effective in solid tumors in a disease model in which triple negative breast cancer in humans has been implanted and studied in zebra fish and have also been shown to eliminate ROR1-carrying leukemia cells in a mouse model of human CLL.

The assessment is that Kancera is a world leader in the development of small molecule 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.

#### ***Events during 2017***

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.

#### ***Events during the first quarter of 2018 and up to the date of this report***

Kancera announced that the article entitled "First-in-class oral small molecule inhibitor of the tyrosine kinase ROR1 (KAN0439834) induced significant apoptosis of chronic lymphocytic leukemia cells" has been published by researchers from Karolinska Institutet and Kancera in Leukemia (Leukemia, 2018) doi: 10.1038 / s41375-018-0113-1 March 27 (E-publ. ahead)). The article documents the molecular mechanisms that cause the small molecule KAN0439834 to produce a potent anti-tumour effect in preclinical models of chronic lymphocytic leukemia (KLL). The basic structure of the drug candidate was identified from the Kancera chemical library from which a set of 110,000 substances were screened against ROR1 and further developed with tests against CLL cells from patients to KAN0439834.

Kancera reported that KAN0441571 penetrates the bone marrow where it achieves an expected pharmacologically

active concentration for several hours. This property may be of significant importance for the treatment of blood cancers that originate from the bone marrow and in the treatment of ROR-dependent bone metastases.

## **PFKFB3-project**

- blocks cancer cells' ability to repair themselves

*Product profile – PFKFB3-inhibitors*

| 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   |
| Administration          | Peroral/Intravenous  |
| Product differentiation | <p><i>Effect:</i> Synergistic effect with PARP-inhibitors, radiation or chemotherapy.</p> <p><i>Safety:</i> PFKFB3 is mainly found in hypoxic tissue and in cancer cells which is why a PFKFB3 selective drug can be expected to give a low level of side effects.</p> <p><i>New mechanism of action:</i> Adds effect to existing drugs.</p> |

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.

PFKFB3 is an enzyme that acts as a gas pedal in the metabolism of sugar to energy. Kancera has 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 support the continuation of the work by Kancera to develop a drug candidate against PFKFB3 and test it in combination with

radiation treatment to combat resistant cancers.

Radiation therapy is an effective method to treat cancer but it is challenged by the fact that cancer cells exhibit resistance and by 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 these requirements.

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 a mechanism of action different from that of the compounds that AstraZeneca have published. Regarding the PFKFB3 inhibitors from Advanced Cancer 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 2017***

DNA damage response (DDR) is one of the most promising research areas for the development of new anti-cancer drugs today, against cancer which is currently untreatable. An example of drugs acting through the DDR are the new so-called PARP inhibitors against treatment-resistant mutated ovarian cancer.

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.

Kancera has received prior notification from patent authorities in the EU and the US that patents on the PFKFB3 inhibitor KAN0438757 will be granted.

#### ***Events during the first quarter of 2018 up to the date of this report***

No events have been reported in the PFKFB3 project during the first quarter of 2018 and up to the reporting date.

## HDAC6-project

– acts against cancer by controlling the cancer cells' ability to spread

*Product profile – HDAC6-inhibitors*

| Property                | Summary of “Target Product Profile” (TPP)   |
|-------------------------|---|
| Primary indication      | Glioblastoma  |
| Secondary indication    | Pain  |
| Administration          | Peroral   |
| Product differentiation | <p><b>Effect:</b> 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.</p> <p><b>Safety:</b> 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.</p> <p><b>New mechanism of action:</b> Combination of effect on HDAC6 and Kancera's "Target 2".</p> |

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.

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 high. Kancera's discovery of selective HDAC6 inhibitors may provide a solution to how the healthcare system 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 2015 and 2016. 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.

Kancera AB has developed a selective HDAC6 inhibitor that combines good killing effect on cancer cells in the laboratory with significantly improved uptake and stability in blood circulation in mice on oral administration compared

with the furthest-developed, competing HDAC6 inhibitor ACY-1215. Kanceras HDAC6 inhibitor is now being evaluated in disease models.

New animal studies show that KAN0440262 effectively passes through the blood-brain barrier and resides in the brain at significantly higher concentrations and for longer than in the bloodstream. This combination of properties allows Kancera to exploit the substance against multiple brain disorders, including brain tumor (glioblastoma) and neuropathic pain. Kancera has also been able to demonstrate that treatment that has given relevant exposures in the brain of KAN0440262 does not lead to notable effects on animal behavior or general health. The so-far positive safety profile of KAN0440262 is further supported by studies conducted without a remark on 44 safety markers in vitro. However, before clinical trials can take place, extended toxicological studies are required.

