ARROWHEAD
BUSINESS AND INVESTMENT DECISIONS

# Due Diligence and Valuation Report

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|---|---|
| Arrowhead Code: | 69-10-01 |
| Coverage initiated: | July 01, 2020 |
| This document: | July 01, 2020 |
| Fair share value bracket: | EUR 0.95 and EUR 1.16 |
| Share price (June 30, 2020): | EUR 0.57[i] |


**Analysts**

Sumit Wadhwa
sumit.wadhwa@arrowheadbid.com

Manish Purohit
Manish.purohit@arrowheadbid.com


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|---|---|
| Company: | NOXXON PHARMA |
| Ticker: | EPA:ALNOX |
| Headquarters: | Berlin, Germany |
| CEO | Aram Mangasarian |
| Sr. Medical Advisor | Jarl Ulf Jungnelius |
| Website: | www.noxxon.com |

## Market Data

| | |
|---|---|
| 52-Week Range: | EUR 0.26 – EUR 1.23[ii] |
| Average Daily Volume (3M Avg.): | 2,259,888[iii] |
| Market Cap (June 30, 2020): | EUR 22.8 million (mn) |

## Financial Forecast (in EUR) (FY Ending – Dec

| EUR '000 | '20E | '21E | '22E | '23E | '24E | '25E |
|---|---|---|---|---|---|---|
| High Revenue | 419 | 72,523 | 654 | 40,752 | 1,859 | 2,632 |
| High EPS (EUR) | (0.34) | 0.80 | (0.24) | 0.31 | (0.43) | (0.39) |
| Low Revenue | 419 | 64,523 | 654 | 34,752 | 1,543 | 2,165 |
| Low EPS (EUR) | (0.35) | 0.69 | (0.25) | 0.21 | (0.40) | (0.36) |

**Company Overview:** Founded in 1997, NOXXON Pharma is a biotechnology company headquartered in Germany that specializes in immuno-oncology therapies. The company leverages its proprietary technology, "Spiegelmer", while developing its product candidates. The company's current pipeline focuses on the tumor microenvironment. There are two product candidates under development for three different indications: (1) NOX-A12 + radiotherapy for first-line brain cancer, (2) NOX-A12 + immunotherapy for metastatic pancreatic and colorectal cancer, and (3) NOX-E36 for pancreatic and lung cancer. The company's product candidates work most effectively in combination with other treatments.

## Innovative approach to targeting the tumor microenvironment

NOXXON Pharma's Spiegelmer technology is an innovative approach that targets the tumor microenvironment by 1) preventing repair of damaged tumors, and 2) breaking the protective wall that excludes immune system cells from the tumor by neutralizing the CXCL12 chemokine, thus allowing the immune cells to destroy the tumor cells. The Spiegelmer technology is being tested in different combinations: with immunotherapy for pre-treated pancreatic and colorectal cancer patients and with radiotherapy for treating first-line brain cancer (glioblastoma and glioma) indications. The technology has the following advantages: 1) Spiegelmers are chemically synthesized compounds that can bind to target molecules with high affinity, similar to the way in which antibodies bind to antigens; 2) they are synthesized in a process that is extensible, in contrast to antibodies which require a complex biological production process; and 3) they are stable and are immunologically passive, offering a good safety profile.

## Encouraging results from Phase I/II study of NOX-A12, in combination with Keytruda® (pembrolizumab), for metastatic pancreatic and colorectal cancers

NOXXON Pharma's study was run on patients who had failed multiple lines of treatment for metastatic pancreatic cancer (average 3 lines) and metastatic colorectal cancer (average 5 lines). The company has reported the results from its Phase I/II study of NOX-A12 in combination with Keytruda® (from Merck & Company/MSD), an anti-PD-1. All patients were confirmed as Micro-Satellite-Stable (MSS), a setting where anti-PD-1 fails.

NOX-A12 was tolerated well, both as a monotherapy and as part of combination therapy, showing a good safety profile. The overall survival rate was 42% at six months and 22% at 12 months. The combination treatment induced a stable disease in 25% of the patients. It induced prolonged time on therapy versus prior therapy for 35% of the patients. Globally, the estimated pancreatic cancer incidence cases in 2018 were 0.46 mn and this is expected to increase to 0.82 mn in 2040, at a CAGR of 2.6%. In the U.S. the number of incident cases is expected to increase from 0.05 mn to 0.08 mn (2018 to 2040), while in Europe the number of cases is expected to rise from 0.13 mn to 0.17 mn during the same period. The estimated colorectal cancer incidence in 2018 was 1.8 mn globally and this is expected to increase to 3.1 mn by 2040, at a CAGR of 2.5%. The incident cases were estimated at 0.15 mn in the U.S. and 0.49 mn in Europe, in 2018. The incidence figures for both indications highlight the large market size. Given the positive results from the Phase I/II study, NOX-A12 could become the second-line treatment for pancreatic cancer and third-line treatment for colorectal cancer.

**NOX-A12, in combination with radiotherapy, undergoing Phase I/II study for brain cancer**

Brain cancer (including glioblastoma and glioma) and cancers of the central nervous system (CNS) present a large market, with an estimated 0.30 mn incidence cases globally in 2018 and an expected 0.44 mn cases in 2040. For the U.S. and Europe, incidence cases were estimated at 0.02 mn and 0.06 mn, respectively, in 2018. NOX-A12 is undergoing Phase I/II trials for the indication in combination with radiotherapy as a first line treatment and has already received orphan drug designation from the U.S. Food and Drug Administration (US FDA) for glioblastoma and from the European Medical Agency (EMA) for glioma, making it a promising and potentially highly profitable drug candidate.

**NOX-A12 under evaluation by one of the leading pharmaceutical companies of the world**

NOX-A12 is currently being evaluated by one of the top ten pharmaceutical companies in the world, for an undisclosed indication with a market worth more than EUR 1 bn.

**Another product candidate - NOX-E36 to be developed for cancer indications**

There are plans for NOX-E36, previously tested for non-oncology indications, to undergo studies for development for pancreatic and/or liver cancer, after positive results from animal studies were reported. The incidence of this indication are estimated to increase from 0.84 mn to 1.36 mn globally from 2018 to 2040.

**Collaboration with leading pharma companies can potentially help gain access to very large markets**

The company is in talks with leading pharma companies to combine NOX-A12 with their proprietary immune checkpoint inhibitors and develop it as a combination treatment for cancer for multiple indications. The company has already collaborated scientifically with Merck & Company/MSD on developing a combination treatment using Keytruda®, a drug that is currently used as an immunotherapy treatment for multiple cancer indications. With USD 11.1 billion (bn) in worldwide sales, Keytruda® was the second-largest selling drug in the world in 2019, and is indicated for the treatment of several types of cancer including melanoma, non-small-cell and small-cell lung cancer, head and neck squamous cell cancer, classical Hodgkin's lymphoma, as well as gastric, esophageal and cervical cancer. Subject to the successful development of NOX-A12 as a combination therapy, NOXXON can potentially leverage the global reach of Keytruda® (and Merck & Company/MSD) to tap into the huge broader oncology market.

**Licensing deals and partnerships with leading pharma companies globally**

The company aims to market its products in the U.S. and Europe through licensing deals with potential partners. The deals can generate revenue in the form of an upfront fee and/or milestone payments. We assume the company will also earn revenues via royalties. After entry into the U.S. and Europe, the company plans to tap the global market via partnerships with global players or local pharma companies.

**Secured financing of up to ~EUR 21.0 mn to carry out clinical activity into 2022**

The company secured financing of up to EUR 14.2 mn in April 2020 and followed it up with a private placement of approximately EUR 5.5 mn and EUR 1.3 mn, which is expected to allow it to fund clinical activities into 2022, including the NOX-A12/Radiotherapy brain cancer study and the manufacturing of additional drug supply for future trials. The company's fundraising activities not only ensure the development of its pipeline products but also serve as a testament to its potential.

**Valuation and Assumptions[iv]:** Based on due diligence and valuation estimates, Arrowhead believes that NOXXON Pharma's fair market value lies in the EUR 38.0–46.3 mn bracket. We have valued the company using a Risk Adjusted Net Present Value (rNPV) method and company comparable analysis. We have given a 65% weightage to rNPV and 35% weightage to comparable analysis. Our model suggests a fair value bracket of EUR 0.95–1.16 per share.

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## 1. Business Overview[v]

We are initiating coverage on NOXXON Pharma, which is a biotechnology company with a pipeline focused on oncology. NOXXON Pharma has two product candidates, NOX-A12 (for metastatic pancreatic and colorectal cancer, and brain cancer – glioblastoma/glioma) and NOX-E36 (for pancreatic and liver cancer).

NOXXON Pharma, founded in 1997, is headquartered in Germany. It is focused on developing oncology compounds for improving cancer therapies. The company has two compounds in the clinical stages of development for three different indications.

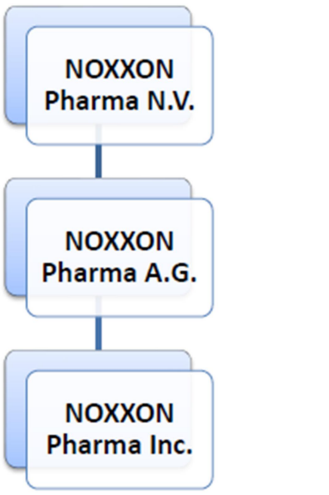
NOXXON Pharma uses its proprietary drug discovery technology, the Spiegelmer platform, to improve the effectiveness of checkpoint inhibitors and other standards of care such as radiotherapy and chemotherapy. The company's approach is to target the tumor microenvironment and thereby disrupt the cancer's ability to defend itself from the immune system, and/or repair itself following anti-cancer therapy.

NOX-A12, the company's leading candidate, is being developed for multiple indications, and for use in different therapeutic combinations. The company has had encouraging data from its Phase I/II study for NOX-A12, used in combination with Keytruda® in heavily pre-treated metastatic pancreatic and colorectal cancer patients who have progressed (i.e. the cancer has continued to develop) after an average 3 lines of therapy in pancreas cancer and 5 lines of therapy in colorectal cancer. NOX-A12 is undergoing another Phase I/II trial, in combination with radiotherapy, for brain cancer as a first-line treatment, and has received orphan drug status in the U.S. from the FDA for glioblastoma and in Europe from the EMA for glioma. The company is also developing another product candidate, NOX-E36, for use in the treatment of pancreatic and liver cancer.

The company is looking to make NOX-A12 a combination partner for a wide range of treatments, and to make it the standard of care, alongside conducting trials for NOX-E36. To achieve this, the company is planning to raise funds and to partner with other companies to accelerate the clinical development and commercialization process.

### 1.1 Corporate Structure[vi]

**Exhibit 1: Corporate Structure**




NOXXON Pharma N.V. is the parent company based in Germany, with two subsidiaries: NOXXON Pharma AG, also based in Germany, and NOXXON Pharma Inc., based in the U.S. (100% subsidiary of NOXXON Pharma AG).

## 1.2 Approach and Technology

NOXXON Pharma's model revolves around developing oncology product candidates for use in combination with other forms of treatment. Currently, the company is conducting studies of its products in combination with immunotherapy and radiotherapy.

The company follows an approach which focuses on the tumor microenvironment, which is the ecosystem in which tumor cells reside. The tumor microenvironment includes blood vessels, immune cells, fibroblasts, and the extracellular matrix; the cells of a tumor communicate with each other and their environment via soluble proteins – chemokines and cytokines. The tumor microenvironment contributes actively to cancer progression, blood vessel growth (angiogenesis & vasculogenesis), spread of tumor, and metastasis.

Chemokines are protein molecules that modulate the movement of cells.[vii] In humans, one function of chemokines is to enable the immune cells to move to the infection site and destroy the invading bodies. However, certain types of chemokines such as CXCL12 can contribute to the proliferation of tumor cells in the human body.[viii] These chemokines lead to tumor growth and send signal to tumor cells that enable them to escape immune system detection and cancer treatments. Chemokines and the tumor microenvironment play a significant role in inhibiting the immune system's response and are an important target of immunotherapy treatments. Certain types of chemokines play an important role in the regrowth of tumors after treatment.

NOXXON Pharma has an innovative approach for treating cancer. NOXXON Pharma's compounds focus on neutralizing key chemokines in the tumor microenvironment. CXCL12, the target of NOX-A12 creates an immunosuppressive tumor microenvironment, by building a 'biochemical' wall, which prevents immune cells from entering the tumor microenvironment. Additionally, it binds with its receptors (CXCR4 and CXCR7) and promotes tumor growth and metastasis. Inhibiting CXCL12 can improve the immune cells' ability to penetrate the tumor environment.

Another important effect of CXCL12 is its pivotal role in the process of vasculogenesis, i.e. the formation of new blood vessels through recruitment of bone marrow-derived cells. This process is fundamentally different from angiogenesis which relies on new blood vessels sprouting from existing vessels. Both vasculogenesis and angiogenesis are induced by hypoxia (lack of oxygen), and both are important processes that lead to regrowth and recurrence of tumors. However, since angiogenesis (which is stimulated by VEGF) requires the presence of intact blood vessels, it is not relevant in irradiated tumors because radiotherapy destroys not only tumor cells but also blood vessels. The resulting hypoxia in the tumor induces increased expression of CXCL12 which recruits building blocks of new blood vessels from the bone marrow, i.e. myeloid cells and endothelial progenitor cells. These cells carry both receptors of CXCL12, CXCR4 and CXCR7. By inhibiting the interaction of CXCL12 with its receptors, NOX-A12 thus prevents the regrowth (recurrence) of the tumor and makes the treatment with radiotherapy more effective and sustainable.[ixxxi]

## 1.3 Proprietary Technology

NOXXON Pharma's proprietary technology generates compounds called Spiegelmers, which are mirror-image oligonucleotides consisting of L-stereoisomer RNA or L-stereoisomer DNA and hence, have stereochemistry which is the mirror-image of that of naturally occurring RNA or DNA.

Spiegelmers can bind to target molecules with high affinity, in a similar way to how antibodies bind to antigens. However, they are synthesized in a chemical synthesis process that is extensible, in contrast to antibodies which require a complex biological production process. Spiegelmers are stable and are immunologically passive, offering a good safety profile, as proven in the NOX-A12 and NOX-E36 studies.

**Exhibit 2: Spiegelmers – mirror image of oligonucleotides**

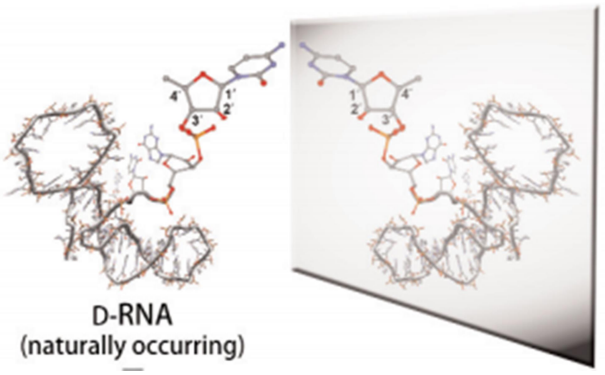
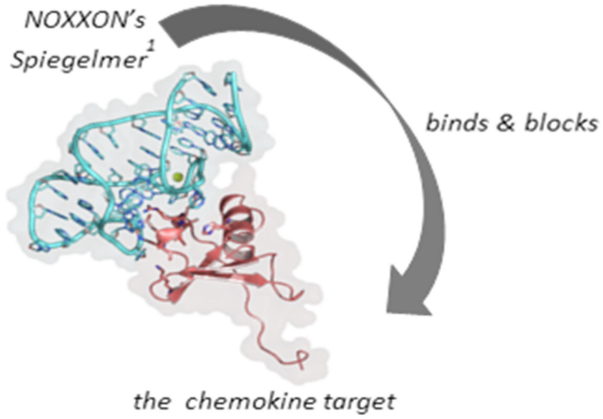



**Exhibit 3: Spiegelmers bind to the chemokine targets**




Spiegelmers bind with and neutralize the protein targets, such as chemokines, preventing cancers from manipulating these molecular "signposts" in the body that guide moving cells.

Chemokines have two distinct functional domains. With the first domain, they anchor themselves to cell surfaces in tissue to form a chemotactic concentration gradient that directs the migration of cells. The second domain binds and activates their receptors on the migrating cells.

The Spiegelmers NOX-A12 and NOX-E36 both bind to the two domains of their respective target molecule. They prevent the interaction of chemokines (CXCL12 and CCL2, respectively) with their receptors - CXCR4 and CXCR7 in the case of NOX-A12, and CCR2 for NOX-E36. In addition, both Spiegelmers strip the chemokines from cell surfaces, destroying the chemotactic concentration gradient. As a result, they are very efficient in preventing the migration of cells that are responsive to these chemokines. This dual action of the two compounds puts them in a dominant position when compared with pure receptor antagonists, such as the receptor antagonist Mozobil (a therapy approved for patients with non-Hodgkin lymphoma) which only acts on CXCR4 but doesn't disrupt the CXCL12 gradient.[xiixiii]

### 1.4 Key Programs and Catalysts

NOXXON Pharma has two compounds in the pipeline:

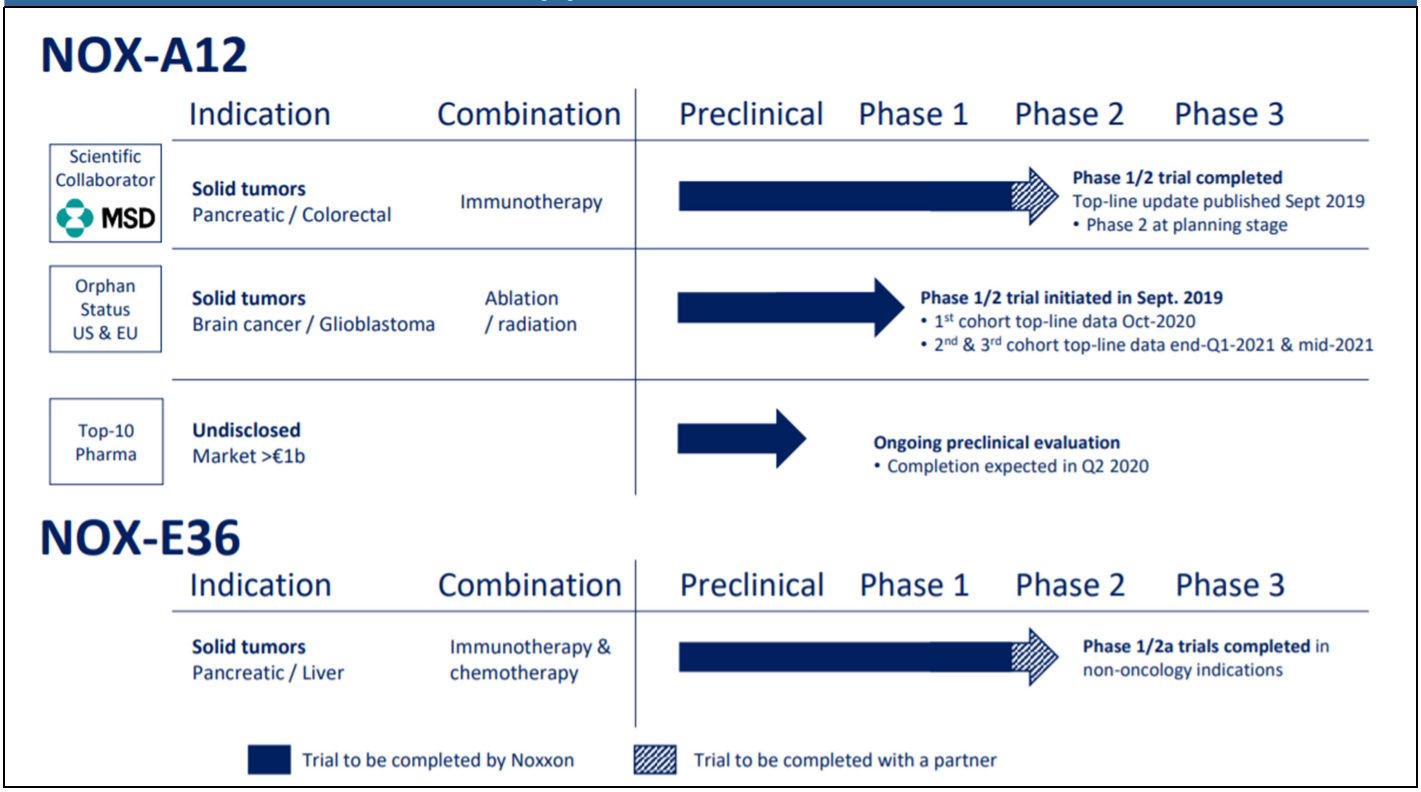
- NOX-A12: The compound, in combination with radiotherapy for brain cancer, is undergoing a Phase I/II trial (conducted on three dose cohorts) with the data on the third cohort expected in mid-2021.

- NOX-A12, in combination with Keytruda®, showed positive results in a Phase I/II study for metastatic pancreatic and colorectal cancer. The company is planning to progress to the next stage of development.

Additionally, NOX-A12 is undergoing a preclinical evaluation by one of the global top ten pharmaceutical companies an undisclosed indication with a market worth reported to be over USD 1 bn.

NOX-E36 is NOXXON Pharma's second clinical-stage product candidate. NOX-E36 has prior positive data in non-oncology indications. NOXXON Pharma is planning to develop NOX-E36 for pancreatic and/or liver cancer. While the Phase I/IIa trials for NOX-E36 have been completed by NOXXON in non-oncology indications, the route to the next stage of Phase II trials is expected to begin with the company engaging a potential partner.

**Exhibit 4: NOXXON Pharma's clinical pipeline**




### 1.4.1 How NOX-A12 works[xiv]

NOX-A12 is NOXXON Pharma's leading candidate and is being developed for multiple cancer indications in combination therapy with other leading drug candidates. NOX-A12 works as a CXCL12 (chemokine) inhibitor. CXCL12 acts as a communication channel between the tumor environment and tumor cells, and promotes tumor proliferation, new blood vessel formation and metastasis. NOX-A12 binds to two key sites in CXCL12 in order to neutralize it. CXCL12 also acts as a chemoattractant for myeloid and endothelial cells, which in turn, leads to regrowth of the tumor.

**Exhibit 5: CXCL12 prevents anti-cancer immune cells from getting into contact with tumor cells and thus inhibits tumor cell killing**

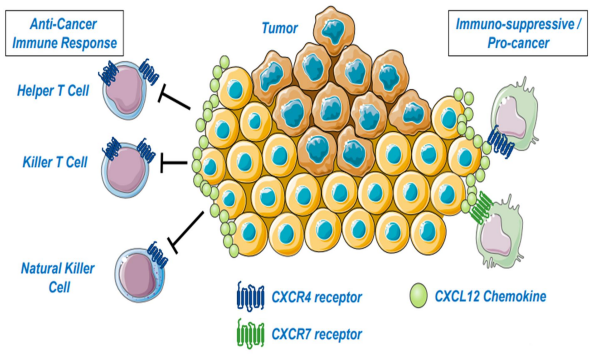
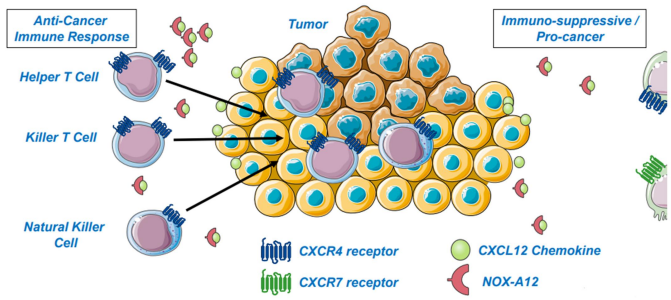



**Exhibit 6: NOX-A12 acting on CXCL12 chemokine**




CXCL12 binds and activates the receptor CXCR4 (involved in tumor cell growth, survival and metastasis), which leads to proliferation of tumor cells, angiogenesis/vasculogenesis (growth of new blood vessels leading to tumor growth), and migration of cancer cells.

CXCL12 establishes an immunosuppressive tumor microenvironment and manages to keep the T-cells out of the tumor microenvironment (by building up a biochemical wall). CXCL12 has another receptor, CXCR7 (involved in tumor cell growth, survival and neovascularization), which it binds to promote tumor cell growth and metastasis.[xv] NOX-A12, binds to CXCL12, preventing it from binding to CXCR4 and CXCR7, and breaks down the biochemical wall, allowing T-cells to enter the tumor microenvironment and attack the tumor cells.

Treatment methods such as radiotherapy have been proven to be effective in killing tumor cells and starving tumors by destroying their blood vessels. However, tumors tend to recur by re-growing tumor cells and by re-establishing their blood supply through the process of vasculogenesis. This process is a response of the tumor to hypoxia (lack of oxygen supply in the tumor) which follows the radiotherapy: under hypoxic conditions, tumor cells produce large amounts of CXCL12 which directs repair cells to the tumor in order to form new blood vessels. NOX-A12 neutralizes CXCL12, preventing the process of vasculogenesis, and consequently, the recurrence of the tumor.[xvixviixviiixixxx]

NOX-A12 provides a novel and more effective approach to treat cancer indications which have low survival rates.

**NOX-A12, in combination with Keytruda®, is being tested for metastatic pancreatic and colorectal cancer.**

**Pancreatic Cancer[xxixxiixxiii] and Colorectal Cancer[xxiv]**

In early-stage pancreatic cancer, the tumor is limited to the pancreas itself, but in advanced stages (Stage IV or metastatic) it can spread to distant organs like the liver, lungs, bowel, spleen, and the stomach. It is a tumor with very poor prognosis, with a 5-year survival rate of 9% for all stages combined.

Although in its early stages the cancer can be resected which leads to better prognosis, the majority of patients present with metastatic, non-resectable disease at diagnosis. Unfortunately, treatment of metastatic pancreatic cancer is only palliative, with the focus on improving the quality of life of a patient.

**Standard of care for pancreatic cancer**

The patient usually undergoes surgery to remove the tumor. However, when the cancer has reached an advanced stage, parts of the tumor are unresectable.

The standard of care for treating pancreatic cancer includes various chemotherapy options as first- and second-line treatments, such as 5-fluorouracil (5FU), leucovorin (folinic acid; LV), irinotecan, and oxaliplatin (FOLFIRINOX) or nab-paclitaxel/gemcitabine. Chemotherapy options, however, are highly toxic, and advanced pancreatic cancer is known to show resistance to them. Targeted therapy options (Erlotinib) are limited, while immunotherapy options (pembrolizumab) are effective only in a small fraction of patients. [xxv]

Colon cancer and rectal cancer are grouped together as they share common characteristics. Colorectal cancer normally starts in the inner lining of the rectum or colon as a growth called 'polyp'. The cancer can grow in the lymph nodes and the distant parts of the body. Metastatic colorectal cancer commonly spreads to the liver and can spread to the lungs, spinal cord and brain.

**Standard of care for colorectal cancer**

Similar to pancreatic cancer, surgery is the first step in the treatment of colorectal cancer. To treat the unresectable part of the tumor, the standard of care for colorectal cancer includes chemotherapy options such as capecitabine (Xeloda), fluorouracil (5-FU), irinotecan (Camptosar), oxaliplatin (Eloxatin), trifluridine/tipiracil (Lonsurf). Targeted therapy options include cetuximab (Erbitux), bevacizumab (Avastin), regorafenib (Stivarga), or panitumumab (Vectibix). The drugs may be used in combination with each other or in combination with immunotherapy options such as pembrolizumab (Keytruda), nivolumab (Opdivo), and nivolumab and ipilimumab (Yervoy).[xxvi]

**Market**

The global market for pancreatic cancer treatment stood at USD 1.9 bn in 2017 and is expected to grow to USD 4.7 bn by 2026 at a CAGR of 10.7%. The global market for colorectal cancer treatment stood at USD 13.7 bn in 2018 and is expected to grow to USD 18.5 bn by 2024 at a CAGR of 6.1%.

The growing market, combined with scope for better treatment methods, provides a sizeable market opportunity for NOXXON Pharma. It can capitalize on this due to its proprietary superior technology and its approach.

**NOXXON Pharma's treatment of microsatellite-stable, metastatic pancreatic and colorectal cancer in collaboration with Merck & Company/MSD**

NOXXON Pharma has collaborated with Merck & Company/MSD (one of the leading pharma players) to use Keytruda®, a checkpoint inhibitor which blocks the programmed cell death protein 1 (PD-1) pathway. PD-1 is a protein which is present on immune cells and acts as an "off switch" to prevent immune cells from attacking the other cells in the body. Programmed death-ligand 1 (PD-L1) is a protein on tumor cells that interacts with PD-1, "pressing the 'off switch'" and preventing T-cells from attacking tumor cells. Keytruda® blocks the pathway of PD-L1, preventing it from attaching to PD-1 and allowing immune cells to do their job and attack the cancer cells. Keytruda® is approved for various cancer indications.

**Immune checkpoint inhibitors**

Immune checkpoint inhibitors (ICI) have historically proven to be ineffective as a monotherapy in metastatic pancreatic and colorectal cancer, due to an immunosuppressive tumor microenvironment. Although there is a small subpopulation of patients that benefit from ICI treatment – those whose tumors display microsatellite instability or mismatch repair deficiency – the vast majority of patients (>95%) are "microsatellite stable" and do not profit from such treatment.

One reason for the ineffectiveness of checkpoint inhibitors like Keytruda® is the immunosuppressive environment created by CXCL12 (to which NOX-A12 binds) which prevents immune cells from penetrating the tumor microenvironment, rendering it ineffective.[xxvii]

**About Keytruda®[xxviiixxix]**

Keytruda® is an approved immunotherapy that works with the immune system to fight tumor cells in the human body. It is Merck & Company/MSD's top selling drug and generated sales of USD 11.1 bn in FY 2019. It is currently being used as a treatment for a number of cancer diseases including: melanoma, non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), head and neck squamous cell cancer (HNSCC), classical Hodgkin's lymphoma

(cHL), primary mediastinal large B-Cell lymphoma (PMBCL), urothelial carcinoma, microsatellite instability-high cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma (HCC), Merkel cell carcinoma (MCC), renal cell Carcinoma (RCC) and endometrial carcinoma. The drug is also being used in combination with chemotherapy and other forms of treatment for several of the above-mentioned indications. However, the immune system released by the drug, during the course of the treatment or after the treatment, can also attack healthy organs and tissues in the body, thus affecting their normal functionality which can sometimes be life-threatening.

NOX-A12, by binding the CXCL12 chemokine and breaking the protection wall it creates, allows immune cells (T-cells) to penetrate the tumor where Keytruda® activates them to attack the cancer cells. In microsatellite stable, metastatic pancreatic and colorectal cancers Keytruda® is not effective as a standalone cancer therapy, but there is now good evidence from the Phase I/II trial that in combination with NOXXON's compound it can prolong survival.

**NOX-A12 + Keytruda® Phase I/II Study design[xxx]**

The study involved the enrolment of 20 heavily pretreated patients to evaluate NOX-A12 as a monotherapy (Part 1) and subsequently in combination with Keytruda® (Part 2). The patients recruited, of whom 11 were metastatic colorectal cancer patients and 9 metastatic pancreatic cancer patients, had the following demographics (PD is Progressive Disease, SD is Stable Disease, MSS is microsatellite-stable):

**Exhibit 7: Demographics of patients enrolled**

| | Colorectal Cancer | Pancreatic Cancer |
|---|---|---|
| N | 11 | 9 |
| Male/Female | 7 / 4 | 8 / 1 |
| Age, mean (range) | 63 (55 – 73) | 67 (48 - 82) |
| Stage at study entry | 100% stage IV (metastatic) | |
| Microsatellite status at study entry | All patients MSS | |
| Prior lines of systemic treatment, mean (range)* | 5 (2 – 9) | 3 (1 – 5) |
| Patients with prior surgery (# of surgeries) | 7 (1 – 4) | 3 (1 – 2) |
| Best response last treatment | PD (10), SD (1) | PD (9) |
| Time since last systemic prior treatment (mean) | 2.0 months | 1.5 months |

* excluding surgery

The monotherapy part of the study, which involved treatment for two weeks, was conducted to examine the ability of NOX-A12 to modulate the tumor microenvironment and the safety and tolerability profile of NOX-A12 as a monotherapy treatment. Before and after the monotherapy part, tumor biopsies were collected and analyzed.

After the monotherapy, the patients were switched to treatment with a combination of NOX-A12 and Keytruda® until tumor progression or intolerable toxicity, with the objective of evaluating the safety and tolerability (primary) of the treatment, along with the efficacy of the treatment.

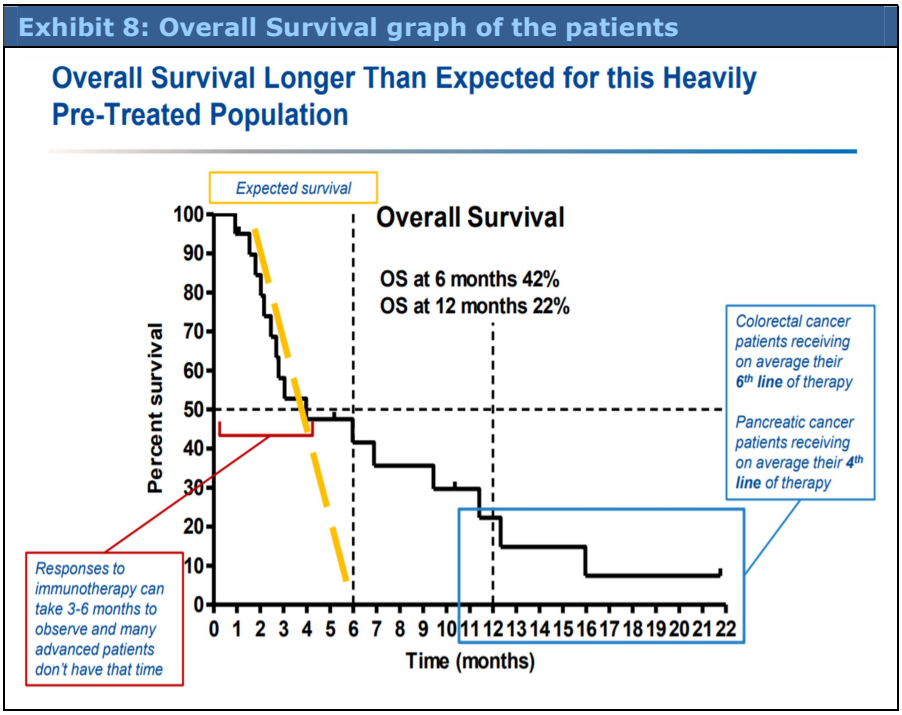
**Monotherapy results[xxxi]**

- NOX-A12 was able to infiltrate the tumor tissue in metastatic pancreatic and colorectal cancer.
- A comparison in cytokine levels before and after the study revealed that NOX-A12 induces a Th-1-like immune response in approximately 50% of the patients with analyzable biopsies.
- A correlation was found between the degree of target inhibition in tumor tissue and the changes in the cytokine and chemokine immune profiles.
- A potential biomarker for predicting immune response on use of NOX-A12 was identified: a cell population, double-positive for the surface markers CD14 and CD15.

**Combination study**[xxxii]

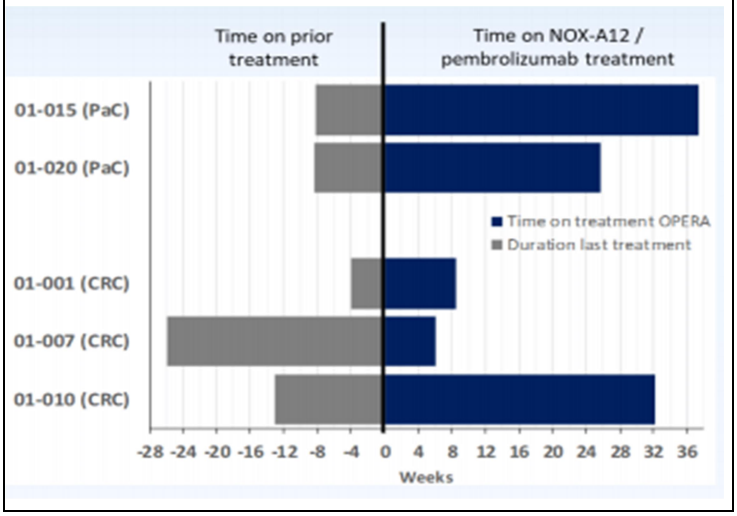
- Of the patients alive after three months, 70% were alive at 24 weeks and 50% were alive at 36 weeks. Overall survival was 42% at 6 months and 22% at 12 months.