#### **Events during 2017**

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.

Vinnova has part-financed the HDAC6 project for two years with a grant of SEK 2 million up until 30th June 2017. Kancera's final report has been submitted and approved during July 2017.

#### **Events during the first quarter 2018 and up to the date of this report**

New animal studies show that KAN0440262 effectively passes through the blood-brain barrier and resides in the brain at significantly higher concentrations and for longer than in the bloodstream. This combination of properties allows Kancera to exploit the substance against multiple brain disorders, including brain tumor (glioblastoma) and neuropathic pain. Kancera has also been able to demonstrate that treatment that has given relevant exposures in the brain of KAN0440262 does not lead to notable effects on animal behavior or general health. The so-far positive safety profile of KAN0440262 is further supported by studies conducted without a remark on 44 safety markers in vitro. However, before clinical trials can take place, extended toxicological studies are required.

The EPO (The European Patent Office) has, in a report (International Preliminary Report on Patentability), assessed that the patent application comprising KAN0440262 is both innovative and has sufficient inventiveness. Following such a positive report, several countries also offer the possibility of a faster handling of patent applications, a so-called "Patent Prosecution Highway". This patent application, which includes KAN0440262, enters the national registration phase in June 2018.

#### **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 2017***

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.

#### ***Events in the first quarter of 2018 and up to the date of this report***

No events have been reported in the anti-parasitic project during the first quarter of 2018 and up to the date of this report.

## 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. Timelines for the first patent application is determined from case to case depending 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 AB currently has nine patent families for small molecules: two for Fractalkine blockers, two for ROR inhibitors, three for PFKFB3 inhibitors and two for HDAC6 inhibitors. In addition, Kancera AB has two patent families covering antibodies to ROR1. However, these are not being developed commercially at the current time.

| Project/<br>Patent family | Description        | Status  | Application-/ Patent<br>number | Filing date<br>(YYYY-MM-DD) |
|---------------------------|--------------------|---|--------------------------------|-----------------------------|
| Fractalkine               | Substance patent 1 | Approved in:<br>China<br>Germany<br>France<br>Great Britain<br>Italy<br>Japan<br>Sweden<br>USA  | US 7947693                     | 2006-04-03                  |
| Fractalkine               | Substance patent 2 | Approved in:<br>China<br>Germany<br>France<br>Great Britain<br>Italy<br>Japan<br>Sweden<br>USA  | US 7960395                     | 2007-09-27                  |
| Fractalkine               | Process patent     | Application in:<br>Great Britain.<br>International<br>application is next<br>step   | GB1807898.0                    | 2008-05-15                  |
| ROR1                      | Substance patent 1 | International<br>application in:<br>Australia<br>Brazil<br>Europe<br>Hong Kong*<br>India<br>Israel<br>Japan<br>Canada<br>China<br>Mexico<br>New Zealand<br>South Africa<br>South Korea<br>USA | PCT/EP2016/052091              | 2016-02-01                  |

|        |  |   |                    |            |
|--------|--|---|--------------------|------------|
| ROR1   | Substance patent 2   | International application   | PCT/EP2017/067262  | 2016-07-10 |
| ROR1   | Antibodies from mouse  | Approved in:<br>Europe<br>China<br>USA  | PCT/EP/2010/007524 | 2010-12-10 |
| ROR1   | Human antibodies   | Approved in:<br>Europe<br>China<br>USA<br><br>Application in:<br>India  | PCT/EP2011/072490  | 2011-12-12 |
| PFKFB3 | Patent family<br>"Sulphoneamide<br>compounds"  | Approved in:<br>Europe<br>USA<br><br>Application in:<br>Hong Kong<br>India  | PCT/EP2011/066250  | 2011-09-19 |
| PFKFB3 | Patent family<br>"Biarylsulphoneamides"  | Approved in:<br>Australia<br>Europe<br>Japan<br>China<br>Mexico<br>New Zealand<br>South Africa<br>USA<br><br>Application in:<br>Brazil<br>Hong Kong<br>India<br>Israel<br>South Korea | PCT/EP2012/076836  | 2012-12-21 |
| PFKFB3 | Patent family<br>"Biarylsulphoneamides in<br>combination with radiation<br>therapy". | USA (continuation<br>in part)   | PCT/EP2012/076836  | 2012-12-21 |
| HDAD6  | Substance patent 1   | Application in:<br>Australia<br>Europe<br>Canada<br>New Zealand<br>USA  | PCT/EP2015/0603293 | 2015-05-11 |
| HDAC6  | Substance patent 2   | International application in:<br>Australia*<br>Europe*<br>India*<br>Japan*<br>Canada*<br>China*<br>New Zealand*<br>South Africa*<br>USA*  | PCT/EP2016/077914  | 2016-11-16 |