**Exhibit 8: Overall Survival graph of the patients**




- A high number of patients, who had progressed quickly on prior therapy and had a best response to prior therapy of progressive disease, were able to stay on this therapy for an extended time and achieved stable disease status. 25% of the patients in the trial achieved stable disease compared to 5% of the patients during their therapy just prior to trial entry.

**Exhibit 9: Time on prior therapy versus time on NOX-A12**



**Conclusion**[xxxiii]

1. NOX-A12 monotherapy, as well as the combination of NOX-A12 + Keytruda®, was tolerated well and had a good safety profile.
2. The overall survival data, prolonged time on therapy, and ability to induce a stable response were impressive, especially given that the patients were at a highly advanced stage (with metastatic colorectal patients having undergone a mean of five lines of prior therapy, and metastatic pancreatic patients having undergone a mean of three lines of prior therapy) and the best response to prior therapy for 95% of the patients was disease progression.
3. NOX-A12 was able to modulate the immunosuppressive environment, allowing Keytruda® to take effect.

The results from the study were encouraging and warrant the progression of NOX-A12 to the next phase of development in the indications.

In addition to that, the results from the monotherapy study give an indication of the potential of NOX-A12 to be used in combination with other treatment methods for various other oncological indications.

**Developments**[xxxiv]

NOXXON Pharma, after positive results from the prior study, is looking to conduct larger-scale randomized trials with less-advanced patient populations, hoping to gain approval from the FDA for second-line treatment for pancreatic cancer and third-line treatment for colorectal cancer by 2026.

The company has started having discussions with possible partners with whom it could continue the development of the therapy and move to the next phases of the study.

**NOX-A12/radiotherapy in Brain cancer indication**[xxxv]

Tumors in the brain can be primary or secondary. Primary tumors start in the brain and can be low-grade (growing slowly) but can transform into high-grade (growing quickly). Secondary tumors have their origin in other parts of the body (such as the breast, lung, or colon) and then spread to the brain. Gliomas are tumors that grow from glial cells or glial precursor cells, and are found in the spinal cord or the brain. Glial cells are supportive cells in the brain that help hold the nerve cells in place, supply oxygen and nutrients to neurons, destroy pathogens and remove dead neurons and allow them to perform their proper functions. Gliomas can be sub-divided into astrocytoma, oligodendroglioma, or ependymoma. Astrocytoma is more common than other gliomas and is more common in children. Astrocytoma cells are cells that look like astrocytes that are found in the cerebellum or cerebrum. Glioblastoma is an aggressive form of astrocytoma (Stage IV).

NOXXON Pharma is targeting the most aggressive form of brain cancer, i.e., patients affected with glioblastoma, through a combination treatment of NOX-A12 plus radiotherapy.

**Standard of care for glioblastoma**

The standard of care for glioblastoma includes, a) surgery to resect the maximum possible amount of the primary tumor, followed by b) radiotherapy, and c) chemotherapy (temozolomide). It is known that approximately 50% of patients with the biomarker "unmethylated MGMT promoter" detectable prior to treatment will not benefit clinically from the temozolomide chemotherapy. Consequently, chemotherapy can be left out of any clinical trial targeting unmethylated MGMT promoter patients.

Although the standard of care can modestly prolong survival, glioblastoma almost inevitably recurs in nearly all patients, reiterating the need for better treatment methods.[xxxvi]

**Market**

The global market for brain tumor therapeutics is expected to increase to USD 2.7 bn between 2018 and 2023 at a CAGR of 11%. The market for glioblastoma, which is a huge part of the total market, is expected to increase from USD 997.0 mn in 2018 to USD 1.7 bn in 2025 at a CAGR of 7.4%.

**NOX-A12 for glioblastoma in combination with radiotherapy**[xxxviixxxviiixxxix]

NOXXON Pharma is conducting a Phase I/II study of NOX-A12 in brain cancer (glioblastoma) with radiotherapy, after having successfully conducted studies in animals. NOX-A12 has received orphan drug designation from FDA in the U.S. for glioblastoma with radiotherapy, and from the EMA in Europe for glioma. NOX-A12 helps to improve anti-cancer activity by preventing tumor repair after radiotherapy.

Glioblastoma tends to recur in almost all of the patients, explaining the poor prognosis associated with it.

Radiotherapy destroys the tumor cells and damages the tumor vasculature, further preventing angiogenesis in the process.

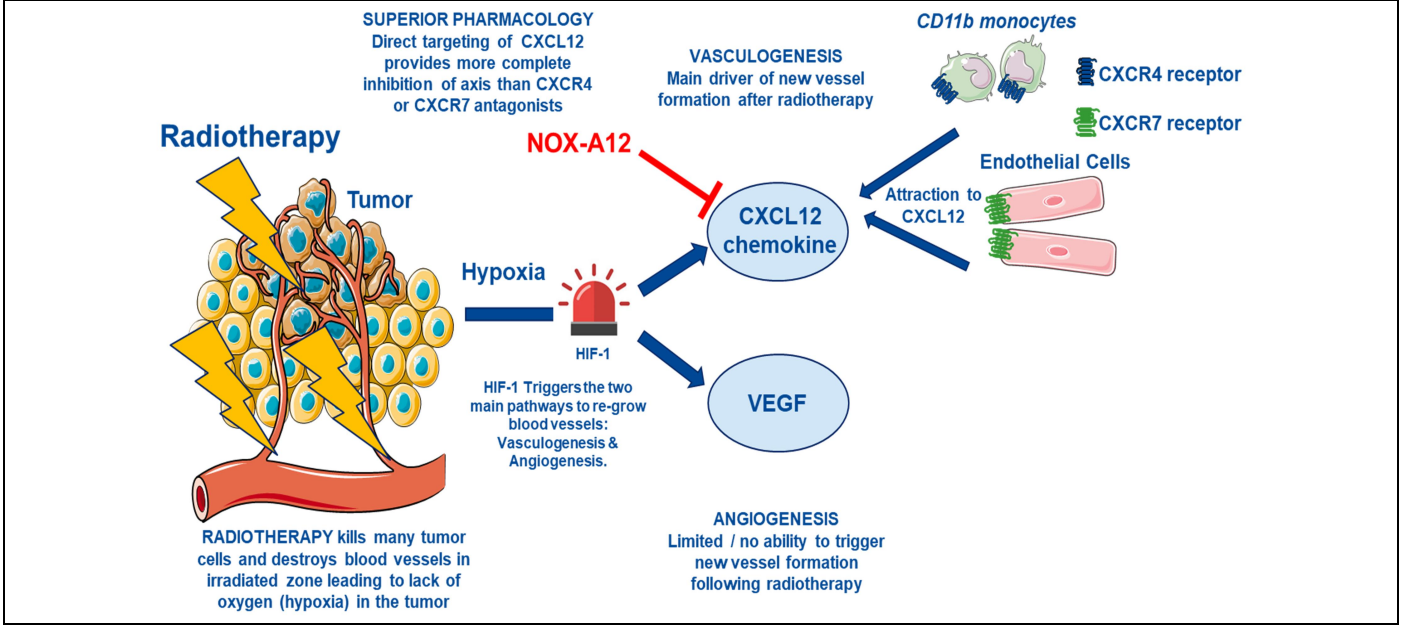
However, tumor irradiation leads to tumor hypoxia (lack of oxygen in the tumor cells), which, in turn, increases levels of Hypoxia-Inducible Factor-1 (HIF-1), a transcription factor that responds to hypoxia in the tumor by upregulating CXCL12. Then, CXCL12 attracts myeloid cells (through CXCR4) and endothelial cells (through CXCR7) from the bone marrow, which, in turn, leads to the formation of new blood vessels. The process is called vasculogenesis and it leads to regrowth and recurrence of glioblastoma in nearly all of the patients.

NOX-A12 inhibits CXCL12, and not just one of the receptors, blocking the CXCL12-CXCR4 pathway and CXCL12-CXCR7 pathway. This impedes the process of vasculogenesis and prevents the tumor from re-growing and recurring. Thus NOX-A12, in combination with radiotherapy, can provide a more effective treatment option than the current first-line standard-of-care treatment in glioblastoma.

The orphan drug designation provides NOXXON Pharma with regulatory support and monetary benefits for the development of the therapy.

NOXXON Pharma progressed to Phase I/II of the study of NOX-A12 for glioblastoma in combination with radiotherapy after animal models showed that NOX-A12 works on CXCL12 and can prevent the recurrence of brain tumors after treatment with radiotherapy.

**Exhibit 10: NOX-A12 prevents recurrence of glioblastoma**



**Study Design**[xl]

The study involves the enrolment of nine first-line glioblastoma patients divided into three cohorts (of three patients each) to evaluate NOX-A12, in combination with radiotherapy in a Phase I/II study.

The first, second and third cohort patients will receive three different doses of NOX-A12 (200, 400 and 600 mg/week, respectively) for a period of six months. In May 2020, patients were being recruited for the middle dose cohort, i.e., 400 mg/week.

**Developments**[xli]

The data from the study for the first, second and third cohorts are expected in October 2020, Q1 2021 and mid-2021, respectively.

NOXXON Pharma has started discussions with possible partners and investors for the development of the therapy and its commercialization, and will look to secure a partnership/investment in 2021. NOXXON Pharma, having already been granted the orphan drug designation status for the indication, will look to expedite the process of gaining FDA approval for the therapy through a single trial after the completion of the current trial. Following successful studies, **NOXXON Pharma could gain FDA approval by 2025.**

**Potential in non-small-cell lung cancer**

The company is part of a consortium, along with a number of university clinicians who have applied to the EU for financing for a Phase I/II study of NOX-A12 in patients with non-small-cell lung cancer who have progressed on Anti PD-1/PD-L1 checkpoint inhibition. Preliminary work in untreated patients with non-small-cell lung cancer suggested that the areas in which T-cells are excluded correspond with areas with high CXCL12 expression. Patients who have such areas of exclusion (of T-cells) can be treated with Anti PD-1/PD-L1 checkpoint inhibition plus NOX-A12. If the results of the study are positive, the company will look to seek advice from competent authorities for development of NOX-A12 and Anti-PD1/PD-L1 for this indication.

### 1.4.2 NOX-E36

NOXXON Pharma's second product candidate NOX-E36 is being developed for pancreatic cancer and liver cancer as a monotherapy or in combination with some other form of treatment.

**Liver cancer**[xlii]

Liver tumors can be primary cancer or secondary/metastatic cancer, i.e., have spread from other parts of the body to the liver; in fact, most tumors in the liver are metastases of primary tumors in other organs. Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, and affects 75% of the primary liver cancer patients. 83% of all new cases of HCC (2012) were reported in low- and middle-income countries. Another type of liver cancer known as cholangiocarcinoma (which develops from cells in the bile duct of the liver) affects about 10%-20% of primary cancer patients. About 1% of primary liver cancers in adults are angiosarcomas (start in the blood vessels of the liver).

**NOX-E36**[xliii]

NOX-E36, a chemokine inhibitor, works on CCL2 and some related chemokines, CCL8, CCL11 and CCL13. CCL2 chemokine binds to the receptor CCR2 and regulates the movement and infiltration of monocytes/macrophages. Macrophages are white blood cells which locate and ingest foreign material and stimulate other functions of the immune system. CCL2 plays the role of recruiting tumor associated macrophages (TAMs), creating an immunosuppressive tumor microenvironment, and leading to growth of the tumor and angiogenesis. NOX-E36 works by binding to and neutralizing CCL2, preventing the recruitment of TAMs and preventing cancer from growing and spreading. It allows for an improved immune response against cancer.

NOX-E36 has data from Phase I/IIa studies in non-oncology indications which indicate that NOX-E36 has a good safety profile and showcase its ability to target monocytes/macrophages.

NOXXON Pharma, in February 2019, published data related to a series of experiments conducted to check the potential of mNOX-E36, a rodent version of NOX-E36, in liver cancer. The data showed that mNOX-E36 was able to inhibit the infiltration of TAMs, which led to profound changes in the tumor microenvironment, pathological vascularization, and reduction in tumor volume. The data exhibited the effectiveness of mNOX-E36 in heptacellular cancer as a monotherapy.

NOXXON Pharma is planning to conduct studies for the development of NOX-E36 as a monotherapy or as a part of combination therapy in pancreatic and liver cancer.

The strategy to pursue the research program for NOX-E36 is dependent on the company's ability to enter into a partnership with an interested party.

**Discussions for undisclosed indication**

NOXXON Pharma, in addition to the above-mentioned pipeline, is in discussion to use NOX-A12 for an undisclosed indication with a market potential reported to be worth more than EUR 1 bn. The discussions are being held with one of the global top ten pharmaceutical companies. After receiving the study results, the parties may enter into negotiations for the rights to NOX-A12

## 1.5 Financial Overview[xliv]:

**H1 2020**

### Fund raising activities to continue development of product candidates

According to the current business plan, the company expects a cash utilization of EUR 0.4 mn each month, including the costs of the NOX-A12/Radiotherapy study for brain cancer. In order to meet the cash requirements, the company raised a total of EUR 1.0 mn at the beginning of 2020 in two separate private placements of EUR 0.5 mn each, at a price of EUR 0.51 per share, from two different groups of European investors. The company followed this up by securing access to a convertible bond financing vehicle with capacity of up to EUR 14.2 mn (gross amount before issuance discount and transaction fees) from Atlas Special Opportunities (ASO) LLC. The company will have access to capital through 21 tranches, as well as to additional tranches for drug manufacturing, through issuance of convertible bonds to ASO. The first tranche, which the company accessed in April, is EUR 1.3 mn. The second tranche received in May 2020 was EUR 475k, and the remaining tranches will also be EUR 475k each. The additional tranches for drug manufacturing for clinical studies will total EUR 3.4 mn, and will be subject to the achievement of certain milestones:

The company further raised ~EUR 5.5 mn in May 2020, from a private placement to European investors through an accelerated bookbuilding process. The company followed it up by raising EUR 1.3 mn in June 2020 by issuing 2,245,000 shares to European investors at a price of EUR 0.58 per share.

The financing is expected to allow NOXXON Pharma to fund its clinical activities including the NOX-A12/Radiotherapy brain cancer indication study and manufacturing of additional drug supply for other studies until the beginning of 2022. This also allows NOXXON to spread out the timing of draws from the convertible bond vehicle, which should reduce pressure on the share price.

**FY 2019**

### Decrease in operating expenses as personnel expenses fell on lower share-based payments

Research and Development (R&D) expenses decreased by 4.4% YoY to EUR 2.1 mn in FY 2019. The increase in costs of production for drug substances and other costs related to preclinical and clinical studies, along with higher patents and consulting services costs, were offset by lower personnel costs.

General and Administrative expenses decreased by 15.1% YoY to EUR 2.1 mn. Higher legal, consulting and audit fees partly offset the lower personnel expenses and public relations expenses, which caused the decline.

Lower personnel expenses in FY 2019 were partly due to a decrease in share-based payments made to employees, by 72.8% YoY to EUR 0.1 mn.

### Net financial income saw a significant increase

Financial income (non-cash) saw a substantial increase in FY 2019 to EUR 3.1 mn (from EUR 0.4 mn in FY 2018) as a decrease in exercise price of warrants reduced the financial liability due to Acuitas by EUR 3.0 mn. The rest was

contributed by changes in the fair value of warrants of Yorkville and other investors, and the exercise of warrants by Acuitas.

Financial costs (non-cash) decreased to EUR 3 k in FY 2019 from EUR 6.8 mn. The high Financial costs in FY 2018 were due to an increase in the fair value of financial liabilities, high financial costs due to notes issued to Yorkville, the consideration paid for cancellation of warrants, and the costs of issuing convertible bonds.

### Lower expenses led to substantial decline in net loss

The fall in operating and non-operating expenses of the company saw its net loss shrink to EUR 0.9 mn in FY 2019 from EUR 10.7 mn in FY 2018.

### Change in nominal value of shares led to decrease in issued capital and increase in share premium

The company reduced the nominal value of its shares from EUR 1.0 to EUR 0.01, which led to a fall in the issued capital to EUR 131 k from EUR 10.1 mn. The decrease was adjusted by adding it to additional paid-in capital account which increased to EUR 29.7 mn in FY 2019 from EUR 18.1 mn in FY 2018.

The current financial liabilities fell to EUR 1.6 mn in FY 2019 from EUR 4.7 mn in FY 2018, due to a decrease in the exercise price of warrants of Acuitas, which led to a fall in the amount due to them.

### Minimal fund-raising activities reduced cash and cash equivalents

The company raised EUR 1.5 mn in FY 2019 through a rights issue and private placement, as compared to EUR 7.8 mn raised in FY 2018. The slowdown in fund-raising activities led to a decline in cash and cash equivalents to EUR 1.4 mn in FY 2019 from EUR 4.3 mn in FY 2018.

**FY 2018**

### Increased outsourcing of manpower lowered R&D and G&A expenses

The R&D expenses were lower by 8.5% YoY at EUR 2.2 mn in FY 2018, from EUR 2.4 mn in FY 2017, mainly on account of a 25.3% YoY decrease in personnel expenses due to increased outsourcing of clinical activities and a decrease in staff numbers.

The G&A expenses were EUR 2.5 mn, down by 3.4% YoY from EUR 2.6 mn in FY 2017, due to a 45.7% YoY decrease in legal, consulting and audit fees.

### Non-cash finance income and finance-cost

The non-cash finance income in FY 2018 was lower by 61.9% YoY at EUR 0.4 mn, The company's finance cost rose to EUR 6.8 mn in FY 2018 a rise of 302.7% YoY, from EUR 1.7 mn in FY 2017, primarily due to the revaluation of financial liability by EUR 2.1 mn to the fair value of EUR 4.7 mn, and a cost of EUR 2.6 mn incurred on issuing new notes (EUR 1.2 mn) and shares (EUR 1.3 mn notes converted to shares) and warrants (EUR 1.2 mn) to Yorkville.

The finance costs also included a cost of EUR 0.8 mn incurred in relation to the modification of an issuance agreement with Yorkville, a cost of EUR 0.5 mn incurred against the issuance of convertible bonds and shares to other investors, and issuance of shares (debt conversion) of EUR 0.4 mn in relation to venture loans (raised from Kreos Capital).

Higher finance-costs increased the net loss for NOXXON to EUR 10.7 mn in FY 2018, an increase of 99.2% YoY.

### Issue of shares raised cash for clinical trials

The company issued a total of 7.8 mn ordinary shares that raised the subscribed capital and additional paid-in capital by EUR 7.8 mn and EUR 5.4 mn (excluding 0.07 mn of issuance costs), respectively. The cash inflow from financing activities increased by 201.5% YoY from EUR 2.5 mn in FY 2017 to EUR 7.6 mn in FY 2018, driven by proceeds from issuance of shares, warrants and convertible bonds.

### 1.6 Company Milestones

| Exhibit 11: NOXXON Pharma's milestones | |
|---|---|
| **Year/ Period** | **Event** |
| **2010** | • Raised EUR 35 mn under series D round of financing<br>• Initiated multiple-dose phase I clinical trial of SDF-1 inhibitor NOX-A12<br>• Received permission to begin Phase Ib clinical trial of MCP-1 Inhibitor NOX-E36<br>• Announced successful competition of first-in-human clinical trial with Spiegelmer® NOX-A12 |
| **2011** | • Completed phase I single- and multiple-dose clinical trials of SDF-1 inhibitor NOX-A12 |
| **2013** | • Presented interim data for Spiegelmer® olaptesed pegol (NOX-A12) in CLL and MM studies at the American Society of Hematology (ASH) 2013 |
| **2014** | • Presented Phase IIa results for Spiegelmer® olaptesed pegol (NOX-A12) in MM and CLL at ASH 2014<br>• Received orphan drug designation for olaptesed pegol (NOX-A12) from FDA |
| **2016** | • Signed an agreement with Merck & Company to study NOX-A12, combined with Keytruda®, for the treatment of pancreatic and colorectal cancer<br>• Presented preclinical data showing synergy of NOX-A12 with natural killer cell mediated therapies at ASH conference<br>• Presented the data for CXCL12 inhibition by NOX-A12 at the ESMO<br>• Listed the shares of the company on Alternext Paris |
| **2017** | • Issued ODIRNANE bond of EUR 2 mn<br>• Announced the treatment of first patients in Phase I/II clinical trial of NOX-A12/Keytruda®<br>• Signed an agreement with National Center for Tumor Diseases for NOX-A12/Keytruda® Phase I/II combination trial<br>• Converted Kreos debt of ~EUR 0.84 mn into 54,263 ordinary shares at EUR 15.5 per share<br>• Raised EUR 1 mn through private placement of shares |
| **2018** | • Issued ODIRNANE bond of EUR 0.9 mn<br>• Raised EUR 6.2 mn through equity financing and ~EUR 0.6 mn by issuing convertible bonds to existing investors |
| **2019** | • Announced the safety results for the first brain cancer patient, who reached 10 weeks of treatment by NOX-A12 & Radiotherapy<br>• Started recruitment of patients for Phase I/II clinical trial combining NOX-A12 and Radiotherapy for the treatment of brain cancer<br>• Raised EUR 1 mn through private placement of shares<br>• Launched a rights issue financing for an amount of up to EUR 3.9 mn, and raised ~EUR 0.52 mn<br>• Signed agreement with leading pharmaceutical company to evaluate NOX-A12 in new indication<br>• Filed an application for Phase I/II clinical trial combining NOX-A12 & Radiotherapy for the treatment of brain cancer with the Federal Institute for Drugs and Medical Devices |
| **2020** | • Raised EUR 1.3 mn through a private placement to European investors<br>• Raised EUR 6.5 mn in three separate private placements to European investors<br>• Approval received to recruit patients for second dose of NOX-A12 in NOX-A12/Radiotherapy brain cancer study after the completion of the first dose cohort with good safety data<br>• Secured financing of EUR 14.2 mn, to be received in tranches by issuance of convertible bonds to Atlas Special Opportunities LLC |

## 1.7 Corporate strategy and future outlook

### 1.7.1 Strategy[xlv]

NOXXON Pharma's long-term strategy is to focus on the development and commercialization of its product candidates.

In the short run, NOXXON Pharma will look for suitable partners/investors to help in the development of its NOX-A12 and NOX-E36 product candidates. The company is expected to focus more on the development of NOX-A12 in combination therapies for multiple cancer indications.

The company, with its impressive pipeline, has garnered interest from Merck & Company/MSD. It is in discussion with other pharmaceutical companies in the world to test NOX-A12 and NOX-E36 in combination with their treatment methods to make possible advances on the current standards of care for different indications. The partnerships can be on a profit-sharing basis or on a royalty payment basis. The company may also receive upfront and/or milestone-based payments depending on the structure of the deal. NOXXON Pharma will also look to secure non-dilutive funding from investors for the development of its product candidates.

NOXXON Pharma will look to obtain approvals and commercialize its product candidates in the U.S. and Europe, before expanding into other geographies, possibly through a licensing deal with either a global or local pharma company.

### 1.7.2 Outlook

NOXXON Pharma will look to finalize a partnership in 2020 to conduct a further trial for NOX-A12 for metastatic pancreatic and colorectal cancer. After conducting a further study, the company will file for an approval from FDA, in order to develop it as the second-line treatment in pancreatic cancer and third-line treatment in colorectal cancer.

NOX-A12 is undergoing a Phase I/II study, in combination with radiotherapy, for glioblastoma. The company is conducting the study on the first cohort of patients, with recruitment process for the second cohort in progress. Data from the first cohort, second cohort and the third cohort are expected in October 2020, Q1 2021 and mid-2021, respectively. NOXXON Pharma will consult the authorities for its orphan drug designation in the U.S. and Europe on how to proceed further with the development of the product candidate. The company will, however, look at a partnership agreement for NOX-A12 in glioblastoma.

NOXXON Pharma will also look to develop its second product candidate, NOX-E36, for pancreatic and liver cancer. The company is planning to conduct a study for the development of NOX-E36 in those indications.

The impact of the COVID-19 pandemic on the operations and finances of the company has been manageable. After a thorough evaluation as requested by the European Medicines Agency (EMA), NOXXON Pharma has decided to continue he treatment of patients enrolled in the NOX-A12/Radiotherapy study in all centers, in addition to continuing recruitment of new patients in two of the three centers. In response to the delay in recruitment caused by COVID-19, the company is expected to add new centers to guard against more potential delays. The company is also likely to continue to engage with investors in Europe, the U.S. and Asia, with a preference for raising capital through equity financing. During the turbulent market conditions in April and May, the company obtained commitments through an alternative financing vehicle and a private placement in order to guarantee access to financing for its clinical trials.

## 1.8 Company premiums[xlvi]

**Greater scope due to poor prognosis:** Low survival rates are associated with metastatic pancreatic, colorectal and glioblastoma/glioma/cancers. This indicates the inability of the current standards of care to effectively provide a treatment for the indications, presenting opportunities in the markets for new approaches and treatments, on which NOXXON Pharma can capitalize.

**Huge potential:** The NOX-A12 monotherapy lead-in period in NOXXON Pharma's Phase I/II study in metastatic pancreatic and colorectal cancer patients highlighted the ability of NOX-A12 to modulate the tumor microenvironment (inducing a Th-1-like immune response in approximately 50% of the patients). The results from the study brought forward the potential and versatility of NOX-A12 to be used in combination with other treatment options for various other oncological indications.

**Unique approach and proprietary technology:** NOXXON Pharma's approach is novel and unique, allowing it to address the unmet needs in treatment of the targeted indications. The company's product candidates focus on targeting the tumor microenvironment, which, as a part of a combination therapy, could be groundbreaking. The proprietary technology, which allows NOXXON Pharma to produce compounds called 'Spiegelmers', gives it a competitive advantage. Spiegelmers' characteristics allow them to be considered as an upgrade to antibodies: (i) they can bind to target molecules with high affinity, similar to the way in which antibodies bind to antigens; (ii) Spiegelmers are synthesized via a chemical synthesis process that is extensible, while antibodies require a complex biological production process; (iii) Spiegelmers are stable and are immunologically passive, offering a good safety profile.

**Promising pipeline:** NOXXON Pharma's pipeline consists of its two product candidates, NOX-A12 and NOX-E36. NOX-A12 has already completed a Phase I/II trial in combination with Keytruda® (developed by Merck & Company/MSD) for metastatic pancreatic and colorectal cancer indications, reporting promising results. NOX-A12, additionally, is in a Phase I/II trial, in combination with radiotherapy, for brain cancer (glioblastoma), having received orphan drug designation from in the U.S. and in Europe. NOX-E36, NOXXON Pharma's second product candidate, has shown encouraging signs in animal studies for liver cancer. It will likely be developed for pancreatic or liver cancer. Additionally, NOXXON Pharma's NOX-A12 is being tested by one of the top ten pharmaceutical companies in the world for an undisclosed indication with a market reported to be over EUR 1 bn.

**Experienced management personnel:** Between them, NOXXON Pharma's CEO and Senior Medical Advisor have over forty years of experience in the biotechnology industry, having played pivotal roles in the clinical development and commercialization of various drugs and therapies.

## 1.9 Company risks[xlviixlviii]

**Safety risk associated with polyethylene glycol:** The compound is a water soluble and biocompatible polymer, which has been used for drug delivery. Therapeutic agents containing polyethylene glycol, developed by other companies, have had safety issues. NOXXON Pharma's Spiegelmer compounds connect site-specifically to polyethylene glycol, which poses a threat to the safety profile of the company's product candidates.

**Potential dilution of investors' stake:** NOXXON Pharma obtained financing from ASO in April, 2020, through issuance of convertible bonds. The convertible bonds can lead to the dilution of the shareholders' stake by up to 52%.

**Clinical trial risk:** All biotechnology companies run the risk of clinical failure. The success of the company is completely dependent on the successful clinical development of its drugs. Failure of a clinical study may lead to the abandonment of the program and can pose a risk to the existence of the company.

**Regulatory risk:** Development of drugs and their commercialization require the approval of regulatory bodies at various stages of the process. The procedure for getting approval can be long and drawn out, which may lead to delays and these, in turn, could have a significant impact on the business of the company. Delays in getting regulatory approvals may give enough time to competitors to develop a similar product, impacting the competitive edge or the first mover advantage of the company.

**Funding risk:** Most biotechnology companies, at one point or the other, need to raise funds or find a partner to support the development of their product candidates. In order to attract investors and partners, companies need to have positive data on the product candidates which favors their further development. Lack of a suitable investor and

partner might lead to lack of funds required for the development of the product candidates, which might bring the company's operations to a halt.

**Reimbursement and commercialization risk:** The company might not be able to secure a suitable licensing agreement or might fail in successfully commercializing its product candidates, which could lead to reduced sales and margins, impacting the financial performance of the company.

**Competition:** The biotechnology industry is marked by a high level of innovation and competition. Companies in the industry are focused on upgrading their existing drugs and developing new drugs to improve the standard of care, in addition to exploring orphan disease indications. This ensures that competition in the industry remains high and substitute drugs for a particular indication can be developed. Delays in development and approval attainment might give a competitor enough time to develop a substitute product.

**Patent protection risk:** The company might not be able to protect its patents and intellectual property in some countries and regions. Different regions have different laws on patent protection and the strictness of the laws may differ from region to region. Patents can be infringed on humanitarian grounds if no other treatment for the disease is available.

### 1.10 Shareholding Pattern

The company had 39,937,419 shares of common stock issued and outstanding on July 01, 2020.

**Exhibit 12: Shareholding breakdown (as on July 01, 2020)[xlix]**

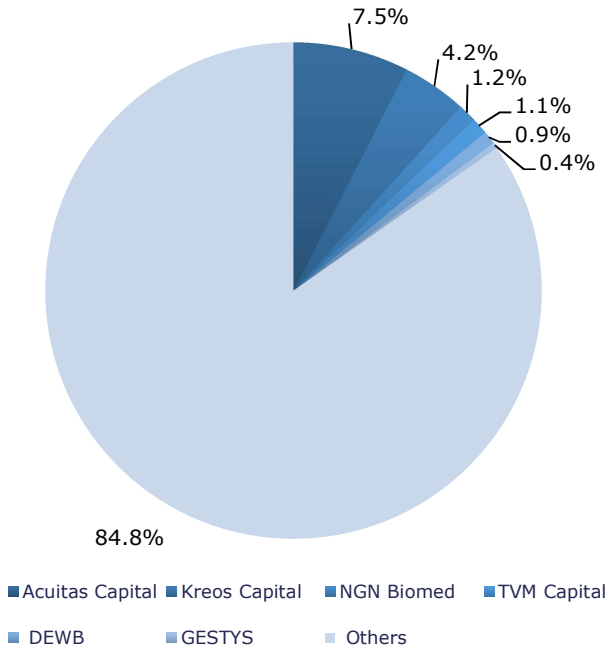



**Exhibit 13: Shareholding breakdown (as on July 01, 2020)[l]**

| Shareholders | No. of Shares | % of total |
|---|---|---|
| Acuitas Capital | 2,999,300 | 7.51% |
| Kreos Capital | 1,677,372 | 4.20% |
| NGN Biomed | 471,262 | 1.18% |
| TVM Capital | 431,324 | 1.08% |
| DEWB | 339,468 | 0.85% |
| GESTYS | 171,731 | 0.43% |
| Others | 33,846,963 | 84.75% |

### 1.11 Listing and contact details[li]

NOXXON Pharma is listed on the Euronext Growth Paris (EPA: ALNOX).

**Company contact details**

Address: Max-Dohrn-Strasse 8-10
10589 Berlin, Germany
Contact No: +49 30 726247 0
Fax: +49 30 726247 225
Website: www.noxxon.com

## 2. News[lii]

**Product news:**

- **The latest data from NOX-A12/Keytruda® study presented at American Association for Cancer Research (AACR) virtual annual meeting 2020**: On April 27, 2020, at AACR, NOXXON Pharma presented the latest data from the Phase I/II study of NOX-A12, in combination with Keytruda®, in patients with metastatic pancreatic and colorectal cancer. The AACR virtual annual meeting was held in two segments, April 27–28, 2020, and June 22–24, 2020.

- **DSMB approved second dose of NOX-A12 in brain cancer study:** On April 24, 2020, NOXXON Pharma announced that DSMB had validated dose escalation in the Phase I/II study of NOX-A12 in combination with radiotherapy for brain cancer. The decision was made after analysis of the safety of all the patients in the first dose cohort once they had completed four weeks of treatment. NOXXON Pharma has now initiated recruitment of patients for the second dose.

- **Recruitment of patients for the first cohort of brain cancer trial completed**: On April 02, 2020, NOXXON Pharma announced that it had completed the recruitment of the three patients for the first cohort of the brain cancer study.

- **Update on clinical trial recruitment provided**: On March 31, 2020, NOXXON Pharma provided an update on the ongoing trial of NOX-A12 in combination with radiotherapy for brain cancer, in lieu of a report of the impact of COVID-19 on the operations of the business. After a thorough assessment and discussion with the coordinating investigators, NOXXON Pharma decided to continue with the treatment and recruitment of patients for the trial.

- **Announcement that first patient enrolled in NOX-A12 with radiotherapy brain cancer trial had completed 10 weeks**: On December 20, 2019, NOXXON Pharma announced that the first patient enrolled in the NOX-A12 with radiotherapy brain cancer trial had completed 10 weeks. The 10 weeks' safety data confirmed that it would be appropriate to continue recruitment of patients for the trial.

- **Announcement of first patient enrolment for NOX-A12 with radiotherapy brain cancer trial**: On October 16, 2019, NOXXON Pharma announced the enrolment of the first patient for the NOX-A12 with radiotherapy brain cancer trial. The study was to investigate increasing doses of NOX-A12 with external beam radiotherapy.

- **Latest data from Phase I/II NOX-A12/Keytruda® combination trial at ESMO congress**: On September 16, 2019, NOXXON Pharma presented the latest data from the Phase I/II study of NOX-A12 in combination with Keytruda® in patients with metastatic pancreatic and colorectal cancer at the ESMO congress in Barcelona, Spain. The combination induced an immune response, stable disease in 25% of patients and prolonged time on therapy compared to prior treatment in 35% of the patients. The study confirmed that NOX-A12 is tolerated well in advanced cancer patients as a monotherapy and in combination with Keytruda®.

- **Started recruitment of patients for NOX-A12/radiotherapy combination brain cancer trial**: On September 12, 2019, NOXXON Pharma announced that it had started the recruitment of patients for the Phase I/II trial of NOX-A12/radiotherapy combination in patients with brain cancer.

- **Announcement of evaluation of NOX-A12 by a leading pharmaceutical company**: On June 24, 2019, NOXXON Pharma announced that a leading pharmaceutical company (one of the top ten in terms of worldwide revenue) had signed an agreement with NOXXON Pharma for the evaluation of NOX-A12 in a new indication (with a market value of more than EUR 1 bn). After receiving the results of the study, the companies might sign an agreement for rights to NOX-A12.

- **Updated results from Phase I/II NOX-A12/Keytruda® combination trial presented at American Association for Cancer Research (AACR) 2019**: On April 01, 2019, NOXXON Pharma announced the latest results from the Phase I/II NOX-A12/Keytruda® combination trial at the AACR Annual Meeting. The results confirmed that NOX-A12 is tolerated well in advanced cancer patients, both as monotherapy and in combination with Keytruda®. The overall survival for the combination was 48% at 6 months and 33% at 12 months. The results suggested that the trials should move ahead to the next stage of development.

- **Data published supporting monotherapy activity of NOX-E36 in liver cancer**: On February 01, 2019, NOXXON Pharma announced the publication of a series of experiments exploring the potential of CCL2 inhibition on liver cancer with mNOX-E36, a rodent version of NOX-E36. The research suggested that mNOX-E36 led to changes in the tumor microenvironment, reduced pathogenic vascularization, and reduced liver tumor volume.

- **Top-line data from the second part of Phase I trial of NOX-A12/Keytruda® published**: On December 14, 2018, NOXXON Pharma published top-line data from the second part of its Phase I NOX-A12/Keytruda® trial. Of the patients who were alive after three months, 70% were alive at 24 weeks and 50% were alive at 36 weeks. Nearly 25% of the patients achieved stable disease according to the response evaluation criteria in solid tumors (RECIST); 22% in pancreatic cancer, and 27% in colorectal cancer.