\*In the process of being submitted

## Market outlook for Kancera's products

2017 was a strong year for the industry with a 19% increase in the biotech index on Nasdaq. The number of acquisitions and the total size of these were comparable to 2016. The IPO market as well as venture investments in early R & D companies continue to be strong. Technology breakthroughs in immuno-oncology have generated the first approved drugs (in addition to Check-Point inhibitors now also cell-treatment with CAR-T). In December, the first gene therapy was approved that could cure a serious eye disease. This type of breakthrough (CAR-T and gene therapy) has also resulted in records for drug pricing of about 400 KUSD for cancer treatment up to 1 MUSD for gene therapy (Genetic Engineering News 2017 overview <https://cen.acs.org/articles/95/i48/year-in-pharma-2017.html>). Overall, this support continued strong development of the market for innovative drugs.

It is also gratifying that the proportion of options that are actually used to acquire projects during the period 2010-2013 is 40% and the term of 2-3 years, which indicates that many collaborations relatively quickly lead to decisions to continue product development (Thomson Reuters Life Science Report 2015). IMS Health reports that the forecast for the use of pharmaceuticals and 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-year period. The driving factors behind this growth are an increased access to new, good, patent-protected specialized drugs (such as cancer drugs) for more and more patients and an increasing proportion of the world's population who are over 65.

During 2017, the European Medicines Agency EMA approved 92 new drugs, of which 35 were of a brand new class. The US Medicines Agency (FDA) approved 46 new drugs in 2017, which after the decline in 2016 was again higher than the average of around 31 per year for the period 2006 to 2016. Of these 46, 32% were of a brand new class and 39% were orphan drugs. Of the 46 approved drugs in the United States in 2016, the percentage receiving some form of accelerated evaluation process was 61%.

Both in the United States and Europe, cancer was the disease against which most new drugs were registered (11 new cancer drugs were approved in the United States and as many in Europe) (Source: EMA and FDA). Kancera contributed to the development of one of these approved drugs, Enasidenib against Acute Myeloid Leukemia (AML). Kancera's contribution consisted of, as paid expert consultants, developing the substance that became the marketed drug now available from Agios Inc. and Celgene Inc.

Kancera AB's primary market is based on selling business-to-business drug candidates for further clinical development and marketing by internationally established pharmaceutical companies. The priority deal is based on an option model where Kancera AB concludes agreements in the pre-clinical or early clinical phase, with a selected international partner that has the resources and capacity for effective clinical development and marketing on an international basis. The option model gives Kancera AB a cash flow under more costly parts of the project's development while allowing the partner to influence the project's focus during the critical phase between late pre-clinical development and registration-based clinical development. This also increases the possibilities for a quick introduction of a clinical program. A quick and successful transition from Kancera AB's preclinical and early clinical development to the partner's further registration-based clinical development also increases the likelihood that the schedule for milestone payments to Kancera AB will be held.

There are several reasons why development projects in the late pre-clinical or early clinic meet increased interest from the major pharmaceutical companies. The development departments of the pharmaceutical companies 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 reached Phase III proves to be suboptimal or insufficiently adapted to its task. Time and money are lost if a clinical study needs to be repeated from the start. Historically, there are many examples of projects that need to be corrected and where the clinical trial needs to be restarted. At the same time, pharmaceutical companies sometimes choose to run multiple parallel explorative clinical trials to ensure that several patient groups and diseases are covered, as well as treatment schedules, thus optimally positioning the product for costly clinical Phase III studies.

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

The trend in cancer 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.

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). 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. Both the European Medicines Agency EMA and the American FDA include a high proportion of drugs to treat rare diseases in their total number of approved drugs in 2017. 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, for example, different forms of blood cancer. The definition of Orphan disease in the United States is diseases affecting fewer than 200,000 individuals.



For more information, contact:

Thomas Olin, CEO: +46 73 520 40 01

**Kancera AB (publ)**  
Karolinska Institutet Science Park  
Banvaktsvägen 22  
SE 171 48 Solna

Visit our home page at: [www.kancera.se](http://www.kancera.se)