- **Top-line data from monotherapy part of NOX-A12 trial in metastatic pancreatic and colorectal cancer published**: On October 02, 2018, NOXXON Pharma published top-line data for the monotherapy part of NOX-A12 in metastatic pancreatic and colorectal cancer. The data show that NOX-A12 penetrates the tumor microenvironment and binds with CXCL12. NOX-A12 induces an immune-stimulatory Th-1-like immune response in approximately 50% of the patients.

- **Update on recruitment of patients for NOX-A12 study for metastatic and pancreatic cancer indications**: On June 28, 2018, NOXXON Pharma provided an update on the recruitment of patients for NOX-A12 study as a monotherapy and in combination with Keytruda® for metastatic pancreatic and colorectal cancer indications.

**Finance and operations news:**

- **Raised EUR 1.3 mn in a private placement to European investors**: On June 16, 2020, NOXXON Pharma raised EUR 1.3 mn in a private placement by issuing 2,245,000 shares at a price of EUR 0.58 per share to European investors.

- **Issued third and fourth tranche of EUR 1.0 mn each to Atlas Special Opportunities**: On June 12, 2020, Noxxon Pharma issued 967 convertible notes (including 17 convertible notes in relation to the transaction fee) with a nominal price of EUR 1k each to Atlas Special Opportunities, in relation to the financing agreement it had announced on April 23, 2020.

- **Raised ~EUR 5.5 mn in a private placement to European investors**: On May 08, 2020, NOXXON Pharma announced that it had raised ~EUR 5.5 mn in a private placement to European investors through an accelerated book-building process.

- **Secured financing of up to EUR 14.2 mn through flexible convertible bonds agreement:** On April 23, 2020, NOXXON Pharma announced that it had entered into a flexible convertible bonds agreement of up to EUR 14.2 mn with ASO LLC, allowing it to receive the funding in 25 tranches over a period of 24 months and subject to achievement of certain milestones. The first tranche of EUR 1.3 mn was received on April 22, 2020, followed by the second tranche on May 06, 2020, of EUR 475k. The remaining tranches will also have a nominal value of EUR 0.5 mn. Drug manufacturing tranches, for a total nominal value of EUR 3.4 mn, can be drawn on achievement of certain milestones in the brain cancer study. This financing will allow the company to fund its activities until the beginning of 2022.

- **FY 2019 results:** On April 22, 2020, NOXXON Pharma announced its FY 2019 results. The company's product candidates are in the development stage and are not expected to generate any revenue until their commercialization. NOXXON Pharma generated other operating income of EUR 0.3 mn in FY 2019, decreasing by 26.2% YoY due to a partial waiver of management's remuneration due in FY 2019. R&D costs decreased by 4.4% YoY to EUR 2.1 mn in FY 2019, due to lower personnel costs. NOXXON Pharma had cash resources of EUR 1.4 mn at the end of FY 2019, as compared with EUR 4.3 mn at FY 2018 end.

- **Converted warrants of Acuitas:** On April 20, 2020, NOXXON Pharma announced that it had converted the remaining warrants of Acuitas Capital to shares after receiving the final exercise notice. Following the conversion Acuitas no longer holds any warrants. The warrants were issued in connection with the EUR 6.2 mn capital raise transaction in November 2018.

- **Raised a total of EUR 1.0 mn:** In two separate private placements of EUR 0.5 mn each on January 20, 2020 and January 14, 2020, NOXXON Pharma was able to raise a total of EUR 1.0 mn from the same investor. The issue

price was EUR 0.51 per share, a 26% discount on the average price of the last 7 trading days from December 31, 2019.

- **H1 2019 results**: On October 24, 2019, NOXXON Pharma announced its H1 2019 results. NOXXON Pharma reported a 255.8% YoY increase in its other operating income to EUR 0.27 mn, due to the sale of raw materials and a partial waiver of supervisory and management board remuneration due in 2019. The company reported a 10.7% YoY decrease in its R&D expenses to EUR 1.1 mn in H1 2019, due to lower personnel expenses, patent costs and consulting services. NOXXON Pharma reported a net loss of EUR 2.0 mn in H1 2019, compared with EUR 4.1 mn in H1 2018.

- **Raised EUR 1.0 mn in a private placement**: On August 15, 2019, NOXXON Pharma announced that it had raised EUR 1.0 mn in a private placement of shares without warrants.

- **Raised EUR 0.52 mn through a rights issue**: On July 19, 2019, NOXXON Pharma announced that it had issued 801,494 shares at a price of EUR 0.65 per share, raising EUR 0.52 mn through the rights issue.

- **FY 2018 results**: On April 12, 2019, NOXXON Pharma announced its FY 2018 results. Other operating income increased from EUR 0.26 mn in FY 2017 to EUR 0.38 mn in FY 2018, up 44.8% YoY. R&D expenses decreased from EUR 2.4 mn in FY 2017 to EUR 2.2 mn in FY 2018, down 8.5% YoY. G&A expenses fell to EUR 2.5 mn, decreasing by 3.4% YoY. The company's net loss increased to EUR 10.7 mn in FY 2018. The company had cash resources of EUR 4.3 mn at the end of FY 2018.

- **Raised EUR 6.2 mn through issuance of shares**: On November 16, 2018, NOXXON Pharma announced that it had secured an equity capital raise of EUR 6.2 mn, with approximately USD 5 mn being invested by Acuitas Capital LLC, a US-based family office. Acuitas Capital LLC agreed to purchase 3,783,201 shares at a price of EUR 1.17 per share.

- **H1 2018 results**: On October 11, 2018, NOXXON Pharma announced its H1 2018 results. The company earned other operating income of EUR 0.08 mn, down by 68.6% YoY, as the sale of assets held for sale in H1 2018 had generated less income than the release of financial liability in H1 2017. R&D expenses decreased by 2.1% YoY to EUR 1.2 m in H1 2018. Net losses increased to EUR 4.1 mn in H1 2018, as compared with EUR 2.2 mn in H1 2017. The company had cash resources of EUR 0.80 mn at the end of H1 2018.

- **Listed existing bonds and raised funds**: On September 18, 2018, NOXXON Pharma announced that it had listed previously issued convertible bonds on the Euronext Access market in Paris. The company secured an additional EUR 0.42 mn worth of investment in the notes.

- **Amended agreement with YA II PN and raised EUR 0.65 mn**: On August 14, 2018, NOXXON Pharma announced that it had amended its agreement with investor YA II PN, with suspension till January 31, 2019, regarding YA II PN's ability to subscribe to subsequent tranches. The investor will only be able to subscribe to half of subsequent trances if NOXXON Pharma raises EUR 1.0 mn through equity financing, and the ability to subscribe at all to subsequent tranches will be removed if NOXXON Pharma raises EUR 5.0 mn. In FY 2018, NOXXON Pharma raised EUR 0.65 mn in one tranche from the investor.

- **Raised EUR 0.20 mn from ODIRNANE bonds (convertible bonds)**: On August 01, 2018, NOXXON Pharma announced that it had raised EUR 0.20 mn by issuing convertible bonds. These will be converted into equity shares of the company at the price of a future equity financing round or from October 01, 2018, at the investor's option at the market price, which will be reset quarterly to the 10-day volume-weighted average price.

## 3. Management and governance[liii]

The management and governance teams have significant experience in the field of biotech R&D, as well as in sales, business development and M&A for multiple businesses.

**Exhibit 14: Management and governance**

| Name | Position | Past Experience |
|---|---|---|
| Dr. Aram Mangasarian | Chief Executive Officer | • Dr. Aram Mangasarian graduated with a Bachelor of Science (biochemistry, molecular chemistry and English literature) from University of Wisconsin-Madison<br>• He obtained a PhD in biology from University of California - San Diego for research carried out at Salk Institute and an MBA from INSEAD<br>• He served in a variety of roles at ExonHit Therapeutics from 2000 to 2005, eventually heading the business development function as the Vice-President, driving a number of strategic alliances, including the USD 30 mn strategic alliance with Allergan<br>• He served as Vice-President Business Development for Novexel from October 2005 to March 2010, leading the EUR 150 mn licensing agreement with Forest Laboratories for North American rights to a beta-lactamase inhibitor now known as Avibactam<br>• He negotiated the acquisition by Novexel of AstraZeneca for USD 505 mn. He joined NOXXON Pharma in 2010 as the Chief Business Officer and currently serves as the Chief Executive Officer (appointed in 2015) |
| Dr. Jarl Ulf Jungnelius | Senior Medical Advisor | • Dr. Jarl Ulf Jungnelius is an oncologist and has more than twenty-five years of experience at large pharmaceutical companies<br>• He obtained Bachelor of Science and Doctor of Medicine (MD) degrees from the Karolinska Institute in Stockholm, Sweden<br>• He held leadership positions at Takeda, Pfizer, Eli Lilly & Company and VAXIMM, where he oversaw clinical development and business<br>• He has played an important role in the clinical development of successful oncology drugs, including Abraxane®, Gemzar®, Alimta® and Revlimid®<br>• He served as the Vice-President of Clinical R&D, Solid Tumors, from 2007 to 2014. He is currently CEO of Isofol Medical AB and serves on the boards of Biovica International AB and Monocl AB and is a director at Oncopeptides AB |

# 4. Industry overview

## 4.1 Introduction[livlvlvilviilviii]

Globally, in 2018, around 18.1 mn new cancer cases were diagnosed, of which 9.5 mn cases were among men and 8.6 mn among women. Deaths related to cancer were estimated at 9.6 mn in 2018, with prevalence of the disease at 43.8 mn cases in the preceding five years.

Of the 9.6 mn deaths, 70% occurred in low- and middle-income countries. One-third of the total deaths were related to high body mass index, low fruit and vegetable intake, lack of physical activity, and tobacco and alcohol use. The use of tobacco accounted for around 22% of the total deaths.

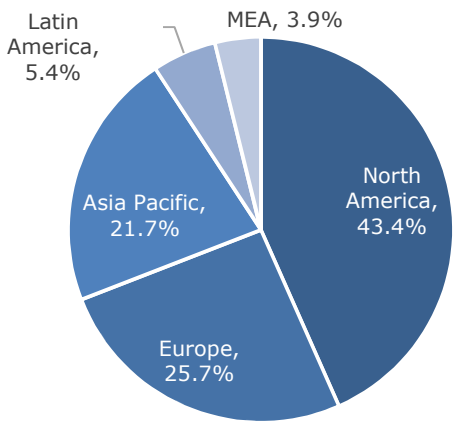
The economic costs of cancer are huge, and in 2015 it is estimated to have cost the U.S. nearly USD 94 bn in lost earnings (the amount that could have been earned by patients, excluding costs associated with cancer), according to a study done by JAMA Oncology. Lost earnings because of colorectal and pancreatic cancer were estimated at USD 9.4 bn and USD 6.1 bn, respectively.

Cancer, if untreated, can progress through stages I to IV. Stage IV is when the cancer is metastatic, i.e., it has spread from the area of origination to other body parts. In many cases, the cancer can recur if not completely treated.

### 4.1.1 Market size expected to grow exponentially [lix]

Along with a rise in the number of cancer cases due to increasingly sedentary lifestyles, rapid growth in the global oncology market is being driven by factors such as an increase in disposable income and upgrading of medical technologies. The global oncology market, estimated at USD 120 bn in 2018, is expected to grow at a CAGR of 12.6% during the period 2019-2025 and reach a value of ~USD 275 bn. North America has the largest share of the global market at approximately 43%.

**Exhibit 15: Global Oncology Market - geographical breakdown**




### 4.1.2 Metastasis (metastatic cancer)[lx]

The spread of cancer from its area of origination to different parts of the body is termed metastasis. It is also termed metastatic cancer, advanced cancer or stage IV cancer. This spread occurs through the lymph system or bloodstream. NOXXON's drug candidate NOX-A12 is targeted (as a combination therapy) at metastatic pancreatic and colorectal cancer.

Regional metastasis is the spread of cancer to areas near the primary site, and distant metastasis occurs when cancer spreads to body parts far away from the primary site.
The following are some possible cases of metastasis:

- Colon and rectal cancers tend to spread to the liver and lungs
- Pancreatic cancer tends to spread to lungs and liver
- Breast cancer tends to spread to the bones, liver, lungs, chest wall, and brain
- Lung cancer tends to spread to the brain, bones, liver, and adrenal glands
- Prostate cancer tends to spread to the bones

Most cancer types tend to spread to the brain in the advanced stage.

### 4.2 Current forms of treatment and their market size

| Type of treatment | Current market size (in USD bn) | Forecast size (in USD bn) | CAGR (%) |
|---|---|---|---|
| Chemotherapy[lxi] | 32.8 (2019) | 56.5 (2024) | 11.5 |
| Radiotherapy[lxii] | 5.6 (2018) | 6.8 (2023) | 4.1 |
| Immunotherapy[lxiii] | 36.8 (2016) | 101.6(2023) | 14.8 |

#### 4.2.1 Factors leading to increased spending on cancer treatment

**1) Increasing numbers of patient assistance programs[lxiv]:** The patient assistance programs in the U.S. are created by pharmaceutical companies, non-profit organizations and government entities to remove the financial burden on the people who cannot afford to bear the cost of treatment. As of February 2020, there are around 372 programs and companies that are covering more than 4,100 drugs. The supporting entity either provides payment assistance to the patient or provides the drugs for free.

**2) Growing government initiatives for cancer awareness[lxv]:** Several initiatives are being taken by governments to benefit their citizens. Governments work with several health agencies, territories, and other key organizations to develop effective strategies and measures to create cancer awareness.

**3) Rising prevalence of cancer worldwide:** Changing lifestyles, eating habits, and a geriatric population are the key causes of an increase in the prevalence rate of cancer.

**4) Strong R&D initiatives from key players:** Companies such as Roche Holding AG, Celgene Corporation, Novartis AG, Merck & Company/MSD, Pfizer, and Amgen continue to spend heavily on R&D by working with new and upcoming companies that are keen to develop new therapies for cancer treatment.

### 4.3 Immunotherapy

Immunotherapy focuses on stimulating an immune response from the immune system or suppressing an anti-immune response. Immunotherapy is a new type of treatment which may be used in isolation or as part of a combination therapy with one of the conventional types of treatment. Revolutionizing the current oncology treatments market, immunotherapy has been relatively effective in oncology indications that have been resistant to chemotherapy and radiotherapy (for example, melanoma), with immunotherapy options having been approved in 17 oncological indications by the FDA.[lxvilxvii]

Immunotherapy has gained prominence as a treatment option for cancer, and its use has been growing in the last few years.[lxviii]

The body's immune system comprises organs, special cells, and substances which protect the body from infections and diseases. However, cancer cells originate and grow among normal cells and the immune cells may fail to recognize and attack them, offering little resistance to the growth of the cancer cells.[lxix] Immunotherapy helps boost the immune system's response to unhealthy cells, leaving lasting results. Immunotherapy can be administered intravenously, orally, through topical applications (cream rubbed on to the skin), or intravesically (directly into the bladder).

**Immunotherapy treatment can be of many types:**[lxx] These include: checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, cytokines, immunomodulators, cancer vaccines, monoclonal antibodies, and oncolytic viral immunotherapy.

**Checkpoint inhibitors:** Cancer cells evade the body's innate checkpoints that destroy the antibodies. Checkpoint inhibitors play a role by allowing the T-cells to attach to the cancer cells.

Yervoy (Ipilimumab), Opdivo (nivolumab), Keytruda® (pembrolizumab), and Tecentriq (atezolizumab) are some of the approved checkpoint inhibitors – each having a different mechanism for different checkpoints. NOXXON Pharma has tied up with Merck & Company/MSD to make Keytruda® an effective combination product along with NOX-A12, with clinical trials currently underway.

Like other forms of treatment, immunotherapy can have side-effects such as flu-like symptoms, diarrhea, low or high blood pressure, and organ inflammation. In some cases, the process may also result in the immune system attacking healthy body parts.

So far there has been limited success in the use of immunotherapy for the treatment of pancreatic and colorectal cancer. Immunotherapy has shown a positive response in colorectal patients with microsatellite instability tumors. However, removing the barriers to effective immunotherapy treatment can have lasting results, which is where NOXXON Pharma's NOX-A12 has an important role to play. [lxxi]

### 4.4 Pancreatic cancer[lxxii]

Pancreatic cancer is one of the leading causes of cancer-related deaths worldwide, with the numbers being higher in developed countries. In the U.S., it is the third leading cause of cancer deaths.

Pancreatic cancer starts in the tissues of the pancreas, and can take the form of exocrine or neuroendocrine (endocrine) tumors, depending on the type of cells in which it starts. About 45%-55% of pancreatic cancer cases turn metastatic, as the cancer may spread to other body parts such as the liver, lungs, or distant parts of the abdomen.

#### 4.4.1 Growing market for treatment, with huge scope for investment and research[lxxiii]

The market for pancreatic cancer treatment was estimated to be worth USD 1.9 bn in 2017 and expected to grow to USD 4.7 bn by 2026 at a CAGR of 10.6%. Increasing research, advancement of technology and rising healthcare expenditure are expected to drive this growth. However, factors such as limited accessibility of costly treatment, low success rate of clinical trials of treatments and lack of stable repayment strategies may inhibit growth to some extent.

In 2018, 0.46 mn new cases of pancreatic cancer were recorded globally, and 0.43 mn deaths were recorded. An increase in the number of people with obesity or diabetes, and an ageing population are factors that can increase the number of patients diagnosed with pancreatic cancer. The number of patients with pancreatic cancer is expected to increase to 0.82 mn in 2040, with 0.78 mn deaths.

The majority of patients with pancreatic cancer do not exhibit symptoms at early stages and the cancer only gets detected when it has reached an advanced stage. This represents tremendous potential for NOXXON Pharma which mainly targets treatment for metastatic cancer patients.

#### 4.4.2 Increase in survival rate offers a glimmer of hope as incidence rate and mortality rate also increase[lxxiv]

The incidence rate of pancreatic cancer was the highest in Europe and U.S. at 7.7 per 100,000 people each, with 132,559 cases in Europe and 50,846 cases in the US, respectively, in 2018. The lowest incidence rate was observed in Africa at 2.2 cases per 100,000 people (16,059 cases) in 2018.

Pancreatic cancer is more common in men (5.5 per 100,000) than in women (4.0 per 100,000). Pancreatic cancer is normally diagnosed in people above the age of 55, and the highest incidence rate is observed in people above the age of 70. The highest mortality rate has been reported in Western Europe (7.6 per 100,000 people), Central and Eastern Europe (7.3 per 100,000 people), followed by Northern Europe and North America (equally 6.5 per 100,000). More than 90% of the deaths were reported among people above the age of 50.

The 5-year survival rate increased from 6% in 2014 to 9% in 2018. While the survival rate has increased in recent years, the increase in incidence rate and mortality rate in the last decade indicates that pancreatic cancer remains a malignant form of cancer. This calls for urgent prioritization of the awareness and treatment of the disease. Another worrying issue, which emphasizes the need for prioritization, is that pancreatic cancer is normally diagnosed at an advanced stage, and 80-90% of the people diagnosed have unresectable tumors, as pancreatic cancer has silent symptoms in its earlier stages.

### 4.4.3 Standard of Care (treatments) - limited options with limited effectiveness[lxxv]

Treatment method depends on the performance status (PS) of the patient. As a first-line therapy for patients with PS 0-1, according to Eastern Cooperative Oncology Group (ECOG) criteria, the National Comprehensive Cancer Network (NCCN), American Society for Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) have approved the use of 5-fluorouracil (5FU), leucovorin (folinic acid, LV), irinotecan, and oxaliplatin (FOLFIRINOX) or nab-paclitaxel/GEM. For patients with PS 2, single-agent GEM is the approved option.

For the next line of therapy, the treatments which were not administered in the first line of therapy are recommended. Single-agent 5FU or capecitabine, 5FU/LV/irinotecan (FOLFIRI), 5FU/LV/liposomal irinotecan, and 5FU/LV/oxaliplatin (FOLFOX) may be used. GEM/erlotinib is used often for patients with endothelial growth factor receptor–positive (EGFR+) tumors, whereas GEM/cisplatin is used for patients with BRCAI/II-mutated tumors. Chemotherapy options are highly toxic and are normally faced with a high level of resistance from pancreatic cancer.

Targeted therapy which destroys cancer cells without affecting normal cells might be used in some cases. Erlotinib is a targeted therapy treatment which is used in pancreatic cancer.
Immunotherapy options might be used in some cases. Pembrolizumab is recommended for microsatellite instability–high (MSI-H) tumors, or tumors with deficiencies in mismatch repair mechanisms (dMMR). Targeted therapy and immunotherapy methods might be used in conjunction with other methods.

Supportive/Palliative care should be used to improve the quality of life of the patients, while treatment is underway to cure or improve their condition.

**Development of immunotherapy treatment options**

In addition to pembrolizumab, which is a PD-1 antibody, other checkpoint inhibitors such as CTLA-4 antibodies are under clinical trials for the pancreatic cancer. Immune checkpoint inhibitors are approved for other types of cancer such as melanoma and lung cancer. Immunotherapy treatments, when used alone, have only been successful in some cases, and generally not had success in treating pancreatic cancer. Various clinical studies are being conducted to test immunotherapy options in combination with radiotherapy, chemotherapy or other immunotherapy options.

## 4.5 Colorectal Cancer[lxxvi]

Depending on the origin of the cancer it can either be colon cancer or rectal cancer. This type of cancer usually starts off as a growth called a polyp in the inner lining of the colon or rectum. Only a few polyps eventually convert into cancer:
1) Adenomatous polyps (adenomas) sometimes convert into cancer and are termed pre-cancerous conditions.
2) Hyperplastic polyps and inflammatory polyps are very common and usually are not pre-cancerous.

### Colorectal Metastasis

Cancer in the form of polyps can grow into the wall of the colon or rectum over time and begins in the innermost layer of the wall and extends outward through other layers. When the cancer cells in the wall meet blood vessels or lymph vessels, they can travel to other body parts such as liver, lungs, bones, brain or spinal cord, turning the case metastatic or into stage IV cancer.

Around 50% of colorectal cancer patients develop liver metastasis.

**Types of Colorectal Cancers**

- **Adenocarcinomas:** (96% of colorectal cancers) start off in the cells that make mucus that lubricates the inner colon and rectum.
- **Carcinoid tumors:** arise from the special hormone-making cells in the intestine.
- **Gastrointestinal stromal tumors (GISTs):** usually start off from special cells in the colon wall.
- **Lymphomas:** are cancers of immune cells and often start in lymph nodes but can also occur in the colon, rectum and other organs
- **Sarcomas:** chances of these cancers occurring in the colon and rectum are low.

### 4.5.1 Colorectal cancer incidence cases set to increase ~72% by 2040

In 2018, 1.8 mn cases of colorectal cancer were estimated, of which 1.1 mn were colon cancer and 0.7 mn rectal cancer. The overall number of colorectal cases is expected to reach 3.1 mn in 2040, with 1.9 mn cases of colon cancer and 1.2 mn of rectal cancer.[lxxvii]

In 2020, it has been estimated that ~0.10 mn and ~0.32 mn of new colon cancer cases will be detected in the U.S. and Europe, respectively, and ~0.05 mn and ~0.18 mn new rectal cancer cases.[lxxviii]

Asia witnessed the highest incidence of 0.94 mn cases, and the lowest incidence occurred in Oceania with 0.02 mn cases. Asia also witnessed the highest number of mortality cases of 0.45 mn while Oceania had the lowest at 0.08 mn cases. [lxxix]

There were ~0.86 mn deaths because of colorectal cancer globally in 2018, which accounted for 9.2% of the total cancer deaths.

Approximately 4.6% of men and 4.2% of women get diagnosed with colorectal cancer in their lifetimes. The risk of colorectal cancer increases with age. About 68 years is the median age at which colon cancer gets detected in men while the corresponding age in women is 72. About 63 years is the median age at which rectal cancer gets diagnosed in both men and women.[lxxx] The 5-year survival rate of colorectal cancer which has reached an advanced stage is around 14%.[lxxxi]

### 4.5.2 Global market size set to grow at 6.1% CAGR to USD 18.5 bn by 2023

The global colorectal cancer market was valued at USD 13.7 bn in 2018 and is expected to reach USD 18.5 bn by 2023, at a CAGR of 6.1%.[lxxxii]The market is expected to be driven by factors such as the launch of better therapeutics, rise in disposable incomes, and increasing awareness of symptoms among people.

Novartis AG, Bayer AG, Merck & Company/MSD, Pfizer Inc., and Sanofi are the key players in the market which are involved in manufacturing drugs related to colorectal cancer.

### 4.5.3 Current treatment methods[lxxxiii]

In the U.S., the FDA has approved the following drugs which can be used for chemotherapy: capecitabine (Xeloda), fluorouracil (5-FU), irinotecan (Camptosar), oxaliplatin (Eloxatin), and trifluridine/tipiracil (Lonsurf). Some common treatment courses may include: 5-FU alone; 5-FU with leucovorin (folinic acid), a vitamin that improves the effectiveness of 5-FU; capecitabine, an oral form of 5-FU; FOLFOX, which is 5-FU with leucovorin and oxaliplatin; FOLFIRI, 5-FU with leucovorin and irinotecan; irinotecan alone; XELIRI/CAPIRI, capecitabine with irinotecan; and XELOX/CAPEOX: capecitabine with oxaliplatin.

The above drugs may be used in combination with cetuximab (Erbitux), bevacizumab (Avastin), regorafenib (Stivarga) or panitumumab (Vectibix) in targeted therapy treatment.

Immunotherapy treatment includes pembrolizumab (Keytruda®), nivolumab (Opdivo), and nivolumab and ipilimumab (Yervoy) in combination.

### 4.6 Brain cancer (glioblastoma/glioma)

There are more than 120 different types of brain tumors. Brain tumors can be primary (start in the brain) or secondary.
Secondary brain cancers start in other parts of the body and metastasize to the brain and are termed metastatic brain cancers. Lung cancer, breast cancer, colorectal cancer, melanoma, kidney cancer, thyroid cancer and uterine cancers are known to metastasize to the brain, with lung cancer being the most common origin of metastatic brain cancers.

**Common types of primary brain tumors** are pituitary tumors, medulloblastoma, meningioma and glioma.

**Glioma**: Glioma is a type of brain tumor which may arise from the glial cells. Around 33% of all primary brain tumors and central nervous system tumors, and 81% of malignant brain tumors are gliomas. Grade IV tumors, the most malignant form of astrocytoma, are called **glioblastoma**. These account for more than 50% of primary malignant brain tumors.

#### Exact causes unknown but radiation and genetic conditions can lead to brain cancer[lxxxiv]

While the exact causes of brain cancer are unknown, some factors are associated with increasing the risk of getting diagnosed with brain cancer:

- Radiation: People who are exposed to ionizing radiation have an increased risk of getting brain cancer.
- Genetic conditions: The risk of getting diagnosed with brain cancer increases if the person has one of the following genetic conditions and syndromes:
    - neurofibromatosis (NF) type 1 and type 2
    - tuberous sclerosis (TSC)
    - Li-Fraumeni syndrome
    - Von Hippel-Lindau syndrome (VHL)
    - Turner syndrome
    - Turcot syndrome
    - Gorlin syndrome

#### 4.6.1 Brain cancer therapeutics market to increase to USD 2.7 bn by 2023 as incidence rates rise[lxxxv]

The global market for brain tumor therapeutics is forecast to increase to USD 2.7 bn from 2018 to 2023 at a CAGR of 11%, driven by the increase in incidence rate around the world and rising R&D expenditure by pharmaceutical companies to develop precision medicines that are tailored to the individual patient. There being few brain-cancer specific drugs and the high cost of treatment may act as deterrents to growth.

North America is expected to dominate the market due to increasing incidence rates and advancement in technologies, while the Asia-Pacific region is likely to witness growth due to easier accessibility to healthcare facilities and a rise in the geriatric population.

The key players in the market are Novartis, F-Hoffman La Roche, Novocure, Merck & Company/MSD and Co and Immunocellular Therapeutics.

In 2018, a total of 0.3 mn cases of brain and CNS cancer were diagnosed globally. This number is expected to increase at a CAGR of 1.8% to 0.44 mn by 2040. The U.S. saw 0.02 mn new cases of brain and CNS cancer in 2018, which is expected to increase to 0.03 mn in 2040 at a CAGR of 1.2%, while Europe is forecast to see a rise from 0.06 mn cases to 0.07 mn cases over the same period at a CAGR of 0.5%.

#### 4.6.2 Market for glioblastoma set to increase as poor prognosis shows need for better research[lxxxvilxxxviilxxxviiilxxxix]

The market for Glioblastoma treatments is expected to increase from USD 1.03 mn in 2018 to USD 1.7 bn in 2025 at a CAGR of 7.4%. The increasing occurrence of glioblastoma, along with a hike in R&D expenditure and rising adoption

of chemotherapy options will underpin the growth. As with the brain cancer market, the high cost of treatment may limit growth. Failure in clinical trials of potential treatments might impact growth.

North America is expected to account for the greater part of the market in the forecast period, followed by Europe. The Asia-Pacific market is expected to grow faster than any other regions.

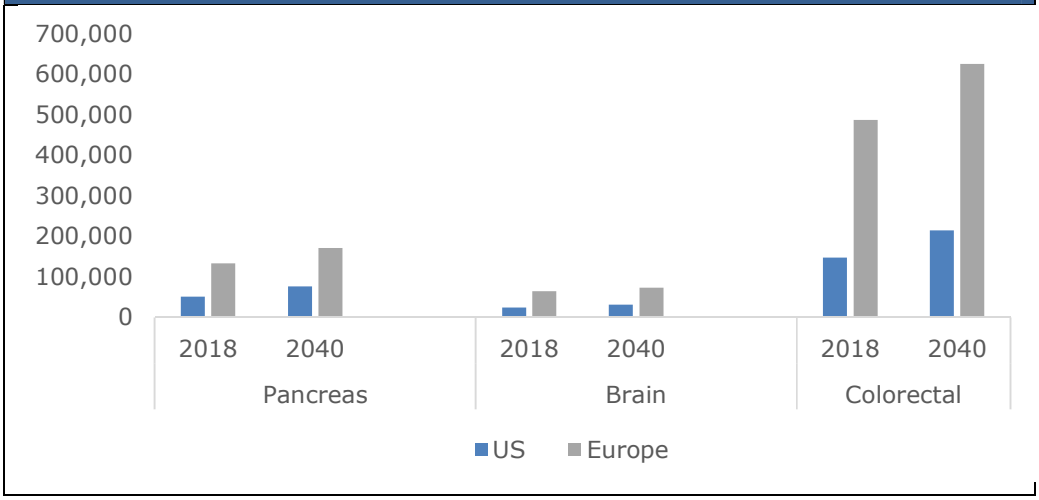
Glioblastoma has an age adjusted incidence rate of 3.2 patients per 100,000 people and a prevalence rate of 1 patient per 100,000 people. The incidence rate in North America and Europe is 2–5 patients per 100,000 people. Around 250,000 new cases of glioblastoma are diagnosed each year. An increase in the number of cases is anticipated in the near future with a rise in the geriatric population.

The indication has a poor prognosis, with a 1-year survival rate of 37.2%, 5-year survival rate of 5.1% and median survival rate of approximately ten months. More than 70% of patients face disease progression within one year.

Around 0.2 mn patients die each year from glioblastoma, including approximately 15,000 in Europe and, in the U.S. 9,000.

Glioblastoma can occur at any age, but 70% of the time it is diagnosed in patients between the ages of 45 and 70, with a median age of 64 years at the time of diagnosis.

**Exhibit 16: Incidence cases of pancreatic, brain and colorectal cancer – U.S. and Europe**




### 4.6.3 Current treatment methods[xc]

After surgical resection, radiotherapy and chemotherapy are used.

Chemotherapy options include the drug Carmustine given through gliadel wafers. A combination of three drugs (lomustine – Gleostine, procarbazine – Matulane, and vincristine – Vincasar) is used in combination with radiotherapy for patients with Grade III oligodendroglioma with a 1p19q co-deletion.

The standard of care for glioblastoma is the combination of radiotherapy and daily low-dose temozolomide (Temodar), followed by monthly doses of temozolomide after radiation therapy for 6 months to 1 year.

Targeted therapy options include larotrectinib (Vitrakvi), which is approved for some forms of tumors. Bevacizumab (Avastin and biosimilar Mvasi) is another targeted therapy treatment used for glioblastoma when the above-mentioned treatment does not work.

Electric Field Therapy, which is admissible through a portable device called "Opune", interferes with parts of cells that are required for tumors to exist and grow. Research has shown that patients newly diagnosed with glioblastoma or those with recurrent glioblastoma live as long as patients treated with chemotherapy, with lesser side effects.

For brain metastases, targeted therapy options include osimertinib (Tagrisso) and alectinib (Alecensa) for non-small cell lung cancer (NSCLC), lapatinib (Tykerb) for HER2-positive breast cancer and dabrafenib (Tafinlar) alone or in combination with trametinib (Mekinist), and vemurafenib (Zelboraf) for melanoma.

Immunotherapy options including ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda®) have shown potential for treating brain metastases in lung cancer and melanoma.

### 4.7 Regulatory framework[xci]

The global biotechnology industry is highly regulated. The biotech drugs are authorized based on a scientific risk assessment undertaken by a national agency, such as the FDA in the U.S. or the European Medical Agency (EMA) in Europe. However, there is no global standard for industry products and their usage, which means that the products and therapies may differ significantly from nation to nation.

The process of drug approval is very rigorous and there are very few drugs which get approval from the FDA and are allowed for human use. It is estimated that, on average, a drug takes 8-12 years from its early laboratory phase to be available for human use.

Ultimately, if a product is found to be safe for human, animal or plant life and health, as well as the environment, it is passed for use and sale. In cases where scientific evidence is insufficient, inconclusive or uncertain, and where possible risks are judged unacceptable, regulators generally rule on the side of caution. Procedures for authorization in major biotech producing countries are generally predictable, efficient and transparent. In line with the speedy adoption of technology and technological processes used by the industry, guidelines in the U.S. and European Union (EU) are frequently amended to encourage biotechnological expansion and discovery within the context of humanitarian and environmentally responsible operations.

Biotechnology patents are usually awarded by the U.S. Patent and Trademark Office (USPTO) in the Department of Commerce and the European Patent Office. A patent application is generally judged on four criteria. The invention must be useful, novel, non-obvious and enabled (the invention must be described in detail to enable one skilled in the field to use it for the stated purpose). Patents are enforced and protected for 20 years from the filing date, and patent priority is based on the "first to invent" principle: whoever made the invention first (and can prove it) is awarded property and monopoly rights for the 20-year period. Patents are especially crucial for the burgeoning biopharmaceutical aspect of industry operations since healthcare costs can be extremely high in some countries, the U.S. for example.

#### 4.7.1 Regulatory body in the U.S.

The sponsors submit the drugs to the Center for Drug Evaluation and Research (CDER)/Center for Biologics Evaluation and Research (CBER) and pay user fees to start the clinical trial process.

The early phase of clinical trials evaluates the drug based on safety and identifies the evidence of any biological drug activity, e.g., shrinkage of tumor. The later phase of clinical trials checks whether the drug provides any clinical benefit or not (survival rate and improvements in the symptoms). The standard FDA procedure for conducting clinical trials for the approval of new drugs includes three phases. Phase I clinical trials test the drugs on a small number of patients, generally 20 to 80 volunteers. Phase II tests the drug's effectiveness in treating the disease on 12 to 100 volunteers. Phase III is the largest of all the trials and involves 100 to 1,000 volunteers on whom the drug is tested, and the effectiveness of the drug is measured. Additionally, these trials gather data about appropriate dosing and interaction of the drug with other medicines.

The CDER/CBER analyzes the cancer drugs and biologics based on some endpoints, such as overall survival, symptom endpoints, disease-free survival or event-free survival, objective response rate, complete response, and progression-free survival or time to progression. Once the clinical trials are over, the sponsors are required to submit a New Drug Application (NDA) to the FDA, which includes complete results of trials, information about manufacturing, labeling, biological and chemical information. After the submission of the NDA, the FDA has 60 days to decide whether to file the NDA and whether to open it for review. Once the NDA is filed, the FDA starts reviewing it and checks the drug safety and effectiveness. The FDA takes around 10 months to act upon the NDA filing, unless the drug is on priority review, in which case it takes ~6 months. Only drugs that receive approval from the FDA can be marketed for human

use. Based on the findings, the FDA can either approve the drug or can issue a complete response letter outlining its decision. After receiving the approval, the sponsor is responsible for conducting additional post-market research to ensure safety, effectiveness and optimal use of the drug.

**Orphan Drugs:** Some drugs which are used for the treatment of rare diseases, and are ignored by developers due to their lower return capacity, are considered "orphan drugs", a special status provided by the FDA. Under the Orphan Drug Act, 1983, these drugs are allowed incentives, including tax credit while conducting clinical trials and extended market exclusivity. The FDA also provides expedited review programs and extra FDA resources for the review and development of orphan drugs.

### 4.7.2 Regulations for Europe (EMA)[xcii]

In Europe, there are two ways of receiving marketing approval. The first is authorization from the EMA and the other is a national authorization procedure. National authorization is a process where the member of the EU authorizes the use of a medicine in its territory only, while authorization from the EMA results in a centralized authorization, which is valid in all the EU member states and in the European Economic Area countries (Iceland, Liechtenstein and Norway).

Authorization from the EMA is compulsory for human medicines containing active substances to treat HIV, cancer, diabetes, neurodegenerative diseases, viral diseases and auto immune diseases, and for medicines derived from biotechnological processes. The results provided by the agency are used by the European Commission to decide whether to allow the marketing of medicines in the EU. Only after receiving authorization from the EMA can the company sell or market the medicine in EU member states. The EMA also monitors the safety of the authorized medicines in the EU region and takes corrective measures if the latest information on the medicine indicates that the it is no longer safe for humans. At the request of member states or the European Commission, the EMA can also provide scientific opinions on the medicines. Once the company receives approval from the European Commission, the EMA has no role to play in the pricing and reimbursement decisions as these decisions are made at national and regional levels.

**Exhibit 17: Legal and regulatory framework for biological products in Europe[xciii]**

| Type of product | Legal framework | Regulatory Organism |
|---|---|---|
| **Advanced therapy medicinal products:**<br>- Somatic cell therapy products<br><br>**Combination products** | - Directive 2001/83/EC (relating to medicinal products for human use)<br>- Directive 2009/120/EC (relating to medicinal products for human use as regards advanced therapy medicinal products)<br>- Regulation 726/2004/EC (community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing an EMA)<br>- Regulation 1394/2007/EC (on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004)<br>- Regulation (EC) No 14I/II000 for orphan drugs | - Clinical trials are under the competent national authorities of each member state where the clinical trial will take place<br>- Product positive opinion: CHMP (Committee for Human Medicinal Products)<br>- Draft opinion: CAT (Committee for Advanced Therapies) |

The assessment of a developer's drug is done by the EMA's Committee for Human Medicinal Products (CHMP), which makes the decision on the grant of authorization. The CHMP also coordinates with other EMA committees during the assessment process; these are the Committee for Advanced Therapies (for advanced therapy medicines), the Pharmacovigilance Risk Assessment Committee (for medicine safety and risk management), the Pediatric Committee (medicine use for children), and the Committee for Orphan Medicinal Products (for orphan-designated medicine).

Just like the FDA, the EMA supports the development of orphan medicines, and the legal framework for orphan medicines is based on "Regulation (EC) No 14I/II000". Orphan medicines are allowed a number of incentives by the EMA, which are:

- Protocol assistance: The EMA provides scientific advice, specifically to the developers of orphan drugs and this is known as protocol assistance.
- Centralized authorization: Every orphan medicine has access to centralized authorizations in the EU.
- 10 years of market exclusivity: Every authorized orphan medicine has a benefit of protection from competition from similar medicines with a similar indication for 10 years.
- Additional incentives for micro, small, medium-sized enterprises (SMEs): If the developer of an orphan medicine belongs to the SME category, then it is allowed further incentives, which include administrative and procedural assistance, and fee reduction.
- Fee reduction: The regulatory fees for orphan drugs are less than those for other medicines.

Grants: The EMA does not offer any grants but the European Commission offers funding options to the developers.

## 4.8 Clinical pipeline of global product candidates of peer companies[xciv]

| Company | Indications | Type of Product | Clinical Stage |
|---|---|---|---|
| **Glycostem** | Acute Myeloid Leukemia; Multiple Myeloma; Solid Tumors (e.g., colorectal cancer, head-neck cancer, lung cancer and breast cancer) | Natural killer cell therapy | Phase I study completed for acute myeloid leukemia |
| **Gritstone Oncology** | Common solid tumors, including metastatic non-small-cell lung cancer, microsatellite stable colorectal cancer, gastroesophageal cancer, and bladder cancer ("Granite");<br>Metastatic non-small-cell lung cancer, colorectal cancer, pancreatic cancer, and other mutation-positive tumors ("Slate") | Tumor-specific antigens – Neoantigen based immunotherapy through two products, namely Granite and Slate | Undergoing Phase I/II study for Granite and Slate |
| **iTeos Therapeutics** | Advanced solid tumors (EOS-850); Solid Tumors (EOS-448) | Receptor based Immunotherapy (EOS-850); Checkpoint inhibitors (EOS-448) | Completed Phase I/Ib study for EOS-850; Undergoing Phase I/II study for EOS-448 |
| **Neon Therapeutics** | Metastatic melanoma, metastatic ovarian cancer (NEO-PTC-01); RAS pancreatic cancer, undisclosed solid tumors (NEO-SCS-01) | Adipose-derived MSC + scaffold Antigen based Immunotherapy | Completed preclinical development for NEO-PTC-01 in metastatic melanoma; preclinical development in other indications has not been completed |
| **PsiOxus Therapeutics** | Metastatic or advanced epithelial tumors (NG-641 and NG-350); Advanced solid tumors with a focus on non-small-lung cell cancer, colorectal cancer and squamous cell cancer of the head and neck); solid tumors (NG-348) | Gene Therapy | All the product candidates are undergoing Phase I study |
| **Unum Therapeutics** | Various solid tumor indications (BOX-1030); Relapsed or refractory non-Hodgkin lymphoma (ACTR707) | T-cell based Immunotherapy | BOX-1030 in preclinical development; ACTR707 in Phase I study |
| **Vaccinex** | Advanced solid tumors, advanced non-small-cell lung cancer | Anti-Semaphorin 4D immunotherapy | Pepinemab (VX15/2503) completed Phase I study for advanced solid tumors and is undergoing Phase Ib/II study for advanced non-small cell lung cancer |
| **X4 Pharma** | Clear cell renal carcinoma (Mavorixafor); Glioblastoma (X4P-002) | Anti-CXCR4 based immunotherapy | Undergoing Phase Ib study for Mavorixafor for clear cell renal carcinoma; Completed preclinical development of X4P-002 in glioblastoma |

## 5. Valuation

Our valuation approach is based on rNPV and Company Comparable Analysis. The Fair Market Value for all of the company's publicly traded shares stood between EUR 38.0 mn and EUR 46.3 mn on July 01, 2020, and the Fair Market Value of a single share was between EUR 0.95 and EUR 1.16.

### 5.1 rNPV Analysis

| Pancreatic Indication (US & EUROPE) (EUR '000) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **High Scenario** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** | **2028E** |
| NOXXON Target Population | - | - | - | - | - | 2,600 | 5,268 | 8,005 |
| Royalty Revenue from Drugs | - | - | - | - | - | 32,957 | 66,977 | 102,132 |
| Upfront Payment | 40,000 | - | - | - | - | - | - | - |
| Milestone Payment | - | - | - | - | - | 20,000 | - | - |
| **Risk-Adjusted Cash Flows** | **1,019** | **(115)** | **(154)** | **(346)** | **(346)** | **1,301** | **1,848** | **2,820** |
| **rNPV of Cash Flows** **6,864** | | | | | | | | |
| **In the model, we have calculated rNPV until 2032.* | | | | | | | | |

| Pancreatic Indication (US & EUROPE) (EUR '000) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Low Scenario** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** | **2028E** |
| NOXXON Target Population | - | - | - | - | - | 2,698 | 4,966 | 7,910 |
| Royalty Revenue from Drugs | - | - | - | - | - | 21,781 | 43,072 | 68,703 |
| Upfront Payment | 36,000 | - | - | - | - | - | - | - |
| Milestone Payment | - | - | - | - | - | 16,000 | - | - |
| **Risk-Adjusted Cash Flows** | **806** | **(77)** | **(109)** | **(205)** | **(205)** | **715** | **1,034** | **1,649** |
| **rNPV of Cash Flows** **3,987** | | | | | | | | |
| **In the model, we have calculated rNPV until 2032.* | | | | | | | | |

**Probability of success used is 3.2%*

| Colorectal Indication (US & EUROPE) (EUR '000) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **High Scenario** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** | **2028E** |
| NOXXON Target Population | - | - | - | - | - | 5,726 | 10,128 | 20,637 |
| Royalty Revenue from Drugs | - | - | - | - | - | 49,491 | 94,894 | 178,700 |
| Upfront Payment | - | - | 40,000 | - | - | - | - | - |
| Milestone Payment | - | - | - | - | - | 30,000 | - | - |
| **Risk-Adjusted Cash Flows** | **(295)** | **(295)** | **2,165** | **(886)** | **(886)** | **4,520** | **5,836** | **10,990** |
| **rNPV of Cash Flows** **31,799** | | | | | | | | |
| **In the model, we have calculated rNPV until 2032.* | | | | | | | | |

| Colorectal Indication (US & EUROPE) (EUR '000) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Low Scenario** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** | **2028E** |
| NOXXON Target Population | - | - | - | - | - | 2,807 | 7,064 | 17,258 |
| Royalty Revenue from Drugs | - | - | - | - | - | 23,050 | 64,817 | 141,972 |
| Upfront Payment | - | - | 34,000 | - | - | - | - | - |
| Milestone Payment | - | - | - | - | - | 24,000 | - | - |
| **Risk-Adjusted Cash Flows** | **(344)** | **(344)** | **1,734** | **(968)** | **(968)** | **2,402** | **3,986** | **8,731** |
| **rNPV of Cash Flows** **23,623** | | | | | | | | |
| **In the model, we have calculated rNPV until 2032.* | | | | | | | | |

**Probability of success used is 8.2%*

| Brain & CNS Indication (US & EUROPE) (EUR '000) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **High Scenario** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** | **2028E** |
| NOXXON Target Population | - | - | - | 539 | 2,100 | 2,755 | 3,702 | 4,541 |
| Royalty Revenue from Drugs | - | - | - | 7,443 | 19,488 | 25,750 | 34,645 | 40,630 |
| Upfront Payment | 32,000 | - | - | - | - | - | - | - |
| Milestone Payment | - | - | 10,000 | - | 10,000 | - | - | - |
| **Risk-Adjusted Cash Flows** | **1,163** | **(342)** | **(410)** | **540** | **1,175** | **1,101** | **1,481** | **1,737** |
| **rNPV of Cash Flows** **5,810** | | | | | | | | |
| **In the model, we have calculated rNPV until 2032.* | | | | | | | | |

| Brain & CNS Indication (US & EUROPE) (EUR '000) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Low Scenario** | **2021E** | **2022E** | **2023E** | **2024E** | **2025E** | **2026E** | **2027E** | **2028E** |
| NOXXON Target Population | - | - | - | 298 | 1,625 | 2,249 | 3,150 | 3,950 |
| Royalty Revenue from Drugs | - | - | - | 3,903 | 13,295 | 18,776 | 26,531 | 31,607 |
| Upfront Payment | 28,000 | - | - | - | - | - | - | - |
| Milestone Payment | - | - | - | 8,000 | 8,000 | - | - | - |
| **Risk-Adjusted Cash Flows** | **958** | **(382)** | **(462)** | **216** | **782** | **803** | **1,134** | **1,351** |
| **rNPV of Cash Flows** **4,105** | | | | | | | | |
| **In the model, we have calculated rNPV until 2032.* | | | | | | | | |

**Probability of success used is 5.7%*

## 5.2 Comparable Company Analysis

The Fair Market Value of NOXXON Pharma's total publicly traded shares stood at EUR 49.6 mn on July 01, 2020, according to the relative valuation method.

| Company Name | Market Cap (EUR mn) | Enterprise Value (EUR mn) | R&D Expenditure FY2019 (EUR mn) | EV/R&D |
|---|---|---|---|---|
| BioLineRx | 30.1 | 19.6 | 20.9 | 0.94 |
| Kura Oncology | 811.5 | 622.6 | 42.7 | 14.57 |
| Gritstone Oncology | 220.4 | 142.6 | 74.1 | 1.93 |
| Oncolytics Biotech inc | 67.8 | 48.4 | 7.5 | 6.46 |
| X4 Pharma Cambridge | 134.0 | 54.5 | 26.9 | 2.02 |
| Transgene SA | 124.8 | 110.1 | 31.4 | 3.51 |
| NuCana PLC | 156.5 | 103.5 | 22.5 | 4.60 |
| Mustang Bio Inc | 152.1 | 115.9 | 32.4 | 3.57 |
| CTI BioPharma Corp | 76.1 | 27.2 | 21.5 | 1.26 |
| **Average** | | | | **4.3** |

### Listed Comparable Analysis

| Relative Valuation based on: | Weights | Multiple | R&D Expenditure (FY 2020) (EUR `000) | Implied Enterprise Value (EUR `000) | Implied Equity Value (EUR `000) |
|---|---|---|---|---|---|
| EV/R&D | 100.0% | 4.32 | 12,100 | 52,248 | 49,599 |

**Estimation of Final Equity Value**

The fair value of NOXXON Pharma's equity has been calculated using two approaches – Comparable Company Analysis and rNPV Analysis. The risk Adjusted NPV Analysis has been given a 65% weightage, and Comparable Company Analysis has been given a 35% weightage. The results are summarized in the tables below:

| Equity Value: HIGH Scenario (EUR '000) | | |
|---|---|---|
| **Valuation Approach** | **Weight** | **Value** |
| **Risk Adjusted NPV:** | | |
| Pancreatic | | 6,864 |
| Colorectal | | 31,799 |
| Brain | | 5,810 |
| Value from risk Adjusted NPV Analysis | 65.0% | 44,473 |
| Value from Comparable Company Analysis | 35.0% | 49,599 |
| **Weighted Average Target Market Cap** | | **46,267** |
| Shares o/s ('000) | | 39,937 |
| **Intrinsic Value per share (EUR)** | | **1.16** |
| Current Market Price *30-June-20* | | 0.57 |
| Upside/Downside | | 103% |

| Equity Value: LOW Scenario (EUR '000) | | |
|---|---|---|
| **Valuation Approach** | **Weight** | **Value** |
| **Risk Adjusted NPV:** | | |
| Pancreatic | | 3,987 |
| Colorectal | | 23,623 |
| Brain | | 4,105 |
| Value from risk Adjusted NPV Analysis | 65.0% | 31,715 |
| Value from Comparable Company Analysis | 35.0% | 49,599 |
| **Weighted Average Target Market Cap** | | **37,975** |
| Shares o/s ('000) | | 39,937 |
| **Intrinsic Value per share (EUR)** | | **0.95** |
| Current Market Price *30-June-20* | | 0.57 |
| Upside/Downside | | 67% |

Below is the detailed methodology for our two valuation approaches:

### 1. rNPV Analysis (65% weightage)

- **Valuation Methodology:** The Arrowhead fair valuation for NOXXON Pharma is based on the rNPV analysis of the three different indications of NOX-A12.
- **Time Horizon:** The time period used for valuation is 13 years (2020E to 2032E). We believe NOX-A12 is the only revenue generator for the company in the near future.
- **Royalty Rate:** We have used a royalty rate of 10% to calculate royalty revenues
- **Prudential Nature of Valuation:** This Arrowhead Fair Value Bracket estimate is a relatively prudential estimate, as it is based on the company's key treatment, NOX-A12, and excludes the value of other treatments, which are in pre-clinical testing phase.

The discount rate for the rNPV Analysis has been assumed to be 12%, based on empirical market data. NOX-A12 is expected to be introduced in the market in the U.S. in 2024 and in Europe in 2025 for glioblastoma/glioma. The treatment will subsequently be introduced for the other two indications (pancreatic and colorectal cancer) in the following two years, the last being in 2026. The following tables show cash flows from the different indications up till 2028. Please refer our model for cash flow projections beyond 2028.

### 2. Comparable Company Analysis (35% weightage)

The Comparable Company Analysis method operates under the assumption that similar companies will have similar valuation multiples, such as EV/R&D. We have shortlisted companies that are comparable to NOXXON Pharma, based on parameters such as market size, drug pipeline, etc.

A list of available statistics for the companies was compiled, and the EV/R&D multiple was calculated for each of the comparable companies. Since most of the data was not normalized, we have left outliers in our calculations.

### Important information on Arrowhead methodology

The principles of the valuation methodology employed by Arrowhead BID are variable to a certain extent, depending on the sub-sectors in which the research is conducted. But all Arrowhead due diligence and valuation reports possess an underlying set of common principles and a generally common quantitative process.

With Arrowhead commercial and technical due diligence, Arrowhead researches the fundamentals, assets and liabilities of a company, and builds estimates for revenue and expenditure over a coherently determined forecast period.

Elements of past performance such as price/earnings ratios, indicated as applicable, are mainly for reference. Still, elements of real-world past performance enter the valuation through their impact on the commercial and technical due diligence.

We have presented the Risk Adjusted NPV and Comparable Company Analysis. The fair value bracket is built on the basis of these two methods.

### Arrowhead BID Fair Market Value Bracket

The Arrowhead Fair Market Value is given as a bracket. This is based on quantitative key variable analyses such as key price analysis for revenue and cost drivers or analysis and discounts on revenue estimates for projects, especially relevant to projects estimated to provide revenue near the end of the chosen forecast period. Low and high estimates for key variables are produced as a valuation tool.

In principle, an investor comfortable with the high brackets of our key variable analysis will align with the high bracket in the Arrowhead Fair Value Bracket, and, likewise, in terms of low estimates. The investor will also note the company intangibles to analyze the strengths and weaknesses, and other essential company information. These intangibles serve as supplementary decision factors for adding or subtracting a premium in the investor's own analysis.

The bracket should be taken as a tool provided by Arrowhead BID for the reader of this report and the reader should not solely rely on this information to make his decision on any particular security. The reader must also understand that while on the one hand global capital markets contain inefficiencies, especially in terms of information, on the other hand, corporations and their commercial and technical positions evolve rapidly. This present edition of the Arrowhead valuation is for a short to medium-term alignment analysis (one to twelve months).

# 6. Appendix

## 6.1 NOXXON Pharma's Financial Summary

**Exhibit 18: Financial Summary**

*Low Bracket Estimates*

| *Year Ending Dec* | 2025E | 2026E | 2027E | 2028E | 2029E | 2030E | 2031E | 2032E |
|---|---|---|---|---|---|---|---|---|
| Revenue (EUR '000) | 2,165 | 7,184 | 9,336 | 16,862 | 22,248 | 24,803 | 32,684 | 33,138 |
| Operating Profit (EUR '000) | (20,162) | 3,810 | 5,732 | 13,012 | 18,134 | 20,407 | 27,987 | 28,118 |
| Net Income (EUR'000 | (19,451) | 2,889 | 4,412 | 9,994 | 14,102 | 16,182 | 22,298 | 22,987 |
| EPS (EUR) | (0.36) | 0.05 | 0.08 | 0.18 | 0.26 | 0.30 | 0.41 | 0.42 |
| EBITDA (EUR '000) | (23,063) | (20,108) | 3,870 | 5,797 | 13,084 | 18,212 | 20,492 | 28,079 |
| **Growth rates (%)** | | | | | | | | |
| Revenue | 40% | 232% | 30% | 81% | 32% | 11% | 32% | 1% |
| Operating Profit | (13%) | (119%) | 50% | 127% | 39% | 13% | 37% | 0% |
| Net Income | (10%) | (115%) | 53% | 126% | 41% | 15% | 38% | 3% |
| EPS | (10%) | (115%) | 53% | 126% | 41% | 15% | 38% | 3% |
| EBITDA | NM | (13%) | (119%) | 50% | 126% | 39% | 13% | 37% |
| **Margins (%)** | | | | | | | | |
| Operating Profit | NM | NM | NM | NM | NM | NM | NM | NM |
| Net Profit Margin | NM | NM | NM | NM | NM | NM | NM | NM |
| EBITDA Margins | (1494%) | (929%) | 54% | 62% | 78% | 82% | 83% | 86% |
| **Ratios** | | | | | | | | |
| ROA | NM | 60.7% | 46.9% | 51.0% | 41.5% | 32.1% | 30.6% | 23.9% |
| ROE | NM | 82.7% | 122% | NM | NM | NM | NM | NM |

**Exhibit 19: Financial Summary**

*High Bracket Estimates*

| *Year Ending Dec* | 2025E | 2026E | 2027E | 2028E | 2029E | 2030E | 2031E | 2032E |
|---|---|---|---|---|---|---|---|---|
| Revenue (EUR '000) | 2,632 | 10,727 | 13,029 | 21,458 | 28,432 | 32,808 | 41,648 | 42,323 |
| Operating Profit (EUR '000) | (22,542) | 7,695 | 9,848 | 18,120 | 24,930 | 29,133 | 37,792 | 38,276 |
| Net Income | (21,446) | 6,040 | 7,830 | 14,242 | 19,722 | 23,399 | 30,515 | 31,684 |
| EPS (EUR) | (0.39) | 0.11 | 0.14 | 0.26 | 0.36 | 0.43 | 0.56 | 0.58 |
| EBITDA (EUR '000) | (24,937) | (22,488) | 7,754 | 9,913 | 18,192 | 25,008 | 29,218 | 37,884 |
| **Growth rates (%)** | | | | | | | | |
| Revenue | 42% | NM | 21% | 65% | 33% | 15% | 27% | 2% |
| Operating Profit | (10%) | (134%) | 28% | 84% | 38% | 17% | 30% | 1% |
| Net Income | (7%) | (128%) | 30% | 82% | 38% | 19% | 30% | 4% |
| EPS | (7%) | (128%) | 30% | 82% | 38% | 19% | 30% | 4% |
| EBITDA | (217%) | (10%) | (134%) | 28% | 84% | 37% | 17% | 30% |
| **Margins (%)** | | | | | | | | |
| Operating Profit | NM | NM | NM | NM | NM | NM | NM | NM |
| Net Profit Margin | NM | NM | NM | NM | NM | NM | NM | NM |
| EBITDA Margins | (1341%) | (854%) | 72% | 76% | 85% | 88% | 89% | 91% |
| **Ratios** | | | | | | | | |
| ROA | (201.9%) | 34.8% | 30.9% | 36.0% | 33.1% | 28.1% | 26.8% | 21.7% |
| ROE | NM | 143.7% | 185% | NM | NM | NM | NM | NM |


See important disclosures on page 45 of this report

## 6.2 NOXXON Pharma's Balance Sheet Forecast

**Exhibit 20: Consolidated Balance Sheet** All figures in EUR '000, unless stated differently *Low Bracket estimates*

| *Year Ending Dec* | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E | 2027E |
|---|---|---|---|---|---|---|---|---|
| Total current assets | 116 | 94 | 70 | 93 | 119 | 146 | 174 | 201 |
| Total non-current assets | (1,884) | 43,476 | 29,871 | 41,894 | 20,555 | 1,442 | 4,584 | 9,211 |
| **TOTAL ASSETS** | **(1,767)** | **43,570** | **29,942** | **41,988** | **20,675** | **1,588** | **4,757** | **9,413** |
| Total current liabilities | (4,259) | 41,023 | 27,384 | 39,153 | 17,606 | (1,738) | 1,258 | 5,777 |
| Total non-current liabilities | 52 | 31 | 4 | 4 | 4 | 4 | 4 | 4 |
| **TOTAL LIABILITIES** | **(4,207)** | **41,054** | **27,389** | **39,157** | **17,611** | **(1,733)** | **1,263** | **5,782** |
| Total shareholder's equity | 2,439 | 2,516 | 2,553 | 2,831 | 3,064 | 3,322 | 3,495 | 3,631 |
| **TOTAL LIABILITIES & EQUITY** | **(1,767)** | **43,570** | **29,942** | **41,988** | **20,675** | **1,588** | **4,757** | **9,413** |

**Exhibit 21: Consolidated Balance Sheet** All figures in EUR '000, unless stated differently *High Bracket estimates*

| *Year-Ending Dec* | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E | 2027E |
|---|---|---|---|---|---|---|---|---|
| Total current assets | 116 | 94 | 70 | 93 | 119 | 146 | 174 | 201 |
| Total non-current assets | (1,644) | 50,094 | 36,794 | 54,293 | 31,563 | 10,475 | 17,172 | 25,100 |
| **TOTAL ASSETS** | **(1,528)** | **50,188** | **36,864** | **54,386** | **31,683** | **10,621** | **17,346** | **25,301** |
| Total current liabilities | (4,020) | 47,481 | 34,307 | 51,317 | 28,330 | 6,992 | 13,138 | 21,075 |
| Total non-current liabilities | 52 | 31 | 4 | 4 | 4 | 4 | 4 | 4 |
| **TOTAL LIABILITIES** | **(3,968)** | **47,512** | **34,311** | **51,321** | **28,335** | **6,996** | **13,143** | **21,079** |
| Total shareholder's equity | 2,439 | 2,676 | 2,553 | 3,065 | 3,348 | 3,625 | 4,203 | 4,222 |
| **TOTAL LIABILITIES & EQUITY** | **(1,528)** | **50,188** | **36,864** | **54,386** | **31,683** | **10,621** | **17,346** | **25,301** |

## 7. Analyst Certifications

I, Sumit Wadhwa, certify that all the views expressed in this research report accurately reflect my personal views about the subject security and the subject Company, based on the collection and analysis of public information and public company disclosures.

I, Manish Purohit, certify that all the views expressed in this research report accurately reflect my personal views about the subject security and the subject Company, based on the collection and analysis of public information and public company disclosures.

### Important disclosures

Arrowhead Business and Investment Decisions, LLC has received fees in 2019-20 and will receive further fees in 2020 from NOXXON Pharma for researching and drafting this report and for a series of other services to NOXXON Pharma including distribution of this report and networking services. Neither Arrowhead BID nor any of its principals or employees own any long or short positions in NOXXON Pharma. Arrowhead BID's principals intend to seek a mandate for investment banking services from NOXXON Pharma in the near-term and intend to receive compensation for investment banking activities for NOXXON Pharma in 2020 or 2021.

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## 8. Notes and Reference

[i] Source: Bloomberg, retrieved on July 01, 2020
[ii] Source: Bloomberg: 52 weeks to July 01, 2020
[iii] Source: Bloomberg: 3 months to July 01, 2020
[iv] Source: Arrowhead Business and Investment Decisions Fair Value Bracket-AFVBTM. See information on valuation on pages 40-42 of this report and important disclosure on pages 45 of this report
[v] Source: Company Website and Company Filings
[vi] Source: Company filings
[vii] Source: https://www.news-medical.net/health/Chemokine-Function.aspx
[viii] Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6414456/
[ix] Source: https://www.sciencedirect.com/topics/neuroscience/vasculogenesis
[x] Source: https://www.ncbi.nlm.nih.gov/pubmed/24338942
[xi] Source: https://ashpublications.org/blood/article/123/7/952/105655/NOX-A12-mobilizing-CLL-away-from-home
[xii] Source: https://www.noxxon.com/fr/downloads/investor/2017-07-10_NOXXON_Pharma_NV-Prospectus.pdf
[xiii] Source: https://ajp.amjpathol.org/article/S0002-9440(17)30006-8/fulltext
[xiv] Source: https://clincancerres.aacrjournals.org/content/16/1I/II927
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3175097/
[xv] Source: https://www.nature.com/articles/onc2011633
[xvi] Source: http://www.noxxon.com/downloads/presentation/2019-09-23_NOXXON_Gliobalstoma_Trial_Webinar_Script_EN.pdf
[xvii] Source: https://www.noxxon.com/downloads/presentation/2020-03-04_NOXXON_Corporate_Deck.pdf
[xviii] Source: http://www.noxxon.com/downloads/presentation/2019-09-23_NOXXON_Gliobalstoma_Trial_Webinar.pdf
[xix] Source: https://pubmed.ncbi.nlm.nih.gov/24338942/
[xx] Source: https://pubmed.ncbi.nlm.nih.gov/24338942/
[xxi] Source: https://www.spandidos-publications.com/10.3892/ol.2017.7512#
[xxii] Source: https://www.ncbi.nlm.nih.gov/pubmed/30834048
[xxiii] Source: https://www.medicalnewstoday.com/articles/323740
[xxiv] Source: https://www.cancer.org/cancer/colon-rectal-cancer/about/what-is-colorectal-cancer.html
[xxv] Source: https://www.mayoclinic.org/diseases-conditions/pancreatic-cancer/diagnosis-treatment/drc-20355427
https://www.pancan.org/facing-pancreatic-cancer/treatment/treatment-types/treatment-by-stage/
https://www.ajmc.com/journals/supplement/2019/managed-care-considerations-pancreatic-cancer/current-treatment-landscape--and-e
[xxvi] Source: https://www.cancer.net/cancer-types/colorectal-cancer/types-treatment
[xxvii] Source: www.bccresearch.com/market-research/pharmaceuticals/colorectal-cancer-therapeutics.html
[xxviii] Source: https://www.keytruda.com/how-does-keytruda-work/
[xxix] Source: https://www.futuremedicine.com/doi/10.2217/imt-2019-0164 https://www.cancernetwork.com/colorectal-cancer/immunotherapy-colorectal-cancer
[xxx] Source: Company Website
[xxxi] Source: Company Website
[xxxii] Source: Company Website
[xxxiii] Source: Company Website

[xxxiv] Source: Company Website
[xxxv] Source: https://www.cancer.net/cancer-types/brain-tumor/introduction
https://www.cancer.gov/publications/dictionaries/cancer-terms/def/glial-cell
[xxxvi] Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6468743/
[xxxvii] Source: Company Website
[xxxviii] Source: http://www.noxxon.com/downloads/presentation/2019-09-23_NOXXON_Gliobalstoma_Trial_Webinar.pdf
[xxxviii] Source: https://pubmed.ncbi.nlm.nih.gov/24338942/
[xl] Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6468743/
[xl] Source: Company Website
[xli] Source: Company Website
[xlii] Source: https://www.cancer.net/cancer-types/liver-cancer/introduction
https://www.webmd.com/cancer/understanding-liver-cancer-basic-information#1
[xliii] Source: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/macrophage
https://jhoonline.biomedcentral.com/articles/10.1186/s13045-019-0760-3
[xliv] Source: Company Filings and Press Releases
[xlv] Source: Company Filings
[xlvi] Source: Company Filings
[xlvii] Source: Company Filings
[xlviii] Source: https://www.sciencedirect.com/science/article/pii/S1818087615000860
[xlix] Source: Bloomberg
[l] Source: Bloomberg
[li] Source: Company Website
[lii] Source: Company Website
[liii] Source: Company Website
[liv] Source: https://www.who.int/cancer/PRGlobocanFinal.pdf
[lv] Source: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf
[lvi] Source:https://www.who.int/news-room/fact-sheets/detail/cancer
[lvii] Source: https://www.cancer.gov/about-cancer/understanding/what-is-cancer
[lviii] Source: https://www.ascopost.com/News/60247
[lix] Source: https://www.industryarc.com/Report/18335/oncology-market.html
[lx] Source: https://www.cancercenter.com/metastasis
[lxi] Source :https://www.marketresearchfuture.com/reports/chemotherapy-market-5791
[lxii] Source :https://www.marketsandmarkets.com/Market-Reports/radiotherapy-monitoring-devices-market-567.html?gclid=EAIaIQobChMIjaSq2L736AIV1DUrCh2qQQIKEAAYASAAEgIc0_D_BwE
[lxiii] Source :https://www.marketresearchfuture.com/reports/global-cancer-immunotherapy-market-567
[lxiv] Source: https://www.pharmacytimes.com/publications/Directions-in-Pharmacy/2020/February2020/patient-assistance-programs-a-lifeline-for-patients-with-cancer

[lxvlxvlxv] Source: https://www.cdc.gov/cancer/dcpc/about/programs.htm
[lxvi] Source: www.cancerresearch.org/immunotherapy/why-immunotherapy
[lxvii] Source: www.uclahealth.org/u-magazine/how-immunotherapy-became-the-next-big-thing
[lxviii] https://www.cancer.gov/about-cancer/treatment/types/immunotherapy
[lxix] https://voice.ons.org/news-and-views/what-oncology-nurses-need-to-know-about-immunotherapy-agents
[lxx] https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/what-is-immunotherapy.html
[lxxi] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6036358/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5848033/
[lxxii] Source: https://www.webmd.com/cancer/pancreatic-cancer/default.htm
[lxxiii] Source: https://www.openpr.com/news/1939845/pancreatic-cancer-market-2020-to-growth-us-13-billion-by-2025
https://www.prnewswire.com/news-releases/global-pancreatic-cancer-market-to-2026---advancement-of-technology-in-therapeutic-devices-and-expanding-prevalence-of-cancer-growth-300929743.html
[lxxiv] Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6396775/#R01
[lxxv] Source: https://www.mayoclinic.org/diseases-conditions/pancreatic-cancer/diagnosis-treatment/drc-20355427
https://www.pancan.org/facing-pancreatic-cancer/treatment/treatment-types/treatment-by-stage/
https://www.ajmc.com/journals/supplement/2019/managed-care-considerations-pancreatic-cancer/current-treatment-landscape--and-e
[lxxvi] Source: https://www.cancer.org/cancer/colon-rectal-cancer/about/what-is-colorectal-cancer.html
[lxxvii] Source: https://gco.iarc.fr/tomorrow/graphic-isotype?type=0&type_sex=0&mode=population&sex=0&populations=905_908_840&cancers=8&age_group=value&apc_male=0&apc_female=0&print=0#collapse-group-0-2
[lxxviii] Source: https://gco.iarc.fr/tomorrow/graphic-isotype?type=0&type_sex=0&mode=population&sex=0&populations=905_908_840&cancers=9&age_group=value&apc_male=0&apc_female=0&print=0#collapse-group-0-2
[lxxix] Source: https://www.wcrj.net/wp-content/uploads/sites/5/2019/11/e1433-Worldwide-incidence-and-mortality-of-colorectal-cancer-and-Human-Development-Index-HDI-an-ecological-study.pdf
[lxxx] Source: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2017-2019.pdf
[lxxxi] Source: https://www.ccalliance.org/colorectal-cancer-information/statistics-risk-factors
[lxxxii] Source: https://www.bccresearch.com/market-research/pharmaceuticals/colorectal-cancer-therapeutics.html
[lxxxiii] https://www.cancer.net/cancer-types/colorectal-cancer/types-treatment
[lxxxiv] Source: www.cancerresearchuk.org/about-cancer/brain-tumours/risks-causes
[lxxxv] Source: www.marketwatch.com/press-release/global-brain-tumor-therapeutics-market-size-share-and-forecast-2020-to-2023-research-report-by-industry-types-applications-and-latest-trend-and-growth-analysis-2020-03-13
[lxxxvi] Source: www.marketwatch.com/press-release/glioblastoma-market-2019-to-2025--overview-global-industry-trends-share-size-and-forecast-report-2019-10-16
[lxxxvii] Source: www.frontiersin.org/articles/10.3389/fonc.2019.00963/full
[lxxxviii] Source :www.gliocure.com/en/patients/glioblastoma/
[lxxxix] Source: www.ncbi.nlm.nih.gov/pmc/articles/PMC5123811/

[xc] Source: www.cancer.net/cancer-types/brain-tumor/types-treatment
[xci] Source: https://www.fda.gov/media/71195/download;
Source: https://www.focr.org/fda-regulatory-policy;
Source: https://www.fda.gov/drugs/special-features/frequently-asked-questions-about-fda-drug-approval-process#2
[xcii] Source: https://www.ema.europa.eu/en/about-us/frequently-asked-questions
[xciii] Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6728416/
[xciv] Source: https://www.x4pharma.com/
https://www.ctibiopharma.com/pacritinib/
http://neontherapeutics.com/product-pipeline/
https://gritstoneoncology.com/our-pipeline/